

**STUDIES ON THE EPOXIDATION OF BROMOALLENES,
BIOMIMETIC TRANSANNULAR REARRANGEMENTS AND
THE TOTAL SYNTHESIS OF MEMBERS OF THE
LAURENCIA NATURAL PRODUCT FAMILY**

A thesis submitted by

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the requirements for the degree of

DOCTOR OF PHILOSOPHY

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1 Front Matter

1.1 Declarations

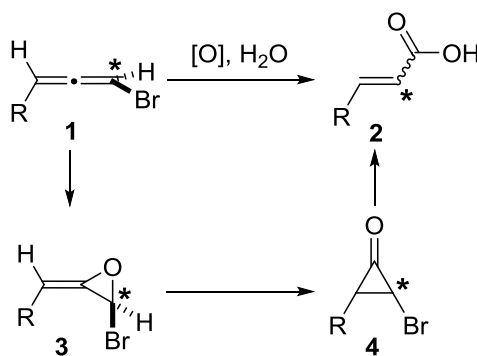
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1.2 Abstract

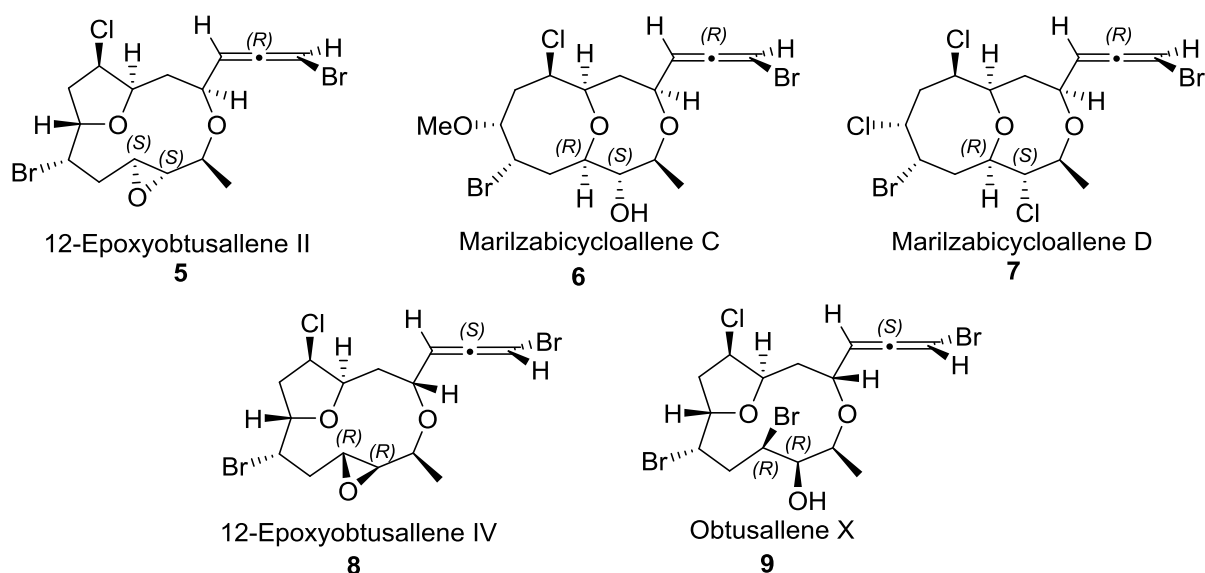
The research presented here regards the biosynthetic origins of several secondary metabolites isolated from red algae of the genus *Laurencia*. This thesis has been separated into two major parts, and includes an appendix cataloguing the experimental procedures and spectroscopic data.

Part I covers the epoxidation of bromoallenes, as inspired by the previously unknown biosynthetic link between two natural products isolated from *Laurencia obtusa*, one bearing a bromoallene and the other an α,β -unsaturated ester. Employing model bromoallene **1** and a range of epoxidation methods, a procedure was developed that would generate α,β -unsaturated acids **2** in low, but reproducible yields. Isotopic labelling of the substrate with deuterium and carbon-13 allowed elucidation of the mechanism, by observation of the migration of these atoms.



Scheme 1.2.1: Bromoallenes are linked to α,β -unsaturated carboxylic acids *via* epoxidation and formation of a bromocyclopropanone (**4**) that can undergo a Favorskii-like rearrangement.

Part II of this thesis reports the completion of the total synthesis of a range of *Laurencia* secondary metabolites. The initial targets of this project proved to be unobtainable, most likely due to the sensitivity of the allyl ether group under reductive conditions. An alternative route was successfully applied to bypass this problematic step, allow the synthesis of a range of *Laurencia* natural products and provide insights into their biosynthesis. Positive identification of these compounds was achieved by a $\Delta\delta$ analysis of the collected ^1H & ^{13}C NMR spectra, with that reported in literature.



Scheme 1.2.2: The *Laurencia* secondary metabolites synthesised during this project.

1.3 Contents

1 Front Matter.....	2
1.1 Declarations	2
1.2 Abstract	3
1.3 Contents	5
1.4 Acknowledgements	9
1.5 Abbreviations	10
1.6 Preface	14
2 Introduction.....	15
2.1 Discovery of Polyhalogenated Marine Natural Products from <i>Laurencia</i> Species.....	15
2.2 The Proposed Biogenesis of <i>Laurencia</i> Natural Products.....	21
2.3 The Proposed Biogenesis of the Obtusallene Family of Natural Products	25
2.3.1 Biomimetic Bromoetherification to Form a Model of the THF Motif	33
2.3.2 Investigation of the Bromination and Nucleophilic Trapping of Obtusallene II (15) core models	35
2.3.3 Isolation and Proposed Biogenesis of [5.5.1] Fused Core Species, the Marilzabicycloallenes	40
2.3.4 Isolation and Proposed Biogenesis of 12-Epoxyobtusallene IV (8), Obtusallene X (9) and Methyl Ester 27	43
2.4 The Epoxidation of Allenes	46
2.4.1 Favorskii Rearrangements in Nature	49
2.5 Progress Towards the Total Synthesis of Obtusallene Natural Products.....	52
2.5.1 Initial Attempt - Biomimetic Ring-Closing <i>via</i> Bromoetherification	52
2.5.2 Second Attempt - Ring-Closing <i>via</i> Grubbs' RRCM	57
2.5.3 Third Attempt - Functionalisation <i>via</i> a One-Pot Cyanoetherification.....	63
2.5.4 Formation of Obtusallene Core Macrocycles 182 & 183 <i>via</i> RCM	67

3 Results & Discussion Part I: The Epoxidation of Bromoallenes	70
3.1 Aims and Objectives Part I	70
3.1.1 Possible Mechanisms Linking Bromoallenes and α,β -Unsaturated Esters ..	70
3.1.2 Epoxidation Reagents.....	72
3.1.3 Synthesis of Model Bromoallenes.....	74
3.1.4 Synthesis of Isotopically Labelled Model Bromoallenes.....	76
3.2 Results & Discussion Part I.....	79
3.2.1 Synthesis of Model Bromoallene 1	79
3.2.2 Assay of Epoxidation Reagents	84
3.2.3 Synthesis of Deuterium Labelled Bromoallene (1- ^2H)-1	93
3.2.4 Epoxidation of Deuterium Labelled Bromoallene (1- ^2H)-1	96
3.2.5 Synthesis of ^{13}C Labelled Propargylic Alcohol (1- ^{13}C)-195.....	100
3.2.6 Derivation to ^{13}C Labelled Bromoallene (1- ^{13}C)-1.....	125
3.2.7 Epoxidation of ^{13}C Labelled Bromoallene (1- ^{13}C)-1	130
3.2.8 Further Investigation Into the Mechanism of Bromoallene Epoxidation ...	138
3.2.9 Conclusion	141
 4 Results & Discussion Part II: Completion of the Total Synthesis of Obtusallene and Marilzabicycloallenes	 144
4.1 Aims and Objectives Part II: Completion of the Total Synthesis of	
Obtusallene Natural Products	144
4.1.1 Expected Synthetic Route Towards Completed Obtusallenes and Marilzabicycloallenes	144
4.1.2 Further Derivation to other Obtusallenes and Marilzabicycloallenes	150
4.2 Results & Discussion Part II	152
4.2.1 Replication of the Cyanoetherification of Aldehyde 163	152
4.2.2 Optimisation of the Cyanation of Acetal 267	165
4.2.3 Hydrogenation of Alkynes 268a & 268b.....	167
4.2.4 DIBAL-H Reduction of Cyanoethers 286a & 286b	168

4.2.5 Alternatives to DIBAL-H Reduction.....	179
4.2.6 Further Investigation Into the Sensitivity of the Cyanoether Group to DIBAL-H	185
4.2.7 Synthesis of Dienes 180 & 181	196
4.2.8 Grubbs' RCM of Dienes 180 & 181 to Form Obtusallene Core Macrocycles 182 & 183	200
4.2.9 Epoxidation of Macrocyclic Nitrile 182 & Total Synthesis of Marilzabicycloallene C (6)	210
4.2.10 Transannular Dichlorination of Macrocyclic Olefin 182 & the Total Synthesis of Marilzabicycloallene D (7).....	228
4.2.11 Epoxidation of Macrocyclic Nitrile 183	236
4.2.12 Total Synthesis of 12-Epoxyobtusallene IV (8)	240
4.2.13 Attempt at Total Synthesis of Marilzabicycloallene B (77)	251
4.2.14 Further Reactivity of 12-Epoxyobtusallene IV (8) & the Total Synthesis of Obtusallene X (9).....	255
4.2.15 Attempts at the Deoxidation of Epoxides with Titanocene(III) Chloride as a Route to Obtusallenes II & IV (15 & 19).....	265
4.2.16 Attempts at Corey-Winter Olefination as a Route to Obtusallenes II & IV (15 & 19).....	271
4.2.17 Attempts at Oxidation and Asymmetric Reduction of Propargylic Alcohol 350 to Increase the Diastereopurity of Obtusallene Natural Products.....	279
4.2.18 Conclusion	286
5 Experimental	290
5.1 General Experimental.....	290
5.2 Procedures and Characterising Data Part I.....	292
5.3 Procedures and Characterising Data Part II	316
6 References.....	373

7 Appendices.....	379
7.1 Published Manuscript - Epoxidation of bromoallenes connects red algae metabolites by an intersecting bromoallene oxide - Favorskii manifold.....	382
7.2 Unpublished Manuscript - Epimeric Face-Selective Oxidations and Diastereodivergent Transannular Oxonium Ion Formation-Fragmentations: Computational Modelling & Total Syntheses of 12-Epoxyobtusallene IV, 12-Epoxyobtusallene II, Obtusallene X, Marilzabicycloallene C and Marilzabicycloallene D.....	380

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Lastly, I will be forever grateful to Luciana, who has been my greatest supporter during the most difficult time of my doctorate.

1.5 Abbreviations

δ	chemical shift	br.	broad
σ	bonding orbital	Bu	butyl
σ^*	anti-bonding orbital	BV	Baeyer-Villiger
<i>i</i>	iso	Bz	benzoyl
<i>J</i>	coupling constant	calcd.	calculated
<i>m/z</i>	mass/charge ratio	CBS	Corey-Bakshi-Shibata
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid	CHP	cumene hydroperoxide
<i>n</i>	normal	CI	chemical ionisation
<i>p</i>	para	cm ⁻¹	wavenumber
<i>t/tert</i>	tertiary	CODO	9-oxabicyclo[6.1.0]non-4-ene (cycloocta-1,5-diene oxide)
[H]	reduction	COSY	correlation spectroscopy
[O]	oxidation	CSA	camphorsulfonic acid
Ac	acetyl	Cy	cyclohexyl
AD	asymmetric dihydroxylation	d	doublet
AOS	allene oxide synthase	d.r.	diastereomeric ratio
aq.	aqueous	DBU	1,8-diazabicycloundec-7-ene
Ar	aryl	dd	doublet of doublets
BDSB	bromodiethylsulfonium bromopentachloro-antimonate	ddd	doublet of doublet of doublets
BPO	bromoperoxidase		

ddt	doublet of doublet of triplets	ent	enantiomer
		epi	epimeric
dddd	doublet of doublet of doublet of doublets	equiv.	equivalents
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	ESI	electrospray ionisation
DEPT	distortionless enhancement by polarisation transfer	fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate
DET	diethyltartrate	g	grams
DIBAL-H	diisobutylaluminium hydride	G I	Grubbs' 1 st generation catalyst
dm	decimetre	G II	Grubb's 2 nd generation catalyst
DMAP	4-dimethylaminopyridine	h	hours
DMF	<i>N,N</i> -dimethylformamide	HG I	Hoveyda-Grubbs' 1 st generation catalyst
DMP	Dess-Martin periodinane		
DMDO	dimethyldioxirane	HG II	Hoveyda-Grubbs' 2 nd generation catalyst
DMSO	dimethyl sulfoxide		
dq	doublet of quartets	HMDS	hexamethyldisilazane
dt	doublet of triplets	HPLC	high pressure liquid chromatography
e.e.	enantiomeric excess	HRMS	high resolution mass spectroscopy
e.r.	enantiomeric ratio		
EDTA	ethylenediaminetetraacetic acid	HSQC	heteronuclear single quantum coherence
EI	electron ionisation		

Hz	hertz	ppm	parts per million
IR	infrared spectroscopy	PTSA	<i>p</i> -toluenesulfonic acid
LA	Lewis acid	Pr	propyl
LPO	lactoperoxidase	qd	quartet of doublets
M	moles per dm ³	quant.	quantitative
m	multiplet	R	alkyl group
Me	methyl	R _f	retention factor
mg	milligrams	r.t.	room temperature
min	minutes	RCM	ring-closing metathesis
mL	millilitres	RRCM	relay ring-closing metathesis
mmol	millimole	RMS	root-mean-square
MS	mass spectroscopy	s	singlet
NBS	<i>N</i> -bromosuccinimide	SG	Stewart-Grubbs' catalyst
NCS	<i>N</i> -chlorosuccinimide	t	triplet
NMR	nuclear magnetic resonance	TBAF	tetra- <i>n</i> -butylammonium fluoride
NOE	nuclear Overhauser effect	TBCO	2,4,4,6- tetrabromocyclohexa-2,5- dienone
NOESY	nuclear Overhauser effect spectroscopy		
Nu	nucleophile	TBDPS	<i>tert</i> -butyldiphenylsilyl
Ph	phenyl	TBS	<i>tert</i> -butyldimethylsilyl
PMB	<i>para</i> -methoxy benzyl	td	triple doublet
ppb	parts per billion		

TES	triethylsilyl	TMG	<i>N,N,N'N'</i> - tetramethylguanidine
Tf	trifluorosulfonyl		
TFA	trifluoroacetic acid	TMS	trimethylsilyl
THF	tetrahydrofuran	Tris	2,4,6-triisopropylbenzene sulfonyl
TLC	thin layer chromatography		

1.6 Preface

Within the experimental, all compounds are named according to IUPAC convention. However, within the main text, obtusallenes, marilzabicycloallenes & their precursor compounds are numbered sequentially from the terminal bromoallene carbon to the terminal methyl group. An example is given in figure 1.6.1.

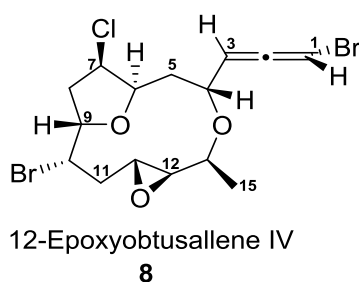


Figure 1.6.1: Example of the numbering system used within this thesis

This is to reflect the contiguous carbon chain of the C₁₅ acetogenin precursor that they all derive from, but also to simplify discussion and comparison between compounds.

2 Introduction

2.1 Discovery of Polyhalogenated Marine Natural Products from *Laurencia* Species

The study of natural products has been a focus of organic chemistry from the very beginning, but those from a marine source were not scrutinised until the mid 20th century when the use of SCUBA equipment opened up new frontiers for exploration. Since then, marine environments have proven to be a rich source of organic compounds. Valued not only for their diversity and unique structures, but also the numerous examples of bioactivity, the number of secondary metabolites isolated from marine organisms is estimated to be around 18,000.¹

Rhodomelaceae, commonly described as red algae, are perhaps the most fascinating source of novel compounds. Although difficult to describe taxonomically, a major order of Rhodomelaceae is *Ceramiales* and is the source of over 500 isolated compounds.¹ Natural products from these organisms are of scientific interest due to the high degree of halogenation of the many aromatics and terpenoids (**10** & **13**, figure 2.1.1), often responsible for biological activity and relatively rare in land species.² Found within *Ceramiales* is the genus *Laurencia*, which may be the most fruitful source of halogenated secondary metabolites.³ *Laurencia* has proven a challenge to describe taxonomically due to the near identical appearance and overlapping habitat of each species. There have been several cases of misidentification and reclassification occurring in the literature.⁴ For this reason, the distinct secondary metabolites found in a specimen are often used as more useful chemotaxonomic markers for a given species.⁵ Distinct species show a profile of compounds with similar structural features, e.g. terpenoid, aromatic, ring-size and degree of

halogenation.⁶ Brominated metabolites predominate, but many also contain chlorine and even four examples bear iodine.⁷

A major class of *Laurencia* compounds are the C₁₅ acetogenins, the first of which, laurencin **11**, was discovered by Irie in Japan in 1965.⁸ In the following 50 years, more than 200 acetogenins have been described. Mostly isolated from Rhodomelaceae, but also from the digestive system of sea-hares of the genus *Aplysia*.³ Some *Laurencia* species contain large intracellular vesicles known as 'corps en cerise', or 'cherry bodies'. These are considered to be the cellular origin of halogenated metabolites, as *Laurencia* species with absent corps en cerise do not produce such halogenated compounds. Whether these are the site of production or only storage is not known.⁹ Such secondary metabolites have been shown to be antimicrobial, insecticidal, antifungal, antiviral, antifeedant, antihelminthic and cytotoxic, so are considered broad-spectrum antiepipibiosis compounds, able to repel or deter predatory or pathogenic species.^{3, 10}

Three major types of these acetogenins are frequently isolated from *Laurencia* species, with examples given in figure 2.1.1. The first is comprised of the subgroups laurenans & lauthisans, **11** & **12** respectively, both containing an 7, 8 or 9-membered cyclic ether and divided by the relative stereochemistries around the macrocyclic ether linkage.¹¹ Collectively they are referred to as medium-ring ethers. The second group, marilzabicycloallenes such as **14**, are distinguished by their bicyclic fused [5.5.1] ring ethers.¹² The last group are the obtusallenes, such as **15**, with a 12-membered macrocyclic ether, often with a fused THF moiety, at least one bromine and often including chlorine.¹³

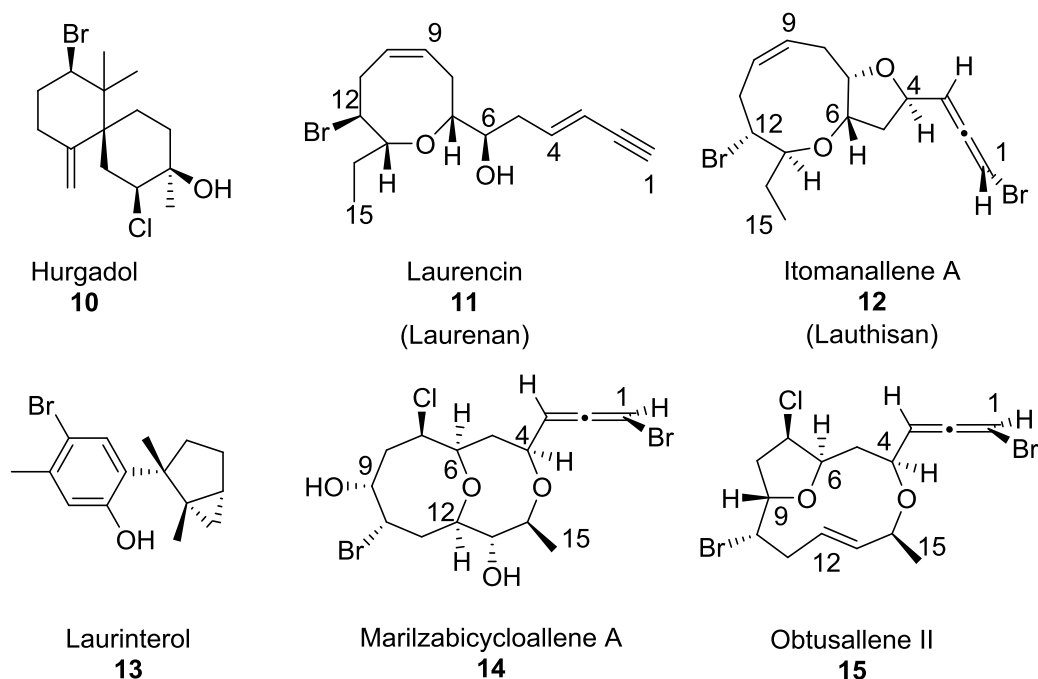


Figure 2.1.1: Examples of *Laurencia* natural products.

To date, sixteen compounds in the obtusallene family have been isolated (figure 2.1.3). All contain a bromoallene moiety, apart from notable exceptions marilzanin (**29**) and the unnamed methyl esters **27** & **28**. However, they shall be included in the list of obtusallenes as they have the same biosynthetic origins and give insights into some novel reactivity.

The first members were isolated in 1982 by Imre.^{13a} An isolation of *Laurencia obtusa* yielded two bromoallenes. One structure was unambiguously defined by X-ray crystallography and named obtusallene I (**16**), with the bromoallene functionality characteristic of *Laurencia* compounds, but a previously unseen 12-membered fused ring. The second was not as fully characterised, so the structure was only tentatively assigned as **15^a** (figure 2.1.2).¹⁴ The analogous 10-bromoobtusallene I (**17**) was also co-isolated with obtusallene I (**16**) in a subsequent extraction of *Laurencia obtusa* by Imre.^{13e}

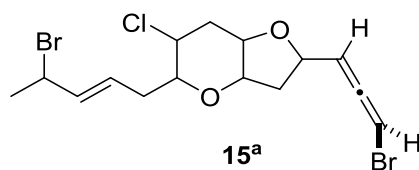


Figure 2.1.2: The initial structural assignment of obtusallene II (**15^a**).

It wasn't until 1991 when Imre re-isolated *Laurencia obtusa*, that the structure was positively identified as that of obtusallene II (**15**) by X-ray crystallography, along with the simultaneous isolation of obtusallene III (**18**).^{13b} With all three bearing many of the same novel features, a series of related compounds had been established.

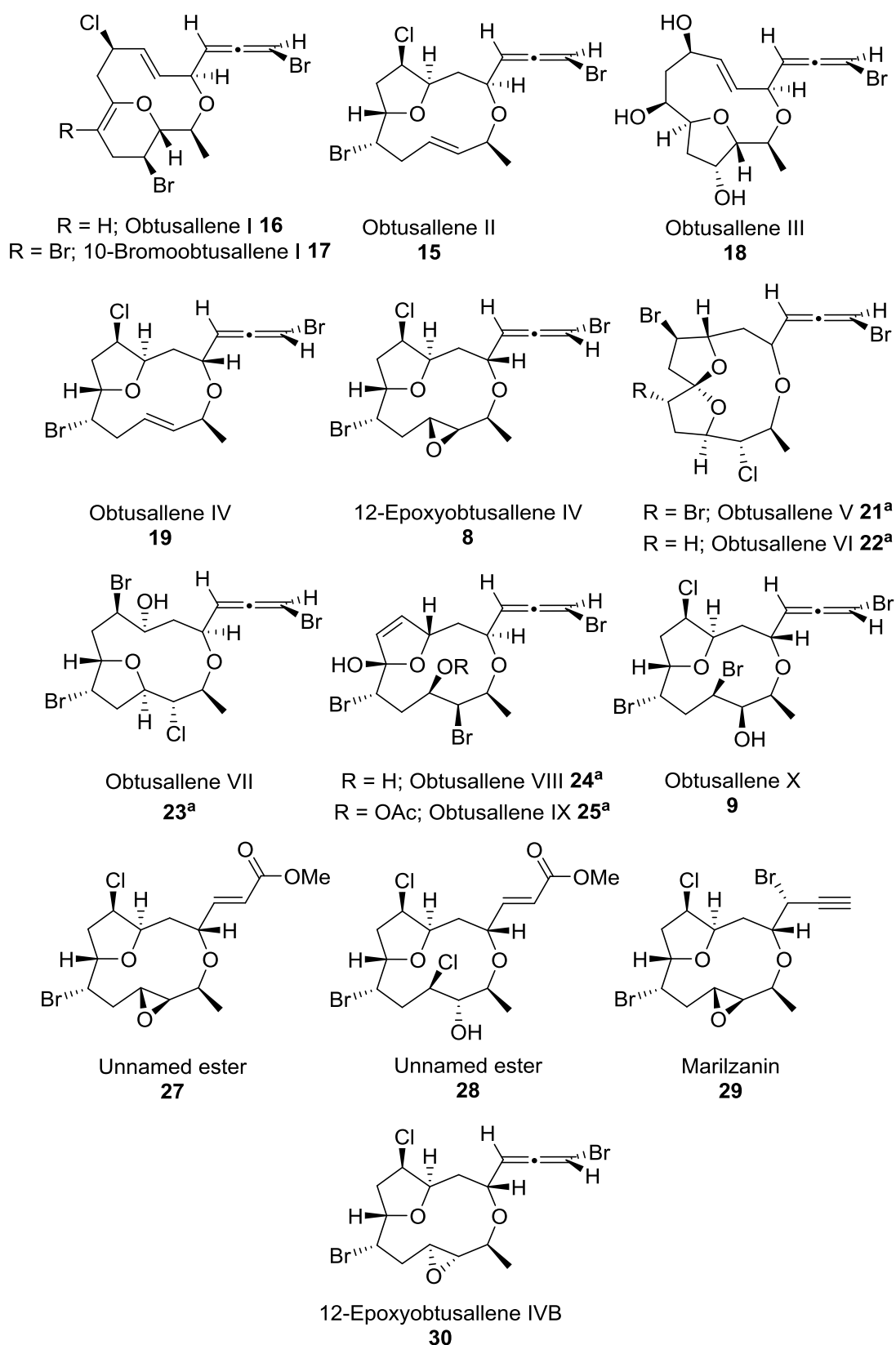


Figure 2.1.3: Sixteen known members of the obtusallene family (n.b. compounds labelled with ^a are represented by their originally proposed structures, *vide infra* section 2.3).

In 1997, Ciavatta and Guella simultaneously discovered an epimer of obtusallene II (**15**), showing the opposing absolute stereochemistry at C₄ and the reverse axial chirality along the bromoallene.^{13c, 13d} Ciavatta had extracted the digestive glands of the opisthobranch molluscs *Aplysia dactylomela*, known to graze on *Laurencia* algae, and obtained a polyhalogenated compound. The structure was defined by X-ray crystallography and although Ciavatta acknowledged the diastereomeric relationship to obtusallene II (**15**), she named the new compound dactylallene after the mollusc. Guella discovered the same compound in *Laurencia obtusa* and named it obtusallene IV (**19**), matching the nomenclature of the other compounds in the series.

Obtusallenes V-IX (**21^a** - **25^a**) were discovered simultaneously by Guella in 2000.^{13f} There were no X-ray studies performed on these compounds, perhaps due to the small quantities collected from the extractions. Instead, characterisation and structure elucidation was largely performed by NMR spectroscopic techniques and Mosher esters derivatisation.¹⁵

More recent was the discovery of obtusallene X (**26**), 12-epoxyobtusallene IV (**20**) and unnamed ester **27** by Norte in 2011, this time from closely related algae *Laurencia marilzae*, all appearing to be derivatives of obtusallene IV (**19**).^{13g}

The latest discoveries in the obtusallene family are marilzanin (**29**), 12-epoxyobtusallene IVB (**30**) and unnamed ester **28** in 2016. Again, all seemingly derived from obtusallene IV (**19**).^{13h}

With such complex connectivity, sensitive moieties, varying macrocycle size and up to nine stereocentres, the obtusallenes are daunting yet appealing synthetic targets. Perhaps due to these obstacles, there have been no previous attempts at the total synthesis of any of these compounds.

2.2 The Proposed Biogenesis of *Laurencia* Natural Products

All of the obtusallenes, as well as the laurenans and lauthisans, bear very similar features. All have a C₁₅ skeleton, showing two or three degrees of unsaturation between C₁ & C₄ in the form of a bromoallene or an enyne and have incorporated heteroatoms at key positions. It is therefore reasonable to presume that all are derived from a similar precursor. The discovery of laurediols (**31**) by Irie in 1972, laurencenyne (**32**) by Yamada in 1981 and more recently, adrienynes (**33**) by Gutierrez-Cepeda in 2011, gave clues to the structure of the precursor.^{13g, 16} (The numbering of the contiguous C₁₅ chain of these linear precursors is also applied to the other *Laurencia* natural products throughout this thesis and highlights the relationship).

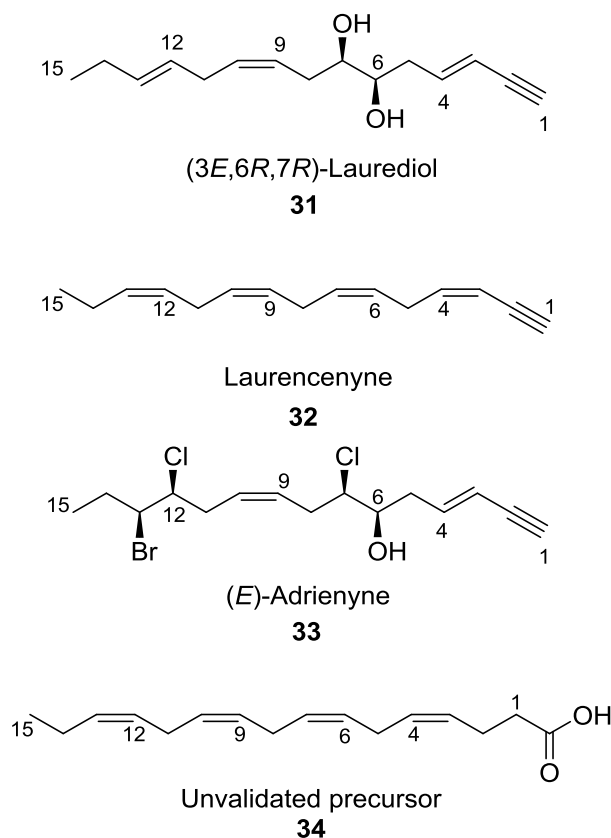


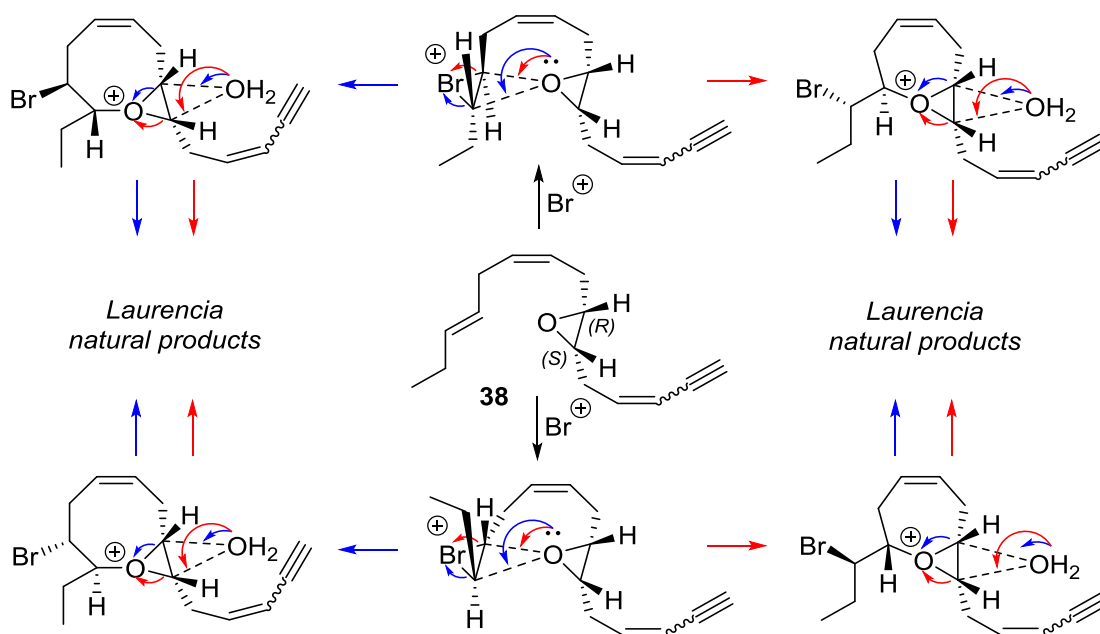
Figure 2.2.1: Examples of straight-chained *Laurencia* natural products.

Polyunsaturated compounds similar to laurencenyne (**32**), isolated from the closely related species of algae *L. okamurae*, are the presumed precursors to the entire family of acetogenins.^{16b} Further back in the biogenesis, the source of **32** is theorised by Sir Ewart Jones to be known fatty acid **34**, although no experimental evidence or even mechanistic proposal has been made.¹⁷ This compound is known in other algae species,¹⁸ but has not yet been observed in *Laurencia*.

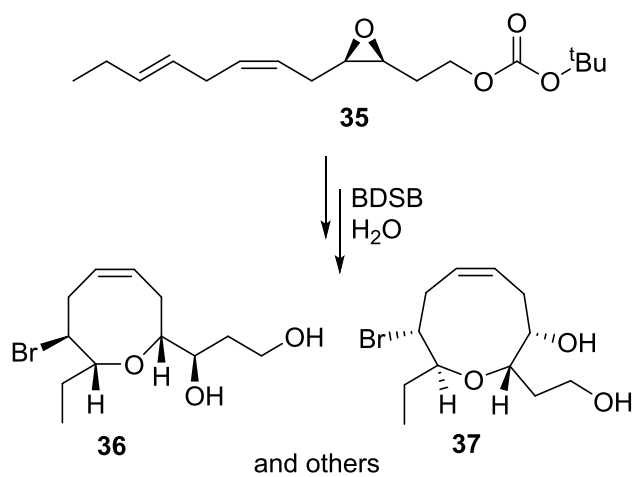
A biosynthesis for all the *Laurencia* compounds can be envisaged to require only epoxidation and bromination, a source of chloride and an aqueous medium, all of which exist in an algal cellular environment. Certain members of the cytochrome P450 hemoprotein superfamily are known to catalyse a range of epoxidation reactions, often with distinct stereospecificity due to the minor variations in the active site and variable nature of the oxidation state of the iron.¹⁹ Biosynthetic brominations are often facilitated by vanadium bromoperoxidase (VPO), a protein often found in seaweeds and marine algae.²⁰ This enzyme does not have a traditional active site, but instead oxidises the bromide present in seawater to provide a source of electrophilic bromine. In a very similar manner to brominating reagents such as *N*-bromosuccinimide, the bromination is non-specific and any π -bonds will be brominated. However, further reaction will only occur if a suitable nucleophile is in the correct proximity and orientation. The nature of the nucleophile is integral to the connectivity of the resulting skeleta and the natural products thus produced.

Work by Murai using the cow's milk enzyme lactoperoxidase, established that select laurenans and lauthisans could be produced from laurediols, such as **31** in the presence of electrophilic bromine.²¹ Braddock built upon this hypothesis in 2012, by the use of a model system to show that the biosynthesis was more satisfactorily explained by the use of an epoxide such as compound **38** in scheme 2.2.1., instead of a diol. A model epoxide and the

brominating agent $\text{Et}_2\text{SBr}\cdot\text{SbCl}_5\text{Br}$ (BDSB) were employed to demonstrate that a much wider range of laurenans and lauthisans could be produced.²² This was proven by demonstrating that a single linear epoxide model (**35**, scheme 2.2.2) could be cyclised to a range of C_7 & C_8 skeleta in the presence of BDSB. Several core structures were also identified that had no analogue in the literature. Braddock proposed that they corresponded to undiscovered natural products. With this, the biogenesis of a major group of *Laurencia* natural products had been elucidated with experimental data and a new reaction established, the Intramolecular Bromonium Ion Assisted Epoxide Ring Opening (IBIAERO).²³ The origins of the obtusallenes were not yet as firmly established.



Scheme 2.2.1: Braddock's hypothesis for the synthesis of *Laurencia* laurenans and lauthisans.



Scheme 2.2.2: Proof-of-principle cyclisation of linear epoxide to form **36** & **37**, representing the cores of laurencin (**11**) and itomanallene A (**12**).

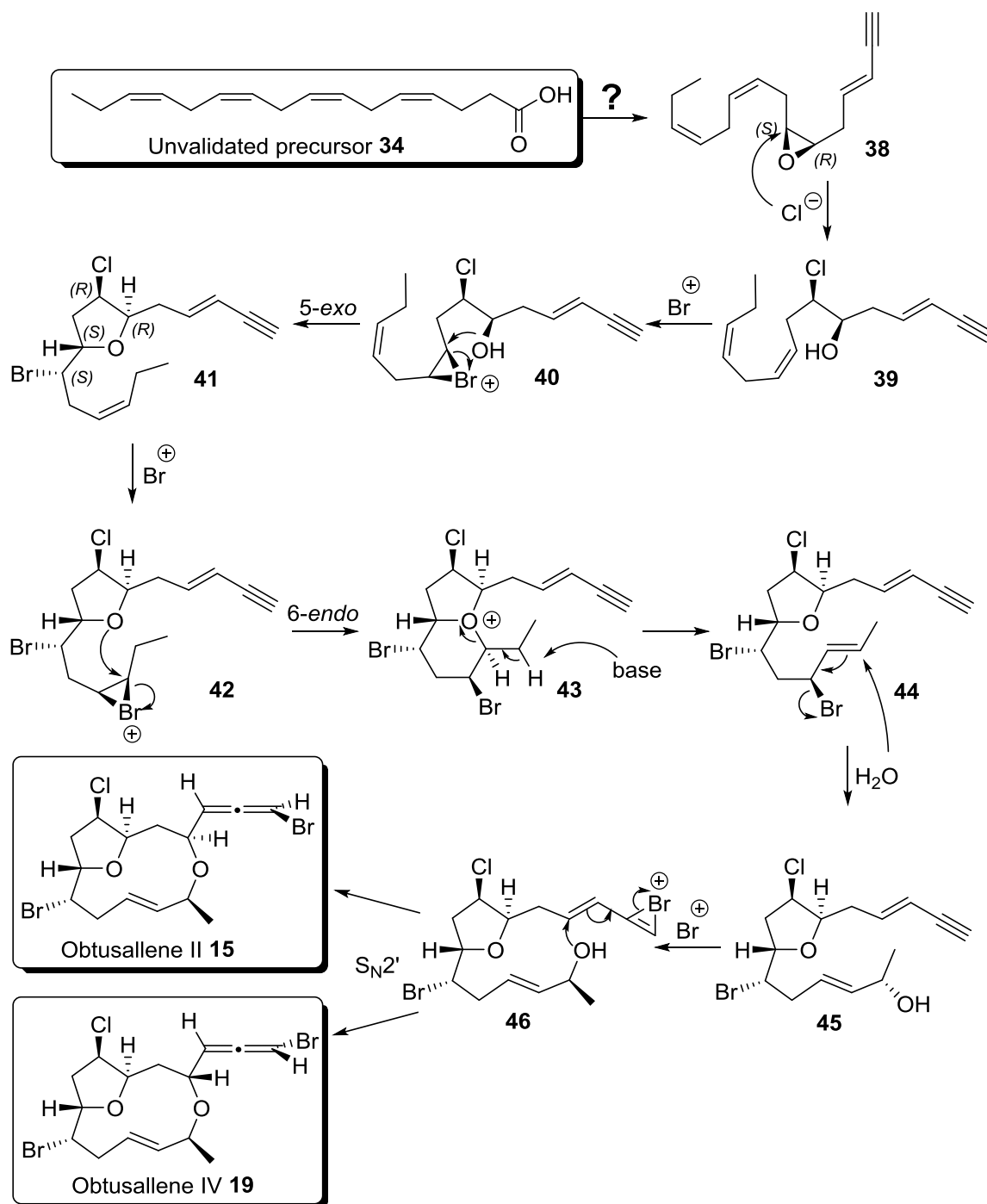
2.3 The Proposed Biogenesis of the Obtusallene Family of Natural Products

In 2006, Braddock published a further hypothesis concerning the biosynthesis of all the obtusallene members known at the time (obtusallenes I - IX, **15** - **25**^a, figure 2.1.3).²⁴ This proposal convincingly described the source of all the complex obtusallene functional groups and stereochemistries observed, whilst invoking only the simple brominative cyclisation reactions discussed earlier. Apart from VPO to oxidise bromide to an electrophilic state, there is no need for any enzyme mediation. The complexity observed is proposed to be a product of the conformation of the intermediates and inherent regioselectivities & stereoselectivities of these reactions.

Conceivably, it is epoxide **38** and its fate that determine whether the end products are obtusallenes or the medium-ring ethers. The (*S,R*)-epoxide in scheme 2.2.1 can directly attack a bromonium ion to form a medium-ring ether. Alternatively, precursor epoxide **38** (scheme 2.3.1), could undergo regioselective and stereospecific opening by a chloride ion to form *syn*-chlorohydrin **39**. This might now have the conformational flexibility to open a bromonium ion across the C₉-C₁₀ olefin. An electrophilic bromination across this bond could be followed by 5-*exo-tet* opening of the bromonium ion of **40**, by the appropriately positioned alcohol to form the characteristic THF core of **41**. The conformation of the alcohol relative to the bromonium may be the source of the high selectivity for the observed relative and absolute stereochemistries, i.e. (6*R*,7*R*,9*S*,10*S*), across the THF motif. Baldwin's rules support the observed preference for 5-*exo-tet* cyclisation over the alternative 6-*endo-tet* attack at C₁₀.²⁵

The oxolane oxygen could then act as a nucleophile in the second bromination event across the C₁₂-C₁₃ olefin, in a 6-*endo-tet* cyclisation to produce oxonium **43**. Deprotonation by adventitious base would yield allyl bromide **44** and S_N2' substitution by water gives alcohol

45. Upon bromination of the alkyne to give bromonium ion **46**, the alcohol could facilitate macrobromoetherification *via* a *syn* S_N2' attack upon C₄.²⁶ Thus, the 12-membered macrocycle is closed with simultaneous formation of the bromoallene. The stereochemistries of diastereomeric obtusallene II (**15**) and IV (**19**) appear to arise from attack on each face of the enyne following bromination.



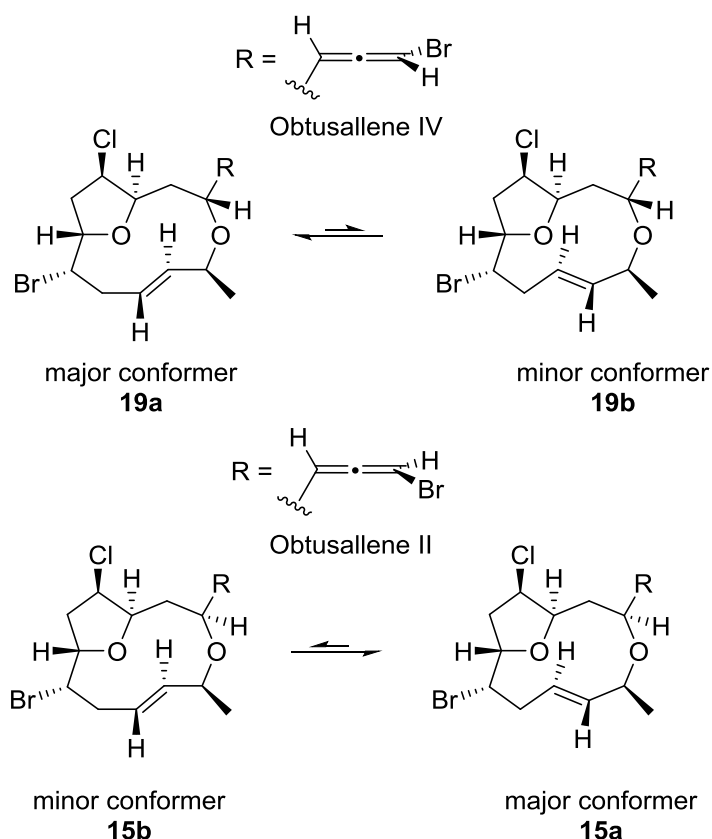
Scheme 2.3.1: Braddock's proposed biosynthesis of obtusallenes II & IV (15 & 19).

These two macrocycles seemingly act as precursors to all the remaining obtusallenes, *via* bromination of the remaining C_{12} - C_{13} olefin. The stereoselectivity of this bromination would be dependent on which face of the olefin is exposed to solvent. When Guella isolated

obtusallene IV (**19**), it was observed that there was significant broadening of the NMR signals, most pronounced across the C₁₁-C₁₅ fragment with a 15 - 20 Hz linewidth.^{13d} This was rationalised as an effect of two slowly interconverting conformers, due to rotation of the C₁₂-C₁₃ double bond, known as a D process.²⁷ Reducing the temperature to -20 °C, the slow exchange limit, led to some sharpening of the signals. Raising the temperature to +50 °C also resulted in signal sharpening as the fast exchange limit was approached.

In the same work, molecular mechanics (MM) calculations predicted two conformations, major **19a** and minor **19b**, with a difference in energy of less than 3 kcal mol⁻¹. Using the equation $K = e^{-\Delta E/RT}$, a relative population of 65 : 35 was calculated, in favour of the *Re* face exposed to solvent.

Furthermore, in the case of obtusallene II (**15**), MM calculations found five distinct conformers. As well as the rotation of the C₁₂-C₁₃ olefin, the C₁₀ bromine atom transitions between axial and equatorial orientations and the THF oxygen undergoes S-type flipping.²⁷ However, the bromine and THF interconversions were comparatively fast enough to have no effect on the spectra. Considering only the olefin rotation, a similar relative population of 61 : 39 was predicted. However, in this case the orientation of the olefin was opposite to that in obtusallene IV (scheme **2.3.2**) as the *Si* face is exposed to solvent in the major conformer.



Scheme 2.3.2: Conformations of obtusallene IV (19) and obtusallene II (15).

In the same paper, similar calculations were performed on obtusallene I (16), 10-bromoobtusallene I (17) and obtusallene III (18). All were found to have distinct conformational effects. The line broadening was not reported in previous isolations of these compounds. Guella presumed that the broad spectra had been overlooked as simply being impure.

