MONASH University

The Asymmetric Synthesis of 2-*epi*-Prevezol C and the Diastereoisomers of *Quercivorol*

A thesis submitted to the Faculty of Science, Monash University,
in fulfilment of the requirements for the degree of
Doctor of Philosophy

by

Michael Blair

BSc. (Hons) Monash University

School of Chemistry
Monash University
Melbourne, Australia

November 2009

“There are no general reactions”

- R. B. Woodward

Table of Contents

Acknowledgements

I wish to extend to my deepest and sincerest gratitude to my supervisor Dr. Kellie Tuck for her mentorship and personal support over the past three and half years whilst working on the Prevezol project. The freedom you bestowed upon me to explore avant-garde chemistry (when nothing else worked), has allowed me to mature into the chemist I am today. The work contained in this dissertation would not have been possible without your support, and the financial assistance of the School of Chemistry. Likewise, to the skilled technical staff Dr Peter Nichols, Sally Duck and Dr Craig Forsyth, thank you for all your help which enabled the elucidation and characterisation of the compounds described in this thesis.

During my time as a PhD student, I have had the amazing opportunity to befriend many talented chemists who share a similar passion for chemistry as I do, some of which are my dearest friends today, all of whom have taught me so much. I especially wish to thank Matt Belousoff, Anthony Chesman, Ben Fraser, Kevin Fraser, Chintan Jani, Amanda Lee, Anna Leung, David Lupton, Max Massi, Brad Wilman and past and present Tuck group members.

In particular, I wish to acknowledge Dr. Clint Woodward for his patience and persistence in the editing of this thesis; I am deeply grateful for yours and Ruth's friendship over the years.

I dedicate this thesis to my loving mother Jill, my brother Kris and his partner Rebecca, my grandmother and my aunty for their stability and support in all the diverse endeavors I pursue; your unwavering support and warm-heartedness has been indispensable through this period in my life.

Finally to Natalie, I hope one day I can repay all the love and support you (and your family) have shown me, you are the love of my life.

Abstract

The brominated secondary metabolites isolated from the polar fractions of the macroalga *Laurencia Obtusa* (Lamoroux), termed 'Prevezols' posses cytotoxic properties against a range of human carcinoma lines. These novel diterpenes contain unique molecular architectures with an incredibly rare and challenging *syn*-bromohydrin motif, to date unaddressed *via* total synthesis.

This dissertation discloses the synthesis of the diterpene framework of Prevezol C, *via* a stereoconvergent allylic alkylation strategy of two monoterpene chirons, derived from the optically pure commercial mixture of *cis*- and *trans*- limonene oxide. The first part of this thesis is concerned with the separation and isolation of both the *cis*- and *trans*-limonene oxide isomers *via* a hydrolytic kinetic separation, to the corresponding limonene *trans*-diaxial and -diequatorial diols (Chapter 2), which are implemented as part of the synthesis of the 2-bromo epimer of Prevezol C (Chapter 3, Part 1).

A novel free radical hydrodebromination strategy (Chapter 3, Part 2) was successfully employed as a means of accessing the naturally occurring *syn*-bromohydrin relationship found in the Eastern domain of the Prevezols, and several other secondary metabolites derived from the red algae species of *Laurencia.*

Finally, a second total synthesis of the major and minor constituents of the ambrosia beetle *Platypus quercivorus* was also achieved (Chapter 4) *via* a palladium catalysed deoxygenation strategy of the limonene *trans*-diaxial and -diequatorial diols.

Part A: Monash Research Graduate School General Declaration:

Declaration for thesis based or partially based on conjointly published or unpublished work.

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 3 original papers published in peer reviewed journals and 1 unpublished publication. The core theme of the thesis is synthetic organic chemistry. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Chemistry under the supervision of Kellie Tuck, and our collaborators, Phil Andrews, Peter Junk, Max Massi, Ben Fraser and Craig Forsyth.

In the case of chapters 2, 3 and 4 my contribution to the work involved intellectual input, the execution and analysis of experiments and drafting the experimental data into a manuscript format.

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution
2	*"Water soluble lanthanoid benzoate complexes for the kinetic separation of cis/trans-limonene oxide"*	Published	Intellectual input. Execution and analysis of experiments (10%)
2	*"Facile methods for the separation of the cis and trans diastereomers of Limonene 1,2-Oxide and convenient routes to diequatorial and diaxial 1,2-Diols"*	Published	Intellectual input. Execution and analysis of experiments. Manuscript drafting. (50%)
3	*A new diastereoselective entry to the (1S,4R)- and (1S,4S)-Isomers of 4-isopropyl-1-Methyl-2-cyclohexan-1-ol, Aggregation pheromones of The ambrosia beetle Platypus quercivorous*	Published	Intellectual input. Execution and analysis of experiments. Manuscript drafting 70%
4	*Towards the Synthesis of Prevezol C: An Efficient Route to 2-Epi-Prevezol C*	Submitted	Intellectual input Execution and analysis of experiments. Manuscript drafting 70%

I have / ~~have not~~ renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

[redacted]
Michael Blair

Wednesday, November 25th, 2009

Copyright Notices

Notice 1

Notice 2

Abbreviations

2°	secondary
2D	two dimensional
Ac	acetyl
Acac	acetylacetonate
AIBN	azobisisobutyronitrile
AIP	aluminium *iso*propoxide
ATP	adenosine triphosphate
BAIB	bis(acetoxy)iodobenzene
COSY	Correlation Spectroscopy
d	doublet
DBU	diaza(1,3)bicyclo[5.4.0]undecane
DCM	dichloromethane
de	diastereomeric excess
DEPT	Distortionless Enhancement by Polarisation Transfer
DIBAL-H	diisobuytlaluminium hydride
DIPA	diisopropylamine
dmdba	dimethoxydibenzylideneacetone
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EtOAc	ethyl acetate
FCC	flash column chromatography
FGI	functional group interconversion
h	hour(s)
His	histidine
HMBC	Heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence

HRMS	high resolution mass spectrometry
hν	light
Hz	Hertz
IBA	2-iodosobenzoic acid
IBX	iodoxybenzoic acid
Im	imidazole
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LO	limonene oxide
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
mins.	minutes
MS	mass spectrometry
Ms	methanesulfonyl
MVK	methyl vinyl ketone
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-butyl lithium
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
N.R.	no reaction
[O]	oxidation event
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
Ph	phenyl
PHOX	2-[2-[Bis(2-tolyl)phosphino]phenyl]-4-*tert*-butyl-2-oxazoline
PMB	*p*-methoxybenzyl
PMBTCA	*p*-methoxybenzyl trichloroacetimadate
PP	pyrophosphate

ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
Py.	pyridine
RCM	Ring Closing Metathesis
RT	room temperature
s	singlet
S.M.	starting material
TBAF	*n*-tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TCIA	trichloroisocyanuric acid
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TfOH	triflic acid
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
TTMSS	*tris*(trimethylsilyl)silane
V-BrPO	vanadium bromoperoxidase
q	quartet

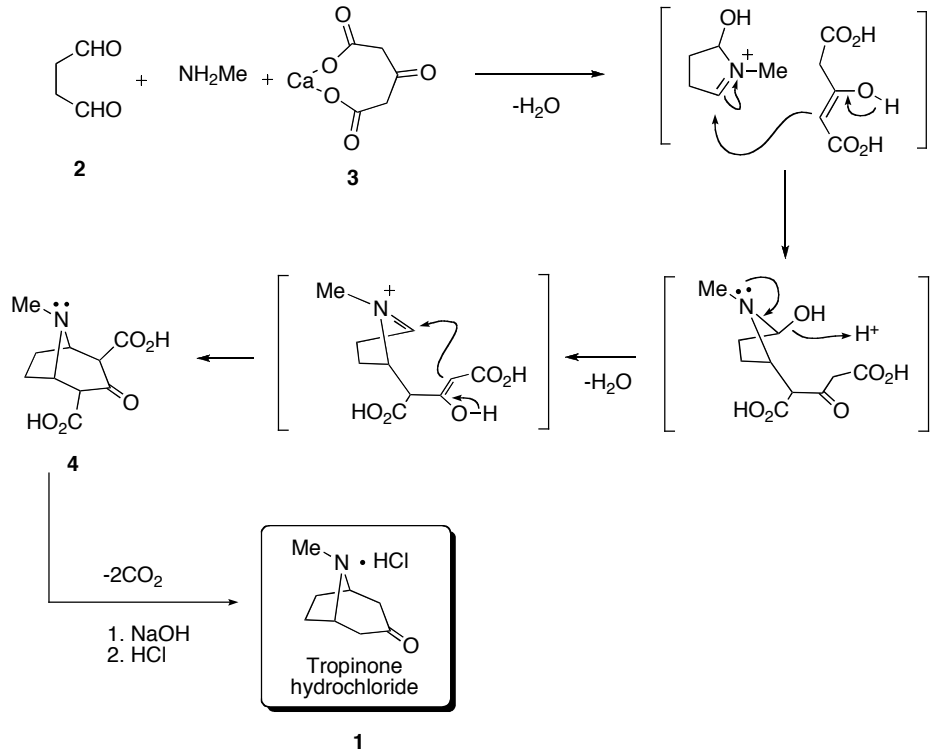
1.0 Natural Product Synthesis: Structural Confirmation and Revision through Total Synthesis.

Natural products represent a unique area in our scientific culture, shaping and influencing fields as diverse as biology, medicine, spectroscopy and instrumentation, through to the subject of this dissertation: natural product syntheses.[1] A key issue that continues to surround this field of science, and will continue to play an underpinning role is the structural elucidation of natural products. The process of elucidation has evolved considerably over the last century moving away from structural determination *via* degradation studies to modern spectroscopic techniques, and when combined with total synthesis, unequivocal structural elucidation can be obtained.[2]

The advent of modern spectroscopic techniques in the late 1950's, particularly NMR spectroscopy and mass spectrometry, heralded a new era of natural product characterisation, so much so, structural elucidation became commonplace.[3] Complex secondary metabolites could be successfully elucidated in both a fraction of the time and the quantity of the natural product previously required, without a single degradation experiment.[3] Simple destructive methods of characterisation such as melting point analyses were now considered a prohibitive waste of material.[3] Moreover, technological advancements in X-ray crystallography permitted the structural determination and absolute configuration of complex natural products with just a single crystal.[1] Such advances in modern spectroscopy beckon the ever-pertinent question of why a practitioner performs the art of total synthesis? To answer this, a brief overview of natural product isolation, characterisation and synthesis will be discussed below.

The modern era of natural product synthesis supplanted more than a century and a half of characterisation that relied almost entirely on the utility of chemical synthesis; synthesis which revealed many examples of new reactions particularly aromatic and heterocyclic chemistry.[4] Pioneers in the early to mid 20th century include Nobel Laureates such as Sir Robert Robinson and Robert Burns Woodward.[1, 5] Robinson's timeless, bio-inspired multi-component total synthesis of tropinone **1** (Scheme 1.0) demonstrated biological processes can be mimicked in a round bottom flask, without the aid of enzymes (1917).[6] Robinson's synthesis used the readily available reagents succinaldehyde **2**, methylamine and the

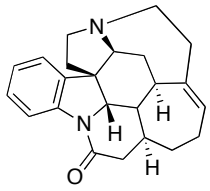
calcium salt of acetone dicarboxylic acid **3**. By initiating a series of intermolecular and intramolecular Mannich reactions, access to the bicyclic dicarboxylic acid **4** was readily obtained. Treatment of diacid **4** with sodium hydroxide to affect a double decarboxylation followed by acidification yielded the hydrochloride salt of tropinone **1** in high yields (>90%).[6] Such synthetic feats as demonstrated by Robinson, were achieved through a prior knowledge of complex degradation studies, yielding in what could only be described as unlocking natures most intriguing, and challenging molecular puzzles.[3]



Scheme 1.0: Robinson's synthesis of tropinone hydrochloride 1[6]

A milestone in the area of structural elucidation, was the assignment of strychnine **5** (Fig 1.0); a highly toxic alkaloid (oral LD_{50} 16 mg/kg rat) isolated from the beans of *Strychnos ignatii*, indigenous to both the Coromandel Coast of India and the rain forests of the South-East Asian archipelagos.[7] Its structural assignment was first reported in 1946; a culmination of a 40-year collaborative effort between Sir Robert Robinson and Herman Leuchs.[8] Less than 5 years later, crystallographic studies[9] revealed the correct gross structure of strychnine thereby supporting Robinson and Leuchs proposed structure, in which Robinson commented "for its molecular size it is the most complex substance known".[10] These reports were quickly followed by Woodward and co-workers' seminal total synthesis of (-)-strychnine **5** in 1954.[5] Woodward had demonstrated for the first time

that Natures most complex targets could be obtained *via* total synthesis, ushering in the golden era of total synthesis.[4]

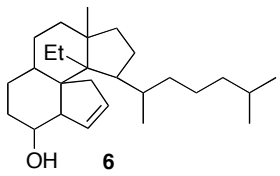


5

Fig 1.0: Strychnine 5 as determined by X-ray crystal analysis[11]

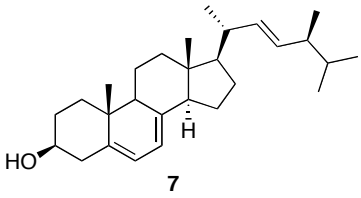
1.1 Structural Misassignment

A classic example of misassignment is that of the originally proposed structure of cholesterol **6** (Fig 1.1) by Wieland and Windaus earning them the 1927 and 1928 Nobel prize in chemistry respectively, only discover 5 years later that their originally proposed structure was incorrect![12, 13] An X-ray crystal structure of ergosterol **7** (which had also been misassigned, by way of the position of the pendant alcohol) provided the framework for the revised structure of cholesterol **8**.[3, 14-17]



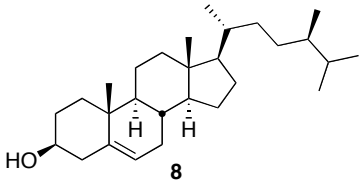
6

The Wieland and Windaus structure of cholesterol **1927**[12, 13]



7

Correct structure of ergosterol derived from X-ray analysis **1932**[14]



8

Revised structure of cholesterol **1932**[15-17]

Fig 1.1: Evolution of the correct gross structure of cholesterol

More than half a century on, isolation through to structural assignment of natural products is still plagued with the same problems of misassignment.[3] Despite the fact that modern spectroscopic methods are considered well advanced, errors can never be completely ruled out, this is attributed primarily to human error and the deductive nature of these spectroscopic techniques. Although an X-ray crystal structure can be considered a

definitive proof of structure, errors can still arise. For example, the position of hydrogen atoms cannot be determined *via* X-ray crystallographic analysis, furthermore, the possibility of misassignment of heteroatoms, particularly nitrogen and oxygen is also an issue specific to this spectroscopic technique. A recent review by Nicolaou and Snyder, surveyed the literature from 1990 to 2004 and revealed a staggering number of structural revisions (well over 300 in fact!) which extended beyond simple stereochemical problems.[3] Two recent examples of structure revisions made possible through total synthesis are: Sclerophytin A (**9** and **9a**)[18] revised by both Overman and Paquette and co-workers[19] and Annuionene A (**10** and **10a**),[20] revised by the Takikawa group,[21] both are depicted below in Fig 1.2.

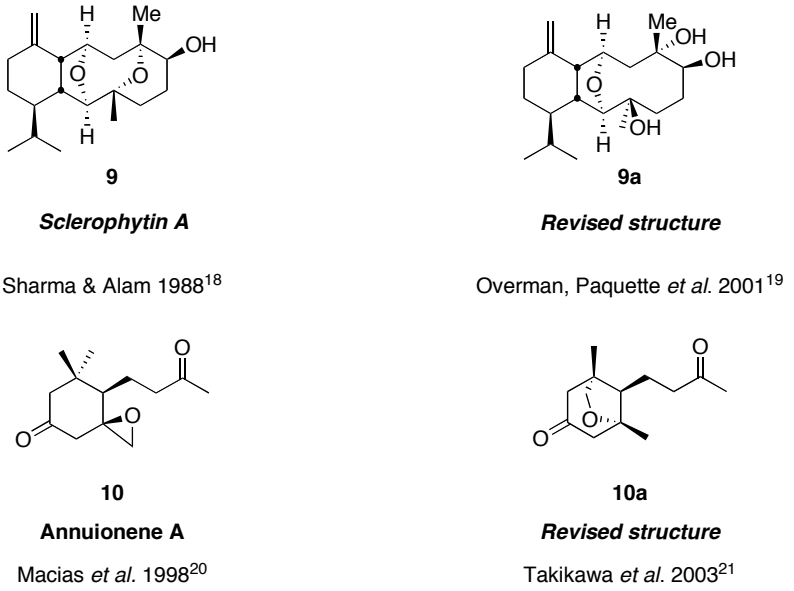
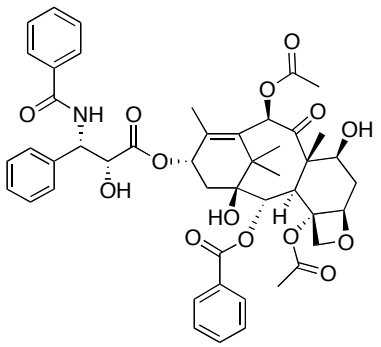


Fig 1.2 Structural revision through total synthesis

Nicoloau and Snyder's review clearly underscores the necessity of total synthesis both as a definitive means of structural determination and revision, but also the investigation of new strategies, reagents and undiscovered reactions, which is the topic of this dissertation.

1.2 Natural Products as Anticancer Lead Compounds: The Prevezols

Cancer is the second leading cause of mortality in the developed world.[22] It results in one out of five deaths worldwide, second to cardiovascular diseases, with 6 million cases per year.[22] Current chemotherapeutic natural products have been developed predominantly from terrestrial plants and microorganisms, such as paclitaxel **11** (Fig 1.3).[23] Such natural products and their synthetic derivatives continue to constitute the vast majority of chemotherapeutic agents for the treatment of all types of cancer, displaying various modes of action that disrupt cellular division and proliferation.[24] With the marine ecosystem accounting for more than 95% of the planets biosphere, it remains a largely untapped resource for new potent cytotoxic agents.[23] Recent examples of potent marine cytotoxins include the bryostatins, eluthrobin, discodermalide and jaspamide to name a few.[25]



11

Fig 1.3: Paclitaxel 11

Recently a novel class of potent cytotoxic brominated diterpenes (**12** to **18**; Fig. 1.4) were isolated from the secondary metabolites of the red algae, *Laurencia obtusa,* native to the coastal rocks of Preveza, Greece.[26, 27] Prior to the isolation of metabolites (**13** to **18**) Mihopoulos and Illopoulou *et al.* disclosed another metabolite, Prevezol A **12**, which formed the basis for both the stereochemical and carbocycle assignment of Prevezol B **13** and Prevezol C **14**.[27] The structural assignment of Prevezol A **12** will be discussed further in Section 1.3.

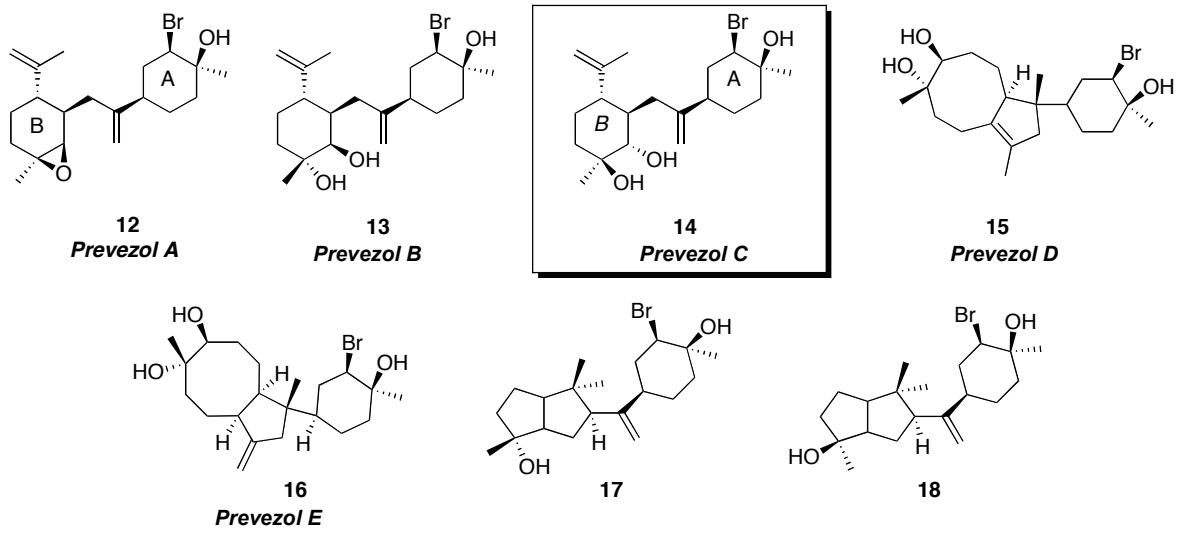


Fig 1.4: The proposed structure of Prevezol 12-18 [26, 27]

The secondary metabolites of *Laurencia obtusa*, termed 'Prevezols' were tested for cytotoxicity against five human cell lines. Two metabolites, Prevezol C **14** and compound **17** have exhibited moderate cytotoxicity against common forms of carcinomas (Table 1.0).[26]

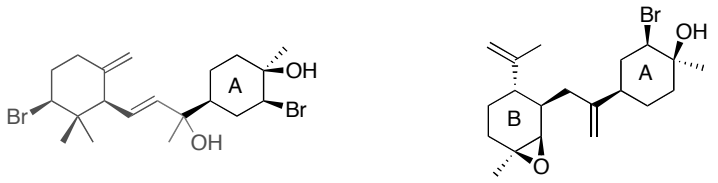
		IC_{50} μM				
Cell line	Origin	**13**	**Prevezol C 14**	**15**	**16**	**17**
MCF7	Breast	140.5	135.6	>200	>200	172.3
PC3	Prostate	158.5	80.4	>200	>200	50.8
HeLa	Cervix	80.5	78.0	120.6	>200	34.4
A431	Epidermis	78.4	65.2	135.5	>200	65.8
K562	Myelogenic	123.5	76.4	156.9	>200	76.4

Table 1.0: In vitro antitumor activity of the Prevezols 13-14 against common cell lines[26, 27]

Prevezol C **14**, has been selected as an initial candidates for total synthesis, due to the structural homology shared with Prevezol A **12** and Prevezol B **13** which may be accessed at a later stage in the Tuck group laboratories, along with mapping their pharmacophore and understanding their mode of action.

1.3 Structural Elucidation of Prevezol A

As mentioned earlier, the structure of Prevezol C **14** was inferred from the prior assignment of Prevezol A **12**. The elucidation of Prevezol A **12** was sought *via* a combination of standard 1D and 2D NMR spectroscopy, EI-HRMS measurements and IR spectroscopy.[27] EI-HRMS supported the molecular formula $C_{20}H_{31}BrO_2$, with two molecular ions $(M+H)^+$ at *m/z* 382 and 384 in a 1:1 ratio, indicative of one bromine atom.[27] Furthermore with an unsaturation degree of 5, it was proposed the metabolite contained two double bonds and three rings; one of which an oxirane. Distortionless Enhancement by Polarization Transfer (DEPT) ^{13}C NMR spectroscopy revealed the proton multiplicity of the carbon scaffold indicating four quaternary, five methine, eight methylene and three methyl carbons. Two of the eight methylenes were assigned as exocyclic olefins as determined *via* IR and ^{13}C NMR spectroscopy vibrating at 3080, 1650 and 880 cm^{-1}; and resonating at δ 111.6 and 110.1 ppm respectively. Two of the three methyl carbons were deshielded as determined by ^1H NMR spectroscopy, resonating as broad singlets (integrating for 3H) at δ 1.27 and 1.31 ppm indicating direct attachment to an oxygenated quaternary centre; the remaining methyl group resonates at δ 1.63 ppm, suggesting a vinylic methyl group. Whilst Prevezol A's **12** gross structure bared little resemblance to other *Laurencia* diterpenes; the Eastern hemisphere (ring **A**) was observed to share the same ^{13}C NMR values of the Eastern domain of the *syn*-bromohydrin containing natural products obtusadiol **19**.[28, 29]



Obtusadiol **19** ***Prevezol A*** **12**

Fig 1.5: The proposed structures of obtusadiol 19, and Prevezol A 12[26, 27]

Obtusadiol's **19** gross structure and relative stereochemical assignment was sought *via* a series of degradation experiments and standard physical analysis techniques.[28] Boiling obtusadiol **19** in the presence of potassium hydroxide/methanol showed no epimerization

of the asymmetric centre bearing the allylic side chain, determined *via* coupling constant analysis of the ^{1}H NMR spectrum. This is consistent with a thermodynamically preferred equatorial substituent.[28]

The stereochemistry of the 2° bromide substituents of obtusadiol **19** were inferred from coupling constant analysis of the ^{1}H NMR spectrum revealing two doublets of doublets centered at 4.18 ppm (12 and 4 Hz respectively, 2H); thereby supporting two bromo methine protons, both orientated axially (Fig 1.6).

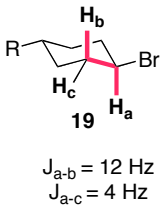
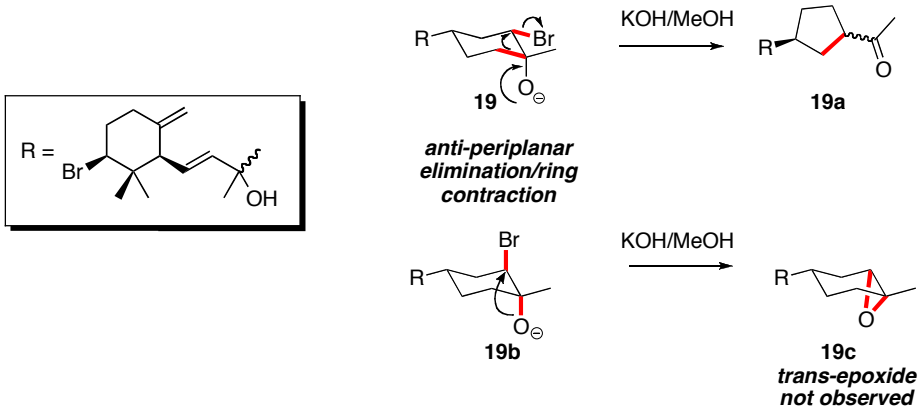


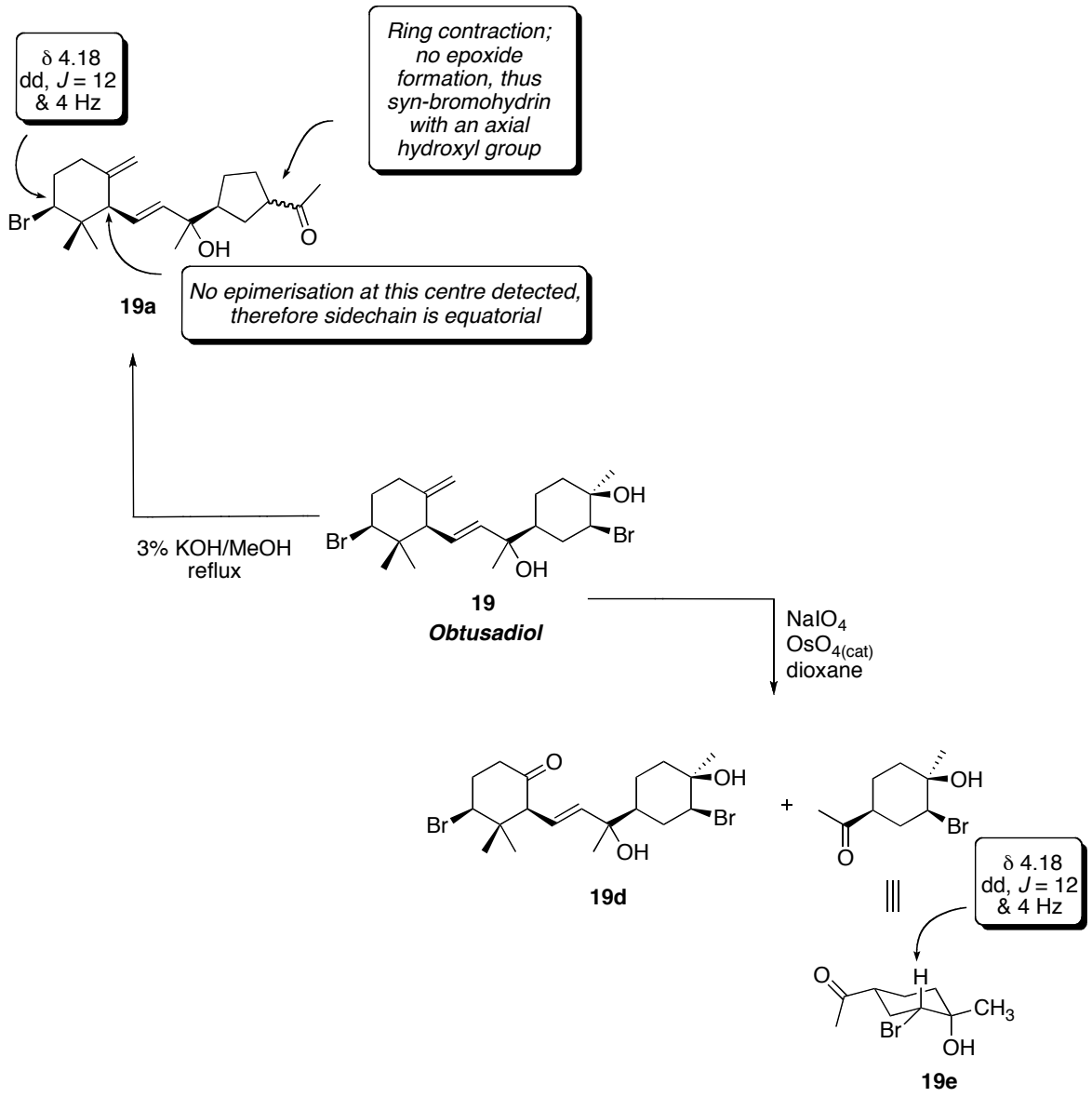
Fig 1.6: Indicative coupling constants of an axial bromo methine proton on a cyclohexane ring

More importantly however, the relative stereochemistry of the bromohydrin moiety on the Eastern hemisphere was assigned as *syn* based on the observation of the ring contracted metabolite **19a** of obtusadiol **19**; and not the epoxide **19c** (Scheme 1.1). This type of ring contraction process is indicative of an anti-periplanar arrangement of the highlighted bonds of the alkoxide **19** that leads directly to the ring contracted cyclopentane; and not the expected *trans*-epoxide from the trans diaxial bromo-alkoxide **19b**.[28]



Scheme 1.1: Ring contraction and ring closure of the bromohydrin 19[28]

Other notable outcomes of Howard and Fenical's degradation and physical analysis are summarized below in Scheme 1.2.



Scheme 1.2: Obtusadiol 19 Degradation studies[28]

Mihopolous *et al*. assigned the relative stereochemistry of the Western (***B***) ring of Prevezol A **12** *via* conformational searching using the Macromodel software suite.[27] A Monte Carlo conformational search gave a low energy conformation which showed good correlation to the observed nOes (Fig 1.7), allowing the relative assignment of the asymmetric centres of the B ring as either (*R, S, S, R)* or as the enantiomeric form (*S, R, R, S*). The absolute configuration of the Western domain is as yet unknown.[27]

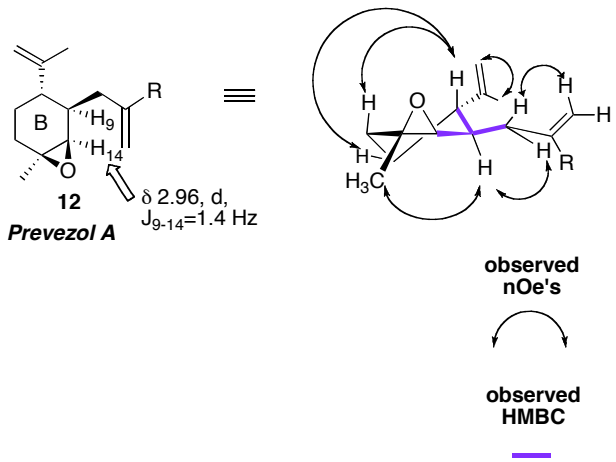


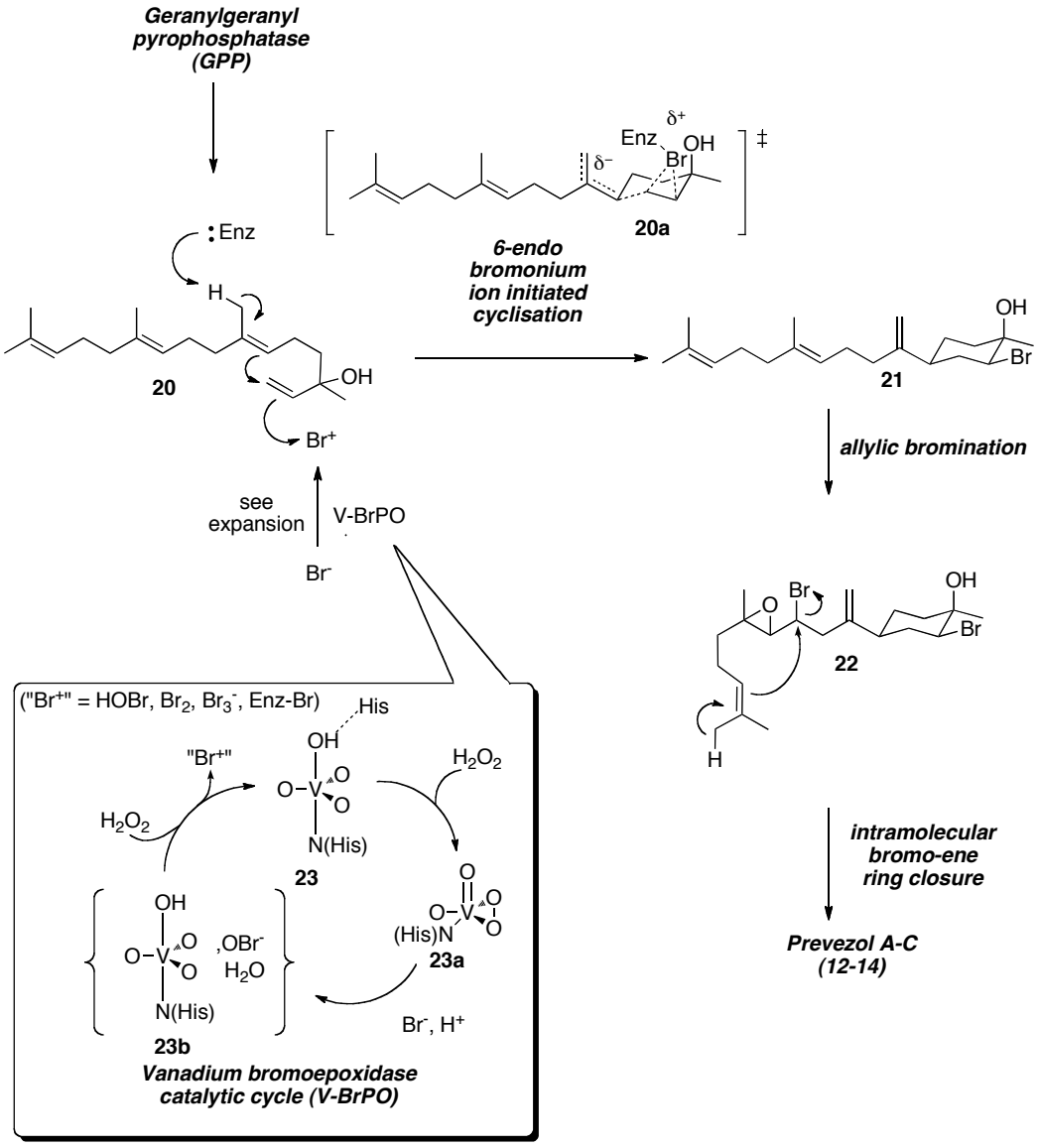
Fig 1.7: Selected nOe interactions and HMBC correlations of the Western ring of Prevezol A 12[27]

1.4 The Hypothetical Biogenetic Pathway to Prevezol A-C

Geranylgeranyl pyrophosphate derived from the putative mevalonic acid pathway (discussed further in Chapter 2) yields the diterpene **20** (Scheme 1.3).[30] Bromination of the acyclic diterpene **20** *via* the recently discovered vanadium bromoperoxidase catalyst cycle (see expansion, Scheme 1.3) and subsequent 6-*endo* bromonium ion initiated cyclisation leads to the formation the hemicyclised diterepene **21**. Subsequent allylic bromination of hemicyclised diterepene **21** is thought to yield the brominated cyclisation precursor **22**, which undergoes further ring closure to form Prevezol A. Subsequent functional group interconversions are proposed to yield the Prevezol B **13** and Prevezol C **14** congeners.[26]

We were interested by this family of Prevezols, as these metabolites contain an incredibly rare *syn*-bromohydrin moiety which is infrequently reported in the chemical literature.[28, 29, 31] This functionality, and other brominated sesqui and diterpenoid secondary metabolites are unique to the red algal genus *Laurencia* and the herbivorous mollusks which feed on this macroalgae.[30] The proposed biogenic cascade which leads to this interesting *syn*-bromohydrin is mediated by the *de novo* production of bromonium ion equivalents, produced from the oxidation of bromide ions in sea water.[32, 33] This process is mediated by the redox active vandatate co-factor **23** (Scheme 1.3) contained at the heart of the (V-BrPO) enzyme. The vanadium co-factor **23** (Scheme 1.3) acted upon hydrogen peroxide as the re-oxidant in this catalytic process. This is summarized in the catalytic cycle expansion, Scheme 1.3.[33] The production of a bromonium ion source such as HOBr, Br_2,

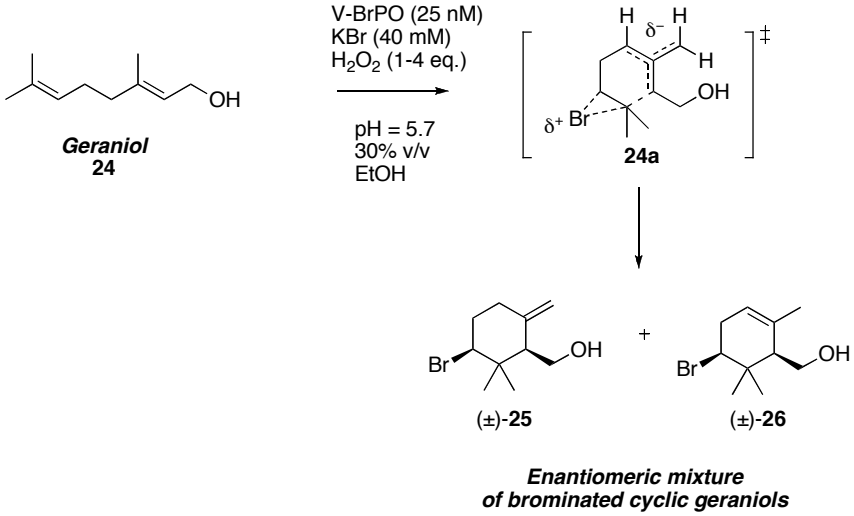
Br_3^-, Enz-Br etc. is proposed to initiate the biogenic 6-*endo* bromonium ion cyclisation described in Scheme 1.3.[26, 32]



Scheme 1.3: Proposed biogenic pathway to Prevezol A-C (12-14), and the V-BrPO catalytic cycle[26, 32]

Carter-Franklin *et al.* isolated and cloned the V-BrPO enzyme expressed by the algal families which produce halogenated terpene secondary metabolites (i.e *Plocamium cartilagineum, Laurencia pacifica, Corallina officinalis*) and performed a range of biomimetic bromonium ion initiated cyclisations of monoterpene substrates under physiological conditions.[33] One such example of a biogenetic cyclisation is depicted in Scheme 1.4.[33] Whilst a yield was not reported this for reaction; complete consumption of

the geraniol **24** starting material was observed. Finally, it is noted that both the cyclised isomers **25** and **26** were isolated as a single diastereoisomer, however as the racemate.



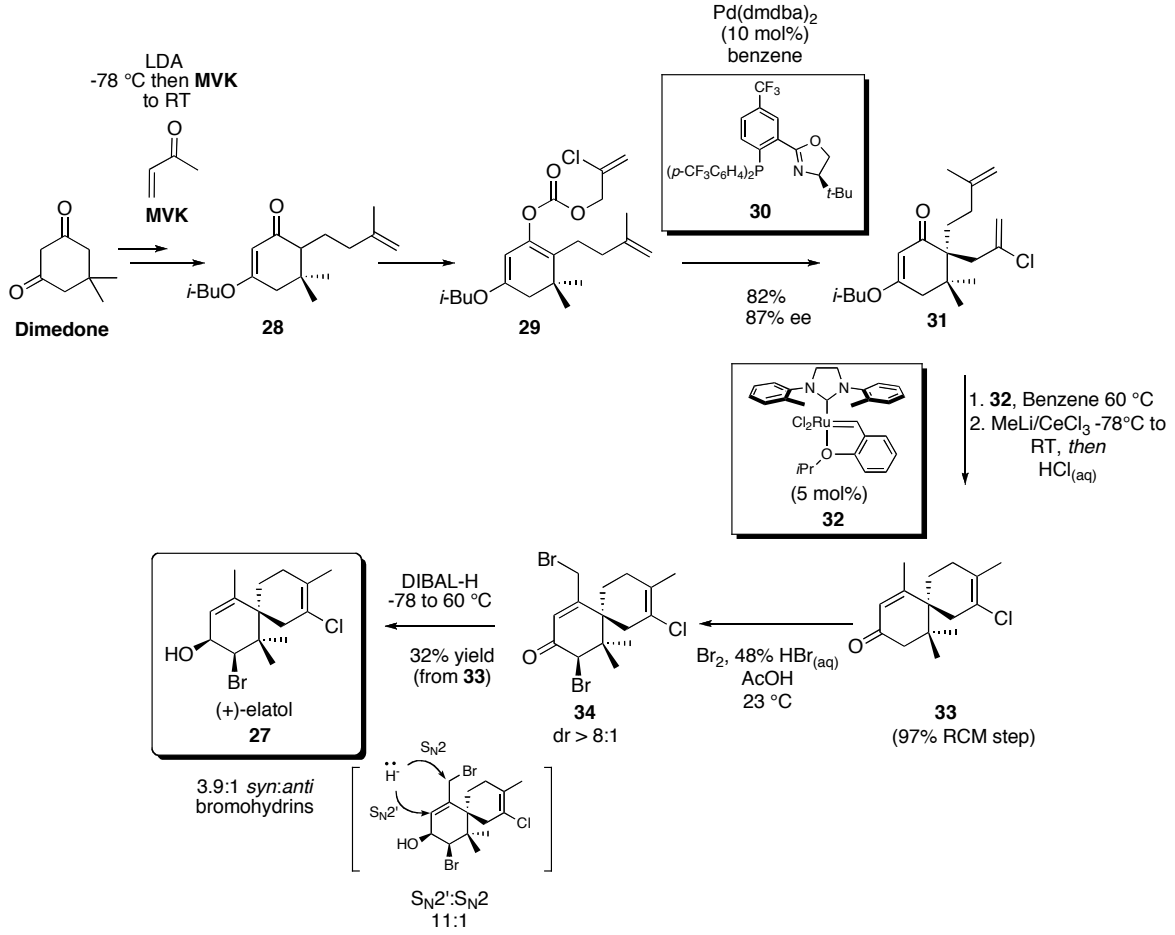
Scheme 1.4: V-BrPO (P. cartilagineum, L. pacifica, C. officinalis) catalysed biogenetic cyclisation of geraniol[33]

Although implementation of the V-BrPO enzyme as a strategy to access brominated cyclic terpene natural products such as Prevezol C **14** would be considered state of the art, there is little data available for substrate scope and enantioselectivity, thus, such a strategy at this stage would be premature. Furthermore, the high price and availability of such enzymes will undoubtedly see the slow acceptance of such catalysts by the wider synthetic community.

1.5 Conventional Routes to Cyclic Brominated Terpenes

One recent example of a compound which has attracted considerable attention from the synthetic community is elatol **27**.[34] A brominated sesquiterpene natural product isolated from the red algal genus *Laurencia*, belongs to the large chamigrene family of natural products.[35] The first catalytic asymmetric synthesis of this *syn*-bromohydrin containing sesquiterpene was disclosed by Stoltz research group in 2007, accessing the natural product in 9 steps and 11% overall yield with a reported enantiomeric excess of 87% (Scheme 1.5).[34] The key features of this synthesis involve the elaboration of dimadone *via* a Michael reaction with methyl vinyl ketone (MVK) to afford the alkene **28** after functional group conversion (FGI). Subsequent formation of the activated vinyl carbonate **29**, sets the stage for a palladium catalysed Tsuji-Trost reaction in the presence of the

activated trifluoromethane derivative of the PHOX ligand **30**. This was reported to yield a moderate trade-off in enantioselectivity for reactivity, as this reaction was reported as being sluggish at best. This asymmetric allylic alkylation afforded the vinylogous ester **31** in good isolated yields (82%) and enantiomeric excess (87% ee). A ring closing metathesis (RCM) reaction between the pendant olefins of the vinylogous ester **31** using the Grubb's Hoveyda 2nd generation catalyst variant **32**, with subsequent functional group manipulation afforded the spirocycle **33**. A double bromination of spirocycle **33** in the presence of both Br_2 and HBr/AcOH yielded dibromide **34**, in a moderate diastereomeric excess (>8:1). An interesting domino reduction with DIBAL-H of the dibromide **34** was achieved *via* first 1,2 addition of a hydride ion into the carbonyl of **34** at -78 °C with a diastereoselectivity of 3.9:1 (*syn*:*anti*). Subsequent warming to 60 °C afforded the S_N2': S_N2 reduced species in a 11:1 ratio, furnishing the synthetic elatol **27**.

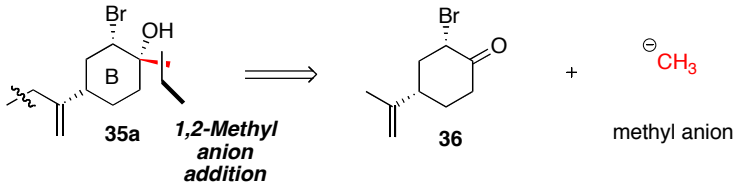


Scheme 1.5:The Stoltz et al. route to the bromohydrin containing sesquiterpene elatol 27[34]

Stoltz's synthesis of elatol **27** lends itself as an elegant route to other such bromohydrin containing natural products, yet, the DIBAL-H ketone reduction was not as selective as

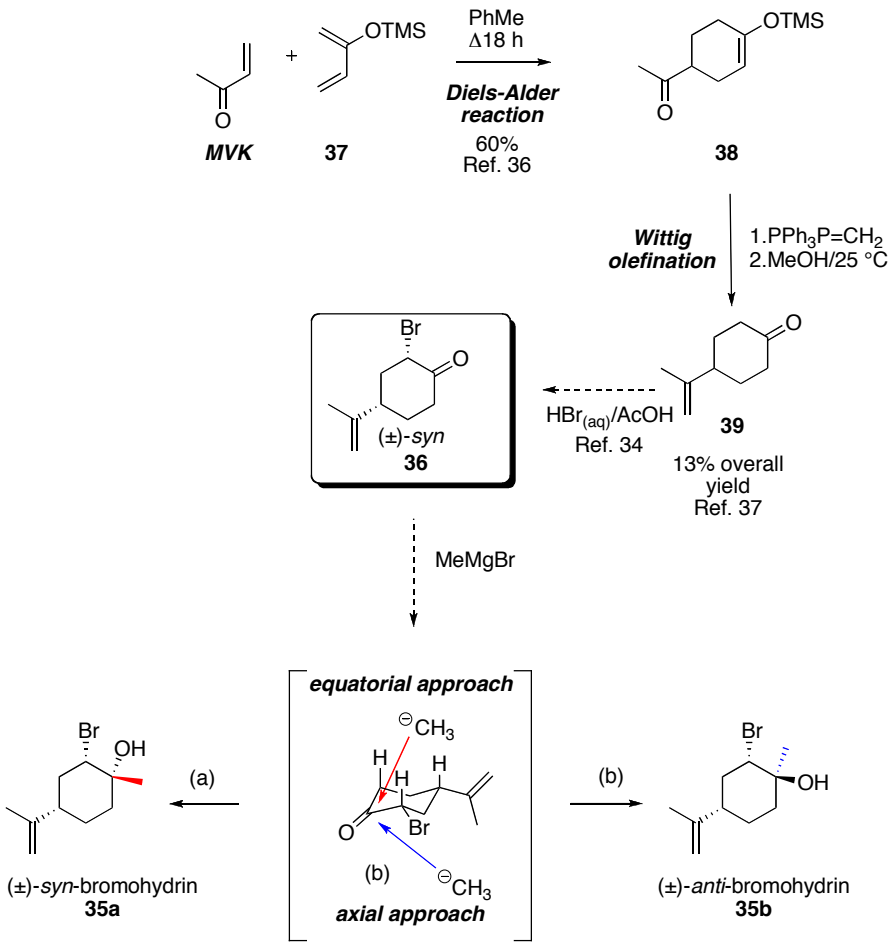
they would have hoped considering the 3.9:1 *syn:anti* selectivity.

In the retrosynthetic analysis of the B ring of the Prevezol congeners **35a**, one could envisage a methyl anion addition to 2-bromo-4-*i*-propenyl cyclohexanone **36** substrate to reveal the oxygenated quaternary centre of the *syn*-bromohydrin (Scheme 1.6).



Scheme 1.6: Applying Stoltz's strategy to the synthesis of syn-bromohydrin 35

Preparation of the bromo ketone **36** could be derived from the known Diels-Alder reaction[36] between 2-trimethylsilylxy-1,3-butadiene **37** and MVK followed by a Wittig methylenation of exocyclic ketone of **38**, and subsequent hydrolysis of the silylenol ether, which is reported to furnish ketone **39** in an overall yield of just 13% (Scheme 1.7).[37] Finally, a thermodynamically controlled bromination of the enol of **39** formed under acid-catalysed conditions,[34] would yield the methyl anion addition precursor **36**. The addition of organometallic reagents such as methylmagnesium bromide (MeMgBr) or methyl lithium (MeLi) to relatively unhindered 4-substituted cyclohexanones such as **39**, is well studied and proceeds through an equatorial reaction coordinate; favouring an axial orientated alcohol product.[38] However substitution at the α-position of **39** with an atom larger than hydrogen, (i.e. bromide, *see* bromo ketone **36**, Scheme 1.7) is known to perturb this selectively; giving rise to a mixture of methyl adducts, such as bromohydrins **35a** and **35b**.[38] Thus, novel routes towards the challenging *syn*-bromohydrin **35a**, which address the low yields and diastereo- and enantio- selectivities which current methods offer, are highly sought after.

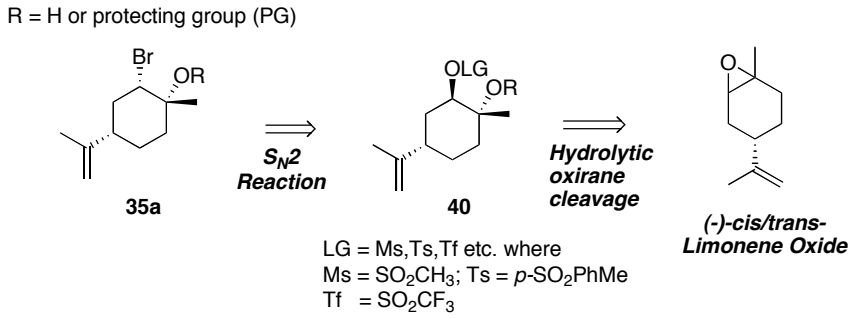


Scheme 1.7: A proposed racemic route to the syn-bromohydrin 35a

1.6 Retrosynthetic Analysis of Prevezol C 14

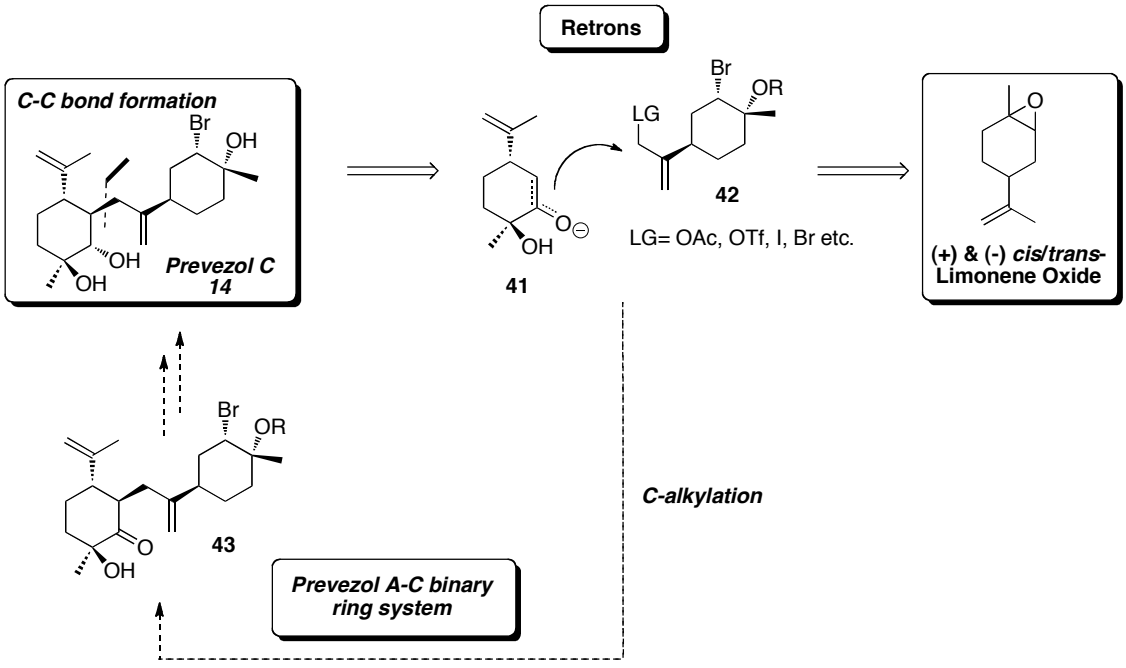
Our proposed approach to the *syn*-bromohydrin **35a** is derived from the commercially available *cis/trans* mixture of (+)- or (-)-limonene oxide (LO); a chiral pool building block, which has been slow to be adopted as a chiron in total synthesis as it is supplied as a mixture of *cis/trans* isomers. Separation and isolation of the respective *cis* and *trans* isomers of this mixture must first be addressed by this project on the onset, and will be further discussed in Chapter 2.

S_N2 reaction approach will be employed to invert the stereochemistry of the activated alcohol of **40** (derived *via* an oxirane opening of limonene oxide). It is anticipated such a strategy will furnish the desired *syn*-bromohydrin **35a** (Scheme 1.8).



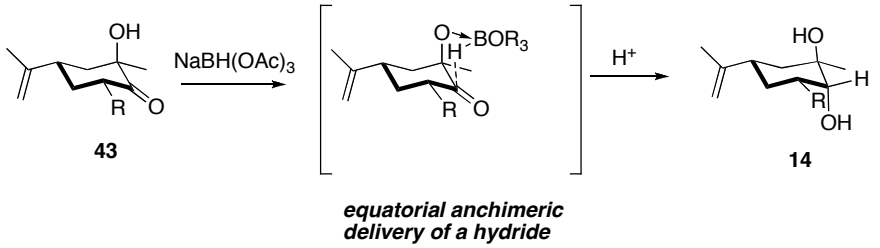
Scheme 1.8: Alternate retrosynthetic analysis of the syn-bromohydrin 35a

Retrosynthetic analysis of Prevezol C **14** (Scheme 1.9) reveals both the Eastern and Western domains share a great deal of structural homology. It was recognised that the diterpene core of **14** could be assembled from the same chiral pool building block - limonene oxide. With the appropriate functional group manipulations performed on the required enantiomers of limonene oxide; it is anticipated the retrons **41** and **42** could give access to hydroxy ketone **43**. The union of the two optically active retrons (**41** and **42**) to form ketone **43** is envisaged to react through a diastereoselective allylic alkylation. To the best of our knowledge this type of disconnection utilizing a highly stereoconvergent alkylation strategy to unite the Eastern and Western domains of Prevezol C **14** would be unprecedented.



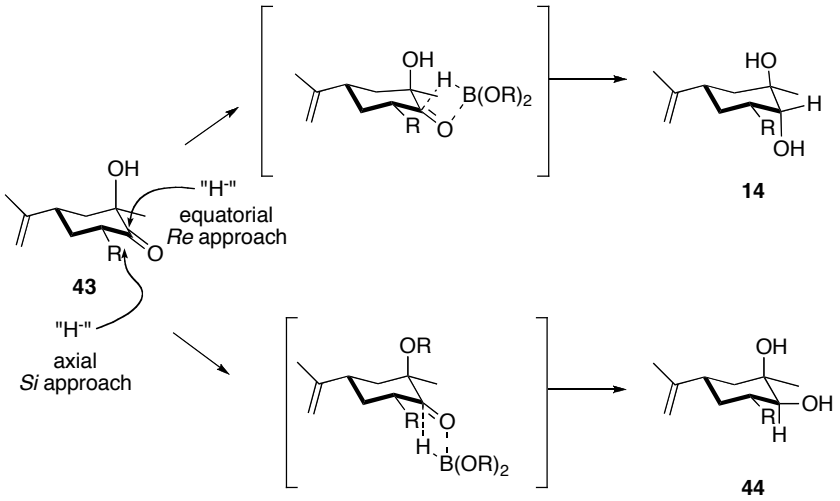
Scheme 1.9: Retrosynthetic analysis of Prevezol C 14

Finally, an equatorial reduction of the hydroxy keto-diterpene **43** to gain access to the *trans*-diaxial diol contained in the Western domain of Prevezol C **14** can be rationalized by a chelate controlled diastereoselective reduction (utilising the oxygenated quaternary centre as an anchimeric group) with an appropriate reagent that participates in such reactions such as sodium *tris*(acetoxy)borohydride (Scheme 1.10).[39]



Scheme 1.10:Chelate controlled diastereoselective reduction of hydroxy ketone 43

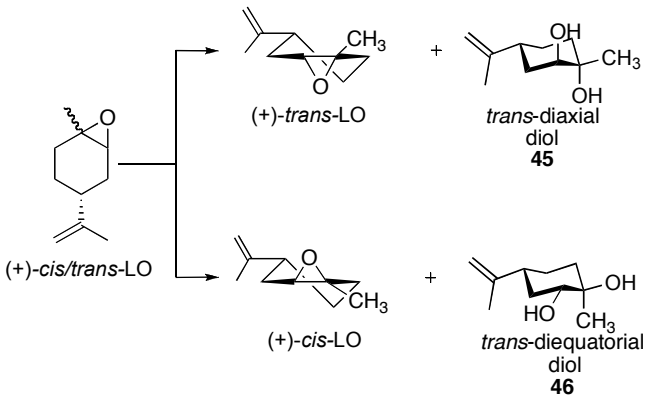
In the absence of chelate control, the preferred axial approach of the relatively small hydride source (i.e sodium borohydride) would predominate; yielding a mixture of the undesired diol **44** and the natural diol **14** (Scheme 1.11).[40]



Scheme 1.11: Non-chelate controlled reduction of hydroxy ketone 43[40]

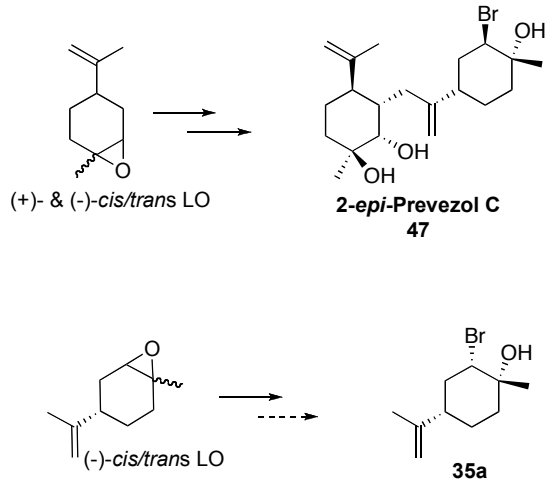
1.7 Chapters 2-4 Overview

As mentioned previously, Chapter 2 will detail the kinetic separation of the commercial mixture of *cis*/*trans*-limonene oxide (LO) and the hydrolytic glycol by-products (**45** and **46**), required for the stereoselective synthesis of Prevezol C **14**.[41, 42]



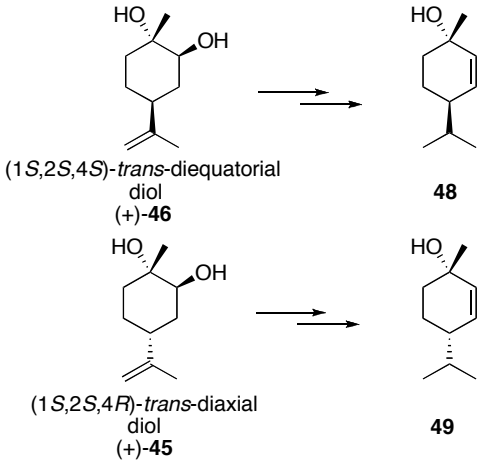
Scheme 1.12: Overview of Chapter 2

Chapter 3 discloses the total synthesis of 2-*epi*-Prevezol C **47**, a Prevezol congener *en route* to the natural Prevezol C **14**. Furthermore, the synthesis of the Eastern fragment **35a** of Prevezol C **14** and the metabolites **12-18** are communicated in the second part of this chapter (Scheme 1.13).



Scheme 1.13: Overview of Chapter 3

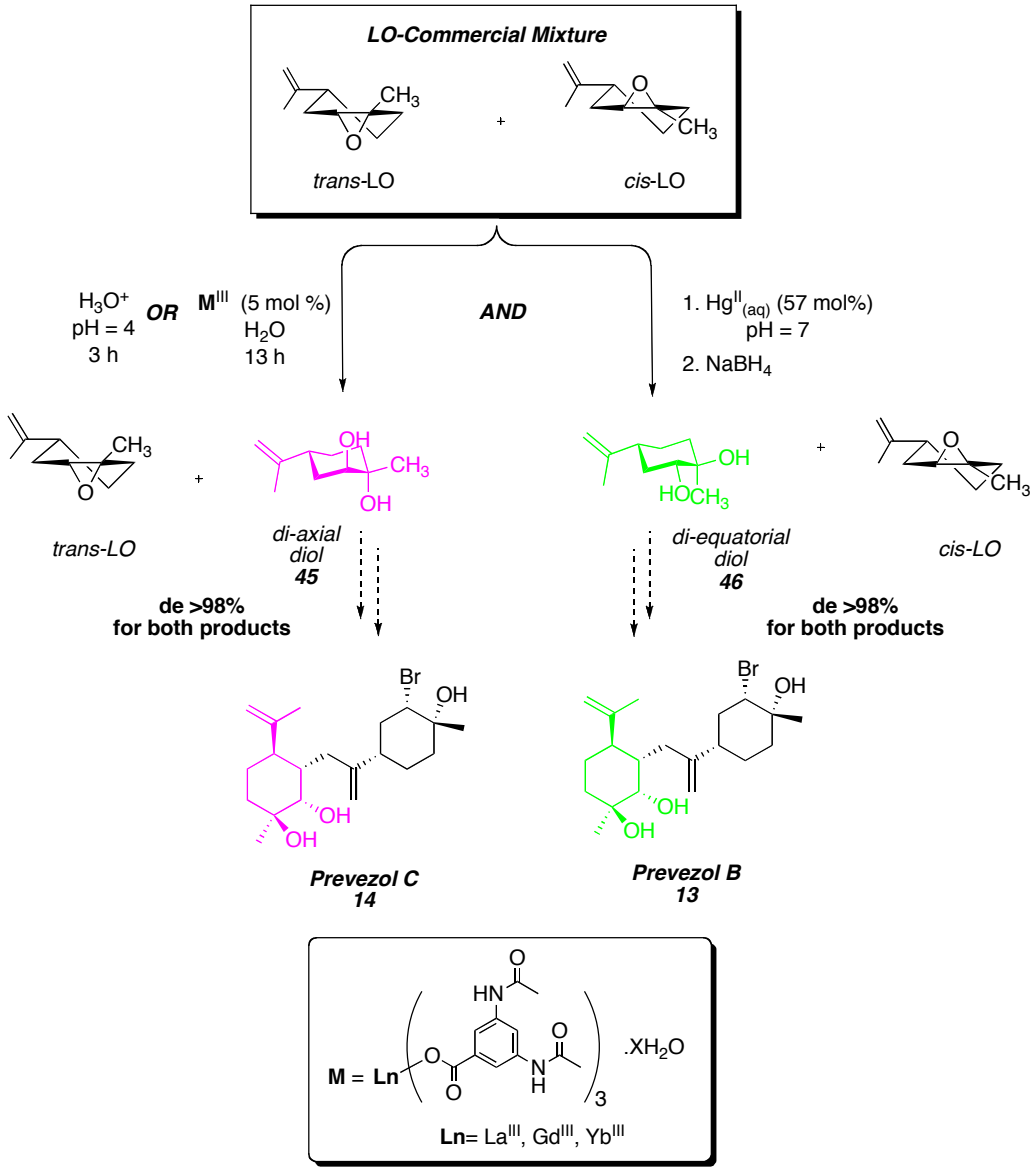
Chapter 4 describes a new entry into the total synthesis of the major and minor aggregation pheromones (**48** and **49** respectively) of the semiochemicals excreted by the ambrosia beetle (*Platypus quercivorus*).[43] It was recognized that utilizing the chiral glycols ((+)-**46** and (+)-**45**) described in Chapter 2, a highly enantio- and diastereo- selective synthesis of **48** and **49** could be achieved employing a novel palladium deoxygenation strategy of a vinyl triflate (derived from the glycols **45** and **46**) as means of accessing the *endo*cyclic allylic alcohol of the natural pheromones **48** and **49** (Scheme 1.14).



