

Enantiopure Bromonium Ion-Induced Cation- π Cyclisations

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Declarations

Declaration of originality

I Jared Stephen Marklew hereby declare that the work presented in this thesis is my own and all else is appropriately referenced, with a list of these cited works provided in the section entitled 'References'.

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Abstract

There has been an astonishing variety of sesqui- and diterpene metabolites isolated—mainly from *Laurencia* species, or their predators—which possess the enantiopure α,α -dimethylcyclohexyl bromide moiety. The key step in their biogenesis is generally considered to be an enzyme-mediated formation of an asymmetric bromonium ion which initiates a cation- π cyclisation. This diverse array of terpene natural products is explored in the introduction to this thesis and their biogenesis *via* cation- π cyclisations analysed. Synthetic sources of electrophilic bromine such as NBS, TBCO and BDSB have been shown to initiate brominative polyene cyclisations with excellent control of relative stereochemistry albeit as necessarily racemic products. At the start of this work no asymmetric bromonium ion-induced polyene cyclisations had been demonstrated.

Studies on a model system for the key *in situ* enantiopure bromonium ion generation and *intramolecular* trapping are described. Sharpless asymmetric dihydroxylation provides access to enantiopure diols of a trisubstituted alkene which can be manipulated to enantiopure bromohydrins. These are activated as 2,3,4,5-tetrafluorobenzoate esters which cyclise cleanly under the action of catalytic triflic acid to give enantiopure bromo-bicycles without racemisation from bromonium ion to alkene transfer. The mechanism of this reaction is investigated, it is practically demonstrated and shorter routes are explored.

The synthesis of high purity linear terpene: homogeranyl 4-methoxybenzene is discussed, from which the synthesis of enantiopure bromo-tetrafluorobenzoate esters is carried out. The use of Lewis acid, in this case dimethylaluminium triflate, was found to successfully enact the cyclisation of these alkene containing substrates. Full conversion to cyclic products was achieved and the desired tricyclic product was isolated as a mixture of enantiopure diastereomers. Absolute and relative configuration of both diastereomers were determined by radical dehalogenation and comparison of the sign of the optical rotation of the product to literature values.

Finally, the synthesis of homofarnesyl 4-methoxybenzene derived substrates is detailed. The cyclisation of which has the potential to generate tetracyclic compounds. This forms the basis of future work to be carried out.

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Abbreviations

Ac	acetyl	GCMS	gas chromatography mass spectrometry
AD	asymmetric dihydroxylation	GPP	geranyl pyrophosphate
aq.	aqueous	h	hour(s)
Ar	aryl	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
ATR	attenuated total reflection	HMPA	hexamethylphosphoramide
BDSB	bromodiethylsulfide bromopentachloroantimonate	HPLC	high-performance liquid chromatography
Bn	benzyl	HRMS	high resolution mass spectrometry
br.	broad	HSQC	heteronuclear single quantum coherence
Bu	butyl	Hx	hexyl
Bz	benzoate	Hz	Hertz
calc'd	calculated	IPP	isopentenyl pyrophosphate
CI	chemical ionisation	<i>i</i>	<i>iso</i>
COSY	correlation spectroscopy	IR	infrared spectroscopy
Cy	cyclohexyl	IUPAC	International Union of Pure and Applied Chemistry
d	doublet	<i>J</i>	coupling constant
DBH	1,3-dibromo-5,5-dimethylhydantoin	k	rate constant
DBU	1,8-diazobicycloundec-7-ene	L.A.	Lewis acid
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide	M	moles per litre
dd	doublet of doublets	m	multiplet
ddd	doublet of doublet of doublets	<i>m</i>	<i>meta</i>
dddd	doublet of doublet of doublet of doublets	<i>m</i>CPBA	<i>meta</i> -chloroperoxybenzoic acid
ddt	doublet of doublet of triplets	M.p.	melting point
DEPT	distortionless enhancement by polarisation transfer	<i>m/z</i>	mass to charge ratio
dm	decimetre	Me	methyl
DMAP	4-dimethylaminopyridine	mg	milligram(s)
DMAPP	dimethylallyl pyrophosphate	MHz	megahertz
DME	dimethoxyethane	min	minute(s)
DMF	dimethylformamide	mL	millilitre(s)
DMSO	dimethylsulfoxide	mmol	millimole(s)
d.t.	diastereomeric ratio	Ms	methane sulfonyl
dt	doublet of triplets	MS	mass spectrometry
DTBP	di- <i>tertiary</i> -butylpyridine	MW	microwave
dtd	doublet of triplet of doublets	<i>n</i>	normal
dtg	doublet of triplet of triplets	NBS	<i>N</i> -bromosuccinimide
e.e.	enantiomeric excess	NGP	neighbouring group participation
EI	electronic ionisation	NIS	<i>N</i> -iodosuccinimide
eq.	equivalents	NMP	<i>N</i> -methyl-2-pyrrolidone
e.r.	enantiomeric ratio	NMR	nuclear magnetic resonance
Et	ethyl	Nu	nucleophile
FPP	farnesyl pyrophosphate	O/N	overnight
g	gram(s)		

<i>p</i>	<i>para</i>
PEG	polyethylene glycol
PFTB	perfluoro- <i>tert</i> -butanol
Ph	phenyl
PhMe	toluene
ppb	parts per billion
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
quant.	quantitative yield
R	alkyl group
r.t.	room temperature
RCM	ring closing metathesis
R_r	retention factor
s	singlet
t	triplet
TBCO	2,4,4,6-tetrabromocyclohexa-2,5-dienone
<i>t</i>	<i>tertiary</i>
td	triplet of doublets
tdd	triplet of doublet of doublets
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluene sulfonyl
δ	chemical shift
σ	<i>ortho</i>

1 Introduction

In modern pharmaceutical science, chemical compounds produced by living organisms *i.e.* metabolites, found in nature from marine¹ and terrestrial environments are the source, or the inspiration, for drug discovery and design.² For example, since the 1940's, the area of small-molecule anti-cancer therapeutics has seen the introduction of 175 different compounds, half of which are directly derived from known natural products.³ This is still the case in 2010 where the natural products field is responsible for 50% of all new small molecule therapeutics.⁴ The process of isolating and characterising natural products often only provides a small quantity of the compound, insufficient for complete biological evaluation. Consequently the synthetic chemist's ability to prepare natural products and their structural analogues is essential to the investigation and development of more effective drug molecules and to enable production of pharmaceuticals on an industrial scale.

1.1 Terpenes and cyclic terpenoids

Resins and essential oils have been used since ancient times as medicines, fragrances, flavourings and rubber.⁵ Turpentine; the distillate of resin obtained from live trees, usually pines and historically named after the terebinth tree from which it was obtained,⁶ and other essential oils compose mainly of terpenes and their derivatives: terpenoids. Terpenes can be found in all classes of living organisms⁷ and they represent the largest group of natural products with over 55,000 having been isolated up to 2007.^{5a} Terpenes consist of five-carbon isoprene units that are often joined in a head-to-tail fashion first described by the isoprene rule in the late 19th century.⁸ Depending on the number of isoprene subunits they are described as *hemi-* (C₅),⁹ *mono-* (C₁₀),¹⁰ *sesqui-* (C₁₅),¹¹ *di-* (C₂₀),¹² *sester-* (C₂₅),¹³ *tri-* (C₃₀),¹⁴ *sesquar-* (C₃₅),¹⁵ *tetra-* (C₄₀)¹⁶ and polyterpenes (C₅)_n where n > 8.¹⁷ In *mono-*, *sesqui-*, *di-* and *sesterterpenes* the isoprene units are linked to each other from head-to-tail, *tri-* and *tetraterpenes* contain one tail-to-tail connection in the centre (*e.g.* squalene (C₃₀) see Figure 1).^{5b}

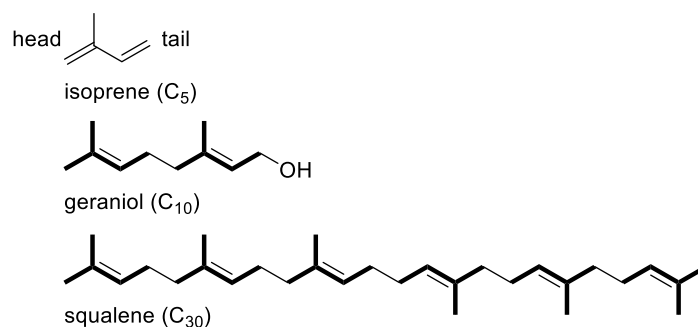


Figure 1 - Linear terpenes and their relation to isoprene

Many terpenoids differ not only in their functional group substituents but also in their basic carbon skeletons. In nature these compounds are arranged from units of isopentyl pyrophosphate (IPP) and its regioisomer: dimethylallyl pyrophosphate (DMAPP) (Figure 2).¹⁸ DMAPP represents a good S_N2 electrophile and alkylating agent and IPP reacts as a nucleophile to form geranyl pyrophosphate (GPP).¹⁹ The reaction of a further IPP unit generates farnesyl pyrophosphate, and its coupling by squalene synthase produces squalene.²⁰ Oxidation by squalene monooxygenase to 2,3-oxidosqualene²¹ and then terpene cyclase enzymes such as lanosterol synthase initiate a cation- π cascade to form polycyclic cholesterol-like structures such as lanosterol.²²

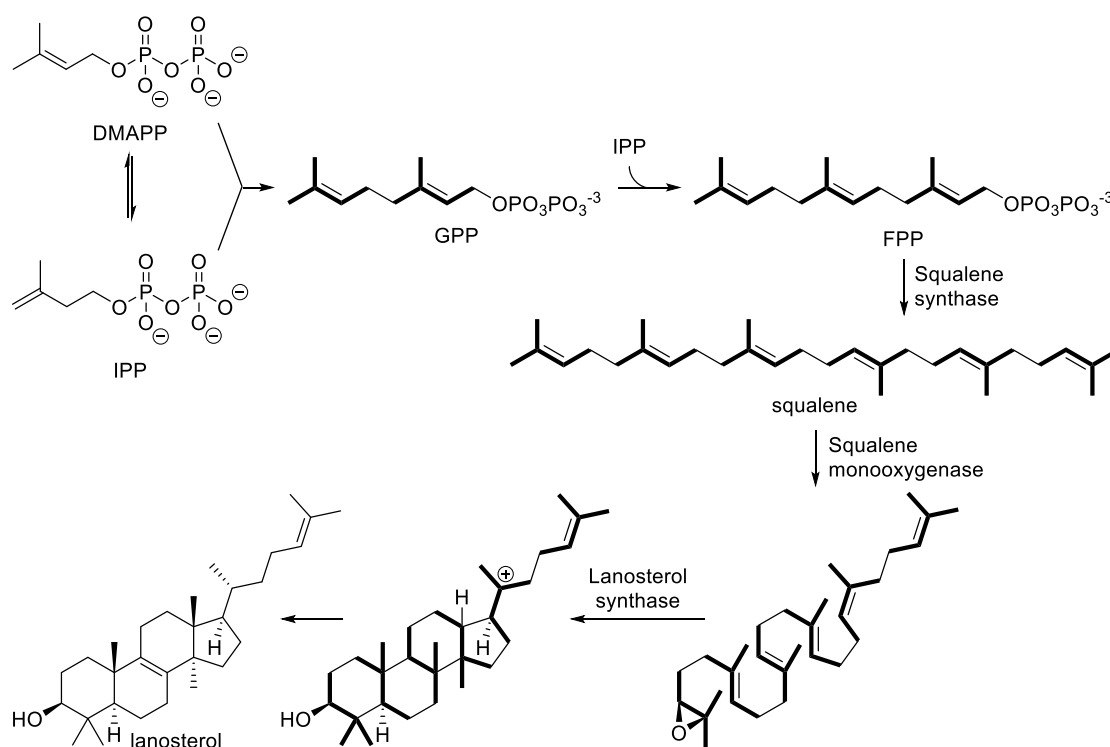


Figure 2 - Overview of lanosterol biosynthesis from dimethylallyl pyrophosphate and isopentyl pyrophosphate

Terpene cyclase enzymes assemble simple linear terpenes such as geranyl pyrophosphate and squalene into an exotic array of chiral, carbocyclic skeletons²³ *via* a cation- π cyclisation cascade, where further modification by oxidation and rearrangement can lead to an almost endless array of conceivable structures, Figure 3.^{5a}

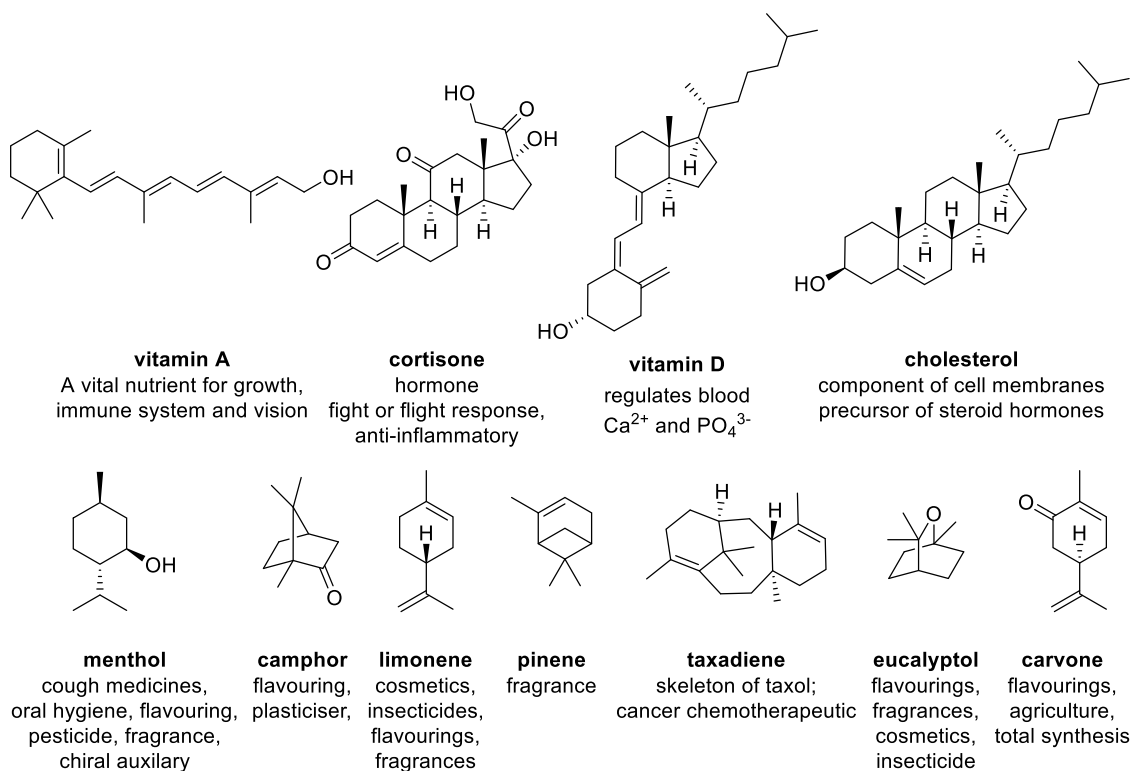


Figure 3 - Examples of terpenoid natural products demonstrating the diversity of structure.²⁰

The enormous structural diversity of terpenoid compounds²³⁻²⁴ provides a broad range of properties²⁵ and functions demonstrated by Figure 3.²⁶ The biosynthesis of these compounds *via* cation- π cyclisations, and the rapid access to complex enantiopure structures that are the basis for so many biologically active compounds, therefore makes this reaction very appealing to the synthetic organic chemist.

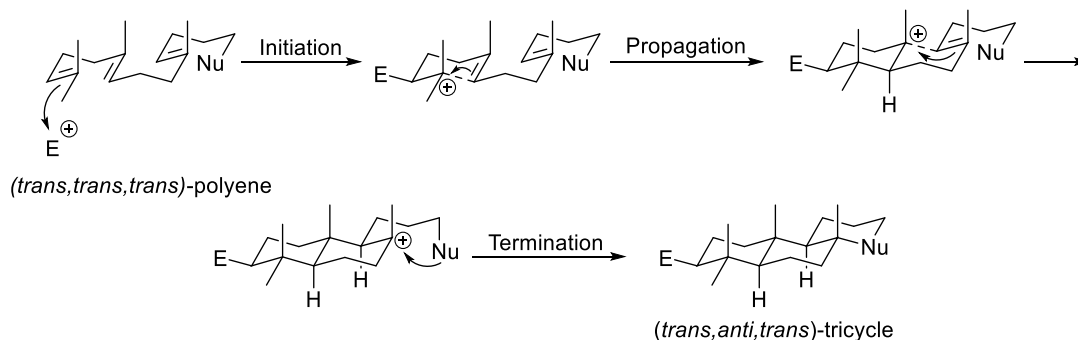
1.2 Cation- π cyclisations

In nature cation- π cyclisations provide the simultaneous formation of several carbon-carbon bonds in one step, creating a number of quaternary carbon centres. The reaction has multifaceted selectivity, in terms of both ring-size and relative and absolute stereochemistry. Up to nine stereocentres are formed in one step, resulting in rapid generation of molecular complexity^{27, 28}

In the laboratory, cation- π cyclisations are initiated by the electrophilic activation of an alkene (Scheme 1). Brønsted²⁹ and Lewis acids³⁰ have been the most frequently used electrophiles but effective cyclisations have also been achieved with oxygen,³¹ iodine,³² sulfur,³³ selenium,³³ mercury,³⁴ and transition metals such as gold,³⁵ iridium,³⁶ palladium,³⁷ and platinum.³⁸

Once initiated with an electrophile the build-up of positive charge results in attack of an *intramolecular* alkene,^{39, 27c} forming a carbocycle and causing migration of the positive charge.

Subsequent ring formations can occur with up to five new rings possible.⁴⁰ Termination of the cascade is achieved by elimination and/or attack by an internal or external nucleophile. To be synthetically useful, polyene cyclisations would ideally be terminated by one mechanism giving a single product.⁴¹



Scheme 1 - Representation of a cation- π cyclisation

The Stork-Eschenmoser hypothesis states that “when a cation- π cyclisation proceeds under stereoelectronic control (either as a ‘concerted’ process or, what is stereochemically equivalent, as a stepwise process *via* carbocationic intermediates that retain stereochemical information), then the stereochemical outcome will correspond to stereospecific *trans*-additions at C=C bonds. When extrapolated to the cyclisation of all-*trans*-polyolefinic isoprenoids, such a steric course produces the *trans-anti-trans*-configuration characteristic of the structure of the natural polycyclic terpenoids and steroids.”^{27, 42, 31a} Therefore, developing a successful polyene cyclisation (forming multiple rings) relies on the stereoselective synthesis of alkenes, efficient initiation, propagation and control over termination.^{41a}

Of particular interest is the initiation of cation- π cyclisations with electrophilic bromine, where despite significant effort, challenges in stereoselective control still remain. Such a transformation would be of great value given the existence of hundreds of brominated natural products (Figure 6) that could be accessed, as well as the potential ability to use the installed bromine atom as a handle to further elaborate the cyclised product.^{41b}

1.3 Brominated cyclic terpene natural products and their biosynthesis

It is estimated that more than 16,000 natural products have been isolated and reported from marine organisms.⁴³ Approximately 15-20% of all newly discovered marine natural products are organohalogens.⁴⁴ These are carbon-based molecules containing fluorine, chlorine, bromine or iodine atoms (Figure 4). A particular class of these organohalogens have been isolated from species of the marine red algae, *Laurencia* (Figure 5).⁴⁵

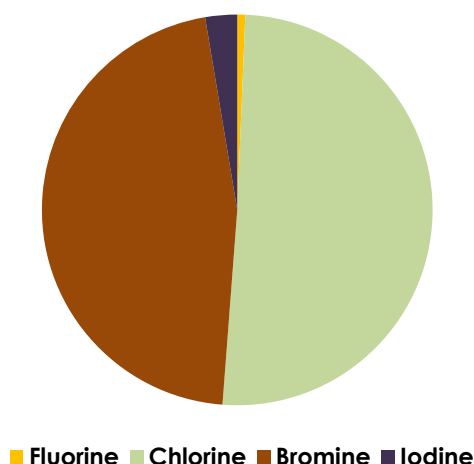


Figure 4 - Organohalogens in nature⁴⁶



Figure 5 - *Laurencia nidifica* attached to a *Porites lobata* coral head.⁴⁷

They all possess a unique chemical motif – a six-membered carbocycle bearing a bromine atom and two adjacent methyl groups (shown in red, Figure 6). To date there are more than 135 bromine-containing members of this natural product family.⁴⁸ Although only a small number of these have been tested in biological assays many have potent biological activity, including anti-tumour,⁴⁹ anti-bacterial,⁵⁰ anti-inflammatory⁵¹ and anti-HIV⁵² activity. For example, aplysisstatin, isolated from an Australian South Pacific Ocean sea hare (*Aplysia angasi*) was found to significantly inhibit progression of murine lymphocytic leukemia.⁴⁹ Majapolene B, isolated from *Laurencia mujuscula* (Harvey) Lucas, collected off Apo Island in the Philippines,^{50b} showed moderate anti-bacterial activity against a range of bacterial strains.^{50a} Peyssonol A, a secondary metabolite obtained from the Red Sea marine algae *Peyssonnelia* species, has been shown to act as an allosteric inhibitor of the reverse transcriptases of HIV types 1 and 2.^{52b} This family of natural products therefore has great potential in drug discovery.

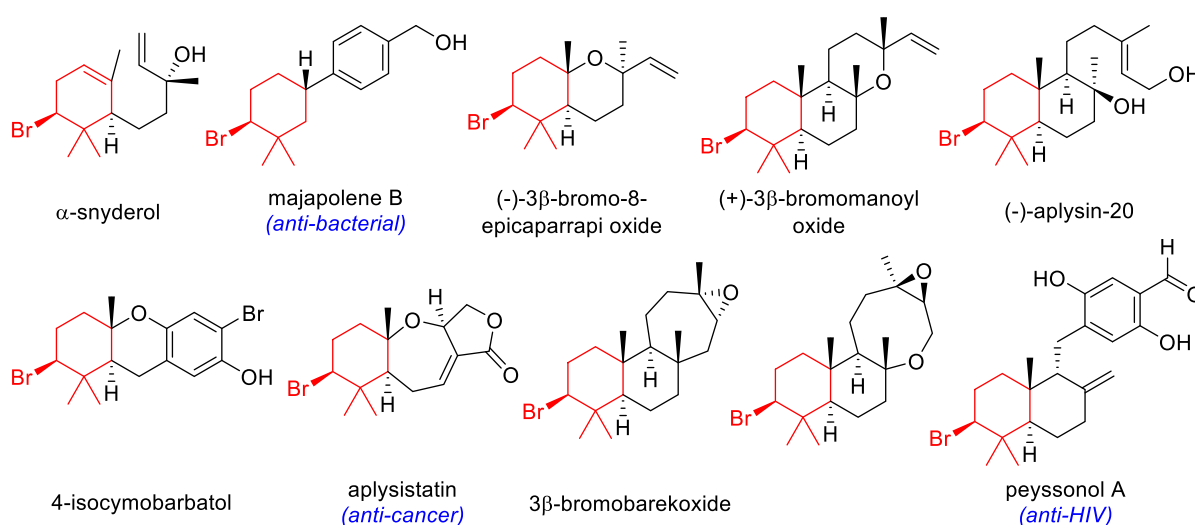


Figure 6 - Representative examples of sesqui- and diterpene metabolites isolated from *Laurencia* species, or their predators, which possess the enantiopure α,α -dimethylcyclohexyl bromide moiety

These compounds are isolated from nature as single enantiomers and their biosynthesis is known to occur by the action of vanadium bromoperoxidase^{53, 46a} – an abundant and robust enzyme found in all classes of marine algae. In the active site of vanadium bromoperoxidase, the vanadate(V) ion is coordinated to the protein scaffold by a single histidine residue positioned at the bottom of a deep active-site channel. Multiple amino acid side-chains hydrogen bond to the vanadate oxygen atoms (Figure 7).^{54, 53d}

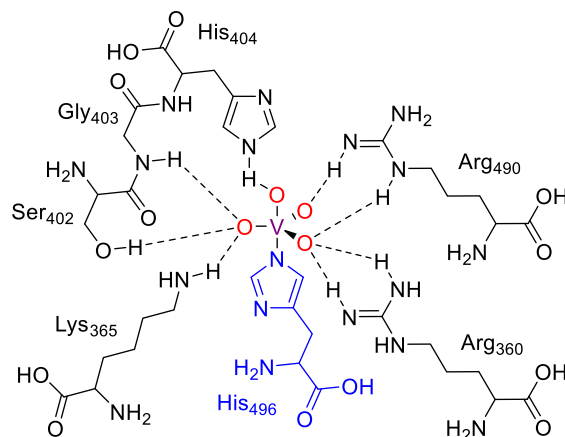
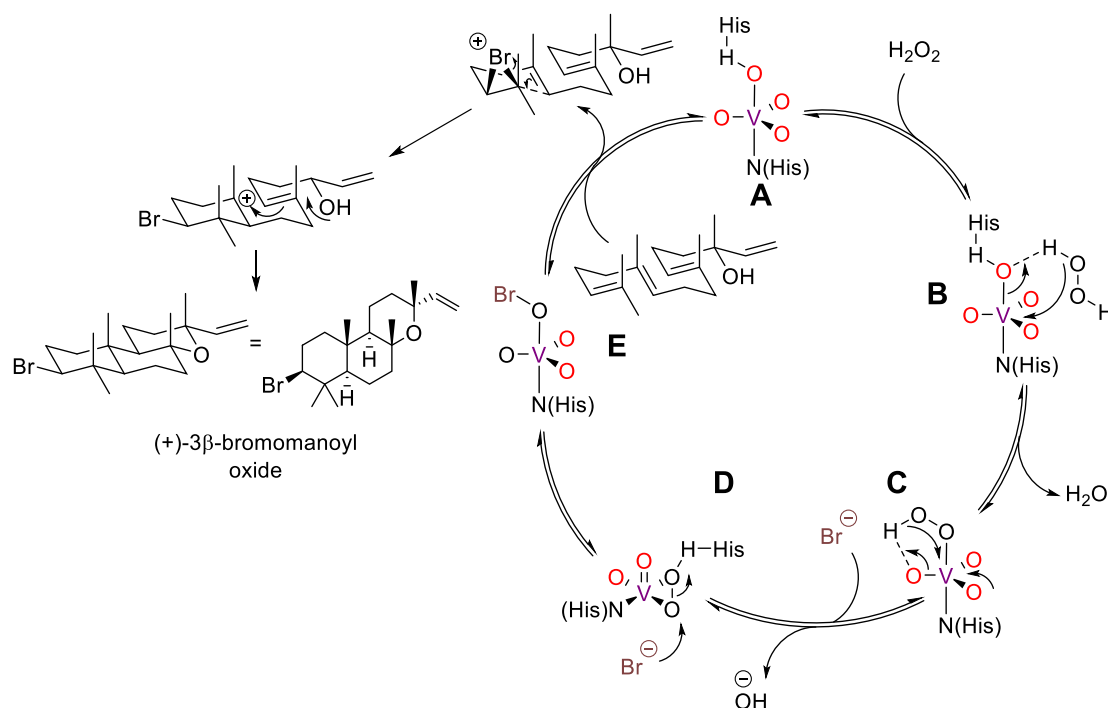


Figure 7 - Representative example of the active site of native vanadium chloroperoxidase from *Curvularia inaequalis*. Possible hydrogen bonds are drawn as dashed lines.^{55, 53d}

Although the process is poorly understood it is proposed that the vanadate(V) first coordinates to hydrogen peroxide in a side-on bound fashion, producing a square-based pyramidal oxo-peroxo-vanadium(V) intermediate (**D**, Scheme 2).⁵⁶ In vanadium *bromoperoxidases* it is thought that a histidine residue alters the redox potential of the vanadium-peroxo complex **D** in such a way that the oxidation of chloride ions is no longer possible, providing chemoselectivity.^{54a} Detection or isolation of the oxidised bromine intermediate **E** is hampered due to its reaction with organic substrates or with excess hydrogen peroxide to produce singlet oxygen, preventing its build-up in solution.⁵⁷ Therefore the nature of the oxidised bromine intermediate as either enzyme-trapped, bound or freely diffusible depends on the nature of the organic substrate.⁵⁸ Recent evidence has shown that bromide ion unambiguously binds within the active site of vanadium bromoperoxidase from the red algae *Corallina piluliferad* in the presence of its known substrates, phenol red and phloroglucinol.⁵⁹



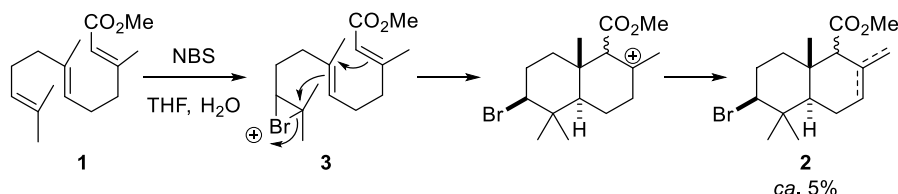
Scheme 2 - Proposed reaction mechanism for bromide oxidation by vanadium bromoperoxidases in the biosynthesis of (+)-3β-bromomanoyl oxide.^{54a 53a}

In nature vanadium bromoperoxidases accomplish bromonium ion-induced polyene cyclisations where a number of new C-C bonds, rings and quaternary stereocentres are formed stereoselectively, to give complex molecules from linear substrates. In the last 50 years, this reaction has been demonstrated in the chemical laboratory.

1.4 History and precedent

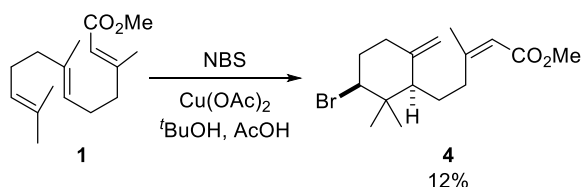
1.4.1 Polyene cyclisations triggered by direct bromination

The first report of a bromonium-ion induced cation- π cyclisation from a synthetic laboratory came in 1966⁶⁰ when van Tamelen and Hessler found that the reaction of NBS with methyl farnesate **1** (Scheme 3) in a water-ethylene glycol mixture or THF solution gave rise to 12-15% yield of bromo-cyclised material, as observed by ¹H NMR analysis of the crude reaction mixture, where mono-bromohydrins of the terminus alkene represented the major product. Isolated from this mixture, as a non-saponifiable fraction was bicycle **2** as a mixture of endo- and exocyclic alkenes in approximately 5% yield. It was suggested that the most likely mechanism for this reaction is the formation of a racemic bromonium ion **3** which cyclises in a synchronous fashion to the bicyclic product.



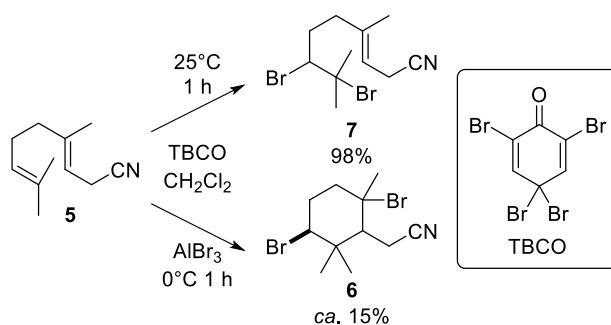
Scheme 3 - Brominative cyclisation of methyl farnesate **1** using NBS

A decade later research into brominative polyene cyclisations continued. This was driven by an increasing number of halogenated mono-, sesqui-, and diterpenoids being isolated from the secondary metabolites of red algae,^{61, 45a} sponges⁶² and sea hares.^{63, 45f} Copper(II) acetate was used as an additive in *tert*-butanol and acetic acid to improve on van Tamelen's conditions.⁶⁴ Monocyclic adduct **4** was isolated in 12% yield (Scheme 4).



Scheme 4 - Brominative cyclisation of methyl farnesate **1** using NBS and Cu(OAc)₂

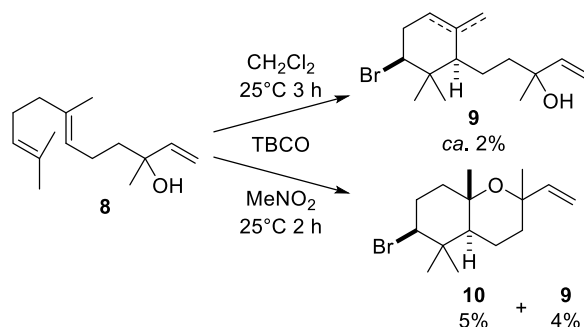
Kato used homogeranitrile **5** as a model polyene (Scheme 5) and under van Tamelen's conditions it was converted to a bromohydrin adducts without formation of any cyclised product. Kato found that 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) in the presence of a Lewis acid such as AlBr₃ could be used to cyclise homogeranitrile **5** into bromo-adduct **6**, albeit in low yield (*ca.* 15%).⁶⁵



Scheme 5 - Brominative cyclisation of homogeranitrile **5** using TBCO

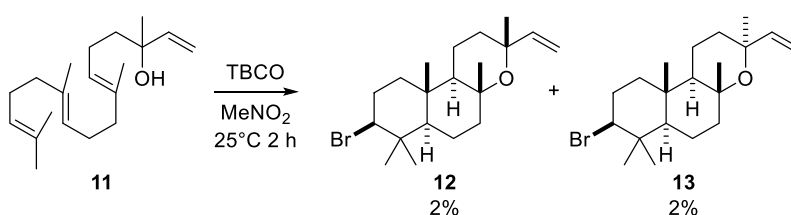
Without AlBr₃, TBCO efficiently brominates homogeranitrile to give dibromide **7**.⁶⁶ It is expected by Kato that action of the Lewis acid on TBCO liberates a bromonium ion and the resulting tribromophenoxide-AlBr₃ complex anion is less reactive towards the carbocation initially formed by attack of the olefin onto bromonium ion. Therefore ring formation by the neighbouring double bond occurs instead.⁶⁵

When applying this method to a more complicated system (Scheme 6) Kato obtained without the aid of a Lewis acid a low (*ca.* 2%) but isolable yield of bromo-cycloadducts with the bromo-cyclisation of nerolidol **8** into racemic synderol **9**.⁶⁷



Scheme 6 - Brominative cyclisation of (±)-nerolidol **8** using TBCO

Use of the more polar solvent nitromethane produced 2% yield of each olefinic regioisomers α and β synderol **9**, and also 5% of the bicyclic bromoether: 3-bromo-8-epicaparrapi oxide **10** (Scheme 6).^{45h} When (±)-geranyl-linalool **11** was also treated with TBCO under these conditions, remarkably isolable quantities (2%) of both **12** and **13** tricyclic bromo ethers were obtained.

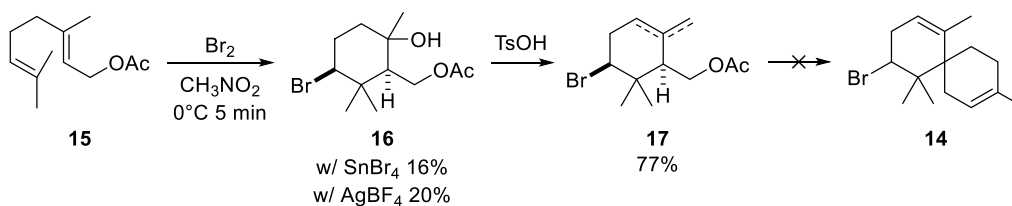


Scheme 7 - Brominative cyclisation of (±)-geranyl-linalool **11** using TBCO

Kato *et al.* have demonstrated the use of TBCO in a number of natural product syntheses⁶⁸ and have shown that it is a useful reagent for the brominative cyclisation of polyene precursors to synthesise up to three rings, in a presumed biomimetic fashion, albeit in low yields.

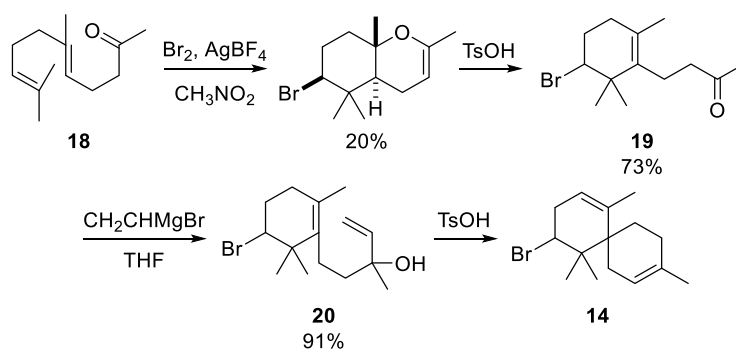
Wolinsky and Faulkner later set out to synthesise the simplest naturally-occurring brominated chamigrene: 10-bromo- α -chamigrene (**14**, Scheme 8),⁶⁹ which also contains the α,α -dimethylcyclohexyl bromide moiety. Investigations were carried out into the use of reagent systems where no nucleophile was present to trap the presumed bromonium ion. The use of molecular bromine and stannic bromide in nitromethane on geranyl acetate **15** at 0°C for 5 minutes yielded 16% of the desired cyclised bromoacetate **16** (Scheme 8). Large quantities of dibrominated materials were also isolated and so silver tetrafluoroborate was substituted for stannic bromide in order to sequester the bromide ions as they were produced. This improved the yield of **16** to 20%. Elimination of tertiary alcohol **16**, ready for a second ring-cyclisation was carried out using tosic

acid. Unfortunately an inseparable mixture of undesired olefins **17** were returned in 77% yield which did not allow for further cyclisation to chamigrene **14**.



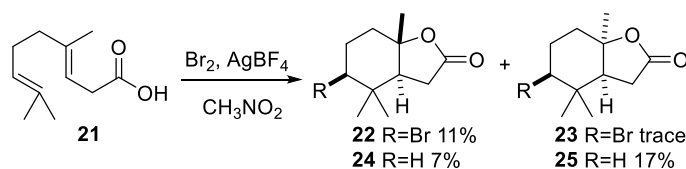
Scheme 8 - Bromo-cyclisation of geranyl acetate **15** using molecular bromine and silver tetrafluoroborate

However, brominative cyclisation and acid catalysed rearrangement of geranylacetone **18** did give the desired tetrasubstituted olefin **19** (Scheme 9). Addition of a two carbon fragment *via* a Grignard reaction provided tertiary alcohol **20**, allowing the second cyclisation to proceed to the desired 10-bromo- α -chamigrene **14** on treatment with tosic acid.



Scheme 9 - Bromo-cyclisation of geranyl acetone **18** using molecular bromine and silver tetrafluoroborate

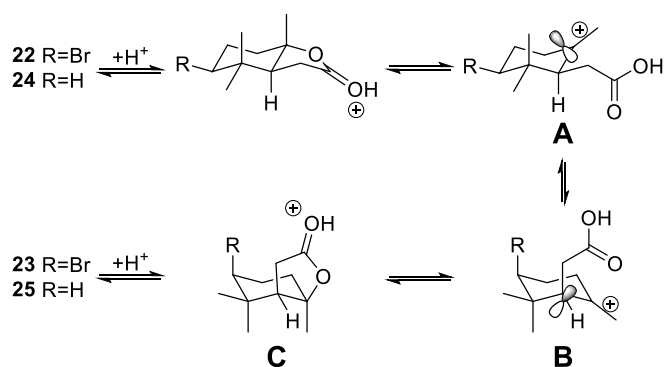
In expanding the scope of this reaction, Hoyer and Kurth carried out the bromolactonisation of homogeranic acid **21**, using the same conditions, with the desire of synthesising brominated bicycles **22** and **23** (Scheme 10). However, as well as producing bromine containing adducts **22** and **23**, they found that the predominant reaction was the formation of norbromo lactones **24** and **25**.⁷⁰



Scheme 10 - Hoyer and Kurth's bromo-cyclisation of homogeranic acid **21** using molecular bromine and silver tetrafluoroborate

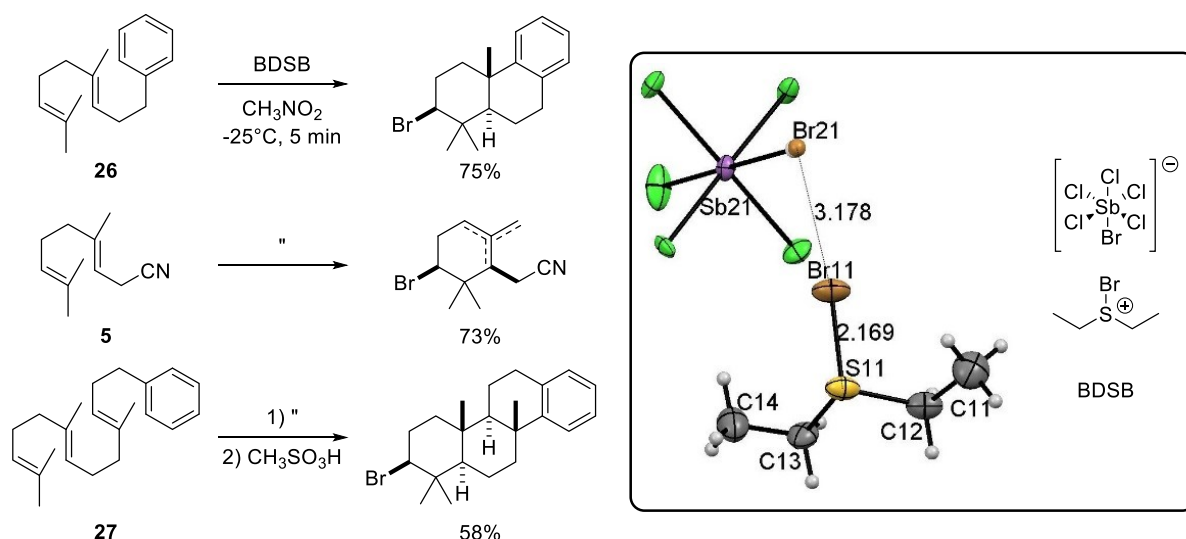
This observation provided Hoyer and Kurth with insight into the reaction's mechanism. Investigation using different acids and conditions allowed them to determine if the undesired norbromo products **24** and **25** were arising *via* a competing cyclisation catalysed by acid, presumably generated as the brominative cyclisation proceeded. Hoyer and Kurth found that

proton initiated cyclisation of homogeric acid **21** led to the *trans*-fused lactone **24**, the kinetically-favoured product. This then isomerised to the thermodynamically favoured *cis*-fused lactone **25** in the presence of both Lewis and Brønsted acids. It was found that this cyclisation and isomerisation was favoured in nitromethane solvent as opposed to less polar solvents. However, isomerisation of bromide containing *trans*-**22** to *cis*-**23** only occurred to a minute extent under the same conditions. Both of these results can be rationalised by a common mechanism: ring-opening of *trans* lactones **22** and **24** (Scheme 11) to planar carbenium ion **A** which can ring-close to the thermodynamic *cis*- lactone **C** *via* attack on the opposite face of the carbenium ion by the carboxyl group (**A** to **B**). This requires a conformational change which would result in severe 1,3-diaxial strain (**B**) in the case of **22** and so this mechanism is comparatively unfavoured resulting in just trace amounts of **23** being isolated.



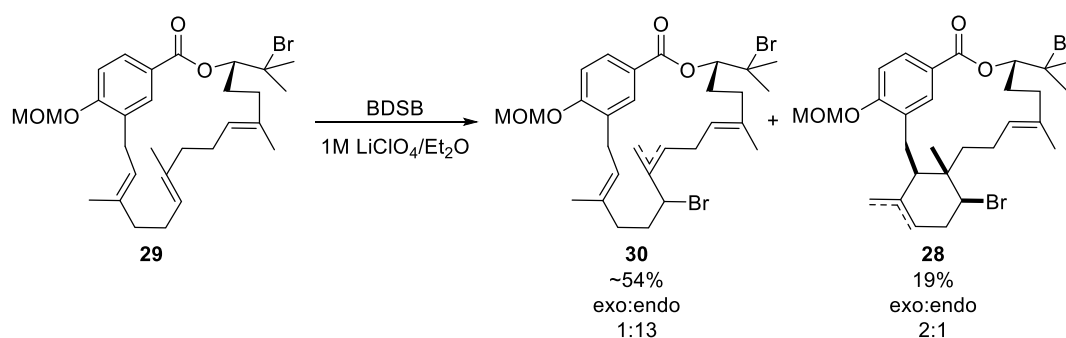
Scheme 11 - Isomerisation of *trans* lactones to *cis* derivatives⁷⁰

Up until now, most methods of direct brominative cyclisation have been low-yielding. This must arise in part from the requirement of the reagent to react regioselectively with the olefin at the terminus of the polyene chain. The recent introduction of the powerful reagent bromodiethylsulfide bromopentachloroantimonate (BDSB, Scheme 12) by Snyder and Treitler—a highly-activated source of electrophilic bromine, free from any additional nucleophilic species—now allows for highly efficient bromonium ion induced cation- π cyclisations of a diverse set of polyenes derived from geraniol (such as **26**) and farnesol (such as **27**), in >55% yield, usually within 5 minutes. Larger polyenes derived from farnesol required diastereoselective cyclisation of the third ring using methanesulfonic acid.⁴⁸ This process is diastereoselective, forming a single product with the relative stereochemistry shown, however these cyclisations necessarily result in racemic cyclic adducts.



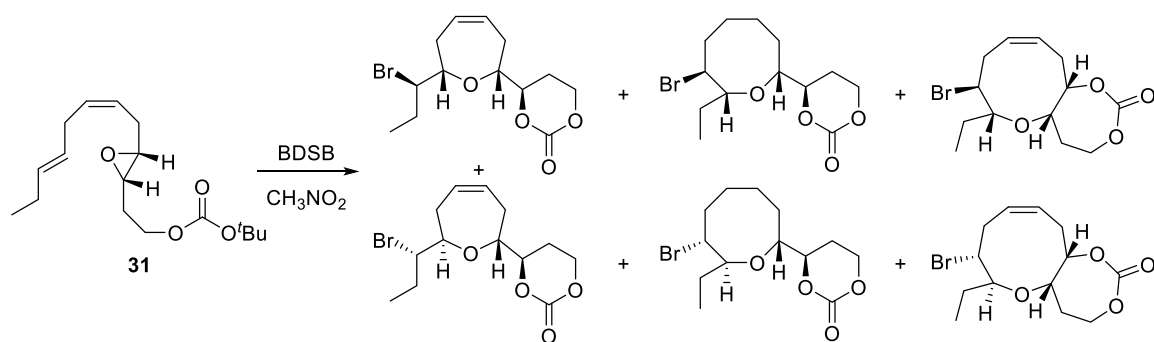
Scheme 12 - BDSB brominative polyene cyclisations⁴⁸

Bromonium ion-induced cyclisations using BDSB have recently formed part of a number of studies towards the synthesis of natural products. For example, the construction of alkenic regioisomers, bromophycolide A and D skeletons **28** (Scheme 13), *via* diastereoselective bromonium ion-induced cyclisation of triene **29** has been achieved in low yield with competitive elimination pathways to alkene isomers **30**.⁷¹



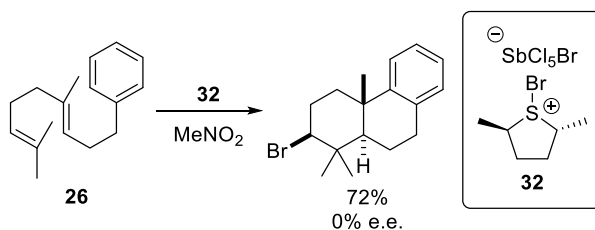
Scheme 13 - The use of BDSB in the synthesis of bromophycolide A and D skeletons

The Braddock group have also used BDSB for an intramolecular bromonium ion assisted epoxide ring-opening reaction.⁷² Enantiomerically-enriched epoxide **31** (Scheme 14), when treated with BDSB, formed a number of constitutional isomeric halogenated C₁₅-acetogenin medium-ring ether compounds that represent the core structures of a number of natural products from *Laurencia* species.



Scheme 14 - BDSB mediated synthesis of halogenated C₁₅-acetogenin medium-ring ethers

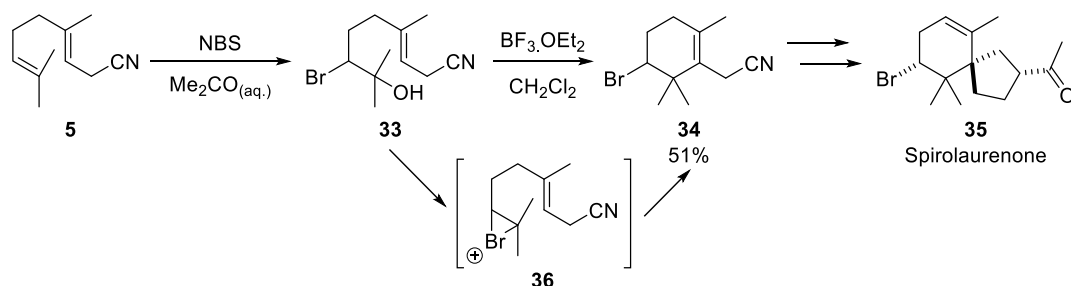
In an endeavour to render these reactions enantioselective, Snyder and co-workers prepared C₂-symmetric chiral sulfonium bromide **32** (Scheme 15).^{45b, 73} The use of this reagent with substrate **26** led to the formation of the expected product in good yield (72%) but unfortunately as a racemic mixture.



Scheme 15 - A chiral BDSB analogue

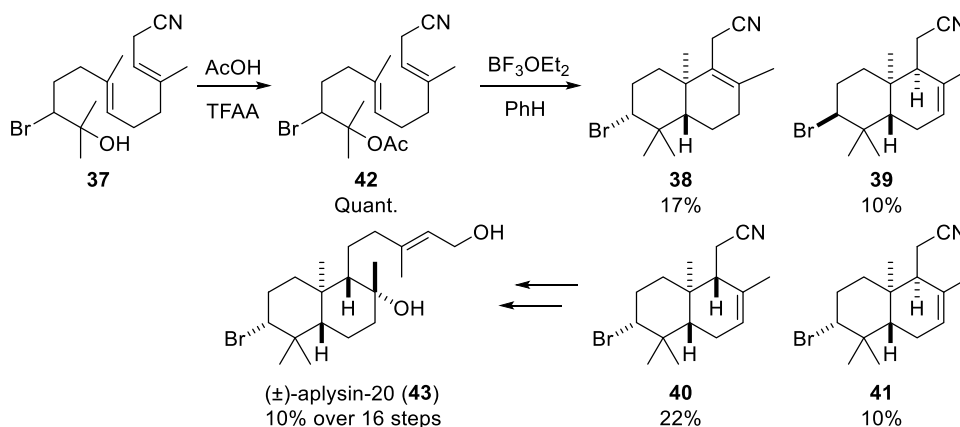
1.4.2 Polyene cyclisations triggered by activation of a bromohydrin

In 1982 Murai reported excellent yields (up to 94%) of bromo-cyclised adducts by the action of a Lewis acid on (racemic) bromohydrins. For example, bromohydrin **33** was cyclised to monocyclic bromo-adducts in 64% yield, (Scheme 16) of which **34** was isolated in 51% yield and elaborated to the antifungal agent, spirolaurenone **35** which possesses a unique spiroaurane skeleton.⁷⁴ Although not explicitly stated in his paper, it is likely that this reaction proceeds through bromonium ion **36** by elimination of Lewis acid activated alcohol through neighbouring group participation of bromine.



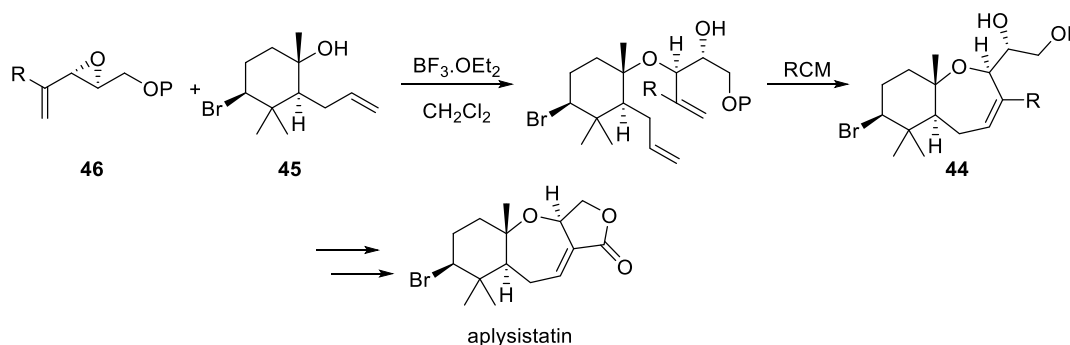
Scheme 16 - Brominative cyclisation of homogeronitrile **5** using boron trifluoride diethyl etherate

This approach was further extended to the cyclisation of bromohydrin polyenes such as **37** to give *bicyclic* ring systems (**38-41**, Scheme 17). The formation of two rings required further activation of the alcohol as acetate **42**, in order to obtain reasonable isolated yields of bicycle **40**. This methodology was used as the key-step in the synthesis of racemic aplysin-20 (**43**), in 16 steps and 10% overall yield.⁷⁵



Scheme 17 - Murai's total synthesis of (±)-aplysin-20 (**43**)

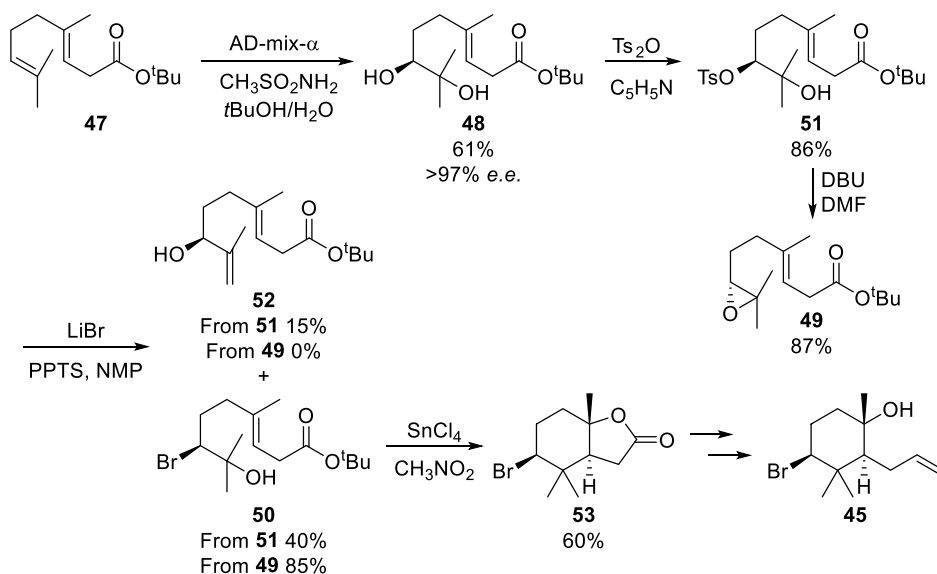
Murai has demonstrated good yields for bromo-cyclisation of polyenes by the action of a Lewis acid on bromohydrin or acetate derivatives to give monocyclic and bicyclic adducts such as **34** and **40** as necessarily racemic products. In 2004 Couladouros and Vidal⁷⁶ used this methodology as part of a new, stereocontrolled method for the formation of *trans*-anti cyclogeranyl-oxepene systems such as **44** (Scheme 18). In this case, the Lewis acid activation of an enantiopure bromohydrin provided the key chiral building block **45** which underwent stereospecific $\text{S}_{\text{N}}2$ attack onto a 1,2-unsymmetrically substituted epoxide **46**. Ring-closing metathesis was employed to form the highly strained 7-membered oxepene ring before diversification into a number of natural products such as aplysinstatin.



Scheme 18 - Couladouros and Vidal's synthesis of aplysinstatin

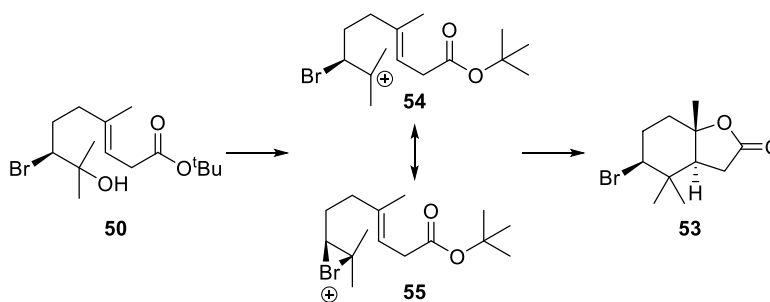
The asymmetric synthesis of enantiopure α,α -dimethylcyclohexyl bromide moiety **45** began with Sharpless asymmetric dihydroxylation of polyene **47** to give diol **48** in good regio- (61% yield)

and excellent enantioselectivity (>97% e.e.) (Scheme 19). Formation of the epoxide **49** and regio- and diastereoselective ring-opening with LiBr and PPTS in NMP was reported to produce bromohydrin **50** with good anti-Markovnikov selectivity and in excellent yield. Attempted direct S_N2 displacement of tosylate **51** with bromide anion led to competing elimination to allyl alcohol **52** in 15% yield. Couladouros and Vidali then activated the tertiary alcohol **50** towards cyclisation with tin(IV) chloride using Gosselin's conditions,⁷⁷ to give bromocyclodecane **53** in 60% yield and in optically active form.



Scheme 19 - Couladouros and Vidali's synthesis of an enantiopure bromohydrin

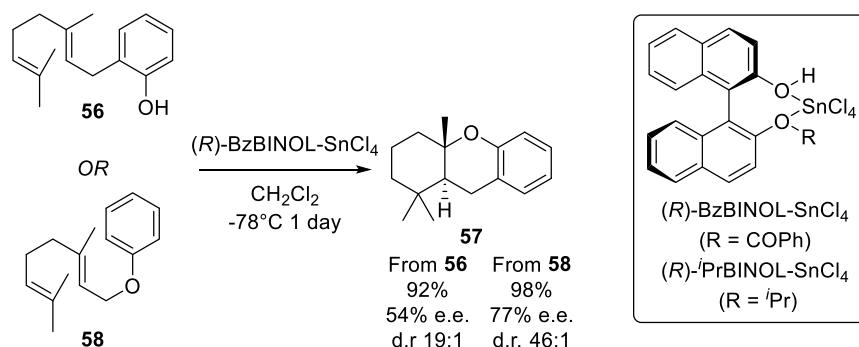
For cyclisation of **50** to **53** there are two possible mechanistic scenarios. One involves cyclisation onto tertiary carbocation **54** (Scheme 20), whereas the other invokes a neighbouring group participation to form enantiopure bromonium ion **55** before cyclisation. Interestingly, Couladouros does not speculate on the mechanism, and does not invoke a bromonium ion. In any event, the mechanism will depend on the relative stabilities of the bromonium ion in comparison to the cationic intermediate which is inherently stabilised by its tertiary nature.



Scheme 20 - Possible mechanisms for cyclisation of asymmetric bromohydrin **50**

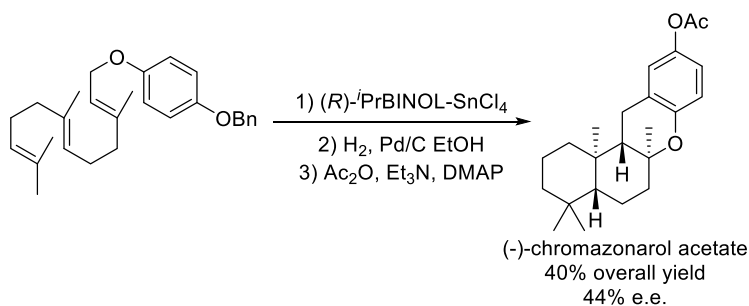
1.4.3 Enantioselective polyene cyclisations

The first enantioselective biomimetic cyclisation of polyprenoids was reported in 1999 by Yamamoto, Ishihara and Nakamura, who combined a system of a Lewis acid and a chiral Brønsted acid.⁷⁸ One equivalent of (*R*)-BzBINOL- SnCl_4 (Scheme 21) was found to give the best yields for cyclisation of 2-geranyl phenol **56** to *trans*-decalin **57** at 92%. This was isolated with moderate enantio- and diastereoselectivity (54% e.e. and 19:1 d.r.). However, it was found that **57** was isolated with much better selectivity from the reaction of geranyl phenyl ether **58** even with only 20 mol% of (*R*)-BzBINOL- SnCl_4 to give **57** in 77% e.e. and 46:1 d.r.



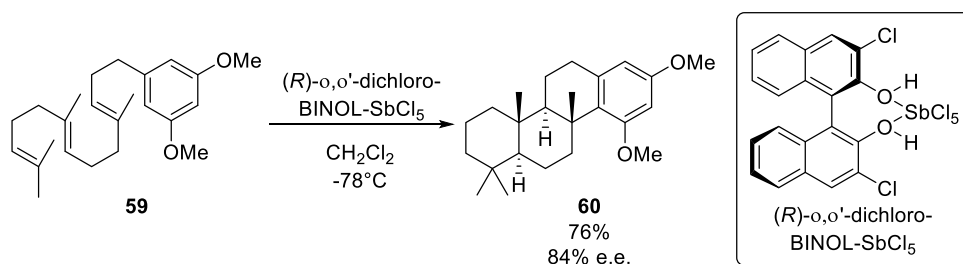
Scheme 21 - The first enantioselective cyclisation of polyprenoids

This methodology was demonstrated in the asymmetric synthesis of (-)-chromazonarol acetate (Scheme 22), a minor constituent of the brown Pacific seaweed, *Dictyopteris undulate*.⁷⁹ In this case one equivalent of (*R*)-*i*PrBINOL- SnCl_4 gave the desired compound as the major diastereomer in 44% e.e. and 40% overall yield.



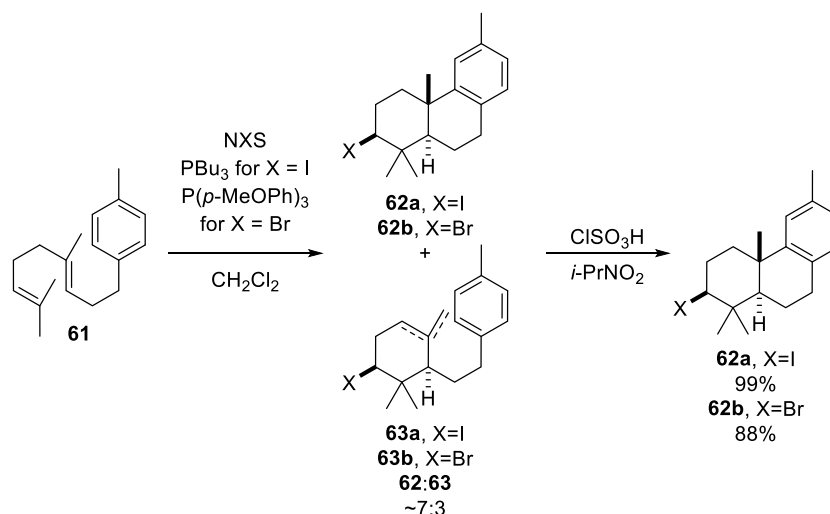
Scheme 22 - Asymmetric synthesis of (-)-chromazonarol acetate

The substrate scope of this reaction was enhanced by the Yamamoto group when new BINOL ligands were tested in combination with SnCl_4 .⁸⁰ However, it wasn't until very recently that Corey and Karavadhi discovered a method to improve the enantioselectivity of this reaction. They observed that a 1:1 complex of *o,o'*-dichloro-BINOL and antimony pentachloride in reaction with triene **59** gave tetracycle **60** in 84% e.e. with complete diastereoselectivity (Scheme 23). This was a consequence of the increased acidity of the BINOL ligand and a bulkier, stronger Lewis acid, antimony pentachloride.



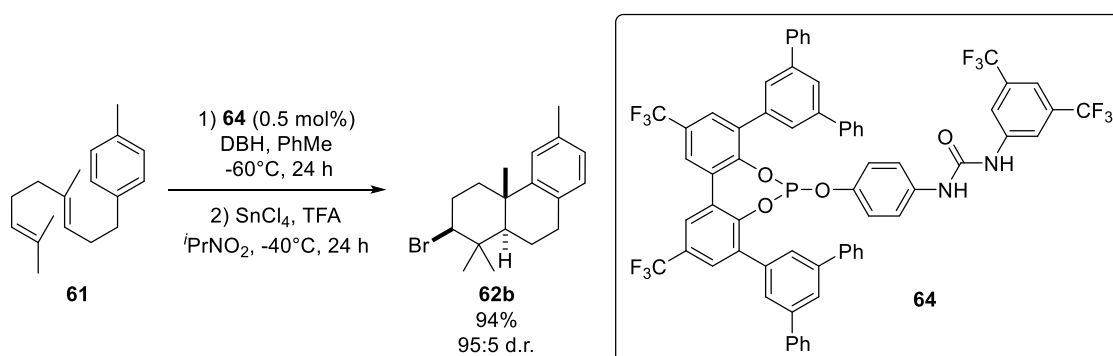
Scheme 23 - Enantioselective proton-initiated polyene cyclisation

Recently, Ishihara and Sakakura demonstrated the use of BINOL ligands in the development of polyene halo-cyclisation reactions. Initially, Ishihara found that racemic halo-cyclisation of 4-(homogeranyl)toluene **61** was extremely efficient using NIS or NBS in the presence of a nucleophilic phosphine catalysts such as tributylphosphine or tri(4-methoxyphenyl)-phosphine (30 mol%) in dichloromethane, producing **62a** and **62b** respectively in excellent yields (>80%, Scheme 24). Albeit after diastereoselective cyclisation of the initially produced monocyclic adducts **63a** and **63b** with chlorosulfonic acid.³²



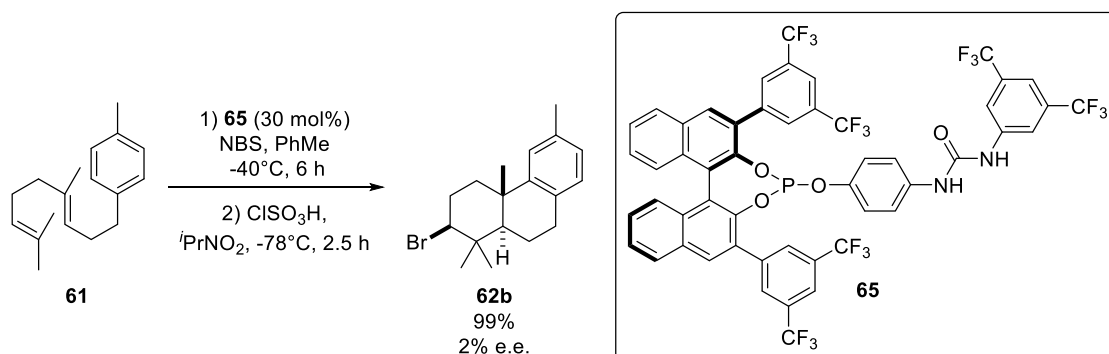
Scheme 24 - Cyclisation of **61** with NXS and a nucleophilic phosphine catalyst

The racemic bromo-cyclisation of **61** was later optimised by Ishihara and co-workers using 1,3-dibromo-5,5-dimethylhydantoin, a more reactive brominating reagent than NBS and a highly active nucleophilic phosphine catalyst containing urea and bulky aryl groups, **64**, to give 94% yield of **62b** with excellent diastereoselectivity also being reported (95:5 d.r., Scheme 25).⁸¹ Acid catalysed cyclisation of the second ring was optimised using trifluoroacetic acid and additional Lewis acid, tin(IV) chloride. It is proposed that urea binds to succinimide that is produced during the course of the reaction, thus preventing it from reacting with the active catalytic species to produce anionic bromide which is responsible for dibromide containing by-products.



Scheme 25 - Bromo-cyclisation of **61** with DBH and a nucleophilic phosphine urea catalyst

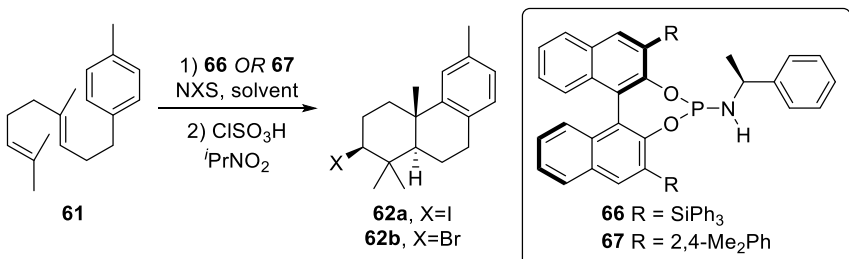
Attempts to render this reaction asymmetric using a BINOL derived catalyst **65** were unsuccessful (Scheme 26). The reaction of diene **61** with NBS and chiral catalyst **65** gave essentially full conversion to tricyclic **62b** after chlorosulfonic acid catalysed cyclisation. However, only minor asymmetric induction was observed (2% e.e.).



Scheme 26 - Attempted asymmetric bromo-cyclisation using a chiral nucleophilic phosphine urea catalyst

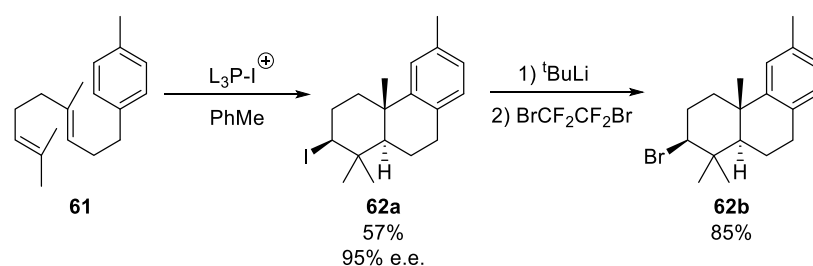
Ishihara and co-workers were however able to demonstrate the asymmetric *iodo*-cyclisation of diene **61** using chiral phosphoramidite **66** at stoichiometric loading to give iodide **62a**. Remarkably, in toluene, 57% yield and 95% e.e. was observed (after treatment with chlorosulfonic acid, Table 1, entry 1). Interestingly, in dichloromethane no asymmetric induction was observed, although a 95% yield of racemate **63a** was isolated (entry 2). Similarly high enantioselectivities (>90% e.e.) were also found in the iodination cyclisations of 3-(homogeranyl)toluene, 4-(homogeranyl)anisole and 4-(homofarensyl)toluene. However, when using NBS and catalytic quantities of chiral phosphoramidite **66**, bromide **62b** was only isolated with 4% enantiomeric excess and 29% yield (entry 3), which could only be improved to 75% yield and 36% e.e. with stoichiometric loading of a more bulky phosphoramidite ligand **67** (entry 4).

Table 1 - Asymmetric halo-cyclisation of diene **61** with NXS and a nucleophilic phosphine catalyst



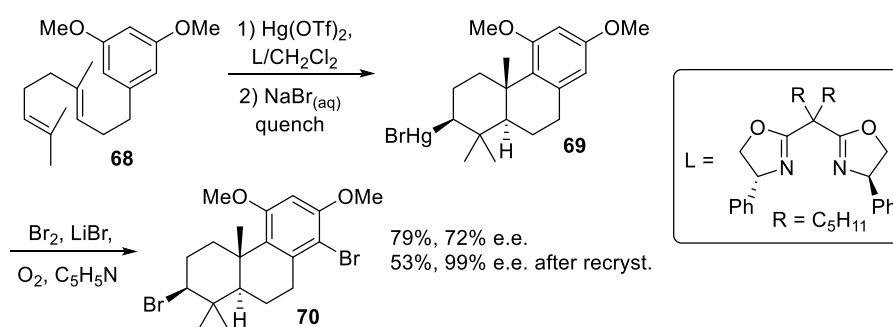
Entry	NXS	Nu. cat. (mol%)	Solvent	Product	Yield (%)	e.e. (%)
1	NIS	66 (100)	MePh	62a	57	95
2	NIS	66 (100)	CH ₂ Cl ₂	62a	95	0
3	NBS	66 (20)	MePh	62b	29	4
4	NBS	67 (100)	MePh	62b	75	36

Therefore, to access enantiomerically-enriched bromide and chloride products, which are more common in nature, Ishihara and co-workers converted the chiral iodides into the corresponding bromides through lithiation and stereo-retentive halide capture (Scheme 27).