Scheme 2.3.3 shows the continuation of Braddock's proposed biosynthesis.²⁴ Bromination on the *Si* face of the C₁₂-C₁₃ olefin of obtusallene II (15) gives bromonium ion 47. The THF oxygen is appropriately positioned to open this bromonium ion, forming either oxonium ions 48 or 49, depending on whether it undergoes a 6-*endo* (blue) or 5-*exo* (red) cyclisation. Beginning with the 6-*endo* route, oxonium ion 48 could follow one of the two

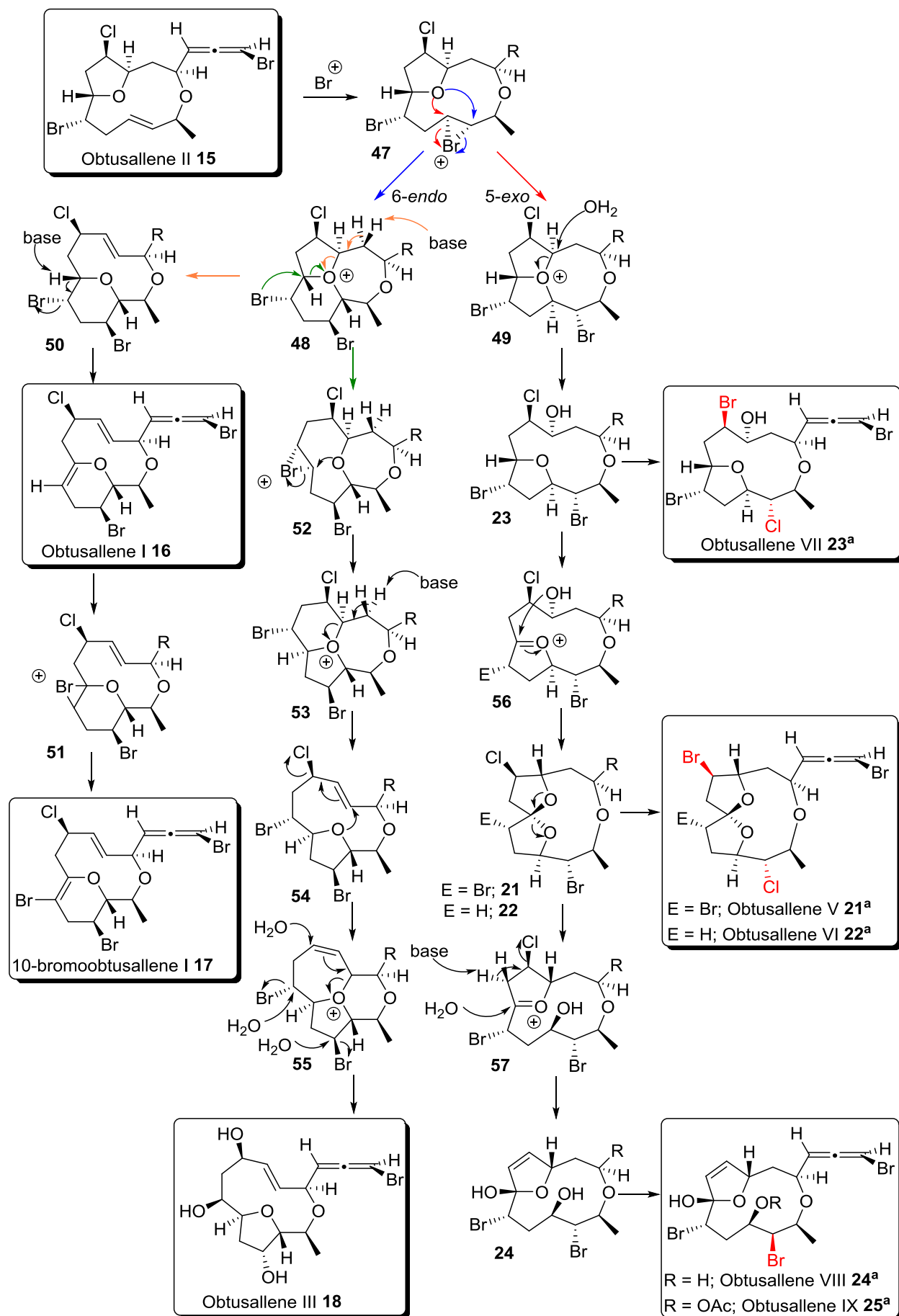
proposed routes. Successive base mediated eliminations (orange), first across the C₅-C₆ bond to collapse the oxonium ion and give the new [7.3.1] fused structure **50**, then across C₉-C₁₀ to give obtusallene I (**16**). This compound could be further brominated across the new C₉-C₁₀ olefin, open with the assistance of the dihydropyran oxygen and eliminate across the same bond to yield 10-bromoobtusallene I (**17**).

Alternatively, the C₁₀ bromine of compound **48** can perhaps relieve the oxonium ion (green), resulting in new bromonium ion **52**, which is subsequently opened by the THF oxygen in a 5-*exo* manner to form oxonium ion **53**. Deprotonation at C₅ releases the oxonium ion and forms a double bond across C₅-C₆. The THF oxygen can attack the double bond in an S_N2' manner to remove the chloride, resulting in oxonium ion **55**, which is then replaced by a molecule of water. This would be a two-step process, unlike the direct S_N2 substitutions of the two bromine atoms, as demonstrated by the retention of stereochemistry in the former and inversion in the latter when considering the completed obtusallene III (**18**).

If we now consider the alternative 5-*exo* cyclisation pathway (red) possible for bromonium ion **47**, water may open the oxonium ion of **49** at C₆ to give the core structure of obtusallene VII (**23**). However, examination of the halogens at C₇ and C₁₃ shows a discrepancy between Braddock's predicted structure **23** and Guella's assignment **23^a**. This will be discussed in more detail later.

Continuing from obtusallene VII (**23**), antiperiplanar elimination of HBr across C₉-C₁₀, followed by electrophilic bromination or protonation of the resulting olefin, opening with the assistance of the THF oxygen and intramolecular trapping by the hydroxyl would result in the spiroketal cores of obtusallene V (**21**) and VI (**22**), depending of the nature of the electrophile. Again, note that the same C₇ and C₁₃ halogens are exchanged when comparing **22** & **23** with **22^a** & **23^a**.

Spiroketal **21** could then collapse to yield oxonium ion **57**, with a similar core to obtusallene II (**15**). The oxonium ion is vulnerable to attack by water and HCl elimination, which would give the skeleton of obtusallene VIII (**24**). Subsequent acetylation would lead to obtusallene IX (**25**). In this case, the predicted stereochemistry of the bromine at C₁₃ does not match that reported (**24^a** & **25^a**).



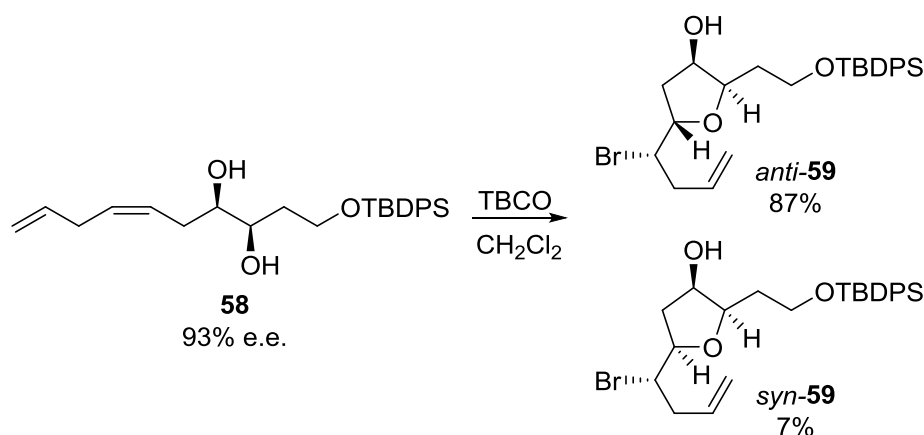
Scheme 2.3.3: Derivation from obtusallene II (15) to obtusallenes I, III & V-IX (16, 18 & 21-25) (n.b. compounds labelled with ^a are represented by their originally proposed structures) Braddock's biosyntheses correctly predicted the structures of obtusallenes I-IV (16 - 19).

Structural elucidation of obtusallenes I - IV (**15** - **19**) came unambiguously from X-ray crystallography and accordingly validated this scheme.^{13a-d} The structures of obtusallenes V - IX (**21** - **25**) predicted by Braddock, do not match those reported by Guella.^{13f} There are major discrepancies between the C₇ and C₁₃ halogens in **21^a**, **22^a** & **23^a** and the inversion of C₁₃ stereochemistry in **24^a** & **25^a**. All of these compounds were isolated together and the structures assigned by NMR spectroscopic techniques alone. Guella relied only on ¹³C and HMQC spectral data to assign the halogen regiochemistry of obtusallenes V - VII (**21^a** - **25^a**) and NOE analysis to designate the C₁₂-C₁₃ stereochemistries of obtusallenes VIII & IX (**24^a** & **25^a**). No X-ray crystallographic experiments were performed to confirm these assignments. If Braddock's hypothesis was to be upheld and the structures of several obtusallene reassigned, experimental data would need to be acquired.

2.3.1 Biomimetic Bromoetherification to Form a Model of the THF Motif

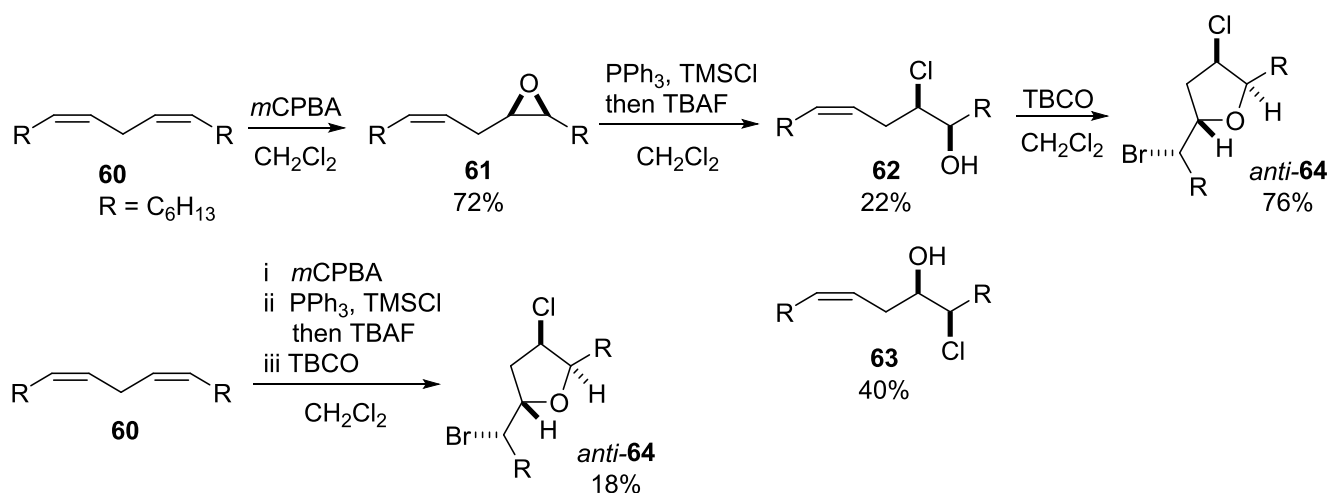
Without access to authentic samples of the natural products, corroboration of Braddock's proposed positioning of the C₇ & C₁₃ halogens required a model system that could be subjected to similar electrophilic bromination conditions as those shown to be successful in medium-ring ethers (scheme **2.2.2**).²⁸

(*R,R*)-Diol **58** was prepared *via* Sharpless asymmetric dihydroxylation in a 93% enantiomeric excess. Treating **58** with electrophilic brominating reagent 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) gave the expected *anti*-THF core *anti*-**59** in 87% yield, as well as 7% of the undesired analogue *syn*-**59**. The *anti*-stereochemistry was confirmed by X-ray crystallography and matched that observed in obtusallenes.



Scheme 2.3.1.1: Bromoetherification of diol **58** to form bromoallene core *anti*-**59** & its diastereomer *syn*-**59**.

As such, the key THF-forming cyclisation was performed with the regio- and stereochemistry matching that of the obtusallenes. The next step was to investigate the opening of a model epoxide (**61**) with chloride and determine if the resulting chlorohydrin (**62**) could then be similarly cyclised.



Scheme 2.3.1.2: Biomimetic synthesis of the obtusallene THF motif *anti*-**64**

Skipped-diene **60** was prepared and monoepoxidised to yield both enantiomers of epoxide **61**. This epoxide could be opened by using TMSCl as a chloride source and PPh₃ as

a Lewis base, then quenching with TBAF to give chlorohydrins **62** and **63** in a roughly 1 : 2 ratio as mixtures of regioisomers. Although chlorohydrin **62** was the minor product, it could be separated then subjected to a TBCO mediated bromoetherification to give *anti*-**64**, as a single diastereomer in 76% yield. As all the reactions in scheme 2.3.1.2 were performed in dichloromethane, it seemed prudent to attempt a one-pot synthesis of compound *anti*-**64**. Diene **60** was concurrently monoepoxidised, opened with chloride and brominated to yield *anti*-**64** in 18% yield. A bromonium ion formed on the free olefin of chlorohydrin **63** has only a 4-*exo* and 5-*endo* ring closure options, neither of which are favourable, so it presumably does not undergo bromoetherification.

With this, the biogenesis of the obtusallene THF-core motif was elucidated and the regiochemistry of the C₇ chloride explained. In addition, the hypothesis that the biosynthesis is not enzymatically controlled was supported by the derivation of skipped diene **60** to THF-core *anti*-**64** using only epoxidation, chloride and bromination reagents in a one-pot reaction.

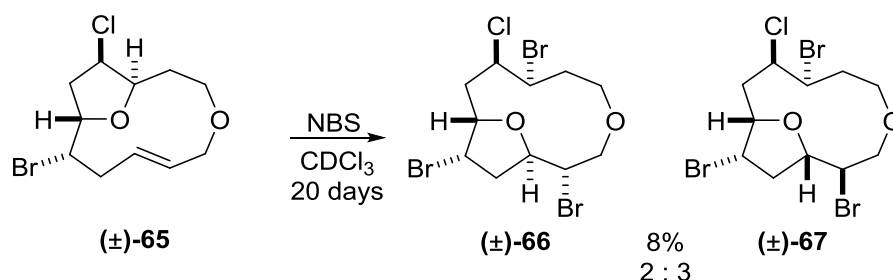
2.3.2 Investigation of the Bromination and Nucleophilic Trapping of Obtusallene

II (15) Core Models

The regiochemical origin of the C₇ chloride in obtusallene II (**15**) had been experimentally elucidated, however if the same was to be so for the succeeding obtusallenes in scheme 2.3.3, a direct link to obtusallene VII (**23**) needed to be found. If successful, the probable identity of the halogen at C₁₃ would also be ascertained.

A racemate of the chloro-substituted obtusallene analogue (±)-**65** and enantiopure acetate obtusallene analogue **68** were both synthesised.²⁹ Both models lacked the C₁₅ methyl group and a synthetic handle at C₄, but were adequate analogues for the macrocyclic

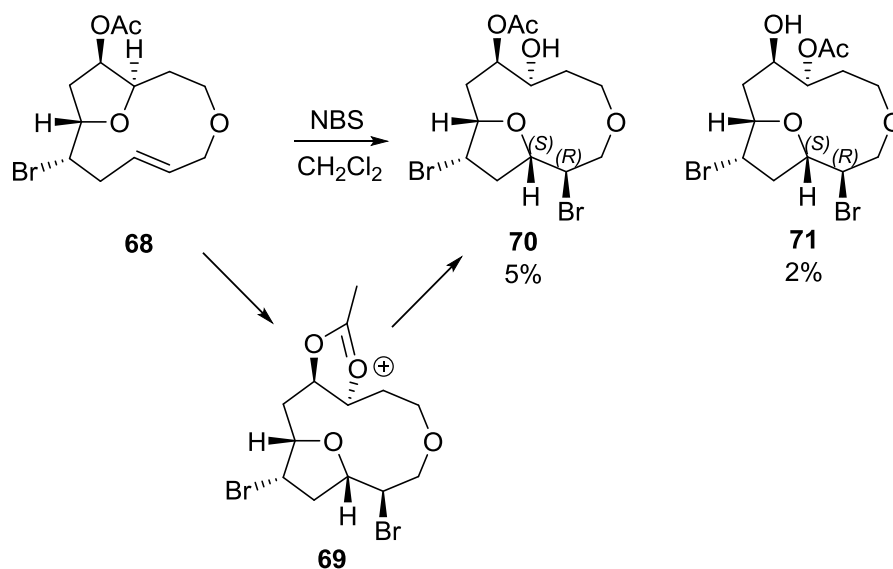
structure. Both were subjected to an electrophilic bromination reaction with *N*-bromosuccinimide (NBS) and the results shown in schemes 2.3.2.1 & 2.3.2.2.



Scheme 2.3.2.1: Treatment of obtusallene II model (±)-65 with NBS to form obtusallene VII (23) type structures.

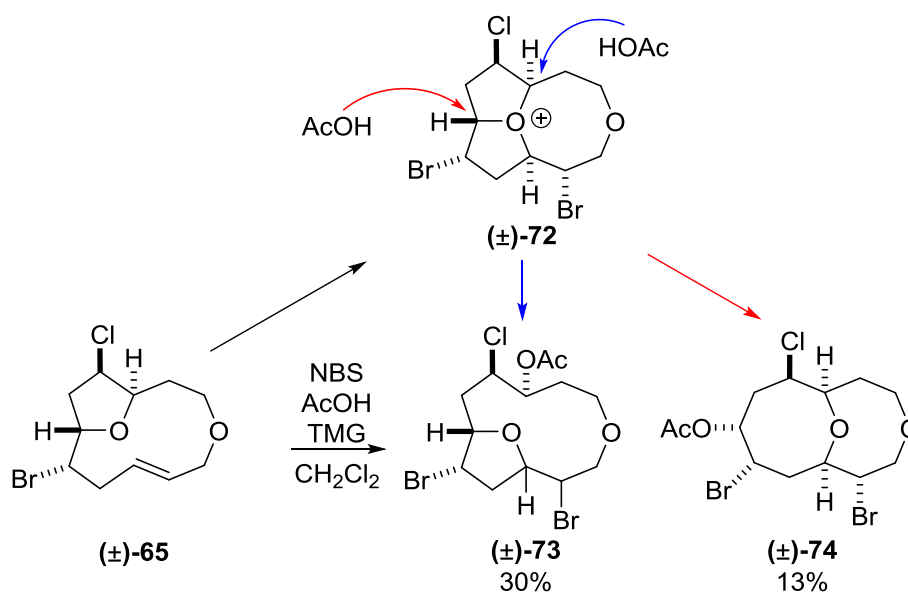
Macrocycle (±)-65 was combined with NBS in wet deuterated chloroform for 20 days. The aim was to brominate the C₁₂-C₁₃ olefin and rely on water to act as a nucleophile to trap the resulting oxonium ion. However, a complex mixture of products was found and after careful column chromatography, the only structures identified were (±)-66 & (±)-67. The desired bromination had occurred with the expected inversion of stereochemistry, but the nucleophilic trapping was performed by bromide, presumably from the slow reduction of NBS to molecular bromine and bromide. In addition, the C₁₂-C₁₃ stereochemistry of the major product (±)-67 (determined by X-ray crystallography) did not match that of obtusallene VII (23). In this case, it is clear that both faces of the olefin are accessible for bromination, as predicted by Guella's observation of slow rotation of obtusallene macrocycles.^{13d} Perhaps the lack of C₁₅ methyl group and bromoallene side chain allows a greater conformational freedom for the THF oxygen to open the bromonium ion *via* a 5-*exo* cyclisation and result in both (±)-66 & (±)-67. Still, the presence of (±)-66 proved the concept of a transannular rearrangement reaction linking obtusallenes II & VII (15 & 23). The

regiochemistry of the new bromine at C₁₃ also supports a reassignment of Guella's proposed structure of **23**^a (scheme 2.3.3).



Scheme 2.3.2.2: Treatment of enantiopure acetate **68** with NBS to form obtusallene VII (**23**) type structures (**70** & **71**).

Scheme 2.3.2.2 shows that similar treatment of enantiopure acetate **68** with NBS gave a mixture of products **70** and **71**. In this case, the macrocyclic structure resembled obtusallene VII (**23**), but the C₁₂-C₁₃ stereochemistry was exclusively (*S,R*) and did not match that of the natural product. In addition, the regiochemistry of the acetate and trapped nucleophilic oxygen was interchangeable. It is likely that the intermediate oxonium ion is opened by the acetate by neighbouring group participation to form Woodward-type intermediate **69**. This can then be attacked at either C₆ or C₇ by adventitious water to give products **70** or **71** respectively.



Scheme 2.3.2.3: Trapping of intramolecular bromonium ions in obtusallene model (±)-65 to form obtusallene VII (23) type structure (±)-73 and a previously unseen [5.5.1] fused core (±)-74.

Chloride bearing macrocycle (±)-65 was revisited to attempt to reduce reaction times, increase yield and ensure incorporation of an oxygen nucleophile at C₆. A catalytic amount of *N,N,N',N'*-tetramethylguanidine (TMG) was added to aid the transfer of electrophilic bromine.²⁹ Pleasingly, the reaction time was dramatically reduced from 20 days to 1 hour with an increased yield of desired product (±)-73, with the correct incorporation of acetate at C₆ and a greatly improved yield. Unfortunately, the stereochemistry at C₁₂ & C₁₃ could not be assigned. Interestingly another product was identified, that of (±)-74, bearing a novel [5.5.1] fused core, previously unseen in *Laurencia* metabolites. This compound seemingly forms *via* trapping of oxonium (±)-72 by acetate at C₉ (red). Evidently, both routes are possible and competitive. This structure was predicted to be the core of an undiscovered natural product and subsequently validated with the discovery of the marilzabicycloallenes in 2011.¹²

In addition, Braddock acquired an authentic sample of obtusallene V (**21**) and employed halogen induced isotopic shift ^{13}C NMR spectroscopy experiments to confirm the identity of the halogens at C_7 and C_{13} . This technique analyses the minute differences between the NMR spectral signals of the isotopomeric molecules bearing different halogen isotopes. In the case of chlorine, the 3 : 1 ratio of naturally occurring ^{35}Cl & ^{37}Cl means that a sample will contain two isotopomers. In the ^{13}C NMR spectrum, the signal for the carbon bearing this halogen will show two peaks, separated by several parts per billion (ppb), in the same 3 : 1 ratio.³⁰ Similarly, the signal for a bromine bearing carbon will be split into two equally sized signals by the relative proportions of ^{79}Br & ^{81}Br .³¹ The results of these experiments unambiguously assigned the C_7 substituent of obtusallene V (**21**) as a chlorine and the C_{13} substituent as bromine. The ^{13}C spectrum resulting from this experiment is shown in figure 2.3.2.1.

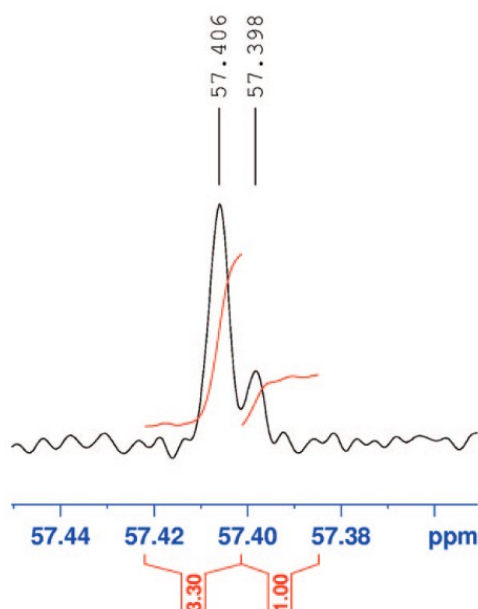


Figure 2.3.2.1: Results of chlorine induced isotopic shift experiment of an authentic sample of obtusallene V (**21**).

Based on these results, it was prudent to reassign the structure of obtusallenes V and VII (**21** & **23**). The updated structures are shown in figure 2.3.2.2. In addition, as obtusallenes VI, VIII and IX (**22**, **24** & **25**) are the likely derivatives, it follows that these should be similarly reassigned. However, without experimental evidence being acquired, such a claim cannot be made.

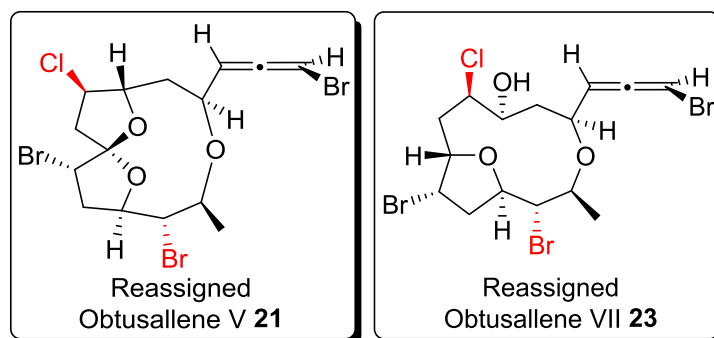
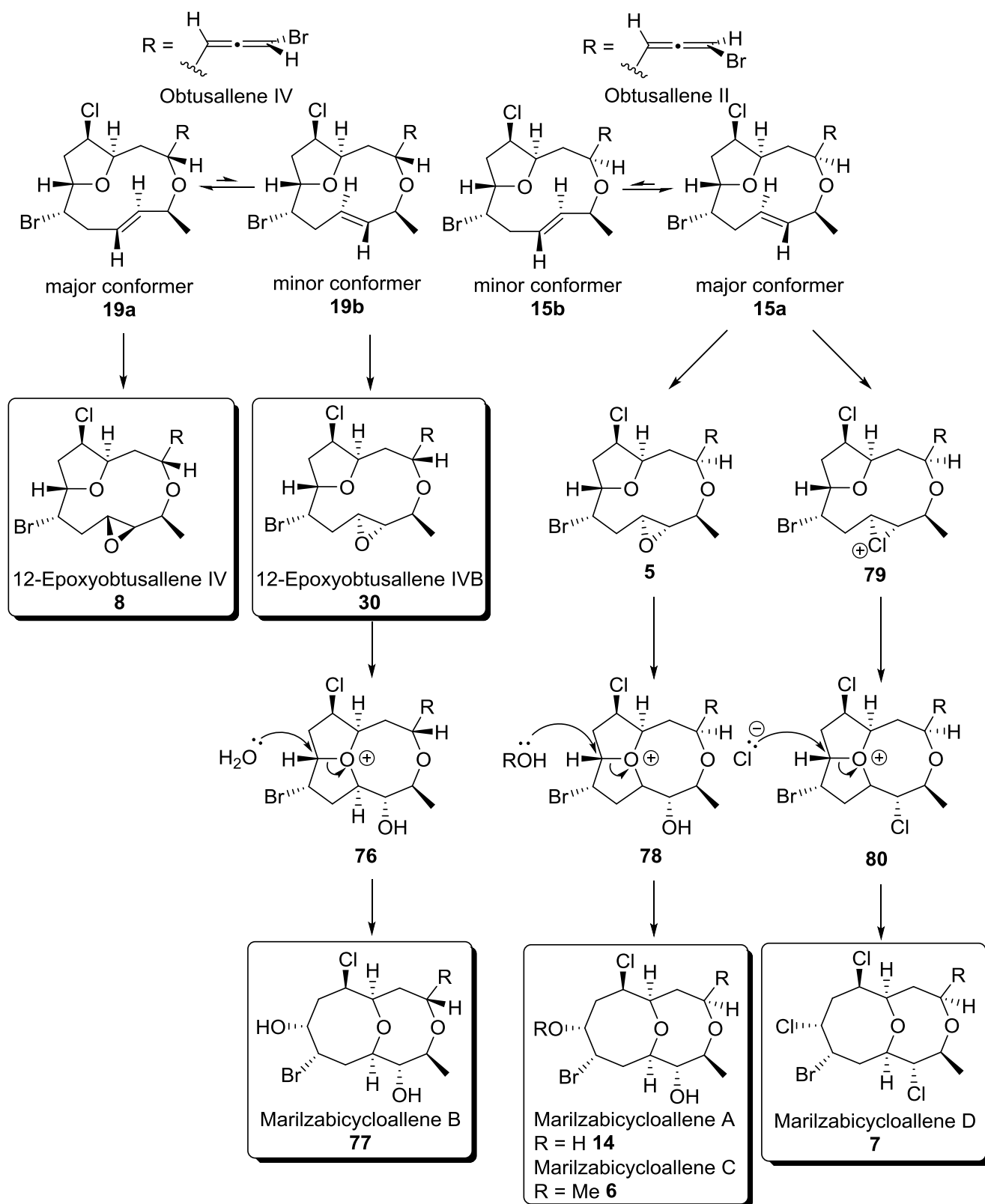


Figure 2.3.2.2: Reassigned structures of obtusallenes V and VII (**21** & **23**).

2.3.3 Isolation and Proposed Biogenesis of [5.5.1] Fused Core Species, the Marilzabicycloallenes

Braddock's prediction of an undiscovered natural product bearing the [5.5.1] tridecane motif was soon validated with the discovery of the marilzabicycloallenes by Norte and co-workers in 2011.¹² An isolation of *Laurencia marilzae* (recently reclassified as *Laurenciella marilzae* after phylogenetic analysis),³² a newly identified *Laurencia* species yielded four new bromoallene containing C₁₅ acetogenins. They do not bear bromine at C₁₃ as with the structure observed by Braddock ((±)-**74**), but instead have either an oxygen or chloride. Nonetheless, they must be products of a similar electrophilic functionalisation of the same olefin. The stereochemistry of the bromoallene indicates which obtusallene core is the precursor, **15** or **19**. Norte proposed a biosynthesis of these compounds, drawing on

Braddock's work with electrophilic brominations and Guella's observations of slowly interconverting olefin atropisomers.



Scheme 2.3.3.1: Norte's proposed biosynthesis of marilzabicycloallenes A - D (14, 77, 6 & 7).

In the above scheme, epoxidation of obtusallene IV **19** is proposed to give two products. The first of which is the known 12-epoxyobtusallene IV (**8**),^{13g} derived from the major conformer **19a** and the second is the C₁₂-C₁₃ epimeric epoxide 12-epoxyobtusallene IVB (**30**),^{13h} from minor conformer **19b**. This second epoxide can potentially undergo 5-*exo* cyclisation to open the epoxide and form the oxonium ion of **76**. This could be trapped by adventitious water to give the fused bicyclic marilzabicycloallene B **77**. It is possible that 12-epoxyobtusallene IV (**8**) does not undergo a similar rearrangement due to an unfavourable orientation of the THF oxygen. A very similar route can be envisaged for obtusallene II major conformer **15a** to form epoxide **5**. THF oxygen assisted epoxide opening, followed by trapping by water or methanol to yield marilzabicycloallenes A & C (**14** & **6**). In this isolation work, no natural products were observed that derived from minor conformer **15b**. This may be because the relative population of **15b** is too low to allow any considerable quantity of the corresponding epoxide to form, or they may simply have not been isolated in this study.

An alternative route, seemingly *via* a previously unseen electrophilic chlorination at C₁₂-C₁₃, is proposed. A chloronium ion stereochemically consistent with being derived from major conformer **15a**, can undergo a 5-*exo* cyclisation to form an oxonium ion that can be trapped by chloride to give trichloride marilzabicycloallene D (**7**). Such compounds have as yet only been observed in isolations of *Laurenciella marilzae* and their likely biosynthesis differs from the other obtusallenes in that they achieve further derivation without the need for electrophilic bromine.

2.3.4 Isolation and Proposed Biogenesis of 12-Epoxyobtusallene IV (8), Obtusallene X (9) and Methyl Ester 27

A separate isolation of *Laurenciella marilzae* by Norte, published just a month earlier, yielded eight new C₁₅ acetogenins, three of which are shown below, as well as the previously discovered obtusallene IV (19).^{13g}

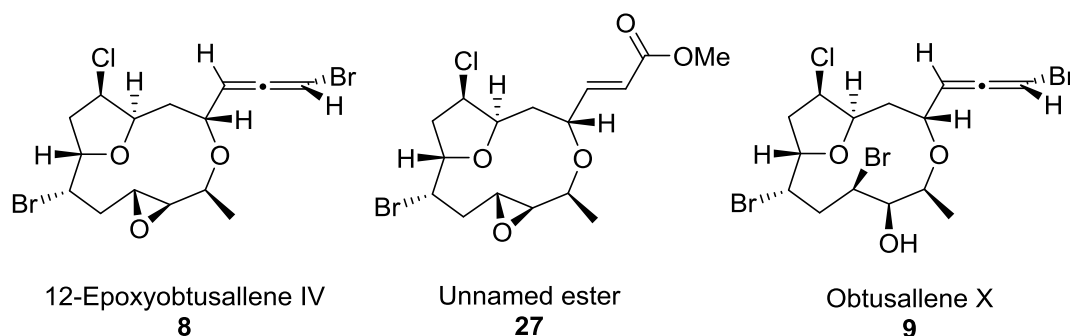
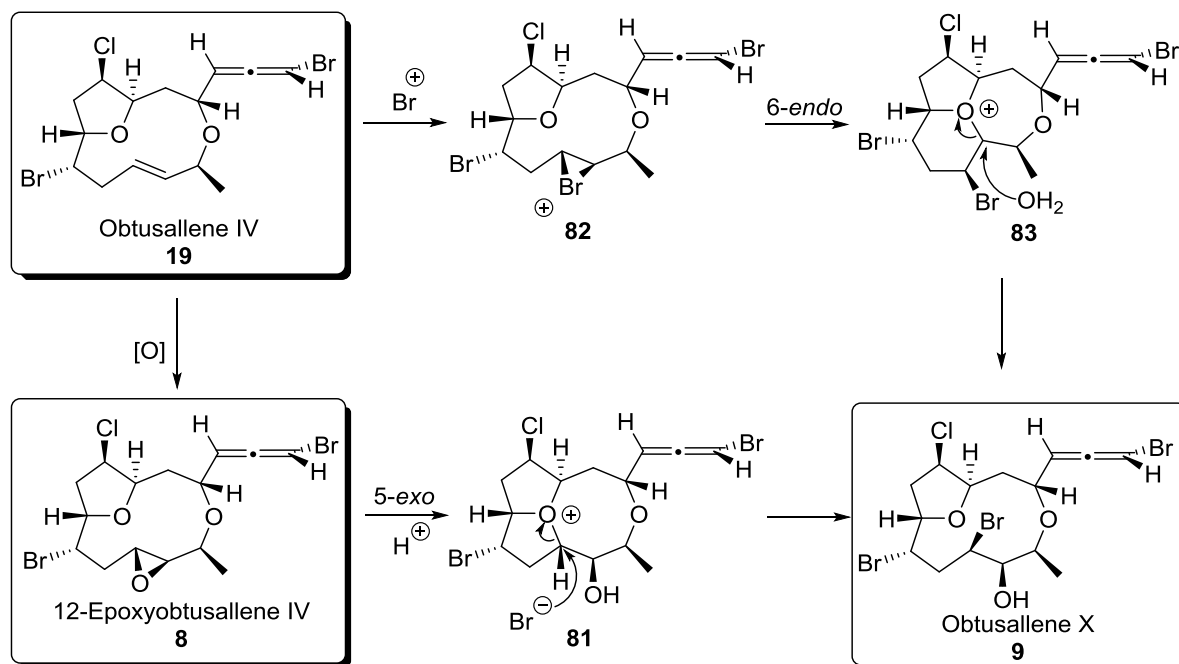


Figure 2.3.4.1: Three obtusallene macrocycles isolated by Norte.

Seemingly all derived from obtusallene IV (19), subjected to further epoxidation and trapping, the proposed biosynthesis of two of the compounds above can be visualised in scheme 2.3.4.1. Epoxidation of obtusallene IV (19) would lead directly to 12-epoxyobtusallene IV (8). Note that the stereochemistry of the epoxidation would be that resulting from the major olefin atropisomer (19a). From here, it may be possible to undergo a 5-*exo* cyclisation in the presence of acid to open the epoxide and form oxonium ion 81. Attack by bromide at C₁₂ would break the oxonium ion to give obtusallene X (9). Why the nucleophile would not attack at C₉, as with the marilzabicycloallenes, is unknown. An alternative pathway can be described. Bromination of obtusallene IV (19) gives bromonium ion 82, again with the same stereochemistry as 12-epoxyobtusallene IV (19), based on

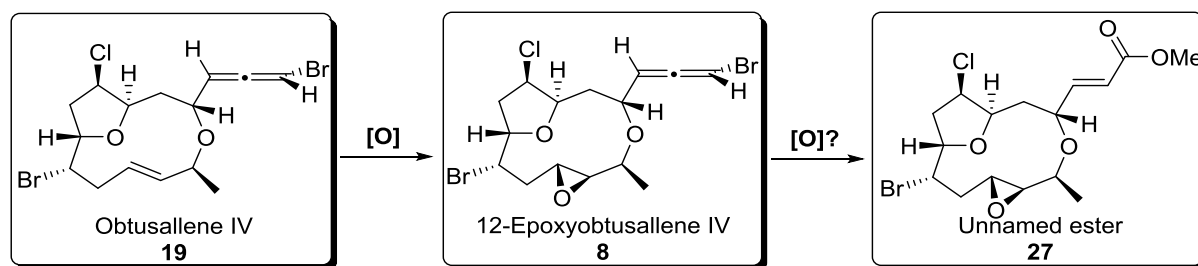
exposure of the *Re* face of the olefin to solvent. 6-*Endo* opening of the bromonium ion of **82** by the THF oxygen gives oxonium ion **83** and attack by water at C₁₃ leads to obtusallene X (**9**). Analysis of the bromohydrin stereochemistry and the corresponding inversion/retention of each mechanism in scheme 2.3.4.1 show that both are possibilities. The bromonium ion route is a strong candidate as the role of electrophilic bromine in the derivation of obtusallenes has already been established (schemes 2.3.1 & 2.3.3). However, the epoxide route is well supported by the isolation of 12-epoxyobtusallene IV (**8**), which is a necessary intermediate on this path. However, the use of bromide as a nucleophile has not been previously invoked in a biosynthesis of an obtusallene.



Scheme 2.3.4.1: Possible biosyntheses of 12-epoxyobtusallene IV (**8**) and obtusallene X (**9**).

The other compound isolated by Norte, unnamed ester **27**, does not bear the bromoallene associated with other members of the obtusallenes. Instead, it has an α,β -unsaturated methyl ester, but still clearly fits within the family. Bearing identical

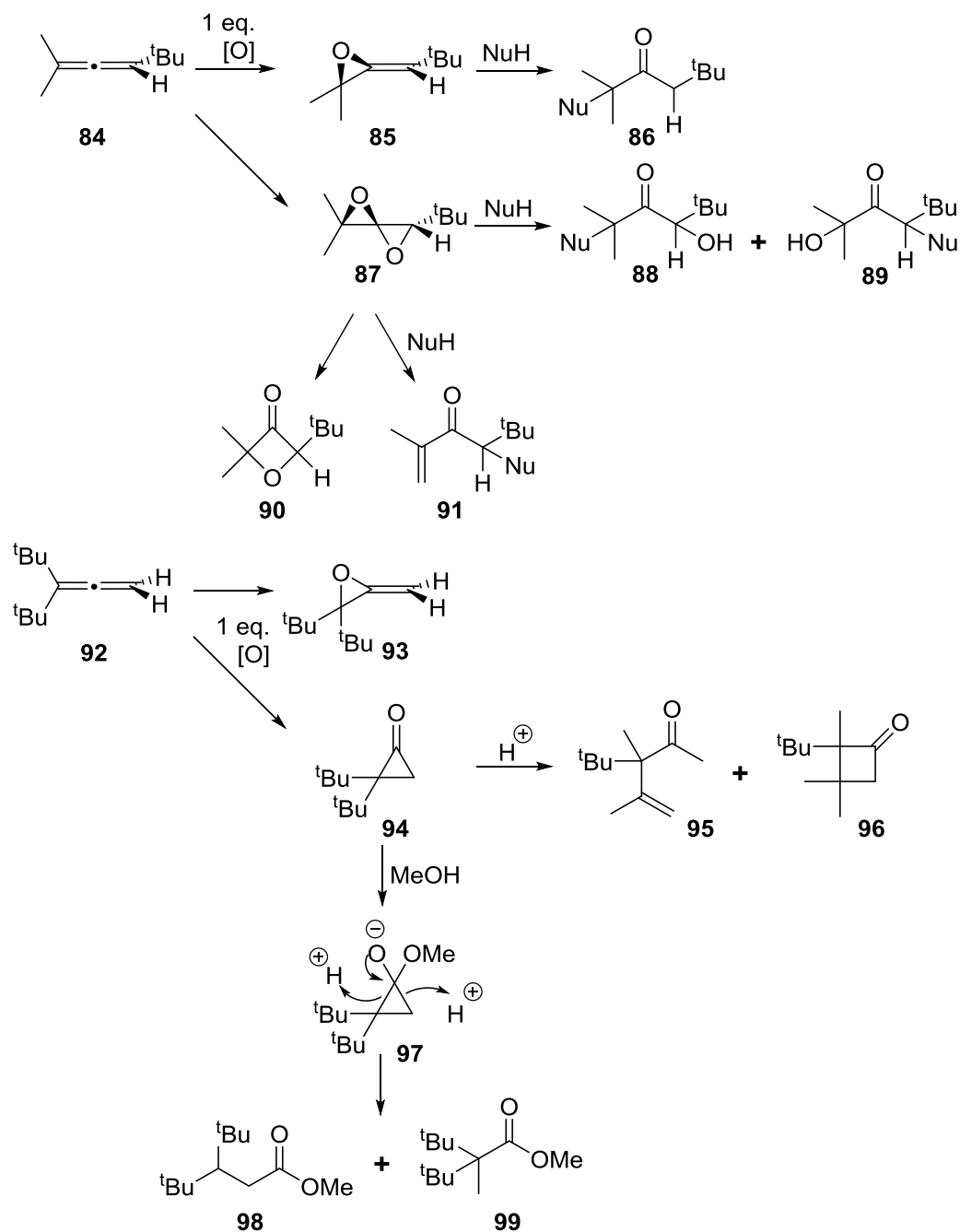
stereochemistry to 12-epoxyobtusallene IV (8) at both the epoxide and C₄, it is logical to assume that **27** is a derivative of **8**. It is also logical to extrapolate that the epoxidation event that transforms obtusallene IV (**19**) to 12-epoxyobtusallene IV (**8**) will subsequently produce methyl ester **27**. However, such a mechanism was unknown in the literature.



Scheme 2.3.4.2: Proposed link between obtusallene IV (**19**) and unnamed ester **27**.

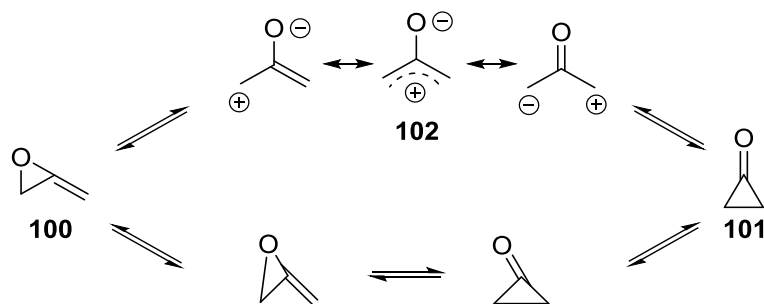
2.4 The Epoxidation of Bromoallenes

While the epoxidation of alkyl substituted allenes has been extensively studied,³³ similar research on bromoallenes is non-existent. Some examples of the reactivity of allene oxides is shown in scheme 2.4.1. It has been well established that the epoxidation of allenes with a variety of epoxidants leads to such allene oxides as **85** & **93**, and because they are more electron rich than the starting allene, rapidly epoxidise a second time to give spiro dioxides such as **87**.³⁴ The high strain of allene oxides and spiro dioxides means that they readily rearrange and acquire adventitious nucleophiles, inter- or intramolecularly, to form a multitude of other products.³⁵ These products include **88**, **89**, **98** & **99**. However, bulky substituents are used to protect the sensitive species from nucleophilic attack, rendering them isolable with great care. Note that the regiochemistry of the first epoxidations of **84** & **92** are selective for the most substituted end of the allene, regardless of steric factors and on the least hindered face.³³



Scheme 2.4.1: Literature examples of the outcome of the epoxidation of allenes.^{34c, 35b}

Allene oxides and cyclopropanones are valence isomers of each other and so will spontaneously equilibrate between each structure. Even allene oxides with very bulky substituents will rearrange at elevated temperatures.³⁶ The likely intermediate of this process is a third valence isomer, the oxyallyl cation.



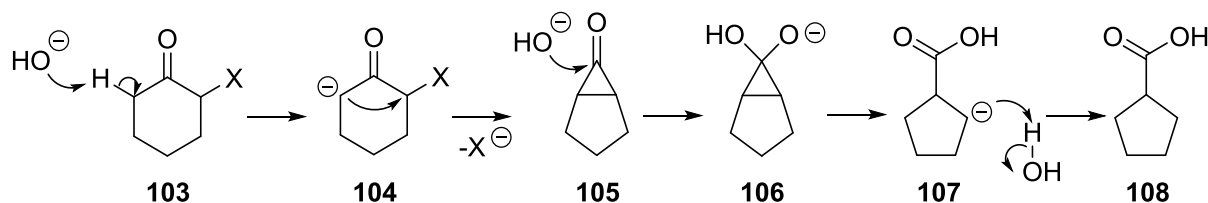
Scheme 2.4.2: Equilibration of allene oxide (**100**) and cyclopropanone (**101**), *via* oxyallyl cation **102**.

The equilibration of these three species has been proved experimentally to be reversible.^{35a} Cyclopropanone **101** has been calculated to be slightly lower in energy than allene oxide **100**, therefore the equilibrium lies to this side.³⁷ The same calculations have also shown that oxyallyl cation **102** is between 75 - 240 kcal.mol⁻¹ higher in energy and so there is some debate if the cation is an intermediate or even exists as a transition state. It has therefore been postulated that the transition between allene oxide **100** and cyclopropanone **101** follows a lower energy pathway where the molecule is simply 'bent' between the two structures.

However, these calculations do not match experimental data, whereby an alkyl substituent at C₁ of an allene oxide greatly reduces the rate of cyclopropanation, while an aryl substituent increases the rate. This suggests that the rate determining step is the breaking of the C₁-O bond with the simultaneous development of a positive charge.³⁷

2.4.1 Favorskii Rearrangements in Nature

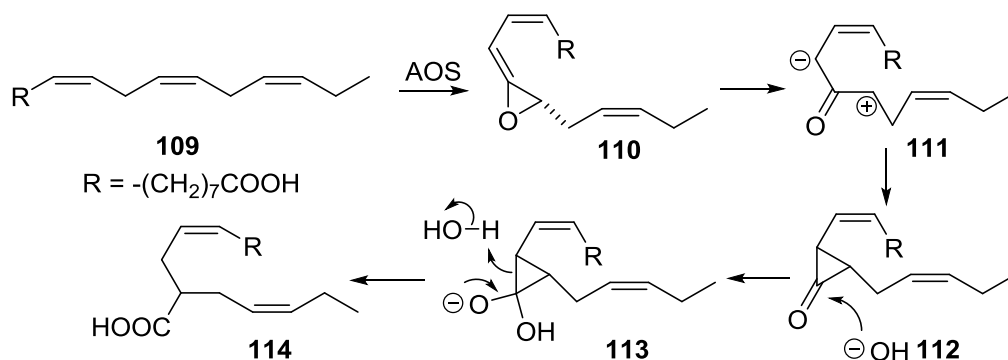
The highly strained and electrophilic cyclopropanone is a common intermediate in the Favorskii rearrangement. This reaction has been known for over 100 years and a representative example given in scheme 2.4.1.1.³⁸



Scheme 2.4.1.1: The Favorskii rearrangement of α -bromocyclohexanone 103.

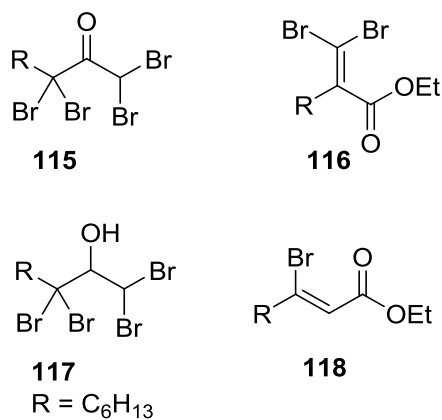
This reaction proceeds *via* initial formation of a cyclopropanone (105), followed by nucleophilic attack at the carbonyl carbon, followed by reformation of the carbonyl, fragmentation of the cyclopropanone and protonation to yield a ring-contracted carboxylic acid (108). The manner of formation of the cyclopropanone can vary and the nature of nucleophile is mutable, but the important comparison is the contraction, for reasons that will be explained later (section 3.1.1).