Scheme 1.14: Overview of Chapter 4

2.0 Utilising the Chiral Pool: Accessing the Diastereomerically Pure cis/trans Isomers of Limonene Oxide

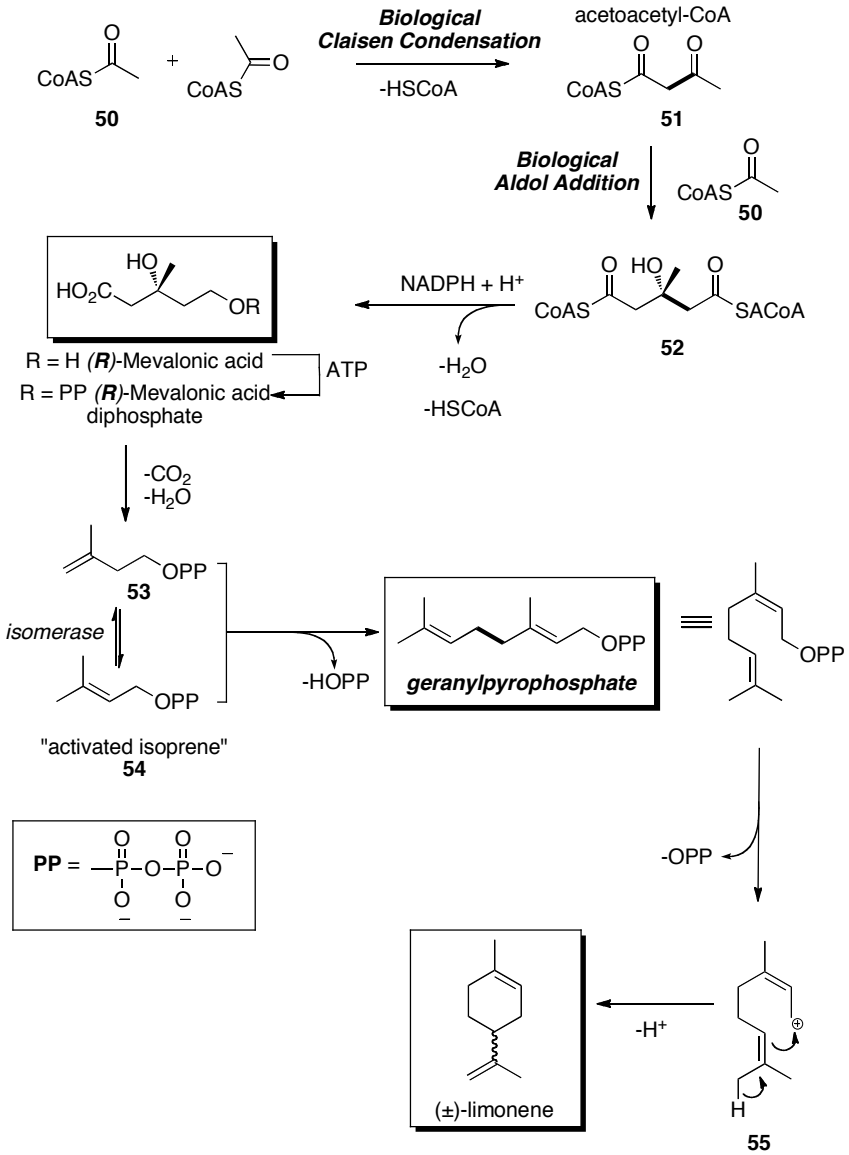
This chapter describes the facile and novel methodology developed for the kinetic separation of the commercial mixture of cis/trans-limonene oxide (LO) and their corresponding hydrolytic trans-diaxial and trans-diequatorial limonene glycols ***45*** *and* ***46*** *(Scheme 2.0), all are achieved in high yields and diastereomeric excesses (>96% de).*[41, 42] *The findings from our studies are disclosed over two journal articles contained at the end of this chapter. Both diol and epoxide constituents isolated from the commercial mixture are applied in the total synthesis of Prevezol C* ***14****.*



Scheme 2.0: The kinetic separation of cis/trans-LO

2.1 The Biosynthesis of Terpenes

Limonene oxide and all other terpenes, be it hemi (C_5), mono (C_{10}), sesqui (C_{15}) or diterpene (C_{20}) etc. are derived from the generally accepted acetate mevalonate pathway which is depicted in Scheme 2.1.[30] The biogenesis begins with a bio-Claisen condensation with two activated acetic acids (acetyl-CoA) units **50**, yielding the acetoacetyl-CoA intermediate **51**. This acetoacetyl-CoA intermediate undergoes further reaction with another equivalent of acetyl-CoA **50** in a bio-aldol type addition affording the aldol adduct **52**. An enzymatic NADPH/H^+ (nicotinamide adenine dinucleotide phosphate) double reduction generates the optically active intermediate *(R)*-mevalonic acid.



Scheme 2.1: Biogenetic pathway to cyclic monoterpenes[30]

Subsequent ATP (adenosine triphosphate) phosphorylation/decarboxylation affords the activated isoprene equivalents **53** and **54**, dimerisation and loss of ATP affords the monoterpene precursor geranylpyrophosphate. Redrawing this monoterpene, and dissociation of a pyrophosphate anion reveals the allylic carbenium ion **55**. Cationic olefin cyclisation of this intermediate is believed to afford cyclic monoterpenes such as limonene.[30]

2.2 Limonene Oxide as a Chiron in Total Synthesis.

Limonene oxide (LO) occurs naturally in the essential oils of *Cymbopogon densiflorus*.[44] It is sold primarily as a relatively inexpensive mixture of (57:43) *cis*:*trans* isomers ($127/50 g Sigma-Aldrich) and both enantiomers (>98% ee) are available.[45] Given the price and the availability of both these enantiomers, LO remains a relatively under utilized chiral building block. Unlike many other monoterpene building blocks that have been popularized in total synthesis, such as carvone,[46] perillyl alcohol,[47, 48] isopulegol[7] and limonene,[49] that have been in use for some time (Fig 2.0), only recently has LO begun to enjoy widespread use as a chiral pool reagent (Scheme 2.2).[50-56] It is believed that LO has been slow to be adopted as an optically pure building block both in total synthesis and of related bioactive compounds, as it is supplied as a diastereomeric mixture of *cis* and *trans* epoxide isomers. Furthermore, given the relatively few practical and preparative routes to obtain the desired diastereoisomer of choice, the vast majority of reports (Scheme 2.2), forego purification/kinetic separation to isolate the respective *cis* or *trans*-limonene epoxide in pure form.

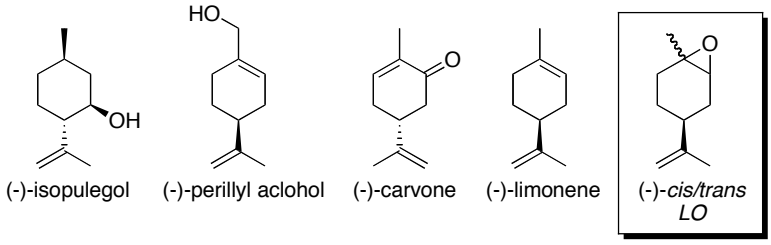
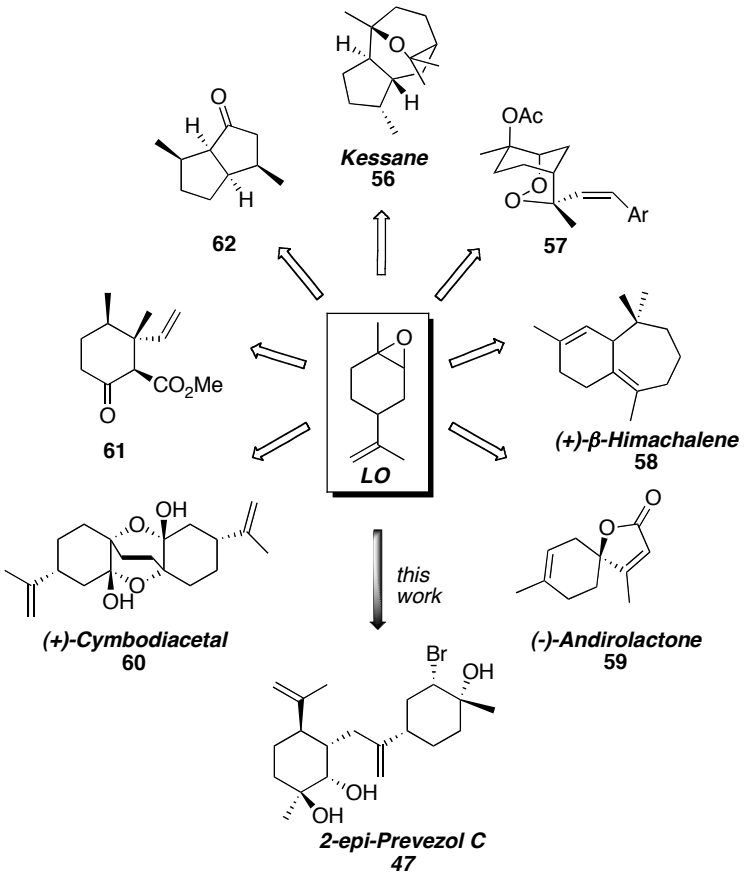


Fig 2.0: Commercially available chiral building blocks

Of the natural and unnatural products **56-62** outlined in Scheme 2.2, only three of which, Kessane **56** (the desired limonene epoxide is isolated *via* fractional distillation),[57] Andirolactone **59** and the work contained in this dissertation exploit one of the diastereomerically enriched epoxides contained in the commercial mixture.[50-56]

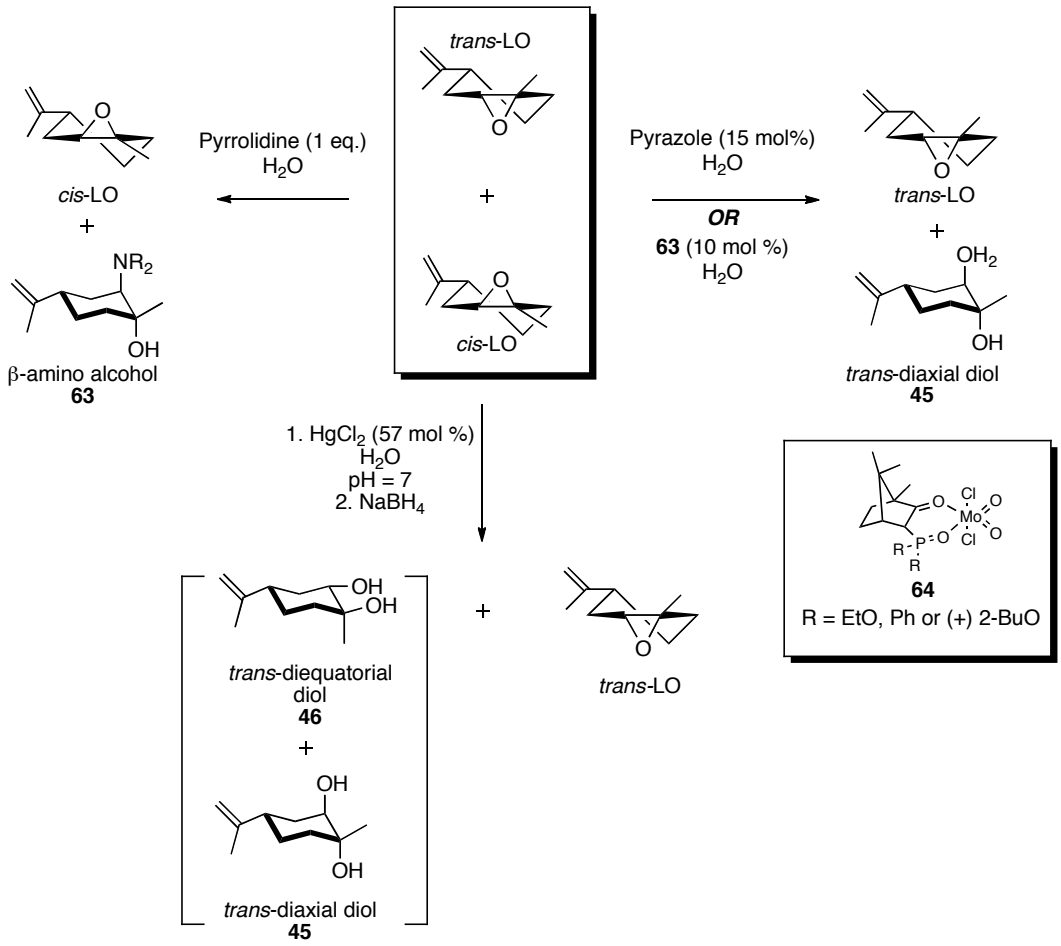


Scheme 2.2: Limonene oxide as an optically pure source to natural and unnatural products

2.3 Kinetic Separation of the Commercial Mixture of Limonene Oxide

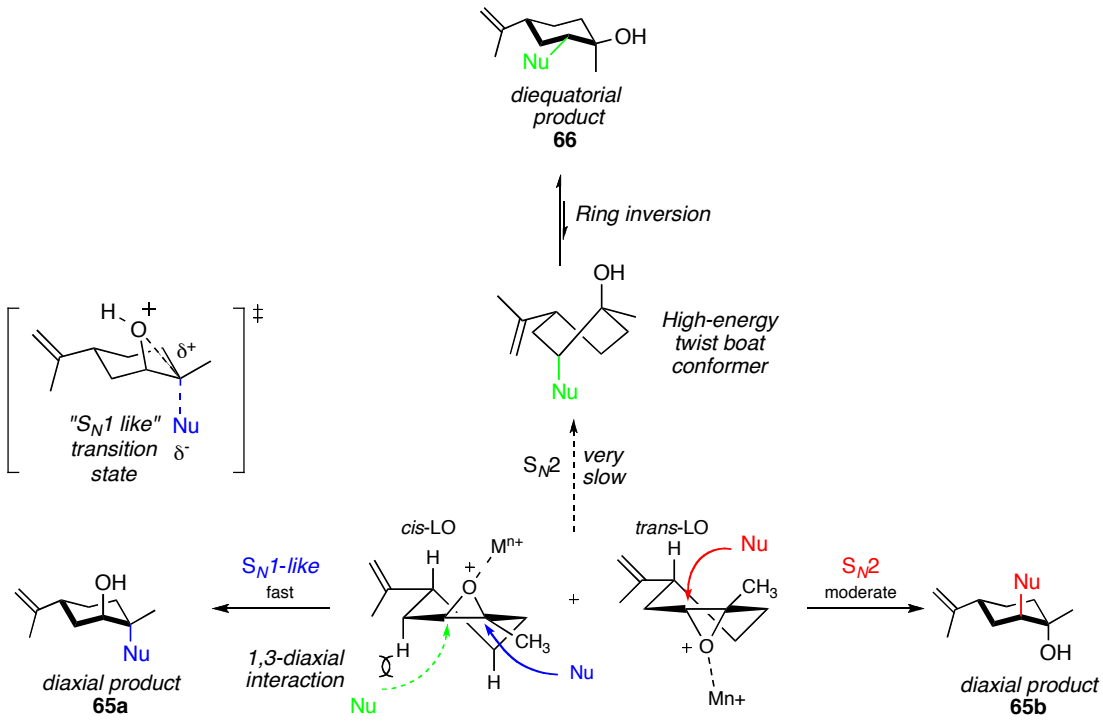
The prior art surveyed in this section will focus on recent methods reported to gain access to the cis or trans limonene oxide and the various by-products via chemical means of separation. Physical methods will not be discussed, however, it has been reported that this mixture of epoxides can be separated utilizing fractional distillation to separate the respective isomers by their 3°C boiling point differential after chemical derivitisation.[57]

Current chemical methods are summarized below (Scheme 2.3) for the kinetic separation of the commercial mixture of *cis/trans*-LO, typically yielding the *trans*-diaxial diol **45** and in some instances, the amino alcohol **63** as the oxirane cleavage products.[58-60]



Scheme 2.3: Methods for the kinetic separation of cis/trans LO[58-60]

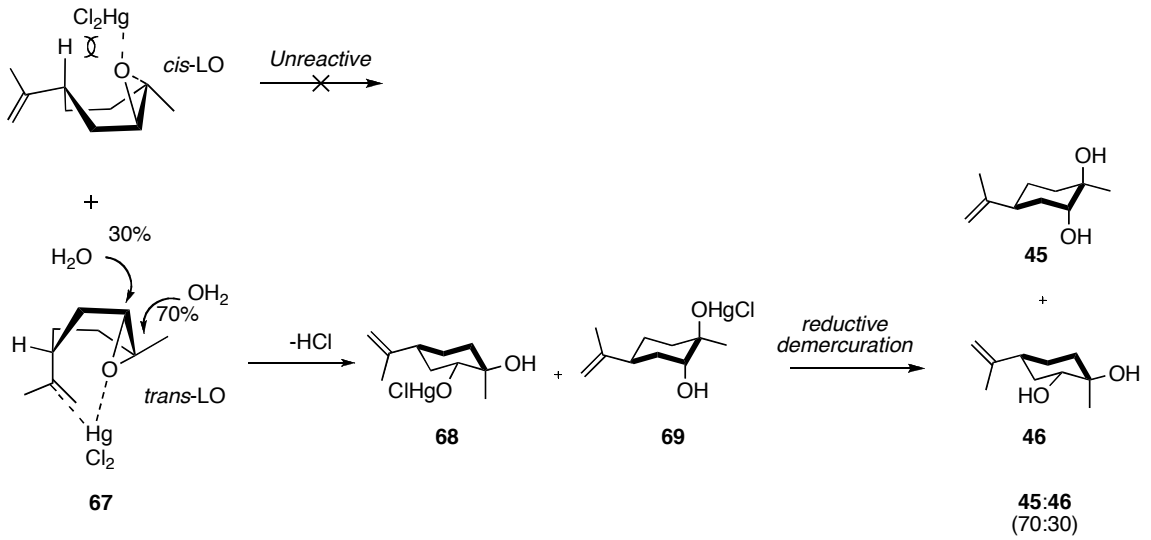
Both Lewis and Brønsted acid catalysed methods (Mo^{VI} reagents **64**,[58] pyrazole[59]) for the hydrolytic kinetic separation of the *cis/trans* mixture relies on the higher reactivity of the *cis* isomer towards nucleophilic attack at the quaternary centre under an S_N1 like mechanism, to yield the diaxial product **65a** (Scheme 2.4). Conversely, the higher reactivity of the *trans*-LO isomer under S_N2 reaction kinetics (i.e pyrrolidine or H_2O nucleophiles) is predicted by the Fürst-Platner rule. This rule stipulates that a diaxial approach is the preferred mode of cyclohexene oxide opening when ring locking substituents are present (i.e. a 4-isoprenyl group), thereby forbiding ring inversion; favouring the formation of the other diaxial isomer **65b**.[61] On the other hand, an S_N2 reaction of the *cis* isomer is an extremely unfavourable process. Nucleophilic approach through the underside of the ring is met with steric repulsion by the 1,3-diaxial hydrogens, coupled with the high-energy twist-boat conformation in order to conform to the Fürst-Platner rule of diaxial oxirane opening, thereby essentially shutting down this reaction pathway.[62] This is reflected experimentally by the low isolated yield of diequatorial product **66** (<5%) under both acid and base mediated openings of the *cis*-epoxide (Scheme 2.4).[44]



Scheme 2.4: Stereo-electronic analysis of cis/trans LO under S_N1 and S_N2 reaction kinetics

Due to these stereo-electronic factors described (*vida supra*), there is larger number of reports exploiting the uniquely different reactivities of the *cis*/*trans* epoxides to perform a kinetic separation of the reaction mixture to either isolate pure *cis* or *trans* isomers of limonene oxide (96% de) and the corresponding *trans* axial cleavage products (amino alcohol **63**, diol **65a** and **65b**).[58-60]

A report by Van der Werf and co-workers[60] piqued our interest in this kinetic separation reaction, as they were able to favour the formation of a *trans*-diequatorial diol **46**, albeit as a diastereomeric mixture of diols in 70:30 (*trans*-diaxial **45**:*trans*-diequatorial **46**), by the addition of 57 mol% Hg^{II} ions under buffered conditions (pH = 7). The stoichiometry of this system reflects the 57:43 ratio of *cis*:*trans* LO. Under these conditions, a simultaneous kinetic separation took place, attributed to the reported unreactivity of the *trans*-LO isomer towards Hg^{II} due to a conformational restriction preventing a bridging mercury ion as depicted in Scheme 2.5. The bridging mercuric ion **67** (which does undergo reaction), is required for the diastereoselective introduction of a hydroxyl group; interestingly however, the unreacted *trans* isomer was not reported to undergo normal S_N1 opening mediated by Hg^{II} ions. This is perhaps reflected again by the higher reactivity of this *cis* isomer towards Hg^{II}, due to its ability to competitively bind such ions in a bridging manner. Van der Werf and co-workers postulated that the diastereoselectivity of this reaction towards the diequatorial diol **46** was a result of a statistical attack of water biased towards the incipient tertiary carbenium ion yielding chloromercurial **68**, as opposed to the less stable secondary carbenium ion, which produces the other diastereomeric chloromercurial **69**. Lastly, in the absence of a buffer or pH < 4, normal acid catalysed conditions prevail, thereby out-competing Hg^{II} mediated oxirane opening, thus significantly decreasing both the yield of the diequatorial diol **46** and the recovery of the unreacted *trans*-LO. The reaction mixture under these conditions was reported to be predominately the *trans*-diaxial diol **45** and unreacted *cis*-LO.



Scheme 2.5: The proposed mechanism under Hg^{II} complexation, leading to the formation of diol 46[60]

With this knowledge in hand, a thorough investigation was performed on the commercial mixture of *cis*/*trans*-LO under both Brønsted and Lewis acid catalysed conditions, several of which employed novel, water soluble lanthanoid benzoate catalysts as detailed in the article entitled "*Water soluble lanthanoid benzoate complexes for the kinetic separation of cis/trans-limonene oxide*".[41] We have also demonstrated that all four possible products (diol **45** and **46**, and the respective *cis* and *trans* LO isomers) from this kinetic separation are now accessible in high yields and diastereoselectivities, communicated as a full paper, entitled "*Facile Methods for the Separation of the cis- and trans-Diastereomers of Limonene-1,2-Oxide and Convenient Routes to Diequatorial and Diaxial 1,2-Diols*".[42] Both articles covering this work can be found at the end of this section.

Monash University

Declaration for Chapter 2, Paper 1: Water Soluble Lanthanoid Benzoate Complexes for the Kinetic Separation of *cis/trans*-Limonene Oxide. Tetrahedron: *Asymmetry* 17, 2006, 2833–2838.

Declaration by candidate

In the case of Chapter 2, Paper 1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Experimental design, manuscript preparation/editing and intellectual input	10%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
P. C. Andrews	Manuscript preparation/editing and intellectual input	
B. H. Fraser	Experimental design, execution of reaction(s), characterisation/isolation of reaction products and manuscript preparation/editing	
P. C. Junk	Manuscript preparation/editing and intellectual input	
M. Massi	Experimental design, execution of reaction(s), characterisation/isolation of reaction products and manuscript preparation/editing	
K. L. Tuck	Manuscript preparation/editing and intellectual input	

Candidate's Signature	[redacted]	Date: 26/11/09

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash University Clayton, School of Chemistry

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	**Date** 16.11.09
Signature 2		
Signature 3		16/11/09
Signature 4		
Signature 5		26/11/09

Location(s)	Monash University Clayton, School of Chemistry

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	**Date**
Signature 2		16/11/09
Signature 3		
Signature 4		
Signature 5		

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1		**Date**
Signature 2		
Signature 3		
Signature 4	[redacted]	16/11/09
Signature 5		
Signature 6		

Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
ELSEVIER
Tetrahedron: *Asymmetry* 17 (2006) 2833–2838

Water soluble lanthanoid benzoate complexes for the kinetic separation of *cis*/*trans*-limonene oxide

Philip C. Andrews,* Michael Blair, Benjamin H. Fraser, Peter C. Junk, Massimiliano Massi and Kellie L. Tuck

School of Chemistry, Monash University, PO Box 23, Victoria 3800, Australia

Received 2 October 2006; accepted 19 October 2006

Abstract—A new class of water soluble, environmentally friendly, lanthanoid 3,5-diacetamidobenzoate complexes (Ln = La, Gd, Yb) have been synthesized. The La and Gd complexes selectively catalyse hydrolysis of the *cis*-isomer of limonene oxide allowing for the separation of the *trans*-isomer (>98:2 dr) in up to 74% yield. Comparative studies with the corresponding chlorides and triflates reveal the lanthanoid benzoate complexes to be more active than the chlorides, but less active, though more selective, than the triflates.

1. Introduction

Homogeneous catalysis in non-volatile organic solvents is currently a field of active research due to interest in sustainable synthetic methods with low environmental impact.[1] In this respect, epoxide ring opening reactions in water have great potential owing to the vast number of enantiomerically pure compounds that are accessible via this simple transformation.[2] As catalysts, lanthanoid triflates appear to be an obvious choice since they have already been shown to be effective in a number of other aqueous based organic procedures.[3] From an industrial perspective though, triflates may not be ideal because of the highly corrosive nature of triflic acid. Lanthanoid benzoates[4] are a possible alternative with the potential to provide similar reactivity with improved selectivity. However, the relative insolubility of simple benzoates has inhibited comparative studies in this area.

The pure diastereomers **1** and **2** of limonene oxide (Fig. 1), a naturally occurring epoxide, have been used in the total syntheses of a number of natural products.[5–7] Although pure **1** and **2** are commercially available, they are expensive and are more commonly purchased and used as a mixture of the *cis*/*trans* (47:53) diastereomers. Efficient and commercially viable methods for separating the diastereomers have, therefore, been of some interest to both academic and industrial researchers and as such, a number of procedures now currently exist, with varying efficiencies, for their separation. These fall largely into two categories: (1) separation and recovery of each diastereomer based upon differing physical properties, for example, chromatography or distillation,[8] and (2) kinetic separation where one diastereomer reacts faster than the other, allowing for recovery of the pure unreacted diastereomer, for example, photo-assisted kinetic separation[9] and biocatalysis,[10] electrophilic mercuration,[11] amine addition[12] and molybdenum(VI) catalysis.[13]

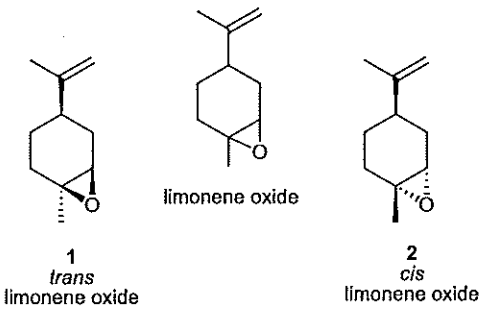


Figure 1. Limonene oxide.

While the degree of separation in these chemical processes is generally >90%, they suffer from various drawbacks including being non-catalytic, requiring high reaction temperatures, the use of toxic reagents/catalysts, a need for derivatisation, and air/moisture sensitivity.

* Corresponding author. Tel.: +61 3 9905 5509; fax: +61 3 9905 4597; e-mail: phil.andrews@sci.monash.edu.au

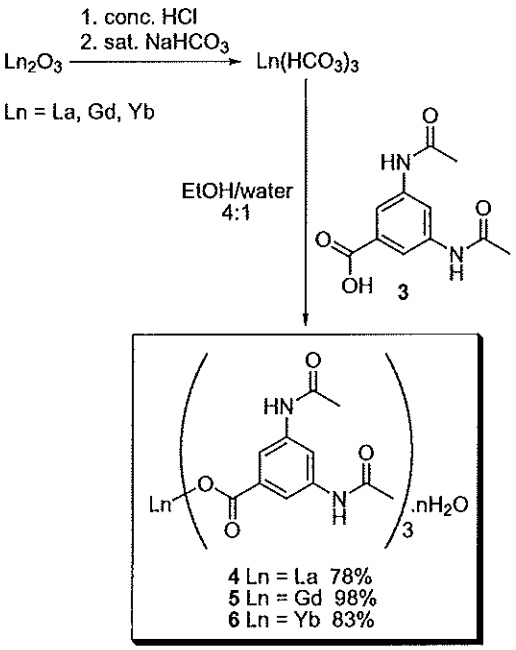
0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.10.026

Herein, we report the first application of water soluble lanthanoid (Ln = La, Gd, Yb) benzoate complexes, derived from 3,5-diacetamidobenzoic acid, and their application as catalysts in the ring opening and consequent kinetic separation of limonene oxide.

2. Results and discussion

To establish the effectiveness of lanthanoid benzoate catalysts in an aqueous medium, the ligands first had to be designed to allow solubility and stability. Convenient targets were the complexes derived from 3,5-diacetamidobenzoic acid **3**. The ligand was efficiently prepared by the acylation of 3,5-diaminobenzoic acid with acetic anhydride. Subsequent treatment of **3** with lanthanoid bicarbonate, prepared from the lanthanoid oxide, gave the appropriate La, Gd and Yb complexes **4–6** in good yield (Scheme 1).

For examination as catalysts in the ring opening and kinetic separation of *cis*/*trans*-limonene oxide, complexes **4–6** were dissolved in water (5 mol %, relative to total limonene oxide) and the 53:47 mixture of limonene oxides **1** and **2** added (Scheme 2).

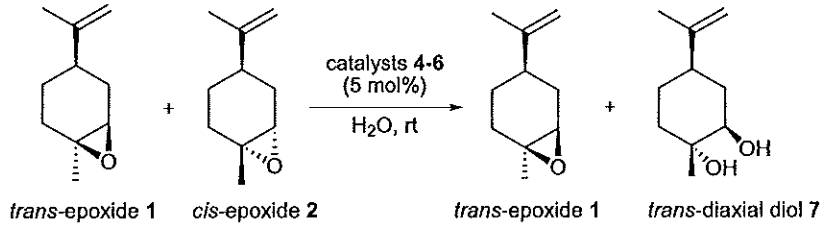


Scheme 1. Synthesis of 3,5-diacetamidobenzoate complexes **4–6**.

Since limonene oxide is only sparingly soluble in water (4.6×10^{-3} mol L^{-1} at 25 °C), the reaction mixtures are best described as dispersions rather than homogeneous solutions. The suspensions were vigorously stirred at room temperature and the reaction progress was monitored by ^1H NMR spectroscopy. A reliable analytical procedure involving extraction with ethyl acetate and in vacuo concentration was initially hindered by the volatility and significant loss of limonene oxide. After some experimentation, the most reliable and reproducible method involved an initial extraction with $CDCl_3$, to efficiently remove all the unreacted epoxide, followed by a second extraction with ethyl acetate to remove the remaining diol **7**. The ethyl acetate extraction was then evaporated to dryness leaving the non-volatile solid diol. This was re-combined with the $CDCl_3$ extract to form the sample for NMR analysis. With a good procedure for monitoring the reaction progress established, it was discovered that the only product of the reaction was the water soluble *trans*-diaxial diol **7** (Scheme 2), which was not unexpected since both *cis*- and *trans*-limonene oxides have been reported to open through a diaxial mechanism to yield the same diol.[14] Further NMR analysis revealed that the *cis*-diastereomer **2** reacts at a much faster rate than the *trans*-diastereomer **1** and that a kinetic separation of *trans*-limonene oxide **1** could be obtained if the reaction was stopped at the appropriate time. Under normal, non-analytical, reaction conditions the remaining unreacted *trans*-limonene oxide **1** could be isolated by pentane extraction of the aqueous layer (pure by NMR and >98:2 dr by GC analysis). The aqueous phase containing the catalyst was used for three consecutive reactions and extraction cycles without any significant reduction in the yield of diol or loss in the recovered fraction of *trans*-epoxide.

Figure 2 shows the reaction profile of the commercially available mixture of limonene oxides **1** and **2** with the lanthanum catalyst **4**. At $t = 0$, the species fractions of limonene oxide are *trans* = 0.53 and *cis* = 0.47. As the reaction proceeds there is a fast consumption of the *cis*-epoxide and a slow consumption of the *trans*-epoxide. After 13 h, the *cis*-epoxide is completely transformed to the diol and 74% of the original fraction of *trans*-epoxide is recovered.

The gadolinium complex **5** gave a similar reaction profile (Fig. 3) where complete consumption of the *cis*-epoxide **2** was achieved in ca. 15 h. In contrast to the La catalysed reaction, the fraction of *trans*-epoxide recovered, decreased to 0.25 (47%).



Scheme 2. Separation of *cis*/*trans*-limonene oxide **1**.

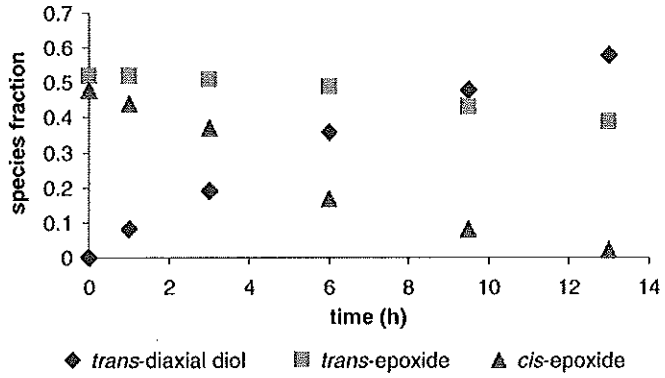


Figure 2. Reaction profile for the hydrolytic ring opening of limonene oxide mixtures 1 and 2 in the presence of 5% lanthanum catalyst 4.

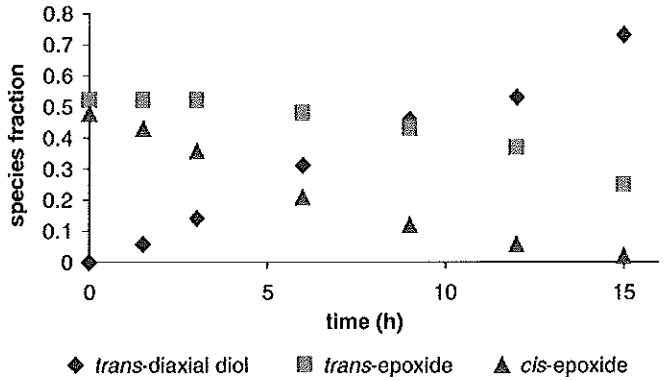


Figure 3. Reaction profile for the hydrolytic ring opening of limonene oxide mixtures 1 and 2 in the presence of 5% gadolinium catalyst 5.

Surprisingly, the Yb complex 6 gave no appreciable reaction over a period of 2 days. Monitoring over a further period of 2 days revealed a very slow, and non-selective reaction which was not studied further.

It was important to compare the reactivity and selectivity of complexes 4–6 with their corresponding lanthanoid chlorides and triflates. The lanthanoid chlorides (La, Gd, Yb) proved to be inefficient catalysts with very little reaction occurring at room temperature over a period of 5 days. The triflates were prepared using an adaptation of the procedure described by Kobayashi.[15] The mixture of limonene oxides 1 and 2 were added to the lanthanoid triflates (5 mol %) in water and stirred vigorously. The reaction progress was again monitored by ^{1}H NMR spectroscopy. The reaction catalysed by La(OTf)$_3$ (Fig. 4) was faster than that catalysed by lanthanum benzoate complex 4 and complete consumption of the *cis*-epoxide 2 was achieved in a reaction time of 11 h. However, there was a decrease in the amount of *trans*-epoxide recovered (65%).

Gadolinium triflate also catalysed the hydrolysis of limonene oxide faster than the corresponding gadolinium benzoate complex 5 (Fig. 5). Complete consumption of the *cis*-epoxide 2 was achieved in 7 h, but again, increased reactivity of the *trans*-epoxide led to an inferior recovery of this diastereomer (61%).

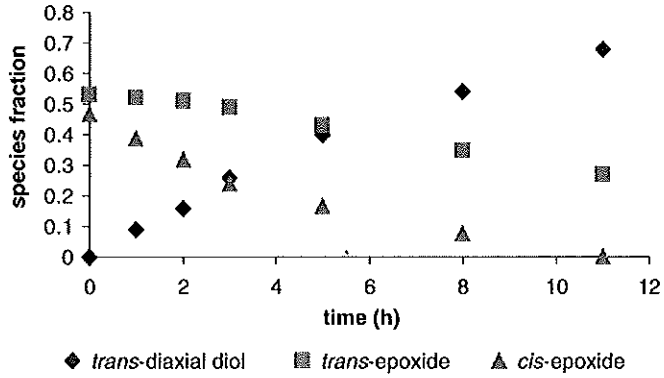


Figure 4. Reaction profile for the hydrolytic ring opening of limonene oxide mixtures 1 and 2 in the presence of 5% La(OTf)$_3$.

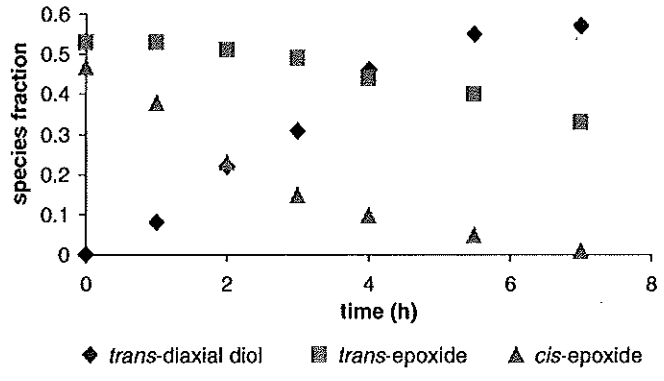


Figure 5. Reaction profile for the hydrolytic ring opening of limonene oxide mixtures 1 and 2 in the presence of 5% Gd(OTf)$_3$.

The increased reactivity of gadolinium triflate (7 h for completion) over lanthanum triflate (11 h for completion) is rationalised by the contraction in ionic radius and increased Lewis acidity of gadolinium over lanthanum. As was observed for the benzoates, the ytterbium triflate proved to be much less reactive (Fig. 6) than the La and Gd analogues. The reaction profile shows that after 9 h only ca. 50% of the *cis*-epoxide 2 had been hydrolysed. This observation is consistent with that obtained with ytterbium complex 6 and most likely results from the epoxide sub-

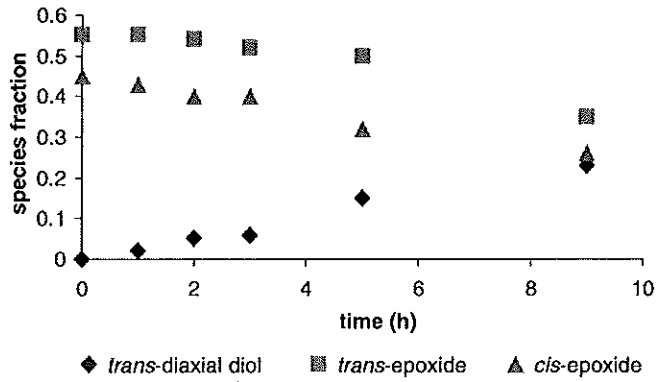


Figure 6. Reaction profile for the hydrolytic ring opening of limonene oxide mixtures 1 and 2 in the presence of 5% Yb(OTf)$_3$.

Table 1. Summary of reaction times, yields and dr for the separation of commercially available (+)-*cis*/*trans*-limonene oxide

Catalyst	Time (h)	dr (1:2)[a]	Fraction of *trans*-epoxide **1** recovered (%)	Yield of diol **7** (%)
4	13	>98:2	39[b] (74)[c]	61
5	15	>98:2	25[b] (47)[c]	75
6	>36	53:47[d]	—	<5
$LaCl_3$	>120	53:47[d]	—	<5
$GdCl_3$	>120	53:47[d]	—	<5
$YbCl_3$	>120	53:47[d]	—	<5
$La(OTf)_3$	11	>98:2	27[b] (65)[c]	73
$Gd(OTf)_3$	7	>98:2	32[b] (61)[c]	68
$Yb(OTf)_3$	>24	35:26	—	23

[a] Diastereomeric ratio of *trans*/*cis*-limonene oxide after given reaction time (h).
[b] Yield as % of total limonene oxide starting material (max = 53%).
[c] Yield as % of only *trans*-limonene oxide starting material.
[d] No appreciable reaction with no change in limonene oxide fraction.

strate not being able to successfully compete with water and the sulfonate ligands for co-ordination to the smaller, more Lewis acidic ytterbium centre.

The reaction times and yields obtained with each of the lanthanoid 3,5-diacetamidobenzoate complexes **4**–**6** and the lanthanoid triflates and chlorides are summarised in Table 1. As can be seen, the La benzoate catalyst **4** is the most efficient, followed by the La and Gd triflates, both of which are marginally better than the Gd benzoate complex **5**, while the chlorides are ineffective.

3. Conclusion

This new procedure provides a high yielding and environmentally benign procedure for the formation of *trans*-axial diol **7** and consequent kinetic separation of *trans*-limonene oxide. The La benzoate complex proved to be the most efficient, outperforming all three metal triflate complexes. While the degree of kinetic separation may not be as high as those reported for other chemical systems this new reaction process provides the benefits of being catalytic in water, can be carried out at ambient temperature, minimizes the use of volatile organic compounds with no need for reagent derivatisation, and importantly does not involve the use of toxic reagents/catalysts. Significantly, lanthanide tris-2,5-diacetamidobenzoate complexes represent a new class of water soluble catalysts, for which this study provides an initial assessment. Further investigations are currently underway in our laboratories to develop and test analogous complex systems in ring opening reactions, and to compare the reactivity and selectivity of these catalysts with lanthanoid triflates in a variety of other organic transformations.

4. Experimental

4.1. General

^1H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, on a Bruker AM 300 spectrometer. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS. Infrared spectra (IR) were recorded on a Bruker Equinox 55 ATR spectrometer. GC–MS were performed on a Varian 3700 gas chromatograph using a 30QC5/BPX5 1.0 μm column of internal diameter 0.53 mm and length 30 m at a linear velocity of 40.6 cm/s. Elemental microanalyses were performed by the University of Otago, Dunedin, New Zealand. Lanthanoid oxides and (+)-limonene oxide, mixture of *cis*/*trans*-diastereomers were obtained from Sigma–Aldrich and used as supplied.

4.2. 3,5-Diacetamidobenzoic acid 3

To a stirred suspension of 3,5-diaminobenzoic acid (5.0 g, 32.9 mmol) in distilled water (150 mL) was added K_2CO_3 (13.3 g, 98.7 mmol). After stirring for 0.5 h, the solution became homogeneous and acetic anhydride (7.80 mL, 82.6 mmol) was slowly added. The reaction was stirred at rt o/n after which time all the water was removed under reduced pressure and the residual solid re-crystallised from boiling ethanol/water (5:1) to give a grey solid (7.06 g, 91%). ^1H NMR (300 MHz): δ 2.04 (s, 6H), 7.89 (d, $J = 1.8$ Hz, 2H), 8.10 (t, $J = 1.8$ Hz, 1H), 10.08 (br s, 2H). ^{13}C NMR (75 MHz): δ 23.0, 113.5, 114.6, 131.4, 139.7, 167.1, 168.6. IR (ATR) 3313s, 2894m, 1684s, 1627s, 1572m, 1533s, 1479m, 1452m, 1353m, 1321m, 1286s, 1158m, 1115w, 1036s, 934w, 912m, 871m, 645m, 625m cm^{-1}. MS calcd for $C_{11}H_{12}N_2O_4Na^+ = 259.1$, found: 259.0. HRMS calcd for $C_{11}H_{12}N_2O_4Na^+ = 259.0695$, found: 259.0695.

4.3. General procedure for the synthesis of benzoate complexes

To solid Ln_2O_3 (0.5 mmol) was added concd HCl (12 M, 1 mL). Stirring was continued until all the solid had dissolved and then satd $NaHCO_3$ (~40 mL) was added until the pH reached 8.5. The precipitated $Ln(HCO_3)_3$ was collected on a sintered funnel and washed with distilled water (3 × 5 mL), acetone (3 × 5 mL) and ether (3 × 5 mL) and then dried under vacuum for 2 h at rt. It was then added to a solution of 3,5-diacetamidobenzoic acid (2 mmol) in refluxing ethanol/water (4:1, 300 mL). The reaction was heated at reflux for a further 3 h after which any unreacted solid was removed by filtration and the ethanol/water removed under reduced pressure. The residual solid was suspended in THF and heated to reflux for 1 h before being filtered and washed with boiling THF (3 × 50 mL). The resulting grey powdery solid was dried under reduced pressure at rt for 2 days.

4.4. Lanthanum tris-3,5-diacetamidobenzoate 4

Following the general procedure as above with 3,5-diacetamidobenzoic acid **2** (1.00 g, 4.23 mmol) and La_2O_3 (173 mg, 0.53 mmol), lanthanum tris-3,5-diacetamido benzoate **4** was obtained as a greyish pink powder (0.7 g, 78%).

Mp 250 °C (decomp.). ^{1}H NMR (300 MHz): δ 2.03 (s, 6H), 7.78 (d, $J = 1.9$ Hz, 2H), 8.07 (t, $J = 1.9$ Hz, 1H), 9.91 (br s, 2H). ^{13}C NMR (75 MHz): δ 23.9, 112.1, 114.8, 137.4, 138.9, 168.2. IR (ATR) 3270s, 3090s, 1660s, 1612s, 1530s, 1493s, 1367s, 1266s, 1037m, 992m, 878m, 787m, 710m cm^{-1}. MS calcd for $C_{33}H_{33}N_6O_{12}LaNa^+ = 867.1$, found: 867.0. Calcd for $C_{33}H_{34}N_6O_{12}La^+ = 845.1$, found: 845.0. Anal. Calcd for $C_{33}H_{33}N_6O_{12}La{\cdot}3H_2O$ = C, 45.01; H, 4.24; N, 9.54. Found: C, 45.22; H, 4.56; N, 9.50.

4.5. Gadolinium tris-3,5-diacetamidobenzoate 5

Following the general procedure above with 3,5-diacetamidobenzoic acid **2** (2.08 g, 8.8 mmol) and Gd_2O_3 (400 mg, 1.10 mmol), gadolinium tris-3,5-diacetamido benzoate **5** was obtained as a greyish pink powder (2.01 g, 98%). Mp 250 °C (decomp.). IR (ATR) 3270s, 3095s, 1662s, 1612s, 1532s, 1444s, 1368s, 1269s, 1169m, 1037w, 991w, 878w, 789m, 698w cm^{-1}. MS calcd for $C_{33}H_{33}N_6O_{12}GdNa^+ =$ 886.1, found: 886.2. HRMS calcd for $C_{33}H_{34}N_6O_{12}Gd^+ = 864.1476$, found: 864.1462. Anal. Calcd for $C_{33}H_{33}N_6O_{12}Gd{\cdot}H_2O$ = C, 44.99; H, 4.00; N, 9.54. Found: C, 45.15; H, 4.21; N, 9.39.

4.6. Ytterbium tris-3,5-diacetamidobenzoate 6

Following the general procedure above with 3,5-diacetamidobenzoic acid **2** (0.80 g, 3.37 mmol) and Yb_2O_3 (250 mg, 0.63 mmol), Ytterbium tris-3,5-diacetamido benzoate **6** was obtained as a greyish pink powder (0.65 g, 83%). Mp 300 °C (decomp.). IR (ATR) 3263s, 3094s, 1659s, 1616s, 1540s, 1367s, 1271s, 1242s, 1170m, 995w, 878, 788m, 693w cm^{-1}. MS calcd for $C_{33}H_{34}N_6O_{12}Yb^+ = 880.1$, found: 880.0. HRMS calcd for $C_{33}H_{34}N_6O_{12}Yb^+ =$ 880.1623. Anal. Calcd for $C_{33}H_{33}N_6O_{12}Yb{\cdot}5H_2O$ = C, 40.91; H, 4.47; N, 8.67. Found: C, 40.90; H, 4.20; N, 8.50.

4.7. General procedure for reaction optimisation in the kinetic separation of (+)-*trans*-limonene oxide 1

The catalyst (**4**–**6** or $Ln(OTf)_3$) (0.017 mmol, 5 mol %) was dissolved in water (20 mL) and commercially available *cis*/*trans* (47:53) limonene oxide **1** or **2** (50 mg, 0.33 mmol) is added. The suspension was vigorously stirred for a given time period and then extracted with $CDCl_3$. The extraction mainly contains all the unreacted epoxide and some of the product diol **7**. The aqueous phase is then exhaustively extracted with EtOAc (2 × 20 mL) and the solvent removed under reduced pressure. This extract contains the residual diol and is dissolved using the $CDCl_3$ extract. Benzonitrile is added (0.033 mL, 0.33 mmol) as an internal NMR standard. A sample for ^{1}H NMR analysis is taken from this solution. The amount of *trans*-epoxide **1** was determined by integration of the methine doublet at 2.98 ppm. The amount of *cis*-epoxide **2** was determined by integration of the methine triplet at 3.05 ppm, and the *trans*-diaxial diol **7** by integration of the methine doublet at 3.63 ppm. All integrations were measured relative to the five hydrogens of benzonitrile.

4.8. Ring opening and kinetic separation of *trans*-limonene oxide 1 by lanthanum catalyst 4

Catalyst **4** (0.153 mmol, 5 mol %) was dissolved in water (180 mL) and *cis*/*trans* (47:53) limonene oxides **1** and **2** (0.45 g, 2.97 mmol) added. The suspension was vigorously stirred for 13 h and then extracted with pentane (2 × 50 mL). The organic phase was washed with brine (2 × 10 mL) and the solvent then carefully removed under reduced pressure to yield the (+)-*trans*-limonene oxide as a colourless liquid (0.18 g, 74%). $[\alpha]_D$ =+78 (neat) (lit.[9] +77). ^{1}H NMR (200 MHz): δ 1.32 (s, 3H), 1.67 (s, 3H), 1.41–1.51 and 1.71–2.29 (m, 6H), 2.98 (d, J 5.0 Hz, 1H), 4.65 (br s, 2H).

4.9. Synthesis of lanthanoid triflates

An adaptation of the procedure of Kobayashi was followed.[15] Trifluoromethanesulfonic acid (0.5 mL, 5.65 mmol) was added to a suspension of lanthanoid oxide (0.34 g, 1.03 mmol) in water (2 mL). The suspension was stirred at reflux for 1 h and was then filtered to remove unreacted oxide. The remaining filtrate was concentrated under reduced pressure and the residual solid dried under reduced pressure (1 mmHg, 2 h) to yield the appropriate lanthanoid triflate hydrate as a white powder.

Lanthanum triflate. ^{13}C NMR (50 MHz): δ 120.2 (q, J 315 Hz, O_3SCF_3) IR (ATR) 3409s, 2228s, 1659w, 1633w, 1225s, 1185s, 1026s, 632w cm^{-1}.

Gadolinium triflate. IR (ATR) 3404s, 2538s, 2654s, 1457w, 1224s, 1183s, 1025s, 632w cm^{-1}.

Ytterbium triflate. ^{13}C NMR (50 MHz): δ 120.2 (q, J 316 Hz, O_3SCF_3). IR (ATR) 3382s, 2495s, 1650w, 1458w, 1222s, 1173s, 1022s, 631m cm^{-1}.

Acknowledgements

The authors acknowledge the support of Monash University and the Australian Research Council.

References

1. For reviews of 'green' solvents in catalysis see: (a) Keim, W. *Green Chem.* **2003**, *5*, 105–111; (b) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267–278.
2. For reviews of asymmetric epoxide ring opening see: (a) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1–29; (b) De Vries, E. J.; Jannsen, D. B. *Curr. Opin. Biotechnol.* **2003**, *14*, 1414–1420; (c) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421–431; (d) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Ed.; Springer: Berlin, 1999; pp 1309–1326; (e) Armstrong, R. N. *Comp. Nat. Prod. Chem.* **1999**, *5*, 51–70; (f) Hodgon, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384; (g) Paterson, I.; Berrisford, D. J. *Angew. Chem.* **1992**, *104*, 1204–1205; (h) Buchanan, J. G.; Sable, H. Z. *Select. Org. Trans.* **1972**, *2*, 1–95; (i) Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1934–1937.
3. Kobayashi, S. *Top. Organomet. Chem.* **1999**, *2*, 63–118.

4. (a) Tsaryuk, V.; Zhuravlev, K.; Zolin, V.; Gawryszewska, P.; Legendzlewicz, J.; Kudryashova, V.; Pekareva, I. *J. Photochem. Photobiol. A* **2006**, *177*, 314–323; (b) Rieter, W. J.; Taylor, K. M. L.; An, H.; Lin, W.; Lin, W. *J. Am. Chem. Soc.* **2006**, *128*, 9024–9025; (c) Ferenc, W.; Walkow-Dzlewulska, A. *J. Therm. Anal. Calorim.* **2002**, *70*, 949–958.
5. Grimm, E. L.; Methot, J.; Shamji, M. *Pure Appl. Chem.* **2002**, *75*, 231–234.
6. Tius, M. A.; Kerr, M. A. *Synth. Commun.* **1988**, *18*, 16–17.
7. Yamasaki, M. *J. Chem. Soc., Chem. Commun* **1972**, *10*, 606a–607a.
8. Kergomard, A.; Veschambre, H. *Sci. Chim.* **1974**, *274*, 155–157.
9. Bettadaiah, B. K.; Srinivas, P. *J. Photochem. Photobiol., A.* **2004**, *167*, 137–140.
10. De Carvalho, C. C. R.; Van Keulen, Frederik.; Da Fonseca, M. M. R. *Biocatal. Biotransform.* **2000**, *18*, 223–235.
11. Van der Werf, M. J.; Jongejan, H.; Franssen, M. C. R. *Tetrahedron Lett.* **2001**, *42*, 5521–5524.
12. Steiner, D.; Ivison, L.; Goralski, C. T.; Appel, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359–2363.
13. Salles, L.; Nixon, A. F.; Russel, N. C.; Clarke, R.; Pogorzelec, P.; Cole-Hamilton, D. J. *Tetrahedron: Asymmetry* **1999**, *10*, 1471–1476.
14. Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1937–1944.
15. Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623–11636.

Monash University

Declaration for Chapter 2, Paper 2: Methods for the Separation of the cis and trans Diastereomers of Limonene 1,2-Oxide and Convenient Routes to Diequatorial and Diaxial 1,2-Diols, Synthesis, 10, 2007, 1523-1527

Declaration by candidate

In the case of Chapter 2, Paper 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Experimental design, execution of reaction(s), characterisation/isolation of reaction products and manuscript preparation/editing	50%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
P. C. Andrews	Manuscript editing and intellectual input	
B. H. Fraser	Experimental design, execution of reaction(s), characterisation/isolation of reaction products and manuscript preparation/editing	
P. C. Junk	Manuscript preparation/editing and intellectual input	
M. Massi	Manuscript preparation/editing and intellectual input	
C. M. Forsyth	X-ray crystal structure determination	
K. L. Tuck	Research guidance/experimental design, financial support, manuscript preparation/editing	

Candidate's Signature [redacted] **Date:** 26/11/09

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Monash University Clayton, School of Chemistry

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	Date 16.11.09
Signature 2	[redacted]	
Signature 3	[redacted]	16/11/09
Signature 4	[redacted]	
Signature 5	[redacted]	17/11/09
Signature 6	[redacted]	26/11/09

Location(s)	Monash University Clayton, School of Chemistry

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	Date
Signature 2		16/11/09
Signature 3		
Signature 4		
Signature 5		

Location(s)	Monash University Clayton, School of Chemistry	

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1		
Signature 2		
Signature 3		
Signature 4	[redacted]	16/11/09
Signature 5		

Facile Methods for the Separation of the *cis*- and *trans*-Diastereomers of Limonene 1,2-Oxide and Convenient Routes to Diequatorial and Diaxial 1,2-Diols

Michael Blair, Philip C. Andrews, Benjamin H. Fraser, Craig M. Forsyth, Peter C. Junk, Massimiliano Massi, Kellie L. Tuck*

School of Chemistry, Monash University, Clayton, Victoria, Australia 3800
Fax +61(3)99054597; E-mail: kellie.tuck@sci.monash.edu.au

Received 9 January 2007; revised 1 March 2007

Abstract: Facile methods are described for accessing four diastereomerically pure products from the commercial mixture of limonene oxide. The use of either an aqueous mercury(II)-mediated or H^+-catalysed hydration, afforded a kinetic separation of (+)-limonene oxide (*cis*- or *trans*-isomer could be respectively recovered) from the commercially available diastereomeric mixture in good recovery yields and high diastereoselectivity (>98% de). The hydrolysed limonene oxide products, either *trans*-diequatorial or *trans*-diaxial diols, are also formed in good conversion yields and high diastereoselectivity (>98% de).

Key words: kinetic separation, diastereomer resolution, limonene oxide, mercury, diols

Optically pure epoxides and their corresponding 1,2-diols are important building blocks in asymmetric synthesis. Limonene oxide (Figure 1) is one such epoxide, which has not only been used in natural product synthesis, but also as a chiral ligand/auxiliary in asymmetric synthesis.[1] The epoxidation of limonene (see Figure 1 for structure) most often leads to a mixture of the *cis*- and *trans*-diastereomers,[2] and although both individual isomers are commercially available, they are expensive, and hence more commonly sold as a diastereomeric mixture (53:47). Efficient methods for separation of these diastereomers are therefore of academic and commercial interest. Physical methods for separation generally involve fractional distillation or chromatography and are expensive and not trivial.[3] The alternative, kinetic separation, which utilises a difference in reactivity of the two diastereomers, has been developed based upon photo-assisted kinetic resolution,[4] hydrolysis with $HClO_4$ or $NaHSO_3$,[5,6] biocatalysis,[7] molybdenum(VI),[8] electrophilic mercuration,[9] amine addition,[10,11] or biotransformation.[12] We have recently described the use of lanthanoid benzoate complexes for the kinetic separation of *cis*/*trans*-limonene oxide.[13]

The hydrolysis of limonene oxide, theoretically, can yield four possible diol stereoisomers, but in practice, predominantly affords the *trans*-diaxial diol **3** and to a much lesser extent, the *trans*-diequatorial diol **4**. Although both have been used in a number of syntheses,[7,10,14,15] they are not commercially available, and there is no selective, high yielding synthesis known for the *trans*-diequatorial diol **4**.

Figure 1 Structure of limonene oxide and limonene

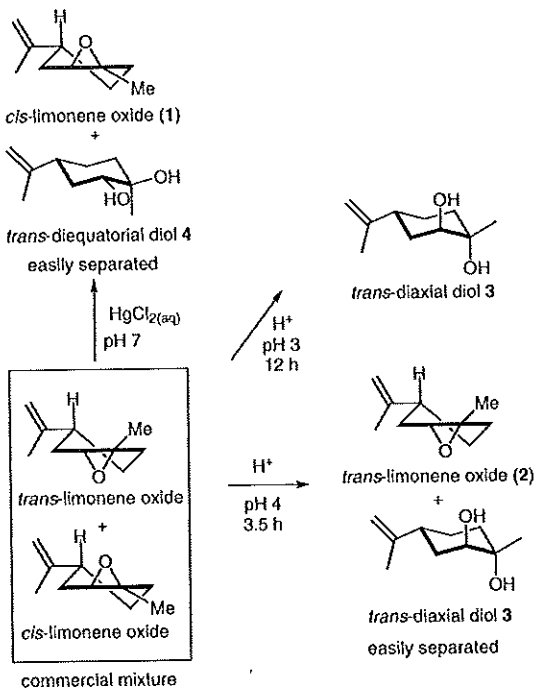
Herein, we describe the results of a two-part study into the stereoselective transformations of *cis*/*trans*-limonene oxide. Firstly, acid hydrolysis at pH 4 (NaOAc buffered solution) yields pure unreacted *trans*-limonene oxide (**2**) and *trans*-diaxial diol **3** which are easily separated. Secondly, in a completely complementary fashion, treatment with $HgCl_2$ at pH 7 yields pure unreacted *cis*-limonene oxide (**1**) and the *trans*-diequatorial diol **4** which are also easily separated. When applied in tandem, these procedures afford both *cis*- and *trans*-limonene oxide (**1** and **2**), and the diaxial and diequatorial diols (**3** and **4**) in excellent recovery yields and diastereoselectivities (Scheme 1).

Acid-Catalysed Separation of *trans*-Limonene Oxide (2)

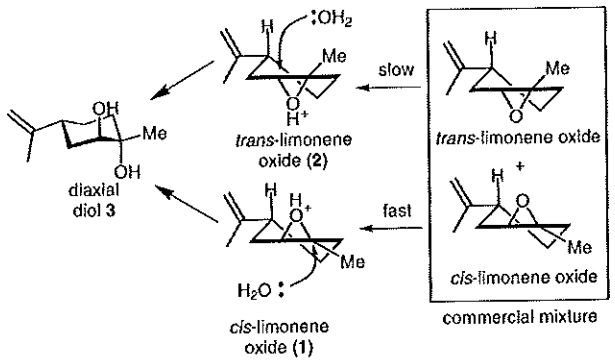
Previously it has been reported that reaction of both the *cis*- and *trans*-limonene oxide (**1** and **2**), under acidic conditions lead to the same *trans*-diaxial diol **3**.[16] It was reasoned that this occurs due to selective axial nucleophilic attack that can be rationalised by the Fürst–Plattner rule.[2,17] It is therefore postulated that due to steric hindrance and electronic effects, under these conditions, the *cis*-isomer **1** would react at a substantially quicker rate than the *trans*-isomer **2** (Scheme 2). As there is no data on the relative reactivities of the *cis*- and *trans*-isomers under acidic conditions, it was of interest to investigate the reactivity of the *cis*-isomer under these conditions.

The reaction mixture (NaOAc buffered solution, pH 4), was analysed by GC analysis over 1.5 hours. It was revealed that the *cis*-epoxide **1** reacted at a quicker rate than the *trans*-epoxide **2** (Figure 2), which is consistent with that *postulated* in the literature. If the reaction was ceased

SYNTHESIS 2007, No. 10, pp 1523–1527
Advanced online publication: 02.05.2007
DOI: 10.1055/s-2007-966033; Art ID: P00407SS



Scheme 1 Separation of diastereomerically pure *cis*- and *trans*-(+)-limonene oxide (**1** and **2**) and the synthesis of the 1,2-*trans*-diols **3** and **4**



Scheme 2 Acid-catalysed hydrolysis of *cis*/*trans*-(+)-limonene oxide (**1** and **2**)

after 3.5 hours (NaOAc buffered solution, pH 4), the unreacted (+)-*trans*-limonene oxide (**2**) could be obtained via extraction of the reaction mixture with hexane [recovery yield based on (+)-*trans*-limonene oxide (**2**) 87%, de >98%]. Subsequent extraction of the reaction mixture with ethyl acetate gave the diaxial diol **3** [76% based on initial amount of (+)-*cis*-limonene oxide, >98% de]. When the mixture was subjected to hydrolysis at pH 3 (KH_2PO_4 buffered aqueous solution, pH 3, 12 h), the diaxial diol **3** was the major hydrolysis product [70% based on the initial amount (+)-limonene oxide, >98% de]. This is consistent with the findings in the literature at pH <1,[9,16] however, we observed only nominal amounts of the diequatorial diol **4**. Thus, this method is a facile method for separation of (+)-*trans*-limonene oxide (**2**) and/or the formation of optically pure diaxial diol **3**.

