

**Dual-Biomimetic Meroterpenoid
Syntheses. A Study of Acetylenic
Terpenes in Polyene Cyclizations Applied
to the Synthesis of Resorcylate Natural
Products.**

A thesis submitted by

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DOCTOR OF PHILOSOPHY in the Faculty of Natural Sciences
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DECLARATIONS

Declaration of Originality

I, Thomas Mies, declare that the work in this thesis was carried out under the supervision of Prof. Anthony G. M. Barrett. Except where indicated by specific references in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of others is indicated as such.

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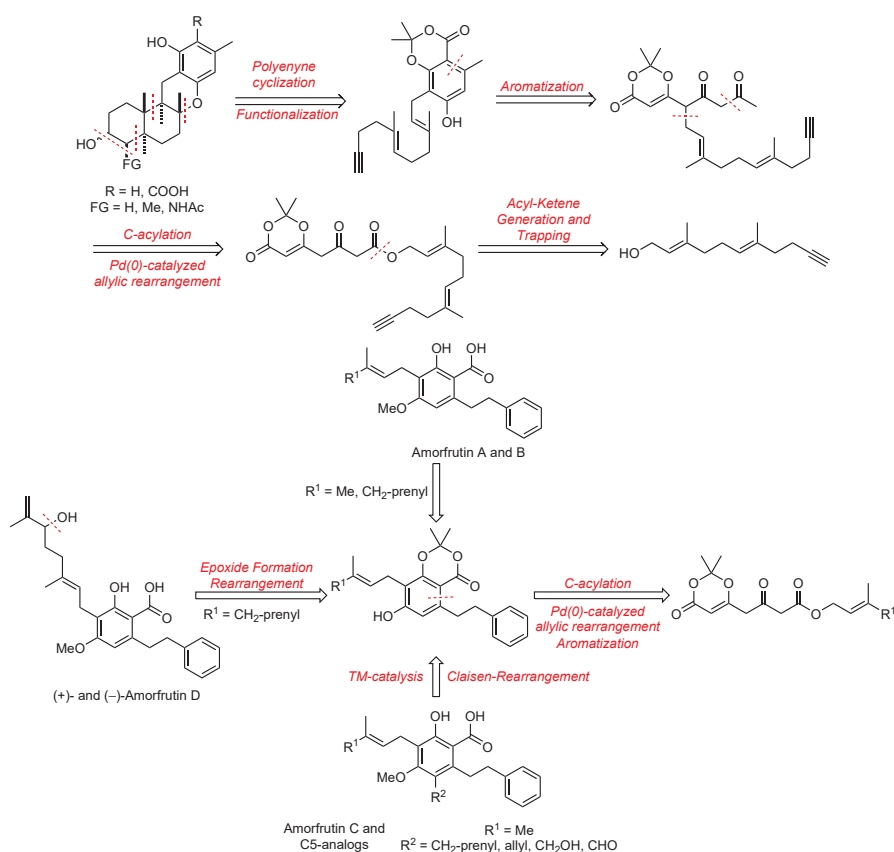
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External Reviewer: Prof. Darren Dixon

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Abstract

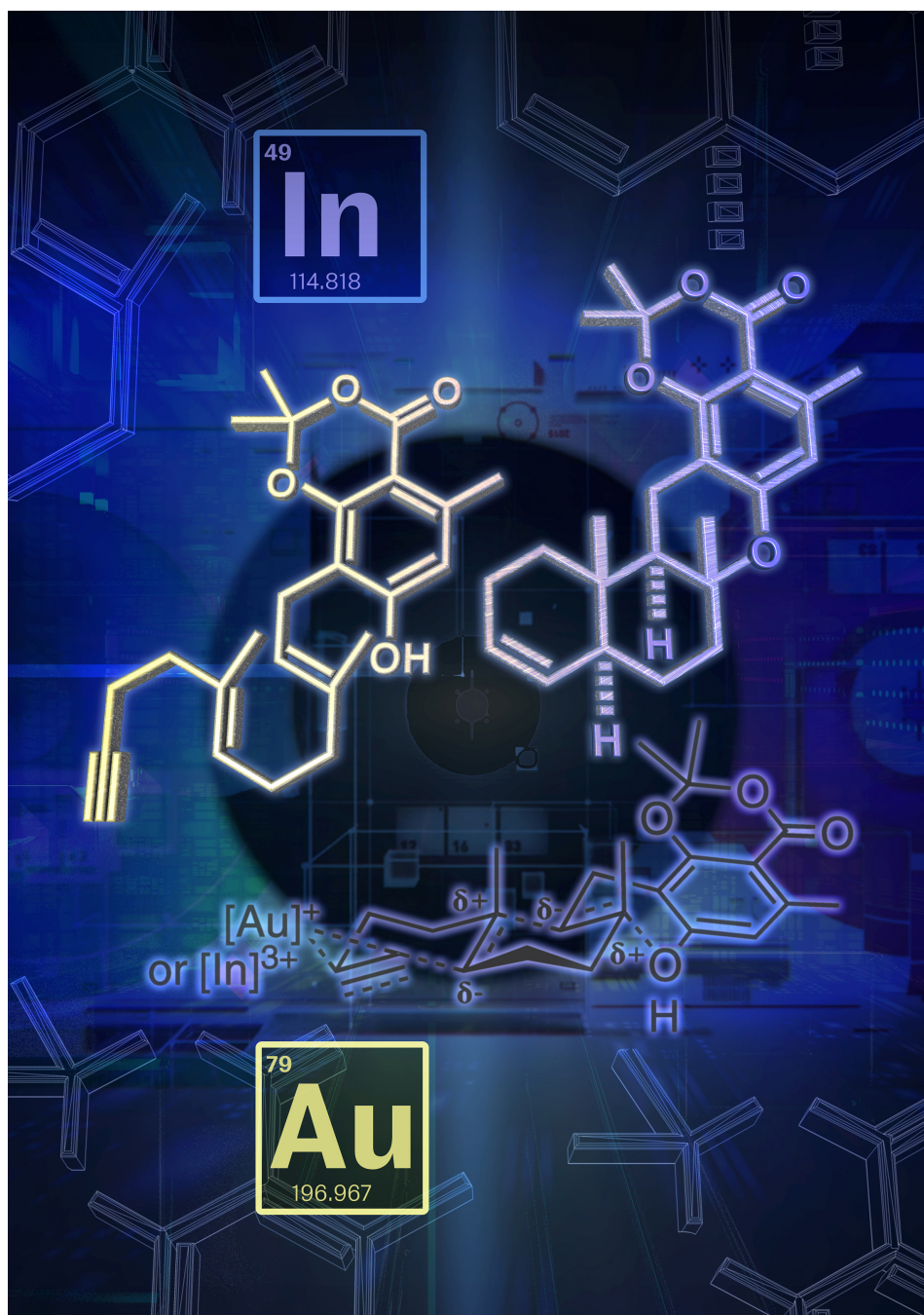
Meroterpenoids are a class of natural products derived from a mixed biosynthetic origin, with an arene entity originating from the polyketide pathway and the polyene unit originating from the terpene pathway. These natural products display a multitude of biological activities. The Barrett group has reported successful syntheses of meroterpenoid natural products, including those derived from polyene cyclizations. The first part of this thesis studied the chemical space around non-natural acetylenic polyene resorcyates for their reactivity in biomimetic polyene cyclizations, which were synthesized by means of remote terpene functionalization, acetylene installation with *in situ* deprotection and established biomimetic polyketide aromatization procedures developed within the Barrett group. The results should be of interest for structure-activity-relationship (SAR) studies and enable future derivatization studies. The second part of this thesis concerns the synthesis



of amorfrutin natural products, which was done in collaboration with a final year undergraduate student. Natural products isolated from *Amorpha fruticosa* display a range of bioactivities with unusual specificity. For

SAR purposes, a unified approach was designed to synthesize these natural products. The syntheses followed a biosynthetic proposal of interconversion between the amorfrutins. Thus, the biomimetic strategy of polyketide aromatization enabled the synthesis of amorfrutin B, which in turn displays the core structure of (*S*)- and (*R*)-amorfrutin D. Amorfrutin A to amorfrutin C conversion and the synthesis of C₅ analogs are described.

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joyable and fruitful and therefore a particular mention to some past and present co-workers is in order, who have helped me expand my chemical knowledge with their experience over the years. In chronological order: I have learnt a great deal during my undergraduate studies from Dr. Felix Hartrampf, educating me in practical organic chemistry and showing me every little trick to solve practical problems. Dr. Sarah Goldstein and Dr. Joshua Almond-Thynne for their endless patience with me during my first two years in the Barrett group. They have been fundamental to my work with their support and knowledge they shared with me, even after leaving the group. Dr. Samuel Spreadbury for countless occasions of after-work beverages and casual discussion about chemistry and life. Dr. Lewis Allen from the Parsons group has been very helpful on various occasions ever since I joined IC in 2016. Calum Patel has been an outstanding undergraduate student. It was hugely enjoyable mentoring Calum on his final year project and working with him very successfully on the Amorfrutin project.

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LIST OF ABBREVIATIONS

Ac - Acetyl = $\text{CH}_3\text{--C(O)--R}$

AD - Asymmetric Dihydroxylation (Sharpless Dihydroxylation)

Ar - Aryl

BDSB - Bromodiethylsulfonium bromopentachloroantimonate(V)

BINOL - 1,1'-Bi-2-naphthol

Bn - Benzyl = $\text{C}_6\text{H}_5\text{--CH}_2\text{--R}$

Boc - *tert*-butoxycarbonyl = $(\text{CH}_3)_3\text{C--C(O)--R}$

BrettPhos -

2-Dicyclohexylphosphino-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl

Bz - Benzoyl = $\text{C}_6\text{H}_5\text{--C(O)--R}$

tert-Bu - *tert*-butyl = 1,1-dimethylethyl; $(\text{CH}_3)_3\text{C--R}$

CBS-catalyst - Corey-Bakshi-Shibata oxazaborolidine based catalyst

CDSC - Chlorodiethylsulfonium hexachloroantimonate (V)

cod - Cycloocta-1,5-diene

DA - Diels-Alder

DCC - *N,N'*-Dicyclohexylcarbodiimide

DCM - Dichloromethane

dba - Dibenzylideneacetone

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

DDQ - 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone

DIAD - Diisopropyl azodicarboxylate

DIPEA - *N,N*-Diisopropylethylamine

DMAP - IUPAC: *N,N*-Dimethylpyridin-4-amine; Trivial Name:

4-Dimethylaminopyridine

DMB - 3,4-Dimethoxybenzyl

DMF - *N,N*-Dimethylformamide

DMP - Dess-Martin periodinane

DMSO - Dimethyl sulfoxide

DPPE - Ethane-1,2-diylbis(diphenylphosphane)

d.r. - Diastereomeric ratio

ds - Diastereoselectivity

e.e. - Enantiomeric excess

e.r. - Enantiomeric ratio

Et - Ethyl

EtOAc - Ethyl Acetate = $\text{CH}_3\text{CH}_2\text{OC(O)CH}_3$

eq./equiv. - equivalent

FG - Functional Group

HFIP - 1,1,1,3,3,3-Hexafluoro-propan-2-ol, Hexafluoroisopropanol

Hz - Hertz

im - 1*H*-Imidazole

iPr - *iso*-Propyl = 1-methylethyl; $(\text{CH}_3)_2\text{CH}-\text{R}$

IR - Infrared

KOTMS - Potassium trimethylsilanolate

LDA - Lithium diisopropylamide

LiHMDS - Lithium hexamethyldisilazide

Mander's Reagent - Methyl cyanoformate = $\text{CH}_3\text{OC(O)CN}$

m - *meta*

m-CPBA - *m*-chloroperoxybenzoic acid = $m\text{-Cl-C}_6\text{H}_4\text{-C(O)-O-OH}$

Me - Methyl

MOM - Methoxymethyl

NBS - *N*-Bromosuccinimide

NMR - Nuclear Magnetic Resonance

NOE - nuclear Overhauser effect

Nu - Nucleophile

Ns - *p*-nitrobenzenesulfonyl = $p\text{-O}_2\text{N-C}_6\text{H}_4\text{-SO}_2\text{-R}$

NTf₂⁻ - bis(trifluoromethane)sulfonimide anion

o - *ortho*

p - *para*

PG - Protecting group

Ph - Phenyl

PKS - Polyketide Synthase

PMB - *p*-Methoxy-benzyl = $p\text{-H}_3\text{CO-C}_6\text{H}_4\text{-CH}_2\text{-R}$

ppm - parts per million

PPP - Bis(diphenylphosphinoethyl)phenylphosphine

p-TsOH - 4-Methylbenzene-1-sulfonic acid

RAL - Resorcylic Acid Lactones

Ra-Ni - Raney-Nickel

R.T. - Room Temperature

SCoA - Acetyl-S Coenzyme A

TBAF - Tetra-*n*-butylammonium fluoride

TBDMS/TBS - *tert*-butyl dimethyl silyl

THF - Tetrahydrofuran

Tf - Triflyl/Trifluoromethanesulfonyl = $\text{F}_3\text{C}-\text{SO}_2-\text{R}$

TMS - Trimethylsilyl

Ts - *p*-toluenesulfonyl = $p-\text{H}_3\text{C}-\text{C}_6\text{H}_4-\text{SO}_2-\text{R}$

XPhos - 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Part I

INTRODUCTION

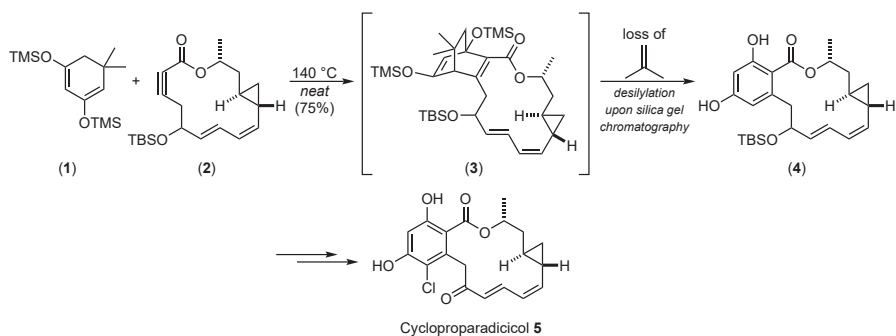
BACKGROUND

1.1 AROMATIZATION METHODS

The concept of aromaticity is a cornerstone of the education of undergraduate chemists, owing to the abundance of arene cores found in the chemical world. Indeed, aromatic entities are ubiquitous in natural products, drugs, molecular machines and polymers.^[1,2] In the early stages of chemical history, aromatic compounds like benzenes, phenols, anilines or polycyclic aromatic hydrocarbons (PAH) were extracted from crude oil or coal tar.^[3] Understanding the conversion of benzene into the above named derivatives prompted the discovery of radical- or ionic-nucleophilic or -electrophilic substitution reactions.^[3,4] Perhaps due to the chronological order of discovery, the lecture courses on aromatic compounds often start with these methods. However, due to the distinct electronic natures of arenes required for nucleophilic or electrophilic aromatic substitution reactions, the products are often limited to either *o*-, *m*- or *p*-substituted derivatives of higher complexity.

On the other hand, the synthesis of arene entities from (non-)cyclic non-aromatic precursors provides a suitable alternative to overcome these limitations, as it can furnish products with controlled selectivity often not accessible through the above mentioned, classical arene functionalization methods.^[3,5,6] In addition, cheaper starting materials and less expensive or sophisticated catalysts or reagents add further beneficial effects to this approach.^[2,7] This strategy is often found in the synthesis of heteroaromatic compounds, and, thus, more commonly found in advanced chemistry lectures.

The chemical literature contains a myriad of aromatization methods and reviews thereof.^[2,3,5-14] The following section will present a selection of common aromatization methods, focussing on heavily substituted arenes, and, in most cases, applied to the total syntheses of resorcyate natural products.

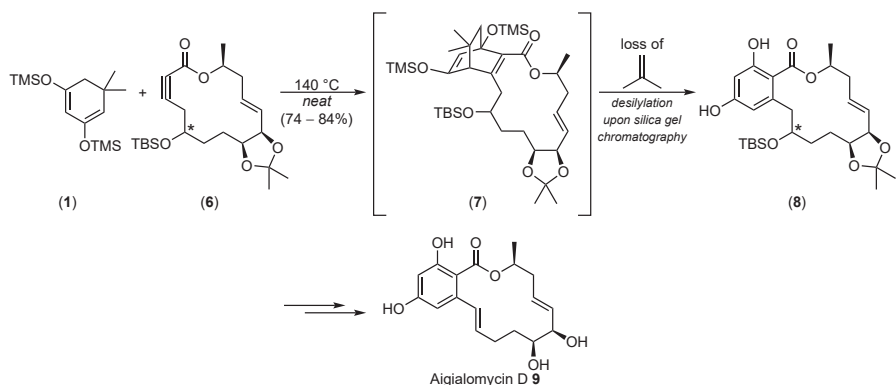


Scheme 1.1: Danishefsky's aromatization reaction in the total synthesis of cycloproparadicicol **5**.

For a more comprehensive selection of current methods of aromatization see the addendum.^[15]

Danishefsky and co-workers reported the total syntheses of the resorcylic acid lactone (RAL) natural products cycloproparadicicol **5** and aigialomycin D **9** via a late stage aromatization strategy, Schemes 1.1 and 1.2.^[16–18] The reaction of ynolide (**2**) with the dimedone derived diene, 5,5-dimethyl-1,3-bis-trimethylsilyloxycyclohexa-1,3-diene (**1**), gave the initial Diels-Alder (DA) adduct (**3**), which upon a retro-Diels-Alder (rDA) reaction and concomitant loss of isobutylene gas gave resorcyate (**4**) in 75% yield. Functional group interconversion gave cycloproparadicicol **5** in five additional steps and an overall yield of 33% from arene (**4**).

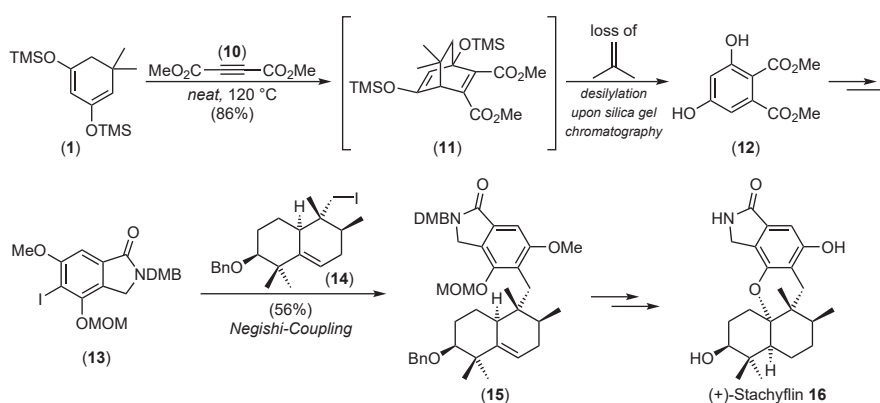
For the synthesis of aigialomycin D **9**, the separate reaction of disiloxidiene (**1**) with the individual epimers of ynolide (**6**) gave the two arene epimers (**8**) in 74% and 84% yield after the DA-rDA sequence with expulsion of isobutylene gas, Scheme 1.2. Deprotection and desaturation gave aigialomycin D **9**.



Scheme 1.2: Danishefsky's aromatization reaction in the total synthesis of aigialomycin D **9**.

in 38% - 42% yield from arenes (8).

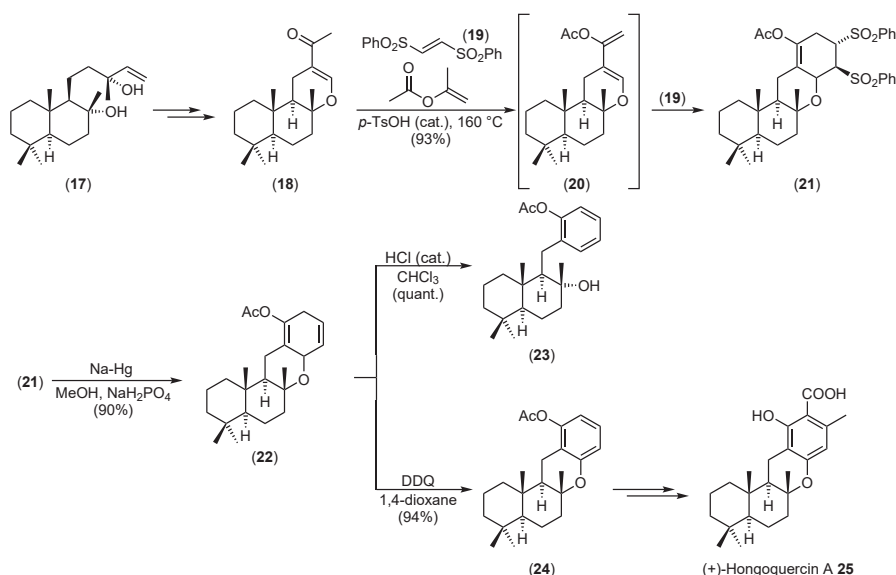
Magauer and co-workers successfully employed Danishefsky's protocol to furnish the arene entity of (+)-stachyflin **16**, a potent anti-viral meroterpenoid, Scheme 1.3.^[19,20] The reaction of diene (**1**) with dimethyl acetylenedicarboxylate (DMAD) (**10**) gave arene (**12**) after the DA-rDA reaction sequence with loss of isobutylene gas. Further functional group interconversion gave lactam (**13**) which was coupled to iodide (**14**) *via* a key Negishi-coupling reaction to give the advanced intermediate (**15**). Deprotection and cyclization gave the natural product (+)-stachyflin **16** with a *cis*-decalin core and a pentasubstituted arene moiety.



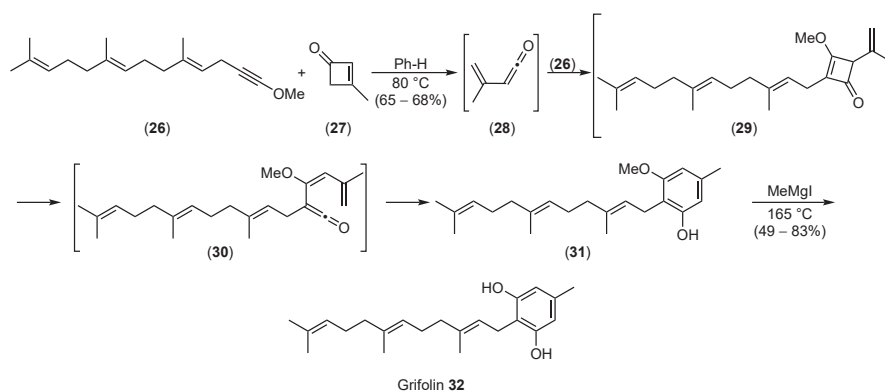
Scheme 1.3: Magauer's aromatization reaction in the total synthesis of (+)-stachyflin **16**.

Recently, Alvarez and co-workers reported the total synthesis of (+)-hongoquercin A **25** employing a Diels-Alder and oxidative aromatization strategy, Scheme 1.4.^[21] The reaction of enone (**18**) with isopropenyl acetate gave intermediate diene (**20**), which reacted with olefin (**19**) to give the Diels-Alder adduct (**21**) in excellent yields (93%), as an inconsequential mixture of diastereoisomers. Reductive desulphonation gave diene (**22**), which was aromatized with a catalytic amount of hydrochloric acid to arene (**23**). Alternatively, oxidative aromatization with DDQ gave arene (**24**), which was subsequently converted into the natural product **25**.

Danheiser and co-workers developed a strategy to synthesize arenes from cyclobutenones and acetylenes, Scheme 1.5.^[22] For the synthesis of grifolin **32**, heating cyclobutenone (**27**) in the presence of farnesyl substituted acetylene (**26**) gave cyclobutenone (**29**) after thermal 4π -electrocyclic ring-opening and a thermal [2+2]-cycloaddition reaction between ketene (**28**) and acetylene (**26**).



Scheme 1.4: Alvarez's aromatization reaction in the synthesis of meroterpenoids.

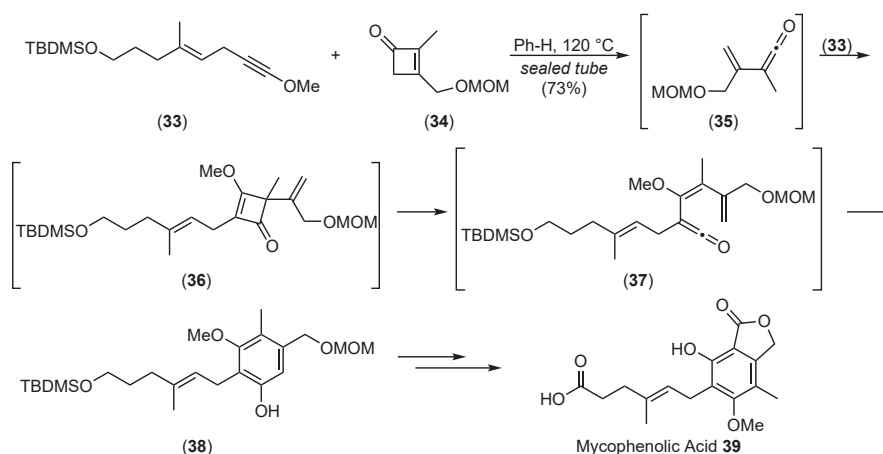


Scheme 1.5: Danheiser's benzannulation reaction in the total synthesis of grifolin 32.

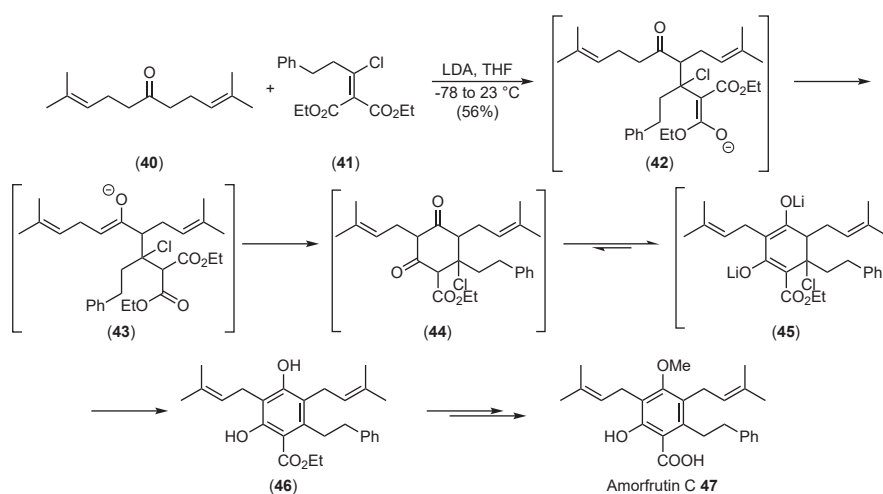
A subsequent 4π -electrocyclic opening gave triene (30) which in turn cyclized and aromatized to (31) *via* a 6π -electrocyclic ring-closure and tautomerization. Demethylation employing excess methyl magnesium iodide^[23,24] at elevated temperatures gave grifolin 32 in 32 - 56% yield from acetylene (26).

The methodology was subsequently applied to the total synthesis of mycophenolic acid 39, Scheme 1.6.^[25] Reaction of acetylene (33) with cyclobutenone (34) gave arene (38), probably *via* a similar mechanism. Selective arene halogenation,^[26] acid formation, lactonization and oxidation state adjustment gave mycophenolic acid 39 in 26% yield from acetylene (33).

Sauer and co-workers reported the synthesis of amorfrutin C 47 *via* a key base-mediated cyclization and aromatization, Scheme 1.7.^[27] Reaction of the enolate derived from ketone (40) with chloride (41) gave the 1,4-adduct



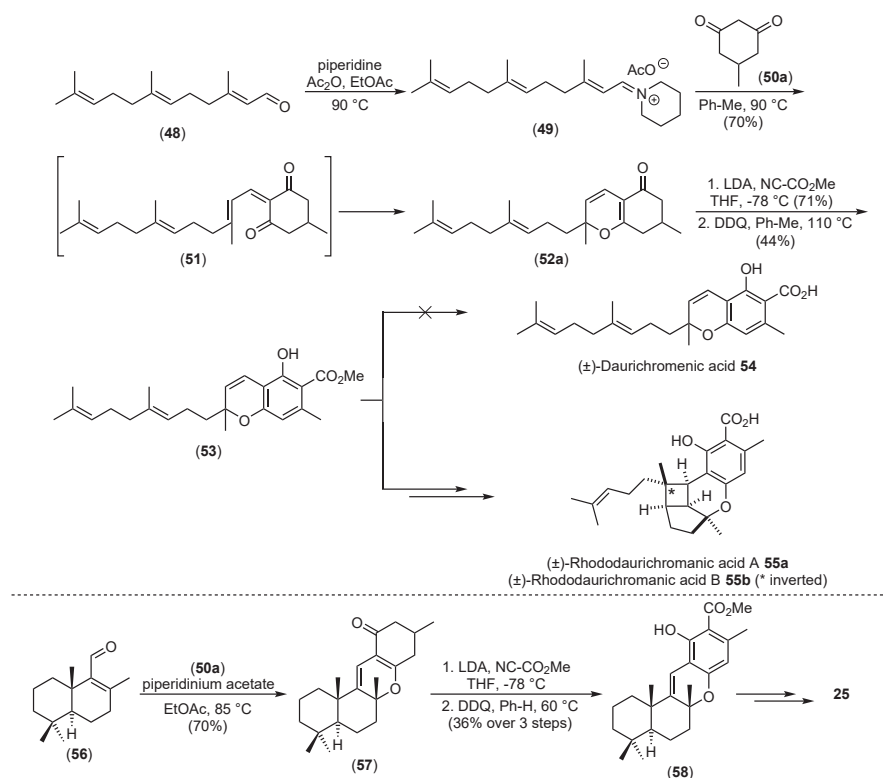
Scheme 1.6: Danheiser's benzannulation reaction in the total synthesis of mycophenolic acid **39**.



Scheme 1.7: Sauer's aromatization reaction in the synthesis of amorfrutin C **47** and analogs.

(43) after protonation and deprotonation of **(42)**. Dieckmann cyclization and tautomerization gave diene **(45)**. Dehydrohalogenation, driven by aromatization, furnished the hexasubstituted amorfrutin core **(46)**. Subsequent phenol protection and acid deprotection completed the total synthesis.

Hsung and co-workers synthesized the arene core of three natural products isolated from *Rhododendron dauricum*, Scheme 1.8 top.^[28] Farnesal (**48**) was reacted with piperidine to give α,β -unsaturated imminium ion **(49)**, which gave oxatriene **(51)** upon reaction with 1,3-diketone (**50a**). A subsequent 6π -electrocyclic ring-closure gave the core unit **(52a)** in 70% yield. Reaction with Mander's reagent^[29] and DDQ mediated oxidative aromatization furnished daurichromenic acid methyl ester (**53**). Noteworthy,

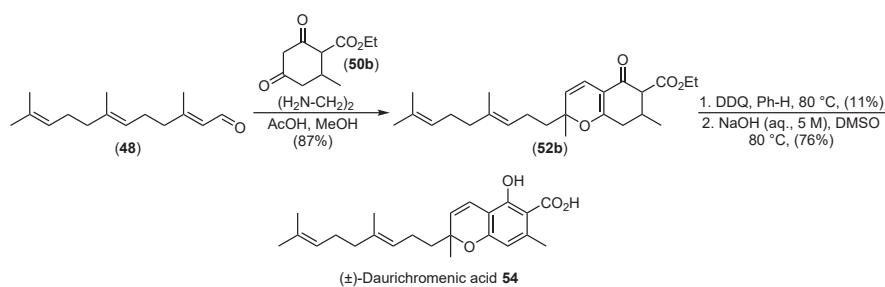


Scheme 1.8: Hsung's aromatization reaction in the total syntheses of rhododaurichromanic acid A 55a, B 55b and (+)-hongoquercin A 25.

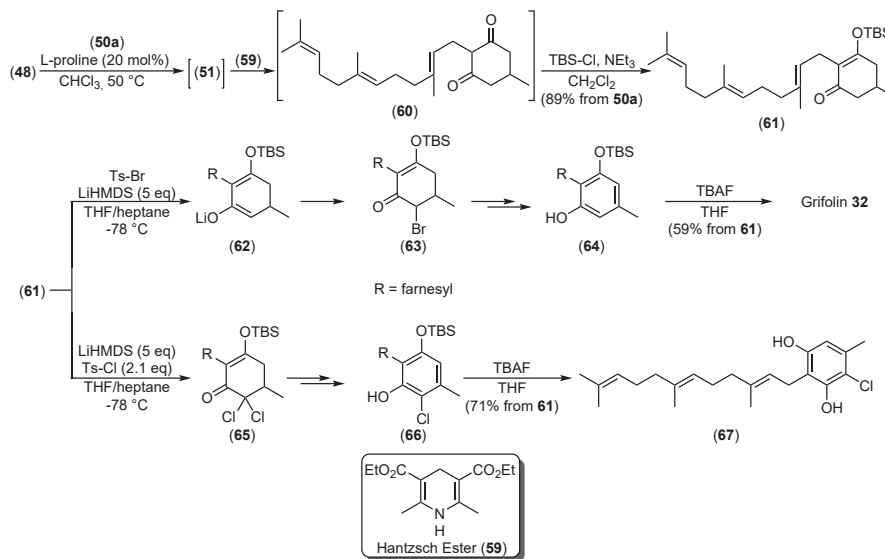
attempts to saponify the ester resulted in decarboxylation instead of desired demethylation. However, photolytic [2+2]-cycloaddition and saponification gave the two (±)-rhododaurichromanic acids A 55a and B 55b. In a separate report, Hsung also synthesized rhododaurichromanic acid A 55a *via* a cationic formal [2+2]-cycloaddition reaction of (53) in a trifluoroacetic acid-dichloromethane solution.^[30] Furthermore, Hsung reported the total synthesis of (+)-hongoquercin A 25 after applying the same methodology with enal (56), Scheme 1.8 bottom.^[30]

Recently, Wilson employed a similar strategy in his total synthesis of daurichromenic acid 54, Scheme 1.9.^[31] Reaction of farnesal (48) with 1,2-ethylenediamine and diketo-ester (50b) gave bicyclic compound (52b), presumably *via* similar intermediates as in Scheme 1.8. Wilson successfully completed the total synthesis of 54 after DDQ mediated oxidative aromatization and saponification.

Mohr and co-workers reported the total syntheses of the natural products grifolin 32, grifolic acid 68, LL-Z1272β 69, ilicicolinic acid A 70 and LL-Z1272α 71 using farnesal (48) and diketone (50a), Schemes 1.10 and 1.11.^[32] In the

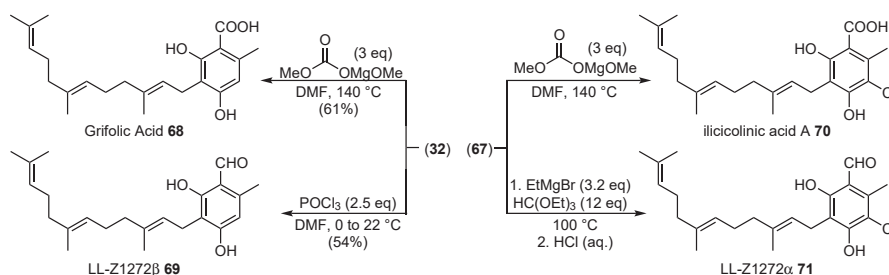


Scheme 1.9: Wilson's aromatization reaction in the synthesis of daurichromenic acid **54** and analogs.



Scheme 1.10: Mohr's aromatization reaction in the total synthesis of grifolin **32** and advanced intermediate **(67)**.

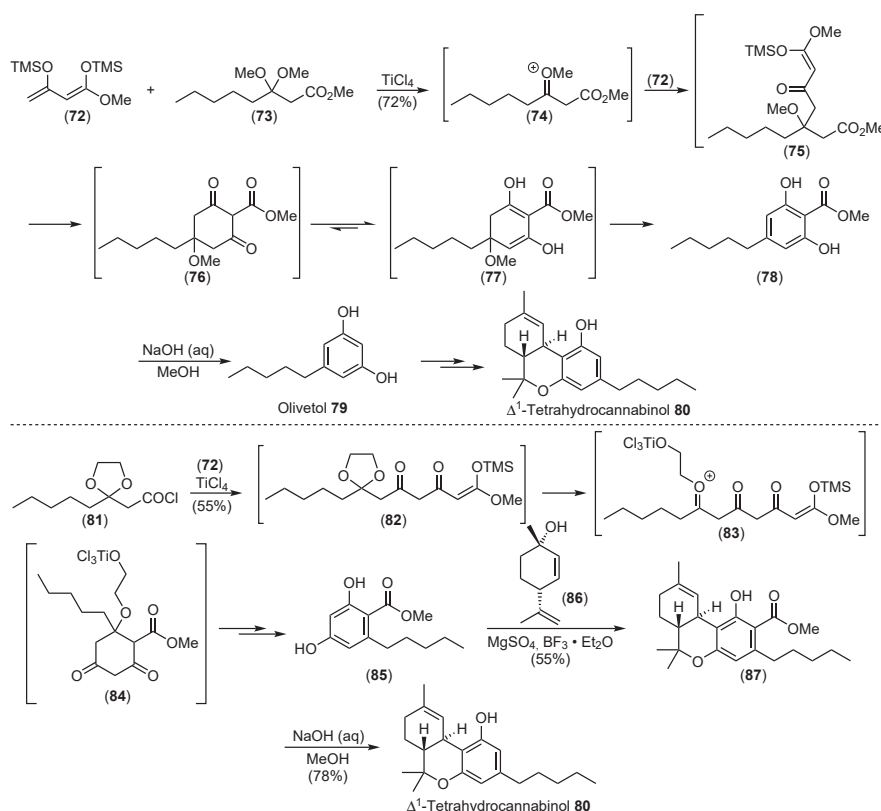
presence of Hantzsch ester (**59**), the initial Knoevenagel condensation product (**51**) was reduced and the resulting enolate (depicted as the diketo-tautomer (**60**)) was trapped as silyl enol ether (**61**), in a three step one pot process from diketone (**50a**) in 89% yield. Subsequently, reaction of the α -enolate (**62**) with 1 equiv. of Ts-Br gave the monohalogenated product (**63**),^[33,34] which, with excess of base, dehydrohalogenated and keto-enol tautomerized to the phenol silyl ether (**64**). Deprotection with tetra *n*-butylammonium fluoride in tetrahydrofuran solution gave grifolin **32** in moderate yields (59%). In addition, with a slight excess of halogenating agent, dihalogenation of enolate (**62**) was observed to give (**65**) which following a mono-dehydrohalogenation and keto-enol tautomerization gave arene (**67**) in 71% yield after tetra *n*-butylammonium fluoride mediated silyl-ether deprotection of intermediate (**66**).



Scheme 1.11: Mohr's arene functionalization in the total syntheses of grifolic acid **68**, LL-Z1272β **69**, ilicicolinic acid A **70** and LL-Z1272α **71**.

Further arene substitution reactions completed the total syntheses of the penta-substituted natural products grifolic acid **68** and LL-Z1272β **69** and the hexa-substituted natural products ilicicolinic acid A **70** and LL-Z1272α **71**.

Chan reported the reaction of methyl acetoacetate derived diene, 1,3-bis-(trimethylsiloxy)-1-methoxybutadiene (**72**), with various electrophiles for the synthesis of carbocycles^[35–38] which also finds use in the Mukaiyama aldol reactions.^[39–41] Furthermore, Chan disclosed the reaction of diene (**72**) with acetal ester (**73**), which gave γ -resorcyate (**78**) through selective reaction with the acetal unit followed by cyclization *via* reaction with the ester entity and subsequent aromatization, Scheme 1.12.^[42] Saponification and decarboxylation gave olivetol **79**, a building block commonly employed in total syntheses of tetrahydrocannabinol (THC) **80** through biomimetic reaction with allylic alcohol (**86**).^[43–45] On the other hand, reaction of Chan's diene (**72**) with the acid chloride derivative (**81**) reversed the regioselectivity and gave β -resorcyate (**85**) after selective reaction at the acid chloride entity followed by aldol-type cyclization onto the acetal. A subsequent Lewis-acid mediated addition of resorcyate (**85**) to allylic alcohol (**86**) gave tetrahydrocannabinol methyl ester (**87**) which was saponified and decarboxylated to the natural product **80**. Chan, thus, completed a dual biomimetic synthesis of THC mimicking the biosynthesis of the arene entity,^[46–48] from a β,δ -diketo ester, and the terpene cyclization onto the arene. In the following section, this biomimetic synthesis of resorcyates is further discussed.



Scheme 1.12: Chan's biomimetic aromatization reaction in the total synthesis of tetrahydrocannabinol **80**.

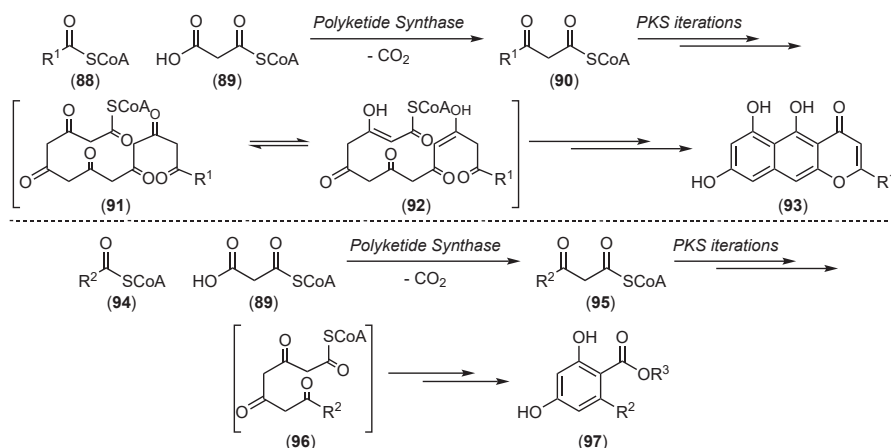
1.2 INTRODUCTION TO BIOMIMETIC SYNTHESIS

The synthesis of complex natural products starting from simple building blocks is a common strategy in the laboratory and in nature. Over several hundreds of thousands of years, nature optimized the design of catalysts to efficiently and selectively synthesize molecules.^[49] These catalysts are enzymes and are by far the most selective ones known to mankind.^[50] In the laboratory, the methods of synthesizing these molecules are ever expanding. One strategy of natural product synthesis is the linear assembly of the molecule, with a continuous increase in molecular complexity.^[51,52] With the creation of new methods, chemists could investigate proposed biosynthetic pathways and transformations when synthesizing natural products, which ultimately promoted the development of new synthetic methodologies. This concept is called biomimetic synthesis.^[52-54] In many ways, biosynthetic reaction cascades that rapidly build up molecular complexity in a (diastereo-, enantio- or regio-)selective way are optimal for biomimetic syntheses,^[55-57] although not

limited to this as natural products originating from these cascades may also be racemates.^[58,59] Most commonly, the prearrangement of linear precursors promotes the observed selectivity of the resulting polycyclic products, with only few side-reactions taking place.^[55] As such, mimicking the biosynthesis can often reduce the step-count and thus time, money, labour and waste of a synthetic sequence and this strategy can significantly increase the overall efficiency and the yield of the final natural product.^[51,55,60] In the following, two biomimetic strategies are discussed: Biomimetic Aromatization and Polyolefin Cyclizations.

1.3 BIOMIMETIC AROMATIZATION METHODS

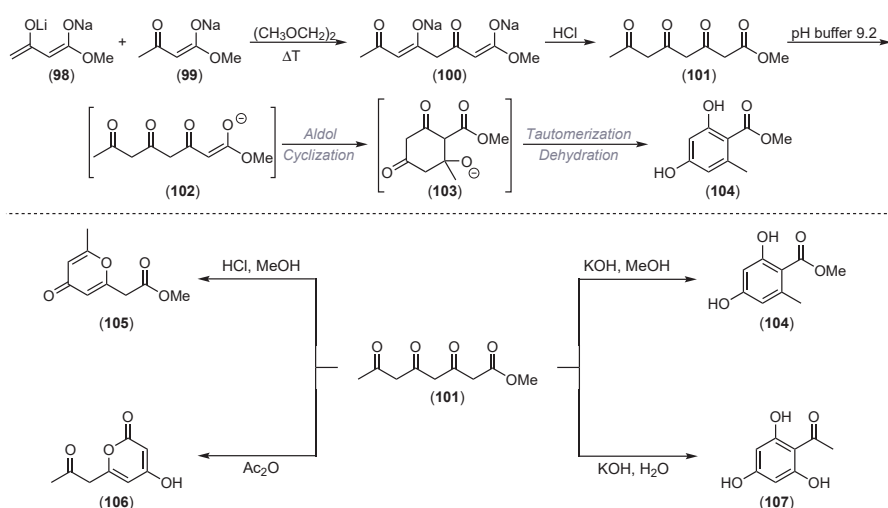
In nature, a plethora of natural products contain aromatic rings, often quite heavily substituted. This can be compared to a chemist's tool box, whereby nature can incorporate aromatic rings starting from existing aromatic precursors and converting those into products of higher complexity and substitution through a series of C-H activation reactions.^[61] The amino acids phenylalanine, tyrosine or tryptophan (all originating from the shikimate pathway) can be used in those examples.^[62,63] On the other hand, another method nature employs is the conversion of linear precursors into aromatic products. For this purpose, nature relies on the polyketide synthase enzyme complex.^[64,65] This enzyme bears several domains to promote the iterative coupling of acyl-units and post-coupling transformation reactions (stereoselective reduction, dehydration and olefin formation or cyclization) to build up an abundance of diverse bioactive natural products.^[66,67] Collie first proposed this link between acyl units arising from acetic acid (derivatives) and polyketides in 1907,^[68] while Birch provided evidence for this in 1953 through radioactive labelled ¹⁴C experiments.^[69] Simplistically depicted in Scheme 1.13 at the top, a decarboxylative Claisen-condensation reaction couples the acyl-group (**88**) to malonyl-CoA **89**. The subsequent PKS iterations build up a linear 1,3-keto system like (**91**) with varying chain lengths. Finally, upon termination and SCoA removal, a series of aldol-condensation reactions can take place giving aromatic compounds, such as (**93**). In the case of orsellinic or resorcylic acid



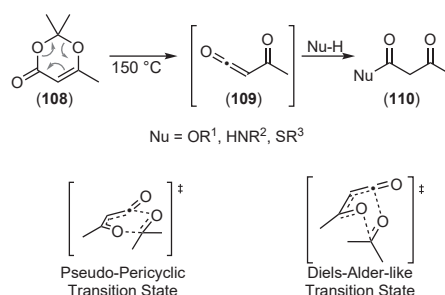
Scheme 1.13: Biosynthesis of arenes and resorcylicates.

derivatives, the PKS enzyme complex builds up a triketto-chain (96), which in a related manner cyclizes and aromatizes to the natural products (97), c.f. Chan's THC synthesis in Scheme 1.12.

Barton and Barrett were able to show, that the synthesis of a triketto ester of type (101) is possible through the condensation of the two enolates (98) and (99) followed by cyclization and aromatization into resorcylic ester (104), as shown in Scheme 1.14 top.^[70] Earlier work by Weiler, and Harris and Harris showed that triketto-ester (101) can be converted into arene (104) with KOH in MeOH, while other conditions, such as HCl in MeOH, Ac₂O, KOH in H₂O yielded different, common natural product moieties: 4-Pyrones (105), 4-hydroxy-2-pyrones (106) or acylphloroglucinol (107), respectively, Scheme 1.14 bottom.^[71,72]



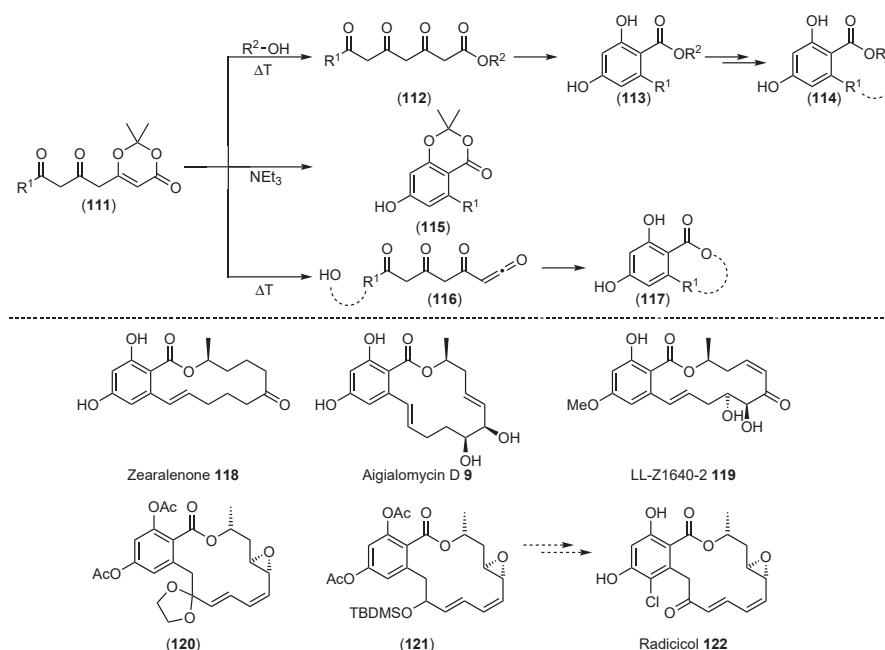
Scheme 1.14: Barton's and Weiler's, Harris and Harris' biomimetic aromatization studies.



Scheme 1.15: Hyatt's acyl-ketene formation and transition states for the ring-opening/ring-closing.

Hyatt developed a method to synthesize 1,3-diketo moieties through the thermal opening of 1,3-dioxin-4-one (**108**) in the presence of various nucleophiles (Scheme 1.15).^[73,74] Following this, several independent studies concluded that the mechanism of this reaction, or more precisely the reversed reaction of formation, is a pseudo-pericyclic reaction with nucleophilic attack of the carbonyl oxygen onto the ketene and concerted attack of the acyl-ketene carbonyl oxygen onto the carbonyl carbon.^[75–79] Conversely, in the transition state these six atoms are in plane, rather than the expected out of plane transition state known for Diels-Alder reactions. In turn, it can be expected, that the reversed reaction which gives the acyl-ketene intermediate (**109**) would follow a similar mechanism.

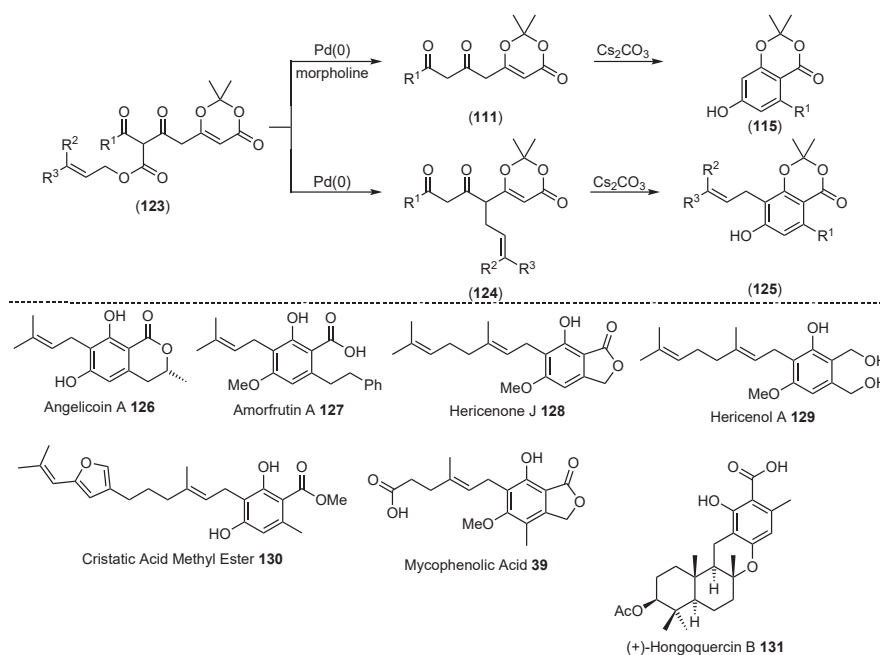
With the foundation work set, the Barrett group employed commercially available 1,3-dioxin-4-one (**108**) as the starting material in the total syntheses of many resorcyate natural products.^[80] Iterative biomimetic acylation reactions of (**108**) furnished a diketo-chain (**111**). With this at hand, heating in the presence of alcohols *via* an inter- (**112**) or intramolecular sequence (**116**) gave the triketo-ester chain, which readily aromatized. Alternatively, in the presence of non-nucleophilic bases, the β,δ -diketo-dioxinone compound (**111**) could aromatize with the dioxinone group acting as a protecting group for the phenol and acid moiety (**115**) (Scheme 1.16).^[81] This methodology was successfully applied in the total synthesis of resorcylic acid lactone (RAL) natural products, such as zearalenone **118**,^[82,83] aigialomycin D **9**,^[84] LL-Z1640-2 **119**^[85] and also in synthetic studies towards radicicol **122**.^[86] These RAL natural products are of interest as they exhibit anti-cancer, anti-viral, anti-inflammatory, antibiotic and anti-fungal properties.



Scheme 1.16: Overview of past synthetic methods towards RAL natural products.

In subsequent studies, it was found that Pd(o) was able to mediate a regioselective allylation reaction of β,δ -dioxinone diketo ester (**123**) to β,δ -diketo dioxinone (**124**) with expulsion of carbon dioxide, in the absence of an allyl trapping agent - e.g. morpholine.^[87–89] Such a Tsuji-Trost-Carroll^[90–95] type reaction facilitated the incorporation of allyl and terpene based carbon chains, regioselectively in the C₃-position (**125**). This method was applied to the syntheses of meroterpenoid natural products, a class of compounds originating from two different biosynthetic pathways (terpene and polyketide). Examples of successful meroterpenoid syntheses employing a key Pd(o)-promoted regioselective decarboxylative allylic rearrangement reaction are depicted in Scheme 1.17.^[88,96–100] These natural products possess antibiotic, anti-inflammatory, anti-viral, anti-tumor, anti-fungal and antimicrobial bioactivities.

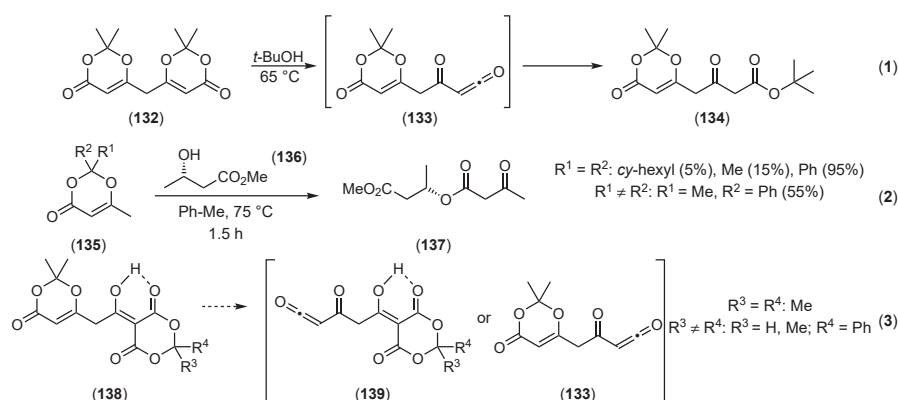
Kiegel showed that dioxinone dimers, like (**132**), mildly heated in the presence of *tert*-butanol selectively form the β -keto ester (**134**), Scheme 1.18 eq (1).^[101] This reaction can be enhanced through the choice of variable substituents on the dioxinone scaffold (**135**).^[102] Benzaldehyde ($R^1 = H$, $R^2 = Ph$) or acetophenone ($R^1 = Me$, $R^2 = Ph$) significantly improved the rate of reaction when reacted with alcohol (**136**), presumably through beneficial delocalization of the π -orbitals into the σ^* -CO orbital. Based on work by



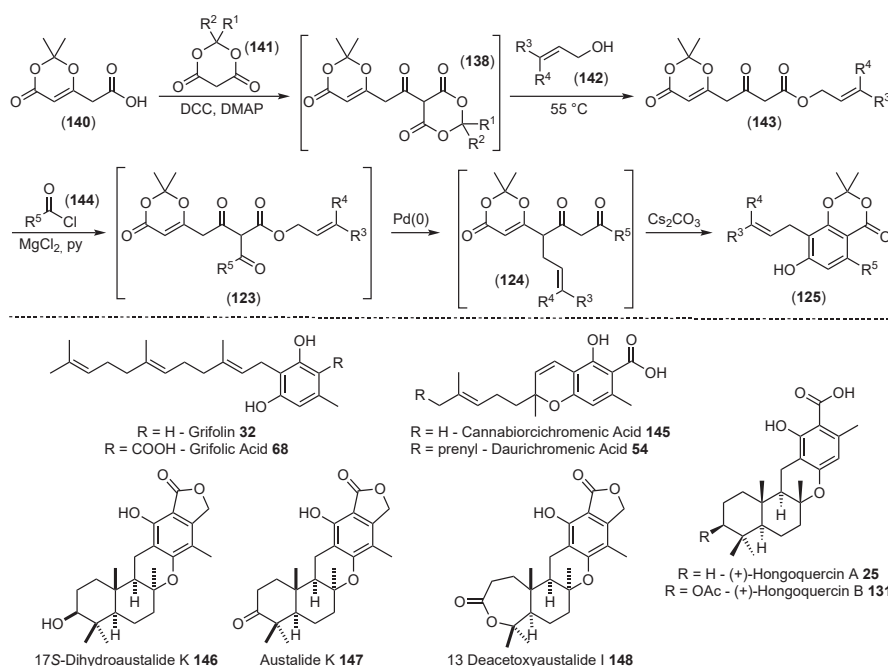
Scheme 1.17: Selected examples of resorcyate meroterpenes synthesized in recent years in the Barrett group.

Oikawa, Sugano and Yonemitsu,^[103] who reported that, upon heating, acylated Meldrum's acid derivatives reacted with alcohols to β -keto-esters, a complementary method to synthesize β,δ -keto-dioxinone esters was developed. Regioselective fragmentation of the Meldrum's acid group to acyl ketene (**133**) over the dioxinone fragmentation product (**139**) was facilitated through the use of benzaldehyde or benzophenone Meldrum's acid adducts (**138**).^[104]

Finally, hinging on this strategy, the Barrett group developed a method that rapidly assembled the key β,δ -diketo-dioxinone moiety starting from



Scheme 1.18: Overview of acyl-ketene generation methods developed in the Barrett group.



Scheme 1.19: Current method for the syntheses of meroterpenes and application towards various natural products.

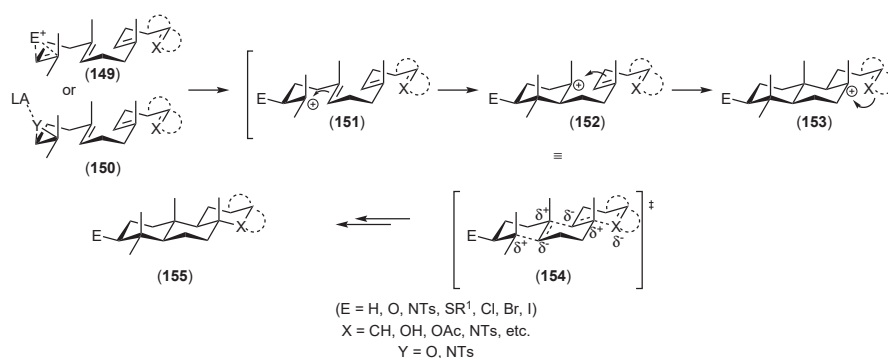
dioxinone carboxylic acid (**140**, Scheme 1.19).^[104] A coupling reaction of acid (**140**) with the benzaldehyde- ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$)^[105] or acetophenone- ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$) Meldrum's acid derivative (**141**) gave dioxane-4,6-dione keto dioxanone (**138**), which was shown to give various allylic β,δ -keto-dioxinone esters (**143**) after heating dioxane-4,6-dione keto dioxanone (**138**) in the presence of allylic alcohols (**142**). A subsequent Mg(II) mediated regioselective C-acylation to give β,δ -dioxinone diketo-ester (**123**) and regioselective Pd(0)-catalyzed decarboxylative, allylic rearrangement reaction gave β,δ -diketo-dioxinone (**124**). Cyclization and aromatization furnished acid-phenol protected meroterpenes (**125**). This methodology was successfully applied to various meroterpenoids, such as grifolin **32** and grifolic acid **68** as well as chromenes **54** and **145**.^[104,105] Terpene chains, such as geranyl or farnesyl are routinely employed in polyene cyclization. This cyclization is easily induced through the use of π -Lewis or Brønsted acids, or alternatively under radical-anion conditions. (+)-Hongoquercin-A **25** and - B **131** and various austalide natural products **146**,^[106,107] **147** and **148** (amongst others) were synthesized by employing such a bioinspired polyene cyclization.

1.4 POLYENE AND CATIONIC CYCLIZATIONS

Terpenes are one of the most widely known classes of natural products.^[108] Their common structural units are isoprenes which are either attached in a head-to-head or head-to-tail fashion to produce geranyl- and/or farnesyl-chains.^[109,110] Higher terpenes like squalene or tetraterpenes are biosynthesized from these intermediates on the way to crucial natural products like steroids, and hormones or carotenoids.^[111,112] Due to this diversity of linear combination, cyclization and/or post-cyclization transformations a myriad of natural products originating from the terpene pathway are known - or hypothesized to exist.^[113]

A common trait of these terpenes is the ability to cyclize, upon activation.^[110,114]

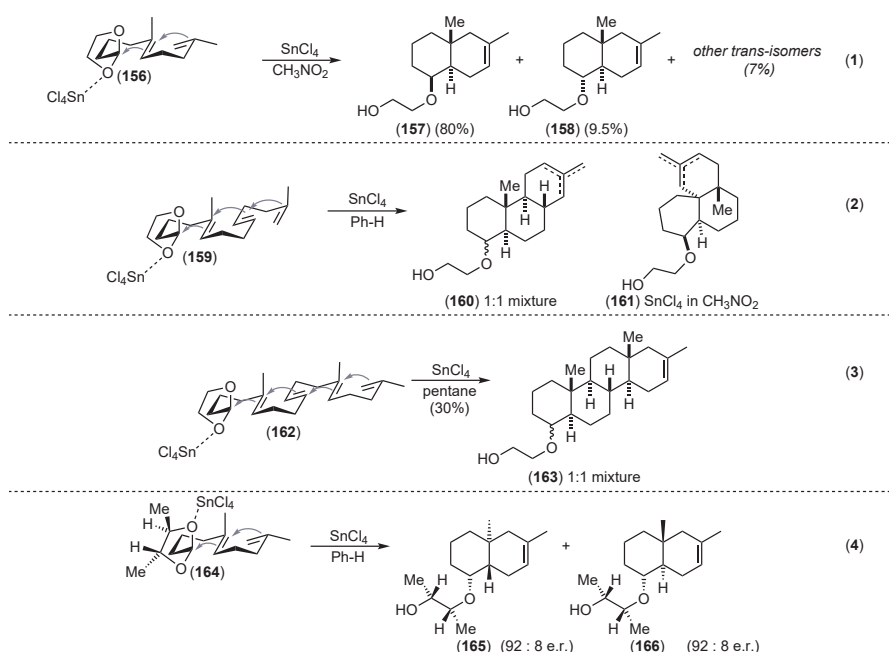
It is postulated, that an initial electrophilic addition (protonation) to the terminal olefin promotes the formation of a short-lived, tertiary carbenium ion,^[115] as indicated in Scheme 1.20. It remains unclear, however, if this initial ring closure could also happen *via* a loose S_N2-type transition state in a concerted fashion. Particularly, in the case of epoxides, the general consensus is a concerted epoxide-opening-A-ring closure.^[116,117] Secondly, the pre-arrangement of the molecule in the enzyme pocket facilitates the cyclization of the proximal olefin onto the carbenium ion, resulting in the formation of a new carbenium ion further down the chain.^[115,118,119] Subsequently, this process can be repeated until a termination reaction (rearrangement, elimination, nucleophilic addition) takes place on the final intermediate. π -Interactions with aromatic amino acids such as phenylalanine or tyrosine stabilize these point charges of the carbenium ions, as was shown through independent residue alteration studies by Poralla, Schulz and Hoshino *et al.*^[115,120–124] Due to the controlled and defined environment of cyclase enzymes (and specifically the catalytic pocket), which controls these cationic cascades, the polycyclization products that are produced show remarkable diastereoselectivity. For example, lanosterol, a precursor to cholesterol, is synthesized as only one enantiomer and one diastereoisomer out of 128 possible diastereoisomers.^[125] (Note the here discussed mode of cyclization is typical for cyclase class II enzymes which propagate the formation of the carbenium ion from head-to-tail. Cyclase class I enzymes initiate the



Scheme 1.20: Origin of the stereoselectivity observed in polyolefin cyclization of *trans*-olefins.

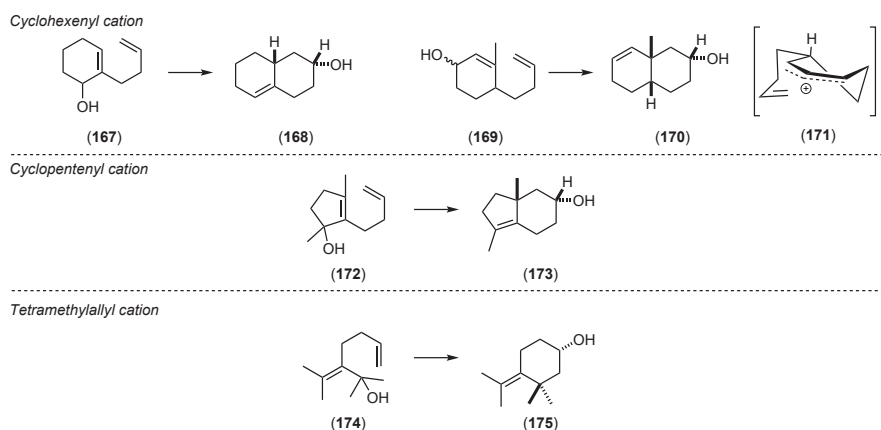
sequence from tail-to-head - usually through the elimination of a pyrophosphate unit in the allylic position).^[110,113,126,127] This remarkable control in the synthesis of *trans*- or *cis*-decalin derivatives promoted the investigation by Eschenmoser, Johnson and Stork who realised (based on foundation work by Bloch and Barton)^[128–131] in their seminal work that the prearrangement of the *E*- or *Z*-polyene precursor in the *pseudo*-chair-chair or *pseudo*-chair-chair-chair conformation allows for a series of anti-periplanar attacks to form the polycyclic compounds. This is hypothesized to be the lowest energy pathway, as it allows, in part, a delocalization of the charge over the molecule and hence postulated to be the reason for the high degree of diastereoselectivity in the biosynthesis of these natural products.^[132–134] Examples, where *trans*-decalins are obtained starting from *cis*-olefins necessarily go *via* a discrete carbenium ion such as (152) or (153). In summary, the evidence suggest that the polyene precursors contain inherent predefined relative stereochemical information, as they are pro-chiral yet diastereo-defined (*cis*- and *trans*-olefin bonds). This information is propagated along the chain as the polycyclization takes place *via* discrete carbenium ions,^[135,136] which, in enzymes are stabilized through aromatic residues.

In the case of the biomimetic terpene cyclization, commonly, the creation of a carbenium ion is the initiator of the cascade, which can be achieved as shown by Eschenmoser and Stork (through protonation), Lewis acids (metal or halonium based) or via opening of an oxirane.^[57,137–140] The following Schemes of this section show a selection of historic milestones in polyolefin cyclizations.



Scheme 1.21: Johnson's polyene cyclization studies from acetal polyolefins.

Johnson studied the use of acetal opening for the initiation of polyene cyclizations. In his studies, various *trans*-polycyclic structures were synthesized from the corresponding linear *trans*-olefin precursors by reacting the corresponding acetals with SnCl_4 . When studying the formation of bicyclic structures, Johnson found that the two epimers (**157**) and (**158**) were formed, next to other elimination products.^[141,142] Strikingly, the ether in an axial position (**157**) was isolated as the major compound. This is indicated in Scheme 1.21. Stereoelectronically controlled opening in case of a concerted mechanism could account for this observation. On the other hand, the tricyclic structure (**160**) was obtained as a mixture of epimers in the C2-position,^[143] indicating the intermediacy of a carbenium (or resonance stabilized oxonium) ion. When a SnCl_4 solution in nitromethane was used, the rearranged product (**161**) was isolated, indicative of a discrete carbenium intermediate. Furthermore, the tetracyclic product (**163**) was accessible through a tetracyclization of linear precursor (**162**) with SnCl_4 in pentane.^[144,145] Finally, Johnson disclosed a stereoselective biomimetic polyene cyclization by employing a chiral auxiliary on the acetal (**164**),^[146] contrary to the above reactions, which all produced racemic mixtures of the cyclization products. The reaction of acetal (**164**) with SnCl_4 in benzene lead to the separable mixture of the diastereoisomeric axial ether (**165**) and equatorial ether (**166**)



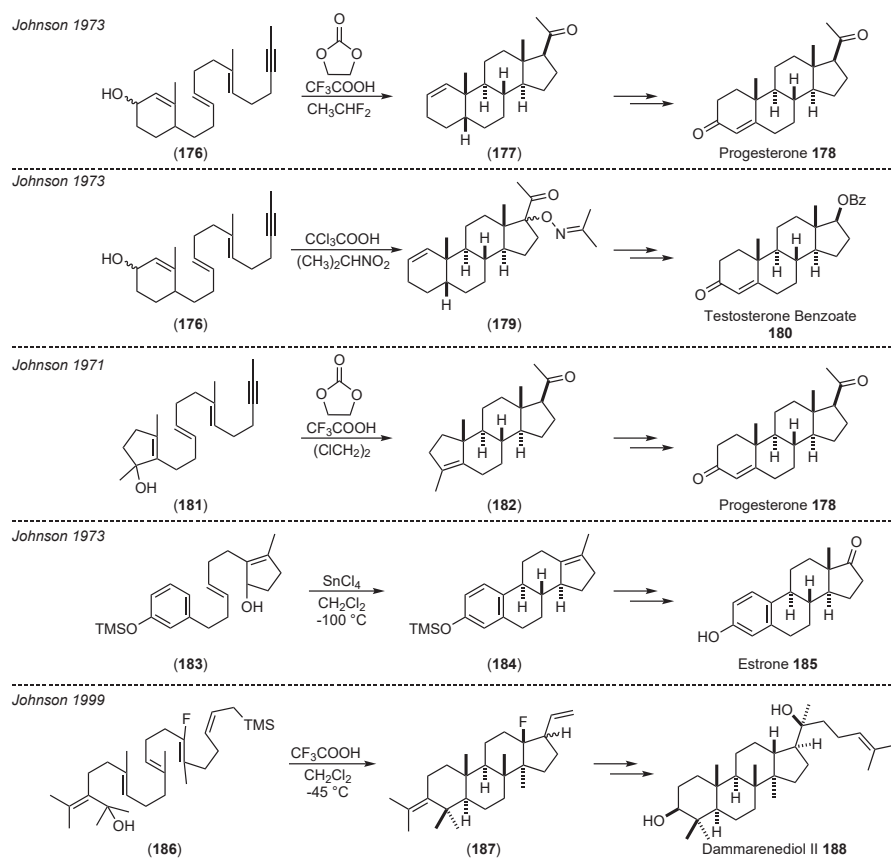
Scheme 1.22: Johnson's polyene cyclization studies from allyl carbenium ions.

with their respective mirror images. By means of degradation studies, it was found that both ethers (**165**) and (**166**) consisted of a 92 : 8 ratio, in favour of the displayed structures over their corresponding mirror images.

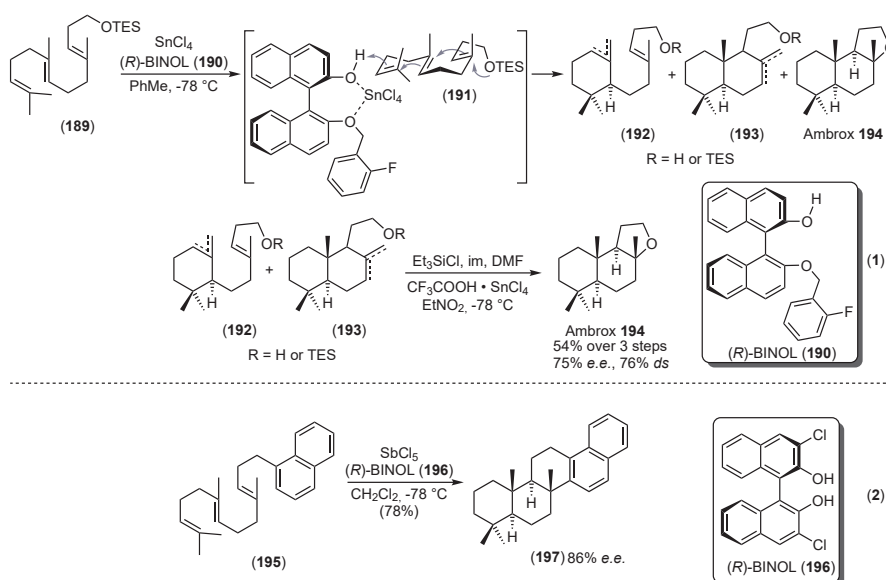
Furthermore, Johnson investigated allyl carbenium ions at the initiation site. These could be of varying ring size (cyclohexenyl (**167**) or cyclopentenyl (**172**))^[147–150] or substitution (tetramethylallyl **174**).^[151,152] In the case of an allylic alcohol of type (**169**) the reaction selectively lead to *cis*-fused ring systems, presumably due to the preference of cyclohexenyl cations to form a pseudo-axial bond with a nucleophile.^[152–154] Scheme 1.22 gives an overview of these cyclizations, which were applied to the syntheses of polycyclic ring structures similar to the ones in Scheme 1.21 or in steroid total syntheses (Scheme 1.23).

Progesterone **178**, testosterone benzoate **180**, estrone **185** and dammarene-diol II **188** are just a few examples where this biomimetic polyene cyclization was employed by Johnson, Scheme 1.23.^[155–160]

It is noteworthy to point out the key acetylene unit at the tail position of polyenes (**176**) and (**181**). Johnson intensively studied the use of styryl- and acetylene units for the selective syntheses of five-membered rings due to the preferred 5-exo attack.^[152,154] The selective synthesis of five-membered D-rings were of particular importance given the presence in many steroid cores. In addition, Johnson found an example where the acetylene unit was substituted with a TMS-group (instead of a methyl group) which lead to the formation of a six-membered ring.^[152]



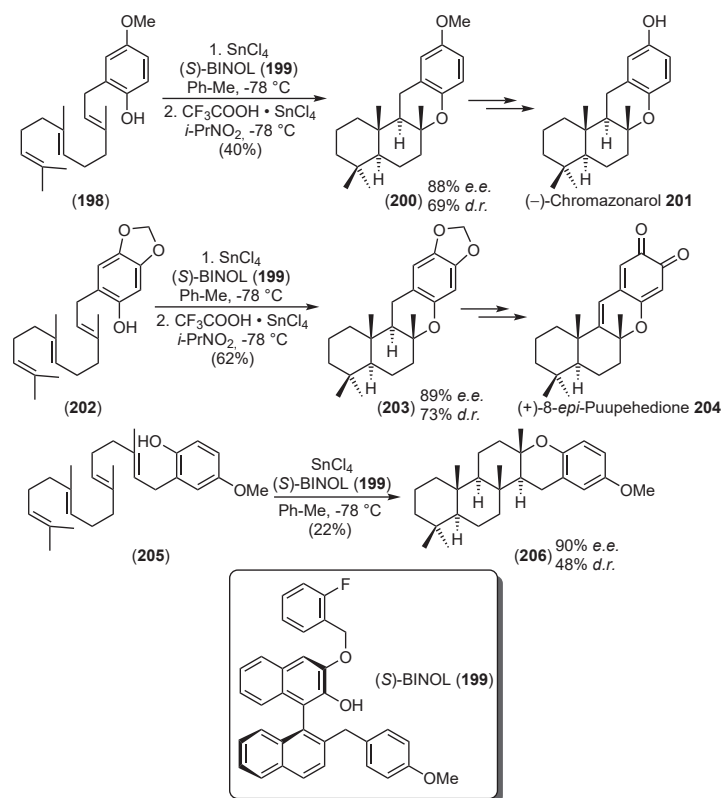
Scheme 1.23: Johnson's polyene cyclization in the total syntheses of steroid natural products.



Scheme 1.24: Lewis acid enhanced Brønsted acid catalysis for enantioselective polyene cyclizations.

In 1999, Yamamoto disclosed a truly biomimetic cationic polyene cyclization.^[161] Combining a Lewis acid, such as SnCl_4 , and one enantiomer of a stereodefined Brønsted acid such as BINOL (190), facilitated an enantioselective protonation reaction similar in nature to the enantioselective protonation of the polyenes in enzymes. Scheme 1.24 top, (1), highlights just one application of this reaction by Yamamoto,^[162] where farnesyl silyl ether (189) was cyclized to the natural product ambrox 194 and partially cyclized products (192) and (193) (which in turn were also partially desilylated). Thus, resilylation (which was shown to increase the yield) and a combination of an achiral Lewis acid - Brønsted acid mixture gave the fully cyclized natural product 194 in 54% with 75% enantiomeric excess. Subsequently, Corey developed a similar strategy (Scheme 1.24 bottom, (2)) based on the use of SbCl_5 as Lewis acid and BINOL (196) as Brønsted acid.^[163] With this, Corey successfully disclosed a series a of polycyclization products (bi-, tri- and tetracyclic) as well as the pentacyclic product (197) with excellent enantioselectivities (e.g. 86% e.e. for (197)).

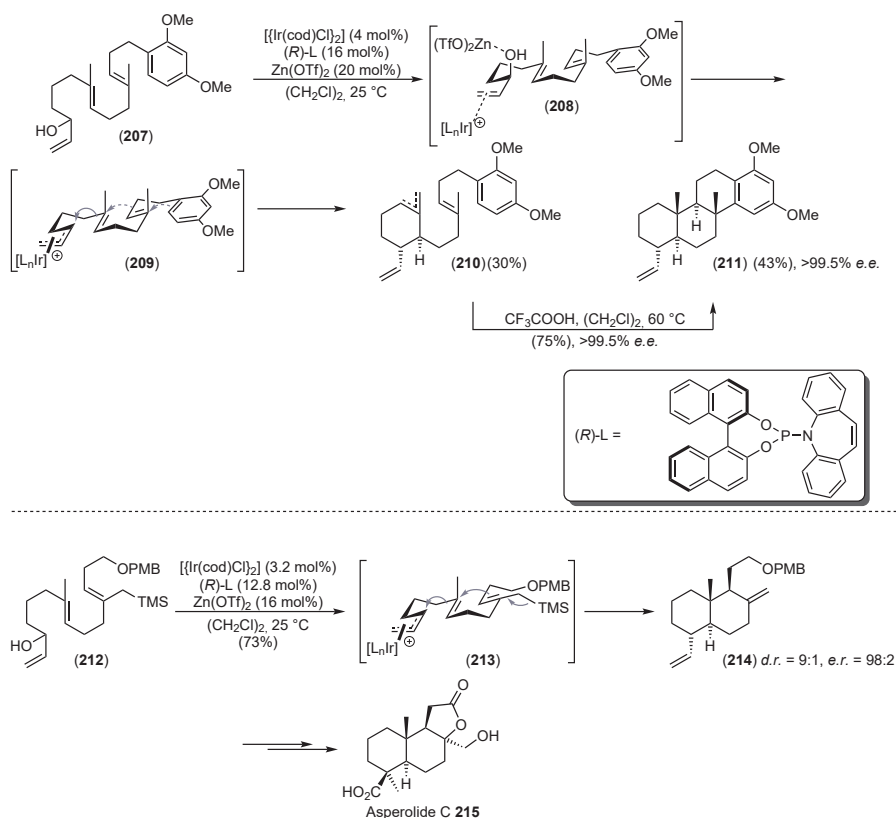
Amongst many other application,^[164,165] Yamamoto employed this pioneering work to the total syntheses of the tetracyclic natural products (–)-chromazonarol 201 and (+)-*epi*-puupehedione 204 as well as the pentacyclic compound (206) from the corresponding precursors, Scheme 1.25.^[166] The



Scheme 1.25: Yamamoto's Lewis acid enhanced Brønsted acid catalysis applied to the total syntheses of natural products.

combination of SnCl_4 and BINOL (**199**) initiated an enantioselective protonation reaction on polyenes (**198**), (**202**) and (**205**), which were subsequently fully cyclized to the advanced intermediates (**200**) and (**203**) through use of a combination of trifluoroacetic acid and SnCl_4 .

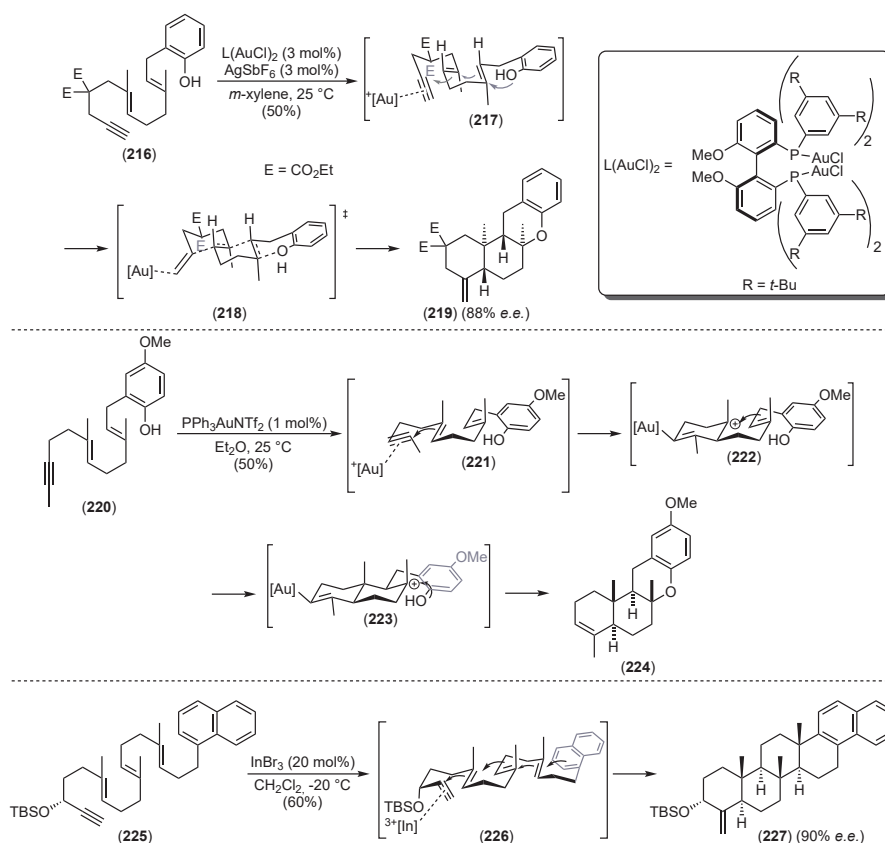
Based on this seminal foundation work further sophisticated methods were developed, such as the Carreira enantioselective, iridium-catalyzed polyene cyclization, Scheme 1.26.^[167] Reaction of allylic alcohol (**207**) with a catalytic mixture of an iridium-complex and one enantiomer of ligand (*R*)-**L** as π -activator, and $\text{Zn}(\text{OTf})_2$ as Lewis-acid alcohol activator, induced an enantioselective polyene cyclization. It was hypothesized, that the initial dehydration gave allylic cation (**209**) as Ir-complex, which subsequently reacted with the proximal olefin. This eliminated a proton to give partially cyclized product (**210**). Alternatively, further cyclization gave tetracyclic compound (**211**) in excellent enantioselectivity. Brønsted-acidic conditions fully cyclized intermediate (**210**) to the tetracyclic product (**211**) in good yield and enantioselectivity. Further examples with variable aryl groups



Scheme 1.26: Carreira's polyene cyclization.

were disclosed. The method was subsequently applied in the total synthesis of asperolide C **215**,^[168] with the key intermediate (**214**) derived from the enantioselective, iridium-catalyzed polyene cyclization of polyene (**212**).

A valuable alternative to the Lewis and Brønsted acid induced cyclizations, described above, is the use of π -Lewis acid transition metals as initiators in polyene cyclization. Historically, mercuric salts were used, often in stoichiometric amounts, which poses health risks.^[169–173] To this end, developments were made in the investigations of late transition metals such as Au or Pt and In (main group element) with polyene's and polyenyne's for bioinspired cyclizations by Toste, Michelet and Corey, Scheme 1.27 and Gagné, Scheme 1.28. Toste developed an enantioselective cyclization of a polyenyne with a 1,6-relationship of the acetylene and the olefin and 1,5-relationships of the olefins.^[174] Reaction of acetylenic polyolefin (**216**) with the activated gold catalyst, prepared by mixing $\text{L}(\text{AuCl})_2$ with AgSbF_6 , furnished the tetracyclic product (**219**) in moderate yields but with great enantioselectivity (88% e.e.). Coordination of the dimeric gold catalyst to the acetylene unit (**217**) initiated

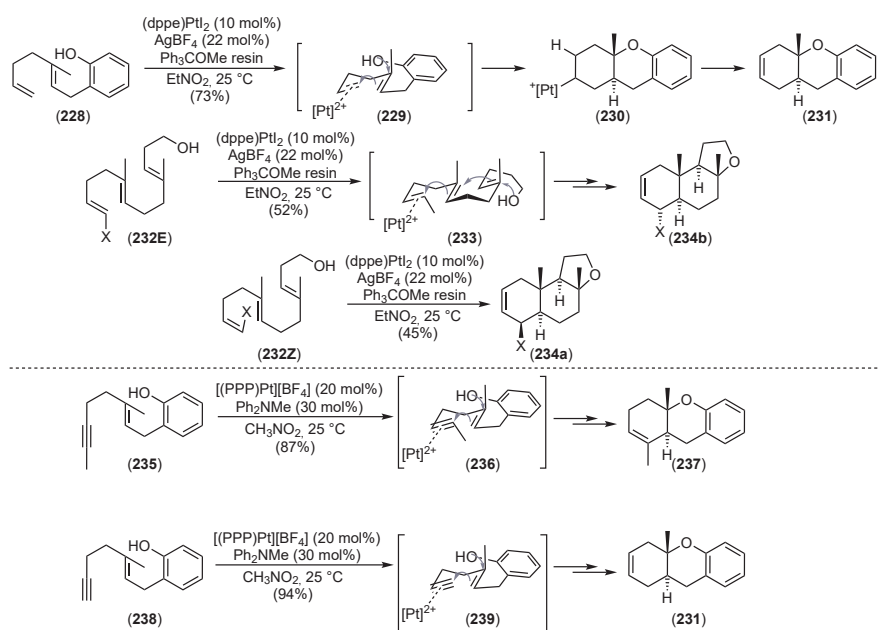


Scheme 1.27: Toste's, Michelet's and Corey's polyenyne cyclizations.

a cyclization possibly *via* a structure like (218). Alternative bi- and tricyclic products were also prepared from the corresponding precursors.

Michelet investigated the reaction of polyenyynes with a 1,5-relationship. Reaction of phenol (220) with PPh_3AuNTf_2 in ether solution gave the tetracyclic product (224) as a single diastereoisomer, possibly *via* the intermediates (222) and (223) after initial gold coordination (221).^[175] Alternative bi- and tricyclic products were also prepared from the corresponding precursors.

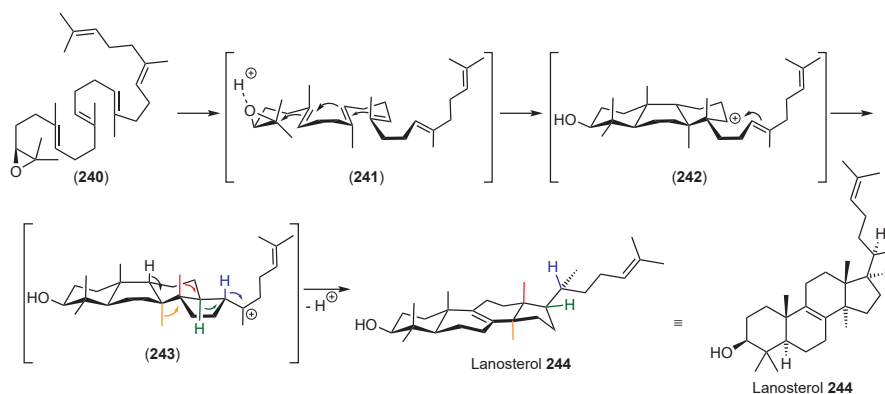
Corey employed a substrate controlled, enantioselective polyenyne cyclization by reacting one enantiomer of silyl propargyl ether (225) with $InBr_3$,^[176] as opposed to Toste, who investigated enantioselective polyenyne cyclizations *via* stereinduction from the catalyst. Reaction of propargyl ether (225) with $InBr_3$ at low temperatures gave the hexacyclic product (227) after initial coordination of In^{3+} to the acetylene unit. The subsequent polycyclization *via* a possible intermediate such as (226) gave the product in good yields and excellent enantioselectivity (90% *e.e.*).



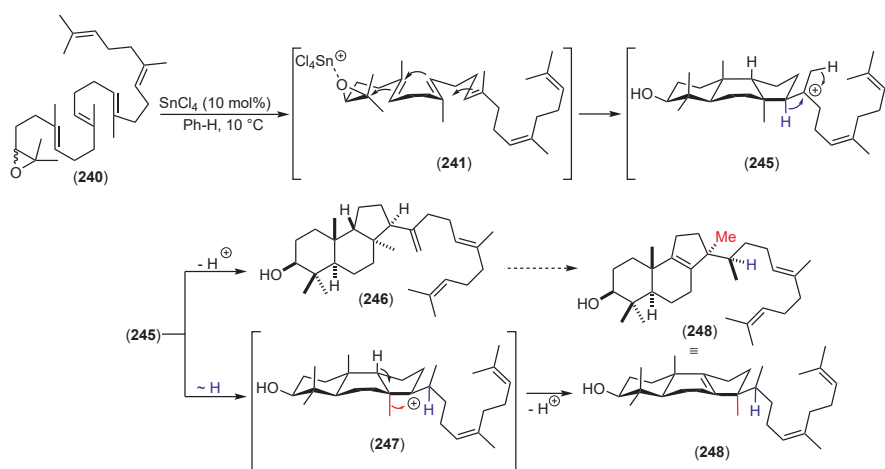
Scheme 1.28: Gagné's polyene and polyenyne cyclizations.

Gagné demonstrated the effective use of electrophilic Pt-catalysts for the bioinspired polyene cyclizations^[177] of precursors (**228**) and (**232**), Scheme 1.28.^[178] Initial activation of the less-substituted olefin gave the platinum compound (**230**) *via* intermediate (**229**). β -Hydride elimination subsequently gave the tricyclic product (**231**). Furthermore, Gagné demonstrated a tricyclizations of olefins (**232**) *via* a similar reaction pathway. Noteworthy, the terminal (*E*)-olefin (**232E**; X = Me) gave the β -product (**234b**; X = Me) while the diastereoisomeric (*Z*)-olefin (**232Z**; X = Et) gave the α -epimer of tricyclic product (**234a**; X = Et), possibly *via* a pathway as shown with complex (**233**). This retention of relative stereochemistry from the starting material to the products is indicative of a concerted A-ring closure. Furthermore, substituted and unsubstituted enynes (**235**) and (**238**) were reacted with an electrophilic Pt-complex.^[179] In the first case, the reaction gave the tricyclic product (**237**) while in the latter case, an olefin isomerization occurred to give ether (**231**). Similar reactivity was observed upon reaction of the platinum intermediate with HBF_4 , while the non-isomerized product was observed upon reaction with LiHBEt_3 .

Polyene cyclizations initiated through epoxide openings are a valuable extension to the classical carbocyclization reactions. One major difference is that the oxirane ring can contain stereochemical information, which is

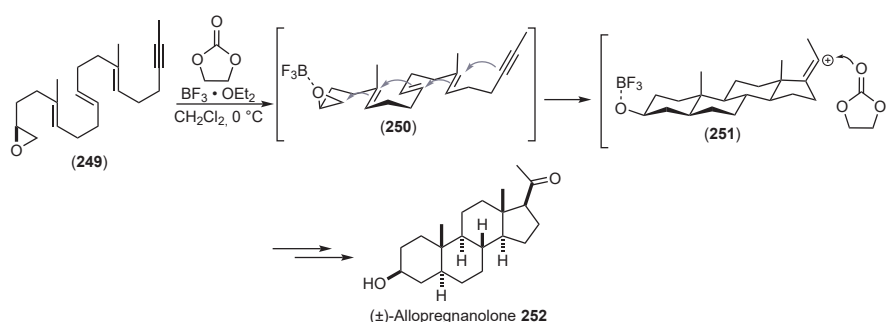
Scheme 1.29: Biosynthesis of Lanosterol **244**.

subsequently propagated during the cyclization compared to the necessary stereoselective protonation during carbocyclizations. It should be noted, that biomimetic epoxide opened polyene cyclizations differ from their biosynthetic counterparts in certain ways. For instance, in the active pocket of oxidosqualene cyclase, the polyene precursor takes up a chair-boat-chair conformation (**241** in Scheme 1.29).^[180,181] Secondly, the biosynthetic cyclization usually results in a 6-6-5 ring system (not shown in Scheme 1.29) followed by ring expansion to a 6-6-6 system, additional cyclopentane-ring formation followed by a series of anti-periplanar 1,2-methyl and hydride shifts (highlighted in Scheme 1.29).^[118,182–187] In nature, these shifts happen readily and are only guided by the enzyme through the conformational lock (and protection from quenching agents like water).^[50] The hydride and methyl shifts are a consequence of the spatial arrangement as the initial tricyclization results in a secondary carbenium ion (**242**), which is higher in energy.



Scheme 1.30: Van Tamelen's racemic epoxysqualene cyclization.

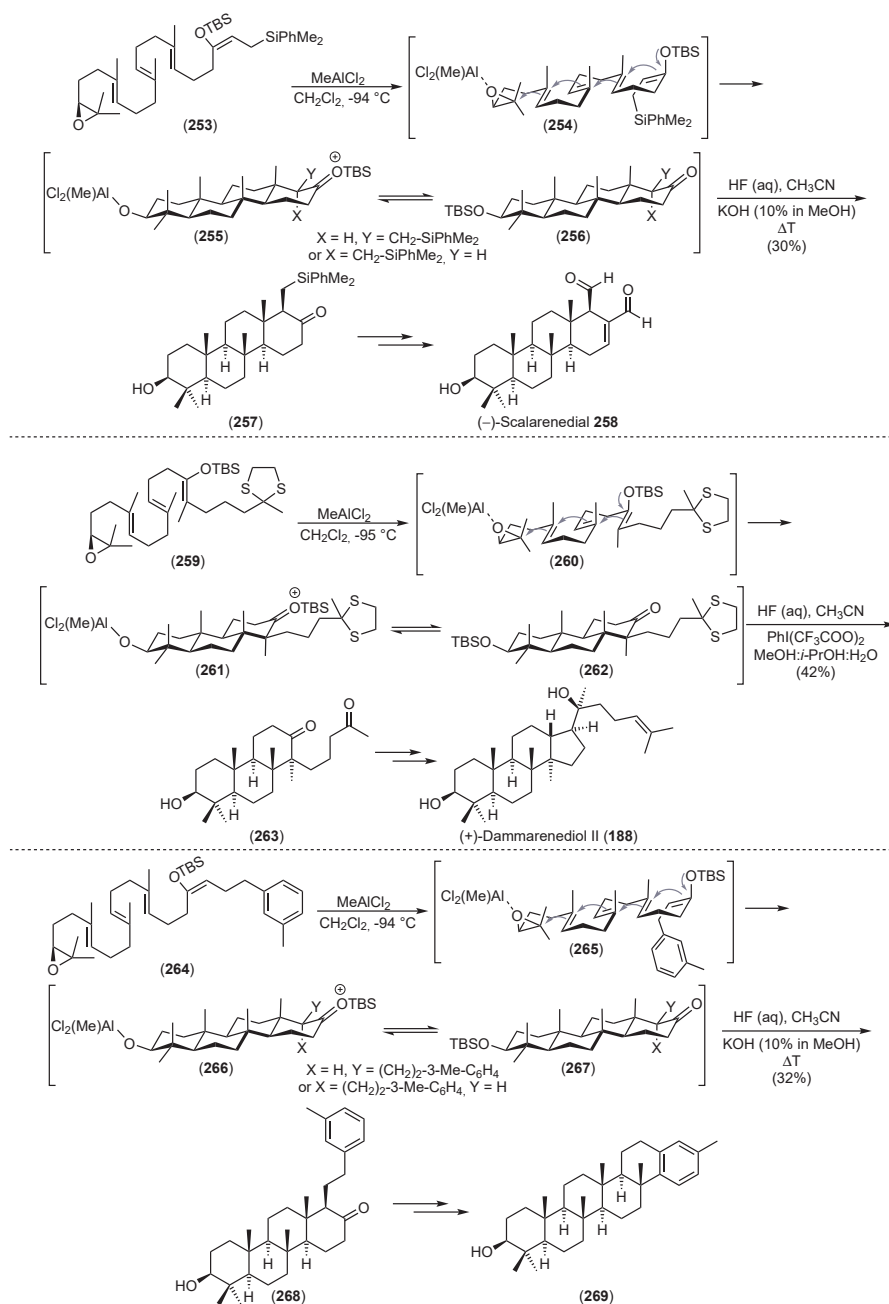
A rapid reaction with the proximal olefin sets the stage (**243**) for various stereoelectronically controlled 1,2-shifts. Van Tamelen could show that these shifts happen very readily even in non-enzymatic environments, Scheme 1.30.^[188] Reaction of oxidosqualene (**240**) with SnCl_4 smoothly induced the conversion into the two tricyclic compounds (**246**) and (**248**). While (**246**) could possibly arise *via* proton abstraction from intermediate (**245**), product (**248**) necessitates the intermediacy of another tertiary carbenium ion (**247**) and subsequent 1,2-methyl shift and proton abstraction. Additionally, the authors speculated if (**248**) may also arise from (**246**) directly *via* reprotonation.



Scheme 1.31: Van Tamelen's steroid synthesis.

On the contrary, in biomimetic epoxide polyene cyclizations, these shifts are not easily to control. Furthermore, as shown by van Tamelen, biomimetic epoxysqualene cyclization gave a five-membered rather than the desired six-membered C-ring.^[189] As such, biomimetic polyene cyclizations use a slightly different precursor, one that already contains a methyl group in the correct position (e.g. comparing the position of the C14 methyl in epoxysqualene in Scheme 1.30 vs the C14 methyl group of epoxide (**249**) in Scheme 1.31 or the C15 methyl group of epoxide (**253**) in Scheme 1.32).^[50] With this strategy, van Tamelen achieved the total synthesis of steroid allopregnanolone **252** from precursor (**249**), Scheme 1.31.^[190] Similar to Johnson (Scheme 1.23) the final ketone functionality was introduced by quenching the polyene cyclized product (**251**) with ethylene carbonate.

Corey completed the total synthesis of scalaredial **258** *via* the key cationic polyene cyclization of epoxide (**253**) with methyl aluminium dichloride, Scheme 1.32.^[191] Aluminium alkyl chloro Lewis acids have substantial precedence in polyene cyclizations due to the combined Lewis acidic nature as



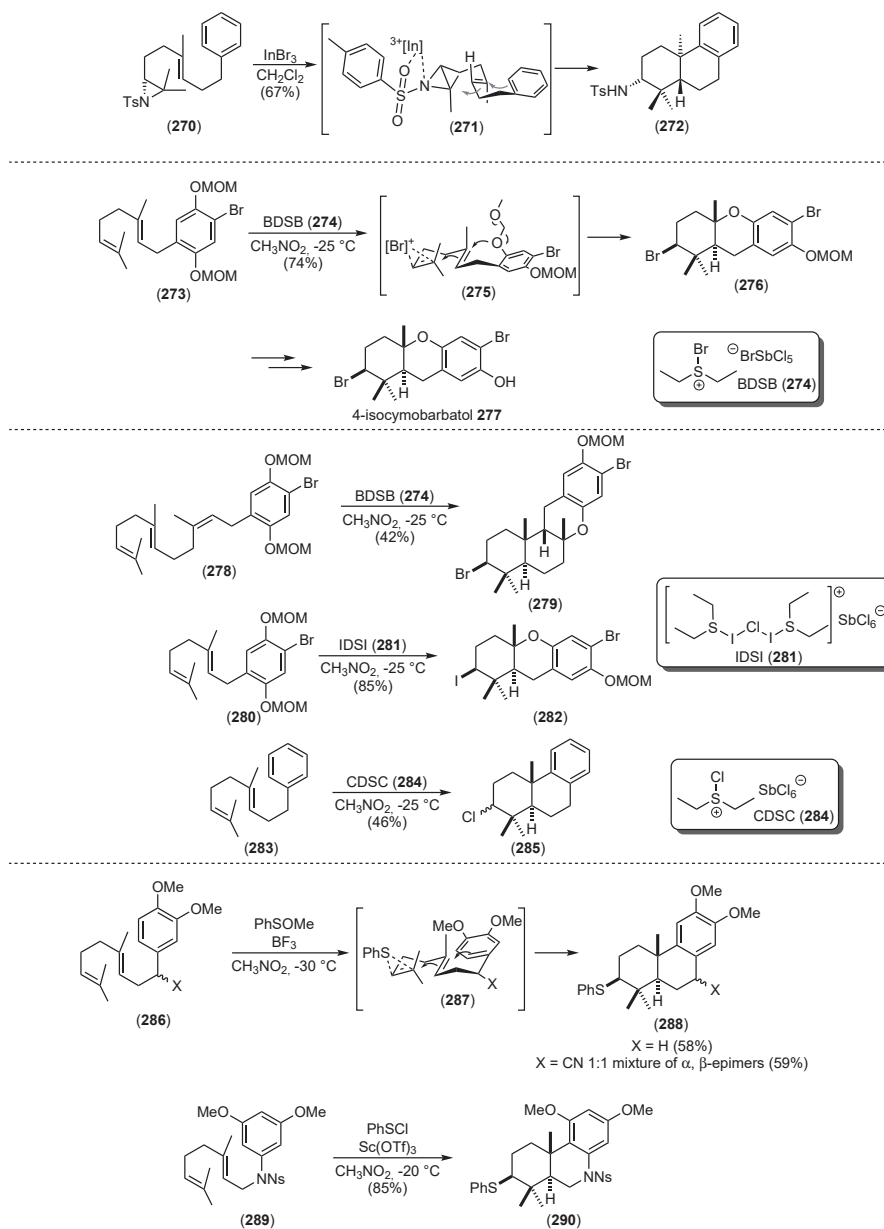
Scheme 1.32: Corey's total synthesis of polycyclic hydrocarbons *via* key epoxide polyene cyclizations.

well as basic functionality for final proton abstraction. Initial cyclization gave a mixture of epimers (**256**) α to the ketone. Desilylation and epimerization under basic conditions gave the tetracyclic ketone (**257**) in 32% yield as key intermediate in the synthesis of scalarenedial **258**. A similar strategy by Corey afforded the tricyclic product (**263**) in 42% yield from epoxide (**259**) *en route* to enantiomerically pure (+)-dammaranediol II **188**.^[192] In addition, this methodology was applied to the total synthesis of hexacyclic product (**269**) starting from arene (**264**).^[193]

Recent developments in polyene cyclizations have seen the discovery of new activating groups at the initiation site. For example, Loh *et al.* showed that aziridines (**270**) can be efficiently used as an alternative to epoxides, Scheme 1.33 top.^[194]

Halogenated natural products often originate from marine origin due to the high saline content and thus the abundance of chloride, bromide and iodide ions available.^[195] In nature, these halogenated natural products are often created through the action of a vanadium- or iron-Heme-dependant enzyme that uses peroxide or molecular oxygen as oxidizing agent.^[196–199] Snyder *et al.* reported that the highly electrophilic brominating agent BDSB (**274**) could mimic the natural bromonium-activation of alkenes to promote cationic polyene cyclizations on a variety of substrates, which was a substantial improvement in yield over alternative methods (Scheme 1.33 middle). The method was applied to the total syntheses of 4-isocymobarbatol **277**, the tetracyclic bromide (**279**) and various other bi- and tricyclic compounds.^[200] Furthermore, Snyder and co-workers disclosed the iodinating agent IDSI (**281**) and the chlorinating agent CDSC (**284**) as complementary electrophilic halonium ions used as initiators for polyene cyclizations on arenes (**280**) and (**285**).^[201]

Edstrom and Livinghouse disclosed the first use of episulfides as activating groups in polyene cyclizations.^[202] A mixture of PhSOMe and BF₃ gave the episulfide electrophile PhS⁺, which promoted the polyene cyclization of arene (**286**) towards sulfide (**288**), Scheme 1.33 bottom. Shaw and co-workers established a similar strategy to create the episulfide precursor PhS⁺ by mixing PhSCl and Sc(OTf)₃.^[203] In addition, further selenide derived products of aniline polycycles (**290**) were synthesized by employing PhSeCl



Scheme 1.33: Recent developments of new activating groups for biomimetic polyene cyclizations.

as selenium-source.

Polyene cyclizations remain at the cutting edge of synthetic organic chemistry due to the copious number of natural products derived from this cascade cyclization process. As a consequence, novel, more sophisticated methods are constantly developed to access these natural products, making it a timeless field of research in organic chemistry - a true classic. For a summary of recent developments in polyene cyclizations, please see the addendum.^[204]

AIMS AND OBJECTIVES

2.1 AIMS AND OBJECTIVES

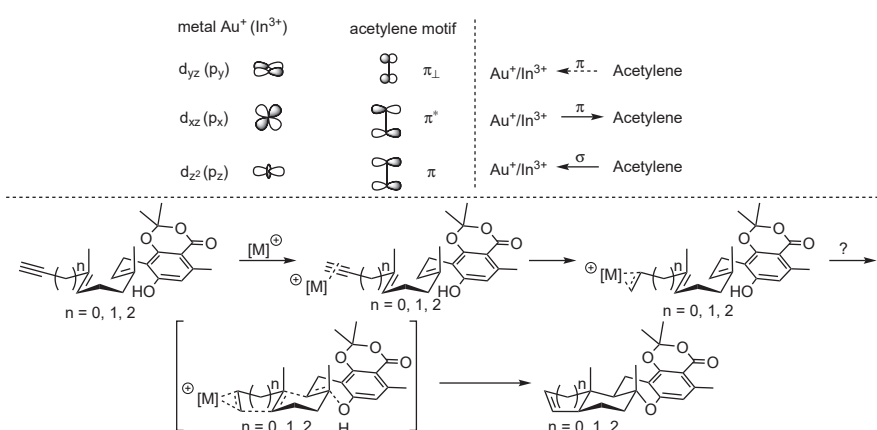
The scientific field of polyene cyclizations has vastly enriched chemical knowledge. The Stark-Eschenmoser hypothesis emerged as an underlying attempt to rationalize the observed outcome of *trans*- or *cis*-fused decalin systems starting from *trans*- or *cis*-olefins, ubiquitous as the product of such processes in nature (steroids, meroterpenes, etc.). Furthermore, these reactions are not only highly diastereoselective (*cis*- and *trans*-fused ring systems) but also enantioselective when an additional stereocenter is present at the initiation site (such as in epoxides, episulfides, aziridines or in intermediately formed, highly reactive haloniums). This can lead to as little as 2 and to 10 or more continuous stereocenters with control of absolute stereochemistry.

Past examples of activating groups include, but are not limited to, cyclic acetals, allylic alcohols, strained three-membered rings (oxirane, thiirane, aziridine, halonium) and stereoselective protonations. As a result, it was envisioned to employ further novel initiators for polyene cyclizations. For example, one objective was to investigate the role of various acetylenic polyolefin chains on their cyclization behaviour. As mentioned in section 1.4, Johnson found acetylene units in the tail region of the polyolefin chain can be harnessed when they are in a 1,5-relationship to the olefin to promote the formation of five-membered rings.^[152,154] In this study, we wanted to investigate the behaviour of such enyne entities in the head region.

Firstly, it was aimed to expand the field of acetylenic groups in polyen(yne) cyclizations. Such enynes have already been successfully used in polyene cyclizations, c.f. work by Toste, Michelet or Gagné in Schemes 1.27 and 1.28.^[174,175,177] However, these studies often focused on a 1,5- or 1,6-relationship between the alkyne and olefin. In those cases the sole product observed is a six-membered ring with an internal- or exo-double bond, respectively. As

such, expanding the area of research to the lower chain derivatives, the 1,3- and 1,4-enynes, next to the 1,5-enyne would provide a valuable insight. The 1,5-enyne will act as a control measure, as its constitutional relation to a typical 1,5-terpene unit is evident from its structure. In a study employing InI_3 as activating Lewis acid, Corey found the selective formation of a six- over a five-membered ring of various 1,5-enyne containing compounds.^[205] Furthermore, the formation of seven- or eight-membered rings from the corresponding precursors was not observed at all or very slowly. Corey, thus, postulated, that π -Lewis acids (such as In or Au) with low-lying d-orbitals, could mix with the empty p-orbital to produce a hybrid orbital.^[176] This could complex an acetylene unit in a bidentate fashion by mixing with both π -bonds of the alkyne,^[206] which enhances the electrophilicity of the acetylene entity as it lowers the bond order, Scheme 2.1 top. As a result, this coordination can bend the $\text{C}-\text{C}\equiv\text{C}$ bond in such a way that it promotes six-membered ring formation. With this in mind, polyenyynes of varying chain length were studied for the possibility of different cyclization behaviour according to this proposed bending of the $\text{C}-\text{C}\equiv\text{C}$ bond, Scheme 2.1 bottom. The results of these investigations and their application are discussed in the chapter titled "Enyne Precursors".

Finally, the resulting cyclization products and their analogs should be transferred to collaborators in the biological fields to investigate their biological profiling which would enable valuable SAR information and possibly new avenues for medicinal chemistry purposes.



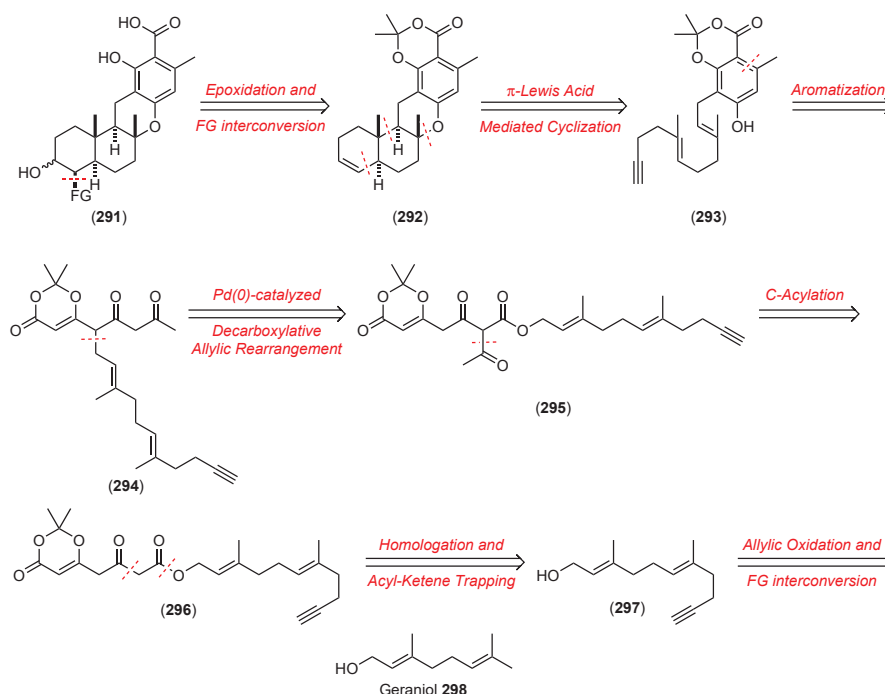
Scheme 2.1: Explanation for the metal-acetylene bonding model and application to the aim of this project for the investigation of various acetylene terpenes in polyenyne cyclizations.

Part II

RESULTS AND DISCUSSION

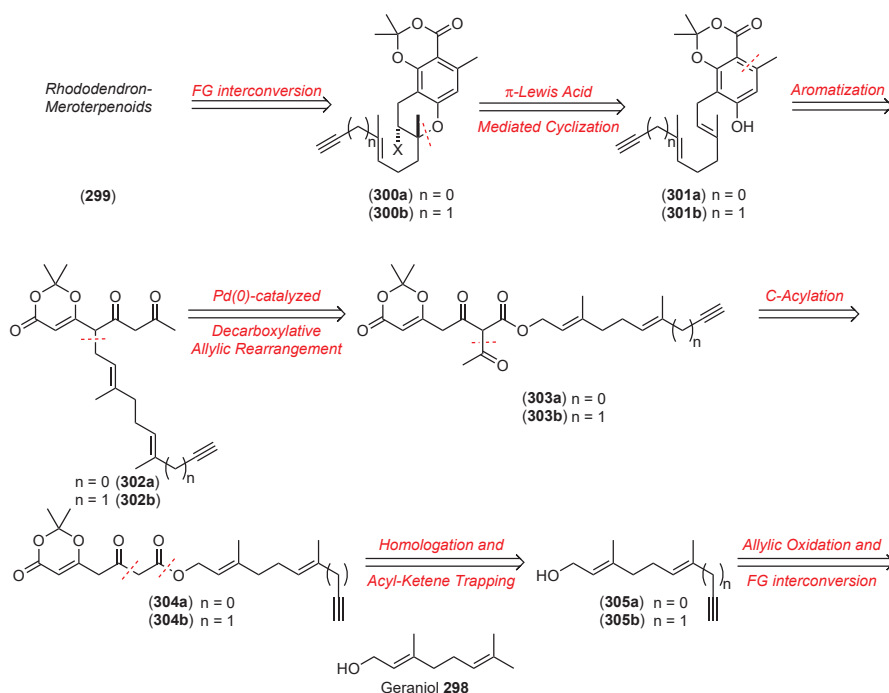
ENYNE PRECURSORS

The syntheses of meroterpenoids would rely on established group methodology employing β,δ -diketo-dioxinones to assemble the arene subunit in a biomimetic fashion.^[80] In the case of the 1,5-dienyne resorcyate, it was anticipated that a rigid core structure such as in (292) could be expected.^[175] This would be applied to the syntheses of various analogs of Hongoquercin A and B (291), as the carbon framework was already in place. It was envisioned to include a late stage diversification through diastereoselective epoxidation, opening of the epoxide with various nucleophiles and functional group interconversion, Scheme 3.1. The cyclized product (292) would be available through a π -Lewis acid (such as $[\text{Au}]^+$ or In(III)) mediated cyclization of (293).^[175,205] Biomimetic aromatization of the β,δ -diketo-dioxinone chain (294) would be possible after the regioselective Pd(0) -mediated Tsuji-Carroll rearrangement of (295) and C-acylation reaction of (296).^[104] The β,δ -keto-



Scheme 3.1: Retrosynthetic analysis for the synthesis of hongoquercin analogs.

dioxinone ester (**296**) should be available from an *in situ* homologation of β -dioxinone acid (**140**) with a benzaldehyde Meldrum's acid derivative (**141**) to regioselectively produce a reactive acyl-ketene intermediate, which can be trapped with the allylic, terpene alcohols (c.f. Scheme 1.19). The β -dioxinone acid in turn can be traced back to commercially available dioxinone through enolate chemistry.^[104,105] Finally, the preparation of the 1,5-dienyne terpene alcohol (**297**) could be facilitated through allylic oxidation and FG interconversion of geraniol **298**.^[207–211] Similar manipulations were envisioned when employing the shorter 1,3- and 1,4-enyne resorcyates. π -Lewis acid (such as $[\text{Au}]^+$,^[212–216] In(III) ^[217,218] or Br^+ ^[219–221]) mediated cyclizations were envisioned to provide a fully or partially cyclized core-structure (**300**), Scheme 3.2. The linear meroterpenoid (**301**) would be available through a similar, biomimetic aromatization of (**302**), Pd(o)-catalyzed decarboxylative rearrangement of (**303**) and C-acylation reaction of the β,δ -keto-dioxinone ester (**304**),^[104] which, conversely, should be accessible from geraniol **298** through allylic functionalization reactions and acyl-ketene trapping.^[207,211,222]



Scheme 3.2: Retrosynthetic analysis for the synthesis of *rhododendron* meroterpenoids.

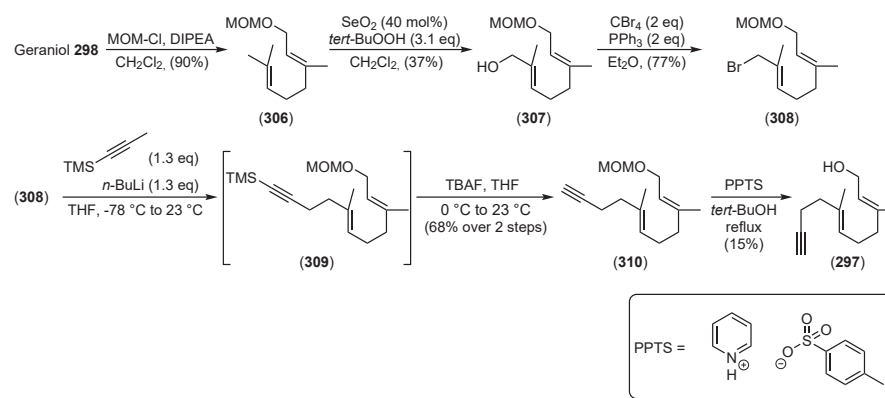
3.1 SYNTHESIS OF ANALOGS OF HONGOQUERCIN *via* A π -LEWIS ACID
MEDIATED CYCLIZATION

With geraniol **298** identified as a suitable, commercially available starting material, the outlined sequence commenced through alcohol protection as MOM-ether under basic conditions, which provided ether (**306**) in 90% yield on several gram scale, Scheme 3.3.^[223]

MOM-ether (**306**) was subjected to two different conditions with selenium dioxide in catalytic amounts and *tert*-butyl hydroperoxide as a stoichiometric oxidant. Initially, catalytic amount of selenium dioxide (0.2 equiv.) with excess of co-oxidant for an extended reaction time (24 h) gave rise to allylic alcohol (**307**) in 30% yield.^[207,224] A new method by Garg suggested raising the amount of selenium dioxide to sub-stoichiometric (0.4 equiv.) with approximately same amount of co-oxidant for 1.5 h.^[225] This indeed gave rise to the allylic alcohol (**307**) in 37% yield next to the overoxidized aldehyde (**390**) in 9% yield. Alcohol (**307**) was envisioned to serve as a divergent precursor to the 1,3- (**305a**, $n = 0$), 1,4- (**305b**, $n = 1$) and 1,5-enyne alcohols (**297**).

Subsequent conversion of alcohol (**307**) into bromide (**308**) employing Appel-conditions worked well (77% yield).^[210,226] Organolithium addition of the lithium acetylide generated from TMS-propyne and *n*-BuLi was successfully accomplished and gave ether (**309**), which following a TBAF mediated de-silylation furnished the 1,5-enyne (**310**) in 68% yield over 2 steps.^[209,227] However, deprotection of the MOM-group proved to be troublesome. HCl in dioxane, even over an extended period of time (3 days) did not afford the deprotected alcohol (**297**) in acceptable yields. When PPTS was used, a similar slow reaction was observed.^[228,229] Heating and excess of PPTS did not accelerate the reaction but allowed transformation to unidentified, possibly cyclized side-products. Thus, benzoyl groups (Bz) were selected as an alternative protecting group. It was postulated that the benzoyl group could be removed with the installation of the acetylene unit through excess of the derived organolithium compound.

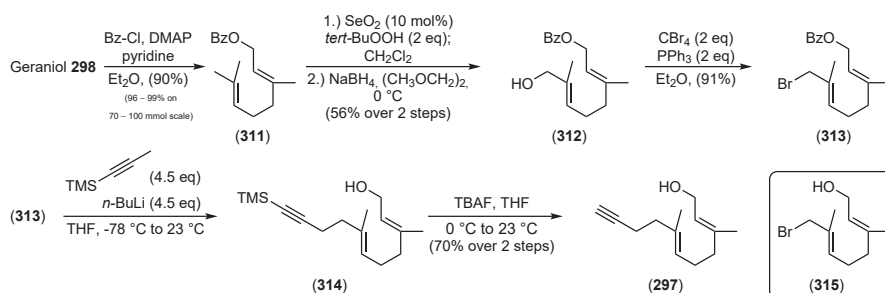
Protection of geraniol **298** as literature known benzoyl ester (**311**) was accomplished in high yields (96 - 99%), Scheme 3.4.^[207] Subsequent allylic



Scheme 3.3: Attempts to synthesize dienynol (**297**) using MOM-protecting groups.

oxidation with different variations of selenium dioxide/*tert*-BuOOH ratios were investigated to find the optimum yield. Garg's method (0.4 equiv. of SeO_2 , 3.1 equiv. of *tert*-BuOOH) was well yielding for allylic alcohol (**307**) and hence, the same conditions were employed for the substrate (**311**). After 2 h, alcohol (**312**) was obtained in 20% yield and 80% yield of recovered starting material. This was very encouraging - however it did not match the reported yield nor the obtained yield of alcohol (**307**) under the same conditions. A method published by Corey (0.1 equiv. of SeO_2 , 2.0 equiv. of *tert*-BuOOH) employed a longer reaction time, which was examined next.^[211] These conditions resulted in a yield of 30 - 37% for alcohol (**312**) and 12 - 20% for aldehyde (**392**). Including a reduction step, to convert aldehyde (**392**) to alcohol (**312**) and reductively cleave any organoselenides, allylic alcohol (**312**) was obtained in 51% yield with 20% yield of recovered starting material. Upon scale-up (100 mmol) the reduction step produced significant amounts of the deprotected alcohol, presumably through methoxide mediated benzoyl-deprotection as evidenced by the isolation of methyl benzoate in 54% yield. In this case on that scale, dimethoxyethane was used as a suitable alternative, giving rise to allylic alcohol (**312**) in 56% combined yield over 2 steps.

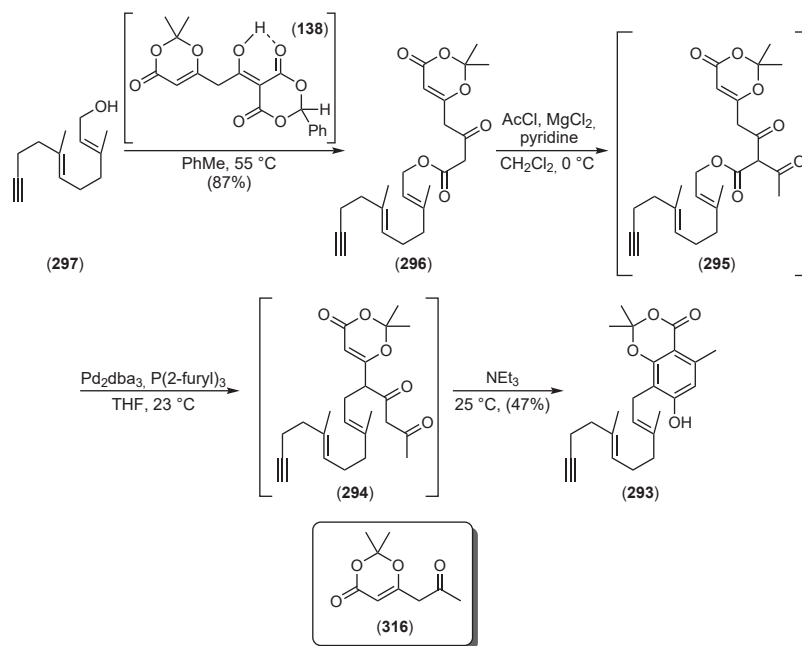
Subsequently, allylic bromide (**313**) was formed under Appel conditions, as this proved to give better yields for bromide (**313**) (91%) compared to using PBr_3 (56%).^[210] Next, installation of the acetylene entity was investigated. Initially, only 1 - 2 equiv. of the lithium acetylide species, derived from TMS-propyne and *n*-BuLi, were allowed to react with bromide (**313**), based on the results observed with the MOM-protected bromide (**308**). The reaction

Scheme 3.4: Synthesis of the dienynol (**297**).

gave a mixture of compounds, which after TBAF mediated deprotection was complex to analyse. Allylic bromide (**315**) was one of the major products. Noteworthy, this suggests that the addition of the TMS-methyl propynyl lithide to the carbonyl of the benzoyl ester was faster than the $\text{S}_{\text{N}}2$ displacement at the allylic position. However, this may find usage as a convenient way to deprotect an ester with a carbon based nucleophile in the presence of an allylic bromide. Eventually, upon using an excess of the lithium acetylide species, derived from TMS-propyne and *n*-BuLi, the reaction gave alcohol (**314**). A subsequent TBAF-mediated deprotection furnished dienyl alcohol (**297**) in 90% yield over 2 steps.^[209] Upon scale-up, this yield converged to 70%.

With allylic alcohol in hand, it was possible to follow established group methodology to synthesize the resorcyate core. Literature-known carboxylic acid (**140**) was prepared according to the method by Barrett *et al.*^[105] and activated and homologated with the benzaldehyde-Meldrum's acid derivative to give dioxane-4,6-dione keto dioxanone (**138**). Upon heating to 55°C , this intermediate produced acyl-ketene (**133**), which was trapped with the allylic alcohol (**297**) and gave dioxinone- β -keto ester (**296**) in good yields (87%), Scheme 3.5. Keto-dioxinone (**316**) was often isolated as side product during the keto-ester preparation, in agreement with the previously reported method development from Ma's thesis.^[230] It was proposed, that the compound (**316**) might arise from the undesired trapping of the acyl-ketene intermediate with H_2O , to give dioxinone- β -keto acid, which decarboxylated to produce acyl-dioxinone (**316**). A following regioselective C-acylation reaction of β -keto ester (**296**), mediated by MgCl_2 and pyridine, Pd(o)-catalyzed decarboxylative, allylic rearrangement reaction of β,δ -diketo-ester (**295**), base

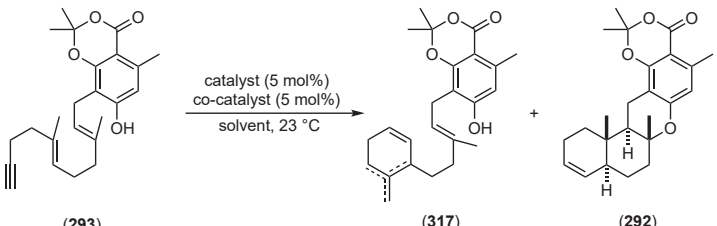
mediated cyclization and final aromatization of β,δ -diketo-dioxinone (**294**) gave the meroterpenoid (**293**) in moderate yield (47%).



Scheme 3.5: Synthesis of the 1,5-enyne resorcyate (**293**).

To mediate a bioinspired polyenyne cyclization,^[175,205] (**293**) was subjected to various conditions, Table 1. Initially, a combination of silver and gold salts was used.^[231] However, it was noticed, that yields and ratios were only moderate. Possibly, the phenol moiety was prone to oxidation in the presence of Ag^I. A different, weakly coordinating counterion was therefore chosen for the Au-catalyst: NTf₂⁻.^[232] Subjecting (**293**) to two catalysts of this type in different solvents gave two compounds: the partially cyclized resorcyate (**317**) and the fully cyclized resorcyate (**292**) in varying yields. Overall, XPhos AuNTf₂ provided a better mass balance (combined yields in the above 80% region) and higher selectivity towards the fully cyclized product in 1,2-dichloroethane. This is in agreement with literature, as XPhos is a sterically less demanding ligand and makes the [Au]⁺-species more alkynophilic.^[233,234]

Compound (**317**) gives some insight into the mechanism of formation of the fully cyclized product (**292**). Following the hypothesis by Corey (c.f. section 2.1), coordination of [Au]⁺ or In³⁺ to the alkyne produced a metal-alkyne complex, which lowered the bond-order of the alkyne and, thus,

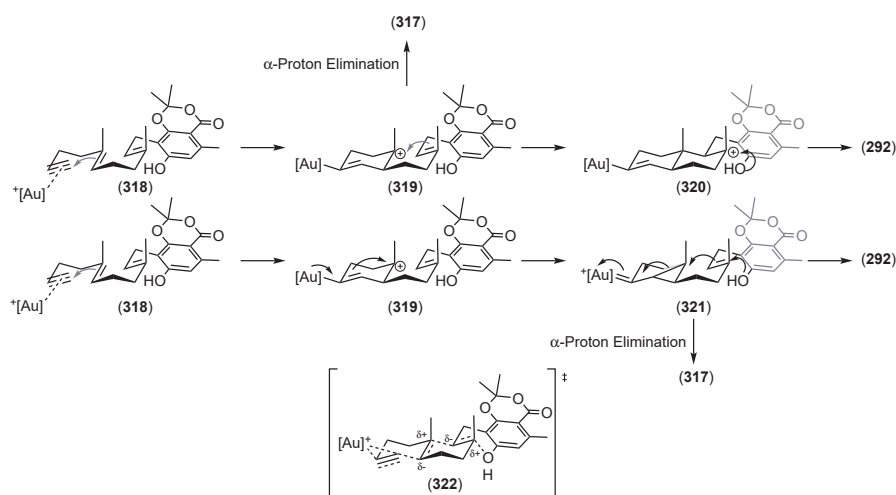


Solvent	Catalyst	Co-Catalyst	Ratio SM : P (Yield)
CH ₂ Cl ₂	(SMe ₂)AuCl	AgSbF ₆	1:1.5 (48%)
CH ₂ Cl ₂	(SMe ₂)AuCl	AgOTf	1:2 (50%)
(CH ₂ Cl) ₂	BrettPhos AuNTf ₂	-	1:5 (75%)
Ph-Me	BrettPhos AuNTf ₂	-	1:1.5 (60%)
(CH ₂ Cl) ₂	Xphos AuNTf ₂	-	1:10.5 (81%)
Ph-Me	XPhos AuNTf ₂	-	1:1.4 (90%)
(CH ₂ Cl) ₂	InBr ₃	-	1:8 (55%)

Table 1: Screening conditions for the bioinspired polyenyne cyclization.

induced bending of the alkyne into a more favourable conformation. This enabled a concerted attack from the proximal olefin to give the first six-membered ring, resulting in the formation of a tertiary carbenium ion (**319**) available for cationic polyene cyclization or alternatively the partially cyclized product (**317**) through α -proton abstraction, Scheme 3.6. On the other hand, Echavarren proposed that coordination by [Au]⁺ to the acetylene promoted a cyclization to (**319**), followed by rearrangement to the cyclopropyl-gold-carbene (**321**).^[235] Intermediate (**321**) could either open to produce the same derived tertiary carbenium ions (**319** or **320**) available for classical terpene cyclization or alternatively eliminate a proton to release ring-strain, giving the partially cyclized product (**317**). An idealised transition state for a full cyclization is depicted as structure (**322**).

Taken from Table 1, solvent effects appear to play a role in this reaction. Polar solvents, like 1,2-dichloroethane, could be hypothesized to stabilize the charge intermediates, and/or promote further cyclization through aggregating the hydrophobic terpene chain in the preferred conformation (although it was not tried, HFIP or ionic liquids are known example for this).^[236–238] Toluene on the other might not be able to stabilize the charged intermediates as well as 1,2-dichloroethane, other than through π -interaction, and may have attractive interactions with the terpene-chain. This might lead to conformational flexibility, which enables the terpene chain to adopt a different conformation which could crucially be different to the desired chair-chair-chair



Scheme 3.6: Possible mechanisms for the formation of the two resorcyate products.

conformation. The observed lower yield and lower ratios between full and partial cyclization from the reactions in toluene would be in agreement with this explanation. While the solvents were bought and stored under inert atmosphere over molecular sieves, the gold-bis(trifluoromethanesulfonyl)imide salts are deemed air- and moisture-stable^[232] and the reactions were performed in oven-dried glassware, it can never be ruled out that residual water, unsolvated in the organic solvent and thus highly reactive, may have been responsible for the deprotonation and formation of the partially cyclized product (317). Finally, the rigid *trans-trans*-ring system of resorcyate (292),

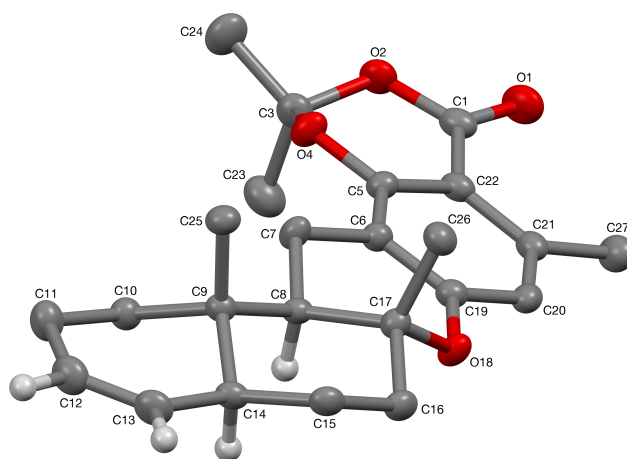
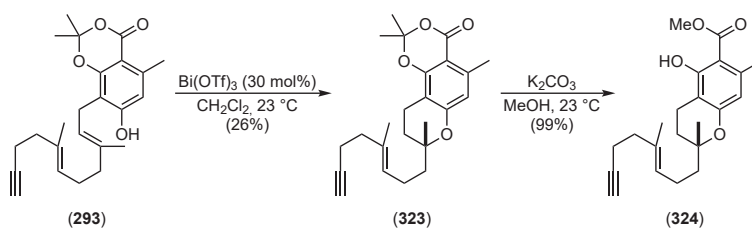


Figure 1: X-Ray crystal structure of the fully cyclized resorcyate (292). Reprinted (adapted) with permission from *J. Org. Chem.* **2021**, *86*, 1802-1817. Copyright 2021 American Chemical Society.

isolated as a single diastereoisomer, was unambiguously characterized using single crystal X-Ray diffraction analysis, Figure 1.

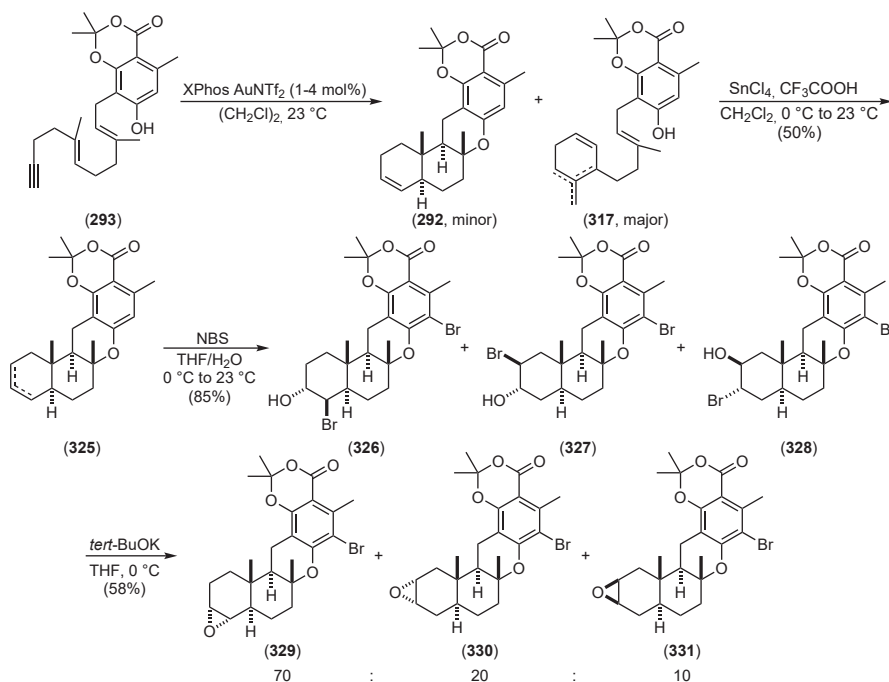
Other Lewis acid such as InBr_3 ,^[176,205] $\text{In}(\text{OTf})_3$ or $\text{Bi}(\text{OTf})_3$ ^[239,240] were inferior in producing the fully cyclized compound (**292**). In fact, with $\text{Bi}(\text{OTf})_3$ the chromane (**323**) was isolated in 26% yield, Scheme 3.7. Transesterification



Scheme 3.7: $\text{Bi}(\text{OTf})_3$ mediated cyclization.

with K_2CO_3 in MeOH furnished chromane methyl ester (**324**) in excellent yields (99%). Resorcyates (**293**) and (**324**) are structural analogs of grifolic acid **68** and the chromanes **54**, bearing a key alkyne functionality. This could have potential applications in proteomics through alkyne-tag chemistry for target identification (see future work).

Moreover, when lower gold-catalyst ratios were employed (1-4 mol-%) and on larger scale reaction, the ratio of resorcyate (**292**) over partially cyclized resorcyate (**317**) deteriorated and diene (**317**) was isolated as the major product, Scheme 3.8. Different solvents (Et_2O , CH_2Cl_2 , Ph-Me) did not improve this ratio. Literature precedence for partial cyclization in cationic



Scheme 3.8: Synthesis of bromo-epoxides.

polyene cyclizations (c.f. Yamamoto's and Carreira's polyene cyclizations in Schemes 1.24 and 1.25, and 1.26, respectively)^[162,164–167] suggests resubmitting the crude mixture of partial and fully cyclized products to a mixture of Lewis-acid enhanced Brønsted-acid conditions.

Thus, examination of such conditions gave the desired product (292), although obtained as a mixture of isomers. This was demonstrated by reaction of resorcyate (325) with NBS in aqueous THF (85% yield), followed by reaction with potassium *tert*-butoxide (58% yield), Scheme 3.8. The isolated bromo-epoxides were an inseparable mixture between the α -C1-C2 epoxide (329) and a mixture of α -epoxide (330) and β -epoxide (331) in the C2-C3-position in ratios of 70:20:10, as further evidenced by single crystal X-ray diffraction analysis, Figure 2. Contrary to literature precedence,^[241–243]

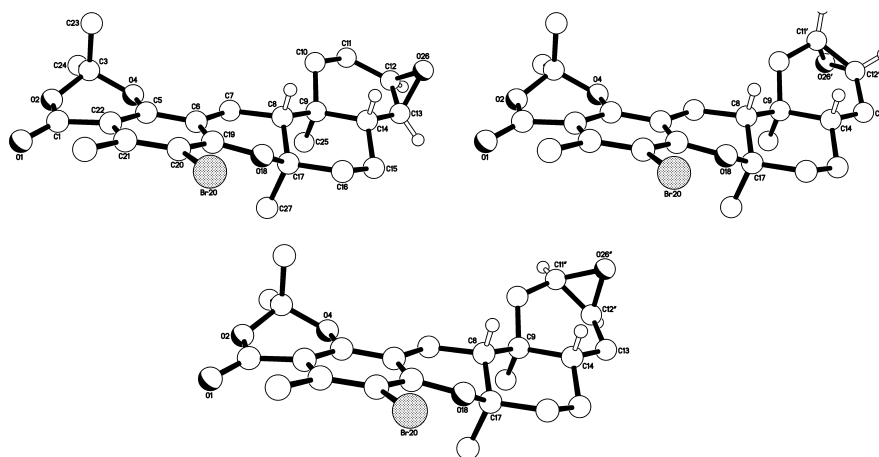


Figure 2: X-Ray crystal structure of the bromo-epoxides.

the relative stereochemical configuration of dibromohydrin (326) and the derived epoxide (329) are the same as the *m*-CPBA derived epoxide (342) and bromohydrin (366), although literature precedence suggests they should be of opposite nature, especially in the absence of a directing group. Figure 3 depicts the relative energy diagram for the formation of the bromohydrin (326) and the opposite diastereoisomer.^[244] As the bromonium ion formation is reversible, the energy barrier can be easily overcome to establish an equilibrium between the formation of the bromohydrin below the plane, the starting material and the bromohydrin above the plane. Due to steric interactions, the bromonium formation above the plane is less favourable than the bromonium formation below the plane ($\Delta G_{TS1}^\ddagger$). The following

nucleophilic attack of water, however, is the rate-determining step. The attack from above the plane, onto the bromohydrin below the plane, will undergo sterically unfavourable interactions with the methyl-groups (shown on the left side), while attack from below the plane onto the bromohydrin above the plane can happen more readily (shown on the right side of the figure, ($\Delta G_{TS2}^\ddagger$)). Thus, as a consequence of the relative levels of the transition states for the opening of the bromohydrins, only the product with less sterically unfavourable interactions is isolated.

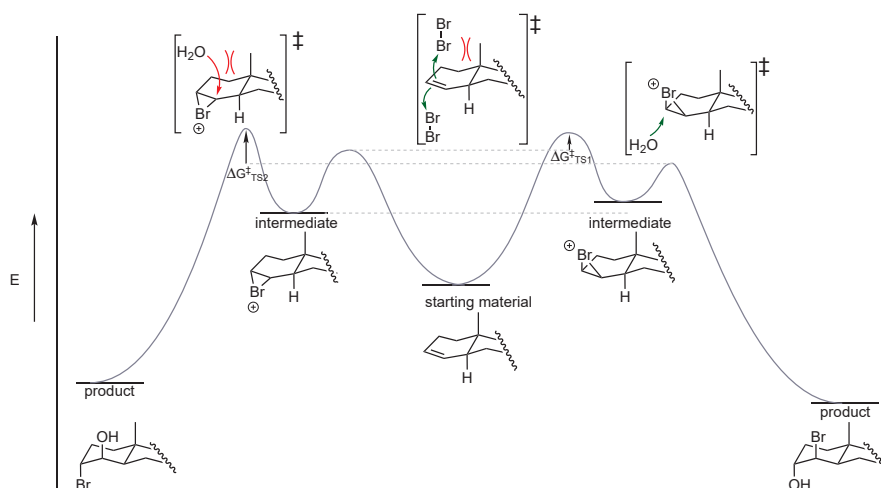
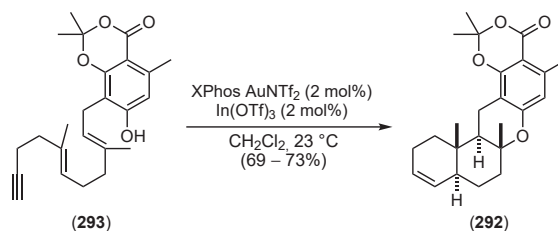


Figure 3: Proposed energy diagram to visualize the formation of the bromohydrin (326) according to the Curtin-Hammett principle.^[244]

To rationalize the olefin isomerization, the strongly acidic conditions possible protonated the olefin of pentacyclic resorcyate (292),^[179] or possibly at an earlier cyclization stage such as partially cyclized resorcyate (317). While protonation in the C2 position will most likely lead to recovery of resorcyate (292), protonation in the C1 position can lead to olefin isomerization, as a proton from the C3 position could be abstracted. Since both derived carbenium ions are of secondary nature, they should have equal probability of formation and, thus, the relative energies of the two products could be the determining factor. It is noteworthy to point out that no rearranged product was observed, which could be derived from protonation at the C2 position and subsequent 1,2-shifts to form a more favourable, tertiary carbenium ion.

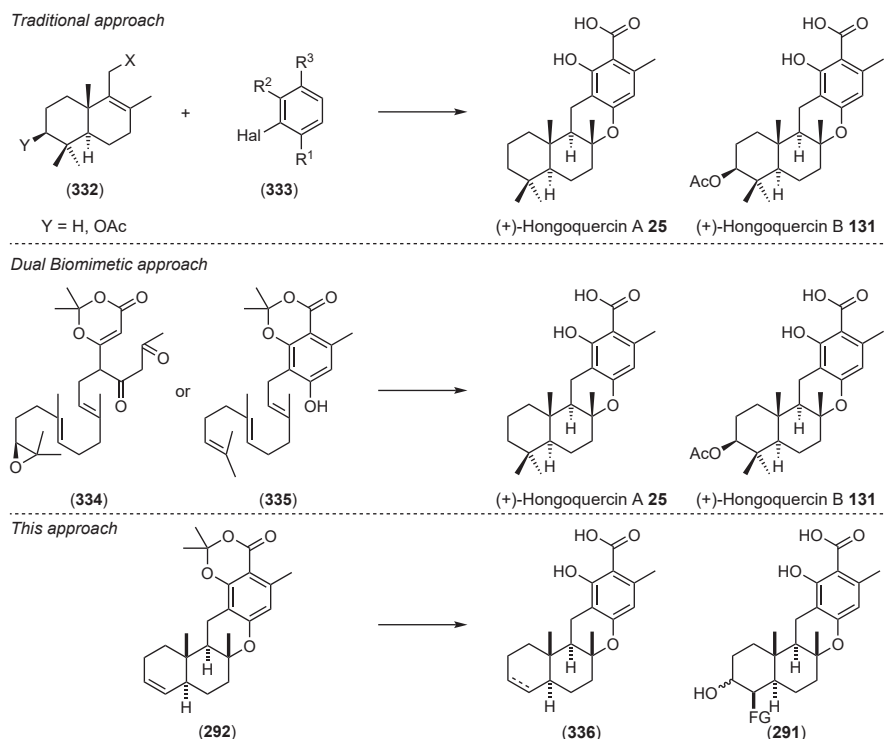
Evidently, the issue of olefin isomerization would have further downstream effects, especially due to the difficulty of separation. Inspired by the Lewis- and Brønsted-acid mixture, a dual catalyst system between the gold salt

XPhos AuNTf₂ (2 mol-%) and an additional π -Lewis acid In(OTf)₃ (2 mol-%) was postulated to further promote the cyclization of the partially cyclized compound (**317**) or promote the opening of the cyclopropyl-gold carbene intermediate (**321**) towards cationic polyene cyclization rather than elimination. Pleasingly, this method gave pentacyclic resorcyate (**292**) over several individual attempts on different scales as the major product (69 - 73% yield) with only trace amounts of the partially cyclized diene (**317**), Scheme 3.9.



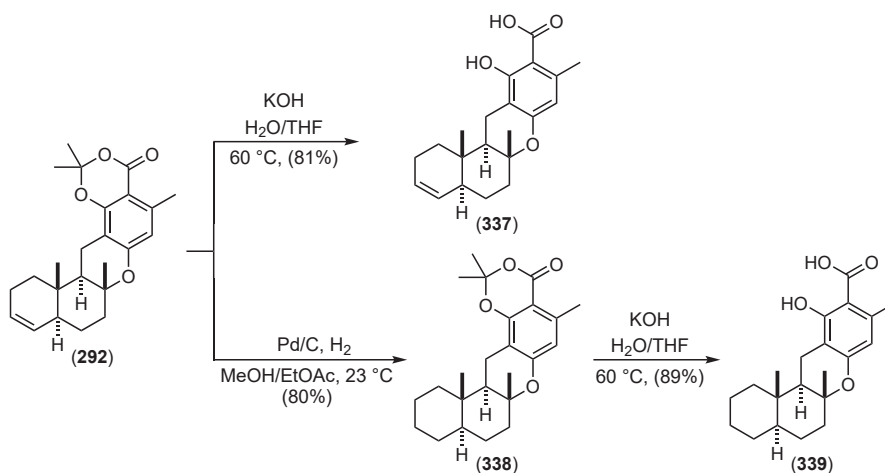
Scheme 3.9: Dual-Lewis acid catalysis for the polyenyne cyclization of (**293**).

With a scalable method at hand to efficiently synthesize the all-*trans*-fused ring system (**292**), the attention turned to synthesizing hongoquercin analogs, as they share a common structural motif. Hongoquercin A **25** and B **131** were found to have antibiotic properties against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, with hongoquercin A **25** showing better activity.^[245,246] Abbanat postulated that the antibiotic properties arise from disruptive bacterial membrane binding. Furthermore, the hongoquercins contain a synthetically challenging rigid core system with four continuous stereocenters and additionally a pentasubstituted arene core. Conventional methods to synthesize hongoquercins **25** and **131** couple the *trans*-decalin entity (**332**) to an arene unit of type (**333**) (c.f. Scheme 1.8), which employs substantial use of protecting groups and limits the possibility of derivatization, Scheme 3.10.^[21,30,247–250] The Barrett group further disclosed two independent syntheses of hongoquercin **131**, employing an early-(**334**) and late-stage terpene functionalization strategy (**335**).^[100,106] Consequently, applying the polyenyne cyclization method to the syntheses of hongoquercin analogs was an attractive target as it complements the established syntheses in the group through late-state derivatization to better understand the antibiotic properties.

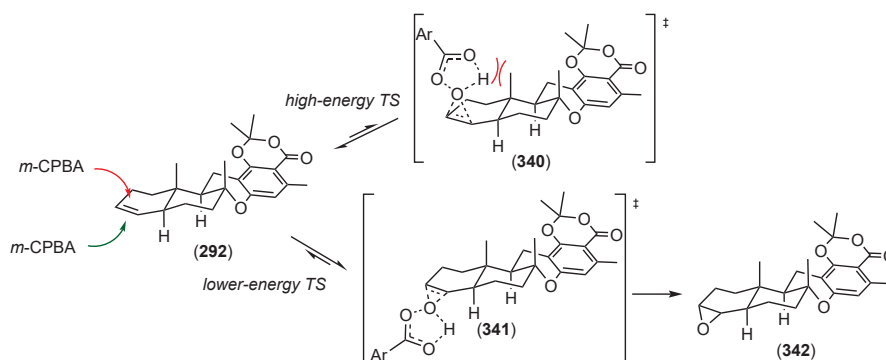


Scheme 3.10: Past methods to synthesize Hongoquercin A and B.

Saponification of resorcyate (**292**) gave acid (**337**) in 81% yield, Scheme 3.11. Additionally, reduction over palladium on carbon gave the saturated pentacyclic compound (**338**) in 80% yield. A subsequent dioxinone ester hydrolysis gave acid (**339**) in good yield (89%).

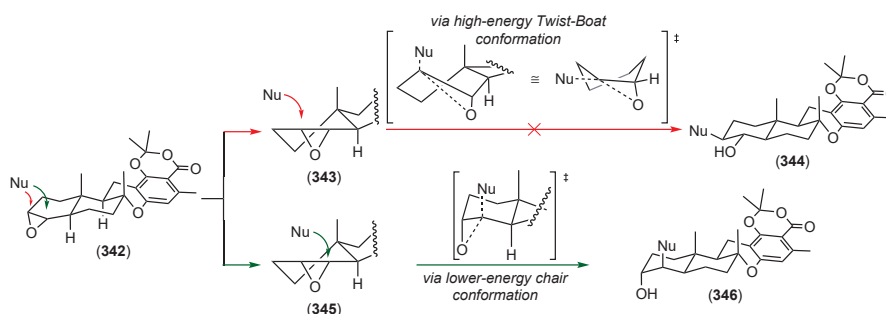
Scheme 3.11: Synthesis of resorcylic acids (**337**) and (**339**).

Epoxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave α -epoxide (**342**) in good yields (86%),^[205,251] as evidenced by nOe-correlation experiments, Scheme 3.14. The observed diastereoselectivity of this Prilezhaev



Scheme 3.12: Rationalization for the observed relative stereochemical configuration of the epoxidation reaction.

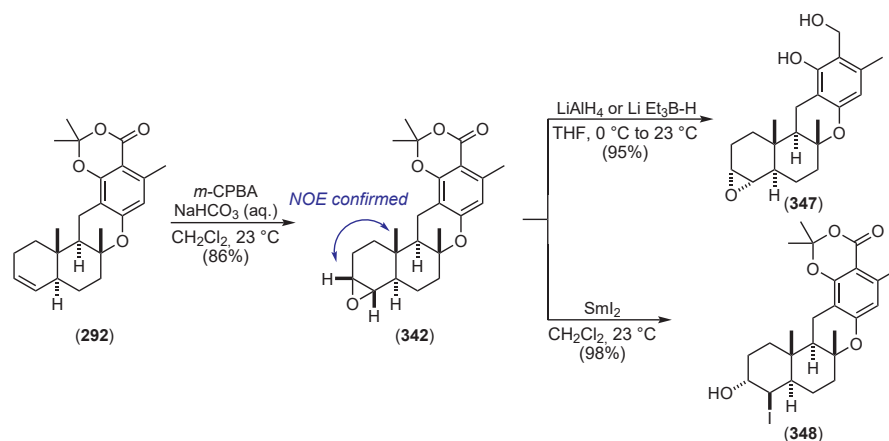
reaction can be rationalized as depicted in Scheme 3.12,^[252] where epoxidation *via* a spirocyclic Butterfly transition state from the top face would result in unfavourable steric interactions (340), while the bottom face (341) is accessible for epoxidation.^[253]



Scheme 3.13: Rationalization for the observed relative stereochemical configuration of the epoxide-opening reaction according to the Fürst-Plattner rule.

The stereoelectronics of the Fürst-Plattner rule dictate a *trans*-diaxial opening of the epoxide in the desired C1-position to give the alcohol in the C2-position.^[254] This is a consequence of the kinetically controlled opening mechanism, as attack in the C2-position (343), following the red pathway in Scheme 3.13, would proceed *via* an unfavourable, high energy twist-boat conformation to give the di-equatorial product (344). Opening in the C1-position (345) would proceed *via* an energetically favourable chair-transition state (along the green pathway in Scheme 3.13) giving rise to the *trans*-diaxial product (346).

Initially, methods to reductively open epoxide (342) with metal-hydrides (lithium aluminium hydride or lithium triethylborohydride) gave the benzylic alcohol (347) in 95% yield, Scheme 3.14.^[255] SmI₂-mediated reduction with



Scheme 3.14: Synthesis of iodohydrin (348).

triethylsilane gave no product evidenced of a reductive opening.^[256] In fact, the iodohydrin (348) was isolated as sole product (82% yield). In the absence of triethylsilane, iodohydrin (348) was isolated in 98% yield. Single crystal

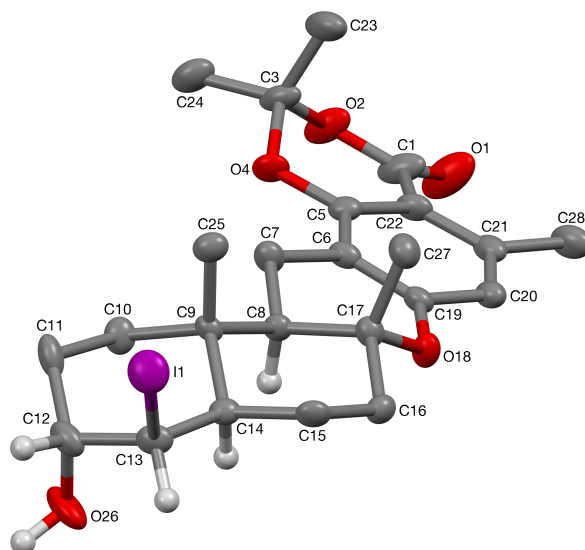
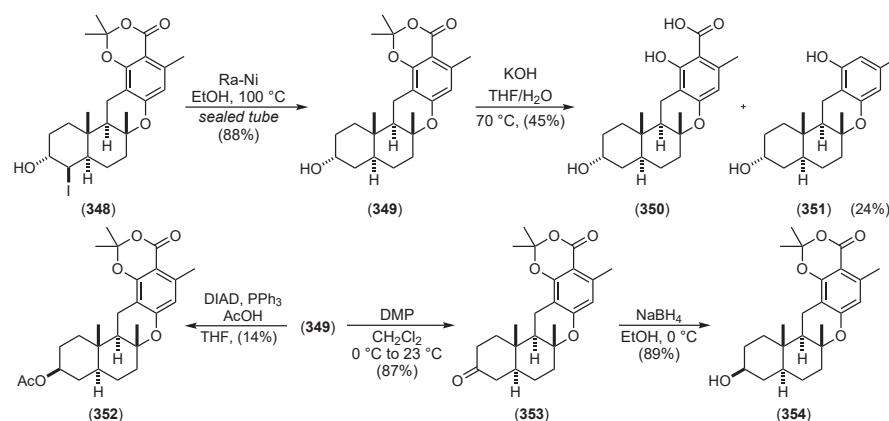


Figure 4: X-Ray crystal structure of iodohydrin (348). Reprinted (adapted) with permission from *J. Org. Chem.* **2021**, *86*, 1802-1817. Copyright 2021 American Chemical Society.

X-ray diffraction analysis confirmed the relative stereochemical configuration of iodohydrin (348) (see Figure 4) and unambiguously determining the *trans*-diaxial relationship of the alcohol and iodide moiety.

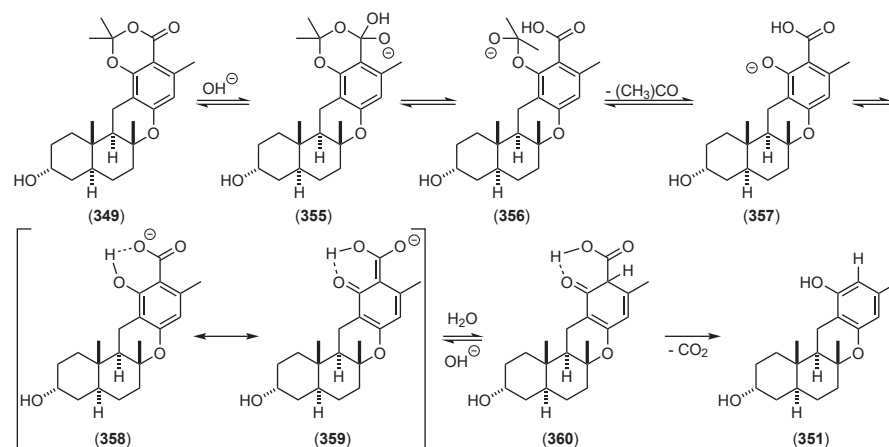
Raney-Nickel mediated dehalogenation of iodohydrin (348) gave alcohol (349) in excellent yields (88%),^[251] Scheme 3.15, while attempts to invert the stereochemistry under Mitsunobu-conditions (DIAD, PPh_3 and AcOH) produced β -alcohol acetate (352) in unsatisfactory yields (14%).^[257-259] Alter-



Scheme 3.15: Synthesis of unsubstituted derivatives.