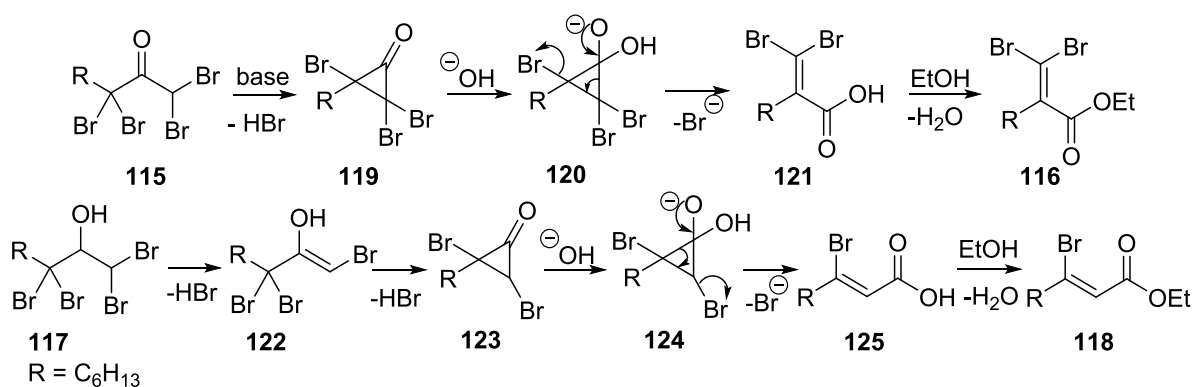
A similar reaction is known to occur in nature. The enzyme allene oxide synthase (AOS), common in many plant species, has been shown to act on α -linoleic acid (109) and related molecules to give secondary carboxylic acids, such as 114.³⁹ The action of the enzyme results in the formation of an allene oxide (110) and rearrangement to a cyclopropanone (112). This rearrangement is likely to be spontaneous, but can be encouraged by the use of a Lewis acid. Attack by hydroxide at the carbonyl, subsequent rearrangement and abstraction of a proton from water gives carboxylic acid 114.



Scheme 2.4.1.2: Allene oxide synthase (AOS) biosynthesis of secondary carboxylic acids from α -linoleic acid (**109**)

In an assay of the metabolites to be found in members of the red algae genus *Bonnemaisonia*, McConnell and co-workers found compounds that resemble more traditional Favorskii substrates (**115** & **117**), as well as their α,β -unsaturated ester derivatives (**116** & **118**).⁴⁰





Scheme 2.4.1.3: Examples of metabolites found in *Bonnemaisonia* red algae and their possible biosynthesis.

The metabolites were comprised of poly α -halogenated carbonyls, alcohols and α,β -unsaturated ethyl esters. The two former groups resemble synthons in the allene oxide-cyclopropanone equilibration pathway. A possible biosynthesis involves a deprotonation, followed by loss of bromide and cyclopropanation, in a very similar fashion to the Favorskii reaction. From here, the cyclopropanones (**119** & **123**) can undergo attack by a nucleophile and collapse. Instead of protonation, the collapse of the intermediates (**120** & **124**) allows a simultaneous elimination pathway, resulting in an α,β -unsaturated esters **116** & **118**.

McConnell proposed in this publication that the likely natural products are the carboxylic acids **121** & **125**, but the collected compounds are esterified during storage, reflux and extraction of the algae in ethanol. An alternative possibility is that the carboxylic acids are not formed and the esters are isolation artefacts. If the above biosynthesis took place during isolation, the hydroxide nucleophile could be replaced with ethanol and still produce the ethyl esters **116** & **118**. It is interesting to note that Norte's extraction of unnamed ester **27** was performed in methanol and the natural product bore a methyl ester.^{13g}

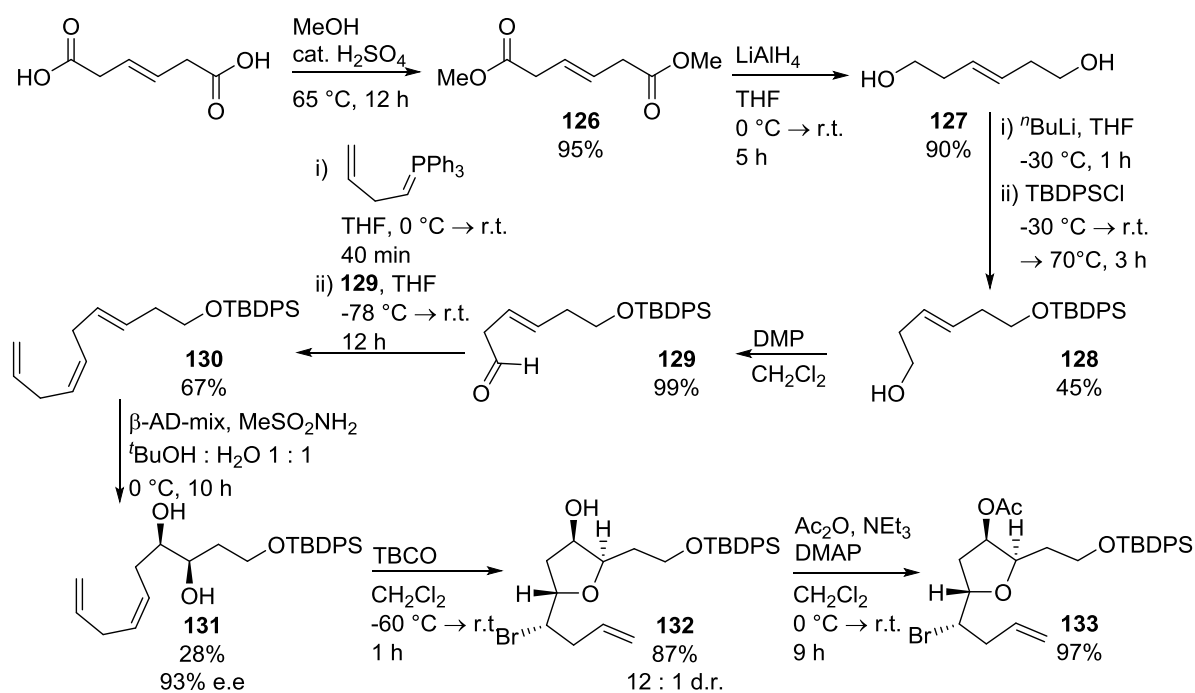
2.5 Progress Towards the Total Synthesis of Obtusallene Natural Products

At the conclusion of the bromoallene epoxidation study, work will begin on total synthesis of *Laurencia* natural products. The clear target for the total synthesis of any obtusallene, and the marilzabicycloallenes, are obtusallenes II & IV (**15** & **19**). With all known obtusallenes and marilzabicycloallenes hypothesised to derive from these two precursors, the most efficient route for a total synthesis of the entire obtusallene family, while also allowing insights into the biosyntheses proposed by Braddock and Norte, is to produce sufficient quantities of **15** & **19** and then perform divergent biomimetic reactions to target the remaining compounds.

Installation of the THF unit would be integral to the success of this total synthesis, as its formation is responsible for four of the eight stereocentres in the finished products. The ideal route would be to synthesise an enantiopure THF core, with adequate functionality to close the macrocycle and later affix the bromoallene.

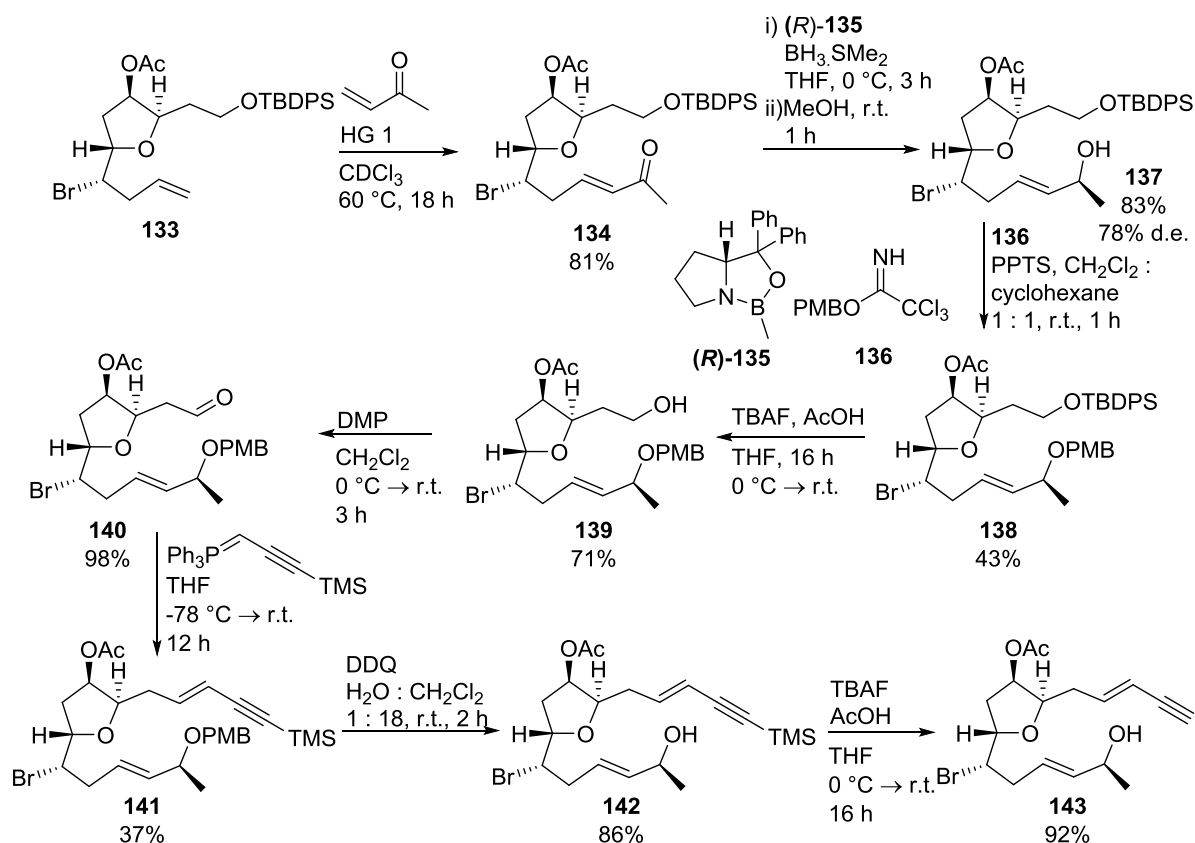
2.5.1 Initial Attempt - Biomimetic Ring-Closing *via* Bromoetherification

The first attempt at this was performed in the Braddock group by Bhuva, a previous PhD student, in 2005.⁴¹ If subsequent steps had been successful, it was planned to later exchange the hydroxyl at C₇ for a chloride with retention of stereochemistry.



Scheme 2.5.1.1: Start of Bhuva's route to precursor **143**.

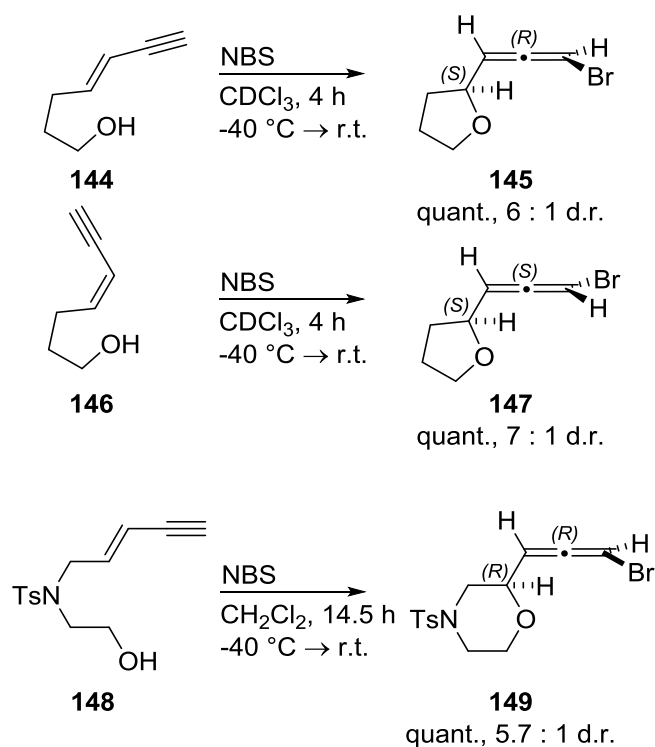
Starting with *trans*- β -hydromuconic acid, the THF core motif was synthesised with a 93% e.e. and 12 : 1 d.r. (scheme 2.5.1.1).²⁸ Bis-methyl esterification of *trans*- β -hydromuconic acid gave diester **126**, which was fully reduced with LiAlH₄ to diol **127**, both steps achieving high yields. Monoprotection with *tert*-butyldiphenylchlorosilane (TBDPSCI) produced silyl ether **128** in moderate yield. This allowed single oxidation of the free alcohol with Dess-Martin periodinane (DMP) to produce aldehyde **129** in high yield. Wittig olefination with a 3-butenyl ylid produced triene **130**, which underwent *E*-selective Sharpless asymmetric dihydroxylation to give diol **131**, in low yield but a good e.e. of 93%. Diol **131** is able to undergo a 5-*exo* cyclisation, as previously established (scheme 2.3.1), to give THF core **132** in a good d.r. of 12 : 1. Protection of the free alcohol resulted in acetate **133**, ready for further functionalisation.



Scheme 2.5.1.2: Completion of Bhuvu's route to precursor **143**.

Olefin **133** was submitted to cross-metathesis with methyl vinyl ketone using Hoveyda-Grubbs 1st generation catalyst (HG I) to generate *E*-enone **134** in 81% yield. Corey-Bakshi-Shibata (CBS) reduction of enone **134** with (*R*)-oxazaborolidine **135** gave enol **137** in 83% yield and a 78% d.e. Protection of the new hydroxyl as *para*-methoxybenzyl (PMB) ether **138** and removal of the silyl protecting group with tetra-*n*-butylammonium fluoride (TBAF) gave compound **139**, followed by Dess-Martin oxidation and Wittig olefination to install the enyne of compound **141**. Successive deprotection of the PMB ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the silane with TBAF gave the enyne substrate **143**, ready for attempts at macrobromoetherification.

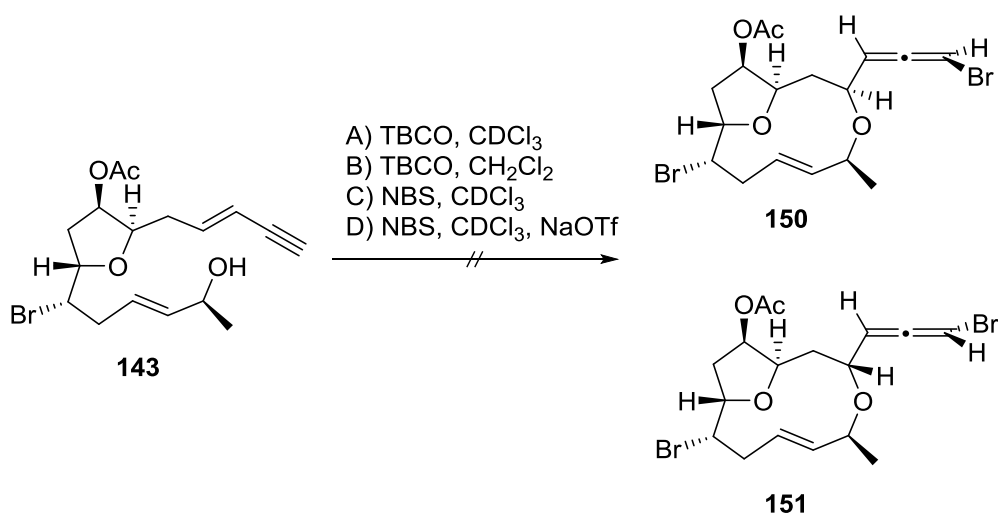
The use of the bromoetherification of chlorohydrins and diols to form rings had already been well established in the Braddock group (schemes 2.3.1.1 & 2.3.1.2).^{22, 28} Studies on the ring closing bromoetherification of enynes **144**, **146** & **148** had also been conducted, with the conclusion that the addition proceeds in a *syn*-fashion (scheme 2.5.1.3).²⁶ Compounds **145** & **149** match the relative axial and C₄ stereochemistries of bromoallene containing natural products. This allows the nature of the biogenetic precursor to be assigned an *E*-enyne **38** (Scheme 2.3.1)



Scheme 2.5.1.3: Stereochemical course of the bromoetherification of enynes.

It therefore seemed probable that submitting *E*-enyne **143** to similar conditions would be successful and give the 7-acetoxy analogues (**150** & **151**) of obtusallenes II & IV (**15** & **19**). The results are summarised in scheme 2.5.1.4.

Several attempts were made using both TBCO and NBS. In the case of TBCO (conditions A & B), no reaction was seen, even after extended reaction time and warming from -60 °C to room temperature. The brominating reagent was changed to NBS, which had proved to be more reactive in the above bromoetherifications (scheme 2.5.1.3). In this case (condition C), extended reaction time only resulted in decomposition of the starting material. Adding sodium triflate to the reaction, to act as a metal template and bring the THF and hydroxyl oxygens into closer proximity and perhaps encourage cyclisation, had no effect.



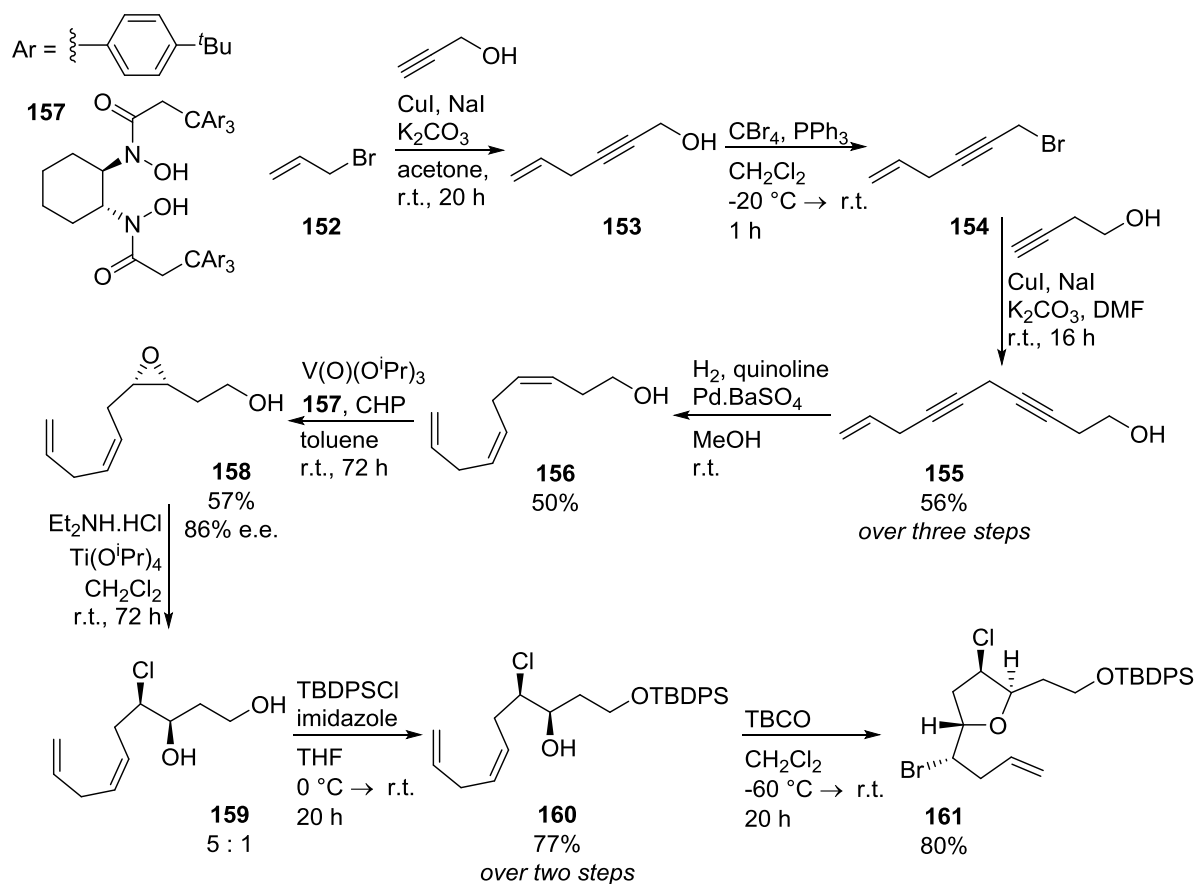
Scheme 2.5.1.4: Attempted macrobromooetherification of alcohol **143**.

This route was abandoned due to lack of further material. Several problems were identified. Firstly, the dihydroxylation of triene **130** was too low yielding due to off-target reactivity of the other olefins. The dihydroxylation also left an oxygen containing moiety at C₇, potentially interfering with the macrobromooetherification. The multiple protection/deprotection steps were also deemed too inefficient. It also appeared that the

entropy of ring closure was too high to overcome. A new route with a more conventional ring closure method was then sought.

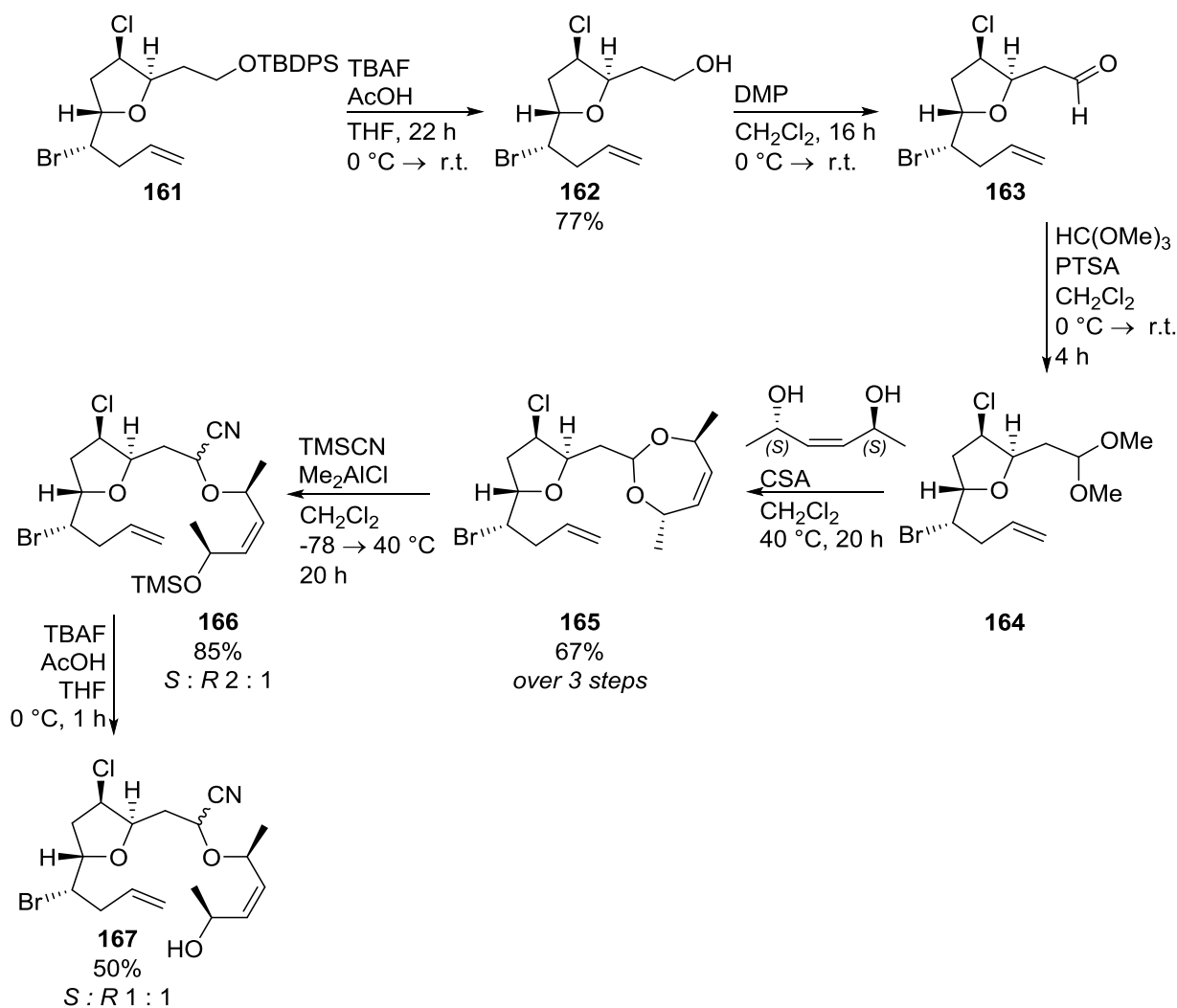
2.5.2 Second Attempt - Ring-Closing *via* Grubbs' RRCM

With the main problems identified, another route was designed. In this attempt, the crucial ring closure would be facilitated by a Grubbs' metathesis of precursor **167**. Having extensive literature precedent and a range of catalysts to select from would increase the chance of success. This non-biomimetic method did not have the advantage of simultaneously installing the bromoallene and so another technique for this important functionality would have to be found.



Scheme 2.5.2.1: Start of Solanki's route to precursor **167**.

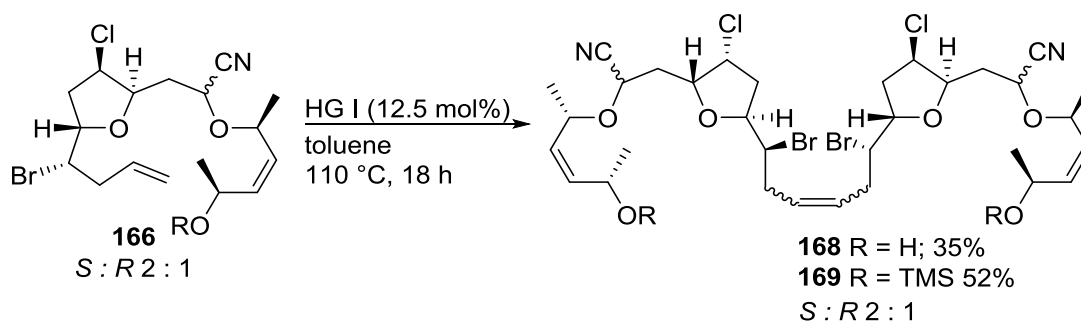
The work shown in scheme 2.5.2.1 was performed by Solanki, another PhD student in the Braddock group.⁴² In a similar manner to Braddock's synthesis of medium-ring ether cores,²² starting with allyl bromide (**152**), successive copper(I) mediated alkyne coupling reactions gave diyne **155** in 56% yield over three steps. This compound was reduced to (Z,Z)-skipped triene **156** by employing hydrogenation with palladium on barium sulfate, poisoned by quinoline. Although this reaction invariably left a mixture of compounds, with varying degrees of unsaturation, the desired (Z,Z)-skipped triene **156** was purified with the use of silver nitrate impregnated silica gel column chromatography. Triene **156** was then asymmetrically and regioselectively epoxidised at the homoallylic position with 57% yield and 86% e.e., with the use of cumene hydroperoxide (CHP), vanadium(V) oxytriisopropoxide and Yamamoto ligand **157**.⁴³ The e.e. of epoxide **158** was calculated by protecting the alcohol with a trityl group and measuring the ratio by chiral HPLC. The epoxide of **158** could be opened with diethylammonium chloride and titanium tetraisopropoxide as a Lewis acid. This gave chlorohydrin **159** in as an inseparable 5 : 1 mixture of regioisomers, that were protected as *tert*butyldiphenylsilyl ether **160** in a 77% yield over the two steps. At this point, the minor chlorohydrin regioisomer could be separated by column chromatography. The major chlorohydrin was then subjected to the previously established bromoetherification procedure with TBCO to compound **161**.²⁸ Thus, the THF core had been installed, bearing a chloride at C₇ and an assumed e.e. of 86%, based on the measured ratio of the trityl derivative of epoxide **158**. Compared to the similar stage of Bhuva's synthesis (scheme 2.5.1.1), whereby the C₇ acetoxy analogue **133** had been collected in 5.5% overall yield, Solanki had produced the C₇ chloro substituted THF-core **161** in a 10% overall yield.



Scheme 2.5.2.2: Completion of Solanki's route to precursor **167**.

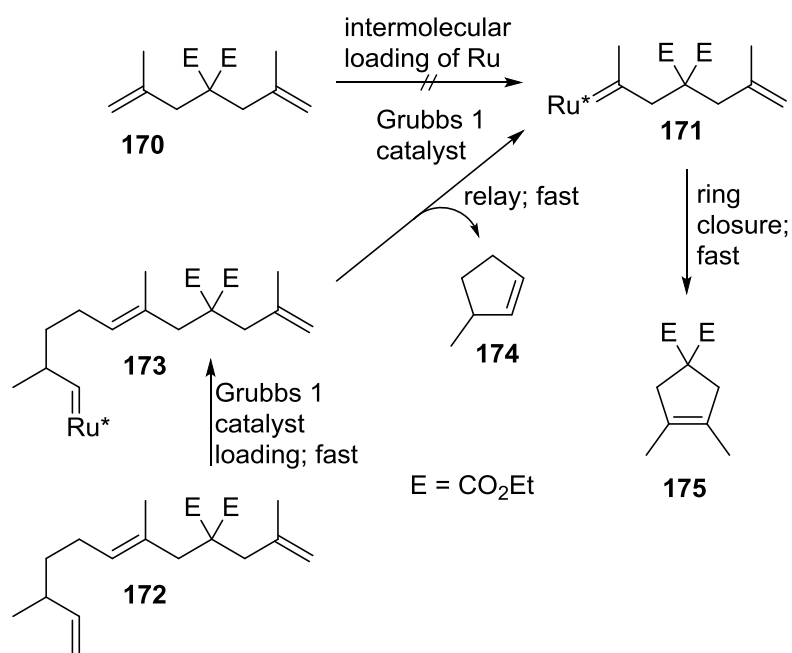
With the THF-core of **161** installed, bearing the correct stereochemistry and substituents, the silyl ether was removed with TBAF and oxidised using DMP to give aldehyde **163**. This was converted to dimethyl acetal **164** with trimethyl orthoformate and *p*-toluenesulfonic acid (PTSA) and subsequently transacetalised with (2*S*,3*Z*,5*S*)-hex-3-ene-2,5-diol to compound **165** in 67% yield over 3 steps. The use of trimethylsilyl (TMS) cyanide and dimethylaluminium chloride as a Lewis acid opened the acetal to give a inseparable 2 : 1 mixture of *S*- and *R*-cyanoethers **166**. The *S*-epimer bears a nitrile with the same stereochemistry at C₄ as the bromoallene in obtusallene II (**15**), while the *R* epimer

corresponds to obtusallene IV (**19**). *S*- and *R*-dienes **166** were now ready to attempt ring-closing metathesis (RCM) to form the macrocycles of each obtusallene.



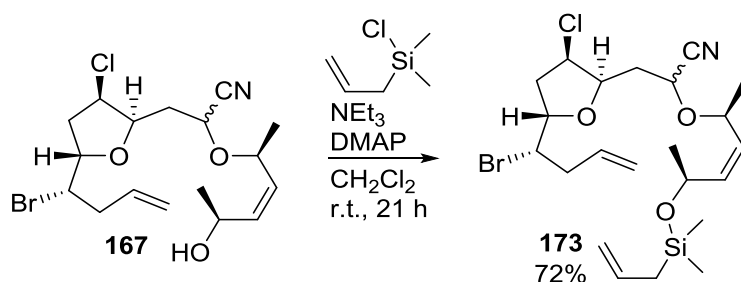
Scheme 2.5.2.3: Attempted ring-closing metathesis of precursor **166**.

Unfortunately, the only products observed after treating substrate **166** with Hoveyda-Grubbs 1st generation catalyst were dimers **168** & **169**. Presumably, there is a large entropic cost to closing such a macrocycle, making dimerisation the more favourable outcome. Alternatively, the unfavourable sterics and deactivation of the disubstituted alkene impedes ring closure. All of these problems could potentially be solved with the use of relay ring-closing metathesis (RRCM), a technique developed by Hovey and co-workers.⁴⁴



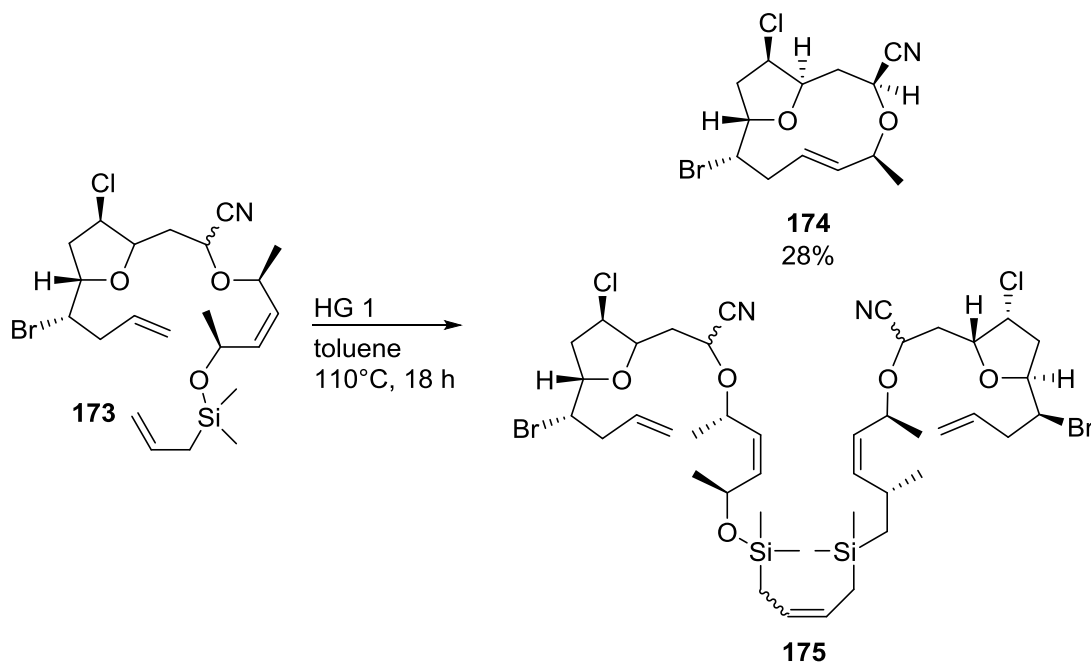
Scheme 2.5.2.4: Noye's RRCM model schematic.

RRCM is employed when substrates are inherently sterically hindered or electronically deactivated. In the example above, substrate **170** is known to be unreactive in the presence of Grubbs catalysts, which will not engage the geminally disubstituted olefin. By tethering a five carbon chain, terminated with a monosubstituted alkene (**172**), the ruthenium species easily initiates at the monosubstituted olefin and can now perform a rapid cyclisation to extrude 3-methylcyclopentene (**174**) and generate ruthenium alkylidene **171**. A second rapid cyclisation yields the desired cyclopentene **175**. This effect could be replicated by affixing an olefin to the hydroxyl of **167** (scheme 2.5.2.5)



Scheme 2.5.2.5: Allyl silyl protection of cyclisation precursor **167**.

Attempts to couple a conventional allyl group on to the free hydroxyl of **167** failed, but the use of an allyl silyl ether was successful in producing cyclisation precursor **173**. Similar allyl silanes have proved to be effective RCM substrates.⁴⁵

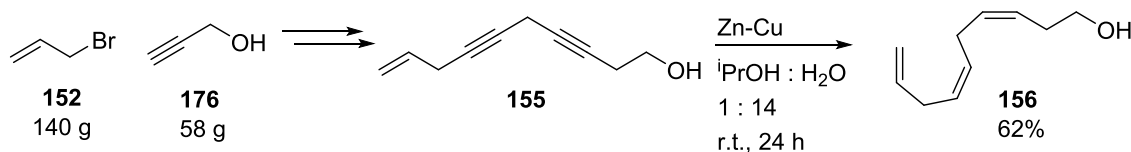


Scheme 2.5.2.6: Attempted RRCM with allyl silyl ether **173**.

Pleasingly, scheme **2.5.2.6** shows that the RRCM proved to be moderately successful, and a small quantity of compound was isolated that presented NMR spectral data very similar to that of obtusallene II (**15**). The remainder of the mass appeared to be dimer **175**, this time coupled *via* the allyl silane. Compound **174** proved to be crystalline, allowing X-ray analysis to establish it bore identical relative and absolute stereochemistries to that of obtusallene II (**15**). Unfortunately, only a total of 1.5 mg macrocycle **174** was prepared and so the synthetic scheme had to be restarted in a larger scale.

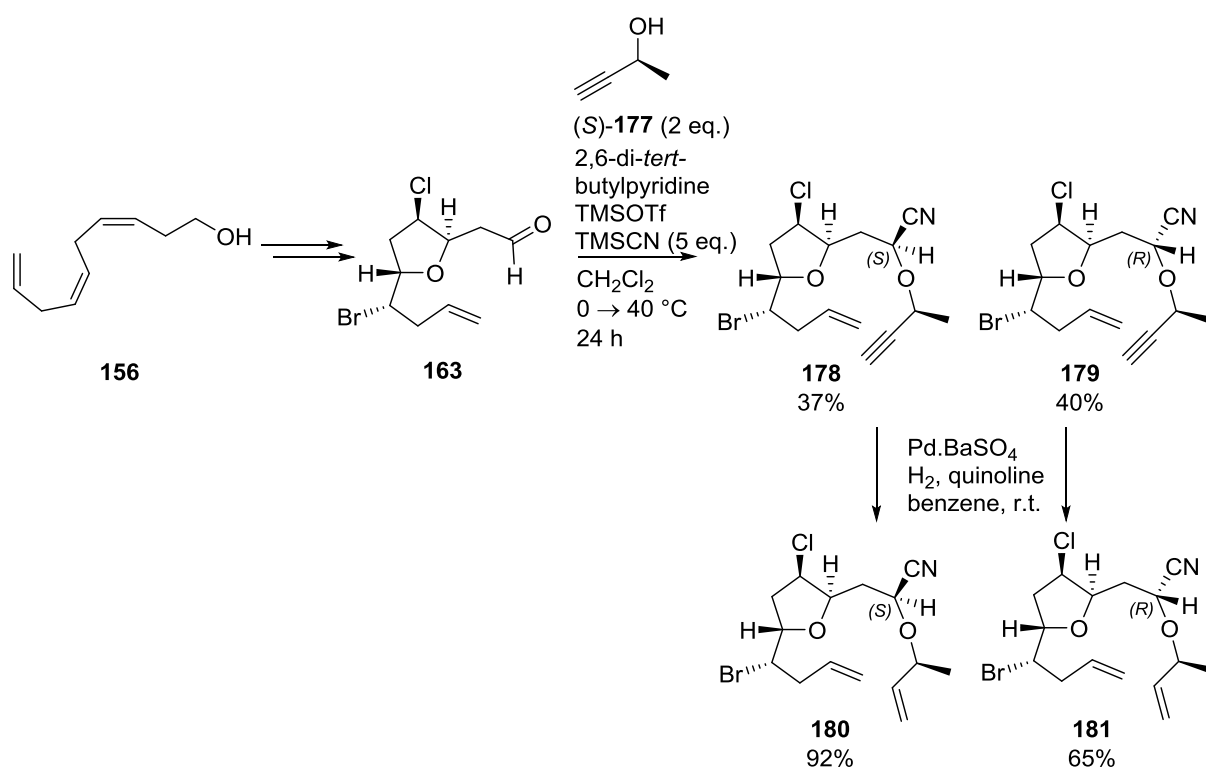
2.5.3 Third Attempt - Functionalisation *via* a One-Pot Cyanoetherification

A larger scale synthesis of triene **156** was begun by Yaqoob, employing 140 g of allyl bromide **152** and 58 g of propargylic alcohol **176**. Few changes were made to Solanki's route (scheme 2.5.2.1) apart from the use of zinc-copper couple in a transfer hydrogenation reaction.⁴⁶



Scheme 2.5.3.1: Large scale synthesis of triene **156**.

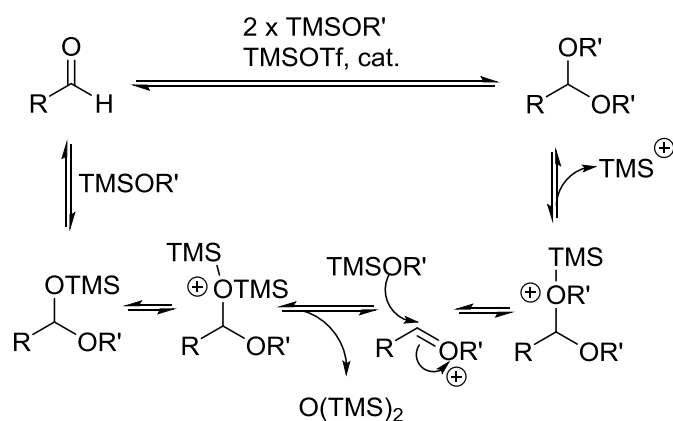
This alternative gave a slight improvement to yield, but more importantly, prevented over reduction of the olefins and thus negated the need of laborious purification with silver nitrate impregnated silica. Triene **156** was elaborated to aldehyde **163** as before, but from here, a new method of introducing the C₁₄ methyl stereochemistry was pursued.



Scheme 2.5.3.2: Cyanoetherification of aldehyde **163** to form epimeric nitriles **178** & **179** and their subsequent hydrogenation to dienes **180** & **181**.

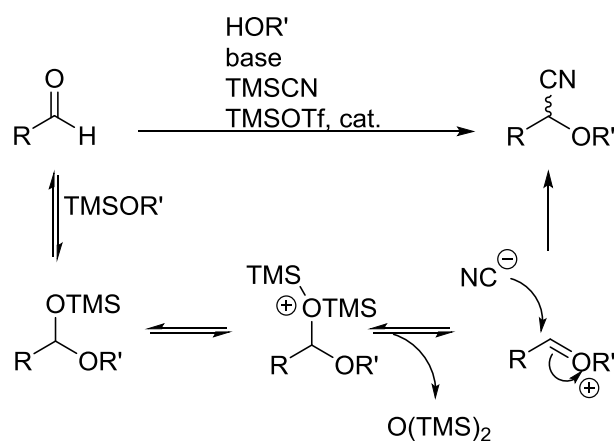
This one-pot cyanoetherification, using commercially available (*S*)-(-)-3-butyn-2-ol ((*S*)-**177**), allowed direct incorporation of a methyl group at C₁₄. This gave the correct stereochemistry and a terminal alkyne that could be easily hydrogenated to give alkenes **180** & **181**, suitable for RCM. This route facilitated the preparation of two substrates ready for RCM in two steps, as opposed to five previously (scheme 2.5.2.2).

The key cyanoetherification was a modification of a procedure to produce acetals under aprotic conditions *via* carbonyls, alkoxyasilanes (TMSOR') and trimethylsilyl triflate (TMSOTf).⁴⁷



Scheme 2.5.3.3: Noyori's aprotic acetalisation.

Aprotic conditions are necessary when using enantiopure alcohols, as aqueous protons may cause racemisation. Work conducted by Yaqoob and Bonney established that by including trimethylsilyl cyanide (TMSCN) in the reaction, the oxonium intermediate could be trapped by a cyanide anion.⁴⁸

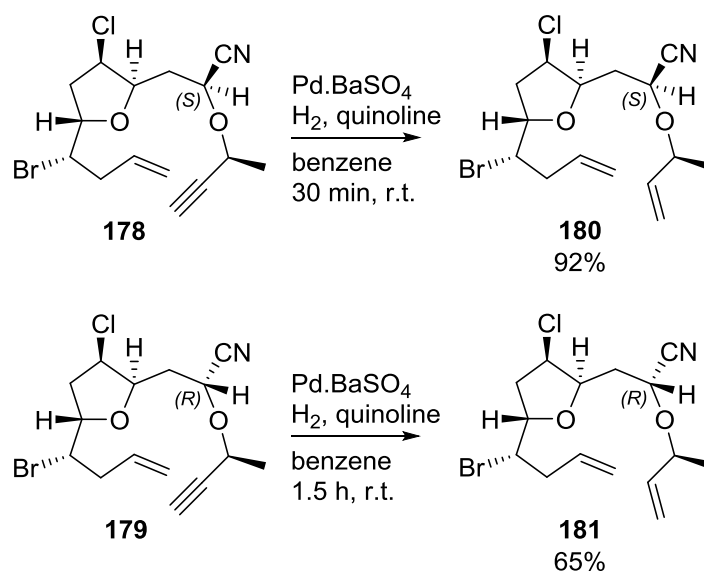


Scheme 2.5.3.4: Modified one-pot cyanoetherification.

All of the steps in scheme 2.5.3.3 are reversible, meaning that an equilibrium is formed. Increased yield is achieved by increasing the equivalents of alkoxy silane ($TMSOR'$). Scheme 2.5.3.4, conversely, is irreversible after the addition of cyanide, theoretically

increasing yield while using fewer equivalents of the expensive enantiopure alcohol (S)-**177**. To avoid having to synthesise the trimethylsilyl analogue of alcohol (S)-**177**, Yaqoob and Bonney added the alcohol directly with hindered base 2,6-di-*tert*-butylpyridine, to generate the alkoxide and sequester the proton. The non-stereospecific addition of nitrile produces two epimeric nitriles, **178** & **179**, bearing the stereochemistry of obtusallenes II & IV (**15** & **19**), respectively.

Thus, in one-step the C₁₄ methyl group would be installed with correct stereochemistry, along with an epimeric nitrile at C₄ that could be employed as a handle for bromoallene installation and an alkyne that could be easily reduced to form a substrate for RCM.



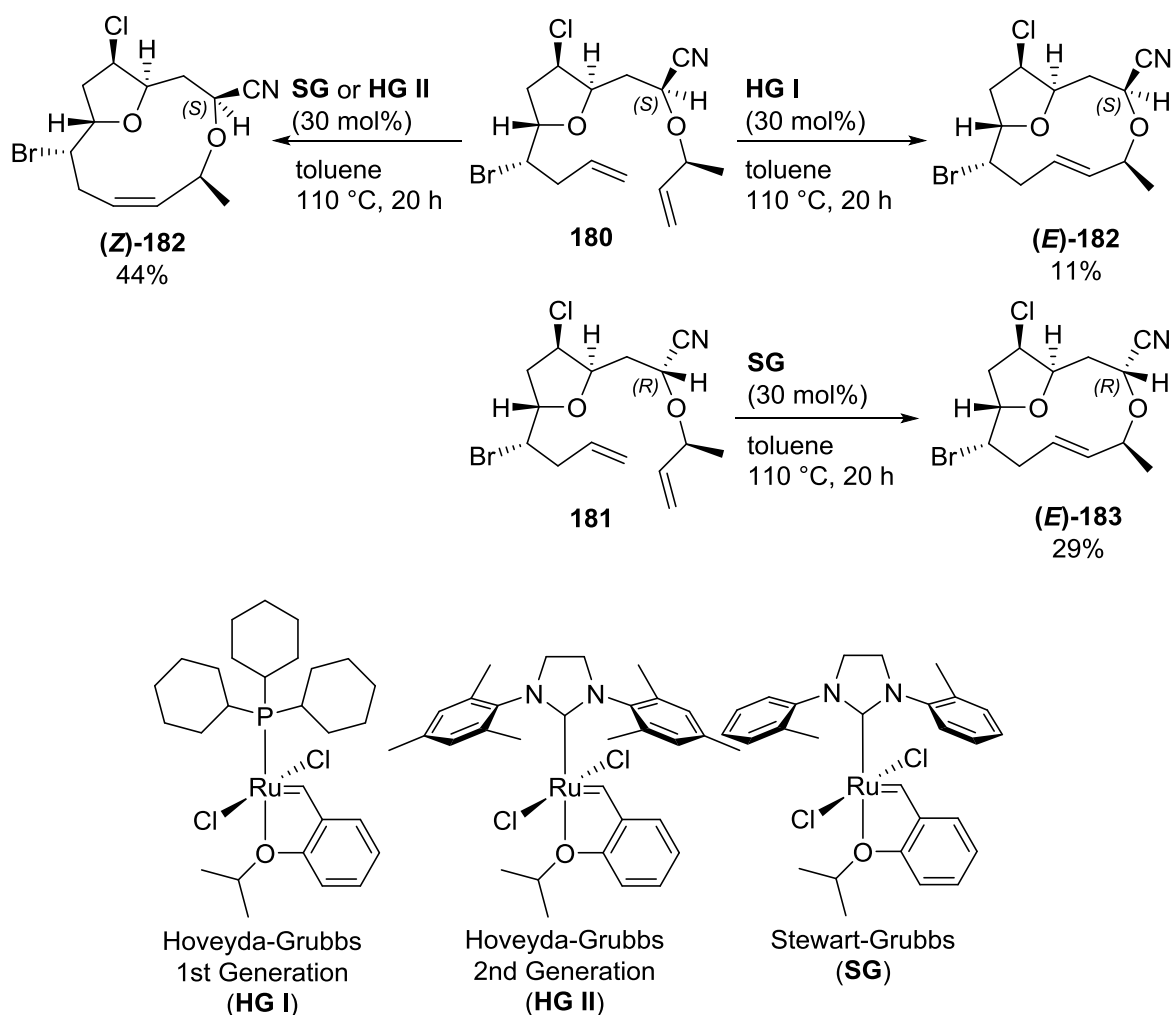
Scheme 2.5.3.5: Palladium catalysed hydrogenation of alkynes **178** & **179**.