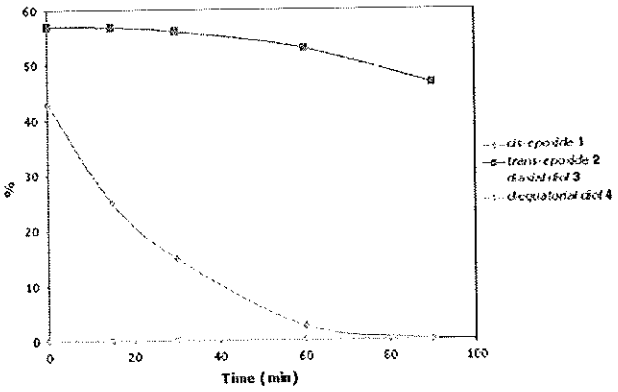
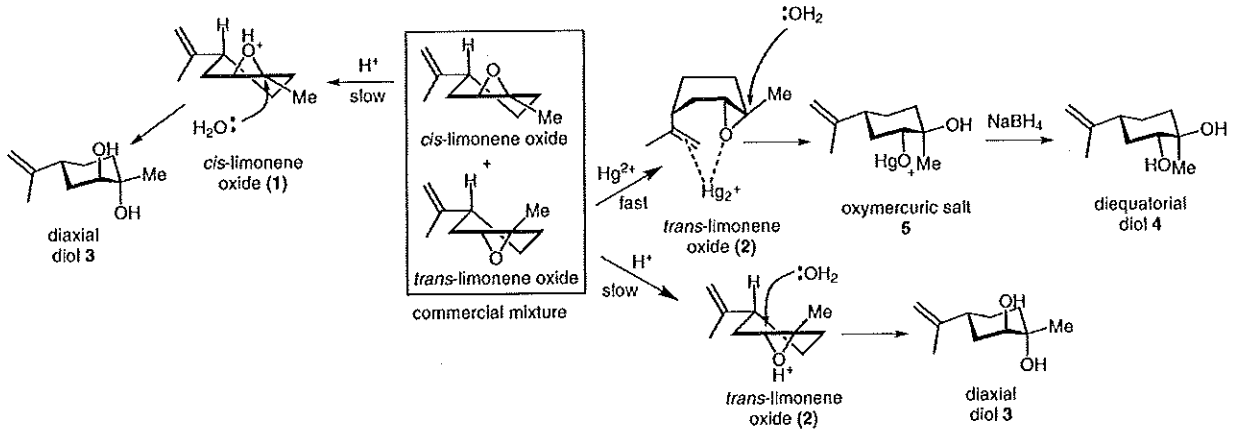


Figure 2 Reaction profile for the kinetic separation of *cis*/*trans*-(+)-limonene oxide in NaOAc buffered solution (pH 4)

$HgCl_2$-Promoted Separation of *cis*-Limonene Oxide (1) and Synthesis of *trans*-Diequatorial Diol 4

The kinetic separation of commercially available *cis*- and *trans*-limonene oxides (**1** and **2**) has been previously described by Van der Werf and co-workers.[9] They report that the optimum conditions [$Hg(OAc)_2$ in 1:1 acetone–50 mM tris buffer, pH 7.0] gives *cis*-limonene oxide (**1**, >98% de) and a mixture of the diequatorial (**4**) and diaxial (**3**) diols in a 7:3 ratio.[9] They concluded that mercuration of *trans*-limonene oxide (**2**) occurs rapidly to give a mixture of diaxial (**3**) and diequatorial (**4**) diols, with water attacking at the tertiary site, to give the diequatorial diol **4** preferentially, after reaction of the oxymercuric salt with $NaBH_4$.[9] From our results obtained with the acid-catalysed separation of limonene oxide, the diaxial diol **3** is a by-product and is formed via acid-catalysed opening of the *cis*-epoxide **1** (Scheme 3). This was most likely due to insufficient buffering capacity, and to prevent this, the buffer concentration was increased from 50 mM to 300 mM. Reaction of *cis*- and *trans*-(+)-limonene oxides (**1** and **2**), with $HgCl_2$ in buffer alone resulted in almost exclusive formation of the diequatorial diol **4**. The use of $Hg(OAc)_2$ in acetone–tris buffer in our hands was unsuccessful, whereas $HgCl_2$ in aqueous conditions afforded reproducible results. The diaxial diol **3** was formed in less than 5% yield according to ^1H NMR spectroscopy and 1% yield as detected by GC. It was also observed that a decrease in pH of the solution was accompanied by an increase in the yield of the diaxial diol **3** (Table 1). This is presumably due to the acid opening of the *cis*-epoxide **1** competing with mercuration of the *trans*-epoxide **2**, and does not occur via formation of a *trans*-oxymercuric salt **5** as previously proposed.[9] Reaction of *cis* and *trans*-(+)-limonene oxides (**1** and **2**) with $HgCl_2$ is summarised in Scheme 3.



Scheme 3 Diastereoselective electrophilic mercuration of *cis*/*trans*-(+)-limonene oxide

Table 1 Effect of the pH on the Diastereoselection of the Diols 3 and 4

Conditions	pH	Yield (%) of diol 4[a]	Ratio of diols 3/4
330 mM tris–67 mM $HgCl_2$	7	90	1:20
330 mM NaOAc–67 mM $HgCl_2$	5	50	2:3
330 mM KH_2PO_4–67 mM $HgCl_2$	3	33	2:1

[a] After 2 h at 25 °C. Yields of limonene 1,2 diequatorial diol via kinetic separation are calculated from the initial percent composition of *cis*-limonene oxide.

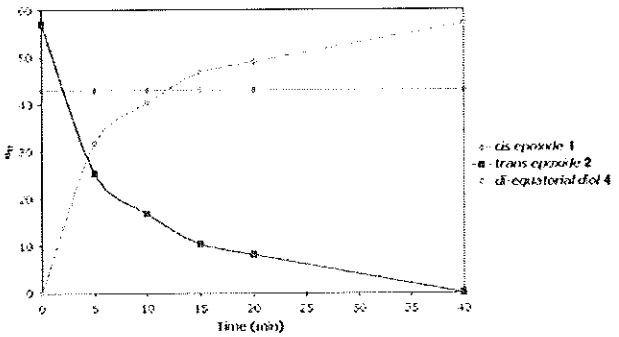


Figure 3 Reaction profile for the kinetic separation of *cis*/*trans*-(+)-limonene oxide, with aq $HgCl_2$. The amount of the diequatorial diol formed was calculated from the disappearance of the *trans*-epoxide, as the oxymercuric intermediate was unable to be detected by GC analysis.

The optimum buffer for the Hg(II) opening of limonene oxide was 330 mM tris buffer. With this information in hand, the reactivities of the *cis*- and *trans*-isomers of (+)-limonene oxide were investigated (Figure 3). It was observed by GC analysis that (+)-*trans*-limonene oxide (**2**) underwent complete conversion to the highly water soluble oxymercuric intermediate in 40 minutes. The unreacted (+)-*cis*-limonene oxide (**1**) was recovered in high yield and diastereoselectivity [96% based on initial (+)-*cis*-limonene oxide, >98% de]. Subsequent reaction of the aqueous solution with $NaBH_4$ gave the diequatorial diol **4** (99% recovery yield, 91% de). Recrystallisation increased the diastereomeric excess to >98%. As a final confirmation of the stereochemistry of **4** an X-ray crystal structure revealed that the *trans*-OH groups and the propenyl group were in equatorial positions (Figure 4).

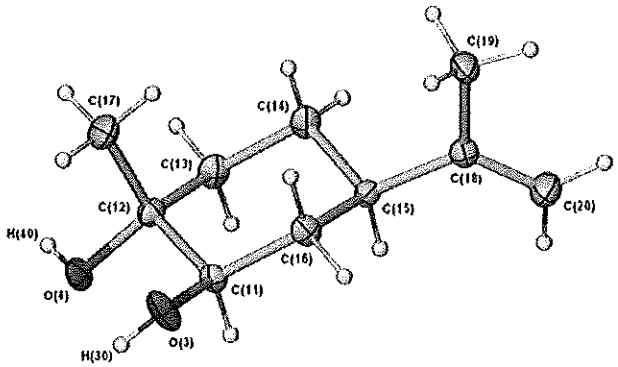


Figure 4 X-ray crystal structure of the *trans*-diequatorial diol **4**

In conclusion, it has been demonstrated that *cis*- and *trans*-limonene oxide hydrolyse at very different rates in a dilute acid solution, and therefore can be exploited to provide one of the most efficient and simple methods for the kinetic separation of the *trans*-diastereomer. In a complementary fashion, it was found that an adequately buffered $HgCl_2$ solution allows complete separation of the *cis*-epoxide, and exclusive formation of the diequatorial diol **4**, in excellent yield and diastereoselectivity (>98% de).

This work highlights a facile method for accessing four diastereomerically pure products from the commercially available limonene oxide mixture.

Chemical shifts are expressed in parts per million (δ). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 and 75 MHz, respectively. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. IR spectra were recorded on a Bruker Equinox 55 ATR spectrometer. GC analyses were performed on a Varian 3700 with a SGE 30 QC5 BPX5 (1.0 μm column of internal diameter, 0.53 mm × 30m) (He carrier gas, 85 °C for 3 min, then ramped to 280 °C at 8 °C/min). Optical rotations were obtained using a PolAAR 2001 automatic polarimeter, using a 1 dm cell with $CHCl_3$ as solvent, at a wavelength of 589 nm (sodium D line). (+)-Limonene oxide (*cis/trans* mixture, 53:47, Aldrich) was used as received.

(1*S*,2*S*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (3)

(+)-Limonene oxide (*cis/trans* isomers **1** and **2**, 1.0 g, 6.57 mmol) was added to a solution of NaOAc (200 mL, 100 mM, pH 4). Stirring was continued until total consumption of the *cis*-epoxide occurred (ca. 3.5 h) as detected by GC analysis. The mixture was neutralised with aq sat. $NaHCO_3$, extracted with hexane (3 × 100 mL), dried (Na_2SO_4) and concentrated in vacuo to afford the unreacted *trans*-epoxide **2** [373 mg, 87% recovery yield based on initial (+)-*trans*-limonene oxide, de >98%, yields of *cis*- or *trans*-limonene oxide via kinetic separation are calculated from the initial percent composition (i.e., 53:47)]. The residual aqueous phase was extracted EtOAc (3 × 100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the diaxial diol **3** [487 mg, 76% based on initial (+)-*cis*-limonene oxide, >98% de].

Mp 68–70 °C; $[\alpha]_D^{20}$ +18.1 (*c* 0.01, $CHCl_3$); t_R = 10.81 min (SGE 30 QC5 BPX5).

IR (solid sample): 3354, 3081, 2931, 2235, 1644, 1448, 1371, 1240 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (s, 3 H), 1.54–1.61 (m, 4 H), 1.62–1.68 (m, 1 H), 1.71–1.74 (m, 3 H), 1.87–98 (m, 1 H), 2.22–2.28 (m, 1 H), 3.61–3.64 (m, 1 H), 4.72–4.73 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3, 26.45, 26.9, 33.9, 34.3, 37.7, 71.5, 74.2, 109.2, 149.6.

Spectral data was consistent to that previously reported.[10]

(+)-*trans*-Limonene Oxide (2)

$[\alpha]_D^{20}$ +78 (neat) {Lit.[4] $[\alpha]_D$ +77 (neat)}; t_R = 7.46 min (SGE 30 QC5 BPX5).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (s, 3 H), 1.35–1.40 (m, 2 H), 1.66–1.67 (m, 3 H), 1.69–1.70 (m, 2 H), 1.84–1.87 (m, 2 H), 2.98 (d, *J* = 4.0 Hz, 1 H), 4.65–4.67 (m, 2 H).

Complete Conversion of *cis/trans*-Limonene Oxide Mixture to (1*S*,2*S*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (3)

(+)-Limonene oxide (*cis/trans* isomers **1** and **2**, 5.0 g, 32.9 mmol) in potassium phosphate buffer (200 mL, 200 mM, pH 3) was stirred at r.t. for 12 h. During this time the product, the diaxial diol, precipitated. The diaxial diol **3** was removed by filtration and the aqueous solution was concentrated to a quarter of its original volume. The solution was allowed to stand overnight at 5 °C to afford a second crop of diaxial diol **3** [3.93 g, 70% based on initial (+)-limonene oxide, >98% de]. The spectroscopic data of the title compound **3** was identical to that obtained when NaOAc was the buffer.

(1*R*,2*R*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (4)

To a solution of $HgCl_2$ (250 mL, 67 mM in 330 mM tris buffer, pH 7) was added (+)-limonene oxide (*cis/trans* epoxides **1** and **2**, 4.0 g, 26.3 mmol) dropwise. The mixture was stirred at r.t. and the progress of the reaction was followed by GC. Aliquots (1 mL) were diluted with aq sat. $NaHCO_3$ (1 mL) followed by extraction with EtOAc (2 mL). The samples were then analysed by GC analysis. After 40 min, the *trans*-epoxide **2** was completely consumed. The mixture was extracted with hexane (3 × 70 mL), to remove unreacted *cis*-(+)-limonene oxide (**1**; 1.64 g, maximum theoretical yield 96%, >98% de) and $NaBH_4$ (3.20 g, 84.6 mmol) was subsequently added to the aqueous phase. After stirring at r.t. for 3 h, the mixture was extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a white crystalline solid [2.52 g, 99% based on starting *trans*-(+)-limonene oxide, yields of *cis*- or *trans*-limonene oxide via kinetic separation are calculated from the initial percent composition (i.e., 53:47)]. A mixture of the diequatorial and diaxial diols (20:1) was observed by ^{1}H NMR spectroscopy. Recrystallisation from water afforded the diastereomerically pure diequatorial diol **4** (68%, >98% de).

Mp 74–76 °C; $[\alpha]_D^{20}$ –5.5 (*c* 0.01, $CHCl_3$); t_R = 11.03 min (SGE 30 QC5 BPX5).

IR (solid sample): 3330, 3251, 3075, 2981, 2864, 1697, 1644, 1434, 1374 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20 (s, 3 H), 1.21–1.26 (m, 2 H), 1.29–145 (m, 2 H), 1.67 (s, 3 H), 1.72 (dt, *J* = 2.4, 9.6 Hz, 1 H) 1.85–1.95 (m, 2 H), 2.05 (tt, *J* = 2.9, 9.3 Hz, 1 H), 2.91 (s, 1 H), 3.20 (s, 1 H), 3.56 (dd, *J* = 3.3, 9.0 Hz, 1 H), 4.71 (s, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.9, 20.8, 28.7, 36.1, 38.5, 43.6, 74.0, 77.2, 109.1, 148.5.

X-ray Data

For X-ray crystal data of **4**, please see ref. 18.

(+)-*cis*-Limonene Oxide (1)

$[\alpha]_D^{20}$ +48.1 (*c* 0.01, $CHCl_3$) {Lit.[10] $[\alpha]_D$ +44 (neat)}; t_R = 7.40 min (SGE 30 QC5 BPX5).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (s, 3 H), 1.45–1.68 (m, 3 H), 1.69–1.72 (m, 3 H), 1.80–1.96 (m, 2 H), 1.85–1.95 (m, 2 H), 2.10–2.20 (m, 1 H), 3.04–3.06 (m, 1 H), 4.65–4.67 (m, 1 H), 4.67–4.73 (m, 1 H).

Acknowledgment

The authors acknowledge the support of Monash University, the School of Chemistry, Monash University, VICS, and the Australian Research Council for a LIEF grant.

References

(1) For example, see: (a) Kido, F.; Abiko, T.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2989. (b) Ho, T.; Chein, R. *Helv. Chim. Acta* **2006**, *89*, 231. (c) Baker, R.; Borges, M.; Cooke, N. G.; Herbert, R. H. *J. Chem. Soc., Chem. Commun.* **1987**, 414. (d) Ho, T.; Lee, K. *Tetrahedron Lett.* **1995**, *36*, 947. (e) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807. (f) Chrisman, W.; Camara, J. N.; Marcellini, K.; Singaram, B.; Goralski, C. T.; Hasha, D. L.; Rudolf, P. R.; Nicholson, L. W.; Borodychuk, K. K. *Tetrahedron Lett.* **2001**, *42*, 5805.

(2) Leffingwell, J. C.; Royals, E. E. *Tetrahedron Lett.* **1965**, 3829.

(3) Newhall, W. F. *J. Org. Chem.* **1959**, *24*, 1673.

(4) Bettadaiah, B. K.; Srinivas, P. *J. Photochem. Photobiol., A* **2004**, *167*, 137.
(5) Jones, J.; dos Santos, A. G.; de Lima Castro, F. *Synth. Commun.* **1996**, *26*, 2651.
(6) Leffingwell, J. C.; Shackelford, R. E. (R. J. Reynolds Tobacco Co.) French Patent FR2002595, **1969**.
(7) De Carvalho, C. C. R.; Van Keulen, F.; Da Fonseca, M. M. R. *Biocatal. Biotransform.* **2000**, *18*, 223.
(8) Salles, L.; Nixon, A. F.; Russell, N. C.; Clarke, R.; Pogorzelec, P.; Cole-Hamilton, D. J. *Tetrahedron: Asymmetry* **1999**, *10*, 1471.
(9) van der Werf, M. J.; Jongejan, H.; Franssen, M. C. R. *Tetrahedron Lett.* **2001**, *42*, 5521.
(10) Steiner, D.; Ivison, L.; Goralski, C. T.; Appel, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359.
(11) Voronkov, M. V.; Gontcharov, A. V.; Kanamarlapudi, R. C.; Richardson, P. F.; Wang, Z. *Org. Process Res. Dev.* **2005**, *9*, 221.
(12) Hamada, H.; Kondo, Y.; Ishihara, K.; Nakajima, N.; Hamanda, H.; Kurihara, R.; Hirata, T. *J. Biosci. Bioeng.* **2003**, *96*, 581.
(13) Andrews, P. C.; Blair, M.; Fraser, B. H.; Junk, P. C.; Massi, M.; Tuck, K. L. *Tetrahedron: Asymmetry* **2006**, *17*, 2833.
(14) For example, see: (a) Kaufmant, T. S.; Srivastava, R. P. R.; Sindelart, D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 501. (b) Kido, F.; Yamaji, K.; Sinha, S. C.; Abiko, T.; Kate, M. *Tetrahedron* **1995**, *51*, 7697.
(15) (a) Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1991**, *32*, 243. (b) Valente, A. A.; Seixas, J. D.; Gonçalves, I. S.; Abrantes, M.; Pillinger, M.; Romão, C. C. *Catal. Lett.* **2005**, *101*, 249.
(16) Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1937.
(17) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.
(18) The X-ray crystal data of **4** (CCDC-627386) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

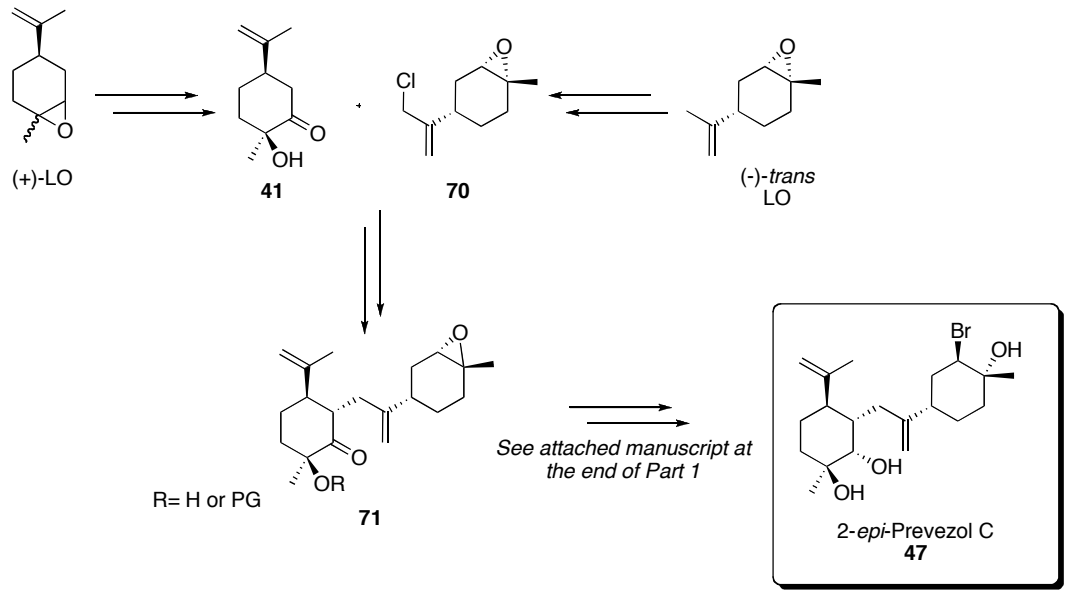
Synthesis 2007, No. 10, 1523–1527

3.0 Progress Towards the Total Synthesis of Prevezol C: Synthesis of 2-epi-Prevezol C and Routes to syn-Bromohydrin Terpenoids.

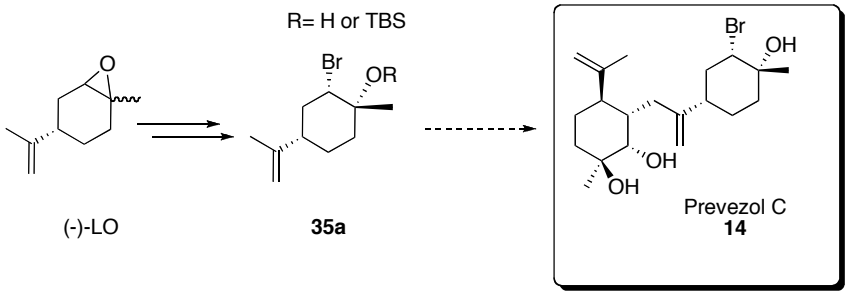
*This first part of this chapter describes the preparation and coupling of the key Eastern **70** and Western domains **41** of the diterpene core **71**. Elaboration of the diterpene core **71** to reveal 2-bromo epimer of Prevezol C **47**, is disclosed at the end of this chapter as a letter submitted to Organic Letters.*

*The second part of this chapter focuses on the synthesis of the syn-bromohydrin monoterpene **35a**, through an array of approaches. It is anticipated these strategies will be implemented in the future to yield the required stereochemistry of the naturally occurring Prevezol C **14**.*

Chapter 3: Part 1



Chapter 3: Part 2



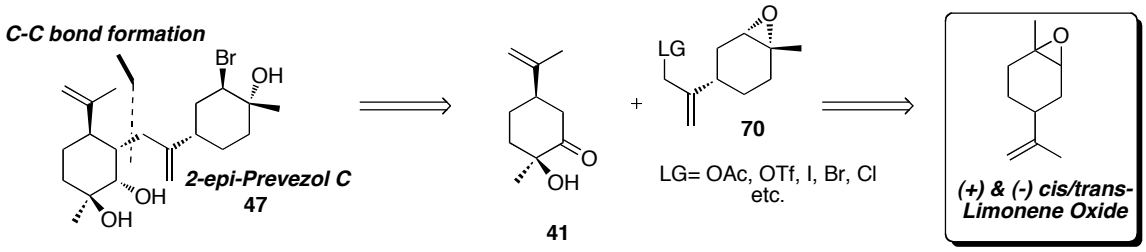
Scheme 3.0: The Stereo-Convergent Strategy to the Prevezol C Ring System

Chapter 3

Part 1: Preparation of the Eastern and Western Domains of 2-epi-Prevezol C

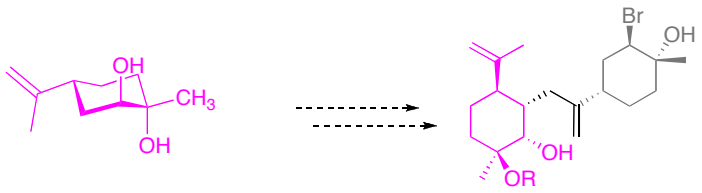
3.1 Model Alkylation Studies to the Preparation of the Western domain

The synthetic strategy towards the preparation of the diterpene core **71** of 2-*epi*-Prevezol C **47** relied upon recognizing the structural homology of the Eastern and Western domains of 2-*epi*-Prevezol C **47** (Scheme 3.1). It was envisaged that the chiron limonene oxide could be utilized to synthesise the Eastern and Western domains, giving retrons **41** and **70** respectively. As introduced in Chapter 1, coupling of these two domains **41** and **70**, would then furnish the required diterpene framework of Prevezol C **14** and its 2-bromo *epimer* **47**.



Scheme 3.1: Retrosynthetic analysis of the 2-epi-Prevezol C 47 ring system

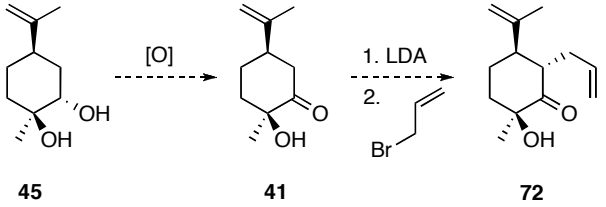
The chiral limonene glycols **45** and **46** were discussed in Chapter 2. It is recognized that the (1*S*,2*S*,4*R*) diaxial isomer **45** could be utilized to establish the 4 contiguous stereogenic centres contained in the Western domain of the natural product (Scheme 3.2). A substrate controlled α-allylic alkylation reaction of the corresponding ketone derived from diaxial diol **45**, would see the installation of the fourth stereocentre in the Western hemisphere.



Scheme 3.2: Elaboration of the limonene 1,2-diaxial diol to the 2-epi-Prevezol C 47 ring system

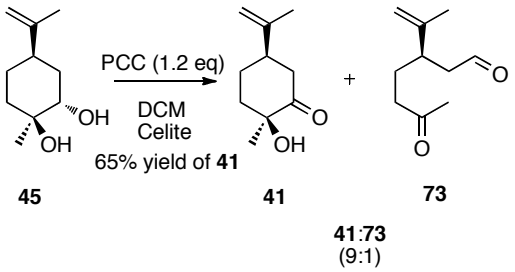
To validate the alkylative strategy towards the binary ring system of 2-*epi*-Prevezol C **47**, work commenced towards the preparation of the alkylated model substrate **72**, and its ketone precursor **41** (Scheme 3.3). The desired ketone **41** would be obtained *via* oxidation of the diaxial-diol **45**, followed by deprotonation with an appropriate lithium amide base,

and subsequent treatment with the allyl bromide electrophile to generate the α-allylated ketone **72**.



Scheme 3.3:Proposed alkylative strategy to the model substrate 72

Conditions towards the oxidation of the *trans*-diaxial diol **45** were investigated. As this was one of the initial transformations in a medium length synthesis, there was a requirement for this transformation to be clean, amenable to large scale, and high yielding. A Swern oxidation of the diol **45** gave moderate yields of the ketol **41** (*ca* 65% isolated yield),[63] however the associated malodor and toxicity of dimethylsulfide on larger scale reactions posed a hazard, and precluded further use of this oxidant system. Pyridinium chlorochromate (PCC) affected the oxidation of the diol **45** to the ketol **41** in moderate isolated yields (65%); however oxidative cleavage of the vicinal diol also occurred affording the ring opened aldehyde **73** (Scheme 3.4) in 10% yield. The analytical data of the aldehyde **73** obtained as by-product from this oxidation was consistent with the literature ^{1}H NMR and MS analysis data previously reported.[64] Separation of the desired ketol **41** from the aldehyde **73** on silica gel was not trivial, and hence other oxidation conditions were sought.

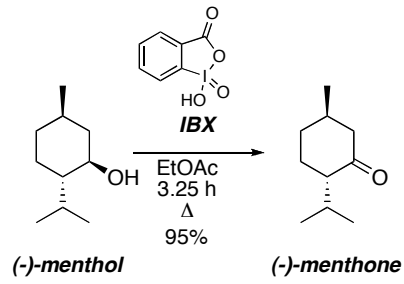


Scheme 3.4: Oxidation to the ketol 41, and oxidative cleavage of the limonene vicinal diol 45 to the aldehyde 73

Recently, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a stable nitroxyl free radical has garnered much attention from the synthetic community as it possesses the ability to

catalyse the oxidation of both primary and secondary alcohols to the corresponding aldehyde or ketone under mild conditions.[65-67] These reactions are performed in the presence of a terminal oxidant such as sodium hypochlorite (NaOCl),[68] [bis(acetoxy)iodo]benzene (BAIB),[69] *m*-chloroperbenzoic acid (*m*CPBA),[70] Oxone[71] or trichloroisocyanuric acid (TCIA).[72] When the conditions of De Luca *et al*. (TEMPO/TCCA)[72] or Anellie *et al.* (TEMPO/NaOCl)[68] were applied to the diaxial diol **45**, no conversion to the desired ketol **41** was observed as determined by ^{1}H NMR and TLC analysis, with only starting material remaining.

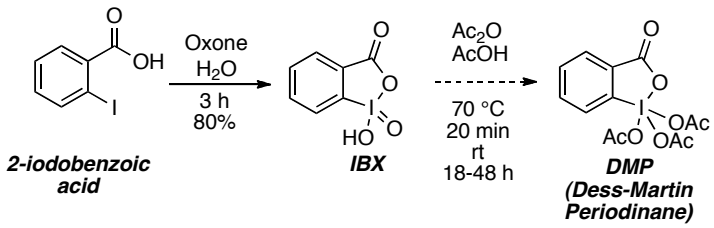
Recently, More and Finney demonstrated the use of IBX (o-iodoxybenzoic acid) as an effective heterogeneous oxidant in refluxing ethyl acetate,[73] whereby high yields, on a large scale (30 mmol) were obtained on the relatively hindered menthol substrate (Scheme 3.5). Furthermore a simple filtration of the reaction mixture was deemed to be sufficient purification, as it removes the insoluble IBX/IBA (2-iodosobenzoic acid by-products) furnishing the desired ketone. Furthermore, Frigerio and Santagostino have noted that IBX in DMSO safely oxidizes diols to their corresponding hydroxy-ketone and dione counterparts without oxidative cleavage of the vicinal diol C-C bond.[74] Undesired oxidative cleavage of vicinal diols is characteristic of oxidants such as tetrapropylammonium perruthenate (TPAP), MnO_2 and as earlier described, PCC.[74]



Scheme 3.5: The IBX oxidation of menthol[73]

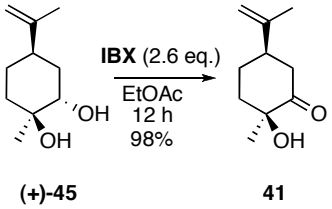
Although IBX has been known for over a century, it has experienced limited use in organic synthesis owing to its remarkable insolubility in most organic solvents, and its sensitivity to shock and heat. [75, 76] For these reasons, DMP (Dess-Martin Periodinane) has enjoyed wide spread use, particular for its ability to oxidize primary alcohols chemoselectively to their corresponding aldehyde in the presence of several other sensitive functional groups.[77] However, oxidative cleavage of vicinal diols are known to occur in the presence of DMP

and therefore IBX was selected in favour of DMP for this sensitive oxidation.[78] Until recently, previous syntheses for the preparation of IBX have not been trivial, having employed the use of the unappealing carcinogen $KBrO_3$, in boiling sulfuric acid, which is reported to liberate copious amounts of obnoxious bromine vapors, undoubtedly a hazard to the user.[75] Frigerio and co-workers recently disclosed a "user-friendly entry to 2-iodoxybenzoic acid (IBX)", utilizing Oxone® monopersulfate ($2KHSO_5{-}KHSO_4{-}K_2SO_4$) in water at 75 °C for 3 h, in place of $KBrO_3/H_2SO_4$ (Scheme 3.6). Application of their protocol was indeed "user-friendly", and IBX was routinely prepared in our laboratories on a 50 g scale (0.2 mol), with reproducibly high yields, in line with those reported by Frigerio *et al*.[75] In addition, there were no air or moisture sensitivity issues which required consideration, as there is with the triacetoxylated, Dess-Martin congener.



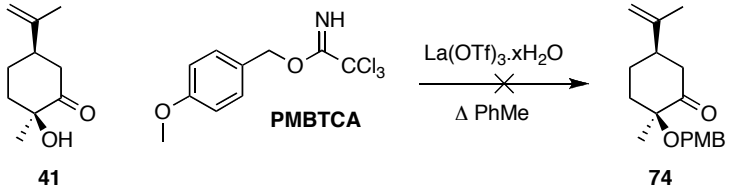
Scheme 3.6: Preparation of IBX by protocol of Frigerio et al.[75]

With IBX in hand, an oxidation utilizing the conditions of More and Finney[73] was performed on the limonene glycol substrate, utilizing 2.6 molar equivalents of IBX in boiling EtOAc for 12 h (Scheme 3.7). Analysis of the ^{1}H NMR spectrum of an aliquot taken from the reaction mixture, confirmed complete consumption of the diol starting material **45**, judged by the disappearance of the carbinol resonance centered at δ 3.63 ppm. Furthermore this was accompanied by the appearance of a downfield doublet of doublets centered at δ 2.76 ppm, integrating for 1H; indicative of an axial α-proton adjacent to the carbonyl. Analysis of the ^{13}C NMR spectrum revealed a carbonyl resonance at 213.7 ppm, which was also supported by IR spectroscopy, whilst HRMS confirmed the formation of **41**. Pleasingly, no oxidative cleavage aldehyde product **73** was detected in any of the analyses aforementioned, and the ketol product **41** was used without purification (*see* Blair, M.; Tuck, K. L., *Tetrahedron: Asymmetry* **2009,** *20*, 2149-2153; Chapter 4).



***Scheme 3.7: IBX oxidation of diaxiol diol* 45**

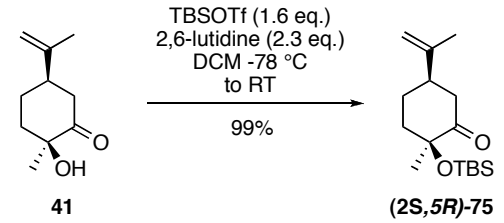
As the next step in this sequence was α-alkylation of the ketol **41**; the undesired alkylation of the tertiary alcohol oxygen was of concern, and thus, efforts towards the protection of this functionality were investigated. Our initial attempts to form the *p*-methoxybenzyl (PMB) ether of the tertiary alcohol with *p*-methoxybenzyl trichloroacetimadate (PMBTCA) in the presence of $La(OTf)_3$ (Scheme 3.8) was met with no detectable conversion to the expected PMB-ether **74** via ^{1}H NMR analysis of an aliquot of the reaction mixture.[79] Employing triflic acid in place of $La(OTf)_3$ showed some promise, as the desired product was observed via ^{1}H NMR analysis of an aliquot of the reaction mixture, albeit in a trace quantity.[80] Therefore, implementation of the PMB protecting group was soon thereafter abandoned.



Scheme 3.8: Attempted formation of the PMB-ether

Employing the general protocol of Corey *et al.* for the protection of hindered alcohols; the formation of the *tert*-butyldimethylsilyl (TBS)-ketone **75**, TBSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate) in the presence of 2,6-lutidine, at low temperature afforded the protected congener derived from **41** in high yields (Scheme 3.9).[81] Successful formation of the novel TBS-ketone **75** was confirmed by the appearance of two diastereotopic silylmethane resonances at 0.02 and 0.12 ppm (each integrating for 3H), and the appearance of a *tert*-butyl resonance appearing at 0.91 ppm (integrating for 9H). The IR spectrum showed the loss of a broad hydroxyl stretch, typically centered at 3157 cm^{-1}. It is noteworthy that the addition of TBSOTf to the reaction mixture at the literature prescribed (room) temperature incurred decomposition of the ketol substrate as observed by TLC

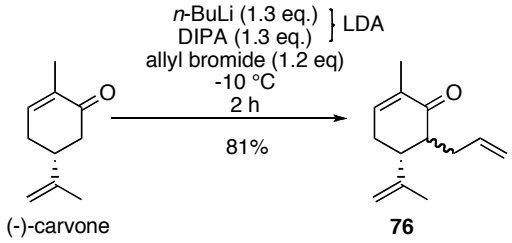
analysis; thus, addition at -78 °C was essential for the successful incorporation of the TBS protecting group.



41 **(2S,5R)-75**

Scheme 3.9: Successful TBS protection of the tertiary alcohol

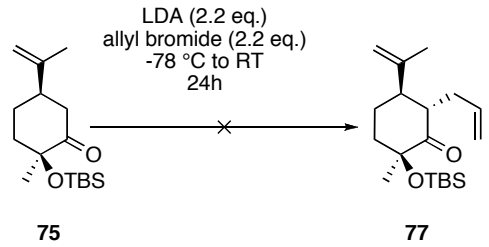
Using the TBS-ketone **75**, the model allylic alkylation reaction in the presence of a strong lithium amide base and the allyl bromide electrophile, was investigated. Gesson and co-workers have demonstrated mild α-allylation of (-)-carvone employing LDA in THF at -10 °C for 2 h (Scheme 3.10). This reaction is reported to yield a mixture of α-allylated carvone epimers **76**, in good yields (81%).[82]



(-)-carvone **76**

Scheme 3.10: LDA mediated alkylation of (-)-carvone[82]

With this literature precedent, alkylation of the TBS-ketone **75** was performed under Gessons conditions,[82] with less than promising results (Scheme 3.11). No conversion to the expected allylated model substrate **77** was observed by ^{1}H NMR spectroscopic analysis, with only starting material remaining. Increasing the reaction time or stoichiometry of the lithium amide base and/or the stoichiometry of the allyl bromide electrophile did not result in formation of the allylated product **77**. Quenching the lithium enolate mixture with methyl iodide also failed to yield the α-methylated congener as observed by ^{1}H NMR spectroscopic analysis of the reaction mixture.

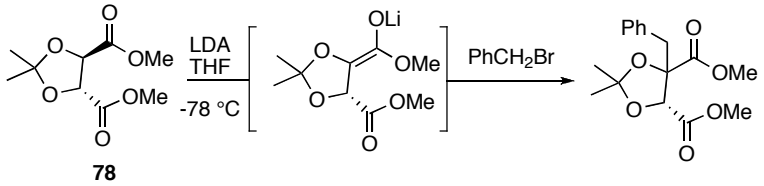


75 **77**

Scheme 3.11: Attempted LDA mediated alkylation of TBS-ketone 74

Due to either the lack of formation of the lithium enolate derived from the TBS-ketone **75**, and/or complete unreactivity with allylic and alkyl electrophiles, it was pertinent to validate the air and moisture sensitive techniques employed for the formation of LDA, and handling of the reagents under the required reaction conditions. By replicating the conditions of Gesson *et al.* on the literature substrate carvone, similar conversions were obtained (80% conversion, 5:1 mixture of epimers as determined by ^{1}H NMR spectroscopic analysis) to that previously reported.[82]

The replacement of the highly toxic, carcinogen hexamethylphosphoramide (HMPA), with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as a co-solvent in a number of reactions was first demonstrated by Mukhopadhyay and Seebach.[83] These reactions include Wittig, enol ester alkylations and the nucleophilic addition of organolithiums to oxiranes. Most notably, and of relevance to this chapter, is the improved reactivity of so called 'unreactive' substrates such as **78** in the presence of either HMPA or DMPU (Scheme 3.12).[83, 84]

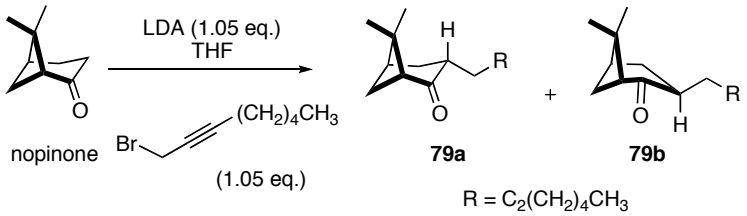


78

Co-solvent (% vol)	Yield (%)
-	<5
HMPA (17)	54
DMPU (33)	52

Scheme 3.12: The comparison of chemical yield in the presence of HMPA or DMPU[83]

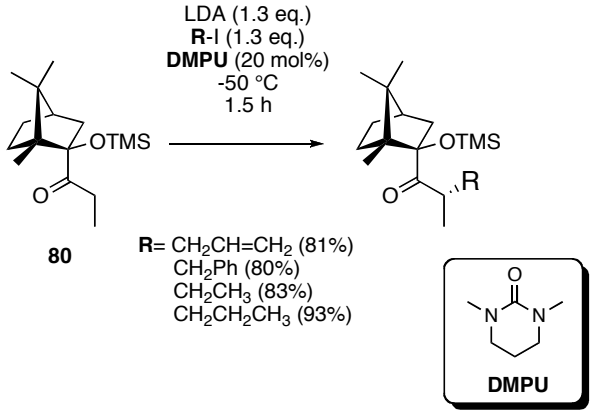
The pronounced effect on the chemical yield when DMPU is employed as a co-solvent or an additive in stoichiometric amounts has also been recently noted by Campos *et al*.[85] The alkylation of the relatively hindered nopinone substrate with 1-bromooctyne showed a marked improvement with the addition of 1 molar equivalent of DMPU as depicted in Scheme 3.13.[85]



Additive (mol %)	Yield (%)	**78a:78b**
-	30	98:2
DMPU(100)	89	99:1

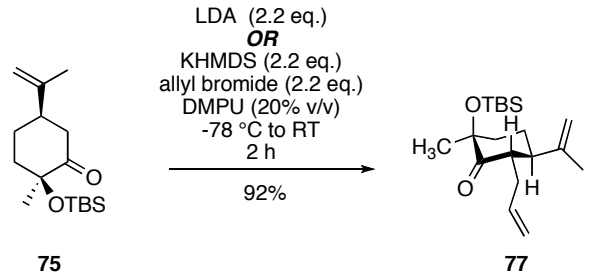
Scheme 3.13: DMPU assisted alkylation of nopinone[85]

Palomo and co-workers, recently reported the alkylation of a camphor derivative **80** with a diverse array of unreactive and reactive alkyl, allyl and benzyl iodide electrophiles (Scheme 3.14).[84] Whilst Palomo's conditions were somewhat reminiscent of Gesson and co-workers protocol, (i.e stoichiometry, and electrophile scope); the addition of 20 mol% of DMPU, was crucial for the reactivity of 'unreactive electrophiles'.[84]



Scheme 3.14: Alkylation of camphor silyloxy ketone derivatives[84]

When a modified variant of the protocol of Palomo *et al.* was applied to the TBS ketone **75** substrate utilizing either LDA or KHMDS in the presence of 20% *v/v* DMPU, excellent isolated yields of the allylated product **77** were recovered (Scheme 3.15). Whilst only a single diastereoisomer was observed *via* ^{1}H NMR spectroscopic analysis. The ^{1}H NMR spectrum indicated the successful incorporation of an allyl group with the appearance of three new signals in the olefinic region (terminal methylene protons resonating at 4.91 and 4.98 ppm, and a vinyl methine proton resonating at 5.80 ppm), whilst HRMS was consistent with the expected molecular weight of the allylated product **77**.



Scheme 3.15: Alkylation of the TBS-ketone 75 utilizing the protocol of Palomo et al.[84]

Analysis of the coupling constant of the resonance ascribed to the α-proton of the ketone, H_a (Fig 3.2) of the newly alkylated asymmetric centre reveals a doublet of doublet of doublets (J=11.8, 9.5 and 2.5 Hz, 1H). The large coupling constants (11.8 and 9.5 Hz) are characteristic of diaxial coupling between H_a-H_b and the large dihedral angle between H_a and H_c.[86] The smaller coupling between H_a-H_d is attributed to the small dihedral angle between these protons, indicative of an equatorially orientated substituent.

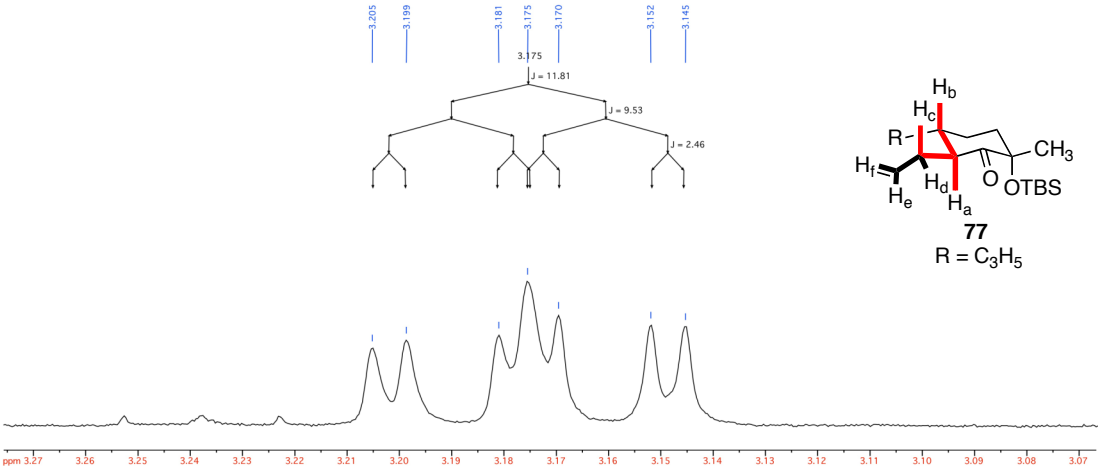


Fig 3.2: $J_{a\text{-}d}$ coalesce doublet of doublet of doublet's characteristic of an equatorially orientated substituent

Assignment of the proximal protons to the newly formed asymmetric centre was sought via ^{1}H-^{1}H correlation spectroscopy (COSY). Highlighted in Fig. 3.3 are relevant ^{1}H correlations of the homoallylic methine proton resonances, H_a coupling to both H_b and the allylic methylene protons, H_c and H_d.

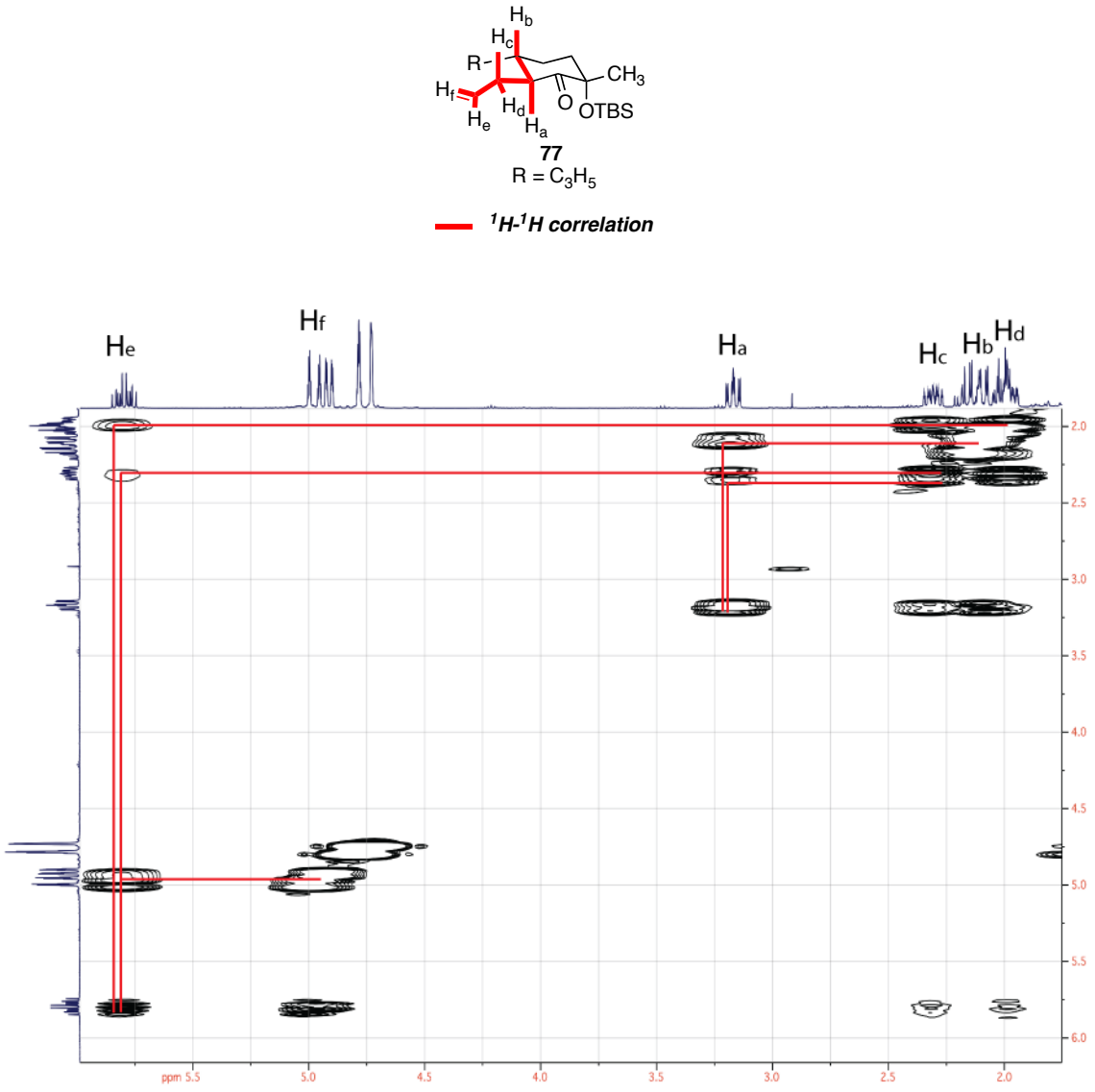


Fig 3.3:^{1}H-^{1}H COSY expansion of the resonances relevant to the newly formed asymmetric centre of compound 77

The stereochemistry of the newly allylated asymmetric centre was assigned as being *trans* in respect to the isoprenyl group based on coupling constant analysis (*vida supra*). To further support this claim, the reaction mixture was stirred in the presence of 5% *w/v* NaOMe in MeOH over 5 days. No change in the ^{1}H NMR spectrum was observed of the allyl ketone **77** at room temperature (Fig 3.4). The epimerization experiment is consistent with an equatorially orientated allyl substituent, which is the thermodynamically favored orientation on a cyclohexanone system.[28]

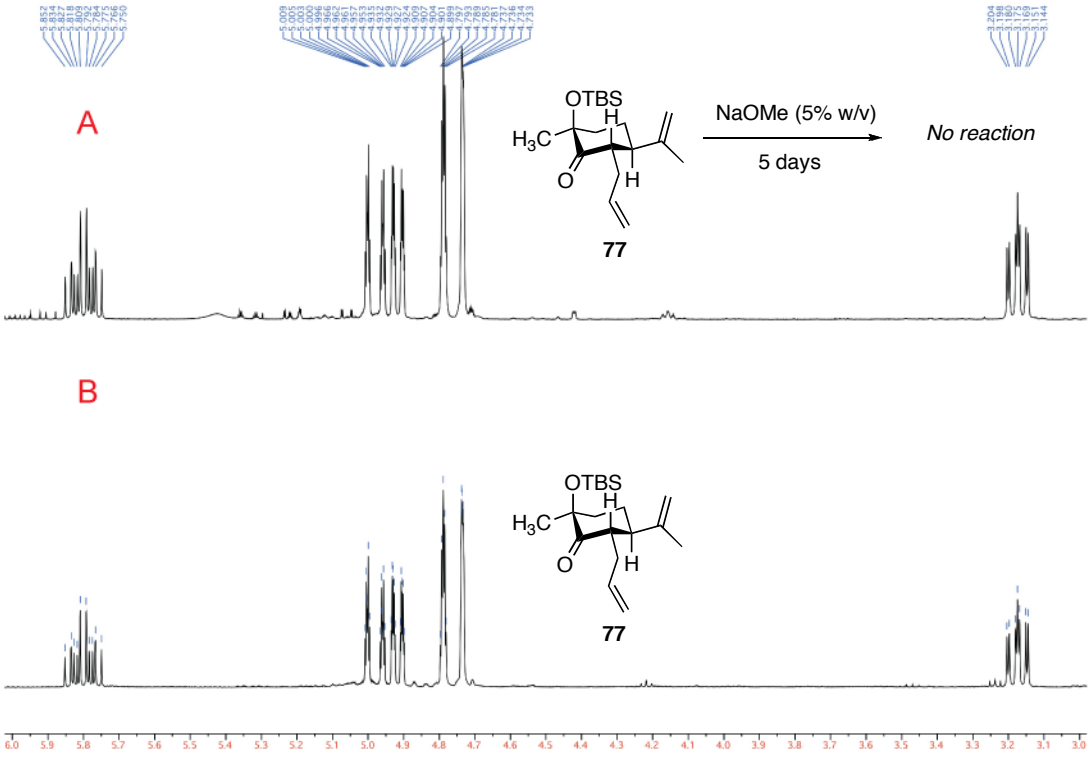
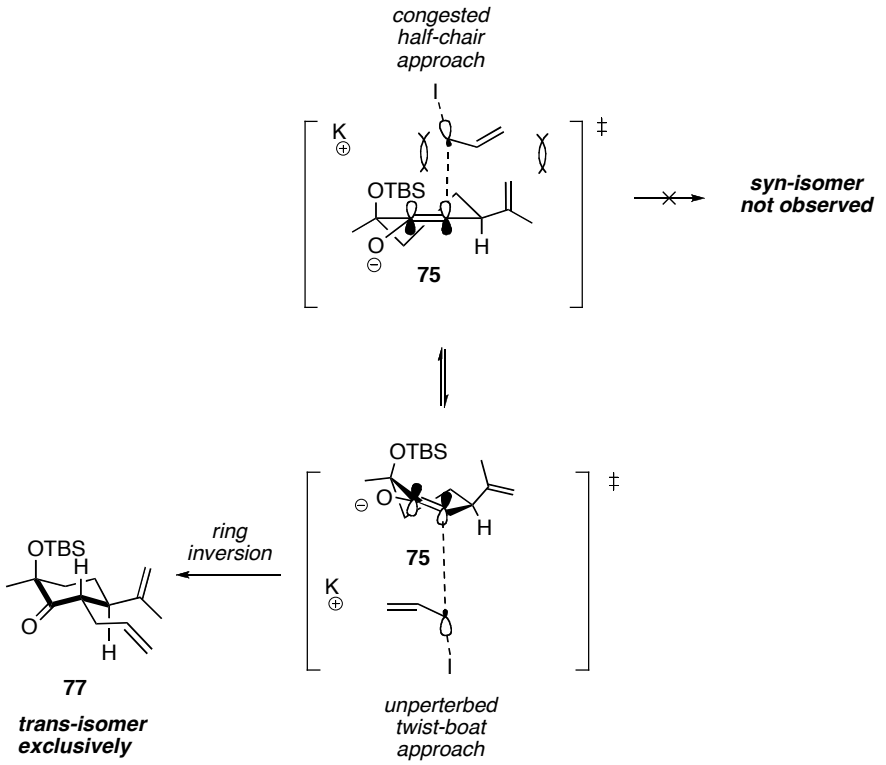


Fig 3.4:Spectrum (A):Compound 77 after to exposure to NaOMe/MeOH for 5 days
Spectrum (B): Compound 77 prior to exposure to NaOMe/MeOH

It is postulated that excellent diastereofacial control for the allylated ketone **77** was obtained due to a 1,3-diaxial steric interaction[87] encountered by the incoming allylic electrophile and the TBS group, and not base catalysed epimerization of the kinetic *syn*-allylated isomer.[††] Thereby alkylating through a twist boat conformation depicted in Scheme 3.16.

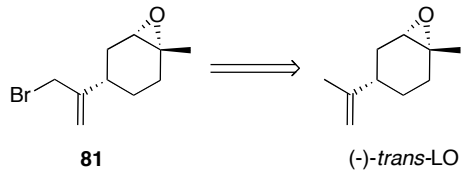


Scheme 3.16: The hypothesized diastereomorphic transition states for substrate control to the desired allylated ketone 77

[††]Quenching at −40 °C with saturated ammonium chloride to destroy residual KHMDS afforded the equatorial product exclusively *via* ^{1}H NMR analysis of the reaction mixture

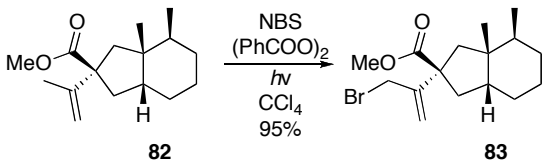
3.2 Direct Installation of the Allylic Nucleofuge

It was anticipated that functionalization of the epoxide at the allylic position required to the bromo oxide **81**, as required for the preparation of the diterpene core, could be sought directly from the corresponding (-)-*trans*-LO isomer (Scheme 3.17).



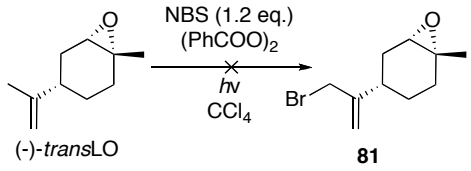
Scheme 3.17: Retrosynthetic analysis of the key allyl bromide 81 electrophile

The Wohl-Ziegler bromination is a well studied method for the allylic bromination of olefins, which is known to take place in the presence of other functional groups.[88] This reaction was first reported in 1919 by Wohl,[89] and later popularized by Ziegler.[88, 90] Recently, Constantino and co-workers employed a late stage Wohl-Ziegler bromination of the alkene **82** to the Bakenolide A precursor **83** (Scheme 3.18). Smooth bromination in excellent yields (95%) took place in 3 h under facile conditions.[91]



Scheme 3.18: Wohl-Ziegler bromination of the Bakenolide A precursor 82[91]

When the above conditions were applied to (-)-*trans*-LO (Scheme 3.19), only trace conversion to the bromo oxide **81** was observed in the ^{1}H NMR and MS spectra; whereby the reaction mixture was comprised of complex degradation products. All attempts to isolate the desired bromide **81** by either flash column chromatography on silca gel, or bulb to bulb distillation were unsuccessful.



Scheme 3.19: Attempted Wohl-Ziegler bromination of trans-LO

Measures taken to effect conversion of *trans*-LO to the desired bromide **81** included purification of the reaction solvent (CCl_4) and reagents *via* degassing and distillation from P_2O_5, and recrystallisation of NBS prior to use. Furthermore, performing the reaction under strictly anhydrous conditions under an atmosphere of nitrogen, resulted in only a negligible increase in conversion to the bromide **81**, as judged by ^{1}H NMR analysis. A representative ^{1}H NMR spectrum of the reaction mixture upon work-up is shown in Fig 3.5.

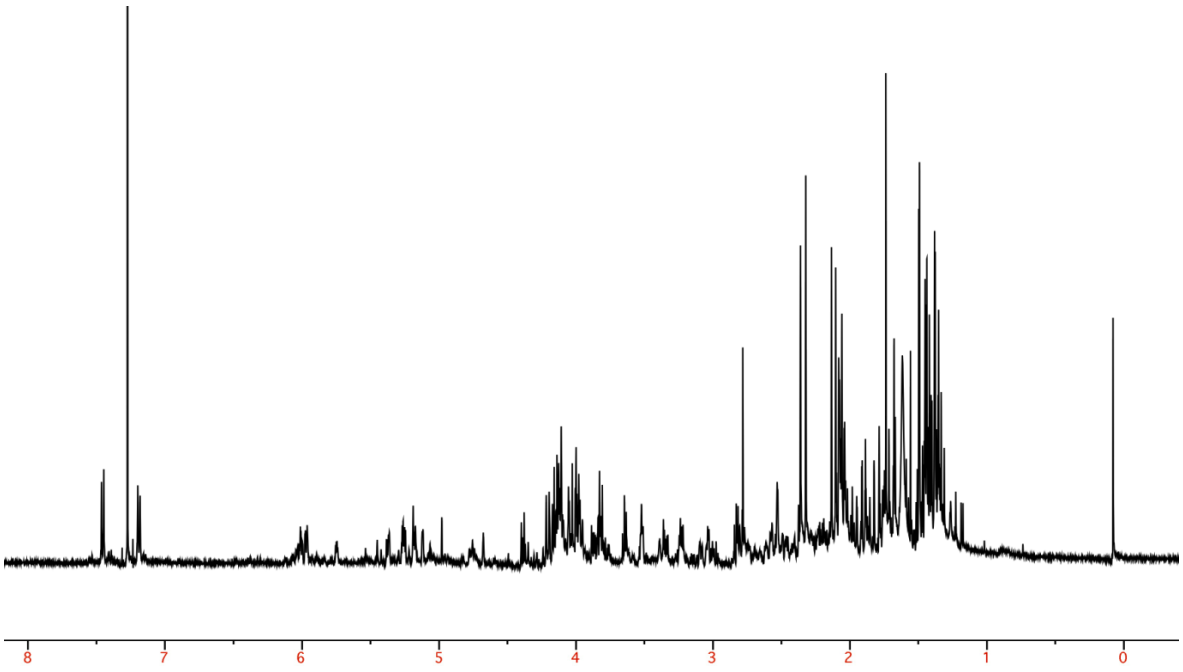
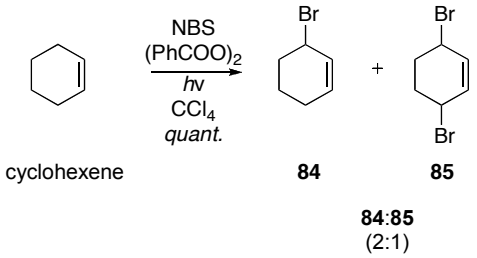


Fig 3.5: ^{1}H NMR spectrum of the crude reaction mixture of a typical Wohl-Ziegler bromination of (-)-trans LO

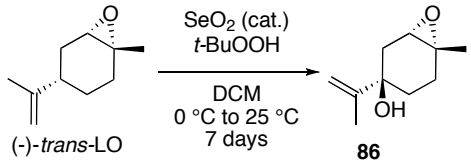
To validate both the reagents and technique used, the standard Wohl-Ziegler protocol was applied to a simple model substrate – cyclohexene (Scheme 3.20). Allylic bromination of

cyclohexene occurred, affording a mixture of mono and bis brominated products (**84**:**85**; 2:1), as determined by ^{1}H NMR spectral analysis, which is consistent with that reported in the literature.[92] This suggested that the reagents where of a suitable quality, and that the (-)-*trans*-LO substrate was not suitable for this transformation.



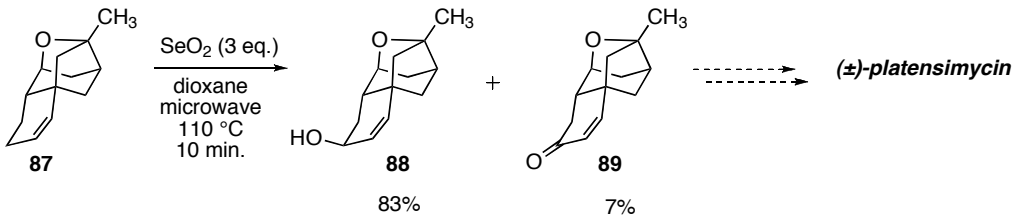
Scheme 3.20: Validation of reagents and conditions in the Wohl-Ziegler reaction

As a direct route to the bromide **81** was proving problematic, an alternate strategy to the key coupling intermediate **42** was investigated. Reaction of *trans*-LO with Sharpless' catalytic SeO_2 system in the presence of *t*-BuOOH as the terminal oxidant,[93] is known to yield the corresponding allylic alcohol, albeit with the undesired regioselectivity (Scheme 3.21).[94]



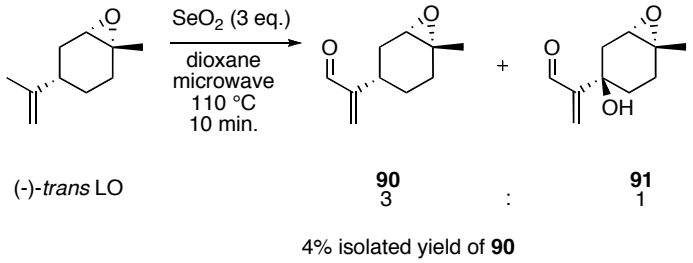
Scheme 3.21:SeO_2 catalysed allylic oxidation of (-)-trans-LO to the tertiary allylic alcohol 86[94]

There are reports that utilizing an excess quantity of SeO_2, under microwave irradiation, rapidly effects allylic oxidation to furnish the corresponding secondary allylic alcohol. This was demonstrated by Snider and co-worker's final step in their formal total synthesis of (±)-platensimycin (Scheme 3.22). Oxidation of the alkene **87** to the desired allylic alcohol **88** was isolated in 83% yield, however it was accompanied with 7% of the over oxidized enone **89**.