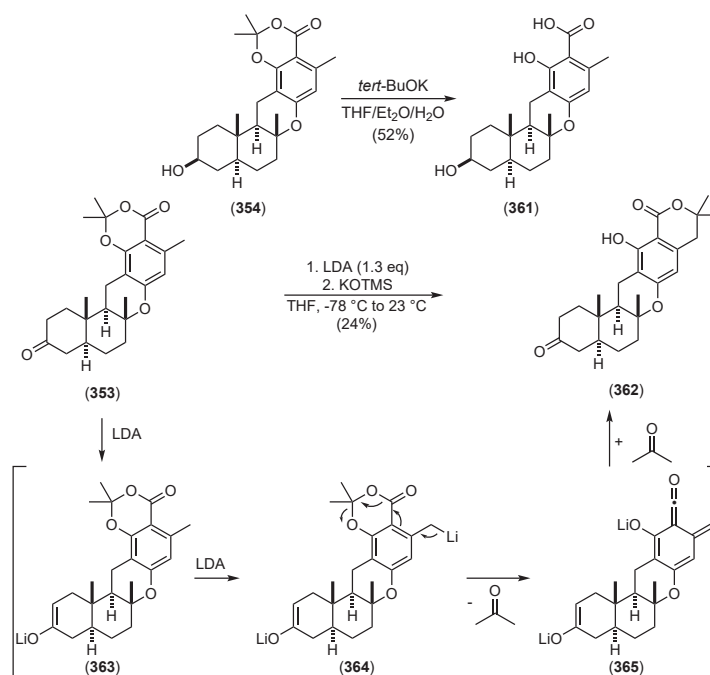
natively, oxidation with Dess-Martin periodinane (DMP) gave ketone (**353**) in 87% yield. Reduction of ketone (**353**) with sodium borohydride furnished β -alcohol (**354**) in 89% yield.^[260–262] While it is acknowledged that this sequence is not redox-economic and can produce noxious side-products,^[263] especially when scaled-up, it further enabled the synthesis of a hongoquercin B analog containing an H-bond acceptor in the C2 position. Saponification of α -alcohol (**349**) using potassium hydroxide gave acid (**350**) in 45% yield next to the decarboxylated product (**351**) in 24% yield.

Decarboxylation is commonly observed with meroterpenoids at elevated temperatures.^[28,104,105,264] A widely studied example is the decarboxylation of tetrahydrocannabinolic acid to the active psychoactive component of cannabis: tetrahydrocannabinol **80** (c.f. Scheme 1.12 and the conversion of resorcyates (**87**) to **80**).^[42] Literature precedence suggests keto-enol tau-

Scheme 3.16: Proposed mechanism for the decarboxylation of (**350**) to (**351**).

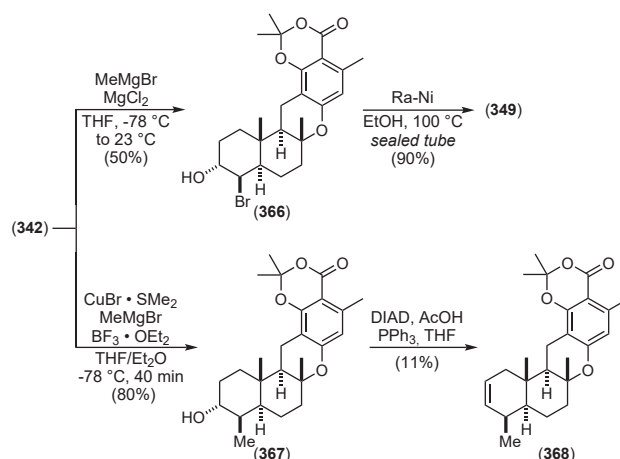
tomertization of the adjacent phenol, with concomitant loss of aromaticity, is followed by entropy-driven decarboxylation and re-aromatization.^[265,266] A similar mechanism could be postulated here: Under basic conditions, saponification and loss of acetone gave phenolate (357), which tautomerized through proton transfer to the H-bond stabilized phenol-carboxylate (358), Scheme 3.16. A possible resonance structure of this can be depicted as (359), which gave intermediate (360) through facile α -protonation. Loss of carbon dioxide as entropic driving force furnished decarboxylated phenol (351). This is notwithstanding that a possible radical mechanism, involving oxygen as radical initiator, could be competing, similarly to the decarboxylation of tetrahydrocannabinolic acid to cannabinoid 80, which can also be initiated through light. For example, Moreno and co-workers found a profound relationship between the presence of oxygen and the decarboxylation kinetics of tetrahydrocannabinolic acid to THC 80.^[266]

Potassium *tert*-butoxide in wet ether or THF was successfully applied as saponification method in the synthesis of (+)-hongoquercin A and B.^[106] This method was therefore chosen to suppress the decarboxylation.^[267] Under these conditions, saponification of β -alcohol (354) gave acid (361) in 52% yield, Scheme 3.17. Hydrolysis of the dioxinone group of resorcyate (353) was anticipated to be more troublesome, due to possible self-aldol reactions under standard saponification methods. As such, it was envisioned to mask ketone (353) as its enolate through reaction with LDA, followed by saponification of the dioxinone group with KOTMS. Serendipitously, it was found that through the slight excess of LDA used, lactone (362) was formed in 24% yield, Scheme 3.17. It is postulated that, after enolate formation (363), LDA deprotonated the benzylic methyl group (364), which induced an anionic accelerated retro-DA reaction to open the dioxinone group to form *ortho*-quinone methide ketene (365) which is trapped with acetone to form lactone (362), possibly *via* a pseudo-pericyclic transition state, where attack by the methide ketene onto the carbonyl carbon is rapidly followed by the attack of the carbonyl oxygen onto the ketene carbon centre, as depicted in Scheme 1.15. This unexpected reaction was further studied in section 3.4.



Scheme 3.17: Synthesis of resorcylic acid (361), resorcylic lactone (362) and proposed mechanism of formation.

Reaction of α -epoxide (342) with methyl magnesium bromide, to incorporate a methyl group in the C₁-position, was unsuccessful - while also displaying poor chemoselectivity with the dioxinone ester group. Addition of a mild Lewis acid (MgCl₂) gave the bromohydrin (366, 50% yield) instead of any product containing methyl group incorporation, Scheme 3.18. The structure of bromohydrin (366) was confirmed by single crystal X-ray



Scheme 3.18: Synthesis of substituted derivatives.

diffraction, see Figure 5. Alternative methylation protocols, like AlMe₃ or the methyl Normant cuprate derived from MeMgBr and CuBr · SMe₂ at

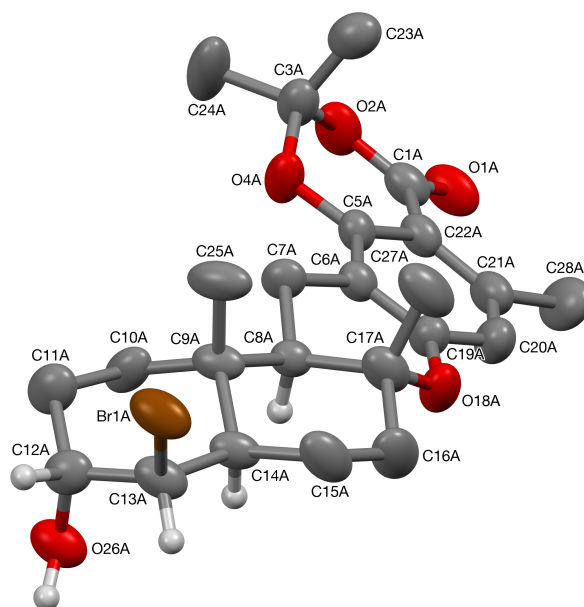
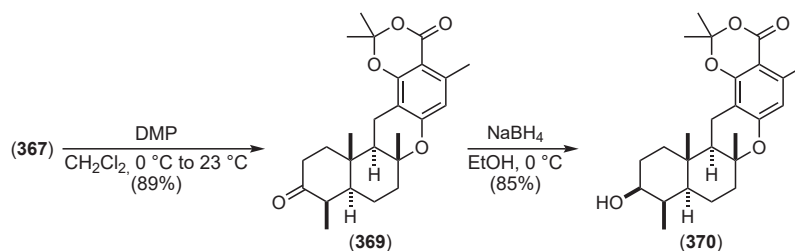


Figure 5: X-Ray crystal structure of bromohydrin (**366**). Reprinted (adapted) with permission from *J. Org. Chem.* **2021**, *86*, 1802-1817. Copyright 2021 American Chemical Society. Note this is only one of two independent molecules that crystallized in the asymmetric unit. Please see the addendum for the second structure.

variable temperatures failed to produce a structure correlating to (**367**) in viable amounts.^[268] Literature precedence suggest that the addition of BF_3 to Gilman cuprates of type $(\text{Me}_2\text{CuLi})_2$ can have beneficial effects, presumably *via* forming the highly reactive methylating species $\text{Me}_3\text{Cu}_2\text{Li}$.^[269–271] It was anticipated that the structurally related Normant cuprate should react in a similar fashion. Mixing the methyl Normant cuprate with $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C followed by addition of α -epoxide (**342**) gave the methyl-branched alcohol (**367**) in excellent yields (80%).^[272] It was found that a reversed order of addition, i.e. addition of $\text{BF}_3 \cdot \text{OEt}_2$ to a mixture of epoxide (**342**) and the methyl Normant cuprate gave almost equimolar amounts of methyl-branched alcohol (**367**) and bromohydrin (**366**). Dehalogenation of bromohydrin (**366**) with Ra-Ni gave alcohol (**349**, 90% yield),^[251] thus permitting to recycle the halohydrin side-product. Reaction of the methyl-branched α -alcohol (**367**) under Mitsunobu-conditions gave no product corresponding to the methyl-branched β -alcohol acetate. In fact, olefin (**368**, 11% yield) was isolated. The steric hindrance of the axial methyl group could account for this. Due to the steric congestion, a *trans*-diaxial-elimination, i.e. E_2 -type, could be kinetically favoured over the nucleophilic displacement. Dehydrative Mit-



Scheme 3.19: Synthesis of methyl-branched ketone (369) and β -alcohol (370).

sunobu procedures have otherwise been used at higher temperatures or with stronger bases and the *gem*-dimethyl group in various terpenoid synthetic studies.^[273–276]

DMP oxidation of methyl-branched α -alcohol (367) gave ketone (369) in excellent yields (89%), Scheme 3.19. The structure of ketone (369) was unambiguously confirmed by means of single crystal X-ray diffraction analysis, see Figure 6. Reduction with sodium borohydride gave methyl-branched β -alcohol (370) in good yields (85%).

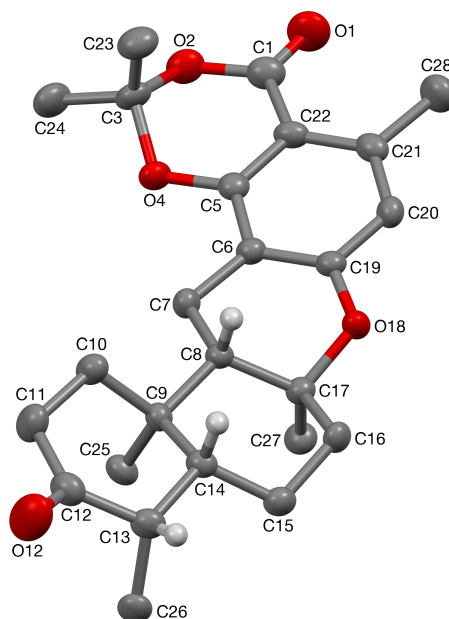
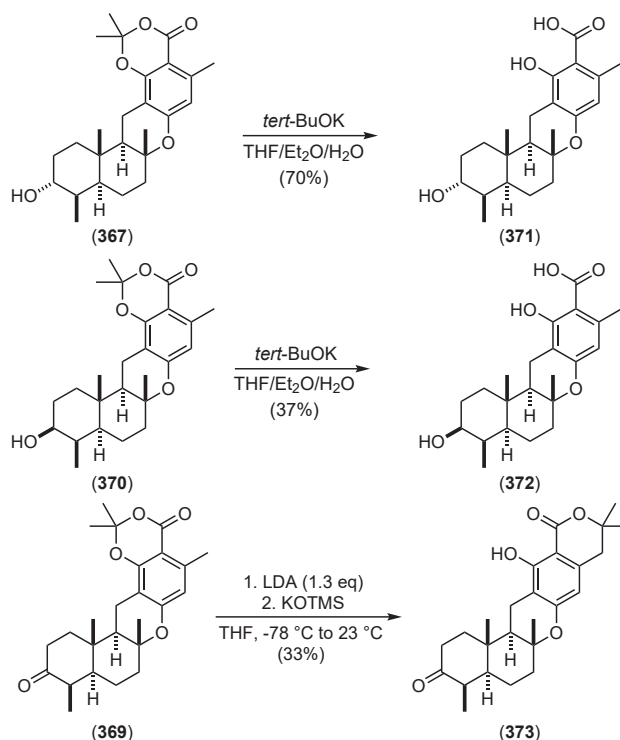


Figure 6: X-Ray crystal structure of methyl-branched ketone (369). Reprinted (adapted) with permission from *J. Org. Chem.* **2021**, *86*, 1802-1817. Copyright 2021 American Chemical Society. Note: by means of separate crystallization and crystal picking, the opposite diastereoisomer is displayed.

Saponification of methyl branched- α -alcohol (367) and - β -alcohol (370) gave acids (371) and (372) in 70% and 37% yields, respectively (Scheme 3.20), while saponification of methyl-branched ketone (369) with LDA and KOTMS gave lactone (373) in 33% yield.

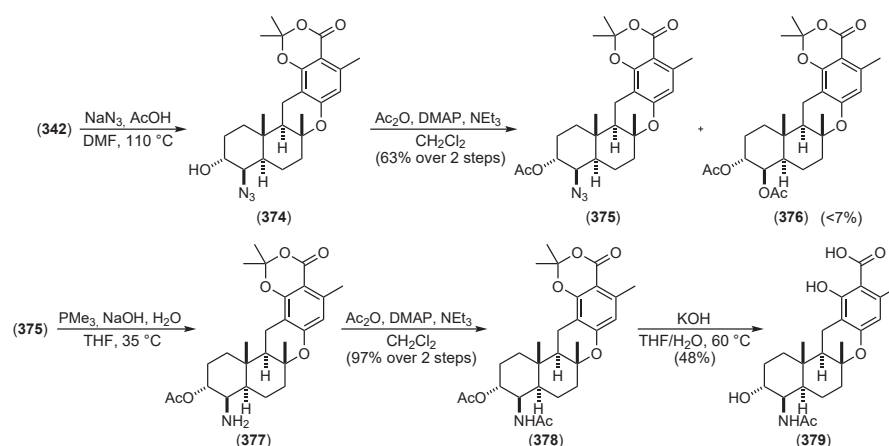


Scheme 3.20: Synthesis of resorcylic acids (371), (372) and resorcylic lactone (373).

α -Methylation of ketone (369) in the C1-position could be postulated to produce the *gem*-dimethyl group found in hongoquercin B **131**. Literature precedence suggest this is possible, although alkylation in the C3 position might be favoured and would require blocking.^[277] Analysis of the conformation of ketone (369), see Figure 6, shows that the C-H acidic proton resides in the equatorial position, where it has little stereoelectronic overlap which is required to produce the enolate to give the *gem*-dimethyl group through methylation. Deprotonation would therefore require strongly basic conditions, which may react undesirably at the benzylic position, similar to the LDA-induced rearrangement. Consequently, this strategy to synthesize hongoquercin **131** was not further investigated as undesired C3-methylation was expected.

Over the course of this study, it was found that epoxide (342) showed good reactivity with halide nucleophiles while showing slower reactivity with organometallic reagents. This reactivity trend was extended to the pseudo-halide azide to give azido- and amino-analogs of hongoquercin. Reaction of α -epoxide (342) with sodium azide gave azido alcohol (374), Scheme 3.21. Various synthetic protocols, including reduction with H₂ over palladium

on carbon or over palladium hydroxide on carbon, AcSH,^[278] Raney-Nickel (with and without AcSH) or Staudinger-type conditions like PPh₃ in wet THF failed to give the amino-alcohol.^[279] Reaction of PMe₃ with azido alcohol (374) gave epoxide (342), rather than the expected aziridine.^[280] This might explain the observed reactivity in the other failed reactions, although no epoxide was isolated in those cases. Due to the presumed alcohol reactivity interference, azido-alcohol (374) was further protected as the acetate (375) by reaction with acetic anhydride in 63% yield over two steps.^[281] Minor amounts of the diacetate (376) were isolated as side-product. Reaction



Scheme 3.21: Synthesis of amino-derivatives.

of acetoxyl azide (375) with PMe₃ in wet THF failed to give the acetoxyl amine (377).^[281] Different temperatures did not improve the outcome of this reaction. Eventually, it was found that addition of aqueous NaOH to the Staudinger reduction with PMe₃ promoted the formation of acetoxyl amine (377),^[282] which was protected as the acyl amide (378) by reaction with acetic anhydride in 97% yield over two steps. Saponification of the acetate and dioxinone ester gave chemoselectively the acylamide resorcylic acid (379) in 48% yield.

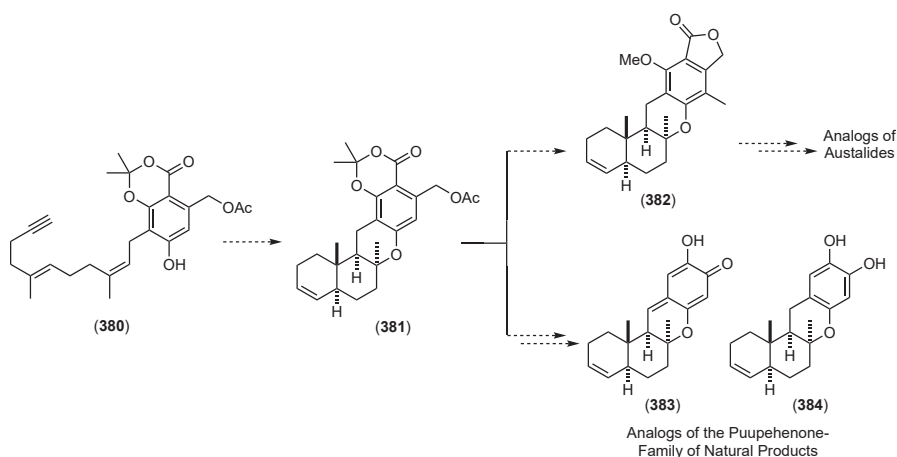
Conclusion

In conclusion, a series of analogs of the hongoquercins **25** and **131** were synthesized *via* a key dual π -Lewis acid catalyzed enyne carbocyclization

cascade and subsequent late-stage derivatization. The synthesis of alcohol (297) was optimized by means of dual enyne installation and alcohol deprotection within the same procedure. A subsequent biomimetic aromatization strategy gave the precursor for the cascade cyclization. Functional-group interconversion from a common precursor furnished a series of analogs. Where applicable, rationals for the observed diastereoselectivities are given.

Future Outlook

Biological profiling of the synthesized analogs is anticipated to give a better insight into the antibiotic properties of the hongoquercins and their analogs as well as other biologic activities (amongst others: anti-viral, anti-tumor, anti-fungal properties) seen from sesquiterpene meroterpenoids. Further-

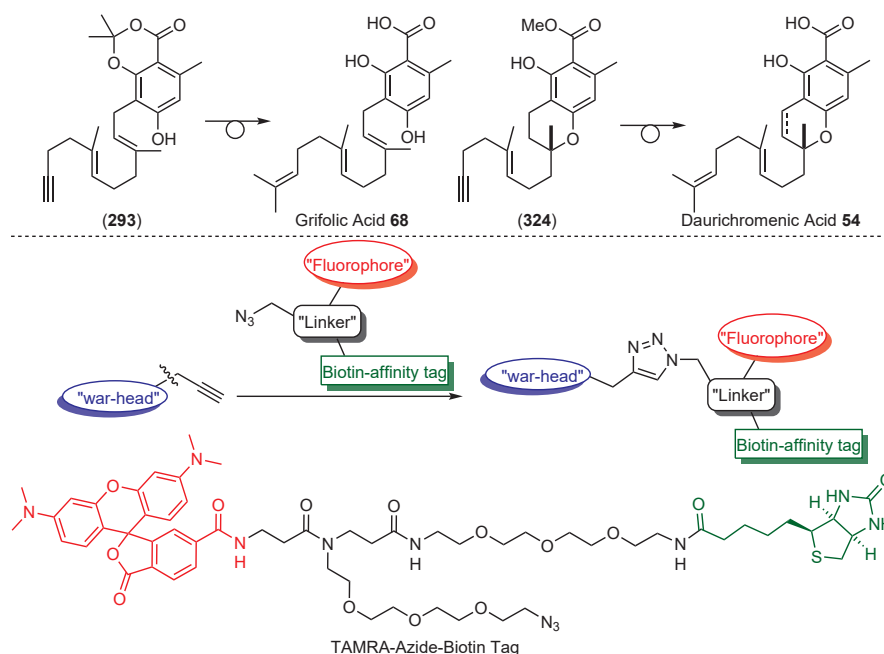


Scheme 3.22: Future studies on incorporation of *cis*-olefins and applications.

more, incorporation of *cis*-olefins like in (380) could expand the scope of the polyenyne cyclization, which, based on the Stork-Eschenmoser hypothesis, should give the rigid core structures (381) with a *trans-anti-cis*-relation, Scheme 3.22. This may enable the synthesis of analogs of the australides and puupehenone and puupehenol natural product family, which could give further insight into the biosynthesis of these natural products. In addition, the synthesis of derivatives could give a better understanding of the biological properties of these natural products.

In addition, resorcyates (293) and (324) can be seen as structural analogs to Grifolin 32 or Grifolic acid 68 or the chromenic acids bearing an additional

acetylene unit. These natural products display antitumor, antibiotic and antiviral (HIV) properties. These compounds could be further employed in

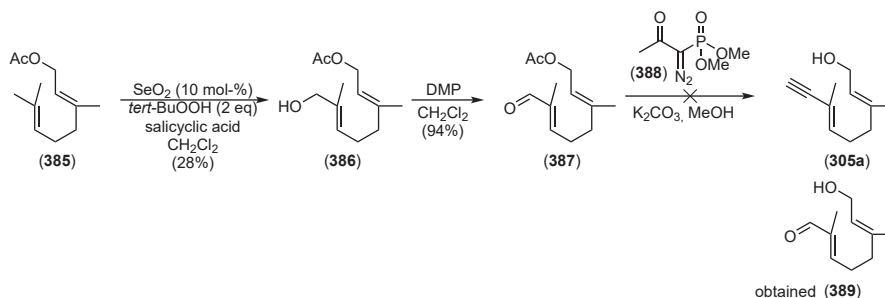


Scheme 3.23: Possible application of the acetylene-containing compounds (293) and (324) in target-ID proteomic studies.

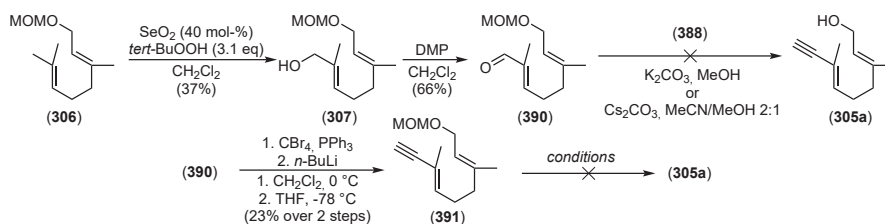
proteomic studies for target-identification of the above mentioned biological activities by using the acetylenic resorcyates as probes for pull-down experiments, utilising the alkyne entity in a click-reaction with an azide, Scheme 3.23.^[283] To give a specific example for such a reaction, one could consider use of the TAMRA-azide biotin tag for specific read out. Finally, the strange observation of the LDA induced rearrangement demands further investigation. The results of this are shown in section 3.4.

3.2 1,3-ENYNE'S IN POLYENE CYCLIZATIONS

As outlined in Scheme 3.2 geraniol **298** was identified as the common precursor for the 1,3- (**305a**, $n = 0$), 1,4- (**305b**, $n = 1$) and 1,5-enynol's (**297**). The synthesis of 1,3-enynol (**305a**) commenced with commercially available geraniol acetate (**385**). Allylic oxidation with selenium dioxide gave allylic alcohol (**386**) in 28% followed by formation of literature known enal (**387**) with DMP in excellent yields (94%), Scheme 3.24.^[224,284] α,β -Unsaturated aldehyde (**387**) was also formed in 10% yield during the selenium dioxide-mediated allylic oxidation. Reaction of aldehyde (**387**) with the Ohira-Bestman^[285–288] reagent (**388**) did not form any product containing an acetylene unit, instead, the deprotected alcohol (**389**) was isolated. Although the formation of alcohol (**389**) was partly anticipated, it was hypothesized that deprotection and homologation to the acetylene could be accomplished within the same reaction. An orthogonal protecting group was therefore required to furnish 1,3-enynol (**305a**) under Ohira-Bestman conditions.

Scheme 3.24: Attempts to synthesize 1,3-enynol (**305**).

MOM-ether (**306**) was reinvestigated for this purpose. Following the established route to the MOM-protected allylic alcohol (**307**), reaction with DMP gave aldehyde (**390**) in 66% yield, Scheme 3.25. Aldehyde (**390**) was initially subjected to the Ohira-Bestman reagent but again no alkyne was observed under the more common K_2CO_3 in MeOH conditions. Stronger conditions were explored with Cs_2CO_3 in 2:1 MeCN/MeOH. Unfortunately, only traces of the alkyne were isolated. The use of potassium *tert*-butoxide could potentially produce the 1,3 enyne (**305a**) in satisfactory yields. Koskinen and co-workers reported, that conjugated aldehydes can be unreactive towards the Ohira-Bestman conditions and might produce methyl ethers through

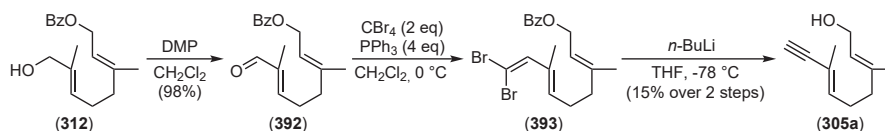


Scheme 3.25: Attempts to synthesize 1,3-enynol (**305a**) using MOM-protecting groups.

conjugate addition.^[289] While this was not observed in the aforementioned reactions, it might explain why aldehydes (**387**) and (**390**) were not converted to alcohol (**305a**) under these conditions.

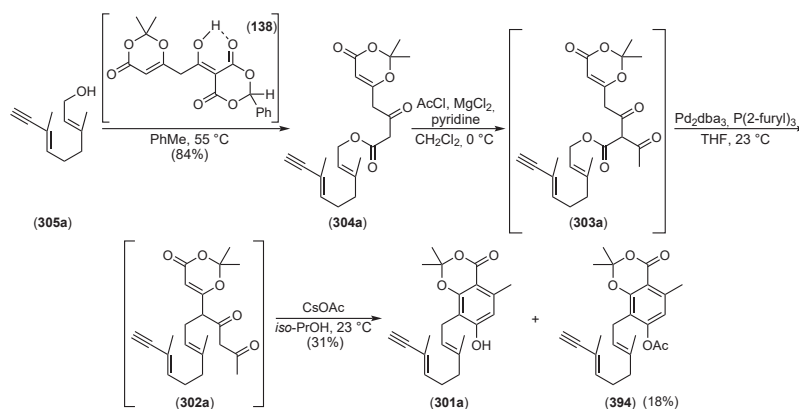
Corey and Fuchs reported a suitable method to synthesize alkynes from conjugated aldehydes.^[222] Adopting this method, reaction of aldehyde (**390**) with the carbene-phosphine adduct derived from CBr_4 and PPh_3 and subsequent $n\text{-BuLi}$ mediated rearrangement gave the 1,3-enyne (**391**) in 23% over 2 steps. Unfortunately, the MOM-ether was resistant to deprotection under various acidic conditions (HCl in dioxane, PPTS in MeOH or *tert*-BuOH), similarly to 1,5-dienynol (**310**).

Encouraged by the success of the Corey-Fuchs reaction and the observed deprotection of the benzoyl group with excess organolithium reagent (c.f. Scheme 3.4), it was hypothesized that excess of $n\text{-BuLi}$ in the Corey-Fuchs reaction could have similar effects. Benzoyl protected allylic alcohol (**312**) was reacted with DMP to give allylic aldehyde (**392**) in excellent yields (98%), Scheme 3.26. Reaction of aldehyde (**392**) under Corey-Fuchs conditions gave the 1,3-enyne alcohol (**305a**), *via* the dibromide (**393**), in good yields (85% on 3 mmol scale) with *in situ* deprotection of the benzoyl group through excess of $n\text{-BuLi}$. Upon scale up (>10 mmol) the yield decreased significantly to 15%, possibly due to the more difficult separation of OPPh_3 from the product at larger scale.



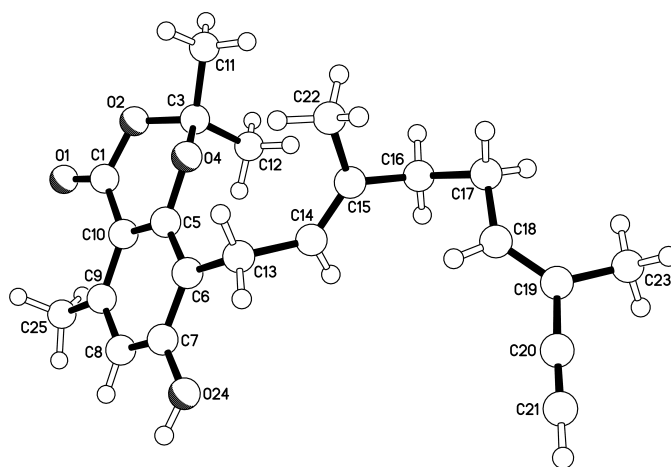
Scheme 3.26: Synthesis of 1,3-enynol (**305a**).

Homologation of carboxylic acid (**140**) with Meldrum's acid derivative (**141**) gave dioxane-4,6-dione keto dioxanone (**138**), which, upon heating to 55 °C,

Scheme 3.27: Synthesis of 1,3-enyne resorcyate (**301a**).

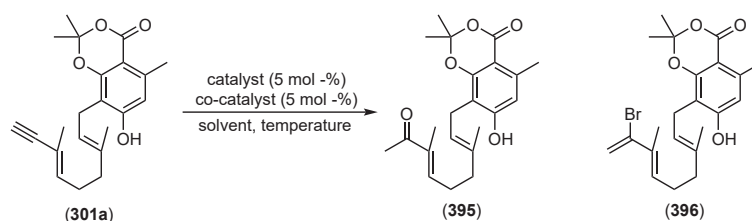
produced the highly reactive acyl-ketene intermediate (**133**). Trapping of acyl ketene (**133**) with 1,3-enyne alcohol (**305a**) afforded β -keto ester (**304a**) in good yields (84%), Scheme 3.27. Regioselective, MgCl_2 -mediated C-acylation of (**304a**) gave β,δ -diketo ester (**303a**), which subsequently underwent a Pd(o)-catalyzed decarboxylative, allylic rearrangement reaction to give β,δ -diketo dioxinone (**302a**). Addition of CsOAc in *iso*-PrOH promoted a base mediated cyclization and aromatization and gave the meroterpenoid (**301a**) in moderate yields (31%). Exchanging the base to NEt_3 did not improve the yield of resorcyate (**301a**). It was noticed that fresh acetyl chloride was paramount for the formation of the resorcyate (**301a**).

Over time, more acyl-protected resorcyate (**394**) was isolated. It is assumed this arises from the formation of acetic anhydride from acetyl chloride with moisture in the air or residual water in the reaction mixture (although dry solvents stored over molecular sieves were used). Alternatively, residual

Figure 7: X-Ray crystal structure of 1,3-enyne resorcyate (**301a**).

amounts of carboxylic acid (**140**) may have reacted with acetyl chloride to form a mixed anhydride. The formed anhydrides would be less reactive and thus favour O-acylation over C-acylation.^[290] The *trans*-olefin-alkyne relationship of resorcyate (**301a**) was unambiguously characterized using single crystal X-Ray diffraction, Figure 7.

Investigation on the cyclization behaviour of 1,3-enyne resorcyate (**301a**) with a variety of different gold and silver co-catalysts are summarized in Table 2. Having ensured that the negative control studies were in place (gold- and silver-catalyst on their own, entry 1 and 2), mixing of the Ag(I) and Au(I) salts with the substrate lead primarily to recovered starting material (labelled as x in the Table) next to ketone (**395**). The formation of ketone (**395**), however, was highly promising as it implied that the initial coordination of the gold catalyst was taking place. Increased temperatures, so as to promote reactivity of the adjacent olefins, only recovered ketone (**395**). Hypothesizing that the



Solvent	Catalyst	Co-Catalyst	Temperature	Yield
CH ₂ Cl ₂	AuCl(SMe) ₂	-	23 °C	x
CH ₂ Cl ₂	-	AgSbF ₆	23 °C	x
CH ₂ Cl ₂	AuCl(SMe) ₂	AgSbF ₆	23 °C	x + ketone (395)
CH ₂ Cl ₂	BrettPhos AuNTf ₂	-	23 °C	x + ketone (395)
CH ₂ Cl ₂	BrettPhos AuNTf ₂	-	40 °C	ketone (395)
CH ₂ Cl ₂	BrettPhos AuNTf ₂	-	23 °C to 40 °C	x + y
CH ₂ Cl ₂	AuCl(SMe) ₂	AgOTf	23 °C	y
(CH ₂ Cl) ₂	XPhos AuNTf ₂	-	23 °C	y
(CH ₂ Cl) ₂	XPhos AuNTf ₂	-	90 °C	y
(CH ₂ Cl) ₂	InBr ₃	-	23 °C	bromide (396) + ketone (395)

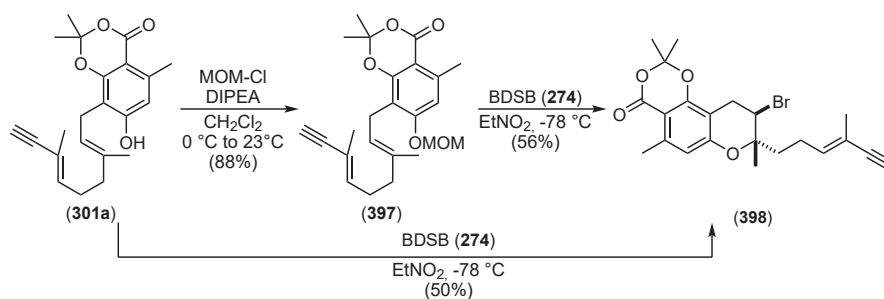
x indicates recovery of starting material. y indicates complex mixture.

Table 2: Screening conditions for the attempted cyclization of 1,3-enyne resorcyate (**301a**).

water was coming from the hygroscopic silver salts, changing the counter anion of the gold catalyst to the weakly coordinating triflate (OTf) and bistriflimide (NTf₂) salts was studied. The sterically demanding BrettPhos

AuNTf₂ reacted very slowly and eventually lead to the formation of (395) due to repeated exposure to air when taking aliquots for reaction TLC's. The addition of activated molecular sieves did not improve the reaction outcome. Exchanging the silver salt for the less hygroscopic AgOTf gave rise to a complex mixture with a very low mass balance (2% of recovered SM and complex mixture of products). Similarly to the results of Table 1, it is possible that the phenol moiety is sensitive to oxidation in the presence of silver salts. In order to establish this, the reaction was repeated in darkened glassware, however, a similar reaction outcome was observed. Variation of the solvent and ligand had no effect, as indicated with XPhos AuNTf₂ in 1,2-dichloroethane furnishing a complex mixture. It was thus concluded, that having screened a selection of various combinations of gold and silver salts at different temperatures in different solvents, no promising formation of a cyclized compound could be observed. Other π -Lewis acids like InBr₃ gave vinyl bromide (396).

With these results in mind attention was turned to other possible initiators more commonly found for unsubstituted 1,3-enynes: Bromocyclizations.^[220,221] Due to the possibility of bromoetherification with the phenol moiety, it was anticipated that phenol protection could be necessary. MOM-groups have often been shown to be labile during (bromonium induced) polyene-cyclization's (c.f. Scheme 1.33).^[200,201,291] MOM-protection of resorcyate (301a) was accomplished in 88% yield, Scheme 3.28. Resorcyate (397) was reacted with Snyder's brominating agent BDSB (274) in nitroethane at -78 °C in anticipation of a bromo-allene formation. However, this furnished bromochromane (398), *via* cyclization of the internal olefin bond. Treatment of



Scheme 3.28: Bromocyclization of 1,3-enyne resorcyates (301a) and (397).

resorcyate (301a) directly with BDSB (274) in nitroethane at -78 °C equally

formed the chromane (**398**) in 50% yield, rather than any product derived of bromo-allene formation and macro-etherification. As the bromocyclization selectively gave chromane (**398**), it was sought to use this for the 6-6-5-4 ring system in *rhododendron* meroterpenoids (see Figure 8).^[292–295]

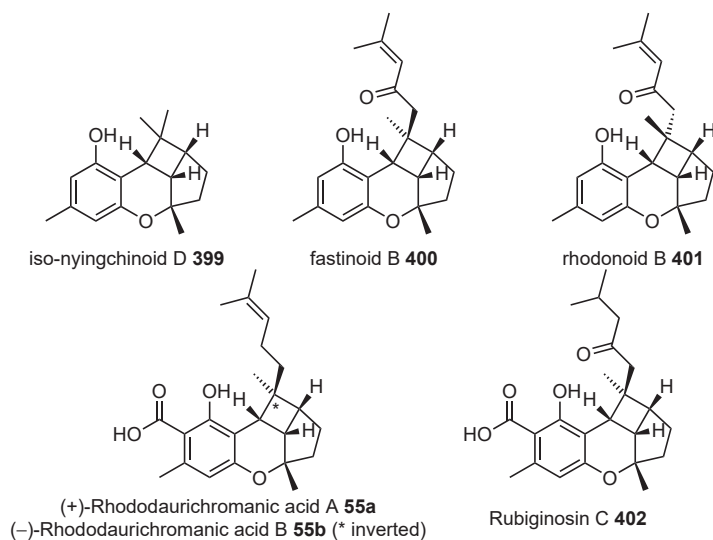
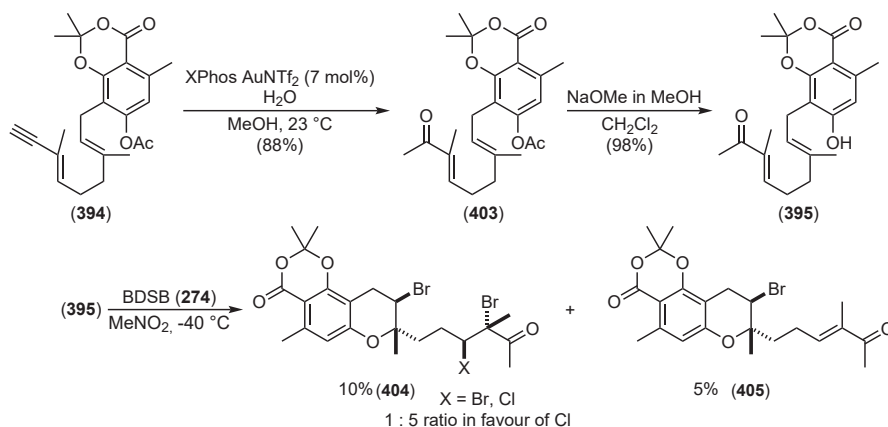


Figure 8: Representative examples of meroterpenoids isolated from *rhododendron* plants.

As shown previously, the hydration of resorcyate (**301a**) lead to ketone (**395**), ketone (**395**) was therefore investigated to see if it behaved similarly with BDSB (**274**). For this purpose, acyl protected resorcyate (**394**) was hydrated to give ketone (**403**), followed by deprotection to give ketone (**395**) in 86% over two steps. The reaction of ketone (**395**) with BDSB (**274**) in



Scheme 3.29: Attempted bromocyclization of ketone (**395**).

nitromethane at -40°C gave polyhalogenated products (**404**) as one diastereoisomer next to minor amounts of the desired mono-bromo chromane

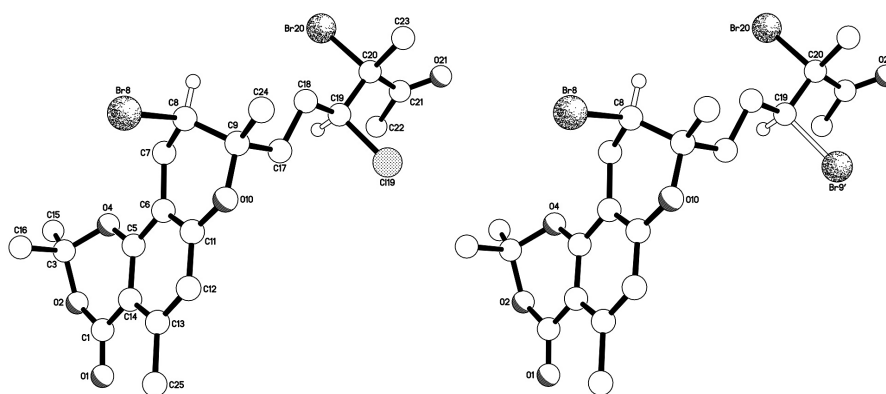
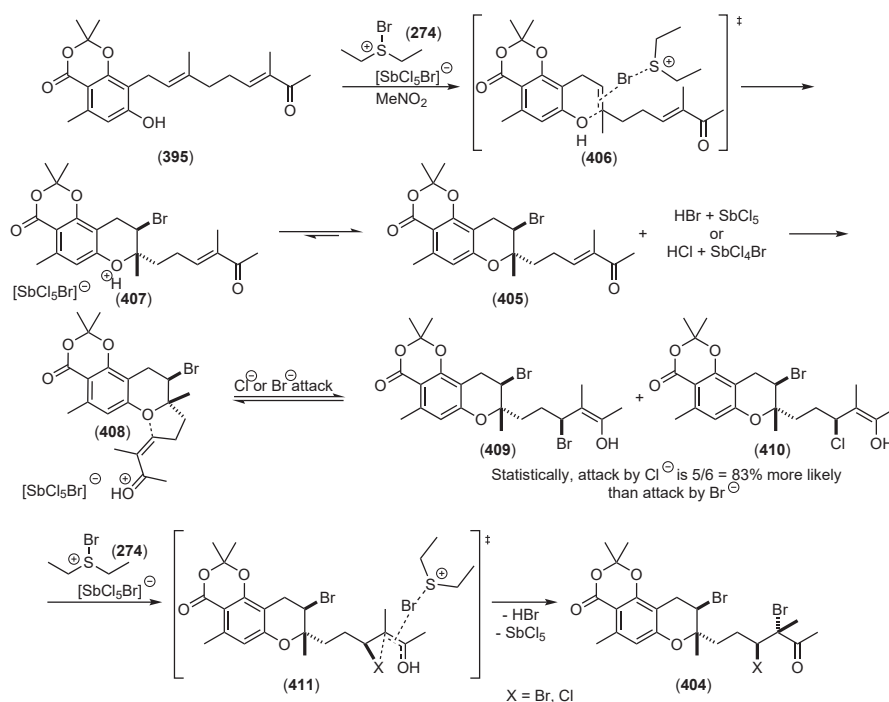


Figure 9: Crystal structures of polyhalogenated products (**404**).

(**405**) and recovery of starting material. Of particular note is the ratio of Cl vs. Br incorporation in polyhalogenated products (**404**), which showed a similar ratio (82 : 18 in favour of Cl) as the Cl vs. Br distribution in the bromopentachloroantimonate(V) anion $[\text{BrSbCl}_5]^-$ in BDSB. This was determined by means of single crystal X-ray analysis, see Figure 9. It is assumed that the crystallization process was slow, such that the estimated ratio of Cl vs. Br in the crystals displays the ratio in solution, which is expected to be the case as the crystallization took several days to give visually observable crystals.

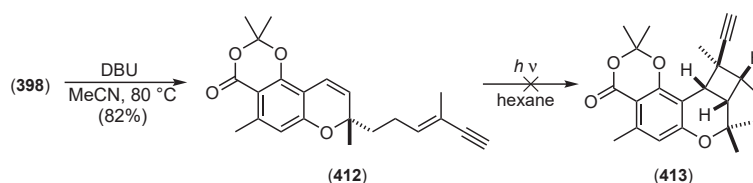
Scheme 3.30 depicts a postulated mechanism to rationalize the formation of polyhalogenated products (**404**) as well as the remarkably selective formation of 1 out of 16 possible diastereoisomers of polyhalogenated products (**404**). Bromination of the more electron-rich, internal olefin of (**395**), possibly *via* a transition state as in (**406**), gave chromane-oxonium ion (**407**), which exists in equilibrium with the deprotonated species (**405**), HBr or HCl and the derived Sb(V) compound, Scheme 3.30. Protonation of the ketone-carbonyl oxygen might include a neighbouring group participation of the chromane oxygen to produce the tricyclic compound (**408**). This facilitated a Michael-addition from the convex face, which is more accessible, of either a chloride or bromide ion to give (**409**) and (**410**). Attack of a chloride ion is statistically more likely, given the 5 : 1 ratio of chloride ions over bromide ions in the $[\text{SbCl}_5\text{Br}]^-$ anion. This is well reflected in the obtained ratio in the crystal structure. Finally, α -bromination of (**409**) and (**410**) with another equivalent of BDSB (**274**), possibly guided by another neighbouring group participation



Scheme 3.30: Postulated mechanism of formation of polyhalogenated products (404).

of the adjacent halogen atom blocking the alpha face *via* a transition state as depicted in (411), furnished polyhalogenated products (404).

As the desired chromane was obtained in unsatisfactory yields, (398) was investigated for the formation of the 6-6-5-4 ring system. Dehydrobromination with DBU gave styrene (412) in good yields (82%).^[296,297] Subsequently, an attempted photolytic [2+2]-cycloaddition^[28,298] gave no product which showed signs of cyclobutane formation and instead gave a very complex mixture with dioxinone deprotection.



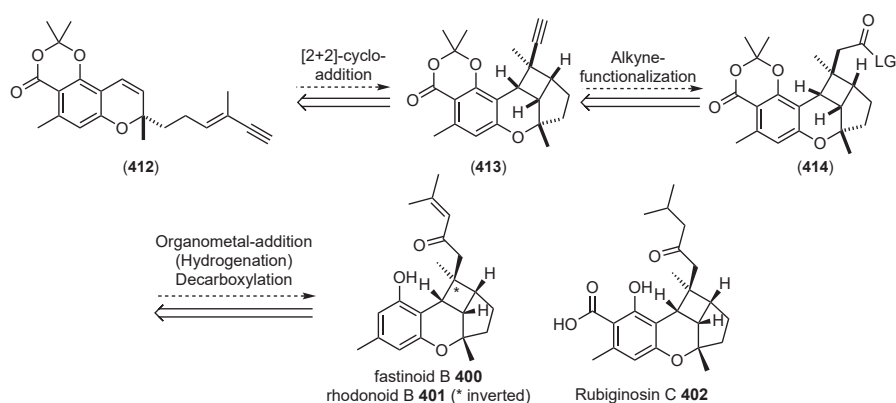
Scheme 3.31: Attempted photolytic cycloaddition reaction of styrene (412).

As this was formerly only achieved with diphenyl-dioxinones, a model system was designed to further study this hypothesis.^[299-303]

Conclusion

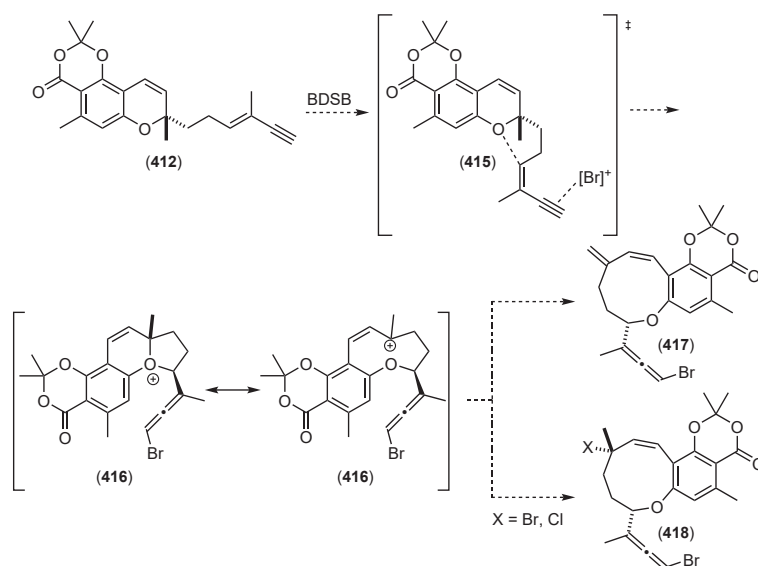
In conclusion, a series of π -Lewis acids were investigated to induce a polyenyne cyclization of a 1,3-enyne resorcyate. In most cases, only reaction at the acetylene entity was observed. Alternative reaction with an electrophilic brominating agent led to the formation of a chromane. Reaction of the electrophilic brominating agent with the derived ketone yielded a polyhalogenated product. Initial photolytic attempts to use the derived styrene resorcyate (**412**) for the total synthesis of several meroterpenoids from *rhododendron* plants failed to give the desired 6-6-5-4 ring system, and instead resulted in dioxinone deprotection. This is further discussed in the next section.

Future Outlook



Scheme 3.32: Possible future avenues to use styrene (**412**).

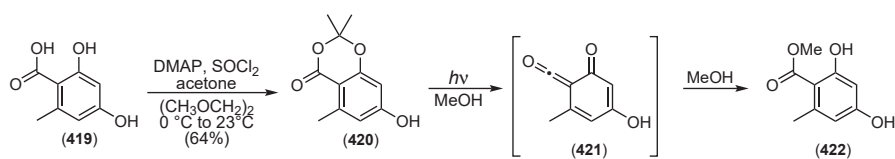
For future work, the desired 6-6-5-4 ring system may be obtained through Lewis acid mediated cyclizations, Scheme 3.32, such as $\text{Fe}(\text{OTf})_3$,^[304] FeCl_3 ,^[305] or TFA (as shown by Hsung, see Scheme 1.8).^[30,306] Alternatively, after transesterification, it may be possible to achieve a photolytic [2+2]-cycloaddition, either by means of UV-light^[28,298] or *via* photoredox catalysis.^[307,308] Subsequent alkyne functionalisation could lead to (**414**) which may be converted to the natural products fastinoid B **400**, rhodonoid B **401** or rubiginosin C **402** *via* selective organometallic-addition, reduction and saponification or decarboxylation.



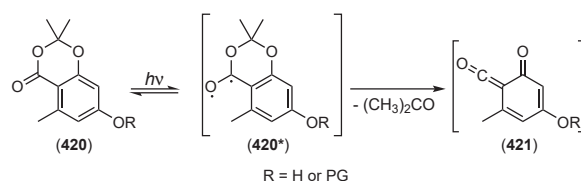
Scheme 3.33: Possible macrocyclization of styrene (412).

In addition, the previously anticipated macrocyclization could be further investigated, Scheme 3.33; Chromane (412) could be treated with an electrophilic bromonium source to induce a ring-expansion reaction *via* a bromo-allene formation and macroetherification.

3.3 PHOTOLYTIC KETENE GENERATION EXPERIMENTS ON A MODEL SUBSTRATE



Scheme 3.34: UV-studies on aryl-ketene generation and synthesis of protected resorcyates.



Scheme 3.35: UV-studies on aryl-ketene generation of protected resorcyates.

Orsellinic acid **419** was protected as the dimethyl-dioxinone (**420**) with SOCl_2 and acetone in moderate yield (64%, Scheme 3.34).^[309] Irradiating (**420**) with UV-A and UV-B light in methanol at different concentrations was examined to determine optimal light triggered ketene generation conditions. The proposed rational is depicted in Scheme 3.35, where, initiated by the absorption of UV light, an excited state is formed, which generates the ketene intermediate (**421**) possibly through direct release of acetone or *via* a bi-radical intermediate. Further mechanistic details of formation of the ketene intermediate are discussed below, Scheme 3.43. After irradiation for 24 h and evaporation, analysis of the crude-NMR spectra were made using changes in chemical shift and the appearance of new peaks. The starting material displayed two aromatic proton signals at 6.48 ppm and 6.29 ppm and a methyl group at 2.55 ppm, while in the product the aromatic protons were shifted upfield to 6.29 ppm and 6.23 ppm, the methyl group was shifted to 2.46 ppm and the methoxy-proton signal appears at 3.91 ppm. As shown in Figure 10, at higher reaction concentrations (0.2 M or 0.1 M) a lower conversion was observed, with the peaks at 6.48 ppm and 6.23 ppm in a 2 : 1 ratio. Under more dilute reaction conditions more conversion to the methyl ester (**422**) was observed. At 0.007 M the methyl ester (**422**) was observed in a 2.7 : 1 ratio of (**422**) to (**420**) according to the signals at

6.48 ppm and 6.23 ppm. Photolytic conditions were proven necessary with a negative control reaction, where only SM was observed after 24 h at 0.02 M under standard incandescent lights, Figure 10. These results are in agreement with results obtained by Tidwell, who investigated the aryl-ketene formation from the corresponding benzaldehyde dioxinone. Furthermore, Tidwell also reported a 1st order kinetic dependence on the trapping nucleophile and diffusion controlled reactivity of the ketene intermediate.^[300]

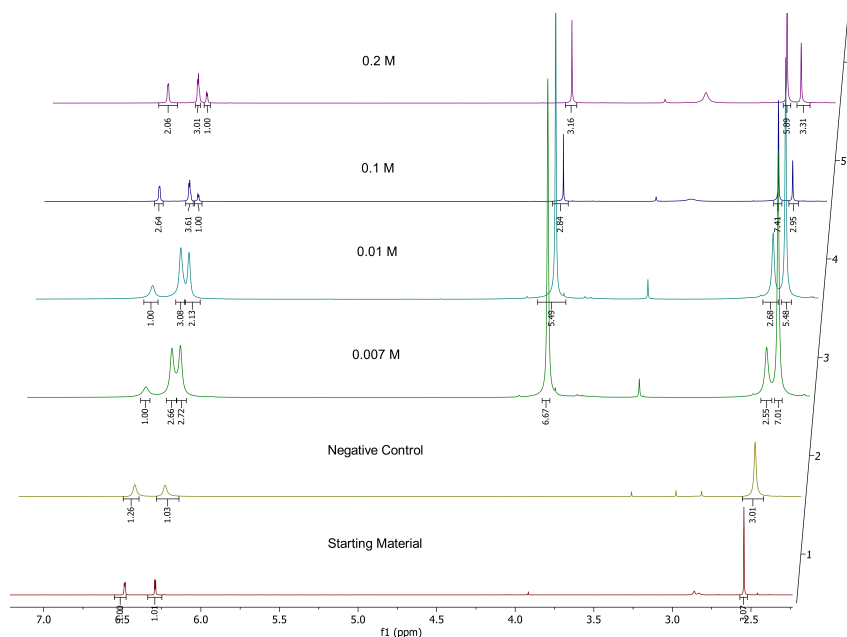
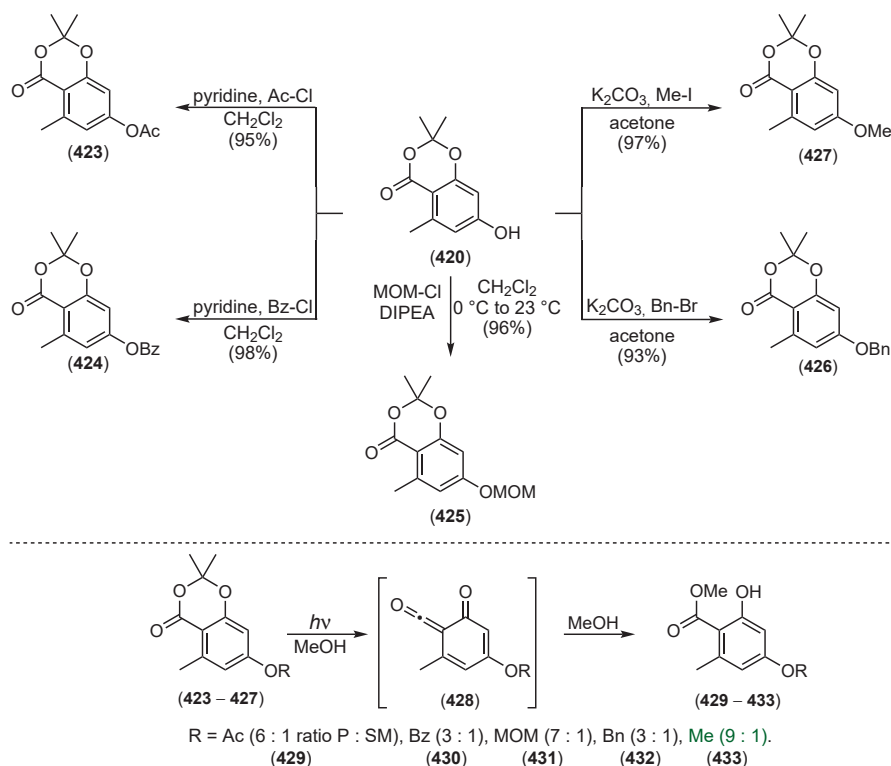


Figure 10: Comparison of the concentration dependence on the photolytic conversion of (420) to (422). All spectra were recorded in $(\text{CD}_3)_2\text{CO}$.

The results suggest that the diquino-methide aryl-ketene intermediate (421) is highly reactive and requires a protecting group to improve the reaction outcome. This could be beneficial for several reasons: Improved solubility in organic solvents due to decreased polarity. Furthermore, introduction of a protecting group may improve the stability of the diketo intermediate, as it locks the molecule in its enolate form. The diketo resonance form might undergo undesired side-reactions, including reactions with itself leading to polymerization.

In order to establish the relative order of reactivity and stabilities, the experiment was repeated with different protecting groups. For this purpose, the phenol moiety was protected as acyl-ester (423, 95%), benzoate-ester (424,

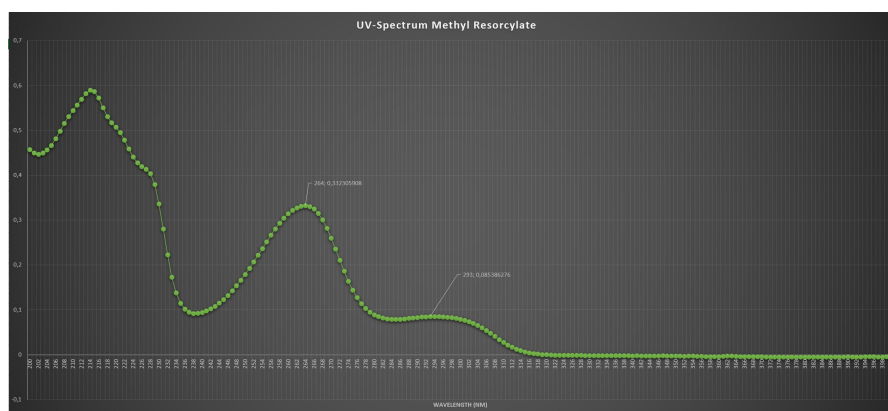
98%), MOM-ether (**425**, 96%), benzyl-ether (**426**, 93%) and methyl ether (**427**, 95%), Scheme 3.36.



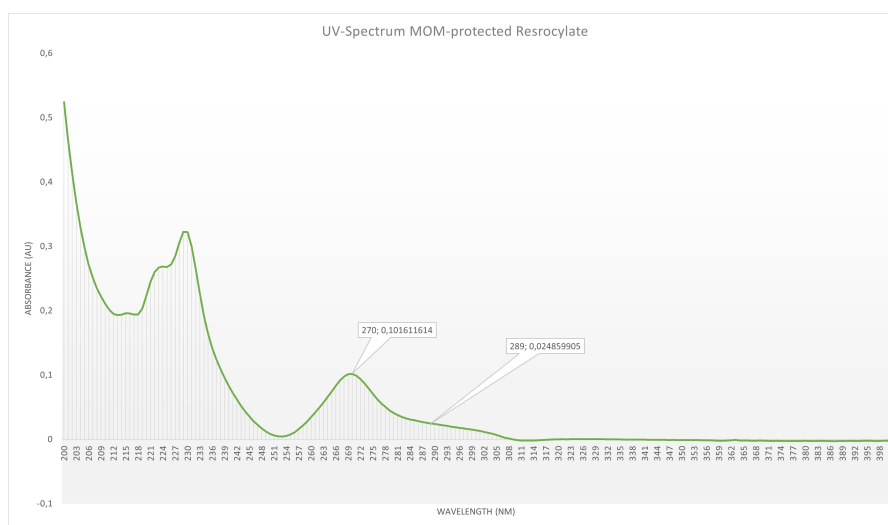
Scheme 3.36: UV-studies on aryl-ketene generation of protected resorcyates.

After irradiation for 24 h resorcyate (**425**) and (**427**) gave the best results, with a 7 : 1 and 9 : 1 ratio of product to starting material, respectively, while the resorcyates (**423**), (**424**) and (**426**) gave a ratio of 6 : 1, 3 : 1 and 3 : 1, respectively. This suggests that electron donating groups are better able to stabilize the aryl-ketene intermediate than the electron-withdrawing, ester groups. The UV-spectrum of resorcyate (**427**) displays two local maxima at 264 nm and 293 nm, Figure 11. Taking standard textbook information into account, the maxima at 264 nm is most probably related to the absorption of the benzene ring, while the maxima at 293 nm is most likely related to the dioxinone carbonyl group, which is of interest in this study. According to the Beer-Lambert Law; $\epsilon = A/L \times c$, with $A(293 \text{ nm}) = 0.0853$, $l = 1 \text{ cm}$ and $M = 0.00003 \text{ M}$, resorcyate (**427**) displays a molar extinction coefficient of $\epsilon = 2846 \text{ M}^{-1} \text{ cm}^{-1}$.

Similarly, the UV-spectrum of resorcyate (**425**) displays two local maxima at 270 nm and 289 nm, Figure 12. Consequently, the local maxima at 270 nm

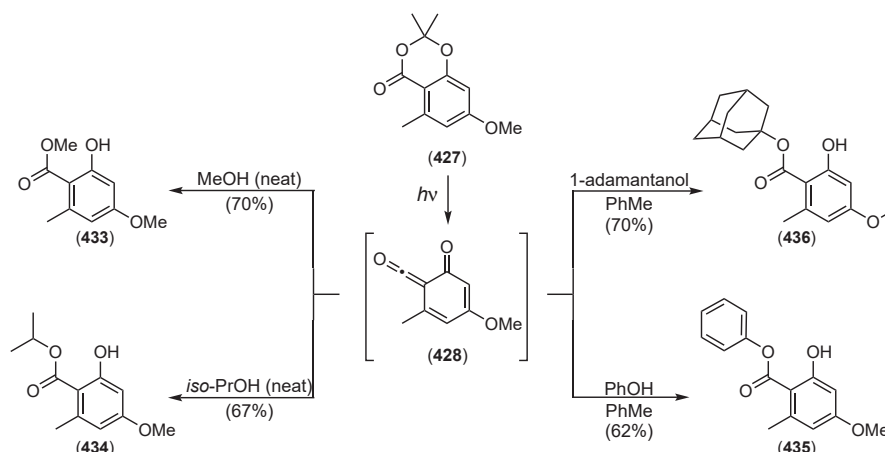
Figure 11: UV-spectrum of methyl resorcyate (**427**).

is related to the absorption of the benzene ring, while the local maxima at 289 nm is related to the dioxinone carbonyl group. With the Beer-Lambert Law; $\epsilon = A/L \times c$, with $A(289 \text{ nm}) = 0.0249$, $l = 1 \text{ cm}$ and $M = 0.00003 \text{ M}$, resorcyate (**425**) displays a molar extinction coefficient of $\epsilon = 941 \text{ M}^{-1} \text{ cm}^{-1}$. Given this, narrowing the band by employing only a UV-B light would be most effective going forward.

Figure 12: UV-spectrum of MOM-protected resorcyate (**425**).

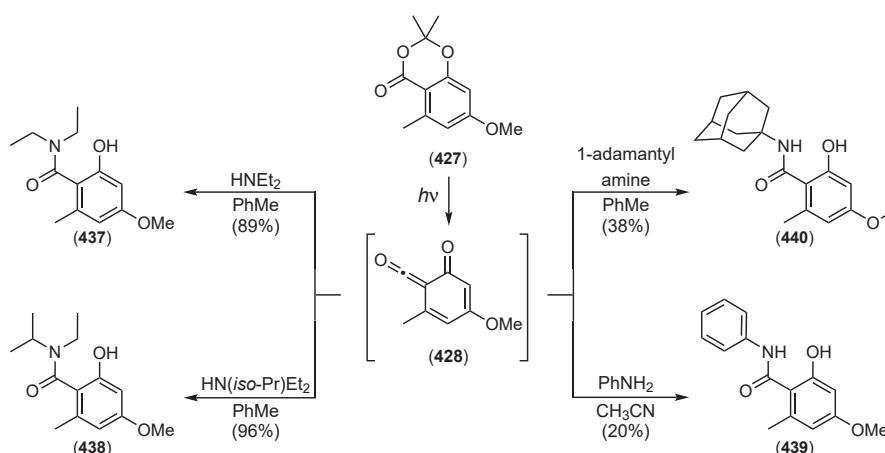
After optimization of the reaction conditions (concentration and light source) and the protecting group, attention was turned to investigate which nucleophiles would react with the ketene intermediate. Examination of alcohol nucleophiles was conducted with MeOH, *iso*-PrOH, 1-adamantanol and phenol (Scheme 3.37) as examples of primary, secondary, tertiary and aromatic-substituted alcohols. Methyl-ester (**433**, 70%), *iso*-propyl ester (**434**,

67%), phenol ester (**435**, 62%) and 1-adamantanol ester (**436**, 70%) were obtained in good yields.



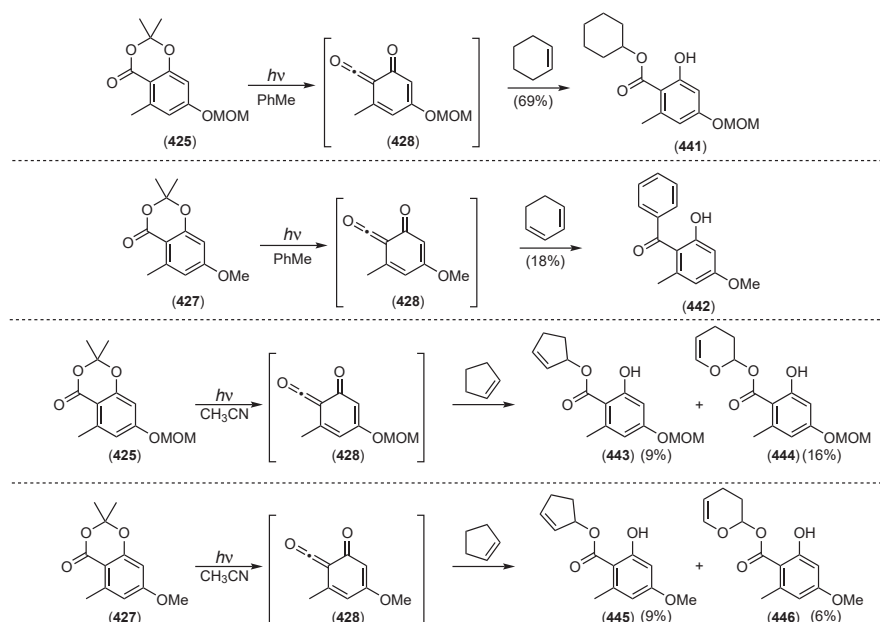
Scheme 3.37: UV-studies on aryl-ketene generation and trapping with alcohols.

Next, various primary and secondary, aromatic or aliphatic amines were tested, Scheme 3.38. Reaction of 3 equiv. of amine in toluene gave the symmetrical, tertiary diethyl amide (**437**, 89%), the unsymmetrical, tertiary isopropyl-ethyl amide (**438**, 96%) and the secondary adamantyl-amide (**440**, 38%). The lower yield of the adamantyl amide could be rationalised by the low solubility of 1-adamantyl amine in PhMe, although the reaction was not re-examined in acetonitrile to support this hypothesis. When aniline was examined in toluene no reaction was observed. In acetonitrile, the reaction of resorcylic anhydride (**427**) with aniline gave amide (**439**) in 20% yields. Efforts with tertiary amines, such as 4-*tert*-butyl-benzyl-*N,N*-dimethylamine were unsuccessful, despite evidence in literature.^[310]



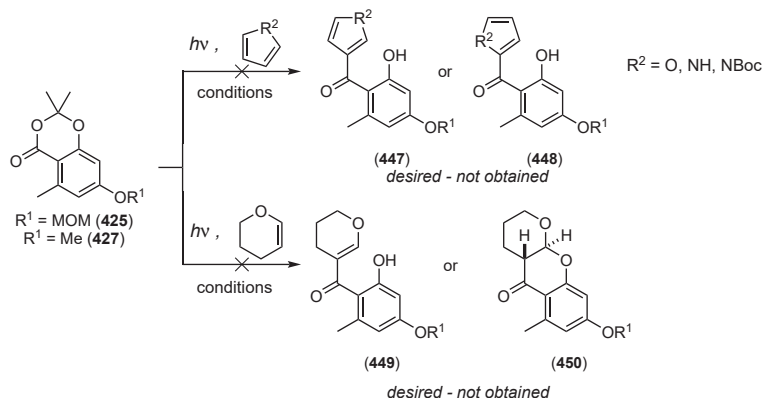
Scheme 3.38: UV-studies on aryl-ketene generation and trapping with amines.

Subsequently, the reactivity behaviour with olefin nucleophiles was explored. Reaction of methyl-protected resorcyate (**427**) with cyclohexene was fruitless and at no occasion furnished the desired product in more than trace amounts. On the other hand, reaction of the MOM-protected resorcyate (**425**) with cyclohexene proceeded to give the cyclohexanol ester (**441**) in 69% yield. Aerobic oxidation may account for this observation.^[311–313] In strictly deoxygenated solvents, starting material was mostly recovered. Other cycloalkenes were thus examined for similar reaction behaviour, Scheme 3.39. Reaction of resorcyate (**427**) with 1,3-cyclohexadiene furnished the benzophenone derivative (**442**) in 18% yield. Possibly, aerobic oxidation of the initial adduct may explain the isolation of (**442**). Reactions with cyclopentene and 1-methyl cyclopentene were examined next. The reaction of (**427**) with 1-methyl cyclopentene proved to be unsuccessful under various conditions (including 3 and 10 equiv. of 1-methyl cyclopentene). The reaction of (**425**) with 3 and 10 equiv. of cyclopentene was equally unfruitful. In agreement with the initial concentration studies, it was concluded that the lower reactivity of C-nucleophilic trapping agents required a change in conditions to a high concentration of trapping reagent. When the reaction was conducted with a large excess of cyclopentene, allylic ester (**443**) was isolated in low yield. When this reaction was performed with the ketene



Scheme 3.39: UV-studies on aryl-ketene generation and trapping with olefin-based nucleophiles.

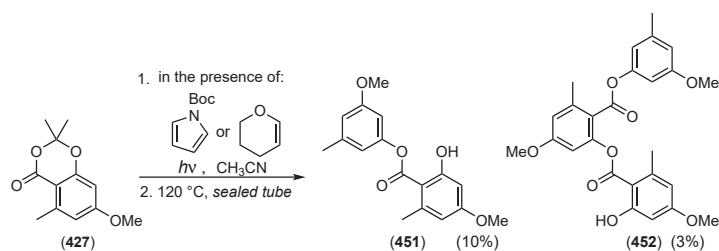
precursor (**427**) the corresponding product (**445**) was isolated. In addition, two products (**444**) and (**446**), respectively, were produced, the structures of which were tentatively assigned, in agreement with literature,^[311,312,314–317] as no corresponding mass-spec m/z peak or fragmentation products were observed. In both cases the reaction mostly recovered starting material.



Scheme 3.40: Unsuccessful trapping reactions with aromatic enol ethers and enamines.

Next, enol ethers such as 3,4-dihydropyran or furan, and enamines like pyrrole or *N*-Boc pyrrole were examined as trapping agents, Scheme 3.40. The reactions of ketene precursor (**425**) and (**427**) with 3,4-dihydropyran, furan, pyrrole and *N*-Boc pyrrole proved to be unsuccessful and mainly recovered starting material next to trace amounts of unidentifiable products. Variations in the light source were examined (UV-A + UV-B, UV-B and UV-C) as well as different solvents (CH_2Cl_2 , PhMe, Et_2O and CH_3CN) and addition of CuOTf as Lewis acids,^[318,319] but all attempts resulted in recovery of starting material.

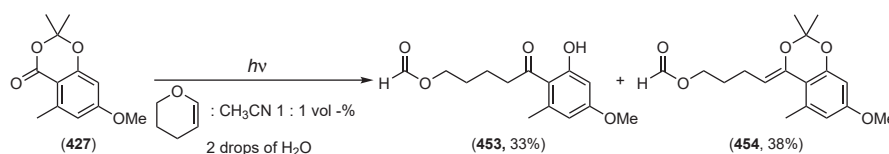
DeBrabanders conditions of employing an excess of the ketene-precursors, while using the trapping reagent as limiting reagent, were examined.^[301,302] This resulted in recovery of starting material. When the reaction was per-



Scheme 3.41: Reaction of resorcyate (**427**) with itself under photolytic conditions.

formed with additional UV-C irradiation a similar result was obtained. When the reaction was performed with UV-A and UV-B light for 24 h, followed by heating to 120 °C, in the absence of UV-light, the dimeric (**451**) and trimeric structures (**452**) were isolated in low yields, see Scheme 3.41. Dimer (**451**) and trimer (**452**) presumably originate *via* photolytic induction, reaction with itself, trapping of the terminal ketene with trace amount of water,^[320] and final decarboxylation, most likely under thermal conditions.^[105,265] Altering the concentrations, solvents and addition of CuOTf as Lewis acid did not affect the outcome of this reaction. Further examinations into the thermal generation of cyclohexadiene ketene (**428**) should be conducted, possibly enabling a complementary method for the ketene generation. Wentrup, for example, reported the thermal generation of cyclohexadiene α -oxo ketenes at high temperatures (>250 °C).^[303]

Once more, high concentrations of trapping agents were examined. While the reaction with furan and pyrrole was unsuccessful, even in 1 : 1 vol-% mixtures with acetonitrile, the reaction of resorcyate (**427**) in a 1 : 1 vol-% mixture of acetonitrile and 3,4-dihydropyran under UV-irradiation gave two products (**453**) and (**454**), Scheme 3.42. Initial isolation of these products were



Scheme 3.42: UV-studies on aryl-ketene generation and trapping with 3,4-dihydropyran.

in low yields. The evidence of an additional H₂O entity to the molecular mass required the presence of water, which may have originated from repeated exposure to moisture in the air when taking TLC samples. Indeed, when 2 drops of H₂O were added to the reaction mixture, arenes (**453**) and (**454**) were isolated in 33% and 38% yield, respectively. The structure of (**453**) was further confirmed through single crystal X-Ray diffraction analysis, see Figure 13.

Formation of the ketene intermediate could occur *via* two pathways. Initial excitation of (**427**) gives the excited species (**427***), which is in equilibrium with (**427**) through thermal relaxation, Scheme 3.43 top. Direct pseudo-

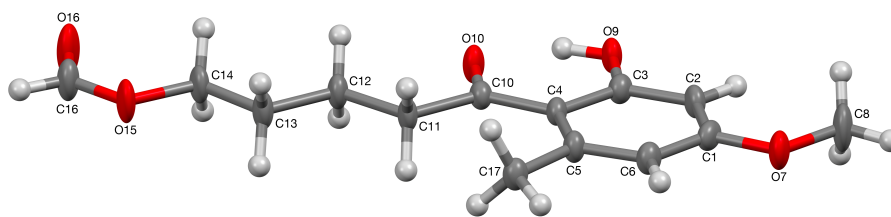
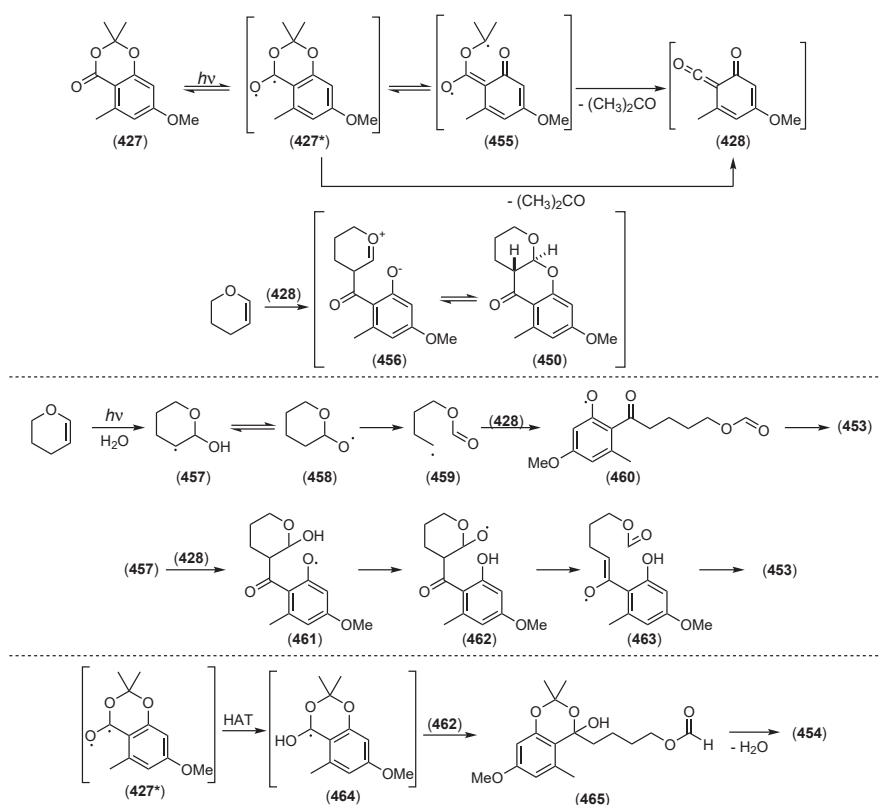


Figure 13: X-Ray crystal structure of formate ester (453).

pericyclic elimination of acetone *via* a retro [4+2] reaction leads to the formation of ketene (428). Alternatively, C-O bond fission and formation of bisradical intermediate (455) could lead to elimination of acetone and formation of the reactive ketene intermediate (428).^[321] The subsequent reaction of ketene (428) with 3,4-dihydropyran is of particular note. Direct reaction of (428) with 3,4-dihydropyran to give compounds of structure (456) or (450), or any products derived from these intermediates, was not observed at low concentrations (3 or 10 equiv. of 3,4-dihydropyran). At high concentrations, the direct addition might be more probable. Furthermore, no derived resorcylic acid was observed when the reaction was performed in the presence of water, which indicates that the 3,4-dihydropyran likely preforms the hydrate as otherwise one would expect to see a resorcylic acid as ketene (428) should react more quickly with water than 3,4-dihydropyran.

It could therefore be reasoned that the hydrated species (457) derived from the addition of water to 3,4-dihydropyran is the active nucleophile. In acidic media, the species (457) would decompose to an aldehyde and a terminal alcohol, as shown by Gilbert and Inomata,^[322,323] products which were not observed in this reaction. The most plausible formation of formate ester (453) would involve a Suarez-type fragmentation,^[324-330] produced by the alkoxyradical (458) derived from the initial radical adduct (457). Upon β -scission, alkoxyradical (458) gives radical (459) that adds to ketene (428) to give phenolate radical (460), which upon H-abstraction leads to formate ester (453). Alternatively, but less likely due to the fast tautomerization and β -scission of radicals (457) to alkoxyradical (458) and primary radical (459), would be the direct addition of radical (457) to ketene (428), which could furnish intermediate (461). Alternatively, intermediate (461) might also be derived from nucleophilic attack of water to (456), although the likelihood of this is reduced due to above mentioned reasons. Intramolecular

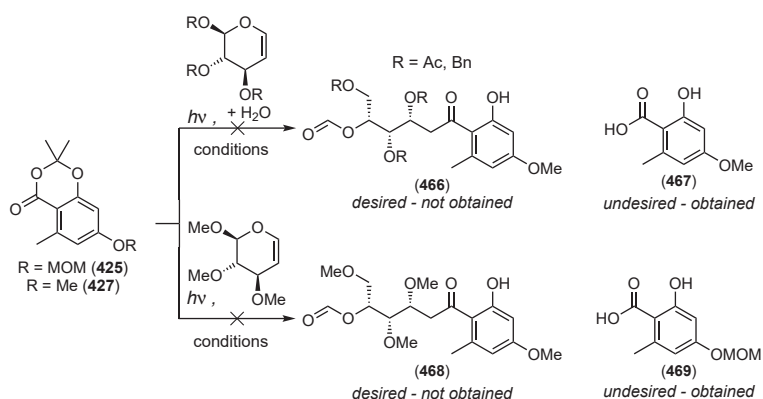


Scheme 3.43: Proposed mechanism of formation for formate esters (453) and (454).

hydrogenatom-transfer (HAT) of intermediate (461) would lead to alkoxy radical (462). As the β -scission is now in conjugation with the ketone, formate ester formation is consequently favoured over the formation of the analogues aldehyde and terminal alcohol. Thus decay to the formyl-ester according to literature known pathways,^[331–336] could furnish enolate radical (463), which can be converted into (453) by means of H-abstraction and tautomerization, or reduction (enolate formation) and protonation. For the formation of (454) it could be reasoned that under the applied conditions, radical (459) adds to the excited state (427*) or the derived alcohol (464) to give intermediate (465). Subsequent elimination of water gives rise to formate ester (454). Alternatively, as acetone absorbs in the UV-B region, it could be reasoned that the excited state of acetone may abstract a hydrogen atom to form a heteroatom stabilized, isopropyl radical. Reaction of this radical intermediate with (463) could lead to an O-adduct, C-O bond fission and acetonide formation *via* a heteroatom stabilized, isopropyl radical cation to furnish formate ester (454). The likelihood of the later proposed mechanism is, however, diminished, as the relative concentration of acetone is low, which

does not support the fact that (454) was isolated as the major product with a higher yield (38%).

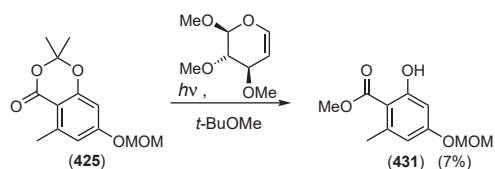
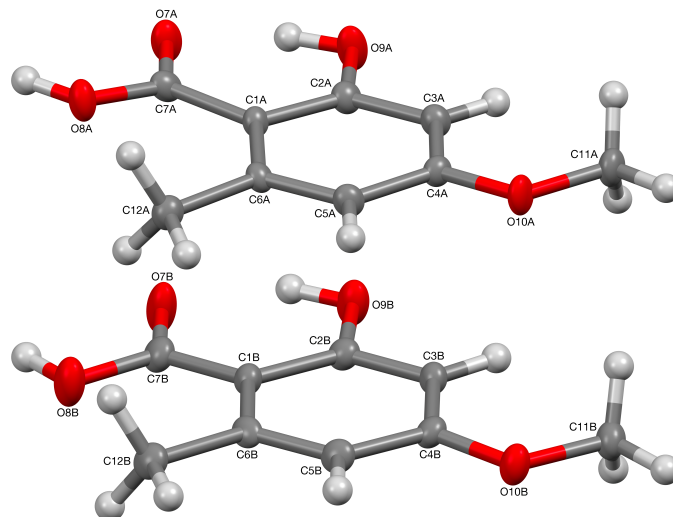
Given the reactivity of 3,4-dihydropyran, it was investigated whether glucals would behave similarly, Scheme 3.44. Reactions of ketene precursor (427) with tri-*O*-acetyl D-glucal and tri-*O*-benzyl D-glucal (3, 10 and 100 equiv.) in acetonitrile in the presence and absence of water were examined. These reaction proved to be unfruitful and in most cases the corresponding



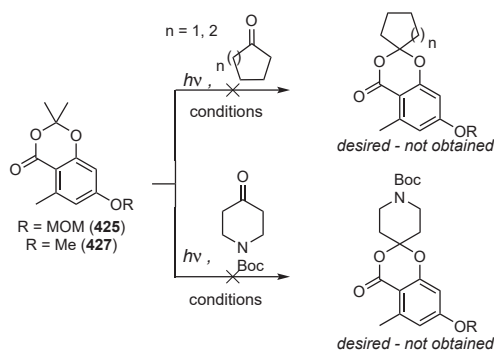
Scheme 3.44: Unsuccessful trapping reactions with D-glucal derived enol ethers.

resorcylic acid (467) was isolated as major product. The structure of acid (467) was further demonstrated *via* single-crystal X-Ray diffraction analysis, Figure 14. It was hypothesized, that tri-*O*-acetyl D-glucal could have a diminished reactivity, relative to 3,4-dihydropyran, due to the electron withdrawing acetoxy groups. While being more electron rich than tri-*O*-acetyl D-glucal, tri-*O*-benzyl D-glucal may absorb undesirably in the required UV-region, thus reducing the likelihood of reaction. As a consequence, tri-*O*-methyl D-glucal was examined. Reaction of resorcylic ketenes (425) or (427) with tri-*O*-methyl D-glucal (3, 10, 100 equiv. or neat) in the absence of H₂O were unsuccessful, while in the presence of H₂O the corresponding resorcylic acids (467) and (469) were isolated. Examination of other solvents (PhMe or CH₂Cl₂) did not lead to a better reaction outcome. When the reaction was performed in *tert*-butyl methyl ether, the methoxy ester (431) was isolated, see Scheme 3.45, presumably *via* elimination of the allylic methoxy group, followed by trapping of the ketene species with methoxide.

Finally, cross-over experiments with other ketones were investigated, Scheme 3.46. Initial reaction of resorcylic ketenes (425) or (427) with cyclopent-

Scheme 3.45: Synthesis of methoxyester (**431**) with tri-O-methyl D-glucal.Figure 14: X-Ray crystal structures of the two independent molecules of acid (**467**) in the unit cell.

tanone, cyclohexanone and *N*-Boc-4-piperidone (10 equiv. in all cases) gave complex mixtures. Examination with a lower loading (3 equiv.) and strictly deoxygenated solvent was examined. However, this also proved to be unsuccessful. Variations in solvents did not improve the outcome of this reaction.



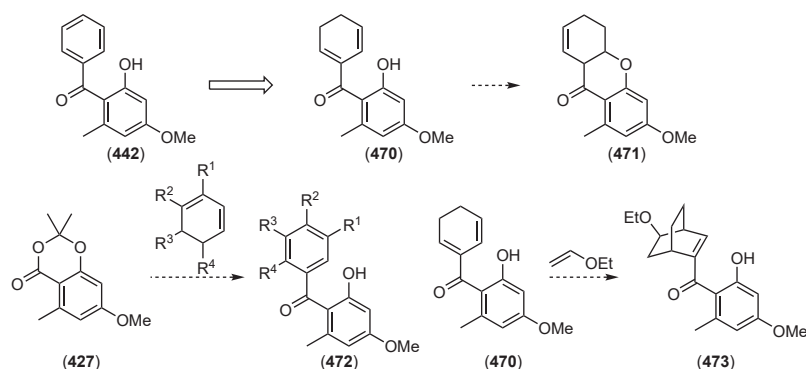
Scheme 3.46: Attempted photolytic cross-over experiments.

Conclusion

In conclusion, the photolytic behaviour of some β -resorcyates were investigated. It was demonstrated that the 4-alkoxy substituted resorcyates can lead to a highly reactive *o*-oxo ketene species, which were successfully trapped with various oxygen and nitrogen based nucleophiles, of varying substitution degree. Furthermore, the reactivity of olefin nucleophiles was studied and successfully demonstrated with cyclohexene, cyclohexadiene, cyclopentene and 3,4-dihydropyran. Cross-over experiments with ketones as well as aromatic enol-ethers and enamines proved to be unsuccessful under the examined conditions.

Future Outlook

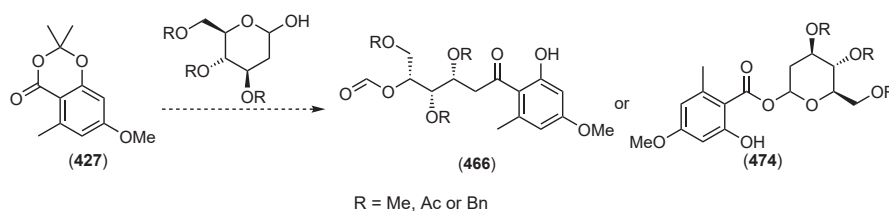
Further work in the elucidation of the formation of benzophenone (**442**) would be of interest. The reaction most probably goes through an intermediate of type (**470**), which could be proven through a conjugate addition reaction and ultimately enable the synthesis of a variety of chromone resorcylic core structures (**471**), Scheme 3.47. Furthermore, exploring the scope of substituents on the cyclohexadiene ring, to study the regioselectivity of addition is of interest. Finally, the intermediate (**470**) could be used in an inverse electron demand Diels-Alder reaction, with an electron-donating dienophile such as ethyl vinyl ether, which would give bicycles of type (**473**).



Scheme 3.47: Future work on the elucidation of formation of (**442**).

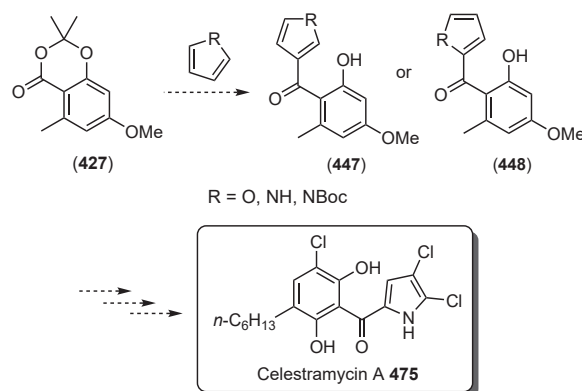
In addition, further investigations into the mechanism of formation of compounds (**453**) and (**454**), see Scheme 3.43, as well as improving the reactivity

of the D-glucal substrates could be performed by reacting tetrahydro-2*H*-pyran-2-ol, or the 2-deoxy-D-glucopyranose derived hemiacetals, with the ketene precursors (425) and (427), Scheme 3.48. This may lead to the desired compounds (466) or simple esterification to compounds (474). Furthermore, (454) could be hydrolyzed to the terminal alcohol under acidic conditions which should lead to the formation of a spirocyclic derivative, thus further validating the structural assignment of (454).



Scheme 3.48: Future work on the formate esters.

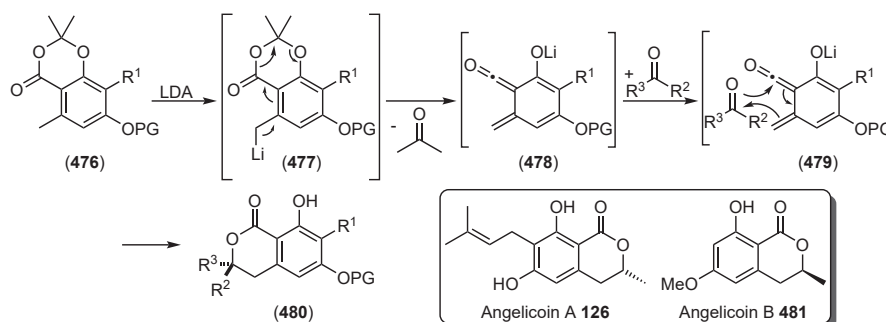
Finally, examinations to expand the scope of these studies to reactions of ketene (428) with imines, carbodiimides and isocyanides as trapping agents, and further explore the reactivity of the ketene precursor with furan and pyrrole, possibly under thermal conditions would be of interest, Scheme 3.49. This chemistry could ultimately be used to synthesize celestramycin A 475, a natural product with strong immunosuppressive properties.^[337,338]



Scheme 3.49: Future work on on the trapping with furan and pyrrole.

3.4 LDA-INDUCED REARRANGEMENT OF β -RESORCYLATES TO LACTONES

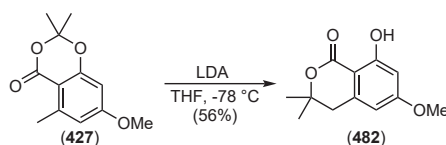
The previously reported LDA induced rearrangement is further expanded in this section (c.f. section 3.1). The formation of γ -resorcylic lactones is of interest, as natural products containing this motif,^[339–342] such as angelicoin A **126** and B **481** show promising bioactivities.^[88,97,343] The rearrangement was therefore envisioned to serve as a complementary entry to various analogs of these natural products. In analogy to the photolytic preparation of *o*-oxo cyclohexadiene ketene (**428**), c.f. Scheme 3.36, past methods employed flash photolysis (or thermolysis) of benzocyclobutenones to prepare cyclohexadiene methide ketenes of type (**478**) and applied to the synthesis of isocoumarin natural products.^[344–349] Kinetic measurements with several nucleophiles have indicated a similar first order kinetic dependence on the trapping agents and diffusion controlled reactivity of cyclohexadiene methide ketenes,^[344,349] as observed for the photolytic *o*-oxo cyclohexadiene ketene measurements.^[300] In addition, Suzuki reported the reaction of benzocyclobutenones with LiTMP and various benzaldehyde derivatives to give isochroman-3-ones derivatives,^[350] which was further utilized for the syntheses of benzocarbo-cycles and benzodiazepines.^[351,352]



Scheme 3.50: Proposed general mechanism for the formation of lactones (**479**).

As shown in Schemes 3.17 and 3.18 reaction of the ketones (**353**) and (**369**) with LDA, in an attempt to mask off the ketones as their enolates, resulted in the formation of lactones (**362**) and (**373**), respectively. In Scheme 3.17, a mechanism is proposed for this reaction. A simplistic view of this is given in Scheme 3.50: Benzylic deprotonation with LDA, gives the lithiated

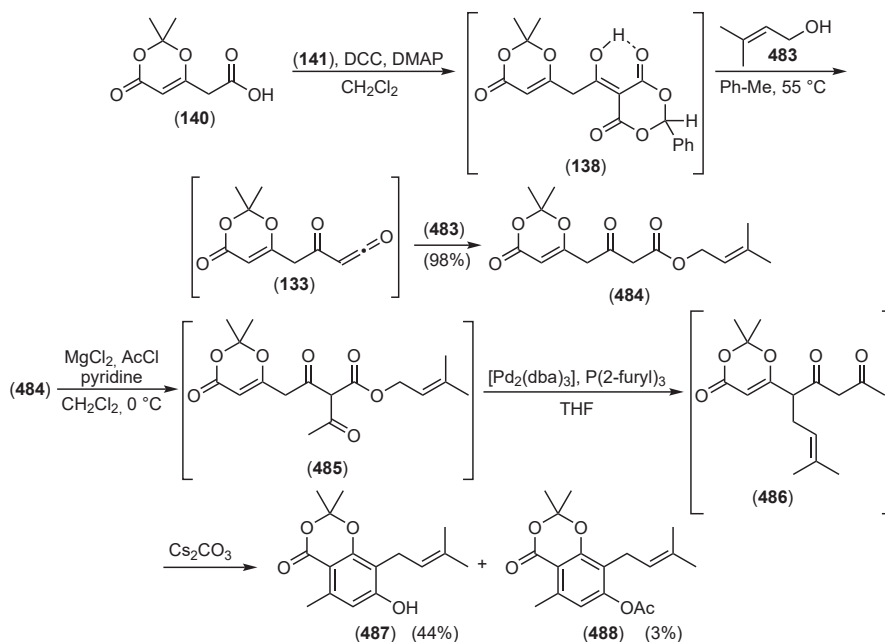
species (**477**). Supported by several literature examples of anionic accelerated rearrangement reactions,^[353–359] it is thought that the species (**477**) promotes the formation of *o*-quinomethide ketene (**478**), which can react with either the released carbonyl-containing species (acetone) or with a different carbonyl-moiety to give the lactones (**480**), possibly *via* a pseudo-pericyclic transition state of type (**479**).



Scheme 3.51: Reaction of model resorcyate (**427**) with LDA.

To examine this, the model substrate (**427**) was reacted with LDA, Scheme 3.51, which gave rise to lactone (**482**) in 56% yield, an analog of angelicin B **481**.

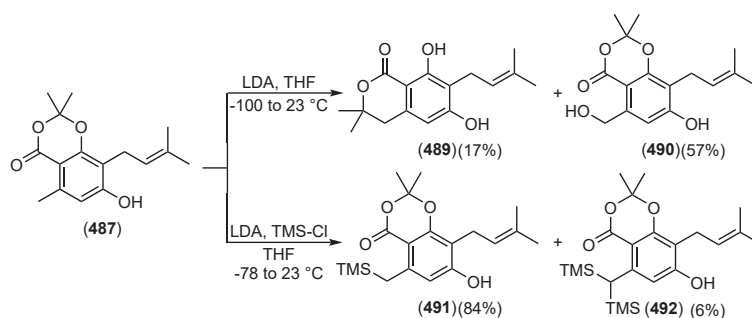
Encouraged by this result, further derivatives were studied. Synthesis of prenol resorcyate (**487**) was accomplished according to literature procedures.^[104] Reaction of dioxinone acid (**140**) with Meldrum's acid derivative (**141**) *via* DCC-mediated coupling, followed by regioselective acyl ketene (**133**) formation and trapping with prenol **483** gave β -keto ester in 98% yield, Scheme 3.52. Lewis acid promoted regioselective C-acylation, palladium-



Scheme 3.52: Biomimetic synthesis of resorcyate (**487**).

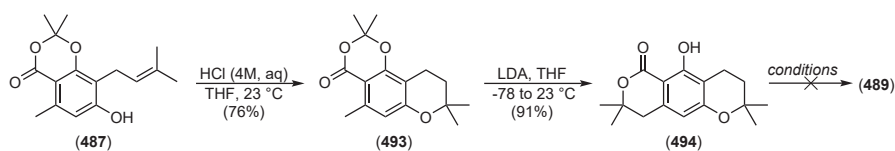
catalyzed allylic migration of intermediate (**485**) and base promoted cyclization and aromatization of intermediate (**486**) gave prenol resorcyate (**487**) in 44% with only 3% of the acylated resorcyate side product (**488**).

Initial trials on the deprotected resorcyate resulted in low yields of the desired product (**489**), an analog of angelicoic acid, with the benzylic alcohol (**490**) as the major isolated product in 57% yield, Scheme 3.53, presumably *via* reaction of the methide-ketene with oxygen.^[360] Thus, in an attempt to latently protect the resorcyate as TMS-ether, which was expected to cleave upon chromatography on silica gel, the LDA-induced rearrangement reaction of resorcyate (**487**) with TMS-Cl or TMSOTf was attempted. This resulted in the formation of the benzylic silane (**491**) in 84% yield, and minor amounts of the disilane side product (**492**). When the TMS-ether



Scheme 3.53: Attempted route to angelicoic acid analog (**489**).

intermediate was synthesized separately, followed by work-up, solvation in THF and addition of LDA, the same benzylic silane (**491**) was isolated.^[361,362] Treatment of benzylic silane (**491**) with CsF according to Kessar's method was also unsuccessful.^[347] Examination of acylated resorcyate (**488**) as a suitable substrate for the LDA-induced rearrangement failed to give any products with a lactone motif.

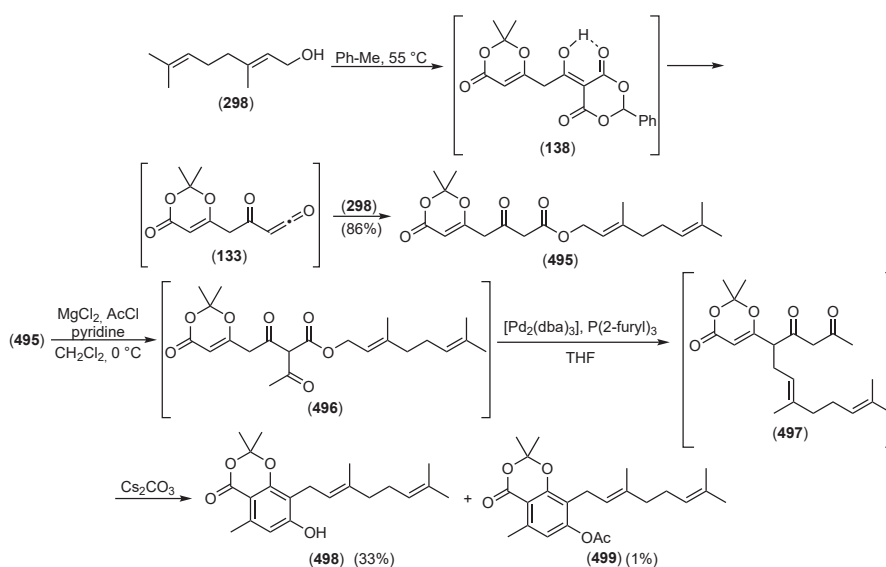


Scheme 3.54: Protecting group free route to angelicoic acid analog (**489**).

To avoid the necessity of a protecting group,^[363] resorcyate (**487**) was cyclized with 4M aqueous HCl in 76% yield, Scheme 3.54. Reaction of (**493**) with LDA gave the desired lactone (**494**) in 91% yield. However, acid-

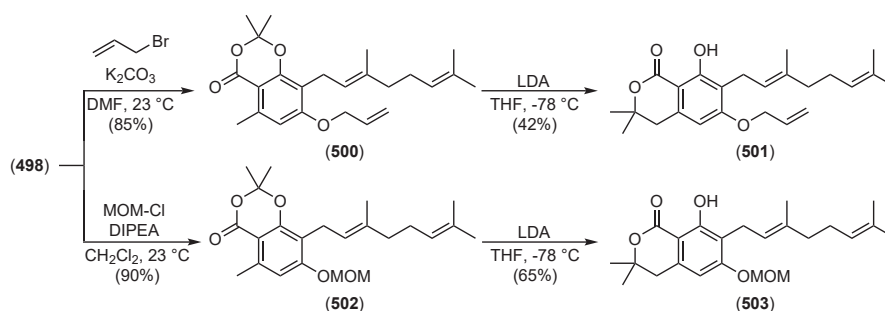
catalyzed opening reactions (H_2SO_4 in PhMe or TMSOTf/TfOH in CH_2Cl_2) all failed to give lactone (489).^[364]

The synthesis of geraniol resorcyate (498) was accomplished in a similar manner to resorcyate (487).^[104] Activation and homologation of dioxinone acid (140) by means of DCC-mediated coupling to malonate (141), followed by regioselective generation of acyl ketene (133) and trapping with geraniol 298 gave β -keto ester (495) in 86% yield, Scheme 3.55. MgCl_2 -mediated regioselective C-acylation of β -keto ester (495), followed by palladium-catalyzed regioselective allylic rearrangement of intermediate (496) and base mediated cyclization and aromatization of β,δ -diketo dioxinone (497) gave resorcyate (498) in 33% yield with only 1% of the acylated resorcyate side product (499).



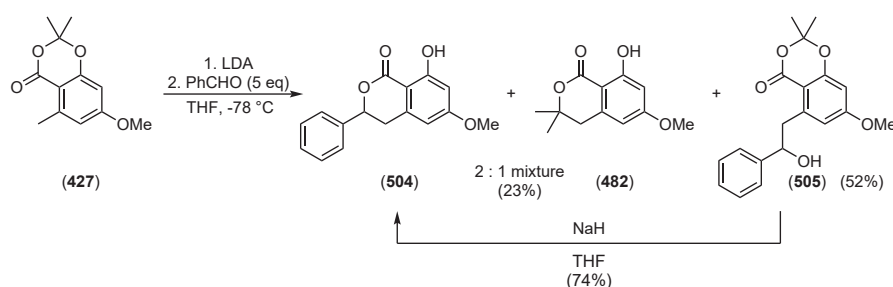
Scheme 3.55: Biomimetic synthesis of resorcyate (498).

Protection as allyl (500) and MOM ether (502) was done according to standard procedures in 85% and 80% yield, respectively, Scheme 3.56. The allyl-protected, geraniol substituted resorcyate (500) was examined next. Upon addition of LDA at -78°C , the anticipated rearrangement took place and gave lactone (501) in 42% yield. The somewhat lower yield may be attributed to deprotonation at the allylic position of the allyl protecting group, commonly seen in the Wittig-rearrangement.^[365–367] On the other hand, the MOM-protected resorcyate (502) was reacted with LDA at -78°C , which furnished lactone (503) in 65% yield.



Scheme 3.56: Synthesis of allyl and MOM protected, 3-geraniol substituted resorcylic lactones (501) and (503).

Next, variable, non-enolizable carbonyl-compounds were explored. Reaction of (427) with benzaldehyde was examined first, Scheme 3.57. Initially, since benzaldehyde is not enolizable, LDA was added to a mixture of the resorcylic lactone and benzaldehyde. This reaction was not successful. Thus, LDA was added first to resorcylic lactone (427) followed by quick addition of benzaldehyde. Dihydroisocoumarin (504) was isolated in a 2 : 1 mixture next to lactone (482).



Scheme 3.57: Reaction of resorcylic lactone (427) with LDA and benzaldehyde.

In addition, the adduct (505) was isolated in 52% yield. Possibly, the direct addition of the derived lithiated species of type (477) to benzaldehyde, rather than the intramolecular rearrangement with expulsion of acetone may account for this observation. Alcohol (505) was converted into lactone (504) with NaH in THF in 74% yield. The structure of lactone (504) was unambiguously characterized by means of single crystal X-Ray diffraction analysis, see Figure 15. Dihydroisocoumarins such as (504), and their analogs, are of interest as they display anti-allergic properties.^[368,369]

Furthermore, the behaviour of the intermediately formed ketene of type (478) with enolizable carbonyl compounds was examined, Scheme 3.58. Reaction of resorcylic lactone (427) with LDA, followed by addition of cyclohexanone,

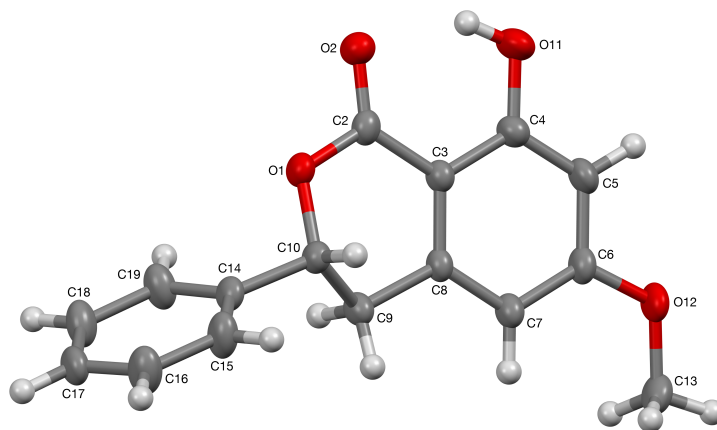
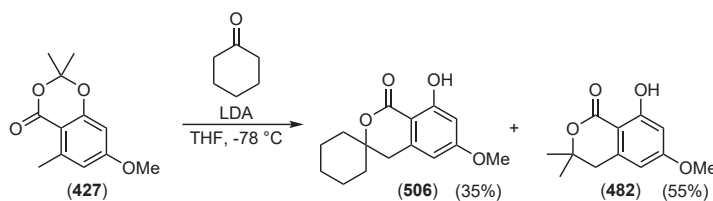


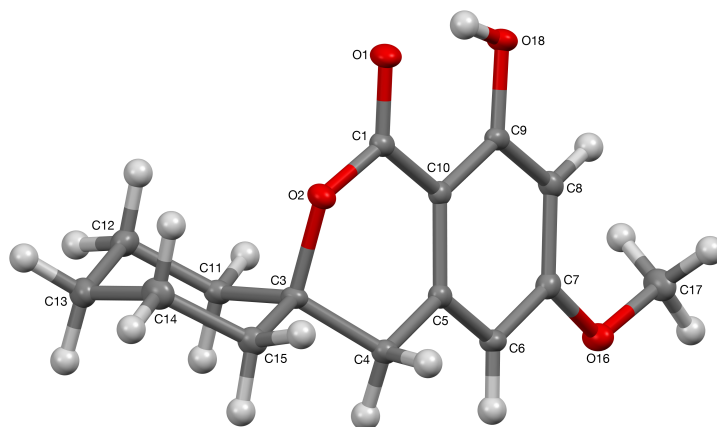
Figure 15: X-Ray diffraction structure of resorcyate (**504**). Note this is one of two independent crystal systems lactone (**504**) crystallized in, with the molecule from the asymmetric unit shown here. Please see the appendix for the alternative crystal system.

as a model example of enolizable carbonyls, gave two products: the desired spiro compound (**506**) and the previously obtained lactone (**482**). The structure of (**506**) was unambiguously characterized by means of single crystal X-Ray diffraction analysis, see Figure 16.



Scheme 3.58: Reaction of resorcyate (**427**) with enolizable carbonyl compounds.

In addition, non-carbonyl compounds were examined. To the LDA-rearrangement reaction of resorcyate (**427**) were added cyclohexene, cyclohexadiene and 3,4-dihydropyran. Unfortunately, in all cases the reaction gave rise to lactone (**482**). It appeared that the ketene diene is electron-rich in nature and preferably reacts with electron-deficient dienophiles.^[344] Furthermore, the relative levels of the LUMO of the dienophiles appear to play a role here, see Figure 17. The C=C π^* -LUMO of cyclohexene is higher in energy than the C=O π^* -LUMO of acetone, thus, the preferred product is the lactone as evidenced in the experimental result. The cyclohexadiene C=C π^* -LUMO is of slightly similar level as in cyclohexene therefore a similar reaction outcome was observed. Finally, in the case of electron-rich 3,4-dihydropyran: While the interaction of the non-bonding orbital on oxygen

Figure 16: X-Ray diffraction structure of resorcyate (**506**).

lowers the HOMO, it consequently raises the LUMO in energy thus the reaction with acetone is preferred.

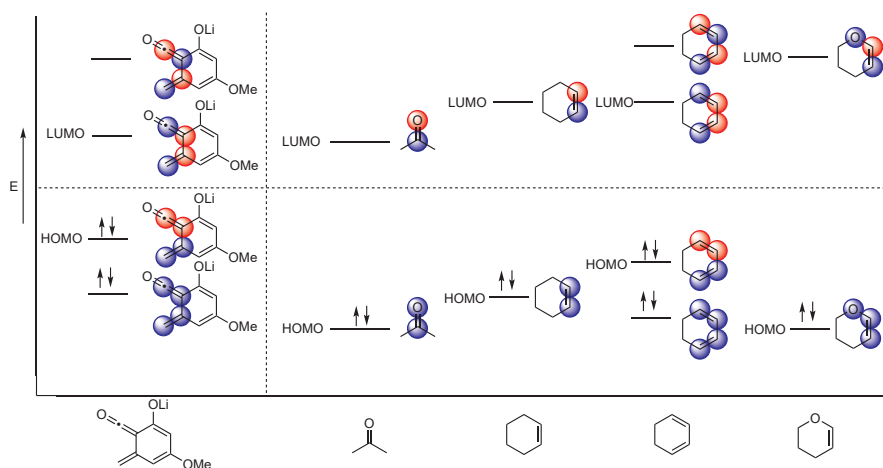
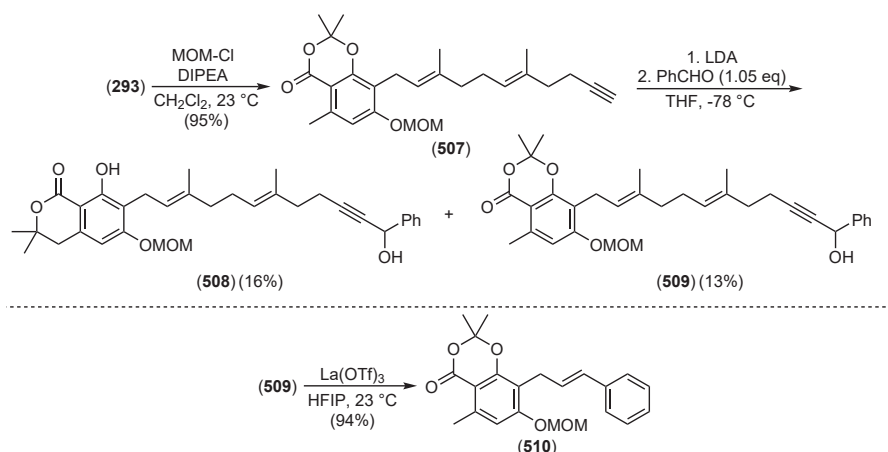


Figure 17: Relative energy levels of the frontier orbitals of acetone, cyclohexene, cyclohexadiene and 3,4-dihydropyran.

Interestingly, when TIPSOTf was added to this reaction to trap acetone in its enolate form, the reaction still proceeded and gave the TIPS protected resorcyate, indicating the rapid kinetics of this reaction. Thirdly, the oxophilicity of ketene intermediates may also play a role.

Finally, the competitive reaction of enyne resorcyate (**507**) with LDA and benzaldehyde was attempted, Scheme 3.59. Preparation of resorcyate (**507**) was accomplished according to standard procedures in 95% yield from resorcyate (**293**). Upon reaction of LDA to resorcyate (**507**), followed by addition of PhCHO, two compounds (**508**) and (**509**) were isolated, both in low yields. In both cases acetylene-addition was observed. The desired

LDA rearrangement was also observed to give lactone (**508**) in 16% yield. Obtaining a mixture of products is a direct consequence of LDA deprotonat-

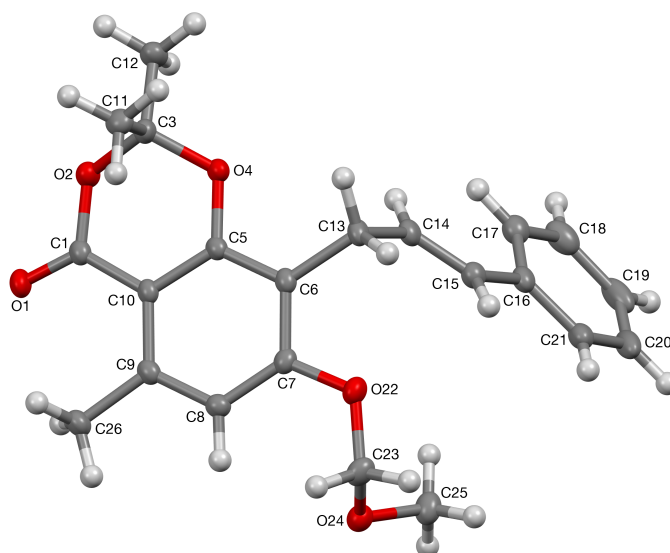


Scheme 3.59: Reaction of enyne resorcyate (**507**) with LDA and benzaldehyde and subsequent attempted polyenyne cyclization.

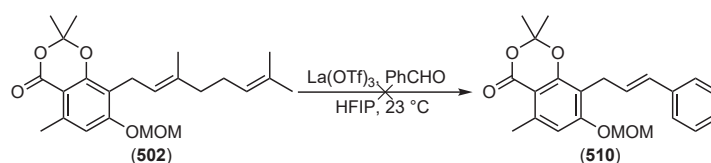
ing two positions, the benzylic and the acetylenic position. Normally, the $\text{p}K_{\text{a}}$ of a terminal acetylene is around 25, while a benzylic proton is around 41.^[370] It concludes, that the dioxinone carbonyl oxygen must be H-bonding to one of the benzylic protons, therefore lowering the $\text{p}K_{\text{a}}$, similarly to the change in $\text{p}K_{\text{a}}$ value in heteroatom-stabilized lateral-metallation studies of toluene-amides and -esters.^[370,371] Furthermore, the ability of the deprotonated species of type (**477**), from Scheme 3.50, to delocalize the charge into the aromatic ring, and further enabling the rearrangement to a methide ketene of type (**478**), lowers the $\text{p}K_{\text{a}}$ of the benzylic position due to the inductive effects of the anion stabilization. As a consequence, the $\text{p}K_{\text{a}}$ of the benzylic proton was sufficiently lowered to observe deprotonation at both positions.

Compound (**509**) is of interested as it contains an acetylenic alcohol moiety. Inspired by Carreira's dehydration of allylic alcohols to induce a polyene cyclization,^[167,168] alkyne (**509**) was reacted with lanthanum triflate in HFIP to induce a polyenyne cyclization. This reaction surprisingly gave rise to resorcyate (**510**) in 94% yield, the structure of which was unambiguously defined by X-ray single crystal diffraction analysis, Figure 18.

A trial reaction to probe the mechanism of this transformation was done: A mixture of resorcyate (**502**) and benzaldehyde was reacted with lanthanum triflate in HFIP, Scheme 3.60. This reaction cleanly recovered starting material,

Figure 18: X-Ray diffraction structure of resorcyate (**510**).

suggesting the acetylene adduct of benzaldehyde might be crucial for this reaction.

Scheme 3.60: Trial reaction of resorcyate (**502**) towards the olefin-carbonyl metathesis product (**510**).

Conclusion

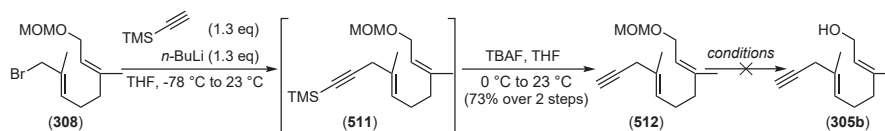
In conclusion, a series of γ -resorcyate lactones were synthesized *via* an LDA induced rearrangement. The syntheses of the precursors were accomplished *via* a biomimetic polyketide aromatization reaction. The LDA induced rearrangement reaction was examined with several different protecting groups and substituents in the C3 position, which were all well tolerated. This method enables the syntheses of various analogs of angelicin A and B. In addition, the methodology was applied to the synthesis of dihydroisocoumarins and spirocyclic products. Finally, a competitive reaction gave rise to two products, one of which was examined for its behaviour in polyene cyclizations.

Future Outlook

To investigate the relative reactivity of the ketene intermediate with electron-deficient dienophiles and heterodienophiles, reactions with 1,4-benzoquinone, DIAD, nitroso compounds or Isatin (Indole-2,3-dione) could be attempted. This would give further kinetic information about the relative reactivity compared to acetone as well as a broader diversification of the scope of the reaction. Furthermore, the reaction with benzaldehyde (Scheme 3.57) could be diversified with variable substituents on the benzaldehyde aromatic core to improve the kinetics of benzaldehyde addition. This could ultimately be applied to the total synthesis of dihydroisocoumarin natural products similar to the method employed by Kessar and co-workers.^[347] Moreover, improved conditions for the formation of angelicin A analog (489) could see the use of a suitable protecting group. Finally, the olefin-carbonyl metathesis reaction (Scheme 3.59 bottom) requires further experiments to investigate the mechanism, which may include the use of 2-methylbut-3-yn-2-ol or 1-phenyl-2-propyn-1-ol as acetylene-alcohols similar in type to (509).

3.5 1,4-ENYNE'S IN BIOMIMETIC POLYENE CYCLIZATIONS

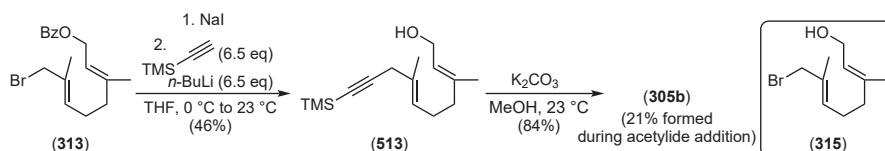
Previously, geraniol **298** was identified as the common precursor for the 1,3- (**305a**, $n = 0$), 1,4- (**305b**, $n = 1$) and 1,5-enynol's (**297**), Scheme 3.2. In accordance with the syntheses of 1,3-enynol (**305a**) and 1,5-enynol (**297**), the formation of 1,4-enynol (**305b**) was attempted in a similar fashion. Preparation of bromide (**308**) was accomplished as in Scheme 3.3. Reaction of allylic bromide (**308**) with 1-TMS lithium acetylide,^[372] generated from TMS-acetylene and *n*-BuLi, followed by TBAF mediated silyl deprotection of intermediate (**511**), gave MOM-protected 1,4-enyne alcohol (**512**) in good yields (73% yield over two steps), Scheme 3.61. Deprotection of the MOM-protecting group of ether (**512**) under various acidic conditions (HCl in dioxane, PPTS/*tert*-BuOH, aq. HCl 1 M) proved to be unsuccessful and failed to give the desired alcohol (**305b**) in more than just trace amounts.



Scheme 3.61: Attempts to synthesize 1,4-enyne alcohol (**305b**) using MOM-protecting groups.

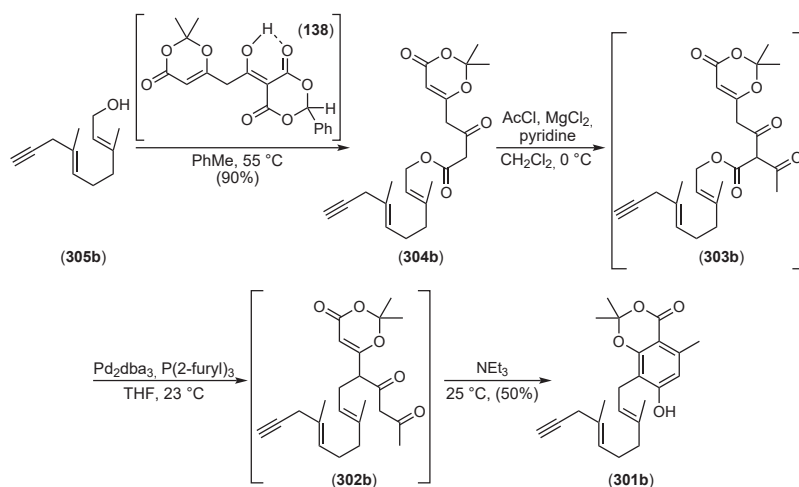
Consequently, benzoyl-protected bromide (**313**) was examined, in an attempt to deprotect within the same procedure akin to the preparation of 1,5-enynol (**297**). The synthesis of bromide (**313**) is outlined in Scheme 3.4. Reaction of bromide (**313**) with 4 equiv. of 1-TMS lithium acetylide gave the deprotected alcohol (**513**) as the major compound (44% yield),^[372] while also producing the partially deprotected alcohol (**315**) in 37% yield. Furthermore, the side product of this reaction was isolated, where the organolithium species added twice to the benzoyl ester giving rise to a tertiary alcohol. An increase to 6 equiv. of 1-TMS lithium acetylide improved the ratio between the desired 1,4-enyne alcohol (**513**) and bromide (**315**). Employing TMEDA as a declustering agent for the acetylene derived organolithide species did not affect the ratio substantially. Addition of sodium iodide, to produce the more reactive allylic iodide *in situ*, gave TMS protected 1,4-enyne alcohol (**513**) as major product (46% yield), while partial deprotection of alcohol (**513**) to alcohol (**305b**) was also observed (21% yield), Scheme 3.62. Subsequent

base mediated desilylation produced the skipped-enyne alcohol (**305b**) in 84% yield, 64% combined yield over two steps. Base mediated deprotection proved to be superior than TBAF-mediated desilylation, which resulted in partial allene formation.^[373]



Scheme 3.62: Synthesis of 1,4-enyne alcohol (**305b**).

Preparation of β -dioxinone keto ester (**304b**) was accomplished in a similar fashion to β -keto ester (**304a**), Scheme 3.63. Reaction of acid (**140**) with the Meldrum's acid derivative (**141**) by means of DCC-mediated coupling gave dioxane-4,6-dione keto dioxanone (**138**). Heating to 55 °C produced the highly reactive acyl ketene intermediate (**133**), which was trapped in the presence of 1,4-enyne alcohol (**305b**) and furnished β -dioxinone keto ester (**304b**) in 90% yield. The conversion of β -dioxinone keto ester (**304b**) to resorcyate (**301b**) was executed in analogy to resorcyate (**301a**). Addition of



Scheme 3.63: Biomimetic synthesis of 1,4-enyne resorcyate (**301b**).

pyridine and MgCl₂ to β -dioxinone keto ester (**304b**), followed by addition of acetyl chloride promoted a regioselective C-acylation to give β,δ -dioxinone diketo ester (**303b**), which upon action of Pd₂dba₃ and P(2-furyl)₃ underwent a Pd(o)-catalyzed, decarboxylative allylic rearrangement reaction to furnish β,δ -diketo dioxinone (**302b**). Base mediated cyclization and aromatization gave resorcyate (**301b**) in 50% yield. Resorcyate (**301b**) was unambiguously

characterized by means of single-crystal X-Ray diffraction analysis, see Figure 19.

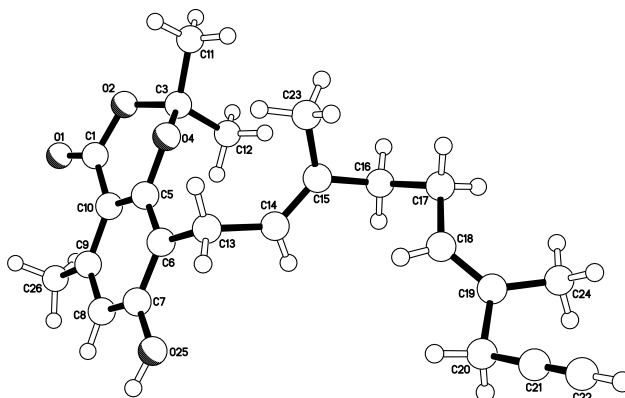
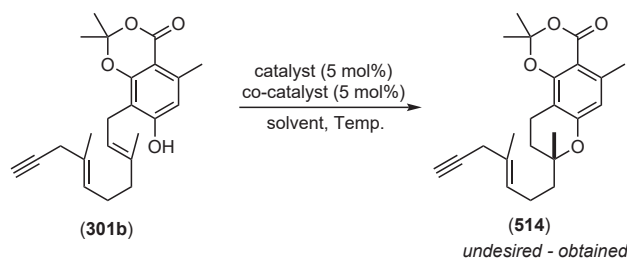


Figure 19: X-Ray structure of 1,4-enyne resorcyate (**301b**).



Solvent	Catalyst	Co-Catalyst	Temperature	Yield
CH ₂ Cl ₂	AuCl(SMe) ₂	-	23 °C	x
CH ₂ Cl ₂	-	AgSbF ₆	23 °C	x
CH ₂ Cl ₂	AuCl(SMe) ₂	AgSbF ₆	23 °C	y
CH ₂ Cl ₂	AuCl(SMe) ₂	AgOTf	23 °C	y
CH ₂ Cl ₂	AuCl(PPh ₃)	AgOTf	23 °C	y + z
(CH ₂ Cl) ₂	AuCl(PPh ₃)	AgOTf	23 °C to 40 °C	y + z
(CH ₂ Cl) ₂	AuCl(PPh ₃)	AgOTf	80 °C	z
(CH ₂ Cl) ₂	BrettPhos AuNTf ₂	-	23 °C	z
(CH ₂ Cl) ₂	XPhos AuNTf ₂	-	23 °C	z
(CH ₂ Cl) ₂	XPhos AuNTf ₂	-	23 °C	z
CH ₂ Cl ₂	InBr ₃	-	23 °C	z

x indicates recovery of starting material. Y indicates complex mixture. z indicated partial cyclization to give (**514**).

Table 3: Screening conditions for the attempted cyclization of 1,4-enyne resorcyate (**301b**).

Examination of different Lewis acids to induce a biomimetic polyenyne cyclization on 1,4-enyne resorcyate (**301b**) are summarized in Table 3. Correspondingly to the 1,3-enyne resorcyate (**301a**), after ensuring the negative control studies were in place, any combination of gold and silver salts failed to provide a fully cyclized product in viable amounts, while in some cases the partially cyclized resorcyate (**514**) was isolated. Unfortunately, not even

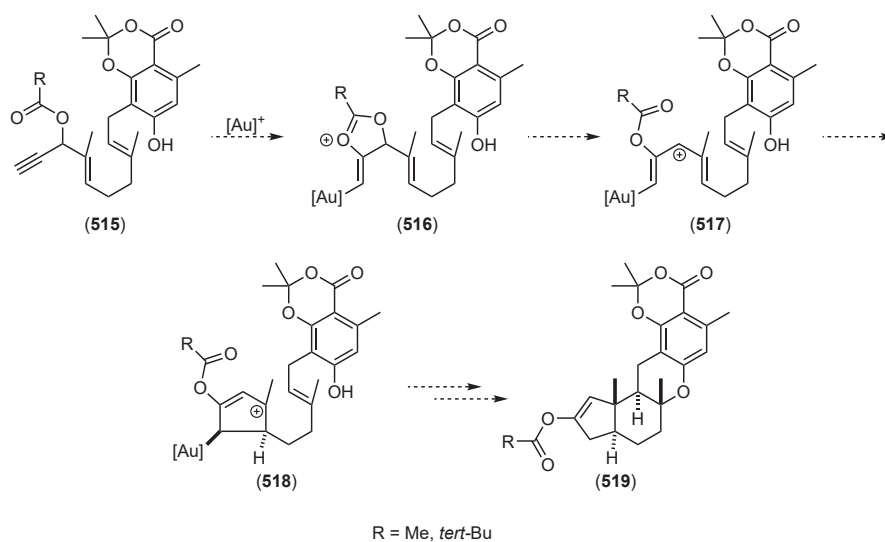
a ketone formation was observed, indicative of initial coordination of the gold catalyst to the alkyne. Exchanging the silver salt for the less hygroscopic AgOTf provided a complex mixture. Similar results were obtained when the more reactive (PPh₃)Au(Cl) was used. Usage of 1,2-dichloroethane as solvent both at RT and elevated temperatures lead to the partially cyclized product (**514**). It should be noted, that in all cases, the mass balance was significantly affected, as already seen with the 1,3-enyne resorcyate (**301a**), possibly due to undesired phenol oxidation with the silver salts. Exchanging the counter anion of the gold catalysts to NTf₂, using BrettPhos AuNTf₂ and XPhos AuNTf₂ at variable temperatures, also lead to formation of the partially cyclized product (**514**). Further examinations on this cyclization are necessary (see future outlook), however, due to time constraints this was not possible.

Conclusion

In conclusion, the 1,4-enyne resorcyate displayed poor reactivity with variable Lewis acids in an attempt to induce a polyene cyclization. The synthesis of the resorcyate was accomplished according to the previous protocols of the 1,3- and 1,5-enyne resorcyates. The corresponding enyne alcohol was obtained in a step-economic fashion with *in situ* deprotection during the installation of the acetylene group.

Future Outlook

Possible further efforts could be directed towards Pt-catalyzed cycloisomerizations or dual Au/In-catalysis. In addition, the usage of the Rautenstrauch rearrangement to induce a polyene cyclization could be considered,^[374,375] Scheme 3.64.^[216,376–378] A key intermediate of the Rautenstrauch rearrangement on a substrate like (**515**) would be the carbenium ion (**517**),^[377,378] which could be of interest in a biomimetic polyene cyclization towards (**519**). Extending this to a polyenyne cyclization could be a complementary entry



Scheme 3.64: Biomimetic synthesis of 1,4-enyne resorcyate (**301b**).

point to 5,6,6-fused ring systems. Alternatively, the limited reactivity of the 1,4-enyne resorcyate could be due to the preferred formation of *cis*-fused 5,6 ring systems. The enyne motif of resorcyate (**301b**) is in a *trans* relationship, which would provide a *trans*-fused 5,6 ring system. Further investigations of this hypothesis *via* the formation of a 1,4-enyne with a *cis* relationship need to be performed to validate this.

SUMMARY

In summary, the syntheses of a 1,3-, 1,4- and 1,5-enyne alcohol was accomplished in a step-efficient procedure from a common precursor, with *in situ* deprotection during the acetylene formation. The derived alcohols were subsequently used in a biomimetic polyketide-aromatization sequence, thereby extending the substrate scope around the aromatization reaction to non-natural acetylenic polyenes. When comparing the reactivity behaviour of the acetylenic resorcyates, it can be noted that the substrates prefer the formation of 6-membered rings, possibly due to the lower energy of the six-membered chair transition states. This is highlighted with the formation of the 6-6-6-6 ring system in the reaction of the 1,5-enyne resorcyate (**293**) with various π -Lewis acids, while the 1,3-enyne resorcyate (**301a**) and 1,4-enyne resorcyate (**301b**) showed preferred reaction on the internal olefin to form chromanes (**398**) and (**514**) rather than any product derived from activation at the terminal acetylene. Conversely, as previously mentioned in the aims section (c.f. 2.1), Corey found that formation of seven- or eight membered rings from the corresponding precursors was also not favoured and therefore not observed or in trace amounts.^[205] It is, thus, of interest that such acetylenic terpenes have a narrow chemical window of reactivity towards polyene cyclizations. Application of the observed reactivity of the 1,5-enyne resorcyate (**293**) has seen the syntheses of various analogs of hongoquercin,^[264] as a complementary method to enhance the chemical space around the previously synthesized hongoquercins,^[106] while creative efforts to employ the bromochromane (**398**) may lead to the synthesis of meroterpenoids isolated from *rhododendrom* plants (c.f. Scheme 3.32) while the 1,4-enyne resorcyate may see usage in an interrupted Rautenstrauch rearrangement, polyene cyclization cascade (Scheme 3.64).

AMORFRUTINS

5.1 AMORFRUTIN NATURAL PRODUCT ISOLATION, BIOLOGICAL ACTIVITIES AND PAST SYNTHESSES

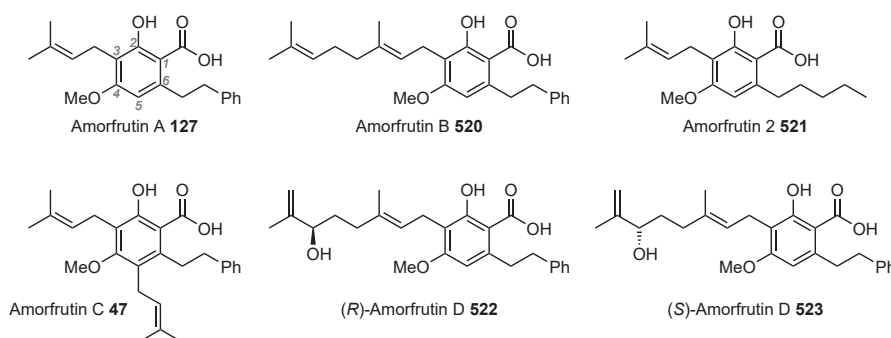
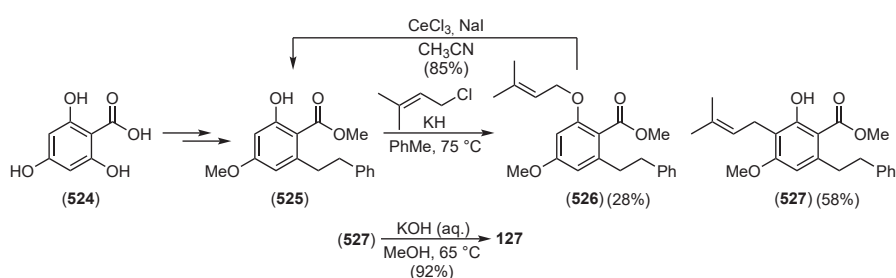


Figure 20: Amorfrutin natural products.

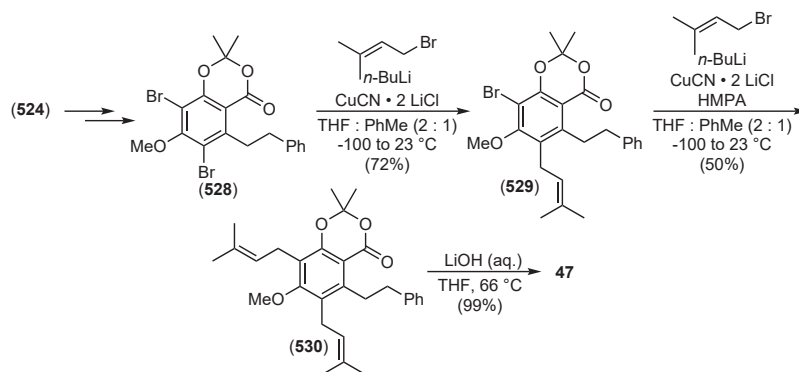
The amorfrutins (amorfrutin A, B, C, D and 2) are meroterpenoid natural products isolated from *Amorpha fruticosa* and *Glycyrrhiza acanthocarpa*.^[379–382] The core structure of the amorfrutins comprises a bibenzyl entity and β -resorcyate unit, which is further substituted with terpene motifs, such as prenyl, geranyl and remote terpene functionalized geranyl chains, Figure 20.^[27] Biological profiling of amorfrutin A **127** and B **520** revealed potent peroxisome proliferator-activated receptor gamma (PPAR- γ) activation, with amorfrutin A showing low-micromolar affinity while amorfrutin B displayed nanomolar affinity.^[383–387] The PPAR γ receptor is a key element in metabolism and is therefore associated with type 2 diabetes and obesity.^[388–391] Sauer and co-workers reported the selective PPAR γ activation by amorfrutin A **127** and amorfrutin B **520** and few downstream side effects were observed.^[384] This is an improvement relative to known PPAR γ modulating drugs, such as rosiglitazone or ciglitazone, which are reported to cause severe cardiovascular side effects and weight gain.^[392,393] Continued biological profiling of amorfurтин **127** showed anti-tumor properties as well

as narrow-spectrum antimicrobial activities.^[379,394,395] Amorfrutin **520** was reported to display micromolar antibiotic activities with minimum inhibition concentration (MIC) against methicillin-resistant strains of *Staphylococcus aureus* of 12.5 μM , vancomycin-resistant strains of *Enterococcus faecium* of 6.3 μM and *Enterococcus faecalis* of 6.3 μM .^[382] Accordingly, amorfrutin **520** may serve as an important candidate in the continuing fight against antibiotic resistant microbes and for the discovery of new antibiotics. Amorfrutin C **47** was reported to show anti-cancer activities in human colon, prostate and breast cancer cell lines.^[381] Amorfrutin D has not been studied for its biological activities so far.^[382]



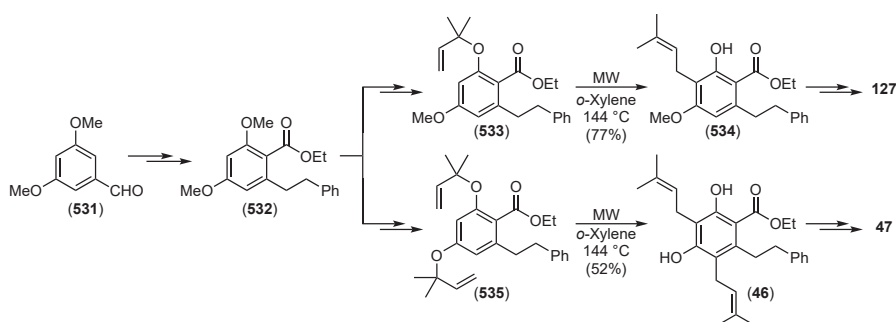
Scheme 5.1: Weidner's total synthesis of amorfrutin A **127**.

With the myriad of biological activities and selectivities, the amorfrutins might be promising new pharmaceutical candidates. As a consequence, several different syntheses have been reported,^[396–401] which can be broadly categorized into arene functionalization studies starting from existing aromatic precursors, and *de novo* syntheses of substituted arenes. Weidner and co-workers reported the total synthesis of amorfrutin A **127** starting from trihydroxybenzoic acid (**524**) and a late-stage introduction of the prenyl-chain, Scheme 5.1.^[384]



Scheme 5.2: Wu's total synthesis of amorfrutin C **47**.

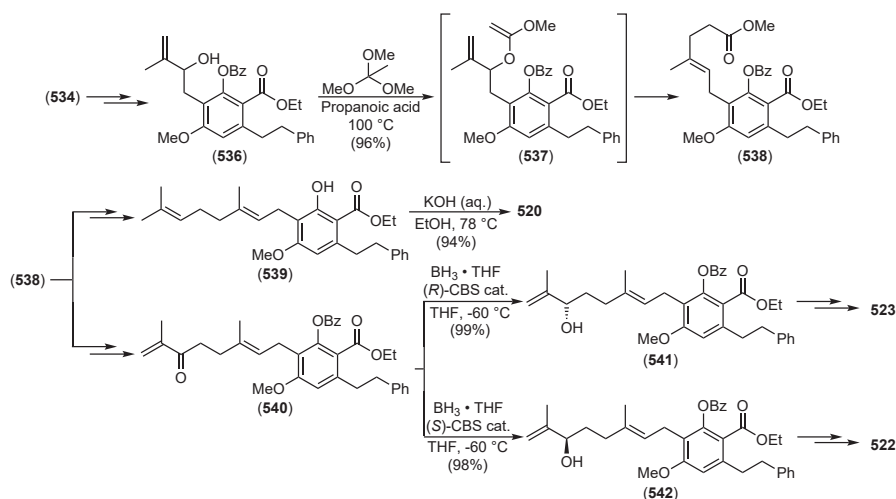
Wu and co-workers reported a similar strategy towards the synthesis of amorfrutin C **47**,^[402] employing a series of transition metal mediated aryl-prenyl coupling reactions on dibromide (**528**) starting from phenol (**524**), Scheme 5.2. It was found that prenylation occurred initially at the C5 position which was further utilized to synthesize *pseudo*-amorfrutin A (prenyl group attached in the C5 position). No further C5 derivatives were reported. Ogura and co-workers reported the use of dimethoxybenzaldehyde as common precursor in the syntheses of amorfrutin A **127** and amorfrutin C **47** employing a Claisen-rearrangement^[403–405] reaction as key step to introduce one or two prenyl units.^[406] Furthermore, Ogura reported the



Scheme 5.3: Ogura's total syntheses of amorfrutins **127** and **47**.

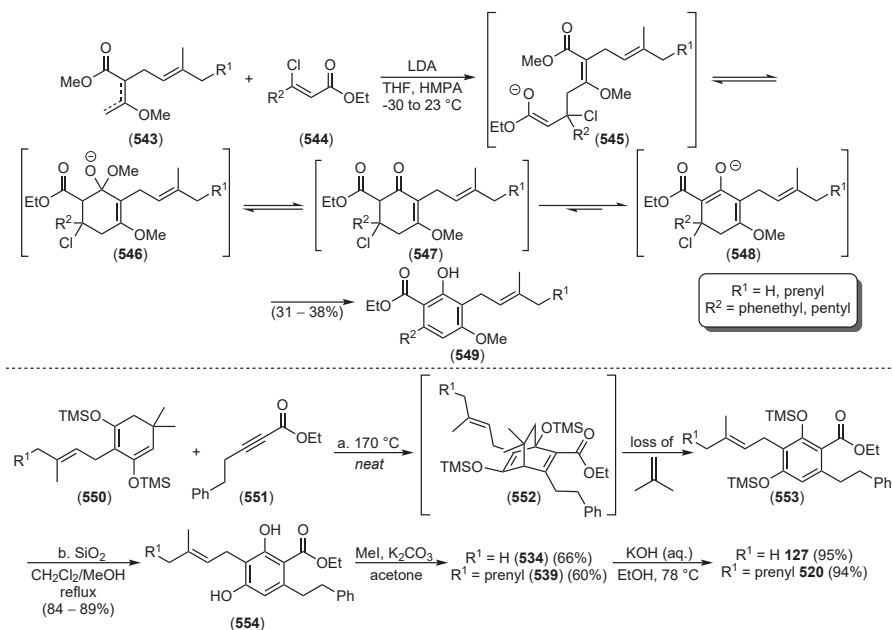
synthesis of amorfrutin B **520**, as well as (*R*)- **522** and (*S*)-amorfrutin D **523**,^[407] employing a Johnson-Claisen rearrangement^[408] on allylic alcohol (**536**) as key step to synthesize the geranyl moiety, after initial Claisen-rearrangement reactions furnished undesired (*E*)/(*Z*)- mixtures, Scheme 5.4. In Ogura's study, it was found that the synthetic (*S*)-amorfrutin D displayed a different optical rotation sign (–) compared to the natural one, which was proposed to be of (*S*)-configuration.^[382] Synthetic (*R*)-amorfrutin D **522** on the other hand was in agreement with the sign of natural amorfrutin D.

Alternatively, employing a *de novo* benzene synthesis approach can circumvent the extensive use of protecting groups that are required in the above mentioned conversion of aromatic compounds to those of higher complexity. For example, Sauer employed such a strategy in the synthesis of amorfrutin **47** and analogs (c.f. Scheme 1.7).^[27] This procedure displayed undesired issues in regioselectivity. Schroeder recently reported an improved synthesis using a one-pot Michael addition of the derived enolate of ester (**543**) on Michael acceptor (**544**), followed by a Dieckmann cyclization to give ester



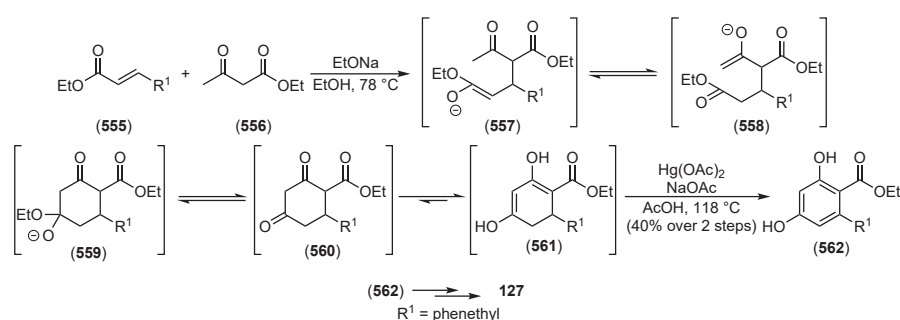
Scheme 5.4: Ogura's total syntheses of amorfrutins 520, 522 and 523.

(546) which after double elimination and concomitant aromatization *via* tautomerization gave resorcyate (549), Scheme 5.5 top.^[409] Furthermore, a Diels-Alder approach was reported, using terpene substituted derivatives of the dimedone derived diene 5,5-dimethyl-1,3-bis-trimethylsilyloxycyclohexa-1,3-diene (550), and ynolides (551), Scheme 5.5 bottom. Loss of butylene gas gave resorcyate disilyl ether (553), which upon addition of silica gel in a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ suspension gave the amorfrutin core (554). Methylation and saponification gave amorfrutins 127 and 520, as well as other cannabinoids. Deng and co-workers reported a Michael-addition, Claisen condensation,



Scheme 5.5: Schroeder's total syntheses of amorfrutins 127 and 520.

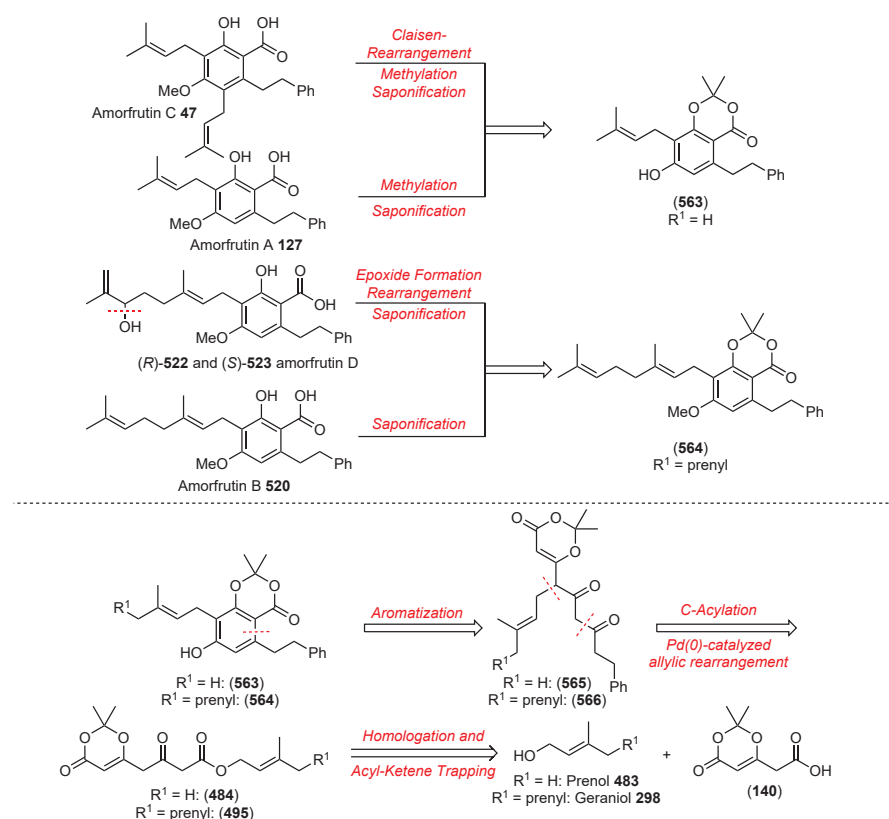
Hg(OAc)₂-mediated oxidation strategy to assemble to core of amorfrutin A **127**, Scheme 5.6.^[410] Treatment of Michael-acceptor (**555**) and ethyl acetoacetate (**556**) with sodium ethoxide in ethanol gave the Michael adduct (**557**), which upon protonation and deprotonation gave enolate (**558**). Intramolecular Claisen condensation reaction of enolate (**558**) gave cyclohexadione (**560**) *via* the tetrahedral intermediate (**559**). Diketo-ester (**560**) exists as a mixture of keto (**560**) and enol (**561**) tautomers. Oxidation with Hg(OAc)₂ furnished the amorfrutin A core structure (**562**), which was subsequently converted into the natural product amorfrutin A **127** in four additional steps and an overall yield of 42% from resorcyate (**562**). The biomimetic polyketide aromatization



Scheme 5.6: Deng's total synthesis of amorfrutins **127**.

strategy (c.f. Scheme 1.17)^[96] was used to synthesize **127** in 16% overall yield. Amorfrutin A **127** contains the core structure of amorfrutin C **47**, hence a working hypothesis of amorfrutin interconversion from common precursors was established, Scheme 5.7. Calum Patel, a final year undergraduate student, devised a retrosynthetic analysis that employed the synthesis of the core structure (**563**), followed by Claisen-rearrangement or transition metal mediated coupling reactions to derivatize the C5 position.^[411] Results of this are discussed in section 5.2.^[412] Derived from this work, the conversion into amorfrutin B and (S)-D and (R)-D was examined that relied on the synthesis of the core structure (**564**), followed by remote terpene functionalization. The results of this are discussed in section 5.3. The amorfrutin cores (**563**) and (**564**) should be available *via* a biomimetic polyketide aromatization reaction involving base promoted cyclization and aromatization, regioselective palladium catalyzed allylic rearrangement reaction and regioselective C-acylation reaction.^[80,104] The β -dioxinone keto esters (**484**) and (**495**), in turn, should be

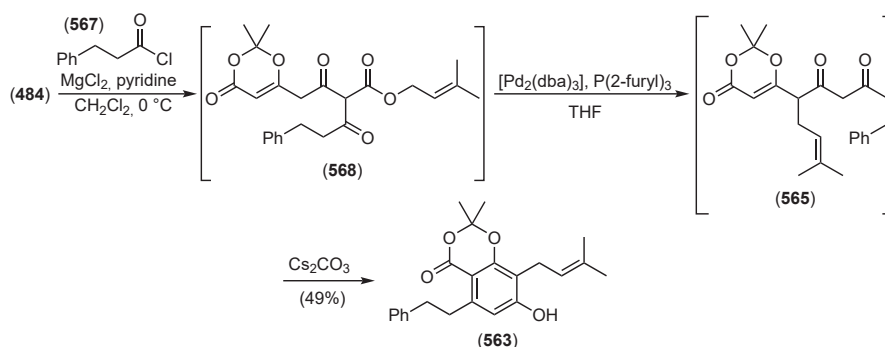
available from prenol **483** or geraniol **298** and dioxinone acid **140**, according to established procedures,^[104,105] c.f. Schemes 3.52 and 3.55.



Scheme 5.7: Unified retrosynthetic analysis from common precursors for amorfrutins **47**, **127**, **520**, **522** and **523**.

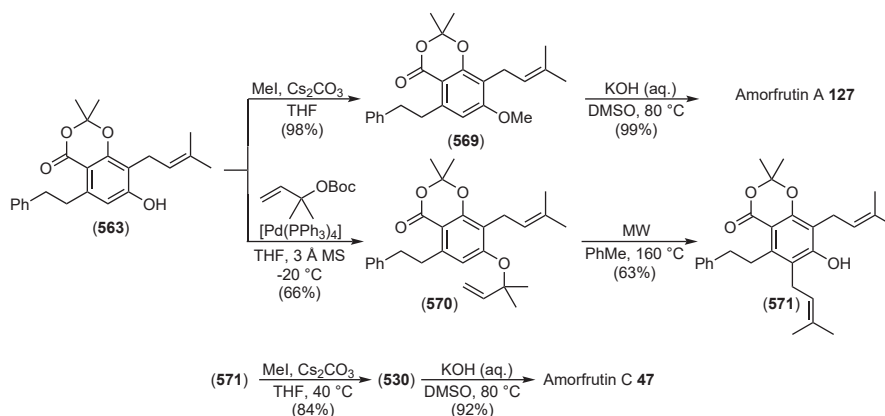
5.2 TOTAL SYNTHESIS OF AMORFRUTIN C AND C5 ANALOGS

The synthesis of the core of amorfrutin A and C commenced with the preparation of prenyl keto ester (**484**), as outlined in Scheme 3.52, and was independently performed by Calum Patel.^[412] Biomimetic polyketide aromatization reaction followed the outlined process from Scheme 3.52 employing dihydrocinnamoyl chloride (**567**). The following synthetic procedures were executed by Calum Patel,^[411,412] except where indicated: $MgCl_2$ promoted regioselective C-acylation gave β,δ -diketo dioxinone ester (**568**), which in the presence of palladium underwent a prenyl migration reaction to give β,δ -diketo dioxinone (**565**). Addition of Cs_2CO_3 furnished the core structure (**563**) in 49% yield, Scheme 5.8. It was found that Cs_2CO_3 performed better than NEt_3 and $CsOAc$. Methylation with MeI and Cs_2CO_3 gave methyl ether (**569**)



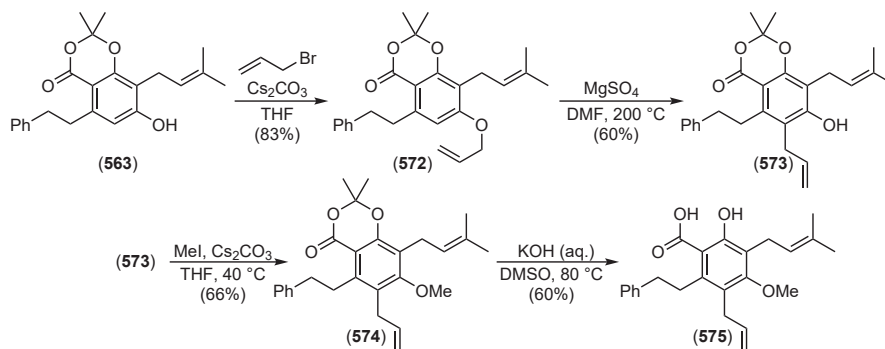
Scheme 5.8: Biomimetic synthesis of the core structure (563).

in 98% yield, Scheme 5.9. Saponification of (569) by means of KOH (aq.) in DMSO completed the total synthesis of **127** in 99% yield.^[96,239,396,398,401,406,409] Reverse prenylation under palladium catalysis with Boc-protected alcohol gave O-allylated resorcyate (570) in 66% yield, *via* a Tsuji-Trost allylic alkylation reaction.^[91,93,413,414] Microwave assisted Claisen-rearrangement reaction furnished the core structure of amorfrutin C (571) in 63% yield. Methylation (84%) and saponification (92%) gave amorfrutin C **47**.^[406] The last two steps were independently confirmed by the author of this thesis. ^1H -NMR and $^{13}\text{C}\{^1\text{H}\}$ -NMR-data obtained from synthetic **47** were in agreement with those reported for natural **47**,^[381] see Table 5. Alkylation of resorcyate (563) gave

Scheme 5.9: Divergent completion of the total syntheses of amorfrutins **47** and **127**.