Hydrogenation of alkynes **178** & **179** with palladium on barium sulfate, poisoned by quinoline gave dienes **180** & **181**. The inclusion of quinoline and choice of catalyst substrate effectively prevented over hydrogenation.

With this, Bonney and Yaqoob had designed a route and successfully employed it the synthesis of multi-gram quantities of RCM precursors **180** & **181**.

2.5.4 Formation of Obtusallene Core Macrocycles (*E*)-182** & **183** *via* RCM**

Yaqoob and Bonney performed a brief screen of Grubbs' catalysts. It was found by Yaqoob that in the case of diene **181**, refluxing in toluene overnight with Stewart-Grubbs catalyst (SG) achieved ring closure to *E*-macrocycle **183** in low yield. Conversely, when Bonney trialled SG catalyst with diene **180**, *Z*-macrocycle **182** was produced exclusively. The same was observed with Hoveyda-Grubbs 2nd generation catalyst (HG II). Only Hoveyda-Grubbs 1st generation catalyst (HG I) gave the desired *E*-macrocycle **182**, but in only an 11% yield.



Scheme 2.5.4.1: Results of ring-closing metathesis of dienes **180** and **181**.

Differing only in the conformation of the nitrile at C₄, it is surprising that the reactivity with respect to RCM is so markedly different. Clearly, a change in the orientation of this pendant group can drastically alter the reactivity of the whole molecule. The observation of major and minor conformers existing for these macrocycles suggests that each will require a different catalyst as the orientation of the dienes will of course be different. This also has implications for the reactivity of each macrocycle in later steps and it was not expected that each would behave in similar manners.

At this point, X-ray crystallography had been performed for both macrocycles, (*E*)-**182** & **183**, so the absolute and relative stereochemistries could be conclusively confirmed as matching obtusallenes II & IV (**15** & **19**).

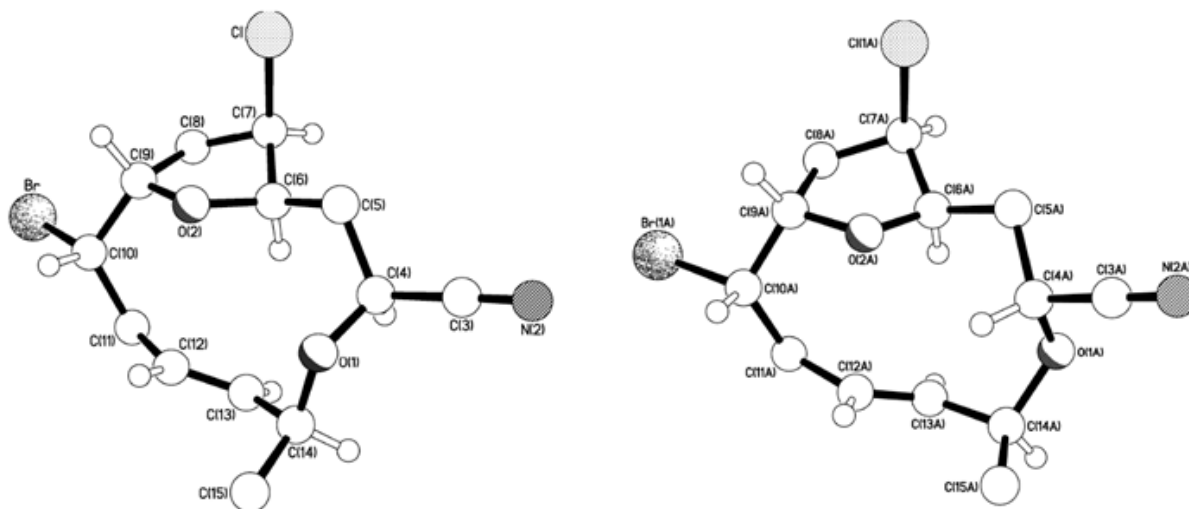


Figure 2.5.4.1: X-ray crystal structures of macrocycles (*E*)-**182** & **183** (left & right), corresponding to obtusallenes II & IV (**15** & **19**) respectively.

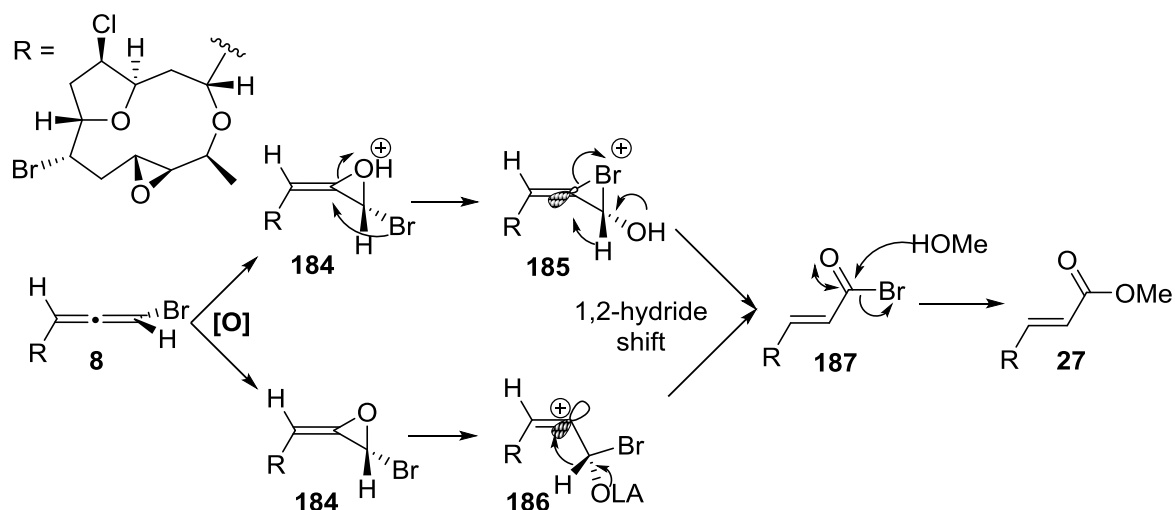
^1H NMR spectroscopy showed significant line broadening, especially for macrocycle (*E*)-**182**, in line with the observations in the isolation papers. Conducting the NMR experiments at higher temperature alleviated much of the broadening, but recording accurate *J*-values for comparison to literature data was not possible. Fortunately, the high temperature experiments allowed sufficient sharpening to measure the coupling constants across the olefin and definitively identify them as the *E*-isomers. It was at this point that Bonney completed his research and the current study began.

3 Results & Discussion Part I: The Epoxidation of Bromoallenes

3.1 Aims and Objectives Part I

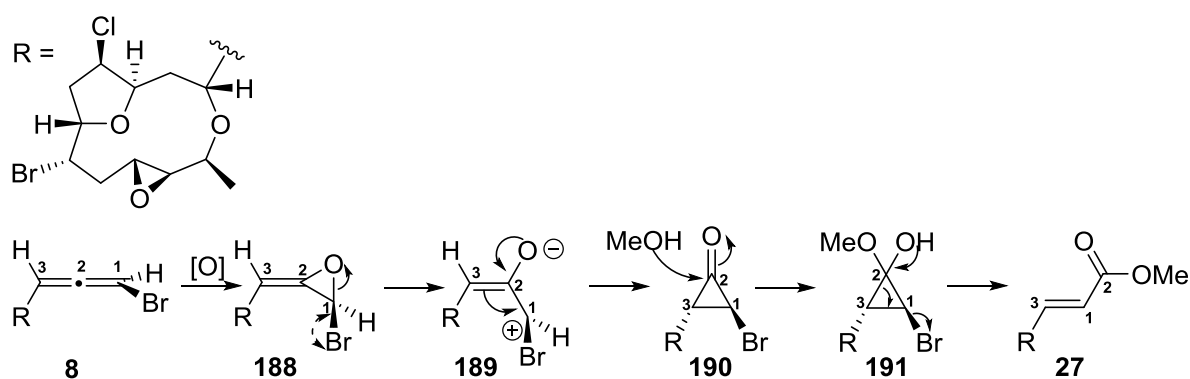
3.1.1 Possible Mechanisms Linking Bromoallenes and α,β -Unsaturated Esters

Likely mechanisms linking bromoallenes to α,β -unsaturated esters were considered. Initial thought involved the interchange of the protonated epoxide of bromoallene oxide **184** for a bromonium ion (**185**) would be followed by a 1,2-hydride shift to acyl bromide **187**. However, analysis of models of these system suggests that the relevant C-H σ and C-O σ^* orbitals are orthogonal, making this route unlikely. The next option considered involved an initial Lewis acid (LA) assisted opening of epoxide **184**, allowing rotation and alignment of the hydride with the empty p-orbital. Indeed, this has been shown to proceed with the use of indium chloride and aliphatic terminal epoxides to give aldehydes.⁴⁹ However, the intended mechanism when applied to a bromoallene oxide **184**, results in vinylic cation **186**, putting a formal charge on an sp carbon and is considerably higher in energy than the alternative, an oxyallyl cation.



Scheme 3.1.1.1: Initial thoughts of the biogenesis of unnamed ester **27**.

With the examples in section 2.4, there is literature precedent for the formation of allene oxides in biological systems, observed equilibration to cyclopropanones and evidence of an unsaturated product pathway in cyclopropanone bromides *via* a Favorskii-like rearrangement. Thus, we can propose a mechanism for the synthesis of α,β -unsaturated esters from bromoallenes. Initial epoxidation of 12-epoxyobtusallene IV (8) (regiochemistry is uncertain as the system is 1,3-disubstituted) would give allene oxide **188**. This will likely rapidly rearrange to cation **189**, perhaps with neighbouring group participation from the bromine, and on to cyclopropanone **190**. From what has been established of the effects of solvolysis of cyclopropanones (scheme 2.4.1.3), we can expect a collapse of the ring and protonation to yield methyl ester **27**. The difference to a standard Favorskii rearrangement is the presence of an α -bromide allows elimination to form a α,β -unsaturated ester, rather than a branched aliphatic analogue.



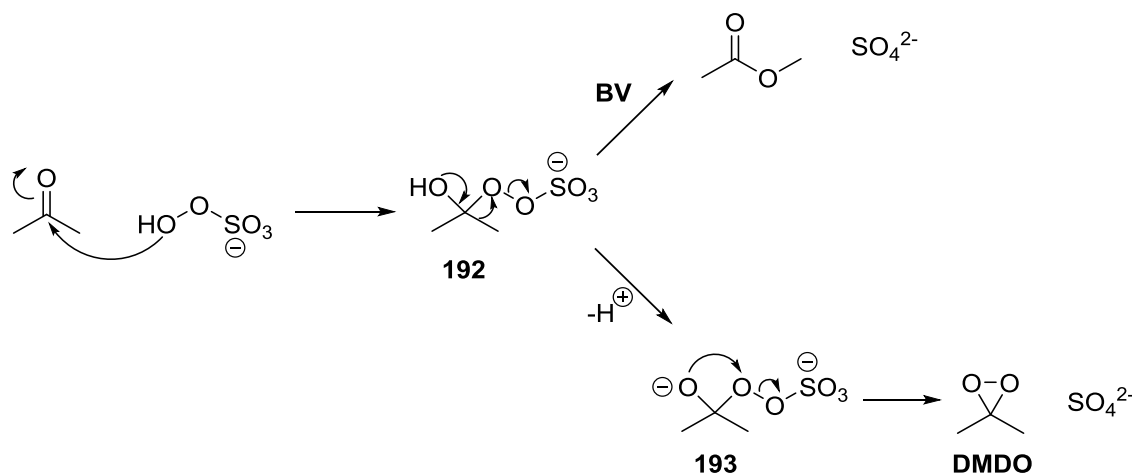
Scheme 3.1.1.2: Predicted biosynthesis of unnamed ester **27**.

One important consequence of this mechanism is the interchange of C_1 & C_2 . In a similar manner to the ring contraction in scheme 2.4.1.1, the formation and subsequent collapse of the cyclopropanone switches the regiochemistry of these carbons. This will be of

great use in validating the mechanism, as the alternatives in scheme 3.1.1.1 do not undergo a similar interchange. The use of isotopically labelled model substrates will allow us to observe the fate of these carbons.

3.1.2 Epoxidation Reagents

With no existing literature precedent for the epoxidation of bromoallenes, a range of epoxidants that have already been used for allenes and other unsaturated bonds were considered.^{35c} The first choice will be the electrophilic epoxidant, dimethyl dioxirane (DMDO).⁵⁰ This reagent is formed by the oxidation of acetone by Oxone[™], a proprietary formulation comprised of a triple salt with the formula 2KHSO₅.KHSO₄.K₂SO₄. The active compound is the peroxymonosulfate ion, which has reactivity similar to other peracids.

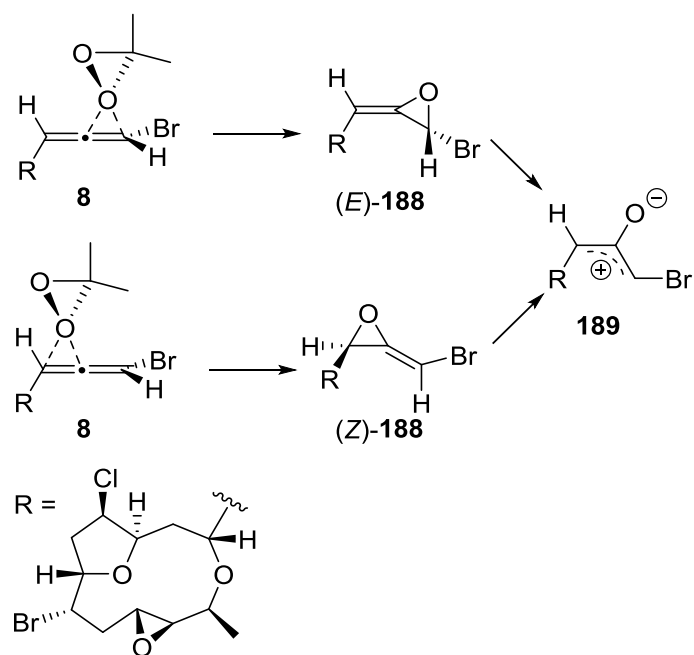


Scheme 3.1.2.1: Generation of DMDO with Oxone[™].

The peroxysulfate nucleophilically attacks the carbonyl carbon to form an alkyl peroxysulfate (**192**). At low pH, this intermediate will undergo Baeyer-Villiger (BV) oxidation.⁵¹ Here, intermediate **192** collapses with 1,2-migration of the alkyl group to yield

methyl ethanoate and sulfate. It is for this reason that Oxone[™] is also formulated with a potassium bisulfate buffer. At neutral pH, intermediate **192** is deprotonated allowing a three-membered ring cyclisation with elimination of sulfate to give DMDO. Due to the alternative pathways and high reactivity of DMDO, the synthesis is highly inefficient, with yields of 3% considered high.^{50c} For this reason, a large excess of Oxone[™] is used to ensure sufficient quantities of DMDO are produced. The reagent can be produced *in situ*, or if more careful stoichiometric control is required, can be produced in bulk and distilled, allowing iodometric titration to determine concentration and storage at low temperatures.

The epoxidation would proceed through a spiro transition state, with the dioxirane ring perpendicular to that of an olefin in **8**.⁵² The steric demand of the methyl groups will invariably place the DMDO *anti* to the R group of bromoallene **8** and thus give the *E*-allene oxide **188** if the C₁-C₂ olefin is attacked. Conversely, if the C₂-C₃ olefin is epoxidised, (*Z*)-**188** will result. However, there is little to suggest the outcome of the regiochemistry of the epoxidation. Both olefins appear equally likely to epoxidise, but it may be the case that the electron donating power of the bromine renders the C₁-C₂ olefin slightly more electron rich and therefore the favoured site of epoxidation. Ultimately, the outcome would be the same as both allene oxides can collapse to the same oxyallyl cation (**189**).

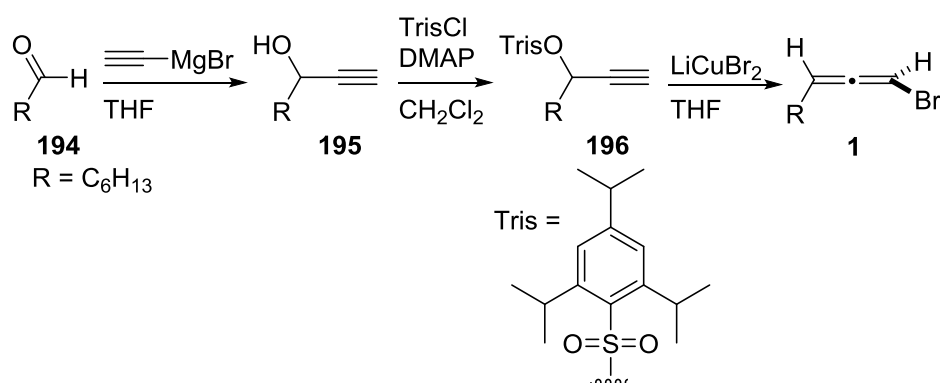


Scheme 3.1.2.2: Spiro transition state of DMDO epoxidation.

Another alternative is *meta*-chloroperoxybenzoic acid (*m*CPBA), also successfully used in the epoxidation of allenes. This works in a similar manner to DMDO in that it affects a facial epoxidation at electron rich olefins.

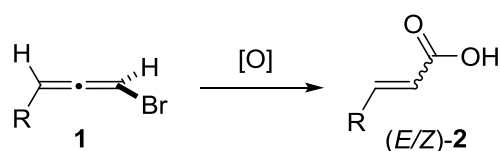
3.1.3 Synthesis of Model Bromoallenes

Any fully elaborated obtusallene compounds will of course be very valuable, only available in small amounts and likely to be sensitive to decomposition. They are certainly not suitable for an epoxidation methodology study. For these reasons, a model bromoallene will be prepared from heptaldehyde (**194**).



Scheme 3.1.3.1: Planned route to model bromoallene **1**.

This route is based on the proven method of installing bromoallenes, as performed by Kim in the successful synthesis of (+)-Itomanallene A (**12**) and commonly referred to as the Overman protocol.⁵³ Ethynylmagnesium bromide is used in the nucleophilic addition of acetylide to heptaldehyde (**194**) to give a racemic mixture of propargylic alcohol **195**. These are then converted to 2,4,6-triisopropylbenzosulfonates (Tris) (**196**), which act as a leaving group for the $\text{S}_{\text{N}}2'$ substitution of bromide with treatment of LiCuBr_2 , to yield a racemic mixture of bromoallene **1**. These bromoallenes will be inseparable, but is of no consequence, as examination of our proposed epoxidation-rearrangement mechanism, (scheme 3.1.1.2) suggests that epoxidation of both bromoallene stereoisomers will result in the same product. This model system is fast and efficient to produce and so can be used for multiple test reactions at any scale.

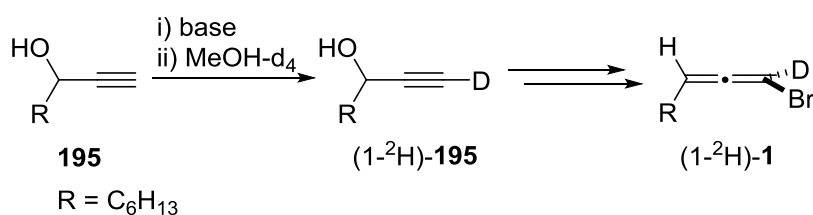


Scheme 3.1.3.2: Planned epoxidation of model bromoallene **1** to give α,β -unsaturated acids (*E*)-**2** & (*Z*)-**2**.

This substrate will allow the success of bromoallene epoxidation to be evaluated. Several epoxidants will be trialled and the conditions optimised until the products can be reliably generated and characterised. Although the inspiration for this study was the α,β -unsaturated methyl ester **27**, the reaction will be replicated in water to produce α,β -unsaturated acids (**2**). Many of the epoxidation methods are conducted in water, so this will be the likely nucleophile in any case, but producing a very polar product will allow for easier isolation and separation from the relatively non-polar bromoallenes starting material **1** and any side-products. Both the *E*- and *Z*- α,β -unsaturated acids ((*E*)-**2** & (*Z*)-**2**) are known in the literature, so comparison to existing spectral data will be possible.^{52, 54}

3.1.4 Synthesis of Isotopically Labelled Model Bromoallenes

Unfortunately, this alone will give little information about the mechanism. For this reason, analogues that have been isotopically labelled at C₁ will need to be produced. In the case of deuterium, this is trivial.

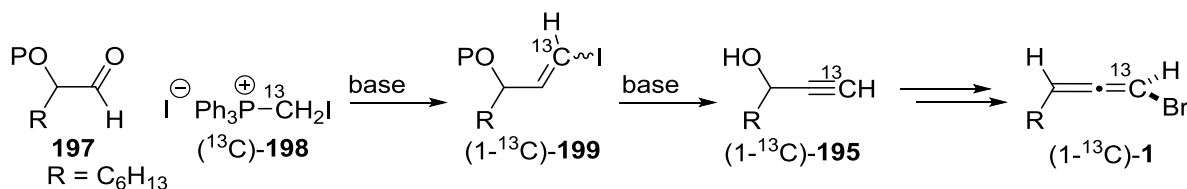


Scheme 3.1.4.1: Route to deuterated bromoallene (1-²H)-**1**.

Deprotonation of the alkyne and alcohol of compound **195** with a suitable base, followed by quenching with deuterated methanol would give alkyne (1-²H)-**195**, which can be submitted to the previously established bromoallene synthesis to generate bromoallene

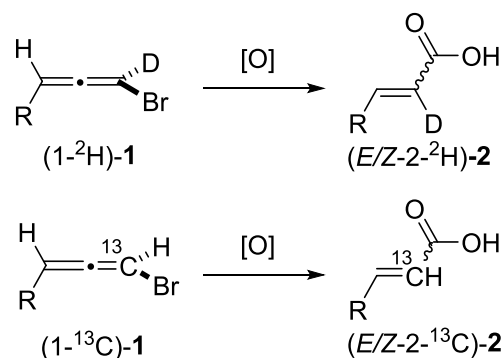
(1-²H)-**1**. After epoxidation, the fate of the deuterium can be monitored by ¹H-NMR spectroscopy. Although deuterium is not directly observable in NMR spectra, the adjacent protons will show larger and more complex coupling constants. A positive result here will not disprove the alternative hydride shift mechanism, but allow us to proceed with the synthesis of a ¹³C labelled compound with more confidence in our hypothesis.

Labelling with ¹³C will not be as trivial. The carbon isotope can be incorporated using a Wittig reaction using (¹³C)-labelled iodomethylphosphonium salt (¹³C)-**198** and a suitably protected aldehyde (**197**) to give vinyl iodide (¹³C)-**199**, both of which have very limited literature precedent. β-Elimination across the vinyl group will yield alkyne (¹³C)-**195**, which can then be further derived using the bromoallene installing procedure and subsequently epoxidised.



Scheme 3.1.4.2: Proposed route to achieve incorporation of a ¹³C label and further derivation to (1-¹³C)-**1**.

The position of the carbon isotope can be directly monitored by ¹³C NMR spectroscopy, as one resonance will have an intensity 100 times greater than that of the others. In addition, the ¹H NMR spectra will show very large splitting patterns due to ¹H-¹³C coupling. Both isotopically labelled bromoallenes can be submitted to the chosen epoxidation method.



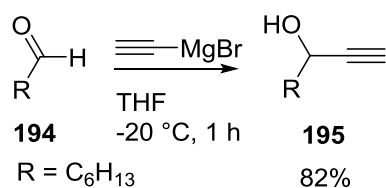
Scheme 3.1.4.3: Migration of the labelled carbons of (1-²H)-1 & (1-¹³C)-1 upon epoxidation.

Observing these isotopically induced resonances at C₂ of the product α,β-unsaturated acids (2-²H)- & (2-¹³C)-2, will confirm that the proposed Favorskii-like mechanism is occurring. As such, these model systems will give insight into the biogenesis of several *Laurencia* natural products, but also allow experience to be gained in key steps in the completion of natural product total syntheses.

3.2 Results & Discussion Part I

3.2.1 Synthesis of Model Bromoallene 1

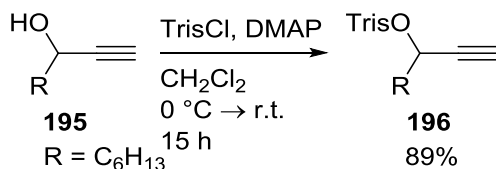
Following the procedure developed in Kim's synthesis of (+)-Itomanallene A (**12**),^{53a} bromoallene **1** was prepared. The first step was a nucleophilic ethynyl Grignard addition to heptaldehyde (**194**) to yield propargyl alcohol **195**.



Scheme 3.2.1.1: Synthesis of propargylic alcohol **195**.

This reaction proceeded well with an 82% yield, and could be performed on multi-gram scales. Distillation of aldehyde **194** was essential in preventing the formation of aldol-type side-products.

The next reaction required protection of the alcohol as a trisylate. This bulky sulfonate group provides a suitable leaving group for the following $\text{S}_{\text{N}}2'$ bromination, while simultaneously protecting C_3 from $\text{S}_{\text{N}}2$ attack.

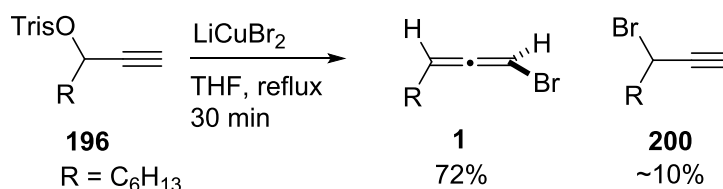


Scheme 3.2.1.2: Trisylation of propargylic alcohol **195**.

Kim's original procedure called for 3 equivalents of TrisCl and 6 equivalents of DMAP.^{53a} However, when these conditions were replicated, the crude product was left with

large residual amounts of these reagents. DMAP, its protonated form and the sulfonic acid were easily removed by column chromatography, but the residual TrisCl had an almost identical R_f to trisylate **196** and could not be removed. It was found that reducing the amounts of each reagent to a single equivalent apiece was not detrimental to the yield and that after removal of the protonated DMAP salt by silica plug, minimal purification was necessary.

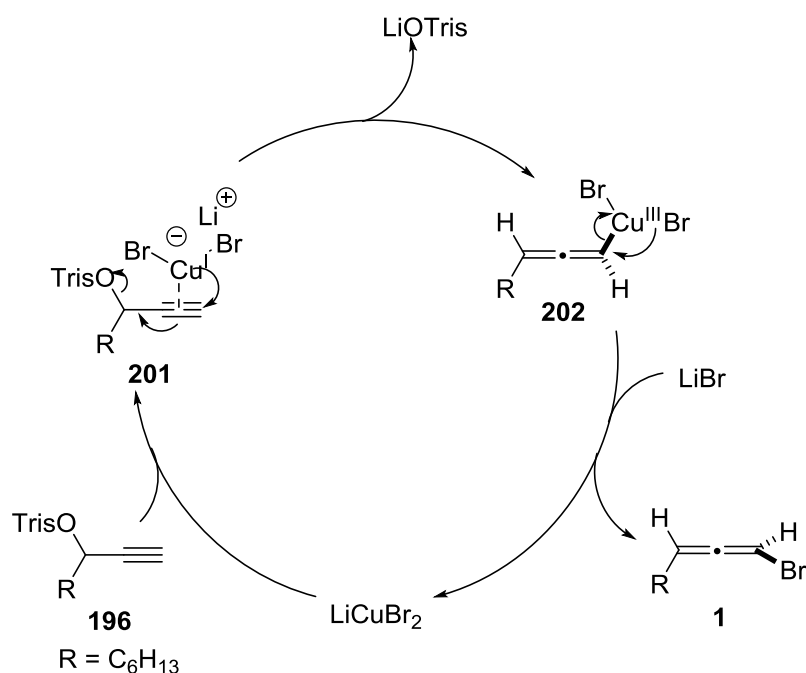
With propargylic trisylate in hand, we could now brominate the alkyne *via* a copper catalysed S_N2' reaction.



Scheme 3.2.1.3: Synthetic route to bromoallene **1**.

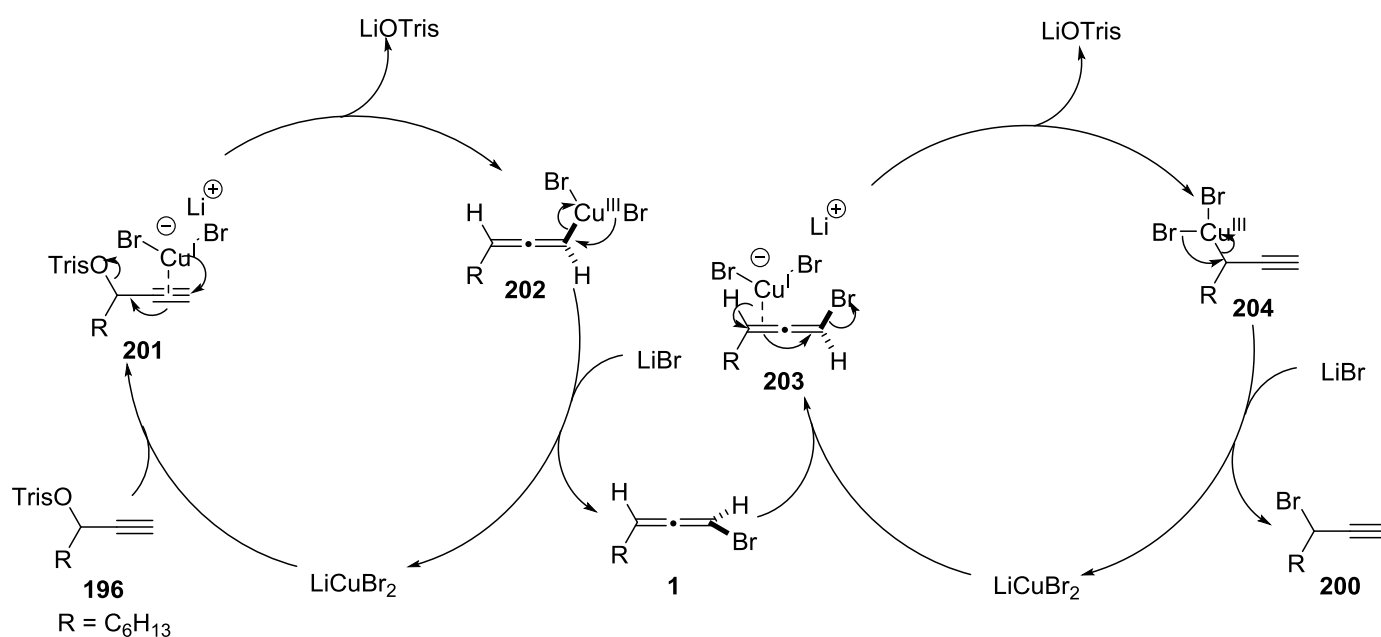
This reaction proceeded cleanly, with high yield. Mass was invariably lost due to the volatility of the product and the formation of apparent S_N2 product, propargylic bromide **200**. This isomer could be removed through careful column chromatography, but could not be isolated due to its high volatility.

The reaction employs an anionic copper complex and the trisylate group to direct the regiochemistry, as shown in the catalytic cycle in scheme 3.2.1.4. The bulk of the trisylate is thought to sterically shield C_3 , preventing S_N2 reaction, while the copper coordinates to the alkyne to give intermediate **201**, directing S_N2 substitution of copper to the terminal carbon. The metallated intermediate **202** can reductively eliminate to give bromoallene **1**, with retention of stereochemistry.



Scheme 3.2.1.4: LiCuBr_2 bromination catalytic cycle.

Synthesis papers employing the same reaction often report that bromoallenes are isolated along with the $\text{S}_{\text{N}}2$ product (7 - 9%) when derived from trisylates.^{53a, 55} Conversely, when a mesylate is used as a leaving group, the yield of the propargylic bromide is much higher at 20 - 30%.^{53b, 56} From this, we can infer that the trisylate group is important in preventing direct $\text{S}_{\text{N}}2$ substitution. However, a much larger difference in the ratio of $\text{S}_{\text{N}}2$: $\text{S}_{\text{N}}2'$ products might be expected when considering the vastly different steric profile of these two leaving groups. An alternative explanation invokes a second catalytic cycle.



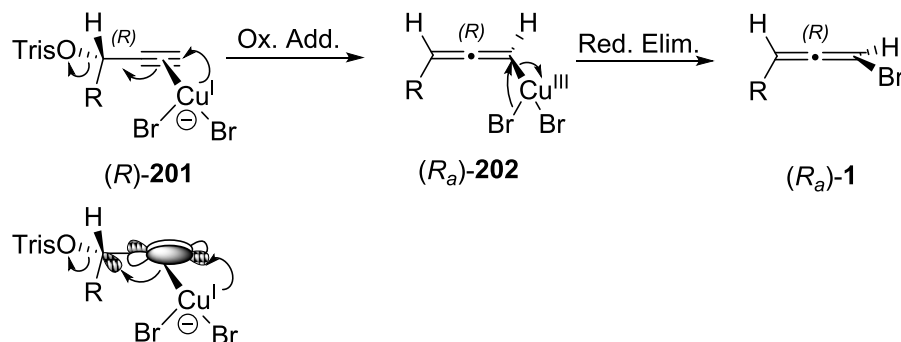
Scheme 3.2.1.5: Second catalytic cycle reversing the reaction from bromoallene **1** to propargylic bromide **200**.

By a similar sequence of oxidative addition at C₃ and reductive elimination, we can envisage a reverse reaction to form propargylic bromide **200**. Furthermore, propargylic bromide **200** can be brominated a further time to return bromoallene **1**. This would explain why the proportion of propargylic bromide was consistently 5 - 10%, even with the very large trisylate leaving group. The ratio represents the relative stability of bromoallene **1** and propargylic bromide **200**, and the equilibrium ratio of the two. Although, when this reaction was applied to the diastereomerically pure obtusallene macrocycles, there was some evidence of direct S_N2 substitution (*vide infra*, section 4.2.9).

Although this model system produced a mixture of inseparable bromoallene isomers, it is important to consider the stereochemical implications of the reaction.

Initial coordination of [Cu^IBr₂]⁻ to alkyne **196** is followed by oxidative addition to a Cu(III) allene species (**202**). Similarly to biomimetic electrophilic brominations (scheme 2.5.1.3), the above reaction is stereospecific. The oxidative addition of copper and

elimination of trisylate must proceed in an *anti* fashion due to the alignment of alkyne π^* & π and trisylate σ^* orbitals.⁵⁷ Scheme 3.2.1.6 demonstrates how these orbitals overlap with respect to one of the alkynes π^* & π orbitals.



Scheme 3.2.1.6: Stereochemical implications of the oxidation addition of $[\text{Cu}^{\text{I}}\text{Br}_2]^-$ to trisylate **(R)-196**.

The above scheme shows that the substitution of the copper species for trisylate must proceed with both groups in an antiperiplanar geometry. Trisylate **(R)-196** yields copper allene **(R_a)-1** and vice versa. The reductive elimination retains stereochemistry to give a bromoallene with the same geometry. As the stereochemistry of the bromoallene will have no effect on the later epoxidation reaction, racemic trisylate **196** was used and so produced racemic bromoallene **1**. If the stereochemistry of the bromoallene is important (e.g. during the completion of obtusallenes, *vide infra*, section 4.2.9), the trisylates must first be separated before bromination.

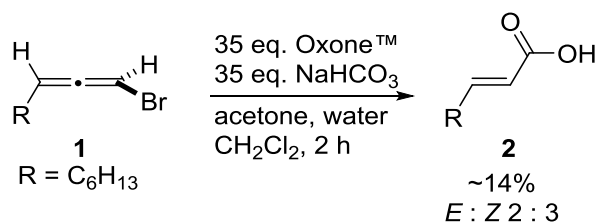
To minimise the risk of free bromide being present in the solution, which may cause off target reactivity, the catalyst was prepared separately, paying close attention to stoichiometry before adding to the substrate. Strictly speaking, without an excess of LiBr , this reaction is no longer catalytic as the cycle terminates with the production of

bromoallene **1** and CuBr. For this reason, three equivalents of the catalyst were used. A standard aqueous work up was not effective at removing the spent copper bromide, which appeared to cause decomposition of bromoallene **1**. Again, the use of a silica plug was effective at completely removing the spent copper compounds and lithium trisylate.

Bromoallene **1**, proved to be volatile and so material was often lost during solvent removal. The compound would also turn brown over time, thought to be due to hydrolysis and generation of HBr, which was subsequently oxidised to elemental bromine. However, it was prepared in sufficient quantities for multiple epoxidation attempts and if used within a week, decomposition was minimal. With bromoallene **1** in hand, several different epoxidation methods were trialled.

3.2.2 Assay of Epoxidation Reagents

The first attempt was an *in situ* generation of DMDO using oxone and NaHCO₃ in acetone, water and dichloromethane, as employed by Crandall in epoxidations of β - and γ -hydroxy allenes.⁵⁸ This procedure called for seventy equivalents of OxoneTM, which seemed excessive, meaning that each mmol of bromoallene **1** required 21.2 g of OxoneTM. However, the preparation of DMDO is very inefficient, with yields of 3% considered high,^{50c} so a large excess of OxoneTM was needed to ensure sufficient generation of DMDO. We began with thirty-five equivalents for the sake of economy and safety.

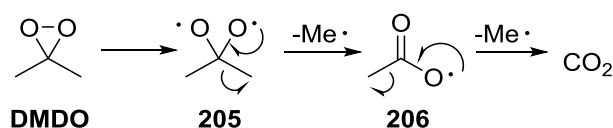


Scheme 3.2.2.1: Epoxidation of bromoallene **1** using *in situ* generation of DMDO.

The first results of this reaction were encouraging, with ~14% yield of a 2 : 3 mixture of *E*- & *Z*-acids **2** obtained, the remainder composed of starting material and a multitude of unidentified side-products. The combined mass of these side-products was very large, exceeding that of the intended α,β -unsaturated acid products (**2**).

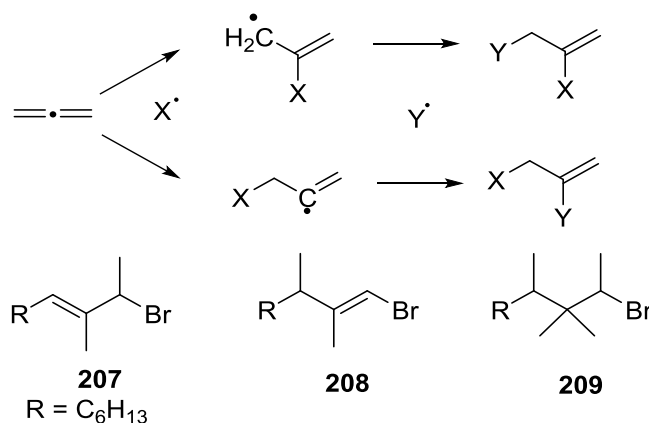
Further trials were made to optimise this reaction, including varying the amount of OxoneTM added (2 – 35 eq.), changing the solvent, rate of addition and excluding dichloromethane to render the reaction monophasic. However, changes to these conditions had little effect on the outcome of the reaction, with yields not exceeding 20%, the remainder composed of a considerable amount of unreacted bromoallene **1** and the same array of side-products. Although it was noted that using fewer equivalents of OxoneTM resulted in fewer side-products.

Although none of these side products were successfully identified, it is thought that they are brought about by radical decomposition. DMDO is known to decompose to methyl radicals with subsequent generation of an acetate radical and then carbon dioxide.⁵⁹



Scheme 3.2.2.2: Radical decomposition of DMDO.

Initial formation of biradical **205** is quickly followed by elimination of a methyl radical, then decarboxylation to produce a second. Allenes are known to be very reactive towards alkyl radicals.⁶⁰ The sensitive and electron rich bromoallene **1** would be susceptible to attack in multiple locations, with the potential for multiple products. This may also explain the observation that yield is unaffected by increased quantities of oxone™. The α,β -unsaturated acid products **2** provide a proton that may catalyse the initial homolytic cleavage. Once the reaction reaches a critical pH, DMDO will be rapidly decompose, precluding further epoxidation and instead destroying bromoallene **1** *via* radical addition. Attempts to neutralise the acidity with sodium bicarbonate resulted in no reaction. Presumably, as the higher pH promoted a Baeyer-Villiger reaction to rearrange DMDO to methyl acetate.

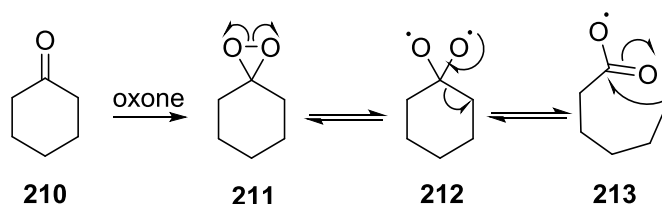


Scheme 3.2.2.3: Radical addition to allene.

Applying the above scheme to bromoallene **1**, with $\text{X}^{\bullet}$ and $\text{Y}^{\bullet}$ as methyl radicals, suggests that the side products may include 1,2- and 2,3-dimethyl adducts, **207** & **208** respectively. They may also include the 1,2,2,3 tetramethyl adduct **209** formed by a second radical addition across the remaining double bond. $\text{X}^{\bullet}$ and $\text{Y}^{\bullet}$ could feasibly be hydrogen

or bromine radicals, brought about by abstraction of these species *via* propagation steps. A study of radical brominations shows that allenes are also susceptible to bromine radicals and this can lead to chain extension when combined with suitable olefins.⁶¹ This goes some way to show the variety of side products possible during the treatment of bromoallene **1** with DMDO.

Considering the issue at hand may be the generation of destructive radicals, attention was turned to employing a dioxirane that would not decompose. We believed that the use of a cyclic ketone would prevent the formation of free radicals.

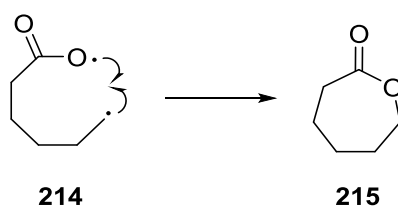


Scheme 3.2.2.4: Formation and reversibility of cyclohexanone dioxirane biradical.

Assuming that generation of radicals is unavoidable, it would be preferable to tether the compound as a biradical. Instead of producing a methyl radical that would proceed to destroy bromoallene **1**, the use of cyclohexanone (**210**) would give biradical **213**, which would have a greater chance of recombining. This intramolecular recombination reaction would ideally proceed before the alkyl radicals facilitate the destruction of bromoallene **1**.

A paper was found detailing the generation of a variety of dioxiranes from various parent ketones, including cyclohexanone, menthone and other cyclic ketones.^{50b} This paper also described a novel approach to preparing dioxiranes as concentrated solution in their parent ketones. The usual method for this involves distillation at low temperature and for

low boiling point ketones, this is the method of choice. However, with the increased mass and boiling point of larger cyclic ketones, a different procedure was employed. The paper described a salting-out process of the dioxirane/ketone mixture that removed water and dissolved salts to allow collection of pure dioxirane solutions in their parent ketones. By ensuring that all the glassware was chilled beforehand, the concentration of dioxirane was maintained. Murray and co-workers described the collection of dioxiranes in a range of concentrations from 0.2 – 0.8 M. Indeed, when his work was replicated with cyclohexanone, we attained a concentration of 0.7 M, as determined by iodometric titration. Two equivalents of this cyclohexanone dioxirane solution was added to bromoallene **1** and stirred in the dark for 2 h. TLC showed the appearance of a spot, roughly at the R_f expected for α,β -unsaturated acids **2**. However, NMR analysis of the crude product showed no evidence of this target compound, but instead a large amount of ϵ -caprolactam. Murray had also observed the formation of this cyclic lactone, as well as ϵ -caprolactone polymers, under certain conditions.

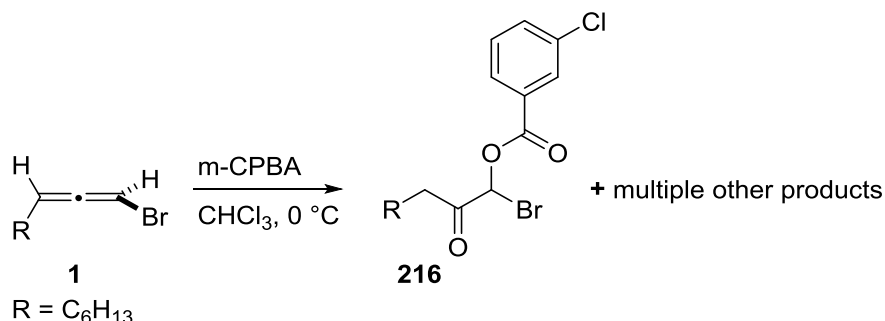


Scheme 3.2.2.5: Formation of ϵ -caprolactone **215**.

The biradical had indeed recombined, but not in the manner that we had hoped. Instead of radical addition from the alkyl radical to the carbonyl carbon (scheme 3.2.2.4), recombination proceeded directly to the oxygen radical, leaving the above cyclic lactone. This process must be occurring faster than either epoxidation or radical addition as the

crude material contained only this lactone (**215**), cyclohexanone (**210**) and bromoallene **1**. As such, the formation of destructive radicals had been prevented, but also any useful reaction.

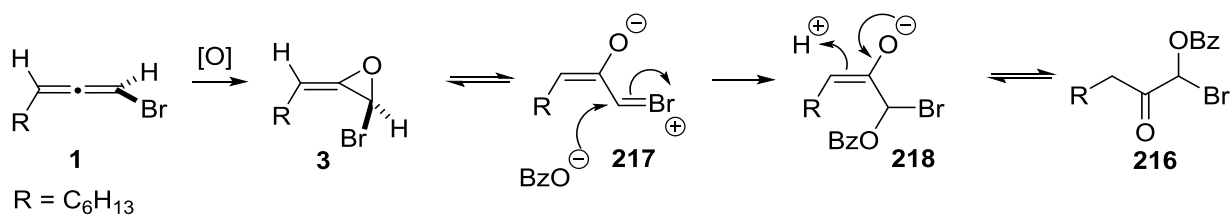
Another epoxidation method trialled was *m*CPBA.



Scheme 3.2.2.6: Attempted epoxidation of **1** using *m*CPBA.

The above reaction also gave many products, none of which was the desired compound. The number of side-products made individual separation and identification unfeasible, but the major product is thought to be the above benzoate adduct **216**, tentatively assigned by the distinct singlet at 6.25 ppm, corresponding to the proton geminal to bromide and benzoate.

A similar compound has been observed in the epoxidation of allenamides with *m*CPBA,⁶² and is presumably formed by trapping of a oxyallylic bromonium ion intermediate **189** with the 3-chlorobenzoic acid by-product.

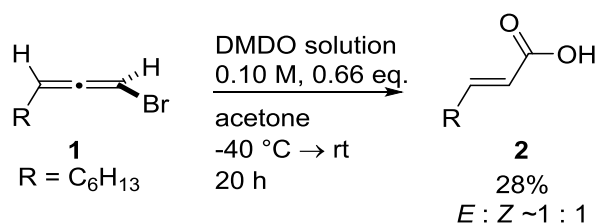


Scheme 3.2.2.7: Proposed mechanism for the trapping of bromonium oxyallylic intermediate

217 with a benzoate nucleophile.