Scheme 3.22: Allylic oxidation of the alkene 87 to functionalized intermediates 88 and 89[95]

When Snider and co-worker's protocol was performed on (-)-*trans* LO substrate, (SeO_2, absolute dioxane, microwave irradiation; 225W, 10 min); the desired primary allylic position was oxidized to produce the enal **90**, in a poor isolated yield of 4% (Scheme 3.23). The major impurities are ascribed as highly water soluble organo-selenic acid by-products. Furthermore, substantial over oxidation also occurred to give a bisoxygenated product **91**, as determined by GCMS analysis (calcd. *m/z* for $C_{10}H_{13}O_3^-$ $[M - H]^-$ 181.1; found 181.0). Structural elucidation of enal **90** was performed after flash column chromatography of the reaction mixture on silica gel. The ^1H NMR of the purified product contained diagnostic features suggesting formation of the enal, such as a downfield shifted peak at 9.45 ppm, suggesting the presence of an aldehyde, accompanied by the disappearance of an allylic methyl group typically centred at 1.71 ppm. Importantly, the epoxy methine resonance centred at 3.07 ppm remained, whilst a downfield-shifted allylic methine resonance was observed at 2.71 ppm, which was assigned as H3, supporting enal **90**, and not the over oxidized product **91**.



Scheme 3.23: Allylic oxidation of (-)-trans LO in the presence of SeO_2 under microwave irradiation

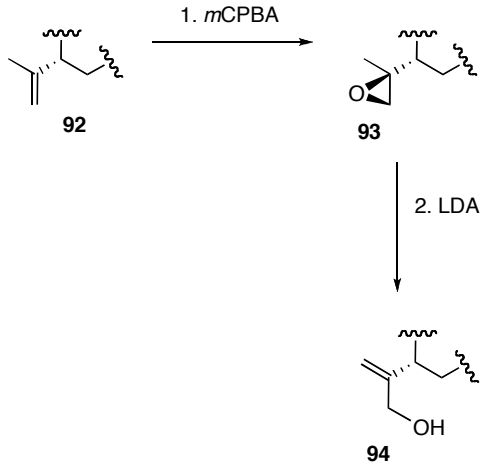
Efforts to improve the chemical efficiency of this reaction by the systematic variation of stoichiometry of SeO_2, reaction time and temperature, showed no overall increase in yield. Conventional heating was also attempted, which provided the enal **90** as the exclusive

allylic oxidation product, as determined by the occurrence of only one aldehydic proton resonance. However the chemical efficiency for this reaction was exceedingly low (< 5%), whereby the majority of the reaction mixture was comprised of organoselenic acid by-products. It is postulated that in the absence of microwave irradiation, the thermal [2,3]-sigmatropic rearrangement, which produces **90**, proceeds sluggishly.

Owing to the low conversion of this transformation, it was deemed as a non-viable route towards the generation of the key Eastern-domain coupling partner **70**, which was required for the assembly of the diterpene core. Thus, an alternative strategy was investigated.

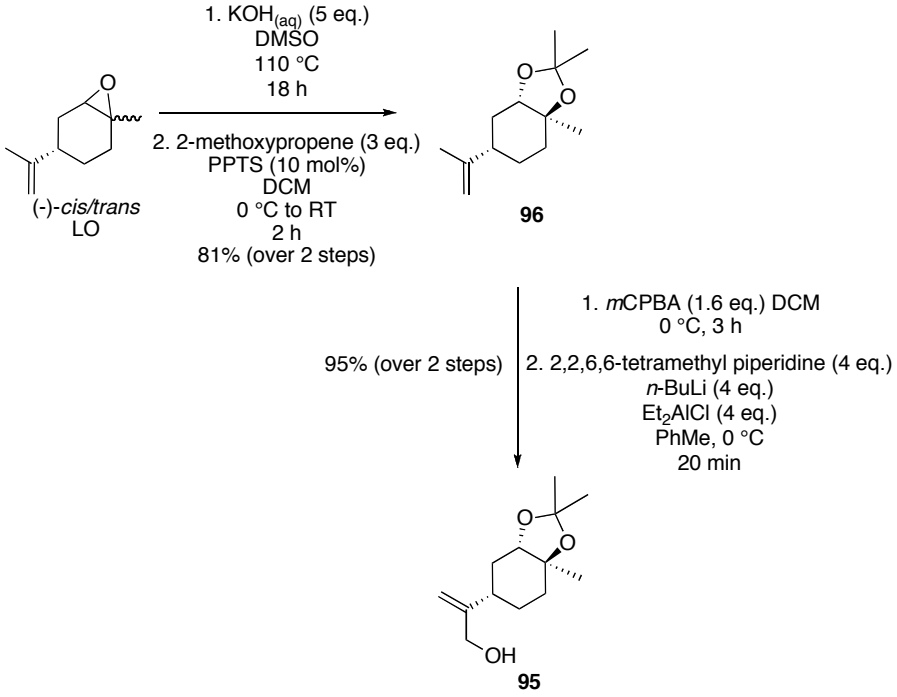
3.3 Indirect Methods to the Allylic Nucleofuge

Given the limited success of the allylic bromination of *trans*-LO (*vida supra*), a step-wise approach was devised whereby an epoxidation of compound **92** would reveal the epoxide **93**, which was anticipated to undergo rearrangement to the desired *exo*-cyclic allylic alcohol **94** (Scheme 3.24).



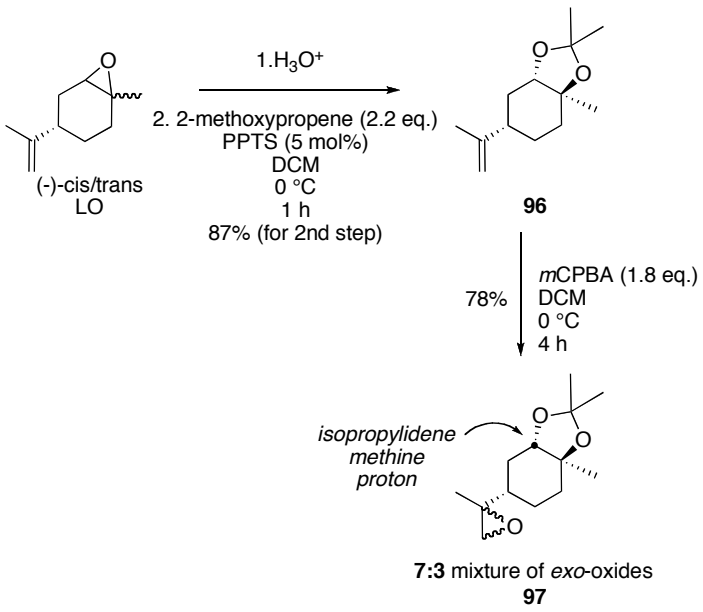
Scheme 3.24: Epoxidation/base induced rearrangement to an allylic alcohol

Pleasingly, such a sequence to the allylic alcohol had already been carried out by Kido *et al*. (Scheme 3.25).[96] Their synthesis to the allylic alcohol **95** commences with the nucleophilic oxirane opening in aqueous KOH/DMSO to afford a mixture of diols, which was subsequently treated with 2-methoxypropene/pyridinum *p*-toluenesulfonate (PPTS) yielding the isopropylidene acetal **96**. Epoxidation of the acetal **96** in the presence of *m*CPBA in DCM, followed by a base induced rearrangement of the epoxide intermediate in the presence of diethylaluminium chloride/*n*-butyl lithium and 2,2,6,6-tetramethylpiperidine gave the allylic alcohol **95** in excellent yields, however, as a mixture of diastereoisomers.[96]



Scheme 3.25: Kido and co-workers preparation of the allyic alcohol 95[96]

Following a modified version of Kido and co-workers protocol,[54] the diastereomerically pure *trans*-diaxial diol **45**[42] derived from the commercial mixture of (-)-*cis/trans*-LO was carried (*see* Blair, M *et al*., *Synthesis* **2007,** *2007*, 1523-1527; Chapter 2) through Kido's sequence (Scheme 3.26). Epoxidation however of the acetonide **96** afforded an inseparable mixture of epoxides **97** diastereoisomers (in a 7:3 ratio) as determined *via* ^{1}H NMR analysis. The ratio of epoxide **97** diastereoisomers were assigned by integration of the diastereotopic isopropylidene methine resonance at δ 2.65 ppm and 2.78 ppm (Fig 3.6).



Scheme 3.26: Preparation of the rearrangement precursor 97

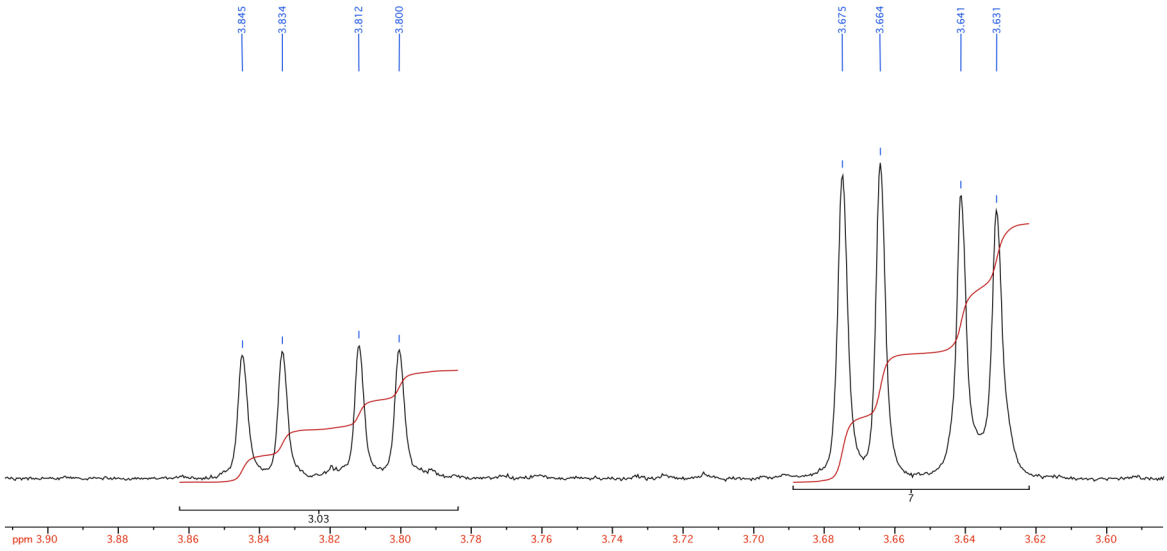
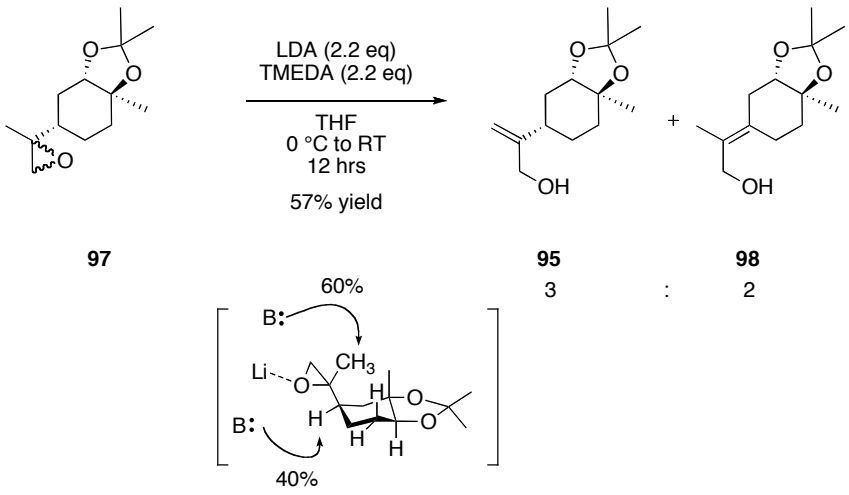


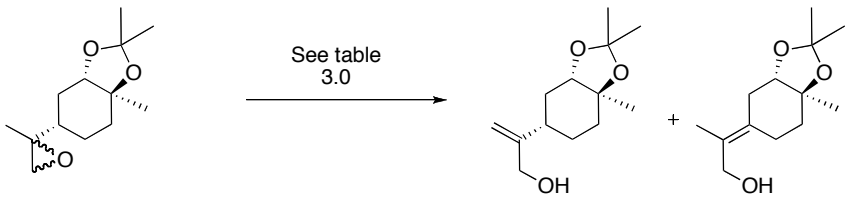
Fig 3.6: ^{1}H NMR spectrum of the diastereotopic isopropylidene methine resonances of epoxide 97

Due to the lack of availability of diethylaluminium chloride and 2,2,6,6-tetramethylpiperidine to replicate Kido's conditions; lithium diisopropylamide (2.5 eq.)/*N,N,N',N'*-tetramethylethylenediamine (TMEDA; 2.2 eq.) in THF was selected in place of this reagent. Whilst LDA/TMEDA was effective for the rearrangement of epoxide **97** (57% isolated yield), an inseparable regioisomeric mixture of allylic alcohols ensued (**95**:**98**, 3:2) upon ^{1}H NMR spectral analysis of the purified product (Scheme 3.27).



Scheme 3.27: Unselective LDA/TMEDA rearrangement of epoxide 97

It is known that aluminium alkoxide salts are also capable of isomerising epoxides to their corresponding allylic alcohols, and thus, aluminum *sec*-butoxide and aluminium isopropoxide (AIP) were screened for their ability to promote the selective rearrangement of epoxide **97** to the allylic alcohol **95** in place of LDA/TMEDA.[97] An increased biased towards the desired allylic alcohol **95** (*via* ^{1}H NMR spectroscopic analysis of the region between δ 3.45 to 3.70 ppm (*vida supra*), was observed when aluminum *sec*-butoxide (3.0 eq.) and the epoxide **97** were refluxed overnight in toluene (**95**:**98**, 2:1; 60% yield). AIP rearranged the epoxide **97**, with complete regioselectivity to the desired allylic alcohol **95** with good mass recovery (70%). The results from the optimization study are summarized below in Table 3.0.



97 **95** **98**

Entry	Conditions	Ratio (**95**:**98**); Crude Yield%[*‡‡]
1	LDA/TMEDA (2.2 eq) 0 °C to RT 12 h	3:2 57%
2	Aluminium *sec*-butoxide (3.0 eq) PhMe 12 h reflux	2:1 60%
3	Aluminium *iso*propoxide (3.0 eq) PhMe 12 h reflux	1:0 70%

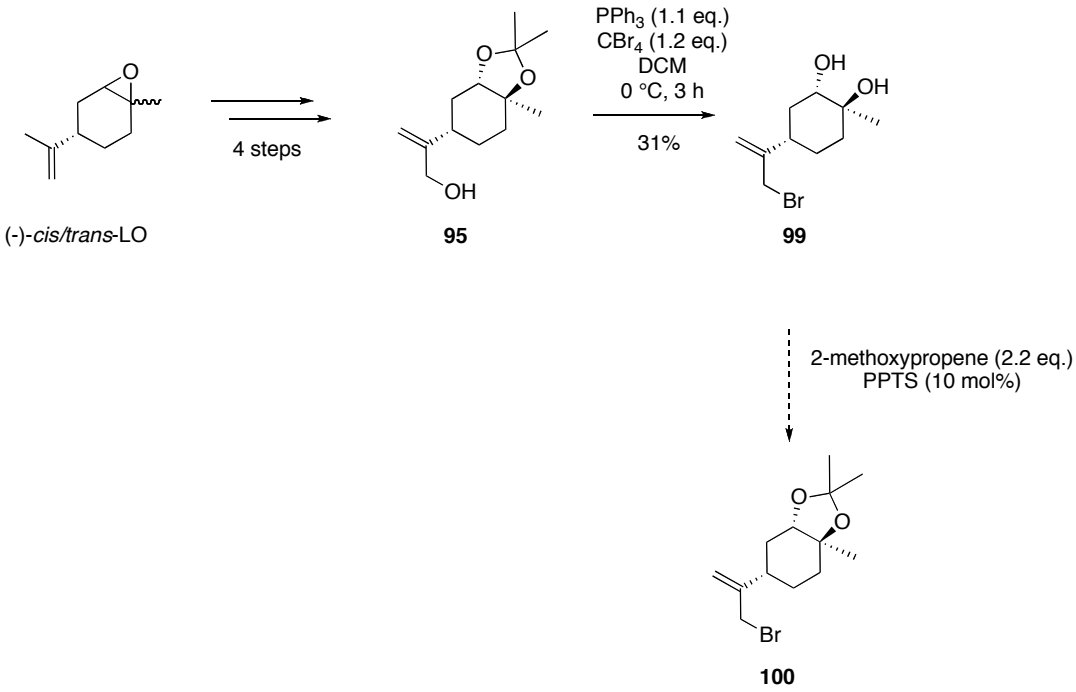
[*] Ratio of diastereoisomers determined *via* ^{1}H NMR analysis

Table 3.0: Selected optimization studies towards the rearrangement of epoxide 97 to allylic alcohol 95

Subsequent Appel bromination (CBr_4/PPh_3) of the allylic alcohol **95** (Scheme 3.28),[98] was accompanied by the loss of the acetal protecting group to afford the bromo-diol **99** in poor isolated yields (31%). As such, the bromo-diol **99** required subsequent reinstatement of isopropylidene acetal moiety to afford the alkylation precursor **100**.

The use of the bromo diol **99** for subsequent reactions was hampered by its instability, whereby complete decomposition occurred (*ca.* 4 h, RT), unidentifiable by ^{1}H NMR spectral analysis. For these reasons, and coupled with the poor overall synthetic efficiency to prepare the bromo acetonide **100**, an alternate strategy to the key Eastern domain coupling intermediate was investigated.

[‡‡] Isolated yields of the allylic alcohol **95** after flash column chromatography are somewhat lower than that quoted in Table 3.0, presumably owing to the acid labile nature of the isopropylidene acetal protecting group on silica gel. Consequently, the crude reaction mixture was deemed of sufficient purity for subsequent chemical transformation, as determined by H ^{1}NMR analysis.

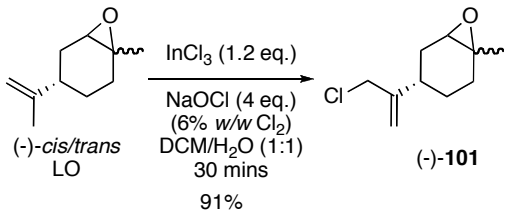


Scheme 3.28: The 6-step route to the required bromo acetonide 100

3.4 Electrophilic Chlorination of the Exocyclic Olefin

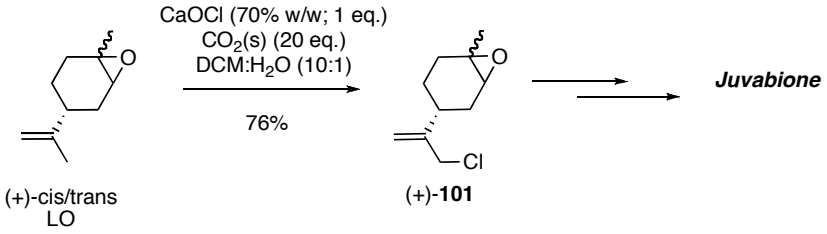
As the above synthetic strategy suffered from reduced yields, poor regiocontrol and instability of the acetonide protecing group, and was procedurally intensive; a new method to the allylically derivatised key intermediate was sought.

An extensive re-examination of the chemical literature revealed a simple procedure for the direct installation of a 10-chloro substituent on the limonene oxide chiral pool starting material, reported by Ceschi *et al.* that was amenable to a large scale synthesis (Scheme 3.29).[99] The authors report an *in situ* generation of electrophilic chlorine from the decomposition of NaOCl utilising $InCl_3$ as the Lewis acid, in a biphasic DCM/H_2O system affording the chloro-limonene *cis*/*trans* oxide **101** in high yields of 91%. This method described a direct electrophilic mechanism, which was independent of a radical pathway, and more importantly, did not require a elaborate multi-step sequence involving a epoxide rearrangement to an allylic alcohol.



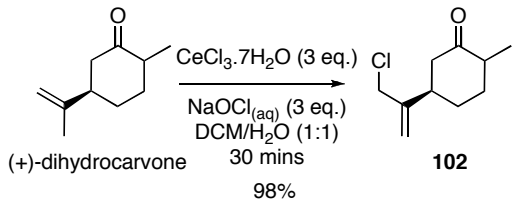
Scheme 3.29: Electrophilic chlorination of cis/trans-LO[99]

Such electrophilic procedures for the chlorination of alkenyl substrates such as LO, however, employing CaOCl (1 mole eq.) and solid CO_2 (20 mole eq.) in place of $InCl_3/NaOCl_{(aq)}$ (Scheme 3.30), have been previously reported in the chemical literature by Wolinsky *et al.*[†100] This reaction was showcased as a key step in their formal total synthesis of juvabione.



Scheme 3.30: Key allylic chlorination strategy of (+)-cis/trans-LO in the formal total synthesis of Juvabione[100]

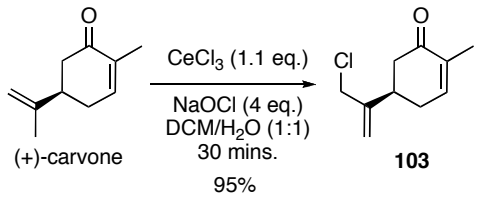
Prior to Ceschi and co-workers report for the use of $InCl_3/NaOCl_{(aq)}$ as a chlorinating system;[99] Massanet and co-workers were the first to optimise this protocol.[101] When Massanet *et al*. substituted $CaOCl/CO_{2(s)}$ with the cheap and readily available lanthanide Lewis acid $CeCl_3.7H_2O$ (3 molar eq.) and $NaOCl_{(aq)}$ solution (3 molar eq.) excellent yields were reported for the allylic chlorination of dihydrocarvone to the corresponding allylic chloride **102** (Scheme 3.31).[101]



Scheme 3.31: The electrophilic allylic chlorination of dihydrocarvone[101]

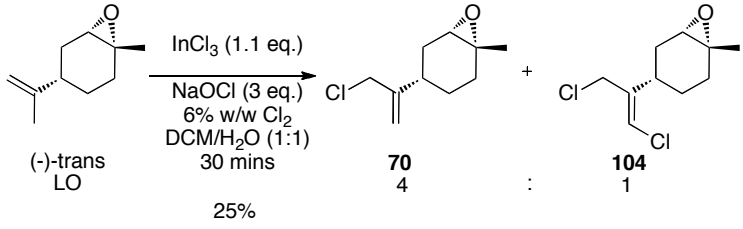
[†]Structure searching for the chloro epoxide **101** using CAS's SciFinder "Get Reactions" tool collects exclusively reference 52.

Ceschi and co-workers report that the above protocol ($CeCl_3.7H_2O/NaOCl_{(aq)}$) was unsuccessful for the electrophilic chlorination of (+)-carvone (Scheme 3.32).[99] However, the use of a stoichiometric quantity of the Lewis acid $CeCl_3$ or $InCl_3$ in the presence of $NaOCl_{(aq)}$ cleanly effected allylic chlorination of carvone to the corresponding allylic chloride **103** in excellent yields (95%).[99]



Scheme 3.32: The electrophilic allylic chlorination of carvone[99]

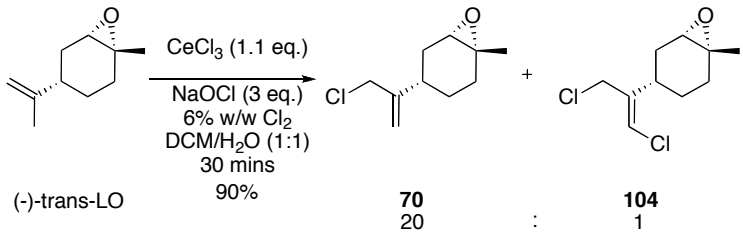
Aware of the above findings, the conditions of Ceschi and co-workers were applied to the kinetically enriched (-)-*trans*-LO substrate (Scheme 3.33).[99] However the yields obtained were much lower than that reported by Ceshi *et al.* for similar substrates.[99] The major by-product observed was the dichloride **104**, tentatively assigned *via* ^{1}H NMR spectroscopy due to the appearance of a downfield shifted vinyl methine resonance (δ 6.2 ppm, integrating for 1H) and an allylic methylene resonance (4.4 ppm, integrating for 2H), however this compound was not isolated as it was inseparable from the monochloride **70**.



Scheme 3.33: Allylic chlorination of (-)-trans LO employing Ceschi and co-workers conditions[99]

In order to optimize this reaction, the conditions were systematically varied, including the use of a sub-stoichiometric quantity of Lewis acid, quenching the reaction with various reductants (Na_2SO_3 vs. $Na_2S_2O_3$), shortened reaction times and different batches of sodium hypochlorite solutions. Since the main by-product from this reaction was the presumed bis chloride **104**, it was of interest to investigate the stoichiometry of NaOCl on the selectivity of this transformation. Interestingly, current routes to allylic chlorides utilise an excess

molar ratio of aqueous sodium hypochlorite, yet with little comment on the available chlorine content at the time of use.[99, 101] Depending on the age, grade and manufacturer, free chlorine content can be in a wide range of 6-15%.‡ It was therefore of the utmost importance to iodometrically quantitate the chlorine content of our sodium hypochlorite solution. Using a standard protocol for back titration sodium hypochlorite against sodium thiocyanate and potassium iodide,[102] it was determined that the optimal stoichiometry for this reaction was in fact 1 equivalent of aqueous sodium hypochlorite, rather than the reported 3-4 equivalents.[99, 101] Thus, the reaction was extremely sensitive to the stoichiometry of $NaOCl_{(aq)}$; over chlorination could be abated with a limiting quantity of $NaOCl_{(aq)}$ using these conditions. The desired allylic chloride **70** was reproducibly produced in high yields (90%) and monochloride selectivity (**70:104**, 20:1; Scheme 3.34). Pleasingly, $CeCl_3.7H_2O$ gave comparable results to $InCl_3$, given the current price of indium(III) salts per gram, cerium(III) lent itself as a cost effective substitute and allowed multi-gram scale reactions of this chlorination to be carried out.

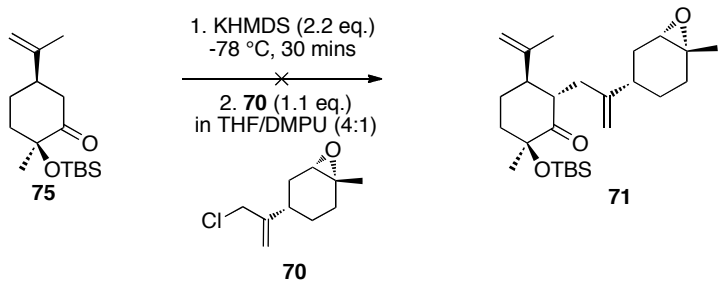


Scheme 3.34: Optimised allylic chlorination protocol

‡Available chlorine is defined as chlorine capable of releasing an equivalent amount of atomic oxygen according to the following reaction equations: $Cl_2 + 2OH^- \rightarrow OCl^- + Cl^- + H_2O$ (Eq.1) $HOCl \rightarrow HCl + ½ O_2$ (Eq.2)

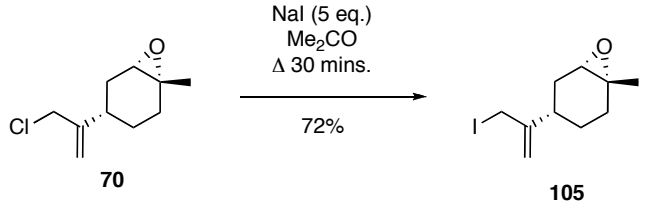
3.5 Alkylation of the Eastern and Western Domains of 2-epi-Prevezol C 47

With the key Eastern and Western domains in hand, the allylic chloride **70**, and the TBS-ketone **75** respectively, the optimized alkylation conditions discussed earlier in Section 3.1, could be applied. Formation of the potassium enolate from the TBS-ketone **75**, with KHMDS (2.2 molar equivalents) at -78 °C in THF over 30 minutes, followed by the addition of the allylic chloride (1.1 molar equivalents); reduced from the model system (2.2 eq.) in a THF/DMPU solvent system, whilst allowing to warm to RT overnight failed to give the expected diterpene oxide product **71** as observed by ^{1}H NMR spectroscopy (Scheme 3.35).



Scheme 3.35: Attempted alkylation of the TBS ketone 75 and the allylic chloride 70 to the diterpene 71

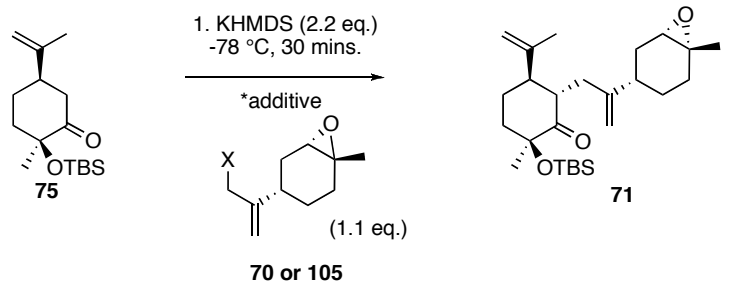
It was assumed the lack of formation of the diterpene **71** was attributed the lower reactivity of the chloride nucleofuge (*c.f.* bromide); thus, the allylic chloride **70** was exchanged to give the allylic iodide **105** alkylation partner, under standard Finkelstein conditions (Scheme 3.36),[103] then re-subjected to the alkylation protocol previously described.



Scheme 3.36: Finkelstein exchange of the chloride leaving group to the allylic iodide 105

Optimization of the allylic alkylation reaction is outlined below in Table 3.1. Greater yields were isolated when KHMDS was used in a stoichiometric quantity (1.1 eq.), whilst DMPU reduced the reaction time to 1 h (*c.f.* 3 h in the absence of DMPU). Therefore its use was not vital for the formation of the desired diterpene oxide **71**.

Eq. 1

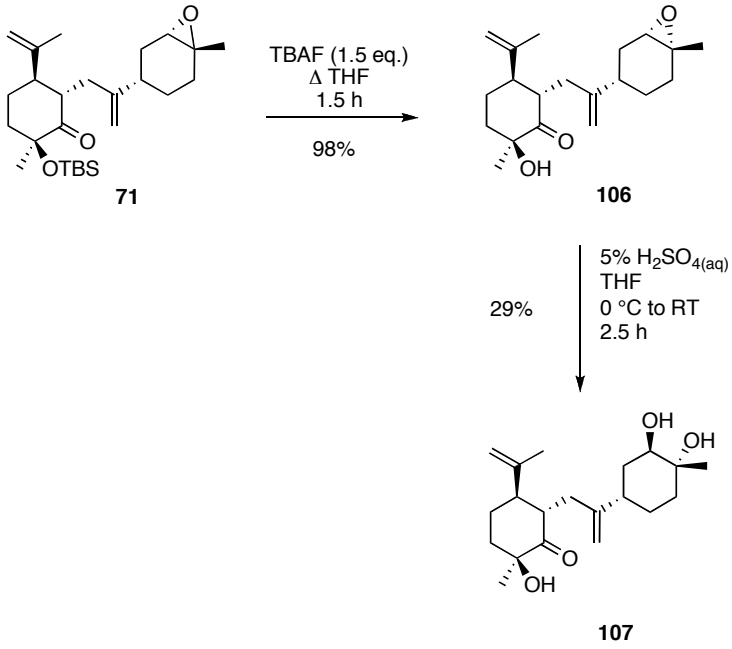


Entry	Eq. KHMDS	X	Additive	Yield
1	2.2	Cl	DMPU (20% *v/v*)	_
2	2.2	Cl	DMPU (20% *v/v*)	25%
			NaI (1.2 eq.)	
3	2.2	I	DMPU (20% *v/v*)	51%
4	1.1	I	DMPU (20% *v/v*)	>95%*
5	1.1	I	-	93%

*Determined by ^{1}H NMR spectroscopy

Table 3.1: Optimised allylic alkylation conditions

A definitive proof for the diastereoselectivity of this reaction was obtained *via* a two-step sequence of deprotection of the tertiary alcohol with *n*-tetrabutylammonium fluoride (TBAF) in refluxing THF over 1.5 h to afford the ketol **106**, which was confirmed by ^{1}H, ^{13}C NMR and HRMS analysis (Scheme 3.37). Subsequent oxirane opening in the presence of 5% aqueous H_2SO_4 in THF rapidly afforded the crystalline triol **107** in a low isolated yield (29%) after 2.5 h (Scheme 3.37). Recrystallisation of the triol **107** from water furnished single crystals suitable for X-ray crystallographic analysis (the structure of **107** is depicted in Fig. 3.7). This allowed the unequivocal determination of the newly formed asymmetric centre from the allylic alkylation reaction, thereby confirming the equatorial arrangement of the Eastern domain, which were consistent with the multidimensional NMR studies performed on the model substrate, allyl ketone **77**.



Scheme 3.37: Accessing the crystalline triol 107 via deprotection/hydrolysis strategy of 71

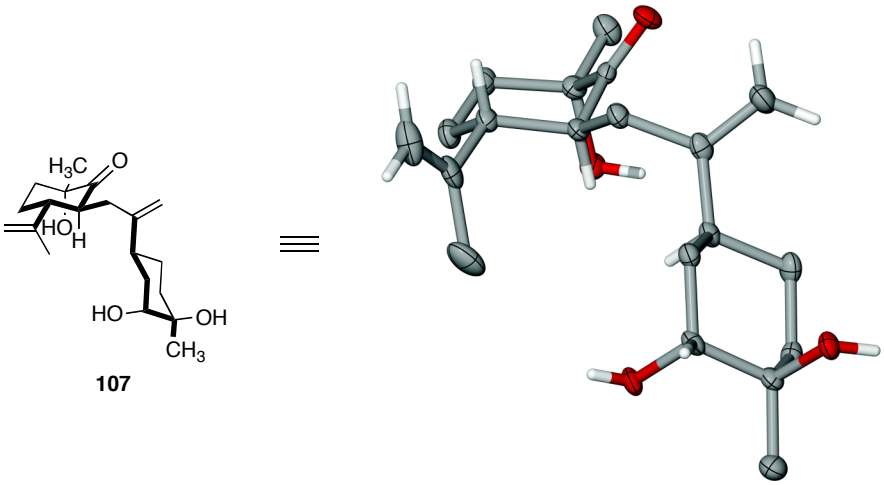


Fig 3.7: The X-ray crystal structure of triol 107

The final component of Section 1 discloses the total synthesis of 2-epi-Prevezol C ***47*** *as an article submitted to Organic Letters entitled "Towards the Synthesis of Prevezol C: An Efficient Route to 2-Epi-Prevezol C"; utilizing the key monoterpene Eastern* ***105*** *and Western* ***75*** *domains as discussed in this chapter.*

Monash University

Declaration for Chapter 3, Paper 3: "Towards the Synthesis of Prevezol C: An Efficient Route to 2-Epi-Prevezol C"- Paper in submission.

Declaration by candidate

In the case of Chapter 3, Part 1 Paper 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Experimental design, execution of reaction(s), characterisation/isolation of reaction products and manuscript preparation/editing	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
K. L. Tuck	Research guidance/experimental design, financial support, manuscript preparation/editing	

Candidate's Signature  **Date:** 26/11/09

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) Monash University Clayton, School of Chemistry

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	**Date**
Signature 2		26/11/09

Towards the Synthesis of Prevezol C: An Efficient Route to 2-*Epi*-Prevezol C

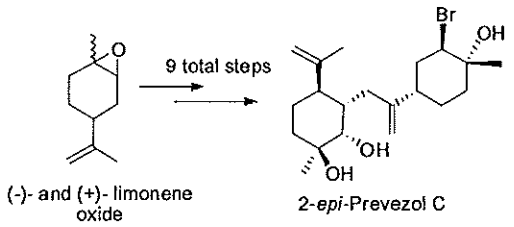
Michael Blair and Kellie L. Tuck

School of Chemistry Monash University Clayton, Melbourne, Vic, 3800, Australia

Kellie.Tuck@sci.monash.edu.au

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



2-*epi*-Prevezol C was readily accessed from the chirons (-)- and (+)-limonene oxide in a total of nine steps in 24% yield. A highly stereoconvergent, substrate-controlled allylic alkylation strategy was utilized to rapidly assemble the diterpene core.

Recently, a family of novel cytotoxic brominated diterpenes, termed 'Prevezols', were isolated from the organic extracts of the alga *Laurencia obtusa* Lamoroux, collected from the coastal rocks of Preveza in the Ionean Sea, Greece.[1] Structural elucidation of these secondary metabolites, by extensive ^{1}H and ^{13}C spectroscopic analyses, revealed a family of *syn*-bromohydrin natural products. The carbocyclic framework possessed by these metabolites is unprecedented in the literature. Whilst modern spectroscopic techniques have advanced, regio and stereoselective synthesis remains at the forefront for structural confirmation of natural products. This was underscored in an excellent review by Nicolaou and Snyder[2] and more relevant to the metabolites of the *Laurecia* species, in an article by Burton and co-workers[3,4] In light of this, these metabolites, in particular Prevezol C **1** (Figure 1), piqued our interest as a candidate for total synthesis. The halogenated metabolites of the red algae *L. Obtusa* species are usually regarded as having a dearth of bioactivity;[5] and the development of strategies for the formation of this unique carbon skeleton is required in order to futher investigate their bioactivity.

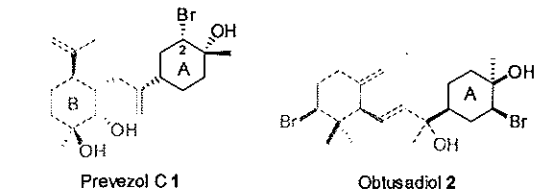


Figure 1. Structure of Prevezol C 1 and Obtusadiol **2**.

(1) Iliopoulou, D.; Mihopoulos, N; Vagias, C.; Papazafiri, P.; Roussis, V. *J. Org. Chem.* **2003**, *68*, 7667-7674.

[2] Nicolaou, K. C.; Snyder, S. A., *Angew. Chem. Int. Ed.* **2005**, *44*, 1012-1044.

(3) Sheldrake, H. M.; Jamieson, C.; Burton, J. W. *Angew. Chem. Int. Ed.* **2006**, *45*, 7199-7202.

(4) Sheldrake, H. M.; Jamieson, C.; Pascu, S. I.; Burton, J. W. *Org. Biomol. Chem.* **2009**, *7*, 238-252.

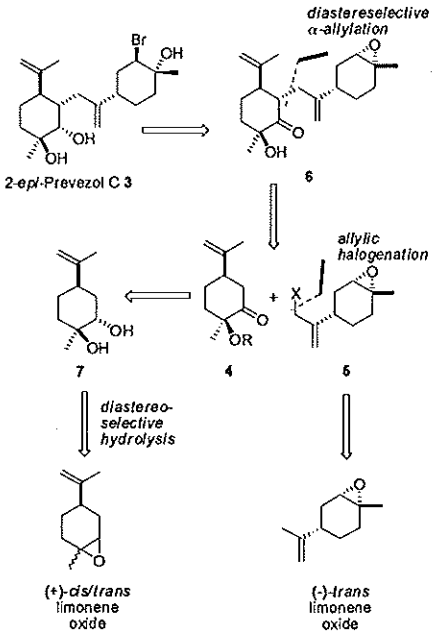
(5) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1R-49R.

Illiopoulou, Mihopoulos and co-workers assigned the Eastern ring (ring A) of Prevezol C **1** based on good spectral agreement to the literature values previously reported for the isolation and characterisation of Obtusadiol A **2** (Figure 1).[1,6] The relative stereochemistry of the Western ring (ring B) was assigned based on NOESY correlations. It was therefore of interest to synthesise the Western ring, as a first step in the synthesis of these complex natural products. The more facile *anti*-bromohydrin of Prevezol C **3**, epimeric at C2, was synthesised as methodology for the synthesis of *syn*-bromohydrins with a quaternary hydroxyl group is not established.

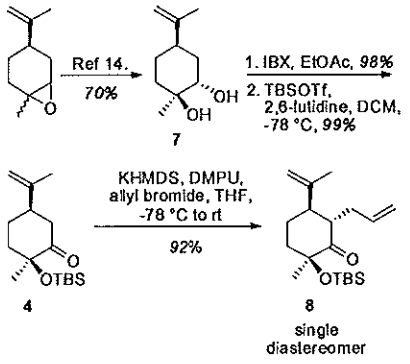
The Western hemisphere of Prevezol C **1**, contains four contiguous stereocentres, and includes an oxygenated quaternary centre. Due to the structural homology shared by the two hemispheres of Prevezol C **1**, we envisaged a stereoconvergent approach to the synthesis of *epi*-Prevezol C **3** utilising limonene oxide as a common precursor. The key disconnection in this approach is a diastereoselective carbon-carbon bond forming allylic alkylation reaction of the ketone **4** and the allylic halide **5** to give the alkylated product **6** (Scheme 1). Recent efforts in our laboratories have focused on accessing the *trans*-diaxial and *trans*-diequatorial diols, derived from a commercially available diasteromeric mixture of *cis*/*trans*-limonene oxide in high yields and diastereoselectivities.[7] We hoped to employ the *trans*-diaxial diol **7** in the total synthesis of *epi*-Prevezol C **3** as a means of accessing the oxygenated quaternary center contained in the western hemisphere and relaying this stereochemical information to the key allylic alkylation carbon-carbon bond forming reaction.

The synthesis of the key *tert*-butyldimethylsilyloxy-ketone **4**, and model allylic alkylations thereof are outlined in Scheme 2. An IBX-mediated oxidation of the *trans*-diaxial diol **7** to the corresponding hydroxy ketone followed by TBS protection of the tertiary alcohol[8] rapidly provided the precursor for the western hemisphere in high yields. Standard allylic alkylation conditions of the lithium enolate of the silyloxy ketone **4**, formed at -78 °C with LDA,[9] failed to give satisfactory yields. Employing a modified version of the conditions reported by Palomo *et al*,[10] utilising excess potassium bis(trimethylsilyl)amide (KHMDS) in the presence of 20% v/v DMPU, gratifyingly afforded the *trans*-α-allylated species **8** in excellent conversion and as a single diastereomer by ^{1}H NMR spectroscopy. The allylated product **8** was also obtained via a reaction of the potassium enoxyborate of the ketone **4** with the palladium π-allyl complex of allyl acetate utilizing the conditions of Negishi and co-workers.[11]

Scheme 1. Retrosynthesis of *epi*-Prevezol C **3**



Scheme 2. Synthesis of the model alkylated product **8**



The stereochemistry at the α-carbon of the allylated product **8** was elucidated to be the thermodynamic *trans* product via a combination of COSY and NOESY analysis

(6) Howard, B. M.; Fenical, W *Tetrahedron Lett.* **1978**, *28*, 2453-2456.
(7) Blair, M.; Andrews, P. C.; Fraser, B. H.; Forsyth, C. M.; Junk, P. C.; Massi, M.; Tuck, K. L. *Synthesis* **2007**, *10*, 1523.
(8) Blair, M.; Tuck, K. L. *Tetrahedron Asymmetr.* **2009**, *20*, 2149–2153.
(9) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165-168.
(10) Palomo, C.; Oiarbide, M.; Mielgo, A.; Gonzalez, A.; Garcia, J. M.; Landa, C.; Lecumberri, A.; Linden, A. *Org. Lett.* **2001**, *3*, 3249-3252.
(11) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188-3190.
(16) House, H.O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502-2512.

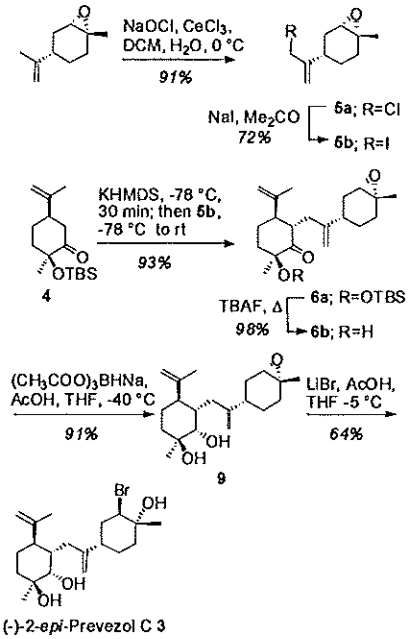
of the proximal proton coupling constants to the allylated centre (δ 3.18, J = 11.8 and 9.5 Hz) which is consistent with diaxially opposed protons. Reaction of **8** with 5% NaOMe (5 days) showed no change in the ^{1}H NMR spectrum, consistent with an equatorial allyl chain. It is postulated that excellent diastereofacial control was obtained due to the 1,3-diaxial interaction encountered by the incoming electrophile with the axial TBS group, thereby alkylating in a twist boat conformation,[16] and not due to base catalysed epimerisation of an axially alkylated intermediate.[17]

Given the positive outcome of the model allylic alkylation studies, we moved forward with the synthesis of the key electrophile, 10-halo-*trans*-limonene oxide **5**. Preparation of the allylic halide **5** was not trivial, as traditional Wohl-Ziegler conditions (NBS, CCl_4, AIBN or dibenzoylperoxide)[18] and derivatives thereof (NBS, AcOH)[19] gave complex mixtures. However optimization of Moreno-Dorado's conditions,[20] utilising a stoichiometric quantity of iodometrically titrated sodium hypochlorite,[21] in the presence of either $CeCl_3$ (1.1 eq) or $InCl_3$ (1.1 *eq.*),[22] in a binary solvent system (1:1 DCM:H_2O) afforded the allylic chloride **5a** in high yields. Furthermore, utilising this modified procedure, minimal amounts of the bis-chloro by-product were observed by ^{1}H NMR spectroscopic analysis.

Recently Jastrzebska and co-workers demonstrated that the palladium catalysed complex of allylic chlorides, utilising Negishi's potassium enoxyborate alkylative conditions can be used as an alternative to the more routinely employed allylic acetate and carbonate electrophiles.[23] Unfortunately however, the application of these conditions with our allylic chloride **5a** was unsuccessful. The use of KHMDS/DMPU (2.2 *eq*/20% v/v), the conditions for the model alkylation, were also unsuccessful. Pleasingly, conversion of the allylic chloride **5a** to the corresponding iodo epoxide species **5b** yielded an extremely reactive electrophile which rapidly participated in an allylic alkylation reaction with the ketone **4**, even in the absence of DMPU (Scheme 3).

Treatment of the diterpene oxide **6a** with TBAF (1.5 *eq.*) in refluxing THF readily cleaved the *tert*-butyldimethylsilyl group in excellent yields. Access to the required *trans*-diol **9** of the penultimate *epi*-Prevezol C intermediate was sought exclusively via a chelation controlled stereoselective ketone reduction employing sodium tri(acetoxy)-borohydride in acetic acid/acetonitrile at -40 °C (Scheme 3).[24,25] A regiospecific acid catalysed nucleophilic oxirane opening was achieved with LiBr/AcOH in cold THF,[26] affording the 2-bromo-epimer of Prevezol C (**3**) in a 64% yield.[27]

Scheme 3. Synthesis of *epi*-Prevezol C **3**.



Comparison of the ^{13}C NMR spectroscopy resonances of 2-*epi*-Prevezol C **3** to Prevezol C **1** showed excellent correlation, with the expected exceptions of the resonance of the epimeric carbon and its neighbours (Supporting Information). In the Western ring the resonances of the stereogenic centres C9, C10, C13 and C14 closely correspond with that reported for Prevezol C (<0.6 ppm difference, Figure 2 and Supporting Information). Methodology to synthesise the *syn*-bromohydrin is ongoing.

(17) Quenching at –40 °C with saturated ammonium chloride afforded the equatorial product exclusively.

(18) Constantino, M. G.; de Oliveira, K. T.; Polo, E. C.; da Silva, G. V. J.; Brocksom, T. J. *J. Org. Chem.* **2006**, *71*, 9880-9883.

(19) Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883-4887.

(20) Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691-6693.

(21) Mendham, J.; Denney, R.C.; Barnes, J. D.; Thomas, M. J. K. *Vogel's Quantitative Chemical Analysis*, 6th ed.; Prentice Hall: England, 2000; Chapter 10, pp 437.

(22) Pisoni, D. S.; Gamba, D.; Fonseca, C. V.; da Costa, J. S.; Petzhold, C. L.; de Oliveira, E. R.; Ceschi, M. A. *J. Braz. Chem. Soc* **2006**, *17*, 321-327.

(23) Jastrzebska, I.; Scaglione, J. B.; DeKoster, G. T.; Rath, N. P.; Covey, D. F. *J. Org. Chem.* **2007**, *72*, 4837-4843.

(24) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868.

(25) With $NaBH_4$/MeOH (-5 °C; 5 min) a 5:1 (*trans*:*cis*) mixture of diols was obtained (determined by ^{1}H NMR analysis).

(26) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021-3024.

(27) Brønsted acid mediated oxirane opening of *cis*-limonene oxide afforded the undesired *trans*-bromohydrin (2-bromo-2-methyl-5-(isopropenyl) cyclohexanol), determined ^{1}H NMR spectroscopy.

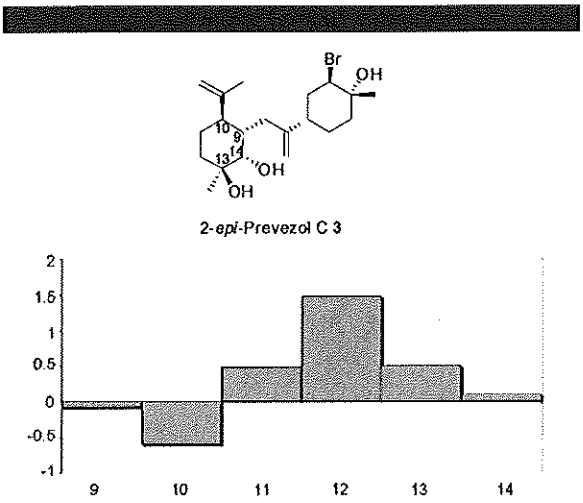


Figure 2. Comparison of the Western Hemisphere ^{13}C NMR signals of Prevezol C **1** and 2-*epi*-Prevezol C **3**. Horizontal and vertical axes show carbon number and $\Delta\delta$ values. The numbering of the rings are consistent with that used by Illiopolou, Mihopoulos and co-workers.[1]

In conclusion we have synthesized 2-*epi* Prevezol C **3** in 8 steps and 31% overall yield from *trans*-limonene oxide and the (*1S,2S,4R*) isomer of limonene glycol (**7**). This work represents the first total synthesis of a Prevezol analogue, and the synthetic construction of their unique carbocyclic framework.

Acknowledgment The authors acknowledge the support of the School of Chemistry, Monash University and Monash University.

Supporting Information Available Experimental procedures and proton and carbon NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

An Efficient Route to 2-*Epi*-Prevezol C

Michael Blair and Kellie L. Tuck*

School of Chemistry Monash University Clayton, Melbourne, Vic, 3800, Australia

Kellie.Tuck@sci.monash.edu.au

Supporting Information

Contents

General Experimental

All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Solvents were dried, when necessary, by standard methods. Organic solutions were dried over $MgSO_4$.The progress of the reactions was monitored by thin layer chromatography (TLC) on Merck 60 F240 precoated silica gel polyester plates, and products were visualized with vanillin dip. Flash chromatography was performed with Davisil LC60A, 40-63 µm silica media.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ on either a Bruker AM300, Bruker AV400 or Varian DRX500 spectrometer operating at 300, 400 and 500 MHz respectively for proton and 75, 100 and125 MHz for carbon nuclei. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to residual solvent signal as the internal standard. Infrared spectra (v_{max}) were recorded on a Perkin-Elmer RXI FTIR Spectrometer as thin films on NaCl plates. Low resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on either a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration or a Waters GC-TOF. Low resolution (EI) mass spectra were recorded on a VG Micromass 70/70F mass spectrometer with an ion source temperature of 200 ºC and electron impact energy (70 eV). Optical rotations were obtained using a PolAAR 2001 automatic polarimeter, using a 1 dm cell with chloroform as solvent, at a wavelength of 589 nm (sodium D line).

(2S,5R,6S)-6-allyl-2-(tert-butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 8

Potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution is toluene; 3.0 mL, 1.5 mmol) was slowly added to a -78 °C magnetically stirred solution of the tertbutyldimethylsilyloxy-ketone[1] **4b** (282 mg, 1 mmol) in absolute THF: DMPU (4:1) (4.0 mL: 800 μL) under an inert atmosphere. After 45 min at this temperature, a solution of allyl bromide (259.2 μL, 3.0 mmol) in THF (2 mL) was slowly introduced through a rubber septa. The ensuing mixture was allowed to warm to room temperature whilst stirring over the course of 3 h; after which complete consumption of the *tert*-butyldimethylsilyloxy-ketone **4b** was observed by TLC analysis (20:1 hexanes:EtOAc). Quenching with cold saturated $NH_4Cl_{(aq)}$ (10 mL) and extraction into diethyl ether (10 mL), followed by drying ($MgSO_4$), concentration *in vacuo* and subjection to flash column chromatography (20:1 hexanes:EtOAc) afforded the *title compound* as a colourless oil (297 mg, 92%).

$[\alpha]_D^{20}$ =+38.0 (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz) δ 0.07 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.32 (s, 3H), 1.21-1.48 (m, 2H), 1.7 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.95-2.05 (m, 2H), 2.08-2.21 (m, 2H), 2.36-2.37 (m, 1H), 3.175(ddd, *J* = 11.8, 9.5, 2.5 Hz, 1H) 4.734-4.739 (m, 1H), 4.78-4.80 (m, 1H) 4.92 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 4.98 (ddt, *J* = 17.2, 2.1,1.5 Hz, 1H) 5.80 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H).

^{13}C NMR (125 MHz) δ-2.8, -1.8, 18.4, 24.1, 26.1, 26.7, 30.8, 42.24, 48.0, 54.5, 78.34, 112.8, 115.6, 137.4, 146.2, 212.5.

IR (film): 3409 (b), 2932 (s), 1719 (s), 1643 (m), 1439 (w), 1375(m 1254 (s), 1171 (s), 1050 (s), 959 (m), 835 (m).

HRMS (ESI) calcd for $C_{19}H_{34}NaO_2Si$ $(M+Na)^+$ 345.2226; found: 345.2214.

(1R,4S,6S)-4-(3-chloroprop-1-en-2-yl)-1-methyl-7-oxabicyclo[4.1.0] heptane 5a

To a magnetically stirred solution of the kinetically separated (-)-*trans*-epoxide[2] (1.52 g, 10 mmol) in DCM:H_2O (1:1, 200 mL) was added $CeCl_3.7H_2O$ (3.91 g, 10.48 mmol) at 0 °C with the aid of an external ice bath. Iodometrically titrated[3] sodium hypochlorite solution (7.7% w/w NaOCl; 8.39 mL) was diluted to twice its volume with deionized water and slowly introduced over the course of 5 min. Analysis of an aliquot via ^{1}H NMR spectroscopy indicated complete consumption of the starting epoxide after 30 min. Partitioning, and washing the organic phase with cold saturated $Na_2SO_{3(aq)}$ (200 mL) followed by saturated brine (200 mL), and drying the organic phase with

($MgSO_4$) afforded the title compound (1.69 g, 91% yield) after evaporative removal of the reaction solvent; which was used without further purification.

$[\alpha]_D^{20}$ =-63.0 (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz) δ1.33 (s, 3H), 1.38-1.49 (m. 2H), 1.6-1.78 (m, 2H), 2.03-2.12 (m, 3H), 2.14-2.20 (m, 1H), 3.01 (d, *J* = 5.0 Hz, 1H), 4.05 (t, *J* = 1.2 Hz, 2H), 4.97 (t, *J* = 0.9 Hz, 1H), 5.13 (d, *J* = 0.9 Hz, 1H).

^{13}C NMR (75 MHz) δ23.2, 24.8, 30.7, 30.9, 36.1, 47.8, 57.6, 59.2, 113.8, 149.1.

(1R,4S,6S)-4-(3-iodoprop-1-en-2-yl)-1-methyl-7-oxabicyclo[4.1.0] heptane 5b

The allylic chloride **5a** (3.00 g, 14.87 mmol), NaI (11.2 g, 74.36 mmol) in dry acetone was brought to reflux for 30 min. The reaction mixture was diluted with hexanes (200 mL); partitioned and washed successively with saturated brine and 10% w/w aqueous sodium metabisulfite (100 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure, and subjected to a short silica plug (10:1) to afford the allylic iodide **5b** as a colourless oil (3.21 g, 72%).

$[\alpha]_D^{20}$ = -70.5 (*c* 1.0, $CHCl_3$)

^{1}H NMR (300 MHz) δ1.34 (s, 3H), 1.40-1.51 (m, 2H), 1.70-1.81 (m, 2H), 2.02-2.23 (m, 3H), 3.04 (d, *J* = 4.8 Hz, 1H), 3.93 (s, 2H), 4.91 (s, 1H), 5.23 (d, *J* = 0.6 Hz, 1H).

^{13}C NMR (125 MHz) δ10.5, 23.1, 25.1, 30.7, 30.8, 36.9, 57.7, 59.2, 112.9, 150.3.

IR (film): 3468 (w), 2975 (s), 2930 (s), 1632 (m), 1448 (s), 1432 (s), 1378 (s), 1312 (w), 1210 (w), 1157 (s), 1021 (w), 903 (s), 842 (s).

HRMS (ESI) calcd. $C_{12}H_{19}INO^+$ $(M+MeCN+H^+)^+$ 320.0506; found 320.0503

(2S,5R,6S)-2-(tert-butyldimethylsilyloxy)-2-methyl-6-(2-((1S,3S,6R)-6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)allyl)-5-(prop-1-en-2-yl) cyclohexanone 6a

Potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution is toluene; 14.10 mL, 7.05 mmol) was slowly added to a -78 °C magnetically stirred solution of the *tert*-butyldimethylsilyloxy-ketone **4b** (1.66 g, 5.88 mmol) in absolute THF (35 mL) under an inert atmosphere. After 30 min had elapsed at this temperature; an anhydrous THF solution (35 mL) of the allylic iodide **5b** (1.82 g, 6.54 mmol)

was slowly introduced through a rubber septa via aid of a syringe over the course of 3 min. The reaction mixture was allowed to slowly warm to ambient temperature, whilst stirring for 12 h. Quenching with cold saturated $NH_4Cl_{(aq)}$ (75 mL) and extraction into diethyl ether (100 mL), followed by washing with saturated brine (100 mL), drying ($MgSO_4$), concentration *in vacuo* and directly subjected to flash column chromatography (20:1 hexanes:EtOAc) afforded the title compound as a colourless oil (2.37 g, 93%).

$[\alpha]_D^{20}$ = -8.9 (*c* 1.0, $CHCl_3$)

^{1}H NMR (500 MHz) δ 0.03 (s, 3H), 0.147 (s, 3H), 0.94 (s, 9H), 1.30 (s, 3H), 1.31 (s, 3H), 1.42-1.48 (m, 3H) 1.61-1.67 (m, 2H), 1.71 (s, 3H) 1.77-1.87 (m, 3H), 1.99-2.08 (m, 4H), 2.15-2.21 (m, 1H), 2.28 (dd, *J* = 15.9, 10.8 Hz, 1H), 2.97 (d, *J* = 5.5 Hz, 1H), 3.39-3.43 (m, 1H), 4.57 (s, 1H), 4.66 (s, 1H), 4.73 (s, 1H), 4.79 (t, *J* = 1.5 Hz, 1H).

^{13}C NMR (125 MHz) δ-2.3, 1.8, 18.4, 23.3, 24.0, 24.8, 26.1, 26.8, 30.5, 30.6, 31.2, 40.2, 42.1, 46.7, 55.1, 57.7, 59.6, 78.8, 107.4, 112.8, 146.3, 152.3, 212.3.

IR (film): 3076 (w), 2932 (bs), 2858 (m), 1720 (s)m 1644 (s), 1472 (m) 1448 (m), 1376 (m), 1254 (s), 1210 (w), 1170 (m), 1132 (m), 1095 (m), 1050 (m), 1005 (m), 956 (m), 893 (w), 861 (m), 835 (s).

HRMS (ESI) calcd for $C_{26}H_{44}NaO_3Si$ $(M+Na)^+$ 455.2957; found 455.2957

(2S,5R,6S)-2-hydroxy-2-methyl-6-(2-((1S,3S,6R)-6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)allyl)-5-(prop-1-en-2-yl)cyclohexanone 6b

A 1.0 M THF solution of tetrabutylammonium fluoride (748 μL, 0.75 mmol) was introduced through a rubber septa via the aid of a syringe to a anhydrous THF solution (7 mL) of the TBS-diterpene oxide **6a** (216 mg, 0.50 mmol) under an inert atmosphere. The reaction mixture was brought to reflux for 1.5 h, after which it was cooled, concentrated and directly subjected to flash column chromatography (4:1 hexanes: EtOAc), to afford the title compound as a clear oil (150 mg, 94%).

$[\alpha]_D^{20}$ = -4.9 (*c* 1.0, $CHCl_3$)

^{1}H NMR (500 MHz) δ1.308 (s, 3H), 1.31 (s, 3H), 1.37 (td, *J* = 12.4, 4.2 Hz, 1H), 1.41-1.44 (m, 2H), 1.54-1.62 (m, 3H), 1.65-1.70 (m, 2H), 1.72 (s, 3H), 1.84 (dq, *J* = 9.2, 3.0 Hz, 1H), 1.87-1.91 (m. 2H), 1.98-2.15 (m, 7H), 2.26 (dd, *J* = 16.2, 10.4 Hz, 1H), 2.99 (d, *J* = 5.4 Hz, 1H), 3.405 (td, *J* = 10.6, 2.6 Hz, 1H), 4.53 (s, 1H), 4.67 (s, 1H), 4.73 (s, 1H), 4.79 (t, *J* = 1.5 Hz, 1H).

^{13}C NMR (100 MHz) δ 18.62, 23.2, 24.4, 24.9, 26.5, 30.5, 30.8, 40.5, 40.6, 46.9, 54.1, 57.8, 59.6, 107.1, 112.8, 146.2, 152.2, 213.0.

IR (film): 3435 (bs), 3075 (w) 2931 (s), 2864 (s), 1718 (s), 1644 (m), 1449 (m), 1433 (m), 1378 (m), 1318(w), 1211 (w), 1317 (w), 1094 (m), 1022, 891 (s), 840 (s) cm^{-1}.

HRMS (ESI) calcd for $C_{20}H_{34}NO_3$ $(M+NH_4)^+$ 336.2539; found 336.2533

(1S,2S,3S,4R)-1-methyl-3-(2-((1S,3S,6R)-6-methyl-7-oxabicyclo-[4.1.0]heptan-3-yl)allyl)-4-(prop-1-en-2-yl)cyclohexane-1,2-diol 9

To a cooled -20 °C solution of sodium triacetoxyborohydride (190 mg, 895 μmol) in 1:1 solution of acetonitrile/acetic acid (1 mL) was added a solution of the epoxide **6b** (57 mg, 179 μmol) in acetonitrile (3 mL). The reaction temperature was maintained at this temperature for 72 h, after which it was quenched with the addition cold saturated $NaHCO_{3(aq)}$ (10 mL), and diluted/ partitioned with diethylether (30 mL) followed by further washing with $NaHCO_{3(aq)}$ (2 x 10mL) and saturated brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduce pressure to afford the title diol as a pale waxy solid (52 mg, 91%).

$[\alpha]_D^{20}$ =-41.6 (*c* 1.0, $CHCl_3$)

^{1}H NMR (500 MHz) δ1.25 (s, 3H), 1.31 (s, 3H), 1.37-1.41 (m, 3H), 1.43-1.41 (m, 3H), 1.43-1.48 (m, 1H), 1.52 (dd, *J* = 15.2, 12.0 Hz, 1H), 1.66 (s, 3H), 1.68-1.81 (m, 4H), 1.88 (dd, *J* = 14.1, 11.3 Hz, 1H) 2.00-2.07 (m, 2H), 2.10-2.15 (m, 2H), 2.96 (d, *J* = 5.4 Hz, 1H), 3.31 (s, 1H), 4.72-4.78 (m, 4H).

^{13}C NMR (125 MHz) δ23.1, 24.3, 27.1, 28.4, 30.8, 31.2, 33.2, 35.1, 36.1, 37.6, 44.2, 57.8, 59.4, 71.8, 73.7, 109.5, 111.8, 148.0, 142.0.

IR (film): 3458 (bs), 3072 (w), 2930 (s), 2862 (m), 1642 (s), 1450 (s), 1434 (s), 1379 (s), 1260 (m), 1214 (m), 1100 (m), 1032 (s), 1032 (s), 891 (s), 754 (s).

