TOTAL SYNTHESIS OF ALKYL CITRATE AND RESORCYLATE NATURAL PRODUCTS

A Thesis Submitted by

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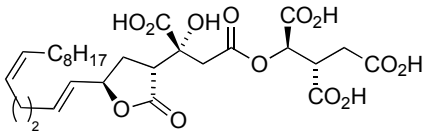
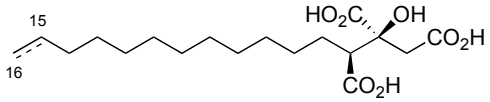
Abstract: Total synthesis of alkyl citrate and resorcylate natural products

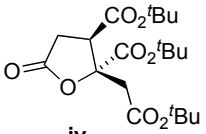
The total synthesis of citrafungin A (**i**),[1] the determination of the absolute stereochemistry[2] of CJ-13,981 (**ii**) and CJ-13,982 (**iii**) and the formal total synthesis of (–)-trachyspic acid, by making lactone **iv**,[3] were achieved from a common intermediate (**v**).



citrafungin A (**i**)

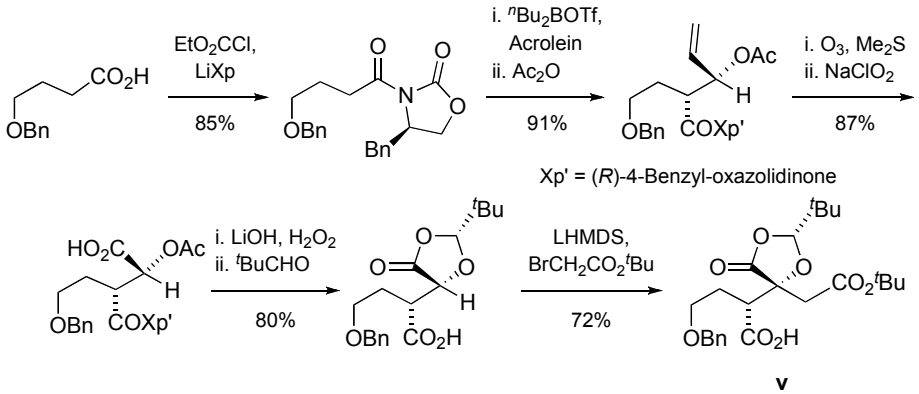


CJ-13,981 (**ii**) (15,16-olefin)
CJ-13,982 (**iii**) (15,16-dihydro)



iv

Dioxolanone **v** was prepared on a multigram scale starting from commercially available 4-benzyloxy-butyric acid using, as key steps, an enantioselective *syn*-aldol reaction of a chiral oxazolidinone and a diastereoselective Seebach alkylation of a 1,3-dioxolan-2-one derivative.

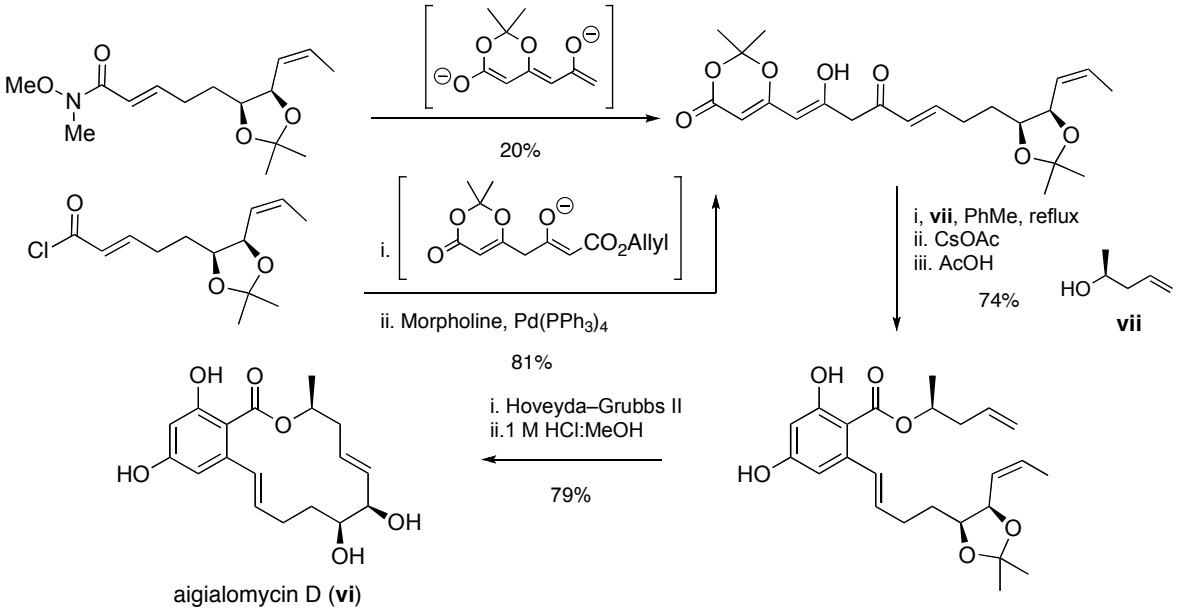


Xp' = (*R*)-4-Benzyl-oxazolidinone

v

From dioxolanone **v**, citrafungin A (i) was synthesised in 13 steps, CJ-13,981 (**ii**) and CJ-13,982 (**iii**) in 9 steps and the intermediate lactone (**iv**) for the formal synthesis of (–)-trachyspic acid in 5 steps.

Based on our recent advances on resorcylates metabolites,[4] we carried out the total synthesis of aigialomycin D (**vi**),[5] a potent 14-membered resorcylic macrolide, without the need for phenol protection, using the *C*-acylation of a keto-dioxinone dianion (or mono-anion), a cascade sequence consisting of ketene generation, alcohol (**vii**) trapping and aromatization, and ring closing metathesis.



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(1) Calo, F.; Richardson, J.; Barrett, A. G. M. *J. Org. Chem.* **2008**, *73*, 9292.

(2) Calo, F.; Bondke. A.; Richardson, J.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2009**, *50*, 3388.

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This thesis is dedicated to my grandmother **Nelly**.

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Abbreviations

$[\alpha]_D$	specific rotation
Å	Angstrom (10^{-10})
Ac	acetyl
Anal.	analysis
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3,3,1]nonane
BINOL	1,1'-bi-2,2'-naphthol
Bn	benzyl
BOP-Cl	*bis*(2-oxo-3oxazolidinyl)phosphonic chloride
b.p.	boiling point
br.	broad
Bu	butyl
BuLi	butyllithium
Bz	benzoyl
°C	degrees Celsius
CAN	ceric ammonium nitrate
cat.	catalytic
CI	chemical ionisation
CM	cross-metathesis
COD	1,5-cyclooctadiene
conc.	Concentrated
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
δ	chemical shift
d	doublet
DCC	dicyclohexyl carbodiimide
DCE	dichloroethane
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

d.e.	diastereomeric excess
DEAD	diethyl azodicarboxylate
DHP	3,4-dihydro-2H-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminium hydride
DIC	diisopropyl carbodiimide
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
dt	doublet of triplets
dq	doublet of quartets
EDA	ethylenediamine
e.e.	enantiomeric excess
EI	electron ionisation
EOM	ethoxymethyl
eq.	equivalent
ES	electrospray
Et	ethyl
h	hour
HBTU	O-Benzotriazole-*N,N,N',N'*tetramethyluronium-hexafluorophosphate
HMPA	hexamethylphosphoramide
HOBT	1-hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	*iso*
IMES	1,3-dimesitylimidazol-2-ylidene
imid.	imidazole
IR	infrared spectroscopy

J	coupling constant
KHMDS	potassium *bis*(trimethylsilyl)amide
L	litre
$LiAlH_4$	lithium aluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
μ	micro (10^{-6})
m	multiplet
M	molar
m	multiplet
m	*meta*
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
MOM	methoxylmethyl
min	minute(s)
mL	millilitre(s)
mol	mole(s)
mmol	millimole(s)
m.p.	melting point
Ms	mesyl
MS	mass spectrometry
MTPA	methoxy(trifluoromethyl)phenylacetyl
m/z	mass to charge ratio
n	*normal*
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
o	*ortho*
p	*para*
P	general protecting group

PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PS	polymer supported
PT	1-phenyl-1-H-tetrazol-yl
Py.	pyridine
q	quartet
quin	quintet
R	general substituent
RALs	resorcylic acid lactones
R_f	retention factor
RCM	ring-closing metathesis
Red-Al	sodium *bis*(2-methoxyethoxy) aluminium hydride
RT	room temperature
s	singlet
Salen	*N*,*N*'-ethylene*bis*(salicylideneiminato)*bis*(salicylidene)-ethylenediamine
sat.	saturated
t	tertiary
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
Tf	trifluoromethanesulfonyl
tt	triplet of triplets
TES	triethylsilyl

Tf	trifluoromethanesulfonyl (triflic)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl (tosyl)

0. General introduction

0.1. Natural products in drug discovery

For thousands of years, medicine and natural products have played a crucial role in treatment and prevention of human diseases.[1-3] Clinical, pharmacological, and chemical studies of traditional medicines, predominantly derived from plants, were the basis of the most early drugs such as aspirin (**1**), digitoxin (**2**), morphine (**3**), quinine (**4**), and pilocarpine (**5**). (Figure 1)

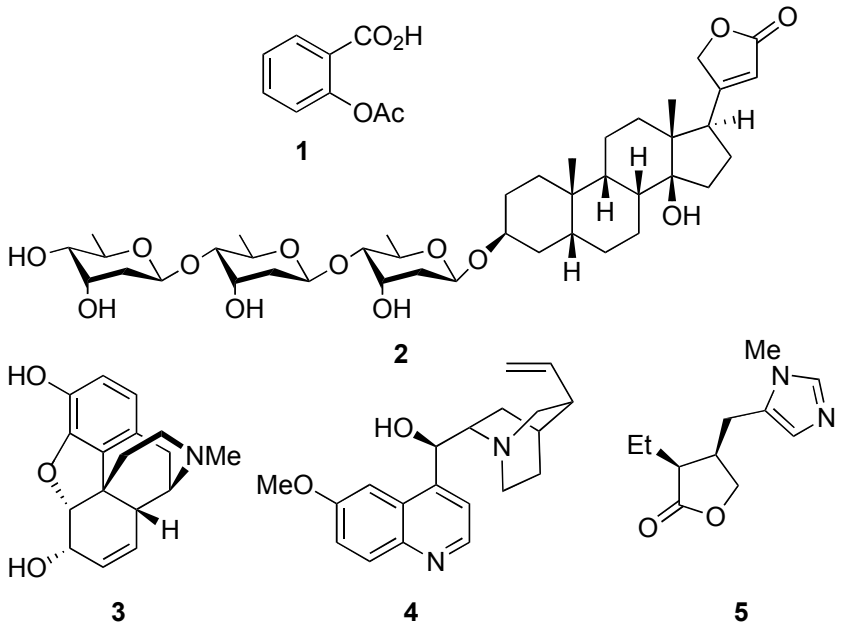


Figure 1. Example of early drugs.

The discovery of the antibacterial filtrate Penicillin[4] by Alexander Fleming in 1928, as well as its chemical structure determination by Dorothy Hodgkin[5] and the commercialisation of synthetic penicillins revolutionised drug discovery research (Figure 2).

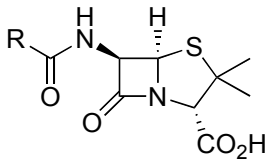


Figure 2. Core structure of penicillin

Following the success of penicillin, drug companies and research groups assembled large microorganism culture collections with a view to discover new antibiotics. The output from the early years of this antibiotic research was enormous and included examples such as streptomycin (**6**),[6] chloramphenicol (**7**),[7] chlortetracycline (**8**)[8] and cephalosporin C (**9**)[9] which are still used as drugs today (Figure 3).

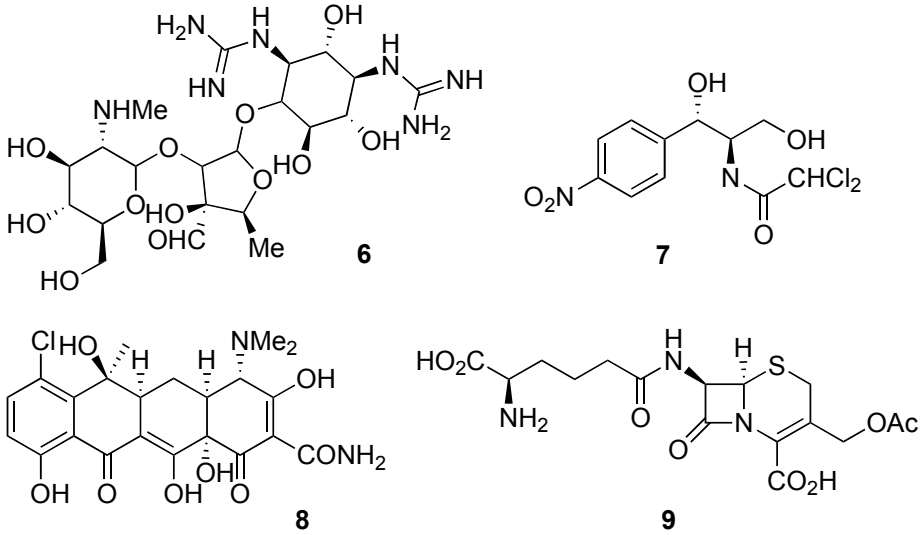


Figure 3. Examples of drugs discovered in the early years of antibiotic research

Between 1981 and 2002, natural products or natural product-derived drugs represented 28% of all new chemical entities (NCEs) launched onto the market.[10] In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products. Those results show how important natural products are as sources of new drugs and how they also are good lead compounds suitable

for further modification during drug development. Between 2000 and 2005, 25 new drugs derived from natural products were launched on the market (Table 1, Figure 4) as products for the treatment of common human diseases such as cancer, neurological, infectious, immunological, cardiovascular and metabolic diseases.[11-13]

Year	Generic Name (trade name)	Natural Product	Targeted Disease
2000	Arteether (Artemotil®)	Artemisinin	Malaria
2001	Ertapenem (Invanz®)	Thienamycin	Bacterial
2001	Telithromycin (Ketek®)	Erythromycin	Bacterial
2001	Pimecrolimus (Elidel®)	Ascomycin	Atopic dermatitis
2002	Ertapenem (Invanz™)	Thienamycin	Bacterial
2002	Fluvestrant (Faslodex®)	Estradiol	Cancer
2002	Galantamine (Reminyl®)	Galantamine	Alzheimer's
2002	Micafungin (Funguard®)	FR901379	Fungal
2002	Nitisinone (Orafadin®)	Leptospermone	Tyrosinaemia
2002	Biapenem (Omegacin®)	Thienamycin	Bacterial
2003	Daptomycin (Cubicin™)	Daptomycin	Bacterial
2003	Miglustat (Zavesca®) (**10**)	1-deoxynojirimycin	Type 1 Gaucher
2003	Mycophenolate sodium (Myfortic®) (**11**)	Mycophenolic acid	Immunosuppresion
2003	Pitavastatin (Livalo®) (**12**)	Mevastatin	Dyslipidemia
2003	Rosuvastatin (Crestor®) (**13**)	Mevastatin	Dyslipidemia
2004	Everolimus (Certican™)	Sirolimus	Immunosuppresion
2005	Doripenem (Finibax®)	Carbapenem	Bacterial
2005	Pramlintide acetate (Symlin®)	Amylin	Diabetic
2005	Tigecycline (Tigacil®)	Tetracycline	Bacterial
2005	Ziconotide (Prialt™)	MVIIA	Pain

Table 1. Examples of drugs launched on the market between 2000 and 2005.

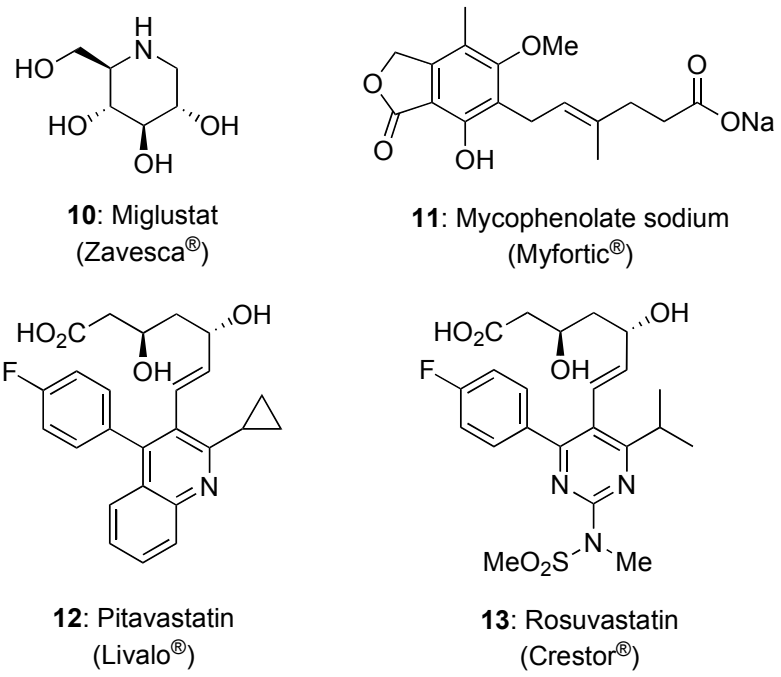


Figure 4. Examples of drugs derived from natural products.

From these observations, it is not surprising to find out that natural products and related drugs are used to treat 87% of all categorised human diseases. Besides new drugs launched on the market from 2000 to present, in 2005, there were 70 new candidates undergoing oncology clinical trials, all obtained from natural sources such as plants, microorganisms and marine organisms.[14,15]

0.2. Previous work in the Barrett group

During the last decades, the Barrett group has carried out extensive research on the synthesis of bio-active natural products and the underlying synthetic methodology. For example, it has reported the first total synthesis of nikkomycin B (**14**),[16] and the first total syntheses and full stereochemical elucidation of the marine macrocyclic alkaloids papuamine (**15**),[17] papulacandin D (**16**),[18] the structurally unusual serial cyclopropane

antifungal agent FR-900848 (**17**)[19,20] and the related CETP inhibitor U-106305 (**18**)[21] and the γ–lactam pramanicin (**19**).[22] The group has also reported an enantioselective route to the palmarumycin and preussomerin antifungal natural products, which allowed for the synthesis of nine natural products including CJ-12,371 (**20**)[23] and preussomerin G (**21**)[24] and completed the first synthesis of the unusual alkaloid CJ-12662 (**22**),[25] a highly active anthelmintic agent.

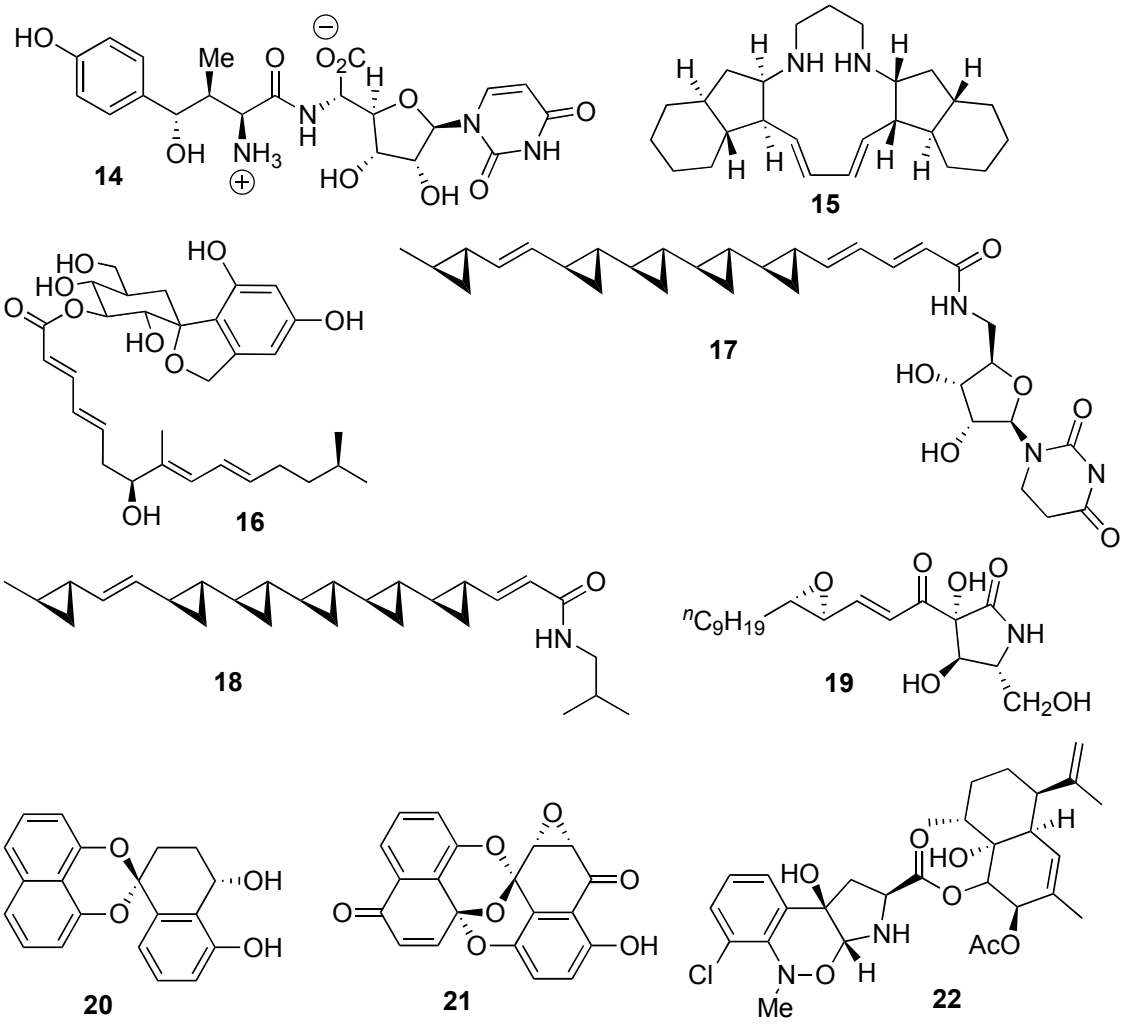


Figure 5. Examples of natural products made in the Barrett group.

0.3. Description of thesis

The first chapter of this PhD thesis is a description of the total synthesis of alkyl citrate natural products from a common precursor using, as key steps, a stereoselective Seebach Self-Regeneration of Stereocenter alkylation reaction of a chiral dioxolanone and a stereoselective Evans aldol reaction. Two different ways to open the dioxolanone ring were developed (in either acidic or basic condition) and will be presented in this section alongside different strategies to perform the total synthesis of citrafungin A (**23**), which required the manipulation of different protecting groups. The formal total synthesis of (–)-trachyspic acid (**24**) and the determination of the absolute stereochemistry of CJ-13,981 (**25**) and CJ-13,982 (**26**) were realised by applying the discoveries made during the synthesis of citrafungin A (Figure 6).

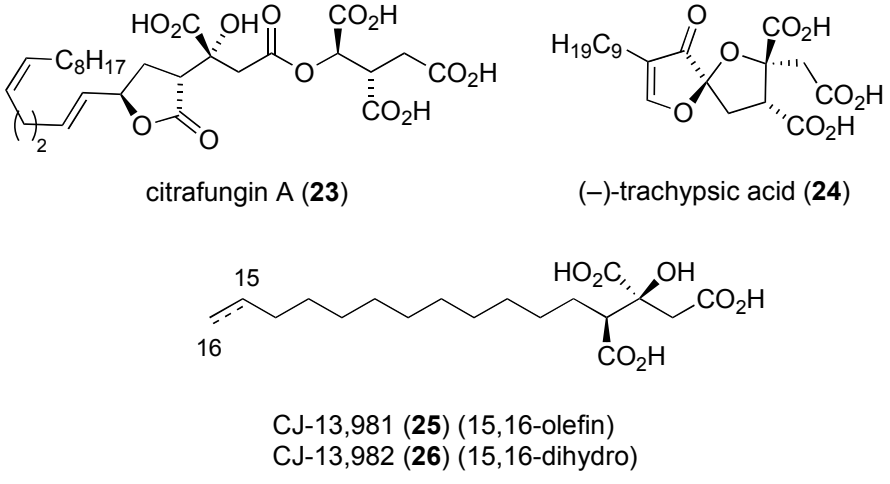
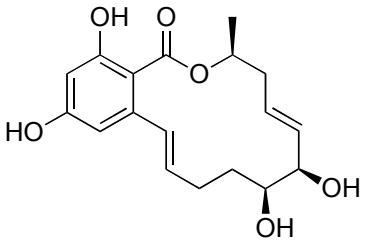


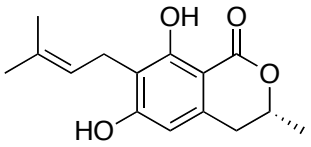
Figure 6. Structures of citrafungin A, (–)-trachyspic acid, CJ-13,981 and CJ-13,982.

The second part of this PhD thesis is a description of the total synthesis of resorcylic acid macrolactone using a biomimetic synthesis. The aromatic ring in aigialomycin D (**27**) was

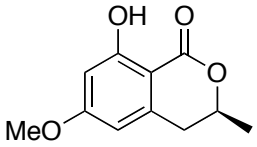
assembled at a later stage by a one-pot ketene formation–trapping–aromatisation sequence starting from a diketo-dioxinone (Figure 7). The application of this methodology was further developed and applied to the allyl- and prenyl-substitution reactions and in particular interest towards the total synthesis of angelicoin A (**28**) and angelicoin B (**29**)



aigialomycin D (**27**)



angelicoin A (**28**)



angelicoin B (**29**)

Figure 7. Structures of aigialomycin D, angelicoin A and angelicoin B.

Part 1

Total Synthesis of Alkyl Citrate Natural Products

Total Synthesis of Citrafungin A

Total Synthesis of (–)-Trachyspic acid

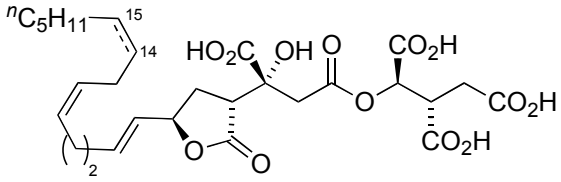
Total Synthesis and Determination of the Absolute Stereochemistry of CJ-13,981 and CJ-13,982

I.1. CITRAFUNGIN A

I.1.1. Introduction

I.1.1.1. Structure and isolation of citrafungin A

In 2004, the Rahway Merck group reported the isolation and structural determination of two novel alkyl citrate natural products, citrafungin A (**23**) and the structurally related citrafungin B (**29**) (Figure 8) from the fermentation broth of fungal sterile mycelium (MF6339) isolated from a cow dung sample in Alaska.[26]

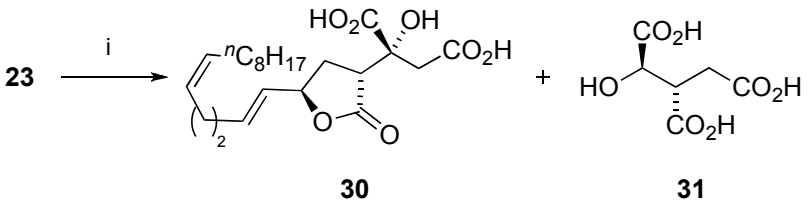


citrafungin A (**23**) (14,15-dihydro)
citrafungin B (**29**) (14,15-*cis*-olefin)

Figure 8. Structures of citrafungins A and B

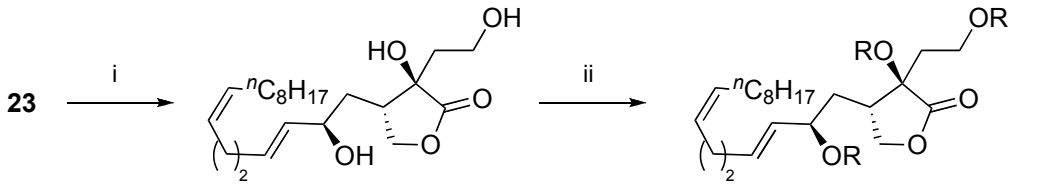
Citrafungins A and B have characteristic structures in which a citric acid moiety, having the γ-lactone attached to a C-14 unsaturated long chain, is connected to an isocitric acid unit. The structure and the absolute configuration of citrafungin A were determined by chemical degradation under basic condition to reveal the citric acid derived lactone **30** and the isocitric acid unit **31** (Scheme 1) and by spectroscopic analysis of Mosher esters **32** and **33** obtained from triol **34** (Scheme 2).

Scheme 1. Degradation of citrafungin A with LiOH.



Reagents and conditions: i) aq. LiOH, THF.

Scheme 2. Reduction of citrafungin A followed by Mosher ester formation.



Reagents and conditions: i) $LiAlH_4$, THF; ii) (*R*)- or (*S*)-MTPACl, NEt_3, CH_2Cl_2.

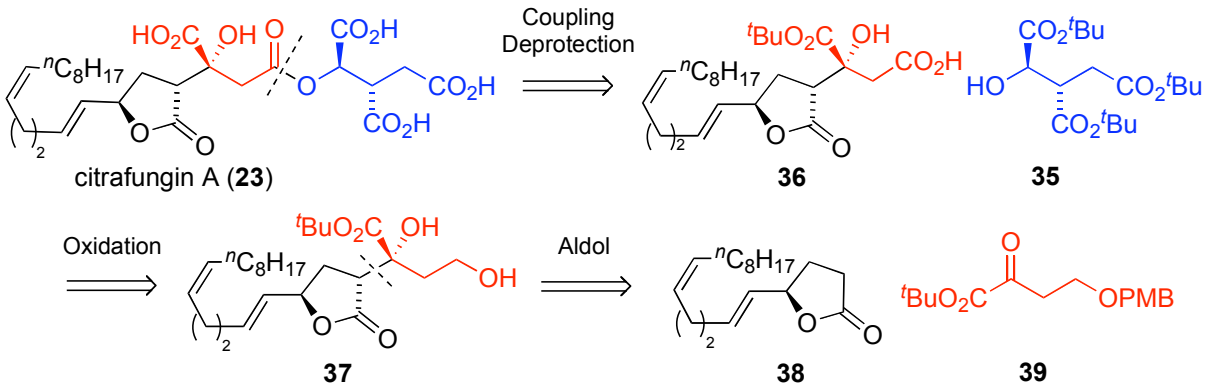
Citrafungins A and B are potent inhibitors of fungal geranylgeranyltransferase I (GGTase I) enzymes, which catalyse the transfer of a terpene side chain to a cysteine residue of the proteins Rho1p and Cdc42p, thereby promoting their membrane localisation and biological activity. Rho1p is a regulatory sub-unit of the crucial enzyme 1,3-β-D-glucan synthase, which is involved in fungal cell wall biosynthesis. Since there are only low levels of homology between fungal and human GGTase I, inhibition of the fungal enzyme is likely to provide novel fungicidal agents of low toxicity.

Citrafungin A inhibits a range of fungal pathogens including strains of *Candida albicans*, *Candida neoformans* and *Aspergillus fumigatus* with MIC values of 0.4–13 μM. It is clear from these results that the citrafungins are intriguing hit structures for the development of new classes of antifungal drugs.

I.1.1.2. First total synthesis of citrafungin A by the Hatakeyama group

In January 2007, the Hatakeyama group reported the first total synthesis of citrafungin A (**23**).[27] In their approach, the alkyl citrate natural product was assembled by a coupling reaction between alcohol **35** and acid **36** obtained by oxidation of alcohol **37**. The quaternary center in **37** was constructed by the aldol condensation between lactone **38** and α-ketoester **39** (Scheme 3).

Scheme 3. Key disconnections in the Hatakeyama total synthesis of citrafungin A.



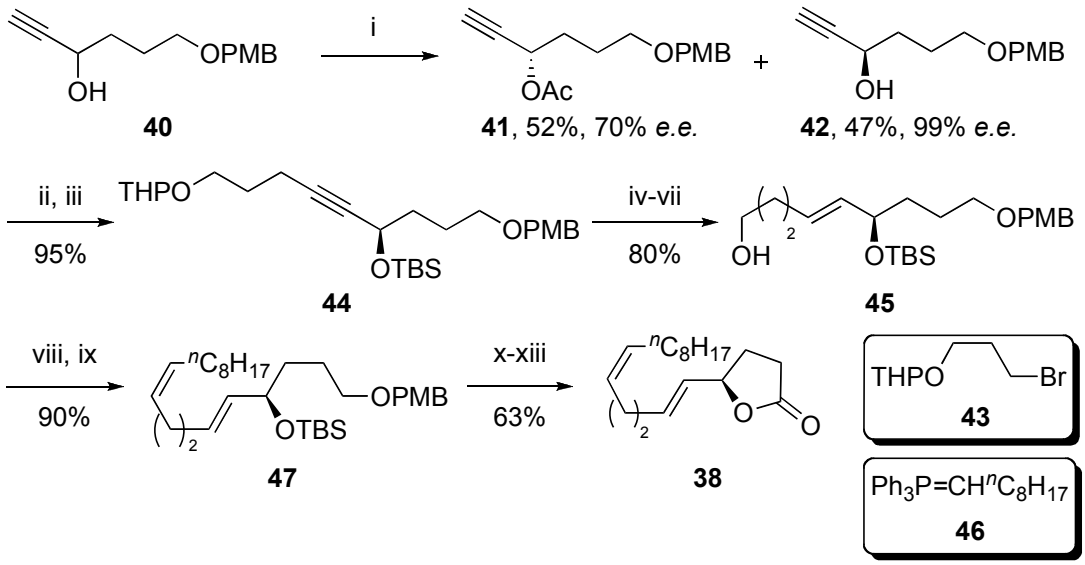
I.1.1.2.1. Synthesis of lactone 38

The introduction of the stereocenter in lactone **38** was realised by a lipase mediated kinetic resolution of racemic propargyl alcohol **40** and afforded (*S*)-acetate **41** (70% *e.e.*) and (*R*)-alcohol **42** (99% *e.e.*) in 52% and 47% yields, respectively.[28] Protection of **42**, followed by alkylation of the terminal acetylene with bromide **43** gave alkyne **44**. Sequential desilylation, Red-Al reduction, reprotection of the alcohol with *tert*-butyl dimethylsilyl chloride and selective removal of the THP group gave (*E*)-alkene **45** in 80%

yield over the sequence (Scheme 4). Swern oxidation[29-33] of **45** followed by Wittig reaction[34-37] using ylide **46** gave selectively the *E*,*Z*-diene **47** in 90% yield. Final deprotection, oxidation and cyclisation steps gave lactone **38** (63%).

The synthesis of lactone **38** required thirteen steps including nine protection/deprotection/oxidation steps in an overall yield of 20%.

Scheme 4. Synthesis of lactone **38**.



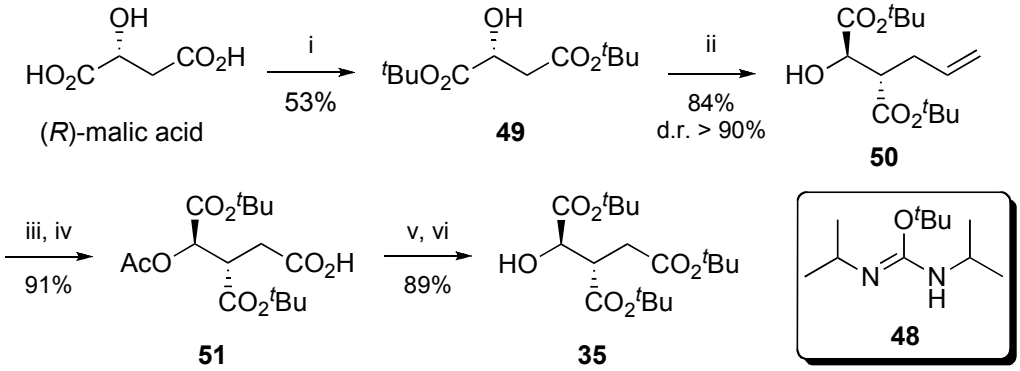
Reagents and conditions: i) Novozyme 435, CH_2=CHOAc, $^{i}Pr_2O$; ii) $^{t}BuMe_2SiCl$, imidazole, DMF; iii) $^{n}BuLi$, **43**, THF-HMPA, –20 °C to RT; iv) Bu_4NF, THF; v) Red-Al, THF, 50 °C; vi) $^{t}BuMe_2SiCl$, imidazole, DMF; vii) PPTS, $^{i}PrOH$, 60 °C; viii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then NEt_3, 0 °C; ix) **46**, THF, 0 °C; x) DDQ, CH_2Cl_2-H_2O; xi) PCC, CH_2Cl_2; xii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^{t}BuOH$-H_2O (5:1); xiii) 47% HF, MeCN-THF.

I.1.1.2.2. Synthesis of alcohol 35

Alcohol **35** was made in 6 steps starting from (*R*)-malic acid. Esterification with *N*,*N*'-di*iso*propyl-*O*-*tert*-butyl-*iso*-urea (**48**)[38] gave ester **49** which was converted to alcohol **50** by a diastereoselective alkylation with allyl bromide.[39-41] Acetate formation and oxidation of

the terminal double bond with *in situ* generated RuO_4 gave carboxylic acid **51** in 41% yield over the four steps (Scheme 5).[42] Esterification of acid **51** with reagent **48** followed by removal of the acetate group by methanolysis gave alcohol **35** in 89% yield over the two steps.

Scheme 5. Synthesis of alcohol **35**.



Reagents and conditions: i) **48**, CH_2Cl_2, reflux, 2 days; ii) LDA, THF, –78 °C then allyl bromide; iii) Ac_2O, DMAP, NEt_3, CH_2Cl_2; iv) $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O (5:5:8); v) **48**, CH_2Cl_2, reflux; vi) K_2CO_3, MeOH.

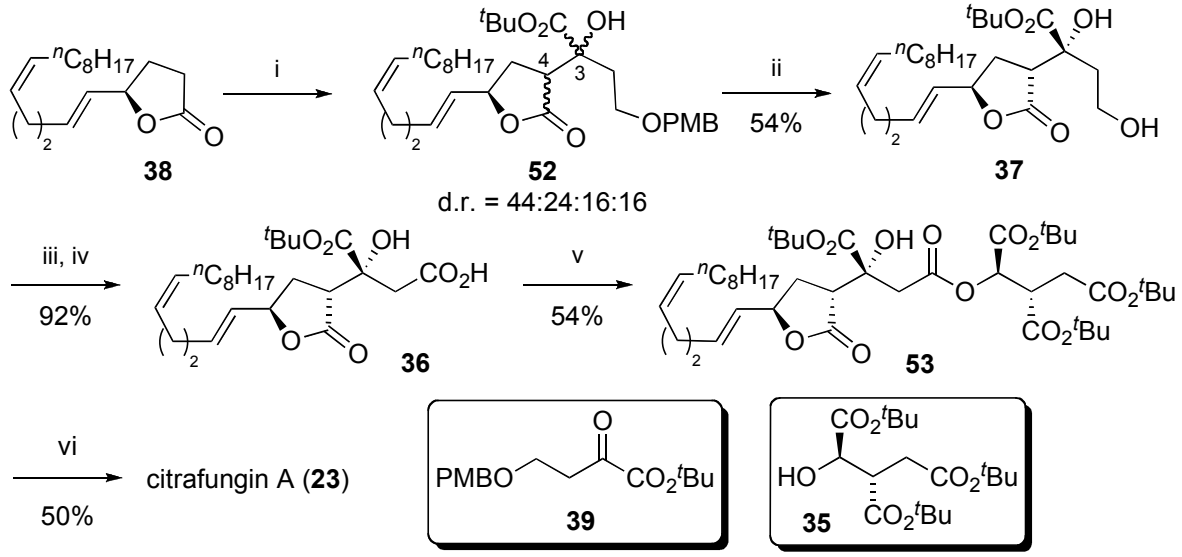
I.1.1.2.3. Aldol and coupling reactions

The main limitation in Hatakeyama's synthesis was the key aldol reaction to construct the C3–C4 bond. Indeed, the aldol reaction between α-ketoester **39** and the lithium enolate of lactone **38** led to a mixture of four diastereoisomers **52** (44:24:16:16), in favour of the desired lactone, which were only separable after deprotection of the *p*-methoxybenzyl group. Only the (3*R*,4*R*)-isomer **37** was kept in 24% yield over the two steps. The stereochemistry at the C4-position of each isomer was unambiguously determined by NOE experiments. PCC oxidation of alcohol **37** followed by Pinnick oxidation[43,44] gave carboxylic acid **36** in 92% yield over the two steps. In the late stages of

the synthesis, the Japanese group used the Keck esterification[45,46] between carboxylic acid **36** and alcohol **35** to form the tetra-*tert*-butyl ester **53** (54%). Final deprotection using trifluoroacetic acid gave citrafungin A (**23**) in a moderate 50% yield due to difficulties in isolation of the tetracarboxylic acid.

Overall, the Hatakeyama synthesis required 19 synthetic steps with an overall yield of 1.2%.

Scheme 6. Synthesis of citrafungin A (**23**) from the Hatakeyama group.



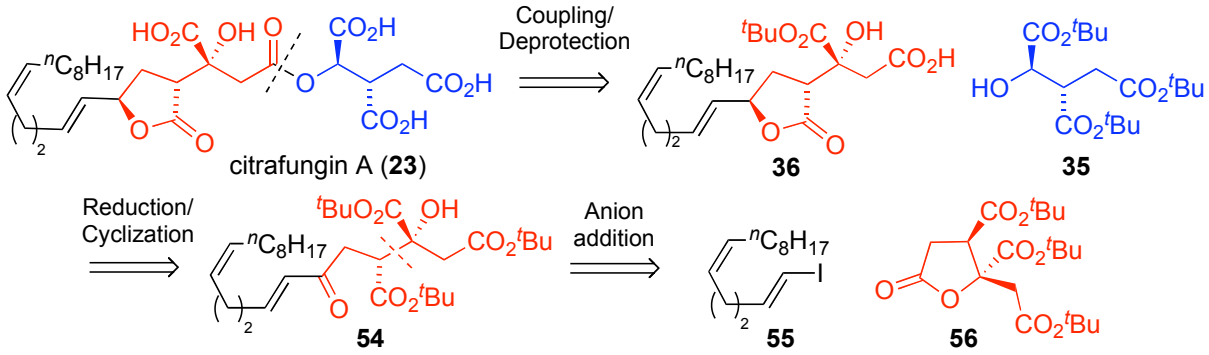
Reagents and conditions: i) LDA, THF, –78 °C then **39**; ii) DDQ, CH_2Cl_2-H_2O; iii) PCC, CH_2Cl_2; iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH-H_2O; v) DCC, DMAP·HCl, **35**; vi) TFA, CH_2Cl_2.

I.1.1.3. Total synthesis of citrafungin A by the Rizzacasa group

More recently, in April 2009, the Rizzacasa group also reported a total synthesis of citrafungin A (**23**).[47] Similarly to the Hatakeyama group, their strategy relied on the coupling between acid **36** and alcohol **35**. Based on previous work done on their enantioselective total synthesis of (–)-trachyspic acid (**24**), key ketone **54** was assembled by the selective anion addition of vinyl iodide **55** to lactone **56** (Scheme 7).[48,49]

The synthesis of lactone **56** is presented in Scheme 65 (*c.f.* formal total synthesis of (–)-trachyspic acid).

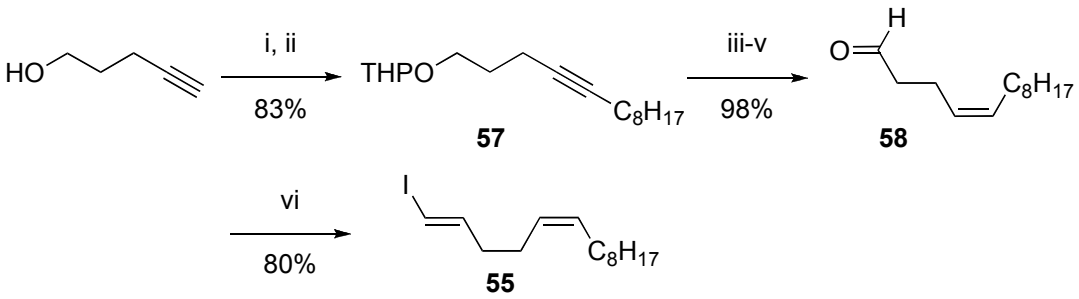
Scheme 7. Key disconnections in the Rizzacasa synthesis.



I.1.1.3.1. Synthesis of vinyl iodide fragment 55

The synthesis of vinyl iodide **55** began with the protection of 4-pentynol with DHP followed by alkylation with 1-bromooctane. Chemoselective reduction of alkyne **57**,[50-53] followed by deprotection and oxidation afforded aldehyde **58** which was converted to vinyl iodide **55** using Takai's conditions (Scheme 8).[54,55]

Scheme 8. Synthesis of vinyl iodide **55**.



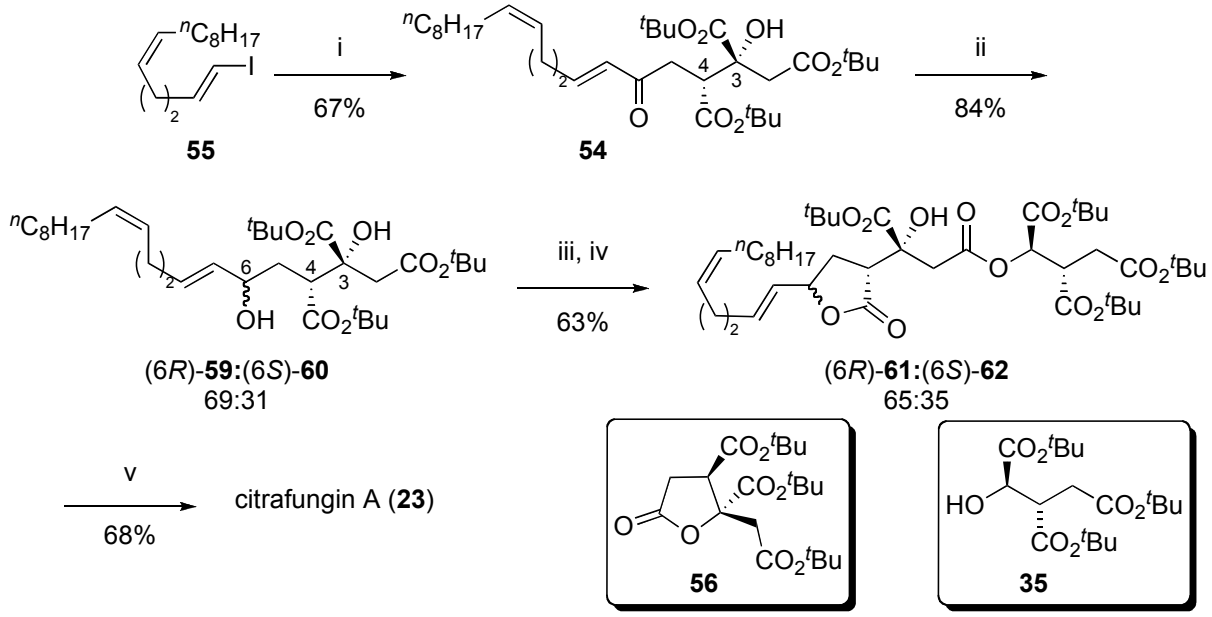
Reagents and conditions: i) DHP, CSA, CH_2Cl_2; ii) LDA, THF-HMPA, 0 °C to RT then 1-bromooctane; iii) P2-Ni, H_2, EDA, EtOH; iv) *p*-TsOH, MeOH; v) DMP, CH_2Cl_2; vi) CHI_3, $CrCl_2$, THF.

I.1.1.3.2. Key anion addition and last steps of the synthesis

Key fragment **54** was formed in good yield (69%) by transmetalation of **55** with ^{t}BuLi followed by the addition of lactone **56**. Reduction of the ketone group in **54**, under Luche's protocol,[56-58] afforded a mixture of allylic alcohols **59** and **60** (69:31) (Scheme 9). Selective γ-lactonisation and concomitant deprotection of the least substituted *tert*-butyl ester gave the carboxylic acids which were immediately converted to the tetra-*tert*-butyl esters **61** and **62** by coupling with alcohol **35**. Final deprotection using TFA gave citrafungin A (**23**) in 68% yield.

The synthesis of the Rizzacasa group was achieved in 11 linear steps from vinyl iodide **55** with an overall yield of 10%, which is a good improvement of the Hatakeyama's synthesis.

Scheme 9. Synthesis of citrafungin A (**23**) from the Rizzacasa group.



Reagents and conditions: i) ^{t}BuLi, Et_2O, –78 ^{o}C then **56**; ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; iii) TFA, CH_2Cl_2, 0 °C to RT; iv) DCC, DMAP, **35**, CH_2Cl_2, RT; v) TFA, CH_2Cl_2, RT.

I.1.1.4. Previous work undertaken in the Barrett group on the alkyl citrate class of natural product: total synthesis of the viridiofungins

The viridiofungins (**63**, **64** and **65**) are a family of potent anti-fungal agents isolated in 1993 by Merck (Figure 9),[59,60] the absolute structure of which was assigned through total synthesis of the trimethyl ester analogue of viridiofungin A.[61]

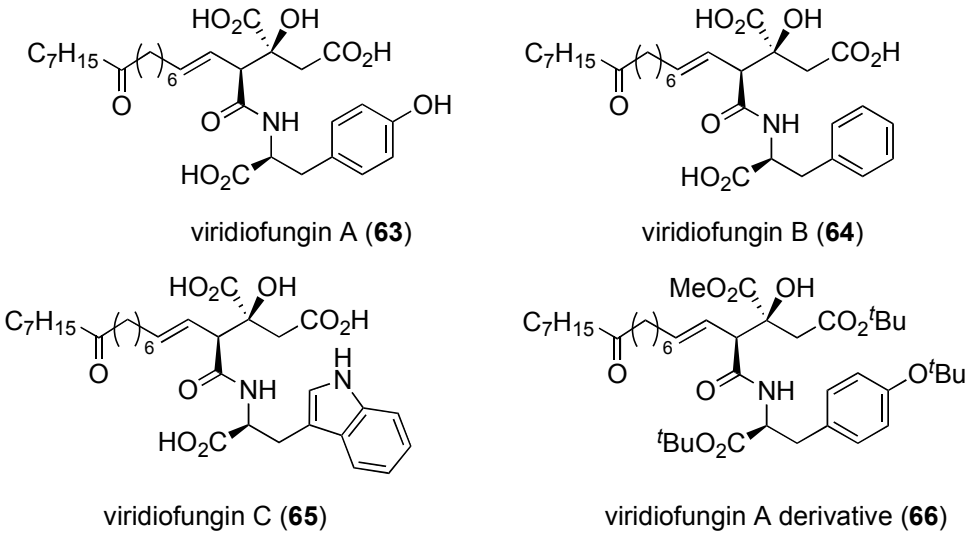
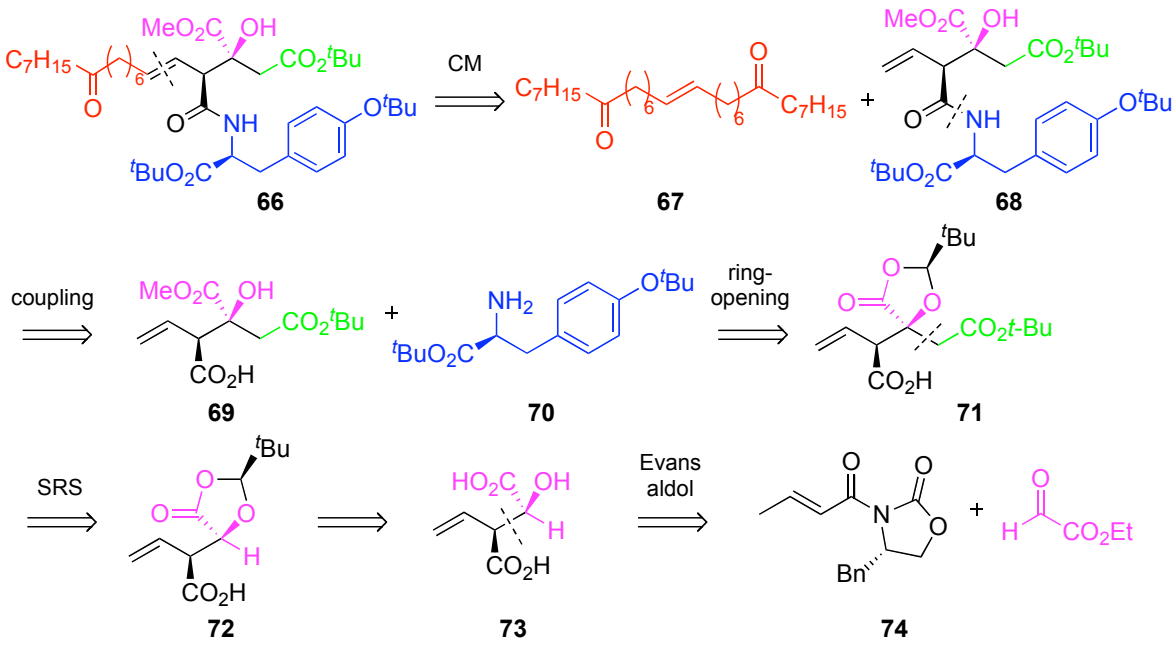


Figure 9. Structures of the viridiofungins and analogue **66**.

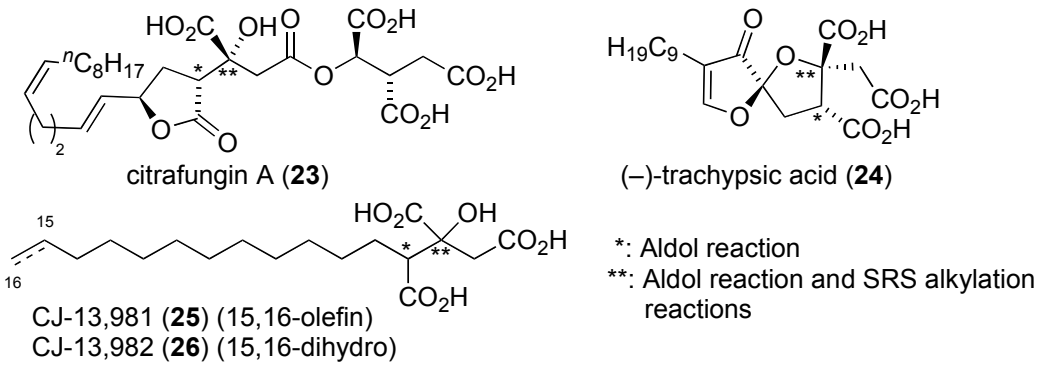
In 2006, the Barrett group reported the total synthesis of the viridiofungin A derivative **66**.[62] The key disconnections consisted of a cross-metathesis reaction between alkenes **67** and **68**, a peptide coupling between carboxylic acid **69** and amide **70**, a Seebach Self-Reproduction or Stereocenter (SRS) alkylation of **72** with *tert*-butyl-bromoacetate to create the quaternary center in **71**. Finally a *syn*-Evans aldol reaction between imide **74** and ethylglyoxylate gave carboxylic acid **73** and built the α-hydroxy acid unit with high diastereomeric excess (Scheme 10).

Scheme 10. Key disconnections for the synthesis of **66**.



The Evans aldol reaction and the Seebach alkylation were the two asymmetric tools that Barrett *et al*. used to create the stereocenters in the viridiofungin A derivative (**66**). As these two methods would also be used for the construction of the stereocenters in citrafungin A, (–)-trachyspic acid, CJ-13,981 and CJ-13,982 (Scheme 11), a short summary of these reactions is described below.

Scheme 11. Construction of the stereocenters in the alkyl citrate natural products.

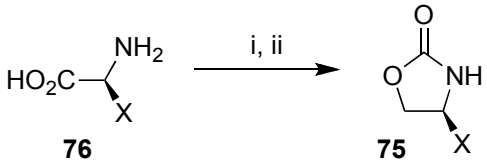


I.1.1.4.1. Brief overview of the aldol reaction using chiral auxiliaries

The aldol reaction is one of the best-known and widely used methods for the generation of carbon-carbon bonds with stereocontrol where chiral auxiliary-mediated processes are probably the most used method for obtaining good stereocontrol.[63,64]

Chiral oxazolidinones **75** (also referred as the "Evans auxiliaries") are readily available in enantiopure form from naturally occurring α-amino acids **76** by reduction and cyclisation (Scheme 12).[65]

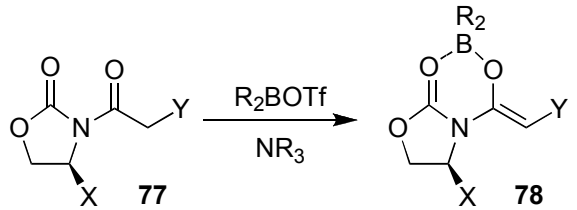
Scheme 12. Synthesis of Evans auxiliaries from α-amino acids.



76 **75**

Reagents and conditions: i) $LiAlH_4$, THF, reflux; ii) diethylcarbonate, K_2CO_3, 80 ºC.

The enolisation of chiral imides such as **77** with dialkyl boron triflates in the presence of a tertiary amine base gives rise, under thermodynamic control, to the corresponding (*Z*)-boron enolates **78** (Figure 10).[66]



77 **78**

Figure 10. Enolisation with dialkylboron triflates.

In 1981, Evans *et al*. reported that the use of boron enolates such as **78** with aldehydes gave a single major *syn*-aldol product, named the "Evans" *syn*-aldol product, with very high diastereoselectivity.[66] The observed diastereoselectivity is rationalised by the Zimmermann–Traxler transition state in which the aldehyde is coordinated by boron (Figure 11). Of the four possible transition states in this model, two, **79** and **80**, place the alkyl substituent of the aldehyde in the preferred equatorial position leading to the two observed diastereoisomers, **81** and **82**, respectively. In major transition state **79**, the oxazolidinone is preferentially oriented to minimise dipole-dipole repulsion giving rise to strong facial selectivity as the large substituent, X, blocks one of the enantiotopic faces of enolate **78**. In minor transition state **80**, the other enantiotopic face of enolate **78** is blocked by X giving rise to **82**. There is a strong preference for transition state **79** and generally a single major isomer is observed with high diastereomeric excess (> 99%).[67]

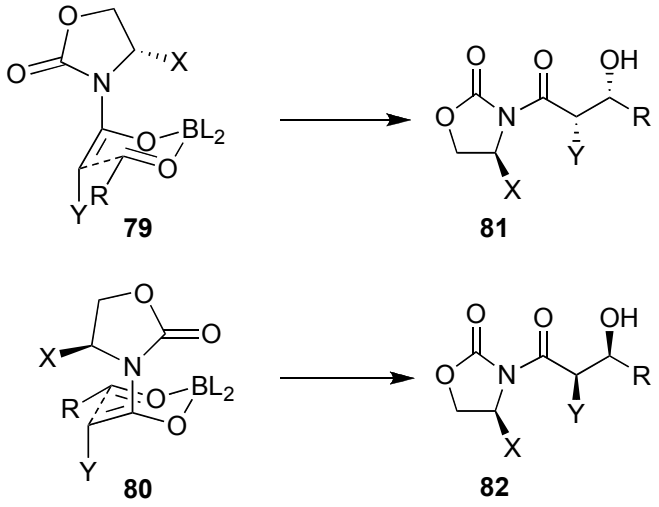


Figure 11. Major transition states in the Evans aldol reaction.

Later, in 1991, Heathcock *et al*. reported that the use of a second Lewis acid in the Evans aldol reaction switches the mechanism from cyclic to acyclic delivery of the enolate

nucleophile.[68] This gives a second *syn* product, which is designated as the "non-Evans" *syn* aldol product (**83**), in the case of small Lewis acids and the "non Evans" *anti* aldol product (**84**) in the case of large Lewis acids (Figure 12). The observed selectivity is rationalised by considering the positioning of the Lewis acid in the transition state with the R-Y repulsion dominating in the case of small Lewis acids (**85**) and the Lewis acid-Y repulsion dominating for larger Lewis acids (**86**). Thus, when $TiCl_4$ is added the "non Evans" *anti* product dominates, while addition of Et_2AlCl results in the "non Evans" *syn* product forming preferentially (Scheme 13).[68]

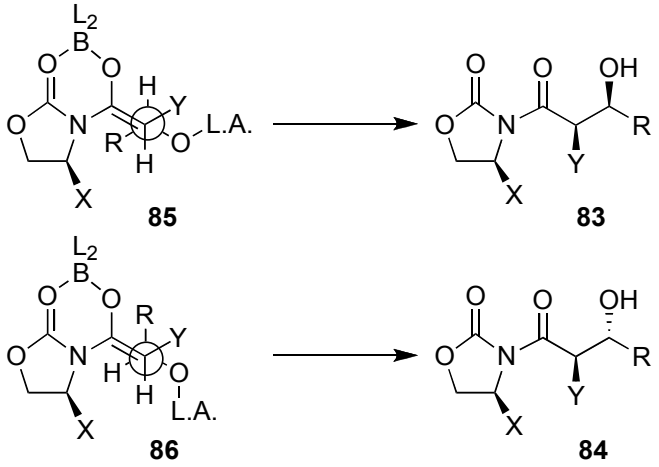
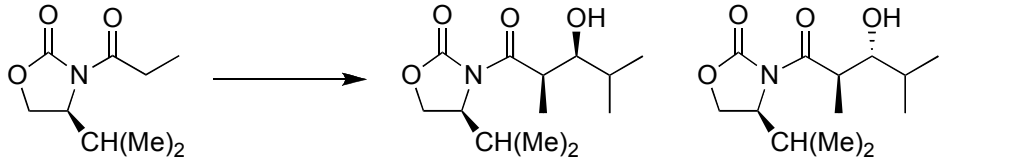


Figure 12. Transition states for Lewis acid mediated boron aldol reactions.

Scheme 13. Use of Lewis acids in Evans aldol reaction



Reagents and conditions: i) $^{n}Bu_2BOTf$, CH_2Cl_2, 0 ºC; $TiCl_4$, –78 ºC; *iso*-butyraldehyde, –78 ºC; ii) $^{n}Bu_2BOTf$, CH_2Cl_2, 0 ºC; *iso*-butyraldehyde, Et_2AlCl, CH_2Cl_2, –78 ºC.

Crimmins *et al*. reported, in 1997, the use of $TiCl_4$ with imides derived from oxazolidinones or the related oxazolidinethiones to allow the preparation of either the "Evans" *syn* (**87**) or "non-Evans" *syn* (**88**) product depending on the number of equivalents of Lewis acid and base employed.[67] The switch in diastereoselectivity in this case is attributed from dipole-controlled orientation of the auxiliary (**89**) to chelated orientation (**90**) allowed by abstraction of a chloride from the titanium center by the excess of Lewis acid (Figure 13).

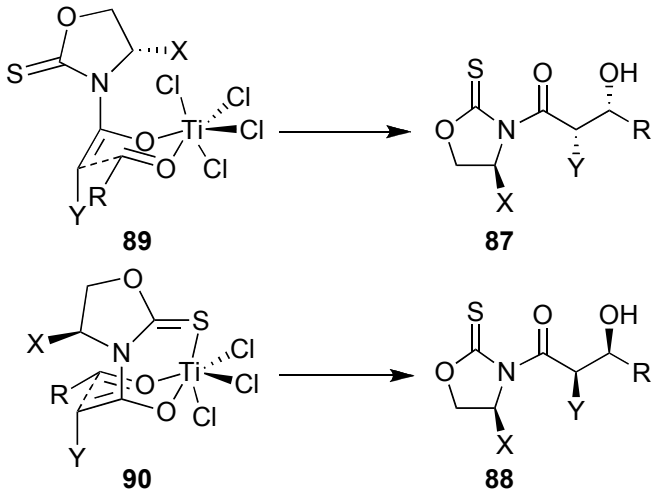
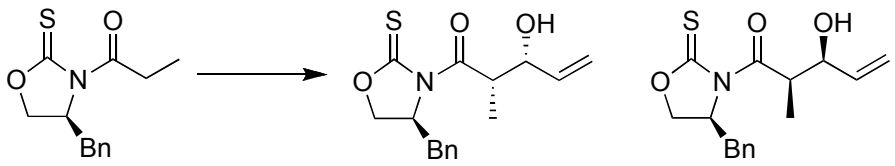


Figure 13. Stereoselectivity in $TiCl_4$ mediated aldol reactions.

Thus, use of one equivalent of $TiCl_4$ results in the expected "Evans" *syn* (**91**) product, while addition of a second equivalent of $TiCl_4$ gives rise to the "non Evans" *syn* (**92**) diastereoisomer (Scheme 14).

Scheme 14. Example in the use of $TiCl_4$ in Evans aldol reactions.

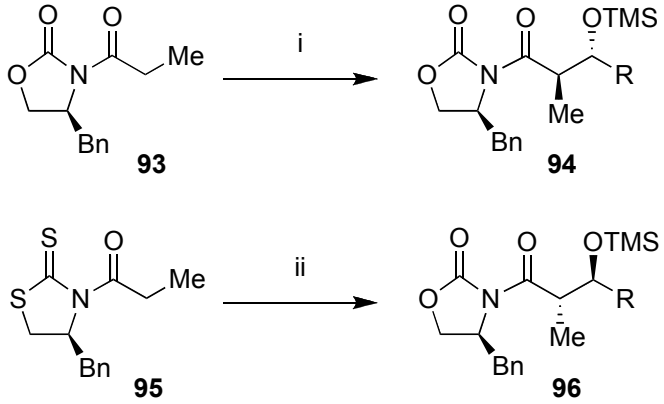


i	98.9	:	1.1	80%
ii	0.7	:	99.3	44%

Reagents and conditions: i) 1.0 equiv of $TiCl_4$, (–)-sparteine, CH_2Cl_2, 0 ºC, propenal, 0 ºC; ii) 2.0 equiv of $TiCl_4$, DIPEA, CH_2Cl_2, 0 ºC; propenal, 0 ºC.

More recently, Evans *et al*. developed an auxiliary-mediated aldol reactions requiring catalytic amount of a magnesium salt. *N*-acyloxazolidinones **93** gave the *anti*-product **94** whereas *N*-acylthiazolidinethiones **95** gave the other *anti*-aldol product **96** (Scheme 15).[69,70]

Scheme 15. Selective formation of *anti*-aldol products.

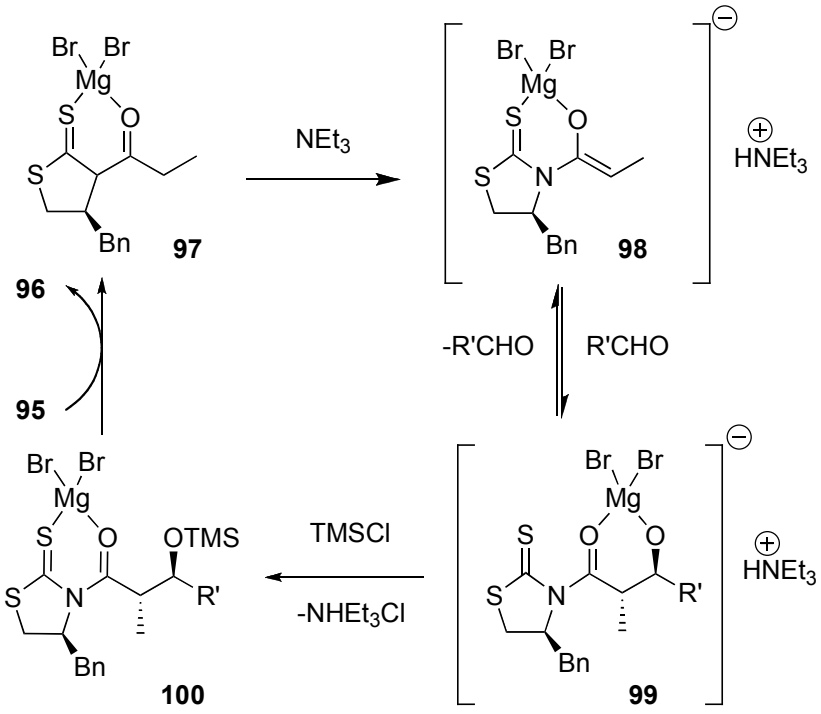


Reagents and conditions: i) cat. $MgCl_2$, NEt_3, TMSCl, RCHO, EtOAc, RT; ii) cat. $MgBr_2{\cdot}OEt_2$, NEt_3, TMSCl, RCHO, EtOAc, RT.

They demonstrated that this process does not proceed through a Mukaiyama aldol pathway, as the enolsilane of **93** or **95** are not formed under the reaction conditions. Furthermore, it was also demonstrated that independently prepared enolsilane of **93** does

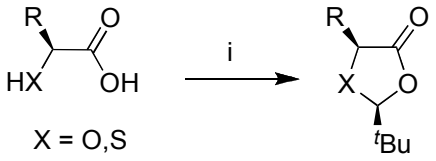
not react with benzaldehyde under $MgCl_2$ catalysis. A proposed catalytic cycle is outlined in Scheme 16. Thiazolidinethione-magnesium complex **97** reacts with triethylamine, yielding magnesium enolate **98**, which adds reversibly to the aldehyde, forming the magnesium aldolate **99**. Chlorotrimethylsilane then irreversibly traps this aldolate to form **100**, which is subsequently displaced from the metal center by another molecule of *N*-acylthiazolidinethione **95** to form the *anti*-aldol product **96**.

Scheme 16. Proposed catalytic cycle by Evans *et al*.



I.1.1.4.2. The Seebach Self-Regeneration of Stereocenter: formation, alkylation and opening of the dioxolanone ring

In 1983 Seebach and co-workers described the diastereoselective cyclisation of chiral α-hydroxy and α-mercapto acids with pivaldehyde to give either the 2-*tert*-butyl-4-substituted-1,3-dioxolanones or the corresponding 1,3-oxathiolanones (Table 2) usually in favour of the *syn*-isomer which can be isolated by recrystallisation.[71]

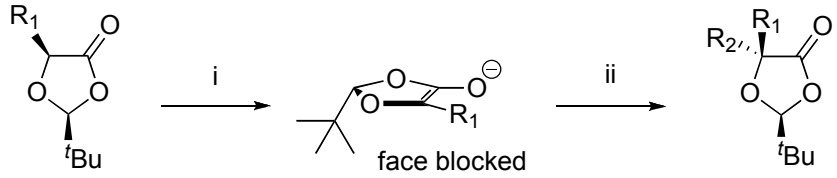


Reagents and conditions: i) Pivaldehyde, *p*-TsOH, H_2SO_4, Pentane, Dean-Stark, reflux.

Entry	R	X	Yield (%)	*d.r.* (*syn*:*anti*)
1	Me	O	93	4:1
2	Bn	O	87	5:1
3	^{i}Pr	O	82	20:1
4	Ph	O	50	5:1
5	CH_2CO_2H	O	95	50:1
6	Me	S	92	2.5:1
7	CH_2CO_2H	S	72	1:1

Table 2. Examples of dioxolanone ring-formation.

The original stereocenter in **101** is then destroyed by using a strong base such as LHMDS to form a trigonal carbon (**102**) which is chiral due to the stereogenic center of the acetal. The approach of the electrophile (R_2–X) is controlled by the *tert*-butyl substituent shielding one face of the enolate to form dioxolanone **103**. The reaction proceeds with good diastereoselectivity under the influence of this temporary stereogenic center with overall retention of stereochemistry (Table 3).[71-73]



101 **102** **103**

Reagents and conditions: i) LDA or LHMDS, THF, –78 ºC; ii) R^2-X, –30 ºC to –15 ºC.

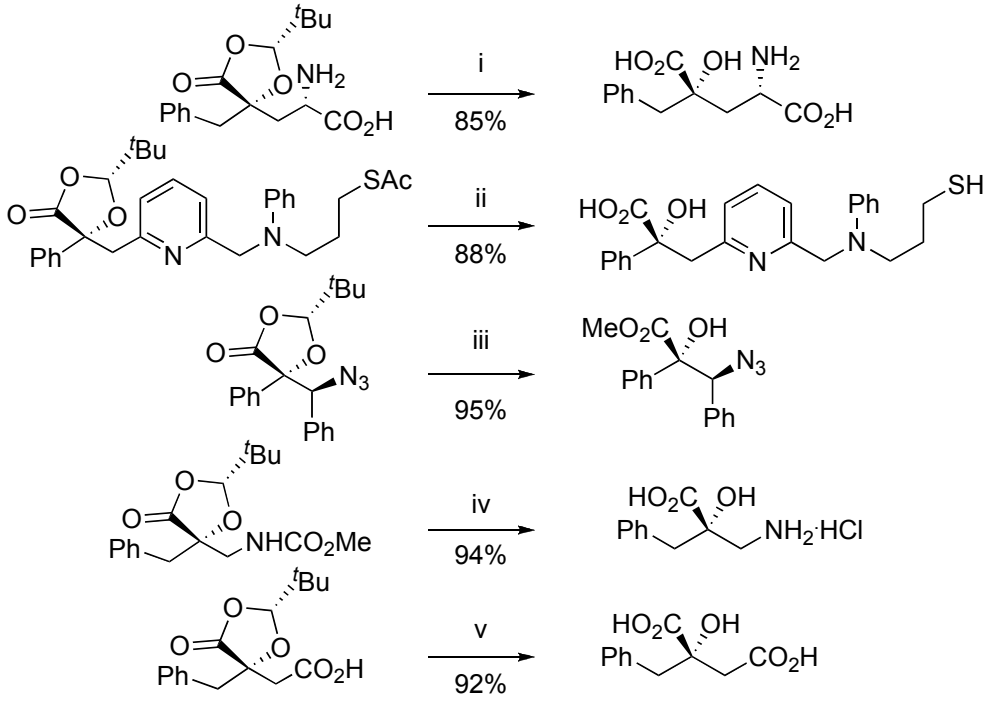
Entry	R^1	R^2-X	Yield (%)	*d.e.* (%)
1	Me	Et-I	82	97
2	Me	CH_2=$CHCH_2Br$	77	96
3	Me	BnBr	81	95
4	Bn	EtI	45	>95
5	Bn	^{n}PrI	40	>95
6	Bn	CH_2=$CHCH_2Br$	40	>95
7	CH_2CO_2H	MeI	79	>95
8	CH_2CO_2H	CH_2=$CHCH_2Br$	76	>95
9	CH_2CO_2H	BnBr	77	>95

Table 3. Seebach SRS alkylation of dioxolanones.

The most commonly reagent used for the acetalisation step is pivaldehyde and thus for several reasons: the bulky ^{t}Bu group results in particularly high diastereoselectivity in the acetalisation step with usually good yields. It also leads to high diastereoselectivities in subsequent reactions at the trigonal center. Since the ^{1}H NMR signal of the ^{t}Bu group is one sharp singlet, it does not overlap with signals in large areas of the spectrum and serves as a reference in ^{1}H NMR analysis of the crude product. Finally, pivaldehyde is available on large scale and can be easily removed (b.p.: 74 ^{o}C).

The opening of the dioxolanone ring is usually done using harsh conditions such as strong acidic or basic aqueous solutions. Some examples are shown in Scheme 17.[74-79]

Scheme 17. Examples of dioxolanones opening.

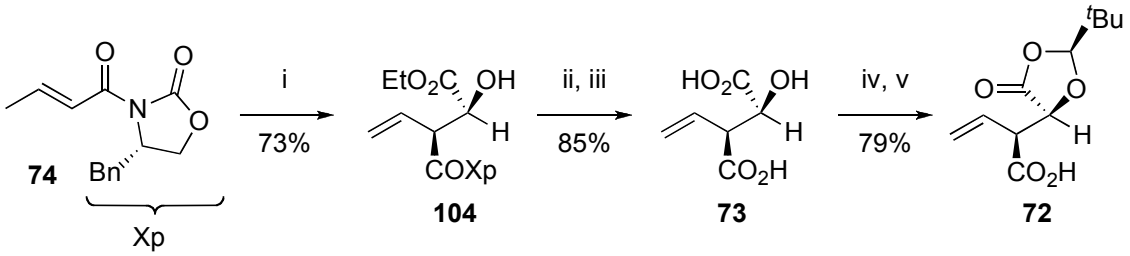


Reagents and conditions: i) 0.1 M HCl, HCO_2H, reflux, ii) LiOH, H_2O-THF, reflux; iii) NaOMe, MeOH, RT; iv) 6 M HCl, sealed tube, 120 ^{o}C; v) 50% TFA, 95 ^{o}C.

I.1.1.4.3. Synthesis of dioxolanone 72

The asymmetric aldol reaction of chiral oxazolidinone **74** with ethyl glyoxylate allowed the formation of secondary alcohol **104** as a single diastereoisomer (Scheme 18). Double saponification, to remove the chiral auxiliary and to convert the ethyl ester to the carboxylic acid, gave diacid **73** which was converted to dioxolanone **72**, exclusively as the *cis*-isomer, using Hoye's modified protocol.[80]

Scheme 18. Synthesis of dioxolanone **72**.



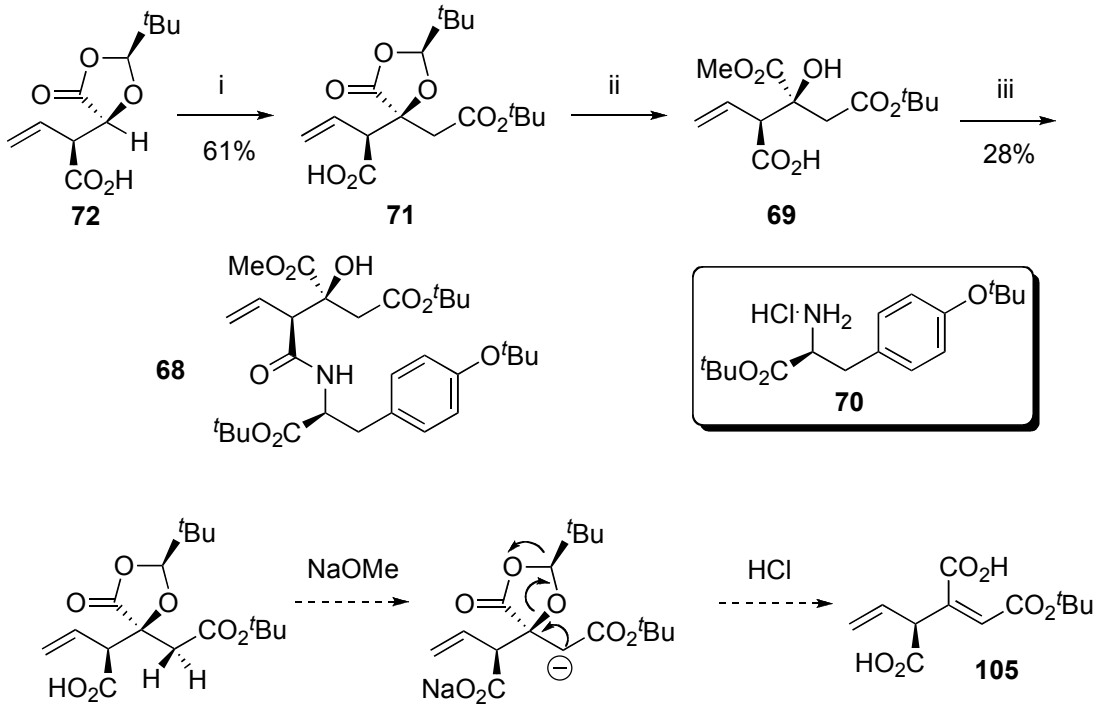
Reagents and conditions: i) $^{n}Bu_2BOTf$, NEt_3, CH_2Cl_2, –78 ºC to 0 ºC then ethyl glyoxylate, –78 ºC to 0 ºC; ii) LiOH, H_2O_2, THF-H_2O (3:1), 0 ºC; iii) LiOH, MeOH-H_2O (1:1), 0 ºC to 25 ºC; iv) TMSCl, DIPEA, THF, RT; v) Pivaldehyde, TMSOTf (20 mol %), CH_2Cl_2, –35 ºC.

I.1.1.4.4. Synthesis of amide 68 *via* a Seebach SRS alkylation reaction

The previous work undertaken in the Barrett group demonstrated that the alkylation of dioxolanone **72** with retention (or regeneration) of stereocenter worked best in dry DMF using LHMDS as a base and *tert*-butyl bromoacetate as the electrophile. This method enabled the construction of the quaternary center and dioxolanone **71** was isolated as a single diastereoisomer (Scheme 19). The dioxolanone ring was then opened using K_2CO_3 and MeOH to afford methyl ester **69**. Final peptide coupling between carboxylic acid **69**

and amine **70** gave key amide **68** in 28% yield over the two steps. The disappointing yield could be explained by the elimination reaction forming alkene by-product **105** (Scheme 19).[62]

Scheme 19. Synthesis of amide **68**.