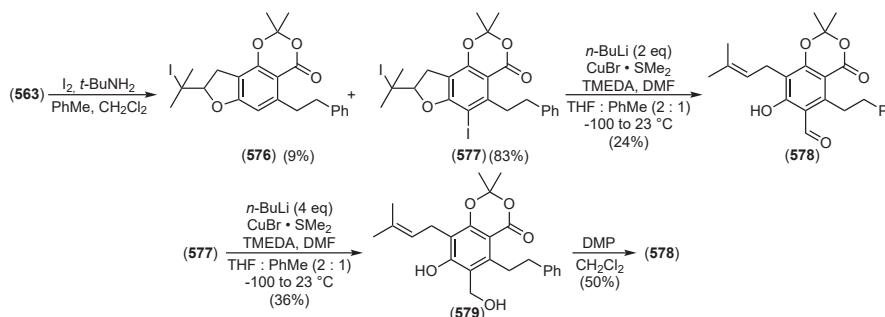
allyl ether (572) in 83% yield, Scheme 5.10. Heating resorcyate (572) in a DMF solution to 200°C promoted the Claisen-rearrangement reaction to give phenol (573). It was found that higher temperatures were detrimental to the stability of the dioxinone group,^[411] resulting in decarbonylation or decarboxylation *via* an intermediately formed ketene species. The difference

in temperature and kinetics of the reaction relative to the microwave assisted reaction of (565) are attributed to the Thorpe-Ingold effect.^[415-418] The author of this thesis independently confirmed the result - addition of MgSO_4 as drying agent improved the outcome of the reaction. Methylation with MeI and Cs_2CO_3 was accomplished in 66% yield of (574), followed by saponification of (574) by means of KOH (aq.) in DMSO ,^[96] which gave allyl substituted resorcylic acid (575) in 60% yield, both reactions executed by the author of this thesis.



Scheme 5.10: Synthesis of C5 allyl substituted amorfrutin derivative (575).

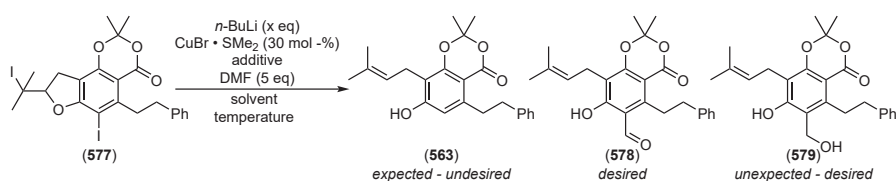
Transition metal catalyzed processes were envisioned as an additional method to derivatize the C5 position.^[411] Treatment of resorcyate (563) with iodine and *tert*-butyl amine gave diiodide (577) in 83% yield next to monoiodide (576) in 9% yield,^[26,99] Scheme 5.11, independently confirmed by the author of this thesis. Reaction of diiodide with *n*-BuLi, $\text{CuBr} \cdot \text{SMe}_2$ and TMEDA in a 2 : 1 PhMe : THF solution at -100 °C,^[402] followed by addition of DMF gave aldehyde (578) in 24%, next to the opened resorcyate (563).



Scheme 5.11: Synthesis of C5 substituted amorfrutin derivatives (577), (578) and (579).

The following synthetic procedures were executed by the author of this thesis: Systematic investigation revealed a narrow window of reactivity, see

Table 4. Substituting THF with diethyl ether was not tolerated, neither was performing the reaction solely in THF or PhMe. In all cases the opened resorcyate (**563**) was the major product. Performing the reaction in a diethyl ether/THF mixture was also unsuccessful and furnished resorcyate (**563**). In the absence of TMEDA the reaction failed to proceed entirely to give aldehyde (**578**). When the reaction was carried out at a higher temperature (-78°C), the opened resorcyate (**563**) was the sole product. When the number of molar equiv. of *n*-BuLi was increased to 4, the reaction proceeded to give the alcohol (**579**) in 36% yield, next to (**563**) in 38% yield.



Solvent	Additive	<i>n</i> -BuLi eq	Temperature	Yield
Et ₂ O : PhMe 2 : 1	TMEDA	2	-100°C	x
THF	TMEDA	2	-100°C	x
PhMe	TMEDA	2	-100°C	x
Et ₂ O : THF 1 : 1	TMEDA	2	-100°C	x
THF : PhMe 2 : 1	-	2	-100°C	x
THF : PhMe 2 : 1	TMEDA	2	-78°C	x
THF : PhMe 2 : 1	TMEDA	4	-100°C	y

x indicates recovery of starting material with less than 10% of aldehyde (**578**) formed. y indicates formation of alcohol (**579**).

Table 4: Screening conditions for the attempted formylation of diiodide (**577**).

It is hypothesized, that the intermediately formed aldehyde, or its resonance *o*-quinone methide structure, is reduced by excess of *n*-BuLi, facilitated by the presence of TMEDA. Treatment of alcohol (**579**) with DMP furnished aldehyde (**578**) in 50% yield, Scheme 5.11. Once more, it is possible that the yield of the oxidation reaction was affected by the formation of an *o*-quinone methide species. The structure of amorfrutin aldehyde (**578**) was unambiguously characterized by means of single crystal X-Ray diffraction analysis, see Figure 21.

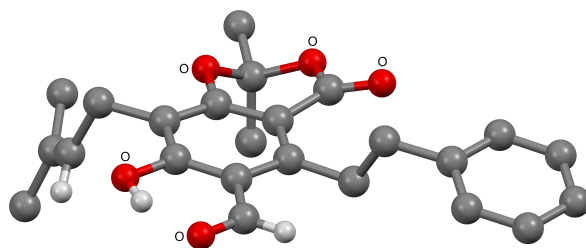
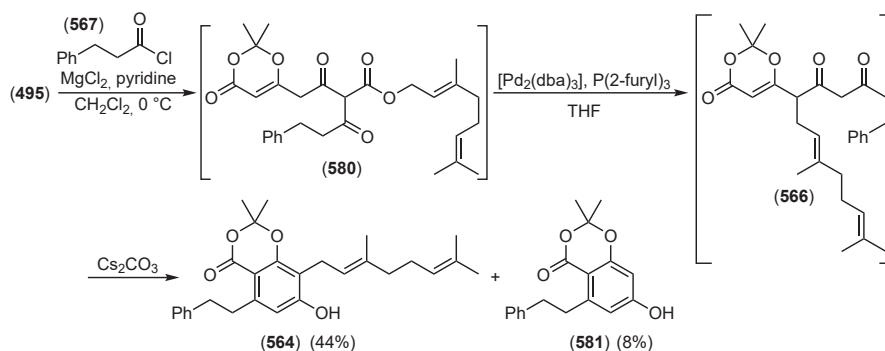


Figure 21: X-Ray crystal structure of aldehyde (578).

5.3 TOTAL SYNTHESIS OF AMORFRUTIN B, (*R*)- AND (*S*)-AMORFURTIN D

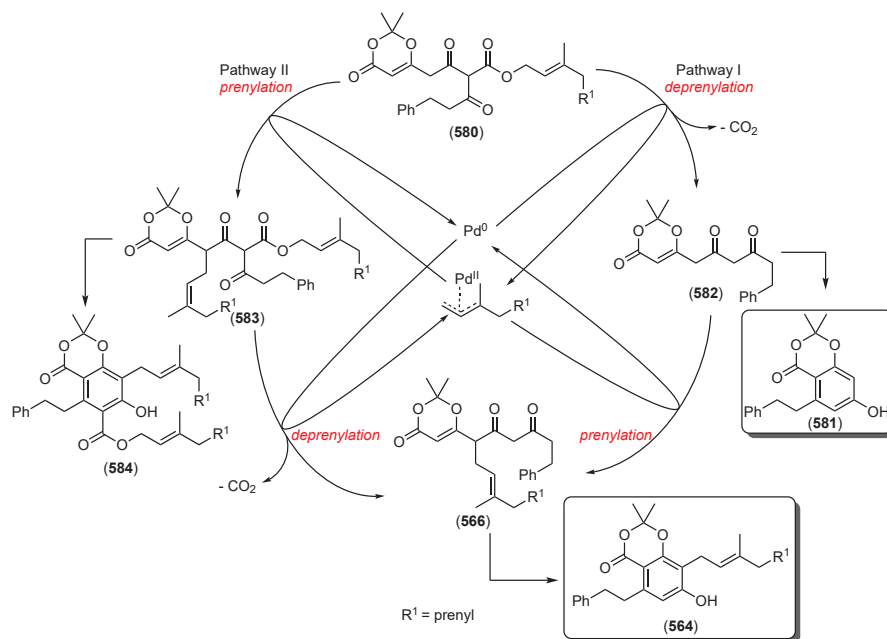
The synthesis sequence commenced with the preparation of geraniol keto ester (495), as described in Scheme 3.55. Conversely, the biomimetic aromatization cascade followed the outlined procedure of Scheme 3.55, with dihydrocinnamoyl chloride (567) as acid chloride unit. Reaction of keto ester (495) with acid chloride (567) in the presence of MgCl_2 promoted a regioselective C-acylation to give β,δ -dioxinone diketo ester (580), which upon addition of catalytic amounts of $\text{Pd}(\text{o})$ formed β,δ -diketo dioxinone (566) *via* a regioselective, decarboxylative, allylic rearrangement reaction, Scheme 5.12. Addition of Cs_2CO_3 furnished the amorfrutin B and D core (564) in 44% yield, as well as the unsubstituted resorcyate (581) in 8% yield.



Scheme 5.12: Biomimetic synthesis of the core structure (564).

Mechanistic studies within the group revealed a catalytic cycle as shown in Scheme 5.13.^[89,96,419] The observation of resorcyate (581) without allylic entities, next to those with two (584) and the desired resorcyate (564) are a consequence of the intermolecular reaction mechanism, which has the possibility of prenylation (used as a general term here) before deprenylation

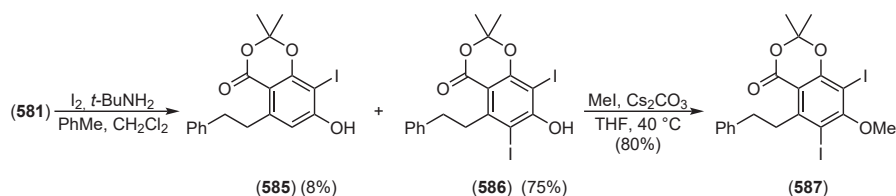
(and decarboxylation, pathway II) or after (pathway I). It follows, that it is



Scheme 5.13: Proposed reaction mechanism of the palladium-catalyzed decarboxylative, allylic rearrangement reaction, applied to the synthetic sequence from Scheme 5.12.

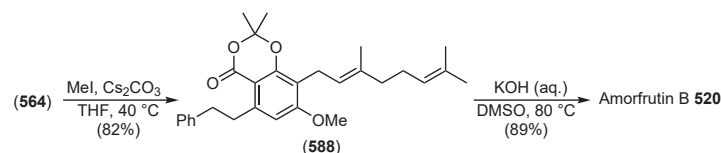
possible, that the intramolecular cyclization and aromatization of β,δ -diketo dioxinone (582) to furnish the unsubstituted resorcyate (581) is quicker than the intermolecular prenylation reaction, as this is dependent on the relative concentration of the Pd-allyl complex. The mechanistic studies further revealed optimal conditions for the formation of (564) to be at 0.2 M reaction concentration.

The corresponding methyl ether of (581) was a key intermediate in Wu's total synthesis of amorfrutin C 47,^[402] thus an alternative approach was examined. Iodination of phenol (581) with iodine and *tert*-butylamine gave the diiodide (586) in 75% yield next to the mono-iodinated product (585) in 8% yield, the structure of which was tentatively assigned based on ^1H -NMR-analysis. Methylation of (586) gave resorcyate (587) in 80% yield. Resorcyate (587) is expected to display similar reactivity in the transition metal mediated aryl-prenyl coupling reactions by Wu and co-workers, thus concluding a formal synthesis of amorfrutin C 47 while also enabling the possibility of synthesizing further C5 analogs, complementary to the approach discussed in section 5.2.



Scheme 5.14: Synthesis of diiodide (587), the iodo-analog of the bromo-intermediate (528) from Wu's amorfrutin C total synthesis.

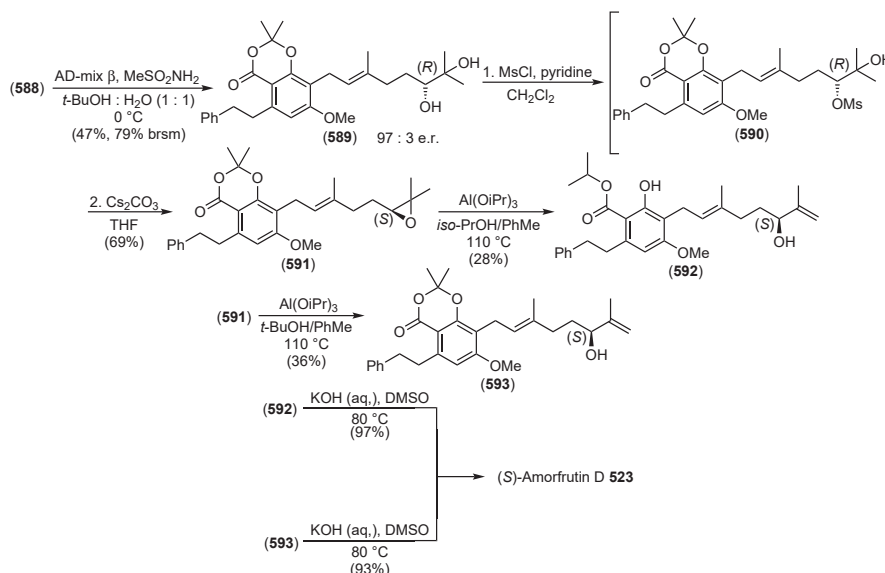
The conversion of resorcyate (564) into amorfrutin B 520 is shown in Scheme 5.15. Methylation (82% yield) followed by saponification of (588) by means of KOH (aq.) in DMSO (89%) completed the total synthesis of 520.^[96] ^1H -NMR and $^{13}\text{C}\{^1\text{H}\}$ -NMR-data obtained from synthetic 520 were in agreement with those reported for natural 520,^[394] see Table 6.



Scheme 5.15: Endgame in the total synthesis of amorfrutin 520.

Transformation of the amorfrutin B and D core (588) into (S)- and (R)-amorfrutin D is displayed in Scheme 5.16 and 5.17, employing a regio- and enantiospecific Sharpless asymmetric dihydroxylation (AD) reaction,^[420,421] mesylation and epoxide formation strategy.^[106,422,423] Reaction of (588) with AD-mix- β furnished (R)-diol (589) in 47% yield (79% corrected for recovered starting material), Scheme 5.16. Mosher's ester formation of (R)-diol (589) revealed an enantiomeric ratio of 97 : 3 for the AD reaction as determined *via* ^{19}F -NMR-analysis.^[424] Treatment of (R)-diol (589) with MsCl and pyridine gave the intermediately formed mesylate (590), which without isolation was reacted with Cs_2CO_3 ,^[106,422,423] which gave rise to (S)-epoxide (591) in 69% yield. An epoxide rearrangement reaction of (S)-epoxide (591), employing $\text{Al}(\text{OiPr})_3$ in an *iso*-propanol/ PhMe mixture gave ester (592) in 28% yield.^[425] Substituting *iso*-propanol for *tert*-butanol successfully suppressed the dioxinone transesterification reaction and gave (S)-allylic alcohol (593) in 36% yield. Saponification of (S)-allylic alcohol (593), and independent saponification of (S)-ester (592), by means of KOH (aq.) in DMSO gave (S)-amorfrutin D 523 in 93% and 97% yield, respectively.^[96,407] In agreement with the results obtained in Ogura's study,^[406] synthetic (S)-amorfrutin D 523 displayed an

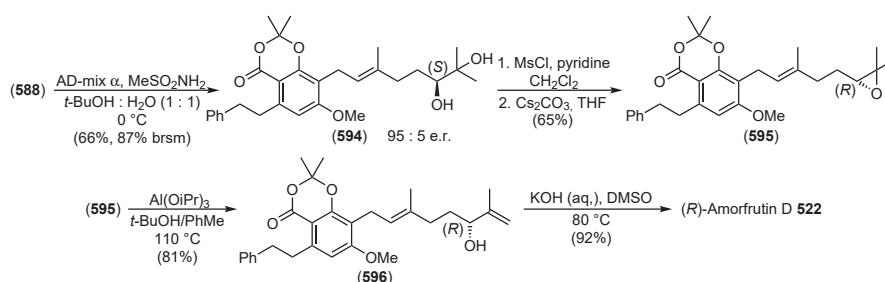
optical rotation of $[\alpha]_D^{26} -4.5^\circ$ ($c = 0.40$, acetone), which is different in sign and value to the one reported for natural amorfrutin D $[\alpha]_D^{22} +31^\circ$ ($c = 0.14$, acetone), but similar to the one obtained by Ogura $[\alpha]_D^{21} -3.5^\circ$ ($c = 0.41$, acetone).



Scheme 5.16: Endgame in the total synthesis of amorfrutin **523**.

The synthesis of (R)-amorfrutin D **522** uneventfully proceeded a similar way. Treatment of methyl ether (**588**) with AD-mix- α gave (S)-diol (**594**) in 66% yield (87% corrected for recovered starting material), with an enantiomeric ratio of 95 : 5 as determined *via* the formation of Mosher's ester as determined *via* ^{19}F -NMR-analysis, Scheme 5.17. Reaction of (S)-diol (**594**) with mesyl chloride and pyridine in CH_2Cl_2 , followed by the addition of Cs_2CO_3 gave (R)-epoxide (**595**) in 65% yield. Epoxide rearrangement reaction by treatment of (R)-epoxide (**595**) with $\text{Al}(\text{OiPr})_3$ in *tert*-butanol and PhMe furnished (R)-allylic alcohol (**596**) in 81% yield. Saponification of (R)-allylic alcohol (**596**) by means of KOH (aq.) in DMSO gave (R)-amorfrutin D **522** in 92% yield, thus completing the total synthesis of both enantiomers of amorfrutin D. Synthetic (R)-amorfrutin D **522** displayed an optical rotation of $[\alpha]_D^{25.7} +2.1^\circ$ ($c = 0.40$, acetone), which is agreement with the result obtained for synthetic (R)-amorfrutin D **522** by Ogura $[\alpha]_D^{21} +4.0^\circ$ ($c = 0.42$, acetone)^[407] and similar in sign to natural amorfrutin D $[\alpha]_D^{22} +31^\circ$ ($c = 0.14$, acetone).^[382] Finally, the ^1H -NMR and $^{13}\text{C}\{^1\text{H}\}$ -NMR-data obtained from synthetic (S)-amorfrutin D **523** matched those reported for synthetic **523** by Ogura,^[407] see

Table 7, while the ^1H -NMR and $^{13}\text{C}\{^1\text{H}\}$ -NMR-data obtained from synthetic (R)-amorfrutin D **522** were in agreement with the ones reported for natural amorfrutin D,^[382] see Table 8.



Scheme 5.17: Endgame in the total synthesis of amorfrutin **522**.

Conclusion

In conclusion, this work, together with Calum Patel's work demonstrates the utility of biomimetic polyketide aromatization reactions to synthesize the amorfrutins **47**, **127**, **520**, **522** and **523** from common precursors. The study followed a biosynthetic proposal of amorfrutin interconversion where core structures of amorfrutin A and C were synthesized and derivatized at a late stage towards the natural products. Conversely, the late stage conversion of a common precursor of amorfrutin B and D followed this strategy. Furthermore, a useful secondary aromatization product was isolated, which was converted into a diiodo analog, thereby concluding a formal synthesis of amorfrutin C as well as enabling the synthesis of other C₅ derivatives.

Future Outlook

For future work, transfer of all synthesized amorfrutin natural products, analogs and their intermediates to collaborators for biological evaluation should provide valuable information for further pharmaceutical hit and lead optimisation studies. Furthermore, the synthetic protocol could be applied to the synthesis of amorfrutin **2** **521**,^[380] as well as other bioactive resorcyate

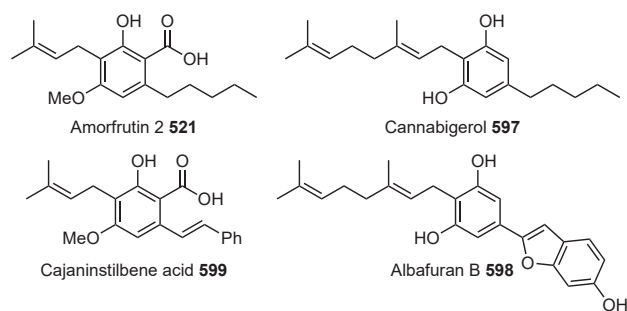
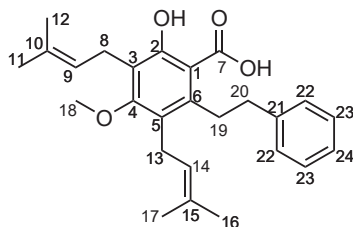


Figure 22: Possible future targets.

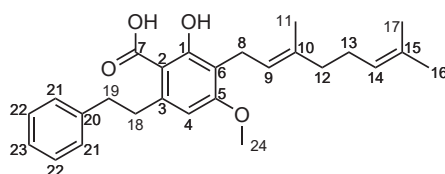
natural products, such as cannabigerol **597**, albufuran B **598** or cajaninstilbene acid **599** and their analogs, Figure 22.^[398,399,426–428]

NMR Data Comparison



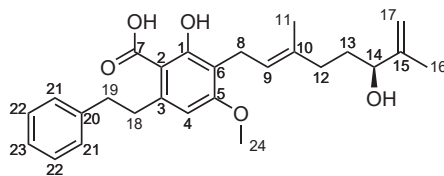
Position	Literature data ^[402]		synthetic 47	
	δ_C	δ_H (mult, <i>J</i> in Hz)	δ_C	δ_H (mult, <i>J</i> in Hz)
1	110.7		111.0	
2	162.5		162.6	
3	126.8		126.8	
4	161.8		161.8	
5	126.8		126.8	
6	143.7		143.7	
7	174.9		175.1	
8	24.3	3.36 - 3.33 (m)	24.3	3.38 - 3.34 (m)
9	122.0	5.24 (t, <i>J</i> = 6.6)	122.0	5.27 - 5.18 (m)
10	132.0		132.1	
11	25.8	1.77 (s)	25.8	1.78 (d, <i>J</i> = 1.3)
12	18.0	1.65 (s)	18.0	1.68 (s)
13	26.3	3.36 - 3.33 (m)	26.2	3.38 - 3.34 (m)
14	124.3	5.02 (m)	124.4	5.05 - 4.97 (m)
15	131.9		131.9	
16	25.9	1.70 (s)	25.9	1.73 (d, <i>J</i> = 1.3)
17	18.2	1.67 (s)	18.2	1.68 (s)
18	61.9	3.66 (s)	61.9	3.69 (s)
19	34.3	3.25 - 2.98 (m)	34.4	3.24 - 3.16 (m)
20	38.7	2.78 - 2.76	38.7	2.83 - 2.74 (m)
21	143.5		143.4	
22	129.2	7.23 (t, <i>J</i> = 7.4)	129.3	7.29 - 7.22 (m)
23	129.2	7.19 - 7.17 (m)	129.3	7.22 - 7.13 (m)
24	125.7	7.13 (t, <i>J</i> = 7.2)	125.8	7.22 - 7.13 (m)

Table 5: ^1H -NMR (400 MHz, CD_3OD) and $^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CD_3OD) data comparison of synthetic amorfrutin C 47 and natural 47 from literature.^[402]



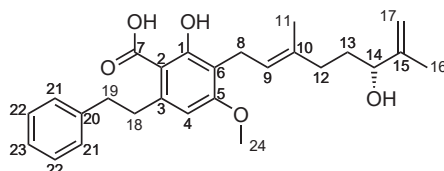
Position	Literature data ^[394]		synthetic 520	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)
1	160.0		163.1	
2	108.4		103.8	
3	144.5		145.9	
4	108.3	6.01 (s)	106.6	6.23 (s)
5	161.2		162.3	
6	114.5		115.6	
7	176.8		175.9	
8	22.3	3.26 (d, $J = 6.8$)	22.1	3.37 (d, $J = 7.1$)
9	123.1	5.03 (t, $J = 6.8$)	122.2	5.27 – 5.19 (m)
10	134.9		135.4	
11	16.2	1.71 (s)	16.3	1.80 (d, $J = 1.4$)
12	40.0	1.87 (s)	40.0	1.99 (dd, $J = 9.4, 6.0$)
13	27.0	1.99 (m)	26.9	2.07 (t, $J = 8.1$)
14	124.7	5.16 (t, $J = 6.8$)	124.6	5.09 (dddd, $J = 8.5, 7.0, 2.8, 1.4$)
15	131.2		131.3	
16	25.8	1.62 (s)	25.8	1.66 (d, $J = 1.5$)
17	17.8	1.53 (s)	17.8	1.59 (d, $J = 1.3$)
18	37.8	3.16 (m)	39.4	3.32 – 3.25 (m)
19	37.9	2.73 (m)	38.3	2.97 – 2.91 (m)
20	142.7		142.0	
21	128.5	7.01 – 6.99 (m)	128.7	7.25 – 7.17 (m)
22	128.3	7.01 – 6.99 (m)	128.5	7.36 – 7.28 (m)
23	124.7	7.01 – 6.99 (m)	126.1	7.25 – 7.17 (m)
24	55.4	3.66 (s)	55.7	3.80 (s)

Table 6: ^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3) data comparison of synthetic amorfrutin B **520** and natural **520** from literature.^[394]



Position	Literature data ^[407]		synthetic 523	
	δ_C	δ_H (mult, <i>J</i> in Hz)	δ_C	δ_H (mult, <i>J</i> in Hz)
1	162.0		162.1	
2	103.6		104.0	
3	145.6		145.8	
4	106.3	6.20 (s)	106.5	6.20 (s)
5	162.9		163.0	
6	115.0		115.2	
7	174.9		175.5	
8	21.9	3.35 (d, <i>J</i> = 7.2)	22.0	3.36 (d, <i>J</i> = 7.1)
9	122.8	5.28 - 5.23 (m)	123.1	5.31 - 5.23 (m)
10	134.9		135.0	
11	16.0	1.80 (s)	16.2	1.83 - 1.79 (m)
12	35.9	2.10 - 1.98 (m)	36.1	2.10 - 1.99 (m)
13	32.9	1.73 - 1.59 (m)	33.1	1.70 - 1.62 (m)
14	75.8	4.03 (t, <i>J</i> = 6.3)	76.0	4.05 (t, <i>J</i> = 6.3)
15	147.3		147.4	
16	17.7	1.73 - 1.59 (m)	17.9	1.71 (s)
17	110.9	4.89 (t, <i>J</i> = 0.9), 4.80 (<i>J</i> = 1.5)	111.1	4.89 (s, <i>Htrans</i>), 4.81 (t, <i>J</i> = 1.7, <i>Hcis</i>)
18	39.2	3.25 (dd, <i>J</i> = 9.3, 6.6)	39.4	3.30 - 3.22 (m)
19	38.1	2.91 (dd, <i>J</i> = 9.3, 6.6)	38.3	2.91 (dd, <i>J</i> = 9.5, 6.3)
20	141.9		142.1	
21	128.5	7.22 - 7.17 (m)	128.7	7.20 (dt, <i>J</i> = 9.3, 3.0)
22	128.3	7.31 - 7.27 (m)	128.5	7.34 - 7.26 (m)
23	125.9	7.22 - 7.17 (m)	126.0	7.20 (dt, <i>J</i> = 9.3, 3.0)
24	55.5	3.78 (s)	55.7	3.78 (d, <i>J</i> = 3.4)

Table 7: ^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3) data comparison of synthetic (*S*)-amorfrutin D **523** and **523** from literature (recorded at: ^1H -NMR (600 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR (150 MHz, CDCl_3)).^[407]



Position	Literature data ^[382]		synthetic 522	
	δ_C	δ_H (mult, J in Hz)	δ_C	δ_H (mult, J in Hz)
1	162.5		163.0	
2	103.2		104.0	
3	14.4		145.9	
4	105.9	6.20 (s)	106.5	6.20 (s)
5	161.7		162.2	
6	114.7		115.3	
7	174.2		175.5	
8	21.7	3.36 (d, $J = 7.0$)	22.1	3.36 (d, $J = 7.1$)
9	122.7	5.25 (t, $J = 7.0$)	123.1	5.26 (tq, $J = 7.1, 1.4$)
10	134.5		135.0	
11	15.8	1.80 (s)	16.2	1.80 (d, $J = 1.3$)
12	35.6	2.03 (m)	36.1	2.03 (hept, $J = 7.0$)
13	32.6	1.65 (m)	33.1	1.67 (dtd, $J = 8.3, 6.9, 4.6$)
14	75.6	4.03 (t, $J = 6.2$)	76.1	4.08 - 4.01 (m)
15	147.0		147.4	
16	17.3	1.70 (s)	17.9	1.71 (t, $J = 1.2$)
17	110.6	4.89 (s), 4.80 (s)	111.1	4.89 (dt, $J = 1.9, 1.0$, H _{trans}), 4.81 (p, $J = 1.6$, H _{cis})
18	39.0	3.25 (m)	39.3	3.30 - 3.21 (m)
19	37.8	2.92 (m)	38.3	2.97 - 2.88 (m)
20	141.7		142.1	
21	128.5	7.20 (m)	128.7	7.19 (ddd, $J = 7.4, 3.7, 2.4$)
22	128.3	7.29 (m)	128.5	7.31 - 7.26 (m)
23	125.7	7.20 (m)	126.1	7.19 (ddd, $J = 7.4, 3.7, 2.4$)
24	55.2	3.78 (s)	55.7	3.78 (s)

Table 8: ^1H -NMR (400 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3) data comparison of synthetic (R)-amorfrutin D **522** and natural **522** from literature (recorded at: ^1H -NMR (600 MHz, CDCl_3) and $^{13}\text{C}\{^1\text{H}\}$ -NMR (150 MHz, CDCl_3)).^[382]

Part III

EXPERIMENTAL

GENERAL EXPERIMENTAL

6.1 GENERAL EXPERIMENTAL METHODS

CH_2Cl_2 , $(\text{CH}_2\text{Cl})_2$, $(\text{CH}_3\text{OCH}_2)_2$, Et_2O , CH_3CN , MeOH , EtOH , DMF , THF , and toluene were obtained by filtration through activated alumina columns (Grubbs apparatus) or purchased as extra dry solvents from Acros Organics and stored over 4 Å molecular sieves. HNiPr_2 , NiPr_2Et , NEt_3 , and pyridine were purchased as extra dry reagents and stored over 4 Å molecular sieves. Petroleum ether refers to the fraction of petroleum ether boiling between 40 °C and 60 °C. Commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**108**) was purified by short-path distillation (b.p. 65 - 67 °C at 2 mmHg). *n*-BuLi was titrated against diphenylacetic acid according to the procedure by Kofron and Baclawski.^[429]

Reactions were carried out in oven-dried glassware (200 °C oven temperature) under a nitrogen or argon atmosphere using standard Schlenk techniques. Reactions were magnetically stirred unless otherwise noted. For reactions at elevated temperatures, DrySyn heating mantels and electric heating plates were used. Stated reaction temperatures refer to the external DrySyn temperature. For transfer of reagents or solvents, cannulas and syringes were used, which were flooded with nitrogen or argon before use.

Purification by column chromatography (CC) was performed under elevated pressure (flash CC) on Geduran[®] Si60 silica gel (40 – 63 μm) from Merck KGaA or Fluorochem. After CC, the concentrated fractions were filtered once through cotton wool to remove residual silica. For monitoring reactions, analyzing fractions of CC and measuring R_f values, silica gel F₂₅₄ thin layer chromatography (TLC) plates from Merck KGaA were used. To visualize the analytes, TLC plates were irradiated with UV-light and developed with potassium permanganate or acidic vanillin and warming, where applicable.

6.2 EQUIPMENT AND INSTRUMENTS

Nuclear Magnetic Resonance spectroscopy (NMR) ^1H -NMR, $^{13}\text{C}\{^1\text{H}\}$ -NMR and ^{19}F -NMR spectra were recorded at 25 °C on a *Bruker* AVANCE III HD 400 or 500 MHz spectrometer with cryoprobe. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance as internal standard (for the corresponding data see: H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.* **1997**, 62, 7512-7515).^[430] All NMR spectra were analyzed using MestReNova 12.0 software developed by the *Mestrelab Research S. L.* company. The signals derived from the ^1H -NMR spectra are reported with chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, m = multiplet or a combination of these descriptions), coupling constant (Hz), integration and assignment. Data for $^{13}\text{C}\{^1\text{H}\}$ -NMR are reported with chemical shift and assignment. Assignments of the ^1H -NMR and $^{13}\text{C}\{^1\text{H}\}$ -NMR spectra were made by the analysis of chemical shift and coupling constant values, COSY, DEPT-135, HSQC and HMBC as appropriate. Note that the atom numbering of the signal assignment does not correspond to IUPAC rules.

Mass Spectrometry (MS) High resolution MS spectra were recorded by the Imperial College mass spectrometry service under conditions of electrospray ionization (ES), chemical ionization (CI) or electron ionization (EI).

X-Ray Crystallography Single crystal X-ray diffraction analyses were recorded by the Imperial College X-ray crystallography service.

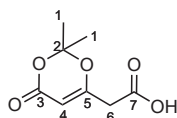
IR Spectroscopy (IR) Spectra of solids and liquids were recorded on a *PerkinElmer* Spectrum BX II FT-IR or *Agilent* Cart 630 FTIR device. The neat substance was directly applied as thin film on the ATR unit. The IR data are reported as measured wavenumbers (cm^{-1}) followed by the corresponding relative band intensities in brackets. The abbreviations vs (very strong), s (strong), m (medium) and w (weak), vw (very weak) and br (broad) stand for relative intensities.

Optical Rotations $[\alpha]$ Measurements were performed on a *Bellingham + Stanley* ADP400+ polarimeter with specific temperatures and concentrations.

Melting Points (mp) Melting points were recorded on a *Lambda* SRS MPA100 OptiMelt melting point apparatus and are uncorrected.

Elemental Analysis Combustion microanalysis were performed by the University of Cambridge Microanalysis Department.

SYNTHESIS OF COMPOUNDS

2-(2,2-DIMETHYL-4-OXO-4*H*-1,3-DIOXIN-6-YL)ACETIC ACID (**140**)

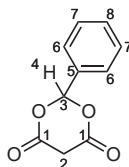
Synthesized according to literature procedure by Barrett et. al.^[105] To a solution of $(\text{Me}_3\text{Si})_2\text{NH}$ (52.4 mL, 250 mmol, 1.10 eq) in THF (200 mL) at -78°C was added *n*-BuLi in hexane (2.5 M; 100 mL, 250 mmol, 1.100 eq), the resulting mixture was gradually warmed to 0°C for 30 min and re-cooled back to -78°C . 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (**108**) (30.2 mL, 227 mmol, 1.00 eq) was added dropwise with stirring at -78°C . After 1 h, CO_2 gas was bubbled through the solution for 20 min and the resulting mixture was warmed to 0°C for over 2 h. An aqueous hydrochloric acid solution (4 M) was added until a pH ~ 1 was reached and the mixture was diluted with EtOAc (200 mL). The aqueous phase was extracted with EtOAc (5 x 150 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate concentrated under reduced pressure to afford 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid (**140**) (40.0 g, 215 mmol, 95%) as a white solid.

^1H -NMR (400 MHz, CDCl_3): δ (ppm) 10.51 (s, 1H, -OH), 5.44 (d, $J = 0.7$ Hz, 1H, H4), 3.33 (d, $J = 0.6$ Hz, 2H, H6), 1.72 (s, 6H, H1).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 171.3 (C7), 162.8 (C5), 160.6 (C3), 107.3 (C2), 96.6 (C4), 38.7 (C6), 24.7 (2 x C1).

mp.: 104°C - 105°C .

Analytic data were in good agreement with literature values.^[105]

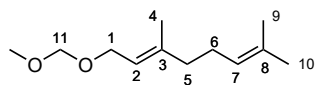
2-PHENYL-1,3-DIOXANE-4,6-DIONE (**141**)

Synthesized according to literature procedure by Barrett et. al.:^[105] To a suspension of malonic acid (52.0 g, 500 mmol, 1.00 eq) in Ac_2O (142 mL, 3.00 eq) was added concentrated H_2SO_4 (0.500 mL) and the resulting mixture was stirred for 15 h. PhCHO (51.0 mL, 500 mmol, 1.00 eq) was added dropwise with stirring at 25 °C. After 1 h, the resulting mixture was left to stand at 5 °C for over 18 h. PhMe (150 mL) was added and the reaction mixture was concentrated under reduced pressure (excess Ac_2O and AcOH were removed by the addition and co-evaporation with PhMe until a solid mixture was obtained). The solid was filtered off and washed with H_2O (2 x 100 mL) and Et_2O (25 mL). The solid was dissolved in acetone (300 mL) and an ice-water mixture (500 mL) was added with stirring. After 15 min, the precipitate was filtered off, washed with ice-cold water (100 mL), Et_2O (25 mL) and dried *in vacuo* to afford 2-phenyl-1,3-dioxane-4,6-dione (**141**) (49.3 g, 257 mmol, 51%) as a white powder.

^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 7.60 – 7.53 (m, 2H, H6), 7.53 – 7.46 (m, 3H, H7 + H8), 6.80 (s, 1H, H4), 3.83 (d, J = 18.8 Hz, 1H, H2), 3.66 (d, J = 18.8 Hz, 1H, H2).
 $^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 163.2 (C1), 132.3 (C5), 131.2 (C8), 129.2 (2 x C7), 126.5 (2 x C, C6), 98.1 (C3), 39.2 (C2).

mp.: 145 °C-146 °C.

Analytic data were in good agreement with literature values.^[105]

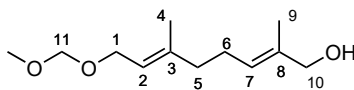
(E)-1-(methoxymethoxy)-3,7-dimethylocta-2,6-diene (**306**)

Synthesized according to a modified literature procedure by Bode et. al.^[223] To an ice-cold solution of *(E)*-3,7-dimethylocta-2,6-dien-1-ol **298** (1.54 g, 1.75 mL, 10.0 mmol, 1.00 eq) in CH₂Cl₂ (25.0 mL) NiPr₂Et (6.46 g, 8.71 mL, 50.0 mmol, 5.00 eq) were added in one portion. MOMCl (1.61 g, 1.52 mL, 20.0 mmol, 2.00 eq) was added dropwise. The resulting suspension was stirred for 20 h at RT. The reaction was quenched with a saturated aqueous ammonium chloride solution (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (2 * 20 mL). The combined organic layers were dried over sodium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3:1 pentane:Ether) afforded *(E)*-1-(methoxymethoxy)-3,7-dimethylocta-2,6-diene (**306**) (2.03 g, 10.2 mmol, 90%) as colourless oil.

R_f (hexane:EtOAc 3:1) = 0.59.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.36 (tq, *J* = 7.0, 1.3 Hz, 1H, H₂), 5.09 (dddt, *J* = 6.9, 4.4, 2.9, 1.6 Hz, 1H, H₇), 4.63 (s, 2H, H₁₁), 4.12 – 4.03 (m, 2H, H₁), 3.38 (s, 3H, -OMe), 2.16 – 2.07 (m, 2H, H₆), 2.07 – 2.01 (m, 2H, H₅), 1.68 (t, *J* = 1.6 Hz, 6H, H₄ and H₉), 1.60 (d, *J* = 1.3 Hz, 3H, H₁₀).

Analytic data were in good agreement with literature values.^[223]

(2*E*,6*E*)-8-(methoxymethoxy)-2,6-dimethylocta-2,6-dien-1-ol (**307**)

Synthesized according to a modified literature procedure by Garg et. al.:^[225] To a suspension of SeO_2 (226 mg, 20.4 mmol, 0.40 eq) in CH_2Cl_2 (25.0 mL) was added *tert*-butyl hydroperoxide (5.5 M in decane; 29.0 mL, 15.8 mmol, 3.10 eq) in one portion. The resulting mixture was stirred for 10 min at RT after which (*E*)-1-(methoxymethoxy)-3,7-dimethylocta-2,6-diene (**306**) (1.01 g, 5.09 mmol, 1.00 eq) was added in one portion. The resulting suspension was stirred for 1.5 h at RT. The reaction was concentrated under reduced pressure and the residue was taken up in EtOAc (20 mL). The organic layer was washed with water (2 * 20 mL), a saturated aqueous sodium hydrocarbonate solution (20 mL), water (20 mL) and a saturated aqueous sodium chloride solution (20 mL). The combined aqueous layers were re-extracted with EtOAc (20 mL) and the combined organic layers were dried over magnesium sulphate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : Et_2O -> 1 : 1 -> 1 : 2) afforded (2*E*,6*E*)-8-(methoxymethoxy)-2,6-dimethylocta-2,6-dien-1-ol (**307**) (403 mg, 1.88 mmol, 37%) as colourless to pale-yellow oil.

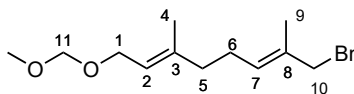
R_f (hexane : EtOAc 3 : 1) = 0.09.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 5.36 (dtq, J = 9.6, 7.0, 1.4 Hz, 2H, H₂ and H₇ overlap), 4.63 (s, 2H, H₁₁), 4.07 (dq, J = 6.9, 0.7 Hz, 2H, H₁), 3.99 (d, J = 5.3 Hz, 2H, H₁₀), 3.38 (s, 3H, -OMe), 2.22 – 2.12 (m, 2H, H₆), 2.09 (dd, J = 8.9, 6.2 Hz, 2H, H₅), 1.68 (d, J = 1.3 Hz, 3H, H₄), 1.66 (d, J = 1.3 Hz, 3H, H₉).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 140.5 (C₃), 135.3 (C₈), 125.8 (C₇), 120.7 (C₂), 95.7 (C₁₁), 69.2 (C₁₀), 63.8 (C₁), 55.3 (-OCH₃), 39.3 (C₅), 25.9 (C₆), 16.5 (C₄), 13.8 (C₉).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3430 (br, s), 2919 (m), 2881 (m), 1669 (w), 1443 (m), 1384 (m), 1213 (m), 1147 (s), 1100 (s), 1041 (vs), 921 (m).

HRMS (ES-ToF) m/z : $[\text{M} - \text{OH}]^+$ calc. for $(\text{C}_{12}\text{H}_{21}\text{O}_2)^+$: 197.1536, found: 197.1547.

(2*E*,6*E*)-1-bromo-8-(methoxymethoxy)-2,6-dimethylocta-2,6-diene (**308**)

Synthesized according to a modified literature procedure by Kobayashi et. al.^[210] To an ice-cold solution of (2*E*,6*E*)-8-(methoxymethoxy)-2,6-dimethylocta-2,6-dien-1-ol (**307**) (488 mg, 2.28 mmol, 1.00 eq) in Et₂O (13.0 mL) CBr₄ (1.51 g, 4.55 mmol, 2.00 eq) was added in one portion. PPh₃ (1.19 g, 4.55 mmol, 2.00 eq) was added in two portions. The resulting suspension was stirred for 16 h at RT. The reaction was diluted with CH₂Cl₂ (15 mL) and quenched with a saturated aqueous sodium hydrogen carbonate solution (20 mL). The aqueous layer was extracted with CH₂Cl₂ (2 * 20 mL) and the combined organic layers were dried over magnesium sulphate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in a small amount of CH₂Cl₂ and loaded onto a column through a Celite pad. Purification by flash column chromatography (9 : 1 pentane : Et₂O) afforded (2*E*,6*E*)-1-bromo-8-(methoxymethoxy)-2,6-dimethylocta-2,6-diene (**308**) (489 mg, 1.76 mmol, 77%) as colourless oil.

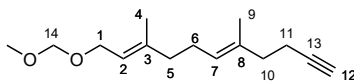
R_f (hexane : EtOAc 3 : 1) = 0.55.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.62 – 5.54 (m, 1H, H7), 5.36 (ddq, *J* = 8.2, 6.9, 1.3 Hz, 1H, H2), 4.63 (s, 2H, H11), 4.07 (dq, *J* = 6.9, 0.7 Hz, 2H, H1), 3.96 (d, *J* = 0.7 Hz, 2H, H10), 3.38 (s, 3H, -OMe), 2.21 – 2.12 (m, 2H, H6), 2.08 (dd, *J* = 9.0, 6.3 Hz, 2H, H5), 1.75 (dt, *J* = 1.5, 0.9 Hz, 3H, H9), 1.69 (d, *J* = 1.0 Hz, 3H, H4).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 140.2 (C3), 132.4 (C8), 130.8 (C7), 120.9 (C2), 95.7 (C11), 63.7 (C1), 55.3 (O-CH₃), 41.8 (C10), 38.8 (C5), 26.7 (C6), 16.5 (C4), 14.8 (C9).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2979 (w), 2925 (m), 2881 (m), 1666 (vw), 1440 (m), 1387 (m), 1206 (m), 1148 (s), 1103 (s), 1044 (vs), 920 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₂H₂₂BrO₂)⁺: 277.0798, found: 277.0791.

(5*E*,9*E*)-11-(methoxymethoxy)-5,9-dimethylundeca-5,9-dien-1-yne (**310**)

Synthesized using a modified literature procedure by Wulff et. al.^[209] To a dry-ice cold solution of 1-trimethylsilyl propyne (257 mg, 0.330 mL, 2.29 mmol, 1.30 eq) in THF (2.00 mL) *n*-BuLi (2.30 M; 1.00 mL, 2.29 mmol, 1.30 eq) was added dropwise. The resulting solution was stirred at -78°C for 2 h. A solution of (2*E*,6*E*)-1-bromo-8-(methoxymethoxy)-2,6-dimethylocta-2,6-diene (**308**) (489 mg, 1.76 mmol, 1.00 eq) in THF (2.00 mL) was added dropwise. The resulting suspension was stirred for 7 h at -78°C and then allowed to warm to RT where it was further stirred for 13 h. The reaction was quenched with an aqueous 10% (w:v) citric acid solution (5 mL) and the aqueous layer was extracted with Et₂O (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. This afforded a pale-yellow oil containing ((5*E*,9*E*)-11-(methoxymethoxy)-5,9-dimethylundeca-5,9-dien-1-yn-1-yl)trimethylsilane (**309**) which was used for the next step without further purification.

To an ice-cold solution of the obtained oil in THF (4.00 mL) was added a solution of TBAF in THF (1 M; 2.65 mL, 2.65 mmol, 1.50 eq) dropwise. The reaction mixture was stirred for 20 h at RT. The reaction was quenched with an aqueous 10% (w:v) citric acid solution (5 mL) and the aqueous layer was extracted with Et₂O (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by column chromatography (pentane : Et₂O 9 : 1) afforded (5*E*,9*E*)-11-(methoxymethoxy)-5,9-dimethylundeca-5,9-dien-1-yne (**310**) (284 mg, 1.20 mmol, 68%) as colourless oil.

R_f (hexane : EtOAc 6 : 1) = 0.46.

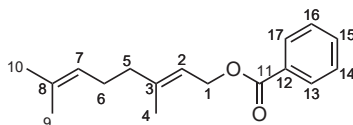
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.36 (dddd, J = 7.0, 5.6, 2.7, 1.4 Hz, 1H, H₂), 5.23 – 5.12 (m, 1H, H₇), 4.63 (s, 2H, H₁₄), 4.09 – 4.05 (m, 2H, H₁), 3.38 (s, 3H, -OMe), 2.30 – 2.24 (m, 2H, H₁₁), 2.20 (d, J = 6.9 Hz, 2H, H₁₀), 2.16 – 2.09 (m, 2H, H₆), 2.09 – 2.03 (m, 2H, H₅), 1.94 (t, J = 2.5 Hz, 1H, H₁₂), 1.68 (d, J = 1.2 Hz, 3H, H₄), 1.61 (d, J = 1.2 Hz, 2H, H₉).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 140.8 (C₃), 133.7 (C₈), 125.3 (C₇), 120.5 (C₂), 95.6 (C₁₄), 84.5 (C₁₃), 68.5 (C₁₂), 63.8 (C₁), 55.3 (-OCH₃), 39.6 (C₅), 38.5 (C₁₀),

26.4 (C6), 17.7 (C11), 16.5 (C4), 15.9 (C9).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3313 (w), 2953 (m), 2922 (vs), 2853 (m), 1735 (m), 1458 (m), 1379 (m), 1149 (s), 1101 (s), 1047 (vs), 921 (m), 630 (m).

HRMS (ES-ToF) m/z : $[\text{M}]^+$ calc. for $(\text{C}_{15}\text{H}_{24}\text{O}_2)^{+}$: 236.1771, found: 236.1770.

(E)-3,7-dimethylocta-2,6-dien-1-yl benzoate (311)

Synthesized according to literature procedure by Armstrong and Weiler:^[207] To a solution of (*E*)-3,7-dimethylocta-2,6-dien-1-ol **298** (6.16 g, 7.00 mL, 40.0 mmol, 1.00 eq) in Et₂O (120 mL) pyridine (6.33 g, 6.48 mL, 80.0 mmol, 2.00 eq) and DMAP (978 mg, 8.00 mmol, 0.20 eq) were added in one portion. Benzoyl chloride (6.19 g, 5.11 mL, 44.0 mmol, 1.10 eq) was added dropwise. The resulting suspension was stirred for 20 h at RT. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution (30 mL), the layers were separated and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution (2 * 40 mL), an aqueous hydrochloric acid solution (1 M; 3 * 30 mL) and a saturated aqueous sodium chloride solution (2 * 40 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure to afford (*E*)-3,7-dimethylocta-2,6-dien-1-yl benzoate (**311**) (9.23 g, 35.7 mmol, 90%) as colourless oil.

R_f (hexane : EtOAc 6 : 1) = 0.46.

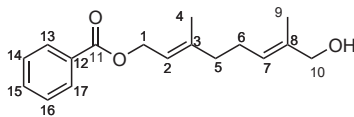
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 8.08 – 8.03 (m, 2H, H₁₃ + H₁₇), 7.58 – 7.53 (m, 1H, H₁₅), 7.43 (dd, *J* = 8.4, 7.0 Hz, 2H, H₁₄ + H₁₆), 5.47 (tp, *J* = 7.0, 1.3 Hz, 1H, H₂), 5.09 (ddq, *J* = 8.3, 5.6, 1.5 Hz, 1H, H₇), 4.84 (dq, *J* = 7.1, 0.7 Hz, 2H, H₁), 2.19 – 2.10 (m, 2H, H₆), 2.10 – 2.04 (m, 2H, H₅), 1.77 (d, *J* = 1.7 Hz, 3H, H₄), 1.67 (d, *J* = 1.3 Hz, 3H, H₉), 1.61 (d, *J* = 1.3 Hz, 3H, H₁₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 166.8 (C₁₁), 142.5 (C₃), 132.9 (C₁₅), 132.0 (C₇), 130.7 (C₁₂), 129.7 (C₁₃ + C₁₇), 128.4 (C C₁₄ + C₁₆), 123.9 (C₇), 118.5 (C₂), 62.0 (C₁), 39.7 (C₅), 26.5 (C₆), 25.8 (C₉), 17.9 (C₁₀), 16.7 (C₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2918 (m), 1716 (vs), 1601 (w), 1450 (m), 1375 (m), 1313 (m), 1267 (vs), 1107 (s), 1069 (m), 1026 (m), 934 (m), 710 (vs).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₇H₂₃O₂)⁺: 259.1693, found: 259.1705.

Analytical data were in good agreement with literature values.^[207] *Note*: When the reaction was carried out on a 70 mmol scale, the yield was 96%. On a 100 mmol scale the yield was converging to 99%.

(2*E*,6*E*)-8-HYDROXY-3,7-DIMETHYLOCTA-2,6-DIEN-1-YL BENZOATE (**312**)

Synthesized according to literature procedure by Corey et. al.:^[211] To a solution of (*E*)-3,7-dimethylocta-2,6-dien-1-yl benzoate (**311**) (10.0 g, 38.7 mmol, 1.00 eq) in CH_2Cl_2 (150 mL) SeO_2 (429 mg, 3.87 mmol, 0.1 eq) and *tert*-butyl hydroperoxide (70 wt. % in H_2O ; 15.7 mL, 77.4 mmol, 2.00 eq) were added in one portion. The resulting emulsion was stirred for 30 h at RT. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 * 50 mL). The combined organic layers were washed with water (50 mL) and a saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure (excess of *tert*-butyl hydroperoxide was removed by the addition and co-evaporation with toluene). The obtained crude oil was used without further purification.

To an ice-cold solution of the crude oil in MeOH (110 mL) was added NaBH_4 (350 mg, 9.28 mmol, 0.24 eq) in several portions over 30 min. The reaction was stirred at 0 °C for 2 h. The reaction was concentrated under reduced pressure, the residue was taken up in Et_2O (100 mL) and the mixture was quenched with water (50 mL). The aqueous layer was extracted with Et_2O (3 * 50 mL) and the combined organic layers were washed with water (50 mL) and a saturated aqueous sodium chloride solution. The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (2 : 1 pentane : Et_2O -> 1 : 1) afforded (2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl benzoate (**312**) (6.07 g, 22.1 mmol, 57%) as colourless oil.

R_f (hexane : EtOAc 4 : 1) = 0.19.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 8.11 – 8.00 (m, 2H, H₁₃ + H₁₇), 7.60 – 7.50 (m, 1H, H₁₅), 7.43 (t, J = 7.7 Hz, 2H, H₁₄ + H₁₆), 5.47 (tq, J = 7.0, 1.4 Hz, 1H, H₂), 5.37 (tt, J = 7.0, 1.5 Hz, 1H, H₇), 4.84 (d, J = 7.0 Hz, 2H, H₁), 3.97 (s, 2H, H₁₀), 2.26 – 2.14 (m, 2H, H₆), 2.16 – 2.06 (m, 2H, H₅), 1.77 (d, J = 1.2 Hz, 3H, H₄), 1.66 (d, J = 1.3 Hz, 3H, H₉), 1.43 (s, 1H, -OH).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 166.8 (C₁₁), 141.9 (C₃), 135.4 (C₈), 133.0 (C₁₅), 130.6 (C₁₂), 129.7 (C₁₃ + C₁₇), 128.5 (C₁₄ + C₁₆), 125.4 (C₇), 119.0 (C₂),

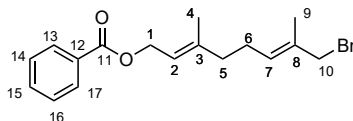
69.0(C10), 62.0 (C1), 39.2 (C5), 25.8 (C6), 16.7 (C4), 13.8 (C9).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3417 (m, br), 2916 (m), 1857 (m), 1715 (vs), 1601 (w), 1450 (m), 1320 (m), 1269 (vs), 1108 (m), 1070 (m), 1025 (m), 1014 (w), 936 (m), 711 (vs).

HRMS (ES-ToF) m/z : [M + Na]⁺ calc. for (C₁₇H₂₂O₃ + Na)⁺: 297.1461, found: 297.1471.

Analytical data were in good agreement with literature values.^[207,211]

Note: On larger scale reactions (100 mmol) the yield of allylic alcohol (**312**) significantly decreased, presumably due to deprotection, as methyl benzoate (4.70 g, 54%) was obtained. 1,2-Dimethoxyethane was a suitable substitute for MeOH as solvent for the reduction step: To a solution of (*E*)-3,7-dimethylocta-2,6-dien-1-yl benzoate (**311**) (25.6 g, 99.1 mmol, 1.00 eq) in CH₂Cl₂ (300 mL) was added SeO₂ (1.10 g, 9.91 mmol, 0.10 eq), and *tert*-butyl hydroperoxide (70 wt % in H₂O; 40.2 mL, 198 mmol, 2.00 eq) sequentially in one portion. After stirring for 30 h at RT, workup as described above and removal of volatiles *via* co-evaporation with PhMe gave a crude oil which was used in the next step without further purification. To the ice-cold crude oil in 1,2-dimethoxyethane (100 mL) was added NaBH₄ (900 mg, 23.8 mmol, 0.24 eq) in several portions over 30 min. Workup as described above and flash column chromatography (2 : 1 pentane : Et₂O → 1 : 1) gave (*2E,6E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl benzoate (**312**) (15.0 g, 54.7 mmol, 56%) as a colourless oil.

(2*E*,6*E*)-8-BROMO-3,7-DIMETHYLOCTA-2,6-DIEN-1-YL BENZOATE (**313**)

Synthesized using a modified literature procedure by Kobayashi et. al.:^[210] To an ice-cold solution of (2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl benzoate (**312**) (1.30 g, 4.05 mmol, 1.00 eq) in Et₂O (50.0 mL) was added CBr₄ (3.14 g, 9.46 mmol, 2.00 eq) in one portion. PPh₃ (2.48 g, 9.46 mmol, 2.00 eq) was added in several portions over 15 min. The resulting suspension was stirred for 18 h at RT. The reaction was diluted with CH₂Cl₂ (20 mL) and quenched with a saturated aqueous sodium hydrogen carbonate solution (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 * 40 mL) and the combined organic layers were washed with a saturated aqueous sodium hydrogen carbonate solution (30 mL) and dried over magnesium sulphate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in a small amount of CH₂Cl₂ and loaded onto a column through a Celite pad. Purification by flash column chromatography (100 % pentane → 4 : 1 pentane : Et₂O) afforded (2*E*,6*E*)-8-bromo-3,7-dimethylocta-2,6-dien-1-yl benzoate (**313**) (1.44 g, 4.28 mmol, 91%) as colourless oil.

R_f (hexane : EtOAc 3 : 1) = 0.61.

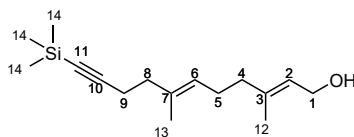
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 8.11 – 7.98 (m, 2H, H₁₃ + H₁₇), 7.61 – 7.50 (m, 1H, H₁₅), 7.49 – 7.39 (m, 2H, H₁₄ + 16), 5.63 – 5.53 (m, 1H, H₇), 5.47 (ddq, *J* = 7.1, 5.6, 1.3 Hz, 1H, H₂), 4.91 – 4.79 (m, 2H, H₁), 3.95 (d, *J* = 0.7 Hz, 2H, H₁₀), 2.23 – 2.15 (m, 2H, H₆), 2.15 – 2.08 (m, 2H, H₅), 1.77 (d, *J* = 1.3 Hz, 3H, H₄), 1.76 (q, *J* = 0.9 Hz, 3H, H₉).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 166.8 (C₁₁), 141.6 (C₃), 133.0 (C₁₅), 132.6 (C₈), 130.6 (C₇), 130.6 (C₁₂), 129.7 (C₁₃ + C₁₇), 128.5 (C₁₄ + C₁₆), 119.1 (C₂), 61.9 (C₁), 41.8 (C₁₀), 38.7 (C₅), 26.5 (C₆), 16.7 (C₄), 14.8 (C₉).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2933 (m), 2853 (w), 1715 (vs), 1601 (m), 1205 (m), 1313 (m), 1268 (vs), 1205 (m), 1175 (m), 1107 (s), 1097 (s), 1070 (m), 1025 (m), 938 (m), 711 (vs), 608 (m).

HRMS (ES-ToF) *m/z*: [M – OBz]⁺ calc. for (C₁₀H₁₆Br)⁺: 215.0430, 215.0441.

Analytic data were in good agreement with literature values.^[207]

(2*E*,6*E*)-3,7-DIMETHYL-11-(TRIMETHYLSILYL)UNDECA-2,6-DIEN-10-YN-1-OL (**314**)

Synthesized according to literature procedure by Wulff et. al.:^[209] To a dry-ice cold solution of 1-(trimethylsilyl) propyne (2.33 g, 3.07 mL, 20.7 mmol, 4.50 eq) in THF (95.0 mL) *n*-BuLi (2.36 M; 8.75 mL, 20.7 mmol, 4.50 eq) was added dropwise. The resulting solution was stirred at -78°C for 2 h. A solution of (2*E*,6*E*)-8-bromo-3,7-dimethylocta-2,6-dien-1-yl benzoate (**313**) (1.55 g, 4.61 mmol, 1.00 eq) in THF (38.0 mL) was added dropwise. The resulting suspension was stirred for 16 h while gradually warming up to RT. The reaction was quenched with a saturated aqueous ammonium chloride solution (50 mL) and the aqueous layer was extracted with Et₂O (2 * 50 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (pentane : Et₂O 5 : 1 $\rightarrow$ 3 : 1) afforded a crude mixture containing (2*E*,6*E*)-3,7-dimethyl-11-(trimethylsilyl)undeca-2,6-dien-10-yn-1-ol (**314**) as yellow oil, which was used for the next step without further purification.

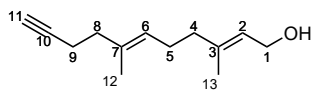
R_f (hexane : EtOAc 3 : 1) = 0.30.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.41 (tq, J = 6.9, 1.3 Hz, 1H, H₂), 5.16 (dddd, J = 6.9, 5.6, 2.6, 1.3 Hz, 1H, H₆), 4.19 – 4.12 (m, 2H, H₁), 2.30 (ddd, J = 7.7, 6.9, 1.1 Hz, 2H, H₉), 2.21 – 2.16 (m, 2H, H₁₀), 2.16 – 2.08 (m, 2H, H₅), 2.07 – 2.00 (m, 2H, H₄), 1.68 (dd, J = 1.3, 0.7 Hz, 3H, H₁₂), 1.60 (q, J = 0.9 Hz, 3H, H₁₃), 1.17 (s, -OH), 0.14 (s, 9H, -SiMe₃).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 139.8 (C₃), 134.0 (C₇), 125.2 (C₆), 123.6 (C₂), 107.5 (C₁₀), 84.8 (C₁₁), 59.6 (C₁), 39.6 (C₄), 38.7 (C₈), 26.4 (C₅), 19.4 (C₉), 16.4 (C₁₂), 16.0 (C₁₃), 0.3 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3330 (s, br), 2956 (m), 2913 (m), 2851 (m), 2173 (m), 1925 (w), 1666 (w), 1441 (m), 1382 (m), 1248 (s), 997 (m), 837 (vs), 759 (s), 697 (m), 646 (m), 638 (m).

HRMS (ES-ToF) m/z : [M – OH]⁺ calc. for (C₁₆H₂₇Si)⁺: 247.1877, found: 247.1890.

(2*E*,6*E*)-3,7-DIMETHYLUNDECA-2,6-DIEN-10-YN-1-OL (**297**)

Synthesized according to literature procedure by Wulff et. al.:^[209] To the above crude oil of (2*E*,6*E*)-3,7-dimethyl-11-(trimethylsilyl)undeca-2,6-dien-10-yn-1-ol (**314**) was added TBAF (1 M in THF; 13.0 mL, 13.0 mmol, 2.82 eq) dropwise. The resulting intense orange-brown solution was stirred for 19 h at RT. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution (20 mL) and the aqueous layer was extracted with Et₂O (2 * 40 mL). The combined organic layers were washed with a saturated aqueous sodium hydrogen carbonate solution (20 mL) and a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (pentane : Et₂O 3 : 1) afforded (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-ol (**297**) (838 mg, 4.36 mmol, 95%) as yellow oil.

R_f (hexane : EtOAc 3 : 1) = 0.26.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.42 (tq, *J* = 6.9, 1.3 Hz, 1H, H₂), 5.18 (ddq, *J* = 8.3, 5.5, 1.3 Hz, 1H, H₆), 4.15 (dd, *J* = 7.2, 3.5 Hz, 2H, H₁), 2.31 – 2.25 (m, 2H, H₉), 2.23 – 2.17 (m, 2H, H₈), 2.17 – 2.10 (m, 2H, H₅), 2.05 (dd, *J* = 9.2, 6.1 Hz, 2H, H₄), 1.95 (t, *J* = 2.6 Hz, 1H, H₁₁), 1.68 (d, *J* = 1.3 Hz, 3H, H₁₃), 1.61 (t, *J* = 1.1 Hz, 3H, H₁₂), 1.13 (s, 1H, -OH).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 139.7 (C₃), 133.7 (C₇), 125.3 (C₆), 123.6 (C₂), 84.5 (C₁₀), 68.5 (C₁₁), 59.6 (C₁), 39.5 (C₄), 38.5 (C₈), 26.3 (C₅), 17.7 (C₉), 16.4 (C₁₃), 16.0 (C₁₂).

IR (Diamond-ATR, neat) *ν*_{max} (cm⁻¹) = 3341 (s, br), 2957 (m), 2917 (m), 2170 (m), 1668 (w), 1437 (m), 1416 (m), 1382 (m), 1288 (2), 1249 (s), 1019 (s), 839 (vs), 759 (s), 697 (m), 654 (m), 917 (w).

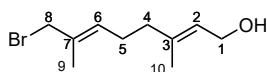
HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₃H₂₁O)⁺: 193.1587, found: 193.1587. Major peak *m/z*: [M – OH]⁺ calc. for (C₁₃H₁₉)⁺: 175.1481, found: 175.1481. Analytical data were in good agreement with literature values.^[209]

Note: For larger scale reactions (>8 mmol) the yield converged to 67 – 72%.

Alternatively this compound was obtained from MOM-ether (**310**) according to the following procedure: To a solution of (5*E*,9*E*)-11-(methoxymethoxy)-5,9-dimethylundeca-5,9-dien-1-yne (**310**) (198 mg, 0.838 mmol, 1.00 eq) in *tert*-butanol (5.00 mL) pyridinium para-toluenesulfonate (PPTS) (842 mg, 3.35 mmol, 4.00 eq) was added in one portion.

The reaction mixture was stirred for 96 h at 85 °C. The reaction was quenched with a saturated aqueous sodium chloride solution (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (2 * 20 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et₂O -> 6 : 1 -> 2 : 1) afforded (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-ol (**297**) (24.0 mg, 0.125 mmol, 15%) as colourless oil.

(2*E*,6*E*)-8-BROMO-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL (**315**)



Synthesised according to the procedure above with 1.2 eq of 1-(trimethylsilyl) propyne and n-BuLi, respectively. Purification by flash column chromatography (pentane : Et₂O 9 : 1 -> 4 : 1 -> 2 : 1) afforded (2*E*,6*E*)-8-bromo-3,7-dimethylocta-2,6-dien-1-ol (**315**) (265 mg, 1.14 mmol, 37%) as pale-yellow oil.

R_f (hexane : EtOAc 3 : 1) = 0.18.

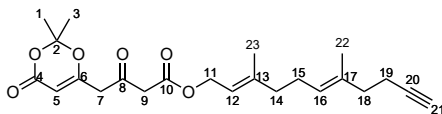
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.57 (td, *J* = 7.0, 1.5 Hz, 1H, H₆), 5.41 (tq, *J* = 6.9, 1.3 Hz, 1H, H₂), 4.15 (d, *J* = 6.9 Hz, 2H, H₁), 3.97 (d, *J* = 0.7 Hz, 2H, H₈), 2.17 (q, *J* = 7.6 Hz, 2H, H₅), 2.07 (dd, *J* = 8.7, 6.4 Hz, 2H, H₄), 1.75 (d, *J* = 1.2 Hz, 3H, H₉), 1.67 (d, *J* = 1.7 Hz, 3H, H₁₀), 1.19 (s, 1H, -OH).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 139.0 (C₃), 132.5 (C₇), 130.8 (C₆), 124.1 (C₂), 59.5 (C₁), 41.9 (C₈), 38.7 (C₄), 26.6 (C₅), 16.4 (C₁₀), 14.8 (C₉).

IR (Diamond-ATR, neat) *ν*_{max} (cm⁻¹) = 3378 (s, br), 2915 (s), 1665 (m), 1437 (s), 1385 (s), 1236 (m), 1204 (vs), 1100 (w), 1070 (w), 999 (vs), 843 (m), 763 (w), 701 (w), 608 (vs).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₂H₁₉O)⁺: 179.1430, found: 179.1440.

(2*E*,6*E*)-3,7-DIMETHYLUNDECA-2,6-DIEN-10-YN-1-YL 4-(2,2-DIMETHYL-4-OXO-4*H*-1,3-DIOXIN-6-YL)-3-OXOBUTANOATE (**296**)



Synthesized using a modified literature procedure by Barrett et. al.^[105] To a solution of 2-phenyl-1,3-dioxane-4,6-dione (**141**) (728 mg, 3.79 mmol, 1.82 eq) and DCC (781 mg, 3.79 mmol, 1.82 eq) in CH₂Cl₂ (32.0 mL) was added DMAP (463 mg, 3.79 mmol, 1.82 eq) in one portion. The solution was stirred for 15 min at RT before 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid (**140**) (705 mg, 3.79 mmol, 1.82 eq) was added in one portion. The resulting yellow-white suspension was stirred for 18 h at RT. The reaction mixture was cooled to 0 °C, the precipitate was filtered off and the solid was washed with small portions of CH₂Cl₂ until the precipitate appeared colourless. The filtrate was washed with an aqueous hydrochloric acid solution (1 M, 2 x 20 mL). The organic layer was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in PhMe (8.00 mL) and a solution of (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-ol (**297**) (400 mg, 2.08 mmol, 1.00 eq) in PhMe (8.00 mL) was added in one portion. The resulting pale yellow solution was heated to 55 °C for 4 h after which the solution was concentrated. Purification by flash column chromatography (9 : 1 pentane : EtOAc -> 7 : 1 -> 4 : 1) afforded (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**296**) (730 mg, 1.81 mmol, 87%) as orange oil.

R_f (hexane : EtOAc 4 : 1) = 0.09.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.36 (d, *J* = 0.6 Hz, 1H, H₅), 5.33 (tq, *J* = 7.2, 1.3 Hz, 1H, H₁₂), 5.15 (ddd, *J* = 5.4, 4.1, 2.8 Hz, 1H, H₁₆), 4.66 (d, *J* = 7.3 Hz, 2H, H₁₁), 3.51 (s, 2H, H₉), 3.50 (s, 2H, H₇), 2.31 – 2.24 (m, 2H, H₁₉), 2.23 – 2.16 (m, 2H, H₁₈), 2.15 – 2.10 (m, 2H, H₁₅), 2.10 – 2.04 (m, 2H, H₁₄), 1.94 (t, *J* = 2.5 Hz, 1H, H₂₁), 1.71 (s, 9H, H₁ + H₃ + H₂₃ overlapping), 1.61 (d, *J* = 1.3 Hz, 3H, H₂₂).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 195.8 (C₈), 166.5 (C₁₀), 163.7 (C₆), 160.6 (C₄), 143.5 (C₁₃), 133.9 (C₁₇), 124.9 (C₁₆), 117.6 (C₁₂), 107.5 (C₂), 97.3 (C₅), 84.5 (C₂₀), 68.6 (C₂₁), 62.8 (C₁₁), 49.3 (C₉), 47.1 (C₇), 39.5 (C₁₄), 38.5 (C₁₈), 26.2 (C₁₅), 25.2 (C₁ + C₃), 17.7 (C₁₉), 16.6 (C₂₃), 16.0 (C₂₂).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3288 (m), 2923 (m), 2855 (w), 2120 (vw), 1724 (vs), 1638 (s), 1389 (s), 1375 (s), 1315 (m), 1272 (s), 1252 (m), 1202 (s), 1154 (m), 1089

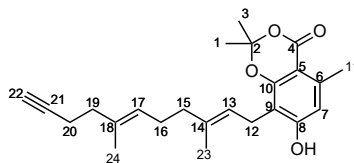
(w), 1059 (w), 1016 (s), 978 (m), 902 (m), 809 (m), 632 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{23}H_{31}O_6)^+$: 403.2115, found: 403.2106.

Major peaks m/z : $[M + Na]^+$ calc. for $(C_{22}H_{30}O_6Na)^+$: 425.1935, found: 425.1947 and

m/z : $[M + K]^+$ calc. for $(C_{22}H_{30}O_6K)^+$: 441.1674, found: 441.1892.

8-((2*E*,6*E*)-3,7-DIMETHYLUNDECA-2,6-DIEN-10-YN-1-YL)-7-HYDROXY-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**293**)



Synthesized using a modified literature procedure by Barrett et. al.^[105] To an ice-cold solution of (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**296**) (289 mg, 0.718 mmol, 1.00 eq) in CH₂Cl₂ (3.60 mL) was added MgCl₂ (68.0 mg, 0.718 mmol, 1.00 eq) and pyridine (114 mg, 120 μL, 1.44 mmol, 2.00 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (85.0 mg, 76.6 μL, 1.08 mmol, 1.50 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (4.30 mL) and tri(2-furyl)phosphine (53.0 mg, 0.228 mmol, 0.32 eq) and Tris(dibenzylideneacetone)dipalladium(o) (35.0 mg, 0.0382 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 1.5 h at RT before caesium acetate (413 mg, 2.15 mmol, 3.00 eq) in 2-propanol 4.30 mL) was added in one portion. The resulting orange-brown solution was stirred for 1.5 h at RT. The reaction mixture was quenched an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc -> 15 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**293**) (129 mg, 0.337 mmol, 47%) as yellow-white solid which solidified upon standing.

Alternatively: To an ice-cold solution of (2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**296**) (401 mg, 0.996 mmol, 1.00 eq) in CH₂Cl₂ (5.00 mL) was added MgCl₂ (95.0 mg, 0.996 mmol,

1.00 eq) and pyridine (158 mg, 161 μ L, 1.99 mmol, 2.00 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (117 mg, 106 μ L, 1.49 mmol, 1.50 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (4.30 mL) and tri(2-furyl)phosphine (69.0 mg, 0.299 mmol, 0.30 eq) and Tris(dibenzylideneacetone)dipalladium(o) (46.0 mg, 0.0498 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 1.5 h at RT before triethylamine (302 mg, 417 μ L, 2.99 mmol, 3.00 eq) was added in one portion. The resulting orange-brown solution was stirred for 20 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc $\rightarrow$ 16 : 1 $\rightarrow$ 12 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**293**) (176 mg, 0.460 mmol, 46%) as yellow-white oil which solidifies upon standing.

R_f (hexane: EtOAc 7 : 3) = 0.33.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.40 (d, J = 0.9 Hz, 1H, H7), 5.91 (s, 1H, -OH), 5.22 – 5.15 (m, 1H, H13), 5.12 (tt, J = 5.6, 1.4 Hz, 1H, H17), 3.32 (d, J = 7.3 Hz, 2H, H12), 2.59 (d, J = 0.8 Hz, 3H, H11), 2.29 – 2.21 (m, 2H, H20), 2.21 – 2.15 (m, 2H, H19), 2.15 – 2.09 (m, 2H, H16), 2.06 (dt, J = 7.3, 3.1 Hz, 2H, H15), 1.93 (t, J = 2.5 Hz, 1H, H22), 1.79 (d, J = 1.3 Hz, 3H, H23), 1.69 (s, 6H, H1 + H3), 1.59 (d, J = 1.3 Hz, 3H, H24).

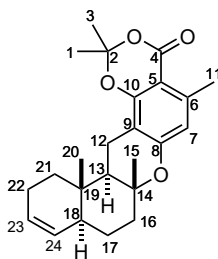
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.0 (C4), 160.1 (C8), 156.1 (C10), 143.1 (C6), 138.6 (C14), 134.0 (C18), 125.0 (C17), 121.1 (C13), 113.8 (C7), 112.7 (C9), 105.6 (C5), 105.0 (C2), 84.5 (C21), 68.5 (C22), 39.7 (C15), 38.5 (C19), 26.3 (C16), 25.9 (C1 + C3), 22.2 (C12), 22.0 (C11), 17.7 (C20), 16.4 (C23), 16.0 (C24).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3294 (s, br), 2989 (m), 2960 (m), 2922 (m), 2851 (m), 2114 (vw), 1726 (s), 1692 (vs), 1607 (vs), 1590 (vs), 1513 (m), 1451 (s), 1409 (s), 1388 (s), 1376 (s), 1295 (vs), 1275 (vs), 1209 (vs), 1166 (s), 1107 (s), 1067 (m), 672 (m), 908 (w), 850 (w), 641 (m), 624 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{24}H_{31}O_4)^+$: 383.2217, found: 383.2234.

Elemental Analysis: calc. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.29; H, 7.80

(±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*A*][1,3]dioxino[5,4-*j*]xanthen-4-one (**292**)



To XPhos gold(I) bis(trifluoromethanesulfonyl)imide (53.0 mg, 3.92 μmol , 0.05 eq) was added a solution of 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**293**) (30.0 mg, 78.4 μmol , 1.00 eq) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1.00 mL) dropwise. The resulting wine-red solution was stirred for 17 h at RT. The reaction mixture was filtered through a silica plug (CH_2CHCl_2 2 x 5.00 mL, EtOAc 1 x 5.00 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (17 : 1 Pentane : EtOAc $\rightarrow$ 9 : 1) afforded (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**292**) (22.0 mg, 57.5 μmol , 73%) as white solid.

Alternatively: To a solution of 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**293**) (444 mg, 1.16 mmol, 1.00 eq) in CH_2Cl_2 (250 mL) was added XPhos gold(I) bis(trifluoromethanesulfonyl)imide (28 mg, 0.029 mmol, 0.025 eq) in one portion. The resulting intense yellow-orange solution was stirred for 30 min after which indium(III) trifluoromethanesulfonate (16 mg, 0.029 mmol, 0.025 eq) was added in one portion. The resulting yellow-orange solution was stirred for 17 h at RT. The reaction mixture was quenched with water (20 mL), the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (40 mL) and dried over magnesium sulphate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (15 : 1 pentane : EtOAc) afforded (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**292**) (325 mg, 0.85 mmol, 73%) as white solid.

R_f (hexane : EtOAc 4 : 1) = 0.61.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.34 (d, J = 0.9 Hz, 1H, H7), 5.58 (dq, J = 10.0,

3.2 Hz, 1H, H23), 5.38 (dq, $J = 9.9, 2.1$ Hz, 1H, H24), 2.66 (dd, $J = 16.8, 4.9$ Hz, 1H, H12eq), 2.57 (s, 3H, H11), 2.33 – 2.23 (m, 1H, H12ax), 2.13 (ddq, $J = 5.2, 3.9, 2.7, 1.9$ Hz, 2H, H22), 2.07 (dt, $J = 12.9, 3.4$ Hz, 1H, H16eq), 2.03 (dt, $J = 3.2, 1.6$ Hz, 1H, H18), 1.87 (dt, $J = 12.8, 4.0$ Hz, 1H, H21eq), 1.79 – 1.70 (m, 1H, H16ax), 1.73 (s, 3H, H1), 1.69 (s, 3H, H3), 1.66 – 1.62 (m, 1H, H17eq), 1.59 (td, $J = 6.5, 5.9, 3.7$ Hz, 1H, H13), 1.50 – 1.42 (m, 1H, H17ax), 1.27 (d, $J = 1.0$ Hz, 3H, H15), 1.22 (dd, $J = 5.0, 4.1$ Hz, 1H, H21ax), 0.82 (d, $J = 0.8$ Hz, 3H, H20).

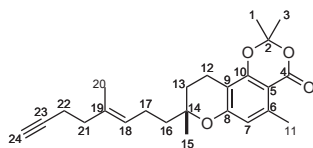
$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 161.0 (C4), 159.1 (C8), 156.2 (C10), 142.3 (C6), 129.9 (C24), 126.1 (C23), 114.6 (C7), 108.6 (C9), 104.9 (C2), 104.2 (C5), 78.9 (C14), 48.8 (C13), 46.0 (C18), 40.2 (C16), 35.2 (C19), 35.0 (C21), 26.3 (C1), 25.6 (C3), 25.2 (C17), 23.2 (C22), 22.1 (C11), 21.5 (C15), 17.0 (C12), 11.5 (C20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2991 (w), 2926 (m), 2859 (w), 1727 (vs), 1616 (s), 1573 (vs), 1493 (w), 1451 (m), 1387 (m), 1376 (m), 1353 (w), 1305 (s), 1289 (vs), 1279 (vs), 1208 (s), 1167 (vs), 1129 (vs), 1085 (w), 1066 (m), 1036 (m), 915 (w), 900 (m), 732 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{31}\text{O}_4)^+$: 383.2217, found: 383.2223.

mp. (recrystallized from CH_2Cl_2 /Pentane): 198 °C–200 °C.

(±)-2,2,5,8-TETRAMETHYL-8-(4-METHYLOCT-3-EN-7-YN-1-YL)-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE (**323**)



To bismuth(III) trifluoromethanesulfonate (15.0 mg, 23.5 μmol , 0.30 eq) was added a solution of 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**293**) (30.0 mg, 78.4 μmol , 1.00 eq) in CH_2Cl_2 (1.00 mL) dropwise. Purification by flash column chromatography (17 : 1 pentane : Et_2O $\rightarrow$ 9 : 1) afforded (±)-2,2,5,8-tetramethyl-8-(4-methyloct-3-en-7-yn-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**323**) (8.00 mg, 0.0209 mmol, 26%) as pale-yellow oil.

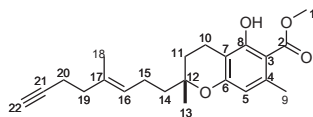
R_f (hexane : EtOAc 3 : 1) = 0.47.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.36 (d, J = 2.2 Hz, 1H, H7), 5.26 – 5.14 (m, 1H, H18), 2.89 (d, J = 6.5 Hz, 1H, H12eq), 2.58 (s, 4H, H11 + H12ax overlapping), 2.29 – 2.25 (m, 2H, H17), 2.20 (d, J = 6.9 Hz, 1H, H13eq), 2.12 (q, J = 7.5 Hz, 1H, H13ax), 2.08 – 1.98 (m, 1H, H16), 1.94 (dq, J = 3.9, 2.4, 1.7 Hz, 1H, H24), 1.79 (dq, J = 23.1, 6.8 Hz, 2H, H21), 1.70 (s, 9H, H1 + H3 + H16 + H22), 1.61 (d, J = 1.3 Hz, 3H, H15), 1.30 (s, 3H, H20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3301 (w), 2967 (w), 2929 (w), 2856 (w), 1728 (vs), 1617 (m), 1574 (s), 1451 (m), 1388 (m), 1376 (m), 1361 (m), 1282 (vs), 1206 (m), 1156 (m), 1040 (m), 891 (w).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{31}\text{O}_4)^+$: 383.2217, found: 383.2208.

(±)-METHYL 5-HYDROXY-2,7-DIMETHYL-2-(4-METHYLOCT-3-EN-7-YN-1-YL)CHROMANE-6-CARBOXYLATE (**324**)



To a solution of (±)-2,2,5,8-tetramethyl-8-(4-methyloct-3-en-7-yn-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**323**) (8.00 mg, 0.0209 mmol, 1.00 eq) in MeOH (2.00 mL) was added K_2CO_3 ((3.00 mg, 0.0209 mmol, 1.00 eq) in one portion. The resulting yellow suspension was stirred for 24 h at RT. The reaction mixture was concentrated under reduced pressure, the crude material was taken up in EtOAc (5.00 mL) and quenched with a saturated aqueous ammonium chloride solution (20 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (5 : 1 pentane : Et₂O) afforded (±)-methyl 5-hydroxy-2,7-dimethyl-2-(4-methyloct-3-en-7-yn-1-yl)chromane-6-carboxylate (**324**) (7.00 mg, 0.0207 mmol, 99%) as pale-yellow oil.

R_f (hexane : EtOAc 4 : 1) = 0.56.

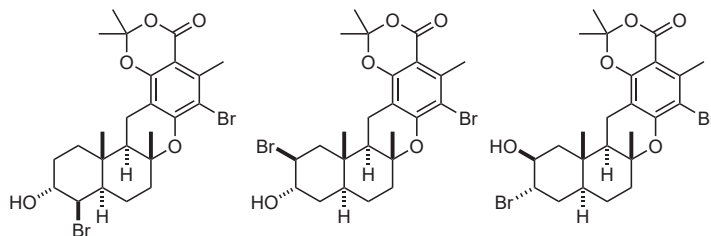
¹H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 12.08 (d, J = 2.8 Hz, 1H, OH), 6.22 – 6.18 (m, 1H, H₅), 5.22 – 5.14 (m, 1H, H₁₆), 3.91 (s, 3H, H₁), 2.88 (t, J = 6.6 Hz, 1H), 2.63 (q, J = 6.6 Hz, 2H), 2.44 (s, 3H), 2.26 (tdd, J = 4.7, 3.4, 1.8 Hz, 2H), 2.19 (t, J = 7.5 Hz, 1H), 2.13 – 2.07 (m, 1H), 1.95 – 1.90 (m, 1H, H₂₂), 1.87 – 1.73 (m, 2H), 1.72 – 1.64 (m, 1H), 1.61 (d, J = 1.3 Hz, 3H, H₁₈), 1.29 (s, 3H).

¹³C{¹H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 172.9 (C₂), 162.9 (C₈), 158.6 (C₆), 140.2 (C₄), 133.7 (C₁₇), 126.5, 125.4 (C₁₆), 112.5 (C₅), 107.0 (C₇), 104.0 (C₃), 84.5, 68.5 (C₂₂), 51.9 (C₁), 39.4, 38.5, 30.4, 24.2 (C₉), 16.4 (C₁₈).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3925 (m), 2969 (m), 2934 (m), 2855 (w), 2119 (vw), 1646 (vs), 1623 (s), 1577 (vs), 1437 (s), 1409 (m), 1377 (m), 1318 (vs), 1265 (vs), 1247 (vs), 1195 (s), 1152 (vs), 1107 (m), 978 (m), 805 (m).

HRMS (ES-ToF) m/z : [M + H]⁺ calc. for (C₂₂H₂₉O₄)⁺: 357.2060, found: 357.2076.

MIXTURE OF (±)-6,10-DIBROMO-11-HYDROXY- (326), (±)-6,12-DIBROMO-11-HYDROXY- (327) AND (±)-6,11-DIBROMO-12-HYDROXY-2,2,5,7A,13A-PENTAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (328)



To an ice-cold solution of (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (292) (168 mg, 0.439 mmol, 1.00 eq) in THF (4.00 mL), CH₃CN (1.50 mL) and H₂O (2.00 mL) was added NBS (82.0 mg, 0.461 mmol, 1.05 eq) in one portion. The resulting solution was stirred for 24 h at RT after which NBS (70.0 mg, 0.393 mmol, 0.90 eq) was added again. The reaction mixture was stirred for another 4 h at RT before NBS (30.0 mg, 0.169 mmol, 0.38 eq) was added. After 3 h stirring at RT the reaction mixture was quenched with an aqueous sodium thiosulfate (10 %, 20 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were washed a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (2 : 1 pentane : Et₂O → 1 : 1) afforded a mixture of dibromohydrins (326), (327) and (328) (209 mg, 0.374 mmol, 85%) as white solid.

R_f (hexane : EtOAc 3 : 1) = 0.11.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 4.39 – 4.31 (m, 1H), 4.27 (t, *J* = 3.2 Hz, 1H), 4.19 (s, oH), 4.11 (dt, *J* = 4.1, 2.0 Hz, 1H), 4.01 (s, oH), 2.79 (d, *J* = 1.4 Hz, 4H), 2.77 – 2.66 (m, oH), 2.65 – 2.55 (m, 1H), 2.53 – 2.43 (m, oH), 2.42 – 2.31 (m, 1H), 2.31 – 2.25 (m, oH), 2.23 (dt, *J* = 6.0, 3.1 Hz, 1H), 2.10 (dt, *J* = 11.6, 3.0 Hz, 1H), 2.06 – 1.89 (m, 1H), 1.88 – 1.77 (m, 1H), 1.73 (d, *J* = 1.7 Hz, 3H), 1.70 (d, *J* = 5.8 Hz, 3H), 1.68 – 1.60 (m, 1H), 1.52 (dd, *J* = 14.3, 4.2 Hz, 1H), 1.28 – 1.24 (m, 3H), 1.14 – 1.10 (m, 2H).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 160.6, 160.5, 155.8, 155.7, 155.6, 155.6, 154.9, 154.8, 154.7, 141.2, 141.2, 141.1, 110.4, 110.4, 110.3, 109.8, 109.6, 109.4, 109.3, 108.7, 105.4, 105.3, 104.9, 80.2, 79.9, 79.8, 76.4, 75.4, 71.8, 71.2, 66.8, 66.5, 62.0, 57.1, 54.9, 54.8, 52.1, 50.4, 50.0, 49.8, 49.5, 49.2, 48.6, 43.1, 42.9, 40.6, 39.9, 39.6, 39.6, 38.9, 36.6, 36.3, 36.1, 36.0, 34.0, 33.7, 33.6, 33.0, 31.6, 31.4, 31.1, 29.6, 29.3, 28.3, 28.0, 27.4, 26.8,

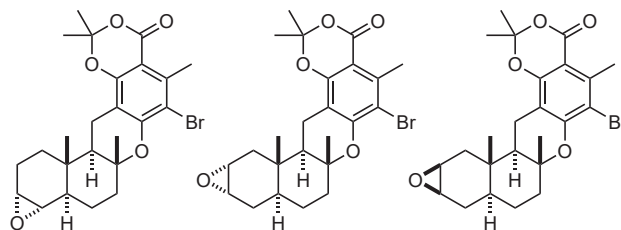
26.2, 26.2, 26.1, 25.8, 25.7, 25.5, 25.5, 25.4, 25.4, 25.3, 25.1, 23.6, 23.1, 22.4, 21.5, 21.3, 21.3, 21.2, 20.2, 17.3, 16.9, 16.7, 16.5, 14.9, 14.4, 14.0.

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3452 (br, s), 2944 (w), 2938 (m), 2867 (w), 1706 (s), 1597 (s), 1558 (s), 1457 (s), 1448 (s), 1388 (m), 1378 (m), 1349 (m), 1295 (s), 1277 (vs), 1207 (s), 1131 (s), 1060 (m), 906 (s), 732 (m).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₂₄H₃₁Br₂O₅)⁺: 557.0533, found 557.0527.

mp. (recrystallized from CH₂Cl₂/Pentane): 125 °C-130 °C.

MIXTURE OF (±)-5-BROMO-3A,6,9,9,11B-PENTAMETHYL-1A,1B,3,3A,11,11A,11B,12,13,13A-DECAHYDRO-2H,7H-[1,3]DIOXINO[4,5-A]OXIRENO[2',3':5,6]BENZO[1,2-J]XANTHEN-7-ONE (**329**), (±)-6-BROMO-2,2,5,7A,12A-PENTAMETHYL-7A,8,9A,10,10A,11A,12,12A,12B,13-DECAHYDRO-4H,9H-[1,3]DIOXINO[4,5-A]OXIRENO[2',3':4,5]BENZO[1,2-J]XANTHEN-4-ONE (**330**) AND (**331**)



To an ice-cold solution a mixture of dibromohydrins (**326**), (**327**) and (**328**) (209 mg, 0.374 mmol, 1.00 eq) in THF (5.00 mL) was added *tert*-BuOK (63.0 mg, 0.561 mmol, 1.50 eq) in one portion. The resulting solution was stirred for 7 h while gradually warming up to RT. The reaction mixture was diluted with Et₂O (10 mL) and quenched with a saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was further extracted with Et₂O (2 x 20 mL). The combined organic layers were washed a saturated aqueous sodium chloride solution (25 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 Pentane : EtOAc → 4 : 1) afforded a mixture of bromoepoxides (**329**), (**330**) and (**331**) (104 mg, 0.218 mmol, 58%) as yellow-white solid.

R_f (hexane : EtOAc 7 : 3) = 0.32.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 3.20 – 3.15 (m, 1H), 3.13 (t, J = 4.8 Hz, 1H), 3.06 (dd, J = 4.2, 1.2 Hz, 1H), 2.98 (dd, J = 4.0, 1.4 Hz, 1H), 2.78 (s, 3H), 2.68 (dd, J = 16.9, 4.7 Hz, 1H), 2.54 (dd, J = 17.0, 5.0 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.24 – 2.09 (m, 1H), 2.02 – 1.91 (m, 2H), 1.91 – 1.80 (m, 2H), 1.80 – 1.73 (m, 1H), 1.72 (d, J = 2.9 Hz,

3H), 1.68 (s, 3H), 1.66 – 1.56 (m, 1H), 1.56 – 1.36 (m, 2H), 1.23 (d, $J = 8.5$ Hz, 3H), 1.12 – 1.02 (m, 1H), 0.98 (s, 1H).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 160.3, 155.6, 155.4, 154.9, 154.8, 141.3, 141.3, 110.4, 110.2, 109.8, 109.5, 105.6, 104.9, 104.9, 80.1, 79.6, 58.0, 57.1, 50.7, 50.4, 49.6, 49.3, 46.7, 40.5, 38.6, 35.9, 35.6, 34.3, 26.3, 26.3, 26.1, 25.6, 25.4, 24.0, 23.7, 22.5, 21.5, 20.6, 20.4, 17.0, 16.9, 14.1.

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2935 (m), 2866 (w), 1730 (vs), 1597 (m), 1559 (s), 1457 (m), 1388 (m), 1378 (m), 1275 (vs), 1208 (m), 1133 (m), 1058 (m).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{30}\text{BrO}_5)^+$: 477.1271, found 477.1274.

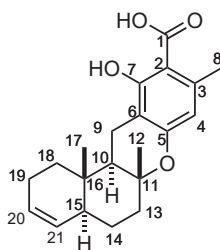
mp. (recrystallized from CH_2Cl_2 /Pentane): 190 °C–200 °C.

Some "cleaner" analytical data could be obtained for ($\pm$)-5-bromo-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12, 13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthen-7-one (**329**), although the $^{13}\text{C}\{^1\text{H}\}$ -NMR suggests further impurities of (**330**) and (**331**): ^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 3.20 (t, $J = 3.4$ Hz, 1H), 2.80 (dd, $J = 4.0, 1.2$ Hz, 1H), 2.78 (s, 3H), 2.62 (ddd, $J = 17.9, 12.1, 5.7$ Hz, 1H), 2.41 – 2.27 (m, 1H), 2.27 – 2.19 (m, 1H), 2.14 – 2.05 (m, 1H), 1.98 – 1.82 (m, 2H), 1.72 (s, 2H), 1.71 (d, $J = 4.6$ Hz, 1H), 1.68 (s, 3H), 1.66 – 1.59 (m, 1H), 1.59 – 1.48 (m, 2H), 1.28 (d, $J = 0.8$ Hz, 2H), 1.10 – 0.96 (m, 1H), 0.84 (s, 2H).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 160.3, 155.7, 154.8, 141.4, 110.5, 109.5, 109.4, 105.6, 105.0, 104.9, 80.0, 79.8, 54.8, 51.8, 47.7, 47.6, 39.8, 34.4, 31.9, 26.3, 25.4, 24.5, 21.7, 21.2, 20.8, 17.7, 14.2, 12.7.

mp. (recrystallized from CH_2Cl_2 /Pentane): 225 °C–232 °C (decomposition).

(±)-11-HYDROXY-6A,9,12B-TRIMETHYL-1,4A,5,6,6A,12,12A,12B-OCTAHYDRO-2H-BENZO[A]XANTHENE-10-CARBOXYLIC ACID (**337**)



To a solution of (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4H,9H-benzo[a][1,3]dioxino[5,4-j]xanthen-4-one (**292**) (22 mg, 0.058 mmol, 1.00 eq) in THF (1.5 mL) was added aqueous KOH (5 M; 1.5 mL, 7.5 mmol, 129 eq) in one portion. The resulting colorless-yellow bilayer system was vigorously stirred 6 days at 60 °C. The reaction mixture was diluted with water (5 mL) and EtOAc (5 mL) and acidified with aqueous hydrochloric acid (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 2 : 7 EtOAc : CH₂Cl₂ : pentane) afforded (±)-11-hydroxy-6a,9,12b-trimethyl-1,4a,5,6,6a,12,12a,12b-octahydro-2H-benzo[a]xanthene-10-carboxylic acid (**337**) (16 mg, 0.047 mmol, 81%) as an off-white solid.

R_f (hexane : EtOAc 7 : 3) = 0.12.

¹H-NMR (400 MHz, CD₃OD): δ (ppm) = 6.12 (dd, *J* = 2.2, 0.9 Hz, 1H, H₄), 5.66 – 5.53 (m, 1H, H₂₀), 5.39 (dq, *J* = 9.8, 2.1 Hz, 1H, H₂₁), 2.80 – 2.67 (m, 1H, H_{9eq}), 2.46 (s, 3H, H₈), 2.39 – 2.26 (m, 1H, H_{9ax}), 2.14 (dq, *J* = 5.8, 3.2 Hz, 2H, H₁₉), 2.06 – 2.01 (m, 1H, H₁₅), 2.00 – 1.94 (m, 1H, H_{13eq}), 1.94 – 1.84 (m, 1H, H_{14eq}), 1.73 (ddd, *J* = 16.3, 8.9, 4.1 Hz, 1H, H_{13ax}), 1.68 – 1.59 (m, 1H, H_{18eq}), 1.59 – 1.54 (m, 1H, H₁₀), 1.54 – 1.44 (m, 1H, H_{18ax}), 1.35 – 1.31 (m, 1H, H_{14ax}), 1.26 (d, *J* = 0.9 Hz, 3H, H₁₂), 0.85 (d, *J* = 0.9 Hz, 3H, H₁₇).

¹³C{¹H}-NMR (101 MHz, CD₃OD): δ (ppm) = 164.1 (C₁), 159.0 (C₅), 154.3 (C₇), 141.8 (C₃), 131.0 (C₂₁), 126.9 (C₂₀), 112.9 (C₄), 109.0 (C₆), 105.2 (C₂), 79.3 (C₁₁), 50.4 (C₁₀), 47.2 (C₁₅), 41.4 (C₁₃), 36.1 (C₁₄), 36.0 (C₁₆), 26.2 (C₁₈), 24.2 (C₈), 24.1 (C₁₉), 21.7 (C₁₂), 18.1 (C₉), 11.8 (C₁₇).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3056 (w), 2927 (vs, br), 2856 (m), 1728 (w),

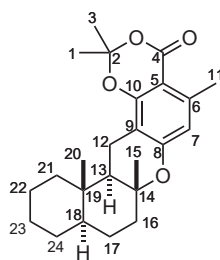
1621 (vs), 1578 (m), 1454 (s), 1370 (m), 1264 (vs), 1168 (m), 1122 (m), 1060 (w).

HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{21}H_{27}O_4)^+$: 343.1904, found: 343.1905. Also found m/z : $[M + D]^+$ $(C_{21}H_{26}DO_4)^+$: 344.1965; calc.: 344.1967.

mp. (recrystallized from CH_2Cl_2 /Pentane): 158 °C-162 °C.

Elemental Analysis calc. for $C_{21}H_{26}O_4 \cdot 0.5 H_2O$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.49.

(±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*J*]xanthen-4-one (**338**)



To a solution of (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**292**) (25 mg, 0.063 mmol, 1.00 eq) in MeOH (3.0 mL) and EtOAc (1.0 mL) was added Pd/C (5%, 10 mg) in one portion. The black suspension was purged with Hydrogen-gas three times, after which the mixture was stirred for 17 h at RT. The reaction mixture was filtered through Celite® and rinsed with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et₂O) afforded (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**338**) (20 mg, 0.052 mmol, 80%) as white solid.

R_f (hexane : EtOAc 7 : 3) = 0.58.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.33 (d, *J* = 1.0 Hz, 1H, H₇), 2.61 (dd, *J* = 17.0, 5.1 Hz, 1H, H_{12eq}), 2.57 (s, 3H, H₁₁), 2.28 – 2.18 (m, 1H, H_{12ax}), 2.00 (dt, *J* = 12.5, 3.2 Hz, 1H, H_{16eq}), 1.82 – 1.75 (m, 1H, H_{21eq}), 1.72 (s, 3H, H₁), 1.70 (d, *J* = 2.1 Hz, H_{16ax}), 1.69 (s, 3H, H₃), 1.57 (d, *J* = 5.0 Hz, 1H, H₁₃), 1.53 (t, *J* = 4.9 Hz, 2H, H₁₇), 1.41 (d, *J* = 9.6 Hz, 1H, H_{24eq}), 1.39 – 1.33 (m, 2H, H₂₃), 1.32 – 1.28 (m, 2H, H₂₂) 1.28 (dd, *J* = 4.3, 3.3 Hz, H_{24ax}), 1.24 (d, *J* = 8.1 Hz, H₁₈), 1.21 (d, *J* = 0.9 Hz, 3H, H₁₅), 1.02 – 0.91 (m, 1H, H_{21ax}), 0.83 (s, 3H, H₂₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 159.0 (C₈), 156.2 (C₁₀), 142.2 (C₆), 114.6 (C₇), 108.6 (C₉), 104.9 (C₂), 104.1 (C₅), 78.9 (C₁₄), 49.9 (C₁₃), 47.7 (C₁₈), 40.2 (C₁₆), 38.8 (C₂₁), 36.5 (C₁₉), 28.1 (C₂₃), 26.8 (C₂₂), 26.6 (C₂₄), 26.3 (C₁), 25.6 (C₃), 22.1 (C₁₁), 21.3 (C₁₇), 21.1 (C₁₅), 16.7 (C₁₂), 12.2 (C₂₀).

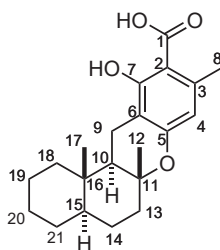
IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2924 (m), 2859 (m), 1724 (vs), 1615 (s), 1572 (vs), 1450 (s), 1387 (m), 1375 (s), 1359 (m), 1299 (s), 1282 (vs), 1207 (s), 1171 (s), 1129 (vs), 901 (s), 730 (s).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₂₄H₃₃O₄)⁺: 385.2373, found: 385.2370.

mp. (recrystallized from CH_2Cl_2 /Pentane): 162 °C-164 °C.

Elemental Analysis calc. for $\text{C}_{24}\text{H}_{32}\text{O}_4$: C, 74.97; H, 8.39. Found: C, 75.29; H, 8.59.

(±)-11-HYDROXY-6A,9,12B-TRIMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2H-BENZO[A]XANTHENE-10-CARBOXYLIC ACID (**339**)



To a solution of (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4H,9H-benzo[a][1,3]dioxino[5,4-j]xanthen-4-one (**338**) (20 mg, 0.052 mmol, 1.00 eq) in THF (1.0 mL) was added aqueous KOH (5 M; 1.0 mL, 5 mmol, 100 eq) and the resulting colorless-yellow bilayer system was vigorously stirred at 60 °C for 6 days. The reaction mixture was diluted with water (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 4 : 5 EtOAc : CH₂Cl₂ : pentane) afforded (±)-11-hydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H-benzo[a]xanthene-10-carboxylic acid (**339**) (16 mg, 0.046 mmol, 89%) as an off-white solid.

R_f (hexane : EtOAc 7 : 3) = 0.15.

¹H-NMR (400 MHz, CD₃OD): δ (ppm) = 6.13 – 6.09 (m, 1H, H₄), 2.70 (dd, *J* = 16.9, 5.0 Hz, 1H, H_{9eq}), 2.46 (d, *J* = 2.9 Hz, 3H, H₈), 2.26 (ddd, *J* = 15.9, 13.6, 6.7 Hz, 1H, H_{9ax}), 1.97 (dt, *J* = 12.5, 3.2 Hz, 1H, H_{13eq}), 1.84 – 1.77 (m, 1H, H_{21eq}), 1.77 – 1.70 (m, 1H, H_{18eq}), 1.68 (d, *J* = 11.7 Hz, 1H, H_{13ax}), 1.60 – 1.56 (m, 1H, H_{19eq}), 1.55 – 1.50 (m, 1H, H₁₀), 1.47 – 1.41 (m, 2H, H₁₅ + H_{18ax} overlapping), 1.40 (d, *J* = 2.8 Hz, H_{14eq}), 1.34 – 1.30 (m, 4H, H_{19ax} + H_{14ax} + H₂₀ overlapping), 1.27 – 1.24 (m, 1H), 1.21 (d, *J* = 0.9 Hz, 3H, H₁₂), 1.02 (s, 1H, H_{21ax}), 0.88 (d, *J* = 0.8 Hz, 3H, H₁₇).

¹³C{¹H}-NMR (101 MHz, CD₃OD): δ (ppm) = 175.6 (C₁), 164.5 (C₇), 159.0 (C₅), 141.8 (C₃), 112.9 (C₄), 109.0 (C₆), 104.9 (C₂), 79.2 (C₁₁), 51.6 (C₁₀), 47.8 (C₁₅), 41.3 (C₁₃), 40.0 (C₂₁), 37.5 (C₁₆), 30.8 (C₁₄), 29.2 (C₂₀), 27.7 (C₁₈), 24.2 (C₈), 22.4 (C₁₉), 21.2 (C₁₂), 17.8 (C₉), 12.4 (C₁₇).

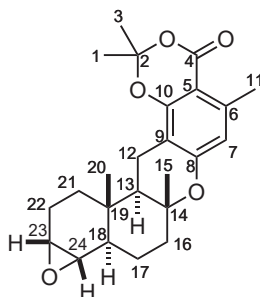
IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2973 (w), 2927 (vs, br), 2855 (m), 1616 (vs), 1595 (vs), 1576 (vs), 1454 (vs), 1370 (m), 1269 (vs), 1263 (vs), 1183 (s), 1109 (s), 1033

(m), 904 (m), 800 (s), 654 (m).

HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{21}H_{29}O_4)^+$: 345.2060, found: 345.2068.

mp. (recrystallized from CH_2Cl_2 /Pentane): 183 °C-185 °C.

($\pm$)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2H,7H-[1,3]dioxino[4,5-a]oxireno[2',3':5,6]benzo[1,2-j]xanthen-7-one (**342**)



To an emulsion of ($\pm$)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4H,9H-benzo[a][1,3]dioxino[5,4-j]xanthen-4-one (**292**) (106 mg, 0.277 mmol, 1.00 eq) in CH_2Cl_2 (3.00 mL) and aqueous NaHCO_3 (0.5 M; 0.84 mL) was added *m*-CPBA (65.0 mg, 0.291 mmol, 1.05 eq) in two portions. The resulting emulsion was stirred for 3 h at RT after which *m*-CPBA (18.0 mg, 83.1 μmol , 0.3 eq) was added again. The reaction mixture was stirred for 1.5 h at RT. The reaction mixture was quenched with water (10 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (1 x 10 mL). The combined organic layers were washed with an aqueous sodium hydroxide solution (1 M; 15 mL), water (10 mL) and a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (6 : 1 pentane : EtOAc $\rightarrow$ 4 : 1) afforded ($\pm$)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2H,7H-[1,3]dioxino[4,5-a]oxireno[2',3':5,6]benzo[1,2-j]xanthen-7-one (**342**) (95.0 mg, 0.238 mmol, 86%) as white foam.

R_f (hexane : EtOAc 4 : 1) = 0.18.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.32 (d, J = 0.2 Hz, 1H, H7), 3.19 (t, J = 3.4 Hz, 1H, H23), 2.79 (dt, J = 4.0, 0.9 Hz, 1H, H24), 2.59 (dd, J = 17.0, 4.8 Hz, 1H, H12eq), 2.56 (s, 3H, H11), 2.27 – 2.10 (m, 1H, H12ax), 2.16 – 2.09 (m, 1H, H16eq), 2.06 (ddd, J = 12.8, 6.6, 2.5 Hz, 1H, H17eq), 1.94 – 1.88 (m, 1H, H17ax), 1.87 (td, J = 5.0, 4.0, 2.3 Hz, 1H, H22ax), 1.71 (d, J = 5.6 Hz, 1H, H16ax), 1.71 (d, J = 0.7 Hz, 3H, H1), 1.67 (d, J = 0.7 Hz, 3H, H3), 1.67 – 1.60 (m, 1H, H21eq), 1.57 (dd, J = 13.2, 3.3 Hz, 1H, H22ax), 1.53 – 1.50 (m, 1H, H13), 1.50 (m, 1H, H18), 1.26 (d, J = 1.0 Hz, 3H, H15), 1.03 – 0.95 (m, 1H, H21ax), 0.83 (d, J = 0.6 Hz, 3H, H20).

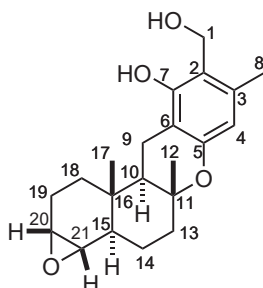
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 160.8 (C4), 158.8 (C8), 156.1 (C10), 142.2 (C6), 114.5 (C7), 108.2 (C9), 104.9 (C2), 104.2 (C5), 78.2 (C14), 54.8 (C24), 51.8 (C23),

47.9 (C13), 47.5 (C18), 40.0 (C16), 34.3 (C19), 31.7 (C21), 26.3 (C1), 25.5 (C3), 24.5 (C22), 22.0 (C11), 21.4 (C15), 20.8 (C17), 17.2 (C12), 12.6 (C20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2973 (w), 2929 (m), 2865 (w), 1718 (vs), 1615 (s), 1571 (s), 1492 (m), 1450 (m), 1375 (m), 1289 (vs), 1279 (vs), 1206 (s), 1172 (m), 1128 (vs), 1036 (s), 1005 (m), 919 (s), 900 (s), 824 (m), 727 (vs).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{31}\text{O}_5)^+$: 399.2166, found. 399.2176.

(±)-7-(HYDROXYMETHYL)-3A,6,9B-TRIMETHYL-1A,1B,3,3A,9,9A,9B,10,11,11A-DECAHYDRO-2*H*-OXIRENO[2',3':3,4]BENZO[1,2-*A*]XANTHEN-8-OL (347)



To an ice-cold solution of (±)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthene-7-one (342) (40.0 mg, 0.100 mmol, 1.00 eq) in THF (1.00 mL) was added LiBHEt₃ (1 M in THF; 0.110 mL, 0.105 mmol, 1.05 eq) dropwise. The reaction mixture was stirred for 2 h while gradually warming up to RT after which the reaction mixture was quenched with an aqueous saturated ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : Et₂O → 1 : 1) afforded (±)-7-(hydroxymethyl)-3a,6,9b-trimethyl-1a,1b,3,3a,9,9a,9b,10,11,11a-decahydro-2*H*-oxireno[2',3':3,4]benzo[1,2-*a*]xanthene-8-ol (347) (33.0 mg, 0.0958 mmol, 95%) as transparent film.

*R*_f (hexane : EtOAc 1 : 1) = 0.43.

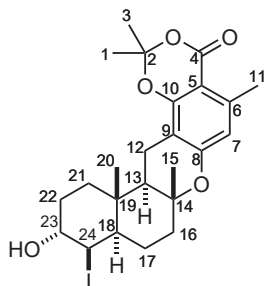
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.31 (s, 1H, H₄), 4.94 (s, 2H, H₁), 3.20 (t, *J* = 3.5 Hz, 1H, H₂₁), 2.80 (d, *J* = 3.8 Hz, 1H, H₂₀), 2.75 (d, *J* = 5.0 Hz, 1H, H_{9eq}), 2.25 (dd, *J* = 16.9, 13.3 Hz, 1H, H_{9ax}), 2.13 – 2.09 (m, 1H, H_{14eq}), 2.09 – 2.04 (m, 1H, H_{13eq}), 2.03 (s, 3H, H₈), 1.97 – 1.90 (m, 1H, H_{14ax}), 1.89 – 1.84 (m, 1H, H_{18eq}), 1.81 – 1.68 (m, 1H, H_{13ax}), 1.68 – 1.60 (m, 1H, H_{19eq}), 1.57 (d, *J* = 3.5 Hz, 1H, H₁₅), 1.53 (t, *J* = 3.4 Hz, 1H, H_{18ax}), 1.50 (d, *J* = 2.8 Hz, 1H, H₁₀), 1.25 (s, 3H, H₁₂), 0.99 (s, 1H, H_{19ax}), 0.84 (s, 3H, H₁₇).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 152.9 (C₅), 146.9 (C₇), 132.3 (C₃), 112.6 (C₄), 111.7 (C₂), 109.3 (C₉), 77.4 (C₁₁), 61.5 (C₁), 55.1 (C₂₀), 52.0 (C₂₁), 48.4 (C₁₀), 47.7 (C₁₅), 40.3 (C₁₃), 34.4 (C₁₆), 31.8 (C₁₉), 24.7 (C₁₈), 21.4 (C₁₂), 20.9 (C₁₄), 17.7 (C₈), 17.4 (C₉), 12.7 (C₁₇).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm^{-1}) = 2927 (vs), 2866 (s), 1732 (w), 1627 (s), 1585 (s), 1457 (vs), 1421 (vs), 1350 (vs), 1227 (vs), 1217 (vs), 1191 (vs), 1107 (s).

HRMS (ESI) m/z : $[\text{M} - \text{OH}]^+$ calc. for $(\text{C}_{21}\text{H}_{27}\text{O}_3)^+$: 327.1955, found. 327.1955.

(±)-11-HYDROXY-10-iodo-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*A*][1,3]dioxino[5,4-*J*]xanthen-4-one (348)



To a solution of (±)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthen-7-one (342) (69 mg, 0.17 mmol, 1.00 eq) in CH₂Cl₂ (5.0 mL) was added Et₃Si-H (48 mg, 70.066 mL, 0.42 mmol, 2.4 eq) and SmI₂ (0.1 M in THF; 3.2 mL, 0.32 mmol, 1.88 eq) dropwise. The resulting dark-blue solution was stirred for 20 min at RT until the color faded. The reaction mixture was diluted with Et₂O (5 mL) and quenched with H₂O (5 mL). Saturated aqueous sodium hydrogencarbonate solution (5 mL) was added and the organic layer was separated. The aqueous layer was further extracted with Et₂O (2 x 10 mL). The combined organic layers were washed a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3 : 1 pentane : Et₂O -> 3 : 1 pentane : EtOAc) afforded (±)-11-hydroxy-10-iodo-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (348) (75 mg, 0.14 mmol, 82%) as a white solid.

Alternatively: To a solution of (±)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthen-7-one (342) (50 mg, 0.13 mmol, 1.00 eq) in CH₂Cl₂ (8.0 mL) was added SmI₂ (0.1 M in THF; 2.3 mL, 0.23 mmol, 1.8 eq) dropwise. The resulting dark-blue solution was stirred for 1 h at RT. The reaction mixture was diluted with Et₂O (10 mL) and quenched with H₂O (10 mL). Saturated aqueous sodium hydrogencarbonate solution (10 mL) was added and the organic layer was separated. The aqueous layer was further extracted with Et₂O (2 x 10 mL). The combined organic layers were washed a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 1 : 8

pentane : EtOAc : CH₂Cl₂) afforded (±)-11-hydroxy-10-iodo-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**348**) (65 mg, 0.12 mmol, 98%) as a white solid.

R_f (hexane : EtOAc 7 : 3) = 0.21.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.31 (s, 1H, H7), 4.39 (q, *J* = 2.7 Hz, 1H, H23), 4.26 (dt, *J* = 3.9, 2.1 Hz, 1H, H24), 2.99 (s, 1H, -OH), 2.56 (d, *J* = 6.9 Hz, 1H, H12eq, overlapping with H11), 2.54 (s, 3H, H11), 2.34 – 2.28 (m, 1H, H21eq), 2.28 – 2.23 (m, 1H, H12ax), 2.07 (d, *J* = 10.3 Hz, 1H, H16eq), 1.90 – 1.79 (m, 1H, H16ax), 1.71 (s, 3H, H1), 1.69 (s, 1H, H21ax), 1.67 (s, 3H, H3), 1.62 (dd, *J* = 5.5, 4.2 Hz, 1H, H18), 1.61 – 1.59 (m, 1H, H17eq), 1.58 (d, *J* = 3.3 Hz, 1H, H22eq), 1.55 (d, *J* = 4.5 Hz, 1H, H13), 1.51 (d, *J* = 3.7 Hz, 1H, H22ax), 1.39 – 1.37 (m, 1H, H17ax), 1.22 (s, 3H, H15), 1.12 (s, 3H, H20).
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.2 (C4), 158.8 (C8), 156.2 (C10), 142.2 (C6), 114.5 (C7), 108.0 (C9), 105.0 (C2), 104.1 (C5), 78.3 (C14), 73.1 (C23), 51.0 (C13), 42.3 (C18), 39.5 (C16), 37.3 (C24), 36.7 (C19), 31.5 (C22), 28.5 (C17), 26.3 (C1), 25.6 (C3), 23.2 (C21), 22.1 (C11), 21.0 (C15), 15.9 (C12), 14.2 (C20).

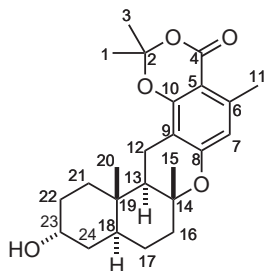
IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3425 (s, br), 2988 (w), 2929 (m), 2863 (w), 1727 (s), 1701 (vs), 1619 (s), 1573 (vs), 1450 (m), 1377 (m), 1307 (vs), 1293 (vs), 1284 (vs), 1207 (m), 1171 (s), 1130 (vs), 1047 (vs).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₂₄H₃₂IO₅)⁺: 527.1289, found: 527.1284.

mp. (recrystallized from CH₂Cl₂/Pentane): 117 °C-120 °C (decomposition).

Elemental Analysis: calc. for C₂₄H₃₁IO₅: C, 54.76; H, 5.94. Found: C, 54.66; H, 5.88.

(±)-11-HYDROXY-2,2,5,7A,13A-PENTAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (349)



To a solution of (±)-11-hydroxy-10-iodo-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (348) (75 mg, 0.14 mmol, 1.00 eq) in EtOH (7.0 mL) was added Ra-Ni (50% aqueous, 1.4 mL) dropwise. The resulting grey suspension was refluxed for 3 h. The reaction mixture was filtered through Celite® and rinsed with EtOH (20 mL). The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in EtOAc (20 mL) and washed with water (10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3 : 1 pentane : Et₂O → 1 : 1 pentane : Et₂O) afforded (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (349) (50 mg, 0.12 mmol, 88%) as a white solid.

R_f (hexane : EtOAc 7 : 3) = 0.12.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.32 (s, 1H, H₇), 4.07 (q, *J* = 2.9 Hz, 1H, H₂₃), 2.61 (dd, *J* = 16.8, 4.9 Hz, 1H, H_{12eq}), 2.55 (s, 3H, H₁₁), 2.29 – 2.18 (m, 1H, H_{12ax}), 2.00 (dt, *J* = 12.6, 3.2 Hz, 1H, H_{16eq}), 1.81 – 1.78 (m, 1H, H₁₈), 1.77 – 1.73 (m, 1H, H_{17eq}), 1.71 (s, 3H, H₁), 1.73 (s, 1H, H_{16ax}), 1.67 (s, 3H, H₃), 1.64 (d, *J* = 5.0 Hz, 1H, H_{17ax}), 1.61 (d, *J* = 4.7 Hz, 1H, H₁₃), 1.56 (dt, *J* = 7.9, 2.5 Hz, 1H, H_{22eq}), 1.53 – 1.46 (m, 2H, H₂₄), 1.47 – 1.40 (m, 1H, H_{22ax}), 1.40 – 1.30 (m, 2H, H₂₁), 1.21 (s, 3H, H₁₅), 0.82 (s, 3H, H₂₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 159.0 (C₈), 156.2 (10), 142.1 (C₆), 114.6 (C₇), 108.5 (C₉), 104.9 (C₂), 104.1 (C₅), 78.7 (C₁₄), 66.1 (C₂₃), 49.4 (C₁₃), 40.0 (C₁₆), 39.4 (C₁₈), 36.3 (C₁₉), 35.1 (C₂₄), 32.7 (C₂₂), 28.4 (C₂₁), 26.3 (C₁ + C₁₇ overlapping), 25.5 (C₃), 22.1 (C₁₁), 21.0 (C₁₅), 16.7 (C₁₂), 11.1 (C₂₀).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3430 (br, s), 2975 (w), 2928 (m), 2862 (w), 1707 (s), 1614 (s), 1570 (vs), 1450 (m), 1376 (m), 1282 (vs), 1207 (s), 1170 (vs), 1127 (vs), 1097

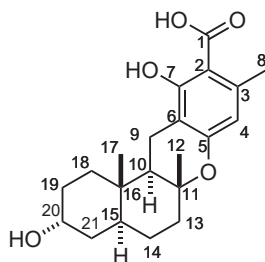
(s), 907 (vs), 727 (vs).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{24}H_{33}O_5)^+$: 401.2323, found: 401.2330.

mp. (recrystallized from CH_2Cl_2 /Pentane): 97 °C-100 °C.

Note: When bromohydrin (**366**) was reacted according to the above procedure a yield of 90% was obtained for alcohol (**349**).

(±)-3,11-DIHYDROXY-6A,9,12B-TRIMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2H-BENZO[A]XANTHENE-10-CARBOXYLIC ACID (**350**)



To a solution of (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**349**) (37 mg, 0.092 mmol, 1.00 eq) in THF (1.0 mL) was added aqueous KOH (5 M; 1.0 mL) dropwise. The resulting yellow-orange biphasic system was heated to 60 °C in a sealed vial under vigorous stirring for 6 days. The reaction mixture was diluted with H₂O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 → 2 : 8 → 3 : 7 EtOAc : CH₂Cl₂) afforded (±)-3,11-dihydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (**350**) (15 mg, 0.042 mmol, 45%) as a yellow-transparent film.

R_f (hexane : EtOAc 1 : 1) = 0.09.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.92 (s, 1H, OH), 6.22 (d, *J* = 0.8 Hz, 1H, H₄), 4.11 (d, *J* = 3.3 Hz, 1H, H₂₀), 2.76 (dd, *J* = 16.8, 4.9 Hz, 1H, H_{9eq}), 2.51 (s, 3H, H₈), 2.30 (dd, *J* = 16.8, 13.3 Hz, 1H, H_{9ax}), 2.05 – 2.00 (m, 1H, H_{13eq}), 1.80 (dd, *J* = 13.2, 3.1 Hz, 1H, H_{14eq}), 1.77 – 1.74 (m, 1H, H₁₅), 1.72 (d, *J* = 6.0 Hz, 1H, H_{13ax}), 1.67 (d, *J* = 4.5 Hz, 1H, H_{14ax}), 1.64 (d, *J* = 5.7 Hz, 1H, H_{19eq}), 1.63 (d, *J* = 4.3 Hz, 1H, H₁₀), 1.60 – 1.46 (m, 2H, H₂₁), 1.41 (s, 1H, H_{19ax}), 1.38 (dd, *J* = 9.7, 2.7 Hz, 2H, H₁₈), 1.23 (d, *J* = 0.9 Hz, 3H, H₁₂), 0.84 (s, 3H, H₁₇).

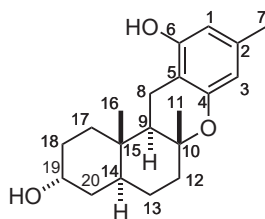
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 175.6 (C₁), 163.9 (C₇), 159.0 (C₅), 141.6 (C₃), 112.8 (C₄), 108.2 (C₂), 102.7 (C₆), 78.7 (C₁₁), 66.4 (C₂₀), 49.7 (C₁₀), 40.1 (C₁₃), 39.6 (C₁₅), 36.4 (C₁₆), 35.1 (C₂₁), 32.8 (C₁₉), 28.5 (C₁₈), 26.4 (C₁₄), 24.3 (C₈), 21.1 (C₁₂), 17.0 (C₉), 11.1 (C₁₇).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3478 (br, m), 2928 (vs), 2862 (s), 1621 (vs), 1578

(s), 1452 (s), 1380 (m), 1262 (vs), 1175 (s), 1124 (m).

HRMS (ES-ToF) m/z : $[M - H]^-$ calc. for $(C_{21}H_{27}O_5)^-$: 359.1864, found: 359.1867.

(±)-6A,9,12B-TRIMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2H-BENZO
[A]XANTHENE-3,11-DIOL (**351**)



To a solution of (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**349**) (37 mg, 0.092 mmol, 1.00 eq) in THF (1.0 mL) was added aqueous KOH (5 M; 1.0 mL) dropwise. The resulting yellow-orange biphasic system was heated to 60 °C in a sealed vial under vigorous stirring for 6 days. The reaction mixture was diluted with H₂O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 → 2 : 8 → 3 : 7 EtOAc : CH₂Cl₂) afforded (±)-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H-benzo[*a*]xanthene-3,11-diol (**351**) (7.0 mg, 0.022 mmol, 24%) as a yellow-white film.

R_f (hexane : EtOAc 1 : 1) = 0.29.

¹H-NMR (500 MHz, CDCl₃): δ (ppm) = 6.24 (s, 1H, H₃), 6.17 (d, J = 1.6 Hz, 1H, H₁), 4.68 (s, 1H, OH), 4.13 – 4.06 (m, 1H, H₁₉), 2.67 (dd, J = 16.2, 5.1 Hz, 1H, H_{8eq}), 2.37 – 2.29 (m, 1H, H_{8ax}), 2.20 (s, 3H, H₇), 2.00 (dt, J = 12.6, 3.3 Hz, 1H, H_{12eq}), 1.81 – 1.78 (m, 1H, H_{17eq}), 1.77 (dd, J = 4.4, 2.3 Hz, 1H, H₁₄), 1.74 (dd, J = 4.7, 3.4 Hz, 1H, H_{12ax}), 1.72 – 1.66 (m, 1H, H₉), 1.66 – 1.62 (m, 1H, H_{17ax}), 1.61 – 1.58 (m, 1H, H_{18eq}), 1.53 – 1.44 (m, 2H, H₂₀), 1.41 (t, J = 4.3 Hz, 1H, H_{18ax}), 1.39 – 1.34 (m, 2H, H₁₃), 1.22 (d, J = 1.0 Hz, 3H, H₁₁), 0.85 – 0.81 (m, 3H, H₁₆).

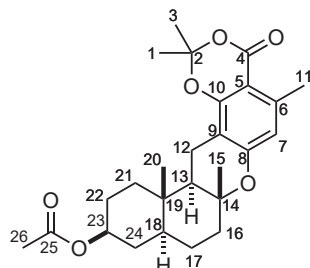
¹³C{¹H}-NMR (126 MHz, CDCl₃): δ (ppm) = 154.2 (C₆), 153.9 (C₄), 137.4 (C₂), 110.4 (C₃), 107.2 (C₁), 106.8 (C₅), 77.0 (C₁₀), 66.4 (C₁₉), 50.0 (C₉), 40.3 (C₁₂), 39.6 (C₁₄), 36.3 (C₁₅), 35.2 (C₂₀), 32.9 (C₁₈), 28.5 (C₁₇), 26.4 (C₁₃), 21.3 (C₇), 21.0 (C₁₁), 16.9 (C₈),

11.1 (C16).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3381 (br, s), 1733 (m), 1710 (m), 1625 (m), 1587 (s), 1445 (s), 1333 (s), 1260 (s), 1172 (s), 1059 (s), 1035 (s), 1018 (s), 988 (s), 822 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{20}\text{H}_{29}\text{O}_3)^+$: 317.2111, found: 317.2102.

(±)-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*A*][1,3]dioxino[5,4-*J*]xanthen-11-yl acetate (**352**)



To a solution of (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**349**) (33.0 mg, 0.0824 mmol, 1.00 eq) in THF (1.0 mL) were added acetic acid (11.8 μ mol, 12.4 mg, 0.201 mmol, 2.50 eq) and PPh_3 (54.0 mg, 0.201 mmol, 2.50 eq) in one portion. DIAD (16.2 μ L, 16.7 mg, 0.201 mmol, 2.50 eq) was added dropwise and the resulting yellow suspension was stirred for 17 h at RT. The reaction mixture was diluted with Et_2O (5 mL) and quenched with H_2O (5 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (7 : 3 pentane : Et_2O $\rightarrow$ 1 : 1) afforded (±)-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (**352**) (5.00 mg, 0.0113 mmol, 14%) as a white film.

R_f (hexane : EtOAc 7 : 3) = 0.14.

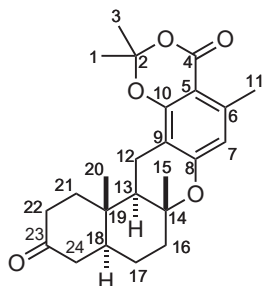
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.34 (d, J = 0.9 Hz, 1H, H7), 4.72 (dq, J = 11.0, 5.2 Hz, 1H, H23), 2.64 – 2.57 (m, 1H, H12eq), 2.57 (s, 3H, H11), 2.34 – 2.27 (m, 1H, H12ax), 2.04 (s, 3H, H26), 2.01 (t, J = 3.3 Hz, 1H, H16eq), 1.92 – 1.83 (m, 2H, H21ax + H24eq overlapping), 1.73 (s, 6H, H1 + H16ax + H21eq + H22eq overlapping), 1.69 (s, 3H, H3), 1.64 – 1.50 (m, 3H, H24ax + H13 + H17eq), 1.45 (d, J = 9.4 Hz, H17ax), 1.41 – 1.34 (m, 1H, H18), 1.22 (d, J = 0.9 Hz, 3H, H15), 1.21 – 1.13 (m, 1H, H22ax), 0.92 – 0.87 (m, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 170.8 (C25), 161.0 (C4), 158.9 (C8), 156.2 (C10), 142.4 (C6), 114.6 (C7), 108.2 (C9), 105.0 (C2), 104.2 (C5), 78.6 (C14), 73.2 (C23), 49.4 (C13), 45.2 (C18), 40.0 (C16), 37.0 (C21), 35.8 (C19), 33.2 (C22), 26.7 (C24), 26.4 (C17), 26.3 (C1), 25.6 (C3), 22.1 (C11), 21.5 (C26), 21.1 (C15), 17.1 (C12), 12.2 (C20).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2937 (m), 2866 (w), 1729 (vs), 16116 (s), 1574 (s), 1452 (m), 1397 (m), 1375 (s), 1299 (s), 1281 (vs), 1244 (vs), 1210 (m), 1130 (s), 1034 (s).

HRMS (ES-ToF) m/z : [M + H]⁺ calc. for (C₂₆H₃₅O₆)⁺: 443.2428, found: 443.2439.

(±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*A*][1,3]dioxino[5,4-*J*]xanthene-4,11(10*H*)-dione (**353**)



To an ice-cold solution of (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**349**) (95.0 mg, 0.237 mmol, 1.00 eq) in CH₂Cl₂ (5.0 mL) was added DMP (201 mg, 0.474 mmol, 2.00 eq) in two portions over the course of 5 min. The resulting yellow suspension was stirred for 1.5 h at RT. The reaction mixture was concentrated and loaded onto a column with a Celite® pad. Purification by flash column chromatography (1 : 1 pentane : CH₂Cl₂ → 1 : 2) afforded (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (**353**) (82.0 mg, 0.206 mmol, 87%) as a white solid.

R_f (hexane : EtOAc 7 : 3) = 0.22.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.32 (s, 1H, H₇), 2.63 (dd, *J* = 16.7, 5.0 Hz, 1H, H_{12eq}), 2.54 (s, 3H, H₁₁), 2.49 – 2.35 (m, 2H, H₂₂), 2.35 – 2.29 (m, 1H, H_{12ax}), 2.28 – 2.18 (m, 2H, H₂₁), 2.17 – 2.09 (m, 1H, H_{24eq}), 2.04 (dt, *J* = 12.9, 3.2 Hz, 1H, H_{16eq}), 1.74 (d, *J* = 5.1 Hz, 1H, H_{16ax}), 1.71 (s, 3H, H₁), 1.68 (s, 1H, H₁₈), 1.67 (s, 3H, H₃), 1.65 – 1.57 (m, 1H, H₁₃), 1.55 – 1.45 (m, 2H, H₁₇), 1.45 – 1.38 (m, 1H, H_{24ax}), 1.25 (s, 3H, H₁₅), 1.05 (s, 3H, H₂₀).

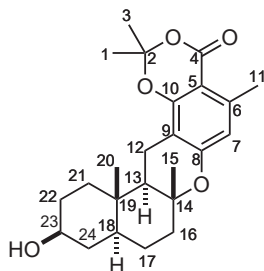
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 210.5 (C₂₃), 160.8 (C₄), 158.6 (C₈), 156.1 (C₁₀), 142.4 (C₆), 114.5 (C₇), 107.9 (C₉), 104.9 (C₂), 104.2 (C₅), 78.2 (C₁₄), 49.0 (C₁₃), 46.3 (C₁₈), 43.9 (C₂₁), 39.5 (C₁₆), 38.3 (C₂₄), 37.2 (C₂₂), 35.8 (C₁₉), 26.3 (C₁), 25.5 (C₃), 22.0 (C₁₁), 20.8 (C₁₅), 17.3 (C₁₂), 11.5 (C₂₀).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2935 (m), 2865 (m), 2246 (vw), 1709 (vs), 1615 (s), 1572 (vs), 1451 (s), 1387 (m), 1376 (m), 1299 (s), 1279 (vs), 1206 (s), 1170 (vs), 1128 (vs), 1077 (m), 1066 (m), 1038 (s), 912 (s), 899 (vs), 725 (vs).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₂₄H₃₁O₅)⁺: 399.2166, found: 399.2174.

Elemental Analysis calc. for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.19; H, 7.52.

(±)-11-HYDROXY-2,2,5,7A,13A-PENTAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (354)



To an ice-cold solution of (±)-2,2,5,7a,13a-pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (353) (19 mg, 0.048 mmol, 1.00 eq) in EtOH (1.0 mL) was added NaBH₄ (2.3 mg, 0.062 mmol, 1.30 eq) in one portion. The resulting yellow suspension was stirred for 1 h at 0 °C. The reaction mixture was diluted with Et₂O (5 mL) and quenched with a saturated aqueous ammonium chloride solution (3 mL). The organic layer was separated and the aqueous layer was further extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 1 : 8 EtOAc : pentane : CH₂Cl₂) afforded (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (354) (17 mg, 0.042 mmol, 89%) as a white foam.

R_f (hexane : EtOAc 7 : 3) = 0.08.

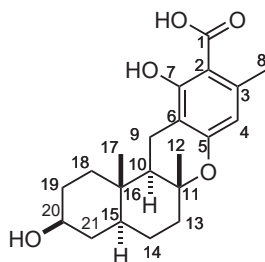
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.33 (d, *J* = 1.0 Hz, 1H, H₇), 3.65 (tt, *J* = 10.6, 4.8 Hz, 1H, H₂₃), 2.63 – 2.58 (m, 1H, H_{12eq}), 2.56 (s, 3H, H₁₁), 2.28 (dd, *J* = 16.8, 13.3 Hz, 1H, H_{12ax}), 2.02 (dt, *J* = 12.6, 3.0 Hz, 1H, H_{16eq}), 1.90 – 1.85 (m, 1H, H_{24eq}), 1.85 – 1.81 (m, 1H, H_{21eq}), 1.72 (s, 3H, H₁), 1.70 (d, *J* = 1.0 Hz, 1H, H_{16ax}), 1.68 (s, 3H, H₃), 1.65 (dd, *J* = 4.8, 2.2 Hz, 1H, H_{21ax}), 1.59 – 1.51 (m, 1H, H₁₃), 1.51 – 1.46 (m, 1H, H_{24ax}), 1.48 – 1.34 (m, 2H, H₁₇), 1.30 (dd, *J* = 11.3, 1.5 Hz, 1H, H_{22eq}), 1.27 – 1.23 (m, 1H, H₁₈), 1.22 (d, *J* = 0.9 Hz, 3H, H₁₅), 1.13 – 1.03 (m, 1H, H_{22ax}), 0.87 (s, 3H, H₂₀).
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 158.9 (C₈), 156.2 (C₁₀), 142.3 (C₆), 114.6 (C₇), 108.3 (C₉), 104.9 (C₂), 104.2 (C₅), 78.7 (C₁₄), 71.1 (C₂₃), 49.5 (C₁₃), 45.3 (C₁₈), 40.1 (C₁₆), 37.2 (C₂₁), 37.2 (C₂₂), 35.8 (C₁₉), 30.7 (C₂₄), 26.4 (C₁₇), 26.3 (C₁), 25.6 (C₃), 22.1 (C₁₁), 21.0 (C₁₅), 17.1 (C₁₂), 12.3 (C₂₀).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3440 (br, s), 2984 (w), 2930 (s), 2863 (m), 1718 (vs), 1615 (vs), 1572 (vs), 1452 (s), 1388 (s), 1376 (s), 1287 (vs), 1209 (s), 1172 (m), 1145

(m), 1129 (vs), 1042 (vs), 902 (vs), 731 (vs).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{24}H_{33}O_5)^+$: 401.2323, found: 401.2318.

(±)-3,11-DIHYDROXY-6A,9,12B-TRIMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2H-BENZO[A]XANTHENE-10-CARBOXYLIC ACID (**361**)



To an ice-cold suspension of *tert*-BuOK (162 mg, 1.44 mmol, 34.0 eq) in Et₂O (0.50 mL) was added water (0.30 mL, 299 mg, 16.6 mmol, 391 eq). After 5 min, a solution of (±)-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**354**) (17 mg, 0.0424 mmol, 1.00 eq) in THF (0.4 mL) and Et₂O (0.4 mL) was added dropwise. The flask was rinsed with 0.4 mL of THF and Et₂O, which was added dropwise to the yellow reaction mixture. After 48 h at RT, the reaction mixture was diluted with water (10 mL) and EtOAc (10 mL) and acidified with aqueous hydrochloric acid solution (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (2 : 8 EtOAc : CH₂Cl₂) afforded (±)-3,11-dihydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (**361**) (8.00 mg, 0.0222 mmol, 52%) as a transparent-white film.

R_f (hexane : EtOAc 1 : 1) = 0.06.

¹H-NMR (400 MHz, CD₃OD): δ (ppm) = 6.11 (d, *J* = 0.8 Hz, 1H, H₄), 3.63 – 3.50 (m, 1H, H₂₀), 2.70 (dd, *J* = 16.9, 5.0 Hz, 1H, H_{9eq}), 2.46 (s, 3H, H₈), 2.37 – 2.23 (m, 1H, H_{9ax}), 1.98 (dt, *J* = 11.8, 3.1 Hz, 1H, H_{13eq}), 1.84 (q, *J* = 5.2, 4.3 Hz, 1H, H_{18eq}), 1.82 – 1.77 (m, 1H, H_{19eq}), 1.78 – 1.64 (m, 1H, H_{13ax}), 1.61 (dtd, *J* = 7.4, 4.7, 2.1 Hz, 1H, H_{21eq}), 1.53 – 1.48 (m, 1H, H₁₀), 1.48 – 1.40 (m, 1H, H_{14eq}), 1.31 – 1.29 (m, 1H, H_{19ax}), 1.28 – 1.28 (m, 3H, H_{14ax} + H₁₅ + H_{21ax}), 1.21 (d, *J* = 0.9 Hz, 3H, H₁₂), 1.18 – 1.04 (m, 1H, H_{18ax}), 0.90 (d, *J* = 0.7 Hz, 3H, H₁₇).

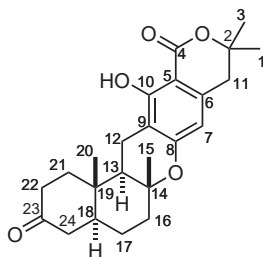
¹³C{¹H}-NMR (101 MHz, CD₃OD): δ (ppm) = 175.6 (C₁), 164.5 (C₇), 159.0 (C₅), 141.8 (C₃), 112.9 (C₄), 108.9 (C₆), 104.9 (C₂), 79.2 (C₁₁), 71.6 (C₂₀), 51.1 (C₁₀), 46.5 (C₁₅), 41.3 (C₁₃), 38.3 (C₁₈), 37.9 (C₂₁), 36.8 (C₁₆), 31.4 (C₁₉), 27.5 (C₁₄), 24.2 (C₈), 21.2

(C12), 18.2 (C9), 12.5 (C17).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3437 (br, s), 2925 (vs), 2853 (s), 1735 (m), 1618 (s), 1577 (s), 1453 (s), 1262 (s), 1034 (s).

HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_{21}\text{H}_{27}\text{O}_5)^-$: 359.1864, found: 359.1863.

(±)-13-HYDROXY-6A,10,10,14B-TETRAMETHYL-1,4,4A,5,6,6A,9,14,14A,14B-DECAHYDRO-2H,10H-BENZO[A]PYRANO[4,3-I]XANTHENE-3,12-DIONE (**362**)



To a dry ice-cold solution of *iso*Pr₂NH (45.7 μ L, 33.0 mg, 0.326 mmol, 1.30 eq) in THF (1.5 mL) was added *n*-BuLi (2.3 M; 0.140 mL, 0.326 mmol, 1.30 eq) dropwise. After 30 min, the reaction was warmed up to 0 °C and after an additional 30 min cooled back down to –78 °C. (±)-2,2,5,7a,13a-Pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (**353**) (100 mg, 0.251 mmol, 1.00 eq) in THF (2.5 mL) was added dropwise. After stirring for 1 h at –78 °C, KOTMS (322 mg, 2.51 mmol, 10.0 eq) was added in one portion. The resulting yellow suspension was gradually warmed up to RT over 13 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (20 mL), the organic layer was separated, and the aqueous phase was further extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (30 mL), the washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 CH₂Cl₂ : EtOAc) afforded (±)-13-hydroxy-6a,10,10,14b-tetramethyl-1,4,4a,5,6,6a,9,14,14a,14b-decahydro-2*H*,10*H*-benzo[*a*]pyrano[4,3-*i*]xanthene-3,12-dione (**362**) (20.0 mg, 0.0603 mmol, 24%) as a white foam.

R_f (hexane : EtOAc 1 : 1) = 0.43.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.63 (s, 1H, OH), 6.16 – 6.09 (m, 1H, H7), 2.86 (d, *J* = 2.4 Hz, 2H, H11), 2.81 (dd, *J* = 16.8, 4.9 Hz, 1H, H12eq), 2.49 (dt, *J* = 8.6, 2.8 Hz, 1H, H12ax), 2.46 – 2.41 (m, 1H, H24eq), 2.41 – 2.35 (m, 1H, H24ax), 2.32 (dd, *J* = 15.5, 1.6 Hz, 1H, H22eq), 2.27 – 2.21 (m, 1H, H22ax), 2.21 – 2.14 (m, 1H, H21eq), 2.10 – 2.03 (m, 1H, H16eq), 1.83 – 1.70 (m, 1H, H16ax), 1.71 – 1.65 (m, 1H, H18), 1.65 – 1.57 (m, 1H, H13), 1.51 (ddt, *J* = 7.3, 4.0, 2.4 Hz, 1H, H17eq), 1.46 (s, 3H, H1), 1.45 (d, *J* = 4.1 Hz, 5H, H3 + H17ax + H21ax overlapping), 1.30 (d, *J* = 0.9 Hz, 3H, H15), 1.08 (s, 3H, H20).

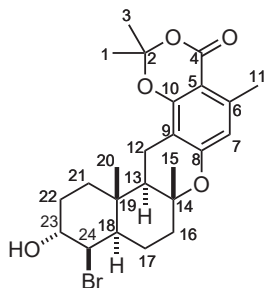
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 210.8 (C23), 169.8 (C4), 161.8 (C10), 159.5

(C8), 137.3 (C6), 108.5 (C9), 108.1 (C7), 100.1 (C5), 81.7 (C2), 78.4 (C14), 49.2 (C13), 46.5 (C18), 44.0 (C22), 39.7 (C16), 39.4 (C11), 38.5 (C21), 37.3 (C24), 36.0 (C19), 27.5 (C1), 27.3 (C3), 26.5 (C17), 21.0 (C15), 17.3 (C12), 11.6 (C20).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm^{-1}) = 2974 (w), 2930 (m), 2865 (w), 1709 (s), 1652 (vs), 1631 (vs), 1584 (s), 1388 (s), 1357 (vs), 1297 (vs), 1267 (s), 1222 (s), 1168 (vs), 1100 (vs), 731 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{31}\text{O}_5)^+$: 399.2166, found: 399.2162.

(±)-10-BROMO-11-HYDROXY-2,2,5,7A,13A-PENTAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (**366**)



To a solution of (±)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthene-7-one (**342**) (77 mg, 0.19 mmol, 1.00 eq) in THF (2.0 mL) and MgCl_2 (7.5 mg, 0.079 mmol, 0.40 eq) was added MeMgBr (3 M in Et_2O ; 0.070 mL, 0.20 mmol, 1.05 eq) dropwise. The resulting mixture was stirred for 24 h while gradually warming up to RT. The reaction mixture was diluted with Et_2O (5 mL) and quenched with a saturated aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with distilled water (10 mL) and a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (6 : 1 pentane : EtOAc $\rightarrow$ 3 : 1) afforded (±)-10-bromo-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (**366**) (46 mg, 0.096 mmol, 50%) as a pale-yellow oil which solidified to a white solid.

R_f (hexane : EtOAc 7 : 3) = 0.23.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.32 (d, J = 1.0 Hz, 1H, H7), 4.25 (q, J = 2.7 Hz, 1H, H24), 4.14 – 4.09 (m, 1H, H23), 2.58 (dd, J = 5.0, 2.8 Hz, 1H, H12eq), 2.55 (s, 3H, H11), 2.34 – 2.26 (m, 1H, H12ax), 2.26 – 2.18 (m, 1H, H21eq), 2.12 – 2.09 (m, 1H, H16eq), 2.08 – 2.05 (m, 1H, H18), 1.80 (d, J = 9.4 Hz, 1H, H17eq), 1.75 (d, J = 12.9 Hz, 1H, H16ax), 1.72 (s, 3H, H1), 1.68 (s, 3H, H3), 1.63 (d, J = 4.4 Hz, 1H, 21ax), 1.61 (d, J = 3.2 Hz, 1H, H22eq), 1.59 (dd, J = 4.8, 2.2 Hz, 1H, H13), 1.56 – 1.49 (m, 1H, H22ax), 1.49 – 1.44 (m, 1H, H17ax), 1.23 (s, 3H, H15), 1.10 (s, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.1 (C4), 158.8 (C8), 156.2 (10), 142.3 (C6), 114.6 (C7), 108.1 (C9), 105.0 (C2), 104.2 (C5), 78.4 (C14), 71.3 (C24), 57.2 (C23), 50.7 (C13), 43.3 (C18), 39.9 (C16), 36.7 (C19), 31.7 (C22), 26.3 (C1), 25.9 (C17), 25.6 (C3),

23.2 (C21), 22.1 (C11), 21.0 (C15), 16.1 (C12), 14.5 (C20).

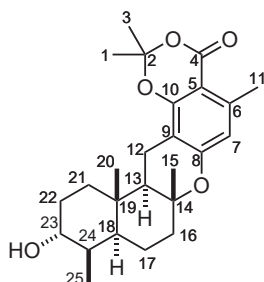
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3439 (s, br), 2993 (w), 2928 (m), 2863 (w), 1701 (vs), 1616 (s), 1571 (vs), 1495 (w), 1450 (m), 1388 (m), 1378 (m), 1296 (vs), 1284 (vs), 1205 (s), 1195 (s), 1168 (vs), 1129 (vs), 1066 (m), 1047 (s), 910 (s), 898 (s), 731 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{32}\text{BrO}_5)^+$: 479.1428, found. 479.1423.

mp. (recrystallized from CH_2Cl_2 /Pentane): 120 °C (decomposition).

Elemental Analysis: calc. for $\text{C}_{24}\text{H}_{31}\text{BrO}_5$: C, 60.13; H, 6.52. Found: C, 59.98; H, 6.48.

(±)-11-HYDROXY-2,2,5,7A,10,13A-HEXAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (367)



To a dry-ice cold suspension of $\text{CuBr} \cdot \text{SMe}_2$ (16 mg, 0.079 mmol, 0.46 eq) in THF (1.0 mL) was added MeMgBr (3 M in Et_2O ; 0.13 mL, 0.40 mmol, 2.4 eq) dropwise. After stirring for 1 h at -78°C , $\text{BF}_3 \cdot \text{OEt}_2$ (46.5%, 0.20 mL) was added dropwise and after 5 min a solution of (±)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthene-7-one (342) (67 mg, 0.17 mmol, 1.00 eq) in THF/ Et_2O (1 : 2; 6.0 mL) was added dropwise. The resulting intense yellow solution was stirred at -78°C for 40 min. The reaction mixture diluted with ether and poured onto an ice-water mixture (30 mL) which was slightly acidified with an aqueous hydrochloric acid solution (1 M, 5 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3 : 1 pentane : Et_2O → 1 : 1) afforded (±)-11-hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (367) (56 mg, 0.14 mmol, 80%) as a white solid.

R_f (hexane : EtOAc 7 : 3) = 0.17.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.33 (d, J = 1.0 Hz, 1H, H7), 3.82 (q, J = 2.6 Hz, 1H, H23), 2.56 (s, 3H, H11), 2.52 (d, J = 5.0 Hz, 1H, H12eq), 2.28 – 2.19 (m, 1H, H12ax), 2.07 (dt, J = 12.3, 3.1 Hz, 1H, H16eq), 1.95 – 1.87 (m, 1H, H17eq), 1.85 (ddd, J = 10.2, 4.9, 2.4 Hz, 1H, H24), 1.82 – 1.76 (m, 1H, H18), 1.72 (s, 3H, H1), 1.68 (s, 3H, H3), 1.67 – 1.63 (m, 1H, H13), 1.63 – 1.59 (m, 1H, H17ax), 1.58 – 1.56 (m, 1H, H22eq), 1.59 – 1.52 (m, 1H, H21eq), 1.46 (dd, J = 13.8, 4.2 Hz, 1H, H21ax), 1.39 – 1.30 (m, 1H, H22ax), 1.20 (d, J = 0.9 Hz, 3H, H15), 0.93 (d, J = 7.6 Hz, 3H, H25), 0.89 (s, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.0 (C4), 158.9 (C7), 156.2 (C10), 142.1 (C6), 114.5 (C7), 108.3 (C9), 104.9 (C2), 104.0 (C5), 78.7 (C14), 71.7 (C23), 50.6 (C13),

42.6 (C18), 41.2 (C24), 40.5 (C16), 36.5 (C19), 32.3 (C21), 26.3 (C1), 25.5 (C3), 24.6 (C22), 24.3 (C17), 22.1 (C11), 20.8 (C15), 16.2 (C12), 14.8 (C20), 14.4 (C25).

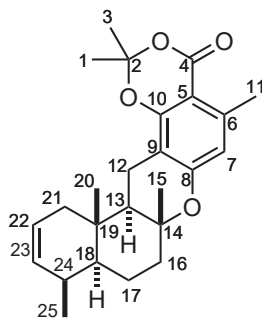
IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3456 (br, s), 2930 (m), 2865 (m), 1707 (s), 1614 (s), 1570 (vs), 1450 (m), 1387 (m), 1283 (vs), 1206 (s), 1197 (s), 1128 (vs), 1042 (vs), 908 (vs), 727 (vs).

HRMS (ES-ToF) m/z : [M - H]⁻ calc. for (C₂₅H₃₃O₅)⁻: 413.2333, found: 413.2334.

mp. (recrystallized from CH₂Cl₂/Pentane): 97 °C-100 °C.

Elemental Analysis: calc. for C₂₅H₃₄O₅: C, 72.44; H, 8.27. Found: C, 72.03; H, 8.07.

(±)-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*A*][1,3]dioxino[5,4-*j*]xanthen-4-one (**368**)



To a solution of (±)-11-hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**367**) (39.0 mg, 0.0941 mmol, 1.00 eq) in THF (1.4 mL) were added acetic acid (7.00 μ L, 7.34 mg, 0.122 mmol, 1.30 eq) and PPh₃ (32.0 mg, 0.122 mmol, 1.30 eq) in one portion. DIAD (24.1 μ L, 25.0 mg, 0.122 mmol, 1.30 eq) was added dropwise and the resulting yellow suspension was stirred for 18 h at RT. The reaction mixture was diluted with Et₂O (5 mL) and quenched with water (5 mL). The organic layer was separated, and the aqueous layer was further extracted with ether (2 x 5 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (7 : 3 pentane : Et₂O $\rightarrow$ 1:1) afforded (±)-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**368**) (4.0 mg, 0.01 mmol, 11%) as a yellow-white solid.

R_f (hexane : EtOAc 1 : 1) = 0.75.

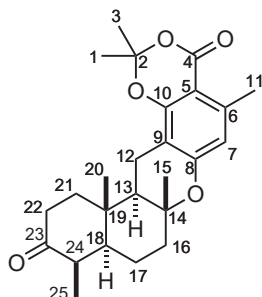
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.34 (s, 1H, H₇), 5.68 (dt, *J* = 10.2, 3.4 Hz, 1H, H₂₃), 5.58 (ddt, *J* = 9.9, 5.8, 1.9 Hz, 1H, H₂₂), 2.57 (s, 3H, H₁₁), 2.53 (dd, *J* = 16.8, 5.0 Hz, 1H, H_{12eq}), 2.35 – 2.28 (m, 1H, H_{12ax}), 2.27 (d, *J* = 3.2 Hz, 1H, H₂₄), 2.17 – 2.11 (m, 1H, H_{16eq}), 2.11 – 2.07 (m, 1H, H_{21eq}), 1.77 (d, *J* = 13.7 Hz, 1H, H_{16ax}), 1.73 (s, 3H, H₁), 1.72 (s, 1H, H_{21ax}), 1.70 (s, 3H, H₃), 1.68 – 1.63 (m, 1H, H₁₈), 1.63 – 1.58 (m, 2H, H₁₇), 1.57 (s, 1H, H₁₃), 1.23 (s, 3H, H₁₅), 0.99 (d, *J* = 7.6 Hz, 3H, H₂₅), 0.92 (d, *J* = 1.0 Hz, 3H, H₂₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 158.8 (C₈), 156.2 (C₁₀), 142.3 (C₆), 133.0 (C₂₃), 123.1 (C₂₂), 114.5 (C₇), 108.3 (C₉), 104.9 (C₂ + C₅ overlapping), 78.5 (C₁₄), 50.0 (C₁₃), 44.9 (C₁₈), 40.5 (C₁₆), 40.1 (C₂₁), 35.7 (C₁₉), 33.9 (C₂₄), 26.3 (C₁), 25.7 (C₃), 24.0 (C₁₇), 22.1 (C₁₁), 20.3 (C₁₅), 16.4 (C₁₂), 15.5 (C₂₅), 15.4 (C₂₀).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2930 (m), 2865 (w), 1728 (vs), 1616 (s), 1574 (vs), 1451 (m), 1387 (m), 1288 (vs), 1208 (s), 1171 (s), 1132 (s), 1038 (m), 901 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{25}\text{H}_{33}\text{O}_4)^+$: 397.2373, found: 397.2386.

(±)-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*A*][1,3]dioxino[5,4-*J*]xanthene-4,11(10*H*)-dione (**369**)



To an ice-cold solution of (±)-11-hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**367**) (68.0 mg, 0.164 mmol, 1.00 eq) in CH₂Cl₂ (4.00 mL) was added DMP (139 mg, 0.328 mmol, 2.00 eq) in two portions over the course of 5 min. The resulting yellow suspension was stirred for 1.5 h at RT. The reaction mixture was concentrated and loaded onto a column with a Celite® pad. Purification by flash column chromatography (1 : 1 pentane : CH₂Cl₂ → 1 : 2) afforded (±)-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (**369**) (60.0 mg, 0.145 mmol, 89%) as a white solid.

R_f (hexane : EtOAc 7 : 3) = 0.26.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.39 – 6.31 (m, 1H, H7), 2.70 – 2.63 (m, 1H, H22eq) 2.63 – 2.58 (m, 1H, H12eq), 2.57 (s, 3H, H11), 2.52 – 2.43 (m, 1H, H24), 2.39 – 2.35 (m, 1H, H22ax), 2.35 – 2.30 (m, 1H, H12ax), 2.15 (dd, *J* = 6.6, 3.2 Hz, 1H, H16eq), 2.1 (dd, *J* = 7.0, 3.7 Hz, 1H, H21eq), 1.89 – 1.79 (m, 1H, H18), 1.77 – 1.75 (m, 1H, H17eq), 1.74 (s, 3H, H1), 1.73 (d, *J* = 1.9 Hz, 1H, H16ax), 1.69 (s, 3H, H3), 1.67 – 1.58 (m, 1H, H13), 1.52 (dd, *J* = 13.3, 6.0 Hz, 1H, H21ax), 1.49 – 1.41 (m, 1H, H17ax), 1.26 (d, *J* = 1.4 Hz, 3H, H15), 1.15 (d, *J* = 7.8 Hz, 3H, H25), 1.11 (s, 3H, H20).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 215.0 (C23), 160.8 (C4), 158.5 (C8), 156.0 (C10), 142.3 (C6), 114.4 (C7), 107.7 (C9), 104.9 (C2), 104.1 (C5), 78.1 (C14), 50.1 (C13), 48.4 (C18), 48.4 (C24), 39.9 (C16), 38.3 (C21), 36.1 (C19), 34.3 (C22), 26.2 (C1), 25.5 (C3), 23.6 (C17), 22.0 (C11), 20.6 (C15), 16.6 (C12), 14.6 (C20), 13.6 (C25).

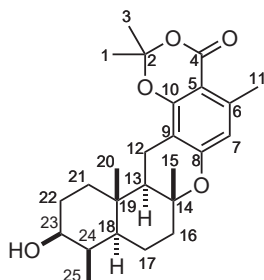
IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2987 (w), 2937 (m), 2867 (w), 1726 (vs), 1616 (s), 1575 (vs), 1452 (m), 1387 (m), 1396 (m), 1288 (vs), 1207 (m), 1170 (s), 1130 (s), 1041 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₂₅H₃₃O₅)⁺: 413.2323, found: 413.2321.

mp. (recrystallized from CH_2Cl_2 /Pentane): 170 °C-171 °C.

Elemental Analysis: calc. for $\text{C}_{25}\text{H}_{32}\text{O}_5$: 72.79; H, 7.82. Found: C, 72.75; H, 7.81.

(±)-11-HYDROXY-2,2,5,7A,10,13A-HEXAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (370)



To an ice-cold solution of (±)-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (369) (21 mg, 0.051 mmol, 1.00 eq) in EtOH (1.0 mL) was added NaBH₄ (2.3 mg, 0.066 mmol, 1.3 eq) in one portion. The resulting yellow suspension was stirred for 1 h at 0 °C. The reaction mixture was diluted with Et₂O (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (3.0 mL). The organic layer was separated and the aqueous layer was further extracted with Et₂O (3 x 5.0 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 2 pentane : Et₂O) afforded (±)-11-hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (370) (18 mg, 0.043 mmol, 85%) as a white foam.