Scheme 27 - Lithiation and stereo-retentive bromide capture of enantiopure iodides

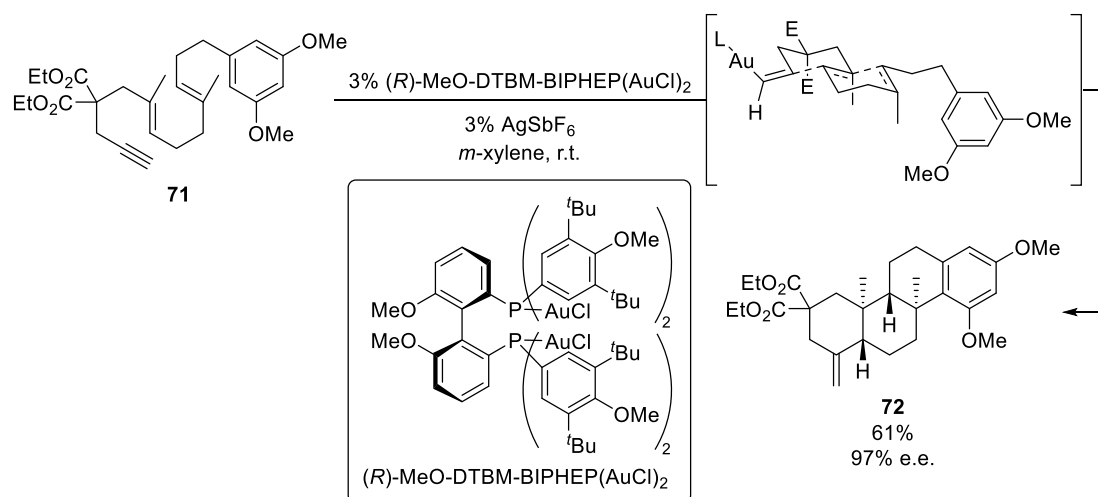
Snyder has also recently employed a similar two-step mimic for asymmetric bromonium ion induced polyene cyclisations.^{34a} Snyder developed methodology to synthesise chiral organomercury cyclic adducts which could then be substituted by bromine in a stereo-retentive fashion.



Scheme 28 - Snyder's two-step mimic for direct asymmetric bromonium ion induced polyene cyclisation

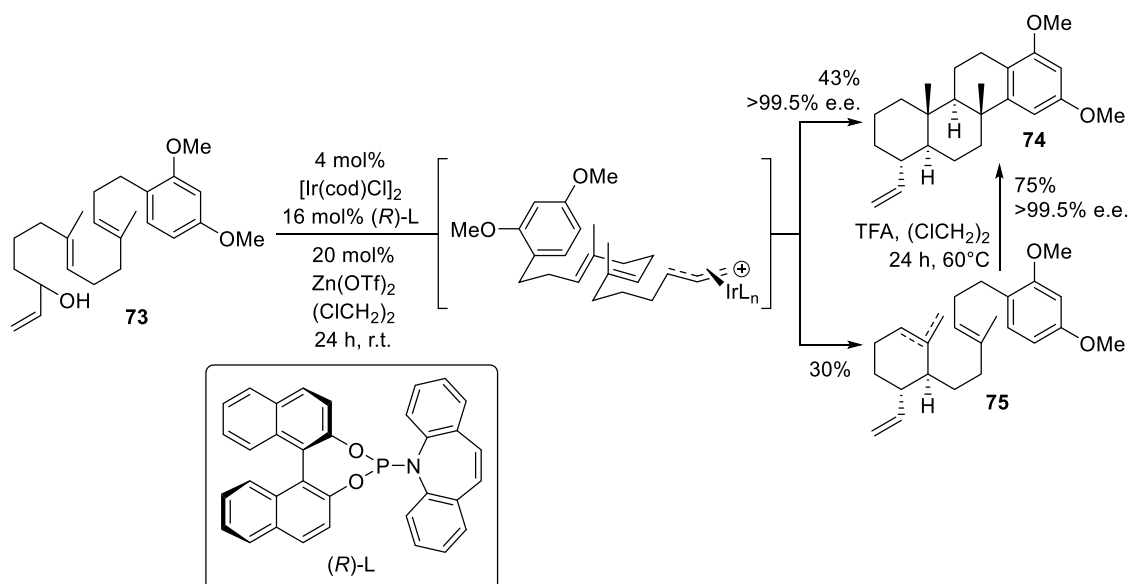
As a representative example, diene **68** was treated with mercury triflate and C_2 -symmetric chiral oxazoline ligand (L) to give cyclised product **69** (Scheme 28). Subsequent treatment with an excess of bromine in oxygenated pyridine, according to the procedure by Hoye and Kurth,⁸² generated the desired product **70** in 79% overall yield and 72% e.e. After recrystallisation of the intermediate organomercury **69**, bromo-cyclised product **70** was afforded in 99% e.e and 53% yield. Although high yielding and enantioselective, this method requires stoichiometric quantities of toxic mercury salts. Also it can be noted that with electron rich aromatics such as **68**, bromination of the aromatic ring is likely with the use of molecular bromine.

Very recently there has been a number of metal-initiated enantioselective polyene cyclisation reactions reported by groups such as Toste,⁸³ Carreira³⁶ and Gagné.⁸⁴ Toste *et al.* report a highly enantioselective gold(I)-catalysed polyene cyclisation in which transition metal-promoted alkyne activation serves as the cyclisation initiating event. Excellent yields were even obtained in the tricyclisation of dienyne **71** to form tetracycle **72** in 61% yield and 97% e.e. (Scheme 29).



Scheme 29 - Gold(I)-catalysed enantioselective polycyclisation reaction

Carreira *et al.* report the highly enantioselective initiation of allylic alcohols, catalysed by iridium and promoted by zinc triflate forming cyclic products in greater than 99.5% e.e. and with excellent yields. The Ir-catalysed cyclisation of **73** was shown to afford tetracyclic product **74** in 43% isolated yield and >99.5% e.e. as a single diastereomer (Scheme 30) and, with careful separation, isomeric trienes **75** in 30% yield. With an additional acid catalysed cyclisation, **75** was fully cyclised to tetracycle **74** in 75% isolated yield to give an overall combined yield of 65% for **74** and with identical enantioselectivity. It was concluded by Carreira *et al.* that the formation of tetracycle **74** from triene **73** in such high stereoselectivity would suggest that this catalyst system has direct stereocontrol of the first cyclisation event. The subsequent ring closures are then stereospecific in accordance with the Stork-Eschenmoser hypothesis.



Scheme 30 - Iridium-catalysed enantioselective polyene cyclisation

Very recently, asymmetric electrophilic platinum(II) cation- π cascades developed by Gagné and co-workers - which would normally be susceptible to β -hydride elimination to produce **76** or **77**⁸⁴ – have been intercepted by a Pt-C fluorination reaction to form asymmetric fluorinated bicycles **78** and **79** (Scheme 31).⁸⁵ The use of silver tetrafluoroborate, perfluorobenzonitrile and commercially available chiral paracyclophane derived ligand (*S*)-xylyl-phanephos (**80**) form the active species for this transformation: $[(S)\text{-(xylyl-phanephos)Pt(NCC}_6\text{F}_5)_2][\text{BF}_4)_2]$.

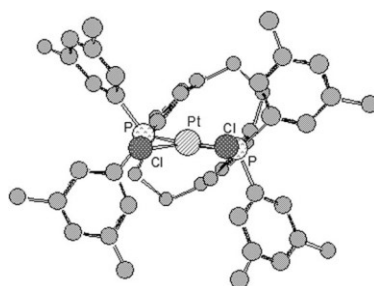
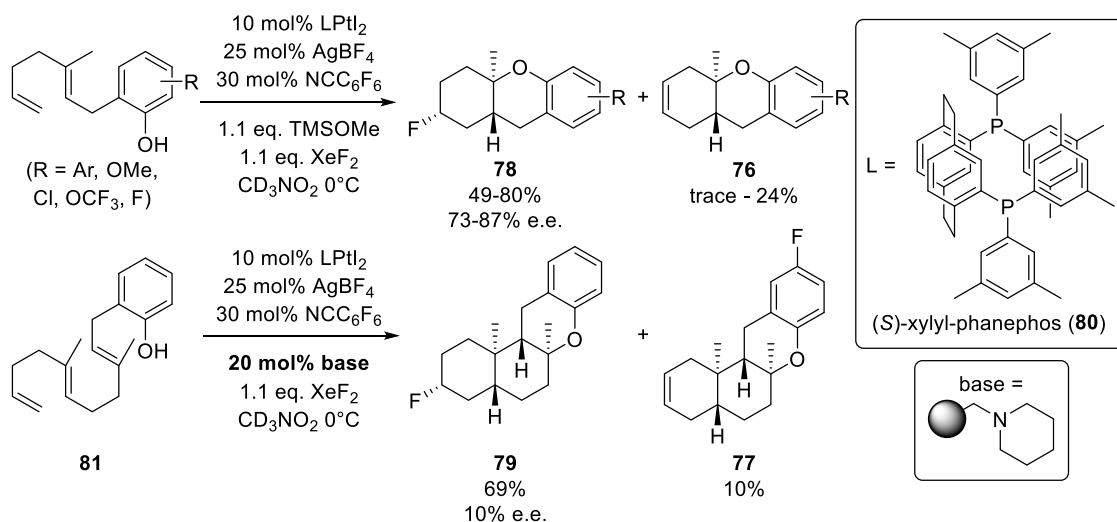


Figure 8 - X-ray crystallographic structure of (*S*)-(xylyl-phanephos)PtCl₂⁸⁴

Addition of base (TMSOMe) facilitates cyclisation and an electrophilic fluorine source provides good enantioselectivity with up to 87% e.e. and 80% yield, where β -hydride elimination is responsible for the major by-products.



Scheme 31 - Catalytic enantioselective cyclisation and C3-fluorination of polyenes

It can be noted that in the case of trienyl phenol **81**, polystyrene-bound piperidine base was used instead of TMSOMe to improve the yields of tetracycle **79**, however the enantioselectivity was greatly reduced to 10 % e.e.

Although these examples of enantioselective polyene cyclisations by high-profile research groups such as Toste, Corey and others⁸⁶ are not triggered by a bromonium ion, they demonstrate the high interest, importance and potential of polyene cyclisations. They suggest that if a cation- π cyclisation can be triggered by an enantiopure bromonium ion, then it is likely that the subsequent ring forming events will occur diastereoselectively. They also demonstrate the increasing difficulty in cyclising multiple rings, with the employment of acid-catalysed ring-closure steps necessary to form tetracyclic compounds. Recent advancements involving enantioselective iodonium ions, mercurinium ions and platinum(II)-induced cation- π cyclisations have provided access to chiral halogenated carbocycles in good yields, however there still remains a need for an enantioselective *bromonium* ion-induced cation- π cyclisation to yield the desired enantiopure bromo-cycles directly.⁸⁷

1.5 Configurational stability of bromonium ions

A cyclic bromonium ion was first proposed by Roberts and Kimball in 1937 to account for the well-established *anti*-stereochemistry observed for the addition of molecular bromine to olefins.⁸⁸ The existence of a cyclic symmetrical species was proven by Winstein and Lucas in 1939 with the loss of optical activity in the reaction of *erythro*- and *threo*-3-bromo-2-butanols with hydrobromic acid where the term “bromonium ion” was first coined (Figure 9).⁸⁹

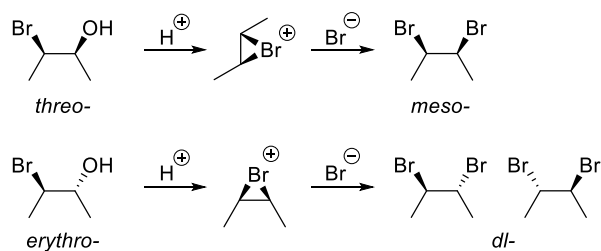


Figure 9 - Winstein and Lucas proving the existence of a bromonium ion

Olah *et al.* were the first to observe a bromonium ion by NMR.⁹⁰ The first stable bromonium ion was isolated by Wynberg *et al.*⁹¹ using adamantylideneadamantane which was subsequently characterised crystallographically (Figure 10) and studied by Brown and co-workers.⁹²

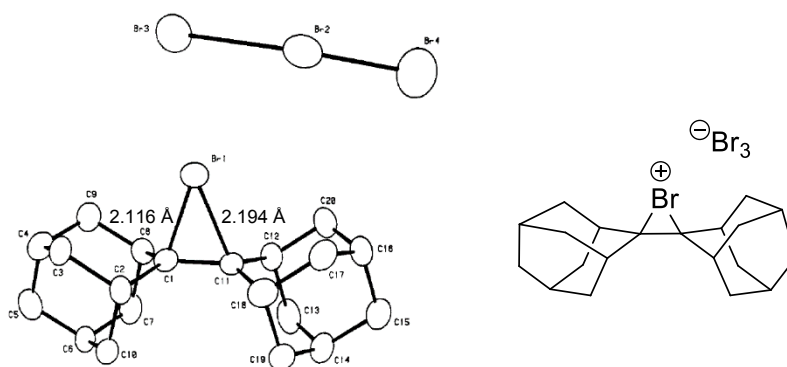


Figure 10 - X-ray crystal structure of the bromonium ion derivative of adamantylideneadamantane^{92a}

The exact structure of bromonium ions in a broader context, depends strongly on any substituents and on the solvent, and it is understood that a continuum of ionic intermediates are possible, of which the cyclic bromonium ion and the open β -bromocarocation are the extremes (Figure 11).⁹³ It is also known that bromonium ions of adamantylideneadamantane can transfer to acceptor olefins, presumably without transfer of stereochemical information.^{92b, 94}

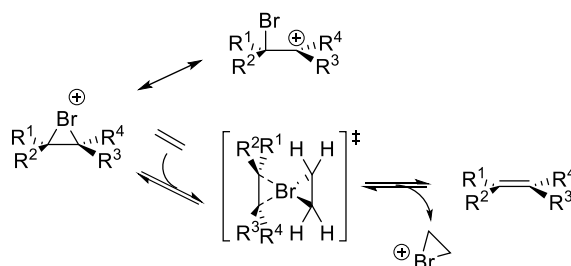


Figure 11 - Cyclic bromonium ion and open β -bromocarocation extremes and the transfer of bromonium ion to acceptor olefins

Denmark has further demonstrated that racemisation of enantiopure bromonium ions *via* olefin-olefin transfer is competitive with *intermolecular* capture by anionic nucleophiles.⁹⁵ The acetolysis of bromotosylate **82** in hexafluoroisopropanol—which provides a strong ionising medium of low nucleophilicity⁹⁶—at room temperature with sodium acetate gave good yields and

complete retention of configuration. However, when alkene **83** was introduced into the reaction, bromoacetate **84** was produced with a diminished enantiomeric ratio (blue markers, Figure 12). With one equivalent of alkene the percentage retention of configuration was reduced to 26%. A large excess of sodium acetate (5 eq.) did not alter this affect significantly (red markers, Figure 12).

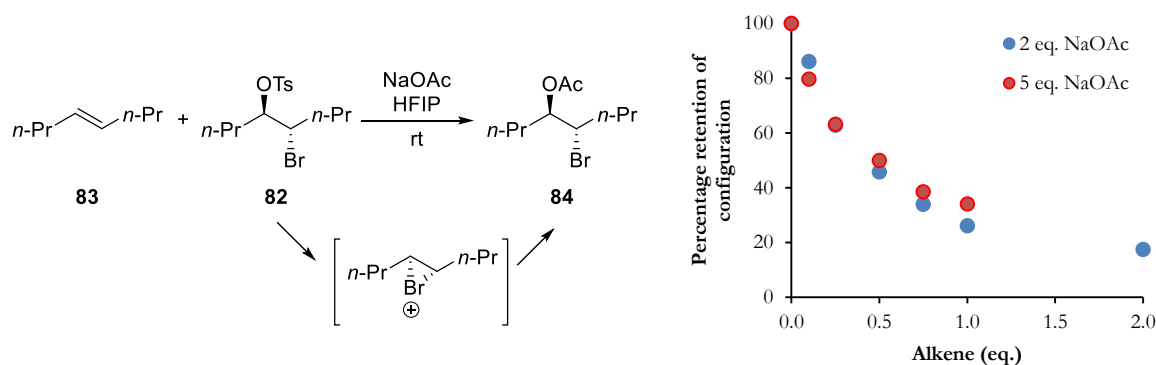
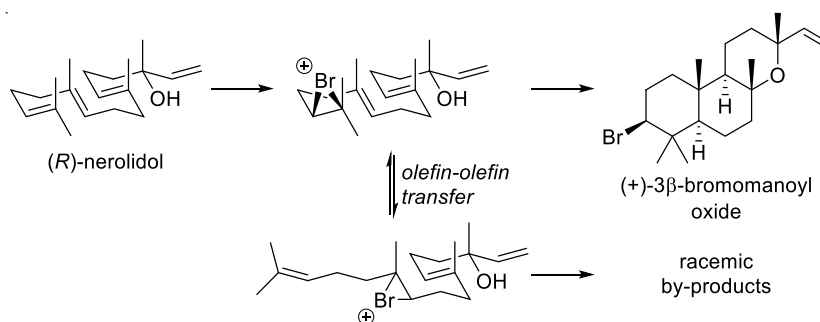


Figure 12 - Racemisation of enantiopure bromonium ion *via* olefin-to-olefin transfer

Since by definition a polyene cyclisation substrate will always contain alkene functional groups, it is not unreasonable to ask if such asymmetric cyclisations are therefore inherently compromised when not under enzymatic control. The close proximity of an intra- or intermolecular olefin may result in the transfer of an enantiopure bromonium ion to another alkene to give a racemic bromonium ion. This could increase the number of by-products and as it is a reversible process, the enantiomeric excess of the bromonium ion leading to the desired product could also be eroded (Scheme 32).

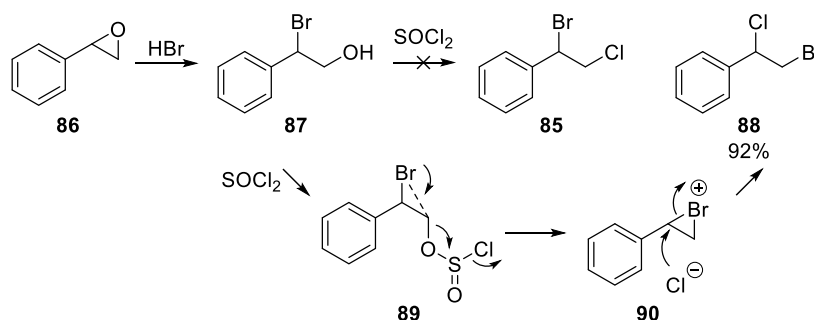


Scheme 32 - Asymmetric brominative polyene cyclisation of (*R*)-nerolidol to (+)-3β-bromomanoyl oxide

Previous research from the Braddock group has shown that an enantiopure bromonium ion can be prepared *in situ* and trapped with an intermolecular nucleophile.

1.6 Previous work in the Braddock group

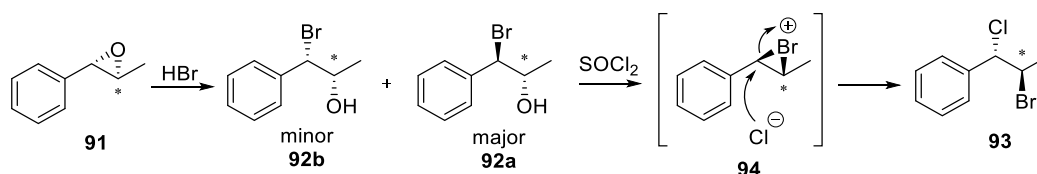
In the attempted synthesis of bromochloride **85** (Scheme 33) racemic styrene oxide **86** was ring-opened with excellent regio-control to bromohydrin **87** by the action of HBr. Alcohol **87** was then treated with thionyl chloride.⁹⁷ However, instead of the expected bromochloride **85**, the corresponding regioisomer **88** was formed in excellent yield. This product must arise *via* the alkyl chlorosulfite **89**, and intervention of a bromonium ion **90** *via* neighbouring group participation,⁸⁹ followed by attack of liberated chloride at the benzylic carbon.⁹⁸ The structure of bromochloride **88** was unambiguously confirmed by X-ray crystallography.



Scheme 33 - Racemic styrene oxide reaction with HBr followed by thionyl chloride to benzylic chloride **88**

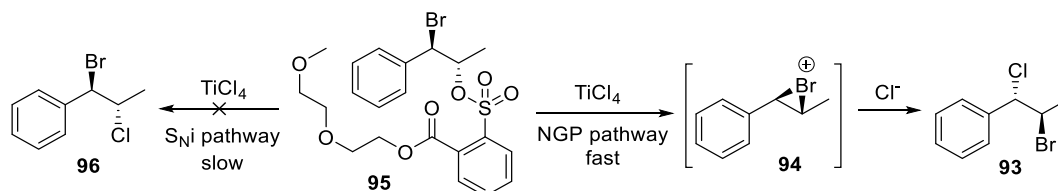
1.6.1 An asymmetric bromo-chlorination reaction

The group then explored this sequence using an enantiopure epoxide (Scheme 34). Starting with enantiopure β -methylstyrene oxide **91**, ring-opening of the epoxide to bromohydrin **92a** proceeded smoothly *via* backside attack. Although some minor diastereoisomer **92b** (*ca.* 20%) was obtained through the participation of the free benzylic cation, the stereochemical integrity of the homobenzylic stereocentre (marked with an asterisk in Scheme 34) was preserved as proven by the formation of the Mosher ester derivative (and comparison with the Mosher ester derived from racemic epoxide). On treatment with thionyl chloride the desired rearranged chlorohydrin **93**—evidently *via* enantiomerically pure bromonium ion **94**—was obtained as a single enantiomer as determined by chiral HPLC (>98% e.e.). The structure of **93** was also unambiguously solved by X-ray crystallography.⁹⁷



Scheme 34 - The trapping of an enantiomerically pure bromonium ion using thionyl chloride

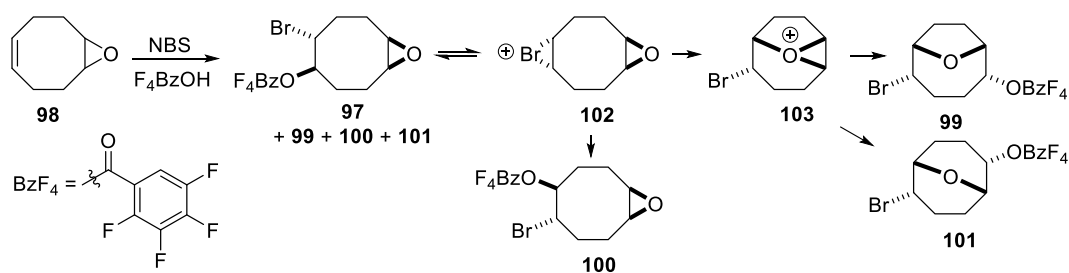
The group have also used PEG-sulfonate **95** to generate an enantiopure bromonium ion **94** by reacting it with TiCl_4 (Scheme 35).⁹⁷ Under these conditions Lepore had previously reported that chlorination of PEG-sulfonate occurs *via* an $\text{S}_{\text{N}}\text{i}$ mechanism⁹⁹ and bromochloride **96** might have been expected to result. The group discovered that bromochloride **93** was obtained instead, which proved to be enantiomerically pure – evidently *via* enantiomerically pure bromonium ion **94** and trapping by chloride nucleophile.⁹⁷



Scheme 35 - The use of PEG-sulfonate and TiCl_4 to generate an enantiopure bromonium ion

1.6.2 An interesting rearrangement on standing

In recent investigations by the group,¹⁰⁰ bromobenzoate **97** was isolated from the reaction of cyclooctene epoxide **98** with NBS and 2,3,4,5-tetrafluorobenzoic acid. Upon standing, neat, this compound was found to rearrange to **99**, **100** and **101** (Scheme 36). This must proceed *via* neighbouring group participation of the bromine and loss of tetrafluorobenzoate. The resultant bromonium ion **102** can now be trapped by the earlier expelled tetrafluorobenzoate to form **100**. Alternatively, transannular attack by the epoxide to give oxonium ion **103**, and attack of tetrafluorobenzoate gives bicyclic adducts **99** and **101**.

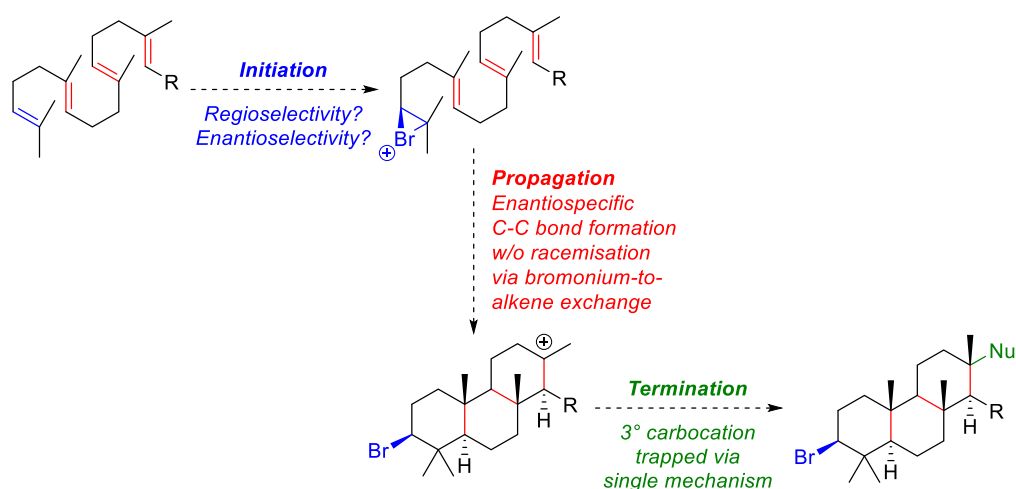


Scheme 36 - Demonstration of 2,3,4,5-tetrafluorobenzoate as a labile leaving group¹⁰⁰

It was noted¹⁰⁰ that this observation may be useful in designing further systems for the generation of enantiopure bromonium ions starting from enantiopure bromo-tetrafluorobenzoates. The enantiopure bromonium ion could then be trapped by a nucleophile intramolecularly to form cyclic compounds.

1.7 Aims and objectives

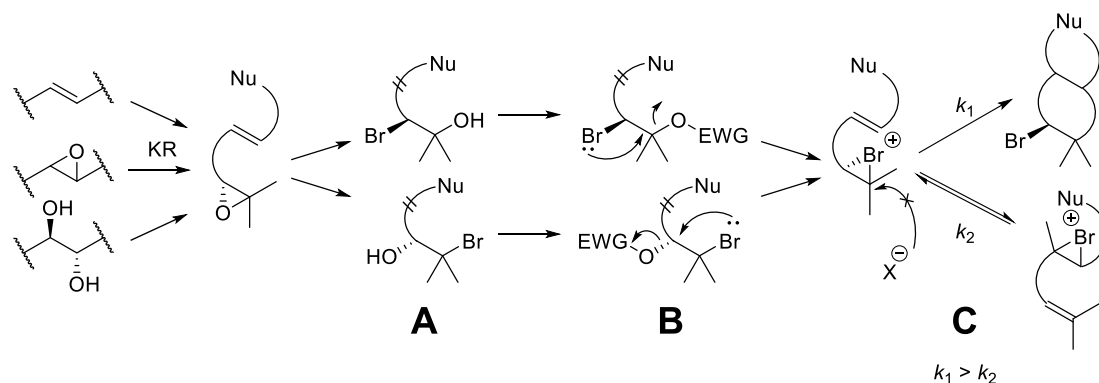
The overall aim of this project is to achieve the first polyene cyclisation triggered by an enantiomerically pure bromonium ion. To be successful, challenges in each of the fundamental steps of initiation, propagation and termination will need to be overcome (Scheme 37). In any initiation step, an enantiopure bromonium ion must be formed regioselectively at the terminus alkene of the polyene (in blue, Scheme 37). Currently, there is no widely applicable method for the formation of enantiopure bromonium ions by direct bromination of a simple trisubstituted alkene (even before considering the required regioselectivity of the process).^{87, 101}



Scheme 37 - Challenges for enantiospecific polyene cyclisation initiated by an enantiopure bromonium ion

In the propagation step(s) intramolecular C-C bond formation must occur preferentially to intra- and/or intermolecular bromonium ion-to-alkene transfer¹⁰² and methods to analyse the extent of racemisation must also be developed. Termination needs to occur *via* a single mechanism, to give one polyene cyclisation product. The synthetic approach used to tackle these challenges is demonstrated in Scheme 38 and will require:

- A.** Preparation of an enantiomerically pure bromine-containing substrate such as the bromohydrins shown in Scheme 38. These can be readily prepared by the anionic bromide ring-opening of an epoxide, the asymmetric synthesis of which can be accessed by a number of routes.
- B.** Formation of an enantiopure bromonium ion by activation of the alcohol as a suitable leaving group, in the absence of a strong nucleophile, X⁻.
- C.** Effective enantiospecific intramolecular trapping without erosion of enantiopurity by rapid bromonium ion-alkene exchange; whereby the rate of intramolecular trapping; k_1 is greater than the rate of racemisation by olefin-olefin transfer; k_2 .



Scheme 38 - Overview of synthetic strategy

In the first instance, racemic model systems will be utilised to develop the necessary synthetic methodology whilst chiral HPLC methods can be investigated to assess the extent of racemisation in a future asymmetric synthesis. This model system should:

1. Provide substrates in good yields and in a small number of synthetic steps;
2. Determine the required nature of the leaving group to form a bromonium ion;
3. Determine the conditions and reagents needed to activate the leaving group;
4. Provide chiral HPLC conditions for analysis of enantiomeric excess;
5. Be reproducible in an asymmetric strategy and without degradation of enantiopurity.

Realisation of the above chemistry will allow an asymmetric route to be undertaken and demonstrate that enantiomerically pure bromonium ions can be generated in a controlled fashion and be employed in synthesis. This methodology could then be applied in the biomimetic synthesis of naturally occurring sesqui-^{45a} and diterpene^{45d,45g} metabolites which possess the α,α -dimethylcyclohexyl bromide moiety (highlighted in red in Figure 13).

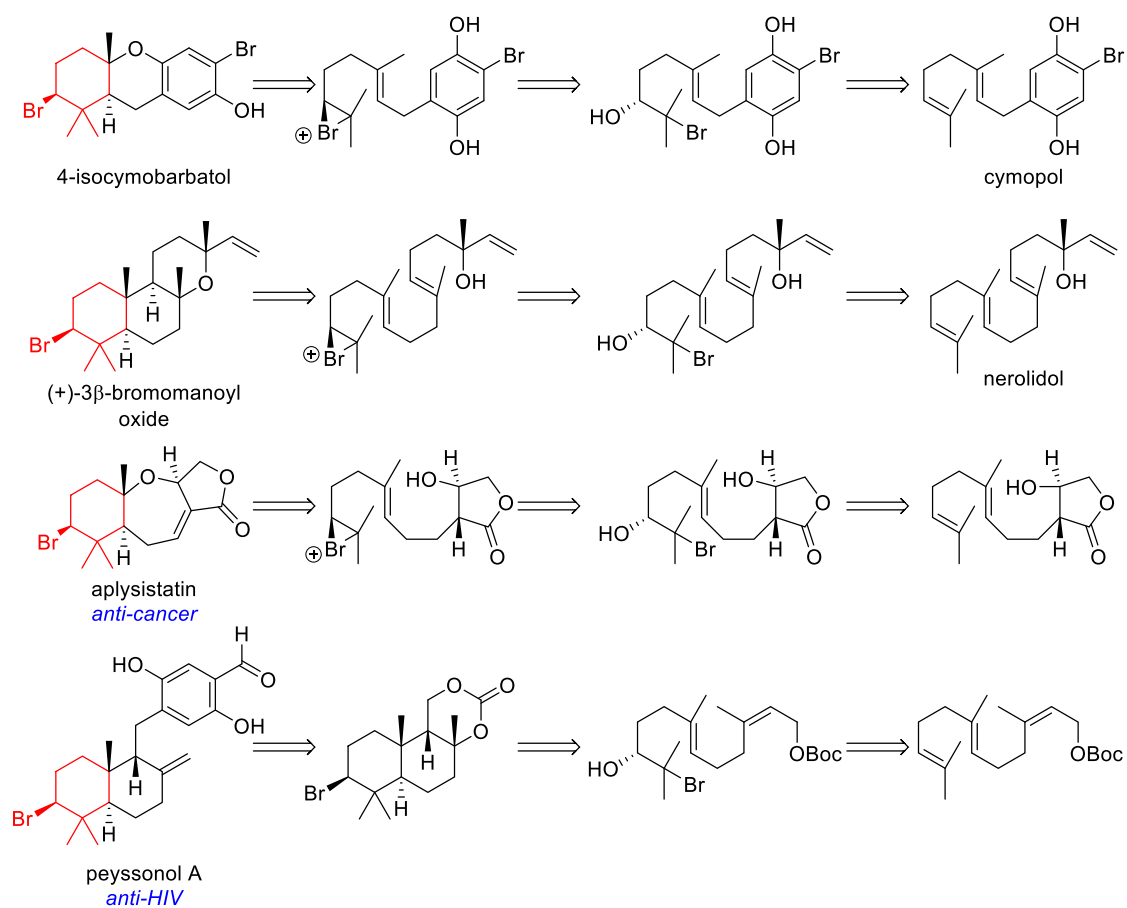


Figure 13 - Representative disconnections for brominated polycyclic natural products

2 Results and discussion

2.1 Synthesis of racemic substrates for mono-cyclisation

The overall aim of this research was to develop general methodology for the asymmetric synthesis of natural products containing an α,α -dimethylcyclohexyl bromide moiety *via* a biomimetic bromonium ion-induced polyene cyclisation. However, when considering cation- π cyclisations of substrates containing an increasing number of isoprene units we anticipated increasing complexity arising from olefin selectivity and difficulties in the closure of multiple rings (Figure 14).

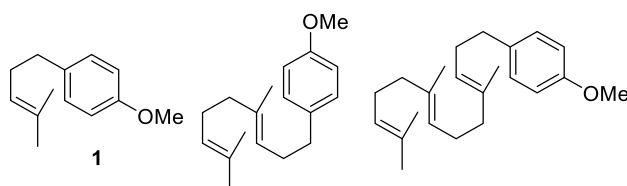
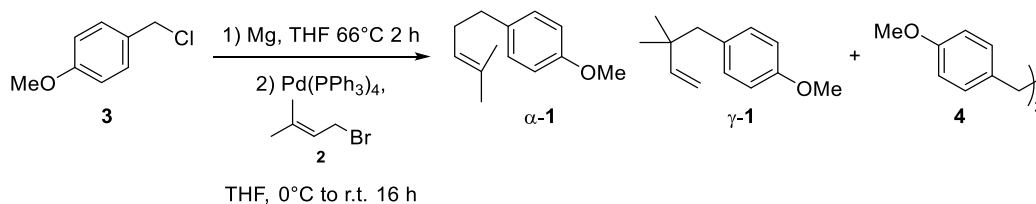


Figure 14 - Homoprenyl, homogeranyl and homofarnesyl *p*-methoxybenzene substrates

Initially we chose to investigate homoprenyl *p*-methoxybenzene (**1**), which allows for the investigation of cyclisation conditions without complications arising due to olefin selectivity. The cation- π cyclisation of this substrate will terminate by attack of the aromatic group; this was preferred over other nucleophilic groups because the remaining positive charge after cyclisation can only be quenched *via* one mechanism: rearomatisation (and therefore producing only one cyclisation product). The aromatic group also allows analysis by UV spectroscopy, which will be necessary for the determination of enantiopurity by chiral HPLC. *Para*-methoxy substitution of the aromatic ring also provides greater nucleophilicity for faster trapping of a bromonium ion during cyclisation and increases the polarity of the compound, aiding separation by analytical chiral HPLC.

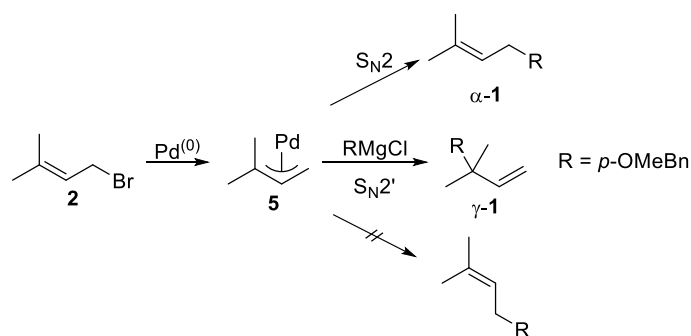
Homoprenyl *p*-methoxybenzene (**1**) was synthesised using methodology developed by Demuth.¹⁰³ In our hands, 76% isolated yield was obtained by alkylation of prenyl bromide **2** with 1.3 equivalents of *p*-methoxybenzyl Grignard reagent in the presence of 5 mol% Pd(PPh₃)₄ (Table 2, entry 1) along with homodimer **4** in 13% yield. Increasing the number of equivalents of Grignard reagent from 1.3 to 1.5 did not improve the yield of **1** (entry 2) and on a larger scale (10 g of prenyl bromide), the catalytic loading of Pd(PPh₃)₄ could be reduced to 1.5 mol% without compromising the yield (80%, entry 3).

Table 2 - Synthesis of homoprenyl *p*-methoxybenzene (**1**)

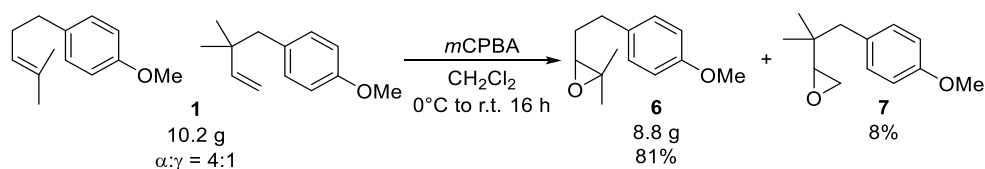
Entry	2 mmol	3 (eq.)	Pd(PPh ₃) ₄ (mol%)	Yield 1 ^a (%)	α:γ	Yield 4 ^a (%)
1	18	1.3	5.0	76	35:1	13
2	4	1.5	5.0	73	11:1	18
3	67	1.3	1.5	80	4:1	0
4	67	1.1	1.0	73	55:1	nd
5	34	0.95	1.0	78	50:1	nd

nd = not determined. ^aIsolated yield after column chromatography

In this reaction (Table 2, entry 3), the desired α -alkylated product **α -1** was isolated with inseparable **γ -1** in a 4:1 ratio. This undesired constitutional isomer is formed by S_N2' attack of the Grignard reagent at the more sterically hindered carbon of the intermediate (η^3 -allyl)Pd complex **5** (Scheme 39) which can be suppressed by decreasing the amount of Grignard reagent (1.1 or 0.95 equivalents) and Pd(PPh₃)₄ (1 mol%) (entries 4 and 5).

**Scheme 39** - Potential products of Demuth's allylic alkylation reaction

Epoxidation of olefin **1** was achieved with *m*CPBA in dichloromethane to give epoxide **6** in 81% yield (Scheme 40) together with isomeric epoxide **7** in 8% yield. This compound results from the epoxidation of **γ -1** present in the starting material.

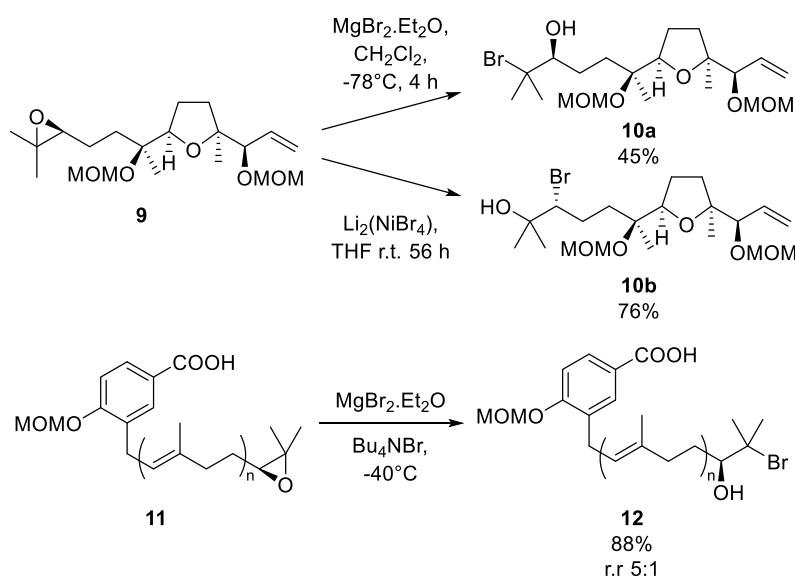


Scheme 40 - Epoxidation of homoprenyl *p*-methoxybenzene (**1**)

Analysis of racemic epoxide **6** by chiral HPLC using available chiral columns (CHIRALCEL OD-H or CHIRALPAK AD) provided incomplete baseline separation of enantiomers. Therefore the enantiopurity of this compound cannot be determined in future asymmetric synthesis of epoxide **6**. This simple two step procedure provided a quick route to over 8.5 grams of pure racemic epoxide **6**.

2.1.1 Anionic bromide epoxide ring-opening

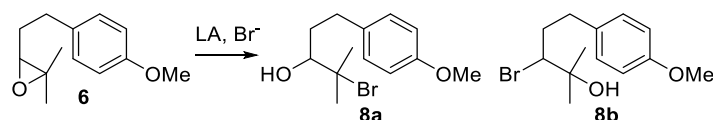
Attention then turned to conditions for the installation of bromide by epoxide ring-opening where two regioisomeric bromohydrin products are possible; **8a** and **8b** (Table 3). There are several reported methods for regioselective ring-opening of epoxides, for example, Morimoto¹⁰⁴ carried out the regioselective ring-opening of trisubstituted epoxide **9** using magnesium bromide etherate in the total synthesis of (+)-intricatetraol,¹⁰⁵ giving the Markovnikov product **10a** in 45% yield. Morimoto also carried out the ring-opening of epoxide **9** to give *anti*-Markovnikov addition **10b** using dilithium tetrabromonickelate¹⁰⁶ in THF in 76% yield. Magnesium bromide etherate was also used by Krauss⁷¹ to carry out the ring-opening of a trisubstituted epoxide in polyene cyclisation substrate **11**. In this case, tetrabutylammonium bromide was added to suppress polyene cyclisation, from the action of Lewis acid on the epoxide. This method gave predominantly the Markovnikov product **12** in 88% with a ratio of regioisomers 5:1.



Scheme 41 - Regioselective ring-opening of epoxides

In this work on bromonium ion-induced cation- π cyclisations, both bromohydrin regioisomers will re-converge onto the same bromonium ion. For this reason, regioselective epoxide ring-opening is not a priority, and there is not necessarily any need for them to be separated. Our aim however, was to discover a practically simple method for the isolation of each bromohydrin regioisomer, **8a** and **8b** in high yield. This would allow conditions for the activation of secondary and tertiary alcohols towards cyclisation to be investigated separately.

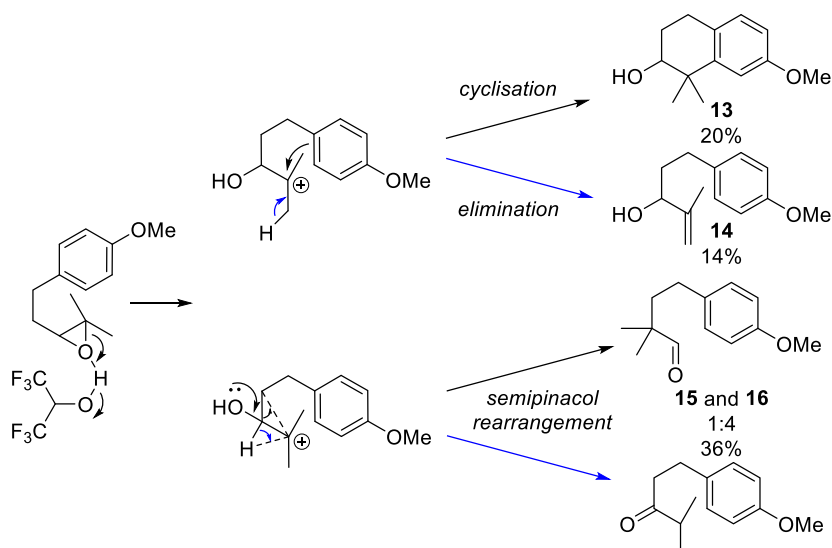
Table 3 - Anionic bromide reagents tested for use in the ring-opening of epoxide **6**



Entry	Reagents	Solvent (T / °C, t / h)	Recovered 6	Yield (%) 8a + 8b ^a	8a:8b ^b
1	(<i>n</i> -hexyl) ₄ NBr	HFIP (58, 16)	12	0	N/A
2	Bu ₄ NBr, Mg(NO ₃) ₂	CH ₂ Cl ₂ (40, 6)	35	39	1:2
3	PPh ₃ /Br ₂	CH ₂ Cl ₂ (r.t. 16)	0	42	2:1
4	PPh ₃ /Br ₂ (excess PPh ₃)	CH ₂ Cl ₂ (r.t. 16)	0	50	2:1
5	Me ₂ SBr ⁺ Br ⁻	MeCN (r.t., 0.5)	0	46	2:1
6	LiBr, PPTS	NMP (r.t., 3)	6	71 ^c	1:1

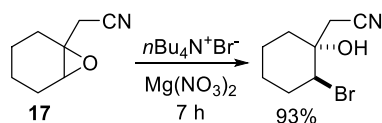
^aIsolated yield after chromatography, ^bdetermined by inspection of the ¹H NMR spectrum, ^cfrom reaction of (R)-**6**

To this end, epoxide **6** was reacted with tetrahexylammonium bromide in hexafluoroisopropanol which acts as a powerful hydrogen-bond donor,¹⁰⁷ previously used in work by Denmark (Table 3, entry 1).⁹⁵ HFIP was anticipated to assist in activation of the epoxide oxygen and the observed reaction products indicated that this assumption was correct. However, competitive elimination, semi-pinacol rearrangement or cyclisation processes were faster than attack by bromide anion giving: cycloadduct **13** (20%, Scheme 42), allyl alcohol **14** (14%), aldehyde **15** (8%) and ketone **16** (28%).



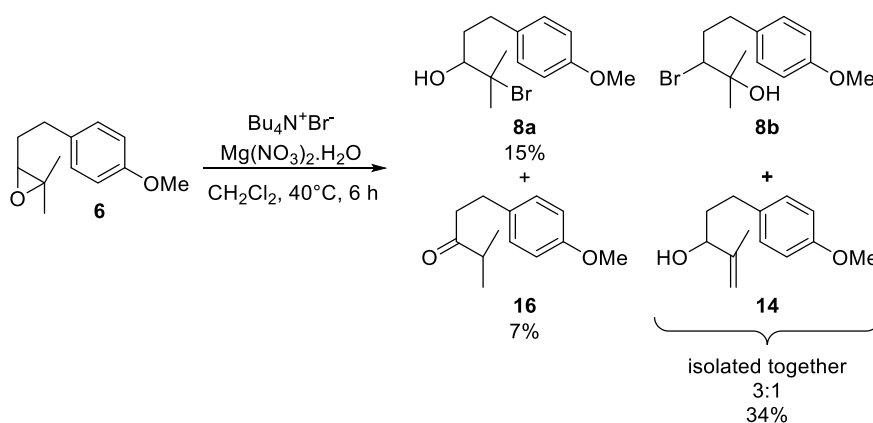
Scheme 42 - Rearrangement of epoxide **6** with (hexyl)₄NBr in HFIP

Tetrabutylammonium bromide was then used in conjunction with *catalytic* quantities of Lewis acid, magnesium nitrate (Table 3, entry 2). This methodology was originally developed by Suh *et al.*¹⁰⁸ who found that magnesium nitrate catalysed the regioselective ring-opening of a number of primary epoxides and one trisubstituted cyclohexene oxide **17** (Scheme 43).



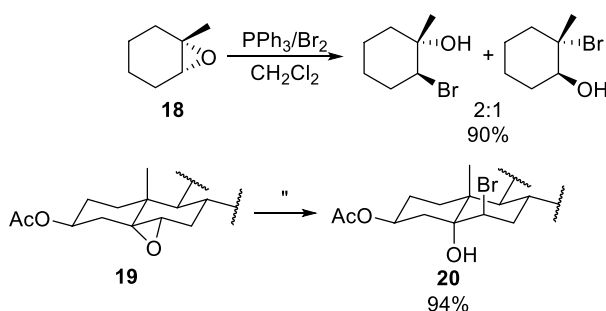
Scheme 43 - Regioselective ring-opening of trisubstituted epoxide **17** using magnesium nitrate Lewis acid

Suh's work showed that bromide attacks preferentially at the least hindered carbon of a trisubstituted epoxide which is activated by magnesium nitrate. Accordingly epoxide **6** was heated at reflux for 6 hours with *n*-Bu₄N⁺Br⁻ and Mg(NO₃)₂, giving 39% yield of bromohydrin **8a** and **8b** in a 1:2 ratio in preference for the *anti*-Markovnikov adduct as found by Suh *et al.* It must be noted that the desired bromohydrin regioisomers **8a** and **8b** could be separated by column chromatography, however bromohydrin **8b** was contaminated with allyl alcohol **14** in 10% yield. Ketone **16** was also isolated in 7% yield (Scheme 44).



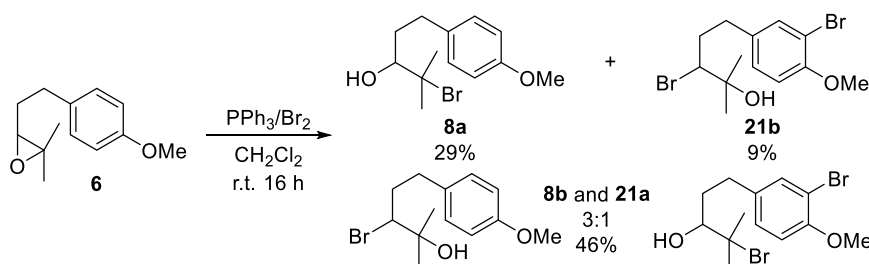
Scheme 44 - Ring-opening of epoxide **6** using $n\text{-Bu}_4\text{N}^+\text{Br}^-$ and $\text{Mg}(\text{NO}_3)_2$

Palumbo, Ferreri and Caputo:¹⁰⁹ reported the use of a 1:1 mixture of triphenylphosphine and molecular bromine which react to give a partially ionic complex¹¹⁰ that preferentially attacks the *less-substituted* carbon atom of trisubstituted epoxide **18** (Scheme 45) leading them to postulate a $\text{S}_{\text{N}}2$ mechanism. In later experiments by the same group,¹¹¹ trisubstituted cholesterol based epoxides (**19**) was shown to give *trans*-diaxial ring-opening of the epoxide to give **20**, consistent with an $\text{S}_{\text{N}}2$ mechanism.



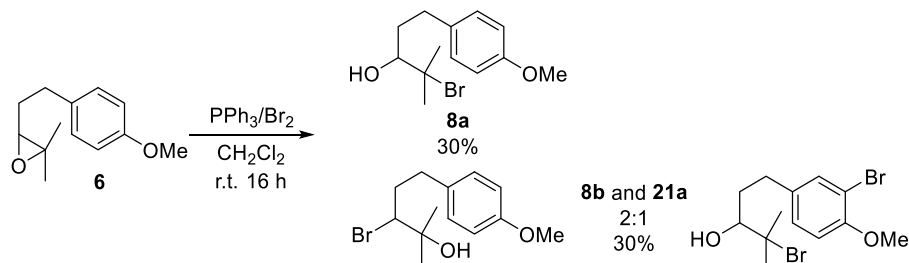
Scheme 45 - Anionic bromide epoxide ring-opening of 1-methylcyclohexene oxide **18** and trisubstituted cholesterol based steroid **19** using PPh_3/Br_2

In our hands these reaction conditions gave bromohydrins **8a** and **8b** in an overall yield of 42% with a *ca.* 2:1 ratio favouring Markovnikov addition (Table 3, entry 3). Unfortunately, considerable quantities of aryl bromides **21a** and **21b** were also isolated (Scheme 46) with secondary bromide **8b** being contaminated with aryl bromide **21a**.



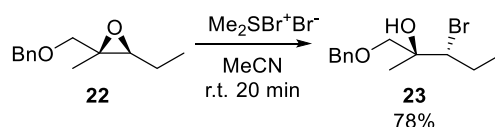
Scheme 46 - PPh_3/Br_2 epoxide ring-opening of **6**

These aromatic bromination by-products were presumably formed by the presence of uncomplexed molecular bromine in the reaction mixture. Subsequently, the use of excess triphenylphosphine reduced the yield of undesired aryl bromide products to *ca.* 10% (Scheme 47) and improved the yield of the desired bromohydrin adducts **8a** and **8b** to 50% (Table 3, entry 4).



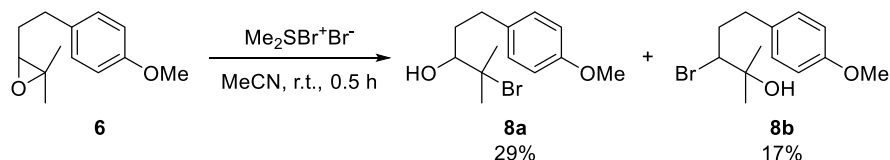
Scheme 47 - PPh_3/Br_2 epoxide ring-opening of **6** with excess of PPh_3

A conceptually similar reagent, (bromodimethyl)sulfonium bromide has been employed by Das, Krishnaiah and Venkateswarlu.¹¹² Its reaction with primary, 1,2-disubstituted cyclic and *trans*-epoxides gives bromohydrins in up to 98% yield with no observed side products and high regioselectivities for attack at the least hindered carbon. Anionic bromide ring-opening of trisubstituted epoxide **22** for example was reported under these conditions to give *anti*-Markovnikov adduct **23** in 78% yield.



Scheme 48 - (Bromodimethyl)sulfonium bromide ring-opening of trisubstituted epoxide

Discovered by Meerwein,¹¹³ (bromodimethyl)sulfonium bromide was synthesised as a light-orange crystalline solid by the original method¹¹⁴ and reacted with epoxide **6** using conditions by Das *et al.*¹¹² Bromohydrins **8a** and **8b** were produced in 46% yield, in a 2:1 ratio (Scheme 49 & Table 3, entry 5).

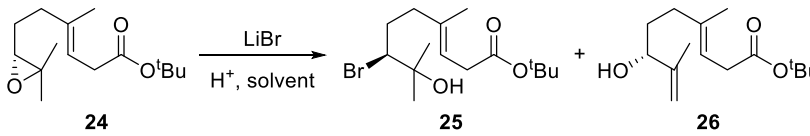


Scheme 49 - Ring-opening of epoxide **6** using $\text{Me}_2\text{SBr}^+\text{Br}^-$

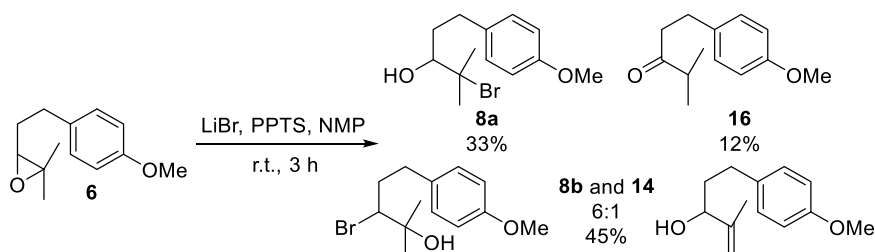
Couladouros and Vidali in their research on the stereocontrolled synthesis of *trans*-fused oxepene-cyclogeranyl systems⁷⁶ (Chapter 1.4.2, page 34) achieved regioselective ring-opening of enantiopure trisubstituted epoxide **24** using lithium bromide and camphorsulfonic acid in

hexamethylphosphoramide, giving the desired *anti*-Markovnikov adduct **25** in 53% yield with allyl alcohol **26** in 18% yield (Table 4, entry 1).

Table 4 - Couladouros and Vidal bromide ring-opening of epoxide conditions

				
Entry	H ⁺	Solvent	Yield 25 (%)	Yield 26 (%)
1	CSA	HMPA	53	18
2	PPTS	NMP	85	<5

The formation of the elimination product **26** was reduced to less than 5% by the use of milder conditions, namely lithium bromide and PPTS in *N*-methyl-2-pyrrolidone. This gave an improved, 85% yield of bromohydrin **25** with less than 5% yield of **26**. In our hands these conditions produced bromohydrins **8a** and **8b** in 71% overall yield in a ratio of *ca.* 1:1 (Table 3, entry 6) and ketone **16** (12%). Bromohydrin **8b** could only be isolated contaminated with *ca.* 12-15% allyl alcohol **14** (Scheme 50). The method of Couladorous⁷⁶ using inexpensive lithium bromide became the method of choice to access both regioisomeric bromohydrins in high yield.



Scheme 50 - Ring-opening of epoxide **6** using LiBr, PPTS and NMP

2.1.2 Characterisation of bromohydrin regioisomers

Once separated and purified bromohydrin regioisomers **8a** and **8b** can be distinguished by characteristic ¹H and ¹³C NMR resonances. Figure 15a and Figure 16a show the ¹³C NMR resonances of carbon atoms bearing a heteroatom for each bromohydrin regioisomer. Below are the corresponding ¹³C DEPT NMR spectrums (Figure 15b and Figure 16b). From this data for the first bromohydrin regioisomer, (Figure 15, a and b) it can be deduced that the carbon resonance at 78.7 ppm bears a proton, whereas the carbon resonance at 75.6 ppm is a quaternary carbon. For the second bromohydrin regioisomer (Figure 16, a and b) there is a quaternary carbon at 72.5 ppm and a tertiary carbon at 70.3 ppm.

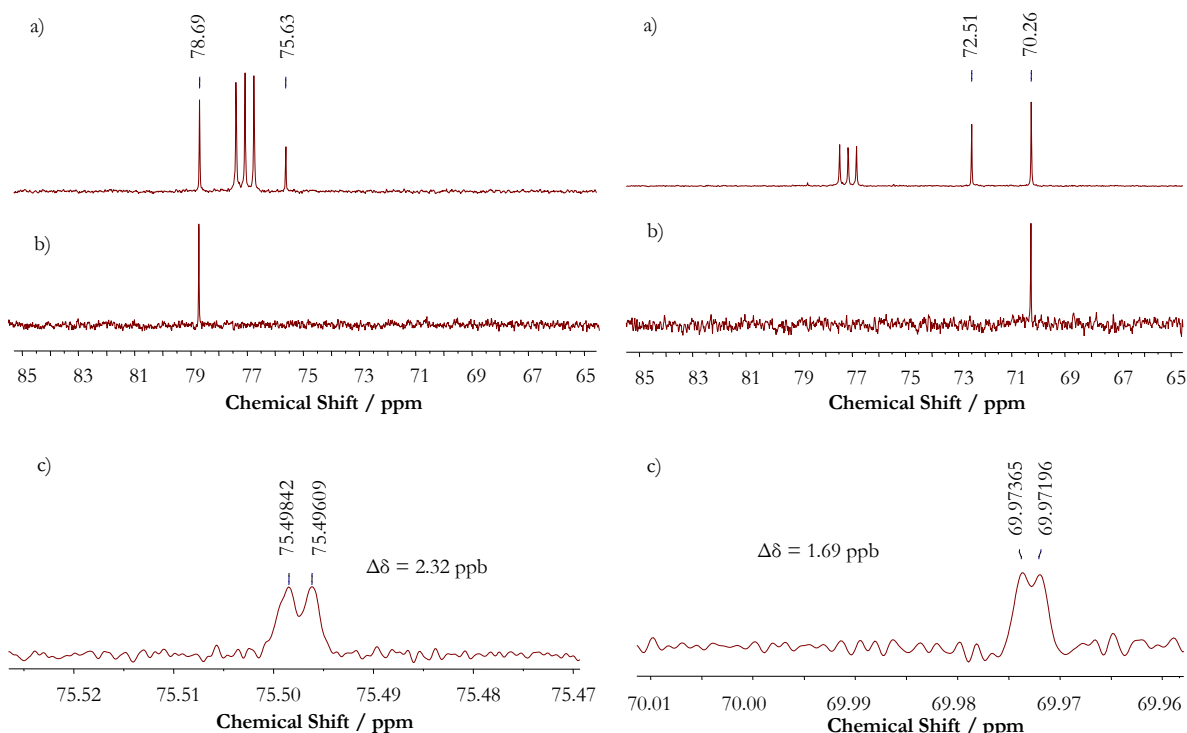


Figure 15 - a) ^{13}C NMR spectrum; b) ^{13}C DEPT NMR spectrum; c) ^{13}C high resolution spectrum of bromine isotope effect of bromohydrin **8a**.

Figure 16 - a) ^{13}C NMR spectrum; b) ^{13}C DEPT NMR spectrum; c) ^{13}C high resolution spectrum of bromine isotope effect of bromohydrin **8b**.

Figure 15c and Figure 16c show high resolution analysis of the ^{13}C NMR resonances at 75.6 ppm and 70.3 ppm for each regioisomer, the patterns shown are characteristic of a carbon bearing a bromine atom, a consequence of the two naturally-occurring isotopes of bromine, ^{79}Br and ^{81}Br , with 50% abundance of each, and their effect on the ^{13}C NMR chemical shift of the carbons attached to each isotope. If bromine is present on a given carbon the ^{13}C NMR resonance will appear as two signals of equal intensity separated by *ca.* 2 ppb.¹¹⁵

Furthermore, with the aid of ^{13}C HSQC NMR experiments it is possible to identify the characteristic ^1H NMR resonances of a proton alpha to a secondary alcohol (in bromohydrin **8a**) and a proton alpha to a bromine atom (in bromohydrin **8b**). The proton alpha to the hydroxyl group was determined to have a ^1H NMR resonance at 3.43 ppm (Figure 17) and the proton alpha to a bromine atom has a ^1H NMR resonance at 3.98 ppm.

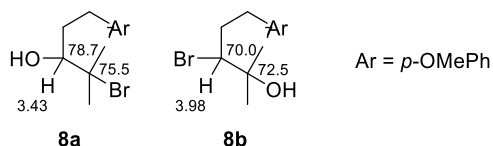


Figure 17 - ^1H and ^{13}C NMR resonances of bromohydrin regioisomers **8a** and **8b**

With careful chromatography samples of bromohydrin **8a** and **8b** could also be analysed by chiral HPLC. In the event of erosion of e.r. in the asymmetric synthesis of bromo-esters this may prove diagnostic.

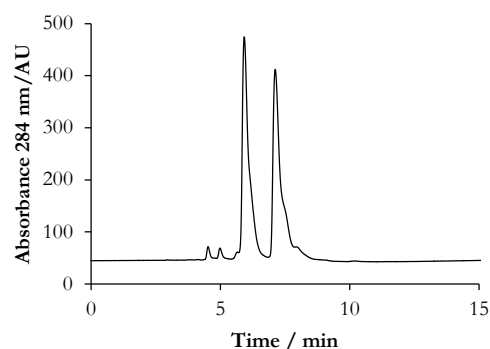


Figure 18 - Chiral HPLC chromatogram showing separation of enantiomers of bromohydrin (±)-**8a**

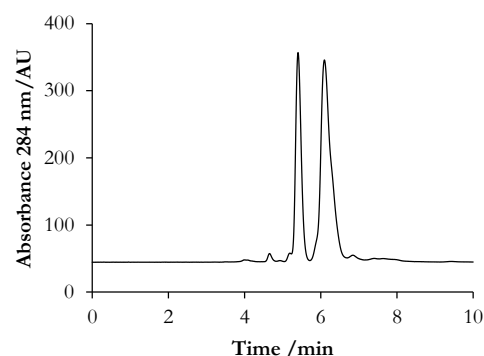
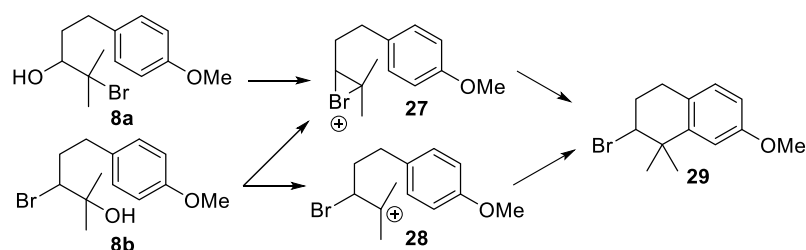


Figure 19 - Chiral HPLC chromatogram showing separation of enantiomers bromohydrin (±)-**8b**

Isolation and characterisation of pure tertiary bromide **8a** would allow us to demonstrate the formation of a bromonium ion in future cyclisations. This regioisomer must necessarily proceed through bromonium ion **27** in order for the bromide to shift from its tertiary position in **8a** to a secondary position in cyclised product **29** (Scheme 51), whereas secondary bromide **8b** could cyclise *via* tertiary carbocation **28** (investigated in Chapter 2.2.4).

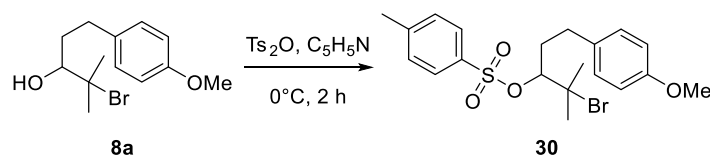


Scheme 51 - Cyclic bromonium ion and open β -bromocarocation extremes of cyclisation intermediates

2.1.3 Esterification

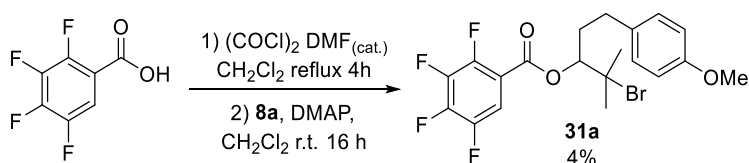
The alcohols present in bromohydrins **8a** and **8b** require activation as a suitable leaving group in order to form a bromonium ion, in the absence of another nucleophile, to trigger clean reaction pathways to cyclisation.

Secondary tosylate **30** was successfully synthesised using 4-toluenesulfonic anhydride in pyridine (Scheme 52). Unfortunately, the product was found to be unstable to chromatography. As tertiary tosylate esters are likely to be more reactive, it was concluded that tosylate esters of **8a** and **8b** would be unsuitable as cyclisation substrates.



Scheme 52 - Synthesis of secondary-tosylate **30**

Based on previous work within the Braddock group (1.6.2, page 45) it was decided that tetrafluorobenzoate esters could be a facile leaving group, stable enough for isolation by column chromatography. The synthesis of secondary tetrafluorobenzoate ester **31a** was first attempted by forming the acid chloride of 2,3,4,5-tetrafluorobenzoic acid using oxalyl chloride and catalytic DMF (Scheme 53). Subsequent reaction with secondary alcohol **8a** and stoichiometric DMAP gave the desired tetrafluorobenzoate ester **31a** in very low yield (4%) along with epoxide **6** (33%), ketone **16** (19%) and recovered starting material **8a** (7%).



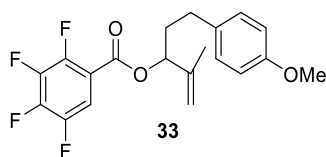
Scheme 53 - Formation of tetrafluorobenzoic acid chloride and esterification of secondary alcohol **8a**

Secondary alcohol **8a** was instead esterified using Steglich esterification¹¹⁶ using a small excess of tetrafluorobenzoic acid (1.2 eq), DCC (1.3 eq) and a substoichiometric amount of DMAP (30 mol%) over one hour gave the desired tetrafluorobenzoate ester **31a** in 88% yield (Table 5, entry 1). The more sterically hindered tertiary alcohol **8b** gave 42% yield of ester **31b** under the same conditions over sixteen hours (entry 2). Increasing the number of equivalents of tetrafluorobenzoic acid and DCC employed to two and three equivalents, respectively, gave an improved yield of 69% of the tertiary tetrafluorobenzoate ester **31b** as a mixture with allyl ester **33** (entry 3). Allyl ester **33** was isolated as the esterification product of allyl alcohol **14** present in the starting material.

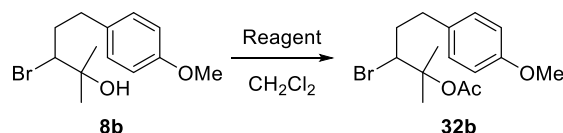
Table 5 - Steglich esterification

Entry	Substrate	Product	<i>t</i> /h	ROH (eq.)	DCC (eq.)	Yield (%)
1	8a	31a	1	1.2	1.3	88
2	8b	31b	16	1.2	1.3	42
3	8b	31b	16	2	3	69 ^a
4	8a	32a	16	1.2	1.3	95
5	8b	32b	48	6	9	0

^a Containing ca. 10% allyl tetrafluorobenzoate **33**

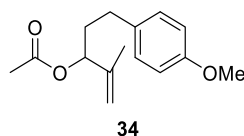


For comparison in cyclisation studies, the more atom-economical acetate esters **32a** and **32b** were also targeted for synthesis using Steglich esterification. Acetylation of secondary alcohol **8a** using acetic acid (1.2 eq.) and DCC (1.3 eq.) over sixteen hours gave 95% yield of the desired acetate ester **32a** (Table 5, entry 4). However, reaction of the more sterically hindered tertiary alcohol **8b** with acetic acid (2 eq.) and DCC (3 eq.) gave poor conversion after 16 h and despite two further additions of the two reagents after 16 h each none of the desired acetate ester **32b** was observed (Table 5, entry 5). Therefore alternative conditions were investigated for the synthesis of tertiary acetate **32b** (Table 6).

Table 6 - Investigating tertiary alcohol acetylation conditions

Entry	Reagent (eq.)	T (°C)	<i>t</i> (h)	Yield (%)
1	AcCl (1.3×2), NEt ₃ (3×2), DMAP (0.3)	0 to r.t	16 then 2	17
2	AcCl (2×3), NBS (2×0.05)	40	8 then 16	32 ^a
3	Ac ₂ O (25), NEt ₃ (19), DMAP (0.1)	0 to r.t.	16	29
4	AcOH (1), TFAA (6)	r.t.	2	63

^aContaminated with 21% yield of allyl acetate **34**



The use of acetyl chloride and triethylamine with catalytic DMAP overnight produced none of the desired tertiary acetate **32b** (Table 6, entry 1), however, when a second equivalent of acetyl chloride and triethylamine was added the desired product was isolated in 17% yield after 2 hour.