HRMS (ESI) calcd for $C_{20}H_{33}O_3$ $(M+H)^+$ 321.2424; found 321.2423

***2-epi-Prevezol C* 3**

LiBr (72 mg, 829 μmol) in anhydrous THF (2 mL) was introduced through a rubber septa via the aid of a syringe to solution of diterpene diol **9** (49 mg, 152.9 μmol) in THF (1.5 mL) and AcOH (28.4 μL, 458.7 μmol) at 0°C under an inert atmosphere. The reaction was allowed to warm to ambient

temperatures, and was deemed complete after 2 h via TLC analysis (1:1 EtOAc:Hexanes). The reaction mixture was quenched with saturated $NaHCO_{3(aq)}$ (5 mL), partitioned with diethyl ether (15 mL), washed with saturated brine (20 mL) and dried over $MgSO_4$. Concentration under reduced pressure afforded the title compound as colourless oil (39 mg, 64%), which did not require further purification.

$[\alpha]_D^{20}$ =-18.0 (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz) δ 1.41 (s, 3H), 1.45-1.49 (m, 2H), 1.56-1.69 (m, 6H) 1.69 (s, 3H), 1.72-1.79 (m, 3H), 1.89 (m, 8H) 2.16 (d, *J* = 14.5 Hz, 1H), 2.39-2.47 (m, 1H), 3.36 (s, 1H), 4.14-4.16 (m, 1H), 4.74-4.78 (m, 2H), 4.85 (s, 1H), 4.87 (s, 1H).

^{13}C NMR (125 MHz) δ18.9, 26.0, 27.1, 28.4, 29.8, 33.1, 33.3, 35.3, 35.6, 36.2, 36.9, 44.3, 60.2, 71.79, 71.84, 73.7, 110.4, 111.9, 148.1, 151.0.

IR (film): 3424 (bs), 3072 (w), 2928 (s), 2857 (m), 1702 (w), 1640 (m),1451 (m), 1376 (m), 1260 (m), 1180 (m), 1099 (m), 1030 (m), 924 (w), 891 (m), 798 (m), 759 (m).

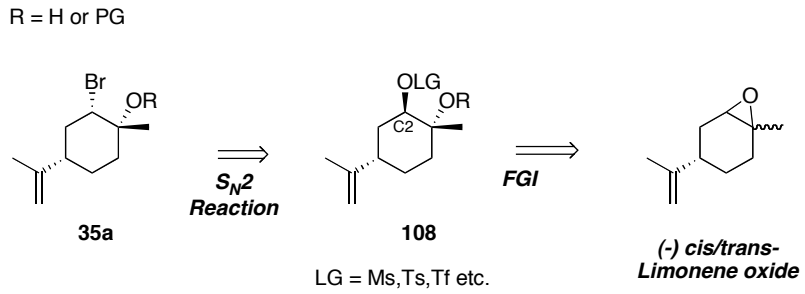
HRMS (ESI) calcd for $C_{20}H_{32}BrO_3$ $(M-H)^-$ 399.1535; found 399.1536.

Chapter 3

Part 2: Preparation of the Western Domain of Prevezol C

3.6 An Inversion Strategy at the C2 Stereocentre to the syn-Bromohydin Moiety

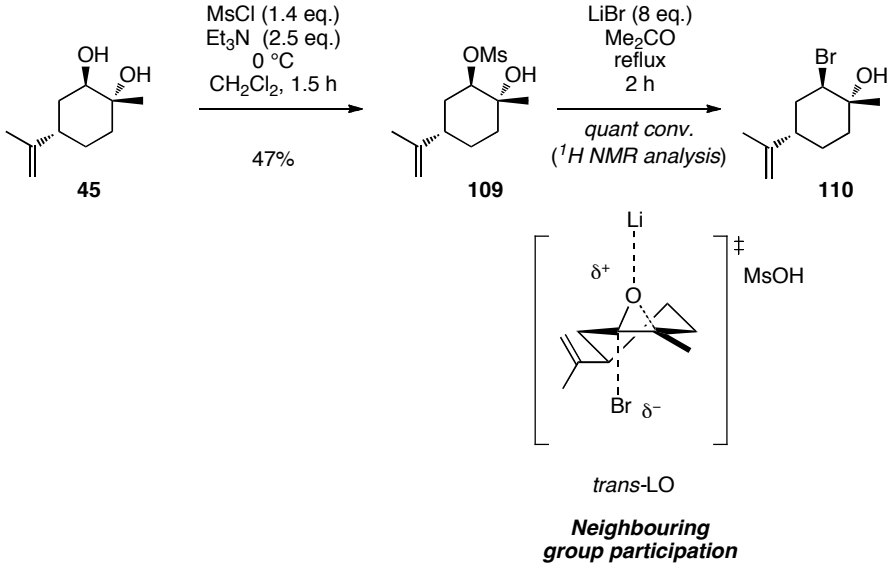
A S_N2 inversion strategy of the C2 stereocentre of the activated alcohol of **108** (derived via an S_N2 oxirane opening of limonene oxide) was envisaged to facilitate the formation of the desired *syn*-bromohydrin **35a**, as discussed in Chapter 1.



Scheme 3.38: Inversion of the activated alcohol 108 to the syn-bromohydrin 35a

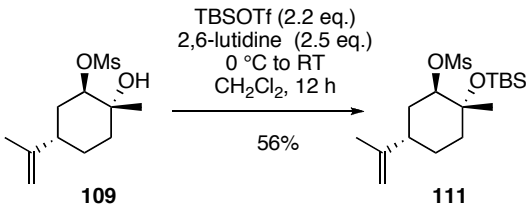
Conversion of the secondary alcohol of the diaxial diol **45** to the mesylate with methanesulfonyl chloride (MsCl) in the presence of triethylamine (TEA) in DCM rapidly afforded the activated mesylhydrin **109** (Scheme 3.39).[104] ^{1}H NMR spectroscopic analysis of the reaction mixture revealed a new methyl resonance at δ 3.04 ppm (integrating for 3H), accompanied with a pronounced downfield shift of the carbinol resonance of the secondary alcohol from δ 3.63 ppm to δ 4.60 ppm, consistent with the formation of a sulfate ester. When the mesylate **109** was subjected to LiBr (8 molar eq.), in refluxing acetone,[105] the exclusive product observed was the *anti*-bromohydrin **110**; not the desired *syn*-bromohydrin isomer **35a** (Scheme 3.39). The ^{1}H NMR spectrum as expected, was devoid of the resonances associated with the mesylate. Instead, an upfield multiplet splitting pattern was observed (δ 4.2 ppm, 1H; reminiscent of the proton previously bound at C2 attributed to the mesylate). Furthermore, the expected doublet of doublets, characteristic of an axial bromomethine *syn*-bromohydrin **35a** (*ca* δ 4.0 ppm, J = 12 and 4Hz) was absent. The lack of the expected proton multiplicity resonances indicated retention of stereochemistry at C2, and thus, it was rationalized the tertiary alcohol at C1 of **108** was lending anchimeric assistance for the formation of bromide **110**.[106] The putative neighbouring group mechanism involves the transient formation of *trans*-LO, which

undergoes nucleophilic attack by a bromide ion yielding net retention of stereochemistry at C2 (S_N2_i reaction; Scheme 3.39).[106]



Scheme 3.39: The S_N2i reaction of 45 leading to retention of stereochemistry in bromohydrin 110

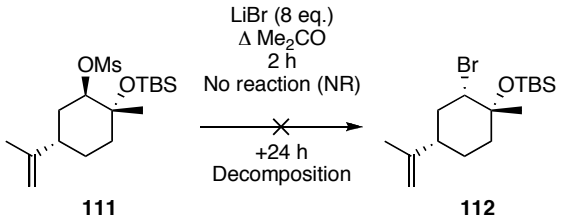
To overcome the formation of the transient epoxide, it was hypothesised that the strategic installation of a tertiary alcohol protecting group would sequester the undesired S_N2_i reaction kinetics (described above in Scheme 3.39) from occurring. As much success had been achieved with the installation of a TBS ether protecting group at the hindered tertiary alcohol, it was logical to implement this protecting group once again in our strategy. Treatment of the mesylhydrin **109** (employing a modified procedure to that previously described for the ketol **41**, *see* Section 1), with a large excess of TBSOTf and 2,6-lutidine, and stirring from 0 °C to RT overnight, afforded the TBS-mesylate **111** in modest yields (*ca*. 56%), after chromatographic purification on SiO_2 (Scheme 3.40).



Scheme 3.40: Protection of the mesylate 109 to the TBS mesylate 111

With the TBS-mesylate **111** in hand, nucleophilic displacement of the 2° mesylate group was attempted in the presence of LiBr in refluxing acetone for 2h (Eq. 1 Table 3.2).[105] However formation of the desired bromide was not observed by TLC and ^{1}H NMR analysis of an aliquot of the reaction mixture. When prolonged reaction times were employed (>24 h), complete decomposition of the TBS-mesylate **111** occurred. This was confirmed by GCMS analysis of the reaction mixture whereby no bromide isotopes were observed in the expected mass-range region. A range of conditions were investigated, including alternate bromide sources such as *n*-tetrabutylammonium bromide (*n*Bu_4Br)[104] to effect conversion to the desired bromide **112**. The conditions screened for the formation of bomide **112** are summarized in Table 3.2; unfortunately, none of which resulted in conversion to the desired bromide **112**.

Eq. 1

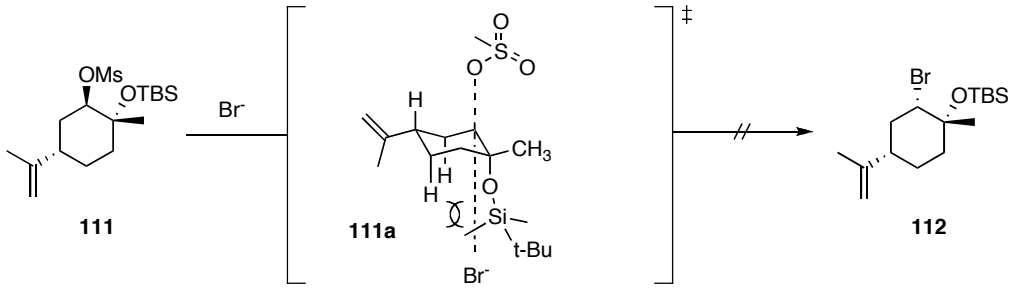


Entry	Conditions	Comment
1	LiBr (8 eq.) Me_2CO, RT, 2 h	NR
2	LiBr (8 eq.) Me_2CO, reflux, 24 h	Decomposition
3	*n*Bu_4Br (2.6 eq.) THF, reflux 24 h[107]	NR
4	*n*Bu_4Br (2.6 eq.) PhMe, reflux, 120 h	NR
5	*n*Bu_4Br (2.6 eq.) DMSO, RT, 24 h	NR
6	*n*Bu_4Br (2.6 eq.) DMSO, 80-100°C, 24 h	Decomposition[§]
7	*n*Bu_4Br (1 eq.), KBR (5 eq.) DCM:H_2O (1:1), 72 h[104]	NR

Table 3.2: Attempts to invert the C2 stereocentre under a range of conventional conditions

[§] 10 h at 60 °C *via* ^{1}H NMR analysis showed no conversion to the bromide **112** (entry 6), see Appendix 2 for selected spectra from this temperature experiment.

It is hypothesised that nucleophilic approach of a bromide ion into the *anti* bonding orbital of the mesylate nucleofuge is met with significant steric shielding both from the 1,3-diaxial hydrogens and the *pseudo*-neopentyl *tert*-butyldimethylsilyl group (Scheme 3.41). For these reasons formation of the bromide does not occur under a range of conditions as illustrated in Table 3.2 (*vida supra*).



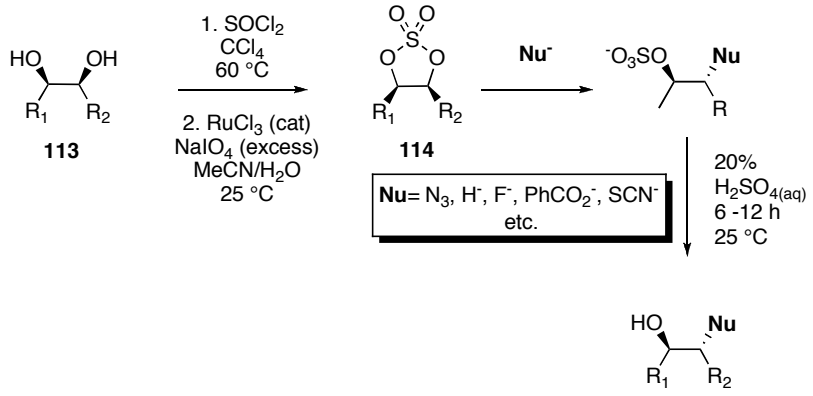
Scheme 3.41: Obscured back-side approach of the bromide nucleophile into the TBS-mesylate 111

As an inversion strategy of the TBS-mesylate **111** towards the bromide **112** was proving unfruitful; attention was turned to an alternate strategy.

3.7. The Gao and Sharpless Cyclic Sulfate Approach to the syn-Bromohydrin Moiety.

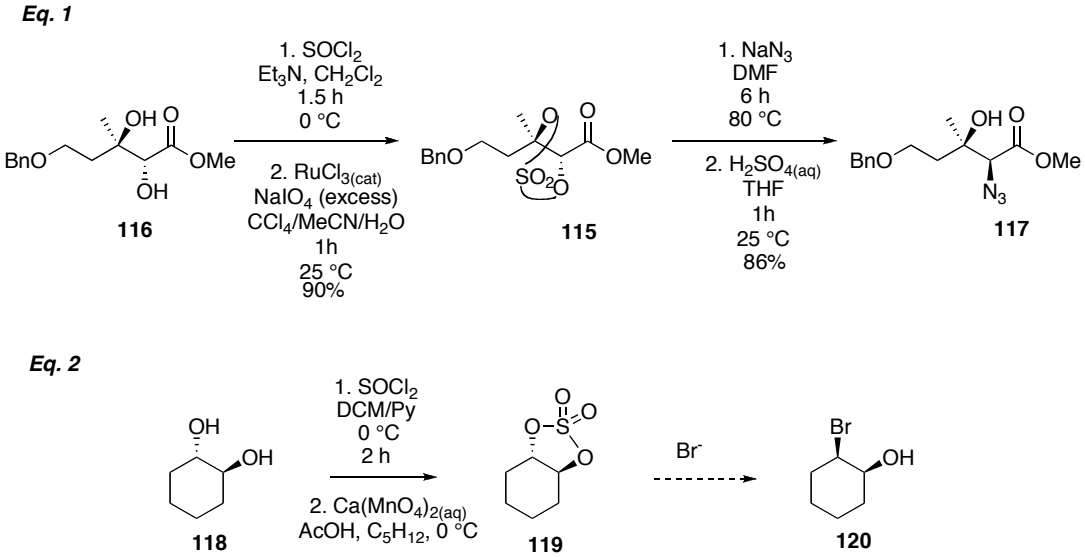
In 1988 Gao and Sharpless published an article entitled "Vicinal Diol Cyclic Sulfates: Like Epoxides Only More Reactive", disclosing the activation of vicinal diols, as the corresponding cyclic sulfate, towards an array of nucleophiles.[108] Formation of the cyclic sulfate was achieved *via* treatment of the vicinal diol **113** with thionyl chloride, followed by a catalytic oxidation to the S(VI) congener with $RuCl_3/NaIO_4$ (Scheme 3.42).[108] Sharpless' work was considered seminal for two reasons: The direct preparation of 1,2-cyclic sulfates such as **114** from reagents such as SO_2Cl_2 was not considered facile due to the 5-6 kcal/mol ring strain energy involved in this cyclisation process. Sharpless addressed this *via* a $RuCl_3/NaIO_4$ catalytic oxidation of the corresponding S(IV) sulfite**,** in place of RuO_4 or MnO_4^- as a stoichiometric oxidant. The latter of these reagents, is reported to give reduced yields and product purity. Furthermore, Sharpless demonstrated

the highly electrophilic nature of these cyclic sulfates towards a diverse range of nucleophiles (Scheme 3.42), behave in a strikingly similar fashion to an epoxide moiety.



Scheme 3.42: Typical reaction conditions for the formation of cyclic sulfates, and nucleophile scope[108]

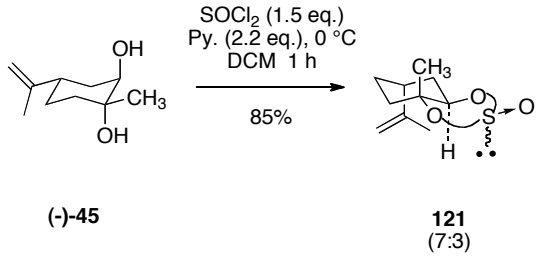
There are examples for the formation of cyclic sulfates **115**, derived from acyclic *trans*-1,2 diols **116**, participating as electrophiles in the presence of nucleophiles such as sodium azide (NaN_3) to form azide **117** (Eq. 1, Scheme 3.43).[109] To the best of our knowledge, there is only one report for the formation of a cyclohexane *trans*-1,2-cyclic sulfate **118**, derived from cyclohexane *trans*-1,2-diol **119**, furthermore, no known reports for the transformation of the sulfate **119** to the bromohydrin **120** (Eq. 2, Scheme 3.43).[110]



Scheme 3.43: The use of cyclic sulfates as a means of accessing syn-orientated functional group moieties[109]

Undeterred by this lack of literature precedent, we attempted the installation of a cyclic sulfite moiety on the (1*R*,2*R*,4*S*)-diaxial-diol **45** substrate, with promising results. Preparation of the *trans*-sulfite **121** proceeded smoothly in 1 h in the presence of thionyl chloride/pyridine in anhydrous DCM in 85% yield (Eq. 1, Fig 3.8). ^{1}H NMR spectroscopic analysis revealed a 7:3 mixture of sulfite diastereoisomers, as determined *via* integration of the sulfite-methine doublet of doublets (δ 3.94 and 4.43 ppm, J = 13.3 and 3.6 Hz each; Fig 3.8). This suggested ring inversion of the *trans*-diaxiol diol (-)-**45**, allowing ring closure to the *trans*-diequatorial cyclic sulfite **121**.

Eq. 1



(-)-45 **121** (7:3)

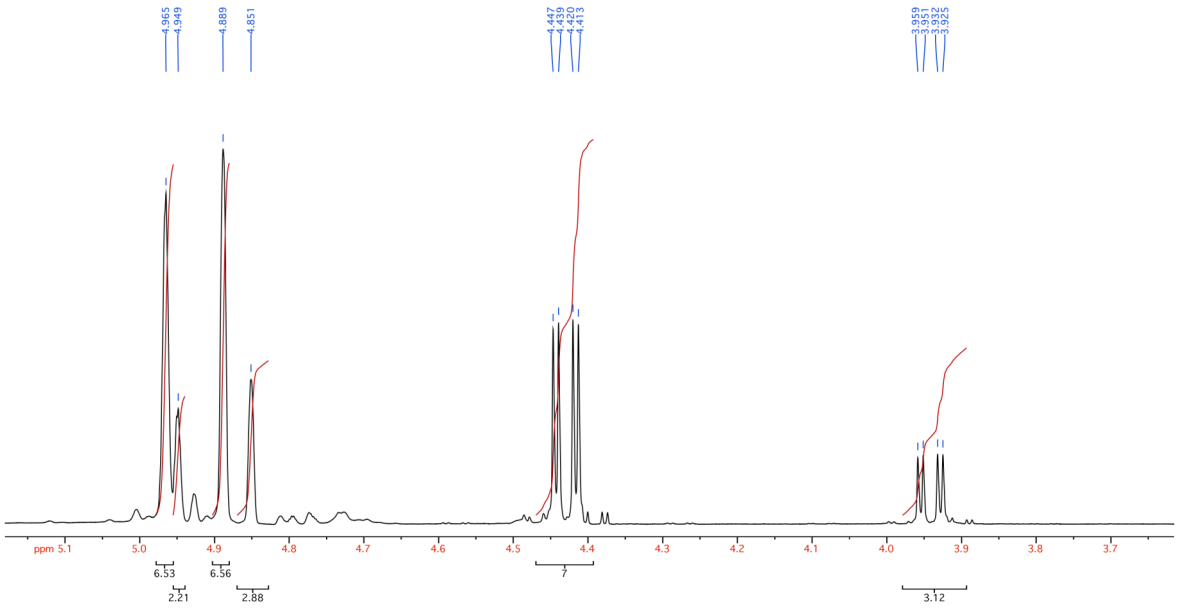
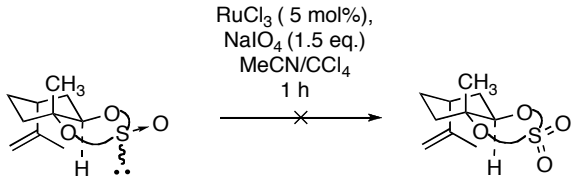


Fig 3.8: The diastereotopic sulfite methine proton resonances of 121

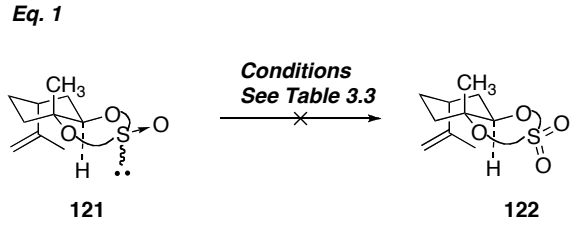
With the cyclic sulfite **121** in hand, this substrate was directly subjected to Sharpless' catalytic $RuCl_3/IO_4^-$ oxidant system[108] in acetonitrile (MeCN)/carbon tetrachloride (CCl_4) without purification (Scheme 3.44). Interestingly, no new product was observed *via* TLC analysis after the prescribed 1 h reaction time, whilst ^{1}H NMR spectroscopic analysis

showed no coalescence of the sulfite methine resonances, as one would expect as symmetrisation of the S(IV) **121** to the S(VI) cyclic sulfate **122** congener occurred.



Scheme 3.44: Attempted oxidation of the cyclic sulfite 121 to the cyclic sulfate 122

When reaction times of up to 5 days were employed, no change was observed in the ^{1}H NMR spectrum of an aliquot taken from the reaction mixture. Several common oxidant systems for the conversion of cyclic sulfites to cyclic sulfates were screened with little success in effecting the oxidation of sulfite **121** to sulfate **122** (Table 3.3).

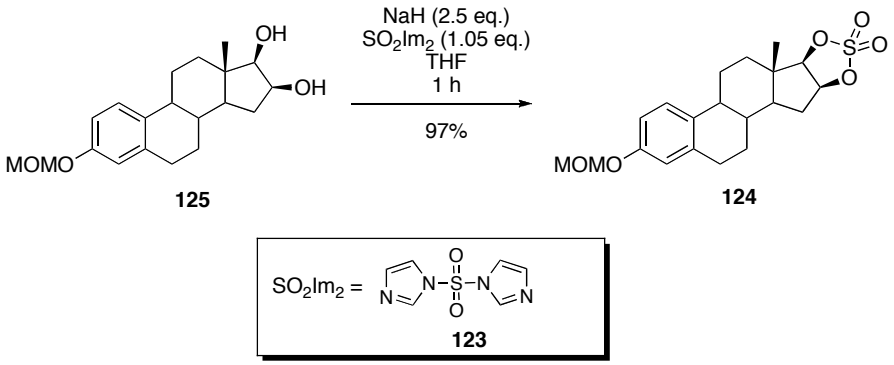


Entry	Oxidant	Comment
1	$RuCl_3$ (5 mol%), $NaIO_4$ (1.5 eq.) 5 days[108]	NR
2	$RuCl_3$ (1mol%), Oxone (1.5 eq.), MeCN/H_2O 3 days[111]	NR
3	$RuCl_3$ (5 mol%), 1:1 $NaOCl_{(aq)}$ (12% *w/v*):DCM 5 days[112]	Allylic chlorination (*ca*. 50%)
4	$KMnO_4$, $H_2SO_{4(aq)}$, DCM 12 h	NR
5	$KMnO_4$ (2.5 eq.), AcOH 30 mins.[110]	Decomposition. (<5% SM recovery)

Table 3.3: Oxidant screening to effect conversion of the cyclic sulfite 121 to the cyclic sulfate 122

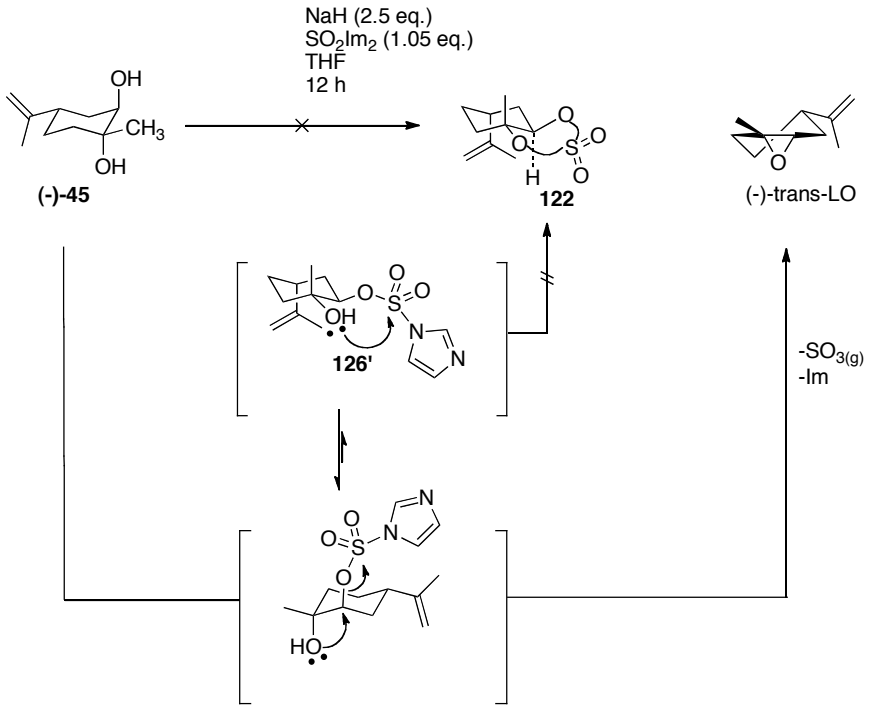
Encouraged by the ease in which the diol (-)-**45** underwent ring closure to the cyclic sulfite in the presence of or $SOCl_2$/Py. It was worthy to investigate the analogous reaction with the S(VI) sulfonyl diimidazole (SO_2Im_2) **123**, as this reagent was used to prepare the

*anti*estrogen cyclic sulfate intermediate **124**, from the *syn*-diol **125** in the presence of sodium hydride in excellent yields (Scheme 3.45).[113] It was anticipated this approach would by-pass the problematic oxidation of the limonene derived cyclic sulfite **121** to the cyclic sulfate **122**.



Scheme 3.45: Direct formation of the cyclic sulfate 124 in the presence of SO_2Im_2 123

Treatment of the diaxial diol (-)-**45** with sodium hydride (NaH) (2.5 eq.) in THF in the presence of SO_2Im_2 (1.05 eq) overnight did not afford the cyclic sulfate **122** as expected (Scheme 3.46). Interestingly the *trans*-isomer of LO was the sole product observed by ^{1}H NMR analysis as determined by the appearance of a doublet centered at δ 2.98 ppm (J = 4.0 Hz, 1H), characteristic of the epoxy-methine resonance of *trans*-LO. Comparisons of the ^{1}H NMR spectral data of the product from this reaction mixture to the literature values of *trans*-LO, displayed excellent agreement, and it was therefore reasoned ring closure to the oxirane derived from intermediate **126** is lower in energy than that of the ring closed sulfate **122**.

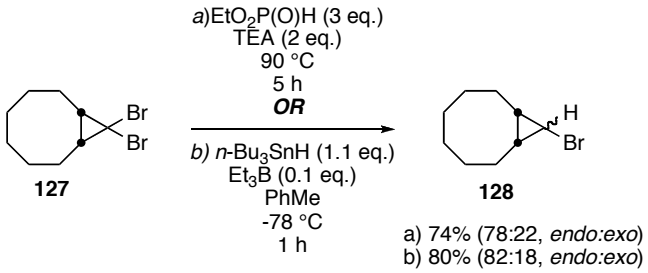


Scheme 3.46: Proposed reaction mechanism for the formation of trans-LO from diaxial diol (-)-45

When alternative method for the formation of cyclic sulfate **122** employing the amidine base diaza(1,3)bicyclo[5.4.0]undecane (DBU; 4 molar eq.) in place of NaH,[114] no formation of either the cyclic sulfate **122** or (-)-*trans*-LO**,** was observed after 24 h at room temperature. Given the lack of success associated for the formation of the cyclic sulfate **122** as a surrogate to the bromohydrin **35a**, an alternate strategy was once again investigated.

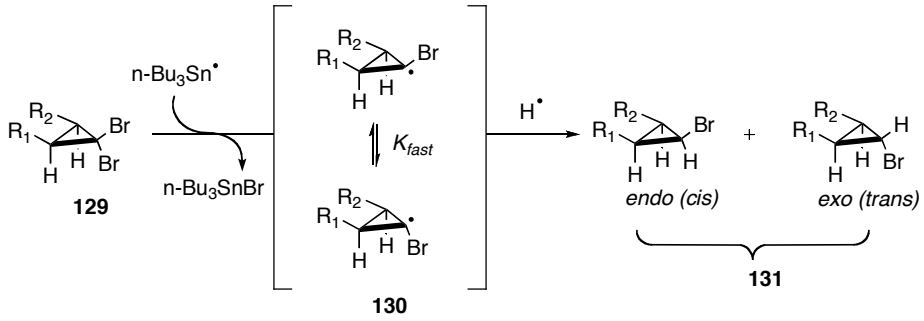
3.8 A Mono Hydrodehalogenation Approach Towards the syn-Bromohydrin Moiety of the Prevezol Congeners

It is known that geminal dibromides such as dibromide **127** undergo hydrodebromination, under a range of mild conditions (Scheme 3.47).[115, 116] Oshiro *et al*. demonstrated this when an excess diethyl phosphite in the presence of triethylamine affords the monobromide **128**, without over-reduction to the corresponding bicycloalkane (Scheme 3.46).[115] Alternatively, the use of *n*-Bu_3SnH at low temperature in the presence of triethylborane (Et_3B) as an initiator, or at 40 ºC in diethyl ether in the absence of an initiator is also an effective protocol for the monohydrodebromination of *gem*-dibromides (Scheme 3.47).[116, 117]



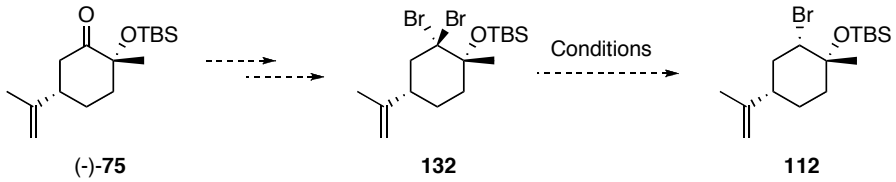
Scheme 3.47: Methods for monodehalogenation of the gem-dibromide 127 to the bromide 128[115, 116]

Oshima and co-workers postulate the abstraction of a bromide atom by a tin radical from dibromide **129**, and subsequent equilibration of the carbon centered radicals **130** occurs rapidly, and does not have a bearing on the stereochemical course of the reaction (Scheme 3.48).[116] Whilst addition of a hydrogen atom occurs at a slower rate, and is influenced by the steric demand of the bulky *n*-tributylstannane in regards to the substrate, affording a stereoisomeric mixture of monobromides **131**, favouring the *endo* product.[116]



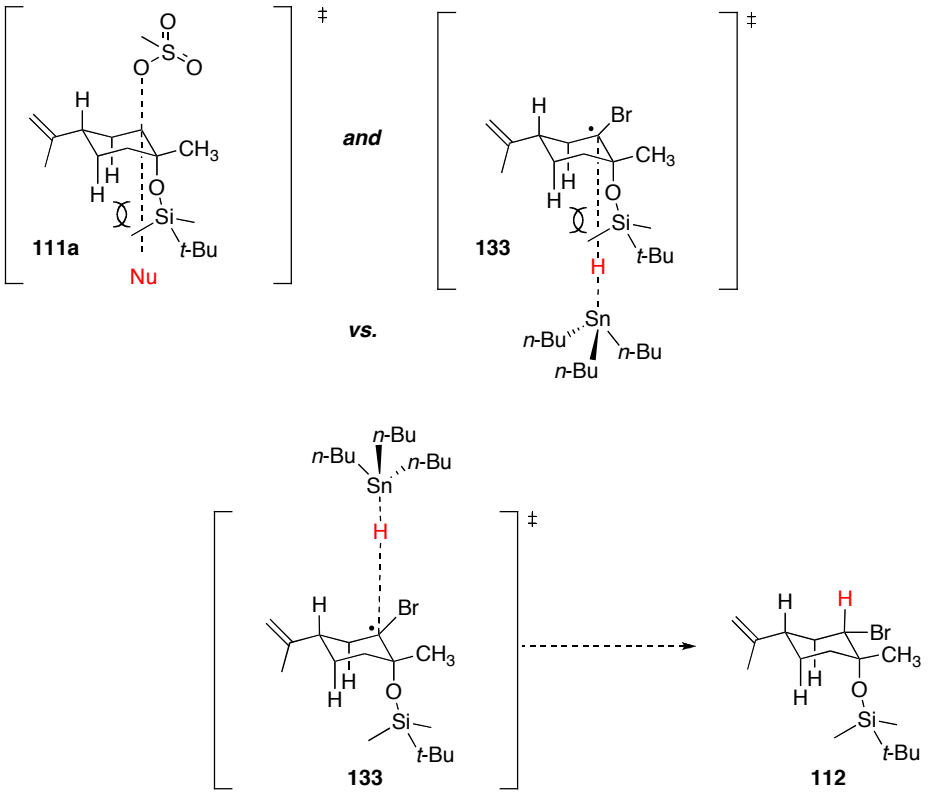
Scheme 3.48: Formation and equilibration of the carbon centred radicals 130 and subsequent reduction to the bromides 131[116]

It was postulated that employing either the conditions of Oshima *et al*. (*n*-Bu_3SnH/Et_3B) or Oshiro *et al*. ($EtO_2P(O)H$/TEA), that reduction of the *gem*-dibromide **132** could be achieved with good stereoinduction at the 2-bromo position of the bromide **112** (Scheme 3.48).



Scheme 3.49: Proposed strategy to the latent syn-bromohydrin 112

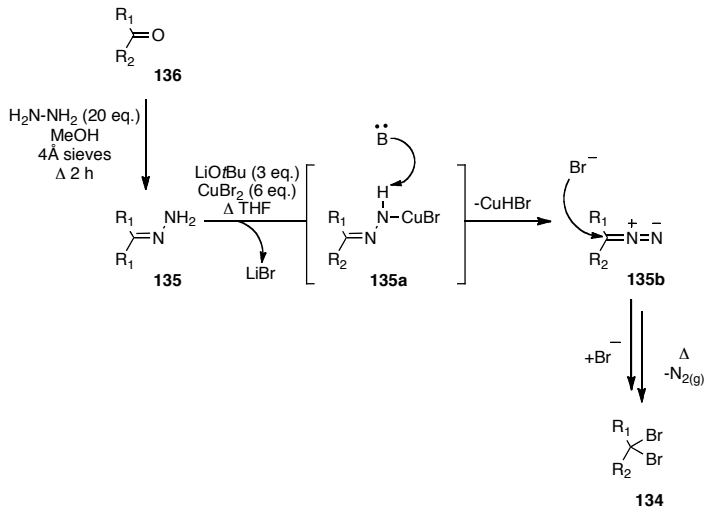
The hypothesis towards obtaining the desired diastereoisomer contained within the bromide **112** was based upon the observation that backside nucleophilic attack of the TBS-mesylate was not a facile process. Similarly, it was hoped that approach of reducing reagent such as *n*-Bu_3SnH would encounter similar electrostatic repulsion (Scheme 3.50). Thus, reduction would occur *anti* to the congested *tert*-butyldimethylsilyl group **133**, forming the latent *syn*-bromohydrin **112** (Scheme 3.50).



Scheme 3.50: Proposed diastereofacial reduction to the desired bromide 112

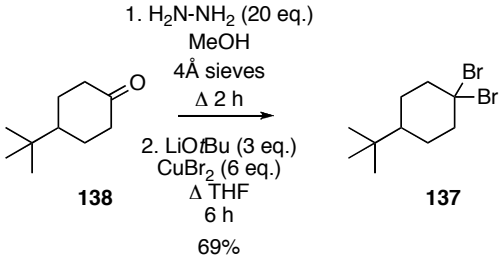
In order to validate this hypothesis, a synthetic strategy towards the key *gem*-dibromide **132** was required. Although there are a number of reported methods available for the transformation of ketones to their corresponding *gem*-dibromo analogues,[118-120] only one such method described by Takeda *et al.* demonstrated mild conditions for the formation of acyclic, cyclic and benzylic *gem*-dibromides in good yields.[13] Furthermore, this method is reported to be selective for the formation of the desired *gem*-dibromide, and not the undesired vinyl bromide by-products, which is common to other methods for this transformation[13]

Formation of the *gem*-dibromide **134**, involves the stepwise formation of the hydrazone **135**, derived from the corresponding ketone **136** (Scheme 3.51). Upon double deprotonation of the hydrazone **135** with excess lithium *tert*-butoxide (*t*-BuOLi)/*tert*-butoxycopper(II) bromide to form the diazonium **135b**, it is hypothesized this species undergoes stepwise reduction to the *gem*-dibromide **134** (Scheme 3.51).[13]



Scheme 3.51: Takeda's procedure and postulated mechanism to the gem-dibromide 134[13]

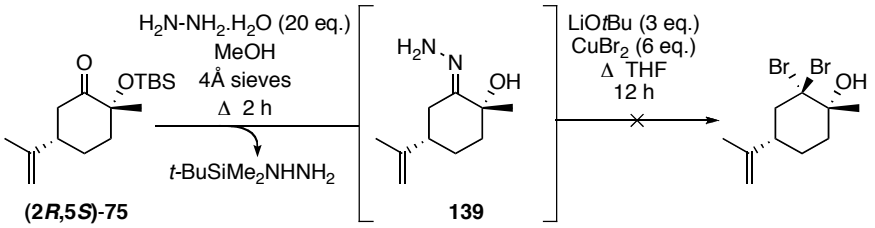
Although the vast majority of Takeda and co-workers' substrates were devoid of sensitive functionality; one such entry, *gem*-dibromide **137** derived from cyclohexanone **138** bared a vague resemblance to the terpenoid backbone of interest (Scheme 3.52).[13]



Scheme 3.52: Preparation of the cyclohexyl gem-dibromide 137[13]

The required TBS-ketone (2*R*,5*S*)-**75**, was therefore prepared from (-)-*cis/trans*-LO employing the conditions previously described (See Chapter 3: Part 1) in excellent yields. Derivatisation to the corresponding hydrazone employing the conditions of Takeda *et al*. was attempted,[13] however on analysis of the intermediary hydrazone (*via* ^{1}H NMR spectroscopy), complete loss of the *tert*-butyldimethylsilyl resonances were observed. It is presumed hydrazinaloysis of the silyl protecting group occurred, affording the deprotected hydrazone **139** (Scheme 3.53). Subjecting the crude hydrazone **139** to the second component of Takeda's protocol (LiO*t*Bu/$CuBr_2$) resulted in a complex mixture of unidentifiable products as observed by both TLC and ^{1}H NMR spectroscopic analysis

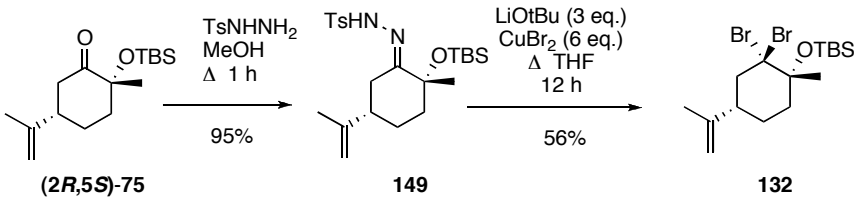
(when either LiO*t*Bu or TEA was used as the base in this reaction). It is reasoned that the neighbouring tertiary hydroxyl group of the hydrazone **139** is sensitive to the somewhat vigorous reaction conditions, and thus, retention of the silyl protecting group was deemed essential for the success of this reaction.



Scheme 3.53: Application of Takeda's protocol on the TBS-ketone (-)-75

Aware that tosylhydrazones also decompose to yield intermediary diazonium homologues, such as diazonium **135b** (*vida supra*, Scheme 3.51), we opted to explore the corresponding tosylhydrazone of (2*R*,5*S*)-**75**, **149** (Eq. 1. Fig 3.9) as a surrogate to the desired *gem*-dibromide **132**. Preparation of the tosylhydrazone **149** proceeded smoothly in the presence of tosylhydrazide (1.05 molar eq.) in refluxing methanol giving excellent yields (>95%). Furthermore, ^{1}H NMR spectroscopic analysis of the reaction mixture pleasingly revealed retention of the silyl-protecting group. Subjecting the intermediary tosylhydrazone **149** to the protocol of Takeda *et al*, however, stirring at room temperature for 18 h opposed to reflux, saw complete consumption of starting material *via* TLC analysis.[13] Purification, and isolation of the major component of the reaction mixture *via* flash column chromatography, revealed a product completely devoid of all resonances on the ^{1}H NMR time scale attributed to the toluenesulfonyl group (δ 2.42, 7.30 and 7.84 ppm, Fig 3.9: Spectrum B). Furthermore the ^{1}H NMR spectrum of *gem*-dibromide **132** was accompanied by the appearance of a downfield doublet of doublets due to the axial proton adjacent to *gem*-dibromide (δ 2.81 ppm, 1H). The ^{13}C NMR spectrum obtained for the product **132** revealed a key new resonance at δ 78.4 ppm, assigned as the geminal dibromo quaternary centre. Attempts to obtain mass spectral data on this substrate were unsuccessful, limiting characterization chiefly to NMR spectroscopy.

Eq. 1



(2*R*,5*S*)-75 **149** **132**

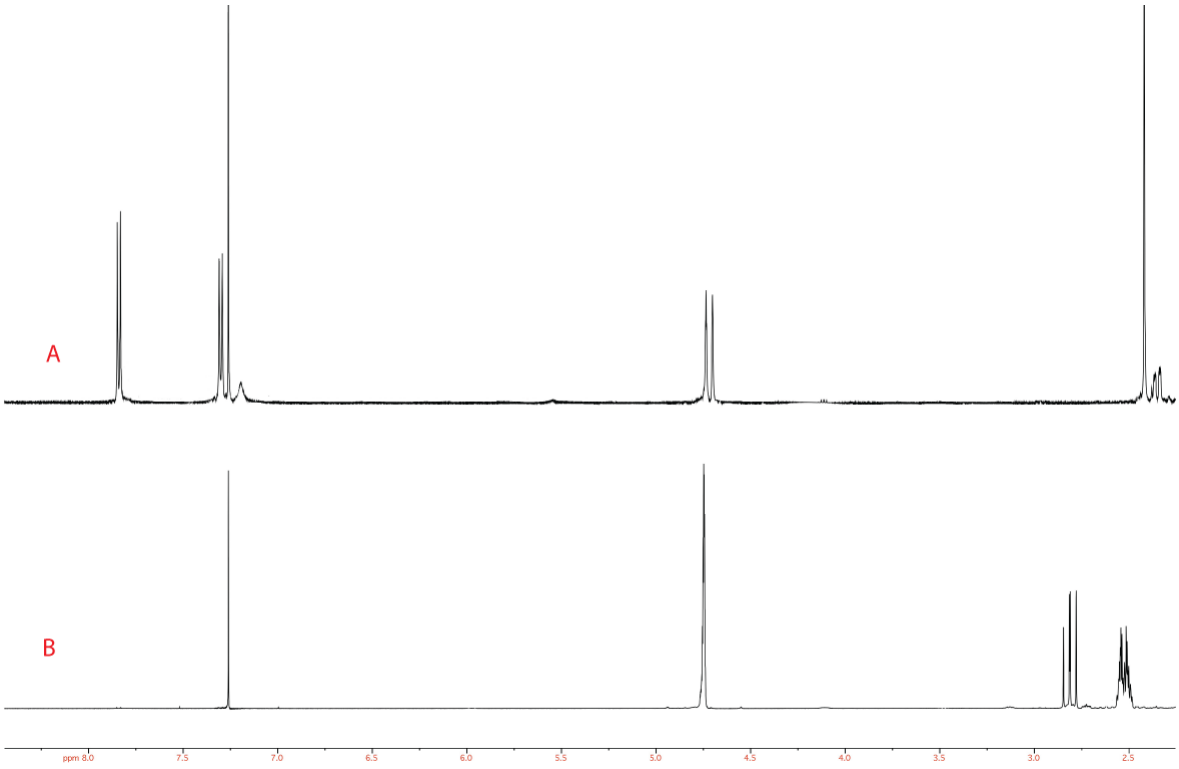


Fig 3.9: ^{1}H NMR expansions of the tosylhydrazone 149 (spectrum A) and the gem-dibromide 132 (spectrum B)

With the tentatively assigned *gem*-dibromide **132** in hand, it was subjected the conditions of Oshiro (diethylphosphite/TEA in THF); TLC analysis of the reaction mixture after the prescribed period (5h) at reflux, showed that no new hydrodebrominated product had formed.[115] The ^{1}H NMR spectrum of the reaction mixture after 7 days revealed no detectable formation of the desired bromide **112**, as only the proton resonances of the *gem*-dibromide **132** were observed.

Following the work of Oshima *et al.* and Chatgilialoglu *et al*., the *gem*-dibromide **132** was subjected to a modified reducing system, employing tris(trimethylsilyl)silane (TTMSS, 1.1 molar equivalents), in favour of *n*-Bu_3SnH in deuterated benzene (C_6D_6).[117,12] Monitoring the progress of the reaction on the ^{1}H NMR time scale over 30 minutes at 72 ºC revealed the formation of the desired *syn*-bromide **112**, in a diastereoselective manner (Fig 3.10). Assignment of the newly formed asymmetric centre was determined by the appearance of a doublets of doublets resonating at δ 3.62 ppm, J = 12.31 and 4.1 Hz, 1H. These values were in close accordance to the literature *syn*-bromohydrin neorgioldiol δ (C_6D_6) 3.73, J=12.5 and 4.4 Hz, 1H.[121] Analysis of the high-resolution electron impact time of flight mass (EI-TOF) spectrum revealed two isotopic bromide ions at 346.1331 and 348.1338 in a 1:1.1 relative abundance (calculated mass for $C_{16}H_{31}BrOSi$ is 346.1328 and 348.1307), further supporting the formation of the bromide **112**.

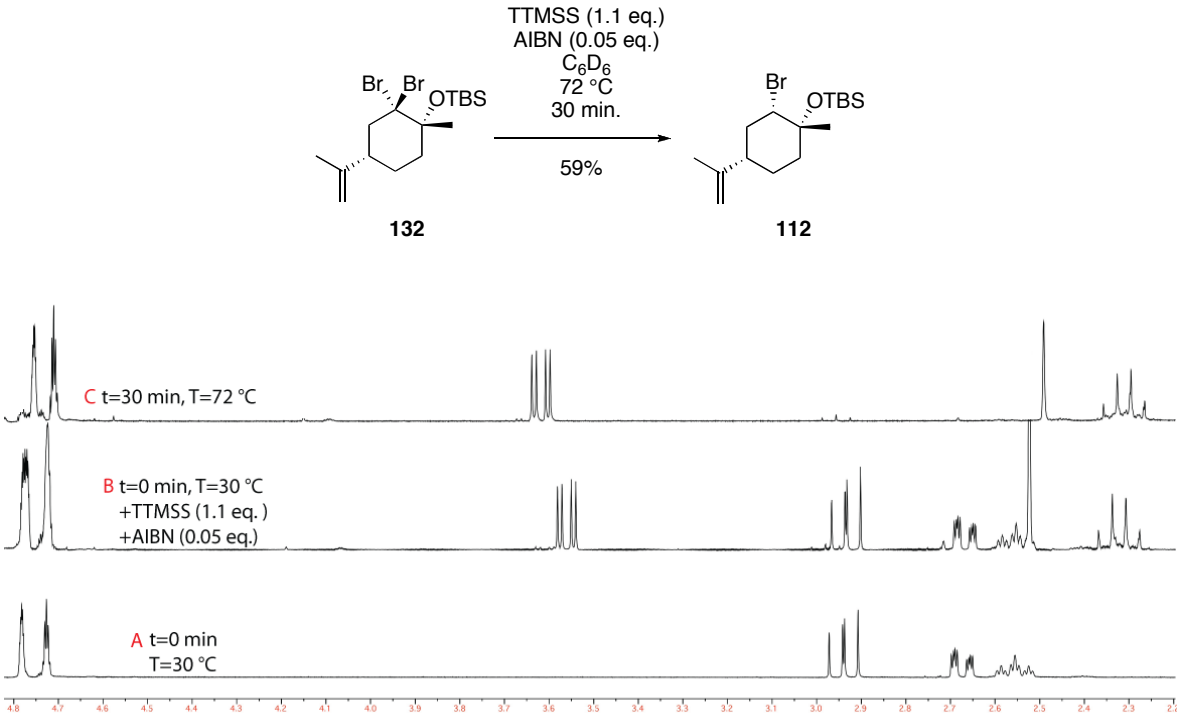


Fig 3.10: The diastereoselective reduction of gem-dibromide 132 (A) to the monobromide 112 (C)

Comparison of the ^{13}C NMR spectral data of the synthetic TBS-bromide **112** to that of the natural Eastern domain of Prevezol C **14** revealed excellent correlation particularly at the tertiary carbon bearing the bromide (C2), resonating within 1.1 ppm deviation of the natural bromide, Fig 3.11.[26] As expected the TBS protected oxygenated quaternary centre of **112** and its neighbour showed poor correlation. Preliminary experiments to remove the silyl protecting group to reveal **35a** have thus far been unsuccessful employing TBAF for a direct spectroscopic comparison of the synthetic bromohydrin **35a** to the natural ^{13}C resonances. Although warranting further investigation, additional examination of this issue extended beyond the scope of this dissertation, and will not be discussed further.

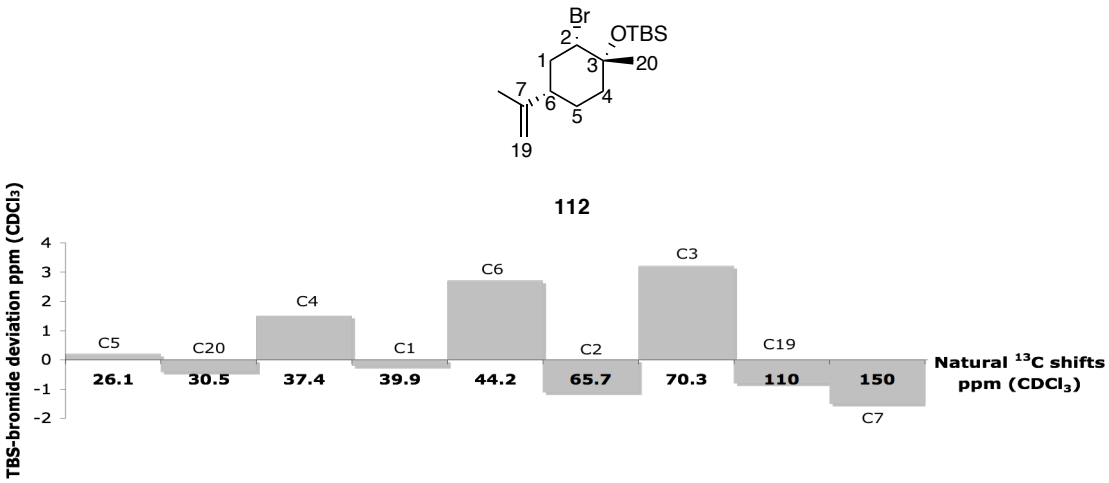
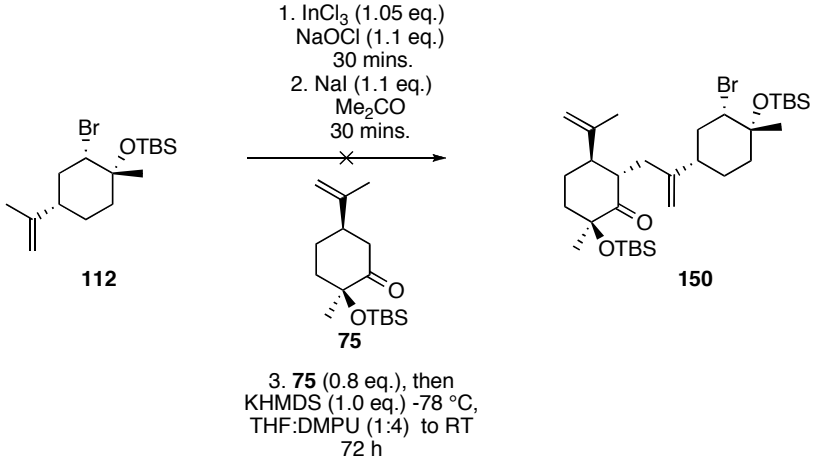


Fig 3.11: Correlation chart of the natural Prevezol C 14 Eastern domain vs. the synthetic bromide 112 ^{13}C resonances

3.9 Future Work

Recent attempts to alkylate the allylic iodinated derivative of the *syn*-silyloxy bromide **112** with the TBS-ketone **75** to form the bis-silyloxy-diterpene **150** have been unfruitful employing the previously reported conditions (Scheme 3.54). Future work within the group will aim to address this issue, and shed light on the structural assignment reported by Illipolou *et al.* through a combination of total synthesis and computer modeling.[26]



Scheme 3:54: Attempted formation of the bis-silyloxy-diterpene 150 under the previously optimised allylic alkylation conditions

Experimental Section

General Experimental

All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Solvents were dried, when necessary, by standard methods.[122] Organic solutions were dried over $MgSO_4$. The progress of the reactions was monitored by thin layer chromatography (TLC) on Merck 60 F240 precoated silica gel polyester plates, and products were visualized with vanillin dip. Flash chromatography was performed with Davisil LC60A, 40-63 μm silica media.

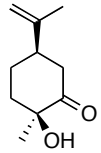
Proton (^1H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ on either a Bruker AM300, Bruker AV400 or Varian DRX500 spectrometer operating at 300, 400 and 500 MHz respectively for proton and 75, 100 and 125 MHz for carbon nuclei. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to residual solvent signal as the internal standard. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer RXI FTIR Spectrometer as thin films on NaCl plates.

Low resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on either a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration or a Waters GC-TOF. Low resolution (EI) mass spectra were recorded on a VG Micromass 70/70F mass spectrometer with an ion source temperature of 200 ºC and electron impact energy (70 eV). GC-MS were performed on a Varian 3700 gas chromatograph using a 3QC5/BPX5 1.0 μM column of internal diameter 0.53 mm abd length 30 cm at a linear velocity of 46.6 cm/sec. A temperature gradient of 80 ºC for 10 mins, increased to 280 ºC for mins at 10 ºC/min was used. Injector temperature = 250 ºC; detector temperature = 300 ºC. Measurements were recorded on a HP 3396A Integrator.

Optical rotations were obtained using a PolAAR 2001 automatic polarimeter, using a 1 dm cell with chloroform as solvent, at a wavelength of 589 nm (sodium D line).

Compound names were generated using the ChemBioDraw® 11 software suite.

(2S,5R)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 45



41

Pyridinium chlorochromate (8.89 g, 41.20 mmol) and Celite (6.00 g) were suspended in dichloromethane (150 mL), the (1*S*,2*S*,4*R*)-diaxial diol **45** (5.85 g, 34.33 mmol) in 50 ml of CH_2C1_2 was rapidly added at room temperature. The ensuing mixture was stirred for 3.5 h, and was subsequently eluted through a short silica gel column and concentration *in vacuo* to afford (4.09 g, 70%) of the oxidized product. ^{1}H NMR spectral analysis revealed quantitative consumption of the diol **45** to the title compound, and typically 10% of a oxidatively cleaved product, keto-aldehyde **75**, (which was consistent to literature values).[64] Flash chromatography (20:80 EtOAc: hexanes) and concentration *in vacuo* to afford (3.74 g, 64%) of the hydroxy ketone **41** as a clear oil.

$[\alpha]_D^{20}$ -49.2 (*c* 1.0, $CHCl_3$).

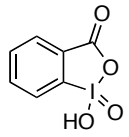
^{1}H NMR (500 MHz) δ 1.36 (s, 3H), 1.70 (m, Hz, 3H), 1.75-2.05 (complex, 4H), 2.58 (dd, *J* = 5.6, 13.6 Hz, 1H), 2.66 (m, 1H), 2.78 (ddd, *J* = 1.6, 5.4, 13.6 Hz, 1H), 2.96 (bs, 1H), 4.69 (d, *J* = 0.5 Hz, 1H), 4.86 (d, *J* = 0.5 Hz, 1H).

^{13}C NMR (125 MHz) δ 21.8, 25.3, 25.5, 37.4, 41.7, 44.3, 75.9, 112.2, 146.3, 213.7.

IR (film): 3348 (bs), 3157 (m) 3057 (w), 2860 (w), 1711 (s) cm^{-1}.

HRMS (ESI) calcd for $C_{10}H_{16}NaO_2$ $(M+Na)^+$ 191.1043, found 191.1041.

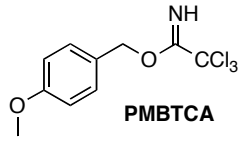
Iodoxybenzoic acid



Following the protocol of Frigerio *et al*,[75] 2-Iodobenzoic acid (25.0 g, 0.1 mol) was added all at once to an aqueous solution (375 mL) of Oxone® (90.5 g, 0.15 mol). The resulting mixture was warmed to 70-75 °C over 20 mins. and maintained at this temperature for 3 h. The ensuing heterogeneous mixture was allowed to cool (with the aid of an external ice bath) over 1.5 h, after which the reaction mixture was filtered through a sintered glass-funnel. The white precipitate was repeatedly washed with water (6 x 50 mL) and acetone (2 x 50 mL). After the white solid was dried in a desiccator for 16 h, the title compound was afforded as a free flowing white powder (20.8 g, 74 %), which was identical *via* ^{1}H NMR analysis to that reported by Frigerio *et al*.[75]

^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.84 (complex, 1H), 7.99 (complex, 1H), 8.03 (complex, 1H), 8.14 (complex, 1H).

4-Methoxyphenyl 2,2,2-trichloroethanimidate



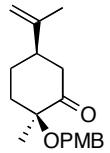
PMBTCA

Following the method described by Audia *et al*,[123] a solution of *p*-methoxybenzyl alcohol (5.2g, 37.60 mmol) in diethyl ether (35 mL) was added to a suspension of 60% dispersion of sodium hydride in mineral oil (0.15g, 3.8 mmol) in diethyl ether (40 mL) at RT under an inert atmosphere. The ensuing mixture was stirred at RT for 30 mins and cooled to 0 °C, trichloroacetonitrile (3.8 mL, 37.6 mmol) was added dropwise and allowed to warm to RT over a course of 4 h. The mixture was filtered through a pad of Celite and concentrated *in*

vacuo to afford the title compound as an orange syrup (8.49 g, 84%). which was identical *via* ^{1}H NMR spectroscopy to that reported by Audia *et al*.[123]

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3H), 5.27 (s, 2H), 6.91 (m, 2H), 7.37 (m, 2H).

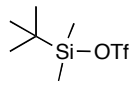
Attempted formation of (2S,5R)-2-(4-methoxybenzyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 74



74

Following a modified procedure to that reported by Rai and Basu,[79] The (1*S*,2*S*,4*R*)-diaxial diol **45** (150 mg, 0.89 mmol), 4-methoxyphenyl-trichloroethanimidate (378 mg, 1.34 mmol) and La(OTf).XH_2O (52 mg, 89 μmol) were heated at reflux in toluene (10 mL) for 16 h. ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after this period revealed no detectable conversion of the diol **45** to the title compound.

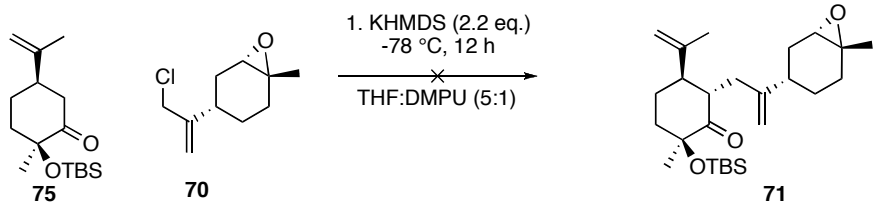
tert-Butyldimethylsilyl trifluoromethanesulfonate



Following a modified method described by Corey *et al.*,[81] trifluoromethanesulfonic (10.0 g, 66.63 mmol) acid was added dropwise to *tert*-butyldimethylsilyl chloride (10.04 g, 66.63 mmol), under an inert atmosphere and heated to 75 °C for *ca.* 10 h. The resulting *tert*-butyldimethylsilyl trifluoromethanesulfonate was directly distilled from the reaction flask (75°C at 10 mbar) to afford a colourless liquid (14 mL, 91%). which was identical *via* ^{1}H NMR spectroscopy to that reported by Corey *et al*.[81]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.46 (s, 6H), 1.00 (s, 9H).

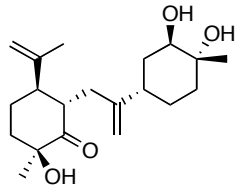
(2S,5R,6S)-2-(tert-Butyldimethylsilyloxy)-2-methyl-6-(2-((1S,3S,6R)-6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)allyl)-5-(prop-1-en-2-yl) cyclohexanone 71



75 **70** **71**

Potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M solution in toluene; 4.4 mL, 2.20 mmol) was slowly added to a -78 °C magnetically stirred solution of the *tert*-butyldimethylsilyloxy-ketone **75** (282 mg, 1 mmol) in absolute THF (10 mL) under an inert atmosphere. After 30 min had elapsed at this temperature; an anhydrous THF:DMPU solution (5 mL, 4:1) of the allylic chloride **70** (223 mg, 1.20 mmol) was slowly introduced through a rubber septa via aid of a syringe over the course of 3 min. The reaction mixture was allowed to slowly warm to ambient temperature, whilst stirring for 12 h. Quenching an aliquot of the reaction mixture with cold sat. $NH_4Cl_{(aq)}$, followed by ^{1}H NMR spectroscopic analysis of the organic fraction revealed no detectable conversion to the diterpene oxide **71**.

(1S,2S,3S,4R)-1-Methyl-3-(2-((1S,3S,6R)-6-methyl-7-oxabicyclo[4.1.0] heptan-3-yl)allyl)-4-(prop-1-en-2-yl)cyclohexane-1,2-diol **107**



107

A of 5% *v/v* $H_2SO_{4(aq)}$ (1.6mL) was slowly introduced to a cooled (*via* the aid of an external ice bath) of the epoxide **106** (512 mg, 1.61 mmol) in THF (25 mL). The reaction mixture was stirred, whilst warming to ambient temperature for 3 h after which, TLC analysis indicated complete consumption of the epoxide. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ (25 mL), extracted with EtOAc (40 mL) and finally washed with sat. $brine_{(aq)}$ (30 mL). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and directly subjected to flash column chromatography (50:50 hexanes:EtOAc) to afforded the title compound as a fluffy white solid (158 mg, 29%). Single crystal X-ray analysis was performed on a recrystallised sample of **107** from de-ionised water.

$[\alpha]_D^{20}$ 10.1 (*c* 1.1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.32 (s, 3H), 1.51-1.61 (m, 6H), 1.71-1.73 (m, 4H) 1.84-2.23 (m, 7H), 2.40 (dd, *J* = 15.9, 10.2 Hz, 1H), 3.427 (td, *J* =10.6, 2.4 Hz, 1H), 3.63 (t, *J* = 2.8 Hz, 1H) 4.62 (s, 1H), 4-73-4.78 (m, 2H), 4.801 (t, *J* = 1.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 24.5, 26.7, 26.85, 26.9, 31.5, 34.0, 34.7, 36.6, 40.5, 47.2, 54.4, 71.5, 74.2, 76.2, 107.4, 113.0, 146.3, 152.6, 213.5.

IR (film):3502 (w), 3399 (s), 2929 (s), 1711 (s), 1643 (m), 1502 (m), 1434 (w), 1377 (m), 1332 (w), 1124 (m), 1100 (m), 1051 (s), 1034 (s) 992 (m), 926 (m), 906 (m), 848 (w).

HRMS (ESI) *m/z* calcd. for $C_{20}H_{32}NaO_4$ $(M+Na)^+$ 359.2198; found 359.2195.