R_f (hexane : EtOAc 7 : 3) = 0.09.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.33 (s, 1H, H₇), 3.76 (ddd, *J* = 9.5, 7.3, 5.6 Hz, 1H, H₂₃), 2.56 (s, 3H, H₁₁), 2.52 (dd, *J* = 17.5, 5.8 Hz, 1H, H_{12eq}), 2.26 – 2.20 (m, 1H, H_{12ax}), 2.08 (dd, *J* = 9.2, 2.9 Hz, 1H, H_{16eq}), 2.06 – 1.98 (m, 1H, H₂₄), 1.82 (dt, *J* = 13.1, 3.5 Hz, 1H, H_{21eq}), 1.75 (s, 1H, H_{17eq}), 1.73 (s, 1H, H_{16ax}), 1.72 (s, 3H, H₁), 1.68 (s, 3H, H₃), 1.65 (dd, *J* = 9.3, 3.5 Hz, 2H, H₂₂), 1.51 (dd, *J* = 13.2, 5.0 Hz, 1H, H₁₃), 1.38 (q, *J* = 2.7, 1.9 Hz, 1H, H_{17ax}), 1.36 (d, *J* = 3.2 Hz, 1H, H₁₈), 1.20 (d, *J* = 1.1 Hz, 3H, H₁₅), 1.09 (dtd, *J* = 13.3, 8.8, 8.2, 3.4 Hz, 1H, H_{21ax}), 0.92 (s, 3H, H₂₅), 0.90 (s, 3H, H₂₀).

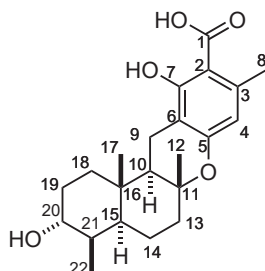
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 158.8 (C₈), 156.2 (C₁₀), 142.3 (C₆), 114.5 (C₇), 108.1 (C₉), 104.9 (C₂), 104.1 (C₅), 78.7 (C₁₄), 73.7 (C₂₃), 50.8 (C₁₃), 48.9 (C₁₈), 40.6 (C₁₆), 40.0 (C₂₄), 37.9 (C₂₁), 36.1 (C₁₉), 26.3 (C₁), 25.8 (C₂₂), 25.6 (C₃), 25.1 (C₁₇), 22.1 (C₁₁), 20.8 (C₁₅), 16.6 (C₁₂), 15.5 (C₂₀), 9.0 (C₂₅).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3438 (br, s), 2930 (m), 2865 (m), 1711 (vs), 1615

(vs), 1572 (vs), 1450 (s), 1388 (s), 1307 (m), 1284 (vs), 1205 (s), 1129 (vs), 1046 (vs), 914 (s), 731 (s).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{25}H_{35}O_5)^+$: 415.2479, found: 415.2474.

(±)-3,11-DIHYDROXY-4,6A,9,12B-TETRAMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2H-BENZO[A]XANTHENE-10-CARBOXYLIC ACID (**371**)



To an ice-cold suspension of *tert*-BuOK (129 mg, 1.15 mmol, 14.4 eq) in Et₂O (0.50 mL) was added water (100 µL, 0.554 mmol, 6.95 eq). After 5 min, a solution of (±)-11-hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**367**) (33.0 mg, 0.0796 mmol, 1.00 eq) in THF (0.8 mL) and Et₂O (0.4 mL) was added dropwise. After 2 weeks at RT, the reaction mixture was diluted with EtOAc (5 mL) and acidified with aqueous hydrochloric acid solution (1 M; 5 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc : CH₂Cl₂ → 3 : 7) afforded (±)-3,11-dihydroxy-4,6a,9,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (**371**) (21.0 mg, 0.0561 mmol, 70%) as a white foam.

R_f (hexane : EtOAc 1 : 1) = 0.05.

¹H-NMR (400 MHz, CD₃OD): δ (ppm) = 6.11 (s, 1H, H₄), 3.73 (q, *J* = 2.7 Hz, 1H, H₂₀), 2.64 (dd, *J* = 16.9, 5.0 Hz, 1H, H_{9eq}), 2.46 (s, 3H, H₈), 2.35 – 2.21 (m, 1H, H_{9ax}), 2.14 – 1.97 (m, 1H, H_{13eq}), 1.97 – 1.89 (m, 1H, H_{19eq}), 1.86 (ddd, *J* = 9.6, 4.6, 2.7 Hz, 1H, H₂₁), 1.81 – 1.76 (m, 1H, H₁₅), 1.76 – 1.73 (m, 1H, H_{14eq}), 1.72 (d, *J* = 9.2 Hz, 1H, H_{13ax}), 1.59 (t, *J* = 4.5 Hz, 1H, H_{19ax}), 1.57 – 1.53 (m, 1H, H₁₀), 1.53 – 1.41 (m, 2H, H₁₈), 1.35 – 1.32 (m, 1H, H_{14ax}), 1.19 (s, 3H, H₁₂), 0.95 (d, *J* = 7.9 Hz, 3H, H₂₂), 0.93 (s, 3H, H₁₇).

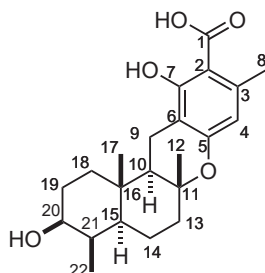
¹³C{¹H}-NMR (101 MHz, CD₃OD): δ (ppm) = 174.9 (C₁), 163.9 (C₇), 158.3 (C₅), 141.1 (C₃), 112.2 (C₄), 108.1 (C₆), 10.49 (C₂), 78.6 (C₁₁), 71.9 (C₂₀), 51.9 (C₁₀), 43.3 (C₂₁), 41.6 (C₁₅), 41.2 (C₁₃), 36.9 (C₁₆), 33.0 (C₁₈), 25.1 (C₁₄), 24.1 (C₁₉), 23.6 (C₈), 20.4 (C₁₂), 16.7 (C₉), 14.5 (C₂₂), 14.1 (C₁₇).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3420 (br, m), 2927 (s), 2864 (m), 1711 (w), 1621

(vs), 1578 (s), 1453 (s), 1264 (vs), 1170 (s).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{22}H_{31}O_5)^+$: 375.2166, found: 375.2176.

(±)-3,11-DIHYDROXY-4,6A,9,12B-TETRAMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2H-BENZO[A]XANTHENE-10-CARBOXYLIC ACID (**372**)



To an ice-cold suspension of *tert*-BuOK (160 mg, 1.43 mmol, 32.8 eq) in Et₂O (0.50 mL) was added water (300 mL, 16.6 mmol, 382 eq). After 5 min, a solution of (±)-11-hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (**370**) (18.0 mg, 0.0434 mmol, 1.00 eq) in THF (0.4 mL) and Et₂O (0.4 mL) was added dropwise. The flask was rinsed with 0.6 mL of THF and Et₂O, which was added dropwise to the yellow reaction mixture. After 48 h at RT, the reaction mixture was diluted with EtOAc (5 mL) and acidified with aqueous hydrochloric acid solution (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc : CH₂Cl₂ → 3 : 7) afforded (±)-3,11-dihydroxy-4,6a,9,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (**372**) (6.0 mg, 0.0160 mmol, 37%) as a white film.

R_f (hexane : EtOAc 1 : 1) = 0.07.

¹H-NMR (400 MHz, CD₃OD): δ (ppm) = 6.11 (d, *J* = 0.9 Hz, 1H, H₄), 3.72 (dt, *J* = 11.6, 5.0 Hz, 1H, H₂₀), 2.67 – 2.57 (m, 1H, H_{9eq}), 2.46 (s, 3H, H₈), 2.35 – 2.24 (m, 1H, H_{9ax}), 2.08 – 2.02 (m, 1H, H_{13eq}), 2.01 – 1.98 (m, 1H, H₂₁), 1.81 (dd, *J* = 8.6, 4.9 Hz, 1H, H_{18eq}), 1.77 (d, *J* = 6.0 Hz, 1H, H_{13ax}), 1.75 – 1.66 (m, 1H, H_{14eq}), 1.62 (tt, *J* = 9.2, 4.2 Hz, 1H, H_{19eq}), 1.49 (dd, *J* = 13.1, 5.0 Hz, 1H, H₁₀), 1.46 – 1.38 (m, 3H, H_{14ax} + H₁₅ + H_{19ax} overlapping), 1.19 (d, *J* = 0.8 Hz, 3H, H₁₂), 1.18 – 1.07 (m, 1H, H_{18ax}), 0.94 (d, *J* = 0.7 Hz, 3H, H₁₇), 0.91 (d, *J* = 7.5 Hz, 3H, H₂₂).

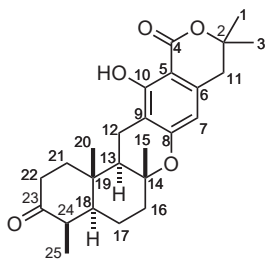
¹³C{¹H}-NMR (101 MHz, CD₃OD): δ (ppm) = 175.6 (C₁), 164.5 (C₇), 158.9 (C₅), 141.8 (C₃), 112.8 (C₄), 108.7 (C₆), 105.4 (C₂), 79.2 (C₁₁), 74.5 (C₂₀), 52.5 (C₁₀), 50.1 (C₁₅), 41.8 (C₁₃), 41.5 (C₂₁), 39.0 (C₁₈), 37.2 (C₁₆), 33.1 (C₁₉), 26.2 (C₁₄), 24.2 (C₈), 21.0

(C12), 17.7 (C9), 15.9 (C17), 9.5 (C22).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3421 (br, s), 2922 (s), 2852 (m), 1651 (s), 1622 (s), 1456 (s), 1264 (s), 1045 (s).

HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_{22}\text{H}_{29}\text{O}_5)^-$: 373.2020, found: 373.2010.

($\pm$)-13-HYDROXY-4,6A,10,10,14B-PENTAMETHYL-1,4,4A,5,6,6A,9,14,14A,14B-DECAHYDRO-2H,10H-BENZO[A]PYRANO[4,3-I]XANTHENE-3,12-DIONE (**373**)



To a dry ice-cold solution of *iso*Pr₂NH (25.6 μ L, 19.0 mg, 0.189 mmol, 1.30 eq) in THF (0.5 mL) was added *n*-BuLi (2.3 M; 0.0800 mL, 0.189 mmol, 1.30 eq) dropwise. After 30 min, the reaction was warmed up to 0 °C and after an additional 30 min cooled back down to –78 °C. ($\pm$)-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4H,9H-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10H)-dione (**369**) (60.0 mg, 0.145 mmol, 1.00 eq) in THF (1.0 mL) was added dropwise. After stirring for 1 h at –78 °C, KOTMS (187 mg, 1.45 mmol, 10.0 eq) was added in one portion. The resulting yellow suspension was gradually warmed up to RT over 12 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL), the organic layer was separated, and the aqueous phase was further extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 CH₂Cl₂ : EtOAc) afforded ($\pm$)-13-hydroxy-4,6a,10,10,14b-pentamethyl-1,4,4a,5,6,6a,9,14,14a,14b-decahydro-2H,10H-benzo[*a*]pyrano[4,3-*i*]xanthene-3,12-dione (**373**) (20.0 mg, 0.0485 mmol, 33%) as a white film.

R_f (hexane : EtOAc 1 : 1) = 0.55.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.62 (s, 1H, OH), 6.12 (d, *J* = 1.0 Hz, 1H, H7), 2.86 (d, *J* = 2.5 Hz, 2H, H11), 2.80 (dd, *J* = 16.8, 5.0 Hz, 1H, H12eq), 2.56 – 2.45 (m, 1H, H22eq), 2.44 – 2.40 (m, 1H, H12ax), 2.40 – 2.35 (m, 1H, H22ax), 2.37 – 2.27 (m, 1H, H24), 2.23 – 2.14 (m, 1H, H21eq), 2.09 (dq, *J* = 13.1, 3.0 Hz, 1H, H16eq), 1.84 (dq, *J* = 11.0, 3.5, 2.6 Hz, 1H, H17eq), 1.73 – 1.62 (m, 1H, H16ax), 1.62 – 1.55 (m, 1H, H13), 1.46 (s, 3H, H1), 1.44 (s, 3H, H3), 1.40 (dt, *J* = 7.2, 3.6 Hz, 1H, H21ax), 1.36 (dq, *J* = 5.3, 2.4 Hz, 1H, H17ax), 1.33 (d, *J* = 2.1 Hz, 1H, H18), 1.29 (d, *J* = 0.9 Hz, 3H, H15), 1.14 (s, 3H, H20), 1.04 (d, *J* = 6.6 Hz, 3H, H25).

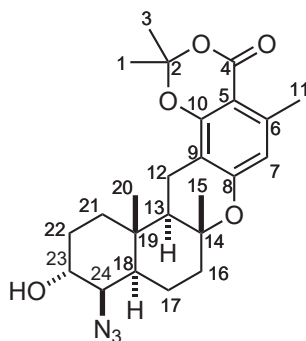
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 212.3 (C23), 169.8 (C4), 161.8 (C10), 159.5

(C8), 137.3 (C6), 108.5 (C9), 108.1 (C7), 100.1 (C5), 81.7 (C2), 78.0 (C14), 53.1 (C18), 49.5 (C13), 44.7 (C24), 39.9 (C16), 39.4 (C11), 39.0 (C21), 37.2 (C22), 36.8 (C19), 27.5 (C1), 27.3 (C3), 23.3 (C17), 20.9 (C15), 17.3 (C12), 12.8 (C20), 11.8 (C25).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2974 (w), 2932 (m), 2865 (m), 1707 (s), 1653 (vs), 1631 (vs), 1585 (s), 1388 (s), 1357 (vs), 1297 (vs), 1285 (vs), 1223 (m), 1169 (vs), 1100 (vs), 732 (s).

HRMS (ES-ToF) m/z : [M + H]⁺ calc. for (C₂₅H₃₃O₅)⁺: 413.2323, found: 413.2325.

(±)-AZIDO-11-HYDROXY-2,2,5,7A,13A-PENTAMETHYL-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-4-ONE (374)



To a solution of (±)-3a,6,9,9,11b-pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthene-7-one (342) (85.0 mg, 0.213 mmol, 1.00 eq) in DMF (3.5 mL) and glacial acetic acid (0.5 mL) was added NaN_3 (166 mg, 2.56 mmol, 12.0 eq) in one portion. The reaction mixture was heated to 110 °C for 15 h after which the reaction mixture was poured onto an ice water – saturated sodium hydrogen carbonate mixture (1 : 1; 100 mL). The reaction mixture was diluted with EtOAc and stirred for 30 min. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium hydrogencarbonate solution (20 mL), water (20 mL) and a saturated aqueous sodium chloride solution (25 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Filtering through a small silica plug with EtOAc gave crude (±)-azido-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4-one (374) which was used without further purification in the next step.

R_f (hexane : EtOAc 4 : 1) = 0.18.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.32 (s, 1H, H7), 4.05 (q, J = 2.8 Hz, 1H, H23), 3.58 (td, J = 3.0, 1.4 Hz, 1H, H24), 2.57 (s, 4H, H11 and H12eq overlapping), 2.36 (s, 1H), 2.25 (dd, J = 16.8, 13.1 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.06 – 2.00 (m, 1H), 1.96 (ddd, J = 14.9, 4.6, 2.2 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.82 (dd, J = 13.0, 10.2 Hz, 1H), 1.78 (d, J = 5.3 Hz, 1H), 1.72 (s, 3H, H1), 1.68 (s, 3H, H3), 1.65 – 1.48 (m, 3H), 1.25 (s, 3H, H15 overlapping with grease), 1.01 (s, 3H, H20).

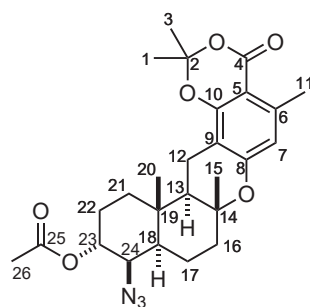
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.1 (C4), 158.8 (C8), 156.2 (C10), 142.2 (C6), 114.5 (C7), 108.1 (C9), 104.9 (C2), 104.1 (C5), 78.4 (C14), 67.9 (C23), 66.8 (C24), 50.2 (C13), 43.4 (C18), 40.1 (C16), 36.1 (C19), 32.0 (C21), 26.2 (C1), 25.6 (C3), 24.3 (C22),

24.0 (C17), 22.1 (C11), 21.0 (C15), 16.2 (C12), 13.7 (C20).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3466 (br, s), 2924 (s), 2856 (m), 2099 (vs), 1728 (s), 1706 (s), 1616 (s), 1573 (vs), 1452 (m), 1377 (m), 1288 (vs), 1209 (m), 1130 (m), 1052 (m).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₂₄H₃₂N₃O₅)⁺: 442.2336, found: 442.2336.

(±)-10-AZIDO-2,2,5,7A,13A-PENTAMETHYL-4-OXO-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-11-YL ACETATE (375)



To a solution of crude (±)-azido-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (374) in CH₂Cl₂ (2.5 mL) was added NEt₃ (0.595 mL, 432 mg, 4.27 mmol, 20.0 eq) dropwise, followed by dropwise addition of Ac₂O (0.202 mL, 218 mg, 2.13 mmol, 10.0 eq). To this mixture DMAP (26.1 mg, 0.213 mmol, 1.00 eq) was added in one portion. The yellow-orange reaction mixture was stirred for 2 h at RT. The reaction mixture was diluted with CH₂Cl₂ (5.0 mL) and quenched with a saturated aqueous sodium hydrogencarbonate solution (20 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (25 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 5 : 4 EtOAc : pentane : CH₂Cl₂) gave (±)-10-azido-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (375) (65.0 mg, 0.134 mmol, 63%) as a yellow-white solid.

R_f (hexane : EtOAc 4 : 1) = 0.18.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.32 (s, 1H, H7), 4.98 (q, J = 2.9 Hz, 1H, H23), 3.61 (td, J = 2.9, 1.3 Hz, 1H, H24), 2.55 (s, 3H, H11), 2.52 (d, J = 4.9 Hz, 1H, H12eq),

2.25 (dd, $J = 16.8, 13.3$ Hz, 1H, H12ax), 2.10 (ddd, $J = 14.2, 8.4, 2.7$ Hz, 1H, H16eq), 2.05 (s, 3H, H26), 1.98 – 1.89 (m, 1H, H22eq), 1.84 – 1.76 (m, 1H, H17eq), 1.72 (s, 1H, H16ax), 1.71 (d, $J = 4.4$ Hz, 5H, H1 + H18 + H22ax overlapping), 1.68 (d, $J = 2.7$ Hz, 1H, H21eq), 1.66 (s, 3H, H3), 1.61 (dd, $J = 13.2, 4.8$ Hz, 1H, H13), 1.52 (dd, $J = 9.2, 3.1$ Hz, 1H, H17ax), 1.33 (d, $J = 10.2$ Hz, 1H, H21ax), 1.24 (s, 3H, H15), 1.01 (s, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 170.0 (C25), 160.9 (C4), 158.7 (C8), 156.2 (C10), 142.3 (C6), 114.4 (C7), 108.0 (C9), 104.9 (C2), 104.2 (C5), 78.3 (C14), 70.2 (C23), 63.9 (C24), 50.3 (C13), 44.7 (C18), 40.1 (C16), 35.8 (C19), 32.6 (C21), 26.2 (C1), 25.6 (C3), 23.9 (C17), 22.1 (C11), 21.5 (C26), 21.4 (C22), 21.1 (C15), 16.2 (C12), 13.9 (C20).

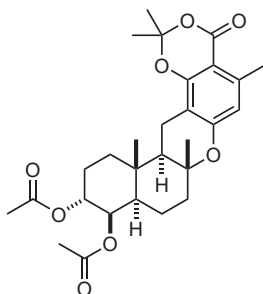
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2994 (w), 2937 (m), 2866 (w), 2100 (s), 1727 (vs), 1616 (s), 1574 (s), 1451 (m), 1375 (s), 1286 (vs), 1232 (s), 1206 (s), 1170 (s), 1129 (s), 1047 (m), 910 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{26}\text{H}_{34}\text{N}_3\text{O}_5)^+$: 484.2442, found: 484.2444.

mp. (recrystallized from CH_2Cl_2 /Pentane): 74 °C–79 °C.

Elemental Analysis: calc. for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_5$: C, 64.58; H, 6.88; N, 8.69. Found: C, 64.16; H, 6.81; N, 8.62.

($\pm$)-2,2,5,7A,13A-PENTAMETHYL-4-OXO-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4H,9H-BENZO[A][1,3]DIOXINO[5,4-J]XANTHENE-10,11-DIYL DIACETATE (376)



Synthesis according to the procedure above. Purification by flash column chromatography (1 : 5 : 4 EtOAc : pentane : CH_2Cl_2) gave ($\pm$)-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4H,9H-benzo[a][1,3]dioxino[5,4-j]xanthene-10,11-diyl diacetate (376) (7.0 mg, 0.014 mmol, 7%) as a yellow-white film.

R_f (hexane : EtOAc 4 : 1) = 0.25

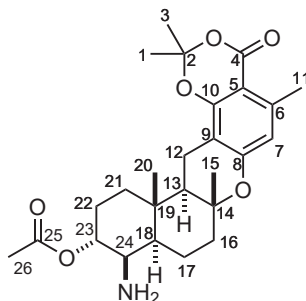
^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 6.33 (s, 1H), 4.95 – 4.90 (m, 1H), 4.86 (p, $J = 2.8$ Hz, 1H), 2.57 (s, 5H), 2.35 – 2.20 (m, 1H), 2.08 (d, $J = 1.7$ Hz, 2H), 2.05 (d, $J = 5.3$ Hz, 4H), 2.03 – 1.87 (m, 2H), 1.88 – 1.75 (m, 1H), 1.72 (d, $J = 3.0$ Hz, 4H), 1.68 (s, 4H), 1.66 – 1.50 (m, 4H), 1.44 – 1.30 (m, 1H), 1.26 (d, $J = 7.2$ Hz, 4H), 1.02 (s, 2H).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 169.9, 169.7, 160.9, 158.7, 156.2, 142.3, 114.5, 108.0, 104.9, 104.2, 78.3, 72.8, 69.3, 50.3, 44.4, 40.1, 35.8, 32.7, 29.8, 26.4, 25.5, 23.1, 21.8, 21.3, 21.2, 21.1, 16.3, 14.0.

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2994 (w), 2928 (m), 2964 (w), 1723 (vs), 1615 (s), 1572 (s), 1450 (s), 1366 (s), 1279 (vs), 1225 (vs), 1206 (vs), 1196 (vs), 1169 (vs), 1128 (vs), 1024 (vs), 909 (s), 728 (vs).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{28}\text{H}_{37}\text{O}_8)^+$: 501.2483, found: 501.2493.

(±)-10-AMINO-2,2,5,7A,13A-PENTAMETHYL-4-OXO-7A,8,9A,10,11,12,13,13A,13B,14-
DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-11-YL ACETATE
(377)



To a solution of (±)-10-azido-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (375) (20 mg, 0.041 mmol, 1.00 eq) in THF (3.0 mL) and water (5.0 μ L) was added PMe_3 (1 M in THF; 0.10 mL, 0.10 mmol, 2.5 eq) dropwise. The reaction mixture was warmed to 35 °C after which after which aqueous NaOH (2 M; 0.10 mL) was added dropwise. The reaction mixture was stirred at 35 °C for 5 h after which the reaction mixture was poured onto a water – EtOAc mixture (1 : 1, 15 mL). The reaction mixture was neutralized to pH = 7 with a saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (25 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure to give crude (±)-10-amino-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (377) which was used without further purification in the next step.

R_f (hexane : EtOAc 7 : 3) = 0.01.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.33 (d, J = 0.9 Hz, 1H, H7), 5.08 – 4.90 (m, 5H, NH₂), 4.84 (q, J = 2.7 Hz, 1H, H, H23), 3.04 (d, J = 3.3 Hz, 1H, H24), 2.56 (s, 5H, H11 + H12eq + H22eq overlapping), 2.53 (d, J = 5.1 Hz, 1H, H22ax), 2.31 – 2.20 (m, 1H, H12ax), 2.16 – 2.06 (m, 1H, H16eq), 2.04 (s, 3H, H26), 1.83 – 1.76 (m, 2H, H16ax + H17eq overlapping), 1.72 (s, 4H, H1 + H18 overlapping), 1.69 (s, 1H, H21eq), 1.67 (s, 4H, H3 + H13 overlapping), 1.48 (ddd, J = 9.3, 7.1, 4.6 Hz, 1H, H17ax), 1.37 – 1.33 (m, 1H, H21ax), 1.23 (s, 3H, H15), 1.07 (s, 3H, H20).

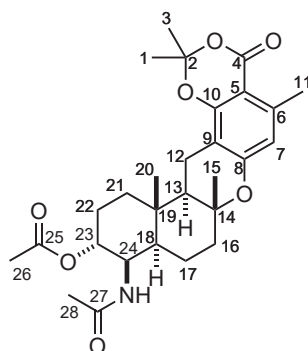
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 170.3 (C25), 161.0 (C4), 158.7 (C8), 156.2 (C10), 142.3 (C6), 114.5 (C7), 108.0 (C9), 104.9 (C2), 104.2 (C5), 78.4 (C14), 73.2 (C23),

54.4 (C24), 50.5 (C13), 44.2 (C18), 40.3 (C16), 35.8 (C19), 33.0 (C21), 26.3 (C1), 25.6 (C3), 23.6 (C17), 22.1 (C11), 21.5 (C26), 21.0 (C22), 20.9 (C15), 16.2 (C12), 14.8 (C20).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3430 (br, m), 2926 (m), 2863 (w), 1727 (vs), 1618 (s), 1573 (vs), 1452 (m), 1375 (m), 1282 (vs), 1243 (m), 1203 (m), 1170 (m), 1129 (vs) 1042 (m).

HRMS (ES-ToF) m/z : [M + H]⁺ calc. for (C₂₆H₃₆NO₆)⁺: 458.2537, found: 458.2554; Also found m/z : [M + CH₃CN + H]⁺ (C₂₈H₃₉N₂O₆)⁺: calc. 499.2803, found: 499.2844.

(±)-10-ACETAMIDO-2,2,5,7A,13A-PENTAMETHYL-4-OXO-7A,8,9A,10,11,12,13,13A,13B,14-DECAHYDRO-4*H*,9*H*-BENZO[*A*][1,3]DIOXINO[5,4-*J*]XANTHEN-11-YL ACETATE (378)



To a solution of crude (±)-10-amino-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-11-yl acetate (377) in CH₂Cl₂ (2.0 mL) was added NEt₃ (29 μ L, 21 mg, 0.21 mmol, 5.0 eq) dropwise, followed by dropwise addition of Ac₂O (8.0 μ L, 8.6 mg, 0.083 mmol, 2.0 eq). To this mixture DMAP (5.0 mg, 0.041 mmol, 1.00 eq) was added in one portion. The yellow-orange reaction mixture was stirred for 2 h at RT. The reaction mixture was diluted with CH₂Cl₂ (5.0 mL) and quenched with a saturated aqueous sodium hydrogencarbonate solution (10 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (7 : 3 EtOAc : CH₂Cl₂) gave (±)-10-acetamido-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-11-yl acetate (378) (20 mg, 0.040 mmol, 97%) as a white foam.

R_f (hexane : EtOAc 1 : 2) = 0.09.

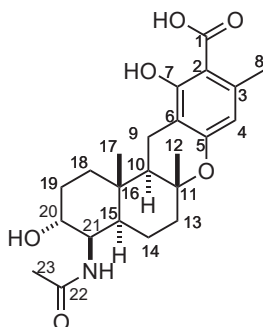
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.34 (s, 1H, H7), 5.49 (d, J = 9.2 Hz, 1H, NH), 4.86 (q, J = 2.7 Hz, 1H, H23), 4.15 (dd, J = 10.1, 3.9 Hz, 1H, H24), 2.57 (s, 3H, H11), 2.56 (d, J = 4.6 Hz, 1H, H12eq), 2.31 – 2.20 (m, 1H, H12ax), 2.14 – 2.09 (m, 1H, H16eq), 2.04 (s, 3H, H26), 2.01 (s, 3H, H28), 1.95 (d, J = 11.0 Hz, 1H, H22eq), 1.87 – 1.84 (m, 1H, H18), 1.83 (d, J = 8.3 Hz, 1H, H16ax), 1.78 (dd, J = 11.7, 6.2 Hz, 1H, H22ax), 1.72 (s, 3H, H1), 1.69 (d, J = 8.7 Hz, 1H, H13), 1.67 (s, 3H, H3), 1.66 (s, 1H, H21eq), 1.58 (d, J = 3.8 Hz, 1H, H17eq), 1.43 – 1.28 (m, 1H, H21ax), 1.27 (d, J = 2.9 Hz, 1H, H17ax), 1.21 (s, 3H, H15), 1.01 (s, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 169.8 (C25), 169.7 (C27), 160.9 (C4), 158.6 (C8), 156.2 (C10), 142.5 (C6), 114.5 (C7), 107.6 (C9), 105.0 (C2), 104.2 (C5), 78.1 (C14), 70.6 (C23), 51.6 (C24), 50.4 (C13), 43.3 (C18), 39.9 (C16), 35.8 (C19), 32.2 (C21), 26.4 (C1), 25.5 (C3), 23.8 (C28), 23.1 (C17), 22.1 (C11), 21.5 (C26), 21.4 (C22), 20.9 (C15), 16.2 (C12), 14.4 (C20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3331 (br, m), 2926 (m), 2858 (w), 1728 (vs), 1653 (m), 1616 (s), 1573 (vs), 1452 (m), 1375 (m), 1281 (vs), 1238 (vs), 1206 (s), 1170 (s), 1129 (vs), 1044 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{28}\text{H}_{38}\text{NO}_7)^+$: 500.2643, found: 500.2635. Also found m/z : $[\text{M} + \text{CH}_3\text{CN} + \text{Na}]^+$ ($\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_7 + \text{Na}$) $^+$: calc. 563.2733, found: 563.2762.

(±)-4-ACETAMIDO-3,11-DIHYDROXY-6A,9,12B-TRIMETHYL-1,3,4,4A,5,6,6A,12,12A,12B-DECAHYDRO-2*H*-BENZO[*A*]XANTHENE-10-CARBOXYLIC ACID (**379**)



To a solution of (±)-10-acetamido-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (**378**) (30 mg, 0.060 mmol, 1.0 eq) in THF (2.0 mL) was added aqueous KOH (2*M*; 2.0 mL, 4.0 mmol, 67 eq) in one portion. The yellow-orange biphasic reaction mixture was vigorously stirred at 60 °C for 4 days. The reaction mixture was diluted with EtOAc (5.0 mL) and water (5.0 mL) acidified to pH = 1 with aqueous hydrochloric acid (1*M*). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (100% EtOAc) gave (±)-4-acetamido-3,11-dihydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (**379**) (12 mg, 0.028 mmol, 48%) as a white foam.

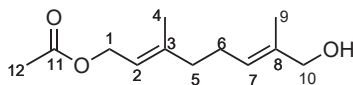
R_f (EtOAc 100%) = 0.01.

$^1\text{H-NMR}$ (400 MHz, CD_3OD): δ (ppm) = 7.14 (d, J = 9.2 Hz, 1H, NH), 6.12 (d, J = 0.9 Hz, 1H, H₄), 4.09 – 4.01 (m, 1H, H₂₁), 3.75 (q, J = 2.8 Hz, 1H, H₂₀), 2.66 (dd, J = 16.9, 5.0 Hz, 1H, H_{9eq}), 2.51 (d, J = 2.8 Hz, 1H, H_{19eq}), 2.46 (s, 3H, H₈), 2.29 (dd, J = 16.9, 13.2 Hz, 1H, H_{9ax}), 2.03 (d, J = 9.6 Hz, 1H, H_{13eq}), 2.01 (s, 1H, H_{19ax}), 2.00 (s, 3H, H₂₃), 1.97 – 1.89 (m, 1H, H₁₅), 1.73 (tt, J = 11.8, 6.2 Hz, 1H, H_{13ax}), 1.63 (d, J = 24.2 Hz, 1H, H_{14eq}), 1.58 (d, J = 6.6 Hz, 1H, H₁₀), 1.56 (s, 2H, H_{14ax} + H_{18eq} overlapping), 1.48 – 1.39 (m, 1H, H_{18ax}), 1.20 (s, 3H, H₁₂), 1.02 (s, 3H, H₂₀).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CD_3OD): δ (ppm) = 173.2 (C₂₂), 164.5 (C₁), 158.8 (C₅), 155.5 (C₇), 141.8 (3), 112.8 (C₄), 109.8 (C₆), 108.6 (C₂), 78.8 (C₁₁), 69.5 (C₂₀), 55.5 (C₂₁), 52.1 (C₁₀), 44.5 (C₁₅), 41.4 (C₁₃), 36.9 (C₁₆), 33.1 (C₁₈), 24.9 (C₁₉), 24.5 (C₁₄), 24.2 (C₈), 22.8 (C₂₃), 21.0 (C₁₂), 17.3 (C₉), 14.1 (C₁₇).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm^{-1}) = 3392 (br, s), 2932 (m), 2867 (m), 1651 (vs), 1645 (vs), 1634 (vs), 1622 (vs), 1576 (s), 1456 (s), 1418 (s), 1377 (m), 1297 (m), 1262 (s), 1171 (m), 1125 (m), 1053 (m). .

HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{23}\text{H}_{32}\text{NO}_6)^+$: 418.2224, found: 418.2218.

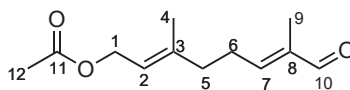
(2*E*,6*E*)-8-HYDROXY-3,7-DIMETHYLOCTA-2,6-DIEN-1-YL ACETATE (**386**)

Synthesized according to a modified literature procedure by Sharpless et. al.:^[224] To a suspension of SeO_2 (283 mg, 2.50 mmol, 0.10 eq) and salicylic acid (353 mg, 2.50 mmol, 0.10 eq) in CH_2Cl_2 (100 mL) was added *tert*-butyl hydroperoxide (70 wt. % in H_2O ; 10.0 mL, 50.0 mmol, 2.00 eq) in one portion. To the ice cold reaction mixture was added (*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate (**385**) (5.35 mL, 25.0 mmol, 1.00 eq) dropwise over the course of 5 min. The reaction mixture was stirred for 6 h at RT after which it was diluted with EtOAc (50 mL) and quenched with an aqueous sodium hydrocarbonate solution (5 wt. %; 100 mL). The organic layer was separated and washed with a saturated aqueous copper(II) sulfate solution (70 mL), a saturated aqueous sodium thiosulfate solution (100 mL), water (50 mL) and a saturated aqueous sodium chloride solution (70 mL). The combined aqueous layers were dried over magnesium sulphate. The dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc $\rightarrow$ 3 : 1) afforded (2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (**386**) (1.47 g, 6.92 mmol, 28%) as colourless to pale-yellow oil.

R_f (hexane : EtOAc 4 : 1) = 0.14.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 5.35 (dtp, J = 11.1, 7.1, 1.2 Hz, 2H, H₂ + H₇ overlapping), 4.58 (d, J = 7.1 Hz, 2H, H₁), 4.02 – 3.96 (m, 2H, H₁₀), 2.17 (q, J = 7.4, 6.9 Hz, 2H, H₆), 2.09 (d, J = 7.8 Hz, 2H, H₅), 2.05 (s, 3H, H₁₂), 1.70 (d, J = 1.5 Hz, 3H, H₄), 1.66 (d, J = 1.6 Hz, 3H, H₉), 1.62 – 1.57 (m, 1H, OH).

Analytic data was in agreement with literature values.^[225]

(2*E*,6*E*)-3,7-DIMETHYL-8-oxoocta-2,6-dien-1-yl acetate (387)

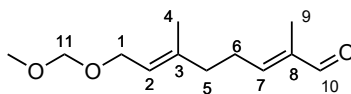
Synthesized according to a modified literature procedure by Cole and Hsung.^[284] To an ice-cold solution of (2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (**386**) (1.47 g, 6.92 mmol, 1.00 eq) in CH₂Cl₂ (30.0 mL) was added DMP (3.52 g, 8.30 mmol, 1.20 eq) in several portions over the course of 5 min. The resulting yellow suspension was stirred for 1 h at RT. The reaction mixture was concentrated and loaded onto a column with a Celite[®] pad. Purification by flash column chromatography (4 : 1 pentane : EtOAc) afforded (2*E*,6*E*)-3,7-dimethyl-8-oxoocta-2,6-dien-1-yl acetate (**387**) (1.37 g, 6.52 mmol, 94%) as colourless to pale-yellow oil.

R_f (hexane : EtOAc 4 : 1) = 0.32.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 9.38 (d, *J* = 1.7 Hz, 1H, H₁₀), 6.44 (tt, *J* = 7.3, 1.4 Hz, 1H, H₇), 5.38 (ddt, *J* = 8.7, 7.0, 1.6 Hz, 1H, H₂), 4.59 (d, *J* = 7.0 Hz, 2H, H₁), 2.49 (q, *J* = 7.5 Hz, 2H, H₆), 2.23 (t, *J* = 7.6 Hz, 2H, H₅), 2.07 – 2.02 (m, 3H, H₁₂), 1.78 – 1.71 (m, 6H, H₄ + H₉ overlapping).

(2*E*,6*E*)-3,7-Dimethyl-8-oxoocta-2,6-dien-1-yl acetate (**387**) (525 mg, 2.50 mmol, 10%) was also formed during the SeO₂ oxidation of geraniol acetate (**385**).

Analytic data was in agreement with literature values.^[284]

(2*E*,6*E*)-8-(METHOXYMETHOXY)-2,6-DIMETHYLOCTA-2,6-DIENAL (**390**)

Synthesized using a modified literature procedure by Cole and Hsung.^[284] To an ice-cold solution of (2*E*,6*E*)-8-(methoxymethoxy)-2,6-dimethylocta-2,6-dien-1-ol (**307**) (147 mg, 0.686 mmol, 1.00 eq) in CH₂Cl₂ (3.00 mL) was added DMP (349 mg, 0.823 mmol, 1.20 eq) in one portion. The reaction mixture was stirred for 1.5 h at RT. The mixture was loaded onto a column through a Celite[®] pad. Purification by flash column chromatography (4 : 1 pentane : Et₂O) afforded (2*E*,6*E*)-8-(methoxymethoxy)-2,6-dimethylocta-2,6-dienal (**390**) (97.0 mg, 0.457 mmol, 66%) as colourless to pale-yellow oil.

R_f (hexane : EtOAc 3 : 1) = 0.30.

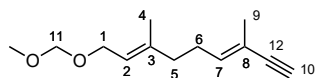
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 9.39 (d, *J* = 0.7 Hz, 1H, H₁₀), 6.46 (tt, *J* = 7.3, 1.4 Hz, 1H, H₇), 5.41 (tq, *J* = 7.0, 1.3 Hz, 1H, H₂), 4.63 (d, *J* = 0.8 Hz, 2H, H₁₁), 4.09 (d, *J* = 6.9 Hz, 2H, H₁), 3.38 (d, *J* = 0.8 Hz, 3H, -OMe), 2.56 – 2.46 (m, 2H, H₆), 2.23 (t, *J* = 7.6 Hz, 2H, H₅), 1.75 (d, *J* = 1.2 Hz, 3H, H₉), 1.72 (d, *J* = 1.2 Hz, 3H, H₄).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 195.3 (C₁₀), 153.8 (C₇), 139.8 (C₈), 139.2 (C₃), 121.7 (C₂), 95.8 (C₁₁), 63.7 (C₁), 55.4 (-OMe), 38.0 (C₅), 27.2 (C₆), 16.5 (C₄), 9.4 (C₉).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2941 (m), 2920 (m), 1889 (w), 1685 (vs), 1148 (s), 1102 (m), 1046 (vs), 1085 (w).

HRMS (ES-ToF) *m/z*: [M – H][–] calc. for (C₁₂H₁₉O₃)[–]: 211.1340, found: 211.1339.

(2*E*,6*E*)-8-(Methoxymethoxy)-2,6-dimethylocta-2,6-dienal (**390**) (102 mg, 0.480 mmol, 9%) was also formed during the SeO₂ oxidation of MOM-protected geraniol (**306**).

(3*E*,7*E*)-9-(METHOXYMETHOXY)-3,7-DIMETHYLNONA-3,7-DIEN-1-YNE (**391**)

Synthesized using a modified literature procedure by de Lera et. al.:^[431] To an ice-cold solution of CBr_4 (319 mg, 0.961 mmol, 2.00 eq) in CH_2Cl_2 (3.00 mL) was added PPh_3 (504 mg, 1.92 mmol, 4.00 eq) in one portion. The intense-yellow orange solution was stirred for 10 min at 0°C . A solution of (2*E*,6*E*)-8-(Methoxymethoxy)-2,6-dimethylocta-2,6-dienal (**390**) (102 mg, 0.480 mmol, 1.00 eq) in CH_2Cl_2 (2.00 mL) was added dropwise. The resulting solution was stirred for 15 min at 0°C . The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution (10 mL) and warmed to RT. The mixture was poured into a mixture of a saturated aqueous sodium hydrogen carbonate solution and CH_2Cl_2 (1:1 vol %; 20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 * 20 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The resulting white solid was suspended in a hexane : Et_2O mixture (1 : 1 vol%; 50 mL) and filtered through a Celite[®] pad. This process was repeated two times. The combined organic fractions were concentrated under reduced pressure which afforded a pale-yellow oil which was used for the next step without further purification.

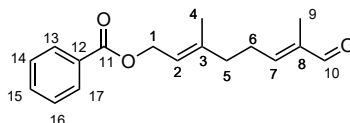
To a dry-ice cold solution of the crude oil in THF (3.50 mL) *n*-BuLi (2.3 M; 0.440 mL, 1.01 mmol, 2.10 eq) was added dropwise. The dark yellow-orange solution was stirred for 1 h at -78°C . The reaction was quenched with a saturated aqueous ammonium chloride solution (10 mL) and warmed to RT. The mixture was poured into a mixture of a saturated aqueous ammonium chloride solution and Et_2O (1 : 1 vol%; 20 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by column chromatography (pentane : Et_2O 7 : 1) afforded (3*E*,7*E*)-9-(methoxymethoxy)-3,7-dimethylnona-3,7-dien-1-yne (**391**) (23.0 mg, 0.110 mmol, 23%) as colourless oil.

R_f (hexane) = 0.21.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 5.92 (ddt, J = 8.9, 7.3, 1.6 Hz, 1H, H7), 5.37 (tdt, J = 5.3, 2.5, 1.3 Hz, 1H, H2), 4.63 (s, 2H, H11), 4.09 (dd, J = 9.5, 6.9 Hz, 2H, H1),

3.38 (s, 3H, -OMe), 2.75 (s, 1H, H₁₀), 2.31 – 2.19 (m, 2H, H₆), 2.14 – 2.00 (m, 2H, H₅), 1.79 (d, $J = 1.4$ Hz, 3H, H₉), 1.68 (t, $J = 1.9$ Hz, 3H, H₄).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 140.0 (C₃), 139.1 (C₇), 121.0 (C₂), 117.3 (C₈), 95.7 (C₁₁), 86.9 (C₁₂), 73.7 (C₁₀), 63.7 (-OMe), 38.6 (C₅), 26.8 (C₆), 17.2 (C₉), 16.5 (C₄).

(2*E*,6*E*)-3,7-DIMETHYL-8-OXOOCTA-2,6-DIEN-1-YL BENZOATE (**392**)

Synthesized using a modified literature procedure by Cole and Hsung.^[284] To an ice-cold solution of (2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl benzoate (**312**) (2.09 g, 7.61 mmol, 1.00 eq) in CH₂Cl₂ (30.0 mL) was added DMP (3.87 g, 9.13 mmol, 1.20 eq) in several portions over the course of 5 min. The reaction mixture was stirred for 1.5 h at RT. The mixture was loaded onto a column through a Celite[®] pad. Purification by flash column chromatography (4 : 1 pentane : Et₂O) afforded (2*E*,6*E*)-3,7-dimethyl-8-oxoocta-2,6-dien-1-yl benzoate (**392**) (2.03 g, 7.44 mmol, 98%) as colourless oil.

R_f (hexane : EtOAc 4 : 1) = 0.35.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 9.38 (s, 1H, H₁₀), 8.09 – 7.98 (m, 2H, H₁₃ + H₁₇), 7.62 – 7.52 (m, 1H, H₁₅), 7.51 – 7.40 (m, 2H, H₁₄ + H₁₆), 6.46 (tq, *J* = 7.2, 1.4 Hz, 1H, H₇), 5.52 (tq, *J* = 7.1, 1.4 Hz, 1H, H₂), 4.85 (d, *J* = 7.0 Hz, 2H, H₁), 2.58 – 2.45 (m, 2H, H₆), 2.26 (t, *J* = 7.6 Hz, 2H, H₅), 1.81 (d, *J* = 1.3 Hz, 3H, H₄), 1.75 (q, *J* = 1.0 Hz, 3H, H₉).

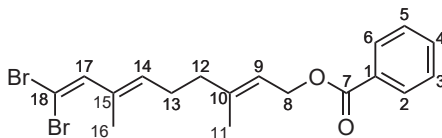
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 195.3 (C₁₀), 166.7 (C₁₁), 153.5 (C₇), 140.7 (C₃), 139.8 (C₈), 133.0 (C₁₅), 130.5 (C₁₂), 129.7 (C₁₃ + C₁₇), 128.5 (C₁₄ + C₁₆), 119.9 (C₂), 61.7 (C₁), 37.9 (C₅), 27.1 (C₆), 16.7 (C₄), 9.4 (C₉).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2922 (w), 1714 (vs), 1683 (vs), 1643 (m), 1450 (m), 1313 (m), 1267 (vs), 1098 (s), 1107 (s), 1070 (m), 1025 (m), 936 (w), 712 (vs).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₇H₂₁O₃)⁺: 273.1485, found: 273.1500.

(2*E*,6*E*)-3,7-Dimethyl-8-oxoocta-2,6-dien-1-yl benzoate (**392**) (284 mg, 1.04 mmol, 13%) was also formed during the SeO₂ oxidation of benzoyl-protected geraniol (**311**).

Analytic data were in good agreement with literature values.^[207]

(2*E*,6*E*)-9,9-DIBROMO-3,7-DIMETHYLNONA-2,6,8-TRIEN-1-YL BENZOATE (**393**)

Synthesized using a modified literature procedure by de Lera et. al.^[431] To an ice-cold solution of CBr_4 (901 mg, 2.72 mmol, 2.00 eq) in CH_2Cl_2 (7.00 mL) PPh_3 (1.43 g, 5.43 mmol, 4.00 eq) was added in one portion. The intense-yellow orange solution was stirred for 10 min at 0°C . A solution of (2*E*,6*E*)-3,7-dimethyl-8-oxoocta-2,6-dien-1-yl benzoate (**392**) (370 mg, 1.36 mmol, 1.00 eq) in CH_2Cl_2 (5.00 mL) was added dropwise. The resulting solution was stirred for 10 min at 0°C . The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution (10 mL) and warmed to RT. The mixture was poured into a mixture of a saturated aqueous sodium hydrogen carbonate solution and CH_2Cl_2 (1:1 vol%; 20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 * 20 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The resulting white solid was suspended in a hexane:ether mixture (1:1 vol%; 50 mL) and filtered through a Celite[®] pad. This process was repeated two times. The combined organic fractions were concentrated under reduced pressure which afforded a colourless oil which was used for the next step without further purification. For larger scale reactions (>5 mmol of (2*E*,6*E*)-3,7-dimethyl-8-oxoocta-2,6-dien-1-yl benzoate (**392**)) the reactions was quenched with silica gel and loaded onto a column. Purification by flash column chromatography (1 : 1 pentane : Et_2O) afforded (2*E*,6*E*)-9,9-dibromo-3,7-dimethylnona-2,6,8-trien-1-yl benzoate (**393**) (50-70%) as yellow to orange oil.

R_f (hexane : EtOAc 6 : 1) = 0.60.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 8.08 – 8.01 (m, 2H, $\text{H}_2 + \text{H}_6$), 7.59 – 7.52 (m, 1H, H_4), 7.49 – 7.40 (m, 2H, $\text{H}_3 + \text{H}_5$), 6.91 (s, 1H, H_{17}), 5.61 (tt, $J = 7.1, 1.4$ Hz, 1H, H_{14}), 5.49 (tq, $J = 7.0, 1.3$ Hz, 1H, H_9), 4.84 (d, $J = 7.0$ Hz, 2H, H_8), 2.23 (q, $J = 7.3$ Hz, 2H, H_{13}), 2.18 – 2.12 (m, 2H, H_{12}), 1.86 (d, $J = 1.3$ Hz, 3H, H_{16}), 1.78 (d, $J = 1.4$ Hz, 3H, H_{11}).

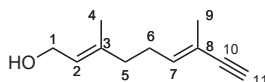
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 166.8 (C7), 141.5 (C10), 140.8 (C17), 134.7 (C14), 133.0 (C4), 132.1 (C15), 130.6 (C1), 129.7 (C2 + C6), 128.5 (C3 + C5), 119.3 (C9), 86.0 (C18), 61.9 (C8), 38.6 (C12), 26.4 (C13), 16.7 (C11), 15.4 (C16).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2923 (m), 1713 (vs), 1600 (m), 14449 (m), 1379

(m), 1265 (vs), 1105 (s), 1095 (s), 1025 (m), 933 (m), 708 (vs).

HRMS (APCI) m/z : $[M + H_2O + H]^+$ calc. for $(C_{18}H_{23}Br_2O_3)^+$: 445.0008, found 444.9808.

(2*E*,6*E*)-3,7-DIMETHYLNONA-2,6-DIEN-8-YN-1-OL (305a)



Synthesized using a modified literature procedure by de Lera et. al.:^[431] To a dry-ice cold solution of the crude oil in THF (6.00 mL) *n*-BuLi (2.26 M; 1.26 mL, 2.85 mmol, 2.10 eq) was added dropwise. The dark yellow-orange solution was stirred for 1 h at -78°C . The reaction was quenched with a saturated aqueous ammonium chloride solution (10 mL) and warmed to RT. The mixture was poured into a mixture of a saturated aqueous ammonium chloride solution and Et_2O (1:1 vol%; 20 mL) and the aqueous layer was extracted with ether (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (7 : 1 pentane : Et_2O) afforded (2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-ol (**305a**) (189 mg, 1.15 mmol, 85%) as colourless oil.

R_f (hexane : EtOAc 4 : 1) = 0.13.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 5.92 (td, J = 7.3, 1.6 Hz, 1H, H7), 5.43 (tq, J = 6.8, 1.4 Hz, 1H, H2), 4.16 (t, J = 5.7 Hz, 2H, H1), 2.76 (s, 1H, H11), 2.23 (q, J = 7.5 Hz, 2H, H6), 2.09 (dd, J = 8.8, 6.4 Hz, 2H, H5), 1.79 (q, J = 1.1 Hz, 3H, H9), 1.68 (d, J = 1.2 Hz, 3H, H4), 1.16 (d, J = 4.9 Hz, 1H, -OH).

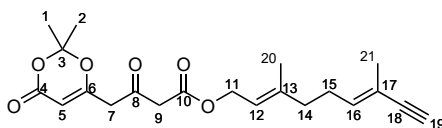
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 139.0 (C7), 139.0 (C3), 124.2 (C2), 117.3 (C8), 86.9 (C10), 73.8 (C11), 59.5 (C1), 38.5 (C5), 26.8 (C6), 17.2 (C9), 16.4 (C4).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3289 (s, br), 3019 (w), 2919 (s), 2855 (s), 2093 (w), 1667 (m), 1437 (s), 1379 (s), 1236 (m), 1097 (w), 1080 (m), 997 (vs), 862 (m), 634 (s), 603 (s).

HRMS (ES-ToF) m/z : $[M - OH]^+$ calc. for $(C_{11}H_{15})^+$: 147.1168, found: 147.1180.

Note: When this was repeated on a 15 mmol scale the yield dropped to 14%. On a 4 mmol scale the yield was around 40%.

(2*E*,6*E*)-3,7-DIMETHYLNONA-2,6-DIEN-8-YN-1-YL 4-(2,2-DIMETHYL-4-OXO-4*H*-1,3-DIOXIN-6-YL)-3-OXOBUTANOATE (**304a**)



Synthesized using a modified literature procedure by Barrett et. al.^[105] To a solution of 2-phenyl-1,3-dioxane-4,6-dione (**141**) (702 mg, 3.65 mmol, 1.82 eq) and DCC (754 mg, 3.65 mmol, 1.82 eq) in CH₂Cl₂ (30.0 mL) was added DMAP (446 mg, 3.65 mmol, 1.82 eq) in one portion. The solution was stirred for 15 min at RT before 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid (**140**) (680 mg, 3.65 mmol, 1.82 eq) was added in one portion. The resulting yellow-white suspension was stirred for 20 h at RT. The reaction mixture was cooled to 0 °C, the precipitate was filtered off and the solid was washed with small portions of CH₂Cl₂ until the precipitate appeared colourless. The filtrate was washed with an aqueous hydrochloric acid solution (1 M; 2 x 20 mL). The organic layer was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in PhMe (7.50 mL) and a solution of (2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-ol (**305a**) (360 mg, 2.01 mmol, 1.00 eq) in PhMe (7.50 mL) was added in one portion. The resulting pale yellow solution was heated to 55 °C for 4 hour after which the solution was concentrated. Purification by flash column chromatography (9 : 1 pentane : EtOAc → 7 : 1 → 4 : 1) afforded (2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**304a**) (634 mg, 1.69 mmol, 84%) as pale-yellow to orange oil.

R_f (hexane : EtOAc 4 : 1) = 0.08.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.88 (ddt, *J* = 8.8, 7.2, 1.6 Hz, 1H, H₁₆), 5.36 (s, 1H, H₅), 5.34 (dq, *J* = 7.2, 1.4 Hz, 1H, H₁₂), 4.67 (d, *J* = 7.2 Hz, 2H, H₁₁), 3.52 (s, 2H, H₉), 3.50 (s, 2H, H₇), 2.76 (s, 1H, H₁₉), 2.28 – 2.19 (m, 2H, H₁₅), 2.14 – 2.07 (m, 2H, H₁₄), 1.78 (t, *J* = 1.2 Hz, 3H, H₂₁), 1.71 (s, 9H, H₁ + H₂ + H₂₀ overlapping).

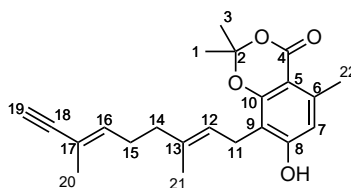
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 195.8 (C₈), 166.5 (C₁₀), 163.7 (C₄), 160.6 (C₆), 142.6 (C₁₃), 138.5 (C₁₆), 118.2 (C₁₂), 117.5 (C₁₇), 107.5 (C₃), 97.3 (C₅), 86.8 (C₁₈), 73.9 (C₁₉), 62.6 (C₁₁), 49.2 (C₉), 47.1 (C₇), 38.5 (C₁₄), 26.6 (C₁₅), 25.2 (C₁ + C₂), 17.2 (C₂₁), 16.6 (C₂₀).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3282 (m), 2994 (w), 2928 (m), 2854 (w), 2092 (vw), 1718 (vs), 1636 (s), 1550 (m), 1389 (s), 1375 (s), 1314 (m), 1231 (vs), 1252 (s), 1201

(vs), 1154 (m), 1088 (w), 1015 (s), 902 (m), 807(m), 626 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{21}H_{27}O_6)^+$: 375.1802, found: 375.1814.

8-((2*E*,6*E*)-3,7-DIMETHYLNONA-2,6-DIEN-8-YN-1-YL)-7-HYDROXY-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**301a**)



Synthesized using a modified literature procedure by Barrett et. al.:^[105] To an ice-cold solution of (2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**304a**) (322 mg, 0.860 mmol, 1.00 eq) in CH₂Cl₂ (4.50 mL) was added MgCl₂ (82.0 mg, 0.860 mmol, 1.00 eq) and pyridine (136 mg, 140 μL, 0.860 mmol, 2.00 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (101 mg, 90.0 μL, 1.29 mmol, 1.50 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1-2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (5.00 mL) and tri(2-furyl)phosphine (59.9 mg, 0.258 mmol, 0.30 eq) and Tris(dibenzylideneacetone)dipalladium(o) (39.4 mg, 0.0430 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 1 h at RT before caesium acetate (495 mg, 2.58 mmol, 3.00 eq) in 2-propanol (5.00 mL) was added in one portion. The resulting orange-brown solution was stirred for 1.5 h at RT. The reaction mixture was quenched an aqueous hydrochloric acid solution (1 M; 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc → 17 : 1 → 12 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301a**) (95.0 mg, 0.268 mmol, 31%) as yellow-white solid.

R_f (hexane : EtOAc 7 : 3) = 0.29.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.40 (d, J = 0.9 Hz, 1H, H₇), 5.88 (td, J = 7.3, 1.6 Hz, 1H, H₁₆), 5.22 – 5.16 (m, 1H, H₁₂), 3.31 (d, J = 7.2 Hz, 2H, H₁₁), 2.75 (s, 1H,

H19), 2.59 (d, $J = 0.7$ Hz, 3H, H22), 2.20 (q, $J = 7.4$ Hz, 2H, H15), 2.11 – 2.04 (m, 2H, H14), 1.78 (d, $J = 1.3$ Hz, 3H, H21), 1.77 (d, $J = 1.4$ Hz, 3H, H20), 1.69 (s, 6H, H1 + H3).

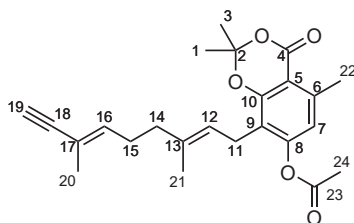
$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 161.1 (C4), 159.8 (C8), 156.2 (C10), 143.0 (C6), 139.0 (C16), 137.1 (C13), 121.8 (C12), 117.3 (C17), 113.7 (C7), 113.0 (C9), 105.6 (C5), 105.0 (C2), 86.9 (C18), 73.8 (C19), 38.7 (C15), 26.9 (C14), 25.9 (C1 + C3), 22.1 (C22), 22.0 (C11), 17.2 (C20), 16.3 (C21).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3286 (s,br), 2989 (m), 2926 (s), 2852 (m), 2092 (w), 1724 (s), 1695 (vs), 1607 (vs), 1591 (vs), 1512 (s), 1451 (s), 1409 (s), 1388 (s), 1376 (s), 1324 (s), 1295 (vs), 1275 (vs), 1208 (vs), 1167 (s), 1107 (s), 1058 (m), 1045 (m), 972 (m), 851 (m), 642 (m), 601 (m), 523 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{22}\text{H}_{27}\text{O}_4)^+$: 355.1904, found: 355.1920.

mp. (recrystallized from CH_2Cl_2 /pentane): 114 °C–116 °C.

8-((2*E*,6*E*)-3,7-DIMETHYLNONA-2,6-DIEN-8-YN-1-YL)-2,2,5-TRIMETHYL-4-OXO-4*H*-BENZO[*D*][1,3]DIOXIN-7-YL ACETATE (**394**)



According to the procedure above. Purification by flash column chromatography (19 : 1 pentane : EtOAc → 17 : 1 → 12 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**394**) (60.0 mg, 0.151 mmol, 18%) as yellow oil which solidified upon standing.

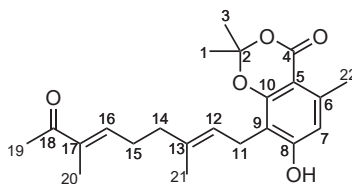
R_f (hexane : EtOAc 7 : 3) = 0.44.

^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 6.68 (d, $J = 0.9$ Hz, 1H, H7), 5.94 – 5.86 (m, 1H, H16), 5.11 – 5.02 (m, 1H, H12), 3.22 (d, $J = 7.1$ Hz, 2H, H11), 2.76 (s, 1H, H19), 2.66 (d, $J = 0.8$ Hz, 3H, H22), 2.35 (s, 3H, H24), 2.23 – 2.14 (m, 2H, H15), 2.04 (t, $J = 7.6$ Hz, 2H, H14), 1.79 (q, $J = 1.1$ Hz, 3H, H20), 1.76 (d, $J = 1.3$ Hz, 3H, H21), 1.72 (s, 6H, H1 + H3).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 168.8 (C23), 160.4 (C4), 156.2 (C10), 153.6 (C8), 142.2 (C6), 139.1 (C16), 135.2 (C13), 121.6 (C12), 120.6 (C17), 119.8 (C7), 115.9 (C9), 110.5 (C5), 105.5 (C2), 86.9 (C18), 73.7 (C19), 38.6 (C14), 26.9 (C15), 25.9 (C1 + C3), 22.8 (C11), 22.1 (C22), 21.1 (C24), 17.2 (C20), 16.2 (C21).

HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_{24}\text{H}_{27}\text{O}_5)^-$: 395.1864, found: 395.1866.

8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**395**)



To a solution of 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**403**) (130 mg, 0.314 mmol, 1.00 eq) in CH₂Cl₂ (3.00 mL) was added NaOMe (0.5 M in MeOH; 0.630 mL, 0.314 mmol, 1.00 eq) dropwise. After 3 h at RT, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution (5.00 mL) and diluted with an aqueous lithium chloride solution (10%; 10 mL). The organic layer was separated and the aqueous layer was further extracted with Et₂O (2 x 10 mL) and EtOAc (1 x 10 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : EtOAc) afforded 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**395**) (114 mg, 0.306 mmol, 98%) as a pale-yellow oil.

Alternatively: To a solution of 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301a**) (13 mg, 0.04 mmol, 1.00 eq) in CH₂Cl₂ (1.0 mL) was added BrettPhos AuNTf₂ (2 mg, 0.002 mmol, 0.05 eq). The reaction was heated to 37 °C for 12 h. The reaction was diluted with Et₂O (2 mL) and quenched with water (5.0 mL). The organic layer was separated and the aqueous layer was further extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : EtOAc) afforded 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**395**) (4 mg, 0.01 mmol, 26%) as colorless film.

Alternatively: To a -40 °C solution of InBr₃ (3.0 mg, 0.008 mmol, 0.2 eq) in CH₂Cl₂ (0.4 mL) was added 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301a**) (15 mg, 0.04 mmol, 1.00 eq) in CH₂Cl₂ (0.1 mL) dropwise. The reaction was stirred 12 h while gradually warming up to RT.

The reaction was diluted with CH_2Cl_2 (5 mL) and quenched with a saturated aqueous sodium hydrogencarbonate solution (10 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by preparative TLC (4 : 1 pentane : EtOAc) afforded 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**395**) (6 mg, 0.02 mmol, 38%) as colorless film.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.08.

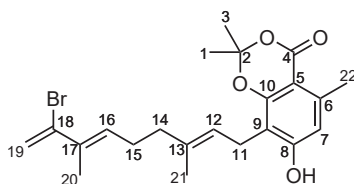
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.58 – 6.53 (m, 1H, H16), 6.40 (d, J = 3.3 Hz, 1H, H7), 5.24 – 5.17 (m, 1H, H12), 3.31 (d, J = 7.2 Hz, 2H, H11), 2.58 (d, J = 0.9 Hz, 3H, H22), 2.36 (q, J = 7.2 Hz, 2H, H15), 2.22 (s, 3H, H19), 2.17 (t, J = 7.4 Hz, 2H, H14), 1.80 (d, J = 1.3 Hz, 3H, H21), 1.74 (t, J = 1.1 Hz, 3H, H20), 1.68 (s, 6H, H1 + H3).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 201.7 (C18), 161.1 (C4), 159.9 (C8), 156.2 (C6), 143.3 (C16), 143.0 (C6), 137.9 (C17), 136.0 (C13), 122.6 (C12), 113.6 (C7), 113.2 (C9), 105.5 (C5), 104.9 (C2), 38.4 (C14), 27.4 (C15), 25.9 (C1 + C3), 25.5 (C19), 22.1 (C22), 21.9 (C11), 16.2 (C21), 11.4 (C20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3276 (br, s), 2996 (w), 2926 (m), 1725 (vs), 1692 (vs), 1666 (s), 1641 (m), 1607 (vs), 1593 (vs), 1513 (m), 1452 (s), 1410 (m), 1388 (m), 1327 (s), 1293 (s), 1275 (vs), 1209 (s), 1172 (m), 1107 (m), 1036 (m).

HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_{22}\text{H}_{27}\text{O}_5)^-$: 371.1864, found 371.1852.

8-((2*E*,6*E*)-8-bromo-3,7-dimethylnona-2,6,8-trien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**396**)



To a -40°C solution of InBr_3 (3.0 mg, 0.008 mmol, 0.2 eq) in CH_2Cl_2 (0.4 mL) was added 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301a**) (15 mg, 0.04 mmol, 1.00 eq) in CH_2Cl_2 (0.1 mL) dropwise. The reaction was stirred 12 h while gradually warming up to RT. The reaction was diluted with CH_2Cl_2 (5 mL) and quenched with a saturated aqueous sodium hydrogencarbonate solution (10 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by preparative TLC (4 : 1 pentane : EtOAc) afforded 8-((2*E*,6*E*)-8-bromo-3,7-dimethylnona-2,6,8-trien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**396**) (8.0 mg, 0.018 mmol, 23%) as colorless film.

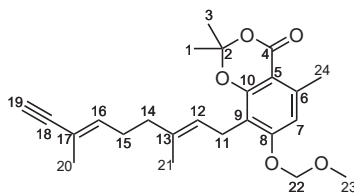
R_f (Petrol Ether : EtOAc 4 : 1) = 0.50.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.39 (d, J = 0.9 Hz, 1H, H7), 6.05 – 5.96 (m, 1H, H16), 5.73 (d, J = 1.9 Hz, 1H, H19 *trans* to bromide), 5.70 (s, 1H, OH), 5.54 (d, J = 1.9 Hz, 1H, H19 *cis* to bromide), 5.24 – 5.17 (m, 1H, H12), 3.32 (d, J = 7.3 Hz, 2H, H11), 2.59 (d, J = 0.8 Hz, 3H, H22), 2.26 (td, J = 8.4, 7.4, 5.9 Hz, 2H, H15), 2.13 (t, J = 7.5 Hz, 2H, H14), 1.82 (d, J = 1.1 Hz, 3H, H20), 1.80 (t, J = 1.4 Hz, 3H, H21), 1.68 (s, 6H, H1 + H3).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3306 (br, s), 2924 (m), 1724 (vs), 1696 (vs), 1607 (s), 1591 (vs), 1512 (m), 1495 (m), 1452 (s), 1409 (m), 1376 (s), 1275 (vs), 1206 (vs), 1167 (s), 1107 (vs), 1036 (s).

HRMS (APCI) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_{22}\text{H}_{26}\text{BrO}_4)^-$: 433.1020, found: 433.1016.

8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**397**)



To an ice-cold solution of 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301a**) (127 mg, 0.358 mmol, 1.00 eq) in CH_2Cl_2 (4.00 mL) was added NiPr_2Et (463 mg, 0.620 mL, 3.58 mmol, 10.0 eq) in one portion. To this pale yellow solution was added MOM-Cl (155 mg, 146 μL , 1.79 mmol, 5.00 eq) dropwise. The resulting intense yellow solution was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (5.00 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : Et_2O) afforded 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**397**) (125 mg, 0.314 mmol, 88%) as a pale-yellow oil.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.47.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.65 (d, J = 0.9 Hz, 1H, H7), 5.95 – 5.82 (m, 1H, H16), 5.25 (s, 2H, H22), 5.13 (tq, J = 7.3, 1.3 Hz, 1H, H12), 3.49 (s, 3H, H23), 3.28 (d, J = 7.2 Hz, 2H, H11), 2.73 (s, 1H, H19), 2.63 (d, J = 0.7 Hz, 3H, H24), 2.22 – 2.09 (m, 2H, H15), 2.02 (q, J = 7.1 Hz, 2H, H14), 1.79 – 1.72 (m, 6H, H20 + H21 overlapping), 1.68 (s, 6H, H1 + H3).

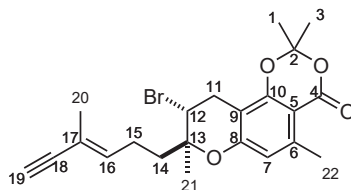
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.0 (C4), 159.8 (C8), 155.8 (C10), 142.8 (C6), 139.3 (C16), 134.4 (C13), 122.6 (C12), 117.0 (C17), 116.4 (C9), 111.2 (C7), 106.6 (C5), 104.9 (C2), 94.1 (C22), 87.0 (C18), 73.7 (C19), 56.5 (C23), 38.7 (C14), 27.0 (C15), 25.9 (C1 + C3), 22.6 (C24), 22.0 (C11), 17.2 (C21), 16.1 (C20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3283 (w), 2993 (w), 2927 (m), 2855 (w), 2095 (vw), 1728 (vs), 1607 (s), 1577 (s), 1451 (m), 1388 (m), 1375 (m), 1321 (m), 1279 (vs), 1207 (s), 1152 (s), 1074 (vs), 1036 (s), 964 (m), 906 (m).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{31}\text{O}_5)^+$: 399.2166, found: 399.2168. Also

found major peak at m/z : $[M - \text{acetone} + H]^+$ calc. for $(C_{21}H_{25}O_4)^+$: 341.1747, found: 341.1750.

(±)-9-BROMO-2,2,5,8-TETRAMETHYL-8-((*E*)-4-METHYLHEX-3-EN-5-YN-1-YL)-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE (**398**)



To a dry-ice cold solution of 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**397**) (54.0 mg, 0.136 mmol, 1.00 eq) in EtNO₂ (6.8 mL) was added BDSB (78.0 mg, 0.142 mmol, 1.05 eq) in one portion. The resulting orange-brown solution was stirred for 8 h at −78 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (15 mL) and warmed to RT. The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et₂O) afforded (±)-9-bromo-2,2,5,8-tetramethyl-8-((*E*)-4-methylhex-3-en-5-yn-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**398**) (33.0 mg, 0.0762 mmol, 56%) as colourless oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.50.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.40 (d, *J* = 0.9 Hz, 1H, H7), 5.95 (tq, *J* = 7.4, 1.6 Hz, 1H, H16), 4.24 (dd, *J* = 9.9, 5.8 Hz, 1H, H12), 3.25 (dd, *J* = 17.2, 5.7 Hz, 1H, H11eq), 3.00 (dd, *J* = 17.2, 9.9 Hz, 1H, H11ax), 2.78 (s, 1H, H19), 2.61 – 2.57 (m, 3H, H22), 2.27 (tq, *J* = 16.0, 7.4 Hz, 2H, H15), 1.98 – 1.84 (m, 2H, H14), 1.82 (dd, *J* = 1.7, 0.8 Hz, 3H, H20), 1.72 (s, 3H, H1), 1.69 (s, 3H, H3), 1.39 (s, 3H, H21).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 160.5 (C4), 158.1 (C8), 155.5 (C10), 143.4 (C6), 138.2 (C16), 117.9 (C17), 114.6 (C7), 106.2 (C9), 105.3 (C2), 105.0 (C5), 86.6 (C18), 79.5 (C13), 74.1 (C19), 48.9 (C12), 38.1 (C14), 28.4 (C11), 26.2 (C1), 25.7 (C3), 22.2 (C22), 22.0 (C15), 19.6 (C21), 17.1 (C20).

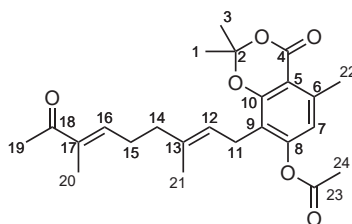
IR (Diamond-ATR, neat) ν_{max} (cm^{−1}) = 3290 (m), 2988 (m), 2927 (m), 2854 (w), 2092 (vw), 1728 (vs), 1617 (s), 1577 (vs), 1494 (m), 1452 (s), 1377 (s), 1295 (s), 1280 (vs), 1207 (vs), 1170 (m), 1142 (s), 1067 (m), 1040 (s), 895 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₂₂H₂₆BrO₄)⁺: 433.1009, found: 433.1012.

Also found fragmentation's as major peaks: *m/z*: [M - acetylene]⁺ calc. for (C₂₀H₂₄BrO₄)⁺:

407.0852, found: 407.0852 and m/z : $[M - \text{acetone} + H]^+$ calc. for $(C_{19}H_{20}BrO_3)^+$:
375.0590, found: 375.0589.

8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-2,2,5-trimethyl-4-oxo-4*H*-benzo[*D*][1,3]dioxin-7-yl acetate (**403**)



To a solution of 8-((2*E*,6*E*)-3,7-dimethylnona-2,6-dien-8-yn-1-yl)-2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**394**) (198 mg, 0.50 mmol, 1.00 eq) in MeOH (2.0 mL) and H₂O (1.0 mL) was added XPhos AuNTf₂ (33.0 mg, 0.035 mmol, 0.07 eq) in one portion. The resulting yellow solution was stirred for 29 h at RT. The reaction mixture was diluted with EtOAc (10 mL) and quenched with an aqueous lithium chloride solution (10 wt.%; 30 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (7 : 1 pentane : EtOAc → 4 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**403**) (183 mg, 0.44 mmol, 88%) as pale-yellow oil.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.21.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.65 (d, *J* = 0.9 Hz, 1H, H₇), 6.53 (tq, *J* = 7.1, 1.4 Hz, 1H, H₁₆), 5.07 (tq, *J* = 7.2, 1.3 Hz, 1H, H₁₂), 3.20 (d, *J* = 7.1 Hz, 2H, H₁₁), 2.63 (d, *J* = 0.7 Hz, 3H, H₂₂), 2.31 (d, *J* = 4.4 Hz, 5H, H₂₄ and H₁₅ overlapping), 2.21 (s, 3H, H₁₉), 2.14 – 2.08 (m, 2H, H₁₄), 1.76 (d, *J* = 1.3 Hz, 3H, H₂₀), 1.73 (q, *J* = 1.0 Hz, 3H, H₂₁), 1.69 (s, 6H, H₁ + H₃).

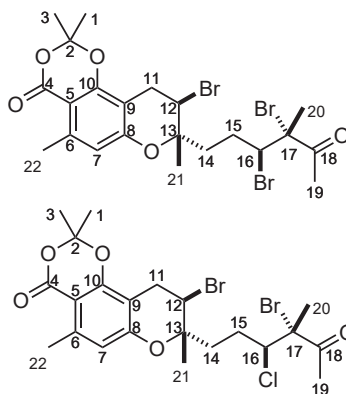
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 199.9 (C₁₈), 168.8 (C₂₃), 160.3 (C₄), 156.1 (C₁₀), 153.6 (C₈), 143.0 (C₁₆), 142.3 (C₆), 137.9 (C₁₇), 134.9 (C₁₃), 121.9 (C₁₂), 120.4 (C₉), 119.9 (C₇), 110.5 (C₅), 105.4 (C₂), 38.4 (C₁₄), 27.5 (C₁₅), 25.9 (C₁ + C₃), 25.4 (C₁₉), 22.8 (C₁₁), 22.1 (C₂₂), 21.0 (C₂₄), 16.2 (C₂₀), 11.3 (C₂₁).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2994 (w), 2928 (w), 1771 (s), 1732 (vs), 1663 (s), 1640 (m), 1610 (m), 1581 (s), 1448 (s), 1388 (s), 1368 (s), 1277 (vs), 1193 (vs), 1154 (s), 1092 (vs), 1038 (s), 899 (m).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₂₄H₃₁O₆)⁺: 415.2115, found: 415.2112. Also

found fragmentation's as major peaks: m/z : $[M - \text{acetone} + H]^+$ calc. for $(C_{21}H_{25}O_5)^+$:
357.1697, found: 357.1696.

($\pm$)-9-BROMO-8-(3,4-DIBROMO-4-METHYL-5-OXOHXYL)-2,2,5,8-TETRAMETHYL-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE AND ($\pm$)-9-BROMO-8-(-4-BROMO-3-CHLORO-4-METHYL-5-OXOHXYL)-2,2,5,8-TETRAMETHYL-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE (**404**)



To a -40°C cold solution of 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**395**) (155 mg, 0.420 mmol, 1.00 eq) in MeNO_2 (11 mL) was added BDSB (251 mg, 0.460 mmol, 1.10 eq) in two portion. The resulting orange-brown solution was stirred for 2 h while gradually warming up to RT. The reaction mixture was quenched with a saturated aqueous sodium hydrogencarbonate solution (15 mL) and a saturated aqueous sodium thiosulfate solution (10 mL) and stirred for 15 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et_2O) afforded a mixture of ($\pm$)-9-bromo-8-(3,4-dibromo-4-methyl-5-oxohexyl)-2,2,5,8-tetramethyl-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one and ($\pm$)-9-bromo-8-(-4-bromo-3-chloro-4-methyl-5-oxohexyl)-2,2,5,8-tetramethyl-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**404**) (25.0 mg, 0.04 mmol, 10%) as a white film which was recrystallized with CH_2Cl_2 /pentane for X-Ray crystallography analysis.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.46.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.42 (dd, J = 2.7, 0.9 Hz, 1H, H7), 4.45 (dd, J = 10.8, 1.6 Hz, 1H, H16), 4.30 – 4.20 (m, 1H, H12), 3.28 (ddd, J = 17.1, 5.8, 2.8 Hz, 1H, H11eq), 3.01 (ddd, J = 17.0, 10.4, 6.6 Hz, 1H, H11ax), 2.71 – 2.52 (m, 4H, H22 and H14 overlapping), 2.45 (d, J = 1.4 Hz, 3H, H19), 2.33 (dddd, J = 18.7, 14.0, 11.3, 4.3 Hz, 1H, H15), 1.97 (tdd, J = 13.7, 4.5, 1.7 Hz, 1H, H15), 1.92 – 1.87 (m, 1H, H14), 1.87 (d, J =

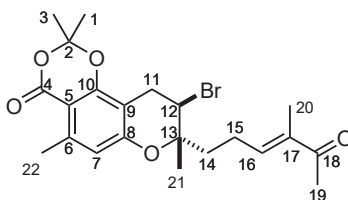
2.1 Hz, 3H, H₂₀), 1.73 (s, 3H, H₁), 1.70 (s, 3H, H₃), 1.44 (t, $J = 1.9$ Hz, 3H, H₂₁).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 199.40 (C₁₈), 199.01 (C₁₈), 160.48 (C₄), 157.90 (C₈), 157.85 (C₈), 155.49 (C₁₀), 155.41 (C₁₀), 143.47 (C₆), 114.63 (C₇), 114.58 (C₇), 106.43 (C₉), 106.28 (C₉), 105.35 (C₂), 105.09 (C₅), 79.61 (C₁₃), 79.50 (C₁₃), 68.93 (C₁₇), 68.84 (C₁₇), 65.25 (C₁₆), 65.19 (C₁₆), 49.13 (C₁₂), 48.25 (C₁₂), 37.19 (C₁₅), 36.74 (C₁₅), 28.39 (C₁₁), 26.91 (C₁₄), 26.70 (C₁₄), 26.24 (C₁), 26.16 (C₁), 25.70 (C₃), 25.63 (C₃), 23.97 (C₁₉), 23.95 (C₁₉), 22.16 (C₂₂), 20.21 (C₂₀), 20.11 (C₂₀), 19.36 (C₂₁), 19.30 (C₂₁).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2986 (w), 2932 (w), 1720 (vs), 1618 (s), 1577 (vs), 1494 (m), 1450 (m), 1388 (m), 1377 (s), 1360 (s), 1300 (s), 1280 (vs), 1206 (s), 1171 (s), 1144 (s), 1127 (s), 1041 (m), 895 (m), 732 (m).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₂₂H₂₈Br₃O₅)⁺: 612.9940, found: 612.9426.
Major peak m/z : [M + H]⁺ calc. for (C₂₂H₂₈Br₂ClO₅)⁺: 566.9966, found: 566.9954.

(±)-9-BROMO-2,2,5,8-TETRAMETHYL-8-((*E*)-4-METHYL-5-OXOHX-3-EN-1-YL)-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE (**405**)



To a -40°C cold solution of 8-((2*E*,6*E*)-3,7-dimethyl-8-oxonona-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**395**) (155 mg, 0.420 mmol, 1.00 eq) in MeNO_2 (11 mL) was added BDSB (251 mg, 0.460 mmol, 1.10 eq) in two portion. The resulting orange-brown solution was stirred for 2 h while gradually warming up to RT. The reaction mixture was quenched with a saturated aqueous sodium hydrogencarbonate solution (15 mL) and a saturated aqueous sodium thiosulfate solution (10 mL) and stirred for 15 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et_2O) afforded (±)-9-bromo-2,2,5,8-tetramethyl-8-((*E*)-4-methyl-5-oxohex-3-en-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**405**) (9.0 mg, 0.0199 mmol, 5%) as a white film.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.36.

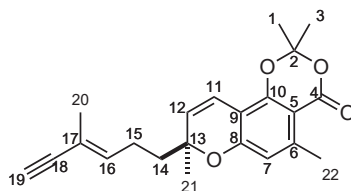
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.66 (td, J = 7.2, 1.5 Hz, 1H, H16), 6.41 – 6.37 (m, 1H, H7), 4.25 (dd, J = 10.3, 5.8 Hz, 1H, H12), 3.27 (dd, J = 17.1, 5.7 Hz, 1H, H11eq), 3.01 (dd, J = 17.1, 10.3 Hz, 1H, H11ax), 2.62 – 2.57 (m, 3H, H22), 2.51 – 2.39 (m, 2H, H15), 2.31 (s, 3H, H19), 2.07 – 1.91 (m, 2H, H14), 1.80 (d, J = 1.4 Hz, 3H, H20), 1.72 (s, 3H, H1), 1.70 (s, 3H, H3), 1.42 (s, 3H, H21).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 199.9 (C18), 160.5 (C4), 158.0 (C8), 155.5 (C10), 143.5 (C6), 142.2 (C16), 138.4 (C17), 114.5 (C7), 106.3 (C9), 105.4 (C2), 105.0 (C5), 79.6 (C13), 48.6 (C12), 38.0 (C14), 28.4 (C11), 26.2 (C1), 25.7 (C3), 25.6 (C19), 22.7 (C15), 22.2 (C22), 19.4 (C21), 11.3 (C20).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2987 (w), 2924 (w), 2850 (w), 1727 (vs), 1666 (s), 1618 (s), 1577 (vs), 1451 (s), 1388 (s), 1377 (s), 1361 (m), 1280 (vs), 1206 (s), 1144 (s), 1040 (s), 895 (m).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{22}\text{H}_{28}\text{BrO}_5)^+$: 451.1115, found: 451.1123.

(±)-(E)-2,2,5,8-tetramethyl-8-((E)-4-methylhex-3-en-5-yn-1-yl)-4*H*,8*H*-[1,3]dioxino[4,5-*F*]chromen-4-one (**412**)



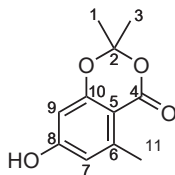
To a solution of (±)-9-bromo-2,2,5,8-tetramethyl-8-((E)-4-methylhex-3-en-5-yn-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**398**) (45.0 mg, 0.104 mmol, 1.00 eq) in CH₃CN (2.0 mL) was added DBU (4 drops). The resulting orange-brown solution was heated to 80 °C for 4 h. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et₂O) afforded (±)-(E)-2,2,5,8-tetramethyl-8-((E)-4-methylhex-3-en-5-yn-1-yl)-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**412**) (30.0 mg, 0.085 mmol, 82%) as colourless oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.38.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.60 – 6.52 (m, 1H, H₁₁), 6.35 (t, *J* = 0.9 Hz, 1H, H₇), 5.91 (tq, *J* = 7.5, 1.6 Hz, 1H, H₁₆), 5.55 – 5.45 (m, 1H, H₁₂), 2.75 (s, 1H, H₁₉), 2.59 (d, *J* = 0.8 Hz, 3H, H₂₂), 2.20 (dt, *J* = 10.6, 5.8 Hz, 2H, H₁₅), 1.86 – 1.75 (m, 2H, H₁₄), 1.75 (q, *J* = 1.1 Hz, 3H, H₂₀), 1.70 (d, *J* = 1.3 Hz, 6H, H₁ + H₃), 1.41 (s, 3H, H₂₁).
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 160.6 (C₄), 158.5 (C₈), 153.1 (C₁₀), 145.1 (C₆), 138.8 (C₁₆), 127.4 (C₁₂), 117.4 (C₁₇), 116.3 (C₁₁), 114.0 (C₇), 107.3, 105.2 (C₂), 105.1 (C₅), 86.8 (C₁₈), 80.0 (C₁₃), 73.9 (C₁₉), 40.6 (C₁₄), 27.3 (C₂₁), 26.0 (C₁), 25.8 (C₃), 23.3 (C₁₅), 22.5 (C₂₂), 17.1 (C₂₀).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3286 (w), 2965 (w), 2924 (m), 2854 (w), 2093 (w), 1725 (vs), 1635 (m), 1611 (s), 1566 (vs), 1491 (w), 1452 (s), 1388 (s), 1375 (s), 1317 (s), 1282 (vs), 1205 (s), 1171 (s), 1152 (vs), 1067 (s), 1040 (s), 897 (s).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₂₂H₂₅O₄)⁺: 353.1747, found: 353.1756.

7-HYDROXY-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**420**)

Synthesized according to literature procedure by Watanabe et. al.:^[309] To an ice-cold solution of 2,4-dihydroxy-6-methylbenzoic acid (**419**) (3.61 g, 19.8 mmol, 1.00 eq) in dimethoxyethane (60.0 mL) was added DMAP (242 mg, 0.198 mmol, 0.10 eq) and acetone (2.59 g, 3.27 mL, 44.6 mmol, 2.25 eq) followed by SOCl_2 (7.07 g, 4.34 mL, 59.4 mmol, 3.00 eq). The resulting mixture was stirred for 3 days at RT. The reaction mixture was placed in an ice-bath, and carefully quenched with a saturated aqueous sodium hydrogencarbonate solution (30 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (20 mL) and a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : EtOAc $\rightarrow$ 1 : 1) afforded 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**420**) (2.66 g, 12.8 mmol, 64%) as an off-white solid.

R_f (Petrol Ether : EtOAc 7 : 3) = 0.24.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.40 (dq, J = 2.4, 0.8 Hz, 1H, H7), 6.26 (d, J = 2.5 Hz, 1H, H9), 5.46 (d, J = 3.5 Hz, 1H, OH), 2.63 (t, J = 0.6 Hz, 3H, H11), 1.69 (s, 6H, H1+H3).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.4 (C4), 160.9 (C8), 159.1 (C10), 146.2 (C6), 113.7 (C7), 105.6 (C5), 105.3 (C2), 101.6 (C9), 25.8 (C1+C3), 22.4 (C11).

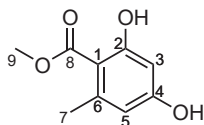
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3326 (s, br), 1682 (vs), 1614 (m), 1577 (vs), 1479 (m), 1283 (vs), 1197 (s), 1170 (vs), 1065 (s), 987 (m), 850 (vs), 718 (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{11}\text{H}_{13}\text{O}_4)^+$: 209.0808, found: 209.0820.

mp. (recrystallized from EtOAc): 199 °C-200 °C.

Elemental Analysis: calc. for $\text{C}_{11}\text{H}_{12}\text{O}_4$: C, 63.45; H, 5.81. Found: C, 63.06; H, 5.76.

Analytic data were in good agreement with literature values.^[309]

2,4-DIHYDROXY-6-METHYLBENZOATE (**422**)

A solution of 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**420**) (20 - 25 mg, 0.096 - 0.12 mmol) in MeOH (0.007, 0.01, 0.1 and 0.2 M) was prepared in a sealed vial. The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The reaction mixture was concentrated and analysed according to crude-NMR integration. The various reactions were combined, concentrated under reduced pressure and loaded onto a column. Purification by flash column chromatography (5 : 1 Pent : EtOAc) afforded methyl 2,4-dihydroxy-6-methylbenzoate (**422**) (43 mg, 0.24 mmol, 23%) as a white solid.

R_f (Petrol Ether : EtOAc 7 : 3) = 0.36.

$^1\text{H-NMR}$ (400 MHz, $(\text{CD}_3)_2\text{CO}$): δ (ppm) = 11.64 (s, 1H, OH), 9.11 (s, 1H, OH), 6.28 (dq, J = 2.4, 0.8 Hz, 1H, H5), 6.23 (dd, J = 2.5, 0.5 Hz, 1H, H3), 3.90 (s, 3H, H9), 2.49 - 2.39 (m, 3H, H7).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, $(\text{CD}_3)_2\text{CO}$): δ (ppm) = 173.0 (C8), 166.3 (C2), 163.3 (C4), 144.4 (C6), 112.3 (C5), 105.4 (C1), 101.6 (C3), 52.2 (C9), 24.3 (C7).

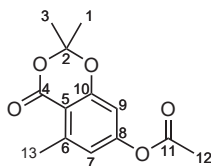
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3366 (m), 3298 (s, br), 2954 (w), 1643 (s), 1609 (vs), 1580 (s), 1497 (m), 1437 (s), 1379 (m), 1307 (s), 1251 (vs), 1198 (m), 1159 (vs), 1109 (s), 1061 (m), 995 (m), 951 (m), 833 (m), 798 (m), 699 (m).

HRMS (APCI) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_9\text{H}_9\text{O}_4)^- = 181.0506$, found: 181.0498.

mp. (recrystallized from EtOAc/pentane): 140 °C-141 °C.

Elemental Analysis: calc. for $\text{C}_9\text{H}_{10}\text{O}_4$: C, 59.34; H, 5.53. Found: C, 59.47; H, 5.45.

Analytic data were in good agreement with literature values.^[81]

2,2,5-TRIMETHYL-4-OXO-4*H*-BENZO[*D*][1,3]DIOXIN-7-YL ACETATE (**423**)

To a suspension of 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**420**) (50 mg, 0.24 mmol, 1.00 eq) in CH₂Cl₂ (3.0 mL) was added pyridine (38 mg, 39 μ L, 0.48 mmol, 2.0 eq) in one portion. To the colorless solution was added acetyl chloride (25 mg, 22 μ L, 0.31 mmol, 1.3 eq) dropwise. The resulting yellow solution was stirred for 18 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : Et₂O) afforded 2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**423**) (57 mg, 0.23 mmol, 95%) as a white solid.

R_f (Petrol Ether : EtOAc 7 : 3) = 0.34.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.68 (dq, J = 2.3, 0.8 Hz, 1H, H7), 6.62 (dd, J = 2.3, 0.6 Hz, 1H, H9), 2.67 (t, J = 0.7 Hz, 3H, H13), 2.30 (s, 3H, H12), 1.70 (s, 6H, H1+H3).

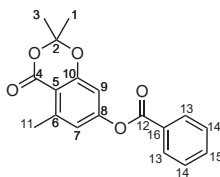
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 168.6 (C11), 160.1 (C4), 158.2 (C10), 155.5 (C8), 145.6 (C6), 119.2 (C7), 110.1 (C5), 108.6 (C9), 105.6 (C2), 25.8 (C1+C3), 22.3 (C13), 21.3 (C12).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2993 (w), 2928 (w), 2947 (w), 1752 (s), 1723 (vs), 1605 (m), 1586 (m), 1451 (m), 1381 (m), 1273 (s), 1257 (s), 1197 (vs), 901 (s).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₁₃H₁₅O₅)⁺: 251.0914, found 251.0903.

mp. (recrystallized from CH₂Cl₂/pentane): 120 °C-121 °C.

Elemental Analysis: calc. for C₁₃H₁₄O₅: C, 62.39; H, 5.64. Found: C, 62.34; H, 5.51.

2,2,5-TRIMETHYL-4-OXO-4*H*-BENZO[*D*][1,3]DIOXIN-7-YL BENZOATE (**424**)

To a suspension of 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**420**) (50 mg, 0.24 mmol, 1.00 eq) in CH_2Cl_2 (3.0 mL) was added pyridine (38 mg, 39 μL , 0.48 mmol, 2.0 eq) in one portion. To the colorless solution was added benzoyl chloride (41 mg, 33 μL , 0.29 mmol, 1.2 eq) dropwise. The resulting yellow solution was stirred for 18 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 10 mL). The organic layer was separated and the aqueous layer was further extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with an aqueous saturated sodium hydrogencarbonate solution (15 mL) and an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : Et_2O) afforded 2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl benzoate (**424**) (74 mg, 0.23 mmol, 98%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.38.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 8.22 – 8.12 (m, 2H, H₁₃), 7.71 – 7.62 (m, 1H, H₁₅), 7.52 (ddt, J = 7.9, 6.6, 1.1 Hz, 2H, H₁₄), 6.82 (dq, J = 2.3, 0.8 Hz, 1H, H₇), 6.76 (dd, J = 2.2, 0.6 Hz, 1H, H₉), 2.70 (d, J = 0.7 Hz, 3H, H₁₁), 1.72 (s, 6H, H₁ + H₃).

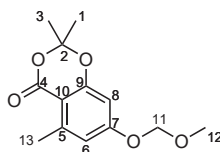
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 164.3 (C₁₂), 160.1 (C₄), 158.2 (C₁₀), 155.8 (C₈), 145.6 (C₆), 134.2 (C₁₅), 130.4 (C₁₃), 128.8 (C₁₄), 119.3 (C₇), 110.1 (C₅), 108.7 (C₉), 105.6 (C₂), 25.8 (C₁ + C₃), 22.3 (C₁₁).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2995 (m), 2929 (m), 1730 (vs), 1607 (s), 1586 (s), 1450 (s), 1377 (s), 1331 (s), 1273 (vs), 1238 (vs), 1204 (s), 1178 (m), 1131 (vs), 1060 (vs), 1023 (s), 703 (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{18}\text{H}_{17}\text{O}_5)^+$: 313.1071, found: 313.1085. Major peak m/z : $[\text{M} + \text{CH}_3\text{CN} + \text{H}]^+$ calc. for $(\text{C}_{20}\text{H}_{20}\text{NO}_5)^+$: 354.1336, found: 354.1346.

mp. (recrystallized from CH_2Cl_2): 111 °C–112 °C.

Elemental Analysis: calc. for $\text{C}_{18}\text{H}_{16}\text{O}_5$: C, 69.22; H, 5.16. Found: C, 69.26; H, 5.10.

7-(METHOXYMETHOXY)-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**425**)

To an ice-cold solution of 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**420**) (299 mg, 1.44 mmol, 1.00 eq) in CH_2Cl_2 (15.0 mL) was added NiPr_2Et (1.86 g, 2.50 mL, 14.4 mmol, 10.0 eq) in one portion. To this colorless solution was added MOM-Cl (621 mg, 0.590 mL, 7.18 mmol, 5.00 eq) dropwise. The resulting yellow solution was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (15.0 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : Et_2O) afforded 7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**425**) (349 mg, 1.38 mmol, 96%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.36.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.59 – 6.54 (m, 1H, H6), 6.45 (d, J = 2.5 Hz, 1H, H8), 5.18 (s, 2H, H11), 3.47 (s, 3H, H12), 2.63 (t, J = 0.6 Hz, 3H, H13), 1.69 (s, 6H, H1 + H3).

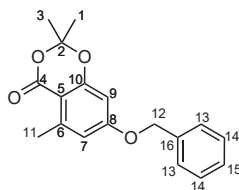
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.4 (C7), 160.6 (C4), 158.8 (C9), 145.6 (C5), 114.1 (C6), 106.3 (C10), 105.2 (C2), 101.7 (C8), 94.1 (C11), 56.5 (C12), 25.8 (C1 + C3), 22.5 (C13).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2993 (w), 2933 (w), 1725 (vs), 1610 (vs), 1577 (vs), 1454 (s), 1388 (m), 1376 (m), 1320 (m), 1297 (m), 1273 (vs), 1208 (s), 1144 (vs), 1081 (vs), 1067 (vs), 1041 (vs), 1008 (s), 941 (m), 910 (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{13}\text{H}_{17}\text{O}_5)^+$: 253.1071, found: 253.1071.

mp. (recrystallized from CH_2Cl_2 /pentane): 88 °C–89 °C.

UV-Vis: 289 nm (ϵ = 941).

7-(BENZYLOXY)-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**426**)

To an ice-cold solution of 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**420**) (50 mg, 0.24 mmol, 1.00 eq) and K_2CO_3 (66 mg, 0.48 mmol, 2.0 eq) in $(CH_3)_2CO$ (3.0 mL) was added benzyl bromide (62 mg, 43 μ L, 0.36 mmol, 1.5 eq) dropwise. The resulting yellow-white suspension was stirred for 20 h at RT. The reaction mixture was filtered through Celite[®] and rinsed with EtOAc (3 x 10 mL). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4:1 Pentane : Et₂O) afforded 7-(benzyloxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**426**) (67 mg, 0.22 mmol, 93%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.44.

¹H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.38 (m, 4H, H₁₃+H₁₄), 7.35 (tdd, J = 8.5, 3.2, 1.9 Hz, 1H, H₁₅), 6.54 (dd, J = 2.6, 0.8 Hz, 1H, H₇), 6.37 (d, J = 2.5 Hz, 1H, H₉), 5.06 (s, 2H, H₁₂), 2.64 (s, 3H, H₁₁), 1.69 (s, 6H, H₁+H₃).

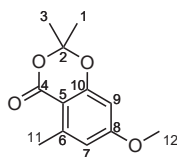
¹³C{¹H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 163.9 (C8), 160.5 (C4), 158.9 (C10), 145.4 (C6), 135.9 (C16), 128.8 (C14), 128.4 (C15), 127.6 (C13), 113.5 (C7), 105.5 (C5), 105.1 (C2), 100.2 (C9), 70.2 (C12), 25.7 (C1+C3), 22.4 (C11).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2994 (w), 2929 (w), 1718 (vs), 1608 (vs), 1452 (s), 1375 (m), 1272 (vs), 1151 (vs), 1047 (s), 908 (m), 735 (m), 695 (s).

HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{18}H_{19}O_4)^+$: 299.1278, found: 299.1269.

mp. (recrystallized from CH_2Cl_2 /pentane): 86 °C–88 °C.

Elemental Analysis: calc. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.04; H, 6.01.

7-METHOXY-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (427)

To a suspension of 7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (420) (1.82 g, 8.78 mmol, 1.00 eq) and K_2CO_3 (2.43 g, 17.6 mmol, 2.0 eq) in $(CH_3)_2CO$ (84 mL) was added methyl iodide (2.49 g, 1.09 mL, 17.6 mmol, 2.0 eq) dropwise. The resulting yellow-white suspension was stirred for 20 h at RT. The reaction mixture was filtered through Celite[®] and rinsed with EtOAc (3 x 80 mL). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4:1 Pentane : Et₂O) afforded 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (427) (1.89 g, 8.49 mmol, 97%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.39.

¹H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.46 (dq, J = 2.5, 0.8 Hz, 1H, H7), 6.29 (dd, J = 2.5, 0.6 Hz, 1H, H9), 3.82 (s, 3H, H12), 2.64 (t, J = 0.6 Hz, 3H, H11), 1.69 (s, 6H, H1+H3).

¹³C{¹H}-NMR (101 MHz, $CDCl_3$): δ (ppm) = 164.9 (C8), 160.6 (C4), 159.1 (C10), 145.5 (C6), 112.9 (C7), 105.5 (C5), 105.1 (C2), 99.4 (C9), 55.7 (C12), 25.8 (C1+C3), 22.5 (C11).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2995 (w), 2943 (w), 2846 (vw), 1728 (vs), 1612 (vs), 1577 (s), 1453 (m), 1325 (m), 1275 (vs), 1202 (s), 1157 (vs), 1059 (s), 852 (m).

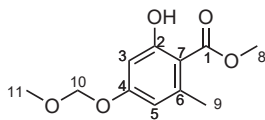
HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{12}H_{15}O_4)^+$: 223.0965, found: 223.0958.

mp. (recrystallized from CH_2Cl_2 /pentane): 78 °C-80 °C.

Elemental Analysis: calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.93; H, 5.76.

UV-Vis: 293 nm (ϵ = 2846).

Analytic data were in good agreement with literature values.^[432]

2-HYDROXY-4-(METHOXYMETHOXY)-6-METHYLBENZOATE (**431**)

A solution of 7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**425**) (15 mg, 0.059 mmol) in MeOH (8.0 mL) was prepared in a sealed vial. The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was concentrated under reduced pressure. Purification by flash column chromatography (3 : 1 Pent : EtOAc) afforded methyl 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoate (**431**) (9.0 mg, 0.040 mmol, 67%) as a white foam.

R_f (Petrol Ether : EtOAc 7 : 3) = 0.55.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.67 (s, 1H, -OH), 6.49 (d, J = 2.6 Hz, 1H, H₃), 6.38 (dd, J = 2.6, 0.9 Hz, 1H, H₅), 5.17 (s, 2H, H₁₀), 3.93 (s, 3H, H₈), 3.46 (s, 3H, H₁₁), 2.50 (d, J = 0.7 Hz, 3H, H₉).

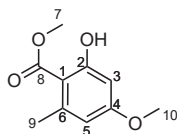
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 172.2 (C₁), 165.3 (C₂), 161.5 (C₄), 143.5 (C₆), 112.0 (C₅), 106.4 (C₇), 101.6 (C₃), 94.0 (C₁₀), 56.4 (C₁₁), 52.1 (C₈), 24.5 (C₉).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2954 (w), 2829 (vw), 1653 (s), 1617 (s), 1577 (s), 1441 (s), 1421 (m), 1322 (s), 1257 (vs), 1211 (s), 1148 (vs), 1079 (m), 1061 (m), 1019 (s), 941 (m).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₁₁H₁₅O₅)⁺: 227.0914, found: 227.0913.

Analytic data were in good agreement with literature values.^[433]

METHYL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE (433)



Two solutions of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (20 and 25 mg, 0.090 and 0.11 mmol) in MeOH (9.1 and 15 mL) were prepared in sealed vials. The sealed vials were placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions were combined and concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 Pent : Et₂O) afforded methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**433**) (28 mg, 0.14 mmol, 70%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.53.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.78 (s, 1H, OH), 6.33 (d, *J* = 2.6 Hz, 1H, H₃), 6.28 (dt, *J* = 2.7, 0.8 Hz, 1H, H₅), 3.92 (s, 3H, H₇), 3.80 (s, 3H, H₁₀), 2.49 (t, *J* = 0.6 Hz, 3H, H₉).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 172.4 (C₈), 165.7 (C₂), 164.1 (C₄), 143.3 (C₆), 111.3 (C₅), 105.4 (C₁), 98.8 (C₃), 55.4 (C₁₀), 52.0 (C₇), 24.5 (C₉).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2976 (m), 2957 (w), 2937 (w), 2853 (w), 1643 (vs), 1620 (vs), 1581 (s), 1534 (m), 1454 (s), 1437 (s), 1327 (vs), 1262 (vs), 1220 (s), 1205 (vs), 1162 (vs), 1040 (s), 950 (s), 837 (m), 804 (m), 969 (m).

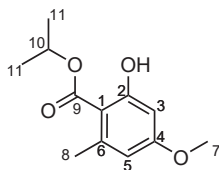
HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₀H₁₃O₄)⁺: 197.0808, found: 197.0814.

mp. (recrystallized from CH₂Cl₂/pentane): 64 °C–66 °C.

Elemental Analysis: calc. for C₁₀H₁₂O₄: C, 61.22; H, 6.17. Found: C, 61.34; H, 6.09.

Analytic data were in good agreement with literature values.^[434]

ISOPROPYL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE (434)



A solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol) in *iso*-propanol (15 mL) was prepared in a sealed vial. The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 Pent : Et₂O) afforded isopropyl 2-hydroxy-4-methoxy-6-methylbenzoate (**434**) (17 mg, 0.076 mmol, 67%) as a colourless oil.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.53.

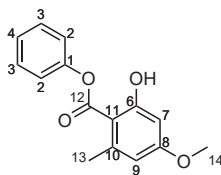
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.93 (s, 1H, OH), 6.33 (d, J = 2.7 Hz, 1H, H₃), 6.27 (dt, J = 2.7, 0.9 Hz, 1H, H₅), 5.28 (hept, J = 6.3 Hz, 1H, H₁₀), 3.79 (s, 3H, H₇), 2.51 (t, J = 0.6 Hz, 3H, H₈), 1.39 (d, J = 6.2 Hz, 6H, 2 × H₁₁).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 171.4 (C₉), 165.7 (C₂), 163.9 (C₄), 143.3 (C₆), 111.2 (C₅), 105.8 (C₁), 98.9 (C₃), 69.3 (C₁₀), 55.4 (C₇), 24.7 (C₈), 22.2 (2 × C₁₁).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2978 (w), 2936 (w), 2846 (vw), 1645 (s), 1612 (s), 1577 (s), 1466 (m), 1443 (m), 1375 (m), 1350 (m), 1315 (s), 1300 (m), 1256 (vs), 1213 (s), 1202 (s), 1158 (vs), 1101 (vs), 1041 (m), 913 (m), 804 (m).

HRMS (ES-ToF) m/z : [M + H]⁺ calc. for (C₁₂H₁₇O₄)⁺: 225.1121, found: 225.1129.

PHENYL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE (435)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol, 1.0 eq) in PhMe (15 mL) in a sealed vial was added phenol (32 mg, 0.34 mmol, 3.0 eq). The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 Pent : Et₂O) afforded phenyl 2-hydroxy-4-methoxy-6-methylbenzoate (**435**) (18 mg, 0.070 mmol, 62%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.56.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.51 (s, 1H, OH), 7.49 – 7.43 (m, 2H, H₃), 7.34 – 7.28 (m, 1H, H₄), 7.22 – 7.18 (m, 2H, H₂), 6.45 – 6.30 (m, 2H, H₇ + H₉ overlapping), 3.84 (s, 3H, H₁₄), 2.67 (t, *J* = 0.6 Hz, 3H, H₁₃).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 170.6 (C₁₂), 166.5 (C₆), 164.8 (C₈), 150.1 (C₁), 143.6 (C₁₀), 129.7 (C₃), 126.4 (C₄), 121.9 (C₂), 111.9 (C₉), 104.7 (C₁₁), 99.0 (C₇), 55.5 (C₁₄), 24.8 (C₁₃).

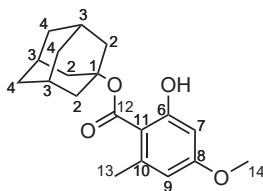
IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3426 (w), 3064 (w), 2979 (w), 1653 (s), 1617 (s), 1590 (s), 1573 (s), 1495 (s), 1417 (s), 1293 (s), 1267 (s), 1188 (vs), 1162 (vs), 1083 (s).

HRMS (ES-ToF) *m/z*: [M – C₆H₅OH]⁺ calc. for (C₉H₉O₃)⁺: 165.0546, found: 165.0545.

mp. (recrystallized from CH₂Cl₂/pentane): 108 °C–109 °C.

Elemental Analysis: calc. for C₁₅H₁₄O₄: C, 69.76; H, 5.76. Found: C, 69.66; H, 5.45.

ADAMANTAN-1-YL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE (436)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (427) (25 mg, 0.11 mmol, 1.0 eq) in PhMe (15 mL) in a sealed vial was added 1-adamantanol (51 mg, 0.34 mmol, 3.0 eq). The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 Pent : Et₂O) afforded adamantan-1-yl 2-hydroxy-4-methoxy-6-methylbenzoate (436) (25 mg, 0.079 mmol, 70%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.53.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.99 (d, *J* = 1.7 Hz, 1H, OH), 6.31 (t, *J* = 2.1 Hz, 1H, H₇), 6.25 (t, *J* = 2.1 Hz, 1H, H₉), 3.78 (d, *J* = 1.7 Hz, 3H, H₁₄), 2.49 (d, *J* = 1.6 Hz, 3H, H₁₃), 2.31 – 2.26 (m, 6H, 3 × H₂), 2.23 (s, 3H, 3 × H₃), 1.73 – 1.69 (m, 6H, 3 × H₄).

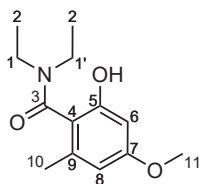
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 171.1 (C₁₂), 165.6 (C₆), 163.5 (C₈), 143.1 (C₁₀), 111.0 (C₉), 106.8 (C₁₁), 98.9 (C₇), 83.5 (C₁), 55.4 (C₁₄), 41.9 (C₂), 36.3 (C₄), 31.1 (C₃), 25.0 (C₁₃).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2907 (s), 2850 (m), 1639 (s), 1610 (s), 1577 (s), 1441 (m), 1329 (vs), 1298 (m), 1251 (vs), 1202 (vs), 1156 (vs), 1122 (s), 1048 (vs), 952 (m), 806 (m), 697 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₉H₂₅O₄)⁺: 317.1747, found: 317.1764.

mp. (recrystallized from CH₂Cl₂/pentane): 97 °C-99 °C.

Elemental Analysis: calc. for C₁₉H₂₄O₄: C, 72.13; H, 7.65. Found: C, 72.17; H, 7.53.

N,N-DIETHYL-2-HYDROXY-4-METHOXY-6-METHYLBENZAMIDE (**437**)

To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol, 1.0 eq) in PhMe (15 mL) in a sealed vial was added diethylamine (25 mg, 35 μ L, 0.34 mmol, 3.0 eq). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (2 : 8 EtOAc : CH₂Cl₂) afforded *N,N*-diethyl-2-hydroxy-4-methoxy-6-methylbenzamide (**437**) (24 mg, 0.10 mmol, 89%) as a colourless oil.

R_f (Petrol Ether : EtOAc 1 : 1) = 0.09.

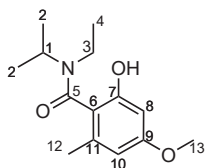
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.21 (d, *J* = 2.3 Hz, 1H, H8), 6.11 (d, *J* = 2.4 Hz, 1H, H6), 3.66 (s, 3H, H11), 3.47 (s, 2H, H1'), 3.27 (dq, *J* = 14.2, 7.1 Hz, 2H, H1), 2.16 (s, 3H, H10), 1.13 (t, *J* = 7.2 Hz, 6H, H2).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 170.3 (C3), 160.6 (C7), 154.8 (C5), 136.1 (C9), 117.2 (C4), 108.2 (C8), 100.0 (C6), 55.1 (C11), 41.3 (C1 + C1'), 19.3 (C10), 13.5 (C2).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3167 (s, br), 2970 (w), 2933 (w), 1584 (vs), 1459 (s), 1437 (s), 1328 (s), 1279 (s), 1197 (s), 1154 (vs).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₃H₂₀NO₃)⁺: 238.1438, found 238.1446.

Elemental Analysis: calc. for C₁₃H₁₉NO₃: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.36; H, 8.20; N, 5.45.

N-ETHYL-2-HYDROXY-*N*-ISOPROPYL-4-METHOXY-6-METHYLBENZAMIDE (**438**)

To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol, 1.0 eq) in PhMe (15 mL) in a sealed vial was added *N*-ethylisopropylamine (29 mg, 41 μ L, 0.34 mmol, 3.0 eq). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (2 : 8 EtOAc : CH₂Cl₂) afforded *N*-ethyl-2-hydroxy-*N*-isopropyl-4-methoxy-6-methylbenzamide (**438**) (27 mg, 0.11 mmol, 96%) as a colourless oil.

R_f (Petrol Ether : EtOAc 1 : 1) = 0.08.

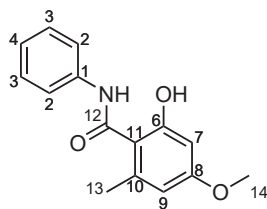
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.22 (d, *J* = 2.3 Hz, 1H, H₁₀), 6.15 (d, *J* = 2.4 Hz, 1H, H₈), 4.16 – 4.02 (m, 1H, H₁), 3.67 (s, 3H, H₁₃), 3.57 – 3.42 (m, 1H, H₃ rotamer), 3.33 – 3.12 (m, 1H, H₃ rotamer), 2.18 (s, 3H, H₁₂), 1.23 – 1.11 (m, 9H, H₂ + H₄ overlapping).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 170.4 (C₅), 160.5 (C₉), 154.6 (C₇), 136.0 (C₁₁), 117.8 (C₆), 108.2 (C₁₀), 100.1 (C₈), 55.1 (C₁₃), 49.5 (C₁), 36.7 (C₃), 21.3 (C₂), 21.2 (C₂), 19.3 (C₁₂), 15.1 (C₁).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3166 (br, s), 2972 (w), 2933 (w), 1582 (vs), 1457 (s), 1429 (s), 1333 (s), 1197 (s), 1160 (s), 1148 (s), 1041 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₄H₂₂NO₃)⁺: 252.1594, found: 252.1598.

Elemental Analysis: calc. for C₁₄H₂₁NO₃: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.42; H, 8.45; N, 5.68.

2-HYDROXY-4-METHOXY-6-METHYL-*N*-PHENYLBENZAMIDE (439)

To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (427) (34 mg, 0.15 mmol, 1.0 eq) in CH₃CN (15 mL) in a sealed vial was added aniline (142 mg, 0.14 mL, 1.53 mmol, 10 eq). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 Pent : Et₂O) afforded 2-hydroxy-4-methoxy-6-methyl-*N*-phenylbenzamide (439) (8.0 mg, 0.03 mmol, 20%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.20.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.39 (s, 1H, OH), 7.59 – 7.53 (m, 2H, H₂), 7.42 – 7.36 (m, 2H, H₃), 7.22 – 7.17 (m, 1H, H₄), 6.39 (d, *J* = 2.7 Hz, 1H, H₇), 6.33 (dd, *J* = 2.6, 0.8 Hz, 1H, H₉), 3.81 (s, 3H, H₁₄), 2.66 – 2.61 (m, 3H, H₁₃).

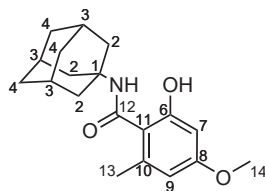
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 169.1 (C₁₂), 163.5 (C₆), 162.9 (C₈), 137.0 (C₁), 136.8 (C₁₀), 129.4 (2 × C₂), 125.4 (C₄), 121.1 (2 × C₃), 111.0 (C₉), 110.4 (C₁₁), 99.9 (C₇), 55.5 (C₁₄), 23.1 (C₁₃).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3308 (br, s), 2933 (w), 1498 (s), 1610 (s), 1595 (vs), 1534 (vs), 1498 (s), 1442 (vs), 1320 (s), 1256 (m), 1198 (s), 1159 (vs), 1038 (m).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₅H₁₆NO₃)⁺: 258.1125, found: 258.1125.

mp. (recrystallized from CH₂Cl₂/pentane): 173 °C–174 °C.

Elemental Analysis: calc. for C₁₅H₁₅NO₃: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.80; H, 5.80; N, 5.31.

N-(ADAMANTAN-1-YL)-2-HYDROXY-4-METHOXY-6-METHYLBENZAMIDE (**440**)

To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol, 1.0 eq) in PhMe (15 mL) in a sealed vial was added 1-adamantylamine (51 mg, 0.34 mmol, 3.0 eq). The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 Pent : Et₂O) afforded *N*-(adamantan-1-yl)-2-hydroxy-4-methoxy-6-methylbenzamide (**440**) (12 mg, 0.038 mmol, 34%) as a white solid.

R_f (Petrol Ether : EtOAc 1 : 1) = 0.74.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.74 (s, 1H, OH), 6.33 (d, *J* = 2.6 Hz, 1H, H₇), 6.23 (dd, *J* = 2.6, 0.8 Hz, 1H, H₉), 5.65 (s, 1H, NH), 3.77 (s, 3H, H₁₄), 2.48 (s, 3H, H₁₃), 2.12 (s, 9H, H₃ + H₂), 1.72 (d, *J* = 2.7 Hz, 6H, H₄).

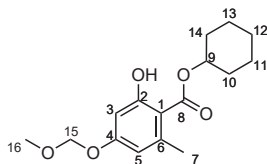
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 170.0 (C₁₂), 163.1 (C₆), 162.1 (C₈), 136.4 (C₁₀), 110.3 (C₉), 99.7 (C₇), 55.4 (C₁₄), 53.3 (C₁), 42.0 (C₂), 36.5 (C₄), 29.6 (C₃), 23.1 (C₁₃).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3310 (br, s), 2906 (vs), 2848 (m), 1629 (vs), 1607 (vs), 1594 (vs), 1577 (vs), 1525 (vs), 1497 (s), 1453 (s), 1407 (m), 1371 (m), 1359 (s), 1344 (m), 1306 (s), 1275 (s), 1200 (s), 1162 (vs), 1088 (s).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₉H₂₆NO₃)⁺: 316.1907, found 316.1909.

mp. (recrystallized from CH₂Cl₂/pentane): 177 °C-178 °C.

Elemental Analysis: calc. for C₁₉H₂₅NO₃ · 0.5 H₂O: C, 70.34; H, 8.08; N, 4.32. Found: C, 70.33; H, 7.90; N, 4.18.

CYCLOHEXYL 2-HYDROXY-4-(METHOXYMETHOXY)-6-METHYLBENZOATE (**441**)

To a solution of 7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**425**) (20 mg, 0.079 mmol) in PhMe (11 mL) in a sealed vial was added cyclohexene (10 mg, 24 μ L, 0.24 mmol, 3.00 eq). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 26 h. The crude material was concentrated under reduced pressure. Purification by preparative TLC (3 : 1 Hexane : EtOAc) afforded cyclohexyl 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoate (**441**) (16 mg, 0.054 mmol, 69%) as a white foam.

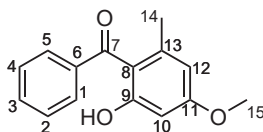
R_f (Petrol Ether : EtOAc 7 : 3) = 0.65.

¹H-NMR (400 MHz, **CDCl₃**): δ (ppm) = 11.86 (s, 1H, -OH), 6.49 (d, J = 2.6 Hz, 1H, H₃), 6.38 (dd, J = 2.6, 0.8 Hz, 1H, H₅), 5.17 (s, 2H, H₁₅), 5.09 (tt, J = 8.5, 3.8 Hz, 1H, H₉), 3.46 (s, 3H, H₁₆), 2.54 (s, 3H, H₇), 1.96 (t, J = 7.9 Hz, 2H, H₁₀+H_{14eq}), 1.81 – 1.72 (m, 2H, H₁₁+H_{13eq}), 1.66 – 1.59 (m, 2H, H₁₀ + H_{14ax}), 1.57 (s, 1H, H_{12eq}), 1.52 – 1.39 (m, 2H, H₁₁+H_{13ax}), 1.35 (dt, J = 9.6, 3.2 Hz, 1H, H_{12ax}).

¹³C{¹H}-NMR (101 MHz, **CDCl₃**): δ (ppm) = 171.3 (C₈), 165.3 (C₂), 161.3 (C₄), 143.4 (C₆), 111.9 (C₅), 106.9 (C₁), 101.7 (C₃), 94.0 (C₁₅), 74.2 (C₉), 56.4 (C₁₆), 31.8 (C₁₀ + C₁₄), 25.5 (C₁₂), 24.9 (C₇), 23.8 (C₁₁ + C₁₃).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2935 (m), 2854 (w), 1644 (s), 1614 (s), 1577 (s), 1449 (m), 1380 (m), 1322 (m), 1253 (vs), 1209 (s), 1147 (vs), 1112 (m), 1079 (s), 1060 (m), 1018 (vs), 943 (s), 803 (m).

HRMS (APCI) m/z : [M – H][–] calc. for (C₁₆H₂₁O₅)[–]: 293.1394, found: 293.1396.

(2-HYDROXY-4-METHOXY-6-METHYLPHENYL)(PHENYL)METHANONE (**442**)

To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (30 mg, 0.13 mmol) in CH₃CN (7 mL) in a sealed vial was added 1,3-cyclohexadiene (8.0 mL). The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solution was concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 Pent : Et₂O) afforded (2-hydroxy-4-methoxy-6-methylphenyl)(phenyl)methanone (**442**) (6.0 mg, 0.025 mmol, 18%) as a white film.

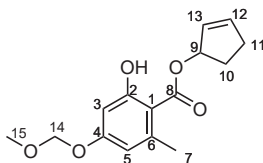
R_f (Petrol Ether : EtOAc 4 : 1) = 0.32.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 10.95 (s, 1H, OH), 7.61 – 7.57 (m, 2H, H1 + H5), 7.57 – 7.51 (m, 1H, H3), 7.48 – 7.41 (m, 2H, H2 + H4), 6.40 (d, *J* = 2.5 Hz, 1H, H10), 6.32 – 6.25 (m, 1H, H12), 3.84 (s, 3H, H15), 1.89 (d, *J* = 0.7 Hz, 3H, H14).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 201.3 (C7), 164.4 (C11), 164.0 (C9), 141.8 (C13), 141.5 (C6), 132.2 (C3), 128.7 (C2 + C4), 128.5 (C1 + C5), 115.7 (C8), 111.0 (C12), 99.0 (C10), 55.6 (C15), 23.7 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3383 (br, s), 2924 (m), 1652 (m), 1613 (vs), 1595 (vs), 1577 (s), 1447 (s), 1325 (s), 1274 (vs), 1201 (s), 1162 (vs), 1145 (s), 701 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₅H₁₅O₃)⁺: 243.1016, found: 243.1034.

CYCLOPENT-2-EN-1-YL 2-HYDROXY-4-(METHOXYMETHOXY)-6-METHYLBENZOATE
(443)

To a solution of 7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (425) (21 mg, 0.080 mmol) in CH₃CN (5.0 mL) in a sealed vial was added cyclopentene (2.5 mL). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was concentrated under reduced pressure. Purification by preparative TLC (20 : 1 Hexane : EtOAc) afforded cyclopent-2-en-1-yl 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoate (443) (2.0 mg, 0.007 mmol, 9%) as a white film.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.31.

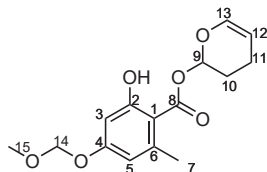
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.78 (d, *J* = 0.8 Hz, 1H, OH), 6.48 (d, *J* = 2.5 Hz, 1H, H₃), 6.36 (d, *J* = 2.6 Hz, 1H, H₅), 6.18 (dt, *J* = 5.4, 2.3 Hz, 1H, H₁₃), 6.01 – 5.91 (m, 2H, H₉ + H₁₂ overlapping), 5.17 (d, *J* = 0.9 Hz, 2H, H₁₅), 3.46 (d, *J* = 0.8 Hz, 3H, H₁₆), 2.90 – 2.53 (m, 1H, H_{10eq}), 2.47 (s, 3H, H₇), 2.41 (dd, *J* = 9.3, 6.8 Hz, 1H, H_{10ax}), 2.39 – 2.30 (m, 1H, H_{11eq}), 2.06 – 1.83 (m, 1H, H_{11ax}).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 171.7 (C₈), 165.3 (C₄), 161.4 (C₂), 143.5 (C₆), 138.4 (C₁₃), 129.2 (C₁₂), 124.9 (C₁), 111.9 (C₅), 101.7 (C₃), 94.0 (C₁₄), 81.9 (C₉), 56.4 (C₁₅), 31.2 (C₁₀), 30.1 (C₁₁), 24.6 (C₇).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2924 (m), 1730 (m), 1648 (vs), 1617 (s), 1577 (s), 1449 (s), 1312 (s), 1254 (vs), 1211 (s), 1150 (vs), 1019 (s), 943 (s).

HRMS (APCI): calc. for carboxylic acid fragmentation *m/z*: [M - C₅H₇]⁺ (C₁₀H₁₃O₅)⁺: 213.0757, found: 213.0763.

3,4-DIHYDRO-2*H*-PYRAN-2-YL 2-HYDROXY-4-(METHOXYMETHOXY)-6-METHYLBENZOATE
(444)



To a solution of 7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (425) (21 mg, 0.080 mmol) in CH₃CN (5.0 mL) in a sealed vial was added cyclopentene (2.5 mL). The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was concentrated under reduced pressure. Purification by preparative TLC (20 : 1 Hexane : EtOAc) afforded 3,4-dihydro-2*H*-pyran-2-yl 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoate (444) (4.0 mg, 0.014 mmol, 16%) as a transparent film.

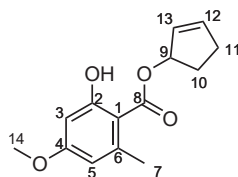
R_f (Petrol Ether : EtOAc 4 : 1) = 0.35.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.58 (s, 1H, OH), 6.61 (d, *J* = 2.7 Hz, 1H, H₉), 6.50 (d, *J* = 2.5 Hz, 1H, H₃), 6.41 – 6.37 (m, 1H, H₅), 6.35 – 6.24 (m, 1H, H₁₃), 5.18 (s, 2H, H₁₄), 4.93 (t, *J* = 6.0 Hz, 1H, H₁₂), 3.46 (d, *J* = 0.7 Hz, 3H, H₁₅), 2.53 (s, 3H, H₇), 2.52 – 2.15 (m, 1H, H_{11eq}), 2.14 – 2.01 (m, 3H, H_{11ax} + H₁₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 170.6 (C₈), 165.8 (C₂), 161.8 (C₄), 143.5 (C₆), 140.5 (C₁₃), 112.0 (C₅), 106.0 (C₁), 101.9 (C₁₂), 101.6 (C₃), 93.8 (C₁₄), 90.5 (C₉), 56.3 (C₁₅), 24.9 (C₁₀), 24.2 (C₇), 15.2 (C₁₁).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2926 (m), 1731 (m), 1654 (s), 1616 (s), 1577 (s), 1320 (s), 1260 (s), 1227 (s), 1151 (vs), 1062 (s), 1034 (vs), 1017 (vs), 942 (s).

CYCLOPENT-2-EN-1-YL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE (445)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (30 mg, 0.13 mmol) in CH₃CN (7 mL) in a sealed vial was added cyclopentene (8.0 mL). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solution was concentrated under reduced pressure. Purification by preparative TLC (20 : 1 Hex : EtOAc) afforded cyclopent-2-en-1-yl 2-hydroxy-4-methoxy-6-methylbenzoate (**445**) (3.0 mg, 0.012 mmol, 9%) as a white film.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.29.

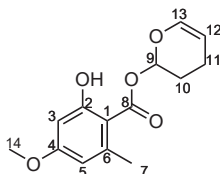
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.93 (s, 1H, OH), 6.35 (d, *J* = 2.6 Hz, 1H, H₃), 6.29 (qt, *J* = 1.5, 0.7 Hz, 1H, H₅), 6.20 (ddt, *J* = 5.6, 2.4, 1.2 Hz, 1H, H₁₃), 6.01 – 5.92 (m, 2H, H₉ + H₁₂ overlapping), 3.82 (d, *J* = 1.0 Hz, 3H, H₁₄), 2.65 – 2.54 (m, 1H, H_{10eq}), 2.49 (t, *J* = 0.6 Hz, 3H, H₇), 2.47 – 2.41 (m, 1H, H_{10ax}), 2.41 – 2.31 (m, 1H, H_{11eq}), 2.09 – 1.97 (m, 1H, H_{11ax}).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 171.8 (C₈), 165.7 (C₄), 163.9 (C₂), 143.3 (C₆), 138.4 (C₁₃), 129.3 (C₁₂), 121.0 (C₁), 111.2 (C₅), 98.8 (C₃), 81.8 (C₉), 55.4 (C₁₄), 31.2 (C₁₀), 29.8 (C₁₁), 24.6 (C₇).

IR (Diamond-ATR, neat) *ν*_{max} (cm⁻¹) = 2930 (m), 1730 (w), 1645 (s), 1614 (s), 1577 (s), 1443 (m), 1342 (s), 1255 (vs), 1213 (s), 1204 (s), 1158 (vs), 1117 (m), 1041 (s).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₄H₁₇O₄)⁺: 249.1121, found: 249.1120.

3,4-DIHYDRO-2*H*-PYRAN-2-YL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE
(**446**)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (30 mg, 0.13 mmol) in CH₃CN (7 mL) in a sealed vial was added cyclopentene (8.0 mL). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The resulting pale-yellow solutions was concentrated under reduced pressure. Purification by preparative TLC (20 : 1 Hex : EtOAc) afforded 3,4-dihydro-2*H*-pyran-2-yl 2-hydroxy-4-methoxy-6-methylbenzoate (**446**) (3.0 mg, 0.012 mmol, 6%) as a transparent film.

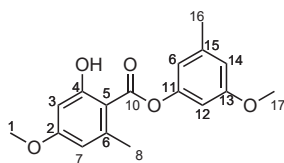
R_f (Petrol Ether : EtOAc 4 : 1) = 0.37.

¹H-NMR (500 MHz, CDCl₃): δ (ppm) = 11.71 (s, 1H, OH), 6.60 (dt, J = 2.6, 1.5 Hz, 1H, H₉), 6.34 (d, J = 2.6 Hz, 1H, H₃), 6.29 (dt, J = 3.5, 2.7, 1.2 Hz, 2H, H₅ and H₁₃ overlapping), 4.95 – 4.91 (m, 1H, H₁₂), 3.80 (s, 3H, H₁₄), 2.52 (t, J = 0.6 Hz, 3H, H₇), 2.31 – 2.19 (m, 1H, H_{11eq}), 2.13 – 2.00 (m, 3H, H_{11ax} + H₁₀).

¹³C{¹H}-NMR (126 MHz, CDCl₃): δ (ppm) = 170.9 (C₈), 166.3 (C₂), 164.5 (C₄), 143.5 (C₆), 140.6 (C₁₃), 111.6 (C₅), 105.1 (C₁), 102.1 (C₁₂), 98.9 (C₃), 90.6 (C₉), 55.5 (C₁₄), 25.1 (C₁₀), 24.3 (C₇), 15.4 (C₁₁).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2924 (s), 2852 (s), 1379 (m), 1653 (vs), 1617 (s), 1577 (s), 1443 (s), 1321 (s), 1260 (vs), 1211 (vs), 1159 (vs), 1033 (vs).

3-METHOXY-5-METHYLPHENYL 2-HYDROXY-4-METHOXY-6-METHYLBENZOATE
(451)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (427) (50 mg, 0.22 mmol, 2.0 eq) in CH₃CN (1.5 mL) in a sealed vial was added either *N*-Boc pyrrole (19 mg, 19 μL, 0.11 mmol, 1.0 eq) or 3,4-Dihydro-2*H*-pyran (9.5 mg, 10 μL, 0.11 mmol, 1.0 eq) in one portion. The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was heated to 100 °C for 15 h and subsequently concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 pentane : Et₂O) afforded 3-methoxy-5-methylphenyl 2-hydroxy-4-methoxy-6-methylbenzoate (451) (7.0 mg, 0.023 mmol, 10%) as a colorless oil.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.42.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.49 (s, 1H, OH), 6.67 (ddd, *J* = 2.2, 1.5, 0.8 Hz, 1H, H₁₄), 6.61 (ddd, *J* = 2.2, 1.4, 0.7 Hz, 1H, H₆), 6.55 (t, *J* = 2.1 Hz, 1H, H₁₂), 6.40 – 6.34 (m, 2H, H₃ and H₇ overlapping), 3.83 (s, 3H, H₁), 3.81 (s, 3H, H₁₇), 2.64 (d, *J* = 0.6 Hz, 3H, H₈), 2.36 (t, *J* = 0.7 Hz, 3H, H₁₆).

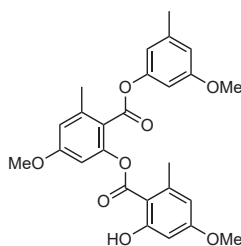
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 170.6 (C₁₀), 166.5 (C₄), 164.8 (C₂), 160.6 (C₁₃), 150.8 (C₁₁), 143.6 (C₆), 140.7 (C₁₅), 114.9 (C₆), 113.1 (C₁₄), 111.9 (C₇), 105.0 (C₁₂), 104.8 (C₅), 99.0 (C₃), 55.6 (C₁₇), 55.5 (C₁), 24.7 (C₈), 21.7 (C₁₆).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2999 (w), 2935 (w), 2846 (w), 1670 (s), 1618 (s), 1577 (s), 1443 (m), 1320 (s), 1294 (s), 1249 (vs), 1210 (s), 1158 (vs), 1135 (vs), 1063 (m), 1038 (m), 952 (w).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₇H₁₉O₅)⁺: 303.1227, found: 303.1240.

Elemental Analysis: calc. for C₁₇H₁₈O₅: C, 67.54; H, 6.00. Found: C, 67.41; H, 5.97.

5-METHOXY-2-((3-METHOXY-5-METHYLPHENOXY)CARBONYL)-3-METHYLPHENYL
2-HYDROXY-4-METHOXY-6-METHYLBENZOATE (**452**)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (50 mg, 0.22 mmol, 2.0 eq) in CH₃CN (1.5 mL) in a sealed vial was added either *N*-Boc pyrrole (19 mg, 19 μ L, 0.11 mmol, 1.0 eq) or 3,4-Dihydro-2*H*-pyran (9.5 mg, 10 μ L, 0.11 mmol, 1.0 eq) in one portion. The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was heated to 100 °C for 15 h and subsequently concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 pentane : Et₂O) afforded 5-methoxy-2-((3-methoxy-5-methylphenoxy)carbonyl)-3-methylphenyl 2-hydroxy-4-methoxy-6-methylbenzoate (**452**) (7.0 mg, 0.0064 mmol, 3%) as a colorless oil.

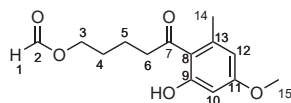
R_f (Petrol Ether : EtOAc 3 : 1) = 0.24.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.43 (s, 1H), 6.77 (dd, *J* = 2.6, 0.7 Hz, 1H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.54 (ddd, *J* = 2.2, 1.4, 0.7 Hz, 1H), 6.39 (ddd, *J* = 2.0, 1.4, 0.7 Hz, 1H), 6.36 – 6.32 (m, 2H), 6.29 (t, *J* = 2.3 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 2.63 (d, *J* = 0.7 Hz, 3H), 2.58 (s, 3H), 2.24 (d, *J* = 0.7 Hz, 3H).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 166.6, 165.0, 160.4, 151.3, 150.2, 143.9, 141.6, 140.5, 125.7, 115.0, 114.5, 113.3, 112.0, 106.6, 104.0, 99.0, 55.8, 55.6, 55.3, 30.5, 24.7, 21.5.

HRMS (ES-ToF) *m/z*: [M – H][–] calc. for (C₂₆H₂₅O₈)[–]: 465.1555, found: 465.1553.

5-(2-HYDROXY-4-METHOXY-6-METHYLPHENYL)-5-OXOPENTYL FORMATE (453)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol) in CH₃CN (8.0 mL) and 3,4-Dihydro-2*H*-pyran (7.0 mL) in a sealed vial were added two drops of water. The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 48 h. The crude material was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 → 4 : 1 pentane : Et₂O) afforded 5-(2-hydroxy-4-methoxy-6-methylphenyl)-5-oxopentyl formate (**453**) (10 mg, 0.038 mmol, 33%) as a white solid.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.24.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 13.32 (s, 1H, OH), 8.06 (s, 1H, H₁), 6.31 (d, *J* = 2.7 Hz, 1H, H₁₀), 6.28 (dd, *J* = 2.7, 0.8 Hz, 1H, H₁₂), 4.21 (td, *J* = 6.2, 0.9 Hz, 2H, H₃), 3.81 (s, 3H, H₁₅), 2.95 (t, *J* = 6.9 Hz, 2H, H₆), 2.57 (s, 3H, H₁₄), 1.88 – 1.79 (m, 2H, H₄), 1.76 (tdd, *J* = 11.6, 5.9, 4.4 Hz, 2H, H₅).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 206.0 (C₇), 166.8 (C₉), 164.3 (C₁₁), 161.2 (C₂), 141.3 (C₁₃), 115.4 (C₈), 112.1 (C₁₂), 99.3 (C₁₀), 63.8 (C₃), 55.5 (C₁₅), 43.3 (C₆), 28.2 (C₅), 25.4 (C₁₄), 21.3 (C₄).

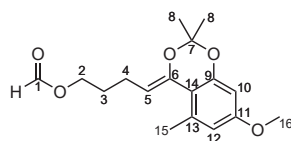
IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3210 (w), 2939 (m), 1719 (vs), 1610 (vs), 1576 (s), 1444 (m), 1420 (m), 1377 (m), 1254 (m), 1204 (vs), 1159 (vs), 834 (m).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₄H₁₉O₅)⁺: 267.1227, found: 267.1228. Also found *m/z*: [M – H₂O]⁺ calc. for (C₁₄H₁₇O₄)⁺: 249.1121, found: 249.1122. Major peak *m/z*: [M – HC(O)O]⁺ calc. for (C₁₃H₁₇O₃)⁺: 221.1172, found: 221.1173.

mp. (recrystallized from CH₂Cl₂/pentane): 77 °C–78 °C.

Elemental Analysis: calc. for C₁₄H₁₈O₅: C, 63.15; H, 6.81. Found: C, 63.16; H, 6.82.

(*Z*)-4-(7-Methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-ylidene)butyl formate (**454**)



To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (25 mg, 0.11 mmol) in CH₃CN (8.0 mL) and 3,4-Dihydro-2*H*-pyran (7.0 mL) in a sealed vial were added two drops of water. The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 48 h. The crude material was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 → 4 : 1 pentane : Et₂O) afforded (*Z*)-4-(7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-ylidene)butyl formate (**454**) (13 mg, 0.042 mmol, 38%) as a colorless oil.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.52.

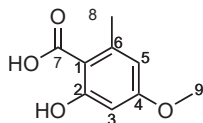
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 8.08 (t, *J* = 0.7 Hz, 1H, H₁), 6.38 (dd, *J* = 2.2, 0.7 Hz, 1H, H₁₂), 6.27 (d, *J* = 2.7 Hz, 1H, H₁₀), 5.26 (t, *J* = 7.3 Hz, 1H, H₅), 4.23 (td, *J* = 6.7, 0.9 Hz, 2H, H₂), 3.76 (s, 3H, H₁₆), 2.42 (s, 3H, H₁₅), 2.36 (q, *J* = 7.4 Hz, 2H, H₄), 1.82 (p, *J* = 7.0 Hz, 2H, H₃), 1.54 (s, 6H, H₈).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.3 (C₁), 159.3 (C₁₁), 152.6 (C₉), 143.7 (C₆), 136.5 (C₁₃), 111.9 (C₁₂), 110.6 (C₁₄), 109.9 (C₅), 100.2 (C₇), 99.9 (C₁₀), 64.0 (C₂), 55.3 (C₁₆), 29.0 (C₃), 25.4 (C₈), 24.4 (C₁₅), 21.6 (C₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2991 (w), 2938 (w), 1724 (vs), 1612 (vs), 1575 (m), 1457 (m), 1384 (m), 1373 (m), 1325 (m), 1201 (vs), 1150 (vs), 1066 (s), 1058 (s), 841 (m).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₇H₂₃O₅)⁺: 307.1540, found: 307.1538.

Elemental Analysis: calc. for C₁₇H₂₂O₅·H₂O: C, 62.95; H, 7.46. Found: C, 62.65; H, 7.08.

2-HYDROXY-4-METHOXY-6-METHYLBENZOIC ACID (**467**)

To a solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (30 mg, 0.13 mmol) in CH₃CN (7.0 mL) and furan (8.0 mL) were added two drops of water. The sealed vial was placed in a Luzchem® UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 → 2 : 1 pentane : EtOAc) afforded 2-hydroxy-4-methoxy-6-methylbenzoic acid (**467**) (21 mg, 0.012 mmol, 85%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.01.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.52 (s, 1H, OH), 6.34 (q, *J* = 2.5 Hz, 2H, H₃ + H₅), 3.82 (d, *J* = 1.0 Hz, 3H, H₉), 2.57 (s, 3H, H₈).

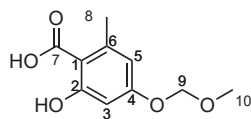
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 175.9 (C₇), 166.7 (C₂), 165.1 (C₆), 144.9 (C₆), 111.8 (C₅), 104.1 (C₁), 98.9 (C₃), 55.5 (C₉), 24.5 (C₈).

IR (Diamond-ATR, neat) *ν*_{max} (cm⁻¹) = 2920 (br, s), 1611 (vs), 1577 (s), 1457 (s), 1442 (s), 1416 (m), 1361 (s), 1318 (m), 1259 (vs), 1221 (s), 1199 (vs), 1159 (vs), 1031 (s), 837 (s), 797 (s).

HRMS (APCI) *m/z*: [M - H]⁻ calc. for (C₉H₉O₄)⁻: 181.0506, found: 181.0504.

mp. (recrystallized from CH₂Cl₂/pentane): 165 °C-167 °C.

Analytic data were in good agreement with literature values.^[435]

2-HYDROXY-4-(METHOXYMETHOXY)-6-METHYLBENZOIC ACID (**469**)

To a solution of 7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**425**) (50 mg, 0.20 mmol, 1.0 eq) in CH₃CN (14 mL) and two drops of water was added 3,4,6-Tri-*O*-Methyl- β -glucal (750 mg, 3.98 mmol, 20 eq). The sealed vial was placed in a Luzchem[®] UV-reactor and irradiated with UV-A and UV-B light for 24 h. The crude material was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 $\rightarrow$ 2 : 1 pentane : EtOAc) afforded 2-hydroxy-4-(methoxymethoxy)-6-methylbenzoic acid (**469**) (30 mg, 0.014 mmol, 71%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.02.

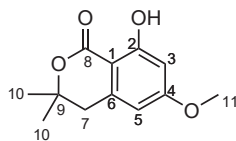
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.38 (s, 1H, OH), 6.51 (d, J = 2.5 Hz, 1H, H₃), 6.43 (dd, J = 2.6, 0.9 Hz, 1H, H₅), 5.19 (s, 2H, H₉), 3.48 (s, 3H, H₁₀), 2.58 (s, 3H, H₈).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 175.9 (C₇), 166.3 (C₂), 162.5 (C₄), 145.1 (C₆), 112.5 (C₅), 105.1 (C₁), 101.7 (C₃), 94.0 (C₉), 56.5 (C₁₀), 24.6 (C₈).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₁₀H₁₃O₅)⁺: 213.0757, found: 213.0765.

mp. (recrystallized from CH₂Cl₂/pentane): 150 °C-151 °C.

Analytic data were in good agreement with literature values.^[436]

8-HYDROXY-6-METHOXY-3,3-DIMETHYLISOCHROMAN-1-ONE (**482**)

To a dry-ice cold solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (100 mg, 0.450 mmol, 1.0 eq) in THF (5.0 mL) was added LDA (1 M in THF/hexanes; 0.90 mL, 0.90 mmol, 2.0 eq). The reaction mixture was stirred for 2 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 pentane : EtOAc) afforded 8-hydroxy-6-methoxy-3,3-dimethylisochroman-1-one (**482**) (56.0 mg, 0.250 mmol, 56%) as a transparent oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.32.

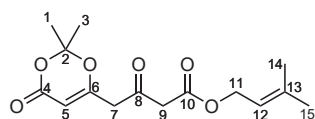
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.34 (s, 1H, OH), 6.33 (d, J = 2.4 Hz, 1H, H₃), 6.22 (dt, J = 2.2, 1.0 Hz, 1H, H₅), 3.80 (s, 3H, H₁₁), 2.91 – 2.88 (m, 2H, H₇), 1.44 (s, 6H, H₁₀).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 169.3 (C₈), 165.9 (C₄), 164.5 (C₂), 140.2 (C₆), 106.9 (C₅), 101.2 (C₁), 99.4 (C₃), 81.6 (C₉), 55.6 (C₁₁), 39.5 (C₇), 27.3 (C₁₀).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2976 (m), 1653 (vs), 1623 (vs), 1582 (s), 1507 (m), 1440 (m), 1388 (m), 1373 (s), 1355 (vs), 1313 (vs), 1284 (vs), 1219 (s), 1178 (vs), 1157 (vs), 1094 (vs), 1033 (s), 952 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{12}\text{H}_{15}\text{O}_5)^+$: 223.0965, found: 223.0974. Minor peak m/z : $[\text{M} + \text{CH}_3\text{CN} + \text{H}]^+$ calc. $(\text{C}_{14}\text{H}_{18}\text{NO}_4)^+$: 264.1230, found: 264.1211.

3-METHYLBUT-2-EN-1-YL 4-(2,2-DIMETHYL-4-OXO-4H-1,3-DIOXIN-6-YL)-3-OXOBUTANOATE
(484)



Synthesized according to a modified literature procedure by Barrett et. al.^[105] To a solution of 2-phenyl-1,3-dioxane-4,6-dione (**141**) (350 mg, 1.82 mmol, 1.82 eq) and DCC (376 mg, 1.82 mmol, 1.82 eq) in CH_2Cl_2 (15 mL) was added DMAP (222 mg, 1.82 mmol, 1.82 eq) in one portion. The solution was stirred for 15 min at RT before 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetic acid (**140**) (339 mg, 1.82 mmol, 1.82 eq) was added in one portion. The resulting yellow-white suspension was stirred for 18 h at RT. The reaction mixture was cooled to 0 °C, the precipitate was filtered off and the solid was washed with small portions of CH_2Cl_2 until the precipitate appeared colourless. The filtrate was washed with an aqueous hydrochloric acid solution (1 M, 2 x 10 mL). The organic layer was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in PhMe (7.5 mL) and 3-methyl-2-buten-1-ol (**483**) (86.0 mg, 0.12 mL, 1.08 mmol, 1.00 eq) was added in one portion. The resulting pale yellow solution was heated to 55 °C for 4 h after which the solution was concentrated. Purification by flash column chromatography (9 : 1 pentane : EtOAc $\rightarrow$ 7 : 1 $\rightarrow$ 4 : 1) afforded 3-methylbut-2-en-1-yl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (**484**) (314 mg, 1.95 mmol, 98%) as yellow-orange oil.

R_f (hexane : EtOAc 4 : 1) = 0.12.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 5.36 (d, J = 0.6 Hz, 1H, H5), 5.33 (dddd, J = 7.3, 5.8, 3.1, 1.6 Hz, 1H, H12), 4.67 – 4.63 (m, 2H, H11), 3.51 (s, 2H, H9), 3.50 (d, J = 0.6 Hz, 2H, H7), 1.77 (q, J = 1.1 Hz, 3H, H15), 1.71 (s, 3H, H14), 1.71 (s, 6H, H1 + H3).

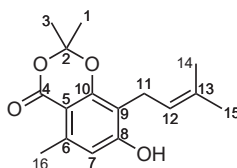
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 195.6 (C8), 166.4 (C10), 163.6 (C6), 160.5 (C4), 140.4 (C13), 117.6 (C12), 107.4 (C2), 97.1 (C5), 62.6 (C11), 49.1 (C9), 47.0 (C7), 25.8 (C15), 25.0 (C1 + C3), 18.1 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 1721 (vs), 1636 (s), 1390 (s), 1271 (s), 1202 (s), 1014 (s).

HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for $(\text{C}_{15}\text{H}_{19}\text{O}_6)^-$: 295.1187, found: 295.1194.

Analytic data were in good agreement with literature values.^[88,104]

7-HYDROXY-2,2,5-TRIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**487**)



Synthesized according to a modified literature procedure by Barrett et. al.:^[105] To an ice-cold solution of 3-methylbut-2-en-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**484**) (294 mg, 0.99 mmol, 1.00 eq) in CH₂Cl₂ (5.00 mL) was added MgCl₂ (189 mg, 1.98 mmol, 2.00 eq) and pyridine (212 mg, 0.20 mL, 2.68 mmol, 2.70 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (93.0 mg, 0.080 mL, 1.19 mmol, 1.20 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (5.00 mL) and tri(2-furyl)phosphine (46.0 mg, 0.20 mmol, 0.20 eq) and tris(dibenzylideneacetone)dipalladium(o) (45.0 mg, 0.005 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 2 h at RT before caesium carbonate (970 mg, 2.98 mmol, 3.00 eq) was added in one portion. The resulting orange-brown solution was stirred for 1.5 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc -> 16 : 1 -> 12 : 1) afforded 7-hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one (**487**) (121 mg, 0.438 mmol, 44%) as yellow-white solid.

R_f (hexane: EtOAc 4 : 1) = 0.31.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.41 (d, *J* = 0.9 Hz, 1H, H₇), 6.15 (s, 1H, OH), 5.18 (dddd, *J* = 8.7, 5.9, 2.8, 1.4 Hz, 1H, H₁₂), 3.31 (d, *J* = 7.3 Hz, 2H, H₁₁), 2.58 (d, *J* = 0.7 Hz, 3H, H₁₆), 1.79 (d, *J* = 1.4 Hz, 3H, H₁₅), 1.73 (q, *J* = 1.3 Hz, 3H, H₁₄), 1.68 (s,

6H, H₁ + H₃).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.3 (C₄), 160.1 (C₈), 156.2 (C₁₀), 142.9 (C₆), 134.8 (C₁₃), 121.1 (C₁₂), 113.7 (C₇), 113.0 (C₉), 105.5 (C₅), 105.0 (C₂), 25.9 (C₁₅), 25.9 (C₁ + C₃), 22.1 (C₁₆), 22.1 (C₁₁), 18.0 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3274 (br, s), 2926 (m), 1726 (m), 1690 (vs), 1607 (vs), 1591 (vs), 1513 (m), 1452 (s), 1410 (s), 1388 (m), 1375 (s), 1325 (s), 1295 (vs), 1276 (vs), 1209 (s), 1166 (s), 1107 (s), 1046 (m).

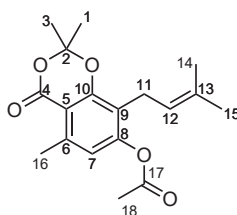
HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₆H₂₀O₄)⁺: 277.1434, found: 277.1443.

mp. (recrystallized from CH₂Cl₂/pentane): 125 °C-127 °C.

Elemental Analysis: calc. for C₁₆H₂₀O₄: C, 69.55; H, 7.30. Found: C, 69.32; H, 7.30.

Analytic data were in good agreement with literature values.^[89,104]

2,2,5-TRIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-4-OXO-4*H*-BENZO[*D*][1,3]DIOXIN-7-YL ACETATE (**488**)



According to the procedure described above. Purification by flash column chromatography (19 : 1 pentane : EtOAc → 16 : 1 → 12 : 1) afforded 2,2,5-trimethyl-8-(3-methylbut-2-en-1-yl)-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**488**) (10 mg, 0.031 mmol, 3%) as white film.

R_f (hexane : EtOAc 4 : 1) = 0.57.

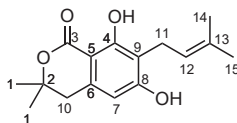
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.65 (d, *J* = 0.9 Hz, 1H, H₇), 5.01 (ddq, *J* = 8.7, 5.8, 1.5 Hz, 1H, H₁₂), 3.18 (d, *J* = 7.2 Hz, 2H, H₁₁), 2.63 (d, *J* = 0.7 Hz, 3H, H₁₇), 2.32 (s, 3H, H₁₈), 1.73 (d, *J* = 1.3 Hz, 3H, H₁₄), 1.69 (s, 6H, H₁ + H₃), 1.67 – 1.65 (m, 3H, H₁₅).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 168.8 (C₁₇), 160.5 (C₄), 156.2 (C₁₀), 153.5 (C₈), 142.1 (C₆), 132.5 (C₁₃), 121.0 (C₁₂), 120.7 (C₉), 119.8 (C₇), 110.5 (C₅), 105.4 (C₂), 25.9 (C₁ + C₃), 25.8 (C₁₅), 23.0 (C₁₁), 22.1 (C₁₆), 21.0 (C₁₈), 18.0 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2927 (m), 1771 (s), 1733 (vs), 1582 (s), 1448 (s), 1375 (s), 1278 (vs), 1195 (vs), 1157 (s), 1090 (s), 1039 (s).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₈H₂₃O₅)⁺: 319.1540, found: 319.1536.

6,8-DIHYDROXY-3,3-DIMETHYL-7-(3-METHYLBUT-2-EN-1-YL)ISOCHROMAN-1-ONE
(489)



To a -100°C cold solution of 7-hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one (**487**) (30 mg, 0.11 mmol, 1.0 eq) in THF (1.0 mL) was added LDA (1 M in THF/hexanes; 0.33 mL, 0.33 mmol, 3.0 eq). The reaction mixture was stirred for 2 h at -100°C followed by gradually warming up to RT over 1 h. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 $\rightarrow$ 4 : 1 $\rightarrow$ 2 : 1 pentane : EtOAc) afforded 6,8-dihydroxy-3,3-dimethyl-7-(3-methylbut-2-en-1-yl)isochroman-1-one (**489**) (5.0 mg, 0.02 mmol, 17%) as a white film.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.17.

$^1\text{H-NMR}$ (400 MHz, C_6D_6): δ (ppm) = 12.64 (s, 1H, OH), 5.83 (s, 1H, H7), 5.60 (s, 1H, OH), 5.32 (ddp, J = 8.9, 5.9, 1.5 Hz, 1H, H12), 3.52 (d, J = 7.3 Hz, 2H, H11), 2.15 (s, 2H, H10), 1.60 (d, J = 1.3 Hz, 3H, H14), 1.51 (d, J = 1.4 Hz, 3H, H15), 1.37 (s, 6H, H1).

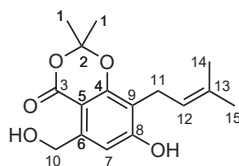
$^1\text{H-NMR}$ (400 MHz, CD_3OD): δ (ppm) = 6.43 (s, 1H, H7), 5.13 (ddd, J = 9.6, 4.9, 3.4 Hz, 1H, H12), 3.23 (s, 2H, H11), 3.21 (d, J = 2.4 Hz, 2H, H10), 1.76 (d, J = 1.3 Hz, 3H, H14), 1.66 (q, J = 1.4 Hz, 3H, H15), 1.63 (s, 6H, H1).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CD_3OD): δ (ppm) = 163.0 (C3), 162.9 (C8), 157.8 (C4), 146.9 (C6), 132.1 (C13), 123.2 (C12), 115.8 (C9), 114.0 (C7), 106.0 (C2), 104.8 (C5), 36.4 (C10), 25.9 (C15), 25.9 (C1), 22.7 (C11), 18.0 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3265 (br, s), 2991 (w), 2924 (m), 1722 (s), 1694 (vs), 1605 (vs), 1592 (s), 1511 (m), 1418 (s), 1375 (m), 1297 (vs), 1277 (vs), 1210 (s), 1166 (s), 1106 (m), 1051 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{16}\text{H}_{21}\text{O}_4)^+$: 277.1434, found: 277.1432.

7-HYDROXY-5-(HYDROXYMETHYL)-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-
4H-BENZO[D][1,3]DIOXIN-4-ONE (**490**)



According to the procedure above. Purification by flash column chromatography (9 : 1 $\rightarrow$ 4 : 1 $\rightarrow$ 2 : 1 pentane : EtOAc) afforded 7-hydroxy-5-(hydroxymethyl)-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-4H-benzo[d][1,3]dioxin-4-one (**490**) (18 mg, 0.062 mmol, 57%) as a transparent oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.04.

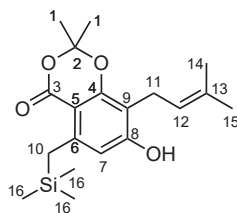
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 8.36 (s, 1H, OH), 6.66 (s, 1H, H₇), 5.15 (tdt, J = 5.8, 2.8, 1.4 Hz, 1H, H₁₂), 4.66 (s, 2H, H₁₀), 3.30 (d, J = 7.3 Hz, 2H, H₁₁), 1.77 (d, J = 1.4 Hz, 3H, H₁₄), 1.71 (s, 6H, H₁), 1.69 (d, J = 1.4 Hz, 3H, H₁₅).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.9 (C₃), 161.8 (C₈), 157.0 (C₄), 142.2 (C₆), 133.3 (C₁₃), 121.1 (C₁₂), 116.5 (C₉), 113.4 (C₇), 105.7 (C₂), 104.3 (C₅), 64.2 (C₁₀), 25.9 (C₁₅), 25.7 (2 $\times$ C₁), 22.1 (C₁₁), 18.0 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3225 (br, s), 2921 (m), 1690 (vs), 1605 (vs), 1513 (m), 1420 (s), 1388 (s), 1375 (s), 1297 (vs), 1279 (s), 1207 (s), 1165 (s), 1107 (s), 1025 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{16}\text{H}_{21}\text{O}_5)^+$: 293.1384, found: 293.1371.

7-HYDROXY-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-5-((TRIMETHYLSILYL)METHYL)-4H-BENZO[D][1,3]DIOXIN-4-ONE (**491**)



To a solution of 7-hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-en-1-yl)-4H-benzo[d][1,3]dioxin-4-one (**487**) (19 mg, 0.069 mmol, 1.0 eq) in THF (1.0 mL) was added DIPEA (9.0 mg, 0.01 mL, 0.069 mmol, 1.0 eq) and TMS-Cl (8.2 mg, 0.01 mL, 0.076 mmol, 1.05 eq). The reaction was stirred for 1 h at RT before the reaction was cooled to -78°C . LDA (1 M in THF/hexanes; 0.21 mL, 0.21 mmol, 3.0 eq) was added dropwise and the reaction was stirred for 3 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (4 M; 10 mL). The reaction was left to stir for 1 h, before the organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 $\rightarrow$ 4 : 1 pentane : EtOAc) afforded 7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-((trimethylsilyl)methyl)-4H-benzo[d][1,3]dioxin-4-one (**491**) (20 mg, 0.0057 mmol, 84%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.64.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.23 (s, 1H, H7), 6.14 (s, 1H, OH), 5.19 (tdd, J = 6.4, 2.9, 1.5 Hz, 1H, OH), 3.29 (d, J = 7.2 Hz, 2H, H11), 2.75 (s, 2H, H10), 1.79 (d, J = 1.4 Hz, 3H, H14), 1.75 – 1.70 (m, 3H, H15), 1.67 (s, 6H, H1), -0.02 (s, 9H, H16).