It has been reported that NBS can act as an acid catalyst for acetylation of alcohols using acetic anhydride.¹¹⁷ It was shown by Rezaei *et al.* that NBS could be used as an effective catalyst specifically for the synthesis of tertiary esters using acyl halides in good yield.¹¹⁸ In our hands, when tertiary alcohol **8b** was heated at reflux with catalytic NBS and acetyl chloride for 16 h a mixture of acetate ester **32b** and allylic acetate **34** were isolated in 32% and 21% yield, respectively (Table 6, entry 2).

Acetic anhydride was then used in a large excess with triethylamine and catalytic DMAP (Table 6, entry 3) which gave 29% isolated yield of desired acetate ester **32b** after 16 h at room temperature.

The use of acetic acid and trifluoroacetic anhydride was first demonstrated by Bourne *et al.* in the acetylation of a range of aromatic carboxylic acids.¹¹⁹ The scope and limitations of the reaction were later investigated with more hindered acids but more importantly, good yields were observed with the esterification of hindered alcohols such as *tert*-butanol.¹²⁰ This method was later used in the synthesis of (±)-Aplysin-20.⁷⁵ Under these conditions tertiary acetate ester **32b** was

accomplished in 72% isolated yield after 3 hours at room temperature (Table 6, entry 4). These reaction conditions provided pure **32b**, free from **34** for analysis by chiral HPLC.

Cyclisation substrates **31a**, **31b**, **32a**, and **32b** have now been synthesised in good yield and all four sets of enantiomers were shown to be separable by chiral HPLC (see Figure 20-Figure 23). This allows the determination of enantiomeric excess of these compounds in a future asymmetric route (2.3.1, page 77).

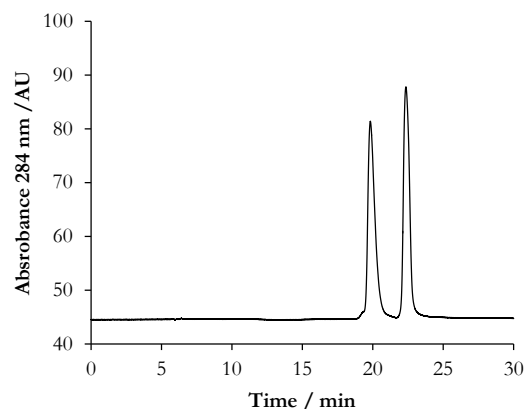


Figure 20 - Chiral HPLC chromatogram showing separation of enantiomers of tetrafluorobenzoate ester (±)-**31a**

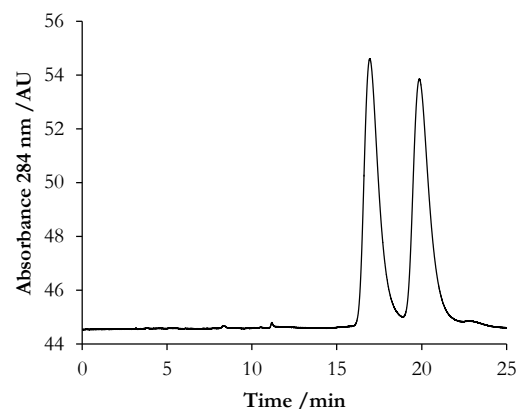


Figure 21 - Chiral HPLC chromatogram showing separation of enantiomers of tetrafluorobenzoate ester (±)-**31b**

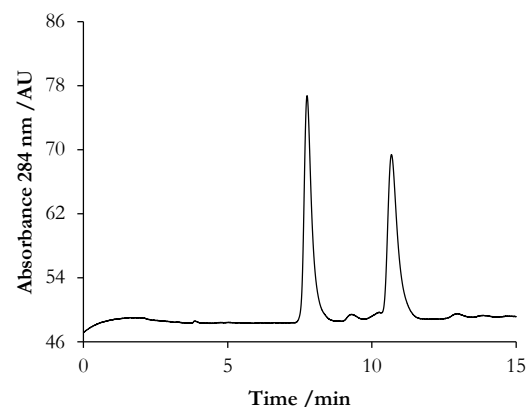


Figure 22 - Chiral HPLC chromatogram showing separation of enantiomers of acetate ester (±)-**32a**

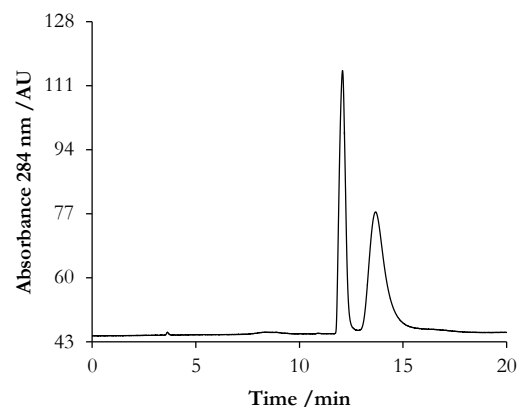


Figure 23 - Chiral HPLC chromatogram showing separation of enantiomers of acetate ester (±)-**32b**

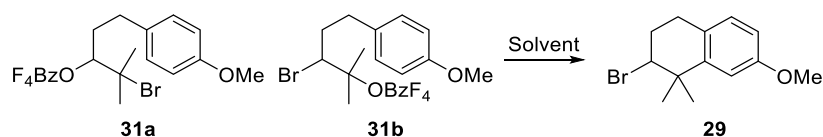
2.2 Investigation of mono-cyclisation reaction conditions

It is now necessary to investigate conditions and reagents to promote the formation of a bromonium ion for tetrafluorobenzoate esters **31a** and **31b**, and acetate esters **32a** and **32b**. This investigation will allow us to establish the required nature of the leaving group.

2.2.1 Solvolysis

As the Braddock group has previously observed the spontaneous formation of a bromonium ion on standing from an isolable 1-bromo-2-tetrafluorobenzoate (1.6.2, 45).¹⁰⁰ It was reasoned that **31a** and **31b** may also spontaneously generate a bromonium ion by solvolysis. Accordingly, a range of solvents and conditions were explored using **31a** and/or **31b**.

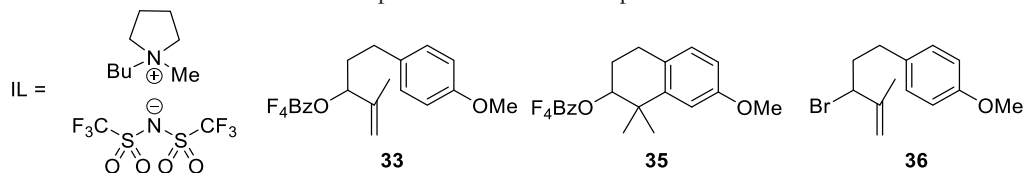
Table 7 - Attempted cyclisation of **31a** or **31b** into **29** under various solvolytic conditions



Entry	Substrate	Solvent	T (°C)	<i>t</i> (h)	Recovered SM	Yield (%)			
						29	33	35	36
1	31a	CDCl ₃	61	3	100 ^a	0	0	0	0
2	31a	CD ₃ NO ₂	100	3	100 ^a	0	0	0	0
3	31a	HFIP	60	16	0	0	26 ^b	39 ^b	0
4	31b	HFIP	60	16	<i>complicated mixture of components</i>				
5	31a	NFTB	45	16	100 ^a	0	0	0	0
6	31b	NFTB	45	16	28	<i>complicated mixture of components</i>			
7	31a	HCO ₂ H	101	6	<i>complicated mixture of components</i>				
8	31b	HCO ₂ H	101	6	<i>complicated mixture of components</i>				
9	31a	IL	90 → 120	16 & 2	95	trace	0	0	0
10	31b	IL	90	4	34	19	0	0	6

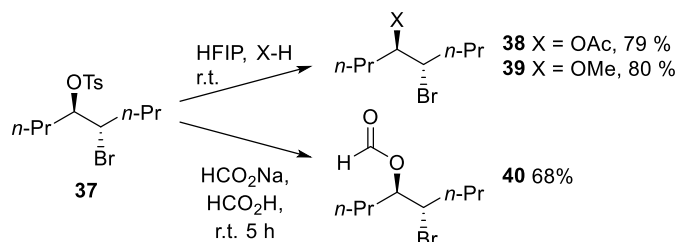
^a inspection of the ¹H NMR spectrum after work-up revealed no reaction and only recovered starting material;

^b inseparable mixture of components



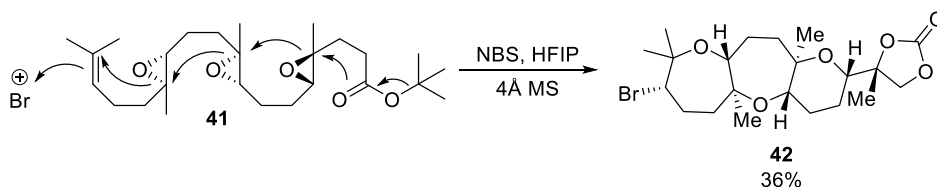
Initially, secondary tetrafluorobenzoate ester **31a** was left standing in deuterated chloroform overnight, inspection of the ¹H NMR spectrum showed that no reaction had occurred. Both heating the same sample at reflux for 3 h (Table 7, entry 1) and exchanging the solvent for deuterated nitromethane as a polar solvent and heating at reflux for 3 h gave no product (entry 2).

As previously discussed (1.5, Figure 12, page 41) hexafluoroisopropanol is a well-known polar solvent¹²¹ of high ionising power, low nucleophilicity⁹⁶ and is a powerful hydrogen-bond donor.¹⁰⁷ It is capable of strongly solvating anions but not cations, and so carbocations and cationic radicals persist in solution. This property makes HFIP an optimal solvent for the promotion of neighbouring group participation in solvolysis reactions which generate cationic halonium ions.¹²² HFIP has therefore been used in cationic cyclisation reactions¹²³ and as discussed previously Denmark⁹⁵ has shown that enantiopure bromonium ions can be generated from 1,2-bromotosylates in HFIP, which are then trapped in the presence of stoichiometric quantities of nucleophile (Scheme 54). The solvolysis of enantiomerically enriched (4*R*,5*S*)bromo-tosylate **37** with a solution of nucleophile (NaOAc, or MeOH) in HFIP produced the products **38** or **39** in high yields and high enantiopurity.



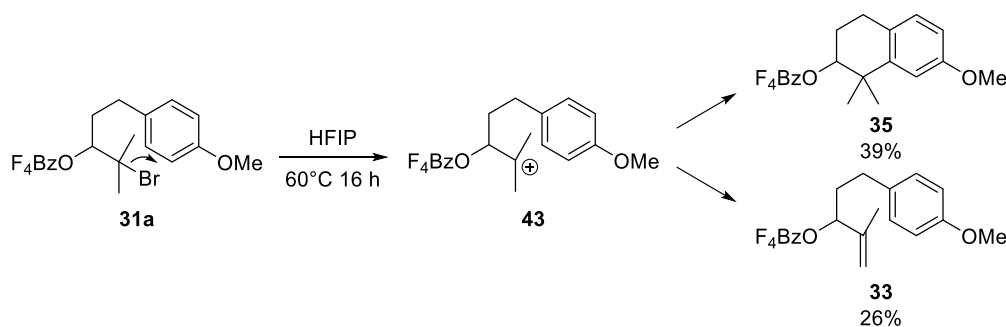
Scheme 54 - Denmark solvolytic substitution with (4*R*,5*S*)-**37**

HFIP has also been used by Jamison *et al.*¹²⁴ to facilitate bromonium ion initiated poly-epoxide ring-opening of alkene **41** and maximised the directing influence of the methyl groups to form the cyclised product **42** (Scheme 55).



Scheme 55 - Jamison *et al.* bromonium ion initiated poly-epoxide ring-opening cascade

Accordingly, HFIP could reasonably be foreseen to promote bromonium ion formation and cyclisation of bromo-tetrafluorobenzoate esters **31a** and **31b**. However utilising HFIP as a solvent at 60°C (Table 7, entry 3) gave non-bromine containing compounds **35** (39%) and **33** (26%, Scheme 56). These must result from solvent assisted bromide separation to produce tertiary carbocation **43** (which may be stabilised anchimerically by the benzoate), this could then cyclise to form **35** or eliminate to form **33**. Under the same conditions tetrafluorobenzoate ester **31b** (Table 7, entry 4) produced a complex mixture of products.



Scheme 56 - Cyclisation of tetrafluorobenzoate **31a** using HFIP at reflux

The use of nonafluoro *tert*-butanol (NFTB) as the solvent was also unsuccessful at promoting clean cyclisation of **31a/31b** to product **29**. No reactivity was observed in reaction with secondary tetrafluorobenzoate ester **31a** (Table 7, entry 5). Only low conversion was observed of **31b** to a mixture of non-bromine containing cyclised and un-cyclised tetrafluorobenzoate esters (entry 6).

Formic acid was also used by Denmark⁹⁵ in the solvolysis of enantiomerically enriched bromo-tosylates **37** (Scheme 54) and so it could reasonably be foreseen to promote bromonium ion formation and cyclisation of bromo-tetrafluorobenzoate esters **31a** and **31b**. However the reaction produced a very complicated mixture of products, presumably a number of formate esters, tetrafluorobenzoate esters, and bromide containing compounds (Table 7, entries 7 and 8).

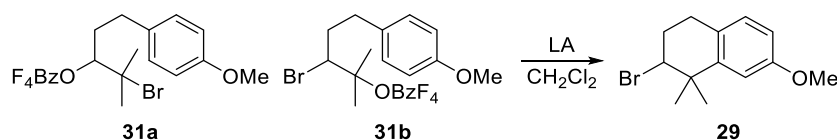
Research into the use of ionic liquids in organic synthetic chemistry is being pioneered by the Welton group at Imperial College.¹²⁵ The use of 1-butyl-1-methylpyrrolidinium bis[(trifluoromethyl)sulfonyl]imide (IL) as a solvent was investigated to promote bromonium ion formation and cyclisation of bromo-tetrafluorobenzoate esters **31a** and **31b** as the ionic nature of the liquid possibly stabilises any charged intermediates formed. Unfortunately, no reactivity was observed at elevated temperatures, for the cyclisation of secondary tetrafluorobenzoate ester **31a** (Table 7, entry 9). However, when IL was used as a solvent in the cyclisation of tertiary tetrafluorobenzoate ester **31b**, 19% yield of the desired cyclised product **29** was obtained along with 6% yield of the allyl bromide **36** (Table 7, entry 10).

Minimal success was achieved using solvolysis to promote bromonium ion formation and cyclisation of bromo-tetrafluorobenzoate esters **31a** and **31b**, and attention turned to the attempted cyclisation of **31a/31b** using stoichiometric quantities of oxophilic Lewis acids.

2.2.2 Oxophilic Lewis acids

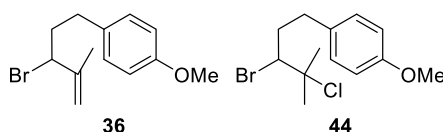
A selection of four oxophilic Lewis acids in dichloromethane at low temperatures were chosen for the attempted cyclisation of tetrafluorobenzoate esters **31a/31b** to brominated bicycle **29** (Table 8).

Table 8 - Lewis acid effect on cyclisation



Entry	Substrate	Reagents	T (°C)	t (h)	Recovered SM	Yield (%)		
						29	36	44
1	31a	BF ₃ .OEt ₂	-40	0.5	100	0	0	0
2	31b	BF ₃ .OEt ₂	-40	0.5	80 ^a	0	20 ^a	0
3	31a	TiCl ₄ (2 eq)	-78	1	100	0	0	0
4	31b	TiCl ₄ (2 eq)	-78	1	5	55	0	12
5	31a	Me ₂ AlCl	-78 to r.t.	16	20	33	0	23
6	31b	Me ₂ AlCl	-78 to r.t.	4	0	56	0	6
7	31a	TMSOTf	-78	6	95	0	0	0
8	31b	TMSOTf	-78	6	0	44	0	0
9	32b	TMSOTf	-78	16	0	43	0	0
10	30	TMSOTf	-78	6	0	48	0	0
11	31b	TMSOTf (2.1 eq) DTBP (1 eq)	-78 to r.t.	96	100	0	0	0

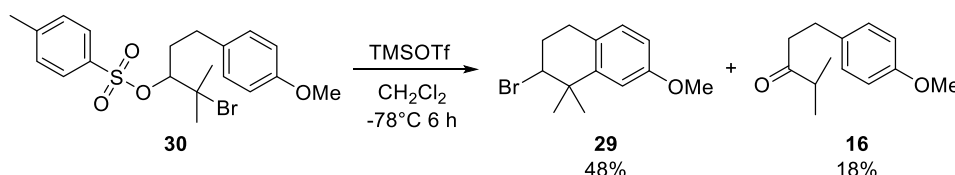
All reactions were carried out with 1.1 eq. of Lewis acid unless stated otherwise. ^adetermined by inspection of the ¹H NMR spectrum



Boron trifluoride etherate was ineffective for cyclisation of substrate **31a** (Table 8, entry 1) under these conditions, and the starting material was recovered. Reaction of tertiary tetrafluorobenzoate ester **31b** however, gave 20% yield of eliminated product **36**, although no bromo-cyclisation was observed (entry 2). Titanium tetrachloride was able to effect the desired cyclisation of tertiary tetrafluorobenzoate ester **31b** in 55% yield (entry 4) with 12% yield of inseparable bromochloride **44**. Regioisomeric bromochloride **44** was identified by the characteristic ¹H NMR absorbance for a proton alpha to a bromine atom at 4.03 ppm, which was bonded to a carbon atom at 65.0 ppm in the ¹³C NMR spectrum by analysis of the HSQC NMR spectrum. Titanium tetrachloride was ineffective at cyclisation of secondary ester **31a** (entry 3).

Dimethylaluminium chloride affected the desired cyclisation of both tetrafluorobenzoate regioisomers **31a** and **31b** in good yield, 33% and 56% yield respectively, however both reactions also produced inseparable chloride **44** (entries 5 and 6).

Trimethylsilyl triflate showed promising activity having cleanly promoted the bromo-cyclisation of tertiary tetrafluorobenzoate ester **31b** in 44% yield (entry 8), but not secondary tetrafluorobenzoate ester **31a** (entry 7). TMSOTf was also found to initiate the cyclisation of acetate ester **32b** in 43% yield (entry 9) and bromo-tosylate **30** in 48% yield (Synthesis: Scheme 52). Also produced in reaction of bromo-tosylate **30** was 18% yield of ketone **16** (entry 10). However, tosylate esters of **8a** and **8b** would be unsuitable as cyclisation substrates as sulfonate esters are too unstable for purification by column chromatography.

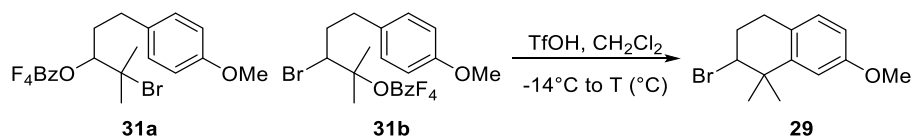


Scheme 57 - TMSOTf catalysed cyclisation of secondary-tosylate **30**

For the successful cyclisation of tertiary tetrafluorobenzoate **31b** using TMSOTf, control experiments containing non-nucleophilic base: 2,6-di-*tert*-butylpyridine were carried out (entry 11). The loss of reactivity signified that TMSOTf was not active in the original reaction and instead it was the presence of triflic acid which must be promoting the reaction. Based on this result, investigations into the use of triflic acid as a cyclisation initiator began.

2.2.3 Triflic acid

The use of 30 mol% catalytic loading of triflic acid was tested on both secondary and tertiary tetrafluorobenzoate esters **31a** and **31b**. Pleasingly, both regioisomers were found to cyclise smoothly to the desired product **29** (Table 9, entries 2 and 3). Tertiary tetrafluorobenzoate ester **31b** reacted over 16 h at room temperature to give bicycle **29** in 51% isolated yield (entry 2). However, no conversion was observed for secondary tetrafluorobenzoate ester **31a** over the same period (entry 1). After heating the reaction mixture at reflux for 6 h in dichloromethane, full conversion to bicycle **29** was accomplished in 73% isolated yield (entry 3).

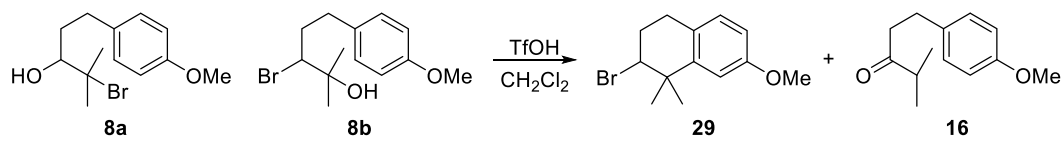
Table 9 - Investigation of triflic acid loading on cyclisation of tetrafluorobenzoate esters **31a** and **31b**


Entry	Substrate	TfOH (mol%)	T (°C)	t (h)	% Conversion ^a
1	31a	30	r.t.	16	0
2	31b	30	r.t.	16	79 (51)
3	31a	30	40	6	97 (73)
4	31a	10	40	16	81 (65)
5	31a	5	40	16	20 (15)

^aAs determined by inspection of the ¹H NMR spectrum after aqueous work-up. Figure in parentheses is isolated yield after column chromatography.

The catalyst loading of triflic acid could be reduced to 10 mol% without compromising the yield of the reaction (65%, Table 9, entry 4), however, 5 mol% catalyst loading of triflic acid was less effective (15% entry 5).

Having successfully triggered a cation- π cyclisation with bromo-tetrafluorobenzoate esters **31a** and **31b** with catalytic quantities of triflic acid, the question posed was whether bromohydrins **8a** and **8b** would also be suitable substrates under these conditions. To analyse the use of these earlier substrates, bromohydrin **8a** and **8b** were treated with 30 mol% triflic acid in dichloromethane at reflux for 3 hours (Table 10, entry 1 and 2).

Table 10 - Triflic acid mediated cyclisation on bromohydrins **8a** and **8b**


Entry	Substrate	TfOH (mol%)	T (°C)	t (h)	Yield 29 (%)	Yield 16 (%)
1	8a	30	40	3	57	30
2	8b	30	40	3	67	14 ^a
3	8a	10	40	16	34	66 ^a
4	8a	5	40	16	31	69 ^a

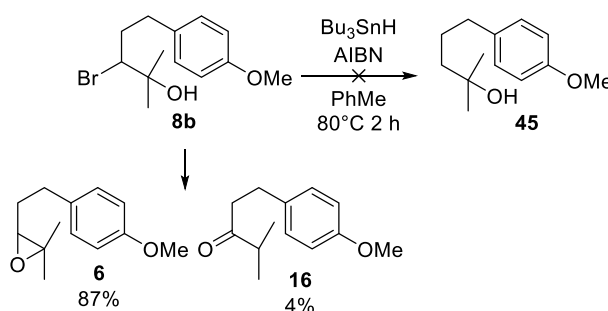
^adetermined by ¹H NMR analysis of crude reaction mixture

In the reaction of secondary alcohol **8a** the desired bromo bicycle **29** was isolated in 57% yield (entry 1), whereas tertiary alcohol **8b** gave an improved yield of 67% (entry 2). The major by-product of both reactions was found to be ketone **16** which was isolated in 30% yield from reaction of bromohydrin **8a** and identified by ^1H NMR analysis of the crude reaction mixture from bromohydrin **8b** (entry 2). Unfortunately, lower than 30 mol% loadings of triflic acid with secondary alcohol **8a** gave ketone **16** as the major product (entries 3 and 4).

In summary, conditions for activation of bromo-tetrafluorobenzoate esters **31a** and **31b** and also bromohydrins **8a** and **8b** towards bromo-cyclisation have been optimised using catalytic triflic acid. However, a number of questions regarding the mechanism of this reaction still remain.

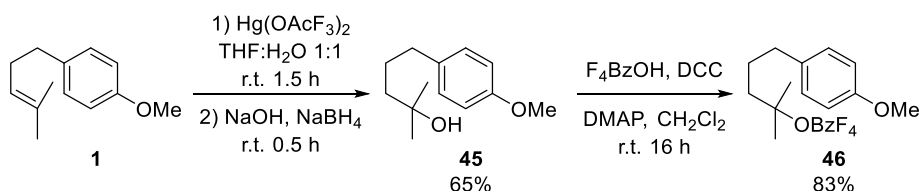
2.2.4 Mechanistic investigation

As mentioned previously, (Scheme 20) the activation of tertiary alcohol or ester derivatives and any subsequent cyclisation can invoke one of two intermediates, either a tertiary carbocation or cyclic bromonium ion. In order to probe whether bromine neighbouring group participation was required for cyclisation to occur in tertiary substrates such as **8b** or **31b**, it was necessary to synthesise the tertiary alcohol **45** without bromine. Attempts to synthesise this compound from bromohydrin **8b** *via* a radical dehalogenation reaction using tributyltin hydride and azobisisobutyronitrile in anhydrous toluene were unsuccessful and the thermal degradation products epoxide **6** and ketone **16** were isolated in 87% and 4% yields (Scheme 58). This unexpected reaction outcome proved to be reproducible.



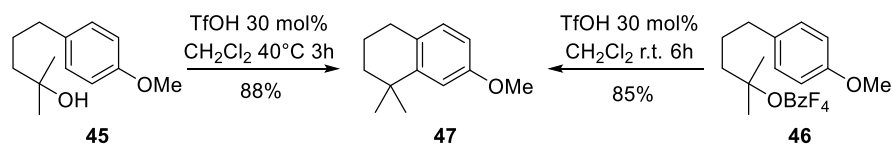
Scheme 58 - Treatment of bromohydrin **8b** with tributyltin hydride

However, oxymercuration-reduction of homoprenyl *p*-methoxybenzene (**1**) yielded 65% of the desired tertiary alcohol **45** (Scheme 59). This could be activated as a tetrafluorobenzoate ester using 2 equivalents of 2,3,4,5-tetrafluorobenzoic acid and 3 equivalents of DCC, catalytic DMAP in dichloromethane at room temperature overnight to give the desired tetrafluorobenzoate ester **46** in 83% yield.



Scheme 59 - Oxymercuration reduction of homoprenyl *p*-methoxybenzene **1**

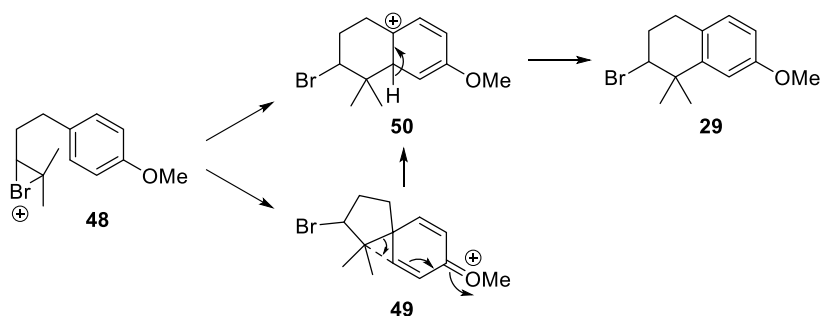
Reaction of both tertiary alcohol **45** and tetrafluorobenzoate ester **46** with catalytic triflic acid gave excellent yields of cyclohexane **47** (Scheme 60).



Scheme 60 - Cyclisation of *des*-bromo tertiary alcohol **45** and tertiary tetrafluorobenzoate ester **46**

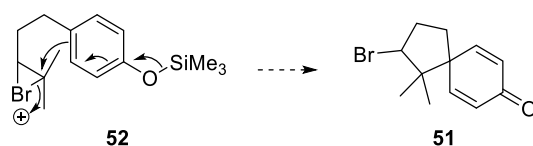
This shows that cyclisation of tertiary leaving groups with triflic acid can certainly occur without neighbouring group participation by bromine. As the yield is higher than the respective bromine-containing compounds **8b** and **31b**, it is possible that the bromine may even be sterically hindering the cyclisation. This demonstrates the stability of the tertiary carbocation in the fact that it can be readily formed using triflic acid and trapped by an intramolecular nucleophile.

After consideration of the substitution of the aromatic ring it became apparent that attack of the aromatic onto bromonium ion **48** may occur at either the *meta*- or the *para*-positions relative to the methoxy group (Scheme 61). Direct attack of the *meta*-position relative to the methoxy group would furnish bicycle **29** after rearomatisation, attack of the more favoured *para*-position would give a spiro quinone type intermediate **49**, which would rearrange and re-aromatise *via* the same carbocation **50** to give the desired bicycle **29**.



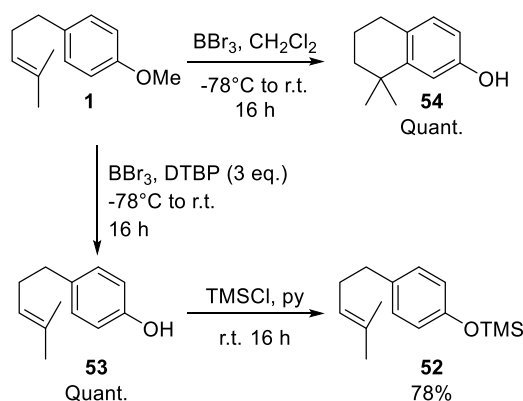
Scheme 61 - Possible mechanisms of attack of a *para*-methoxy substituted aromatic

In an attempt to trap any spiro quinone type intermediate such as **51** (Scheme 62), silyl ether **52** was sought.



Scheme 62 - Cyclisation of silyl ether **52** to a spiro quinone **51**

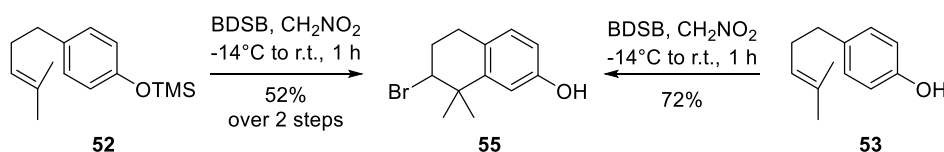
The use of boron tribromide for demethylation of **1** failed to give the desired phenol **53** and instead catalytic, proton initiated cyclisation under these reaction conditions gave bicycle **54** in quantitative yield.



Scheme 63 - Boron tribromide demethylation of **1**

When the demethylation reaction was instead carried out with three equivalents of 2,6-di-*tert*-butylpyridine (DTBP)—a non-nucleophilic proton scavenger—the desired phenol **53** was isolated in quantitative yield. Silylation of **53** with chlorotrimethylsilane in pyridine produced the desired silyl ether **52** in 78% yield, but again the silyl ether was found to be unstable to chromatography and so was used directly after work-up in bromo-cyclisation reaction with Snyder's reagent: BDSB.⁴⁸

With one equivalent of BDSB in nitromethane at -14°C for 1 h, TMS ether **52** gave bromo-bicyclic phenol **55** in 52% isolated yield over two steps. The cyclisation of phenol **53** gave the same product in 72% under the same bromo-cyclisation reaction conditions. There was no evidence for the presence of a compound such as a spiro-quinone **51**, in either reaction. Therefore it seems likely that if such an intermediate were to be formed it rearranges to the observed bicyclic phenol **55**.

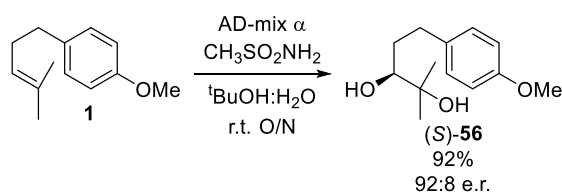


Scheme 64 - Mechanistic studies using phenol **53** and its trimethylsilyl ether derivative **52**

To conclude, it cannot be ruled out that cyclisation of tertiary leaving groups such as those in bromohydrin **8a** and tetrafluorobenzoate ester **31b** are proceeding through a tertiary carbocation. However, secondary leaving group substrates must necessarily proceed through NGP of bromine. Further experimentation would be needed to determine if cyclisation proceeds through attack of the aromatic from the *para*- position, as products such as spiro quinone **51** could not be isolated.

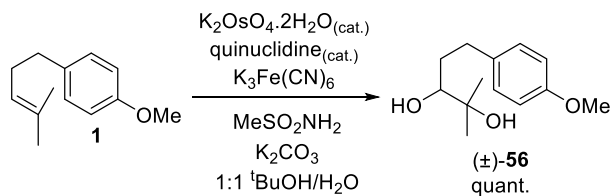
2.3 Enantioselective synthesis of mono-cyclisation substrates and reactions

So far, the synthesis of a range of racemic substrates has been optimised and the conditions needed for activation of the leaving group towards cyclisation have been identified. It was then necessary to investigate the reactions in an asymmetric synthesis and determine the enantiomeric ratio of the products. Sharpless asymmetric dihydroxylation provides access to both *R* and *S*-enantiomeric diols, and these 1,2-diols can then be converted to epoxides *via* Corey conditions.¹²⁶ Initially, scalemic diol (*S*)-**56** was synthesised from alkene **1** using Sharpless' AD-mix α ¹²⁷ in 92% isolated yield (Scheme 65). The absolute configuration of diol (*S*)-**56** was assigned on the basis of the Sharpless mnemonic.¹²⁷⁻¹²⁸



Scheme 65 - Sharpless asymmetric dihydroxylation using AD-mix α

The enantiomeric ratio was 92:8 (Figure 25) as determined by chiral HPLC separation of enantiomers and comparison with a racemic sample (Figure 24). Racemic diol **56** was synthesised using modified Sharpless asymmetric dihydroxylation conditions, whereby the chiral ligand was substituted by achiral quinuclidine, a method developed by Warren *et al.*¹²⁹ Quantitative yields of ($\pm$)-**56** were obtained (Scheme 66).



Scheme 66 - Dihydroxylation of homoprenyl *p*-methoxybenzene (**1**) to give racemic diol **56**

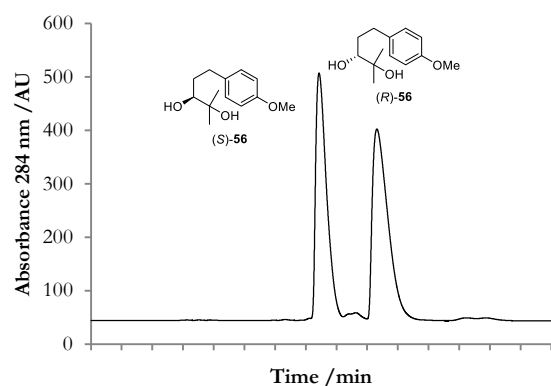


Figure 24 - Chiral HPLC chromatogram showing separation of enantiomers of diol (±)-**56**

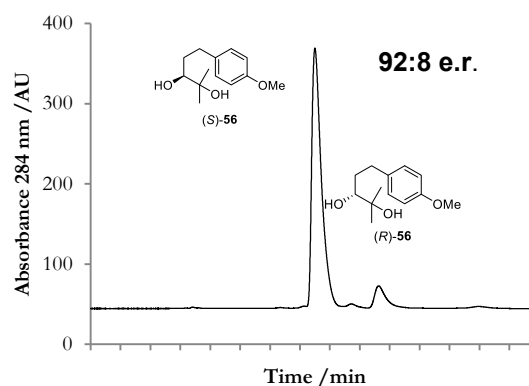
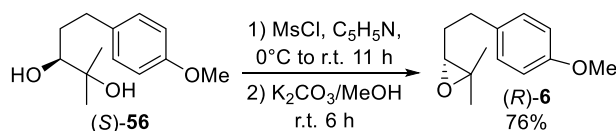


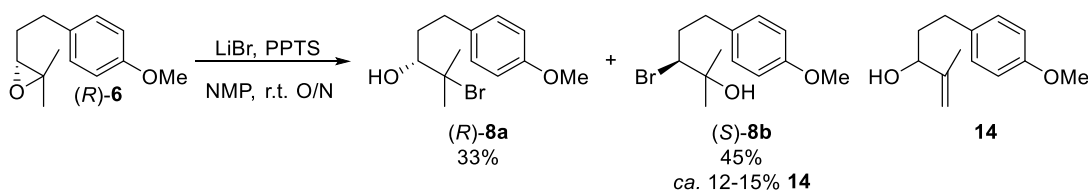
Figure 25 - Chiral HPLC chromatogram showing enantiopurity of (S)-**56**

Mesylation of diol (S)-**56** at the less hindered secondary alcohol and treatment with base produced epoxide (R)-**6** in 76% yield.



Scheme 67 - Mesylation and base mediated closing to epoxide (R)-**6**

Ring-opening of epoxide (R)-**6** with lithium bromide and pyridinium *p*-toluenesulfonate in *N*-methylpyrrolidone produced bromohydrins (R)-**8a** and (S)-**8b** in 71% overall yield (Scheme 68).



Scheme 68 - Ring-opening of epoxide (R)-**6** with lithium bromide

The enantiomeric ratio of bromohydrin regioisomers, **8a** and **8b** was determined by chiral HPLC analysis (Figure 26 and Figure 27) to be 91:9 which is comparable to the enantiomeric ratio of diol (S)-**56** at 92:8. This discrepancy is likely to be in the margin of error.

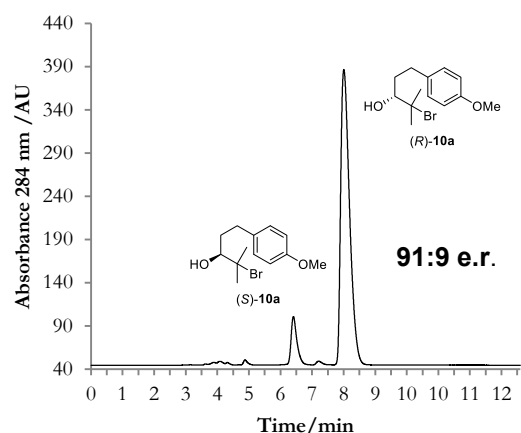


Figure 26 - Chiral HPLC chromatogram showing enantiopurity of bromohydrin (*R*)-**8a**

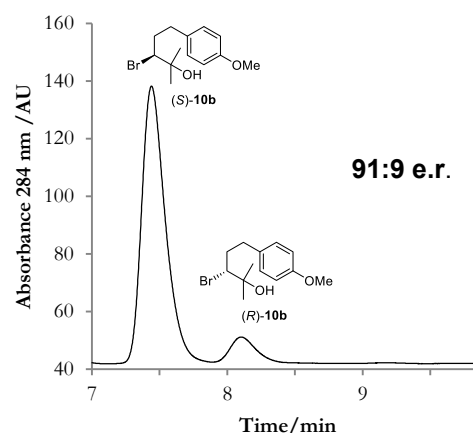
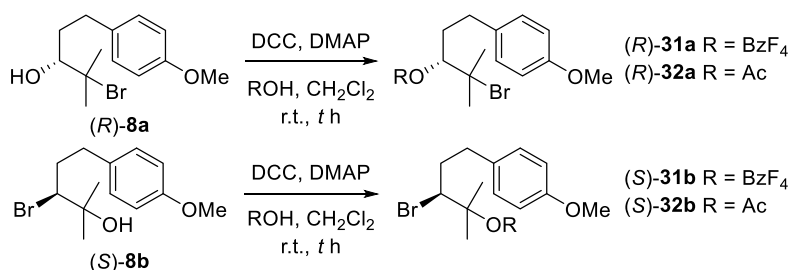


Figure 27 - Chiral HPLC chromatogram showing enantiopurity of bromohydrin (*S*)-**8b**

Esterification of bromohydrin regioisomers (*R*)-**8a** and (*S*)-**8b** as tetrafluorobenzoate esters was achieved using Steglich conditions.¹¹⁶ Bromohydrin (*R*)-**8a** was reacted with a small excess of 2,3,4,5-tetrafluorobenzoic acid and DCC over 4 h in excellent yield, 88% for the synthesis of secondary tetrafluorobenzoate ester (*R*)-**31a** (Table 11, entry 1). Bromohydrin (*S*)-**8b** was reacted with two equivalents of tetrafluorobenzoic acid and three equivalents of DCC. Under these conditions tertiary tetrafluorobenzoate ester (*S*)-**31b** was isolated in 62% with *ca.* 15% of allyl tetrafluorobenzoate ester **33** (entry 2).

Table 11 - Steglich esterification

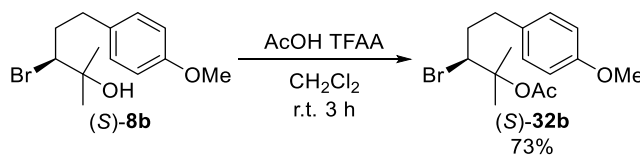


Entry	Substrate	Desired Product	DCC (eq.)	Acid (eq.)	<i>t</i> (h)	Yield (%)
1	(<i>R</i>)- 8a	(<i>R</i>)- 31a	1.3	1.2	4	88
2	(<i>S</i>)- 8b	(<i>S</i>)- 31b	3	2	16	62 ^a
3	(<i>R</i>)- 8a	(<i>R</i>)- 32a	1.3	1.2	62	52

^acontaining *ca.* 15% allyl tetrafluorobenzoate **33**

The synthesis of secondary acetate (*R*)-**32a** (entry 3) using the Steglich method (1.3 eq. DCC, 1.2 eq. acetic acid) over 62 h gave a low 52% yield, showing that this reaction could be capricious when forming acetate esters, possibly due to the volatility of the carboxylic acid. The previous

optimised conditions for synthesis of racemic tertiary acetate **32b** using acetic acid and trifluoroacetic anhydride in dichloromethane at room temperature for 3 hours provided clean tertiary acetate (*S*)-**32b** in 73% yield.

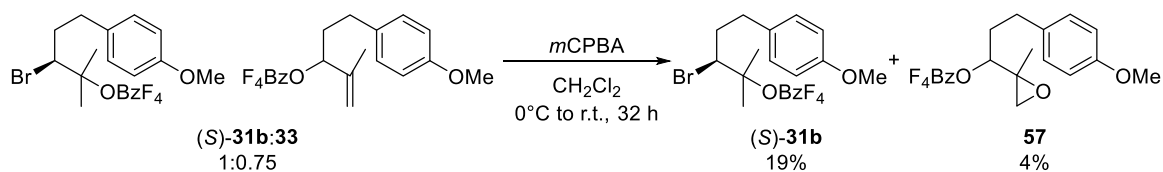


Scheme 69 - Acetylation of tertiary alcohol (*R*)-**8b** using mixed anhydride

With access to scalemic tetrafluorobenzoate esters (*R*)-**31a** and (*S*)-**31b**, and acetate esters (*R*)-**32a** and (*S*)-**32b** in good yield it is necessary to determine the enantiomeric ratio of each bromo-ester before carrying out any cyclisation reactions with triflic acid. This is to determine if the route following Sharpless asymmetric dihydroxylation was enantiospecific and if cyclisation of the bromo esters with triflic acid is also enantiospecific. For an accurate enantiomeric ratio to be determined *via* chiral HPLC separation the following is required:

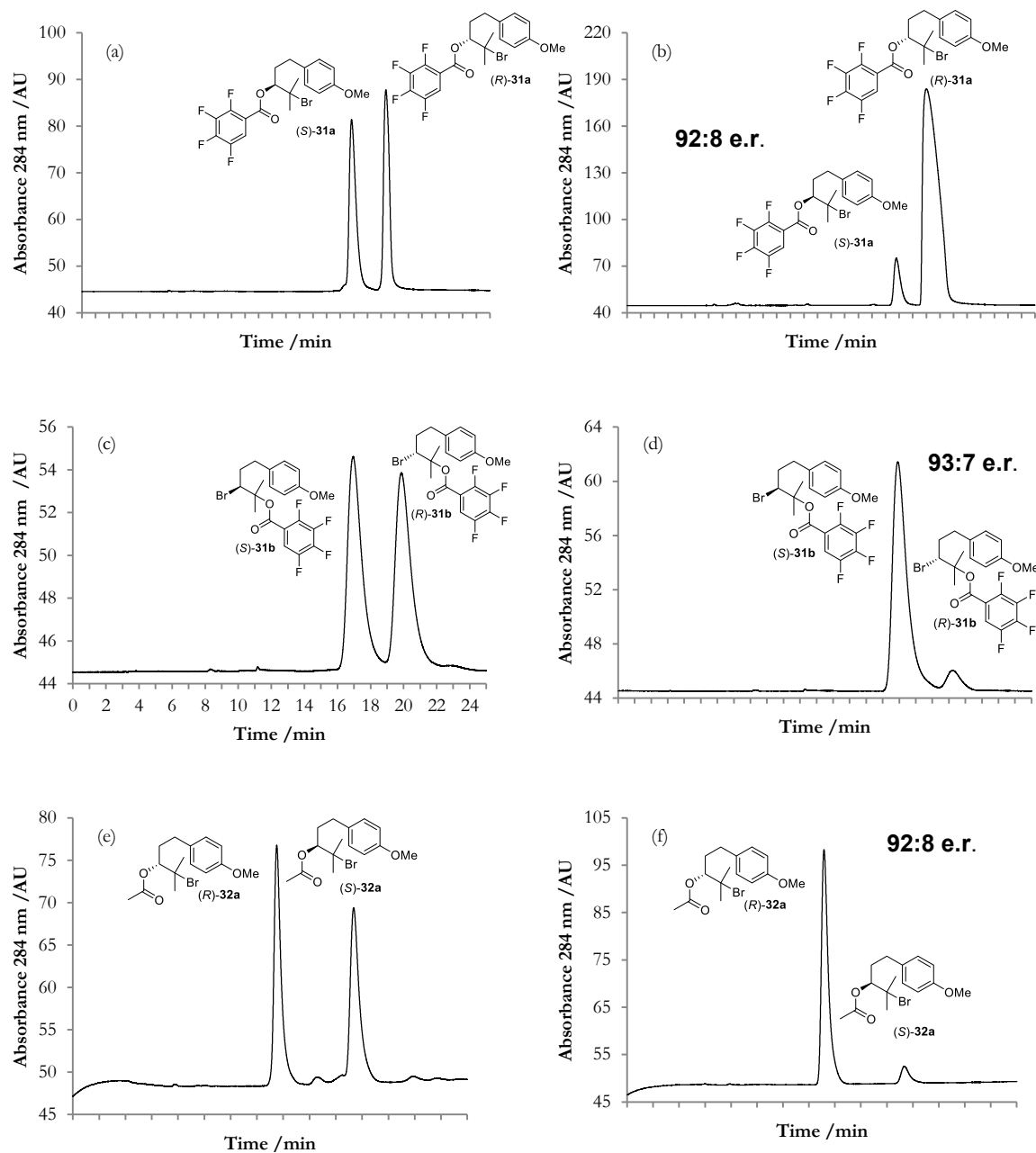
- Baseline separation of enantiomers.
- A sample which is free from impurities present in greater quantities than the minor enantiomer.
- Retention times of enantiomers which are equal to those of a racemic sample.

This was complicated by the presence of alkene-containing impurities mainly in tertiary esters (*S*)-**31b** and (*S*)-**32b**, although some samples of (*R*)-**32a** were also contaminated. These impurities were difficult to remove by column chromatography and even in small proportions relative to desired material were enough to affect baseline separation of enantiomers and the ability to identify the minor enantiomer. When it was not possible to obtain analytically pure samples by careful chromatography a further reaction was needed to remove the impurities. Epoxidation with *m*CPBA was chosen in order to react with olefinic impurities and produce more polar oxidation products which would be separable from the desired bromo-esters. This was carried out successfully, for example, a 1:0.75 mixture of (*S*)-**31b** and **33** was reacted with *m*CPBA to give analytically pure (*S*)-**31b** in 19% yield and a 4% yield of the corresponding epoxide **57**.



Scheme 70 - Removal of allyl tetrafluorobenzoate **33** by reaction with *m*CPBA

Figure 28 shows the enantiomeric ratios of both tetrafluorobenzoate ester regioisomers (*R*)-**31a** and (*S*)-**31b** (chromatograms b and d) and acetate esters (*R*)-**32a** and (*S*)-**32b** (chromatograms f and h) as determined by chiral HPLC chromatography in comparison to a racemic reference samples (chromatograms a, c, e and g).



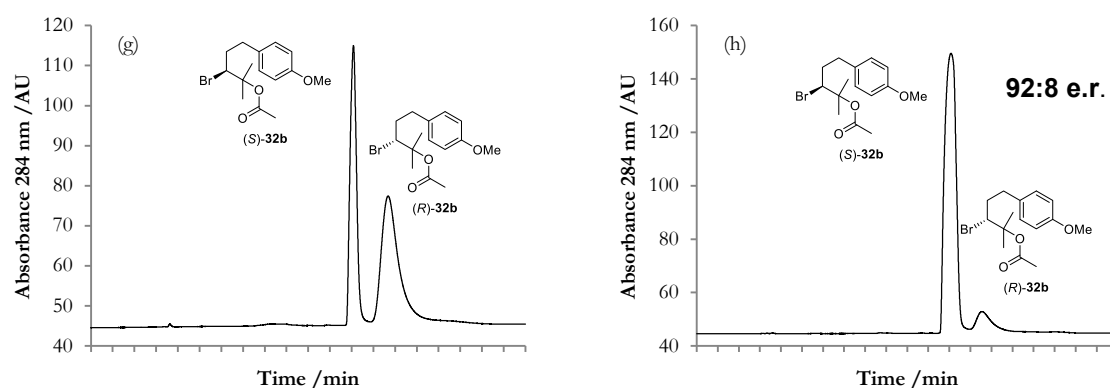
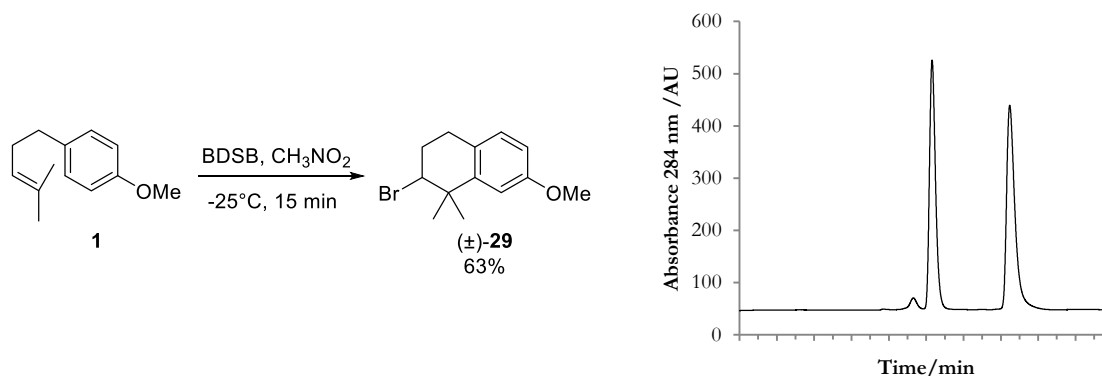


Figure 28 - Chiral HPLC chromatograms showing separation of enantiomers in a) ($\pm$)-**31a**, b) (*R*)-**31a**, c) ($\pm$)-**31b**, d) (*S*)-**31b**, e) ($\pm$)-**32a**, f) (*R*)-**32a**, g) ($\pm$)-**32b**, h) (*S*)-**32b**

With enantiomeric ratios of all the substrates proven to be $92:8 \pm 1$, in line with that achieved by Sharpless asymmetric dihydroxylation in the first step of this synthesis it is now possible to investigate activation of these esters in order to generate enantiopure bromonium ions. We can then be confident that any erosion of enantiomeric excess will have occurred under cyclisation conditions.

2.3.1 Enantiospecific mono-cyclisation

In order to determine the enantiopurity of cyclisation reactions carried out with scalemic substrates a racemic sample of bromocyclohexane **29** was needed. This was obtained by direct BDSB-mediated cyclisation of alkene **1** giving ($\pm$)-**29** in 63% yield in 15 minutes (Scheme 71).



Scheme 71 - BDSB bromo-cyclisation of homoprenyl *p*-methoxybenzene (**1**) and chiral HPLC analysis of bicycle ($\pm$)-**29**

Cyclisation of secondary tetrafluorobenzoate (*R*)-**31a** with 30 mol% TfOH at reflux in dichloromethane proceeded quantitatively to bromo-bicycle (*S*)-**29** (Table 12, entry 1). This process was completely enantiospecific as determined by chiral HPLC analysis (Figure 29). Tertiary tetrafluorobenzoate (*S*)-**31b** was also efficiently cyclised under these conditions, in excellent conversion and without racemisation at reflux (entry 2).

Table 12 - Investigation of triflic acid loading on cyclisation of tetrafluorobenzoate esters (*R*)-**31a** and (*S*)-**31b** and acetate esters (*R*)-**32a** and (*S*)-**32b**

$$\begin{array}{c} \text{Substrates} \\ (R)\text{-}\mathbf{31a}, (S)\text{-}\mathbf{31b} \\ (R)\text{-}\mathbf{32a}, (S)\text{-}\mathbf{32b} \end{array} \xrightarrow[\text{-14}^{\circ}\text{C to T (}^{\circ}\text{C)}]{\text{TfOH (30 mol\%)} \\ \text{CH}_2\text{Cl}_2} \text{Br} \begin{array}{c} \diagup \diagdown \\ \text{C} \\ \diagdown \diagup \end{array} \begin{array}{c} \diagup \diagdown \\ \text{C} \\ \diagdown \diagup \end{array} \text{OMe}$$

(*S*)-**29**

Entry	Substrate	e.r.	T (°C)	<i>t</i> (h)	% Conversion ^a	e.r. ^b
1	(<i>R</i>)- 31a	92:8	40	3	97 (84)	91:9
2	(<i>S</i>)- 31b	93:7	40	4	94 (67)	92:8
3	(<i>R</i>)- 32a	92:8	40	3	92 (53)	84:16
4	(<i>S</i>)- 32b	92:8	r.t.	5	35 (30 ^c)	nd

^aAs determined by inspection of the ¹H NMR spectrum after aqueous work-up. Figure in parentheses is isolated yield after column chromatography. ^bAs determined by HPLC analysis by reference to a racemic sample. ^cIsolated as a mixture of products

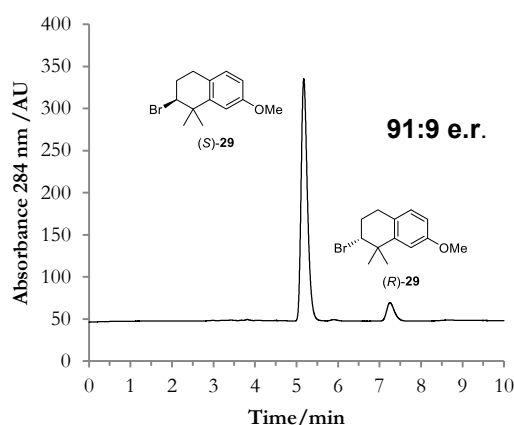


Figure 29 - Chiral HPLC chromatogram showing the enantiopurity of (*S*)-**29** for entry 1 Table 12

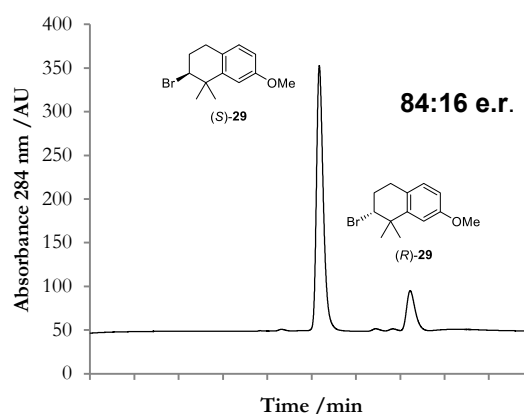


Figure 30 - Chiral HPLC chromatogram showing the enantiopurity of (*S*)-**29** for entry 3 Table 12

Secondary acetate ester (*R*)-**32a** was also efficiently cyclised under these conditions (entry 3) with a slight erosion in enantiomeric ratio of the product observed by chiral HPLC analysis (Figure 30). In the ¹H NMR spectrum of the crude product mixture small quantities of alkene (*ca.* 2-5%) were observed, and presumably some erosion of enantiomeric ratio is occurring by transfer of bromonium ion to these olefins.⁹⁵ Tertiary acetate ester (*S*)-**32b** gave complex and varied mixtures of product and rearranged compounds at room temperature (entry 4). This demonstrates that a non-nucleophilic counterion, such tetrafluorobenzoate is required for clean cyclisation to (*S*)-**29**.

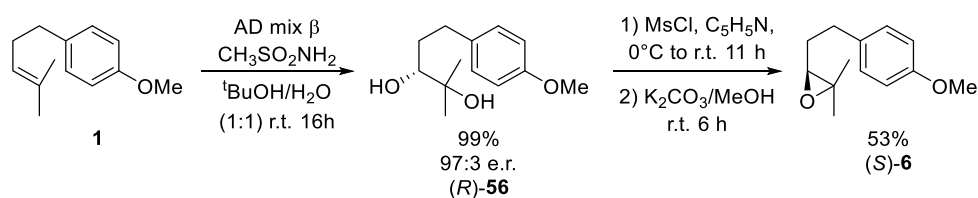
The reaction profiles of tetrafluorobenzoate derivatives cyclised using triflic acid at reflux were extremely clean, gave complete conversion to desired product **29**, without the formation of alkene products and without erosion of enantiopurity. So, tetrafluorobenzoate derivatives of either (*R*)-

8a or (*S*)-**8b** bromohydrins represent excellent choices for the formation of scalemic bromonium ions.

It became apparent that in a practical synthesis of (*S*)-**29** it would be desirable to esterify bromohydrins (*R*)-**32a** and (*S*)-**32b** without separation and so a full synthesis of (*S*)-**29** was set out without separation of these regioisomers.

2.3.2 Demonstration of practical utility

To show the preparative utility of this method alkene **1** was dihydroxylated using AD-mix β which gave (*R*)-**56** in 99% yield, and with an improved enantiomeric ratio of 97:3 e.r. over AD-mix α . Epoxide formation as before gave (*S*)-**6** in 53% isolated yield.



Scheme 72 - Synthesis of the opposite enantiomer (*S*)-**6** epoxide

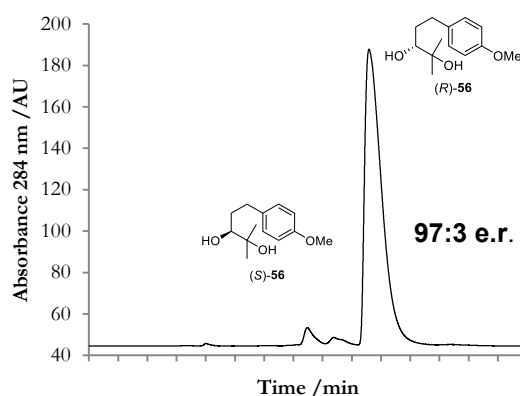
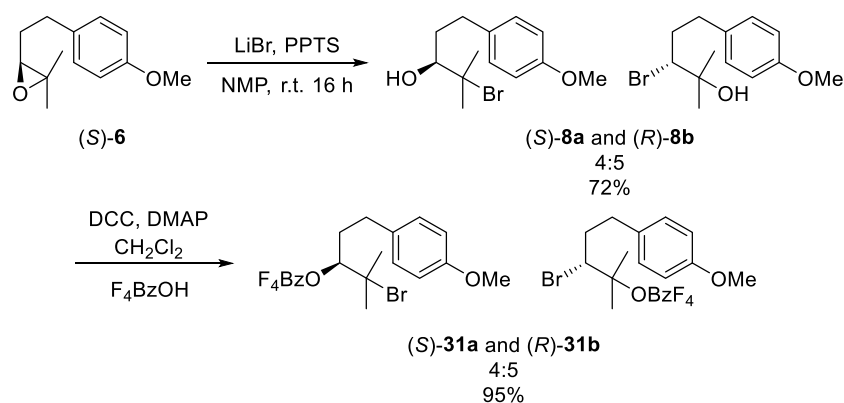


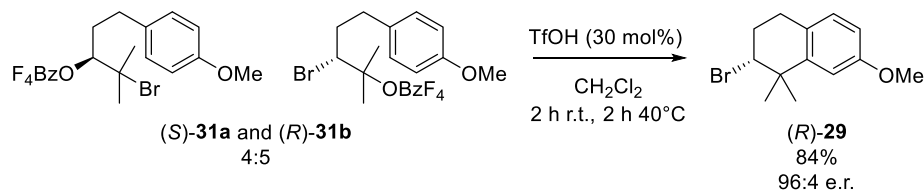
Figure 31 - Chiral HPLC analysis of (*R*)-**56**

Anionic bromide ring-opening of epoxide (*S*)-**6** produced bromohydrins (*S*)-**8a** and (*R*)-**8b** which were isolated as a mixture in 72% yield and converted to tetrafluorobenzoate esters (*S*)-**31a** and (*R*)-**31b** in 95% overall yield (Scheme 73).



Scheme 73 - Synthesis of tetrafluorobenzoate esters (*S*)-**31a** and (*R*)-**31b** without separation of regioisomers

Triflic acid catalysed cyclisation of the mixture in dichloromethane at reflux over 3 h gave (*R*)-**29** in high yield without racemisation of the products (84%, 96:4 e.r.).

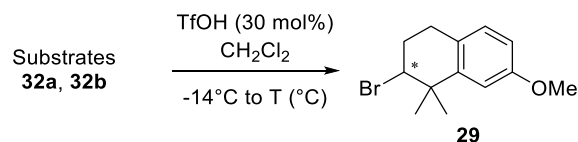


Scheme 74 - Cyclisation of a mixture of regioisomeric tetrafluorobenzoate esters (*S*)-**31a** and (*R*)-**31b**

The epoxide ring-opening method produces *ca.* 9% of allyl alcohol **14**, which is carried through in the esterification to give allyl tetrafluorobenzoate ester **33**. This material can be removed by treating the mixture with *m*CPBA followed by chromatography. If the cyclisation is conducted in the presence of the allylic ester, (*R*)-**29** is obtained in lower yield (53%) with slight erosion of e.r. (92:8), presumably some leakage of ee is occurring by bromonium ion-to-olefin transfer.⁹⁵

2.3.3 Investigation into racemisation in the cyclisation of acetate esters

It was at this point, when substrates of both enantiomeric series, from AD-mix α and β , that the cyclisation of scalemic acetate esters with catalytic triflic acid was investigated further. Table 13, entries 1 and 5 detail the cyclisation of acetate esters (*R*)-**32a** and (*S*)-**32b**, derived from dihydroxylation using AD-mix α , that were previously discussed in Chapter 2.3.1.

Table 13 - Investigation of triflic acid loading on cyclisation of scalemic acetate esters **32a** and **32b**

Entry	Substrate	e.r.	T (°C)	t (h)	% Conversion ^a	e.r. ^b
1	(R)- 32a	92:8	40	3	92 (53)	84:16
2	(S)- 32a	96:4	40	3	86 (59)	89:11
3	(S)- 32a	96:4	40	2	100 (78)	96:4
4	(S)- 32a	96:4	40	2.5	97(66)	96:4
5	(S)- 32b	92:8	r.t.	5	35 (30)	nd
6	(R)- 32b	96:4	40	2	92 (30)	72:28
7	(R)- 32b	96:4	40	2	95 (39)	89:11
8	(R)- 32b	96:4	40	2	85 (56)	90:10

^aAs determined by inspection of the ¹H NMR spectrum after aqueous work-up. Figure in parentheses is isolated yield after column chromatography. ^bAs determined by HPLC analysis by reference to a racemic sample.

Secondary acetate ester (R)-**32a**, discussed previously (Table 12, entry 3) and re-examined here (Table 13, entry 1) cyclised efficiently in 3 h at reflux. However, erosion of enantiomeric ratio of the product was observed, from 92:8 to 84:16 e.r. This was accounted for by the presence of small quantities of alkene produced during the reaction which caused erosion of enantiomeric ratio by bromonium ion-to-olefin transfer.⁹⁵

This was also the case in entry 2 where secondary acetate ester (S)-**32a** derived from dihydroxylation using AD-mix β, with enantiomeric ratio of 96:4, showed a lower enantiomeric ratio of 89:11 in its cyclisation with triflic acid, the crude ¹H NMR spectrum also contained 7% of alkene.

However, two subsequent runs using (S)-**32a**, gave quantitative conversion with undiminished e.r.'s where no alkene was apparent in the crude ¹H NMR spectrum (entries 3 and 4). Evidently, using this substrate produces variable quantities of alkene during the reaction which cause unpredictable erosion of enantiomeric ratio.

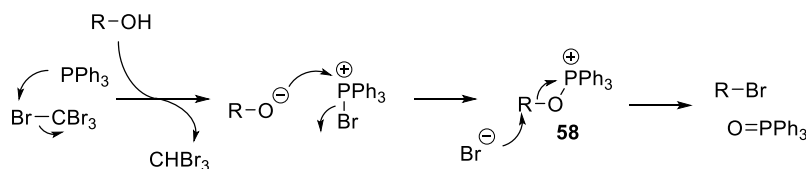
Tertiary acetate ester (S)-**32b** discussed previously (Table 12, entry 4) and re-examined here (entry 5) gave complex and varied mixtures of product and rearranged compounds. However,

three runs were also carried out using the opposite enantiomer (*R*)-**32b** (e.r. 96:4). (*R*)-**32b** giving essentially the same results in which the product (*R*)-**29** was observed in all cases, along with varying amounts of starting acetate **32b**, secondary acetate **32a**, elimination products and ketone **16**. Enantiomer ratios of the isolated product (*R*)-**29** were recorded as 72:28, 89:11 & 90:10 in each case. Not surprisingly, the formation of many different side products has led to variable erosion of enantiomeric excess.

It has very clearly been demonstrated that the presence of alkenes in cyclisation reactions, either from the starting material or produced during the reaction, has a profound effect on the enantiomeric ratio of the products and so the use of pure tetrafluorobenzoate esters is critical. As an activated leaving group they provide clean conversion to desired cyclised products without undesirable alkene by-products which results in completely enantiospecific reactions.

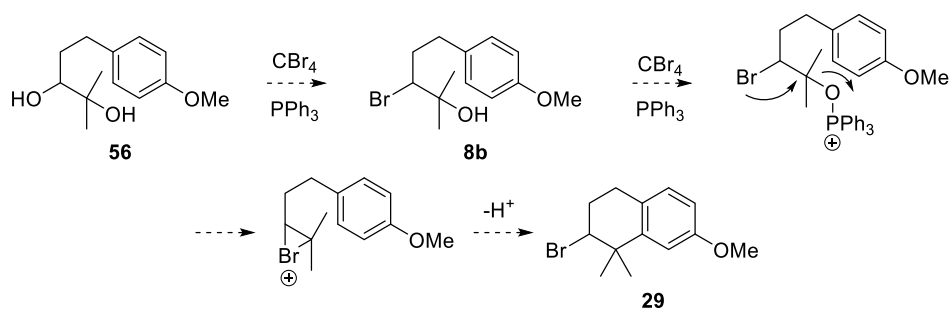
2.3.4 Are shorter routes possible?

The Appel reaction is used to convert primary and secondary alcohols to halides using triphenylphosphine and tetrahalomethane in high yield and under mild conditions.¹³⁰ In the example of bromination, triphenylphosphine reacts with tetrabromomethane to give CBr_3^- which deprotonates the alcohol (Scheme 75), the resulting alkyl oxide attacks at phosphorus to form an oxyphosphonium intermediate **58**. This activated alcohol is reactive towards attack by the resulting bromide anion to give the desired alkyl bromide.



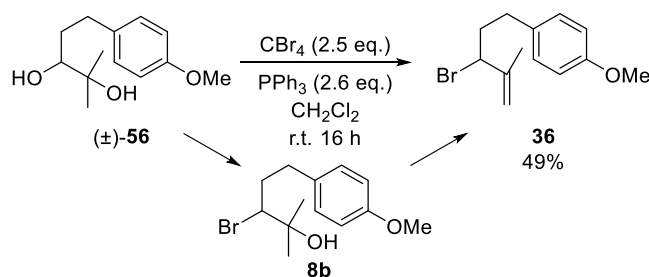
Scheme 75 - Generalised Appel bromination reaction

There are examples of Appel reactions being carried out on tertiary alcohols¹³¹ and so it was proposed that in the case of a 1,2-bromohydrin **8b**, under these reaction conditions, that the activated alcohol may undergo intramolecular cyclisation (Scheme 76). The reaction of diol **56** with triphenylphosphine and tetrabromomethane could also be expected to give bromohydrin (Scheme 76). Therefore reaction of diol **56** with two equivalents of triphenylphosphine and tetrabromomethane could provide the desired cyclised product in one step.



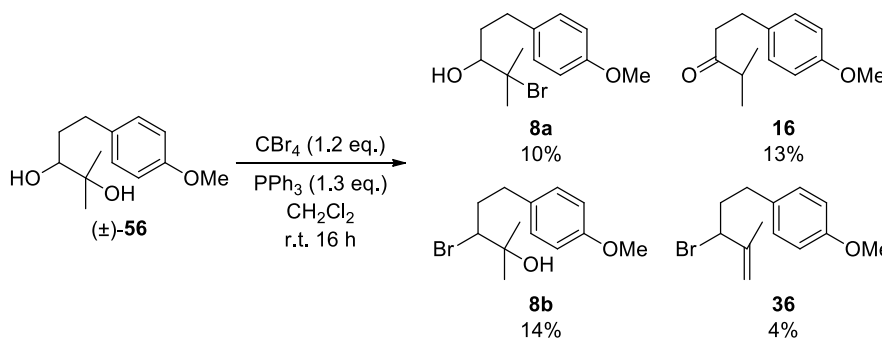
Scheme 76 - Postulated Appel reaction of diol **56**

Accordingly, ($\pm$)-**56** was reacted with 2.5 equivalents of tetrabromomethane and 2.6 equivalents of triphenylphosphine at room temperature overnight. Unfortunately none of the desired cyclised product **29** was isolated. Instead allyl bromide **36** was isolated as the major product in 49% yield (Scheme 77), presumably this results from the bromination of diol **56** to give bromohydrin **8b**. Activation of the tertiary alcohol and elimination would then provide allyl bromide **36**.



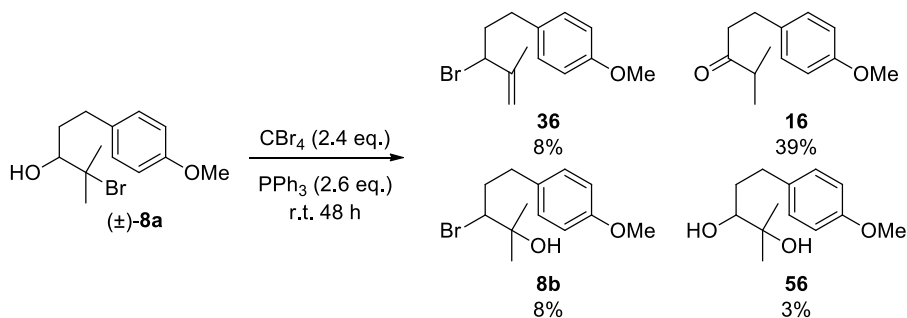
Scheme 77 - Appel reaction of diol ($\pm$)-**56** with two equivalents of tetrabromomethane and triphenylphosphine

In order to investigate the first step in this reaction, from diol **56** to presumed bromohydrin **8b**, ($\pm$)-**56** was reacted with only 1.2 and 1.3 eq. of tetrabromomethane and triphenylphosphine respectively. This gave both bromohydrin regioisomers **8a** and **8b** in 24% overall yield (Scheme 78). This supports our previous hypothesis that they are intermediates to allyl bromide **36** in the previous reaction and although, the conversion was low, heating may improve the yields of bromohydrin.