X-Ray Crystallography Structure determination

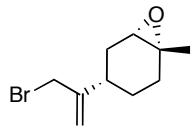
A representative, colourless prismatic crystal of dimensions 0.18 × 0.10 × 0.05 mm was covered in viscous oil and mounted on a glass fibre. A sphere ($2q_{max}$ 55°) of CCD area-detector diffractometer data was measured (Bruker X8 Apex CCD, 0.5° frames, f and ω-

scans, monochromatic Mo *K*α radiation, λ = 0.71073 Å; *T ca*. 123 K) yielding N_t reflections, these merging to *N* independent data (R_{int} as quoted) after empirical/multi-scan absorption correction (SADABS). Full matrix least squares refinement on F^2 (SHELX97) with anisotropic displacement parameter forms for non-hydrogen atoms yielded final residuals *R* and wR_2. Hydrogen atoms attached to carbon were placed in calculated positions, constrained to ride on the parent atoms, whilst those associated with the alcohol and water moieties were located and freely refined. The molecule crystallized in the non-centrosymmetric space group $P2_1$ with two molecules and two lattice water molecules in the ASU; no additional symmetry was indicated by PLATON. Due to the absence of a heavy (>Si) atom, the absolute strucutre was not determined (stereochemistry was inferred from the synthetic method) and Friedel opposites were merged for the final refinement cycle.

Crystal Refinement Data

$C_{20}H_{34}O_5$ *M* = 354.47, monoclinic, space group $P2_1$, *Z* = 4. *a* = 8.9326(4), *b* = 24.6259(10), *c* = 9.1377(4)Å, *b* = 90.256(2), *V* = 2010.03(15)Å^3. D_c = 1.171 g cm^{-3}. μ_{Mo} = 0.082 mm^{-1}; $T'_{min,max}$ = 0.99, 0.97, N_t = 29130, *N* = 4923 (R_{int} = 0.0508), *R* = 0.041 wR_2 = 0.081 (for 4046 reflections with *I*>2s*I*), *R* = 0.059 wR_2 = 0.089 (all data).

Attempted formation of (1R,4S,6S)-4-(3-bromoprop-1-en-2-yl)-1-methyl-7-oxabicyclo[4.1.0]heptane 81

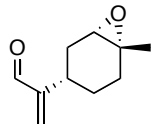


81

Freshly distilled (-)-*trans*-LO (152 mg, 1.0 mmol) and recrystallised NBS (267 mg, 1.5 mmol) were dissolved in degassed, anhydrous CCl_4 (10 mL, 0.1 M). The reaction mixture was brought to reflux and maintained at this temperature for 40 mins. The insolubles (NBS/succinimide) were filtered through a bed of Celite, and the reaction mixture was concentrated *in vacuo* to afford a viscous orange syrup. ^{1}H NMR and GCMS spectral

analysis of this residue revealed a complex mixture of degradation/polymerization products, none of which were reminiscent of the expected title compound.

2-((1S,3S,6R)-6-Methyl-7-oxabicyclo[4.1.0]heptan-3-yl)acrylaldehyde 90



90

(-)-*trans*-LO (1.0 g, 6.57 mmol) and SeO_2 (1.09 g, 9.85 mmol) were dissolved in absolute dioxane (50 mL) and brought to reflux and maintained at this temperature for 12 h. After this period, the ensuing mixture was allowed to cool to ambient temperature, diluted with diethyl ether (50 mL) and washed successively with 5% $KOH_{(aq)}$ (3 x 30 mL) and sat. $brine_{(aq)}$ (30 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow syrup (856 mg). Subjecting this residue to flash column chromatography on silica gel (25:75: EtOAc: hexanes) afforded the title enal as colourless oil (43 mg, 4%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53-1.60 (m, 1H), 1.74-1.81 (m, 1H), 2.05 (dt, *J* = 14.5, 3.2 Hz, 1H), 2.27-2.22 (m, 1H), 2.40-2.47 (m, 1H), 3.00 (d, *J* = 5.4 Hz, 1H), 5.97 (s, 1H), 6.22 (d, *J* = 0.8 Hz, 1H), 9.49 (s, 1H).

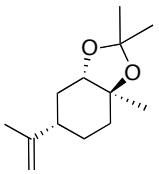
Due to the instability of the enal **90**, subjecting this compound (44 mg, 264 μmol) to $NaBH_4$ (80 mg, 2.12 mmol) in MeOH (4 mL) for 1.5 h at 0 °C, rapidly reduced the enal **90** to the corresponding allylic alcohol (43 mg, 97%) in excellent yield. This compound was stable for the purpose of further characterization.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H) 1.38-1.45 (m, 3H), 1.67-1.74 (m, 2H), 1.93-1.99 (m, 1H), 2.02-2.06 (m, 1H), 2.09-2.14 (m, 1H), 3.00 (d, *J* = 5.4 Hz, 1H), 4.08 (s, 2H), 4.87 (t, *J* = 1.0 Hz, 1H), 5.02 (d, *J* = 1.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8, 24.6, 30.0, 32.0, 32.3, 36.7, 59.8, 66.0, 109.0, 152.9.

MS (ESI) *m/z* calcd. for $C_{10}H_{15}O_2$ $(M-H)^-$ 167.1; found 166.8.

(3aR,6S,7aR)-2,2,3a-Trimethyl-6-(prop-1-en-2-yl) hexahydrobenzo[d][1,3]dioxole 96

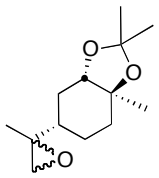


96

Following a modified procedure of Kido *et al*,[96] to a stirred solution of (1*R*,2*R*,4*S*)-limonene diol (6.26 g, 36.77 mmol; $[\alpha]_D^{20}$ -26.1, *c* 1.05, $CHCl_3$), in anhydrous DCM (100 mL), was added 2-methoxy-propene (7.75 mL, 80.89 mmol) and PPTS (462 mg, 3.68 mmol) at ambient temperature. Complete consumption of the diol substrate typically occurred over 2 h *via* TLC analysis. The reaction mixture was quenched (100 mL) sat. $NaHCO_{3(aq)}$, and washed successively with sat. $brine_{(aq)}$ (100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (6.77 g, 88%) as a straw yellow viscous oil, which was used without purification, and was spectroscopically identical to that reported by Kido *et al.*[96]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.64-1.75 (m, 3H), 1.77-1.79 (m, 3H), 1.79-1.85 (m, 1H), 1.99-2.04 (m, 1H), 2.13-2.18 (m, 1H), 2.49-2.52 (m, 1H), 3.59 (dd, *J* = 13.2, 3.5 Hz, 1H), 4.88-4.91 (m, 2H).

(3aR,6S,7aR) 2,2,3a Trimethyl 6 (2-methyloxiran-2-yl) hexahydrobenzo[d][1,3] dioxole 97



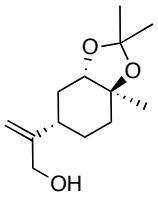
97

7:3 mixture of *exo*-oxides

Following a modified procedure of Kido *et al.*,[96] *m*CPBA (80% *w/w* 15.93 g, 64.62 mmol) was added portion wise over 10 mins. to a 0 °C cooled stirred solution of the acetonide **96** (7.55 g, 35.90 mmol) in DCM (125 mL), and maintained at this temperature for a further 5 h. After this period, the reaction mixture was neutralised by the addition of sat. $Na_2SO_{3(aq)}$ (125 mL), successively washed with sat. $NaHCO_{3(aq)}$ (3 x 100 mL) followed by sat. brine (100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless, viscous oil (6.36 g, 78%; 7:3 mixture of diastereoisomers) as the title compound which was spectroscopically identical to that reported by Kido *et al.*[96]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 3H). 1.39 (br s, 6H), 1.50 (s, 3H), 1.55-1.68 (m, 3H), 1.73-1.89 (m, 3H), 2.03-2.15 (m, 2H), 2.54-2.79 (m, 1H), 3.64-3.85 (m, 1H).

2-((3aR,5S,7aR)-2,2,7a-Trimethylhexahydrobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol 95



95

Rearrangement of 97 with LDA

n-BuLi (1.4 M hexanes; 20.9 mL, 29.2 mmol) was added to a cooled solution (with the aid of an external ice bath) of diisopropylamine (4.10 mL, 29.2 mmol) and tetramethylethylene diamine (4.94 mL, 29.2 mmol) in anhydrous THF (30 mL) under an inert atmosphere. The ensuing mixture was allowed to stir for at this temperature for 15 mins. after which a solution of the epoxide **97** (3.0 g, 13.26 mmol) in THF (15 mL) was slowly introduced, and allowed to warm to ambient temperature, whilst stirring for 12 h. The reaction mixture was quenched with water (100 mL), washed with brine (100 mL), and the organic extracts were dried ($MgSO_4$) after which the resulting residue was subjected to flash column chromatography (50:50 EtOAc:hexanes) to afford a colourless oil (1.73 g, 57%; **95**:**98**, 5:3 mixture of allylic alcohols)

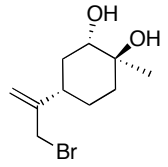
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s 3H; **95**), 1.195 (s, 3H; **98**), 1.34 (s, 3H; **95**), 1.37 (s, 3H; **98**), 1.49 (s, 3H; **95**), 1.52 (s, 3H; **95**), 1.68-1.79 (m, 3H; **95** & **98**), 1.85 - 2.01 (m, 3H; **95** & **98**), 2.08-2.12 (m, 1H; **95** & **98**), 2.67 (dd, *J* = 15.5, 6 Hz 1H; **98**), 2.72 (t, *J* = 5.1 Hz, 1H; **95**), 3.05 (dd, *J* = 13.3, 4.2 Hz 1H; **98**), 3.49 (dd, *J* = 13.4, 4.3 Hz, 1H; ; **98**), 3.60 (dd, *J* = 13.2, 3.5 Hz, 1H; ; **95**), 4.09-4.22 (m, 2H; **95** & **98**), 5.11 (s, 1H; **95**), 5.24 (s, 1H; **95**).

Rearrangement of 97 with AIP

The epoxide **97** (4.0 g, 17.67 mmol) in a toluene aluminium *iso*propoxide solution (53 mL, 53.0 mmol; 1M) was heated at reflux for 12 h. After this period the reaction was allowed to cool to ambient temperature and water was added (10 mL), this caused substantial precipitation of a white volumous aluminium hydroxide species which was removed *via* vacuum filtration. The organic phase was washed with sat. $brine_{(aq)}$ (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title allylic alcohol (crude) as a colourless, highly viscous oil (2.83 g). Subsequent flash column chromatography on silica gel (35:65: EtOAc: hexanes) yielded a higher purity allylic alcohol (1.37 g, 34%) which was spectroscopically identical to that reported by Kido *et al.*[96]

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.34 (s, 3H), 1.49 (s, 3H), 1.68-1.87 (m, 4H) 1.97 - 2.10 (m, 3H), 2.72 (t, *J* = 5.1 Hz, 1H), 3.60 (dd, *J* = 13.2, 3.3 Hz, 1H), 4.13 (s, 2H), 5.11 (s, 1H), 5.24 (s, 1H).

(1R,2R,4S)-4-(3-Bromoprop-1-en-2-yl)-1-methylcyclohexane-1,2-diol 99

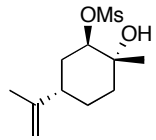


99

To a stirred solution of the allylic alcohol **95** (1.45 g, 6.41 mmol**)** in DCM (50 mL) at 0 °C (with the aid of an external ice bath), was added all at once triphenylphosphine (1.85 g, 7.05 mmol) and carbon tetrabromide (2.55 g, 7.69 mmol). The reaction mixture was allowed to warm to RT over 3.5 h, after which it was concentrated to a fifth of its original volume. Successive trituration/filtration with cold diethyl ether was performed to remove the triphenylphosphine oxide by-product. This light yellow oil was analysed by ^{1}H NMR spectroscopy, whereby loss of the acetal protecting group was observed, along with exchange of the alcohol group for a bromide. Subsequent flash column chromatography on silica gel of this oil (25:75: EtOAc: hexanes) afforded the deprotected bromo diol **99** (499 mg, 31%), which rapidly underwent decomposition to a black residue (unidentifiable by ^{1}H NMR analysis) before further physical analysis could be performed.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 3H). 1.52-1.84 (m, 5H), 1.92-1.98 (m, 1H), 2.57-2.62 (m, 1H), 3.65 (s, 1H), 4.02 (s, 2H), 5.05 (s, 1H), 5.23 (s, 1H).

(1R,2R,5S)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl methanesulfonate 109



109

Methanesulfonyl chloride (878.3 μL, 11.35 mmol) was added dropwise to a 0 °C (with the aid of an external ice bath) stirred solution of (1*R*,2*R*,4*S*)-limonene diol (1.61 g, 9.46 mmol; $[\alpha]_D^{20}$ -26.1, *c* 1.05, $CHCl_3$) and triethylamine (1.32 mL, 9.46 mmol) in anhydrous DCM (25 mL) under an atmosphere of nitrogen. TLC analysis after 1.5 h confirmed complete consumption of the limonene 1,2-diol, after which the reaction mixture was diluted with water (5 mL), washed with sat. NH_4Cl (3 x 50 mL) followed by sat. brine (50 mL). The organic extact was dried ($MgSO_4$), concentrated *in vacuo* and subjected to flash column chromatography on silica gel (40:60: EtOAc: hexanes) to afford a colourless oil (1.11 g, 47%) as the title compound. Owing to the instability of this compound, it was typically formed prior to use in subsequent reactions, and was not stored for any prolonged periods.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, *J* = 1.5 Hz, 3H), 1.59-1.70 (m, 4H), 1.74 (s, 3H), 1.96- 2.07 (m, 2H), 2.25-2.31 (m, 1H), 3.05 (s, 3H), 4.59-4.62 (m, 1H), 4.73-4.77 (m, 2H).

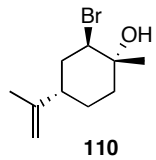
^{13}C NMR (75 MHz, $CDCl_3$):δ 21.1, 22.9, 27.0, 32.2, 34.4 37.8, 38.9, 70.1, 63.9, 109.8, 148.3.

IR (film): 3522 (bs), 3083 (m), 2939 (s), 1705 (w), 1644 (m), 1455 (s), 1343 (bs), 1174 (s), 1003 (m), 959 (s), 893 (s).

MS (ESI) *m/z* 271.2 $(M+Na)^+$.

HRMS (ESI) *m/z* cacld for $C_{11}H_{24}NO_4S$ $(M+NH_4)^+$ 266.1426; found 266.1426.

(1R,2R,4S)-2-Bromo-1-methyl-4-(prop-1-en-2-yl)cyclohexanol 110



110

The mesylate **109** (0.510 g, 2.05 mmol) was refluxed for 12 h in the presence of lithium bromide (1.43 g, 16.43 mmol) in acetone (50 mL). After this period, the reaction was allowed to cool, and was diluted with sat. $NaHCO_{3(aq)}$ (50 mL). Extraction of the organics into ethyl acetate (75 mL), followed by washing with sat. $brine_{(aq)}$ (75 mL) and drying over $MgSO_4$ afforded 421 mg of a light brown oil after concentration *in vacuo*. Subjecting this residue to flash column chromatography on silica gel afforded 57 mg (12%) of the *anti*-bromohydrin which was consistent with that of previously reported data.[124]

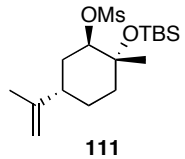
$[\alpha]_D^{20}$ -33.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.57-1.70 (m, 3H), 1.73-1.75 (m, 3H), 1.94-2.05 (m, 2H), 2.27 (ddd, *J* = 14.3, 11.0, 3.3 Hz, 1H),) 2.41-2.47 (m, 1H), 4.20 (td, *J* = 3.69 Hz and 1.12 Hz, 1H) 4.74-4.77 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 26.2, 29.6, 33.3, 35.9, 38.5, 60.2, 71.9, 109.6, 148.6.

MS (ESI): Parent and/or daughter ions not detected.

(1R,2R,5S)-2-(tert-Butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexyl methanesulfonate 111



111

TBS triflate (858 μL, 1.73 mmol) was added dropwise to a 0 °C (with the aid of an external ice bath) stirred solution of the mesylate **109**, 2,6-lutidine (501 μL, 4.33 mmol) in anhydrous DCM (10 mL) under an atmosphere of nitrogen. The reaction mixture was allowed to warm to RT, and stirred overnight. After this period, the reaction was quenched with cold 1M HCl (3 x 50 mL), washed with sat. $brine_{(aq)}$ (50 mL) and subjected to flash column chromatography on silica gel (50:50: EtOAc: hexanes) to afford a colourless oil (340 mg, 56%) as the title compound.

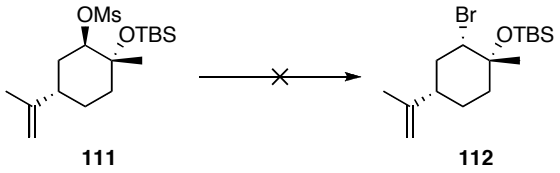
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.32 (s, 3H), 1.49 - 1.51 (m, 1H), 1.58-1.63 (m, 3H), 1.710 (s, 3H), 1.88-1.99 (m, 1H), 2.03 (td, J = 13 Hz, 2.5 Hz, 1H), 2.20-2.45 (m, 1H), 3.02 (s, 3H), 4.51 (t, J = 2.5 Hz, 1H), 4.71-4.72 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ -1.9, -1.6, 18.5, 21.0, 26.0, 26.1, 27.2, 32.0, 37.9, 39.1, 72.6, 84.2, 109.5, 149.2.

IR (film): 2954 (m), 2932 (m), 2857 (m), 2259 (w), 1644 (w), 1471 (w), 1360 (bs), 1257 (m), 1201 (s), 1056 (s), 971 (w), 909 (bs), 808 (m).

MS (ESI) *m/z* calcd. for $C_{17}H_{34}NaO_4SSi$ $(M+Na)^+$ 385.2; found 385.2.

Attempted formation of ((1R,2S,4S)-2-bromo-1-methyl-4-(prop-1-en-2-yl)cyclohexyloxy)(tert-butyl)dimethylsilane 112



111 **112**

Procedure A

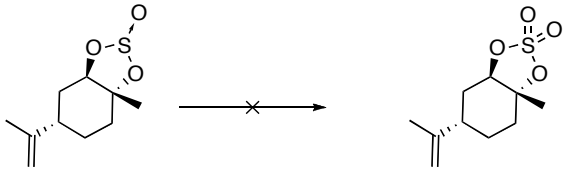
A representative procedure for the attempted formation of the title compound is as follows: The TBS-mesylate **111** (25 mg, 69 μmol), *n*-tetrabutylammonium bromide (58 mg, 179 μmol) in DMSO-d_6 (3 mL) was heated to 80 -100 °C with the aid of an oil bath. Analysis *via* ^{1}H NMR spectroscopy revealed complete decomposition of the TBS-mesylate **111** after 12 h at this temperature. Running this reaction at 60 °C and monitoring over 10 h revealed no formation of the title compound *via* ^{1}H NMR spectral analysis; whereby, only the TBS-mesylate **111** remained.

Procedure B

Following a modification of the literature protocol,[104] The TBS-mesylate **111** (40 mg, 110 μmol), *n*-tetrabutylammonium bromide (36 mg, 110 μmol) and potassium bromide (66 mg, 550 μmol) in DCM:H_2O (4 ml, 1:1) were stirred at ambient temperature for 72 h. ^{1}H NMR spectral analysis of the reaction mixture after this period revealed no conversion to the desired bromide **112**.

Attempted formation of (1R,2R,4S)-limonene cyclic sulfate 122

Procedure A:



121 **122**

Thionyl chloride (109 μL, 1.5 mmol) was added dropwise to a 1:1 pyridine:DCM solution (10 mL) of the (1*R*,2*R*,4*S*)-limonene diol **45** (173 mg, 1.0 mmol; $[\alpha]_D^{20}$ = -26.1, *c* = 1.05, $CHCl_3$) at 0 °C under a positive flow of nitrogen which was bubbled beneath the surface of the reaction solvent. TLC analysis after 1.5 h indicated complete consumption of the diol **45**. The reaction mixture was diluted with diethyl ether (25 mL) washed with 1M $HCl_{(aq)}$ (3 x 25 mL) and lastly with sat. $brine_{(aq)}$ (25 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford as colourless oil as the title sulfite **121** **(**170 mg, 73%; 7:3 mixture of diastereoisomers).

(1R,2R,4S)-limonene cyclic sulfite 121

$[\alpha]_D^{20}$ -38.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (s, 3H, *major*), 1.59 (s, 3H, *minor*), 1.65-1.71 (m, 2 H, *major* & *minor*), 1.77-1.78 (m, 3H, *minor*), 1.78-1.79 (m, 3H, *major*), 1.87-2.11 (m, 3 H, *major* & *minor*), 2.35 (ddt, *J* = 12.8, 3.6, 1.8 Hz, 1H, *minor*), 2.43 (ddt, *J* = 12.8, 3.6, 1.8 Hz, 1H, *major*), 2.59-2.61 (m, 1H, *major* & *minor*), 3.95 (dd, *J* = 13.2, 3.6 Hz, 1H, *minor*), 4.43 (dd, *J* = 13.2, 3.6 Hz, 1H *major*), 4.85-4.86 (m, 1H, *minor*), 4.89-4.90 (m, 1H, *major*), 4.94-4.96 (m, 1H, *minor*), 4.97-4.98 (m, 1H *major*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 19.9, 22.7, 25.1, 25.4, 27,2, 27.9, 33.3, 38.8, 39.9, 78.9, 84.3, 91.4, 111.8, 112.2, 145.3.

IR (film): 3087 (m), 2963 (s), 1643 (s), 1450 (s), 1383 (s), 1320 (w), 1214 (s), 1158 (m), 1070 (w), 1013 (s), 950 (s).

MS (ESI): *m/z* 239.1 $(M+Na)^+$.

HRMS (ESI) *m/z* calcd. for $C_{10}H_{16}NaO_3S$ $(M+Na)^+$ 239.0718; found 239.0721.

***Oxidation A:*[108]**

The cyclic sulfite **121** was redissolved in MeCN:CCl_4 (7 mL, 1:1) and cooled to 0 °C by the aid of an external ice bath. $RuCl_3.H_2O$ (10 mg) and $NaIO_4$ (278 mg, 1.3 mmol) were added all at once, and the reaction mixture was allowed to stir at this temperature for 1.5 h. Analysis of an aliquot of this reaction mixture at this time or after 5 days showed no change by ^{1}H NMR spectrum to that of the starting material proton resonances.

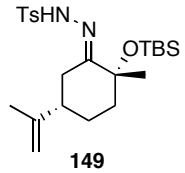
***Oxidation B:*[110]**

An aqueous solution (*ca*. 1 mL) of potassium permangenate (90 mg, 570 μmol) was slowly introduced to a vigorously stirred solution of the cyclic sulfite **121** (50 mg, 231 μmol) in glacial acetic acid (2.5 mL) at 0 °C (by the aid of an external ice bath). The reaction mixture gradually turned brown (from pink), and was quenched after 1 h *via* the addition of sat. $NaHCO_{3(aq)}$ (6 mL), followed by solid sodium metabisulphite to decompose excess permangenate. Extraction of the ensuing reaction mixture into EtOAc (7 mL), followed by standard work-up procedure yielded the cyclic sulfite **121** (15 mg) as the sole product from this reaction mixture, as determined by ^{1}H NMR spectroscopic analysis of this crude residue.

Procedure B:

Following the literature protocol, sodium hydride 60% dispersion (50 mg, 1.5 mmol) was added to a stirred solution of the diol (1*R*,2*R*,4*S*)-limonene diol **45** (85 mg, 0.5 mmol) in anhydrous THF (5 mL), and was allowed to stir at ambient temperature for 10 mins, under an inert atmosphere. A THF solution (3 mL) of sulfonyl diimidazole (104 mg, 525 μmol) was slowly introduced, and the ensuing mixture was allowed to stir overnight. ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture, indicated no conversion to the desired cyclic sulfate **122**; instead *trans*-LO was the sole product of the reaction mixture showing excellent agreement to literature values for this epoxide.[42]

(Z)-N'-((2S,5R)-2-(tert-Butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexylidene)-4-methylbenzenesulfonohydrazide



149

p-Toluenesolfonyl hydrazide (1.04 g, 5.59 mmol) was added to a methanol solution (50 mL) of (2*S*,5*R*)-TBS-ketone (1.58 g, 5.59 mmol; $[\alpha]_D^{20}$ -53.7, *c* 1.2, $CHCl_3$) and was heated at reflux for 1 h. The reaction mixture was cooled, diluted with toluene (to 30% *v/v*) and concentrated *in vacuo* to afford an off-white waxy solid (2.4 g, 95%) as the tosyl hydrazone, which was used directly in the next part of the reaction.

$[\alpha]_D^{20}$ -52.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.46 (s, 3H). -0.08 (s, 3H), 0.79 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 2H), 1.33 (s, 3H), 1.50-1.53 (m, 2H), 1.70 (s, 3H), 1.88-1.92 (m, 1H), 1.94-1.99 (m, 1H), 2.13 (t, *J* = 13.1 Hz, 1H), 2.33-2.38 (m, 1H), 2.42 (s, 3H), 4.70-4.74 (m, 2H), 7.31-7.29 (m, 2H), 7.84 (d, *J* = 8.3 Hz, 2H).

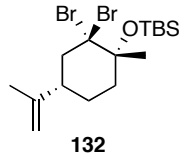
^{13}C NMR (400 MHz, $CDCl_3$) δ -3.7, -2.1, 20.4, 21.7, 25.9, 25.9, 26.05, 26,1, 26.2, 28.0, 74.9, 110.1, 125.4, 128.5, 129.5, 144.2, 148.1, 161.7.

IR (film): 2929 (m), 2339 (w), 1598 (w), 1376 (w), 1335 (w), 1258 (w), 1165 (w), 1091 (w).

MS (ESI): *m/z* 473.1 $(M + Na)^+$.

HRMS (ESI) *m/z* calcd. for $C_{23}H_{39}N_2O_3SSi^+$ $(M + H)^+$ 451.2445; found: 451.2446.

tert-Butyl((1S,4R)-2,2-dibromo-1-methyl-4-(prop-1-en-2-yl) cyclohexyloxy)dimethylsilane 132



132

n-Butyl lithium (1.45M in hexanes; 11.0 mL, 15.97 mmol) was slowly introduced through a rubber septum to a cooled 0 °C (with the aid of an external ice bath) THF solution (25 mL) of anhydrous *tert*-butanol (1.53 mL, 15.97 mmol) under an inert atmosphere. After stirring at this temperature for 15 mins, granular $CuBr_2$ (5.95 g, 26.62 mmol) was added all at once to the ensuing mixture, whereby the green reaction mixture gradually became brown. The tosyl hydrazone **149** (2.40 g, 9.67 mmol) in THF (25mL) of was added over the course of 5 mins. Gentle evolution of nitrogen gas was observed, and the reaction mixture was allowed to warm to RT, whilst stirring for 12 hours. The reaction mixture was diluted with *n*-hexane (150 mL), quenched with 10% $NH_4OH_{(aq)}$ (3 x 40 ml), and the organic phase was washed with sat. brine (100 mL), dried ($MgSO_4$) and eluted through a short plug of silica gel to remove residual copper salts. Concentration *in vacuo* afforded a turbid oil, which was subjected to flash column chromatography (100% *n*-pentane) to afford a colourless oil (1.12 g, 56%).

$[\alpha]_D^{20}$ -36.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 0.02 (m, 3H), 0.16 (m, 3H),. 0.98 (m, 9H) , 1.35-1.41 (m, 2H), 1.44-1.50 (m, 1H) , 1.57 (s, 3H), 1.60 (s, 3H), 1.73-1.84 (m, 1H), 2.08 (td, *J* = 13.8, 4.0 Hz, 1H), 2.52-2.59 (m, 1H), 2.67 (ddd, *J* = 13.8, 3.3, 1.9 Hz, 1H), 2.94 (dd, *J* = 13.8, 12.1 Hz, 1H), 4.72-4.73 (m, 1H), 4.77-4.78 (m, 1H).

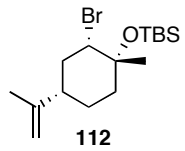
^{13}C NMR (100 MHz, $CDCl_3$): δ -2.4, -1.7, 18.79, 18.8, 21.2, 25.6, 26.2, 27.6, 29.9, 34.8, 43.4, 49.7, 78.4, 83.9, 110.0, 147.7.

IR (film): 2929 (s), 2856 (s), 1646 (w), 1471 (m), 1376 (s), 1254 (s), 1189 (s), 1052 (s), 1004 (w) 974 (w).

MS (ESI): Parent and/or daughter ions not detected.

Note: The crude ^1H NMR spectrum typically suggested substrate conversion in the order of 80-90%, with acceptable product purity, however FCC usually incurred substantial loss of substrate, perhaps due to instability on silica gel.

((1S,2R,4R)-2-Bromo-1-methyl-4-(prop-1-en-2-yl)cyclohexyloxy)(tert-butyl)dimethylsilane 112



112

Reduction A:

Employing the literature protocol,[115] the geminal dibromide **132** (24 mg, 56 μmol), diethylphosphite (9.4 μL, 73 μmol) and triethylamine (13.45 μL, 96 μmol) were refluxed in THF (2 mL) for 5 h. TLC analysis after this period revealed no product formation, whilst allowing the reaction mixture to stir for an additional 7 days at RT, failed to effect conversion of the dibromide **132** to the title compound *via* ^{1}H NMR spectroscopic analysis.

Reduction B:

Tirs(trimethylsilyl)silane (15.92 μL, 51.61 μmol) was added to a benzene-d_6 solution (0.8 mL, 0.005 M) of the geminal-dibromide (20 mg, 46.92 μmol) and AIBN (10 mol%, 1 mg) in an NMR tube which was sealed with the aid of Teflon tape. The reaction mixture was warmed to 72 °C and analysed at time intervals of 15 mins. Near quantitative conversion was observed after 30 mins. to the title compound, as judged by the relative ratio of the bromomethine (δ 3.62 ppm) to the allylic methine (δ 2.95 ppm) resonance of the starting material. Subsequent flash column chromatography (100% *n*-pentane) afforded the title compound pure (9 mg, 59%).

$[\alpha]_D^{20}$ -36.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (d, *J* = 2.8 Hz, 3H), 0.17-0.18 (m, 3H) 0.94 (d, *J* = 5.4 Hz, 9H), 1.37 (s, 3H), 1.44-1.52 (m, 2H), 1.71 (d, *J* = 4.0 Hz, 3H), 1.74 (d, *J* = 3.8 Hz, 1H) , 1.92-1.96 (m, 1H), 2.00 (s, 1H), 2.03-2.07 (m, 1H), 2.20 (t, *J* = 12.3 Hz, 1H), 3.94 (dd, *J* = 12.3, 4.0 Hz, 1H), 4.70 (dt, *J* = 4.4, 1.2 Hz, 2H).

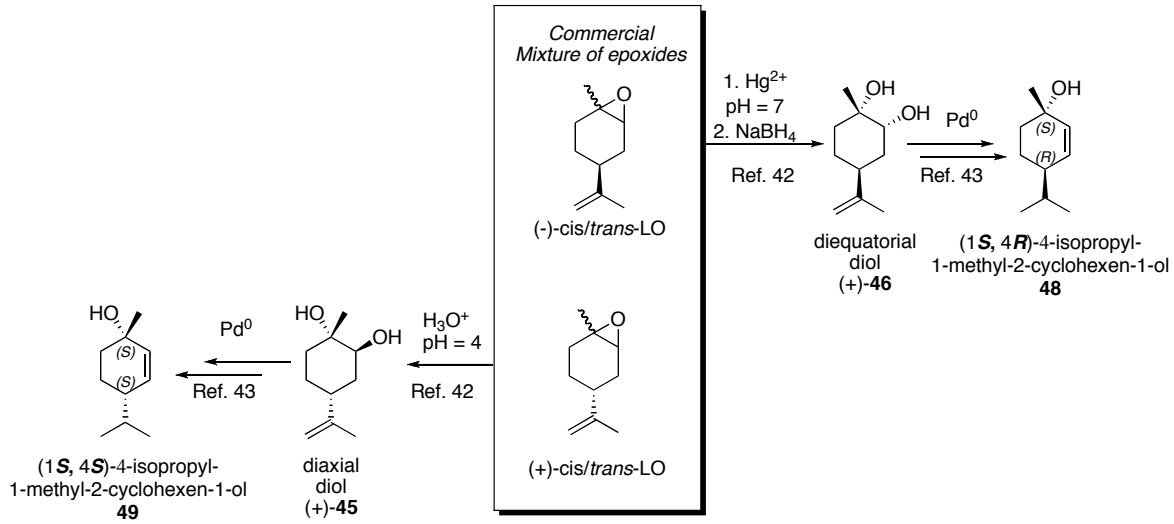
^{13}C NMR (125 MHz, $CDCl_3$): δ -2.1, -1.7, 18.8, 20.7, 26.2, 26.3, 30.1, 38.9, 39.7, 46.9, 64.6, 73.5, 109.4, 148.7.

IR (film): 2957 (s), 2932 (s), 2856 (m), 1693 (w), 1645 (m), 1471 (m), 1452 (m) 1252 (s), 1176 (m), 1159 (m), 1139 (s), 1054 (s), 1005 (m), 980 (m), 939 (w), 891 (m), 836 (s), 802 (s).

HRMS (EI-TOF) *m/z* calcd. for $C_{16}H_{31}BrOSi^{\bullet+}$ 346.1328 (100%) and 348.1307 (97%); found 346.1331 (91%) and 348.1338 (100%).

4.0 Limonene 1,2-Glycol's as Surrogates to tertiary-Endocyclic Allylic Alcohol Containing Natural Products

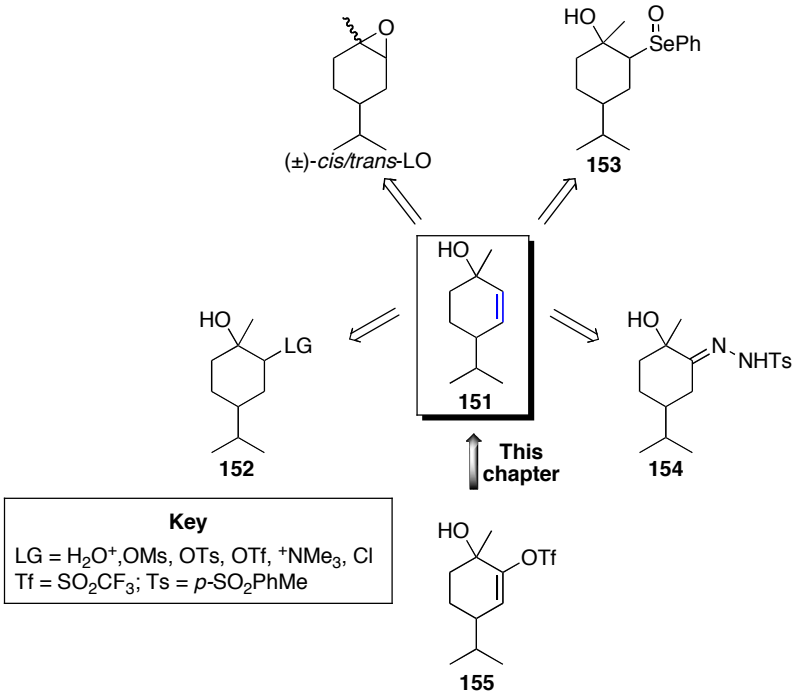
This chapter describes the use of the hydrolytic by-products (the limonene-1,2 glycols (+)-***45*** *&* (+)-***46****) derived from* (+)-*and* (-)-*limonene oxide (see Chapter 2) to access the diastereomeric forms of the oxygenated quaternary centres contained in terpenoid natural products* ***48*** *and* ***49*** *(Scheme 4.0).*[42] *This methodology was applied in a highly diastereo- and enantio-selective (>98% de and ee) total synthesis of the major and minor constituents of the ambrosia beetle sex pheromone 4-isopropyl-1-methyl-2-cyclohexen-1-ol. As published in Tetrahedron: Asymmetry (****2009****, 20, 2149-2153) appended at the end of this chapter.*



Scheme 4.0: Palladium catalysed monodeoxygenation of the limonene glycols* (+)-*45* & (+)-46 *to optically active tertiary endocyclic allylic alcohols 48 & 49

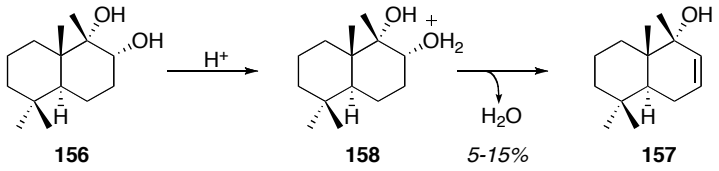
4.1 Common Routes to Endocyclic Olefins

The installation of an endocyclic allylic alcohol **151** may be achieved utilizing functional group interconversions from moieties such as activated diols **152**, epoxides, selenoxides **153** and hydrazones **154** (Scheme 4.1).[125-127] Recently the work conducted in our laboratories concerning the palladium catalysed deoxygenation of enol triflates **155**, has also been demonstrated to afford endocyclic allylic alcohols.[43]



Scheme 4.1: Common routes to endocylic olefins

When Lopez and co-workers attempted an acid catalysed elimination of diol **156** as a means of accessing the allylic alcohol **157** (Scheme 4.2); elimination of the protonated secondary diol **158** was not facile (5-15% yield).[126] As a multitude of carbenium ions can exist in such an acid catalysed elimination (due to methyl and hydride shifts); it is not surprising the isolated yield for this reaction was exceedingly low.

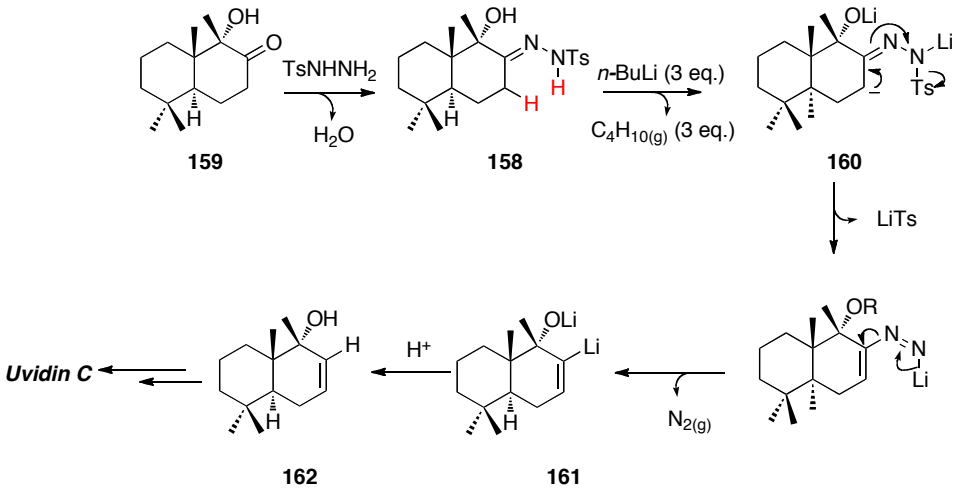


Scheme 4.2: Dehydration of diol 156 to the allylic alcohol 157[126]

With these considerations in mind, there is need for facile routes to *endo*cylic allylic alcohol substrates such as **151** and **157**, which will be discussed in this chapter.

4.2 Organolithium/Tosyl Hydrazone Mediated Decompositions to Allylic Alcohols

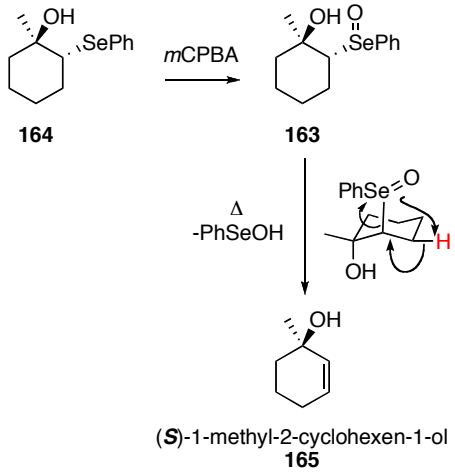
The Bamford-Stevens and more recently the Shapiro reaction have gained popularity as a means of installing olefins in both cyclic and acyclic substrates (Scheme 4.3).[45] An example of the use of this reaction *en route* to the total synthesis of Uvidin C, depicted in Scheme 4.3.[126] Formation of the tosylhydrazone **158**, derived from the corresponding ketone **159**, followed by the treatment with *n*-butyl lithium (*n*-BuLi; 3 molar eq.), gives rise to the trianion **160**. Loss of lithium toluenesulfinate and expulsion of dinitrogen yields the olefin precursor **161**. Protonolysis of the vinyl lithium intermediate **161**, affords the required allylic alcohol **162** in 91% yield.[126] Given the high nucleophilicity of the organometallic base *n*-BuLi, in some cases functional group compatibility and/or choice of appropriate organolithium base may require optimisation.



Scheme 4.3: The use of the Shapiro reaction in the synthesis of Uvidin C[126]

4.3 Organoselenium Decompositions to Allylic Alcohols and Mori's Total Synthesis of the 4-isopropyl-1-Methyl-2-Cyclohexen-1-ol Isomers

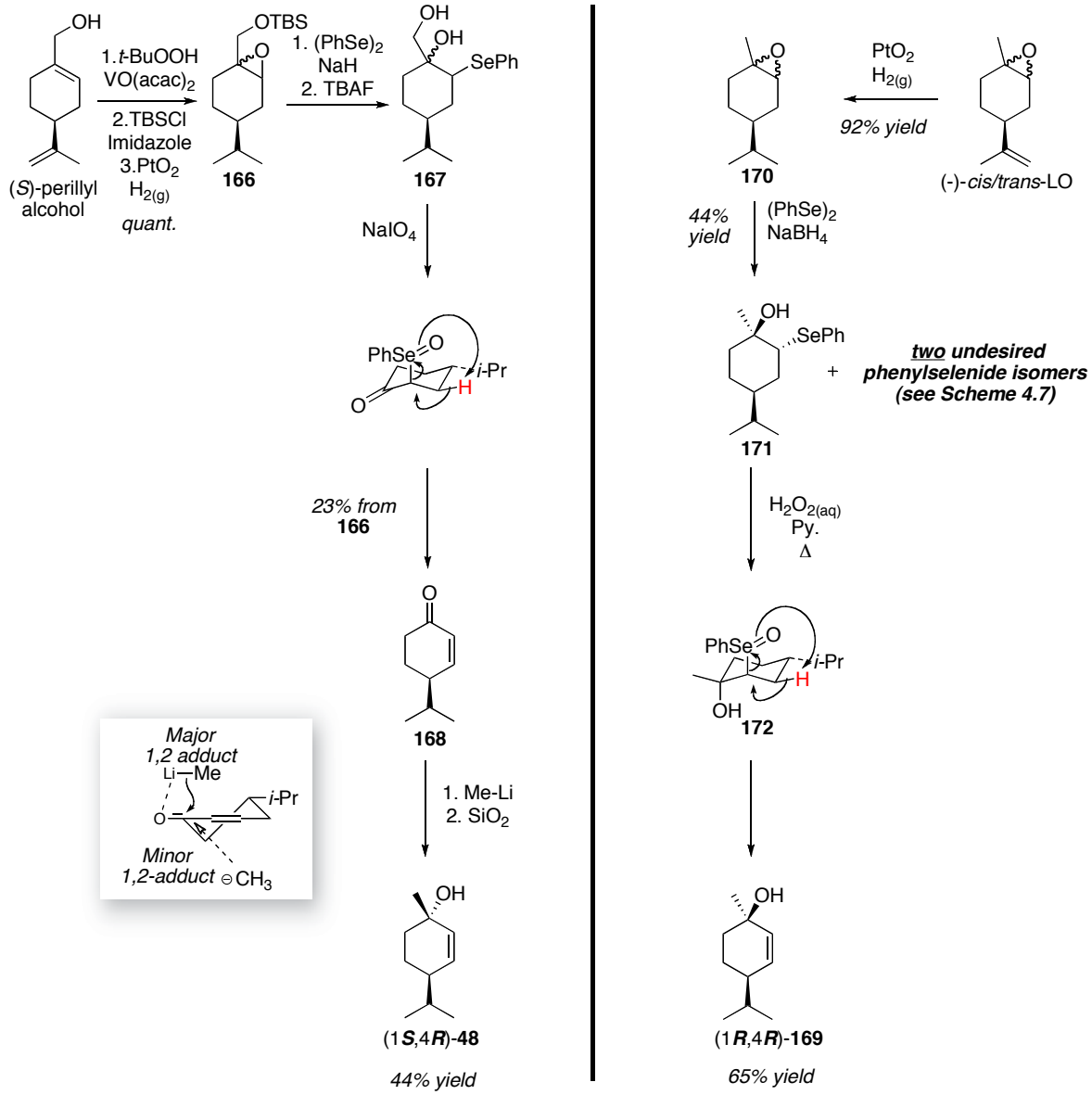
Elimination of organoselenoxides to form alkenyl substrates is another example of a modernized reaction protocol which circumvents the elimination of protonated alcohols to form alkenes. The degradation of an activated selenoxide **163** *via* the oxidation (i.e. hydrogen peroxide (H_2O_2), $NaIO_4$, *m*CPBA etc.) of the phenylselenide **164** was utilised *en route* to (*S*)-1-methyl-2-cyclohexen-1-ol **165**, a constituent of the aggregation pheromone of *Dendroctonus pseudotsugae* (Scheme 4.4).[128] The reaction proceeds *via* a thermally driven *syn*-phenylselenoxide elimination to reveal the allylic alcohol of the natural product.



Scheme 4.4: Sharpless' selenoxide decomposition chemistry for the synthesis of methyl-2-cyclohexen-1-ol 165[128]

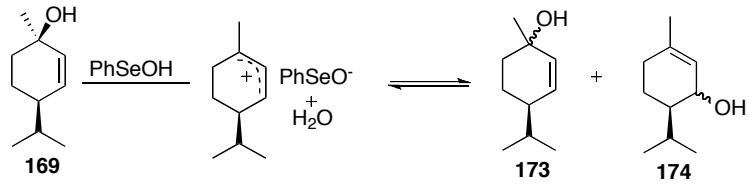
Mori's total synthesis of the major and minor pheromones of the frass volatiles isolated from the *Platyputus quercivourous*, namely *4-isopropyl-1-methyl-2-cyclohexen-1-ol* (i.e **48**), employed two distinctly different routes to prepare the respective isomers, *via* a selenoxide elimination (Scheme 4.4).[127] The first of Mori's syntheses of the pheromone **48**, utilized the chiron, (*S*)-perillyl alcohol to access the optically active isoprenyl group contained at the C4 position along with the monoterpene framework (Scheme 4.5). A *t*-BuOOH/vanadyl acetoacetate ($VO(acac)_2$) catalysed endocyclic selective epoxidation of (*S*)-perillyl alcohol followed by silylation and lastly PtO_2 catalysed hydrogenation of the remaining *exo*-olefin afforded the TBS-epoxide **166**. A regioselective oxirane opening with sodium phenylselenide (formed *via* the treatment of diphenyldiselenide $(PhSe)_2$ in

THF/HMPA with sodium hydride), and cleavage of the TBS-ether revealed the diol **167**. A one pot oxidative cleavage of the vicinal diol **167** followed by oxidation of the intermediate selenide and subsequent elimination at ambient temperature revealed the cyclohexenone **168** in 23% over 3-steps from the TBS-epoxide **166**. Completion of total synthesis was executed *via* the installation of the required C1-oxygenated quaternary stereocentre, *via* a 1,2-addition of methyl lithium with **168** in the presence of lithium bromide. This gave the (1*S*,4*R*) isomer **48** after separation on silica gel (SiO_2), albeit in low yields (44%) and diastereoselectivity which was unspecified by Mori.[127]



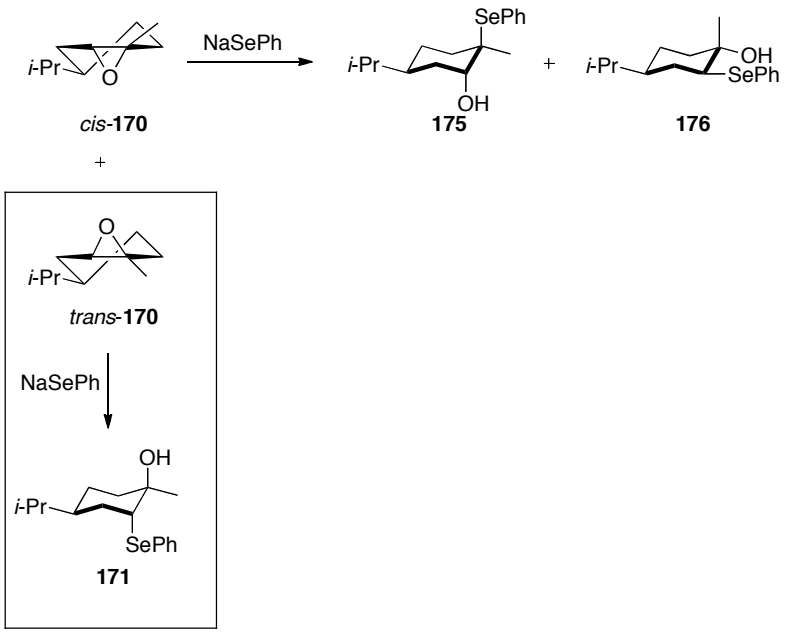
Scheme 4.5: Mori's common selenoxide elimination to the synthetic pheromones 48 & 169[127]

The minor pheromone (1*R*, 4*R*)-**169** (Scheme 4.5) was accessed from the commercial mixture of (**-**)-*cis/trans*-LO. Hydrogenation in the presence of Adam's catalyst (PtO_2) and nucleophilic opening of the oxirane *cis*/*trans*-**170** with sodium phenylselenide (formed from diphenyldiselenide $(PhSe)_2$ and $NaBH_4$) revealed both a diastereo- and regio-meric mixture of selenohydrins. The desired isomer **171**, was isolated *via* chromatography of the reaction mixture on SiO_2. An alternate protocol was employed for the oxidative elimination of the selenoxide **172**; utilizing hydrogen peroxide in the presence of pyridine, resulted in higher selectivity for the desired allylic alcohol **169**. In the absence of pyridine, a complex mixture of rearrangement isomers ensued (Scheme 4.6; **173** and **174**). The role of pyridine in this reaction was essential to buffering the phenylselenic acid (PhSeOH) by-product, circumventing the protonation/elimination reaction of the labile tertiary allylic alcohol of **169**.[127]



Scheme 4.6: Acid catalysed allylic alcohol rearrangement in the presence of PhSeOH[127]

As Mori did not perform a separation of the *cis*/*trans*-**170** prior to the nucleophilic opening with sodium selenide, the intrinsic relative reactivities of *cis* and *trans* alkyl substituted cyclohexene oxides (*see* Chapter 2), expectedly gave rise to a mixture of selenohydrins **171**, **175** and **176** (Scheme 4.7).[127] Mori notes that the *trans*-**170** reacts with a higher regioselectivity to afford the desired *trans*-diaxial selenohydrin **171**; whilst the *cis*-**170**, reacts to yield an unspecified regioisomers of *trans*-diaxial **175** and *trans*-diequatorial **176** selenohydrins.[127] The latter *trans*-diequatorial selenohydrin **176** arises from a high-energy twist boat nucleophilic opening of *cis*-**170**; thus, it can be assumed that the *trans*-diequatorial selenohydrin **176** is formed to a lesser extent.[44]

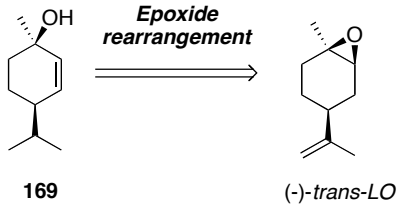


Scheme 4.7: Sodium selenide opening of cis/trans 170[127]

Mori's achieved the first total synthesis of the pheromones **48** and **169**, however his syntheses were marred by diastereo- and regio-selectivity issues particularly the nucleophilic introduction of the phenylselenide group and installation of the oxygenated quaternary centre. A second-generation synthesis was aimed to address these issues, whilst providing a general route to all four possible natural and unnatural stereoisomers of *4-isopropyl-1-methyl-2-cyclohexen-1-ol.*

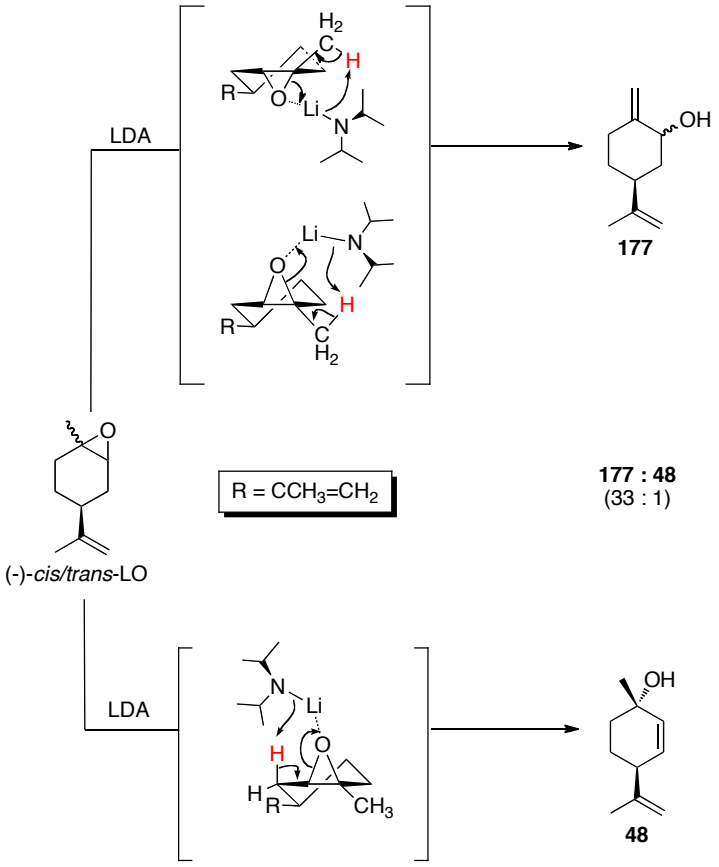
4.4 Epoxide Rearrangements to Allylic Alcohols

It was recognized that an exceedingly short route to the pheromones (i.e **169**) could be potentially accessed *via* an epoxide rearrangement (Scheme 4.8) from either one of our kinetically enriched epoxides described in Chapter 2.



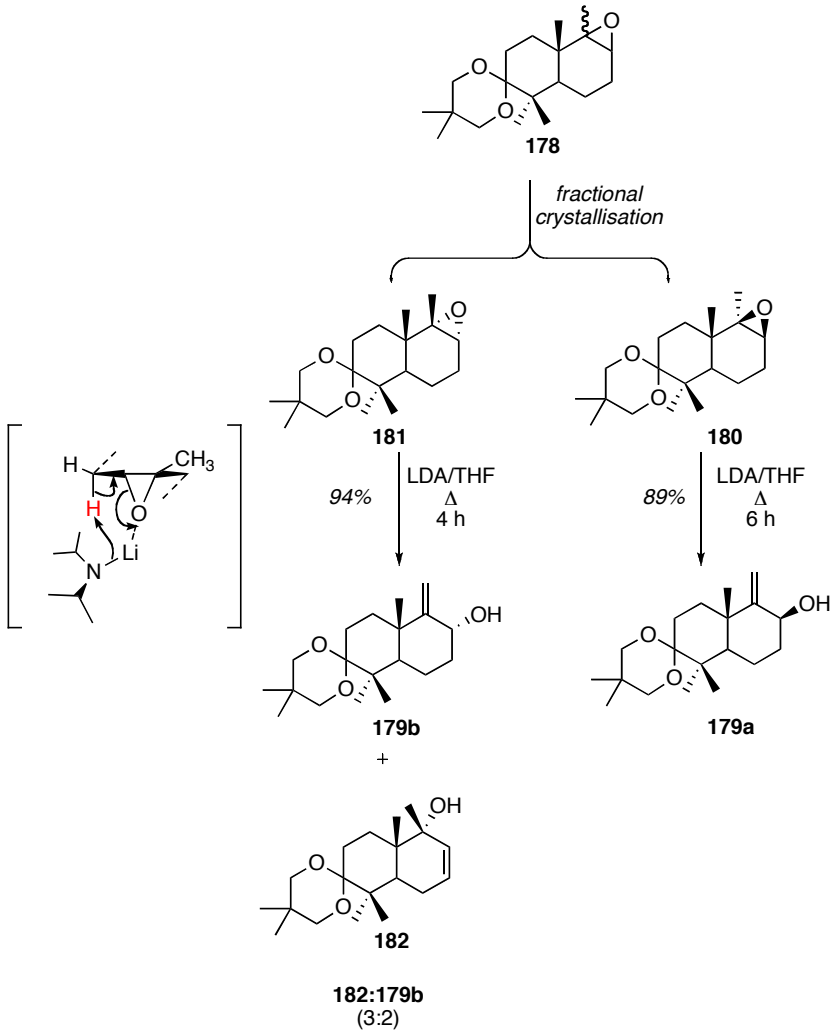
Scheme 4.8: Retrosynthetic analysis of 169

The base induced isomerisation of cyclohexene oxides to allylic alcohols is an extensively studied reaction,[129, 130] and in general proceeds via the β-deprotonation of an epoxide, followed by isomerisation to the corresponding allylic alcohol. A survey of the literature revealed that this transformation was indeed possible on the limonene oxide starting material; however, the reaction proceeds with the undesired regioselectivity, giving almost exclusive access to the *exo*-alkene **177** (Scheme 4.9).[131] The proposed selectivity of the β-elimination is said to occur from the least substituted carbon.[129] However, this process is influenced upon by factors such as steric demand of the lithium amide base in regards to the epoxide substrate, and the relative configuration of the β-proton with respect to the coordinated base (Scheme 4.9, *syn*-facial protons colourised in red). In the case of *cis*/trans-LO, deprotonation occurs almost entirely at the 1-methyl substituent, depicted in Scheme 4.9.[131] The low amount of the desired tertiary endocyclic allylic alcohol **48** formed, is believed to arise from a *syn*-planar abstraction of the *pseudo* axial proton; this *syn*-planar requirement restricts this process exclusively to the *cis*-isomer of limonene oxide. *Exo*cyclic abstraction of a β-methyl proton and subsequent rearrangement is common to both *cis*- and *trans*-1,2-epoxides of limonene.



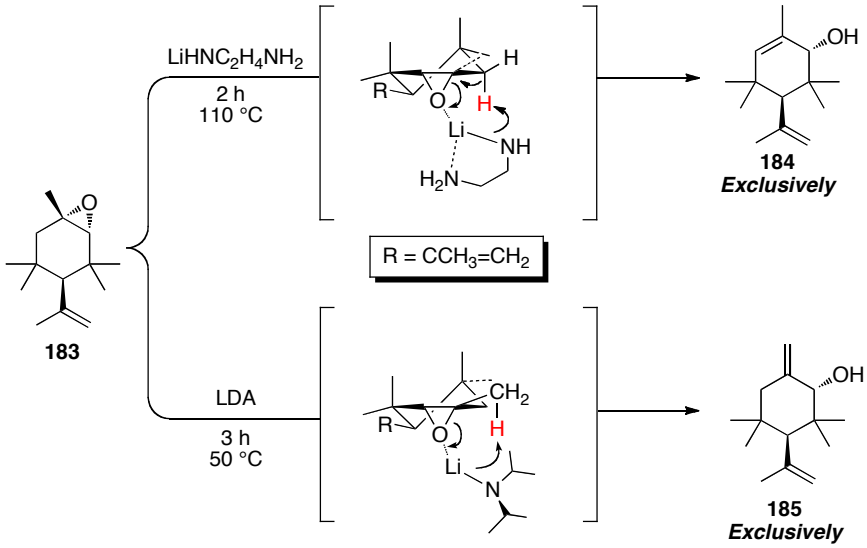
Scheme 4.9: The LDA mediated rearrangement of cis/trans-LO[131]

Heathcock and co-workers exploited the kinetic phenomenon of *syn*-facial deprotonation in their synthesis of the AB ring precursors **178** of pentacyclic triterpenes (Scheme 4.10), and were able to selectively form the *exo*-alkene **179a** from the diastereomerically pure epoxide **180**. Rearrangement of the epoxide **181** afforded a 3:2 mixture of endocyclic allylic alcohols **179b** and **182** (Scheme 4.10).[132]



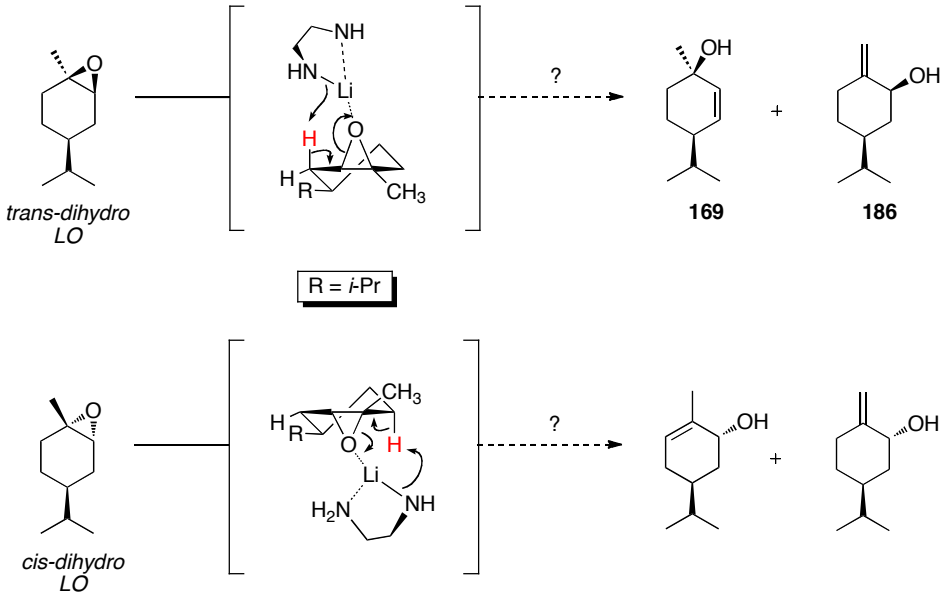
Scheme 4.10: Heathcock's rearrangements of the AB steroid precursor 178[132]

As mentioned, the steric requirement of the lithium amide base has been demonstrated to play an important role in the regioselectivity of the elimination process. When a sterically non-demanding base such as *N*-lithiodiaminoethane was applied to the tetramethyllimonene **183**, complete regio-control occurred to the corresponding endocyclic allylic **184**; whereas, the use of LDA in place of *N*-lithiodiaminoethane furnished the predicted *exo*-allylic alcohol **185** (Scheme 4.11).[133]



Scheme 4.11: N-Lithiodiaminoethane mediated rearrangement tetramethyllimonene 183[133]

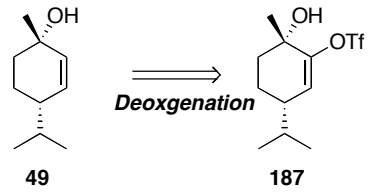
Considering both the steric and stereochemical requirements for the selection of base and substrate respectively, i.e the *trans*-epoxide to undergo a *syn*-planar deprotonation with an unhindered base to yield **169**, whilst the *cis*-isomer would lead to the undesired endocyclic secondary allylic alcohol **186** (Scheme 4.12). The unpredictability of regioisomer control, and separation of the resulting mixture, prompted us to search elsewhere for a general, yet novel strategy towards the tertiary *endo*-cyclic allylic alcohol contained within the of *4-isopropyl-1-methyl-2-cyclohexen-1-ol* natural products.



Scheme 4.12:The theoretical N-lithiodiaminoethane rearrangement of cis- and trans-LO

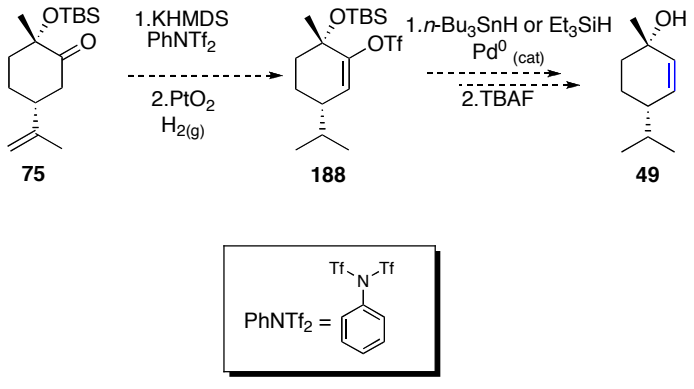
4.5 Palladium Catalysed Deoxygenation of Enol Triflates to Endocylic Olefins

Retrosynthetic analysis of the tertiary allylic alcohol contained within the natural product **49** (or its diastereoisomer **169**) identified that a deoxygenation sequence could be potentially applied to the vinyl triflate substrate **187**, derived from either of the chiral limonene diol **45** (see Chapter 2), shown in Scheme 4.13.