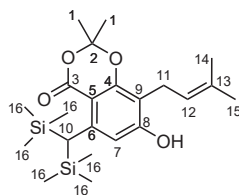
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.7 (C3), 159.9 (C8), 156.1 (C4), 146.8 (C6), 134.5 (C13), 121.4 (C12), 112.0 (C7), 111.4 (C9), 104.6 (C2), 104.4 (C5), 25.9 (C10), 25.9 (2 x C1 + C15), 22.1 (C11), 18.0 (C14), -1.3 (3 x C16).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3271 (br, s), 2952 (m), 2923 (m), 1724 (m), 1685 (vs), 1606 (vs), 1582 (vs), 1506 (s), 1416 (s), 1375 (s), 1332 (m), 1293 (s), 1274 (vs), 1247 (s), 1210 (s), 1165 (s), 1101 (m), 1054 (vs), 847 (vs).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{19}\text{H}_{29}\text{SiO}_4)^+$: 349.1830, found: 349.1825.

mp. (recrystallized from CH_2Cl_2 /pentane): 129°C - 131°C .

5-(BIS(TRIMETHYLSILYL)METHYL)-7-HYDROXY-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**492**)



According to the procedure above. Purification by flash column chromatography (9 : 1 $\rightarrow$ 4 : 1 pentane : EtOAc) afforded 5-(bis(trimethylsilyl)methyl)-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one (**492**) (20 mg, 0.0057 mmol, 84%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.56.

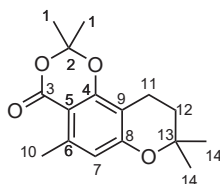
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.22 (s, 1H, H7), 5.75 (s, 1H, OH), 5.20 (ddt, J = 7.2, 5.8, 1.4 Hz, 1H, H12), 3.84 (s, 1H, H10), 3.29 (d, J = 7.3 Hz, 2H, H11), 1.80 (d, J = 1.4 Hz, 3H, H14), 1.76 (d, J = 1.5 Hz, 3H, H15), 1.65 (s, 6H, H1), 0.04 (s, 18H, H16).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 161.8 (C3), 159.5 (C8), 156.6 (C4), 148.8 (C6), 133.9 (C13), 121.4 (C12), 111.9 (C7), 110.4 (C9), 105.5 (C5), 104.2 (C2), 26.0 (C15), 25.7 (2 $\times$ C1), 24.2 (C10), 22.2 (C11), 18.0 (C14), 0.5 (6 $\times$ C16).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3366 (br, s), 2952 (m), 1718 (m), 1685 (vs), 1605 (vs), 1582 (s), 1498 (m), 1412 (s), 1388 (m), 1375 (m), 1275 (vs), 1251 (vs), 1211 (m), 1177 (s), 1165 (s), 1049 (vs), 880 (s), 865 (s), 841 (vs).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{22}\text{H}_{37}\text{Si}_2\text{O}_4)^+$: 421.2225, found: 421.2238.

2,2,5,8,8-PENTAMETHYL-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE (**493**)



To a solution of 7-hydroxy-2,2,5-trimethyl-8-(3-methylbut-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one (**487**) (29 mg, 0.10 mmol, 1.0 eq) in THF (1.0 mL) was added an aqueous hydrochloric acid solution (4 M; 10 mL). The reaction was left to stir for 1 h, before the organic layer was separated and the aqueous phase was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc) afforded 2,2,5,8,8-pentamethyl-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**493**) (22 mg, 0.0080 mmol, 76%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.41.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 6.35 (d, J = 0.9 Hz, 1H, H7), 2.62 – 2.55 (m, 5H, H10 + H11 overlapping), 1.78 (t, J = 6.8 Hz, 2H, H12), 1.69 (s, 6H, H1), 1.33 (s, 6H, H14).

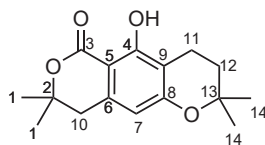
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.0 (C3), 159.6 (C8), 156.1 (C4), 142.2 (C6), 114.7 (C7), 107.1 (C9), 104.9 (C2), 104.1 (C5), 75.7 (C13), 31.8 (C12), 26.8 (2 × C14), 25.9 (2 × C1), 22.1 (C10), 16.5 (C11).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2974 (m), 2928 (m), 1723 (vs), 1618 (s), 1572 (vs), 1494 (m), 1449 (s), 1374 (s), 1359 (s), 1280 (vs), 1206 (s), 1155 (vs), 1116 (vs), 1066 (s), 1038 (vs), 885 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{16}\text{H}_{20}\text{O}_4)^+$: 277.1434, found: 277.1446.

mp. (recrystallized from CH_2Cl_2 /pentane): 99 °C–100 °C.

5-HYDROXY-2,2,8,8-TETRAMETHYL-3,4,8,9-TETRAHYDRO-2*H*,6*H*-PYRANO[3,4-*G*]CHROMEN-6-ONE (**494**)



To a dry-ice cold solution of 2,2,5,8,8-pentamethyl-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**493**) (22 mg, 0.08 mmol, 1.0 eq) in THF (1.0 mL) was added LDA (1 M in THF/hexanes; 0.16 mL, 0.16 mmol, 2.0 eq). The reaction mixture was stirred for 2 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc) afforded 5-hydroxy-2,2,8,8-tetramethyl-3,4,8,9-tetrahydro-2*H*,6*H*-pyrano[3,4-*g*]chromen-6-one (**494**) (22 mg, 0.072 mmol, 91%) as a white solid.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.46.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.59 (s, 1H, OH), 6.13 (d, J = 1.0 Hz, 1H, H7), 2.86 (d, J = 1.0 Hz, 2H, H10), 2.67 (t, J = 6.8 Hz, 2H, H11), 1.80 (t, J = 6.8 Hz, 2H, H12), 1.45 (s, 6H, H1), 1.35 (s, 6H, H14).

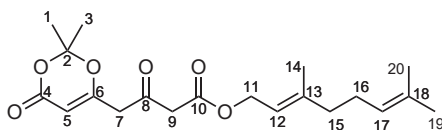
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 169.8 (C3), 161.8 (C4), 160.5 (C8), 137.1 (C6), 108.3 (C7), 107.7 (C9), 99.9 (C5), 81.6 (C2), 75.8 (C13), 39.3 (C10), 32.0 (C12), 27.4 (2 x C1), 26.9 (2 x C14), 16.5 (C11).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2974 (m), 2931 (m), 1727 (w), 1653 (vs), 1633 (s), 1583 (s), 1433 (m), 1388 (s), 1357 (vs), 1308 (vs), 1285 (s), 1257 (s), 1222 (s), 1157 (vs), 1100 (vs), 797 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{16}\text{H}_{20}\text{O}_4)^+$: 277.1434, found: 277.14447.

mp. (recrystallized from CH_2Cl_2 /pentane): 93 °C-95 °C.

(*E*)-3,7-DIMETHYLOCTA-2,6-DIEN-1-YL 4-(2,2-DIMETHYL-4-OXO-4*H*-1,3-DIOXIN-6-YL)-3-OXOBUTANOATE (**495**)



Synthesized using a modified literature procedure by Barrett et. al.^[105] To a solution of 2-phenyl-1,3-dioxane-4,6-dione (**141**) (5.25 g, 27.3 mmol, 1.82 eq) and DCC (5.63 g, 27.3 mmol, 1.82 eq) in CH₂Cl₂ (230 mL) was added DMAP (3.34 g, 27.3 mmol, 1.82 eq) in one portion. The solution was stirred for 15 min at RT before 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid (**140**) (5.08 g, 27.3 mmol, 1.82 eq) was added in one portion. The resulting yellow-white suspension was stirred for 18 h at RT. The reaction mixture was cooled to 0 °C, the precipitate was filtered off and the solid was washed with small portions of CH₂Cl₂ until the precipitate appeared colourless. The filtrate was washed with an aqueous hydrochloric acid solution (1 M, 2 x 20 mL). The organic layer was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in PhMe (115 mL) and (*E*)-3,7-dimethylocta-2,6-dien-1-ol **298** (2.31 g, 2.63 mL, 15.0 mmol, 1.00 eq) was added in one portion. The resulting pale yellow solution was heated to 55 °C for 4 h after which the solution was concentrated. Purification by flash column chromatography (9 : 1 pentane : EtOAc -> 7 : 1 -> 4 : 1) afforded (*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**495**) (4.66 g, 12.8 mmol, 86%) as yellow-orange oil.

R_f (hexane : EtOAc 4 : 1) = 0.13.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.36 (s, 1H, H₅), 5.35 – 5.30 (m, 1H, H₁₂), 5.06 (tq, J = 5.4, 1.5 Hz, 1H, H₁₇), 4.70 – 4.64 (m, 2H, H₁₁), 3.51 (s, 2H, H₉), 3.50 (s, 2H, H₇), 2.14 – 2.07 (m, 2H, H₁₆), 2.06 (s, 2H, H₁₅), 1.71 (s, 9H, H₁ + H₃ and H₁₄ overlapping), 1.67 (d, J = 1.3 Hz, 3H, H₁₉), 1.59 (d, J = 1.4 Hz, 3H, H₂₀).

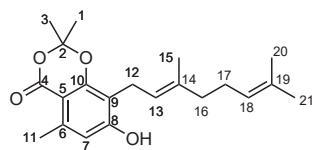
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 195.8 (C₈), 166.5 (C₁₀), 163.7 (C₆), 160.6 (C₄), 143.8 (C₁₃), 132.1 (C₁₈), 123.7 (C₁₇), 117.4 (C₁₂), 107.5 (C₂), 97.3 (C₅), 62.8 (C₁₁), 49.3 (C₉), 47.1 (C₇), 39.6 (C₁₅), 26.4 (C₁₉), 25.8 (C₁₆), 25.1 (C₁ + C₃), 17.8 (C₂₀), 16.7 (C₁₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2966 (w), 2919 (w), 2855 (w), 1718 (vs), 1636 (s), 1388 (s), 1375 (s), 1271 (vs), 1252 (s), 1201 (vs), 1015 (vs), 966 (m), 902 (m).

HRMS (ESI) m/z : [M + Na]⁺ calc. for (C₂₀H₂₈O₆Na)⁺: 387.1778, found: 387.1770.

Analytic data were in good agreement with literature values.^[104]

(*E*)-8-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-7-HYDROXY-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**498**)



Synthesized using a modified literature procedure by Barrett et. al.^[105] To an ice-cold solution of (*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**495**) (3.63 g, 9.96 mmol, 1.00 eq) in CH₂Cl₂ (50.0 mL) was added MgCl₂ (1.89 g, 19.9 mmol, 2.00 eq) and pyridine (2.17 g, 2.17 mL, 26.9 mmol, 2.70 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (938 mg, 0.85 mL, 11.9 mmol, 1.20 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (20 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (50.0 mL) and tri(2-furyl)phosphine (462 mg, 1.99 mmol, 0.20 eq) and Tris(dibenzylideneacetone)dipalladium(o) (456 mg, 0.50 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 2 h at RT before caesium carbonate (9.73 g, 29.9 mmol, 3.00 eq) was added in one portion. The resulting orange-brown solution was stirred for 1.5 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 30 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc → 16 : 1 → 12 : 1) afforded (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**498**) (1.13 g, 3.28 mmol, 33%) as yellow-white solid.

R_f (hexane: EtOAc 4 : 1) = 0.23.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.41 (d, *J* = 0.9 Hz, 1H, H₇), 6.09 (s, 1H, OH), 5.19 (ddq, *J* = 7.3, 5.8, 1.3 Hz, 1H, H₁₃), 5.04 (ddq, *J* = 8.3, 5.7, 1.5 Hz, 1H, H₁₈), 3.32 (d, *J* = 7.2 Hz, 2H, H₁₂), 2.59 (d, *J* = 0.8 Hz, 3H, H₁₁), 2.16 – 2.06 (m, 2H, H₁₇), 2.06 –

1.98 (m, 2H, H16), 1.79 (d, $J = 1.3$ Hz, 3H, H15), 1.68 (s, 6H, H1 + H3), 1.66 (d, $J = 1.5$ Hz, 3H, H21), 1.58 (d, $J = 1.3$ Hz, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 161.2 (C4), 160.3 (C8), 156.1 (C10), 143.0 (C6), 138.7 (C14), 132.1 (C19), 123.9 (C18), 121.0 (C13), 113.8 (C7), 112.9 (C9), 105.5 (C5), 104.9 (C2), 39.8 (C15), 26.6 (C16), 25.9 (C1 + C3), 25.8 (C21), 22.1 (C11), 22.0 (C12), 17.8 (C20), 16.3 (C15).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3304 (br, s), 2925 (m), 1726 (s), 1692 (vs), 1606 (vs), 1591 (vs), 1513 (m), 1452 (m), 1409 (s), 1388 (s), 1375 (s), 1325 (s), 1296 (vs), 1275 (vs), 1209 (s), 1167 (s), 1106 (s), 1046 (s).

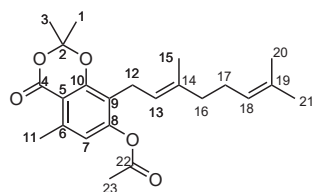
HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{21}\text{H}_{29}\text{O}_4)^+$: 345.2060, found: 345.2057. Major peak m/z : $[\text{M} - \text{acetone} + \text{H}]^+$ calc. for $(\text{C}_{18}\text{H}_{23}\text{O}_3)^+$: 287.1642, found 287.1639.

mp. (recrystallized from CH_2Cl_2 /pentane): 100 °C-102 °C.

Elemental Analysis: calc. for $\text{C}_{21}\text{H}_{28}\text{O}_4$: C, 72.23; H, 8.19. Found: C, 72.89; H, 8.18.

Analytic data were in good agreement with literature values.^[104]

(*E*)-8-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-2,2,5-TRIMETHYL-4-OXO-4*H*-BENZO[*D*][1,3]DIOXIN-7-YL ACETATE (**499**)



According to the procedure described above. Purification by flash column chromatography (19 : 1 pentane : EtOAc $\rightarrow$ 16 : 1 $\rightarrow$ 12 : 1) afforded (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-2,2,5-trimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-7-yl acetate (**499**) (53 mg, 0.014 mmol, 1%) as yellow-white film.

R_f (hexane: EtOAc 4 : 1) = 0.45.

^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 6.65 (d, $J = 0.9$ Hz, 1H, H7), 5.04 (dtdd, $J = 8.4, 7.1, 2.7, 1.4$ Hz, 2H, H13 + H18 overlapping), 3.20 (d, $J = 7.1$ Hz, 2H, H12), 2.63 (d, $J = 0.8$ Hz, 3H, H11), 2.32 (s, 3H, H23), 2.06 – 2.00 (m, 2H, H17), 1.97 (q, $J = 7.0$ Hz, 2H, H16), 1.73 (d, $J = 1.3$ Hz, 3H, H15), 1.69 (s, 6H, H1 + H3), 1.65 (d, $J = 1.3$ Hz, 3H, H21), 1.57 (d, $J = 1.2$ Hz, 3H, H20).

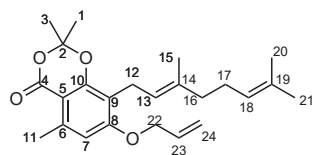
$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 168.7 (C22), 160.5 (C4), 156.3 (C10), 153.6 (C8), 142.1 (C6), 136.2 (C14), 131.7 (C19), 124.2 (C18), 120.8 (C13), 120.8 (C9), 119.8 (C7), 110.5 (C5), 105.4 (C2), 39.8 (C16), 26.7 (C15), 25.9 (C1 + C3), 25.8 (C21), 22.9

(C12), 22.1 (C11), 21.0 (C23), 17.8 (C20), 16.3 (C15).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2924 (m), 1772 (s), 1734 (vs), 1582 (s), 1448 (s), 1375 (s), 1278 (s), 1193 (vs), 1158 (s), 1092 (s), 1038 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{23}\text{H}_{31}\text{O}_5)^+$: 369.2166, found: 369.2066.

(*E*)-7-(ALLYLOXY)-8-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**500**)



To a suspension of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**498**) (330 mg, 0.958 mmol, 1.0 eq) and K_2CO_3 (199 mg, 1.44 mmol, 1.5 eq) in DMF (10 mL) was added allyl bromide (174 mg, 0.12 mL, 1.44 mmol, 1.5 eq) dropwise. The reaction was stirred for 15 h at RT before the reaction was diluted with EtOAc (5.0 mL), quenched with an aqueous hydrochloric acid solution (1 M; 10 mL) and further diluted with an aqueous lithium chloride solution (10 wt-%; 30 mL). The reaction was left to stir for 1 h, before the organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (20 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc in Pentane) afforded (*E*)-7-(allyloxy)-8-(3,7-dimethylocta-2,6-dien-1-yl)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**500**) (314 mg, 0.82 mmol, 85%) as a pale yellow oil.

R_f (hexane: EtOAc 4 : 1) = 0.81.

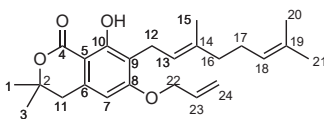
1H -NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.42 (s, 1H, H7), 6.04 (ddt, J = 17.3, 10.4, 5.1 Hz, 1H, H23), 5.42 (dq, J = 17.3, 1.6 Hz, 1H, H24*cis*), 5.30 (dq, J = 10.6, 1.4 Hz, 1H, H24*trans*), 5.13 (ddp, J = 7.3, 5.9, 1.3 Hz, 1H, H13), 5.05 (tdt, J = 7.0, 2.9, 1.4 Hz, 1H, H18), 4.60 (dt, J = 5.1, 1.6 Hz, 2H, H22), 3.29 (d, J = 7.3 Hz, 2H, H12), 2.64 (d, J = 0.7 Hz, 3H, H11), 2.08 – 2.00 (m, 2H, H17), 1.95 (dd, J = 9.3, 6.0 Hz, 2H, H16), 1.75 (d, J = 1.3 Hz, 3H, H15), 1.67 (s, 6H, H1 + H3), 1.64 (q, J = 1.3 Hz, 3H, H21), 1.57 (d, J = 1.5 Hz, 3H, H20).

$^{13}C\{^1H\}$ -NMR (101 MHz, $CDCl_3$): δ (ppm) = 161.1 (C4 + C8), 155.8 (C10), 142.7 (C6), 135.3 (C14), 132.8, (C23) 131.5 (C19), 124.4 (C18), 121.8 (C13), 117.8 (C24), 116.2 (C9), 109.5 (C7), 106.0 (C5), 104.9 (C2), 69.1 (C22), 39.9 (C17), 26.8 (C16), 25.9 (C1 + C3), 25.8 (C21), 22.6 (C11), 21.9 (C12), 17.8 (C20), 16.3 (C15).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2925 (m), 1729 (vs), 1605 (s), 1575 (s), 1449 (m), 1387 (s), 1375 (s), 1327 (s), 1279 (vs), 1208 (vs), 1169 (s), 1115 (s), 1045 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{24}H_{33}O_4)^+$: 385.2373, found: 385.2384.

(*E*)-6-(ALLYLOXY)-7-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-8-HYDROXY-3,3-DIMETHYLISOCHRMAN-1-ONE (**501**)



To a dry-ice cold solution of (*E*)-7-(allyloxy)-8-(3,7-dimethylocta-2,6-dien-1-yl)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**500**) (43 mg, 0.11 mmol, 1.0 eq) in THF (1.2 mL) was added LDA (1 M in THF/hexanes; 0.17 mL, 0.17 mmol, 1.5 eq). The reaction mixture was stirred for 2 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc) afforded (*E*)-6-(allyloxy)-7-(3,7-dimethylocta-2,6-dien-1-yl)-8-hydroxy-3,3-dimethylisochroman-1-one (**501**) (18 mg, 0.05 mmol, 42%) as a pale-yellow oil.

R_f (Petrol Ether : EtOAc 9 : 1) = 0.22.

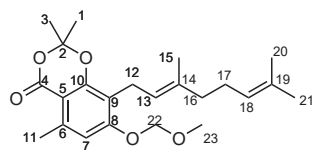
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.43 (s, 1H, OH), 6.20 (s, 1H, H7), 6.04 (ddt, J = 17.3, 10.3, 5.0 Hz, 1H, H23), 5.41 (dq, J = 17.3, 1.7 Hz, 1H, H24cis), 5.29 (dq, J = 10.6, 1.5 Hz, 1H, H24trans), 5.23 (dddt, J = 6.2, 5.2, 2.5, 1.2 Hz, 1H, H13), 5.09 – 5.03 (m, 1H, H18), 4.59 (dt, J = 5.1, 1.6 Hz, 2H, H22), 3.37 (d, J = 7.3 Hz, 2H, H12), 2.92 – 2.88 (m, 2H, H11), 2.05 (q, J = 7.4 Hz, 2H, H17), 1.96 (dd, J = 9.3, 6.0 Hz, 3H, H16), 1.77 (d, J = 1.4 Hz, 3H, H15), 1.63 (d, J = 1.4 Hz, 3H, H21), 1.56 (d, J = 1.3 Hz, 3H, H20), 1.46 (s, 6H, H1 + H3).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 169.6 (C4), 162.2 (C8), 161.2 (C10), 137.5 (C6), 135.4 (C14), 132.8 (C23), 131.3 (C19), 124.6 (C18), 121.9 (C13), 117.7 (C24), 116.2 (C9), 102.9 (C7), 101.7 (C5), 81.5 (C2), 69.1 (C22), 39.9 (C16), 39.8 (C11), 27.4 (C1 + C3), 26.8 (C15), 25.8 (C21), 21.9 (C12), 17.8 (C20), 16.3 (C15).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2922 (m), 1727 (m), 1654 (vs), 1621 (s), 1580 (s), 1510 (m), 1429 (s), 1388 (m), 1320 (s), 1299 (vs), 1223 (s), 1207 (s), 1164 (vs), 1104 (vs), 986 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{24}\text{H}_{33}\text{O}_4)^+$: 385.2373, found: 385.2371.

(*E*)-8-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-7-(METHOXYMETHOXY)-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**502**)



To an ice-cold solution of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**498**) (100 mg, 0.29 mmol, 1.0 eq) and DIPEA (375 mg, 0.51 mL, 2.90 mmol, 10 eq) in CH₂Cl₂ (3.5 mL) was added MOM-Cl (117 mg, 0.11 mL, 1.45 mmol, 5.0 eq) dropwise. The reaction was stirred for 1 h at 0 °C. The reaction was quenched with a saturated aqueous ammonium chloride solution (5.0 mL). The organic layer was separated and the aqueous phase was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc in Pentane) afforded (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**502**) (101 mg, 0.26 mmol, 90%) as a pale yellow oil.

R_f (hexane: EtOAc 3 : 1) = 0.54.

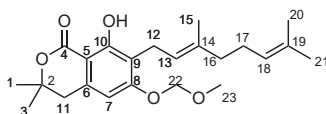
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.64 (d, *J* = 0.9 Hz, 1H, H₇), 5.25 (s, 2H, H₂₂), 5.12 (tq, *J* = 7.2, 1.3 Hz, 1H, H₁₃), 5.05 (dddt, *J* = 7.0, 5.7, 2.9, 1.4 Hz, 1H, H₁₈), 3.49 (s, 3H, H₂₃), 3.29 (d, *J* = 7.3 Hz, 2H, H₁₂), 2.63 (d, *J* = 0.8 Hz, 3H, H₁₁), 2.07 – 2.00 (m, 2H, H₁₇), 1.95 (dd, *J* = 9.2, 6.1 Hz, 2H, H₁₆), 1.76 (d, *J* = 1.3 Hz, 3H, H₁₅), 1.68 (s, 6H, H₁ + H₃), 1.64 (t, *J* = 1.3 Hz, 3H, H₂₁), 1.57 (d, *J* = 1.3 Hz, 3H, H₂₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 159.8 (C₈), 155.9 (C₁₀), 142.7 (C₆), 135.4 (C₁₄), 131.5 (C₁₉), 124.4 (C₁₈), 121.8 (C₁₃), 116.7 (C₉), 111.2 (C₇), 106.7 (C₅), 104.9 (C₂), 94.2 (C₂₂), 56.5 (C₂₃), 39.9 (C₁₆), 26.8 (C₁₇), 25.9 (C₁ + C₃), 25.8 (C₂₁), 22.5 (C₁₁), 22.1 (C₁₂), 17.8 (C₂₀), 16.2 (C₁₅).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2929 (m), 1732 (vs), 1609 (s), 1577 (s), 1452 (s), 1390 (m), 1376 (m), 1322 (s), 1280 (vs), 1208 (s), 1152 (vs), 1116 (vs), 1073 (vs), 965 (s), 907 (m).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₂₃H₃₃O₅)⁺: 389.2323, found: 389.2323.

(*E*)-7-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-8-HYDROXY-6-(METHOXYMETHOXY)-3,3-DIMETHYLISOCHROMAN-1-ONE (**503**)



To a dry-ice cold solution of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**502**) (43 mg, 0.11 mmol, 1.0 eq) in THF (1.1 mL) was added LDA (1 M in THF/hexanes; 0.22 mL, 0.22 mmol, 2.0 eq). The reaction mixture was stirred for 2 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc) afforded (*E*)-7-(3,7-dimethylocta-2,6-dien-1-yl)-8-hydroxy-6-(methoxymethoxy)-3,3-dimethylisochroman-1-one (**503**) (28 mg, 0.07 mmol, 65%) as a pale-yellow oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.33.

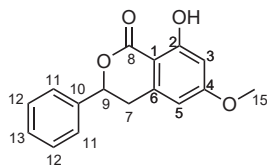
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.46 (s, 1H, OH), 6.43 (s, 1H, H7), 5.24 (s, 2H, H22), 5.22 – 5.16 (m, 1H, H13), 5.06 (dddt, J = 7.0, 5.7, 2.9, 1.4 Hz, 1H, H18), 3.48 (s, 3H, H23), 3.39 – 3.35 (m, 2H, H12), 2.94 – 2.88 (m, 2H, H11), 2.08 – 2.01 (m, 2H, H17), 1.96 (dd, J = 9.5, 6.0 Hz, 2H, H16), 1.78 (d, J = 1.3 Hz, 3H, H15), 1.64 (t, J = 2.2 Hz, 3H, H21), 1.56 (d, J = 1.3 Hz, 3H, H20), 1.46 (d, J = 1.5 Hz, 6H, H1 + H3).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 169.6 (C4), 161.4 (C10), 160.8 (C8), 137.4 (C6), 135.5 (C14), 131.4 (C19), 124.5 (C18), 121.9 (C13), 116.8 (C9), 104.6 (C7), 102.3 (C5), 94.0 (C22), 81.6 (C2), 56.4 (C23), 39.9 (C16), 39.7 (C11), 27.4 (C1 + C3), 26.8 (C17), 25.8 (C21), 22.1 (C12), 17.8 (C20), 16.2 (C15).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2914 (m), 1725 (m), 1653 (vs), 1620 (s), 1580 (s), 1508 (m), 1429 (m), 1292 (vs), 1267 (s), 1226 (s), 1151 (vs), 1103 (vs), 1055 (vs), 965, (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{23}\text{H}_{33}\text{O}_5)^+$: 389.2323, found: 389.2323.

8-HYDROXY-6-METHOXY-3-PHENYLISOCHROMAN-1-ONE (504)



To a dry-ice cold solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (427) (53 mg, 0.24 mmol, 1.0 eq) in THF (2.5 mL) was added LDA (1 M in THF/hexanes; 0.45 mL, 0.45 mmol, 2.0 eq). After 5 min benzaldehyde (129 mg, 0.12 mL, 1.21 mmol, 5.0 eq) was added dropwise. The reaction mixture was stirred for 2 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (85 : 15 pentane : EtOAc) afforded 8-hydroxy-6-methoxy-3-phenylisochroman-1-one (504) (14 mg, 0.06 mmol, 23%) as a transparent oil in a 2 : 1 mixture with 8-hydroxy-6-methoxy-3,3-dimethylisochroman-1-one (482).

Alternatively: To an ice-cold solution of 5-(2-hydroxy-2-phenylethyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (505) (41 mg, 0.12 mmol, 1.00 eq) was added NaH (5.0 mg, 0.13 mmol, 1.05 eq) in one portion. The reaction mixture was stirred for 12 h at RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (15 : 1 -> 9 : 1 pentane : EtOAc) afforded 8-hydroxy-6-methoxy-3-phenylisochroman-1-one (504) (25 mg, 0.09 mmol, 74%) as a white film

R_f (Petrol Ether : EtOAc 4 : 1) = 0.41.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.24 (s, 1H, OH), 7.50 – 7.47 (m, 2H, H₁₂), 7.46 (dd, J = 4.1, 1.8 Hz, 1H, H₁₃), 7.45 – 7.39 (m, 2H, H₁₁), 6.43 (dd, J = 2.4, 0.7 Hz, 1H, H₃), 6.32 (ddd, J = 2.3, 1.4, 0.7 Hz, 1H, H₅), 5.57 (dd, J = 12.1, 3.3 Hz, 1H, H₉), 3.86 (s, 3H, H₁₅), 3.28 (ddt, J = 16.4, 12.1, 1.1 Hz, 1H, H_{7eq}), 3.09 (ddd, J = 16.4, 3.3, 0.7 Hz, 1H, H_{7ax}).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 169.8 (C8), 166.1 (C4), 164.8 (C2), 140.9 (C6), 140.2 (C10), 129.0 (C13), 128.9 (C11), 126.3 (C12), 106.4 (C5), 101.8 (C1), 99.7 (C3), 80.4 (C9), 55.8 (C15), 35.6 (C7).

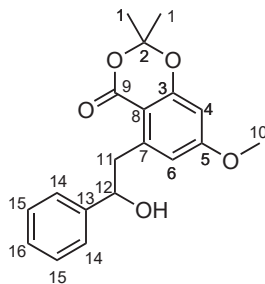
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2927 (m), 1660 (vs), 1624 (vs), 1582 (s), 1437 (s), 1359 (s), 1310 (s), 1241 (vs), 1204 (s), 1156 (vs), 1101 (s), 699 (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{16}\text{H}_{15}\text{O}_4)^+$: 271.0965, found: 271.0983.

mp. (recrystallized from CH_2Cl_2 /pentane): 102 °C–104 °C.

Elemental Analysis: calc. for $\text{C}_{16}\text{H}_{14}\text{O}_4$: C, 71.10; H, 5.22. Found: C, 71.5; H, 5.24.

5-(2-HYDROXY-2-PHENYLETHYL)-7-METHOXY-2,2-DIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (505)



According to the procedure above. Purification by flash column chromatography (85 : 15 pentane : EtOAc) afforded 5-(2-hydroxy-2-phenylethyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (505) (41 mg, 0.12 mmol, 52%) as a transparent oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.14.

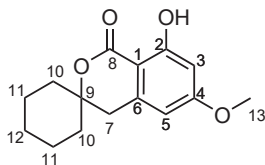
^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 7.48 – 7.41 (m, 2H, H14), 7.36 – 7.32 (m, 2H, H15), 7.29 – 7.23 (m, 1H, H16), 6.38 (d, J = 2.5 Hz, 1H, H6), 6.35 (d, J = 2.6 Hz, 1H, H4), 5.00 (dt, J = 8.3, 3.9 Hz, 1H, H12), 3.77 (s, 3H, H10), 3.54 (dd, J = 13.0, 4.0 Hz, 1H, H11*pseudoequatorial*), 3.34 (dd, J = 13.0, 8.7 Hz, 1H, H11*pseudoaxial*), 3.14 (d, J = 4.5 Hz, 1H, OH), 1.72 – 1.70 (m, 3H, H1), 1.69 (s, 3H, H1).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 164.9 (C5), 161.9 (C9), 159.2 (C3), 145.3 (C7), 144.5 (C13), 128.4 (C15), 127.4 (C16), 125.9 (C14), 113.9 (C6), 105.7 (C8), 105.3 (C2), 100.6 (C4), 75.2 (C12), 55.7 (C10), 44.4 (C11), 26.0 (C1), 25.4 (C1).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3442 (br, s), 2938 (m), 1718 (vs), 1607 (vs), 1575 (vs), 1432 (s), 1388 (m), 1377 (m), 1356 (m), 1277 (vs), 1197 (vs), 1154 (vs), 1051 (vs), 1026 (s), 910 (s), 699 (vs).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{19}H_{21}O_5)^+$: 329.1384, found: 329.1404.

Major peak m/z : $[M - H_2O]^+$ calc. for fragmentation $(C_{19}H_{18}O_4)^+$: 311.1278, found: 311.1288.

8'-HYDROXY-6'-METHOXYSPIRO[CYCLOHEXANE-1,3'-ISOCHROMAN]-1'-ONE (**506**)

To a dry-ice cold solution of 7-methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**427**) (29 mg, 0.13 mmol, 1.0 eq) in THF (1.0 mL) was added LDA (1 M in THF/hexanes; 0.21 mL, 0.21 mmol, 1.6 eq). After 5 min cyclohexanone (51 mg, 0.05 mL, 0.52 mmol, 3.96 eq) was added dropwise. The reaction mixture was stirred for 1.5 h while gradually warming up to RT. The reaction was diluted with EtOAc (5.0 mL) and quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc) afforded 8'-hydroxy-6'-methoxyspiro[cyclohexane-1,3'-isochroman]-1'-one (**506**) (12 mg, 0.05 mmol, 23%) as a white film which was recrystallized from CH₂Cl₂/pentane for X-ray analysis, next to 8-hydroxy-6-methoxy-3,3-dimethylisochroman-1-one (**482**) (16 mg, 0.07 mmol, 55%).

R_f (Petrol Ether : EtOAc 4 : 1) = 0.50.

¹H-NMR (500 MHz, CDCl₃): δ (ppm) = 11.37 (s, 1H, OH), 6.35 (d, *J* = 2.4 Hz, 1H, H₃), 6.23 (dt, *J* = 2.2, 1.0 Hz, 1H, H₅), 3.82 (s, 3H, H₁₃), 2.90 (d, *J* = 0.8 Hz, 2H, H₇), 1.93 (dd, *J* = 13.1, 5.5 Hz, 2H, H_{10eq}), 1.75 (ddd, *J* = 13.5, 9.9, 3.9 Hz, 2H, H_{11eq}), 1.60 (d, *J* = 11.6 Hz, 1H, H_{12eq}), 1.56 (s, 7H, H_{10ax} + H₂O overlapping), 1.50 (d, *J* = 14.9 Hz, 2H, H_{11ax}), 1.35 (d, *J* = 15.4 Hz, 1H, H_{12ax}).

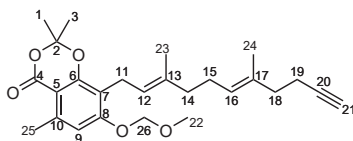
¹³C{¹H}-NMR (126 MHz, CDCl₃): δ (ppm) = 169.2 (C₈), 165.9 (C₄), 164.5 (C₂), 139.9 (C₆), 107.1 (C₅), 101.7 (C₁), 99.3 (C₃), 82.8 (C₉), 55.7 (C₁₃), 38.3 (C₇), 35.9 (C₁₀), 25.4 (C₁₂), 21.7 (C₁₁).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2927 (vs), 2852 (s), 1732 (m), 1662 (vs), 1627 (vs), 1584 (s), 1457 (m), 1437 (m), 1374 (s), 1312 (s), 1273 (s), 1242 (vs), 1205 (s), 1161 (vs), 1102 (s).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₁₅H₁₉O₄)⁺: 263.1278, found: 263.1288.

mp. (recrystallized from CH₂Cl₂/pentane): 104 °C-107 °C.

8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**507**)



To an ice-cold solution of 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**293**) (120 mg, 0.314 mmol, 1.0 eq) and DIPEA (405 mg, 0.550 mL, 3.14 mmol, 10 eq) in CH₂Cl₂ (3.00 mL) was added MOM-Cl (136 mg, 0.13 mL, 1.57 mmol, 5.0 eq) dropwise. The reaction was stirred for 1 h at 0 °C. The reaction was quenched with a saturated aqueous ammonium chloride solution (5.00 mL). The organic layer was separated and the aqueous phase was further extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 4 Et₂O in Pentane) afforded 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**507**) (127 mg, 0.298 mmol, 95%) as a pale yellow oil.

R_f (hexane: EtOAc 3 : 1) = 0.47.

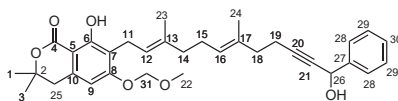
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.66 – 6.62 (m, 1H, H₉), 5.25 (s, 2H, H₂₆), 5.12 (dddd, *J* = 8.7, 7.4, 5.8, 1.4 Hz, 2H, H₁₂ and H₁₆ overlapping), 3.49 (s, 3H, H₂₂), 3.28 (d, *J* = 7.3 Hz, 2H, H₁₁), 2.63 (d, *J* = 0.7 Hz, 3H, H₂₅), 2.25 – 2.19 (m, 2H, H₁₉), 2.15 (dd, *J* = 9.0, 5.6 Hz, 1H, H₁₈), 2.06 (q, *J* = 6.9 Hz, 2H, H₁₄), 1.96 (dd, *J* = 9.0, 6.0 Hz, 2H, H₁₅), 1.93 (t, *J* = 2.5 Hz, 1H, H₂₁), 1.76 (d, *J* = 1.3 Hz, 3H, H₂₃), 1.68 (s, 6H, H₁ + H₃), 1.57 – 1.56 (m, 3H, H₂₄).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0 (C₄), 159.7 (C₈), 155.8 (C₆), 142.7 (C₁₀), 135.2 (C₁₃), 133.4 (C₁₇), 125.5 (C₁₆), 121.9 (C₁₂), 116.6 (C₇), 111.2 (C₉), 106.6 (C₅), 104.9 (C₂), 94.1 (C₂₆), 84.5 (C₂₀), 68.5 (C₂₁), 56.5 (C₂₂), 39.8 (C₁₅), 38.5 (C₁₈), 26.6 (C₁₆), 25.9 (C₁ + C₃), 22.6 (C₂₅), 22.1 (C₁₁), 17.7 (C₁₉), 16.2 (C₂₃), 15.9 (C₂₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3295 (w), 2988 (m), 2926 (m), 2854 (m), 2117 (w), 1728 (vs), 1607 (s), 1576 (s), 1450 (s), 1388 (s), 1375 (s), 1321 (s), 1279 (vs), 1206 (s), 1151 (vs), 1115 (s), 1072 (vs), 1036 (s), 964 (s), 907 (m), 633 (m).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₂₆H₃₅O₅)⁺: 427.2479, found. 427.2471.

8-HYDROXY-7-((2*E*,6*E*)-12-HYDROXY-3,7-DIMETHYL-12-PHENYLDODECA-2,6-DIEN-10-YN-1-YL)-6-(METHOXYMETHOXY)-3,3-DIMETHYLISOCHROMAN-1-ONE (**508**)



To a dry-ice cold solution of 8-((2*E*,6*E*)-3,7-dimethylundeca-2,6-dien-10-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**507**) (127 mg, 0.30 mmol, 1.0 eq) in THF (2.0 mL) was added LDA (1 M in THF/hexanes; 0.31 mL, 0.31 mmol, 1.05 eq). After 1 h, a solution of benzaldehyde (38 mg, 36.3 μ L, 0.36 mmol, 1.3 eq) in THF (2.0 mL) was added dropwise. The reaction mixture was stirred for 2 h while gradually warming up to RT. The reaction was diluted with EtOAc (15 mL) and quenched with a saturated aqueous ammonium chloride solution (20 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (20 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3 : 1 $\rightarrow$ 2 : 1 pentane : Et₂O) afforded 8-hydroxy-7-((2*E*,6*E*)-12-hydroxy-3,7-dimethyl-12-phenyldodeca-2,6-dien-10-yn-1-yl)-6-(methoxymethoxy)-3,3-dimethylisochroman-1-one (**508**) (25 mg, 0.047 mmol, 16%) as a transparent oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.09.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.46 (s, 1H, OH), 7.55 – 7.49 (m, 2H, H₂₈), 7.40 – 7.33 (m, 2H, H₂₉), 7.32 – 7.27 (m, 1H, H₃₀), 6.43 (s, 1H, H₉), 5.42 (d, J = 2.1 Hz, 1H, H₂₆), 5.23 (s, 2H, H₃₁), 5.19 (dq, J = 7.1, 1.2 Hz, 1H, H₁₂), 5.16 – 5.09 (m, 1H, H₁₆), 3.47 (s, 3H, H₂₂), 3.36 (d, J = 7.1 Hz, 2H, H₁₁), 2.93 – 2.86 (m, 2H, H₂₅), 2.32 – 2.22 (m, 2H, H₁₉), 2.15 (t, J = 7.5 Hz, 2H, H₁₈), 2.07 (q, J = 7.2 Hz, 2H, H₁₅), 1.96 (dd, J = 8.9, 6.1 Hz, 2H, H₁₄), 1.78 (d, J = 1.3 Hz, 3H, H₂₃), 1.56 (d, J = 1.4 Hz, 3H, H₂₄), 1.45 (s, 6H, H₁ + H₃).

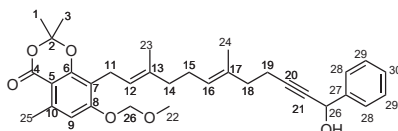
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 169.6 (C₄), 161.4 (C₆), 160.7 (C₈), 141.4 (C₂₇), 137.5 (C₁₀), 135.1 (C₁₃), 133.4 (C₁₇), 128.6 (C₂₉), 128.3 (C₃₀), 126.7 (C₂₈), 125.6 (C₁₆), 122.2 (C₁₂), 116.7 (C₇), 104.6 (C₉), 102.3 (C₅), 94.0 (C₃₁), 87.5 (C₂₀), 81.7 (C₂), 80.3 (C₂₁), 64.9 (C₂₆), 56.4 (C₂₂), 39.7 (C₂₅), 39.6 (C₁₄), 38.6 (C₁₈), 27.4 (C₁ + C₃), 26.5 (C₁₅), 22.0 (C₁₁), 18.1 (C₁₉), 16.2 (C₂₃), 15.9 (C₂₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3463 (br, s), 2920 (m), 1727 (vs), 1607 (s), 1577 (s), 1493 (m), 1450 (s), 1388 (s), 1375 (m), 1321 (m), 1280 (vs), 1207 (s), 1151 (vs), 1115

(s), 1074 (vs), 1037 (s).

HRMS (ES-ToF) m/z : $[M + Na]^+$ calc. for $(C_{33}H_{40}O_6Na)^+$: 555.2717, found: 555.2736.

8-((2*E*,6*E*)-12-HYDROXY-3,7-DIMETHYL-12-PHENYLDODECA-2,6-DIEN-10-YN-1-YL)-7-(METHOXYMETHOXY)-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE
(509)



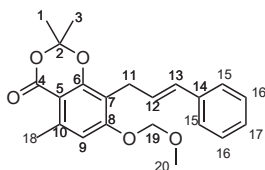
According to the procedure above. Purification by flash column chromatography (85 : 15 pentane : EtOAc) afforded 8-((2*E*,6*E*)-12-hydroxy-3,7-dimethyl-12-phenyldodeca-2,6-dien-10-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**509**) (20 mg, 0.038 mmol, 13%) as a transparent oil.

R_f (Petrol Ether : EtOAc 4 : 1) = 0.13.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.57 – 7.49 (m, 2H, H₂₈), 7.39 – 7.33 (m, 2H, H₂₉), 7.33 – 7.27 (m, 1H, H₃₀), 6.64 (s, 1H, H₉), 5.43 (s, 1H, H₂₆), 5.25 (s, 2H, H₃₁), 5.13 – 5.07 (m, 2H, H₁₂ + H₁₈ overlapping), 3.48 (s, 3H, H₂₂), 3.28 (d, J = 7.3 Hz, 2H, H₁₁), 2.63 (s, 3H, H₂₅), 2.31 – 2.23 (m, 2H, H₁₉), 2.16 (t, J = 7.5 Hz, 2H, H₁₈), 2.05 (q, J = 7.1 Hz, 2H, H₁₅), 2.00 – 1.91 (m, 2H, H₁₄), 1.75 (d, J = 1.3 Hz, 3H, H₂₄), 1.67 (s, 6H, H₁ + H₃), 1.57 – 1.55 (m, 3H, H₂₃).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{33}H_{41}O_6)^+$: 533.2898, found: 533.2885.

8-CINNAMYL-7-(METHOXYMETHOXY)-2,2,5-TRIMETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**510**)



To an ice-cold solution of 8-((2*E*,6*E*)-12-hydroxy-3,7-dimethyl-12-phenyldodeca-2,6-dien-10-yn-1-yl)-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**509**) (20 mg, 0.38 mmol, 1.0 eq) in HFIP (3.0 mL) was added La(OTf)₃ (98 mg, 0.17 mmol, 4.5 eq) in one portion. After 4 days, the reaction was diluted with CH₂Cl₂ (15 mL) and quenched with a saturated aqueous ammonium chloride solution (20 mL). The organic layer was separated and the aqueous phase was further extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (25 mL), the washed solution was dried, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : Et₂O) afforded 8-cinnamyl-7-(methoxymethoxy)-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**510**) (13 mg, 0.035 mmol, 94%) as a white film which was recrystallized from CH₂Cl₂/pentane for X-Ray analysis.

R_f (Petrol Ether : EtOAc 3 : 1) = 0.54.

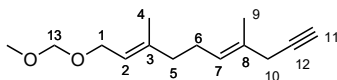
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.29 – 7.25 (m, 4H, H₁₅ + H₁₆), 7.18 (ddd, *J* = 9.4, 5.5, 2.4 Hz, 1H, H₁₇), 6.68 (d, *J* = 0.8 Hz, 1H, H₉), 6.34 (dt, *J* = 15.8, 1.3 Hz, 1H, H₁₃), 6.22 (dt, *J* = 15.7, 6.2 Hz, 1H, H₁₂), 5.27 (s, 2H, H₁₉), 3.49 (dd, *J* = 6.0, 1.1 Hz, 2H, H₁₁), 3.47 (s, 3H, H₂₀), 2.66 (d, *J* = 0.7 Hz, 3H, H₁₈), 1.68 (s, 6H, H₁ + H₃).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 160.9 (C₄), 159.8 (C₈), 156.1 (C₆), 143.4 (C₁₀), 137.7 (C₁₄), 130.3 (C₁₃), 128.6 (C₁₆), 127.7 (C₁₂), 127.1 (C₁₇), 126.0 (C₁₅), 114.7 (C₇), 111.2 (C₉), 106.7 (C₅), 105.1 (C₂), 94.0 (C₁₉), 56.6 (C₂₀), 26.2 (C₁₁), 26.0 (C₁ + C₃), 22.6 (C₁₈).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2928 (m), 1728 (vs), 1607 (s), 1576 (s), 1450 (m), 1321 (m), 1280 (vs), 1206 (s), 1152 (s), 1117 (vs), 1074 (vs), 1036 (s), 964 (s).

HRMS (ES-ToF) *m/z*: [M + H]⁺ calc. for (C₂₂H₂₅O₅)⁺: 369.1697, found : 369.1697.

mp. (recrystallized from CH₂Cl₂/pentane): 116 °C–117 °C.

(4*E*,8*E*)-10-(methoxymethoxy)-4,8-dimethyldeca-4,8-dien-1-yne (**512**)

Synthesized using a modified literature procedure by Kotoku et. al.:^[372] To a dry-ice cold solution of trimethylsilyl acetylene (191 mg, 0.270 mL, 1.95 mmol, 1.41 eq) in THF (2.00 mL) was added *n*-BuLi (2.30 M; 0.780 mL, 1.80 mmol, 1.30 eq) dropwise. The resulting solution was stirred at -78°C for 2 h. A solution of (2*E*,6*E*)-1-bromo-8-(methoxymethoxy)-2,6-dimethylocta-2,6-diene (**308**) (383 mg, 1.38 mmol, 1.00 eq) in THF (2.00 mL) was added dropwise. The resulting suspension was stirred for 7 h at -78°C and then allowed to warm to RT where it was further stirred for 4 h. The reaction was quenched with an aqueous citric acid solution (10% (w:v); 5 mL) and the aqueous layer was extracted with Et₂O (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. This afforded a pale-yellow oil which was used for the next step without further purification.

To an ice-cold solution of the obtained oil in THF (4.00 mL) was added a solution of TBAF in THF (1 M, 2.07 mL, 2.07 mmol, 1.50 eq) dropwise. The reaction mixture was stirred for 5 h at RT. The reaction was quenched with an aqueous citric acid solution (10% (w:v); 5 mL) and the aqueous layer was extracted with Et₂O (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by column chromatography (pentane : Et₂O 9 : 1) afforded (4*E*,8*E*)-10-(methoxymethoxy)-4,8-dimethyldeca-4,8-dien-1-yne (**512**) (225 mg, 1.01 mmol, 73%) as colourless oil.

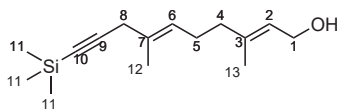
R_f (hexane : EtOAc 7 : 1) = 0.32.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.41 (dddd, J = 7.0, 5.6, 2.9, 1.4 Hz, 1H, H7), 5.36 (tq, J = 7.0, 1.2 Hz, 1H, H2), 4.63 (s, 2H, H13), 4.08 (dq, J = 7.0, 0.8 Hz, 2H, H1), 3.38 (s, 3H, -OCH₃), 2.87 (dd, J = 2.8, 1.4 Hz, 2H, H10), 2.20 – 2.12 (m, 2H, H6), 2.09 (t, J = 2.5 Hz, 1H, H11), 2.10 - 2.04 (m, J = 6.9 Hz, 2H, H5 and H11 overlap), 1.71 – 1.66 (m, 6H, H4 and H9).

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) = 140.8 (C3), 129.9 (C8), 125.8 (C7), 120.5 (C2), 95.6 (C11), 82.2 (C12), 70.3 (C11), 63.8 (C1), 55.3 (-OCH₃), 39.4 (C5), 28.7 (C10), 26.5 (C6), 16.5 (C4), 16.1 (C9).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3297 (m), 2979 (m), 2929 (m), 2882 (m), 1668 (w), 1441 (m), 1385 (m), 1213 (w), 1148 (s), 1101 (s), 1044 (vs), 944 (m), 920 (s), 636 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{14}\text{H}_{23}\text{O}_2)^+$: 223.1693, found: 223.1700.

(2*E*,6*E*)-3,7-DIMETHYL-10-(TRIMETHYLSILYL)DECA-2,6-DIEN-9-YN-1-OL (**513**)

To a dry-ice cold solution of trimethylsilyl acetylene (1.51 g, 2.13 mL, 15.3 mmol, 5.00 eq) in THF (80.0 mL) was added *n*-BuLi (2.36 M; 6.48 mL, 15.3 mmol, 5.00 eq) dropwise. The resulting solution was stirred at 0 °C for 1 h. A solution of (2*E*,6*E*)-8-bromo-3,7-dimethylocta-2,6-dien-1-yl benzoate (**313**) (1.04 g, 3.07 mmol, 1.00 eq) in THF (10.0 mL) was added dropwise. The resulting suspension was stirred for 16 h while gradually warming up to RT. The reaction was quenched with a saturated aqueous ammonium chloride solution (50 mL) and the aqueous layer was extracted with Et₂O (2 * 50 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (pentane : Et₂O 9 : 1 -> 4 : 1 -> 2 : 1) afforded (2*E*,6*E*)-3,7-dimethyl-10-(trimethylsilyl)deca-2,6-dien-9-yn-1-ol (**513**) (344 mg, 1.37 mmol, 45%) as yellow oil.

Alternatively: To a dry-ice cold solution of trimethylsilyl acetylene (1.18 g, 1.60 mL, 12.0 mmol, 6.00 eq) in THF (40.0 mL) was added *n*-BuLi (2.22 M; 5.41 mL, 12.0 mmol, 5.00 eq) dropwise. The resulting solution was stirred at 0 °C for 1 h. To a solution of (2*E*,6*E*)-8-bromo-3,7-dimethylocta-2,6-dien-1-yl benzoate (675 mg, 2.00 mmol, 1.00 eq) in THF (20.0 mL) was added NaI (300 mg, 2.00 mmol, 1.00 eq) in one portion. The resulting white suspension was stirred for 1 h at RT. The allyl iodide solution was transferred to the acetylide solution dropwise at 0 °C. The resulting suspension was stirred for 16 h while gradually warming up to RT. The reaction was quenched with a saturated aqueous ammonium chloride solution (50 mL) and the aqueous layer was extracted with Et₂O (2 * 50 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (pentane : Et₂O 9 : 1 -> 2 : 1) afforded (2*E*,6*E*)-3,7-dimethyl-10-(trimethylsilyl)deca-2,6-dien-9-yn-1-ol (**513**) (200 mg, 0.800 mmol, 46%) and (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-ol (**305b**) (74.0 mg, 0.420 mmol, 21%) as pale -yellow oils.

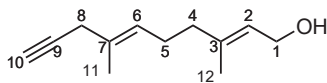
R_f (hexane : EtOAc 3 : 1) = 0.27.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 5.46 – 5.33 (m, 2H, H2 + H6 overlapping), 4.14(d, J = 6.9 Hz, 2H, H1), 2.90 (d, J = 1.6 Hz, 2H, H8), 2.19 – 2.10 (m, 2H, H5), 2.05 (dd, J = 9.2, 6.1 Hz, 2H, H4), 1.67 (d, J = 1.3 Hz, 3H, H13), 1.65 (d, J = 1.3 Hz, 3H, H12), 1.34 (s, 1H, -OH), 0.15 (s, 9H, -SiMe₃).

$^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 139.5 (C3), 130.1 (C7), 125.5 (C6), 123.7(C2), 104.7 (C9), 86.9 (C10), 59.5 (C1), 39.3 (C4), 30.0 (C8), 26.4 (C5), 16.4 (C13), 16.2(C12), 0.2 (3 $\times$ C11).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3296 (s, br), 2914 (s), 2852 (m), 2115 (w), 1666 (m), 1437 (s), 1430 (s), 1382 (s), 1237 (m), 1085 (m), 994 (vs), 843 (m), 626 (vs).

HRMS (APCI) m/z : $[\text{M} - \text{H}]^-$ calc. for ($\text{C}_{15}\text{H}_{25}\text{OSi}$)⁻: 249.1680, found: 249.1670. Major peak m/z : $[\text{M} - \text{CH}_2\text{O}]^-$ calc. for ($\text{C}_{14}\text{H}_{23}\text{Si}$)⁻: 219.1575, found. 219.1562.

(2*E*,6*E*)-3,7-DIMETHYLDECA-2,6-DIEN-9-YN-1-OL (**305b**)

To a solution of (2*E*,6*E*)-3,7-dimethyl-10-(trimethylsilyl)deca-2,6-dien-9-yn-1-ol (**513**) (344 mg, 1.37 mmol, 1.00 eq) in THF (7.00 mL) was added TBAF (1 M in THF, 3.13 mL, 3.13 mmol, 2.28 eq) dropwise. The resulting intense orange solution was stirred for 15 h at RT. The reaction was quenched with a saturated aqueous sodium hydrogen carbonate solution (15 mL) and the aqueous layer was extracted with Et₂O (2 * 20 mL). The combined organic layers were washed with a saturated aqueous sodium hydrogen carbonate solution (15 mL) and a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (pentane : Et₂O 70 : 30) afforded (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-ol (**305b**) (234 mg, 1.31 mmol, 96%) as pale-yellow oil.

Alternatively: To a solution of (2*E*,6*E*)-3,7-dimethyl-10-(trimethylsilyl)deca-2,6-dien-9-yn-1-ol (**513**) (250 mg, 0.998 mmol, 1.00 eq) in MeOH (10.0 mL) was added K₂CO₃ (100 mg, 698 mmol, 0.7 eq) in one portion. The resulting intense orange solution was stirred for 15 h at RT. The reaction was concentrated *in vacuo* and the resulting brown slurry was quenched with a saturated aqueous ammonium chloride solution (15 mL) and diluted with EtOAc (20 mL). The organic phase was separated and the aqueous layer was further extracted with EtOAc (2 * 20 mL) and the combined organic layers were washed with a saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (pentane : Et₂O 70 : 30) afforded (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-ol (**305b**) (149 mg, 0.840 mmol, 84% - 64% combined over 2 steps) as pale-yellow oil.

R_f (hexane : EtOAc 3 : 1) = 0.18.

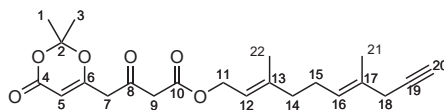
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.41 (dddq, *J* = 8.4, 7.1, 5.7, 1.4 Hz, 2H, H₂ + H₆ overlapping), 4.15 (d, *J* = 6.4 Hz, 2H, H₁), 2.88 (s, 2H, H₈), 2.15 (dddd, *J* = 12.7, 6.7, 2.3, 1.3 Hz, 2H, H₅), 2.10 (t, *J* = 2.7 Hz, 1H, H₁₀), 2.09 – 2.03 (m, 2H, H₄), 1.68 (d, *J* = 1.4 Hz, 6H, H₁₁ + H₁₂ overlapping), 1.17 (s, 1H, -OH).

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) = 139.6 (C₃), 130.0 (C₇), 125.8 (C₆), 123.7 (C₂), 82.2 (C₉), 70.3 (C₁₀), 59.5 (C₁), 39.3 (C₄), 28.7 (C₈), 26.4 (C₅), 16.4 (C₁₂), 16.1 (C₁₁).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3300 (s, br), 2919 (s), 2883 (m), 1668 (m), 1440 (m), 1420 (m), 1385 (m), 1293 (w), 1237 (w), 1081 (w), 999 (vs), 850 (w), 667 (m), 637 (vs).

HRMS (Es-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{12}\text{H}_{19}\text{O})^+$: 179.1430, found. 179.1440.

(2*E*,6*E*)-3,7-DIMETHYLDECA-2,6-DIEN-9-YN-1-YL 4-(2,2-DIMETHYL-4-OXO-4*H*-1,3-DIOXIN-6-YL)-3-OXOBUTANOATE (**304b**)



Synthesized using a modified literature procedure by Barrett et. al.^[105] To a solution of 2-phenyl-1,3-dioxane-4,6-dione (**141**) (795 mg, 4.13 mmol, 1.82 eq) and DCC (855 mg, 4.13 mmol, 1.82 eq) in CH₂Cl₂ (24.0 mL) was added DMAP (505 mg, 4.13 mmol, 1.82 eq) in one portion. The solution was stirred for 15 min at RT before 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid (**140**) (769 mg, 4.13 mmol, 1.82 eq) was added in one portion. The resulting yellow-white suspension was stirred for 16 h at RT. The reaction mixture was cooled to 0 °C, the precipitate was filtered off and the solid was washed with small portions of CH₂Cl₂ until the precipitate appeared colourless. The filtrate was washed with an aqueous hydrochloric acid solution (1 M, 2 x 20 mL). The organic layer was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in PhMe (8.75 mL) and (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-ol (**305b**) (405 mg, 2.27 mmol, 1.00 eq) in PhMe (8.75 mL) was added in one portion. The resulting pale yellow solution was heated to 55 °C for 4 h after which the solution was concentrated. Purification by flash column chromatography (9 : 1 pentane : EtOAc → 7 : 1 → 4 : 1) afforded (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**304b**) (790 mg, 2.03 mmol, 90%) as yellow-orange oil.

R_f (hexane : EtOAc 4 : 1) = 0.10.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 5.41 – 5.37 (m, 1H, H₁₆), 5.36 (s, 1H, H₅), 5.33 (dq, *J* = 7.2, 1.3 Hz, 1H, H₁₂), 4.67 (d, *J* = 7.2 Hz, 2H, H₁₁), 3.51 (d, *J* = 0.9 Hz, 2H, H₉), 3.50 (s, 2H, H₇), 2.87 (dd, *J* = 2.8, 1.4 Hz, 2H, H₁₈), 2.17 – 2.11 (m, 2H, H₁₅), 2.10 (t, *J* = 2.6 Hz, 1H, H₂₀), 2.07 (d, *J* = 8.9 Hz, 2H, H₁₄), 1.71 (d, *J* = 1.6 Hz, 6H, H₁ + H₃), 1.68 (s, 3H, H₂₂), 1.68 (d, *J* = 1.2 Hz, 3H, H₂₁).

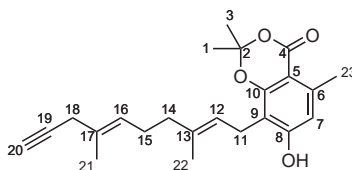
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 195.8 (C₈), 166.5 (C₁₀), 163.7 (C₄), 143.4 (C₁₃), 130.2 (C₁₇), 127.8 (C₆), 125.4 (C₁₆), 117.7 (C₁₂), 107.5 (C₂), 97.3 (C₅), 82.1 (C₁₉), 70.4 (C₂₀), 62.7 (C₁₁), 49.3 (C₉), 47.1 (C₇), 39.3 (C₁₄), 28.6 (C₁₈), 26.3 (C₁₅), 25.1 (C₁ + C₃), 16.7 (C₂₂), 16.1 (C₂₁).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3288 (m), 2990 (m), 2922 (m), 2117 (w), 1935 (w), 1718 (vs), 1636 (s), 1388 (s), 1375 (s), 1314 (m), 1271 (s), 1252 (m), 1200 (s), 1154

(m), 1090 (w), 1059 (w), 1015 (s), 979 (m), 964 (m), 806 (m), 630 (m).

HRMS (ES-ToF) m/z : $[M + Na]^+$ calc. for $(C_{22}H_{28}O_6Na)^+$: 411.1778, found: 411.1790.

8-((2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**301b**)



Synthesized using to a modified literature procedure by Barrett et. al.:^[105] To an ice-cold solution of (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**304b**) (218 mg, 0.561 mmol, 1.00 eq) in CH₂Cl₂ (3.00 mL) was added MgCl₂ (53.0 mg, 0.561 mmol, 1.00 eq) and pyridine (89.0 mg, 90.8 μL, 1.12 mmol, 2.00 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (66.0 mg, 59.9 μL, 0.842 mmol, 1.50 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (3.50 mL) and tri(2-furyl)phosphine (39.0 mg, 0.168 mmol, 0.30 eq) and Tris(dibenzylideneacetone)dipalladium(o) (26.0 mg, 0.0281 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 1.5 h at RT before caesium acetate (323 mg, 1.68 mmol, 3.00 eq) in *iso*-propanol (3.50 mL) was added in one portion. The resulting orange-brown solution was stirred for 1.5 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc → 15 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301b**) (87.0 mg, 0.236 mmol, 42%) as a yellow-white solid.

Alternatively: To an ice-cold solution of (2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**304b**) (329 mg, 0.847 mmol, 1.00 eq) in CH₂Cl₂ (4.00 mL) was added MgCl₂ (81.0 mg, 0.847 mmol, 1.00 eq) and pyri-

dine (134 mg, 137 μ L, 1.69 mmol, 2.00 eq) in one portion. The ice-cold suspension was stirred for 15 min before acetyl chloride (103 mg, 90.3 μ L, 1.27 mmol, 1.50 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with an aqueous saturated sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (4.00 mL) and tri(2-furyl)phosphine (59.0 mg, 0.254 mmol, 0.30 eq) and Tris(dibenzylideneacetone)dipalladium(o) (39.0 mg, 0.0423 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 1.5 h at RT before triethylamine (257 mg, 354 μ L, 2.54 mmol, 3.00 eq) was added dropwise. The resulting orange-brown solution was stirred for 19 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (19 : 1 pentane : EtOAc $\rightarrow$ 15 : 1) afforded 8-((2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301b**) (155 mg, 0.421 mmol, 50%) as a yellow-white solid.

R_f (hexane : EtOAc 7 : 3) = 0.35.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.40 (s, 1H, H7), 5.90 (s, 1H, -OH), 5.35 (tt, J = 5.5, 1.6 Hz, 1H, H16), 5.24 – 5.14 (m, 1H, H12), 3.32 (d, J = 7.2 Hz, 2H, H11), 2.86 (dd, J = 2.8, 1.4 Hz, 2H, H18), 2.59 (s, 3H, H23), 2.13 (t, J = 7.2 Hz, 2H, H15), 2.08 (t, J = 2.7 Hz, 1H, H20 overlapping with H14), 2.06 (d, J = 6.4 Hz, 2H, H14), 1.79 (d, J = 1.3 Hz, 3H, H22), 1.69 (s, 6H, H1 + H3), 1.67 (d, J = 1.3 Hz, 3H, H21).

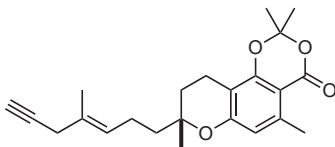
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.1 (C4), 160.1 (C8), 156.1 (C10), 143.0 (C6), 138.4 (C13), 130.1 (C17), 125.6 (C16), 121.2 (C12), 113.7 (C7), 112.8 (C9), 105.6 (C5), 105.0 (C2), 82.2 (C19), 70.3 (C20), 39.5 (C14), 28.7 (C18), 26.5 (C15), 25.9 (C1 + C3), 22.1 (C12), 22.0 (C23), 16.4 (C22), 16.1 (C21).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3295 (s, br), 2988 (m), 2924 (m), 2852 (m), 2129 (vw), 2119 (vw), 1936 (vw), 1726 (m), 1691 (vs), 1607 (vs), 1591 (vs), 1513 (m), 1452 (m), 1409 (m), 1388 (m), 1376 (m), 1325 (s), 1295 (vs), 1277 (vs), 1210 (vs), 1167 (m), 1107 (m), 1046 (m), 972 (w), 850 (w), 641 (m).

HRMS (Es-ToF) m/z : $[M + H]^+$ calc. for $(C_{23}H_{29}O_4)^+$: 369.2060, found. 369.2062.

mp. (recrystallized from CH_2Cl_2 /pentane): 110 °C-114 °C.

(±)-(E)-2,2,5,8-TETRAMETHYL-8-(4-METHYLHEPT-3-EN-6-YN-1-YL)-9,10-DIHYDRO-4*H*,8*H*-[1,3]DIOXINO[4,5-*F*]CHROMEN-4-ONE (**514**)



To a solution of 8-((2*E*,6*E*)-3,7-dimethyldeca-2,6-dien-9-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**301b**) (30.0 mg, 0.11 mmol, 1.00 eq) in CH₂Cl₂ (1.00 mL) was added InBr₃ (8.0 mg, 0.02 mmol, 0.2 eq) in one portion. The resulting solution was stirred for 17 h at RT. The reaction mixture was quenched with H₂O (5 mL), the organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with an aqueous sodium chloride solution (10 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (17 : 1 pentane : EtOAc → 6 : 1) afforded (±)-(E)-2,2,5,8-tetramethyl-8-(4-methylhept-3-en-6-yn-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (**514**) (20 mg, 0.05 mmol, 67%) as pale-yellow oil

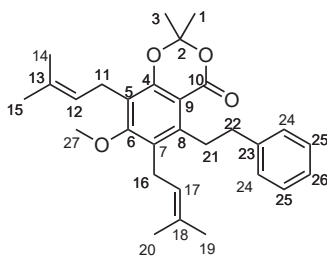
R_f (hexane : EtOAc 4 : 1) = 0.5.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 6.36 (s, 1H), 5.42 (tq, *J* = 7.1, 1.5 Hz, 1H), 2.89 – 2.85 (m, 2H), 2.57 (s, 7H), 2.19 – 2.11 (m, 3H), 2.09 (t, *J* = 2.7 Hz, 1H), 1.88 – 1.72 (m, 3H), 1.70 (s, 10H), 1.68 (d, *J* = 1.7 Hz, 5H), 1.67 – 1.54 (m, 1H).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 161.0, 159.6, 156.1, 142.3, 130.1, 125.7, 114.7, 114.5, 107.2, 104.9, 104.1, 82.0, 70.5, 39.3, 30.1, 29.8, 28.6, 26.0, 25.9, 24.1, 22.2, 22.1, 16.2.

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₂₃H₂₉O₄)⁺: 369.2060, found. 369.2058.

7-METHOXY-2,2-DIMETHYL-6,8-BIS(3-METHYLBUT-2-EN-1-YL)-5-PHENETHYL-4H-BENZO[*D*][1,3]DIOXIN-4-ONE (**530**)



To a solution of 7-hydroxy-2,2-dimethyl-6,8-bis(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[*d*][1,3]dioxin-4-one (**571**) (65.0 mg, 0.150 mmol, 1.00 eq) in THF (2.00 mL) was added Cs_2CO_3 (157 mg, 0.449 mmol, 3.00 eq) in one portion, followed by dropwise addition of MeI (63.7 mg, 27.9 μL , 0.449 mmol, 3.00 eq). The reaction mixture was stirred for 2 h at 40 °C. The reaction mixture was quenched with water (1.0 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 2.0 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (20 : 1 $\rightarrow$ 18 : 1 pentane : EtOAc) afforded 7-methoxy-2,2-dimethyl-6,8-bis(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[*d*][1,3]dioxin-4-one (**530**) (56.0 mg, 0.125 mmol, 84%) as pale-yellow oil.

R_f (hexane : Et_2O 4 : 1) = 0.82.

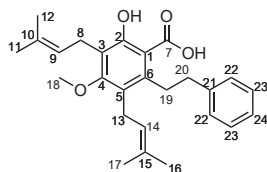
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.36 – 7.27 (m, 4H, H₂₄ + H₂₅), 7.22 – 7.17 (m, 1H, H₂₆), 5.12 (dddd, J = 8.4, 5.6, 2.9, 1.4 Hz, 1H, H₁₂) 5.09 – 5.02 (m, 1H, H₁₇), 3.75 (s, 3H, H₂₇), 3.40 – 3.36 (m, 4H, H₁₁ + H₂₁), 3.34 – 3.29 (m, 2H, H₁₆), 2.85 – 2.77 (m, 1H, H₂₂), 1.78 (d, J = 1.3 Hz, 3H, H₁₅), 1.75 (d, J = 1.3 Hz, 3H, H₁₉), 1.69 (t, J = 1.4 Hz, 6H, H₁₄ + H₂₀), 1.68 (s, 6H, H₁ + H₃).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.5 (C₆), 160.6 (C₁₀), 155.1 (C₄), 144.6 (C₈), 142.5 (C₂₃), 132.0 (C₁₃), 129.8 (C₁₈), 128.8 (C₂₄), 128.4 (C₂₅), 126.0 (C₂₆), 123.8 (C₁₇), 122.4 (C₁₂), 122.0 (C₇), 110.6 (C₅), 109.2 (C₉), 104.6 (C₂), 61.9 (C₂₇), 37.1 (C₂₂), 32.6 (C₂₁), 25.8 (C₁₅ + C₁ + C₃), 25.8 (C₁₉), 25.3 (C₁₆), 23.3 (C₁₁), 18.3 (C₂₀), 18.1 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 1728 (vs), 1571 (vs), 1437 (s), 1375 (s), 1278 (s), 1207 (vs), 1116 (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{29}\text{H}_{37}\text{O}_4)^+$: 449.2686, found: 449.2691.

2-HYDROXY-4-METHOXY-3,5-BIS(3-METHYLBUT-2-EN-1-YL)-6-PHENETHYLBENZOIC
ACID (AMORFRUTIN C) (47)



To a solution of 7-methoxy-2,2-dimethyl-6,8-bis(3-methylbut-2-en-1-yl)-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**530**) (25.0 mg, 0.0557 mmol, 1.00 eq) in DMSO (0.10 mL) was added aqueous KOH (48 vol%; 0.07 mL) in one portion. The resulting orange biphasic reaction mixture was stirred for 18 h at 80 °C. The reaction mixture was diluted with EtOAc (15 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 1 EtOAc : pentane) afforded 2-hydroxy-4-methoxy-3,5-bis(3-methylbut-2-en-1-yl)-6-phenethylbenzoic acid (Amorfrutin C) (**47**) (21.0 mg, 0.0514 mmol, 92%) as a pale-yellow solid.

R_f (hexane : EtOAc 4 : 1) = 0.07.

$^1\text{H-NMR}$ (400 MHz, CD_3OD): δ (ppm) = 7.29 – 7.22 (m, 2H, H₂₂), 7.22 – 7.13 (m, 3H, H₂₃ + H₂₄), 5.27 – 5.18 (m, 1H, H₉), 5.05 – 4.97 (m, 1H, H₁₄), 3.69 (s, 3H, H₁₈), 3.38 – 3.34 (m, 4H, H₈ + H₁₃), 3.24 – 3.16 (m, 2H, H₁₉), 2.83 – 2.74 (m, 2H, H₂₀), 1.78 (d, J = 1.3 Hz, 3H, H₁₁), 1.73 (d, J = 1.3 Hz, 3H, H₁₆), 1.68 (s, 6H, H₁₂ + H₁₇).

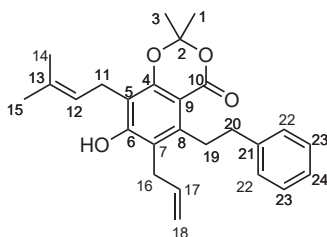
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CD_3OD): δ (ppm) = 175.2 (C₇), 162.5 (C₂), 161.8 (C₄), 143.8 (C₆), 143.5 (C₂₁), 132.1 (C₁₀), 131.9 (C₁₅), 129.3 (C₂₂), 129.3 (C₂₃), 126.9 (C₅), 126.9 (C₃), 125.8 (C₂₄), 124.4 (C₁₄), 122.0 (C₉), 111.0 (C₁), 61.9 (C₁₈), 38.7 (C₂₀), 34.4 (C₁₉), 26.2 (C₁₃), 25.9 (C₁₆), 25.8 (C₁₁), 24.3 (C₈), 18.2 (C₁₇), 18.0 (C₁₂).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2957 (br, s), 1635 (s), 1597 (m), 1448 (m), 1261 (s), 1216 (m), 1092 (s).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for (C₂₆H₃₃O₄)⁺: 409.2373, found: 409.2379.

mp. (recrystallized from CH₂Cl₂/pentane): 112 °C–114 °C.

6-ALLYL-7-HYDROXY-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-5-PHENETHYL-4H-BENZO[*D*][1,3]DIOXIN-4-ONE (573)



To a solution of 7-(allyloxy)-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[*d*][1,3]dioxin-4-one (572) (35.0 mg, 0.0861 mmol, 1.00 eq) in DMF (0.80 mL) in a sealed vial was added MgSO_4 (500 mg) and the resulting suspension was stirred for 8 h at 200 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous lithium chloride solution (10 w/v-%; 5 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Flash column chromatography (pentane : EtOAc 20 : 1 → 18 : 1) afforded 6-allyl-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[*d*][1,3]dioxin-4-one (573) (21.0 mg, 0.0517 mmol, 60%) as pale-yellow oil next to 7-(allyloxy)-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[*d*][1,3]dioxin-4-one (572) (10 mg, 0.024 mmol, 29%) as white film.

R_f (hexane : EtOAc 9 : 1) = 0.58.

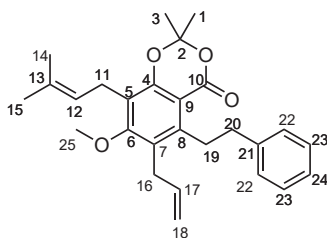
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.39 – 7.27 (m, 4H, H22 – H23), 7.24 – 7.17 (m, 1H, H24), 5.96 (ddt, J = 17.2, 10.1, 5.7 Hz, 1H, H17), 5.22 – 5.15 (m, 1H, H12), 5.13 – 5.08 (m, 1H, H18_{cis}), 5.08 – 5.01 (m, 1H, H18_{trans}), 3.48 – 3.42 (m, 2H, H16), 3.41 – 3.31 (m, 4H, H11 + H19), 2.84 – 2.78 (m, 2H, H20), 1.82 (d, J = 1.3 Hz, 3H, H14), 1.76 (d, J = 1.3 Hz, 3H, H15), 1.68 (s, 6H, H1 + H3).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 160.6 (C10), 159.1 (C6), 154.5 (C4), 144.3 (C8), 142.2 (C21), 136.0 (C17), 135.6 (C13), 128.6 (C22), 128.3 (C23), 125.9 (C24), 120.8 (C12), 120.2 (C7), 116.0 (C18), 113.0 (C5), 105.5 (C9), 104.3 (C2), 36.8 (C20), 32.4 (C19), 29.9 (C16), 25.8 (C15), 25.7 (C1), 25.7 (C3), 22.3 (C11), 17.9 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3396 (br, s), 1724 (vs), 1696 (s), 1576 (s), 1454 (vs), 1280 (s), 1210 (vs).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{26}\text{H}_{31}\text{O}_4)^+$: 407.2217 found: 407.2221.

6-ALLYL-7-METHOXY-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-5-PHENETHYL-4H-BENZO[D][1,3]DIOXIN-4-ONE (574)



To a solution of 6-allyl-7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[d][1,3]dioxin-4-one (573) (19.0 mg, 0.00467 mmol, 1.00 eq) in THF (1.00 mL) was added Cs_2CO_3 (45.7 mg, 0.140 mmol, 3.00 eq) in one portion, followed by dropwise addition of MeI (19.9 mg, 7.89 μL , 0.140 mmol, 3.00 eq). The reaction mixture was stirred for 2 h at 40 °C. The reaction mixture was quenched with water (1.0 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 2.0 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 1 pentane : CH_2Cl_2) afforded 6-allyl-7-methoxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4H-benzo[d][1,3]dioxin-4-one (574) (13.0 mg, 0.0309 mmol, 66%) as colourless oil.

R_f (hexane : Et_2O 4 : 1) = 0.64.

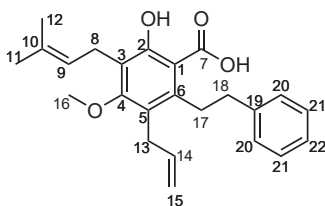
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.36 – 7.24 (m, 4H, H22 + H23), 7.23 – 7.15 (m, 1H, H24), 5.98 (ddt, J = 17.2, 10.2, 5.5 Hz, 1H, H17), 5.16 – 5.08 (m, 1H, H12), 5.07 – 5.01 (m, 1H, H18_{cis}), 4.93 – 4.85 (m, 1H, H18_{trans}), 3.75 (s, 3H, H25), 3.47 – 3.42 (m, 2H, H16), 3.39 – 3.33 (m, 2H, H19), 3.31 (d, J = 7.0 Hz, 2H, H11), 2.84 – 2.76 (m, 2H, H20), 1.77 (d, J = 1.3 Hz, 3H, H14), 1.69 (d, J = 1.4 Hz, 3H, H15), 1.68 (s, 6H, H1 + H3).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.7 (C6), 160.6 (C10), 155.5 (C4), 144.8 (C8), 142.4 (C21), 137.3 (C17), 132.1 (C13), 128.7 (2 x C22), 128.5 (2 x C23), 127.3 (C7), 126.0 (C24), 122.3 (C12), 122.1 (C5), 115.6 (C18), 109.2 (C9), 104.7 (C2), 62.1 (C25), 37.1 (C20), 32.5 (C19), 30.2 (C16), 25.9 (C15), 25.8 (C1 + C3), 23.3 (C11), 18.1 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2922 (m), 1730 (vs), 1588 (m), 1573 (s), 1453 (m), 1440 (s), 1388 (m), 1375 (m), 1280 (s), 1209 (s), 1120 (s), 1052 (s), 910 (m), 700 (m).

HRMS (ES-ToF) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{27}\text{H}_{33}\text{O}_4)^+$: 421.2373, found: 421.2359.

3-ALLYL-6-HYDROXY-4-METHOXY-5-(3-METHYLBUT-2-EN-1-YL)-2-PHENETHYLBENZOIC ACID (**575**)



To a solution of 6-allyl-7-methoxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**574**) (13.0 mg, 0.0309 mmol, 1.00 eq) in DMSO (0.10 mL) was added aqueous KOH (48 vol%; 0.04 mL) in one portion. The resulting orange biphasic reaction mixture was stirred for 18 h at 80 °C. The reaction mixture was diluted with EtOAc (10 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 7 EtOAc : pentane) afforded 3-allyl-6-hydroxy-4-methoxy-5-(3-methylbut-2-en-1-yl)-2-phenethylbenzoic acid (**575**) (7.00 mg, 0.0184 mmol, 60%) as a pale-yellow solid.

R_f (hexane : EtOAc 9 : 1) = 0.02.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.29 (t, J = 7.4 Hz, 2H, H₂₁), 7.25 – 7.17 (m, 4H, H₂₀ + H₂₂), 5.99 (ddt, J = 17.2, 10.4, 5.3 Hz, 1H, H₁₄), 5.26 (th, J = 6.8, 1.6 Hz, 1H, H₉), 5.03 (dq, J = 10.1, 1.8 Hz, 1H, H_{15cis}), 4.89 (dq, J = 17.2, 1.9 Hz, 1H, H_{15trans}), 3.75 (s, 3H, H₁₆), 3.46 (dt, J = 5.4, 1.9 Hz, 2H, H₁₃), 3.41 (d, J = 6.7 Hz, 2H, H₈), 3.30 – 3.21 (m, 2H, H₁₇), 2.90 – 2.80 (m, 2H, H₁₈), 1.80 (d, J = 1.3 Hz, 3H, H₁₂), 1.71 (d, J = 1.6 Hz, 3H, H₁₁).

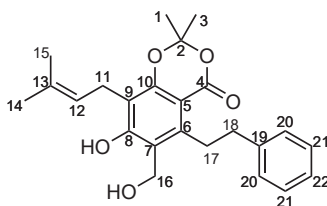
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 175.4 (C₇), 162.8 (C₄), 162.0 (C₄), 143.4 (C₆), 142.1 (C₁₉), 137.4 (C₁₄), 132.0 (C₁₀), 128.4 (2 x C₂₀), 128.2 (2 x C₂₁), 126.0 (C₂₂), 124.1 (C₅), 122.6 (C₉), 121.5 (C₃), 115.1 (C₁₅), 107.9 (C₁), 61.8 (C₁₆), 37.5 (C₁₈), 33.1 (C₁₇), 29.7 (C₁₃), 25.7 (C₁₁), 23.6 (C₈), 18.0 (C₁₂).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2921 (vs), 2851 (s), 1734 (m), 1700 (s), 1653 (s), 1593 (s), 1453 (s), 1437 (s), 1411 (m), 1363 (m), 1256 (s), 1197 (s), 1179 (vs), 1093 (m), 977 (m), 910 (m), 699 (s).

HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for (C₂₄H₂₇O₄)⁻: 379.1915, found: 379.1909.

Elemental Analysis: calc. for $C_{24}H_{28}O_4$: C 75.76, H 7.42, found: C 75.90, H 7.52.

7-HYDROXY-6-(HYDROXYMETHYL)-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (579)



To a -100°C solution of ($\pm$)-6-Iodo-8-(2-iodopropan-2-yl)-2,2-dimethyl-5-phenethyl-8,9-dihydro-4*H*-[1,3]dioxino[4,5-*e*]benzofuran-4-one (577) (80.0 mg, 0.129 mmol, 1.00 eq) in THF (1.4 mL) and PhMe (0.7 mL) was added *n*-BuLi (2 M in cyclohexane; 0.26 mL, 0.518 mmol, 4.00 eq) dropwise. After stirring for 10 min at -100°C , $\text{CuBr} \cdot \text{Me}_2\text{S}$ (8.00 mg, 0.0388 mmol, 0.30 eq) was added in one portion followed by dropwise addition of TMEDA (0.10 mL, 0.647 mmol, 5.00 eq). After 2 min at -100°C , DMF (47.3 mg, 0.05 mL, 0.647 mmol, 5.00 eq) was added dropwise and the resulting reaction mixture was stirred for 18 h while gradually warming to RT. The reaction mixture was quenched with an aqueous saturated ammonium chloride solution (4 mL), the organic layer was separated and the aqueous layer was further extracted with EtOAc (3×10 mL). The combined organic layers were washed with an aqueous hydrochloric acid solution (1 M; 10 mL) and a saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Flash column chromatography (pentane : EtOAc 15 : 1 $\rightarrow$ 10 : 1) afforded 7-hydroxy-6-(hydroxymethyl)-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (579) (18.0 mg, 0.0454 mmol, 36%) as a yellow oil next to 7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (563) (18.0 mg, 0.0491 mmol, 38%) as yellow-white solid.

R_f (hexane : EtOAc 9 : 1) = 0.05.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 8.68 (s, 1H, OH), 7.30 – 7.25 (m, 2H, H21), 7.23 – 7.18 (m, 1H, H22), 7.16 (dd, J = 8.1, 1.4 Hz, 2H, H20), 5.15 (tdt, J = 5.7, 2.8, 1.5 Hz, 1H, H12), 4.66 (s, 2H, H16), 3.51 – 3.33 (m, 1H, H17), 3.30 (d, J = 7.3 Hz, 2H, H11), 2.84 (t, J = 7.5 Hz, 2H, H18), 1.78 (d, J = 1.4 Hz, 3H, H15), 1.69 (d, J = 1.4 Hz, 3H, H15), 1.66 (s, 6H, H1+H3).

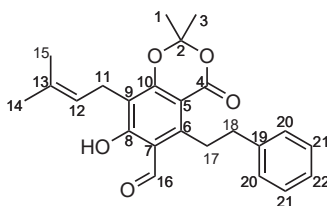
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.3 (C8), 161.0 (C4), 156.3 (C10), 141.9 (C19), 141.8 (C6), 132.6 (C13), 129.2 (2xC, C20), 128.5 (2xC, C21), 126.2 (C22), 121.6 (C12), 119.7 (C7), 115.7 (C9), 104.7 (C5), 104.5 (C2), 60.3 (C16), 37.2 (C18), 31.2 (C17),

25.9 (C₁₄), 25.7 (C₁ + C₃), 22.0 (C₁₁), 18.0 (C₁₅).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3339 (br, s), 2924 (m), 1722 (s), 1691 (vs), 1588 (vs), 1453 (m), 1425 (s), 1388 (s), 1375 (s), 1305 (vs), 1282 (s), 1263 (s), 1211 (vs), 1130 (s), 1028 (m), 700 (m).

HRMS (APCI) m/z : [M + H]⁺ calc. for (C₂₄H₂₉O₅)⁺: 397.2010, found: 397.2002. Major peak m/z : = [M - acetone + H]⁺ calc. for (C₂₁H₂₃O₄)⁺: 339.1591, found: 339.1586. Also found m/z : [M - H₂O]⁺ calc. for (C₂₄H₂₇O₄)⁺: 379.1904, found: 379.1889.

7-HYDROXY-2,2-DIMETHYL-8-(3-METHYLBUT-2-EN-1-YL)-4-OXO-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXINE-6-CARBALDEHYDE (**578**)



To an ice-cold solution of 7-hydroxy-6-(hydroxymethyl)-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**579**) (14.0 mg, 0.035 mmol, 1.00 eq) in CH₂Cl₂ (0.8 mL) was added DMP (22.0 mg, 0.053 mmol, 1.50 eq) in one portion. The resulting reaction mixture was stirred for 2 h at RT. The reaction mixture was concentrated and loaded onto a column with a Celite[®] pad. Purification by flash column chromatography (10 : 1 pentane : EtOAc) afforded 7-hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)-4-oxo-5-phenethyl-4*H*-benzo[*d*][1,3]dioxine-6-carbaldehyde (**578**) (7.0 mg, 0.018 mmol, 50%) as a white solid.

R_f (hexane : Et₂O 4 : 1) = 0.30.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 13.16 (s, 1H, OH), 10.14 (s, 1H, H16), 7.33 – 7.27 (m, 3H, H21 + H22), 7.22 (dt, *J* = 9.9, 1.2 Hz, 2H, H20), 5.17 – 5.09 (m, 1H, H12), 3.72 (d, *J* = 8.4 Hz, 2H, H17), 3.30 (d, *J* = 7.3 Hz, 2H, H11), 2.95 (t, *J* = 8.0 Hz, 2H, H18), 1.77 (d, *J* = 1.3 Hz, 3H, H15), 1.70 (s, 6H, H1 + H3), 1.68 (d, *J* = 1.4 Hz, 3H, H14).

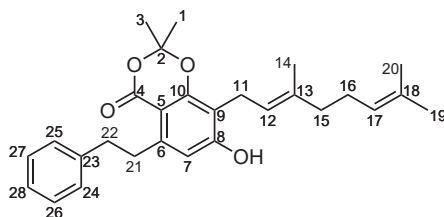
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 194.4 (C16), 166.8 (C8), 159.5 (C4), 151.9 (C10), 145.5 (C19), 140.7 (C6), 132.9 (C13), 128.9 (2 × C20), 128.8 (2 × C21), 126.6 (C22), 120.7 (C12), 116.6 (C7), 114.9 (C9), 105.3 (C2), 105.0 (C5), 38.5 (C18), 29.8 (C17), 26.1 (C1 + C3), 25.9 (C14), 21.4 (C11), 18.0 (C15).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2954 (m), 2922 (s), 1733 (vs), 1634 (s), 1583 (s), 1452 (m), 1388 (m), 1377 (m), 1364 (m), 1264 (s), 12108 (vs), 1049 (m).

HRMS (ES-ToF) *m/z*: [M - H]⁻ calc. for (C₂₄H₂₅O₅)⁻: 393.1707, found 393.1710.

Elemental Analysis: calc. for C₂₄H₂₆O₅: C 73.08, H 6.64. Found: C 73.08, H 7.11.

(*E*)-8-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-7-HYDROXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**564**)



Synthesized using to a modified literature procedure by Barrett et. al.^[105] To an ice-cold solution of (*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (**495**) (500 mg, 1.37 mmol, 1.00 eq) in CH₂Cl₂ (7.00 mL) was added MgCl₂ (261 mg, 2.74 mmol, 1.00 eq) and pyridine (293 mg, 0.30 mL, 3.70 mmol, 2.70 eq) in one portion. The ice-cold suspension was stirred for 15 min before hydrocinnamoyl chloride (278 mg, 0.24 mL, 1.65 mmol, 1.20 eq) was added dropwise to the reaction mixture. The resulting yellow-white suspension was stirred for 1 h at 0°C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL) and the pH was adjusted to 1 - 2 with an aqueous hydrochloric acid solution (1 M). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (7.00 mL) and tri(2-furyl)phosphine (64.0 mg, 0.27 mmol, 0.32 eq) and Tris(dibenzylideneacetone)dipalladium(o) (63.0 mg, 0.0686 mmol, 0.05 eq) were added sequentially in one portion. The resulting yellow solution was stirred for 2 h at RT before Cs₂CO₃ (1.34 g, 4.12 mmol, 3.00 eq) was added in one portion. The resulting orange-brown solution was stirred for 1.5 h at RT. The reaction mixture was quenched with an aqueous hydrochloric acid solution (1 M, 15 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (20 : 1 pentane : EtOAc -> 15 : 1 -> 10 : 1) afforded (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**564**) (260 mg, 0.598 mmol, 44%) as orange oil.

*R*_f (hexane : EtOAc 3 : 1) = 0.43.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.31 - 7.22 (m, 4H, H₂₄-H₂₇), 7.21 - 7.14 (m,

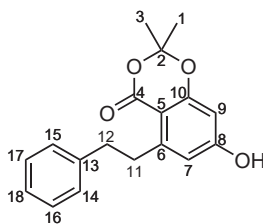
1H, H28), 6.89 (s, OH), 6.47 (s, 1H, H7), 5.26 – 5.19 (m, 1H, H12), 5.07 (tp, $J = 6.9, 1.7$ Hz, 1H, H17), 3.35 (d, $J = 7.3$ Hz, 2H, H11), 3.32 – 3.25 (m, 2H, H21), 2.91 – 2.84 (m, 2H, H22), 2.17 – 2.08 (m, 2H, H16), 2.08 – 1.98 (m, 2H, H15), 1.80 (d, $J = 1.4$ Hz, 3H, H14), 1.70 (s, 6H, H1 + H3), 1.69 – 1.67 (m, 3H, H19), 1.60 (d, $J = 1.4$ Hz, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 161.3 (C4), 160.7 (C8), 156.5 (C10), 146.3 (C6), 142.0 (C23), 137.9 (C13), 131.9 (C18), 128.7 (C24 + C25), 128.4 (C26 + C27), 125.9 (C28), 124.0 (C17), 121.1 (C12), 113.7 (C7), 113.4 (C9), 104.9 (C5), 104.7 (C2), 39.8 (C15), 37.5 (C22), 36.9 (C21), 26.6 (C16), 25.8 (C1 + C3 + C19), 22.0 (C11), 17.8 (C20), 16.3 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3258 (br, s), 2962 (w), 2920 (m), 2854 (m), 1724 (m), 1689 (vs), 1603 (vs), 1591 (vs), 1510 (m), 1452 (m), 1420 (s), 1375 (s), 1295 (vs), 1269 (vs), 1208 (vs), 1165 (s), 1105 (s), 1058 (s), 1047 (s), 698 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{28}\text{H}_{35}\text{O}_4)^+$: 435.2530, found: 435.2522.

7-HYDROXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**581**)



According to the procedure above. Purification by flash column chromatography (20 : 1 pentane : EtOAc $\rightarrow$ 15 : 1 $\rightarrow$ 10 : 1) afforded 7-hydroxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**581**) (32.0 mg, 0.107 mmol, 8%) as pale-orange oil which solidified upon standing.

R_f (hexane : EtOAc 3 : 1) = 0.18.

^1H -NMR (400 MHz, CDCl_3): δ (ppm) = 7.33 – 7.24 (m, 4H, H14 – H17), 7.24 – 7.15 (m, 1H, H18), 6.36 (t, $J = 2.9$ Hz, 1H, H7), 6.30 (t, $J = 2.0$ Hz, 1H, H9), 3.35 – 3.28 (m, 2H, H11), 2.92 – 2.85 (m, 2H, H12), 1.68 (s, 6H, H1 + H3).

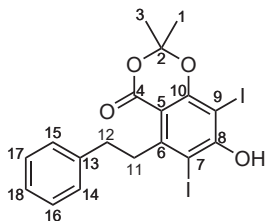
$^{13}\text{C}\{^1\text{H}\}$ -NMR (101 MHz, CDCl_3): δ (ppm) = 162.5 (C8), 161.2 (C4), 159.4 (C10), 149.6 (C6), 141.8 (C13), 128.8 (C14 + C15), 128.4 (C16 + C17), 126.0 (C18), 113.7 (C7), 105.2 (C2), 104.5 (C5), 102.1 (C9), 37.4 (C12), 37.0 (C11), 25.7 (C1 + C3).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3235 (br, s), 2925 (m), 1723 (s), 1689 (vs), 1609 (vs), 1581 (vs), 1446 (s), 1388 (s), 1377 (s), 1355 (s), 1287 (vs), 1268 (vs), 1204 (vs), 1167 (vs), 1053 (s), 699 (s).

HRMS (ESI) m/z : $[M + H]^+$ calc. for $(C_{18}H_{19}O_4)^+$: 299.1278, found: 299.1275.

Analytic data were in good agreement with literature values.^[89]

7-HYDROXY-6,8-DIIODO-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**586**)



To a solution of iodine (54.0 mg, 0.214 mmol, 2.00 eq) in PhMe (1.6 mL) was added *tert*-BuNH₂ (31.4 mg, 45.1 μ L, 0.429 mmol, 4.00 eq) dropwise. The mixture was stirred for 15 min, after which a solution of 7-hydroxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**581**) (32.0 mg, 0.107 mmol, 1.00 eq) in CH₂Cl₂ (0.70 mL) was added dropwise. The reaction mixture was stirred for 16 h at RT. The reaction mixture was diluted with CH₂Cl₂ (10 mL) and quenched with an aqueous hydrochloric acid solution (1 M, 10 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 $\times$ 15 mL). The combined organic layers were washed with a saturated aqueous Na₂S₂O₃ solution (10 mL), dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4 : 1 pentane : EtOAc) afforded 7-hydroxy-6,8-diiodo-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**586**) (44.0 mg, 0.0800 mmol, 75%) as orange oil.

R_f (hexane : EtOAc 7 : 3) = 0.23.

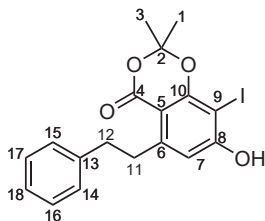
¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.44 – 7.39 (m, 2H, H₁₄ + H₁₅), 7.35 – 7.29 (m, 2H, H₁₆ + H₁₇), 7.25 – 7.18 (m, 1H, H₁₈), 3.64 (d, *J* = 6.6 Hz, 2H, H₁₁), 2.85 (dd, *J* = 9.3, 7.6 Hz, 2H, H₁₂), 1.73 (s, 6H, H₁ + H₃).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 159.2 (C₄), 158.5 (C₈), 158.1 (C₁₀), 150.5 (C₆), 141.3 (C₁₃), 128.8 (C₁₄ + C₁₅), 128.6 (C₁₆ + C₁₇), 126.3 (C₁₈), 106.8 (C₅), 105.9 (C₂), 86.4 (C₇), 71.0 (C₉), 41.7 (C₁₁), 35.1 (C₁₂), 25.8 (C₁ + C₃).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3423 (br, s), 2922 (m), 1727 (vs), 1559 (vs), 1451 (s), 1389 (vs), 1377 (s), 1275 (vs), 1234 (s), 1206 (vs), 1047 (s), 699 (s).

HRMS (APCI) *m/z*: [M + H]⁺ calc. for (C₁₈H₁₇I₂O₄)⁺: 550.9211, found: 550.9203.

7-HYDROXY-6,8-DIIODO-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**586**)



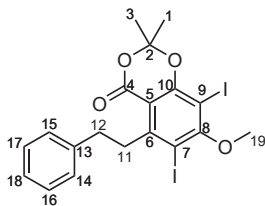
According to the procedure above. Purification by flash column chromatography (4 : 1 pentane : EtOAc) afforded 7-hydroxy-8-iodo-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**585**) (10.0 mg, 0.0182 mmol, 8%) as transparent film.

R_f (hexane : EtOAc 4 : 1) = 0.20.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.35 – 7.25 (m, 4H, H₁₄ - H₁₇), 7.25 – 7.15 (m, 1H, H₁₈), 6.60 (s, 1H, H₇), 6.07 (s, 1H, OH), 3.40 – 3.29 (m, 2H, H₁₁), 2.93 – 2.85 (m, 2H, H₁₂), 1.73 (s, 6H, H₁ + H₃).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 160.7 (C₄), 159.4 (C₈), 157.9 (C₁₀), 149.5 (C₆), 141.5 (C₁₃), 128.8 (C₁₄ + C₁₅), 128.5 (C₁₆ + C₁₇), 126.1 (C₁₈), 112.5 (C₇), 105.9 (C₂), 105.7 (C₅), 73.5 (C₉), 37.3 (C₁₁), 36.7 (C₁₂), 25.8 (C₁ + C₃).

6,8-DIIODO-7-METHOXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**587**)



To a solution of 7-hydroxy-6,8-diiodo-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**586**) (44.0 mg, 0.0800 mmol, 1.00 eq) in THF (1.20 mL) was added Cs_2CO_3 (76.0 mg, 0.240 mmol, 3.00 eq) in one portion, followed by dropwise addition of MeI (34.0 mg, 14.9 μL , 0.240 mmol, 3.00 eq). The reaction mixture was stirred for 13 h at 35 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (9 : 1 pentane : EtOAc) afforded 6,8-diiodo-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**587**) (36.0 mg, 0.0638 mmol, 80%) as orange oil.

R_f (hexane : EtOAc 4 : 1) = 0.64.

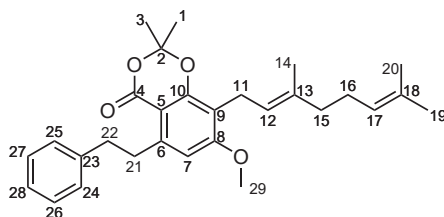
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.45 – 7.41 (m, 2H, H₁₄ + H₁₅), 7.35 – 7.29 (m, 2H, H₁₆ + H₁₇), 7.25 – 7.19 (m, 1H, H₁₈), 3.94 (s, 3H, H₁₉), 3.63 (s, 2H, H₁₁), 2.85 (dd, J = 9.3, 7.6 Hz, 2H, H₁₂), 1.73 (s, 6H, H₁ + H₃).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 164.8 (C8), 158.6 (C4), 158.2 (C10), 150.8 (C6), 141.5 (C13), 128.9 (C14 + C15), 128.5 (C16 + C17), 126.3 (C18), 110.2 (C5), 106.0 (C2), 94.6 (C7), 79.7 (C9), 60.9 (C19), 41.8 (C11), 35.2 (C12), 25.8 (C1 + C3).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2932 (m), 1733 (vs), 1555 (s), 1534 (m), 1452 (s), 1374 (s), 1273 (vs), 1231 (vs), 1206 (s), 1053 (s), 911 (m), 700 (m).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{19}\text{H}_{19}\text{I}_2\text{O}_4)^+$: 564.9367, found: 564.9371. Major peak m/z : $[\text{M} - \text{acetone} + \text{H}]^+$ calc. for $(\text{C}_{16}\text{H}_{13}\text{I}_2\text{O}_3)^+$: 506.8949, found: 506.8954.

(*E*)-8-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-7-METHOXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (588)



To a solution of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (564) (260 mg, 0.598 mmol, 1.00 eq) in THF (8.00 mL) was added Cs_2CO_3 (1.99 g, 1.79 mmol, 3.00 eq) in one portion, followed by dropwise addition of MeI (255 mg, 0.112 mL, 1.79 mmol, 3.00 eq). The reaction mixture was stirred for 1.5 h at 40 °C. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (20 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 1 pentane : CH_2Cl_2) afforded (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (588) (221 mg, 0.493 mmol, 82%) as colourless oil.

R_f (hexane : EtOAc 3 : 1) = 0.57.

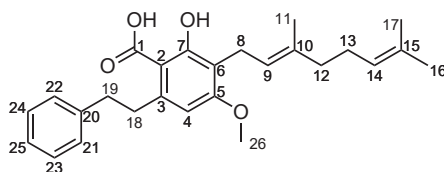
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.27 (d, J = 6.0 Hz, 4H, H₂₄ – H₂₇), 7.18 (ddd, J = 8.6, 5.6, 2.6 Hz, 1H, H₂₈), 6.30 (s, 1H, H₇), 5.13 – 5.08 (m, 1H, H₁₂), 5.08 – 5.03 (m, 1H, H₁₇), 3.79 (s, 3H, H₂₉), 3.37 – 3.30 (m, 2H, H₂₁), 3.25 (d, J = 7.3 Hz, 2H, H₁₁), 2.93 – 2.87 (m, 2H, H₂₂), 2.04 (q, J = 7.4 Hz, 2H, H₁₆), 1.95 (dd, J = 9.3, 6.0 Hz, 2H, H₁₇), 1.75 (d, J = 1.4 Hz, 3H, H₁₄), 1.67 (s, 6H, H₁ + H₃), 1.64 (d, J = 1.4 Hz, 3H, H₁₉), 1.57 (s, 3H, H₂₀).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 161.9 (C₈), 160.7 (C₄), 155.7 (C₁₀), 146.1 (C₆), 141.9 (C₂₃), 135.3 (C₁₃), 131.4 (C₁₈), 128.8 (C₂₄ + C₂₅), 128.3 (C₂₆ + C₂₇), 125.8 (C₂₈), 124.2 (C₁₇), 121.6 (C₁₂), 116.2 (C₉), 108.1 (C₇), 105.3 (C₅), 104.6 (C₂), 55.7 (C₂₉), 39.8 (C₁₅), 37.4 (C₂₂), 37.4 (C₂₁), 26.7 (C₁₆), 25.7 (C₁ + C₃ + C₁₉), 21.7 (C₁₁), 17.7 (C₂₀), 16.1 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2922 (m), 1727 (vs), 1605 (s), 1575 (s), 1455 (m), 1411 (m), 1375 (m), 1334 (m), 1292 (s), 1267 (s), 1209 (s), 1170 (s), 1119 (s), 1052 (m), 699 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{29}H_{37}O_4)^+$: 449.2686, found: 449.2697.

(*E*)-3-(3,7-DIMETHYLOCTA-2,6-DIEN-1-YL)-2-HYDROXY-4-METHOXY-6-PHENETHYLBENZOIC ACID (AMORFRUTIN B) (**520**)



To a solution of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**588**) (21.0 mg, 0.0468 mmol, 1.00 eq) in DMSO (0.40 mL) was added aqueous KOH (48 vol%; 0.40 mL) in one portion. The resulting orange biphasic reaction mixture was stirred for 16 h at 80 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 10 mL). An aqueous lithium chloride solution (10 w/v-%; 25 mL) was added and the solution was stirred for 2 h. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 15 EtOAc : CH₂Cl₂) afforded (*E*)-3-(3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-4-methoxy-6-phenethylbenzoic acid (Amorfrutin B) (**520**) (17.0 mg, 0.0416 mmol, 89%) as a white solid.

R_f (hexane : EtOAc 1 : 1) = 0.35.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 11.59 (s, 1H, OH), 7.36 – 7.28 (m, 2H, H₂₃ + H₂₄), 7.25 – 7.17 (m, 3H, H₂₁ + H₂₂ + H₂₅ overlapping), 6.23 (s, 1H, H₄), 5.27 – 5.19 (m, 1H, H₉), 5.09 (dddd, J = 8.5, 7.0, 2.8, 1.4 Hz, 1H, H₁₄), 3.80 (s, 3H, H₂₆), 3.37 (d, J = 7.1 Hz, 2H, H₈), 3.32 – 3.25 (m, 2H, H₁₈), 2.97 – 2.91 (m, 2H, H₁₉), 2.07 (t, J = 8.1 Hz, 2H, H₁₃), 1.99 (dd, J = 9.4, 6.0 Hz, 2H, H₁₂), 1.80 (d, J = 1.4 Hz, 3H, H₁₁), 1.66 (d, J = 1.5 Hz, 3H, H₁₆), 1.59 (d, J = 1.3 Hz, 3H, H₁₇).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 175.9 (C₁), 163.1 (C₇), 162.3 (C₅), 145.9 (C₃), 142.0 (C₂₀), 135.4 (C₁₀), 131.3 (C₁₅), 128.7 (C₂₁ + C₂₂), 128.5 (C₂₃ + C₂₄), 126.1 (C₂₅), 124.6 (C₁₄), 122.2 (C₉), 115.6 (C₆), 106.6 (C₄), 103.8 (C₂), 55.7 (C₂₆), 40.0 (C₁₂), 39.4 (C₁₈), 38.3 (C₁₉), 26.9 (C₁₃), 25.8 (C₁₆), 22.1 (C₈), 17.8 (C₁₇), 16.3 (C₁₁).

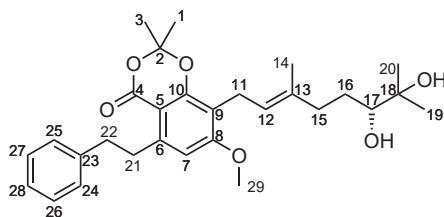
IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 2922 (br, s), 1628 (vs), 1607 (Vs), 1571 (m), 1496 (m), 1453 (s), 1400 (m), 1267 (vs), 1225 (s), 1172 (m), 1114 (s), 699 (m).

HRMS (ES-ToF) m/z : [M - H]⁻ calc. for (C₂₆H₃₁O₄)⁻: 407.2228, found: 407.2232.

mp. (recrystallized from CH_2Cl_2 /pentane): 79 °C-80 °C.

Analytic data were in good agreement with literature values.^[394,407]

(*R,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**589**)



To an ice-cold solution of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**588**) (196 mg, 0.437 mmol, 1.00 eq) in *tert*-BuOH (2.20 mL) and water (2.20 mL) were added MeSO₂NH₂ (42.0 mg, 0.437 mmol, 1.00 eq) and AD-mix-β (612 mg, 0.437 mmol (based on 1.4 g AD-Mix per mmol of SM), 1.00 eq) in one portion. The resulting orange suspension was stirred for 24 h at 0 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and water (5.0 mL), and quenched with NaSO₃ (700 mg). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with an aqueous potassium hydroxide solution (2 M; 20 mL) and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 5 → 1 : 1 EtOAc : pentane) afforded (*R,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**589**) (99.0 mg, 0.205 mmol, 47%, 79% corrected for recovered SM) as a colourless oil.

R_f (hexane : EtOAc 1 : 1) = 0.22.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.31 – 7.24 (m, 5H, H₂₄–27), 7.18 (ddd, *J* = 8.6, 5.6, 2.4 Hz, 1H, H₂₈), 6.31 (s, 1H, H₇), 5.18 (ddt, *J* = 7.3, 6.0, 1.3 Hz, 1H, H₁₂), 3.79 (s, 3H, H₂₉), 3.39 – 3.29 (m, 3H, H₂₁ + H₁₇ overlapping), 3.27 (d, *J* = 7.3 Hz, 2H, H₁₁), 2.94 – 2.87 (m, 2H, H₂₂), 2.28 – 2.17 (m, 1H, H₁₅), 2.11 – 2.01 (m, 1H, H₁₅), 1.77 (d, *J* = 1.3 Hz, 3H, H₁₄), 1.68 (d, *J* = 1.3 Hz, 6H, H₁ + H₃), 1.57 (dddd, *J* = 13.7, 8.8, 6.6, 1.9 Hz, 1H, H₁₆), 1.47 – 1.34 (m, 1H, H₁₆), 1.18 (s, 3H, H₁₉), 1.14 (s, 3H, H₂₀).

¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 162.1 (C₈), 160.7 (C₄), 155.7 (C₁₀), 146.4 (C₆), 142.0 (C₂₃), 135.4 (C₁₃), 128.9 (C₂₄ + C₂₅), 128.4 (C₂₆ + C₂₇), 126.0 (C₂₈), 122.6 (C₁₂), 115.9 (C₉), 108.3 (C₇), 105.4 (C₅), 104.8 (C₂), 78.5 (C₁₇), 73.1 (C₁₈), 55.8 (C₂₉), 37.5 (C₂₁), 37.4 (C₂₂), 37.1 (C₁₅), 29.7 (C₁₆), 26.5 (C₁₉), 25.9 (C₁), 25.9 (C₃), 23.5 (C₂₀), 21.9 (C₁₁), 16.1 (C₁₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3443 (br, s), 2925 (m), 1724 (vs), 1605 (vs), 1574

(vs), 1453 (s), 1410 (s), 1388 (s), 1375 (s), 1335 (s), 1293 (vs), 1268 (vs), 1210 (vs), 1167 (vs), 1119 (vs), 1053 (s), 700 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{29}H_{39}O_6)^+$: 483.2741, found: 483.2728.

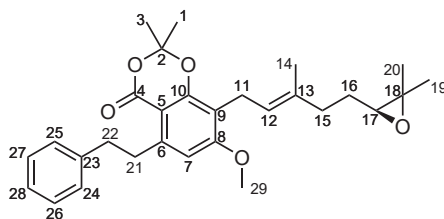
Major peak m/z : $[M + Na]^+$ calc. for $(C_{29}H_{38}O_6Na)^+$: 505.2561, found: 505.2575.

Optical rotation: $[\alpha]_D^{22.3} +26.4^\circ$ ($c = 1.0$, $CHCl_3$).

Determination of the enantiomeric ratio was executed according to a procedure by Corey and Zhang, and found to be 97 : 3 *via* Mosher's ester:^[424] To a solution of (*R,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**589**) (12 mg, 0.025 mmol, 1.0 eq) in CH_2Cl_2 (1.0 mL) were added DMAP (12 mg, 0.099 mmol, 4.0 eq) and (*S*)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride (9.3 μ L, 13 mg, 0.050 mmol, 2.0 eq) in one portion. The reaction was stirred for 1.5 h at RT, before the reaction mixture was loaded onto a pasteur pipette column, and eluted with Et_2O (15 mL). The filtrate was concentrated under reduced pressure and afforded the (*S*)-MTBA resorcyate ester.

^{19}F -NMR (377 MHz, $CDCl_3$): δ (ppm) = -70.71 for the (*R*)-enantiomer, -70.84 for the (*S*)-enantiomer, corresponding to the α -trifluoromethyl group of the ester.

(*S,E*)-8-(5-(3,3-DIMETHYLOXIRAN-2-YL)-3-METHYLPENT-2-EN-1-YL)-7-METHOXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**591**)



To an ice-cold solution of (*R,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**589**) (90.0 mg, 0.186 mmol, 1.00 eq) in CH₂Cl₂ (3.00 mL) were added pyridine (221 mg, 0.23 mL, 2.80 mmol, 15.0 eq) and methanesulfonyl chloride (42.5 mg, 28.7 μ L, 0.371 mmol, 1.99 eq) dropwise. The resulting yellow solution was stirred for 12 h at RT. The reaction mixture was concentrated and redissolved in THF (0.8 mL). Cs₂CO₃ (4.86 g, 14.9 mmol, 80.0 eq) was added in portion and the yellow-white suspension was stirred for 15 h at RT, after which the reaction mixture was diluted with CH₂Cl₂ (7.0 mL) and quenched with water (20 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3 $\times$ 15 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc : pentane) afforded (*S,E*)-8-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**591**) (60.0 mg, 0.129 mmol, 69%) as a colourless oil.

R_f (hexane : EtOAc 1 : 1) = 0.62.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.30 – 7.25 (m, 4H, H₂₄ – H₂₇), 7.18 (ddd, *J* = 8.6, 5.6, 2.4 Hz, 1H H₂₈), 6.31 (s, 1H, H₇), 5.15 (tdd, *J* = 7.2, 2.5, 1.2 Hz, 1H, H₁₂), 3.79 (s, 3H, H₂₉), 3.38 – 3.30 (m, 2H, H₂₁), 3.26 (d, *J* = 7.3 Hz, 2H, H₁₁), 2.94 – 2.86 (m, 2H, H₂₂), 2.66 (t, *J* = 6.3 Hz, 1H, H₁₇), 2.19 – 2.01 (m, 2H, H₁₅), 1.77 (d, *J* = 1.3 Hz, 3H, H₁₄), 1.67 (d, *J* = 2.0 Hz, 6H, H₁ + H₃), 1.67 – 1.55 (m, 2H, H₁₆), 1.24 (s, 3H, H₁₉), 1.23 (s, 3H, H₂₀).

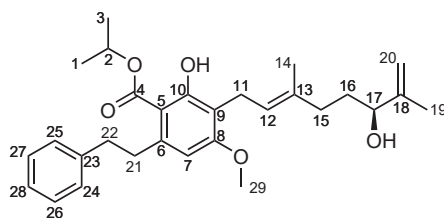
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 162.0 (C₈), 160.7 (C₄), 155.7 (C₁₀), 146.4 (C₆), 142.0 (C₂₃), 134.4 (C₁₃), 128.9 (C₂₄ + C₂₅), 128.4 (C₂₆ + C₂₇), 126.0 (C₂₈), 122.4 (C₁₂), 116.0 (C₉), 108.2 (C₇), 105.4 (C₅), 104.7 (C₂), 64.3 (C₁₇), 58.5 (C₈), 55.8 (C₂₉), 37.5 (C₂₂), 37.4 (C₂₁), 36.5 (C₁₅), 27.5 (C₁₆), 25.9 (C₁), 25.8 (C₃), 24.9 (C₁₉), 21.9 (C₁₁), 18.8 (C₂₀), 16.2 (C₁₄).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 2958 (w), 2923 (m), 2856 (w), 1725 (vs), 1604

(s), 1574 (s), 1496 (w), 1453 (m), 1411 (m), 1375 (s), 1334 (s), 1291 (s), 1268 (s), 1208 (s), 1167 (s), 1119 (s), 1051 (s), 700 (m).

HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{29}H_{37}O_5)^+$: 465.2636, found: 465.2623. Major peak m/z : $[M - \text{acetone} + H]^+$ calc. for $(C_{26}H_{31}O_4)^+$: 407.2217, found: 407.2206.

Optical rotation: $[\alpha]_D^{25.2} -1.7^\circ$ ($c = 1.0$, $CHCl_3$).

ISOPROPYL (*S,E*)-2-HYDROXY-3-(6-HYDROXY-3,7-DIMETHYLOCTA-2,7-DIEN-1-YL)-4-METHOXY-6-PHENETHYLBENZOATE (**592**)

To a solution of (*S,E*)-8-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**591**) (60.0 mg, 0.129 mmol, 1.00 eq) in PhMe (1.70 mL) and *iso*-PrOH (0.34 mL) was added aluminium triisopropoxide (100 mg, 0.490 mmol, 3.80 eq) in one portion. The resulting suspension was stirred for 5 h at 110 °C. The reaction mixture was diluted with EtOAc (10.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 20 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc : pentane) afforded isopropyl (*S,E*)-2-hydroxy-3-(6-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-4-methoxy-6-phenethylbenzoate (**592**) (17.0 mg, 0.0364 mmol, 28%) as a colourless oil.

R_f (hexane : EtOAc 4 : 1) = 0.35.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.90 (s, 1H, OH), 7.31 – 7.25 (m, 2H, H26 + H27), 7.22 – 7.15 (m, 3H, H24 + H25 + H28 overlapping), 6.11 (d, J = 2.5 Hz, 1H, H7), 5.35 (p, J = 6.3 Hz, 1H, H2), 5.25 (tp, J = 5.6, 1.4 Hz, 1H, H12), 4.89 (dt, J = 2.0, 1.0 Hz, 1H, H20*trans*), 4.80 (p, J = 1.6 Hz, 1H, H20*cis*), 4.04 – 3.98 (m, 1H, H17), 3.73 (d, J = 3.1 Hz, 3H, H29), 3.34 (d, J = 7.0 Hz, 2H, H11), 3.25 (ddd, J = 8.3, 6.6, 1.5 Hz, 2H, H21), 2.91 (t, J = 7.9 Hz, 2H, H22), 2.12 – 1.90 (m, 2H, H15), 1.78 (dd, J = 7.4, 1.3 Hz, 3H, H14), 1.71 (t, J = 1.2 Hz, 3H, H19), 1.70 – 1.52 (m, 2H, H16), 1.39 (s, 3H, H1), 1.37 (s, 3H, H3).

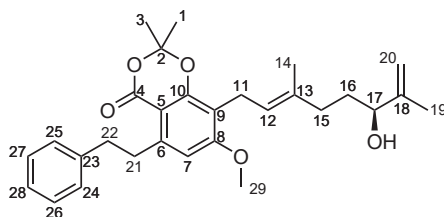
$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 171.4 (C4), 162.1 (C10), 161.1 (C8), 147.7 (C18), 144.0 (C6), 141.9 (C23), 134.8 (C13), 128.5 (C24 + C25), 128.4 (C26 + 27), 126.0 (C28), 123.2 (C12), 115.1 (C9), 110.9 (C20), 106.2 (C7), 105.7 (C5), 75.9 (C17), 69.4 (C2), 55.6 (C29), 38.4 (C21), 38.1 (C22), 36.0 (C15), 33.2 (C16), 22.1 (C1 + C3), 22.1 (C11), 17.9 (C19), 16.2 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3437 (br, s), 2932 (m), 1642 (s), 1608 (s), 1571 (s), 1496 (m), 1464 (m), 1453 (s), 1405 (s), 1374 (s), 1277 (vs), 1228 (s), 1167 (vs), 1103 (vs), 905 (m), 699 (s).

HRMS (APCI) m/z : $[\text{M} + \text{H}]^+$ calc. for $(\text{C}_{29}\text{H}_{39}\text{O}_5)^+$: 467.2792, found: 467.2784. Major peak m/z : $[\text{M} - (\text{CH}_3)_2\text{CHOH} + \text{H}]^+$ calc. for $(\text{C}_{26}\text{H}_{31}\text{O}_4)^+$: 407.2217, found: 407.2209.

Optical rotation: $[\alpha]_{\text{D}}^{25.4}$ -39.1° ($c = 1.0$, CHCl_3).

(*S,E*)-8-(6-HYDROXY-3,7-DIMETHYLOCTA-2,7-DIEN-1-YL)-7-METHOXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**593**)



To a solution of (*S,E*)-8-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**591**) (36.0 mg, 0.0775 mmol, 1.00 eq) in PhMe (1.00 mL) and *tert*-BuOH (0.30 mL) was added aluminium triisopropoxide (32.0 mg, 0.155 mmol, 2.00 eq) in one portion. The resulting suspension was stirred for 23 h at 110 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 15 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (15 : 85 EtOAc : pentane) afforded (*S,E*)-8-(6-Hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**593**) (13.0 mg, 0.0280 mmol, 36%) as a colourless oil.

R_f (hexane : EtOAc 4 : 1) = 0.17.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.30 – 7.24 (m, 4H, H24 – H27), 7.18 (ddd, J = 8.6, 5.5, 2.2 Hz, 1H, H28), 6.30 (s, 1H, H7), 5.14 (tq, J = 7.5, 1.4 Hz, 1H, H12), 4.89 (dt, J = 1.9, 1.0 Hz, 1H, H20*trans*), 4.82 (p, J = 1.7 Hz, 1H, H20*cis*), 4.01 (t, J = 6.4 Hz, 1H, H17), 3.79 (s, 3H, H29), 3.38 – 3.30 (m, 2H, H21), 3.26 (d, J = 7.3 Hz, 2H, H11), 2.95 – 2.86 (m, 2H, H22), 2.09 – 1.93 (m, 2H, H15), 1.77 (d, J = 1.4 Hz, 3H, H14), 1.71 (t, J = 1.2 Hz, 3H, H19), 1.67 (s, 6H, H1 + H3), 1.66 – 1.59 (m, 2H, H16).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.0 (C8), 160.7 (C4), 155.7 (C10), 147.5 (C18), 146.4 (C6), 142.0 (C23), 135.1 (C13), 128.9 (C24 + C25), 128.4 (C26 + C27), 126.0 (C28), 122.3 (C12), 116.0 (C9), 111.1 (C20), 108.2 (C7), 105.4 (C5), 104.7 (C2), 75.8 (C17), 55.8 (C29), 37.5 (C22), 37.5 (C21), 35.9 (C15), 33.2 (C16), 25.9 (C1), 25.9 (C3), 21.9 (C11), 17.8 (C19), 16.2 (C14).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3453 (br, s), 2919 (s), 2855 (m), 1729 (vs), 1604 (vs), 1575 (vs), 1456 (m), 1411 (m), 1387 (m), 1334 (m), 1294 (s), 1268 (m), 1208 (s),

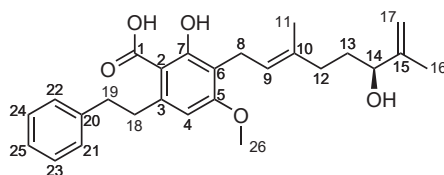
1171 (s), 1051 (m), 984 (m).

HRMS (ES-ToF) m/z : $[M + H]^+$ calc. for $(C_{29}H_{37}O_5)^+$: 465.2636, found 465.2652.

Major peak m/z : $[M + Na]^+$ calc. for $(C_{29}H_{36}NaO_5)^+$: 487.2455, found 487.2441.

Optical rotation: $[\alpha]_D^{26.1}$ -9.3° ($c = 1.0$, $CHCl_3$).

(*S,E*)-2-HYDROXY-3-(6-HYDROXY-3,7-DIMETHYLOCTA-2,7-DIEN-1-YL)-4-METHOXY-6-PHENETHYLBENZOIC ACID ((*S*)-AMORFRUTIN D) (**523**)



To a solution of isopropyl (*S,E*)-2-hydroxy-3-(6-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-4-methoxy-6-phenethylbenzoate (**592**) (17.0 mg, 0.0364 mmol, 1.00 eq) in DMSO (0.30 mL) was added aqueous KOH (48 vol%; 0.30 mL) in one portion. The resulting orange biphasic reaction mixture was stirred for 17 h at 80 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 10 mL). An aqueous lithium chloride solution (10 w/v-%; 25 mL) was added and the solution was stirred for 2 h. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 8.0 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 2 EtOAc : pentane) afforded (*S,E*)-2-hydroxy-3-(6-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-4-methoxy-6-phenethylbenzoic acid ((*S*)-Amorfrutin D) (**523**) (15.0 mg, 0.0353 mmol, 97%) as a white film.

R_f (hexane : EtOAc 4 : 1) = 0.03.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.72 (s, 1H, OH), 7.34 – 7.26 (m, 2H, H₂₃ + H₂₄), 7.20 (dt, J = 9.3, 3.0 Hz, 3H, H₂₁ + H₂₂ + H₂₅ overlapping), 6.20 (s, 1H, H₄), 5.31 – 5.23 (m, 1H, H₉), 4.89 (s, 1H, H_{17trans}), 4.81 (t, J = 1.7 Hz, 1H, H_{17cis}), 4.05 (t, J = 6.3 Hz, 1H, H₁₄), 3.78 (d, J = 3.4 Hz, 3H, H₂₆), 3.36 (d, J = 7.1 Hz, 2H, H₈), 3.30 – 3.22 (m, 2H, H₁₈), 2.91 (dd, J = 9.5, 6.3 Hz, 2H, H₁₉), 2.10 – 1.99 (m, 2H, H₁₂), 1.83 – 1.79 (m, 3H, H₁₁), 1.71 (s, 3H, H₁₆), 1.70 – 1.62 (m, 2H, H₁₃).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 175.5 (C₁), 163.0 (C₅), 162.1 (C₇), 147.4 (C₁₅), 145.8 (C₃), 142.1 (C₂₀), 135.0 (C₁₀), 128.7 (C₂₁ + C₂₂), 128.5 (C₂₃ + C₂₄), 126.0 (C₂₅), 123.1 (C₉), 115.2 (C₆), 111.1 (C₁₇), 106.5 (C₄), 104.0 (C₂), 76.0 (C₁₄), 55.7 (C₂₆), 39.4 (C₁₈), 38.3 (C₁₉), 36.1 (C₁₂), 33.1 (C₁₃), 22.0 (C₈), 17.9 (C₁₆), 16.2 (C₁₁).

IR (Diamond-ATR, neat) ν_{max} (cm⁻¹) = 3500 (br, s), 2925 (s), 1709 (m), 1649 (s), 1605 (vs), 1573 (s), 1495 (m), 1453 (s), 1404 (s), 1268 (vs), 1226 (Vs), 1170 (s), 1114 (vs) 751 (m), 700 (s).

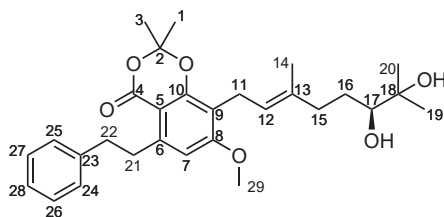
HRMS (ES-ToF) m/z : $[\text{M} - \text{H}]^-$ calc. for (C₂₆H₃₁O₅)⁻: 423.2177, found: 423.2180.

Optical rotation: $[\alpha]_{\text{D}}^{26.0} -4.5^{\circ}$ ($c = 0.4$, acetone).

When the reaction was performed with (*S,E*)-8-(6-Hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**593**) (13.0 mg, 0.0280 mmol, 1.00 eq) in DMSO (0.30 mL) and aqueous KOH (48 vol%; 0.30 mL) for 15 h at 80 °C, followed by work-up and purification as above (*S,E*)-2-hydroxy-3-(6-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-4-methoxy-6-phenethylbenzoic acid ((*S*)-Amorfrutin D) (**523**) (11 mg, 0.0259 mmol, 93%) was obtained as white film.

Analytic data were in good agreement with literature values.^[407]

(*S,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*D*][1,3]dioxin-4-one (**594**)



To an ice-cold solution of (*E*)-8-(3,7-dimethylocta-2,6-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**588**) (80.0 mg, 0.178 mmol, 1.00 eq) in *tert*-BuOH (1.00 mL) and water (1.00 mL) were added MeSO₂NH₂ (17.0 mg, 0.178 mmol, 1.00 eq) and AD-mix- α (250 mg, 0.178 mmol (based on 1.4 g AD-Mix per mmol of SM), 1.00 eq) in one portion. The resulting orange suspension was stirred for 24 h at 0 °C. The reaction mixture was diluted with EtOAc (2.0 mL) and water (2.0 mL), and quenched with NaSO₃ (285 mg). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with an aqueous potassium hydroxide solution (2 M; 15 mL) and saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 $\rightarrow$ 3 : 7 EtOAc : pentane) afforded (*S,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**594**) (57.0 mg, 0.118 mmol, 66%, 87% corrected for recovered SM) as a colourless oil.

R_f (hexane : EtOAc 1 : 1) = 0.22.

¹H-NMR (400 MHz, CDCl₃): δ (ppm) = 7.30 – 7.24 (m, 4H, H₂₄–H₂₇), 7.18 (ddd, J = 8.7, 5.6, 2.3 Hz, 1H, H₂₈), 6.31 (s, 1H, H₇), 5.18 (tq, J = 7.3, 1.3 Hz, 1H, H₁₂), 3.79 (s, 3H, H₂₉), 3.39 – 3.30 (m, 3H, H₂₁ + H₁₇ overlapping), 3.27 (d, J = 7.2 Hz, 2H, H₁₁), 2.96 – 2.86 (m, 2H, H₂₂), 2.35 (s, 1H, OH), 2.29 – 2.17 (m, 1H, H₁₅), 2.10 – 2.01 (m, 1H, H₁₅), 1.78 (d, J = 1.3 Hz, 3H, H₁₄), 1.72 – 1.65 (m, 6H, H₁ + H₃), 1.58 (dddd, J = 13.8, 8.9, 6.7, 1.9 Hz, 1H, H₁₆), 1.47 – 1.38 (m, 1H, H₁₆), 1.19 (s, 3H, H₁₉), 1.15 (s, 3H, H₂₀).
¹³C{¹H}-NMR (101 MHz, CDCl₃): δ (ppm) = 162.1 (C₈), 160.7 (C₄), 155.7 (C₁₀), 146.4 (C₆), 142.0 (C₂₃), 135.4 (C₁₃), 128.9 (C₂₄ + C₂₅), 128.3 (C₂₆ + C₂₇), 125.9 (C₂₈), 122.5 (C₁₂), 116.0 (C₉), 108.3 (C₇), 105.4 (C₅), 104.7 (C₂), 78.4 (C₁₇), 73.0 (C₁₈), 55.8 (C₂₉), 37.5 (C₂₁), 37.3 (C₂₂), 37.1 (C₁₅), 29.7 (C₁₆), 26.5 (C₁₉), 25.8 (C₁), 25.8 (C₃), 23.4 (C₂₀), 21.9 (C₁₁), 16.1 (C₁₄).

IR (Diamond-ATR, neat) $\nu_{\max}$ (cm⁻¹) = 3443 (br, s), 2927 (m), 1718 (vs), 1603 (vs), 1572

(vs), 1452 (s), 1409 (s), 1387 (s), 1375 (s), 1334 (s), 1290 (vs), 1266 (vs), 1207 (vs), 1164 (vs), 1117 (vs), 1051 (s), 908 (m), 730 (m), 699 (m).

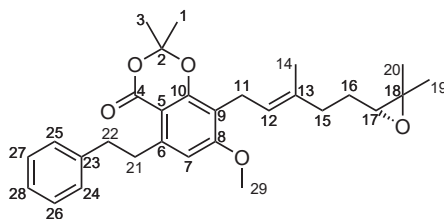
HRMS (ES-ToF) m/z : $[M + Na]^+$ calc. for $(C_{29}H_{38}O_6Na)^+$: 505.2561, found: 505.2575.

Optical rotation: $[\alpha]_D^{23.6}$ -24.8° ($c = 1.0$, $CHCl_3$).

Determination of the enantiomeric ratio was executed according to a procedure by Corey and Zhang, and found to be 95 : 5 *via* Mosher's ester:^[424] To a solution of (*S,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**59**) (7.0 mg, 0.015 mmol, 1.0 eq) in CH_2Cl_2 (0.6 mL) were added DMAP (7.0 mg, 0.058 mmol, 4.0 eq) and (*S*)-(+)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride (5.4 μ L, 7.0 mg, 0.015 mmol, 2.0 eq) in one portion. The reaction was stirred for 1.5 h at RT, before the reaction mixture was loaded onto a pasteur pipette column, and eluted with Et_2O (15 mL). The filtrate was concentrated under reduced pressure and afforded the (*S*)-MTBA resorcyate ester.

^{19}F -NMR (377 MHz, $CDCl_3$): δ (ppm) = -70.72 for the (*R*)-enantiomer, -70.85 for the (*S*)-enantiomer, corresponding to the α -trifluoromethyl group of the ester.

(*R,E*)-8-(5-(3,3-DIMETHYLOXIRAN-2-YL)-3-METHYLPENT-2-EN-1-YL)-7-METHOXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*d*][1,3]DIOXIN-4-ONE (**595**)



To an ice-cold solution of (*S,E*)-8-(6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**594**) (50.0 mg, 0.104 mmol, 1.00 eq) in CH_2Cl_2 (2.00 mL) were added pyridine (123 mg, 0.125 mL, 1.55 mmol, 15.0 eq) and methanesulfonyl chloride (23.6 mg, 16.0 μL , 0.206 mmol, 1.99 eq) dropwise. The resulting yellow solution was stirred for 6 h at RT. The reaction mixture was concentrated and redissolved in THF (0.5 mL). Cs_2CO_3 (2.70 g, 8.29 mmol, 80.0 eq) was added in portion and the yellow-white suspension was stirred for 17 h at RT, after which the reaction mixture was diluted with CH_2Cl_2 (4.0 mL) and quenched with water (15 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 EtOAc : pentane) afforded (*R,E*)-8-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**595**) (31.0 mg, 0.0672 mmol, 64%) as a colourless oil.

R_f (hexane : EtOAc 1 : 1) = 0.58.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.32 – 7.23 (m, 4H, H24 – H27), 7.21 – 7.15 (m, 1H, H28), 6.31 (s, 1H, H7), 5.16 (tq, J = 7.3, 1.3 Hz, 1H, H12), 3.79 (s, 3H, H29), 3.39 – 3.31 (m, 2H, H21), 3.27 (d, J = 7.3 Hz, 2H, H11), 2.94 – 2.87 (m, 2H, H22), 2.67 (t, J = 6.3 Hz, 1H, H17), 2.20 – 2.01 (m, 2H, H15), 1.78 (d, J = 1.3 Hz, 3H, H14), 1.68 (s, 6H, H1 + H3), 1.66 – 1.54 (m, 2H, H16), 1.25 (s, 3H, H19), 1.24 (s, 3H, H20).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.0 (C8), 160.6 (C4), 155.7 (C10), 146.4 (C6), 142.0 (C23), 134.4 (C13), 128.9 (C24 + C25), 128.3 (C26 + C27), 125.9 (C28), 122.4 (C12), 116.0 (C9), 108.2 (C7), 105.4 (C5), 104.7 (C2), 64.2 (C17), 58.4 (C18), 55.8 (C29), 37.5 (C22), 37.4 (C23), 36.5 (C15), 27.5 (C16), 25.9 (C1), 25.8 (C3), 24.9 (C19), 21.9 (C11), 18.8 (C20), 16.2 (C14).

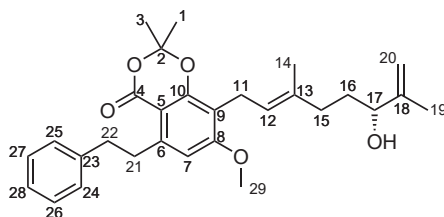
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 2989 (w), 2922 (m), 1724 (vs), 1603 (vs), 1573 (vs), 1453 (m), 1410 (s), 1387 (s), 1333 (s), 1290 (vs), 1267 (vs), 1207 (vs), 1166 (vs), 1118

(vs), 1050 (vs), 982 (m), 908 (m), 699 (s).

HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{29}H_{37}O_5)^+$: 465.2636, found: 465.2629. Major peak m/z : $[M - \text{acetone} + H]^+$ calc. for $(C_{26}H_{31}O_4)^+$: 407.2217, found: 407.2212.

Optical rotation: $[\alpha]_D^{25.4} +1.4^\circ$ ($c = 1.0$, $CHCl_3$).

(*R,E*)-8-(6-HYDROXY-3,7-DIMETHYLOCTA-2,7-DIEN-1-YL)-7-METHOXY-2,2-DIMETHYL-5-PHENETHYL-4*H*-BENZO[*D*][1,3]DIOXIN-4-ONE (**596**)



To a solution of (*R,E*)-8-(5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**595**) (31.0 mg, 0.0667 mmol, 1.00 eq) in PhMe (1.00 mL) and *tert*-BuOH (0.30 mL) was added aluminium triisopropoxide (27.0 mg, 0.133 mmol, 2.00 eq) in one portion. The resulting suspension was stirred for 23 h at 110 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 15 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and a saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (15 : 85 EtOAc : pentane) afforded (*R,E*)-8-(6-Hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**596**) (25.0 mg, 0.0538 mmol, 81%) as a colourless oil.

R_f (hexane : EtOAc 4 : 1) = 0.27.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 7.30 – 7.24 (m, 4H, H24 – H27), 7.18 (pd, J = 5.7, 2.5 Hz, 1H, H28), 6.30 (s, 1H, H7), 5.15 (tq, J = 7.3, 1.3 Hz, 1H, H12), 4.89 (dq, J = 3.1, 2.0, 1.5 Hz, 1H, H20*trans*), 4.81 (p, J = 1.6 Hz, 1H, H20*cis*), 4.01 (t, J = 6.4 Hz, 1H, H17), 3.78 (s, 3H, H29), 3.38 – 3.31 (m, 2H, H21), 3.26 (d, J = 7.3 Hz, 2H, H11), 2.94 – 2.87 (m, 2H H22), 2.10 – 1.92 (m, 2H, H15), 1.77 (d, J = 1.4 Hz, 3H, H14), 1.71 (t, J = 1.2 Hz, 3H, H19), 1.67 (s, 6H, H1 + H3), 1.66 – 1.58 (m, 2H, H16).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 162.1 (C8), 160.7 (C4), 155.8 (C10), 147.6 (C18), 146.3 (C6), 142.0 (C23), 135.1 (C13), 128.9 (C24 + C25), 128.4 (C26 + C27), 125.9 (C28), 122.3 (C12), 116.1 (C9), 111.1 (C20), 108.3 (C7), 105.4 (C5), 104.7 (C2), 75.8 (C17), 55.8 (C29), 37.5 (C22), 37.4 (C21), 35.9 (C15), 33.2 (C16), 25.9 (C1), 25.9 (C3), 21.9 (C11), 17.8 (C19), 16.2 (C14).

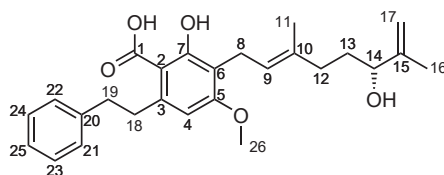
IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3445 (br, s), 2935 (m), 1723 (vs), 1603 (vs), 1573 (vs), 1452 (s), 1410 (s), 1388 (s), 1375 (s), 1334 (s), 1290 (vs), 1267 (vs), 1208 (vs), 1168

(vs), 1118 (vs), 1051 (s), 984 (m), 906 (m), 699 (s). .

HRMS (APCI) m/z : $[M + H]^+$ calc. for $(C_{29}H_{37}O_5)^+$: 465.2636, found: 465.2618. Major peak m/z : $[M - \text{acetone} + H]^+$ calc. for $(C_{26}H_{31}O_4)^+$: 407.2217, found: 407.2199.

Optical rotation: $[\alpha]_D^{26.1} +11.2^\circ$ ($c = 1.0$, $CHCl_3$).

(*R,E*)-2-HYDROXY-3-(6-HYDROXY-3,7-DIMETHYLOCTA-2,7-DIEN-1-YL)-4-METHOXY-6-PHENETHYLBENZOIC ACID ((*R*)-AMORFRUTIN D) (**522**)



To a solution of (*R,E*)-8-(6-Hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-7-methoxy-2,2-dimethyl-5-phenethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**596**) (24.0 mg, 0.0517 mmol, 1.00 eq) in DMSO (0.30 mL) was added aqueous KOH (48 vol%; 0.30 mL) in one portion. The resulting orange biphasic reaction mixture was stirred for 17 h at 80 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and quenched with an aqueous hydrochloric acid solution (1 M; 10 mL). An aqueous lithium chloride solution (10 w/v-%; 25 mL) was added and the solution was stirred for 2 h. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 x 8.0 mL). The combined organic layers were washed with a saturated aqueous sodium chloride solution (15 mL), the washed solution was dried over magnesium sulphate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (3 : 7 EtOAc : pentane) afforded (*R,E*)-2-hydroxy-3-(6-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)-4-methoxy-6-phenethylbenzoic acid ((*R*)-Amorfrutin D) (**522**) (20.0 mg, 0.0471 mmol, 92%) as a white film.

R_f (hexane : EtOAc 7 : 3) = 0.09.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 11.67 (s, 1H, OH), 7.31 – 7.26 (m, 2H, H₂₃ + H₂₄), 7.19 (ddd, J = 7.4, 3.7, 2.4 Hz, 3H, H₂₁ + H₂₂ + H₂₅ overlapping), 6.20 (s, 1H, H₄), 5.26 (tq, J = 7.1, 1.4 Hz, 1H, H₉), 4.89 (dt, J = 1.9, 1.0 Hz, 1H, H_{17trans}), 4.81 (p, J = 1.6 Hz, 1H, H_{17cis}), 4.08 – 4.01 (m, 1H, H₁₄), 3.78 (s, 3H, H₂₆), 3.36 (d, J = 7.1 Hz, 2H, H₈), 3.30 – 3.21 (m, 2H, H₁₈), 2.97 – 2.88 (m, 2H, H₁₉), 2.03 (hept, J = 7.0 Hz, 2H, H₁₂), 1.80 (d, J = 1.3 Hz, 3H, H₁₁), 1.71 (t, J = 1.2 Hz, 3H, H₁₆), 1.67 (dtd, J = 8.3, 6.9, 4.6 Hz, 2H, H₁₃).

$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$ (101 MHz, CDCl_3): δ (ppm) = 175.5 (C₁), 163.0 (C₇), 162.2 (C₅), 147.4 (C₁₅), 145.9 (C₃), 142.1 (C₂₀), 135.0 (C₁₀), 128.7 (C₂₁ + C₂₂), 128.5 (C₂₃ + C₂₄), 126.1 (C₂₅), 123.1 (C₉), 115.3 (C₆), 111.1 (C₁₇), 106.5 (C₄), 104.0 (C₂), 76.1 (C₁₄), 55.7 (C₂₆), 39.3 (C₁₈), 38.3 (C₁₉), 36.1 (C₁₂), 33.1 (C₁₃), 22.1 (C₈), 17.9 (C₁₆), 16.2 (C₁₁).

IR (Diamond-ATR, neat) ν_{max} (cm^{-1}) = 3488 (br, s), 1935 (m), 1635 (s), 1607 (vs), 1571 (s), 1496 (m), 1452 (s), 1403 (s), 1265 (vs), 1225 (vs), 1169 (s), 1113 (vs), 699 (m).

HRMS (ES-ToF) m/z : $[M - H]^-$ calc. for $(C_{26}H_{31}O_5)^-$: 423.2177, found: 423.2186.

Optical rotation: $[\alpha]_D^{25.7} +2.1^\circ$ ($c = 0.4$, acetone).

Analytic data were in good agreement with literature values.^[382,407]

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Part IV

APPENDIX



CRYSTALLOGRAPHY DATA

Formula	$C_{24}H_{30}O_4$
Formula weight	382.48
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 13.4421(4) \text{ Å}$, $\alpha = 90^\circ$ $b = 10.4766(3) \text{ Å}$, $\beta = 107.755(4)^\circ$ $c = 14.8019(5) \text{ Å}$, $\gamma = 90^\circ$
Volume, Z	$1985.22(11) \text{ Å}^3$, 4
Density (calculated)	1.280 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F (ooo)	824
Crystal colour / morphology	Colourless / hexagonal blocks
Crystal size	$0.401 \times 0.305 \times 0.137 \text{ mm}^3$
θ range for data collection	2.512 to 28.281°
Index ranges	$-17 \leq h \leq 17$, $-13 \leq k \leq 13$, $-19 \leq l \leq 17$
Reflns collected / unique	11297 / 4185 [$R(\text{int}) = 0.0258$]
Reflns observed [$F > 4\sigma(F)$]	3320
Absorption correction	Analytical
Max. and min. transmission	0.989 and 0.976
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4185 / 0 / 259
Goodness-of-fit on F^2	1.028
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0421$, $wR_2 = 0.0955$
R indices (all data)	$R_1 = 0.0577$, $wR_2 = 0.1045$
Largest diff. peak, hole	0.282 , -0.190 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.000

Table 9: Crystal data and structure refinement for resorcylate (292).

O(1)-C(1)	1.2048(17)	C(6)-C(7)-C(8)	110.86(11)
C(1)-O(2)	1.3638(18)	C(7)-C(8)-C(17)	110.25(11)
C(1)-C(22)	1.4711(19)	C(7)-C(8)-C(9)	115.18(11)
O(2)-C(3)	1.4368(17)	C(17)-C(8)-C(9)	114.78(11)
C(3)-O(4)	1.4304(16)	C(10)-C(9)-C(25)	107.88(11)
C(3)-C(24)	1.501(2)	C(10)-C(9)-C(14)	106.54(11)
C(3)-C(23)	1.509(2)	C(25)-C(9)-C(14)	111.84(11)
O(4)-C(5)	1.3699(16)	C(10)-C(9)-C(8)	110.10(11)
C(5)-C(6)	1.3933(18)	C(25)-C(9)-C(8)	113.66(11)
C(5)-C(22)	1.3999(19)	C(14)-C(9)-C(8)	106.60(11)
C(6)-C(19)	1.3903(19)	C(11)-C(10)-C(9)	113.16(12)
C(6)-C(7)	1.5031(19)	C(12)-C(11)-C(10)	113.56(13)
C(7)-C(8)	1.5322(17)	C(13)-C(12)-C(11)	123.85(14)
C(8)-C(17)	1.5441(19)	C(12)-C(13)-C(14)	121.85(13)
C(8)-C(9)	1.5501(18)	C(13)-C(14)-C(15)	114.29(11)
C(9)-C(10)	1.5378(19)	C(13)-C(14)-C(9)	111.98(12)
C(9)-C(25)	1.5410(18)	C(15)-C(14)-C(9)	111.90(11)
C(9)-C(14)	1.5476(18)	C(14)-C(15)-C(16)	110.01(11)
C(10)-C(11)	1.535(2)	C(15)-C(16)-C(17)	111.89(11)
C(11)-C(12)	1.492(2)	O(18)-C(17)-C(26)	106.16(11)
C(12)-C(13)	1.326(2)	O(18)-C(17)-C(16)	103.91(10)
C(13)-C(14)	1.501(2)	C(26)-C(17)-C(16)	111.28(12)
C(14)-C(15)	1.5243(19)	O(18)-C(17)-C(8)	107.19(10)
C(15)-C(16)	1.5254(19)	C(26)-C(17)-C(8)	116.44(11)
C(16)-C(17)	1.5254(18)	C(16)-C(17)-C(8)	110.89(11)
C(17)-O(18)	1.4712(16)	C(19)-O(18)-C(17)	116.09(10)
C(17)-C(26)	1.524(2)	O(18)-C(19)-C(6)	121.89(12)
O(18)-C(19)	1.3676(16)	O(18)-C(19)-C(20)	116.09(12)
C(19)-C(20)	1.392(2)	C(6)-C(19)-C(20)	121.99(13)
C(20)-C(21)	1.381(2)	C(21)-C(20)-C(19)	121.69(13)
C(21)-C(22)	1.410(2)	C(20)-C(21)-C(22)	117.89(12)
C(21)-C(27)	1.506(2)	C(20)-C(21)-C(27)	118.62(13)
		C(22)-C(21)-C(27)	123.48(13)
O(1)-C(1)-O(2)	117.43(13)	C(5)-C(22)-C(21)	119.08(12)
O(1)-C(1)-C(22)	126.39(14)	C(5)-C(22)-C(1)	117.93(13)
O(2)-C(1)-C(22)	116.04(12)	C(5)-C(6)-C(7)	121.88(12)
C(1)-O(2)-C(3)	118.97(11)	C(19)-C(6)-C(7)	122.23(12)
O(4)-C(3)-O(2)	109.26(12)	C(19)-C(6)-C(5)	115.87(12)
O(4)-C(3)-C(24)	106.47(12)	C(6)-C(5)-C(22)	123.45(13)
O(2)-C(3)-C(24)	106.54(12)	O(4)-C(5)-C(22)	120.37(12)
O(4)-C(3)-C(23)	110.94(12)	O(4)-C(5)-C(6)	116.17(12)
O(2)-C(3)-C(23)	109.82(12)	C(5)-O(4)-C(3)	114.30(10)
C(24)-C(3)-C(23)	113.61(14)	C(21)-C(22)-C(1)	122.89(13)

Table 10: Bond lengths [Å] and angles [°] for resorcyate (292).

Formula	$C_{24}H_{29}BrO_5$
Formula weight	477.38
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 15.4274(7) \text{ Å}, \alpha = 90^\circ$ $b = 11.0346(7) \text{ Å}, \beta = 95.974(5)^\circ$ $c = 12.7981(8) \text{ Å}, \gamma = 90^\circ$
Volume, Z	$2166.9(2) \text{ Å}^3, 4$
Density (calculated)	1.463 Mg/m^3
Absorption coefficient	1.930 mm^{-1}
F (000)	992
Crystal colour / morphology	Colourless / shards
Crystal size	$0.437 \times 0.229 \times 0.119 \text{ mm}^3$
θ range for data collection	2.443 to 28.337°
Index ranges	$-20 \leq h \leq 18, -8 \leq k \leq 14, -9 \leq l \leq 15$
Reflns collected / unique	7314 / 4357 [R(int) = 0.0211]
Reflns observed [$F > 4\sigma(F)$]	3204
Absorption correction	Analytical
Max. and min. transmission	0.837 and 0.606
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4357 / 68 / 303
Goodness-of-fit on F^2	1.028
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0459, wR_2 = 0.1080$
R indices (all data)	$R_1 = 0.0708, wR_2 = 0.1207$
Largest diff. peak, hole	$1.198, -0.561 \text{ eÅ}^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 11: Crystal data and structure refinement for bromoepoxides (**329**), (**330**) and (**331**).

O(1)-C(1)	1.205(4)	C(25)-C(9)-C(14)	111.2(3)
C(1)-O(2)	1.354(4)	C(8)-C(9)-C(14)	107.3(3)
C(1)-C(22)	1.474(4)	C(9)-C(10)-C(11)	110.5(4)
O(2)-C(3)	1.443(4)	C(9)-C(10)-C(11')	123.8(10)
C(3)-O(4)	1.432(3)	C(9)-C(10)-C(11'')	120(2)
C(3)-C(24)	1.499(5)	C(12)-C(11)-C(10)	117.1(5)
C(3)-C(23)	1.508(5)	O(26)-C(12)-C(13)	59.9(3)
O(4)-C(5)	1.365(4)	O(26)-C(12)-C(11)	119.2(7)
C(5)-C(22)	1.396(4)	C(13)-C(12)-C(11)	118.8(7)
C(5)-C(6)	1.397(4)	O(26')-C(11')-C(12')	59.4(8)
C(6)-C(19)	1.389(4)	O(26')-C(11')-C(10)	114.9(15)
C(6)-C(7)	1.508(4)	C(12')-C(11')-C(10)	110(2)
C(7)-C(8)	1.544(4)	O(26')-C(12')-C(11')	58.7(8)
C(8)-C(17)	1.538(5)	O(26')-C(12')-C(13)	131(2)
C(8)-C(9)	1.552(5)	C(11')-C(12')-C(13)	125(3)
C(9)-C(10)	1.534(5)	O(26'')-C(11'')-C(12'')	59.1(9)
C(9)-C(25)	1.538(5)	O(26'')-C(11'')-C(10)	130(3)
C(9)-C(14)	1.556(4)	C(12'')-C(11'')-C(10)	110(5)
C(10)-C(11)	1.544(6)	O(26'')-C(12'')-C(13)	110(2)
C(10)-C(11')	1.547(15)	O(26'')-C(12'')-C(11'')	59.3(9)
C(10)-C(11'')	1.547(17)	C(13)-C(12'')-C(11'')	123(5)
C(11)-C(12)	1.500(9)	O(26)-C(13)-C(12)	59.5(4)
C(12)-O(26)	1.433(8)	O(26)-C(13)-C(14)	113.2(3)
C(12)-C(13)	1.450(8)	C(12)-C(13)-C(14)	120.7(5)
C(11')-O(26')	1.441(16)	C(12'')-C(13)-C(14)	116(3)
C(11')-C(12')	1.486(17)	C(12')-C(13)-C(14)	114.7(13)
C(12')-O(26')	1.450(17)	C(13)-C(14)-C(15)	113.0(3)
C(12')-C(13)	1.501(15)	C(13)-C(14)-C(9)	111.3(3)
C(11'')-O(26'')	1.445(18)	C(15)-C(14)-C(9)	113.1(3)
C(11'')-C(12'')	1.479(18)	C(14)-C(15)-C(16)	109.9(3)
C(12'')-O(26'')	1.443(18)	C(15)-C(16)-C(17)	111.2(3)
C(12'')-C(13)	1.476(17)	O(18)-C(17)-C(27)	107.2(3)
C(13)-O(26)	1.440(5)	O(18)-C(17)-C(16)	103.4(3)
C(13)-C(14)	1.508(5)	C(27)-C(17)-C(16)	111.3(3)
C(14)-C(15)	1.512(5)	O(18)-C(17)-C(8)	106.2(3)
C(15)-C(16)	1.525(5)	C(27)-C(17)-C(8)	116.4(3)
C(16)-C(17)	1.527(4)	C(16)-C(17)-C(8)	111.2(3)
C(17)-O(18)	1.474(4)	C(19)-O(18)-C(17)	115.7(2)
C(17)-C(27)	1.524(5)	O(18)-C(19)-C(6)	121.6(3)
O(18)-C(19)	1.359(4)	O(18)-C(19)-C(20)	116.9(3)
C(19)-C(20)	1.402(5)	C(6)-C(19)-C(20)	121.4(3)
Br(20)-C(20)	1.893(3)	C(21)-C(20)-C(19)	122.1(3)
C(20)-C(21)	1.387(4)	C(21)-C(20)-Br(20)	121.1(3)
C(21)-C(22)	1.417(5)	C(19)-C(20)-Br(20)	116.8(2)
C(21)-C(28)	1.501(5)	C(20)-C(21)-C(22)	116.7(3)
		C(20)-C(21)-C(28)	120.8(3)
O(1)-C(1)-O(2)	118.2(3)	C(22)-C(21)-C(28)	122.5(3)
O(1)-C(1)-C(22)	126.1(3)	C(5)-C(22)-C(21)	120.1(3)
O(2)-C(1)-C(22)	115.5(3)	C(5)-C(22)-C(1)	117.4(3)
C(1)-O(2)-C(3)	119.3(2)	C(21)-C(22)-C(1)	122.2(3)
O(4)-C(3)-O(2)	108.6(2)	C(12)-O(26)-C(13)	60.6(4)
O(4)-C(3)-C(24)	106.6(3)	C(11')-O(26')-C(12')	61.9(10)
O(2)-C(3)-C(24)	106.5(2)	C(12'')-O(26'')-C(11'')	61.6(11)
O(4)-C(3)-C(23)	111.3(3)	C(10)-C(9)-C(25)	109.7(3)
O(2)-C(3)-C(23)	109.8(3)	C(10)-C(9)-C(8)	109.0(3)
C(24)-C(3)-C(23)	113.7(3)	C(25)-C(9)-C(8)	113.2(3)
C(5)-O(4)-C(3)	114.3(2)	C(10)-C(9)-C(14)	106.1(3)
O(4)-C(5)-C(22)	120.7(3)	C(22)-C(5)-C(6)	122.9(3)
O(4)-C(5)-C(6)	116.4(3)	C(19)-C(6)-C(5)	116.2(3)
C(5)-C(6)-C(7)	121.6(3)	C(19)-C(6)-C(7)	122.2(3)
C(6)-C(7)-C(8)	110.5(3)	C(17)-C(8)-C(7)	108.9(3)
C(7)-C(8)-C(9)	115.1(3)	C(17)-C(8)-C(9)	115.9(3)

Table 12: Bond lengths [Å] and angles [°] for bromoepoxides (329), (330) and (331).

Formula	$C_{24}H_{31}IO_5$
Formula weight	526.39
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, Cc
Unit cell dimensions	$a = 21.5208(8) \text{ Å}, \alpha = 90^\circ$ $b = 7.2834(3) \text{ Å}, \beta = 92.507(3)^\circ$ $c = 14.3068(4) \text{ Å}, \gamma = 90^\circ$
Volume, Z	$2240.36(13) \text{ Å}^3, 4$
Density (calculated)	1.561 Mg/m^3
Absorption coefficient	1.462 mm^{-1}
F (000)	1072
Crystal colour / morphology	Colourless / plates
Crystal size	$0.414 \times 0.267 \times 0.139 \text{ mm}^3$
θ range for data collection	2.850 to 28.227°
Index ranges	$-19 \leq h \leq 28, -6 \leq k \leq 9, -14 \leq l \leq 17$
Reflns collected / unique	3917 / 2861 [R(int) = 0.0202]
Reflns observed [$F > 4\sigma(F)$]	2634
Absorption correction	Analytical
Max. and min. transmission	0.869 and 0.718
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2861 / 3 / 280
Goodness-of-fit on F^2	1.049
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0249, wR_2 = 0.05895$
R indices (all data)	$R_1 = 0.0284, wR_2 = 0.06175$
Absolute structure parameter	-0.03(2)
Largest diff. peak, hole	$0.319, -0.355 \text{ eÅ}^{-3}$
Mean and maximum shift/error	0.000 and 0.001

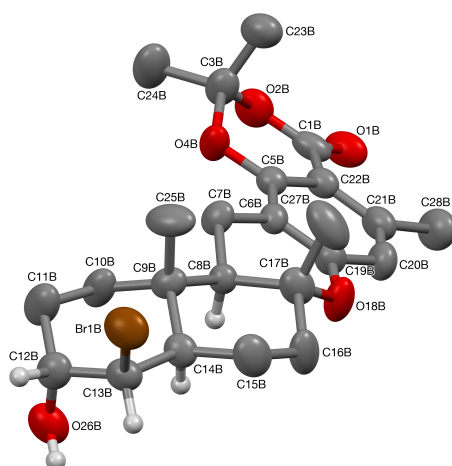
Table 13: Crystal data and structure refinement for iodohydrin (348).