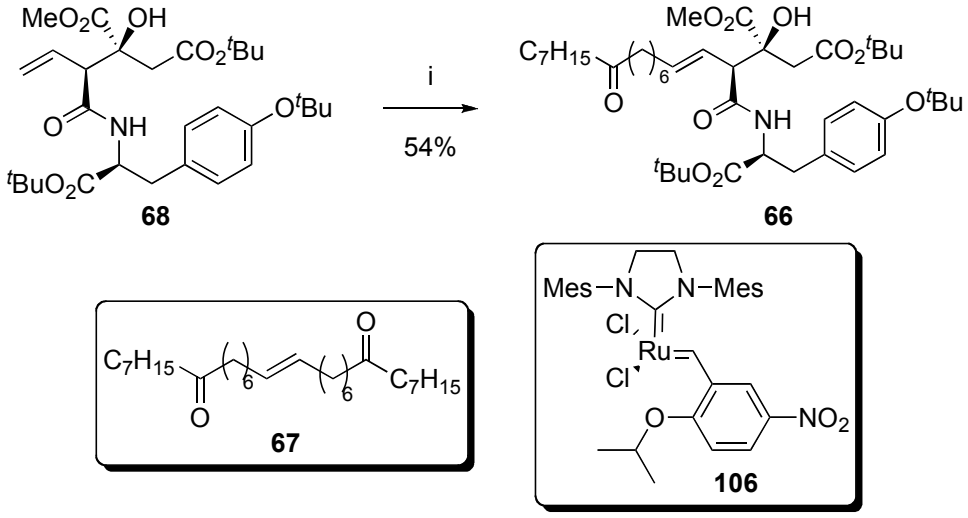
Reagents and conditions: i) LHMDS, DMF, –70 ºC then BrAcO^tBu, –70 ºC; ii) K_2CO_3, MeOH, 0 ºC; iii) **70**, HOBT, HBTU, NEt_3, DMF, 0 ºC.

M. Sefkow also reported the decomposition of a similar dioxolanone under basic condition using the same decomposition pathway. They found that the elimination was very fast and even occurred at very low temperature.[72]

I.1.1.4.5. Synthesis of 66 by cross-metathesis reaction

The geometrically selective alkene cross-metathesis reaction,[81-84] one of the key C-C bond forming steps in this synthesis, was performed between vinyl amide **68** and alkene partner **67** using Grela's catalyst **106** (Scheme 20). Previous work in the group demonstrated that only this catalyst was efficient to perform the cross-metathesis reaction with high conversion. It enabled the formation of the viridiofungin A derivative **66** in 54% yield (95% conversion by crude ^{1}H NMR).[62]

Scheme 20. Synthesis of viridiofungin A derivative **66**.



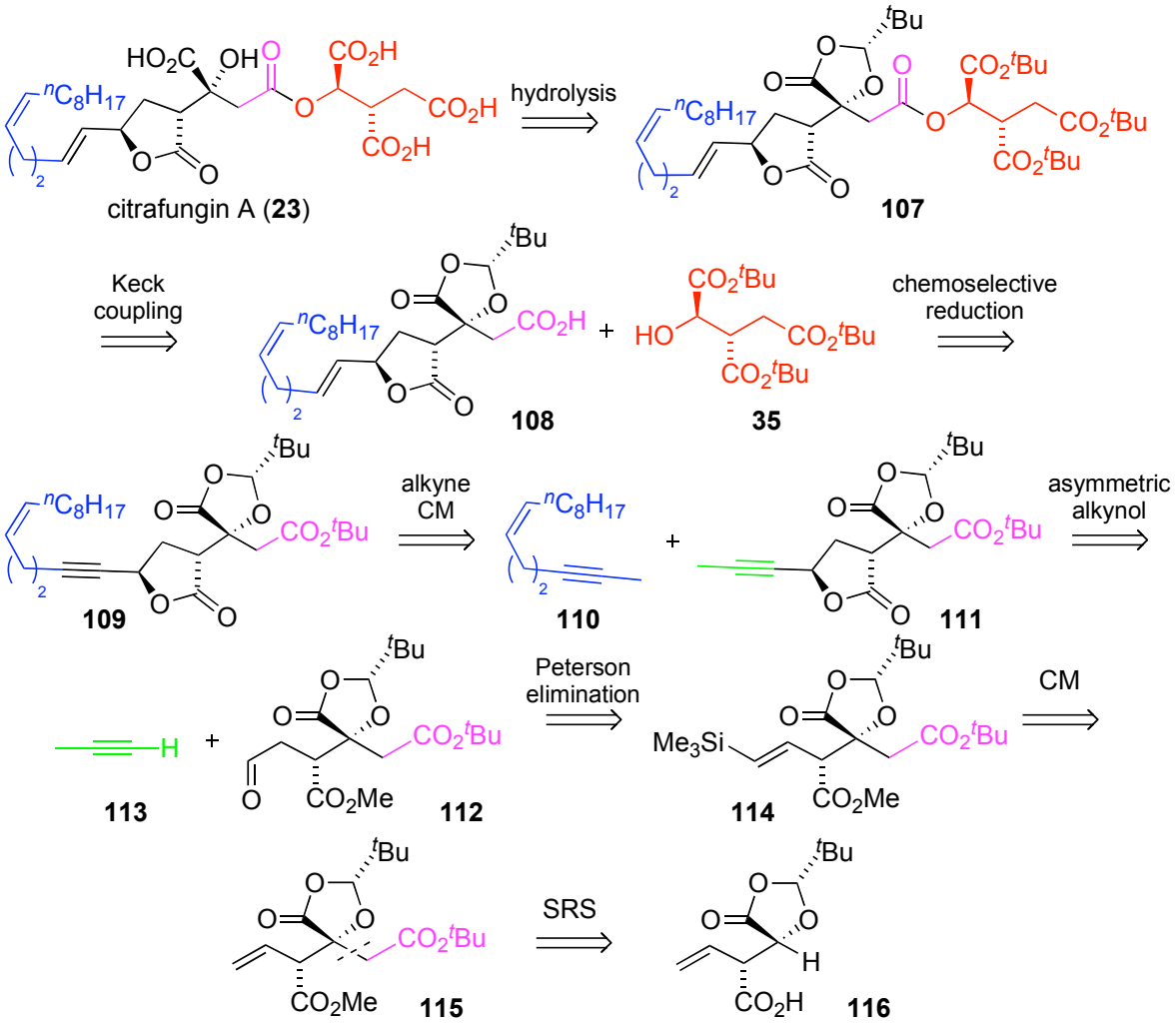
Reagents and conditions: i) **67**, **106** (20 mol %), CH_2Cl_2, microwave.

I.1.1.5. Proposed retrosynthetic analysis for the citrafungin A (23)

The retrosynthetic analysis of citrafungin A is shown in Scheme 21. Citrafungin A (**23**) could be obtained from fully protected ester **107** by hydrolysis of both the *tert*-butyl esters

and the dioxolanone ring. In turn, ester **107** could be synthesised by a Keck esterification between alcohol **35** and carboxylic acid **108** made by a *trans* hydrosilylation-desilylation sequence of alkyne **109**,[85,86] followed by *tert*-butyl ester deprotection. Fürstner tungsten-catalysed cross alkyne-alkyne metathesis of acetylene **110** with alkyne **111** should provide the exchanged enyne **109**.[87,88] Carreira homologation of aldehyde **112** with methyl acetylene **113** should provide the corresponding alkynol,[89] which would readily undergo cyclisation to provide the γ-lactone **111**. In turn, aldehyde **112** could be synthesised by a Peterson elimination reaction (under acidic condition) of the corresponding diol made from vinyltrimethylsilane derivative **114** by hydrosilylation (Scheme 21). Alkene **114** would be synthesised by a cross-metathesis reaction between vinyltrimethylsilane and dioxolanone **115** using the conditions shown in Scheme 20. Dioxolanone **116**, enantiomer of **72**, would be assembled in a similar way (*c.f.* Scheme 18).

Scheme 21. Retrosynthetic analysis.



I.1.2. Studies towards the total synthesis of citrafungin *via* the late stage opening of dioxolanone 107

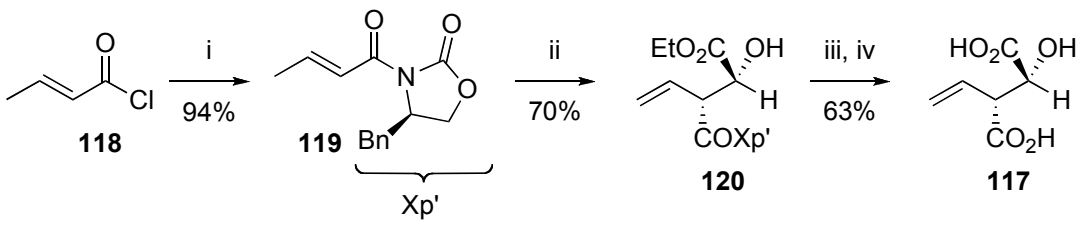
I.1.2.1. Studies towards the synthesis of aldehyde 112 *via* vinylsilane 114

Based on the citrafungin A retrosynthetic analysis (Scheme 21), the first objective was to synthesize dioxolanone **116** by the route employed for the total synthesis of viridiofungin derivative **66**. To introduce the desired stereochemistry, the opposite chiral auxiliary was used.

I.1.2.1.1. Synthesis of α-hydroxy acid 117

Commercially available *trans*-crotonyl chloride **118** was converted into the acyl-oxazolidinone **119** by reaction with (*R*)-4-benzyl-*N*-lithio-2-oxazolidinone at –78 ºC (Scheme 22). Evans *syn*-selective aldol reaction using di-*n*-butylboron triflate, triethylamine and freshly distilled glyoxylic ester gave alcohol **120** in 75% yield with excellent diastereoselectivity (*d.r.* > 99%).[66,69,70] Subsequent cleavage of the auxiliary followed by hydrolysis of the ethyl ester afforded (2*R*,3*R*)-3-vinyl malic acid **117** in 42% overall yield.

Scheme 22. Synthesis of (2*R*,3*R*) 3-vinyl malic acid **117**.

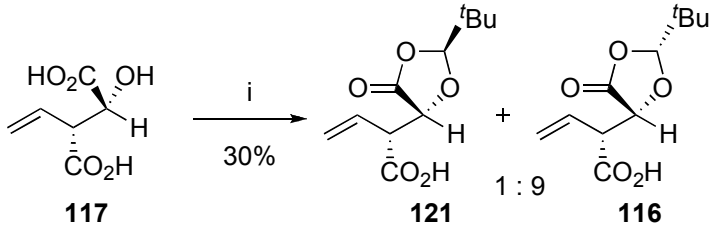


Reagents and conditions: i) ^{n}BuLi, (*R*)-4-benzyl-oxazolidinone then **118**; ii) $^{n}Bu_2BOTf$, NEt_3, CH_2Cl_2, –78 ºC to 0 ºC then ethyl glyoxylate, –78 ºC to 0 ºC; iii) LiOH, H_2O_2, THF-H_2O (3:1), 0 ºC; iv) LiOH, MeOH-H_2O (1:1), 0 ºC to RT.

I.1.2.1.2. Dioxolanone 116 formation: synthesis and optimisation

The synthesis of (2*R*,3*R*) 3-vinyl malic acid **117** being accomplished, our interest was then focused on the formation of dioxolanone **116**. Standard *p*-TsOH catalysed condensation of dicarboxylic acid **117** with pivaldehyde led to the formation of dioxolanones **121** and **116** in 30% yield and as a 9:1 mixture of diastereoisomers in favour of the desired *cis*-product **116** (Scheme 23).[62,71]

Scheme 23. Dioxolanone synthesis using standard conditions.

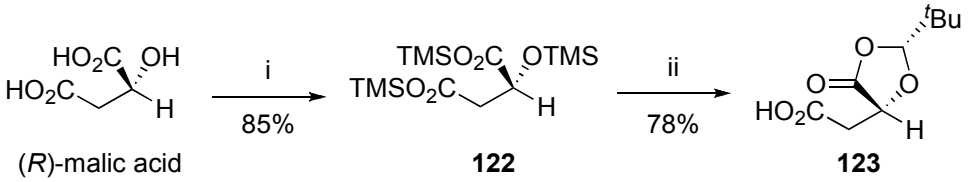


Reagents and conditions: i) Pivaldehyde, *p*-TsOH (30 mol %), pentane, Dean-Stark, reflux.

A similar diastereoselectivity issue was faced by Hoye *et al.* and was overcome by forming the *per*-TMS derivative **122** starting from (*R*)-malic acid. Subsequent cyclisation

using catalytic TMSOTf and pivaldehyde afforded the *cis*-dioxolanone **123** exclusively (Scheme 24).[80]

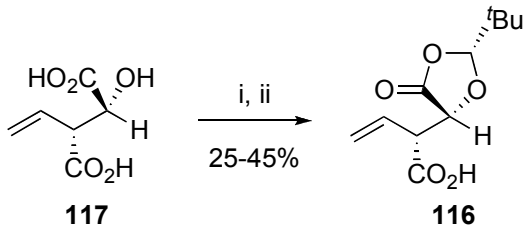
Scheme 24. Hoye's protocol to form *cis*-dioxolanone **123**.



Reagents and conditions: i) TMSCl, DIPEA, THF, RT; ii) Pivaldehyde, TMSOTf (20 mol %), CH_2Cl_2, –35 ºC.

When applied to diacid **117**, this two steps acetalisation procedure led to dioxolanone **116** as a single diastereoisomer in low to moderate yield varying from 20 to 45% (Scheme 25).

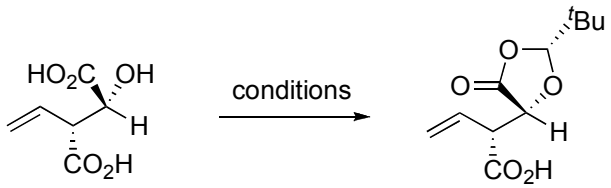
Scheme 25. Hoye's dioxolanone formation applied to diacid **116**.



Reagents and conditions: i) TMSCl, DIPEA, THF, RT; ii) Pivaldehyde, TMSOTf (20 mol %), CH_2Cl_2, –35 ºC.

Due to the limitations of this method (air-sensitivity and stability of the *per*-TMS intermediate), various reaction conditions were screened to improve the yield including variation of solvents and equivalent of reagents. The results are summarised in Table 4. No conversion was observed when chloroform was used (entry 1). Adding THF increased the yield of the reaction by improving the solubility of the α-hydroxy acid (entry 3).

Changing the solvent mixture from pentane:THF (10:1) to hexane:THF (10:1) increased the yield as this new mixture has a higher boiling point. The yield was further increased to 85% by adding more pivaldehyde (entry 5).



117 **116**

Entry	Solvent	*p*-TsOH[a]	Pivaldehyde[b]	Yield
1	Chloroform	0.3	2.5	-
2	Pentane	0.3	2.5	30%
3	Pentane:THF (10:1)	0.3	2.5	55%
4	Hexane:THF (10:1)	0.3	2.5	65%
5	Hexane:THF (10:1)	0.3	5	85%

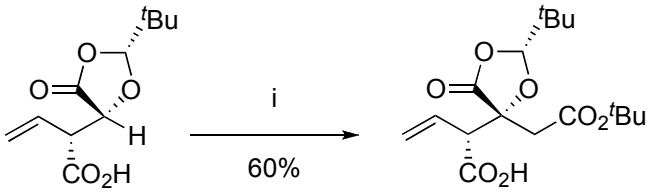
[a]equivalent of *p*-TsOH; [b]equivalent of pivaldehyde.

Table 4. Optimisation of the acetalisation step.

I.1.2.1.3. Seebach SRS alkylation of 116

The Seebach SRS alkylation reaction of dioxolanone **116** with *tert*-butyl bromoacetate worked well and gave dioxolanone **124** in 60% yield with a *d.e.* > 95% (Scheme 26).[62]

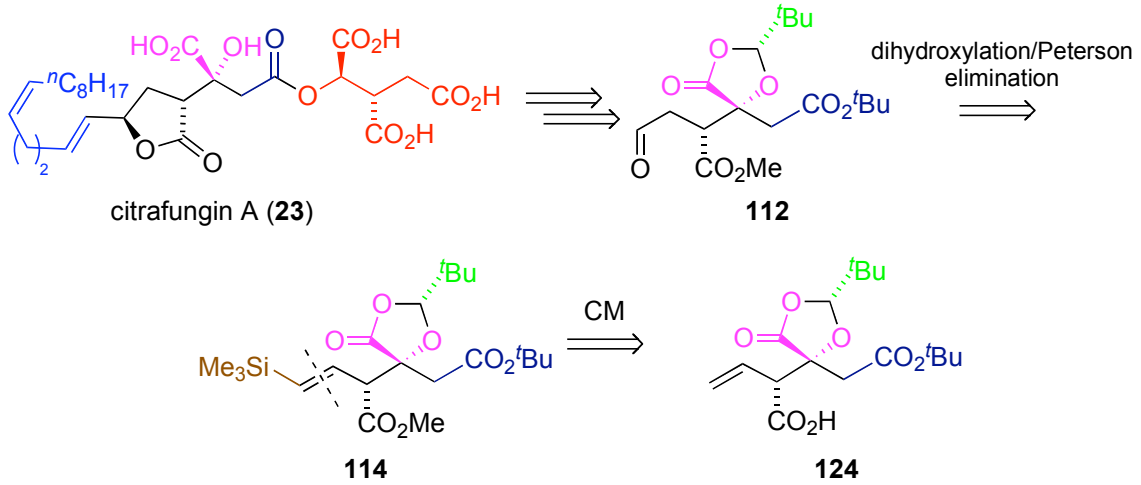
Scheme 26. Alkylation of dioxolanone **116** with *tert*-butyl bromoacetate.



116 **124**

Reagents and conditions: i) 2 eq. LHMDS, DMF, –70 ºC then $BrCH_2CO_2{}^tBu$, –70 ºC.

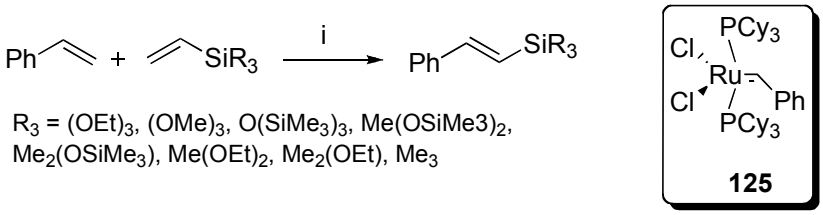
Overall, the synthesis of key dioxolanone **124** was achieved in 7 steps with 21% yield. The major improvement was achieved during the acetalisation step. Using *p*-TsOH and a 10:1 mixture of hexane:THF resulted in formation of dioxolanone **116** as a single diastereoisomer. Having made sufficient quantity of dioxolanone **124**, the key cross-metathesis reaction with vinyltrimethylsilane was then studied to obtain aldehyde **112**.



I.1.2.1.4. Attempted vinylsilane 114 formation

In 2000, Fisher *et al.* reported that the cross-metathesis reaction at room temperature of vinysilanes with styrene, catalysed by the Grubbs I catalyst (**125**), gave (*E*)-silylstyrene with high conversion (Scheme 27).[90]

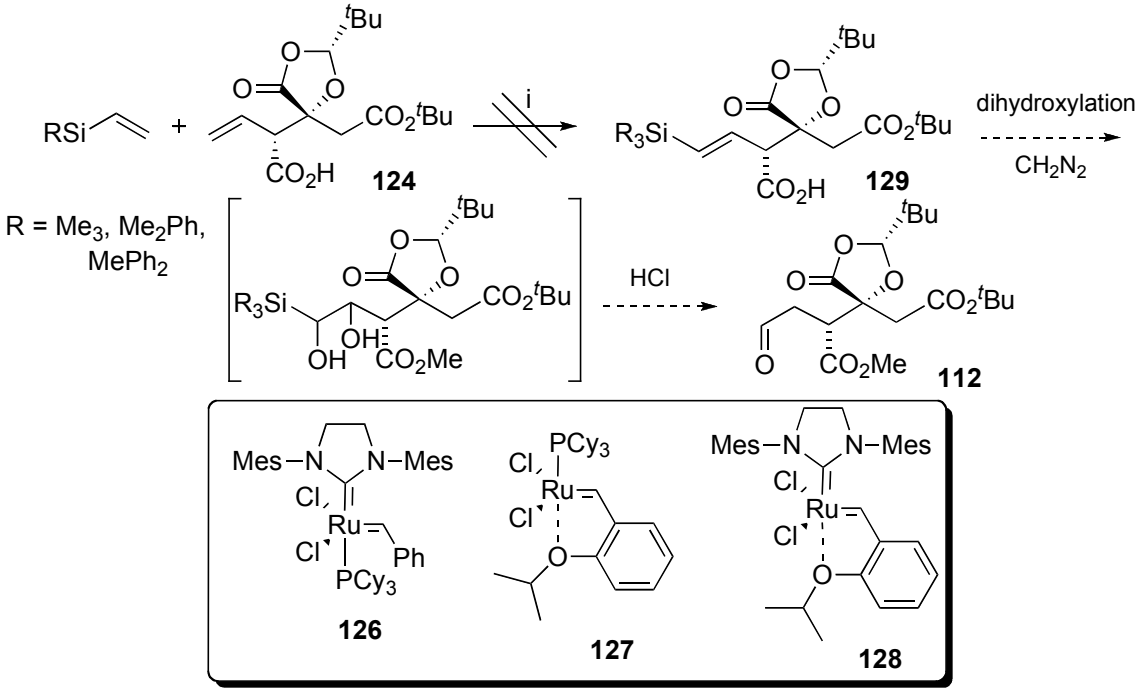
Scheme 27. Cross-metathesis reaction using vinylsilanes.



Reagents and conditions: i) **125** (20-100 mol %), benzene, RT, 6 h.

The cross-metathesis reaction of alkene **124** with a range of vinylsilanes was investigated using either the Grubbs or the Hoveyda–Grubbs catalysts (**125**-**128**). The choice of vinylsilanes was based on the Peterson elimination reaction where trimethylsilyl, dimethylphenylsilyl or diphenylmethylsilyl groups are usually suitable substrates for this transformation (Scheme 28).

Scheme 28. Proposed cross-metathesis and Peterson elimination reactions.

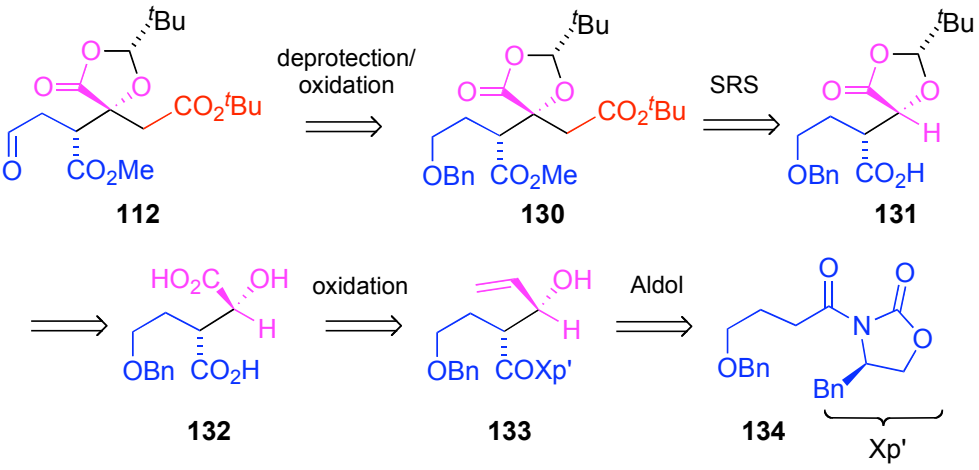


Reagents and conditions: i) catalyst (20-100 mol %), solvent, temperature.

Unfortunately, every attempt to obtain alkene **129** by cross-metathesis reaction of alkene **123** with different vinylsilanes failed. Variation of solvent (CH_2Cl_2, PhMe), temperature (RT, reflux either thermal or under microwave irradiation), concentration (0.15 to 1.5 $mol.L^{-1}$), catalyst (**125-128**) or catalyst loading (20 to 100 mol %) did not improve the reactivity and only the starting material **124** was observed by crude ^1H NMR.

The failure of this reaction led to the development of a new retrosynthetic analysis without the need of a cross-metathesis reaction where aldehyde **112** would be made by a deprotection-oxidation sequence of benzyl protected alcohol **130**. Alcohol **130** would be synthesised similarly to dioxolanone **123**, using a Seebach SRS alkylation of dioxolanone **131**. In turn dioxolanone **131** would be obtained from α-hydroxy acid **132** by oxidation of alkene **133** and Evans aldol reaction of imide **134** with propenal (Scheme 29).

Scheme 29. New retrosynthetic analysis for aldehyde **112**.



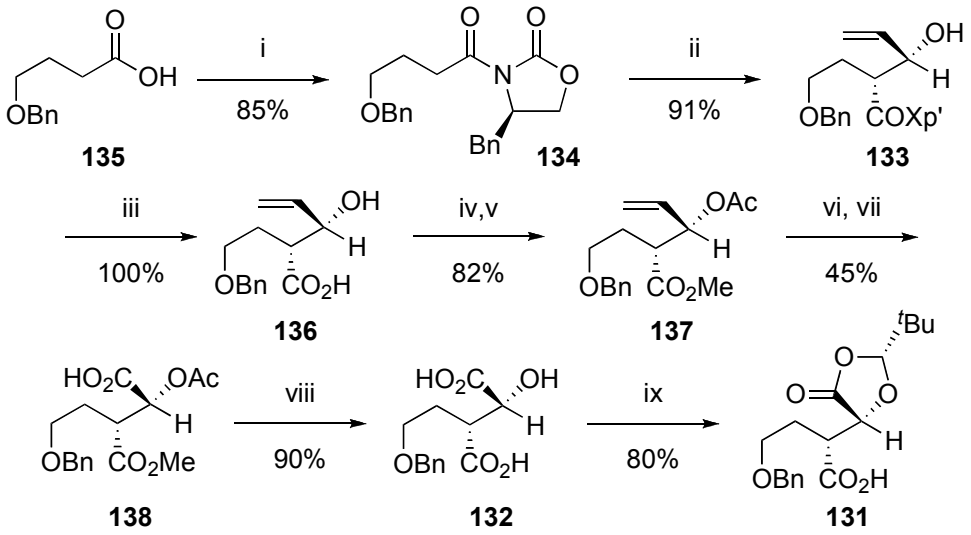
I.1.2.2. Synthesis of aldehyde 112 *via* deprotection/oxidation of 130

I.1.2.2.1. Synthesis of dioxolanone 131

Commercially available 4-benzyloxybutyric acid **135** was converted into the acyl-oxazolidinone **134** by formation of the mixed anhydride with ethyl chloroformate followed by reaction with (*R*)-4-benzyl-*N*-lithio-2-oxazolidinone at –78 ºC.[91] Unfortunately, repeating the Evans *syn*-selective aldol reaction between imide **134** and ethylglyoxylate gave a mixture of four diastereoisomers. This result was in agreement with the work reported by Iseki and co-workers indicating that ethyl glyoxalate was capable of undergoing boron mediated aldol reactions with Evans propionimides but with poor diastereoselectivity.[92] By replacing the electrophile with propenal, the *syn*-aldol reaction gave alcohol **133** in 91% yield with excellent diastereoselectivity (*d.r.* > 99%) (Scheme 30). Removal of the chiral auxiliary with hydrogen peroxide and LiOH gave carboxylic acid **136**. Esterification with diazomethane followed by acetate protection afforded methyl ester **137** in 82% yield over the two steps. Ozonolysis[93] and Pinnick oxidation[44] of alkene **137** gave the carboxylic acid **138** in a moderate 45% yield over the two steps mainly due to difficulties in purification.[94] Final hydrolysis of both the methyl ester and the acetate group led to the formation of diacid **132** which was converted to dioxolanone **131** using the previously optimised conditions in 72% yield over the two steps. In this case, dioxolanone **131** was obtained as a 94:6 mixture in favour of the desired *cis*-isomer, the structure of which was confirmed by NOESY.

The synthesis of dioxolanone **131** was achieved in nine steps with an overall yield of 21%.

Scheme 30. Synthesis of dioxolanone **131**.

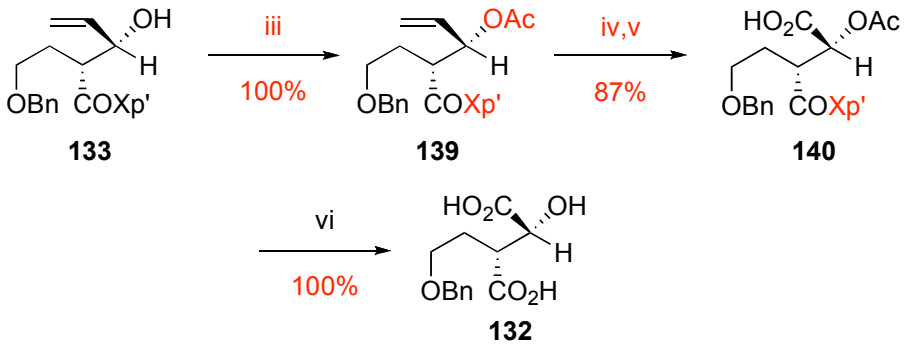


Reagents and conditions: i) EtOCOCl, Et_3N, Et_2O then (*R*)-4-benzyl-*N*-lithio-2-oxazolidinone; ii) $^nBu_2BOTf$, Et_3N, CH_2Cl_2, –78 ºC; CH_2=CHCHO, CH_2Cl_2, –78 to 0 ºC; iii) LiOH, H_2O_2, THF-H_2O (1:1); iv) CH_2N_2, Et_2O; v) Ac_2O, Et_3N, DMAP, Et_2O; vi) O_3, Me_2S, CH_2Cl_2, –78 ºC; vii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH-THF-H_2O (1:1:1); viii) LiOH, THF-H_2O (1:1); ix) ^{t}BuCHO, *p*-TsOH, hexane-THF (10:1).

The synthesis of dioxolanone **131** was optimised by keeping the chiral auxiliary as a protecting group of the carboxyl unit. Acetate protection of **133** gave alkene **139** which was oxidised to carboxylic acid **140** using the same sequence of oxidations (Scheme 31). Saponification of **140** gave diacid **132** in quantitative yield.

By using this approach, the number of steps to synthesise dioxolanone **131** was reduced to seven and the overall yield was increased to 54%.

Scheme 31. Optimised route to diacid **132**.

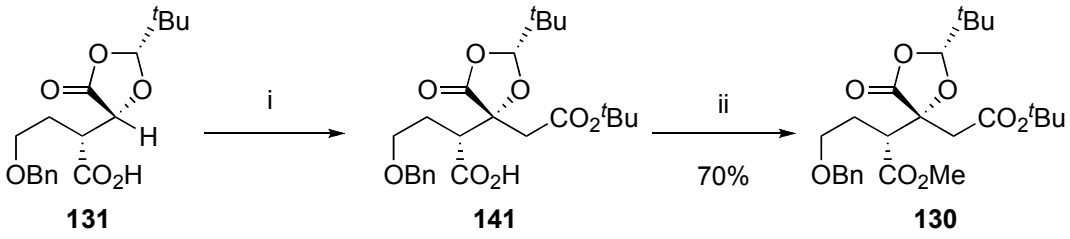


Reagents and conditions: iii) Ac_2O, Et_3N, DMAP, Et_2O; iv) O_3, Me_2S, CH_2Cl_2, –78 ºC; v) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, THF, H_2O (1:1:1); vi) LiOH, H_2O_2, THF, H_2O (1:1).

I.1.2.2.2. Synthesis of dioxolanone 130

The alkylation of dioxolanone **131** was carried out by double deprotonation in dry DMF at –70 °C using lithium hexamethyldisilazide followed by the addition of *tert*-butyl bromoacetate in DMF solution and afforded carboxylic acid **141** (Scheme 32).[62] While the reaction was completely diastereoselective with dioxolanone **116**, for substrate **131** the reaction proceeded with a *d.r.* > 9:1. Crude carboxylic acid **141** was then converted to methyl ester **130** (70%) with a freshly prepared solution of diazomethane in Et_2O.

Scheme 32. Synthesis of methyl ester **130**.

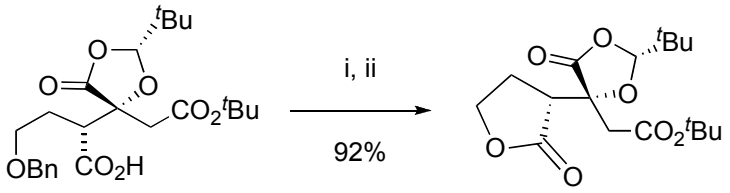


Reagents and conditions: i) 2 eq. LHMDS, DMF, –70 ºC then $BrCH_2CO_2{}^tBu$, –70 ºC; ii) CH_2N_2, Et_2O, 0 °C to RT.

I.1.2.2.3. Proof of the Seebach SRS alkylation

Hydrogenolysis of benzyl ether **130** followed by *in situ* lactonisation reaction using aqueous hydrochloric acid gave lactone **142** as a white solid in 92% yield (Scheme 33). Isolation of a single crystal and X-ray analysis confirmed that the alkylation had proceeded with Self-Regeneration of Stereocenter (Figure 14).

Scheme 33. Synthesis of lactone **142**.



141 **142**

Reagents and conditions: i) Pd/C, H_2, THF; ii) HCl, THF.

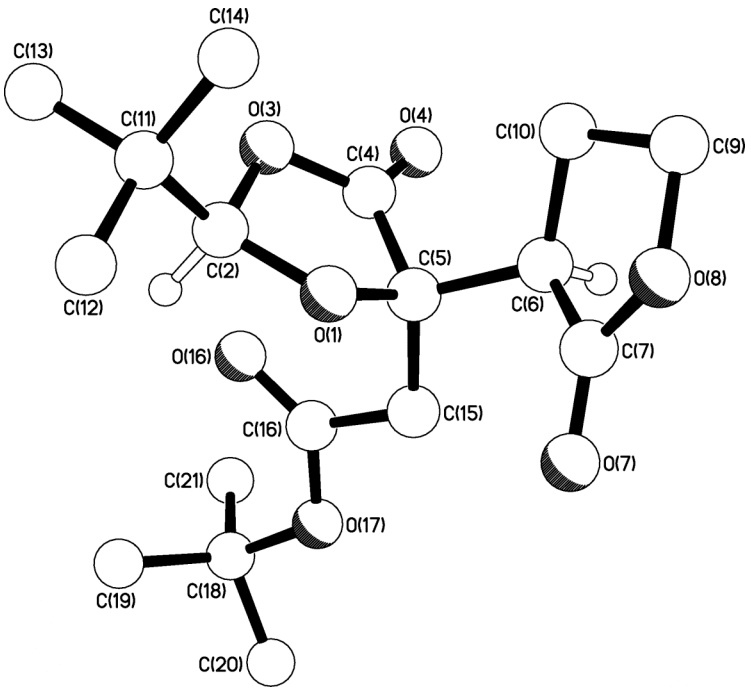
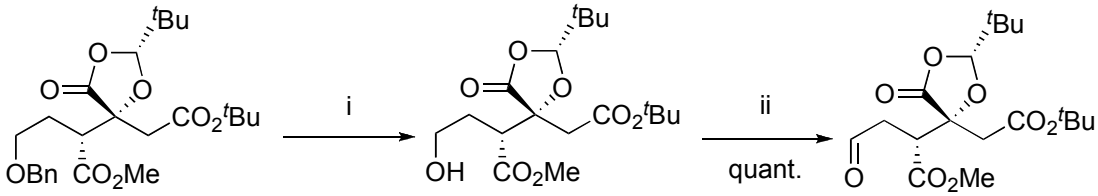


Figure 14. X-ray structure confirmation of lactone **142**.

I.1.2.2.4. Synthesis of key aldehyde 112

Hydrogenolysis[95] of benzyl ether **130** with Pd/C in dry THF gave clean crude alcohol **143** which was immediately oxidised with Dess–Martin periodinane[96] to afford aldehyde **112** in quantitative yield over the two steps (Scheme 34).

Scheme 34. Synthesis of key aldehyde **112**.



Reagents and conditions: i) Pd/C, H_2, THF; ii) DMP, CH_2Cl_2.

Having synthesised key aldehyde **112** using a more conventional approach, our next interest was focused on the addition of different nucleophiles to **112**, and in particular Zn-nucleophiles. Those nucleophiles were chosen, compared to their Mg- or Li- analogues, as they are less basic, less reactive and should avoid side reactions such as additions to other carbonyl groups (methyl and *tert*-butyl esters also present in **112**), dioxolanone opening and epimerisation reactions.

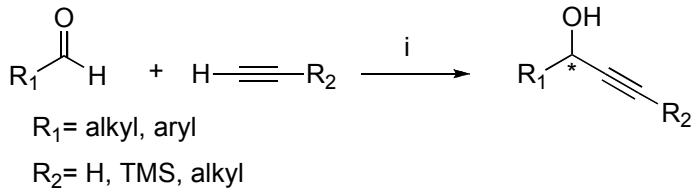
I.1.2.3. Addition of Zinc-nucleophiles to aldehyde 112

I.1.2.3.1. Stereoselective alkynol formation

I.1.2.3.1.1. The Carreira approach

Carreira *et al.* reported the enantioselective addition of terminal acetylenes to aldehydes to afford propargyl alcohols with high enantiomeric excess.[89,97,98] They developed an easy synthetic method which required stoichiometric (or catalytic) quantities of commercially available $Zn(OTf)_2$, (+)- or (–)-*N*-methylephedrine and a base (Scheme 35).[99]

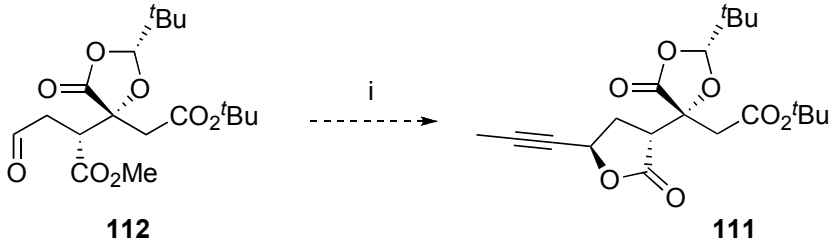
Scheme 35. Addition of Zn-alkynilides to aldehydes.



Reagents and conditions: i) alkyne, $Zn(OTf)_2$, (+)- or (–)-*N*-methylephedrine, NEt_3, PhMe, RT.

Based on our retrosynthetic analysis (Scheme 21), our next target was to synthesize alkynol **111** by using the protocol developed by E. Carreira (Scheme 36).

Scheme 36. Proposed alkynol formation with *in situ* lactonisation.

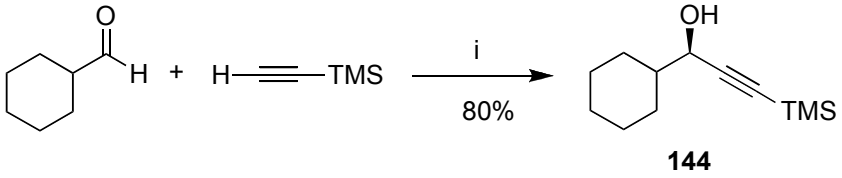


112 **111**

Reagents and conditions: i) Propyne, $Zn(OTf)_2$, (+)-*N*-methylephedrine, DIPEA, PhMe, RT.

First, a test reaction was carried out using commercial cyclohexylcarboxaldehyde and TMS-acetylene. The reaction proceeded very well and gave optically pure propargylic alcohol **144** in 80% yield (Scheme 37).[97]

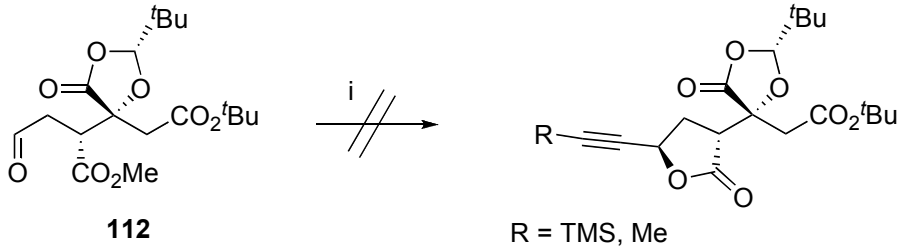
Scheme 37. Addition of TMS-acetylene to cyclohexylcarboxaldehyde.



Reagents and conditions: i) $Zn(OTf)_2$, (+)-*N*-methylephedrine, NEt_3, PhMe, RT.

Unfortunately, when applied to substrate **112**, the reaction did not work and only the starting material was observed by crude ^1H NMR. The same results were observed by increasing the reaction time and the loading of reagents (Scheme 38).

Scheme 38. Attempted addition of alkynes to aldehyde **112**.



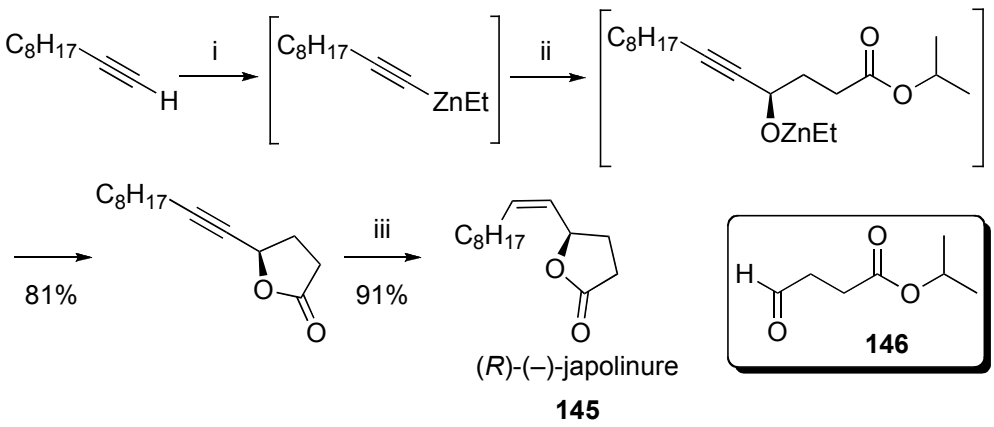
Reagents and conditions: i) Alkyne, $Zn(OTf)_2$, (+)-*N*-methylephedrine, NEt_3, PhMe, RT.

Having failed in applying Carreira's methodology using the mild $Zn(OTf)_2$ reagent to substrate **112**, other methods for the enantioselective addition of acetylenes to aldehydes were investigated.

I.1.2.3.1.2. Pu's methodology

In 2002, Pu *et al.* reported the titanium-catalysed enantioselective alkynylation of aldehydes using catalytic amount of (*S*)- or (*R*)-BINOL with stoichiometric amount of alkyne, $Ti(O^iPr)_4$ and Et_2Zn.[100] Das Santos and Francke applied this methodology to the total synthesis of (*R*)-(–)-japolinure **145**, a sex pheromone of the female Japanese beetle.[101] Lactone **145** was assembled by the chemoselective addition of 1-decynylethylzinc (generated *in situ*) to aldehyde **146** in the presence of (*S*)-(–)-BINOL, followed by immediate cyclisation and chemoselective Lindlar reduction (Scheme 39).

Scheme 39. Total synthesis of (*R*)-(–)-japolinure **145**.



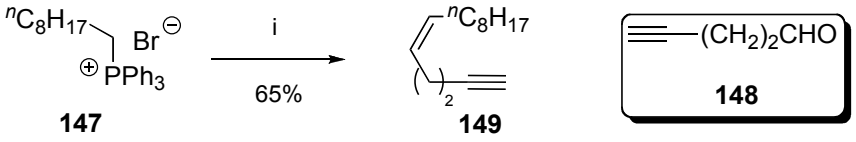
Reagents and conditions: i) Et_2Zn, PhMe, reflux, 12 h; ii) (*S*)-BINOL followed by $Ti(O^iPr)_4$ then slow adition of **146**; iii) Lindlar's catalyst, H_2, pentane.

This method looked very attractive as it could make the total synthesis of the citrafungin A (**23**) shorter. Indeed this one-pot sequence would have the advantage to introduce directly the long lipophilic side chain of the citrafungin A without the need to perform an alkyne-alkyne cross-metathesis reaction.

I.1.2.3.1.3. Attempted synthesis of lactone 109

The citrafungin A lipophilic side chain was synthesised using the Wittig reaction[102] of commercially available 1-nonyltriphenylphosphonium bromide **147** with 4-pentynal[103] **148** and gave alkyne **149** as the (*Z*)-isomer in 65% yield (Scheme 40).

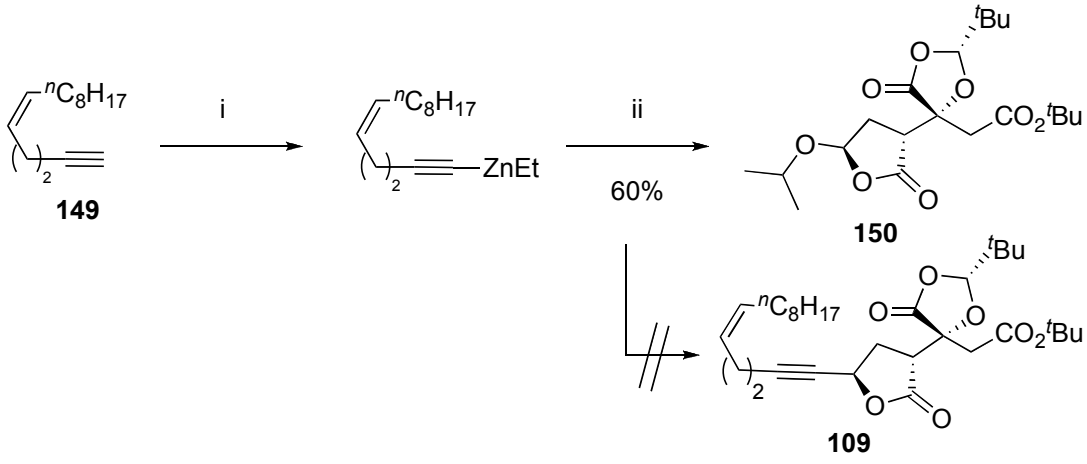
Scheme 40. Synthesis of alkyne **149**.



Reagents and conditions: i) LHMDS, THF, –35 °C then **148**.

Applying the conditions used for the synthesis of (*R*)-(–)-japolinure to aldehyde **112** and alkyne **149** did not afford the desired adduct **109**. Only lactone **150** was obtained in 60% yield and its structure was determined by X-ray analysis (Scheme 41 and Figure 15).

Scheme 41. Synthesis of by-product **150**.



Reagents and conditions: i) Et_2Zn, PhMe, reflux, 12 h; ii) (*S*)-BINOL then $TiO(^iPr)_4$ then **112**.

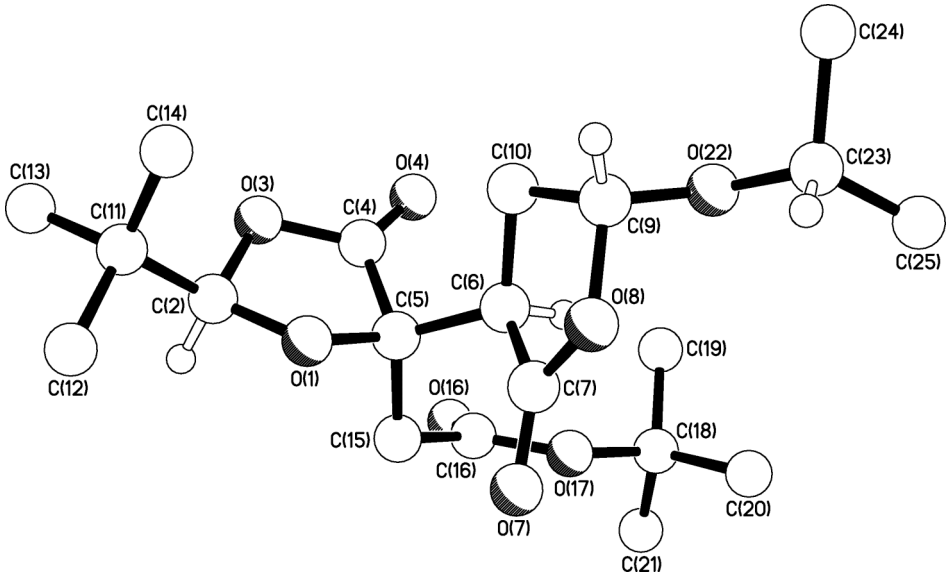
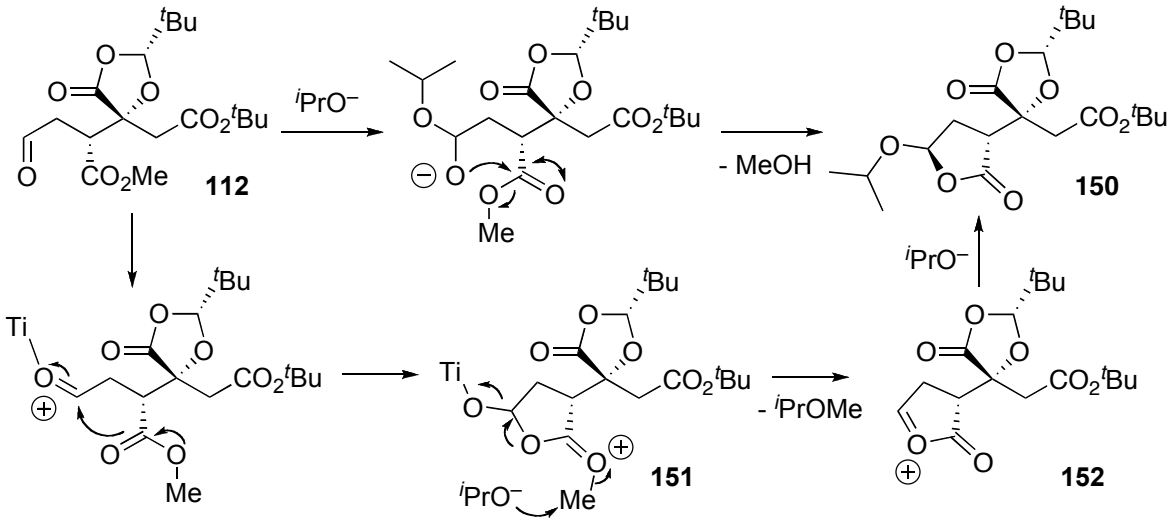


Figure 15. X-ray structure confirmation of lactone **150**.

The formation of lactone **150** could be explained either by the stereocontrolled addition of the *iso*-propyl alkoxide to aldehyde **112** with *in situ* lactonisation and elimination of MeOH or by the activation of the aldehyde to form the oxonium **151** which could be successively converted to oxonium **152** and lactone **150** (Scheme 42).

Scheme 42. Proposed formation of lactone **150**.

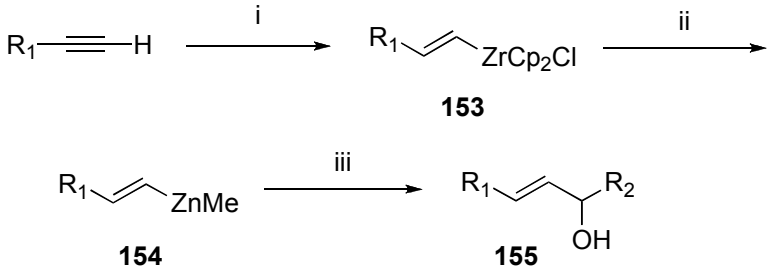


Using a catalytic amount of $Ti(O^iPr)_4$ did not improve the reaction conditions. Failing in obtaining alkyne **109**, a different approach was investigated.

I.1.2.3.2. Stereoselective allylic alcohol formation

In 1994, P. Wipf and co-workers published an efficient way to synthesise (*E*)-allylic alcohols starting from alkynes and aldehydes.[104,105] They demonstrated that alkenyl zirconocenes such as **153**, made by a *syn*-alkyne hydrozirconation reaction with the Schwartz reagent,[106] could be transmetalated at low temperature with solutions of Me_2Zn or Et_2Zn. The *in situ* generated zinc reagent **154** then can selectively add to aldehydes to provide (*E*)-allylic alcohols such as **155** (Scheme 43).

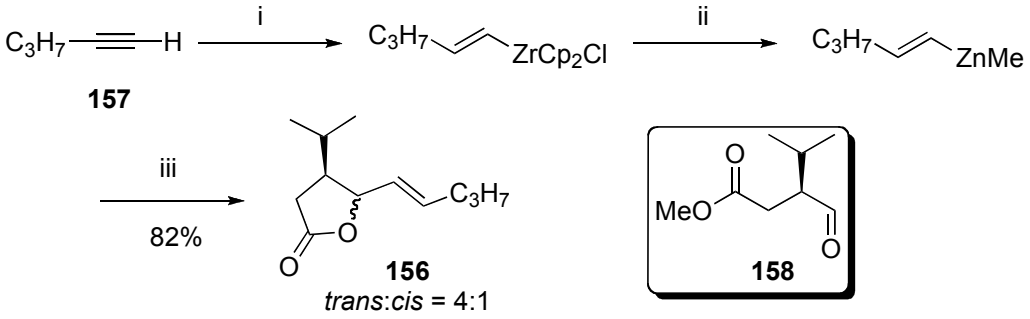
Scheme 43. Allylic alcohol formation.



Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2; ii) Me_2Zn, –65 °C; iii) R_2CHO, 0 °C.

This methodology was used by Nakata *et al.* for the asymmetric synthesis of methyl sarcoate.[107] The synthesis of lactone **156** was realised in a one-pot sequence and in 82% yield starting with the *syn*-hydrozirconation of alkyne **157** followed by transmetalation and addition of aldehyde **158** (Scheme 44).

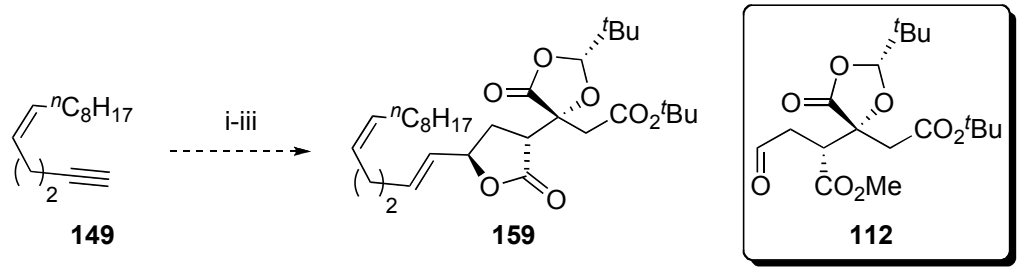
Scheme 44. Synthesis of lactone **156**.



Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2; ii) Me_2Zn, –65 °C; iii) **158**, 0 °C to RT.

This strategy could be a better approach to introduce the lipophilic chain of the citrafungin A. Indeed, it could have the advantage to form directly lactone **159** by adding alkyne **149** to aldehyde **112** hence constructing the core unit of the citrafungin A (**23**) (Scheme 45). This approach would also reduce our synthesis further by not having to perform the alkyne cross-metathesis and hydrosilylation/desilylation sequence of reactions.

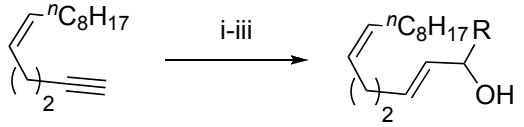
Scheme 45. Proposed synthesis of **159** and construction of the core of the citrafungin A.



Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2; ii) Me_2Zn, –65 °C; iii) **112**, 0 °C to RT.

I.1.2.3.2.1. Test reactions

Before using aldehyde **112**, some trial reactions between alkyne **149** and several aldehydes were performed and the results are presented in Table 5.



149 **160a-c**

Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2; ii) Me_2Zn, –65 °C; iii) RCHO, 0 °C to RT.

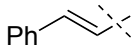
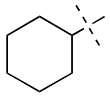
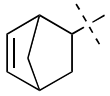
Entry	R-	Product (yield)
1		**160a** (70%)
2		**160b** (73%)
3		**160c** (75%)

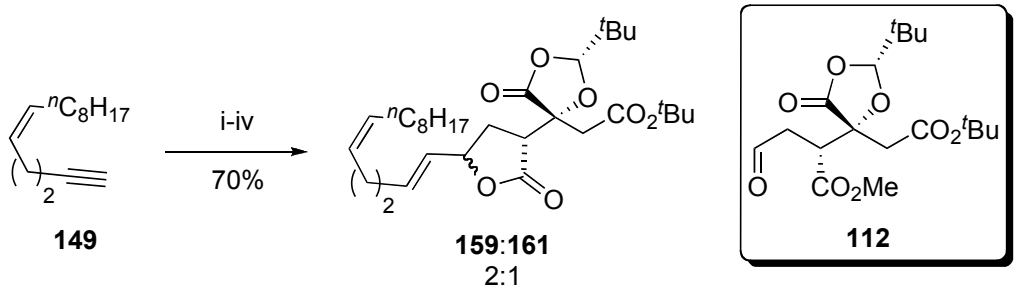
Table 5. Test reactions with commercially available aldehydes.

The *syn*-hydrozirconation of alkyne **149** with the Schwartz reagent proceeded very quickly at 0 ºC and was chemoselective towards the terminal triple bond. The transmetalation reaction was performed by cooling the reaction mixture to –65 ˚C and adding a solution of Me_2Zn in toluene. Warming up the reaction mixture and adding the aldehyde at 0 ˚C gave the (*E*)-allylic alcohol with good yield (entries 1-3).

I.1.2.3.2.2. Synthesis of lactone 159

When this reaction was carried out on aldehyde **112**, it was very rewarding to observe that it proceeded very well. An extra *p*-TsOH catalysed step was needed to promote the lactone formation (Scheme 46). Lactones **159** and **161** were obtained as a 2:1 separable mixture of isomers in favour of the desired *trans*-isomer in 70% yield over the sequence. Their structures were confirmed by NOESY and HMBC experiments.

Scheme 46. One-pot synthesis of lactones **159** and **161**.



Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2; ii) Me_2Zn sol. in PhMe, –65 °C; iii) **112**, 0 °C to RT; iv) *p*-TsOH, Et_2O, reflux.

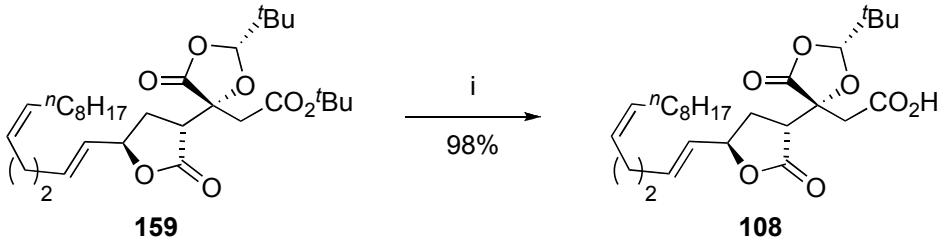
I.1.2.4. Synthesis of fully protected citrafungin A derivative 107

I.1.2.4.1. Deprotection of the *tert*-butyl ester in 159

Our attention was consequently turned to the deprotection of the *tert*-butyl ester group to reveal carboxylic acid **108**. Standard treatment of lactone **159** with trifluoroacetic acid (TFA) in methylene chloride was the most effective method and formed carboxylic acid **108** in 98% yield (Scheme 47). Other deprotection methods including formic acid,[108]

phosphoric acid,[109] $ZnBr_2$,[110,111] TMSOTf[112] or TESOTf[113,114] resulted in no conversion, low yields or decomposition.

Scheme 47. *tert*-Butyl ester deprotection.



Reagents and conditions: i) TFA, CH_2Cl_2, RT.

Starting from 4-benzyloxybutyric acid **135**, the synthesis of acid **108** was achieved in 13 steps with an overall yield of 18%. Only two steps were left to accomplish the total synthesis of citrafungin A (**23**) *i.e.* the coupling with alcohol **35** to form dioxolanone **107** and the final deprotection step. Ultimately, our attention was turned to the synthesis of the right-hand side isocitric alcohol unit **35** and its coupling reaction with acid **108**.

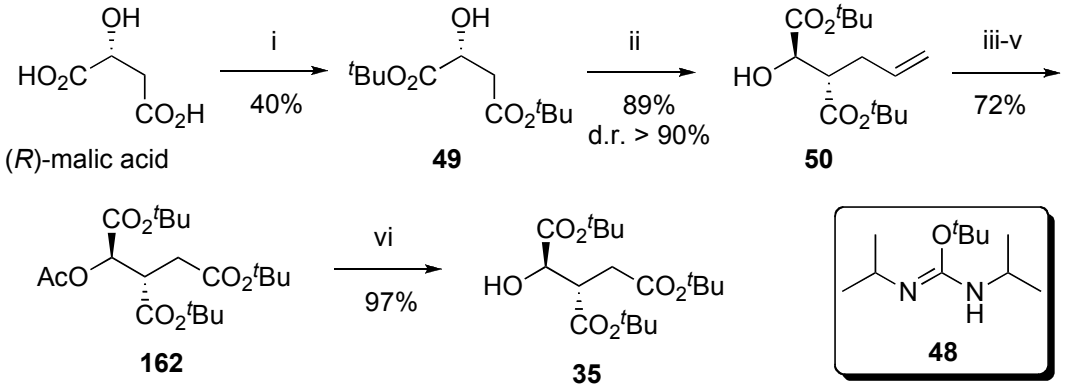
I.1.2.4.2. Synthesis of alcohol 35 and coupling reaction

I.1.2.4.2.1. Synthesis of alcohol 35

(2*R*,3*S*)-Tri-*tert*-butyl isocitrate **35** was prepared from commercially available (*R*)-malic acid following the Hatakeyama precedent. Esterification of (*R*)-malic acid using reagent **48**[115-118] gave di-*tert*-butyl ester **49** in a modest 40% yield after two days. Alkylation with allyl bromide by double deprotonation provided alkene **50** in 89 % yield with a *d.e.*>90 % (Scheme 48).[39,119-121] Sequential acylation, ruthenium tertraoxide

oxidation[122-125] of the alkenic double bond and esterification of **50** gave ester **162** in 72% yield, over the three steps. Hydrolysis of the acetate group with potassium carbonate in methanol cleanly provided alcohol **35** in 97% yield.

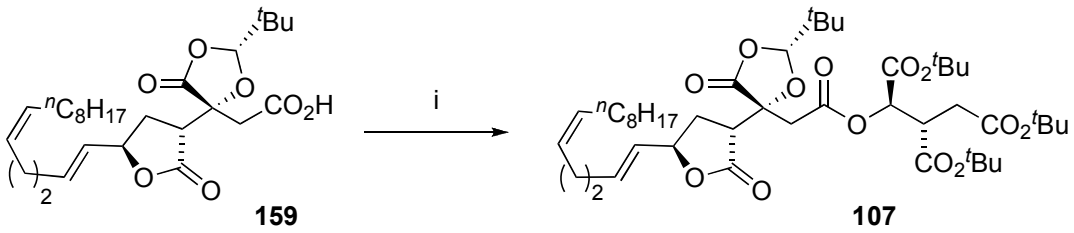
Scheme 48. Synthesis of alcohol **35**.



Reagents and conditions: i) **48**, CH_2Cl_2, reflux; ii) LHMDS, allyl bromide, THF, –78 °C to 0 °C; iii) Ac_2O, NEt_3, DMAP, Et_2O; iv) $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O (5:5:8); v) **48**, CH_2Cl_2, reflux; vi) K_2CO_3, MeOH.

I.1.2.4.2.2. Coupling reaction and formation of ester 107

Having prepared both sides of our target, the coupling reaction between acid **159** and alcohol **35** was studied by using different coupling reagents and the results are shown in Table 6.[126] The reaction did not work using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) or the Yamaguchi protocol (entries 1 and 2). When carbodiimide reagents were used with DMAP·HCl, the formation of ester **107** was achieved (entries 3 and 4). The yield was improved to 70% by replacing the *N*,*N*'-di-*iso*-propylcarbodiimide (DIC) with *N*,*N*'-di-cyclohexylcarbodiimide (DCC).



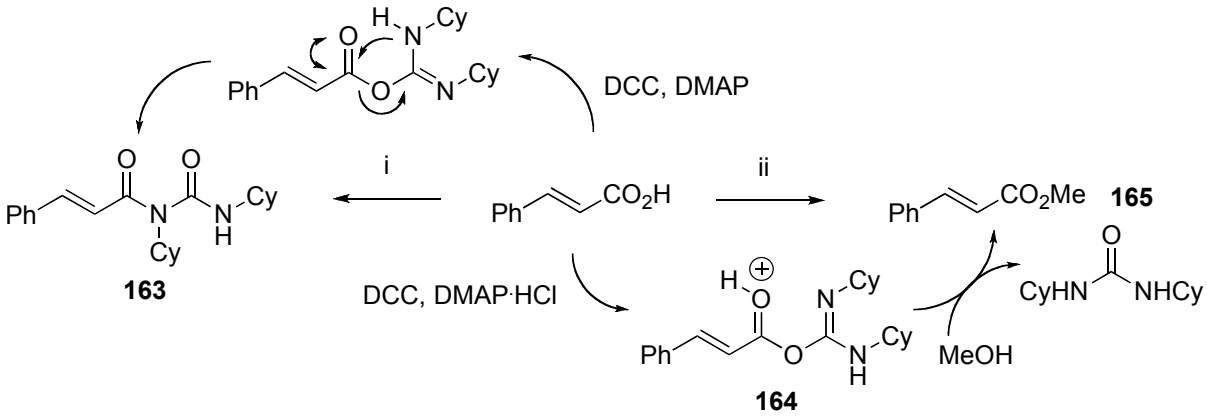
Reagents and conditions: i) **35**, coupling conditions, CH_2Cl_2, RT.

Entry	Coupling conditions	Product	Yield
1	BOPCl, DIEA, CH_2Cl_2	**159**	-
2	Yamaguchi	**159**	-
3	DIC, DMAP·HCl, CH_2Cl_2	**107**	50%
4	DCC, DMAP·HCl, CH_2Cl_2	**107**	70%
5	DIC, DMAP, CH_2Cl_2	**159**	-

Table 6. Esterification of acid **159** with alcohol **35**.

When the reaction was performed with just DMAP, no reaction was observed (entry 5). This result showed the importance of the proton-transfer step in the Steglish esterification that Keck *et al.* reported in 1985 (Scheme 49).[127] They observed that the coupling reaction between cinnamic acid and MeOH with DCC and DMAP afforded only the urea by-product **163**. However, when DMAP·HCl was used, it enabled the formation of intermediate **164** by protonation and the formation of methyl ester **165**.

Scheme 49. Importance of DMAP·HCl in the Keck esterification.

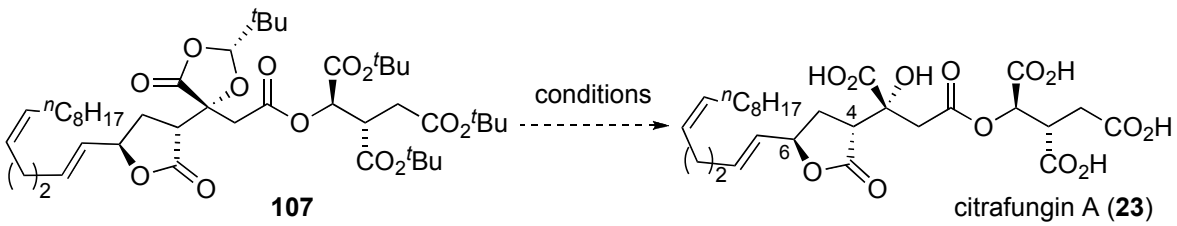


Reagents and conditions: i) DCC, DMAP, CH_2Cl_2; ii) DCC, DMAP·HCl, CH_2Cl_2.

I.1.2.4.2.3. Final hydrolysis step

Having made the fully protected version of citrafungin A **107**, the next and final step was the hydrolysis of both the dioxolanone ring and the *tert*-butyl esters.

Based on the literature precedent (*c.f.* Scheme 17), the final deprotection step was carried out and the results presented in Table 7. This reaction turned out to be very challenging. Most of the literature conditions were unsuccessful and resulted either in decomposition of **107** or in epimerisation of the lactone moiety at the C4 position. This was shown by ^{1}H NMR of the crude mixture where the proton at the C6 position has a chemical shift around 5ppm for the *trans*-isomer and a chemical shift around 4.6 ppm for the *cis*-isomer. Unfortunately, the dioxolanone ring seemed to be very robust. Removing this protecting group required harsh conditions which were not compatible with the fragile nature of compound **107** and therefore this final step could not be achieved.

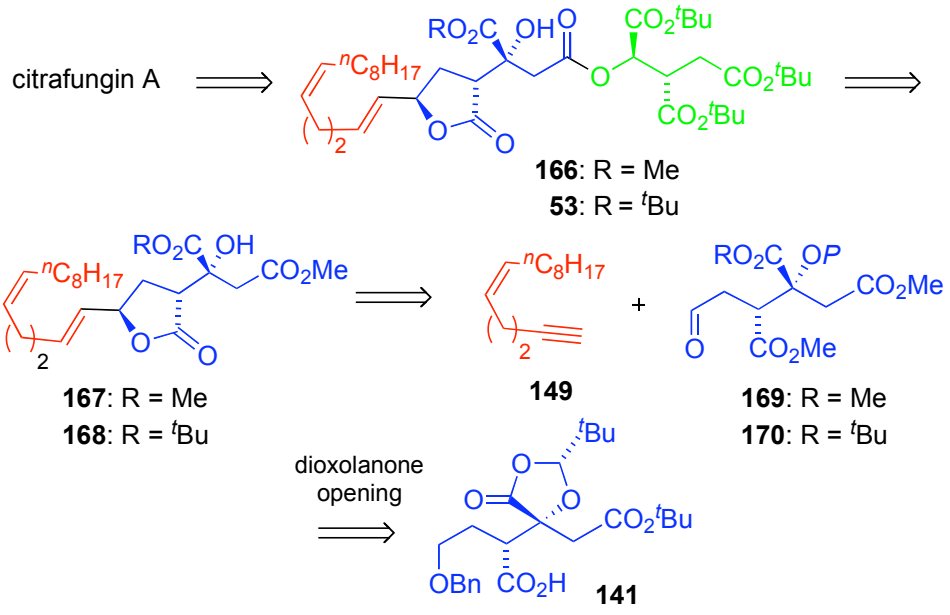


Entry	Conditions	Temperature	Conversion
1	0.1 M HCl, HCO_2H, 12 h	reflux	No conversion
2	1 M HCl, 2 to 12 h	RT or reflux	Decomposition
3	6 M HCl, 2 to 12h	RT or reflux	Decomposition
4	50% TFA, 2 to 12 h	RT or reflux	Decomposition
5	LiOH	reflux	Epimerisation/decomposition
6	KOH	reflux	Epimerisation/decomposition

Table 7. Attempted hydrolysis reaction to reveal the citrafungin A (**23**).

To overcome this problem, it was decided to investigate the opening of the dioxolanone ring at an earlier stage, on a less sensitive and less advanced intermediate. Our new retrosynthetic analysis is shown in Scheme 50. Citrafungin A would be obtained by a final deprotection of tetraester **166** (R = Me) or **53** (R = ^{t}Bu). As previously demonstrated, lactones **167** or **168** could be constructed by the addition of alkyne **149** to aldehydes **169** or **170**, respectively, which would be obtained by the opening of dioxolanone **141**.

Scheme 50. New retrosynthesis with an earlier stage opening of the dioxolanone ring.



I.1.3. Total synthesis of citrafungin A *via* the early opening of dioxolanone 176

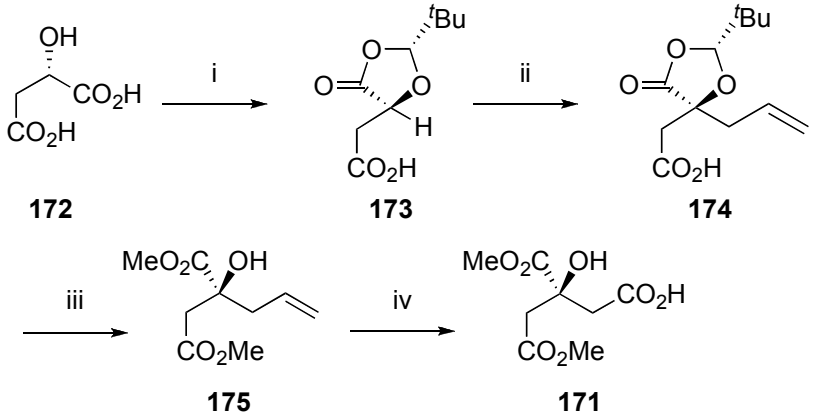
I.1.3.1. Protecting group variation 1: opening of dioxolanone 141 under acidic conditions (R = Me)

I.1.3.1.1. Synthesis of key dioxolanone 176

The opening reaction of dioxolanone **141** under acidic conditions had to be developed as it has been previously shown that the opening under basic conditions led to low conversion due to a competitive elimination reaction affording alkene by-product **105** (*c.f.* Scheme 19).

Shultz *et al.* reported the opening of a similar dioxolanone with $BF_3{\cdot}OEt_2$ for the total synthesis of (*S*)-cupilure **171**, a spider sex pheromone.[128] Starting from (*S*)-malic acid (**172**), dioxolanone **173** was obtained by cyclisation with pivaldehyde. Seebach SRS alkylation of **173** with allyl bromide afforded dioxolanone **174** which was ring-opened with MeOH and $BF_3{\cdot}OEt_2$ to give methyl ester **175**. Final oxidation with RuO_4 produced (*S*)-cupilure **171** (Scheme 51).

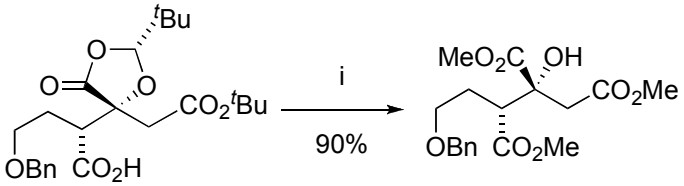
Scheme 51. Shultz's dioxolanone cleavage with MeOH and $BF_3{\cdot}OEt_2$.



Reagents and conditions: i) H^+, pivaldehyde; ii) LHMDS, THF, –78 °C then allyl bromide; iii) $BF_3{\cdot}OEt_2$ (5 equiv), MeOH, reflux; iv) $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O.

Using this procedure on dioxolanone **141** allowed the formation of trimethyl ester **176** in 90% yield. By ^{1}H NMR analysis of the crude reaction mixture over the course of the reaction, it was discovered that the first step was the esterification of the carboxylic acid to the methyl ester followed by the transesterification of the *tert*-butyl ester to the methyl ester and finally by the opening of the dioxolanone ring to reveal the α-hydroxy methyl ester (Scheme 52).

Scheme 52. Opening of dioxolanone **141** MeOH and $BF_3{\cdot}OEt_2$.



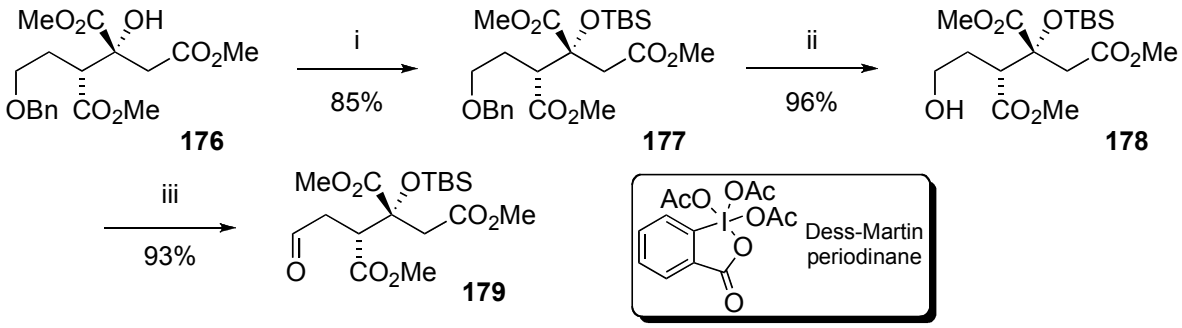
141 **176**

Reagents and conditions: i) $BF_3{\cdot}OEt_2$ (10 equiv), MeOH, reflux.

I.1.3.1.2. Synthesis of dimethyl ester 167

The synthesis of ester **167** started with the TBS protection of the tertiary alcohol **176** to afforded benzyl ether **177**. Hydrogenolysis of **177** gave primary alcohol **178** which was subsequently oxidised to aldehyde **179** with Dess–Martin periodinane in 76% yield over the three steps (Scheme 53).

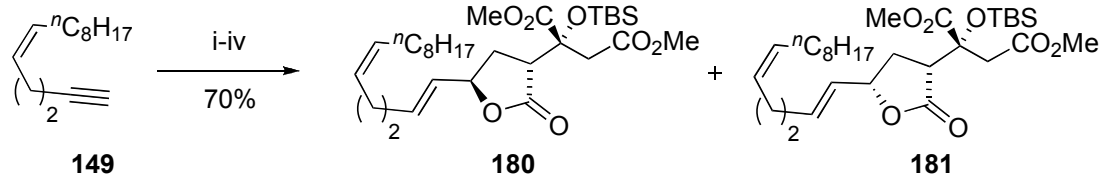
Scheme 53. Synthesis of aldehyde **179**.



Reagents and conditions: i) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT; ii) Pd/C, H_2, THF, RT; iii) DMP, CH_2Cl_2, RT.

Syn-hydrozirconation of alkyne **149** using the Schwartz reagent, followed by transmetalation with Me_2Zn and addition of crude aldehyde **179** gave, after *p*-TsOH lactonisation, a 2:1 mixture of lactones **180** and **181** in 70% yield. ^{1}H NOESY NMR studies confirmed the major diastereoisomer was the desired *trans*-lactone **180** (Scheme 54).

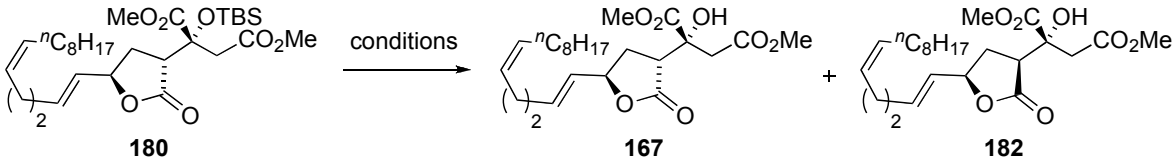
Scheme 54. One-pot synthesis of lactones **180** and **181**.



Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2; ii) Me_2Zn, –65 °C; iii) **179**, 0 °C to RT; iv) *p*-TsOH, Et_2O, reflux.

The deprotection of the TBS group proved to be quite challenging (Table 8). Treatment of lactone **180** with TBAF[129] resulted in deprotection of the tertiary alcohol but lactone **167** was obtained with epimer **182** as an inseparable 1:1 mixture. To overcome the epimerisation reaction, other fluoride sources such as HF,[130,131] H_2SiF_6,[132,133] $BF_3{\cdot}OEt_2$[134] (entries 2-5) or concentrated HCl[135] (entry 6) were tested but unfortunately gave no

conversion. Finally, buffering TBAF with acetic acid allowed the isolation of lactone **167** in 94% yield.[136]



180 **167** **182**

Entry	Conditions	180:167:182	Isolated yield
1	TBAF (1 M in THF), THF, 0 ^{o}C	0:1:1	Inseparable mixture
2	HF, H_2O, THF, 0 ^{o}C to RT	1:0:0	-
3	HF·pyridine, MeCN, 0 ^{o}C to RT	1:0:0	-
4	H_2SiF_6 in H_2O, MeCN, 0 ^{o}C to RT	1:0:0	-
5	$BF_3{\cdot}OEt_2$, MeCN, 0 ^{o}C to RT	1:0:0	-
6	Conc. HCl, MeOH, 0 ^{o}C to RT	1:0:0	-
7	TBAF (1 M, THF), AcOH, THF, 0 ^{o}C	0:1:0	94%

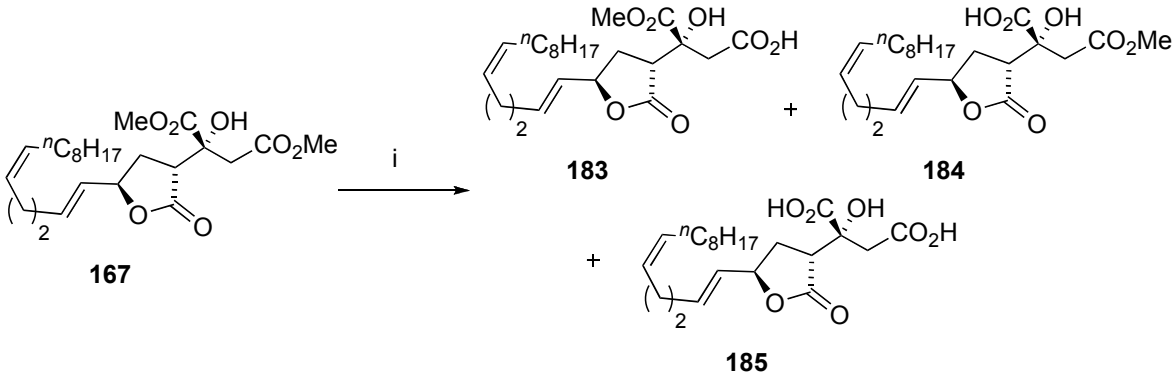
Table 8. Deprotection of the TBS alcohol using fluoride sources.