Scheme 78 - Appel reaction of diol ($\pm$)-**56** with one equivalent of tetrabromomethane and triphenylphosphine

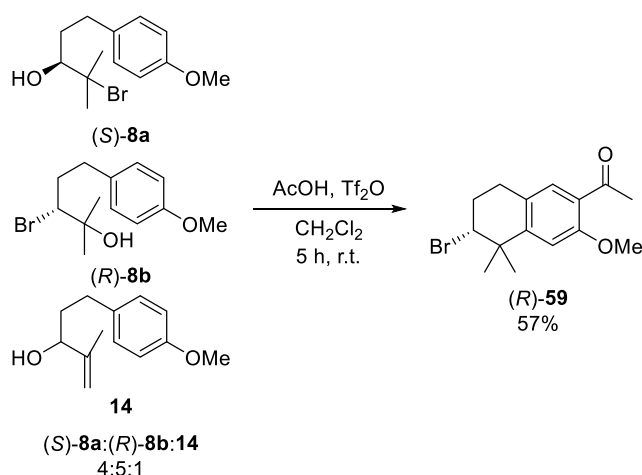
In order to investigate the second part of the reaction, from bromohydrin to allyl bromide, bromohydrin ($\pm$)-**8a** was reacted under the same conditions, but there was no reaction at room temperature overnight. Adding an extra equivalent of each reagent, triphenylphosphine and tetrabromomethane gave ketone **16** as the major product in 29% yield and allyl bromide **36** in 8% yield. (Scheme 79).



Scheme 79 - Reaction of bromohydrin ($\pm$)-**8a** under Appel conditions.

From these reactions it appears possible to react a 1,2-diol under Appel conditions to synthesise allyl bromide **36** (Scheme 77) or bromohydrin (albeit in low yields, Scheme 78). However using these conditions to enact a bromo cyclisation was not possible.

The synthesis of tertiary acetates has been carried out using acetic acid and trifluoroacetic anhydride in dichloromethane. It was proposed that the substitution of trifluoroacetic anhydride with triflic anhydride would further promote cyclisation by the formation of triflic acid in the reaction. Accordingly a mixture of bromohydrin regioisomers was reacted with acetic acid and triflic anhydride at room temperature for 5 hours (Scheme 80)



Scheme 80 - Bromohydrin cyclisation *via* acetylation

Interestingly, the major component isolated from the reaction was Friedel–Crafts adduct **59** in 57% yield, where the desired brominated bicycle **29** was not present in the product mixture. Evidently, bromo-cyclisation of the bromohydrin regioisomers had indeed been induced.

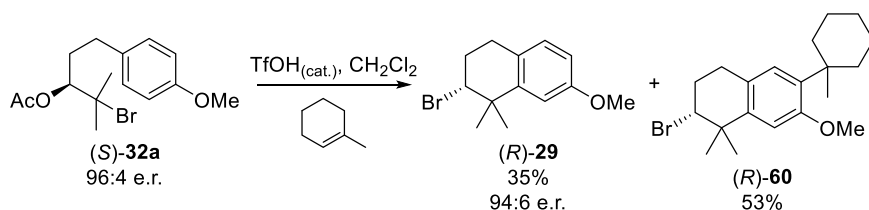
However, further reaction of the desired product with the reagent combination led to Friedel-Crafts acetylation. If further investigation was explored it would be interesting to see if triflic anhydride can enact the cyclisation of alcohols (*S*)-**8a** and (*R*)-**8b** without the presence of acetic acid.

Although the synthesis of tetrafluorobenzoate cyclisation substrates requires a number of reaction steps, the substrates have been proven to undergo clean, efficient, and most importantly enantiospecific cyclisation reactions. The production of pure scalemic cyclisation products was deemed far more beneficial than a shorter route and so these avenues were no longer pursued..

2.3.5 Experimental mono-cyclisation reactions with added alkene

For the development of a *polyene* cyclisation triggered by an enantiopure bromonium ion it is vital to know if the enantiospecific cyclisation onto bromonium ion will be compromised by competitive bromonium ion transfer to alkenes.⁹⁵ Alkenes, which are necessarily present in potential polyene substrates. Accordingly, catalytic triflic acid was added to secondary tetrafluorobenzoate ester (*R*)-**31a** in the presence of one equivalent of 1-methylcyclohexene and no reaction of (*R*)-**31a** was observed even after prolonged heating and a total addition of 60 mol% of triflic acid, instead 1-methylcyclohexene was reacting with the acid to give high molecular weight hydrocarbons.

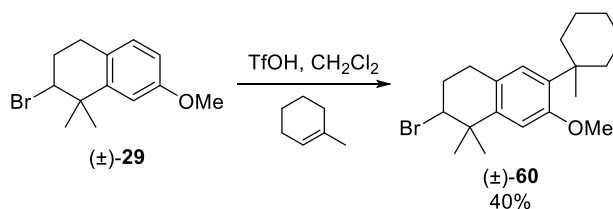
The cyclisation of secondary acetate ester (*S*)-**32a** (e.r. 96:4) was however successful in the presence of one equivalent of 1-methylcyclohexene (Scheme 81) with the desired bromocyclohexane (*R*)-**29** isolated in 35% yield with an essentially undiminished e.r. of 94:6. Therefore no racemisation had occurred in the formation of desired product **29** *via* bromonium ion-to methylcyclohexene transfer. Friedel–Crafts alkylation adduct (*R*)-**60** was also formed in 53% yield.



Scheme 81 - Mono-cyclisation in the presence of alkene.

To analyse the enantiomeric ratio of (*R*)-**60** a racemic sample was synthesised *via* the reaction of bromo bicycle ($\pm$)-**29** with 1-methylcyclohexene and stoichiometric triflic acid, which gave ($\pm$)-**60** in 40% yield together with 56% recovered starting material (Scheme 82). Unfortunately ($\pm$)-**60** was not separable on the available chiral HPLC columns. However it can be assumed by the high

enantiomeric ratio of (R)-**29** obtained from the previous reaction that it is likely to be the same case for (R)-**60**.



Scheme 82 - Synthesis of Friedel-Crafts adduct ($\pm$)-**60**

We have shown that the enantiomeric ratio of bicycle (R)-**29** from bromonium ion-induced cation- π cyclisation of secondary acetate (S)-**32a** is not diminished by the presence of an added alkene under these conditions. Thus, for a bi-cyclisation, with substrates bearing a necessarily present alkene, it can be expected that their cyclisation will be wholly enantiospecific. However the presence of an acid-sensitive trisubstituted alkene in bi-cyclisation substrates renders the use of Brønsted acids to subsequently generate bromonium ions undoubtedly problematic.

2.4 Bi-cyclisation substrates

Bromonium ion-induced cation- π cyclisation of substrates bearing a single olefin have been successfully carried out and the mechanism of the reaction investigated. This synthetic methodology was then applied to polyene substrates containing two alkenes where two C-C bonds are formed during bromonium ion-induced cyclisation. Figure 32 demonstrates this for the cyclisation of nerolidol to bromo-epicaparrapi oxide.

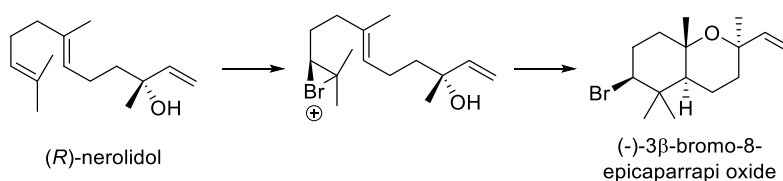


Figure 32 - Polyene cyclisation of nerolidol to (-)-3b-bromo-8-epicaparrapi oxide

Polyene **61** (Figure 33) was selected as the basic carbon framework for investigation of the first polyene cyclisation triggered by an enantiopure bromonium ion. The *para*-methoxy substituted aromatic in the compound will provide a UV chromophore necessary for chiral HPLC analysis. An enantiopure bromonium ion was to be formed on the terminus alkene (in blue), with the second, internal alkene (in red) acting as the propagating olefin, and the polyene cyclisation was to be terminated by the aromatic moiety.

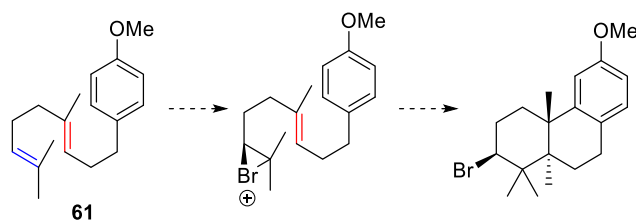
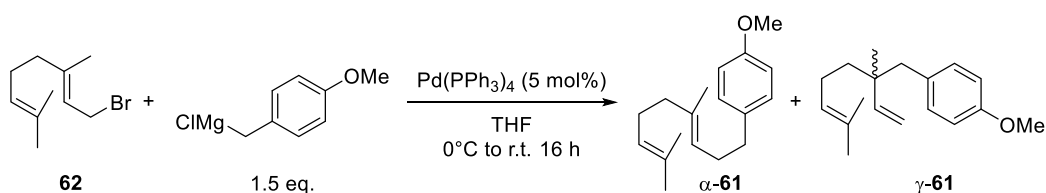


Figure 33 - Polyene **61** and its enantiopure bromonium ion-induced polyene cyclisation

2.4.1 Synthesis of analytically pure polyene **61**

Diene **61** could be prepared by the method of Demuth and co-workers *via* palladium(0) catalysed coupling of commercially available *p*-methoxybenzyl magnesium chloride with geranyl bromide.¹⁰³ In our hands variable and significant quantities of the branched regioisomer γ -**61** were also observed which was inseparable by simple column chromatography. In multiple runs the ratio of α : γ -**61** was found to vary unpredictably from 37:1 to 15:1 (Table 14).

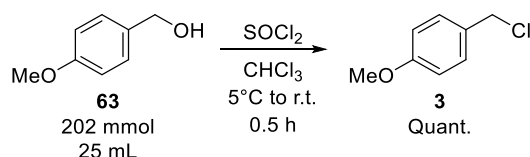
Table 14 - Pd(PPh₃)₄ catalysed alkylation of geranyl bromide **62** using commercial Grignard reagent



Entry	62 (mmol)	Yield 61 (%)	α : γ^a
1	1.0	83	37:1
2	2.5	62	35:1
3	4.6	65	15:1

^aAs determined by ¹H NMR analysis of isolated product

For larger-scale reactions (over 5 mmol) it was more economical to synthesise *p*-methoxybenzyl chloride from the corresponding benzyl alcohol **63** (Scheme 83) and then react this with magnesium turnings to form the Grignard reagent.

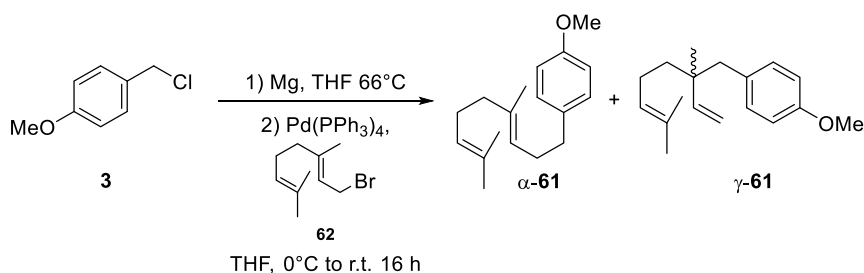


Scheme 83 - Synthesis of *p*-methoxybenzyl chloride

Synthetic Grignard reagent was employed for the alkylation of geranyl bromide using Demuth conditions¹⁰³ (Table 15) and inseparable branched regioisomer γ -**61** was again isolated with the

desired product: α -**61** in a ratio of 1:18 (entry 1). The use of 0.9 equivalents of Grignard reagent (entry 2) and palladium(0) catalyst sourced from Strem gave poorer regioselectivity (9:1 α : γ -**61**).

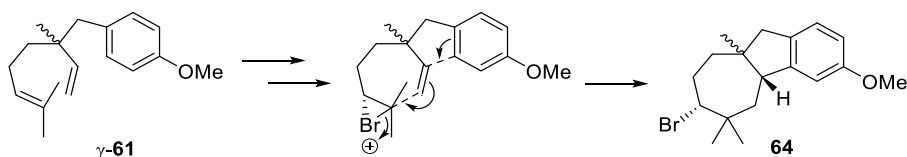
Table 15 - Pd(PPh₃)₄ catalysed alkylation of geranyl bromide **62** with synthetic Grignard reagent



Entry	62 (mmol)	3 (eq.)	Pd(PPh ₃) ₄ (mol%)	Pd(PPh ₃) ₄ Source	Yield 61 (%)	α : γ ^d
1	2.5	1.5	5	Aldrich	63	18:1
2	8.1	0.9	5	Strem	89	9:1
3	100.6	1.1	5	Strem	48	3:1
4	0.2	1.1	100	Synthetic	0	n/a
5	0.7	1.1	1	Synthetic	29	10:1
6	24.2	0.95	1	Synthetic	77	36:1

^dAs determined by ¹H NMR analysis of isolated product

When further reactions were carried out using a 9:1 mixture of linear to branched chain isomers it was found that the branched isomers were inseparable at all stages of the synthesis, culminating in the contamination of cyclisation products with a 7,5,6-membered tricycle **64**, (Scheme 84) formed from bromonium ion-induced cyclisation of γ -**61**. This impurity obscured the desired minor enantiomer signal in the HPLC analysis and so high purity diene α -**61**, free from branched γ -**61**, was therefore found to be essential for subsequent HPLC enantiomeric excess determination of products.

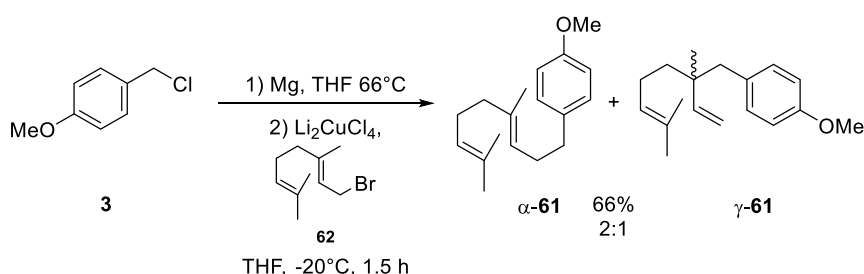


Scheme 84 - Formation of unwanted by-product **64** from γ -**61**

On a 100 mmol scale of geranyl bromide **62** with 1.1 equivalents of Grignard reagent, even poorer regioselectivities of 3:1 α : γ -**61** were observed (entry 3). When freshly prepared tetrakis

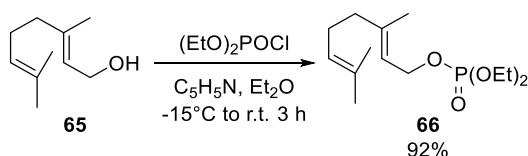
palladium was investigated at stoichiometric loading only homo-coupling by-product **4** was isolated (entry 4). Two further runs using synthetic Pd(PPh₃)₄ at catalyst loadings of 1 mol% continued to give unpredictable ratios of α : γ -**61** (10:1 and 36:1, entries 5 and 6) and so another method for this alkylation was sought.

Dilithium tetrachlorocuprate(II) is frequently used as a catalyst in the reaction of Grignard reagents with electrophiles.¹³² It has been reported to undergo highly regioselective substitution of geranyl bromide to give exclusively α - (S_N2) substitution without any γ - (S_N2') substitution products detectable by NMR.¹³³ In our hands *p*-methoxybenzyl magnesium chloride was reacted with geranyl bromide in the presence of 4 mol% Li₂CuCl₄ catalyst at -20°C for 1.5 h (Scheme 85) to give a 66% yield of the desired product **61**. The regioselectivity of the reaction was poor with an α : γ ratio of 2:1.



Scheme 85 - Li₂CuCl₄ catalysed Grignard alkylation of geranyl bromide

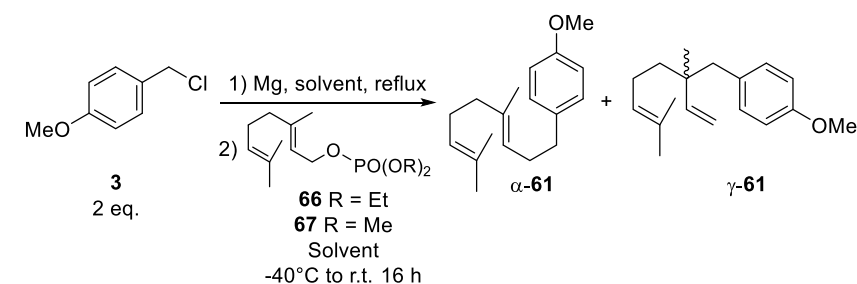
Synder^{10a} has described the non-catalysed coupling of the same Grignard reagent with geranyl diethyl phosphate, a method originally reported by Butsugan *et al.*¹³⁴ Geranyl diethyl phosphate **66** can be synthesised by reaction of geraniol **65** and diethyl chlorophosphate in 92% isolated yield (Scheme 86).



Scheme 86 - Synthesis of geranyl diethyl chlorophosphate

For comparison, geranyl *dimethyl* phosphate **67**¹³⁵ was also investigated as an alternative substrate for Grignard alkylation. Geranyl dimethyl phosphate can be synthesised by reaction of geraniol and dimethyl chlorophosphate *via* the same method and although analysis of the ¹H NMR of the crude reaction mixture showed good conversion to the desired dimethyl phosphate, purification by chromatography led to decomposition on silica. Both geranyl diethyl and dimethyl phosphates could however be used as crude mixtures in subsequent alkylation reactions.

Table 16 - Investigation of non-catalysed Grignard alkylations of geranyl alkyl phosphates using the Butsugan method.¹³⁴



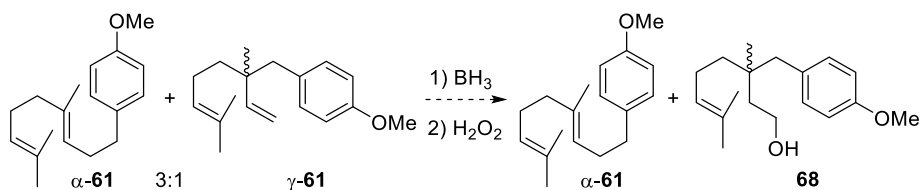
Entry	Substrate	Mg (eq.)	Solvent	Yield 61 (%)	$\alpha:\gamma^a$
1	66	4	THF	Quant.	17:1
2	66	4	THF	82	8:1
3	66	10	THF	90	15:1
4	66	10	Et ₂ O	13	3:1
5	67	4	THF	19	0:1

^aAs determined by ¹H NMR analysis of isolated product

Two reactions using the literature procedure^{10a} and geranyl diethyl phosphate gave excellent yields of **61** (quantitative and 82% yield, entries 1 and 2, Table 16) and reasonable regioselectivities of $\alpha:\gamma$ products (17:1 and 8:1). The use of greater quantities of magnesium turnings did not affect the yield or regioselectivity of the reaction (90% yield and 15:1 $\alpha:\gamma$, entry 3). The use of diethyl ether in the formation of the Grignard reagent and subsequent alkylation reaction gave poor yields and regioselectivity (13% yield, 3:1 $\alpha:\gamma$, entry 4). This is likely due to the precipitation of MgCl₂ and the formation of dialkylmagnesium compounds in the Grignard formation step. Synthesis of the Grignard reagent in THF and then exchanging the solvent for diethyl ether was also attempted, but unfortunately the reagent was not soluble in diethyl ether and so 1,4-dioxane was considered as an alternative however its melting point of 12°C would not allow for temperature control in the reaction and so was expected to give poor regioselectivity. The use of crude geranyl dimethyl phosphate **67** and the literature conditions^{10a} gave 19% yield of $\gamma\text{-61}$ and none of the desired $\alpha\text{-61}$ product (entry 5).

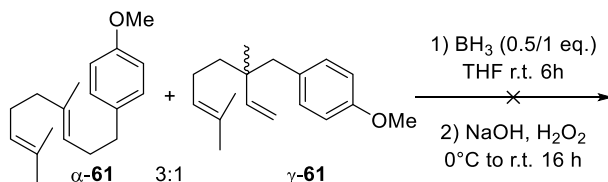
With no improvement in regioselectivity found using different geranyl alkylation substrates, catalysts or conditions, attention turned to reagents which may react selectively at the primary olefin over the trisubstituted alkenes. This will create derivatives of the undesired branched regioisomer, $\gamma\text{-61}$, which could be separated from the linear polyene ($\alpha\text{-61}$) by column

chromatography. A hydroboration-oxidation reaction for example, could be envisaged to react with the less hindered primary alkene of γ -**61** to give an alcohol **68** (Scheme 87) which would be more polar than linear diene α -**61** and so separable by standard chromatography.



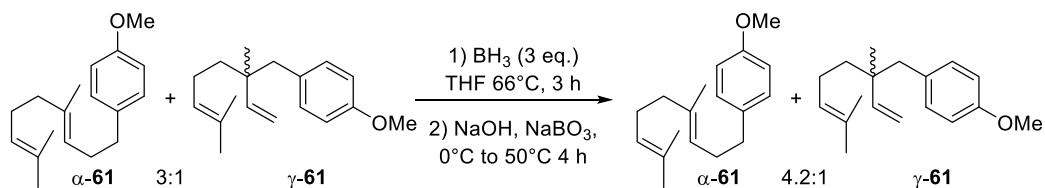
Scheme 87 - Proposed hydroboration of diene mixture α - and γ -**61**

Accordingly a 3:1 mixture of α - and γ -**61** was stirred with 0.5 equivalents of borane at room temperature over 6 h (Scheme 88), unfortunately, no conversion of the starting materials was observed by ^1H NMR analysis of the crude reaction mixture even after doubling the number of equivalents of borane.



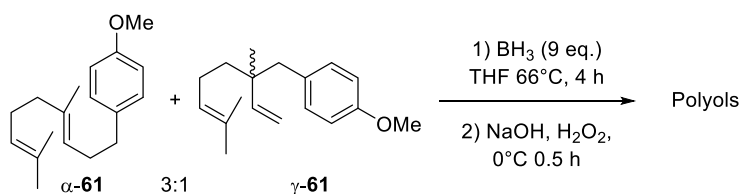
Scheme 88 - Unsuccessful hydroboration-oxidation of **61**

The use of sodium perborate oxidation, as described by Denmark for the hydroboration-oxidation of terminal double bonds,¹³⁶ led to a small improvement in the regioisomeric ratio from 3:1 to 4.2:1 (Scheme 89). This ratio was determined by ^1H NMR analysis of the crude reaction mixture following heating with 3 equivalents of borane at reflux for 3 h and subsequent oxidation with sodium perborate and sodium hydroxide solution at 50°C for 4 h.



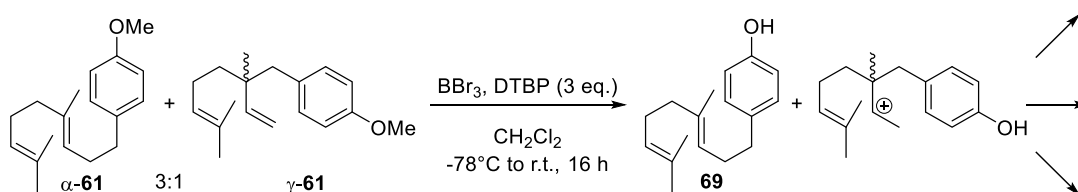
Scheme 89 - Hydroboration and NaBO_3 oxidation of **61**

Evidently, with the use of 3 equivalents of borane, the reagent was reacting poorly with α - and γ -**61** and in an attempt to push the reaction to completion a 3:1 mixture of α - and γ -**61** was heated at reflux with 9 equivalents of borane in THF for 4 h (Scheme 90). Standard oxidation with hydrogen peroxide and sodium hydroxide gave non-alkene containing products.



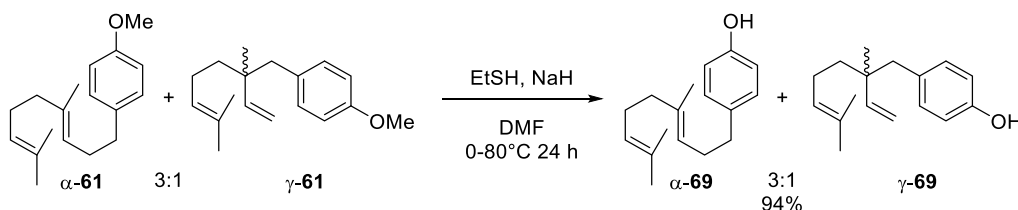
Scheme 90 - Hydroboration/oxidation of **61** to non-alkene containing products

After limited success using reagents which selectively react with primary alkenes, an alternative approach was investigated. The mixture of two constitutional isomers could both be reacted to give more polar products which may be separable by standard column chromatography. To this end, the demethylation of α - and γ -**61** in a 3:1 ratio was carried out with previously used conditions for the synthesis of compound **53** (Scheme 91). However after column chromatography a mixture of compounds was isolated. It was apparent from the ^1H NMR that full conversion to aromatic phenols had occurred, but there were a considerable number of alkyl absorbances between 0.8-2.8 ppm and no primary alkenes, this suggested that protonation of the primary alkene and various cyclisations had occurred to produce inseparable alkyl products. The same product distribution was also observed when five equivalents of DTBP was used.



Scheme 91 - Boron tribromide demethylation of α - and γ -**61**

Yamamoto and co-workers carried out the demethylation of aryl methyl ether **61** using ethanethiol and sodium hydride in DMF.¹³⁷ These conditions gave full conversion to the desired phenols **69**, (Scheme 92) however α - and γ -**69** could not be separated by column chromatography



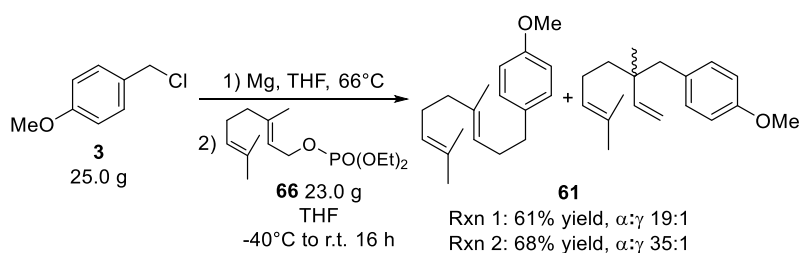
Scheme 92 - Ethanethiolate demethylation of α - and γ -**61**

Having explored the selective synthesis of α -**61**, reactions of primary alkenes and the synthesis of more polar derivatives with minimal success, it became apparent that α - and γ -**61** would *have* to be separated directly. Numerous solvent systems for standard silica gel column chromatography had already been investigated as well as preparative HPLC within our laboratory. Samples of the 3:1 mixture were supplied to AstraZeneca to investigate the use of supercritical fluid

chromatography and their library of chiral HPLC columns. Unfortunately, none of their analytical chiral HPLC columns separated the two constitutional isomers and samples returned after supercritical fluid chromatography contained the same ratio of isomers.

The power of silver nitrate-impregnated silica gel column chromatography has been demonstrated in the separation of hydrocarbons bearing various alkenes, which are inseparable *via* standard techniques due to their high R_f in non-polar solvents.¹³⁸ Using this technique pure samples of both α - and γ -**61** were obtained for characterisation, however, the expense of silver nitrate was prohibitive for isolation of pure α -**61** on a larger scale.

We proposed that as linear and branched constitutional isomers, α - and γ -**61** will differ most in their volatility, and distillation could be a likely method to purify these mixtures. In order to be successful, over 10 mL of α - and γ -**61** was needed for Vigreux distillation to give satisfactory separation of fractions. Butsugan's method¹³⁴ was selected for large-scale synthesis of α - and γ -**61** as the reaction reliably provided good selectivity for the desired linear polyene and the starting materials could be obtained cheaply from geraniol and 4-methoxybenzyl alcohol, subsequently two 80 mmol scale reactions were carried out (Scheme 93), which gave a total of 26.7 g of **61** in an overall ratio of 26:1.



Scheme 93 - Large scale synthesis of α - and γ -**61** for use in distillation

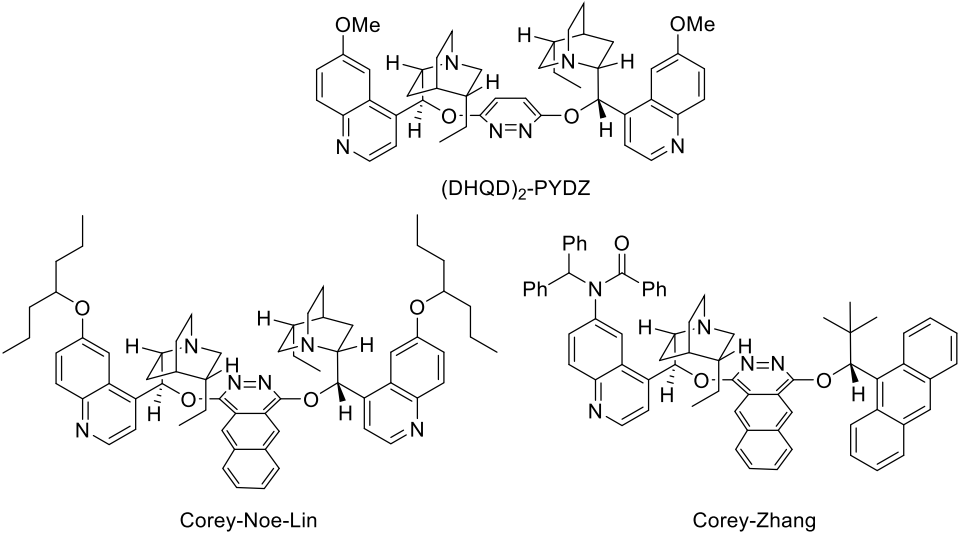
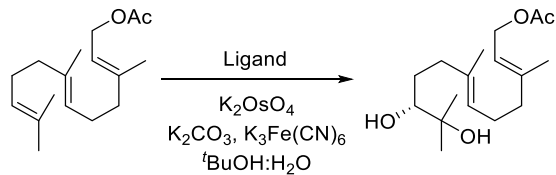
By carrying out fractional distillation of the combined diene mixtures using a vacuum-jacketed Vigreux column, the purity of **61** could be improved to >98%, this involved heating the mixture under vacuum (0.003 mmHg) at 200°C and collecting the fraction at 70°C. This fraction was enriched in branched isomer γ -**61** and the distillation residue remaining was linear diene α -**61** with a mass of 8.2 g.

2.4.2 Optimisation of Sharpless asymmetric dihydroxylation

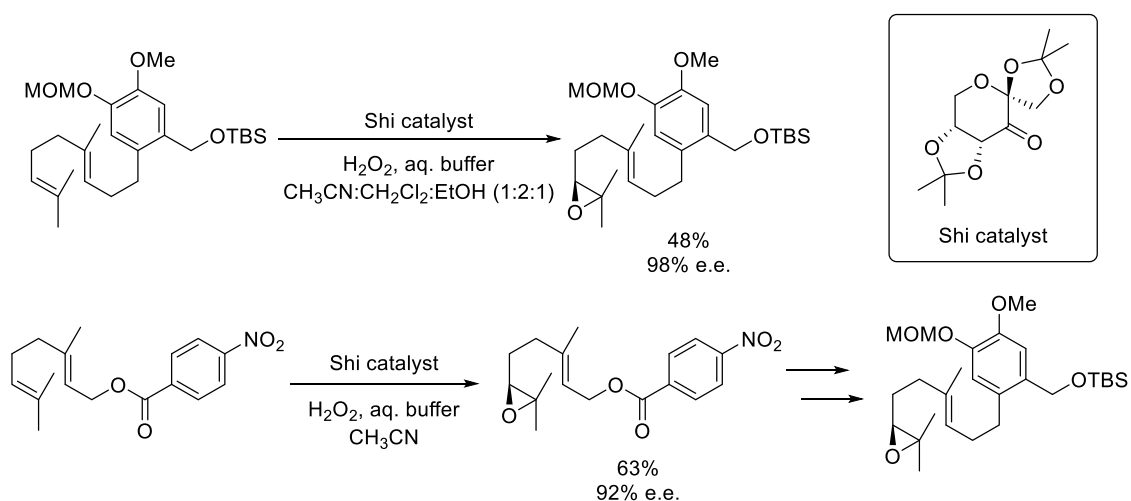
To generate enantiopure bromohydrins at the terminus of the diene, regioselective, asymmetric dihydroxylation would be required. Ligands such as the Corey-Noe-Lin ligand¹³⁹ (Table 17) give improved yields of dihydroxylation at the terminus alkene in comparison to the standard (DHQD)₂-PYDZ ligand found in AD-mix β .¹²⁶ For example in the regioselective asymmetric dihydroxylation of farnesyl acetate, AD-mix β provides 34% yield of the desired diol whereas the

Corey-Noe-Lin ligand increases the yield to 60% and the ligand has therefore been used in the synthesis of a number of natural products.^{71, 140} The development of the Corey-Zhang ligand gave further improvements up to 72% yield for the same substrate¹⁴¹ and the ligand was later used in the synthesis of Germanicol,^{30f} Lupeol,¹⁴² Serratenediol.¹⁴³ and Glisoprenin A.¹⁴⁴

Table 17 - Regioselective dihydroxylation ligands

 (DHQD)₂-PYDZ Corey-Noe-Lin Corey-Zhang		
	Entry	Ligand
	1	(DHQD) ₂ -PYDZ
	2	Corey-Noe-Lin
	3	Corey-Zhang
		Yield (%)
		34
		60
		72

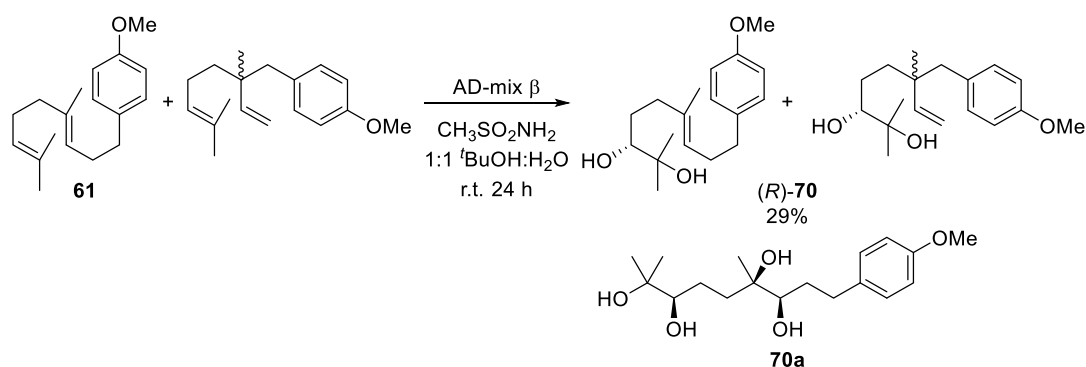
Shi epoxidation¹⁴⁵ using a sugar-derived catalyst has also been found to give good regioselectivity in polyprenoid substrates by Wiemer and co-workers,¹⁴⁶ diene substrates undergoing highly enantioselective Shi epoxidation of the terminus alkene in 48% yield (Scheme 94) which was later improved to 63% yield by epoxidation of an earlier geraniol derivative.¹⁴⁷



Scheme 94 - Regioselective Shi epoxidation of polyprenoid substrates.

(DHQD)₂PHAL, found in AD-mix β , is significantly sterically demanding that a slight preference for the less encumbered olefins nearer the terminus occurs even in substrates such as squalene¹⁴⁸ and has been used to good effect in a number of recent natural product syntheses.¹⁴⁹ Therefore good selectivity for dihydroxylation at the terminus alkene was also assumed for diene substrate **61** using AD-mix β .¹²⁷ In the event, dihydroxylation of diene **61** with AD-mix β and methane sulfonamide at room temperature gave good regioselectivity furnishing the desired diol (R)-**70** in 52% yield, (72% based on recovered starting material, Figure 34) with only a trace of dihydroxylation occurring at the central diol. The absolute configuration of diol (R)-**70** was assigned on the basis of the Sharpless mnemonic.¹²⁷⁻¹²⁸ Although AD-mix is not as high yielding as the use of Corey-Zhang ligand or Shi epoxidation, AD-mix provides a cheap and commercially available reagent which can be used in a simple procedure, thus providing significant practical benefits over more complex reagents. Optimisation of the reaction conditions can be carried out to reduce the quantity of major by-product tetraol **70a** to obtain a good yield based on recovered starting material.

Tetraol **70a**, the major by-product of the reaction was then further investigated. A rudimentary analysis of the conversion of starting material to desired product and tetraol over a 24 h period demonstrated that tetraol is formed in 11% yield within 1 h and only increases to 21% after 24 h. This was carried out by analysis of UV chromatograms from LCMS experiments at various intervals of the reaction.



Entry	Time (h)	61 (%)	70a (%)	(R)- 70 (%)
1	1	79	11	10
2	4	56	11	33
3	5.5	48	11	42
4	24	28	20	52

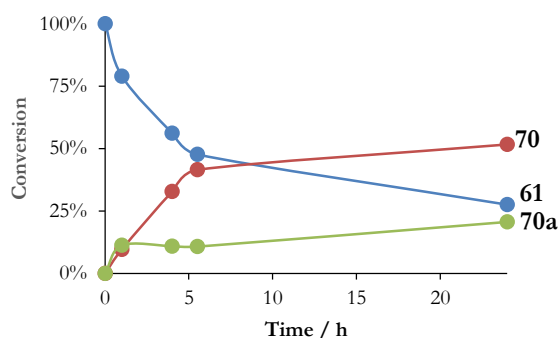
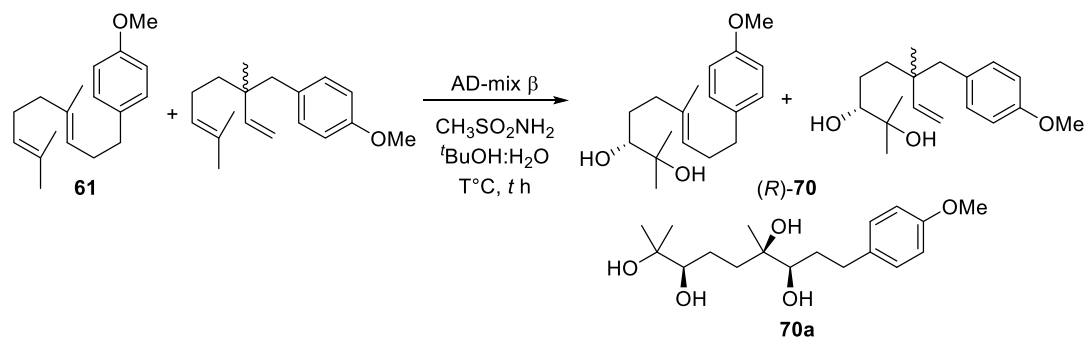


Figure 34 - Initial investigation into the conversion of diene **61** during Sharpless asymmetric dihydroxylation

We felt confident, as the proportion of tetraol **70a** after 24 hours was 21% that stirring the reaction for longer periods of time could improve the conversion of diene **61**. As tetraol **70a** was formed in 11% yield within one hour and was unchanged for the next four and a half hours, we felt that over-dihydroxylation may be occurring as the starting materials are first mixed. To control this we initiated the reaction at 0°C and allowed it to warm to room temperature slowly over three days. As this is a biphasic reaction involving water and $t\text{BuOH}$, it is important to have all the reagents mixing thoroughly at room temperature before cooling the reaction mixture to 0°C. This prevents the solvent from freezing at 0°C at which point the diene starting material can be added. Under these conditions a 63% isolated yield of diol (R)-**70** was obtained (84% BRSM, Table 18, entry 1).

Table 18 - Investigation of conditions for Sharpless asymmetric dihydroxylation of diene **61**

Entry	AD-mix β (gmmol ⁻¹)	CH ₃ SO ₂ NH ₂ (eq.)	T (°C)	<i>t</i> (h)	Recovered 61 (%)	Yield 70a (%)	Yield (<i>R</i>)- 70 (%) ^a
1	1.4	1	0 to r.t.	72	25 ^b	12 ^b	63 (84 ^b)
2	0.7	1	r.t.	72	13 ^b	37 ^b	50 (57 ^b)
3	1.4	0.5	r.t.	72	54 ^b	2 ^b	25 (54 ^b)
4	1.4 ^c	1	0 to r.t.	16	7	nd	31 (33)

^a Figure in parentheses is percentage yield based on recovered starting material. ^b Based on LCMS analysis of crude reaction mixture. ^c Additional 1 mol% K₂OsO₄·2H₂O and 2 mol% (DHQD)₂PHAL. nd = not determined.

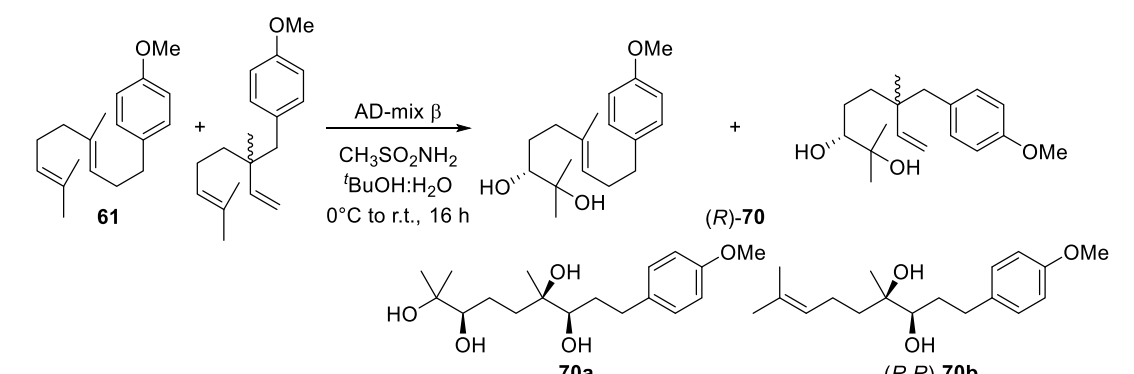
Slowing down the reaction by using half the number of equivalents of AD-mix or methane sulfonamide, over 72 hours, gave reduced yields of 50% and 25% of diol (*R*)-**70** (entries 2 and 3). Adding an extra 1 mol% of potassium osmate and 2 mol% of ligand (entry 4) gave 31% isolated yield of diol (*R*)-**70** (33% BRSM). Presumably such forcing conditions led to over-dihydroxylation to tetraol **70a**. Carrying out the Sharpless asymmetric dihydroxylation reaction at 0°C and warming to room temperature gave both the highest yield of diol (*R*)-**70** (63%) and the highest yield based on recovered starting material (84%). Therefore these conditions were selected for future dihydroxylation reactions.

In these test reactions diene **61** was used with a low linear to branched chain ratio of 13:1. It has to be noted that for the dihydroxylation reactions discussed thus far (excluding entry 4, Table 18) the linear to branched chain ratio of the product diol (*R*)-**70** had reduced to 5:1 in the product. Evidently, while the linear diol α -**70** could further dihydroxylate to tetrol **70a**, thus depleting the amount of (*R*)-**70**, the terminal alkene of the branched isomer diol γ -**70** was more resistant to further dihydroxylation. This accumulation of the branched isomer in this reaction made it even more imperative that the starting material was of high purity. This dramatic effect can be shown in the following example: when 5 g of diene **61** with a linear to branched chain ratio of 3:1 was reacted under our standard Sharpless asymmetric dihydroxylation conditions, the reaction went to

full conversion and a 34% yield of **70** was isolated, however the mixture of isomers had the opposite ratio of linear to branch chain diols, 3:1 in favour of the branched diol, γ -**70**.

Subsequently, 8.2 g of high purity (>98% or 60:1 α : γ) diene **61**, was divided into three reactions and carried out at 0°C and warmed to room temperature overnight to produce diol (R)-**70** in good yield based on recovered starting material (42-60%, Table 19), with isolated yields from 25-40%. The main by-products were tetraol **70a**, isolated in 25% yield (entry 2), and trace quantities of undesired regioisomer (R,R)-**70b** (3% isolated yield, entry 1).

Table 19 - Sharpless asymmetric dihydroxylation using high purity diene **61**



Entry	61 (g)	Recovered 61 (%)	Recovered 61 (α : γ)	Yield 70a (%)	Yield (R,R)- 70b (%)	Yield (R)- 70 (%) ^a	70 (α : γ)
1	1	33	124:1	nd	3	40 (60)	118:1
2	4.1	40	205:1	25	nd	25 (42)	98:1
3	3	34	60:1	nd	nd	37 (56)	63:1

^a Figure in parentheses is percentage yield based on recovered starting material

The Sharpless asymmetric dihydroxylation of diene **61** was found to be highly enantioselective, diol (R)-**70** from entry 2, Table 19 had an enantiomeric ratio of 99:1 (Figure 36) determined by chiral HPLC analysis in comparison to a racemic sample (Figure 35). As the asymmetric dihydroxylation was highly enantioselective (99:1 e.r.) identifying the minor enantiomer in chiral HPLC analysis became difficult as impurities that represent even 1% of the mixture can obscure judgement, it was therefore critical that diol **70** is synthesised in at least 99% purity.

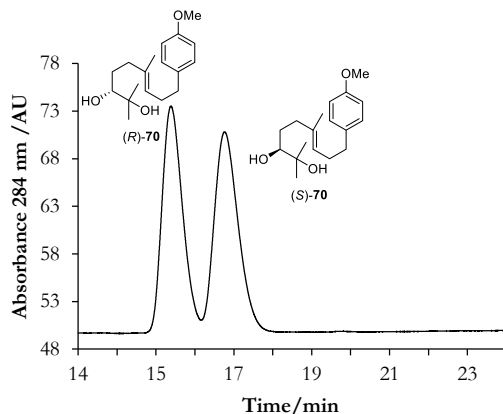


Figure 35 - Chiral HPLC chromatogram showing separation of enantiomers of (±)-70

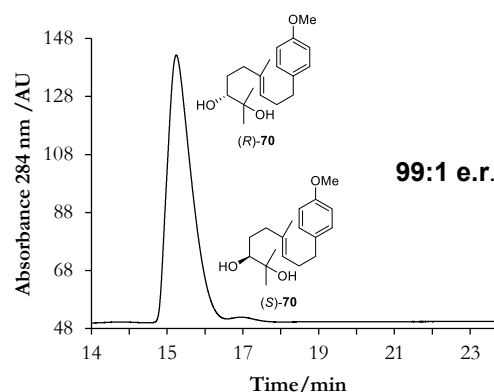
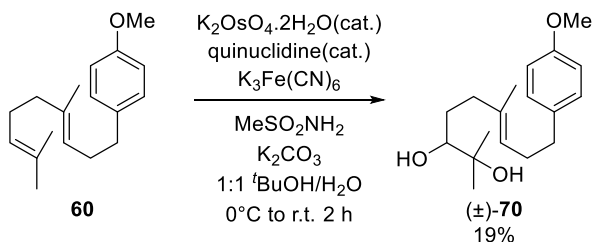


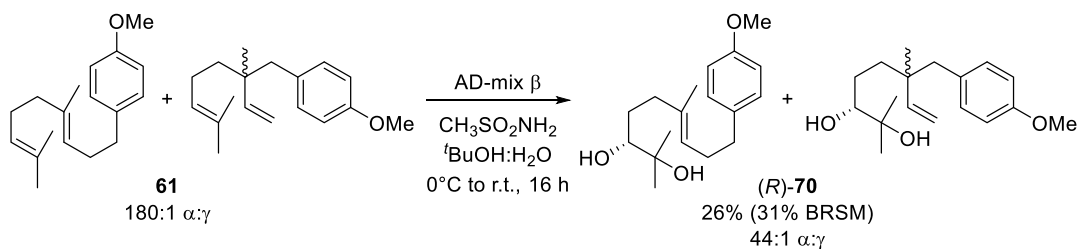
Figure 36 - Chiral HPLC chromatogram showing separation of enantiomers in (R)-70

Racemic diol (R)-70 was synthesised using modified Sharpless asymmetric dihydroxylation conditions, whereby the chiral ligand was substituted by achiral quinuclidine, a method developed by Warren *et al.*¹²⁹ A consequence of using quinuclidine, a less sterically-encumbered ligand than (DHQD)₂PHAL, is that the reaction times are much shorter and so racemic diol (±)-70 was isolated in 19% yield after just two hours (Scheme 95).



Scheme 95 - Racemic dihydroxylation of diene 60

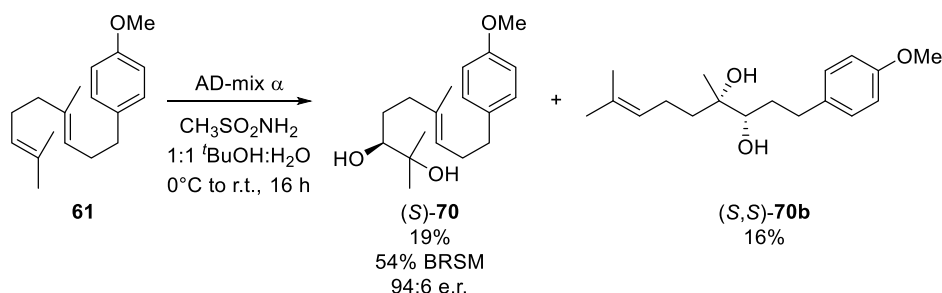
Interestingly, as a direct consequence of the accumulation of the branched isomer in the product diol (R)-70, recovered starting material has a much higher purity, from 60:1, linear to branch chain ratio in diene 61 to over 100:1 in product diol (R)-70 for cases entries 1 and 2, Table 19. It was hoped that combining these two batches of recovered starting material and subjecting them to Sharpless asymmetric dihydroxylation would result in even higher purity diol (R)-70. However this was not the case and diol (R)-70 was isolated in 26% yield (31% based on recovered starting material, Scheme 96) with a linear to branched chain ratio of 44:1.



Scheme 96 - Sharpless asymmetric dihydroxylation of ultra-high purity recovered diene 61

The remaining recovered starting material was dihydroxylated to give a total of 4 g of diol **70**, this represents a 43% overall yield of diol (*R*)-**70** from 8.2 g of diene **61**.

For access to the *S* enantiomer, diene **60** can be treated with AD-mix α to give (*S*)-**70** in 19% yield (Scheme 97) and 94:6 enantiomeric ratio (Figure 37). Under these conditions a 16% yield of central diol regioisomer (*S,S*)-**70b** was also isolated and none of the over dihydroxylation product **70a** was observed. Evidently, (DHQ)₂PHAL is less regioselective for dihydroxylation at the terminus alkene of diene **61**.



Scheme 97 - Asymmetric dihydroxylation of diene **60** to (*S*)-**70** using AD-mix α

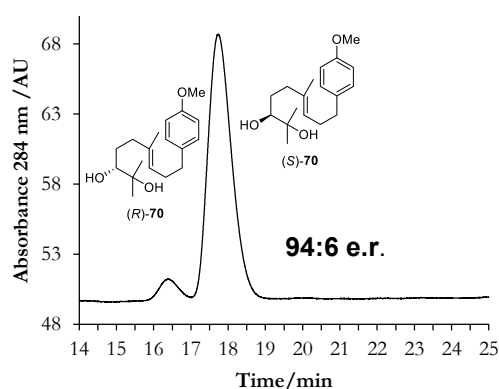
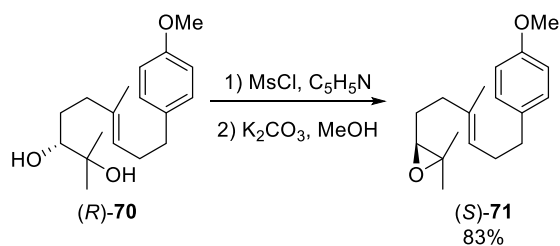


Figure 37 - Chiral HPLC chromatogram showing separation of enantiomers in (*S*)-**70**

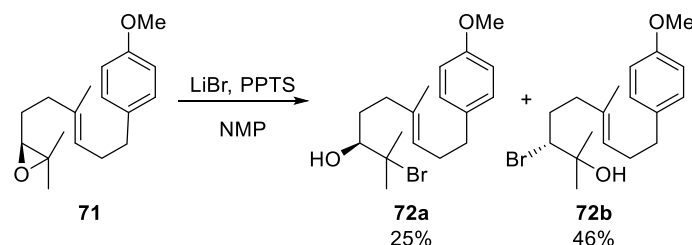
2.4.3 Synthesis of enantiopure bromohydrin derivatives

Diol (*R*)-**70** was converted to epoxide (*S*)-**71** by the Corey *et al.* method¹²⁶ in 83% isolated yield (Scheme 98).



Scheme 98 - Stereospecific formation of epoxide (*S*)-**71**

Stereospecific epoxide ring-opening of (*S*)-**71** by bromide anion provided the separable regioisomeric bromohydrins (*S*)-**72a** and (*R*)-**72b** in 71% overall yield (Scheme 99). The regioisomeric bromohydrins (*S*)-**72a** and (*R*)-**72b** were assigned on the basis of their distinctive chemical shifts at 3.40 and 3.95 ppm in their ¹H NMR spectra respectively, see chapter 2.1.2 page 56.

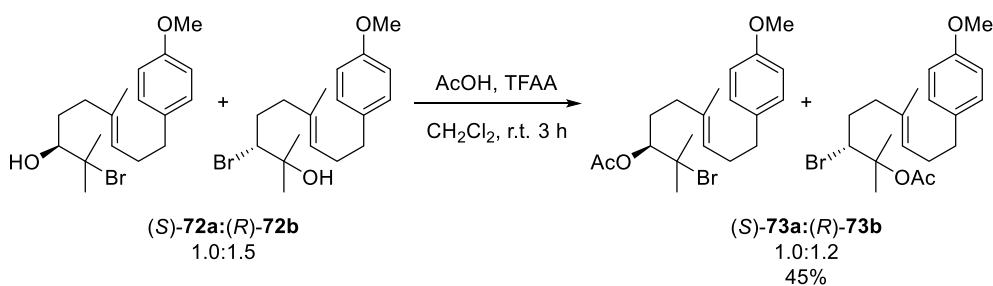


Scheme 99 - Synthesis of enantiopure bromohydrins (*S*)-**72a** and (*R*)-**72b**

In the work on mono-cyclisation reactions (2.3.1, page 77) enantiopure bromonium ions were generated from 2,3,4,5-tetrafluorobenzoate derivatives, followed by activation with catalytic triflic acid. Whilst we could synthesise tetrafluorobenzoate esters of **72a** and **72b**, unfortunately acid-sensitive trisubstituted alkenes present in these substrates would make the use of triflic acid to generate bromonium ions incompatible. In experimental mono-cyclisation reactions with added alkene (Chapter 2.3.5, page 85), tetrafluorobenzoate derivatives did not undergo cyclisation with triflic acid, which instead protonated the added alkene. Acetate derivatives did however show that racemisation was not occurring in the presence of added alkenes.

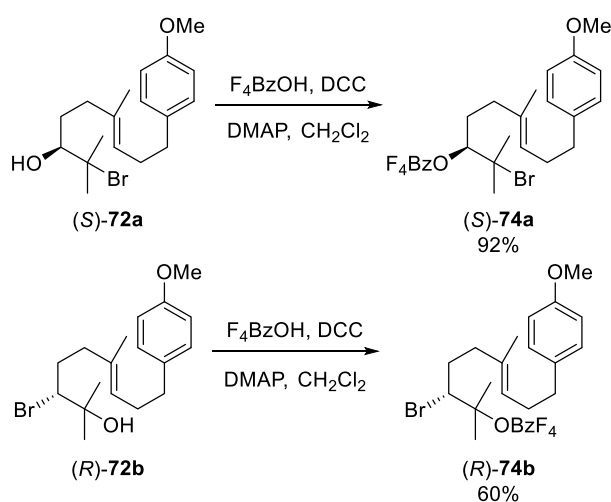
The acetate derivatives, (*S*)-**73a** and (*R*)-**73b** were synthesised for testing alongside tetrafluorobenzoate derivatives, (*S*)-**74a** and (*R*)-**74b**. It was hoped that a suitable Lewis acid would enact the required cyclisation of either acetate or tetrafluorobenzoate derivatives. However tetrafluorobenzoate esters are expected to produce cleaner and enantiospecific cyclisation reactions, based on work previously investigated on mono-cyclisations.

A mixture of acetates (*S*)-**73a** and (*R*)-**73b** were synthesised using the Bourne method^{119a} with acetic acid and trifluoroacetic anhydride in 45% isolated yield (Scheme 100) but it was observed that there was a reduction in the ratio of regioisomers in the acetate products compared to starting material (*S*)-**72a** and (*R*)-**72b**, from 1:1.5 to 1:1.2. This is likely a result of the lower reactivity of the more hindered tertiary alcohol (*R*)-**72b** toward esterification.



Scheme 100 - Acetylation of bromohydrins (*S*)-73a and (*R*)-73b

Tetrafluorobenzoates (*S*)-74a and (*R*)-74b were synthesised using Steglich esterification¹¹⁶ with 2,3,4,5-tetrafluorobenzoic acid in 92% yield and 60% yield (Scheme 101) from alcohols (*S*)-72a and (*R*)-72b respectively.



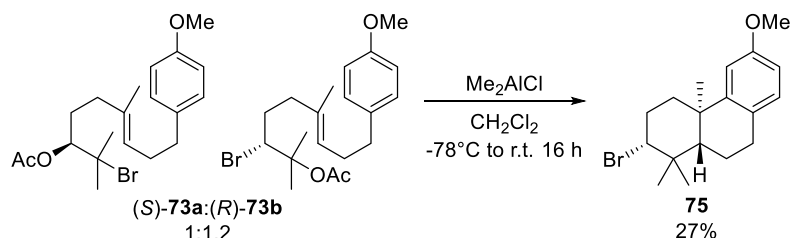
Scheme 101 - Synthesis of enantiopure tetrafluorobenzoate derivatives (*S*)-73a and (*R*)-73b

2.5 Investigation of enantiospecific bi-cyclisation reaction conditions

Attempted bromonium ion-initiated cyclisation of acetates and tetrafluorobenzoates (*S*)-73a, (*R*)-73b, (*S*)-74a or (*R*)-74b with catalytic quantities of triflic acid, led, as predicted (*vide supra*), to extensive decomposition. Previous attempts to generate bromonium ions from bromo-tetrafluorobenzoates **31a** and **31b** by solvolysis were unsuccessful (see chapter 2.2.1 page 63) and so such conditions were not pursued on these bi-cyclisation substrates.

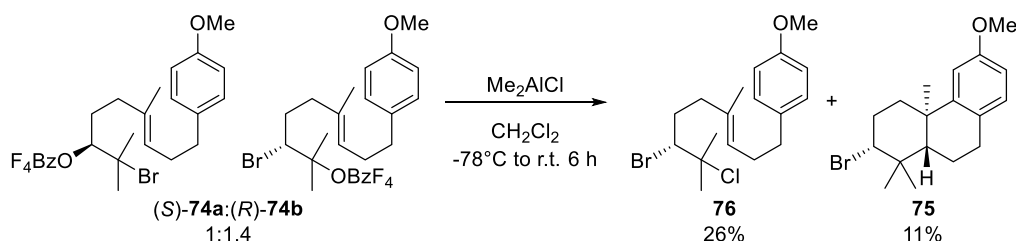
Previously, oxophilic Lewis acids such as titanium(IV) chloride and dimethylaluminium chloride had been successfully used to carry out the mono-cyclisation of bromo-tetrafluorobenzoates (*R*)-**31a** and (*S*)-**31b** in the model system. TiCl_4 however, was rejected as a potential mediator of bi-cyclisation as hydrochloric acid would be generated during the course of the reaction, whereas alkyl aluminium reagents lead to rigorously proton free-solutions¹⁵⁰ and so Me_2AlCl was expected to be more beneficial.

Reaction of a mixture bromo-acetates (*S*)-**73a** and (*R*)-**73b** with dimethylaluminium chloride gave a 27% yield of the desired cyclisation adduct **75** (Scheme 102), however this component of the reaction mixture was not isolated as a pure product and contained other unknown un-cyclised by-products. Furthermore, 27% of the starting material was also recovered.



Scheme 102 - Cyclisation of bromo-acetates (*S*)-**73a** and (*R*)-**73b** using dimethylaluminium chloride

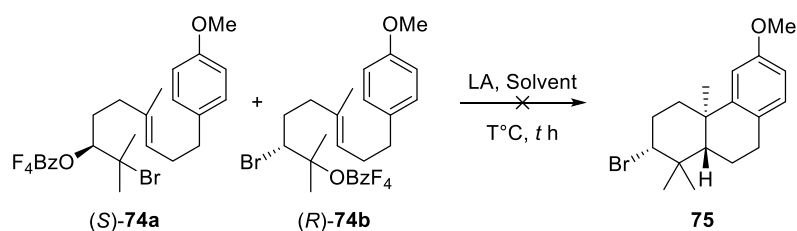
Similarly, cyclisation of a mixture of tetrafluorobenzoate esters (*S*)-**74a** and (*R*)-**74b** using dimethylaluminium chloride gave 11% yield of cyclisation adduct **75** after extensive chromatography. Non-cyclised bromochloride **76** was observed as the major product in 26% yield, evidently competing intermolecular attack of anionic chloride on bromonium ion was occurring.



Scheme 103 - Cyclisation of tetrafluorobenzoates (*S*)-**74a** and (*R*)-**74b** by dimethylaluminium chloride

Initial studies with stoichiometric quantities of $\text{Yb}(\text{OTf})_3$ were ineffective at triggering cyclisation of a mixture of (*S*)-**74a** and (*R*)-**74b** at reflux overnight in dichloromethane and even the addition of a second equivalent of $\text{Yb}(\text{OTf})_3$ and heating at 131°C in chlorobenzene for a second night failed to produce the desired cyclisation products and 15% of the starting material was recovered (entry 1, Table 20). The use of $\text{Eu}(\text{fod})_3$ in chlorobenzene at 60°C overnight with the addition of a second equivalent, and heating at 131°C was also ineffective at initiating the cyclisation with starting material being recovered in 10% yield (entry 2). Heating a solution of both regioisomeric tetrafluorobenzoates at 150°C for 1 h under microwave irradiation was also ineffective, starting material was recovered in 22% yield (entry 3).

Table 20 - The use of Lewis acids, ytterbium triflate and Eu(fod)₃ for the cyclisation of tetrafluorobenzoates (*S*)-**74a** and (*R*)-**74b**



Entry	LA	LA (eq.)	Solvent	T (°C)	t (h)	Recovered	
						(<i>S</i>)- 74a	(<i>R</i>)- 74b (%)
1	Yb(OTf) ₃	1 + 1	CH ₂ Cl ₂	40	16		
			PhCl	131	16		15
2	Eu(fod) ₃	1 + 1	PhCl	60	16		
				131	16		10
3	Eu(fod) ₃	1	PhCl	150 (MW)	1		22

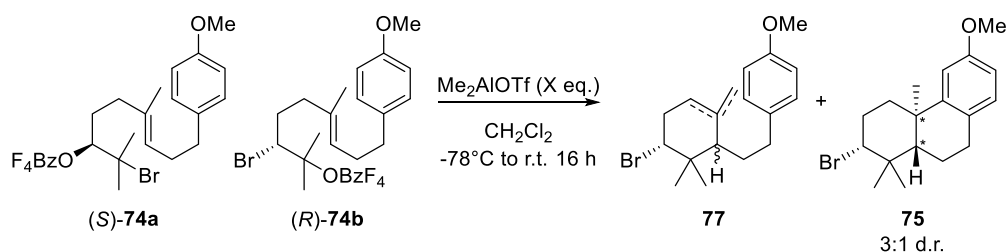
The use of stoichiometric quantities of trimethylaluminium were not effective in mediating the desired cyclisation, instead, decomposition of both of the substrates (*S*)-**74a** and (*R*)-**74b** was observed.

So far, the Lewis acid which has shown the most promise is dimethylaluminium chloride. To reduce competing reaction pathways, the chloride in the Lewis acid was replaced with a non-nucleophilic counterion. Tetrafluorobenzoate esters have acted as good leaving groups in mono-cyclisation reactions with high yields, where no tetrafluorobenzoate containing by-products were observed. Therefore, dimethylaluminium tetrafluorobenzoate was prepared by adding a solution of one equivalent of 2,3,4,5-tetrafluorobenzoic acid in dichloromethane at -78°C to a solution of trimethylaluminium, evolution of methane gas was observed, signifying the formation of the reagent, which was used at -78°C for attempted cyclisation of a mixture of tetrafluorobenzoate substrates (*S*)-**74a** or (*R*)-**74b**. However, no reaction was observed overnight at room temperature and addition of two further equivalents of reagent and heating at reflux overnight, returned 82% recovered starting material.

Formation of tris(tetrafluorobenzoate)aluminium using three equivalents of tetrafluorobenzoic acid to one trimethylaluminium and heating at reflux with a mixture of tetrafluorobenzoate substrates (*S*)-**74a** and (*R*)-**74b** for 2 h again gave 83% recovered starting material. It is apparent that alkylaluminium tetrafluorobenzoate Lewis acids are not reactive enough for cyclisation of bromo-tetrafluorobenzoate substrates, or trimethylaluminium may not be coordinating to the ester but instead methylating the ester to form 1-(2,3,4,5-tetrafluorophenyl)ethanone.

The use of stoichiometric dimethylaluminium triflate – first reported in the 1980s¹⁵¹ and infrequently used¹⁵² – on each of bromide (*S*)-**74a** and (*R*)-**74b** provided clean conversion to cyclised adducts. The desired cyclised product **75** was isolated in 9% and 26% yield respectively (Table 21, entries 1 and 2), in both cases **75** was formed as a 3:1 mixture of diastereoisomers.

Table 21 - Dimethylaluminium triflate activated cyclisation of bromo-tetrafluorobenzoates (*S*)-**74a** and (*R*)-**74b**



Entry	Substrate	X (eq.)	Recovered (<i>S</i>)- 74a (<i>R</i>)- 74b (%)	Yield 77 (%)	Yield 75 (%)
1	(<i>S</i>)- 74a	1.2	44	0	9
2	(<i>R</i>)- 74b	1.2	9	35	26
3	(<i>S</i>)- 74a	2.5	42	23	13
4	(<i>R</i>)- 74b	2.5	0	24	34
5	(<i>S</i>)- 74a	5	0	19	25
6	(<i>R</i>)- 74b	5	0	55	11
5	(<i>S</i>)- 74a	7.5	0	17	19

In the cyclisation of (*R*)-**74b** (entry 2) a mixture of inseparable endo- and exocyclic alkenes **77** were also isolated in 35% yield and identified by inspection of the alkene region of their ¹H NMR spectrum (Figure 38). Two monocycles with endocyclic trisubstituted alkenes [δ_{H} 5.27 (br. s, 1H) and 5.20 (br. s, 1H)] were evident. As well as two monocycles with exocyclic methylene groups [δ_{H} 5.03 (s, 1H), 4.79 (s, 1H) and 4.91 (s, 1H), 4.72 (s, 1H)]. Both endo- and exocyclic alkene monocycles had a diastereomeric ratio of 3:1 and their endo:exocyclic ratio was 1.5:1.

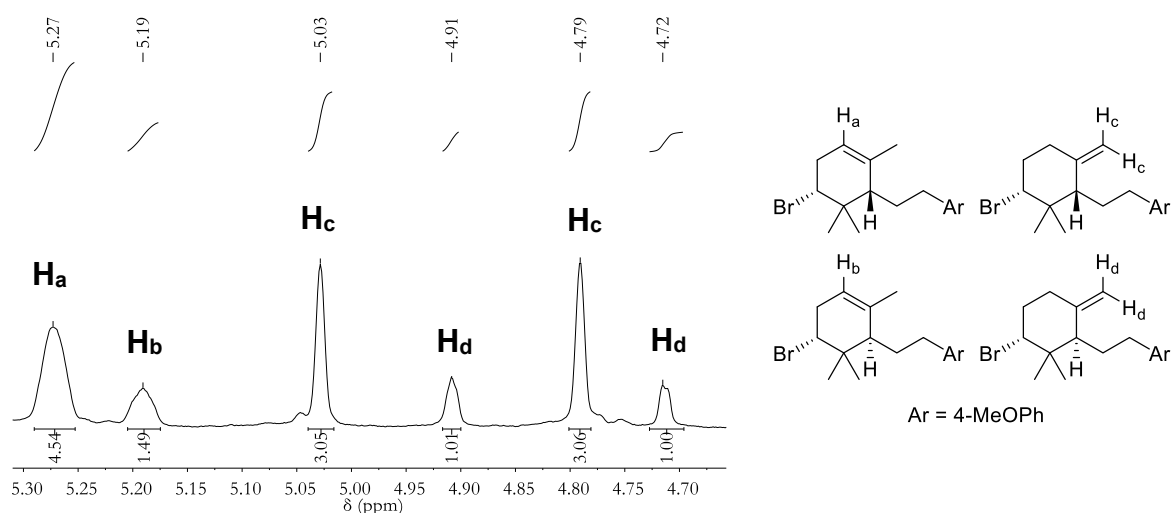


Figure 38 - ^1H NMR Spectrum of **77**, a mixture of endo- and exocyclic diastereomers

Monocyclisation adducts of this type have been ring-closed with chlorosulfonic acid in 2-nitropropane by Ishihara *et al.*,^{32, 81, 153} however, in our hands no reaction was observed under these conditions with mono-cycles **77** after 4 h at room temperature and after 24 h at room temperature polymerisation of the mixture had occurred. Carrying out the acid catalysed second ring-closure on crude cyclisation material also led to polymerisation at -78°C for 4 h.

The use of 2.5 equivalents of dimethylaluminium triflate improved the yield of **75** from both substrates, (*S*)-**74a** and (*R*)-**74b** to 13% and 34% respectively (entries 3 and 4). In the case of entry 4, clean and complete conversion of (*R*)-**74b** was observed with mono-cyclised adducts representing 24% yield.

Increasing the number of equivalents of dimethylaluminium triflate to 5 improved the yield of bromide **75** from secondary tetrafluorobenzoate (*S*)-**74a** to 25% (entry 5), however this was not the case for cyclisation of tertiary tetrafluorobenzoate (*R*)-**74b** whose yield of **75** dropped to 11% (entry 6). Increasing the number of equivalents further to 7.5 did not improve the yield of **75** from (*S*)-**74a** (entry 7).

The highest yield of cyclisation for (*S*)-**74a** of 25% was obtained using 5 equivalents of dimethylaluminium triflate, whereas for (*R*)-**74b** only 2.5 equivalents was needed to obtain a 34% yield, evidently the secondary tetrafluorobenzoate is less readily activated than the tertiary tetrafluorobenzoate. In both these reactions inspection of the ^1H NMR spectrum of the crude reaction mixtures showed clean conversion of all starting material to mono- and bicyclisation products. The relatively low isolated yields were a result of the difficult purification of these non-polar compounds by column chromatography.

It is unclear in cyclisation reactions initiated by Me_2AlOTf which alkyl aluminium species is the *defacto* initiator of the reaction. We know that trimethylaluminium is an inactive species and $\text{Al}(\text{OTf})_3$ will not provide proton-free solutions however methylaluminium ditriflate may also be present in the reaction mixture. To investigate if $\text{MeAl}(\text{OTf})_2$ was the active species secondary tetrafluorobenzoate (*S*)-**74a** was reacted with 2.4 equivalents of $\text{MeAl}(\text{OTf})_2$, as prepared from trimethylaluminium and 2 equivalents of triflic acid, at room temperature overnight. Unfortunately decomposition of substrates was observed.