I(1)-C(13)	2.187(4)	O(4)-C(5)-C(22)	120.5(4)
C(1)-O(1)	1.218(6)	C(6)-C(5)-C(22)	123.0(4)
C(1)-O(2)	1.361(6)	C(19)-C(6)-C(5)	116.1(4)
C(1)-C(22)	1.454(6)	C(19)-C(6)-C(7)	121.7(4)
O(2)-C(3)	1.449(6)	C(5)-C(6)-C(7)	122.2(4)
C(3)-O(4)	1.421(6)	C(6)-C(7)-C(8)	111.2(4)
C(3)-C(23)	1.496(7)	C(7)-C(8)-C(17)	110.1(3)
C(3)-C(24)	1.496(7)	C(7)-C(8)-C(9)	115.7(4)
O(4)-C(5)	1.369(5)	C(17)-C(8)-C(9)	114.0(3)
C(5)-C(6)	1.394(5)	C(25)-C(9)-C(10)	108.2(4)
C(5)-C(22)	1.400(5)	C(25)-C(9)-C(8)	112.8(3)
C(6)-C(19)	1.384(6)	C(10)-C(9)-C(8)	109.2(3)
C(6)-C(7)	1.508(6)	C(25)-C(9)-C(14)	113.8(3)
C(7)-C(8)	1.527(6)	C(10)-C(9)-C(14)	107.2(3)
C(8)-C(17)	1.542(6)	C(8)-C(9)-C(14)	105.5(3)
C(8)-C(9)	1.553(5)	C(11)-C(10)-C(9)	111.9(4)
C(9)-C(25)	1.541(6)	C(12)-C(11)-C(10)	112.4(4)
C(9)-C(10)	1.549(6)	O(26)-C(12)-C(11)	110.0(4)
C(9)-C(14)	1.556(6)	O(26)-C(12)-C(13)	106.0(4)
C(10)-C(11)	1.531(6)	C(11)-C(12)-C(13)	111.2(4)
C(11)-C(12)	1.512(7)	C(12)-C(13)-C(14)	113.3(4)
C(12)-O(26)	1.435(6)	C(12)-C(13)-I(1)	109.0(3)
C(12)-C(13)	1.512(7)	C(14)-C(13)-I(1)	115.7(3)
C(13)-C(14)	1.516(6)	C(13)-C(14)-C(15)	114.3(4)
C(14)-C(15)	1.517(7)	C(13)-C(14)-C(9)	116.7(4)
C(15)-C(16)	1.528(6)	C(15)-C(14)-C(9)	111.7(3)
C(16)-C(17)	1.525(6)	C(14)-C(15)-C(16)	110.4(3)
C(17)-O(18)	1.452(5)	C(17)-C(16)-C(15)	112.6(4)
C(17)-C(27)	1.527(6)	O(18)-C(17)-C(16)	102.9(4)
O(18)-C(19)	1.356(6)	O(18)-C(17)-C(27)	106.1(3)
C(19)-C(20)	1.396(7)	C(16)-C(17)-C(27)	111.9(4)
C(20)-C(21)	1.377(7)	O(18)-C(17)-C(8)	108.6(4)
C(21)-C(22)	1.407(7)	C(16)-C(17)-C(8)	109.9(3)
C(21)-C(28)	1.501(7)	C(27)-C(17)-C(8)	116.5(4)
		C(19)-O(18)-C(17)	116.7(3)
O(1)-C(1)-O(2)	117.1(5)	O(18)-C(19)-C(6)	122.3(4)
O(1)-C(1)-C(22)	126.1(5)	O(18)-C(19)-C(20)	115.7(4)
O(2)-C(1)-C(22)	116.7(4)	C(6)-C(19)-C(20)	122.0(4)
C(1)-O(2)-C(3)	118.4(4)	C(21)-C(20)-C(19)	121.4(4)
O(4)-C(3)-O(2)	108.7(4)	C(20)-C(21)-C(22)	118.1(4)
O(4)-C(3)-C(23)	110.9(4)	C(20)-C(21)-C(28)	118.5(5)
O(2)-C(3)-C(23)	110.0(4)	C(22)-C(21)-C(28)	123.3(4)
O(4)-C(3)-C(24)	106.9(4)	C(5)-C(22)-C(21)	119.2(4)
O(2)-C(3)-C(24)	105.9(4)	C(5)-C(22)-C(1)	117.7(4)
C(23)-C(3)-C(24)	114.2(4)	C(21)-C(22)-C(1)	122.9(4)
C(5)-O(4)-C(3)	114.9(3)	O(4)-C(5)-C(6)	116.4(4)

Table 14: Bond lengths [$\text{\AA}$] and angles [$^\circ$] for iodohydrin (348).

Formula	$C_{24}H_{31}BrO_5 \cdot 0.5 C_5H_{12}$
Formula weight	515.47
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.541 84 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 12.6906(11) \text{ Å}$, $\alpha = 107.196(8)^\circ$ $b = 13.5110(11) \text{ Å}$, $\beta = 107.637(8)^\circ$ $c = 16.5909(14) \text{ Å}$, $\gamma = 98.387(7)^\circ$
Volume, Z	$2501.7(4) \text{ Å}^3$, 4
Density (calculated)	1.369 Mg/m^3
Absorption coefficient	2.515 mm^{-1}
F (000)	1084
Crystal colour / morphology	Colourless / shards
Crystal size	$0.173 \times 0.098 \times 0.008 \text{ mm}^3$
θ range for data collection	3.545 to 73.504°
Index ranges	$-15 \leq h \leq 15$, $-16 \leq k \leq 16$, $-20 \leq l \leq 13$
Reflns collected / unique	14764 / 9510 [R(int) = 0.0658]
Reflns observed [$F > 4\sigma(F)$]	4997
Absorption correction	Analytical
Max. and min. transmission	0.980 and 0.777
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9510 / 125 / 635
Goodness-of-fit on F^2	0.996
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0718$, $wR_2 = 0.1804$
R indices (all data)	$R_1 = 0.1356$, $wR_2 = 0.2310$
Largest diff. peak, hole	0.688 , -0.747 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.005

Table 15: Crystal data and structure refinement for bromohydrin (366).

Figure 23: X-Ray crystal structure of bromohydrin (366). Reprinted (adapted) with permission from *J. Org. Chem.* **2021**, 86, 1802-1817. Copyright 2021 American Chemical Society. Note this is only one of two independent molecules that crystallized in the asymmetric unit. Please see figure 5 for the second structure.

Br(1A)-C(13A)	1.982(5)	O(1B)-C(1B)	1.202(7)
Br(1C)-C(13A)	2.014(9)	O(1B)-C(1B)	1.202(7)
O(1A)-C(1A)	1.216(7)	C(1B)-O(2B)	1.370(8)
C(1A)-O(2A)	1.350(8)	C(1B)-C(22B)	1.457(8)
C(1A)-C(22A)	1.464(8)	O(2B)-C(3B)	1.437(7)
O(2A)-C(3A)	1.440(7)	C(3B)-O(4B)	1.428(7)
C(3A)-O(4A)	1.423(7)	C(3B)-C(23B)	1.491(10)
C(3A)-C(23A)	1.497(10)	C(3B)-C(24B)	1.507(9)
C(3A)-C(24A)	1.502(9)	O(4B)-C(5B)	1.375(7)
O(4A)-C(5A)	1.376(7)	C(5B)-C(6B)	1.400(7)
C(5A)-C(6A)	1.390(7)	C(5B)-C(22B)	1.404(7)
C(5A)-C(22A)	1.392(7)	C(6B)-C(19B)	1.383(8)
C(6A)-C(19A)	1.375(8)	C(6B)-C(7B)	1.500(7)
C(6A)-C(7A)	1.510(7)	C(7B)-C(8B)	1.527(7)
C(7A)-C(8A)	1.531(7)	C(8B)-C(9B)	1.548(7)
C(8A)-C(17A)	1.523(8)	C(8B)-C(17B)	1.550(8)
C(8A)-C(9A)	1.568(7)	C(9B)-C(10B)	1.530(9)
C(9A)-C(25A)	1.529(8)	C(9B)-C(14B)	1.536(8)
C(9A)-C(10A)	1.537(9)	C(9B)-C(25B)	1.541(8)
C(9A)-C(14A)	1.558(8)	C(10B)-C(11B)	1.533(8)
C(10A)-C(11A)	1.539(8)	C(11B)-C(12B)	1.516(9)
C(11A)-C(12A)	1.518(9)	C(12B)-O(26B)	1.417(8)
C(12A)-O(26A)	1.418(7)	C(12B)-C(13B)	1.519(9)
C(12A)-C(13A)	1.533(9)	C(13B)-C(14B)	1.533(7)
C(13A)-C(14A)	1.538(8)	C(14B)-C(15B)	1.535(9)
C(14A)-C(15A)	1.502(9)	C(15B)-C(16B)	1.510(9)
C(15A)-C(16A)	1.541(10)	C(16B)-C(17B)	1.547(9)
C(16A)-C(17A)	1.533(8)	C(17B)-O(18B)	1.469(7)
C(17A)-O(18A)	1.456(8)	C(17B)-C(27B)	1.516(10)
C(17A)-C(27A)	1.514(9)	O(18B)-C(19B)	1.368(7)
O(18A)-C(19A)	1.365(7)	C(19B)-C(20B)	1.389(8)
C(19A)-C(20A)	1.383(8)	C(20B)-C(21B)	1.372(9)
C(20A)-C(21A)	1.381(9)	C(21B)-C(22B)	1.396(9)
C(21A)-C(22A)	1.404(9)	C(21B)-C(28B)	1.515(8)
C(21A)-C(28A)	1.516(8)	C(31)-C(32)	1.471(16)
Br(1B)-C(13B)	1.995(6)	C(32)-C(33)	1.481(16)
Br(1D)-C(13B)	2.051(8)	C(33)-C(34)	1.565(16)
C(34)-C(35)	1.489(15)	C(32')-C(33')	1.478(16)
C(31')-C(32')	1.511(16)	C(33')-C(34')	1.533(16)
C(34')-C(35')	1.502(15)		

Table 16: Bond lengths [Å] for bromohydrin (366).

O(1A)-C(1A)-O(2A)	117.6(5)	O(1B)-C(1B)-O(2B)	116.8(5)
O(1A)-C(1A)-C(22A)	125.2(6)	O(1B)-C(1B)-C(22B)	126.8(6)
O(2A)-C(1A)-C(22A)	117.2(5)	O(2B)-C(1B)-C(22B)	116.3(5)
C(1A)-O(2A)-C(3A)	119.3(4)	C(1B)-O(2B)-C(3B)	119.0(4)
O(4A)-C(3A)-O(2A)	110.1(5)	O(4B)-C(3B)-O(2B)	110.0(5)
O(4A)-C(3A)-C(23A)	111.1(5)	O(4B)-C(3B)-C(23B)	111.9(5)
O(2A)-C(3A)-C(23A)	109.9(5)	O(2B)-C(3B)-C(23B)	110.2(5)
O(4A)-C(3A)-C(24A)	106.3(5)	O(4B)-C(3B)-C(24B)	105.4(5)
O(2A)-C(3A)-C(24A)	106.1(5)	O(2B)-C(3B)-C(24B)	106.2(5)
C(23A)-C(3A)-C(24A)	113.3(6)	C(23B)-C(3B)-C(24B)	112.9(6)
C(5A)-O(4A)-C(3A)	115.1(4)	C(5B)-O(4B)-C(3B)	115.3(4)
O(4A)-C(5A)-C(6A)	115.7(5)	O(4B)-C(5B)-C(6B)	115.8(5)
O(4A)-C(5A)-C(22A)	120.3(5)	O(4B)-C(5B)-C(22B)	120.4(5)
C(6A)-C(5A)-C(22A)	123.8(5)	C(6B)-C(5B)-C(22B)	123.8(5)
C(19A)-C(6A)-C(5A)	115.9(5)	C(19B)-C(6B)-C(5B)	115.0(5)
C(19A)-C(6A)-C(7A)	121.6(5)	C(19B)-C(6B)-C(7B)	121.9(5)
C(5A)-C(6A)-C(7A)	122.5(5)	C(5B)-C(6B)-C(7B)	123.0(5)
C(6A)-C(7A)-C(8A)	109.7(5)	C(6B)-C(7B)-C(8B)	110.7(5)
C(17A)-C(8A)-C(7A)	110.3(5)	C(7B)-C(8B)-C(9B)	115.6(4)
C(17A)-C(8A)-C(9A)	116.1(4)	C(7B)-C(8B)-C(17B)	109.3(5)
C(7A)-C(8A)-C(9A)	114.1(5)	C(9B)-C(8B)-C(17B)	114.9(4)
C(25A)-C(9A)-C(10A)	109.4(6)	C(10B)-C(9B)-C(14B)	106.5(5)
C(25A)-C(9A)-C(14A)	114.3(4)	C(10B)-C(9B)-C(25B)	109.4(5)
C(10A)-C(9A)-C(14A)	106.9(5)	C(14B)-C(9B)-C(25B)	114.6(5)
C(25A)-C(9A)-C(8A)	112.3(5)	C(10B)-C(9B)-C(8B)	108.1(4)
C(10A)-C(9A)-C(8A)	108.9(4)	C(14B)-C(9B)-C(8B)	106.0(4)
C(14A)-C(9A)-C(8A)	104.8(5)	C(25B)-C(9B)-C(8B)	111.9(5)
C(9A)-C(10A)-C(11A)	113.7(5)	C(9B)-C(10B)-C(11B)	113.5(5)
C(12A)-C(11A)-C(10A)	112.0(5)	C(12B)-C(11B)-C(10B)	111.6(5)
O(26A)-C(12A)-C(11A)	106.7(5)	O(26B)-C(12B)-C(11B)	108.1(5)
O(26A)-C(12A)-C(13A)	107.7(5)	O(26B)-C(12B)-C(13B)	108.1(5)
C(11A)-C(12A)-C(13A)	113.5(6)	C(11B)-C(12B)-C(13B)	112.6(6)
C(12A)-C(13A)-C(14A)	114.5(4)	C(12B)-C(13B)-C(14B)	113.3(5)
C(12A)-C(13A)-Br(1A)	108.2(4)	C(12B)-C(13B)-Br(1B)	111.1(4)
C(14A)-C(13A)-Br(1A)	114.4(4)	C(14B)-C(13B)-Br(1B)	112.4(4)
C(12A)-C(13A)-Br(1C)	132.3(6)	C(12B)-C(13B)-Br(1D)	86.1(5)
C(14A)-C(13A)-Br(1C)	102.4(5)	C(14B)-C(13B)-Br(1D)	121.8(5)
C(15A)-C(14A)-C(13A)	114.3(5)	C(13B)-C(14B)-C(15B)	114.6(5)
C(15A)-C(14A)-C(9A)	113.1(5)	C(13B)-C(14B)-C(9B)	116.5(5)
C(13A)-C(14A)-C(9A)	114.5(5)	C(15B)-C(14B)-C(9B)	112.1(5)
C(14A)-C(15A)-C(16A)	109.6(5)	C(16B)-C(15B)-C(14B)	109.9(5)
C(17A)-C(16A)-C(15A)	111.7(6)	C(15B)-C(16B)-C(17B)	111.7(6)
O(18A)-C(17A)-C(27A)	106.6(5)	O(18B)-C(17B)-C(27B)	106.4(5)
O(18A)-C(17A)-C(8A)	107.7(4)	O(18B)-C(17B)-C(16B)	103.1(5)
C(27A)-C(17A)-C(8A)	116.0(6)	C(27B)-C(17B)-C(16B)	112.9(5)
O(18A)-C(17A)-C(16A)	103.2(5)	O(18B)-C(17B)-C(8B)	107.3(4)
C(27A)-C(17A)-C(16A)	111.9(5)	C(27B)-C(17B)-C(8B)	116.8(6)
C(8A)-C(17A)-C(16A)	110.4(5)	C(16B)-C(17B)-C(8B)	109.2(5)
C(19A)-O(18A)-C(17A)	117.7(4)	C(19B)-O(18B)-C(17B)	117.8(5)
O(18A)-C(19A)-C(6A)	122.5(5)	O(18B)-C(19B)-C(6B)	121.9(5)
O(18A)-C(19A)-C(20A)	115.9(5)	O(18B)-C(19B)-C(20B)	115.5(5)
C(6A)-C(19A)-C(20A)	121.6(5)	C(6B)-C(19B)-C(20B)	122.6(5)
C(21A)-C(20A)-C(19A)	122.4(6)	C(21B)-C(20B)-C(19B)	121.4(6)
C(20A)-C(21A)-C(22A)	117.2(5)	C(20B)-C(21B)-C(22B)	118.7(5)
C(20A)-C(21A)-C(28A)	119.3(6)	C(20B)-C(21B)-C(28B)	118.1(6)
C(22A)-C(21A)-C(28A)	123.4(6)	C(22B)-C(21B)-C(28B)	123.2(6)
C(5A)-C(22A)-C(21A)	118.9(5)	C(21B)-C(22B)-C(5B)	118.5(5)
C(5A)-C(22A)-C(1A)	117.8(5)	C(21B)-C(22B)-C(1B)	122.9(5)
C(21A)-C(22A)-C(1A)	123.0(5)	C(5B)-C(22B)-C(1B)	118.5(5)
C(31)-C(32)-C(33)	111.0(16)	C(33')-C(32')-C(31')	106.3(15)
C(32)-C(33)-C(34)	103.3(14)	C(32')-C(33')-C(34')	105.7(15)
C(35)-C(34)-C(33)	104.3(13)	C(35')-C(34')-C(33')	101.9(13)

Table 17: Bond angles [°] for bromohydrin (366).

Formula	$\text{C}_{25}\text{H}_{32}\text{O}_5$
Formula weight	412.50
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.541 84 Å
Crystal system, space group	Orthohomic, $\text{P}2_12_12_1$
Unit cell dimensions	$a = 9.8269(3) \text{ Å}, \alpha = 90^\circ$ $b = 12.5104(4) \text{ Å}, \beta = 90^\circ$ $c = 17.2187(5) \text{ Å}, \gamma = 90^\circ$
Volume, Z	$2116.85(11) \text{ Å}^3, 4$
Density (calculated)	1.294 Mg/m^3
Absorption coefficient	0.0716 mm^{-1}
F (000)	888
Crystal colour / morphology	Colourless / needles
Crystal size	$0.295 \times 0.072 \times 0.046 \text{ mm}^3$
θ range for data collection	4.368 to 73.487°
Index ranges	$-11 \leq h \leq 12, -14 \leq k \leq 15, -20 \leq l \leq 20$
Reflns collected / unique	4526 / 3509 [R(int) = 0.0510]
Reflns observed [$F > 4\sigma(F)$]	2823
Absorption correction	Analytical
Max. and min. transmission	0.970 and 0.878
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3509 / 0 / 278
Goodness-of-fit on F^2	1.051
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0456, wR_2 = 0.1041$
R indices (all data)	$R_1 = 0.0604, wR_2 = 0.1182$
Absolute structure parameter	0.2(3)
Largest diff. peak, hole	$0.210, -0.175 \text{ e Å}^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 18: Crystal data and structure refinement for methyl branched ketone (369).

C(1)-O(1)	1.204(5)	C(5)-O(4)-C(3)	114.9(3)
C(1)-O(2)	1.375(5)	O(4)-C(5)-C(6)	116.0(3)
C(1)-C(22)	1.466(5)	O(4)-C(5)-C(22)	120.2(3)
O(2)-C(3)	1.438(5)	C(6)-C(5)-C(22)	123.8(3)
C(3)-O(4)	1.430(4)	C(5)-C(6)-C(19)	116.6(3)
C(3)-C(24)	1.497(6)	C(5)-C(6)-C(7)	121.8(3)
C(3)-C(23)	1.507(5)	C(19)-C(6)-C(7)	121.6(3)
O(4)-C(5)	1.371(4)	C(6)-C(7)-C(8)	110.8(3)
C(5)-C(6)	1.386(5)	C(7)-C(8)-C(17)	110.0(3)
C(5)-C(22)	1.405(5)	C(7)-C(8)-C(9)	114.7(3)
C(6)-C(19)	1.391(5)	C(17)-C(8)-C(9)	115.3(3)
C(6)-C(7)	1.510(5)	C(25)-C(9)-C(10)	109.1(3)
C(7)-C(8)	1.533(5)	C(25)-C(9)-C(14)	113.8(3)
C(8)-C(17)	1.540(5)	C(10)-C(9)-C(14)	106.2(3)
C(8)-C(9)	1.561(4)	C(25)-C(9)-C(8)	112.5(3)
C(9)-C(25)	1.538(5)	C(10)-C(9)-C(8)	107.4(3)
C(9)-C(10)	1.544(5)	C(14)-C(9)-C(8)	107.5(3)
C(9)-C(14)	1.547(5)	C(9)-C(10)-C(11)	112.6(3)
C(10)-C(11)	1.545(5)	C(12)-C(11)-C(10)	115.9(4)
C(11)-C(12)	1.502(6)	O(12)-C(12)-C(11)	120.2(4)
C(12)-O(12)	1.215(5)	O(12)-C(12)-C(13)	119.5(4)
C(12)-C(13)	1.516(6)	C(11)-C(12)-C(13)	120.2(3)
C(13)-C(14)	1.551(5)	C(12)-C(13)-C(14)	112.9(3)
C(13)-C(26)	1.602(5)	C(12)-C(13)-C(26)	109.0(3)
C(14)-C(15)	1.527(5)	C(14)-C(13)-C(26)	116.5(3)
C(15)-C(16)	1.535(5)	C(15)-C(14)-C(9)	113.3(3)
C(16)-C(17)	1.521(5)	C(15)-C(14)-C(13)	112.0(3)
C(17)-O(18)	1.465(4)	C(9)-C(14)-C(13)	114.5(3)
C(17)-C(27)	1.530(5)	C(14)-C(15)-C(16)	110.2(3)
O(18)-C(19)	1.363(4)	C(17)-C(16)-C(15)	111.1(3)
C(19)-C(20)	1.405(5)	O(18)-C(17)-C(16)	103.6(3)
C(20)-C(21)	1.377(6)	O(18)-C(17)-C(27)	106.3(3)
C(21)-C(22)	1.419(6)	C(16)-C(17)-C(27)	111.9(3)
C(21)-C(28)	1.517(5)	O(18)-C(17)-C(8)	108.3(3)
		C(16)-C(17)-C(8)	110.5(3)
O(1)-C(1)-O(2)	117.8(4)	C(27)-C(17)-C(8)	115.5(3)
O(1)-C(1)-C(22)	126.3(4)	C(19)-O(18)-C(17)	116.8(3)
O(2)-C(1)-C(22)	115.8(3)	O(18)-C(19)-C(6)	122.6(3)
C(1)-O(2)-C(3)	118.3(3)	O(18)-C(19)-C(20)	116.0(3)
O(4)-C(3)-O(2)	109.2(3)	C(6)-C(19)-C(20)	121.3(3)
O(4)-C(3)-C(24)	106.3(3)	C(21)-C(20)-C(19)	121.4(3)
O(2)-C(3)-C(24)	106.6(3)	C(20)-C(21)-C(22)	118.8(3)
O(4)-C(3)-C(23)	111.1(3)	C(20)-C(21)-C(28)	119.2(4)
O(2)-C(3)-C(23)	109.8(3)	C(22)-C(21)-C(28)	122.1(4)
C(24)-C(3)-C(23)	113.7(4)	C(5)-C(22)-C(21)	118.1(3)
C(5)-C(22)-C(1)	118.4(4)	C(21)-C(22)-C(1)	123.4(3)

Table 19: Bond lengths [Å] and angles [°] for methyl branched ketone (**369**).

Formula	$C_{22}H_{26}O_4$
Formula weight	354.43
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 15.4832(10)$ Å, $\alpha = 90^\circ$ $b = 15.7813(7)$ Å, $\beta = 93.715(6)^\circ$ $c = 8.0450$ Å, $\gamma = 90^\circ$
Volume, Z	$1961.6(2)$ Å ³ , 4
Density (calculated)	1.200 Mg/m ³
Absorption coefficient	0.081 mm ⁻¹
F (000)	760
Crystal colour / morphology	Colourless / thin plates
Crystal size	$0.650 \times 0.466 \times 0.026$ mm ³
θ range for data collection	2.637 to 28.344°
Index ranges	$-20 \leq h \leq 19$, $-12 \leq k \leq 20$, $-4 \leq l \leq 10$
Reflns collected / unique	7050 / 3982 [R(int) = 0.0320]
Reflns observed [$F > 4\sigma(F)$]	2626
Absorption correction	Analytical
Max. and min. transmission	0.998 and 0.967
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3982 / 1 / 244
Goodness-of-fit on F^2	1.015
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0501$, $wR_2 = 0.1011$
R indices (all data)	$R_1 = 0.0898$, $wR_2 = 0.1189$
Largest diff. peak, hole	$0.188, -0.199$ eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table 20: Crystal data and structure refinement for 1,3-enyne resorcyate (**301a**).

O(1)-C(1)	1.216(2)	O(4)-C(3)-C(11)	106.51(16)
C(1)-O(2)	1.355(2)	O(2)-C(3)-C(11)	105.78(15)
C(1)-C(10)	1.460(2)	O(4)-C(3)-C(12)	111.28(15)
O(2)-C(3)	1.453(2)	O(2)-C(3)-C(12)	110.15(16)
C(3)-O(4)	1.417(2)	C(11)-C(3)-C(12)	113.84(16)
C(3)-C(11)	1.506(3)	C(5)-O(4)-C(3)	114.22(14)
C(3)-C(12)	1.510(3)	O(4)-C(5)-C(6)	116.67(16)
O(4)-C(5)	1.373(2)	O(4)-C(5)-C(10)	119.46(15)
C(5)-C(6)	1.379(2)	C(6)-C(5)-C(10)	123.81(16)
C(5)-C(10)	1.403(2)	C(5)-C(6)-C(7)	116.39(16)
C(6)-C(7)	1.399(2)	C(5)-C(6)-C(13)	120.61(16)
C(6)-C(13)	1.513(2)	C(7)-C(6)-C(13)	123.00(16)
C(7)-O(24)	1.354(2)	O(24)-C(7)-C(8)	122.13(16)
C(7)-C(8)	1.394(2)	O(24)-C(7)-C(6)	116.69(16)
C(8)-C(9)	1.380(2)	C(8)-C(7)-C(6)	121.16(16)
C(9)-C(10)	1.410(2)	C(9)-C(8)-C(7)	121.79(16)
C(9)-C(25)	1.508(2)	C(8)-C(9)-C(10)	118.29(17)
C(13)-C(14)	1.504(3)	C(8)-C(9)-C(25)	119.01(16)
C(14)-C(15)	1.321(3)	C(10)-C(9)-C(25)	122.68(16)
C(15)-C(22)	1.507(3)	C(5)-C(10)-C(9)	118.53(16)
C(15)-C(16)	1.509(3)	C(5)-C(10)-C(1)	117.78(16)
C(16)-C(17)	1.536(3)	C(9)-C(10)-C(1)	123.66(17)
C(17)-C(18)	1.489(3)	C(14)-C(13)-C(6)	113.03(15)
C(18)-C(19)	1.336(3)	C(15)-C(14)-C(13)	127.99(18)
C(19)-C(20)	1.432(3)	C(14)-C(15)-C(22)	124.20(18)
C(19)-C(23)	1.507(3)	C(14)-C(15)-C(16)	120.62(18)
C(20)-C(21)	1.177(3)	C(22)-C(15)-C(16)	115.18(18)
		C(15)-C(16)-C(17)	114.51(18)
O(1)-C(1)-O(2)	116.67(16)	C(18)-C(17)-C(16)	112.21(18)
O(1)-C(1)-C(10)	126.01(17)	C(19)-C(18)-C(17)	127.9(2)
O(2)-C(1)-C(10)	117.26(16)	C(18)-C(19)-C(20)	119.2(2)
C(1)-O(2)-C(3)	118.70(14)	C(18)-C(19)-C(23)	125.5(2)
O(4)-C(3)-O(2)	109.02(14)	C(20)-C(19)-C(23)	115.35(19)
		C(21)-C(20)-C(19)	177.5(3)

Table 21: Bond lengths [$\text{\AA}$] and angles [$^\circ$] for 1,3-enyne resorcyate (**301a**).

Formula	$C_{22}H_{27}Br_{2.18}Cl_{0.82}O_5$
Formula weight	574.71
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	$a = 10.5862(3) \text{ Å}$, $\alpha = 90^\circ$ $b = 11.7691(4) \text{ Å}$, $\beta = 96.285(3)^\circ$ $c = 18.9783(6) \text{ Å}$, $\gamma = 90^\circ$
Volume, Z	$2350.31(14) \text{ Å}^3$, 4
Density (calculated)	1.624 Mg/m^3
Absorption coefficient	3.878 mm^{-1}
F (000)	1157
Crystal colour / morphology	Colourless / blocks
Crystal size	$0.193 \times 0.175 \times 0.097 \text{ mm}^3$
θ range for data collection	2.596 to 28.295°
Index ranges	$-13 \leq h \leq 14$, $-15 \leq k \leq 14$, $-24 \leq l \leq 22$
Reflns collected / unique	23089 / 5148 [$R(\text{int}) = 0.0597$]
Reflns observed [$F > 4\sigma(F)$]	3460
Absorption correction	Analytical
Max. and min. transmission	0.775 and 0.616
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5148 / 2 / 287
Goodness-of-fit on F^2	1.040
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0534$, $wR_2 = 0.1124$
R indices (all data)	$R_1 = 0.0951$, $wR_2 = 0.1307$
Largest diff. peak, hole	0.753 , -0.659 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.000

Table 22: Crystal data and structure refinement for polyhalogenated products (404).

O(1)-C(1)	1.208(5)	C(5)-O(4)-C(3)	115.3(3)
C(1)-O(2)	1.375(5)	O(4)-C(5)-C(6)	115.9(4)
C(1)-C(14)	1.467(6)	O(4)-C(5)-C(14)	120.4(4)
O(2)-C(3)	1.453(5)	C(6)-C(5)-C(14)	123.7(4)
C(3)-O(4)	1.426(5)	C(5)-C(6)-C(11)	116.4(4)
C(3)-C(15)	1.498(6)	C(5)-C(6)-C(7)	122.0(4)
C(3)-C(16)	1.507(7)	C(11)-C(6)-C(7)	121.6(4)
O(4)-C(5)	1.374(5)	C(6)-C(7)-C(8)	110.0(4)
C(5)-C(6)	1.382(6)	C(7)-C(8)-C(9)	111.3(4)
C(5)-C(14)	1.401(6)	C(7)-C(8)-Br(8)	107.6(3)
C(6)-C(11)	1.393(6)	C(9)-C(8)-Br(8)	109.4(3)
C(6)-C(7)	1.502(6)	O(10)-C(9)-C(24)	105.1(3)
C(7)-C(8)	1.520(6)	O(10)-C(9)-C(8)	109.4(3)
C(8)-C(9)	1.526(6)	C(24)-C(9)-C(8)	112.9(4)
C(8)-Br(8)	1.978(4)	O(10)-C(9)-C(17)	106.0(3)
C(9)-O(10)	1.453(5)	C(24)-C(9)-C(17)	111.0(4)
C(9)-C(24)	1.525(6)	C(8)-C(9)-C(17)	111.9(4)
C(9)-C(17)	1.539(6)	C(11)-O(10)-C(9)	118.6(3)
O(10)-C(11)	1.361(5)	O(10)-C(11)-C(6)	122.4(4)
C(11)-C(12)	1.399(6)	O(10)-C(11)-C(12)	116.3(4)
C(12)-C(13)	1.375(6)	C(6)-C(11)-C(12)	121.3(4)
C(13)-C(14)	1.406(6)	C(13)-C(12)-C(11)	121.3(4)
C(13)-C(25)	1.520(6)	C(12)-C(13)-C(14)	118.8(4)
C(17)-C(18)	1.523(6)	C(12)-C(13)-C(25)	119.2(4)
C(18)-C(19)	1.519(6)	C(14)-C(13)-C(25)	122.1(4)
C(19)-C(20)	1.530(6)	C(5)-C(14)-C(13)	118.4(4)
C(19)-Cl(19)	1.826(6)	C(5)-C(14)-C(1)	117.6(4)
C(19)-Br(9')	1.960(9)	C(13)-C(14)-C(1)	123.8(4)
C(20)-C(23)	1.533(7)	C(18)-C(17)-C(9)	117.1(4)
C(20)-C(21)	1.547(7)	C(19)-C(18)-C(17)	111.6(4)
C(20)-Br(20)	1.990(4)	C(18)-C(19)-C(20)	116.8(4)
C(21)-O(21)	1.204(6)	C(18)-C(19)-Cl(19)	108.1(4)
C(21)-C(22)	1.500(7)	C(20)-C(19)-Cl(19)	105.0(5)
		C(18)-C(19)-Br(9')	115.2(6)
O(1)-C(1)-O(2)	116.4(4)	C(20)-C(19)-Br(9')	102.5(8)
O(1)-C(1)-C(14)	127.1(4)	C(19)-C(20)-C(23)	115.0(4)
O(2)-C(1)-C(14)	116.4(4)	C(19)-C(20)-C(21)	111.2(4)
C(1)-O(2)-C(3)	118.8(3)	C(23)-C(20)-C(21)	112.3(4)
O(4)-C(3)-O(2)	108.3(3)	C(19)-C(20)-Br(20)	106.5(3)
O(4)-C(3)-C(15)	106.4(4)	C(23)-C(20)-Br(20)	107.9(3)
O(2)-C(3)-C(15)	106.2(4)	C(21)-C(20)-Br(20)	103.0(3)
O(4)-C(3)-C(16)	111.0(4)	O(21)-C(21)-C(22)	122.3(5)
O(2)-C(3)-C(16)	109.3(4)	O(21)-C(21)-C(20)	119.2(5)
C(15)-C(3)-C(16)	115.2(4)	C(22)-C(21)-C(20)	118.5(4)

Table 23: Bond lengths [Å] and angles [°] for polyhalogenated products (404).

Formula	$C_{14}H_{18}O_5$
Formula weight	266.28
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.541 84 Å
Crystal system, space group	Monoclinic, $P2_1/m$
Unit cell dimensions	$a = 8.1431(13) \text{ Å}, \alpha = 90^\circ$ $b = 6.8148(18) \text{ Å}, \beta = 107.652(17)^\circ$ $c = 12.6113(19) \text{ Å}, \gamma = 90^\circ$
Volume, Z	$666.9(2) \text{ Å}^3, 2$
Density (calculated)	1.326 Mg/m^3
Absorption coefficient	0.837 mm^{-1}
F (000)	284
Crystal colour / morphology	Colourless / thin platy needles
Crystal size	$0.334 \times 0.111 \times 0.045 \text{ mm}^3$
θ range for data collection	3.678 to 73.561°
Index ranges	$-9 \leq h \leq 9, -8 \leq k \leq 8, -15 \leq l \leq 15$
Reflns collected / unique	3289 / 3289 [R(int) = 0.1158]
Reflns observed [$F > 4\sigma(F)$]	1951
Absorption correction	Analytical
Max. and min. transmission	0.969 and 0.879
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3289 / 1 / 121
Goodness-of-fit on F^2	1.588
Final R indices [$F > 4\sigma(F)$]	$R1 = 0.1061, wR2 = 0.2639$
R indices (all data)	$R1 = 0.1471, wR2 = 0.2849$
Largest diff. peak, hole	$0.773, -0.419 \text{ e Å}^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 24: Crystal data and structure refinement for formate ester (453).

C(1)-O(7)	1.354(8)	C(1)-C(2)-C(3)	120.4(7)
C(1)-C(2)	1.360(11)	O(9)-C(3)-C(2)	116.2(6)
C(1)-C(6)	1.408(12)	O(9)-C(3)-C(4)	122.6(6)
C(2)-C(3)	1.394(9)	C(2)-C(3)-C(4)	121.2(6)
C(3)-O(9)	1.325(9)	C(5)-C(4)-C(3)	116.6(6)
C(3)-C(4)	1.448(10)	C(5)-C(4)-C(10)	127.1(6)
C(4)-C(5)	1.422(10)	C(3)-C(4)-C(10)	116.3(6)
C(4)-C(10)	1.470(9)	C(6)-C(5)-C(4)	120.4(6)
C(5)-C(6)	1.385(9)	C(6)-C(5)-C(17)	115.2(6)
C(5)-C(17)	1.515(10)	C(4)-C(5)-C(17)	124.4(6)
O(7)-C(8)	1.449(11)	C(5)-C(6)-C(1)	121.2(6)
C(10)-O(10)	1.236(9)	C(1)-O(7)-C(8)	116.3(6)
C(10)-C(11)	1.519(10)	O(10)-C(10)-C(4)	120.4(6)
C(11)-C(12)	1.520(9)	O(10)-C(10)-C(11)	116.1(6)
C(12)-C(13)	1.528(10)	C(4)-C(10)-C(11)	123.5(6)
C(13)-C(14)	1.505(10)	C(10)-C(11)-C(12)	112.1(6)
C(14)-O(15)	1.466(8)	C(11)-C(12)-C(13)	113.8(6)
O(15)-C(16)	1.306(9)	C(14)-C(13)-C(12)	108.0(6)
C(16)-O(16)	1.173(11)	O(15)-C(14)-C(13)	110.1(6)
O(7)-C(1)-C(2)	124.9(7)	C(16)-O(15)-C(14)	113.2(6)
O(7)-C(1)-C(6)	114.9(6)	O(16)-C(16)-O(15)	128.6(8)
		C(2)-C(1)-C(6)	120.2(6)

Table 25: Bond lengths [$\text{\AA}$] and angles [$^\circ$] for formate ester (453).

Formula	$\text{C}_9\text{H}_{10}\text{O}_4$
Formula weight	182.17
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 28.979(3) \text{ Å}$, $\alpha = 90^\circ$ $b = 3.8782(7) \text{ Å}$, $\beta = 99.250(10)^\circ$ $c = 15.0099(16) \text{ Å}$, $\gamma = 90^\circ$
Volume, Z	$1665.0(4) \text{ Å}^3$, 8
Density (calculated)	1.453 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F (000)	768
Crystal colour / morphology	Colourless / needles
Crystal size	$0.616 \times 0.065 \times 0.015 \text{ mm}^3$
θ range for data collection	2.727 to 28.285°
Index ranges	$-24 \leq h \leq 37$, $-3 \leq k \leq 5$, $-18 \leq l \leq 17$
Reflns collected / unique	6213 / 3386 [R(int) = 0.0686]
Reflns observed [$F > 4\sigma(F)$]	1502
Absorption correction	Analytical
Max. and min. transmission	0.998 and 0.969
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3386 / 4 / 255
Goodness-of-fit on F^2	0.938
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0641$, $wR_2 = 0.1129$
R indices (all data)	$R_1 = 0.1501$, $wR_2 = 0.1501$
Largest diff. peak, hole	0.236 , -0.252 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.002

Table 26: Crystal data and structure refinement for carboxylic acid (467).

C(1A)-C(2A)	1.412(4)	O(9A)-C(2A)-C(1A)	122.7(3)
C(1A)-C(6A)	1.441(4)	C(3A)-C(2A)-C(1A)	122.4(3)
C(1A)-C(7A)	1.450(5)	C(2A)-C(3A)-C(4A)	119.2(3)
C(2A)-O(9A)	1.364(4)	O(10A)-C(4A)-C(3A)	123.4(3)
C(2A)-C(3A)	1.384(5)	O(10A)-C(4A)-C(5A)	117.3(3)
C(3A)-C(4A)	1.387(4)	C(3A)-C(4A)-C(5A)	119.3(3)
C(4A)-O(10A)	1.347(4)	C(6A)-C(5A)-C(4A)	122.9(3)
C(4A)-C(5A)	1.393(4)	C(5A)-C(6A)-C(1A)	118.9(3)
C(5A)-C(6A)	1.362(4)	C(5A)-C(6A)-C(12A)	118.6(3)
C(6A)-C(12A)	1.510(4)	C(1A)-C(6A)-C(12A)	122.5(3)
C(7A)-O(7A)	1.252(4)	O(7A)-C(7A)-O(8A)	119.5(3)
C(7A)-O(8A)	1.308(4)	O(7A)-C(7A)-C(1A)	121.8(3)
O(10A)-C(11A)	1.426(4)	O(8A)-C(7A)-C(1A)	118.6(3)
C(1B)-C(2B)	1.416(5)	C(4A)-O(10A)-C(11A)	117.6(3)
C(1B)-C(6B)	1.431(4)	C(2B)-C(1B)-C(6B)	117.1(3)
C(1B)-C(7B)	1.436(4)	C(2B)-C(1B)-C(7B)	118.2(3)
C(2B)-O(9B)	1.361(4)	C(6B)-C(1B)-C(7B)	124.6(3)
C(2B)-C(3B)	1.368(4)	O(9B)-C(2B)-C(3B)	115.6(3)
C(3B)-C(4B)	1.373(4)	O(9B)-C(2B)-C(1B)	121.7(3)
C(4B)-O(10B)	1.357(4)	C(3B)-C(2B)-C(1B)	122.7(3)
C(4B)-C(5B)	1.398(5)	C(2B)-C(3B)-C(4B)	119.4(3)
C(5B)-C(6B)	1.373(4)	O(10B)-C(4B)-C(3B)	124.3(3)
C(6B)-C(12B)	1.517(4)	O(10B)-C(4B)-C(5B)	115.8(3)
C(7B)-O(7B)	1.248(4)	C(3B)-C(4B)-C(5B)	119.9(3)
C(7B)-O(8B)	1.330(4)	C(6B)-C(5B)-C(4B)	121.9(3)
O(10B)-C(11B)	1.430(4)	C(5B)-C(6B)-C(1B)	119.0(3)
		C(5B)-C(6B)-C(12B)	117.4(3)
C(2A)-C(1A)-C(6A)	117.2(3)	C(1B)-C(6B)-C(12B)	123.6(3)
C(2A)-C(1A)-C(7A)	118.4(3)	O(7B)-C(7B)-O(8B)	118.8(3)
C(6A)-C(1A)-C(7A)	124.4(3)	O(7B)-C(7B)-C(1B)	123.6(3)
O(9A)-C(2A)-C(3A)	114.9(3)	O(8B)-C(7B)-C(1B)	117.6(3)
		C(4B)-O(10B)-C(11B)	116.5(3)

Table 27: Bond lengths [$\text{\AA}$] and angles [$^\circ$] for carboxylic acid (**467**).

Formula	$C_{16}H_{14}O_4$
Formula weight	270.27
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.541 84 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	$a = 5.4825(7) \text{ Å}, \alpha = 90^\circ$ $b = 9.8450(12) \text{ Å}, \beta = 90^\circ$ $c = 24.380(2) \text{ Å}, \gamma = 90^\circ$
Volume, Z	$1315.9(3) \text{ Å}^3, 4$
Density (calculated)	1.364 Mg/m^3
Absorption coefficient	0.810 mm^{-1}
F (000)	568
Crystal colour / morphology	Colourless / needles
Crystal size	$0.264 \times 0.066 \times 0.031 \text{ mm}^3$
θ range for data collection	4.844 to 73.382°
Index ranges	$-6 \leq h \leq 6, -11 \leq k \leq 11, -23 \leq l \leq 29$
Reflns collected / unique	2952 / 2117 [R(int) = 0.0670]
Reflns observed [$F > 4\sigma(F)$]	1420
Absorption correction	Analytical
Max. and min. transmission	0.975 and 0.896
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2117 / 1 / 186
Goodness-of-fit on F^2	0.982
Final R indices [$F > 4\sigma(F)$]	$R1 = 0.0514, wR2 = 0.1193$
R indices (all data)	$R1 = 0.0832, wR2 = 0.1427$
Absolute structure parameter	0.1(4)
Largest diff. peak, hole	$0.200, -0.185 \text{ e Å}^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Table 28: Crystal data and structure refinement for resorcyate lactone (504).

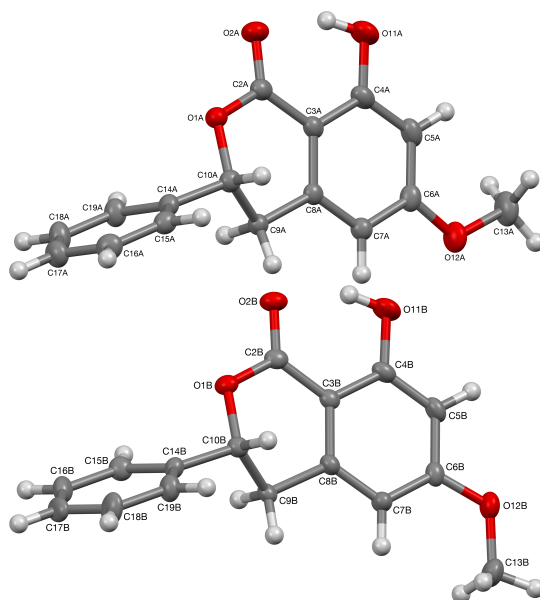
O(1)-C(2)	1.348(5)	C(8)-C(3)-C(2)	121.5(4)
O(1)-C(10)	1.462(6)	C(4)-C(3)-C(2)	119.2(4)
C(2)-O(2)	1.237(6)	O(11)-C(4)-C(5)	118.4(4)
C(2)-C(3)	1.454(6)	O(11)-C(4)-C(3)	121.7(4)
C(3)-C(8)	1.384(6)	C(5)-C(4)-C(3)	120.0(4)
C(3)-C(4)	1.424(6)	C(4)-C(5)-C(6)	120.1(4)
C(4)-O(11)	1.357(6)	O(12)-C(6)-C(5)	114.7(4)
C(4)-C(5)	1.361(7)	O(12)-C(6)-C(7)	124.4(5)
C(5)-C(6)	1.390(7)	C(5)-C(6)-C(7)	120.8(4)
C(6)-O(12)	1.354(5)	C(8)-C(7)-C(6)	118.7(5)
C(6)-C(7)	1.405(6)	C(7)-C(8)-C(3)	121.1(4)
C(7)-C(8)	1.381(6)	C(7)-C(8)-C(9)	121.9(4)
C(8)-C(9)	1.507(6)	C(3)-C(8)-C(9)	116.9(4)
C(9)-C(10)	1.493(6)	C(10)-C(9)-C(8)	110.0(4)
C(10)-C(14)	1.520(6)	O(1)-C(10)-C(9)	110.3(4)
O(12)-C(13)	1.437(7)	O(1)-C(10)-C(14)	106.6(4)
C(14)-C(15)	1.357(7)	C(9)-C(10)-C(14)	112.7(4)
C(14)-C(19)	1.368(7)	C(6)-O(12)-C(13)	118.0(4)
C(15)-C(16)	1.390(7)	C(15)-C(14)-C(19)	119.7(4)
C(16)-C(17)	1.368(8)	C(15)-C(14)-C(10)	119.3(5)
C(17)-C(18)	1.367(8)	C(19)-C(14)-C(10)	121.0(5)
C(18)-C(19)	1.409(7)	C(14)-C(15)-C(16)	120.7(6)
		C(17)-C(16)-C(15)	120.4(6)
C(2)-O(1)-C(10)	117.8(3)	C(18)-C(17)-C(16)	119.2(5)
O(2)-C(2)-O(1)	116.2(4)	C(17)-C(18)-C(19)	120.2(6)
O(2)-C(2)-C(3)	125.1(4)	C(14)-C(19)-C(18)	119.8(6)
O(1)-C(2)-C(3)	118.7(4)	C(8)-C(3)-C(4)	119.2(4)

Table 29: Bond lengths [Å] and angles [°] for resorcylic lactone (**504**).

Formula	$C_{16}H_{14}O_4$
Formula weight	270.27
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 12.3300(5) \text{ Å}$, $\alpha = 90^\circ$ $b = 13.2844(5) \text{ Å}$, $\beta = 95.623(4)^\circ$ $c = 16.2226(7) \text{ Å}$, $\gamma = 90^\circ$
Volume, Z	2644.42 Å^3 , 8
Density (calculated)	1.358 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F (000)	1136
Crystal colour / morphology	Colourless / blocks
Crystal size	$0.659 \times 0.445 \times 0.343 \text{ mm}^3$
θ range for data collection	2.666 to 28.302°
Index ranges	$-10 \leq h \leq 16$, $-17 \leq k \leq 16$, $-21 \leq l \leq 21$
Reflns collected / unique	14828 / 5575 [$R(\text{int}) = 0.0268$]
Reflns observed [$F > 4\sigma(F)$]	3593
Absorption correction	Analytical
Max. and min. transmission	0.970 and 0.955
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5575 / 71 / 381
Goodness-of-fit on F^2	1.036
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0488$, $wR_2 = 0.1028$
R indices (all data)	$R_1 = R_1 = 0.0886$, $wR_2 = 0.1226$
Largest diff. peak, hole	0.242 , -0.197 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.001

Table 30: Crystal data and structure refinement for resorcyate lactone (**504**), separate crystallization.

O(1A)-C(2A)	1.341(2)	O(1A)-C(10A)	1.474(2)
C(2A)-O(2A)	1.231(2)	C(2A)-C(3A)	1.454(3)
C(3A)-C(4A)	1.401(3)	C(3A)-C(8A)	1.404(2)
C(4A)-O(11A)	1.357(2)	C(4A)-C(5A)	1.384(3)
C(5A)-C(6A)	1.380(3)	C(6A)-O(12A)	1.360(2)
C(6A)-C(7A)	1.398(3)	C(7A)-C(8A)	1.375(3)
C(8A)-C(9A)	1.500(2)	C(9A)-C(10A)	1.507(3)
C(10A)-C(14A)	1.501(2)	O(12A)-C(13A)	1.438(2)
C(14A)-C(15A)	1.384(3)	C(14A)-C(19A)	1.389(3)
C(15A)-C(16A)	1.386(3)	C(16A)-C(17A)	1.375(3)
C(17A)-C(18A)	1.374(3)	C(18A)-C(19A)	1.375(3)
O(1B)-C(2B)	1.346(2)	O(1B)-C(10B)	1.482(3)
O(1B)-C(10'')	1.482(4)	C(2B)-O(2B)	1.227(2)
C(2B)-C(3B)	1.452(2)	C(3B)-C(8B)	1.399(2)
C(3B)-C(4B)	1.415(2)	C(4B)-O(11B)	1.351(2)
C(4B)-C(5B)	1.371(3)	C(5B)-C(6B)	1.382(3)
C(6B)-O(12B)	1.358(2)	C(6B)-C(7B)	1.392(2)
C(7B)-C(8B)	1.376(2)	C(8B)-C(9B)	1.513(4)
C(8B)-C(9'')	1.525(5)	O(12B)-C(13B)	1.424(3)
C(9B)-C(10B)	1.504(5)	C(10B)-C(14B)	1.505(4)
C(14B)-C(15B)	1.3900	C(14B)-C(19B)	1.3900
C(15B)-C(16B)	1.3900	C(16B)-C(17B)	1.3900
C(17B)-C(18B)	1.3900	C(18B)-C(19B)	1.3900
C(9'')-C(10'')	1.507(6)	C(10'')-C(14'')	1.517(5)
C(14'')-C(15'')	1.3900	C(14'')-C(19'')	1.3900
C(15'')-C(16'')	1.3900	C(16'')-C(17'')	1.3900
C(17'')-C(18'')	1.3900	C(18'')-C(19'')	1.3900

Table 31: Bond lengths [Å] for resorcylic lactone (**504**), separate crystallization.Figure 24: X-Ray crystal structure of resorcylic lactone (**504**). Note this is one of two independent crystal systems lactone (**504**) crystallized in, with the two independent molecules in the asymmetric unit shown here. Please see figure 15 for the alternative crystal system.

O(12A)-C(6A)-C(7A)	114.97(19)	C(5A)-C(6A)-C(7A)	121.01(19)
C(8A)-C(7A)-C(6A)	119.69(18)	C(7A)-C(8A)-C(3A)	120.25(17)
C(7A)-C(8A)-C(9A)	122.42(16)	C(3A)-C(8A)-C(9A)	117.30(16)
C(8A)-C(9A)-C(10A)	111.74(15)	O(1A)-C(10A)-C(14A)	106.49(14)
O(1A)-C(10A)-C(9A)	110.81(15)	C(14A)-C(10A)-C(9A)	113.61(16)
C(6A)-O(12A)-C(13A)	118.30(18)	C(15A)-C(14A)-C(19A)	118.78(17)
C(15A)-C(14A)-C(10A)	120.39(17)	C(19A)-C(14A)-C(10A)	120.79(17)
C(14A)-C(15A)-C(16A)	120.52(18)	C(17A)-C(16A)-C(15A)	119.68(19)
C(18A)-C(17A)-C(16A)	120.41(19)	C(17A)-C(18A)-C(19A)	119.9(2)
C(18A)-C(19A)-C(14A)	120.67(19)	C(2B)-O(1B)-C(10B)	116.61(18)
C(2B)-O(1B)-C(10")	117.55(18)	O(2B)-C(2B)-O(1B)	117.12(17)
O(2B)-C(2B)-C(3B)	123.58(18)	O(1B)-C(2B)-C(3B)	119.30(16)
C(8B)-C(3B)-C(4B)	118.32(16)	C(8B)-C(3B)-C(2B)	121.43(16)
C(4B)-C(3B)-C(2B)	120.23(16)	O(11B)-C(4B)-C(5B)	118.52(17)
O(11B)-C(4B)-C(3B)	121.16(17)	C(5B)-C(4B)-C(3B)	120.32(17)
C(4B)-C(5B)-C(6B)	120.24(17)	O(12B)-C(6B)-C(5B)	115.05(17)
O(12B)-C(6B)-C(7B)	124.29(18)	C(5B)-C(6B)-C(7B)	120.64(17)
C(8B)-C(7B)-C(6B)	119.36(17)	C(7B)-C(8B)-C(3B)	121.11(17)
C(7B)-C(8B)-C(9B)	122.0(2)	C(3B)-C(8B)-C(9B)	116.3(2)
C(7B)-C(8B)-C(9")	121.4(2)	C(3B)-C(8B)-C(9")	115.9(2)
C(6B)-O(12B)-C(13B)	119.02(16)	C(10B)-C(9B)-C(8B)	106.9(3)
O(1B)-C(10B)-C(9B)	109.9(3)	O(1B)-C(10B)-C(14B)	105.7(2)
C(9B)-C(10B)-C(14B)	114.0(3)	C(15B)-C(14B)-C(19B)	120.0
C(15B)-C(14B)-C(10B)	121.1(3)	C(19B)-C(14B)-C(10B)	118.9(3)
C(16B)-C(15B)-C(14B)	120.0	C(15B)-C(16B)-C(17B)	120.0
C(18B)-C(17B)-C(16B)	120.0	C(17B)-C(18B)-C(19B)	120.0
C(18B)-C(19B)-C(14B)	120.0	C(10")-C(9")-C(8B)	109.2(4)
O(1B)-C(10")-C(9")	108.4(4)	C(2A)-O(1A)-C(10A)	118.28(14)
O(1B)-C(10")-C(14")	107.2(3)	O(2A)-C(2A)-O(1A)	116.87(18)
C(9")-C(10")-C(14")	115.9(4)	O(2A)-C(2A)-C(3A)	123.34(18)
C(15")-C(14")-C(19")	120.0	O(1A)-C(2A)-C(3A)	119.78(17)
C(15")-C(14")-C(10")	121.3(3)	C(4A)-C(3A)-C(8A)	119.00(18)
C(19")-C(14")-C(10")	118.7(3)	C(4A)-C(3A)-C(2A)	119.83(18)
C(14")-C(15")-C(16")	120.0	C(8A)-C(3A)-C(2A)	121.08(16)
C(17")-C(16")-C(15")	120.0	O(11A)-C(4A)-C(5A)	117.93(18)
C(16")-C(17")-C(18")	120.0	O(11A)-C(4A)-C(3A)	121.29(19)
C(17")-C(18")-C(19")	120.0	C(5A)-C(4A)-C(3A)	120.78(19)
C(18")-C(19")-C(14")	120.0	C(6A)-C(5A)-C(4A)	119.26(18)
		O(12A)-C(6A)-C(5A)	124.01(18)

Table 32: Bond angles [°] for resorcylic lactone (**504**), separate crystallization.

Formula	$C_{15}H_{18}O_4$
Formula weight	262.29
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 7.1568(3) \text{ Å}, \alpha = 90^\circ$ $b = 13.1910(5) \text{ Å}, \beta = 93.552(4)^\circ$ $c = 13.6396(5) \text{ Å}, \gamma = 90^\circ$
Volume, Z	$1285.17(9) \text{ Å}^3, 4$
Density (calculated)	1.356 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F (000)	560
Crystal colour / morphology	Colourless / blocks
Crystal size	$0.464 \times 0.459 \times 0.274 \text{ mm}^3$
θ range for data collection	2.852 to 28.271°
Index ranges	$-8 \leq h \leq 6, -17 \leq k \leq 17, -16 \leq l \leq 17$
Reflns collected / unique	7571 / 2707 [R(int) = 0.0236]
Reflns observed [$F > 4\sigma(F)$]	2198
Absorption correction	Analytical
Max. and min. transmission	0.980 and 0.966
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2707 / 1 / 178
Goodness-of-fit on F^2	1.049
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0400, wR_2 = 0.0962$
R indices (all data)	$R_1 = 0.0516, wR_2 = 0.1039$
Largest diff. peak, hole	$0.234, -0.203 \text{ e Å}^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 33: Crystal data and structure refinement for spirocyclic resorcyate (**506**).

O(1)-C(1)	1.2302(15)	O(2)-C(3)-C(15)	104.23(10)
C(1)-O(2)	1.3384(15)	O(2)-C(3)-C(4)	109.19(10)
C(1)-C(10)	1.4519(18)	C(15)-C(3)-C(4)	111.73(11)
O(2)-C(3)	1.4858(15)	O(2)-C(3)-C(11)	108.39(10)
C(3)-C(15)	1.5172(18)	C(15)-C(3)-C(11)	111.25(11)
C(3)-C(4)	1.5177(18)	C(4)-C(3)-C(11)	111.72(11)
C(3)-C(11)	1.5208(19)	C(5)-C(4)-C(3)	112.06(10)
C(4)-C(5)	1.5006(17)	C(6)-C(5)-C(10)	120.09(12)
C(5)-C(6)	1.3736(18)	C(6)-C(5)-C(4)	122.75(11)
C(5)-C(10)	1.4115(17)	C(10)-C(5)-C(4)	117.10(11)
C(6)-C(7)	1.3957(19)	C(5)-C(6)-C(7)	120.02(11)
C(7)-O(16)	1.3582(16)	O(16)-C(7)-C(8)	123.75(12)
C(7)-C(8)	1.3863(18)	O(16)-C(7)-C(6)	115.23(11)
C(8)-C(9)	1.3880(19)	C(8)-C(7)-C(6)	121.01(12)
C(9)-O(18)	1.3524(15)	C(7)-C(8)-C(9)	119.15(12)
C(9)-C(10)	1.4038(18)	O(18)-C(9)-C(8)	117.54(12)
C(11)-C(12)	1.5166(19)	O(18)-C(9)-C(10)	121.78(12)
C(12)-C(13)	1.524(2)	C(8)-C(9)-C(10)	120.68(12)
C(13)-C(14)	1.521(2)	C(9)-C(10)-C(5)	119.01(12)
C(14)-C(15)	1.518(2)	C(9)-C(10)-C(1)	120.15(11)
O(16)-C(17)	1.4250(17)	C(5)-C(10)-C(1)	120.84(12)
		C(12)-C(11)-C(3)	112.94(11)
O(1)-C(1)-O(2)	117.08(12)	C(11)-C(12)-C(13)	110.70(11)
O(1)-C(1)-C(10)	123.22(12)	C(14)-C(13)-C(12)	110.52(12)
O(2)-C(1)-C(10)	119.70(11)	C(15)-C(14)-C(13)	111.39(12)
C(1)-O(2)-C(3)	120.23(10)	C(3)-C(15)-C(14)	113.40(12)
		C(7)-O(16)-C(17)	117.96(10)

Table 34: Bond lengths [Å] and angles [°] for spirocyclic resorcyate (**506**).

Formula	$C_{22}H_{24}O_5$
Formula weight	368.41
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.541 84 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 13.2568(3) \text{ Å}$, $\alpha = 90^\circ$ $b = 15.9740(4) \text{ Å}$, $\beta = 97.032(2)^\circ$ $c = 8.957 59(19) \text{ Å}$, $\gamma = 90^\circ$
Volume, Z	$1882.63(7) \text{ Å}^3$, 4
Density (calculated)	1.300 Mg/m^3
Absorption coefficient	0.747 mm^{-1}
F (000)	784
Crystal colour / morphology	Colourless / plates
Crystal size	$0.353 \times 0.269 \times 0.070 \text{ mm}^3$
θ range for data collection	3.359 to 73.325°
Index ranges	$-16 \leq h \leq 16$, $-19 \leq k \leq 7$, $-9 \leq l \leq 10$
Reflns collected / unique	6116 / 3605 [R(int) = 0.0282]
Reflns observed [$F > 4\sigma(F)$]	2741
Absorption correction	Analytical
Max. and min. transmission	0.962 and 0.843
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3605 / 0 / 248
Goodness-of-fit on F^2	1.026
Final R indices [$F > 4\sigma(F)$]	$R1 = 0.0414$, $wR2 = 0.1034$
R indices (all data)	$R1 = 0.0586$, $wR2 = 0.1192$
Largest diff. peak, hole	0.281 , -0.224 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.000

Table 35: Crystal data and structure refinement for styrene resorcyate (**510**).

O(1)-C(1)	1.2084(19)	O(2)-C(3)-C(12)	106.06(13)
C(1)-O(2)	1.361(2)	O(4)-C(3)-C(11)	110.95(14)
C(1)-C(10)	1.470(2)	O(2)-C(3)-C(11)	110.50(13)
O(2)-C(3)	1.444(2)	C(12)-C(3)-C(11)	112.82(15)
C(3)-O(4)	1.4316(18)	C(5)-O(4)-C(3)	115.25(11)
C(3)-C(12)	1.501(2)	O(4)-C(5)-C(6)	116.75(13)
C(3)-C(11)	1.514(2)	O(4)-C(5)-C(10)	120.04(13)
O(4)-C(5)	1.3741(19)	C(6)-C(5)-C(10)	123.15(14)
C(5)-C(6)	1.389(2)	C(5)-C(6)-C(7)	116.51(13)
C(5)-C(10)	1.406(2)	C(5)-C(6)-C(13)	122.08(14)
C(6)-C(7)	1.396(2)	C(7)-C(6)-C(13)	121.41(14)
C(6)-C(13)	1.514(2)	O(22)-C(7)-C(8)	123.57(15)
C(7)-O(22)	1.3720(19)	O(22)-C(7)-C(6)	114.51(13)
C(7)-C(8)	1.396(2)	C(8)-C(7)-C(6)	121.90(14)
C(8)-C(9)	1.386(2)	C(9)-C(8)-C(7)	120.86(15)
C(9)-C(10)	1.411(2)	C(8)-C(9)-C(10)	118.80(14)
C(9)-C(26)	1.504(2)	C(8)-C(9)-C(26)	118.24(15)
C(13)-C(14)	1.500(2)	C(10)-C(9)-C(26)	122.96(14)
C(14)-C(15)	1.325(2)	C(5)-C(10)-C(9)	118.72(14)
C(15)-C(16)	1.480(2)	C(5)-C(10)-C(1)	118.40(14)
C(16)-C(17)	1.387(3)	C(9)-C(10)-C(1)	122.70(13)
C(16)-C(21)	1.390(3)	C(14)-C(13)-C(6)	111.97(13)
C(17)-C(18)	1.382(3)	C(15)-C(14)-C(13)	125.21(17)
C(18)-C(19)	1.380(4)	C(14)-C(15)-C(16)	126.56(17)
C(19)-C(20)	1.381(4)	C(17)-C(16)-C(21)	118.31(18)
C(20)-C(21)	1.394(3)	C(17)-C(16)-C(15)	123.36(16)
O(22)-C(23)	1.422(2)	C(21)-C(16)-C(15)	118.33(18)
C(23)-O(24)	1.388(2)	C(18)-C(17)-C(16)	121.1(2)
O(24)-C(25)	1.427(2)	C(19)-C(18)-C(17)	120.2(2)
		C(18)-C(19)-C(20)	119.75(19)
O(1)-C(1)-O(2)	117.67(14)	C(19)-C(20)-C(21)	119.9(2)
O(1)-C(1)-C(10)	126.20(15)	C(16)-C(21)-C(20)	120.8(2)
O(2)-C(1)-C(10)	115.98(13)	C(7)-O(22)-C(23)	119.26(13)
C(1)-O(2)-C(3)	119.03(12)	O(24)-C(23)-O(22)	113.08(14)
O(4)-C(3)-O(2)	109.02(13)	C(23)-O(24)-C(25)	112.53(14)
		O(4)-C(3)-C(12)	107.29(13)

Table 36: Bond lengths [$\text{\AA}$] and angles [$^\circ$] for styrene resorcyate (**510**).

Formula	$C_{23}H_{28}O_4$
Formula weight	368.45
Temperature	173(2) K
Diffractometer, wavelength	Agilent PX Ultra A, 1.541 84 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	$a = 15.6361(6)$ Å, $\alpha = 90^\circ$ $b = 15.6509(4)$ Å, $\beta = 95.195(4)^\circ$ $c = 8.4495(3)$ Å, $\gamma = 90^\circ$
Volume, Z	$2059.27(13)$ Å ³ , 4
Density (calculated)	1.188 Mg/m ³
Absorption coefficient	0.641 mm ⁻¹
F (000)	792
Crystal colour / morphology	Colourless / thin platy needles
Crystal size	0.313 × 0.191 × 0.010 mm ³
θ range for data collection	4.005 to 73.194°
Index ranges	-19 ≤ h ≤ 18, -19 ≤ k ≤ 11, -10 ≤ l ≤ 9
Reflns collected / unique	6572 / 3926 [R(int) = 0.0540]
Reflns observed [$F > 4\sigma(F)$]	2438
Absorption correction	Analytical
Max. and min. transmission	0.993 and 0.904
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3926 / 1 / 253
Goodness-of-fit on F^2	1.007
Final R indices [$F > 4\sigma(F)$]	R1 = 0.0602, wR2 = 0.1376
R indices (all data)	R1 = 0.1002, wR2 = 0.1703
Largest diff. peak, hole	0.250, -0.239 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Table 37: Crystal data and structure refinement for 1,4-enyne resorcyate (**3oba**).

C(1)-O(1)	1.210(3)	O(4)-C(3)-C(12)	111.3(2)
C(1)-O(2)	1.354(3)	O(2)-C(3)-C(12)	110.0(2)
C(1)-C(10)	1.468(3)	C(11)-C(3)-C(12)	113.8(2)
O(2)-C(3)	1.451(3)	C(5)-O(4)-C(3)	113.47(19)
C(3)-O(4)	1.422(3)	O(4)-C(5)-C(6)	116.9(2)
C(3)-C(11)	1.504(4)	O(4)-C(5)-C(10)	119.9(2)
C(3)-C(12)	1.513(4)	C(6)-C(5)-C(10)	123.2(2)
O(4)-C(5)	1.370(3)	C(5)-C(6)-C(7)	116.6(2)
C(5)-C(6)	1.388(3)	C(5)-C(6)-C(13)	120.5(2)
C(5)-C(10)	1.404(4)	C(7)-C(6)-C(13)	122.8(2)
C(6)-C(7)	1.392(4)	O(25)-C(7)-C(6)	116.9(2)
C(6)-C(13)	1.507(4)	O(25)-C(7)-C(8)	121.7(2)
C(7)-O(25)	1.350(3)	C(6)-C(7)-C(8)	121.3(2)
C(7)-C(8)	1.407(4)	C(9)-C(8)-C(7)	121.6(2)
C(8)-C(9)	1.383(3)	C(8)-C(9)-C(10)	118.0(2)
C(9)-C(10)	1.411(4)	C(8)-C(9)-C(26)	118.8(2)
C(9)-C(26)	1.506(4)	C(10)-C(9)-C(26)	123.2(2)
C(13)-C(14)	1.506(4)	C(5)-C(10)-C(9)	119.3(2)
C(14)-C(15)	1.338(4)	C(5)-C(10)-C(1)	117.8(2)
C(15)-C(23)	1.495(5)	C(9)-C(10)-C(1)	122.9(2)
C(15)-C(16)	1.506(5)	C(14)-C(13)-C(6)	111.2(2)
C(16)-C(17)	1.527(5)	C(15)-C(14)-C(13)	128.3(3)
C(17)-C(18)	1.504(5)	C(14)-C(15)-C(23)	123.5(3)
C(18)-C(19)	1.328(5)	C(14)-C(15)-C(16)	121.5(3)
C(19)-C(24)	1.497(5)	C(23)-C(15)-C(16)	115.0(3)
C(19)-C(20)	1.512(5)	C(15)-C(16)-C(17)	114.6(3)
C(20)-C(21)	1.469(6)	C(18)-C(17)-C(16)	111.2(3)
C(21)-C(22)	1.184(6)	C(19)-C(18)-C(17)	127.1(3)
		C(18)-C(19)-C(24)	125.4(3)
O(1)-C(1)-O(2)	117.7(2)	C(18)-C(19)-C(20)	118.4(3)
O(1)-C(1)-C(10)	125.9(2)	C(24)-C(19)-C(20)	116.2(3)
O(2)-C(1)-C(10)	116.4(2)	C(21)-C(20)-C(19)	113.0(3)
C(1)-O(2)-C(3)	119.05(18)	C(22)-C(21)-C(20)	177.2(4)
O(4)-C(3)-O(2)	108.7(2)	O(4)-C(3)-C(11)	106.8(2)
		O(2)-C(3)-C(11)	106.0(2)

Table 38: Bond lengths [Å] and angles [°] for 1,4-enyne resorcyate (**301b**).

Formula	$C_{24}H_{26}O_5$
Formula weight	394.45
Temperature	173(2) K
Diffractometer, wavelength	Agilent Xcalibur PX Ultra A, 1.541 84 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	$a = 6.2255(7) \text{ Å}$, $\alpha = 74.118(9)^\circ$ $b = 11.4170(11) \text{ Å}$, $\beta = 85.032(9)^\circ$ $c = 15.1074(17) \text{ Å}$, $\gamma = 89.075(8)^\circ$
Volume, Z	$1028.89(19) \text{ Å}^3$, 2
Density (calculated)	1.273 Mg/m^3
Absorption coefficient	0.718 mm^{-1}
F (000)	420
Crystal colour / morphology	Colourless / thin plates
Crystal size	$0.280 \times 0.161 \times 0.027 \text{ mm}^3$
θ range for data collection	4.026 to 73.495°
Index ranges	$-7 \leq h \leq 5$, $-13 \leq k \leq 14$, $-18 \leq l \leq 18$
Reflns collected / unique	5731 / 3890 [R(int) = 0.0498]
Reflns observed [$F > 4\sigma(F)$]	2248
Absorption correction	Analytical
Max. and min. transmission	0.981 and 0.875
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3890 / 1 / 270
Goodness-of-fit on F^2	1.003
Final R indices [$F > 4\sigma(F)$]	$R_1 = 0.0542$, $wR_2 = 0.1247$
R indices (all data)	$R_1 = 0.1031$, $wR_2 = 0.1630$
Largest diff. peak, hole	0.221 , -0.223 e Å^{-3}
Mean and maximum shift/error	0.000 and 0.002

Table 39: Crystal data and structure refinement for amorfrutin aldehyde (578).

O(1)-C(1)	1.205(4)	O(2)-C(3)-C(11)	106.0(2)
C(1)-O(2)	1.354(3)	C(12)-C(3)-C(11)	114.1(3)
C(1)-C(10)	1.487(4)	C(5)-O(4)-C(3)	114.7(2)
O(2)-C(3)	1.451(3)	O(4)-C(5)-C(6)	116.9(2)
C(3)-O(4)	1.437(3)	O(4)-C(5)-C(10)	119.7(2)
C(3)-C(12)	1.502(4)	C(6)-C(5)-C(10)	123.4(2)
C(3)-C(11)	1.505(4)	C(5)-C(6)-C(7)	116.4(2)
O(4)-C(5)	1.363(3)	C(5)-C(6)-C(13)	122.3(2)
C(5)-C(6)	1.381(4)	C(7)-C(6)-C(13)	121.3(3)
C(5)-C(10)	1.409(4)	O(18)-C(7)-C(6)	117.0(2)
C(6)-C(7)	1.396(4)	O(18)-C(7)-C(8)	121.1(2)
C(6)-C(13)	1.515(4)	C(6)-C(7)-C(8)	121.9(3)
C(7)-O(18)	1.343(3)	C(9)-C(8)-C(7)	120.4(2)
C(7)-C(8)	1.418(4)	C(9)-C(8)-C(19)	121.3(2)
C(8)-C(9)	1.418(4)	C(7)-C(8)-C(19)	118.3(3)
C(8)-C(19)	1.468(4)	C(10)-C(9)-C(8)	117.6(2)
C(9)-C(10)	1.392(4)	C(10)-C(9)-C(20)	121.9(2)
C(9)-C(20)	1.512(3)	C(8)-C(9)-C(20)	120.5(2)
C(13)-C(14)	1.508(4)	C(9)-C(10)-C(5)	120.2(2)
C(14)-C(15)	1.333(4)	C(9)-C(10)-C(1)	122.8(2)
C(15)-C(17)	1.502(5)	C(5)-C(10)-C(1)	116.7(2)
C(15)-C(16)	1.508(5)	C(14)-C(13)-C(6)	110.4(2)
C(19)-O(19)	1.212(4)	C(15)-C(14)-C(13)	128.0(3)
C(20)-C(21)	1.535(4)	C(14)-C(15)-C(17)	120.8(3)
C(21)-C(22)	1.521(4)	C(14)-C(15)-C(16)	124.5(3)
C(22)-C(23)	1.382(5)	C(17)-C(15)-C(16)	114.7(3)
C(22)-C(27)	1.391(5)	O(19)-C(19)-C(8)	124.0(3)
C(23)-C(24)	1.383(5)	C(9)-C(20)-C(21)	112.9(2)
C(24)-C(25)	1.377(5)	C(22)-C(21)-C(20)	110.5(2)
C(25)-C(26)	1.376(6)	C(23)-C(22)-C(27)	118.5(3)
C(26)-C(27)	1.384(5)	C(23)-C(22)-C(21)	121.3(3)
		C(27)-C(22)-C(21)	120.2(3)
O(1)-C(1)-O(2)	117.8(3)	C(22)-C(23)-C(24)	121.1(3)
O(1)-C(1)-C(10)	125.8(3)	C(25)-C(24)-C(23)	120.0(3)
O(2)-C(1)-C(10)	116.2(2)	C(26)-C(25)-C(24)	119.6(3)
C(1)-O(2)-C(3)	119.2(2)	C(25)-C(26)-C(27)	120.6(3)
O(4)-C(3)-O(2)	107.6(2)	C(26)-C(27)-C(22)	120.3(3)
O(4)-C(3)-C(12)	111.7(2)	O(4)-C(3)-C(11)	106.7(2)
		O(2)-C(3)-C(12)	110.4(2)

Table 40: Bond lengths [$\text{\AA}$] and angles [$^\circ$] for amorfrutin aldehyde (578).

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PAPER

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Syntheses of polyfunctional aromatic compounds from non-aromatic precursors

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Syntheses of polyfunctional benzene derivatives from both cyclic and acyclic non-aromatic precursors are reviewed. Such aromatizations include transformations that use Diels–Alder reactions, transition metal-catalyzed reactions, base mediated aldol or Michael addition reactions or electrocyclic and pericyclic reactions. This review is limited to research that has been published since the last reviews in 2006, 2008, 2015 and 2018 and is specifically focused on aromatic and heteroaromatic compounds synthesized by construction of the benzene ring. It excludes heterocyclic compounds that lack a monocyclic benzene core. Applications of such aromatization reactions for the total syntheses of natural products as well as potential medicinal chemical entities are included.

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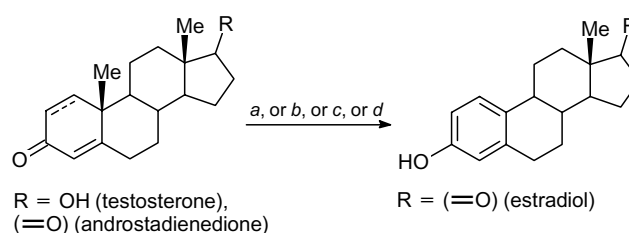
1. Introduction

The classical methods for the synthesis of polyfunctional aromatic compounds depend on the use of a range of reactions including sequential electrophilic aromatic substitution reactions and *o*-metalation with addition or substi-

tution reactions using electrophilic reagents. Additionally, transition metal-catalyzed substitution and C–H activation are also of considerable value in this regard. All these transformations depend on the conversion of an aromatic precursor to another aromatic compound of enhanced complexity. There is an alternative process: the conversion of a non-aromatic precursor, which may be cyclic or acyclic, into an aromatic compound; such transformations are complementary to classical approaches and are often used for the synthesis of arenes with ring substitution patterns not readily available by classical arene derivatizations.

An early example for this type of aromatization is the conversion of testosterone or androstadienedione into estradiol, both enzyme-catalyzed processes *in vivo* (Scheme 1, conditions *a*). Related bioinspired dehydrogenative aroma-

Scheme 1



(a) aromatase enzyme; (b) flash vacuum pyrolysis;
(c) Fe-porphyrin, peroxide; (d) I₂, PPh₃

tizations *via* transition metal-catalyzed oxidations have been reported in the first half of the 20th century.^{1,2} Alternative reactions using oxidants such as iodine have since been extensively studied for the synthesis of many aromatic compounds mainly from functionalized cyclohexane or cyclohexanone precursors (see Scheme 1, conditions *b–d*).^{3–8}

This review aims to complement an overview of these reactions by highlighting additional methods for ring formation and subsequent aromatization processes, which

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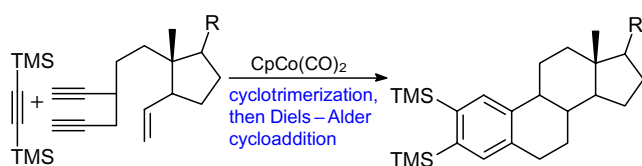
Current research interest of the authors: synthesis of bioactive natural, heterocyclic, organometallic compounds, macrocyclic ethers, lactones and porphyrans, design of novel therapeutic agents for detection and treatment of cancers, catalytic sustainable organic synthesis, application of combinatorial chemistry and parallel synthesis for the development of pharmaceuticals, applications of microfluidic flow reactors in synthesis.

allows for the synthesis of arenes with various functionalities otherwise not readily available from the derivatization of aromatic precursors. These alternative reactions possess a high degree of flexibility for the synthesis of polyfunctional arenes.

Such advantages are reported for the base-catalyzed benzannulation reactions,^{9,10} Diels–Alder cycloadditions^{11–16} and electrocyclic and pericyclic reactions followed by aromatization.^{17–19} These strategies are often employed, since in addition to the above advantages, they can also reduce the costs of scale-up synthesis with the use of inexpensive building blocks and transformations with high atom economy.

The synthesis of aromatic compounds through transition metal-catalyzed reactions, such as ring-closing alkene metathesis (RCM) or cyclotrimerization of alkynes or alkenes and subsequent aromatization, often allows for the synthesis of aromatic compounds with a range of bespoke substituents that would not be easily accessible through other methods.^{20–22} RCM shows remarkable functional group tolerance and can often be carried out under mild reaction conditions. Cyclotrimerization reactions are also often conducted under mild conditions and show broad functional group compatibility.²³ A highlight of this methodology is the Funk and Vollhardt's²⁴ estrone synthesis *via* a [2+2+2]-cyclotrimerization strategy to elaborate the aromatic ring complementing the biomimetic dehydrogenative processes described above (Scheme 2).

Scheme 2



R = OH, (=O); TMS = SiMe₃

The reaction strategies herein described have distinct advantages and disadvantages and are complementary to each other for the synthesis of aromatic compounds. The review covers a selection of methods for cyclization reactions and subsequent aromatizations published between 2016 and early 2020. For a more comprehensive and exhaustive selection of aromatization methods, the authors draw attention to the recently updated Chapter: Formation of Arenes by Aromatization in Comprehensive Organic Transformations by Larock and Pletnev[†] as well as various prior reviews.^{25–33}

The following designations and abbreviations are used:

Ad — adamantyl,

All — allyl,

Atom Economy — ratio of atoms transferred from starting material to products,

BINAP — 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl,

Boc — *tert*-butoxycarbonyl,

[bmim][Cl] — 1-butyl-3-methylimidazolium chloride,

BMIDA — boronic acid *N*-methyliminodiacetic acid ester,

Bn — benzyl,

Cbz — carboxybenzyl,
CDI — 1,1'-carbonyldiimidazole,
Cy — cyclohexyl,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
DCE — 1,2-dichloroethane,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DEC — *N,N*-diethylcarbamoyl,
DMAD — dimethyl acetylenedicarboxylate,
DMP — Dess–Martin periodinane,
E₁CB — elimination unimolecular conjugate base,
FN — functionalized nanoparticle,
Fu — furyl,
FVP — flash vacuum pyrolysis,
HIV — human immunodeficiency virus,
IC — inhibitory concentration,
LC — median lethal dose,
LED — light-emitting diode,
Mes-Acr⁺ClO₄ — 9-mesityl-10-methylacridinium perchlorate,
MIC — minimum inhibition concentration,
MOM — methoxymethyl,
Ms — methylsulfonyl (mesyl),
MTBE — methyl-*tert*-butyl ether,
MW — microwave,
NaBARF — sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate,
Naph — naphthyl,
p-NBA — 4-O₂NC₆H₄COOH,
NBS — *N*-bromosuccinimide,
NFSI — *N*-fluorobenzenesulfonimide,
NHC — *N*-heterocyclic carbene,
Ns — 4-nitrobenzenesulfonyl (nosyl),
o/n — overnight,
PG — protecting group,
PMB — *para*-methoxybenzyl,
Py — pyridyl,
RCM — ring closing alkene metathesis,
SET — single electron transfer,
TBAF — tetra-*n*-butylammonium fluoride,
TBD — 1,5,7-triazabicyclo[4.4.0]dec-5-ene,
TBS — *tert*-butyldimethylsilyl,
TEMPO — (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
TES — triethylsilyl,
Tf — trifluoromethanesulfonate (triflate),
TFA — trifluoroacetic acid,
TFP — tri-2-furylphosphine,
Th — thienyl,
THP — tetrahydropyranyl,
TIPS — triisopropylsilyl,
TMS — trimethylsilyl,
TMTU — tetramethylthiourea,
Ts — 4-toluenesulfonyl (tosyl),
w/u — work-up.

2. Diels–Alder reactions and subsequent aromatization

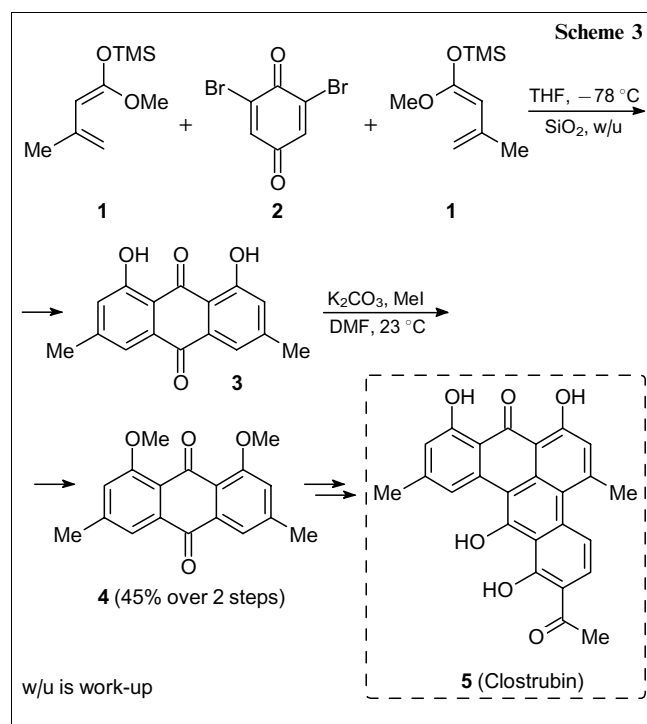
The Diels–Alder cycloaddition is an exceptionally powerful reaction for the synthesis of carbocycles, given the chemo-, regio- and stereoselectivity which is retained from the starting materials in addition to excellent atom economy. By employing a post-cycloaddition oxidation or an elimination reaction, aromatization can be carried out, thereby providing a range of heavily substituted aromatic com-

[†] R.C.Larock, A.Pletnev. In *Comprehensive Organic Transformations*. (Eds R.C.Larock). (Wiley, 2018).

pounds efficiently.^{29, 34} These reactions may be sub-divided according to the diene or dienophile precursors.

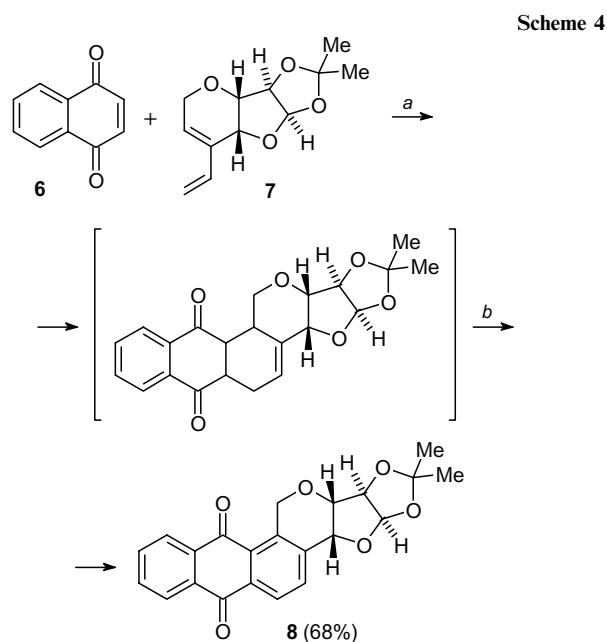
2.1. Quinone precursors

Since previous reviews, Diels–Alder reactions of quinones and quinonimine ketals have been reported to be useful for the syntheses of aromatic compounds. Additionally, Bras-sard's, Danishefsky's and other related dienes remain particularly useful building blocks for the synthesis of α,β -unsaturated cyclohexenones, which are readily converted into phenols by oxidation using oxygen, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), *etc.* For example, Li and co-workers³⁵ reported that the reaction of dibromobenzoquinone **2** with diene **1** and subsequent dehydrobromination gave the northern anthraquinone fragment **3** of clostrubin (**5**) on a multi-gram scale (Scheme 3). The natural product was shown to have strong antibiotic activities with minimum inhibition concentrations (MIC's) at $0.12 \mu\text{mol L}^{-1}$ against methicillin-resistant *Staphylococcus aureus* and $0.97 \mu\text{mol L}^{-1}$ against vancomycin-resistant enterocci.

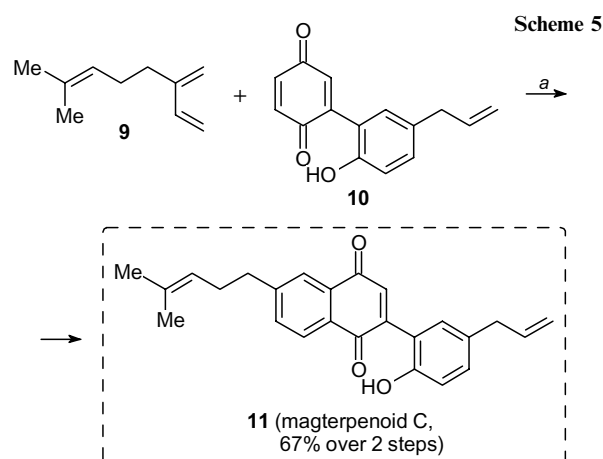
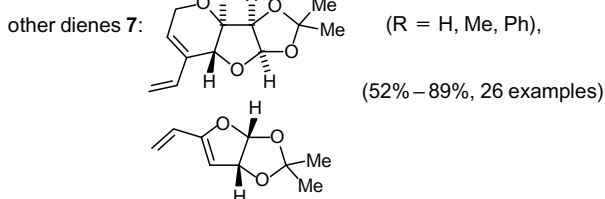


In 2017, Sayyad and Kaliappan³⁶ reported a Diels–Alder reaction and subsequent aromatization for the synthesis of the polycyclic anthraquinones **8** functionalized with delicate sugar moieties (Scheme 4). Other dienophiles that were employed in this sequence included various quinones as well as dimethyl acetylenedicarboxylate (DMAD) together with various sugar functionalized dienes followed by aromatization under aerobic, acidic conditions.

Khan and co-workers³⁷ recently reported the use of the Diels–Alder and aromatization strategy in their synthesis of magterpenoid C (**11**) via a key silica-gel mediated [4 + 2]-cycloaddition reaction followed by oxidative aromatization with manganese dioxide (Scheme 5). The magterpenoids A–C inhibit protein tyrosine phosphatase 1B, and thereby enhance insulin sensitivity in cells. An attempted synthesis of the more complex tricyclic magterpenoid B by the same methodology, however, was not successful.



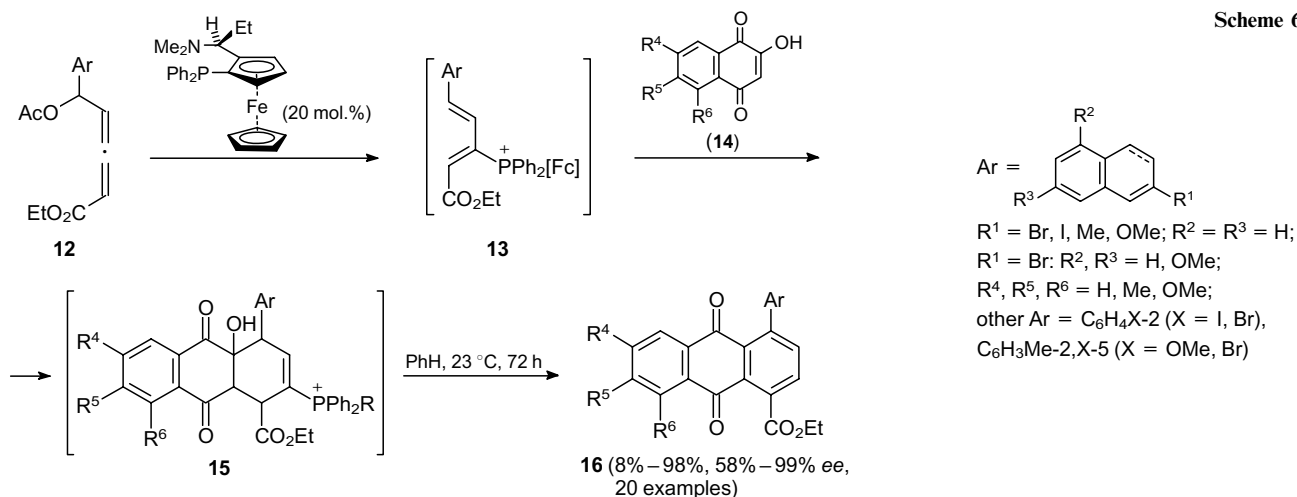
(a) PhMe, 110°C , 12 h; (b) SiO₂, NEt₃, air, 23°C , 2 h;



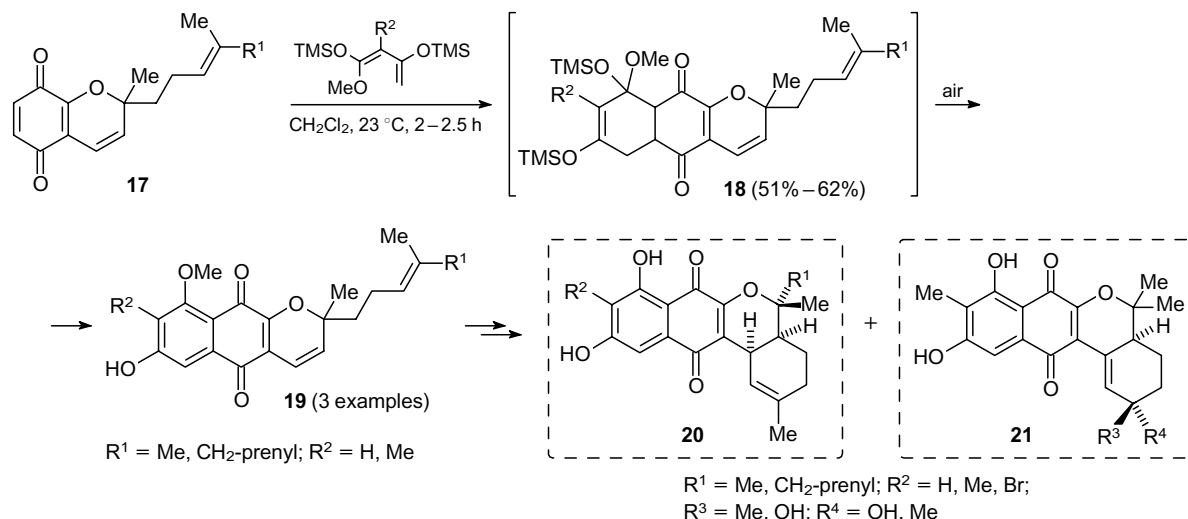
(a) 1) SiO₂, 2.5 h; 2) MnO₂, CH₂Cl₂, 39°C , 4 h

Tong and co-workers³⁸ reported the first atropoisomerically-selective synthesis of conformationally stable 1,1'-naphthyl-anthraquinones **16** from the Diels–Alder reaction of (1-acetoxy-1-(1-naphthyl)methyl)allenoates **12** and 2-hydroxy-1,4-naphthoquinones **14** catalyzed by an enantiomerically pure ferrocene-based phosphine (Scheme 6). These reactions were extended to those of a range of substituted (1-acetoxy-1-(2-mono- and 2,6-disubstituted-phenyl)methyl)allenoates, mono- and disubstituted-2-hydroxy-1,4-benzoquinones and a hydroxybenzo-anthracenequinone to provide the corresponding adducts

Scheme 6



Scheme 7



(16). The postulated mechanism involved phosphine addition to the allene and acetoxy elimination to form the diene **13**, which readily reacted with the dienophile **14** to produce the adduct **15**. Subsequent base mediated ylide formation, phosphine elimination and dehydration induced aromatization.

In his most recent meroterpenoid studies, George and co-workers³⁹ employed a Diels–Alder and aromatization sequence for the synthesis of the racemic aromatic core of the naphterpin and marinone natural products (Scheme 7). Quinones **17** and Brassard's diene (or derivative of Brassard's diene) and subsequent aerobic oxidation gave the tricyclic arenes **19**. Within one to three steps, these products **19** were converted into four different naphterpin (**20** and **21**) and marinone (**20**) natural products.

Hsu and Huang⁴⁰ employed a Diels–Alder reaction of naphthoquinone **22** with diene **23** in the presence of the Lewis acid boron triacetate, followed by methanol elimination, TMS-ether hydrolysis and aerobic oxidation to give anthraquinone **25**, furnishing three of the four rings of parimycin (**26**) (Scheme 8). The use of boron triacetate was critically important for the observed regioselectivity as well as enabling the reaction to proceed at room temperature. Anthraquinone **25** was subsequently converted into racemic parimycin (**26**) and its (*R*)-(-)-enantiomer (**27**) thereby

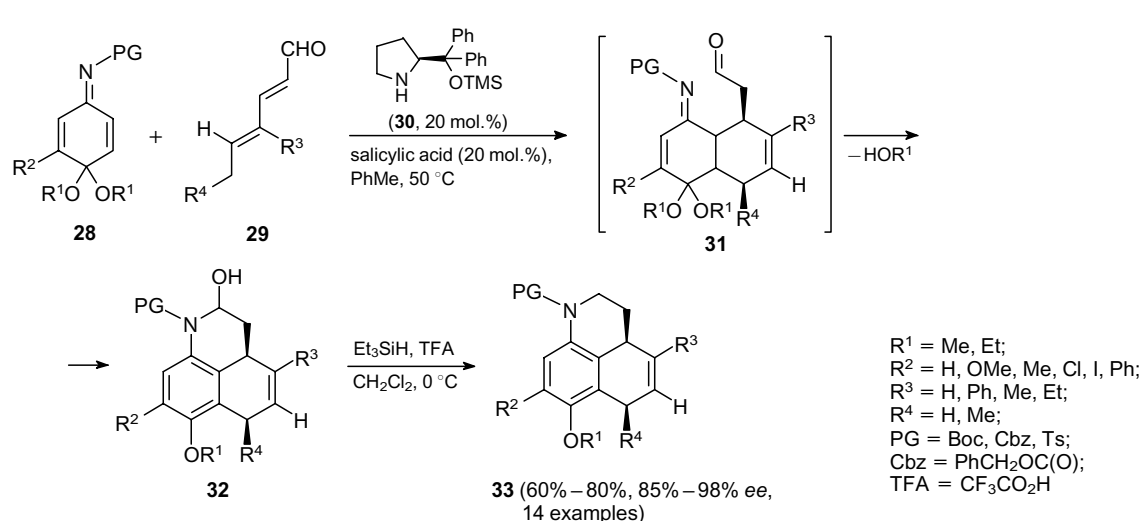
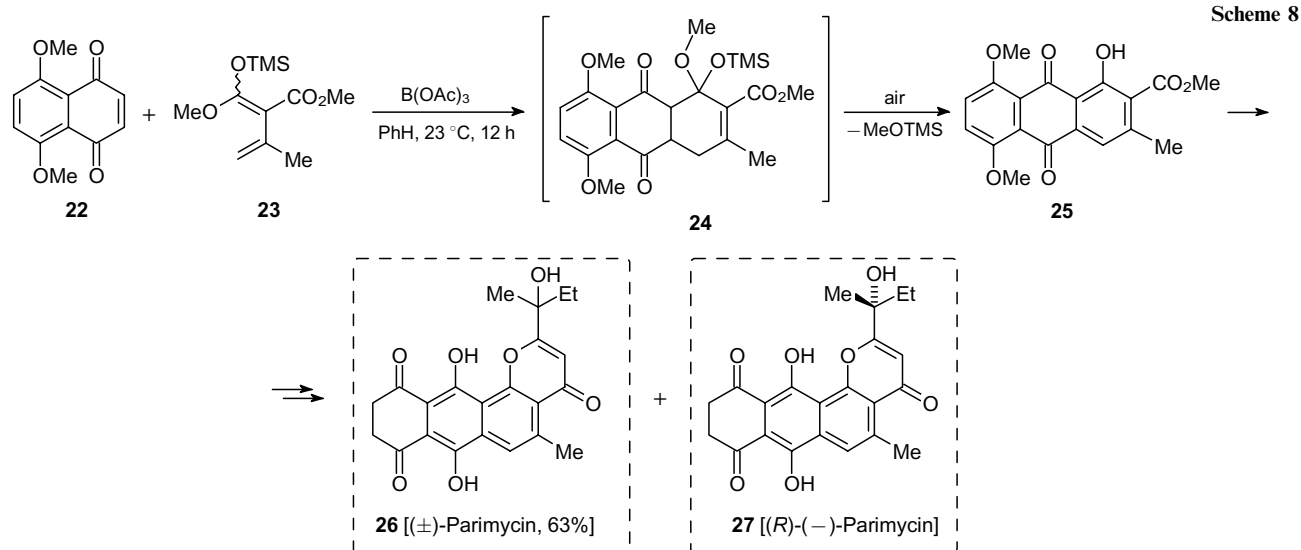
defining the absolute stereochemistry of the natural product as the (*S*)-(+)-enantiomer, a potent antitumour compound with activities against stomach, lung, breast and skin cancers with IC₇₀ values between 0.9 to 6.7 µg mL⁻¹.

Chen and co-workers⁴¹ showed that the formal Diels–Alder reaction of quinone imines **28** with dienals **29** catalyzed by the prolinol derivative **30** provided substituted aromatic compounds **33** with excellent relative and absolute stereochemical control following trimethylsilane mediated dehydroxylation of the carbinolamines **32** (Scheme 9). These products **33** included examples with a broad range of electron-withdrawing and -donating substituents. The method additionally showed good compatibility with a range of protecting groups (PG = Boc, Cbz, Ts) and proceeded with high enantioselectivities.

2.2. Thiophene and furan precursors

Kamimura and co-workers⁴² reported the synthesis of phthalimides **38** from maleimides **35** and furfural hydrazones **34** under microwave irradiation (MW) in ionic liquids (Scheme 10). The only by-product of this reaction is water and the ionic liquids were shown to be repeatedly recyclable with no loss of functionality.

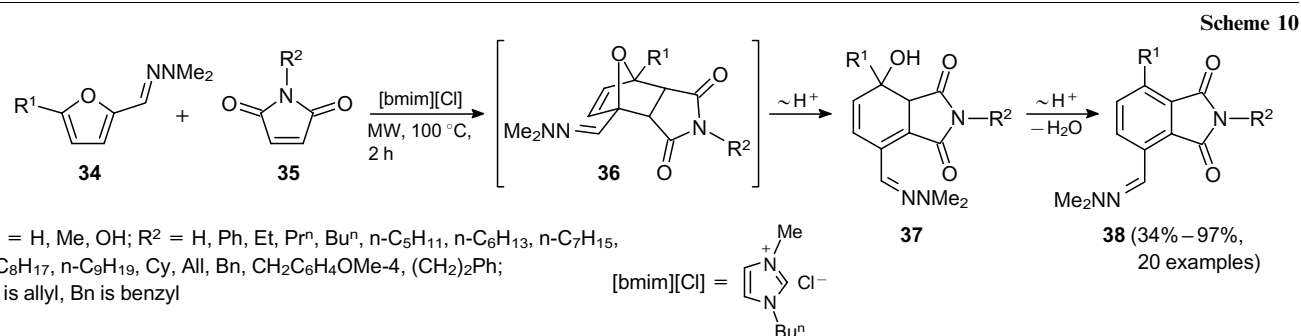
Jérôme and coworkers⁴³ described the synthesis of the *o*- and *m*-xylene derivatives **42** and **43** by allowing the

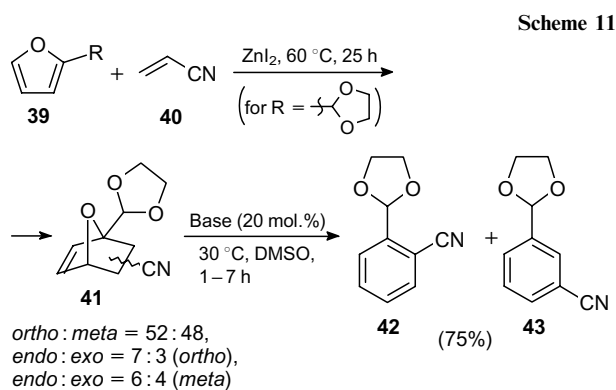


furfural acetal **39** to react with acrylonitrile **40** under Lewis acid catalysis to give the Diels–Alder adduct **41** (Scheme 11).⁴³ This Diels–Alder reaction showed modest selectivity towards the *o*-endo-adducts. Various bases were screened for the conversion of the Diels–Alder adducts into the aromatic compounds **42** and **43**, with regioselectivities ranging from 1.5–3.4:1 in favour of the *m*-product **43**. By prematurely quenching the base induced aromatization reaction of adduct **41**, the selectivity towards the *m*-xylene derivative **43** was further enhanced. Subsequent derivatiza-

tion was used in a new route to *m*-xylenediamine, an important monomer in polymer chemistry.

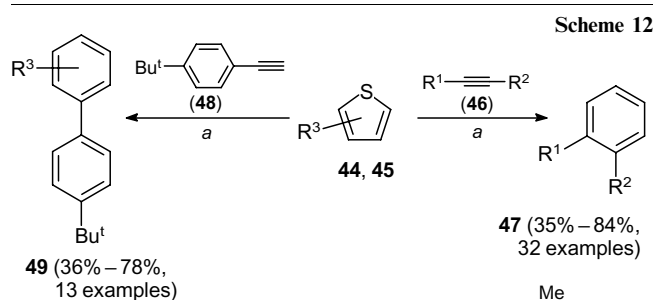
Recently, Lei and co-workers⁴⁴ reported the conversion of thiophenes **44**, **45** and acetylenes **46**, **48** to aromatic compounds **47**, **49** under exceptionally mild photocatalytic conditions using 9-mesityl-10-methylacridinium perchlorate (Mes-Acr⁺ClO₄⁻), with the generation of elemental sulfur as a byproduct (Scheme 12). Related Diels–Alder reactions of thiophene were previously reported to proceed at very high temperatures (typically > 220 °C)⁴⁵ but this was reduced to room temperature with photocatalysis. It was postulated



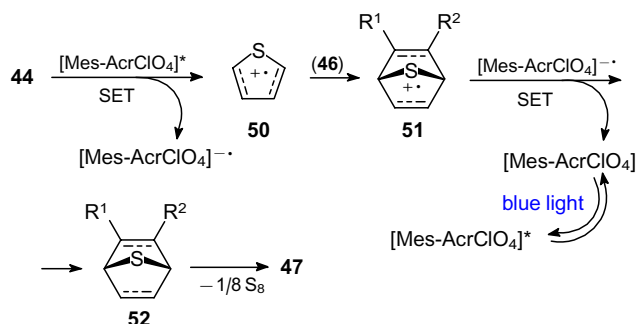
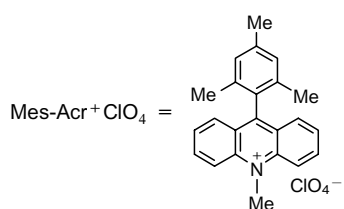


$\text{R} = \text{Me}, \text{CH}_2\text{OEt}, \text{CH}_2\text{OH}$ (38%–86%, 42:43 = 1:1.5–1:3.4);
 Base: NaOMe, NaOBu^t, KOH, NaOH, Amberlyst-26

that the formal [4 + 2] addition was initiated by the oxidation of thiophene (44) to the corresponding radical cation 50 by the excited state of the photocatalyst. Addition of this species to alkynes 46 gave the radical cation adduct 51,



(a) MesAcr⁺ ClO₄[−],
 MeCN, blue LED, 23 °C,
 12 h

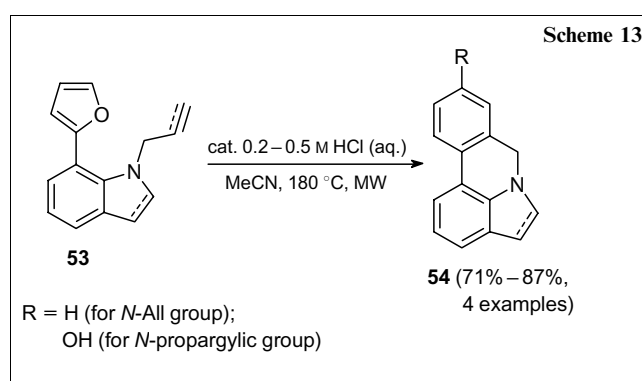


$\text{R}^1 = \text{Ph}, \text{C}_6\text{H}_4\text{X-4}$ (X = Bu^t, Me, Ph, OAc, OMe, F, Cl, Br, CHO, CO₂Me, CF₃, CN), C₆H₄Me-2(3), 3-Th (Th is thienyl), 4-NMe-pyrazole, 1-cyclohexenyl, (CH₂)₂OTBS, (CH₂)₂Ph, 3-biphenyl, Et, estrone, C₆H₄[CH₂CH(NHAc)CO₂Me]-4, sarcosine derivative, C₆H₄-4-CH₂OC(O)C₆H₄(SO₂NPr₂)-4; $\text{R}^2 = \text{H}, \text{Me}, \text{Et}$;
44: $\text{R}^3 = \text{H}$; **45**: $\text{R}^3 = 2\text{-X}$ (X = Me, Cl), 4-X (X = Me, Et, n-C₆H₅, (CH₂)₂OAc, Cl, Br, I, CH₂OMe, 3-Bpin, 3-CO₂Me, C≡CH), 3,4-Me₂

TBS = SiBu^tMe₂, Bpin = , LED is light-emitting diode,
 SET is single electron transfer

which was reduced by a single electron transfer (SET) from the reduced photocatalyst, thereby regenerating the photocatalyst and forming the Diels–Alder adduct **52**, which subsequently underwent elimination of sulfur accompanied by aromatization. The authors reported related syntheses of aromatic compounds from the corresponding selenophenes.

In 2019, Gundersen *et al.*⁴⁶ reported the conversion of *N*-allyl- or *N*-propargyl substituted indole or indoline derivatives **53** into the core of bioactive lycorine alkaloids **54** via a Diels–Alder reaction followed by acid-catalyzed dehydration and aromatization (Scheme 13). When the precursor **53** was functionalized with *N*-allyl groups, the reaction gave rise to arenes (**54**, R = H), whereas the use of precursors **53** with *N*-propargyl groups provided phenols (**54**, R = OH). The authors also reported related intramolecular Diels–Alder and aromatization sequences for *o*-(2-furyl)-*N*-allyl- and *N*-propargylaniline derivatives.



In 2020, Zubkov and co-workers⁴⁷ reported an aromatization method that involves the formation of arenes **67** and **75** from 3-(2-furyl)-allyl amines **56** and **73** and bromomaleic anhydride **55** (Scheme 14). The authors proposed the initial formation of amides **57** and **58**, which subsequently underwent an intramolecular Diels–Alder reaction, with *exo*-control. Amides **57** plausibly undergo reaction *via* intermediates **61**–**66** to produce the final lactams **67**. In a comparable way, amides **58** plausibly undergo reaction *via* intermediates **68**–**72** to produce the same final lactams **67**. The lactams **67** were obtained in moderate to good yields after recrystallization. When the authors used 3-(3-furyl)-allyl amines **73**, the corresponding aromatization product **74** was shown to be sensitive to acidic conditions, which resulted in the opening of the dihydrofuran ring to yield phenols **75** in moderate yields after recrystallization.

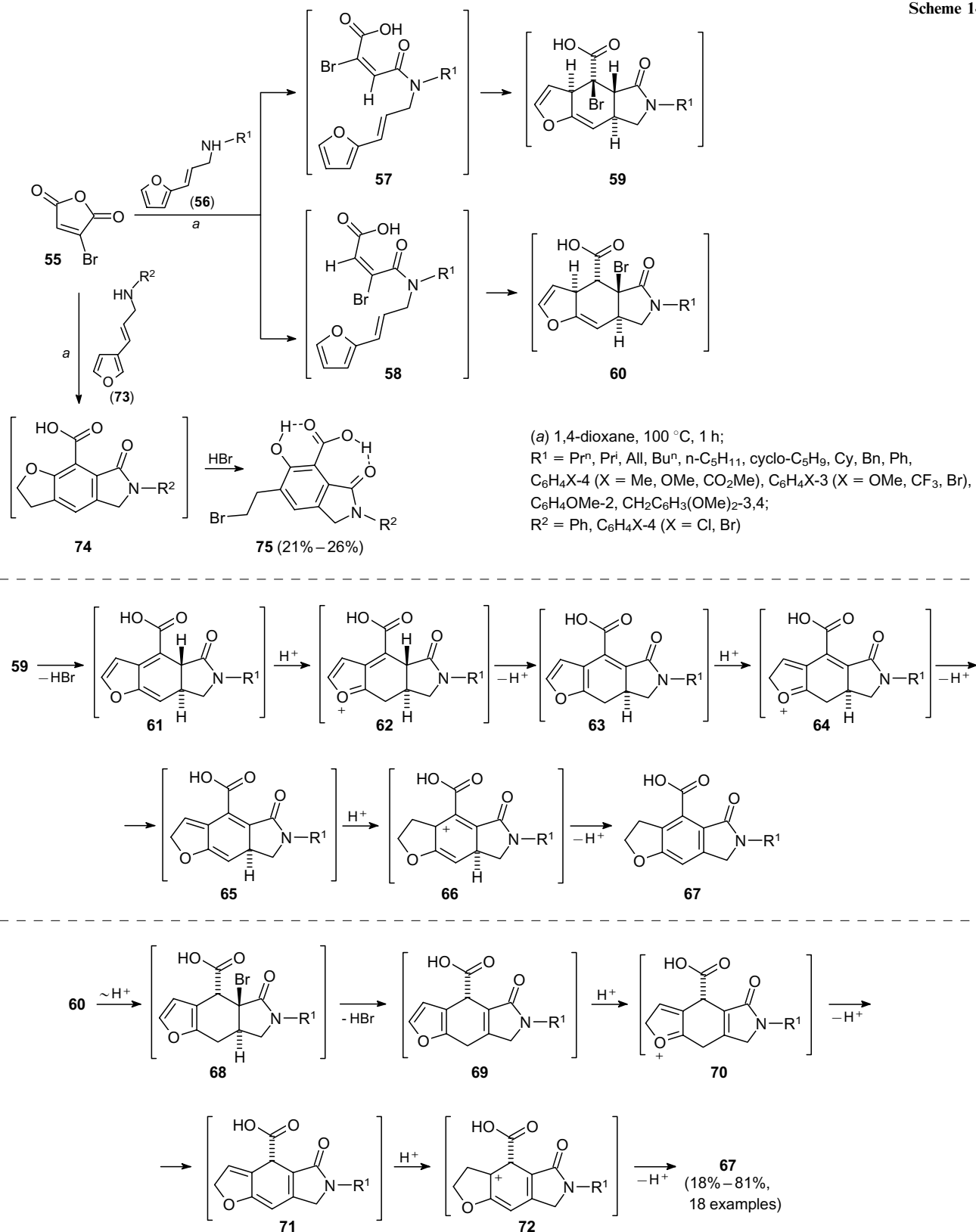
2.3. Pyrone starting material

Pyrone are exceptionally good dienes for the synthesis of aromatic compounds since the initial cycloadducts **77** readily undergo loss of carbon dioxide in the aromatization step (Scheme 15). Snyder and co-workers⁴⁸ synthesized a range of indoline derivatives **78** in excellent yields using this method.

In 2017, Kraus and Wang⁴⁹ synthesized a range of differentially substituted aromatic compounds **82**, **84** by simple variation of the dienophile **80** in the Diels–Alder reaction step and subsequent aromatization by loss of carbon dioxide (Scheme 16). Interestingly in these examples, intermediate Diels–Alder-lactones **81** and **83** were stable and could be isolated.

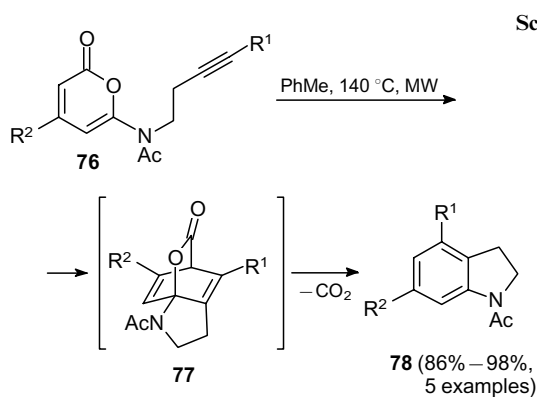
Additionally, Yu and Kraus⁵⁰ expanded the substrate scope of this reaction by including various enamines **85**, **90**,

Scheme 14

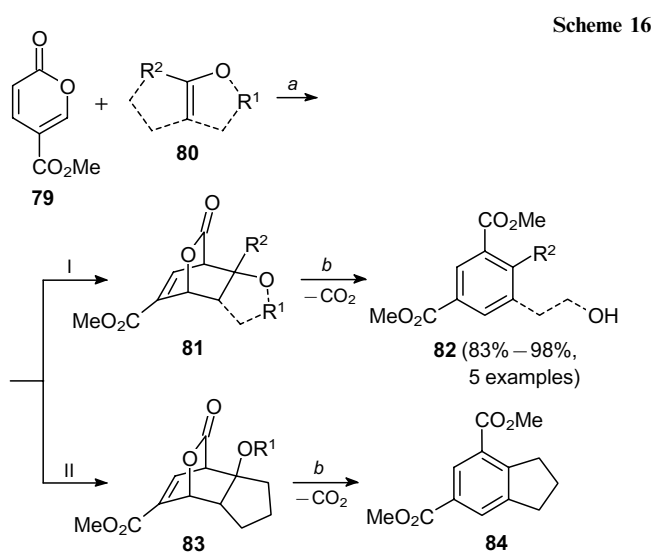


91 as dienophiles to provide the arenes **88**, **93** and **94** (Scheme 17). A range of enamine substrates bearing various alkyl and aryl groups as well as cyclic enamines were used in this reaction. Interestingly, the pyrrolidine enamine adducts **87** rapidly underwent elimination of both carbon dioxide and pyrrolidine and aromatization to provide the tetrahy-

dronaphthalene **88**, whereas the morpholine adducts **92** were stable enough for purification but were aromatized using base-mediated elimination. When the cyclopentene derivative of enamine **86** was used, the reaction gave ketone **89** via a conjugate addition, carbon dioxide elimination and



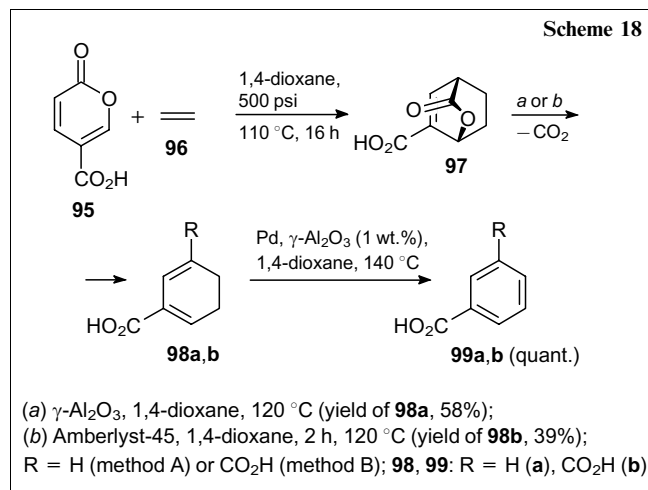
$R^1 = \text{H, Ph, TMS, CF}_3$; $R^2 = \text{Cl, SPh}$



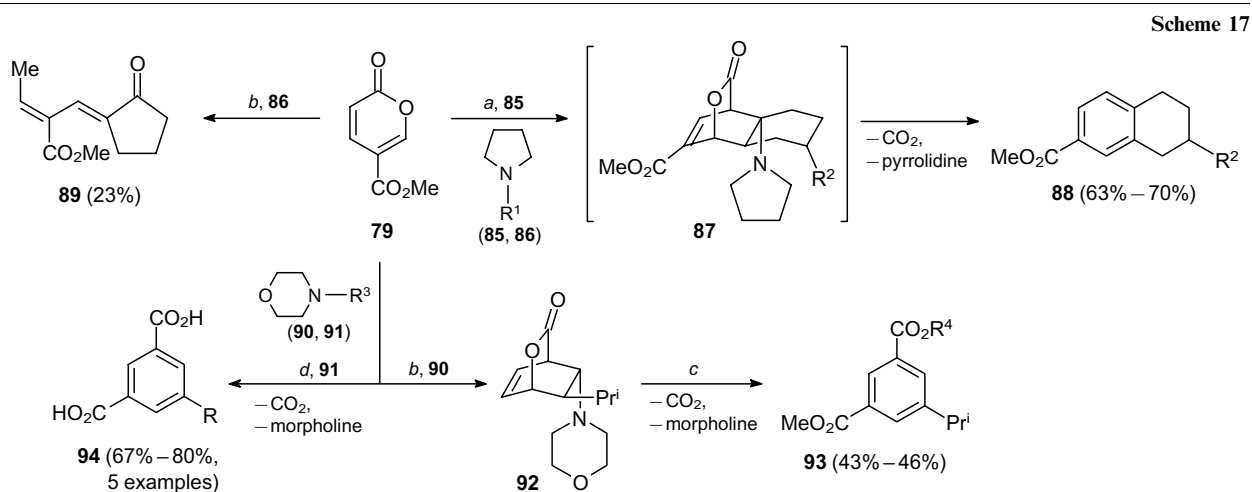
(a) MeCN, 75 °C; (b) TsOH, MeOH, 65 °C;
I: $R^2 = \text{H}$; $R^1 = \text{OBU}^t, (\text{CH}_2)_2$; $R^1 = \text{Me}$; $R^2 = \text{Me, Ph, 2-Th}$;
II: $R^2 = (\text{CH}_2)_2$; $R^1 = \text{OMe, OTMS}$; Ts is tosyl

hydrolysis of the enamine rather than the anticipated Diels–Alder product.

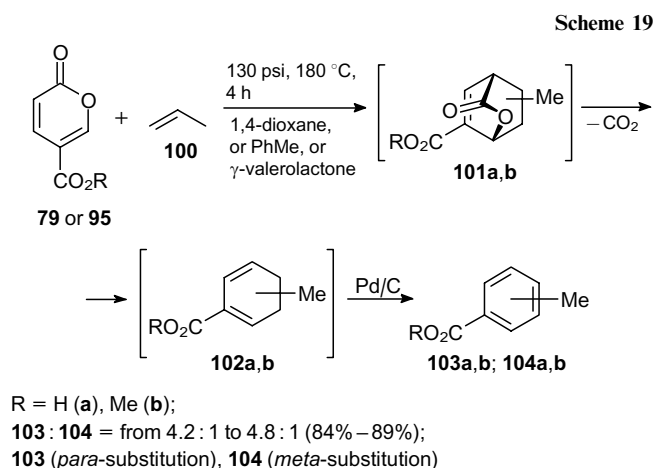
Methyl coumalates **79** (see Scheme 16) and coumalic acid **95** are feedstock chemicals accessible from malic acid through dimerization. Shanks and co-workers⁵¹ investigated the transformation of acid **95** into the bulk chemicals benzoic (**99a**) and isophthalic acids (**99b**) (Scheme 18) *via* a Diels–Alder reaction of **95** with ethylene (**96**) which initially gave lactone **97**. The advanced cyclohexadiene moiety **98** was accessible through either Lewis acid mediated ($R = \text{H}$) or Brønsted acid ($R = \text{CO}_2\text{H}$) mediated lactone decarboxylation. Finally, catalytic dehydrogenation gave benzoic acid **99a** effectively from feedstock biomass.



Subsequently, Shanks and co-workers⁵² were able to expand this methodology to synthesize *p*- or *m*-toluic acids (**103a**, **104a**) or their esters (**103b**, **104b**) in excellent yields starting from methyl coumalate **79** or coumalic acid **95** and propylene (**100**) (Scheme 19). By raising the temperature, the reaction proceeded smoothly to the cyclohexadiene intermediates **102**, which upon addition of Pd/C could be dehydrogenated to compounds **103a,b**, **104a,b**.



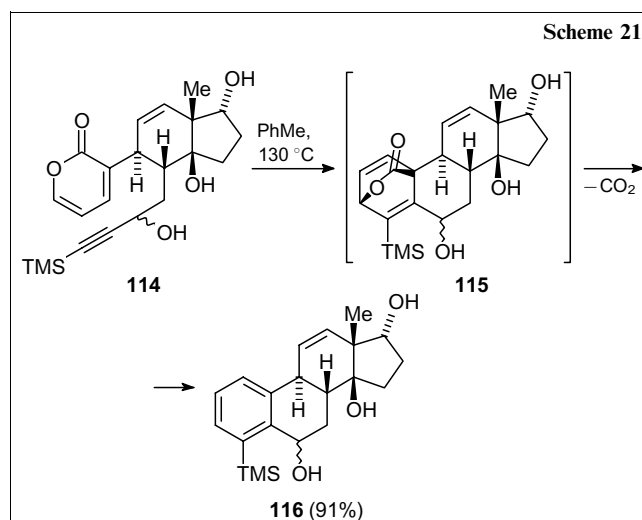
(a) MeOH; (b) CH_2Cl_2 ; $R^1 = \text{---} \text{C}_6\text{H}_4 \text{---} R^2$ ($R^2 = \text{H, CO}_2\text{Et}$, **85, 87, 88**), $\text{---} \text{C}_6\text{H}_4 \text{---}$ (**86**); (c) K_2CO_3 , MeOH; (d) 1) CH_2Cl_2 ; 2) KOH, MeOH– H_2O , reflux; 3) HCl; $R^3 = \text{---} \text{C}_6\text{H}_4 \text{---} R^4$ (**90**), $\text{---} \text{C}_6\text{H}_4 \text{---} R^5$ ($R^5 = \text{Et, Ph, C}_6\text{H}_4\text{OMe-4, C}_6\text{H}_4\text{Me-2, C}_6\text{H}_4\text{Br-3}$, **91**); $R^4 = \text{H, Me}$



In 2018, Cui and co-workers⁵³ synthesized heavily substituted indole derivatives **109** as well as aniline derivatives **113** via a one-pot cascade sequence of alkyne (**106**, **111**, **112a**) and alkynyl-acid **110** coupling to produce pyrones **107**, which underwent a subsequent Diels–Alder and aromatization sequence (Scheme 20). A broad scope of various aliphatic and aromatic substituents were tolerated in these transformations.

In 2019, Nakazaki and co-workers⁵⁴ reported the synthesis of an estrogen analogue **116** using an intramolecular pyrone–Diels–Alder and aromatization sequence of alkynyl-pyrone **114** in their studies on the potential medical chemistry applications of highly oxygenated steroids (Scheme 21).

Garg and co-workers⁵⁵ reported that electron-rich pyrones **121**, which can be synthesized from 6*H*-1,3,4-oxadiazin-6-one (**119**), reacted with the strained azacycloalkyne **118**, generated *in situ* from the silyl-triflate precursors **117** with caesium fluoride, to provide the heterocyclic compounds **123** and **124** after carbon dioxide elimination with concomitant aromatization. The initial cycloaddition with a ratio of precursors **117**:**119** of 1:2 and dinitrogen loss gave both regioisomers **121a,b** but the second adduct underwent selective decomposition with the excess caesium fluoride present to leave only the azapyrone **121a** (74%). When the reaction was carried out with a ratio of precursors **117**:**119**

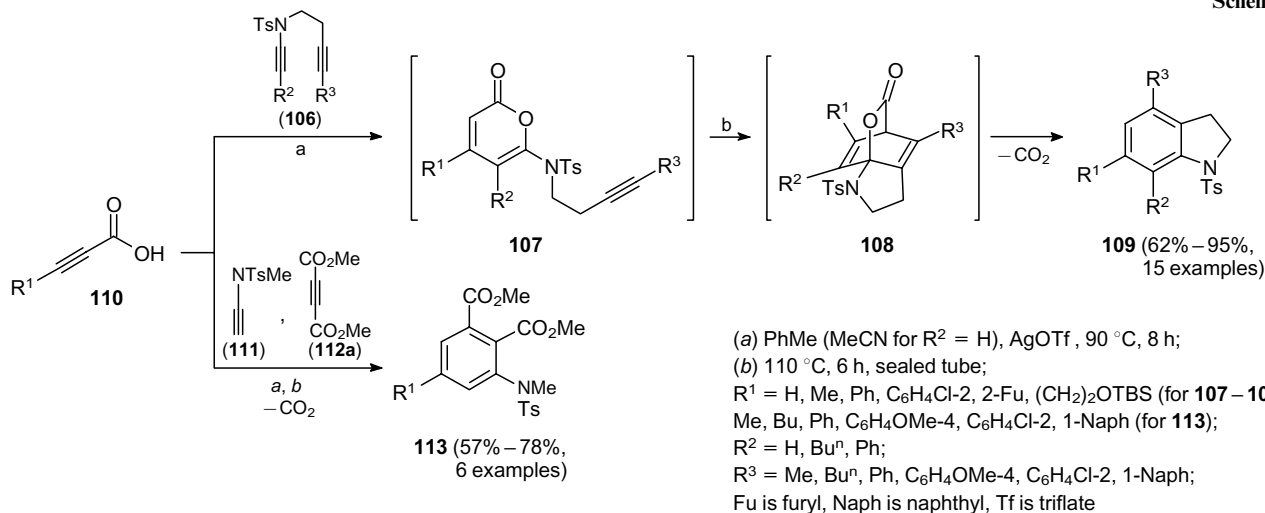


of 2:1, a double cycloaddition and carbon dioxide loss occurred giving both arenes **123** and **124**. The aza-pyrone **121a** was also converted into the corresponding derivatives by reaction with other strained cycloalkynes (cyclohexyne **125** and 4-oxacyclohexyne **126**). These reactions proceeded under mild conditions and in good yields [71% and 62% (**123**:**124** ratio is 1.5:1), respectively] (Scheme 22). Additional examples from the Garg group included related trapping reactions with arynes and heteroarynes but these are outside the scope of this review.

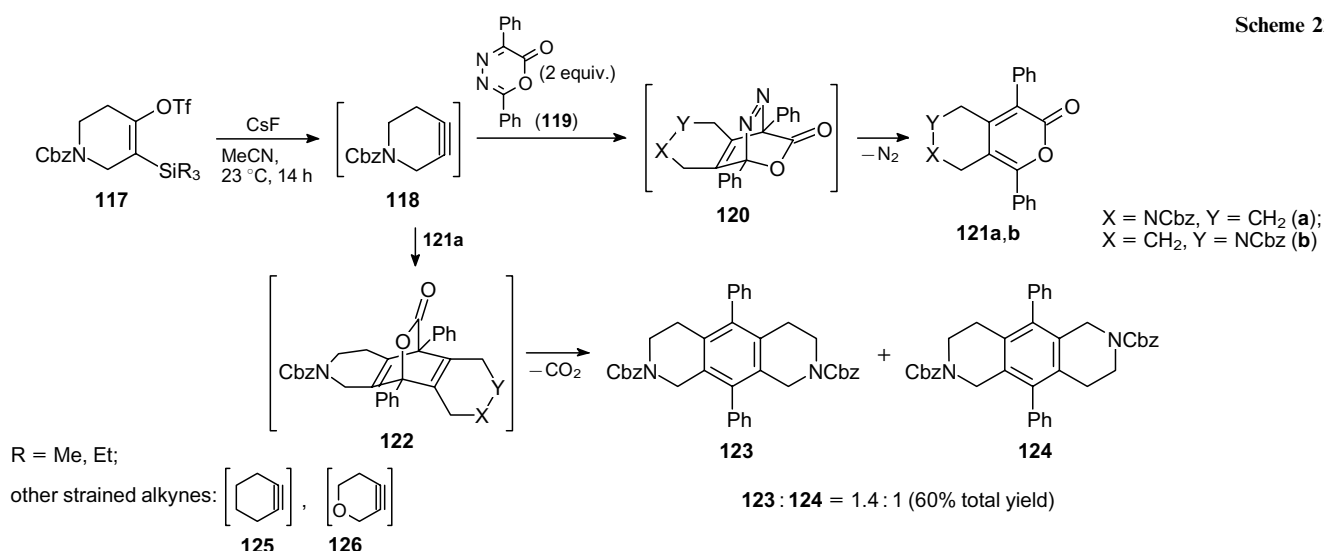
Recently, Wilson *et al.*⁵⁶ reported a cascade sequence of an intramolecular Diels–Alder reaction of the pyridones **127** followed by the elimination of isocyanic acid (**129**) instead of carbon dioxide to synthesize isoindolinones **130**; such heterocyclic compounds are common scaffolds in medicinal chemistry (Scheme 23).

Wang and co-workers⁵⁷ reported the synthesis of benzoate esters **135** (Scheme 24). Initially, the synthesis provided lactones **133** at 120 °C, however raising the temperature to 150 °C resulted in smooth conversion to the cyclohexadienes **134**. Subsequently, this route was extended by addition of DDQ, thereby providing benzoate esters **135**. Finally, employing alkynes **136** instead of alkenes **132** gave the similar arenes **135**.

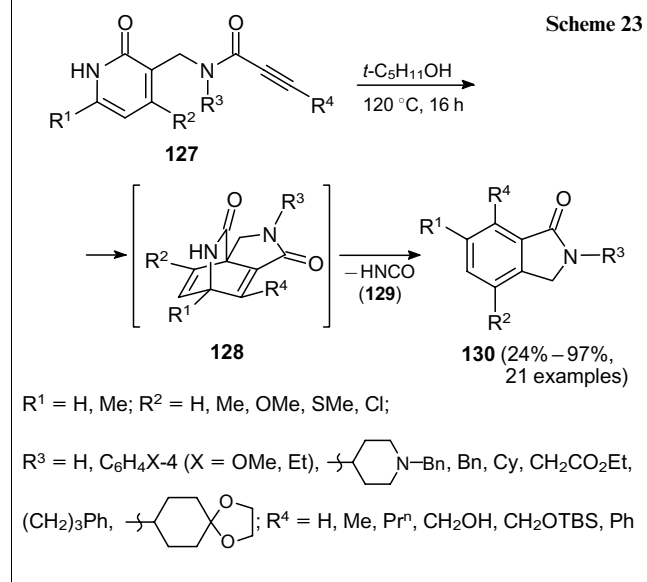
Scheme 20



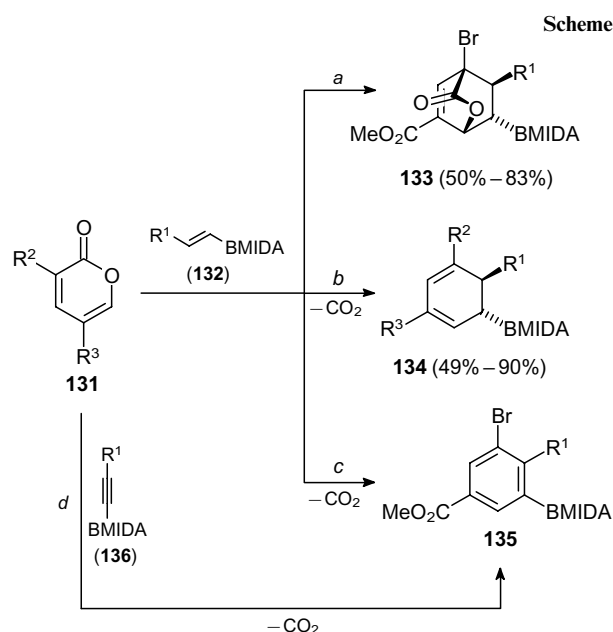
Scheme 22



Scheme 23



Scheme 24



2.4. Miscellaneous substrates

Abae *et al.*⁵⁸ reported a one pot procedure for the synthesis of bicyclic aromatic compounds **142** from enones **137**, aldehydes **138** and acetylenedicarboxylate esters **112a,b** using recyclable, silica-coated magnetite nanoparticle-based catalyst FN-Fe₃O₄ (**139**) followed by aerobic oxidative aromatization (Scheme 25).

In 2017, Philkhana and Reddy⁵⁹ reported the synthesis of fregenedadiol (**146**) and fregenedadiol acetate (**147**) using a Diels–Alder cycloaddition and oxidative (DDQ) aromatization sequence as key steps to elaborate the arene core **145** (Scheme 26). Reaction of diene **143** with dimethylacetylenedicarboxylate **112a** gave the cycloadduct **144** and this was oxidatively aromatized with DDQ to provide the arene **145**, which was converted to the natural products **146** and **147** respectively in two (reduction, hydrogenolysis) and three (reduction, hydrogenolysis, acylation) steps.

Thamattoor and co-workers⁶⁰ reported the synthesis of the reactive intermediate, 3-oxacyclohexyne (**126**), via an unusual photochemical rearrangement reaction (Scheme 27).⁶⁰ In this study, the phenanthrene derived precursor **148** underwent photolytic cleavage and thereby formed carbene **149**, which, in turn, rearranged to the reactive species **126**. Its generation *in situ* in the presence

(a) DCE, 120 °C, 6 h; $\text{R}^2 = \text{Br}, \text{R}^3 = \text{CO}_2\text{Me}$;

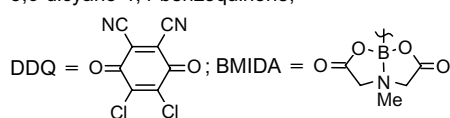
$\text{R}^1 = \text{Ph, C}_6\text{H}_4\text{CO}_2\text{Me-4, C}_6\text{H}_2(\text{OMe})_3\text{-3,4,5, C}_6\text{H}_3\text{Me}_2\text{-2,4, 2-fluorenyl, 2-Th}$;

(b) DCE, 150 °C, 3–9 h; $\text{R}^1 = \text{Ph, C}_6\text{H}_4\text{X-4 (X = CO}_2\text{Me, OMe, Cl), C}_6\text{H}_4\text{X-3 (X = Me, CF}_3\text{), C}_6\text{H}_3\text{F-4, Me-3, C}_6\text{H}_3\text{Me}_2\text{-2,4, 3-Th, 2-fluorenyl, 1-Naph}$; $\text{R}^2 = \text{H, Br, CO}_2\text{Me}; \text{R}^3 = \text{H, CO}_2\text{Me}$;

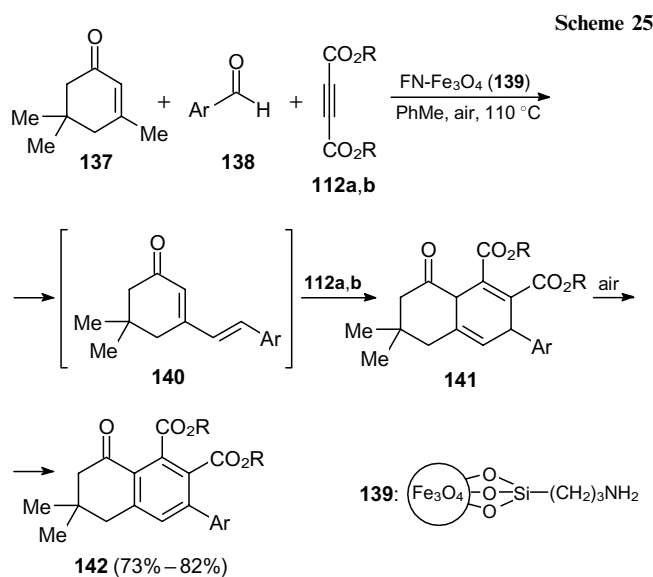
(c) 1) DCE, 150 °C, 5 h; 2) DDQ, 80 °C, 1 h; $\text{R}^2 = \text{Br, R}^3 = \text{CO}_2\text{Me}; \text{R}^1 = \text{Ph, C}_6\text{H}_4\text{X-4 (X = SMe, Bu}^t\text{, Cl, OMe), C}_6\text{H}_4\text{Me-3, 2-fluorenyl (21%–65%)}$;

(d) DCE, 170 °C, 5 h; $\text{R}^2 = \text{Br, R}^3 = \text{CO}_2\text{Me}; \text{R}^1 = \text{Ph, C}_6\text{H}_4\text{X-4 (X = F, CO}_2\text{Me), C}_6\text{H}_4\text{OMe-3, 2-Th (40%–77%)}$;

DCE = Cl(CH₂)₂Cl, DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone;



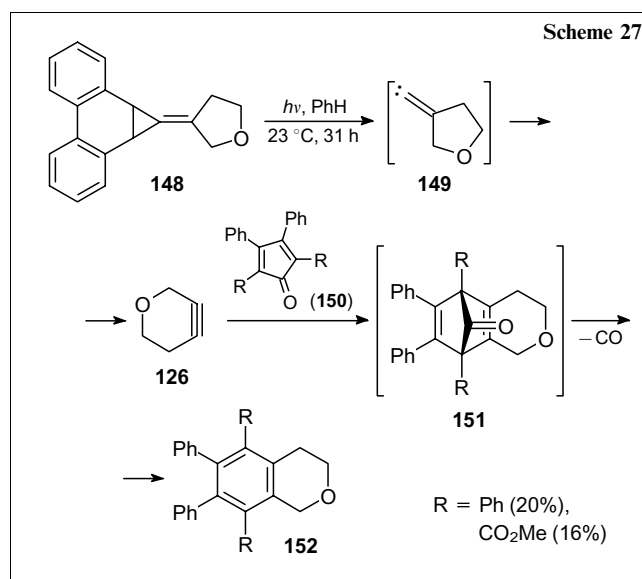
of cyclopentadienones **150** gave the Diels–Alder adduct **151** and this underwent a retro [4 + 1] reaction with loss of carbon monoxide and aromatization to provide the isochromanes **152** in moderate yields.



R = Me (**a**), Et (**b**); Ar = Ph, C₆H₄X-3 (X = Me, OMe), C₆H₄X-4 (X = Me, OMe, Cl), 2-Th

In 2019, Carreira and co-workers⁶¹ reported the completion of the total synthesis of (–)-merochlorin A (**160**) by a late stage introduction of the aromatic core (Scheme 28). Dehydrogenation of ketone **153** by reaction of the derived enolate with imino-sulfonyl chloride **154** gave the enone **155**, which underwent a Diels–Alder reaction with Brassard's diene **156** with hydrolytic cleavage to produce the core cyclohexenone unit **157**. This was converted into the enol trimethylsilyl ether **158**, which underwent Saegusa–Ito oxidation to form the resorcyate **159**. Subsequent de-*O*-methylation of ether **159** completed the synthesis of (–)-merochlorin A (**160**), a potent antibiotic with MIC's of 0.15–0.3 μmol L^{–1} against *C. difficile* and 2–4 μmol L^{–1} against *S. aureus*.

In 2019, Liang and co-workers⁶² synthesized the ABCE ring system of daphenylline **165** using a Diels–Alder reaction of amine-borane complex **161** with dimethyl acetylenedicarboxylate (**112a**) and subsequent aerobic oxidation

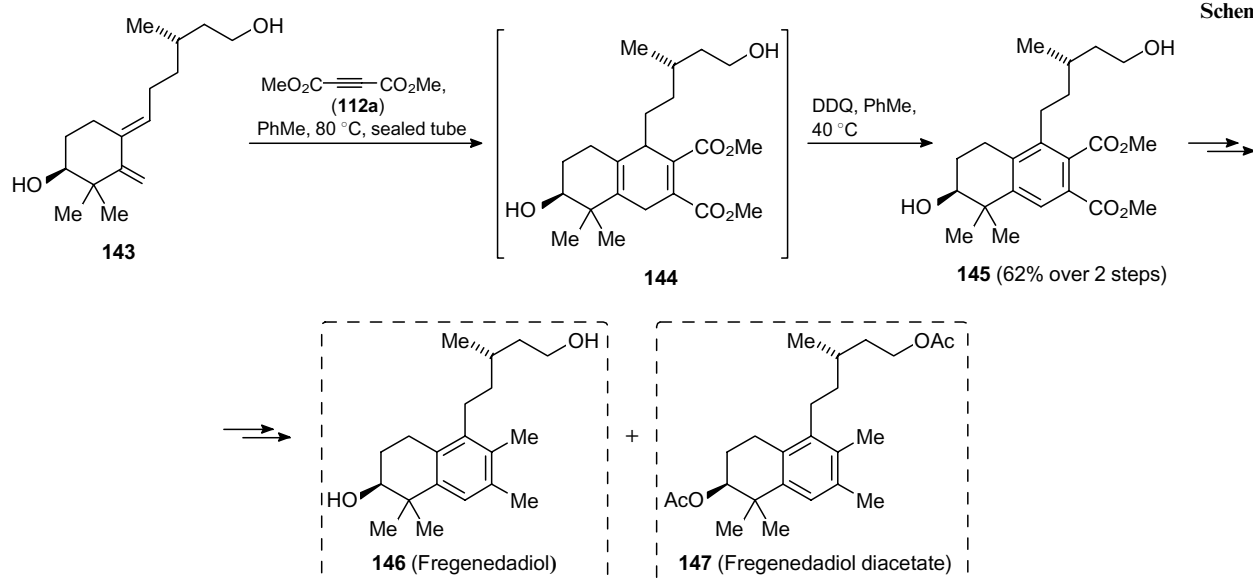


to produce the arene **163**, which was purified as the amine-borane salt (Scheme 29). Without amine coordination with borane as in the complex **161**, the critical Diels–Alder reaction did not occur. Additionally, diverse alternative oxidants for the aromatization reaction of diene **162** to arene **163** were unsuccessful.

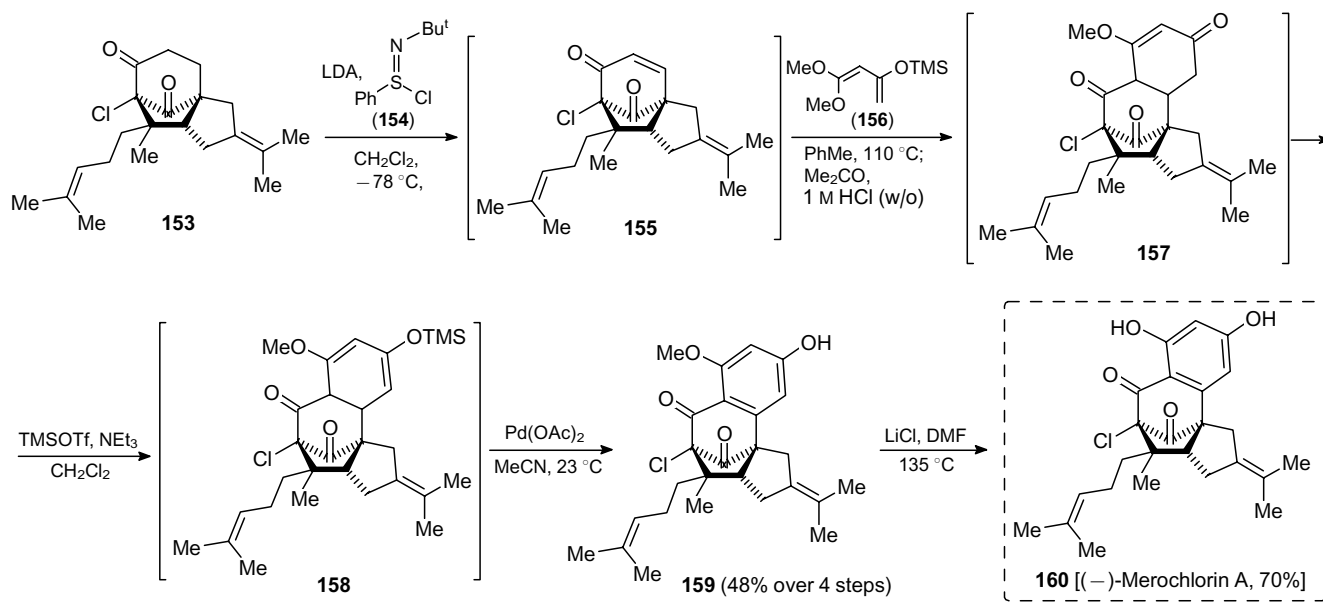
Recently, Yu and co-workers⁶³ synthesized the aromatic core of psymberin (**170**, irciniastatin A) by the reaction of alkynyl-ester **166** with diene **167** and subsequent aromatization by the expulsion of isobutylene following earlier Danishefsky and co-workers^{64–66} precedent (Scheme 30). Psymberin was shown to have high cytotoxic activities against breast cancer, colon cancer and melanoma (LC₅₀ values < 2.5 × 10^{–9} mol L^{–1}).

Moreover, Yuan and co-workers⁶⁷ synthesized a range of bioactive sesquiterpenes **173** through the key intramolecular Diels–Alder and oxidative aromatization sequence of alkyne **171** (Scheme 31) *via* diene **172**. Further functionalization of the ketone at the α-position was used to readily synthesize a range of natural products **174–178**.

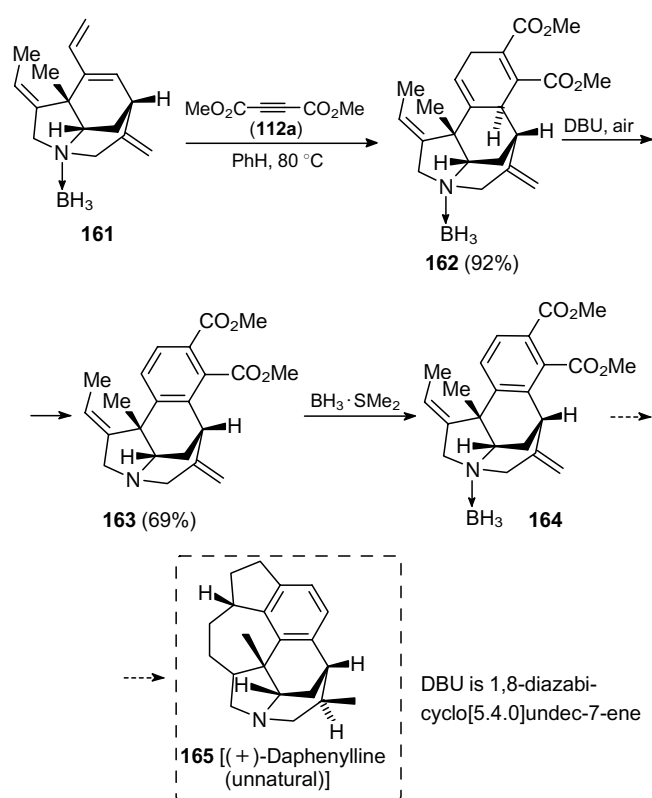
Some benzochromenes exhibit interesting biological properties including antibacterial, antioxidative and anti-



Scheme 28



Scheme 29



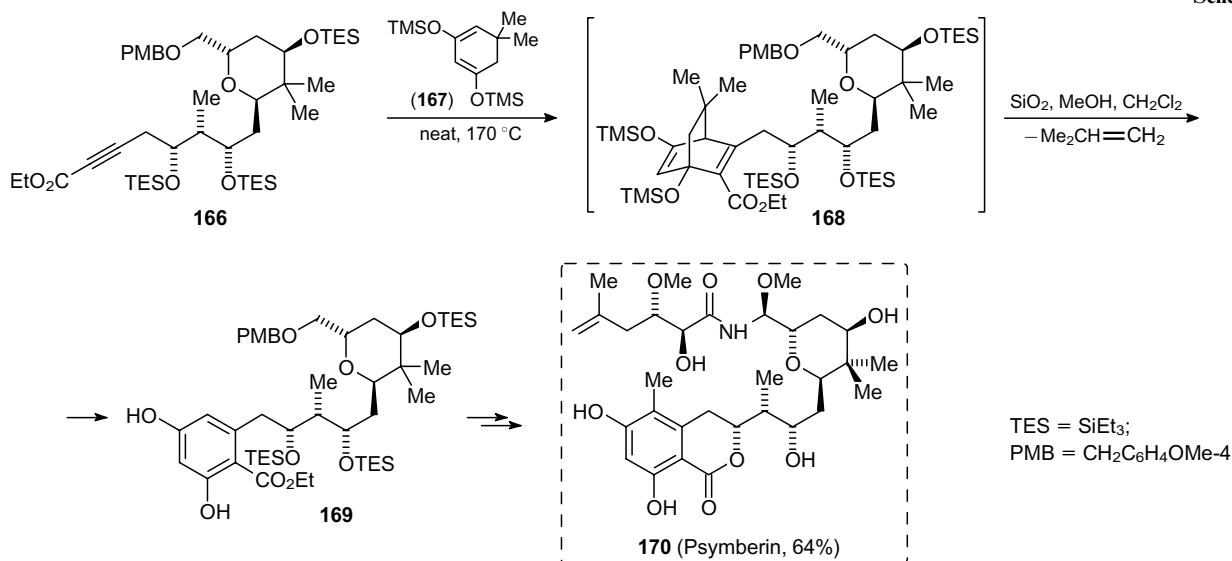
microbial activities and possess material properties useful for the fabrication of photovoltaic devices. Xu and co-workers⁶⁸ reported a synthesis of these heterocyclic compounds through a Wolf-rearrangement of a diazoacetoacetate derivative **179** to the corresponding ketene-based diene **180** (Scheme 32). This reactive intermediate gave 6*H*-benzo[*c*]chromene derivatives **182** following an intramolecular Diels–Alder reaction and subsequent aromatization through tautomerization.

Zhang and co-workers⁶⁹ reported that bifunctional ligands **L**, with a Lewis-basic phosphine coordinating to the metal catalyst as well as a Brønsted-basic amine to act as a proton shuttle, together with a π -Lewis acid such as gold(I) chloride mediated the rearrangement of acetylenic amides **183** into amino-furans **185** (Scheme 33). These highly electron-rich intermediates were trapped, *in situ*, with a dienophile in an inter- or intra-molecular Diels–Alder reaction. Ring opening of the resultant dihydrofuran intermediates **187** and elimination of water gave the tetra-substituted arenes **188** and **190**. The intramolecular reaction affording the latter arene was extended with variation in the tether.

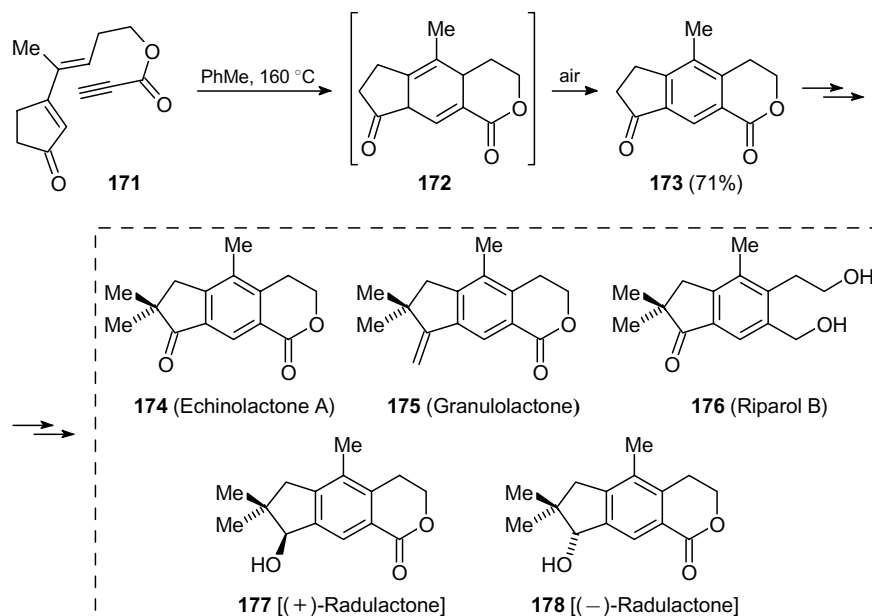
Kirschning and co-workers⁷⁰ reported three different routes to synthesize chromanes, a heterocyclic unit found in various biologically active natural products (Scheme 34). Reaction of vinyl-dihydropyran **191** with nitroalkenyl sulfide **192** gave cyclohexadiene **194** by Diels–Alder reaction and subsequent elimination of phenylsulfenic acid. Without the need of further oxidants, cyclohexadiene **194** underwent aromatization by elimination to yield alcohol **195**. Diels–Alder reaction of vinyl-dihydropyran **196** with keto-acetylene **197** gave cyclohexadienes **198** and **199**, which were subsequently converted into chromane **200** via DDQ mediated oxidation. Reaction using excess DDQ resulted in cleavage of the silyl-ether and oxidation of the benzylic alcohol giving the corresponding ketone. Other acetylenes and additives were examined, but the yield of the Diels–Alder reaction was not significantly better. Subsequently, the use of high pressure was investigated, which gave dihydrobenzenes **198**, **199** in combined 35% yield. In addition, chromane **202** was formed under these conditions, presumably due to a second Diels–Alder reaction of dihydrobenzene **199** with keto-acetylene **197** and subsequent elimination of ethylene from **201** to produce chromane **202**.