I.1.3.1.3. Attempted saponification and coupling reaction

The next step of the synthesis was the hydrolysis of the least hindered methyl ester in **167**. The use of LiOH in H_2O did not give the desired carboxylic acid **183** but an inseparable mixture of mono-protected acids **183** and **184**, and diacid **185** (Scheme 55).[137] The same result was observed using other bases such as NaOH, KOH[138] and $Ba(OH)_2{\cdot}8H_2O$.[139] Full conversion to diacid **185** was achieved using 3.5 equivalents of

LiOH but compound **185** ultimately epimerised (40%). This was a disappointing and surprising result as citrafungin A (**23**) was characterised by cleavage of the isocitric acid unit using LiOH (*c.f* Scheme 1).

Scheme 55. Saponification of **167** using LiOH.



Reagents and conditions: i) LiOH, THF-H_2O, 0 ^{o}C to RT.

In this section, it was demonstrated that it was possible to open the dioxolanone ring to obtain trimethyl ester **176** with no differentiation between the carboxyl groups. Performing Wipf's methodology and subsequent lactonisation allowed the exclusive formation of the 5-membered ring lactone **180** which gave access to dimethyl ester **167**.

Unfortunately, the selective deprotection of the methyl ester prior to the coupling reaction was not possible. It was concluded that the differentiation of the primary and tertiary carboxyl groups was mandatory to be able to complete the total synthesis of citrafungin A.

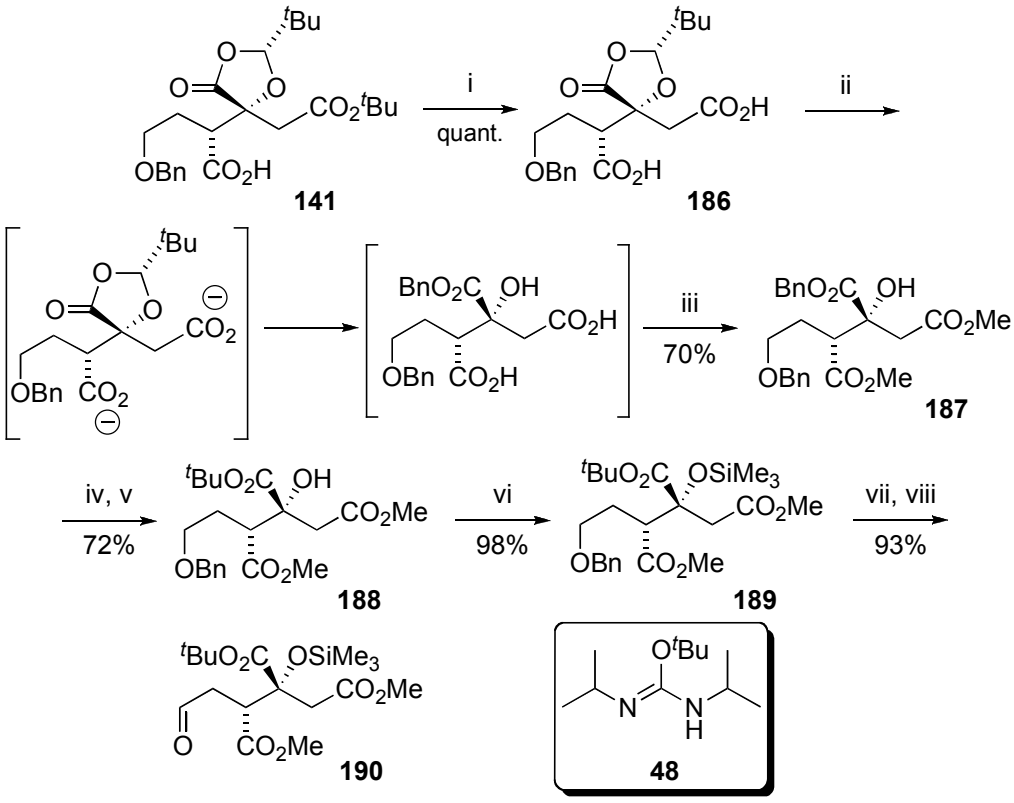
I.1.3.2. Protecting group variation 2: Opening of dioxolanone 141 under basic conditions, R = ^{t}Bu

Only the opening of the dioxolanone ring under basic conditions allowed the formation of a compound having two different ester groups but this reaction was low yielding and accompanied by an elimination reaction (*c.f* Scheme 19). It was hypothesised that the problem of elimination could be overcome by increasing the pKa of the α protons in **141**.

I.1.3.2.1. Synthesis of aldehyde 190

Tert-butyl ester **141** was deprotected with TFA to obtain diacid **186**. It was anticipated that, under basic conditions, the di-carboxylate would be formed, increasing the pKa of the α protons, therefore reducing the likelihood of elimination. Extremely pleasingly, the treatment of diacid **186** with benzyl alcohol and LHMDS smoothly opened the dioxolanone ring and afforded, after diazomethane methylation, ester **187** in 70% yield over the two steps. Selective debenzylation of the benzyl ester was achieved by hydrogenolysis over palladium on carbon. Reprotection of the free carboxylic acid as *tert*-butyl ester **188** was carried out using reagent **48** in 72% yield over the two steps. Protection of the tertiary alcohol with TMSCl afforded compound **189** in 98% yield. Sequential benzyl ether hydrogenolysis (which was slower than the ester **187** hydrogenolysis) and Dess–Martin oxidation of **189** gave aldehyde **190** in 93% yield over the two steps (Scheme 56).

Scheme 56. Synthesis of aldehyde **185**.



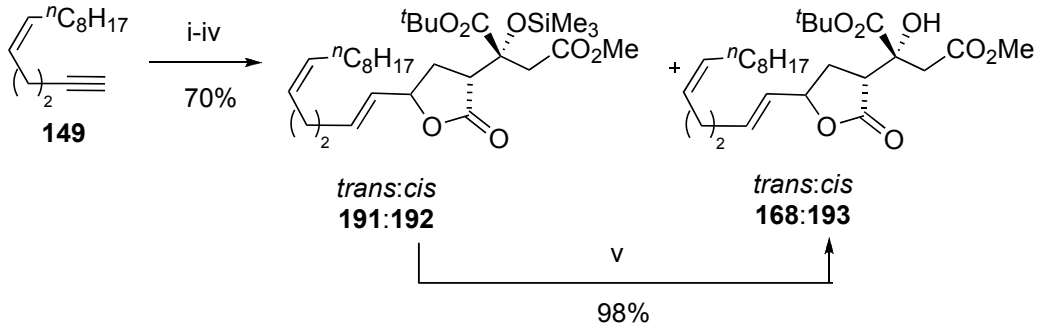
Reagents and conditions: i) TFA, CH_2Cl_2; ii) BnOH, LHMDS, PhMe, 0 °C to RT; iii) CH_2N_2, EtOAc; iv) H_2, Pd/C, THF; v) **48**, CH_2Cl_2, reflux; vi) Me_3SiCl, imidazole, CH_2Cl_2; vii) H_2, Pd/C, THF; viii) DMP, CH_2Cl_2.

I.1.3.2.2. Synthesis of lactone 168

Alkyne **149** *syn*-hydrozirconation using the Schwartz reagent followed by transmetalation at low temperature with Me_2Zn gave selectively the *trans*-alkenylzinc which was directly added to aldehyde **190** at 0 °C. Acidic work up followed by *p*-TsOH catalyzed lactonisation gave a mixture of the *trans*-**191** and the *cis*-**192** lactones (2:1). During chromatographic purification, partial cleavage of the trimethylsilyl group occurred but fortunately the

resultant four lactones were separable (Scheme 57). Treatment of either lactone **191** or **192** with acetic acid buffered TBAF cleanly gave lactones **168** or **193** in 98% yield, respectively. Overall lactones **168** and **193** were obtained in 70% yield starting from alkyne **149** in with the major isomer having the correct *trans*-stereochemistry. Their structures were confirmed by NOESY and HMBC experiments.

Scheme 57. Synthesis of lactone **168**.

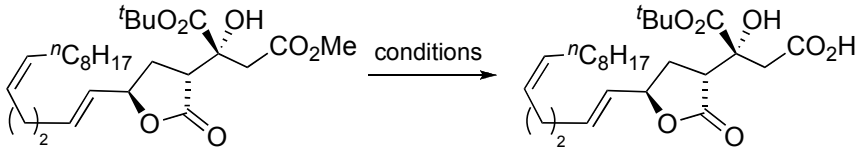


Reagents and conditions: i) Cp_2ZrHCl, CH_2Cl_2, 0 °C to RT; ii) Me_2Zn, –65 °C; iii) **190**, 0 °C to RT; iv) *p*-TsOH, Et_2O, reflux; v) TBAF, AcOH, THF.

I.1.3.2.3. Synthesis of Hatakeyama's acid 36

The final step required to obtain carboxylic acid **36** was the selective deprotection of methyl ester **168** in presence of a *tert*-butyl ester and a delicate lactone susceptible to epimerisation (Table 9). Standard saponification procedures[138-141] were indiscriminate giving a mixture of mono- and di-acids. These results may be explained by a neighbouring group effect of the tertiary alcohol leading to partial hydrolysis of the adjacent *t*-butyl ester *via* the α-lactone or *via* the combined inductive effect of the two adjacent carbonyls and hydroxyl groups enhancing the electrophilicity of the *tert*-butyl ester. Attempted demethylation using lithium iodide[142] or thiophenol and cesium carbonate[143] were too slow

or resulted in partial lactone *trans* to *cis* epimerisation, respectively. However, selective demethylation was achieved using hydroxytrimethylstannane in 1,2-dichloroethane[144] giving Hatakeyama's carboxylic acid **36** in 94% yield.



168 **36**

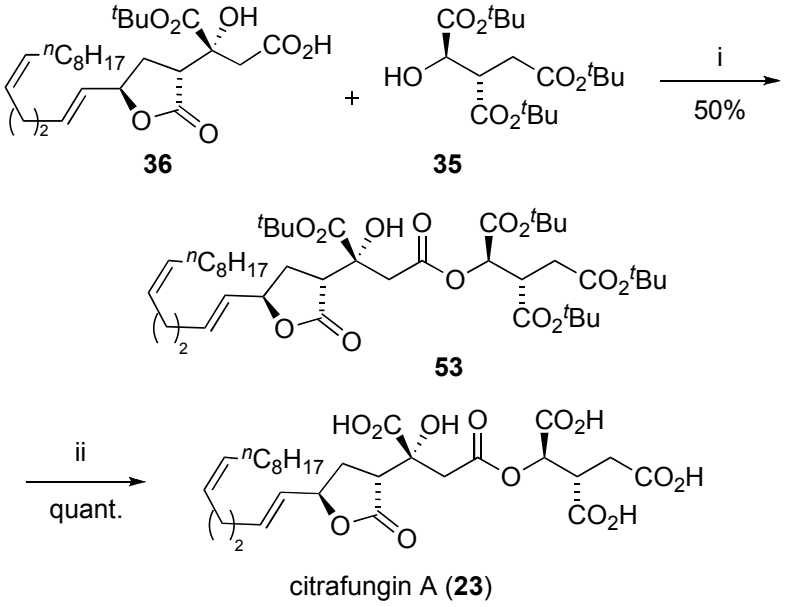
Entry	Conditions	36 (yield)
1	LiOH, THF-H_2O	Diacid formed + epimerisation
2	$Ba(OH)_2 \cdot 8H_2O$, THF-MeOH	Diacid formed + epimerisation
3	LiI, DMF, 80 °C	No conversion
4	PhSH, Cs_2CO_3, DMF, 80 °C	Full conversion with epimerisation (1:1)
5	Me_3SnOH, $Cl(CH_2)_2Cl$, 80 °C	Full conversion (94%)

Table 9. Selective cleavage of the methyl ester.

I.1.3.2.4. Total synthesis of citrafungin A (23)

Following the Hatakeyama precedent, esterification of carboxylic acid **36** with alcohol **35** using Keck's esterification procedure[145] (Scheme 58) gave pentaester **53** in 50% yield which upon global deprotection with trifluoroacetic acid gave citrafungin A (**23**), which was further purified by preparative HPLC.[146] Pleasingly, the ^1H and ^{13}C NMR data were in excellent agreement with the reported data.

Scheme 58. Synthesis of citrafungin A (**23**).



Reagents and conditions: i) DCC, DMAP·HCl, CH_2Cl_2; ii) TFA, CH_2Cl_2.

I.2. (–)-TRACHYSPIC ACID

I.2.1. Structure, isolation and previous total syntheses

Heparanase, an endo-β-glucuronidase that was originally identified in murine B16 melanoma, has the ability to cleave heparansulfate (HS), one of the major components of basement membranes (tissue barrier that tumor cells must penetrate in the process of invasion and metastasis). Their degradation by heparanase is an important step in pathogenesis. In addition, heparanase is able to liberate HS-bound angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGF-1 and FGF-2) thus promoting tumor growth and angiogenesis. Because of its important role in these processes, heparanase is an attractive target for the development of antitumor, antimetastasis or anti-inflammatory drugs.[147] Trachyspic acid (**24**) was isolated from the culture broth of *Talaromyces trachyspermu* SANK 12191 and was identified as a potent inhibitor of heparanase with an IC_{50} of 36 μM. Structurally, this compound is characterised by a spiroketal structure consisting of a 4-nonyl-3-furanone and a tetrahydrofuran containing a citric acid unit. The planar structure was determined by detailed NMR analysis; however, its relative configuration was not elucidated (Figure 16).

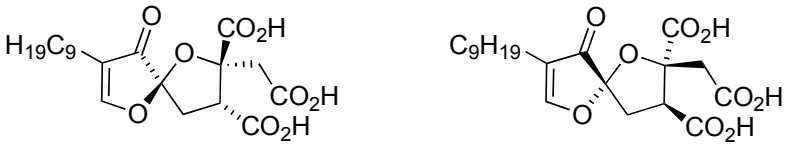
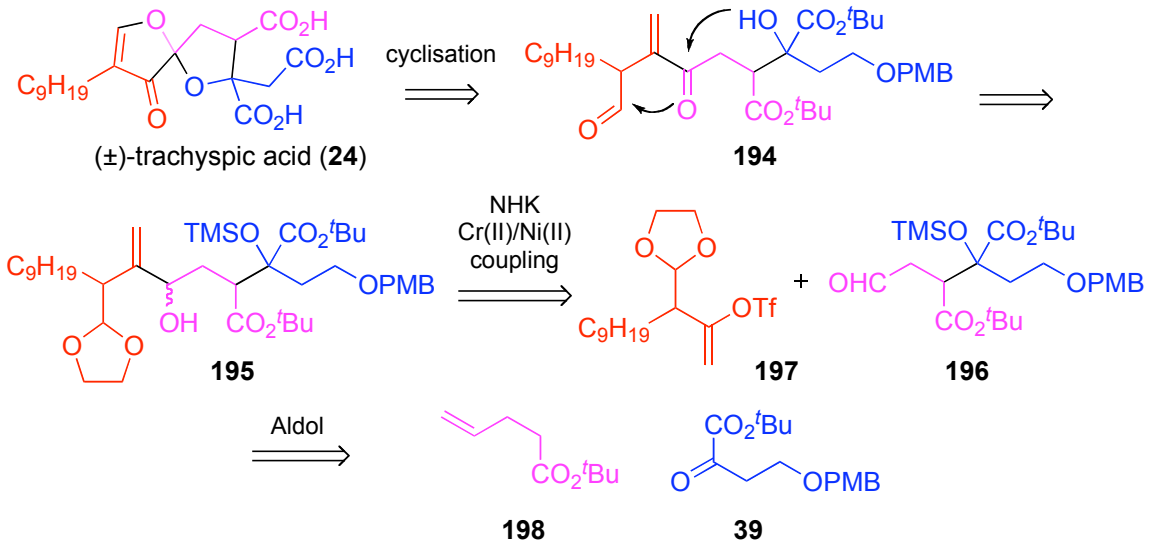


Figure 16. Structure of trachyspic acid (**24**).

I.2.1.1. Total synthesis of (±)-trachyspic acid and determination of its relative stereochemistry by the Hatakeyama group

In 2002, the Hatakeyama group published the first total synthesis of (±)-trachyspic acid and determined its relative stereochemistry.[148] (±)-Trachyspic acid (**24**) was synthesised by cyclisation of ketone **194** made by functional modifications of alcohol **195**. Alcohol **195** was assembled by a Nozaki-Hiyama-Kishi (NHK) coupling between aldehyde **196** and triflate **197**. In turn, aldehyde **196** was made by the aldol condensation of ester **198** with α-ketoester **39** (Scheme 59).

Scheme 59. Key disconnections in the Hatakeyama synthesis.

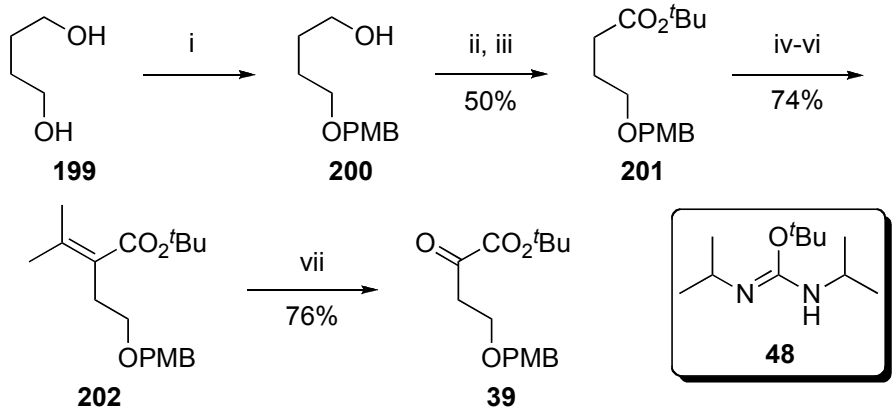


I.2.1.1.1. Synthesis of α-ketoester 39

α-Ketoester **39** was synthesised in 7 steps with an overall yield of 28%. The synthesis began with the mono-protection of 1,4-butanediol (**199**) to afford alcohol **200**. Jones

oxidation followed by ester formation using *N*,*N*'-di-*iso*-propyl-*O*-*tert*-butylisourea (**48**) gave the *tert*-butyl ester **201** in 50% yield over the sequence. Sequential condensation with acetone, dehydration and isomerisation of **201** led to the formation of the α,β-unsaturated ester **202** which was oxidised to the α-ketoester **39** by ozonolysis in 56% yield over the four steps (Scheme 60).

Scheme 60. Synthesis of α-ketoester **39**.

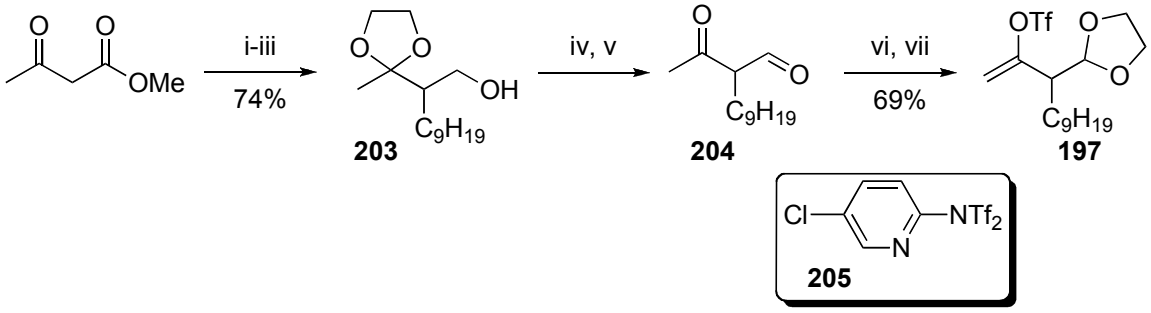


Reagents and conditions: i) PMBCl, NaH, DMSO; ii) CrO_3, aq. H_2SO_4, acetone; iii) **48**, CH_2Cl_2, reflux; iv) LDA, –78 °C, THF then acetone; v) $SOCl_2$, pyridine; vi) ^{t}BuOK, ^{t}BuOH; vii) O_3, –78 °C, CH_2Cl_2 then Me_2S.

I.2.1.1.2. Synthesis of triflate 197

The synthesis of triflate **197** started with the alkylation of methyl acetoacetate, ketone protection and ester reduction to form alcohol **203** in 74% over the three steps (Scheme 61). Swern oxidation and removal of the acetal in **203** gave the di-carbonyl compound **204** which was selectively protected and converted to triflate **197** with reagent **205** in 69% yield over the four steps.

Scheme 61. Synthesis of triflate **197**.

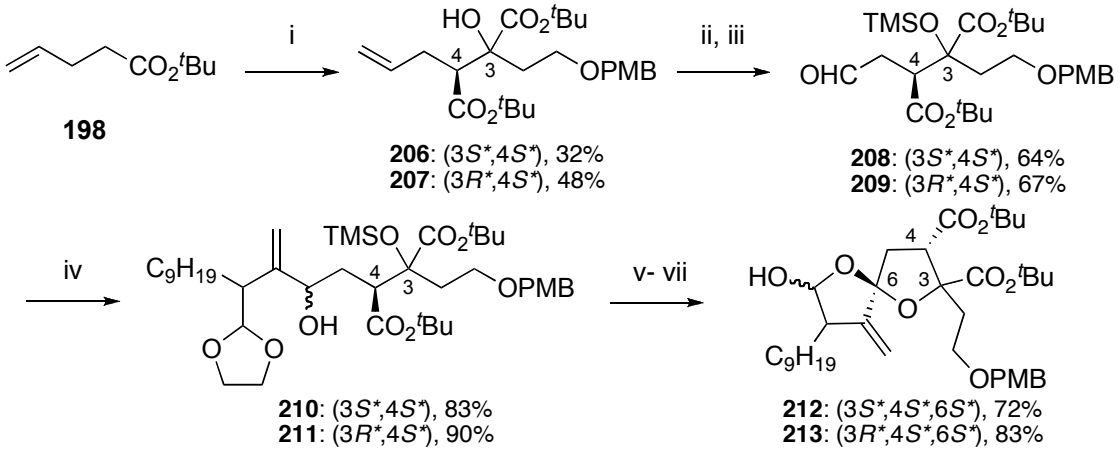


Reagents and conditions: i) Nonyl bromide, NaOMe, MeOH, reflux; ii) ethylene glycol, *p*-TsOH, C_6H_6, reflux; iii) $LiAlH_4$, THF; iv) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then NEt_3, 0 °C; v) 3 M HCl; vi) ethylene glycol, *p*-TsOH, C_6H_6, reflux; vii) LDA, –78 °C, THF then **205**.

I.2.1.1.3. Aldol reaction and NHK coupling

The aldol reaction between α-ketoester **39** and the lithium enolate of **198** led to a separable 2:3 mixture of racemic alcohols **206** and **207**. Silylation and oxidative cleavage of the olefin gave the key aldehydes **208** and **209**, respectively (Scheme 62).

Scheme 62. Synthesis of spiroketals **210** and **211**.

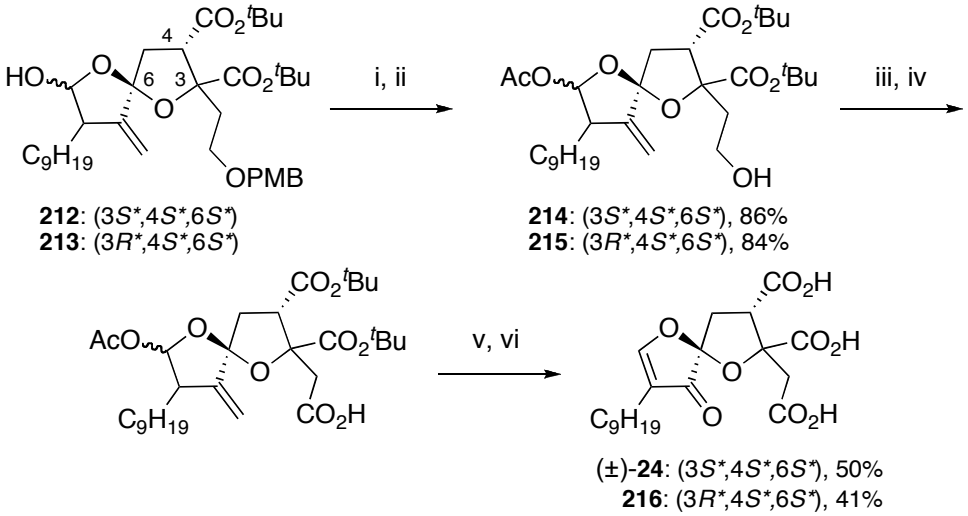


Reagents and conditions: i) LDA, THF, –78 °C then **39**; ii) Me_3SiCl, imidazole, CH_2Cl_2; iii) OsO_4, NMO, THF-H_2O then $NaIO_4$; iv) $CrCl_2$, $NiCl_2$, **197**, DMF; v) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, then NEt_3, 0 °C; vi) aq. HF, pyridine-MeCN; vii) 3 M $HClO_4$.

NHK coupling of triflate **197** with the two aldehydes gave alcohols **210** (83%) and **211** (90%), respectively.[149-151] Sequential Swern oxidation, desilylation, acetal deprotection and cyclisation gave spiroketals **212** (72%) and **213** (73%).

Acetylation and oxidative removal of the *p*-methoxybenzyl protecting group[152-154] in **212** and **213** gave alcohol **214** (86%) and **215** (84%), which were converted to their corresponding carboxylic acids *via* Dess–Martin and Pinnick oxidations. Final ozonolysis and exposure of the resulting ketone to TFA furnished the tricarboxylic acids (±)-**24** and **216** in 50% and 41% yield over the four steps, respectively (Scheme 63).

Scheme 63. Determination of the relative stereochemistry of trachyspic acid.



212: (3*S**,4*S**,6*S**)
213: (3*R**,4*S**,6*S**)

214: (3*S**,4*S**,6*S**), 86%
215: (3*R**,4*S**,6*S**), 84%

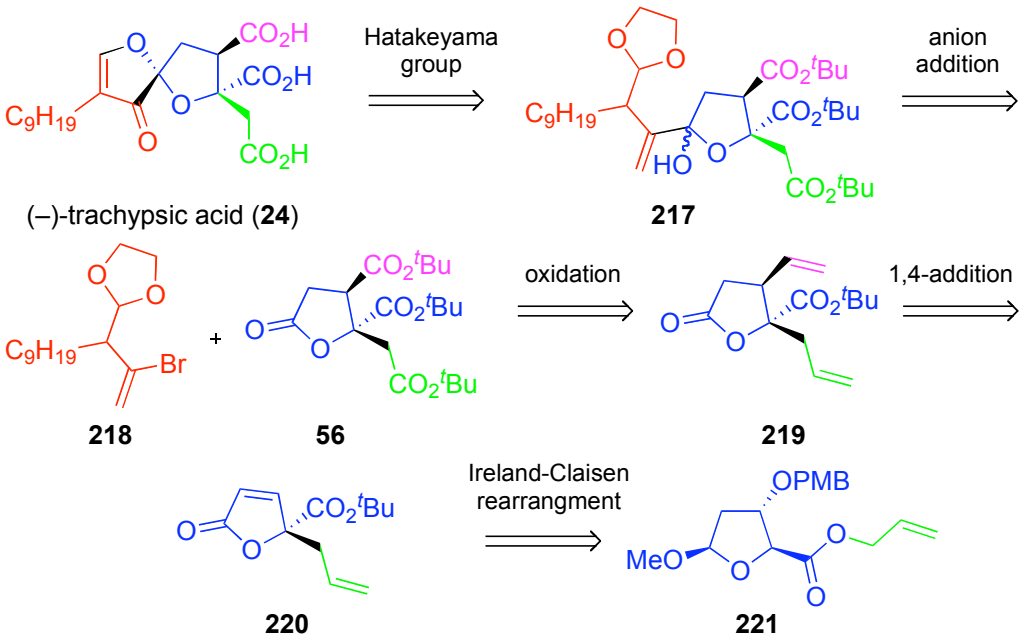
Reagents and conditions: i) Ac_2O, DMAP, pyridine; ii) DDQ, aq. CH_2Cl_2; iii) DMP, CH_2Cl_2; iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq. ^{t}BuOH; v) O_3, –78 °C, CH_2Cl_2-MeOH then Me_2S; vi) TFA, CH_2Cl_2.

I.2.1.2. First enantioselective total synthesis of (–)-trachyspic acid by the Rizzacasa group

After the synthesis of (±)-trachyspic acid by the Hatakeyama group, the Rizzacasa group was the first to publish the first enantioselective total synthesis of (–)-trachyspic acid (**24**) and therefore determining the absolute stereochemistry of natural (+)-trachyspic acid (*ent*-**24**).[48,49]

In the Rizzacasa approach, lactol **217** was assembled by the selective anion addition of vinyl bromide **218** to lactone **56**. Lactone **56** was made by oxidation of alkene **219** which was synthesised by the 1,4-Michael addition to α,β-unsaturated lactone **220**. The latter was constructed by the Ireland-Claisen rearrangement of allyl ester **221** (Scheme 64).

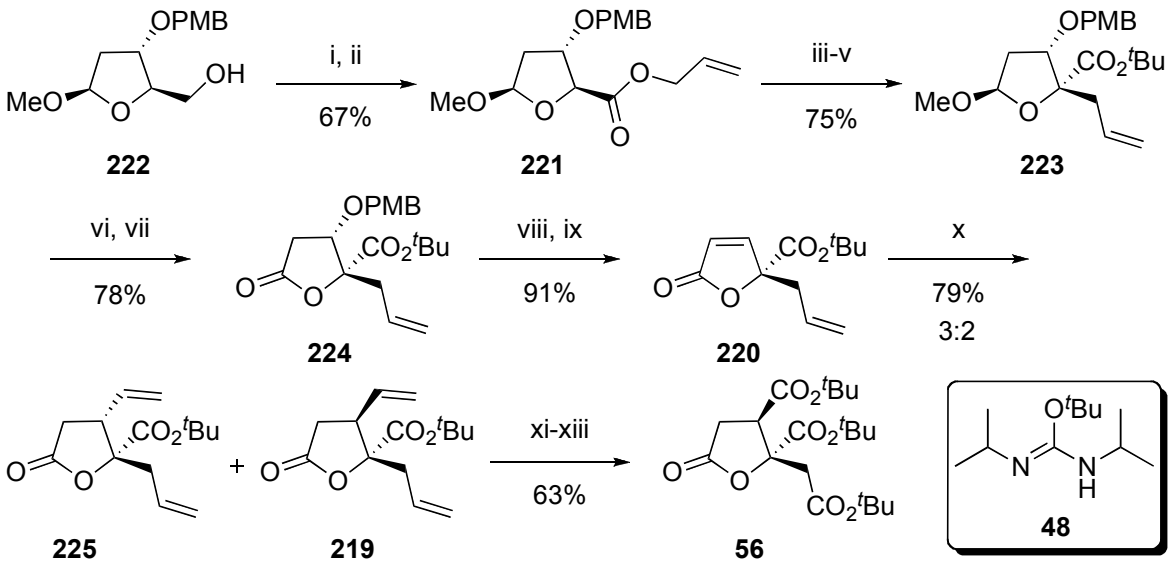
Scheme 64. Key disconnection in the Rizzacasa group.



I.2.1.2.1. Synthesis of lactone 56

Oxidation of alcohol **222** (formed in three steps from 1-*O*-methyl-2-deoxy-D-ribose) followed by esterification with allyl alcohol gave Claisen precursor **221** in 67% yield. Ireland–Claisen rearrangement[155-158] of **221** followed by saponification and esterification with **48** gave *tert*-butyl ester **223** (75%). Acid hydrolysis and oxidation formed lactone **224** in 78% yield over the two steps. Oxidative cleavage of the PMB group followed by mesylation of the resulting alcohol and base induced elimination gave the α,β-unsaturated lactone **220**, which upon treatment with vinylmagnesium bromide afforded two Michael adducts **219** and **225** in a 3:2 ratio in favour of the undesired diastereoisomer.[159-161] Oxidation and esterification of **219** gave key lactone **56** (Scheme 65).

Scheme 65. Rizzacasa's synthesis of lactone **56**.

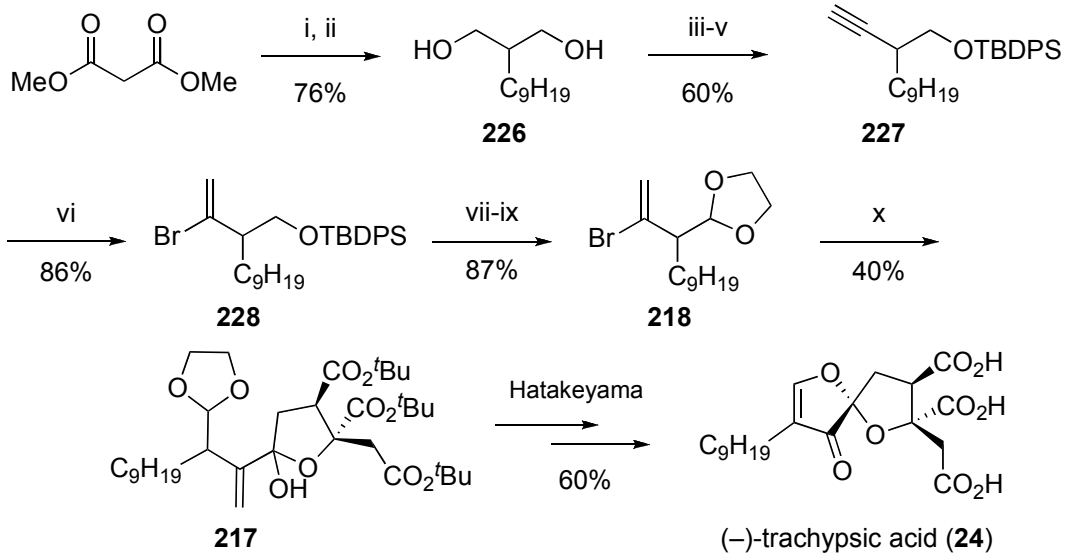


Reagents and conditions: i) NaOCl, $NaClO_2$, TEMPO; ii) DCC, DMAP, allyl alcohol; iii) TMSCl, NEt_3, LDA, THF-HMPA, –95°C; iv) aq. NaOH; v) **48**, CH_2Cl_2; vi) 10% HCl; vii) PCC; viii) DDQ, aq. CH_2Cl_2; ix) MsCl, pyridine; x) CuI, vinylMgBr, Me_2S, –45°C; xi) O_3, –78 °C, CH_2Cl_2-MeOH then Me_2S; xii) $NaClO_2$, NaH_2PO_4; xiii) **48**, CH_2Cl_2.

I.2.1.2.2. Synthesis of bromide 218 and coupling reaction with lactone 56

The synthesis of vinyl bromide **218** began with the alkylation of dimethyl malonate with nonyl bromide followed by ester reduction to afford diol **226** in 76% yield. Monoprotection of **226** with *tert*-butyldiphenylsilyl chloride, Dess–Martin oxidation of the resulting alcohol and alkyne homologation using the Corey–Fuchs procedure[162,163] afforded alkyne **227** in 60% yield over the three steps. Bromoboration and acid induced deboronation gave vinyl bromide **228** which was deprotected, oxidised and converted into bromide **218** by acetal protection. Metal-halogen exchange using ^{t}BuLi generated the vinyl anion which selectively added to the lactone carbonyl to from lactol **217** in 40% yield. Finally, (–)-trachyspic acid (**24**) was made by following the Hatakeyama precedent (Scheme 66).

Scheme 66. Enantioselective synthesis of (–)-trachyspic acid (**24**).

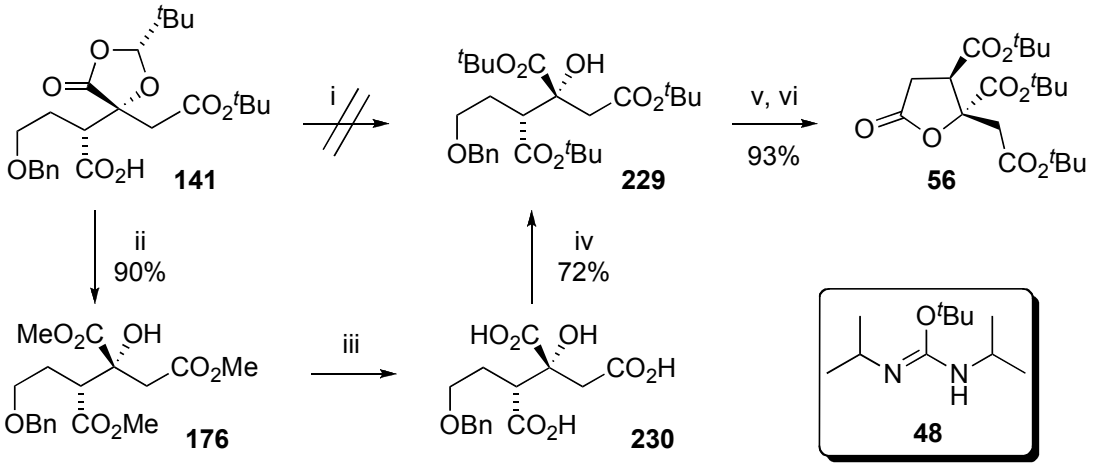


Reagents and conditions: i) nonyl bromide, NaOMe, MeOH, reflux; ii) $LiAlH_4$, THF; iii) TBDPSCl, NaH, THF; iv) DMP, CH_2Cl_2; v) PPh_3, CBr_4, THF, 0 ^{o}C then ^{n}BuLi, –78 °C; vi) *B*-Br-9-BBN, AcOH, 0 ^{o}C; vii) TBAF, THF; viii) DMP, CH_2Cl_2; ix) ethylene glycol, *p*-TsOH, benzene, reflux; x) ^{t}BuLi, Et_2O-hexane, –78 °C then **56**.

I.2.2. Formal total synthesis of (–)-trachyspic acid (23) by making lactone 56

Having successfully opened dioxolanone **141** in refluxing methanol with $BF_3{\cdot}OEt_2$, the same conditions were tried with ^{t}BuOH to obtain directly dioxolanone **229**. Disappointingly, the switch from MeOH to ^{t}BuOH gave no conversion, hence an alternative route was investigated (Scheme 67). Trimethyl ester **176** was converted to tricarboxylic acid **230**, without epimerisation, by saponification with LiOH. Esterification of crude tricarboxylic acid **230** with reagent **48** afforded the tri-*tert*-butyl ester **229** in 72% yield over the two steps. Finally, sequential benzyl ether hydrogenolysis and TPAP/NMO oxidation[164-166] of **229** gave Rizzacasa's lactone **56** in 93% yield over the two steps. Lactone **56** showed identical data as previously reported[48] and its structure was also confirmed by X-ray crystallography (Figure 17). The synthesis of lactone **56** was achieved in 21% yield over 13 steps whereas the Rizzacasa route proceeded with 7% yield over 15 steps.[167]

Scheme 67. Synthesis of Rizzacasa's lactone **56**.



Reagents and conditions: i) ^{t}BuOH, $BF_3{\cdot}OEt_2$, reflux, sealed tube; ii) MeOH, $BF_3{\cdot}OEt_2$, reflux, sealed tube; iii) LiOH, THF-H_2O, 60 ^{o}C ; iv) **48**, CH_2Cl_2, reflux; v) H_2, Pd/C, THF; vi) TPAP, NMO, CH_2Cl_2.

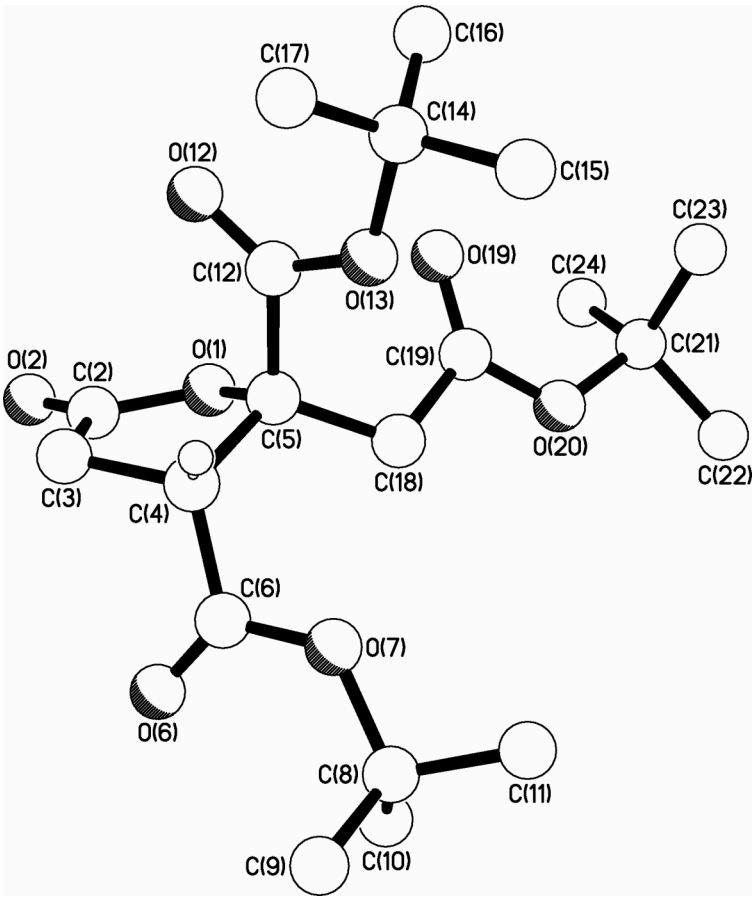
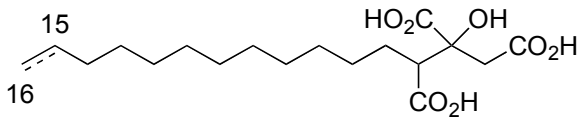


Figure 17. X-ray crystallography of lactone **56**.

I.3. CJ-13,981 AND CJ-13,982[Ω]

I.3.1. Structures and isolation

In 2001, Pfizer scientists in Nagoya isolated two new Squalene Synthase (SSase) inhibitors, CJ-13,981 (**25**) and CJ-13,982 (**26**) from the fermentation broth of an unidentified fungus (CL15036) and identified their structures by FAB-MS and NMR analyses (Figure 18). CJ-13,981 (**25**) and CJ-13,982 (**26**) inhibited human liver microsomal SSase with IC_{50} values of 2.8 and 1.1 μM, respectively. Their relative and absolute stereochemistries were not determined although their optical rotations were reported.[168]



CJ-13,981 (**25**) (15,16-olefin)
CJ-13,982 (**26**) (15,16-dihydro)

Figure 18. Structures of CJ-13,981 (**25**) and CJ-13,982 (**26**).

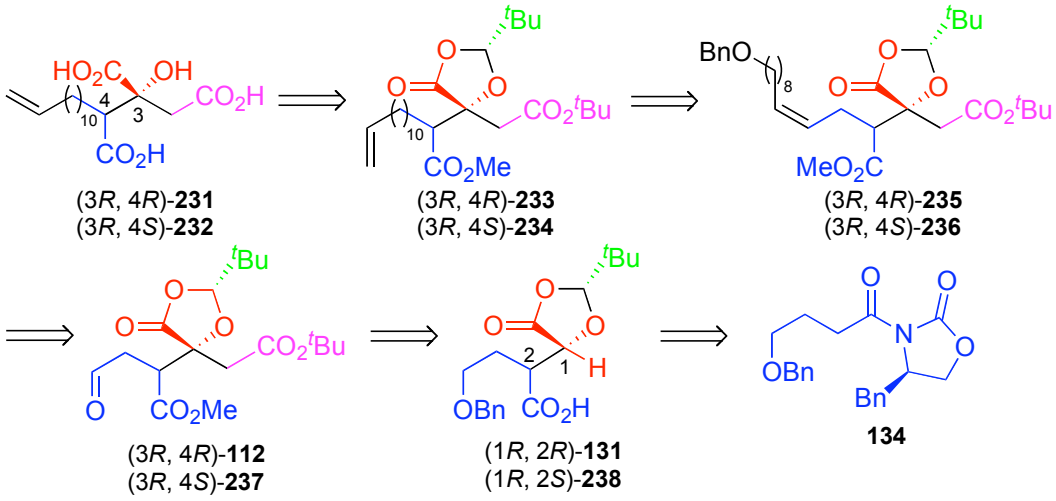
Squalene synthase (SSase) is a key enzyme in the isoprenoid pathway, which catalyzes the biosynthesis of squalene, a key cholesterol precursor, by the reductive dimerisation of two molecules of farnesyl pyrophosphate (FPP) *via* the intermediate presqualene pyrophosphate. Specific inhibition of SSase would suppress cholesterol biosynthesis but not prevent the formation of other essential non-sterol products, such as ubiquinone, dolichol, isopentenyl t-RNA and prenylated proteins and therefore represents an attractive target for pharmaceutical discovery.[168]

[Ω] This work has been conducted with the help of Alexander Bondke, an Erasmus student who joined the Barrett group for a period of six months.

I.3.2. Synthesis of *ent*-CJ-13,981 and *ent*-CJ-13,982

As part of our research on the total synthesis of alkyl citrate natural products,[4] it was decided to determine the full stereochemistries of CJ-13,981 (**25**) and CJ-13,982 (**26**) by total synthesis of two of the four possible stereoisomers. Arbitrarily, the stereochemistry at C-3 was set as *R*. The retrosynthetic analysis for both the (3*R*,4*S*) and (3*R*,4*R*)-15-alkene stereoisomers is shown in Scheme 68.

Scheme 68. Retrosynthetic analysis.



The tricarboxylic acids **231** and **232** should be available from the precursors **233** and **234** by saponification. In turn, the dioxolanones **233** and **234** should be synthesised from aldehydes **112** and **237** by Wittig reaction, hydrogenation and elimination of the benzyloxy substituent in **235** and **236**. These key aldehydes **112** and **237** should be synthesised from oxazolidinone **134** respectively, by either a *syn*- or an *anti*-aldol reaction, dioxolanone **131**

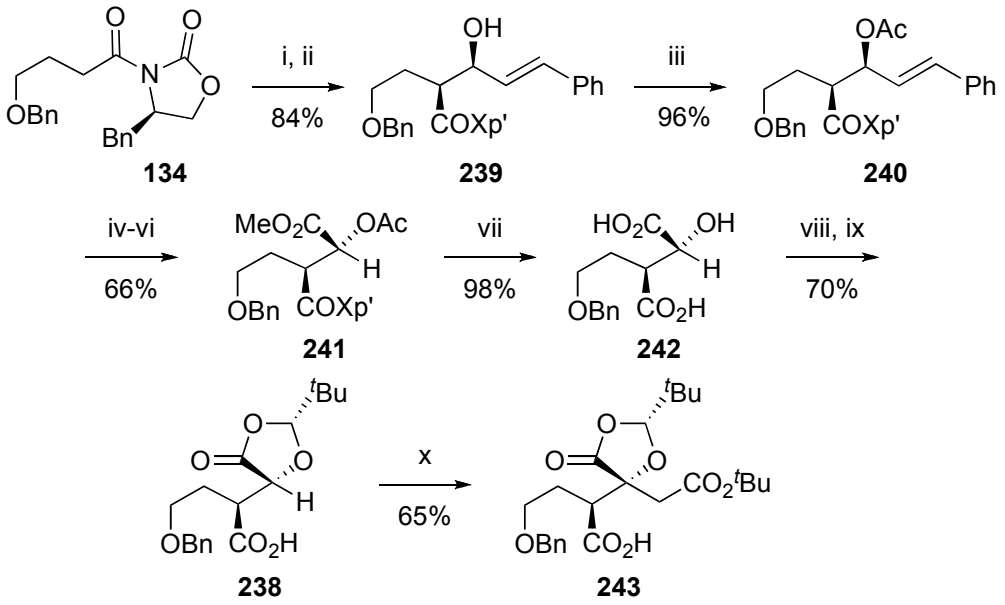
and **238** formation and Seebach Self–Regeneration of Stereocenter (SRS) alkylation using *tert*-butyl bromoacetate.

I.3.2.1. Synthesis of dioxolanone 243

Having successfully synthesised dioxolanone **131** and used it for the total synthesis of citrafungin A and the formal synthesis of (–)-trachyspic acid, it was decided to apply the same strategy to elaborate its diastereoisomer **238** starting from imide **134** by using an *anti*-aldol reaction. Contrary to our expectation, attempted *anti*-aldol reactions of **134** with propenal in the presence of the Lewis acids $^{n}Bu_2BOTf$-Et_2AlCl,[68] $MgCl_2$,[69] *c*-$(C_6H_{11})_2BCl$,[70] or $MgBr_2{\cdot}OEt_2$[69] either failed or gave intractable mixtures of diastereoisomers. However, by changing the electrophile to cinnamaldehyde, the Evans $MgBr_2{\cdot}OEt_2$ catalyzed *anti*-aldol reaction proceeded in 84% yield after TFA-mediated desilylation (Scheme 69). The resultant secondary alcohol **239** was protected as the acetate **240** (96%),[169] the structure of which was confirmed by X-ray crystallography (Figure 19). Ozonolysis using a dimethyl sulfide work-up and subsequent Pinnick oxidation gave the corresponding carboxylic acid which was esterified using diazomethane to give the methyl ester **241**. Triple oxazolidinone, methyl ester and acetate hydrolysis using lithium hydroxide and hydrogen peroxide gave diacid **242**, which was converted into the *cis*-dioxolanone **238** using Hoye acetalisation.[80,170] The structure of **238** was confirmed by NOESY NMR. Attempted acetalisation of **242** using a *p*-TsOH-catalyzed condensation reaction, gave an inseparable 1:1 mixture of **238** and its *trans*-isomer. Seebach SRS alkylation of dioxolanone **238** by double deprotonation using lithium hexamethyldisilazide

in DMF at –70 °C followed by addition of *t*-butyl bromoacetate gave exclusively dioxolanone **243** in 65% yield.[62,71,146,167]

Scheme 69. Synthesis of dioxolanone **243**.



Reagents and conditions: i) $MgBr_2 \cdot OEt_2$, PhCH=CHCHO, Me_3SiCl, EtOAc; ii) TFA, CH_2Cl_2; iii) Ac_2O, DMAP, Et_2O; iv) O_3, Me_2S, CH_2Cl_2, –78 ºC; v) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, THF, H_2O (1:1:1); vi) CH_2N_2, Et_2O; vii) LiOH, H_2O_2, THF, H_2O (1:1); viii) TMSCl, DIPEA, THF, RT; ix) Pivaldehyde, TMSOTf (20 mol %), CH_2Cl_2, –35 ºC, x) LHMDS, DMF, –70 ºC then $BrAcO^tBu$, –70 ºC.

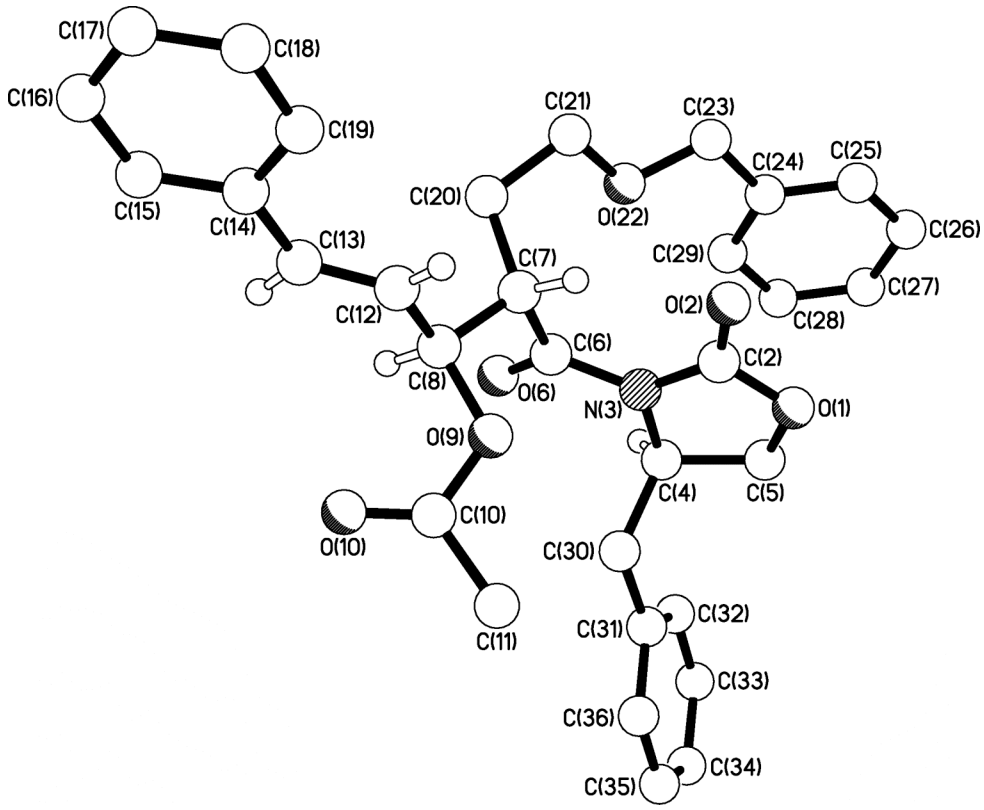


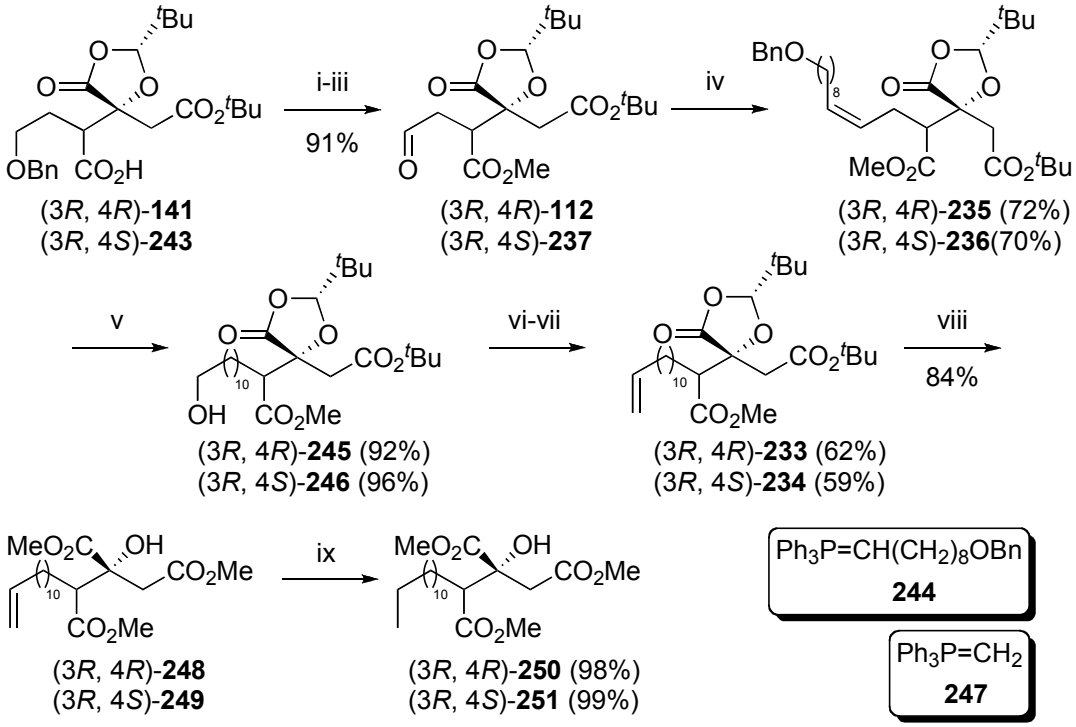
Figure 19. X-ray structure confirmation of acetate **240**.

I.3.2.2. Synthesis of esters 248-251

Diazomethane esterification of carboxylic acids **141** and **243** gave the corresponding methyl esters, which were subjected to benzyl ether hydrogenolysis and Dess–Martin oxidation to give aldehydes **112** and **237**, both in 91% yield over the three steps. Wittig olefination using $Ph_3P{=}CH(CH_2)_8OBn$ (**244**)[171] respectively gave *cis*-alkenes **235** and **236**, which were hydrogenated over palladium on carbon to yield alcohols **245** and **246** in 66% and 67% yield, respectively (Scheme 70). Sequential Dess–Martin oxidation and Wittig olefination with ylide **247** gave alkenes (3*R*, 4*R*)-**233** and (3*R*, 4*S*)-**234** in 62% and 59% yields respectively over the two steps. It is noteworthy in this sequence that the

dioxolanone was used as a protecting group for the α-hydroxy acid as well as the stereocontrolling element in the Seebach alkylation reaction. Dioxolanone ring opening was effected by refluxing in methanol containing $BF_3{\cdot}OEt_2$[128] giving the trimethyl esters **248** and **249** (84%) which were hydrogenated over palladium on carbon to give esters, **250** and **251**, respectively.

Scheme 70. Synthesis of triesters **248** – **251**.



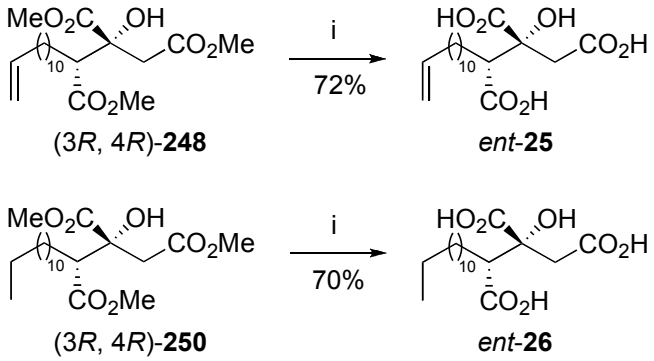
Reagents and conditions: i) CH_2N_2, Et_2O; ii) H_2, Pd/C, THF; iii) DMP, CH_2Cl_2; iv) **244**, CH_2Cl_2; v) H_2, Pd/C, THF; vi) DMP, CH_2Cl_2; vii) **247**, CH_2Cl_2; viii) $BF_3{\cdot}OEt_2$, MeOH, reflux, sealed tube; ix) H_2, Pd/C, THF.

At this stage, the ^{1}H NMR spectra of **248** and **250** exhibited high similarity to those of the natural products **25** and **26**, although containing three extra methyl ester singlets, whereas the corresponding diastereoisomers **249** and **251** did not.

I.3.2.3. Final hydrolysis and synthesis of *ent*-25 and *ent*-26

Saponification of both **248** and **250** using potassium hydroxide at 80 °C in H_2O gave, after purification on reverse phase silica, *ent*-**25** and *ent*-**26** (Scheme 71). In contrast, attempted saponification of **249** and **251** resulted in extensive decomposition. All the analytical data for the synthetic samples of *ent*-CJ-13,981 (**25**) and *ent*-CJ-13,982 (**26**) matched those reported for the natural products except for the opposite sign of the optical rotations therefore it can be concluded that both the natural products have a (3*S*,4*S*) absolute and relative configuration.[172]

Scheme 71. Synthesis of *ent*-**25** and *ent*-**26**.



Reagents and conditions: i) KOH, THF-H_2O, 80 ^{o}C.

Part 2

Total Synthesis of Resorcylic Acid Lactones Natural Products

Total Synthesis of Aigialomycin D

and

Studies Towards the Total synthesis of Angelicoin A and Angelicoin B

II.1. AIGIALOMYCIN D

II.1.1. Introduction

The 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylate unit (**252**) can be found as part of macrocyclic lactone ring systems in a number of biologically active natural products. Examples include lasiodiplodin (**253**),[173-176] zearalenone (**254**),[177-182] aigialomycin D (**27**),[183-192] radicicol (**255**),[193-200] 15G256-β (**256**),[182,201-204] angelicoin A (**28**) and angelicoin B (**29**)[205] (Figure 20).

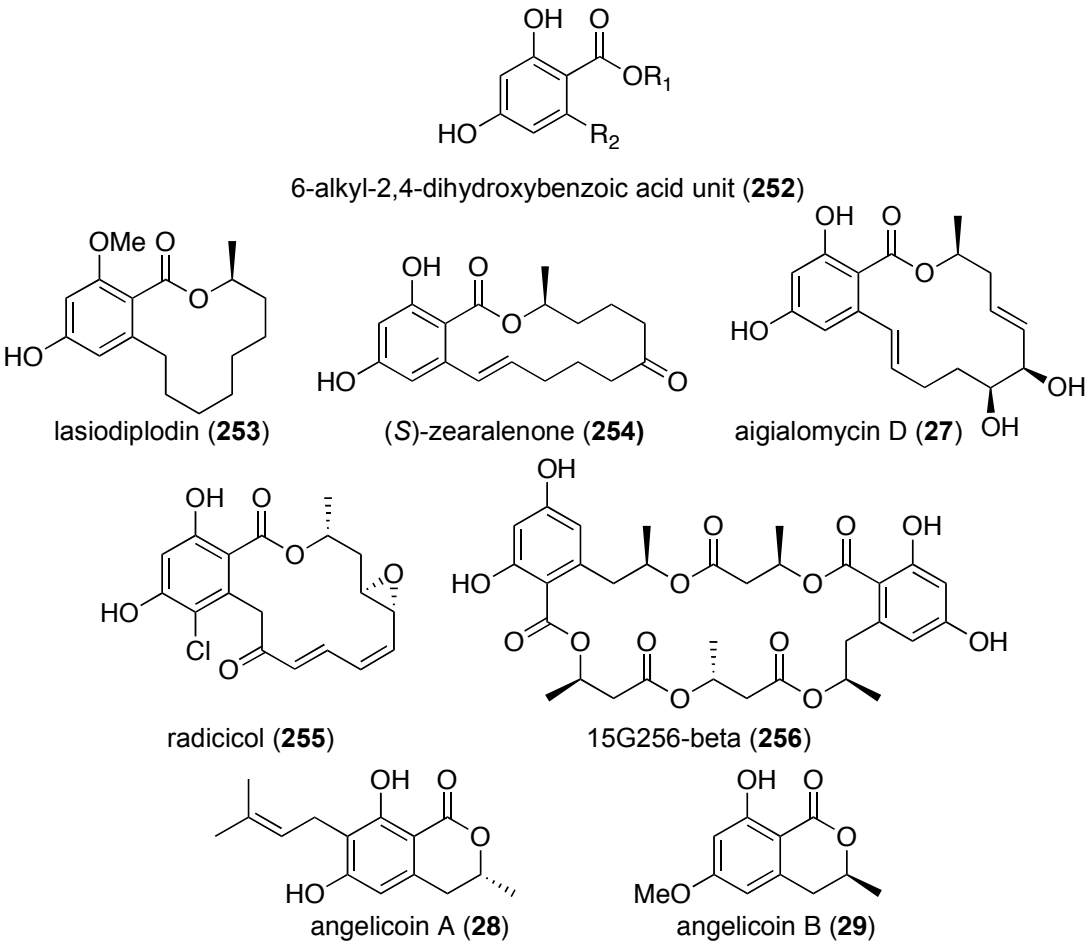


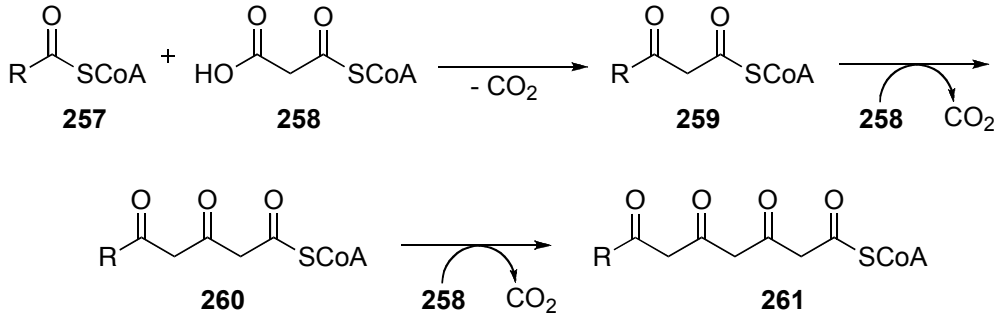
Figure 20. Examples of resorcylic macrolactones.

II.1.1.1. Synthesis of polyketide: the biosynthesis pathway

Biomimetic synthesis has long been a field of interest in organic chemistry, not only to probe in detail the biosynthetic pathway of natural products but also to provide alternative solutions to conventional synthetic problems.

In the 50s, Robinson and Birch[206-210] reintroduced interests in the biosynthesis of polyketides and developed a pathway theory which is still believed today: polyketide chains are constructed by the condensation of coenzyme A esters such as **257** with malonyl coenzyme A ester **258**. After decarboxylation reaction, *β*-keto thioesters **259** were obtained and underwent a Claisen type condensation with malonyl coenzyme A ester **258** to give thioester of 3,5-diketoacids **260**. Repeating this process gave thioesters of 3,5,7-triketoacid derivatives **261** and so on, and thus building the poly-*β*-carbonyl chains (Scheme 72).

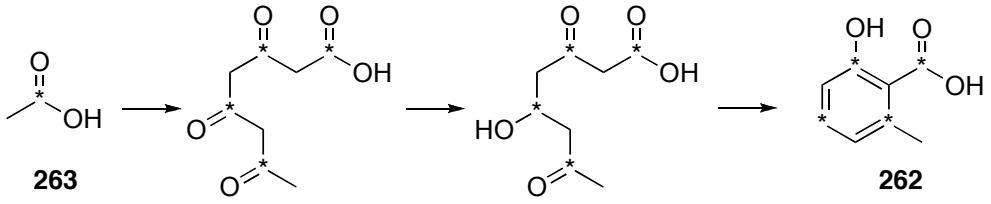
Scheme 72. Biosynthesis pathway of poly-*β*-carbonyl chains.



To validate their theory, Birch *et al*. conducted an *in vivo* experiment which supports the polyketide hypothesis by demonstrating that ^{14}C-labelled 6-methyl salicylic acid (**262**) could be produced biosynthetically from *Penicillium griseofulvum* fed 1-^{14}C-acetic acid

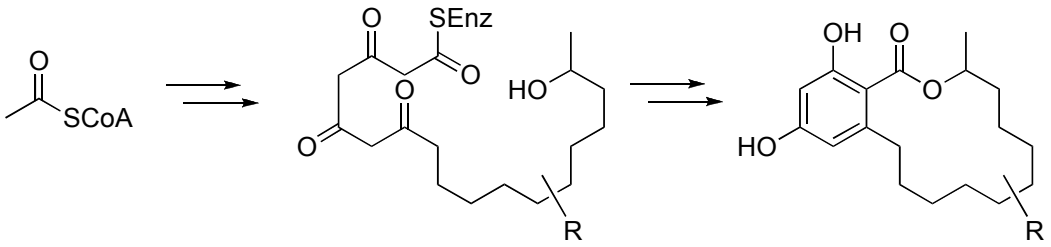
(**263**). Acid **262** presented four alternating ^{14}C labelled sites, as predicted by the polyketide route (Scheme 73).[209]

Scheme 73. Biosynthesis of 6-methyl salicylic acid (**262**). * indicates ^{14}C labelling



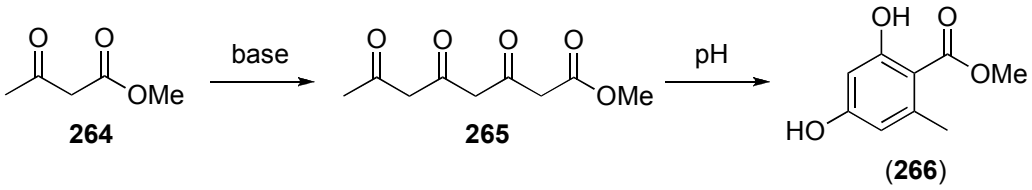
For example, the proposed biosynthesis of zearalenone (**254**) involves two polyketide synthases. The first one assembled the first five acetate units with further processing to arrive at the adequate oxidation state at each carbon. The second one performed the remaining three rounds of condensation without carbonyl reduction. The reactive unreduced ketones engage in a cyclisation-aromatisation sequence followed by lactonisation (Scheme 74). Different combinatorial arrangements of the modules involved in the processing of the *β*-ketones in the first five condensations are possible and are responsible for the diversity of functionality in the resorcylic acid macrolactones (represented by the R-group).

Scheme 74. Biosynthesis of resorcylic acid lactones.



Following the revival of the polyketide hypothesis, several research groups became interested in developing ways to mimic this pathway. The main contributors of the 1970s were C. M. Harris and T. M. Harris.[211-217] They developed a very simple aromatisation reaction involving the self-condensation of methyl acetoacetate **264** to produce methyl 3,5,7-trioxooctanoate **265**. Upon treatment of ester **265** with a range of pH varying from 4 to 12, a rapid aldol condensation-dehydration sequence occurred to give methyl orsellinate (**266**). This procedure was later optimised by Barrett *et al*. using a pH 9.2 buffer and afforded resorcylate **266** in 78% yield (Scheme 75).[218]

Scheme 75. Self-condensation of **264** to produce methyl orsellinate (**266**).

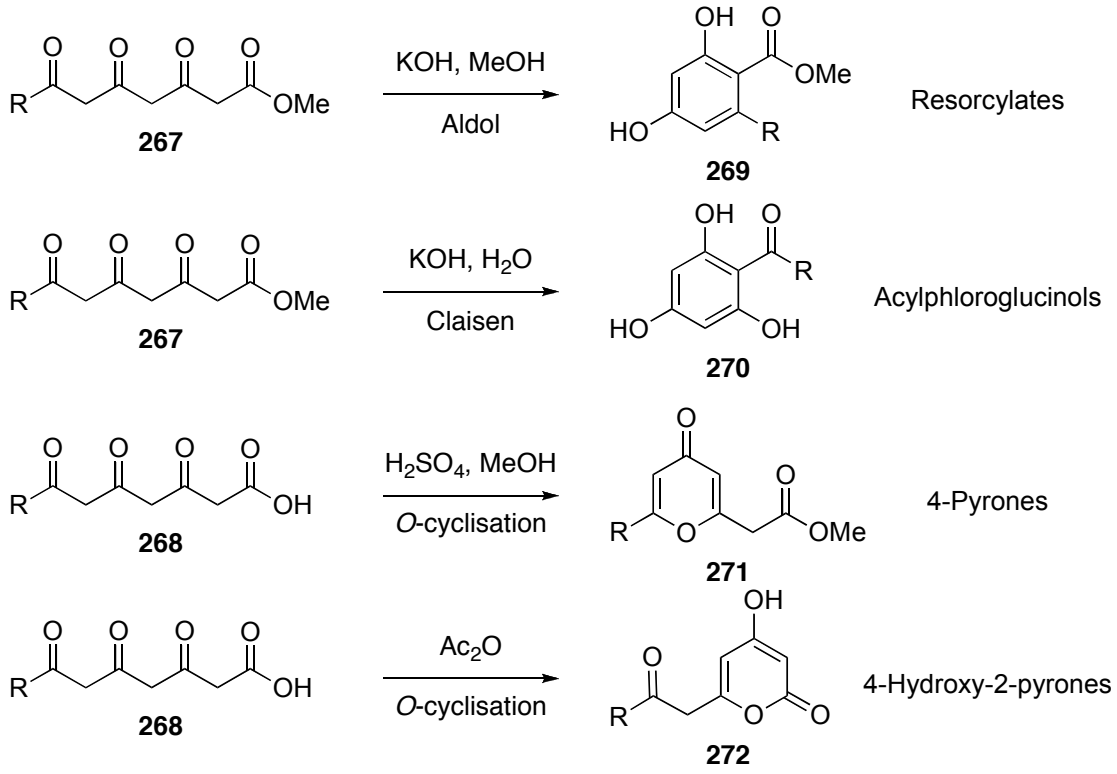


264 **265** (**266**)

Harris *et al.* also demonstrated that poly-β-carbonyl chains could be synthesised and undergo many cyclisation reactions analogous to those carried out in nature, without the need of enzyme catalysis.[211,212,214-217] They have shown that four possible cyclisations can occur from β-triketo acid derivatives (methyl ester **267** and carboxylic acid **268**) (Scheme 76). The aldol condensation-dehydration pathway is predominant under the majority of laboratory reaction conditions to form resorcylates **269**. It is, however, possible to control which cyclisation product is obtained by careful selection of the solvent and pH. From methyl 3,5,7-trioxooctanoate derivatives **267**, the Claisen acylphloroglucinols **270** were obtained by adding an aqueous medium. Derivatives of 3,5,7-trioxooctanoic acid (**268**)

could undergo *O*-cyclisation to give 4-pyrones **271** in strongly acidic conditions and 4-hydroxy-2-pyrones **272** when acetic anhydride was used.

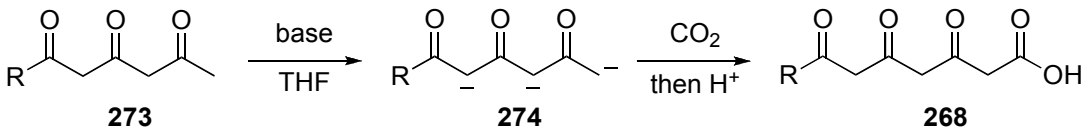
Scheme 76. Possible condensations of β-triketo acid derivatives.



II.1.1.2. Previous syntheses of resorcylates

II.1.1.2.1. From triketo compounds

Starting from 2,4,6-triketo compounds such as **273**, triketo acid derivatives **268** have been synthesised by carboxylation of the corresponding trianions **274**. The best results were observed when the base used was LDA and the solvent THF. Some examples are shown in Table 10.[216]



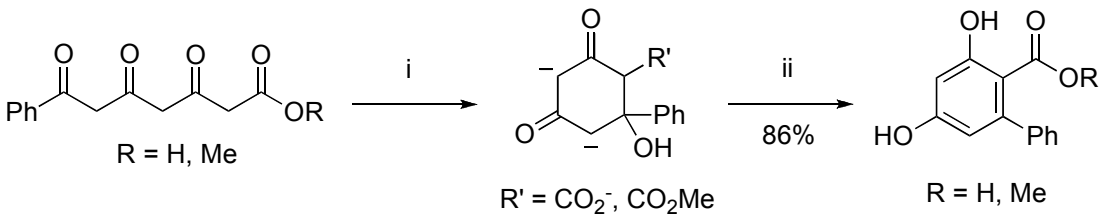
273 274 268

Entry	R-	$NaNH_2$ (yield)	KNH_2 (yield)	LDA (yield)
1	Ph-	46%		82%
2	PhCH=CH-	52%		
3	$PhCH_2CH_2$-	16%	57%	
4	$^nC_7H_{15}$-	>2%	30%	
5	$^nC_5H_{11}$-		16%	44%
6	$^nC_3H_7$-		>5%	28%
7	C_2H_5-			42%
8	CH_3-			47%

Table 10. Carboxylation of trianion using LDA.

Methyl esters **267** were prepared in good yields by treatment of the triketo-acids **268** with diazomethane. Using basic conditions (usually KOH in MeOH) followed by acidic work up, triketo-acids derivatives **267** and **268** afforded the corresponding resorcylates in good yield (Scheme 77).

Scheme 77. Resorcylate formation from triketo-acid or triketo-ester.

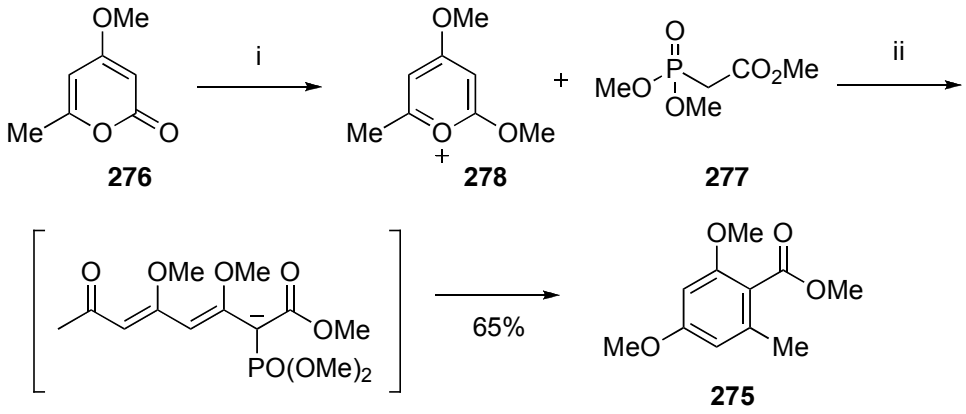


Reagents and conditions: i) KOH, MeOH; ii) aq. HCl.

II.1.1.2.2. From 2-pyrones derivatives

In 1975, Griffin and Staunton synthesised resorcylate **275** starting from 4-methoxy-6-methyl-2-H-pyran-2-one (**276**) by the condensation of trimethyl phosphonoacetate (**277**) with pyrylium ion **278**. The presence of the phosphonate group ensured the regiospecific cyclisation and the reaction proceeded in good yield (65%) (Scheme 78).[219]

Scheme 78. Synthesis of resorcylate **275** from 2-pyrone **276**.



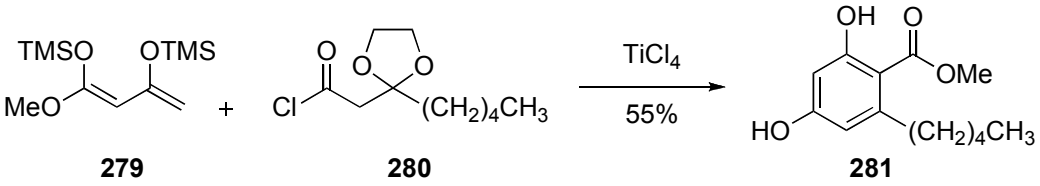
Reagents and conditions: i) FSO_3Me; ii) NaH.

II.1.1.2.3. From silyl enol ethers and activated acids

In the 1980s, Chan *et al*. developed the construction of resorcylates from the intermolecular condensations of silyl enol ethers (such as β-ketoester or β-diketoester equivalents) with activated acids, under Lewis acid catalysis.

In 1982, they condensed silyl enol ether **279** with β-ketal acid chloride **280** to produce resorcylate **281** (55%) after spontaneous ketal deprotection (Scheme 79).[220,221]

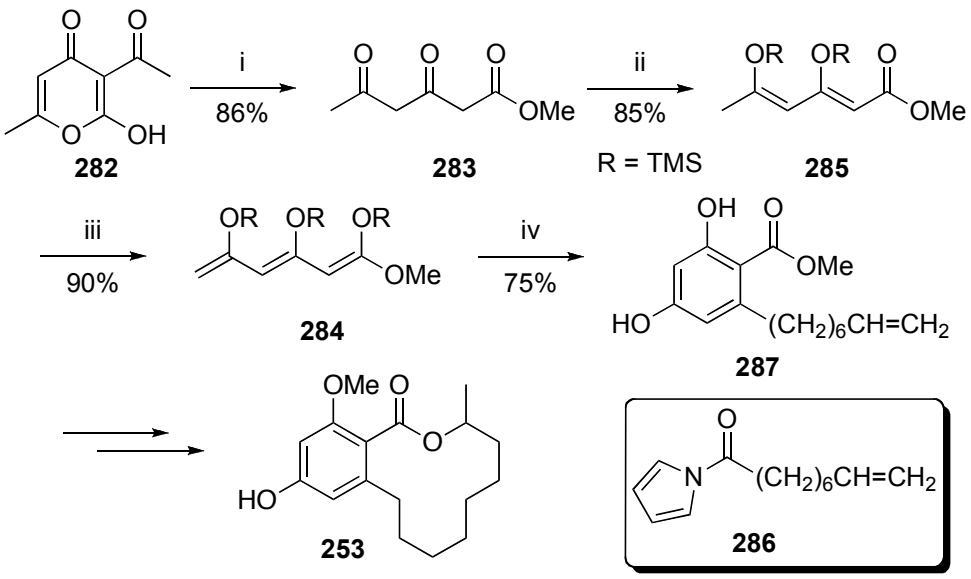
Scheme 79. Chan synthesis of resorcylate using a β-ketoester synthon.



279 **280** **281**

Later in 1986, they applied this strategy to the construction of a more complex resorcylic acid lactone: (±)-lasiodiplodin (**253**). The synthesis started with the conversion of dehydroacetic acid (**282**) to methyl triacetate **283**, which was thus converted to silyl ether **284** (a β-diketo ester trianion equivalent) *via* ester **285**.[222] Reaction with acyl imidazole **286** under Lewis acid catalysis led to the formation of resorcylate **287** in 75% yield, which was further converted to (±)-lasiodiplodin (**253**) (Scheme 80).[223,224]

Scheme 80. Chan synthesis of resorcylate using a β-diketoester synthon.



Reagents and conditions: i) $Mg(OMe)_2$, MeOH; ii) NEt_3, TMSCl, cat. $ZnCl_2$, CH_2Cl_2, RT; iii) LDA, TMSCl, THF, –78 ^oC; iv) $TiCl_2(O^iPr)_2$, CH_2Cl_2 then **286.**

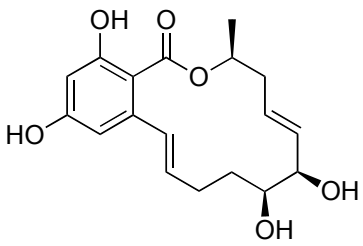
In spite of progress in the latter half of the 20th century, biomimetic strategies for the syntheses of simple resorcylate natural products have failed to develop into methods widely used today. This is principally due to the use of harsh basic or acidic conditions to perform the aromatisation reaction which often showed no substrate compatibility and selectivity. As a result, in today's synthesis of resorcylic lactones, most of the research groups use the resorcylic unit as a building block pre-installed in the natural product.