Scheme 4.13: A Pd catalysed deoxygenation approach to the pheromone 49

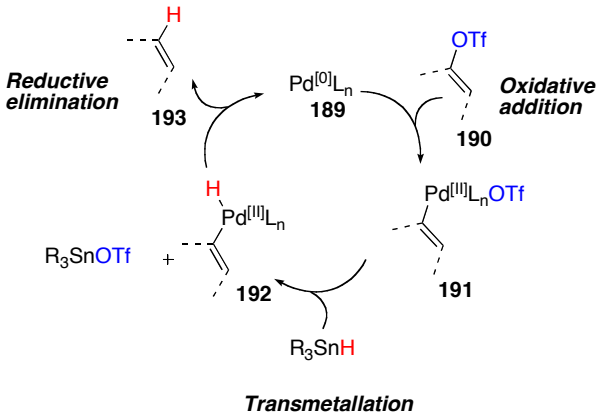
Furthermore, it was recognised that a key intermediate *en route* to 2-*epi*-Prevezol C **47**, namely the TBS-ketone **75** (Scheme 4.13), could serve as the de-oxygenation precursor to the pheromone **49**. Thus, utilizing a two step sequence involving the formation of a vinyl triflate **188** from the corresponding TBS-ketone **75** followed by a palladium catalysed reduction of the vinyl triflate **188** in the presence of a hydride source, (typically a trialkylstannane or silane) and lithium chloride should give access to the allylic alcohol contained within the pheromones **49** (or its diastereoisomer **169**), as outlined in Scheme 4.14.



Scheme 4.14: Proposed synthetic route to the pheromone 49 from the TBS-ketone 75

It is believed the catalytic cycle responsible for the palladium catalysed reduction and cross coupling of vinyl triflates involves the general mechanism described in Scheme 4.15. Oxidative insertion of the Pd(0) **189** species into the vinyl triflate **190** yields the vinyl

palladium species **191**, followed by transmetallation with an appropriate hydride donor, i.e. trialkyltin hydride, and finally loss of trialkyltin triflate to yield the palladium hydride intermediate **192**. Reductive elimination of the alkene **193** and simultaneous regeneration of the active Pd(0) **189** catalyst species resets the catalytic cycle.[134]

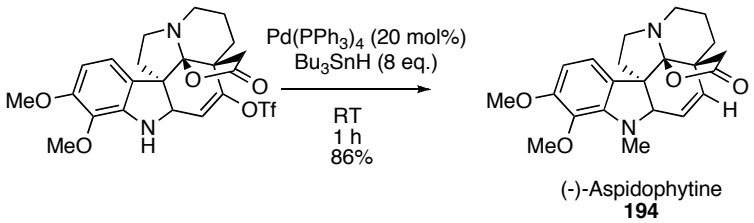


Scheme 4.15: The generally accepted palladium catalysed cycle for the reduction/cross coupling of vinyl triflates

*The preparation of the advanced vinyl triflate intermediate is detailed in a full paper published in Tetrahedron: Asymmetry and is reproduced at the end of this chapter. As a result, this discussion will now be limited to the selection of the appropriate reducing species which facilitated the synthesis of the pheromone **49**.*

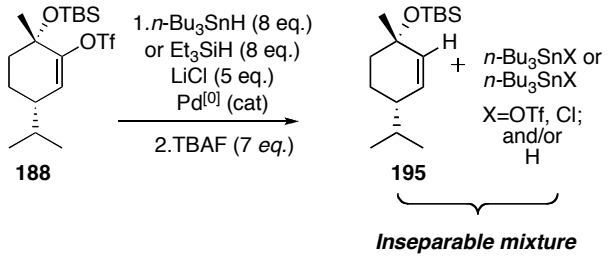
4.6 Conditions for the Reduction of Vinyl Triflates

It was recognized that *n*-tributyltin hydride could serve as the transfer hydrogenation donor as demonstrated by Corey and co-workers in their final step in the preparation of the complex natural product, (-)-aspidophytine **194** (Scheme 4.16).[135]



Scheme 4.16: Corey's preparation of aspidophytine via a Pd catalysed deoxygenation reaction[135]

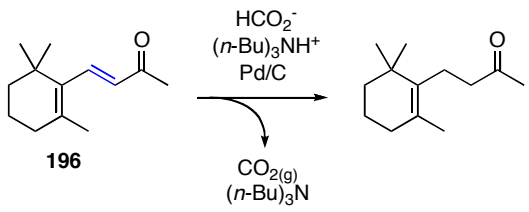
The application of Corey's protocol to our substrate did indeed affect the smooth and rapid deoxygenation of the vinyl triflate **188** substrate, however this procedure was marred by the extreme difficulty associated with the separation of a superstoichiometric quantity of the stannane reductant from the desired latent allylic alcohol **195** when applied to our vinyl triflate substrate **188** (Scheme 4.17). Chromatographic removal of the tributylstannane was unsuccessful due to the strikingly similar R_f values on silica gel of the reduced TBS-pheromone **195** and unreacted tributyltin hydride. Employing fluorolytic removal (precipitation of tributyltin fluoride *via* the reaction between aqueous KF in a bi-phasic ethereal solution) and subsequent purification by distillative methods were unfruitful due to the high boiling points tributyltin chloride and hydride.[136, 137] This is unlike the volatile trimethyltin hydride or its water soluble trimethyltin chloride congener.[138] Employing triethylsilane in place of tributyltin hydride also reduced the vinyl triflate **188** smoothly, however this route was met with similar purification difficulties. In a final attempt to isolate the TBS-pheromone **195** an *in situ* deprotection of the TBS group was performed on the organic extracts of the reaction mixture by treatment with an excess of TBAF (7 molar eq.) to amplify the differences in R_f values of the desired product and the undesired stannanes on silica gel. It was hoped excess TBAF would also aid the precipitation of tributyltin fluoride in a similar manner to aqueous KF; this however not the case, and the deprotected pheromone **195** was not obtained by this route.



Scheme 4.17: Unsuccessful chemical derivatisation methods of the inseparable reaction mixture

The chromatographic difficulties associated with the separation of *n*-tributylstannane from the reduced TBS-pheromone **195**, not to mention severe toxicity both to the user and the environment, prompted us to search for a safer hydride donor to perform this reduction. A requirement for such a reagent system to perform this task needed to offer both a preparatively straight forward work-up/isolation of the reduced species **195**, whilst providing increased atom economy over the conventional superstoichiometric amount (8 molar eq. of *n*-Bu_3SnH or Et_3SiH).

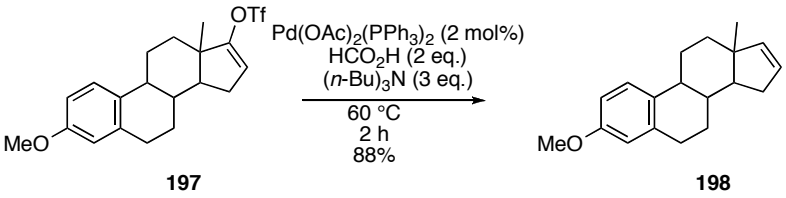
Heck and co-workers, have demonstrated the application, and utility of trialkylammonium formate as a transfer hydrogenation reagent in the presence of palladium in the reduction of complex substrates such as acetylenes and α,β-unsaturated carbonyl compounds **196** (Scheme 4.18). [139, 140]



Scheme 4.18: Heck's transfer hydrogenation of 196[13]

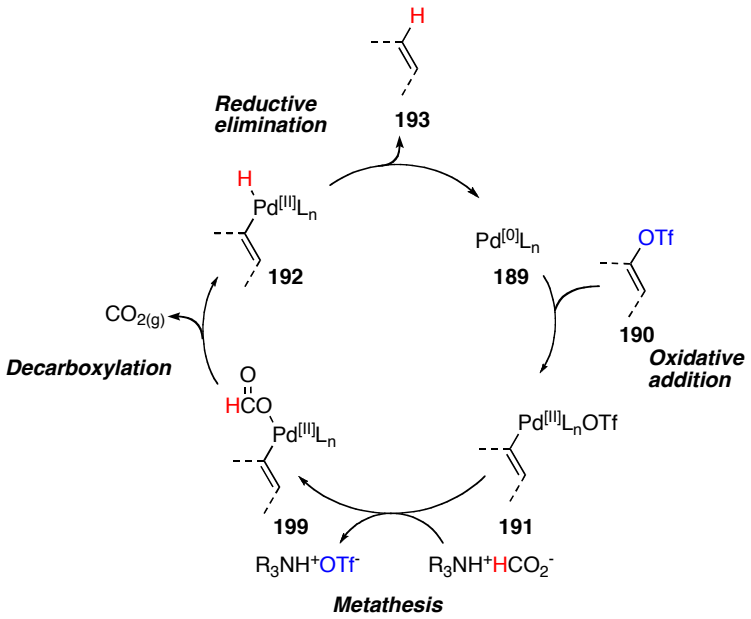
Following this work, and the work of others,[134] Cacchi and co-workers demonstrated that this mild, selective reducing system could be applied to the reduction of vinyl triflates substituting the in vogue *n*-trialkylstannane/silane reagents. This mild transformation was demonstrated on a range of steroidal vinyl triflates. For instance, a selected reduction of

the estronemethylether vinyl triflate derivative **197** under palladium catalysed transfer hydrogenation conditions yielding the alkene **198**, is depicted below in Scheme 4.19.



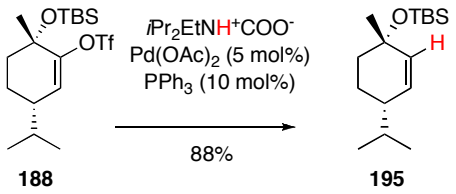
Scheme 4.19: Cacchi and co-workers transfer hydrogenation of vinyl triflate 197[141]

The proposed mechanism for Pd catalysed transfer hydrogenation of vinyl triflates follows the general reaction mechanism depicted in Scheme 4.20. The catalytic cycle begins by the oxidative insertion of the vinyl triflate **190** into the Pd(0) **189** species with a general structure **191**. A metathesis reaction expels the trialkylammonium triflate salt, whilst generating the formylated Pd(II) species **198**. Decarboxylation of the palladium formate **199**, reveals the Pd(II) hydride **192**; reductive elimination releases the olefin **193** and simultaneously regenerating the Pd(0) species **189** and resets the catalytic cycle.[134]



Scheme 4.20: Pd-catalysed transfer hydrogenation of a vinyl triflate 198[134]

As seen in the catalytic cycle depicted above (Scheme 4.20), the major by-products (trialkylammonium formate and CO_2) are benign, and readily removed from the reaction mixture with minimal effort. This was indeed the case when a modified variant of the protocol of Cacchi *et al.* was applied to our substrate **188**.[141] Utilizing diisopropylethylammonium formate, in the presence of the $Pd(OAc)_2(PPh_3)_2$ species (generated *in situ* by reaction between $Pd(OAc)_2$ (5 mol%) and triphenylphosphine (10 mol%)) in DMF, smoothly reduced the vinyl triflate **188** over 2 h at 70 °C (Scheme 4.21).[141] This protocol revealed the TBS-pheromone **195** in excellent isolated yields after its elution through a silica gel plug.



Scheme 4.21: Pd cataylsed transfer hydrogenation of the vinyl triflate 188[43]

Application of Cacchi and co-workers protocol finally granted access to the synthetic pheromones **48** and **49**. This demonstrated for the first time that under facile reaction conditions, with minimal purification, the vinyl triflate **187** could serve as a masked tertiary allylic alcohol utilizing the sequence described above. Importantly this strategy to endocyclic allylic alcohols isn't marred with toxic and difficult to remove by-products such as stannanes or organoselenic acids; whilst, offering a mild and selective method for the installation of alkenes into natural products. For an account of the total synthesis of the pheromones **48** and **49,** please refer to the full publication entitled: "*A new diastereoselective entry to the (1S,4R)- and (1S,4S)-isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol, aggregation pheromones of the ambrosia beetle Platypus quercivorus*" appended at the end of this chapter.

Monash University

Declaration for Chapter 4, Paper 4: "A new diastereoselective entry to the (1S,4R)- and (1S,4S)-isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol, aggregation pheromones of the ambrosia beetle Platypus quercivorus" Tetrahedron: *Asymmetry*, 20, 2009, 2149-2153

Declaration by candidate

In the case of Chapter 4, Paper 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Experimental design, execution of reaction(s), characterisation/isolation of reaction products and manuscript preparation/editing	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
K. L. Tuck	Research guidance/experimental design, financial support, manuscript preparation/editing	

Candidate's Signature [redacted] **Date:** 26/11/09

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) Monash University Clayton, School of Chemistry

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	**Date**
Signature 2		26/11/09

Tetrahedron: Asymmetry 20 (2009) 2149–2153

Contents lists available at ScienceDirect

Tetrahedron: Asymmetry

journal homepage: www.elsevier.com/locate/tetasy

A new diastereoselective entry to the (1*S*,4*R*)- and (1*S*,4*S*)-isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol, aggregation pheromones of the ambrosia beetle *Platypus quercivorus*

Michael Blair, Kellie L. Tuck*

School of Chemistry, Monash University, Clayton, VIC 3800, Australia

ARTICLE INFO

Article history:
Received 16 July 2009
Accepted 11 August 2009
Available online 14 September 2009

ABSTRACT

A concise diastereoselective and enantiopure route to the (1*S*,4*R*)- and (1*S*, 4*S*)-isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol via a palladium-catalysed deoxygenation of the enol triflate derived from limonene glycol.

1. Introduction

Over the past two decades, the epidemic mortality of the deciduous oak *Quercus crispula* has posed a significant threat to Japan's forest ecosystem.[1] The dieback is caused by the fungus *Raffaela quercivorus*, which is transmitted by the ambrosia beetle *Platypus quercivorus* (Murayama). It has recently been revealed that the invasion of *Q. crispula* and subsequent boring by the beetles are mediated by the semiochemicals (1*S*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol (*cis*-2-menthen-1-ol, **1**), and (1*S*,4*S*)- and (1*R*,4*R*)-4-isopropyl-1-methyl-2-cyclohexen-1-ol (*trans*-2-menthen-1-ol, **2** and **2′**) (Fig. 1), first isolated and reported by Nakashima et al.[2] The isomer (1*S*,4*R*)-**1** is the major aggregation pheromone of the ambrosia beetle. (1*S*,4*S*)-**2** and (1*R*,4*R*)-**2′** were also identified as minor components of *P. quercivorus*, although their precise semiochemical role is yet to be determined.

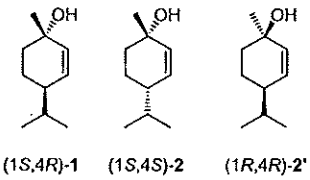
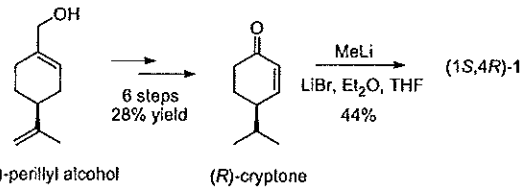


Figure 1. The frass volatiles of *P. quercivorus*.

Mori confirmed the absolute stereochemistry via the total synthesis of all three of these pheromones **1**, **2** and **2′**,[3] thus allowing field bioassays to be conducted on the synthetic pheromone (1*S*,4*R*)-**1** and confirming its role as a conspecific beetle aggregation sex pheromone. The (1*S*,4*R*)-**1** isomer lured 14.4 times as many ambrosia beetles (*P. quercivorus*) versus any other beetle species, and 3.32 times as many males to females.[4]

The synthesis of highly enriched single enantiomers of these molecules **1** and **2** has not been facile.[3] Base-promoted isomerisation of epoxides typically leads to the undesired *exo*-alkene.[5] The (1*S*,4*R*)-**1** isomer can be synthesised in one step by methylation of (*R*)-cryptone. However, this reaction is unselective, and produces a diastereomeric mixture of (1*S*,4*R*)-**1** and (1*R*,4*R*)-**2′** from which (1*S*,4*R*)-**1** could be obtained in a 44% yield after chromatographic purification and distillation (Scheme 1).[3] The enantiomeric purity of (1*S*,4*R*)-**1** was determined as 93.3% ee and it was contaminated with small amounts of (1*R*,4*R*)-**2′**. Furthermore the synthesis of (*R*)-cryptone is accomplished in six steps (28% overall yield), utilising (*S*)-perillyl alcohol as the chiral pool starting material, via a modified literature procedure for the preparation of 4-isopropenyl-2-cyclohexenone.[6]

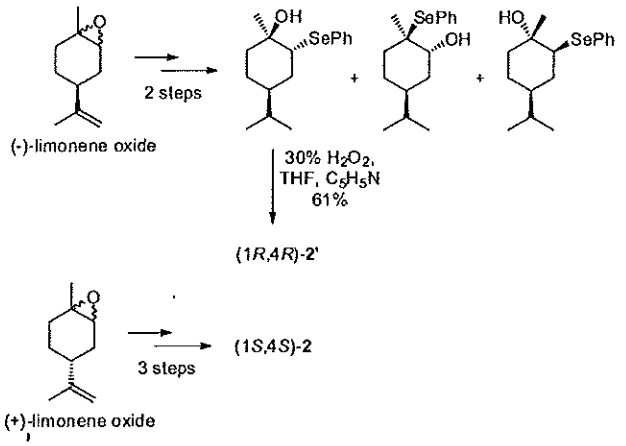


Scheme 1. Mori's methylation of (*R*)-cryptone to afford the synthetic pheromone **1**.[3]

The (1*S*,4*S*)-**2** and (1*R*,4*R*)-**2′** isomers were synthesised by Mori from the desired enantiomer of limonene oxide (3:2 mixture of *cis*- and *trans*-diastereomers) utilising Sharpless' organoselenium chemistry on dihydrolimonene oxide (Scheme 2). A regio- and diastereomeric mixture of phenylselenohydrins was obtained, from which the desired selenide could be separated by chromatography. The presence of pyridine was essential for the success of the

* Corresponding author. Tel.: +61 3 99054510; fax: +61 3 99054597.
E-mail address: kellie.tuck@sci.monash.edu.au (K.L. Tuck).

0957-4166/$ - see front matter Crown Copyright © 2009 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.08.009

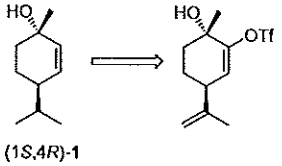


Scheme 2. Mori's synthetic strategy for accessing the minor constituents.

selenoxide elimination, otherwise acid-catalysed allylic rearrangement products of **2** ensued. The enantiomeric purity of (1*S*,4*S*)-**2** and (1*R*,4*R*)-**2'** was 94.5% and 94.3%, respectively.[3]

In light of the problems associated with the current synthesis, we hoped to gain access to the pheromones (1*S*,4*R*)-**1** and (1*S*,4*S*)-**2** both enantiomerically and diastereomerically pure via the hydrolytic by-products isolated from the kinetic separation of the commercial mixture of *cis* and *trans* (+)- or (−)-limonene oxide.

Limonene oxide has only recently begun to enjoy widespread use as a chiral pool reagent, unlike other monoterpene building blocks popularised in total synthesis such as carvone,[7] peryillyl alcohol,[8] isopulegol[9] and limonene.[10] We believe that limonene oxide has not been adopted as an enantiomerically pure building block in total synthesis because the commercially available (+)- or (−)-limonene oxide is a diastereomeric mixture (approximately a 1:1 mixture of *cis* and *trans* epoxides) and there are relatively few practical and preparative routes to obtain the desired diastereoisomer.[11–13] Recently we reported a highly diastereoselective hydrolytic kinetic separation of the commercial mixture of *cis* and *trans* limonene oxide to afford either *trans*-diequatorial-1,2-dihydrolimonene or *trans*-diaxial-1,2-dihydrolimonene, depending on the reaction protocol employed.[14] Herein, we report a highly diastereoselective, novel second total synthesis of the volatile pheromones (1*S*,4*R*)-**1** and (1*S*,4*S*)-**2** of the beetle *P. quercivorus* utilising either the *trans*-diaxial diol or the *trans*-diequatorial diol as the chiral pool building block (Scheme 3). The key step in the synthetic route was a Stille type reduction of the enol triflate with an organostannane/silane (Scheme 4). The deoxygenation of ketones to the corresponding olefin via a $Pd^{[0]}$catalysed enol triflate reduction has been well studied,[15] and it was anticipated that we could utilise similar chemistry in the synthesis of the pheromones **1** and **2**. If successful, this would be a novel route for the synthesis of tertiary endocyclic allylic alcohols, which is complementary to the organoselenium chemistry.



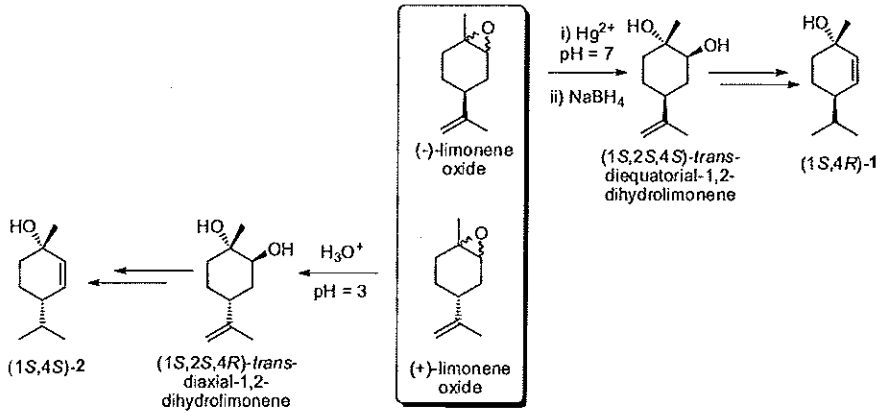
Scheme 4. Key synthetic strategy for the synthesis of compounds **1** and **2**.

2. Results and discussion

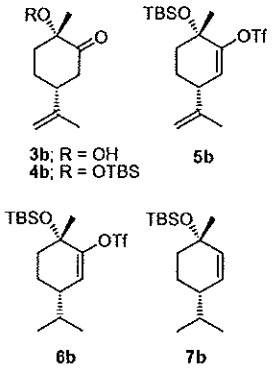
2.1. Total synthesis of the (1*S*,4*R*)- and (1*S*,4*S*)- isomers of 4-isopropyl-1-methyl-2-cyclohexen-1-ol

Our initial attempts to synthesis the required enol triflate were with the unprotected analogue (Scheme 4). The first step was oxidation of the (1*S*,2*S*,4*S*)-*trans*-diequatorial diol to the corresponding hydroxy ketone **3a**. Standard oxidation conditions for secondary alcohols, pyridinium chlorochromate (PCC), Swern conditions and TEMPO/TCCA gave poor product purity and yields of the ketol **3a**. The use of IBX (*o*-iodoxybenzoic acid)[16] gave superior yields and product purity (>95%) while ketol **3a** was typically used without further purification (Scheme 5). Ketol **3b** was obtained in excellent yields using the same conditions.

Our attempts to synthesise the enol triflate directly from either ketol **3a** or **3b** using KHMDS (2 equiv) and *N*-phenylbistrifluorosulfonamide ($PhNTf_2$) were unsuccessful. The corresponding *tert*-butyldimethylsilyl derivatives **4a** and **4b** reacted cleanly under similar conditions, but with 1 equiv of base, to give either the *tert*-butyldimethylsilyloxy enol triflate **5a** or **5b**. Selective reduction of the *exo*-cyclic olefin was achieved with Adam's catalyst (PtO_2)[3] under an atmosphere of hydrogen. Under these conditions, racemisation of the 4-position of the enol triflates **6a** and **6b** does not occur.[17]



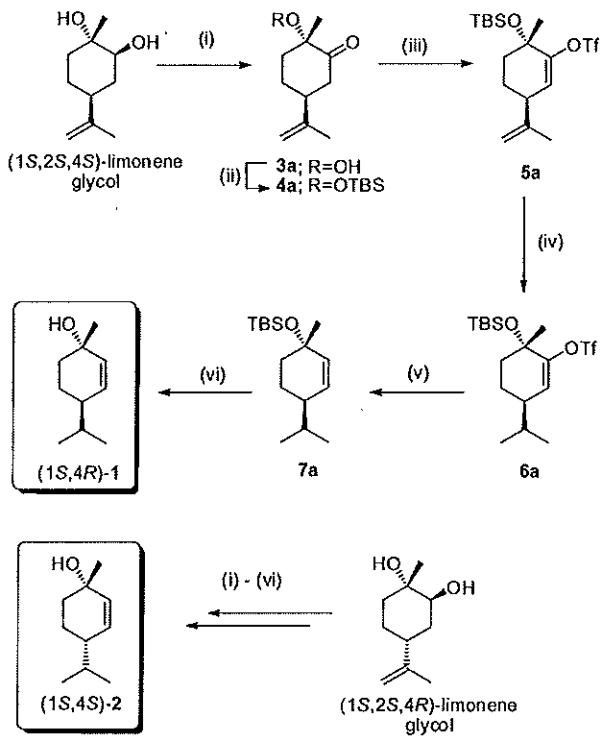
Scheme 3. Complementary routes to compounds **1** and **2** from (+)- or (−)-limonene oxide.



The synthesis of the *endo*-cyclic allylic ether **7a** or **7b** by Stille reduction of the enol triflate was successful [$Pd(PPh_3)_4$ (20 mol %), LiCl and 5 M equiv of either Bu_3SnH or Et_3SiH, in DMF at 75 °C, 2 h,[18] as determined via ^1H NMR analysis of the crude reaction sample. However, the excess starting material and by-products of the reaction (Bu_3SnH/Bu_3SnCl or Et_3SiCl) could not be removed by chromatography due to the similarity of their polarity to the TBS-protected pheromone **7a** or **7b** on silica. Fluorolytic methods ($KF_{(aq)}$ or 10% KF/silica) to remove the excess Bu_3SnCl or Et_3SiCl were investigated; however, neither of these were successful.[19,20] In an effort to separate the alkylsilanes or stannanes, an in situ deprotection of **7a** and **7b** was attempted, thus allowing their separation from the pheromone. However, even 7 equiv of TBAF and prolonged heating were unsuccessful in removing the *tert*-butyldimethylsilyl protecting group. This is presumably due to a competing side reaction of TBAF with residual organostannanes/silanes.

An alternate reagent for the palladium-catalysed reduction of enol triflates is a trialkylammonium formate–palladium complex.[21–23] This reagent can be used for the efficient and straightforward reduction of enol triflates to alkenes, it is also tolerant of a wide range of functional groups including tertiary alcohols and esters. Treatment of enol triflate **6a** or **6b** with HCO_2H and PPh_3 in the presence of $Pd(OAc)_2$ and PPh_3 gave the desired olefin in good yields after a simple extraction and elution through a short silica plug in neat hexane.

Finally, the *tert*-butyldimethylsilyloxy pheromone **7a** or **7b** was deprotected; TBAF (1.5 equiv) in refluxing THF gave the synthetic pheromones (1*S*,4*R*)-**1** or (1*S*,4*S*)-**2**, respectively, in excellent yields (>90%). No racemisation, which would produce diastereomers, was observed throughout the synthesis. The enantiomeric excess of the pheromones (1*S*,4*R*)-**1** or (1*S*,4*S*)-**2** was 98–99% ee, identical to that of the chiral pool reagent (+)- or (−)-limonene oxide. Furthermore, we have established an alternate route for the synthesis of tertiary allylic alcohols that does not use the conventional organoselenium chemistry.



Scheme 5. Total synthesis of the synthetic pheromones **1** and **2**. Reagents and conditions: (i) IBX, EtOAc, reflux, **3a** 93%, **3b** 98%; (ii) TBSOTf, 2,6-lutidine, DCM, −78 °C to rt, **4a** 61%, **4b** 99%; (iii) KHMDS, THF, −78 °C then $PhNTf_2$, −78 °C to rt, **5a** 91%, **5b** 82%; (iv) 1 mol % PtO_2, H_2, MeOH, **6a** 75%, **6b** 88%; (v) 5 mol % $Pd(OAc)_2$, PPh_3, DIPEA, formic acid, DMF, 70 °C, **7a** 75%, **7b** 88%; (vi) TBAF, THF, reflux, **1** 81%, **2** 91%.

3. Conclusion

The pheromones (1*S*,4*R*)-*cis*-2-menthen-1-ol **1** and (1*S*,4*S*)-*trans*-2-menthen-1-ol **2** were synthesised in high diastereoselectivity (>98% de), enantiomeric purity (98–99% ee) and good overall yields (32% **1**, 45% **2** from *trans*-1,2-dihydrolimonene). Utilising this synthetic sequence, the synthesis of all components of the volatiles of *P. quercivorus* in high enantiomeric purity is now possible. This will facilitate further field studies on the roles of the minor constituents of *P. quercivorus*, which will aid in evaluating their activity, with the eventual hope of improved trapping techniques being developed, thereby addressing the invasion and epidemic mortality of the deciduous oak *Q. crispula* by the ambrosia beetle.

4. Experimental

4.1. General

All reagents were purchased from the Aldrich Chemical Co. and used without further purification. Solvents were dried, when necessary, by standard methods. Organic solutions were dried over $MgSO_4$. The progress of the reactions was monitored by thin layer chromatography (TLC) on Merck 60 F240 precoated silica gel polyester plates, and products were visualized with vanillin dip. Flash chromatography was performed with Davisil LC60A, 40–63 μm silica media.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ on either a Bruker AM300, Bruker AV400 or Varian DRX 500 spectrometer operating at 300, 400 and 500 MHz, respectively, for proton and 75, 100 and125 MHz for carbon nuclei. Chemical shifts (δ) are expressed in parts per million (ppm) and referenced to residual solvent signal as the internal standard. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer RXI FTIR Spectrometer as thin films on NaCl plates. Low resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on either a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration or a Waters GC-TOF. Low resolution (EI) mass spectra were recorded on a VG Micromass 70/70F mass spectrometer with an ion source temperature of 200 °C and electron impact energy of 70 eV. Optical rotations were obtained using a PolAAR 2001 automatic polarimeter, using a 1 dm cell with chloroform as a solvent, at a wavelength of 589 nm (sodium D line).

4.2. (2*S*,5*S*)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 3a

To a solution of *trans*-diequatorial-1,2-dihydrolimonene[14] (1.47 g, 8.63 mmol) in EtOAc (40 mL) was added iodoxybenzoic acid (IBX) (6.28 g, 22.4 mmol). After the heterogeneous solution was refluxed for 12 h, it was cooled to ambient temperature and filtered through a sintered funnel. The residue was washed with EtOAc (20 mL), the filtrate dried and concentrated in vacuo to afford the *title compound* as a colourless oil (1.36 g, 93% yield), which was typically used without further purification. An analytical sample was obtained by purification of a small portion by flash column chromatography (25% EtOAc: 75% hexanes). $[\alpha]_D^{20} = +2.5$ (*c* 1.0 $CHCl_3$). ^1H NMR (500 MHz) δ 1.41 (s, 3H), 1.64–1.72 (m, 2H), 1.75 (s, 3H), 1.90 (m, 1H), 2.18 (m, 1H), 2.35–2.40 (m, 2H), 2.52–2.55 (m, 2H), 4.75 (s, 1H), 4.80 (m, 1H). ^{13}C NMR (125 MHz) δ 18.7, 26.5, 30.1, 39.0, 41.3, 42.9, 68.0, 113.2, 145.3, 214.0. IR (film): 3486 (m), 2972 (m), 2856 (w), 1715 (s) cm^{-1}. MS (ESI) *m/z*: 207.10 $(M+K)^+$. HRMS (ESI) calcd for $C_{10}H_{17}O_2$ $(M+H)^+$ *m/z* 169.1223, found: 169.1223.

4.3. (2*S*,5*R*)-2-Hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 3b

The above procedure was repeated with *trans*-diaxial-1,2-dihydrolimonene,[14] the *title compound* was obtained as a colourless oil in a 98% yield. $[\alpha]_D^{20} = -49.2$ (*c* 1.1 $CHCl_3$,). ^1H NMR (500 MHz) δ 1.36 (s, 3H), 1.70 (m, Hz, 3H), 1.75–2.05 (complex, 4H), 2.58 (dd, J = 5.6, 13.6 Hz, 1H), 2.66 (m, 1H), 2.78 (ddd, J = 1.6, 5.4, 13.6 Hz, 1H), 2.96 (br s, 1H), 4.69 (d, J = 0.5 Hz, 1H), 4.86 (d, J = 0.5 Hz, 1H). ^{13}C NMR (125 MHz) δ 21.8, 25.3, 25.5, 37.4, 41.7, 44.3, 75.9, 112.2, 146.3, 213.7. IR (film): 3348 (br s), 3157 (m) 3057 (w), 2860 (w), 1711 (s) cm^{-1}. HRMS (ESI) calcd for $C_{10}H_{16}NaO_2$ $(M+Na)^+$ 191.1043, found: 191.1041.

4.4. (2*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4a

To a solution of the hydroxy ketone **3a** (1.26 g, 7.49 mmol) 2,6-lutidine (2.0 mL, 17.3 mmol) in dry DCM (20 mL), at −78 °C under an atmosphere of nitrogen, was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.2 mL, 3.9 mmol) dropwise. The solution was allowed to warm to room temperature over 1.5 h. The reaction mixture was quenched with cold 1 M $HCl_{(aq)}$ (1 × 20 mL), washed with brine (3 × 20 mL), dried and concentrated in vacuo and subsequently subjected to flash column chromatography (10% EtOAc: 90% hexanes), to afford the *title compound* as a colourless oil (1.29 g, 61%). $[\alpha]_D^{20} = -41.3$ (*c* 2.3, $CHCl_3$). ^1H NMR (200 MHz) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.86 (s, 9H), 1.36 (s, 3H), 1.66 (m, 1H), 1.72 (s, 3H), 1.76 (m, 1H), 1.90–1.97 (m, 2H), 2.39–2.47 (m, 2H), 2.53–2.57 (m, 1H), 4.72 (s, 1H), 4.78 (m, 1H). ^{13}C NMR (125 MHz) δ −2.4, −2.1, 18.6, 21.2, 25.7, 26.2, 27.4, 41.1, 43.6, 45.7, 79.2, 110.7, 147.1, 211.3. IR (film): 2950 (m), 2935 (s), 2856 (m), 1728 (s), 1472 (w), 1462 (m), 1360 (w), 1253 (s), 1207 (m) cm^{-1}.

4.5. (2*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-(prop-1-en-2-yl)cyclohexanone 4b

The above procedure was repeated with the hydroxy ketone **3b**, the *title compound* was obtained as a colourless oil in a 99% yield. $[\alpha]_D^{20} = +59.8$ (*c* 1.25, $CHCl_3$). ^1H NMR (400 MHz) δ 0.02 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.30 (s, 3H), 1.42–1.63 (complex, 2H), 1.73 (s, 3H), 1.95–2.07 (m, 2H), 2.20–2.32 (m, 2H), 2.99 (m, 1H), 4.72–4.76 (m, 2H). ^{13}C NMR (100 MHz) δ −2.9, −1.8, 18.5, 20.6, 23.9, 26.16, 26.23, 41.9, 43.0, 47.6, 110.1, 147.9, 211.7. IR (film): 2857 (s), 1723 (s), 1463 (m), 1375 (m), 1254 (s), 1198 (m) cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{30}NaO_2Si$ $(M+Na)^+$ 305.1913, found: 305.1905.

4.6. (3*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-6-methyl-3-(prop-1-en-2-yl)cyclohex-1-enyl trifluoromethane-sulfonate 5a

A solution of the TBS-ether **4a** (1.10 g, 3.89 mmol) in anhydrous THF (5 mL) was cooled to −78 °C, and potassium bistrimethylsilylamide (0.5 M solution in toluene, 8.6 mL, 4.22 mmol) was added dropwise under an atmosphere of nitrogen; stirring was maintained at this temperature for 30 min, after which *N*-phenyl-bis(trifluoromethanesulfonimide) (1.53 g, 4.28 mmol) in anhydrous THF (5 mL) was introduced via a syringe to the −78 °C solution of the potassium enolate. Stirring was continued whilst warming to ambient temperatures over 2.5 h, after which the reaction was deemed to have gone to completion via TLC analysis. The reaction mixture was quenched with water (10 mL), diluted with ether (50 mL) and was washed with saturated brine (3 × 20 mL). The organic phase was dried, concentrated, and subjected to flash column chromatography (5% EtOAc: 95% hexanes) to yield the *title compound* as colourless oil (1.48 g, 91% yield). Alternatively, dissolution of the crude residue in MeOH precipitated residual *N*-phenyltrifluorosulfonimide, which then afforded the *title compound* after filtration and removal of solvent in vacuo. The material obtained was of acceptable purity (>90% by ^1H NMR analysis). $[\alpha]_D^{20} = -66.15$ (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz) δ 0.11 (s, 3H), 0.13 (s, 3H), 0.87 (s, 9H), 1.43 (s, 3H), 1.56 (m, 1H), 1.75 (s, 3H), 1.83–1.88 (m, 2H), 1.95 (m, 1H), 2.97 (m, 1H), 4.70 (m, 1H), 4.85 (m, 1H), 5.67 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz) δ −2.3, −2.1, 18.4, 21.6, 23.8, 25.8, 25.9, 26.8, 37.7, 42.7, 72.0, 112.7, 120.8, 145.5, 152.8. IR ($CDCl_3$): 2956 (w), 2931 (w), 2858 (w), 1260(m), 1248 (m), 1215 (s), 1143 (s) cm^{-1}. HRMS (EI) calcd for $C_{16}H_{27}F_3O_4SSi$ $(M-CH_4)$. 399.1268, found: 399.1241 (6%), 357.0830 (84), 207.0271 (37), for 133.1351 (100).

4.7. (3*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-6-methyl-3-(prop-1-en-2-yl)cyclohex-1-enyl trifluoromethane-sulfonate 5b

The above procedure was repeated with the TBS-ether **4b**, the *title compound* was obtained as a colourless oil in an 82% yield. $[\alpha]_D^{20} = +5.8$ (*c* 1.25, $CHCl_3$). ^1H NMR (500 MHz) δ 0.047 (s, 3H), 0.054 (s, 3H), 0.08 (s, 9H), 1.36 (s, 3H), 1.60–1.68 (m, 2H), 1.67 (s, 3H), 2.03 (m, 1H), 2.94 (m, 1H) 4.84 (s, 1H), 4.87 (m, 1H), 5.63 (d, J = 2.5 Hz, 1H). ^{13}C NMR (125 MHz) δ −2.3, −2.1, 18.4, 20.8, 24.2, 25.9, 26.6, 38.9, 44.0, 71.6, 112.4, 117.4, 121.7, 146.6, 152.7. IR (film): 2954 (s), 2932 (s), 2859 (s), 1249 (s), 1211 (s), 1145 (s) cm^{-1}. MS (EI) *m/z* 399.1 $((M-CH_4)^+$, 4%)$^+$, 357.1(58), 207.1 (25), 133.2 (100). HRMS (ESI) calcd for $C_{17}H_{33}F_3NO_4SSi$ $(M+NH_4)^+$ 434.1852, found: 432.1848.

4.8. (3*R*,6*S*)-6-*tert*-Butyldimethylsilyloxy)-3-isopropyl-6-methylcyclohex-1-enyl trifluoromethanesulfonate 6a

A solution of enol triflate **5a** (1.38 g, 3.32 mmol) and PtO_2 (7.5 mg, 1 mol %) in absolute methanol (15 mL), under an atmosphere of hydrogen, was stirred at room temperature for 3 h, after which time the reaction had gone to completion (TLC analysis, 100% hexane). Filtration of the crude reaction mixture through a bed of Celite followed by concentration of the filtrate in vacuo afforded the *title compound* as a colourless oil (1.28 g 93% yield), which was used without further purification. $[\alpha]_D^{20} = -21.7$ (*c* 2.65, $CHCl_3$). ^1H NMR (400 MHz) δ 0.11 (s, 6H), 0.88, (s, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.38–1.45 (complex, 4H), 1.66 (m, 1H), 1.75 (m, 1H), 1.85–2.00 (m, 2H), 2.19–2.26 (m, 1H) 5.60 (dd, J = 3.0, 0.6 Hz, 1H). ^{13}C NMR (100 MHz) δ −2.2, −2.1, 18.4, 19.8, 19.9, 23.0, 24.9, 26.8, 31.9, 39.6, 41.8, 72.5,

120.3, 121.3, 152.4. IR (film): 2959 (s), 2933 (s), 2865 (sh), 2859 (s), 1248 (s), 1211, 1146 (s) cm^{-1}. HRMS (EI) calcd for $C_{16}H_{28}F_3O_4SSi$ $(M-CH_4)^{+\cdot}$ 401.1430, found: 401.1408 (11%), 359.1017 (83), 135.1534 (100).

4.9. (3*S*,6*S*)-6-*tert*-Butyldimethylsilyloxy)-3-isopropyl-6-methylcyclohex-1-enyl trifluoromethanesulfonate 6b

The above procedure was repeated with the enol triflate **5b**, the *title compound* was obtained as a colourless oil in an 81% yield. $[\alpha]_D^{20} = -35.5$ (*c* 1.55, $CHCl_3$). ^1H NMR (500 MHz) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.86 (s, 9H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H), 1.4 (s, 3H), 1.51 (m, 1H), 1.60–1.64 (m, 2H), 1.75 (m, 1H), 1.97 (m, 1H), 2.16 (m, 1H), 5.59 (d, $J = 2$ Hz, 1H). ^{13}C NMR (125 MHz) δ −2.4, −2.2, 18.3, 19.4, 19.7, 20.6, 25.9, 26.7, 32.0, 39.6, 42.9, 71.7, 119.1, 122.3, 152.6. IR (film): 2959 (s), 2932 (s), 2859 (s), (s), 1210 (s), 1173 (m), 1145 (s), cm^{-1}. MS (EI) *m/z* 401.1 ($C_{16}H_{28}F_3O_4SSi^{\cdot}-CH_4$, 6%)$^+$, 359.1 (44), 265 (18), 251 (30), 207 (49), 183 (24), 135 (100). HRMS (EI) calcd for $C_{16}H_{28}F_3O_4SSi$ $(M-CH_4)^{+\cdot}$ 401.1430, found: 401.1410 (6%), 359.0930 (90), 265.0194 (26), 251.0470 (52), 207.0099 (78), 135.1462 (100).

4.10. (1*S*,4*R*)-*tert*-Butyl((1*S*,4*S*)-4-isopropyl-1-methylcyclohex-2-enyloxy)dimethylsilane 7a

Following a modified procedure of both Cacchi et al.[21,22] and Liu et al.,[23] to a stirred solution of the dihydroenoltriflate **6a** (1.15 g, 2.76 mmol), DIPEA (2.1 mL, 6.03 mmol), $Pd(OAc)_2$ (31 mg, 148 μmol) and triphenylphosphine (72 mg, 275 μmol) in dry DMF (20 mL), under an atmosphere of nitrogen, was slowly added 98%formic acid (208 μL, 5.50 mmol). The reaction temperature was warmed to 70 °C with the aid of an external oil bath, and maintained at this temperature for 2 h. After this period, complete conversion to the *title compound* was observed via TLC analysis. The reaction mixture was diluted with water (40 mL), extracted into hexanes and dried, after which it was subjected directly to a short silica gel plug in neat hexanes, to afford a clear volatile oil (556 mg, 75% yield) after concentration of the solvent under reduced pressure (330 mbar, 40 °C). $[\alpha]_D^{20} = -77.3$ (*c* 2.07, $CHCl_3$). ^1H NMR (500 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.86 (d, $J = 8.5$ Hz, 3H), 0.88 (d, $J = 8.5$ Hz, 3H), 1.23 (s, 3H), 1.32 (m, 1H), 1.57 (m, 1H), 1.67–1.80 (m, 3H), 1.92 (m, 1H), 5.49 (ddd, $J = 1.0$, 2.4, 10.3 Hz, 1H), 5.60 (ddd, $J = 1.3$, 2.6, 10.3 Hz, 1H). ^{13}C NMR (100 MHz) δ −1.9, −1.8, 19.6, 20.0, 22.9, 24.0, 26.1, 30.3, 32.1, 38.7, 41.9, 72.3, 129.9, 136.1. IR (film): 3021 (w), 2958 (s), 2930 (s), 2858 (s), 1130 (s) cm^{-1}. ESI (MS) *m/z*: 301.08 $(M+MeOH+H)^+$ HRMS (EI) calcd for $C_{15}H_{29}OSi$ $(M-CH_4)^{+\cdot}$ 253.1988 $(M-CH_4)^{+\cdot}$, found: 253.1988 (12%), 211.1770 (31), 135.1405 (28), 93.1008 (73), 75.0529 (100).

4.11. (1*S*,4*S*)-*tert*-Butyl((1*S*,4*S*)-4-isopropyl-1-methylcyclohex-2-enyloxy)dimethylsilane 7b

The above procedure was repeated with the dihydroenoltriflate **6b**, the *title compound* was obtained as a colourless oil in 88% yield. $[\alpha]_D^{20} = -49.75$ (*c* 2.07, $CHCl_3$). ^1H NMR (500 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H) 0.88 (d, $J = 7.0$ Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H), 1.25 (s, 3H), 1.38 (dt, $J = 3.0$, 12.5 Hz, 1H), 1.48–1.66 (m, 3H), 1.78–1.85 (m, 2H) 5.59–5.65 (complex, 2H). ^{13}C NMR (125 MHz) δ −1.7, 14.4, 19.7, 20.1, 21.9, 22.9, 26.1, 31.2, 31.9, 32.2, 39.1, 42.7, 70.0, 132.2, 134.4. IR (film): 3021 (w), 2957 (s), 2930 (s), 2858 (m), 1131 (m) cm^{-1}. MS (EI) 253.2 ($(M-CH_4)^{+\bullet}$, 12%), 211.2 (57), 13.2 (43), 93.1 (44), 75.1 (100). HRMS (EI) calcd for $C_{15}H_{29}OSi$ $(M-CH_4)^{+\cdot}$ 253.1988, found: 253.1956 (7%), 211.1815 (41), 135.1434 (23), 93.1005 (57), 75.0566 (100).

4.12. (1*S*,4*R*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol 1

Tetrabutylammonium fluoride (1.0 M in THF; 1.5 mL, 1.5 mmol) was added to a stirred solution of the *tert*-butyldimethylsilyloxy pheromone **7a** (268 mg, 1 mmol) in anhydrous THF (5 mL) under an atmosphere of nitrogen; the reaction mixture was brought to reflux and maintained at this temperature for 18 h. After this time, the reaction was cooled and carefully concentrated in vacuo (357 mbar, 40 °C), and the resulting residue was subjected directly to flash column chromatography (15% EtOAc: 75% hexanes); affording the synthetic pheromone (140 mg, 91% yield) as a colourless oil. $[\alpha]_D^{20} = -72.4$ (*c* 1.0, $CHCl_3$) lit. −65.9 (Ref. 3 $CHCl_3$ *c* 1.17, 96.67% ee). ^1H NMR (500 MHz) δ 0.86 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 1.27 (s, 3H), 1.38 (m, 1H), 1.55–1.66 (m, 2H), 1.67 (br s, 1H), 1.73 (m, 1H), 1.86 (ddd, $J = 2.8$, 5.9, 12.6 Hz, 1H), 1.94 (m, 1H), 5.58–5.64 (m, 2H). ^{13}C NMR (125 MHz) δ 19.6, 20.0, 23.8, 28.7, 32.0, 38.3, 41.9, 69.9, 131.5, 134.8.

4.13. (1*S*,4*S*)-4-Isopropyl-1-methyl-2-cyclohexen-1-ol 2

The above procedure was repeated with the *tert*-butyldimethylsilyloxy pheromone **7b**, the *title compound* was obtained as a colourless oil in an 81% yield. $[\alpha]_D^{20} = -11.5$ (*c* 1.0, $CHCl_3$) lit. −12.0 (Ref. 3 $CHCl_3$, *c* 2.06, 98.66% ee). ^1H NMR (500 MHz) δ 0.89 (d, $J = 7$ Hz, 3H), 0.91 (d, $J = 7$ Hz, 3H), 1.27 (s, 3H), 1.43 (m, 1H), 1.46 (br s, 1H), 1.52 (dt, $J = 3.0$, 13.5 Hz, 1H), 1.59–1.67 (m, 2H), 1.81–1.90 (m, 2H), 5.64–5.70 (complex, 2H). ^{13}C NMR (125 MHz) δ 19.5, 19.9, 21.8, 29.8, 31.9, 37.5, 42.3, 67.7, 133.5, 133.8.

Acknowledgment

The authors acknowledge the support of the School of Chemistry, Monash University.

References

1. Ito, S. Y. *J. Jpn. For. Soc* **1998**, *80*, 229–232.
2. Nakashima, T. *Aroma Res.* **2005**, *6*, 348–351.
3. Mori, K. *Tetrahedron: Asymmetry* **2006**, *17*, 2133–2142.
4. Kamata, N.; Esaki, K.; Mori, K.; Takemoto, H.; Mitsunaga, T.; Honda, H. *J. For. Res.* **2008**, *13*, 122–126.
5. Qian Wang, S. Y. F.; Wang, H. N. C.; Li, Z.; Fung, B. M.; Twieg, R. J.; Nguyen, H. T. *Tetrahedron* **1993**, *49*, 619–638.
6. Stevens, R. V.; Albizati, K. F. *J. Org. Chem.* **1985**, *50*, 632–640.
7. Nicolaou, K. C.; Pappo, D.; Tsang, K. Y.; Gibe, R.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2008**, *47*, 944–946.
8. Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313–4320.
9. Kreuzer, T.; Metz, P. *Eur. J. Org. Chem.* **2008**, *2008*, 572–579.
10. Haddad, N.; Salman, H. *Tetrahedron Lett.* **1997**, *38*, 6087–6090.
11. Andrews, P. C.; Blair, M.; Fraser, B. H.; Junk, P. C.; Massi, M.; Tuck, K. L. *Tetrahedron: Asymmetry* **2006**, *17*, 2833–2838.
12. Steiner, D.; Ivison, L.; Goralski, C. T.; Appell, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359–2363.
13. Salles, L.; Nixon, A. F.; Russell, N. C.; Clarke, R.; Pogorzelec, P.; Cole-Hamilton, D. J. *Tetrahedron: Asymmetry* **1999**, *10*, 1471–1476.
14. Blair, M.; Andrews, P. C.; Fraser, B. H.; Forsyth, C. M.; Junk, P. C.; Massi, M.; Tuck, K. L. *Synthesis* **2007**, *2007*, 1523–1527.
15. Mc Murry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.
16. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.
17. Pavia, A. G. P.; Olivé, J.-L. *Bull. Soc. Chim. Fr.* **1981**, *1*, 24–27.
18. He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.
19. Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968–1969.
20. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.
21. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821–4824.
22. Cacchi, S.; Morera, E.; Ortar, G. *Org. Synth.* **1990**, *8*, 126.
23. Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562–7563.

References

1. Nicolaou, K. C.; Montagnon, T., *Molecules That Changed The World*. Wiley-VCH Weinheim, 2008; p 385.
2. Maier, M. E., *Nat. Prod. Rep.* **2009,** *26*, 1105-1124.
3. Nicolaou, K. C.; Snyder, S. A., *Angew. Chem. Int. Ed.* **2005,** *44*, 1012-1044.
4. Nicolaou, K. C.; Sorensen, E. J., *Classics in Total Synthesis: Targets, Strategies, Methods*. Wiley VCH: Weinheim, 1996; p 821.
5. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K., *J. Am. Chem. Soc.* **1954,** *76*, 4749-4751.
6. Robinson, R., *J. Chem. Soc., Trans.* **1917,** *111*, 762.
7. Pelletier, P. J.; Caventou, J. B., *Ann. Chim, Phys.* **1818,** *8*, 323.
8. Briggs, L. H.; Openshaw, H. T.; Robinson, R., *J. Chem. Soc.* **1946**, 903.
9. Bokhoven, C.; Schoone, J. C.; Bijvoet, J. M., *Proc. K. Ned. Akad.* **1948,** *51*, 990.
10. Robinson, R., *Prog. Org. Chem.* **1952,** *1*, 2.
11. Peerdeman, A. F., *Acta Crystallogr.* **1956**, 824.
12. Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B., *J. Org. Chem.* **1991,** *56*, 678-683.
13. Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T., *Tetrahedron* **1997,** *53*, 557-556.
14. Bernal, J. D., *Nature* **1932,** *129*, 721.
15. Weiland, H.; Dane, E. Z., *Physiol. Chem.* **1932,** *210*, 268.
16. Rosenheim, O.; King, H., *Chem. Industry* **1932,** *51*, 954.
17. Rosenheim, O.; King, H., *Chem. Industry* **1932,** *51*, 464.
18. Sharma, P.; Alam, M., *J. Chem. Soc. Perkin Trans. 1* **1988**, 2357.
19. Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J., *Org. Lett.* **2000,** *3*, 135-137.
20. Macias, F. A.; Varela, R. M.; Torres, A.; Oliva, R. M.; Molinillo, J. M. G., *Phytochemistry* **1998,** *48*, 631-636.
21. Takikawa, H.; Isono, K.; Sasaki, M.; MacIas, F. A., *Tetrahedron Lett.* **2003,** *44*, 7023-7025.
22. Srivastava, V.; Negi, A. S.; Kumar, J. K.; Gupta, M. M.; Khanuja, S. P. S., *Bioorg. Med. Chem.* **2005,** *13*, 5892.
23. Garciya-Fernandez;, L.; Fernando Reyes; Sanchez-Puelles, J. M., *Pharmaceutical News* **2002,** *9*, 495.
24. Baker, D. D.; Chu, M.; Oza, U.; Rajgarhia, V., *Nat. Prod. Rep.* **2007,** *24*, 1225-1244.
25. Mayer, A. M. S.; Gustafson, K. R., *Eur. J. Cancer* **2004,** *40*, 2676.
26. Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V., *J. Org. Chem.* **2003,** *68*, 7667-7674.
27. Mihopoulos, N.; Vagias, C.; Mikros, E.; Scoullos, M.; Roussis, V., *Tetrahedron Lett.* **2001,** *42*, 3749-3752.
28. Howard, B. M.; Fenical, W., *Tetrahedron Lett.* **1978,** *19*, 2453-2456.
29. Guella, G.; Pietra, F.; Marchetti, F., *Helv. Chim. Acta* **1997,** *80*, 684-694.
30. Breitmaier, E., *Terpenes: Flavours Fragrances, Pharmaca, Pheromones*. Wiley-VCH: Weinheim, 2006.
31. Ji, N.-Y.; Li, X.-M.; Li, K.; Ding, L.-P.; Gloer, J. B.; Wang, B.-G., *J. Nat. Prod.* **2007,** *70*, 1901-1905.
32. Butler, A.; Carter-Franklin, J. N., *Nat. Prod. Rep.* **2004,** *21*, 180-188.

33. Carter-Franklin, J. N.; Parrish, J. D.; Tschirret-Guth, R. A.; Little, R. D.; Butler, A., *J. Am. Chem. Soc.* **2003,** *125*, 3688-3689.
34. White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M., *J. Am. Chem. Soc.* **2007,** *130*, 810-811.
35. Sims, J. J.; Lin, G. H. Y.; Wing, R. M., *Tetrahedron Lett.* **1974,** *15*, 3487-3490.
36. Jung, M. E.; McCombs, C. A., *Tetrahedron Lett.* **1976,** *17*, 2935-2938.
37. Stevens, R. V.; Albizati, K. F., *J. Org. Chem.* **1985,** *50*, 632-640.
38. Ashby, E. C.; Laemmle, J. T., *Chem. Rev.* **1975,** *75*, 521-546.
39. Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S., *J. Am. Chem. Soc.* **1990,** *112*, 866-868.
40. Carey, F. A.; Sundberg, R. J., *Advanced organic chemistry Part B: Reactions and Synthesis*. 5th ed.; Springer: New York, 2007; p 413-414.
41. Andrews, P. C.; Blair, M.; Fraser, B. H.; Junk, P. C.; Massi, M.; Tuck, K. L., *Tetrahedron: Asymmetry* **2006,** *17*, 2833-2838.
42. Blair, M.; Andrews, P. C.; Fraser, B. H.; Forsyth, C. M.; Junk, P. C.; Massi, M.; Tuck, K. L., *Synthesis* **2007,** *2007*, 1523-1527.
43. Blair, M.; Tuck, K. L., *Tetrahedron: Asymmetry* **2009,** *20*, 2149-2153.
44. Royals, E. E.; Leffingwell, J. C., *J. Org. Chem.* **1966,** *31*, 1937-1944.
45. Bamford, W. R.; Stevens, T. S., *J. Chem. Soc* **1952**, 4735–4740.
46. Nicolaou, K. C.; Pappo, D.; Tsang, K. Y.; Gibe, R.; Chen, D. Y.-K., *Angew. Chem., Int. Ed.* **2008,** *47*, 944-946.
47. Marshall, J. A.; Sehon, C. A., *J. Org. Chem.* **1997,** *62*, 4313-4320.
48. Kreuzer, T.; Metz, P., *Eur. J. Org. Chem.* **2008,** *2008*, 572-579.
49. Haddad, N.; Salman, H., *Tetrahedron Lett.* **1997,** *38*, 6087-6090.
50. Booker-Milburn, K. I.; Jenkins, H.; Charmant, J. P. H.; Mohr, P., *Org. Lett.* **2003,** *5*, 3309-3312.
51. D'Souza, A. M.; Paknikar, S. K.; Dev, V.; Beauchamp, P. S.; Kamat, S. P., *J. Nat. Prod.* **2004,** *67*, 700-702.
52. Pisoni, D. S.; Silva, D. B.; Schenato, R. A.; Ceschi, M. A., *J. Braz. Chem. Soc.* **2004,** *15*, 652-657.
53. O'Neill, P. M.; Stocks, P. A.; Pugh, M. D.; Araujo, N. C.; Korshin, E. E.; Bickley, J. F.; Ward, S. A.; Bray, P. G.; Pasini, E.; Davies, J.; Verissimo, E.; Bachi, M. D., *Angew. Chem. Int. Ed.* **2004,** *43*, 4193-4197.
54. Kido, F.; Yamaji, K.; Sinha, S. C.; Abiko, T.; Kato, M., *Tetrahedron* **1995,** *51*, 7697-7714.
55. Ho, T.-L.; Chein, R.-J., *Helv. Chim. Acta* **2006,** *89*, 231-239.
56. Li, Y.; Zhang, T.; Li, Y.-L., *Tetrahedron Lett.* **2007,** *48*, 1503-1505.
57. Delay, F.; Ohloff, G. n., *Helv. Chim. Acta* **1979,** *62*, 2168-2173.
58. Salles, L.; Nixon, A. F.; Russell, N. C.; Clarke, R.; Pogorzelec, P.; Cole-Hamilton, D. J., *Tetrahedron: Asymmetry* **1999,** *10*, 1471-1476.
59. Steiner, D.; Ivison, L.; Goralski, C. T.; Appell, R. B.; Gojkovic, J. R.; Singaram, B., *Tetrahedron: Asymmetry* **2002,** *13*, 2359-2363.
60. van der Werf, M. J.; Jongejan, H.; Franssen, M. C. R., *Tetrahedron Lett.* **2001,** *42*, 5521-5524.
61. Furst, A.; Plattner, P. A., In *12th International of Congress of Pure and Applied Chemistry*, New York, 1951; p 409.
62. Leffingwell, J. C.; Royals, E. E., *Tetrahedron Lett.* **1965,** *6*, 3829-3837.
63. Mancuso, A. J.; Huang, S.-L.; Swern, D., *J. Org. Chem.* **1978,** *43*, 2480-2482.
64. Castro, F. d. L.; Kover, R. X.; Kover, W. B.; Jones Jr, J., *J. Braz. Chem. Soc.* **1999,** *10*, 112-116.

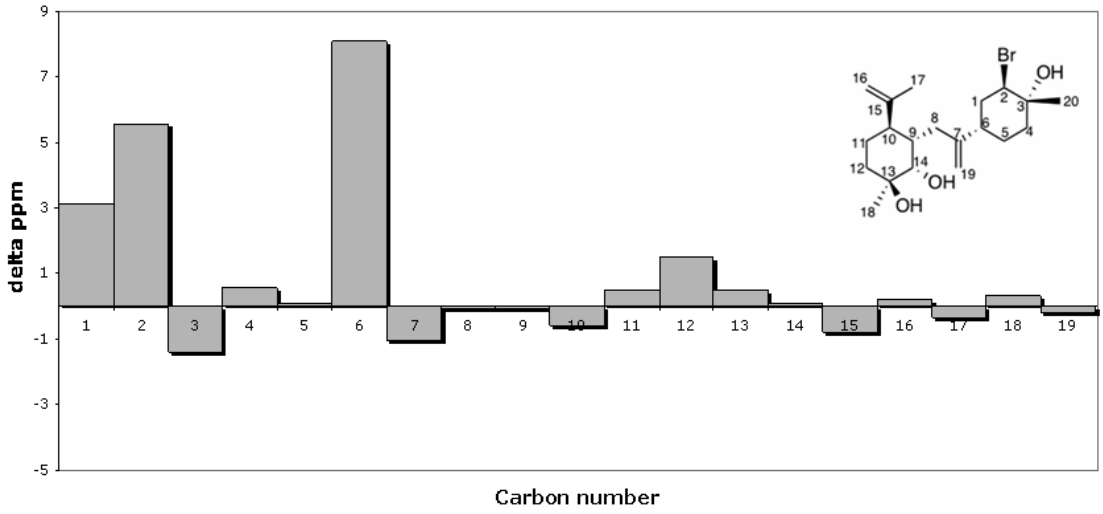
65. Hirano, S.; Ichikawa, S.; Matsuda, A., *J. Org. Chem.* **2007,** *73*, 569-577.
66. Chandrasekhar, S.; Rambabu, C.; Reddy, A. S., *Tetrahedron Lett.* **2008,** *49*, 4476-4478.
67. Yadav, J. S.; Reddy, C. S., *Org. Lett.* **2009,** *11*, 1705-1708.
68. Lucio Anelli, P.; Biffi, C.; Montanari, F.; Quici, S., *J. Org. Chem.* **1987,** *52*, 2559-2562.
69. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G., *J. Org. Chem.* **1997,** *62*, 6974-6977.
70. Rychnovsky, S. D.; Vaidyanathan, R., *J. Org. Chem.* **1998,** *64*, 310-312.
71. Bolm, C.; Magnus, A. S.; Hildebrand, J. P., *Org. Lett.* **2000,** *2*, 1173-1175.
72. De Luca, L.; Giacomelli, G.; Porcheddu, A., *Org. Lett.* **2001,** *3*, 3041-3043.
73. More, J. D.; Finney, N. S., *Org. Lett.* **2002,** *4*, 3001-3003.
74. Frigerio, M.; Santagostino, M., *Tetrahedron Lett.* **1994,** *35*, 8019-8022.
75. Frigerio, M.; Santagostino, M.; Sputore, S., *J. Org. Chem.* **1999,** *64*, 4537-4538.
76. Plumb, J. B.; Harper, D. J., *Chem. Eng. News* **1990,** *16*, 3.
77. Tohma, H.; Kita, Y., *Adv. Synth. Catal.* **2004,** *346*, 111-124.
78. De Munari, S.; Frigerio, M.; Santagostino, M., *J. Org. Chem.* **1996,** *61*, 9272-9279.
79. Rai, A. N.; Basu, A., *Tetrahedron Lett.* **2003,** *44*, 2267-2269.
80. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O., *Tetrahedron Lett.* **1988,** *29*, 4139-4142.
81. Corey, E. J.; Cho, H.; R¸cker, C.; Hua, D. H., *Tetrahedron Lett.* **1981,** *22*, 3455-3458.
82. Gesson, J.-P.; Jacquesy, J.-C.; Renoux, B., *Tetrahedron* **1989,** *45*, 5853-5866.
83. Mukhopadhyay, T.; Seebach, D., *Helv. Chim. Acta* **1982,** *65*, 385-391.
84. Palomo, C.; Oiarbide, M.; Mielgo, A.; Gonzalez, A.; Garcia, J. M.; Landa, C.; Lecumberri, A.; Linden, A., *Org. Lett.* **2001,** *3*, 3249-3252.
85. Campos, K. R.; Lee, S.; Journet, M.; Kowal, J. J.; Cai, D.; Larsen, R. D.; Reider, P. J., *Tetrahedron Lett.* **2002,** *43*, 6957-6959.
86. Williams, D. H.; Flemming, I., Spectroscopic Methods in Organic Chemistry. In 5th ed.; McGraw Hill: New York, 1995; pp 92-100.
87. House, H. O.; Trost, B. M., *J. Org. Chem.* **1965,** *30*, 2502-2512.
88. Djerassi, C., *Chemical Reviews* **1948,** *43*, 271-317.
89. Wohl, A., *Ber.* **1919,** *62*, 51.
90. Ziegler, K.; Shenck, G.; Krockow, E. W.; Siebert, A.; Wenz, A.; Weber, H., *Ann.* **1942,** *661*, 1.
91. Constantino, M. G.; de Oliveira, K. T.; Polo, E. C.; da Silva, G. V. J.; Brocksom, T. J., *J. Org. Chem.* **2006,** *71*, 9880-9883.
92. Blomquist, A. T.; Kwiatek, J., *J. Am. Chem. Soc.* **1951,** *73*, 2098-2100.
93. Umbreit, M. A.; Sharpless, K. B., *J. Am. Chem. Soc.* **1977,** *99*, 5526-5528.
94. Ohloff, G. n.; Giersch, W.; N‰f, R.; Delay, F., *Helv. Chim. Acta* **1986,** *69*, 698-703.
95. Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B., *Org. Lett.* **2007,** *9*, 1825-1828.
96. Kido, F.; Abiko, T.; Michiharu, K., *J. Chem. Soc. Perkin Trans. 1* **1995**, 2989-2994.
97. Eschinasi, E. H., *J. Org. Chem.* **1969,** *35*, 1598-1599.
98. Baughman, T. W.; Sworen, J. C.; Wagener, K. B., *Tetrahedron* **2004,** *60*, 10943-10948.
99. Pisoni, D. S.; Gamba, D.; Fonseca, C. V.; Costa, J. S. d.; Petzhold, C. L.; Oliveira, E. R. d.; Ceschi, M. A., *J. Braz. Che. Soc.* **2006,** *17*, 321-327.