Other alkylaluminium Lewis acids and conditions were tested using secondary tetrafluorobenzoate (*S*)-**74a**, these include:

- 2.5 equivalents of $\text{Me}_2\text{Al}(\text{OTf})$ in polar solvents such as $t\text{BuNO}_2$ led to decomposition;
- carrying out the cyclisation using $\text{Me}_2\text{Al}(\text{OTf})$ at elevated temperatures in 1,2-dichloroethane led to oxidation of the *para*-methoxyphenyl ring in the substrate and also to alkylation with 1,2-dichloroethane;
- the use of 2.9 equivalents of $\text{Me}_2\text{Al}(\text{NTf}_2)$, as prepared from trimethylaluminium and 1 equivalent of bis(trifluoromethane)sulfonimide, in dichloromethane at reflux for 6 h, gave trace quantities of **75**.

The desired product of the cyclisation **75** was isolated as a mixture of two diastereoisomers which were not separable by column chromatography, but could be separated by preparative HPLC. This enabled the enantiomeric purity of each to be determined, without interference from the other, as 98:2.

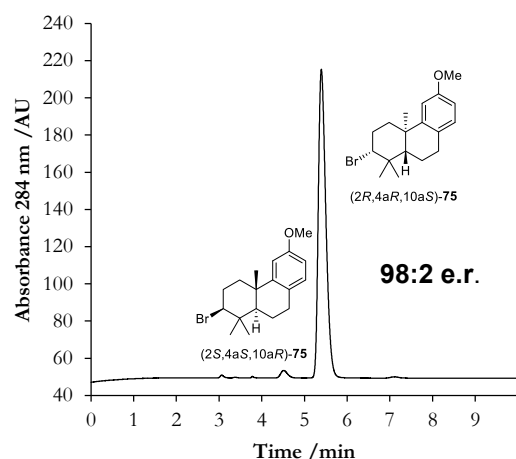


Figure 39 - Chiral HPLC chromatogram showing separation of enantiomers of the desired diastereomer (2R,4aR,10aS)-**75**

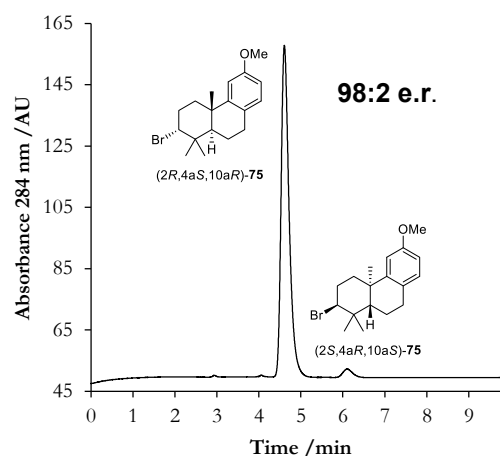
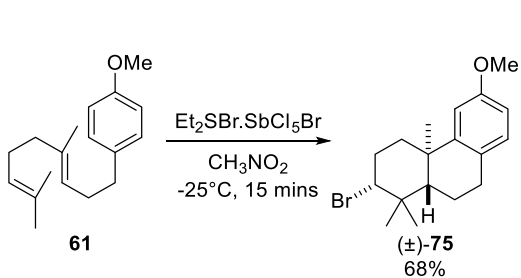


Figure 40 - Chiral HPLC chromatogram showing separation of enantiomers of undesired diastereomer (2R,4aS,10aR)-**75**

The chiral HPLC chromatogram of the desired diastereomer was compared to a racemic sample. This was prepared by the direct action of BDSB on diene **61** as described by Synder⁴⁸ to provide racemic tricyclic bromide ($\pm$)-**75** (Scheme 104) in 68% yield as a single diastereoisomer, which in our hands proved to be crystalline. An X-ray crystal structure (Figure 41) of tricyclic bromide ($2R^*,4aR^*,10aS^*$)-**75** confirms the formation of a *trans*-fused decalin ring system and the equatorial positioning of the bromine atom.



Scheme 104 - BDSB mediated cyclisation of polyene **61** into racemic tricyclic bromide ($\pm$)-**75**.

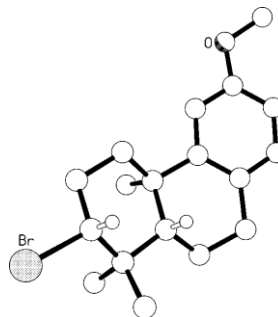
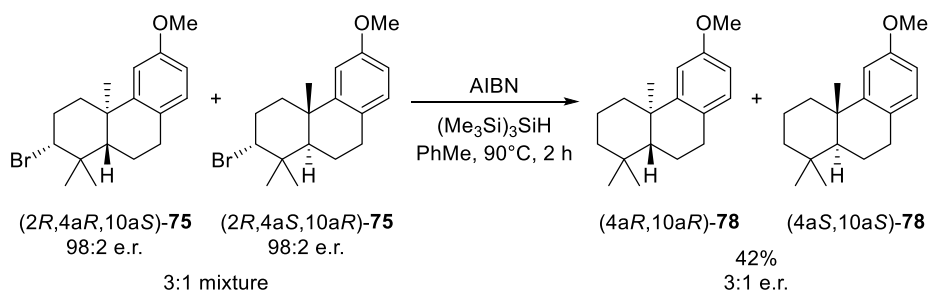


Figure 41 - The crystal structure of ($\pm$)-**75**

With the relative configuration of ($2R,4aR,10aS$)-**75** being established by X-ray crystallography (Figure 41), the assignment of absolute configuration follows from an *R*-configured bromonium ion. The relative configuration of the minor diastereoisomer can be established by dehalogenation of a 3:1 mixture of diastereomers **75**. This was carried out by radical dehalogenation using trimethylsilyl silane in essentially quantitative conversion (43% isolated yield, Scheme 105). A *single* diastereomeric *trans*-decalin-**78** was obtained with a 3:1 enantiomeric ratio. This allows assignment of the absolute configurations as ($4aR,10aR$)-**78** and ($4aS,10aS$)-**78** from ($2R,4aR,10aS$)-**75** and ($2R,4aS,10aR$)-**75** respectively. The absolute configurations were confirmed by comparison of the sign of optical rotation for the 3:1 enantiomeric mixture of ($4aR,10aR$)-**78** and ($4aS,10aS$)-**78** with the rotation already reported for (+)-($4aS,10aS$)-**78**.¹⁵⁴



Scheme 105 - Correlation of absolute and relative configurations by reduction of a 3:1 diastereomeric bromide mixture **75** to *trans*-decalin **78**.

Evidently, the bromonium ion-initiated cyclisations described (Table 21) are proceeding *via* enantiomerically pure bromonium ions without erosion of enantiopurity by intramolecular or

intermolecular bromonium ion-to-alkene transfer.^{87a} A chair-like conformation **C** (Figure 42) can be invoked in the cyclisation leading to (2*R*,4*aR*,10*aS*)-**75**, and a boat-like conformation **B** in the cyclisation leading to (2*R*,4*aS*,10*aR*)-**75**. Both have the same *R*-configured absolute configuration of the bromonium ion.

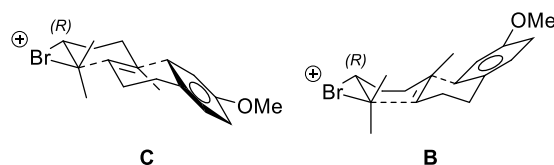
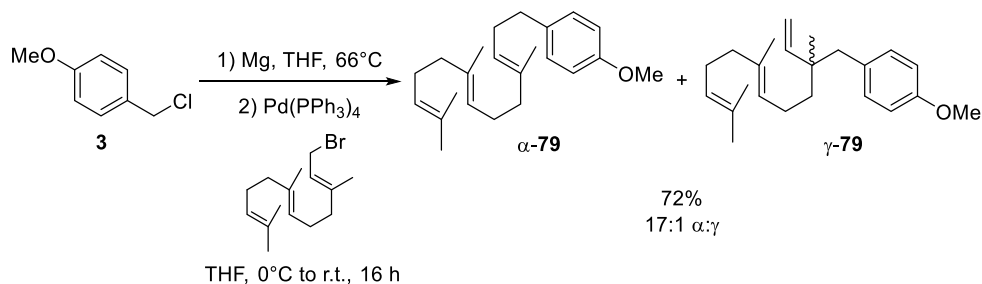


Figure 42 - Chair-like **C** and boat-like **B** geometries in the cyclisations leading to (2*R*,4*aR*,10*aS*)-**75** and (2*R*,4*aS*,10*aR*)-**75** respectively.

The enantiospecific cyclisation of tertiary bromide (*S*)-**74a** has to occur by the formation of an *R*-configured enantiomerically pure bromonium ion, due to the change in position of Br-C bond. Cyclisation of secondary bromide (*R*)-**74b** may instead be occurring directly *via* a tertiary carbocation. As the product distributions for each substrate are identical by analysis of the ¹H NMR spectrum of the crude reaction mixture, a single common intermediate such as a bromonium ion must be implicated.

2.6 Towards an enantiospecific tri-cyclisation

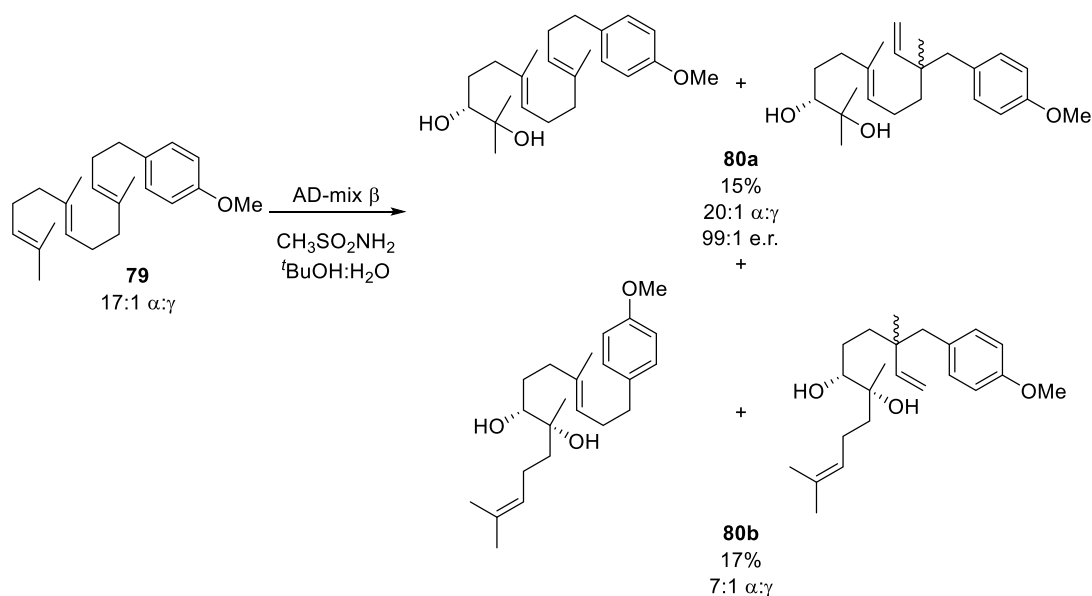
Having successfully carried out the first bromonium ion-induced polyene cyclisation of a diene substrate, the natural progression was to carry out the bromonium ion-induced cyclisation of a triene substrate. To this end, triene **79** was synthesised *via* palladium(0)-catalysed alkylation of farnesyl bromide using conditions reported by Demuth and co-workers¹⁰³ in 72% yield with the desired α -alkylated product isolated with inseparable branched regioisomer γ -**79** in a ratio of 17:1. Unfortunately, the boiling point of **79** was expected to be too high for vacuum distillation using standard stirrer hotplate temperatures ($\leq 300^\circ\text{C}$).



Scheme 106 - Synthesis of homo-farnesyl *p*-methoxybenzene **79**

Triene **79**, as a 17:1 mixture of constitutional isomers was dihydroxylated using Sharpless' AD-mix β ¹²⁷ (Scheme 107) on a 7.6 g scale as the reaction was likely to be low yielding due to

regioselectivity problems, as discussed previously (Chapter 2.4.2, page 93). The desired regioisomeric diol **80a** was isolated in 15% yield with branched diol γ -**80a** in a ratio of 20:1 with regioisomeric diol **80b** in 17% yield. Evidently, the central alkene is just as accessible to dihydroxylation as the terminus alkene. Starting material was recovered in 31% yield (2.4 g) with an α : γ ratio of 23:1. The absolute configuration of diol (*R*)-**80a** and **80b** were assigned on the basis of the Sharpless mnemonic.¹²⁷⁻¹²⁸



Scheme 107 - Sharpless asymmetric dihydroxylation of homo-farnesyl *p*-methoxybenzene **79**

The enantiomeric ratio of **80a** was determined to be 99:1 by chiral HPLC separation of enantiomers (Figure 43) in comparison to a racemic sample (Figure 44). Visible in these chromatograms are a minor impurity, branched chain diol γ -**80a**.

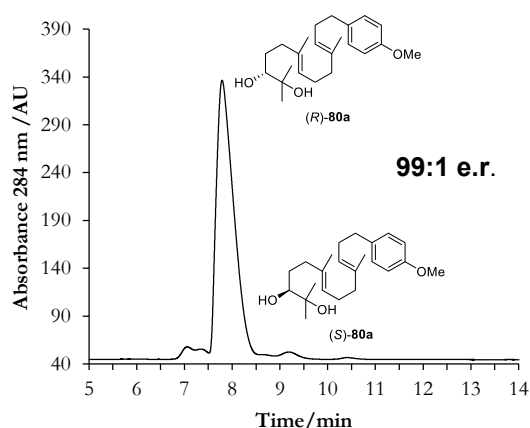


Figure 43 - Chiral HPLC chromatogram showing separation of enantiomers of (*R*)-**80a**

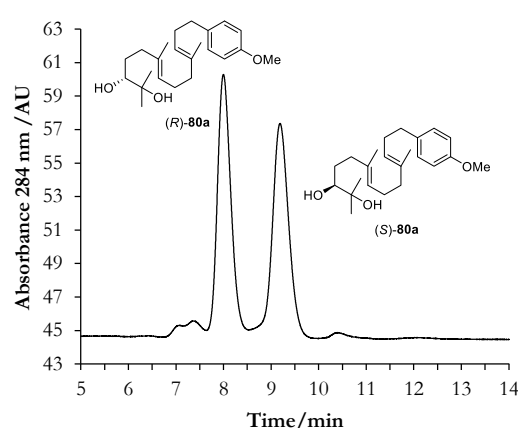
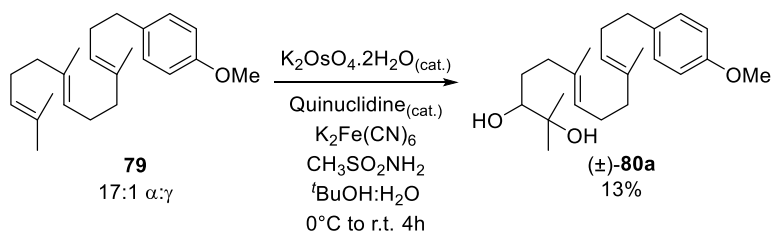


Figure 44 - Chiral HPLC chromatogram showing separation of enantiomers of ($\pm$)-**80a**

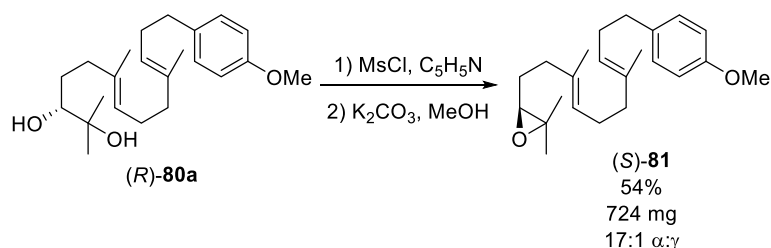
Racemic diol ($\pm$)-**80a** was synthesised using modified Sharpless asymmetric dihydroxylation conditions, whereby the chiral ligand was substituted by achiral quinuclidine, a method developed

by Warren *et al.*¹²⁹ As a consequence of using quinuclidine, a less sterically encumbered ligand than (DHQD)₂PHAL, the reaction time is much shorter, racemic diol ($\pm$)-**80a** was isolated in 13% yield after four hours (Scheme 108).



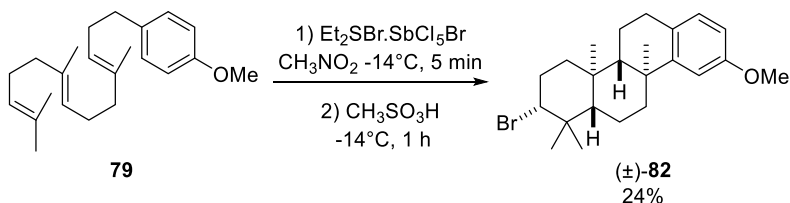
Scheme 108 - Racemic dihydroxylation of homo-farnesyl *p*-methoxybenzene **79**

Diol (*R*)-**80a** was ring-closed to epoxide (*S*)-**81** *via* mesylation and reaction with potassium carbonate in 54% yield (Scheme 109). Progress on tri-cyclisation substrate (*S*)-**81** was halted at the more stable epoxide, as bromohydrins in our hands were found to undergo photolytic dehalogenation over time.



Scheme 109 - Synthesis of epoxide (*S*)-**81**

Racemic bromonium ion-induced polyene cyclisation of **79** was carried out using Snyder's BDSB reagent⁴⁸ with a second acid catalysed ring closure step using methane sulfonic acid in 24% overall yield.



Scheme 110 - BDSB initiated tri-cyclisation of polyene **79**

This provided a racemic sample for chiral HPLC analysis of the enantiomers. This can be used to determine future enantiospecific cyclisation reactions.

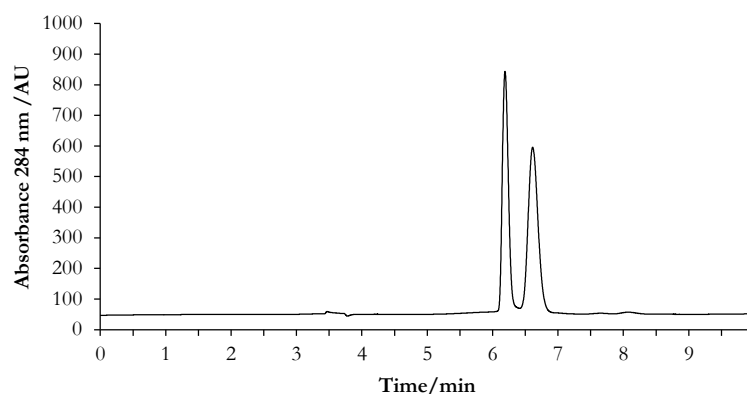


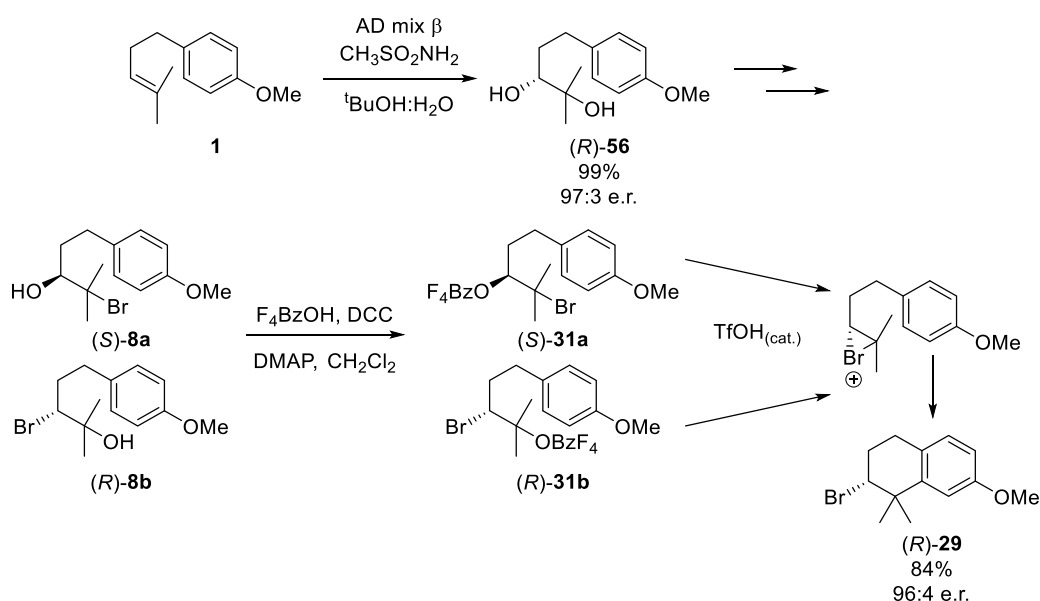
Figure 45 - Chiral HPLC chromatogram showing separation of enantiomers in (±)-**82**

When carrying out a bi-cyclisation reaction using Me_2AlOTf on tetrafluorobenzoate derivatives such as **74a** or **74b**, mono-cyclisation products accounted for 17-55% yield. When considering a tri-cyclisation reaction using these conditions, mono- and bi-cyclisation products are expected to account for the majority of the reaction products where the desired tricycle **82** may only be isolated in trace amounts. Development of our cyclisation conditions will have to be carried out to promote multiple C-C bond forming events.

3 Conclusion

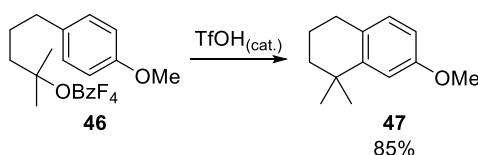
The overall aim of this project was to achieve the first polyene cyclisation triggered by an enantiomerically pure bromonium ion. The chemistry developed in this investigation was expected to demonstrate that enantiomerically pure bromonium ions can be generated in a controlled fashion and be employed in synthesis. The methodology could then be applied to the biomimetic synthesis of naturally occurring sesqui-^{45a} and diterpene^{45d,45g} metabolites which possess the α,α -dimethylcyclohexyl bromide moiety.

Initial studies on a model system bearing a single olefin **1** (Scheme 111), showed that enantiopure bromohydrins (**8a** and **8b**) can be efficiently synthesised utilising Sharpless asymmetric dihydroxylation methodology. Activation as tetrafluorobenzoate esters (**31a** and **31b**) was shown, in comparison to acetate derivatives, to provide substrates which undergo clean, enantiospecific and regioselective cyclisation under the action of catalytic triflic acid. Bromobicycle **29** was therefore synthesised in excellent yield and high enantiomeric excess.



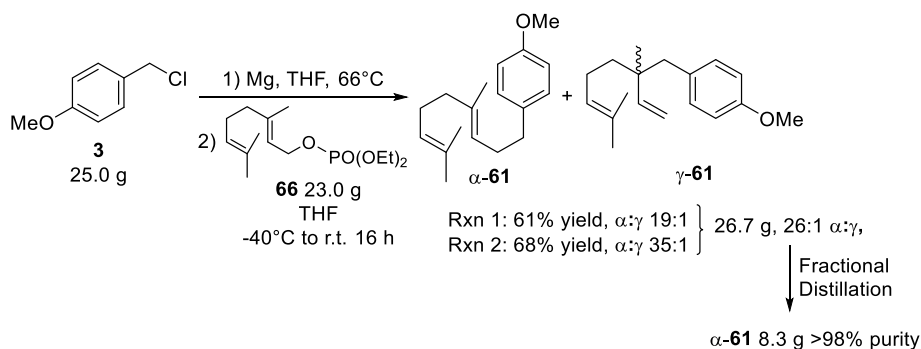
Scheme 111 - Triggering a cation- π cyclisation with an enantiopure bromonium ion

The isolation of each bromohydrin regioisomer separately allowed us to demonstrate that in the cyclisation of **31a** an enantiomerically pure bromonium ion must be invoked. Although the cyclisation of **31b** may instead proceed *via* a tertiary carbocation, as was indeed the case for des-bromo substrate **46** (Scheme 112), the near identical product distributions for each substrate suggests a single common intermediate such as a bromonium ion.



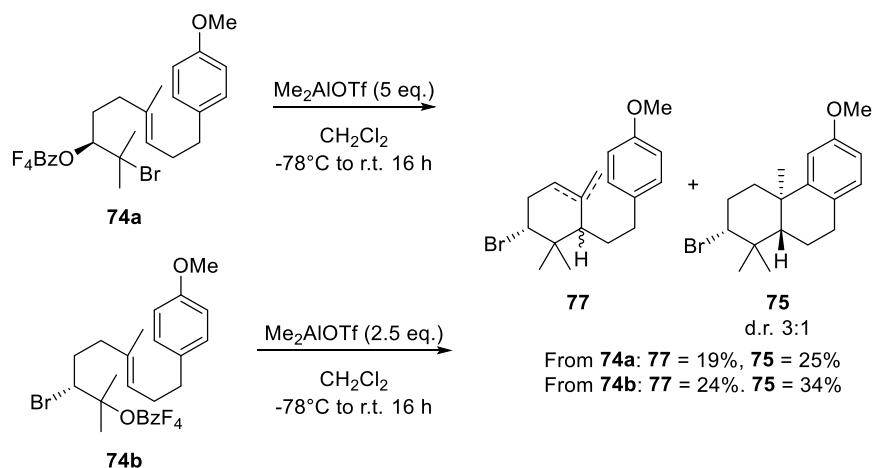
Scheme 112 - Cyclisation of des-bromo tetrafluorobenzoate **46** *via* tertiary carbocation

In preliminary studies using diene **61** it became apparent that high purity α -**61**, free from branched diene γ -**61**, was essential for subsequent dihydroxylation reactions and accurate HPLC enantiomeric excess determination. The branched isomer was inseparable at all stages of the synthesis by standard chromatography techniques and was found to obscure enantiomer signals in chiral HPLC analysis after cyclisation. Extensive investigation into the selective synthesis of α -**61** was carried out and reaction conditions were optimised. Large scale synthesis and fractional vacuum distillation was found to remove the branched diene γ -**61** which provided a small number of grams of >98% purity α -**61** for investigation.



Scheme 113 - Synthesis of high purity diene α -**61**

Sharpless asymmetric dihydroxylation of diene **61** was optimised using AD-mix β and standard conditions. Diol **70** was synthesised in reproducible yields in the range of 25-40% and with excellent enantioselectivity 99:1 e.r. Synthesis of bromo-tetrafluorobenzoate derivatives **74a** and **74b** (Scheme 114) *via* the same methodology developed on the model system provided activated alcohols for investigation of cyclisation conditions. Although triflic acid was shown to be unsuitable for these olefinic substrates, Lewis acid: dimethylaluminium triflate was found to successfully enact the cyclisation.



Scheme 114 - Enantiospecific bromonium ion-induced cyclisation of **74a** and **74b** by the action of Me_2AlOTf

Although clean and complete conversion of **74a** and **74b** to cyclised adducts was achieved with Me_2AlOTf , unfortunately, full conversion to the desired tricycle **75** was not. Mono-cyclisation adducts **77** accounted for 19% and 24% of the product mixtures. Closing of the final ring *via* acid catalysed cyclisation was attempted unsuccessfully using known literature conditions. Bromo tricycle **75**, was isolated as a 3:1 mixture of diastereomers, evidently in this case a boat transition state has a similar energy to that of the more favourable chair transition state.

After preparative HPLC separation of both diastereomers of **75** were shown to be of high enantiopurity: 98:2 e.r. Therefore we have demonstrated that enantiopure bromonium ions can be generated in the presence of alkene without racemisation *via* bromonium ion-to-olefin transfer and used in the synthesis of polyene cyclisation products.

In the beginning we set out to overcome challenges in each of the fundamental steps of initiation, propagation and termination. Using this methodology an enantiopure bromonium ion can be formed regioselectively by taking advantage of Sharpless asymmetric dihydroxylation which is selective for the terminus alkene of the polyene. In propagation intramolecular C-C bonds were formed to give tricycle **75** in high enantiopurity, but with low diastereoselectivity. Unfortunately challenges in termination of this cyclisation *via* one mechanism, to give the desired tricyclic product diastereoselectivity, still need to be addressed.

4 Future Work

In the development of the first polyene cyclisation triggered by an enantiopure bromonium ion a number of hurdles were overcome and novel methodology developed. However there still remains challenges and new avenues to explore.

4.1 Optimisation of bi-cyclisation reaction

In order to improve the overall yield of polycyclic product **75** in the cyclisation of geranyl based substrates such as **74a**, alternative Lewis acid-leaving group combinations could be explored. Although 2,3,4,5-tetrafluorobenzoate derivatives were championed in this work, higher yields may be achieved with other benzoate derivatives such as pentafluorobenzoate, 4-nitrobenzoate, 3,5-dinitrobenzoate or 4-trifluoromethylbenzoate.

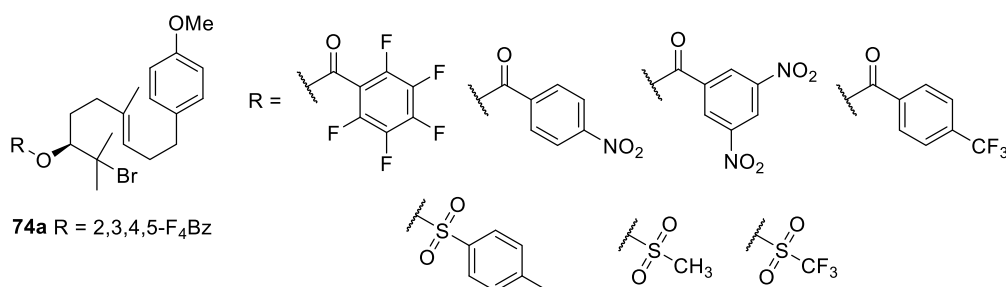
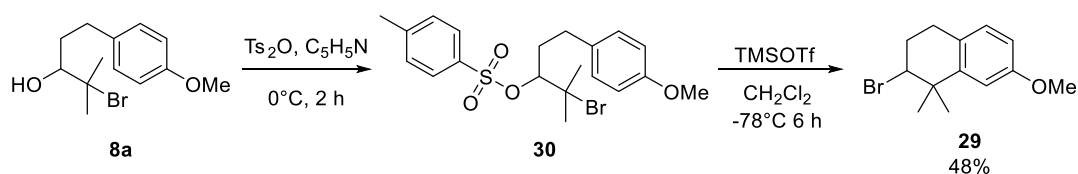


Figure 46 - Suggested leaving groups for development of bromonium ion-induced polyene cyclisation

These suggested leaving groups can be tested with Lewis acids already investigated in this project such as Yb(OTf)₃, Eu(fod)₂ and Me₂AlOTf, or unexplored Lewis acids such as Sc(OTf)₃. Sulfonate esters could also act as good leaving groups. Bromo-tosylate **30** was investigated as a cyclisation substrate in model systems and cyclised successfully using TMSOTf (Scheme 115). Although it is likely that adventitious triflic acid was the active catalyst, bromo-tosylates show potential as cyclisation substrates. Other sulfonate esters could be synthesised and investigated such as methanesulfonate and trifluoromethanesulfonate.

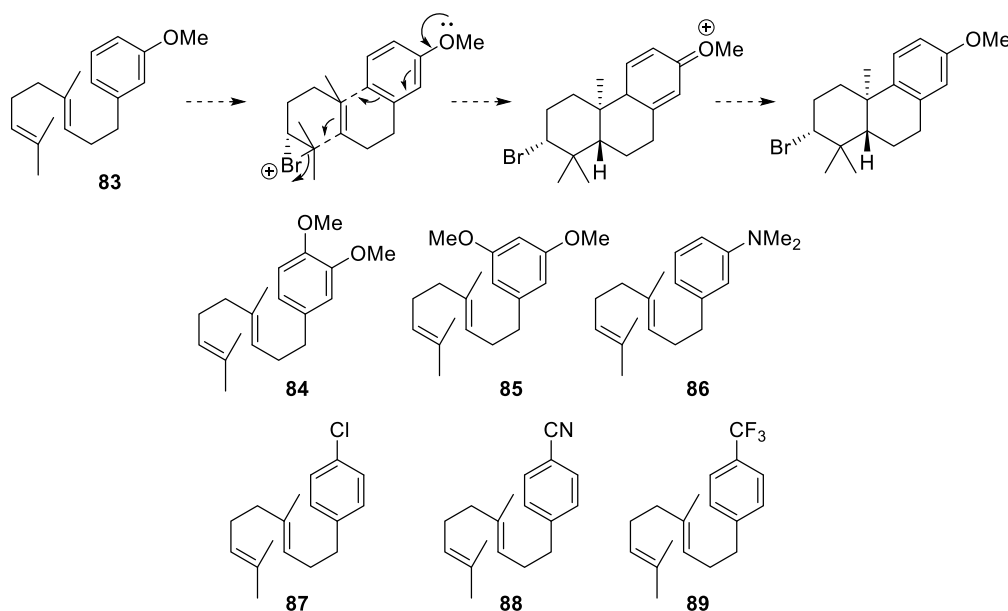


Scheme 115 - Activation of bromohydrins as tosylate esters

4.2 Expansion of substrate scope

Other factors which may improve cyclisation yields include the nucleophilicity of the intramolecular aromatic which terminates the cyclisation. 4-Methoxybenzene has been used

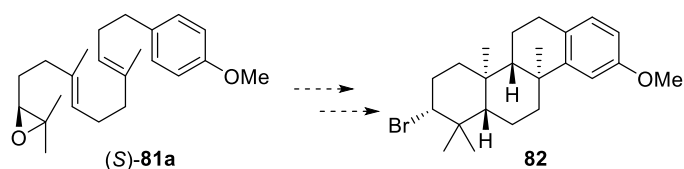
throughout this study however the substrate scope could be broadened to different substitution patterns. 2-Methoxy substitution **83**, for example would be better positioned for stabilisation of the cationic intermediate (Scheme 116). Dimethoxy substitution would increase the nucleophilicity further, such as in substrates **84** and **85**. Dimethyl aniline **86** would take this hypothesis even further.



Scheme 116 - Broadening of substrate scope to different aromatics

To find the boundaries in scope of this methodology, less nucleophilic aromatics could be investigated such as 4-chloro substitution **87**. It should be noted that aromatic substitution should still provide enough polarity for separation of enantiomers of cyclisation products by chiral HPLC analysis. Other electron withdrawing groups to be tested could include cyano- and trifluoromethyl **88** and **89**.

As discussed previously, future work will involve the progression of farnesyl substrate (*S*)-**81a** to bromohydrins using methodology developed in this thesis (Scheme 117). Activation of the bromohydrins as tetrafluorobenzoate esters and triggering with Me_2AlOTf will likely produce only mono- and bicyclic products. Cyclisation of three rings will require a second acid catalysed cyclisation step which as of yet hasn't been proven in this work.

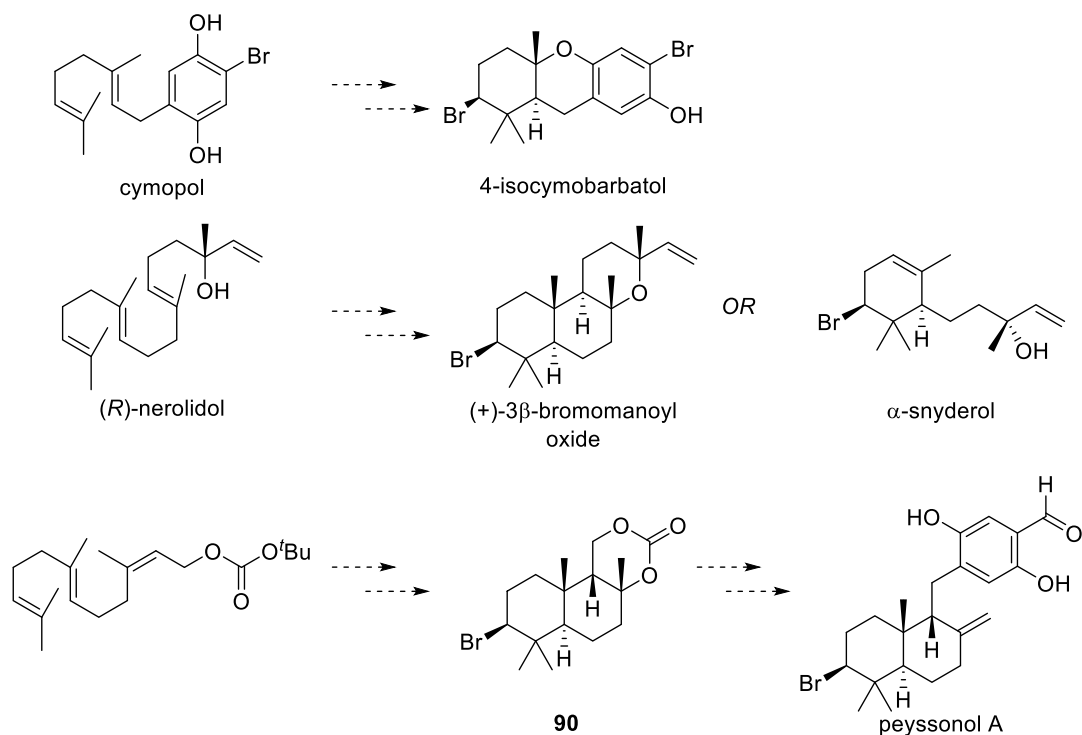


Scheme 117 - Development of farnesyl substrate **81a**

It may also be of interest to understand the product distribution of cation- π cyclisations carried out on olefins that aren't trisubstituted. A disubstituted terminus alkene will produce two stereocentres which will be under stereospecific control of the enantiopure bromonium ion. It will be of interest to know if this affects the diastereoselectivity.

4.3 Synthesis of natural products

Far more interesting may be to investigate the bromonium ion-induced cyclisation of substrates with different functional groups terminating the reaction. Phenols such as cymopol (Scheme 118) would undergo cyclisation to the natural product 4-isocymobarbatol.^{68d} Nerolidol could cyclise to give bromomanoyl oxide or α -snyderol. The synthesis of these natural products would pose new challenges. Activation of the intermediary bromohydrin may result in esterification of the cyclisation terminating alcohols. In such a case the terminating alcohols may need protecting before this step. Trimethylsilyl ether functionality may prove beneficial as deprotection is likely to occur under cyclisation conditions.



Scheme 118 - Bromonium ion-induced polyene cyclisation in the biomimetic synthesis of natural products

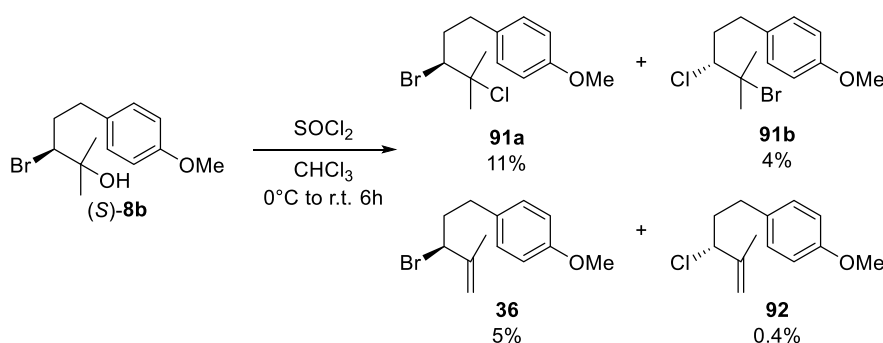
The use of a boc protected alcohol in the synthesis of peyssonol A (Scheme 118) will act as a trigger for the bromonium ion-induced cyclisation. This will favour termination of the cyclisation *via* one mechanism and give tricycle **90** as the major product. This product can be hydrolysed and the diol further functionalised to peyssonol A.

It may be the case that any combination of substrate, Lewis acid-leaving group combination may produce improved yields and diastereoselectivity.

4.4 The synthesis of enantiopure bromo-chlorides

With a simple modification of the protocol an enantiopure fluorohydrin,¹⁵⁵ chlorohydrin or iodohydrins could be synthesised. It would be interesting to investigate the activation of such substrates as tetrafluorobenzoate esters and to cyclise with Me₂AlOTf to form halocyclic analogues of **29** and **75**.

The reaction of enantiopure bromohydrin **8b** with thionyl chloride to give enantiopure bromochloride **91a** has been carried out in 11% yield (Scheme 119). Unfortunately this was isolated with inseparable regioisomeric bromochloride **91b** and elimination by-products **36** and **92**. Optimisation of this reaction could give rise to methodology for the asymmetric synthesis of bromo-chlorides such as **91a**, a common motif found in a wide variety of halogenated natural products.^{104, 156}



Scheme 119 - Synthesis of enantiopure bromo-chlorides

Carrying out this research into bromonium ion-induced cation- π cyclisations has therefore opened up the door to a number of different avenues of research. Long may it continue.

5 Experimental

5.1 General Experimental

Reagents: Tetrakis(triphenylphosphine)palladium(0) was prepared according to the procedure by Coulson *et al.*¹⁵⁷ and stored under nitrogen, without light in the fridge. 4-Methoxybenzyl chloride was prepared from 4-methoxybenzyl alcohol according to a procedure by Yadav *et al.*¹⁵⁸ Bromodiethylsulfide pentachloroantimony bromide (BDSB) was prepared according to the procedure by Snyder and Treitler.^{41b} Methanesulfonamide was purified by recrystallization from EtOH. NBS was purified by recrystallization from water. Pyridine was distilled from CaH₂. Triethylamine was distilled from CaH₂ onto activated 4Å molecular sieves. All other reagents were obtained from commercial sources and used as received.

Solvents: All reactions were carried out in anhydrous solvents unless used in combination with H₂O. CH₂Cl₂, Et₂O, THF and toluene were dried by passing through a column of alumina beads. N-Methyl-2-pyrrolidone was purified by distillation and stored over 4Å molecular sieves. Extraction solvents and chromatography eluents were used as received. MeOH and CH₂Cl₂ were HiPerSolv grade, EtOH was AnalaR grade, and Et₂O, EtOAc, and petroleum ether 40-60 (referred to as pet. ether) were GPR grade. *n*-Hexane and *i*-PrOH for analytical HPLC were HPLC grade and used as received.

Experimental techniques: Reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen, unless otherwise stated. Air and moisture sensitive reagents were transferred by syringe. Reaction temperatures other than room temperature were recorded as aluminium alloy heating block, or bath temperatures. 4Å Molecular sieves were activated by grinding into a powder and heating under vacuum and then cooling under nitrogen. The phrase, concentrated under reduced pressure, refers to rotary evaporation. Brine refers to a saturated aqueous solution of NaCl. Column chromatography was performed on silica gel, particle size 40-63 µm unless otherwise stated. Chiral HPLC was performed on CHIRALCEL OD-H, OJ or CHIRALPAK AD columns detecting at 284 nm. Retention times (*t_R*) are reported in minutes. Analytical TLC was performed on Kieselgel 60 F254 pre-coated aluminium-backed plates which were visualised by ultraviolet light (350 nm) and chemical staining using potassium permanganate solution. Silver nitrate doped silica gel was obtained after slurring silica in aqueous AgNO₃ solution (0.1 M, 4 mLg⁻¹ silica) and concentrating under reduced pressure azeotroping with toluene until dryness.

Characterisation: Fourier transform IR spectra were recorded neat using an ATR-IR spectrometer. ^1H , ^{13}C and ^{19}F NMR spectra were recorded on Bruker AV400 and AV500 spectrometers at 400 MHz and 500 MHz, and 100 MHz and 125 MHz, and 377 (AV500 only) MHz respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent resonance. Coupling constants (J) are quoted in Hertz (Hz). Low resolution MS (EI, CI), GCMS and HRMS, were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service.

Compound naming: Compounds in this experimental section are named according to IUPAC recommendations on nomenclature. ^1H NMR resonances are assigned using the numbering system outlined below. For linear substrates, numbering will begin at the terminus alkene and end at the benzylic position and each of the aromatic ^1H NMR resonances will be labelled “a” and “b” as shown in Figure 47.

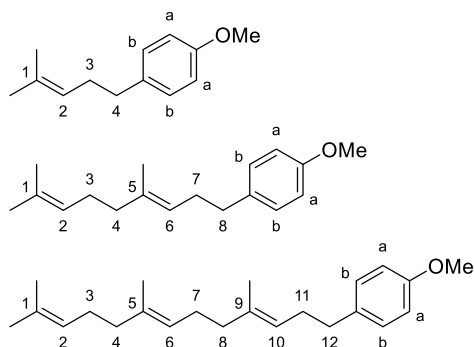


Figure 47 - Representative compound numbering system for linear substrates in assignment of ^1H NMR throughout the experimental section

For cyclic structures, IUPAC nomenclature will be used.

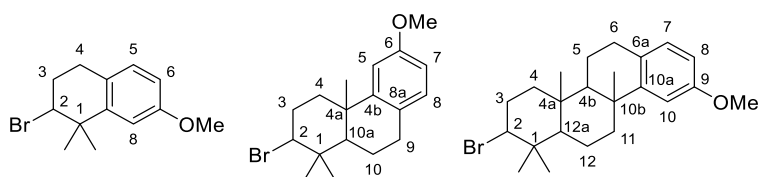
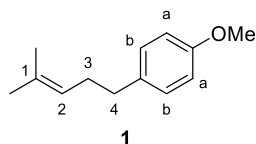


Figure 48 - IUPAC compound numbering system for cyclic structures

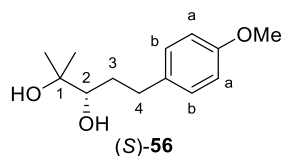
5.2 1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (1)



Prepared according to the procedure used by Zhao and Loh¹⁵⁹ and developed by Demuth.¹⁰³ To a stirred solution of magnesium turnings (2.4 g, 100 mmol) in anhydrous THF (50 mL) was added a few drops of *p*-methoxybenzyl chloride and a few drops of 1,2-dibromoethane to activate the magnesium. The reaction could also be started by gentle heating. Subsequently a solution of *p*-methoxybenzyl chloride (11.3 mL, 83 mmol) in anhydrous THF (50 mL) was added dropwise over 30 min maintaining the reflux. After complete addition reflux was continued for 2 h. The mixture was then added dropwise to a freshly prepared solution of 1-bromo-3-methylbut-2-ene (8.0 mL, 67 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 1.5 mol%) in THF (50 mL) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for 16h and quenched with ice water (100 mL). The mixture was extracted with Et₂O (2 × 100 mL), washed with water (100 mL), brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (5-15% Et₂O in pet. ether) to afford the title compound **1** as a mixture of constitutional isomers with 1-(2,2-dimethylbut-3-en-1-yl)-4-methoxybenzene (**γ-1**) in ratio 4:1 (10.2 g, 54 mmol, 80%) as a colourless oil. 1-(2,2-Dimethylbut-3-en-1-yl)-4-methoxybenzene (**γ-1**) can be identified by characteristic ¹H NMR absorbances at 5.90 (dd, *J* = 17.5, 10.8 Hz, 1H), 4.96 (dd, *J* = 10.6, 1.5 Hz, 1H) and 4.90 (dd, *J* = 17.4, 1.4 Hz, 1H) ppm.

R_f = 0.33 (10% EtOAc in pet. ether); IR *ν*_{max} 2914, 2855, 2835, 1612, 1585, 1511, 1441, 1376, 1300, 1243, 1176, 1109, 1038, 825, 760, 720, 700 cm⁻¹, sp² CH and C=C stretches not observed; ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, *J* = 8.6 Hz, 2H, *H_b*), 6.87 (d, *J* = 8.6 Hz, 2H, *H_a*), 5.21 (t, *J* = 7.1 Hz, 1H, *H₂*), 3.83 (s, 3H, OCH₃), 2.62 (app. t, *J* = 7.8 Hz, 2H, *H₄*), 2.31 (app. q, *J* = 7.8 Hz, 2H, *H₃*), 1.74 (s, 3H, C1(CH₃)), 1.61 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.6, 132.1, 129.3, 123.8, 113.7, 55.3, 35.2, 30.3, 25.7, 17.7 ppm; MS (CI⁺, NH₃) *m/z* 191 [M + H]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₁₉O [M + H]⁺ 191.1436, found 191.1434.

5.3 (-)-(S)-5-(4-Methoxyphenyl)-2-methylpentane-2,3-diol [(S)-56]

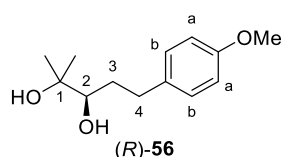


Diol (*S*)-**56** was prepared according to the method of Sharpless,¹²⁷ to a stirred solution of alkene **1** (2.0 g, 10.5 mmol, 1 eq.) and methanesulfonamide (1.0 g, 10.5 mmol, 1 eq.) in water (20 mL) and *tert*-butanol (20 mL) was added AD-mix α (14.7 g, 1.4 gmmol⁻¹) at room temperature and stirred vigorously for 16 h. The reaction mixture was quenched with saturated aqueous Na₂SO₄ solution (60 mL), extracted with EtOAc (2 $\times$ 100 mL), washed with brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50-60% EtOAc in pet. ether) to afford the title product (*S*)-**56** (2.17 g, 92%).

Colourless oil; R_f = 0.37 (50% EtOAc in pet. ether); $[\alpha]_D^{24}$ -27.6 (c 1.4, CH₂Cl₂); IR $\nu_{\max}$ 3700-3050, 2933, 1612, 1584, 1512, 1465, 1382, 1300, 1244, 1177, 1077, 1036, 936, 823 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, J = 8.6 Hz, 2H, *H*_b), 6.86 (d, J = 8.6 Hz, 2H, *H*_a), 3.81 (s, 3H, OCH₃), 3.40 (d, J = 10.5 Hz, 1H *H*₂), 2.90 (ddd, J = 14.3, 9.6, 5.2 Hz, 1H, *H*₄), 2.65 (ddd, J = 13.8, 9.3, 7.2 Hz, 1H, *H*₄), 1.81-1.72 (m, 1H, *H*₃), 1.69-1.59 (m, 1H, *H*₃), 1.21 (s, 3H, C1(CH₃)), 1.17 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 134.0, 129.4, 113.9, 77.8, 73.2, 55.3, 33.7, 32.0, 26.6, 23.2 ppm; MS (CI⁺, NH₃) m/z 242 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₂₄NO₃ [M + NH₄]⁺ 242.1756, found 242.1756; HPLC (CHIRALCEL OD-H; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 7.5 min (major), 9.6 min (minor) – 92:8 e.r. (84% ee).

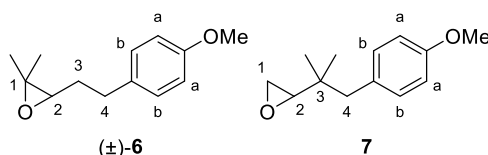
A reference sample of ($\pm$)-diol **56** was prepared following a modified procedure of Warren.¹²⁹ A solution of potassium ferricyanide (2.60 g, 7.9 mmol), potassium carbonate (1.09 g, 7.9 mmol), K₂OsO₄·2H₂O (29 mg, 0.079 mmol), quinuclidine (9 mg, 0.079 mmol, 3 mol%) and methanesulfonamide (250 mg, 2.63 mmol) in water (5 mL) and *tert*-butanol (5 mL) was warmed slightly and stirred until all the solids had dissolved and then allowed to cool to room temperature. Alkene **1** (500 mg, 2.63 mmol) was added and the mixture was stirred vigorously for 16 h. Anhydrous sodium sulfite (3.8 g, 30.2 mmol) was added and the mixture was stirred for 1 h, diluted with water (75 mL) and extracted with CH₂Cl₂ (3 $\times$ 75 mL). The combined organics were washed with aq. NaOH (2M, 100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50-60% EtOAc in pet. ether) to afford ($\pm$)-**56** (594 mg, 100%) as a white solid; m.p. 58-62 °C; HPLC (CHIRALCEL OD-H; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 7.4 min, 9.3 min.

5.4 (+)-(R)-5-(4-Methoxyphenyl)-2-methylpentane-2,3-diol [(R)-**56**]



According to the method of Sharpless,¹²⁷ to a stirred solution of alkene **1** (1.5 g, 7.9 mmol) and methanesulfonamide (750 mg, 7.9 mmol) in water (15 mL) and *tert*-butanol (15 mL) was added AD-mix β (11.0 g, 1.4 gmmol⁻¹) and stirred vigorously for 16 h. The reaction mixture was quenched with saturated aqueous Na₂SO₄ solution (40 mL), extracted with EtOAc (2 $\times$ 75 mL), washed with brine (75 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50:50-60:40 EtOAc:PE) to afford the title product (*R*)-**56** (1.76 g, 99%) as a white solid. m.p. 42-44°C; [α]_D²⁴ +31.8 (*c* 1.1, CH₂Cl₂). HPLC (CHIRALCEL OD-H; 10% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 7.5 min (minor), 9.6 min (major) – 97:3 e.r. (94% ee). All other data identical to that of diol (*S*)-**56**.

5.5 (±)-3-[2-(4-Methoxyphenyl)ethyl]-2,2-dimethyloxirane [(±)-**6**] and (±)-2-[1-(4-methoxyphenyl)-2-methylpropan-2-yl]oxirane (**7**)



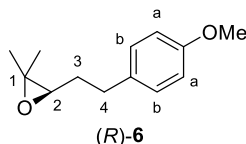
To a stirred solution of alkene **1** as a mixture of constitutional isomers with 1-(2,2-dimethylbut-3-en-1-yl)-4-methoxybenzene (γ -**1**) in ratio 4:1 (10.2 g, 54 mmol, 1 eq) in CH₂Cl₂ (250 mL) at 0 °C was added *meta*-chloroperoxybenzoic acid (13.9 g, 80 mmol 1.5 eq) in one portion and stirred overnight. The reaction was quenched with saturated aqueous solution of Na₂SO₃ (250 mL), extracted and washed with saturated aqueous solution NaHCO₃ (250 mL), brine (250 mL), dried, concentrated under reduced pressure and chromatographed (10% EtOAc in pet. ether) to afford the title product **7**¹⁶⁰ (8.8 g, 81%) and isomeric epoxide **7** (843 mg, 8%).

Epoxide 6: Colourless oil; *R*_f = 0.36 (10% EtOAc in pet. ether); IR $\nu_{\max}$ 2960, 2928, 2859, 2835, 1612, 1584, 1512, 1462, 1378, 1299, 1243, 1177, 1113, 1035, 909, 871, 760, 731, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.86 (d, *J* = 8.6 Hz, 2H, *H*_a), 3.81 (s, 3H, OCH₃), 2.85-2.75 (m, 2H, *H*₄), 2.72-2.63 (m, 1H, *H*₂), 1.93-1.74 (m, 2H, *H*₃), 1.29 (s, 3H, C1(CH₃)) 1.16 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 133.5, 129.4, 113.8, 63.9, 58.5, 55.3, 31.8, 31.0, 24.8, 18.6 ppm; MS (CI⁺, NH₃) *m/z* 224 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₃H₂₂NO₂ [M + NH₄]⁺ 224.1651. Found: 224.1660.

Isomeric epoxide 7: Colourless oil; *R*_f = 0.44 (10% EtOAc in pet. ether); IR $\nu_{\max}$ 2958, 2931, 1711, 1612, 1583, 1512, 1466, 1302, 1245, 1179, 1073, 913, 824, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.10 (d, *J* = 8.5 Hz, 2H, *H*_b), 6.84 (d, *J* = 8.7 Hz, 2H, *H*_a), 3.81 (s, 3H, OCH₃), 2.88-2.51 (m, 3H, *H*₄, *H*₂), 1.08 (d, *J* = 6.9 Hz, 2H, *H*₁), 0.91 (s, 3H, C3(CH₃)) 0.82 (s, 3H, C3(CH₃)) ppm;

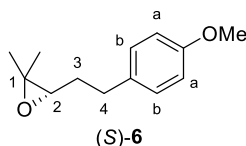
^{13}C NMR (100 MHz, CDCl_3) δ 158.0, 131.5, 130.0, 113.2, 59.0, 55.2, 45.5, 44.3, 34.5, 23.3, 21.7 ppm; MS (CI^+) m/z 224, $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+) calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{NH}_4]^+$ 224.1651. Found: 224.1654.

5.6 (+)-(R)-3-[2-(4-Methoxyphenyl)ethyl]-2,2-dimethyloxirane [(R)-6]



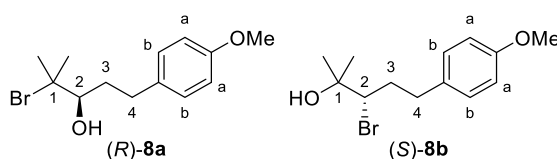
Using a modified procedure of Corey,¹²⁶ to a stirred solution of (*S*)-diol **56** (2.0 g, 8.9 mmol, 1 eq.) and triethylamine (2.46 mL, 17.7 mmol, 2 eq.) in CH_2Cl_2 (40 mL) at 0°C was added methanesulfonyl chloride (0.89 mL, 11.5 mmol, 1.3 eq.). After 0.5 h the mixture was warmed to room temperature and stirred for 3 h. Additional triethylamine (7.4 mL 53 mmol, 6 eq.) was added, the reaction mixture was stirred for 16 h and poured into a suspension of K_2CO_3 (20 g, 145 mmol, 16 eq.) in methanol (80 mL). The reaction mixture was stirred for 5 h, concentrated, diluted with water (100 mL), extracted with EtOAc (3×100 mL), washed with 10% aqueous CuSO_4 solution (200 mL) and brine (200 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (5-15% EtOAc in pet. ether) to afford the title product (R)-6 (1.39 g, 76%) as a colourless oil; $[\alpha]_{\text{D}}^{24} +12.6$ (c 1.1, CH_2Cl_2).

5.7 (-)-(S)-3-[2-(4-Methoxyphenyl)ethyl]-2,2-dimethyloxirane [(S)-6]



Following the method used for the preparation of epoxide (R)-6, (R)-**56** (1.76 g, 7.9 mmol) was converted into (*S*)-epoxide (S)-6 (858 mg, 53%) as a colourless oil: $[\alpha]_{\text{D}}^{24} -14.8$ (c 1.7 CH_2Cl_2).

5.8 (+)-(R)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol [(R)-8a] and (-)-(S)-3-bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol [(S)-8b]

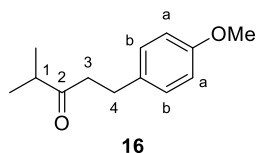


Following the method of Couladouros and Vidal,⁷⁶ to a solution of epoxide (R)-**6** (1.39 g, 6.75 mmol, 1 eq) in *N*-methyl-2-pyrrolidone (2 mL) was added LiBr (763 mg, 8.77 mmol, 1.3 eq) and PPTS (1.69 g, 6.75 mmol, 1 eq) and stirred at room temperature for 3 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (100 mL), extracted with EtOAc (2 × 100 mL), washed with brine (100 mL), dried, concentrated under reduced pressure and chromatographed (10-20% EtOAc in pet. ether) to yield first ketone **16**¹⁶⁰ (172 mg, 12%), second, bromohydrin (R)-**8a** (648 mg, 33%), and third, bromohydrin (S)-**8b** (1.06 g, 45%) containing ca. 12-15% allyl alcohol **14**.¹⁶¹ A sample of analytically pure (S)-**8b** was obtained by careful chromatography. Samples of (±)-**8a** and (±)-**8b** were prepared from (±)-**6** using the above procedure. Bromohydrin (±)-**8a**: HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 5.9 min, 7.1 min. Bromohydrin (±)-**8b**: HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 5.4 min, 6.1 min (major)

Bromohydrin (R)-**8a**: Colourless oil; [α]_D²⁴ +28.5 (*c* 1.4, CH₂Cl₂); *R*_f = 0.64 (10% EtOAc in pet. ether); IR ν_{max} 3600-3200, 2933, 1611, 1584, 1512, 1455, 1387, 1300, 1244, 1177, 1105, 1072, 1035, 972, 824, 741, 704, 532 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.87 (d, *J* = 8.7 Hz, 2H, *H*_a), 3.82 (s, 3H, OCH₃), 3.46 (dd, *J* = 10.4, 1.8 Hz, 1H, *H*₂), 2.94 (ddd, *J* = 14.0, 9.4, 4.8 Hz, 1H, *H*₄), 2.63 (ddd, *J* = 13.8, 9.0, 7.6 Hz, 1H, *H*₄), 2.20 (br. s, 1H, OH), 1.92 (dddd, *J* = 13.7, 9.4, 7.6, 2.1 Hz, 1H, *H*₃), 1.81 (s, 3H, C1(CH₃)), 1.78-1.67 (m, 1H, *H*₃) 1.74 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 133.8, 129.4, 113.9, 78.7, 75.6 (CBr), 55.3, 33.9, 31.7, 31.2, 28.7 ppm; MS (CI⁺) *m/z* 306, 304 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₃H₂₃NO₂⁷⁹Br [M + NH₄]⁺ 304.0912. Found: 304.0918; HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 6.4 min (minor), 8.0 min (major) - 91:9 e.r. (81% e.e.).

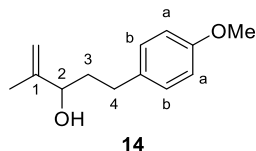
Bromohydrin (S)-**8b**: Colourless oil; [α]_D²⁴ -42.0 (*c* 1.1, CH₂Cl₂); *R*_f = 0.50 (10% EtOAc in pet. ether); IR ν_{max} 3600-3150, 2934, 2835, 1612, 1584, 1512, 1464, 1369, 1336, 1300, 1244, 1177, 1105, 1035, 964, 906, 822, 773, 704, 567, 552, 533, 527 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.88 (d, *J* = 8.6 Hz, 2H, *H*_a), 3.98 (dd, *J* = 11.4, 2.1 Hz, 1H, *H*₂), 3.82 (s, 3H, OCH₃), 3.00 (ddd, *J* = 13.9, 8.4, 4.4 Hz, 1H, *H*₄), 2.68 (ddd, *J* = 13.9, 8.4, 8.3 Hz, 1H, *H*₄), 2.26 (br. s, 1H, OH), 2.23-2.13 (m, 1H, *H*₃), 2.11-2.00 (m, 1H, *H*₃) 1.34 (s, 3H, C1(CH₃)), 1.33 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 132.7, 129.5, 114.0, 72.5, 70.5, 55.3, 35.9, 33.6, 26.6, 26.0 ppm; MS (CI⁺) *m/z* 306, 304 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₃H₂₃NO₂⁷⁹Br [M + NH₄]⁺ 304.0912, found: 304.0915; HPLC (CHIRALCEL OD-H, 1% IPA in *n*-hexane, 1.0 mL/min) *t*_R = 7.6 min (major), 8.3 min (minor) - 91:9 e.r. (82% e.e.).

5.8.1 1-(4-Methoxyphenyl)-4-methylpentan-3-one (16)



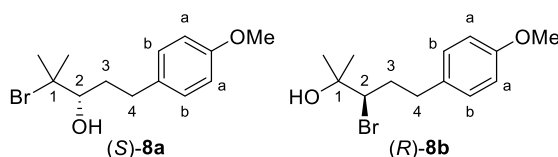
Colourless oil. $R_f = 0.58$ (20% EtOAc in pet. ether); IR $\nu_{\max}$ 2969, 2935, 2834, 1708, 1612, 1584, 1512, 1464, 1409, 1383, 1364, 1300, 1243, 1177, 1110, 1071, 1034, 1001, 963, 729, 705 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.15-7.09 (m, 2H, H_b), 6.87-6.83 (m, 2H, H_a), 3.81 (s, 3H, OCH_3), 2.89-2.83 (m, 2H, H_4), 2.79-2.74 (m, 2H, H_3), 2.59 (sep, $J = 6.9$ Hz, 1H, H_1), 1.10 (s, 3H, $\text{C1}(\text{CH}_3)$), 1.08 (s, 3H, $\text{C1}(\text{CH}_3)$) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 214.0, 157.9, 133.4, 129.3, 113.9, 55.3, 42.3, 41.0, 29.0, 18.1 ppm; MS (CI^+) m/z 224 $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+) calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{NH}_4]^+$ 224.1651, found: 224.1651.

5.8.2 5-(4-Methoxyphenyl)-2-methylpent-1-en-3-ol (14)



Colourless oil. $R_f = 0.50$ (10% EtOAc in pet. ether); IR $\nu_{\max}$ 3421, 2935, 1612, 1513, 1456, 1246, 1178, 1036, 900, 830 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.15 (d, $J = 8.6$ Hz, 2H, H_b), 6.86 (d, $J = 8.7$ Hz, 2H, H_a), 5.01-4.98 (m, 1H, $\text{CH}_2=\text{C}$), 4.91-4.88 (m, 1H, $\text{CH}_2=\text{C}$), 4.11 (t, $J = 6.4$ Hz, 1H, H_2), 3.82 (s, 3H, OCH_3), 2.74-2.57 (m, 2H, H_4), 1.90-1.83 (m, 2H, H_3), 1.77 (s, 3H, $\text{C1}(\text{CH}_3)$), 1.29 (br. s, 1H, OH) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 147.5, 134.0, 129.3, 113.8, 111.2, 55.3, 36.8, 31.0, 29.7, 17.6 ppm; MS (CI^+) m/z 224 $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+) calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{NH}_4]^+$ 224.1651, found: 224.1650.

5.9 (-)-(S)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-ol [(S)-8a] and (+)-(R)-3-bromo-5-(4-methoxyphenyl)-2-methylpentan-2-ol [(R)-8b]



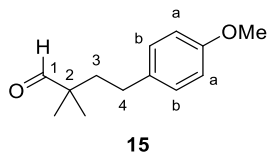
Following the method of Couladouros and Vidali,⁷⁶ to a solution of (S)-epoxide **3** (858 mg, 4.17 mmol) in *N*-methyl-2-pyrrolidone (1.2 mL) was added LiBr (471 mg, 5.41 mmol) and PPTS (1.05 g, 4.17 mmol) and stirred at room temperature for 4 h. Additional LiBr (72 mg, 0.83 mmol) and

PPTS (209 mg, 0.83 mmol) was added and stirred for a further 2 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (50 mL), extracted with EtOAc (2 × 50 mL), washed with brine (50 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-20:80 EtOAc:PE) to yield a 4:5 mixture of bromohydrins (*S*)-**8a** and (*R*)-**8b** (860 mg, 72%) as a colourless oil containing *ca.* 9% allyl alcohol **14**.¹⁶¹ Bromohydrins (*S*)-**8a**: [α]_D²⁴ -27.0 (*c* 0.8, CH₂Cl₂). Bromohydrin (*R*)-**8b**: [α]_D²⁴ +51.0 (*c* 1.5, CH₂Cl₂). The spectral data for (*S*)-**8a** and (*R*)-**8b** were identical to those of (*R*)-**8a** and (*S*)-**8b**.

5.10 Epoxide ring-opening with HFIP and (*n*-hexyl)₄N⁺Br⁻

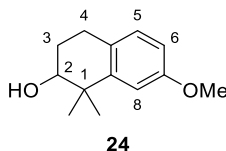
To a stirred solution of epoxide ($\pm$)-**6** (50 mg, 0.24 mmol, 1 eq) and activated 4 Å molecular sieves in HFIP for 1 h, was added *n*-hexyl₄N⁺Br⁻ (385 mg, 0.89 mmol, 3.65 eq) and heated at reflux overnight. The reaction mixture was diluted with EtOAc (10 mL), filtered through a silica plug, washed with brine (50 mL), concentrated under reduced pressure and chromatographed (5-25% EtOAc in pet. ether) to afford ketone **16**¹⁶⁰ (14 mg, 28%) and aldehyde **15**^{162,160} (4 mg, 8%) as a 4:1 mix, as a colourless oil, bicycle **13**^{163,160} (10 mg, 20%) and allyl alcohol **14**¹⁶¹ (7 mg, 14%).

5.10.1 4-(4-Methoxyphenyl)-2,2-dimethylbutanal (**15**)



R_f = 0.58 (20% EtOAc in pet. ether); ¹H NMR (400 MHz, CDCl₃) δ 9.50 (s, 1H *CHO*), 7.09 (d, *J* = 8.6 Hz, 2H, *H_b*), 6.83 (d, *J* = 2H, *H_a*), 3.81 (s, 3H, OCH₃), 2.53-2.47 (m, 2H, *H₄*), 1.82-1.76 (m, 2H, *H₃*), 1.15 (s, 6H, C2(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 206.0, 157.9, 133.9, 129.2, 113.9, 55.3, 45.9, 39.6, 29.8, 29.7, 21.4 ppm; MS (CI⁺) *m/z* 224 [M + NH₄]⁺.

5.10.2 ($\pm$)-7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-ol (**13**)



Colourless oil. *R_f* = 0.42 (20% EtOAc in pet. ether); IR $\nu_{\max}$ 3397, 2935, 1611, 1574, 1504, 1464, 1282, 1242, 1034, 856, 808, 708 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.02 (d, *J* = 8.4 Hz, 1H, *H₅*), 6.91 (d, *J* = 2.7 Hz, 1H, *H₆*), 6.37 (dd, *J* = 8.4, 2.6 Hz, 1H, *H₈*), 3.82 (s, 3H, OCH₃), 3.78 (dd, *J* = 8.7, 3.1 Hz, 1H *H₂*), 2.97-2.77 (m, 2H, *H₄*), 2.03 (tdd, *J* = 9.7, 6.6, 3.4 Hz, 1H, *H₃*), 1.99-1.90 (m,

1H, *H*3), 1.36 (s, 3H, C1(*CH*₃)), 1.32 (s, 3H, C1(*CH*₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.0, 145.6, 129.6, 126.7, 112.4, 111.4, 75.6, 55.3, 39.3, 29.0, 27.0, 26.1, 25.0 ppm; MS (CI⁺) *m/z* 224 [M + NH₄]⁺. HRMS (CI⁺) calc'd for C₁₃H₂₂NO₂ [M + NH₄]⁺ 224.1651, found: 224.1652.

5.11 Epoxide ring-opening with Bu₄N⁺Br⁻ and Mg(NO₃)₂

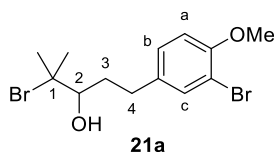
According to the procedure developed by Suh *et al.*,¹⁰⁸ to a stirred solution of epoxide (±)-**6** (50 mg, 0.24 mmol, 1 eq) in CH₂Cl₂ (2.5 mL) was added Bu₄N⁺Br⁻ (156 mg, 0.48 mmol, 2 eq) and Mg(NO₃)₂·6H₂O (41 mg, 0.16 mmol, 0.66 eq) and heated at reflux for 6 h. The suspension was then filtered through a silica plug, concentrated under reduced pressure and chromatographed (15% EtOAc in pet. ether) to yield secondary alcohol bromohydrin **8a** (10 mg, 15%), ketone **16** (4 mg, 7%), secondary bromide bromohydrin **8b** (16 mg, 24%) as a 3:1 mixture with allyl alcohol **14** (4 mg, 10%).

5.12 Epoxide ring-opening with PPh₃/Br₂

The reaction was carried out according to a modified procedure of Palumbo, Ferreri and Caputo.¹⁰⁹ To a solution of bromine (13 μL, 0.27 mmol, 1.1 eq) in anhydrous CH₂Cl₂ (7.8 mL), triphenylphosphine (70 mg; 0.27 mmol, 1.1 eq) was added in one portion. The brown solution turned immediately to a pale yellow colour and then epoxide (±)-**6** (50 mg; 0.24 mmol, 1 eq) was added also in one portion. After stirring overnight the reaction mixture was poured onto ice in a sat. aq. solⁿ NaHCO₃ (25 mL), extracted with CH₂Cl₂ (2 × 20 mL), washed with brine (20 mL), concentrated under reduced pressure and chromatographed (5-25% EtOAc in pet. ether) to afford secondary alcohol bromohydrin **8a** (20 mg, 29%) as a colourless oil, over-brominated secondary alcohol bromohydrin **21a** (29 mg, 33%) and secondary bromide bromohydrin **8b** (9 mg, 13%) as a 3:1 mixture and over-brominated secondary bromide bromohydrin **21b** (8 mg, 9%) as a colourless liquid.