This result is of importance as it supports the proposed cyclopropanone pathway (scheme 3.1.1.2) by suggesting that oxyallylic cationic bromonium ion **217** exists as an intermediate. Indeed, subsequent molecular modelling, showed that the reaction intermediate undergoes significant shortening of the C-Br bond.⁶³ However, it also disqualified *m*CPBA as a suitable epoxidation reagent.

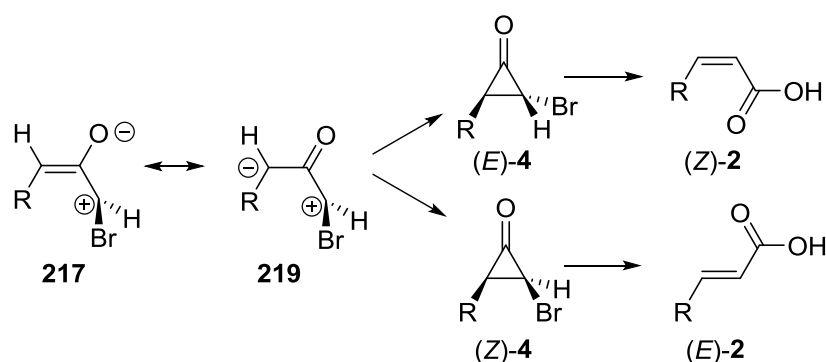
The epoxidation method of choice was found to be the preparation of DMDO solution *via* distillation from a mixture of oxone, Na₂CO₃, acetone and water. DMDO was collected as a solution in acetone at -100 °C, in concentrations between 0.07 M and 0.12 M as determined by iodometric titration. This DMDO solution could then be added to substrates in known quantities. When bromoallene **1** was epoxidised in this manner, it still resulted in low yields, between 12 and 28%, but was found to be much more convenient. DMDO solutions could be produced in large batches, stored for several days, added in accurate stoichiometric amounts and greatly simplified the work up. It did not appear that any dispirodioxide, often seen in literature examples of allene epoxidations, was being formed. This means that the rate of bromonium assisted epoxide opening far exceeded that of a second epoxidation.



Scheme 3.2.2.8: Epoxidation of bromoallene **1** using sub-stoichiometric amounts of DMDO solution.

Again, varying the conditions did not drastically change the yield of the reaction, but it was found that using a sub-stoichiometric amount of DMDO gave the best results. As it is hypothesised that the proton of the product acid promotes radical decomposition and that these radicals destroy the bromoallene starting material, limiting the amount of radicals in the system would be to our advantage. As the yield of epoxidation had not risen above 30%, we first tried adding 0.30 equivalents of DMDO. This gave a much cleaner product, but in a greatly reduced yield. Eventually, up to 0.66 equivalents were added for each epoxidation. This quantity seemed to give the best balance between reducing radical side products and producing a moderate yield, although there was no clear correlation between equivalents added and final yield. The reactions were also conducted in darkness, in the belief that light may promote the initial homolytic cleavage. Excluding light also resulted in a closer 1 : 1 ratio of (*E*)- and (*Z*)-**2**, as opposed to the slight excess of (*Z*)-**2** seen previously.

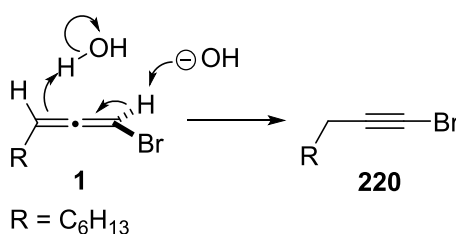
We presumed that the geometry of the double bond is defined by the relative stereochemistry of the alkyl group and bromine of cyclopropanone **4** and as such, equal amount of (*E*)- and (*Z*)-**2** would be produced.



Scheme 3.2.2.9: Stereodefining step in the formation of α,β-unsaturated acids (**2**).

For the cyclopropanone (**4**) to form, C₁ and C₃ must form a new bond. Whether this occurs with the alkyl group and bromine *syn* or *anti* dictates whether the resulting double bond will be *trans* or *cis*, respectively. Although, this is not well supported in the literature. Other studies of hindered and unhindered di-substituted cyclopropanones for which we would product *E*- and racemic products respectively, show no such pattern.^{54, 64} Results vary between very similar substrates and it appears that reaction conditions during the formation of bromocyclobutanone **4** may be more important than steric factors.

Furthermore, the initial work-up for this reaction involved washing with 3M KOH solution, to transfer the product acids into the aqueous layer, before acidification and extraction, in an attempt to remove the majority of side products. While this removed much of the impurities, it also caused the appearance of a new compound, believed to be 1-bromonon-1-yne (**220**).



Scheme 3.2.2.10: Proposed base catalysed formation of 1-bromonon-1-yne (**220**)

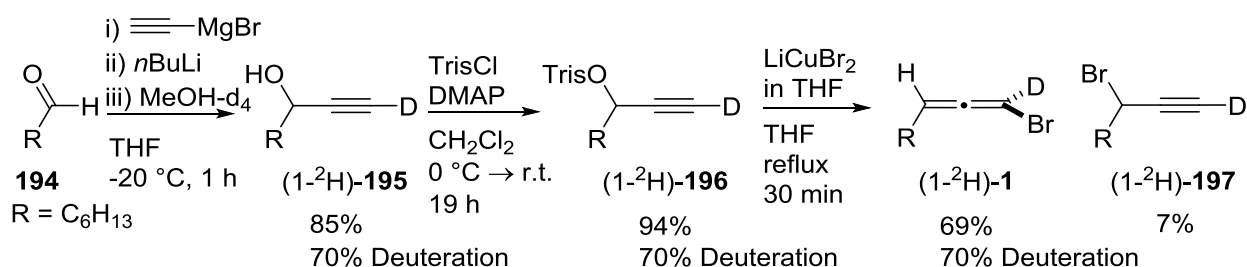
This compound may be formed by deprotonation of the starting bromoallene **1**, so did not affect the yield of the carboxylic acids. However, this compound co-eluted with the product (*E*)-**2**, making it very difficult to separate. Subsequent DMDO epoxidations did not use a base wash as part of the work-up and this compound was no longer observed.

As such, a link between the epoxidation of bromoallenes and α,β -unsaturated acids

had been established and a procedure developed to collect the products in reasonable and reproducible yields. However, these results gave no information about the likely mechanism. Work began on the synthesis of isotopically labelled substrates to clarify the mechanism.

3.2.3 Synthesis of Deuterium Labelled Bromoallene (1-²H)-1

Alkyne **195** was readily converted into alkyne (1-²H)-**195** deprotonation with *n*BuLi followed by treatment with methanol-d₄.



Scheme 3.2.3.1: Route to deuterium labelled bromoallene (1-²H)-1.

Similar yields were obtained to those for the unlabelled substrate **1** in section 3.2.1 and again the propargylic bromide (1-²H)-**197** was formed in 7% yield, but was removable by chromatography. Propargylic alcohol (1-²H)-**195** was found to be 70% deuterated at the alkynic position and as the ¹H NMR spectral peaks for bromoallenes and α,β-unsaturated acids are clearly distinct, it was obvious which position was deuterated by the large decrease in integral.

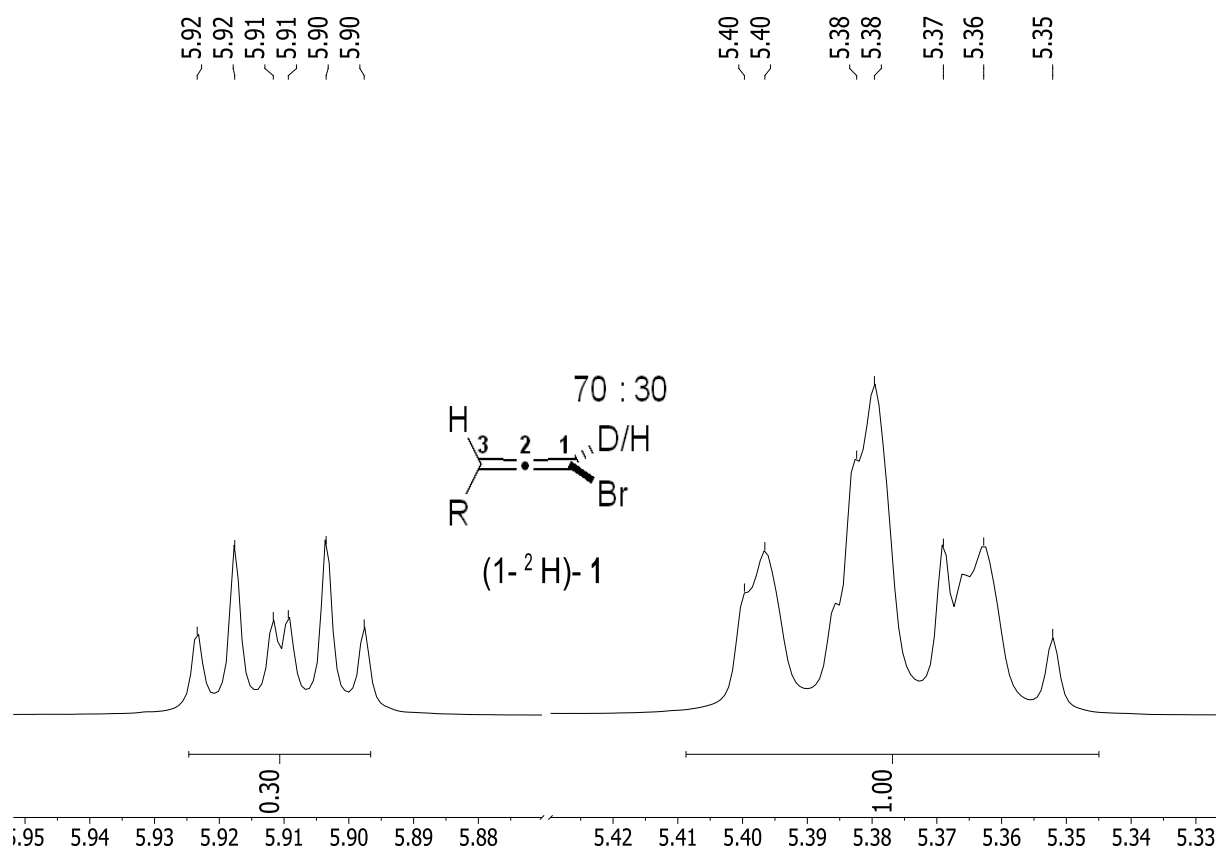


Figure 3.2.3.1: Allenic region of the ^1H NMR spectrum of deuterated bromoallene (1- ^2H)-1.

The above spectrum shows that the peak assigned to the terminal proton at 5.91 ppm has a greatly reduced integral, caused by 70% of the compound now bearing deuterium at this position. In addition to this, comparison of the splitting patterns of the multiplet at 5.41 - 5.35 ppm further proves deuteration.

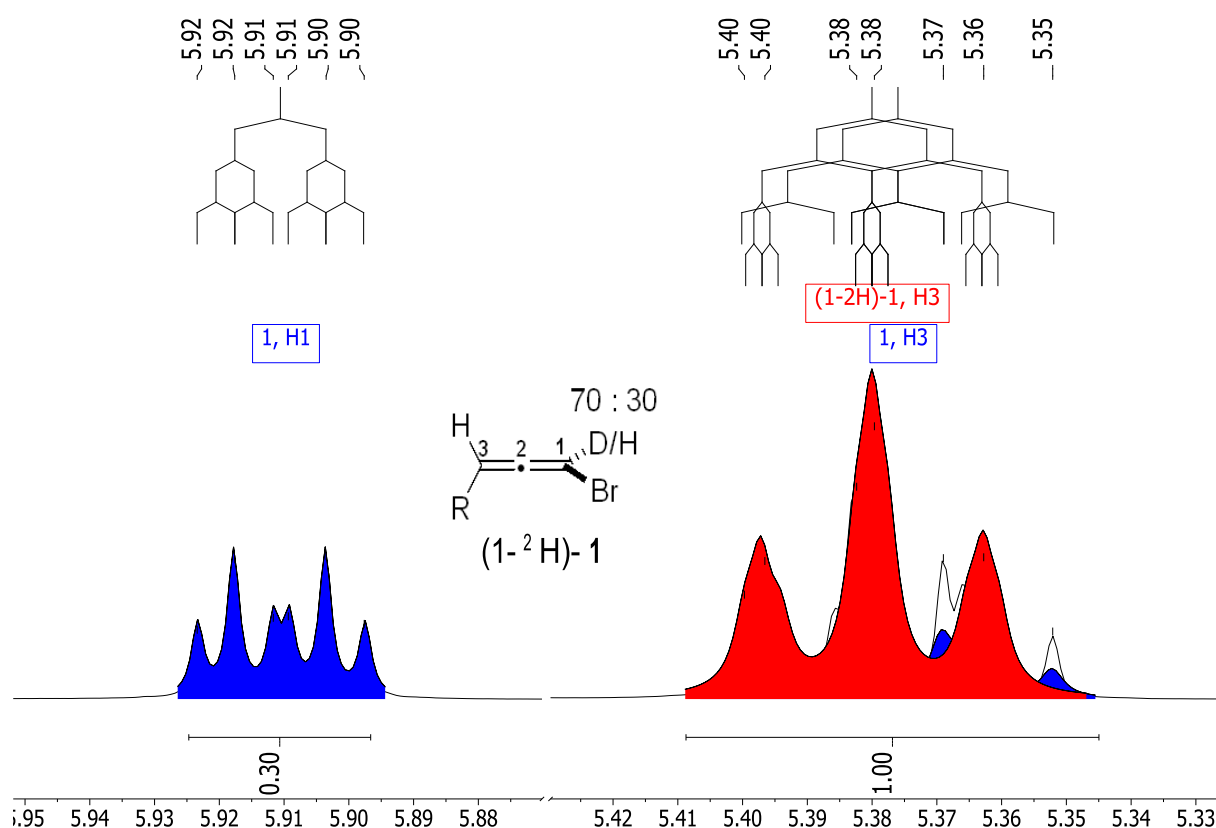


Figure 3.2.3.2: Overlay showing the ^1H NMR spectrum of protonated bromoallene **1** (blue) and deuterated bromoallene (1- ^2H)-**1** (red).

In the protonated compound (blue), the proton on C_3 couples to the adjacent methylene protons, but also the terminal bromoallene proton, C_1 . Each of these coupling constants are close to 6.8 Hz, making a doublet of triplets appear as a quartet. This quartet is still present in the spectrum of the deuterated compound at about 30%. The new, larger resonances in red, is a triplet caused by the proton on C_3 coupling to the adjacent methylene protons and the deuterium. As the magnitude of coupling constants is proportional to the gyromagnetic ratio of a nuclide, coupling constants to deuterium are 6.51 times less than the equivalent to hydrogen, i.e. $J_{\text{H-H}} = \gamma_{\text{H}} / \gamma_{\text{D}} (J_{\text{H-D}}) = 6.51(J_{\text{H-D}})$.⁶⁵ In this case, we know that the coupling constant will be approximately 1.0 Hz. In addition to this, deuterium has a spin

of 1, resulting in a 1:1:1 triplet. We would therefore expect a multiplet with a 1:1:1:2:2:2:1:1:1 pattern, but only observed as a broadened triplet, presumably as 1.0 Hz is too small to distinguish at this resolution.

With labelled bromoallene (1-²H)-1 in hand, this substrate was submitted to the established epoxidation procedure.

3.2.4 Epoxidation of Deuterium Labelled Bromoallene (1-²H)-1

With a sufficient quantity of (1-²H)-1 obtained for several epoxidation attempts, this substrate was subjected to the previously optimised DMDO epoxidation procedure.



Scheme 3.2.4.1: Epoxidation of deuterium labelled (1-²H)-1 with DMDO solution.

As before, a sub-stoichiometric amount of DMDO was used to minimise side-products. The yield and *E* : *Z* ratio did not match that seen previously, but this was largely due to incomplete collection of (*Z*-2-²H)-2. Analysis of the ¹H NMR spectrum showed that C₂ now bore the deuterium.

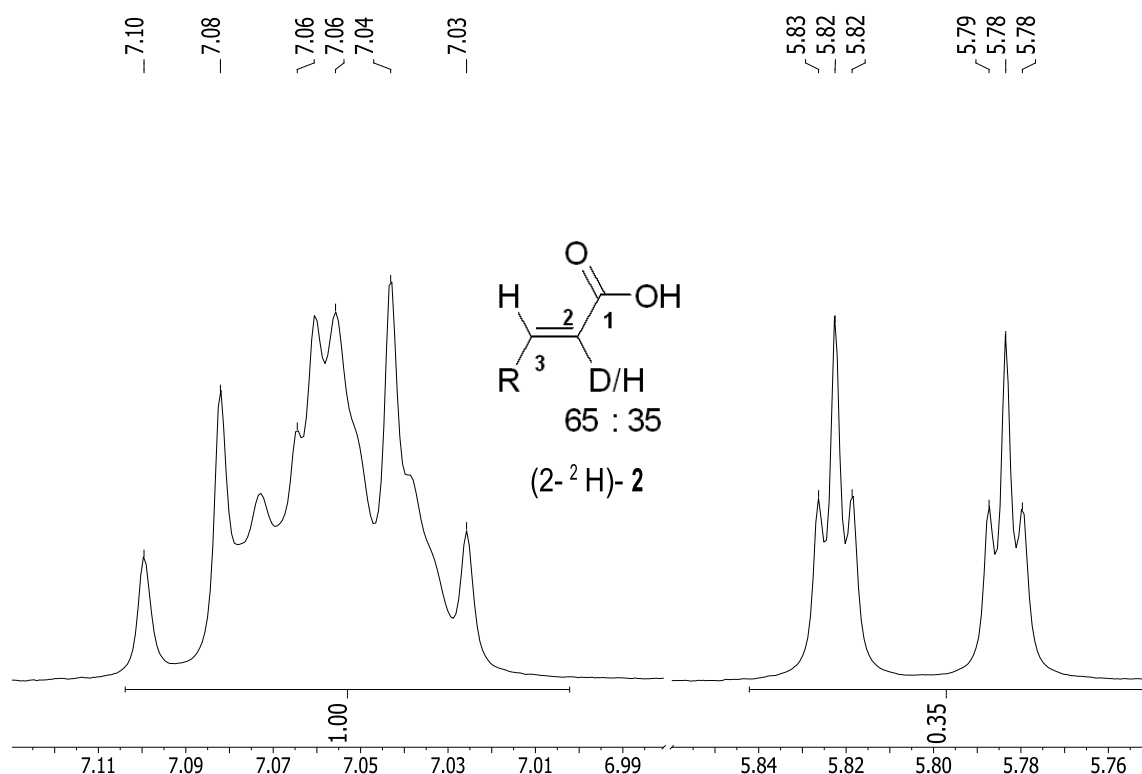


Figure 3.2.4.1: Alkenic region of the ^1H NMR spectrum showing deuteration of the α -position of (*E*-2- ^2H)-**2**.

The spectrum above shows the alkene region of α,β -unsaturated acid (*E*-2- ^2H)-**2**. The peak at 5.8 ppm, assigned to the α -proton, shows a significant decrease in integral, which means deuterium has indeed migrated from C_1 to C_2 . The extent of deuteration had dropped from 70% in bromoallene (1- ^2H)-**1** to 65% in the unsaturated acid products (*E*-2- ^2H)- and (*Z*-2- ^2H)-**2**. This may be due to a kinetic isotope effect favouring the epoxidation of the unlabelled substrate **1**, or may be caused by abstraction of deuterium by a methyl radical and replacement with a hydrogen. Nevertheless, this still allowed the deuterated position to be unequivocally assigned as C_2 .

Similarly to figure 3.2.3.2, we can observe the effect of deuterium coupling on the resonance for the β -proton.

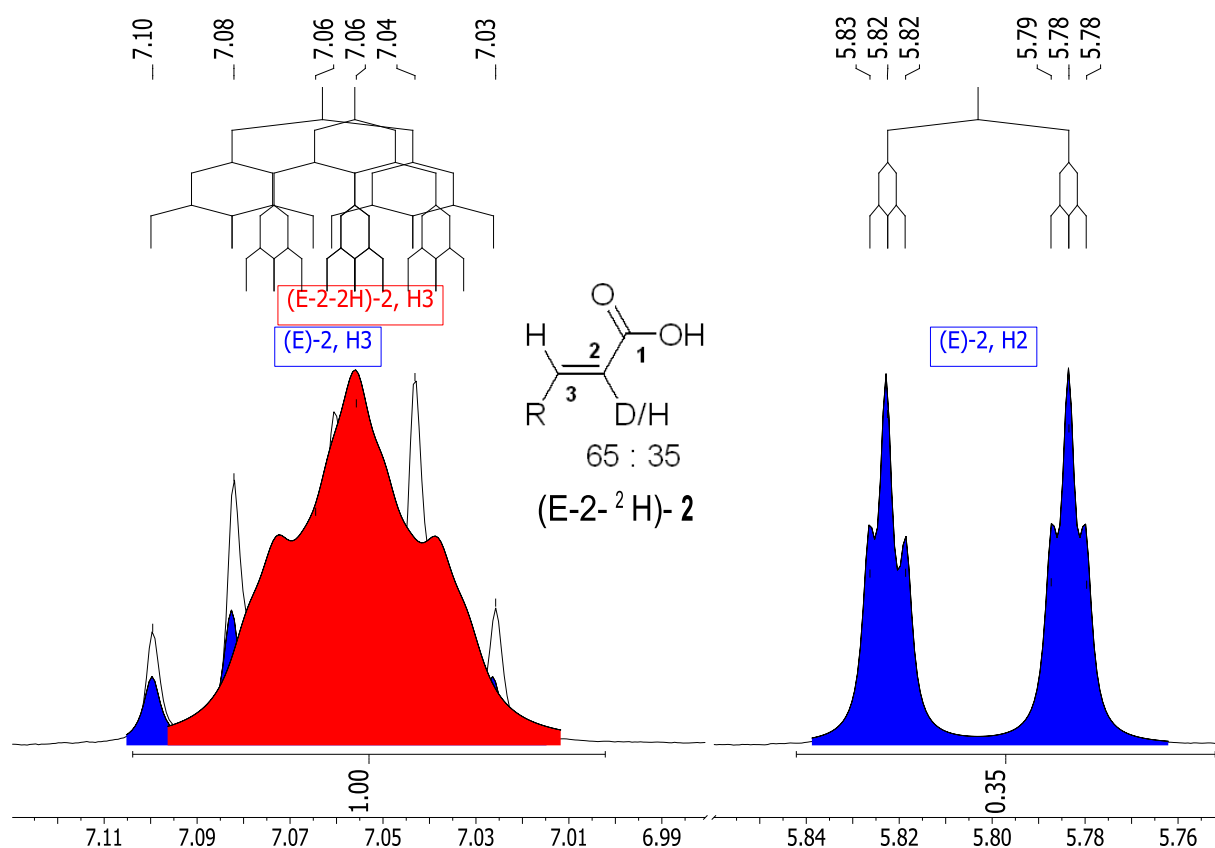


Figure 3.2.4.2: Overlay showing the ^1H NMR spectrum of protonated unsaturated acid (*E*)-2 (blue) and deuterated unsaturated acid (*E*-2- ^2H)-2 (red).

Overlaying the original doublet of triplets shows that the deuterated compound (*E*-2- ^2H)-2 also contains a broadened triplet. As before, this is due to the coupling to deuterium instead of hydrogen, with a coupling constant 6.51 times less than that to hydrogen.

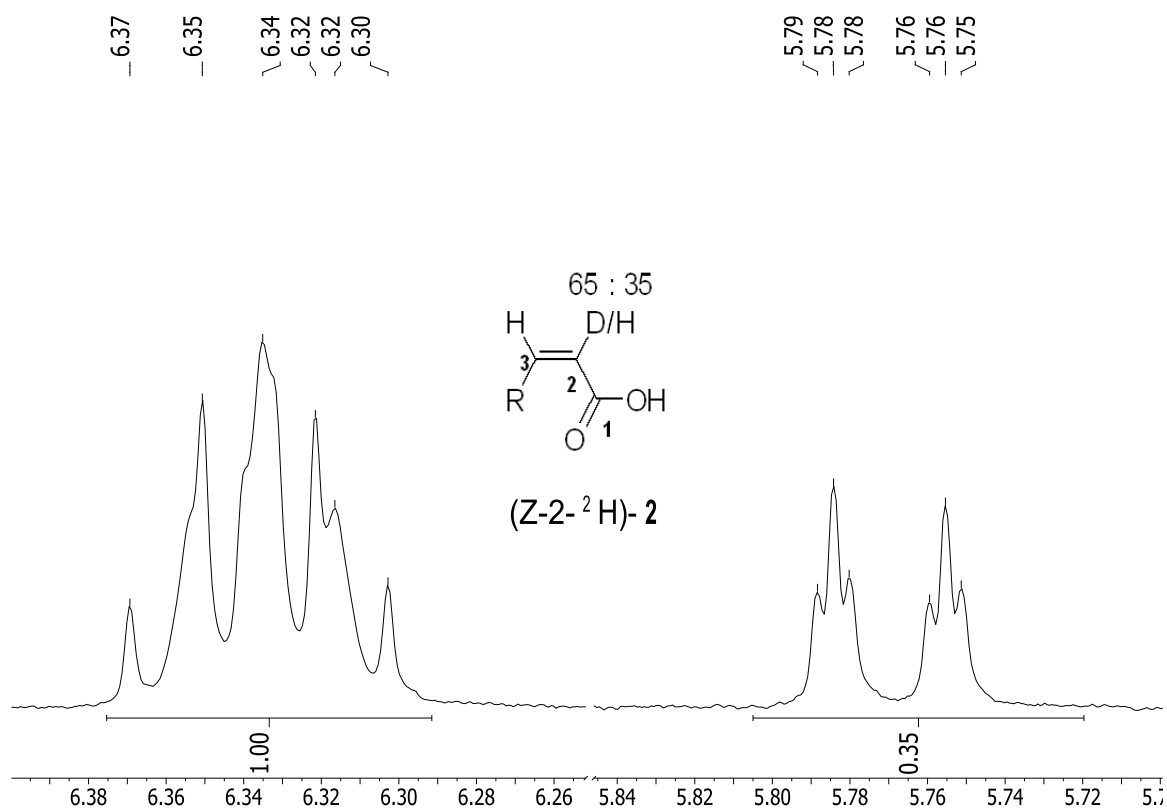


Figure 3.2.4.3: Alkenic region of the ¹H NMR spectrum showing deuteration of the α-position of (Z-2-²H)-2.

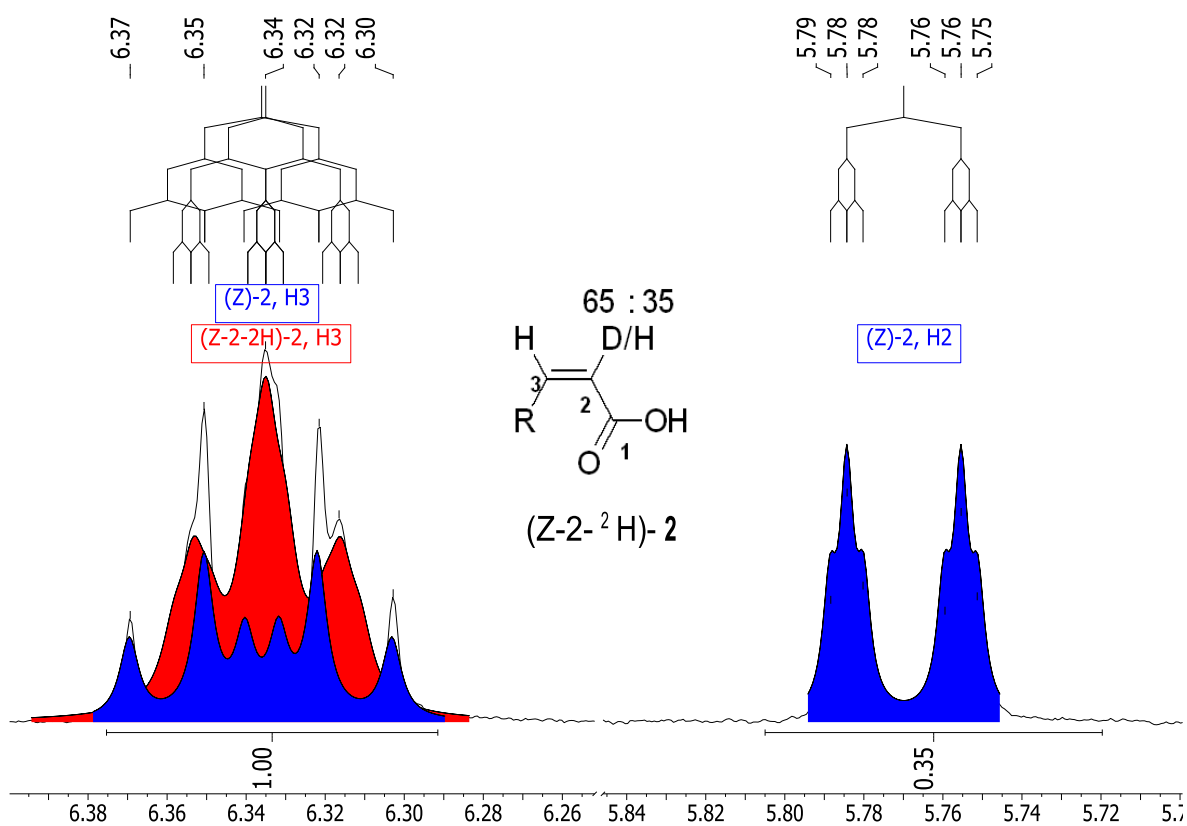


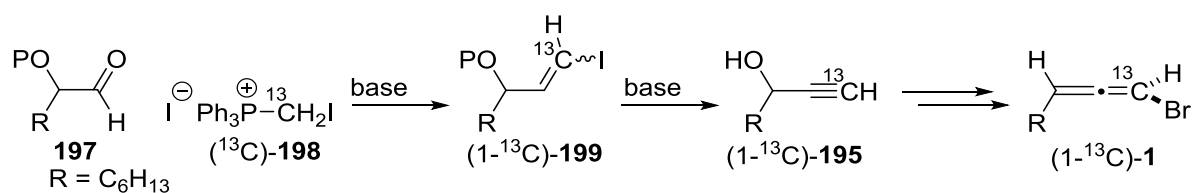
Figure 3.2.4.4: Overlay showing the ¹H spectrum of protonated unsaturated acid (Z)-2 (blue) and deuterated unsaturated acid (Z-2-²H)-2 (red).

Similar analysis can be made for (Z-2-²H)-**2** and is shown in figure 3.2.4.4. It can be seen that the extent of deuteration has also dropped to 65%, as measured by the loss of integral of the α -proton at 5.77 ppm. Coupling of the β -proton to deuterium has also made a complex splitting pattern at 6.34 ppm, that overlaps the resonance from the protonated isotopomer.

This result supports the proposed cyclopropanone mechanism (scheme 3.1.1.2), as it shows a definite migration has occurred. However, it does not disprove the alternative, a 1,2-hydride shift, as whether the C₁ carbon has also moved or only the deuterium cannot be confirmed. A ¹³C-labelled compound was necessary to follow the terminal carbon and discriminate between the two mechanisms.

3.2.5 Synthesis of ¹³C Labelled Propargylic Alcohol (1-¹³C)-**195**

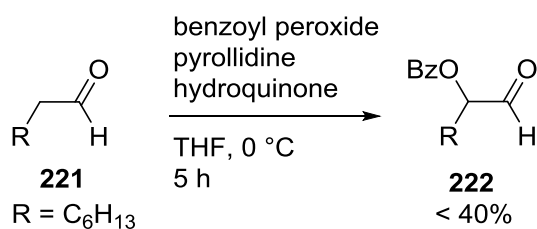
The synthesis of a ¹³C labelled model compound proved to be challenging. Following a similar route to the ethynyl addition in scheme 3.2.1.1 was not possible, as singly labelled acetylene is not commercially available. Even if it were, preparation of a Grignard reagent and addition an aldehyde would result in labelling of both C₁ and C₂. Instead, the route chosen involved a Wittig olefination with a suitably protected α -hydroxy aldehyde and (iodomethyl)phosphonium salt (¹³C)-**198**. Dehydrohalogenation of the resulting vinyl iodide would then give a labelled alkyne that could be submitted to the previously established route (scheme 3.2.5.1).



Scheme 3.2.5.1: Proposed route to achieve incorporation of a ¹³C label and further derivation to (1-¹³C)-1.

The first issue with this proposal is the synthesis of an α-hydroxy aldehyde. Compared to α-hydroxy ketones, very little literature precedent existed for this class of compounds. Secondly, generation of the (¹³C)-labelled phosphonium salt (¹³C)-**198** would have been trivial with ¹³C-diiodomethane. However, the cost of the reagent was prohibitive at almost £500 for 500 mg, considering the low atom economy of such a route, an alternative using ¹³MeI would need to be found.

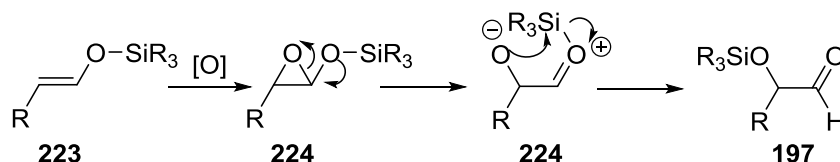
Several routes to α-hydroxy aldehydes were explored. The first was a pyrrolidine promoted benzoylperoxidation based on an asymmetric variant.⁶⁶ The aldehyde used would be octaldehyde (**221**), as only a one carbon synthon is being incorporated, rather than two carbons with an acetylide addition.



Scheme 3.2.5.2: Attempted benzoylperoxidation of octaldehyde (**221**).

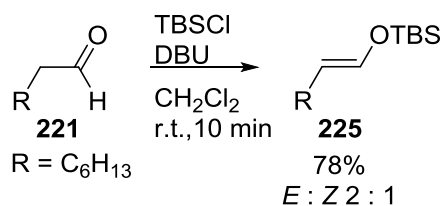
Yields for this reaction were below 40%, and very difficult to purify, so alternatives were sought.

Rubottom oxidation proved to be the most advantageous route. The Rubottom oxidation employs *m*CPBA to epoxidise a silyl enol ether, which subsequently undergoes migration of the silyl group to give a silyl protected α -hydroxy ketone/aldehyde.⁶⁷



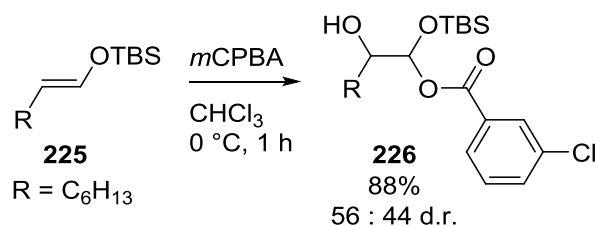
Scheme 3.2.5.3: Mechanism of the Rubottom oxidation.

An initial attempt to generate a silyl enol ether with trimethylsilyl chloride (TMSCl) was abandoned as the work up hydrolysed much of the product. Instead, *tert*-butyldimethylsilyl chloride (TBSCl) with 1,8-diazabicycloundec-7-ene (DBU) as base was employed with more success.⁶⁸ The use of a less labile silyl group also proved to be beneficial in later steps.



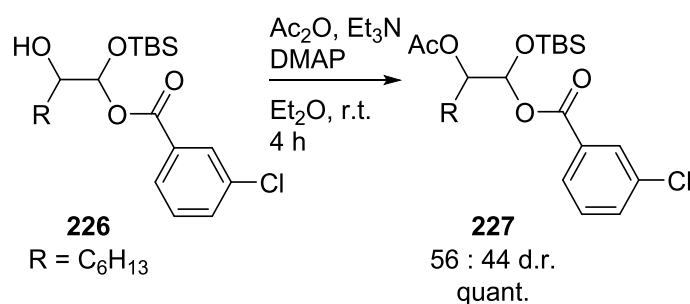
Scheme 3.2.5.4: Generation of TBS enol ether **225** from octaldehyde **221**.

The next step of the Rubottom oxidation involves treatment with *m*CPBA. However, the bulk of the TBS group meant that the intermediate oxonium was trapped by the 3-chlorobenzoic acid by-product before migration could occur, leading to compound **226**. A similar outcome was observed in the *m*CPBA epoxidation of bromoallene **1** (scheme 3.2.2.6).



Scheme 3.2.5.5: Unintended side-product of the Rubottom oxidation of TBS enol ether **225**.

This was fortuitous, as it was found in this study and also known in literature, that unprotected α -hydroxy aldehydes cannot be isolated due to rearrangement to hydroxy ketones, dimerisation and polymerisation.⁶⁹ In this manner the aldehyde is protected as an silyl benzoyl acetal, allowing protection of the hydroxyl, before elimination of the TBS and benzoate groups to reveal the aldehyde.



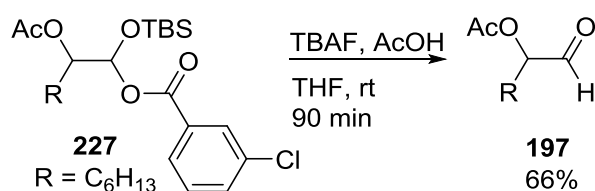
Scheme 3.2.5.6: Acetyl protection of alcohol **226**.

Acetyl protection of **226** proceeded with quantitative yield giving the same ratio of inseparable mixture of diastereomers.

Next, a method for the simultaneous removal of the TBS and 3-chlorobenzoate groups needed to be found. Treatment of compound **227** with tetra-*n*-butylammonium fluoride (TBAF) was unsuccessful. This was thought to be due to fluoride induced

deacetylation involving ketene elimination.⁷⁰ The resulting α -hydroxy aldehyde will rearrange, dimerise and polymerise to leave an intractable mixture of products.

A similar attempt at deprotection with trifluoroacetic acid (TFA) achieved removal of the TBS and benzoate groups, but also resulted in some substitution of the acetate group with trifluoroacetate. Although this substitution only occurred to a very low extent, the two compounds were inseparable. A procedure employing TBAF buffered with excess acetic acid to prevent deacetylation was attempted.⁷¹

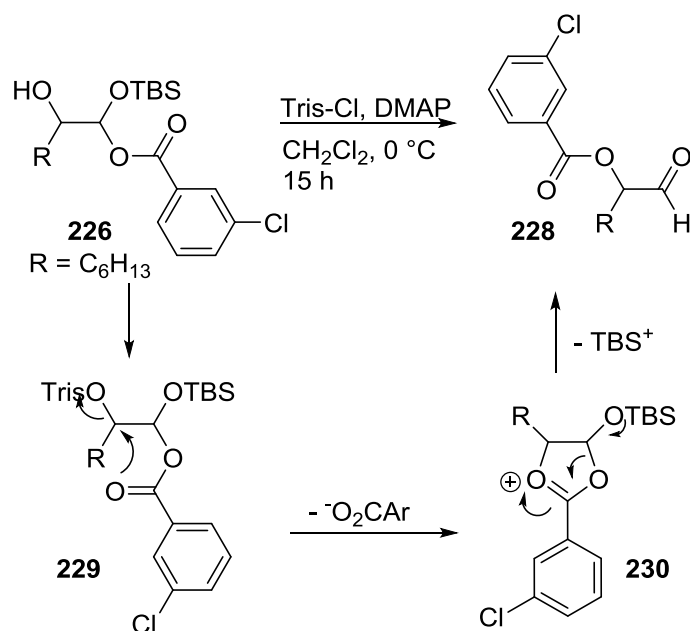


Scheme 3.2.5.7: Elimination of TBS and 3-chlorobenzoate groups to reveal aldehyde **197**.

This reaction was successful, with what appeared initially to be quantitative yields. Considerable mass was lost upon chromatography however, due to the sensitive nature of the aldehyde, leaving the isolated yield at only 66%. Mass spectroscopy of this compound, and other acetate containing compounds (*vide infra*), were hampered by ketene elimination. Many mass spectroscopy techniques are known to cause fragmentation of acetates *via* elimination of ketene.⁷² For compound **197**, this leaves an α -oxyanionic aldehyde, which will immediately react intermolecularly to give cyclic dimers. Indeed, mass spectra of this compound showed no evidence of the molecular ion, but instead peaks assigned to $(2\text{M} - 2\text{Ac})^+$ and $(2\text{M} - \text{Ac})^+$.

An alternative protection of **226** with a trisylate group was trialled in an attempt to reduce the number of steps after the following Wittig reaction. ¹H NMR spectroscopy of the

crude product looked promising, but after chromatography, the intended product had spontaneously eliminated to form compound **228**.

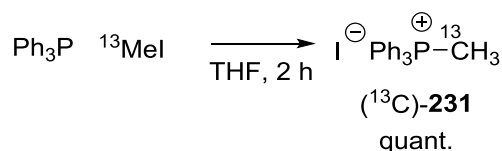


Scheme 3.2.5.8: Prévost-like elimination of the trisylate and TBS groups of compound **299**.

It is likely that this proceeds *via* a Prévost-like reaction. The lability of the trisylate allows substitution by the benzoate carbonyl. Elimination of the TBS group results in formation of the aldehyde with a 1,2-shift of the benzoate. This compound was also observed after chromatography of a large quantity of alcohol **226**. Presumably, long exposure to silica gel caused protonation of the hydroxyl, generating a suitable leaving group for substitution by the benzoate carbonyl.

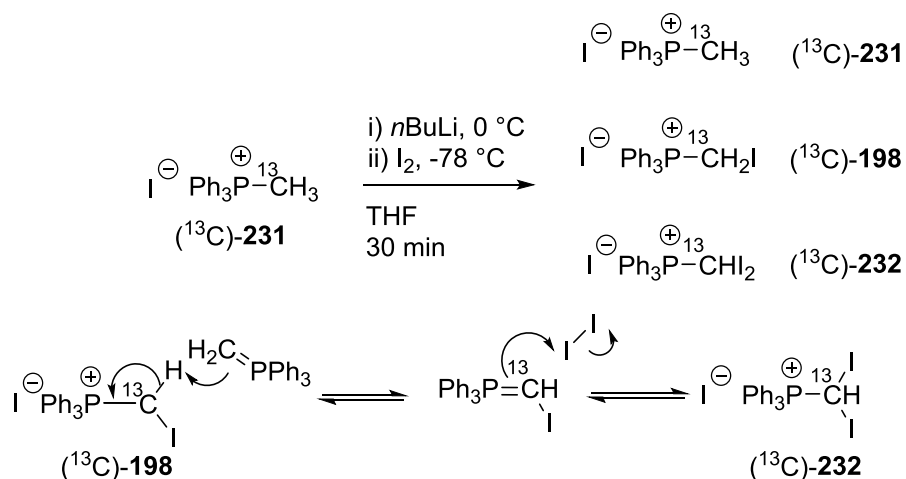
With the protected α -hydroxy aldehyde **197** in hand, attention turned to (iodomethyl)phosphonium salt (¹³C)-**198**. Only one example in the literature could be found for the synthesis of this compound using methyl iodide, a step in the total synthesis of (-)-dictyostatin.⁷³

Initial generation of the labelled methylphosphonium salt (^{13}C)-**231** was achieved by stirring triphenylphosphine with ^{13}C -methyl iodide to give a quantitative yield of (^{13}C)-**231** (scheme 3.2.5.9).



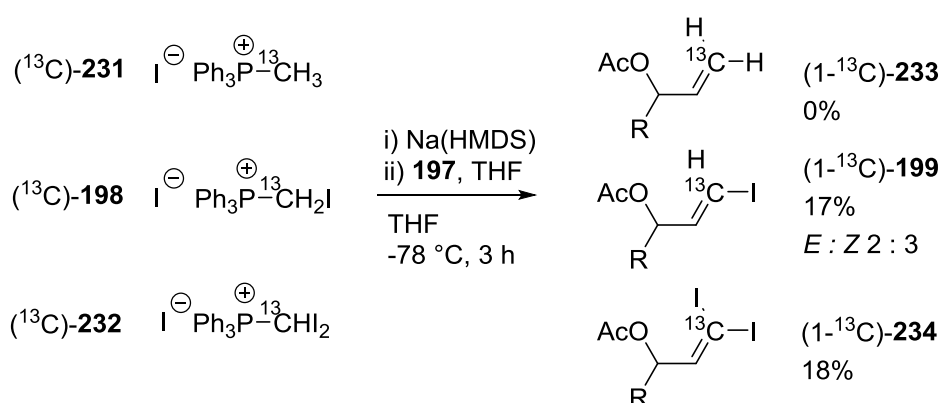
Scheme 3.2.5.9: Preparation of methyl phosphonium salt (^{13}C)-**231**.

This compound was found to be highly hygroscopic and rapidly turned yellow upon exposure to air. This problem was solved by performing the reaction in a Schlenk tube under a nitrogen atmosphere and removing the solvent *via* cannula, before immediately performing the next reaction. The white crystals were then able to be iodinated without any need for purification or coming into contact with air. Iodination was achieved by deprotonation with *n*BuLi followed by treatment with elemental iodine at $-78\text{ }^\circ\text{C}$



Scheme 3.2.5.10: Equilibrium upon deprotonation and iodination of methylphosphonium salt (^{13}C)-**231**.

Complications arose with the above iodination due to product (^{13}C)-**198** being slightly more acidic than the reactant (^{13}C)-**231**. The methyl ylide could deprotonate the (iodomethyl)phosphonium salt (^{13}C)-**231**. This meant that after addition to the iodine solution, double deprotonation and iodination was possible, generating an equilibrium between the three with (diiodomethyl)phosphonium salt (^{13}C)-**232** as the major product. This mechanism is known in literature and is exploited in the synthesis of vinyl dihalides.⁷⁴ Changes to the rate of addition, temperature and concentration of iodine had little effect on the outcome. NMR spectral analysis of the reaction mixture showed that the system reached equilibrium immediately and attempts to isolate (^{13}C)-**198** were hampered as the crystals were too fine to collect by filtration. Extraction and recrystallisation also failed, as the target compound was only soluble in DMSO or hot methanol, but so were starting material (^{13}C)-**231** and side-product (^{13}C)-**232**. The paper from which this procedure was taken performed the subsequent Wittig olefination on the crude reaction mixture, so presumably experienced similar difficulties.



Scheme 3.2.5.11: Wittig olefination of phosphonium salts (^{13}C)-**231**, (^{13}C)-**198** & (^{13}C)-**232**.

Treatment of the mixture of phosphonium salts (^{13}C)-**231**, (^{13}C)-**198** & (^{13}C)-**232**, *in situ* with sodium hexamethyldisilazane (Na(HMDS)) followed by addition of aldehyde **197** gave a 2 : 3 mixture of the (*E*-1- ^{13}C)- and (*Z*-1- ^{13}C)-vinyl iodides **199** as well as an equal amount of the vinyl diiodide (1- ^{13}C -**234**). There was no indication of the presence of (1- ^{13}C)-**233**. It is possible that the higher acidity of the mono- and diiodo-phosphonium salts, (^{13}C)-**198** & (^{13}C)-**232** respectively, kinetically favoured the olefination of these compounds. Careful column chromatography allowed separation of the isomeric vinyl iodides, (*E*-1- ^{13}C)-**199** and (*Z*-1- ^{13}C)-**199**, from each other, but not the vinyl diiodide (1- ^{13}C)-**234** from either.