The next chapter will present the previous total synthesis of aigialomycin D (**27**) from such building blocks.

II.1.1.3. Aigialomycin D: structure, isolation and previous total syntheses

II.1.1.3.1. Structure and isolation

Aigialomycin D (**27**) is a 14-membered resorcylic macrolide (Figure 21) possessing three stereocenters and two double bonds of (*E*)-configuration. It was isolated in 2002 from the marine mangrove fungus *Aigialus parvus* BCC5331 and shows potent antitumor (IC_{50}: 3.0 μg/ml against KB cells) and antimalarial activities (IC_{50}: 6.6 μg/ml against *Plasmodium falciparum*). Recently, cyclin-dependent kinase (CDK) and glycogen synthase kinase 3 (GSK-3) have been identified as its antitumor targets of action. Due to its interesting biological properties, several total syntheses of aigialomycin D have been reported.[184-191,225]



aigialomycin D (**27**)

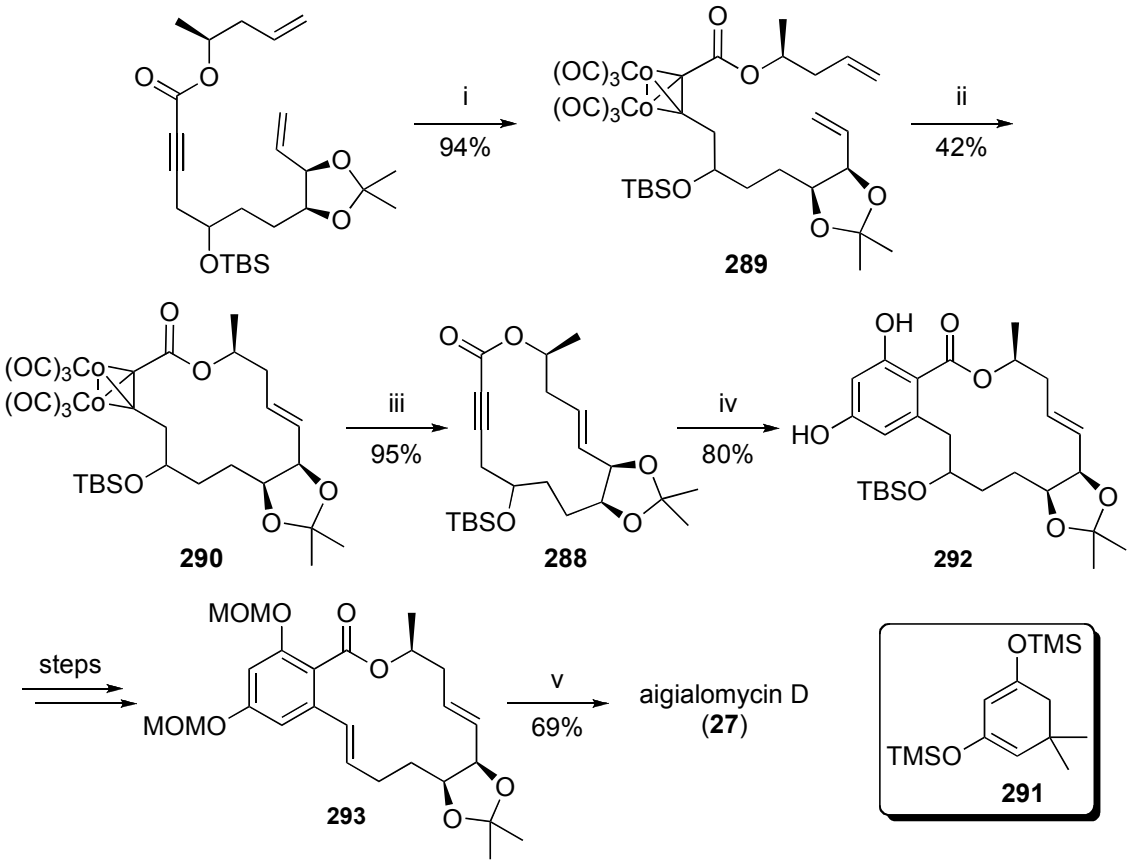
Figure 21. Structure of aigialomycin D (**27**).

II.1.1.3.2. First total synthesis without the use of resorcylate building blocks

In 2004, Danishefsky *et al*. published the first total synthesis of aigialomycin D (**27**).[184] Inspired by their success with the total synthesis of cycloproparadicicol *via* an ynolide protocol and a Diels–Alder reaction,[200] they applied the same strategy for the total synthesis of aigialomycin D. Ynolide **288** was assembled by RCM of protected alkyne **289** and

deprotection of **290**. DielsAlder reaction with disiloxydiene **291** afforded resorcylate **292** in good yield (80%). Protecting group manipulation and formation of the benzylic double bond by elimination gave resorcylate **293** which was converted to aigialomycin D (**27**) by acidic deprotection (Scheme 81). The synthesis was realised in 18 steps with an overall yield of 8%.

Scheme 81. Key steps in Danishefsky's total synthesis of aigialomycin D.



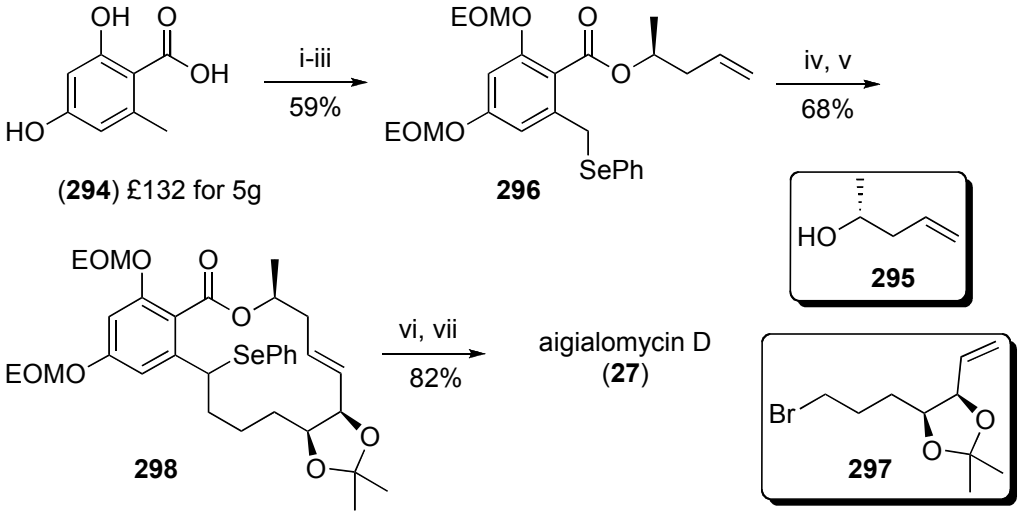
Reagents and conditions: i) $Co_2(CO)_8$, PhMe, RT; ii) Grubbs II (**126**), CH_2Cl_2, RT; iii) CAN, acetone, –10 ^oC; iv) **291**, neat, 140 ^oC; v) 0.5 M HCl, MeOH-H_2O.

II.1.1.3.3. Previous syntheses of aigialomycin D having the resorcylic unit preinstalled

II.1.1.3.3.1. Winssinger's approach

In 2006, Winssinger *et al.* realised a concise total synthesis of aigialomycin D starting from commercially available 2,4-dihydroxy-6-methyl benzoic acid (**294**).[185] Polymer supported Mitsunobu reaction[226-231] with alcohol **295** followed by phenol protection and alkylation with diphenyl diselenide afforded selenoether **296** in 59% yield over the three steps. Alkylation with bromide **297** followed by RCM produced the protected resorcylate **298** in good yield (68%). Final selenium oxidation with *in situ* elimination and deprotection gave aigialomycin D (Scheme 82). The synthesis required only seven linear steps with an overall yield of 32%. It is to date the shortest and the highest yielding synthesis.

Scheme 82. Total synthesis of aigialomycin D from the Winssinger group.

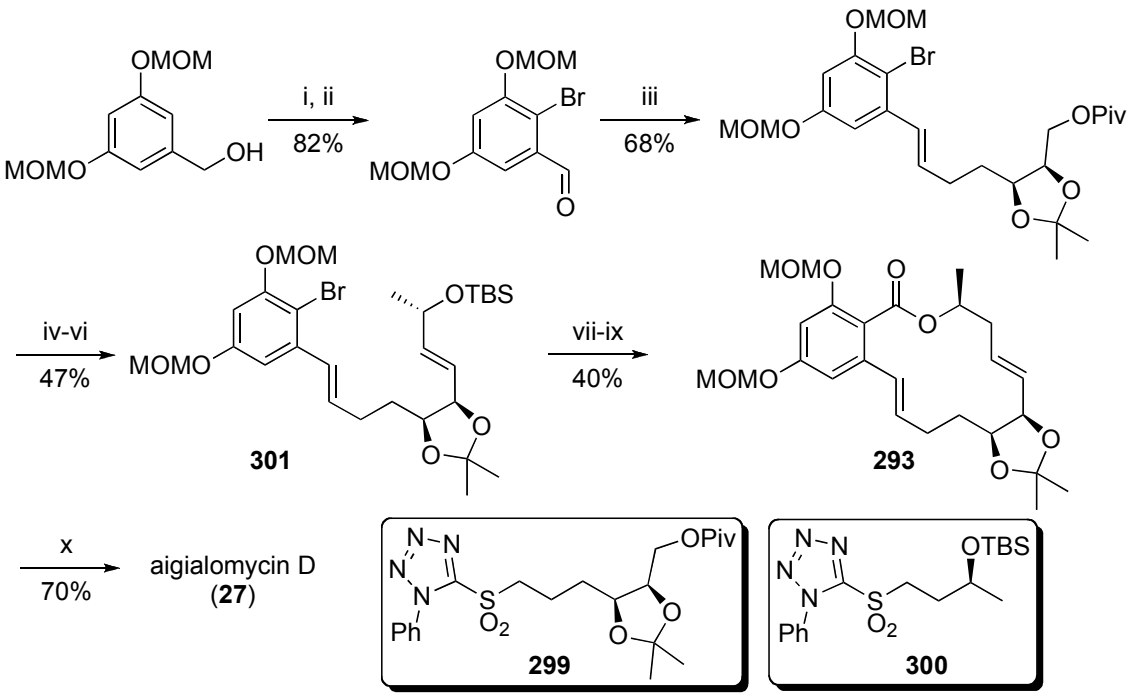


Reagents and conditions: i) **295**, *m*-Cl-Ph_3P, PS-DEAD; ii) $^{i}Pr_2EtN$, EOM-Cl; iii) LDA then $(PhSe)_2$; iv) LDA then **297**; v) Grubbs II (**126**), CH_2Cl_2, reflux; vi) H_2O_2; vii) PS-SO_3H.

II.1.1.3.3.2. Pan's synthesis

At the same time, the group of X. Pan also published a total synthesis of aigialomycin D where the 14-membered resorcylate was assembled by a Yamaguchi lactonisation.[186] The two (*E*)-double bonds were installed stereoselectively by performing two Julia-Kocienski reactions,[232-239] using respectively sulfones **299** and **300** to form bromide **301** (Scheme 83). Carboxylation of **301**, deprotection and Yamaguchi macrolactonisation gave Danishefsky's resorcylate **293**. Pan's synthesis was accomplished in ten linear steps and with 7% yield starting from a non-commercially available precursor.

Scheme 83. Key steps in Pan's synthesis of aigialomycin D.

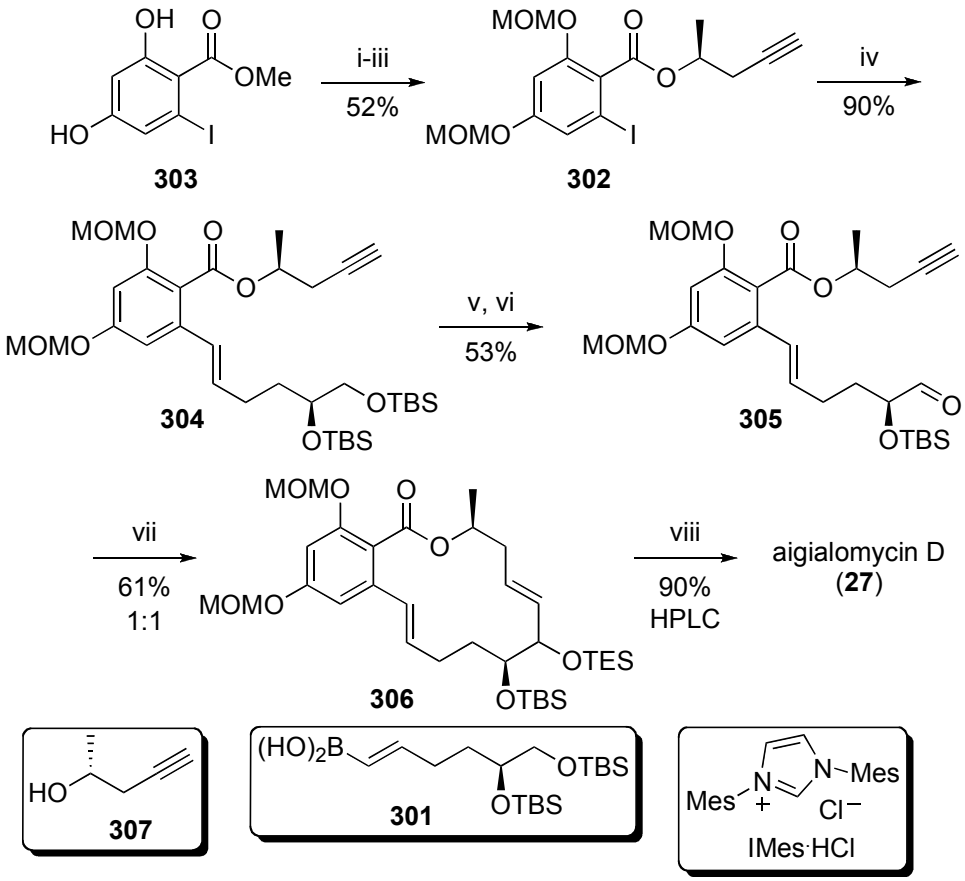


Reagents and conditions: i) NBS, $CHCl_3$, RT; ii) PCC, NaOAc, CH_2Cl_2, RT; iii) **299**, KHMDS, DME, –60 °C to RT; iv) DIBAL-H, CH_2Cl_2, –78 °C; v) DMP, CH_2Cl_2, RT; vi) **300**, KHMDS, DME, –60 °C to RT; vii) TBAF, THF, RT; viii) ^{n}BuLi, CO_2, THF, –78 °C to RT; ix) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF then DMAP, PhMe, reflux; x) 0.5 M HCl, MeOH/H_2O, RT.

II.1.1.3.3.3. Montgomery's synthesis

In 2009, Montgomery *et al*. developed a new strategy for the total synthesis of aigialomycin D.[190] They carried out a nickel-catalysed ynal macrocyclisation which in a single step formed the macrocycle, the disubstituted olefin and the secondary allylic alcohol but as a mixture of diastereoisomers. The Suzuki coupling[240-245] between boronic acid **301** with aryl iodide **302** (made in three steps from known resorcylic iodide **303)** gave resorcylate **304** (Scheme 84). Deprotection and oxidation of **304** allowed the formation of key aldehyde **305** which underwent a the nickel-catalysed reductive coupling and macrocyclisation to produce resorcylate **306** as a 1:1 mixture of diastereoisomers. Final deprotection and HPLC separation gave aigialomycin D (**27**). The overall synthesis required eight linear steps and proceeded with 7% yield starting from non-commercially available precursors.

Scheme 84. Montgomery's total synthesis of aigialomycin D.



Reagents and conditions: i) MOMCl, $^{i}PrEt_2N$, CH_2Cl_2; ii) NaOTMS, CH_2Cl_2, RT; iii) **307**, DEAD, PPh_3, THF, RT; iv) **301**, $Pd(PPh_3)_4$; v) HF·pyr, MeCN; vi) DMP, CH_2Cl_2, RT; vii) Et_3SiH, $Ni(COD)_2$, IMes·HCl, $^{t}BuOK$; viii) aq. HCl, MeOH.

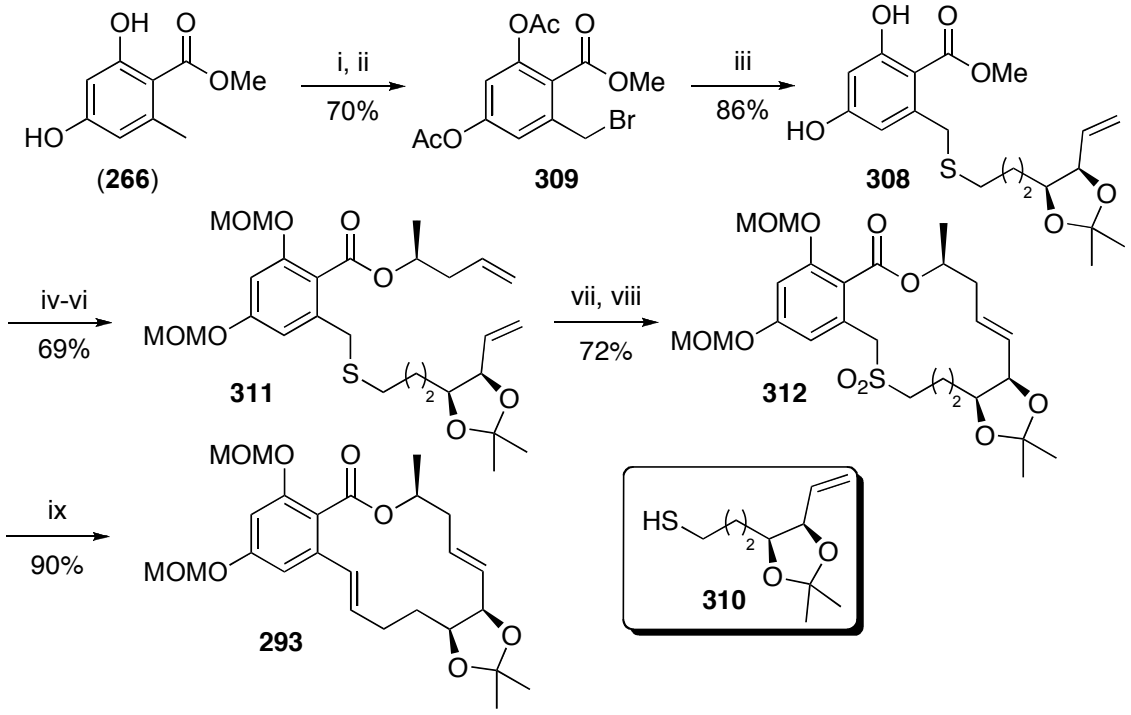
II.1.1.3.3.4. Harvey's synthesis

In 2009, J. E. Harvey *et al.* developed a different approach towards the total synthesis of aigialomycin D using a novel combination of RCM and Ramberg-Bäcklund[246,247] reactions to form the macrocycle and to introduce the benzylic double bond, respectively.[191]

Sulfide **308** was prepared in one step by displacement of bromide **309** (made in two steps from methyl orsellinate (**266**)) with thiol **310** (Scheme 85). Functional group manipulations gave resorcylate **311** which was converted to macrocycle **312** by oxidation and RCM

reactions. The key Ramberg-Bäcklund reaction produced Danishefsky's resorcylate **293** in 90% yield.

Scheme 85. Harvey's formal synthesis of aigialomycin D.



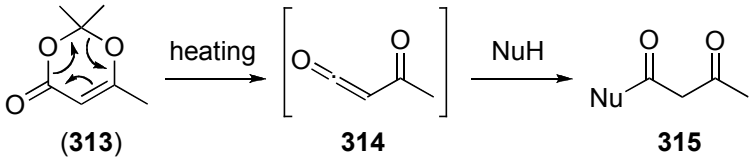
Reagents and conditions: i) Ac_2O, Et_3N, CH_2Cl_2; ii) NBS, $[PhC(O)O]_2$, CCl_4, RT; iii) **310**, K_2CO_3, MeOH, RT; iv) NaH, MOMCl, DMF; v) KOH, H_2O-MeOH; vi) **295**, DIAD, PPh_3, THF, RT; vii) *m*-CPBA, CH_2Cl_2, RT; viii) Grubbs II (**126**), CH_2Cl_2, RT; ix) CCl_4, KOH, ^{t}BuOH, CH_2Cl_2.

II.1.1.3.4. Previous work in the Barrett group

In 1984, Hyatt *et al*. have shown that 2,2,6-trimethyl-4-H-1,3-dioxin-4-one (**313**) could be opened at elevated temperatures with nucleophiles such as alcohols, amines and thiols to provide β-keto esters, β-keto amides or β-keto thio esters, respectively. This reaction

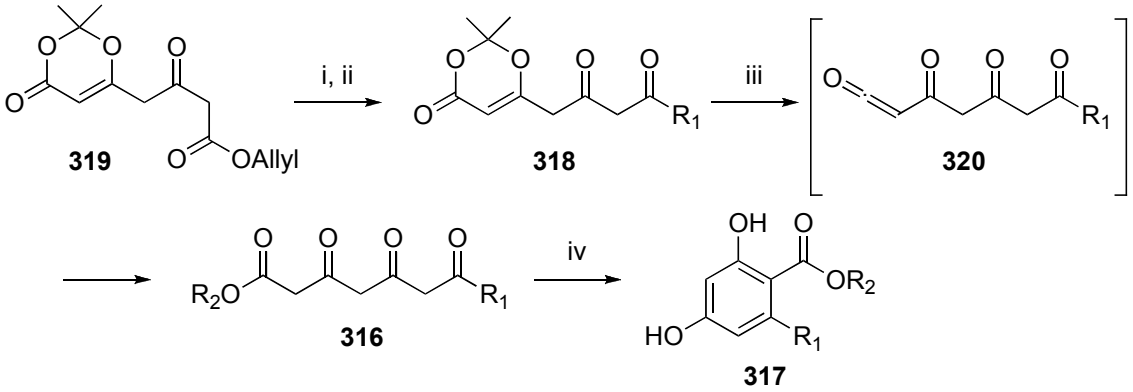
occurred *via* a retro Diels–Alder reaction to form acetylketene **314**, which was trapped with a nucleophile to form the desired product **315** (Scheme 86).[248-250]

Scheme 86. Nucleophilic opening of dioxinone **313**.



Inspired by the work of Hyatt, Barrett *et al.* recently discovered that key triketo-esters **316**, precursors of resorcylates **317** as shown by Harris, could be synthesised from diketo-dioxinones **318** (Scheme 87). These dioxinones (**318**) were constructed by a mild and highly selective *C*-acylation reaction, starting from dioxinone **319**, without using strongly Brönsted basic or Lewis acidic conditions that have hitherto significantly limited the scope of resorcylate biomimetic synthesis.

Scheme 87. Barrett's strategy to construct resorcylates **317**.



Reagents and conditions: i) $MgCl_2$, pyridine, CH_2Cl_2, 0 ^oC then R_1COCl; ii) morpholine, $Pd(PPh_3)_4$, CH_2Cl_2, 0 ^oC; iii) PhMe, 120 ^oC, R_2OH; iv) K_2CO_3, ^iPrOH-CH_2Cl_2 then HCl, MeOH.

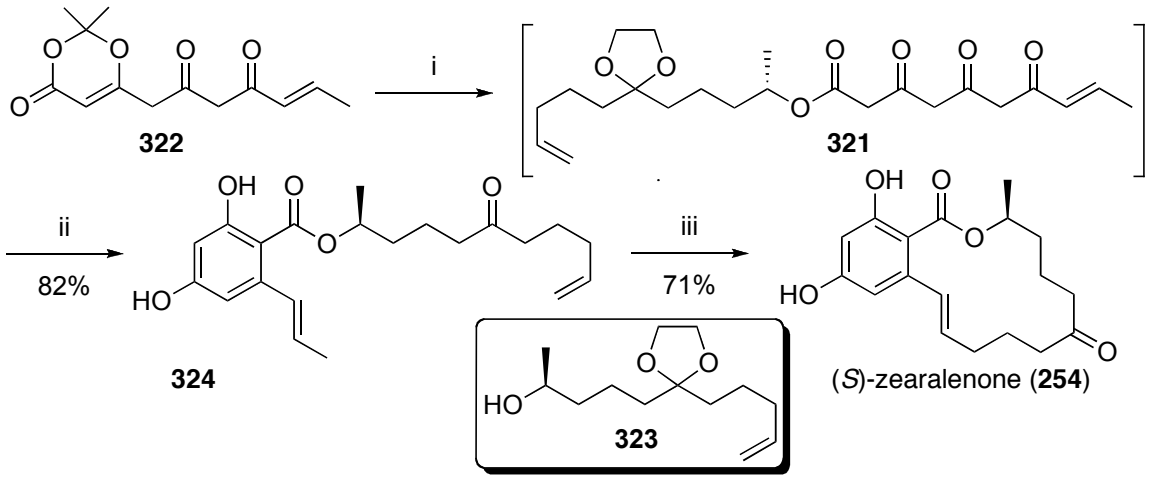
Upon heating, dioxinones **318** underwent a retro Diels–Alder reaction and generated triketo-ketenes **320** which were trapped with alcohols to generate the triketo-esters **316**. Aromatisation by adding successively potassium carbonate and methanolic hydrogen chloride led to resorcylates **317** in good yield (usually between 70 to 85%).

Using this methodology, the total synthesis of (*S*)-zearalenone (**254**) and the first total synthesis of the marine antifungal agent 15G256β (**256**) were recently published.[182]

II.1.1.3.4.1 Total synthesis of (*S*)-zearalenone (254)

The synthesis of triketo-ester **321** was achieved by thermolysis of diketo-dioxinone **322** in the presence of alcohol **323**. Smooth aromatisation and ketal deprotection afforded resorcylate **324** in 82% yield over the two steps (Scheme 88).

Scheme 88. Biomimetic total synthesis of (*S*)-zearalenone (**254**).



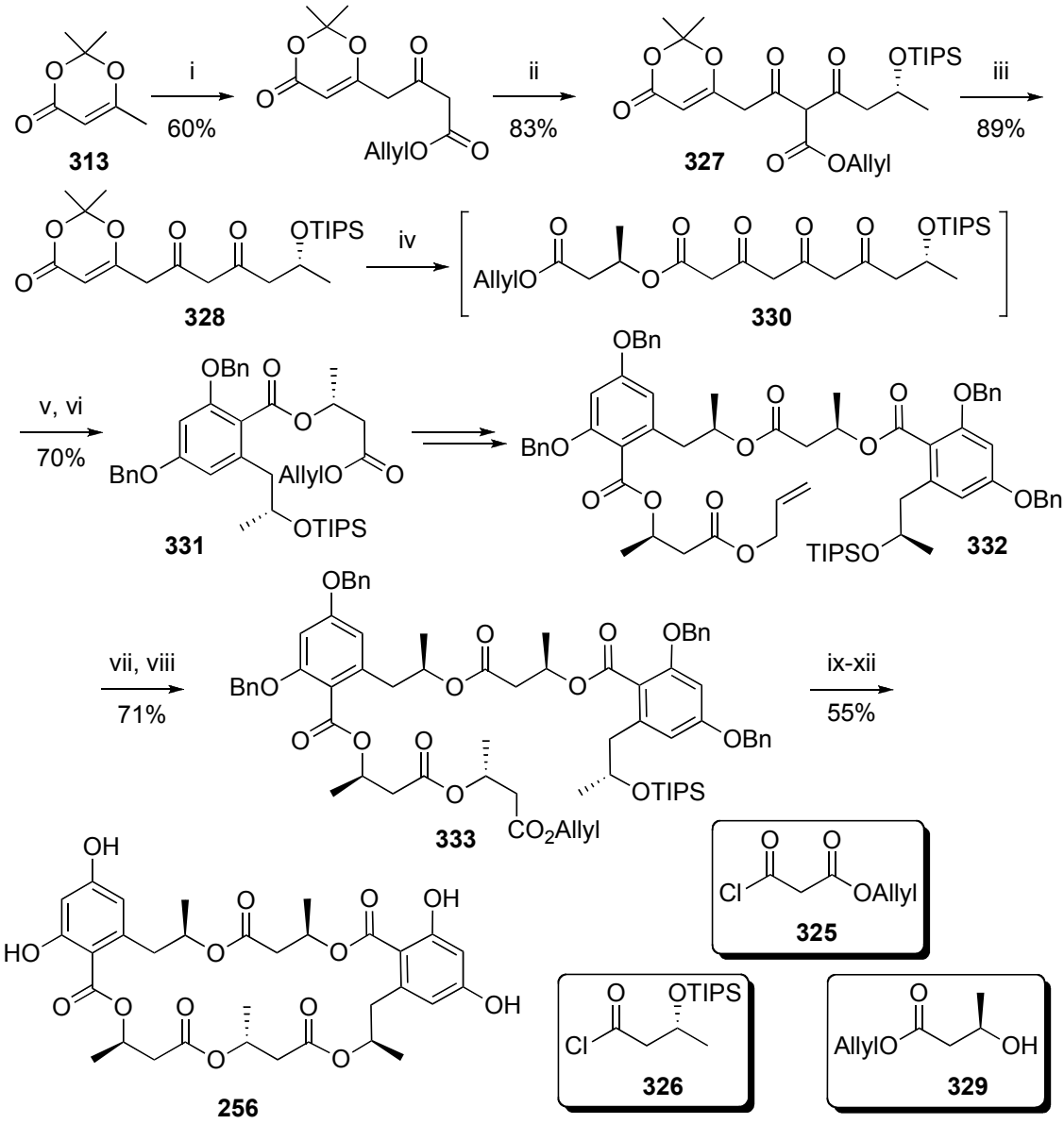
Reagents and conditions: i) **323**, PhMe, 120 °C; ii) KOMe, MeOH then HCl, MeOH; iii) Hoveyda–Grubbs II (**128**) (10 mol %), PhMe, 80 °C.

The latter was subjected to a RCM reaction using the Hoveyda–Grubbs II (**128**) catalyst to give a (*E*):(*Z*) (86:14) mixture of macrolatones from which (*S*)-zearalenone (**254**) was isolated in 71% yield.

II.1.1.3.4.2 Total synthesis of 15G256β (256)

The synthesis of marine antifungal agent 15G256β (**256**) started with sequential double *C*-acylation of commercially available dioxinone **313** with acyl chlorides **325** and **326** to produce diketo-ester **327**. Upon a palladium-catalyzed deallylation-decarboxylation reaction, key diketo-dioxinone **328** was formed in 89% yield (Scheme 89). Thermal decomposition of dioxinone **328** in the presence of alcohol **329** gave triketo-ester **330**, which was aromatised to provide, after phenol group protection, resorcylate monomer **331**. Functional modifications and Yamaguchi esterification afforded dimer **332** which was converted to allyl ester **333** in 71% yield over the two steps. Final deallylation, alcohol deprotection followed by Yamaguchi lactonisation and removal of the benzyl groups by hydrogenolysis led to 15G256β (**256**) in 55% yield over the four steps.

Scheme 89. New biomimetic synthesis of resorcylate 15G256β (**256**).



Reagents and conditions: i) LDA, THF, –78 °C then **325**; ii) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C then **326**, 0 °C to RT; iii) morpholine, $Pd(PPh_3)_4$, CH_2Cl_2, 0 °C; iv) **329**, PhMe, 120 °C; v) K_2CO_3, ^{i}PrOH-CH_2Cl_2 then HCl, MeOH; vi) Cs_2CO_3, BnBr, DMF, RT; vii) morpholine, $Pd(PPh_3)_4$, THF, 0 °C to RT; viii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF then **329**, DMAP, PhMe, reflux; ix) morpholine, $Pd(PPh_3)_4$, THF; x) HF·pyridine, THF; xi) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF then DMAP, PhMe, reflux; xii) H_2, Pd/C, EtOAc, RT.

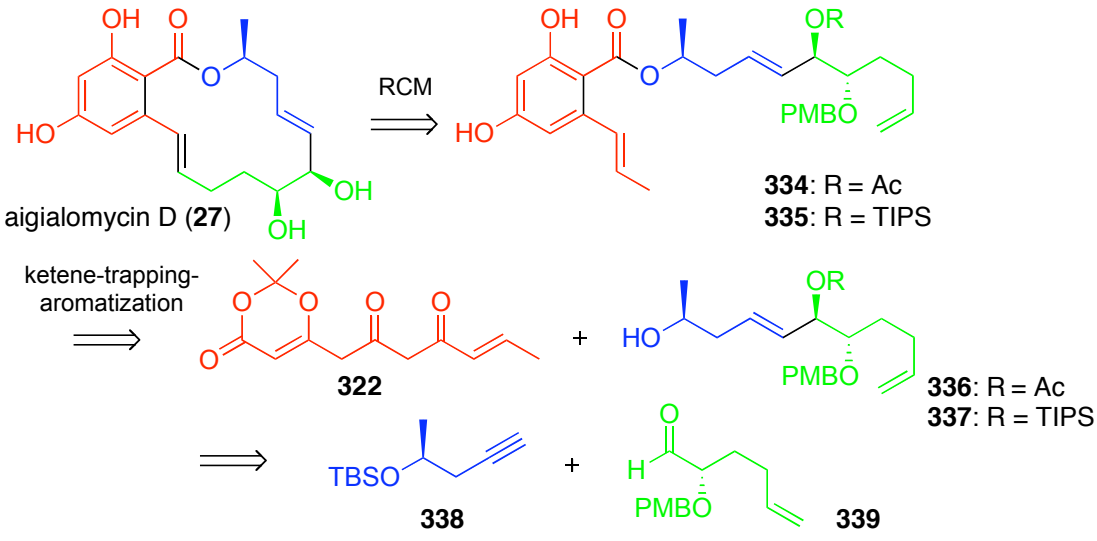
A new strategy for the synthesis of resorcylate natural products, using a biomimetic and a highly selective late-stage aromatisation reaction, having been established by Barrett *et al.*, its application to the synthesis of aigialomycin D was investigated.

II.1.2. Total synthesis of aigialomycin D

II.1.2.1. First retrosynthetic approach

Based on the previous work achieved on resorcylates metabolites, it was decided to apply this new methodology to the total synthesis of aigialomycin D (**27**). The first retrosynthetic analysis is described in Scheme 90 and used similar disconnections as those chosen for the total synthesis of (*S*)-zearalenone (**254**). Aigialomycin D could be obtained by RCM and final deprotection of resorcylates **334** or **335**. These resorcylates would be assembled by ketene formation of diketo-dioxinone **322**, trapping with alcohols **336** or **337** followed by aromatisation reaction. Both alcohols could be prepared from alkyne **338** and aldehyde **339**.

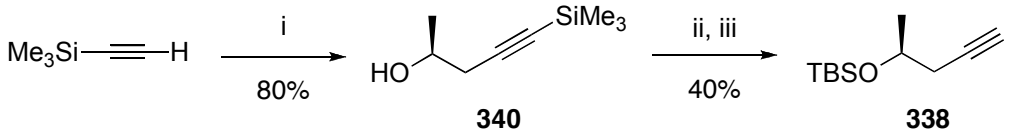
Scheme 90. First retrosynthetic analysis.



II.1.2.1.1. Synthesis of alkyne 338

Alkyne **338** was synthesised in three steps starting from commercially available trimethylsilyl acetylene. Deprotonation at low temperature followed by addition of $BF_3{\cdot}OEt_2$ and (*S*)-propylene oxide gave exclusively the secondary alcohol **340** in 80% yield.[251-253] Protection with TBSCl and selective removal of the trimethylsilyl group by methanolysis gave alkyne **338** in 32% yield over the three steps (Scheme 91).

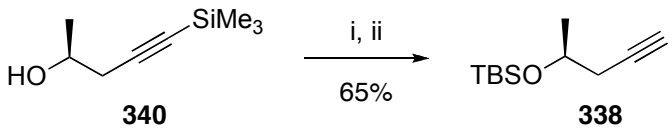
Scheme 91. Synthesis of alkyne **338**.



Reagents and conditions: i) ^{n}BuLi, THF, –78 ^{o}C then $BF_3{\cdot}OEt_2$, (*S*)-propylene oxide, –78 ^{o}C to 0 ^{o}C; ii) TBSCl, imidazole, CH_2Cl_2, RT; iii) K_2CO_3, MeOH.

As the limiting step was the final removal of the TMS group, it was decided to investigate a second route to make alkyne **338**. Simply reversing the protection and deprotection steps allowed the formation of **338** with an overall yield improved to 52% (Scheme 92).

Scheme 92. Improved synthesis of alkyne **338**.

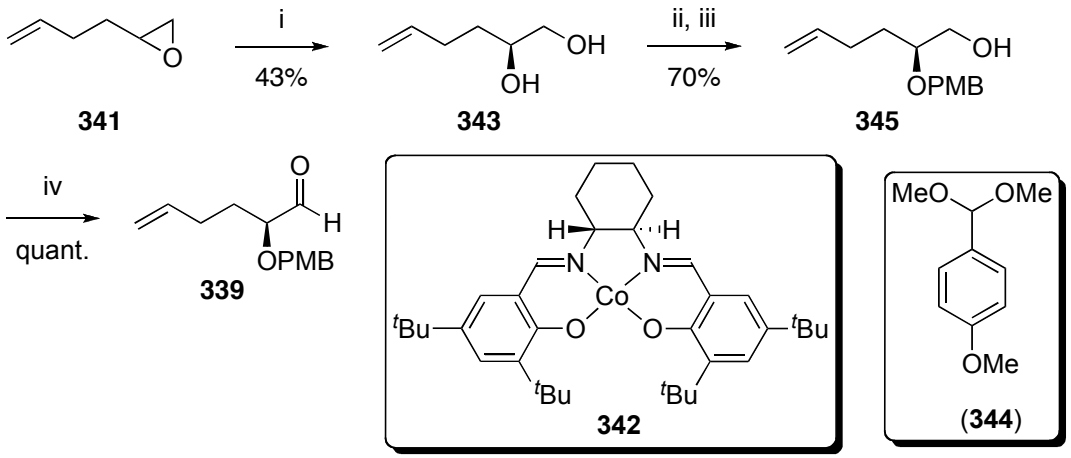


Reagents and conditions: i) TBAF, THF, 0 ^{o}C to RT; ii) TBSCl, imidazole, CH_2Cl_2, RT.

II.1.2.1.2. Synthesis of aldehyde 339

The synthesis of aldehyde **339** started with a Jacobsen hydrokinetic resolution[254-259] of commercially available 1,2-epoxy-5-hexene (**341**) with (*R*,*R*)-Salen **342**, water and AcOH. It enabled the formation of enantio-enriched diol **343** in 43% yield (*e.e.* > 98%). Acetalisation of **343**, by condensation with anisaldehyde dimethyl acetal (**344**) in the presence of a catalytic amount of camphorsulfonic acid (CSA), and regioselective opening of the newly formed acetal with DIBAL-H afforded exclusively protected alcohol **345** in 70% yield over the two steps.[260] Final Dess–Martin oxidation of alcohol **345** gave aldehyde **339** in quantitative yield (Scheme 93). Other oxidation using TPAP/NMO, PCC or the Swern oxidation either failed or gave low conversion due to difficulties in purification.

Scheme 93. Synthesis of aldehyde **339**.



Reagents and conditions: i) **342**, AcOH, THF, H_2O, 0 °C to RT; ii) **344**, CSA (10 mol %), CH_2Cl_2, reflux; iii) DIBAL-H, CH_2Cl_2, –78 °C; iv) DMP, CH_2Cl_2, RT.

II.1.2.1.3. Synthesis of alcohols 336 and 337

Alcohols **336** and **337** were synthesised from a common precursor (**346**). At this stage, two different protective groups were chosen to anticipate potential problems in deprotection at the end of the synthesis of aigialomycin D. Triol **336** will have an acetate and a *para*-methoxybenzyl-protected alcohols whereas triol **337** a tri-*iso*-propylsilyl and a *para*-methoxybenzyl-protected alcohols (Figure 22).

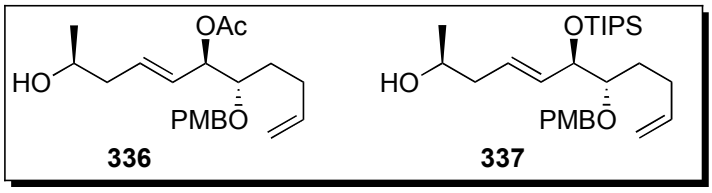
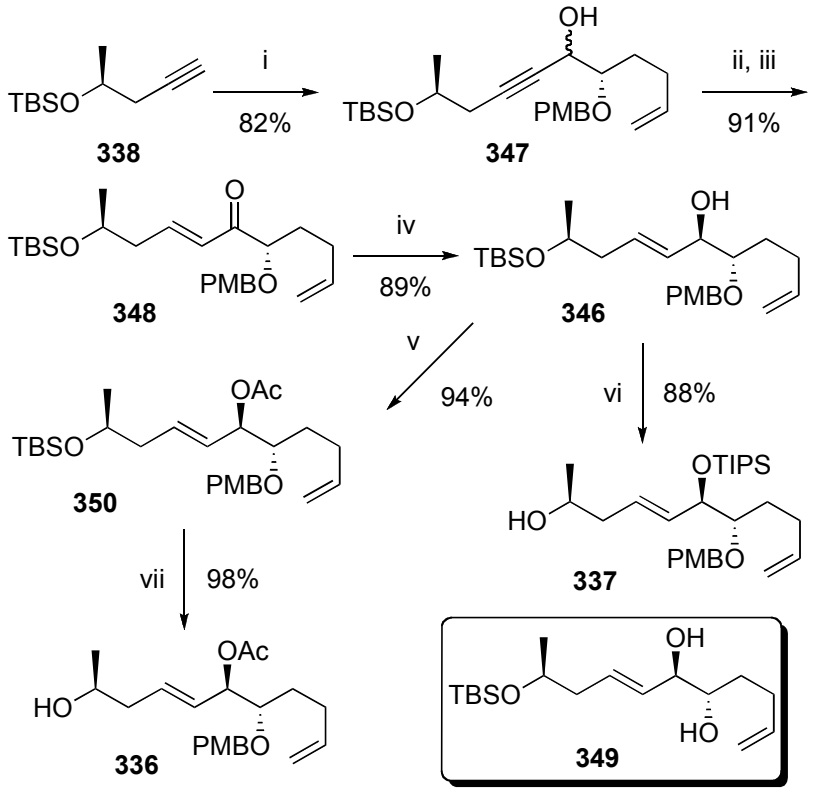


Figure 22. Structures of alcohols **336** and **337**.

The synthesis of both alcohols started with the deprotonation of terminal acetylene **338** with ^{n}BuLi followed by the addition of aldehyde **339** at low temperature. This reaction led to an inseparable 2:1 (*anti*:*syn*) mixture of alcohols **347** in favour of the desired *anti*-diol. The selective reduction of the internal triple bond to the (*E*)-double bond in **347** was achieved with Red-Al and afforded the internal (*E*)-alcohols (still as a 2:1 mixture of the *anti*- and the *trans*-diols).[261-263] Oxidation with TPAP and NMO gave ketone **348** in 91% yield over the two steps (Scheme 94). The stereoselective reduction of the ketone group was realised with Red-Al and led exclusively to the *anti*-diol **346** in 89% yield. Attempted reduction with $Zn(BH_4)_2$ also gave the *anti*-diol **346** (25%) but with a considerable amount of unprotected *anti*-diol **349** (50%).[264-266] Protection of **346** with either Ac_2O or TIPSOTf

afforded alkene **350** and directly alkene **337** after acidic work up, respectively. Final deprotection of **350** with TBAF gave alcohol **336** in 98% yield.

Scheme 94. Synthesis of alcohols **336** and **337**.



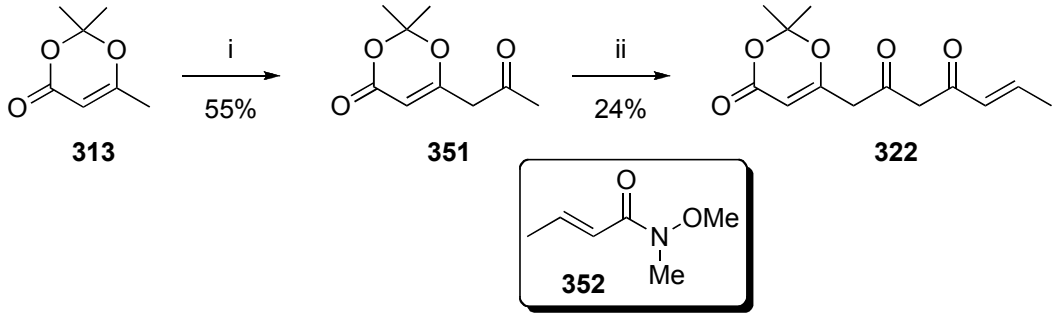
Reagents and conditions: i) ^{n}BuLi, THF, –78 ^{o}C then **339**; ii) Red-Al, CH_2Cl_2, –78 ^{o}C; iii) TPAP, NMO, CH_2Cl_2, 4 Å Molecular sieves; iv) Red-Al, CH_2Cl_2, –78 ^{o}C; v) Ac_2O, Et_3N, Et_2O; vi) TIPSOTf, 2,6-lutidine, CH_2Cl_2 then HCl work up; vii) TBAF, THF, RT.

II.1.2.1.4. Synthesis of diketo-dioxinone 322

Keto-dioxinone **351** was made in one step by acylation of dioxinone (**313**) with AcCl. The best conditions were achieved using LHMDS as the base and 0.6 equivalent of AcCl. As a result, clean keto-dioxinone **351** was obtained in 55% yield. Double deprotonation of

351 followed by addition of Weinreb amide **352** gave diketo-dioxinone **322** in 24% yield (Scheme 95).[192]

Scheme 95. Synthesis of diketo-dioxinone **322**.

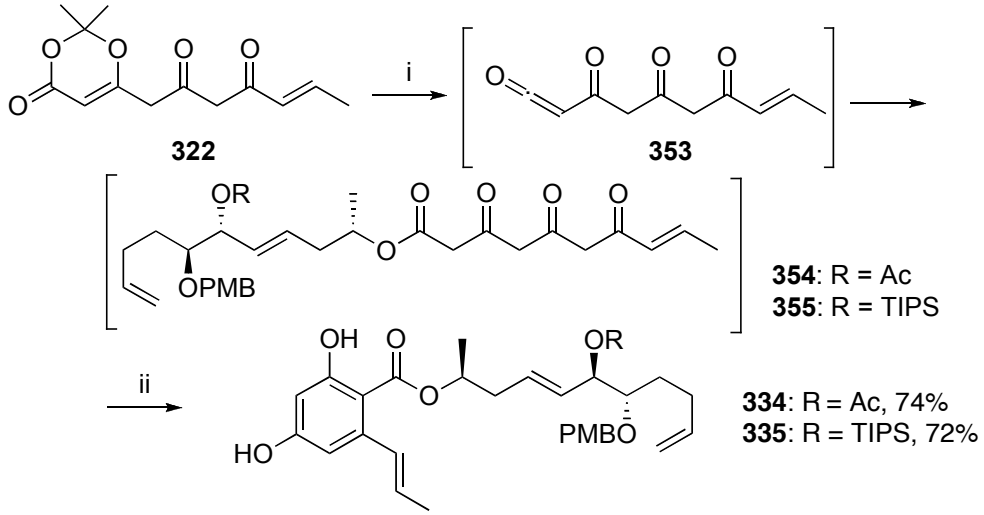


Reagents and conditions: i) LHMDS, THF, –78 °C then AcCl; ii) LDA, THF, –78 °C then **352**, –50 °C to –30 °C.

II.1.2.1.5. Ketene–trapping–aromatisation sequence and formation of resorcylates 334 and 335

Having successfully made our key precursors, our interest was focused on the key ketene generation-trapping-aromatisation sequence. Upon heating in toluene, diketo-dioxinone **322** underwent a retro Diels–Alder reaction to generate triketo-ketene **353** which was immediately trapped with either alcohols **336** or **337** to give triketo-esters **354** and **355**, respectively. Smooth deprotonation with cesium acetate (to perform the intramolecular aldol reaction) followed by acetic acid protonation and elimination of water gave resorcylates **334** and **335**, respectively, in excellent yield (74 and 72%) over the sequence (Scheme 96).

Scheme 96. Synthesis of resorcylates **334** and **335**.



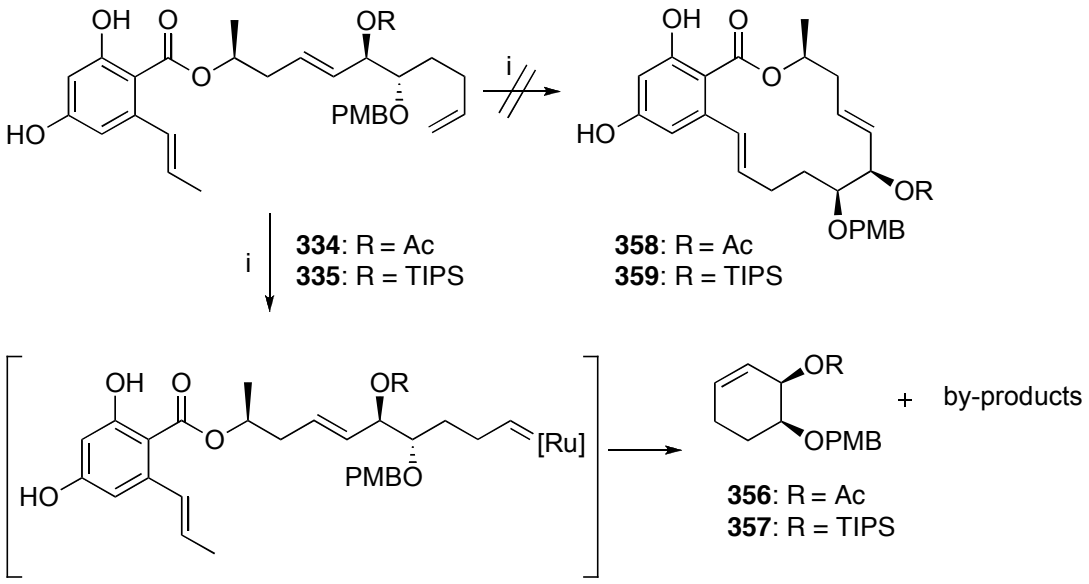
Reagents and conditions: i) **336** or **337**, PhMe, reflux; ii) CsOAc, ^{i}PrOH-CH_2Cl_2, RT then AcOH.

The next RCM reaction of either resorcylate **334** or **335** was investigated.

II.1.2.1.6. Attempted ring-closing metathesis reaction

Treatment of either trienes **334** or **335** with the Hoveyda–Grubbs II (**128**) catalyst led very quickly to the formation of two new products which appeared to be the undesired cyclohexenes **356** or **357**, respectively. Changing the solvent, the catalyst, the temperature and the concentration did not change the selectivity of the reaction and the desired macrocycles **358** and **359** were never observed. This result demonstrated the high reactivity of the terminal double bonds for RCM reaction. Once the ruthenium complexes were formed, the favoured intramolecular reaction could not be avoided and only the *cis*-cyclohexenes were formed (Scheme 97).

Scheme 97. Attempted RCM reaction on trienes **334** and **335**.



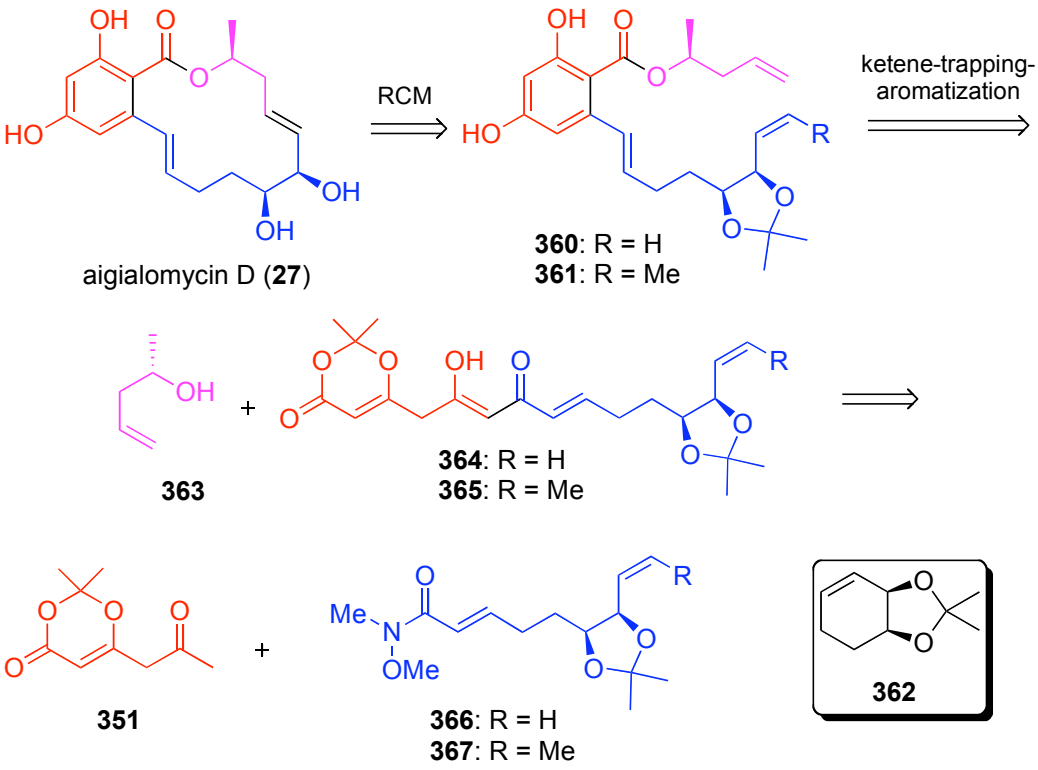
Reagents and conditions: i) catalysts **128** or **126**, PhMe or CH_2Cl_2, RT or reflux, 1 h to 17 h.

Due to the failure of this reaction, a new route had to be designed avoiding a RCM reaction between the benzylic and the terminal double bonds.

II.1.2.2. Second retrosynthetic approach

Our new retrosynthetic analysis is shown in Scheme 98. Aigialomycin D (**27**) should be available by RCM of trienes **360** or **361** without phenol protection. It was postulated that by suitable choice of the alkene substituent R, it should be possible to direct the RCM away from the formation of cyclohexene **362** to favour macrocyclisation.[267-269] Trienes **360** and **361** should be obtained from a one-pot diketo-acyl-ketene generation–trapping–aromatisation sequence using commercially available (*S*)-(+)-4-penten-2-ol (**363**) and the diketo-dioxinones **364** or **365**. The diketo-dioxinones **364** and **365** should be available from the *C*-acylation reaction of keto-dioxinone **351** with Weinreb amides **366** and **367**.

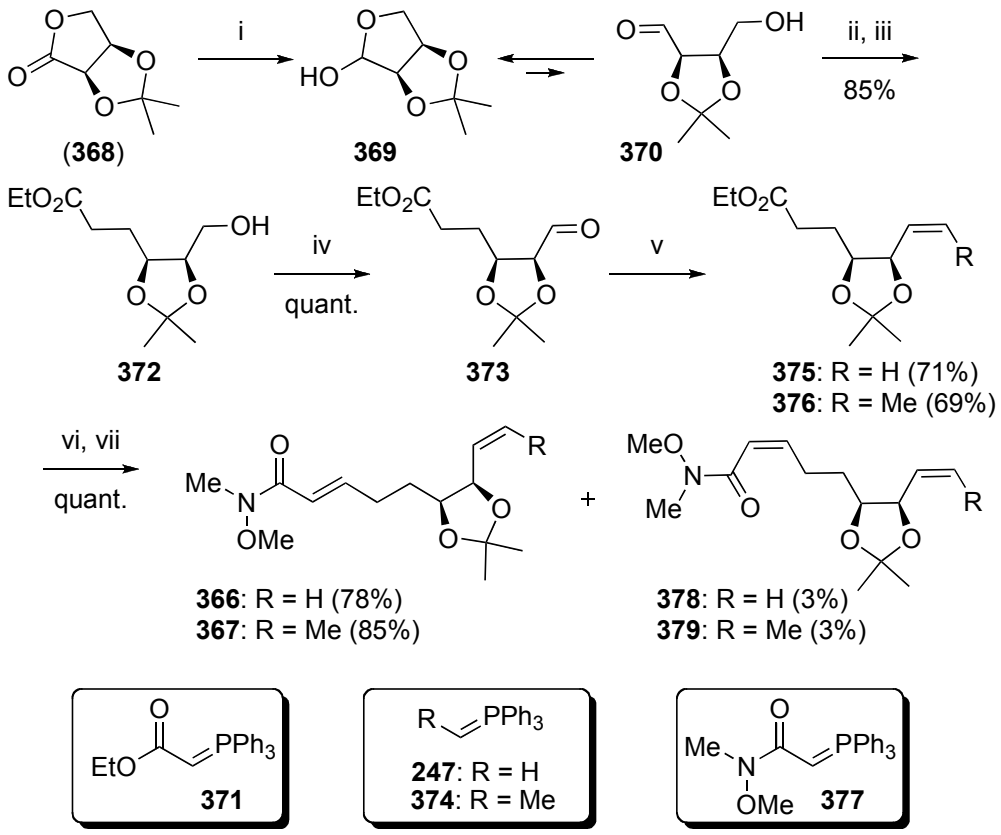
Scheme 98. New retrosynthetic analysis.



II.1.2.2.1. Synthesis of Weinreb amides 366 and 367

The synthesis of the two Weinreb amides started with a DIBAL-H reduction of commercially available 2,3-*O*-isopropylidene-D-erythronolactone (**368**) to form the corresponding lactol.[270] Direct treatment of lactol **369** (in equilibrium with the hydroxy-aldehyde **370**) with ylide **371** gave a 2:1 mixture of the *cis*- and *trans*-α,β-unsaturated esters which were hydrogenated to form alcohol **372** in 85% yield over the three steps (Scheme 99). Dess–Martin oxidation[96] of alcohol **372** gave aldehyde **373** in quantitative yield. Wittig olefination using either methylenetriphenylphosphorane (**247**) or ethylenetriphenylphosphorane (**374**) afforded the known terminal alkene **375**[188] in 71 % yield and alkene **376**[271] as the (*Z*)-isomer in 69% yield over the two steps.

Scheme 99. Synthesis of Weinreb amides **366** and **367**.



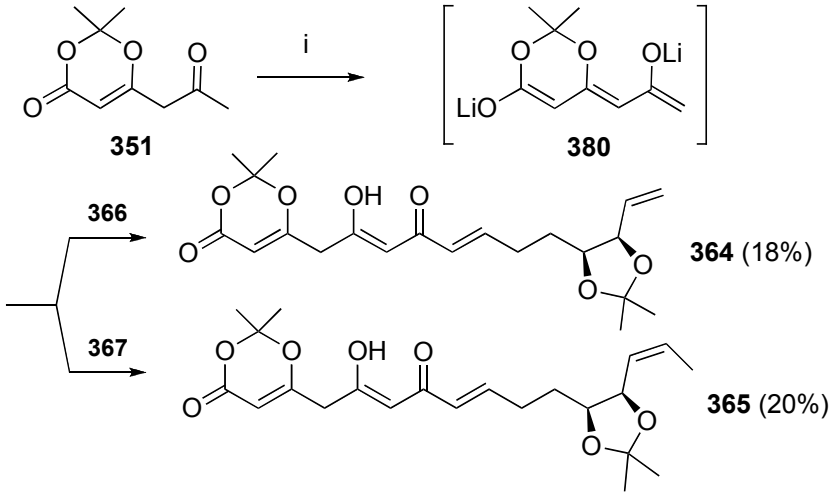
Reagents and conditions: i) DIBAL-H, CH_2Cl_2, –78 °C; ii) **371**, CH_2Cl_2, reflux; iii) H_2, $Pd(OH)_2$, EtOH; iv) DMP, CH_2Cl_2, RT; v) **247** or **374**, THF, 0 °C to RT; vi) DIBAL-H, CH_2Cl_2, –78 °C; vii) **377**, CH_2Cl_2, reflux.

Reduction of the ethyl esters **375** and **376** using DIBAL-H at –78 °C gave the corresponding aldehydes,[272] which were immediately allowed to react with commercially available ylide (**377**)[273-275] in dichloromethane at reflux to afford the *trans*-α,β-unsaturated Weinreb amides **366** (78%) and **367** (85%) along with small quantities of the *cis*-isomers **378** (3%) and **379** (3%).

II.1.2.2.2. *C*-acylation reaction

With both the Weinreb amides **366** and **367** and the keto-dioxinone **351** in hand, the crucial acylation step was investigated (Scheme 100). Solladié *et al*. have previously reported the use of trianion *C*-acylation with the Weinreb amide of cinnamic acid in their biomimetic synthesis of leridiol.[276] Dianion **380**, derived from **351**, was generated using lithium di-*iso*-propylamide at –78 °C and allowed to react with Weinreb amides **366** or **367** at –40 °C to provide the required diketo-dioxinone **364** (18%) or **365** (20%). The low yields resulted from the formation of complex mixtures containing adducts tentatively assigned as 1,4-addition products and from difficulties in the purification by chromatography.

Scheme 100. Synthesis of key diketo-dioxinones **364** and **365**.

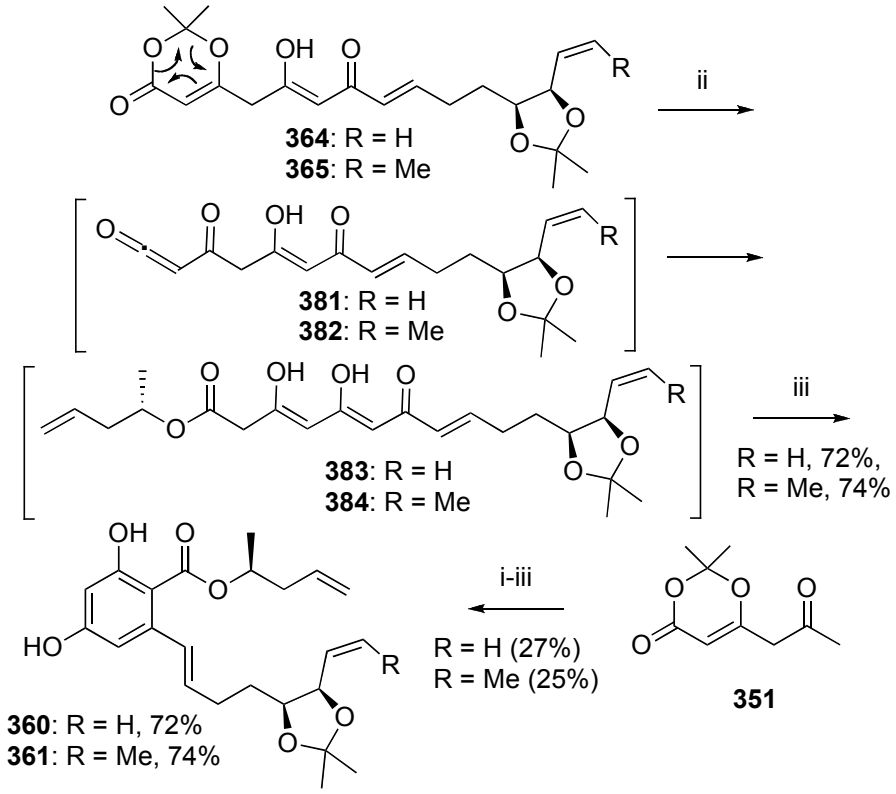


Reagents and conditions: i) LDA, THF, –78 °C then **366** or **367**, –40 °C.

II.1.2.2.3. Ketene–trapping–aromatisation sequence and formation of resorcylates 360 and 361

Upon heating in toluene, diketo-dioxinones **364** and **365** underwent a retro Diels–Alder reaction to generate ketenes **381** and **382**. Trapping with alcohol (**363**) led to the formation of triketo-esters **383** and **384** which were aromatised with cesium acetate followed by acetic acid to give, respectively, resorcylates **360** and **361** in 72% and 74% overall yields (Scheme 101).

Scheme 101. Synthesis of resorcylates **360** and **361**.

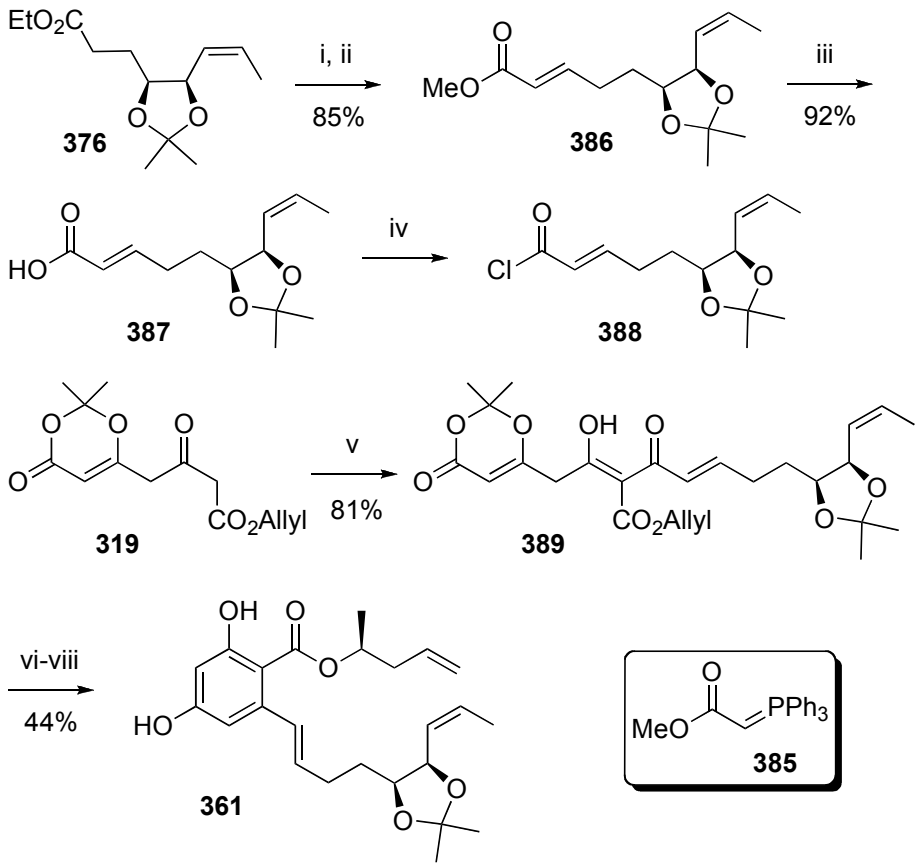


Reagents and conditions: i) LDA, THF, –78 °C then **366** or **367**, –40 °C; ii) **363**, PhMe, reflux; iii) CsOAc, ^{i}PrOH-CH_2Cl_2 then AcOH, RT.

Directly submitting the crude diketo-dioxinones **364** or **365** to the ketene generation-trapping-aromatisation sequence doubled the overall yields for **360** (27%) and for **361** (25%) starting from keto-dioxinone **351**.

To increase the reactivity and the selectivity towards the *C*-acylation only, it was decided to examine the mild Claisen condensation strategy previously used in our group and apply this methodology to the synthesis of resorcylate **361**. The chemistry began with a DIBAL-H reduction of ester **376** followed by a Wittig olefination using ylide **385** to give alkene **386** exclusively as the (*E*)-isomer in 85% yield over the two steps. Saponification using LiOH gave carboxylic acid **387** (92%), which was converted to acyl chloride **388** with oxalyl chloride (Scheme 102). Claisen condensation between the enolate derived from **319**, generated by treatment with $MgCl_2$ and pyridine, and crude acyl chloride **388** gave dioxinone **389** as the only addition product in 81% yield. Subsequent palladium-catalyzed deallylation and decarboxylation using tetrakis(triphenylphosphine)palladium(0) and morpholine gave the desired diketo-dioxinone **365** which was immediately converted to resorcylate **361** using the previous reaction conditions (44%). Using this mild and selective *C*-acylation approach, the overall yield to synthesize resorcylate **361** was improved to 35% starting from carboxylic acid **387**.

Scheme 102. Synthesis of resorcylate **361** using a mild Claisen condensation.



Reagents and conditions: i) DIBAL-H, CH_2Cl_2, –78 °C; ii) **385**, CH_2Cl_2, reflux; iii) LiOH, THF-H_2O, RT; iv) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0 °C to RT; v) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C then **388**, 0 °C to RT; vi) morpholine, $Pd(PPh_3)_4$, CH_2Cl_2, 0 °C; vii) **363**, PhMe, reflux; viii) CsOAc, ^{i}PrOH-CH_2Cl_2 then AcOH, RT.

II.1.2.2.4. RCM and total synthesis of aigialomycin D

During the previous total syntheses of aigialomycin D (**27**), it was shown that RCM of trienes **390** or **391** were not practical due to a competitive reaction giving rise to cyclohexene **362** in addition to the desired macrocycle (Figure 23).[185,189] As a consequence, the styrene unit was masked as a phenyl selenide,[185] a silyl ether,[184] a ketone[188] or as a

sulfone[191] prior to macrocyclisation *via* RCM and late stage introduction of Δ^1 *via* elimination.

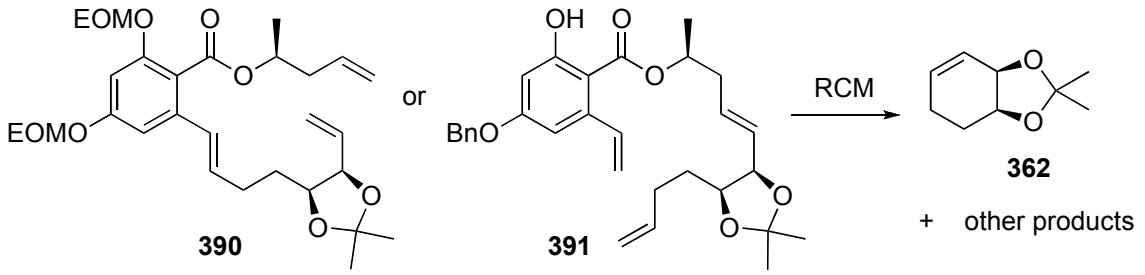
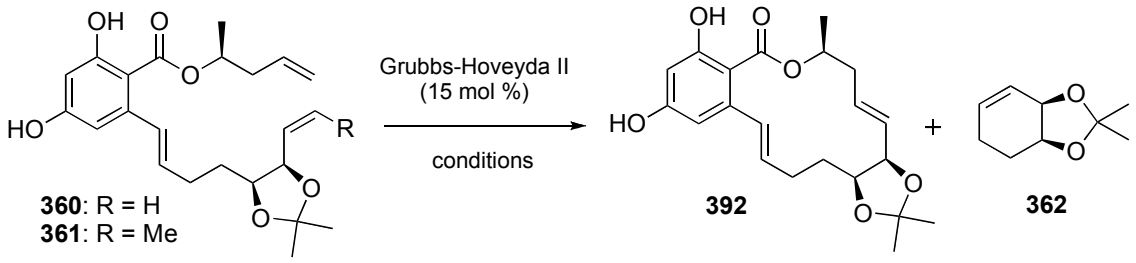


Figure 23. Formation of by-product **362** by RCM

With a potentially optimised substrate in hand (**361**), the key RCM was investigated. The results are presented in Table 11.

Using the Hoveyda-Grubbs II catalyst (15 mol %) at a concentration of 15 x 10^{-4} M and with microwave irradiation at 80 °C in dichloromethane (entry 1), triene **360** was converted into the *trans*-macrocycle **392** in 50% isolated yield. In this case, cyclohexene **362** was also formed (20%). By decreasing the concentration to 6 x 10^{-4} M (entry 2), the ratio of macrocycle **392** to cyclohexene **362** decreased to 1:0.2. When subjected to the same conditions, triene **361** gave macrocycle **392** (81%) with very little co-production of cyclohexene **362** (entry 3). Interestingly, the RCM could also be performed with conventional heating (entry 4) making the reaction amendable to larger scale application.



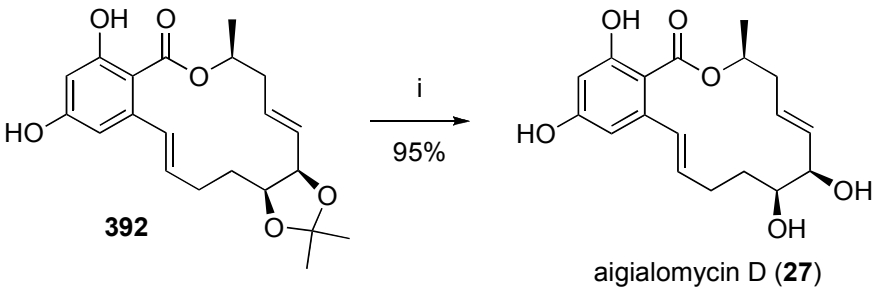
Entry	Triene	Concentration (10^{-4} mol.L^{-1})	Method[a] (°C)	Solvent	Ratio 392:362 (yield)[d]
1	**360**	15	MW (85)	CH_2Cl_2	1:0.40 (50%)
2	**360**	6	MW (85)	CH_2Cl_2	1:0.21
3	**361**	6	MW (85)	CH_2Cl_2	1:0.06 (81%)
4	**361**	6	Thermal (100)	PhMe	1:0.06 (83%)

[a]Microwave irradiation (MW) or conventional heating (thermal). [b]Solvents were degassed with nitrogen. [c]Ratio of **392**:**362** determined from the ^{1}H NMR spectrum of the crude reaction mixture. [d]Yield of isolated product **392**.

Table 11. RCM on trienes **360** and **361**.

Finally, deprotection of the acetonide moiety was achieved using 1 M hydrochloric acid in methanol (1:1) giving aigialomycin D (**27**) (Scheme 103) (95%), the data of which were identical to those previously reported.[192]

Scheme 103. Final deprotection.



Reagents and conditions: i) 1 M HCl, MeOH-H_2O.

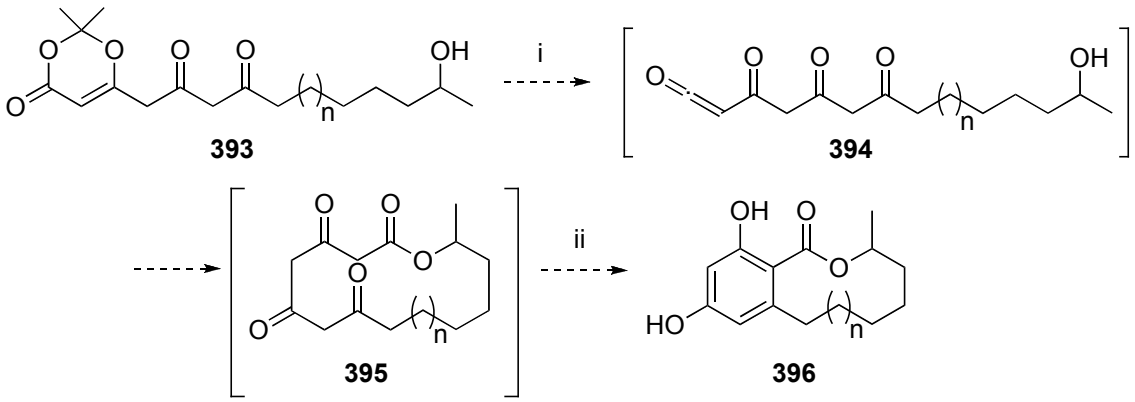
In summary, we managed to perform an eleven step total synthesis of aigialomycin D (**27**) in 15% overall yield from simple chiral pool precursors using a keto-dioxinone C-acylation, a ketene generation-trapping-aromatisation cascade and a RCM macrocyclisation as the key steps.

II.1.3. New approach towards the total synthesis of aigialomycin D: intramolecular ketene–trapping strategy

We managed to perform a concise and short total synthesis of aigialomycin D, using a *C*-acylation reaction, a cascade sequence consisting of ketene generation, alcohol trapping and aromatisation, and ring closing metathesis. Thus, it was decided to expand the scope of this methodology and to develop a new approach towards the total synthesis of resorcylic acid lactones without the use of RCM by performing instead an intramolecular ketene–trapping reaction (Scheme 104).

Indeed, if intermediate **393** could be formed, then upon thermolysis reaction, it would generate ketene **394**, which could undergo an intramolecular trapping reaction and form cyclic triketo-ester **395**. Aromatisation of **395** should directly provide macrocycle resorcylate **396**.

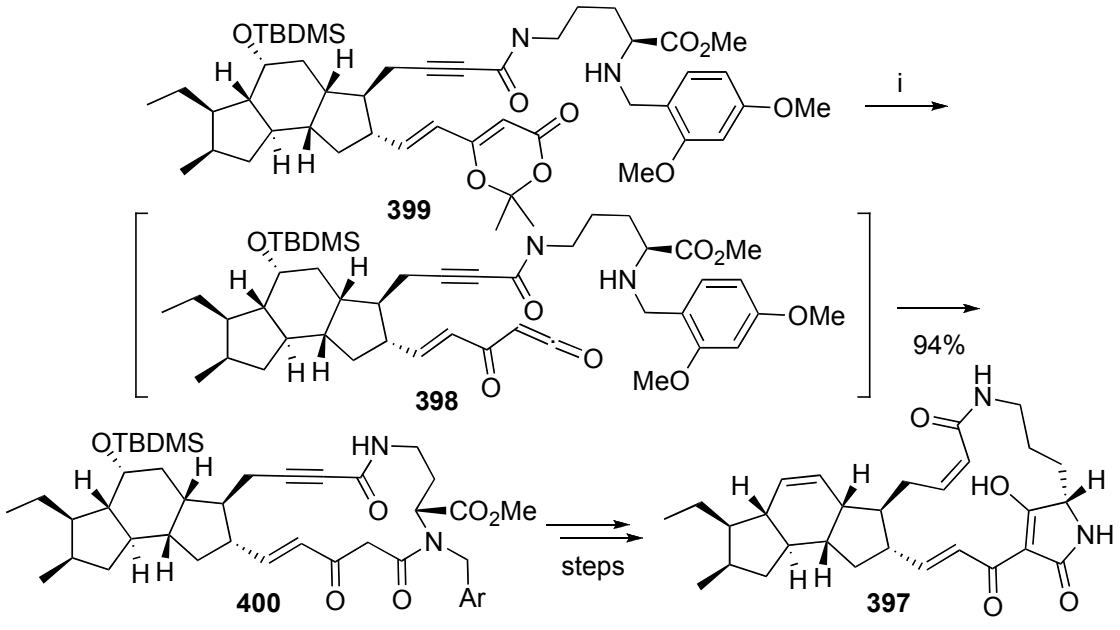
Scheme 104. New strategy: intramolecular trapping of the ketene.



Proposed reagents and conditions: i) PhMe, reflux; ii) CsOAc, ^{i}PrOH-CH_2Cl_2 then AcOH.

In 1990, Paquette *et al*. achieved the total synthesis of (+)-ikarugamycin (**397**) using an intramolecular ketene-trapping reaction (Scheme 105).[277] The formation of acyl ketene **398** was achieved by simply heating dioxinone **399** in toluene. Once formed, ketene **398** was intramolecularly trapped with a secondary amine to give β-keto-lactam **400** in 94% yield.

Scheme 105. Example of intramolecular acyl-ketene trapping.

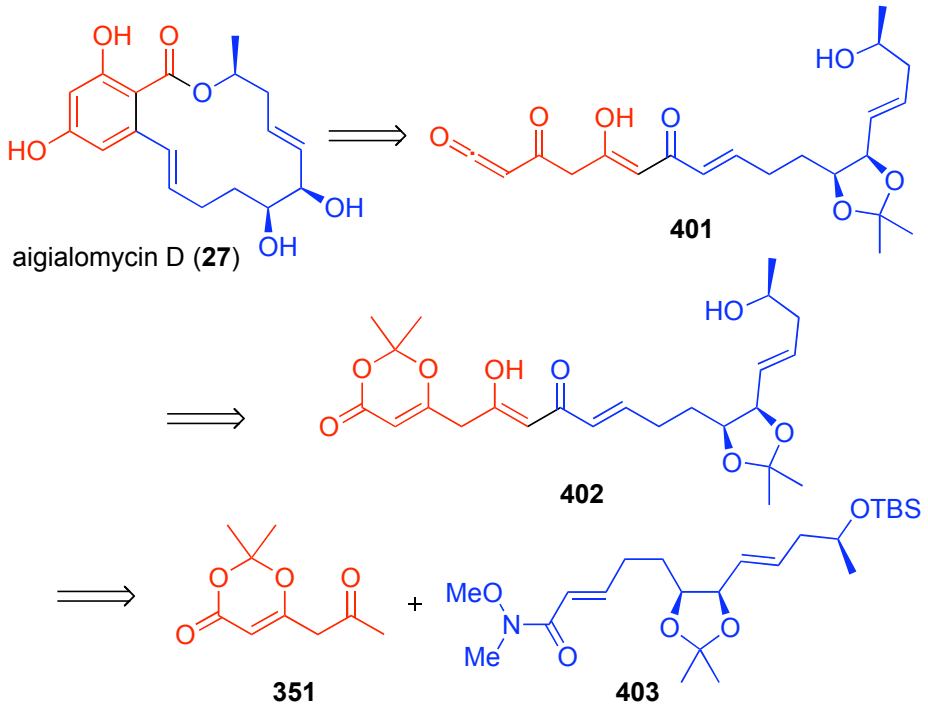


Reagents and conditions: i) PhMe, reflux, 4 h.