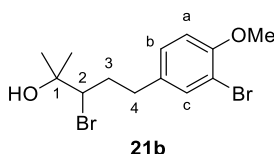
The reaction was repeated under the same conditions but with an excess of triphenylphosphine (114 mg, 0.44 mmol, 1.3 eq), epoxide (±)-**6** (69 mg, 0.34 mmol, 1 eq), bromine (19 μL, 0.37 mmol, 1.1 eq) to produce secondary alcohol bromohydrin **8a** (29 mg, 30%) as a colourless oil and secondary bromide bromohydrin **8b** (19 mg, 20%) and over-brominated secondary alcohol bromohydrin **21a** (12 mg, 10%) as a 5:3 mixture as a colourless oil.

5.12.1 (±)-4-Bromo-1-(3-bromo-4-methoxyphenyl)-4-methylpentan-3-ol (21a)



Colourless oil. $R_f = 0.50$ (10% EtOAc in pet. ether); ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 2.2$ Hz, 1H, H_c), 7.18-7.13 (m, 1H, H_b), 6.89-6.84 (m, 1H, H_a), 3.90 (s, 3H, OCH_3), 3.43 (dd, $J = 10.5, 2.0$ Hz, 1H, H_2), 2.92 (ddd, $J = 14.1, 9.5, 4.8$ Hz, 1H, H_4), 2.72-2.60 (m, 1H, H_4), 1.90 (dddd, $J = 13.7, 9.4, 7.5, 1.9$ Hz, 1H, H_3), 1.81 (s, 3H, $\text{C1}(\text{CH}_3)$), 1.74 (s, 3H, $\text{C1}(\text{CH}_3)$), 1.75-1.64 (m, 1H, H_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 135.4, 133.2, 128.5, 112.0, 111.5, 78.5, 56.3, 31.4, 31.2, 28.6, 21.1 ppm; MS (CI^+) m/z 224, $[\text{M}-\text{Br} + \text{NH}_4]^+$.

5.12.2 (±)-3-Bromo-5-(3-bromo-4-methoxyphenyl)-2-methylpentan-2-ol (21b)



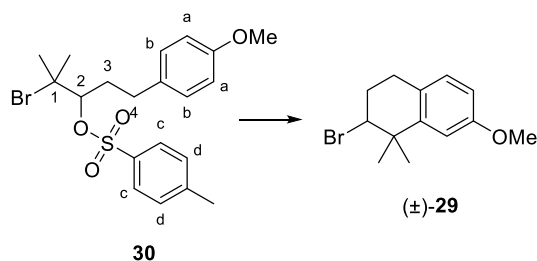
Colourless oil. $R_f = 0.42$ (10% EtOAc in pet. ether); IR ν_{max} 3462, 2929, 1608, 1498, 1463, 1256, 1056, 1022, 811, 748, 579, 557 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 2.1$ Hz, 1H, H_c), 7.15 (dd, $J = 8.3, 2.1$ Hz, 1H, H_b), 6.86 (d, $J = 8.4$ Hz, 1H, H_a), 3.96 (dd, $J = 11.4, 2.1$ Hz, 1H, H_2), 3.91 (s, 3H, OCH_3), 2.99 (ddd, $J = 13.9, 8.6, 4.5$ Hz, 1H, H_4), 2.66 (dt, $J = 14.0, 8.3$ Hz, 1H, H_4), 2.23-2.11 (m, 1H, H_3), 2.10-1.99 (m, 1H, H_3), 1.35 (s, 6H, $\text{C1}(\text{CH}_3)$) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 154.4, 134.4, 133.3, 128.5, 112.0, 111.6, 72.5, 70.0, 56.3, 35.7, 33.3, 26.7, 25.9 ppm; MS (CI^+) m/z 386, 384, 382, $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+) calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_2^{79}\text{Br}_2$ $[\text{M} + \text{NH}_4]^+$ 382.0017, found: 382.0013.

5.13 Epoxide ring-opening with $\text{Me}_2\text{SBr}^+\text{Br}^-$

Synthesis of reagent is carried out according to the procedure of Olah *et al.*¹¹⁴ To a solution of dimethyl sulfide (4.36 mL, 60 mmol, 1 eq) in CH_2Cl_2 (12 mL) at 0 °C was added dropwise over 30 min a solution of bromine (3.070 mL, 60 mmol, 1 eq) in CH_2Cl_2 (12 mL). The light-orange crystals were filtered and washed with dry hexane and dried under reduced pressure. The reagent (10.4 g, 42 mmol, 1 eq) was added to a solution of epoxide (±)-6 (8.57 g, 42 mmol, 1 eq) in MeCN (25 mL) and stirred for 30 min. The reaction was quenched with water (50 mL) and extracted with EtOAc (2×50 mL), concentrated under reduced pressure and chromatographed (5-25% EtOAc

in pet. ether) to afford secondary alcohol bromohydrin **8a** (3.44 g, 29%) and secondary bromide bromohydrin **8b** (2.05 g, 17%).

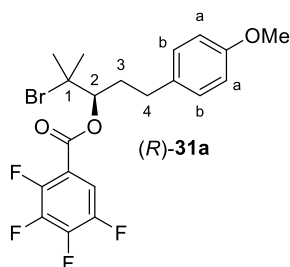
5.14 2-Bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 4-toluenesulfonate (**30**)



To a stirred solution of bromohydrin (±)-**8a** (250 mg, 0.87 mmol, 1 eq.) in pyridine (1 ml) at 0°C was added tosic anhydride (369 mg, 1.13 mmol, 1.3 eq.) and stirred for 2 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with EtOAc (2 × 25 mL), washed with water (3 × 50 mL), brine (50 mL) and concentrated under reduced pressure at 55°C. The crude reaction mixture was dissolved in CH₂Cl₂ (8 mL), stirred at -78°C and TMSOTf (0.17 mL, 0.96 mmol, 1.1 eq.) added dropwise and stirred for 6 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (25 mL), extracted with CH₂Cl₂ (25 mL), washed with a saturated aqueous solution of NaHCO₃ (25 mL), brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-20% CH₂Cl₂ in pet. ether) to give bromo bicycle (±)-**29** (113 mg, 0.42 mmol, 48% yield) and ketone **16** (32 mg, 0.15 mmol, 18% yield).

Tosylate **30** from analysis of the crude reaction mixture before reaction with TMSOTf: *R*_f = 0.45 (5% EtOAc in pet. ether); ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.3 Hz, 2H, *H*_c), 7.38 (d, *J* = 8.2 Hz, 2H, *H*_d), 7.05 (d, *J* = 8.5 Hz, 2H, *H*_b), 6.84 (d, *J* = 8.6 Hz, 2H, *H*_a), 4.74 (dd, *J* = 8.5, 2.3 Hz, 1H, *H*₂), 3.81 (s, 3H, OCH₃), 2.89-2.83 (m, 1H, *H*₄), 2.79-2.73 (m, 1H, *H*₄), 2.48 (s, 3H, PhCH₃), 2.31 (dddd, *J* = 14.7, 10.4, 6.5, 2.2 Hz, 1H, *H*₃), 2.07-1.96 (m, 1H, *H*₃), 1.73 (s, 3H, C1CH₃), 1.71 (s, 3H, C1CH₃) ppm.

5.15 (+)-(R)-2-Bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 2,3,4,5-tetrafluorobenzoate [(R)-**31a**]



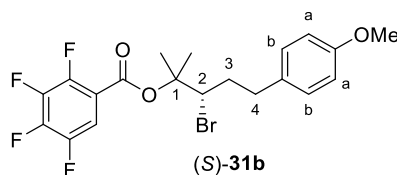
Using the method of Steglich,¹¹⁶ to a stirred solution of secondary alcohol (R)-**8a** (250 mg, 0.87 mmol, 1 eq) in CH₂Cl₂ (5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (203 mg, 1.05 mmol, 1.2 eq), DMAP (32 mg, 0.26 mmol, 30 mol%) and DCC (233 mg, 1.13 mmol, 1.3 eq) and stirred for 4 h. The reaction mixture was then diluted with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (0-10% Et₂O in pet. ether) to afford (R)-**31a** (353 mg, 88%). (±)-**31a** (71 mg, 88% yield) was prepared from (±)-**8a** (50 mg, 0.18 mmol) using the same procedure over 1 h. HPLC (CHIRALPAK AD; 0.25% IPA in *n*-hexane; 0.5 mL/min) *t*_R = 19.8 min, 22.4 min.

Colourless oil; [α]_D²⁴ +16.5 (*c* 1.2, CH₂Cl₂); *R*_f = 0.34 (5% EtOAc in pet. ether); IR ν_{max} 2935, 1725, 1628, 1613, 1526, 1513, 1485, 1371, 1282, 1225, 1178, 1097, 1034, 1000, 977, 922, 882, 829, 775, 743, 705, 623, 581, 541 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.63 (dddd, *J* = 10.5, 8.4, 6.0, 2.5 Hz, 1H, F₄BzH), 7.12 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.82 (d, *J* = 8.6 Hz, 2H, *H*_a), 5.33 (dd, *J* = 10.2, 1.8 Hz, 1H, *H*₂), 3.79 (s, 3H, OCH₃), 2.67 (app. t, *J* = 7.8 Hz, 2H, *H*₄), 2.32-2.23 (m, 1H, *H*₃), 2.18-2.07 (m, 1H, *H*₃) 1.81 (s, 3H, C1(CH₃)), 1.80 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 161.5, 158.0, 148.0 (dd, *J* = 262, 12 Hz), 146.4 (dd, *J* = 250, 10 Hz), 144.0 (ddd, *J* = 232, 14, 14 Hz), 141.0 (ddd, *J* = 228, 14, 14 Hz), 114.6 (m), 113.8, 113.4 (dd, *J* = 21, 3 Hz), 81.5, 65.6, 55.1, 32.9, 31.6, 30.3 ppm; ¹⁹F NMR (377 MHz, CDCl₃) δ -153.2 (t, *J* = 20 Hz, 1F), -146.9 (m, 1F), -137.7 (m, 1F), -133.5 (m, 1F) ppm; MS (CI⁺) *m/z* 482, 480, [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₂₀H₂₃NO₃⁷⁹BrF₄ [M + NH₄]⁺ 480.0797, found: 480.0792. HPLC (CHIRALPAK AD; 0.25% IPA in *n*-hexane; 0.5 mL/min) *t*_R = 19.8 min (minor), 22.0 min (major) – 92:8 e.r. (84% ee).

5.16 Esterification using acid chloride

To a stirred solution of 2,3,4,5-tetrafluorobenzoic acid (135 mg, 0.70 mmol, 2 eq.) in CH₂Cl₂ (10 mL) was added oxalyl chloride (1 mL, 11 mmol, 33 eq.) and a drop of DMF and heated at reflux for 4 h. The reaction mixture was then concentrated under reduced pressure, dissolved in CH₂Cl₂ (2 mL) and added dropwise at 0 °C to a solution of secondary alcohol bromohydrin (±)-**8a** (100 mg, 0.35 mmol, 1 eq.) and DMAP (85 mg, 0.70 mmol, 2 eq.) in CH₂Cl₂ (15 mL), and stirred at room temperature for 16 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (30 mL) extracted with CH₂Cl₂ (2 × 30 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-20% EtOAc in pet. ether) to yield epoxide **6** (23 mg, 0.11 mmol, 33%), ketone **16** (14 mg, 0.07 mmol, 19%) and tetrafluorobenzoate ester **31a** (6 mg, 0.01 mmol, 4%).

5.17 (-)-(S)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate [(S)-31b]



Tertiary alcohol ($\pm$)-**8b** (50 mg, 0.18 mmol) was reacted under the same conditions as used for the esterification of (*R*)-**8a** over 16 h to afford tertiary tetrafluorobenzoate ($\pm$)-**31b** (34 mg, 42%). Optimisation of this reaction gave improved yields with the conditions described below.

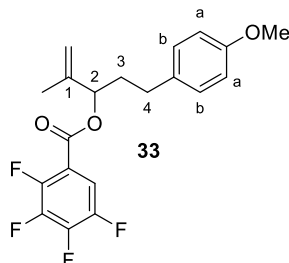
Using the method of Steglich,¹¹⁶ to a stirred solution of tertiary alcohol (*S*)-**8b** containing *ca.* 12-15% allyl alcohol **14** (250 mg, 0.87 mmol, 1 eq) in CH₂Cl₂ (1 mL) was added 2,3,4,5-tetrafluorobenzoic acid (338 mg, 1.78 mmol, 2 eq), DMAP (32 mg, 0.262 mmol, 30 mol%) and DCC (538 mg, 2.61 mmol, 3 eq). After 16 h the reaction mixture was diluted with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (5-20% EtOAc in pet. ether) to afford tetrafluorobenzoate ester (*S*)-**31b** (300 mg, 62%) as a white solid containing *ca.* 15% 5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl tetrafluorobenzoate (**33**). A sample of analytically pure (*S*)-**31b** was obtained by reaction of this mixture with *m*CPBA.

A sample of ($\pm$)-**31b** (111 mg, 69%, containing *ca.* 10% 5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl tetrafluorobenzoate **33**) was prepared from ($\pm$)-**31b** (100 mg, 0.35 mmol) by the same procedure. A sample of analytically pure ($\pm$)-**31b** was obtained by further careful chromatography; m.p. 74-77 °C. HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) *t_R* = 16.9 min, 19.8 min.

White solid; m.p. 72-75 °C; [α]_D²⁴ -37.3 (*c* 1.5, CH₂Cl₂); *R_f* = 0.3 (5% EtOAc in pet. ether); IR ν_{max} 2994, 2937, 2841, 1729, 1717, 1631, 1612, 1583, 1526, 1512, 1485, 1392, 1363, 1325, 1285, 1228, 1176, 1163, 1124, 1107, 1030, 984, 958, 950, 920, 875, 865, 824, 799, 778, 768, 743, 720, 704, 679 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (dddd, *J* = 10.4, 8.4, 6.0, 2.5 Hz, 1H, F₄BzH), 7.16 (d, *J* = 8.6 Hz, 2H, H_b), 6.87 (d, *J* = 8.7 Hz, 2H, H_a), 4.51 (dd, *J* = 11.3, 1.9 Hz, 1H, H₂), 3.83 (s, 3H, OCH₃), 3.03 (ddd, *J* = 13.4, 8.6, 4.5 Hz, 1H, H₄), 2.70 (ddd *J* = 13.9, 8.3, 8.3 Hz, 1H, H₄), 2.25-2.15 (m, 1H, H₃) 2.13-2.03 (m, 1H, H₃) 1.74 (s, 3H, C1(CH₃)), 1.72 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 160.4, 158.1, 147.8 (dddd, *J* = 262, 11, 4, 2 Hz), 146.4 (dddd, *J* = 249, 11, 4, 2 Hz), 143.4 (dddd, *J* = 261, 16, 12, 3 Hz), 141.2 (dddd, *J* = 248, 17, 12, 4 Hz) 132.5, 129.5, 115.8 (m), 113.9, 113.3 (dd, *J* = 20, 3 Hz), 86.1, 61.3, 55.2, 35.5, 33.3, 24.1, 23.1 ppm; ¹⁹F NMR (377 MHz, CDCl₃) δ -153.5 (t, *J* = 20 Hz, 1F), -147.6 (m, 1F), -138.0 (m, 1F), -134.4 (m, 1F)

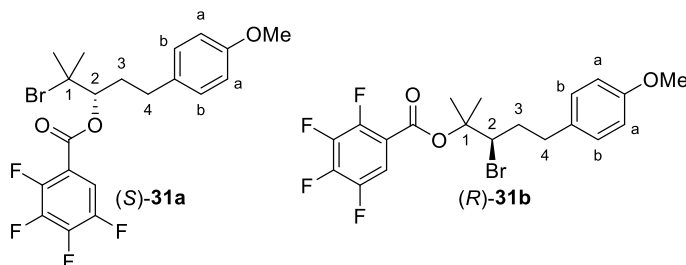
ppm; MS (Cl^+) m/z 482, 480, $[\text{M} + \text{NH}_4]^+$; HRMS (Cl^+) calc'd for $\text{C}_{20}\text{H}_{23}\text{NO}_3^{79}\text{BrF}_4$ $[\text{M} + \text{NH}_4]^+$ 480.0797, found: 480.0821. HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) t_R = 16.9 min (major), 20.2 min (minor) – 93:7 e.r. (86% ee).

5.18 5-(4-Methoxyphenyl)-2-methylpent-1-en-3-yl 2,3,4,5-tetrafluorobenzoate (**33**)



R_f = 0.4 (10% EtOAc in pet. ether); ^1H NMR (400 MHz, CDCl_3) δ_H 7.64–7.54 (m, 1H F_4BzH) 7.12 (d, J = 8.6 Hz, 2H, H_b), 6.84 (d, J = 8.6 Hz, 2H, H_a), 5.47 (dd, J = 7.2, 6.0 Hz, 1H, H_2), 5.08 (s, 1H $\text{C1}=\text{CH}_2$), 5.03–5.01 (m, 1H, $\text{C1}=\text{CH}_2$), 3.80 (s, 3H, OCH_3), 2.99–2.84 (m, 1H, H_4), 2.77–2.59 (m, 1H, H_4), 2.23–2.09 (m, 1H, H_3), 2.09–1.98 (m, 1H, H_3), 1.83 (s, 3H, C1CH_3).

5.19 (-)-(S)-2-Bromo-5-(4-methoxyphenyl)-2-methylpentan-3-yl 2,3,4,5-tetrafluorobenzoate [(S)-**31a**] and (+)-(R)-3-bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate [(R)-**31b**]



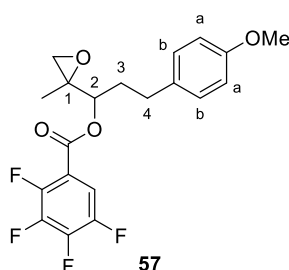
A 4:5 mixture of bromohydrins (*S*)-**8a** and (*R*)-**8b** (860 mg, 3.00 mmol) containing *ca.* 9% allyl alcohol **14** was esterified under the same conditions as used for (*S*)-**31b** to produce a 4:5 mixture of tetrafluorobenzoates (*S*)-**31a** and (*R*)-**31b** (644 mg, 95%) as a white oily solid containing *ca.* 8% allyl tetrafluorobenzoate **33**. Tetrafluorobenzoates (*R*)-**31b**: $[\alpha]_D^{24} +33.1$ (c 1.2, CH_2Cl_2); The spectral data for (*S*)-**31a** and (*R*)-**31b** were identical to those of (*R*)-**31a** and (*S*)-**31b**.

5.20 Removal of olefinic impurities

Olefinic impurities are removed by reaction with *m*CPBA. An exemplary reaction is described below:

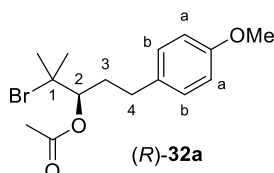
To a stirred solution of a 1:0.75 mixture of (*S*)-**31b** and **33** (175 mg, 0.38 mmol) in CH₂Cl₂ (6 mL) at 0°C was added *m*CPBA (98 mg, 0.57 mmol) and stirred at room temperature for 16 h. To the reaction mixture was added *m*CPBA (98 mg, 0.57 mmol) and stirred at room temperature for a further 16 h. The reaction was quenched with a saturated aqueous solution of Na₂SO₃ (25 mL), extracted with CH₂Cl₂ (25 mL), washed with a saturated aqueous solution of NaHCO₃ (25 mL), brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0–25% Et₂O in pet. ether) to afford pure tetrafluorobenzoate (*S*)-**31b** (32.5 mg, 0.07 mmol, 19%) and 3-(4-methoxyphenyl)-1-(2-methyloxiran-2-yl)propyl 2,3,4,5-tetrafluorobenzoate (6 mg, 0.02 mmol, 4%).

5.21 3-(4-Methoxyphenyl)-1-(2-methyloxiran-2-yl)propyl 2,3,4,5-tetrafluorobenzoate (**57**)



Colourless oil; *R_f* = 0.43 (20% Et₂O in pet. ether); ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dddd, *J* = 10.4, 8.3, 6.0, 2.5 Hz, 1H, F₄BzH), 7.11 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.83 (d, *J* = 8.7 Hz, 2H, *H*_a), 4.94 (dd, *J* = 6.1, 6.9 Hz, 1H, *H*₂), 3.80 (s, 3H), 2.92 (d, *J* = 5.0 Hz, 1H, C1CH₂O), 2.71 (td, *J* = 7.5, 3.0 Hz, 2H, *H*₃), 2.66 (d, *J* = 5.0 Hz, 1H, C1CH₂O), 2.14 (t, *J* = 7.6 Hz, 2H, *H*₄), 1.42 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.0, 132.8, 129.2, 113.9, 113.4, 76.7, 56.2, 55.2, 53.0, 32.5, 31.0, 16.9 ppm; MS (CI⁺) *m/z* 416 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₂₀H₁₉O₄F₄ 399.1219 [M + H]⁺, found: 399.1213.

5.22 (+)-(R)-4-Bromo-1-(4-methoxyphenyl)-4-methylpentan-3-yl acetate [(*R*)-**32a**]

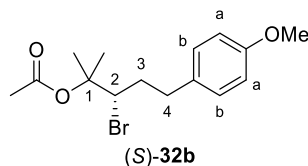


Using the method of Steglich,¹¹⁶ to a stirred solution of secondary alcohol (*R*)-**8a** (129 mg, 0.52 mmol, 1 eq) in CH₂Cl₂ (3 mL) was added acetic acid (35 μL, 0.63 mmol, 1.2 eq), DMAP (19 mg, 0.16 mmol, 30 mol%) and DCC (140 mg, 0.68 mmol, 1.3 eq) and stirred 48 h. The reaction mixture

was then diluted with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (0-15% EtOAc in pet. ether) to afford (*R*)-**32a** (90 mg, 52%). A sample of (±)-**32a** (272 mg, 95% yield) was prepared from (±)-**32a** (250 mg, 0.87 mmol) by the same procedure over 16 h. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 7.6 min, 10.7 min.

Colourless oil; [α]_D²⁴ +8.7 (*c* 1.3, CH₂Cl₂); *R*_f = 0.38 (15% EtOAc in pet. ether); IR ν_{max} 2995, 2963, 2932, 2859, 2835, 1739, 1612, 1584, 1512, 1455, 1371, 1300, 1226, 1177, 1114, 1037, 987, 964, 872, 826, 746, 702, 639, 606, 576; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.86, (d, *J* = 8.6 Hz, 2H, *H*_a), 5.05 (dd, *J* = 10.3, 2.1 Hz, 1H, *H*₂), 3.82 (s, 3H, OCH₃), 2.68-2.52 (m, 2H, *H*₄), 2.20-2.10 (m, 1H, *H*₃), 2.16 (s, 3H, C(O)CH₃) 2.03-1.92 (m, 1H, *H*₃), 1.74 (s, 3H, C1(CH₃)) 1.73 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 158.0, 133.2, 129.3, 113.9, 79.1, 66.5, 55.3, 33.3, 31.5, 30.6, 30.4, 20.9 ppm; MS (CI⁺, NH₃) *m/z* 348, 346 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₅H₂₅NO₃⁷⁹Br [M + NH₄]⁺ 346.1018, found: 346.1017. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 7.6 min (major), 10.7 min (minor) – 92:8 e.r. (84% ee).

5.23 (-)-(S)-3-Bromo-5-(4-methoxyphenyl)-2-methylpentan-2-yl acetate [(S)-**32b**]



Using a modified procedure of Murai.⁷⁵ To a stirred solution of tertiary alcohol (*S*)-**8b** (200 mg, 0.70 mmol, 1 eq.) and acetic acid (40 μ L, 0.70 mmol 1 eq.) in CH₂Cl₂ (2 mL) was added trifluoroacetic anhydride (0.57 mL, 4.11 mmol, 6 eq.) and stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (20 mL) and extracted with CH₂Cl₂ (20 mL). The organic layer was washed with brine (20 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (5-20% Et₂O in pet. ether) to give bromoacetate (*S*)-**32b** (167 mg, 73%). A sample of (±)-**32b** (72 mg, 63%) was prepared from (±)-**8b** (100 mg, 0.35 mmol) by the same procedure over 1.5 h. HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 12.1 min, 13.7 min.

Colourless oil; [α]_D²⁴ -41.9 (*c* 2.1, CH₂Cl₂); *R*_f = 0.34 (10% EtOAc in pet. ether); IR ν_{max} 2951, 1734, 1612, 1512, 1465, 1368, 1300, 1245, 1177, 1124, 1036, 822, 607, 567 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.88 (d, *J* = 6.8 Hz, 2H, *H*_a), 4.58 (dd, *J* = 11.2, 2.0

Hz, 1H, *H*2), 3.82 (s, 3H, OCH₃), 3.01 (ddd, *J* = 13.9, 9.3, 4.5 Hz, 1H, *H*4), 2.65 (ddd, *J* = 13.9, 9.4, 7.3 Hz, 1H, *H*4), 2.18-2.06 (m, 1H, *H*3), 2.05-1.95 (m, 1H, *H*3), 2.02 (s, 3H, C(O)CH₃), 1.59 (s, 3H, C1(CH₃)), 1.57 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 158.1, 132.9, 129.4, 114.0, 83.2, 61.9, 55.3, 35.6, 33.6, 24.2, 23.1, 22.3 ppm; MS (CI⁺, NH₃) *m/z* 348, 346 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₅H₂₅NO₃⁷⁹Br [M + NH₄]⁺ 346.1018, found: 346.1019. HPLC (CHIRALCEL OD-H; 0.25% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 12.1 min (major), 13.6 min (minor) – 92:8 e.r. (84% ee).

5.24 Acetylation of tertiary alcohols using acetyl chloride, triethylamine and DMAP

To a stirred solution of tertiary alcohol (±)-**8b** (350 mg, 1.22 mmol, 1 eq.), DMAP (4.5 mg, 0.37 mmol, 0.3 eq.) and triethylamine (0.5 mL, 3.66 mmol, 3 eq.) in CH₂Cl₂ at 0°C was added acyl chloride (0.11 mL, 1.59 mmol, 1.3 eq.) and warmed to room temperature over 16 h. Acyl chloride (0.11 mL, 1.59 mmol, 1.3 eq.) and triethylamine (0.5 mL, 3.66 mmol, 3 eq.) were added and stirred at room temperature for 3 h. The reaction was quenched with water (25 mL), extracted with CH₂Cl₂ (2 × 25 mL), washed with an aqueous solution of 10% CuSO₄ (50 mL), brine (50 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-30% Et₂O in pet. ether) to give bromo bicycle **29** (67 mg, 0.25 mmol, 17%).

5.25 Acetylation of tertiary alcohols using catalytic NBS

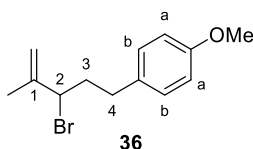
To a stirred solution of tertiary alcohol (±)-**8b** (90 mg, 0.31 mmol, 1 eq.) in CH₂Cl₂ at room temperature was added acetyl chloride (70 μL, 0.94 mmol, 3 eq.) and NBS (3 mg, 0.02 mmol, 5 mol%) and heated at reflux for 8 h. Acetyl chloride (70 μL, 0.94 mmol, 3 eq.) and NBS (3 mg, 0.02 mmol, 5 mol%) were then added and heated at reflux for 16 h. The reaction was quenched with a saturated aqueous solution of Na₂SO₃ (15 mL), extracted with CH₂Cl₂ (20 mL), washed with a saturated aqueous solution of NaHCO₃ (20 mL), brine (20 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-25% Et₂O in pet. ether) to give bromo bicycle **29** and allyl acetate **34** as a 2:1 mixture (50 mg, 32% yield of **29**, 21% yield of **34**).

5.26 Acetylation of tertiary alcohols using acetic anhydride, triethylamine and DMAP

To a stirred solution of tertiary alcohol (*S*)-**8b** (50 mg, 0.17 mmol, 1 eq.), triethylamine (0.45 mL, 3.26 mmol, 18.7 eq.) in CH₂Cl₂ at 0°C was added DMAP (2 mg, 0.02 mmol, 11 mol%) and acetic anhydride (0.42 mL, 4.46 mmol, 25 eq.) and warmed to room temperature over 16 h. The

reaction mixture was concentrated under reduced pressure and chromatographed (10-25% Et₂O in pet. ether) to give bromo bicycle **29** (17 mg, 0.06 mmol, 29% yield).

5.27 1-(3-Bromo-4-methylpent-4-en-1-yl)-4-methoxybenzene (36)



To a stirred solution of diol ($\pm$)-**56** (100 mg, 0.45 mmol, 1 eq.) in CH₂Cl₂ (1.5 mL) at room temperature was added CBr₄ (296 mg, 0.89 mmol, 2 eq.) and dropwise a solution of PPh₃ (246 mg, 0.94 mmol, 2.1 eq.) in CH₂Cl₂ (1 mL) and stirred for 24 h. To the reaction mixture was added CBr₄ (74 mg, 0.22 mmol, 0.5 eq.) and dropwise a solution of PPh₃ (62 mg, 0.22 mmol, 0.5 eq.) in CH₂Cl₂ (0.25 mL) and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and chromatographed (10-25% CH₂Cl₂ in pet. ether) to give allyl bromide **26** (59 mg, 49% yield).

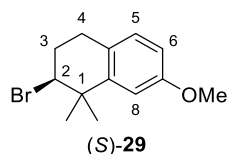
Colourless oil: R_f = 0.62 (40:60 CH₂Cl₂:PE); ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, J = 8.6 Hz, 2H) 6.88 (d, J = 8.6 Hz, 2H), 5.08 (s, 1H), 5.08 (s, 1H), 4.93 (s, 1H), 4.50 (dd, J = 8.1, 6.7 Hz, 1H), 3.82 (s, 3H), 2.80-2.58 (m, 2H), 2.40-2.22 (m, 1H) 2.20-2.10 (m, 2H), 2.22-2.00 (m, 2H), 1.89 (s, 3H) ppm. GCMS (CI⁺, NH₃) t_R = 20.5 min, m/z 288, 286 [M + NH₄]⁺.

To a stirred solution of diol ($\pm$)-**56** (50 mg, 0.22 mmol, 1 eq.) in CH₂Cl₂ (0.75 mL) at -10°C was added CBr₄ (89 mg, 0.27 mmol, 1.2 eq.) and dropwise a solution of PPh₃ (76 mg, 0.29 mmol, 1.3 eq.) in CH₂Cl₂ (0.5 mL) and allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and chromatographed (10-25% CH₂Cl₂ then 5-60% EtOAc in pet. ether) to give allyl bromide **26** (2.4 mg, 4% yield), ketone **16** (6 mg, 13% yield), bromohydrin **8a** (9 mg, 10% yield), bromohydrin **8b** (6.5 mg, 14% yield) and recovered starting material (17 mg, 34%).

To a stirred solution of bromohydrin ($\pm$)-**8a** (100 mg, 0.35 mmol, 1 eq.) in CH₂Cl₂ (1.5 mL) at -10°C was added CBr₄ (139 mg, 0.42 mmol, 1.2 eq.) and dropwise a solution of PPh₃ (118 mg, 0.45 mmol, 1.3 eq.) in CH₂Cl₂ (1 mL) and allowed to warm to room temperature and stirred for 16 h. To the reaction mixture was added CBr₄ (139 mg, 0.42 mmol, 1.2 eq.) and dropwise a solution of PPh₃ (118 mg, 0.45 mmol, 1.3 eq.) in CH₂Cl₂ (1 mL) and stirred for 72 h. The reaction mixture was concentrated under reduced pressure and chromatographed (10-25% CH₂Cl₂ then 5-25% EtOAc in pet. ether) to give allyl bromide **26** (8 mg, 8% yield), ketone **16** (28 mg, 39% yield),

recovered starting material (13 mg, 13% yield), bromohydrin **8b** (8 mg, 8% yield) and diol **56** (3 mg, 3% yield).

5.28 (-)-(S)-2-Bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene [(S)-**29**]



General procedure. To a stirred solution of substrate in CH₂Cl₂ at -14 °C was added a solution of triflic acid (5-30 mol%) in CH₂Cl₂. The reaction was allowed to warm to room temperature and stirred for 16 h or heated to reflux. The reaction was quenched with a saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-15% CH₂Cl₂ in pet. ether) to afford bicycle **29**.

To secondary alcohol (±)-**8a** (100 mg, 0.35 mmol) in CH₂Cl₂ (4 mL, 0.17 M) at -14 °C was added a solution of triflic acid (9.2 μL, 30 mol%) in CH₂Cl₂ (2 mL, 0.05 M) and stirred for 16 h at room temperature, then heated at reflux for 3 h. Work-up using the same method afforded first the desired product (53 mg, 57%), then ketone **16** (21 mg, 30%). Reaction was repeated with 10 mol% TfOH at reflux for 16 h to give (±)-**29** (32 mg, 34%) and with 5 mol% TfOH to give (±)-**29** (29 mg, 31%)

To tertiary alcohol (±)-**8b** (50 mg, 0.17 mmol) in CH₂Cl₂ (2 mL, 0.17 M) at -14 °C was added a solution of triflic acid (4.6 μL, 30 mol%) in CH₂Cl₂ (1 mL, 0.05 M) and stirred for 16 h at room temperature, then heated at reflux for 3 h. Work-up using the same method afforded (±)-**29** (32 mg, 67%).

To secondary tetrafluorobenzoate ester (±)-**31a** (100 mg, 0.22 mmol) in CH₂Cl₂ (4 mL, 0.078 M) at -14°C was added a solution of triflic acid (5.7 μL, 30 mol%) in CH₂Cl₂ (1.24 mL, 0.05 M) and stirred at room temperature for 16 h, then heated at reflux for 6 h. Work-up using the same method afforded the desired product (43 mg, 73%) and recovered starting material (6 mg, 6%). Reaction was repeated with 10 mol% TfOH at reflux for 16 h to give (±)-**29** (38 mg, 65%) and with 5 mol% TfOH to give (±)-**29** (9 mg, 15%). Reaction of (R)-**31a** with 30 mol% TfOH at reflux for 3 h gave (S)-**29** (47 mg 0.17 mmol, 84%). [α]_D²⁴ -5.9 (*c* 2.1, CH₂Cl₂). HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 5.1 min (major), 7.2 min (minor) – 91:9 e.r. (82% ee).

To tertiary tetrafluorobenzoate ester ($\pm$)-**31b** (100 mg, 0.22 mmol) in CH₂Cl₂ (4 mL, 0.078 M) at -14 °C was added a solution of triflic acid (5.7 μ L, 30 mol%) in CH₂Cl₂ (1.24 mL, 0.05 M) and stirred at room temperature for 16 h. Work-up using the same method afforded the desired product (29 mg, 51%). Reaction of (*S*)-**31b** with 30 mol% TfOH at reflux for 4 h gave (*S*)-**29** (38 mg 0.14 mmol, 67%) – 92:8 e.r. (84% ee).

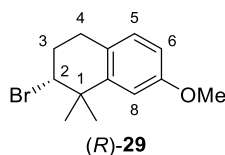
To secondary acetate ester (*R*)-**32a** (90 mg, 0.27 mmol) in CH₂Cl₂ (3 mL) at -14 °C was added a solution of triflic acid (30 mol%) in CH₂Cl₂ (1 mL) and heated at reflux for 3 h. Work-up using the same method afforded (*S*)-**29** (39 mg, 0.15 mmol 53%). HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 4.9 min (major), 6.5 min (minor) – 84:16 e.r. (68% ee).

To tertiary acetate (*S*)-**32b** (146 mg, 0.44 mmol) in CH₂Cl₂ (6.16 mL) at -14 °C was added a solution of triflic acid (30 mol%) in CH₂Cl₂ (3 mL) and stirred at room temperature for 5 h. Work-up using the same method afforded (*S*)-**29** and by-products as a 1:1.25 mixture (81 mg, 30% yield of (*S*)-**29**).

Pale yellow oil; *R*_f = 0.64 (40:60 CH₂Cl₂:PE); [α]_D²⁴ -5.9 (*c* 2.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 8.5 Hz, 1H, *H*5), 6.93 (d, *J* = 2.6 Hz, 1H, *H*6), 6.76 (dd, *J* = 8.5, 2.6 Hz, 1H, *H*8), 4.47 (dd, *J* = 9.2, 3.1 Hz, 1H, *H*2), 3.84 (s, 3H, OCH₃), 3.03 (ddd, *J* = 16.8, 6.0, 6.0 Hz, 1H, *H*4) 2.95-2.85 (m, 1H, *H*4), 2.52-2.33 (m, 2H, *H*3), 1.50 (s, 6H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 144.3, 129.8, 125.9, 112.3, 111.8, 64.8, 55.3, 39.9, 30.5, 30.1, 28.8, 28.4 ppm; MS (CI⁺, NH₃) *m/z* 288, 286 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₂₁NO⁷⁹Br [M + NH₄]⁺ 286.0807, found 286.0815. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 5.1 min (major), 7.2 min (minor) – 91:9 e.r. (82% ee).

A reference sample of ($\pm$)-bromide **29** was prepared by direct brominative cyclisation of alkene **1** using the method of Snyder and Treitler.⁴⁸ To a stirred solution of alkene **1** (100 mg, 0.53 mmol) in CH₃NO₂ (4 mL) at -25 °C was added quickly a solution of BDSB (289 mg, 0.53 mmol) in CH₃NO₂ (2 mL) and stirred for 15 min. The reaction was quenched with a 1:1 mixture of 5% aqueous NaHCO₃ and 5% aqueous Na₂SO₃ (20 mL) solution and stirred for 15 min before being poured into water (20 mL), extracted with CH₂Cl₂ (2 $\times$ 20 mL), dried over MgSO₄, concentrated under reduced pressure and chromatographed (pet. ether) to afford ($\pm$)-bromide **7** (88 mg, 63%) as a pale yellow oil. HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL / min) *t*_R = 5.2 min, 7.2 min.

5.29 (+)-(R)-2-Bromo-7-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene [(R)-29]



To a stirred solution of (*S*)-**31a** and (*R*)-**31b** (200 mg, 0.44 mmol) in CH₂Cl₂ (6 mL) at -14 °C was added a solution of triflic acid (11 μL, 0.13 mmol, 30 mol%) in CH₂Cl₂ (2.8 mL). The reaction was allowed to warm to room temperature and stirred for 7 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (2 × 25 mL), extracted with CH₂Cl₂ (20 mL), washed with brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-15% CH₂Cl₂ in pet. ether) to afford bicycle (*R*)-**29** (63 mg, 53%, 85% e.e.) as a pale yellow oil.

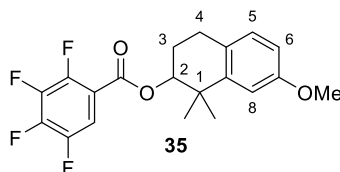
In order to improve the e.e. of (*R*)-**29** purification of tetrafluorobenzoates (*S*)-**31a** and (*R*)-**31b** is required. To remove allyl tetrafluorobenzoate **33** a stirred solution of the mixture (200 mg, 0.44 mmol) in CH₂Cl₂ (4 mL) was added *m*CPBA (74 mg, 0.43 mmol) and stirred at room temperature for 16 h. The reaction was quenched with a saturated aqueous solution of Na₂SO₃ (25 mL), extracted with CH₂Cl₂ (20 mL), washed with an aqueous solution of NaHCO₃ (25 mL), brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-25:75 Et₂O:PE) to afford tetrafluorobenzoates (*S*)-**31a** and (*R*)-**31b** (143 mg, 72%) as a white solid.

To a stirred solution of analytically pure tetrafluorobenzoates (*S*)-**31a** and (*R*)-**31b** (143 mg, 0.31 mmol) in CH₂Cl₂ (4.3 mL) at -14 °C was added a solution of triflic acid (8.2 μL, 0.09 mmol, 30 mol%) in CH₂Cl₂ (2 mL). The reaction was allowed to warm to room temperature and stirred for 2 h then heated at reflux for 2 h. The reaction was quenched with a saturated aqueous solution of NaHCO₃ (2 × 25 mL), extracted with CH₂Cl₂ (20 mL), washed with brine (25 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10:90-15:85 CH₂Cl₂:PE) to afford bicycle *ent*-**7** (70 mg, 84%, 96:4 e.r., 92% e.e.) as a colourless oil. [α]_D²⁴ +6.1 (*c* 1.1, CH₂Cl₂).

5.30 Mono-cyclisation in HFIP

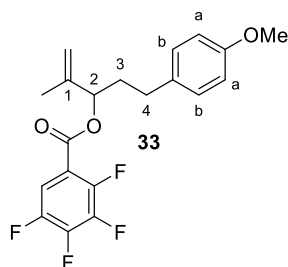
Secondary tetrafluorobenzoate ester ($\pm$)-**31a** (29 mg, 0.063 mmol, 1 eq.) was heated in HFIP (1 mL) at reflux over 16 h. The reaction mixture was quenched with a saturated aqueous solution NaHCO₃ (10 mL), extracted with EtOAc (10 mL), washed with water (10 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10% Et₂O in pet. ether) to afford a 3:2 mixture of bicycle **35** (9 mg, 39%) and allyl tetrafluorobenzoate ester **33** (6 mg, 26%).

5.31 (±)-7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl 2,3,4,5-tetrafluorobenzoate (35)



Colourless oil. $R_f = 0.45$ (10% EtOAc in pet. ether); ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.54 (m, 1H F_4BzH) 7.05 (d, $J = 8.5$ 1H, H_5), 6.90 (d, $J = 2.6$, 1H, H_6), 6.75 (dd, $J = 8.4$, 2.7, 1H, H_8), 5.37 (dd, $J = 8.0$, 3.3, 1H, H_2), 3.83 (s, 3H, OCH_3), 2.99-2.84 (m, 1H, H_4), 2.77-2.59 (m, 1H, H_4), 2.23-2.09 (m, 1H, H_3), 2.08-1.98 (m, 1H, H_3), 1.41 (s, 3H, $\text{C1}(\text{CH}_3)$), 1.40 (s, 3H, $\text{C1}(\text{CH}_3)$) ppm, GCMS (CI^+ , NH_3) $t_R = 23.9$ min, m/z 400 $[\text{M} + \text{NH}_4]^+$.

5.32 (±)-5-(4-Methoxyphenyl)-2-methylpent-1-en-3-yl 2,3,4,5-tetrafluorobenzoate (33)



$R_f = 0.45$ (10% EtOAc in pet. ether); ^1H NMR (400 MHz, CDCl_3) δ 7.64-7.54 (m, 1H F_4BzH) 7.12 (d, $J = 8.6$, 2H, H_b), 6.84 (d, $J = 8.6$, 2H, H_a), 5.47 (dd, $J = 7.2$, 6.0, 1H, H_2), 5.08 (2, 1H $\text{HC}=\text{C1}$), 5.03-5.01 (m, 1H, $\text{HC}=\text{C}$), 3.80 (s, 3H, OCH_3), 2.99-2.84 (m, 1H, H_4), 2.77-2.59 (m, 1H, H_4), 2.23-2.09 (m, 1H, H_3), 2.09-1.98 (m, 1H, H_3), 1.83 (s, 3H, $\text{C1}(\text{CH}_3)$) ppm. GCMS (CI^+ , NH_3) $t_R = 23.3$ min, m/z 400 $[\text{M} + \text{NH}_4]^+$.

5.33 Mono-cyclisation with ionic liquid

A stirred solution of tertiary tetrafluorobenzoate ester (±)-**31b** (100 mg, 0.22 mmol, 1 eq.) in 1-butyl-1-methylpyrrolidinium bis[(trifluoromethyl)sulfonyl]azanide (5 mL) was heated at 90°C for 4 h. The reaction was quenched with a saturated aqueous solution of NaHCO_3 (30 mL), extracted Et_2O (3×30 mL), washed with brine (30 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (0-15% Et_2O in pet. ether) to afford the desired cyclised product **29** (11 mg, 0.04 mmol, 19%) and allyl bromide **36** (3 mg, 0.01 mmol, 6%) as a 7:2 mixture.

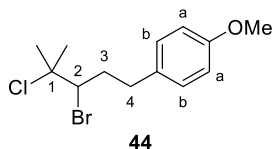
5.34 Mono-cyclisation with $\text{BF}_3 \cdot \text{OEt}_2$

To a stirred solution of tertiary tetrafluorobenzoate ester ($\pm$)-**31b** (100 mg, 0.22 mmol, 1 eq.) in CH_2Cl_2 (1 mL) at -40°C was added $\text{BF}_3 \cdot \text{OEt}_2$ (30 μL , 0.24 mmol, 1.1 eq.) and stirred for 30 mins. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (20 mL), extracted with CH_2Cl_2 (20 mL), washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a 4:1 mixture of starting material ($\pm$)-**31b** and allyl bromide ($\pm$)-**36**.

5.35 Mono-cyclisation with TiCl_4

To a stirred solution of tertiary tetrafluorobenzoate ester ($\pm$)-**31b** (100 mg, 0.22 mmol, 1 eq.) in CH_2Cl_2 (4 mL) at -78°C was added dropwise TiCl_4 (48 μL , 0.43 mmol, 2 eq.) and stirred at -78°C for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (10 mL), extracted with CH_2Cl_2 (10 mL), dried over Na_2SO_4 , passed through a silica plug, concentrated under reduced pressure and chromatographed (0-12% Et_2O in pet. ether) to give the desired cyclised product **29** (32 mg, 0.12 mmol, 55%) as a 4:1 mixture with chlorobromide **44** (8 mg, 0.03 mmol, 12%)

5.36 ($\pm$)-1-(3-Bromo-4-chloro-4-methylpentyl)-4-methoxybenzene (**44**)



R_f = 0.64 (40% CH_2Cl_2 in pet. ether); ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.17 (m, 2H, H_a), 6.90-6.86 (m, 2H, H_b), 4.03 (dd, J = 11.3, 1.6, 1H, H_2), 3.83 (s, 3H, OCH_3), 2.71 (dt, J = 13.6, 8.2, 2H, H_4), 2.66-2.56 (m, 1H, H_3), 2.09 (dddd, J = 14.6, 11.3, 8.4, 4.3, 1H, H_3), 1.79 (s, 3H, $\text{C1}(\text{CH}_3)$), 1.70 (s, 3H, $\text{C1}(\text{CH}_3)$) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 132.5, 129.6, 114.0, 71.9, 65.0, 36.12, 33.3, 33.0, 27.3 ppm; MS (CI^+) m/z 324, 322, $[\text{M} + \text{NH}_4]^+$.

5.37 Mono-cyclisation using Me_2AlCl

To a stirred solution of secondary tetrafluorobenzoate ester ($\pm$)-**31a** (100 mg, 0.22 mmol, 1 eq.) in CH_2Cl_2 (4 mL) at -78°C was added dropwise Me_2AlCl (0.24 mL, 1 M in hexane, 0.24 mmol, 1.1 eq.) and warmed to room temperature over 16 h. The reaction mixture was quenched with HCl (1 M, 10 mL) and extracted with CH_2Cl_2 (10 mL), washed with brine (20 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (10-20% CH_2Cl_2 in pet. ether) to give

the bromo bicycle **29** (19 mg, 0.07 mmol, 33%) as a 5:4 mixture with chlorobromide **44** (15 mg, 0.05 mmol, 23%)

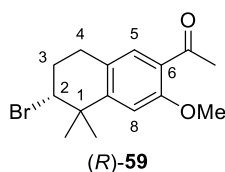
The reaction was repeated with tertiary tetrafluorobenzoate ester ($\pm$)-**31b** (100 mg, 0.22 mmol, 1 eq.) under the same conditions for 4 h to afford bromo cycle **29** (32 mg, 0.12 mmol, 55%) as a 10:1 mixture with chlorobromide **44** (4 mg, 0.01 mmol, 6%).

5.38 Mono-cyclisation with TMSOTf

To a stirred solution of tertiary tetrafluorobenzoate ester ($\pm$)-**31b** (100 mg, 0.22 mmol, 1 eq.) in CH_2Cl_2 (4 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise TMSOTf (43 μL , 0.24 mmol, 1.1 eq.) and stirred for 6 h at $-78\text{ }^\circ\text{C}$ and then room temperature for 16 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (10 mL), extracted with CH_2Cl_2 (10 mL), washed with a saturated aqueous solution of NaHCO_3 (20 mL), brine (20 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (5-20% CH_2Cl_2 in pet. ether) to give bromo bicycle **29** (26 mg, 0.10 mmol, 44%).

The reaction was repeated using tertiary acetate ester ($\pm$)-**32b** (114 mg, 0.35 mmol, 1 eq.) under the same conditions to afford the desired bromo bicycle **29** (40 mg, 0.15 mmol, 43%).

5.39 Mono-cyclisation with acetic acid and triflic anhydride

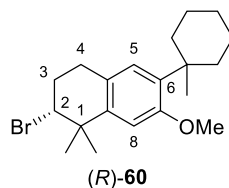


To a stirred solution of bromohydrins (*S*)-**8a** and (*R*)-**8b** containing *ca.* 9% allyl alcohol **14** (100 mg, 0.35 mmol, 1 eq.) in CH_2Cl_2 (1 mL) was added acetic acid (20 μL , 0.35 mmol, 1 eq.) and triflic anhydride (350 μL , 2.06 mmol, 6 eq.) and stirred at room temperature for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (20 mL) extracted with CH_2Cl_2 (20 mL), washed with a saturated aqueous solution of NaHCO_3 (20 mL), brine (20 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (10-30% EtOAc in pet. ether) to give the title product (62 mg, 57% yield).

White solid; R_f = 0.58 (20% EtOAc in pet. ether); IR ν_{max} 2975, 2847, 1661, 1601, 1561, 1494, 1455, 1404, 1334, 1260, 1242, 1232, 1185, 1103, 1039, 993, 912, 877, 865, 698, 635, 622 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.49 (s, 1H, *H*5), 6.91 (s, 1H, *H*8), 4.42 (dd, J = 8.8, 3.0 Hz, 1H, *H*2), 3.93 (s, 3H, OCH_3), 3.04 (dt, J = 17.0, 6.4 Hz, 1H, *H*4), 2.88 (dt, J = 17.0, 7.0 Hz, 1H, *H*4), 2.61

(s, 3H, COCH₃), 2.46 (dtd, *J* = 13.1, 6.5, 3.0 Hz, 1H, *H*3), 2.34 (dtd, *J* = 13.9, 8.3, 6.9 Hz, 1H, *H*3), 1.51 (s, 3H, C1CH₃), 1.49 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 199.4, 157.4, 149.1, 130.9, 126.4, 126.0, 109.5, 63.8, 55.6, 40.2, 31.8, 30.5, 29.6, 28.8, 27.7 ppm; MS (CI⁺, NH₃) *m/z* 313, 311 [M + H]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₅H₂₀O₂Br⁷⁹ 311.0647 [M + H]⁺, found: 311.0638.

5.40 (+)-(R)-2-Bromo-7-methoxy-1,1-dimethyl-6-(1-methylcyclohexyl)-1,2,3,4-tetrahydro naphthalene [(R)-60]



To a stirred solution of acetate (*S*)-**32a** (50 mg, 0.15 mmol, 1 eq., 96:4 e.r.) in CH₂Cl₂ (1 mL) was added a solution of 1-methyl-1-cyclohexene (18 μL, 0.15 mmol, 1 eq.) in CH₂Cl₂ (1 mL), cooled to -14°C, added a solution of triflic acid (4 μL, 0.05 mmol, 30 mol%) in CH₂Cl₂ (1 mL) and heated at reflux for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ (10 mL) extracted with CH₂Cl₂ (10 mL), washed with NaHCO₃ (10 mL), brine (10 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-25% CH₂Cl₂ in pet. ether) to give the title product (30 mg, 53%) and second bicycle (*R*)-**29** (14 mg, 34%).

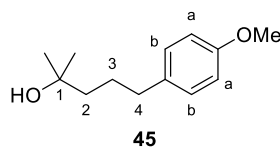
Colourless oil; [α]_D²⁴ +7.0 (*c* 0.4, CH₂Cl₂); *R_f* = 0.5 (10:90 CH₂Cl₂:pet. ether); ¹H NMR (400 MHz, CDCl₃) δ 6.92 (s, 1H), 6.81 (s, 1H), 4.44 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.82 (s, 3H), 2.97-2.82 (m, 2H), 2.48-2.33 (m, 2H), 2.05-1.95 (m, 2H), 1.78-1.68 (m, 2H), 1.63-1.45 (m, 6H), 1.47 (s, 3H), 1.45 (s, 3H), 1.28 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 141.0, 136.4, 127.7, 125.0, 110.1, 65.4, 55.2, 39.6, 37.6, 36.9, 30.7, 30.0, 29.3, 28.5, 26.7, 24.9, 22.8 ppm; MS (CI⁺, NH₃) *m/z* 384, 382 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₂₀H₃₃NO⁷⁹Br [M + NH₄]⁺ 382.1746, found 382.1752; HPLC (CHIRALCEL OD-H; 1% IPA in *n*-hexane; 1.0 mL/min) *t_R* = 5.1 min (minor), 7.2 min (major) – 94:6 e.r. (88% ee).

5.41 Friedel–Crafts alkylation of bicycle [(±)-29]

To a stirred solution of bicycle (±)-**29** (100 mg, 0.37 mmol, 1 eq.) and 1-methyl-1-cyclohexene (44 μL, 0.37 mmol, 1 eq.) in CH₂Cl₂ (5 mL) at -14°C was added a solution of triflic acid (10 μL, 0.11 mmol, 30 mol%) in CH₂Cl₂ (2.5 mL) and stirred at -14°C for 0.5 h, then warmed to room temperature and heated at reflux for 1 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ (20 mL), extracted with CH₂Cl₂ (20 mL), washed with brine (20

mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-20 % CH₂Cl₂ in pet. ether) to give (R)-**60** (54 mg, 40% yield).

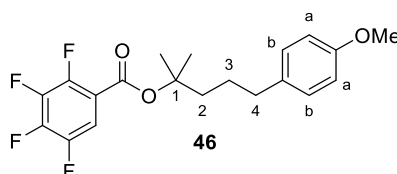
5.42 5-(4-Methoxyphenyl)-2-methylpentan-2-ol (**45**)



According to a modified procedure of Sarandeses *et al.*,¹⁶⁴ to a stirred solution of alkene **1** (250 mg, 1.32 mmol, 1 eq) in THF:H₂O (20 mL 1:1) was added mercury(II) trifluoroacetate (618 mg, 1.45 mmol, 1.1 eq). The mixture was stirred at room temperature for 1.5 h and aqueous NaOH solution (20 mL, 3 M) was added, followed by a solution of NaBH₄ (55 mg, 1.45 mmol, 1.1 eq) in aqueous NaOH (2 mL, 3 M). After stirring for a further 0.5 h brine (20 mL) was added and the mixture extracted with Et₂O (3 × 30 mL), dried, concentrated under reduced pressure and chromatographed (20-50% EtOAc in pet. ether) to yield the title product¹⁶⁵ (177 mg, 65%).

Colourless oil; *R*_f = 0.26 (20% EtOAc in pet. ether); IR *v*_{max} 3600-3100, 2967, 2937, 1613, 1584, 1512, 1465, 1376, 1300, 1245, 1177, 1150, 1123, 1038, 910, 830, 775, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.86 (d, *J* = 8.6 Hz, 2H, *H*_a), 3.82 (s, 3H, OCH₃), 2.60 (t, *J* = 7.6 Hz, 2H, *H*₄) 1.75-1.64 (m, 2H, *H*₃) 1.60-1.50 (m, 2H, *H*₂) 1.23 (s, 6H C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.6, 129.3, 113.7, 70.9, 55.3, 43.5, 35.4, 29.3, 26.5 ppm; MS (CI⁺, NH₃) *m/z* 226 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₂₄NO₂ [M + NH₄]⁺ 226.1807, found: 226.1808.

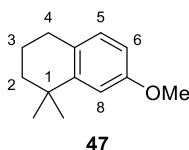
5.43 5-(4-Methoxyphenyl)-2-methylpentan-2-yl 2,3,4,5-tetrafluorobenzoate (**46**)



Using the method of Steglich,¹¹⁶ to a stirred solution of tertiary alcohol **45** (85 mg, 0.41 mmol, 1 eq) in CH₂Cl₂ (2 mL) was added 2,3,4,5-tetrafluorobenzoic acid (159 mg, 0.82 mmol, 2 eq), DMAP (15 mg, 0.12 mmol, 30 mol%) and DCC (253 mg, 1.23 mmol, 3 eq). After 16 h the reaction mixture was diluted with Et₂O, filtered through a silica plug, concentrated under reduced pressure and chromatographed (5-15% Et₂O in pet. ether) to afford the title product (131 mg, 83%)

Colourless oil; $R_f = 0.52$ (10% Et₂O in pet. ether); IR $\nu_{\max}$ 2937, 1716, 1627, 1613, 1584, 1525, 1512, 1483, 1367, 1286, 1243, 1197, 1177, 1120, 1098, 1032, 920, 884, 831, 793, 713, 702, 625, 563, 538, 527 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.54 (dddd, $J = 10.5, 8.4, 6.0, 2.5$ Hz, 1H, F₄BzH), 7.12 (d, $J = 8.6$ Hz, 2H, H_b), 6.86 (d, $J = 8.6$ Hz, 2H, H_a), 3.82 (s, 3H, OCH₃), 2.62 (t, $J = 7.6$ Hz, 2H, H₄), 1.98-1.90 (m, 2H, H₃), 1.78-1.62 (m, 2H, H₂), 1.59 (s, 6H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 161.0, 157.8, 147.9 (dddd, $J = 262, 11, 4, 2$ Hz), 146.4 (dddd, $J = 249, 11, 4, 2$ Hz), 143.1 (dddd, $J = 261, 16, 12, 3$ Hz), 141.2 (dddd, $J = 248, 17, 12, 4$ Hz), 134.1, 129.1, 116.6, 113.8, 113.1 (d, $J = 20$ Hz), 85.7, 55.2, 40.6, 35.1, 26.0, 25.9 ppm; MS (CI⁺, NH₃) m/z 402 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₀H₂₄NO₃F₄ [M + NH₄]⁺ 402.1692, found: 402.1707.

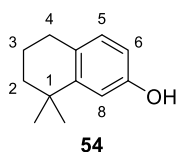
5.44 7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (47)



According to the general procedure for bromo bicycle **29**, tertiary alcohol **45** (80 mg, 0.39 mmol) in CH₂Cl₂ (4.4 mL, 0.09 M) at -14 °C was added a solution of triflic acid (10.2 μ L, 30 mol%) in CH₂Cl₂ (2.2 mL, 0.05 M) and heated at reflux for 3 h. Work-up using the same method afforded first the desired product¹⁶⁶ (64 mg, 88%). Using the same procedure, tertiary tetrafluorobenzoate ester **46** (120 mg, 0.31 mmol) in CH₂Cl₂ (6.1 mL, 0.05 M) at -14 °C was added a solution of triflic acid (8.3 μ L, 30 mol%) in CH₂Cl₂ (1.8 mL, 0.05 M) and stirred at room temperature for 16 h. Work-up using the same method afforded first the desired product (51 mg, 85%).

Pale yellow oil; $R_f = 0.43$ (20% CH₂Cl₂ in pet. ether); IR $\nu_{\max}$ 2928, 2864, 1610, 1572, 1503, 1463, 1287, 1236, 1188, 1163, 1076, 1047, 903, 872, 705 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.04 (d, $J = 8.4$ Hz, 1H, H₅), 6.95 (d, $J = 2.7$ Hz, 1H, H₆), 6.74 (dd, $J = 8.4, 2.7$ Hz, H₈), 3.86 (s, 3H, OCH₃), 2.78 (t, $J = 6.3$ Hz, 2H, H₄), 1.90-1.82 (m, 2H, H₃), 1.75-1.70 (m, 2H, H₂), 1.36 (s, 6H, C1(CH₃)₂) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 147.1, 129.9, 128.4, 112.2, 111.0, 55.2, 39.3, 34.1, 31.9, 30.0, 19.9 ppm; MS (CI⁺, NH₃) m/z 191, [M + H]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₃H₁₉O [M + H]⁺ 191.1436, found 191.1437.

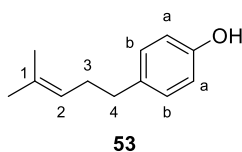
5.45 1,1-Dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (54)



According to the procedure by Braddock *et al.*,¹⁶⁷ to a stirred solution of methyl ether **1** (100 mg, 0.53 mmol, 1 eq.) in CH₂Cl₂ (3 mL) at -78°C and protected from light was added dropwise boron tribromide (0.8 mL, 1M solution in CH₂Cl₂, 0.79 mmol, 1.5 eq) and after 5 minutes was allowed to warm to room temperature overnight. The reaction mixture was quenched with methanol, concentrated under reduced pressure and chromatographed (0-20% EtOAc in pet. ether) to yield the title product (93 mg, 100%).

White solid, m.p. = 98-100°C, lit.¹⁶⁸ 103.5-104.5°C; *R_f* = 0.29 (20% EtOAc in pet. ether); IR ν_{max} 3251, 2959, 2926, 2864, 1621, 1579, 1486, 1456, 1296, 1232, 1217, 1164, 1136, 916, 870, 813, 740, 713, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.96 (d, *J* = 8.2 Hz, 1H, *H*5), 6.87 (d, *J* = 2.6 Hz, 1H, *H*6), 6.65 (dd, *J* = 8.3, 2.7 Hz, 1H, *H*8), 5.63 (s, 1H, OH), 2.74 (t, *J* = 6.4 Hz, 2H, *H*4), 1.87-1.80 (m, 2H, *H*3), 1.71-1.67 (m, 2H, *H*2), 1.30 (s, 6H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 153.5, 147.4, 130.1, 128.4, 113.2, 112.9, 39.2, 34.0, 31.8, 29.9, 19.9 ppm; MS (CI⁺) *m/z* 176 [M]⁺; HRMS (CI⁺) calc'd for C₁₂H₁₆O [M]⁺ 176.1201, found: 176.1199.

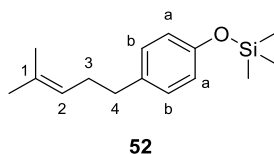
5.46 4-(4-Methylpent-3-en-1-yl)phenol (**53**)



To a stirred solution of methyl ether **1** (500 mg, 2.63 mmol, 1 eq.) in CH₂Cl₂ (20 mL) at -78°C and protected from light was added 2,6-di-*tert*-butylpyridine (2.0 mL, 8.92 mmol, 3.4 eq.), dropwise boron tribromide (2.9 mL, 1M solution in CH₂Cl₂, 2.89 mmol, 1.1 eq.) and after 5 minutes was allowed to warm to room temperature overnight. The reaction mixture was quenched with methanol, concentrated under reduced pressure and chromatographed (10-25% Et₂O in pet. ether) to yield the title product (463 mg, 100%).

Colourless oil; *R_f* = 0.32 (30% Et₂O in pet. ether); IR ν_{max} 3600-3050, 2967, 2925, 2857, 1614, 1513, 1444, 1375, 1230, 1172, 1109, 1017, 988, 825 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, *J* = 8.4 Hz, 2H, *H*b), 6.78 (d, *J* = 8.5 Hz, 2H, *H*a), 5.16 (t, 7.1 Hz, 1H, *H*2), 4.65 (br. s, 1H, OH), 2.59 (t, *J* = 7.4 Hz, 2H, *H*4), 2.32-2.24 (m, 2H, *H*3), 1.72 (s, 3H, C1(CH₃)), 1.59 (s, 3H, C1(CH₃)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 153.5, 134.7, 132.1, 129.5, 123.8, 115.1, 35.2, 30.3, 25.7, 17.7 ppm; MS (CI⁺) *m/z* 194 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₂H₂₀NO [M + NH₄]⁺ 194.1545, found: 194.1546.

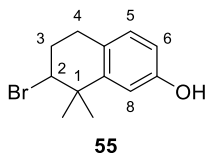
5.47 1-[(Trimethylsilyl)oxy]-4-(4-methylpent-3-en-1-yl)benzene (52)



According to a modified procedure by Holmes *et al.*,¹⁶⁹ to a stirred solution of phenol **53** (100 mg, 0.57 mmol, 1 eq.) in pyridine (1.15 mL, 14.27 mmol, 25 eq.) was added dropwise chlorotrimethylsilane (0.23 mL, 1.81 mmol, 3 eq.) and stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (10 mL), washed with water (15 mL), 10% aqueous CuSO₄ solution (15 mL), water (20 mL), brine (20 mL), dried and concentrated under reduced pressure to give the title product (111 mg, 78%)

Colourless oil; $R_f = 0.27$ (20% Et₂O in pet. ether); IR $\nu_{\max}$ 2962, 2923, 2856, 1609, 1509, 1446.5, 1377, 1249, 1167, 1102, 1016, 911, 840, 733, 549, 540, 529 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, $J = 8.4$ Hz, 2H, *H*_b), 6.78 (d, $J = 8.4$ Hz, 2H, *H*_a), 5.19 (t, $J = 7.1$ Hz, 1H, *H*₂), 2.59 (t, $J = 7.4$ Hz, 2H, *H*₄), 2.28 (dt, $J = 7.4, 7.4$ Hz, 2H, *H*₃), 1.71 (s, 3H, C1(CH₃)), 1.57 (s, 3H, C1(CH₃)), 0.28 (s, 9H, SiCH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 153.1, 135.3, 132.0, 129.3, 123.8, 119.7, 35.3, 30.2, 25.7, 17.6, 0.2 ppm; MS (CI⁺) m/z 266 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₅H₂₅OSi [M + H]⁺ 249.1675, found: 249.1673.

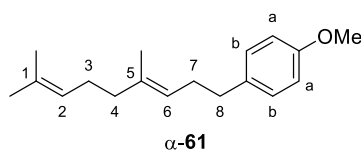
5.48 (±)-2-Bromo-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-7-ol (55)



According to the method of Snyder and Treitler,⁴⁸ to a stirred solution of **53** (100 mg, 0.57 mmol) in CH₃NO₂ (3 mL) at -14°C was added quickly a solution of BDSB (312 mg, 0.57 mmol) in CH₃NO₂ (2 mL) and stirred for 10 min at -14°C, then 45 min at room temperature. The reaction was quenched with a 1:1 mixture of 5% aqueous NaHCO₃ and 5% aqueous Na₂SO₃ (20 mL) solution and stirred for 15 min before being poured into water (20 mL), extracted with CH₂Cl₂ (2 × 20 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0 to 25% Et₂O in pet. ether) to afford cyclic bromide **55** (104 mg, 72%). Reaction was repeated with silyl ether **52** under the same conditions to yield (76 mg, 52 yield over 2 steps)

White solid; $R_f = 0.29$ (20% Et₂O in pet. ether); IR $\nu_{\max}$ 3600-3100, 2970, 1611, 1584, 1502,, 1444, 1289, 1232, 1198, 1161, 948, 905, 881, 864, 732, 704, 691, 568 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.96 (d, $J = 8.1$ Hz, 1H, *H*5), 6.86 (d, $J = 2.6$ Hz, 1H, *H*6), 6.68 (dd, $J = 8.2, 2.6$ Hz, 1H, *H*8), 5.44 (br. s. 1H, OH), 4.44 (dd, $J = 9.2, 3.1$ Hz, 1H, *H*2), 3.04-2.95 (m, 1H, *H*4), 2.92-2.83 (m, 1H, *H*4), 2.45 (dddd, $J = 13.3, 10.1, 6.6, 3.5$ Hz, 1H, *H*3), 2.40-2.31 (m, 1H, *H*3), 1.45 (s, 6H, C1(CH₃)₂) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 153.8, 144.5, 130.0, 125.9, 113.8, 113.3, 64.8, 39.7, 30.4, 30.0, 28.7, 28.3 ppm; MS (CI⁺, NH₃) m/z 272, 274 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₂H₁₉NO⁷⁹Br [M + NH₄]⁺ 272.0650, found 272.0652.

5.49 (E)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methoxybenzene (α -61)

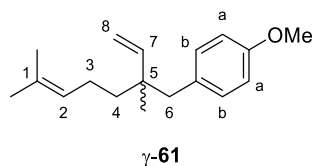


Prepared according to a modified procedure of Snyder and Treitler.⁴⁸ To a stirred solution of geraniol (23 mL, 133 mmol) and pyridine (32 mL, 398 mmol) in diethyl ether (80 mL) at -15°C was added diethyl chlorophosphate (29 mL, 199 mmol) and the mixture was allowed to warm to room temperature over 5 h. The reaction mixture was quenched with 1 M aqueous HCl solution (250 mL), extracted with ethyl acetate (2 × 250 mL), washed with saturated aqueous NaHCO₃ solution (2 × 250 mL), brine (250 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give geranyl diethyl phosphate as a colourless oil (46 g) which was used directly without purification. To magnesium turnings (7.6 g, 318 mmol) stirred in anhydrous THF (200 mL) was added a portion of 4-methoxybenzyl chloride (2.0 mL, 15 mmol), where the reaction could be started by gentle heating. Subsequently a solution of 4-methoxybenzyl chloride (19.5 mL, 144 mmol) in anhydrous THF (200 mL) was added dropwise over 1 h at such a rate as to maintain reflux. After complete addition, reflux was continued for 2 h. The reaction mixture was cooled to -40°C and added dropwise *via* cannula to a stirred solution of geranyl diethyl phosphate (23 g, 80 mmol) in anhydrous THF (250 mL) at -40°C and allowed to warm to room temperature over 16 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (300 mL), extracted with diethyl ether (2 × 300 mL), washed with saturated aqueous NaHCO₃ solution (300 mL), brine (300 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-25% CH₂Cl₂ in pet. ether) to afford the title compound **61** as a mixture of constitutional isomers with branched diene α -**61** in 19:1 ratio (12.7 g, 49 mmol, 61%) as a colourless oil. A second run on the same scale afforded the title product α -**61** as a mixture of constitutional isomers with γ -**61** in ratio 35:1 (14.0 g, 54 mmol, 68%). The purity of **61** could be increased to >98% by fractional distillation

of the combined diene mixtures (27 g, 26:1 α : γ -**61**). Distillation (200 °C, 0.003 mmHg) collecting the fraction at 70 °C was enriched in branched isomer γ -**61** and the distillation residue was linear diene α -**61** (8.2 g, 32 mmol).

Colourless oil, R_f = 0.35 (15% CH₂Cl₂ in pet. ether); IR $\nu_{\max}$ 2919, 2854, 1612, 1584 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, J = 8.5 Hz, 2H, *H*_b), 6.88 (d, J = 8.6 Hz, 2H, *H*_a), 5.24 (t, J = 7.1 Hz, 1H, *H*₆), 5.19-5.13 (m, 1H, *H*₂), 3.82 (s, 3H, OCH₃), 2.60 (t, J = 7.8 Hz, 2H, *H*₈), 2.34 (q, J = 8.5 Hz, 2H, *H*₇), 2.17-2.02 (m, 4H, *H*₃ and *H*₄), 1.75 (s, 3H, C₅CH₃), 1.67 (s, 3H, C₁CH₃), 1.62 (s, 3H, C₁CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 135.7, 134.6, 131.3, 129.4, 124.4, 123.7, 113.7, 55.3, 39.8, 35.3, 30.2, 26.8, 25.7, 17.7, 16.0 ppm; MS (CI⁺) m/z 276 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₈H₂₇O [M + H]⁺ 259.2062. Found: 259.2050. An analytically pure sample of branched diene γ -**61** could be obtained after silver nitrate-doped silica gel chromatography (0:1-3:7 Et₂O:PE).