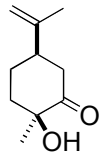
100. Hegde, S. G.; Wolinsky, J., *J. Org. Chem.* **1982,** *47*, 3148-3150.
101. Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M., *Tetrahedron Lett.* **2003,** *44*, 6691-6693.
102. Mendham, J.; Denney, R. C.; Barnes, J. D.; Thomas, M. J. K., *Vogel's Quantitative Chemical Analysis (6th Edition)*. Prentice Hall: 2000.
103. Finkelstein, H., *Berichte der deutschen chemischen Gesellschaft* **1910,** *43*, 1528-1532.
104. Salvati, M.; Cordero, F. M.; Pisaneschi, F.; Bucelli, F.; Brandi, A., *Tetrahedron* **2005,** *61*, 8836-8847.
105. Dei, S.; Budriesi, R.; Sudwan, P.; Ferraroni, M.; Chiarini, A.; Garnier-Suillerot, A.; Manetti, D.; Martelli, C.; Scapecchi, S.; Teodori, E., *Bioorg. Med. Chem.* **2005,** *13*, 985-998.
106. McCortney, B. A.; Jacobson, B. M.; Vreeke, M.; Lewis, E. S., *J. Am. Chem. Soc* **1990,** *112*, 3554.
107. Beaulieu, P. L.; Anderson, P. C.; Cameron, D. R.; Croteau, G.; Gorys, V.; Grand-Maitre, C.; Lamarre, D.; Liard, F.; Paris, W.; Plamondon, L.; Soucy, F.; Thibeault, D.; Wernic, D.; Yoakim, C.; Pav, S.; Tong, L., *J. Med. Chem.* **2000,** *43*, 1094-1108.
108. Gao, Y.; Sharpless, K. B., *J. Am. Chem. Soc.* **1988,** *110*, 7538-7539.
109. Qin, D.-G.; Zha, H.-Y.; Yao, Z.-J., *J. Org. Chem.* **2002,** *67*, 1038-1040.
110. Brimbacombe, J. S.; Foster, A. B.; Hancock, E. B.; Overend, W. G.; Stacey, M., *J. Chem. Soc.* **1960**, 201-211.
111. Kim, S.; Ko, H.; Kim, E.; Kim, D., *Org. Lett.* **2002,** *4*, 1343-1345.
112. Camps, P.; Munoz, M. R.; Vazquez, S., *J. Org. Chem.* **2005,** *70*, 1945-1948.
113. Seimbille, Y.; Benard, F.; Lier, J. E. v., *J. Chem. Soc., Perkin Trans. 1* **2002**, 2275-2281.
114. Moffat, D.; Nichols, C. J.; Riley, D. A.; Simpkins, N. S., *Org. Biomol. Chem.* **2005,** *3*, 2953-2975.
115. Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T., *J. Org. Chem.* **1981,** *46*, 3745-3747.
116. Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K., *Bull. Chem. Soc. Jpn.* **1989,** *62*, 143-147.
117. Seyferth, D.; Yamazaki, H.; Alleston, D. L., *J. Org. Chem.* **1963,** *28*, 703-706.
118. Kabe, Y.; Takata, T.; Ueno, K.; Ando, W., *J. Am. Chem. Soc.* **1984,** *106*, 8174-8180.
119. Napolitano, E.; Fiaschi, R.; Mastrorilli, E., *Synthesis* **1986,** *1986*, 122-125.
120. Furrow, M. E.; Myers, A. G., *J. Am. Chem. Soc.* **2004,** *126*, 5436-5445.
121. Guella, G.; Pietra, F., *Helv. Chim. Acta* **2000,** *83*, 2946-2952.
122. Armarego, W. L. F.; Chai, C. L. L., *Purification of Laboratory Chemicals*. 5th ed.; Elsevier Science: Sydney, 2003.
123. Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J., *J. Org. Chem.* **1989,** *54*, 3738-3740.
124. Bettadaiah, B. K.; Gurudutt, K. N.; Srinivas, P., *J. Org. Chem.* **2003,** *68*, 2460-2462.
125. Hamon, D. P. G.; Tuck, K. L., *Chem. Commun.* **1997**, 941-942.
126. Lopez, J.; Sierra, J.; Cortes, M., *Chem. Lett.* **1986**, 2073-2074.
127. Mori, K., *Tetrahedron: Asymmetry* **2006,** *17*, 2133-2142.
128. Hamon, D. P. G.; Tuck, K. L., *Tetrahedron* **2000,** *56*, 4829-4835.
129. Rickborn, B.; Thummel, R. P., *J. Org. Chem.* **1969,** *34*, 3583-3586.
130. Thummel, R. P.; Rickborn, B., *J. Am. Chem. Soc.* **1970,** *92*, 2064-2067.

131. Wang, Q.; Yan Fan, S.; Wong, H. N. C.; Li, Z.; Fung, B. M.; Twieg, R. J.; Nguyen, H. T., *Tetrahedron* **1993,** *49*, 619-638.
132. Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H., *J. Org. Chem.* **1976 ,** *41*, 2663-2669.
133. Giguere, R. J.; Hoffmann, H. M. R., *Tetrahedron Lett.* **1981,** *22*, 5039-5042.
134. Tsuji, J.; Yamakawa, T., *Tetrahedron Lett.* **1979,** *20*, 613-616.
135. He, F.; Bo, Y.; Altom, J. D.; Corey, E. J., *J. Am. Chem. Soc.* **1999,** *121*, 6771-6772.
136. Harrowven, D. C.; Guy, I. L., *Chem. Commun.* **2004**, 1968-1969.
137. Milstein, D.; Stille, J. K., *J. Am. Chem. Soc.* **1978,** *100*, 3636-3638.
138. Stille, J. K., *Angew. Chem., Int. Ed. Engl.* **1986,** *25*, 508-524.
139. Weir, J. R.; Patel, B. A.; Heck, R. F., *J. Org. Chem.* **1980,** *45*, 4926-4931.
140. Cortese, N. A.; Heck, R. F., *J. Org. Chem.* **1978,** *43*, 3985-3987.
141. Cacchi, S.; Morera, E.; Ortar, G., *Tetrahedron Lett.* **1984,** *25*, 4821-4824.

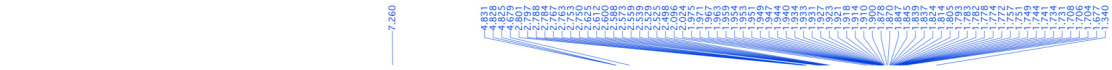
Appendix 1

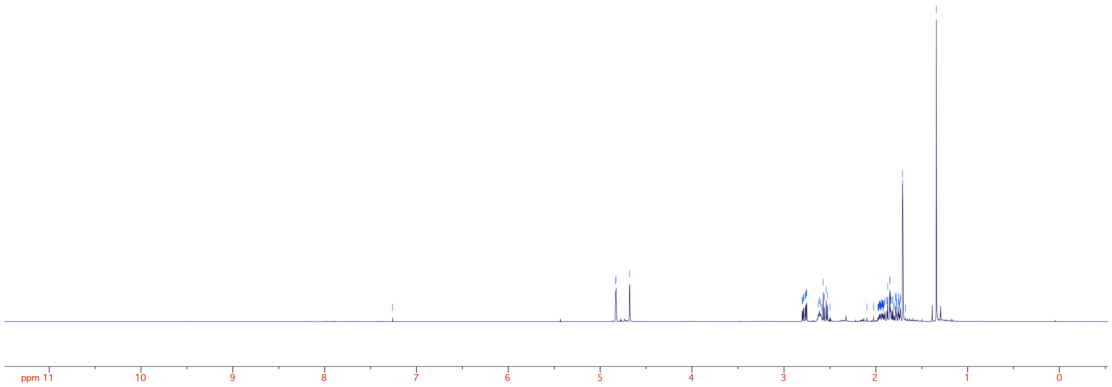
^{13}C NMR comparisons of reported natural Prevezol C **1** and synthetic 2-*epi*-Prevezol C **3**.

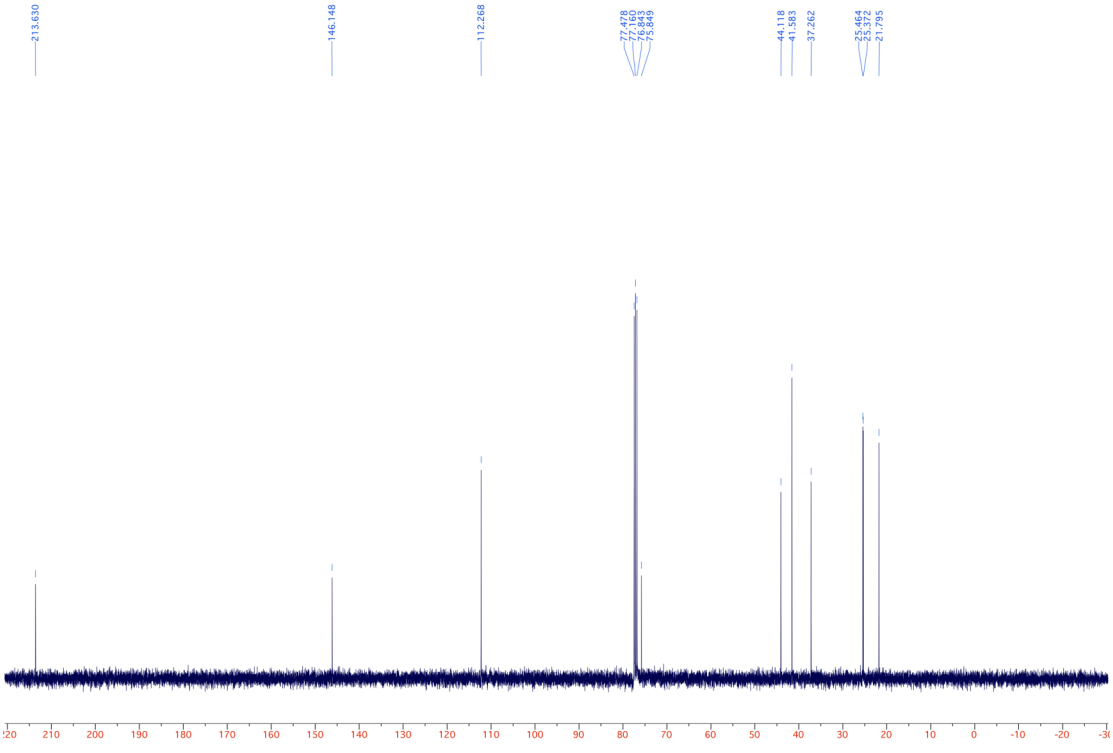


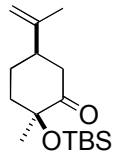

O
OH

4a

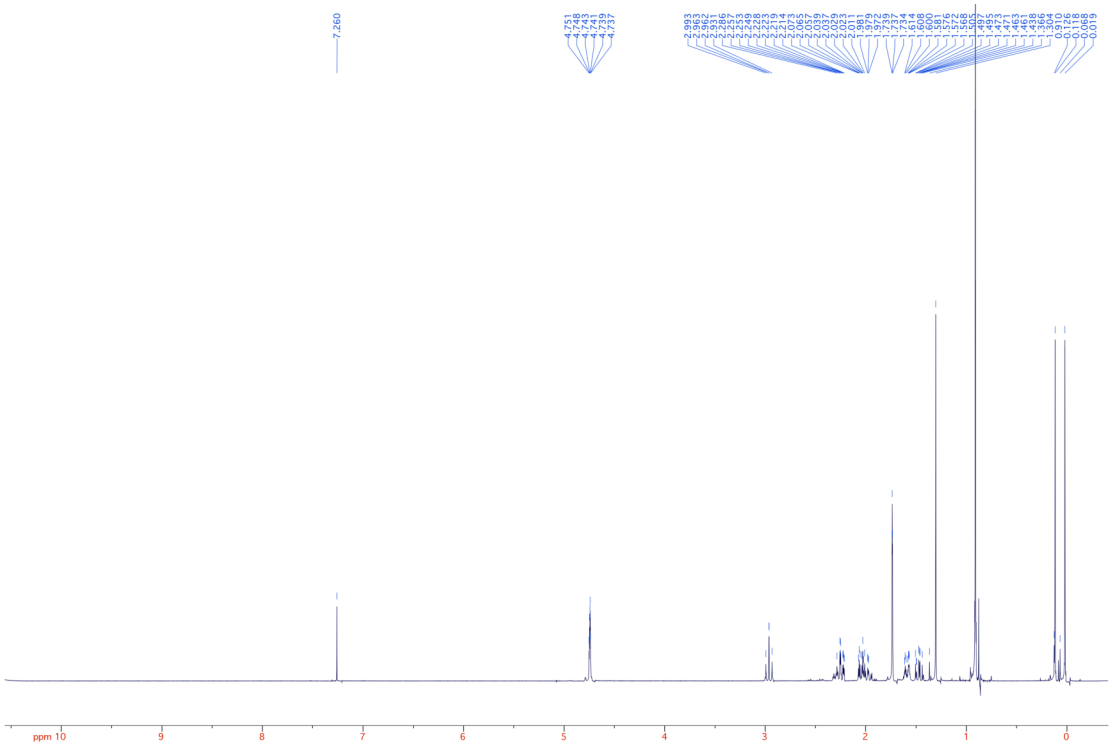


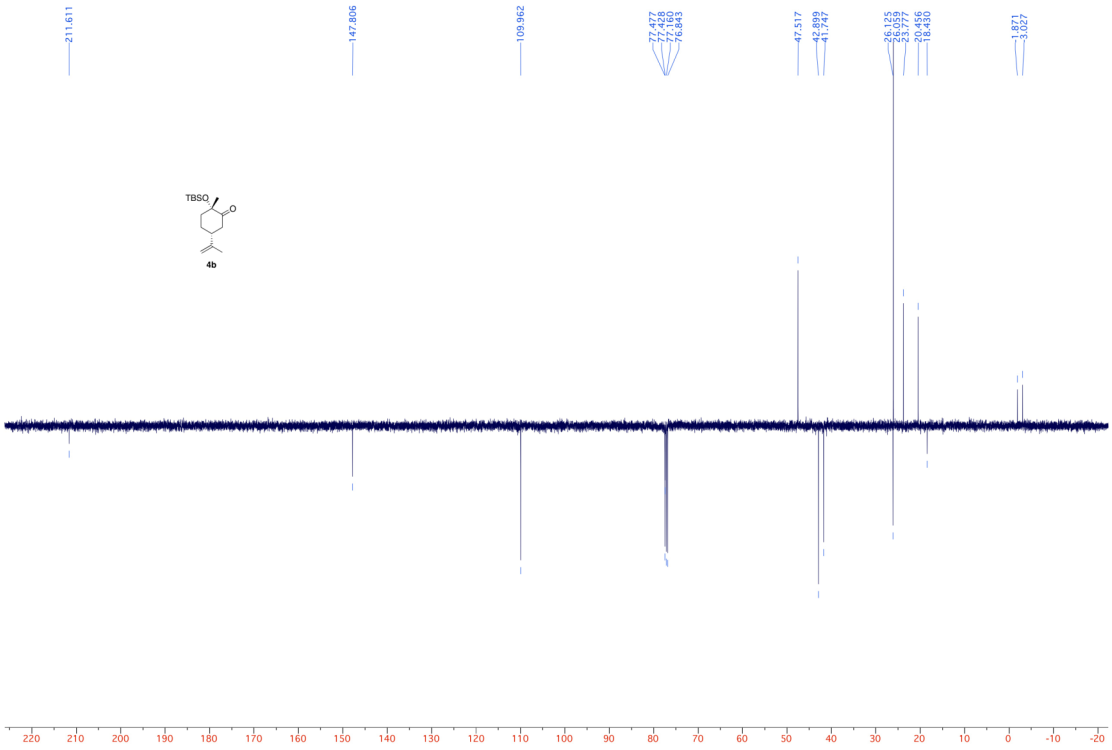

ppm 11
10
9
8
7
6
5
4
3
2
1
0

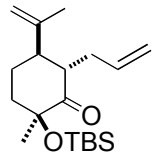

213.630
146.148
112.268
77.478
77.160
76.843
75.849
44.118
41.583
37.262
25.464
25.372
21.795
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20


O
OTBS

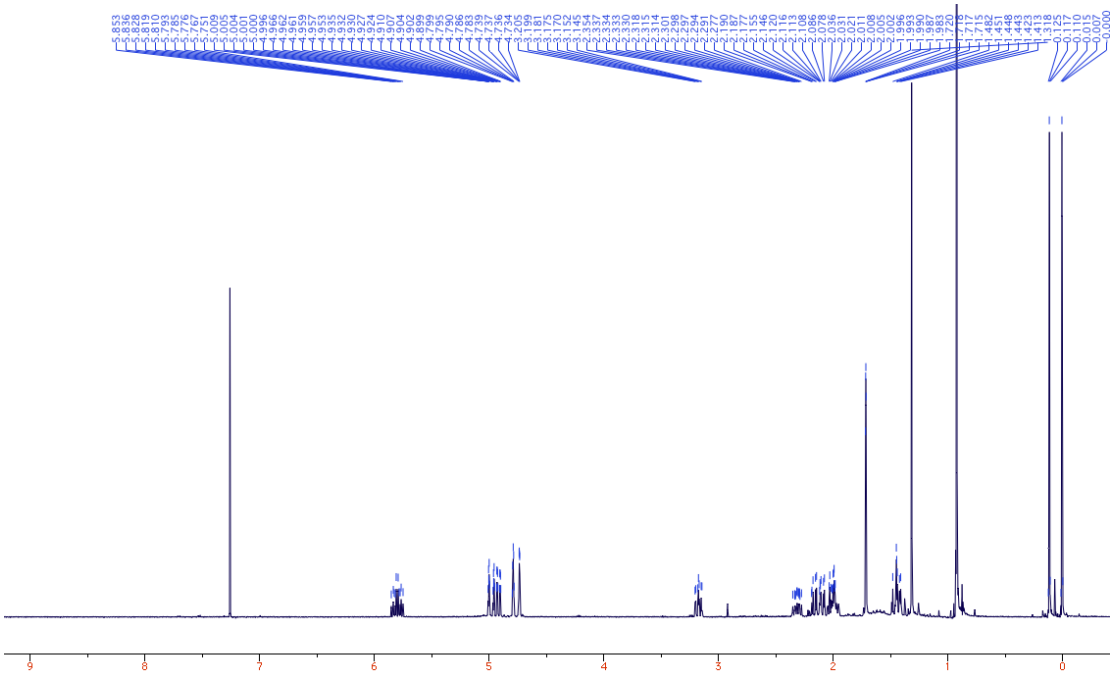
4b

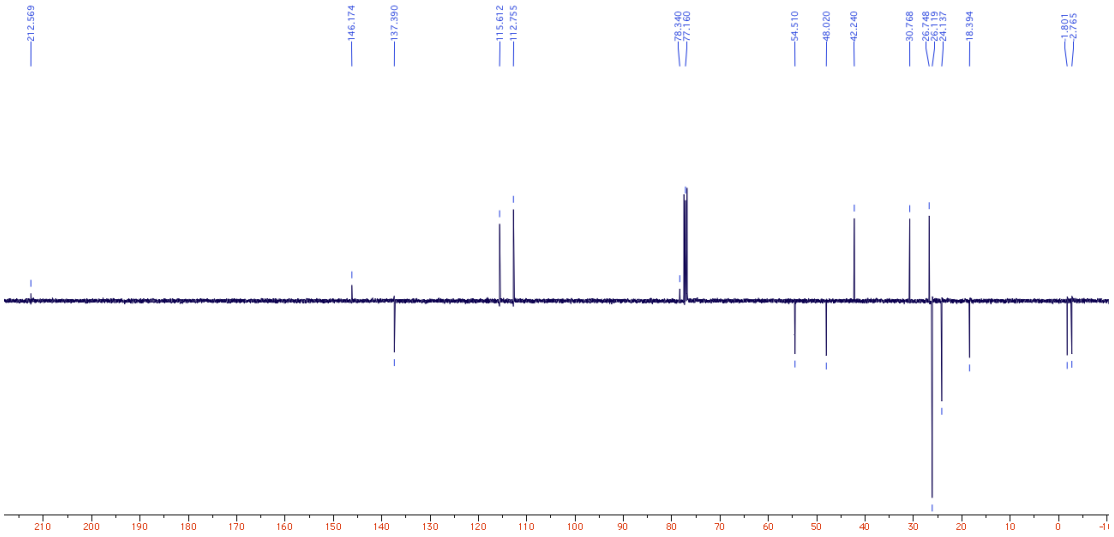

7.260
4.751
4.748
4.743
4.741
4.739
4.737
2.993
2.965
2.962
2.931
2.906
2.257
2.253
2.249
2.228
2.223
2.219
2.214
2.070
2.065
2.059
2.037
2.029
2.023
2.011
1.981
1.979
1.737
1.734
1.614
1.608
1.600
1.581
1.576
1.572
1.568
1.567
1.497
1.475
1.473
1.471
1.463
1.461
1.368
1.366
1.304
3.010
0.126
0.118
0.068
0.019
ppm 10
9
8
7
6
5
4
3
2
1
0

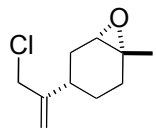

211.611
147.806
109.962
77.477
77.428
77.140
77.013
76.843
47.517
42.899
41.747
26.125
26.059
25.977
23.466
18.430
1.871
3.027
TBSO
4b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20



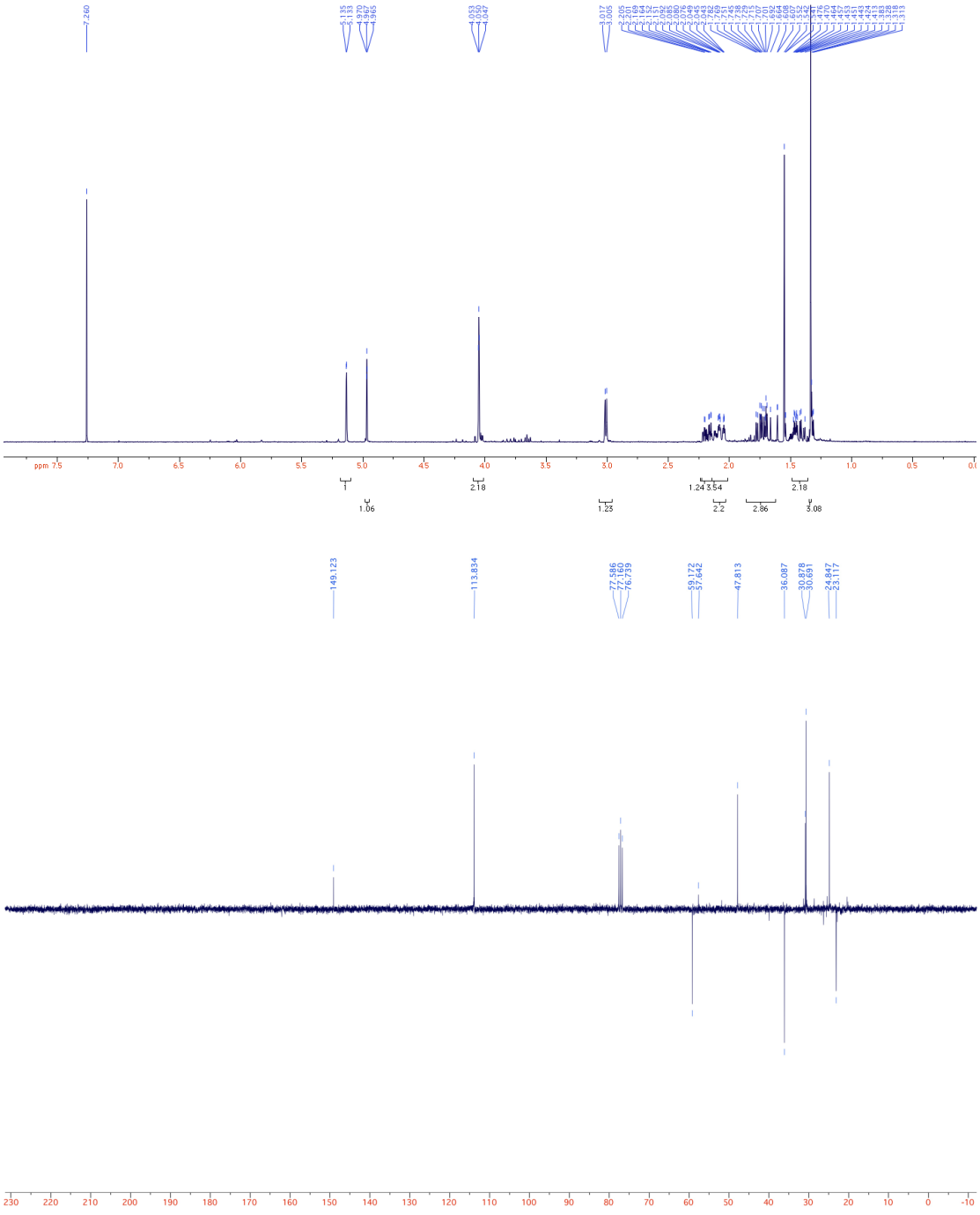
8

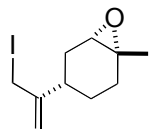




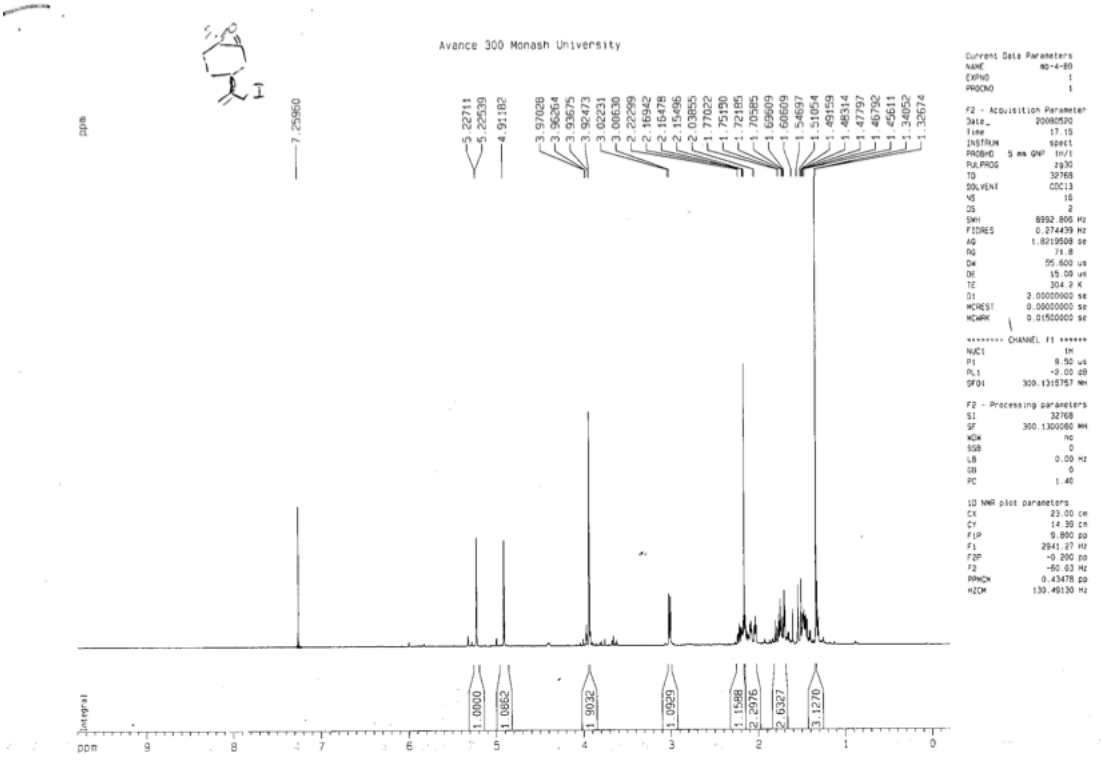


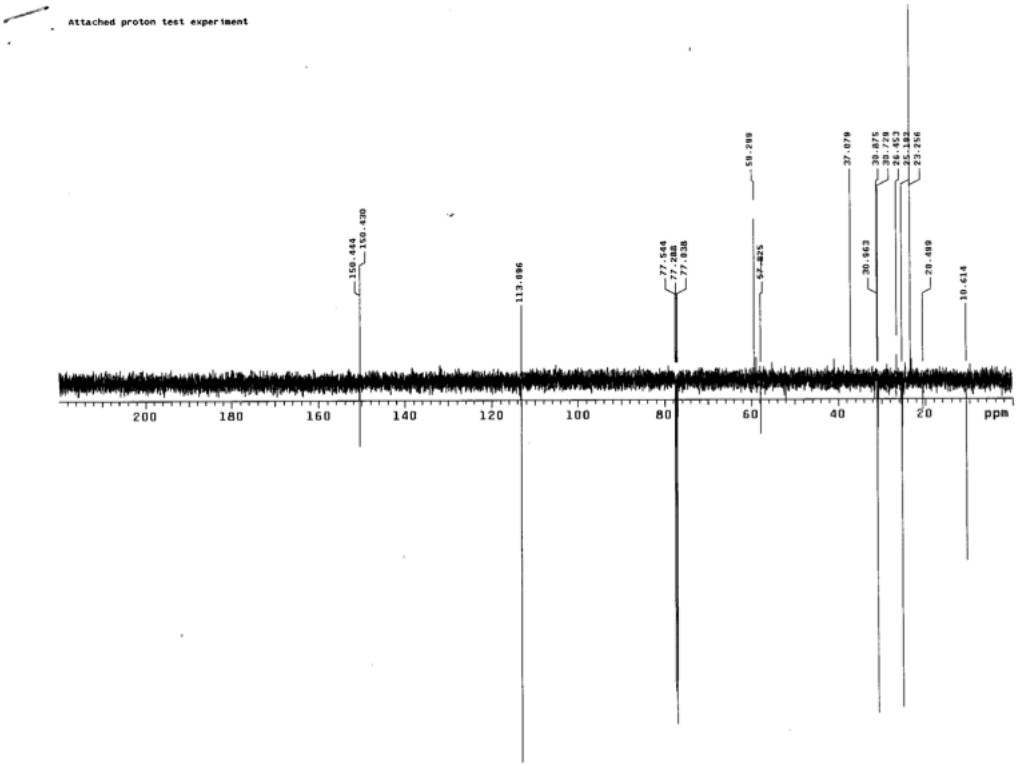
5a

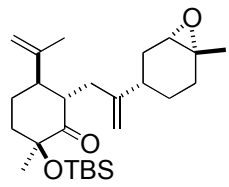




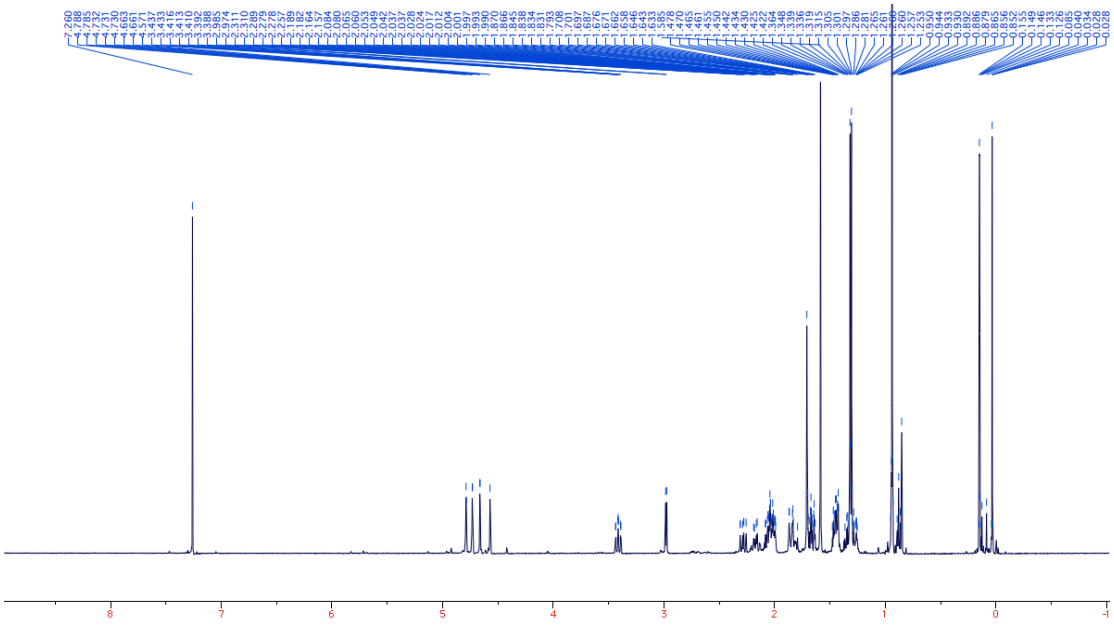
5b

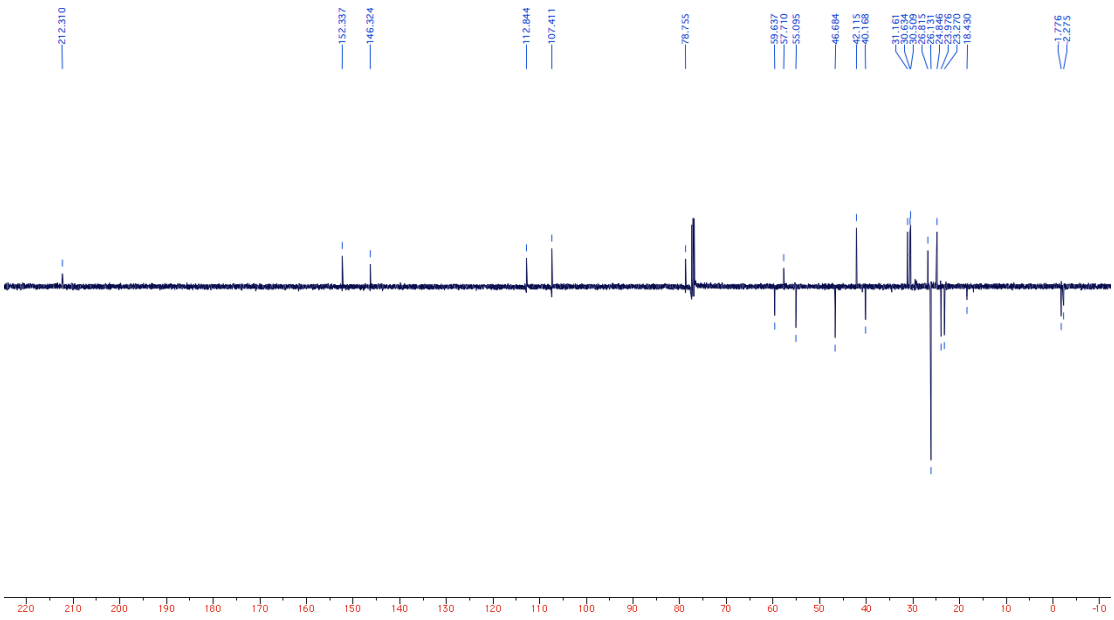

Avance 300 Monash University
ppm
7.25960
5.22711
5.20539
4.91182
3.97028
3.96264
3.93675
3.92473
3.02231
3.00630
2.22299
2.16942
2.16478
2.15496
2.03855
1.77022
1.75130
1.72185
1.70585
1.69609
1.60609
1.54697
1.51054
1.49159
1.48314
1.47797
1.46792
1.45611
1.34052
1.32674
Integral
1.0000
1.0862
1.9036
3.0929
1.1588
2.2976
2.6327
3.1270
ppm
Current Data Parameters
NAME mb-4-80
EXPNO 1
PROCNO 1
F2 - Acquisition Parameter
Date_ 20080520
Time 17.15
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 8992.806 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 se
RG 71.8
DW 55.600 us
DE 15.00 us
TE 304.2 K
D1 2.00000000 se
MCREST 0.00000000 se
MCWRK 0.01500000 se
======== CHANNEL f1 ======
NUC1 1H
P1 8.50 us
PL1 +2.00 dB
SFO1 309.1315757 MH
F2 - Processing parameters
SI 32768
SF 300.1300060 MH
WDW nc
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 23.00 cm
CY 14.30 cm
F1P 9.980 pp
F1 2941.27 Hz
F2P -0.290 pp
F2 -80.03 Hz
PPMCM 0.43478 pp
HZCM 130.49130 Hz

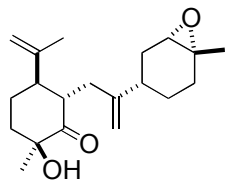

Attached proton test experiment
159.444
159.430
113.086
77.544
77.288
77.038
59.288
59.025
37.670
30.875
30.729
30.563
25.182
23.256
20.489
10.614
200
180
160
140
120
100
80
60
40
20
ppm



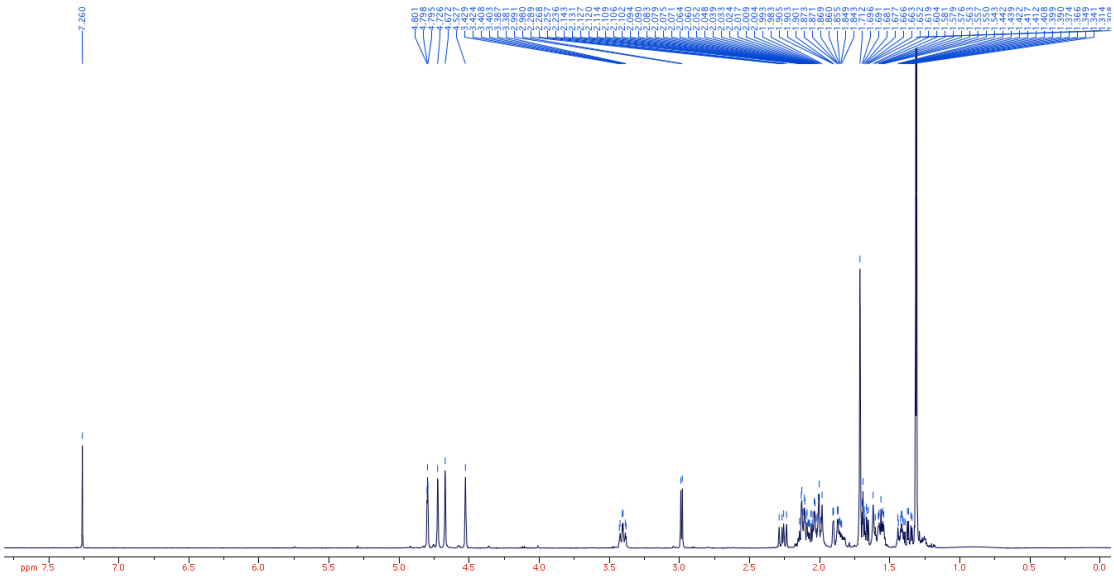
6a

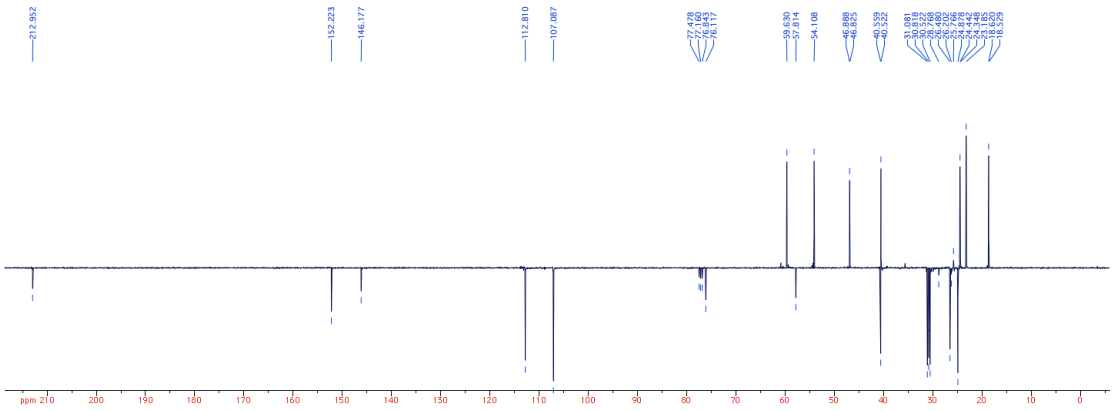


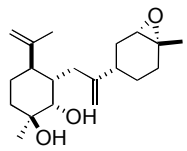




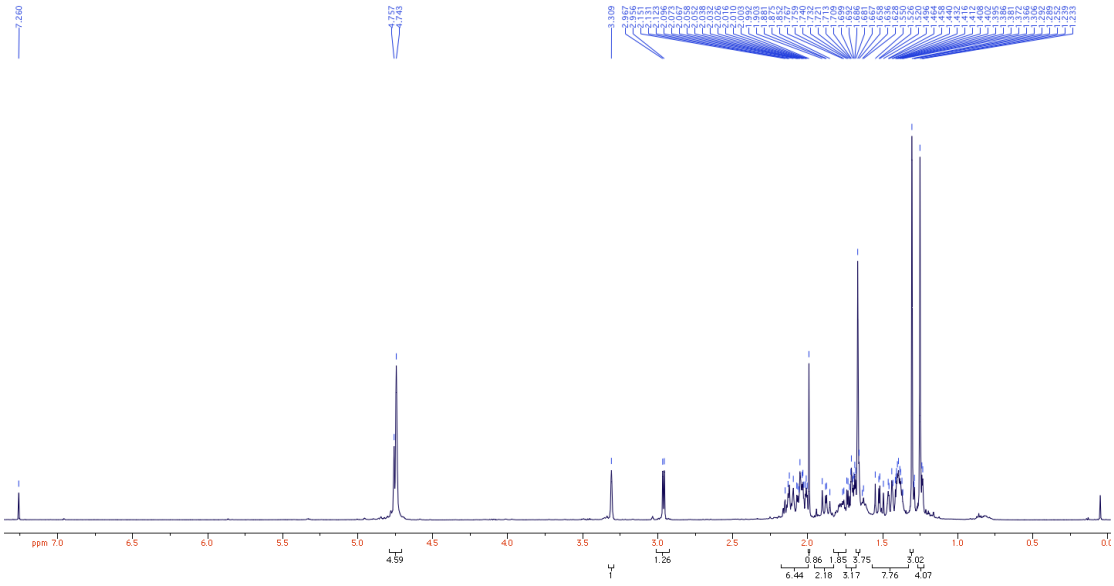
6b

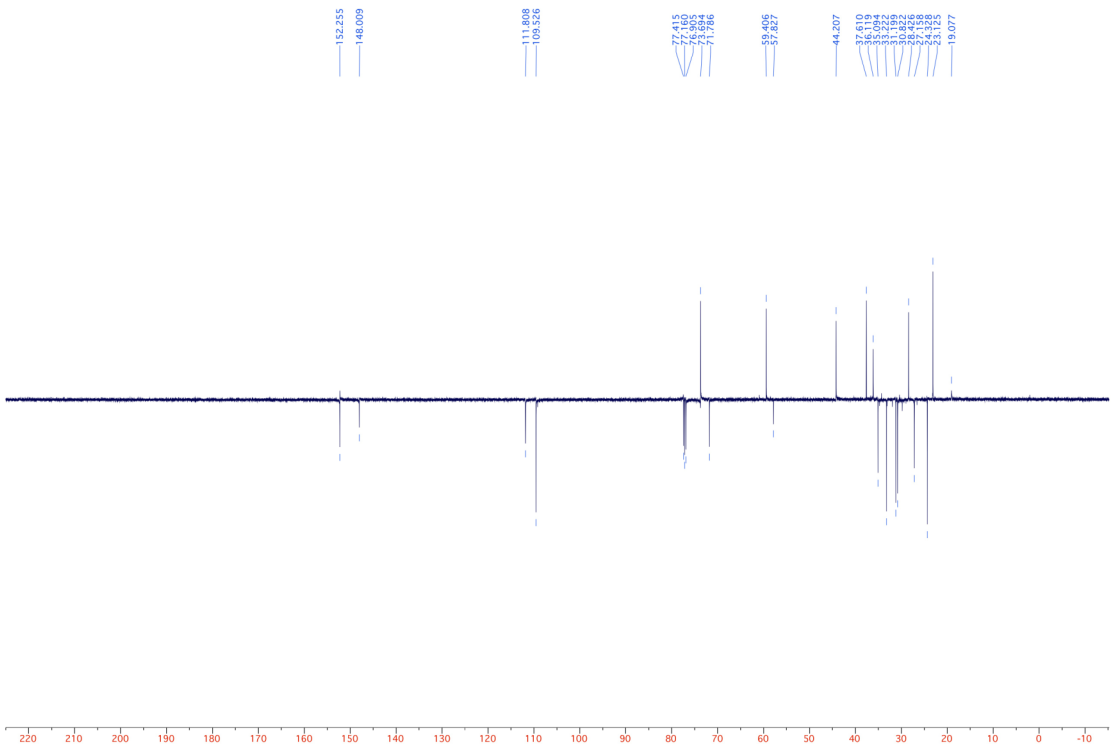


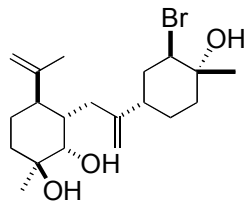




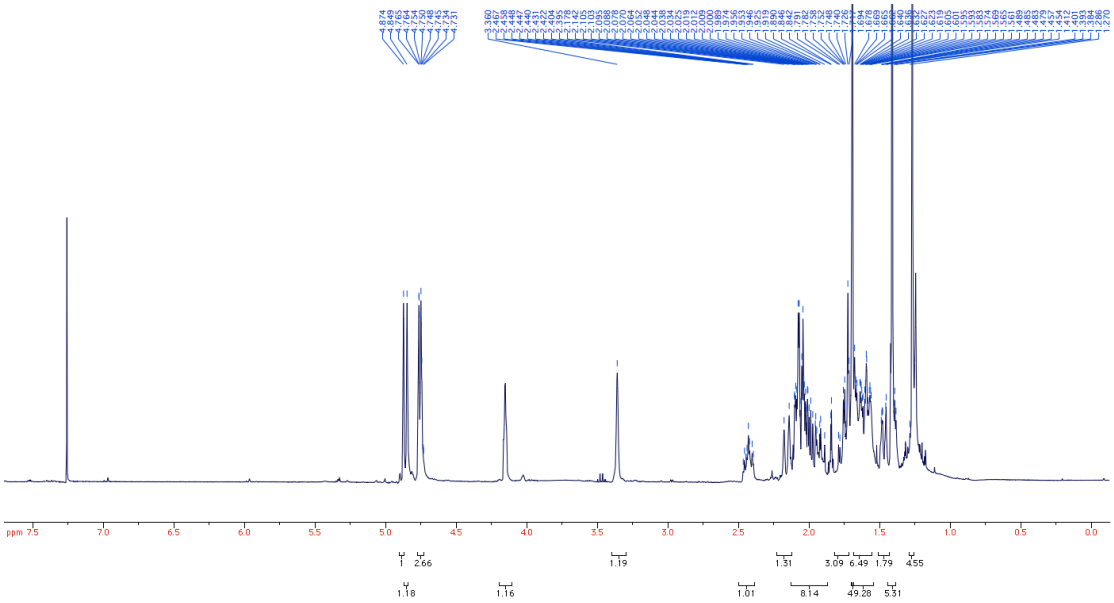
9

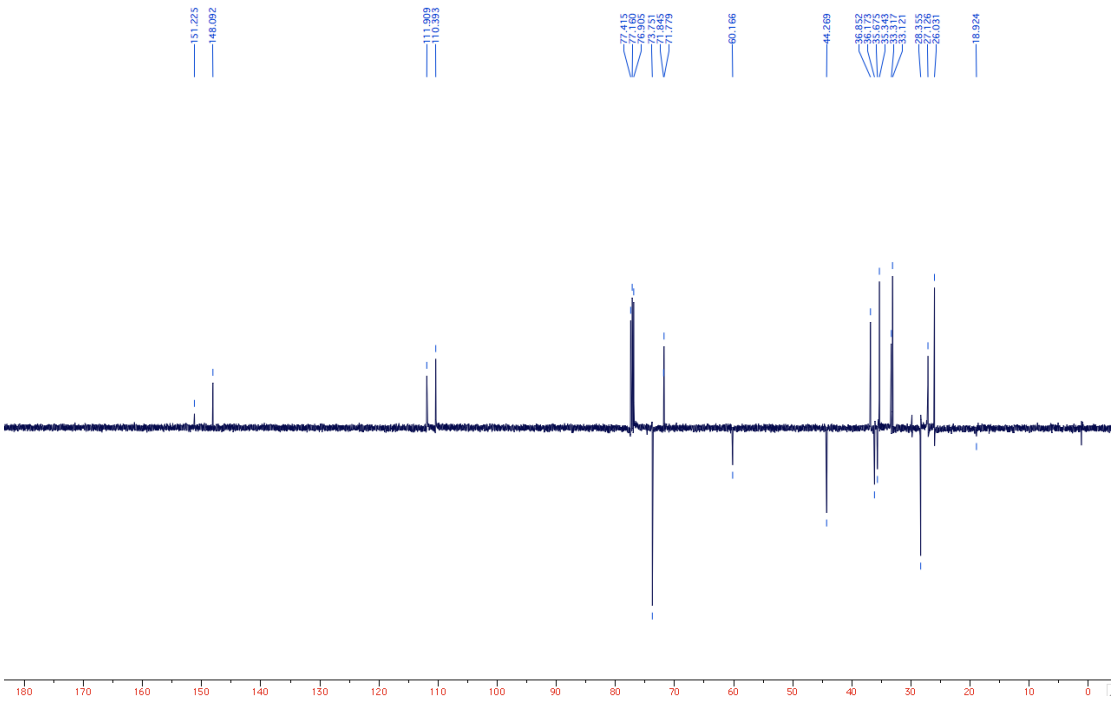


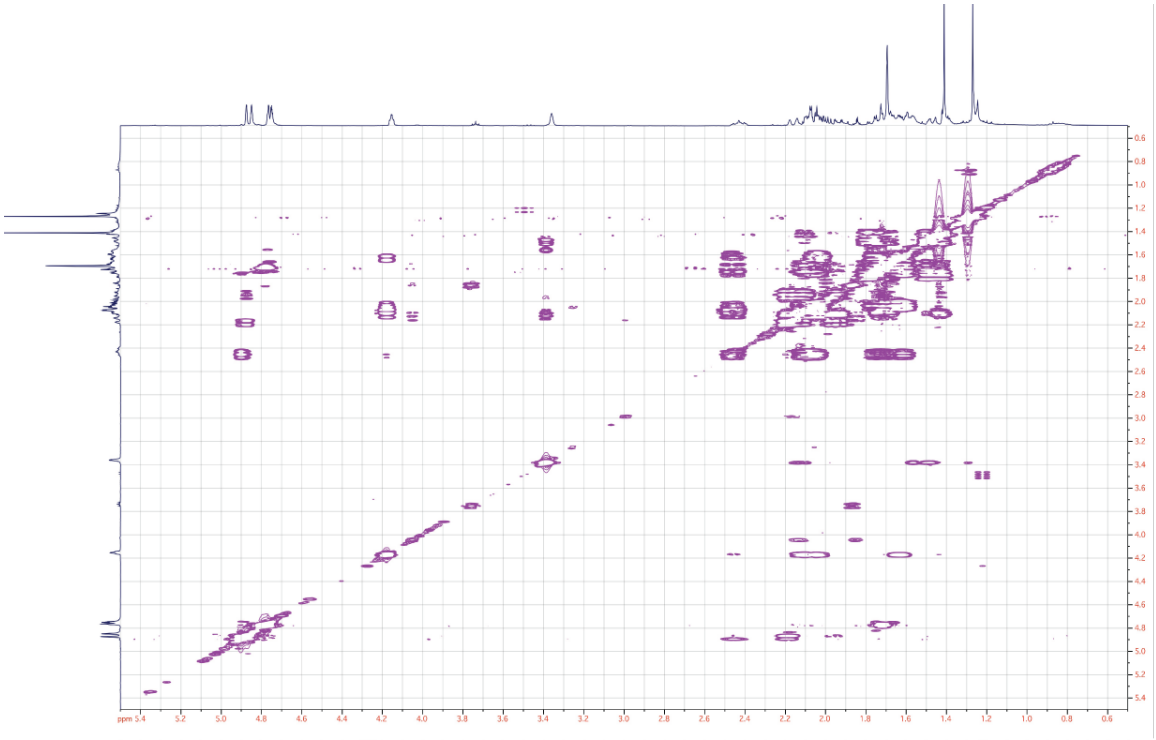




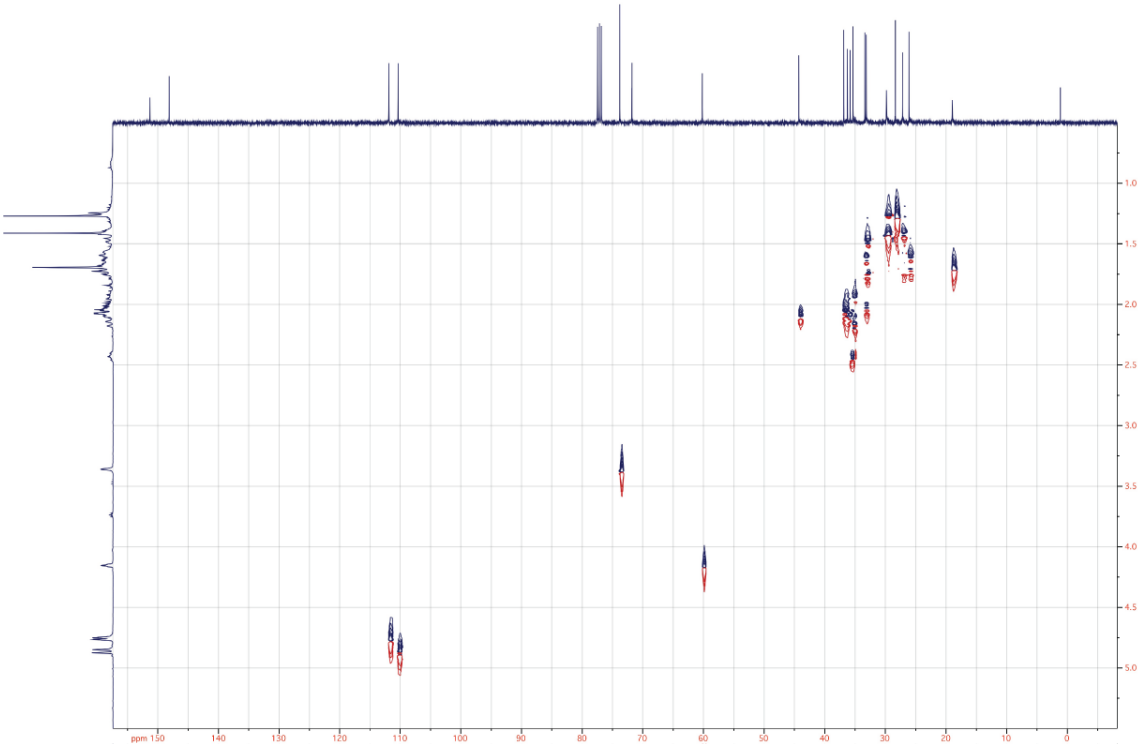
***2-epi*-Prevezol C**



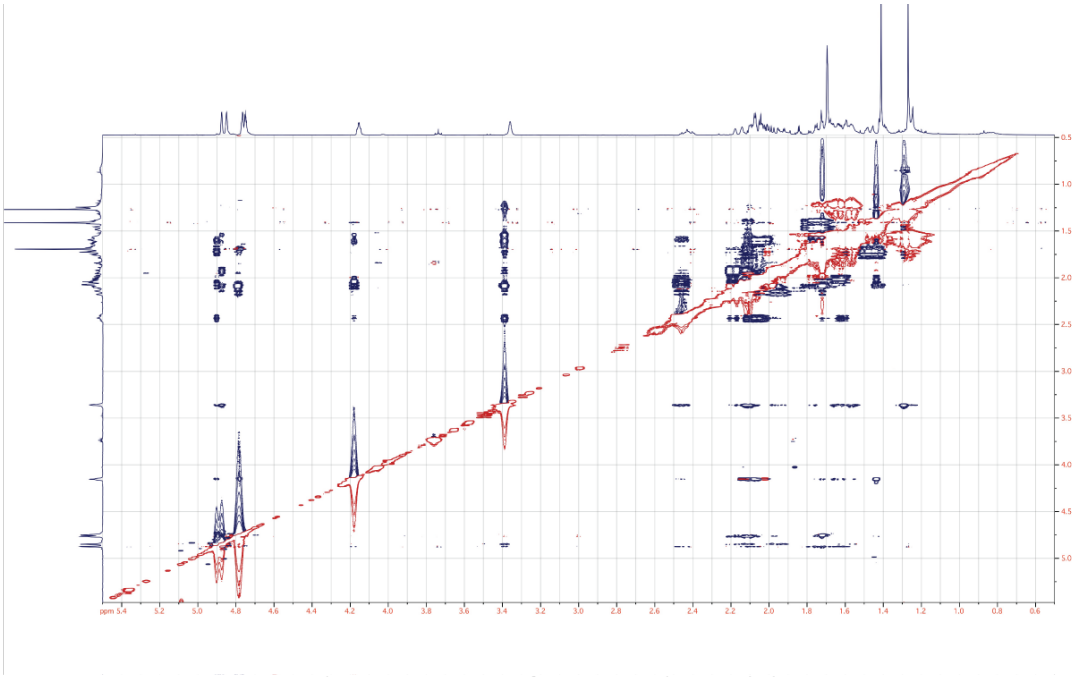




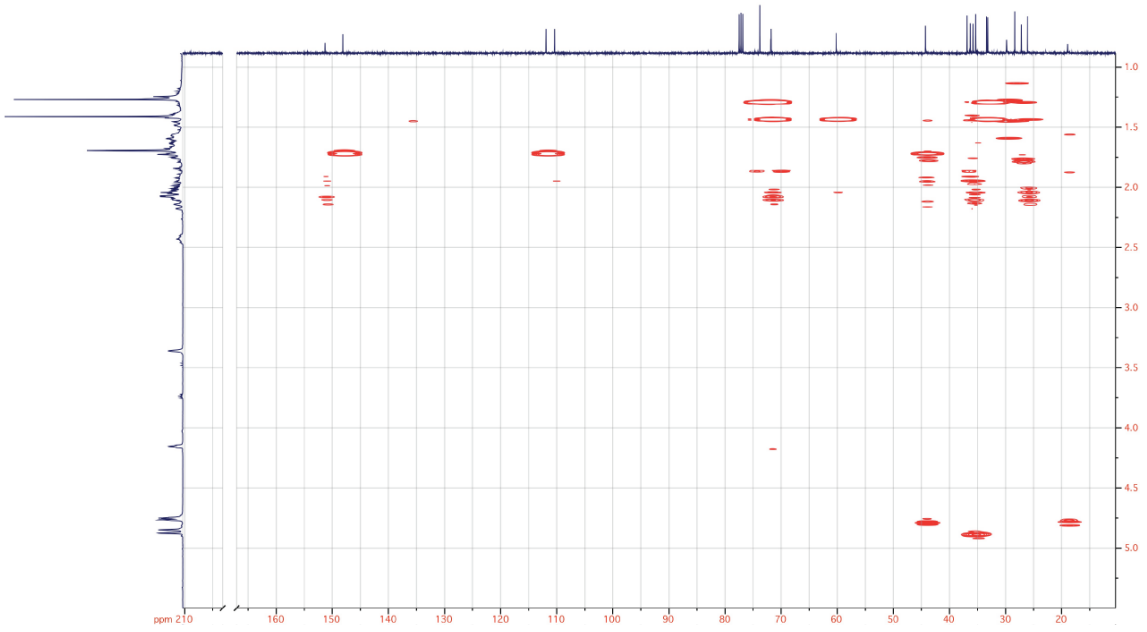
The COSY spectrum of 2-*epi*-Prevezol C recorded at 400 MHz



The HMQC spectrum of 2-*epi*-Prevezol C recorded at 400 MHz



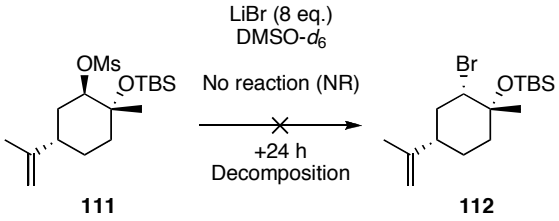
The NOESY spectrum of 2-*epi*-Prevezol C recorded at 400 MHz

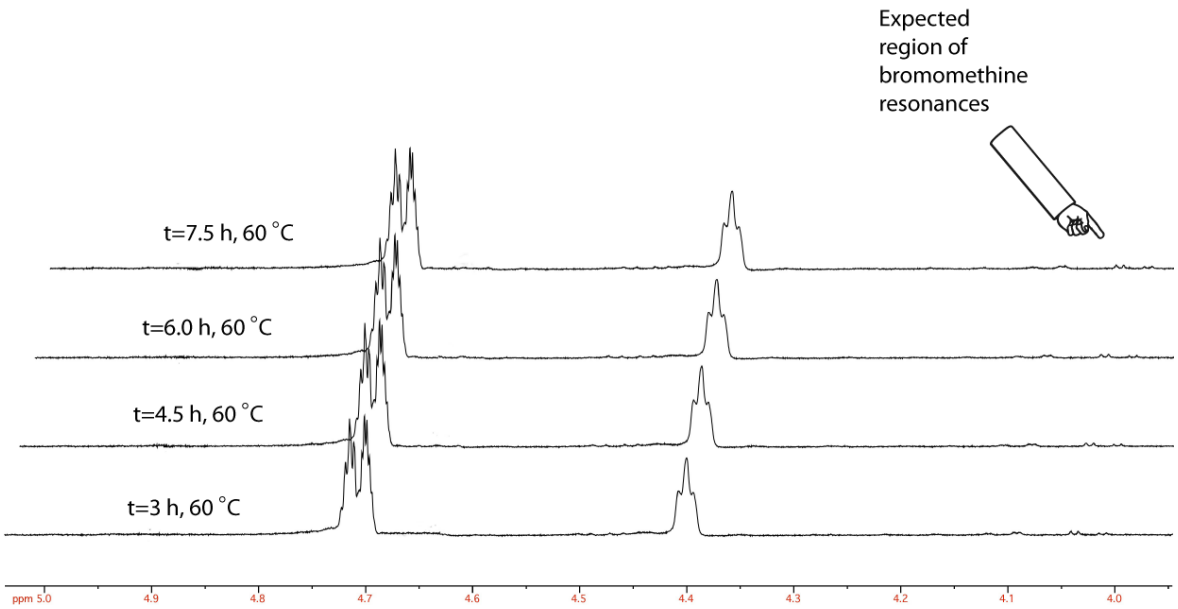


The HMBC spectrum of 2-*epi*-Prevezol C recorded at 400 MHz

Appendix 2

Eq. 1





The ^{1}H NMR spectra recorded at 300 MHz for the attempted formation of bromide 112