II.1.3.1. Retrosynthetic analysis

Inspired by this work, it was decided to use a similar strategy towards the total synthesis of aigialomycin D. The natural product could be obtained from triketo-ketene **401**, which would be made by the thermolysis of diketo-dioxinone **402** followed by intramolecular trapping and *in situ* aromatisation using the previous conditions developed in our group. Diketo-dioxinone **402** would be synthesised by the addition of the dianion derived from keto-dioxinone **351** to Weinreb amide **403**. The new retrosynthetic disconnections are shown in Scheme 106.

Scheme 106. Retrosynthetic analysis of aigialomycin D using an intramolecular ketene–trapping strategy.

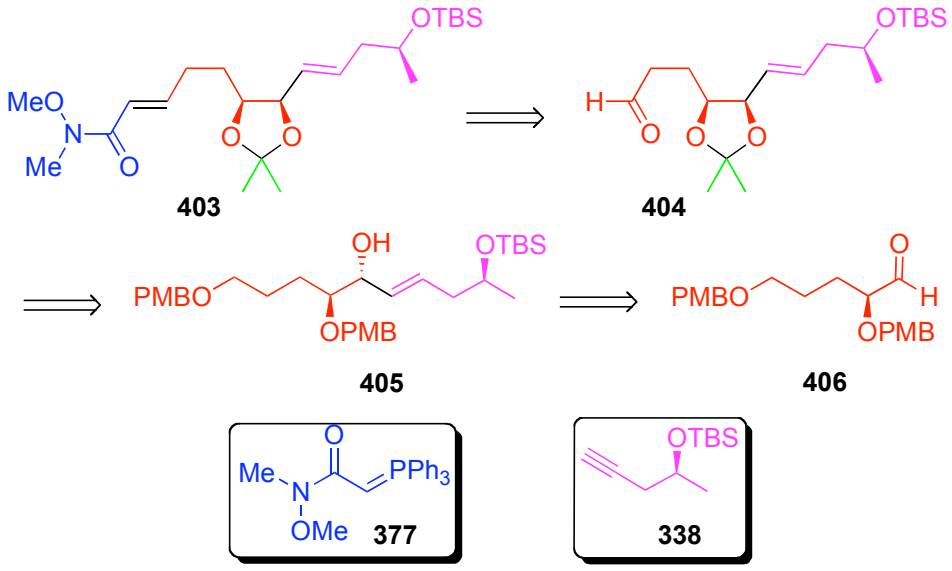


Having already made diketo-dioxinone **351** in large quantities, our research was focused on the synthesis of Weinreb amide **403**.

II.1.3.2. First synthesis of Weinreb amide 403

Our first disconnections were similar to those used in Schemes 94 and 99. It was envisaged that Weinreb amide **403** could be made by a Wittig olefination between ylide **377** and aldehyde **404**. Aldehyde **404** would be synthesised by protective group manipulation of alkene **405** which would be assembled by the addition of alkyne **338** to aldehyde **406** (Scheme 107).

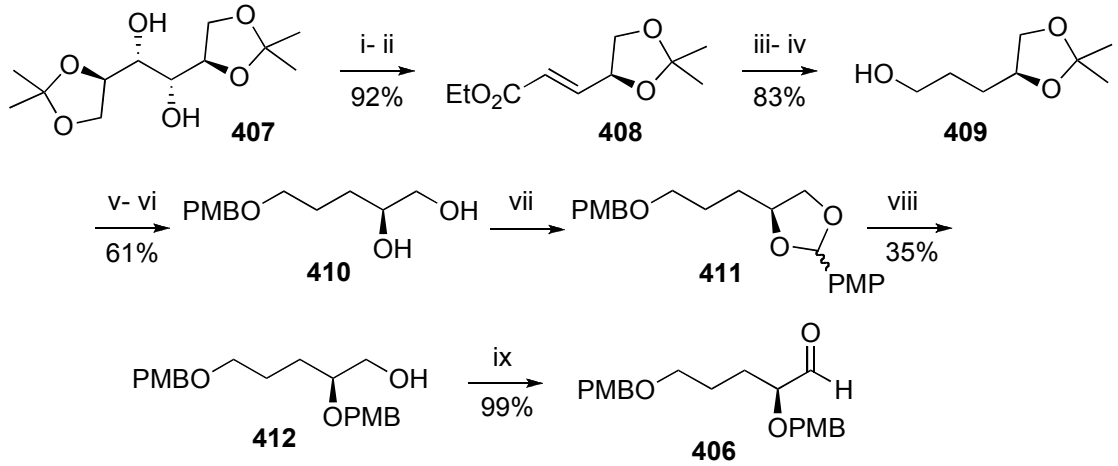
Scheme 107. Retrosynthetic analysis of Weinreb amide **403**.



The synthesis of aldehyde **406** started with the oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**407**) followed by *in situ* Wittig olefination with ylide **371** to form ester **408** in 92% yield over the two steps (Scheme 108). Upon hydrogenolysis and $LiAlH_4$ reduction, alcohol **409** was obtained in 83% yield over the two steps. Sequential PMB protection and diol deprotection gave alcohol **410** in 61% yield. Subsequent diol protection with anisaldehyde dimethyl acetal (**344**) under CSA catalysis and regioselective opening of **411** with DIBAL-H afforded mono-protected alcohol **412** in a moderate 35%

yield over the two steps. Final Dess–Martin oxidation of **412** gave the desired aldehyde **406** in 99% yield.

Scheme 108. Synthesis of aldehyde **406**.

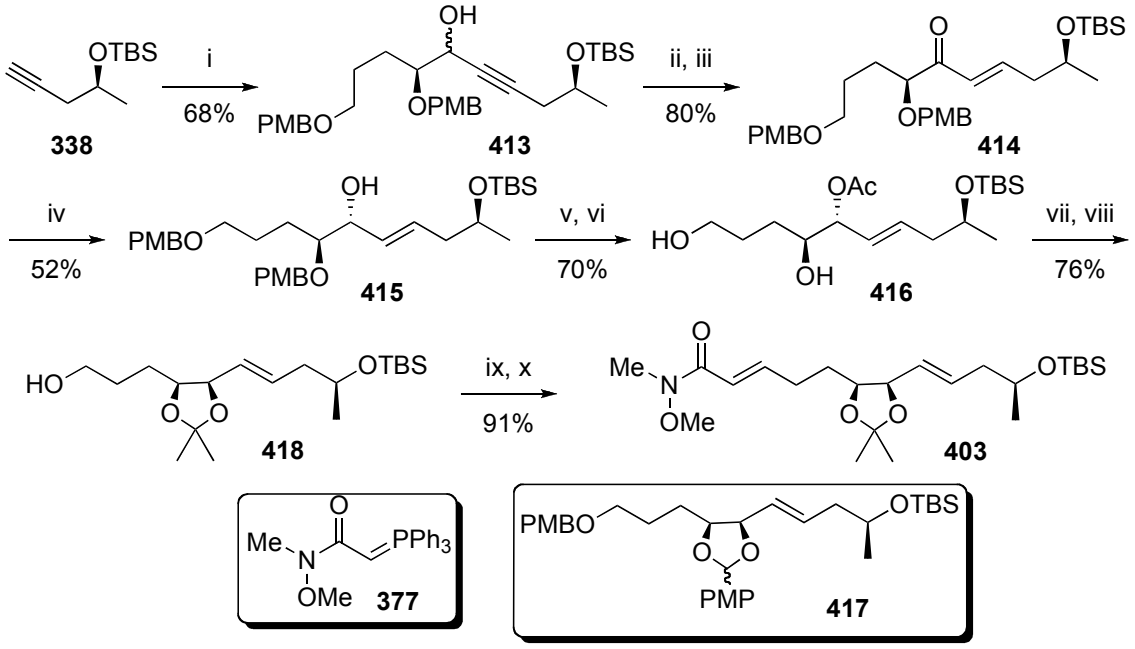


Reagents and conditions: i) aq. $NaHCO_3$, $NaIO_4$, H_2O, 0 ^oC; ii) **371**, H_2O, RT; iii) H_2, Pd/C, EtOH, RT; iv) $LiAlH_4$, THF, –78 ^oC to 0 ^oC; v) NaH, PMBCl, THF; vi) 2 M HCl, THF-H_2O, RT; vii) **344**, CSA (10 mol %), CH_2Cl_2, reflux; viii) DIBAL-H, PhMe, 0 ^oC; ix) DMP, CH_2Cl_2, RT.

Treatment of alkyne **338** with ^{n}BuLi followed by addition of aldehyde **406** gave a mixture of the *syn*- and the *anti*-diols **413**. Similarly to Scheme 94, this mixture of diols was reduced using Red-Al to the corresponding (*E*)-alkenes and, after oxidation with Dess–Martin periodinane, ketone **414** was obtained in 80% yield over the two steps (Scheme 109). Red-Al reduction of ketone **414** gave the *anti*-diol **415**, which was protected with Ac_2O. Deprotection of the PMB groups using DDQ afforded diol **416**. At this stage, it was necessary to have alcohol **415** protected as the acetate before performing the DDQ deprotection to avoid the formation of by-product **417**. Methanolysis of **416** followed by 1,2-diol protection using 2,2-dimethoxypropane gave alcohol **418**. Final Dess–Martin

oxidation and Wittig reaction with ylide **377** gave the required Weinreb amide **403** in 91% yield over the two steps.

Scheme 109. Synthesis of Weinreb amide **403**.

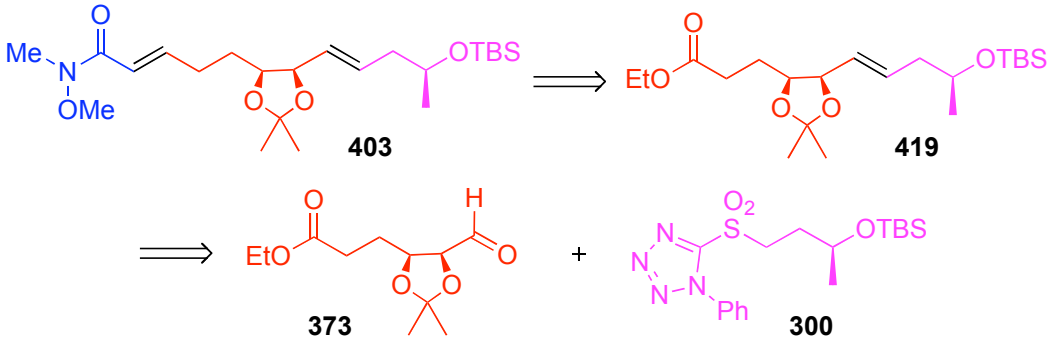


Reagents and conditions: i) ^{n}BuLi then **406**, THF, –78 ^{o}C; ii) Red-Al, PhMe, 0 ^{o}C to RT; iii) DMP, CH_2Cl_2, RT; iv Red-Al, PhMe, –78 ^{o}C to 0 ^{o}C; v) Ac_2O, NEt_3, DMAP, Et_2O, RT; vi) DDQ, CH_2Cl_2-H_2O, RT; vii) K_2CO_3, MeOH, RT; viii) 2,2-dimethoxypropane, CSA (10 mol %), CH_2Cl_2, RT; ix) DMP, CH_2Cl_2, RT, x) **377**, CH_2Cl_2, reflux.

II.1.3.3. Optimised route to synthesise Weinreb amide 403

The first route developed to make Weinreb amide **403** was unacceptably long (19 synthetic steps) with a low overall yield of 2.3%. However, based on the previous total syntheses of aigialomycin D, it was envisaged that **403** could be made from ester **419** which would be assembled by a modified Julia–Kocienski olefination of known sulfone **300** with previously synthesised aldehyde **373** (Scheme 99). The new retrosynthetic analysis is shown in Scheme 110.

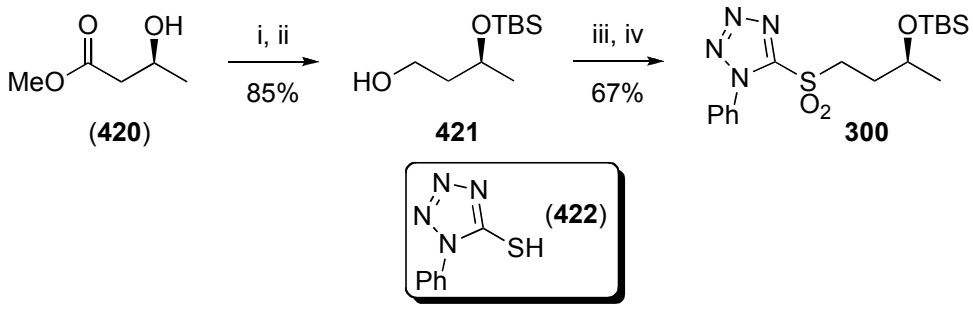
Scheme 110. New retrosynthetic disconnection to synthesize Weinreb amide **403**.



II.1.3.3.1. Synthesis of sulfone 300

Known sulfone **300** was made in four steps from (*S*)-(+)-methyl-3-hydroxybutyrate (**420**) starting with TBS protection followed by reduction with DIBAL-H to produce alcohol **421** (72%).[186] Mitsunobu reaction with commercial 1-phenyl-1-H-tetrazole-5-thiol (**422**) followed by *m*-CPBA oxidation gave sulfone **300** in 67% yield over the two steps (Scheme 111).

Scheme 111. Synthesis of sulfone **300**.



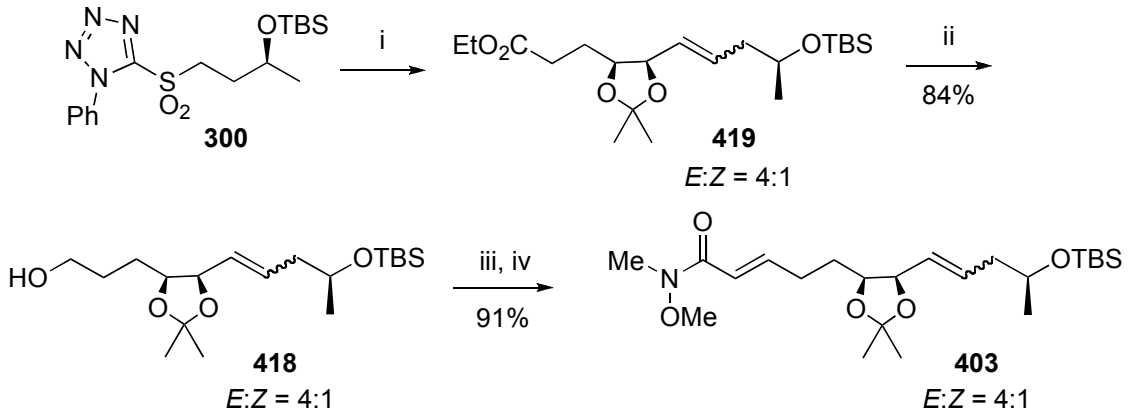
Reagents and conditions: i) TBSCl, imidazole, CH_2Cl_2, RT; ii) DIBAL-H, CH_2Cl_2, –78 °C to 0 °C; iii) DEAD, PPh_3, **422**, THF, RT; iv) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to RT.

II.1.3.3.2. Synthesis of Weinreb amide 403

Having both aldehyde **373** and sulfone **300** in hand, the key Julia-Kocienski reaction was investigated.[186,232-236,238] Using THF as the solvent and LHMDS as a base, the reaction led to the formation of the desired product as a 2:1 inseparable mixture of the (*E*)- and the (*Z*)-isomer. However, by changing the base to KHMDS (solution in PhMe) and the solvent to dimethoxy ethane (DME),[239] the (*E*):(*Z*) ratio increased to 4:1. Making a KHMDS solution in DME did not improve the selectivity. At that stage, it was not possible to isolate pure alkene **419** as it was contaminated with residual sulfone **300**. Nevertheless, alcohol **418** (still as an inseparable 4:1 mixture of isomers) could be isolated after DIBAL-H reduction of ester **419** (Scheme 112). From alcohol **418**, Weinreb amide **403** was formed in two steps according to the procedure shown in Scheme 109.

Using this new route, Weinreb amide **403** was made in only eight linear steps with an overall yield of 65%. However, it was not possible to separate the stereoisomers and **403** was used as a 4:1 mixture of stereoisomers in the next step.

Scheme 112. Second synthesis of Weinreb amide **403**.

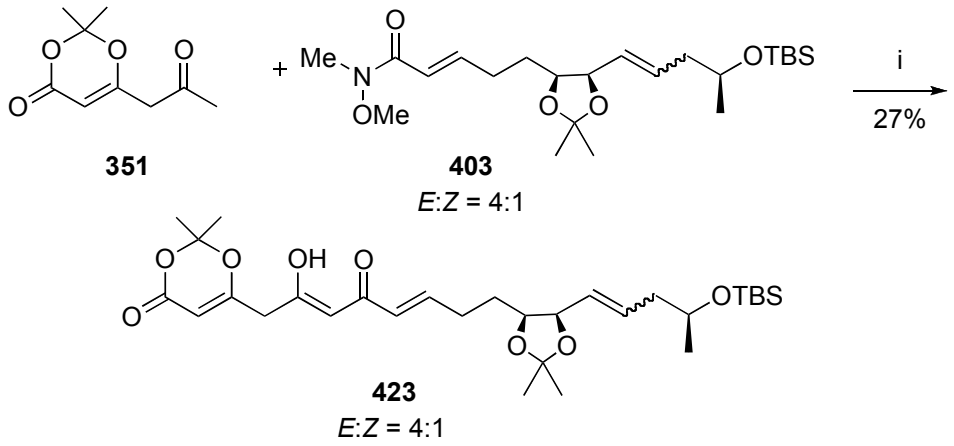


Reagents and conditions: i) KHMDS (0.5 M in PhMe), DME then **373**, –78 °C to 0 °C; ii) DIBAL-H, CH_2Cl_2, –78 °C to 0 °C; iii) DMP, CH_2Cl_2, RT, iv) **377**, CH_2Cl_2, reflux.

II.1.3.4. Final investigations on the intramolecular ketene–trapping strategy

The *C*-acylation reaction between Weinreb amide **403** and keto-dioxinone **351** was then carried out. We were delighted to observe the formation of the diketo-dioxinone adduct **423**, despite the low yield of the reaction (27%). To manage to isolate pure diketo-dioxinone **423**, it was necessary to use two equivalents of the diketo-dioxinone **351** to get full consumption of the Weinreb amide **403** as it was inseparable from the desired adduct **423** (Scheme 113).

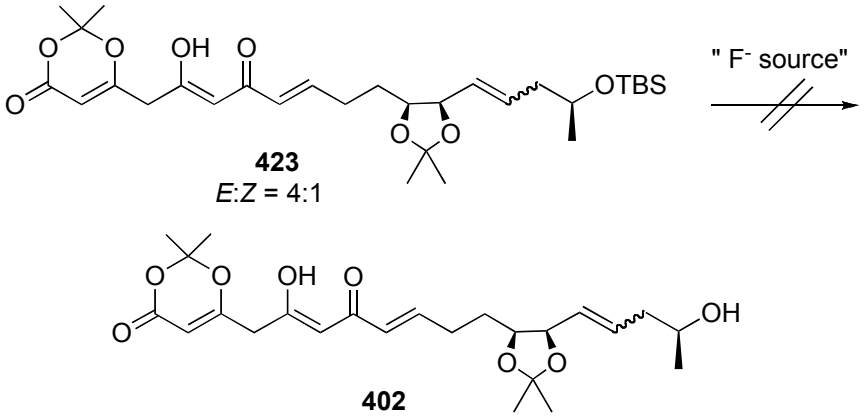
Scheme 113. Formation of diketo-dioxinone **423**.



Reagents and conditions: i) LDA (2 equiv.), THF, –78 °C then **403**, –78 °C to –40 °C.

Our attention was next focused on the deprotection of the TBS group. The use of TBAF, HF in water, HF in pyridine and CsF did not give the desired deprotected product **402** (Scheme 114). Either the starting material was recovered or decomposition occurred.

Scheme 114. Attempted deprotection of **423**.



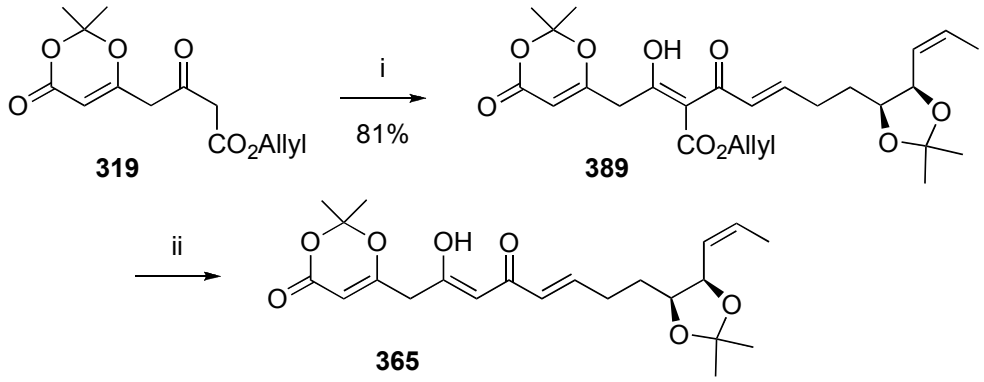
Unfortunately, due to time constraints, this step could not be made successful. Nevertheless, further research in our group to finish the total synthesis of aigialomycin D using this intramolecular ketene-trapping reaction is under investigation.

II.2. ANGELICOINS A AND B[Φ]

II.2.1. Introduction

During the previous work undertaken towards the total synthesis of aigialomycin D (**27**), an interesting discovery was made. As shown in the previous sections, the mild Claisen condensation of dioxinone **319** with acyl chloride **388** led to diketo-dioxinone **389**. This reaction was followed by a one-pot palladium-catalysed deallylation–decarboxylation reaction using morpholine as the trapping agent for the π-allyl cation to produce diketo-dioxinone **365**. The experiment was carried out by first adding morpholine followed by a solution of tetrakis(triphenylphosphine)palladium(0) in THF (Scheme 115).

Scheme 115. Mild *C*-acylation and deallylation–decarboxylation sequence.



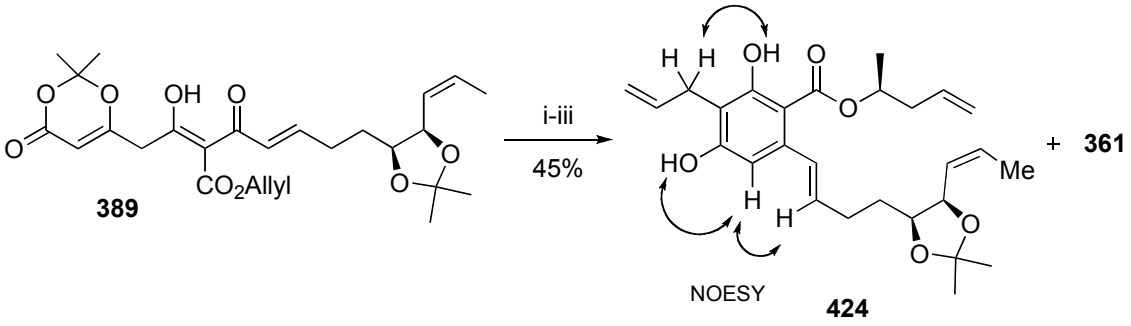
Reagents and conditions: i) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C then **388** 0 °C to RT; ii) morpholine, $Pd(PPh_3)_4$, CH_2Cl_2, 0 °C.

However, when a solution of tetrakis(triphenylphosphine)palladium(0) in THF was added first, followed by morpholine, and after subsequent aromatisation reaction, two products

[Φ] This work has been conducted with the help of Toni Pfaffeneder, a summer student who joined the Barrett group for a period of two months.

were isolated (Scheme 116). Expected resorcylate **361** was obtained in a 1:1 ratio with new resorcylate **424**, the structure of which was confirmed by both NOESY and mass spectroscopy analyses.

Scheme 116. Formation of new resorcylate **424**.

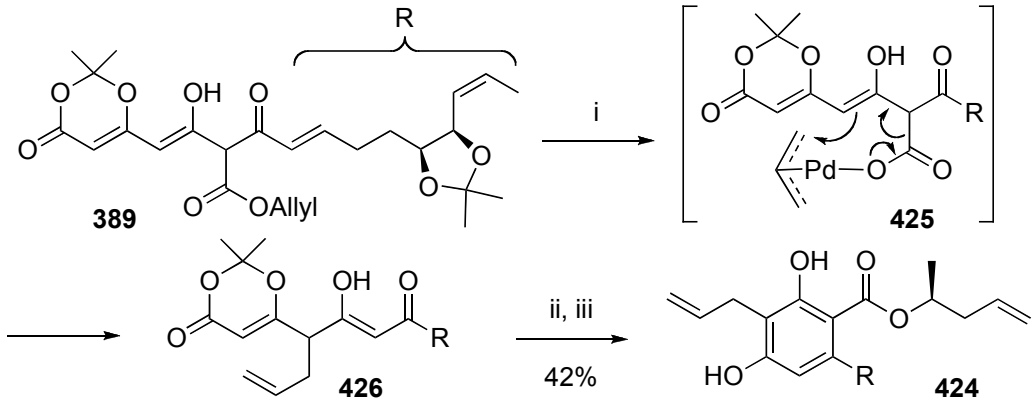


Reagents and conditions: i) $Pd(PPh_3)_4$, THF, 0 ^oC then morpholine; ii) **363**, PhMe, reflux; iii) CsOAc then AcOH.

It was possible to obtain resorcylate **424** as the only product in 42% yield starting from diketo-dioxinone **389** by changing the reaction conditions and not adding morpholine as a π-allyl cation trapping agent.

The proposed mechanism of formation of **424** is shown in Scheme 117. Upon reaction with palladium(0), the π-allyl complex **425** was formed and underwent a Claisen rearrangement to form allyl-substituted dioxinone **426** (allyl transfer reaction), the structure of which was confirmed by COSY of the crude reaction mixture. After aromatisation, the allyl-substituted resorcylate **424** was obtained in 42% yield.

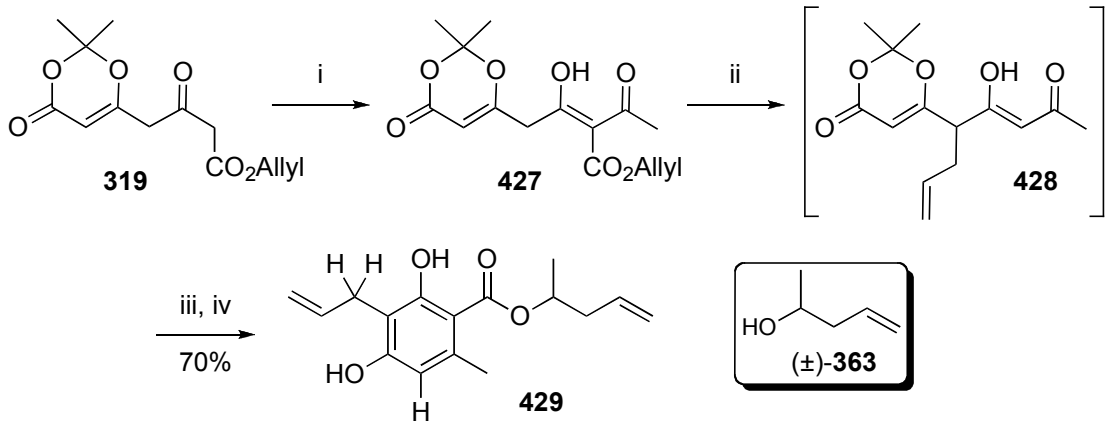
Scheme 117. Proposed mechanism of formation of resorcylate **424**.



Reagents and conditions: i) $Pd(PPh_3)_4$, THF, 0 °C; ii) **363**, PhMe, reflux; iii) CsOAc then AcOH.

To confirm this result, a simple reaction was carried out. Using the Claisen condensation previously described, dioxinone **319** was acylated with AcCl to give diketo-dioxinone **427**. Upon palladium(0)-catalysed allyl transfer and decarboxylation reactions, dioxinone **428** was formed and its structure confirmed by COSY. Ketene formation, trapping with racemic (±)-**363** and aromatisation led to resorcylate **429** in 70% overall yield (Scheme 118).

Scheme 118. Synthesis of resorcylate **429**.



Reagents and conditions: i) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C then AcCl 0 °C to 20 °C; ii) $Pd(PPh_3)_4$, THF, 0 °C; iii) (±)-**363**, PhMe, reflux; iv) CsOAc, ^{i}PrOH-CH_2Cl_2 then AcOH.

To summarize, diketo-dioxinones such as **430**, generated from a Claisen condensation, can give access to two different resorcylates by varying the reaction conditions during the palladium catalysed deallylation–decarboxylation sequence. One route, using morpholine as the π-allyl cation trapping agent, will lead to the formation of 3-H-resorcylic esters **431** and the other route, without the use of morpholine, will lead to the formation of 3-allyl-resorcylic esters **432** *via* an intramolecular trapping of the π-allyl cation (Figure 24).

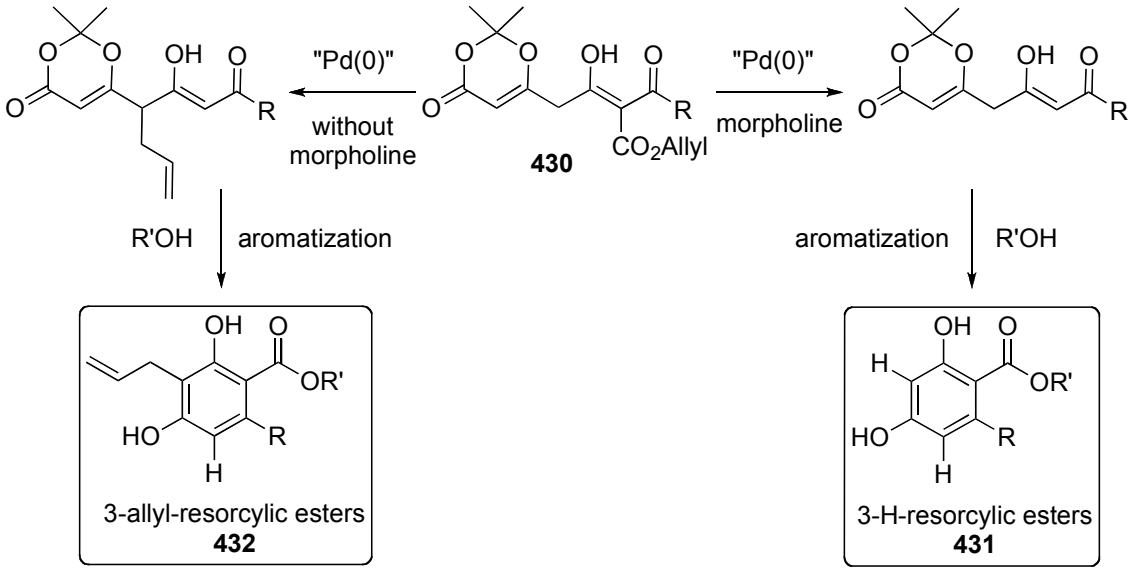


Figure 24. Formation of 3-H-resorcylic esters or 3-allyl-resorcylic esters.

It was decided to apply this new methodology towards the first total synthesis of two new resorcylates (also part of the isocoumarin class of natural product): angelicoin A (**28**) and angelicoin B (**29**) (Figure 25).

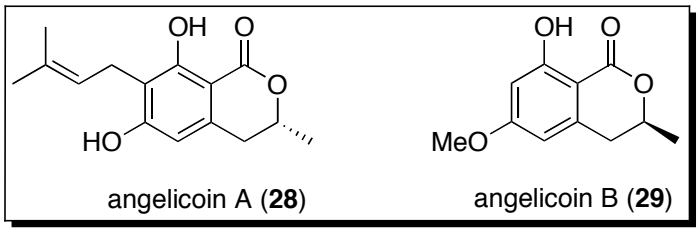


Figure 25. Structures of Angelicoins A and B.

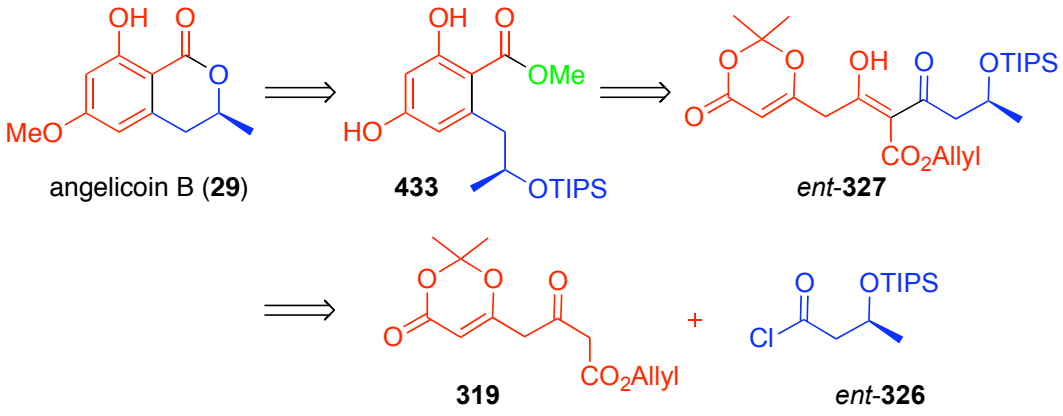
II.2.2. Studies towards the total synthesis of angelicoins A and B

Angelicoins A and B have been recently isolated from the roots of *Pleurospermum Angelicoides* in the Himalaya mountains and can be used as antipyretic and diaphoretic agents for the treatment of typhia and dysentery.[205]

II.2.2.1. Total synthesis of angelicoin B

Based on our findings, angelicoin B (**29**) could be obtained from lactonisation of resorcylate **433**. The latter would be made by palladium(0)-catalysed deallylation-decarboxylation reaction (using morpholine) of diketo-dioxinone *ent*-**327** followed by ketene–trapping with methanol and aromatisation. Dioxinone *ent*-**327** would be assembled by the Claisen condensation of dioxinone **319** with acyl chloride *ent*-**326** (Scheme 119).

Scheme 119. Retrosynthetic analysis of angelicoin B.

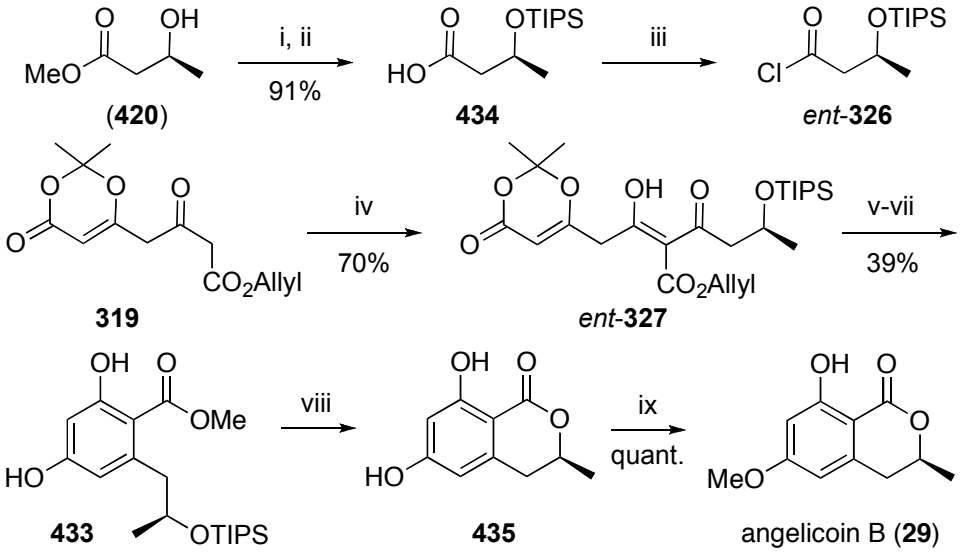


Acyl chloride *ent*-**326** was made in three steps from commercially available (*S*)-(+)-methyl-3-hydroxybutyrate (**420**) by TIPS protection, methyl ester hydrolysis to form

carboxylic acid **434** and acyl chloride formation with oxalyl chloride (Scheme 120). Claisen condensation between dioxinone **319** and acyl chloride *ent*-**326** gave diketo-dioxinone *ent*-**327** in 70% yield. The one-pot palladium(0)-catalyzed deallylation–decarboxylation–ketene–trapping–aromatisation sequence gave the desired resorcylate **433** in 39% overall yield. TIPS deprotection using H_2SiF_6 and cyclisation under *p*-TsOH catalysis gave lactone **435** in quantitative yield. Final methylation with MeI and K_2CO_3 gave angelicoin B (**29**).

The total synthesis of angelicoin B was achieved in only 6 steps with an overall yield of 28%.

Scheme 120. Total synthesis of angelicoin B.



Reagents and conditions: i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, RT; ii) LiOH, THF-H_2O, RT; iii) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0 °C to RT; iv) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C, then *ent*-**326**, 0 °C to RT; v) $Pd(PPh_3)_4$, morpholine, THF, 0 °C; vi) MeOH, PhMe, reflux; vii) CsOAc, ^{i}PrOH-CH_2Cl_2 then AcOH, RT; viii) H_2SiF_6, MeCN then cat. *p*-TsOH, reflux; ix) K_2CO_3, MeI, acetone, reflux.

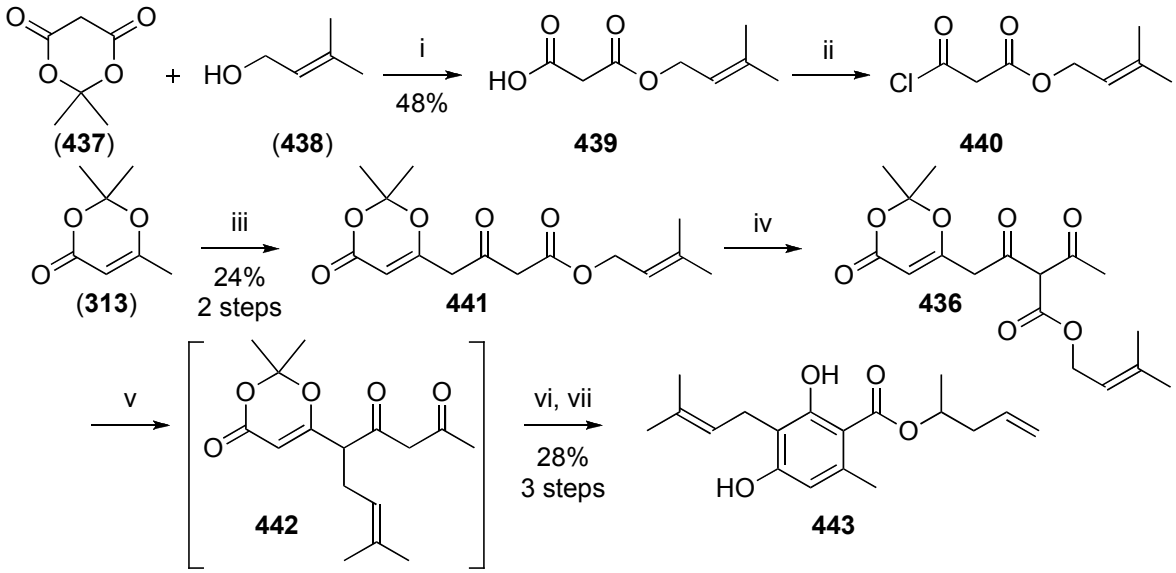
II.2.2.2. Attempted total synthesis of angelicoin A

II.2.2.2.1. Proof of concept

Having successfully performed the synthesis of 3-allyl-resorcylates, we decided to expand the scope of this reaction to prenyl substitution reactions which would give access to 3-prenyl-resorcylates such as angelicoin A (**28**).

To validate this hypothesis, dioxinone **436** was synthesised starting with the opening of Meldrum's acid (**437**) with prenyl alcohol (**438**) to obtain carboxylic acid **439** which was converted to acyl chloride **440**. Deprotonation of dioxinone **313** and addition of **440** gave diketo-dioxinone **441** in 28% yield over the three steps (Scheme 121). Acylation of **441**, using the conditions previously described, gave key dioxinone **436**.

Scheme 121. Synthesis of 3-prenyl-resorcylate **443**.



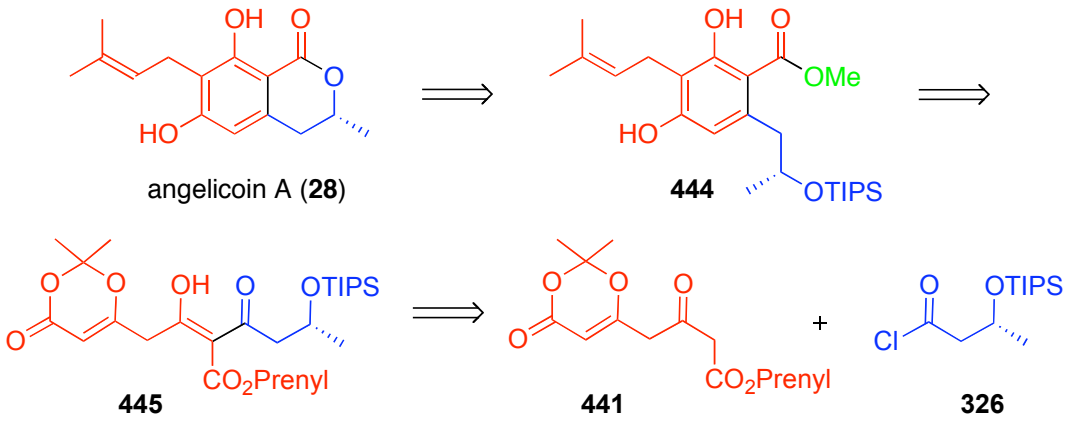
Reagents and conditions: i) neat, reflux; ii) $(COCl)_2$, cat. DMF, CH_2Cl_2; iii) LHMDS, THF, –78 °C then **440**, –78 °C to 0 °C; iv) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C then AcCl, 0 °C to RT; v) $Pd(PPh_3)_4$, THF, 0 °C; vi) (±)-**363**, PhMe, reflux; vii) CsOAc, ^iPrOH-CH_2Cl_2 then AcOH.

Treatment of **436** with a solution of tetrakis(triphenylphosphine)palladium(0) afforded dioxinone **442** which was used immediately as a crude. Sequential heating of **442** in toluene, trapping of the ketene formed with (±)-**363** and aromatisation reaction, allowed the formation of 3-prenyl-resorcylate **443** in 28% yield over the sequence.

II.2.2.2.2. Synthesis of tricyclic resorcylate 447

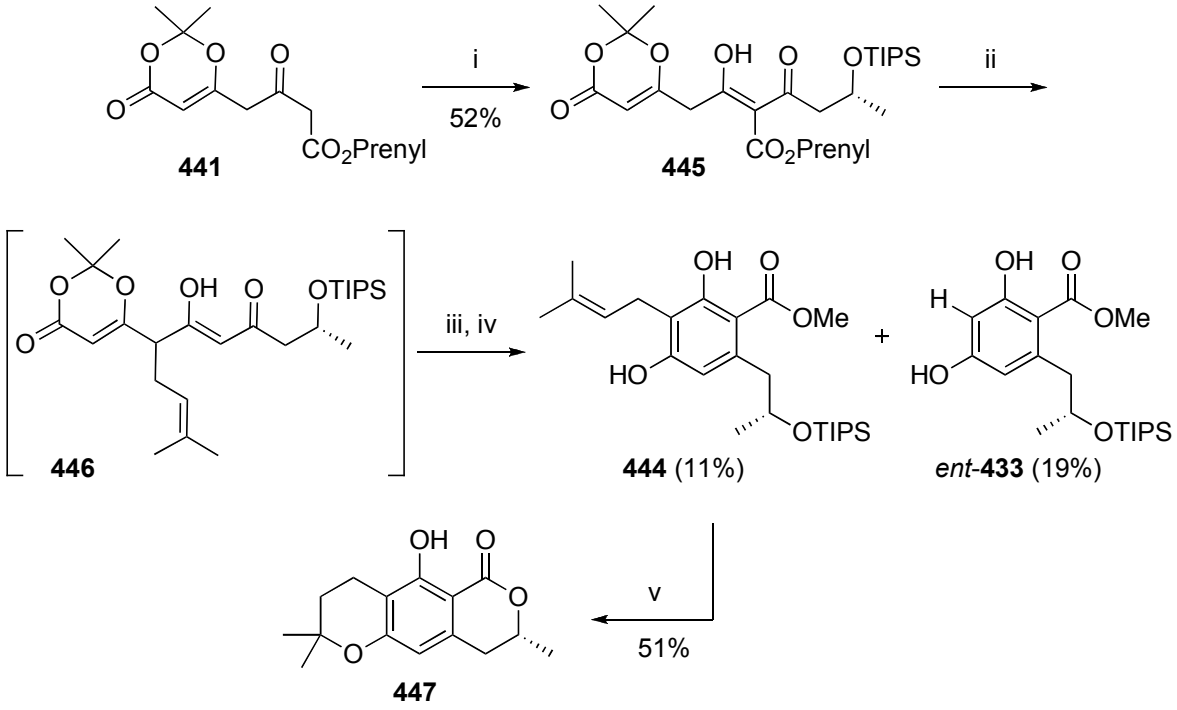
Having demonstrated that this methodology could be applied to a prenyl substitution reaction, it was decided to use this strategy towards the total synthesis of angelicoin A, the retrosynthesis of which is shown in Scheme 122. Similarly to angelicoin B (**29**), angelicoin A (**28**) could be obtained from lactonisation of resorcylate **444** which would be made by palladium(0)-catalysed prenyl rearrangement–decarboxylation reaction of diketo-dioxinone **445** followed by ketene–trapping with methanol and aromatisation. Dioxinone **445** would be assembled by the Claisen condensation of dioxinone **441** with acyl chloride **326**.

Scheme 122. Retrosynthetic analysis of angelicoin A.



Diketo-dioxinone **445** was made in 52% yield by acylation of dioxinone **441** with acyl chloride **326** (made in the same manner as *ent*-**326**). The palladium(0)-catalysed prenyl rearrangement–decarboxylation sequence gave diketo-dioxinone **446** which was immediately aromatised to afford resorcylate **444** albeit in a disappointing low yield of 11%. It is worth noticing that a considerable amount of the 3-H resorcylate *ent*-**433** was also formed (19%) (Scheme 123). Final deprotection of 3-prenyl-resorcylate **444** with H_2SiF_6 and lactonisation reaction led to the undesired tricyclic compound **447** in 51% yield. This reaction is being completed by other group members in our laboratories.

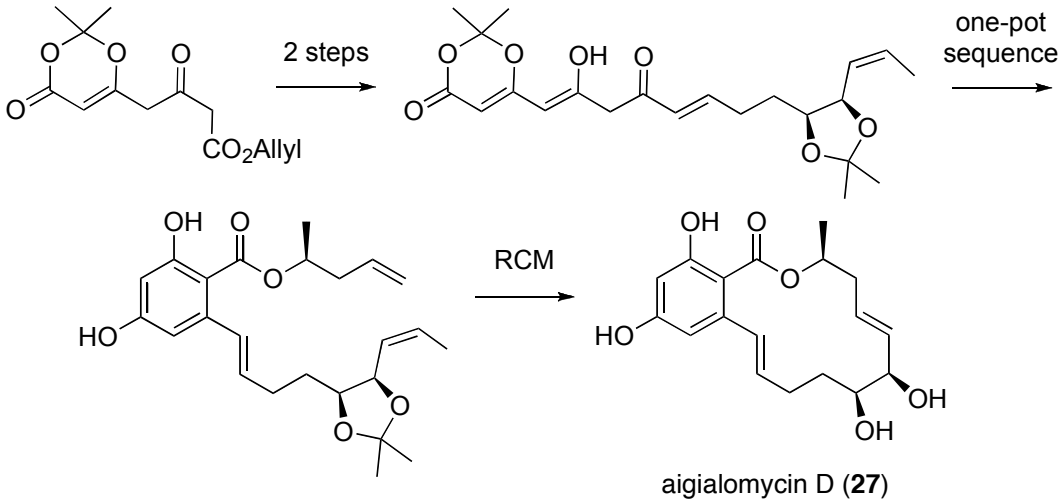
Scheme 123. Formation of tricyclic resorcylate **447**.



Reagents and conditions: i) $MgCl_2$, pyridine, CH_2Cl_2, 0 °C then **326**, 0 °C to RT; ii) $Pd(PPh_3)_4$, THF, 0 °C; iii) MeOH, PhMe, reflux; iv) CsOAc, ^{i}PrOH-CH_2Cl_2 then AcOH, RT; v) H_2SiF_6, MeCN then *p*-TsOH, reflux.

II.3. CONCLUSION

In the second part of this thesis was developed a concise total synthesis of aigialomycin D employing a one-pot ketene–generation–trapping–aromatisation sequence and RCM as key steps.

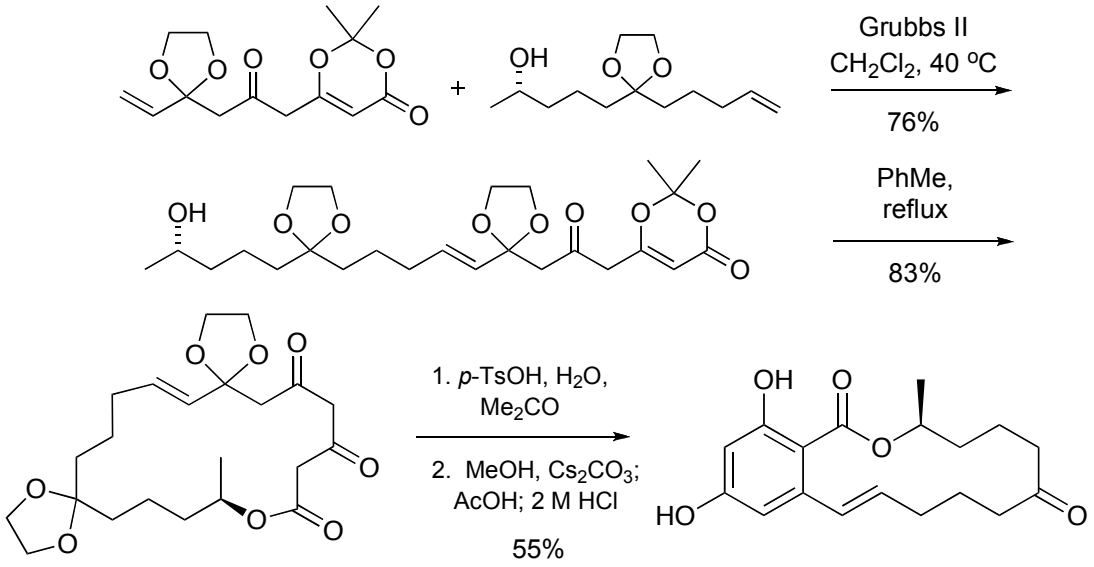


The biological activity and interesting structural features (including a 14-membered resorcylic macrolactone) of aigialomycin D have made it an attractive target and several syntheses have been reported since its isolation in 2002. We demonstrated that the complete carbon backbone, including the embedded resorcinol unit, could be prepared in a highly efficient manner from a relatively simple dioxinone precursor using the methodology developed in our group.

Good progress was also made towards the total synthesis of Aigialomycin D *via* an intramolecular trapping of the ketene. Despite the fact we have not yet been successful in removing the TBS group in **423**, and hence have not attempted the key intramolecular ketene–trapping reaction, we are confident that this approach would be fruitful as the total

synthesis of (*S*)-zearalenone (**254**) has been very recently achieved in our group by one of our co-workers using this strategy (Scheme 124).

Scheme 124. Total synthesis of (*S*)-zearalenone *via* an intramolecular ketene–trapping.



Finally, a new strategy towards the synthesis of new substituted resorcylates has been developed, where the trapping of a π-allyl-cation or a substituted π-allyl-cation was done in an intramolecular fashion. Based on this methodology, new projects have been initiated in our group. For example, Δ^9-THCA and cristatic acid could be obtained *via* the substituted π-allyl-cation intramolecular transfer, ketene-formation-trapping and aromatisation reactions (Figure 26).

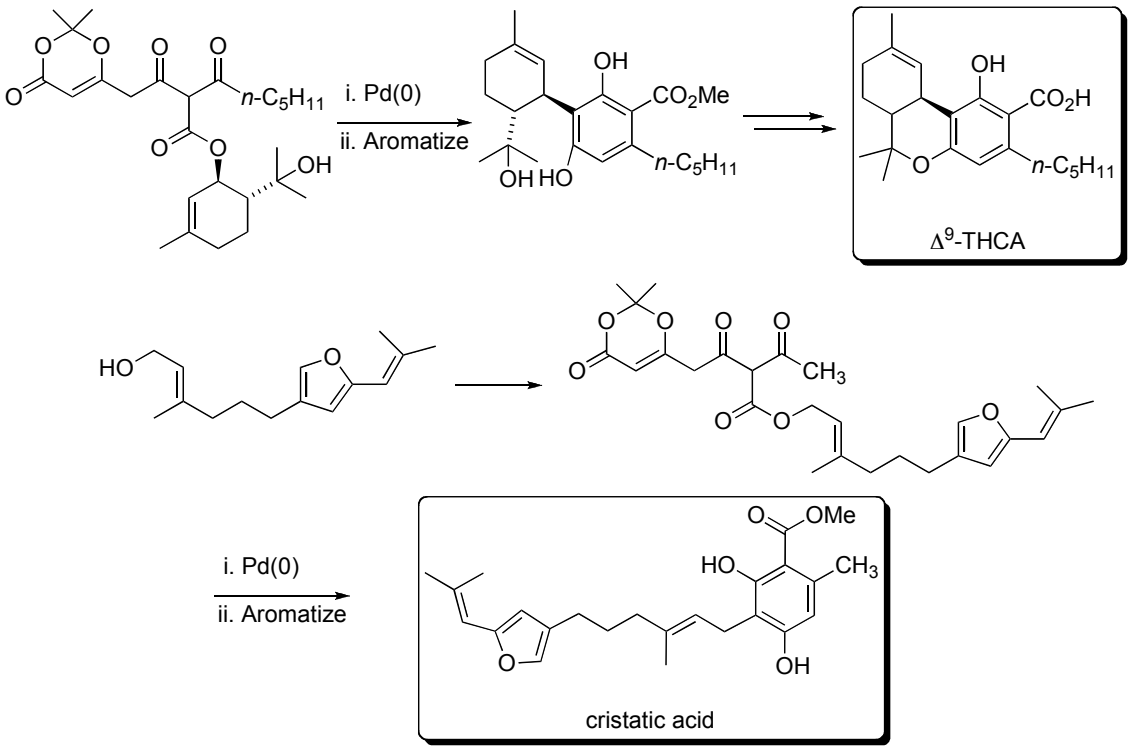


Figure 26. Proposed synthesis of Δ^9-THCA and cristatic acid.

III. EXPERIMENTAL

III.1. General procedure

III.1.1. Instrumental procedures

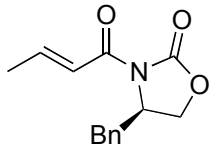
Melting points: obtained using a Reichert-Thermovar melting point apparatus and are uncorrected. **Infrared spectra:** obtained using a Mattson 5000 FTIR apparatus with automatic background subtraction. Indicative features of each spectrum are given with adsorptions reported in wavenumbers (cm^{-1}). Samples were prepared as thin films on sodium chloride plates. **Proton magnetic resonance spectra (^{1}H NMR):** recorded at 300 or 400 MHz on Brüker DRX-300 or Brüker DRX-400 spectrometers respectively, or at 500 MHz on an AM 500 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. Coupling constants (J) recorded in Hertz (Hz) and quoted to the nearest 0.5 Hz. **Carbon magnetic resonance spectra (^{13}C NMR):** recorded at 75 or 100 MHz on Brüker DRX-300 or Brüker DRX-400 spectrometers respectively, or at 125 MHz on an AM 500 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to the residual solvent peak. Spectra recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) were carried out by the Imperial College Department of Chemistry NMR service or by the Eli Lilly NMR service. **Mass spectrometry:** Low and high resolution mass spectra (EI, CI, ESI) were recorded by Imperial College Mass Spectrometry service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. **Microanalysis:** determined by the University of North London analytical service. **Optical Rotations:** recorded at 25 °C on a Perkin-Elmer 241 Polarimeter with a path length of 1 dm, using the 589.3 mn D-line of sodium. Concentrations (*c*) are quoted in

g/100 mL. **X-ray Diffraction:** X-ray diffraction data were recorded by the Imperial College Department of Chemistry X-ray diffraction service.

III.1.2. General experimental procedures

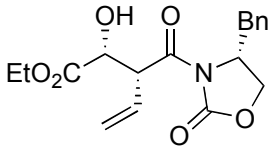
Reaction procedures: All reactions were carried out in flame-dried or oven-dried glassware in an atmosphere of dry nitrogen or argon at ambient temperature unless otherwise stated. Reaction temperatures other than RT were recorded as the bath temperature unless otherwise stated. Prolonged periods of vessel cooling were attained by the use of CryoCool apparatus. **Solvents and reagents:** All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The following reaction solvents were distilled under nitrogen: Et_2O and THF from sodium/benzophenone; PhMe from sodium; CH_2Cl_2 and Et_3N from CaH_2. MeOH was dried by refluxing over magnesium turnings and iodine, followed by distillation from CaH_2 under nitrogen. Hexanes refers to BDH AnalaR® petroleum spirit 40-60 °C. H_2O refers to distilled H_2O. **Chromatography:** Flash column chromatography was performed using BDH silica gel 60, particle size 40-63 mm unless otherwise stated. Thin layer chromatography (TLC) was performed on pre-coated aluminium backed or glass backed plates (Merck Kieselgel 60 F_{254}), visualisation was accomplished by either UV light (254 nm) or chemical staining using basic potassium permanganate ($KMnO_4$), or acidic vanillin stains as deemed appropriate.

(*Z*)-4-Benzyl-3-but-2-enoyl-oxazolidin-2-one (119)



^{n}BuLi (2.5 M in Hexane; 19.9 mL, 49.7 mmol) was added to 4-(*R*)-Benzyl-oxazolidin-2-one (8.8 g, 49.7 mmol) in THF (180 mL) at –78 °C and this solution stirred for 15 min after which time crotonyl chloride (5.73 mL, 59.6 mmol) was added. The reaction was stirred for 30 min and then allowed to warm to 0 °C for 15 min and quenched by the addition of aq. NH_4Cl (sat., 200 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. Recrystallisation from diethyl ether gave oxazolidinone **119** (11.5 g, 46.9 mmol, 94%) as a white solid: $[\alpha]_D^{25}$ –78.5 (*c* 1, $CHCl_3$); IR (KBr) 1776, 1682, 1635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 7H), 4.78 – 4.72 (m, 1H), 4.26 – 4.18 (m, 2H), 3.35 (dd, *J* = 13.0, 3.0 Hz, 1H), 2.82 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.01 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 153.5, 147.0, 135.4, 129.5, 129.0, 127.3, 121.9, 66.1, 55.3, 37.9, 18.6; MS (CI, NH_3) *m/z* 263 $(M + NH_4)^+$, 246 $(M + H)^+$.

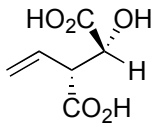
(2,3-*syn*)-3-(4-Benzyl-2-oxo-oxazolidine-3-carbonyl)-2-hydroxy-pent-4-enoic acid ethyl ester (120)



$^{n}Bu_2BOTf$ (1 M in CH_2Cl_2; 22.0 mmol, 22 mL) and NEt_3 (3.6 mL, 25.8 mmol) were added to a solution of **119** (4.90 g, 20.0 mmol) in CH_2Cl_2 (100 mL) at –78 °C and this mixture stirred for 1 h at –78 °C and 15 min at 0 °C. The reaction mixture was recooled to

–78 °C, and freshly distilled ethylglyoxalate (2.8 mL, 30.0 mmol) was added and the reaction stirred for 1 h at –78 °C and 1 h at 0 °C. The mixture was poured into aq. HCl (1 M; 100 mL) and the organic layer washed with aq. $NaHCO_3$ (sat., 100 mL), dried ($MgSO_4$) and the solvent removed. Purification by column chromatography (1:1 Hexanes: EtOAc) gave ester **120** (4.8 g, 14 mmol, 70%) as a viscous oil: $[\alpha]_D^{25}$ –23.7 (*c* 1, $CHCl_3$); IR (KBr) 1784, 1743, 1693, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 5H), 6.13 – 5.97 (m, 1H), 5.37 (d, *J* = 10.5 Hz, 1H), 5.34 (s, 1H), 4.92 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.61 (d, *J* = 4.5 Hz, 1H), 4.36 – 4.15 (m, 4H), 3.53 (*br*s, 1H, OH), 3.27 (dd, *J* = 13.5, 2.5 Hz, 1H), 2.78 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 171.3, 153.0, 135.1, 130.9, 127.4, 121.3, 128.9, 129.5, 71.1, 66.2, 62.2, 55.3, 51.6, 37.6, 14.2.

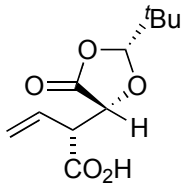
2(*R*)-Hydroxy-3(*R*)-vinyl-succinic acid (117)



LiOH (0.50 g, 12.0 mmol) was added at 0 °C to **120** (0.75 g, 4.0 mmol) in 1:1 MeOH:H_2O (20 mL) and the mixture stirred for 12 h. The reaction was reduced *in vacuo* and the residue extracted with CH_2Cl_2 (20 mL) and the aqueous layer acidified to pH 1 with conc. HCl and extracted with EtOAc (3 x 20 mL). The combined EtOAc extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give **15** (500 mg, 2.5 mmol, 63%) as a colorless oil: $[\alpha]_D^{25}$ +9.7 (*c* 1, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.89 (m, 1H), 5.25 (d, *J* = 9.0 Hz, 1H), 5.18 (s, 1H), 4.64 (d, *J* = 3.5 Hz, 1H), 4.48 (dd, *J* = 9.0, 3.5 Hz,

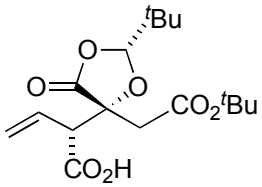
1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 172.7, 130.9, 120.2, 71.8, 53.2; HRMS (CI) calc. for $C_6H_{12}NO_5$: $(M + NH_4)^+$, 178.0715, found: $(M + NH_4)^+$, 178.0705.

2(*R*)-(2(*R*)-*tert*-Butyl-5-oxo-[1,3]dioxolan-4(*R*)-yl)-but-3-enoic acid (116)



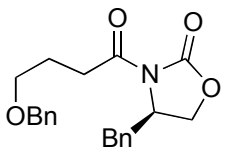
p-TsOH (0.2 g, 0.24 mmol), pivaldehyde (2 mL, 31 mmol) and were added to a suspension of diacid **117** (2.0 g, 12.6 mmol) in Hexane:THF (10:1, 22 mL) and the reaction stirred with azeotropic removal of water using a Dean-Stark apparatus. The reaction was cooled to RT and poured into aq. HCl (1 M; 20 mL), the organic layer dried ($MgSO_4$) and the solvent rotary evaporated to afford dioxolanone **116** (2.42 g, 10.7 mmol, 85%) as a white solid: m.p: 120–122 ºC (Hexane/CH_2Cl_2); $[\alpha]_D^{25}$ +19.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 – 5.93 (m, 1H), 5.45 – 5.34 (m, 2H), 5.16 (s, 1H), 4.76 (d, *J* = 2.5 Hz, 1H), 3.65 (dd, *J* = 9.0, 3.5 Hz, 1H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 171.1, 128.7, 122.3, 109.7, 75.7, 50.5, 34.4, 23.7; HRMS (CI) calc. for $C_{11}H_{20}NO_5$: $(M + NH_4)^+$, 246.1341, found: $(M + NH_4)^+$, 246.1336.

2-(4-*tert*-Butoxycarbonylmethyl-2-*tert*-butyl-5-oxo-[1,3]dioxolan-4-yl)-but-3-enoic acid (124)



LHMDS in THF (1 M; 2 mL, 2 mmol) was added dropwise to acid **116** (228 mg, 1 mmol) in dry DMF (1 mL) and the resulting pale yellow solution stirred at –70 °C for 50 min, when *tert*-butyl bromoacetate (150 μL, 1 mmol) was added. The reaction temperature was maintained at –70 °C for 15 min after which time the solution was poured onto aq. HCl (1 M; 10 mL) and Et_2O (30 mL) was added. The organic phase was washed with brine (3 × 20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 3:1) gave carboxylic acid **124** (200 mg, 0.60 mmol, 60%) as a colorless oil: $[\alpha]_D^{25}$ +67.8; IR (KBr) 3414, 1795, 1723, 1632, 1476 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 – 6.17 (m, 1H); 5.43 (d, *J* = 8.2 Hz, 1H), 5.40 (s, 1H), 5.26 (s, 1H), 3.70 (d, *J* = 9.5 Hz, 1H), 3.00 (d, *J* = 15.9 Hz, 1H), 2.78 (d, *J* = 15.9 Hz, 1H), 1.46 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 172.5, 168.1, 129.4, 123.0, 109.2, 82.3, 79.7, 56.0, 38.8, 34.3, 27.9, 23.7.

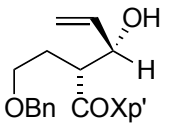
(*R*)-4-Benzyl-3-(4-benzyloxy-butyryl)-oxazolidin-2-one (134)



EtOCOCl (243 μL, 2.5 mmol) was added dropwise with stirring to a solution of 4-(benzyloxy)butyric acid **135** (0.5 g, 2.5 mmol) in dry Et_2O (50 mL) at 0 °C containing

Et_3N (356 μL, 2.5 mmol), resulting in the formation of a thick white precipitate. The mixture was allowed to warm to RT over 1 h. ^{n}BuLi in Hexane (2.5 M; 1 mL, 2.5 mmol) was added dropwise to a solution of (*R*)-4-benzyl-oxazolidin-2-one (452 mg, 2.5 mmol) in THF (50 mL) at –78 °C. This solution was added to the mixed anhydride (cannula) and the mixture stirred for 1 h at –78 °C, warmed to 0 °C, stirred for 1 h and quenched with aq. NH_4Cl (sat., 100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:EtOAc, 6:1) gave amide **134** (700 mg, 2.1 mmol, 85%) as a colorless oil: R*f* 0.20 (EtOAc:Hexanes, 1:6); $[\alpha]_D^{25}$ +44.8 (*c* 1.0, $CHCl_3$); IR (KBr) 1779, 1698, 1454, 1386, 1351, 1211, 1099, 738, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.25 (m, 10H), 4.51 (m, 1H), 4.42 (s, 2H), 4.01 (m, 2H), 3.49 (t, *J* = 6.2 Hz, 2H), 3.16 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.61 (dd, *J* = 13.4, 9.6 Hz, 1H), 1.93 (dt, *J* = 7.2, 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 153.4, 138.4, 135.3, 129.3, 128.9, 128.3, 127.6, 127.5, 127.2, 72.8, 69.2, 66.1, 55.1, 37.8, 32.4, 24.4; HRMS (ESI) calc. for $C_{21}H_{24}NO_4$: $(M + H)^+$, 354.1705, found: $(M + H)^+$, 354.1714.

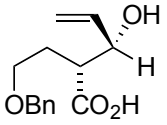
(*R*)-4-Benzyl-3-[2-((*R*)-2-benzyloxyethyl)-(*S*)-3-hydroxy-4-pentenoyl]-oxazolidin-2-one (133)



^{n}Bu_2BOTf in CH_2Cl_2 (1 M; 100 mL, 100 mmol) and Et_3N (15 mL, 50.6 mmol) were added with stirring to oxazolidinone **134** (31.5 g, 89.2 mmol) in CH_2Cl_2 (600 mL) at

–78 °C. After 1 h at –78 °C and 1 h at 0 °C, the mixture was cooled to –78 °C and freshly distilled propenal (7.8 mL, 116 mmol) was added with stirring. After 1 h at –78 °C and 1 h at 0 °C, the mixture was poured onto aq. HCl (1 M; 600 mL), the phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:EtOAc, 4:1) gave alcohol **133** (33.2 g, 91%) as a viscous oil: R*f* 0.30 (Hexanes:Et_2O, 6:1); $[\alpha]_D^{25}$ –29 (*c* 1.0, $CHCl_3$); IR (KBr) 3488, 1778, 1695, 1386, 1351, 1205, 1101, 1018, 738, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 8H), 7.12 – 7.10 (m, 2H), 5.88 (m, 1H), 5.33 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.21 (dt, *J* = 10.6, 1.3 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.46 (d, *J* = 2.6 Hz, 2H), 4.44 – 4.39 (m, 1H), 4.26 (m, 1H), 4.10 (t, *J* = 8.4 Hz, 1H), 4.04 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.60 (dd, *J* = 5.4, 1.5 Hz, 1H), 3.59 (d, *J* = 5.3 Hz, 1H), 3.16 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.81 (d, *J* = 3.1 Hz, 2H), 2.27 – 2.17 (m, 1H), 2.09 (dd, *J* = 13.4, 10.5 Hz, 1H), 2.00 – 1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 153.6, 138.1, 137.3, 135.7, 129.3, 128.8, 128.4, 128.2, 127.7, 127.1, 116.7, 73.6, 73.3, 68.9, 66.0, 55.7, 46.2, 37.2, 28.0; MS (CI) *m/z* 410 $(M + H)^+$, 427 $(M + NH_4)^+$; HRMS (ESI) calc. for $C_{24}H_{28}NO_5$: $(M + H)^+$, 410.1967, found: $(M + H)^+$, 410.1973.

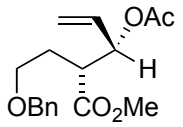
(2*R*)-(2-Benzyloxy-ethyl)-(3*R*)-hydroxy-pent-4-enoic acid (136)



Hydrogen peroxide (30%, 1.27 mL, 11.3 mmol) and LiOH (237 mg, 5.6 mmol) were added with stirring to a solution of **133** (580 mg, 1.4 mmol) in THF:H_2O (4:1, 10 mL). The resultant mixture was stirred for 1 h at 0 °C after which time Na_2SO_3 (2 g, 27.3 mmol) and

$NaHCO_3$ (2.3 g, 34.5 mmol) were added and the solvent removed *in vacuo*. The aqueous residue was diluted with H_2O (50 mL), extracted with CH_2Cl_2 (100 mL) and carefully acidified to pH 1 with conc. HCl. The acidified aqueous layer was extracted with EtOAc (2 x 100 mL), the combined EtOAc extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to give acid **136** (350 mg, 1.4 mmol, 100%) as a colorless oil: $[\alpha]_D^{25}$ –5.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.83 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 4.52 (s, 2H), 4.47 (m, 1H), 3.59 (m, 2H), 2.73 (dt, *J* = 8.4, 4.2 Hz, 1H), 2.02 (ddd, *J* = 20.4, 13.6, 7.2 Hz, 1H), 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 128.5, 127.9, 127.8, 117.0, 76.7, 76.3, 73.3, 72.5, 68.4, 48.0, 26.7, HRMS (CI) calc. for $C_{14}H_{19}O_4$: $(M + H)^+$, 251.1283, found: $(M + H)^+$, 251.1280.

(3*R*)-Acetoxy-(2*R*)-(2-benzyloxy-ethyl)-pent-4-enoic acid methyl ester (137)

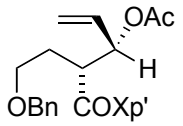


A solution of diazomethane in Et_2O was added to a solution of carboxylic acid **136** (170 mg, 0.7 mmol) in Et_2O (20 mL) until the yellow coloration persisted. Removal of the solvent and purification by column chromatography (Hexanes:EtOAc, 7:3) gave the corresponding methyl ester (175 mg, 0.58 mmol, 82%) as a viscous oil: $[\alpha]_D^{25}$ +5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.82 (m, 1H), 5.29 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.17 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.47 (m, 2H), 4.36 (m, 1H), 3.62 (s, 3H), 3.56 (ddd, *J* = 9.6, 6.4, 5.2 Hz, 1H), 3.48 (ddd, *J* = 9.7, 7.4, 4.9 Hz, 1H), 2.83 (d, *J* = 4.5 Hz, 1H), 2.72 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0,

138.3, 137.8, 128.6, 127.9, 127.9, 116.7, 73.2, 73.2, 68.4, 51.9, 48.7, 27.7; HRMS (CI) calc. for $C_{15}H_{21}O_4$: $(M + H)^+$, 265.1440, found: $(M + H)^+$, 265.1447.

A solution of this methyl ester (165 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (100 μL, 0.744 mmol), DMAP (15 mg, 0.124 mmol) and acetic anhydride (70 μL, 0.744 mmol). The resulting mixture was stirred for 1 h at RT and subsequently quenched with aq. $NaHCO_3$ (sat., 10 mL). The organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed to give acetate **137** (198 mg, 0.62 mmol, 100%) as a colorless oil: $[\alpha]_D^{25}$ +5.16 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.79 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H), 5.45 (t, *J* = 6.6 Hz, 1H), 5.24 (m, 2H), 4.44 (m, 2H), 3.59 (s, 3H), 3.45 (m, 2H), 2.86 (ddd, *J* = 10.3, 6.4, 3.7 Hz, 1H), 2.04 (s, 3H), 1.97 (ddt, *J* = 14.1, 11.0, 5.7 Hz, 1H), 1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.1, 138.5, 133.9, 128.55, 127.9, 127.8, 118.85, 77.4, 74.9, 73.2, 68.1, 52.0, 46.9, 28.2, 21.2; HRMS (CI) calc. for $C_{17}H_{23}O_5$: $(M + H)^+$, 307.1545, found: $(M + H)^+$, 307.1547.

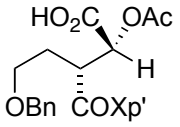
(*R*)-4-Benzyl-3-[2-((*R*)-2-benzyloxyethyl)-(*S*)-3-acetoxy-4-pentenoyl]-oxazolidin-2-one (139)



Et_3N (0.22 mL, 1.55 mmol), DMAP (17 mg, 0.14 mmol) and Ac_2O (0.15 mL, 1.55 mmol) were added with stirring to alcohol **133** (577 mg, 1.41 mmol) in Et_2O (30 mL) at 0 °C. After 5 h at RT, the solution was poured onto aq. HCl (1 M; 30 mL) and the organic layer washed with brine (30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1) gave acetate **139** (553 mg, 1.23 mmol, 87%) as a colorless oil: R*f* 0.40

(Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –29 (*c* 1.0, $CHCl_3$); IR (KBr) 1778, 1741, 1697, 1386, 1230, 1099, 1022, 740, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 8H), 7.13 – 7.11 (m, 2H), 5.88 – 5.80 (m, 1H), 5.60 (t, *J* = 5.4 Hz, 1H), 5.32 (dt, *J* = 17.3, 1.4 Hz, 1H), 5.24 (dt, *J* = 10.5, 1.2 Hz, 1H), 4.55 – 4.50 (m, 1H), 4.46 (q, *J* = 11.8, 2H), 4.35 (ddd, *J* = 11.5, 4.8, 2.8 Hz, 1H), 4.14 (t, *J* = 8.3 Hz, 1H), 4.04 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.57 – 3.45 (m, 2H), 3.12 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.21 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.06 (s, 3H), 1.92 – 1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 170.0, 153.4, 138.2, 135.6, 133.7, 129.3, 128.8, 128.3, 127.9, 127.6, 127.1, 117.9, 74.1, 73.0, 68.4, 66.0, 55.7, 44.2, 37.3, 26.7, 20.9; HRMS (ESI) calc. for $C_{26}H_{30}NO_6$: $(M + H)^+$, 452.2073, found: $(M + H)^+$, 452.2080; Anal. Calc. for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.19; H, 6.41; N, 3.07.

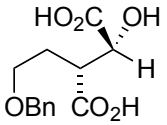
(*R*)-2-Acetoxy-(*R*)-3-((*R*)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-5-benzyloxy-pentanoic acid (140)



Acetate **139** (33 g, 73.2 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 ºC and a stream of ozone was bubbled through the mixture until a deep blue colour persisted. Oxygen was then bubbled through the solution for an additional 20 min to remove excess of ozone. Me_2S (25 mL, 366 mmol) was added at –78 ºC and the solution was allowed to warm to RT. Rotary evaporation gave the crude aldehyde, which was directly oxidized. Solid NaH_2PO_4 (44 g, 366 mmol) and $NaClO_2$ (26.5 g, 293 mmol) were added sequentially with stirring to aldehyde and 2-methyl-2-butene (116 mL, 1.1 mol) in ^{t}BuOH, H_2O, THF (1:1:1;

600 mL) at 0 °C. The mixture was allowed to warm to RT overnight and quenched by the addition of aq. Na_2SO_3 (sat., 600 mL) and aq. NH_4Cl (sat., 200 mL). The mixture was acidified to pH 1 using aq. HCl (conc.), saturated with NaCl and extracted with EtOAc (2 × 500 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (gradient Hexanes:EtOAc, 1:1 to EtOAc:MeOH, 4:1 to 7:3) gave carboxylic acid **140** (30 g, 63.8 mmol, 87%) as a colorless oil: R*f* 0.32 (MeOH:CH_2Cl_2, 1:4); $[\alpha]_D^{25}$ –59.5 (*c* 1.0, MeOH); IR (KBr) 1778, 1751, 1700, 1388, 1213, 1105, 1074, 744, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 8H), 7.12 – 7.10 (m, 2H), 5.55 (d, *J* = 5.4 Hz, 1H), 4.66 – 4.46 (m, 2H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.16 (t, *J* = 8.4 Hz, 1H), 4.04 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.65 – 3.54 (m, 2H), 3.14 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.22 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.13 (s, 3H), 2.07 – 1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.5, 169.9, 153.3, 137.8, 135.3, 129.3, 128.8, 128.4, 128.0, 127.7, 127.1, 73.1, 71.2, 67.9, 66.3, 55.6, 42.3, 37.3, 28.0, 20.5; HRMS (ESI) calc. for $C_{25}H_{28}NO_8$: $(M + H)^+$, 470.1815, found: $(M + H)^+$, 470.1817; Anal. Calc. for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.98. Found: C, 63.92; H, 5.70; N, 2.91.

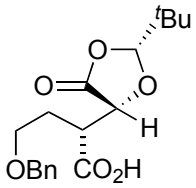
(*R*)-2-((*R*)-2-Benzyloxy-ethyl)-(*R*)-3-hydroxy-succinic acid (132)



H_2O_2 in H_2O (50%, 36 mL, 0.56 mol) and $LiOH{\cdot}H_2O$ (16 g, 0.37 mol) were added with stirring at 0 °C to carboxylic acid **140** (35 g, 74.5 mmol) in THF and H_2O (1:1, 1L). After 2 h, the THF was removed by rotary evaporation and aq. Na_2SO_3 (sat., 500 mL) added

at 0 °C and the mixture extracted with CH_2Cl_2 (3 × 250 mL). The aqueous residue was carefully acidified to pH 1 with aq. HCl (conc.) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were washed with brine (2 x 300 mL), dried ($MgSO_4$) and rotary evaporated to give diacid **132** (19.9 g, 74 mmol, 100%) as a colorless oil: $[\alpha]_D^{25}$ +4.5 (*c* 1.0, MeOH); IR (KBr) 1718, 1454, 1272, 1209, 1089, 1074, 740, 698 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.33 – 7.25 (m, 5H), 4.52 (d, *J* = 4.5 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.0 (m, 1H), 2.13 – 2.04 (m, 1H), 1.89 – 1.82 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 176.3, 176.1, 139.7, 129.3, 128.8, 128.6, 73.7, 72.5, 69.2, 46.9, 27.7; HRMS (ESI) calc. for $C_{13}H_{15}O_6$: $(M - H)^+$, 267.0869, found: $(M - H)^+$, 267.0879.