The pyrone Diels–Alder reaction was investigated by Kirschning and co-workers⁷⁰ initially on a model system, which gave lactones **204** and **205**. Subsequent loss of carbon dioxide gave cyclohexadiene **206** and this was aromatized with DDQ to produce chromane **207** (Scheme 35). Optimum yields were obtained at room temperature and high pressure

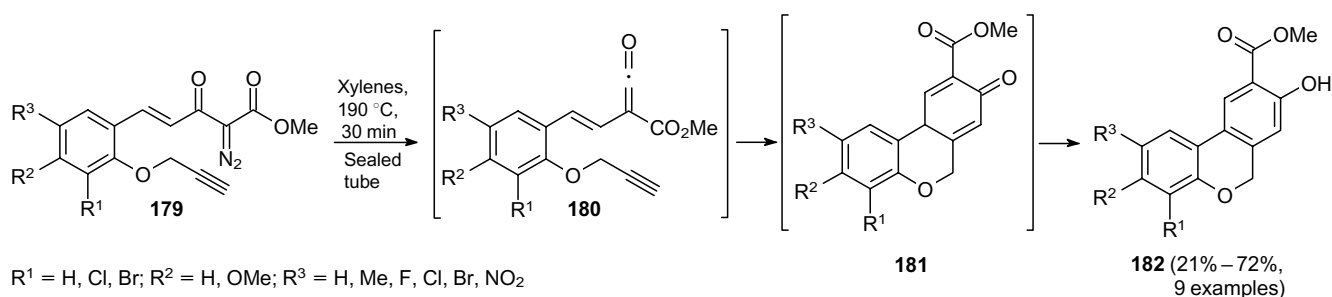
Scheme 30



Scheme 31



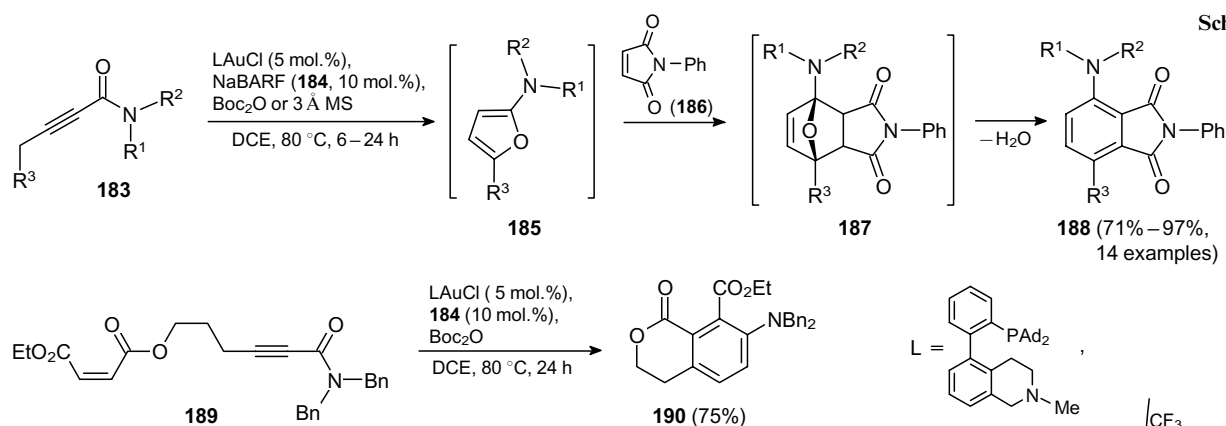
Scheme 32



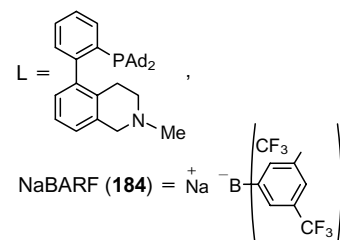
over prolonged reaction times. This method was successfully applied to dihydropyran **208** and methyl coumalate **79** in an inverse electron demand Diels–Alder reaction followed by the loss of carbon dioxide and DDQ mediated oxidative aromatization.

In recent studies on the synthesis of biphenyl and heterobiaryls, Temperini *et al.*⁷¹ employed a Diels–Alder reaction of the enol acetate derived from **211**, via transacylation with *iso*-propenyl acetate (**213**), with acetylene **212** (Scheme 36).⁷¹ Yields were better at 145 °C than 110 °C, and elevated pressure in a closed metal vessel gave dihy-

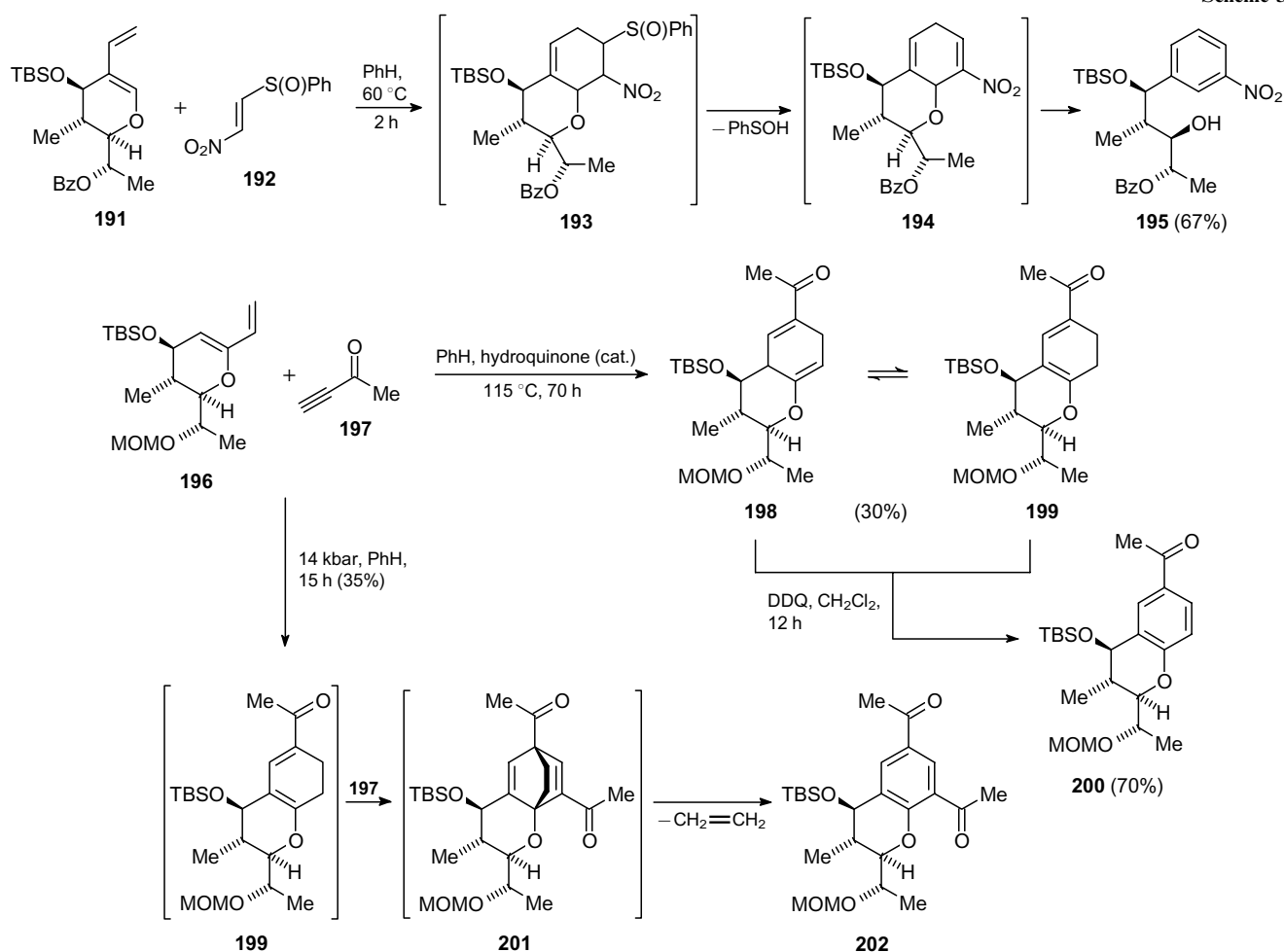
Scheme 33



$\text{R}^1 = \text{Me, Bn, Ph}$; $\text{R}^2 = \text{Me, Bn, Ph}$; cyclic $\text{NR}^1\text{R}^2 = \text{morpholine, piperidine}$;
 $\text{R}^3 = \text{H, Et, Pr}^n, (\text{CH}_2)_2\text{X}$ [$\text{X} = \text{OTIPS, OAc, N(Ts)Boc}$], CH_2OTBS , Cy , $\text{C}_6\text{H}_4\text{OMe-4}$, 3-Th;
 TIPS = SiPr_3 , TBS = SiBu^tMe_2 ; MS are molecular sieves; Boc = C(O)OBu^t



Scheme 34



MOM = CH_2OMe , Bz = $\text{C(O)C}_6\text{H}_5$

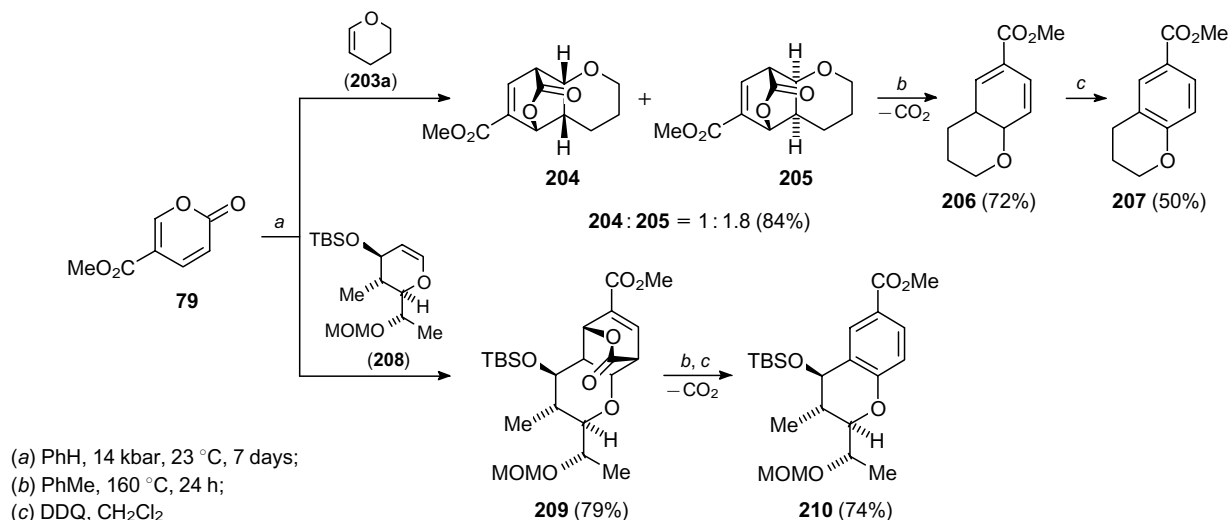
drobenzenes **214**, which upon DDQ mediated oxidative aromatization furnished biaryls and heterobiaryls **215** in moderate to good yields.

Recently, Hu and co-workers⁷² reported that tetra-yne **216** underwent cyclization *via* the arynes **217**, **218**, which were trapped by reaction with oxazolines **219** to give arenes **223**. The authors suggested a plausible mechanism *via*

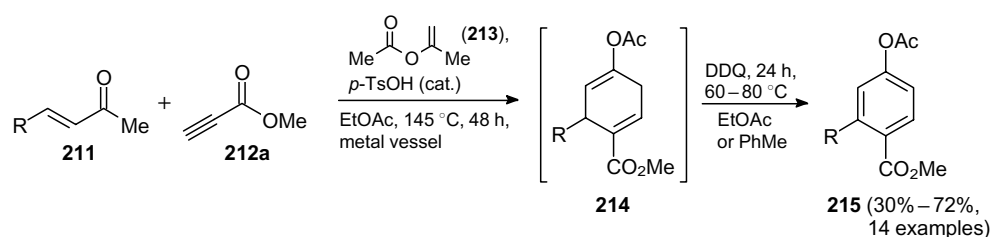
intermediates **220** to **222** (Scheme 37). Equivalent reactions using oxazolines **224** gave the indoles **228**, which were formed presumably *via* the intermediates **225**–**227**.

Also, it was reported that reaction using oxazolines **229** without a substituent at the imine carbon atom gave adducts **232** in good yields (Scheme 38). These reactions

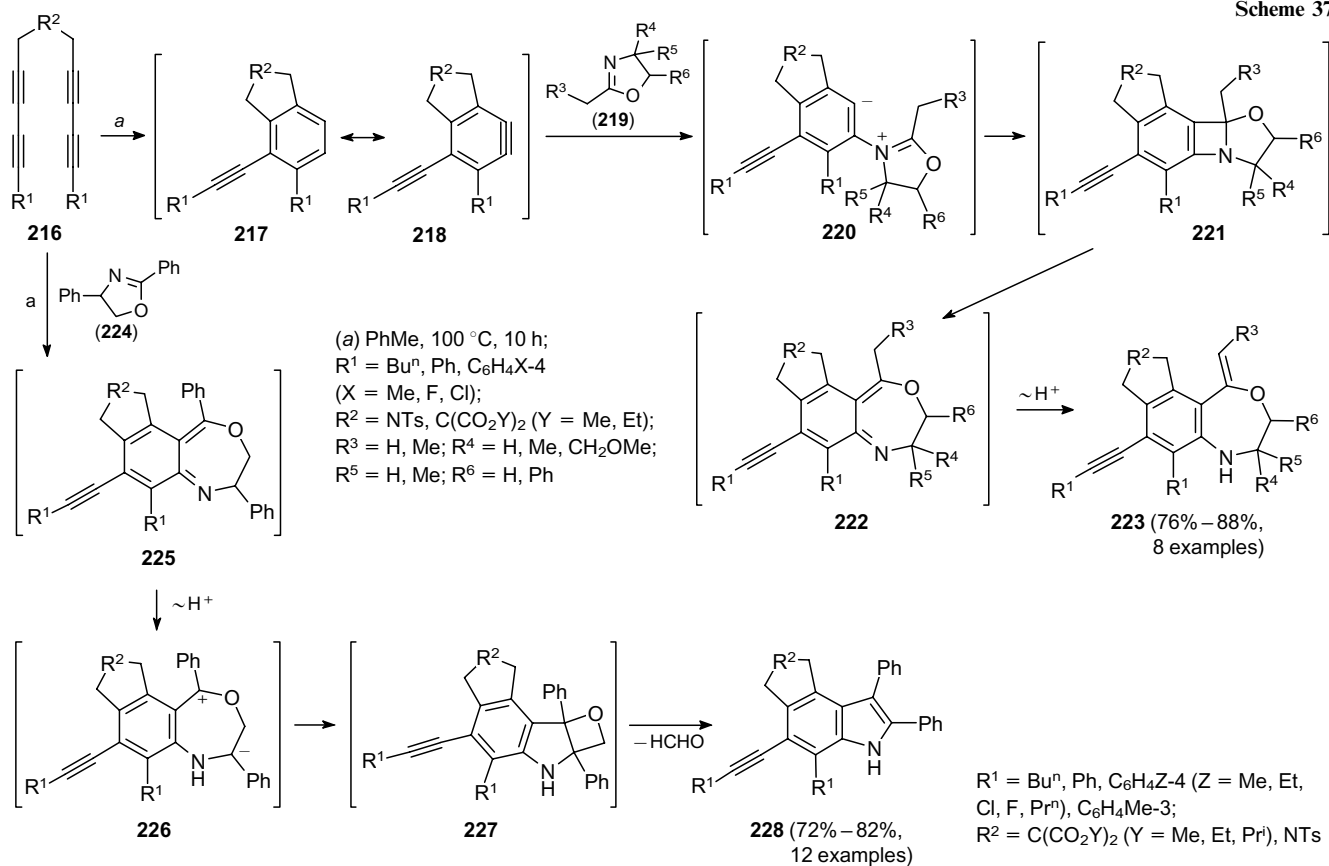
Scheme 35

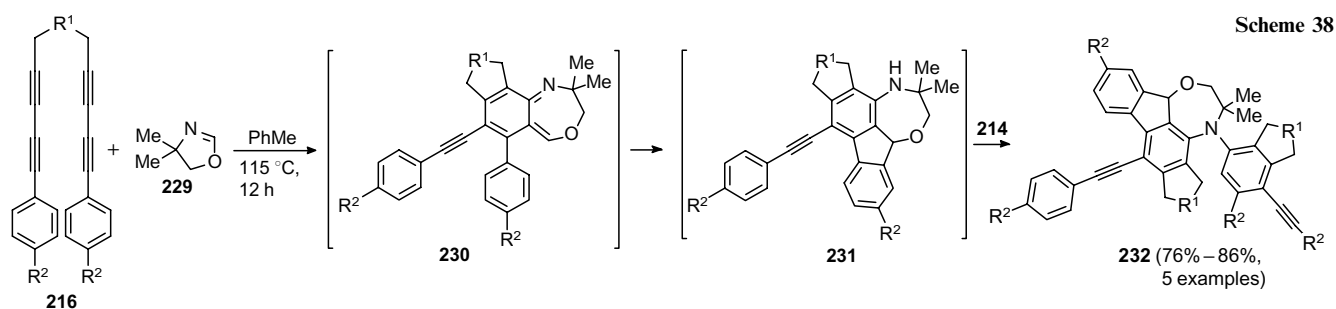


Scheme 36



Scheme 37





were again suggested to proceed *via* intermediates **230** and **231**.

3. Electrocyclic(pericyclic) reactions and aromatization

6 π -Electrocyclic and pericyclic reactions are governed by orbital-symmetry, which controls their mode of cyclization (disrotatory or conrotatory). This stereoelectronic control has been used in highly regioselective and stereoselective syntheses of carbocycles or heterocycles through the simple use of heat or light. Aerobic oxidation or the addition of oxidants was used for aromatization to provide arenes with various substitution patterns with broad functional group compatibility and atom economy.

1,3-Cyclohexadienes are the initial product of 6 π -electrocyclization reactions and were found to be convenient precursors for the synthesis of benzene derivatives by oxidation. Additionally, 6 π -electrocyclizations have been proposed as possible pathways in the biosynthesis of natural products. In conjunction with other $n\pi$ -electrocyclic ($n = 4, 8$) or pericyclic reactions, these cascade reactions have been applied photochemically for the rapid assembly of complex products.⁷³ UV irradiation or thermally initiated 6 π -electrocyclic and pericyclic reactions are therefore useful for the conversion of acyclic precursors into benzene derivatives. This chapter will exclusively focus on the synthesis of all carbon aromatic compounds; equivalent methods for heteroarene syntheses have been reviewed by Ding and Kaufman.^{74, 75}

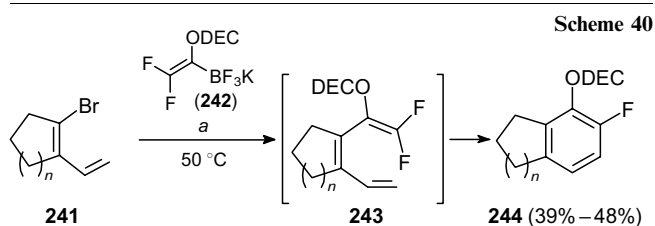
Chuang and co-workers⁷⁶ reported that the (formal) electrocyclization of polyfunctional triene ylides **236**, which were synthesized from enyne-esters **234**, triarylphosphines **235** and imines or aldehydes **233**, gave stabilized ylides **237**

and subsequently oxindole and benzofuranone ylides **238** (X = NR, O, respectively). These were further derivatized to produce isatins **239** and isooxazolinones **240** (Scheme 39).

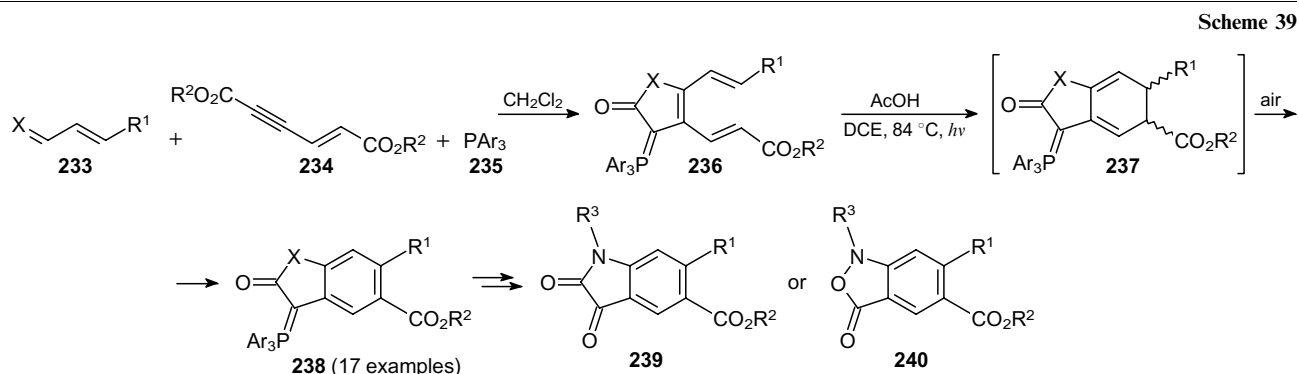
In 2016, Wilson and co-workers⁷⁷ reported that reaction of bromodienes **241** and trifluoroborate **242** under Molander–Suzuki–Miyaura conditions gave trienes **243**, which underwent sequential thermal 6 π -electrocyclization and dehydrofluorination reactions to give indanes, tetralins and benzosuberans **244** (Scheme 40).⁷⁷

Huang and co-workers⁷⁸ applied a 6 π -electrocyclization and aromatization sequence by the addition of amines **246** to ynedienyl-amines **245** and **248** followed by siloxane elimination to synthesize variously substituted 1,3-diaminobenzene derivatives **247**, **249** (Scheme 41). The reaction conditions tolerated a range of amine substituents with both cyclic and acyclic amines as defined below.

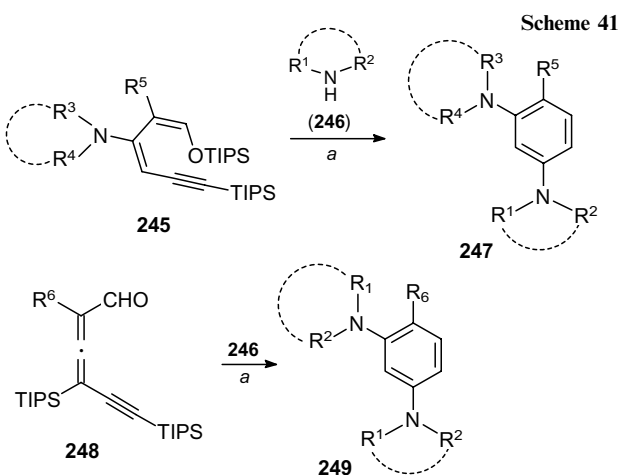
Delavatine A (**254**) and (–)-incarviate A (**255**) are two secondary metabolites from *Incarvillea delavayi*. These plants are found in Southwest China and the Himalayas and have been used in traditional Chinese medicine to treat anemia and dizziness. Both have intriguing biological activities with delavatine A (**254**) possessing anti-cancer activity against several human cancer cell lines. Sarpong and co-



(a) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, Cs_2CO_3 , Bu^tOH , H_2O ; $n = 1–3$; DEC = $\text{Et}_2\text{NC}(\text{O})$



X = NR³ (81%–89%), O (62%); Ar = Ph, C₆H₄Y-4 (Y = OMe, Cl, F, Me); R¹ = C₆H₄Z-4 (Z = NO₂, CN); R² = Me, Et; R³ = Ts, Bs; Bs = PhSO₃



(a) NaOAc, 4-O₂NC₆H₄CO₂H, 4 Å MS, PhCl, 120 °C;
 HNR¹R² = HN(CN₂)₄; R³, R⁴ = Me, Et; HNR³R⁴ = 1-pyrrolidine, piperidine, morpholine, 3-pyrroline, 4-OH-piperidine, *N*-Me piperazine, tetrahydroisoquinoline, azepane, azocane; R⁵ = Bn, (CH₂)₄OBn, (CH₂)₄OTBS, (CH₂)₂O-prenyl, *n*-C₆H₁₃ (**247**: 52%–85% yields);
 R¹ = R² = Et; HNR¹R² = 1-pyrrolidine;
 HNR³R⁴ = 3-OH-pyrrolidine, 3-pyrroline, isoindoline, piperidine, azepane, azocane; R⁵ = Bn (**247**: 51%–74%);
 HNR¹R² = pyrrolidine, azepane, azocane; R⁶ = Bn, *n*-C₆H₁₃, (CH₂)₄OBn (**249**: 52%–82%)

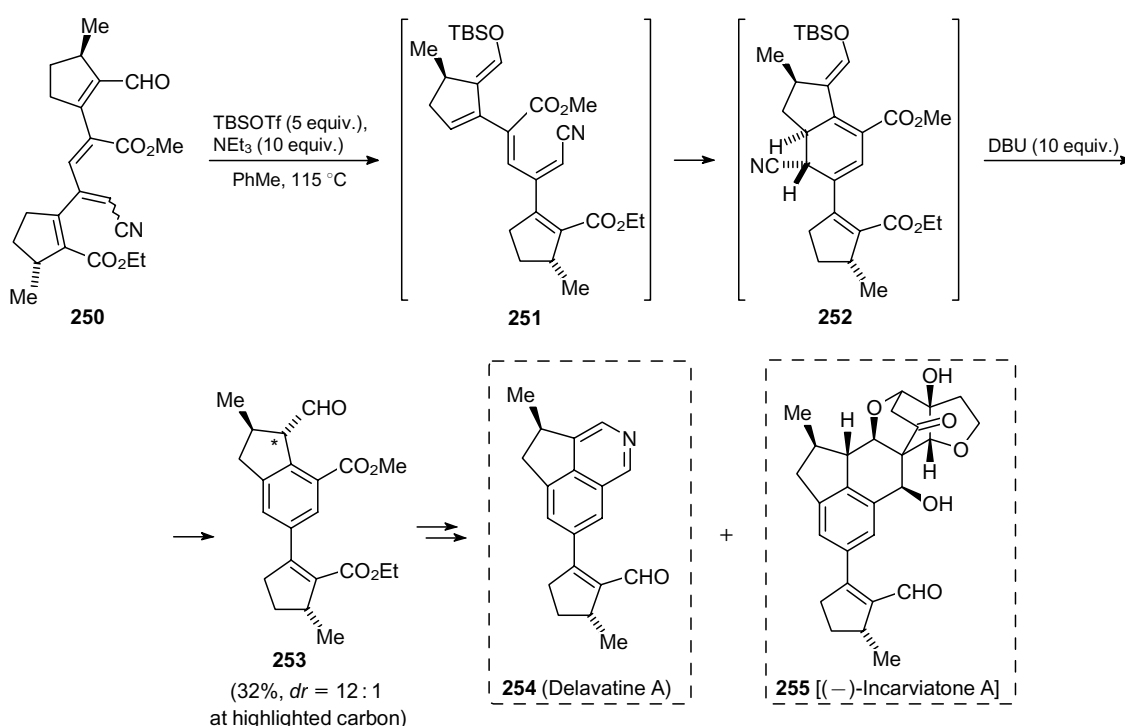
workers⁷⁹ have developed a unified approach for the synthesis of these two natural products as they share a common molecular scaffold (Scheme 42). The polyene precursor **250** upon silylation with TBSOTf or TIPSOTf gave penta-ene **251** with a core triene with the (*Z,Z,E*)-geometry. This polyene **251** underwent a 6 π -electrocyclization reaction and subsequent DBU-mediated aromatization of intermediate **252** to give the polyfunctional indane **253**. Subsequently, it was found that this transformation worked well in a one-

pot procedure with precise base stoichiometry (10 equiv.) to provide indane **253** as a 12:1 mixture of diastereoisomers. Within three steps this indane **253** was subsequently converted into delavatine A (**254**) and also used to complete a formal total synthesis of (–)-incarviate A (**255**).

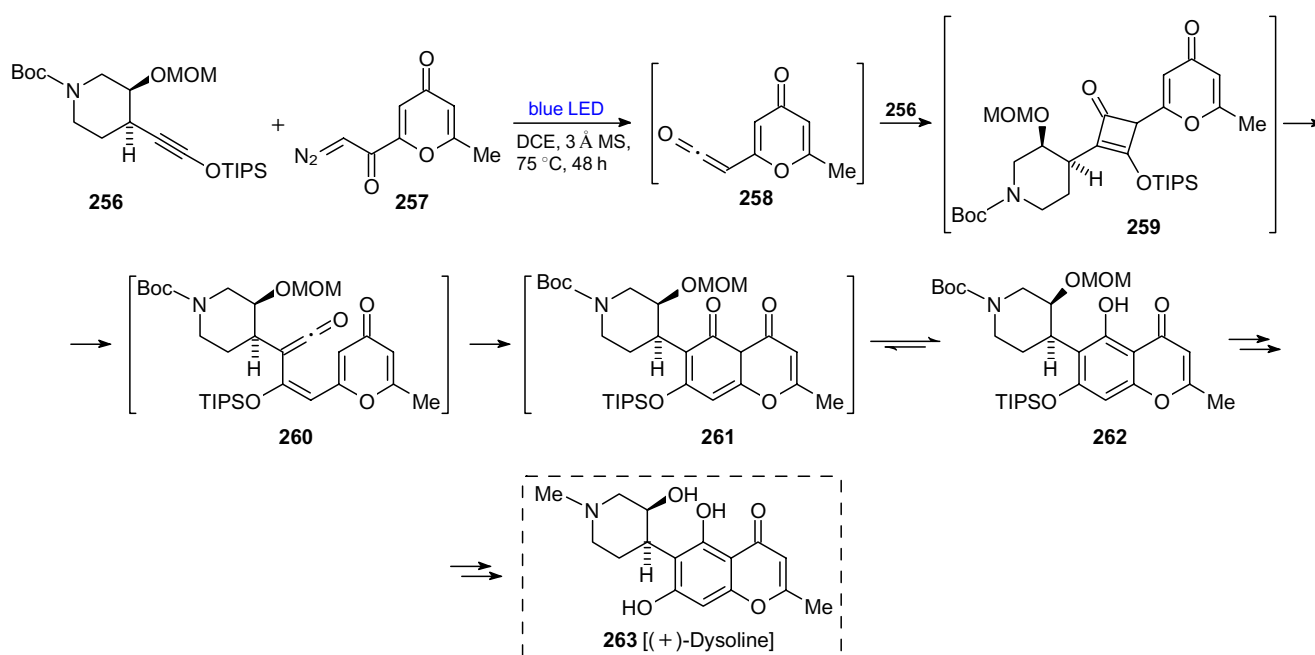
Coffin and Ready⁸⁰ reported the preparation of the advanced intermediate **262** in their enantioselective synthesis of (+)-dysoline (**263**) (Scheme 43). A highly regioselective Danheiser benzannulation between diazoketone **257** and alkyne **256** was used to synthesize the core chromenone **262**. Irradiation with blue light induced a Wolf-rearrangement of diazo-ketone **257** to provide ketene **258**, which, in turn, underwent a selective [2 + 2] addition with alkyne **256** to produce cyclobutenone **259**, followed by a retro-4 π -electrocyclic opening and subsequent 6 π -electrocyclization of triene **260** and aromatization through tautomerization to give the advanced intermediate **262**. The natural product **263** was shown to have cytotoxic activity against HT1080 fibrosarcoma cell lines (IC₅₀ 0.21 μ mol L^{–1}).

In 2015 and 2018, the group of Magauer^{81,82} reported a unified approach for the synthesis of variously substituted phenols **268**, anilines and phenol ethers **269** and polycyclic compounds **271** and **272** through the 2 π -disrotatory electrocyclic ring opening of bicyclo[3.1.0]hexan-2-ones **264** and **270** (Scheme 44). The optimal reaction conditions were applied to the synthesis of phenols **268** tolerating various electron-donating and electron-withdrawing substituents. In addition, a penta-substituted derivative of phenol **268** was synthesized in reasonable yield (53%) after a [1,2]-shift.

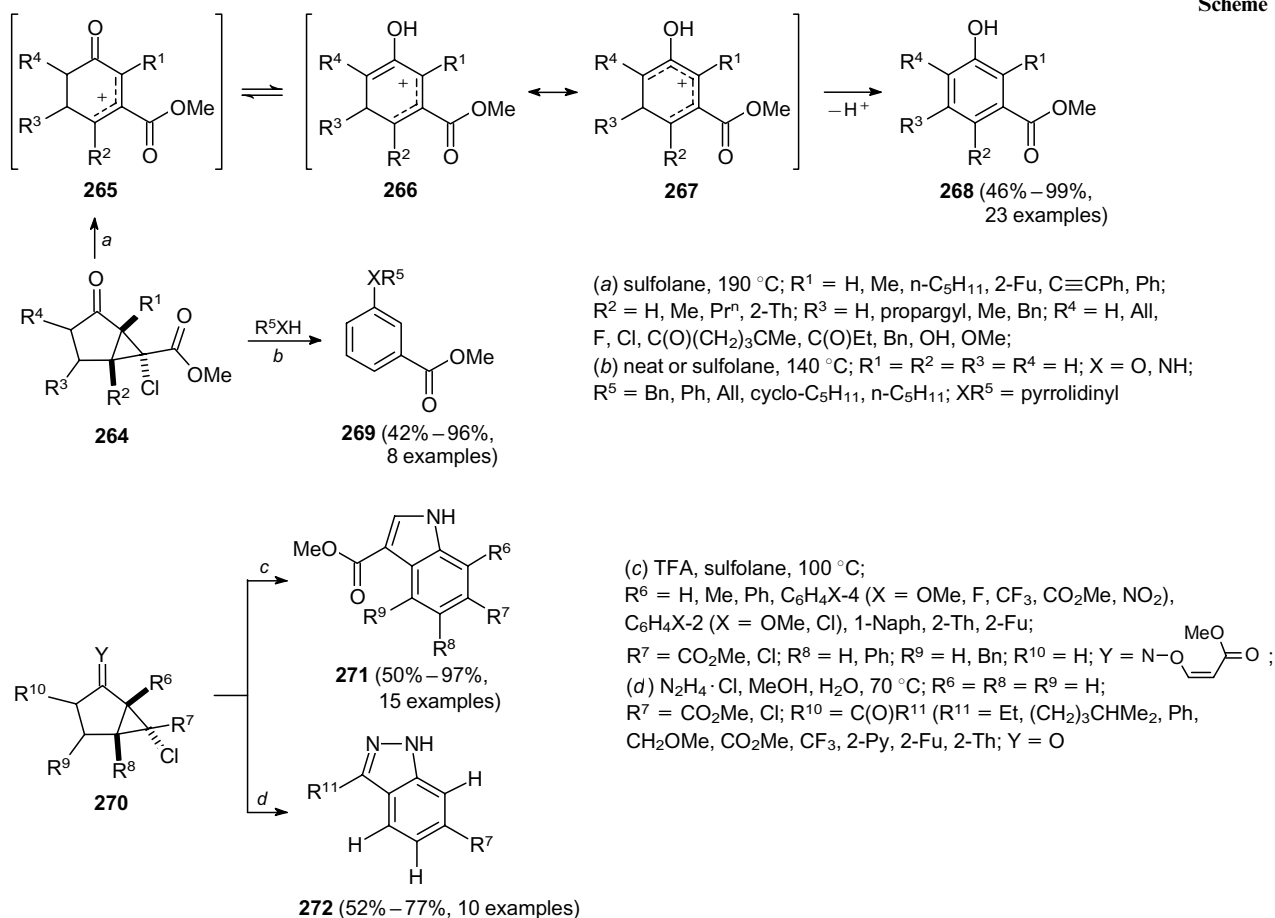
In 2017, Zhu and co-workers⁸³ developed a gold-catalyzed ring expansion including a 6 π -electrocyclization-aromatization sequence to prepare a selection of mono- and bicyclic aromatic compounds **278** (Scheme 45). The authors' proposed mechanism of reaction involved enyne-activation and ring expansion to provide nonacycle **275**, followed by a formal 6 π -electrocyclization of the intermediate hexatriene **276** and subsequent aromatization.



Scheme 43



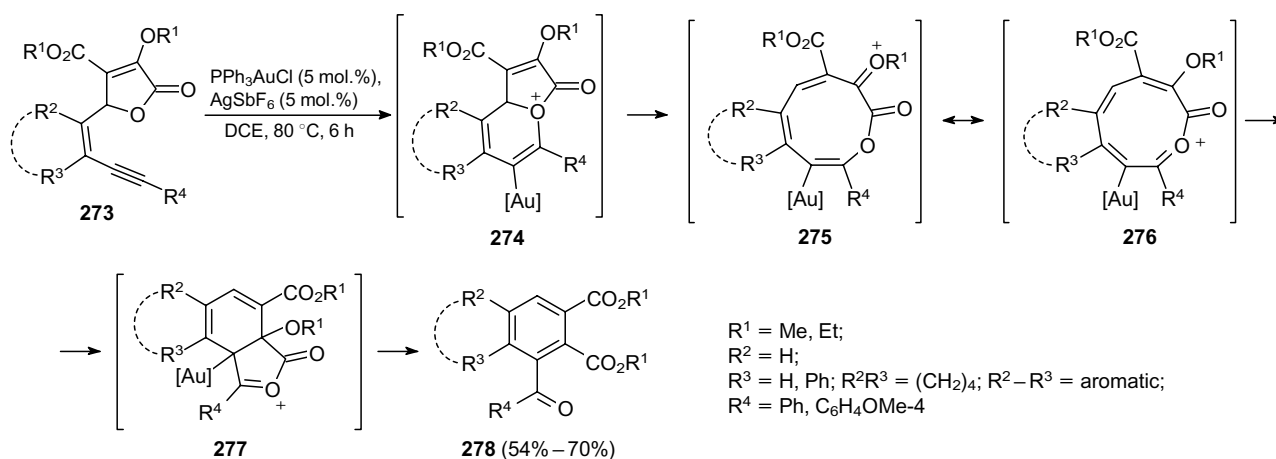
Scheme 44



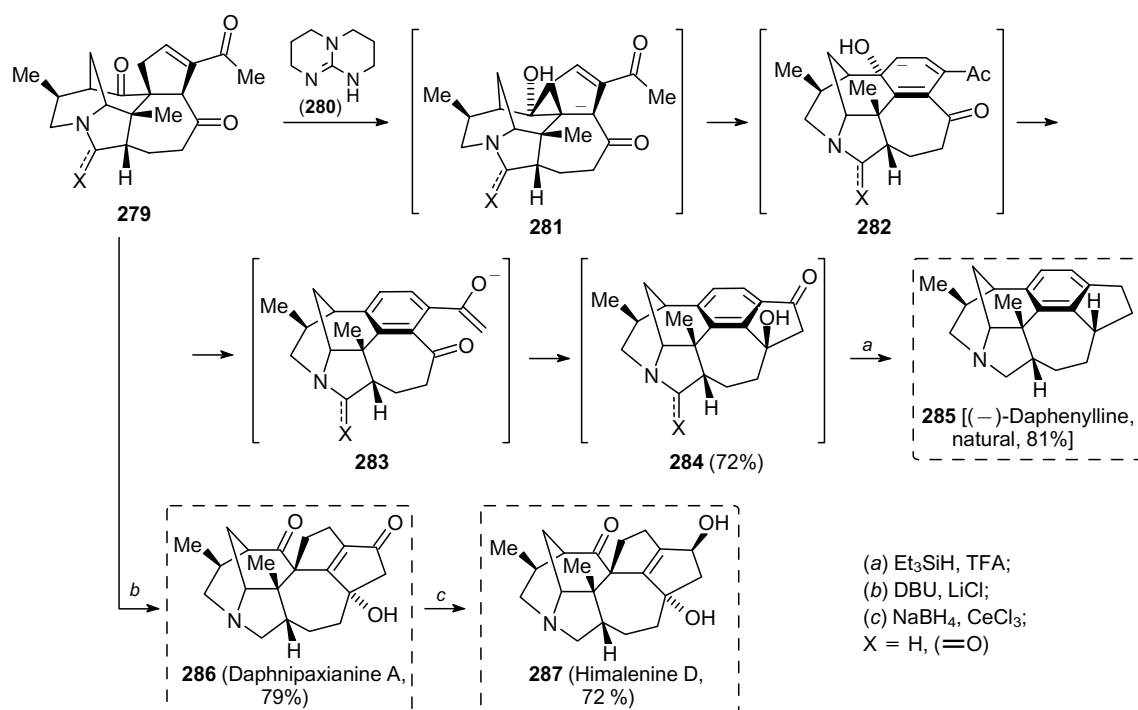
In 2018, Li and co-workers⁸⁴ reported a divergent total synthesis of three *Daphniphyllum* alkaloids, namely, (–)-daphenylline (**285**), daphnipaxianine A (**286**) and himalenine D (**287**) using a late stage aromatization of the common intermediate **279** (Scheme 46). The natural pro-

ducts have been used in traditional Chinese medicine and have a range of biological activities, including antitumour and antiviral properties. Their synthesis of the central aromatic ring of the daphenylline precursor **284** applied a formal 6π-electrocyclization and aromatization sequence.

Scheme 45



Scheme 46



Pentacyclic triketone **279** was allowed to react with guanine **280** (triazabicyclodecene, TBD), which induced a vinyl-ous aldol reaction with the adjacent ketone to produce the cyclopentene-anion **281**. This set the stage for a 6 π -electrocyclic ring expansion, which upon elimination of hydroxide from **282** produced the aromatic core of daphenylline **283**, followed by an additional aldol reaction of the acetophenone moiety with the proximal ketone. This elegant reaction cascade sequence led to the formation of one aromatic and 2 different ring systems in one procedure. Reductive deoxygenation completed the synthesis of the natural product (**285**).

4. Transition metal-catalyzed reactions and aromatization

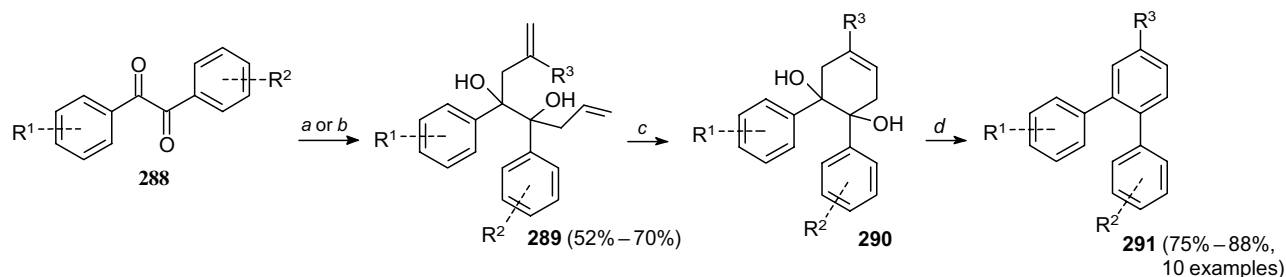
A series of *ortho*-terphenyl derivatives **291** were prepared by Dash and co-workers⁸⁵ utilizing a ring closing alkene metathesis (RCM) reaction as a key step (Scheme 47).

Treatment of diketones **288** with allylmagnesium bromide or sequentially with (allyl)_{1,2}-XBr ($\text{X} = \text{Zn, In}$) and allylmagnesium bromide provided the diallylated compounds **289**, which were subjected to RCM with Grubb's 2nd generation catalyst thereby providing tricyclic diols **290**. Subsequent reaction of these diols **290** with *p*-toluenesulfonic acid resulted in aromatization *via* double dehydration to provide the arenes **291**.

In 2016, Xie and co-workers⁸⁶ reported studies on the total synthesis of (–)-rubrifiordilactone **B** (**295**), a natural product which showed bioactivity against HIV-1 replication (Scheme 48). The key aromatization step in their approach involved a rhodium-catalyzed formal [2 + 2 + 2] cycloaddition of triynes **292** to produce arene **293**, which was subsequently allowed to react with *p*-toluenesulfonic acid to give an advanced lactone intermediate **294**.

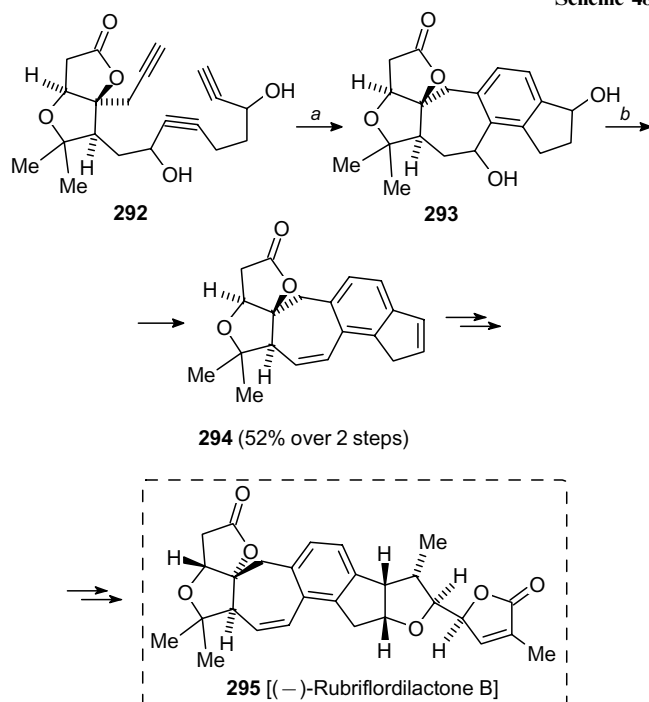
Matsuda and Matsumoto⁸⁷ reported a rhodium(I) catalyzed approach for the synthesis of arenes **301** (Scheme 49). It was found that Wilkinson's catalyst [$(\text{Ph}_3\text{P})_3\text{RhCl}$] medi-

Scheme 47



(a) AlIMgX , THF, from 0 °C to 23 °C, 6 h; (b) AlIBr , NaI, Zn or In, THF:H₂O (4:1), 23 °C, 6 h; (c) Grubbs II (5 mol.%), CH_2Cl_2 , 23 °C, 15 h; (d) TsOH, PhH, 80 °C, 3 h; $\text{R}^1 = \text{R}^2 = \text{H}$, 2-F, 4-F, 4-Cl, 4-Me, 3-OMe, 2,5-(OMe)₂; $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{I}$, OMe; $\text{R}^3 = \text{H}$, Me

Scheme 48



(a) $[\text{RhCl}(\text{PPh}_3)_3]$, DCE, 23 °C; (b) *p*-TsOH, PhH

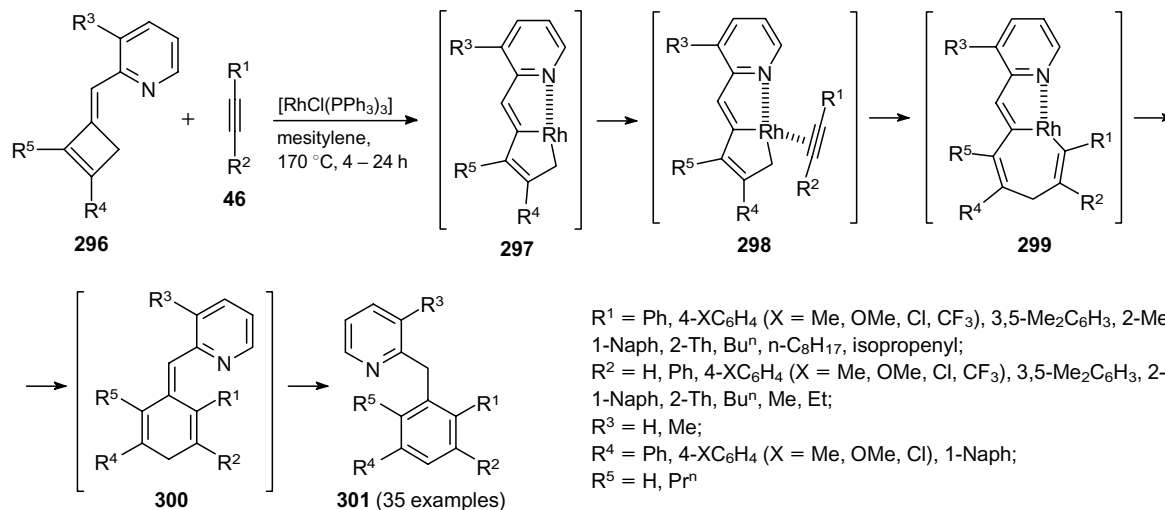
ated the insertion of alkyne **46** into the C–C bond of cyclobutenes **296** to give a range of tetra- and pentasubstituted arenes **301**.

Benzocyclobutenes are valuable synthetic intermediates in organic chemistry. Recently Shi and co-workers⁸⁸ reported a gold(I)-catalyzed dehydrogenative cycloisomerization of 1,5-enynes **302** to produce disubstituted benzocyclobutenes **305** after oxidative aromatization using DDQ (Scheme 50). Furthermore, cyclobutane and cyclohexane but not cyclopentane tethered 1,5-enynes **306** were also aromatized under the reaction conditions to produce arenes **307** as well as enynes with the $\text{R}^1\text{R}^2\text{C}=\text{CH}_2$ tethers (where $\text{R}^1 = \text{R}^2 = \text{Me}$, Et; $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ph}$, $\text{C}_6\text{H}_4\text{Cl-4}$).

A new method for the synthesis of aryl triazoles was reported by Fan and co-workers⁸⁹ (Scheme 51). This involved one pot cascade reactions of alkynes **308** with aliphatic keto-azides **309** and allenic ketones **311**. Firstly, the alkynes **308** and azides **309** underwent copper-catalyzed Huisgen cycloaddition reactions to give triazole intermediates **310**, which were subsequently allowed to react with allenic ketones **311** via Michael addition and intramolecular condensation to yield the aromatic compounds **313**.

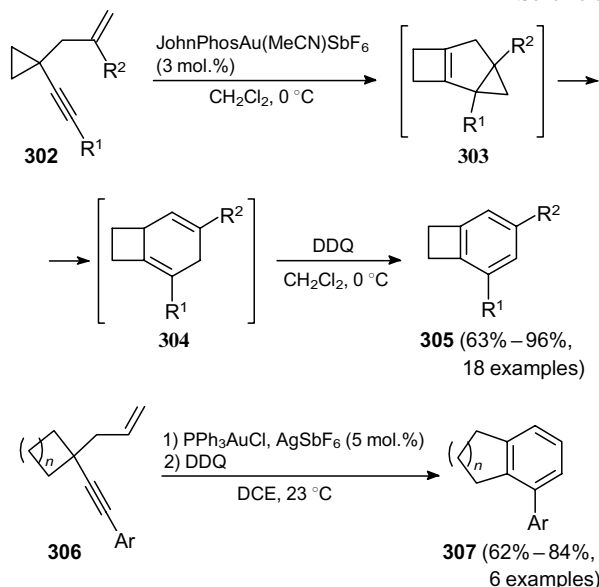
Chan and co-workers⁹⁰ reported that in the presence of DDQ or *N*-fluorobenzenesulfonimide (NFSI) as an oxidant, the known cycloisomerization of 1,4-enyne esters **314** to cyclopropanated cyclopentene-derivatives **315** occurred with oxidative ring expansion to provide phenol derivatives **317** in moderate to good yields (Scheme 52). The reaction tolerated various aliphatic and aromatic substituents in the *meta*-position thereby highlighting the value of synthesizing

Scheme 49



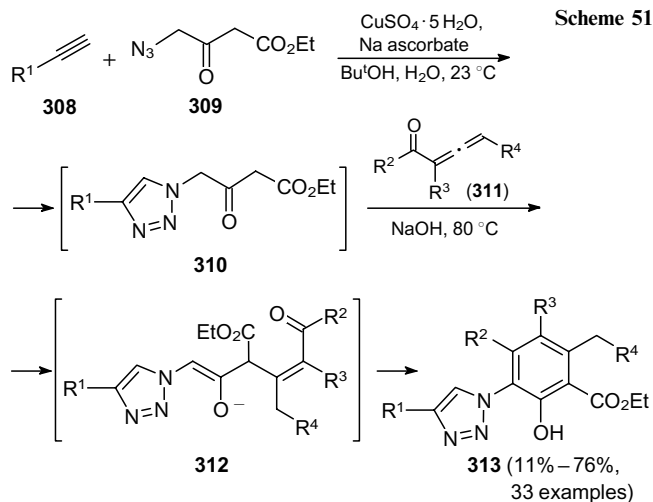
$\text{R}^1 = \text{Ph}$, 4- XC_6H_4 (X = Me, OMe, Cl, CF_3), 3,5- $\text{Me}_2\text{C}_6\text{H}_3$, 2- MeC_6H_4 , 1-Naph, 2-Th, Bu^n , $n\text{-C}_8\text{H}_{17}$, isopropenyl;
 $\text{R}^2 = \text{H}$, Ph, 4- XC_6H_4 (X = Me, OMe, Cl, CF_3), 3,5- $\text{Me}_2\text{C}_6\text{H}_3$, 2- MeC_6H_4 , 1-Naph, 2-Th, Bu^n , Me, Et;
 $\text{R}^3 = \text{H}$, Me;
 $\text{R}^4 = \text{Ph}$, 4- XC_6H_4 (X = Me, OMe, Cl), 1-Naph;
 $\text{R}^5 = \text{H}$, Pr^n

Scheme 50



$\text{R}^1 = \text{Ph}$, 4- XC_6H_4 (X = Me, OMe, Ph, Br, Cl, F, Ac, CF_3), 3- XC_6H_4 (X = Me, OMe), 3,5- $\text{Me}_2\text{C}_6\text{H}_3$, 2,4-(MeO) $_2\text{C}_6\text{H}_3$, 2-Th, *N*-Boc-5-indolyl, 2-Naph, 6-MeO-2-Naph, 9-phenanthryl; $\text{R}^2 = \text{H}$, Me; Ar = Ph, 4-MeOC $_6\text{H}_4$; $n = 1, 2$ (complex mixtures), 3; JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl

Scheme 51

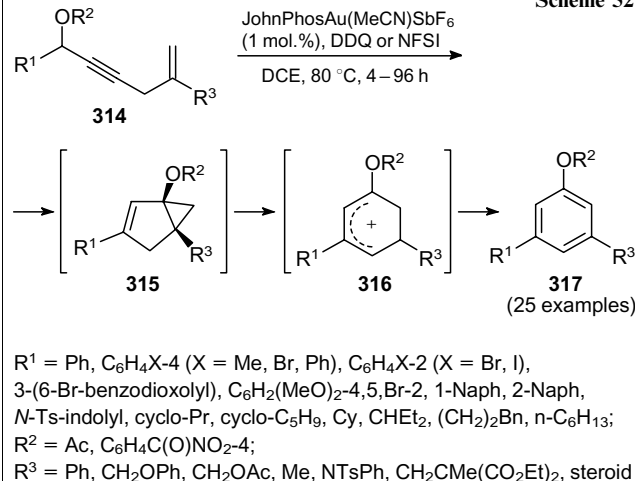


$\text{R}^1 = \text{Ph}$, $\text{C}_6\text{H}_4\text{X-4}$ (X = Cl, F, Br, OMe, Me), $\text{C}_6\text{H}_4\text{Me-3}$, CH_2OH , CH(OH)Ph , $\text{CH(OH)CH}_2\text{C}_6\text{H}_4\text{Br-2}$, Bn, 3-Th, 3-Py; $\text{R}^2 = \text{Ph}$, $\text{C}_6\text{H}_4\text{Br-2}$, $\text{C}_6\text{H}_4\text{X-4}$ (X = Me, CF_3), Bn, Me, CH_2Bn , $\text{C}_6\text{H}_3(\text{MeO})_{2-3,4}$, $\text{C}_6\text{H}_3\text{Br}_{2-2,5}$, $\text{C}_6\text{H}_3\text{Br-2,F-5}$; $\text{R}^3 = \text{H}$, Me; $\text{R}^4 = \text{H}$, Ph

aromatic compounds from acyclic precursors given the preference for *ortho*- and *para*-substitution of phenols on reaction with electrophiles or *via ortho*-lithiation based processes.

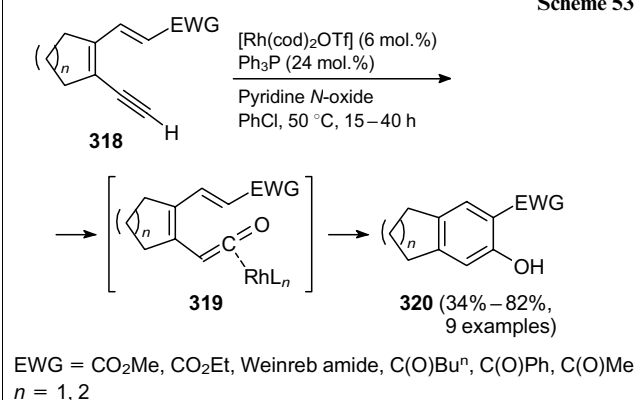
Zi and co-workers⁹¹ reported a *de novo* synthesis of substituted phenols **320** *via* oxidative cycloaromatizations of dienyne **318** (Scheme 53).⁹¹ The key step involved their rhodium-catalyzed conversion into the corresponding metal vinylidenes, which were subsequently oxidized to provide metal ketenes **319**. These reactive intermediates **319** under-

Scheme 52



$\text{R}^1 = \text{Ph}$, $\text{C}_6\text{H}_4\text{X-4}$ (X = Me, Br, Ph), $\text{C}_6\text{H}_4\text{X-2}$ (X = Br, I), 3-(6-Br-benzodioxolyl), $\text{C}_6\text{H}_2(\text{MeO})_{2-4,5}$, Br-2, 1-Naph, 2-Naph, *N*-Ts-indolyl, cyclo-Pr, cyclo- C_6H_9 , Cy, CHET_2 , $(\text{CH}_2)_2\text{Bn}$, $n\text{-C}_6\text{H}_{13}$; $\text{R}^2 = \text{Ac}$, $\text{C}_6\text{H}_4\text{C(O)NO}_2\text{-4}$; $\text{R}^3 = \text{Ph}$, CH_2OPh , CH_2OAc , Me, NTsPh, $\text{CH}_2\text{CMe}(\text{CO}_2\text{Et})_2$, steroid

Scheme 53



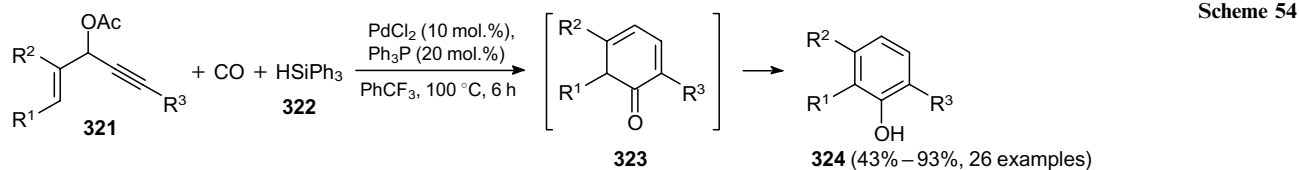
EWG = CO_2Me , CO_2Et , Weinreb amide, C(O)Bu^n , C(O)Ph , C(O)Me ; $n = 1, 2$

went cycloaromatization to provide phenols **320** in fair to good yields.

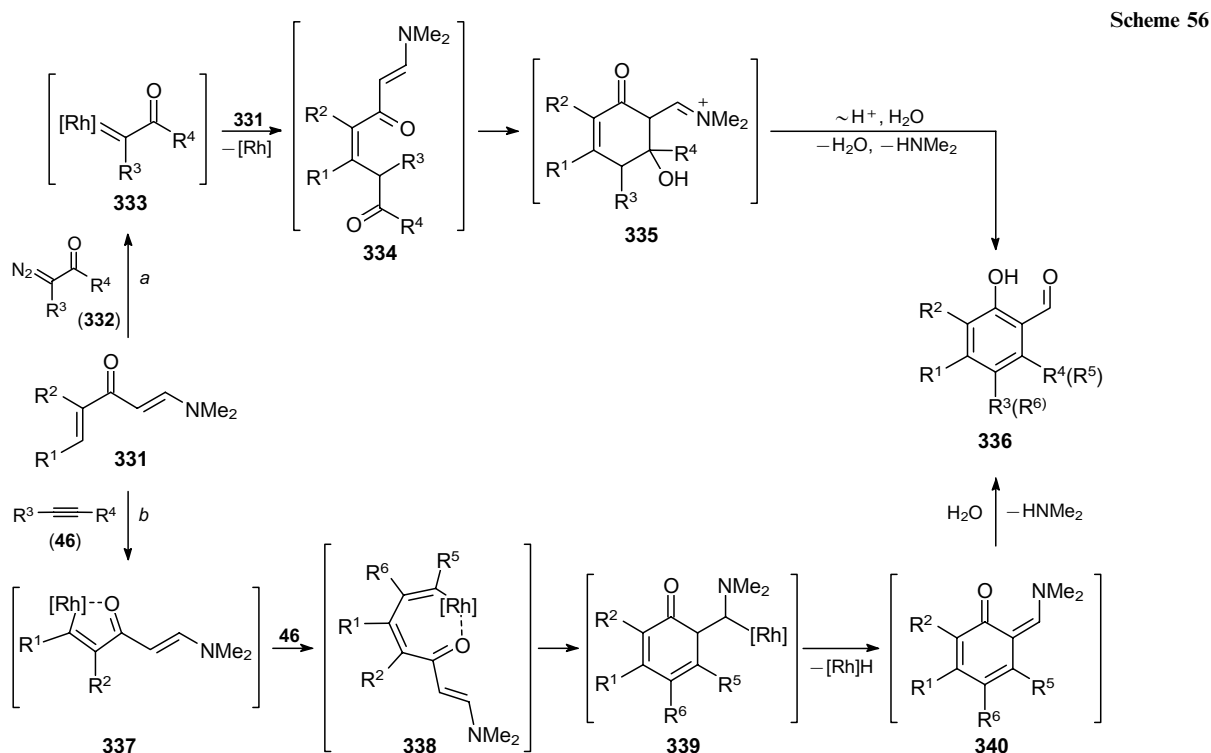
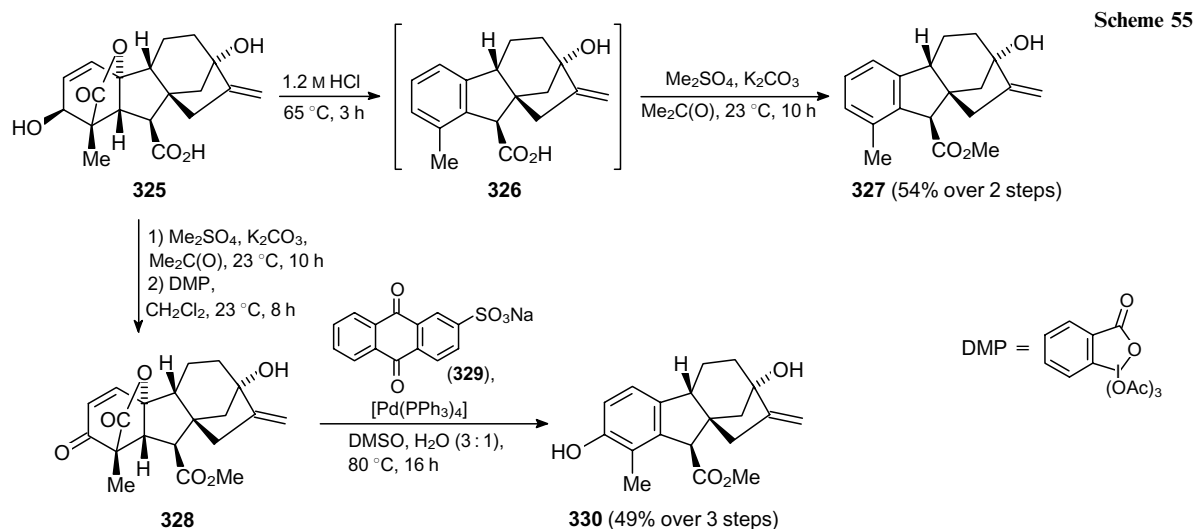
In 2018, Li and co-workers⁹² reported a palladium-catalyzed carbonylative benzannulation approach to synthesize substituted phenols **324** (Scheme 54). Hydrosilane **322** was used to mediate the palladium-catalyzed reductive [5 + 1] cycloaddition of enynes **321** with carbon monoxide to provide a range of substituted phenols **324** with excellent functional group tolerance.

The gibberellins are a family of tetracyclic *ent*-kaurenoid diterpenes that exhibit multiple biological activities including promoting plant germination and growth. When Zhang and co-workers⁹³ prepared triazole derivatives of allogibberic acid **326**, they utilized two different aromatization approaches to elaborate the arene core (Scheme 55). Aromatization of gibberellin **325** with hydrochloric acid provided arene **326**, which was subsequently esterified to produce methyl ester **327**. On the other hand, sequential esterification and Dess Martin periodinane (DMP)-mediated oxidation of gibberellin **325** gave enone **328**, which was subsequently aromatized using quinone **329** and $\text{Pd(PPh}_3)_4$ in aqueous DMSO to give phenol **330**.

In 2018, Loh and co-workers⁹⁴ reported the synthesis of highly substituted salicylaldehydes **336** starting from dialkenyl ketones **331** and diazoketones **332** using rhodium catalysis (Scheme 56, conditions *a*). The authors proposed that the reaction proceeded *via* intermediates **333**–**335**. This reaction tolerated various alkyl, aryl and alkenyl substituents and was also useful for the synthesis of a series of arylene-spaced bic(salicylaldehydes) in moderate yields.



R¹ = H, 4-XC₆H₄ (X = Me, OMe, Cl, CF₃), 3-MeOC₆H₄, 2-MeOC₆H₄, Prⁿ, Ph; R² = H, Me, Et, Ph; R³ = Ph, 4-XC₆H₄ (X = Me, OMe, Cl, Br, Ph), 3-XC₆H₄ (X = Me, OMe, F, CF₃), 2-XC₆H₄ (X = Me, Cl), 3,5-Me₂C₆H₃, 2-Th, Me, Buⁿ, n-C₆H₁₃, cyclo-Pr

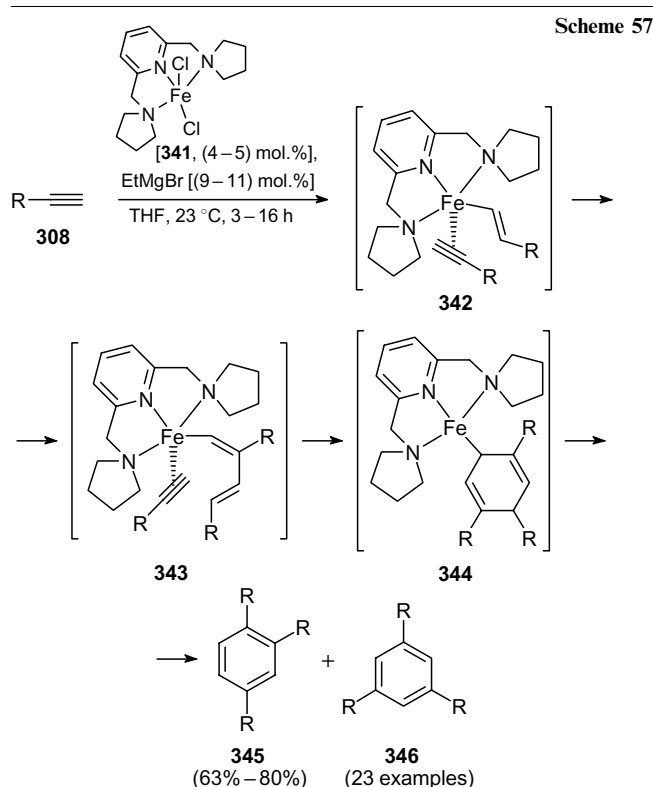


(a) [(RhCp*Cl₂)₂] (2 mol.%), CF₃CO₂Ag (8 mol.%), Zn(OAc)₂, Ac₂O, CF₃CH₂OH, 40 °C, 12 h; R¹ = Me, Buⁿ, Ph, C₆H₄X-2, C₆H₄X-3 (X = Me, F), C₆H₄X-4 (X = Me, OMe, F, Cl, Br, CF₃, NO₂, CH = CHAc), C₆H₃(OMe)₂-3,4, 5-(2,3-dihydro)benzofuryl, 2-Fu, 2-Th, Fe, styryl, 2-propenyl, 1,3-pentadienyl; R¹–R² = (CH₂)₄; R² = H, C₆H₄F-4; R³ = CO₂Me, CO₂Et, CO₂All, Ac; R⁴ = H, Me, Prⁱ, cyclo-Pr, CH₂OMe, Ph, C₆H₄X-4 (X = F, OMe) [**336**: 34 examples, 24%–87% yields; 4 additional examples with polybenzene formation (52%–68%)];

(b) [(RhCp*Cl₂)₂] (2.5 mol.%), AgSbF₆ (10 mol.%), AgOAc, H₂O, DCE, 90 °C, 15–24 h; R¹ = H, C₆H₄Me-4; R² = C₆H₄X-4, (X = OMe, Ph), 2-(7-MeO)-naphthyl, C₆H₃(OCH₂O)-3,4; R⁵ = R⁶ = Ph, C₆H₄X-4 (X = Me, OMe, F, Cl, Br, Ac, CO₂Et, NO₂), C₆H₄X-3 (X = Me, OMe, F, CO₂Me), 2-Naph, 2-Th, 2-(5-Me)-thienyl; R⁵ = Ph; R⁶ = Me, Et (**336**: 50%–92%, 24 examples)

Gao and co-workers⁹⁵ reported the synthesis of the same structures **336** via rhodium catalyzed reaction of similar dienamides **331** with acetylenes **46** (Scheme 56, conditions *b*). The authors suggested that the process proceeded via the organo-rhodium intermediates **337** to **339**, quinomethide **340** and its hydrolysis.

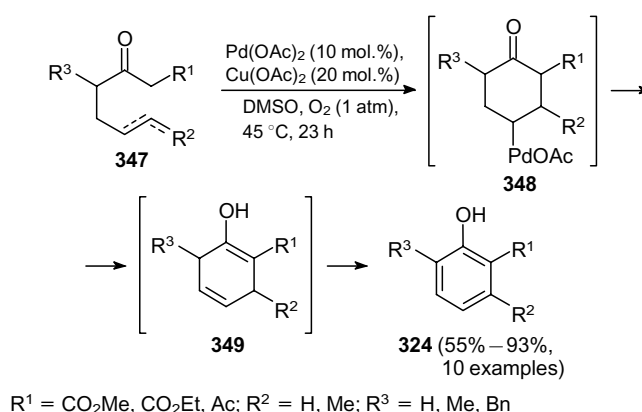
Gawali and Gunanathan⁹⁶ reported that iron-pincer complex **341** catalyzed a regioselective cyclotrimerization to yield trisubstituted benzene derivatives **345**, **346** (Scheme 57). Activation of the iron dichloride in the **341** with ethylmagnesium bromide produced iron(I)-hydride, which was the active catalytic species for the reaction and mediated the stepwise formal [2 + 2 + 2] cycloaddition of aryl alkynes **308** via intermediates **342**–**344** to provide arenes **345** and **346**. The authors also reported that aliphatic alkynes reacted in a similar fashion to yield the corresponding arenes.



Toyota and co-workers⁹⁷ reported a palladium-mediated aromatization of various alkenyl- β -keto-esters **347** to produce substituted phenols **324** (Scheme 58). The authors proposed that the reaction proceeded with the enolate attack of the terminal carbon to form an acetoxy palladium intermediate **348**. Subsequent β -elimination and oxidative aromatization gave phenols **324**.

In 2019, Gong and co-workers⁹⁸ described the total synthesis of dehydrobotrydienal (**355**), dehydrobotrydienol (**356**) and 10-oxodehydrodihydrobotrydienal (**357**). These botryanes are structurally diverse sesquiterpenoids that are isolated from the phytopathogenic fungus *Botrytis cinerea*

Scheme 58



(Scheme 59). Co-tetramethylthiourea (**351**, TMTU)-catalyzed tandem Pauson–Khand and 6π -electrocyclization reactions of triene **350** gave the tricyclic ketone **353**. Subsequent oxidative aromatization mediated by DDQ gave the aromatic ketone **354**, which was subsequently transformed into the above-mentioned botryanes **355**–**357**.

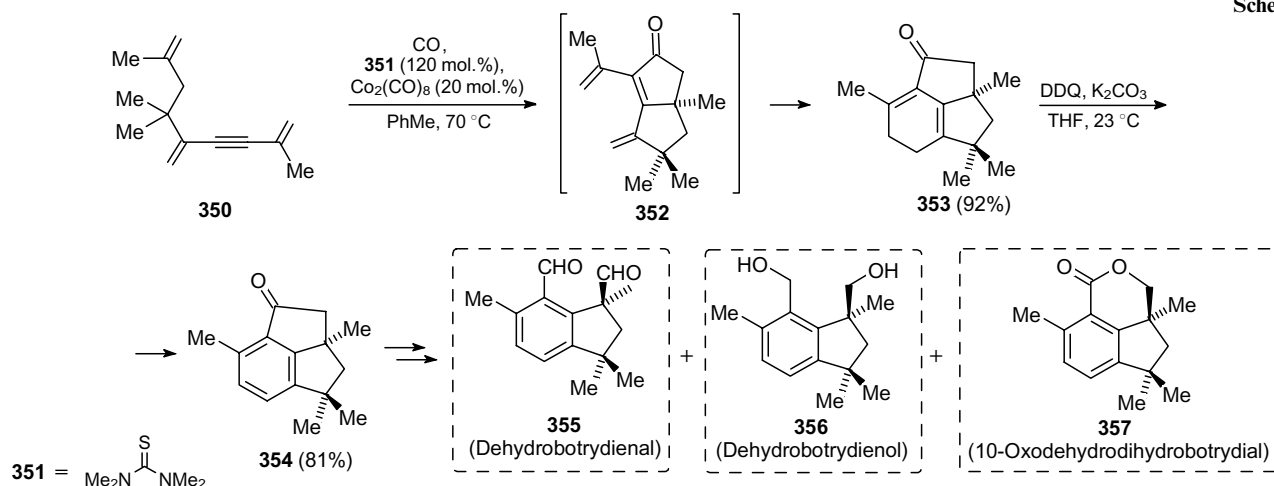
Aryl triazenes are versatile synthetic intermediates since they can be transformed into many different compounds on reaction of the derived arenediazonium salts with different oxygen- and nitrogen-containing nucleophiles. Recently, Cramer and co-workers⁹⁹ reported the synthesis of heavily substituted aromatic triazenes **363** and **365**, which utilized a ruthenium-catalyzed cyclization reaction (Scheme 60). Reaction of tethered diynes **358** with alkynyl triazenes **359** in the presence of a Ru^{II} complex resulted in formal [2 + 2 + 2] cyclotrimerization reactions, producing aryl triazenes **363**. Similarly, 1-diynyl triazenes **364** and alkynes **46** underwent a related [2 + 2 + 2] cycloadditions to produce aryl triazenes **365**. The retention of the triazine unit during these aromatization reactions is noteworthy.

Ma and co-workers¹⁰⁰ reported a palladium-catalyzed synthesis of 1,3-dihydroisobenzofurans **371**, **372** and **374**, **375** ($\text{Z} = \text{O}$) and isoindolines **374** and **375** ($\text{Z} = \text{NTs}$) (Scheme 61). The authors found that palladium acetate and tri-2-furylphosphine (TFP) promoted the cyclization of dienyl carbonates **367** with terminal alkynes **366** to produce dihydroisobenzofurans **371** and **372**, favouring regioisomers **371** due to regioselective double alkyne insertion reactions. Furthermore, a range of oxygen- or nitrogen-tethered carbonates **373** were also cyclized with terminal alkynes **366** to produce arenes **374** and **375**.

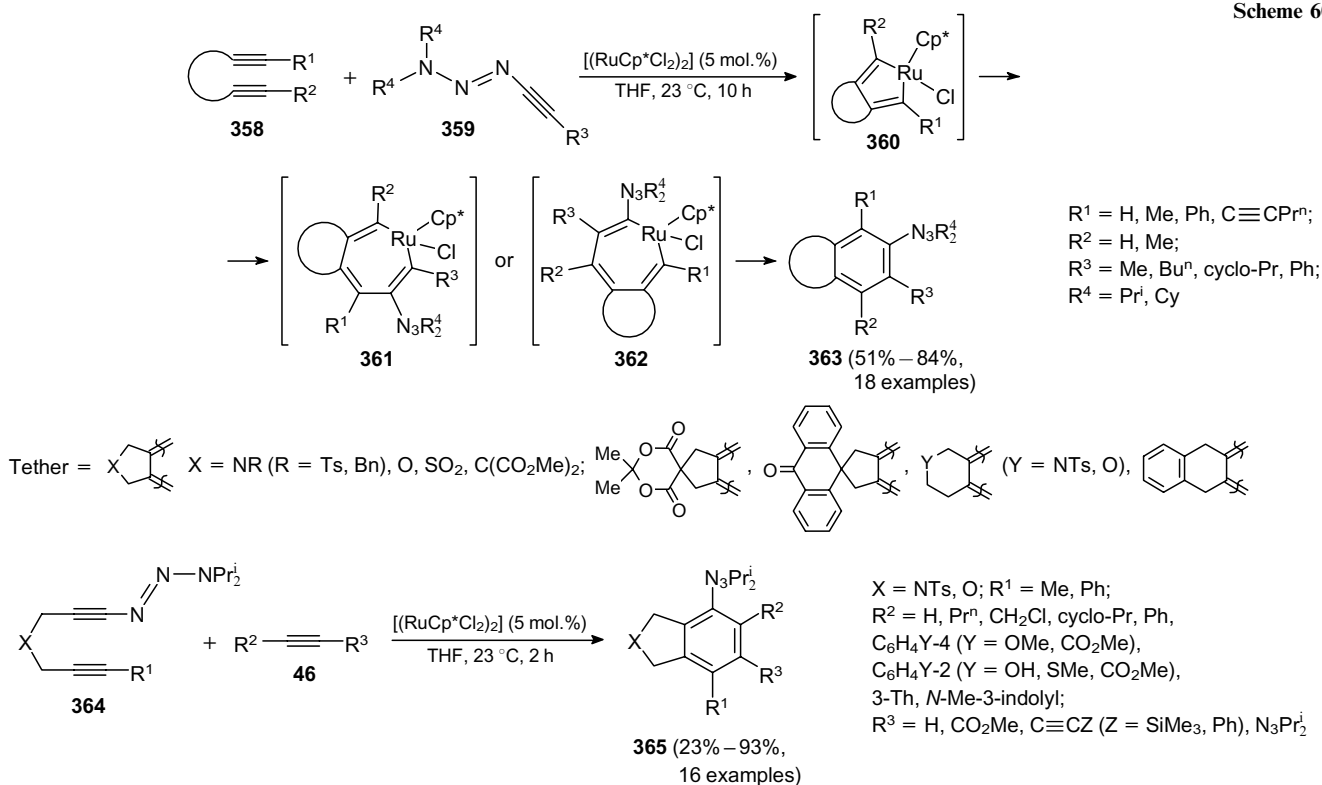
Yang and co-workers¹⁰¹ reported a simple formal [3 + 3] cycloaddition approach to produce polysubstituted terphenyls **382** from vinyl ethylene carbonates **376** (Scheme 62). With palladium catalysis, the latter compounds were converted into the corresponding α,β -unsaturated aldehydes **377**, which were subsequently allowed to react with allylic sulfones **378** to induce a regioselective [3 + 3] oxidative cycloaddition in the presence of DBU to give terphenyl compounds **382**.

Kale and Liu¹⁰² reported that the cyclohexene-bridged diyne **383** underwent gold-catalyzed aromatization reactions with *para*-substituted nitrosobenzenes **384** to give tetrahydronaphthaldehyde derivatives **388** (Scheme 63). It was found that the propargylic oxygen substituent of the 1,6-diyne substrate influenced the reaction outcome with

Scheme 59



Scheme 60



larger silyl groups leading to higher reactivity due to the operation of the Ingold–Thorpe effect.

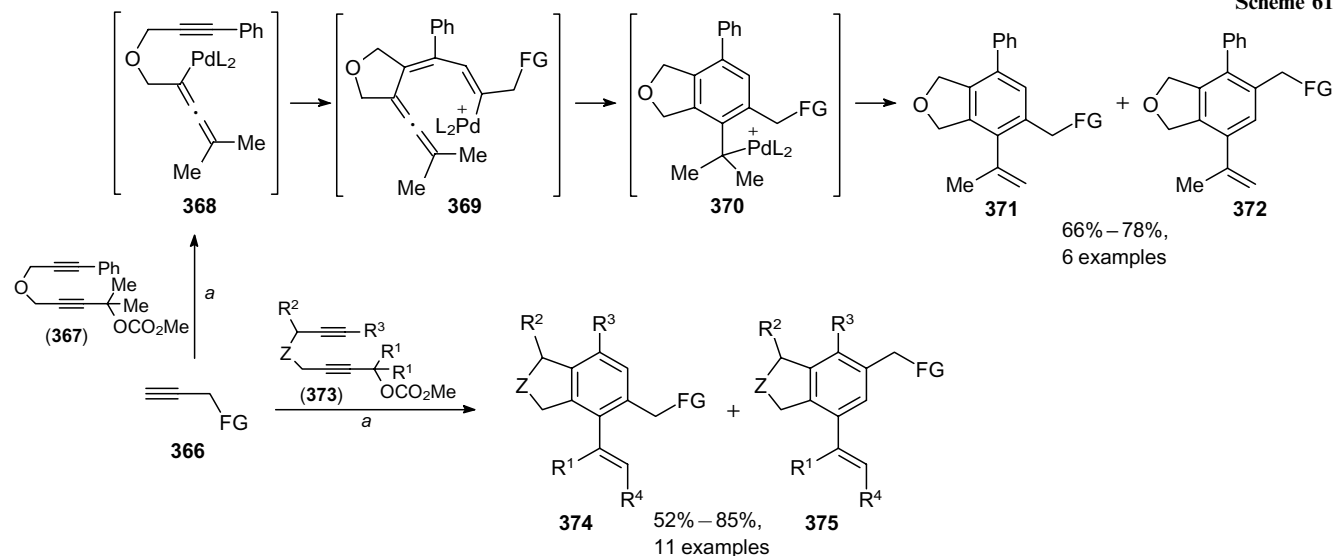
Deng and co-workers¹⁰³ reported a palladium-catalyzed aerobic benzannulation approach for the preparation of highly functionalized anilines **396** (Scheme 64). It was found that these anilines were formed *via* palladium-catalyzed formal [3 + 2 + 1] cycloadditions between amines **389**, aldehydes **138** and β -dicarbonyl compounds **390**. It is important to note that the addition of acetic acid was essential to promote both the condensation process as well as in the oxidative dehydrogenation step.

Ghorai and Lee¹⁰⁴ reported aryne-based multicomponent coupling reactions for the preparation of highly functionalized aromatic compounds **402–406** (Schemes 65, 66). They reported the hexadehydro Diels–Alder reaction of the tetra-ynes **214**, **397** to produce aryne intermediates **398**, which readily underwent reaction with aryl isocyanides to

form nitrilium intermediates **399**. Subsequent trapping of these species with carboxylic acids gave the corresponding imides **401** after Mumm rearrangement. This method was further extended for the syntheses of imide **404**, amidine **405** and amide **406** by respectively replacing the carboxylic acid with an alcohol, sulfonamide or water (see Scheme 66). All these 3-component coupling reactions were generalized by variation in the tetra-yne, alcohol and sulfonamide. Also, the processes could be catalyzed using silver(I) hexafluoroantimonate but yields were better in its absence.

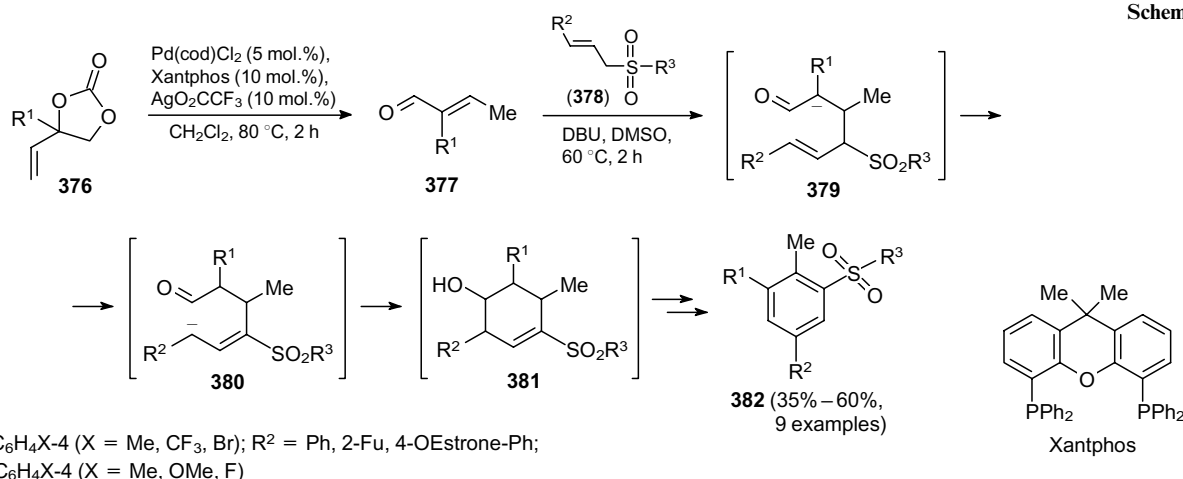
(-)-Rubriflordinolactone B (**295**) is a highly functionalized polycyclic nortriterpenoid extracted from the plants of the *Schisandra* sp. and, as mentioned above, displays antiviral and anticancer activities. Recently, Anderson and co-workers¹⁰⁵ reported a convergent strategy for the total synthesis of this natural product in which the aromatic core was elaborated from a non-aromatic precursor

Scheme 61



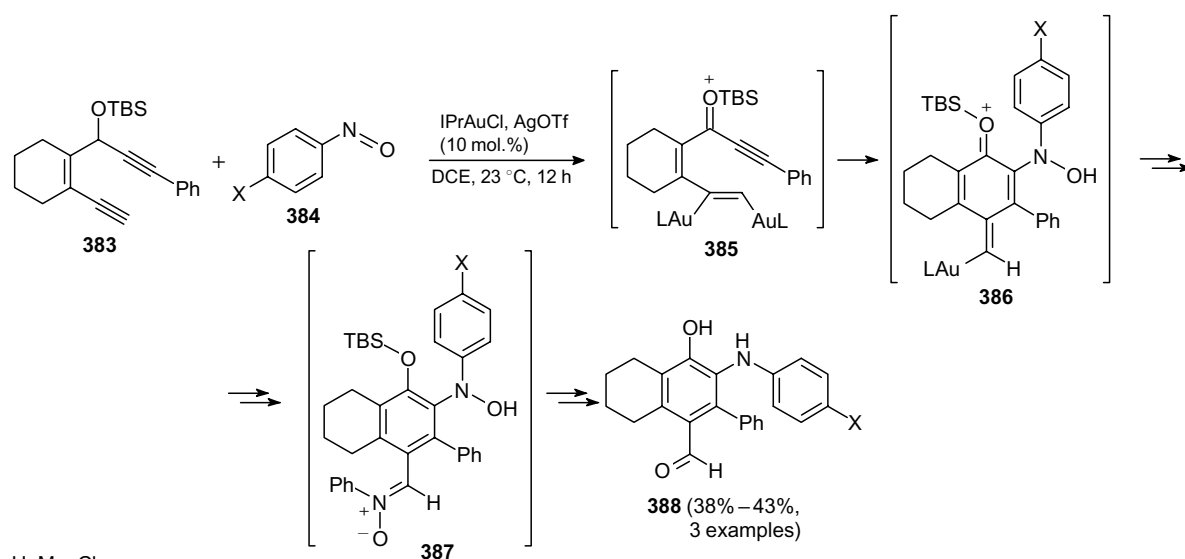
(a) Pd(OAc)₂ (5 mol.%), TFP (10 mol.%) [TFP = P(2-Fu)₃], Na₂CO₃, H₂O, N₂, MeCN, 30 °C; FG = NHTs, OH, 1-indolyl, 2-indolyl, 3-formyl, 6-Br-, 5-Me-1-indolyl; Z = O, NTs; R¹ = Me; R² = H, Prⁿ; R³ = Ph, C₆H₄X-4 (X = Me, OMe, Cl), C₆H₄Me-2, 3-Th, Buⁿ, SiMe₃; R⁴ = H; R¹–R⁴ = (CH₂)₃, (CH₂)₄

Scheme 62



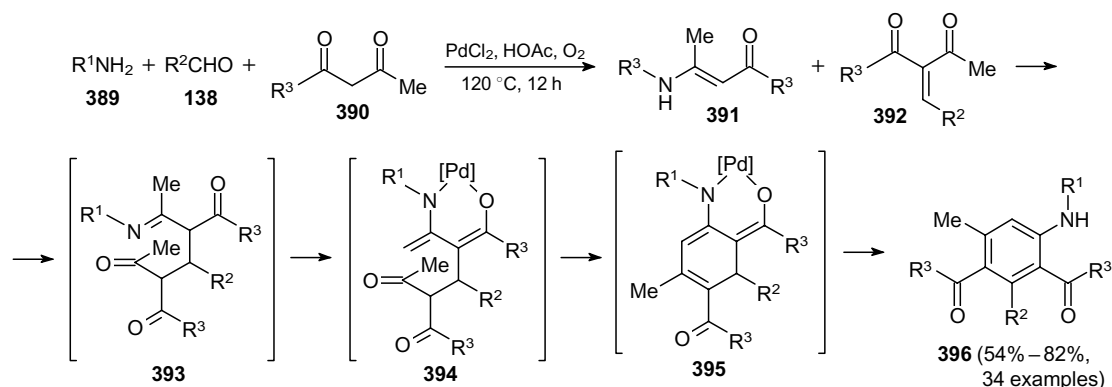
R¹ = Ph, C₆H₄X-4 (X = Me, CF₃, Br); R² = Ph, 2-Fu, 4-OEstrone-Ph;
 R³ = Ph, C₆H₄X-4 (X = Me, OMe, F)

Scheme 63



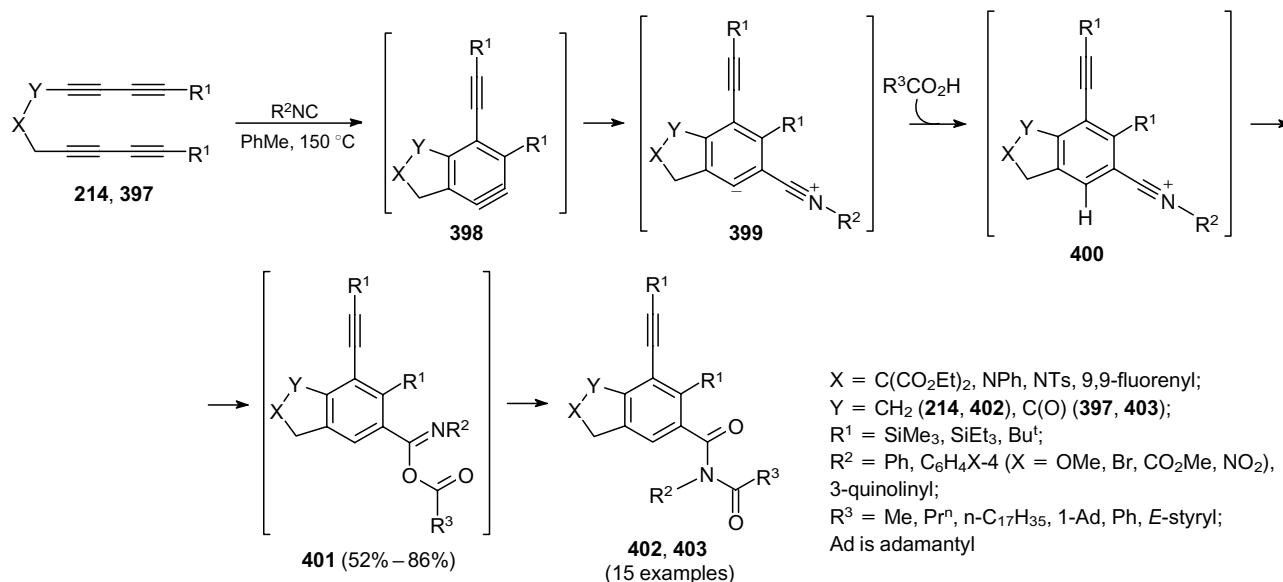
X = H, Me, Cl;
 IPr is 1,3-bis(diisopropylphenyl)imidazol-2-ylidene

Scheme 64

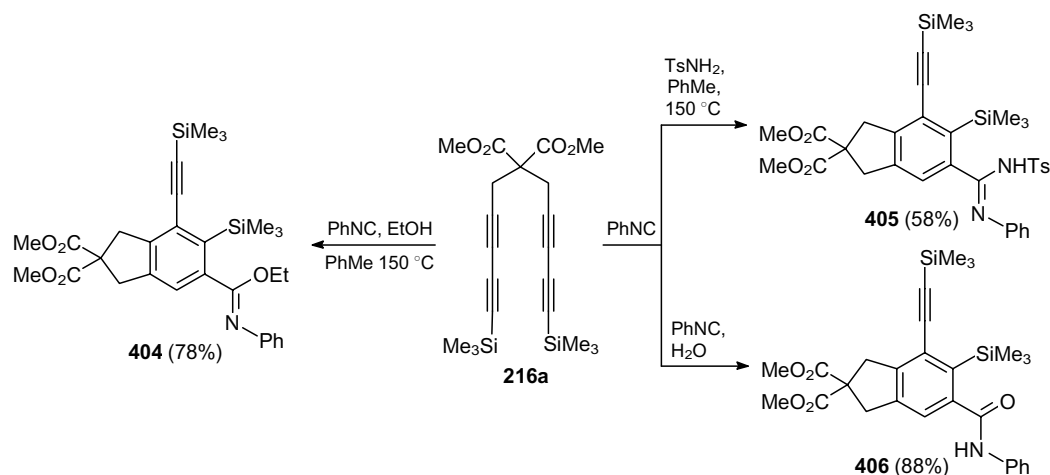


R^1 = Ph, C_6H_4X-4 (X = Me, Pr^i , Bu^t , CF_3 , OMe, OCF_3 , F, Cl, Br, Ph), C_6H_4X-3 (X = Me, Cl), C_6H_4X-2 (X = Me, F, Cl), 2-Py, CH_2-2-Th ;
 R^2 = Ph, C_6H_4X-4 (X = Me, Bu^t , OMe, Cl, Br, Ph), C_6H_4X-3 (X = Me, F, Br), C_6H_4F-2 , 2-Fu; R^3 = Me, OMe, OEt, MeC_6H_4Y (Y = 4-Cl, 3-Cl, 2-Br)

Scheme 65



Scheme 66

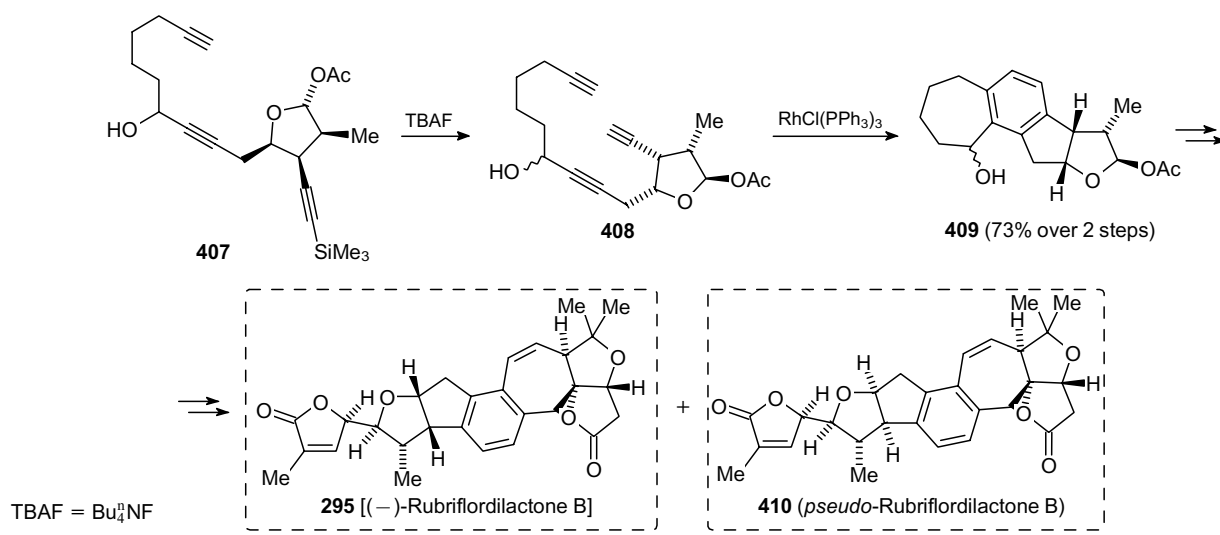


(Scheme 67). Triyne **408**, derived from triyne **407** by desilylation, underwent a rhodium-catalyzed cyclotrimerization reaction in the presence of Wilkinson's catalyst $[(Ph_3P)_3RhCl]$ to give the arene core of alcohol **409**, an advanced intermediate which was further converted into

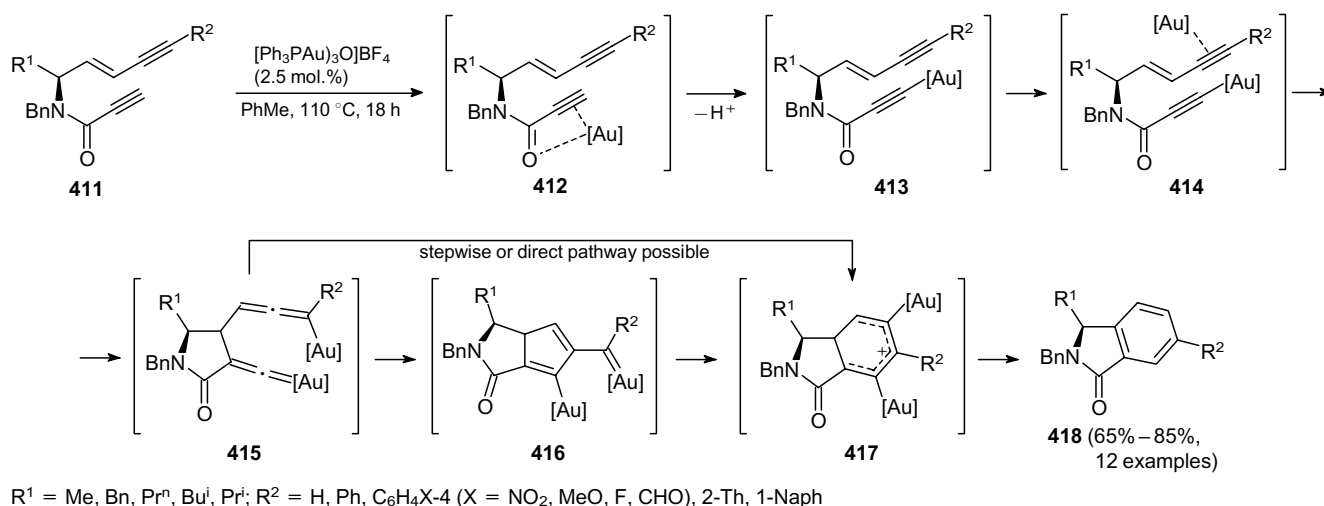
(–)-rubriflordilactone **B** (**295**) and (–)-*pseudo*-rubriflordilactone **B** (**410**).

Hyland and co-workers¹⁰⁶ disclosed the synthesis of isoindolinones **418** via a gold catalyzed cycloisomerization and aromatization of diyne **411** (Scheme 68). The authors

Scheme 67



Scheme 68



suggested that the reaction proceeded *via* gold acetylides **412** and **413**, a second gold incorporation as acetylene complex **414**, and cyclization *via* intermediates **415**–**417**.

As a follow up publication from the earlier dihydroiso-benzofuran synthesis (see Scheme 61), Ma and co-workers¹⁰⁷ reported that the use of α -disubstituted propargylic alcohols **420** gave tricyclic arenes **424** with only minor amounts of the β -elimination products (Scheme 69). The authors suggested a mechanism where Pd-coordination induced the elimination of the carbonate and gave the reactive intermediate **421**, which reacted with propargylic alcohol **420** to give the allene **422**. Arene **423** formation was followed by nucleophilic displacement of the catalyst to release the benzoisofuran derivatives **424** in fair to good yields. The use of enantiomerically pure diynes **367a,b** gave the arenes **424a,b** with retention of configuration at the propargylic position.

Recently, Zhu and co-workers¹⁰⁸ showed that diynes **425** on reaction with a catalytic amount of cobalt dichloride and pinacolborane **426** in the presence of phenanthroline gave vinyl boranes **427** in moderate to good yields (Scheme 70). Vinyl borane **427a** was subsequently converted into cyclohexadienes **428**, employing a Suzuki–Miyaura coupling reaction followed by a thermal 6π -electrocycliza-

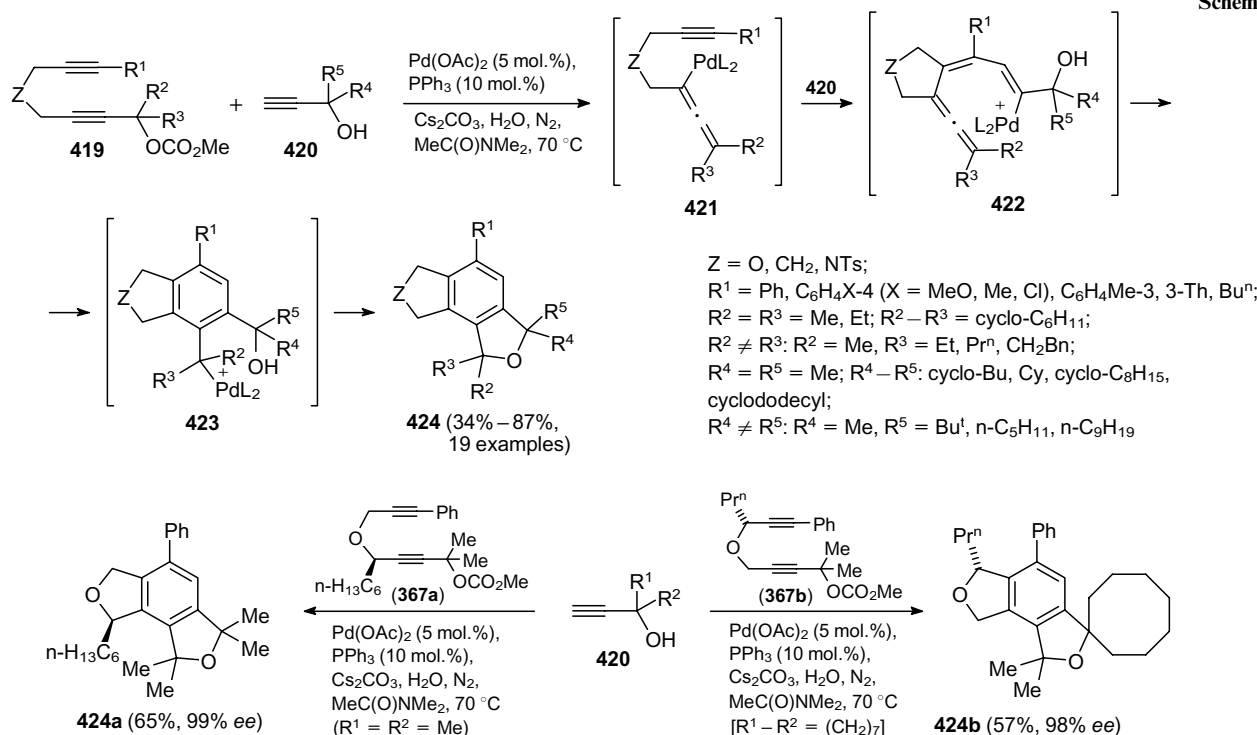
tion. Oxidative aromatization mediated by DDQ gave indanes **429** in good yields.

Lee and co-workers¹⁰⁹ expanded their earlier work¹⁰⁴ on imides **401**, imidates **404**, amidines **405** and amides **406** (see Schemes 65, 66) by trapping the aryne intermediate **432** from triynes **430** by nitriles in the presence of a silver catalyst (Scheme 71). Silver complexed aryne **433** gave rise to two regioisomeric nitrilium ions **434** and **437**, which underwent conversion into the two isomeric quinazolines **436** and **439** on treatment with a second equivalent of nitrile. The observed regioselectivity was controlled by the steric bulk of the R⁵ group with *tert*-butyl favouring nitrilium ion **434** whereas nitrilium ion **437** was favoured with the smaller TMS group. Aromatic substituents resulted in a slight preference of **434** over **437**.

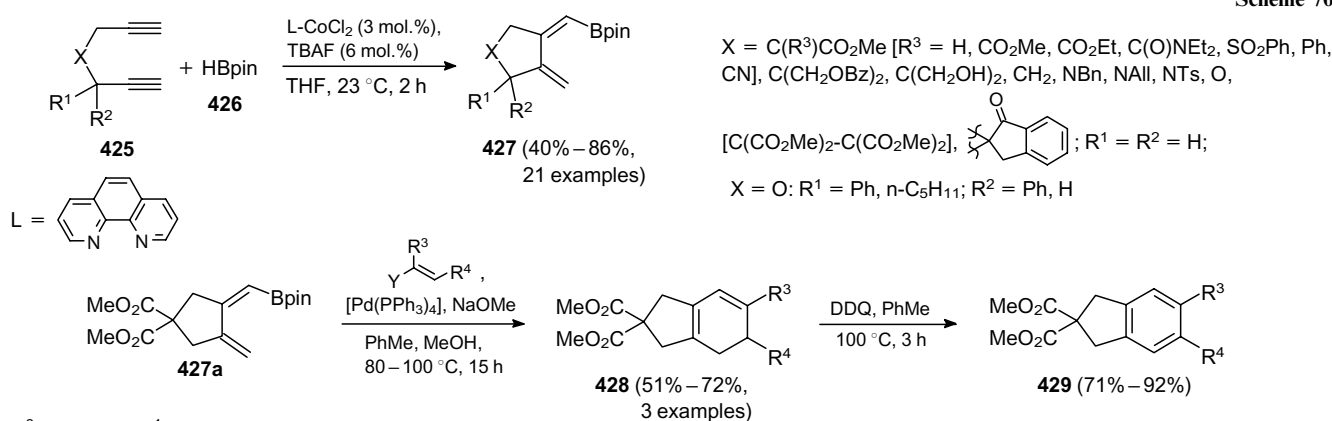
Additionally, the same group¹¹⁰ reported that arynes of type **434** derived from **440** were trapped with isonitriles to give benzocyclobutene-diimines **441** in moderate yields (Scheme 72). Mixed additions of both nitriles and isonitriles were also performed. In this case, reactions gave indolimes **442** in fair yields, as well as the derived hydrate **443** in moderate yields in some cases.

In 2020, B. Wang and co-workers¹¹¹ reported the rhodium catalyzed annulation of heterocyclic amides **444** with

Scheme 69



Scheme 70



diynes **445** (Scheme 73). As a directing group, the amide functionality is known to facilitate Rh–C–H insertion to intermediate **446**, which reacted with diyne **445**. Subsequently, a five-membered rhodacycle **448** was formed, which in the presence of a nucleophile lost the directing group. Concomitant insertion into the other alkyne gave the metallacycle **449**, followed by rhodium elimination to give arenes **450** in low to good yields.

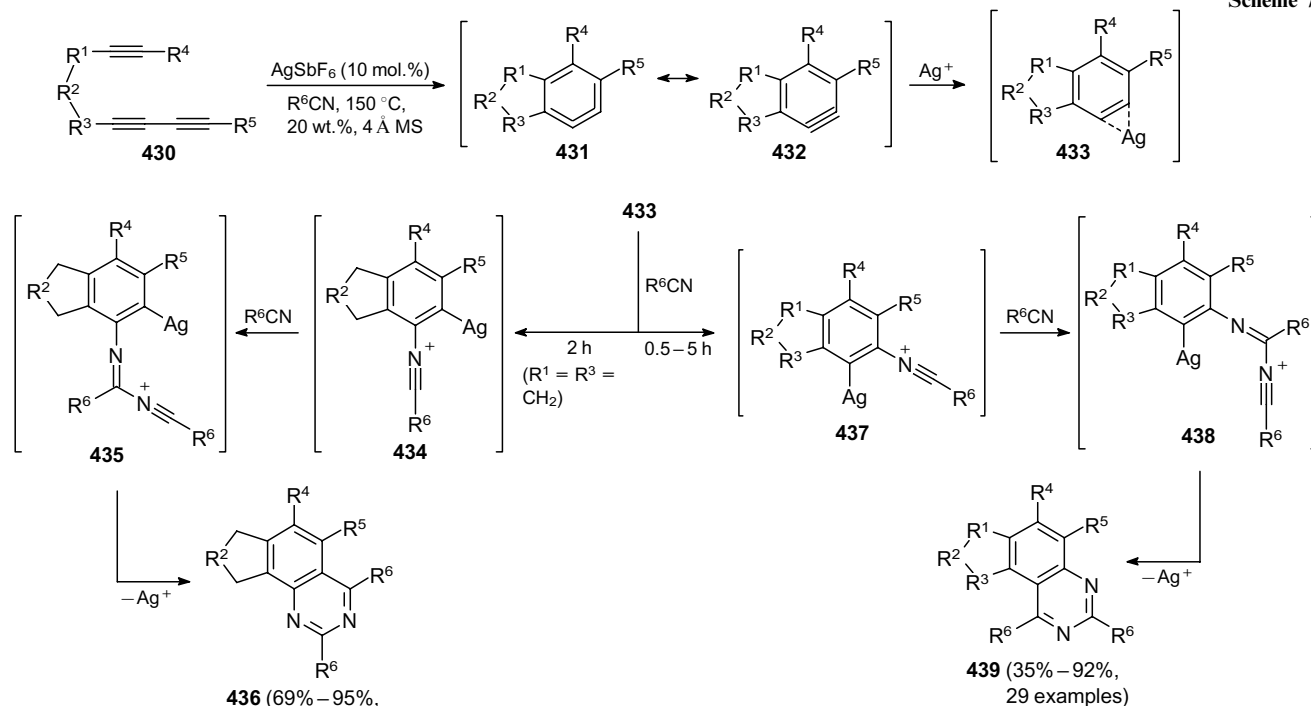
Activation of diynes **451** with rhodium in the presence of 2 equivalents of quinones **452** gave naphthoquinones **457** (Scheme 74).¹¹² Initially, the metallacycle **454** was formed, which reacted with quinone **452** in a cycloaddition type fashion to give diene **456** after rhodium elimination. The intermediate cyclohexadiene **456** was aromatized by reaction with a second equivalent of quinone **452** giving naphthoquinones **457** in fair to good yields. Hexasubstituted arenes were accessible *via* this procedure in moderate yields.

Foubelo and co-workers¹¹³ investigated strategies for the conversion of diynes and enynes into arenes. Firstly,

rhodium catalyzed [2+2+2]-cyclotrimerization of diyne **458** and acetylenes **112** gave tetrahydroisoquinolines **463** (Scheme 75). In addition, enynes **464**, **465** were cyclized using the Hoveyda–Grubbs catalyst to give dienes **466** and **469**. Finally, Diels–Alder reaction of these compounds with dimethyl acetylenedicarboxylate (**112a**) and subsequent DDQ mediated oxidative aromatization gave tetrahydroisoquinolines **468** and **470**.

Li and co-workers¹¹⁴ reported the oxidative coupling of primary alcohols **472** with differently substituted cyclohexanones **471** on Pd/C for the synthesis of *o*-substituted phenols **478** (Scheme 76). Oxidation of the alcohols **472** to the corresponding aldehydes **473** followed by base catalyzed aldol reaction gave alcohols **474**. Dehydration and alkene isomerization gave cyclohexanone **476**, which on aerobic oxidation and tautomerization gave phenols **478** in reasonable yields. Intriguingly, reaction with a steroid triol occurred with regioselective oxidation of the primary alcohol and gave the steroidal phenol **479**.

Scheme 71



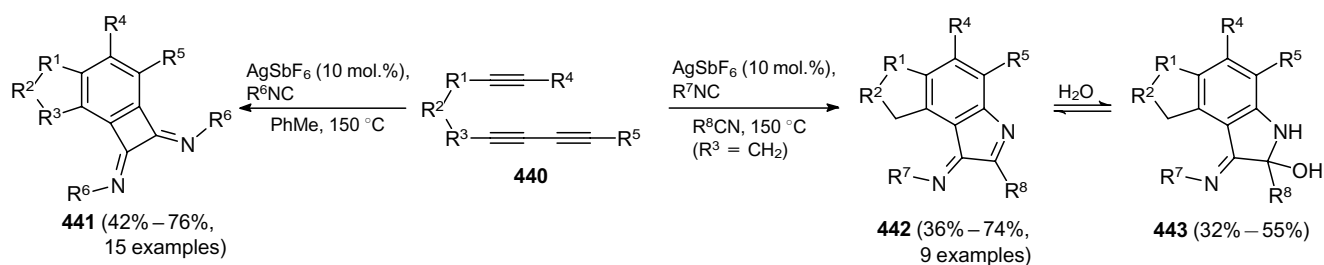
$\text{R}^2 = \text{C}(\text{CO}_2\text{Me})_2, \text{C}(\text{CO}_2\text{Et})_2, \text{CH}_2$;
 $\text{R}^4 = \text{C}\equiv\text{CX}$ ($\text{X} = \text{Bu}^t, \text{CH}_2\text{C}_6\text{H}_4\text{OMe-4}, \text{Ph}$);
 $\text{R}^5 = \text{Bu}^t, \text{CH}_2\text{C}_6\text{H}_4\text{OMe-4}, \text{Ph}$; $\text{R}^6 = \text{Ph}$

$\text{R}^1 = \text{C}(\text{O}), \text{CH}_2$; $\text{R}^2 = \text{NTs}, \text{O}, \text{CH}_2, \text{NPh}, \text{C}(\text{CO}_2\text{Me})_2$;
 $\text{R}^2 = 9,9\text{-fluorenyl}$; $\text{R}^3 = \text{CH}_2, \text{NTs}$;

$\text{R}^1\text{--R}^2\text{--R}^3 =$ ; $\text{R}^4 = \text{H}, \text{SiMe}_3, \text{C}\equiv\text{CX}$ ($\text{X} = \text{SiMe}_3, \text{Bu}^n$);

$\text{R}^5 = \text{SiMe}_3, \text{SiEt}_3$; $\text{R}^6 = \text{Ph}, \text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{OMe}, \text{NMe}_2, \text{F}$),
 piperidyl, morpholyl, vinyl, styryl, Me, Et, Pr^i , cyclo- Pr , 2-Naph

Scheme 72



$\text{R}^1 = \text{CH}_2, \text{C}(\text{O})$; $\text{R}^2 = \text{C}(\text{CO}_2\text{Me})_2, \text{NTs}, \text{NPh}, \text{O}$;
 $\text{R}^2 = 9,9\text{-fluorenyl}$; $\text{R}^3 = \text{CH}_2$;

$\text{R}^1\text{--R}^2\text{--R}^3 =$ ; $\text{R}^4 = \text{H}, \text{C}\equiv\text{CTMS}$; $\text{R}^5 = \text{TMS}, \text{TES}$;

$\text{R}^6 = \text{Ph}, \text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{Me}, \text{OMe}, \text{NMe}_2, \text{CO}_2\text{Me}, \text{NO}_2, \text{Br}$), 2-Naph, 3-quinolyl

$\text{R}^1 = \text{CH}_2, \text{C}(\text{O})$;
 $\text{R}^2 = \text{C}(\text{CO}_2\text{Me})_2, \text{NPh}$;
 $\text{R}^4 = \text{H}, \text{C}\equiv\text{CTMS}$;
 $\text{R}^5 = \text{TMS}, \text{TES}$;
 $\text{R}^7 = \text{Ph}, \text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{Me}, \text{Br}, \text{CO}_2\text{Me}, \text{NO}_2$);
 $\text{R}^8 = \text{Ph}, \text{Pr}^i$

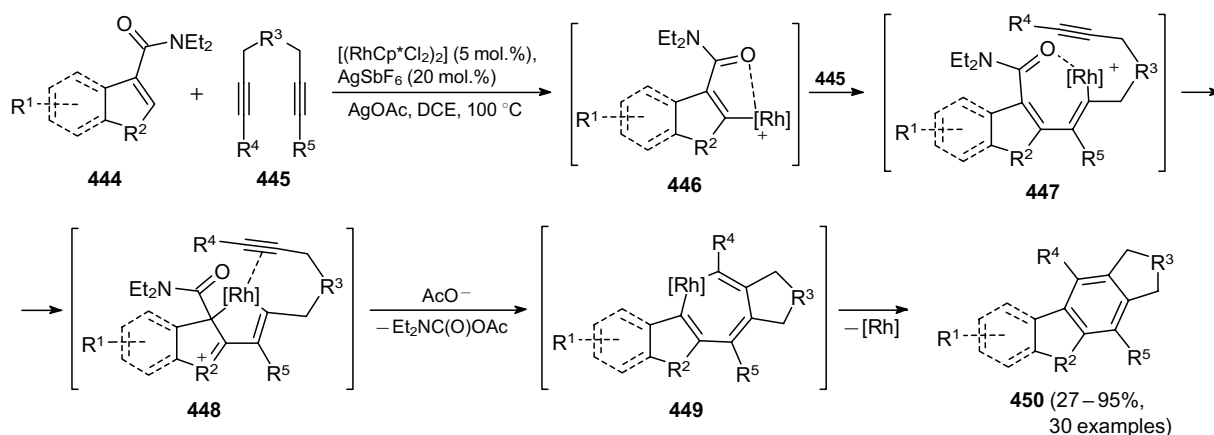
$\text{R}^1 = \text{CH}_2, \text{C}(\text{O})$;
 $\text{R}^2 = \text{C}(\text{CO}_2\text{Me})_2, \text{NPh}$;
 $\text{R}^4 = \text{H}, \text{C}\equiv\text{CTMS}$;
 $\text{R}^5 = \text{TMS}, \text{TES}$;
 $\text{R}^7 = \text{Ph}, \text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{Me}, \text{Br}, \text{CO}_2\text{Me}$);
 $\text{R}^8 = \text{Me}, \text{Et}$

Recently, Deng and co-workers¹¹⁵ reported the synthesis of heavily substituted phenols **487** from allenyl diazoketones **480** (Scheme 77). Upon mixing with a silver salt, allene **481** was cycloisomerized to diazofuran **483**. Under rhodium catalysis conditions, this compound was converted into the rhodium-carbene **484**, which underwent cyclopropanation and ring expansion to give the cyclohexanone **486**. When $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{OEt}$ these underwent tautomerization under the reaction conditions and gave phenols **487** in good yields. In ten other examples when $\text{R}^2 = \text{Ph}$, OEt the

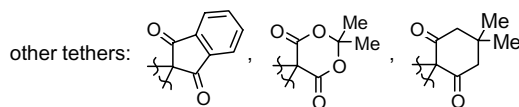
products isolated were the cyclohexenones **486**. Addition of a second Lewis acid mediated the aromatization of seven of those examples ($\text{R}^2 = \text{OEt}$, 50%–86%) while three ($\text{R}^2 = \text{Ph}$ or $\text{R}^1 = \text{H}$ and $\text{R}^2 = \text{OEt}$) did not undergo conversion into the phenols **487**. Further attempts to transform this reaction into a one-pot procedure were unsuccessful since the reaction stopped at the furan **483** stage.

Toyota and co-workers¹¹⁶ reported the conversion of enamines **488** into anilines **491** in moderate to good yields by reaction with copper(II) and palladium(II) acetates in

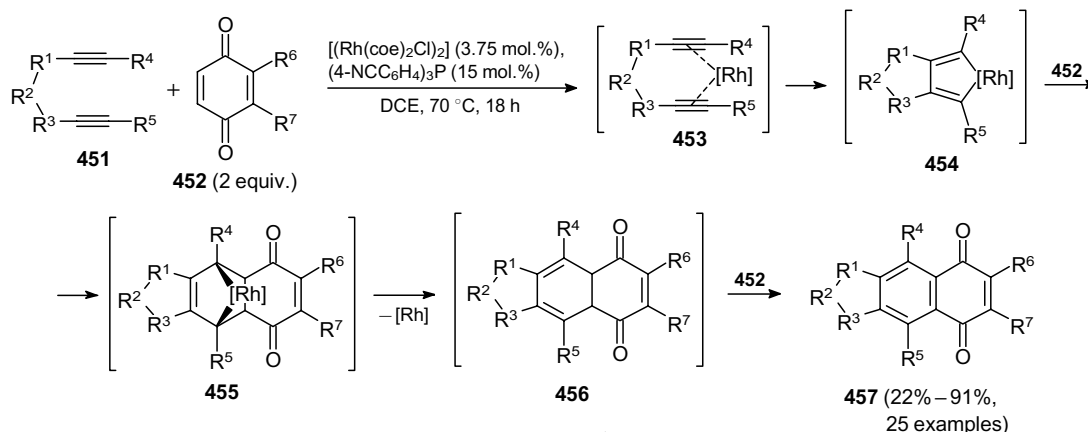
Scheme 73



Ar = indole, benzothiophene, thiophene; $\text{R}^2 = \text{NMe}$; $\text{R}^1 = \text{H}$, 4-OMe, 5-X (X = Br, Me, OMe, F, NO_2), 6-Cl, 7-Me, 7-Cl; $\text{R}^2 = \text{NBn}$, NH, S; $\text{R}^1 = \text{H}$, $\text{R}^3 = \text{C}(\text{CO}_2\text{Et})_2$, $\text{C}(\text{Ac})_2$, NTs, $\text{C}(\text{Ac})\text{CO}_2\text{Et}$, $\text{C}(\text{CN})_2$, O; $\text{R}^4 = \text{R}^5 = \text{Ph}$, $\text{C}_6\text{H}_4\text{X}-4$ (X = Me, OMe, F, Cl), 2-Th, Me; $\text{R}^4 = \text{C}_6\text{H}_4\text{Cl}-4$, $\text{R}^5 = \text{C}_6\text{H}_4\text{MeO}-4$ (major); $\text{R}^4 = \text{C}_6\text{H}_4\text{OMe}-4$, $\text{R}^5 = \text{C}_6\text{H}_4\text{Cl}-4$ (minor);



Scheme 74



$\text{R}^1 = \text{CH}_2$; $\text{R}^2 = \text{C}(\text{CO}_2\text{Me})_2$, CH_2 , O, NTs; $\text{R}^3 = \text{CH}_2$; $\text{R}^1\text{--R}^2\text{--R}^3 = \text{C}_6\text{H}_4\text{Y}$ (Y = NTs, O); $\text{R}^4 = \text{H}$, Me, Bu^n , CH_2OTBS , Ph,

$\text{C}_6\text{H}_4\text{X}-4$ (X = OMe, F); $\text{R}^5 = \text{H}$, Me, Bu^n , Ph, $\text{C}_6\text{H}_4\text{X}-4$ (X = OMe, F); $\text{R}^6 = \text{H}$, Me, OMe, $\text{N}(\text{Me})\text{Ph}$, Cl, Br, I, Ph, $\text{C}_6\text{H}_4\text{X}-2$ (X = OMe, Br), $\text{C}_6\text{H}_4\text{CF}_3-4$; $\text{R}^7 = \text{H}$, Me; coe is cyclooctene

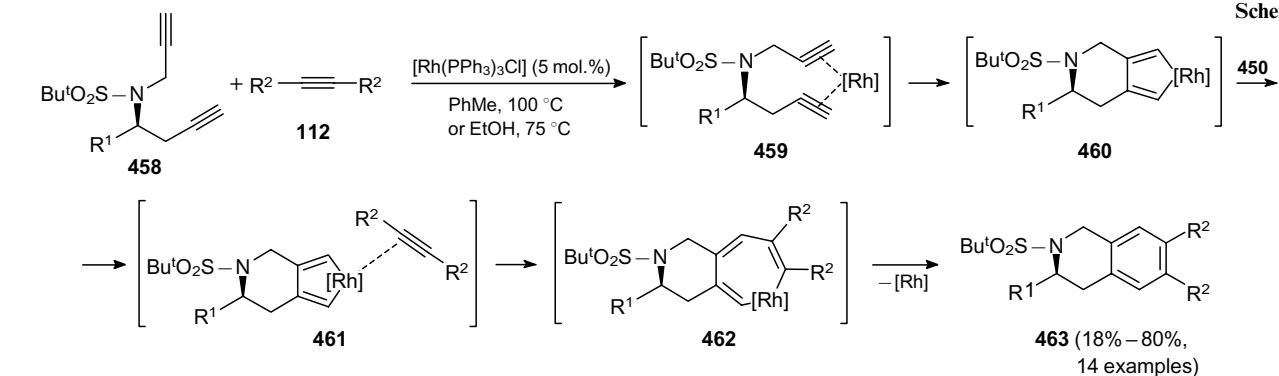
DMSO (Scheme 78). The transformation by $\text{Pd}(\text{OAc})_2$ mediated cyclization to the palladated cyclohexene derivative **489** and subsequent reductive elimination gave cyclohexadiene **490**, which was subsequently converted into the anthranilic acid ester derivatives **491** by further oxidation with $\text{Pd}(\text{OAc})_2$. In these cases, $\text{Cu}(\text{OAc})_2$ was the best co-oxidant. When the amine **488** was only monosubstituted and the alkene was terminal, a mixture of the cyclohexanone imine **489** and the corresponding pyrrolidine was obtained, which gave rise to a mixture of anilines and pyrroles slightly favouring the aniline. Additionally, the authors showed that the procedure was amenable to a one-pot process starting with the acetoacetate and the amine (with oxygen as the oxidant).

5. Other aromatization strategies

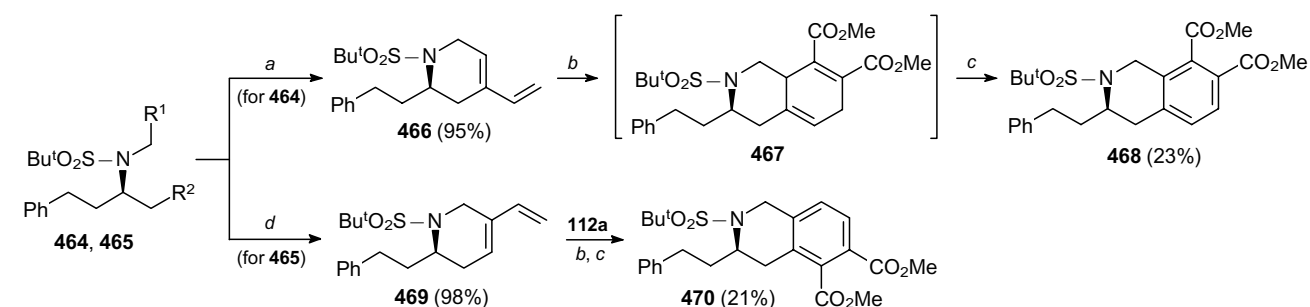
This final section of the review will focus on alternative methods that are not classified according to the sections

above. This includes aromatization reactions that depend on applications of organo-catalysis, base-mediated reactions (Aldol-reactions, Mannich-reactions, *etc.*) and oxidative cyclohexane- or cyclohexanone halide–halonium addition–elimination reactions to form phenols. These methods are highly versatile and applicable for the synthesis of heavily substituted phenols from readily available starting materials. As shown in this chapter, new developments in phenol syntheses have facilitated the synthesis of *m*-substituted derivatives through pre-functionalization and subsequent aromatization. These approaches overcome the limitations of electrophilic aromatic substitution reactions or *ortho*-lithiation reactions of phenols and phenol derivatives, which strongly favour *ortho*- or *para*-substitution reactions and not *meta*. These reactions may be sub-divided according to their reaction type.

Scheme 75

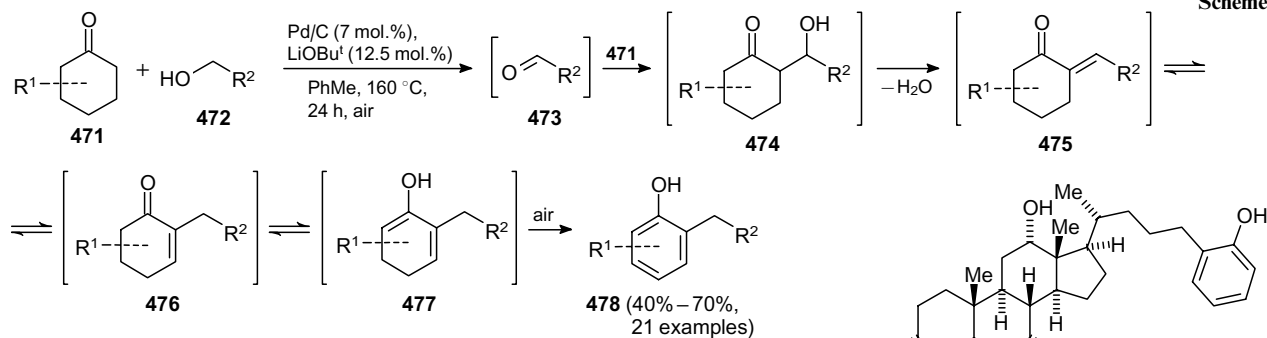


$\text{R}^1 = \text{CH}_2\text{Bn}$, Ph, $n\text{-C}_9\text{H}_{19}$, $(\text{CH}_2)_4\text{OTHP}$, Bu^t ; $\text{R}^2 = \text{Et}$, CH_2OH , CO_2Me ; $\text{R}^2\text{--R}^2 = \text{Bu}^n$, H gives 1 : 1 mixture; THP is tetrahydropyranyl



(a) H-G II (10 mol. %), 1,7-octadiene, CH_2Cl_2 , 40 °C; (b) $\text{MeO}_2\text{C}\equiv\text{CO}_2\text{Me}$ (**112a**), PhMe, 100 °C; (c) DDQ, PhMe, 80 °C; (d) H-G I (20 mol. %), 1,7-octadiene, CH_2Cl_2 , 40 °C (H-G is Hoveyda–Grubbs 1st (I) or 2nd (II) generation catalyst); **464**: $\text{R}^1 = \text{CH}=\text{CH}_2$, $\text{R}^2 = \text{C}\equiv\text{CH}$; **465**: $\text{R}^1 = \text{C}\equiv\text{CH}$, $\text{R}^2 = \text{C}=\text{CH}_2$

Scheme 76



$\text{R}^1 = \text{H}$, 2-Me, 3-Me, 4-Me, 4-Ph, 4- Bu^t ; $\text{R}^2 = \text{Me}$, $n\text{-C}_6\text{H}_{11}$, $n\text{-C}_6\text{H}_{12}$, $n\text{-heptadecyl}$, Ph, CH_2Bn , $(\text{CH}_2)_2\text{Bn}$, $\text{CH}_2\text{CH}(\text{Me})\text{CH}_2\text{Bu}^t$, $(\text{CH}_2)_2\text{-Cy}$, $\text{CH}_2\text{-1-Ad}$, $(\text{CH}_2)_2\text{-3-indolyl}$, $(\text{CH}_2)_3\text{-2-benzofuranyl}$, $(\text{CH}_2)_3\text{-2-Th}$, 2,6-dimethylheptanyl, 11-hydroxyheptadecyl

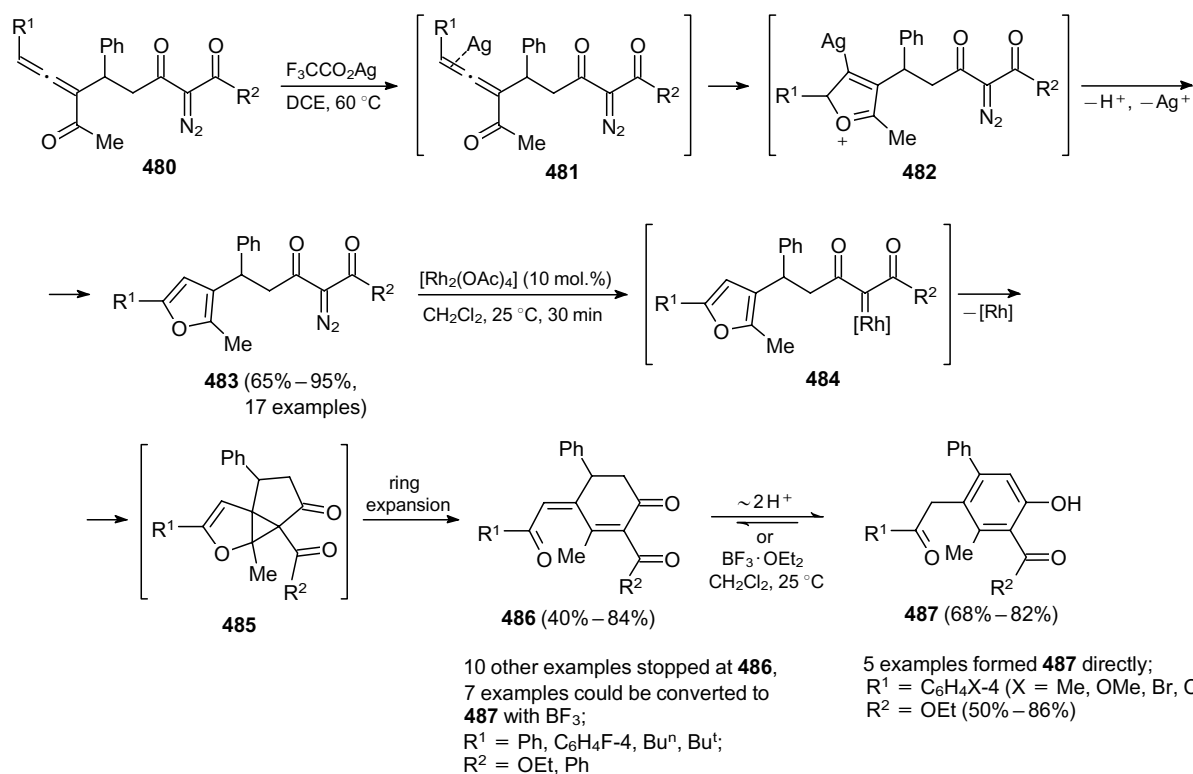
5.1. Halogen-mediated reactions

Luo *et al.*¹¹⁷ showed that substituted cyclohexenones **492** reacted with iodine in DMSO under air to provide phenols **493** (Scheme 79). This procedure was applicable to a broad range of different substitution patterns including for the elaboration of tetra-substituted phenols **493**.

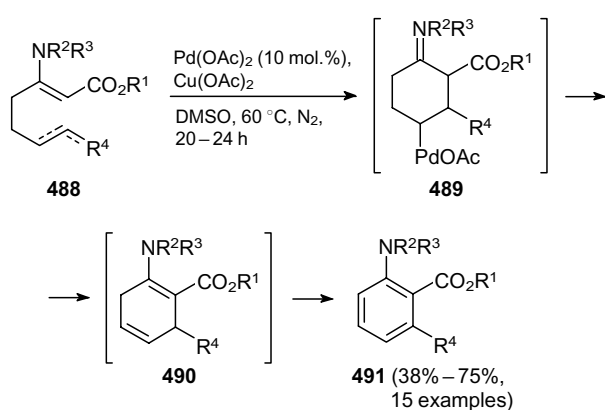
Kang and co-workers¹¹⁸ reported the trimethylsilyl triflate-catalyzed aromatization of Hagemman's esters **494** with NBS as the stoichiometric oxidant. Sixteen examples of phenol derivatives **495** were synthesized *via* this route by simple variation of the aldehyde precursor (RCHO) used in the preparation of the starting cyclohexanone **494** (Scheme 80) from ethyl acetoacetate.

Luo and co-workers¹¹⁹ reported the conversion of α,β -unsaturated oximes **496** with iodine under air to provide anilines **500** (Semmler–Wolf type reaction) (Scheme 81). Improving on recent findings, this method excluded strong acids or transition metal catalysis. A range of aromatic substituents were tolerated with the R^1 and R^2 substituents and the reaction provided the desired products with overall moderate to good yields. The authors suggested that the reaction proceeded *via* the imine radical **497**, its tautomerization to radical **498**, C-iodination and elimination to the aniline tautomer **499** and aromatization. Whilst the authors have shown by reaction inhibition with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) that the process involves radicals, the authors of this review consider that the imine

Scheme 77

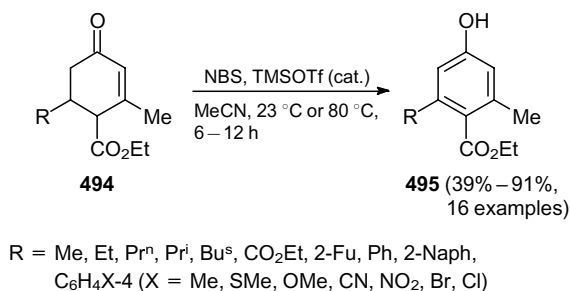


Scheme 78

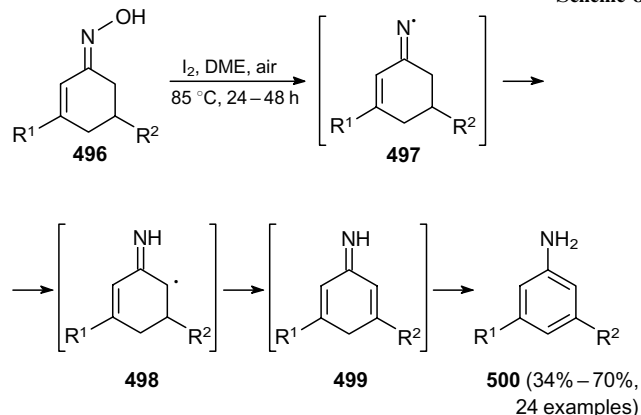


$\text{R}^1 = \text{Me}, \text{Et}$; $\text{R}^2 = \text{H}$, NR^2R^3 : pyrrolidine, piperidine, morpholine, *N*-Me-piperazine, *N*-Ac-piperazine; $\text{R}^3 = \text{Bn}, \text{CH}_2\text{C}_6\text{H}_4\text{X}-4$ ($\text{X} = \text{MeO}, \text{Me}, \text{F}$), $\text{CH}_2\text{Bn}, n\text{-C}_6\text{H}_{13}$; $\text{R}^2 = \text{R}^4 = \text{H}$, $\text{R}^3 = \text{Bn}$ or $\text{CH}_2\text{C}_6\text{H}_4\text{OMe}-4$ 2:1 to 5:3 mixture between aniline and pyrrole;
 $\text{R}^4 = \text{H}, \text{Me}$

Scheme 80

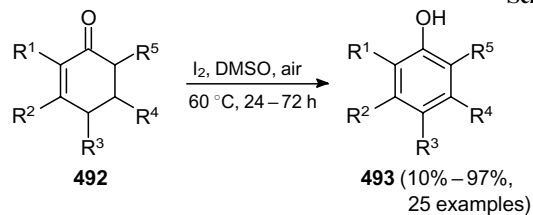


Scheme 81



$\text{R}^1 = \text{H}, \text{Me}, \text{Ph}, \text{C}_6\text{H}_4\text{X}-4$ ($\text{X} = \text{OMe}, \text{Me}, \text{Cl}, \text{SMe}, \text{SO}_2\text{Me}$), 2-Th, 2-Fu, 2-Naph, cyclohex-2-enone oximes;
 $\text{R}^2 = \text{H}, \text{CO}_2\text{H}, \text{CO}_2\text{Et}, \text{C}(\text{O})\text{NHBn}, \text{C}(\text{O})\text{NHPh}, \text{Ph}, \text{C}_6\text{H}_4\text{X}-4$ ($\text{X} = \text{Me}, \text{OMe}, \text{NO}_2, \text{Cl}, \text{Br}$), $\text{C}_6\text{H}_3\text{OCH}_2\text{O}-3,4$

Scheme 79



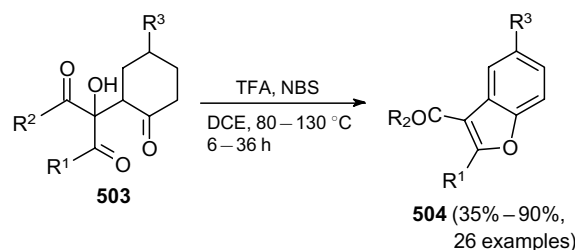
$\text{R}^1 = \text{H}, \text{Me}$; $\text{R}^2 = \text{Ph}, \text{C}_6\text{H}_4\text{X}-4$ ($\text{X} = \text{OMe}, \text{Cl}, \text{Me}, \text{Br}, \text{NHBoc}, \text{OH}$), 2-Fu; $\text{R}^3, \text{R}^5 = \text{H}, \text{Me}, \text{CO}_2\text{Et}$; $\text{R}^4 = \text{Ph}, \text{C}_6\text{H}_4\text{NO}_2-3$, $\text{C}_6\text{H}_3\text{OCH}_2\text{O}-3,4$, 2-Naph, $\text{C}_6\text{H}_4\text{Br}-4$, CO_2H , CO_2Et , $\text{C}(\text{O})\text{NHBn}$, $\text{C}(\text{O})\text{NHPh}$, $\text{C}(\text{O})\text{NHC}_6\text{H}_4\text{OMe}-4$

Scheme 82



$\text{R}^1 = (\text{CH}_2)_2\text{-1-Naph}$, CH_2Bn , $(\text{CH}_2)_2\text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{Bu}^t$, OMe , OBn , Br , F , OH), $(\text{CH}_2)_2\text{C}_6\text{H}_4\text{Y}$ ($\text{Y} = 2\text{-Br}$, 3-Br), $\text{CH}_2\text{CH}(\text{Ph})_2$, $\text{CH}_2\text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{CO}_2\text{H}$, $\text{C}\equiv\text{CH}$), $(\text{CH}_2)_2\text{Bn}$, $(\text{CH}_2)_2\text{C}\equiv\text{CH}$, $\text{CH}_2\text{C}\equiv\text{CPh}$, $\text{cyclo-C}_5\text{H}_9$, $\text{CH}(\text{Et})_2$, CHMe-cyclo-Pr , $2\text{-C}_6\text{H}_{13}$, Cy , $\text{C}_6\text{H}_{10}\text{Me-4}$, $\text{C}_6\text{H}_{10}\text{Pr}^i\text{-2}$, $(\text{CH}_2)_2(4\text{-Me})\text{thiazole}$, menthyl , citronellyl , cholesteryl , borneoyl ;
 $\text{R}^2 = \text{H}$, 3-Me , 3-Ph , 3-(2-Th) , 3-(1-Naph) , $3\text{-CO}_2\text{Me}$, $3,5\text{-Ph}_2$, $3\text{-(5-phenyl)thienyl}$, $2\text{-(C}_6\text{H}_4\text{Me-4)}$, $3\text{-(SC}_6\text{H}_4\text{Cl-4)}$

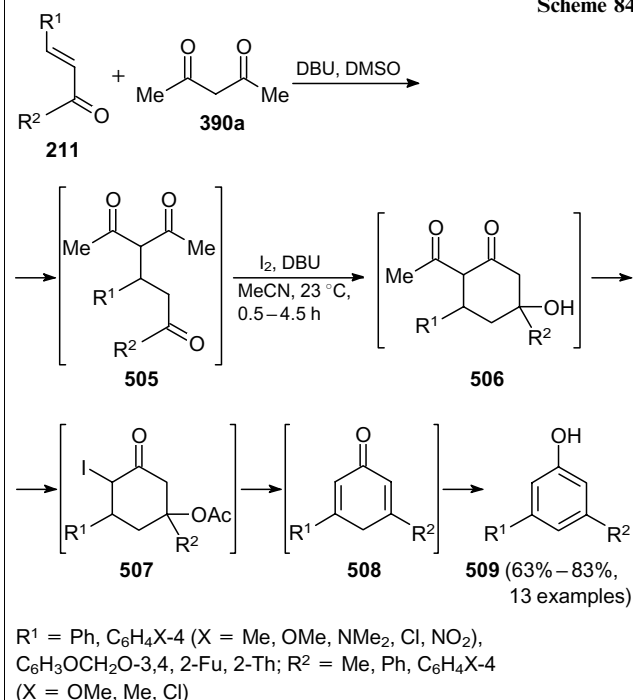
Scheme 83



$\text{R}^1 = \text{Me}$, Pr^n , Pr^i , Bn , Et , Ph , 2-Naph , 2-Th , $\text{C}_6\text{H}_4\text{X-4}$ ($\text{X} = \text{Cl}$, Br);
 $\text{R}^2 = \text{OBn}$, OMe , OEt , $\text{OC}_5\text{H}_{11}\text{-n}$, OBu^s , $\text{MeO}(\text{CH}_2)_2\text{O}$, Me ;
 $\text{R}^3 = \text{H}$, Me , Et , Pr^n , Bu^t , Ph , CO_2Me , NHC(O)Me

radical **497** is an unlikely intermediate and the reaction more likely proceeds *via* an alternative radical pathway and intermediacy of the dihydroaryl hydroxylamine and dehydrative aromatization.

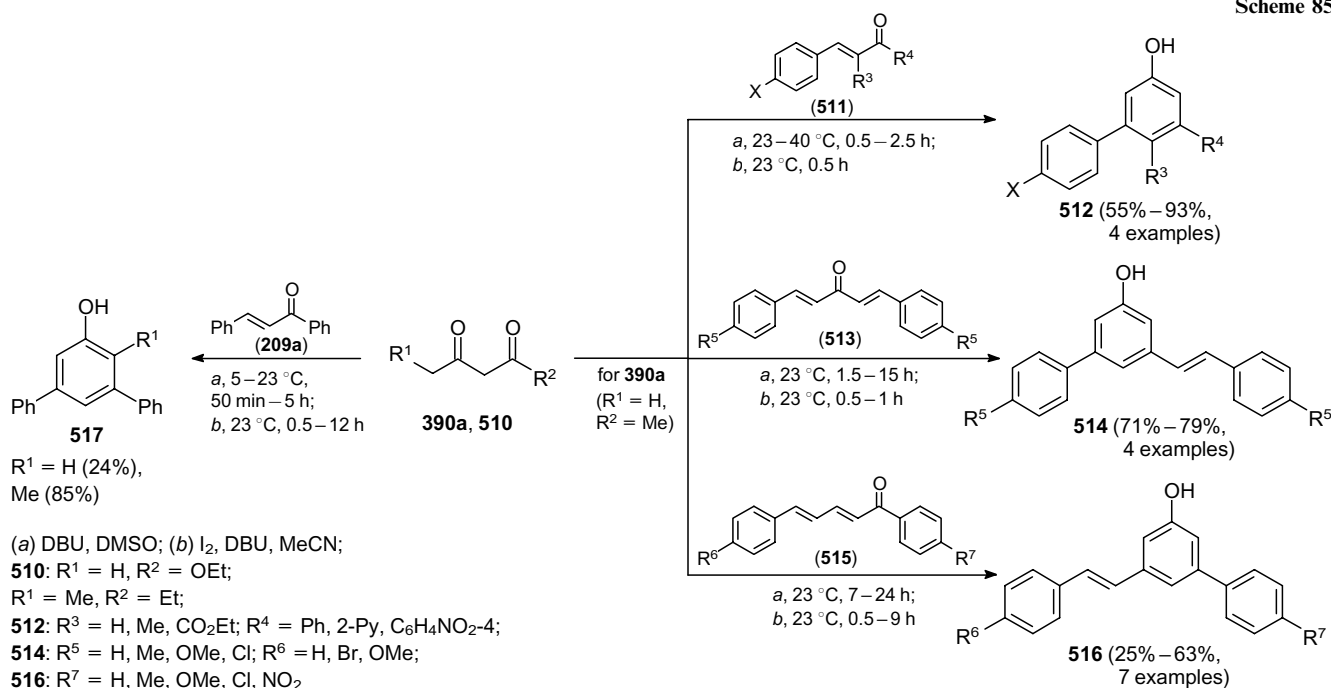
Scheme 84

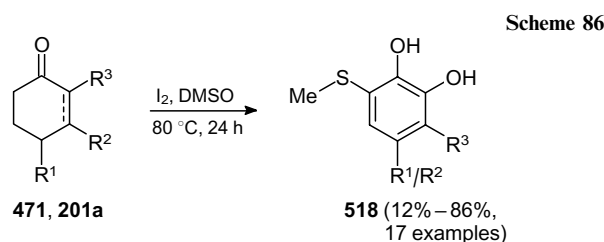


Jiao and co-workers¹²⁰ reported the coupling of cyclohexenones **201** with primary, secondary, terpene based, cyclic, and benzylic alcohols **501** to afford phenol ethers **502** (Scheme 82). The reaction tolerated different substituents on the cyclohexanone scaffold as well, giving tri-substituted phenol ethers in fair to excellent yields.

Sha and Liu¹²¹ discovered a Paal-Knorr based benzofuran synthesis starting from the readily available 2-hydroxy-1,4-diketones **503** (Scheme 83). With the use of trifluoroacetic acid-catalysis, the diketones were converted into the furans; subsequent NBS oxidation resulted in aromatization to produce benzofurans **504**.

Scheme 85





$R^1 = \text{H, Me, Et, 4-oxocyclohexyl, CO}_2\text{H, CO}_2\text{Et, Pr}^n, \text{Bu}^t, n\text{-C}_5\text{H}_{11}, \text{C}(\text{Me})_2\text{Et, OH, OMe, NHAc}$; $R^2 = \text{H, Me}$; $R^3 = \text{H, Me, Bu}^s$

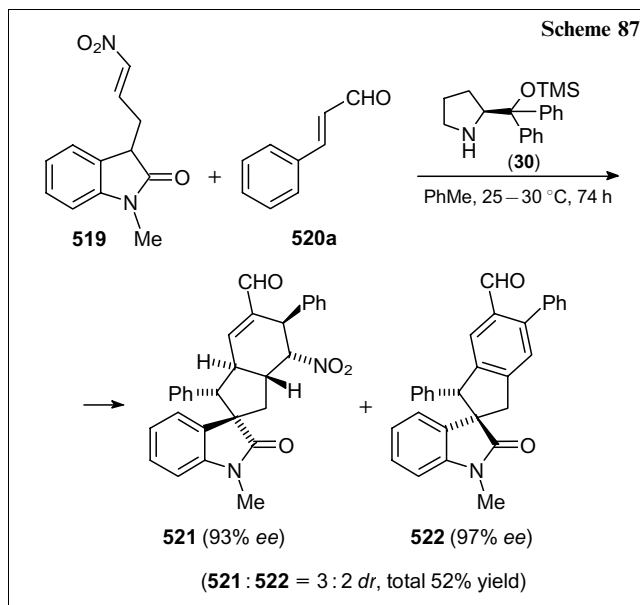
Yang and co-workers¹²² reported a general method for the syntheses of phenols **509** with a varying substitution patterns starting from 1,3-diketone **390a** and enones **209** (Scheme 84). Self-condensation of 1,3-diketones **505** mediated by iodine as catalyst followed by transacylation (*C* to *O*) of intermediate **506** and subsequent iodine promoted oxidation, presumably *via* iodides **507**, provided a variety of biaryl-phenols **509**.

Additionally, the authors showed that 1,3-diketones **390a**, **510** were general precursors for the synthesis of biaryl phenols **512**, **514**, **516** and **517** using α,β -unsaturated ketones **511**, **513**, **515** and **209a**, respectively (Scheme 85). Both symmetrical **513** as well as unsymmetrical ketones (**511**, **515**, **209a**) were found to readily react to produce the corresponding phenols in moderate to good yields using this iodine mediated reaction.

In 2019, Wu *et al.*¹²³ reported the oxidization of cyclohexanones **471** with iodine in the presence of DMSO for the synthesis of 2-sulfanylcatechols **518** (Scheme 86). This method proved to be general and worked with a range of alkyl and carboxylate substituents in the 2, 3 and 4 position of the cyclohexanones **471** and the reaction was also applicable to 2-cyclohexenones (*e.g.*, **201a**) as starting materials.

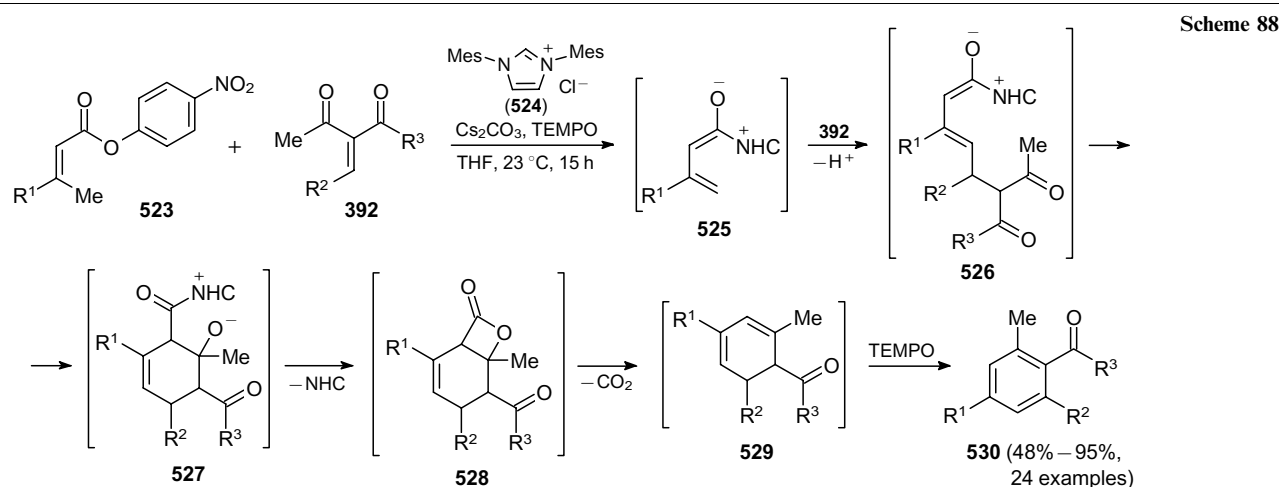
5.2. Organocatalyst-mediated reactions

In 2017, Lee and co-workers¹²⁴ reported the reaction of the nitroalkene **519** and cinnamaldehyde (**520a**) with the proli-



nol catalyst **30** to produce the heavily substituted spirocyclic oxindole derivative **521** as well as the arene **522** (Scheme 87). This reaction proceeded through a catalyst **30** mediated Michael–Michael–Michael–Aldol reaction cascade, a multistep process that proceeded with remarkable enantioselectivity (>96% ee) to provide oxindole **521** and presumably its spirane epimer, which underwent spontaneous aromatization by the elimination of nitrous acid under the reported reaction conditions and directly gave the spiro-arene **522**. The authors noted that other organocatalytic reactions of cinnamaldehyde derivatives with nitroalkenes structurally related to nitroalkene **519** gave spirocyclic oxindole derivatives corresponding to oxindole **521** as mixtures of spirane-epimers and no arene products corresponding to arene **522**. Presumably these cyclohexenes *e.g.*, **521** could be aromatized by reactions at the nitro-group.

In 2018, Chi and co-workers¹²⁵ reported that an *N*-heterocyclic carbene (NHC) derived from a precatalyst **524**



$R^1 = \text{Ph, C}_6\text{H}_4\text{X-4}$ (X = Me, OMe, F, Br, Cl), $\text{C}_6\text{H}_4\text{X-2}$ (X = OMe, Cl, F), $\text{C}_6\text{H}_4\text{X-3}$ (X = Me, OMe, Cl, F), 2-Fu, 2-Th, 2-Naph; $R^2 = \text{Ph, C}_6\text{H}_4\text{F-2,}$

$\text{C}_6\text{H}_4\text{X-4}$ (X = Me, Cl), $\text{C}_6\text{H}_4\text{Br-3, 2-Naph, 2-Th, 1-E-pentenyl}$; $R^3 = \text{Me, Ph}$; TEMPO = , NHC =

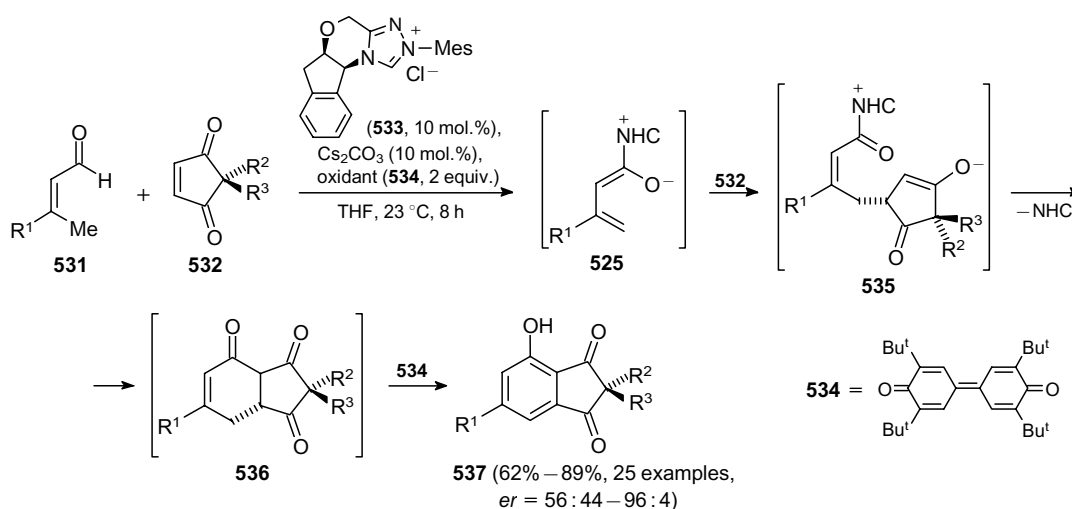
catalyzed the aromatization condensation reaction of α,β -unsaturated *p*-nitrophenol esters **523** with enediones **392** to produce tetrasubstituted benzene derivatives **530** (Scheme 88). The authors proposed that the reaction proceeded *via* the Michael and aldol adducts **526** and **527**, lactone **528** formation and elimination of carbon dioxide to provide cyclohexadiene **529**, with final aromatization carried out with TEMPO as the oxidant. With this method, a broad variety of different biaryl systems **530** were synthesized in moderate to excellent yields.

After their successful synthesis of tetrasubstituted arenes **530** from α,β -unsaturated esters **523** under NHC catalysis, the Chi group¹²⁶ expanded this methodology to prepare stereodefined indane derivatives **537** in good yields and enantiomeric ratios (up to 96:4 *er*) (Scheme 89). The reaction followed a similar pathway as above, however, using the stereodefined NHC-based catalyst **533**, gave the

products **537** with high enantioselectivities (up to 91% *ee*). The scope of reaction allowed for variation of the different substituents R^1 , R^2 and R^3 in substrates **531**, **532**. In addition, several spirocyclic 1,3-dienones **532** gave the corresponding derivatives in good yields and moderate to excellent enantiomeric ratios.