5.50 (±)-(E)-1-(2,6-Dimethyl-2-vinylhept-5-enyl)-4-methoxybenzene (γ -**61**)



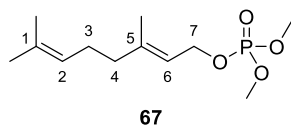
Colourless oil, R_f = 0.35 (15% CH₂Cl₂ in pet. ether); IR $\nu_{\max}$ 2920, 2854, 1612 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, J = 8.6 Hz, 2H, *H*_b), 6.79 (d, J = 8.7 Hz, 2H, *H*_a), 5.76 (dd, J = 17.6, 10.8 Hz, 1H, *H*₇), 5.10-5.05 (m, 1H, *H*₂), 5.00 (dd, J = 10.8, 1.4 Hz, 1H, *H*₆), 4.82 (dd, J = 17.6, 1.4 Hz, 1H, *H*₆), 3.79 (s, 3H, OCH₃), 2.54 (m, 2H, *H*₆), 1.91 (q, J = 8.0 Hz, 2H, *H*₄), 1.67 (s, 3H, C₅CH₃), 1.58 (s, 3H, C₁CH₃), 1.37-1.25 (m, 2H, *H*₃), 0.94 (s, 3H, C₁CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 146.6, 131.6, 131.0, 130.6, 125.0, 112.9, 112.1, 55.2, 47.2, 40.8, 40.4, 25.7, 23.1, 21.9, 17.6 ppm; MS (CI⁺) m/z 276 [M + NH₄]⁺; HRMS (CI⁺) calc'd for C₁₈H₃₀NO [M + NH₄]⁺ 276.2327. Found: 276.2328.

5.51 Li₂CuCl₄ catalysed Grignard alkylation of geranyl bromide

Prepared according to a modified procedure by Steglich and Lang.¹⁷⁰ To magnesium turnings (22 mg, 0.92 mmol, 1.5 eq.) stirred in anhydrous THF (4 mL) was added a portion of 4-methoxybenzyl chloride (10 μ L, 0.07 mmol, 0.12 eq.), where the reaction was started by heating at 50 °C. Subsequently a solution of 4-methoxybenzyl chloride (90 μ L, 0.67 mmol, 1.08 eq.) in anhydrous THF (4 mL) was added dropwise over 30 min at such a rate as to maintain reflux. After complete addition, reflux was continued for 3 h. The reaction mixture was cooled to -20 °C and

added dropwise *via* cannula to a stirred solution of Li_2CuCl_4 (0.25 mL, 0.1 M in THF, 40 mol%) and stirred for 10 minutes. A solution of geranyl bromide (0.12 mL, 0.62 mmol, 1 eq.) in THF (2 mL) was added dropwise and stirred at -20°C for 1.5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL), extracted with Et_2O (10 mL) and washed with NH_4OH (20 mL), brine (20 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (0-30% Et_2O in pet. ether) to give polyene **61** (105 mg, 0.41 mmol, 66% yield) as a 2:1 mixture of constitutional isomers α : γ -**61**.

5.52 (E)-3,7-Dimethylocta-2,6-dien-1-yl dimethyl phosphate (67)



To a stirred solution of geraniol (1 mL, 5.77 mmol, 1 eq.) and pyridine (1.4 mL, 17.32 mmol, 3 eq.) in Et_2O (3 mL) at -15°C was added dropwise dimethyl chlorophosphate (0.95 mL, 8.66 mmol, 1.5 eq.) and warmed to room temperature over 3 h. The reaction mixture was quenched with a 1 M aqueous solution of HCl , extracted with EtOAc (2×30 mL), washed with a saturated aqueous solution of NaHCO_3 (2×50 mL), brine (50 mL), concentrated under reduced pressure and chromatographed (40-100% EtOAc in pet. ether) to give the title product (430 mg, 1.64 mmol, 28% yield).

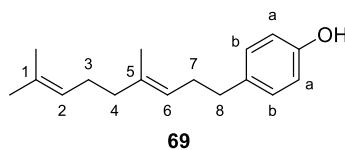
Colourless oil, $R_f = 0.25$ (50% EtOAc in pet. ether); IR ν_{max} 2958, 2920, 2855, 1667, 1449, 1380, 1267, 1187, 1037, 1007, 847, 752 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.39 (t, $J = 7.1$ Hz, 1H, H_6), 5.09-5.02 (m, 1H, H_2), 4.56 (ap. t, $J = 7.8$ Hz, 2H, H_7) 3.75 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.12-2.00 (m, 4 H, H_3 and H_4), 1.69 (s, 3H, C_5CH_3), 1.66 (s, 3H, C_1CH_3), 1.58 (s, 3H, C_1CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 143.0, 131.9, 123.6, 118.7 (d, $J = 6.3$ Hz), 64.3 (d, $J = 5.7$ Hz), 54.1 (d, $J = 6.3$ Hz), 39.5, 26.2, 25.6, 17.6, 16.4 ppm; ^{31}P NMR (162 MHz, CDCl_3) δ 1.9-1.4 (m, 1P) ppm; MS (ES^+) m/z 285 $[\text{M} + \text{Na}]^+$; HRMS (ES^+) calc'd for $\text{C}_{12}\text{H}_{23}\text{O}_4\text{NaP}$ $[\text{M} + \text{Na}]^+$ 285.1232. Found: 285.1228.

5.53 Hydroboration-oxidation of **61**

Carried out according to the procedure by Denmark and co-workers¹³⁶ To a stirred solution of a 3:1 mixture of α : γ -**61** (100 mg, 0.39 mmol, 1 eq.) in THF (1 mL) was added BH_3 (1.2 mL, 1 M in THF, 3 eq.) and heated at reflux for 3h. The reaction mixture was cooled to 0°C and H_2O (0.2 mL), NaBO_3 (350 mg, 3.49 mmol, 9 eq.) and NaOH (140 mg, 3.49 mmol, 9 eq.) added and heated at 50°C for 4 h. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc ($3 \times$

20 mL), washed with brine (50 mL), dried over Na₂SO₄, concentrated under reduced pressure to give a mixture of constitutional isomers α and γ -**61** in a ratio 4.2:1.

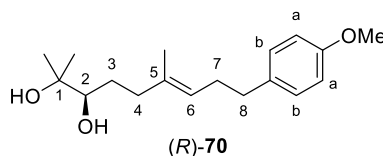
5.54 4-[(*E*)-4,8-Dimethylnona-3,7-dien-1-yl]phenol (**69**)



Prepared according to the procedure by Ishihara and co-workers.¹³⁷ To a stirred solution of NaH (60% in mineral oil, 140 mg, 3.50 mmol, 4.5 eq.) in DMF (2.3 mL) at 0°C was added dropwise over a period of 5 minutes a solution of ethanethiol (0.23 mL, 3.10 mmol, 4 eq.) in DMF (4.6 mL) and stirred at room temperature for 1 h. To this mixture was added dropwise at room temperature a solution of a 3:1 mixture of α : γ -**61** (200 mg, 0.78 mmol, 1 eq.) in DMF (2.3 mL) and stirred at 80°C for 16 h, and reflux for 4 h. The reaction mixture was cooled to 0°C and acidified with a 1 M aqueous solution of HCl, extracted with Et₂O (2 $\times$ 25 mL), washed with brine (50 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-30% Et₂O in pet. ether) to give the title product **69** (178 mg, 0.73 mmol, 94% yield) as a 3:1 mixture of α : γ -**69**.

Colourless oil, R_f = 0.23 (30% Et₂O in pet. ether); ¹H NMR (400 MHz, CDCl₃) δ 7.09 (d, J = 8.4 Hz, 2H, *H*_b), 6.78 (d, J = 8.4 Hz, 2H, *H*_a), 5.78 (dd, J = 17.6, 10.8 Hz, 0.38H, CH=CH₃ γ -**69**), 5.23-5.17 (m, 1H, *H*₆), 5.15-5.09 (m, 1H, *H*₂), 5.03 (dd, J = 10.8, 1.3 Hz, 0.38H, CH=CH₂), 4.84 (dd, J = 17.6, 1.3 Hz, 0.38 Hz, CH=CH₂), 4.55 (br. s, 1H, OH) 2.63-2.55 (m, 2H, *H*₈), 2.29 (q, J = 7.4 Hz, 2H, *H*₇) 2.13-1.90 (m, 4H, *H*₃ and *H*₄), 1.72 (s, 3H, C5CH₃), 1.64 (s, 3H, C1CH₃), 1.58 (s, 3H, C1CH₃) ppm.

5.55 (+)-(*R,E*)-9-(4-Methoxyphenyl)-2,6-dimethylnon-6-ene-2,3-diol [(*R*)-**70**]

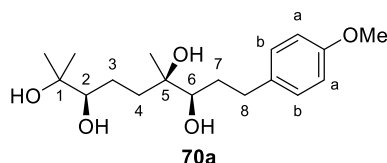


According to the method of Sharpless,¹²⁷ to a stirred solution of AD-mix β (22.3 g, 1.4 gmmol⁻¹) and methanesulfonamide (1.5 g, 16 mmol) in water (40 mL) and *tert*-butanol (40 mL) at 0°C was added alkene **61** (4.1 g, 16 mmol). The reaction mixture was stirred vigorously for 16 h, quenched with saturated aqueous sodium sulfite solution (50 mL), extracted with EtOAc (2 $\times$ 100 mL), washed with brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50-60% EtOAc in pet. ether) to afford first unreacted diene **61** (1.64 g, 6.3

mmol, 40%), the title product (*R*)-**70** (1.16 g, 4.3 mmol, 25%, 42% based on recovered starting material) as a colourless oil, and tetraol **70a** (1.27 g, 3.9 mmol, 25%) as a white solid.

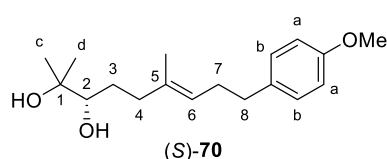
Colourless oil, $R_f = 0.42$ (50% EtOAc in pet. ether); $[\alpha]_D^{24} = +12.3$ (c 1.9, CH_2Cl_2); IR ν_{max} 3600-3100, 2931, 2858 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.13 (d, $J = 8.6$ Hz, 2H, *Hb*), 6.85 (d, $J = 8.6$ Hz, 2H, *Ha*), 5.26 (br t, $J = 7.1$ Hz, 1H, *H6*), 3.81 (s, 3H, OCH_3), 3.32 (dd, $J = 10.5, 2.0$ Hz, 1H, *H2*), 2.63 (t, $J = 7.6$ Hz, 2H, *H8*), 2.38-2.19 (m, 3H, *H7* and C1OH), 2.15-2.01 (m, 3H, *H3* and C2OH), 1.64-1.55 (m, 1H, *H4*) 1.60 (s, 3H, C5CH_3), 1.44 (m, 1H, *H4*), 1.21 (s, 3H, C1CH_3), 1.18 (s, 3H, C1CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 135.5, 134.4, 129.4, 124.5, 113.7, 78.1, 73.0, 55.3, 36.7, 35.1, 30.1, 29.6, 26.4, 23.2, 15.9 ppm; MS (CI^+ , NH_3) m/z 310 $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+ , NH_3) calc'd for $\text{C}_{18}\text{H}_{32}\text{NO}_3$ $[\text{M} + \text{NH}_4]^+$ 310.2382. Found: 310.2384; HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) $t_R = 16.2$ min (major), 18.2 min (minor) - e.r. 99:1.

5.56 (+)-(3*R*,6*R*,7*R*)-2,6-Dimethyl-9-(4-methoxyphenyl)nonane-2,3,6,7-tetraol (**70a**)



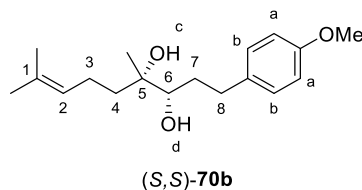
White solid; m.p. 130-131 °C; $R_f = 0.28$ (50% EtOH in pet. ether.); $[\alpha]_D^{24} = +20.0$ (c 1.0, EtOH); IR ν_{max} 3600-3100, 2972, 2952 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.16 (d, $J = 8.4$ Hz, 2H, *Hb*), 6.86 (d, $J = 8.5$ Hz, 2H, *Ha*), 3.81 (s, 3H, OCH_3), 3.41 (d, $J = 9.6$ Hz, 1H, *H6*), 3.30 (d, $J = 9.6$ Hz, 1H, *H2*), 3.29 (br s, 2H, OH), 2.90 (ddd, $J = 13.8, 8.8, 4.9$ Hz, 1H, *H8*), 2.65 (dt, $J = 13.7, 8.2$ Hz, 1H, *H8*), 2.53 (br s, 1H, OH), 2.20 (br s, 1H, OH), 1.81-1.56 (m, 5H, *H3*, *H4*, *H7*), 1.48-1.37 (m, 1H, *H7*), 1.21 (s, 3H, C5CH_3), 1.17 (s, 3H, C1CH_3), 1.13 (s, 3H, C1CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 134.2, 129.4, 113.9, 78.9, 74.6, 73.2, 55.3, 50.7, 35.6, 33.6, 31.9, 26.5, 25.0, 23.3, 20.6 ppm; MS (CI^+ , NH_3) m/z 344 $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+ , NH_3) calc'd for $\text{C}_{18}\text{H}_{31}\text{O}_5$ $[\text{M} + \text{H}]^+$ 327.2171. Found: 327.2164.

5.57 (-)-(S,*E*)-9-(4-Methoxyphenyl)-2,6-dimethylnon-6-ene-2,3-diol [(S)-**70**]



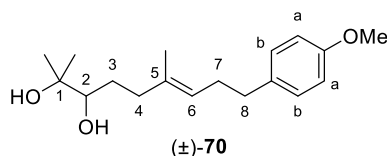
In a run using diene **61** (100mg, 0.39 mmol) and AD-mix α , afforded first was unreacted diene **61** (65 mg, 0.25 mmol, 65% yield), regioisomer (*S,S*)-**70b** (18 mg, 0.06 mmol, 16% yield) and the title product (*S*)-**70** (21 mg, 0.07 mmol, 19%, 54% based on recovered starting material) as a colourless oil: $[\alpha]_D^{24} = -5.9$ (c 1.0, CH_2Cl_2); HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) $t_R = 15.9$ min (minor), 17.1 min (major) – e.r. 6:94.

5.58 (-)-(3*S*,4*S*)-1-(4-Methoxyphenyl)-4,8-dimethylnon-7-ene-3,4-diol [(*S,S*)-**70b**]



Colourless oil, $R_f = 0.46$ (50% EtOAc in pet. ether); $[\alpha]_D^{24} = -18.0$ (c 0.8, CH_2Cl_2); IR ν_{max} 3600-3100, 2927, 2857, 1612, 1511, 1455, 1376, 1300, 1244, 1177, 1074, 1036, 936, 822 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.17 (d, $J = 8.5$ Hz, 2H, *H*_b), 6.87 (d, $J = 8.5$ Hz, 2H, *H*_a), 5.13 (t, $J = 7.0$ Hz, 1H, *H*₂), 3.82 (s, 3H, OCH_3), 3.47 (dd, $J = 10.3, 2.2$ Hz, 1H, *H*₆), 2.90 (ddd, $J = 14.2, 9.3, 5.3$ Hz, 1H, *H*₈), 2.65 (ddd, $J = 13.9, 9.1, 7.2$ Hz, 1H, *H*₈), 2.25-2.10 (br. s, 1H, C6OH), 2.10-1.99 (m, 2H, *H*₃), 1.80- 1.60 (m, 2H, *H*₇), 1.71 (s, 3H, C1CH_3), 1.62 (s, 3H, C1CH_3), 1.59-1.43 (m, 2H, *H*₄), 1.29 (br. s, 1H, C5OH), 1.14 (s, 3H, C5CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 134.1, 132.2, 129.4, 124.2, 113.9, 110.1, 75.1, 55.3, 38.8, 33.5, 32.0, 25.7, 21.9, 21.0, 17.7 ppm; MS (CI^+ , NH_3) m/z 310 $[\text{M} + \text{NH}_4]^+$; HRMS (CI^+ , NH_3) calc'd for $\text{C}_{18}\text{H}_{32}\text{NO}_3$ $[\text{M} + \text{NH}_4]^+$ 310.2382. Found: 310.2378.

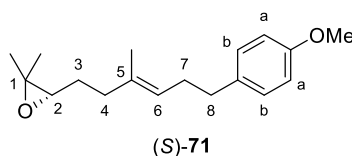
5.59 ($\pm$)-(E)-9-(4-Methoxyphenyl)-2,6-dimethylnon-6-ene-2,3-diol [($\pm$)-**70**]



A reference sample of ($\pm$)-diol **70** was prepared following a modified procedure of Warren.¹²⁹ To a solution of potassium ferricyanide (383 mg, 1.16 mmol), potassium carbonate (161 mg, 1.16 mmol), $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (4 mg, 0.012 mmol), quinuclidine (1 mg, 0.012 mmol) and methanesulfonamide (37 mg, 0.39 mmol) in water (2.5 mL) and *tert*-butanol (2.5 mL) at 0°C was added olefin **1** (100 mg, 0.39 mmol) and stirred vigorously for 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium sulfite (10 mL), extracted with EtOAc (2

× 20 mL), washed with brine (40 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (50-60% EtOAc in pet. ether) to afford (±)-diol **3** (21 mg, 19%) as a colourless oil. HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 16.5 min, 17.8 min.

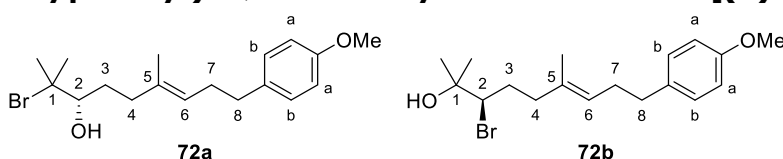
5.60 (-)-(S,E)-3-[-6-(4-Methoxyphenyl)-3-methylhex-3-enyl]-2,2-dimethyloxirane [(S)-71]



Using a modified procedure of Corey,¹²⁶ to a stirred solution of (R)-diol **70** (840 mg, 2.88 mmol) and pyridine (0.46 mL, 5.75 mmol) in CH₂Cl₂ (15 mL) at 0°C was added methanesulfonyl chloride (0.29 mL, 3.72 mmol). After 0.5 h the mixture was allowed to warm to room temperature and stirred for 3 h. Additional pyridine (1.38 mL 17.7 mmol) was added and the reaction mixture stirred for 16 h. The reaction mixture was poured into a suspension of K₂CO₃ (6.63 g, 48 mmol) in methanol (25 mL), stirred for 6 h, concentrated under reduced pressure, diluted with water (50 mL), extracted with EtOAc (2 × 50 mL), washed with 10% aqueous CuSO₄ solution (100 mL), brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (5-20% EtOAc in pet. ether) to afford the title product (S)-**71** (565 mg, 83%).

Colourless oil; *R*_f = 0.34 (10% EtOAc in pet. ether); [α]_D²⁴ -2.5 (*c* 1.6, CH₂Cl₂); IR ν_{max} 2958, 2925, 2835, 1612, 1586 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.85 (d, *J* = 8.6 Hz, 2H, *H*_a), 5.26 (tq, *J* = 5.8, 1.5 Hz, 1H, *H*₆), 3.81 (s, 3H, OCH₃), 2.72 (app. t, *J* = 6.3 Hz, 1H, *H*), 2.62 (t, *J* = 7.5 Hz, 2H), 2.32 (app. q, *J* = 7.6 Hz, 2H), 2.24-2.06 (m, 2H), 1.78-1.62 (m, 2H), 1.61 (s, 3H, C5CH₃) 1.33 (s, 3H, C1CH₃) 1.29 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.8, 134.3, 129.3, 124.3, 113.7, 64.1, 58.3, 55.2, 36.3, 35.1, 30.2, 27.5, 24.9, 18.8, 16.0 ppm; MS (CI⁺, NH₃) *m/z* 292 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₈H₂₇O₂ [M + H]⁺ 275.2011, found 275.2011.

5.61 (-)-(S,E)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-ol [(S)-72a] and (+)-(R,E)-3-bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-ol [(R)-72b]



Following the method of Couladouros and Vidali,⁷⁶ to a solution of (*S*)-epoxide **71** (200 mg, 0.73 mmol) in *N*-methyl-2-pyrrolidone (0.22 mL) was added LiBr (99 mg, 0.95 mmol) and PPTS (183 mg, 0.73 mmol) and stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (15 mL), extracted with EtOAc (2 × 15 mL), washed with brine (30 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-20% EtOAc in pet. ether) to yield first (*E*)-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-one (10 mg, 5%) as a colourless oil, second bromohydrin (*S*)-**72a** (66 mg, 25%) as a colourless oil, and third, bromohydrin (*R*)-**72b** (119 mg, 46%) as a colourless oil.

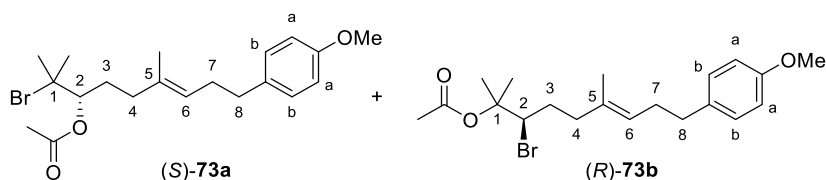
(*E*)-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-one: *R*_f = 0.45 (10% EtOAc in pet. ether); IR $\nu_{\max}$ 2966, 2936, 1710, 1612, 1512, 1456, 1300, 1244, 1177, 1036, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, *J* = 8.5 Hz, 2H, *H*_b), 6.84 (d, *J* = 8.6 Hz, 2H, *H*_b), 5.20 (t, *J* = 7.0 Hz, 1H, *H*₆), 3.81 (s, 3H, OCH₃), 2.68-2.52 (m, 5H, *H*₁, *H*₃, *H*₈), 2.32-2.22 (m, 4H, *H*₄, *H*₇), 1.57 (s, 3H, C5CH₃), 1.12 (s, 3H, C1CH₃), 1.10 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 214.5, 157.7, 134.6, 134.3, 129.3, 124.1, 113.6, 55.3, 40.9, 39.1, 35.1, 33.5, 30.2, 18.3, 16.1, 14.2 ppm; MS (CI⁺, NH₃) *m/z* 292 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₈H₂₇O₂ [M + H]⁺ 275.2006, found 275.2000.

Bromohydrin (*S*)-**72a**: *R*_f = 0.32 (10% EtOAc in pet. ether); [α]_D²⁴ -10.6 (c 1.3, CH₂Cl₂); IR $\nu_{\max}$ 3600-3200, 2958, 2926, 2855, 2835, 1612 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.86 (d, *J* = 8.6 Hz, 2H, *H*_a), 5.27 (tq, *J* = 6.8, 1.4 Hz, 1H, *H*₆), 3.82 (s, 3H, OCH₃), 3.40 (dd, *J* = 10.1, 3.0 Hz, 1H, *H*₂), 2.63 (t, *J* = 7.5 Hz 2H, *H*₈), 2.37-2.25 (m, 3H, OH, *H*₇), 2.17-2.05 (m, 2H, *H*₃), 1.82 (s, 3H, C5CH₃), 1.81-1.72 (m, 1H, *H*₄), 1.75 (s, 3H, C1CH₃), 1.59 (s, 3H, C1CH₃), 1.49 (dddd, *J* = 14.0, 10.3, 8.8, 5.2 Hz, 1H, *H*₄) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 135.1, 134.4, 129.4, 124.6, 113.7, 79.0, 75.4, 55.3, 36.4, 35.1, 31.1, 30.1 (×2), 28.9, 16.0 ppm; MS (CI⁺, NH₃) *m/z* 374, 372 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₈H₃₁NO₂⁷⁹Br [M + NH₄]⁺ 372.1538, found 372.1538.

Bromohydrin (*R*)-**72b**: *R*_f = 0.24 (10% EtOAc in pet. ether); [α]_D²⁴ +35.1 (c 1.3, CH₂Cl₂); IR $\nu_{\max}$ 3600-3250, 2925, 2854, 1612 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, *J* = 8.6 Hz, 2H, *H*_b), 6.86 (d, *J* = 8.6 Hz, 2H, *H*_a), 5.29 (t, *J* = 7.3 Hz, 1H, *H*₆), 3.95 (dd, *J* = 11.6, 1.9 Hz, 1H, *H*₂), 3.82 (s, 3H, OCH₃), 2.63 (td, *J* = 7.4, 3.4 Hz, 2H, *H*₈), 2.39-2.27 (m, 3H, OH, *H*₇), 2.24 (s, 1H, *H*₃), 2.15 (dt, *J* = 14.9, 8.2 Hz, 1H, *H*₃), 1.97 (dtd, *J* = 16.2, 8.0, 1.8 Hz, 1H, *H*₄), 1.85-1.74 (m, 1H, *H*₄), 1.56 (s, 3H, C5CH₃), 1.354 (s, 3H, C1CH₃), 1.347 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.3, 133.7, 129.4, 125.5, 113.7, 72.5, 70.8, 55.3, 38.2, 35.1, 31.8, 30.2, 26.6, 25.9

15.8 ppm; MS (CI^+ , NH_3) m/z 374, 372 [$\text{M} + \text{NH}_4$] $^+$; HRMS (CI^+ , NH_3) calc'd for $\text{C}_{18}\text{H}_{31}\text{NO}_2^{79}\text{Br}$ [$\text{M} + \text{NH}_4$] $^+$ 372.1538, found 372.1540.

5.62 (-)-(S,E)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-yl acetate [(S)-74a] and (+)-(R,E)-3-bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-yl acetate [(R)-73b]

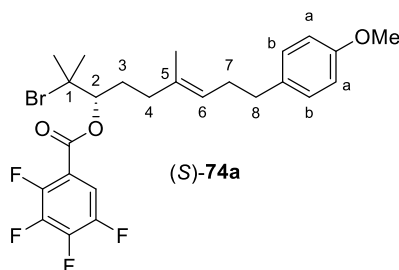


To a stirred solution a 1:1 mixture of (*S*)-**72a** and (*R*)-**72b** (250 mg, 0.70 mmol, 1 eq.) and acetic acid (40 μL , 0.70 mmol, 1 eq.) in dichloromethane (2.5 mL) was added trifluoroacetic anhydride (0.58 mL, 4.15 mmol, 5.9 eq.) and stirred at room temperature for 3 h. The reaction mixture was quenched by a saturated aqueous solution of NaHCO_3 (25 mL), extracted with CH_2Cl_2 (2×25 mL), washed with brine (50 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (0-30% Et_2O in pet. ether) to give the title products, (*S*)-**73a** and (*R*)-**73b** in a ratio of 1.0 :1.2 (126 mg, 0.32 mmol, 45% yield).

Bromoacetate (*S*)-**73a**: R_f = 0.37 (30% Et_2O in pet. ether); IR ν_{max} 2930, 2854, 1736, 1612, 1511, 1457, 1441, 1368, 1237, 1176, 1113, 1036, 819, 605, 560 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.15 (dd, J = 8.5 Hz, 2H, H_b), 6.86 (d, J = 8.6 Hz, 2H, H_a), 5.23 (t, J = 7.1 Hz, 1H, H_6), 4.98 (dd, J = 10.3, 1.8 Hz, 1H, H_2), 3.82 (s, 3H, OCH_3), 2.67-2.58 (m, 2H, H_8), 2.40-2.27 (m, 2H, H_7), 2.16 (s, 3H, $(\text{C}=\text{O})\text{CH}_3$), 1.76 (s, 3H, C1CH_3), 1.75 (s, 3H, C1CH_3) 1.60 (s, 3H, C5CH_3) ppm; MS (CI^+ , NH_3) m/z 416, 414 [$\text{M} + \text{NH}_4$] $^+$; HRMS (CI^+ , NH_3) calc'd for $\text{C}_{20}\text{H}_{33}\text{NO}_3^{79}\text{Br}$ 414.1644 [$\text{M} + \text{NH}_4$] $^+$, found 414.1655.

Bromoacetate (*R*)-**73b**: R_f = 0.37 (30% Et_2O in pet. ether); IR ν_{max} 2934, 1735, 1612, 1584, 1512, 1463, 1370, 1300, 1242, 1177, 1112, 1035, 953, 827 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.14 (d, J = 8.5 Hz, 2H, H_b), 6.85 (d, J = 8.6 Hz, 2H, H_a), 5.28 (t, J = 6.8 Hz, 1H, H_6), 4.53 (dd, J = 11.2, 1.8 Hz, 1H, H_2), 3.81 (s, 3H, OCH_3), 2.63 (t, J = 7.7 Hz, 2H, H_8), 2.39-2.25 (m, 3H, H_3 , H_7), 2.16-2.07 (m, 1H, H_3), 2.04 (s, 3H, $(\text{C}=\text{O})\text{CH}_3$), 1.97-1.86 (m, 1H, H_4), 1.81-1.72 (m, 1H, H_4), 1.61 (s, 3H, C5CH_3), 1.58 (s, 3H, C1CH_3), 1.57 (br. s, 3H, C1CH_3) ppm; MS (CI^+ , NH_3) m/z 416, 414 [$\text{M} + \text{NH}_4$] $^+$; HRMS (CI^+ , NH_3) calc'd for $\text{C}_{20}\text{H}_{33}\text{NO}_3^{79}\text{Br}$ 414.1644 [$\text{M} + \text{NH}_4$] $^+$, found 414.1655.

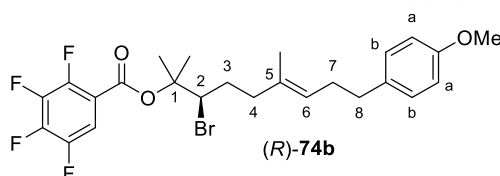
5.63 (-)-(S,E)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-yl 2,3,4,5-tetrafluorobenzoate [(S)-74a]



Using the method of Steglich,¹¹⁶ to a stirred solution of secondary alcohol (S)-72a (380 mg, 1.07 mmol) in CH₂Cl₂ (7.5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (228 mg, 1.18 mmol), DMAP (39 mg, 0.321 mmol, 30 mol%) and DCC (287 mg, 1.39 mmol). After 4 h the reaction mixture was filtered through a silica plug eluting with Et₂O, concentrated under reduced pressure and chromatographed (0-15% Et₂O in pet. ether) to afford bromo tetrafluorobenzoate (S)-74a (520 mg, 92%).

Colourless oil; *R_f* = 0.34 (5% EtOAc in pet. ether); [α]_D²⁴ -22.0 (*c* 1.1, CH₂Cl₂); IR $\nu_{\max}$ 2935, 2861, 2362, 2344, 1729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dddd, *J* = 10.3, 8.3, 6.0, 2.4 Hz, 1H, F₄BzH), 7.13 (d, *J* = 8.5 Hz, 2H, *H*_b), 6.85 (d, *J* = 8.6 Hz, 2H, *H*_a), 5.27 (d, *J* = 9.9 Hz 1H, *H*₂), 5.22 (t, *J* = 7.0 Hz, 1H, *H*₆), 3.82 (s, 3H, OCH₃), 2.61 (app. t, *J* = 7.7 Hz, 2H, *H*₈), 2.37-2.19 (m, 2H, *H*₇), 2.10-2.03 (m, 3H, *H*₃ and *H*₄), 1.99-1.85 (m, 1H, *H*₄), 1.83 (s, 3H, C1CH₃), 1.82 (s, 3H, C1CH₃), 1.58 (s, 3H, C5CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 161.5, 157.7, 148.0 (dddd, *J* = 262, 11, 3, 1 Hz), 146.6 (dddd, *J* = 249, 10, 4, 2 Hz), 143.6 (dddd, *J* = 262, 17, 13, 3 Hz), 141.4 (dddd, *J* = 255, 17, 12, 3 Hz), 134.3, 134.0, 129.4, 125.1, 114.7 (m), 113.7, 113.4 (dd, *J* = 21, 3 Hz), 81.5, 65.8, 55.2, 36.0, 35.0, 30.44, 30.35, 30.15, 29.3, 15.9 ppm; ¹⁹F NMR (377 MHz, CDCl₃) δ -153.1 (t, *J* = 20 Hz, 1F), -147.0 (m, 1F), -137.6 (m, 1F), -133.6 (m, 1F) ppm; MS (CI⁺, NH₃) *m/z* 548, 546 [M + NH₄]⁺; HRMS (EI⁺) calc'd for C₂₅H₂₇O₃⁷⁹BrF₄ [M]⁺ 530.1080, found 530.1080.

5.64 (+)-(R,E)-3-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-yl 2,3,4,5-tetrafluorobenzoate [(R)-74b]

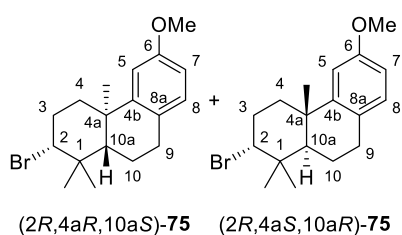


Using the method of Steglich,¹¹⁶ to a stirred solution of tertiary alcohol 5b (350 mg, 0.99 mmol) in CH₂Cl₂ (7.5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (383 mg, 1.97 mmol), DMAP (36 mg, 0.30 mmol, 30 mol%) and DCC (610 mg, 2.96 mmol). After 16 h further 2,3,4,5-

tetrafluorobenzoic acid (191 mg, 0.98 mmol), DMAP (36 mg, 0.30 mmol, 30 mol%) and DCC (305 mg, 1.48 mmol) was added and stirred for 5 h, passed through a plug of silica and chromatographed (0-40% CH₂Cl₂ in pet. ether) to afford tetrafluorobenzoate ester **6b** (316 mg, 60%).

Colourless oil; *R_f* = 0.30 (5% EtOAc in pet. ether); [α]_D²⁴ +14.4 (*c* 1.4, CH₂Cl₂); IR ν_{max} 2931, 2858, 2362, 1719 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.66-7.56 (m, 1H, F₄BzH), 7.15 (d, *J* = 8.6 Hz, 2H, *Hb*), 6.85 (d, *J* = 8.6 Hz, 2H, *Ha*), 5.34 (t, 6.80 Hz, 1H, *H6*), 4.54 (dd, *J* = 11.5, 1.9 Hz, 1H, *H2*), 3.81 (s, 3H, OCH₃), 2.66 (t, *J* = 7.6 Hz, 2H, *H8*), 2.44-2.26 (m, 3H, *H7* and *H3*) 2.21 (dt, *J* = 13.8, 8.0 Hz, 1H, *H3*), 2.09-2.00 (m, 1H, *H4*) 1.94-1.85 (m, 1H, *H4*) 1.79 (s, 3H, C1CH₃), 1.76 (s, 3H, C1CH₃), 1.60 (s, 3H, C5CH₃) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 160.5, 157.7, 147.8 (dddd, *J* = 262, 11, 4, 2 Hz), 146.4 (dddd, *J* = 249, 10, 4, 2 Hz), 143.4 (dddd, *J* = 262, 17, 13, 3 Hz), 141.3 (dddd, *J* = 255, 17, 12, 3 Hz), 134.3, 133.6, 129.3, 125.7, 116.0 (m), 113.6, 113.2 (dd, *J* = 21, 2 Hz), 86.2, 61.6, 55.2, 37.8, 35.0, 31.5, 30.2, 24.1, 23.3, 15.8 ppm; ¹⁹F NMR (377 MHz, CDCl₃) δ -153.5 (t, *J* = 20 Hz, 1F), -147.7 (tt, *J* = 19, 8 Hz, 1F), -138.0 (dt, *J* = 22, 12 Hz, 1F), -134.5 (m, 1F) ppm; MS (CI⁺, NH₃) *m/z* 548, 546 [M + NH₄]⁺; HRMS (EI⁺) calc'd for C₂₅H₂₇NO₃⁷⁹BrF₄ [M]⁺ 530.1080, found 530.1082.

5.65 (-)-(2*R*,4*aR*,10*aS*)- and (-)-(2*R*,4*aS*,10*aR*)-2-Bromo-6-methoxy-1,1,4*a*-trimethyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrenes (**75**) from Me₂Al(OTf) cyclisation of bromotetrafluorobenzoates (*S*)-**74a** and (*R*)-**74b**



Cyclisation of tertiary bromide (*S*)-**74a**: To a stirred solution of Me₃Al (2M in hexanes, 0.25 mL, 0.5 mmol) in CH₂Cl₂ (2 mL) at -78°C was added a solution of trifluoromethanesulfonic acid (43 μ L, 0.5 mmol) in CH₂Cl₂ (4 mL) and stirred at -78°C for 0.5 h and 0°C for 0.5 h. The white suspension of Me₂AlOTf was re-cooled to -78 °C and a solution of bromo tetrafluorobenzoate (*S*)-**74a** (50 mg, 0.292 mmol) in CH₂Cl₂ (2 mL) was added dropwise at -78°C. The reaction was allowed to warm to room temperature over 16 h, quenched with aqueous HCl solution (1M, 10 mL), extracted with CH₂Cl₂ (2 $\times$ 10 mL), washed with saturated aqueous NaHCO₃ solution (10 mL), brine (10 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-30% CH₂Cl₂ in pet. ether) to afford first monocycles **77** as an inseparable

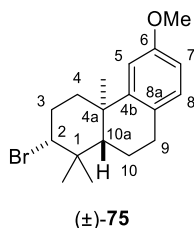
mixture of at least two endocyclic and two exocyclic alkenes (6 mg, 19%) as a colourless oil, $R_f = 0.39$ (20% CH_2Cl_2 in pet. ether), and second bromides (2R,4aR,10aS)-**75** and (2R,4aS,10aR)-**75** as an inseparable mixture of diastereoisomers (d.r. 3:1, 8 mg, 25%) as a white solid: m.p. 92-93 °C; $R_f = 0.64$ (40% CH_2Cl_2 in pet. ether). The major diastereoisomer (2R,4aR,10aS)-**75** was identical to that produced in the BDSB mediated cyclisation of polyene **61**, and the minor diastereoisomer (2R,4aS,10aR)-**75** was identified in the mixture by its characteristic ^1H NMR signal at 4.42 (1H, CHBr) ppm as a broad singlet.

(2R,4aS,10aR)-**75** [as 1:3 mixture with bromide (2R,4aR,10aS)-**75**]: ^1H NMR (400 MHz; CDCl_3) δ 7.01 (d, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 2.8$ Hz, 1H), 6.71 (dd, $J = 8.3, 2.8$ Hz, 1H), 4.42 (br s, 1H), 3.81 (s, 3H), 2.94-2.75 (m, 2H), 2.42-2.38 (m, 1H), 2.21-2.06 (m, 3H), 1.89 (dd, $J = 12.4, 2.5$ Hz, 1H), 1.82-1.67 (m, 2H), 1.22 (s, 3H), 1.12 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3) 157.8, 150.5, 129.8, 127.1, 111.0, 110.0, 69.1, 55.3, 43.5, 38.4, 37.8, 33.4, 32.9, 29.1, 28.7, 25.5, 22.2, 18.5 ppm; GCMS (EI^+) m/z 337, 335 (M-H) $^+$.

The diastereoisomers were inseparable by standard column chromatography on silica gel, but could be separated by preparative HPLC (Prep Si; *n*-hexane; 5 mL/min) $t_R = 145$ min [(2R,4aS,10aR)-**75**], 165 min [(2R,4aR,10aS)-**75**]. Bromide (2R,4aR,10aS)-**75**: $[\alpha]_D^{24} -100$ (c 0.04, CH_2Cl_2). The concentration of this solution was very dilute and so the absolute magnitude of this measurement is liable to large error; HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 4.7$ min (minor), 5.4 min (major), e.r. 98:2. Bromide (2R,4aS,10aR)-**2**: $[\alpha]_D^{24} -43$ (c 0.01, CH_2Cl_2). The concentration of this solution was very dilute and so the absolute magnitude of this measurement is liable to large error; HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 4.7$ min (major), 6.1 min (minor), e.r. 98:2.

Cyclisation of secondary bromide **6b** (135 mg, 0.254 mmol) was conducted as above using 2.5 equivalents of Me_2AlOTf to afford first monocycles **77** as an inseparable mixture of at least two endocyclic and two exocyclic alkenes (21 mg, 25%) as a colourless oil, $R_f = 0.39$ (1:4 CH_2Cl_2 :PE), and second bromides (2R,4aR,10aS)-**75** and (2R,4aS,10aR)-**75** as an inseparable mixture of diastereoisomers (d.r. 3:1, 30 mg, 35%) as a white solid. The diastereomers were separated by preparative HPLC (Prep Si; *n*-hexane; 5 mL/min) $t_R = 145$ min and [(2R,4aS,10aR)-**75**] and 165 min [(2R,4aR,10aS)-**75**]. Bromide (2R,4aR,10aS)-**75**: HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 4.7$ min (minor), 5.4 min (major), e.r. 98:2. Bromide (2R,4aS,10aR)-**75**: HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) $t_R = 4.7$ min (major), 6.1 min (minor), e.r. 98:2.

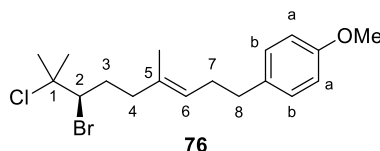
5.66 (±)-(2R*,4aR*,10aS*)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene [(±)-(75)] by direct brominative cyclisation of polyene 61 with BDSB



Prepared by direct brominative cyclisation of diene **61** using the method of Snyder and Treitler.⁴⁸ To a stirred solution of alkene **61** (100 mg, 0.39 mmol) in CH₃NO₂ (6 mL) at -25°C was added quickly a solution of BDSB (213 mg, 0.39 mmol) in CH₃NO₂ (2 mL) and stirred for 5 min. The reaction mixture was quenched with a 1:1 mixture of 5% aqueous NaHCO₃ and 5% aqueous Na₂SO₃ solution (20 mL) and stirred for 15 min before being poured into water (20 mL), extracted with CH₂Cl₂ (2 × 20 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (pet. ether) to afford bromide (±)-**75** (88 mg, 68%).

White crystalline solid ; m.p. 86-87 °C. R_f = 0.64 (40% CH₂Cl₂ in pet. ether); IR ν_{max} 2933, 2851, 1611 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, *J* = 8.3 Hz, 1H, *H*8), 6.77 (d, *J* = 2.8 Hz, 1H, *H*5), 6.71 (dd, *J* = 8.3, 2.8 Hz, 1H, *H*7), 4.07 (dd, *J* = 12.5, 4.1 Hz, 1H, *H*2), 3.80 (s, 3H, OCH₃), 2.98-2.76 (m, 2H, *H*9) 2.48-2.23 (m, 3H, *H*10 and *H*3), 1.98 (ddt, *J* = 13.4, 7.0, 2.2 Hz, 1H, *H*3), 1.88-1.75 (m, 1H, *H*4), 1.69-1.56 (m, 1H, *H*4), 1.48 (dd, *J* = 12.1, 2.2 Hz, 1H, *H*10a), 1.27 (s, 3H, C4aCH₃), 1.18 (s, 3H, C1CH₃), 1.09 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 150.0, 129.9, 127.0, 111.2, 110.2, 68.8, 55.3, 51.3, 40.1, 39.9, 38.1, 31.6, 30.6, 30.0, 24.8, 20.8, 18.3 ppm; MS (CI⁺, NH₃) *m/z* 354, 356 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₈H₂₉NO⁷⁹Br [M + NH₄]⁺ 354.1433, found 354.1433. HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 4.9 min, 5.7 min.

5.67 1-[(7*R*,*E*)-7-Bromo-8-chloro-4,8-dimethylnon-3-en-1-yl]-4-methoxybenzene (76)



To a stirred solution of a 1.0:1.4 mixture of bromotetrafluorobenzoates (*S*)-**74a** and (*R*)-**74b** (131 mg, 0.25 mmol, 1 eq) in CH₂Cl₂ at -78°C was added dropwise Me₂AlCl (0.27 mL, 1 M in

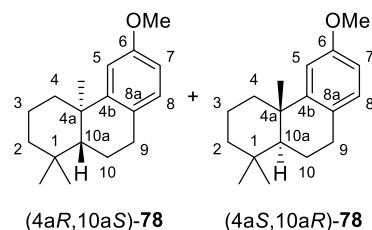
hexanes, 0.27 mmol, 1.1 eq.) and slowly warmed to room temperature over 6 h. The reaction mixture was quenched with a 1 M aqueous solution of HCl (25 mL), extracted with CH₂Cl₂ (2 × 25 mL), washed with H₂O (40 mL), brine (40 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-50% CH₂Cl₂ in pet. ether) to give first the title product **76** (24 mg, 0.06 mmol, 26% yield) and then tricycle **75** (9 mg, 0.02 mmol, 11% yield) as a 3:1 mixture of diastereomers.

Colourless oil; *R_f* = 0.32 (40% CH₂Cl₂ in pet. ether); IR ν_{max} 2931, 2854, 1612, 1511, 1454, 1441, 1387, 1371, 1300, 1244, 1177, 1103, 1038, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.5 Hz, 2H, *Hb*), 6.86 (d, *J* = 8.5 Hz, 2H, *Ha*), 5.31 (t, *J* = 7.2 Hz, 1H, *H6*), 3.98 (dd, *J* = 11.2, 1.2 Hz, 1H, *H2*), 3.82 (s, 3H, OCH₃), 2.67-2.60 (m, 2H, *H8*), 2.47-2.25 (m, 2H, *H7*), 2.23-2.12 (m, 1H, *H3*), 1.87-1.81 (m, 1H, *H3*), 1.80 (s, 3H, C5CH₃), 1.73 (td, *J* = 8.1, 1.2 Hz, 2H, *H4*), 1.70 (s, 3H, C1CH₃), 1.59 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 134.3, 133.7, 129.3, 125.6, 113.7, 72.1, 65.0, 55.3, 37.7, 35.1, 33.1 32.3, 30.1, 27.1, 15.7 ppm; MS (CI⁺, NH₃) *m/z* 392, 390 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₈H₃₀NO⁷⁹Br [M + NH₄]⁺ 390.1199, found 390.1200.

5.68 Me₂AlCl cyclisation of bromoacetates (*S*)-**73a** and (*R*)-**73b**

To a stirred solution of a 1.0:1.2 mixture of bromoacetates (*S*)-**73a** and (*R*)-**73b** (44 mg, 0.11 mmol, 1 eq) in CH₂Cl₂ at -78°C was added dropwise Me₂AlCl (0.12 mL, 1 M in hexanes, 0.12 mmol, 1.1 eq.) and slowly warmed to room temperature over 16 h. The reaction mixture cooled to -78°C and added dropwise was Me₂AlCl (0.12 mL, 1 M in hexanes, 0.12 mmol, 1.1 eq.) and warmed to room temperature over 4 h. The reaction mixture was quenched with a 1 M aqueous solution of HCl (25 mL), extracted with CH₂Cl₂ (2 × 25 mL), washed with H₂O (40 mL), brine (40 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-60% CH₂Cl₂ in pet. ether) to give tricycle **75** (10 mg, 0.03 mmol, 27% yield) and recovered starting material (*S*)-**73a** (12 mg, 0.03 mmol, 27% yield).

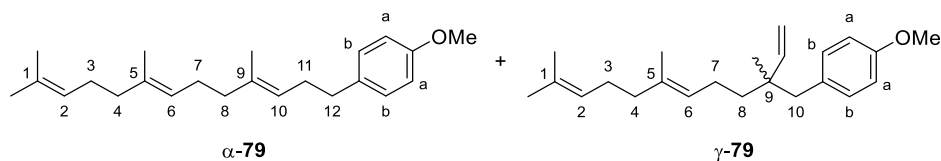
5.69 (-)-(4aR,10aR)- and (+)-(4aS,10aS)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (78) from reduction of a 3:1 mixture of (-)-(2R,4aR,10aS)- and (-)-(2R,4aS,10aR)-2-bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (75)



Using the method of Chatgililoglu *et al.*¹⁷¹ To a stirred solution of (2R,4aR,10aS)-**75** and (2R,4aS,10aR)-**75** (d.r. 3:1, 15 mg, 45 μ mol, 1 eq.) in toluene (2 mL) was added tris(trimethylsilyl)silane (16.5 μ L, 53 μ mol, 1.2 eq.) and azobisisobutyronitrile (0.73 mg, 40 μ mol, 0.1 eq.) and stirred at 90°C for 2 h, concentrated under reduced pressure and chromatographed (0-30% CH₂Cl₂ in pet. ether) to afford (4aR,10aR)-**78** and (4aS,10aR)-**78** as a single diastereomer (5 mg, 0.02 mmol, 43% yield).

Colourless oil; R_f = 0.42 (20% CH₂Cl₂ in pet. ether); $[\alpha]_D^{24}$ -23.0 (c 0.26, CHCl₃); lit.¹⁵⁴ (4aS,10aR)-**78** $[\alpha]_D^{24}$ +64.0 (c 1.0, CHCl₃); IR $\nu_{\max}$ 2997, 2924, 2852, 1686, 1609, 1576, 1502, 1463, 1443, 1390, 1376, 1250, 1227, 1207, 1174, 1074, 1043, 869, 847, 834, 799, 739, 729 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.98 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 2.6 Hz, 1H), 6.68 (dd, J = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H), 2.94-2.75 (m, 2H), 2.67 (ap. dt, J = 12.7 Hz, 1H), 1.89 (ddt, J = 13.3, 7.5, 2.0 Hz, 1H), 1.82- 1.60 (m, 3H), 1.50 (dtd, J = 13.2, 3.2, 1.6 Hz, 1H), 1.43 (td, J = 13.1, 3.7 Hz, 1H), 1.35 (dd, J = 12.5, 2.3 Hz, 1H), 1.26 (dd, J = 13.7, 4.0 Hz, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 151.5, 129.74, 127.5, 110.7, 110.2, 55.3, 50.3, 41.7, 38.8, 38.0, 33.5, 33.3, 29.6, 24.8, 21.7, 19.3, 19.1 ppm; MS (CI⁺, NH₃) m/z 259 [M + H]⁺; HRMS (CI⁺, NH₃) calc'd for C₁₈H₂₆O [M + H]⁺ 259.2062, found 259.2071; HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.12 min, 4.72 min.

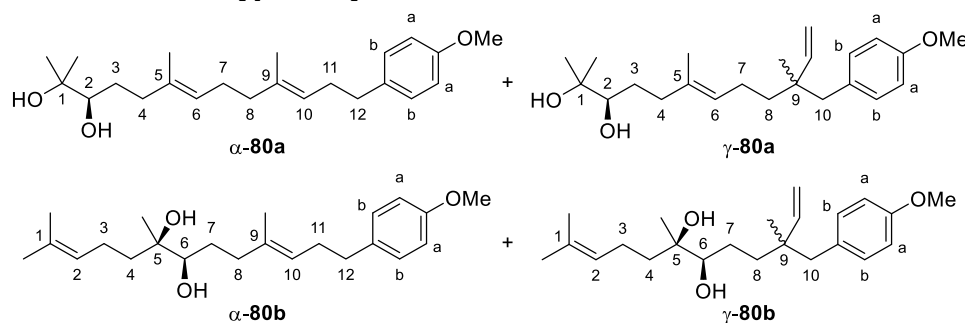
5.70 (3E,7E)-1-(4,8,12-Trimethyltrideca-3,7,11-trienyl)-4-methoxybenzene (α -79) and ($\pm$)-(5E,9E)-1-(2,6,10-trimethyl-2-vinylundec-5,9-dienyl)-4-methoxybenzene (γ -79)



Prepared according to the procedure used by Zhao and Loh¹⁵⁹ and developed by Demuth.¹⁰³ To a stirred suspension of magnesium turnings (927 mg, 38 mmol, 1.25 eq.) in anhydrous THF (50 mL) was added *p*-methoxybenzyl chloride (0.46 mL, 3.36 mmol, 0.11 eq.) and heated at 50°C. When the colourless solution turned cloudy, a solution of *p*-methoxybenzyl chloride (4.09 mL, 30 mmol, 0.99 eq.) in anhydrous THF (50 mL) was added dropwise over 30 min maintaining reflux for 3 h. The mixture was cooled to room temperature and added dropwise at 0°C to a stirred solution of farnesyl bromide (8.27 mL, 31 mmol, 1 eq.) and Pd(PPh₃)₄ (1.76 g, 1.52 mmol, 5 mol%) in THF (50 mL) and allowed to warm to room temperature and stirred for 16h. The reaction mixture was quenched by pouring onto ice water (100 mL) and extracted with Et₂O (2 × 100 mL), washed with water (150 mL), brine (150 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-5% Et₂O in *n*-heptane) to afford the title compound (α)-**79** as a mixture of constitutional isomers with (5*E*,9*E*)-1-(2,6,10-trimethyl-2-vinylundec-5,9-dienyl)-4-methoxybenzene (γ -**79**) in ratio 17:1 (7.19 g, 22 mmol, 72% yield).

Colourless oil; *R*_f = 0.37 (5% Et₂O in pet. ether); IR ν_{max} 2918, 2854, 1612, 1511, 1446, 1379, 1300, 1244, 1177, 1107, 1039, 819 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, *J* = 8.5 Hz, 2H, *H*_b), 6.87 (d, *J* = 8.6 Hz, 2H, *H*_a), 5.24 (t, *J* = 7.2 Hz, 1H, *H*₁₀), 5.20-5.13 (m, 2H, *H*₂ and *H*₆), 3.84 (s, 3H, OCH₃), 2.63 (dd, *J* = 8.9, 6.8 Hz, 2H, *H*₁₂), 2.32 (ap. q, *J* = 7.6 Hz, 2H, *H*₁₁), 2.17-2.09 (m, 4H, *H*₃ and *H*₇), 2.07-2.01 (m, 4H, *H*₄ and *H*₈), 1.74 (s, 3H, C₉CH₃), 1.66 (s, 6H, C₁CH₃), 1.61 (s, 3H, C₅CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 135.7, 135.0, 134.6, 131.3, 129.4, 124.5, 124.3, 123.7, 113.7, 55.3, 39.8, 35.3, 30.3, 26.8, 26.7, 25.7, 17.7, 16.0 ppm; MS (CI⁺, NH₃) *m/z* 344 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₃H₃₅O [M + H]⁺ 327.2688, found 327.2674.

5.71 (+)-(R,6*E*,10*E*)-13-(4-Methoxyphenyl)-2,6,10-trimethyltridec-6,10-diene-2,3-diol (α -80a**), (+)-(R,*E*)-11-(4-methoxyphenyl)-2,6,10-trimethyl-10-vinylundec-6-ene-2,3-diol (γ -**80a**), (+)-(7*R*,8*R*,3*E*)-1-(4-methoxyphenyl)-4,8,12-trimethyltridec-3,11-diene-7,8-diol (α -**80b**) and (+)-(6*R*,7*R*)-11-(4-methoxyphenyl)-2,6,10-trimethyl-10-vinylundec-2-ene-6,7-diol (γ -**80b**)**

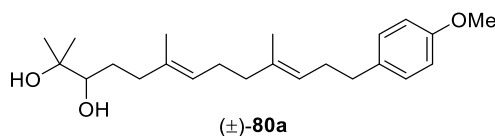


To a stirred solution of triene **79** (7.62 g, 23 mmol, 1 eq.) in *t*BuOH:H₂O (1:1, 150 mL) at 0°C was added methanesulfonamide (2.22 g, 23 mmol, 1 eq.) and AD-mix β (32.66 g, 1.4 mmol⁻¹) and vigorously stirred for 3 h at 0°C before warming to room temperature and stirring over 48 h. The reaction mixture was quenched with a saturated aqueous solution of Na₂SO₃ (75 mL), extracted with EtOAc (2 $\times$ 150 mL), washed with brine (250 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-60% EtOAc in *n*-heptane) to give first recovered starting material (α)-**79** (2.4 g, 7.29 mmol, 31% yield) as a mixture of constitutional isomers with (5*E*,9*E*)-1-(2,6,10-trimethyl-2-vinylundec-5,9-dienyl)-4-methoxybenzene (γ -**79**) in a 23:1 ratio, then diol (α)-**80b** (1.4 g, 3.88 mmol, 17% yield) as a mixture of constitutional isomers with (+)-(6*R*,7*R*,*E*)-11-(4-methoxyphenyl)-2,6,10-trimethyl-10-vinylundec-2-ene-6,7-diol (γ -**80b**) in a ratio 7:1, then diol (α)-**80a** (1.3 g, 3.61 mmol, 15% yield) as a mixture of constitutional isomers with (+)-(R,*E*)-11-(4-methoxyphenyl)-2,6,10-trimethyl-10-vinylundec-6-ene-2,3-diol (γ -**80a**) in a 20:1 ratio.

Diol (α)-**80b**: white solid; m.p. 32-34°C; *R_f* = 0.46 (50% EtOAc in pet. ether); [α]_D²⁴ +12.2 (*c* 2.1, CH₂Cl₂); IR ν_{max} 3600-3100, 2924, 2856, 1612, 1511, 1448, 1378, 1299, 1243, 1177, 1072, 1037, 935, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, *J* = 8.5 Hz, 2H, *Hb*), 6.85 (d, *J* = 8.6 Hz, 2H, *Ha*), 5.27 (t, *J* = 7.2 Hz, 1H, *H10*), 5.16 (t, *J* = 6.9 Hz, 1H, *H2*), 3.81 (s, 3H, OCH₃), 3.39 (dd, *J* = 10.5, 1.3 Hz, 1H, *H6*), 2.70-2.40 (br. s, 1H, OH), 2.62 (t, *J* = 7.8 Hz, 2H, *H12*), 2.32 (ap. q, *J* = 7.3 Hz, 2H, *H11*), 2.17-1.98 (m, 3H, *H3* and *H7*), 1.73 (s, 3H, C9CH₃), 1.68- 1.28 (m, 6H, *H4*, *H7*, *H8*, OH), 1.66 (s, 3H, C1CH₃), 1.60 (s, 3H, C1CH₃), 1.14 (s, 3H, C5CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.71, 135.5, 134.4, 131.8, 129.3, 124.5, 124.4, 113.7, 76.7, 74.9, 55.2, 38.9, 36.8, 35.1, 30.2, 29.6, 25.8, 22.1, 21.0, 17.7, 16.0 ppm; MS (CI⁺, NH₃) *m/z* 378 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₃H₄₀NO₃ [M + NH₄]⁺ 378.3008, found 378.3009.

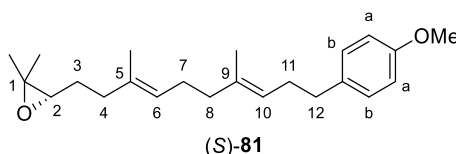
Diol (α)-**80a**: Colourless oil; *R_f* = 0.39 (50% EtOAc in pet. ether); [α]_D²⁴ +12.3 (*c* 1.1, CH₂Cl₂); IR ν_{max} 3600-3100, 2925, 2853, 1612, 1511, 1450, 1381, 1300, 1243, 1176, 1076, 1037, 909, 820, 732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.5 Hz, 2H, *Hb*), 6.86 (d, *J* = 8.7 Hz, 2H, *Ha*), 5.22 (t, *J* = 6.8 Hz, 2H, *H6* and *H10*), 3.81 (s, 3H, OCH₃), 3.38 (d, *J* = 10.0 Hz, 1H, *H2*), 2.80 (br. s, 1H, C1OH), 2.69 (br. s, 1H, C2OH), 2.62 (dd, *J* = 8.8, 6.8 Hz, 2H, *H12*), 2.31 (q, *J* = 7.5 Hz, 3H, *H11* and *H7*), 2.17-2.10 (m, 5H, *H7*, *H8* and *H4*), 1.66 (s, 3H, C9CH₃), 1.65-1.57 (m, 1H, *H4*), 1.60 (s, 3H, C5CH₃), 1.50-1.39 (m, 1H, *H3*), 1.23 (s, 3H, C1CH₃), 1.19 (s, 3H, C1CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 135.6, 134.9, 134.5, 129.4, 124.9, 123.8, 113.7, 78.3, 73.1, 55.3, 39.7, 36.9, 35.2, 30.2, 29.9, 26.6, 26.5, 23.3, 16.0 ppm; MS (CI⁺, NH₃) *m/z* 378 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₃H₄₀NO₃ [M + NH₄]⁺ 378.3008, found 378.3011. HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) *t_R* = 8.78 min (major), 10.19 min (minor) – 99:1 e.r.

5.72 (±)-(6E,10E)-13-(4-Methoxyphenyl)-2,6,10-trimethyltridec-6,10-diene-2,3-diol [(±)-80a]



A reference sample of (±)-diol **80a** was prepared following a modified procedure of Warren.¹²⁹ To a solution of potassium ferricyanide (302 mg, 0.92 mmol, 3 eq.), potassium carbonate (127 mg, 0.92 mmol, 3 eq.), K₂OsO₄·2H₂O (3.4 mg, 9.2 μmol, 3 mol%), quinuclidine (1 mg, 9.2 μmol, 3 mol%) and methanesulfonamide (29 mg, 0.31 mmol, 1 eq.) in water (2.5 mL) and *tert*-butanol (2.5 mL) at 0°C was added olefin **79** (100 mg, 0.31 mmol) and stirred vigorously for 4 h. The reaction mixture was quenched with a saturated aqueous solution of sodium sulfite (10 mL), extracted with EtOAc (2 × 20 mL), washed with brine (40 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (10-60% EtOAc in pet. ether) to afford (±)-diol **80a** (15 mg, 0.04 mmol, 13% yield). HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) *t*_R = 8.99 min, 10.18 min.

5.73 (-)-(S,3E,7E)-3-[10-(4-Methoxyphenyl)-3,7-dimethyldec-3,7-dienyl]-2,2-dimethyloxirane [(S)-81]

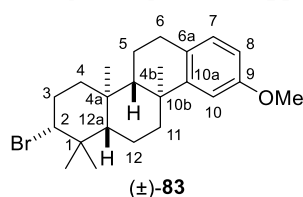


Using a modified procedure of Corey,¹²⁶ to a stirred solution of (*R*)-diol **80a** (1.3 g, 3.6 mmol, 1 eq.) and pyridine (0.58 mL, 7.21 mmol, 2 eq.) in CH₂Cl₂ (23 mL) at 0°C was added methanesulfonyl chloride (0.37 mL, 4.69 mmol, 1.3 eq.). After 0.5 h the mixture was allowed to warm to room temperature and stirred for 6 h. Additional pyridine (1.74 mL 21.6 mmol, 6 eq.) was added and the reaction mixture stirred for 16 h. The reaction mixture was poured into a suspension of K₂CO₃ (8.3 g, 60 mmol, 16.7 eq.) in methanol (40 mL), stirred for 6 h, concentrated under reduced pressure, diluted with water (50 mL), extracted with EtOAc (2 × 50 mL), washed with 10% aqueous CuSO₄ solution (100 mL), brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-20% EtOAc in pet. ether) to afford the title product (*S*)-**81a** (724 mg, 2.11 mmol, 54%) as a 36:1 mixture of constitutional isomers with (-)-(*S,E*)-3-[10-(4-methoxyphenyl)-3,7-dimethyl-7-vinyloct-3-enyl]-2,2-dimethyloxirane (γ)-**81a**.

Colourless oil; *R*_f = 0.37 (20% EtOAc in pet. ether); IR *ν*_{max} 2958, 2920, 2850, 1612, 1512, 1450, 1379, 1300, 1245, 1177, 1115, 1038, 822 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 8.6 Hz,

2H, *Hb*), 6.86 (d, $J = 8.7$ Hz, 2H, *Ha*), 5.20 (ap. q, $J = 7.1$ Hz, 2H, *H6* and *H10*), 3.82 (s, 3H, OCH₃), 2.74 (t, $J = 6.2$ Hz, 1H, *H2*), 2.61 (dd, $J = 8.9, 6.7$ Hz, 2H, *H12*), 2.30 (q, $J = 7.4$ Hz, 2H, *H11*), 2.24-1.94 (m, 6H, *H7*, *H4*, *H8*), 1.75-1.60 (m, 2H, *H3*), 1.65 (s, 3H, C9CH₃), 1.59 (s, 3H, C5CH₃), 1.34 (s, 3H, C1CH₃), 1.30 (s, 3H, C1CH₃), ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 135.6, 134.5, 134.1, 129.4, 124.9, 123.8, 113.7, 64.2, 58.4, 55.3, 39.7, 36.3, 35.2, 30.2, 27.5, 26.6, 24.9, 18.8, 16.0 ppm; MS (CI⁺, NH₃) m/z 360 [M + NH₄]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₃H₃₅O₂ [M + H]⁺ 343.2637, found 343.2646.

5.74 (±)-(2*R**,4*aS**,4*bS**,10*bS**,12*aS**)-2-Bromo-1,2,3,4,4*a*,4*b*,5,6,10*b*,11,12,12*a*-dodecahydro-1,1,4*a*,10*b*-tetramethyl-9-methoxychrysene [(±)-**83**]

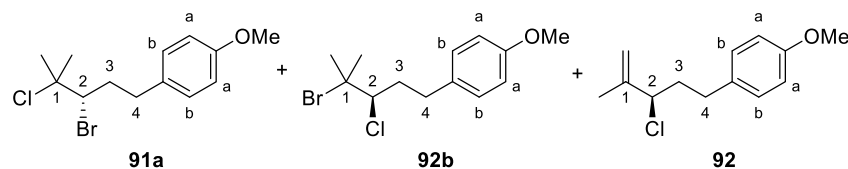


Prepared by direct brominative cyclisation of triene **79** using the method of Snyder and Treitler.⁴⁸ To a stirred solution of triene **79** (100 mg, 0.31 mmol, 1 eq.) in CH₃NO₂ (3 mL) at -14°C was added quickly a solution of BDSB (168 mg, 0.31 mmol, 1 eq.) in CH₃NO₂ (1.5 mL) and stirred for 5 min. At -14°C methanesulfonic acid (0.3 mL, 4.59 mmol, 15 eq.) was added dropwise and stirred for 1 h. The reaction mixture was quenched with a 1:1 mixture of 5% aqueous NaHCO₃ and 5% aqueous Na₂SO₃ solution (20 mL), extracted with CH₂Cl₂ (2 × 20 mL), dried over Na₂SO₄, concentrated under reduced pressure and chromatographed (0-35% CH₂Cl₂ in pet. ether) to afford bromide (±)-**83** (29 mg, 0.07 mmol, 24% yield).

Colourless oil; $R_f = 0.27$ (20% CH₂Cl₂ in pet. ether); IR $\nu_{\max}$ 2923, 2851, 1609, 1575, 1502, 1463, 1379, 1272, 1252, 1229, 1209, 1160, 1090, 1047, 1009, 868, 849, 803, 767, 737, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.98 (d, $J = 8.4$ Hz, 1H, *H7*), 6.81 (d, $J = 2.7$ Hz, 1H, *H10*), 6.69 (dd, $J = 8.5, 2.6$ Hz, 1H, *H8*), 4.04 (dd, $J = 12.8, 4.3$ Hz, 1H, *H2*), 3.80 (s, 3H, OCH₃), 2.91 (ddd, $J = 16.8, 6.6, 1.9$ Hz, 1H, *H6*), 2.77 (ddd, $J = 16.9, 11.4, 7.3$ Hz, 1H, *H6*), 2.39 (dt, $J = 12.7, 3.2$ Hz, 1H, *H5*), 2.29 (qd, $J = 13.4, 3.9$ Hz, 1H, *H5*), 2.14 (dq, $J = 13.8, 3.9$ Hz, 1H, *H*), 1.88 (dt, $J = 13.0, 3.5$ Hz, 1H, *H*), 1.84-1.48 (m, 8H), 1.23 (s, 3H, C10*b*CH₃), 1.11 (s, 3H, C4*a*CH₃), 1.02 (s, 3H, C1CH₃), 1.01 (s, 3H, C1CH₃), ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 151.1, 129.6, 127.1, 110.8, 110.2, 69.8, 56.6, 55.2, 55.0, 41.3, 40.6, 39.7, 38.0, 37.7, 30.9, 30.5, 29.8, 25.8, 20.6, 18.2, 18.1, 16.3 ppm; MS (CI⁺, NH₃) m/z 407, 405 [M + H]⁺; HRMS (CI⁺, NH₃) calc'd for C₂₃H₃₄OBr [M + H]⁺ 405.1774,

found 405.1776; HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 6.19 min, 6.61 min.

5.75 1-[(3*S*)-3-Bromo-4-chloro-4-methylpentyl]-4-methoxybenzene (**91a**), 1-[(3*R*)-4-bromo-3-chloro-4-methylpentyl]-4-methoxybenzene (**91b**) and 1-[(3*R*)-3-chloro-4-methylpent-4-en-1-yl]-4-methoxybenzene (**92**)



To a stirred solution of alcohol (*S*)-**8b** (100 mg, 0.35 mmol, 1 eq.) in CHCl_3 (2 mL), at 0°C was added dropwise thionyl chloride (40 μL , 0.53 mmol, 1.5 eq.) and allowed to warm to room temperature over 4 h. The reaction mixture was cooled to 0°C , a further addition of thionyl chloride was made (40 μL , 0.53 mmol, 1.5 eq.) and the reaction stirred at room temperature for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 (20 mL), extracted with CHCl_3 (20 mL), washed with brine (30 mL), dried over Na_2SO_4 , concentrated under reduced pressure and chromatographed (0-30% CH_2Cl_2 in pet. ether) to give tertiary chloride **91a**, secondary chloride **91b**, allyl bromide **36** and allyl chloride **92** as a 2.4:0.9:1.0:0.3 mixture (23 mg).

Colourless oil; R_f = 0.45 (30% CH_2Cl_2 in pet. ether); ^1H NMR (400 MHz, CDCl_3) δ 7.18 (d, J = 8.5 Hz, 6H, *Hb*), 7.14 (d, J = 8.5 Hz, 3H, *Hb*), 6.90-6.84 (m, 9H, *Ha*), 5.08 (s, 1H, **36** C1=CH), 5.03 (s, 0.3H, **92** C1=CH), 4.95-4.92 (m, 1.3H, **36** C1=CH and **92** C1=CH), 4.53 (dd, J = 8.2, 6.6 Hz, 1H, **36** H2), 4.37 (dd, J = 8.2, 6.3 Hz, 0.3H, **92**, H2), 4.01 (dd, J = 11.2, 1.6 Hz, 2.4H, **91a** H2), 3.95 (dd, J = 11.5, 1.2 Hz, 0.9H, **92b**, H2), 3.83 (s, 13.3H, OCH_3), 3.02 (ddd, J = 13.0, 8.3, 4.3 Hz, 2.6H, *H4*), 2.77-2.55 (m, 9.5H, *H3*), 2.37-2.25 (m, 1.6 H, *H3*), 2.20-2.01 (m, 4.6 H, *H3*), 1.91 (s, 2H, C1CH_3), 1.90 (s, 3.2H, C1CH_3), 1.85 (s, 0.9 H, C1CH_3), 1.79 (s, 2.3H, C1CH_3), 1.78 (s, 6.3 H, C1CH_3), 1.68 (s, 6.3 H, C1CH_3) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ ^{13}C NMR (101 MHz, CDCl_3) δ 158.1, 158.1, 157.9, 133.7, 133.7, 132.6, 132.4, 130.5, 130.0, 129.6, 129.5, 129.4, 114.3, 113.9, 113.8, 77.4, 77.3, 77.1, 76.7, 65.0, 59.2, 55.3, 52.5, 41.7, 38.9, 36.4, 36.1, 34.4, 34.3, 33.3, 33.1, 33.0, 32.4, 30.4, 30.2, 27.3, 17.8, 14.7, 14.1, 1.1 ppm; FTMS m/z 305, 303, [**91** - H] $^+$ 269, 267, [**36** - H] $^+$ 225, 223 [**92** + H] $^+$.