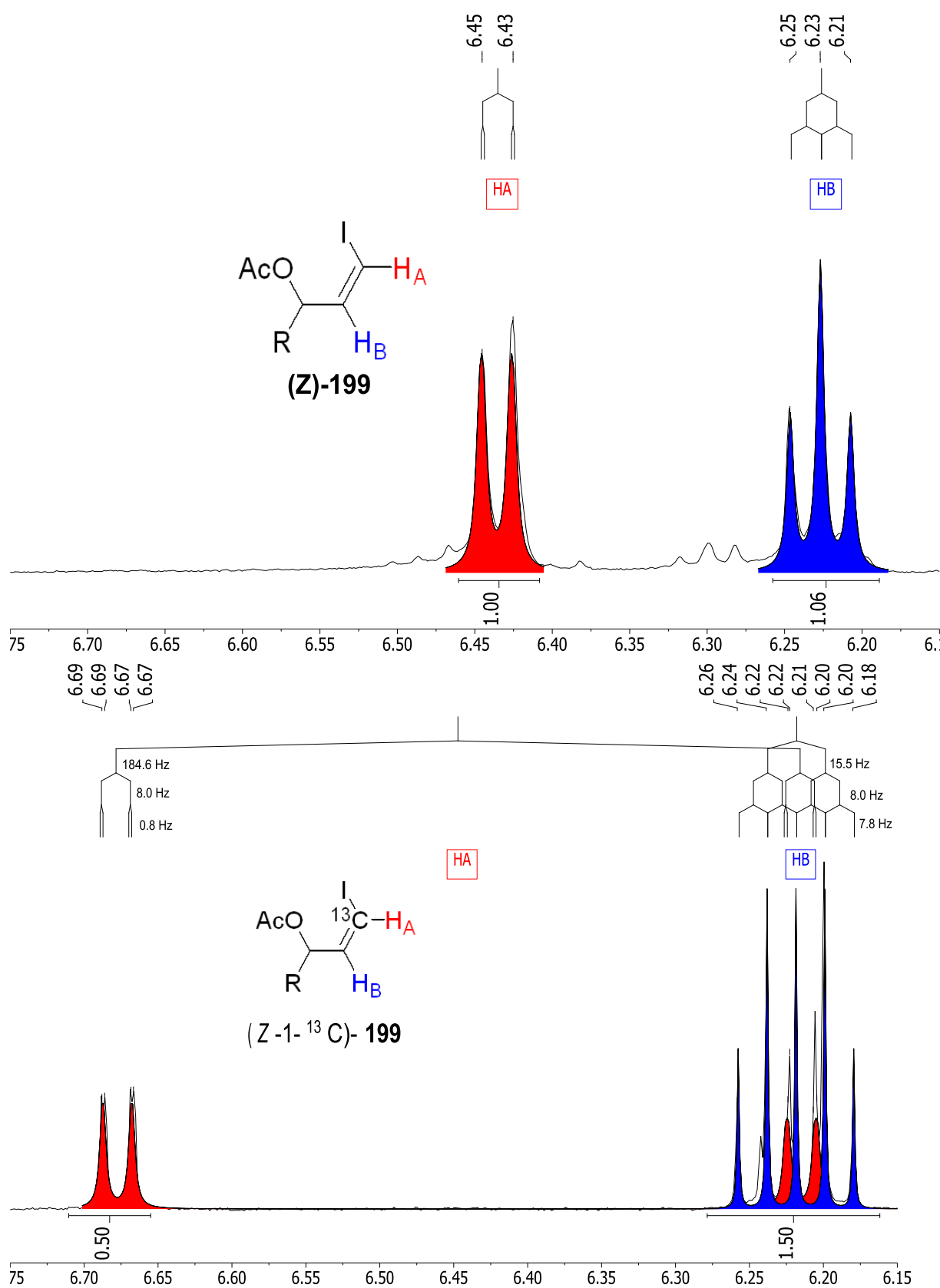


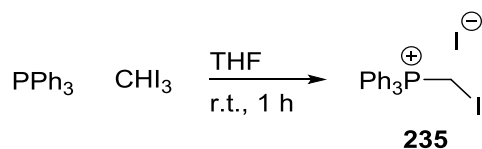
Figure 3.2.5.1: ^1H NMR spectra showing the alkenic region of unlabelled (Z)-199 (above) and labelled (Z-1- ^{13}C)-199 (below).

^1H and ^{13}C NMR spectral analysis confirmed that isotopic purity approached 100%. The spectra could be compared to unlabelled **199**, prepared from non-labelled methyl iodide by the same route. Both (*E*- $1\text{-}^{13}\text{C}$)- & (*Z*- $1\text{-}^{13}\text{C}$)-**199** showed the expected large $^1J_{\text{H-}^{13}\text{C}}$ coupling constants of ~190 Hz and $^2J_{\text{H-}^{13}\text{C}}$ coupling constants of ~16 Hz. Interestingly, the vinyl diiodide ($1\text{-}^{13}\text{C}$)-**234**, exhibited a $^2J_{\text{H-}^{13}\text{C}}$ coupling constant of 0 Hz. This is consistent with the literature which shows that similar $^2J_{\text{H-}^{13}\text{C}}$ coupling constants, especially in 1,1-disubstituted vinyl compounds, is often less than 1 Hz.⁷⁵

With the acetyl protected vinyl iodides in hand, a route to the labelled propargylic alcohol ($1\text{-}^{13}\text{C}$)-**195** was now needed, from which further derivation to a labelled bromoallene ($1\text{-}^{13}\text{C}$)-**1** could be made. This would require three distinct transformations: the deprotection of the acetate group, dehydrohalogenation of the vinyl iodides (*E*- $1\text{-}^{13}\text{C}$)- & (*Z*- $1\text{-}^{13}\text{C}$)-**199**, and as they could not be separated, a simultaneous Corey-Fuchs elimination of the vinyl diiodide ($1\text{-}^{13}\text{C}$)-**200**. Several challenges were thus presented. Firstly, all three reactions are performed with base, but it would be preferable to have some selectivity over each. Test reactions on unlabelled analogues suggested that the use of LDA would satisfactorily achieve dehydrohalogenation of the vinyl iodides, but would also cause deacetylation *via* a ketene elimination. Secondly, it was assumed that the standard conditions for acetate deprotection, K_2CO_3 in methanol, would be successful, but no data was available on if this base was sufficient to dehydrohalogenate. Also, the Corey-Fuchs reaction has a wealth of precedent for vinyl dibromides, but only one example for vinyl diiodides exists and only reports a 28% yield.⁷⁶ It seems logical that the Corey-Fuchs reaction would proceed better with diiodides over dibromides, but the lack of precedent was a

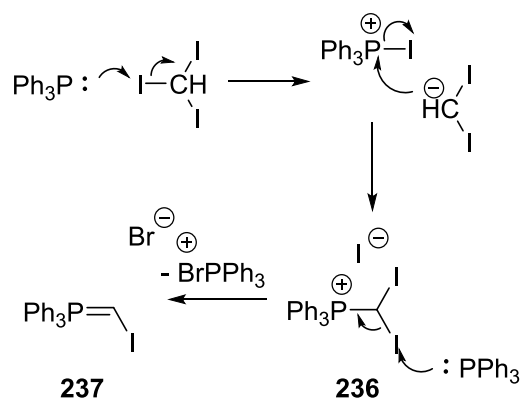
concern. Furthermore, the above example employed $n\text{BuLi}$, whereas we would have to use LDA to prevent lithium-iodine exchange of the vinyl iodides (*E*-1- ^{13}C)- & (*Z*-1- ^{13}C)-**199**, presenting another unknown variable.

To investigate these issues, 1,1-diiodonon-1-ene (**238**) was prepared to perform test reactions. It would have been more preferable to use a compound bearing an α -acetate group to more closely mimic the reactivity, but the α -acetyl aldehyde **197** precursor was in short supply. The first attempt at this compound involved the preparation of (diiodo)phosphonium salt **236** by direct substitution of iodoform by triphenylphosphine. The previous route (scheme 3.2.5.10) *via* deprotection and iodination did not need to be replicated, as there was no need to begin with methyl iodide.



Scheme 3.2.5.12: Attempted preparation of (diiodo)phosphonium salt **236**.

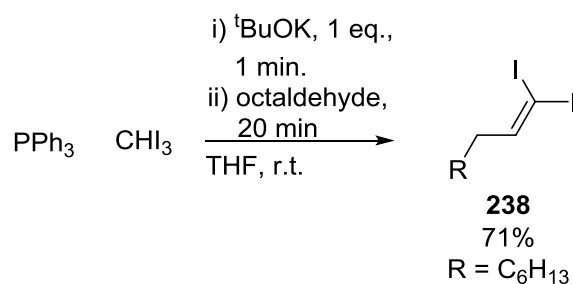
This reaction yielded only the (monoiodo)phosphonium salt **235**. Similarly to the previous attempt (scheme 3.2.5.10), collection of this product was problematic due to the solubility and particle size, with only a 2% collected yield. The formation of the monoiodide compound **235** instead of the required diiodide **236** is explained by analysis of the mechanism and shown in scheme 3.2.5.13.



Scheme 3.2.5.13: Mechanism of phosphonium salt generation.

Initial formation of the desired diiodide **236** takes place, but triphenylphosphine can abstract a further iodide to generate moniodide ylene **237**. For most phosphonium salts, a proton would be removed, but the increased lability of iodide results in the undesired compound being the major product.

Instead, an *in-situ* Wittig reaction was performed. Triphenylphosphine and iodoform were stirred in the presence of potassium *t*butoxide, before octaldehyde (**221**) was added.

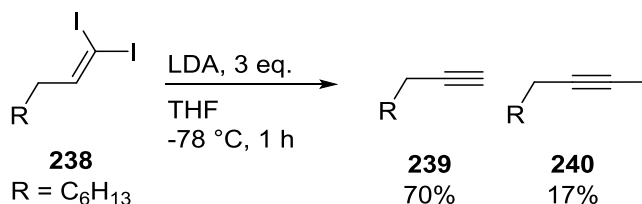


Scheme 3.2.5.14: *In situ* Wittig reaction to form vinyl diiodide **238**.

Scheme 3.2.5.14 shows that this method was more successful, with the desired vinyl diiodide **238** being collected in good yield. The presence of $t\text{BuOK}$ during the initial generation of phosphonium salt **236** means that deprotonation to the ylene takes place

immediately and triphenylphosphine can no longer diiodinate. Addition of octaldehyde (**221**) results in an *in-situ* Wittig reaction and generation of the desired vinyl diiodide **238**.

This compound was then treated with LDA to determine whether the Corey-Fuchs reaction would proceed as planned.



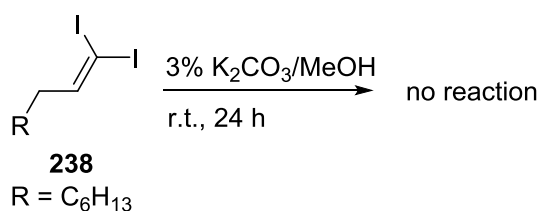
Scheme 3.2.5.15: Corey-Fuchs reaction of vinyl diiodide **238** with LDA.

This result shows that the Corey-Fuchs reaction does indeed proceed well with LDA and vinyl diiodides, two variables that were unknown in literature. The yield was not as high as would have been liked, but this is likely to be due to the volatility of 1-nonyne (**239**). With a boiling point of 150 °C, a noticeable amount of product was lost during solvent removal. Furthermore, yield was again reduced by the presence of a considerable amount of 1-iodonon-1-yne (**240**), presumable formed by dehydrohalogenation instead of the Corey-Fuchs mechanism. LDA is not a suitable reagent for lithium-halogen exchange, so further derivation to 1-nonyne (**239**) does not take place (*vide infra*, scheme 3.2.5.20). If this were to occur during the reaction of our ¹³C-labelled compounds, treatment with a small amount of ⁿBuLi would complete the reaction to propargylic alkyne (1-¹³C)-**195**.

As stated before, treatment of acetates (1-¹³C)-**199** and (1-¹³C)-**234** with LDA would probably cause deacetylation, but the eliminated ketene would likely present problems by further reaction with any π -bonds. It is therefore essential to remove the acetate, while

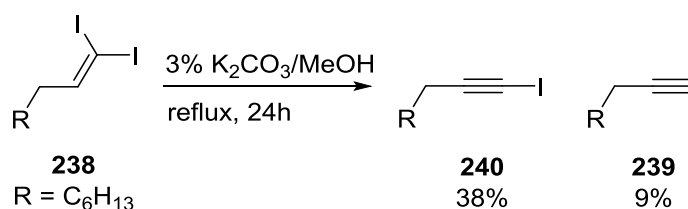
leaving the vinyl iodide groups untouched. Previous test reactions had shown that dehydrohalogenation proceeds well with the alcohol, so having selectivity over these reactions was desirable.

Knowing that the acetate could be removed in high yield with K_2CO_3 and MeOH, but unsure if dehydrohalogenation would also take place, a test reaction was performed.



Scheme 3.2.5.16: Treatment of vinyl diiodide **238** with potassium carbonate in methanol.

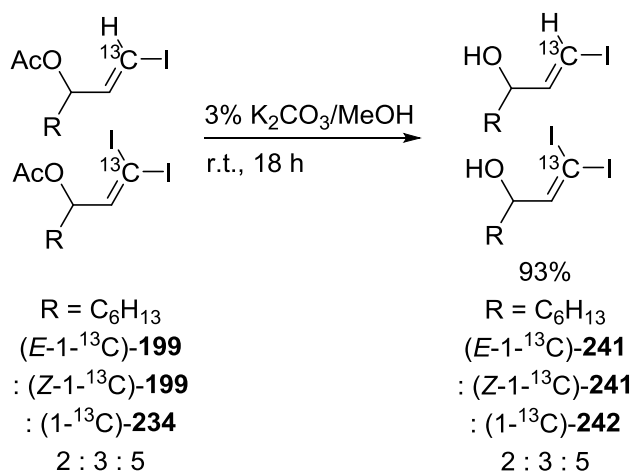
After 24 hours at room temperature, TLC and ^1H NMR spectral analysis showed that no reaction had taken place. From this, it can be inferred that deprotection of the acetate will take place, while leaving the rest of the molecule untouched. For the sake of curiosity, the reaction was then heated to reflux for a further 24 h.



Scheme 3.2.5.17: dehydrohalogenation of vinyl diiodide **238** with potassium carbonate in methanol at elevated temperature.

It was of little surprise that dehydrohalogenation occurred with methoxide at reflux as similar examples with a variety of alkoxides and vinyl dihalides exist in literature.⁷⁷ However, there was a relatively large amount of non-1-yne (**239**) present in the product. Metal-iodine exchange is much less likely with a potassium cation, so it is more likely that methoxide deiodinates compound **240** directly. This is another reaction unknown in literature. Again, yields were considerably reduced by the volatility of the products.

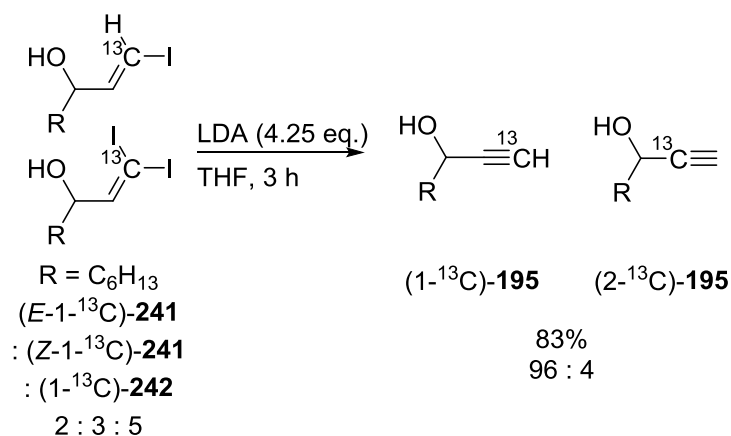
With this result, methods to selectively remove the acetate group and subsequently perform a combined dehydrohalogenation and Corey-Fuchs reaction had been established. This route was applied to the ¹³C-labelled substrates.



Scheme 3.2.5.18: Deprotection of vinyl acetates (E-1-¹³C)-**199**, (Z-1-¹³C)-**199** and (1-¹³C)-**234**, to give vinyl alcohols (E-1-¹³C)-**241**, (Z-1-¹³C)-**241** and (1-¹³C)-**242**.

Scheme 3.2.5.18 shows that stirring vinyl acetates (E-1-¹³C)-**199**, (Z-1-¹³C)-**199** and (1-¹³C)-**234** at room temperature successfully achieved deprotection. This reaction proceeded in high yield, with no change to the ratio of compounds. As expected, performing the reaction

at room temperature prevented any dehydrohalogenation. These compounds were then treated with LDA, in a simultaneous dehydrohalogenation/Corey-Fuchs reaction.



Scheme 3.2.5.19: Dehydrohalogenation and Corey-Fuchs reactions of (E-1-¹³C)-**241**, (Z-1-¹³C)-**241** and (1-¹³C)-**242** with LDA.

Propargylic alcohol (1-¹³C)-**195** was collected in good yield, with no evidence of a corresponding iodoalkyne, as seen in scheme 3.2.5.15. To our surprise, ¹H and ¹³C NMR spectroscopy showed that roughly 4% of the product alkyne now bore the ¹³C label at C₂.

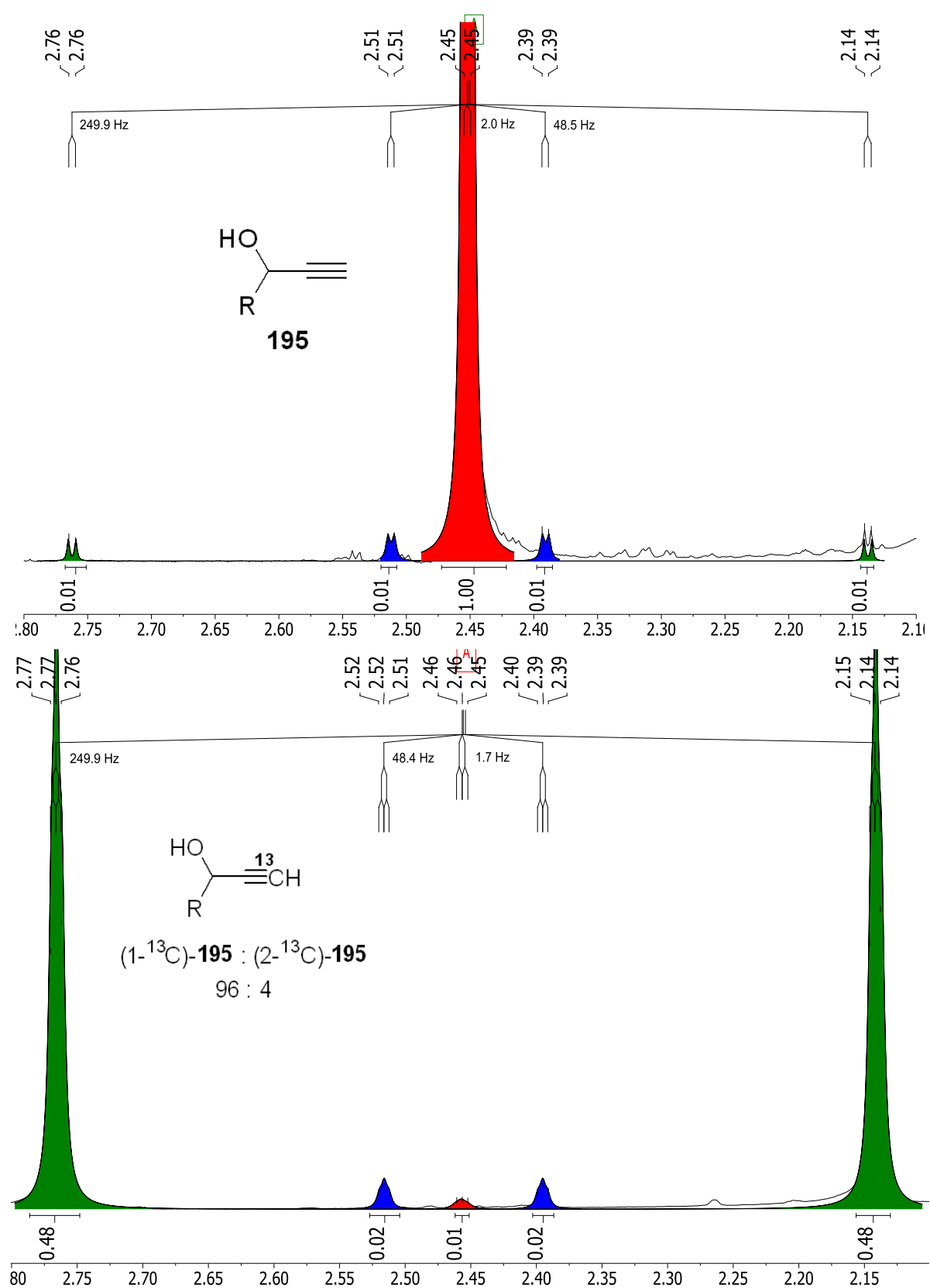


Figure 3.2.5.2: Alkyne region of the ^1H NMR spectrum of unlabelled **195** (above) and ^{13}C labelled $(1-^{13}\text{C})\text{-195}$ (below).

The above spectra compare the alkyne resonance of unlabelled (above) and ^{13}C labelled (above) propargylic alcohols, **195** and (1- ^{13}C)-**195** respectively. The unlabelled compound **195** (red), shows a major resonance at 2.45 ppm, split into a doublet due to $^4J_{\text{H-H}}$ coupling to the proton geminal to the hydroxyl. Compound (1- ^{13}C)-**195** (green) shows a doublet of triplets at the same shift, with a large $^1J_{\text{H-}^{13}\text{C}}$ coupling constant of 250 Hz. Similarly, the compound (2- ^{13}C)-**195** (blue) shows a doublet of triplets with $^2J_{\text{H-}^{13}\text{C}}$ coupling constant of 48 Hz and by integration, it can be calculated that it comprises 4% of the mass. Furthermore, a small multiplet in the centre shows that a trace amount of unlabelled **195** exists in the sample, due to the starting isotopic purity of the ^{13}MeI . The reason that the resonances for the labelled compounds (1- ^{13}C)- and (2- ^{13}C)-**195** present a splitting pattern containing triplets is unknown. Once the hydroxyl had been trisylated, the alkyne resonance reverted to a doublet, so it may be that the above spectrum was poorly shimmed. The baseline of the unlabelled compound **195** (above) shows satellites at the same shift due to the 1% natural abundance of ^{13}C at C₁ and C₂.

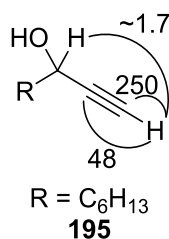


Figure 3.2.5.3: $J_{\text{H-}^{13}\text{C}}$ coupling constants (Hz) in propargylic alcohol **195**.

This interchange of the labelled carbon was confirmed in the ^{13}C NMR spectrum.

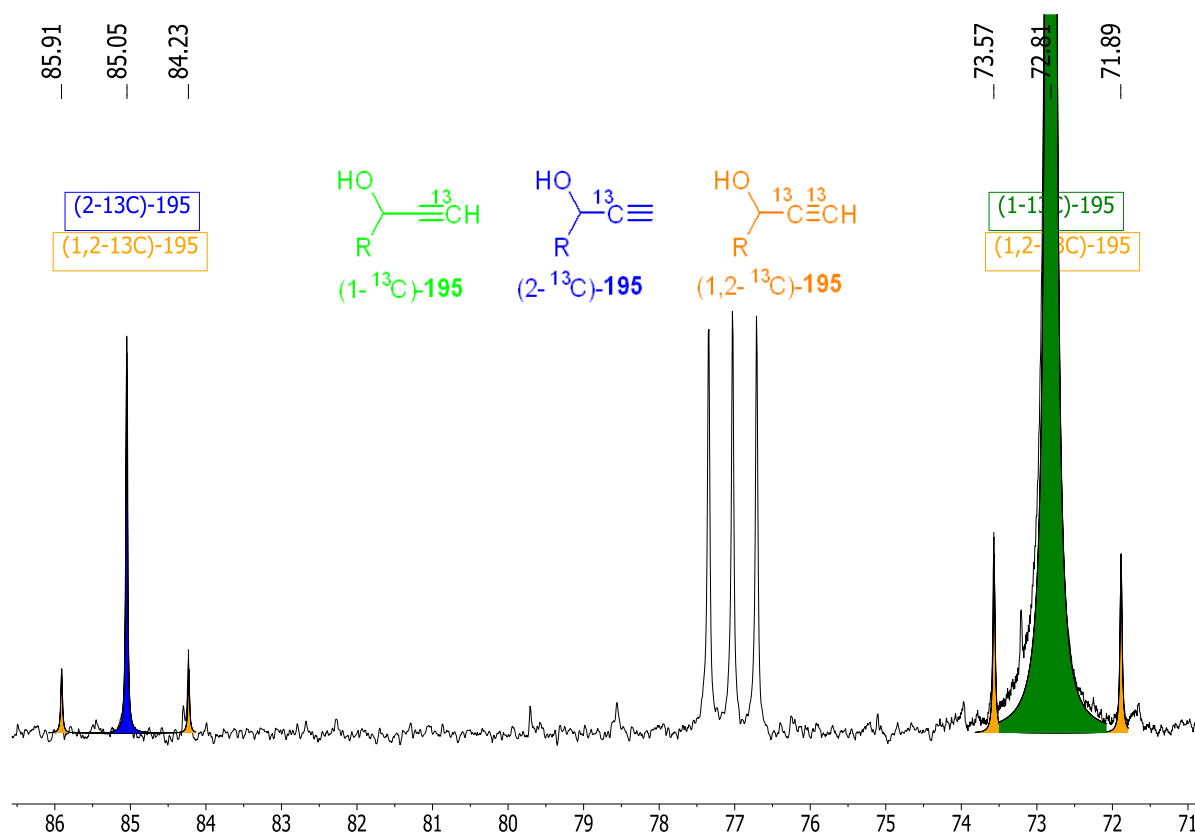
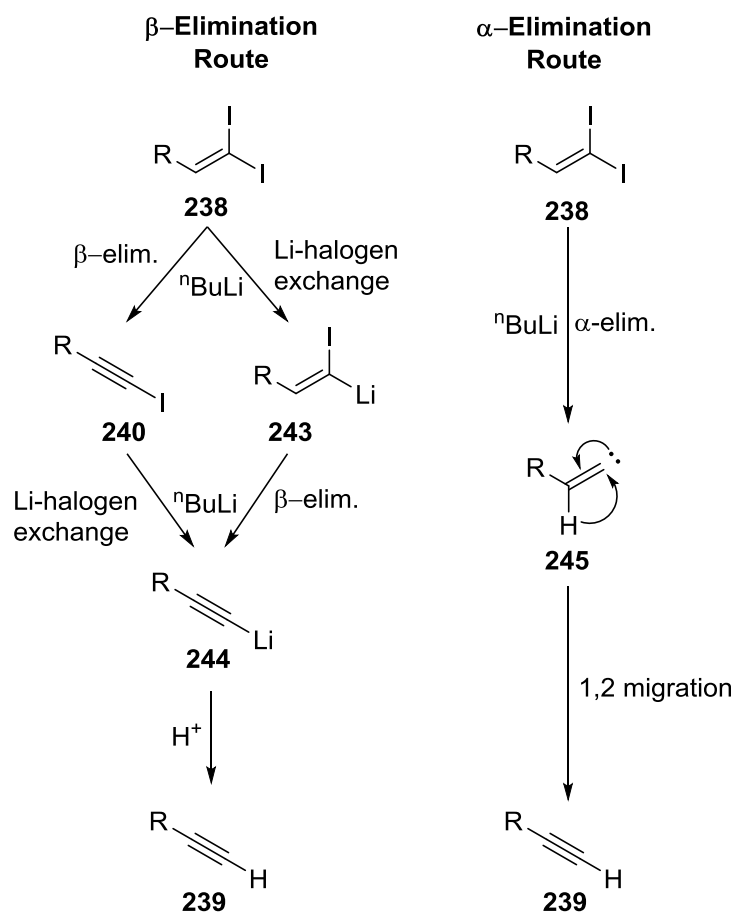


Figure 3.2.5.4: ^{13}C NMR spectrum of ^{13}C labelled propargylic alcohols (1- ^{13}C)- and (2- ^{13}C)-195, showing doubly labelled (1,2- ^{13}C)-195.

The most intense resonance at 72.8 ppm is due to the correctly labelled $^{13}\text{C}_1$ of (1- ^{13}C)-195. The satellites are due to 1% of the compound bearing ^{13}C at both C_1 and C_2 . In the same doubly labelled compound, the resonance for C_2 shows as a doublet at 85.1 ppm, with a $^1J_{^{13}\text{C}-^{13}\text{C}}$ coupling constant of 169 Hz. The compound with the incorrectly labelled $^{13}\text{C}_2$ shows a resonance at 85.0 ppm and will have approximately 4% the integral of the larger at 72.8 ppm.

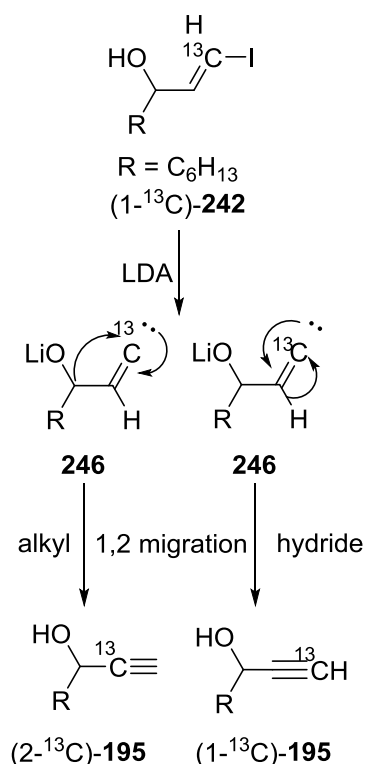
This was certainly an unexpected outcome, but consideration of the Corey-Fuchs mechanism provides an explanation. Two competing mechanistic explanations of the Corey-Fuchs reaction exist.



Scheme 3.2.5.20: The competing Corey-Fuchs mechanisms with vinyl diiodide **238**.

The first possibility involves initial β -elimination to give a haloalkyne **240**, followed by lithium-halogen exchange resulting in a lithioalkyne **244**. Aqueous work-up substitutes the lithium for a proton and yields the alkyne **239**.⁷⁸ The order of the β -elimination and lithium-halogen exchange are interchangeable, however. The alternative proceeds via an α -elimination to give a vinyl carbene **245**. This undergoes a 1,2-migration, with the hydride

shifting to C₁ and the lone pair of electrons forming the π -bond of alkyne **239**. Both mechanisms are possible with ⁿBuLi. However, when LDA is employed as the base, lithium halogen exchange cannot take place. This is supported by the presence of iodoalkyne **240** during the test reaction with vinyl diiodide **238** and LDA (scheme 3.2.5.17). This leaves only the α -elimination route. The mechanism as shown above does not result in a switch of C₁ and C₂. The related Fritsch-Buttenberg-Wiechall rearrangement, involves exactly the same α -elimination, but as this reaction starts with a 1,1-disubstituted alkene, it is an alkyl or aryl group that must migrate.⁷⁹ In our case, the hydrogen is clearly the favoured migrating group, but the rate of alkyl migration must be approximately 4% that of hydride migration and is sufficient to produce an observable amount of (2-¹³C)-**195**.



Scheme 3.2.5.21: Competing alkyl and hydride 1,2-migrations of carbene **246**.

Had the rates of migration been equivalent, we might have found the product to be equally labelled at C₁ and C₂. Epoxidation of an equally labelled bromoallene would have imparted no information about the mechanism, as it is the switching of these carbons that we intend to observe. The only solution would have been to restart this synthetic route and separate the vinyl iodide, (Z-1-¹³C)-**242** from the vinyl diiodide, (1-¹³C)-**243**. Fortunately, the small amount of ¹³C₂ labelled isotopomer (2-¹³C)-**195**, would not prevent the observation of any carbon migration during bromoallene epoxidation and instead made for some interesting spectral analysis.

The ¹³C NMR spectrum of this compound showed an anomalous peak at 114.6 ppm. This could not be assigned to any carbon in the propargylic alcohol (1-¹³C)-**195**, but instead is indicative of a terminal alkene. Expanding the baseline of the ¹H NMR spectrum showed a distinct set of resonances.

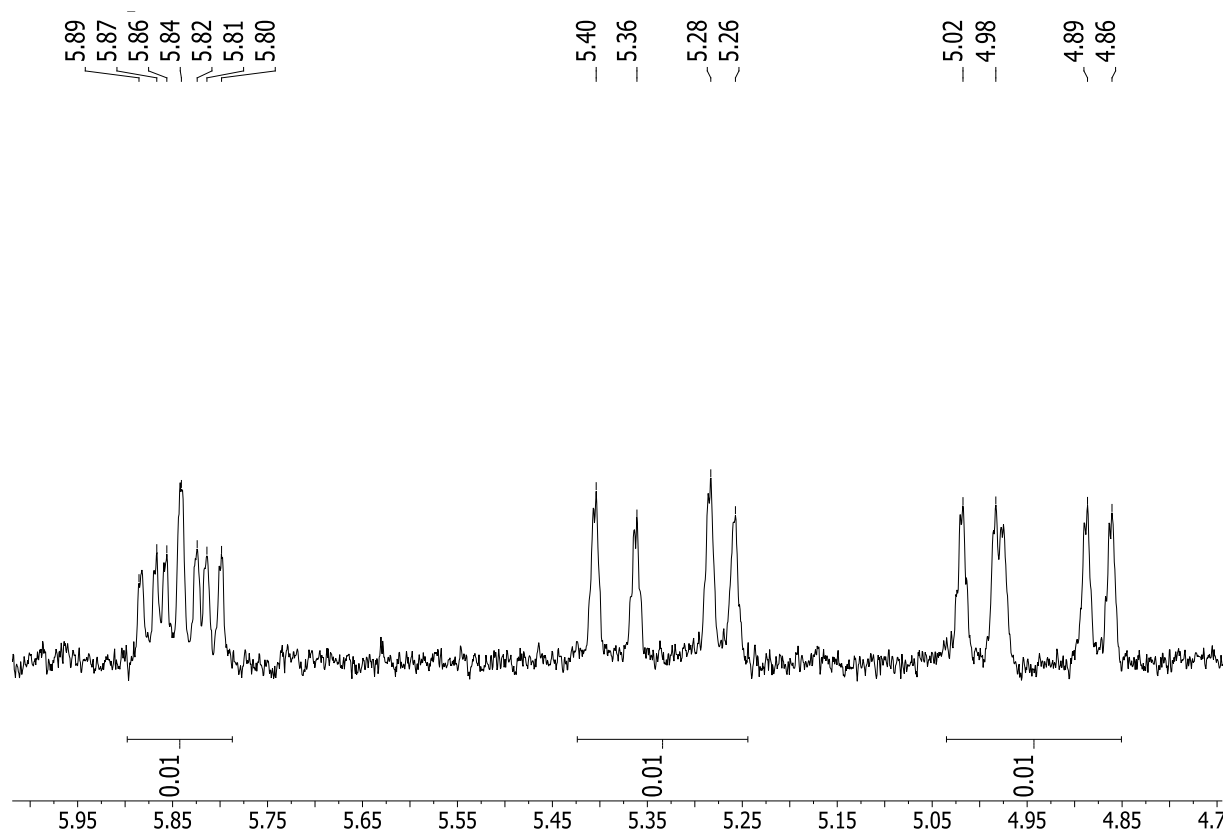
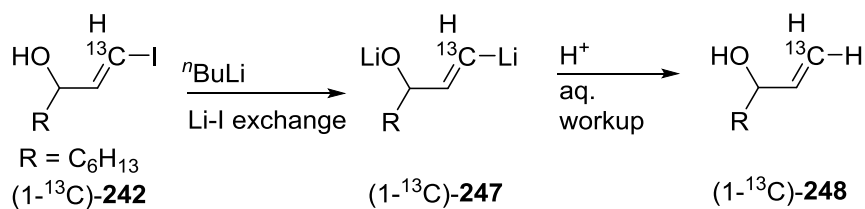


Figure 3.2.5.5: Alkene region of the ^1H NMR spectrum of compound $(1\text{-}^{13}\text{C})\text{-195}$.

Barely visible above the baseline were an array of doublets characteristic of a terminal alkene, assigned to allylic alcohol $(1\text{-}^{13}\text{C})\text{-248}$. This compound is most likely a result of a slight excess of $n\text{BuLi}$ in the LDA solution, allowing lithium-iodine exchange.



Scheme 3.2.5.22: Formation of allylic alcohol $(1\text{-}^{13}\text{C})\text{-248}$.

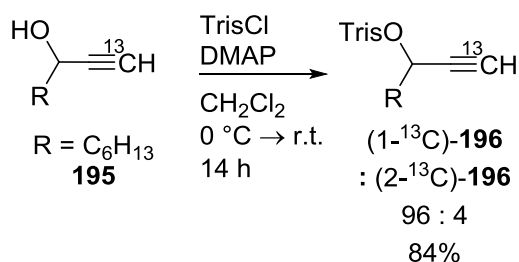
Although the n BuLi was titrated and stoichiometry was strictly controlled during the formation of LDA, it is possible that there was a slight excess of n BuLi available to perform the above reaction. Considering the allylic alcohol (1- ^{13}C)-**248** comprised less than 1% of the yield, this is not an unreasonable explanation. This compound was only noticed due to the increased resonance intensity of the labelled carbon. Had the compound been unlabelled, it most likely would have gone unnoticed. The corresponding allylic trisylate was observed in the ^{13}C NMR spectrum after the next reaction, at a concentration of about 0.1%, and was finally completely removed after bromination.

This was a theme throughout the ^{13}C -labelled synthetic route. Side products and compounds from previous reactions, often in sub parts-per-thousand concentrations, were occasionally seen in the ^{13}C NMR spectra of purportedly pure compounds, even after careful chromatography. These sorts of impurity concentrations are normally negligible as they are all but unobservable by most spectroscopic techniques, but with their increased visibility due to the labelled carbon, an important insight into purity was made.

With this reaction complete, 200 mg of ^{13}C -labelled propargylic alcohol (1- ^{13}C)-**195** had been prepared. In addition to this, a side product of the Wittig reaction had been successfully converted into a desired compound. Was this not possible, not enough ^{13}C -labelled bromoallene (1- ^{13}C)-**1** would have been prepared to allow analysis the products of epoxidation. Considering the low yields of that reaction (and the mass eventually collected), this was a definite possibility. The 4% of $^{13}\text{C}_2$ labelled compound produced by the Corey-Fuchs reaction would not be a negative issue in the elucidation of the mechanism.

3.2.6 Derivation to ^{13}C labelled bromoallene ($1\text{-}^{13}\text{C}$)-1

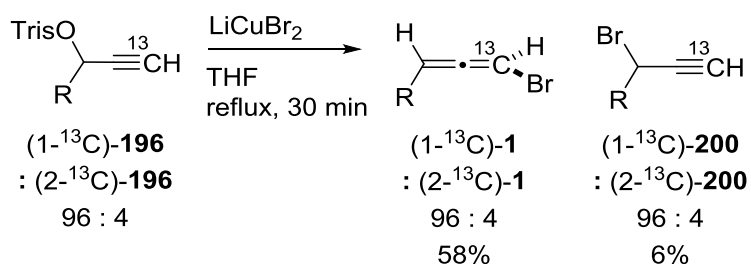
The established route from propargylic alcohol to bromoallene could now be followed.



Scheme 3.2.6.1: Trisylation of propargylic alcohol ($1\text{-}^{13}\text{C}$)-**196**.

Trisylation proceeded well, with similar yields to previous attempts. The product still contained 4% of the $^{13}\text{C}_2$ isotopomer, calculated by the integral of the alkyne resonances in the ^1H NMR spectrum.

Bromination via the established procedure was then conducted.



Scheme 3.2.6.2: Bromination of propargylic trisylate ($1\text{-}^{13}\text{C}$)-**196**.

The yield for this reaction was slightly lower than previous attempts, but as explained earlier, the volatility of this compound meant considerable mass could be lost

during solvent removal. The $^{13}\text{C}_2$ labelled isotopomer, (2- ^{13}C)-**1**, was still present at a 4% concentration.

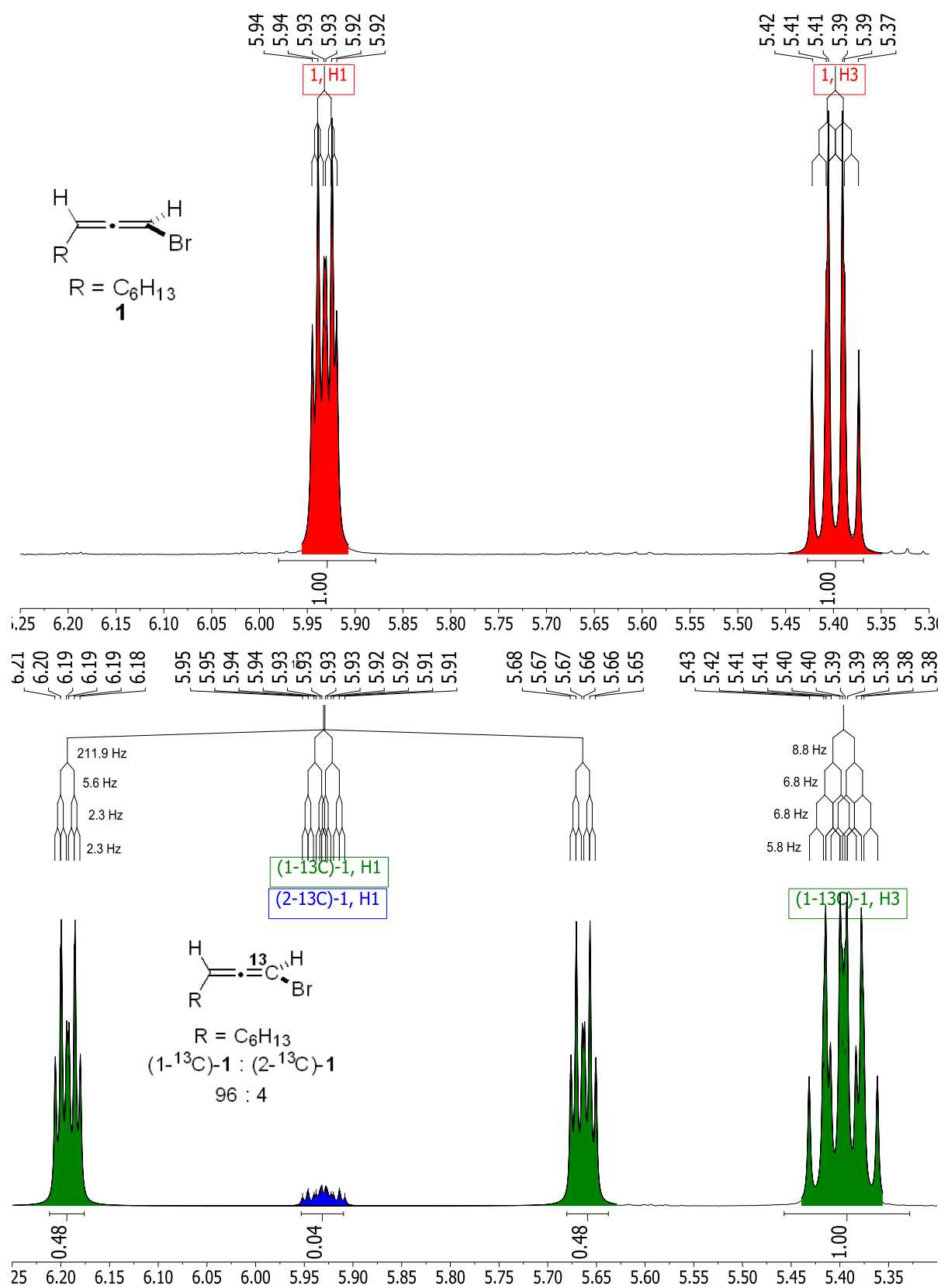


Figure 3.2.6.1: ^1H NMR of unlabelled bromoallene **1** (above) and ^{13}C labelled bromoallene ($1\text{-}^{13}\text{C}$)-**1** (below).

The above spectra show the allenic resonances of compounds **1** and (1-¹³C)-**1**. The resonances at 5.93 ppm correspond to the terminal proton and in the ¹³C₁ labelled compound, show a $^1J_{H-^{13}C}$ coupling constant of 212 Hz. The same proton in the ¹³C₂ compound causes the small multiplet in the middle with a $^2J_{H-^{13}C}$ coupling constant of 7.2 Hz. It appears that the unlabelled compound and ¹³C₂ labelled compound give identical resonances, but we can differentiate between the two by close analysis of the splitting pattern.

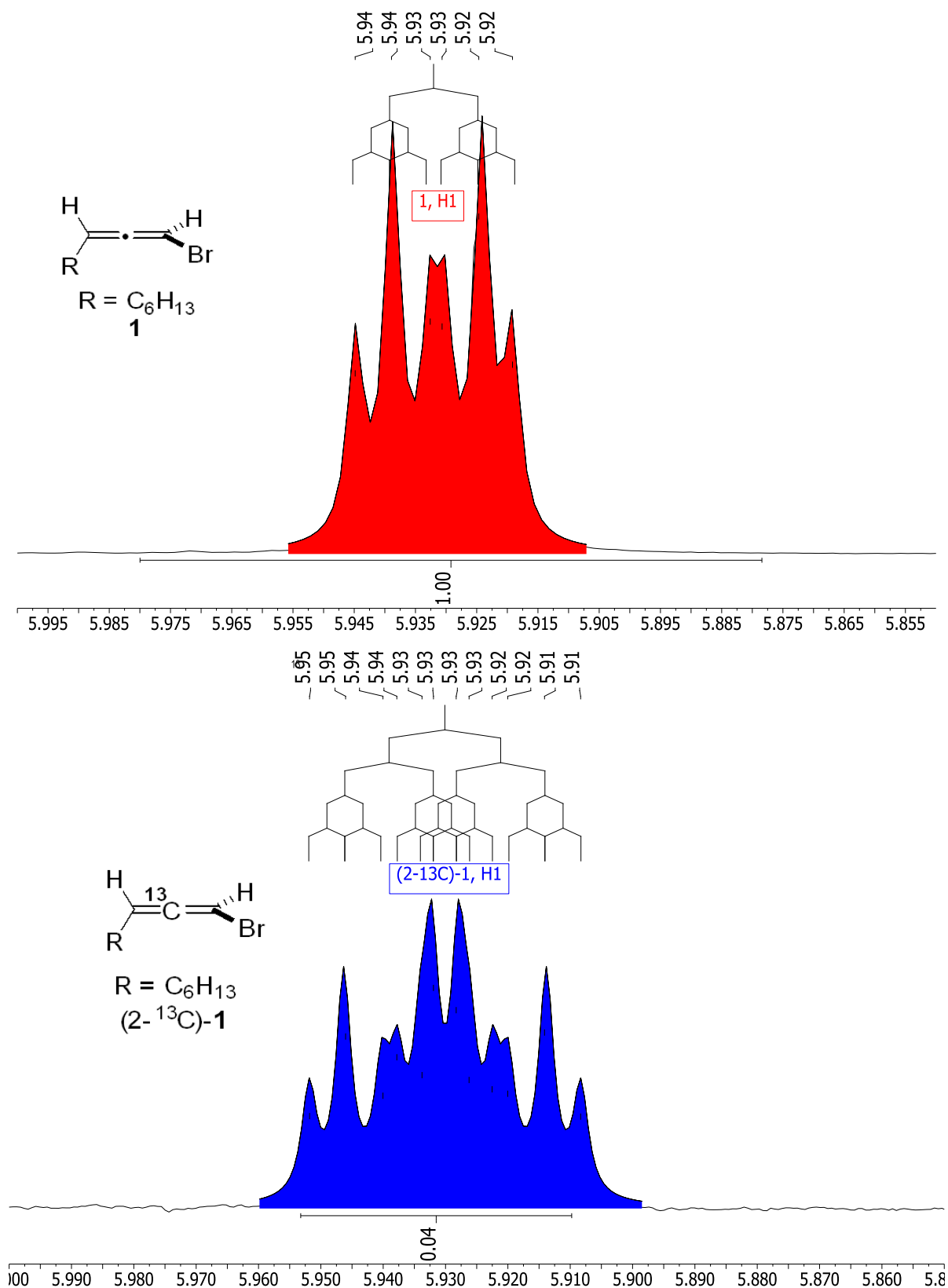


Figure 3.2.6.2: ^1H NMR spectra of the terminal proton of unlabelled bromoallene **1** (above) and ^{13}C labelled bromoallene (2- ^{13}C)-**1** (below).