In addition to the synthesis of arenes **530** and stereo-defined indanes **537**, Chi and co-workers¹²⁷ showed that the method was useful for the synthesis of biaryls such as phenyl benzothiazoles **543** (Scheme 90). Reaction of enal **531** and enone **538** gave phenyl benzothiazoles **543**, which were formed *via* a NHC catalyzed Michael-addition and aldol reaction pathway, followed by lactone formation and loss of carbon dioxide to give **542**. Oxidation with 3,3',5,5'-tetra-*tert*-butyldiphenylquinone (**534**) gave the phenyl benzothiazoles **543** in moderate to excellent yields. Benzothiazoles have been shown to act as directing groups in

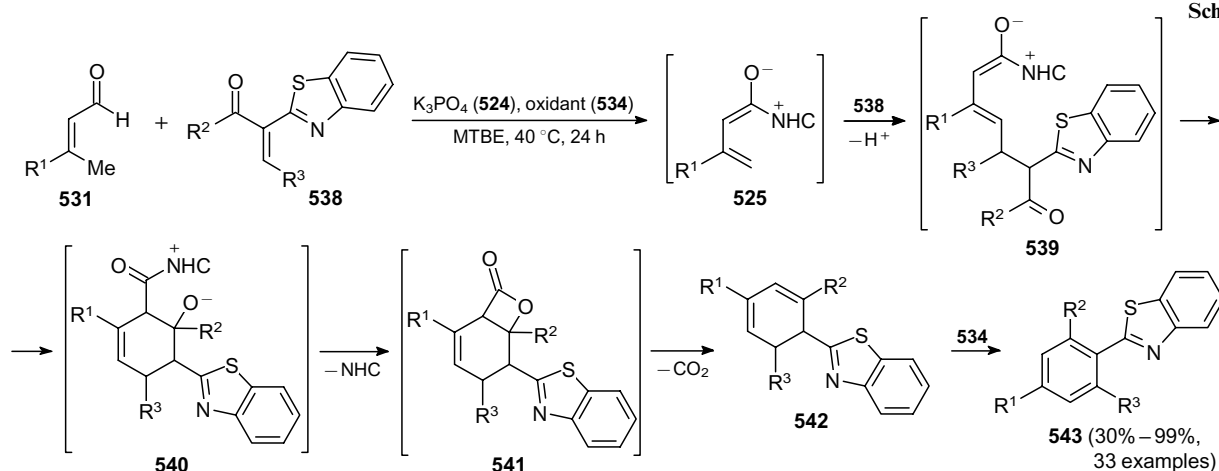
Scheme 89



R^1 = Ph, C_6H_4X-4 (X = Me, OMe, F, Cl, Br), C_6H_4MeO-3 , C_6H_4MeO-2 , $C_6H_3OCH_2O-3,4$, 1-Naph, 2-Naph, 2-Fu, 2-Th; R^2 = Me; R^3 = Bn, $CH_2C_6H_4X-4$ (X = Me, OMe, F, Cl, Br), $CH_2C_6H_4X-3$, $CH_2C_6H_4X-2$ (X = Me, NO_2), $CH_2(3-Naph)$, $CH_2(2-Th)$, $CHPh_2$;

R^2R^3C = 1,2,3,4-tetrahydro-5-naphthylidene; 1-indanylidene, (DEF ring-system of fredericamycin A)

Scheme 90



R^1 = Ph, C_6H_4X-4 , C_6H_4X-2 (X = Me, OMe, Br), C_6H_4X-3 (X = Me, OMe), $C_6H_3Me_2-2,6$, 2-Th, cyclo-Pr, 2-Naph; R^2 = Ph, C_6H_4X-4 (X = Br, F, Me); R^3 = Ph, C_6H_4X-4 (X = Me, F, Cl, Br, NO_2 , CN), C_6H_4X-3 (X = F, Cl), $C_6H_4Cl-3, X-4$ (X = F, Br), $C_6H_3F-2, Br-5$, 3-Th, 3-Py, Me, CH_2Bn ; MTBE = MeOBu^t

transition metal-catalyzed C–H activation reactions and are thus useful intermediates for late-stage functionalization.

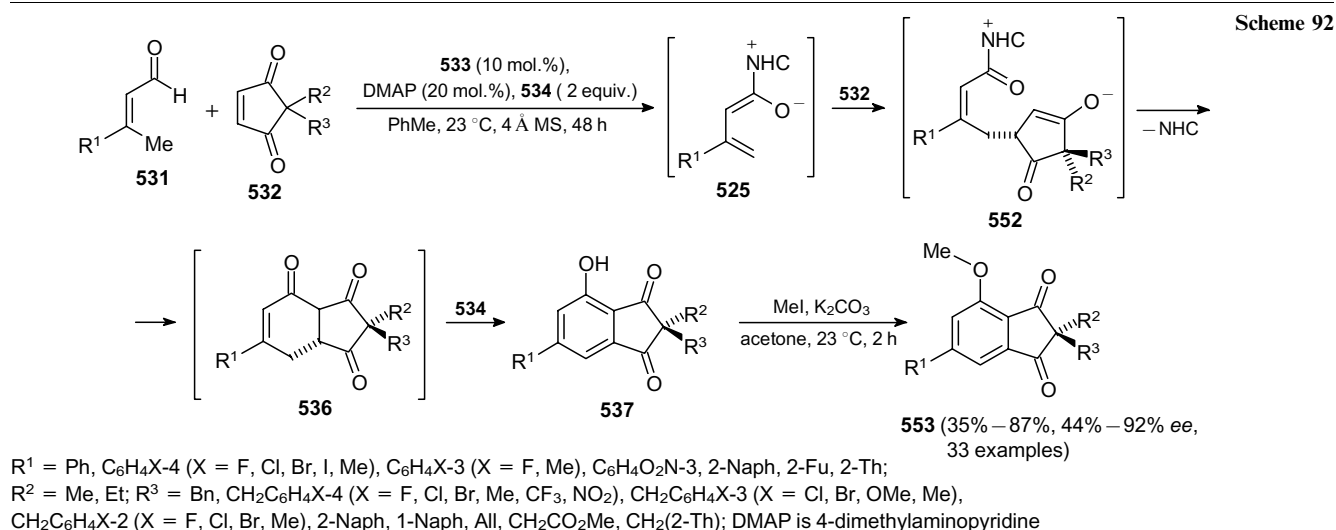
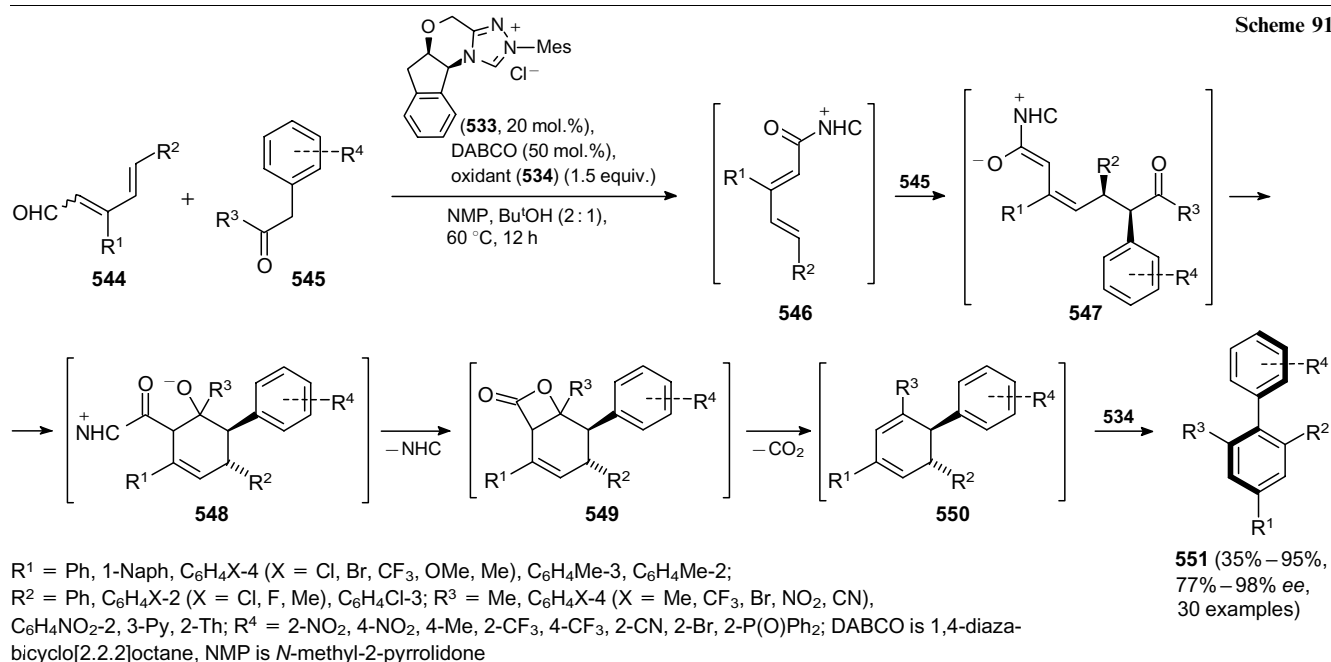
Additionally, Zhu and co-workers^{128,129} applied the same stereodefined NHC based catalyst for the synthesis of biaryls **551** with good levels of atropisomeric control (98% *ee*) (Scheme 91). The reaction proceeded *via* a similar mechanistic pathway as postulated by Chi and co-workers^{125–127} and also tolerated various functional groups in the *ortho* and *para* positions. The resultant biaryls **551** were isolated in good to excellent yields and enantioselectivities.

In 2019, Wang and co-workers¹³⁰ extended the stereoselective NHC catalysed indanone syntheses by employing a stereodefined catalyst to bring about the coupling of various cyclopentene-1,3-diones **532** with α,β -unsaturated enals **531** (Scheme 92). The mechanism, as postulated above, involved a Michael–aldol–aromatization cascade to elaborate the aromatic indanone framework followed by protection of the phenol as the methyl ether. The reaction was shown to tolerate various substituents on the starting

cyclopentenones **532** as well as different aromatic substituents on the enal **531**.

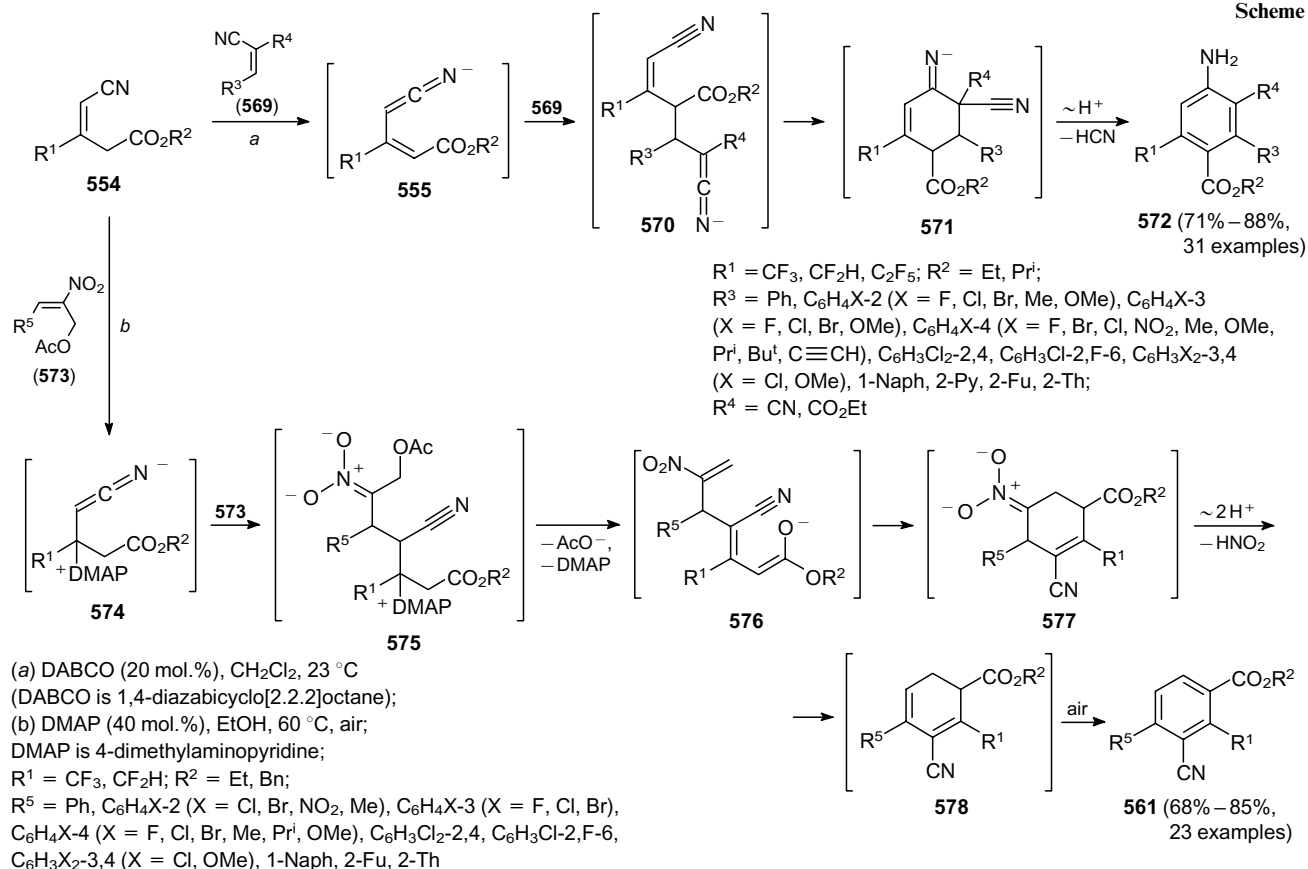
Recently, Han and co-workers¹³¹ published a prolinol catalyzed coupling of acrylonitriles **554** with enals **520** to prepare tetrasubstituted arenes **561** (Scheme 93). Michael-addition of the resonance stabilized anion **555** with the iminium ions **556** gave adducts **557**. Proton transfer and Mannich-type addition gave the cyclohexene derivative **559**, which upon elimination of the catalyst gave cyclohexadiene **560**, which easily underwent oxidation under aerobic conditions to give arene **561**. The authors applied the method to synthesize various trisubstituted R_F containing arenes in an efficient manner.

In addition, Han and co-workers¹³¹ showed that prolinol **30** catalyzed the reaction of β -trifluoromethyl-enones **562** and enals **520** and gave tetrasubstituted benzaldehydes **568** (Scheme 94). A similar reaction pathway as described above gave intermediate **565**, which underwent a prolinol catalyzed aldol reaction to give the cyclohexene core **566**.

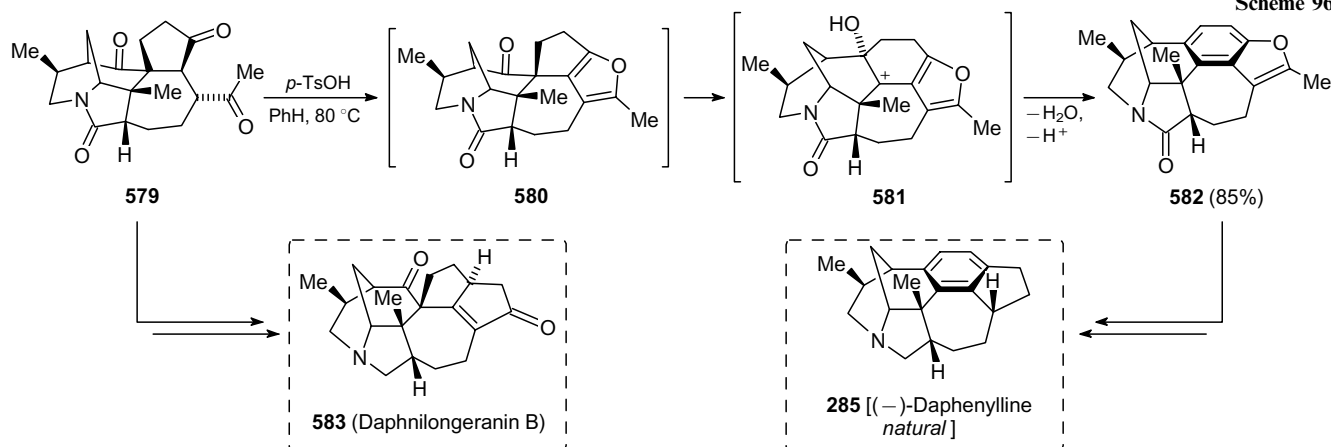


In 2018, Wan and co-workers¹³⁴ reported a method to synthesize *m*- and *p*-substituted benzaldehyde derivatives **589** and **591** from enamines **585** and **590** and enals **584** (Scheme 97). An initial vinyllogous Michael addition of

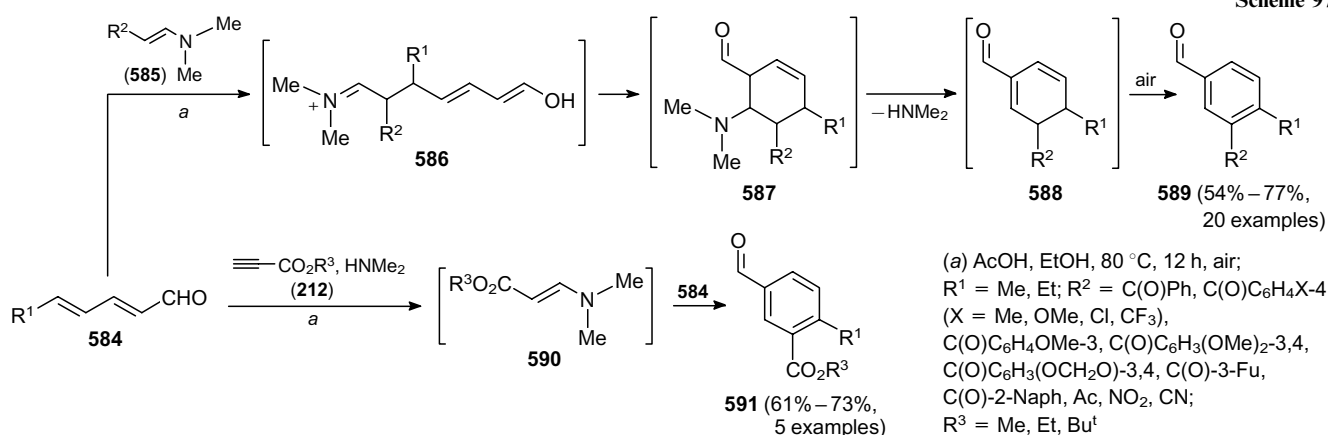
Scheme 95



Scheme 96



Scheme 97



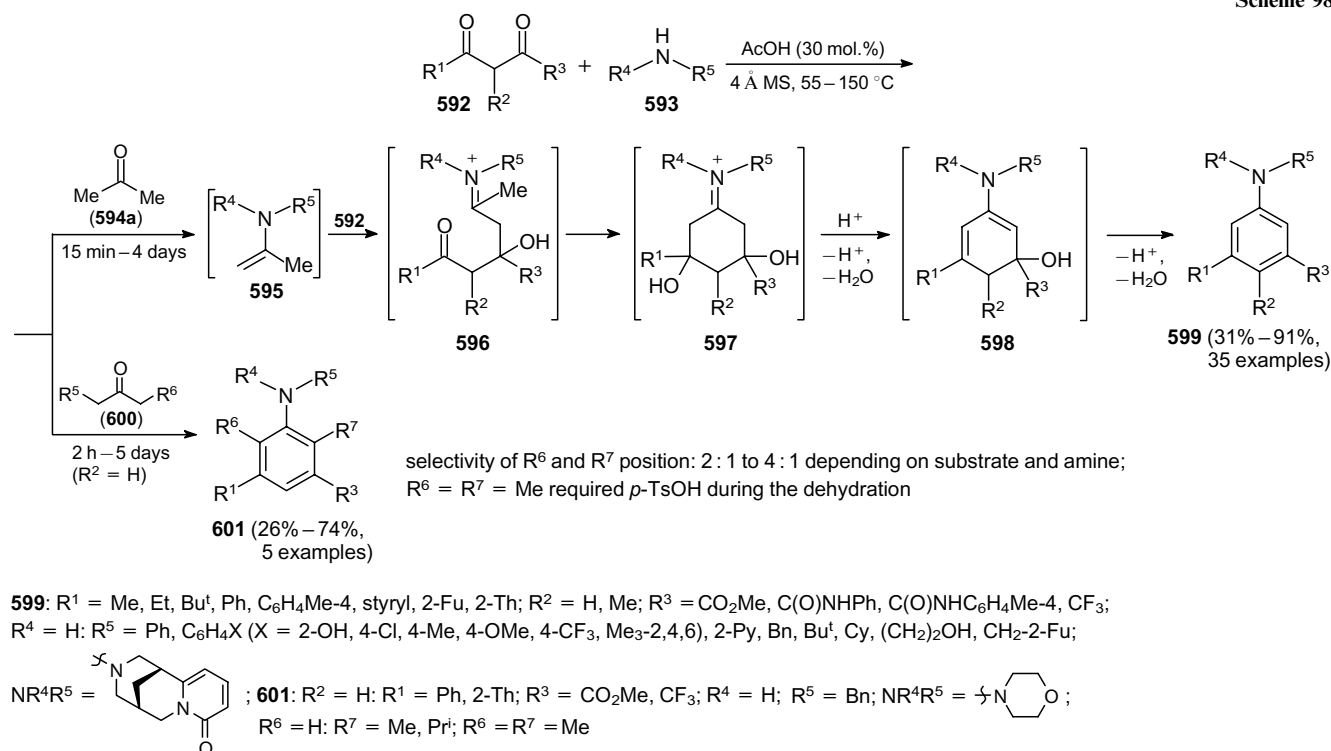
enamine **585** to the protonated enal **584** gave enol **586**, which underwent cyclization to the cyclohexene **587**. Elimination and aerobic oxidation gave the *m*- and *p*-substituted arenes in good yields. In addition, it was shown that the enamines **590** could be formed *in situ* from acetylenes **210** and dimethylamine, which gave the benzoate esters **591** in good yields following a similar reaction pathway.

In 2019, Rubin and co-workers¹³⁵ published a synthesis of aniline derivatives **599** via a three-component coupling of 1,3-diketones **592**, amines **593** and acetone (**594a**) (Scheme 98). The authors suggested that the reaction proceeded by enamine formation and subsequent addition to the 1,3-diketones **592** to give the intermediate **596**. Cyclization gave the cyclohexane **597**, which underwent dehydration to give anilines **599**. A large range of substituents were tolerated under the reaction conditions. Furthermore, penta-substituted anilines **601** could be synthesized with this methodology, albeit requiring longer reaction times

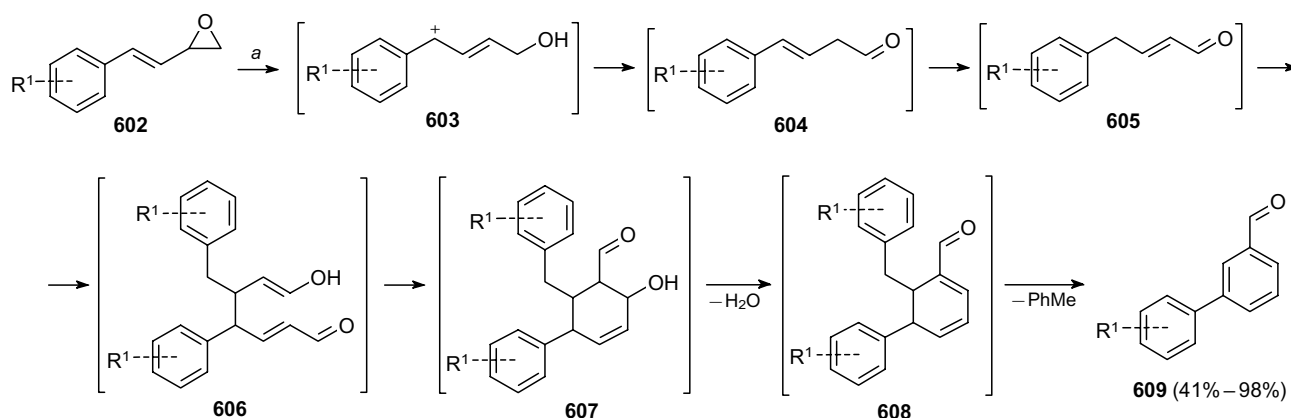
and further addition of the dehydrating agent 4-toluenesulfonic acid.

In 2020, Xu and co-workers¹³⁶ reported the dimerization of various styryl-epoxides **602** to prepare biaryls **609** under microwave accelerated acid-base conditions (Scheme 99). The authors postulated that an initial Meinwald rearrangement took place to give aldehydes **605** or their corresponding enolates. These intermediates underwent dimerization followed by cyclization with an aldol reaction to hydroxyaldehydes **607**. Dehydration gave diene **608**, which underwent aromatization presumably by loss of toluene possibly in a concerted process. Biaryl benzaldehyde derivatives **609** were obtained in moderate to excellent yields and the reaction tolerated various functional groups on the aryl core. Noteworthy, substituents on the alkene in the *cis*-position were not tolerated and the reaction stopped after formation of the Meinwald rearranged product **605**.

Scheme 98



Scheme 99



(a) NEt₃, *p*-TsOH · H₂O, mesitylene, MW, 200 °C, 1 h; R¹ = H, 2-X (X = Cl, F, OMe), 3-X (X = Cl, CF₃), 4-X (X = Cl, F, CF₃, Me), 2,3-(Cl)₂

5.4. Base-catalyzed reactions

Recently, Ye and co-workers¹³⁷ reported a DBU mediated synthesis of tri-substituted arenes **346** from readily available α,β -unsaturated carboxylic acids **610** and α -cyano-enones **611** (Scheme 100). This method was applied for the synthesis of thirty two biaryls **346** in moderate to good yields. Mechanistically, the authors suggested that DBU had a dual role both as base as well as nucleophilic catalyst through a CDI activated acyl transfer of the α,β -unsaturated carboxylic acids to DBU **613**. In their control-experiment without DBU, the reaction only formed traces of the product **346** even from the carboxylic acid CDI adducts. The acylated DBU intermediate **613** was found to react with the cyano-enone **611** (or its derived enolate) to produce the cyclohexenes **614**, which upon β -lactone **615** formation, decarboxylation **616** and cyanide elimination underwent aromatization to produce the product arenes **346**.

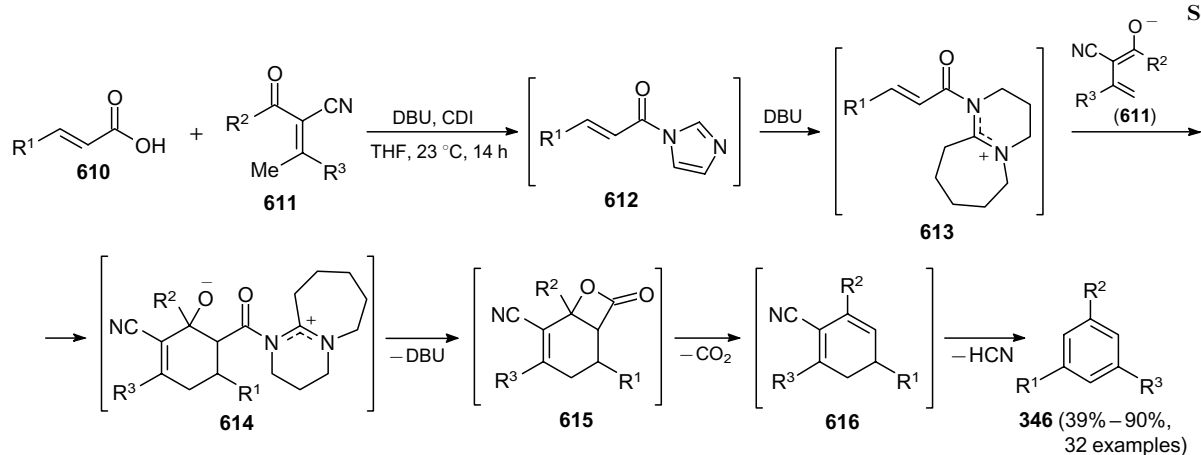
Thorimbert and co-workers¹³⁸ showed that reaction of methyl coumalate **79** with trifluoromethyl-1,3-diketones **617** gave the corresponding trifluoromethylated arenes **622** (Scheme 101). Various aliphatic and aromatic substituents on the starting diketone were tolerated. Mechanistically, the authors suggested that the reaction proceeded by Michael-addition of the enolate derived from **617** followed by ring opening to the linear dienolate **619**. Subsequent ring closure and loss of carbon dioxide and hydroxide in a Grob-type

fragmentation gave the arene **622** in good yields. With this study the authors developed a potentially sustainable transformation of a renewable precursor into trifluoromethyl-functionalized arenes in a simple manner.

In 2018, Shi and co-workers¹³⁹ published a base promoted synthesis of heavily substituted benzonitriles **629** from diketo compounds **392** and α -cyanoenones **623** (Scheme 102). This method was applied for the preparation of biaryl compounds including hexa-substituted arenes **629** in moderate yields. Mechanistically, the synthesis involved a Michael addition of the enolate derived from cyano enones **623** with enones **392**, followed by a tautomerization and aldol ring closure. Subsequent (*C* to *O*) acyl transfer and E1cB elimination of benzoic acid gave cyclohexadienes **628**. Aerobic oxidation produced arenes **629** in fair to good yields.

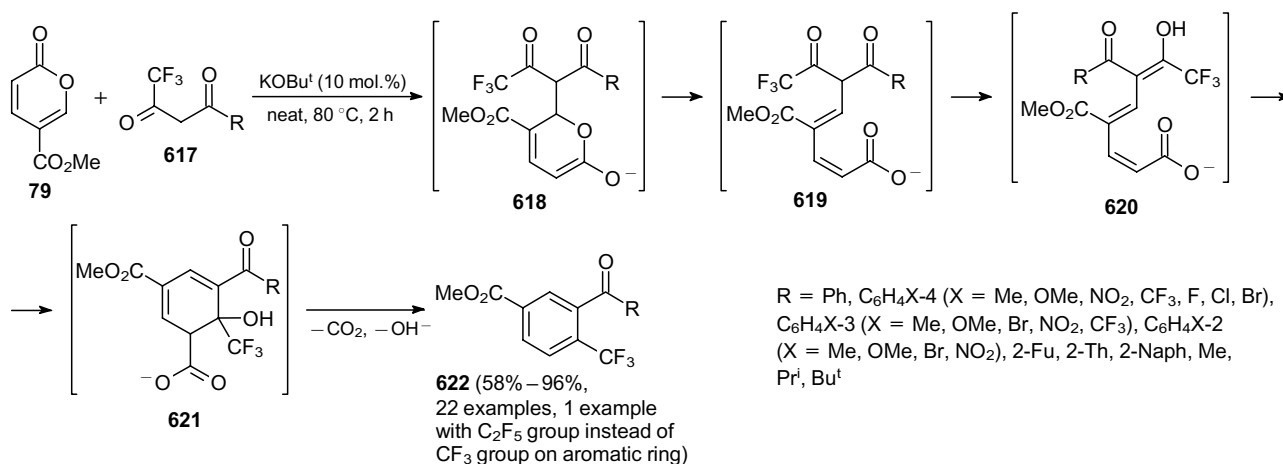
Recently, Qiu and co-workers¹⁴⁰ reported the total synthesis of (–)-daphenylline (**285**) including a key Robinson annulation and aromatization sequence to build up the ABCE ring system (Scheme 103). Diketone **630**, prepared from the corresponding ketone using the Stork-Ganem reagent $\text{MeCOC(=CH}_2\text{)SiMe}_3$, was converted into the aromatic compound **633** in good yield through a base mediated aldol-condensation, dehydration and oxidative aromatization in air.

Scheme 100



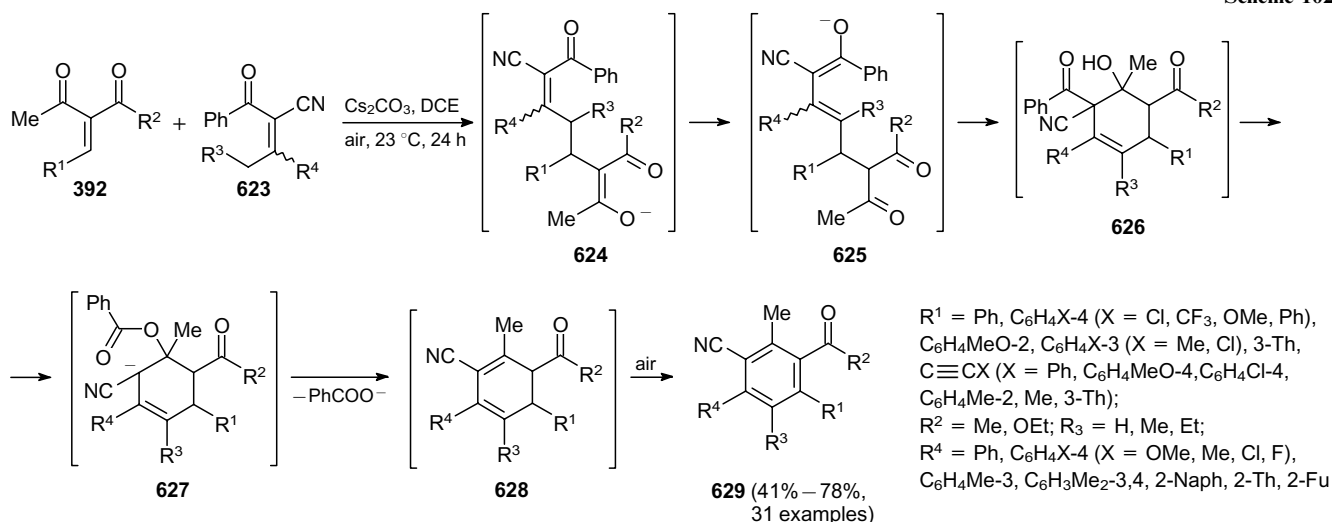
$R^1 = \text{Ph, C}_6\text{H}_4\text{X-4 (X = OMe, Me, Cl, Br, Ac), C}_6\text{H}_4\text{X-3, C}_6\text{H}_4\text{X-2 (X = Me, Br), C}_6\text{H}_3\text{Cl}_2\text{-2,6, C}_6\text{H}_3\text{Cl}_2\text{-3,4, 2-Fu, 3-Py, CO}_2\text{Et}$;
 $R^2 = \text{Ph, C}_6\text{H}_4\text{X-4 (X = OMe, F), 2-Th, Me}$; $R^3 = \text{Ph, C}_6\text{H}_4\text{X-4 (X = OMe, Me, Cl, Br, NO}_2\text{), C}_6\text{H}_4\text{X-3, C}_6\text{H}_4\text{X-2 (X = Me, Cl), 2-Th, 2-Naph, Pr}^n\text{, Bu}^t$; CDI is 1,1'-carbonyldiimidazole

Scheme 101

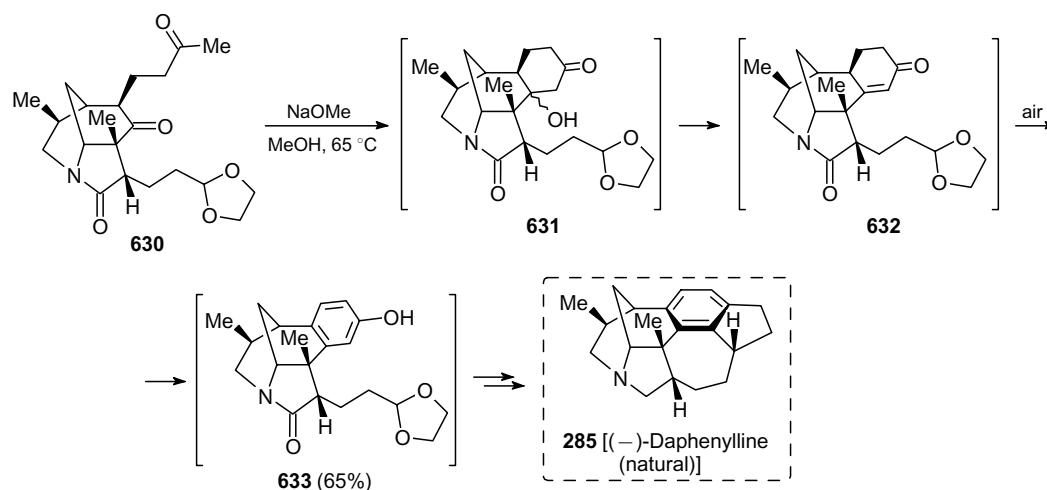


$R = \text{Ph, C}_6\text{H}_4\text{X-4 (X = Me, OMe, NO}_2\text{, CF}_3\text{, F, Cl, Br), C}_6\text{H}_4\text{X-3 (X = Me, OMe, Br, NO}_2\text{, CF}_3\text{), C}_6\text{H}_4\text{X-2 (X = Me, OMe, Br, NO}_2\text{), 2-Fu, 2-Th, 2-Naph, Me, Pr}^n\text{, Bu}^t$

Scheme 102



Scheme 103

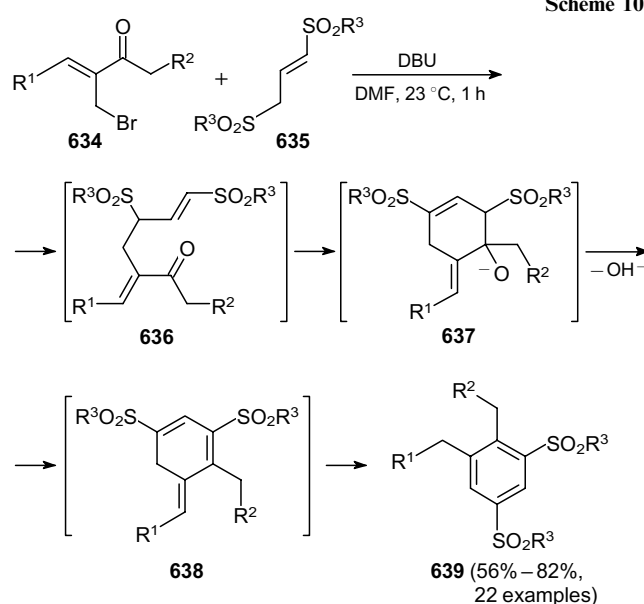


Yadav *et al.*¹⁴¹ reported a formal [3 + 3] benzannulation between bromo-enones **634** and α,β -unsaturated sulfones **635** (Scheme 104). Both of these precursors were readily synthesized from commercially available starting materials through simple functional group interconversions. Subsequent DBU-mediated coupling readily gave tetrasubstituted arenes **639** under mild reaction conditions.

The group of Tummatorn¹⁴² reported the sequential transformation of alkynyl-aryl ketones **640** to provide indenones **641**, which were subsequently aromatized to provide 3-hydroxyfluorenes **644** (Scheme 105). This procedure was also used to synthesize 4-azafluorenes by employing ammonium acetate in methanol in the cyclization process (*via* the corresponding enamine of **641**) and aromatization step.

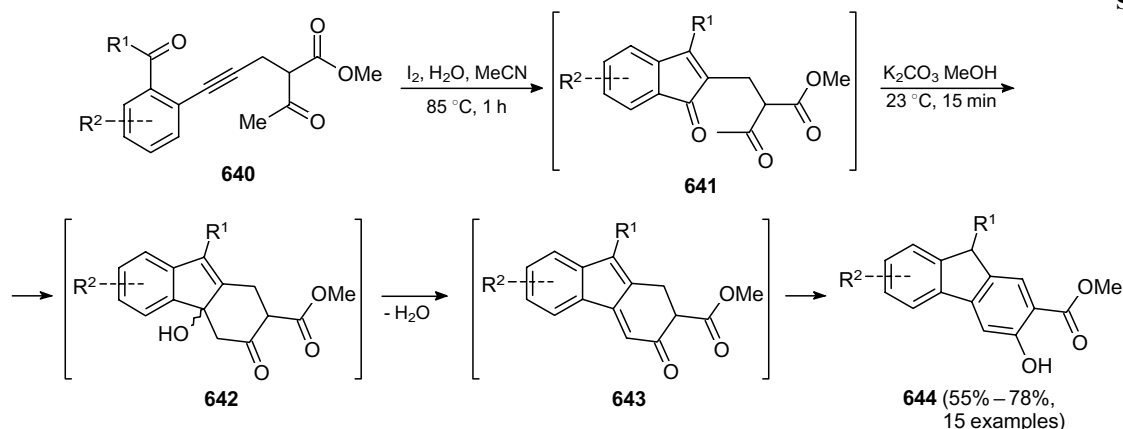
Baidya and co-workers¹⁴³ reported the base-mediated coupling of alkylidene malonitriles **645** with cyclopentene-1,3-diones **532** to produce penta- and hexasubstituted 4-amino-1*H*-indene-1,3(2*H*)-diones **648** (Scheme 106). The authors suggested that this reaction proceeded *via* a vinyl-ogous Michael-addition and subsequent cyclization by addition to the nitrile group, followed by oxidative aromatization. The reaction showed a broad functional group tolerance for aliphatic, aromatic and bulky steroid substituents.

Scheme 104



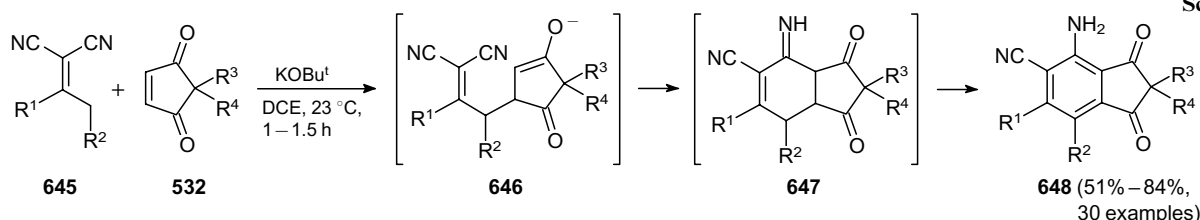
$\text{R}^1 = \text{Ph}, \text{C}_6\text{H}_4\text{X}-4$ (X = Cl, CF_3 , NO_2 , SMe, Prⁱ, OMe), $\text{C}_6\text{H}_4\text{NO}_2-2$, $\text{C}_6\text{H}_4\text{Br}-3$, $\text{C}_6\text{H}_3\text{Br}-2,\text{Cl}-5$, $\text{C}_6\text{H}_3\text{Cl}-5,\text{NO}_2-2$, 2-Th, 2-Fu, Prⁿ, Buⁱ; $\text{R}^2 = \text{Ph}, \text{C}_6\text{H}_4\text{Me}-4$; $\text{R}^3 = \text{H}, \text{Me}$

Scheme 105

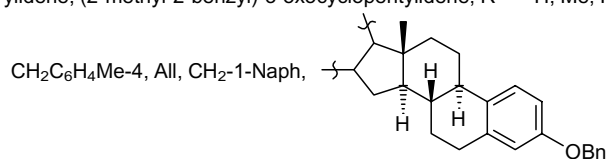


$R^1 = \text{Ph}$, $\text{C}_6\text{H}_4\text{X}-4$ ($\text{X} = \text{Me}$, Cl , F , OMe), $\text{C}_6\text{H}_4\text{X}-3$ ($\text{X} = \text{F}$, OMe), $\text{C}_6\text{H}_2(\text{MeO})_3-2,4,5$, $\text{N}(\text{Ns})-3\text{-indolyl}$; $R^2 = 6\text{-F}$, 7-F , 8-F , 6-Cl , 7-BrO , $\text{Me}-7$

Scheme 106



$R^1 = \text{Ph}$, $\text{C}_6\text{H}_4\text{X}-4$ ($\text{X} = \text{Me}$, OMe , Cl , Br , OAll , $\text{CH}_2\text{C}\equiv\text{CH}$, styryl), $\text{C}_6\text{H}_4\text{Cl}-3$, 2-Naph, 2-Th, 1-Ad, Fc; Fc is ferrocenyl; cyclic $R^1\text{CCHR}^2 = 4\text{-chromanidene}$, 4-thiochromanidene, 1,2,3,4-tetrahydro-1-naphthalidene, 1-indenylidene, O-benzyl-17-deoxyestron-17-ylidene, (2-methyl-2-benzyl)-3-oxocyclopentylidene; $R^2 = \text{H}$, Me ; $R^3 = \text{Me}$; $R^4 = \text{Bn}$, $\text{CH}_2\text{C}_6\text{H}_4\text{X}-2$ ($\text{X} = \text{Me}$, Br , NO_2), $\text{CH}_2\text{C}_6\text{H}_4\text{Me}-3$,



Sosnovskikh and co-workers¹⁴⁴ showed that enamino-diones **649** were dimerized by condensation using lithium hydride and tetraethoxysilane to produce trisubstituted phenolic diketones **653** (Scheme 107). The authors postulated that these reactions proceeded *via* a double-Michael addition to intermediates **651** with subsequent, highly selective retro-Claisen reaction to yield benzophenones after aromatization. This method enabled the authors to rapidly synthesize different phenols **653** from simple precursors in three steps.

Prat and co-workers¹⁴⁵ reported the synthesis of tetrahydroquinolines **659** from 2-pyrone derivatives **654** or **661** as C(4) building blocks and Boc-protected 3-piperidone **655** as a C(2) building block (Scheme 108). This method, following trifluoroacetic acid Boc-deprotection, gave tetrahydroquinolines **660** from easily accessible precursors in good yields. The authors proposed that Michael addition of the enolate derived from **655** with 2-pyrone **654**, followed by ring opening and ring closure to cyclohexadienes **658** and a Grob-type fragmentation with concomitant aromatization gave arenes **659**. Trifluoroacetic acid mediated Boc deprotection completed the synthesis of tetrahydroquinolines **660**.

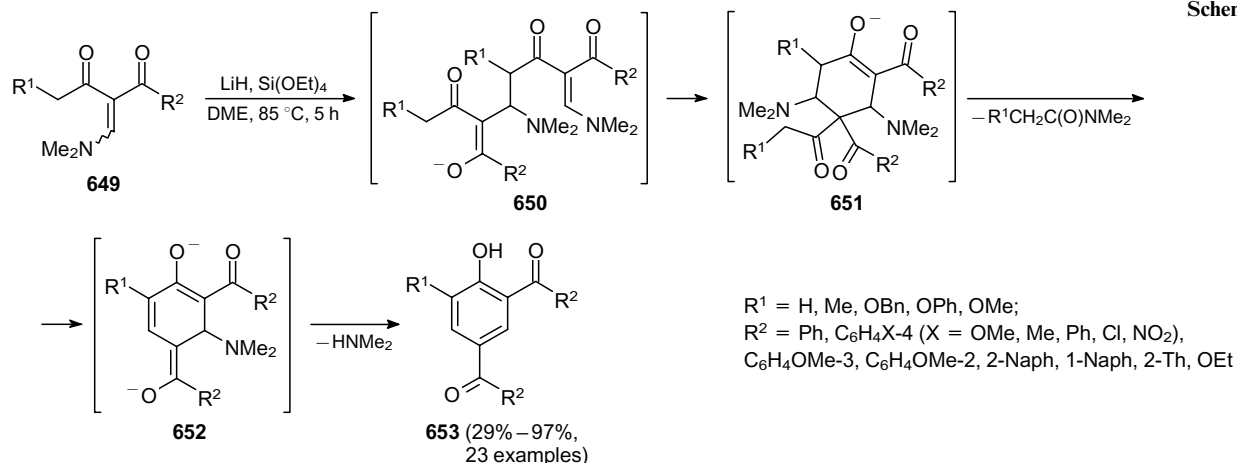
In 2019, Kano and co-workers¹⁴⁶ reported the synthesis of benzophenones **666** *via* base mediated annulation of imino-dienes **662** as C5 building blocks and substituted acetophenones **594** (Scheme 109). The authors proposed reaction mechanism involved Mannich-type additions of the enolates derived from ketones **594** with imines **662**

followed by piperidine elimination to give the trienones **664**. Cyclization of these gave cyclohexadiene **665**. These intermediates underwent aromatization by elimination of a second equivalent of piperidine to give benzophenones **666** in fair to excellent yields. The reaction was extended to 4,4'-diacetyl-biphenyl, 1,3,5-triacetylbenzene and 4,4',4''-triacetyl-triphenylamine derivatives of **594**.

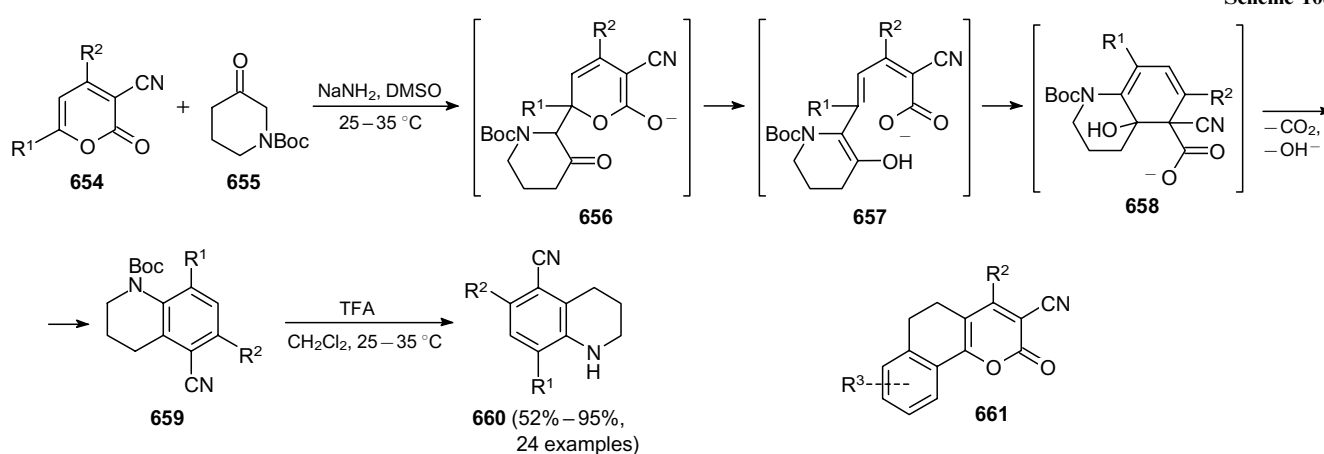
In 2019, Wang and Kraus¹⁴⁷ reported the total synthesis of ($\pm$)-dihydro eurtiumide **B** (**675**), which employed a cascade sequence to build up the arene and lactone ring (Scheme 110). These authors showed that this reaction also worked with other epoxides as well as methyl sorbate, which lacked the epoxide functionality. They proposed that butanolide **667** underwent alkylation *via* the corresponding enolate with subsequent selective Michael addition onto the α,β -unsaturated ester **668**. A subsequent aldol reaction gave the tetrahedral intermediate **670**, which underwent fragmentation to the diketone **671** by thiophenolate elimination. Aromatization by tautomerization gave intermediate **672**. Opening of the styryl epoxide by participation of the electron rich arene gave enolates **673**, which readily underwent aromatization by the diastereoselective addition of thiophenolate. Substitution of the thio ether by sodium methoxide gave dihydro-eurtiumide **B** (**675**) in 41% yield.

Yu and Kraus,¹⁴⁸ in further studies on pyrone Diels–Alder chemistry, reported that electron-poor dienophiles including dihydroxy-*p*-quinones **676** do not undergo Diels–Alder reactions to provide arenes. However, addition of a

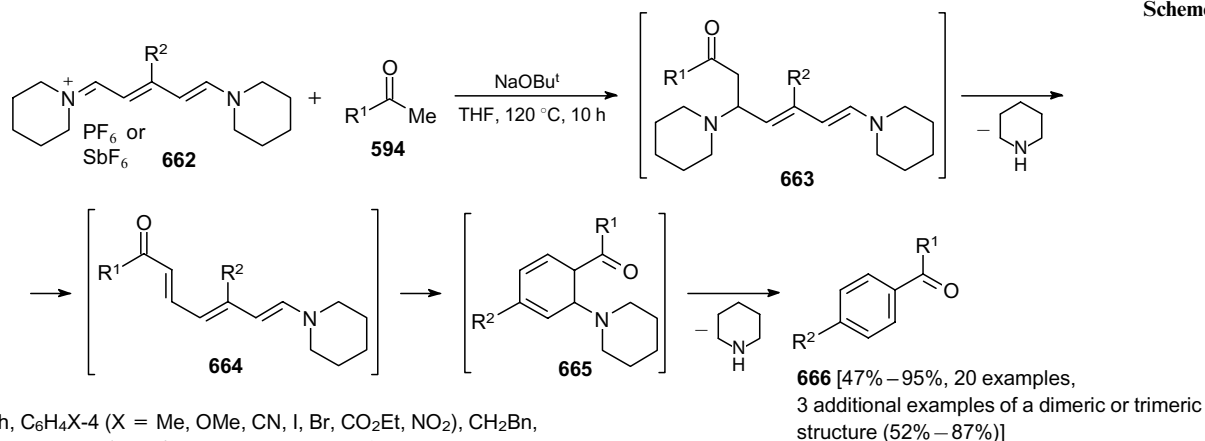
Scheme 107



Scheme 108



Scheme 109

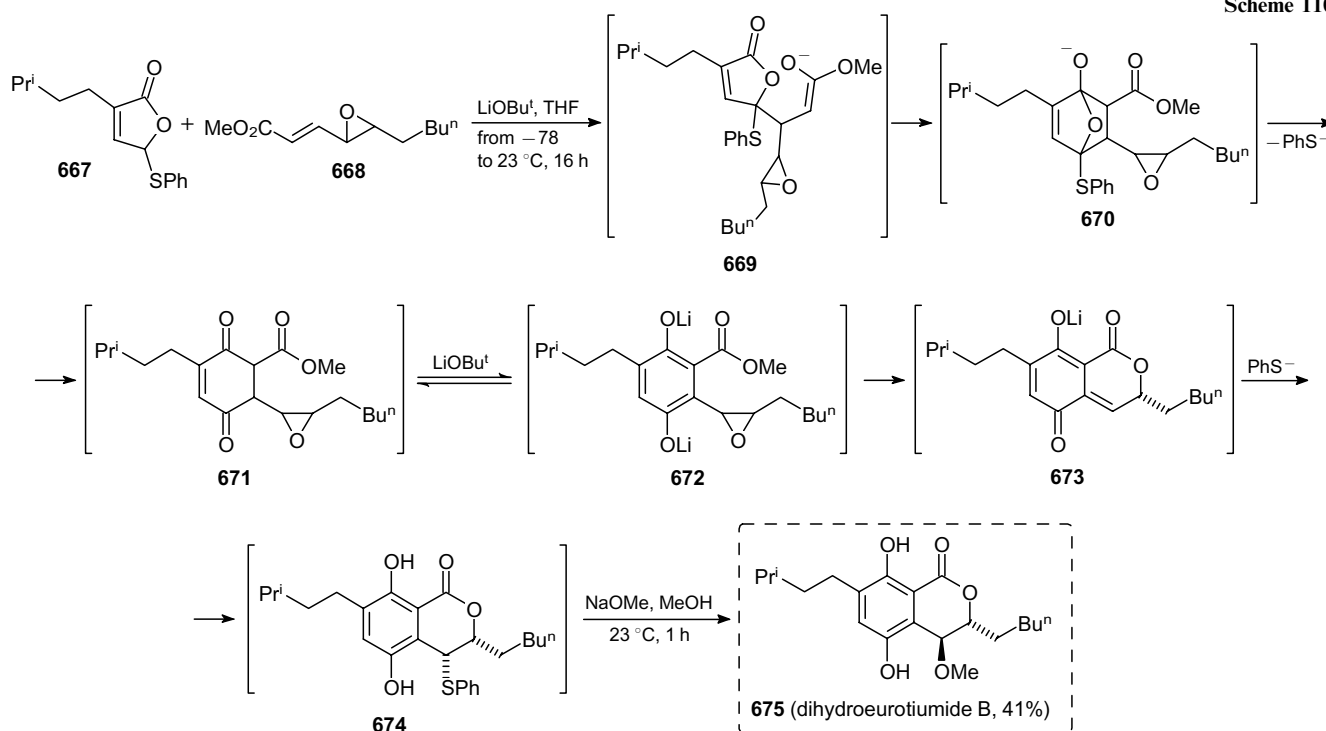


base such as triethylamine mediated the formal Diels–Alder reaction of 2-pyrones **131** with hydroxyquinones **676** and **681** (Scheme 111). The authors suggested that these reactions involved base mediated enolate formation of the hydroxyquinones and subsequent Michael addition to give adducts **677** thereby allowing the aldol reaction to give intermediate **678**. Subsequent decarboxylation and loss of water gave the arenes **680** in fair to excellent yields. In the

case of dihydroxybenzoquinone **676** ($\text{R}^3 = \text{H}$), a double addition was observed giving rise to anthraquinones **683**. Of particular note, acetylene substituents in the R^2 position underwent oxidation to the corresponding ketones during the progress of this reaction, presumably after the elimination of water.

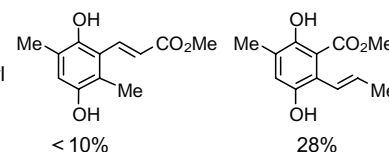
In 2020, Xu and co-workers¹⁴⁹ reported the synthesis of hydronaphthofurans **685** via rhodium catalyzed coupling of

Scheme 110



other epoxide used: $\text{MeO}_2\text{C}-\text{CH}=\text{CH}-\text{O}-\text{Me} \Rightarrow 71\%$ of thioether
 $\Rightarrow 43\%$ of methoxyether

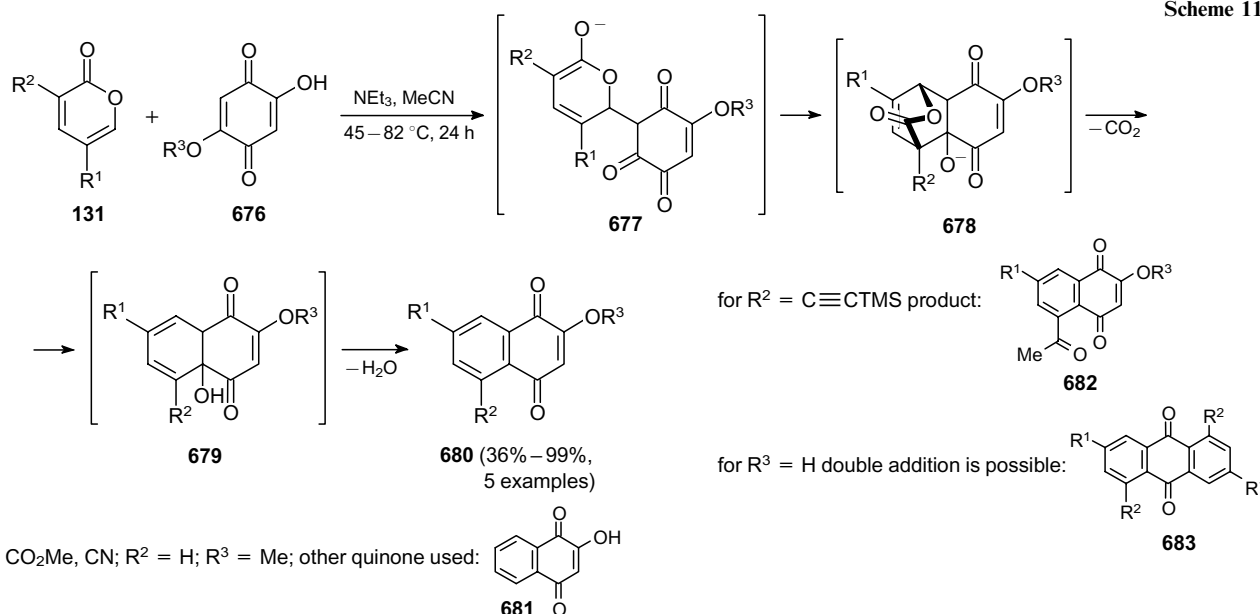
Products from reaction with methyl sorbate instead of epoxide:



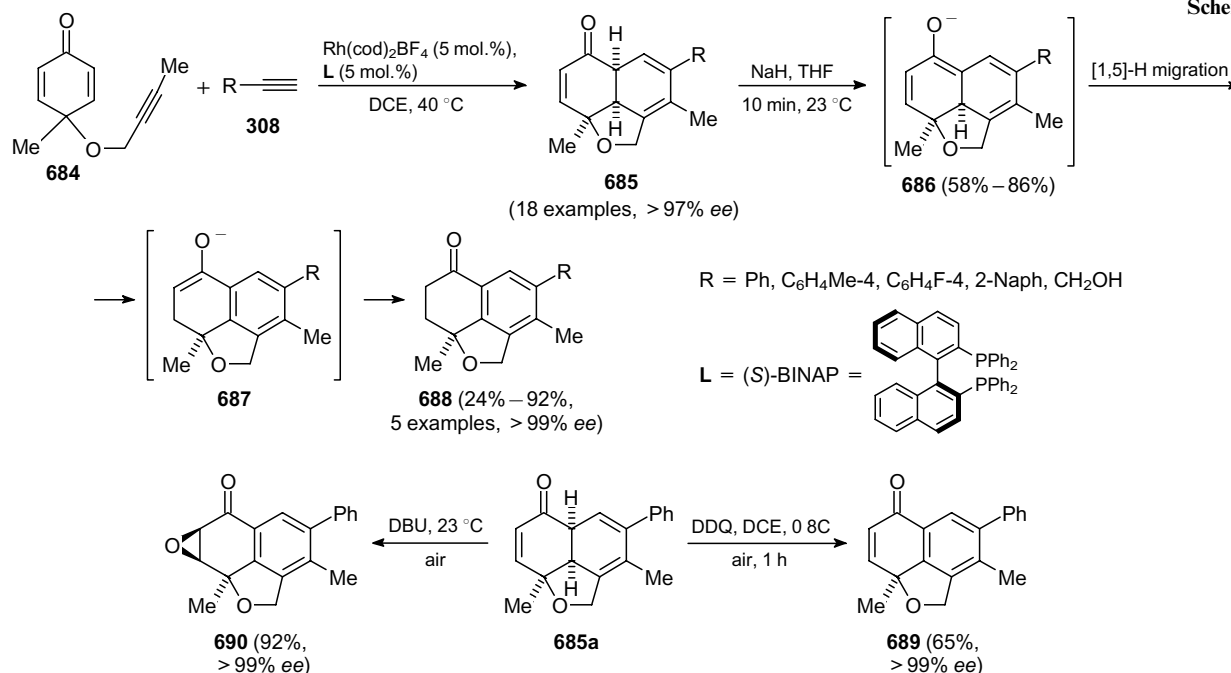
1,6-enynes **684** with acetylenes **308** (Scheme 112). When (*S*)-BINAP was used as a ligand in the [2+2+2] cycloaddition reaction, enones **685** were formed with excellent enantioselectivities ($>97\%$ *ee*). Upon addition of sodium hydride, the derived enolate **686** underwent an oxy-accelerated [1,5]-hydride shift with concomitant aromatization to give arenes **688** in good yields with no reduction in enantiomeric excesses ($>99\%$ *ee*). In one case, the authors showed the reaction could be carried out as a one-pot process in

good yield (62%) and enantioselectivity (99% *ee*). Other standard aromatization procedures, such as with DDQ, gave enone **689**. Furthermore, aerobic oxidation in the presence of DBU gave arene epoxide **690** in excellent yield and enantioselectivity. In this case, oxidation of diene **685a** with oxygen gave rise to hydrogen peroxide, which subsequently underwent reaction with the enone moiety *via* a stereospecific Scheffer–Weitz epoxidation to give epoxide **690**.

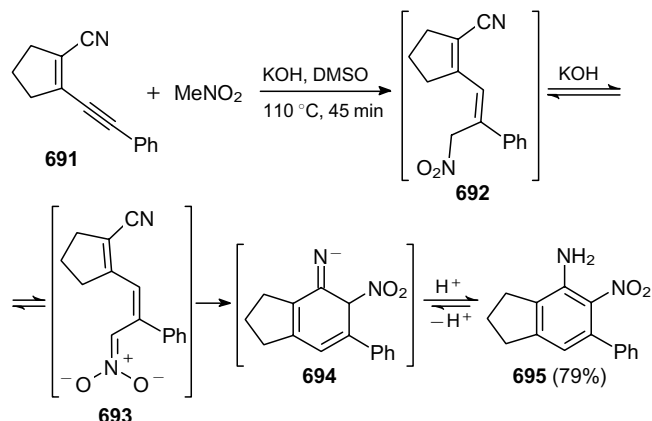
Scheme 111



Scheme 112



Scheme 113



went aromatization to give the nitro-indane **695**. We consider the mechanism involves these intermediates through nitronate addition to the acetylene and protonation by water to **692**, followed by deprotonation to form nitronate **693** and cyclization to **694** and not *via* a vinyl carbanion as suggested by the authors. In addition, the authors reported 37 additional examples for the synthesis of naphthalene derivatives, which is outside of the scope of this review.

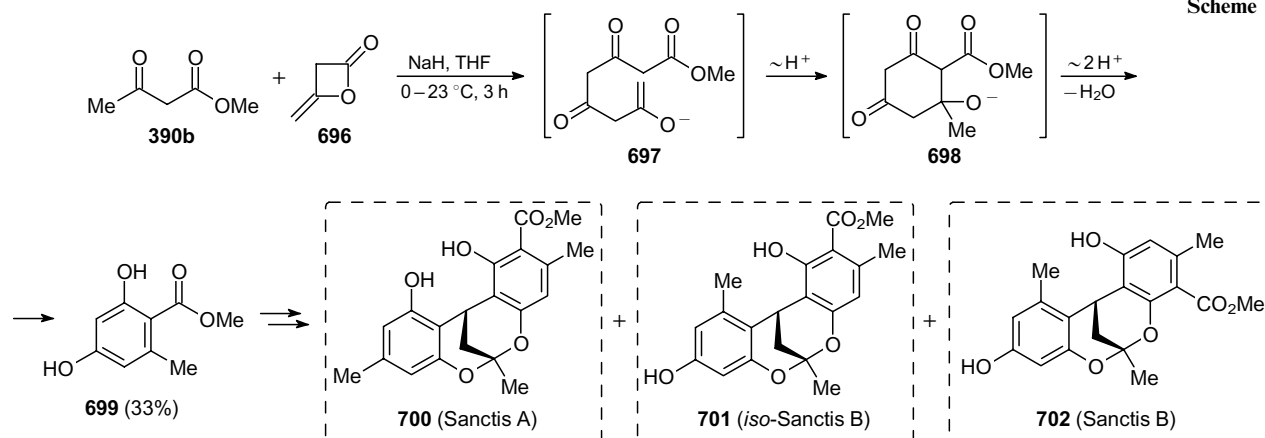
Recently, Tan and co-workers¹⁵¹ reported a biomimetic total synthesis of the natural products sanctis A (**700**), iso-sanctis B (**701**) and sanctis B (**702**) using a classical orsellinate synthesis (Scheme 114).¹⁵² 1,3-Keto-ester **390b** was allowed to react under basic conditions with diketene **696** to provide the triketo-ester **697**, which readily underwent cyclization and aromatization to give resorcyate **699**. This intermediate was converted into the three natural products **700–702**.

Verma and co-workers¹⁵⁰ reported the synthesis of indane **695** *via* an aza-Henry reaction between nitrile **691** and nitromethane (Scheme 113). Reaction of the nitronate from nitromethane with nitrile **691** and tautomerization and cyclization gave cyclohexadiene imine **694**, which under-

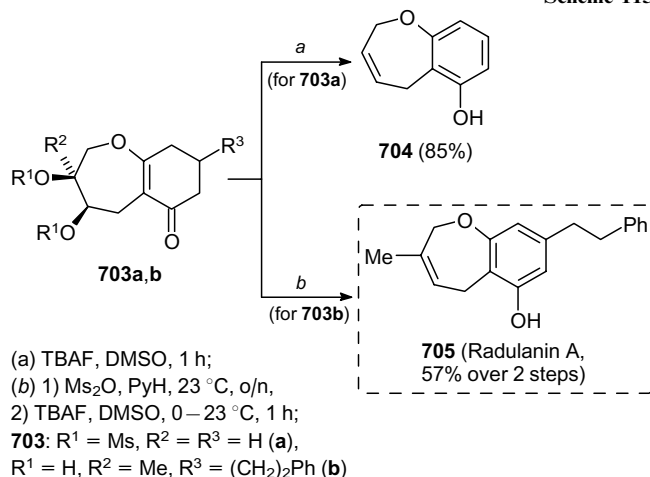
5.5. Other oxidation reactions

Zhang *et al.*¹⁵³ reported a one-pot procedure for the syntheses of 5,7,8,9-tetrahydrobenzo[*b*]oxepin-6(2*H*)-one, which on dihydroxylation using osmium tetroxide and NMO in aqueous acetone and double methanesulfonylation

Scheme 114

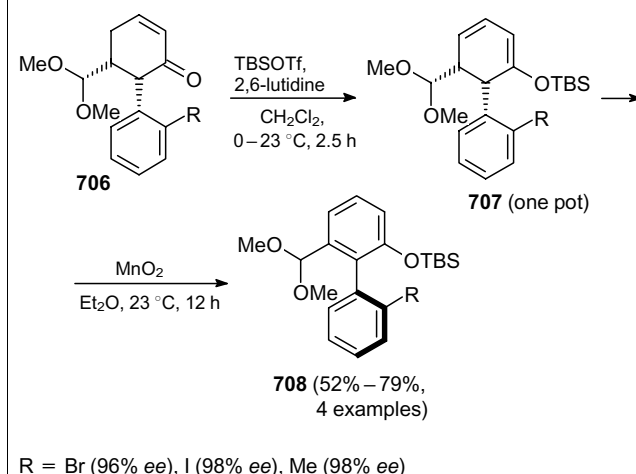


Scheme 115



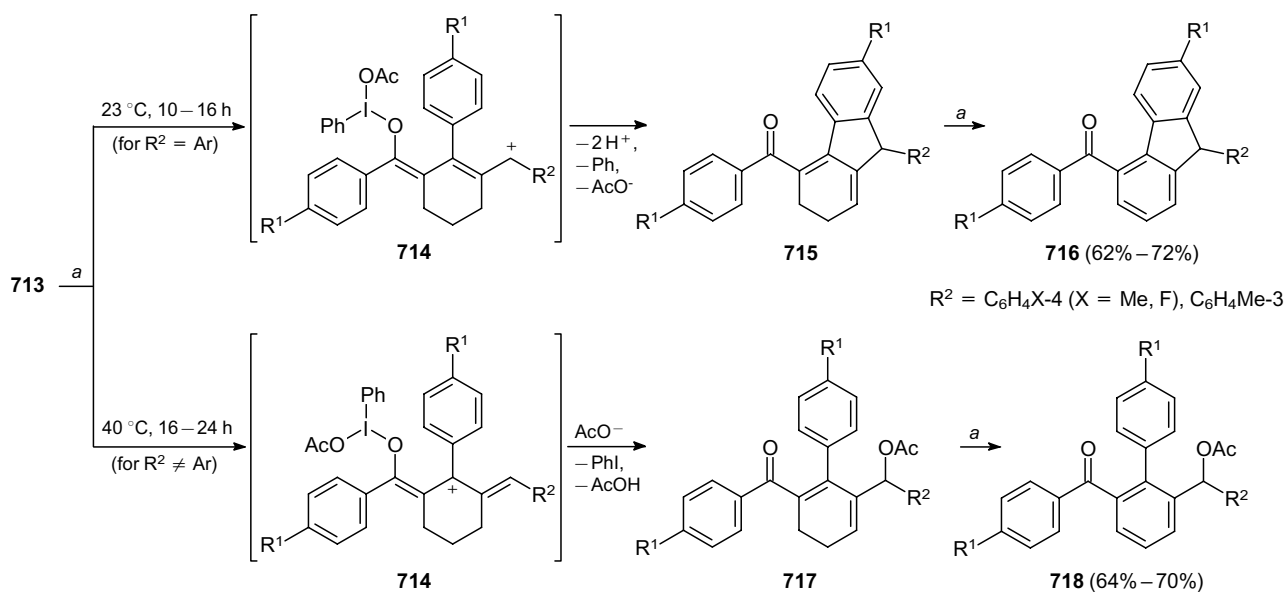
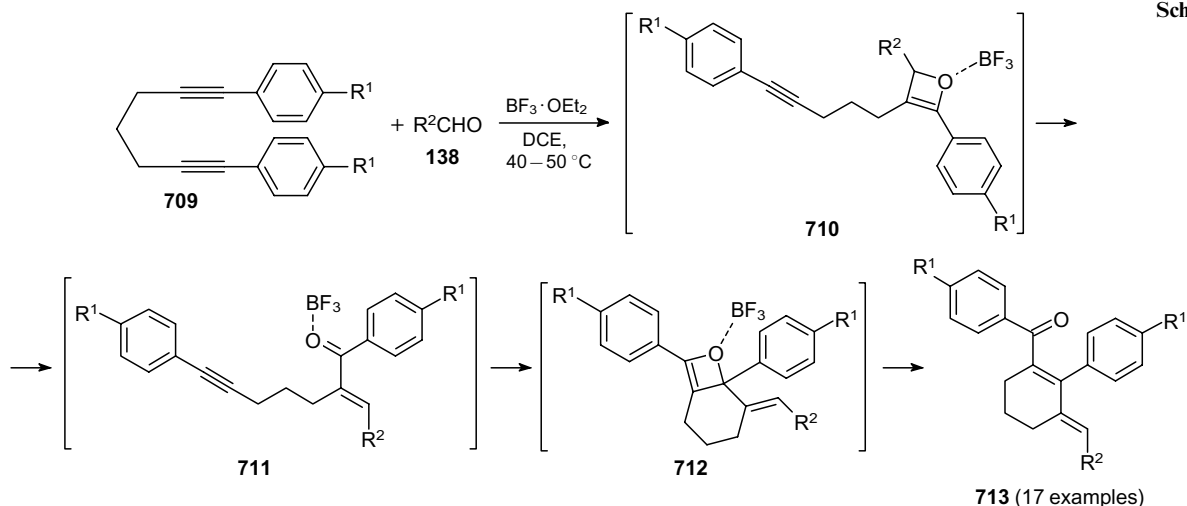
using methanesulfonyl chloride in pyridine was converted into the dimesylate **703a**. Subsequent aromatization was carried out by reaction with tetra-*n*-butylammonium fluo-

Scheme 116



ride (TBAF) to produce the 2,5-dihydrobenzoxepine **704** (Scheme 115). Additionally starting from compound **703b**,

Scheme 117



(a) $\text{In}(\text{OTf})_3$, $\text{PhI}(\text{OAc})_2$; $\text{R}^1 = \text{OMe}, \text{OEt}, \text{OBn}$; $\text{R}^2 = \text{Cy}, \text{cyclo-C}_5\text{H}_9, \text{Bu}^i$

this reaction was successfully applied for the synthesis of radulanin A (**705**), a phenol with phytotoxic activity.

Ishida and co-workers¹⁵⁴ have recently reported the synthesis of atropisomerically enriched biaryls **708** via manganese dioxide mediated aromatization of cyclohexanones **707**, which were readily prepared through an organocatalytic enantioselective (99% *ee*) Michael–Henry reaction (Scheme 116). A one-pot silyl-enol ether **707** formation followed by manganese dioxide oxidation gave the three biaryls **708** in high atroposelectivities (96–98% *ee*) as well as the 1-naphthyl-analogue (56%, 95% *ee*).

Lastly, Yanada and co-workers¹⁵⁵ reported the synthesis of benzophenones **716** and **718** from 1,6-diynes **709** and aliphatic and aromatic aldehydes **138** under Lewis acidic conditions (Scheme 117). The authors suggested that the mechanism of reaction involved a carbonyl–acetylene metathesis and was applied to 17 different benzophenones **713**. Subsequently, in a one-pot procedure, these compounds were converted into indanes **716** and benzyl acetates **718** the ratio of which depended on the R² substituent. When R² was aromatic, upon addition of the oxidant iodobenzene diacetate and indium(III) trifluoromethanesulfonate, the stabilized allylic, benzylic carbenium ion **714** underwent Friedel–Crafts alkylation to give cyclohexadiene **715**. Further oxidation with iodobenzene diacetate gave indanes **716** in good yields. Alternatively, when R² was aliphatic, the same reaction promoted the formation of the allylic, benzylic carbenium ion **714**, which was trapped with acetate, and loss of a proton to produce cyclohexadiene **717**. Further addition of the oxidant iodobenzene diacetate gave benzyl acetate derivatives **718** in good yields.

6. Conclusion

Inspired in part by nature's methods for the biosynthesis of aromatic compounds, chemists have devised procedures for the synthesis of variously substituted benzenes, phenols, anilines, and other aromatic and heteroaromatic compounds from both cyclic and non-cyclic precursors. The underlying synthetic pathways are robust and well understood processes and depend on Diels–Alder, electrocyclic, pericyclic, cross-coupling, RCM, cyclo-isomerization, aldol or Michael addition reactions. The resulting aromatic compounds have diverse applications from medicinal chemistry to materials. Recent applications are in drug discovery and the total syntheses of meroterpenoids, polyketides and *Daphniphyllum* alkaloids with both early and late-stage incorporation of the aromatic units. Furthermore, the use of stereodefined catalysts to generate precursors for aromatization, has proven very valuable for the enantio- and diastereoselective synthesis of biaryl atropisomer systems, stereodefined ligands and compounds relevant to the elaboration of molecular machines. It is, therefore, reasonable to expect future developments in this important area of synthetic organic chemistry, given the extensive use of aromatic compounds in pharmaceuticals, agrochemicals, organic electronics and other materials.

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Recent Developments in Polyene Cyclizations and Their Applications in Natural Product Synthesis

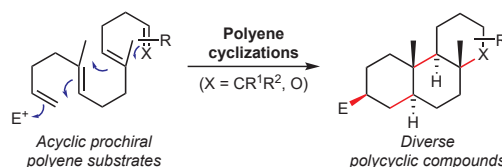
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Abstract Cascade polyene cyclization reactions are highly efficient and elegant bioinspired transformations that involve simultaneous multiple bond constructions to rapidly generate complex polycyclic molecules. This review summarizes the most prominent work on a variety of cationic and radical cascade cyclizations and their applications in natural product synthesis published between 2014 and 2018.

- 1 Introduction
- 2 Cationic Polyene Cyclizations
 - 2.1 Lewis Acid Mediated Polyene Cyclizations
 - 2.2 Brønsted Acid Mediated Polyene Cyclizations
 - 2.3 Halogen Electrophile Initiated Polyene Cyclizations
 - 2.4 Sulfur Electrophile Initiated Polyene Cyclizations
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- 3 Radical Polyene Cyclizations
 - 3.1 Transition-Metal-Mediated Radical Polyene Cyclizations
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- 4 Origin of Stereocontrol in Polyene Cyclizations
- 5 Conclusion

Key words polyene cyclization, cascade reaction, carbon–carbon bond formation, natural products, total synthesis

1 Introduction

Biomimetic strategies are powerful methods in natural product synthesis since they can provide concise methods for the elaboration of structurally complex molecules from significantly simpler precursors. Polyene cyclizations are recognized as unique and efficient ways to build structural complexity from acyclic molecules via concerted and stereocontrolled C–C bond formations. In 1955, Stork and Eschenmoser independently published a hypothesis rationalizing the stereoelectronic aspects that underpin the stereochemical outcomes of polyene cyclizations, which immediately encouraged further studies on these types of



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transformations.¹ In 1968 and 1975, pioneering research on the biomimetic syntheses of steroids was reported by Johnson² and van Tamelen,³ both of whom demonstrated the profound synthetic power of polyene cyclizations in natural product total synthesis.

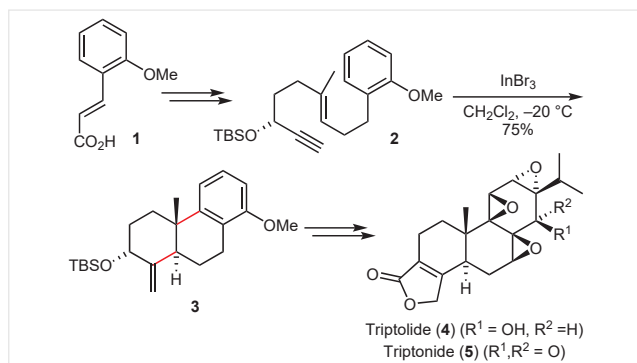
Inspired by these revolutionary investigations into the use of polyene cyclizations in organic synthesis, considerable advancements have been achieved in the past several decades to improve the efficiency of this biomimetic process, develop novel creative variants of the cyclization processes, as well as invent novel chiral reagents and catalysts to induce highly enantioselective and regioselective cyclizations, with comparable selectivity to the enzyme-controlled cyclizations in nature.⁴ Snyder, Gagné, Anderson, and Sarlah previously reviewed this topic from 2000 to 2016.⁴ The aim of this review is to provide an updated over-

view of cascade polyene cyclizations and their applications toward natural product synthesis from 2014 to 2018. These cyclization processes are first divided mechanistically into cationic and radical pathways and are further subcategorized according to the mode of activation.

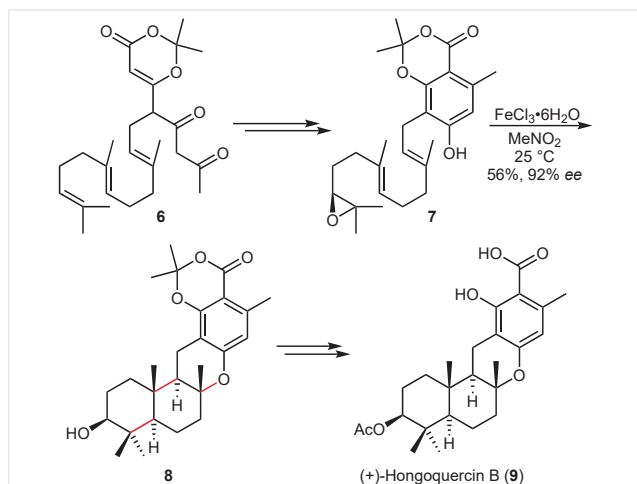
2 Cationic Polyene Cyclizations

2.1 Lewis Acid Mediated Polyene Cyclizations

In 2014, Li and co-workers reported the synthesis of antitumor and anti-inflammatory natural products triptolide (**4**), triptonide (**5**), and related analogues which utilized a series of metal-mediated reactions (Scheme 1).⁵ Functionalization of carboxylic acid **1** provided alkyne **2**. The subsequent key step involved an indium bromide mediated polyene cyclization, which was originally developed by Corey and co-workers,⁶ to furnish the *trans*-fused ring framework **3** (75%).



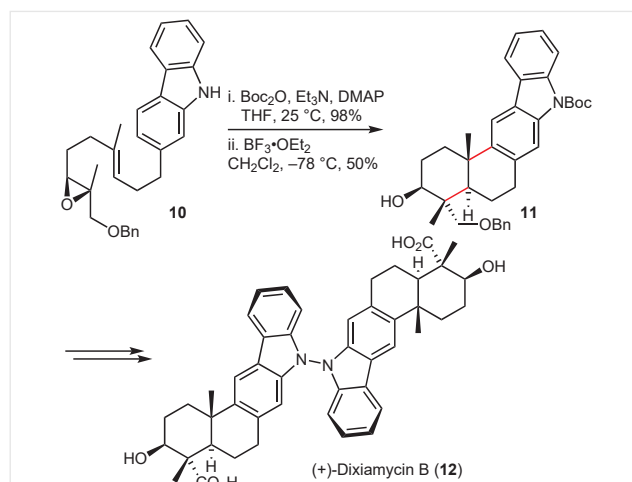
Scheme 1 Synthesis of triptolide and triptonide



Scheme 2 Synthesis of (+)-hongoquercin B

The Barrett group has applied a dual biomimetic approach to the synthesis of (+)-hongoquercin B (**9**) by successive polyketide and polyene cascade cyclizations (Scheme 2).⁷ Cyclo-aromatization of β,δ -diketo-dioxinone **6** and subsequent enantioselective epoxidation provided resorcyate **7**. Reaction of resorcyate **7** with iron(III) chloride hexahydrate catalyzed polyene cyclization to provide the meroterpenoid **8** (56%, 92% ee) as a single diastereomer and demonstrated that the single epoxide stereocenter controlled the resulting five stereocenters formed during this transformation.

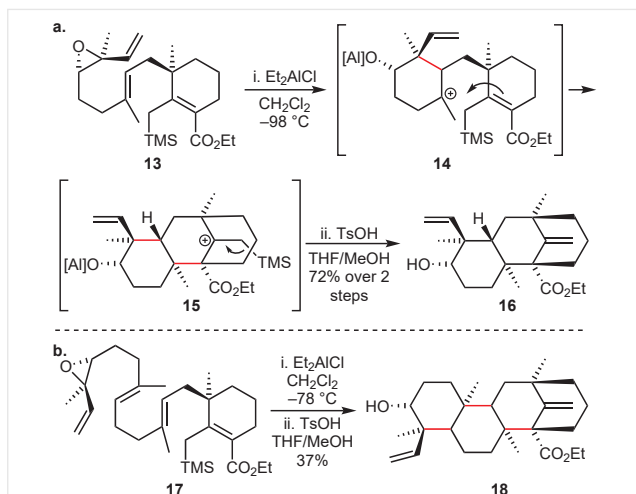
In the synthesis of atropisomeric indoloterpenoid natural product (+)-dixiamycin B (**12**), the Baran group utilized a boron trifluoride–diethyl ether complex mediated cyclization of epoxide **10** into alcohol **11** as the key step to furnish the pentacyclic core (Scheme 3).⁸ It was observed that the *N*-protection with Boc_2O was essential in order to suppress the formation of undesired isomers during polyene cyclization, thereby enhancing the yield of alcohol **11**.



Scheme 3 Synthesis of (+)-dixiamycin B

While polyene cyclization reactions are often used in the synthesis of fused polycyclic ring systems, their use in the construction of bridged polycyclic ring systems was only recently, in 2015, explored by Nakamura and co-workers (Scheme 4).⁹ Exposure of epoxyallylsilane **13** to diethylaluminum chloride resulted in polyene cyclization via carbocation intermediates **14** and **15** to produce bridged tricyclic compound **16** (72%) after hydrolysis. Tetracyclic product **18** (37%) was also obtained under the same conditions from epoxyallylsilane **17**.

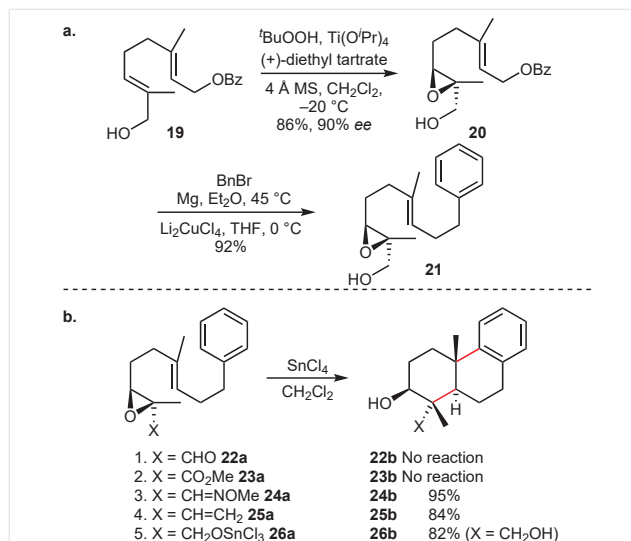
A systematic study of using functionalized unsaturated oxiranes in Lewis acid mediated polyene cyclization was published by Corey and co-workers, providing valuable insight into the electronic effects of neighboring substituents in epoxide initiated cationic π -cyclizations (Scheme 5).¹⁰



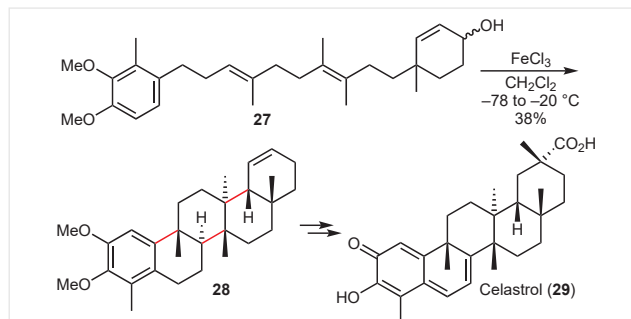
Scheme 4 Syntheses of bridged tri- and tetracyclic compounds

Enantiomerically enriched epoxy alcohol **21** was efficiently prepared from alcohol **19** via enantioselective Katsuki–Sharpless epoxidation to give epoxide **20** (86%, 90% ee). Further derivatization of epoxy alcohol **21** gave functionalized oxiranes **22a–26a**. It was found that aldehyde **22a** (Scheme 5b, entry 1) and ester **23a** (Scheme 5b, entry 2) were unreactive when exposed to tin(IV) chloride. It is postulated that chelation of tin(IV) chloride by the epoxide and carbonyl groups did not facilitate cyclization, but prevent it from occurring as the carbonyl group becomes electron deficient, inhibiting the heterolysis of the oxirane $\alpha\text{--C--O}$ bond. In contrast, reaction of methoxime **24a** (Scheme 5b, entry 3) with tin(IV) chloride resulted in polyene cyclization to give tricyclic product **24b** (95%), which could be explained by the electron-donating nature of the methoxy group, favoring the heterolytic fission of the oxirane $\alpha\text{--C--O}$ bond. Vinyl-oxirane **25a** (Scheme 5b, entry 4) was also smoothly cyclized to provide the tricyclic product **25b** (84%) on reaction with tin(IV) chloride. This result demonstrates that substitution on the epoxide may facilitate the Lewis acid activation of the epoxide moiety; the resulting polyene cyclization is assisted by the π -electron-donating nature of its substituent. Furthermore, it was found that conversion of epoxide alcohol **21** into alkoxytrichlorostannane complex **26a** (Scheme 5b, entry 5) also facilitated epoxide activation by covalently attaching a Lewis acid to the substrate, thereby leading to tricyclic diol **26b** (82%) on destannylation work-up.

Celastroid natural products have a range of promising biological activities and are being studied in clinical trials. Seigel and co-workers reported the first total synthesis of celastrol (**29**) which utilized polyene cyclization as the key step to elaborate the pentacyclic core (Scheme 6).¹¹ Iron(III) chloride catalyzed polyene cyclization of allylic alcohol **27** produced pentacyclic alkene **28** (38%) on a gram scale. The use of tin(IV) chloride for this cyclization was less efficient,



Scheme 5 Synthesis of an epoxy alcohol and derivatization into different substrates for polyene cyclization reactions

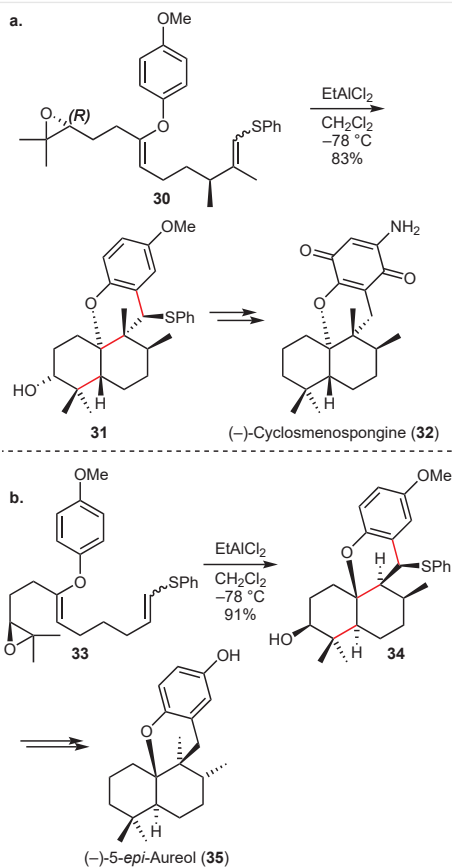
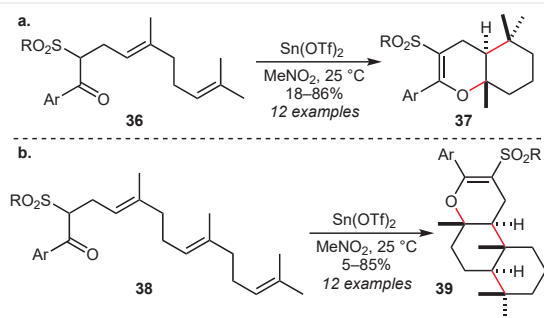


Scheme 6 Synthesis of celastrol

producing alkene **28** only in 15% yield. Further manipulation of alkene **28** was used to complete the total synthesis of celastrol (**29**) in 31 steps overall.

The marine natural product (–)-cyclosmenospongine (**32**) is a tetracyclic meroterpenoid which was synthesized by Magauer and co-workers using polyene cyclizations (Scheme 7).¹² The approach featured an unprecedented stepwise non-biomimetic polyene cyclization of an aryl enol ether **30** catalyzed by ethylaluminum dichloride as the Lewis acid. This led to the closure of three rings with excellent control of four stereocenters on a gram scale to yield alcohol **31** (83%) as a single diastereomer. Excellent stereoselectivity was observed due to the transition state governed by the double-bond geometry of the enol ether, thioenol ether, and epoxide. Utilizing the same strategy, (–)-5-*epi*-aureol (**35**) was also synthesized via alcohol **34** (91%), which was prepared from aryl enol ether **33**.¹⁰

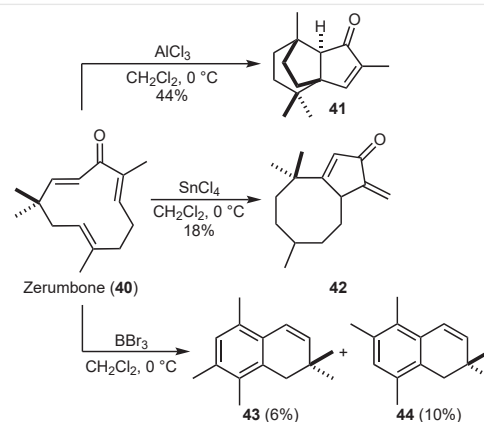
Chang and co-workers reported that tin(II) triflate catalyzed the polyene cyclization of β -keto sulfones (Scheme 8).¹³ It was found that this Lewis acid could catalyze the cy-

Scheme 7 Synthesis of (–)-cyclosmenospongine and (–)-5-*epi*-aureolScheme 8 Bi- and tricyclization reactions of β -keto sulfones

clization of β -keto sulfones **36** and **38**, which were derived from geranyl bromide and farnesyl bromide, to give bi- and tricyclic sulfonyl dihydropyrans **37** and **39**, respectively, as ambrox analogues via six-membered chairlike conformations.

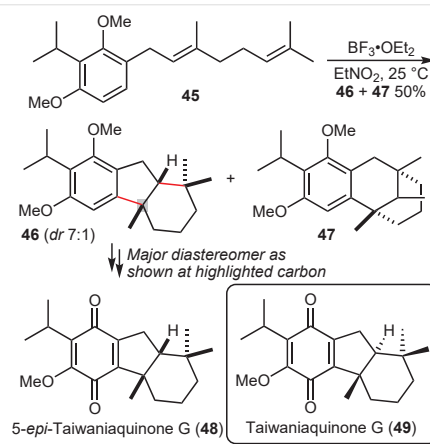
Electrophilic polyene cyclization of zerumbone (**40**), an isoprenoid, via carbonyl activation was reported by Appendino and co-workers (Scheme 9).¹⁴ Carbonyl activation of zerumbone (**40**) with electrophilic reagents resulted in a Nazarov-type polyene cyclization, leading to the formation

of a variety of cyclized products after intramolecular rearrangement. Zerumbone (**40**) is very stable towards mineral acids, but undergoes intramolecular cyclizations upon treatment with a variety of Lewis acids. Reaction of zerumbone (**40**) with aluminum trichloride resulted in the formation of the racemic tricyclic enone **41** (44%), featuring a 5/5/7 ring system as a single product along with recovered starting material. On the other hand, bicyclic dienone **42** (18%) was formed via tin(IV) chloride mediated cyclization. Furthermore, upon treatment of zerumbone (**40**) with boron tribromide, a mixture of isomeric hydrocarbons **43** (6%) and **44** (10%) were formed following a series of rearrangements reactions.



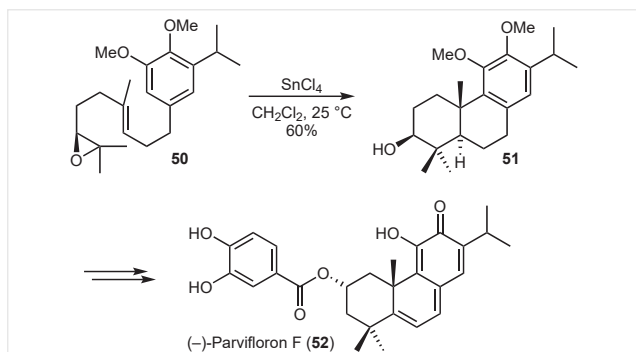
Scheme 9 Polyene cyclizations of zerumbone

McErlean and co-workers reported the first total synthesis of 5-*epi*-taiwaniaquinone G (**48**) via Lewis acid catalyzed polyene cyclization (Scheme 10).¹⁵ Taiwaniaquinone G (**49**) is a diterpene containing a 6/5/6 *trans*-fused ring system. It was envisioned that Lewis acid mediated polyene cyclization of geranylbenzene **45** would lead to the formation of the desired *trans*-fused 5/6 ring system. Surprising-

Scheme 10 Synthesis of (±)-5-*epi*-taiwaniaquinone G

ly, boron trifluoride–diethyl ether complex induced cationic cyclization led to the formation of a mixture of tricyclic products **46** and **47** in 50% combined yield, in which the *cis*-fused 5/6 ring system of tricyclic intermediate **46** was the major diastereomer (dr 7:1). The observed diastereoselectivity was further investigated by a computational study incorporating a conductor-like polarizable continuum model, which led to the conclusion that the observed selectivity was due to steric interactions that destabilized the transition state leading to the *trans*-configured diastereomer.

(–)-Parvifloron F (**52**) was found to be a valuable abietane diterpene that exhibits multiple biological activities such as antibacterial and antiproliferative activity against several human tumor cell lines.¹⁶ Nakagawa-Goto and co-workers achieved the first total synthesis of (–)-parvifloron F (**52**), which utilized tin(IV) chloride mediated polyene cyclization of epoxide **50** to give alcohol **51** (60%), furnishing the tricyclic core of the natural product (Scheme 11).

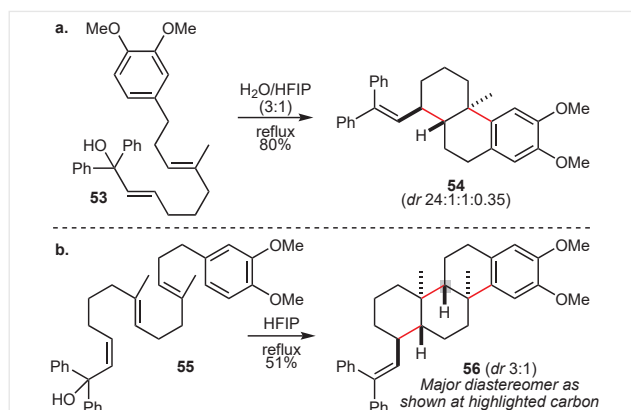


Scheme 11 Synthesis of (–)-parvifloron F

2.2 Brønsted Acid Mediated Polyene Cyclizations

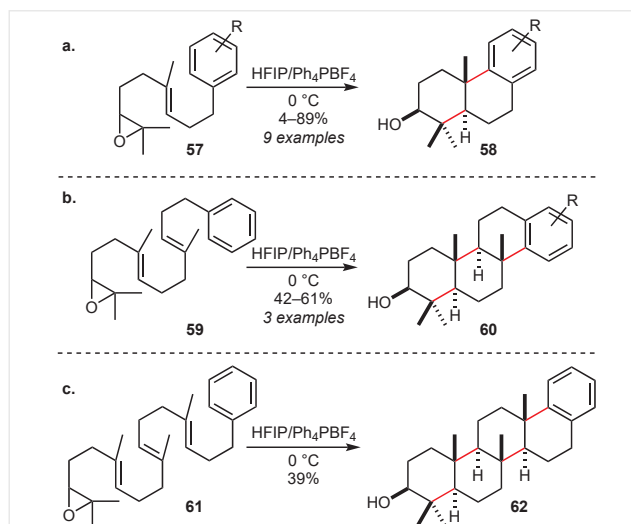
Polyfunctionalized benzhydryl alcohols were found to be able to undergo S_N1 -type ionization thereby triggering polyene cyclization promoted by hot water and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a mildly acidic catalyst (Scheme 12).¹⁷ Stable carbocations, generated from such electron-rich benzylic alcohols by water, react with carbon, sulfur, and nitrogen nucleophiles in aqueous conditions. Qu and co-workers discovered that allylic alcohol **53** underwent polyene cyclization in a 3:1 mixture of refluxing water and HFIP to form octahydrophenanthrene product **54** (80%, dr 24:1:1:0.35) with excellent diastereoselectivity. Equivalent tricyclization of allylic alcohol **55** gave tetracycle **56** (51%, dr 3:1) in higher yield and with better diastereoselectivity when the reaction was performed in neat HFIP.

Further studies by the Qu group discovered that HFIP could act as a Brønsted acid ($pK_a = 9.3$) catalyst to promote epoxide initiated cationic π -cyclizations (Scheme 13).¹⁸ The addition of tetraphenylphosphonium tetrafluoroborate enhanced the rate of reaction presumably due to trace amounts of hydrogen fluoride generated by tetrafluorobo-



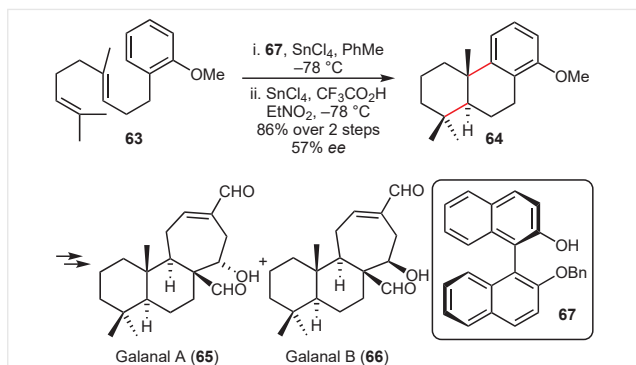
Scheme 12 Di- and tricyclizations promoted by HFIP/hot water

rate anion solvolysis in HFIP. Therefore, the reaction medium acted as both Brønsted acid and solvent to promote epoxides **57**, **59**, and **61** to undergo di-, tri-, and tetracyclizations rapidly to yield polycyclic compounds **58**, **60**, and **62**, respectively.



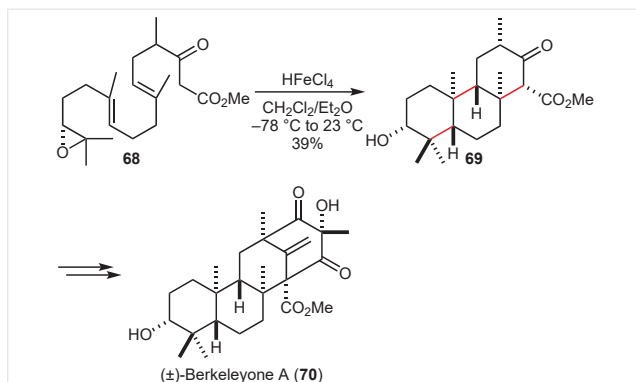
Scheme 13 HFIP/ Ph_4PBF_4 -promoted polyene cyclizations

Following the pioneering work on Lewis acid assisted chiral Brønsted acid (chiral LBA) mediated polyene cyclization from the Yamamoto and Corey groups,¹⁹ Chein and co-workers reported an enantioselective polyene cyclization of 2-(homogeranyl)anisole **63** with the BINOL derivative **67** and tin(IV) chloride *en route* to galanal A (**65**) and B (**66**) (Scheme 14).²⁰ Enantioselective protonation with the complex tin(IV) chloride-**67** provided a mixture of tricyclic compound **64** along with monocyclized products as the major components. Subsequent exposure of the mixture to tin(IV) chloride and trifluoroacetic acid provided octahydrophenanthrene **64** (86% over 2 steps, 57% ee) as the key intermediate, which was converted into galanal A (**65**) and B (**66**).

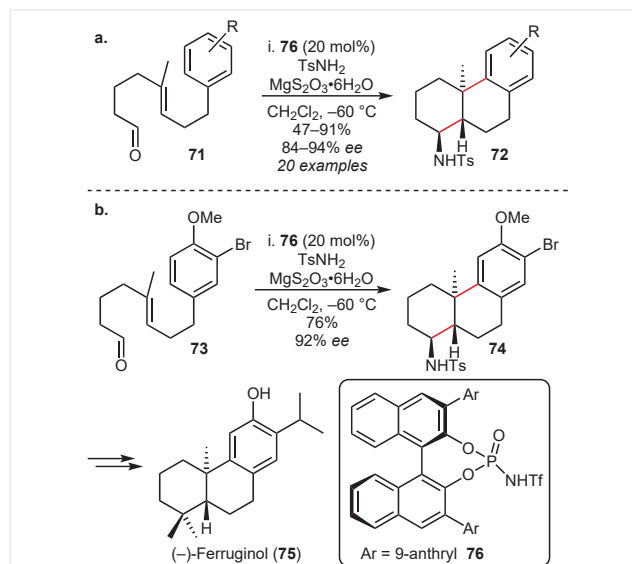


Scheme 14 Synthesis of galanal A and B

Meroterpenoid berkeleyone A (**70**), which is produced by a fungus *Penicillium rubrum*, inhibits caspase-1, a protein associated with Alzheimer's and Parkinson's diseases. Newhouse and co-workers reported a 13-step total synthesis of ($\pm$)-berkeleyone A (**70**) utilizing a Brønsted acid mediated epoxy-diene polyene cyclization as the key step to form the tricyclic framework (Scheme 15).²¹ While most epoxide-initiated polyene cyclizations are activated with Lewis acids, the desired polyene cyclization of epoxide **68** required a Brønsted acid to facilitate the carbon-based nucleophilic attack of the β -keto ester moiety to terminate the cyclization. After extensive screening of Lewis and Brønsted acids promoters for the polyene cyclization of epoxide **68** to alcohol **69**, it was found that the yellow ether solvated complex of HFeCl_4 , prepared in situ by reaction of iron(III) chloride in CH_2Cl_2 with anhydrous hydrogen chloride in diethyl ether, was the best promoter for the desired polyene cyclization to form alcohol **69** (39%). This led to the formation of three C–C bonds and generated six stereogenic centers to furnish the majority of the berkeleyone scaffold. Control experiments showed that the active Brønsted acid $[\text{FeCl}_4]^-$ anion was superior to either iron(III) chloride or anhydrous hydrogen chloride alone.

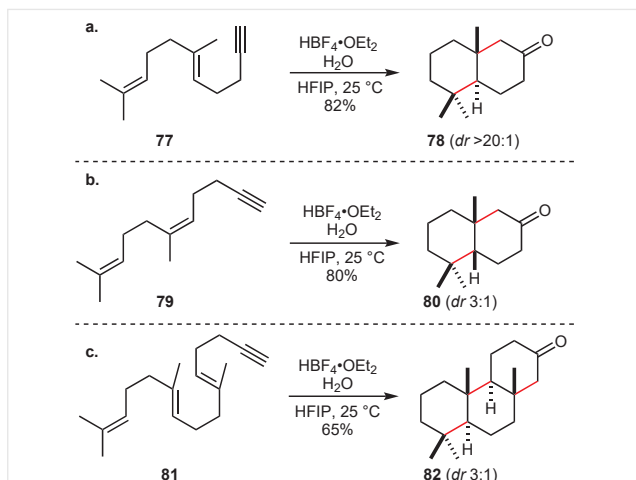
Scheme 15 Synthesis of ($\pm$)-berkeleyone A

Zhao and co-workers developed a chiral Brønsted acid *N*-phosphoramidate from BINOL that catalyzed enantioselective polyene cyclization via protonation (Scheme 16).²² This methodology focused on the protonation of an imine to produce an iminium ion as initiator for the polyene cyclization. It was found that *N*-phosphoramidate **76** provided optimal enantioselectivity and addition of magnesium thio-sulfate hexahydrate improved the reaction rate with enhanced enantioselectivity at -60°C . A broad range of substituted arenes are compatible as terminating nucleophiles under the reaction conditions. Furthermore, its application was showcased in the first total synthesis of (–)-ferruginol (**75**), the enantiomer of diterpene natural product (+)-ferruginol which has antifungal, antimicrobial, antitumor, and anti-inflammatory activities. The *N*-phosphoramidate **76** catalyzed enantioselective protonation of the resulting imine derived from aldehyde **73** with 4-toluene-sulfonamide, which was utilized as the key step to induce polyene cyclization, forming the dicyclized intermediate **74** for the total synthesis of (–)-ferruginol (**75**).



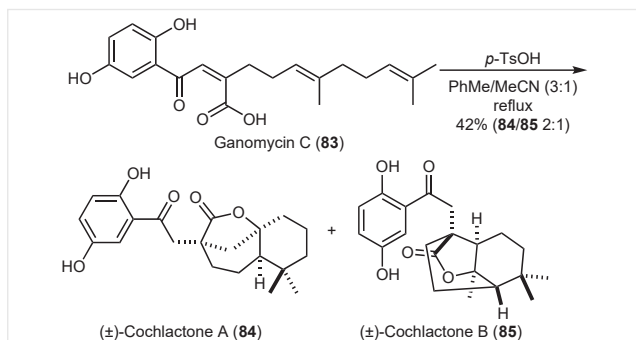
Scheme 16 Synthesis of (–)-ferruginol

A new protocol for the synthesis of cyclohexanones developed by Rodríguez and co-workers,²³ was extended to the cationic polyene cyclization of polyenynes (Scheme 17). Tetrafluoroboric acid acts as the promotor for the cyclization, employing HFIP as the solvent. The reaction was initiated by alkene protonation and terminated by trapping the final alkenyl cation with water. Three different polyenynes derived from geraniol **77**, nerol **79**, and farnesol **81** were cyclized to provide ketones **78** (82%, dr >20:1), **80** (80%, dr 3:1), and **82** (65%, dr 3:1), respectively.

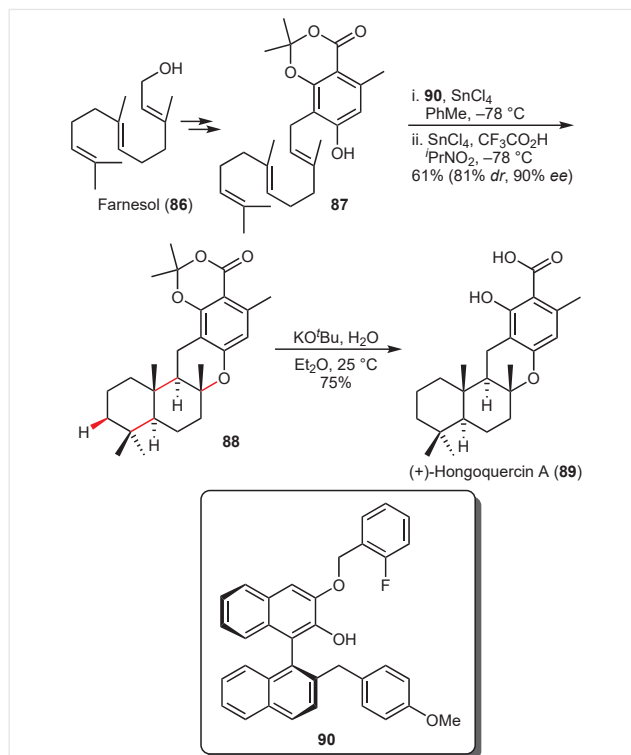


Scheme 17 Cationic polyenyne cyclizations

Qiu and co-workers have isolated new natural meroterpenoids ($\pm$)-cochlactone A (**84**) and B (**85**) that display anti-inflammatory activities (Scheme 18).²⁴ It was postulated that the possible biogenetic pathway for cochlactone A (**84**) could be from ganomycin C (**83**) by acid-catalyzed cyclization. After optimization of the reaction conditions, it was found that exposure of ganomycin C (**83**) to *p*-toluenesulfonic acid resulted in polyene cyclization, thereby producing a product mixture containing ($\pm$)-cochlactone A (**84**) and B (**85**) (42% combined yield) in 2:1 ratio.

Scheme 18 Synthesis of ($\pm$)-cochlactone A and B

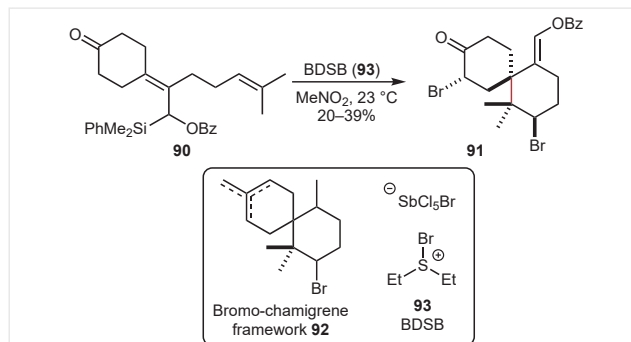
By utilizing sequential biomimetic polyketide and polyene cyclizations, the Barrett group completed a concise 6 step synthesis of (+)-hongoquercin A (**89**) (Scheme 19).^{7b} A farnesol (**86**)-derived resorcyate **87** was protonated enantioselectively and regioselectively at the terminal alkene to promote polyene cyclization with tin(IV) chloride-**90**, developed by the Yamamoto group as a Lewis acid enhanced Brønsted acid,^{19e} thereby producing meroterpenoid **88** (61%, 81% dr, 90% ee). Subsequent saponification of meroterpenoid **88** was used to complete the synthesis of (+)-hongoquercin A (**89**) (75%).



Scheme 19 Synthesis of (+)-hongoquercin A

2.3 Halogen Electrophile Initiated Polyene Cyclizations

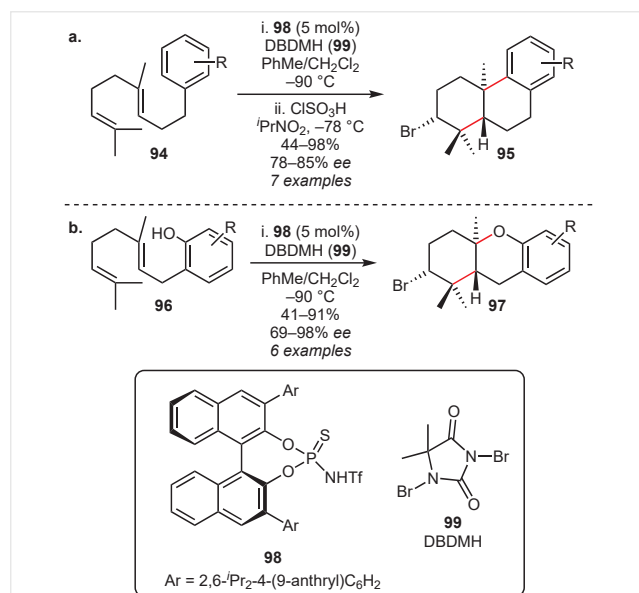
In 2009, the Snyder group invented bromodiethylsulfonium bromopentachloroantimonate ($\text{Et}_2\text{SBr}^+\text{SbCl}_5\text{Br}^-$, BDSB, **93**), which was shown to be an efficient reagent to induce bromonium ion mediated polyene cyclizations and electrophilic aromatic substitution reactions.²⁵ Recent findings by the Snyder group further demonstrated its ability to mediate the cyclization of alkene **90** to produce the spiro[5.5]undecane derivative **91** via bromonium-induced polyene cyclization accompanied by regio- and stereoselective α -bromination of the ketone functionality (Scheme 20).²⁶



Scheme 20 Bromonium-mediated polyene cyclization for the synthesis of the chamigrene framework

Spirocycle **91** possesses the essential framework of bromochamigrene **92**, which could provide access to the chamigrene family of natural products.

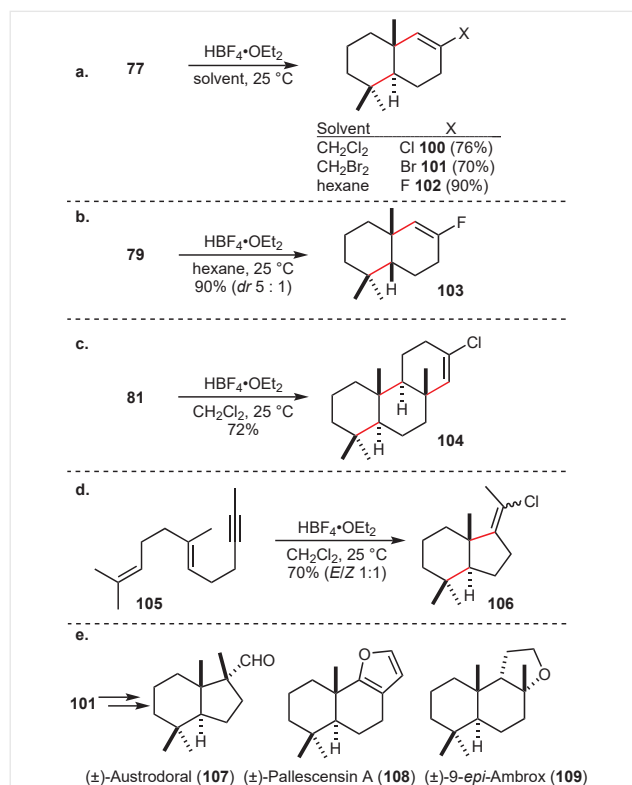
The first reported catalytic enantioselective bromonium-mediated polyene cyclization was developed by the Yamamoto group (Scheme 21).²⁷ This reaction was catalyzed by a chiral thiophosphoramidate **98** and employed 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **99**) as an electrophilic bromine source. Enantioselective bromocyclization of geranylbenzenes **94** provided a mixture of fully and partially cyclized products. Subsequent treatment of the reaction mixture with chlorosulfonic acid promoted the final cyclization of the partially cyclized products to give bromides **95**. On the other hand, bromocyclization of geranylphenols **96** under the same conditions provided fully cyclized bromides **97** as single diastereomers with excellent enantioselectivities without additional treatment with chlorosulfonic acid.



Scheme 21 Catalytic enantioselective bromonium ion mediated polyene cyclizations

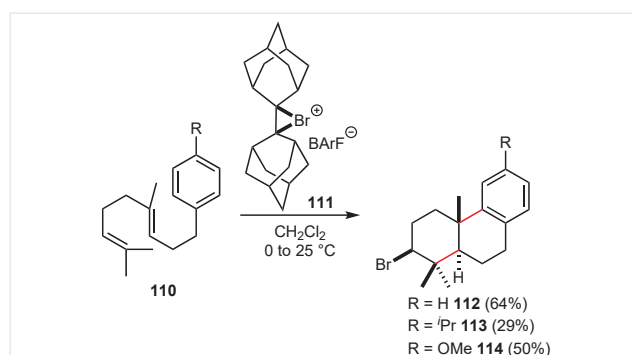
Rodríguez, Fañanás, and co-workers reported an acid-mediated cationic cyclization of polyenyne to form halogen-containing polycyclic compounds (Scheme 22).²⁸ Protonation of the alkene functionality of enyne **77** by tetrafluoroboric acid induced a cationic polyene cyclization which was terminated by the alkyne group to form an intermediate alkenyl cation that reacted with a halide source. It was observed that the dienyne **77** cyclized to give the corresponding chloride **100** (76%), bromide **101** (70%), or fluoride **102** (90%) when the halogenated solvent used in the reaction was changed to dichloromethane, dibromomethane, or hexane. While a geraniol-derived dienyne gave the *trans*-fused compounds **100–102** exclusively, *cis*-fused compound **103** was obtained diastereoselectively from ne-

rol-derived dienyne **79**. Furthermore, cyclization with substrate **105** containing an internal alkyne produced an indane derivative **106** (70%) as a mixture of geometric isomers. It is important to note that bicyclic bromide **101** served as a common intermediate for the total synthesis of (±)-austrodoral (**107**), (±)-palescensin A (**108**), and (±)-9-*epi*-ambrox (**109**).



Scheme 22 Cyclization of polyenyynes

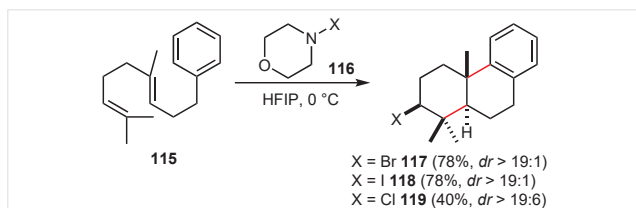
Hennecke and co-workers discovered that a stable bromonium salt **111** underwent electrophilic addition to alkenes that induced halocyclization of polyenes (Scheme 23).²⁹ Bromonium salt **111** is a sterically demanding bromonium ion with the weakly coordinating tetrakis[3,5-



Scheme 23 Bromocyclization with a bromonium salt

bis(trifluoromethyl)phenyl]borate (BArF^-) counterion. Reaction of this salt **111** with homogeranyl arenes **110** effectively furnished fully cyclized bromides **112–114** (29–64%).

The halocyclization of polyenes was also mediated using an electrophilic halogen source in the presence of the Lewis base morpholine with HFIP acting as the Lewis acid according to findings in 2018 by Gulder and co-workers (Scheme 24).³⁰ Reaction of morpholine and either *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), or 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) generates the corresponding *N*-halomorpholine **116**, which acts as the halogenating reagent. Homogeranyl benzene **115** was successfully converted into the corresponding fully cyclized halides **117–119** with excellent diastereoselectivities using *N*-halomorpholines **116**. HFIP was identified as the best solvent for this transformation because of its Lewis acidic, highly polar, and strongly hydrogen-bond donating, but weakly nucleophilic, properties. It is essential for HFIP to activate the *N*-halomorpholine **116** via hydrogen-bonding for halogenation to take place. Furthermore, HFIP could possibly prearrange the aryl-diene **115** via hydrophobic interactions to facilitate the cyclization. Lastly, the Lewis acidity of HFIP allows activation of the halonium ion intermediate to induce polyene cyclization.

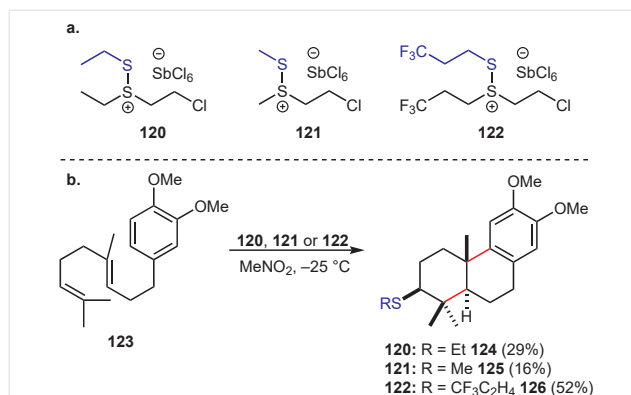


Scheme 24 Halocyclizations of polyene substrates

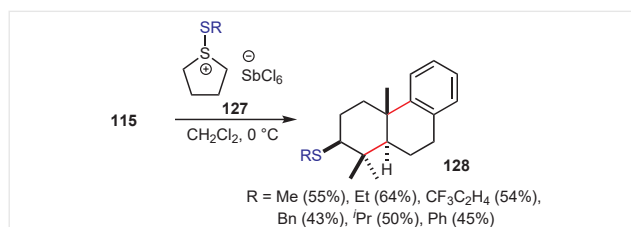
2.4 Sulfur Electrophile Initiated Polyene Cyclizations

The Snyder group reported three electrophilic alkyl-disulfanium salts that are capable of inducing sulfur-mediated cationic polyene cyclizations (Scheme 25).³¹ Alkyl-disulfanium salts **120–122**, effectively serving as electrophilic sources of ethylsulfanium, methylsulfanium, and 3,3,3-trifluoropropylsulfanium cations, respectively, mediate the cyclization of polyene **123** to produce octahydrophenanthrenes **124–126** in modest yields (16–52%).

Further investigations led to the development of alkyl- and aryl-disulfanium salts **127** that could induce thiiranium-mediated polyene cyclizations (Scheme 26).³² Cyclization of homogeranylbenzene **115** with alkyl and aryl sulfide electrophiles produced sulfides **128** with improved yields compared to those obtained with alkyl-disulfanium salts **120–122**.



Scheme 25 Polyene cyclizations with alkyl-disulfanium salts

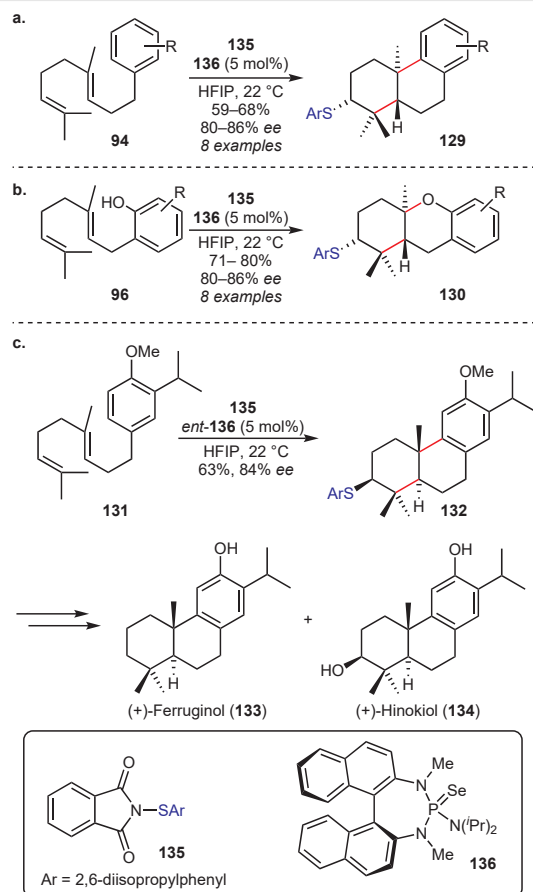


Scheme 26 Polyene cyclizations with alkyl- and aryl-disulfanium salts

The first catalytic and enantioselective thiiranium ion mediated polyene cyclization was reported by Denmark and co-workers (Scheme 27).³³ Homogeranylarenes **94** and *ortho*-geranylphenols **96** were cyclized to give the corresponding polycyclic compounds **129** and **130**, respectively, via the intermediacy of an enantiomerically enriched thiiranium ion in HFIP. This reaction was catalyzed by a chiral Lewis base **136** and sulfenylating reagent **135**. It is important to note that the use of HFIP as the solvent is crucial to suppress sulfenylation of the internal alkene due to solvophobic interactions between the highly polar HFIP medium and the lipophilic polyene substrate, minimizing exposure of internal alkenes. Furthermore, the acidity of HFIP is beneficial to generate the cationic active catalyst. Application of the methodology was used in enantioselective total syntheses of (+)-ferruginol (**133**) and (+)-hinokiol (**134**) from sulfide **132**.

2.5 Transition-Metal-Mediated Cationic Polyene Cyclizations

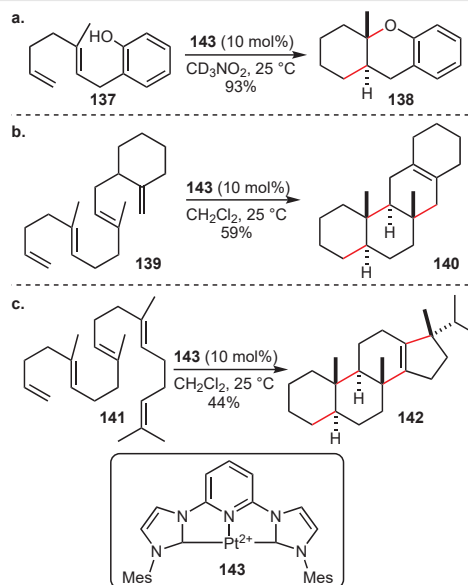
Following the pioneering work by Gagné and co-workers on electrophilic platinum-complex-catalyzed polyene cyclization reactions,^{4c} in 2014 they developed a new platinum(II) complex **143** with an *N*-heterocyclic carbene (NHC) containing pincer ligand for the synthesis of sterol-like polycyclic compounds via sequential electrophilic polyene cyclization and oxidative protonolysis (Scheme 28).³⁴ The terminal alkene of the substrates is activated by the electro-



Scheme 27 Catalytic sulfenylcyclizations of polyenes

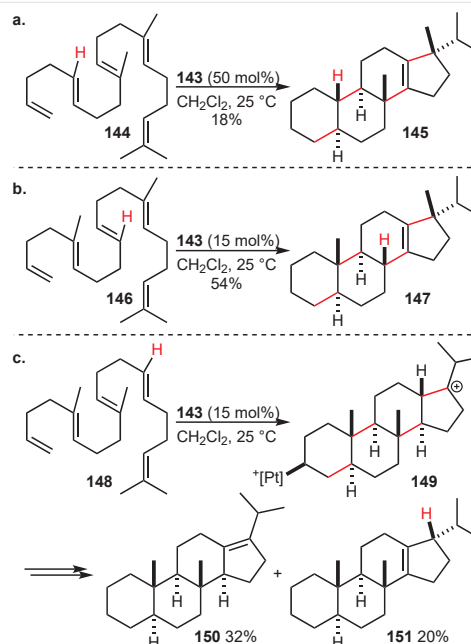
philic platinum(II) complex to initiate the polyene cyclization, followed by protodemetalation to regenerate the Pt catalyst. This methodology has a broad substrate scope and is able to induce di-, tri-, and tetracyclization reactions with a range of polyene substrates **137**, **139**, and **141**. Diphenylamine was added as a proton shuttle to enhance the reaction rate in some cases.

The platinum(II) catalyst **143** was also used in a study on the influence of alkene substitution on pentaene cyclizations (Scheme 29).³⁵ Three unique analogues (**144**, **146**, and **148**) of pentaenes **141**, with different methyl group modification, were synthesized and treated with catalyst **143**, inducing polyene cyclizations to provide the cyclized products **145**, **147**, and **150/151**. It was found that replacement of methyl groups by hydrogen did not affect the efficiency of polyene cyclization compared to that of **141** except to diminish reaction rates. Pentaenes **144** and **146** both underwent the anticipated cyclization to give alkene **145** (18%) and **147** (54%), respectively. On the other hand, cyclization of pentaene **148** provided a mixture of two tetracyclic compounds **150** (32%) and **151** (20%), which were formed from the common intermediate **149** via hydride shifts. Kinetic



Scheme 28 Platinum(II)-mediated polyene cyclizations

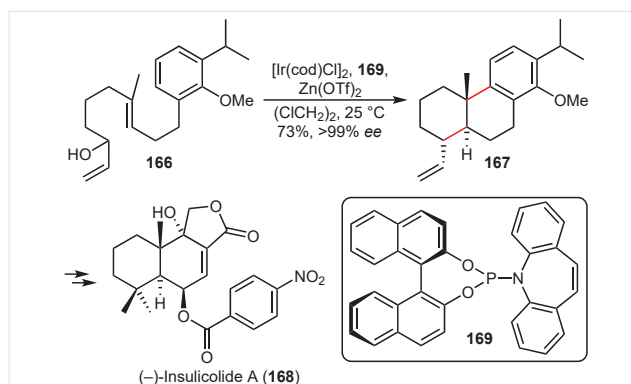
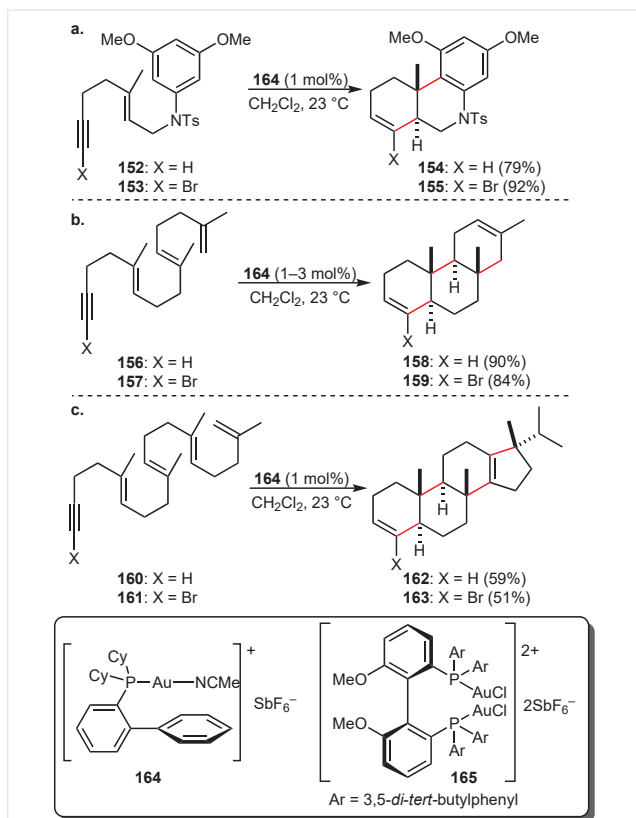
studies showed that the rate of pentaene cyclization of substrates **141**, **144**, **146**, and **148** follows the order **141** > **148** > **146** > **144**. Computational studies suggest that pentaenes **141** and **144** form the first three rings in a concerted mechanism to generate a carbocation intermediate for further cyclizations. Pentaene **146** forms the cyclohexyl ring first, followed by concerted cyclizations to close the second and third rings. Pentaene **148** first undergoes concerted cycliza-



Scheme 29 Study of the influence of alkene substitution in platinum(II)-mediated polyene cyclizations

tions to form the first two rings, followed by stepwise cyclizations to yield products **150** and **151** after different hydride shifts. Pentaenes **141**, **144**, and **146** generate tertiary carbocations while pentaene **148** generates a secondary carbocation after the concerted cyclizations. Furthermore, intrinsic reaction coordinate (IRC) calculations for the cyclization of pentaene **144** indicated that the reaction coordinates of the platinum(II)-catalyzed pentaene cyclizations are similar to those of the enzymatic cyclizations of squalene and oxidosqualene, suggesting that it is essentially an organometallic equivalent of a key biomimetic process.

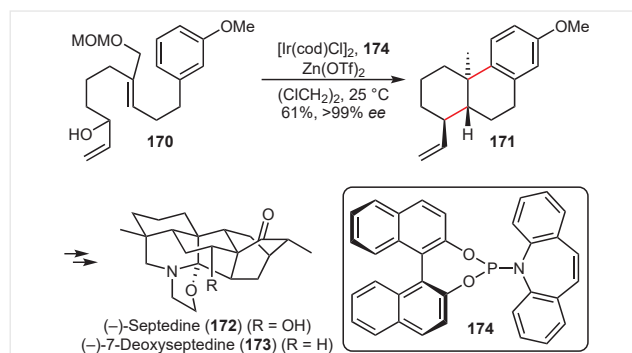
Building upon previous research on gold(I)-catalyzed polyene cyclizations,³⁶ a new advance was reported by Echavarren and Rong (Scheme 30).³⁷ Activation of the enyne of polyene substrates by gold(I) triggered polyene cyclization to produce steroid-like compounds. 1,5-Enyne **152** cyclized to give alkene **154** (79%) with the arene acting as the terminating nucleophile. Additional examples using alcohols, phenols, and heteroarenes as the terminal nucleophiles were also successfully cyclized. Furthermore, di- and tricyclization of polyenynes **156** and **160** gave the tri- and tetracyclic compounds **158** (90%) and **162** (59%), respectively, under the same conditions. It was also found that bromoalkynes could be used as initiators of polyene cyclization to give cyclic bromoalkenes. For instance, the bromoalkyne



analogues **153**, **157**, and **161** were cyclized to give the corresponding synthetically useful bromoalkenes **155** (92%), **159** (84%), and **163** (51%). The use of chiral gold(I) catalysts for the enantioselective variant of this cyclization was also investigated. It was found that moderate enantioselectivity was observed when the dinuclear gold(I) complex of BIPHEP **165** and silver(I) dinitrilylimide were employed in the cyclization of **152** into **154** (85%, 54% ee).

(-)-Insulicolide A (**168**) is a nitrobenzoyloxy-substituted sesquiterpenoids with promising anticancer activity against several human cancer cell lines. The first total synthesis of (-)-insulicolide A (**168**) and related sesquiterpenoids was accomplished by Yang, Chen, and co-workers (Scheme 31).³⁸ A key intermediate **167** in this synthesis was prepared from allylic alcohol **166** by an iridium-catalyzed enantioselective polyene cyclization reaction, developed by Carreira and co-workers,³⁹ in the presence of ligand **169** to furnish the drimane core **167** (73%, >99% ee).

The same strategy was utilized by Li and co-workers in the total synthesis of (-)-septedine (**172**) and (-)-7-deoxyseptedine (**173**) (Scheme 32).⁴⁰ The key enantiomerically pure alkene **171** (61%, >99% ee) was prepared by the iridium-catalyzed polyene cyclization of allylic alcohol **170** employing phosphoramidite **174** as the chiral ligand.

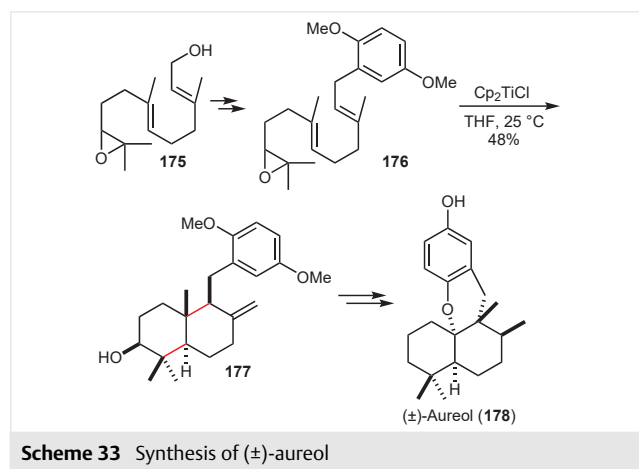


3 Radical Polyene Cyclizations

3.1 Transition-Metal-Mediated Radical Polyene Cyclizations

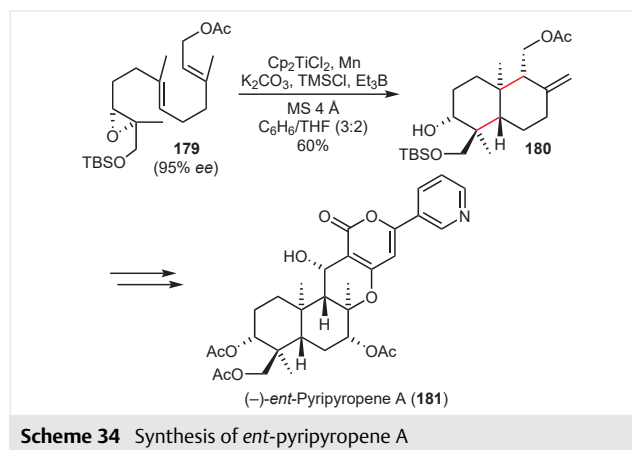
While classical cationic polyene cyclizations dominate the literature on this topic, radical-mediated polyene cyclizations were proposed as early as the 1960s by Breslow.⁴¹ The hypothesis of the biosynthetic pathway for polyene cyclizations was ambiguous, which led Breslow to the formulation of a radical approach, which was subsequently rejected. In contrast to cationic polyene cyclizations, radical processes allow a milder approach towards functionalized decalins, as radicals operate on a lower relative energy level than cationic intermediates. It should be noted that radical mediators can transform highly functionalized polyene precursors into *trans*-decalins with remarkable stereocontrol in a non-concerted mechanism that could be rationalized in terms of the Beckwith–Houk rules.⁴²

In 2015, Oltra, Rosales, and co-workers reported the synthesis of ($\pm$)-aureol (**178**), a marine natural product which exhibits cytotoxicity against A549 human non-small cell lung cancer cells and anti-influenza-A virus activity (Scheme 33).⁴³ Application of a titanocene(III)-mediated reductive polyene cyclization of racemic epoxide **176**, derived from alcohol **175**, provided alcohol **177** with an exocyclic alkene with excellent relative stereochemical control. Subsequent boron trifluoride–diethyl ether catalyzed rearrangement was used in the transformation of alcohol **177** into ($\pm$)-aureol (**178**).

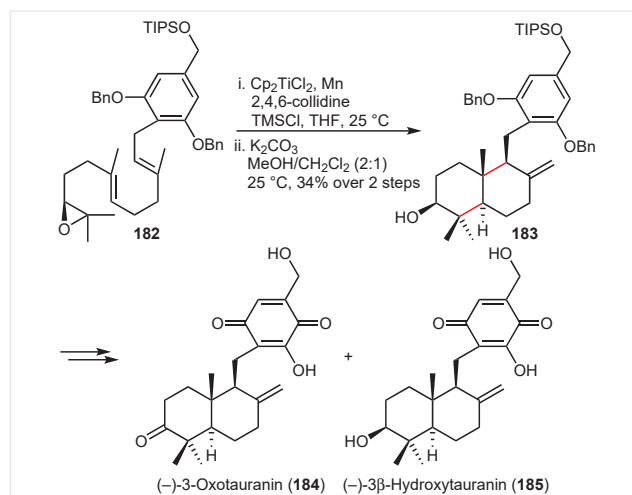


The synthetic power of the titanocene(III)-mediated polyene cyclization was further demonstrated by Takahashi and co-workers in the synthesis of (–)-*ent*-pyripyropene A (**181**) (Scheme 34).⁴⁴ Titanocene(III)-induced polyene cyclization of epoxide **179** gave alcohol **180** (60%). The use of single enantiomer epoxide **179** thereby controls the outcome of the formation of 4 contiguous stereocenters. The choice of ligand in the asymmetric epoxidation allows di-

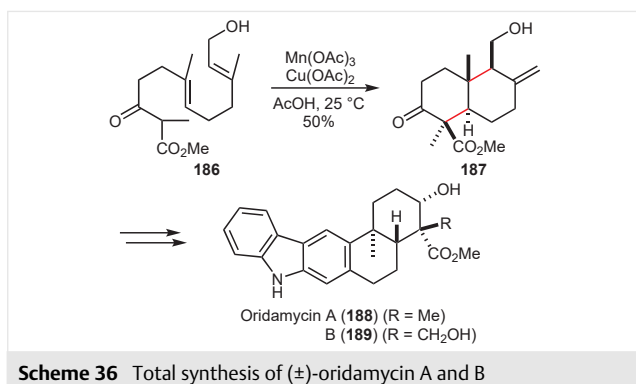
versification towards natural and unnatural derivatives of the pyripyropene family. The titanocene(III)-mediated cyclization was fully automated, reproducibly allowing access to **180**, a common intermediate in terpene natural product synthesis.



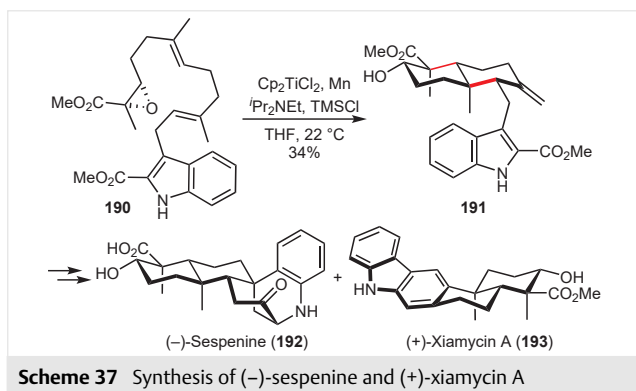
Seifert and Göhl utilized a similar strategy in the synthesis of (–)-3-oxotauranin (**184**) and (–)-3 β -hydroxytauranin (**185**) (Scheme 35).⁴⁵ Titanocene(III)-mediated radical polyene cyclization of epoxide **182** afforded alcohol **183**, subsequent global deprotection and adjustment of oxidation state completed the synthesis of (–)-3-oxotauranin (**184**) and (–)-3 β -hydroxytauranin (**185**).



In 2015, Trotta reported the cyclization of a geranyl β -keto ester **186** under radical conditions employing a Mn(III)/Cu(II) system to provide alcohol **187** (50%) (Scheme 36).⁴⁶ This allowed the preparation of the terpenoid *trans*-decalin core of ($\pm$)-oridamycin A (**188**) and B (**189**) with the methyl ester moiety in the axial position.

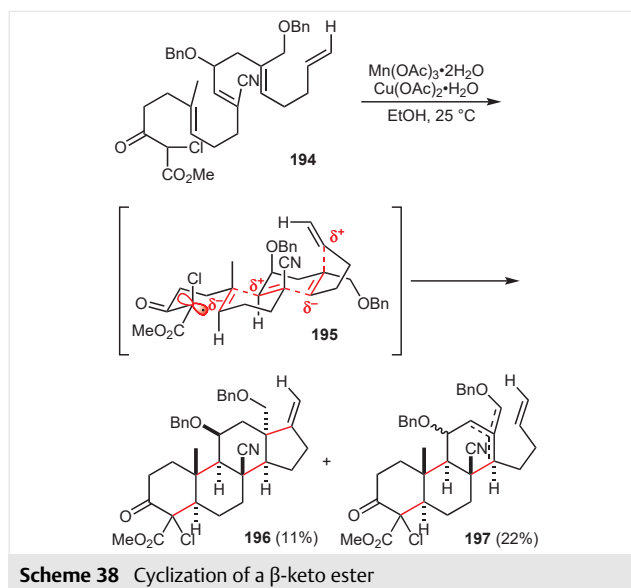


Li and co-workers reported the use of a titanocene(III)-mediated polyene cyclization of epoxide **190**, furnishing the *trans*-decalin core **191** (34%), with the alcohol in equatorial and the methyl ester in equatorial positions (Scheme 37).⁴⁷ Subsequent transformation of alcohol **191** completed the divergent synthesis of (–)-sespenine (**192**) and (+)-xiamycin A (**193**).

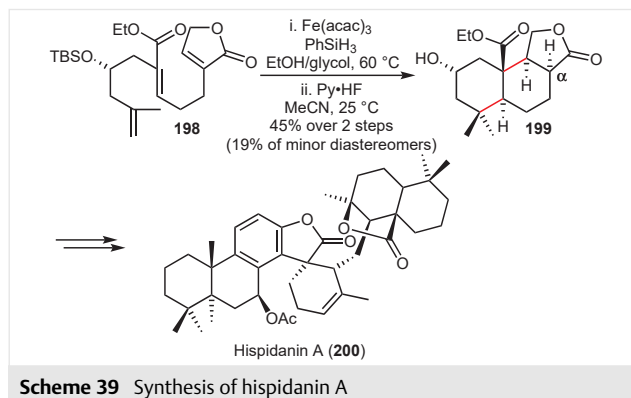


In 2017, Shoji and co-workers reported a radical cyclization of β -keto ester **194** which was mediated by Mn(III)/Cu(II) to give tetracyclic ketone **196** (11%) and tricyclic ketone **197**, as a mixture of regioisomers (22%) via intermediate **195** (Scheme 38).⁴⁸ The functionalization arose from tuning the electron-donating or -demanding properties of the polyene scaffold to allow efficient cyclization between alternating electrophilic radicals with electron-rich trisubstituted olefins.

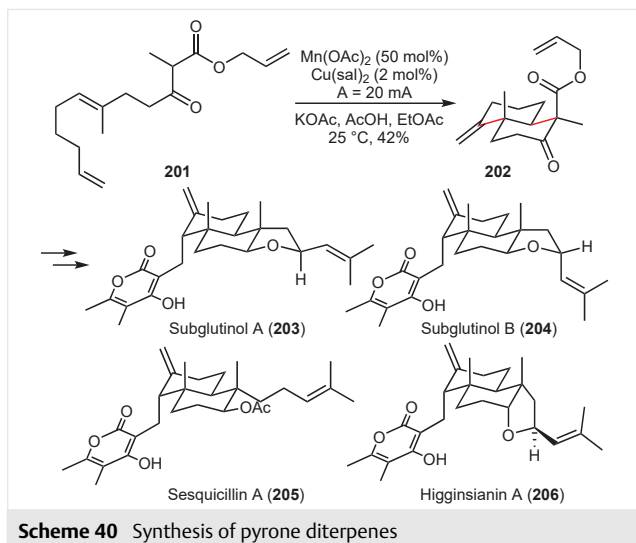
In 2017, Liu and co-workers reported the synthesis of (–)-hispidanin A (**200**), a natural product with promising anticancer properties, via a hydrogen atom transfer (HAT) mediated triene cyclization to construct the tricyclic core of (–)-hispidanin A (**200**) (Scheme 39).⁴⁹ The use of iron(III) acetylacetonate and triphenylsilane as hydrogen source smoothly furnished tricyclic lactone **199** from alkene **198**



(45% over 2 steps) after deprotection, thereby establishing two quaternary and four contiguous stereocenters in one step. In a 2018 follow-up paper, Liu and co-workers reported further mechanistic studies, producing deuteration at the α -position of the lactone, supporting the hypothesis that the reaction involves the formation of an enolate anion.⁵⁰



While most of these transformations are initiated by a radical generated from metal complexes, in 2018 the Baran group exploited electrochemical initiation for a radical polyene cyclization in the divergent synthesis of pyrone diterpenes sesquicillin A (**205**), higginsianin A (**206**), and subglutinol A (**203**) and B (**204**) (Scheme 40).⁵¹ Cyclization of β -keto ester **201** provided key intermediate alkene **202** (42%) which was further derivatized into the different diterpene natural products.

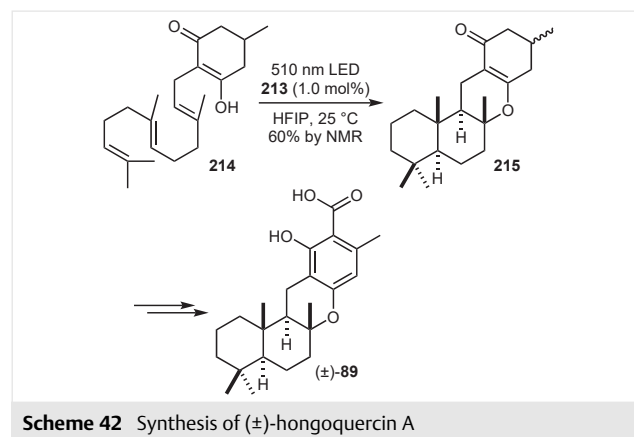
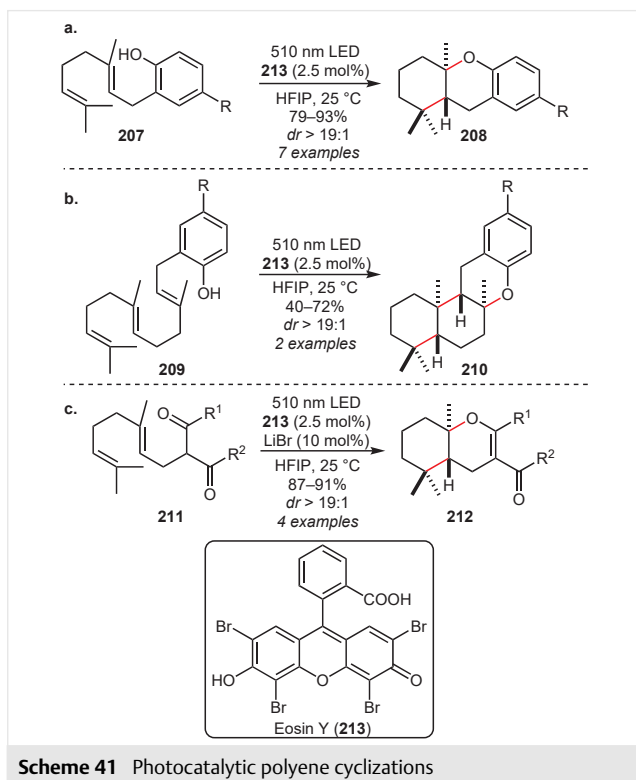


3.2 Photocatalyst-Mediated Polyene Cyclizations

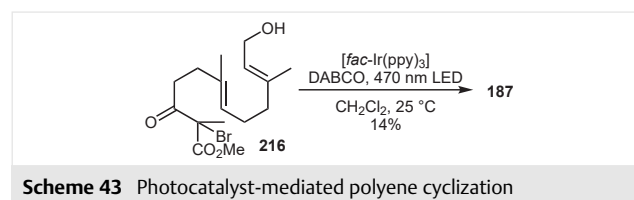
Photoredox catalysis has been an ever-growing field over the last decade with numerous examples of synthetic transformations, and applications in natural product or pharmaceutical synthesis. Since the seminal work published by Demuth and co-workers on photochemically induced electron transfer polyene cyclizations,⁵² the utility of photocatalyst-mediated polyene cyclization has remained

underexplored. One noticeable example of polyene cyclization catalyzed with eosin Y (**213**) was published in 2015 by Zhang, Luo, and co-workers (Scheme 41).⁵³ The mild photoredox-catalyzed transformation tolerated various functionalization and the cyclization proceeded with excellent relative stereochemical control and diastereoselectivity for various ring systems. A selection of solvents and organic and inorganic photoredox catalysts were examined and optimal results were obtained with eosin Y in HFIP. Subsequently, an array of geranylphenols **207** and farnesylphenols **209** with various functional groups in the *para* position were cyclized to produce chromanes **208** and **210**, respectively. 1,3-Diketones **211** also underwent photocatalyzed polyene cyclizations, thereby producing chromenes **212** with various substituents R¹ and R² of different electronic nature.

The synthetic utility of the photocatalyst-initiated polyene cyclization was further demonstrated in the 7-step synthesis of (±)-hongoquercin A (**89**) (Scheme 42).⁵⁴ Cyclization of phenol **214** catalyzed by eosin Y (**213**) provided tetracyclic compound **215** (60% by NMR), a key intermediate with the complete carbon framework of the natural product.



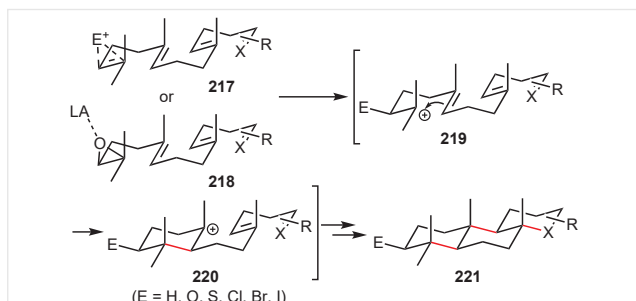
Trotta reported attempts to employ photoredox catalysts as polyene cyclization initiators during his studies on the total synthesis of xiamycin A (**193**).⁵⁵ While earlier work on (±)-oridamycin A (**188**) showed that manganese(III)-mediated cyclization gave the *trans*-decalin **187** with the methoxy ester in the axial position (Scheme 43); photoredox catalysts were able to convert an α-bromo-β-keto ester **216** into the same *trans*-decalin compound **187**.



When the acylated linear precursor was subjected to these conditions, it resulted in complete decomposition. Although the yields were low, the reaction proceeded at catalyst loadings as low as 0.01 mol%.

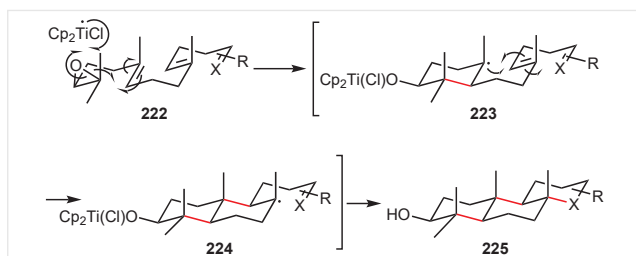
4 Origin of Stereocontrol in Polyene Cyclizations

Several general remarks on the observed stereoselectivity of the various methods of cationic polyene cyclization reactions can be made. The underlying principle of all the cationic cyclization reactions mentioned is that the prearranged *pseudo-chair-chair-(chair)* conformation such as of polyene **217** or **218** allows the efficient preparation of polycyclic compound **221** with predefined relative stereochemistry. This is based on the stereoelectronic arrangement of an olefinic double bond in close proximity to the electrophilic carbenium center in intermediate **219** and subsequently nucleophilic attack by an olefinic bond further down the chain on the intermediately formed carbenium center (Scheme 44). As such the *trans*-substitution of the polyene precursor sets the outcome for the observed *trans*-decalin stereoselectivity in the concerted cationic cyclization through the given prearranged conformation according to the Stork–Eschenmoser hypothesis.^{1a,b} In cases where the reactions are not proceeding in a concerted fashion, a mixture of products are formed.^{1a}



Scheme 44 Cationic polyene cyclizations

On the other hand, the origin of stereocontrol in radical polyene cyclization reactions could be rationalized by the Beckwith–Houk rules in addition to the Stork–Eschenmoser



Scheme 45 Radical polyene cyclizations

hypothesis (Scheme 45).⁴² As an illustration, titanium(III)-mediated cyclization of epoxide **222** would presumably proceed in a non-concerted fashion via radical intermediates **223** and **224** and favored 6-*endo-trig* cyclization via a chair transition state over 5-*exo-trig* cyclization to produce alcohol **225** due to ring strain.

5 Conclusion

Inspired by nature's efficient and highly stereochemically controlled syntheses of primary and secondary metabolites via polyene cyclizations, the use of initiators such as Lewis acids, metal complexes, halonium ion transfer reagents, sulfonium ion transfer reagents, and Brønsted acids have demonstrated the synthetic utility of these bioinspired transformations with comparable selectivities and efficiencies to the enzymatic processes. Recent developments of novel polyene cyclization methodologies have significantly expanded the scope of terpene and polyene functionalization reactions, providing a wide range of unique carbon frameworks. Radical-mediated polyene cyclizations have been further investigated to achieve different modes of cyclization from the cationic pathway, allowing early and late stage functionalization of polyenes for terpene and meroterpenoid total syntheses. Photocatalyst-mediated polyene cyclizations have emerged as new alternatives, which employ milder reaction conditions as well as lower catalyst loadings. It goes without saying that future developments in electrophilic reagents and catalysts will further advance the synthetic utility of polyene cyclizations with excellent enantio- and diastereoselectivities, greatly impacting the area of terpenoid, meroterpenoid, and steroid total syntheses amongst other classes of compounds.

Acknowledgment

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