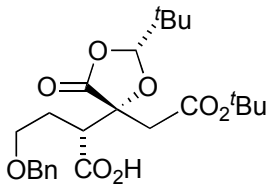
4-Benzyloxy-(*R*)-2-((*R*)-2-*tert*-butyl-(*R*)-5-oxo-[1,3]dioxolan-4-yl)-butyric acid (131)



p-TsOH (3.9 g, 20.5 mmol) and ^{t}BuCHO (22.6 mL, 205.8 mmol) were added with stirring to a solution of carboxylic acid **132** (18.4 g, 68.6 mmol) in Hexane and THF (10:1; 500 mL), and the mixture was stirred under reflux for 5 h with azeotropic removal of water (Dean-Stark). The mixture was cooled to RT and poured onto aq. HCl (1 M; 400 mL). The organic layer was washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (CH_2Cl_2:MeOH, 40:1) gave dioxolanone **131** (18.4 g, 54.8 mmol, 80%) as a white solid: R*f* 0.30 (CH_2Cl_2:MeOH, 20:1); mp: 105–110 ºC (Hexanes/CH_2Cl_2); $[\alpha]_D^{25}$ +10.2 (*c* 1.0, $CHCl_3$); IR (KBr) 1799, 1714, 1484, 1409, 1195,

1091, 971, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 5.14 (d, *J* = 1.0 Hz, 1H), 4.69 (dd, *J* = 3.9, 1.1 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.16 (dt, *J* = 8.8, 3.9 Hz, 1H), 2.24 – 2.15 (m, 1H), 1.95 – 1.88 (m, 1H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 171.6, 137.7, 128.4, 127.74, 127.71, 109.4, 75.1, 73.0, 67.5, 43.3, 34.2, 27.1, 23.5; HRMS (ESI) calc. for $C_{18}H_{23}O_6$: $(M - H)^+$, 335.1495, found: $(M - H)^+$, 335.1506; Anal. Calc. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.23.

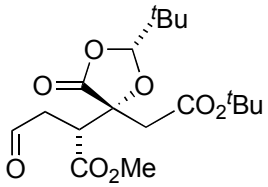
4-Benzyloxy-(*R*)-2-(4-*tert*-butoxycarbonylmethyl-2-(*R*)-*tert*-butyl-(*R*)-5-oxo-[1,3]dioxolan-4-yl)-butyric acid (141)



LHMDS in THF (1 M; 1 mL, 1 mmol) was added dropwise to acid **131** (168 mg, 0.5 mmol) in dry DMF (1 mL) and the resulting pale yellow solution stirred at –70 °C for 50 min, when *tert*-butyl bromoacetate (82 μL, 0.5 mmol) was added. The reaction temperature was maintained at –70 °C for 15 min after which time the solution was poured onto aq. HCl (1 M; 10 mL) and Et_2O (30 mL) was added. The organic phase was washed with brine (3 × 20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (CH_2Cl_2:MeOH, 40:1) gave carboxylic acid **141** (165 mg, 0.37 mmol, 73%), a yellow gum, as a mixture of diastereoisomers (9:1): R*f* 0.32 (CH_2Cl_2:MeOH, 20:1); IR (KBr) 1800, 1730, 1366, 1244, 1192, 1155, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 5.28 (s, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.58 – 3.45 (m, 2H), 3.16 (d, *J* = 16.5

Hz, 1H), 3.10 (dd, *J* = 11.3, 2.6 Hz, 1H), 2.84 (d, *J* = 16.5 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.05 – 1.97 (m, 1H), 1.45 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 172.5, 168.6, 138.0, 128.2, 127.5, 127.5, 109.7, 82.3, 79.6, 72.9, 67.5, 49.4, 38.8, 34.4, 27.9, 23.6; HRMS (ESI) calc. for $C_{24}H_{34}NaO_8$: $(M + Na)^+$, 473.2151, found: $(M + Na)^+$, 473.2157.

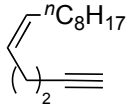
(*R*)-Methyl 2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)-4-oxobutanoate (112)



Diazomethane in Et_2O (excess) was added to the corresponding carboxylic acid (450 mg, 1 mmol) in Et_2O (50 mL) at 0 ºC till the yellow colour persisted. The reaction mixture was flushed with a stream of Nitrogen to remove the excess of diazomethane and the solvent evaporated to afford methyl ester **130** (464 mg, 1 mmol) as a colorless oil. Pd/C (10%, 400 mg) was added to a solution of methyl ester **130** (464 mg, 1 mmol) in dry THF (15 mL) under H_2 pressure and the mixture was stirred for 15 h, filtered through Celite and the solid washed with Et_2O, and rotary evaporated to leave the corresponding alcohol **143**. A solution of alcohol **143** (370 mg, 0.99 mmol) in CH_2Cl_2 (30 mL) was allowed to react with Dess–Martin periodinane (503 mg, 1.19 mmol) at 0 ºC. After 2 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 30 mL) and aq. Na_2SO_3 (sat., 30 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the corresponding crude aldehyde **112** (365 mg, 0.95 mmol, 96%) as a colorless oil: R*f* 0.36

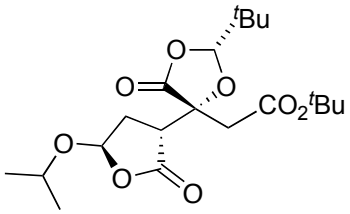
(Et_2O:Hexanes, 1:2); IR (KBr) 1793, 1727, 1365, 1236, 1195, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 5,28 (s, 1H), 3.74 (s, 3H), 3.33 (dd, *J* = 11.0, 3.0 Hz, 1H); 3.15 (dd, *J* = 18.3, 11.0 Hz, 1H), 3.09 (d, *J* = 16.8 Hz, 1H), 2.87 (d, *J* = 16.9 Hz, 1H), 2.78 (dd, *J* = 18.1, 2.9 Hz, 1H), 1.45 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 172.1, 170.7, 168.5, 110.0, 82.5, 79.1, 52.5, 45.7, 41.7, 39.5, 34.4, 27.9, 23.7; HRMS (ESI) calc. for $C_{18}H_{28}NaO_8$: $(M + Na)^+$, 395,1682, found: $(M + Na)^+$, 395.1692

Tetradec-5-en-1-yne (149)



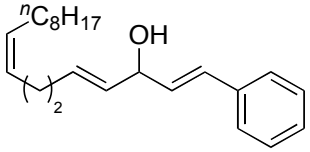
LHMDS in THF (2.5 M; 18.5 mL, 37 mmol) was slowly added with stirring at –40 ºC to (1-nonyl)triphenylphosphonium bromide **147** (17.8 g, 37.9 mmol) in THF (200 mL). The resulting red-orange solution was allowed to warm to –20 ºC, and recooled to –40 ºC. 4-Pentynal (**148**) (2.5 g, 30.5 mmol) in THF (5 mL) was added over 10 min and the mixture was allowed to warm to 0 ºC. The resulting yellow solution was diluted with Et_2O (50 mL) and aq. NH_4Cl (sat., 40 mL) added. The organic layer was washed with brine (40 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (100% Hexanes) gave alkyne **149** (3.8 g, 19.9 mmol, 65%) as a colorless oil: R*f* 0.85 (Hexanes); IR (KBr) 3313, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 – 5.37 (m, 2H), 2.30 – 2.19 (m, 4H), 2.04 (q, *J* = 6.9, 6.8 Hz, 2H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.36 – 1.21 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 127.3, 68.3, 31.9, 29.7, 29.5, 29.3, 27.3, 26.4, 22.7, 18.8, 14.1; HRMS (CI) calc. for $C_{14}H_{24}$: $(M + H)^+$, 192.1878, found: $(M + H)^+$, 192.1871.

[2-*tert*-Butyl-4-(5-isopropoxy-2-oxo-tetrahydro-furan-3-yl)-5-oxo-[1,3]dioxolan-4-yl]-acetic acid tert-butyl ester (150)



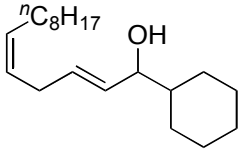
Under an atmosphere of argon, alkyne **149** (100 mg, 0.52 mmol), PhMe (1 mL) and neat Et_2Zn (40 μL, 0.42 mmol) were introduced sequentially into a 25 mL two-necked flask. The mixture was heated for 12 h at reflux and cooled to RT. (*S*)-(-)-BINOL (30 mg, 0.13 mmol), Et_2O (100 mL) and $Ti(O^iPr)_4$ (80 μL, 0.13 mmol) were added sequentially. After stirring for an additional 30 min at RT, a solution of aldehyde **112** (100 mg, 0.26 mmol) in PhMe (1 mL) was added dropwise and the solution stirred at RT for 10 h. Celite was added and the mixture was stirred for an additional 30 min. The slurry was filtered on a Büchner funnel and the residue was extracted with Et_2O (2 x 50 mL). The resulting solution was washed with aq. HCl (1 M; 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by column chromatography (Hexanes:Et_2O, 2:1) gave lactone **150** (60 mg, 0.31 mmol, 60%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (dd, *J* = 5.8, 0.8 Hz, 1H), 5.28 (s, 1H), 3.92 (hept, *J* = 6.2 Hz, 1H), 3.50 (d, *J* = 16.5 Hz, 1H), 3.35 (dd, *J* = 10.2, 9.1 Hz, 1H), 3.06 (d, *J* = 16.5 Hz, 1H), 2.40 (ddd, *J* = 13.2, 10.3, 5.9 Hz, 1H), 2.20 (ddd, *J* = 13.2, 8.9, 0.9 Hz, 1H), 1.44 (s, 9H), 1.16 (dd, *J* = 9.6, 6.2 Hz, 6H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.85, 172.6, 168.8, 109.5, 100.3, 82.6, 79.9, 77.4, 72.0, 44.3, 40.1, 34.6, 31.5, 29.9, 28.1, 24.2, 23.4, 21.7; MS (CI) *m/z* 401 $(M + H)^+$, 418 $(M + NH_4)^+$.

1-Phenyl-heptadeca-1,4,8-trien-3-ol (160a)



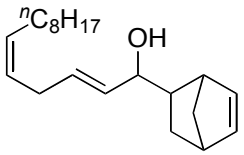
Alkyne **149** (100 mg. 0.52 mmol) in CH_2Cl_2 (2 mL) was kept under an atmosphere of N_2 and treated at RT with zirconocene hydrochloride (134 mg, 0.50 mmol). The mixture was stirred at RT until a homogenous solution formed and cooled to –65 ºC. Dimethyl zinc (1.2 M in PhMe; 0.42 mL) was added over 5 min. The reaction mixture was immersed in an ice bath and a solution of *trans*-cinnamaldehyde (70 mg, 0.53 mmol) in CH_2Cl_2 (2 mL) was added over 10 min. The reaction mixture was stirred at 0 ºC for 1.5 h. After addition of aq. NH_4Cl (sat., 10 mL), the mixture was extracted with Et_2O (10 mL). The organic layer was washed with aq. $NaHCO_3$ (sat., 15 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Hexanes:Et_2O, 4:1) gave **160a** (70 mg, 0.36 mmol, 70%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (m, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 16.0, 6.3 Hz, 1H), 5.75 (dt, *J* = 15.2, 5.9 Hz, 1H), 5.59 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.35 (m, 2H), 4.75 (t, *J* = 6.3 Hz, 1H), 2.12 (m, 4H), 1.99 (dd, *J* = 13.4, 6.6 Hz, 2H), 1.63 (*br*s, 1H, OH), 1.24 (s, 12H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 131.5, 131.2, 130.9, 130.5, 128.8, 127.9, 126.7, 73.9, 32.6, 32.1, 29.9, 29.7, 29.55, 27.5, 27.0, 22.9, 14.3; HRMS (CI) calc. for $C_{23}H_{38}NO$: $(M + NH_4)^+$, 344.2953, found: $(M + NH_4)^+$, 344.2948.

1-Cyclohexyl-pentadeca-2,6-dien-1-ol (160b)



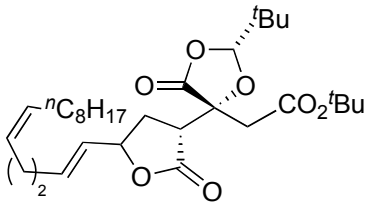
Alkyne **149** (75 mg. 0.39 mmol) in CH_2Cl_2 (2 mL) was kept under an atmosphere of N_2 and treated at RT with zirconocene hydrochloride (100 mg. 0.38 mmol). The mixture was stirred at RT until a homogenous solution formed and cooled to –65 ºC. Dimethyl zinc (1.2 M in PhMe, 0.195 mL) was added over 5 min. The reaction mixture was immersed in an ice bath and a solution of cyclohexylcarboxaldehyde (35 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added over 10 min. The reaction mixture was stirred at 0 ºC for 1.5 h. After addition of aq. NH_4Cl (sat., 10 mL), the mixture was extracted with Et_2O (10 mL). The organic layer was washed with aq. $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Hexanes:Et_2O, 4:1) gave **160b** (64 mg, 0.28 mmol, 73%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dt, *J* = 15.3, 5.9 Hz, 1H), 5.45 (dd, *J* = 15.3, 7.4 Hz, 1H), 5.34 (m, 2H), 3.75 (td, *J* = 7.0, 2.9 Hz, 1H), 2.09 (m, 4H), 1.99 (dd, *J* = 13.4, 6.6 Hz, 2H), 1.84 (*br*d, *J* = 12.6 Hz, 1H), 1.67 (m, 4H), 1.25 (m, 15H), 0.95 (m, 2H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 132.0, 130.8, 129.0, 77.95, 43.9, 32.6, 32.1, 29.9, 29.75, 29.5, 29.0, 28.9, 27.5, 27.2, 26.7, 26.4, 26.3, 22.9, 14.3; HRMS (CI) calc. for $C_{21}H_{42}NO$: $(M + NH_4)^+$, 324.3266, found: $(M + NH_4)^+$, 324.3275.

1-Bicyclo[2.2.1]hept-5-en-2-yl-pentadeca-2,6-dien-1-ol (160c)



Alkyne **149** (75 mg. 0.39 mmol) in CH_2Cl_2 (2 mL) was kept under an atmosphere of N_2 and treated at RT with zirconocene hydrochloride (100 mg. 0.38 mmol). The mixture was stirred at RT until a homogenous solution formed and cooled to –65 ºC. Dimethyl zinc (1.2 M in PhMe, 0.195 mL) was added over 5 min. The reaction mixture was immersed in an ice bath and a solution of 5-norbornene-2-carboxaldehyde (38 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was added over 10 min. The reaction mixture was stirred at 0 ºC for 1.5 h. After addition of aq. NH_4Cl (sat., 10 mL), the mixture was extracted with Et_2O (10 mL). The organic layer was washed with aq. $NaHCO_3$ (sat., 15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Hexanes:Et_2O, 4:1) gave **160c** (74 mg, 0.29 mmol, 75%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 – 6.02 (m, 2H), 5.62 -5.31 (m, 4H), 3.41 – 3.30 (m, 1H), 2.17 – 1.98 (m, 8H), 1.33 – 1.24 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 132.7, 132.5, 132.2, 131.6, 130.5, 130.5, 128.6, 49.5, 49.3, 46.4, 45.5, 45.0, 44.6, 43.8, 42.7, 42.1, 32.3, 31.8, 29.8, 29.7, 29.6, 29.5, 29.3, 27.2, 26.9,14.1; HRMS (CI) calc. for $C_{22}H_{40}NO$: $(M + NH_4)^+$, 334.3110, found: $(M + NH_4)^+$, 334.3097

[2-*tert*-Butyl-5-oxo-4-(2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-3-yl)-[1,3]dioxolan-4-yl]-acetic acid *tert*-butyl esters(159) and (161)



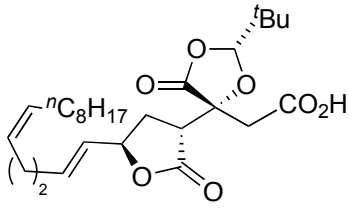
Alkyne **149** (200 mg. 1.04 mmol) in dry CH_2Cl_2 (10 mL) was kept under an atmosphere of N_2 and treated at RT with zirconocene hydrochloride (234 mg. 0.91 mmol). The mixture was stirred at RT until a homogenous solution formed and cooled to –65 ºC. Dimethyl zinc (1.2 M solution in PhMe, 0.76 mL, 0.91 mmol) was added over 5 min. The reaction mixture was immersed in an ice bath and a solution of aldehyde **112** (250 mg, 0.67 mmol) in CH_2Cl_2 (2 mL) was added over 10 min. The reaction mixture was stirred at RT overnight. After addition of aq. HCl (1 M; 20 mL), the mixture was extracted with Et_2O (30 mL). The organic layer was washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL) then transferred into a flask with *p*-TsOH (200 mg, excess) and stirred under reflux for 3 h. Brine (50 mL) was added, the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Hexanes:Et_2O, 6:1 to 4:1) gave first *trans*-lactone **159** as a pale yellow oil (163 mg, 0.47 mmol, 45%) followed by *cis*-lactone **161** (85 mg, 0.25 mmol, 24%) as a colorless gum:

159: R*f* 0.45 (Hexanes:Et_2O, 1:1); $[\alpha]_D^{25}$ +32.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.73 (m, 1H), 5.49 – 5.28 (m, 4H), 4.97 – 4.93 (m, 1H), 3.43 (d, *J* = 16.5 Hz, 1H), 3.25 (t, *J* = 9.2 Hz, 1H), 2.1 (d, *J* = 16.4 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.19 – 2.10 (m, 5H), 1.99 (q, *J* = 13.4, 6.7 Hz, 2H), 1.46 (s, 9H), 1.34 – 1.33 (m, 12H), 1.01 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 131.0, 128.0, 126.8, 110.1, 109.3, 82.3,

79.3, 78.6, 50.6, 46.3, 44.1, 42.7, 39.3, 32.2, 31.8, 30.8, 29.7, 29.5, 29.3, 27.9, 27.3, 26.6, 26.3, 24.1, 22.6, 14.1; HRMS (CI) calc. for $C_{31}H_{54}NO_7$: $(M + NH_4)^+$, 552.3900, found: $(M + NH_4)^+$, 552.3914.

161: R*f* 0.32 (Hexanes:Et_2O, 1:1); $[\alpha]_D^{25}$ +17.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.80 (m, 1H), 5.49 – 5.27 (m, 4H), 4.75 – 4.70 (m, 1H), 3.50 (d, *J* = 16.4 Hz, 1H), 3.31 (q, *J* = 12.6, 8.5 Hz, 1H), 3.10 (d, *J* = 16.4 Hz, 1H), 2.43 – 2.37 (m, 1H), 2.14 – 2.11 (m, 5H), 1.99 (q, *J* = 13.5, 6.7 Hz, 2H), 1.46 (s, 9H), 1.32 – 1.27 (m, 12H), 1.01 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 131.0, 128.0, 126.8, 110.1, 109.3, 82.3, 79.3, 78.6, 50.6, 46.3, 44.1, 42.7, 39.3, 32.2, 31.8, 30.8, 29.7, 29.5, 29.3, 27.9, 27.3, 26.6, 26.3, 24.1, 22.6, 14.1; HRMS (CI) calc. for $C_{31}H_{54}NO_7$ $(M + NH_4)^+$, 552.3900, found: $(M + NH_4)^+$, 552.3909.

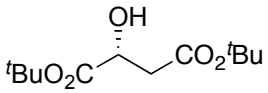
[2-*tert*-Butyl-5-oxo-4-(5-tetradeca-1,5-dienyl-tetrahydro-furan-3-yl)-[1,3]dioxolan-4-yl]-acetic acid (108)



TFA (1 mL) was slowly added to a stirred solution of *tert*-butyl ester **159** (20 mg, 0.038 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at RT for 4 h. PhMe was added (10 mL) and the solvent removed *in vacuo* to give carboxylic acid **109** (18 mg, 0.037 mmol, 98%) as yellow gum: ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.74 (m, 1H), 5.49 -5.27 (m, 4H), 4.99 – 4.94 (m, 1H), 3.58 (d, *J* = 16.9 Hz, 1H), 3.31 (t, *J* = 9.2 Hz, 1H), 3.28 (d, *J* = 16.9 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.20 – 2.11 (m, 5H), 1.99 (q, *J* = 13.5, 6.7 Hz, 2H), 1.26 – 1.22 (m,

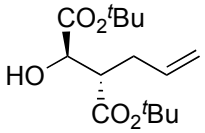
12H), 1.01 (s, 9H), 0.88 (t, J = 6.78 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.7, 171.9, 134.9, 131.0, 128.0, 127.1, 109.3, 79.7, 78.5, 44.2, 37.5, 34.3, 32.1, 31.8, 29.8, 29.6, 29.5, 29.3, 27.2, 26.3, 23.9, 22.6, 14.1; HRMS (ESI) calc. for $C_{27}H_{41}O_7$: $(M - H)^+$, 477.2852, found: $(M - H)^+$, 477.2838.

2-Hydroxy-succinic acid di-*tert*-butyl ester (49)



N,*N*'-di-*iso*-propyl-*O*-tert-butylisourea (**48**) (7 g, 140 mmol) was added to a solution of (*R*)-malic acid (2 g, 14 mmol) in CH_2Cl_2 (20 mL) and the resulting mixture stirred at reflux under N_2 for 2 days. The solvent was removed *in vacuo* and the crude purified by column chromatography (Hexanes:Et_2O, 2:1) to give ester **49** (800 mg, 5.6 mmol, 40%) as a colorless oil: R*f* 0.52 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +14.2 (*c* 1.0, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 – 4.28 (m, 1H), 3.21 (d, J = 5.6 Hz, 1H), 2.69 (dq, J = 16.4, 16.3, 5.2 Hz, 2H), 1.49 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 169.7, 82.6, 81.3, 67.5, 39.8, 28.0, 27.9. HRMS (ESI) calc. for $C_{12}H_{22}NaO_5$: $(M + Na)^+$, 269.1365, found: $(M + Na)^+$, 269.1369.

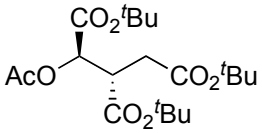
di-*tert*-Butyl (*S*)-2-allyl-(*R*)-3-hydroxy-succinate (50)



LHMDS in THF (1 M; 6.3 mL, 6.3 mmol) was slowly added with stirring at –78 ºC to a solution in THF (15 mL) containing ester **49** (733 mg, 3 mmol) and allyl bromide (0.31

mL, 3.1 mmol). After 1 h at –78 °C and 1 h at 0 °C, the mixture was poured onto aq. HCl (1 M; 40 mL), the phases separated, and the aqueous phase extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:EtOAc, 4:1) gave alcohol **50** (760 mg, 2.7 mmol, 89%) as a colorless oil: R*f* 0.66 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ –5.3 (*c* 1.0, Et_2O); IR (KBr) 3489, 1732, 1368, 1253, 1156, 1066, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.77 (m, 1H), 5.17 – 5.08 (m, 2H), 4.10 (s, 1H), 3.19 (s, 1H), 2.82 – 2.78 (m, 1H), 2.60 -2.53 (m, 1H), 2.42 – 2.35 (m, 1H), 1.49 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.4, 135.2, 117.4, 82.5, 81.5, 70.5, 48.7, 32.7, 28.0, 28.0; HRMS (ESI) calc. for $C_{15}H_{26}NaO_5$: $(M + Na)^+$, 309.1678, found: $(M + Na)^+$, 309.1685.

di-*tert*-Butyl (*R*)-2-acetoxy-(*S*)-3-*tert*-butoxycarbonyl-pentanedioic (162)

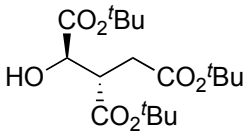


Et_3N (0.44 mL, 3.1 mmol), DMAP (4 mg, 0.32 mmol) and Ac_2O (0.3 mL, 3.1 mmol) were added with stirring to alcohol **50** (760 mg, 2.65 mmol) in Et_2O (30 mL) at 0 °C. After 5 h at RT, the mixture was poured onto aq. HCl (1 M; 30 mL) and the organic layer was washed with brine (30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 4:1) gave the corresponding acetate (840 mg, 2.55 mmol, 96%) as a colorless oil: R*f* 0.50 (Et_2O:Hexanes, 1:4); $[\alpha]_D^{25}$ +7.2 (*c* 1.0, Et_2O); IR (KBr) 1934, 1745, 1371, 1226, 1129, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.73 (m, 1H), 5.11 – 5.05 (m, 3H), 2.95 – 2.90 (m, 1H), 2.52 – 2.44 (m, 1H), 2.30 – 2.23 (m, 1H), 2.11 (s, 3H); 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.9, 167.5, 134.5, 117.6,

82.5, 81.5, 72.3, 46.9, 32.2, 28.0, 20.5; HRMS (ESI) calc. for $C_{17}H_{28}NaO_6$: $(M + Na)^+$, 351.1784, found: $(M + Na)^+$, 351.1793.

$RuCl_3$ (4 mg, 0.08 mmol) and $NaIO_4$ (2.25 g, 10.6 mmol) were added the previous acetate (840 mg, 2.6 mmol) in CCl_4, MeCN and H_2O (5:5:8; 18 mL) and the mixture was stirred vigorously for 2 h at RT. CH_2Cl_2 (10 mL) was added and the layers separated and the upper aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried ($MgSO_4$) and rotary evaporated to give the corresponding carboxylic acid (840 mg, 2.6 mmol, 100%). *N*,*N*'-di-*iso*-propyl-*O*-*t*-butylisourea (**48**) (1.22 g, 6.5 mmol) was added to this acid (840 mg, 2.6 mmol) in CH_2Cl_2 (15 mL) and the mixture stirred under reflux for 12 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 6:1) gave *tert*-butyl ester **162** (730 mg, 1.81 mmol, 75%) as a colorless oil: R*f* 0.45 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ +16.2 (*c* 1.0, Et_2O); IR (KBr) 1739, 1369, 1225, 1160, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (d, *J* = 3.3 Hz, 1H), 3.37 (ddd, *J* = 9.7, 4.9, 3.4 Hz, 1H), 2.68 (dd, *J* = 16.7, 9.7 Hz, 1H), 2.39 (dd, *J* = 16.7, 5.0 Hz, 1H), 2.12 (s, 3H), 1.47 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 169.1, 166.7, 82.8, 81.9, 80.9, 72.0, 43.6, 33.6, 28.0, 20.5; HRMS (ESI) calc. for $C_{20}H_{34}NaO_8$: $(M + Na)^+$, 425.2151, found: $(M + Na)^+$, 425.2141.

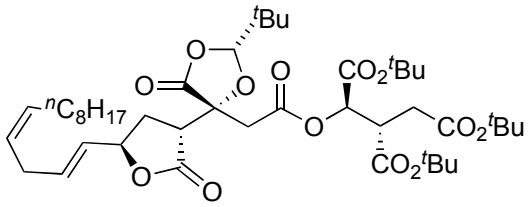
di-*tert*-Butyl (*S*)-3-*tert*-butoxycarbonyl-(*R*)-2-hydroxy-pentanedioate (35)



K_2CO_3 (368 mg, 2.7 mmol) was added with stirring to acetate **162** (715 mg, 1.78 mmol) in MeOH (15 mL) at 0 ºC. After 1 h, the solution was poured onto aq. NH_4Cl (sat., 20 mL)

and extracted with EtOAc (2 x 30 mL). The organic phase was washed with brine (2 x 30 mL) and dried ($MgSO_4$). Rotary evaporation gave alcohol **35** (620 mg, 1.75 mmol, 98%) as a colorless oil: R*f* 0.40 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ +7.6 (*c* 0.67, CH_2Cl_2); IR (KBr) 3496, 1731, 1368, 1254, 1151, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 1H), 3.29 (ddd, *J* = 8.7, 6.3, 2.8 Hz, 1H), 3.15 (brs, 1H), 2.73 (dd, *J* = 16.7, 8.4 Hz, 1H), 2.49 (dd, *J* = 16.8, 6.2 Hz, 1H), 1.50 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.0, 170.2, 83.0, 81.6, 80.7, 70.8, 45.8, 33.8, 28.0; HRMS (ESI) calc. for $C_{18}H_{32}NaO_7$: $(M + Na)^+$, 383.2046, found: $(M + Na)^+$, 383.2063; Anal. Calc. for $C_{18}H_{32}O_7$: C, 59.98; H, 8.95. Found: C, 60.05; H, 8.90.

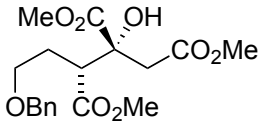
3-*tert*-Butoxycarbonyl-2-{2-[2-*tert*-butyl-5-oxo-4-(2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-3-yl)-[1,3]dioxolan-4-yl]-acetoxy}-pentanedioic acid di-*tert*-butyl ester (107)



DCC (47 mg, 0.30 mmol), DMAP·HCl (1 mg, 0.015 mmol) and alcohol **35** (86 mg, 0.30 mmol) were sequentially added with stirring to acid **159** (55 mg, 0.15 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 2 h at RT and concentrated *in vacuo*. Purification by column chromatography (Hexanes:Et_2O, 4:1) gave ester **107** (65 mg, 0.11 mmol, 70%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.77 (m, 1H), 5.49 – 5.28 (m, 4H), 5.23 (d, *J* = 3.6 Hz, 1H), 4.77 – 4.71 (m, 1H), 3.67 (d, *J* = 16.8 Hz, 1H), 3.40 – 3.34 (m, 2H), 3.37 (d, *J* = 16.8 Hz, 1H), 2.67 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.44 – 2.37 (m,

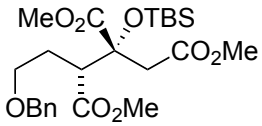
2H), 2.20 – 2.09 (m, 5H), 1.99 (q, *J* = 13.7, 6.9 Hz, 2H), 1.46 – 1.45 (*br* s, 27H), 1.35 – 1.25 (m, 12H), 1.02 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H); HRMS (ESI) calculated for $C_{45}H_{72}O_{13}Na$: $(M + Na)^+$, 843.4871, found: $(M + Na)^+$, 843.4890.

(2*R*,3*R*)-Trimethyl 5-(benzyloxy)-2-hydroxypentane-1,2,3-tricarboxylate (176)



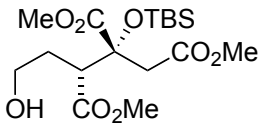
$BF_3{\cdot}OEt_2$ (0.7 mL, 10 mmol) was added to a solution of carboxylic acid **141** (450 mg, 1 mmol) in MeOH (10 mL) and the mixture heated at reflux in a sealed tube overnight. The solvent was rotary removed and Et_2O (20 mL). The etherate solution was washed with aq. HCl (1 M; 20 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by chromatography (Hexanes:Et_2O, 2:1) gave trimethyl ester **176** (335 mg, 0.9 mmol, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 4.51 – 4.41 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.62 (s, 3H), 3.50 – 3.39 (m, 2H), 3.13 (d, *J* = 16.4 Hz, 1H), 2.93 (dd, *J* = 11.5, 2.8 Hz, 1H), 2.73 (d, *J* = 16.4 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.90 – 1.82 (m, 1H), 1.58 (*br*s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.5, 171.0, 138.1, 128.3, 127.62, 127.52, 72.9, 68.0, 53.2, 52.0, 51.0, 40.6; HRMS (ESI) calc. for $C_{18}H_{25}O_8$: $(M + H)^+$, 369.1549, found: $(M + H)^+$, 369.1548.

(2*R*,3*R*)-Trimethyl-5-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)pentane-1,2,3-tricarboxylate (177)



TBSOTf (0.14 mL, 0.49 mmol) was added with stirring to tertiary alcohol **176** (120 mg, 0.33 mmol) and 2,6-lutidine (0.1 mL, 0.66 mmol) in CH_2Cl_2 and the mixture stirred at RT for 48 h and subsequently quenched with aq. $NaHCO_3$ (sat., 15 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 4:1) gave silyl ether **177** (135 mg, 0.28 mmol, 85%) as a colorless oil: R*f* 0.55 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ –17.5 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 7.29 (m, 5H), 4.43 (m, 2H), 3.72 (s, 3H), 3.62 (s, 3H), 3.56 (s, 3H), 3.41 (m, 2H), 3.09 (d, *J* = 15.8 Hz, 1H), 2.92 (dd, *J* = 11.6, 2.2 Hz, 1H), 2.70 (d, *J* = 15.9 Hz, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 0.84 (s, 9H), 0.17 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 174.4, 174.0, 172.1, 129.5, 128.95, 128.8, 80.7, 74.1, 69.45, 54.3, 53.0, 52.5, 52.3, 42.85, 29.0, 26.7, 19.9, –2.4, –2.6; HRMS (ESI) calculated for $C_{24}H_{39}O_8Si$: $(M + H)^+$, 483.2414, found: $(M + H)^+$, 483.2401.

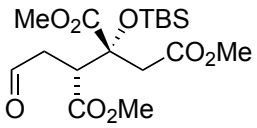
(2*R*,3*R*)-Trimethyl-2-(*tert*-butyldimethylsilyloxy)-5-hydroxypentane-1,2,3-tricarboxylate (178)



Powdered Pd/C (10%, 140 mg) was added to benzyl ether **177** (135 mg, 0.28 mmol) in dry THF (15 mL) under H_2 pressure. The mixture was magnetically stirred for 1 h, filtered

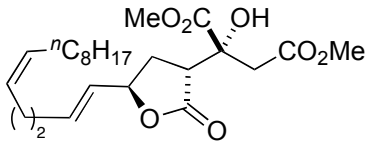
through Celite while being rinsed with Et_2O and rotary evaporated to give alcohol **178** (108 mg, 0.27 mmol, 96%) as a colorless oil: R*f* 0.10 (Et_2O:Hexanes, 1:5); ^1H NMR (400 MHz, MeOD) δ 3.74 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.51 (m, 1H), 3.43 (ddd, *J* = 10.9, 7.5, 5.8 Hz, 1H), 3.10 (d, *J* = 15.8 Hz, 1H), 2.89 (dd, *J* = 11.8, 2.3 Hz, 1H), 2.72 (d, *J* = 15.8 Hz, 1H), 2.02 (dtd, *J* = 17.5, 11.5, 5.7 Hz, 1H), 1.84 (m, 2H), 0.85 (s, 9H), 0.20 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 174.35, 174.0, 172.0, 80.8, 61.2, 53.7, 53.0, 52.5, 52.3, 43.3, 31.8, 26.7, 19.9, –2.3, –2.6; HRMS (ESI) calculated for $C_{17}H_{32}O_8Si$: $(M + H)^+$, 393.1945, found: $(M + H)^+$, 393.1949.

(2*R*,3*R*)-Trimethyl 2-(*tert*-butyldimethylsilyloxy)-5-oxopentane-1,2,3-tricarboxylate (179)



Dess–Martin periodinane (175 mg, 0.41 mmol) was added to alcohol **178** (108 mg, 0.28 mmol) in CH_2Cl_2 (20 mL) at 0 ºC. After 2 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 15 mL) and aq. Na_2SO_3 (sat., 15 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the crude aldehyde **179** (104 mg, 0.26 mmol, 93%) as a colorless oil: R*f* 0.40 (Et_2O:Hexanes, 1:2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.34 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.12 (dd, *J* = 18.6, 11.0 Hz, 1H), 3.04 (d, *J* = 15.9 Hz, 1H), 2.81 (d, *J* = 15.9 Hz, 1H), 2.62 (dd, *J* = 18.6, 2.6 Hz, 1H), 0.81 (s, 9H), 0.18 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 172.51, 171.3, 170.3, 78.7, 52.8, 52.4, 52.0, 47.8, 42.8, 42.2, 26.0, 19.0, –2.7, –3.0.

(2*R*)-Dimethyl-2-hydroxy-2-((3*R*)-2-oxo-(5*R*)-((1*E*,5*Z*)-tetradeca-1,5-dienyl-tetrahydrofuran-3-yl)succinate (167)



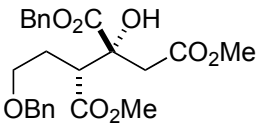
Alkyne **149** (200 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was added dropwise with stirring to Cp_2ZrHCl (244 mg, 0.94 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at RT until a homogenous solution was formed and subsequently cooled to –65 ºC. Me_2Zn in PhMe (1.2 M; 0.79 mL, 0.94 mmol) was added over 5 min after which time the mixture was cooled to 0 ºC and a solution of aldehyde **179** (255 mg, 0.65 mmol) in CH_2Cl_2 (2 mL) was added over 10 min. The reaction mixture was warmed to room RT and stirred for 12 h then poured onto aq. HCl (1 M; 20 mL). Et_2O (30 mL) was added and the layers were separated. The organic layer was washed with brine (30 mL), dried ($MgSO_4$) and *p*-TsOH (200 mg, excess) was added with stirring. After 3 h of reflux in Et_2O, the solvent was removed by rotary evaporation. Purification by chromatography (gradient Hexanes:Et_2O, 6:1 to 4:1 to 2:1) gave in order of increasing polarity first silyl protected *trans*-lactone **180** (150 mg, 0.27 mmol, 42%) as a pale yellow oil followed by silyl protected *cis*-lactone **181** (100 mg, 0.18 mmol, 28%) as a colorless oil:

180: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.38 (m, 3H), 4.88 (dd, *J* = 12.5, 7.6 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.36 (d, *J* = 15.7 Hz, 1H), 3.30 (d, *J* = 15.7 Hz, 1H), 3.19 (dd, *J* = 9.8, 7.4 Hz, 1H), 2.39 (m, 1H), 2.02 (m, 7H), 1.24 (*br*s, 12H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.82 (s, 9H), 0.17 (s, 3H), 0.08 (s, 3H); HRMS (ESI) calc. for $C_{30}H_{53}O_7Si$: $(M + H)^+$, 553.3561, found: $(M + H)^+$, 553.3572.

181: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.37 (m, 3H), 4.66 (dt, *J* = 10.5, 6.8 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.45 (m, 3H), 3.26 (dd, *J* = 12.1, 8.6 Hz, 1H), 2.23 (ddd, *J* = 12.5, 8.6, 6.1 Hz, 1H), 2.10 (m, 5H), 1.98 (dd, *J* = 13.5, 6.9 Hz, 2H), 1.24 (*br*s, 12H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); HRMS (ESI) calc. for $C_{30}H_{53}O_7Si$: $(M + H)^+$, 553.3561, found: $(M + H)^+$, 553.3578.

^{n}Bu_4NF in THF (1 M; 2.35 mL, 2.35 mmol) and AcOH (135 μL, 2.35 mmol) in THF (2.5 mL) were slowly added with stirring to a solution of *trans*-lactone **180** (100 mg, 0.18 mmol) in THF (15 mL) at 0°C. The resulting mixture was stirred for 5 h, diluted with Et_2O (25 mL) and subsequently quenched with aq. $NaHCO_3$ (sat., 15 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1) gave *trans*-alcohol **167** (75 mg, 0.17 mmol, 94%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.37 (m, 3H), 4.98 (q, *J* = 7.0 Hz, 1H), 4.05 (d, *J* = 0.9 Hz, 1H, OH), 3.81 (s, 3H), 3.67 (s, 3H), 3.62 (d, *J* = 17.0 Hz, 1H), 2.97 (d, *J* = 17.0 Hz, 1H), 2.86 (dd, *J* = 9.6, 5.7 Hz, 1H), 2.32 (ddd, *J* = 13.2 Hz, 7.4, 5.8, 1H), 2.09 (m, 4H), 1.97 (m, 3H), 1.25 (s, 12H), 0.86 (t, *J* = 6.8 Hz, 3H); HRMS (ESI) calc. for $C_{24}H_{39}O_7$: $(M + H)^+$, 439.2696, found: $(M + H)^+$, 439.2703

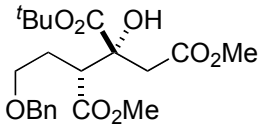
Benzyl-5-benzyloxy-(*R*)-2-hydroxy-(*R*)-3-methoxycarbonyl-(*R*)-2-methoxy-carbonylmethyl-pentanoate (187)



tert-Butyl ester **141** (165 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) was treated at 0 °C with trifluoroacetic acid (1 mL). The mixture was stirred for 4 h at RT and toluene was added

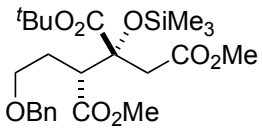
(10 mL) and solvent rotary evaporated to give crude diacid **186** (144 mg, 0.37 mmol, 100%) as a yellow gum, which was dissolved in dry PhMe (15 mL) and cooled to 0 °C. Benzyl alcohol (303 μL, 3 mmol) was added followed by slow addition of LHMDS in THF (1 M; 1.85 mL, 1.87 mmol) and the mixture was stirred at RT. After 12 h, the solution was poured onto aq. $NaHCO_3$ (sat., 20 mL), the aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were discarded. The aqueous layer was slowly acidified with concentrated hydrochloric acid to pH 1 and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and freshly prepared diazomethane (solution in Et_2O) was added until the yellow coloration persisted. Rotary evaporation followed by chromatography (Hexanes:Et_2O, 3:2) gave benzyl ester **187** (111 mg, 0.26 mmol, 70%) as a pale yellow oil: R*f* 0.25 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –0.3 (*c* 1.0, CH_2Cl_2); IR (KBr) 1737, 1436, 1357, 1195, 1172, 1099, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 10H), 5.22 (q, *J* = 12.1 Hz, 2H), 4.42 (dd, *J* = 15.2, 11.9 Hz, 2H), 3.96 (*br*s, 1H), 3.60 (s, 3H), 3.51 (s, 3H), 3.48 – 3.35 (m, 2H), 3.13 (d, *J* = 16.5 Hz, 1H), 2.95 (dd, *J* = 11.5, 2.7 Hz, 1H), 2.73 (d, *J* = 16.5 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.86 – 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.3, 170.9, 138.1, 134.8, 128.6, 128.5, 128.2, 127.6, 127.5, 75.7, 72.8, 68.1, 67.9, 51.9, 51.8, 50.8, 40.6, 27.4; HRMS (ESI) calc. for $C_{24}H_{29}O_8$: $(M + H)^+$, 445.1862, found: $(M + H)^+$, 445.1862.

***tert*-Butyl-5-Benzyloxy-(*R*)-2-hydroxy-(*R*)-3-methoxycarbonyl-(*R*)-2-methoxy-carbonylmethyl-pentanoate (188)**



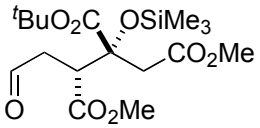
Powdered Pd/C (10%, 300 mg) was added to benzyl ester **187** (390 mg, 0.88 mmol) in dry THF (15 mL) under H_2 pressure. The mixture was magnetically stirred for 1 h, filtered through Celite while being rinsed with Et_2O and rotary evaporated to give crude carboxylic acid (310 mg, 0.87 mmol, 100%) as a colorless oil. This crude acid (310 mg, 0.87 mmol) in CH_2Cl_2 (15 mL) was allowed to react with *N*,*N*'-di-*iso*-propyl-*O*-*tert*-butylisourea **(48)** (2 mL, excess) and the mixture stirred under reflux for 12 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 1:1) gave *tert*-butyl ester **188** (260 mg, 0.63 mmol, 72%) as a colorless oil: R*f* 0.30 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –1.1 (*c* 1.0, CH_2Cl_2); IR (KBr) 1741, 1436, 1369, 1157, 1103, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 4.45 (dd, *J* = 15.6, 12.0 Hz, 2H), 3.87 (*br*s, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.51 – 3.45 (m, 1H), 3.43 – 3.38 (m, 1H), 3.07 (d, *J* = 16.2 Hz, 1H), 2.90 (dd, *J* = 11.6, 2.6 Hz, 1H), 2.71 (d, *J* = 16.2 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.90 – 1.82 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 172.4, 170.7, 138.2, 128.2, 127.6, 127.5, 83.6, 75.2, 72.8, 68.1, 51.8, 51.7, 51.1, 40.7, 27.7, 27.6; HRMS (ESI) calc. for $C_{21}H_{30}NaO_8$: $(M + Na)^+$, 433.1838, found: $(M + Na)^+$, 433.1841.

***tert*-Butyl-5-benzyloxy-(*R*)-3-methoxycarbonyl-(*R*)-2-methoxycarbonylmethyl-(*R*)-2-trimethylsilanyloxy-pentanoate (189)**



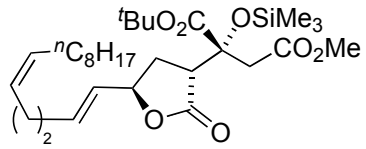
Imidazole (800 mg, 11.7 mmol) and Me_3SiCl (1.5 mL, 11.7 mmol) were sequentially added to alcohol **188** (240 mg, 0.58 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was stirred for 36 h and subsequently quenched with aq. $NaHCO_3$ (sat., 15 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 6:1) gave silyl ether **189** (280 mg, 0.57 mmol, 98%) as a colorless oil: R*f* 0.40 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ –3.9 (*c* 0.7, CH_2Cl_2); IR (KBr) 1745, 1436, 1369, 1247, 1197, 1155, 1118, 844, 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 4.45 (dd, *J* = 11.9, 9.3 Hz, 2H), 3.63 (s, 3H), 3.59 (s, 3H), 3.49 – 3.38 (m, 2H), 3.07 (d, *J* = 15.3 Hz, 1H), 2.89 (dd, *J* = 11.6, 2.3 Hz, 1H), 2.70 (d, *J* = 15.3 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.98 – 1.89 (m, 1H), 1.46 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.1, 170.4, 138.3, 128.2, 127.5, 127.4, 82.3, 78.9, 77.8, 72.8, 68.5, 52.3, 51.5, 51.3, 42.0, 28.0, 27.7, 2.4; HRMS (ESI) calc. for $C_{24}H_{38}O_8NaSi$: $(M + Na)^+$, 505.2234, found: $(M + Na)^+$, 505.2225; Anal. Calc. for $C_{24}H_{38}O_8Si$: C, 59.73; H, 7.94. Found: C, 59.68; H, 7.84.

***tert*-Butyl-(*R*)-3-methoxycarbonyl-(*R*)-2-methoxycarbonylmethyl-5-oxo-(*R*)-2-trimethylsilanyloxy-pentanoate (190)**



Powdered Pd/C (10%, 300 mg) was added to benzyl ether **189** (270 mg, 0.56 mmol) in dry THF (20 mL) under H_2 pressure and the mixture was stirred for 15 h, filtered through Celite while being rinsed with Et_2O, and rotary evaporated to give the crude alcohol (219 mg, 0.56 mmol, 100%) as a colorless oil. This alcohol (219 mg, 0.56 mmol) in CH_2Cl_2 (20 mL) was allowed to react with Dess–Martin periodinane (356 mg, 0.84 mmol) at 0 ºC. After 2 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 15 mL) and aq. Na_2SO_3 (sat., 15 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the crude aldehyde **190** (204 mg, 0.52 mmol, 93%) as a colorless oil: R*f* 0.40 (Et_2O:Hexanes, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 3.30 (dd, *J* = 10.9, 2.9 Hz, 1H), 3.09 (dd, *J* = 18.5, 11.3 Hz, 1H), 3.01 (d, *J* = 15.5 Hz, 1H), 2.79 (d, *J* = 15.5 Hz, 1H), 2.65 (dd, *J* = 18.5, 2.9 Hz, 1H), 1.47 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 171.3, 170.5, 170.0, 82.9, 78.3, 52.0, 51.5, 47.6, 42.5, 42.2, 27.7, 2.3; HRMS (ESI) calc. for $C_{17}H_{30}NaO_8Si$: $(M + Na)^+$, 413.1608, found: $(M + Na)^+$, 413.1590.

1-*tert*-Butyl 4-methyl (*R*)-2-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-(*R*)-2-trimethylsilanyloxy-succinate (191)



Alkyne **149** (160 mg, 0.83 mmol) in CH_2Cl_2 (2 mL) was added dropwise with stirring to Cp_2ZrHCl (180 mg, 0.76 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at RT until a homogenous solution was formed and subsequently cooled to –65 ºC. Me_2Zn in PhMe (1.2 M; 0.55 mL, 0.76 mmol) was added over 5 min after which time the mixture was cooled to 0 ºC and aldehyde **190** (200 mg, 0.51 mmol) in CH_2Cl_2 (2 mL) was added over 10 min. The reaction mixture was stirred at RT for 12 h and poured onto aq. HCl (1 M; 20 mL). Et_2O (30 mL) was added and the layers were separated. The organic layer was washed with brine (30 mL), dried ($MgSO_4$) and *p*-TsOH (200 mg, excess) was added with stirring. After 3 h, rotary evaporation and chromatography (gradient Hexanes:Et_2O, 6:1 to 4:1 to 2:1) gave in order of increasing polarity (1) silyl protected *trans*-lactone **191** (95 mg, 0.17 mmol, 34%) as a pale yellow oil; (2) silyl protected *cis*-lactone **192** (55 mg, 0.10 mmol, 19%) as a colorless oil; (3) *trans*-lactone **168** (33 mg, 0.07 mmol, 14%) as a colorless oil; (4) *cis*-lactone **193** (10 mg, 0.02 mmol, 4%) as a colorless oil.

191: R*f* 0.40 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ +9.8 (*c* 0.8, CH_2Cl_2); IR (KBr) 1770, 1747, 1436, 1369, 1249, 1186, 1153, 1070, 1002, 844, 757, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 15.0, 6.2 Hz, 1H), 5.48 – 5.29 (m, 3H), 4.87 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 3.27 – 3.18 (m, 3H), 2.40 (ddd, *J* = 13.1, 7.6, 5.3 Hz, 1H), 2.11 (*br*m, 4H), 2.04 – 1.98 (m, 3H), 1.47 (s, 9H), 1.27 (*br*s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 170.5, 170.2, 134.7, 130.9, 128.4, 128.2, 82.6, 79.5, 79.3, 51.6,

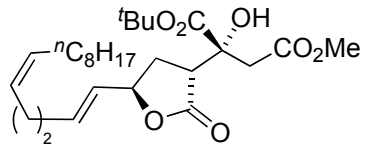
47.4, 41.8, 32.2, 31.9, 31.2, 29.6, 29.5, 29.3, 27.8, 27.3, 26.5, 22.7, 14.1, 2.2; HRMS (ESI) calc. for $C_{30}H_{53}O_7Si$: $(M + H)^+$, 553.3561, found: $(M + H)^+$, 553.3561; Anal. Calc. for $C_{30}H_{52}O_7Si$: C, 65.18; H, 9.48. Found: C, 65.25; H, 9.39.

192: R*f* 0.30 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ +36.7 (*c* 0.8, CH_2Cl_2); IR (KBr) 1774, 1745, 1436, 1369, 1249, 1176, 1157, 1072, 1006, 844, 755, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dt, *J* = 15.0, 6.2 Hz, 1H), 5.50 – 5.30 (m, 3H), 4.68 (dt, *J* = 9.87, 6.99 Hz, 1H), 3.67 (s, 3H), 3.40 (d, *J* = 15.4 Hz, 1H), 3.32 (dd, *J* = 11.4, 8.9 Hz, 1H), 3.29 (d, *J* = 15.4 Hz, 1H), 2.26 (ddd, *J* = 12.8, 8.9, 6.5 Hz, 1H), 2.12 (*br*m, 5H), 2.01 (dd, *J* = 6.9, 6.8 Hz, 2H), 1.47 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 170.6, 170.3, 135.5, 130.8, 128.2, 127.9, 82.5, 78.2, 77.7, 51.5, 47.6, 41.2, 32.2, 31.8, 30.9, 29.6, 29.5, 29.3, 27.8, 27.2, 26.4, 22.6, 14.0, 2.1; HRMS (ESI) calc. for $C_{30}H_{53}O_7Si$: $(M + H)^+$, 553.3561, found: $(M + H)^+$, 553.3568; Anal. Calc. for $C_{30}H_{52}O_7Si$: C, 65.18; H, 9.48. Found: C, 65.18; H, 9.55.

168: R*f* 0.32 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ –18.5 (*c* 0.6, CH_2Cl_2); IR (KBr) 3482, 1768, 1743, 1438, 1269, 1282, 1253, 1189, 1155, 1122, 993, 971, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 14.6, 6.1 Hz, 1H), 5.45 – 5.28 (m, 3H), 4.98 (q, *J* = 7.1 Hz, 1H), 3.99 (*br*s, 1H), 3.68 (s, 3H), 3.57 (d, *J* = 16.6 Hz, 1H), 2.93 (d, *J* = 16.6 Hz, 1H), 2.86 (dd, *J* = 9.8, 5.4, 1H), 2.33 (ddd, *J* = 13.0, 7.4, 5.4 Hz, 1H), 2.11 (*br*m, 4H), 2.02 – 1.93 (m, 3H), 1.49 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 172.0, 171.1, 135.0, 130.9, 128.1, 127.9, 83.7, 79.6, 75.5, 51.8, 46.2, 40.5, 32.1, 31.8, 30.5, 29.6, 29.4, 29.2, 27.7, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calc. for $C_{27}H_{44}O_7Na$: $(M + Na)^+$, 503.2985, found: $(M + Na)^+$, 503.2991; Anal. Calc. for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.47; H, 9.19.

193: R*f* 0.30 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +11.6 (*c* 0.5, CH_2Cl_2); IR (KBr) 3480, 1773, 1743, 1438, 1369, 1284, 1252, 1156, 995, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dt, *J* = 15.2, 6.5 Hz, 1H), 5.55 – 5.30 (m, 3H), 4.71 (dt, *J* = 9.7, 7.0 Hz, 1H), 3.97 (*br*s, 1H), 3.77 (d, *J* = 16.5 Hz, 1H), 3.68 (s, 3H), 2.95 (dd, *J* = 11.5, 8.7 Hz, 1H), 2.89 (d, *J* = 16.5 Hz, 1H), 2.18 (ddd, *J* = 12.7, 8.8, 6.2 Hz, 1H), 2.12 – 2.06 (m, 5H), 1.99 (q, *J* = 6.9 Hz, 2H), 1.50 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.9, 171.0, 136.1, 130.9, 128.1, 127.4, 83.7, 78.7, 74.0, 51.7, 46.9, 40.1, 32.1, 31.8, 30.3, 29.6, 29.4, 29.2, 27.7, 27.2, 26.3, 22.6, 14.1; HRMS (ESI) calc. for $C_{27}H_{44}O_7Na$: $(M + Na)^+$, 503.2985, found: $(M + Na)^+$, 503.2981; Anal. Calc. for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.51; H, 9.27.

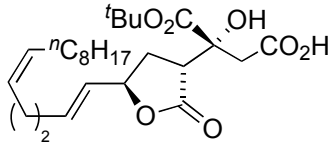
1-*tert*-Butyl 4-methyl (*R*)-2-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-(*R*)-2-hydroxy-succinate (168)



$^nBu_4NF$ in THF (1 M; 2.5 mL, 2.5 mmol) and AcOH (115 μL, 2.5 mmol) in THF (2.5 mL) was slowly added with stirring to lactone **191** (140 mg, 0.25 mmol) in THF (15 mL) at 0°C. The resulting mixture was stirred for 5 h, diluted with Et_2O (25 mL) and subsequently quenched with aq. $NaHCO_3$ (sat., 15 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1) gave alcohol **168** (119 mg, 0.248 mmol, 98%) as a colorless oil: R*f* 0.32 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ –18.5 (*c* 0.6, CH_2Cl_2); IR (KBr) 3482, 1768, 1743, 1438, 1269, 1282, 1253, 1189, 1155, 1122, 993, 971, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 14.6, 6.1 Hz,

1H), 5.45 – 5.28 (m, 3H), 4.98 (q, *J* = 7.1 Hz, 1H), 3.99 (*br*s, 1H), 3.68 (s, 3H), 3.57 (d, *J* = 16.6 Hz, 1H), 2.93 (d, *J* = 16.6 Hz, 1H), 2.86 (dd, *J* = 9.8, 5.4, 1H), 2.33 (ddd, *J* = 13.0, 7.4, 5.4 Hz, 1H), 2.11 (*br*m, 4H), 2.02 – 1.93 (m, 3H), 1.49 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 172.0, 171.1, 135.0, 130.9, 128.1, 127.9, 83.7, 79.6, 75.5, 51.8, 46.2, 40.5, 32.1, 31.8, 30.5, 29.6, 29.4, 29.2, 27.7, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calc. for $C_{27}H_{44}NaO_7$: $(M + Na)^+$, 503.2985, found: $(M + Na)^+$, 503.2991.

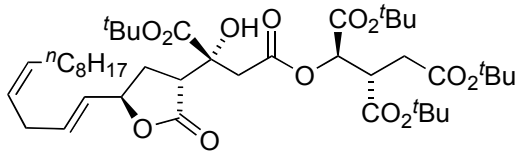
***tert*-Butyl (*R*)-2-hydroxy-(*R*)-2-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-succinate (36)**



Solid Me_3SnOH (213 mg, 1.17 mmol) was added to methyl ester **168** (113 mg, 0.23 mmol) in $ClCH_2CH_2Cl$ (5 mL) and heated at 85 °C in a sealed tube for 12 h. After rotary evaporation, the crude product was dissolved in EtOAc (20 mL) and washed with aq. HCl (1 M; 2 × 20 mL) and brine (20 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (CH_2Cl_2:MeOH, 15:1) gave carboxylic acid **36** (103 mg, 0.22 mmol, 94%) as a pale yellow gum: R*f* 0.30 (CH_2Cl_2:MeOH, 15:1); $[\alpha]_D^{25}$ –9.9 (*c* 1.0, CH_2Cl_2); IR (KBr) 3452, 1728, 1435, 1399, 1370, 1275, 1251, 1191, 1155, 1119, 999, 969, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 15.2, 6.1 Hz, 1H), 5.47 – 5.30 (m, 3H), 4.99 (dd, *J* = 14.0, 7.00 Hz, 1H), 3.97 (*br*s, 1H), 3.58 (d, *J* = 16.8 Hz, 1H), 2.99 (d, *J* = 16.8 Hz, 1H), 2.88 (dd, *J* = 9.8, 5.6 Hz, 1H), 2.33 (ddd, *J* = 13.1, 7.4, 5.6 Hz, 1H), 2.11 (*br*m, 4H), 2.02 – 1.94 (m, 3H), 1.48 (s, 9H), 1.26 (*br*s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 175.1, 174.5, 171.7, 135.2, 130.9, 128.1, 127.8, 84.1, 79.8, 75.3, 46.2, 40.4, 32.1, 31.8, 30.4, 29.6, 29.4, 29.3, 27.7, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calc. for $C_{26}H_{42}O_7Na$: $(M + Na)^+$, 489.2828, found: $(M + Na)^+$, 489.2837; Anal. Calc. for $C_{26}H_{42}O_7$: C, 66.93; H, 9.07. Found: C, 66.86; H, 8.98.

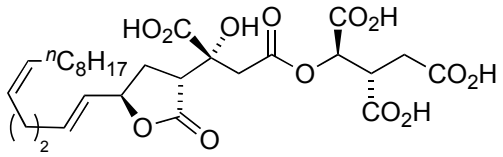
Di-*tert*-butyl-(*S*)-3-*tert*-Butoxycarbonyl-(*R*)-2-[(*R*)-3-t*ert*-butoxycarbonyl-(*R*)-3-hydroxy-(*R*)-3-((*R*)-2-oxo-5-tetradeca-1,5-dienyl-tetrahydro-furan-(*R*)-3-yl)-propanoyloxy]-pentanedioate (53)



DMAP·HCl (66 mg, 0.42 mmol)) and DCC (57 mg, 0.28 mmol) were sequentially added to carboxylic acid **36** (20 mg, 0.043 mmol) and alcohol **35** (31 mg, 0.086 mmol) in CH_2Cl_2 (5 mL) and this mixture stirred for 4 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 4:1) gave tetra-*tert*-butyl ester **53** (17.2 mg, 0.021 mmol, 50%) as a colorless oil: R*f* 0.20 (Et_2O:Hexanes, 1:4); $[\alpha]_D^{25}$ +2.1 (*c* 1, $CHCl_3$); IR (KBr) 3487, 1730, 1369, 1225, 1153, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.75 (m, 1H), 5.47 – 5.30 (m, 3H), 5.18 (d, *J* = 3.2 Hz, 1H), 4.99 (q, *J* = 7.1 Hz, 1H), 4.05 (d, *J* = 0.9 Hz, 1H), 3.72 (d, *J* = 17.4 Hz, 1H), 3.31 (ddd, *J* = 10.1, 4.7, 3.4 Hz, 1H), 3.05 (d, *J* = 17.4 Hz, 1H), 2.83 (dd, *J* = 9.8, 5.3 Hz, 1H), 2.62 (dd, *J* = 16.9, 10.0 Hz, 1H), 2.42 (dd, *J* = 16.8, 4.7 Hz, 1H), 2.34 (ddd, *J* = 12.9, 7.4, 5.3 Hz, 1H), 2.12 – 2.09 (*br*m, 4H), 2.03 – 1.91 (m, 3H), 1.48 – 1.44 (m, 36H), 1.27 (*br*s, 12H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 171.9, 170.4, 169.6, 168.9, 166.4, 135.0, 130.9, 128.2, 128.0, 83.8, 83.0, 81.9, 80.9, 79.7, 77.2, 75.2, 72.2, 46.4, 43.5, 40.4, 33.0, 32.1, 31.8, 30.5, 29.6, 29.4, 29.3, 28.0,

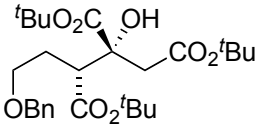
27.6, 27.2, 26.4, 22.6, 14.1; HRMS (ESI) calc. for $C_{44}H_{72}O_{13}Na$: $(M + Na)^+$, 831.4871, found: $(M + Na)^+$, 831.4853.

Citrafungin A (23)



Pentaester **53** (15 mg, 6.3 μmol) in CH_2Cl_2 (5 mL) was treated at 20 °C with trifluoroacetic acid (2 mL). After 4 h, PhMe (10 mL) was added and solvent rotary evaporated to give crude citrafungin A (**23**) (11 mg, 6.3 μmol, 100%). Purification using reverse phase HPLC (column: Xbridge Prep C18 OBD 30cm x 10cm 5μm (P/N186002982) and gradient elution H_2O:MeCN with 0.1% TFA 85:15 to 5.3:94.7 over 12 min) gave citrafungin A (**23**): $[\alpha]_D^{25}$ +3.2 (*c* 0.25, MeOH); IR (KBr) 3453, 1731, 1405, 1250, 1187, 967 cm^{-1}; ^1H NMR (600 MHz, d^6-acetone) δ 5.82 (dt, *J* = 14.9, 6.3 Hz, 1H), 5.58 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.49 (d, *J* = 3.4 Hz, 1H), 4.99 (q, *J* = 7.1 Hz, 1H), 5.41 – 5.33 (m, 2H), 3.70 (d, *J* = 16.3 Hz, 1H), 3.56 (ddd, *J* = 8.8, 4.8, 3.7 Hz, 1H), 3.16 (d, *J* = 16.3 Hz, 1H), 3.05 (dd, *J* = 9.7, 5.8 Hz, 1H), 2.81 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.61 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.39 (ddd, *J* = 13.2, 7.4, 6.0 Hz, 1H), 2.16 – 2.03 (m, 7H), 1.29 (*br*m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, d^6-acetone) δ 175.0, 173.8, 172.3, 171.1, 169.2, 169.0, 134.4, 130.6, 129.2, 128.8, 79.5, 75.6, 71.9, 46.2, 42.7, 40.8, 32.3, 32.0, 31.8, 30.9, 30.3, 27.2, 26.7, 22.7, 13.8; HRMS (ESI) calc. for $C_{28}H_{40}NaO_{13}$: $(M + Na)^+$, 607.2367, found: $(M + Na)^+$, 607.2363, calc. for $C_{28}H_{41}O_{13}$: $(M + H)^+$, 585.2547, found: $(M + H)^+$, 585.2550.

(2*R*,3*R*)-tri-*tert*-Butyl 5-(benzyloxy)-2-hydroxypentane-1,2,3-tricarboxylate (229)

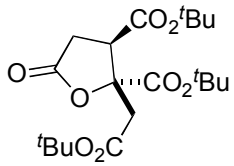


$LiOH{\cdot}H_2O$ (375 mg, 9 mmol) was added to trimethyl ester **176** (330 mg, 0.9 mmol) in THF:H_2O (3:1, 16 mL) and the resulting solution stirred at RT over the week end. The reaction was quenched by the addition of aq. HCl (1 M; 20 mL) and the product extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to give crude carboxylic acid **230** (290 mg, 100%) as a colorless gum: ^{1}H NMR (400 MHz, Acetone d_6) δ 7.37 – 7.24 (m, 5H), 4.52 – 4.44 (m, 2H), 3.65 – 3.45 (m, 2H), 3.16 (d, J = 16.6 Hz, 1H), 2.96 (dd, J = 11.5, 2.8 Hz, 1H), 2.81 (d, J = 16.6 Hz, 1H), 2.16 – 2.04 (m, 1H), 1.98 – 1.88 (m, 1H). ^{13}C NMR (100 MHz, Acetone d_6) δ 175.9, 174.4, 173.2, 140.8, 130.0, 129.4, 129.2, 129.1, 77.2, 74.2, 68.9, 52.0, 42.3; HRMS (ESI) calc. for $C_{15}H_{17}O_8$: $(M - H)^+$, 325.0923, found: $(M - H)^+$, 325.0936;

N, *N*'-di-*iso*-propyl-*O*-*tert*-butylisourea (**48**) (2 mL, excess) was added to carboxylic acid **230** (290 mg, 0.9 mmol) in CH_2Cl_2:THF (1:1, 20 mL) and the resulting suspension heated at refluxed for 12 h. The solvent was rotary evaporated to leave a white solid. Et_2O (20 mL) was added and the solid was filtered and discarded. The solvent was rotary evaporated and the crude product purified by chromatography (Hexanes:Et_2O, 4:1) to afford tri-*tert*-butyl ester **229** (300 mg, 0.6 mmol, 70%) as a colorless oil: $[\alpha]_D^{25}$ –10.6 (*c* 1, CH_2Cl_2); IR (KBr) 1786, 1725, 1347, 1250, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 5H), 4.50 – 4.43 (m, 2H), 3.52 – 3.45 (m, 1H), 3.39 – 3.33 (m, 1H), 2.95 (d, J = 16.4 Hz, 1H), 2.77 (dd, J = 11.7, 2.6 Hz, 1H), 2.63 (d, J = 16.4 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.79 – 1.71 (m, 1H), 1.48 (s, 9H), 1.44 (s, 9H), 1.42(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 171.2,

168.8, 138.4, 128.3, 127.5, 127.45, 82.9, 81.3, 75.5, 72.8, 68.0, 51.1, 42.7, 28.1, 28.0, 27.9; HRMS (ESI) calc. for $C_{27}H_{42}O_8Na$: $(M + Na)^+$, 517.2777, found: $(M + Na)^+$, 517.2762;

(2*R*,3*R*)-di-*tert*-Butyl-2-(2-*tert*-butoxy-2-oxoethyl)-5-oxotetrahydrofuran-2,3-dicarboxylate (56)

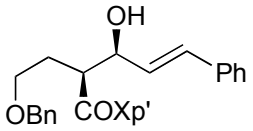


Powdered Pd/C (100 mg, excess) was added to tri-*tert*-butyl ester **229** (65 mg, 0.13 mmol) in dry THF (20 mL) under N_2. Vacuum was applied and N_2 was replaced by H_2. The mixture was magnetically stirred until TLC indicated complete conversion, filtered through Celite while being rinsed with Et_2O and concentred in vacuo to give the corresponding alcohol (53 mg, 0.13 mmol, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 – 3.66 (m, 1H), 3.63 – 3.57 (m, 1H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.75 (dd, *J* = 11.0, 3.3 Hz, 1H), 2.65 (d, *J* = 16.4 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.77 – 1.69 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 171.5, 170.0, 83.0, 81.7, 81.4, 75.5, 61.0, 51.0, 42.3, 30.6, 28.08, 28.0, 27.9; HRMS (ESI) calc. for $C_{20}H_{36}O_8Na$: $(M + Na)^+$, 427.2308, found: $(M + Na)^+$, 427.2309;

NMO (40 mg, 0.39 mmol) followed by TPAP (3.5 mg, 0.011 mmol) were added with stirring to a solution of the alcohol (40 mg, 0.099 mmol) at 0 ºC in CH_2Cl_2 (20 mL). After 2 h, the reaction was stopped, the solvent rotary evaporated and the crude purified by chromatography (Hexanes:Et_2O, 4:1) to give lactone **56** (35 mg, 0.088 mmol, 88%) as a colorless oil: $[\alpha]_D^{25}$ –15.1 (*c* 1, CH_2Cl_2); IR (KBr) 1803, 1735, 1369, 1251, 1147, 1066, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (dd, *J* = 8.6, 3.8 Hz, 1H), 3.09 (d, *J* = 17.3 Hz,

1H), 2.88 (d, *J* = 17.3 Hz, 1H), 2.84 (dd, *J* = 17.8, 8.3 Hz, 1H), 2.76 (dd, *J* = 17.5, 3.8 Hz, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.0, 168.2, 167.6, 83.7, 83.6, 83.1, 81.9, 47.6, 39.0, 32.0, 27.9, 27.9, 27.7; HRMS (ESI) calculated for $C_{20}H_{32}O_8Na$: $(M + Na)^+$, 423.1995, found: $(M + Na)^+$, 423.2004;

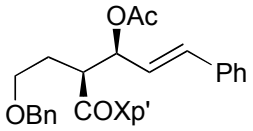
(*R*)-4-Benzyl-3-((3*R*,4*R*,*E*)-3-(2-(benzyloxy)ethyl)-4-hydroxy-6-phenylhex-5-enoyl)oxazolidin-2-one (239)



To a solution of oxazolidinone **134** (200 mg, 0.57 mmol) in freshly distilled EtOAc (1.5 mL) were sequentially added cinnamaldehyde (0.08 mL, 0.62 mmol), dry Et_3N (0.16 mL, 1.13 mmol), freshly distilled Me_3SiCl (0.11 mL, 0.85 mmol) and $MgBr_2{\cdot}OEt_2$ (15 mg, 0.06 mmol). The cloudy, yellow reaction mixture was stirred until complete conversion was indicated by TLC (24 h), filtered and the solids extracted with Et_2O (10 mL). The combined filtrate and washings were concentrated *in vacuo*. MeOH (10 mL) and CF_3CO_2H (3 drops) were added and after 30 min, the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL) and the layers were separated. The organic layer was extracted sequentially with aq. $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Et_2O:Hexanes, 1:2) gave alcohol **239** (231 mg, 84%) as a brown gum: R*f* 0.25 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ –2.5 (*c* 0.4, CH_2Cl_2); IR (KBr) 3447, 1776, 1691, 1386, 1208, 1120, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.00 (m, 13H), 7.00 (m, 2H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 15.9, 5.9, 1H), 4.47 (t, *J* = 5.9 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.38 – 4.34 (m, 1H), 4.32 (d, *J* = 11.4 Hz, 1H), 4.24 (ddd, *J*

= 8.0, 6.4, 3.1 Hz, 1H), 3.73 (dd, *J* = 8.9, 2.8 Hz, 1H), 3.60 (dd, *J* = 7.1, 4.1 Hz, 2H), 3.26 (t, *J* = 8.4 Hz, 1H), 3.11 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.41 – 2.31 (m, 2H), 1.86 (dq, *J* = 14.2, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 153.8, 138.3, 136.2, 135.4, 131.6, 129.8, 129.2, 128.7, 128.6, 128.2, 127.8, 127.5, 127.3, 127.0, 126.5, 74.9, 72.8, 69.1, 65.5, 55.1, 46.1, 37.8, 30.5; HRMS (ESI) calc. for $C_{30}H_{31}NNaO_5$: $(M + Na)^+$, 508.2100, found: $(M + Na)^+$, 508.2107. Anal. calc. for $C_{30}H_{31}NO_5$: C, 74.21; H, 6.43; N, 2.88. Found: C, 74.26; H, 6.49; N, 2.93.

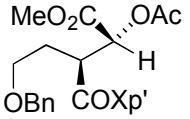
(3*R*,4*R*,*E*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-4-(2-(benzyloxy)ethyl)-6-oxo-1-phenylhex-1-en-3-yl acetate (240)



Et_3N (0.07 mL, 0.49 mmol), DMAP (10 mg, 0.08 mmol) and Ac_2O (0.05 mL, 0.49 mmol) were added with stirring to alcohol **239** (200 mg, 0.41 mmol) in CH_2Cl_2 (7 mL) at 0 °C. After 5 h at RT, the solution was poured onto aq. HCl (1 M; 15 mL) and the organic layer washed with brine (30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:CH_2Cl_2, 1:4) gave acetate **240** (209 mg, 96%) as a white solid: R*f* 0.47 (CH_2Cl_2:Hexanes, 4:1); $[\alpha]_D^{25}$ –1.1 (*c* 0.24, CH_2Cl_2); mp 127–130 ºC (Hexanes/CH_2Cl_2); IR (KBr) 3447, 1777, 1740, 1696, 1389, 1232, 1210 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, 15H), 6.77 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.66 (t, *J* = 8.9 Hz, 1H), 4.56 (dt, *J* = 10.1, 3.0 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.31 – 4.25 (m, 1H), 3.77 (dd, *J* = 8.9, 3.0, Hz, 1H), 3.66 – 3.58 (m, 2H), 3.24 – 3.17 (m, 2H), 2.49 (dd, *J* = 13.2, 10.1 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.00 (s, 3H), 1.85 (dq,

J = 14.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.5, 153.6, 138.3, 135.9, 135.8, 135.4, 129.3, 128.8, 128.6, 128.3, 128.2, 127.6, 127.5, 127.2, 126.8, 124.9, 72.8, 68.9, 65.3, 55.0, 44.7, 38.0, 29.8, 21.1; HRMS (ESI) calc. for $C_{32}H_{33}NNaO_6$: $(M + Na)^+$, 550.2206, found: $(M + Na)^+$, 550.2220. Anal. calc. for $C_{32}H_{33}NO_6$: C, 72.85; H, 6.30; N, 2.65. Found: C, 72.79; H, 6.37; N, 2.62.

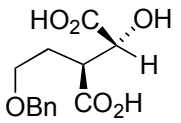
(2*R*,3*S*)-Methyl 2-acetoxy-3-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-(benzyloxy)pentanoate (241)



Acetate **240** (5.62 g, 10.66 mmol) in CH_2Cl_2 (200 mL) was cooled to –78 ºC and a stream of ozone was bubbled through the mixture until a deep blue colour persisted. Oxygen was subsequently bubbled through the solution for an additional 20 min to remove excess of ozone when Me_2S (15.7 mL, 213.3 mmol) was added at –78 ºC and the solution was allowed to warm to RT. Rotary evaporation gave the crude aldehyde, which was directly oxidized. Solid NaH_2PO_4 (12.8 g, 53.32 mmol) and $NaClO_2$ (7.72 g, 42.7 mmol) were added sequentially with stirring to aldehyde and 2-methyl-2-butene (50 mL, 213.3 mmol) in ^{t}BuOH, H_2O, THF (1:1:1; 240 mL) at 0 °C. The mixture was allowed to warm to RT overnight and quenched by the addition of aq. Na_2SO_3 (sat., 300 mL) and aq. NH_4Cl (sat., 200 mL). The mixture was acidified to pH 1 using conc. aq. HCl, saturated with NaCl and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with brine (500 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (gradient Hexanes:EtOAc, 1:1; EtOAc:MeOH, 4:1 to 7:3) gave the

corresponding carboxylic acid which was directly esterified using freshly prepared diazomethane in Et_2O (excess). Evaporation followed by chromatography (Et_2O:Hexanes, 1:3) gave methyl ester **241** (3.40 g, 66%) as a colorless oil: R*f* 0.15 (Et_2O:Hexanes, 1:3); $[\alpha]_D^{25}$ –4.4 (*c* 0.08, CH_2Cl_2); IR (KBr) 1777, 1749, 1700, 1389, 1210, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 10H), 5.24 (d, *J* = 7.6 Hz, 1H), 4.59 – 4.54 (m, 1H), 4.40 (q, *J* = 11.4 Hz, 2H), 4.35 – 4.29 (m, 1H), 3.88 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.76 (s, 3H), 3.66 – 3.57 (m, 2H), 3.45 (t, *J* = 8.5 Hz, 1H), 3.23 (dd, *J* = 13.4, 3.1, Hz, 1H), 2.60 (dd, *J* = 13.3, 10.0 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.11 (s, 3H), 2.02 – 1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.9, 169.1, 153.2, 138.2, 135.2, 129.2, 128.9, 128.2, 127.6, 127.2, 73.3, 72.8, 68.2, 65.6, 55.1, 52.4, 42.2, 37.7, 28.1, 20.4; HRMS (ESI) calc. for $C_{26}H_{30}NO_8$: $(M + H)^+$, 484.1971, found: $(M + H)^+$, 484.1982.

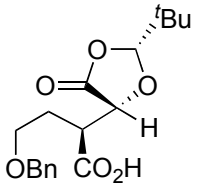
(2*S*,3*R*)-2-(2-(Benzyloxy)ethyl)-3-hydroxysuccinic acid (242)



H_2O_2 in H_2O (50%, 0.12 mL, 1.95 mmol) and $LiOH{\cdot}H_2O$ (49 mg, 1.17 mol) were added with stirring at 0 °C to methyl ester **241** (94 mg, 0.19 mmol) in THF and H_2O (1:1, 20 mL). After 24 h, the THF was removed by rotary evaporation and aq. Na_2SO_3 (sat., 20 mL) added at 0 °C and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The aqueous residue was carefully acidified to pH 1 with conc. aq. HCl and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried ($MgSO_4$) and rotary evaporated to give diacid **242** (51 mg, 98%) as a colorless oil: $[\alpha]_D^{25}$ –1.0 (*c* 0.26, CH_2Cl_2); IR (KBr) 3456, 1454, 1122, 1094, 1028 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.30 – 7.20

(m, 5H), 4.45 (s, 2H), 4.23 (d, J = 4.6 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.01 (td, J = 8.4, 5.21 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.89 – 1.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 177.0, 137.3, 128.6, 128.0, 127.9, 73.4, 70.2, 67.6, 45.6, 27.8; HRMS (ESI) calc. for $C_{13}H_{15}O_6$: $(M - H)^+$, 267.0869, found: $(M - H)^+$, 267.0868.

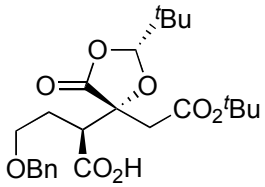
(*S*)-4-(Benzyloxy)-2-((2*R*,4*R*)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)butanoic acid (238)



TMSCl (0.16 mL, 1.23 mmol) and DIPEA (0.21 mL, 1.23 mmol) were added to diacid **242** (100 mg, 0.37 mmol) in THF (10 mL) and the resultant mixture stirred for 2 h at RT when hexane (10 mL) was added and the mixture cooled to –78 ºC. This suspension was filtered, the solid extracted with cold hexane (5 mL) and the combined filtrate and extract evaporated to give the *per*-TMS derivative as a pale yellow oil. This compound was dissolved in dry CH_2Cl_2 (10 mL), cooled at –35 ºC and ^{t}BuCHO (0.06 mL, 0.56 mmol) was added followed by Me_3SiOTf (0.01 mL, 0.08 mmol) and the reaction stirred for 16 h. From this point onwards manipulation were performed without an inert atmosphere. The reaction mixture was poured into aq. HCl (1 M; 10 mL) and stirred for a further 10 min at RT. The mixture was extracted with Et_2O:Hexanes (1:1, 30 mL). The organic extract was washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (CH_2Cl_2:MeOH, 50:1) gave dioxolanone **238** (87 mg, 69%) as a yellow oil: R*f* 0.28 (CH_2Cl_2:MeOH, 50:1); $[\alpha]_D^{25}$ +2.3 (*c* 0.04, CH_2Cl_2); IR (KBr) 1799, 1714, 1196, 1090 cm$^-$

[1]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 5.09 (s, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 4.4 Hz, 1H), 3.61 (t, *J* = 5.9 Hz, 2H), 3.23 (td, *J* = 8.0, 5.4 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.13 – 2.05 (m, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 171.7, 137.8, 128.4, 127.7, 127.6, 109.5, 75.0, 73.0, 67.3, 43.0, 34.2, 27.5, 23.5; HRMS (ESI) calc. for $C_{18}H_{23}O_6$: $(M - H)^+$, 335.1495, found: $(M - H)^+$, 335.1495. Anal. calc. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.28.

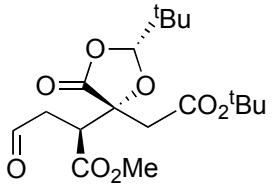
4-Benzyloxy-(*S*)-2-(4-*tert*-butoxycarbonylmethyl-2-(*R*)-*tert*-butyl-(*R*)-5-oxo-[1,3]dioxolan-4-yl)-butyric acid (243)



LHMDS in THF (1 M; 4.29 mL, 4.29 mmol) was added dropwise to acid **238** (720 mg, 2.14 mmol) in dry DMF (5 mL) at –70 °C. After 50 min, *tert*-butyl bromoacetate (0.32 mL, 2.14 mmol) was added and the reaction temperature was maintained at –70 °C. After 15 min, the solution was poured onto aq. HCl (1 M; 20 mL) and Et_2O (40 mL) was added. The organic phase was washed with brine (3 × 30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Et_2O:Hexanes, 1:3 to 2:3) gave dioxolanone **243** (665 mg, 69%) as a yellow oil: R*f* 0.24 (Et_2O:Hexanes, 3:1); $[\alpha]_D^{25}$ +1.2 (*c* 0.06, CH_2Cl_2); IR (KBr) 3447, 1793, 1731, 1364, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 5H), 5.30 (s, 1H), 4.46 (s, 2H), 3.53 – 3.44 (m, 2H), 3.32 (d, *J* = 17.2 Hz, 1H), 2.95 (dd, *J* = 11.5, 2.2 Hz, 1H), 2.90 (d, *J* = 17.2 Hz, 1H), 2.41 – 2.34 (m, 1H), 1.97 – 1.87 (m, 1H), 1.45 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 172.9, 169.2, 137.9, 128.3, 127.5, 110.6, 82.2,

78.5, 72.7, 67.6, 50.5, 37.6, 34.6, 27.9, 27.2, 23.4; HRMS (ESI) calc. for $C_{24}H_{35}O_8$: $(M + H)^+$, 451.2332, found: $(M + H)^+$, 451.2348.