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Appendices

Permission documents

Regarding the use of reference 47 photograph taken by Preskitt, L. Laurencia nidifica attached to a Porites lobata coral head. (accessed 11/01/2013).

http://www.hawaii.edu/reefalgae/invasive_algae/rhodo/M%20TC12%20laurencia1.jpg

Marklew, Jared S

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Hawaii Island Coordinator
Eyes of the Reef Network

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Dear Linda Preskitt,

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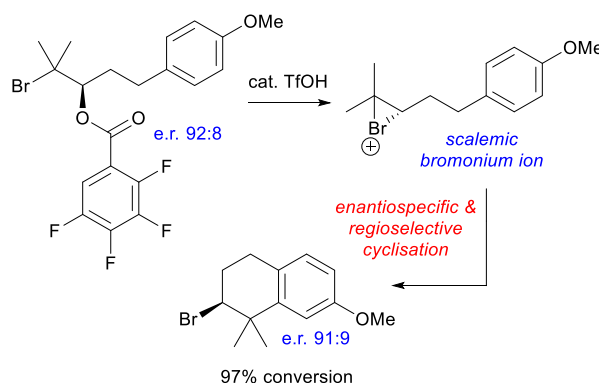
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Enantiospecific bromonium ion generation and intramolecular capture: a model system for asymmetric bromonium ion-induced polyene cyclisations

D. Christopher Braddock, Jared S. Marklew and Alexander J. F. Thomas

Abstract

Scalemic bromonium ions generated enantiospecifically by the action of catalytic triflic acid on scalemic regioisomeric bromohydrin derivatives are trapped intramolecularly, enantiospecifically and regioselectively to give bicyclic brominated carbocycles in excellent yield and high enantiomeric excess. This enantiospecific pathway is not significantly perturbed by the addition of a trisubstituted alkene.



Scalemic bromonium ions can be generated enantiospecifically from scalemic bromohydrin derivatives and then captured intramolecularly in enantiospecific and regioselective fashion.

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COMMUNICATION

Enantiospecific bromonium ion generation and intramolecular capture: a model system for asymmetric bromonium ion-induced polyene cyclisations†

D. Christopher Braddock,^a Jared S. Marklew^a and Alexander J. F. Thomas^b

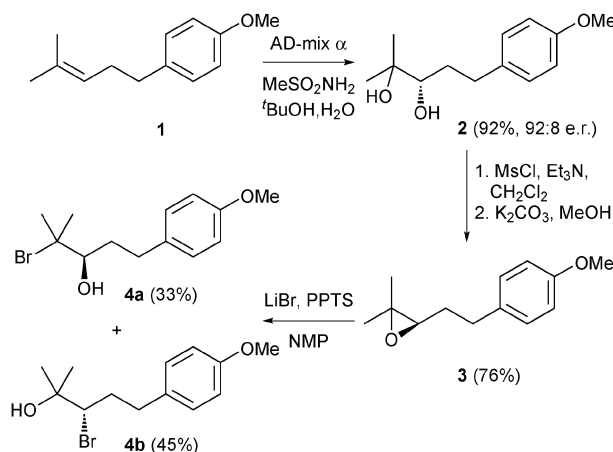
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DOI: 10.1039/c1cc13619d

Scalemic bromonium ions generated enantiospecifically by the action of catalytic triflic acid on scalemic regioisomeric bromohydrin derivatives are trapped intramolecularly, enantiospecifically and regioselectively to give bicyclic brominated carbocycles in excellent yield and high enantiomeric excess. This enantiospecific pathway is not significantly perturbed by the addition of a trisubstituted alkene.

Biomimetic cationic polyene cyclisations of terpenes by electrophilic initiators to give polycyclic terpenoids are tremendously powerful synthetic processes.^{1,2} The first direct bromonium ion-induced polyene cyclisation was described by Van Tamelen in 1966 as initiated by NBS,³ but in this, and other early work,^{4a–e} the cyclisations were necessarily racemic and very low yielding. Later, the use of 2,4,4,6-tetrabromocyclohexadienone (TBCO) in acetonitrile or nitromethane resulted in sufficiently efficient brominative cyclisations to give monocarbocycles and/or bicarbocycles that the total synthesis of a number of naturally occurring compounds could be accomplished.^{4f–k} The recent work of Snyder⁵ has shown that bromodiethylsulphonium bromopentachloroantimonate (BDSB) is an extraordinarily useful reagent for the direct bromonium-induced cyclisation of a wide range of polyenes giving mono-, bi-, tri- and even tetracyclic carbocycles in high yield, but as necessarily racemic products.⁶ A driving force for the development of these reactions is the continual isolation of complex polycyclic brominated natural products⁷—as single

enantiomers—where their biogenesis are generally considered to be enzyme mediated asymmetric bromonium ion-induced polyene cyclisations,⁸ and these isolations continue to date.⁹ Selected cyclisations have been effected enzymatically, giving single enantiomer products.¹⁰ However, a non-enzymatic asymmetric polyene cyclisation as induced by an enantiopure bromonium ion has yet to be reported.^{11,12} We have recently reported the first generation and intermolecular trapping of enantiomerically pure bromonium ions to give enantiomerically pure bromochloride adducts.¹³ In that previous work we had generated enantiopure bromonium ions by the action of thionyl chloride or titanium tetrachloride on enantiopure bromohydrin or sulphonate derivatives respectively with concomitant stereospecific NGP of the bromide. The enantiopure bromonium ions were then captured stereospecifically, and in high yield, by necessarily present chloride anion. In order to extend this methodology to the initiation of polyene cyclisations with a bromonium ion we considered that we would require (i) synthetic access to enantiopure (or enantioenriched) bromohydrins;[†] (ii) efficient activation of the bromohydrin (or derivative) to form a scalemic bromonium ion in the absence of a nucleophilic counterion; (iii) effective enantiospecific intramolecular trapping without catastrophic erosion of enantiomeric purity by rapid bromonium ion-alkene exchange (Scheme 1).¹⁴ We also considered that this overall strategy should be high yielding since the bromonium ion



Scheme 1 Preparation of enantioenriched bromohydrins.

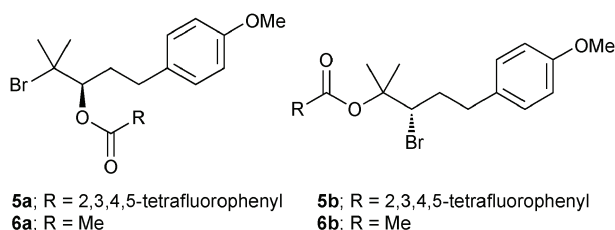
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† Electronic supplementary information (ESI) available: Notes ‡, §, ¶, ¥, ††, **, †††, §§, ¶¶, ¥¥, ††††, ***, ††††, §§§, ¶¶¶ and ¥¥¥, general experimental, experimental details and characterising data for compounds 1–3, 4a–b, 5a–b, 6a–b and 7, ¹H and ¹³C NMR spectra for compounds 1–3, 4a–b, 5a–b, 6a–b and 7 including ¹³C NMR spectra displaying bromine isotopic shifts for 4a and 4b, determination of enantiomer ratios (e.r.) for 2, 5a–b, 6a–b and 7 by HPLC, details for preparation of ent-7 including HPLC traces for ent-2 and ent-7, preliminary investigations for cyclisation of 5a and 5b into 7, optimisation of anionic bromide ring-opening of epoxide 3, procedures and data for preparation and cyclisation of des-bromo 4b, and details of experiment for cyclisation of ent-6a in the presence of added alkene. See DOI: 10.1039/c1cc13619d

would be formed, and only formed, at the terminus of the polyene. Herein, we report on the generation of bromonium ions from scalemic bromohydrin derivatives—derived from anionic bromide ring-opening of scalemic epoxides—as a viable method for initiating cyclisation,^{15,16} and demonstrate regioselective intramolecular trapping with a π -nucleophile to give bicyclic brominated carbocycles with essentially complete enantiospecificity in high yield. We also report that this process occurs *without significant erosion of enantiomeric purity in the presence of added trisubstituted alkene*.

Trisubstituted alkene **1**,^{17,8} was dihydroxylated using AD-mix α ¹⁸ to give diol **2** in excellent yield and high enantiomer ratio (**2**: e.r. 92:8),^{19,¶} and converted into epoxide **3** using the method of Corey (Scheme 1).²⁰ Ring-opening of epoxide **3** with anionic bromide was best achieved using the method of Couladorous and Vidali[¶] to give the separable tertiary bromide **4a** and secondary bromide **4b**. Their regioisomeric assignments were secured on the basis of a bromide induced ¹³C isotopic shift (see ESI)²¹ and their enantiomeric integrity confirmed by analysis of their derivatives (*vide infra*). Thus, the Sharpless dihydroxylation method allows access to enantioenriched bromohydrins of trisubstituted alkenes.



With scalemic bromohydrins **4a** and **4b** in hand, we considered how best to activate them. We had recently observed the spontaneous formation of a bromonium ion from a 1-bromo-2-tetrafluorobenzoate on standing,²² and so we selected the tetrafluorobenzoate as a suitable leaving group for this study. Accordingly, tetrafluorobenzoates **5a** and **5b** were prepared from alcohols **4a** and **4b** by Steglich esterification.²³ Acetates **6a** and **6b** could also be prepared by the same method.^{††} These transformations to give **5a**, **5b**, **6a** and **6b** – and evidently the preceding steps involving epoxide formation (**2** into **3**) and anionic bromide ring-opening (**3** into **4a** + **4b**) *cf.* Scheme 1 – proceeded without loss of any stereochemical integrity.^{¶,***} In the event, cyclisation was effected^{‡‡} by the use of catalytic triflic acid in dichloromethane (Table 1). Much to our delight, cyclisation of secondary bromobenzoate **5a** with 30 mol% TfOH in refluxing dichloromethane proceeded enantio-specifically,[¶] and essentially quantitatively, to bromocyclohexane **7**^{§§} (entry 1), but where lower catalyst loading were increasingly less effective (entries 2,3).

Tertiary bromobenzoate **5b** was also efficiently cyclised under these conditions, again with essentially complete enantio-specificity, in excellent to good conversions either at reflux (entry 4) or at r.t. (entry 5). Thus tetrafluorobenzoates of *either* 2° or 3° bromohydrins derived from trisubstituted alkenes are excellent choices for the formation of scalemic bromonium ions as catalysed by triflic acid. In addition, the reaction profiles of these reactions were extremely clean. Secondary acetate **6a** was also efficiently cyclised under these conditions

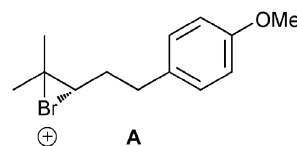
Table 1 Brominative cyclisation of substrates with catalytic TfOH^a

Substrates 4a-b , 5a-b , 6a-b		x mol% TfOH CH ₂ Cl ₂ , T °C, t h				
Entry	Substrate ^b	x	T/°C	t (h)	% Conversion ^c	e.r. ^d
1	5a (92:8)	30	40	3	97 (84)	91:9
2	5a (92:8)	10	40	16	81	nd
3	5a (92:8)	5	40	16	20	nd
4	5b (93:7)	30	40	4	94 (67)	92:8
5	5b (93:7)	30	r.t.	16	79	nd
6	6a (92:8)	30	40	2.5	80 (68)	84:16
7	6b (92:8)	30	40	2	45 (14)	nd

^a See ESI for experimental conditions. ^b The figure in parentheses is the e.r. for this substrate. ^c As determined by inspection of the ¹H NMR spectrum after aqueous work-up. Figure in parentheses is isolated yield after column chromatography. ^d As determined by HPLC analysis by reference to a racemic sample.

but with a slight erosion in enantiomeric ratio of the product (entry 6).^{¶¶} However tertiary acetate **6b** (entry 7) gave complex and varied mixtures of product and rearranged compounds.^{†††} The direct cyclisation of both bromohydrins **4a** and **4b** under these conditions were also attempted, but these substrates gave complex product mixtures, from which the desired product **7** could sometimes be isolated, but where isopropylphenethyl-ketone¹⁷ was usually the major component.

Evidently, the transformation of **5a** (and **6a**) into **7** must necessarily proceed through bromonium ion **A**^{***} by stereo-specific NGP of the bromide—with complete inversion of configuration—on the protonated leaving group and then enantiospecific and regioselective trapping of the bromonium ion by the aromatic nucleus.^{‡‡‡} The same scalemic bromonium ion **A**^{§§§} can be invoked from **5b**.



To show the preparative utility of this method alkene **1** was dihydroxylated with AD-mix β to give *ent*-**2** (99%, 97:3 e.r.[¶]). Epoxide formation as before gave *ent*-**3** (53%), and anionic bromide ring-opening gave *ent*-**4a** and *ent*-**4b** (72%), which were converted—without separation—into a mixture of *ent*-**5a** and *ent*-**5b** (95%). Triflic acid catalysed cyclisation of the mixture in dichloromethane (30 mol% TfOH, 2h r.t. then 2 h at reflux) gave *ent*-**7** in high yield with essentially complete enantiospecificity (84%, 96:4 e.r.^{¶¶}).

In the context of developing asymmetric bromonium ion-induced polyene cyclisations it is vital to know if these enantiospecific intramolecular cyclisations onto bromonium ions will be compromised by competitive intermolecular bromonium ion transfer to alkenes¹⁴ (alkene functionality being necessarily present in potential polyene substrates). Accordingly, triflic acid catalysed cyclisation of secondary acetate *ent*-**6a** (e.r. 96:4) was performed in the presence of one equivalent of 1-methylcyclohexene. Although a Friedel–Crafts alkylation adduct was formed in the reaction mixture,[¶]

the desired bromocyclohexane *ent*-7 was isolated in 35% yield, and with an essentially undiminished e.r. of 94:6.

In conclusion, we have shown that scalemic bromohydrins of trisubstituted alkenes can be readily prepared by application of the Sharpless dihydroxylation method, thereby giving access to both enantiomeric series with high enantioselectivity. Their tetrafluorobenzoate derivatives are excellent substrates for the formation of scalemic bromonium ions of a trisubstituted alkene from *either* 2° or 3° bromohydrins—or as a mixture—on treatment with catalytic quantities of triflic acid, and undergo enantiospecific regioselective cyclisation with a suitably positioned nucleophile. This enantiospecific pathway is not significantly perturbed by the addition of a trisubstituted alkene. The above findings lay the groundwork for the development of polyene cyclisations triggered by enantiomerically pure bromonium ions. Further findings will be reported in due course.

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Notes and references

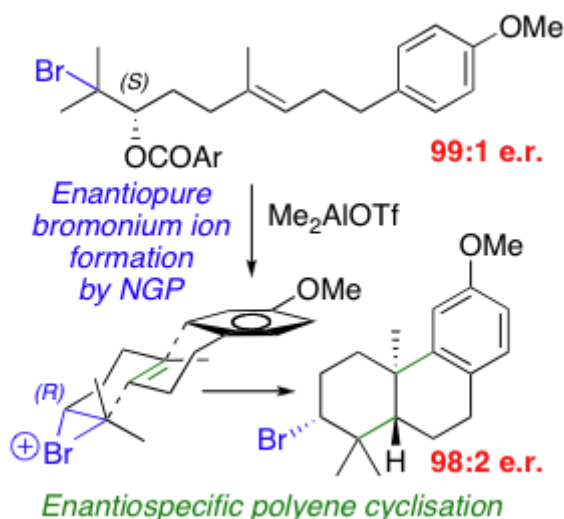
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An enantiospecific polyene cyclization initiated by an enantiomerically pure bromonium ion

D. Christopher Braddock, Jared S. Marklew, Kevin M. Foote and Andrew J. P. White

Abstract

Dimethylaluminum triflate-mediated activation of tetrafluorobenzoates of enantiomerically pure bromohydrins results in enantiospecific polyene cyclizations. The initiation of cyclization by enantiomerically pure bromonium ions and subsequent propagation is not subject to catastrophic erosion of enantiomeric purity by any intramolecular or intermolecular bromonium ion-to-alkene transfer.



An Enantiospecific Polyene Cyclization Initiated by an Enantiomerically Pure Bromonium Ion

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ABSTRACT Dimethylaluminum triflate-mediated activation of tetrafluorobenzoates of enantiomerically pure bromohydrins results in enantiospecific polyene cyclizations. The initiation of cyclization by enantiomerically pure bromonium ions and subsequent propagation is not subject to catastrophic erosion of enantiomeric purity by any intramolecular or intermolecular bromonium ion-to-alkene transfer. *Chirality* 25:692–700, 2013. © 2013 Wiley Periodicals, Inc.

KEY WORDS: bromonium ion; polyene cyclization; enantiospecific

INTRODUCTION

Since the advance of the Stork-Eschenmoser hypothesis,^{1–3} cation-initiated polyene cyclizations as inspired by the enzymatic conversions of squalene to hopene and oxidosqualene to lanosterol have attracted much synthetic attention,^{4–6} with enantioselective variants now representing the state of the art.^{7–15} With the continued isolation^{16–29} of complex single enantiomer brominated (poly)cyclic terpenoid natural products containing the signature α -bromo- β , β -dimethylcyclohexane motif from marine sources,^{30–34} a consensus has arisen that nature employs enzyme-mediated bromonium ion initiated asymmetric polyene cyclizations to so construct them (Fig. 1).³⁵ While van Tamelen and Hessler³⁶ demonstrated the first direct brominative cyclization of polyene methyl farnesate with NBS nearly 50 years ago, the products were necessarily racemic and formed in very low yields (ca. 5%). Over the next 30 years a number of other direct brominative polyene cyclizations have further been reported using a variety of (achiral) reagent-solvent combinations.^{37–48} The low yields generally obtained in these cyclizations must arise in part from the requirement of the reagent to react regioselectively with the olefin at the terminus of the polyene chain. The recent introduction of the powerful bromodiethylsulphonium bromopentachloroantimonate reagent, BDSB, by Snyder and co-workers now allows for highly efficient bromonium ion initiated polyene cyclizations to give bi- tri-, and even tetracyclic adducts, albeit still as racemates.^{41–51,*} Snyder and colleagues have also recently reported a two-step mimic for direct, asymmetric bromonium-induced polyene cyclizations using a chiral Hg(II) salt to mediate the initial cyclization.⁵² However, the demonstration of an enantiospecific, nonenzymatic-mediated, polyene cyclization initiated by an enantiopure bromonium ion remains unreported.[†]

In contemplating such an asymmetric bromonium ion-initiated polyene cyclization, challenges in each of the fundamental steps of initiation and propagation arise (Fig. 2), and a suitable group must also be chosen to terminate the polyene

cyclization. In any initiation step, an enantiopure bromonium ion must be formed regioselectively at the terminus alkene of the polyene. Currently, there is no widely applicable method for the formation of enantiopure bromonium ions by direct bromination of a simple trisubstituted alkene (even before considering the required regioselectivity of the process).^{53–57} In the propagation step(s) intramolecular and/or intermolecular bromonium ion-to-alkene transfer^{58,59} must be avoided, where Denmark et al. have recently demonstrated that racemization of enantiopure bromonium ions via bromonium ion-to-olefin transfer with an added alkene is competitive with *intermolecular* capture by anionic nucleophiles.⁶⁰ Since by definition a polyene cyclization substrate will always contain alkene functional groups, it is not unreasonable to ask if such asymmetric cyclizations are therefore inherently compromised when not under enzymatic control. Thus, methods for the initiation of polyene cyclizations with enantiopure bromonium ions are required to be developed, so that the extent of the racemization via either intramolecular or intermolecular bromonium ion-to-alkene transfer can be assessed. An enantiomerically pure bromonium ion was generated in the formation of a vicinal bromochloride in the total synthesis of (+)-intricatetraol.⁶¹ Lewis acid-mediated carbocyclizations of (racemic) 1,2-bromohydrins (3° alcohol and/or esterified derivatives, 2° bromide) have been demonstrated previously,^{62–66} and a cyclization of an enantiopure 1,2-bromohydrin (3° alcohol, 2° bromide) to an enantiopure 1-bromo-2,2,4-trimethylcyclohexane has been reported,⁶⁷ but bromonium ions were not invoked. Herein, as an extension of our previous work, we report the formation of an enantiopure bromonium ion at the terminus of a polyene by suitable activation of an enantiopure bromohydrin,^{68,69} thereby initiating polyene cyclization to produce tricyclic carbocycles with the characteristic α -bromo- β , β -dimethylcyclohexane motif of (poly)cyclic naturally occurring terpenoids. Under these

Additional Supporting Information may be found in the online version of this article.

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*Chiral versions of BDSB are also reported in Ref. 50. However, no asymmetric induction was observed in the cyclization of a representative polyene.

†Chiral phosphoramidites at stoichiometric loading have delivered high enantiomeric excess for direct iodonium-induced polyene cyclizations (up to 95% ee) using NIS as the electrophilic halide source. With NBS as the halide source instead to effect a bromonium-ion induced cyclization, the asymmetric induction dropped off markedly (36% ee) (Ref. 10).

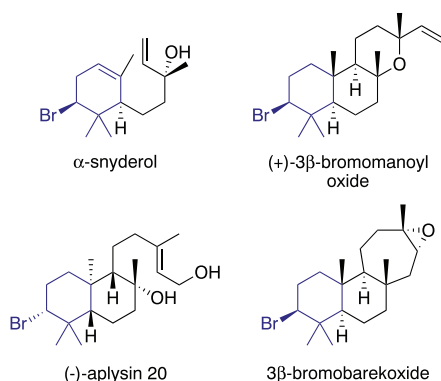


Fig. 1. Selected single enantiomer terpenoid natural products containing the α -bromo- β , β -dimethylcyclohexane motif (highlighted in blue) considered to arise via bromonium ion-initiated polyene cyclization.

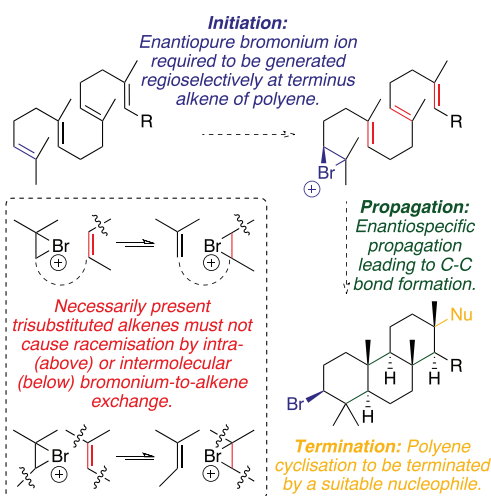


Fig. 2. Challenges for enantiospecific polyene cyclization initiated by an enantiopure bromonium ion.

conditions—even with a necessarily present trisubstituted alkene in the cyclization substrates—the brominated tricyclic carbocycles are isolated in high enantiomeric excess. Racemization via either intramolecular or intermolecular bromonium ion-to-alkene transfer is evidently not in operation, and the cyclizations proceed enantiospecifically.

MATERIALS AND METHODS

General Experimental

Reagents. 4-Methoxybenzyl chloride was prepared from 4-methoxybenzyl alcohol according to a procedure by Yadav and colleagues.⁷⁰ Bromodiethylsulphide pentachloroantimonybromide (BDSB) was prepared according to the procedure by Snyder and Treitler.⁵¹ Pyridine was distilled from CaH₂. Methanesulphonamide was purified by recrystallization from EtOH. All other reagents were obtained from commercial sources and used as received.

Solvents. All reactions were carried out in anhydrous solvents unless used in combination with H₂O. CH₂Cl₂, Et₂O, and THF were dried by passing through a column of alumina beads. *N*-Methyl-2-pyrrolidone was purified by distillation and stored over 4 Å molecular sieves. All other reaction solvents, extraction solvents, and chromatography eluents were used as received. MeOH and CH₂Cl₂ were HiPerSolv grade, EtOH was AnalaR grade, and Et₂O, EtOAc, and petroleum ether 40-60 (referred to as PE) were GPR grade. *n*-Hexane and *i*-PrOH for analytical

high-performance liquid chromatography (HPLC) were HPLC grade and used as received.

Experimental techniques. Reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen, unless otherwise stated. Air and moisture-sensitive reagents were transferred by syringe. Reaction temperatures other than room temperature were recorded as aluminum alloy heating block, or bath temperatures. Concentrated under reduced pressure refers to rotary evaporation. Brine refers to a saturated aqueous solution of NaCl. Column chromatography was performed on silica gel, particle size 40-63 μ m unless otherwise stated. Chiral HPLC was performed on CHIRALCEL OJ or CHIRALPAK AD columns detecting at 284 nm. Retention times (*t_R*) are reported in minutes. Analytical thin-layer chromatography (TLC) was performed on Kieselgel 60 F254 precoated aluminum-backed plates visualized by ultraviolet light (350 nm) and/or chemical staining using potassium permanganate solution. Silver nitrate-doped silica gel was obtained after slurring silica in aqueous AgNO₃ solution (0.1 M, 4 mL g⁻¹ silica) and concentrating under reduced pressure azeotroping with toluene until dryness.

Characterization. Fourier transform IR spectra were recorded neat using an ATR-IR spectrometer. ¹H, ¹³C and ¹⁹F NMR spectra were recorded on Bruker AV400 and AV500 spectrometers at 400 MHz and 500 MHz, and 100 MHz and 125 MHz, and 377 (AV500 only) MHz, respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual solvent resonance. Coupling constants (*J*) are quoted in Hertz (Hz). Low-resolution mass spectroscopy (MS) (EI, CI), gas chromatography MS (GCMS), and high-resolution MS (HRMS) were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service.

(E)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methoxybenzene (1). Prepared according to a modified procedure of Snyder and Treitler.⁴⁹ To a stirred solution of geraniol (23 mL, 133 mmol) and pyridine (32 mL, 398 mmol) in diethyl ether (80 mL) at -15 °C was added diethyl chlorophosphate (29 mL, 199 mmol) and the mixture was allowed to warm to room temperature over 5 h. The reaction mixture was quenched with 1M aqueous HCl solution (250 mL), extracted with ethyl acetate (2 $\times$ 250 mL), washed with saturated aqueous NaHCO₃ solution (2 $\times$ 250 mL), brine (250 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give geranyl diethyl phosphate as a colorless oil (46 g) which was used directly without purification. To magnesium turnings (7.6 g, 318 mmol) stirred in anhydrous THF (200 mL) was added a portion of 4-methoxybenzyl chloride (2.0 mL, 15 mmol), where the reaction could be started by gentle heating. Subsequently, a solution of 4-methoxybenzyl chloride (19.5 mL, 144 mmol) in anhydrous THF (200 mL) was added dropwise over 1 h at such a rate as to maintain reflux. After complete addition, reflux was continued for 2 h. The reaction mixture was cooled to -40 °C and added dropwise via cannula to a stirred solution of geranyl diethyl phosphate (23 g, 80 mmol) in anhydrous THF (250 mL) at -40 °C and allowed to warm to room temperature over 16 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (300 mL), extracted with diethyl ether (2 $\times$ 300 mL), washed with saturated aqueous NaHCO₃ solution (300 mL), brine (300 mL), dried over Na₂SO₄, concentrated under reduced pressure, and chromatographed (0:1-1:3 CH₂Cl₂:PE) to afford the title compound **1** as a mixture of constitutional isomers with branched diene **1a** in 19:1 ratio (12.7 g, 49 mmol, 61%) as a colorless oil. A second run on the same scale afforded the title product **1** as a mixture of constitutional isomers with **1a** in ratio 35:1 (14.0 g, 54 mmol, 68%). The purity of **1** could be increased to >98% by fractional distillation of the combined diene mixtures (27 g, 26:1 **1:1a**). Distillation (200 °C, 0.003 mmHg) collecting the fraction at 70 °C was enriched in branched isomer **1a** and the distillation residue was linear diene **1** (8.2 g, 32 mmol). Diene **1**: *R_f* = 0.35 (15% CH₂Cl₂ in PE); IR ν_{max} 2919, 2854, 1612, 1584 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.24 (t, *J* = 7.1 Hz, 1H), 5.19-5.13 (m, 1H), 3.82 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.34 (q, *J* = 8.5 Hz, 2H), 2.17-2.02 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 135.7, 134.6, 131.3, 129.4, 124.4, 123.7, 113.7, 55.3, 39.8, 35.3, 30.2.

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26.8, 25.7, 17.7, 16.0 ppm; MS (Cl^+) m/z 276 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+) calcd. for $\text{C}_{18}\text{H}_{27}\text{O}$ [$\text{M} + \text{H}$] $^+$ 259.2062. Found: 259.2050. An analytically pure sample of branched diene **1a** could be obtained after silver nitrate-doped silica gel chromatography (0:1:3:7 Et_2O :PE).

(E)-1-(2,6-Dimethyl-2-vinylhept-5-enyl)-4-methoxybenzene (1a).

R_f = 0.35 (15% CH_2Cl_2 in PE); IR ν_{max} 2920, 2854, 1612 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.03 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.76 (dd, J = 17.6, 10.8 Hz, 1H), 5.10–5.05 (m, 1H), 5.00 (dd, J = 10.8, 1.4 Hz, 1H), 4.82 (dd, J = 17.6, 1.4 Hz, 1H), 3.79 (s, 3H), 2.54 (m, 2H), 1.91 (q, J = 8.0 Hz, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.37–1.25 (m, 2H), 0.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 146.6, 131.6, 131.0, 130.6, 125.0, 112.9, 112.1, 55.2, 47.2, 40.8, 40.4, 25.7, 23.1, 21.9, 17.6 ppm; MS (Cl^+) m/z 276 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+) calcd. for $\text{C}_{18}\text{H}_{30}\text{NO}$ [$\text{M} + \text{NH}_4$] $^+$ 276.2327. Found: 276.2328.

(2R*,4aR*,10aS*)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2R*,4aR*,10aS*)-(2) by direct brominative cyclization of polyene 1 with BDSB.

Bromide (**2R*,4aR*,10aS*)-2** was prepared by direct brominative cyclization of diene **1** using the method of Snyder and Treitler.⁴⁹ To a stirred solution of alkene **1** (100 mg, 0.39 mmol) in CH_3NO_2 (6 mL) at -25°C was added quickly a solution of BDSB (213 mg, 0.39 mmol) in CH_3NO_2 (2 mL) and stirred for 5 min. The reaction mixture was quenched with a 1:1 mixture of 5% aqueous NaHCO_3 and 5% aqueous Na_2SO_3 solution (20 mL) and stirred for 15 min before being poured into water (20 mL), extracted with CH_2Cl_2 (2×20 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (PE) to afford bromide (**2R*,4aR*,10aS*)-2** (88 mg, 68%) as a white solid: m.p. $86\text{--}87^\circ\text{C}$. R_f = 0.64 (40:60 CH_2Cl_2 :PE); IR ν_{max} 2933, 2851, 1611 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.00 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 8.3, 2.8 Hz, 1H), 4.07 (dd, J = 12.5, 4.1 Hz, 1H), 3.80 (s, 3H), 2.98–2.76 (m, 2H), 2.48–2.23 (m, 3H), 1.98 (ddt, J = 13.4, 7.0, 2.2 Hz, 1H), 1.88–1.75 (m, 1H), 1.69–1.56 (m, 1H), 1.48 (dd, J = 12.1, 2.2 Hz, 1H), 1.27 (s, 3H), 1.18 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 150.0, 129.9, 127.0, 111.2, 110.2, 68.8, 55.3, 51.3, 40.1, 39.9, 38.1, 31.6, 30.6, 30.0, 24.8, 20.8, 18.3 ppm; MS (Cl^+ , NH_3) m/z 354, 356 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{29}\text{NO}^{79}\text{Br}$ [$\text{M} + \text{NH}_4$] $^+$ 354.1433, found 354.1433. HPLC (CHIRALPAK AD; 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 4.9 min, 5.7 min.

(+)-(R,E)-9-(4-Methoxyphenyl)-2,6-dimethylnon-6-ene-2,3-diol (3).

According to the method of Sharpless,⁷¹ to a stirred solution of AD-mix β (22.3 g, 1.4 gmmol $^{-1}$) and methanesulphonamide (1.5 g, 16 mmol) in water (40 mL) and *tert*-butanol (40 mL) at 0°C was added alkene **1** (4.1 g, 16 mmol). The reaction mixture was stirred vigorously for 16 h, quenched with saturated aqueous sodium sulfite solution (50 mL), extracted with EtOAc (2×100 mL), washed with brine (100 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (1:1:3:2 EtOAc:PE) to afford first unreacted diene **1** (1.64 g, 6.3 mmol, 40%), the title product **3** (1.16 g, 4.3 mmol, 27%, 67% based on recovered starting material) as a colorless oil, and tetraol **3a** (1.27 g, 3.9 mmol, 24%) as a white solid. Diol **3**: R_f = 0.42 (1:1 EtOAc:PE); $[\alpha]_D^{24}$ = +12.3 (*c* 1.9, CH_2Cl_2); IR ν_{max} 3600–3100, 2931, 2858, cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.13 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.26 (br t, J = 7.1 Hz, 1H), 3.81 (s, 3H), 3.32 (dd, J = 10.5, 2.0 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.38–2.19 (m, 3H), 2.15–2.01 (m, 3H), 1.64–1.55 (m, 1H), 1.60 (s, 3H), 1.44 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 135.5, 134.4, 129.4, 124.5, 113.7, 78.1, 73.0, 55.3, 36.7, 35.1, 30.1, 29.6, 26.4, 23.2, 15.9 ppm; MS (Cl^+ , NH_3) m/z 310 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{32}\text{NO}_3$ [$\text{M} + \text{NH}_4$] $^+$ 310.2382. Found: 310.2384; HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 16.2 min (major), 18.2 min (minor) – e.r. 99:1. In a run using AD-mix α , (S)-diol *ent*-**3** was obtained: $[\alpha]_D^{24}$ = –5.9 (*c* 1.0, CH_2Cl_2); HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 15.9 min (minor), 17.1 min (major) – e.r. 6:94.

(+)-(3R,6R,7R)-2,6-Dimethyl-9-(4-methoxyphenyl)nonane-2,3,6,7-tetraol (3a). m.p. $130\text{--}131^\circ\text{C}$. $[\alpha]_D^{24}$ = +20.0 (*c* 1.0, EtOH); R_f = 0.28 (1:1 EtOH:PE); IR ν_{max} 3600–3100, 2972, 2952 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.16 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.41 (d, J = 9.6

Hz, 1H), 3.30 (d, J = 9.6 Hz, 1H), 3.29 (br s, 2H), 2.90 (ddd, J = 13.8, 8.8, 4.9 Hz, 1H), 2.65 (dt, J = 13.7, 8.2 Hz, 1H), 2.53 (br s, 1H), 2.20 (br s, 1H), 1.81–1.56 (m, 5H), 1.48–1.37 (m, 1H), 1.21 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 134.2, 129.4, 113.9, 78.9, 74.6, 73.2, 55.3, 50.7, 35.6, 33.6, 31.9, 26.5, 25.0, 23.3, 20.6 ppm; MS (Cl^+ , NH_3) m/z 344 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{31}\text{O}_5$ [$\text{M} + \text{H}$] $^+$ 327.2171. Found: 327.2164. A reference sample of ($\pm$)-diol **3** was prepared following a modified procedure of Warren and colleagues.⁷² To a solution of potassium ferricyanide (383 mg, 1.16 mmol), potassium carbonate (161 mg, 1.16 mmol), $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (4 mg, 0.012 mmol), quinuclidine (1 mg, 0.012 mmol), and methanesulphonamide (37 mg, 0.39 mmol) in water (2.5 mL) and *tert*-butanol (2.5 mL) at 0°C was added olefin **1** (100 mg, 0.39 mmol) and stirred vigorously for 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium sulfite (10 mL), extracted with EtOAc (2×20 mL), washed with brine (40 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (1:1:3:2 EtOAc:PE) to afford ($\pm$)-diol **3** (21 mg, 19%) as a colorless oil. HPLC (CHIRALCEL OJ; 10% IPA in *n*-hexane; 1.0 mL/min) t_R = 16.5 min, 17.8 min.

(-)-(S,E)-3-[6-(4-Methoxyphenyl)-3-methylhex-3-enyl]-2,2-dimethyloxirane (4).

Using a modified procedure of Corey et al.,⁷³ to a stirred solution of (*R*)-diol **3** (840 mg, 2.88 mmol) and pyridine (0.46 mL, 5.75 mmol) in CH_2Cl_2 (15 mL) at 0°C was added methanesulphonyl chloride (0.29 mL, 3.72 mmol). After 0.5 h the mixture was allowed to warm to room temperature and stirred for 3 h. Additional pyridine (1.38 mL, 17.7 mmol) was added and the reaction mixture stirred for 16 h. The reaction mixture was poured into a suspension of K_2CO_3 (6.63 g, 48 mmol) in methanol (25 mL), stirred for 6 h, concentrated under reduced pressure, diluted with water (50 mL), extracted with EtOAc (2×50 mL), washed with 10% aqueous CuSO_4 solution (100 mL), brine (100 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (1:19:1:4 EtOAc:PE) to afford the title product (*S*)-**4** (565 mg, 83%) as a colorless oil: R_f = 0.34 (1:9 EtOAc:PE); $[\alpha]_D^{24}$ = –2.5 (*c* 1.6, CH_2Cl_2); IR ν_{max} 2958, 2925, 2835, 1612, 1586 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.13 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.26 (tq, J = 5.8, 1.5 Hz, 1H), 3.81 (s, 3H), 2.72 (app. t, J = 6.3 Hz, 1H), 2.62 (t, J = 7.5 Hz, 2H), 2.32 (app. q, J = 7.6 Hz, 2H), 2.24–2.06 (m, 2H), 1.78–1.62 (m, 2H), 1.61 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 134.8, 134.3, 129.3, 124.3, 113.7, 64.1, 58.3, 55.2, 36.3, 35.1, 30.2, 27.5, 24.9, 18.8, 16.0 ppm; MS (Cl^+ , NH_3) m/z 292 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{27}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 275.2011, found 275.2011.

(-)-(S,E)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-ol (5a) and (+)-(R,E)-3-bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-ol (5b).

Following the method of Coulaudouros and Vidali,⁶⁷ to a solution of (S)-epoxide **4** (200 mg, 0.73 mmol) in *N*-methyl-2-pyrrolidone (0.22 mL) was added LiBr (99 mg, 0.95 mmol) and PPTS (183 mg, 0.73 mmol) and stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NaHCO_3 solution (15 mL), extracted with EtOAc (2×15 mL), washed with brine (30 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (1:9:1:4 EtOAc:PE) to yield first (E)-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-one (10 mg, 5%) as a colorless oil, second bromohydrin **5a** (66 mg, 25%) as a colorless oil, and third, bromohydrin **5b** (119 mg, 46%) as a colorless oil. Bromohydrin **5a**: R_f = 0.32 (1:9 EtOAc:PE); $[\alpha]_D^{24}$ = –10.6 (*c* 1.3, CH_2Cl_2); IR ν_{max} 3600–3200, 2958, 2926, 2855, 2835, 1612 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.14 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.27 (tq, J = 6.8, 1.4 Hz, 1H), 3.82 (s, 3H), 3.40 (dd, J = 10.1, 3.0 Hz, 1H), 2.63 (t, J = 7.5 Hz, 2H), 2.37–2.25 (m, 3H), 2.17–2.05 (m, 2H), 1.82 (s, 3H), 1.81–1.72 (m, 1H), 1.75 (s, 3H), 1.59 (s, 3H), 1.49 (dddd, J = 14.0, 10.3, 8.8, 5.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 135.1, 134.4, 129.4, 124.6, 113.7, 79.0, 75.4, 55.3, 36.4, 35.1, 31.1, 30.1 ($\times 2$), 28.9, 16.0 ppm; MS (Cl^+ , NH_3) m/z 374, 372 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{31}\text{NO}_2^{79}\text{Br}$ [$\text{M} + \text{NH}_4$] $^+$ 372.1538, found 372.1538. Bromohydrin **5b**: R_f = 0.24 (1:9 EtOAc:PE); $[\alpha]_D^{24}$ = +35.1 (*c* 1.3, CH_2Cl_2); IR ν_{max} 3600–3250, 2925, 2854, 1612 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.13 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.29 (t, J = 7.3 Hz, 1H), 3.95 (dd, J = 11.6, 1.9 Hz, 1H), 3.82 (s, 3H), 2.63 (td, J = 7.4, 3.4 Hz, 2H), 2.39–2.27 (m, 3H), 2.24 (s, 1H),

2.15 (dt, $J = 14.9, 8.2$ Hz, 1H), 1.97 (dtd, $J = 16.2, 8.0, 1.8$ Hz, 1H), 1.85–1.74 (m, 1H), 1.56 (s, 3H), 1.354 (s, 3H), 1.347 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 134.3, 133.7, 129.4, 125.5, 113.7, 72.5, 70.8, 55.3, 38.2, 35.1, 31.8, 30.2, 26.6, 25.9 15.8 ppm; MS (Cl^+ , NH_3) m/z 374, 372 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{31}\text{NO}_2^+\text{Br}$ [$\text{M} + \text{NH}_4$] $^+$ 372.1538, found 372.1540.

(-)-(S,E)-2-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-3-yl 2,3,4,5-tetrafluorobenzoate (6a). Using the method of Neises and Steglich,⁷⁴ to a stirred solution of secondary alcohol **5a** (380 mg, 1.07 mmol) in CH_2Cl_2 (7.5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (228 mg, 1.18 mmol), DMAP (39 mg, 0.321 mmol, 30 mol%) and DCC (287 mg, 1.39 mmol). After 4 h the reaction mixture was filtered through a silica plug eluting with Et_2O , concentrated under reduced pressure, and chromatographed (0:1.3:17 Et_2O :PE) to afford bromo tetrafluorobenzoate **6a** (520 mg, 92%) as a colorless oil. $R_f = 0.34$ (5:95 EtOAc :PE); $[\alpha]_D^{24} -22.0$ (c 1.1, CH_2Cl_2); IR ν_{max} 2935, 2861, 2362, 2344, 1729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dddd, $J = 10.3, 8.3, 6.0, 2.4$ Hz, 1H), 7.13 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.27 (d, $J = 9.9$ Hz, 1H), 5.22 (t, $J = 7.0$ Hz, 1H), 3.82 (s, 3H), 2.61 (app. t, $J = 7.7$ Hz, 2H), 2.37–2.19 (m, 2H), 2.10–2.03 (m, 3H) 1.99–1.85 (m, 1H), 1.83 (s, 3H), 1.82 (s, 3H) 1.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 161.5, 157.7, 148.0 (dddd, $J = 262, 11, 3, 1$ Hz), 146.6 (dddd, $J = 249, 10, 4, 2$ Hz), 143.6 (dddd, $J = 262, 17, 13, 3$ Hz), 141.4 (dddd, $J = 255, 17, 12, 3$ Hz) 134.3, 134.0, 129.4, 125.1, 114.7 (m), 113.7, 113.4 (dd, $J = 21, 3$ Hz), 81.5, 65.8, 55.2, 36.0, 35.0, 30.44, 30.35, 30.15, 29.3, 15.9 ppm; ^{19}F NMR (377 MHz, CDCl_3) δ -153.1 (t, $J = 20$ Hz, 1F), -147.0 (m, 1F), -137.6 (m, 1F), -133.6 (m, 1F) ppm; MS (Cl^+ , NH_3) m/z 548, 546 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Et^+) calcd. for $\text{C}_{25}\text{H}_{27}\text{O}_3^+\text{BrF}_4$ [M] $^+$ 530.1080, found 530.1080.

(+)-(R,E)-3-Bromo-9-(4-methoxyphenyl)-2,6-dimethylnon-6-en-2-yl 2,3,4,5-tetrafluorobenzoate (6b). Using the method of Neises and Steglich,⁷⁴ to a stirred solution of tertiary alcohol **5b** (350 mg, 0.99 mmol) in CH_2Cl_2 (7.5 mL) was added 2,3,4,5-tetrafluorobenzoic acid (383 mg, 1.97 mmol), DMAP (36 mg, 0.30 mmol, 30 mol%) and DCC (610 mg, 2.96 mmol). After 16 h further 2,3,4,5-tetrafluorobenzoic acid (191 mg, 0.98 mmol), DMAP (36 mg, 0.30 mmol, 30 mol%), and DCC (305 mg, 1.48 mmol) was added and stirred for 5 h, passed through a plug of silica, and chromatographed (0:1.2:3 CH_2Cl_2 :PE) to afford tetrafluorobenzoate ester **6b** (316 mg, 60%) as a colorless oil. $R_f = 0.3$ (5:95 EtOAc :PE); $[\alpha]_D^{24} +14.4$ (c 1.4, CH_2Cl_2); IR ν_{max} 2931, 2858, 2362, 1719 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.66–7.56 (m, 1H), 7.15 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.34 (t, 6.80 Hz, 1H), 4.54 (dd, $J = 11.5, 1.9$ Hz, 1H), 3.81 (s, 3H), 2.66 (t, $J = 7.6$ Hz, 2H), 2.44–2.26 (m, 3H) 2.21 (dt, $J = 13.8, 8.0$ Hz, 1H), 2.09–2.00 (m, 1H) 1.94–1.85 (m, 1H) 1.79 (s, 3H), 1.76 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 160.5, 157.7, 147.8 (dddd, $J = 262, 11, 4, 2$ Hz), 146.4 (dddd, $J = 249, 10, 4, 2$ Hz), 143.4 (dddd, $J = 262, 17, 13, 3$ Hz), 141.3 (dddd, $J = 255, 17, 12, 3$ Hz) 134.3, 133.6, 129.3, 125.7, 116.0 (m), 113.6, 113.2 (dd, $J = 21, 2$ Hz), 86.2, 61.6, 55.2, 37.8, 35.0, 31.5, 30.2, 24.1, 23.3, 15.8 ppm; ^{19}F NMR (377 MHz, CDCl_3) δ -153.5 (t, $J = 20$ Hz, 1F), -147.7 (tt, $J = 19, 8$ Hz, 1F), -138.0 (dt, $J = 22, 12$ Hz, 1F), -134.5 (m, 1F) ppm; MS (Cl^+ , NH_3) m/z 548, 546 [$\text{M} + \text{NH}_4$] $^+$; HRMS (Et^+) calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_3^+\text{BrF}_4$ [M] $^+$ 530.1080, found 530.1082.

(-)-(2R,4aR,10aS)- and (-)-(2R,4aS,10aR)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (2) from cyclization of bromotetrafluorobenzoates 6a and 6b. Cyclization of tertiary bromide **6a**: To a stirred solution of Me_3Al (2M in hexanes, 0.25 mL, 0.5 mmol) in CH_2Cl_2 (2 mL) at -78°C was added a solution of trifluoromethanesulphonic acid (43 μL , 0.5 mmol) in CH_2Cl_2 (4 mL) and stirred at -78°C for 0.5 h and 0°C for 0.5 h. The white suspension of Me_2AlOTf was recooled to -78°C and a solution of bromo tetrafluorobenzoate **6a** (50 mg, 0.292 mmol) in CH_2Cl_2 (2 mL) was added dropwise at -78°C . The reaction was allowed to warm to room temperature over 16 h, quenched with aqueous HCl solution (1M, 10 mL), extracted with CH_2Cl_2 (2×10 mL), washed with saturated aqueous NaHCO_3 solution (10 mL) and brine (10 mL), dried over Na_2SO_4 , concentrated under reduced pressure, and chromatographed (0:1.3:7 CH_2Cl_2 :PE) to afford first monocycles **7** as an inseparable mixture of at least two endocyclic and

two exocyclic alkenes (6 mg, 19%) as a colorless oil, $R_f = 0.39$ (1:4 CH_2Cl_2 :PE), and second bromides (2R,4aR,10aS)-**2** and (2R,4aS,10aR)-**2** as an inseparable mixture of diastereoisomers (d.r. 3:1, 8 mg, 25%) as a white solid: m.p. $92\text{--}93^\circ\text{C}$; $R_f = 0.64$ (40:60 CH_2Cl_2 :PE). The major diastereoisomer (2R,4aR,10aS)-**2** was identical to that produced in the BDSB mediated cyclization of polyene **1**, and the minor diastereoisomer (2R,4aS,10aR)-**2** was identified in the mixture by its characteristic ^1H NMR signal at 4.42 (1H, CHBr) ppm as a broad singlet (see SI 11 for ^1H and ^{13}C NMR spectra). Data for (2R,4aS,10aR)-**2** [as 1:3 mixture with bromide (2R,4aR,10aS)-**2**]: ^1H NMR (400 MHz; CDCl_3) δ 7.01 (d, $J = 8.3$ Hz, 1H), 6.84 (d, $J = 2.8$ Hz, 1H), 6.71 (dd, $J = 8.3, 2.8$ Hz, 1H), 4.42 (br s, 1H), 3.81 (s, 3H), 2.94–2.75 (m, 2H), 2.42–2.38 (m, 1H), 2.21–2.06 (m, 3H), 1.89 (dd, $J = 12.4, 2.5$ Hz, 1H), 1.82–1.67 (m, 2H), 1.22 (s, 3H), 1.12 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 150.5, 129.8, 127.1, 111.0, 110.0, 69.1, 55.3, 43.5, 38.4, 37.8, 33.4, 32.9, 29.1, 28.7, 25.5, 22.2, 18.5 ppm; GCMS (Et^+) m/z 337, 335 [$\text{M} - \text{H}$] $^+$. The diastereoisomers were inseparable by standard column chromatography on silica gel, but could be separated by preparative HPLC (Prep Si; n -hexane; 5 mL/min) $t_R = 145$ min [(2R,4aS,10aR)-**2**], 165 min [(2R,4aR,10aS)-**2**]. Bromide (2R,4aR,10aS)-**2**: $[\alpha]_D^{24} -100$ (c 0.04, CH_2Cl_2) $^+$; HPLC (CHIRALPAK AD; 1% IPA in n -hexane; 1.0 mL/min) $t_R = 4.7$ min (minor), 5.4 min (major), e.r. 98:2. Bromide (2R,4aS,10aR)-**2**: $[\alpha]_D^{24} -43$ (c 0.01, CH_2Cl_2) $^+$; HPLC (CHIRALPAK AD; 1% IPA in n -hexane; 1.0 mL/min) $t_R = 4.7$ min (major), 6.1 min (minor), e.r. 98:2. Cyclization of secondary bromide **6b** (135 mg, 0.254 mmol) was conducted as above using 2.5 equivalents of Me_2AlOTf to afford first monocycles **7** as an inseparable mixture of at least two endocyclic and two exocyclic alkenes (21 mg, 25%) as a colorless oil, $R_f = 0.39$ (1:4 CH_2Cl_2 :PE), and second bromides (2R,4aR,10aS)-**2** and (2R,4aS,10aR)-**2** as an inseparable mixture of diastereoisomers (d.r. 3:1, 30 mg, 35%) as a white solid. The diastereoisomers were separated by preparative HPLC (Prep Si; n -hexane; 5 mL/min) $t_R = 145$ min and [(2R,4aS,10aR)-**2**] and 165 min [(2R,4aR,10aS)-**2**]. Bromide (2R,4aR,10aS)-**2**: HPLC (CHIRALPAK AD; 1% IPA in n -hexane; 1.0 mL/min) $t_R = 4.7$ min (minor), 5.4 min (major), e.r. 98:2. Bromide (2R,4aS,10aR)-**2**: HPLC (CHIRALPAK AD; 1% IPA in n -hexane; 1.0 mL/min) $t_R = 4.7$ min (major), 6.1 min (minor), e.r. 98:2.

(-)-(4aS,10aS)- and (+)-(4aS,10aS)-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (8) from reduction of a 3:1 mixture of (-)-(2R,4aR,10aS)- and (-)-(2R,4aS,10aR)-2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes (2). Using the method of Chatgililoglu and colleagues,⁷⁵ to a stirred solution of (2R,4aR,10aS)-**2** and (2R,4aS,10aR)-**2** (d.r. 3:1, 15 mg, 45 μmol) in toluene (2 mL) was added tris(trimethylsilyl)silane (16.5 μL , 53 μmol) and azobisisobutyronitrile (0.73 mg, 40 μmol) and heated to 90°C for 2 h. The mixture was allowed to cool, concentrated under reduced pressure, and chromatographed (0:1.3:7 CH_2Cl_2 :PE) to give *trans*-decalin **8** (5 mg, 43%) as a single diastereoisomer as a colorless oil. $R_f = 0.42$ (20:80 CH_2Cl_2 :PE); $[\alpha]_D^{24} -23.0$ (c 0.26, CH_2Cl_2); lit.⁷⁶ (4aS,10aS)-**8** $[\alpha]_D +64.0$ (c 1.0, CHCl_3); IR ν_{max} 2997, 2924, 2852, 1686, 1609 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.96 (d, $J = 8.3$ Hz, 1H), 6.81 (d, $J = 2.7$ Hz, 1H), 6.66 (dd, $J = 8.3, 2.7$ Hz, 1H), 3.78 (s, 3H), 2.88 (ddd, $J = 16.8, 6.9, 1.3$ Hz, 1H), 2.78 (ddd, $J = 16.8, 11.2, 7.4$ Hz, 1H), 2.24 (br d, $J = 12.6$ Hz, 1H), 1.86 (dddd, $J = 13.3, 7.5, 2.0, 2.0$ Hz, 1H), 1.80–1.57 (m, 3H), 1.48 (br d, $J = 13.2$ Hz, 1H), 1.41 (td, $J = 13.1, 3.7$ Hz, 1H), 1.32 (dd, $J = 12.5, 2.3$ Hz, 1H), 1.23 (dd, $J = 13.7, 4.0$ Hz, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 157.6, 151.5, 129.7, 127.5, 110.7, 110.2, 55.3, 50.3, 41.7, 38.8, 38.0, 33.5, 33.3, 29.6, 24.8, 21.7, 19.3, 19.1 ppm; MS (Cl^+ , NH_3) m/z 259 [$\text{M} + \text{H}$] $^+$; HRMS (Cl^+ , NH_3) calcd. for $\text{C}_{18}\text{H}_{27}\text{O}$ [$\text{M} + \text{H}$] $^+$ 259.2062, found 259.2071. HPLC (CHIRALPAK AD; 1% IPA in n -hexane; 1.0 mL/min) $t_R = 4.12$ min [(4aS,10aS)-**8**], 4.72 min [(4aR,10aR)-**8**], e.r. 25:75.

RESULTS AND DISCUSSION

Polyene **1**⁴⁹ (Fig. 3) was selected as the basic carbon framework for our investigations, with the enantiopure

[†]The concentration of this solution is very dilute and the absolute magnitude of this measurement is liable to a large error.

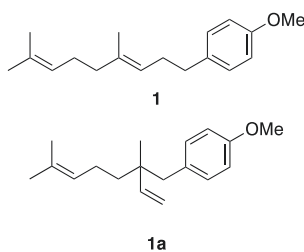
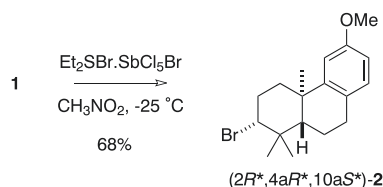


Fig. 3. Polyene **1** and isomer **1a**.



Scheme 1. BDSB mediated cyclization of polyene **1** into racemic tricyclic bromide (*2R**,*4aR**,*10aS**)-**2**.

bromonium ion to be formed on the terminus alkene, the second, internal alkene acting as the propagating olefin, and the polyene cyclization to be terminated by the aromatic nucleus. Diene **1** could be prepared by the palladium(0) catalyzed coupling of *p*-methoxybenzyl magnesium chloride with geranyl bromide,⁷⁷ but in our hands variable and significant quantities of the inseparable branched regioisomer **1a** were also observed.[§] The noncatalyzed coupling of the same Grignard reagent with geranyl diethyl phosphate as described by Synder⁴⁹ gave significantly improved regioselectivity.[¶] The direct action of BDSB on diene **1** as described by Synder⁴⁹ gave racemic tricyclic bromide (*2R**,*4aR**,*10aS**)-**2** (Scheme 1) in good yield as a single diastereoisomer, which in our hands proved to be crystalline. Single crystal x-ray determination (Fig. 4) of tricyclic bromide (*2R**,*4aR**,*10aS**)-**2** confirms the formation of the two six-membered carbocyclic rings as a *trans*-fused decalin ring system, and also the equatorial positioning of the bromine atom.

To the end of generating enantiopure bromohydrins,^{69–78} high purity diene **1**^{**} was first dihydroxylated using AD-mix β^{††} in good regioselectivity to give diol (*R*)-**3**, in excellent

[§]In multiple runs the ratio of **1**:**1a** was found to vary unpredictably from 35:1 to 10:1. The two isomers could not be separated by simple column chromatography.

[¶]In two 80 mmol batch reactions, the ratio of **1**:**1a** was determined to be 19:1 and 35:1. Analytically pure **1a** could be obtained from silver nitrate-doped silica gel column chromatography. The purity of **1** could be improved to >98% by a fractional distillation process (see Experimental).

^{**}High purity diene **1** free from branched **1a** was found to be essential for subsequent HPLC enantiomeric excess determination of products. The branched isomers were inseparable at all stages of the subsequent synthesis and overlapped and/or obscured the minor and/or major enantiomer signal in the HPLC analyses. This was especially problematic since the asymmetric dihydroxylation of diene **1** is so highly enantioselective (99:1 e.r.), and therefore high purity was required for accurate ee assessment. Moreover, in dihydroxylation runs using lower purity diene **1**, the branched isomer actually *accumulated* (e.g., in multiple runs using dienes **1**:**1a** in a 13:1 ratio, the ratio of linear diol **3** to its inseparable branched diol counterpart was 5:1). Evidently, while **3** could be further dihydroxylated to tetraol **3a** thus depleting the amount of **3**, the terminal alkene of the branched isomer diol was more resistant to further dihydroxylation.

Chirality DOI 10.1002/chir

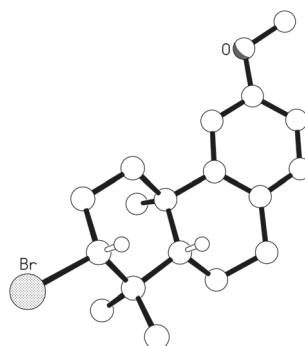
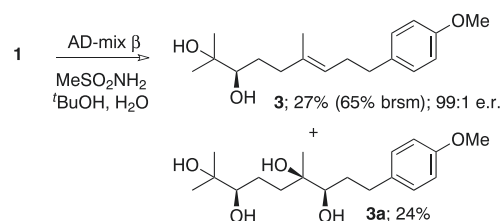


Fig. 4. The crystal structure of (*2R**,*4aR**,*10aS**)-**2**. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 928846). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (Fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

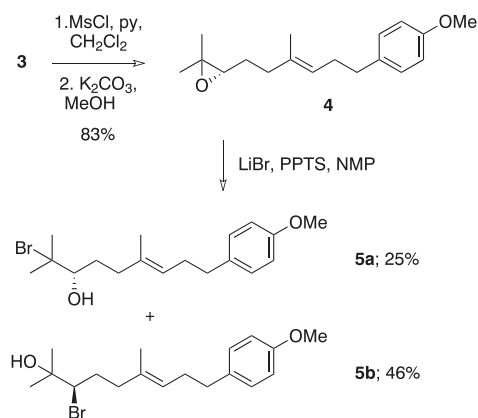


Scheme 2. Asymmetric dihydroxylation of diene **1**.

enantioselectivity (*R*)-**3**; e.r. 99:1)^{††} along with unavoidable formation of tetraol (*3R*,*6R*,*7R*)-**3a** (Scheme 2). The absolute configuration of diol (*R*)-**3** was assigned on the basis of the Sharpless mnemonic.^{71,79} Diol (*R*)-**3** was converted stereospecifically into epoxide (*S*)-**4** by the Corey et al. method,⁷³ followed by stereospecific (but non-regioselective) epoxide ring-opening by bromide anion⁵⁵ providing the separable regioisomeric bromohydrins (*S*)-**5a** and (*R*)-**5b** (Scheme 3). The regioisomeric bromohydrins (*S*)-**5a** and (*R*)-**5b** were assigned on the basis of their distinctive chemical shifts at 3.40 and 3.95 ppm in their ¹H NMR spectra, respectively, where two regioisomeric bromohydrins of a trisubstituted alkene were previously distinguished unambiguously by bromide induced ¹³C isotopic shifts.⁶⁹

In our previous work with non-alkene-containing substrates,⁶⁹ and on the basis of an earlier observation where we had observed the spontaneous formation of a bromonium ion from a 1-bromo-2-tetrafluorobenzoate on standing,⁸⁰ enantiopure bromonium ions had been generated by first converting enantiopure bromohydrins into 2,3,4,5-tetrafluorobenzoates, followed by activation with catalytic amounts of triflic acid. While we were confident that the corresponding tetrafluorobenzoates of bromohydrins (*S*)-**5a** and (*R*)-**5b** could be synthesized, the presence of the acid-sensitive trisubstituted alkenes in these substrates would render the use of triflic acid to subsequently generate bromonium ions undoubtedly problematic. Nevertheless, knowing that a suitable Lewis acid should offer an alternative activation mode, tetrafluorobenzoates (*S*)-**6a** (92%) and (*R*)-**6b** (60%) (Fig. 5) were prepared from alcohols (*S*)-**5a** and (*R*)-**5b**, respectively, by Steglich esterification⁷⁴ with 2,3,4,5-tetrafluorobenzoic acid. On activation—and stereospecific

^{††}The enantiomeric purity was assayed by chiral HPLC methods (see Supporting Information).



Scheme 3. Synthesis of enantiopure bromohydrins (S)-5a and (R)-5b.

displacement of the activated leaving group by neighboring group participation of the bromide—each of (S)-6a and (R)-6b should re-converge on the same *R*-configured enantiomerically pure bromonium ion **A** (Fig. 5).

Attempted bromonium ion initiated cyclization of (S)-6a or (R)-6b with catalytic quantities of triflic acid,⁶⁹ led, as predicted (vide supra), to extensive decomposition, and previous attempts to generate bromonium ions from vicinal bromo tetrafluorobenzoates of trisubstituted alkenes by solvolysis were unsuccessful⁶⁹ and not pursued in this study. Lewis acid activation was then explored, where the use of alkyl aluminum reagents as Lewis acids that lead to rigorously proton-free solutions⁸¹ was expected to be beneficial (oxophilic Lewis acid metal halides were rejected as potential mediators of the cyclization on the basis that hydrohalic acids would be generated during the course of the reaction), and preliminary studies with stoichiometric quantities of Yb(OTf)₃ and/or Eu(fod)₃ in CH₂Cl₂ or chlorobenzene were ineffective in initiating the cyclization even at elevated temperatures and/or under microwave irradiation. The use of stoichiometric quantities of trimethylaluminum to mediate the cyclization was found to be ineffective, leading to decomposition of both of the substrates (S)-6a or (R)-6b. Some cyclization adduct was observed using dimethylaluminum chloride as the Lewis acid activator, but a bromochloride was also observed as the major product, where intermolecular attack of any incipient bromonium ion by anionic chloride from the Lewis acid is evidently competing.^{††} The use of the Lewis acid dimethylaluminum triflate, incorporating the non-nucleophilic triflate anion—first reported in the 1980s⁸² and only infrequently employed⁸³—on either bromide (S)-6a (5 eq. Me₂AlOTf)^{§§} or (R)-6b (2.5 eq. Me₂AlOTf)^{§§} led to clean and complete conversion of substrates into cyclization adducts (Scheme 4).^{¶¶} *** In both cases, enantiopure bromide

^{††}From a run using 131 mg of a mixture of **6a** and **6b** (1:2) 9 mg of cyclization adducts **2** (d.r. 3:1) were isolated after extensive column chromatography. A noncyclized bromochloride (24 mg) was obtained with a characteristic mass spectrometry isotope pattern of 390 (82%), 392 (100%), 394 (49%) (M + NH₄)⁺.

^{§§}The use of less equivalents of Me₂AlOTf led to incomplete consumption of starting tetrafluorobenzoates. Evidently the 2° benzoate **6a** is less readily activated than the 3° benzoate **6b**.

^{¶¶}The use of MeAl(OTf)₂ as prepared from Me₃Al and 2TfOH in CH₂Cl₂ led to decomposition of the substrates.

^{***}Inspection of the ¹H NMR spectrum of the crude reaction mixtures show that all starting material has cleanly been converted to product. The relatively low isolated yields (scheme 4) reflect the difficult chromatographic purification/separation of these non-polar compounds.

(2*R*,4*aR*,10*aS*)-**2** (e.r. 98:2)^{††} was provided as a 3:1 mixture with diastereomeric enantiopure bromide (2*R*,4*aS*,10*aR*)-**2** (e.r. 98:2),^{††,†††} along with monocyclization adducts **7**,^{††† §§§}

The relative configuration of (2*R*,4*aR*,10*aS*)-**2** had already been established by x-ray crystallography (Fig. 4) from direct BDSB mediated cyclization of polyene **1** (Scheme 1), and the assignment of absolute configuration follows from an *R*-configured bromonium ion. The relative configuration of (2*R*,4*aS*,10*aR*)-**2** was established by (Me₃Si)₃SiH mediated dehalogenation of a 3:1 mixture of (2*R*,4*aR*,10*aS*)-**2** and (2*R*,4*aS*,10*aR*)-**2** diastereomers with essentially quantitative conversion (43% isolated yield) to give a *single* diastereomeric *trans*-decalin **8** (Scheme 5). The observed 3:1 e.r. for *trans*-decalin **8** allows assignment of the absolute configurations as (4*aR*,10*aR*)-**8** and (4*aS*,10*aS*)-**8** from (2*R*,4*aR*,10*aS*)-**2** and (2*R*,4*aS*,10*aR*)-**2**, respectively. The absolute configurations were confirmed by comparison of the negative sign of optical rotation for the 3:1 enantiomeric mixture of (4*aR*,10*aR*)-**8** and (4*aS*,10*aS*)-**8** with the rotation already reported for (+)-(4*aS*,10*aS*)-**8**.⁷⁶

Evidently, the bromonium ion initiated cyclizations described herein (Scheme 4) are proceeding enantiospecifically via enantiomerically pure bromonium ions^{68,¶¶,¶¶¶} without problematic intramolecular or intermolecular bromonium ion-to-alkene transfer.⁵³ We invoke a chair-like conformation **C** in the cyclization leading to (2*R*,4*aR*,10*aS*)-**2**, and a boat-like conformation **B** in the cyclization leading to (2*R*,4*aS*,10*aR*)-**2** (Fig. 6), each with the same absolute configuration of the bromonium ion (*R*-configured).^{¶¶,¶¶¶}

CONCLUSION

In conclusion, we have demonstrated the first enantiospecific polyene cyclizations initiated by enantiopure bromonium ions. We have identified the stoichiometric use of dimethylaluminum triflate to activate tetrafluorobenzoates of enantiopure bromohydrins to initiate such processes, where other Lewis and Brønsted acids fail. Notably, under

^{†††}The two diastereoisomers were not separable by column chromatography, but could be separated by preparative HPLC. This enabled the enantiomeric purity of each to be established without interference from the other (see Supporting Information).

^{§§§}A mixture of inseparable monocyclization adducts **7** could be isolated by column chromatography after cyclization. Inspection of the alkene region of the ¹H NMR spectrum reveals two monocycles with exocyclic methylene groups [δ_{H} 5.03 (s, 1H), 4.79 (s, 1H), and 4.90 (s, 1H), 4.17 (s, 1H) in a 3:1 ratio respectively] and two monocycles with endocyclic trisubstituted alkenes [δ_{H} 5.27 (br s, 1H), and 5.20 (br s, 1H) in a 3:1 ratio, respectively]. The endocyclic:exocyclic alkenes ratio is 1.5:1.

^{§§§}Attempts to convert the isolated monocyclic alkene mixture **7** into tricyclic adducts **2** with chlorosulphonic acid in nitromethane as previously demonstrated by Sakakura et al. (Ref. 10) in a similar system, led instead to extensive decomposition.

^{¶¶¶}The exact structure of a “bromonium ion” of an alkene will depend strongly on the substitution pattern of the alkene, the solvent, and its counterion. It is understood that a cyclic bromonium ion and an open β -bromocarocation represent the two extremes of a spectrum of ionic intermediates that are possible.

^{¶¶¶¶}The enantiospecific cyclization of tertiary bromide (S)-**6a** requires the intermediacy of an *R*-configured enantiomerically pure bromonium ion by stereospecific NGP displacement of the tetrafluorobenzoate group, whereas cyclization of secondary bromide (R)-**6b** may proceed instead directly via a tertiary carbocation. The near identical product distributions for each substrate as observed by inspection of the crude reaction mixtures by ¹H NMR implicate a single common intermediate *viz.* a bromonium ion.

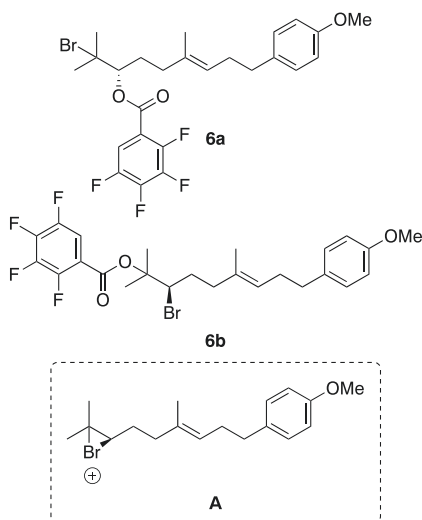
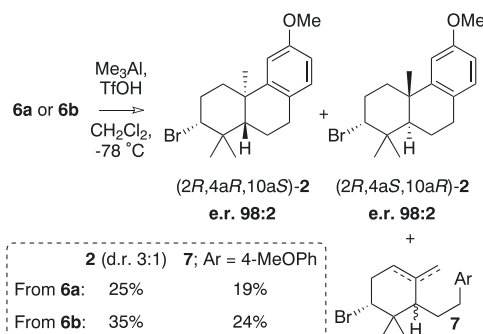
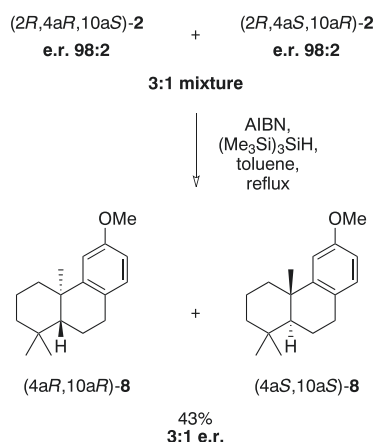


Fig. 5. Tetrafluorobenzoates (S)-**6a** and (R)-**6b** as precursors to the same enantiomerically pure bromonium ion **A**.



Scheme 4. Enantiospecific cyclization of tetrafluorobenzoates (S)-**6a** and (R)-**6b** with stoichiometric dimethylaluminum triflate.



Scheme 5. Correlation of absolute and relative configurations by reduction of a 3:1 diastereomeric bromide mixture **2** to *trans*-decalin **8**.

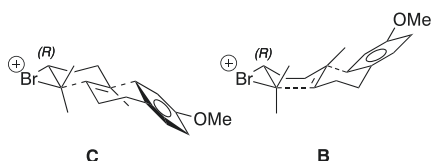


Fig. 6. Chair-like **C** and boat-like **B** geometries in the cyclizations leading to (2R,4aR,10aS)-**2** and (2R,4aS,10aR)-**2**, respectively.

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the reported cyclization conditions, any intramolecular or intermolecular bromonium ion-to-alkene transfer is evidently not in operation. Further work will require the identification of other Lewis acid-leaving group combinations to improve overall yields of polycyclic products and to expand the substrate scope.

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