The resonance for the unlabelled compound presents as a double triplet, caused by $^4J_{H-H}$ coupling to H₃ and $^5J_{H-H}$ to H₄. For the $^{13}\text{C}_2$ labelled compound, the resonance shows an additional splitting of 7.2 Hz, corresponding to a $^2J_{H-^{13}\text{C}}$ interaction.

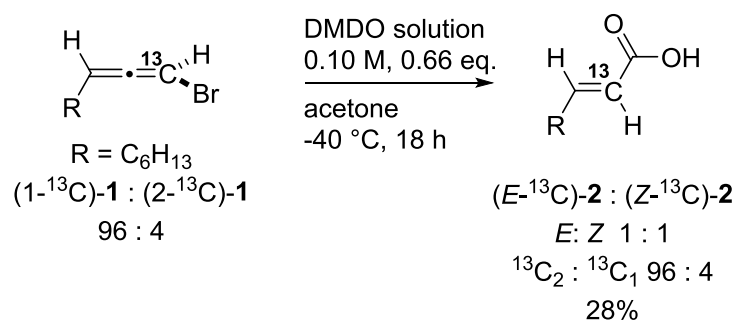
Similarly, the resonance at 5.4 ppm, corresponding to the proton on C₃, shows additional splitting from an (apparent) quartet to a doublet of quartets, due to a $^3J_{H-^{13}\text{C}}$. All resonances also show a slight isotopic shift, the magnitude of which is related to the proximity of the proton to the labelled carbon.

In addition to the intended bromoallene (1- ^{13}C)-**1**, propargylic bromide (1- ^{13}C)-**200** was also collected in a 6% yield, but the majority was lost due to evaporation during column chromatography.

With 145 mg of ^{13}C labelled bromoallene (1- ^{13}C)-**1** in hand, epoxidation could be attempted to determine the likely mechanism of this novel reaction.

3.2.7 Epoxidation of ^{13}C Labelled Bromoallene (1- ^{13}C)-**1**

Following the earlier observation that sub-stoichiometric amounts of DMDO resulted in a cleaner reaction, with no loss in yield, the first epoxidation attempt consisted of 0.30 eq. of DMDO and a 24 h reaction time. After work up and chromatography, 7 mg of each unsaturated acid were collected. This corresponds to an 11% combined yield. The samples of α,β -unsaturated carboxylic acids ((2- ^{13}C)-**2**) were not pure however, with a considerable amount of the unidentified side-products in the (Z)-isomer especially. The mass was deemed too low to attempt a second round of chromatography, so bromoallene (1- ^{13}C)-**1** was recovered and epoxidised again. This time 0.66 eq. of DMDO was employed and the solution stirred in the dark at -40 °C for 18 h.



Scheme 3.2.7.1: Epoxidation of ^{13}C -labelled bromoallene (1- ^{13}C)-1.

Work up and chromatography gave much cleaner samples of each unsaturated acid. A mass of 10 mg of each isomer was collected, which translated to a combined yield of 28% , by far the highest yield obtained for this reaction. More importantly, ^1H and ^{13}C NMR spectra definitively showed that the ^{13}C label was now at C₂.

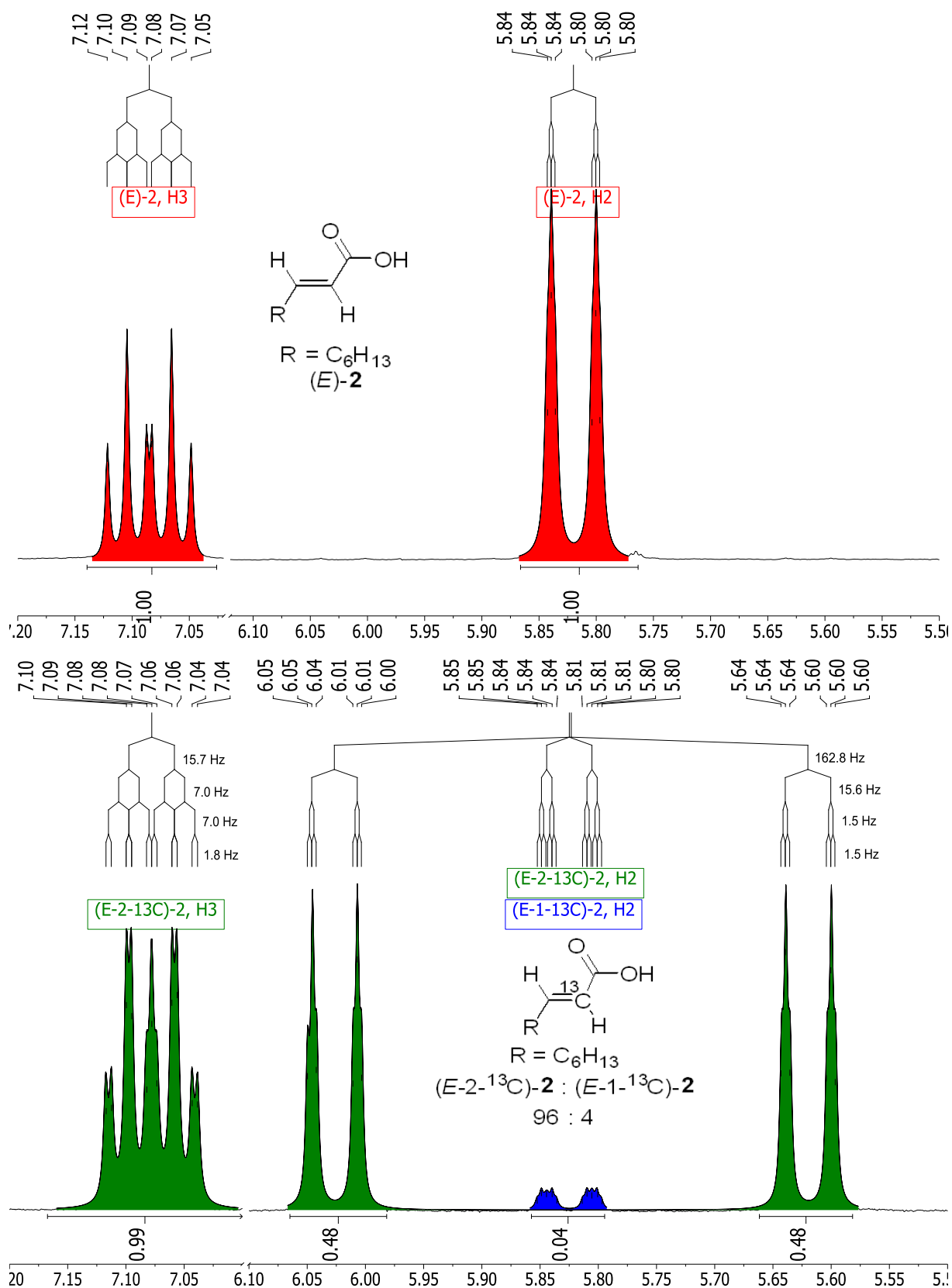


Figure 3.2.7.1: ^1H NMR spectra of unlabelled (E)-2 (above) and ^{13}C labelled (E-2- ^{13}C)-2

(below).

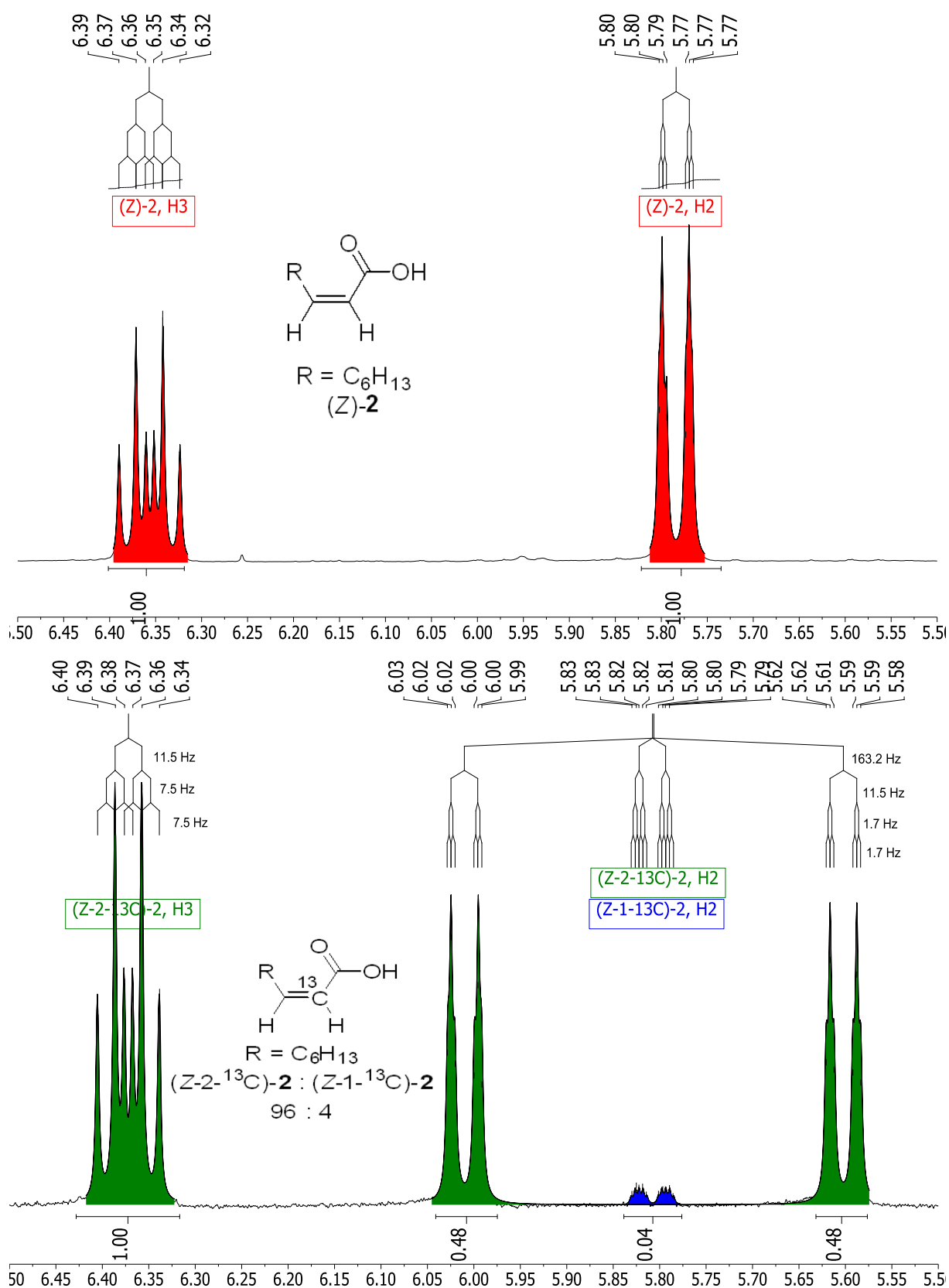
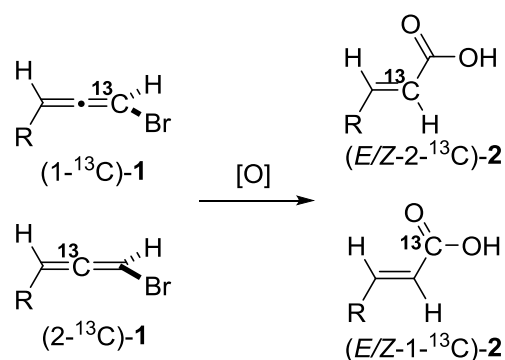


Figure 3.2.7.2: ¹H NMR spectra of labelled (Z)-2 (above) and ¹³C labelled (Z-2-¹³C)-2 (below).

Figures 3.2.7.1 & 3.2.7.2 both show the alkenic region of (*E*)-**2** and (*Z*)-**2** respectively (above). The resonances centred at ~5.8 ppm in both figures have been previously assigned as C₂ in the unsaturated acids. It can be seen that in the labelled compounds (below) that there is an additional splitting of 163 Hz, caused by $^1J_{H-^{13}C}$ coupling. The other resonances at 7.07 and 6.38 ppm are from the protons on C₃ and show $^2J_{H-^{13}C}$ coupling constants of 1.8 and 0 Hz for (*E*-2-¹³C)-**2** & (*Z*-2-¹³C)-**2** respectively. We have seen from previous ¹³C-labelled compounds that, depending on the hybridisation of the intermediate carbons, $^1J_{H-^{13}C}$ constants tend to be in the range of 250 – 150 Hz, while $^2J_{H-^{13}C}$ constants lie between 50 – 0 Hz. Had the ¹³C label been at C₁, we would expect the resonance at 5.8 ppm to have a much smaller coupling constant. Indeed, we can see the spectra that would be expected if the labelled carbon was at C₁ by the 4% integral peaks isotopomer peaks in the centre.



Scheme 3.2.7.2: Migration of the ¹³C labelled carbon during epoxidation of bromoallenes (1-¹³C)-**1** and (2-¹³C)-**1**.

We can observe in figures 3.2.7.1 & 3.2.7.2 that the minor isotopomer is still present at 4% concentration and has a $^2J_{H-^{13}C}$ coupling constant of 11.4 Hz, which is expected of such

a ^2J coupling. Rather than being a hindrance to our investigation, this unintended isotopomer has provided further evidence to our proposal by demonstrating a migration of C₂ to C₁. The fact that the amount of this isotopomeric compound remains constant at 4% also suggests that there are no competing mechanisms, such as the hydride shift (scheme 3.1.1.1), taking place.

^{13}C NMR spectroscopy confirms the conclusion reached from in the ^1H NMR spectrum.

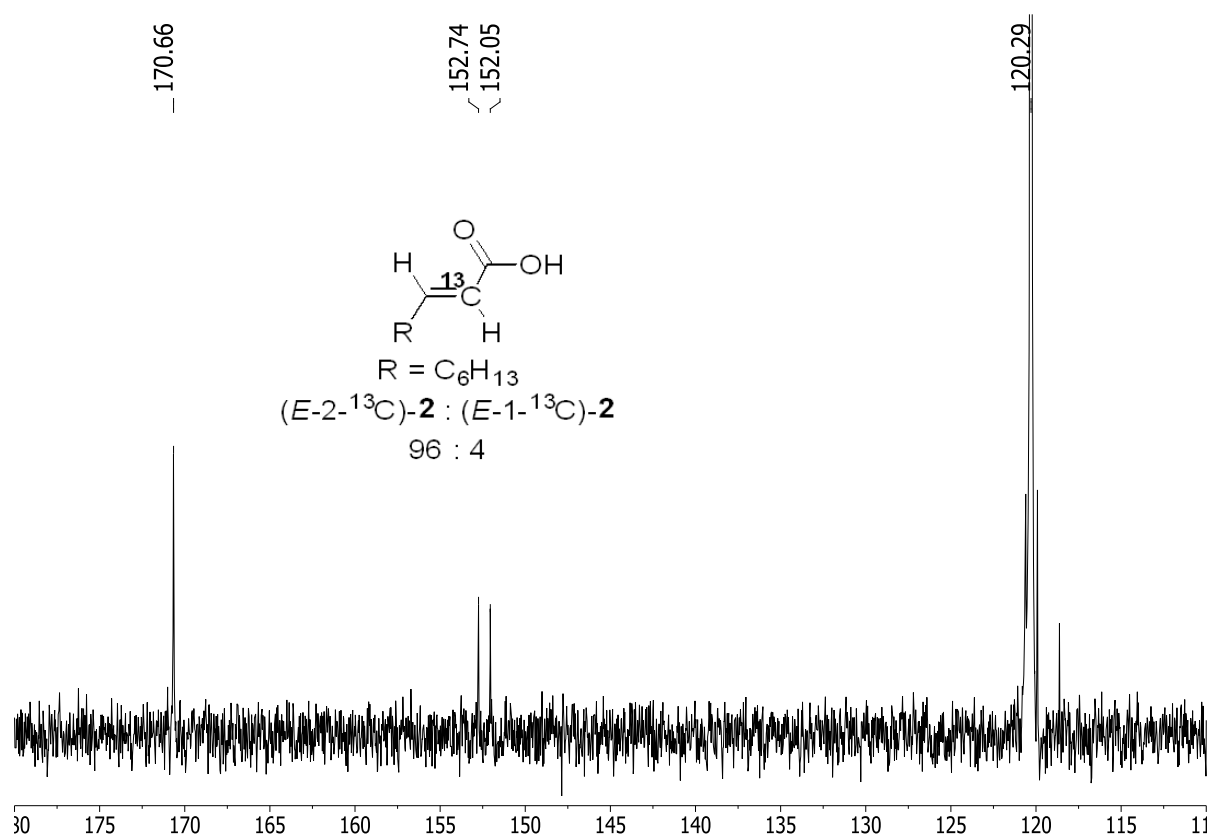
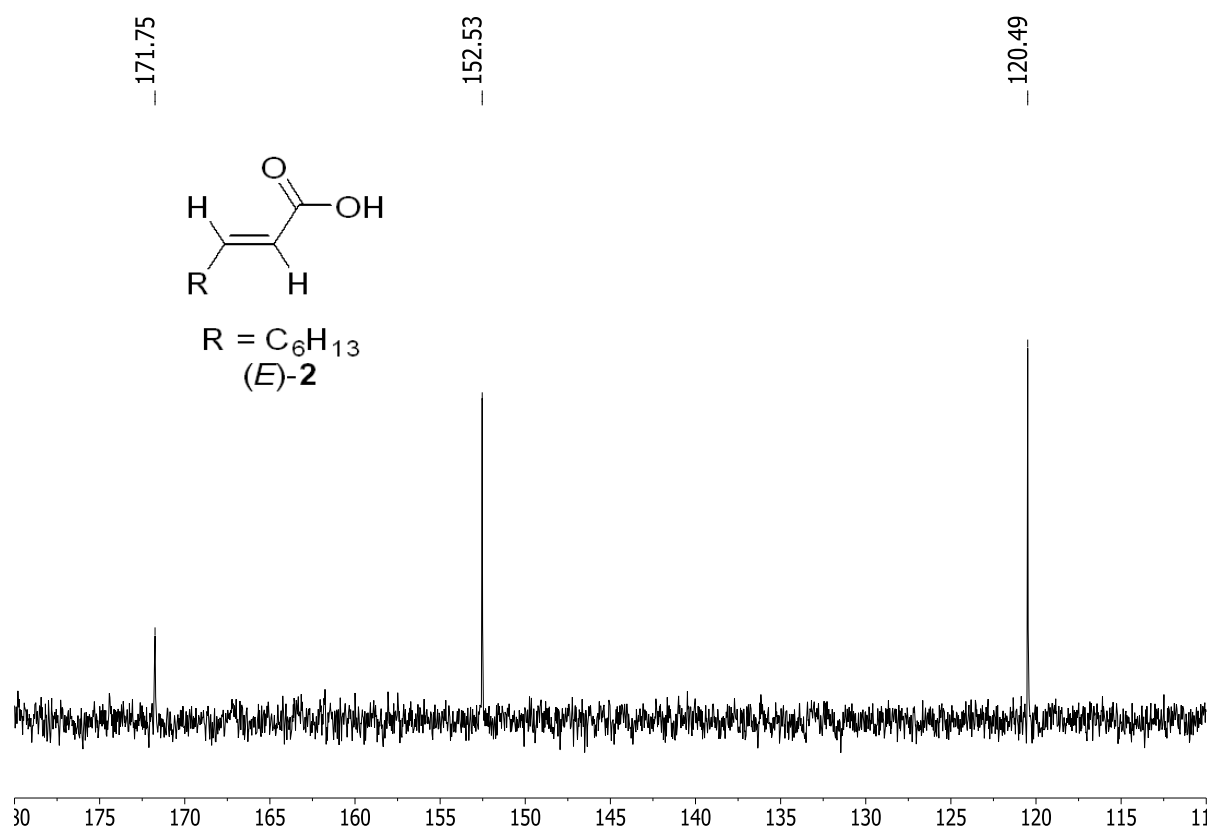


Figure 3.2.7.3: ^{13}C NMR spectra of unlabelled *(E)*-2 (above) and ^{13}C labelled *(E)*-2- ^{13}C -2

(below).

The resonances at 120 ppm correspond to C₂. The increased intensity of the resonance in the lower spectrum demonstrates that the ¹³C label is incorporated at this position. Also of note is the doublet at 152 ppm of the lower spectrum, caused by coupling of C₃ to ¹³C₂. Lastly, in the spectrum of unlabelled (*E*)-**2**, the carbonyl carbon produces a much lower intensity due to slow relaxation. In the lower spectrum the resonance is much stronger, due to the 4% of (*E*-1-¹³C)-**2** present in the sample.

Regarding the many side-products observed during these epoxidations, when using unlabelled bromoallene **1** as a substrate, these unwanted compounds are observed only by a long streak between starting material and product on TLC plates. Attempts to collect these compounds gave nothing that could be identified or quantified by NMR spectroscopy as the concentration of each one does not reach an amount that would allow individual observation. When using labelled bromoallene (1-¹³C)-**1**, these side-products were much more visible.

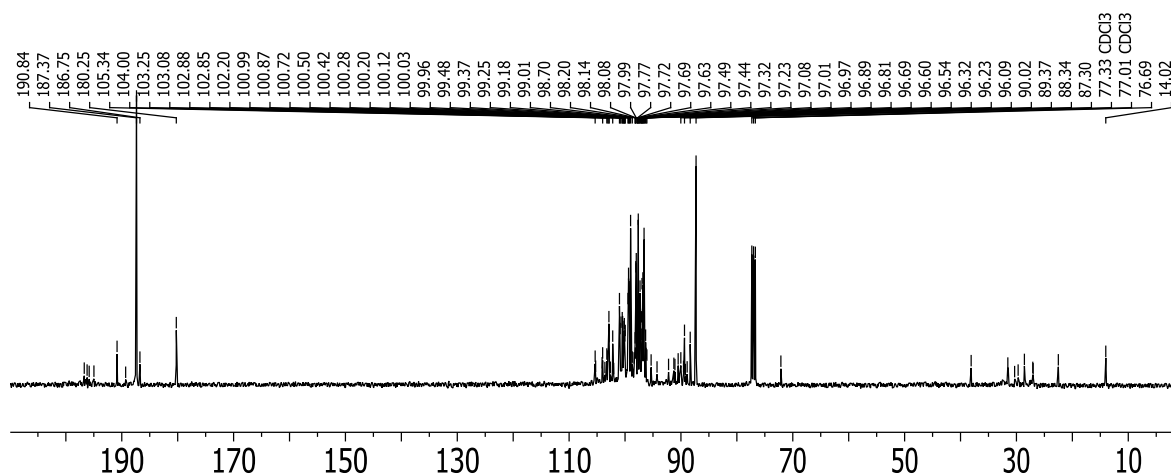


Figure 3.2.7.4: ¹³C NMR spectrum of the side products generated during the epoxidation of ¹³C-labelled bromoallene (1-¹³C)-**1**.

The above spectrum is the ^{13}C NMR of the fractions collected between the elution of bromoallene (1- ^{13}C)-**1** and unsaturated acids (E-2- ^{13}C)- and (Z-2- ^{13}C)-**2**. Now that the compounds contain an isotopic carbon label, each one presents a distinct peak. This suggests that there may be more than 50 side products from this reaction. It is very fortunate that the starting material and product of this reaction lie on opposite ends of the polarity scale, as this makes them elute first and last respectively. The multitudes of side products, with intermediate polarity, are eluted between them. Had this not been the case, purification may have been impossible.

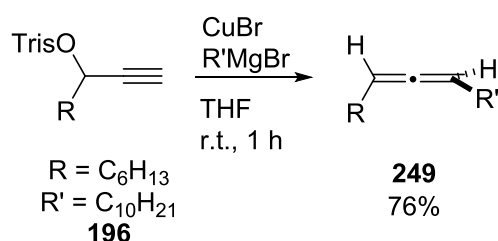
Analysis of the NMR spectroscopic data leaves no doubt the C_2 migrates to C_1 , and *vice versa*, during the epoxidation. This provides excellent evidence for the proposed Favorskii-like mechanism and as such, the biogenesis of the α,β -unsaturated methyl ester compound **27** found in *Laurencia obtusa*.

3.2.8 Further Investigation Into the Mechanism of Bromoallene Epoxidation

The mechanism of the bromoallene epoxidation - cyclopropanone - Favorskii rearrangement had been elucidated, but there was still a question of the regiochemistry of the epoxidation. As epoxidation of either olefin of bromoallene **1** can lead to cyclopropanone **4**, the experiments conducted so far could give no indication on which olefin this was. There was no possibility of observing a reaction intermediate, either isolated or during an NMR spectroscopy experiment, as the rearrangement was too fast. Comparison to aromatic bromides and their influence on electrophilic aromatic substitution suggest that the bromide in bromoallene **1** would deactivate the $\text{C}_1\text{-C}_2$ olefin through inductive electron withdrawal, but simultaneously direct the epoxidation by resonance donation. Although, computational

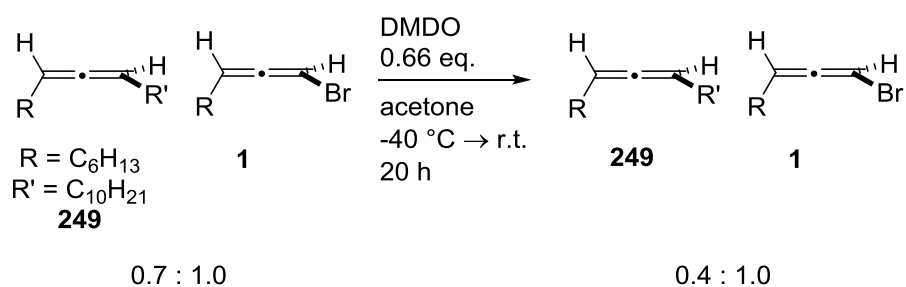
analysis of the transition states suggests that the C₂-C₃ is of lower energy and therefore the preferred site of epoxidation.⁶³

A competition reaction was devised whereby bromoallene **1** and 1,3-dialkylallene **249** would be epoxidised together to determine if such a deactivation was correct. Based on modified procedures, 1,3-dialkylallene **249** was synthesised by exploiting the same copper-catalysed Gilman chemistry used in the generation of bromoallenes.^{61, 80}



Scheme 3.2.8.1: Synthesis of 1,3-dialkylallene **249** *via* copper catalysed alkylation.

Decylmagnesium bromide was chosen as the Grignard reagent, as a longer chain length would raise the boiling point of the product, preventing volatility. The reaction proceeds through a similar activated copper species to the previous brominations, presumably of the form (BrMg)CuR'Br, which coordinates to the alkyne before delivering a nucleophile in an S_N2' reaction. The carbanion is a better nucleophile than bromide so is preferentially transferred. Although, there was a small amount of bromoallene **1** present in the crude mixture, but this could be largely removed *in vacuo*. This compound was combined with further bromoallene **1** and subjected to the same DMDO epoxidation procedure as previously, in a competition experiment.



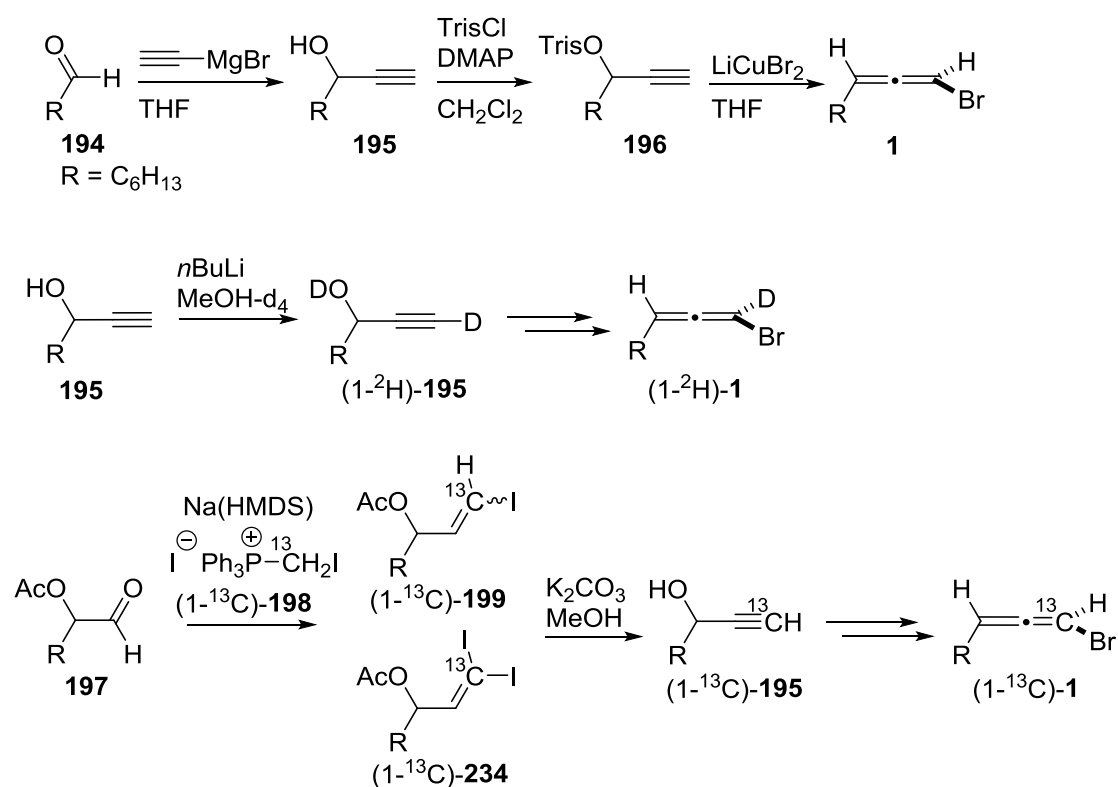
Scheme 3.2.8.2: Competition reaction between the epoxidation of 1,3-dialkylallene **249** and bromoallene **1**.

The first attempt at the above reaction gave unsatisfactory results because after an attempt was made to purify the products, but much of the bromoallene was lost during solvent removal. Instead, the ratios of each component was measured by ^1H NMR spectra taken as samples from the reaction over time. It was seen that the ratio decreased considerably, with the 1,3-dialkylallene **249** clearly being the preferred substrate for epoxidation. This supports the hypothesis that the bromine deactivates the olefins towards electrophiles. In addition, there was no sign of any of the radical decomposition products in the spectra. This suggests that in the absence of bromoallene epoxidation, no acidic products are formed and DMDO decomposition does not occur to the same extent. Indeed, the reaction was repeated with 0.5 equivalents of (*E*)-**2** and after the same time period the spectral baseline showed large amounts of the same radical addition side-products previously seen.

Unfortunately, no further insights could be made as to the regiochemistry of this reaction. Work is currently underway by other members of the Braddock group to epoxidise a highly hindered bromoallene in an attempt to slow the rearrangement and observe intermediates. However, no solid conclusions have yet been made in this new study.

3.2.9 Conclusion

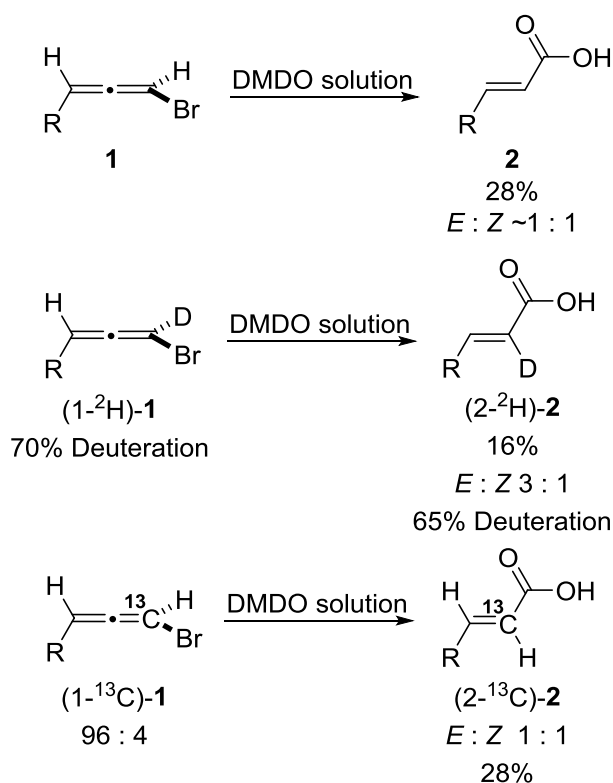
This project was begun with the question of how *Laurencia* achieves the conversion of bromoallenes to α,β -unsaturated esters, as posed by the co-isolation of obtusallene IV (19), 12-epoxyobtusallene IV (8) and unnamed ester 27. This was answered by developing a model bromoallene (1), which could be tested with a range of epoxidation methods. Isotopically labelled substrates (1- ^2H)-1 & (1- ^{13}C)-1 were also synthesised as a method of probing the mechanism.



Scheme 3.2.9.1: Synthesis of bromoallene model substrates **1**, (1- ^2H)-**1** & (1- ^{13}C)-**1**.

Scheme 3.2.9.1 summarises the route to each of these model bromoallenes. Substrates **1** & (1- ^2H)-**1** could be generated using the Overman protocol,^{53b} as exemplified in Kim's synthesis of (+)-itomanallene (**12**),^{53a} in a sufficiently large scale to allow multiple test

reactions of the novel epoxidation. Compound (1-¹³C)-**1** proved to be a more challenging target, due to the limitation of starting with ¹³C-methyl iodide. However, a route involving Rubottom oxidation and a Corey-Fuchs reaction allowed substrate (1-¹³C)-**1** to be prepared in a sufficient quantity to epoxidise and examine the products. The results of such epoxidation are summarised in scheme 3.2.9.2.

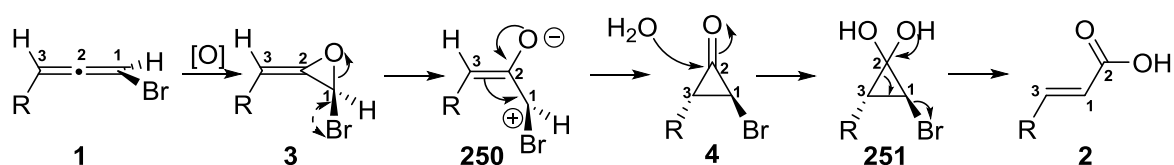


Scheme 3.2.9.2: Results of the epoxidation of model substrates **1**, (1-²H)-**1** & (1-¹³C)-**1**.

It was found that a solution of DMDO in acetone, prepared by distillation of a mixture of water, acetone, oxone™ & NaHCO₃ and adding sub-stoichiometric quantities gave the most reliable results. The reaction was prone to side-reactions, possibly brought about by decomposition of DMDO to methyl radicals, but the product acids could be easily separated

and purified. In addition, unreacted bromoallenes could be recovered and recycled, allowing multiple repeats of the reaction to be conducted.

Acids **2**, (2-²H)-**2** & (2-¹³C)-**2** were collected in low yields and were produced in a 1 : 1 ratio of *E* : *Z* olefins. Thorough analysis of the NMR spectra showed that the isotopic labels had migrated from C₁ to C₂. This allows a mechanism for the epoxidation of bromoallenes to be proposed.



Scheme 3.2.9.3: Proposed mechanism for the epoxidation of bromoallenes.

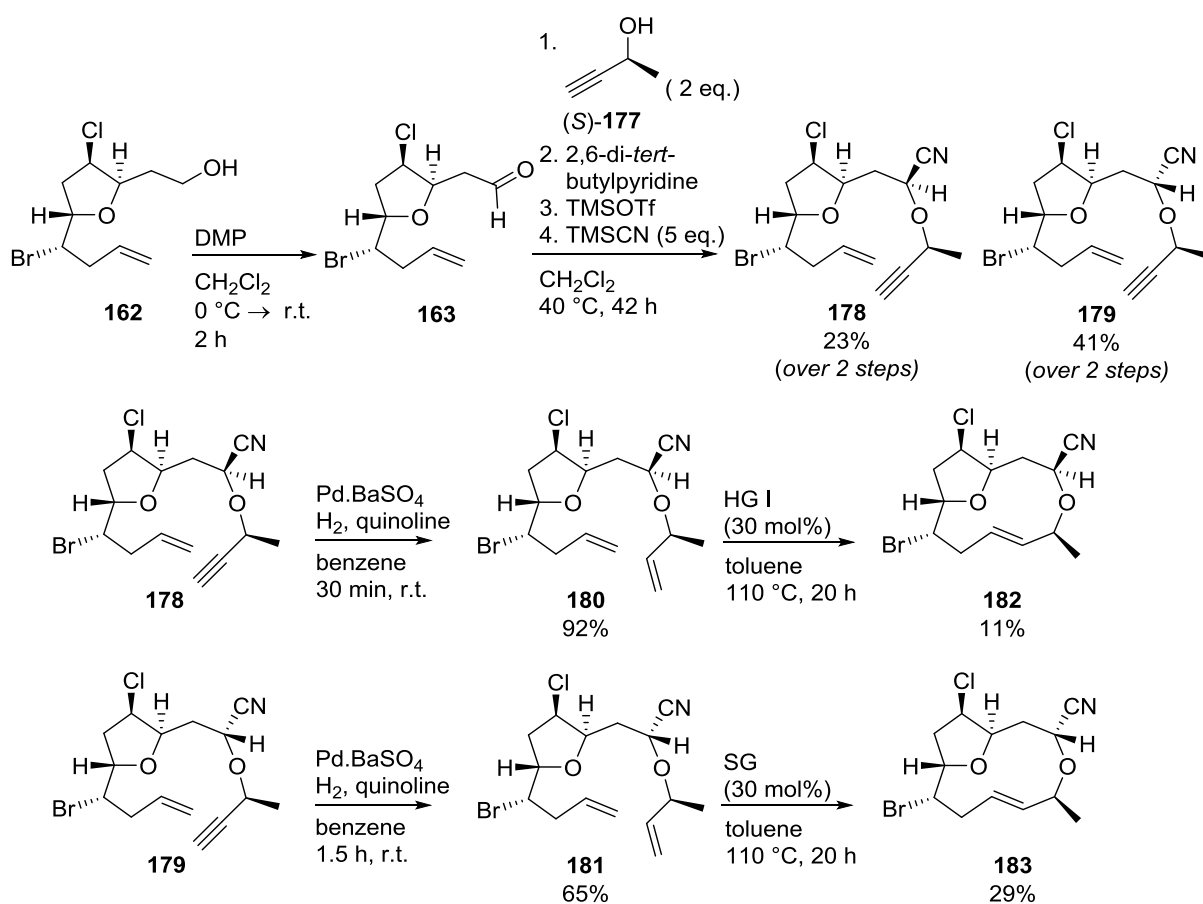
Epoxidation of one of the bromoallene olefins can be followed by epoxide opening and formation of bromocyclopropanone. This is sensitive to solvolysis and rapidly reacts with adventitious water to join a Favorskii reaction manifold, which could allow elimination of the bromine and formation of α,β-unsaturated acids. As such, the biogenesis of unnamed ester **27** had been elucidated.

4 Results & Discussion Part II: Completion of the Total Synthesis Of Obtusallenes And Marilzabicycloallenes

4.1 Aims and Objectives Part II: Completion of the Total Synthesis of Obtusallenes and Marilzabicycloallenes

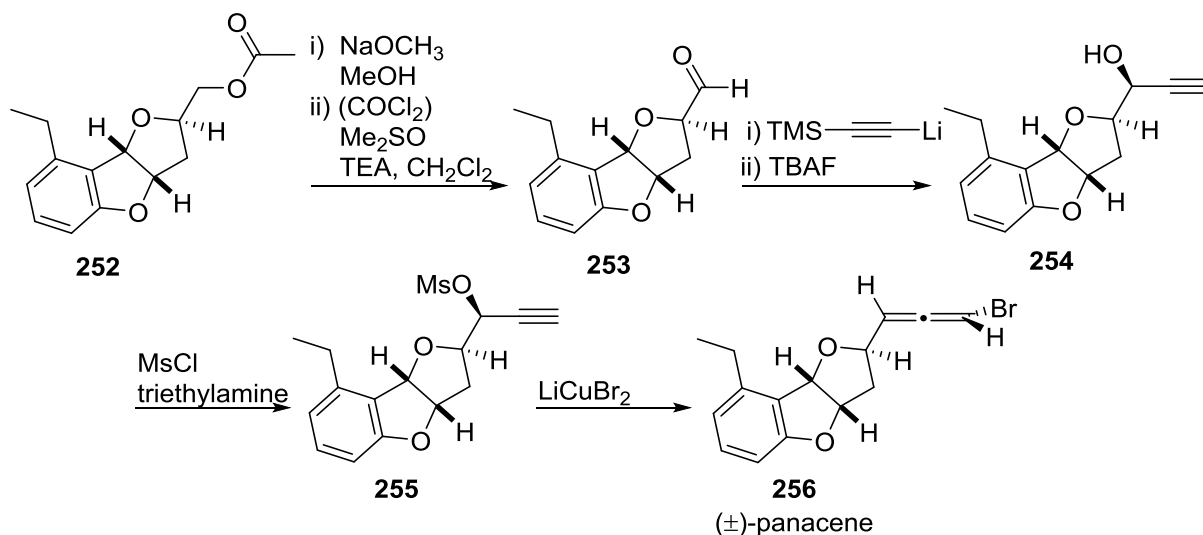
4.1.1 Expected Synthetic Route Towards Completed Obtusallenes and Marilzabicycloallenes

At the culmination of the synthetic studies by Yaqoob and Bonney, the remainder of the material comprised of approximately 1.50 g (5.29 mmol) of alcohol **162** & 300 mg (0.827 mmol) of diene **180**.^{46, 48} Compare this to the 140 g (1160 mmol) of propargylic bromide with which Yaqoob began the synthesis. Building on the work by Bonney, this material would be elaborated to nitriles **182** & **183** *via* the established cyanoetherification and RCM route (scheme 4.1.1.1).



Scheme 4.1.1.1: Expected route to macrocycles **182** & **183**, with previously observed yields.

Assuming that the yields recorded by Yaqoob and Bonney were replicable, we could expect 71.3 mg (0.213 mmol) of **182** & 137 mg (0.409 mmol) of **183**. From here, an established synthetic route, used widely in the total synthesis of a range of bromoallene bearing natural products will be followed.^{53, 55a, 55b, 81}



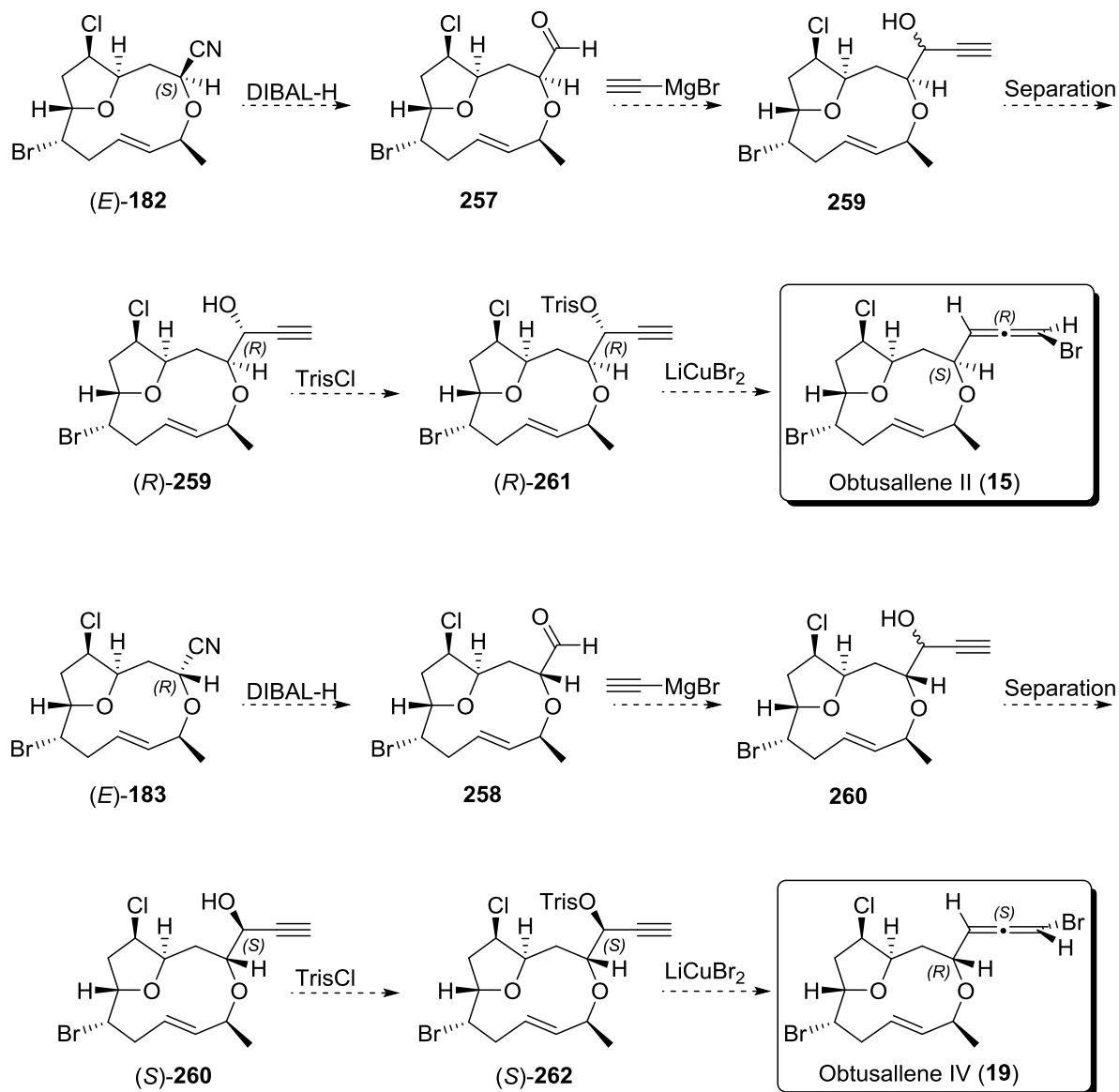
Scheme 4.1.1.2: Bromoallene installation in Feldman's synthesis of (±)-panacene **256**.

The first example that could be found of a such a protocol being used in a natural product total synthesis is Feldman's synthesis of (±)-panacene **256**.^{81a} In this protocol, acetate **252** is solvolysed and Swern oxidised to aldehyde **253**. Trimethylsilyl protected acetylide addition and TBAF deprotection gave propargylic alcohol **254** in an 86 : 14 ratio with its epimer. Mesylation and copper catalysed S_N2' bromination gave (±)-panacene **256**.

In other natural product total syntheses, the precursor to the aldehyde and the nature of the metal cation used for the acetylide addition is variable, but the sulfonylation and bromination is ubiquitous and well established. This route is often generically referred to as the Overman protocol, after he used it in a total synthesis of (±)-kumausallene.^{53b}

A very similar route starting from nitriles **182** & **183** (scheme 4.1.1.3) was envisaged. DIBAL-H reduction of the pendant nitriles of **182** & **183** will yield aldehydes **257** & **258**. Acetylide addition with an ethynyl Grignard reagent will give mixtures of epimeric propargylic alcohols **259** & **260**. Test reactions conducted by Yaqoob and Bonney had showed these steps to be low yielding and so would require optimisation. Trisylation and subsequent copper catalysed S_N2' bromination will give obtusallenes II & IV (**15** & **19**). Due

to the stereospecific nature of the bromination, (i.e. alcohol (*R*)-**259** leads to *R_a*-configured obtusallene II (**15**)), it would be essential to separate the epimers at the alcohol stage, or at least encourage the acetylide addition to have a high selectivity for the correct product.