(*S*)-Methyl-2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)-4-oxobutanoate (237)

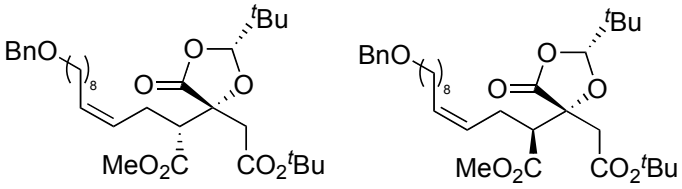


Diazomethane in Et_2O (excess) was added to a solution of carboxylic acid **243** (450 mg, 1 mmol) in Et_2O (50 mL) at 0 ºC till the yellow colour persisted. The reaction mixture was flushed with a stream of Nitrogen to remove the excess of diazomethane and the solvent evaporated to afford cleanly the corresponding methyl ester (464 mg, 1 mmol) as a colorless oil. Pd/C (10%, 400 mg) was added to the methyl ester (464 mg, 1 mmol) in dry THF (15 mL) under H_2 pressure and the mixture was stirred for 15 h, filtered through Celite and the solid washed with Et_2O, and rotary evaporated to leave the corresponding alcohol. The alcohol (370 mg, 0.99 mmol) in CH_2Cl_2 (30 mL) was allowed to react with Dess–Martin periodinane (503 mg, 1.19 mmol) at 0 ºC. After 2 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 30 mL) and aq. Na_2SO_3 (sat., 30 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to crude aldehyde **237** (339 mg, 0.41 mmol, 91%) as a white solid which was used directly in the next step: mp 137–140 ºC (Hexanes/CH_2Cl_2); R*f* 0.36 (Et_2O:Hexanes, 1:2); IR (KBr) 1793, 1727, 1365, 1236,1195, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 5.28 (s, 1H), 3.76 (s, 3H), 3.33 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.26 (dd, *J* = 18.5, 2.7 Hz, 1H), 3.07 (d, *J*

= 16.8 Hz, 1H), 2.91 (dd, *J* = 18.5, 11.2 Hz, 1H), 2.83 (d, *J* = 16.8 Hz, 1H), 1.45 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 172.7, 171.0, 168.6, 110.7, 82.4, 78.3, 52.4, 45.5, 41.4, 38.0, 34.6, 27.9, 23.4; HRMS (ESI) calc. for $C_{18}H_{28}NaO_8$: $(M + Na)^+$, 395,1682, found: $(M + Na)^+$, 395.1694.

(*R*,*Z*)-Methyl-13-(benzyloxy)-2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)tridec-4-enoate (235)

(*S*,*Z*)-Methyl-13-(benzyloxy)-2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)tridec-4-enoate (236)



*n*BuLi (1.6 M; 1 mL) was added to a solution of $Ph_3P(CH_2)_9OBn{\cdot}Br$ (1 g, 1.7 mmol) in dry THF (50 mL) at –78 ºC giving an orange solution of the ylide **244**. The mixture was allowed to warm up to 0 ºC recooled to –78 ºC, when a solution of aldehyde **112** or **237** (420 mg, 1.1 mmol) in THF (5 mL) was slowly added and the mixture stirred for 30 min at –78 ºC and 30 min at 0 ºC then quenched with aq. NH_4Cl (sat., 100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 5:1) gave the corresponding alkene **235** or **236**:

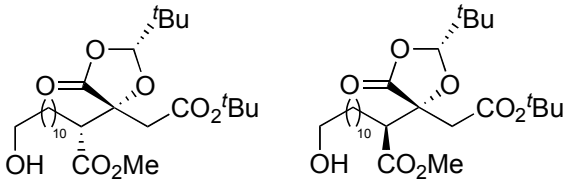
235 (465 mg, 0.79 mmol, 72%) as a colorless oil; R*f* 0.25 (Et_2O:Hexanes, 1:5); $[\alpha]_D^{25}$ +4.8 (*c* 1.0, CH_2Cl_2); IR (KBr) 1800, 1736, 1454, 1366, 1237, 1193, 1156, 1127, 1100, 968, 734, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 5H), 5.46 (m,

1H), 5.30 (s, 1H), 5.21 (m, 1H), 4.50 (s, 2H), 3.67 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.26 (d, *J* = 16.9 Hz, 1H), 2.84 (d, *J* = 16.9 Hz, 1H), 2.77 (dd, *J* = 11.7, 3.3 Hz, 1H), 2.59 (m, 1H), 2.41 – 2.37 (m, 1H), 1.61 (m, 2H), 1.45 (s, 9H), 1.37 – 1.25 (m, 12H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.6, 168.9, 138.6, 133.3, 128.3, 127.6, 127.4, 124.3, 110.0, 82.1, 79.4, 72.8, 70.4, 52.8, 51.9, 38.4, 34.4, 29.7, 29.5, 29.4, 29.4, 29.2, 27.9, 27.1, 26.1, 25.3, 23.6; HRMS (ESI) calc. for $C_{34}H_{52}NaO_8$: $(M + Na)^+$, 611.3560, found: $(M + Na)^+$, 611.3548. Anal. calc. for $C_{34}H_{52}O_8$: C, 69.36; H, 8.90. Found: C, 69.43; H, 8.83.

236 (450 mg, 0.77 mmol, 70%) as a colorless oil: R*f* 0.20 (Et_2O:Hexanes, 20:1); $[\alpha]_D^{25}$ +4.7 (*c* 0.06, CH_2Cl_2); IR (KBr) 1794, 1736, 1365, 1194, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 5H), 5.47 – 5.40 (m, 1H), 5.28 (s, 1H), 5.20 – 5.13 (m, 1H), 4.50 (s, 2H), 3.70 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.39 (d, *J* = 17.2 Hz, 1H), 2.96 (d, *J* = 17.3 Hz, 1H), 2.75 – 2.69 (m, 2H), 2.39 – 2.30 (m, 1H), 2.02 – 1.94 (m, 2H), 1.65 – 1.55 (m, 4H), 1.45 (s, 9H), 1.37 – 1.27 (m, 8H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.9, 169.5, 138.7, 133.4, 128.3, 127.6, 127.4, 124.2, 110.6, 82.1, 78.7, 72.9, 70.5, 53.4, 51.8, 37.5, 34.7, 29.8, 29.5, 29.4, 29.2, 28.0, 27.2, 26.2, 25.5, 23.5; HRMS (ESI) calc. for $C_{34}H_{52}NaO_8$: $(M + Na)^+$, 611.3560, found: $(M + Na)^+$, 611.3568. Anal. calc. for $C_{34}H_{52}O_8$: C, 69.26; H, 8.90. Found: C, 69.40; H, 9.02.

(*R*)-Methyl-2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)-13-hydroxytridecanoate (245)

(*S*)-Methyl-2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)-13-hydroxytridecanoate (246)



Pd/C (10%, 150 mg) was added to benzyl ether **235** or **236** (130 mg, 0.21 mmol) in dry THF (20 mL) under H_2 and the mixture was stirred for 15 h, filtered through Celite while being rinsed with Et_2O, and rotary evaporated to leave the corresponding primary alcohol:

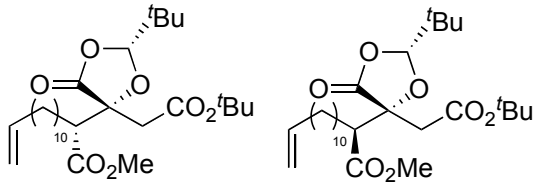
245 (95 mg, 0.19 mmol, 92%) as a colorless oil: R*f* 0.42 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +11.2 (*c* 1.0, CH_2Cl_2); IR (KBr) 3438, 1800, 1735, 1462, 1367, 1194, 1157, 1083, 969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 3.70 (s, 3H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.23 (d, *J* = 16.8 Hz, 1H), 2.80 (d, *J* = 16.8 Hz, 1H), 2.75 (dd, *J* = 11.8, 3.2 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.68 – 1.60 (m, 1H), 1.59 – 1.53 (m, 2H), 1.44 (s, 9H), 1.25 (*br*s, 16H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.3, 169.0, 109.9, 82.0, 79.6, 63.0, 52.7, 51.9, 38.4, 34.4, 32.7, 29.5, 29.4, 29.4, 29.3, 29.2, 29.1, 27.9, 27.6, 27.2, 25.6, 23.6; HRMS (ESI) calc. for $C_{27}H_{48}NaO_8$: $(M + Na)^+$, 523.3247, found: $(M + Na)^+$, 523.3266. Anal. calc. for $C_{27}H_{48}O_8$: C, 64.77; H, 9.66. Found: C, 64.85; H, 9.71.

246 (101 mg, 0.202 mmol, 96%) as a colorless oil: R*f* 0.22 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +3.3 (*c* 0.04, CH_2Cl_2); IR (KBr) 3456, 1796, 1736, 1462, 1366, 1198, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (s, 1H), 3.73 (s, 3H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.35 (d, *J* = 17.3 Hz, 1H), 2.93 (d, *J* = 17.3 Hz, 1H), 2.71 (dd, *J* = 12.1, 2.6 Hz, 1H), 2.01 – 1.92 (m,

1H), 1.60 – 1.45 (m, 5H), 1.44 (s, 9H), 1.29 – 1.20 (m, 14H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.5, 169.6, 110.5, 82.0, 78.9, 63.1, 53.6, 51.8, 37.6, 34.7, 32.8, 29.6, 29.5, 29.4, 29.3, 29.2, 28.0, 27.8, 27.4, 25.7, 23.5; HRMS (ESI) calc. for $C_{27}H_{48}NaO_8$: $(M + Na)^+$, 523.3247, found: $(M + Na)^+$, 523.3231. Anal. calc. for $C_{27}H_{48}O_8$: C, 64.77; H, 9.66. Found: C, 64.81; H, 9.71.

(*R*)-Methyl 2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)tetradec-13-enoate (233)

(*S*)-Methyl 2-((2*R*,4*R*)-4-(2-*tert*-butoxy-2-oxoethyl)-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)tetradec-13-enoate (234)



A solution of alcohol **245** or **246** (100 mg, 0.2 mmol) in CH_2Cl_2 (20 mL) was allowed to react with Dess–Martin periodinane (170 mg, 0.4 mmol) at 0 ºC. After 2 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 15 mL) and aq. Na_2CO_3 (sat., 15 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the corresponding aldehyde. ^{n}BuLi (1.6 M; 0.2 mL, 0.32 mmol) was added to a solution of $Ph_3PMe{\cdot}Br$ (130 mg, 0.36 mmol) in dry THF (50 mL) at –78 ºC giving a yellow solution of ylide (**247**). The mixture was allowed to warm to 0 ºC and after 30 min was recooled to –78 ºC. Aldehyde (90 mg, 0.18 mmol) in THF (2 mL) was slowly added with stirring and, after 30 min at –78 ºC and 30 min at 0 ºC, was quenched with aq. NH_4Cl (sat., 100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts

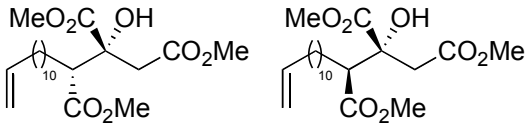
were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 20:1) gave the corresponding alkene **233** or **234**.

233 (62 mg, 0.13 mmol, 62%) as a colorless oil: R*f* 0.60 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +13.8 (*c* 1.0, MeOH); IR (KBr) 1801, 1736, 1461, 1366, 1240, 1194, 1157, 1095, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.96 (m, 2H), 3.70 (s, 3H), 3.23 (d, *J* = 16.9 Hz, 1H), 2.80 (d, *J* = 16.9 Hz, 1H), 2.75 (dd, *J* = 11.8, 3.1 Hz, 1H), 2.03 (dd, *J* = 14.4, 6.9 Hz, 2H), 1.86 – 1.78 (m, 1H), 1.68 – 1.60 (m, 1H), 1.44 (s, 9H), 1.25 (*br*s, 16H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.3, 169.0, 139.2, 114.0, 109.9, 82.0, 79.6, 52.7, 51.9, 38.3, 34.4, 33.7, 29.5, 29.4, 29.2, 29.1, 29.1, 28.9, 27.9, 27.6, 27.2, 23.6; HRMS (ESI) calc. for $C_{28}H_{48}NaO_7$: $(M + Na)^+$, 519.3298, found: $(M + Na)^+$, 519.3304. Anal. calc. for $C_{28}H_{48}O_7$: C, 67.71; H, 9.74. Found: C, 67.77; H, 9.86.

234 (58 mg, 0.117 mmol, 58%) as a colorless oil: R*f* 0.32 (Et_2O:Hexanes, 1:20); $[\alpha]_D^{25}$ +4.1 (*c* 0.2, CH_2Cl_2); IR (KBr) 1796, 1736, 1365, 1196, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, 16.9, 10.1, 6.7 Hz, 1H), 5.27 (s, 1H), 5.02 – 4.90 (m, 2H), 3.73 (s, 3H), 3.36 (d, *J* = 17.3 Hz, 1H), 2.93 (d, *J* = 17.3 Hz, 1H), 2.71 (dd, *J* = 12.1, 2.7 Hz, 1H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.60 – 1.58 (m, 2H), 1.44 (s, 9H), 1.31 – 1.12 (m, 16H), 0.96 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.5, 169.6, 139.3, 114.1, 110.5, 82.0, 78.9, 53.6, 51.8, 37.5, 34.7, 33.8, 29.7, 29.5, 29.5, 29.3, 29.2, 29.1, 28.9, 28.0, 27.8, 27.4, 23.5; HRMS (ESI) calc. for $C_{28}H_{48}NaO_7$: $(M + Na)^+$, 519.3298, found: $(M + Na)^+$, 519.3312.

(2*R*,3*R*)-Trimethyl 2-hydroxypentadec-14-ene-1,2,3-tricarboxylate (248)

(2*R*,3*S*)-Trimethyl 2-hydroxypentadec-14-ene-1,2,3-tricarboxylate (249)



$BF_3{\cdot}OEt_2$ (0.1 mL, 4.4 mmol) was added to a dioxolanone **233** or **234** (22 mg, 0.44 mmol) in dry MeOH (5 mL) and the mixture was stirred in a sealed tube under reflux overnight. Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave triester **248** or **249** (15 mg, 0.37 mmol, 84%) as a pale yellow oil:

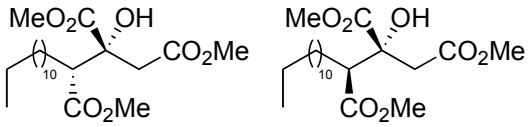
248: R*f* 0.23 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +9.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3504, 1742, 1437, 1353, 1201, 1175, 1118, 997, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.96 (m, 2H), 3.90 (*br*s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.10 (d, *J* = 16.4 Hz, 1H), 2.71 (d, *J* = 16.4 Hz, 1H), 2.70 (dd, *J* = 11.8, 3.1 Hz, 1H), 2.03 (dd, *J* = 14.3, 6.9 Hz, 2H), 1.85 – 1.76 (m, 1H), 1.51 – 1.43 (m, 1H), 1.38 – 1.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.8, 171.0, 139.2, 114.0, 75.8, 53.7, 53.1, 51.9, 51.8, 40.7, 33.7, 29.4, 29.4, 29.3, 29.1, 28.9, 27.7, 27.0; HRMS (ESI) calc. for $C_{21}H_{36}NaO_7$: $(M + Na)^+$, 423.2359, found: $(M + Na)^+$, 423.2379. Anal. calc. for $C_{21}H_{36}O_7$: C, 62.98; H, 9.06. Found: C, 63.02; H, 9.16.

249: R*f* 0.28 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +0.40 (*c* 0.2, CH_2Cl_2); IR (KBr) 2926, 2854, 1741, 1437, 1201, 1173, 1125, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.02 – 4.90 (m, 2H), 4.11 (*br*s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.01 (d, *J* =16.4 Hz, 1H), 2.92 (d, *J* =16.5 Hz, 1H), 2.77 (dd, *J* = 11.7, 3.3 Hz, 1H), 2.07 – 2.01 (m, 2H), 1.76 – 1.53 (m, 3H), 1.31 – 1.16 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 173.2, 171.5, 139.3, 114.1, 76.1, 53.0, 52.7, 52.1, 52.0, 39.5, 33.8, 29.7,

29.5, 29.4, 29.1, 28.9, 27.7, 26.5, HRMS (ESI) calc. for $C_{21}H_{37}O_7$: $(M + H)^+$, 401.2539, found: $(M + H)^+$, 401.2529. Anal. calc. for $C_{21}H_{36}O_7$: C, 62.98; H, 9.06. Found: C, 63.07; H, 8.97.

(2*R*,3*R*)-Trimethyl 2-hydroxypentadecane-1,2,3-tricarboxylate (250)

(2*R*,3*S*)-Trimethyl 2-hydroxypentadecane-1,2,3-tricarboxylate (251)



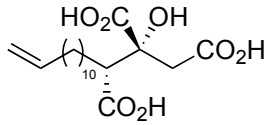
Pd/C (10%, 150 mg) was added to alkene **248** or **249** (130 mg, 0.21 mmol) in dry THF (20 mL) under H_2 and the mixture was stirred for 15 h, filtered through Celite while being rinsed with Et_2O, and rotary evaporated to leave the corresponding trimethyl ester:

250 as a white solid (148 mg, 98%): mp 40 – 42 ºC (Hexanes/CH_2Cl_2); R*f* 0.23 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +10.1 (*c* 1.0, $CHCl_3$); IR (KBr) 1742, 1437, 1353, 1201, 1174, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.10 (d, *J* = 16.4 Hz, 1H), 2.71 (d, *J* = 16.4 Hz, 1H), 2.69 (dd, *J* = 11.8, 3.0 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.51-1.44 (m, 1H), 1.23 (m, 20H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 172.9, 171.1, 53.8, 53.1, 51.9, 40.8, 31.9, 29.62, 29.58, 29.5, 29.3 (2C), 27.7, 27.0, 22.7, 14.1; HRMS (ESI) calc. for $C_{21}H_{38}NaO_7$: $(M + Na)^+$, 425.2515, found: $(M + Na)^+$, 425.2509;

251 as a white gum (149 mg, 98%): R*f* 0.29 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +0.40 (*c* 0.1, CH_2Cl_2); IR (KBr) 1741, 1437, 1202, 1176 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 4.11 (*br*s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.01 (d, *J* = 16.5 Hz, 1H), 2.92 (d, *J* = 16.5 Hz, 1H), 2.77 (dd, *J* = 11.6, 3.2 Hz, 1H), 1.80 – 1.54 (m, 3H), 1.29 – 1.21 (m, 20H), 0.88 (t, *J* =

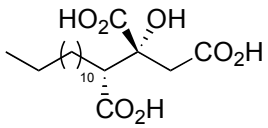
6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.2, 171.4, 76.1, 52.9, 52.6, 51.9, 51.9, 39.5, 31.8, 29.6, 29.5, 29.5, 29.3, 27.6, 26.4, 22.6, 14.0; HRMS (ESI) calc. for $C_{21}H_{39}O_7$: $(M + H)^+$, 403.2696, found: $(M + H)^+$, 403.2697.

***ent*-CJ-13,981 (25)**



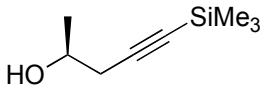
Trimethyl ester **248** (20 mg, 0.05 mmol) and KOH in H_2O (0.1 M; 2.5 mL, 0.25 mmol) were stirred at 90 °C overnight. The mixture was acidified to pH 1 using 1 M HCl and the product was extracted with EtOAc (10 mL), dried ($MgSO_4$) and purified using a reverse phase silica gel column (100 C_{18}, MeCN:H_2O, 2:1 with 1% CF_3CO_2H) to give *ent*-**25** (14 mg, 0.036 mmol, 72%) as a white solid: R*f* 0.44 (C_{18} silicagel, MeCN:H_2O, 2:1 with 1% CF_3CO_2H); $[\alpha]_D^{25}$ +16.5 (*c* 0.77, acetone); IR (KBr) 1699, 1460, 1420, 1249, 1117, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.93 (m, 2H), 3.08 (d, *J* = 16.5 Hz, 1H), 2.70 (d, *J* = 16.5 Hz, 1H), 2.66 (dd, *J* = 11.8, 2.8 Hz, 1H), 2.04 (dd, *J* = 14.1, 6.9 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.51 – 1.46 (m, 1H), 1.40 – 1.18 (m, 16H); ^{13}C NMR (100 MHz, MeOD) δ 176.6, 176.3, 173.9, 140.2, 114.7, 76.8, 54.7, 42.4, 34.9, 30.7, 30.6, 30.6, 30.4 (2C), 30.2, 30.1, 28.8, 28.1; HRMS (ESI) calc. for $C_{18}H_{29}O_7$: $(M - H)^+$, 357.1913, found: $(M - H)^+$, 357.1912.

***ent*-CJ-13,982 (26)**



Trimethyl ester **250** (20 mg, 0.05 mmol) and KOH in H_2O (0.1 M; 2.5 mL, 0.25 mmol) were stirred at 90 °C overnight. The mixture was acidified to pH 1 using 1 M HCl and the product was extracted with EtOAc (10 mL), dried ($MgSO_4$) and purified using a reverse phase silica gel column (100 C_{18}, MeCN:H_2O, 2:1 with 1% CF_3CO_2H) to give *ent*-**26** (13 mg, 0.035 mmol, 70%) as a white solid: mp 133 – 135 ºC (Hexanes/CH_2Cl_2); R*f* 0.40 (C_{18} silicagel, MeCN:H_2O, 2:1 with 1% CF_3CO_2H); $[\alpha]_D^{25}$ +16.6 (*c* 0.5, Me_2CO); IR (KBr) 1698, 1472, 1418, 1249, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.02 (d, *J* = 16.4 Hz, 1H), 2.64 (d, *J* = 16.4 Hz, 1H), 2.60 (dd, *J* = 11.9, 2.5 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.46 – 1.41 (m, 1H), 1.23 (m, 20H), 0.85 (t, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, MeOD) δ 176.7, 176.2, 173.9, 76.9, 54.9, 42.3, 33.1, 30.8 (2C), 30.7, 30.5 (2C), 30.4 (2C), 28.9, 28.2, 23.8, 14.5; HRMS (ESI) calc. for $C_{18}H_{31}O_7$: $(M - H)^+$, 359.2070, found: $(M - H)^+$, 359.2066. Anal. Calc. for $C_{18}H_{32}O_7$: C, 59.98; H, 8.95. found: C, 59.92; H, 9.00.

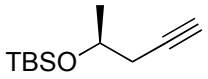
(*S*)-5-(Trimethylsilyl)pent-4-yn-2-ol (340)



^{n}BuLi (1.6 M in hexane, 29 mL, 44 mmol) was slowly added to a solution of (trimethylsily1)acetylene (4.17 g, 43 mmol) in THF (50 mL) at –78 ºC. After 5 min, $BF_3{\cdot}OEt_2$ (4 mL) was added followed by *(S)*-propylene oxide (3.2 mL, 46.0 mmol). The mixture was allowed to warm to 0 ºC over 6 h and stirred at ambient temperature for 10 h. H_2O was added (50 mL), the product extracted with Et_2O and dried ($MgSO_4$).

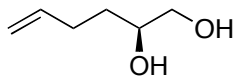
Chromatography (Et_2O:Hexanes, 1:1) gave alcohol **340** (5.45 g, 80%) as a colorless oil: $[\alpha]_D^{25}$ +13.5 (*c* 3.0, CH_2Cl_2); IR (KBr) 3400, 2950, 3170, 1250,1120 cm^{-1}; 'H NMR (400 MHz, $CDC1_3$) δ 3.93 (m, 1 H), 2.65 (m, 1 H), 2.65 (*br*s, 1 H), 2.39 (d, *J* = 6.6 Hz, 2H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.16 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.4, 87.2, 66.2, 30.4, 22.2, 0.1.

(*S*)-*tert*-Butyldimethyl(pent-4-yn-2-yloxy)silane (338)



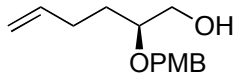
A solution of alcohol **340** (2.5 g, 30 mmol) in THF (20 mL) was treated with a solution of TBAF (1 M; 36 mL, 60 mmol) and the mixture was stirred at RT for 1 h. The solvent was removed in vacuo and the crude alcohol was filtered through a pad of silica eluted with Et_2O. After evaporation of the solvent, the crude was dissolved in CH_2Cl_2 (60 mL). TBSCl (5.25 g, 35 mmol) and imidazole (3 g, 45 mmol) were added and the mixture stirred overnight. The reaction mixture was washed with brine (60 mL), the layers separated and the organic phase dried ($MgSO_4$). Chromatography (100% Hexanes) gave alkyne **338** (5.5 g, 92%) as a colorless oil: $[\alpha]_D^{25}$ –1.2 (c 10.0 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (tq, *J* = 6.7, 6.0 Hz, 1H), 2.33 (ddd, *J* = 16.5, 5.6, 2.6 Hz, 1H), 2.22 (ddd, *J* = 16.4, 7.1, 2.7 Hz, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.21 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.059 (s, 3H), 0.052 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.8, 69.6, 67.4, 29.3, 25,7, 23.1, 18.0, –4.8, –4.9.

(*S*)-Hex-5-ene-1,2-diol (343)



A 100 mL flask equipped with a stirring bar was charged with (*R*,*R*)-**342** (302 mg, 0.5 mmol, 0.005 equiv). The catalyst was treated with (±)-1,2-epoxy-5-hexene (11.3 mL, 9.81 g, 100 mmol), AcOH (120 μL, 2.1 mmol, 0.02 equiv) and 1 mL THF. The solution was cooled to 0 ºC and H_2O (1.0 mL, 55 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to RT and stir for 16 h after which time the (*S*)-epoxide was removed by evaporation. Purified of the crude alcohol by chromatography (Hexanes:Et_2O 1:4) afforded (*S*)-1,2-epoxy-5-hexene **343** (4.23 g, 43.1 mmol, 43%) as a colorless oil: $[\alpha]_D^{25}$ +9.2 (*c* 10.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.1, 6.6, 1H), 5.11 – 4.88 (m, 2H), 3.75 – 3.67 (m, 1H), 3.63 (dd, *J* = 11.2, 2.7, 1H), 3.42 (dd, *J* = 11.2, 7.7, 1H), 2.29 – 2.00 (m, 2H), 1.56 – 1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 115.1, 71.7, 66.6, 32.1, 29.8. HRMS (CI) calc. for $C_6H_{16}NO_2$: $(M + NH_4)^+$, 134.1181, found: $(M + NH_4)^+$, 134.1181.

(*S*)-2-(4-Methoxybenzyloxy)hex-5-en-1-ol (345)

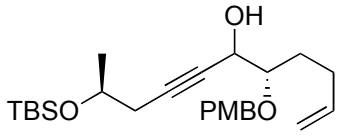


A solution of diol **343** (1.40 g, 12.1 mmol), *p*-methoxybenzaldehyde dimethyl acetal (**344**) (4.40 g, 24.2 mmol) and CSA (279 mg, 1.20 mmol) in CH_2Cl_2 (40 mL) was refluxed for 14 h. The reaction was quenched with Et_3N before all volatiles were evaporated and the

residue was purified by chromatography (Hexanes:EtOAc, 19:1) to afford the corresponding acetal (1.67 g, 59%) as a colorless liquid.

DIBAL-H (1 M in toluene; 9.0 mL, 9.0 mmol) was slowly added to a solution of the acetal (1.06 g, 4.52 mmol) in toluene (40 mL) at 0 ºC. The mixture was allowed to warm to RT over 3 h. The reaction mixture was filtered through a short pad of silica to remove the aluminium salts and the solvent was removed. Purification by chromatography (Hexanes:Et_2O, 4:1) gave primary alcohol **345** (885 mg, 83%) as a colorless liquid: $[\alpha]_D^{25}$ –19.3 (c 3 Et_2O); IR (KBr) 3429, 2998, 2935, 1640, 1612, 1514, 1248, 1036, 998, 912, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.24 (m, 2H), 6.96 – 6.79 (m, 2H), 5.78 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.04 – 4.93 (m, 2H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 3.79 (s, 3H), 3.68 (dt, *J* = 8.8, 5.7 Hz, 1H), 3.54 – 3.46 (m, 2H), 2.18 – 2.03 (m, 2H), 1.77 – 1.66 (m, 1H), 1.62 – 1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 138.2, 130.5, 129.4, 114.9, 113.9, 78.7, 71.3, 64.1, 55.3, 30.1, 29.5.

(5*S*,10*S*)-10-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)undec-1-en-7-yn-6-ol (347)

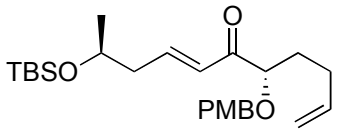


Dess–Martin periodinane (4.3 g, 10.3 mmol) was added with stirring to alcohol **345** (2 g, 6.84 mmol) in CH_2Cl_2 (25 mL). After 5 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 50 mL) and aq. Na_2SO_3 (sat., 50 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give aldehyde **339** (1.82 g, 6.3 mmol) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 8.6 Hz,

2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (m, 2H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 2.16 (m, 2H), 1.74 (m, 2H).

*n*BuLi (1.6 M; 2.8 mL, 4.5 mmol) was added to a solution of alkyne **338** (1.1 g, 5.55 mmol) in dry THF (50 mL) at –78 ºC. The mixture was allowed to warm to 0 ºC and after 30 min recooled to –78 ºC. Aldehyde **339** (1.3 g, 4.48 mmol) in THF (2 mL) was slowly added with stirring. After 30 min at –78 ºC and 30 min at 0 ºC, the reaction was quenched with aq. NH_4Cl (sat., 100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 2:1) gave alcohol **347** (1.41 g, 3.3 mmol, 74%) as a mixture of diastereoisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.85 (m, 2H), 5.78 (m, 1H), 4.98 (m, 2H), 4.56 (m, 2H), 3.91 (m, 1H), 3.79 (s, 3H), 3.47 (m, 1H), 2.38 (m, 1H), 2.33 (m, 2H), 2.16 (m, 2H), 1.74 (m, 2H), 1.20 (m, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 159.6, 138.5, 129.8, 129.8, 115.1, 114.1, 81.65, 80.9, 80.55, 79.6, 73.15, 72.2, 67.8, 65.1, 64.0, 55.5, 30.5, 30.05, 29.9, 29.6, 29.15, 26.0, 23.6, 18.3, –4.45, –4.5.

(5*S*,10*S*,*E*)-10-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)undeca-1,7-dien-6-one (348)

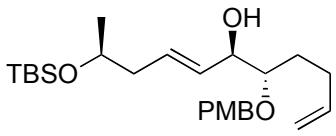


REDAl-H (65% wt in PhMe; 3.2 mL, 7.4 mmol) was slowly added to alkyne **347** (1.4 g, 2.32 mmol) in THF (30 mL) at 0 ºC then warmed to RT and stirred for 48 h. Aqueous HCl

(1 M; 25 mL), brine (25 mL) and Et_2O (25 mL) were added. The aqueous layer was extracted with Et_2O (25 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 3:1) gave the corresponding *trans*-alkene (1.25 g, 2.9 mmol, 89%) as a mixture of diastereoisomers.

NMO (810 mg, 6.9 mmol) and TPAP (100 mg, 0.28 mmol) were sequentially added to this *trans*-alkene (1.20 g, 2.7 mmol) in CH_2Cl_2 (100 mL). The solution was stirred for 1 h and the solvent rotary evaporated. Purification by chromatography (Hexanes:Et_2O 5:1) afforded ketone **348** (1.1 g, 2.5 mmol, 93%) as a colorless oil: $[\alpha]_D^{25}$ –11.0 (*c* 1 MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.06 – 6.96 (m, 1H), 6.88 – 6.83 (m, 2H), 6.54 – 6.45 (m, 1H), 5.74 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.01 – 4.90 (m, 2H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 3.98 – 3.84 (m, 2H), 3.78 (s, 3H), 2.38 – 2.29 (m, 2H), 2.24 – 2.03 (m, 2H), 1.82 – 1.61 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.85 (d, *J* = 2.7 Hz, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 159.4, 146.0, 137.5, 129.7, 129.6, 126.6, 115.4, 113.8, 83.1, 71.8, 67.6, 55.3, 43.0, 31.7, 29.4, 25.8, 23.8, 18.1, –4.5, –4.8; HRMS (ESI) calc. for $C_{25}H_{41}O_4Si$: $(M + H)^+$, 433.2774, found: $(M + H)^+$, 433.2769.

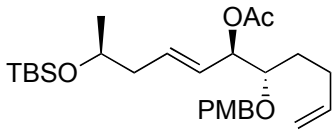
(5*S*,6*R*,10*S*,*E*)-10-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)undeca-1,7-dien-6-ol (346)



REDAl-H (65% wt in PhMe; 0.67 mL, 7.4 mmol) was slowly added to ketone **348** (0.8 g, 1.85 mmol) in THF (30 mL) at 0 °C then warmed to RT and stirred for 1 h. The

reaction was slowly poured into aq. HCl (1 M; 50 mL) and Et_2O (50 mL) was added. The aqueous was extracted with 50 mL of Et_2O and the organic combined dried ($MgSO_4$). Chromatography (Et_2O:Hexanes, 1:3) gave alcohol **346** (700 mg, 1.6 mmol, 89%) as a colorless oil and as a single diastereoisomer: $[\alpha]_D^{25}$ –33.5 (*c* 1 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.24 (m, 2H), 6.89 – 6.83 (m, 2H), 5.75 (ddt, *J* = 22.4, 15.1, 6.7 Hz, 2H), 5.48 (dd, *J* = 15.5, 6.7 Hz, 1H), 5.01 – 4.90 (m, 2H), 4.55 (d, *J* = 11.1 Hz, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 4.25 (dd, *J* = 6.6, 3.1 Hz, 1H), 3.82 (dd, *J* = 12.1, 6.1 Hz, 1H), 3.79 (s, 3H), 3.41 (dt, *J* = 8.2, 3.4 Hz, 1H), 2.24 – 2.11 (m, 3H), 2.04 (dt, *J* = 14.6, 7.1 Hz, 1H), 1.73 – 1.58 (m, 1H), 1.57 – 1.45 (m, 1H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.5, 130.5, 130.2, 129.5, 114.8, 113.9, 81.3, 73.1, 71.8, 68.4, 55.3, 42.8, 29.9, 28.5, 25.9, 23.4, 18.1, –4.5, –4.7; HRMS (ESI) calc. for $C_{25}H_{43}O_4Si$: $(M + H)^+$, 435.2931, found: $(M + H)^+$, 435.2935.

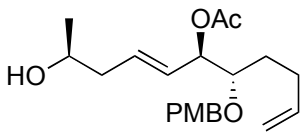
(5*S*,6*R*,10*S*,*E*)-10-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)undeca-1,7-dien-6-yl acetate (350)



Et_3N (0.07 mL, 0.49 mmol), DMAP (10 mg, 0.08 mmol) and Ac_2O (0.05 mL, 0.49 mmol) were added with stirring to a solution of alcohol **346** (200 mg, 0.41 mmol) in CH_2Cl_2 (7 mL) at 0 °C. After 17 h of stirring at RT, the solution was poured onto aq. HCl (1 M; 15 mL) and the organic layer washed with brine (30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 3:1) gave acetate **350** (209 mg, 98%) as a colorless oil: $[\alpha]_D^{25}$ –22.8 (*c* 1 Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.24 (m, 2H),

6.90 – 6.79 (m, 2H), 5.80 – 5.67 (m, 2H), 5.51 (dd, *J* = 15.1, 7.1 Hz, 1H), 5.46 – 5.42 (m, 1H), 5.00 – 4.89 (m, 2H), 4.64 (d, *J* = 11.0 Hz, 1H),), 4.39 (d, *J* = 11.0 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.79 (s, 3H), 3.49 – 3.42 (m, 1H), 2.29 – 2.13 (m, 3H), 2.08 – 1.97 (m, 1H), 2.05 (s, 3H), 1.68 – 1.55 (m, 2H), 1.54 – 1.45 (m, 1H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.4, 138.5, 132.8, 130.7, 129.9, 126.6, 115.15, 114.0, 79.5, 75.7, 72.3, 68.45, 55.5, 42.9, 30.2, 30.0, 26.1, 23.7, 21.5, 18.3, -4.3, -4.5; HRMS (ESI) calc. for $C_{27}H_{44}O_5SiNa$: $(M + Na)^+$, 499.2856, found: $(M + Na)^+$, 499.2852.

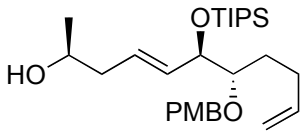
(5*S*,6*R*,10*S*,*E*)-10-Hydroxy-5-(4-methoxybenzyloxy)undeca-1,7-dien-6-yl acetate (336)



TBAF (1 M; in THF, 0.8 mL, 0.8 mmol) was slowly added to a solution of TBS protected alcohol **350** (250 mg, 0.53 mol) in THF (30 mL). The reaction was stirred at RT for 17 h then quench with aq. HCl (1 M; 30 mL). The layers were separated and the aqueous extracted with Et_2O (25 mL). The combined organic layers were dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:Et_2O, 2:1) gave alcohol **336** (179 mg, 0.50 mmol) as a colorless oil: $[\alpha]_D^{25}$ –40.2 (*c* 1 Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 6.88 – 6.83 (m, 2H), 5.80 – 5.67 (m, 2H), 5.63 – 5.55 (m, 1H), 5.39 (dd, *J* = 7.1, 2.8 Hz, 1H), 5.01 – 4.90 (m, 2H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.79 (s, 3H), 3.48 (dt, *J* = 9.0, 3.5 Hz, 1H), 2.29 – 2.11 (m, 3H), 2.05 (s, 3H), 1.67 – 1.55 (m, 3H), 1.55 – 1.43 (m, 1H), 1.16 (d, *J* = 6.3 Hz,

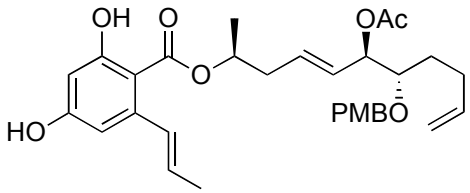
3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.25, 138.1, 131.5, 130.4, 129.6, 127.95, 115.0, 113.8, 79.2, 75.8, 72.2, 67.0, 55.3, 42.2, 30.0, 29.8, 22.8, 21.3; HRMS (ESI) calc. for $C_{21}H_{30}O_5Na$: $(M + Na)^+$, 385.1991, found: $(M + Na)^+$, 385.1996.

(2*S*,6*R*,7*S*,*E*)-7-(4-Methoxybenzyloxy)-6-(tri*iso*propylsilyloxy)undeca-4,10-dien-2-ol (337)



TIPSOTf (0.183 mg, 1.2 mmol) and imidazole (200 mg, 3.6 mmol) were added with stirring to alcohol **346** (47 mg, 0.69 mmol) in CH_2Cl_2 (20 mL). The reaction was let to stir at RT for 72 h and quenched with aq. HCl (1 M; 25 mL). The layers were separated and the aqueous washed with CH_2Cl_2 (30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:Et_2O, 2:3) gave alcohol **337** (29 mg, 0.61 mmol, 88%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 6.92 – 6.78 (m, 2H), 5.82 – 5.53 (m, 3H), 4.95 (dt, *J* = 10.3, 5.4, 2H), 4.76 (d, *J* = 11.1, 1H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.21 (dd, *J* = 6.7, 2.8 Hz, 1H), 3.84 – 3.75 (m, 5H), 3.46 (dt, *J* = 8.9, 3.4 Hz, 1H), 2.28 – 2.11 (m, 3H), 2.03 (dq, *J* = 14.5, 7.2 Hz, 1H), 1.59 (s, 3H), 1.58 – 1.41 (m, 2H), 1.19 – 1.13 (m, 4H), 1.05 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.6, 133.8, 131.2, 129.4, 128.0, 114.7, 113.6, 82.6, 77.2, 73.0, 67.2, 55.3, 42.2, 31.0, 30.1, 22.8, 18.1, 12.4; HRMS (ESI) calc. for $C_{28}H_{48}O_4SiNa$: $(M + Na)^+$, 499.3220, found: $(M + Na)^+$, 499.3206.

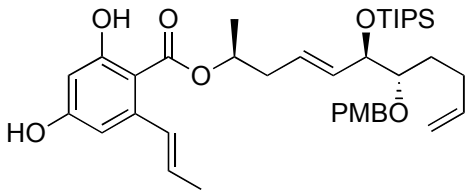
(2*S*,6*R*,7*S*,*E*)-6-Acetoxy-7-(4-methoxybenzyloxy)undeca-4,10-dien-2-yl-2,4-dihydroxy-6-((*E*)-prop-1-enyl)benzoate (334)



Diketo-dioxinone **322**[182] (70 mg, 0.27 mmol) and alcohol **326** (130 mg, 0.36 mmol) in PhMe (5 mL) were heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (1:1; 16 mL). CsOAc (300 mg, 1.56 mmol) was added and the mixture was stirred at RT for 3 h. The solution was acidified with AcOH (1 mL, 15.9 mmol) and stirred overnight. The mixture was poured into aq. $NaHCO_3$ (sat., 15 mL), extracted with Et_2O (2 x 20 mL) and the combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave resorcylate **334** (105 mg, 2.0 mmol, 74%) as a pale yellow oil: R*f* 0.68 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +12.0 (*c* 1, CH_2Cl_2); IR (KBr) 3336, 1643, 1611, 1581, 1380, 1354, 1314, 1255, 1157, 1111, 1050, 1116, 923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (s, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.89 (dd, *J* = 15.5, 1.7 Hz, 1H), 6.85 (d, J = 8.6, 2H), 6.32 (d, *J* = 2.5 Hz, 1H), 6.27 (d, *J* = 2.5 Hz, 1H), 5.73 (m, 4H), 5.38 (dd, *J* = 7.3, 2.6 Hz, 1H), 5.20 (h, *J* = 6.3 Hz, 1H), 4.92 (m, 2H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 2.44 (m, 2H), 2.13 (m, 1H), 2.03 (s, 3H), 1.96 (m, 2H), 1.83 (m, 1H), 1.82 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.56 (m, 1H), 1.41 (m, 1H), 1.32 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 165.0, 160.6, 159.5, 144.6, 138.3, 132.6, 130.7, 130.65, 129.85, 128.4, 127.3, 115.2, 114.0, 108.6, 104.4, 102.3, 79.5, 77.4, 76.0, 72.5, 71.75, 55.5, 39.1, 30.2,

30.0, 21.5, 19.9, 18.7; HRMS (ESI) calc. for $C_{31}H_{38}O_8Na$: $(M + Na)^+$, 561.2464, found: $(M + Na)^+$, 561.2449.

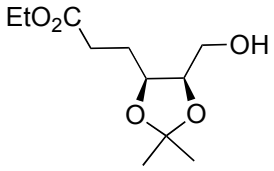
(2*S*,6*R*,7*S*,*E*)-7-(4-Methoxybenzyloxy)-6-(tri*iso*propylsilyloxy)undeca-4,10-dien-2-yl 2,4-dihydroxy-6-((*E*)-prop-1-enyl)benzoate (335)



Diketo-dioxinone **322**[182] (253 mg, 1 mmol) and alcohol **337** (435 mg, 0.91 mmol) in PhMe (10 mL) were heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and *iso*-PrOH (1:1; 32 mL). CsOAc (1.4 g, 7.3 mmol) was added and the mixture was stirred at RT for 3 h. The solution was acidified with AcOH (2 mL, 32 mmol) and stirred overnight. The mixture was poured into aq. $NaHCO_3$ (sat., 30 mL), extracted with Et_2O (2 x 30 mL) and the combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 1.5:1) gave resorcylate **335** (430 mg, 6.58 mmol, 72%) as a pale yellow oil: R*f* 0.68 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –0.6 (*c* 1, CH_2Cl_2); IR (KBr) 3336, 1643, 1611, 1581, 1380, 1354, 1314, 1255, 1157, 1111, 1050, 1116, 923 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.73 (s, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 6.91 (dd, *J* = 15.4, 1.5 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 3H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.27 (d, *J* = 2.5 Hz, 1H), 5.70 (m, 4H), 5.15 (m, 1H), 4.91 (m, 2H), 4.76 (d, *J* = 11.0 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.17 (dd, *J* = 7.3, 2.4 Hz, 1H), 3.78 (s, 3H), 3.43 (m, 1H), 2.47 (m, *J* = 13.8, 6.9 Hz, 1H), 2.38 (m, 1H), 2.13 (m, 1H), 1.97 (m, 1H), 1.81 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.50 (m, 1H), 1.37 (m, 1H), 1.33 (d, *J* = 6.2 Hz,

3H), 1.02 – 0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.0, 160.6, 159.2, 144.6, 138.8, 134.0, 132.7, 131.5, 129.7, 127.2, 114.85, 113.9, 108.5, 104.4, 102.2, 83.0, 73.4, 72.4, 66.15, 55.5, 39.3, 31.1, 30.35, 20.2, 18.7, 18.3, 18.3, 15.4, 12.6; HRMS (ESI) calc. for $C_{38}H_{56}O_7SiNa$: $(M + Na)^+$, 675.3693, found: $(M + Na)^+$, 675.3720.

Ethyl 3-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (372)



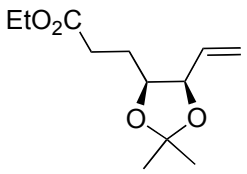
Ethyl(triphenylphosphoranylidene)acetate (**371**) (12.5 g, 36.0 mmol) and benzoic acid (0.10 g, 0.82 mmol) were added to known lactol **369**[188] (4.74 g, 29.6 mmol) in CH_2Cl_2 (150 mL). The solution was heated under reflux for 17 h. The solvent was evaporated and the residue purified by chromatography (Hexanes:Et_2O, 1:1) to give the corresponding α,β-unsaturated ester (5.7 g, 85%) as a colorless liquid as mixture of *E* and *Z*-isomers (*E*:*Z*, 1:2): IR (film) 3441, 2986, 2938, 1714, 1645, 1456, 1416 cm^{-1}; HRMS (CI) calc. for $C_{11}H_{19}O_5$: $(M + H)^+$, 231.1232, found: $(M + H)^+$, 231.1241.

(*Z*)-isomer: R*f* 0.43 (EtOAc:Hexanes, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, *J* = 11.6, 7.0 Hz, 1H), 5.93 (dd, *J* = 11.6, 1.7 Hz, 1H,), 5.60 (ddd, *J* = 7.2, 7.0, 1.7 Hz, 1H), 4.58 (ddd, *J* = 7.2, 5.1, 3.8 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.56 (dd, *J* = 11.8, 3,8 Hz, 1H), 3.44 (dd, *J* = 11.8, 5.1 Hz, 1H), 2.14 (*br*s, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 147.3, 121.1, 108.9, 78.8, 74.9, 61.5, 60.7, 27.4, 24.7, 14.2;

(*E*)-isomer: R*f* 0.33 (EtOAc:Hexanes, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 15.6, 5.6 Hz, 1H), 6.13 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.81 (ddd, *J* = 7.1, 5.7, 1.6 Hz, 1H), 4.37 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.56 (dd, *J* = 11.8, 3.8 Hz, 1H), 3.44 (dd, *J* = 11.8, 5.1 Hz, 1H), 1.89 (*br*s, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 142.1, 123.3, 109.7, 78.4, 62.0, 60.8, 27.8, 25.4, 14.4;

Pd on charcoal (10%, 1.50 g) was added to a solution of the above unsaturated ester (7.20 g, 31.3 mmol) in EtOH (150 mL). The black mixture was evacuated and back-filled with a balloon of hydrogen for four cycles and then stirred under H_2 for 2.5 h. The mixture was diluted with EtOH (20 mL) and filtered through a pad of Celite, and the residue was washed with EtOH (2 x 30 mL). The filtrates were evaporated under reduced pressure to give the alcohol **372** (7.04 g, 97%) as a colorless liquid: R*f* 0.42 (EtOAc:Hexanes, 2:1); $[\alpha]_D^{25}$ +21.4 (*c* 2.0, EtOH); IR (film) 3514, 2986, 2937, 1733, 1448, 1373, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.63 (m, 2H), 2.50 (m, 1H), 2.37 (m, 1H), 1.94 (*br*s, 1H), 1.80 (m, 2H), 1.42 (s, 3H), 1.32 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 108.5, 78.0, 76.2, 61.8, 60.7, 31.4, 28.3, 25.6, 24.9, 14.4; HRMS (CI) calc. for $C_{11}H_{21}O_5$: $(M + H)^+$, 233.1389, found: $(M + H)^+$, 233.1390.

Ethyl 3-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propanoate (375)



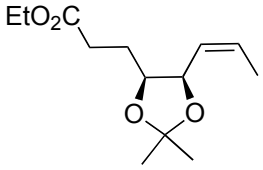
Alcohol **372** (1 g, 4.30 mmol) in CH_2Cl_2 (30 mL) was allowed to react with Dess–Martin periodinane (2.37 g, 5.6 mmol) at RT. After 3 h, the reaction was quenched with aq.

$NaHCO_3$ (sat., 50 mL) and aq. Na_2SO_3 (sat., 50 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the corresponding aldehyde (900 mg, 3.91 mmol, 91%) as a colorless oil: R*f* 0.27 (Et_2O:Hexanes, 1:1); IR (KBr) 1731, 1371, 1219, 1181, 1159, 1072, 1036, 984, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.9 Hz, 1H), 4.39 – 4.32 (m, 1H), 4.28 (dd, *J* = 7.2, 3.1 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.53 – 2.34 (m, 2H), 1.92 (dddd, *J* = 13.9, 8.3, 7.3, 3.8 Hz, 1H), 1.73 (dddd, *J* = 14.0, 9.6, 8.0, 6.1 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 172.8, 110.9, 82.0, 77.6, 60.8, 31.1, 27.7, 25.5, 25.45, 14.4; HRMS (CI) calc. for $C_{11}H_{19}O_5$: $(M + H)^+$, 231.1240, found: $(M + H)^+$, 231.1232. Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.88. Found: C, 57.48; H, 7.75.

*n*BuLi (1.6 M; 3.2 mL, 5.12 mmol) was added to a solution of $Ph_3PMe^+Br^-$ (1.8 g, 6.07 mmol) in dry THF (50 mL) at –78 ºC to produce a yellow solution of ylide (**247**), which was allowed to warm up to 0 ºC and stirred at this temperature for 30 min and recooled to –78 ºC. Aldehyde (900 mg, 3.91 mmol) in THF (2 mL) was slowly added with stirring. After 30 min at –78 ºC and 12 h at RT, the mixture was quenched with aq. NH_4Cl (sat., 100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 4:1) gave alkene **375** (720 mg, 2.95 mmol, 71%) as a colorless oil: R*f* 0.61 (EtOAc:Hexanes, 1:1); $[\alpha]_D^{25}$ +20.6 (c 2.0, EtOH); IR (film) 3010, 2986, 2936, 1737, 1449, 1371, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.3, 10.3, 7.7 Hz, 1H), 5.27 (m, 2H), 4.51 (dd, *J* = 7.3, 6.5 Hz, 1H), 4.11 (m, 3H), 2.45 (ddd, *J* = 16.1, 8.1, 6.6 Hz, 1H), 2.35 (m, 1H), 1.72 (m, 2H), 1.45 (s, 3H), 1.33 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 134.1, 118.8, 108.6, 79.75, 77.45,

60.6, 31.1, 28.4, 26.3, 25.8, 14.4; HRMS (CI) calc. for $C_{12}H_{21}O_4$: $(M + H)^+$, 229.1440, found: $(M + H)^+$, 229.1449.

Ethyl 3-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)propanoate (376)

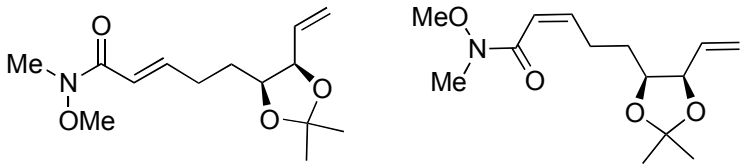


Alcohol **373** (1 g, 4.30 mmol) in CH_2Cl_2 (30 mL) was allowed to react with Dess–Martin periodinane (2.37 g, 5.6 mmol) at RT. After 3 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 50 mL) and aq. Na_2SO_3 (sat., 50 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the corresponding aldehyde (900 mg, 3.91 mmol, 91%) as a colorless oil: R*f* 0.27 (Et_2O:Hexanes, 1:1); IR: 1731, 1371, 1219, 1181, 1159, 1072, 1036, 984, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.9 Hz, 1H), 4.39 – 4.32 (m, 1H), 4.28 (dd, *J* = 7.2, 3.1 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.53 – 2.34 (m, 2H), 1.92 (dddd, *J* = 13.9, 8.3, 7.3, 3.8 Hz, 1H), 1.73 (dddd, *J* = 14.0, 9.6, 8.0, 6.1 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 172.8, 110.9, 82.0, 77.6, 60.8, 31.1, 27.7, 25.5, 25.45, 14.4; HRMS (CI) calc. for $C_{11}H_{19}O_5$: $(M + H)^+$, 231.1240, found: $(M + H)^+$, 231.1232. Anal. calc. for $C_{11}H_{18}O_5$: C, 57.39; H, 7.88. Found: C, 57.48; H, 7.75.

*n*BuLi (1.6 M; 3.2 mL, 5.12 mmol) was added to $Ph_3PEt{\cdot}Br$ (2.25 g, 6.07 mmol) in dry THF (50 mL) at –78 °C to produce an orange solution of ylide (**374**), which was allowed to warm up to 0 °C and, after 30 min, re-cooled to –78 °C. Aldehyde (900 mg, 3.91 mmol) in THF (2 mL) was slowly added with stirring. After 30 min at –78 °C and 12 h at RT, the

mixture was quenched with aq. NH_4Cl (sat., 100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 4:1) gave *Z*-alkene **376** (650 mg, 2.95 mmol, 69%) as a colorless oil: R*f* 0.86 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –55.8 (*c* 1, CH_2Cl_2); IR: 1734, 1369, 1250, 1215, 1161, 1060, 1021, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.44 (m, 1H), 4.92 (m, 1H), 4.11 (m, 3H), 2.44 (m, 1H), 2.34 (m, 1H), 1.70 (m, 5H), 1.44 (s, 3H), 1.34 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 129.2, 126.3, 108.3, 77.35, 73.8, 60.6, 31.05, 28.5, 26.2, 25.9, 14.4, 13.6; HRMS (ESI) calc. for $C_{12}H_{19}O_4$: $(M - Me)^+$, 227.1283, found: $(M - Me)^+$, 227.1284. Anal. calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.54; H, 9.08.

(*E*)-*N*-Methoxy-*N*-methyl-5-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)pent-2-enamide (366) and (*Z*)-*N*-methoxy-*N*-methyl-5-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)pent-2-enamide (378)



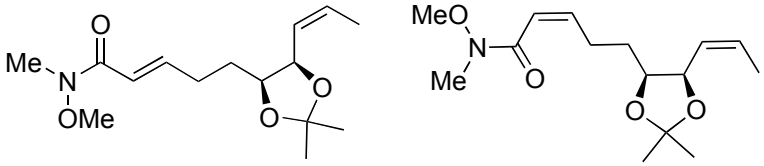
DIBAL-H in CH_2Cl_2 (1 M; 1.8 mL, 1.8 mmol) was added dropwise with stirring to ester **375** (400 mg, 1.75 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 1.5 h, MeOH (1 mL) was carefully added and the mixture allowed to warm up to RT. Aqueous HCl (1 M; 15 mL), brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated to give the crude aldehyde (320 mg, 100%) as a colorless oil. Ylide **377** (870 mg, 2.4 mmol) was added to the crude aldehyde (320 mg, 1.75 mmol) in CH_2Cl_2 (30 mL) and the mixture stirred at reflux for 14 h. Rotary evaporation and

chromatography (Hexanes:Et_2O, 1:1) gave (*Z*)-Weinreb amide **378** (13 mg, 0.048 mmol, 3%) and the more polar (*E*)-Weinreb amide **366** (370 mg, 1.37 mmol, 79%) both as a colorless oils:

378: R*f* 0.24 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +25.7 (*c* 1, $CHCl_3$); IR: 1661, 1427, 1270, 1350, 1248, 1213, 1169, 1050, 999, 926, 877 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, *J* = 11.5 Hz, 1H), 6.11 (dt, *J* = 11.6, 7.4 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.20 (dd, *J* = 10.3, 0.9 Hz, 1H), 4.48 (m, 1H), 4.17 (m, 1H), 3.65 (s, 3H), 3.18 (s, 3H), 2.69 (q, *J* = 7.4 Hz, 2H), 1.58 (m, 2H), 1.46 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 134.6, 118.9, 118.5, 108.4, 79.95, 78.0, 61.7, 30.2, 28.4, 26.1, 25.85; HRMS (ESI) calc. for $C_{14}H_{23}NO_4Na$: $(M + Na)^+$, 292.1525, found: $(M + Na)^+$, 292.1512.

366: R*f* 0.11 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –10.0 (*c* 1, CH_2Cl_2); IR: 1663, 1633, 1379, 1248, 1215, 1167, 1048, 994, 928, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 15.2, 7.0 Hz, 1H), 6.40 (d, *J* = 15.4 Hz, 1H), 5.77 (ddd, *J* = 17.2, 10.3, 7.8 Hz, 1H), 5.29 (m, 1H), 5.22 (m, 1H), 4.48 (m, 1H), 4.13 (ddd, *J* = 9.5, 6.2, 4.4 Hz, 1H), 3.67 (s, 3H), 3.21 (s, 3H), 2.39 (m, 1H), 2.26 (m, 1H), 1.64 (m, 1H), 1.52 (m, 1H), 1.46 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 134.4, 119.5, 118.7, 108.5, 79.9, 61.9, 32.6, 29.5, 29.3, 28.4, 25.8; HRMS (ESI) calc. for $C_{14}H_{23}NO_4Na$: $(M + Na)^+$, 292.1525, found: $(M + Na)^+$, 292.1525. Anal. calc. for $C_{14}H_{23}O_4N$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.56; H, 8.53; N, 5.13.

(2*E*)-*N*-Methoxy-*N*-methyl-5-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)pent-2-enamide (367) and (2*Z*)-*N*-methoxy-*N*-methyl-5-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)pent-2-enamide (379)



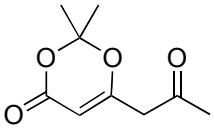
DIBAL-H in CH_2Cl_2 (1 M; 1.6 mL, 1.6 mmol) was added dropwise with stirring to ester **376** (360 mg, 1.49 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 1.5 h, MeOH (1 mL) was carefully added and the mixture allowed to warm up to RT. Aqueous HCl (1 M; 15 mL), brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated to give the crude aldehyde (300 mg, 100%) as a colorless oil. Ylide **377** (760 mg, 1.94 mmol) was added to the crude aldehyde (300 mg, 1.5 mmol) in CH_2Cl_2 (30 mL) and the mixture stirred at reflux for 14 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 1:1) gave (*Z*)-amide **379** (12 mg, 0.042 mmol, 3%) and the more polar (*E*)-amide **367** (360 mg, 1.27 mmol, 85%) both as colorless oils:

379: R*f* 0.24 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –17.0 (*c* 1, $CHCl_3$); IR: 1659, 1442, 1368, 1246, 1215, 1167, 1058, 869, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 11.5 Hz, 1H), 6.10 (dt, *J* = 11.6, 7.4 Hz, 1H), 5.68 (m, 1H), 5.43 (m, 1H), 4.89 (m, 1H), 4.14 (m, 1H), 3.65 (s, 3H), 3.18 (s, 3H), 2.66 (q, *J* = 7.4 Hz, 2H), 1.66 (dd, *J* = 7.0, 1.9 Hz, 3H), 1.64 (m, 1H), 1.51 (m, 1H), 1.45 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 128.8, 126.7, 118.8, 108.1, 77.9, 73.8, 61.7, 30.1, 28.6, 26.1, 26.0, 13.4; HRMS (ESI) calc. for $C_{15}H_{25}NO_4Na$: $(M + Na)^+$, 306.1681, found: $(M + Na)^+$, 306.1671.

367: R*f* 0.13 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –51.3 (*c* 1, CH_2Cl_2); IR: 1663, 1633, 1379, 1368, 1243, 1215, 1164, 1033, 995, 979, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (dt, *J* =

15.2, 7.0 Hz, 1H), 6.39 (d, *J* = 15.4 Hz, 1H), 5.69 (m, 1H), 5.41 (ddq, *J* = 11.1, 9.3, 1.8 Hz, 1H), 4.89 (m, 1H), 4.11 (ddd, *J* = 9.5, 6.0, 4.4 Hz, 1H), 3.67 (s, 3H), 3.21 (s, 3H), 2.37 (m, 1H), 2.23 (m, 1H), 1.66 (m, 4H), 1.50 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 128.95, 126.6, 119.4, 108.2, 77.4, 73.75, 61.9, 32.6, 29.4, 29.2, 28.6, 25.9, 13.5; HRMS (ESI) calc. for $C_{15}H_{25}NO_4Na$: $(M + Na)^+$, 306.1681, found: $(M + Na)^+$, 306.1670. Anal. calc. for $C_{15}H_{25}O_4N$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.59; H, 8.82; N, 4.88.

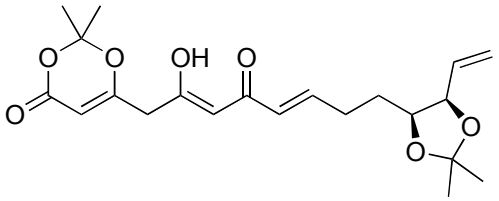
2,2-Dimethyl-6-(2-oxopropyl)-4*H*-1,3-dioxin-4-one (351)



LHMDS in THF (1 M; 21 mL, 21 mmol) was added dropwise with stirring to dioxinone **313** (3.0 g, 21 mmol) in THF (60 mL) and the resulting pale yellow solution stirred at –78 °C for 50 min, when AcCl (0.9 mL, 12.6 mmol) was added. The reaction temperature was maintained at –78 °C for 30 min after which time the solution was poured onto aq. HCl (1 M; 50 mL) and Et_2O (40 mL) was added. The organic phase was washed with brine (3 × 50 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Et_2O:Hexanes, 1:1 to 2:1) gave keto-dioxinone **351** (2.1 g, 11.6 mmol, 55%) as a white solid: mp 47-50 °C (Hexanes/CH_2Cl_2); R*f* 0.13 (Et_2O:Hexanes, 1:1); IR: 1733, 1714, 1639, 1379, 1317, 1270, 1253, 1197, 1160, 1011, 904, 862, 821, 794 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 3.31 (s, 2H), 2.21 (s, 3H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 164.5, 160.8, 107.4, 96.9, 48.15, 30.3, 25.2; HRMS (CI) calc. for $C_9H_{13}O_4$: $(M + H)^+$, 185.0814,

found: $(M + H)^+$, 185.0812. Anal. calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.75; H, 6.63.

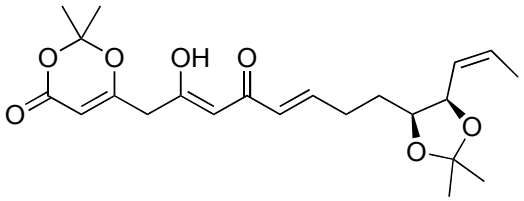
6-((2*Z*,5*E*)-2-Hydroxy-8-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-4-oxoocta-2,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (364)



LDA in THF (1 M; 0.93 mL, 0.93 mmol) was added dropwise with stirring to keto-dioxinone **351** (82 mg, 0.445 mmol) in THF (8 mL) at –70 °C and the resulting cloudy yellow solution was slowly allowed to warm up to –40 °C. Weinreb amide **366** (82 mg, 3 mmol) in THF (2 mL) was slowly added and the mixture stirred at –40 °C for 1 h and poured into aq. HCl (1 M; 25 mL). Et_2O was added (25 mL), the layers separated and the aqueous phase extracted with Et_2O (25 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:3) gave diketo-dioxinone **364** (21 mg, 0.535 mmol, 18%) as a colorless oil: R*f* 0.16 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –7.6 (*c* 0.5, CH_2Cl_2); IR: 1727, 1579, 1391, 1371, 1271, 1250, 1202, 1128, 1014, 970, 927, 901, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.74 (*br*s, 1H), 6.89 (m, 1H), 5.84 (d, *J* = 15.2 Hz, 1H), 5.79 (m, 1H), 5.49 (s, 1H), 5.37 (s, 1H), 5.27 (dd, *J* = 27.6, 13.7 Hz, 2H), 4.50 (t, *J* = 6.9 Hz, 1H), 4.12 (m, 1H), 3.25 (s, 2H), 2.41 (m, 1H), 2.26 (m, 1H), 1.68 (s, 6H), 1.63 (m, 1H), 1.52 (m, 2H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 177.6, 165.25, 160.9, 145.3, 134.2, 125.6, 118.8, 108.6,

107.35, 99.5, 96.6, 79.8, 45.1, 29.6, 29.55, 28.4, 25.8, 25.2; HRMS (ESI) calc. for $C_{21}H_{28}O_7Na$: $(M + Na)^+$, 415.1733, found: $(M + Na)^+$, 415.1724.

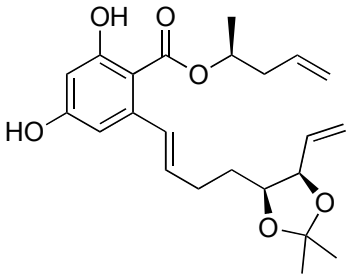
6-((2*Z*,5*E*)-2-Hydroxy-8-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)-4-oxoocta-2,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (365)



LDA in THF (1 M; 0.93 mL, 0.93 mmol) was added dropwise with stirring to keto-dioxinone **351** (82 mg, 0.445 mmol) in THF (8 mL) at –70 °C and the resulting cloudy yellow solution was slowly allowed to warm up to –40 °C. Weinreb amide **367** (82 mg, 2.9 mmol) in THF (2 mL) was slowly added and the mixture stirred at –40 °C for 1 h and poured into aq. HCl (1 M; 25 mL). Et_2O was added (25 mL), the layers separated and the aqueous phase extracted with Et_2O (25 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:3) gave diketo-dioxinone **365** (24 mg, 0.59 mmol, 20%)[3] as a colorless oil: R*f* 0.19 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –32.5 (*c* 0.2, CH_2Cl_2); IR: 1733, 1643, 1580, 1378, 1275, 1207, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.74 (*br*s, 1H), 6.89 (dt, *J* = 14.1, 7.0 Hz, 1H), 5.84 (d, *J* = 15.4 Hz, 1H), 5.71 (m, 1H), 5.49 (s, 1H), 5.42 (ddd, *J* = 11.0, 9.3, 1.7 Hz, 1H), 5.37 (s, 1H), 4.91 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.09 (m, 1H), 3.24 (s, 2H), 2.37 (m, 1H), 2.24 (m, 1H), 1.65 (m, 10H), 1.50 (m, 1H), 1.47 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 177.65, 165.2, 160.9, 145.45, 129.1, 126.4, 125.5, 108.31, 107.3, 99.4,

96.6, 73.8, 45.1, 29.6, 29.5, 28.6, 25.9, 25.2, 13.6; HRMS (ESI) calc. for $C_{22}H_{30}O_7Na$: $(M + Na)^+$, 429.1889, found: $(M + Na)^+$, 429.1890.

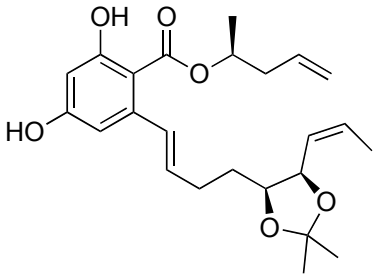
(*S*)-Pent-4-en-2-yl 2,4-dihydroxy-6-((*E*)-4-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)but-1-enyl)benzoate (360)



Diketo-dioxinone **364** (20 mg, 0.051 mmol) and commercially available alcohol **363** (50 mg, 0.58 mmol) in PhMe (5 mL) were heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (1:1; 16 mL). CsOAc (300 mg, 1.56 mmol) was added and the mixture was stirred at RT for 3 h. The solution was acidified with AcOH (1 mL, 15.9 mmol) and stirred overnight. The mixture was poured into aq. $NaHCO_3$ (sat., 15 mL), extracted with Et_2O (2 x 20 mL) and the combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave resorcylate **360** (15 mg, 0.0367 mmol, 72%) as a pale yellow oil: R*f* 0.52 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +15.0 (*c* 0.5, CH_2Cl_2); IR: 3336, 1643, 1611, 1581, 1380, 1354, 1314, 1255, 1157, 1111, 1050, 1116, 923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 6.96 (d, *J* = 15.5 Hz, 1H), 6.36 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 5.83 (m, 3H), 5,65 (s, 1H), 5.26 (m, 3H), 5.11 (m, 2H), 4.53 (t, *J* = 6.3 Hz, 1H), 4.19 (ddd, *J* = 9.5, 6.1, 4.4 Hz, 1H), 2.40 (m, 3H), 2.22 (m, 1H), 1.67 (m, 1H), 1.54 (m, 1H), 1.49 (s, 3H), 1.37 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 165.0, 160.6, 144.4,

134.4, 133.5, 131.9, 131.8, 118.8, 118.5, 108.6, 104.5, 102.4, 80.0, 77.9, 72.15, 40.4, 30.5, 29.8, 28.5, 25.9, 19.9; HRMS (CI) calc. for $C_{23}H_{34}NO_6$: $(M + NH_4)^+$, 420.2386, found: $(M + NH_4)^+$, 420.2406.

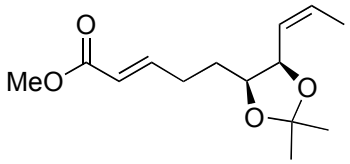
(*S*)-Pent-4-en-2-yl 2,4-dihydroxy-6-((1*E*)-4-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)but-1-enyl)benzoate (361)



Diketo-dioxinone **365** (20 mg, 0.049 mmol) and commercially available alcohol **363** (50 mg, 0.58 mmol) in PhMe (5 mL) were heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and *iso*-PrOH (1:1; 16 mL). CsOAc (300 mg, 1.56 mmol) was added and the mixture was stirred at RT for 3 h. The solution was acidified with AcOH (1 mL, 15.9 mmol) and stirred overnight. The mixture was poured into aq. $NaHCO_3$ (sat., 15 mL), extracted with Et_2O (2 x 20 mL) and the combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave resorcylate **361** (15 mg, 0.036 mmol, 74%) as a pale yellow oil: R*f* 0.56 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –15.5 (*c* 1, CH_2Cl_2); IR: 3316, 1644, 1609, 1581, 1449, 1381, 1353, 1316, 1258, 1199, 1160, 1113, 1051, 1017, 962, 922, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.70 (s, 1H), 6.95 (d, *J* = 15.5 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 5.77 (m, 4H), 5.46 (ddd, *J* = 10.9, 9.4, 1.6 Hz, 1H), 5.22 (m, 1H), 5.10 (m, 2H), 4.94 (dd, *J* = 8.7, 6.7 Hz, 1H), 4.17 (m, 1H), 2.39 (m, 3H), 2.20 (m, 1H), 1.67 (m, 4H),

1.54 (m, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.33 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 165.0, 160.6, 144.3, 133.5, 131.9, 131.8, 129.1, 126.5, 118.5, 108.6, 108.3, 104.5, 102.4, 77.8, 73.8, 72.1, 40.4, 30.35, 29.8, 28.65, 26.0, 19.85, 13.5; HRMS (CI) calc. for $C_{24}H_{33}O_6$: $(M + H)^+$, 417.2277, found: $(M + H)^+$, 417.2293.

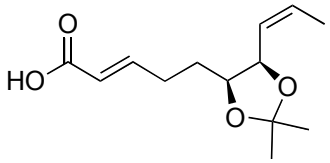
(2*E*)-Methyl 5-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)pent-2-enoate (386)



DIBAL-H in CH_2Cl_2 (1 M; 2 mL, 2 mmol) was added dropwise with stirring to alkene **376** (450 mg, 1.85 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 1.5 h, MeOH (1 mL) was carefully added and the mixture allowed to warm up to RT. Aqueous HCl (1 M; 15 mL), brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated to give the crude aldehyde (366 mg, 100%) as a colorless oil. Ylide (**385**) (800 mg, 2.6 mmol) was added to the crude aldehyde (366 mg, 2 mmol) in CH_2Cl_2 (30 mL) and the mixture stirred at reflux for 14 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 7:1) gave ester **386** (430 mg, 1.70 mmol, 85%) as a colorless oil: Rf 0.69 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –54.5 (c 1, $CHCl_3$); IR: 1725, 1660, 1438, 1383, 1371, 1275, 1213, 1166, 1044, 980, 873 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dt, J = 15.6, 6.9 Hz, 1H), 5.87 (dt, J = 15.7, 1.5 Hz, 1H), 5.75 (dqd, J = 10.9, 6.9, 0.9 Hz, 1H), 5.47 (ddq, J = 10.8, 9.3, 1.7 Hz, 1H), 4.95 (ddd, J = 9.2, 6.3, 0.7 Hz, 1H), 4.14 (m, 1H), 3.76 (s, 3H), 2.41 (m, 1H), 2.25 (m, 1H), 1.72 (dd, J = 7.0, 1.8 Hz, 3H), 1.66 (m, 1H), 1.54 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 148.9,

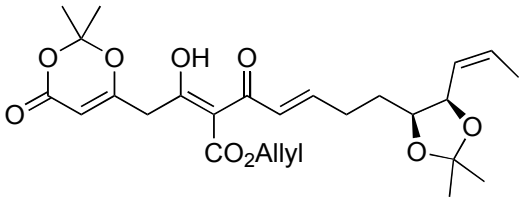
129.1, 126.5, 121.5, 108.3, 77.4, 73.8, 51.65, 29.2, 29.0, 28.6, 25.9, 13.5; HRMS (CI) calc. for $C_{14}H_{23}O_4$: $(M + H)^+$, 255.1596, found: $(M + H)^+$, 255.1598. Anal. calc. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.09; H, 8.85.

(2*E*)-5-((4*S*,5*R*)-2,2-Dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)pent-2-enoic acid (387)



$LiOH{\cdot}H_2O$ (280 mg, 6.66 mmol) was added with stirring to methyl ester **386** (340 mg, 1.33 mmol) in THF and H_2O (1:1, 20 mL). After 8 h, the mixture was carefully acidified with aq. HCl (1 M, 10 mL) and EtOAc was added (20 mL). The layers were separated and the aqueous re-extracted with EtOAc (30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:EtOAc, 1:1) gave carboxylic acid **387** (294 mg, 1.22 mmol, 92%) as a colorless oil: R*f* 0.17 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –63.8 (*c* 1, $CHCl_3$); IR: 1698, 1651, 1422, 1379, 1371, 1289, 1244, 1217, 1165, 1058, 1035, 981, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.71 (dqd, *J* = 11.2, 6.9, 0.9 Hz, 1H), 5.42 (ddq, *J* = 10.8, 9.1, 1.7 Hz, 1H), 4.91 (ddd, *J* = 8.9, 6.1, 0.7 Hz, 1H), 4.09 (m, 1H), 2.39 (m, 1H), 2.24 (m, 1H), 1.67 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.63 (m, 1H), 1.50 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 151.5, 129.2, 126.4, 121.1, 108.4, 77.4, 73.8, 29.14, 29.1, 28.6, 25.9, 13.55; HRMS (ESI) calc. for $C_{13}H_{19}O_4$: $(M - H)^+$, 239.1283, found: $(M - H)^+$, 239.1288. Anal. calc. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.92; H, 8.30.

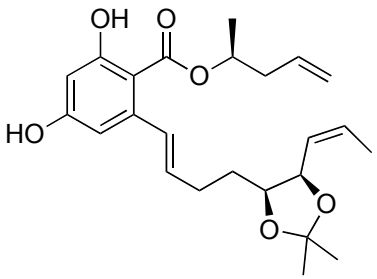
6-((2*Z*,5*E*)-2-Hydroxy-8-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)-4-oxo-3-((2-propen-1-yloxy)carbonyl)-octa-2,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (389)



Pyridine (60 μL, 0.74 mmol) was added with stirring to a suspension of dioxinone **319** (100 mg, 0.37 mmol) and $MgCl_2$ (33 mg, 0.37 mmol) in CH_2Cl_2 at 0 °C. After 30 min, acyl chloride **388**[a] (97 mg, 0.37 mmol) in CH_2Cl_2 (1 mL) was slowly added and, after a further 1 h at RT, aq. HCl (1 M; 15 mL), brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated to give allyl ester **389** (147 mg, 0.30 mmol, 81%) as a pale yellow oil: R*f* 0.31 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –34.7 (*c* 0.5, CH_2Cl_2); IR: 1732, 1639, 1596, 1544, 1391, 1377, 1273, 1250, 1206, 1070, 1016, 976, 938, 902, 870, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (dt, *J* = 15.0, 7.0 Hz, 1H), 6.64 (dd, *J* = 15.3, 1.2 Hz, 1H), 5.97 (ddt, *J* = 16.5, 10.4, 5.9 Hz, 1H), 5.71 (m, 1H), 5.39 (m, 4H), 4.91 (dd, *J* = 8.8, 6.3 Hz, 1H), 4.71 (d, *J* = 5.9 Hz, 2H), 4.10 (ddd, *J* = 9.8, 6.0, 4.2 Hz, 1H), 3.68 (s, 2H), 2.44 (m, 1H), 2.28 (m, 1H), 1.64 (m, 10H), 1.51 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 182.5, 166.3, 165.3, 161.0, 149.6, 131.6, 129.2, 126.4, 124.0, 119.9, 108.3, 107.4, 107.3, 96.8, 73.8, 66.3, 44.2, 30.1, 29.4, 28.6, 25.9, 25.2, 13.6; HRMS (ESI) calc. for $C_{26}H_{34}O_9Na$: $(M + Na)^+$, 513.2101, found: $(M + Na)^+$, 513.2098.

[a] Acid choride **388** was prepared by the addition of oxalyl choride (43 μL, 0.48 mmol) and 1 drop of dry DMF to acid **387** (90 mg, 0.37 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 1.5 h and the solvent was evaporated under vacuum. The crude material was used directly in the acylation step.

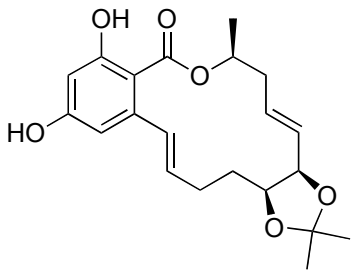
Synthesis of (*S*)-pent-4-en-2-yl 2,4-dihydroxy-6-((1*E*)-4-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)but-1-enyl)benzoate (361) from 6-((2*Z*,5*E*)-2-hydroxy-8-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)-4-oxo-3-((2-propen-1-yloxy)carbonyl)-octa-2,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (389)



Morpholine (28 μL, 0.32 mmol) was added with stirring to allyl ester **389** (80 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) at 0 °C followed immediately by the addition of $Pd(PPh_3)_4$ (9.2 mg, 0.016 mmol) in CH_2Cl_2 (1 mL). After 30 min at 0 °C, aq. HCl (1 M; 15 mL), brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated to give diketo-dioxinone **365** as a pale yellow oil. PhMe (5 mL) and alcohol **363** (100 mg, 1.16 mmol) were added and the mixture heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (1:1; 16 mL) when CsOAc (500 mg, 2.6 mmol) was added and the mixture stirred at RT for 3 h. The solution was acidified with AcOH (1 mL, 15.9 mmol), stirred overnight, added to aq. $NaHCO_3$ (sat., 15 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave resorcylate **361** (30 mg, 0.072 mmol, 44%) as a pale yellow oil: R*f* 0.56 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –15.5 (*c* 1, CH_2Cl_2); IR: 3316, 1644, 1609, 1581, 1449, 1381, 1353, 1316, 1258, 1199, 1160, 1113, 1051, 1017, 962, 922, 864 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.70 (s, 1H), 6.95 (d, *J* = 15.5 Hz, 1H), 6.35 (d, *J* =

2.3 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 5.77 (m, 4H), 5.46 (ddd, *J* = 10.9, 9.4, 1.6 Hz, 1H), 5.22 (m, 1H), 5.10 (m, 2H), 4.94 (dd, *J* = 8.7, 6.7 Hz, 1H), 4.17 (m, 1H), 2.39 (m, 3H), 2.20 (m, 1H), 1.67 (m, 4H), 1.54 (m, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.33 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 165.0, 160.6, 144.34, 133.5, 131.9, 131.8, 129.1, 126.5, 118.5, 108.6, 108.3, 104.5, 102.4, 77.8, 73.8, 72.1, 40.4, 30.35, 29.8, 28.65, 26.0, 19.85, 13.5; HRMS (CI) calc. for $C_{24}H_{33}O_6$: $(M + H)^+$, 417.2277, found: $(M + H)^+$, 417.2293.

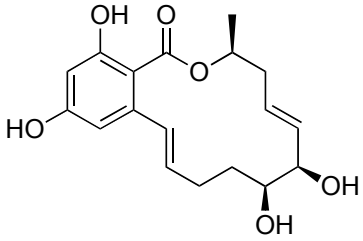
***iso*-Propylidene-aigialomycin D (392)**



Hoveyda–Grubbs II catalyst (2.25 mg, 0.0036 mmol) in PhMe (1 mL) was added to resorcylate **361** (10 mg, 0.024 mmol) in PhMe (40 mL) and the mixture was stirred at 100 °C for 1 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave macrolactone **392** (7.5 mg, 0.020 mmol, 83%) as a colorless oil: R*f* 0.38 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +15.0 (*c* 1, CH_2Cl_2); IR: 3323, 1644, 1609, 1582, 1457, 1382, 1359, 1314, 1258, 1164, 1111, 1039, 976 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.70 (s, 1H), 6.90 (d, *J* = 15.3 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.29 (d, *J* = 2.6 Hz, 1H), 5.92 (m, 1H), 5.80 (m, 2H), 5.71 (dd, *J* = 15.5 Hz, 6.4, 1H), 5.31 (m, 1H), 4.64 (t, *J* = 6.1 Hz, 1H), 4.16 (m, 1H), 2.63 (ddd, *J* = 9.6, 6.2, 2.8 Hz, 1H), 2.48 (m, 1H), 2.24 (m, 1H), 2.03 (m, 1H), 1.80 (m, 2H), 1.48 (s, 3H), 1.43 (d, *J* = 6.3 Hz, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

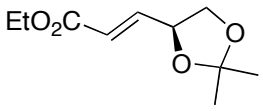
171.5, 165.2, 160.6, 143.8, 132.4, 130.6, 128.4, 128.2, 108.1, 107.7, 104.8, 102.5, 78.8, 77.8, 72.3, 38.4, 30.6, 29.3, 28.3, 25.9, 19.3; HRMS (CI) calc. for $C_{21}H_{27}O_6$: $(M + H)^+$, 375.1808, found: $(M + H)^+$, 375.1804.

Aigialomycin D (27)



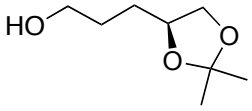
Aqueous HCl (1 M; 1 mL) was added with stirring to macrolactone **392** (10 mg, 0.0267 mmol) in MeOH (1 mL) at RT. After 1 h, EtOAc (10 mL) and brine (10 mL) were added, the layers separated and the organic layer was dried ($MgSO_4$) and rotary evaporated. Chromatography (100% EtOAc) gave aigialomycin D (**27**) (8.5 mg, 0.0254 mmol, 95%) as a white solid: R*f* 0.49 (100% EtOAc); $[\alpha]_D^{25}$ –24.2 (*c* 0.5, MeOH); IR: 3287, 1642, 1608, 1581, 1449, 1385, 1354, 1312, 1257, 1201, 1169, 1128, 1110, 1055, 1033, 973, 1019, 850, 806 cm^{-1}; ^1H NMR (400 MHz, *d6*-acetone) δ 11.67 (s, 1H), 9.11 (s, 1H), 7.16 (d, *J* = 15.9 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 2.4 Hz, 1H), 6.09 (dt, *J* = 15.8, 5.5 Hz, 1H), 5.88 (m, 1H), 5.69 (dd, *J* = 15.7, 5.0 Hz, 1H), 5.44 (m, 1H), 4.35 (*br*s, 1H), 3.77 (d, *J* = 3.8 Hz, 1H, OH), 3.63 (m, 1H), 3.56 (d, *J* = 6.3 Hz, 1H, OH), 2.57 (ddd, *J* = 14.15, 7.4, 3.2 Hz, 1H), 2.44 (m, 1H), 2.34 (m, 2H), 2.15 (m, 1H), 1.58 (m, 1H), 1.39 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, *d6*-acetone) δ 172.3, 166.0, 163.2, 144.5, 135.90, 133.8, 130.8, 125.5, 107.9, 104.5, 102.6, 76.6, 73.3, 73.1, 38.05, 28.7, 28.1, 19.2; HRMS (CI) calc. for $C_{18}H_{26}NO_6$: $(M + NH_4)^+$, 352.1760, found: $(M + NH_4)^+$, 352.1761.

(*S*,*E*)-Ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (408)



Sodium periodate (9.8 g, 45 mmol) in H_2O (50 mL) was slowly added with stirring to diol **407** (10 g, 38 mmol) in H_2O (100 mL) at 0 ºC. The reaction was stirred at RT for 2 h then recooled to 0 ºC. Ethyl(triphenylphosphoranylidene)acetate **371** (35 g, 100 mmol) was added and the reaction stirred at RT for 6 h. EtOAc (200 mL) was added and the layer separated. The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (EtOAc:Hexanes, 1:1 to 1.5:1) gave *E*-alkene **408** (7.5 g, 35 mmol, 92%) as a colorless oil: R*f* 0.6 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +109.8 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 11.6, 6.6 Hz, 1H), 5.81 (dd, *J* = 11.6, 1.7 Hz, 1H), 5.47 (qd, *J* = 6.8, 1.7 Hz, 1H), 4.35 (dd, *J* = 8.2, 7.0 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 8.2, 6.7 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.85, 149.4, 121.0, 109.9, 73.7, 69.6, 60.6, 26.8, 25.6, 14.4.

(*S*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)propan-1-ol (409)

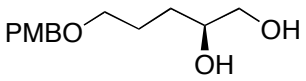


Pd on charcoal (10%, 2.50 g) was added to a solution of the unsaturated ester **408** (12.50 g, 62.4 mmol) in EtOH (250 mL). The black mixture was evacuated and back-filled with hydrogen for four cycles and then stirred under H_2 (ca. 1 atm) for 2.5 h. The mixture was diluted with EtOH (100 mL) and filtered through a pad of Celite, and the residue was

washed with EtOH (2 x 30 mL). Rotary evaporation gave the saturated ester (12.15 g, 60 mmol, 96%) as a colorless liquid: R*f* 0.42 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ +5.1 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (m, 4H), 3.52 (dd, *J* = 7.8, 6.7 Hz, 1H), 2.39 (m, 2H), 1.85 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 109.2, 75.2, 69.3, 60.6, 30.65, 29.0, 27.1, 25.8, 14.4.

$LiAlH_4$ (1 M in THF; 65 mL, 65 mmol) was slowly added with stirring to the saturated ester (12 g, 59 mmol) in THF (200 mL) at –78 °C. After 30 min, the reaction was warmed up to 0 ºC and stirred for 1.5 h. Et_2O (200 mL) was added followed by the very slow addition of H_2O (2.7 mL), NaOH (15%, 2.7 mL), H_2O (8.1 mL) and $MgSO_4$. Filtration of the salts, removal of the solvent and purification by chromatography (Hexanes:Et_2O, 1:4) afforded the terminal alcohol **409** (8.1 g, 50.6 mmol, 86%) as a colorless oil: R*f* 0.14 (Et_2O:Hexanes, 2:1); $[\alpha]_D^{25}$ +12.1 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.08 (m, 1H), 4.02 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.63 (dd, *J* = 7.4, 2.8 Hz, 2H), 3.49 (t, *J* = 7.3 Hz, 1H), 2.21 (t, *J* = 5.6 Hz, 1H), 1.63 (m, 4H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.15, 76.2, 69.7, 62.8, 30.4, 29.4, 27.1, 25.9.

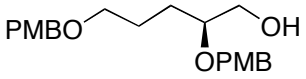
(*S*)-5-(4-Methoxybenzyloxy)pentane-1,2-diol (410)



NaH (60% in oil, 1.5 g, 37 mol) was added with stirring to alcohol **409** (5.0 g, 31 mmol) in THF at 0 ºC. After 1 h, TBAI (500 mg, 1.35 mol) and PMBCl (5 mL, 32 mmol) were added and the reaction stirred at 60 ºC for 6 h. The crude reaction mixture was cooled to RT and slowly added to aq. HCl (2 M; 100 mL) and stirred for 2 h. EtOAc (100 mL) and brine (200 mL) were added and the layers separated. The aqueous was extracted with EtOAc

(100 mL) and the combined organic layers dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:EtOAc, 1:1 to 1:5) gave diol **410** (4.55 g, 18.9 mmol, 61%) as a colorless oil: R*f* 0.12 (Et_2O:Hexanes, 2:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 1H), 6.85 (m, 1H), 4.42 (s, 2H), 3.78 (s, 3H), 3.66 (m, 1H), 3.56 (dt, *J* = 6.0, 3.0 Hz, 1H), 3.47 (td, *J* = 6.1, 1.8 Hz, 1H), 3.40 (dd, *J* = 11.0, 7.4 Hz, 1H), 1.71 (m, 2H), 1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 130.2, 129.6, 114.1, 73.0, 72.1, 70.4, 67.0, 55.5, 31.0, 26.3; LCMS, 100%, $(M + Na)^+$, 263.2.

(*S*)-2,5-bis(4-Methoxybenzyloxy)pentan-1-ol (412)

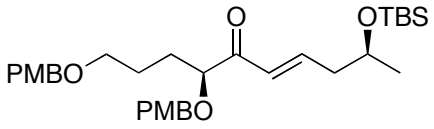


A solution of diol **410** (4.5 g, 18.8 mmol), *p*-methoxybenzaldehyde dimethyl acetal (**344**) (5.7 mL, 34 mmol) and CSA (450 mg, 1.9 mmol) in CH_2Cl_2 (40 mL) was refluxed for 14 h. The reaction was quenched with Et_3N before all volatiles were evaporated and the residue was purified by flash chromatography (Hexanes:Et_2O, 2:1 to 1:1) to afford acetal **411** (5.12 g, 13.8 mol, 73%) as an orange oil.

DIBAL-H (1 M in toluene; 20 mL, 20 mmol) was slowly added to a solution of acetal **411** (3.5 g, 10 mmol) in toluene (40 mL) at 0 ºC. The mixture was allowed to warm to RT. After 3 h, MeOH (3 mL) was carefully added and the mixture was stirred at RT for 30 min. Aqueous HCl (1 M; 150 mL), brine (300 mL) and Et_2O (500 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated. Purification by chromatography (Hexanes:Et_2O, 1:3) gave primary alcohol **412** (1.8 g, 4.8 mmol, 48%) as a colorless oil: R*f* 0.18 (Et_2O:Hexanes, 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 4H), 6.85 (m, 4H), 4.48 (dd, *J* = 24.7, 11.2 Hz, 2H), 4.41 (s, 2H), 3.78 (s, 6H), 3.65 (dt, *J* = 10.1

Hz, 6.5, 1H), 3.47 (m, 4H), 1.95 (dd, *J* = 6.9, 5.2 Hz, 1H), 1.65 –1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 159.4, 130.8, 130.7, 129.6, 129.45, 114.1, 114.0, 79.3, 72.8, 71.4, 70.1, 64.4, 55.5, 27.75, 25.8; LCMS, 100%, $(M + Na)^+$, 383.2.

(4*S*,9*S*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxybenzyloxy)dec-6-en-5-one (414)



Dess–Martin periodinane (3.1 g, 7.3 mmol) was added with stirring to a solution of alcohol **412** (1.73 g, 4.8 mmol) in CH_2Cl_2 (50 mL). After 5 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 50 mL) and aq. Na_2SO_3 (sat., 50 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give aldehyde **406** (1.70 g, 4.75 mmol, 99%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, *J* = 2.1 Hz, 1H), 7.23 (m, 4H), 6.85 (m, 4H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.38 (s, 2H), 3.78 (s, 6H), 3.73 (m, 1H), 3.40 (t, *J* = 5.3 Hz, 2H), 1.75 – 1.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.85, 159.7, 159.4, 130.7, 130.0, 129.9, 129.6, 129.4, 114.1, 114.0, 83.0, 72.7, 72.4, 69.5, 55.5, 27.0, 25.3; LCMS, $(M + Na)^+$, 381.2.

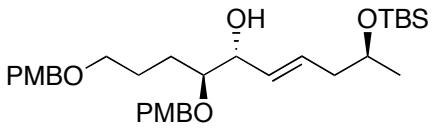
*n*BuLi (2.5 M; 2.1 mL, 5.3 mmol) was added to a solution of alkyne **338**[189] (1.23 g, 6.2 mmol) in dry THF (50 mL) at –78 ºC. The mixture was allowed to warm to 0 ºC and after 30 min recooled to –78 ºC. Aldehyde **406** (1.7 g, 4.75 mmol) in THF (2 mL) was slowly added with stirring. After 30 min at –78 ºC and 30 min at 0 ºC, the reaction was quenched with aq. HCl (1 M; 30 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and rotary

evaporated. Chromatography (Hexanes:Et_2O, 3:1 to 1:1) gave alcohol **413** (1.8 g, 3.23 mmol, 68%) as a mixture of diastereoisomers.

REDAl-H (65% wt in PhMe; 4.55 mL, 10.6 mmol) was slowly added to a solution of alkyne **413** (1.7 g, 3.05 mmol) in PhMe (100 mL) at 0 ºC. The reaction mixture was warmed to RT and stirred for 6 h. Aqueous HCl (0.5 M; 150 mL), brine (100 mL) and Et_2O (250 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (25 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1) gave the corresponding *trans*-alkene (1.4 g, 2.9 mmol, 82%) as a colorless oil and as a mixture of diastereoisomers.

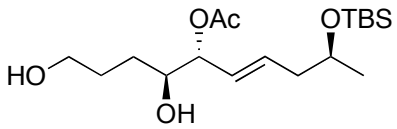
Dess–Martin periodinane (1.6 g, 3.7 mmol) was added with stirring to a solution of the above *trans*-alkene (1.4 g, 2.46 mmol) in CH_2Cl_2 (100 mL) at 0 ºC. After 5 h, the reaction was quenched with aq. $NaHCO_3$ (sat., 50 mL) and aq. Na_2SO_3 (sat., 50 mL) and the mixture stirred for 30 min. The organic layer was dried ($MgSO_4$) and rotary evaporated to give ketone **414** (1.34 g, 2.40 mmol, 97%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 4H), 7.00 (dt, *J* = 15.3, 7.5 Hz, 1H), 6.84 (m, 4H), 6.49 (dt, *J* = 15.6, 1.3 Hz, 1H), 4.46 (t, *J* = 12.5 Hz, 1H), 4.37 (s, 2H), 4.26 (d, *J* = 11.3 Hz, 1H), 3.89 (ddd, *J* = 12.5, 10.6, 6.2 Hz, 2H), 3.78 (d, *J* = 0.9 Hz, 6H), 3.37 (m, 2H), 2.32 (m, 2H), 1.66 (m, 4H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.85 (s, 9H), 0.02 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 159.6, 159.3, 146.1, 130.8, 130.0, 129.8, 129.4, 126.9, 114.0, 114.0, 83.7, 72.7, 72.0, 69.7, 67.8, 55.5, 43.2, 29.4, 26.0, 25.8, 24.0, 18.3, –4.3, –4.6; LCMS, 100%, $(M + Na)^+$, 579.4.

(4*S*,5*R*,9*S*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxybenzyloxy)dec-6-en-5-ol (415)



REDAl-H (65% wt in PhMe; 0.87 mL, 2.9 mmol) was slowly added to a solution of ketone **414** (1.34 g, 2.41 mmol) in PhMe (50 mL) at 0 ºC then warmed to RT and stirred for 1 h. The reaction was slowly poured into aq. HCl (1 M; 50 mL), Et_2O (50 mL) was added and the layers separated. The aqueous was extracted with 50 mL of Et_2O and the organic combined dried ($MgSO_4$). Chromatography (SiO_2, Et_2O:Hexanes, 1:3) gave alcohol **415** (700 mg, 1.25 mmol, 52%) as a colorless oil and as a single diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 4H), 6.85 (m, 4H), 5.70 (dtd, *J* = 7.8, 7.0, 0.8 Hz, 1H), 5.49 (dd, *J* = 15.5, 6.6 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.39 (s, 2H), 4.23 (dt, *J* = 6.7, 3.4 Hz, 1H), 3.83 (m, 1H), 3.79 (s, 6H), 3.38 (m, 2H), 2.16 (m, 2H), 1.64 (m, 4H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.02 (d, *J* = 0.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 159.3, 130.9, 130.7, 130.6, 130.4, 129.7, 129.4, 114.1, 114.0, 81.9, 73.4, 72.7, 72.0, 70.2, 68.6, 55.5, 43.0, 26.2, 26.2, 26.1, 23.65, 18.35, –4.3, –4.5; LCMS, 100%, $(M + Na)^+$, 581.3.

(4*S*,5*R*,9*S*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-1,4-dihydroxydec-6-en-5-yl acetate (416)

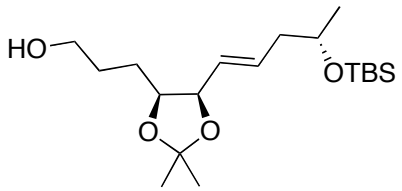


Et_3N (0.2 mL, 1.44 mmol), DMAP (14 mg, 0.12 mmol) and Ac_2O (0.14 mL, 1.44 mmol) were added with stirring to a solution of alcohol **415** (670 mg, 1.20 mmol) in Et_2O (30 mL).

After 12 h at RT, the solution was poured onto aq. HCl (1 M; 50 mL) and the organic layer washed with aq. $NaHCO_3$ (sat., 50 mL), brine (50 mL), dried ($MgSO_4$) and rotary evaporated to give the corresponding acetate (700 mg, 1.16 mmol, 97%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 4H), 6.84 (m, 4H), 5.73 (dt, *J* = 14.5, 7.1 Hz, 1H), 5.50 (dd, *J* = 15.1, 7.2 Hz, 1H), 5.42 (dd, *J* = 7.2, 2.8 Hz, 1H), 4.61 (t, *J* = 9.0 Hz, 1H), 4.38 (d, *J* = 10.9 Hz, 1H), 4.38 (s, 2H), 3.82 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.42 (m, 3H), 2.15 (m, 2H), 2.04 (s, 3H), 1.75 (m, 1H), 1.53 (m, 3H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 159.45, 159.35, 132.75, 130.9, 130.8, 129.85, 129.4, 126.7, 114.0, 80.0, 75.8, 72.7, 72.3, 70.1, 68.5, 55.5, 42.9, 27.5, 26.3, 26.1, 23.7, 21.5, 18.3, –4.3, –4.5; LCMS, 100%, $(M + Na)^+$, 623.3.

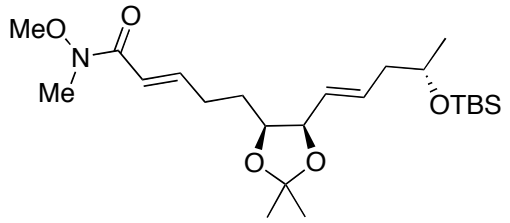
DDQ (880 mg, 3.88 mmol) was added with stirring to the above acetate (903 mg, 1.55 mmol) in CH_2Cl_2:H_2O (9:1, 30 mL). After 4 h at RT, aq. $NaHCO_3$ (sat., 50 mL) and Et_2O (50 mL) were added and the layers separated. The aqueous was extracted with Et_2O (50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1 to 100% Et_2O) gave diol **416** (400 mg, 1.11 mmol, 72%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.50 (ddt, *J* = 15.5, 7.7, 1.2 Hz, 1H), 5.17 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.83 (m, 1H), 3.68 (m, 3H), 2.17 (m, 2H), 2.06 (s, 3H), 1.64 (m, 3H), 1.43 (m, 1H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 134.1, 125.8, 78.1, 73.2, 68.3, 63.0, 42.85, 29.7, 29.45, 26.1, 23.6, 21.5, 18.3, –4.3, –4.5; LCMS, 100%, $(M + Na)^+$, 383.2.

3-((4*S*,5*R*)-5-((*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (418)



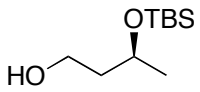
K_2CO_3 (460 mg, 3.33 mmol) was added with stirring to acetate **416** (400 mg, 1.11 mmol) in MeOH (30 mL). After 2 h, the solvent is removed and Et_2O (30 mL) and aq. $NaHCO_3$ (sat., 50 mL) were added and the layers separated. The organic phase was washed with brine (50 mL), dried ($MgSO_4$) and the solvent rotary evaporated. CH_2Cl_2 (50 mL), 2,2-dimethoxypropane (0.21 mL, 1.66 mmol) and CSA (80 mg, 0.33 mmol) were added and the mixture stirred for 3 h at RT. Aqueous $NaHCO_3$ (sat., 50 mL) was added and the layers separated. The organic phase was dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1) afforded acetal **418** (300 mg, 0.84 mmol, 76%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.44 (ddt, *J* = 15.3, 8.2, 1.1 Hz, 1H), 4.48 (dd, *J* = 8.2, 6.3 Hz, 1H), 4.10 (dt, *J* = 7.4, 6.0 Hz, 1H), 3.83 (m, 1H), 3.64 (m, 2H), 2.17 (m, 2H), 1.99 (t, *J* = 5.7 Hz, 1H), 1.66 (m, 3H), 1.51 (m, 1H), 1.46 (s, 3H), 1.34 (s, 3H), 1.09 (d, *J* = 6.1 Hz, 3H), 0.85 (s, 9H), 0.02 (d, *J* = 1.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.5, 128.1, 108.2, 80.0, 78.6, 68.4, 62.9, 42.85, 30.05, 28.5, 27.8, 26.1, 25.9, 23.7, 18.3, –4.3, –4.5; LCMS, 100%, $(M + Na)^+$, 381.2.

(*E*)-5-((4*S*,5*R*)-5-((*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-methoxy-*N*-methylpent-2-enamide (403)



NMO (117 mg, 1 mmol) and TPAP (27 mg, 0.0756 mmol) were sequentially added to alcohol **418** (275 mg, 0.77 mmol) in CH_2Cl_2 (100 mL). The solution was stirred for 2 h and the solvent rotary evaporated. The crude material was dissolved in Et_2O (5 mL) and filtered through a short pad of silica eluted with Et_2O to give the corresponding aldehyde (265 mg, 0.745 mmol, 84%) as a colorless oil. Ylide **377** (280 mg, 0.77 mmol) was added to the above aldehyde (265 mg, 0.745 mmol) in CH_2Cl_2 (30 mL) and the reaction stirred at reflux for 14 h. Rotary evaporation and chromatography (Hexanes:Et_2O, 1:1) gave (*E*)-amide **403** (300 mg, 0.68 mmol, 91%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 15.1, 7.0 Hz, 1H), 6.40 (d, *J* = 15.4 Hz, 1H), 5.72 (m, 1H), 5.43 (dd, *J* = 15.4, 8.3 Hz, 1H), 4.46 (dd, *J* = 8.1, 6.3 Hz, 1H), 4.08 (ddd, *J* = 9.9, 6.0, 4.3 Hz, 1H), 3.82 (dt, *J* = 14.1, 7.0 Hz, 1H), 3.67 (s, 3H), 3.21 (s, 3H), 2.38 (m, 1H), 2.27 (dt, *J* = 23.4, 8.0 Hz, 1H), 2.18 (m, 2H), 1.64 (m, 1H), 1.51 (m, 1H), 1.46 (s, 3H), 1.33 (s, 3H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 146.9, 132.6, 127.9, 119.45, 108.2, 79.7, 68.4, 61.9, 42.8, 32.6, 29.7, 29.3, 28.5, 26.1, 25.9, 23.65, 18.3, –4.3, –4.5; HRMS (ESI) calc. for $C_{23}H_{43}NO_5SiNa$: $(M + Na)^+$, 464.2808, found: $(M + Na)^+$, 464.2789; Anal. Calc. for $C_{23}H_{43}NO_5Si$: C, 62.54; H, 9.82; N, 3.17. Found C, 62.63; H, 9.85; N, 3.17.

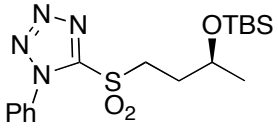
(*S*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol (421)



2,6-Lutidine (3.05 mL, 26.1 mmol) was added to a solution of methyl 3(*S*)-hydroxybutanoate **420** (1.80 mL, 16.3 mmol) in CH_2Cl_2 (50 mL) at 0 ºC followed by the dropwise addition of TBSOTf (5.0 g, 16.3 mmol) over 30 min. The resulting mixture was warmed to RT and stirred for 3 h. Aqueous HCl (1 M; 50 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the protected ester (11.6 g, 16.3 mmol) as a pale yellow oil.

DIBAL-H in CH_2Cl_2 (1 M; 20 mL, 20 mmol) was added dropwise with stirring to the above ester (4 g, 17.2 mmol) in CH_2Cl_2 (100 mL) at –78 °C. After 1.5 h, the reaction was warmed up to 0 ºC and stirred at this temperature for 1 h. MeOH (2 mL) was carefully added and the mixture allowed to warm up to RT. Aqueous HCl (1 M; 50 mL), brine (50 mL) and Et_2O (150 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:2) gave alcohol **421** (3 g, 14.7 mmol, 85%) as a colorless oil: R*f* 0.23 (Et_2O:Hexanes, 2:1); $[\alpha]_D^{25}$ +25.1 (*c* 2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (pd, *J* = 6.2, 4.1 Hz, 1H), 3.82 (m, 1H), 3.70 (m, 1H), 2.53 (t, *J* = 5.3 Hz, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.87 (s, 9H), 0.07 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.6, 60.7, 40.7, 26.0, 23.6, 18.2, –4.1, –4.7; LCMS, 100%, $(M + H)^+$, 205.2.

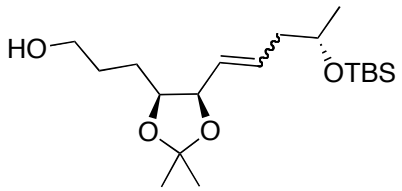
(*S*)-5-(3-(*tert*-Butyldimethylsilyloxy)butylsulfonyl)-1-phenyl-1*H*-tetrazole (300)



DEAD (5.55 mL, 35 mmol) in THF (20 mL) was slowly added with stirring to a solution containing alcohol **421** (5.6 g, 27 mmol), PPh_3 (9.25 g, 35 mmol) and 1-phenyl-1H-tetrazole-5-thiol (**422**) (6.3 g, 35 mmol) in THF (250 mL). The reaction mixture was stirred for 2 h before being quenched with aq. $NaHCO_3$ (sat., 250 mL), and extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried ($MgSO_4$) and rotary evaporated to give the corresponding sulfide (9.2 g, 25,2 mmol, 93%) as a colorless oil directly used in the next step.

$NaHCO_3$ (2.3 g, 28 mmol) and *m*-CPBA (70%, 6.7 g, 28 mmol) were added with stirring at 0 ºC to a solution of the above sulfide (4.6 g, 12.6 mmol) in CH_2Cl_2 (100 mL) and the mixture was stirred at RT for 12 h. Aqueous $Na_2S_2O_3$ (sat., 200 mL) and EtOAc (200 mL) were added and the layers separated. The aqueous was extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:Et_2O, 2:1) gave sulfone **300** (3.6 g, 9.1 mmol, 72%) as a colorless oil: R*f* 0.25 (Et_2O:Hexanes, 1:2); $[\alpha]_D^{25}$ +12.5 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 5H), 4.02 (m, 1H), 3.80 (m, 2H), 2.03 (m, 2H), 1.18 (d, *J* = 6.1 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 133.3, 131.7, 129.9, 125.3, 66.45, 53.0, 31.5, 26.0, 25.85, 23.7, 18.2, –4.15, –4.65; LCMS, 100%, $(M - H)^+$, 395.1.

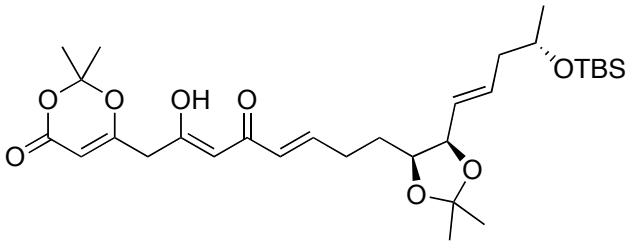
3-((4*S*,5*R*)-5-((*S*)-4-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (418)



KHMDS in PhMe (0.5 M; 1 mL, 0.5 mmol) was added dropwise to sulfone **300** (300 mg, 0.5 mmol) in dry DME (10 mL) and the resulting pale yellow solution stirred at –78 °C for 1 h after which time aldehyde **373** (155 mg, 0.5 mmol) in DME (1 mL) was added. The reaction temperature was maintained at –78 °C for 30 min and warmed up to 0 ºC. After 1 h, the mixture was poured onto aq. HCl (1 M; 10 mL) and Et_2O (30 mL) was added. The organic phase was washed with brine (3 × 30 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O 3:1) gave the corresponding alkene (210 mg, 0.53 mmol) as a colorless oil and as a mixture of regioisomers (*E*:*Z* = 4:1) contaminated with residual sulfone **300**. DIBAL-H in CH_2Cl_2 (1 M; 1.5 mL, 1.5 mmol) was added dropwise with stirring to a solution of the above mixture of regioisomers (400 mg, 1.75 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 1.5 h, MeOH (1 mL) was carefully added and the mixture allowed to warm up to RT. Aqueous HCl (1 M; 15 mL), brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:1) afforded alcohol **418** (150 mg, 0.42 mmol, 84%), a colorless oil, as a mixture of regioisomers (*E*:*Z* = 4:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.44 (ddt, *J* = 15.3, 8.2, 1.1 Hz, 1H), 4.86 (ddd, J = 9.1, 6.1, 0.8, 0.2H), 4.48 (dd, *J* = 8.2, 6.3 Hz, 0.8H), 4.10 (dt, *J* = 7.4, 6.0 Hz, 1H), 3.83 (m, 1H), 3.64 (m, 2H), 2.17 (m, 2H), 1.99 (t, *J* = 5.7 Hz, 1H), 1.66 (m, 3H), 1.51 (m, 1H), 1.46 (s, 3H), 1.34 (s, 3H), 1.09

(d, J = 6.1 Hz, 3H), 0.85 (s, 9H), 0.02 (d, J = 1.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.5, 128.1, 108.2, 80.0, 78.6, 68.4, 62.9, 42.85, 30.05, 28.5, 27.8, 26.1, 25.9, 23.7, 18.3, –4.3, –4.5; LCMS, 100%, $(M + Na)^+$, 381.2.

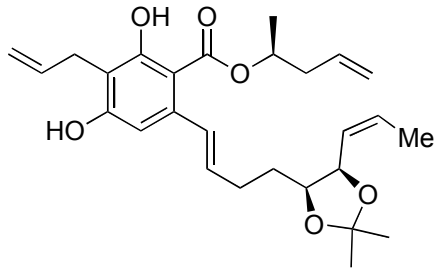
6-((2*Z*,5*E*)-8-((4*S*,5*R*)-5-((*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxy-4-oxoocta-2,5-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (423)



LDA in THF (1 M; 0.9 mL, 0.9 mmol) was added dropwise with stirring to keto-dioxinone **351** (84 mg, 0.45 mmol) in THF (8 mL) at –70 °C and the resulting cloudy yellow solution was slowly allowed to warm up to –40 °C. Weinreb amide **403** (100 mg, 0.23 mmol) in THF (2 mL) was slowly added and the mixture stirred at –40 °C for 1 h and poured into aq. HCl (1 M; 25 mL). Et_2O was added (25 mL), the layers separated and the aqueous layer washed with Et_2O (25 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 1:3) gave diketo-dioxinone **423** (35 mg, 0.062 mmol, 27%) as a colorless oil: R*f* 0.33 (Et_2O:Hexanes, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (dt, J = 14.3, 6.5 Hz, 1H), 5.83 (d, J = 15.5 Hz, 1H), 5.71 (m, 1H), 5.48 (s, 1H), 5.42 (m, 1H), 5.37 (s, 1H), 4.48 (dd, J = 8.0, 6.3 Hz, 1H), 4.06 (m, 1H), 3.83 (m, 1H), 3.24 (s, 2H), 2.38 (m, 1H), 2.32 (m, 1H), 2.17 (m, 2H), 1.67 (s, 6H), 1.59 (m, 1H), 1.51 (m, 1H), 1.44 (s, 3H), 1.33 (s, 3H), 1.09 (d, J = 6.1 Hz, 3H), 0.85 (s, 9H), 0.02 (d, J = 1.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 177.6,

165.2, 160.9, 145.4, 132.9, 127.7, 125.5, 108.3, 107.3, 99.45, 96.6, 79.7, 68.4, 45.1, 42.9, 29.75, 29.6, 28.5, 26.1, 25.9, 25.2, 23.7, 18.3, –4.3, –4.5; LCMS, 100%, $(M + NH_4)^+$, 582.3.

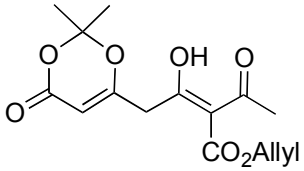
(*S*)-Pent-4-en-2-yl 3-allyl-6-((*E*)-4-((4*S*,5*R*)-2,2-dimethyl-5-((*Z*)-prop-1-enyl)-1,3-dioxolan-4-yl)but-1-enyl)-2,4-dihydroxybenzoate (424)



A solution of the $Pd(PPh_3)_4$ (9.2 mg, 0.016 mmol) in CH_2Cl_2 (1 mL) was added with stirring to a solution of allyl ester **389** (80 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min at 0 °C, brine (30 mL) and Et_2O (50 mL) were added and the organic layer separated, dried ($MgSO_4$) and rotary evaporated to give diketo-dioxinone **426** as a pale yellow oil. PhMe (5 mL) and alcohol **363** (100 mg, 1.16 mmol) were added and the mixture heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (1:1; 16 mL) when CsOAc (500 mg, 2.6 mmol) was added and the mixture stirred at RT for 3 h. The solution was acidified with AcOH (1 mL, 15.9 mmol), stirred overnight, added to aq. $NaHCO_3$ (sat., 15 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave resorcylate **424** (30 mg, 0.072 mmol, 42%) as a pale yellow oil: R*f* 0.60 (Et_2O:Hexanes, 1:1); $[\alpha]_D^{25}$ –29.4 (*c* 1, CH_2Cl_2); IR: 3338, 1639, 1613, 1590, 1315, 1266, 1216, 1120, 993, 965, 865 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 6.94 (d, *J* = 15.5 Hz, 1H), 6.38 (s, 1H), 5.97 (ddt, *J* = 16.1, 10.1, 6.1 Hz,

1H), 5.76 (m, 3H), 5.46 (m, 1H), 5.40 (s, 1H), 5.24 (hept, *J* = 6.3 Hz, 1H), 5.15 (ddd, *J* = 9.1, 3.2, 1.5 Hz, 1H), 5.10 (m, 3H), 4.93 (dd, *J* = 8.9, 6.3 Hz, 1H), 4.16 (ddd, *J* = 9.6, 5.9, 4.5 Hz, 1H), 3.45 (d, *J* = 6.0 Hz, 2H), 2.40 (m, 3H), 2.20 (m, 1H), 1.68 (dd, *J* = 7.0, 1.7 Hz, 3H), 1.67 (m, 2H), 1.47 (s, 3H), 1.37 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 162.5, 159.1, 141.9, 136.0, 133.6, 131.89, 131.4, 128.9, 126.7, 118.45, 116.1, 111.4, 108.4, 108.2, 104.4, 77.8, 73.8, 72.1, 40.4, 30.4, 29.8, 28.7, 27.4, 26.0, 19.9, 13.5; HRMS (CI) calc. for $C_{27}H_{36}O_6Na$: $(M + Na)^+$, 479.2410, found: $(M + Na)^+$, 479.2422.

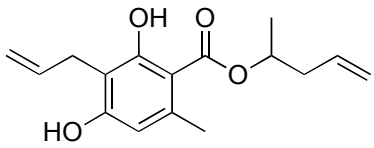
Allyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybut-2-enoate (427)



Pyridine (80 μL, 0.99 mmol) was added with stirring to a suspension of dioxinone **319**[182] (100 mg, 0.37 mmol) and $MgCl_2$ (42 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC. After 30 min, acetic chloride (40 μL, 0.56 mmol) was slowly added and, after a further 30 min at RT, aq. HCl (1 M; 5 mL) and brine (5 mL) were added. The mixture was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried ($MgSO_4$). Rotary evaporation gave diketo-dioxinone **427** (104 mg, 0.34 mmol, 91%) as a pale yellow oil and was used in the next step without further purification: R_f 0.36 (Et_2O:Hexanes, 2:1); IR: 3421, 2924, 2852, 1726, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.92 (m, 1H), 5.41 – 5.30 (m, 3H), 4.71 (d, *J* = 6.0 Hz, 2H), 3.74 (s, 2H), 2.43 (s, 3H), 1.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 193.8, 165.9, 165.1, 160.7, 131.5, 119.7, 108.2,

107.2, 96.5, 65.9, 43.2, 25.6, 24.9; HRMS (ESI) calc. for $C_{15}H_{19}O_7$: $(M + H)^+$, 311.1131, found: $(M + H)^+$, 311.1123.

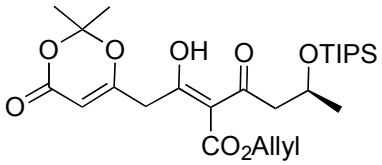
Pent-4-en-2-yl 3-allyl-2,4-dihydroxy-6-methylbenzoate (429)



A solution of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in THF (2 mL) was added with stirring to a solution of allyl ester **427** (104 mg, 0.34 mmol) in THF (5 mL) at 0 °C. After 15 min at 0 °C followed by 15 min at RT, brine (5 mL) was added and the mixture extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give a pale yellow oil. PhMe (5 mL) and pent-4-en-2-ol (±)-**363** (0.2 mL, 1.94 mmol) were added and the mixture heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (5:3; 8 mL) then CsOAc (200 mg, 1.04 mmol) was added and the mixture stirred at RT for 2 h. The solution was acidified with AcOH (0.5 mL, 8.74 mmol) and stirred 4 h at RT. Aqueous $NaHCO_3$ (sat., 10 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 3:1) gave resorcylate **429** (70 mg, 0.24 mmol, 70%) as a pale yellow oil: R_f 0.58 (Hexanes:Et_2O, 3:1); IR: 3400, 1638, 1597, 1454, 1423, 1311, 1270, 1163, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H), 6.23 (s, 1H), 6.04 – 5.94 (m, 1H), 5.87–5.77 (m, 1H), 5.46 (s, 1H), 5.28 (sex, J = 6.4 Hz, 1H), 5.18 – 5.15 (m, 2H), 5.13 – 5.09 (m, 2H), 3.46 (d, J = 6.0 Hz, 2H), 2.54 – 2.40 (m, 2H), 2.48 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 162.9, 158.7, 141.3, 135.9,

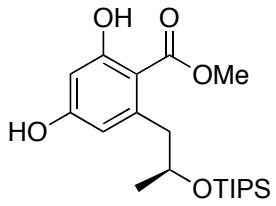
133.4, 118.2, 115.7, 111.1, 110.0, 105.7, 71.7, 40.3, 27.1, 24.5, 19.6; HRMS (ESI) calc. for $C_{16}H_{21}O_4$: $(M + H)^+$, 277.1440, found: $(M + H)^+$, 277.1445.

(5*S*)-Allyl 2-(2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl)-3-oxo-5-(tri*iso*propyl-silyloxy)hexanoate (*ent*-327)



Pyridine (120 μL, 1.51 mmol) was added with stirring to a suspension of dioxinone **319**(150 mg, 0.56 mmol) and $MgCl_2$ (64 mg, 0.67 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C giving a bright yellow solution. After 20 min, a solution of acyl chloride *ent*-**326**[182] (97 mg, 0.67 mmol) in CH_2Cl_2 (1 mL) was slowly added and, after further 15 min at 0 °C and 15 min at RT, water (25 mL) was added and the pH was adjusted to 3 by with aq. HCl (1 M). The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine and dried ($MgSO_4$). Rotary evaporation gave diketo-dioxinone *ent*-**327** (200 mg, 0.39 mmol, 70%) as a pale yellow oil and was used in the next step without further purification: R_f 0.66 (Et_2O:Hexanes, 2:1); IR: 3401, 2926, 2867, 1732, 1639, 1588, 1460, 1392, 1273, 1204, 1124, 1016, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02–5.87 (m, 1H), 5.45–5.25 (m, 3H), 4.71 (d, J = 6 Hz, 2H), 4.47 (sex, J = 6.8 Hz, 1H), 3.67 (s, 2H), 3.00 (dd, J = 14.8, 6.8 Hz, 1H), 2.81 (dd, J = 14.4, 6.0, 1H), 1.69 (s, 6H), 1.25 (s, 3H), 1.03 (*br*s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 193.2, 166.0, 164.9, 160.7, 131.4, 119.8, 109.4, 107.2, 96.6, 66.5, 66.0, 47.2, 43.0, 24.9, 24.3, 18.0, 12.4; HRMS (ESI) calc. for $C_{26}H_{43}O_8Si$: $(M + H)^+$, 511.2727, found: $(M + H)^+$, 511.2717.

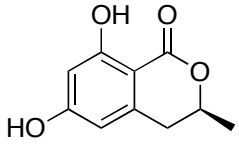
(*S*)-Methyl 2,4-dihydroxy-6-(2-(tri*iso*propylsilyloxy)propyl)benzoate (433)



Morpholine (110 μL, 1.27 mmol) was added with stirring to a solution of diketo-dioxinone *ent*-**327** (200 mg, 0.39 mmol) in THF (4 mL) at 0 °C followed immediately by the addition of $Pd(PPh_3)_4$ (65 mg, 0.06 mmol) in THF (3 mL). After 25 min at 0 °C and 30 min at RT the reaction was quenched with aq. NH_4Cl (sat., 5 mL). Water (10 mL) was added and the pH was adjusted to 4 by adding aq. HCl (1 M). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to give a pale yellow oil. PhMe (5 mL) and MeOH (130 μL, 3.08 mmol) were added and the mixture heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (5:3; 8 mL) when CsOAc (300 mg, 1.56 mmol) was added and the mixture stirred at RT for 2.5 h. The solution was acidified with AcOH (0.5 mL, 8.74 mmol) and stirred overnight. Aqueous $NaHCO_3$ (sat., 10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 2:1) gave resorcylate **433** (58 mg, 0.15 mmol, 39%) as a colourless solid: R_f 0.38 (Et_2O:Hexanes, 1:3); $[\alpha]_D^{25}$ +35.5 (*c* 0.3, $CHCl_3$); IR: 3365, 2926, 2866, 1652, 1625, 1586, 1462, 1386, 1318, 1263, 1194, 1173, 1134, 1108, 1082, 1025, 995, 952, 884 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 2.8 Hz, 1H), 5.75 (s, 1H), 4.14 (sex, *J* = 6.4 Hz, 1H), 3.91 (s, 3H), 3.13 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.93 (dd, *J* = 13.2, 8.0 Hz, 1H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.97 (*br*s, 21H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 165.1, 160.2, 145.0, 113.2, 105.3, 101.8, 69.8, 52.0, 46.7, 24.3, 18.0, 12.6; HRMS (ESI) calc. for $C_{20}H_{35}O_5Si$: $(M + H)^+$, 383.2254, found: $(M + H)^+$, 383.2263.

(*S*)-6,8-Dihydroxy-3-methylisochroman-1-one (435)

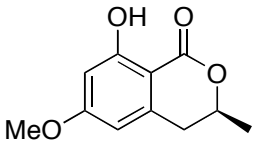


H_2SiF_6 in H_2O (20% w/w; 60 μL, 0.09 mmol) was added with stirring to resorcylate **433** (53 mg, 0.14 mmol) in MeCN (2.1 mL) at 0 °C. After 2 h at RT, the reaction mixture was poured into EtOAc (20 mL), washed with H_2O (3 x 5 mL) and dried ($MgSO_4$). Rotary evaporation gave the deprotected alcohol (32 mg, 0.14 mmol, 100%) as a colourless solid which was used in the next step without further purification: ^{1}H NMR (400 MHz, CD_3CN) δ 11.42 (s, 1H), 7.71 (s, 1H), 6.23 (s, 2H), 4.66 (sex, *J* = 4 Hz, 1H), 3.88 (s, 3H), 3.07 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.79 (dd, *J* = 12.8, 7.6 Hz, 1H), 2.33 (s, 1H), 1.43 (d, *J* = 6.4 Hz, 3H); HRMS (ESI) calc. for $C_{11}H_{15}O_5$: $(M + H)^+$, 227.0919, found: $(M + H)^+$, 227.0923.

A catalytic amount of *p*-TsOH was added with stirring to a solution of the above deprotected alcohol (32 mg, 0.14 mmol) in THF (5 mL). The mixture was heated at reflux for 2 h, cooled to RT and aq. $NaHCO_3$ (sat., 10 mL) was added. The mixture was extracted with Et_2O (3 x 25 mL) and dried ($MgSO_4$). Rotary evaporation gave resorcylate **435** (27 mg, 0.14 mmol, 100%) as a colourless solid which was used in the next step without further purification: R_f 0.32 (Et_2O:Hexanes, 2:1); IR: 3016, 2971, 2929, 1739, 1634, 1440, 1366, 1229, 1217, 1209 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 11.20 (s, 1H), 7.85 (s, 1H), 6.24 (s, 2H), 4.70 – 4.62 (m, 1H), 2.89 (dd, *J* = 16.4, 4.0 Hz, 1H), 2.81 (dd, *J* = 16.4,

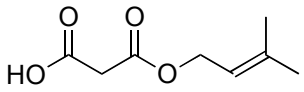
11.2 Hz, 1H), 1.43 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 170.9, 165.1, 164.7, 143.5, 118.2, 107.3, 101.9, 76.6, 34.9, 20.7; HRMS (ESI) calc. for $C_{10}H_{11}O_4$: $(M + H)^+$, 195.0657, found: $(M + H)^+$, 195.0665. Anal. calc. for $C_{10}H_{10}O_4$: C 61.85, H 5.19; found: C 61.90, H 5.21.

Angelicoin B (29)



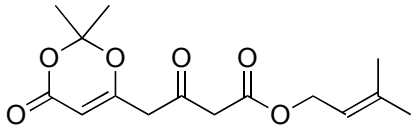
A solution of methyl iodide (4.7 μL, 0.08 mmol) in dry acetone (2 mL, dried over $CaCl_2$) was slowly added to a solution of resorcylate **435** (10 mg, 0.05 mmol) in dry acetone (1 mL) containing dry potassium carbonate (7.1 mg, 0.05 mmol). The reaction mixture was refluxed under nitrogen for 2.5 h then water was added. The mixture was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$). Rotary evaporation and chromatography (Hexanes:Et_2O, 1:2) gave angelicoin B (**28**) (11 mg, 0.05 mmol, 100%) as a colourless solid: R_f 0.25 (Et_2O:Hexanes, 1:3): $[\alpha]_D^{25}$ +21.1 (*c* 0.2, $CHCl_3$); IR: 3428, 1634, 1422, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.24 (m, 1H), 4.67 (m, 1H), 3.82 (s, 3H), 2.86 (m, 2H), 1.51 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 165.8, 164.6, 140.9, 106.2, 101.6, 99.4, 75.5, 55.5, 34.8, 20.7; HRMS (ESI) calc. for $C_{11}H_{13}O_4$: $(M + H)^+$, 209.0814, found: $(M + H)^+$, 209.0811.

3-(3-Methylbut-2-enyloxy)-3-oxopropanoic acid (439)



A solution of Meldrum's acid (**437**) (13.56 g, 94 mmol) in 3-methylbut-2-en-1-ol (**438**) (14.3 mL, 141 mmol) was refluxed for 8 h. After this period the volatiles were removed by rotary evaporation and the residue was dissolved in aq. $NaHCO_3$ (sat., 250 mL). The excess of the allylic alcohol was removed by extraction with EtOAc (3 x 200 mL). The pH of the aqueous layer was adjusted to 3 by adding aq. HCl (1 M) and the solution was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL) and dried ($MgSO_4$). Rotary evaporation gave compound **439** (7.81 g, 45.36 mmol, 48%) as a colourless oil: R_f 0.45 ($MeOH:CH_2Cl_2$, 1:9); IR: 2978, 1714, 1416, 1378, 1339, 1312, 1277, 1151, 1048, 975, 904, 830, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (t, J = 7.6 Hz, 1H), 4.67 (d, J = 7.6 Hz, 2H), 3.43 (s, 2H), 1.77 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.2, 140.4, 117.6, 62.9, 40.6, 25.7, 18.0; HRMS (CI) calc. for $C_8H_{16}NO_4$: $(M + NH_4)^+$, 190.1079, found: $(M + NH_4)^+$, 190.1081.

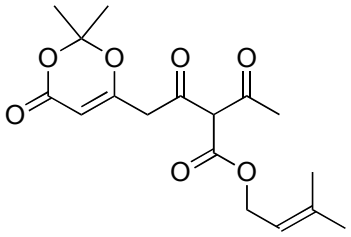
3-Methylbut-2-enyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (441)



A solution of LHMDS (1 M in THF; 20 mL, 20 mmol) was added dropwise to dioxinone **313** (2.9 mL, 21.75 mmol) in 100 mL dry THF at ~–78 °C and the mixture was stirred for 3.5 h. After this period a solution of acid chloride **440** (2.76 g, 14.50 mmol) in dry THF (7 mL) was slowly added and the temperature was raised to 0 °C for 3 h. The reaction was quenched by addition of aq. NH_4Cl (sat., 5 mL). Water (75 mL) was added and the pH was

adjusted to 4 by adding aq. HCl (1 M). The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (Et_2O:Hexanes, 2:1) afforded dioxinone **441** (1.05 g, 3.54 mmol, 24%) as a pale yellow oil: R_f 0.29 (Et_2O:Hexanes, 2:1); IR: 2971, 2924, 2857, 1738, 1730, 1640, 1376, 1274, 1229, 1217, 1205, 1017, 903 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.34 – 5.32 (m, 1H), 4.65 (d, *J* = 7.6 Hz, 2H), 3.50 (s, 2H), 3.49 (s, 2H), 1.77 (s, 3H), 1.72 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 166.3, 163.5, 160.5, 140.4, 117.6, 107.3, 97.1, 62.6, 49.1, 47.0, 25.7, 25.0, 18.0; HRMS (CI) calc. for $C_{15}H_{24}NO_6$: $(M + NH_4)^+$, 314.1604, found: $(M + NH_4)^+$, 314.1608.

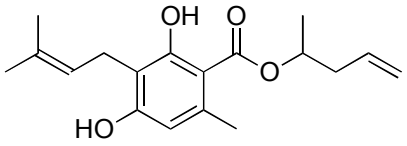
(*E*)-3-Methylbut-2-enyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybut-2-enoate (436)



Pyridine (80 μL, 0.99 mmol) was added with stirring to a suspension of dioxinone **441** (110 mg, 0.37 mmol) and $MgCl_2$ (42 mg, 0.44 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. After 30 min, acetic chloride (50 μL, 0.70 mmol) was slowly added and, after 15 min at 0 °C and 15 min at RT, aq. HCl (1 M, 15 mL) and brine (15 mL) were added. The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). Rotary evaporation gave diketo-dioxinone **436** (121 mg, 0.54 mmol, 97%) as a pale yellow oil used in the next step without further purification: R_f 0.54 (Et_2O:Hexanes, 2:1); IR: 3003, 2971, 2927, 1737, 1640, 1575, 1374, 1272, 1231,

1218, 1205, 1077, 1016, 901, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (t, *J* = 7.6 Hz, 1H), 5.34 (s, 1H), 4.71 (d, *J* = 7.2 Hz, 2H), 3.72 (s, 2H), 2.41 (s, 3H), 1.78 (s, 3H), 1.75 (s, 3H), 1.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 193.4, 166.3, 165.2, 160.8, 140.2, 117.9, 108.5, 107.2, 96.4, 61.9, 43.1, 25.8, 25.5, 24.9, 18.1; HRMS (ESI) calc. for $C_{17}H_{23}O_7$: $(M + H)^+$, 339.1444, found: $(M + H)^+$, 339.1431.

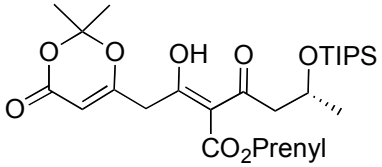
Pent-4-en-2-yl 2,4-dihydroxy-6-methyl-3-(3-methylbut-2-enyl)benzoate (443)



A solution of $Pd(PPh_3)_4$ (38 mg, 0.03 mmol) in THF (2.5 mL) was added with stirring to a solution of diketo-dioxinone **436** (111 mg, 0.33 mmol) in THF (2.5 mL) at 0 °C. After 15 min at 0 °C followed by 30 min at RT, brine (20 mL) was added and the mixture extracted with EtOAc (3 x 25 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give a pale yellow oil. PhMe (5 mL) and pent-4-en-2-ol (±)-**363** (0.2 mL, 1.94 mmol) were added and the mixture heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^iPrOH (5:3; 8 mL) and CsOAc (200 mg, 1.04 mmol) was added and the mixture stirred at RT for 2 h. The solution was acidified with AcOH (0.5 mL, 8.74 mmol) and stirred 2.5 h at RT after which time aq. $NaHCO_3$ (sat., 10 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 3:1) gave resorcylate **443** (28 mg, 0.09 mmol, 28%) as a pale yellow oil: R_f 0.67 (Hexanes:Et_2O, 3:1); IR: 3400, 2927, 1641, 1615, 1451, 1419, 1270, 1164, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H), 6.21 (s, 1H), 5.87–5.77 (m, 2H), 5.31–5.24

(m, 2H), 5.15–5.09 (m, 2H), 3.41 (d, J = 6.8 Hz, 2H), 2.54 – 2.39 (m, 2H), 2.47 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 162.7, 159.0, 140.9, 135.0, 133.4, 121.6, 118.1, 111.5, 111.2, 105.5, 71.6, 40.3, 25.8, 24.4, 22.1, 19.6, 17.9; HRMS (ESI) calc. for $C_{18}H_{25}O_4$: $(M + H)^+$, 305.1753, found: $(M + H)^+$, 305.1765.

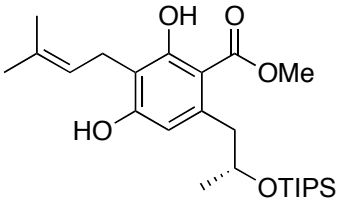
(*R*,*E*)-3-methylbut-2-enyl 2-(2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-1-hydroxyethyl-idene)-3-oxo-5-(tri*iso*propylsilyloxy)hexanoate (445)



Pyridine (80 μL, 0.99 mmol) was added with stirring to a suspension of dioxinone **441** (110 mg, 0.37 mmol) and $MgCl_2$ (70 mg, 0.74 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C giving a bright yellow solution. After 25 min, a solution of acyl chloride **326**[182] (124 mg, 0.44 mmol) in CH_2Cl_2 (0.8 mL) was slowly added. The mixture was allowed to warm to 10 °C over 2 h and then stirred at RT for 10 min. Aqueous HCl (1 M; 5 mL) and brine (20 mL) were added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:EtOAc, 4:1) gave diketo-dioxinone **445** (103 mg, 0.19 mmol, 52%) as a pale yellow oil used in the next step without further purification: R_f 0.74 (Et_2O:Hexanes, 2:1); IR: 2943, 2867, 1733, 1712, 1641, 1464, 1391, 1273, 1250, 1204, 1126, 1068, 1015, 883, 809, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (t, J = 7.2 Hz, 1H), 5.33 (s, 1H), 4.71 (d, J = 7.6 Hz, 2H), 3.66 (s, 2H), 2.94 (dd, J = 14.4, 6.8 Hz, 1H),

2.81 (dd, J = 14.4, 6.0 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.68 (s, 6H), 1.02 (m, 21H); HRMS (ESI) calc. for $C_{28}H_{47}O_8Si$: $(M + H)^+$, 539.3040, found: $(M + H)^+$, 539.3023.

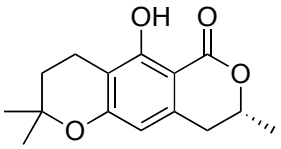
(*R*)-Methyl 2,4-dihydroxy-3-(3-methylbut-2-enyl)-6-(2-(tri*iso*propylsilyl-oxy)propyl)benzoate (444)



A solution of $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) in THF (2 mL) was added with stirring to a solution of diketo-dioxinone **445** (95 mg, 0.18 mmol) in THF (5 mL) at 0 °C. After stirring for 20 min at 0 °C and 20 min at RT, brine (20 mL) was added and the mixture extracted with EtOAc (3 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered through SiO_2 to remove the catalyst and rotary evaporated to give a pale yellow oil. PhMe (5 mL) and MeOH (0.2 mL, 4.94 mmol) were added and the mixture was heated at reflux for 1 h. After rotary evaporation, the residue was dissolved in CH_2Cl_2 and ^{i}PrOH (5:3; 4 mL) and CsOAc (110 mg, 0.57 mmol) was added and the mixture stirred at RT for 2 h. The solution was acidified with AcOH (0.25 mL, 4.37 mmol) and stirred at RT for 4 h after which time aq. $NaHCO_3$ (sat., 20 mL) was added and the mixture extracted with Et_2O (3 x 25 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated. Chromatography (Hexanes:Et_2O, 5:1) gave first resorcylate **444** (10 mg, 0.02 mmol, 11%) as a pale yellow oil followed by *ent*-**433** (13 mg, 0.03 mmol, 19%) as a colourless solid: R_f 0.81 (Hexanes:Et_2O, 3:1); $[\alpha]_D^{25}$ +15.4 (*c* 1.0, CH_2Cl_2); IR: 3395, 1594, 1418, 1122 cm^{-}1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H), 6.27 (s, 1H), 5.23 (t, J = 7.2 Hz, 1H), 4.12

(sex, J = 6.4 Hz, 1H), 3.91 (s, 3H), 3.41 (d, J = 3.6 Hz, 2H), 3.08 (dd, J = 12.8, 5.2 Hz, 1H), 2.94 (dd, J = 13.2, 7.2 Hz, 1H) 1.81 (s, 3H), 1.74 (s, 3H), 1.15 (d, J = 6.0 Hz, 3H), 0.97 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.4, 162.5, 158.9, 135.1, 125.5, 121.5, 112.9, 112.1, 69.8, 51.9, 46.6, 30.3, 25.8, 24.3, 22.1, 18.0, 12.6; HRMS (ESI) calc. for $C_{25}H_{43}O_5Si$: (M + H), 451.2880, found: (M + H), 451.2868.

Attempted synthesis of angelicoin A (28)



H_2SiF_6 in H_2O (20% w/w; 50 μL, 0.08 mmol) was added with stirring to a solution of resorcylate **444** (10 mg, 0.02 mmol) in MeCN (4 mL) at 0 °C. After 15 min at 0 °C, the reaction mixture was heated at reflux for 45 min after which time a spatula of *p*-TsOH was added and the mixture heated at reflux for 2 h. The reaction was cooled to RT and poured into aq. $NaHCO_3$ (sat., 20 mL). The mixture was extracted with Et_2O (3 x 25 mL), dried ($MgSO_4$) and the solvent rotary evaporated. Chromatography (Hexanes:Et_2O, 3:1) gave tricyclic resorcylate **447** (2.7 mg, 0.01 mmol, 51%) as a colourless solid: R_f 0.49 (Hexanes:Et_2O, 3:1); $[\alpha]_D^{25}$ +33.0 (*c* 0.2, $CHCl_3$); IR: 3432, 2925, 1659, 1634, 1584, 1434, 1370, 1311, 1253, 1235, 1157, 1118, 1041, 918, 875, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H), 6.14 (s, 1H), 4.67 – 4.61 (m, 1H), 2.82–2.80 (m, 2H), 2.67 (td, J = 6.8, 3.2 Hz, 2H), 1.80 (t, J = 6.8 Hz, 1H), 1.49 (d, J = 6.4 Hz, 3H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 137.8, 107.5, 100.1, 75.6, 34.6, 31.8, 26.8, 26.6, 20.8, 16.3 (4 carbons missing); HRMS (ESI) calc. for $C_{15}H_{19}O_4$: $(M + H)^+$, 263.1283, found: $(M + H)^+$, 263.1294.

III.2. Appendices

III.2.1. Crystal data and structure refinement for lactone 142.

Empirical formula	$C_{17}H_{26}O_7$
Formula weight	342.38
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.94340(11) Å a = 90°
	b = 13.4581(3) Å b = 90°
	c = 22.8780(4) Å g = 90°
Volume, Z	1829.95(10) $Å^3$, 4
Density (calculated)	1.243 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	736
Crystal colour / morphology	Colourless blocky needles
Crystal size	0.33 x 0.17 x 0.14 mm^3
q range for data collection	3.75 to 32.54°
Index ranges	-8<=h<=8, -19<=k<=19, -32<=l<=32
Reflns collected / unique	26284 / 6146 [R(int) = 0.0400]
Reflns observed [F>4s(F)]	3909
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.89148
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6146 / 0 / 217
Goodness-of-fit on F^2	0.930
Final R indices [F>4s(F)]	R1 = 0.0366, wR2 = 0.0802
	R1+ = 0.0366, wR2+ = 0.0802
	R1- = 0.0366, wR2- = 0.0803
R indices (all data)	R1 = 0.0595, wR2 = 0.0855

Absolute structure parameter	x+ = 0.0(6), x- = 1.0(6) Absolute structure indeterminate, enantiomer assigned by internal reference on known chirality at C(6)
Largest diff. peak, hole	0.235, -0.170 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.000

O(1)-C(2)	1.4180(14)	O(1)-C(5)	1.4343(13)
C(2)-O(3)	1.4404(12)	C(2)-C(11)	1.5223(15)
O(3)-C(4)	1.3500(14)	C(4)-O(4)	1.2014(14)
C(4)-C(5)	1.5248(15)	C(5)-C(15)	1.5319(15)
C(5)-C(6)	1.5404(16)	C(6)-C(7)	1.5224(17)
C(6)-C(10)	1.5235(16)	C(7)-O(7)	1.1986(14)
C(7)-O(8)	1.3440(16)	O(8)-C(9)	1.4518(17)
C(9)-C(10)	1.5140(19)	C(11)-C(12)	1.5244(17)
C(11)-C(14)	1.5250(17)	C(11)-C(13)	1.5276(18)
C(15)-C(16)	1.5007(16)	C(16)-O(16)	1.1982(14)
C(16)-O(17)	1.3347(13)	O(17)-C(18)	1.4878(14)
C(18)-C(19)	1.5024(18)	C(18)-C(21)	1.5117(19)
C(18)-C(20)	1.5123(18)		
C(2)-O(1)-C(5)	107.62(8)	O(1)-C(2)-O(3)	105.09(8)
O(1)-C(2)-C(11)	112.26(9)	O(3)-C(2)-C(11)	111.65(9)
C(4)-O(3)-C(2)	108.13(9)	O(4)-C(4)-O(3)	123.38(11)
O(4)-C(4)-C(5)	127.91(11)	O(3)-C(4)-C(5)	108.47(9)
O(1)-C(5)-C(4)	102.47(9)	O(1)-C(5)-C(15)	112.88(9)
C(4)-C(5)-C(15)	113.72(9)	O(1)-C(5)-C(6)	107.88(9)
C(4)-C(5)-C(6)	108.96(9)	C(15)-C(5)-C(6)	110.51(9)
C(7)-C(6)-C(10)	103.06(9)	C(7)-C(6)-C(5)	111.75(9)
C(10)-C(6)-C(5)	116.00(10)	O(7)-C(7)-O(8)	121.40(12)
O(7)-C(7)-C(6)	128.66(12)	O(8)-C(7)-C(6)	109.94(10)

C(7)-O(8)-C(9)	110.03(11)	O(8)-C(9)-C(10)	105.14(10)
C(9)-C(10)-C(6)	102.41(10)	C(2)-C(11)-C(12)	107.21(9)
C(2)-C(11)-C(14)	112.69(10)	C(12)-C(11)-C(14)	109.86(10)
C(2)-C(11)-C(13)	107.74(9)	C(12)-C(11)-C(13)	109.31(11)
C(14)-C(11)-C(13)	109.93(11)	C(16)-C(15)-C(5)	114.54(9)
O(16)-C(16)-O(17)	125.23(11)	O(16)-C(16)-C(15)	124.65(10)
O(17)-C(16)-C(15)	110.09(9)	C(16)-O(17)-C(18)	120.55(9)
O(17)-C(18)-C(19)	110.11(10)	O(17)-C(18)-C(21)	109.94(10)
C(19)-C(18)-C(21)	112.31(12)	O(17)-C(18)-C(20)	101.41(9)
C(19)-C(18)-C(20)	112.38(12)	C(21)-C(18)-C(20)	110.15(12)

Table 1. Bond lengths [Å] and angles [°] for **142**.

III.2.2. Crystal data and structure refinement for lactone 150.

Empirical formula	$C_{20}H_{32}O_8$	
Formula weight	400.46	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.2871(3) Å	a = 90.0°
	b = 11.8600(3) Å	b = 90.0°
	c = 30.1108(11) Å	g = 90.0°
Volume, Z	2245.2(3) $Å^3$, 4	
Density (calculated)	1.185 Mg/m^3	
Absorption coefficient	0.757 mm^{-1}	
F(000)	864	
Crystal colour / morphology	Colourless needles	
Crystal size	0.25 x 0.01 x 0.01 mm^3	
q range for data collection	2.94 to 63.18°	
Index ranges	-7<=h<=7, -13<=k<=12, -34<=l<=33	

Reflns collected / unique	12291 / 3561 [R(int) = 0.0895]
Reflns observed [F>4s(F)]	2286
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3561 / 0 / 253
Goodness-of-fit on F^2	0.990
Final R indices [F>4s(F)]	R1 = 0.0594, wR2 = 0.1193
	R1+ = 0.0594, wR2+ = 0.1193
	R1- = 0.0595, wR2- = 0.1194
R indices (all data)	R1 = 0.1038, wR2 = 0.1341
Absolute structure parameter	x+ = 0.2(4), x- = 0.8(4)
	Absolute structure indeterminate, enantiomer assigned by internal reference on known chirality at C(6)
Largest diff. peak, hole	0.239, -0.182 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.000

O(1)-C(2)	1.428(4)	O(1)-C(5)	1.438(4)
C(2)-O(3)	1.447(5)	C(2)-C(11)	1.504(5)
O(3)-C(4)	1.351(4)	C(4)-O(4)	1.203(4)
C(4)-C(5)	1.509(5)	C(5)-C(15)	1.524(5)
C(5)-C(6)	1.539(5)	C(6)-C(7)	1.502(5)
C(6)-C(10)	1.520(5)	C(7)-O(7)	1.196(5)
C(7)-O(8)	1.361(5)	O(8)-C(9)	1.467(5)
C(9)-O(22)	1.392(5)	C(9)-C(10)	1.512(5)
C(11)-C(14)	1.501(6)	C(11)-C(12)	1.528(7)
C(11)-C(13)	1.548(6)	C(15)-C(16)	1.527(5)
C(16)-O(16)	1.186(4)	C(16)-O(17)	1.352(4)
O(17)-C(18)	1.488(4)	C(18)-C(21)	1.499(6)
C(18)-C(19)	1.503(6)	C(18)-C(20)	1.521(6)

O(22)-C(23)	1.448(5)	C(23)-C(25)	1.496(7)
C(23)-C(24)	1.509(7)		
C(2)-O(1)-C(5)	106.2(3)	O(1)-C(2)-O(3)	104.6(3)
O(1)-C(2)-C(11)	112.0(3)	O(3)-C(2)-C(11)	112.5(4)
C(4)-O(3)-C(2)	108.0(3)	O(4)-C(4)-O(3)	122.6(4)
O(4)-C(4)-C(5)	128.5(3)	O(3)-C(4)-C(5)	108.9(3)
O(1)-C(5)-C(4)	101.9(3)	O(1)-C(5)-C(15)	109.4(3)
C(4)-C(5)-C(15)	111.4(3)	O(1)-C(5)-C(6)	108.0(3)
C(4)-C(5)-C(6)	110.0(3)	C(15)-C(5)-C(6)	115.3(3)
C(7)-C(6)-C(10)	103.7(3)	C(7)-C(6)-C(5)	112.9(3)
C(10)-C(6)-C(5)	115.7(3)	O(7)-C(7)-O(8)	121.0(4)
O(7)-C(7)-C(6)	130.2(4)	O(8)-C(7)-C(6)	108.8(4)
C(7)-O(8)-C(9)	110.7(3)	O(22)-C(9)-O(8)	108.6(3)
O(22)-C(9)-C(10)	108.6(3)	O(8)-C(9)-C(10)	104.1(3)
C(9)-C(10)-C(6)	102.5(3)	C(14)-C(11)-C(2)	112.1(4)
C(14)-C(11)-C(12)	110.7(4)	C(2)-C(11)-C(12)	107.1(4)
C(14)-C(11)-C(13)	111.5(5)	C(2)-C(11)-C(13)	106.5(3)
C(12)-C(11)-C(13)	108.7(4)	C(5)-C(15)-C(16)	114.8(3)
O(16)-C(16)-O(17)	126.7(3)	O(16)-C(16)-C(15)	125.1(3)
O(17)-C(16)-C(15)	108.2(3)	C(16)-O(17)-C(18)	122.0(3)
O(17)-C(18)-C(21)	109.2(3)	O(17)-C(18)-C(19)	109.0(3)
C(21)-C(18)-C(19)	113.1(4)	O(17)-C(18)-C(20)	101.0(3)
C(21)-C(18)-C(20)	111.6(4)	C(19)-C(18)-C(20)	112.3(4)
C(9)-O(22)-C(23)	114.2(3)	O(22)-C(23)-C(25)	106.8(4)
O(22)-C(23)-C(24)	107.7(5)	C(25)-C(23)-C(24)	114.2(5)

Table 2. Bond lengths [Å] and angles [°] for **150**.

III.2.3. Crystal data and structure refinement for lactone 56.

Empirical formula	$C_{20}H_{32}O_8$	
Formula weight	400.46	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å	
Crystal system, space group	Monoclinic, P2(1)	
Unit cell dimensions	a = 11.1924(3) Å	a = 90°
	b = 19.4545(3) Å	b = 117.717(3)°
	c = 11.8870(3) Å	g = 90°
Volume, Z	2291.31(9) $Å^3$, 4	
Density (calculated)	1.161 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	864	
Crystal colour / morphology	Colourless blocky needles	
Crystal size	0.30 x 0.15 x 0.09 mm^3	
q range for data collection	3.76 to 32.26°	
Index ranges	-16<=h<=16, -27<=k<=28, -17<=l<=16	
Reflns collected / unique	19594 / 12427 [R(int) = 0.0281]	
Reflns observed [F>4s(F)]	8530	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.85343	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12427 / 31 / 518	
Goodness-of-fit on F^2	0.955	
Final R indices [F>4s(F)]	R1 = 0.0410, wR2 = 0.0892	
	R1+ = 0.0410, wR2+ = 0.0892	
	R1- = 0.0410, wR2- = 0.0893	
R indices (all data)	R1 = 0.0634, wR2 = 0.0982	
Absolute structure parameter	x+ =0.5(5), x- = 1.5(5)	

	Absolute structure not determined. Assigned based on known centres at C(4) and C(5)
Largest diff. peak, hole	0.220, -0.171 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.000

O(1)-C(2)	1.3564(19)	O(1)-C(5)	1.4408(18)
C(2)-O(2)	1.198(2)	C(2)-C(3)	1.504(2)
C(3)-C(4)	1.523(2)	C(4)-C(6)	1.518(2)
C(4)-C(5)	1.565(2)	C(5)-C(18)	1.515(2)
C(5)-C(12)	1.539(2)	C(6)-O(6)	1.200(2)
C(6)-O(7)	1.332(2)	O(7)-C(8)	1.479(2)
C(8)-C(11)	1.510(3)	C(8)-C(9)	1.516(3)
C(8)-C(10)	1.526(3)	C(12)-O(12)	1.1978(19)
C(12)-O(13)	1.3287(18)	O(13)-C(14)	1.4791(19)
C(14)-C(17)	1.501(2)	C(14)-C(15)	1.514(3)
C(14)-C(16)	1.518(3)	C(18)-C(19)	1.505(2)
C(19)-O(19)	1.2028(19)	C(19)-O(20)	1.3377(18)
O(20)-C(21)	1.4760(19)	C(21)-C(23)	1.506(2)
C(21)-C(22)	1.520(3)	C(21)-C(24)	1.521(3)
		C(2)-O(1)-C(5)	110.60(11)
O(2)-C(2)-O(1)	120.67(15)	O(2)-C(2)-C(3)	129.05(15)
O(1)-C(2)-C(3)	110.28(13)	C(2)-C(3)-C(4)	104.37(13)
C(6)-C(4)-C(3)	110.99(13)	C(6)-C(4)-C(5)	114.50(12)
C(3)-C(4)-C(5)	101.56(12)	O(1)-C(5)-C(18)	108.04(12)
O(1)-C(5)-C(12)	107.75(12)	C(18)-C(5)-C(12)	112.28(12)
O(1)-C(5)-C(4)	104.57(11)	C(18)-C(5)-C(4)	116.80(13)
C(12)-C(5)-C(4)	106.82(12)	O(6)-C(6)-O(7)	125.83(16)
O(6)-C(6)-C(4)	124.35(16)	O(7)-C(6)-C(4)	109.80(13)
C(6)-O(7)-C(8)	123.23(13)	O(7)-C(8)-C(11)	102.15(15)

O(7)-C(8)-C(9)	107.42(14)	C(11)-C(8)-C(9)	111.81(19)
O(7)-C(8)-C(10)	111.40(15)	C(11)-C(8)-C(10)	111.43(18)
C(9)-C(8)-C(10)	112.13(18)	O(12)-C(12)-O(13)	127.31(15)
O(12)-C(12)-C(5)	123.36(14)	O(13)-C(12)-C(5)	109.17(12)
C(12)-O(13)-C(14)	122.37(12)	O(13)-C(14)-C(17)	109.73(14)
O(13)-C(14)-C(15)	101.19(13)	C(17)-C(14)-C(15)	110.89(17)
O(13)-C(14)-C(16)	109.12(14)	C(17)-C(14)-C(16)	113.68(17)
C(15)-C(14)-C(16)	111.49(16)	C(19)-C(18)-C(5)	113.49(13)
O(19)-C(19)-O(20)	125.62(14)	O(19)-C(19)-C(18)	125.56(14)
O(20)-C(19)-C(18)	108.80(13)	C(19)-O(20)-C(21)	121.85(13)
O(20)-C(21)-C(23)	110.15(14)	O(20)-C(21)-C(22)	101.66(15)
C(23)-C(21)-C(22)	110.58(16)	O(20)-C(21)-C(24)	110.01(14)
C(23)-C(21)-C(24)	112.36(16)	C(22)-C(21)-C(24)	111.57(18)

Table 3. Bond lengths [Å] and angles [°] for **56**.

III.2.4. Crystal data and structure refinement for imide 240.

Empirical formula	$C_{32}H_{33}NO_6$	
Formula weight	527.59	
Temperature	173(2) K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Monoclinic, P2(1)	
Unit cell dimensions	a = 13.7285(3) Å	a = 90°
	b = 6.58582(13) Å	b = 98.2220(18)°
	c = 15.2218(3) Å	g = 90°
Volume, Z	1362.11(5) $Å^3$, 2	
Density (calculated)	1.286 Mg/m^3	
Absorption coefficient	0.719 mm^{-1}	
F(000)	560	

Crystal colour / morphology	Colourless needles
Crystal size	0.19 x 0.04 x 0.02 mm^3
q range for data collection	2.93 to 71.57°
Index ranges	-16<=h<=16, -8<=k<=7, -18<=l<=18
Reflns collected / unique	20173 / 5024 [R(int) = 0.0765]
Reflns observed [F>4s(F)]	3156
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.80385
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5024 / 1 / 354
Goodness-of-fit on F^2	0.864
Final R indices [F>4s(F)]	R1 = 0.0377, wR2 = 0.0742
	R1+ = 0.0377, wR2+ = 0.0742
	R1- = 0.0378, wR2- = 0.0745
R indices (all data)	R1 = 0.0709, wR2 = 0.0840
Absolute structure parameter	x+ = 0.0(2), x- = 1.1(2)
	Enantiomer assignment based on known chirality at C(4)
Extinction coefficient	0.0010(2)
Largest diff. peak, hole	0.190, -0.168 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

O(1)-C(2)	1.351(3)	O(1)-C(5)	1.448(3)
C(2)-O(2)	1.205(3)	C(2)-N(3)	1.374(3)
N(3)-C(6)	1.391(3)	N(3)-C(4)	1.467(3)
C(4)-C(5)	1.522(3)	C(4)-C(30)	1.534(3)
C(6)-O(6)	1.221(3)	C(6)-C(7)	1.517(4)
C(7)-C(8)	1.537(3)	C(7)-C(20)	1.541(3)
C(8)-O(9)	1.471(3)	C(8)-C(12)	1.497(4)
O(9)-C(10)	1.363(3)	C(10)-O(10)	1.202(3)

C(10)-C(11)	1.495(3)	C(12)-C(13)	1.333(3)
C(13)-C(14)	1.467(3)	C(14)-C(15)	1.388(3)
C(14)-C(19)	1.394(3)	C(15)-C(16)	1.396(4)
C(16)-C(17)	1.375(4)	C(17)-C(18)	1.389(3)
C(18)-C(19)	1.382(4)	C(20)-C(21)	1.512(3)
C(21)-O(22)	1.423(3)	O(22)-C(23)	1.432(3)
C(23)-C(24)	1.488(3)	C(24)-C(29)	1.379(4)
C(24)-C(25)	1.384(3)	C(25)-C(26)	1.382(4)
C(26)-C(27)	1.388(4)	C(27)-C(28)	1.377(4)
C(28)-C(29)	1.394(4)	C(30)-C(31)	1.506(3)
C(31)-C(32)	1.379(4)	C(31)-C(36)	1.399(3)
C(32)-C(33)	1.384(4)	C(33)-C(34)	1.383(4)
C(34)-C(35)	1.371(4)	C(35)-C(36)	1.375(4)
		C(2)-O(1)-C(5)	110.5(2)
O(2)-C(2)-O(1)	120.9(2)	O(2)-C(2)-N(3)	130.0(2)
O(1)-C(2)-N(3)	109.0(2)	C(2)-N(3)-C(6)	127.6(2)
C(2)-N(3)-C(4)	111.97(19)	C(6)-N(3)-C(4)	120.4(2)
N(3)-C(4)-C(5)	101.3(2)	N(3)-C(4)-C(30)	109.74(19)
C(5)-C(4)-C(30)	113.3(2)	O(1)-C(5)-C(4)	105.5(2)
O(6)-C(6)-N(3)	118.4(2)	O(6)-C(6)-C(7)	121.1(2)
N(3)-C(6)-C(7)	120.5(2)	C(6)-C(7)-C(8)	106.9(2)
C(6)-C(7)-C(20)	109.5(2)	C(8)-C(7)-C(20)	113.49(19)
O(9)-C(8)-C(12)	111.4(2)	O(9)-C(8)-C(7)	102.13(18)
C(12)-C(8)-C(7)	111.7(2)	C(10)-O(9)-C(8)	117.20(19)
O(10)-C(10)-O(9)	122.8(2)	O(10)-C(10)-C(11)	126.2(2)
O(9)-C(10)-C(11)	111.0(2)	C(13)-C(12)-C(8)	122.7(3)
C(12)-C(13)-C(14)	127.6(3)	C(15)-C(14)-C(19)	118.5(3)
C(15)-C(14)-C(13)	119.1(2)	C(19)-C(14)-C(13)	122.2(2)
C(14)-C(15)-C(16)	120.7(3)	C(17)-C(16)-C(15)	120.2(3)
C(16)-C(17)-C(18)	119.5(3)	C(19)-C(18)-C(17)	120.5(3)

C(18)-C(19)-C(14)	120.6(2)	C(21)-C(20)-C(7)	110.8(2)
O(22)-C(21)-C(20)	108.3(2)	C(21)-O(22)-C(23)	111.66(18)
O(22)-C(23)-C(24)	110.7(2)	C(29)-C(24)-C(25)	118.5(3)
C(29)-C(24)-C(23)	122.7(2)	C(25)-C(24)-C(23)	118.8(2)
C(26)-C(25)-C(24)	121.0(3)	C(25)-C(26)-C(27)	120.3(3)
C(28)-C(27)-C(26)	119.1(3)	C(27)-C(28)-C(29)	120.3(3)
C(24)-C(29)-C(28)	120.8(2)	C(31)-C(30)-C(4)	114.7(2)
C(32)-C(31)-C(36)	117.5(2)	C(32)-C(31)-C(30)	124.3(2)
C(36)-C(31)-C(30)	118.1(2)	C(31)-C(32)-C(33)	121.9(3)
C(34)-C(33)-C(32)	119.7(3)	C(35)-C(34)-C(33)	119.1(3)
C(34)-C(35)-C(36)	121.2(3)	C(35)-C(36)-C(31)	120.6(3)

Table 4. Bond lengths [Å] and angles [°] for **240**.

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