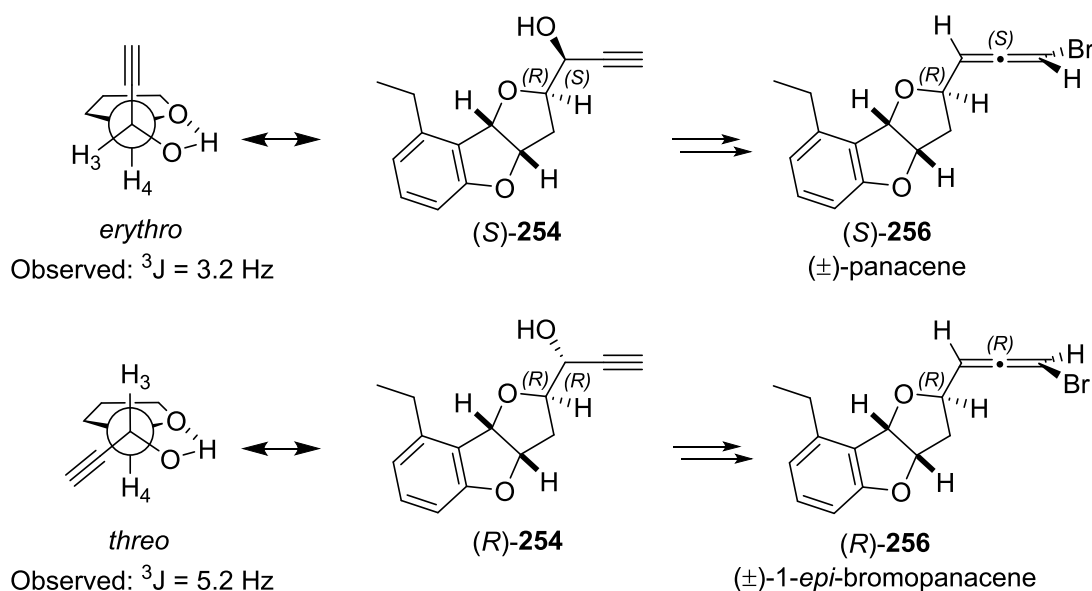


Scheme 4.1.1.3: Final reactions to complete the synthesis of obtusallenes II & IV (**15** & **19**).

There will be difficulty in assigning the stereochemistry of each epimer of alcohols **259** & **260**, and therefore it is not likely that we will know the correct epimer without

carrying the material forward to the bromoallene and comparing to the relevant natural product data. We will therefore be producing a natural product and its 1-*epi*-counterpart when possible. Although its formation in *Laurencia* is impossible due to the stereospecific bromoetherification of the enyne (scheme 2.3.1), it will still be of use to isolate and characterise the 1-*epi*-compounds, as it will act as a negative control for our claim to have synthesised any natural product.

Feldman postulated that the coupling constants of the alcohols could be used to predict the correct stereochemistry.^{81a}



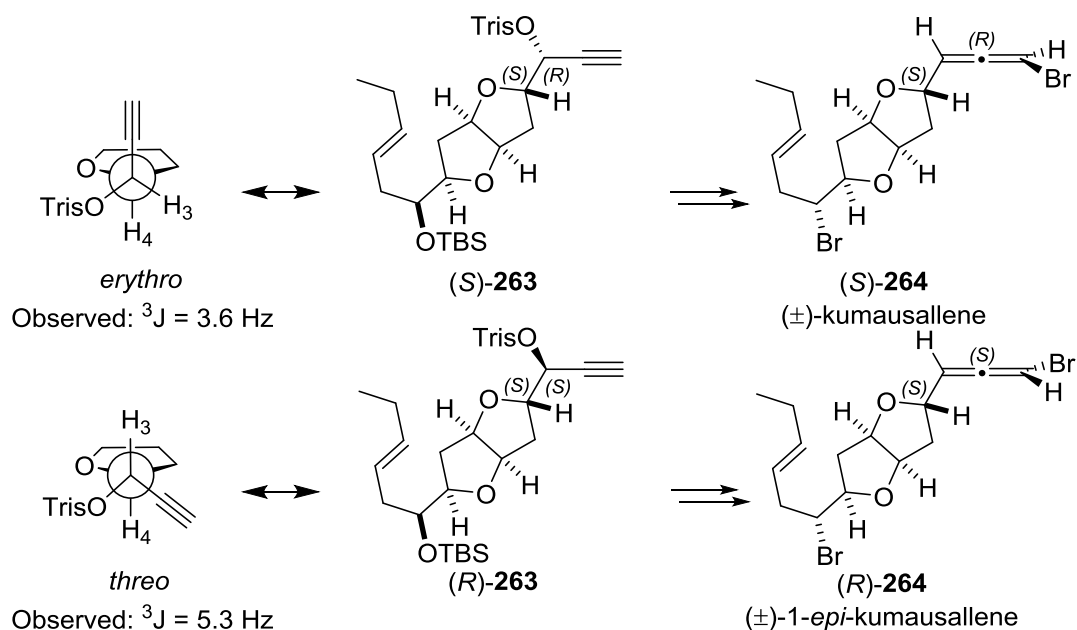
Scheme 4.1.1.4: Newman projection analysis of the epimeric alcohols (S)-254 & (R)-254 leading to (±)-panacene (256).

Feldman predicted that intramolecular hydrogen bonding by the alcohol and the THF oxygen will cause alcohols (S)-254 & (R)-254 to adopt certain conformations. In the case of the *erythro* isomer (R)-254, hydrogen bonding leaves the alkyne group perpendicular to the ring and antiperiplanar to the THF proton, H₄. The propargylic proton, H₃, is therefore

gauche to H₄. Using the Karplus equation and a dihedral angle of 60°, we can expect the coupling constant between such protons to be in the range of 2 - 4 Hz. Conversely, the orientation of H₃ and H₄ in the *threo* isomer is antiperiplanar. Again, the Karplus equation predicts a coupling constant of 6 - 8 Hz. This effect can be increased with the use of a metal template, such as Eu(fod)₃, to coordinate the two oxygens and lock the conformation.⁸²

Indeed, Feldman observed coupling constants of 3.2 Hz for one epimer and 5.2 Hz for the other. From this, one compound was assigned as *erythro*-**254** and after derivation to the bromoallene, was proven to be the precursor to the natural product (±)-panacene (*S*)-**256**. Of course, *threo*-**254** was also converted to its 1-*epi*-analogue, (*R*)-**254**, for the sake of completion and spectroscopic confirmation of the structure.

Overman performed a similar analysis on the trisylate precursors (*S*)-**263** & (*R*)-**263** in a total synthesis of (±)-kumausallene (*S*)-**264**.^{53b}



Scheme 4.1.1.5: Newman projection analysis of the epimeric alcohols (*S*)-**263** & (*R*)-**263** leading to (±)-kumausallene (**264**).

Again, the trisylate with the lowest observed vicinal coupling constant correctly predicted the *erythro*- and *threo*-isomers of **263** and was proven by full derivation to natural product (S)-**264** and its 1-*epi*-analogue (R)-**264**.

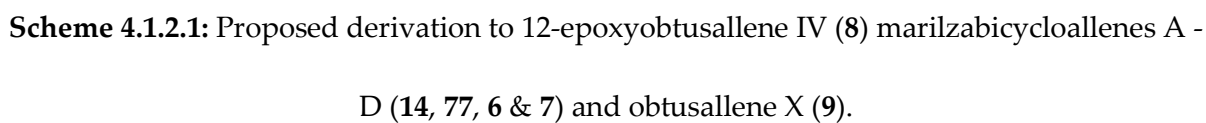
In the present synthesis, the products of acetylide addition and trisylation, (R)-**261** & (S)-**262**, can be similarly evaluated to predict which epimer will lead to a natural obtusallene. Although a compelling argument, the two above example were performed on very similar α -tetrahydrofurylpropargylic alcohols. This same theory may not translate to the much more conformationally flexible macrocyclic ethers (R)-**261** & (S)-**262**, so this assignment alone cannot be relied upon and all epimers should be produced for the sake of certainty.

4.1.2 Further Derivation to Other Obtusallenes and Marilzabicycloallenes

If the synthesis of obtusallenes II & IV (**15** & **19**) was successful, then the biosynthesis of other obtusallenes and marilzabicycloallenes could be explored.

If the biosynthesis of marilzabicycloallenes is correct,¹² obtusallenes II & IV (**15** & **19**) or an appropriate precursor, would need to have been epoxidised in the presence of a suitable nucleophile. DMDO had shown to be an effective epoxidant for the model system (section 3.2.2). However, the risk of radical side-products or alkyl oxidations meant that more mild reagents would be necessary. An alternative, *m*CPBA, had shown itself to undergo nucleophilic addition to epoxides (scheme 3.2.2.6), but this would not be an issue for the sterically protected macrocycles.

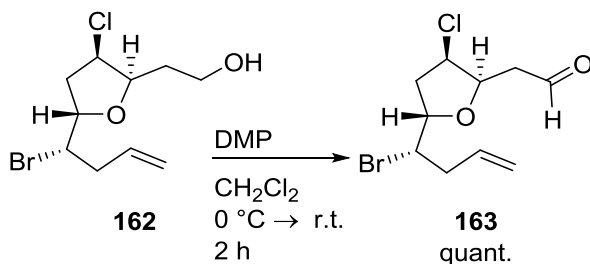
Further to this, a dichlorination procedure could be pursued, based on the previous work by Braddock on the IBIAERO reaction.²³ The biogenesis of obtusallene X (**9**) can also be investigated using 12-epoxyobtusallene IV (**8**).



4.2 Results and Discussion Part II

4.2.1 Replication of Cyanoetherification of Aldehyde 163

The first step of this project would be to replicate the reactions outlined by Yaqoob and Bonney to ensure that they are repeatable.^{46, 48}



Scheme 4.2.1.1: Dess-Martin oxidation of alcohol **162**.

Oxidation with Dess-Martin periodinane proceeded very well, often with quantitative yield. However, the crude product was heavily contaminated with iodine by-product **265**.

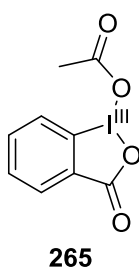
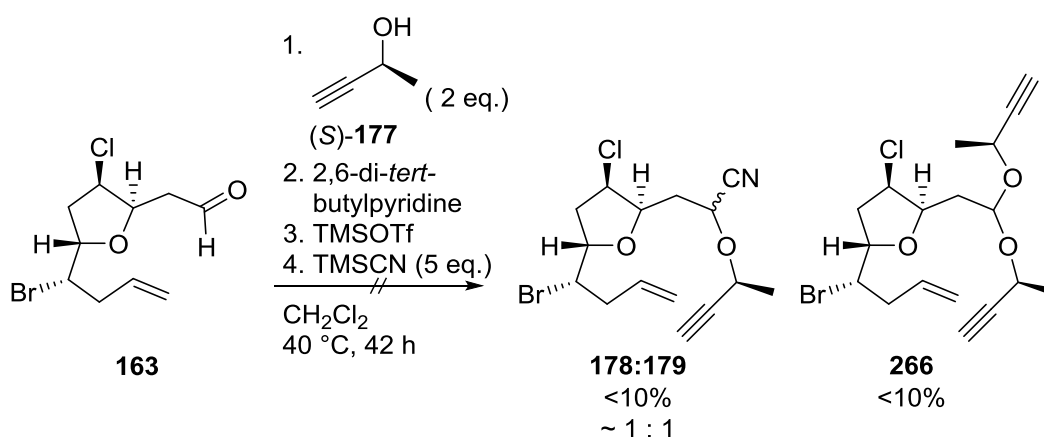


Figure 4.2.1.1: Iodine by-product of Dess-Martin oxidation.

The sodium bicarbonate work-up described by Bonney did not entirely remove iodine **265** and as the product was a sensitive aldehyde, purification by column

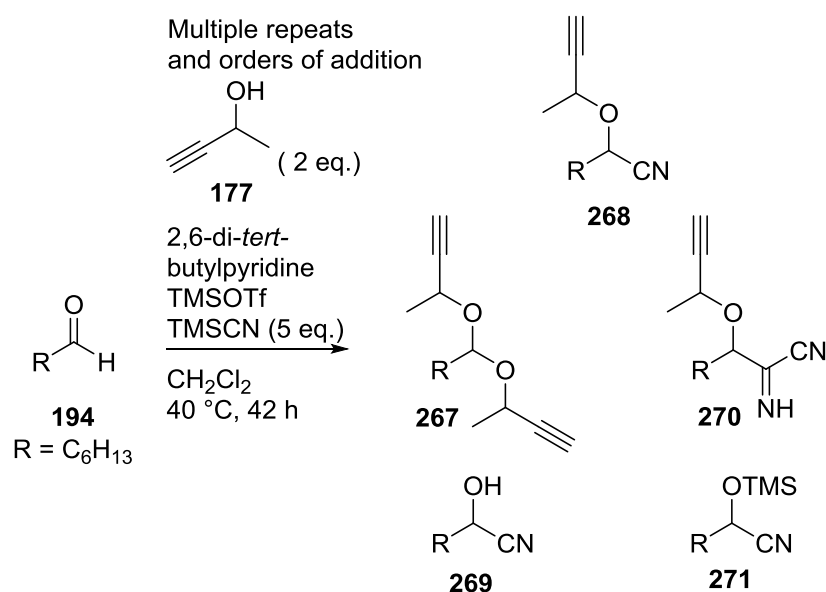
chromatography would result in a loss of yield. This problem was solved by substituting the liquid-liquid extraction work up for a simple silica plug. This allowed isolation of aldehyde **163** in high yield and purity with no need for further purification.

Continuing with Yaqoob and Bonney's route, the one-pot cyanoetherification was attempted.



Scheme 4.2.1.2: Attempted cyanoetherification of aldehyde **163**.

Unfortunately, when Bonney's conditions were replicated, multiple unidentified compounds were produced. The only structure that was identifiable was acetal **266** in very low yield. To spare aldehyde **163** from wasteful test reactions, a model system was developed and investigated. Heptaldehyde (**194**) and racemic alcohol **177** were subjected to the same conditions to try and identify some of the side-products. All subsequent reactions in scheme 4.1.1.3 were also to be replicated to build familiarity with the procedure, but also to identify any other problematic steps.



Scheme 4.2.1.3: Products of the cyanoetherification of a heptaldehyde (**194**) model system.

As well as the expected cyanoether **268**, multiple additional products were formed. The outcome was often a combination of acetal **267** and starting aldehyde **194**, or a complex mixture of cyanohydrins **269** & **271** and cyanoimine **270**. From this, we can assume that similar functionalities were present in the combination of products seen in the reaction with aldehyde **163**.

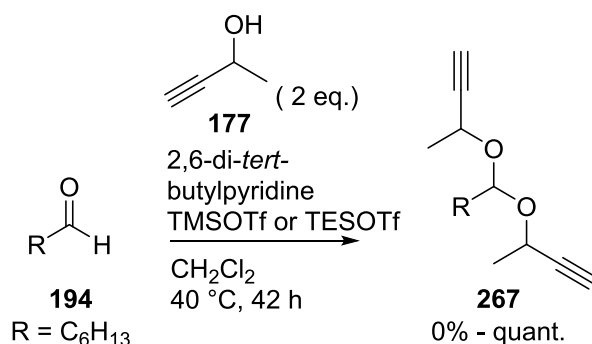
A reaction as capricious as this would be ruinous for the end stages of a total synthesis. Had we submitted the bulk of our precursor alcohol **162** to this protocol and found only cyanohydrins or cyanoimines were produced, this would have meant the end of the project. However, the formation of acetals **266** & **267** was promising.

Being an intermediate in the expected cyanoetherification reaction, it is of no surprise that it was often isolated as the major product. If the reaction could be driven to produce only an acetal product, purify and separately incorporate cyanide, greater control over the products formed would be given. By splitting the one-pot cyanoetherification into a two-

step process, increased yield, milder conditions and greater control over reactivity would be allowed.

Heptaldehyde (**194**) model system was revisited to determine conditions that will maximise acetalisation. Formation of an acetal is usually a trivial matter with the use of a protic catalyst, but the use of enantiopure alcohol (*S*)-**177** when transferring to the real system, could have presented problems. Allowing (*S*)-**177** and TMSOTf to react for too long risked racemisation of the secondary alcohol. Presumably, a protic acid will promote the same racemisation.

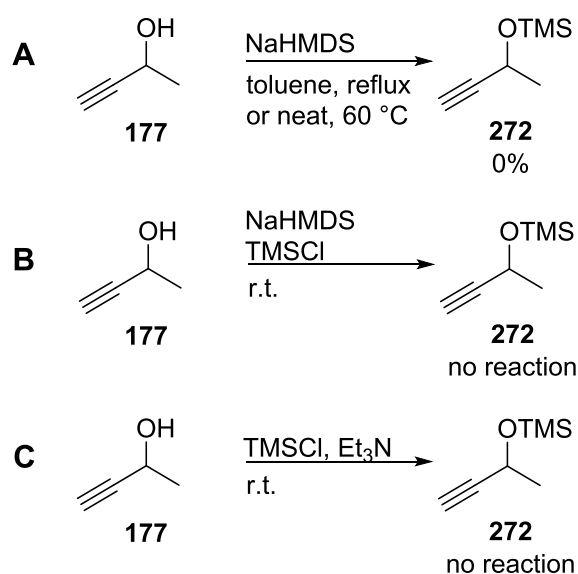
With this limitation, the search commenced using the same TMSOTf, Lewis acid catalyst as well as its analogue, triethylsilyl triflate (TESOTf)



Scheme 4.2.1.4: Attempt at forming acetal **267**.

Although TESOTf was found to give better results, this reaction was just as unpredictable. Repeats of the same reaction, with identical conditions would give either quantitative conversion, no reaction or decomposition of heptaldehyde (**194**).

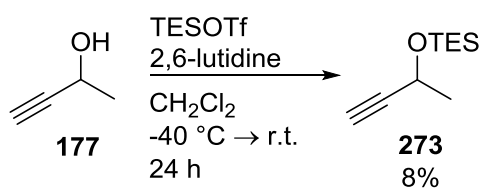
It was reasoned that relying on the *in situ* formation of the reactive silyl ether (**272**) may be complicating matters and so attempts to isolate this intermediate and employ it as a reactant in more controlled manner were made.



Scheme 4.2.1.5: Attempted formation of trimethylsilyl ether **272**.

The above procedures, adapted from similar syntheses,⁸³ employing HMDS, TMSCl or both, either resulted in no reaction (**B** and **C**) or initial success but loss of product due to evaporation (**A**).

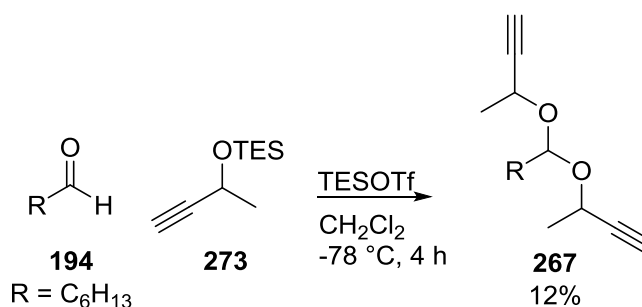
Our target changed to the triethylsilyl (TES) analogue **273**, in an effort to reduce volatility. Literature precedent could be found for a similar protection.⁸⁴



Scheme 4.2.1.6: Attempted formation of triethylsilyl ether **273**.

Scheme 4.2.1.6 shows that combining alcohol **177** with 2,6-lutidine and TESOTf at -40 °C gave a very low yield of triethylsilyl ether **273**. Although the volatility of this compound was less problematic and analysis of the crude product from this reaction looked promising,

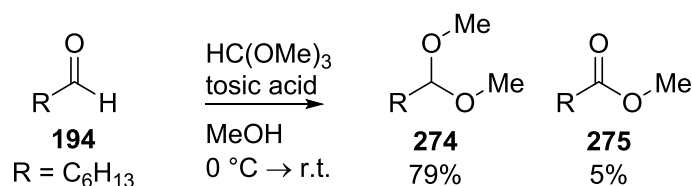
it was heavily contaminated by (TES)₂O. Having an identical R_f value and similar boiling point to silyl ether **273**, the repeated distillations required to remove (TES)₂O meant that only a few milligrams of triethylsilyl ether **273** were collected. Despite this, the small amount of **273** collected was combined with heptaldehyde (**194**) in an attempt to form acetal **267**.



Scheme 4.2.1.7: Attempted formation of acetal **267**.

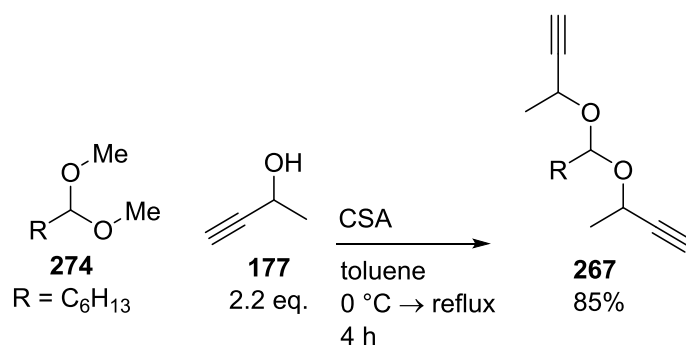
Attempting an acetalisation with triethylsilyl ether **273** & heptaldehyde (**194**), resulted in only a 12% yield of acetal **267**. Again, purification was complicated by the similar polarity of side-product (TES)₂O.

At this point, the silyl ether route was abandoned, in favour of a more conventional acetal formation, similar to that performed by Solanki in the second attempt at synthesising obtusallenes (scheme 2.5.2.2).



Scheme 4.2.1.8: Methyl acetalisation of heptaldehyde (**194**).

First, methyl acetal **274** was prepared using an established technique, as shown in scheme 4.2.1.8.^{42, 85} Trimethyl orthoformate was stirred with heptaldehyde (**194**) and tosic acid as a catalyst. Dimethyl acetal was formed in good yield, but with a slight impurity of methyl ester **275**, which was inseparable due to very similar polarity.



Scheme 4.2.1.9: Transacetalisation to form diyne **267**.

Initial results, shown in scheme 4.2.1.9, were promising. Successful transacetalisation with racemic alcohol **177** gave an 85% yield of acetal **267**. However, as optimisation of the reaction was begun, it became clear that it was as unpredictable as the others.

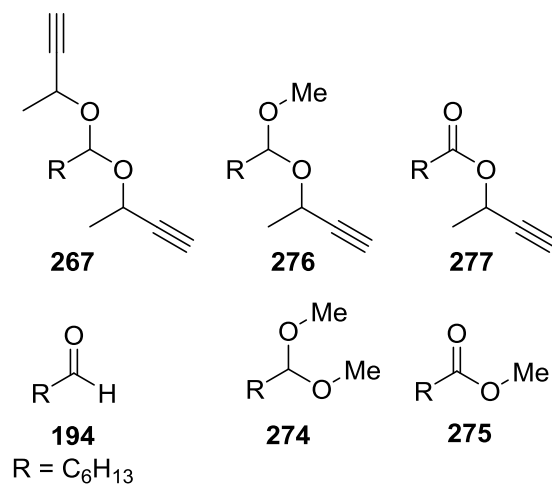
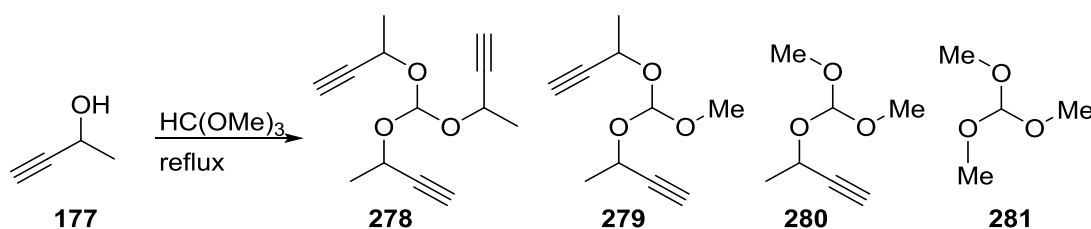


Figure 4.2.1.2: Observed products of the transacetalisation of dimethyl acetal **274**.

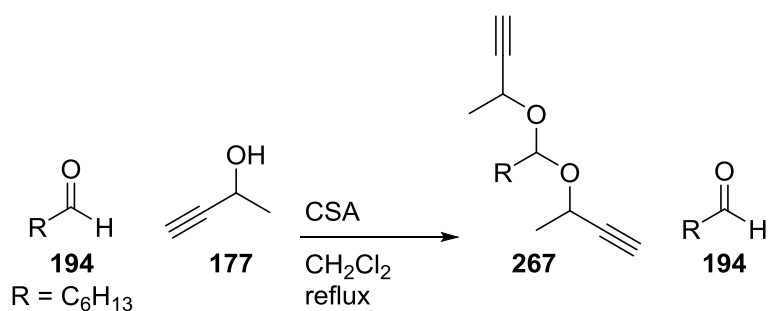
Figure 4.2.1.2 shows the products observed during repeats of the same reaction, with nearly identical conditions. A mixture of acetals **267**, **274** & **276**, starting aldehyde **194** and esters **275** & **277** were observed in varying ratios. The similar polarity of all of these species made individual isolation almost impossible. Fortunately, all of these products are recoverable, mixed acetals can be resubmitted to acetalisation and esters can be reduced to aldehydes. But when using the valuable obtusallene macrocycles, such inefficiencies are not acceptable. Once more, a more reliable route was sought.



Scheme 4.2.1.10: Attempted formation of orthoformate **278**.

Having seen the relative ease that dimethyl acetal **274** had been formed with trimethyl orthoformate, attempts to synthesise tri(but-3-yn-2-yloxy) orthoformate **278** were made, in an effort to create an acetalisation reagent.⁸⁶ Refluxing neat trimethyl orthoformate and a large excess of propargylic alcohol **177** for 48 hours in distillation apparatus to remove the methanol, only left a complex mixture of orthoformates (**278** - **281**) seen in scheme 4.2.1.10. Adding more equivalents of propargylic alcohol **177** pushed the ratio of products towards the desired compound **278**, but with diminishing returns. As purification of these substrates was not a possibility, due to their sensitivity to silica and the presence of any of the mono-, di- or trimethyl orthoformates (**279** - **281**) being highly undesirable, this route was also discarded.

It was chosen to simplify the acetalisation as much as possible. Heptaldehyde (**194**) was heated in dichloromethane and an excess of alcohol **177** with CSA as a catalyst, under a variety of conditions (scheme 4.2.1.11, table 4.2.1.1). Being a reversible reaction, it was unlikely for the acetalisation to go to completion, but the aim was to develop conditions that would maximise conversion. Due to the moderate volatility of heptaldehyde (**194**) and its instability to silica gel, the reaction was assessed by the ratio of acetal **267** to aldehyde **194** in the crude NMR spectra.



Scheme 4.2.1.11: Direct acetalisation with heptaldehyde (**194**) & racemic alcohol **170**.

Conditions	Conc. / mM	177 / eq.	CSA / mol %	Additives	Time / h	267 : 194
A	0.66	6.5	3	4 Å mol. sieves	7	65 : 35
B	0.66	6.5	3	4 Å mol. sieves	20	75 : 25
C	neat	12.8	3	4 Å mol. sieves	24	85 : 15
D	0.66	6.5	1	4 Å mol. sieves	24	55 : 45
E	Neat → 0.66	6.5	3	4 Å mol. sieves	48	85 : 15
F	0.66	((S)-177) 6.5	12	4 Å mol. sieves	48	85 : 15
G	0.66	6.5	0	Silica gel	24	20 : 80
H	neat	10.4	3	4 Å mol. sieves	24	65 : 35
I	0.66	6.5	3	4 Å mol. sieves	6	60 : 40
J	0.66	6.5	3	4 Å mol. sieves	20	55 : 45
K	0.66	6.5	3	4 Å mol. sieves	6	65 : 35
L	0.66	6.5	3	4 Å mol. sieves	20	55 : 45
M	0.5	12.8	3	4 Å mol. sieves	24	70 : 30
N	neat	6.5	3	-	1	55 : 45
O	neat	6.5	3	4 Å mol. sieves	1	40 : 60

Table 4.2.1.1: Results of initial screen of acetalisation conditions with aldehyde **194** and propargylic alcohol **177**.

Based on these results, some conclusions were reached. Firstly, incorporating 4 Å molecular sieves into the reaction generally increase yield, as would be expected when water is removed from the reaction, but not dramatically so. It was observed that the **267 : 194** ratio would often increase between the crude NMR and after column chromatography, so silica gel was trialled as a catalyst, but without great success (entry **G**). Neat reactions, using

alcohol **177** as a solvent generally produced higher yields of acetal **267** (entries **C**, **H**, **N** & **O**). Entry **F** used enantiopure alcohol (*S*)-**177**, larger amounts of CSA and increased reaction time, without any observation of racemisation. Contrary to what was expected, it was discerned that the enantiopurity of the acetal would be retained. However, all the conditions employed gave a yield of acetal **267** of approximately 55 to 85%. As the reaction forms a reversible equilibrium, this explains the moderate excess of acetal **267**. The real complication with this reaction is the fact that a non-trivial amount of heptaldehyde **194** was left remaining. In the real systems of aldehyde **163**, any remaining starting material may have been lost upon chromatography. In addition, several side products emerged, all of which co-eluting with starting material **194** & product **267**, making them exceedingly difficult to remove (figure 4.2.1.3).

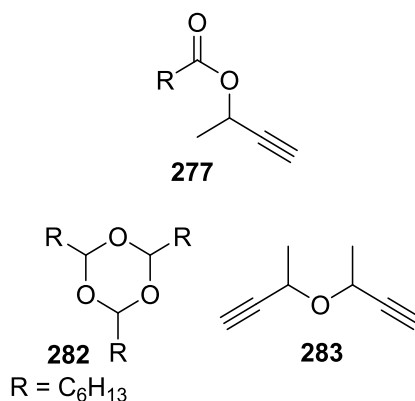
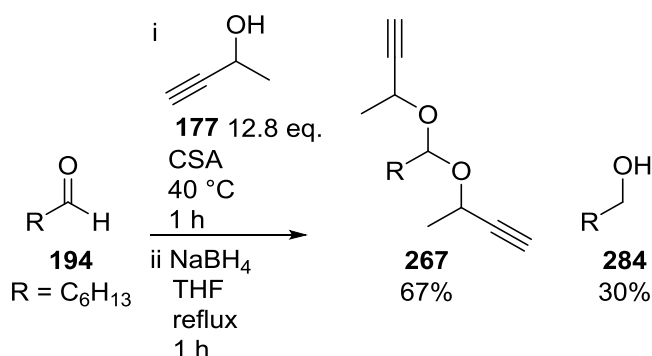


Figure 4.2.1.3: Side product of the acetalisation of heptaldehyde (**194**) and propargylic alcohol **177**.

Although not isolated and characterised, the side products were tentatively assigned as trioxane **282**, ester **277** & ether **283**. All represent a loss of material that could not be tolerated in the real system. In order to recover as much material as possible, a method of reduction, immediately following the acetalisation would allow any remaining

heptaldehyde (**194**) to be reverted to 1-heptanol (**284**) and recovered more easily. Ideally, the reduction would also allow recycling of ester and trioxane side products **277** & **282**. The acetalisation reaction was repeated, followed by NaBH₄ as a quenching agent. This reducing agent is not typically suitable for the reduction of esters, but it is known in the literature that a mixture of NaBH₄ and methanol in refluxing THF is effective at reducing esters.⁸⁷ It is possible that the propargylic alcohol **177** would mimic the role of methanol in this reduction.



Scheme 4.2.1.12: Acetalisation of heptaldehyde (**194**), employing a NaBH₄ quench.

It was found that using a reductive quench such as this gave a moderate yield of acetal **267** at 67% (scheme 4.2.1.12). But more importantly, the remaining mass could be separated and isolated as 1-heptanol (**284**). In the real system, alcohol **162** could be reoxidised and submitted for acetalisation a second time. The side products described in figure 4.2.1.3 were also no longer observed, suggesting that the NaBH₄-alcohol **177** system was an effective reductant for these functionalities. It was not expected for an ether such as **283** to be reduced, but it was certainly not present in the crude mixture. It is possible that the electronic influence of the two alkynes make it more sensitive to NaBH₄. Trioxane **282** was present in trace amounts, but we reasoned that the increased sterics of the real system would effectively preclude the formation of this in the real system. It is possible that the yield of

acetal **267** could have been increased with an extended reaction time, but it was deemed to be more efficient to perform shorter reaction times and focus on the recovery of as much starting material as possible.

Acetal **267** was collected as 52 : 35 : 12 mixture of inseparable diastereomers, calculated by comparison of the ratio of alkyne resonances around 2.40 ppm. The major diastereomer was known to be (*S*^{*},*S*^{*})-acetal **267A** by comparison to the product obtained with enantiopure alcohol (*S*)-**177** (entry F, table 4.2.1.1). In this compound, the central acetal carbon is not chiral and all of the 1-butyn-3-yl resonances overlap, making it simple to characterise. The minor diastereomers **267B** & **267C** must arise from mismatch of the stereochemistry of the 1-butyn-3-yl groups resulting in the acetal carbon showing pseudo-chirality. In these cases, the resonances are slightly different, resulting in a complex pattern of alkyne peaks. When this reaction would be repeated on the obtusallene system and aldehyde **163**, the diastereomeric purity of the resulting acetal could be assessed by observing the alkyne resonances. Such signals are distinct enough that the diastereopurity of acetal **266** could be assessed by observing the pattern of alkyne resonances.

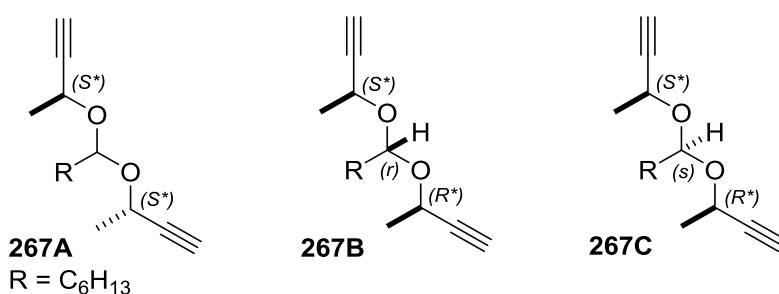
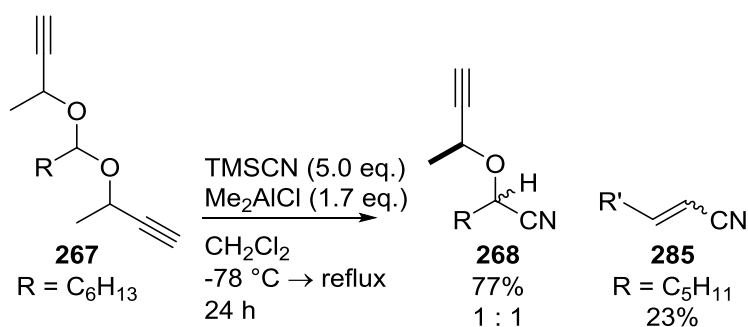


Figure 4.2.1.4: The three diastereomers of acetal **267** observed in the acetalisation of heptaldehyde (**194**) with racemic alcohol **177** (n.b. the absolute and relative stereochemistries of these compounds in arbitrary).

The reaction was repeated with enantiopure alcohol (*S*)-**177** for confirmation and the only product seen was acetal **267A**, confirming that racemisation would not be a complication.

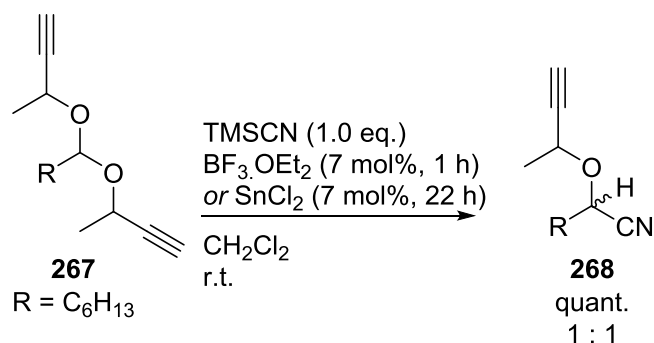
4.2.2 Optimisation of the Cyanation of Acetal **267**

With an appropriate method of acetalisation finalised, work moved towards optimising the cyanation step. Starting with dimethylaluminium chloride (Me_2AlCl), the catalyst used in Bonney's one-pot cyanoetherification, and optimising the equivalents of TMSCN, we found a set of conditions that effected cyanation in good yield.



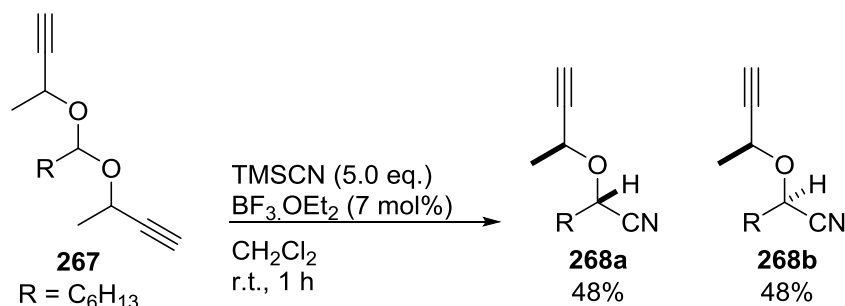
Scheme 4.2.2.1: Cyanation of acetal **267** with TMSCN and Me₂AlCl.

As scheme **4.2.2.1** shows, although there was a considerable amount of eliminated product **285**, the high yield of cyanoethers **268** in a roughly 1 : 1 ratio was promising. However, when repeated and scaled up, it became evident that the yield was highly variable, with the ratio of products **268**, acetal **267** & vinyl nitrile **285** being highly inconsistent. Two other Lewis acid catalysts were trialled, based on literature precedent (scheme **4.2.2.2**).⁸⁸



Scheme 4.2.2.2: Screening of Lewis acid catalysts for cyanation of acetal **267**.

It was found that using either boron trifluoride diethyletherate ($\text{BF}_3 \cdot \text{OEt}_2$) or tin(II) chloride in much lower catalyst loading, cyanide equivalents, temperature and duration, gave the desired cyanoethers **268** with full conversion. The reaction with $\text{BF}_3 \cdot \text{OEt}_2$ proved to be the fastest and so this catalyst was carried forward for optimisation. Although the original aim was to reduce the amount of TMSCN in the reaction for reasons of safety, it was found that 5.0 equivalents gave more reliable results. When moving to the obtusallene system, the reaction scale would be so small as to minimise the risk of using a higher number of equivalents of TMSCN.

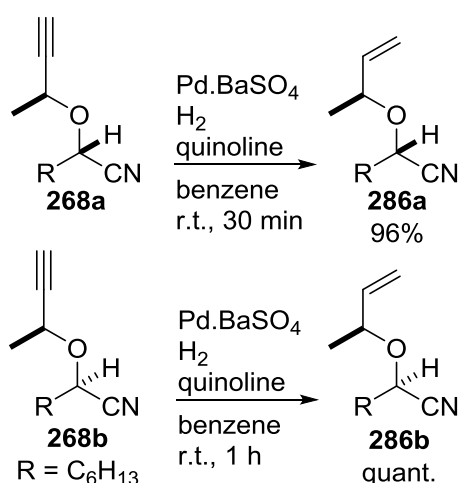


Scheme 4.2.2.3: Optimised cyanation of acetal **267**.

Using 5.0 equivalents of TMSCN with 7 mol% of $\text{BF}_3 \cdot \text{OEt}_2$ at room temperature and a short reaction time of 1 hour, an almost quantitative yield of a cyanoethers **268a** and **268b** could be attained reproducibly. Each diastereomer was collected in a 48% yield. The diastereomers in scheme 4.2.2.3 and all following reactions have been arbitrarily assigned as the stereochemistry of each stereocentre could not be confirmed.

4.2.3 Hydrogenation of Alkynes **268a** & **268b**

Partial hydrogenation was then replicated by the same method as employed by Bonney.⁴⁸

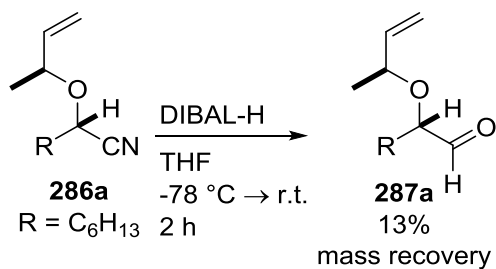


Scheme 4.2.3.1: Partial hydrogenation of alkynes **268a** & **268b**.

Bonney's hydrogenation proceeded as expected, with the only alteration being changing the work-up to include a silica plug and hydrochloric acid wash. This completely removed the catalyst and quinoline, leaving the products analytically pure without need for further purification.

4.2.4 DIBAL-H Reduction of Cyanoethers **286a** & **286b**

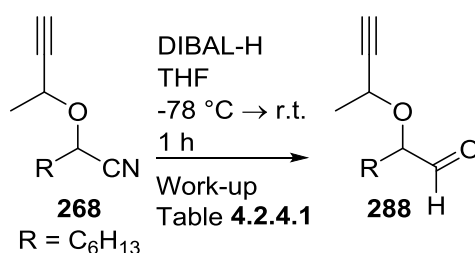
Focus now moved onto replicating the DIBAL-H reduction of the nitrile group, which would be the crucial handle for the installation of a bromoallene.



Scheme 4.2.4.1: Attempted DIBAL reduction of nitrile **286a**.

Treating cyanoethers **286a** & **286b** with DIBAL-H, followed by the tartaric acid work up standard for such reductions, it was found that only a fraction of the intended aldehyde was recovered. Scheme 4.2.4.1 shows a yield of 13%, which was typical for both diastereomers of **286**. Repeated extractions of the aqueous phase yielded no further product. In addition, the peaks in the ¹H NMR spectrum appeared broad, showing that two similar aldehydes were present, suggesting that some epimerisation had occurred and also showed an imine-like peak at 7.45 ppm. The reasons for this were not immediately apparent. Bonney and Yaqoob had similarly found test reactions on the obtusallene system and macrocyclic nitriles **182** & **183**, gave very low isolated yields of between 10 - 15%, but no explanations had been forthcoming. A screen of reduction procedures and work ups was begun, alongside a close analysis of any side-products to determine the reason for such mass loss. The alkynes **268a** & **268b** were found to be more stable during storage and were more resistant to epimerisation than alkenes **286a** & **286b**, so these were used for test reactions.

As we observed significant mass loss in the crude product and the ^1H NMR spectrum showed an unidentified peak at 7.37 ppm, it was presumed that the tartaric acid was not sufficient to hydrolyse the aluminium imine intermediate of the DIBAL-H reduction, meaning a significant amount of material remained in the aqueous layer. Table 4.2.4.1 gives the ranges of work up conditions that were trialled. The ratio of the peaks corresponding to the aldehyde of **288**, its epimer and the imine-like resonance were calculated from the crude ^1H NMR spectrum in each case. In some examples, an aldol-type product was also observed, but it was not possible to isolate or characterise it.

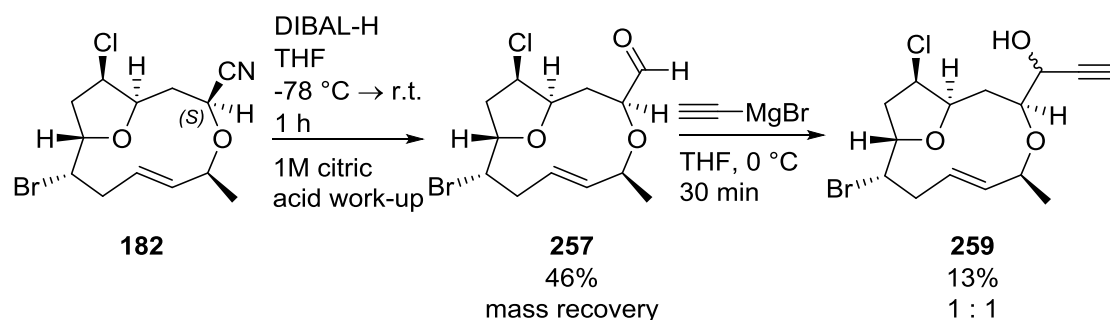


Scheme 4.2.4.2: Attempts at DIBAL-H reduction of alkyne **268**, followed by different work-up reagents.

Entry	Work up Reagent	Aldehyde 288	C ₄ -Epimer	Imine-type Product	Aldol-type Product	Mass recovery / %
A	1M tartaric acid	80	6	14	0	36
B	Rochelle's Salt	0	0	100	0	98
C	2M KOH	51	0	11	38	92
D	Sat. EDTA	100	0	0	0	20
E	1M citric acid	94	0	6	0	58
F	1M malic acid	79	9	12	0	49
G	0.1M EDTA	71	14	15	0	37
H	Silica gel	10	0	18	72	100
I	TFA	44	20	36	0	57

Table 4.2.4.1: Results of DIBAL-H reduction of nitrile **268** with different work-up reagents.

All entries in table 4.2.4.1 were conducted with 1.5 equivalents of DIBAL-H added dropwise at -78 °C and allowed to warm to room temperature over 1 hour. It had been observed previously that the reaction did not proceed if the temperature was maintained at -78 °C or -40 °C. We can see that KOH (entry C) and silica gel (entry H) caused an aldol-type addition, but with good mass recovery. EDTA and TFA caused epimerisation of the ether (entries G & I) and most entries showed the presence of an imine-like product to be present in the crude material. Mass recovery varied considerably, a saturated EDTA work up (entry D) gave exclusively the intended aldehyde **288**, but at only 20% mass recovery. The best option was clearly the citric acid work up (entry E) as it gave a high mass recovery, with minimal amounts of the undesired side-products. This work-up procedure was tested on the real system of obtusallene core nitrile **182** (see section 4.2.8 for synthesis).



Scheme 4.2.4.3: DIBAL-H reduction and acetylide addition to nitrile **182**.

Scheme 4.2.4.3 shows that after submitting nitrile **182** to the DIBAL-H reduction with a citric acid aqueous work up, aldehyde **257** was collected and analysed without further purification. The success of the DIBAL-H reduction was assessed by inspection of the ^1H NMR spectrum of this crude material. There was no evidence of epimerisation at C₄ and the imine-like product only made up approximately 20% of the material (as calculated by ^1H NMR spectroscopy of the crude sample). Mass recovery was only 46% and a second extraction of the aqueous phase yielded no further material. This material was directly submitted for acetylide addition with ethynylmagnesium bromide. After chromatography, only 1.4 mg of an impure 1 : 1 mixture of inseparable propargylic alcohols was isolated, corresponding to a 13% yield. This was similar to the yield observed by Bonney in test reactions of the other nitrile epimer **183**.⁴⁸

Clearly, such a low yield is unacceptable in the late stages of a total synthesis such as this. In order to resolve this issue, the problem with the DIBAL-H reduction needed to be identified to determine the reason for such mass loss.

A DIBAL-H reduction was performed on alkyne **268** with the only work up being a water wash in an attempt to recover as many of the side products as possible. The crude

NMR spectrum showed a much larger imine-like resonance at 7.37 ppm, of a roughly equal integration to that of the aldehyde **268**. This sample was studied with a range of techniques to attempt to identify this unknown compound.

Firstly, the ^1H NMR spectrum showed the imine-like peak presented as a broadened doublet at 7.37 ppm. ^{13}C NMR spectroscopy showed an unidentified peak at 177 ppm. The IR spectrum had a new peak at 1680 cm^{-1} and mass spectroscopy using chemical ionisation displayed two unknown peaks at 226 and 243 m/z . From this, we propose an aluminium-substituted oxazole **289**.

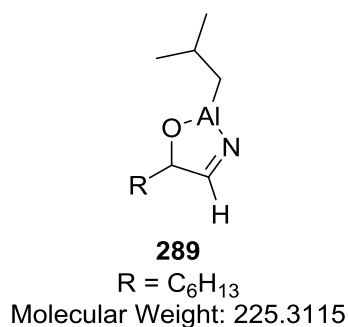


Figure 4.2.4.1: Proposed aluminium oxazole **289**.

Although appearing to be a highly improbable structure, especially as it could withstand acidic work-ups, the molecular weight matches that seen in mass spectroscopy. In addition, the IR peak at 1680 cm^{-1} is indicative of an imine and distinct enough to discriminate from an aldehyde peak. Comparison of the ^1H and ^{13}C NMR spectral data to other known examples, also lends support to our proposal.

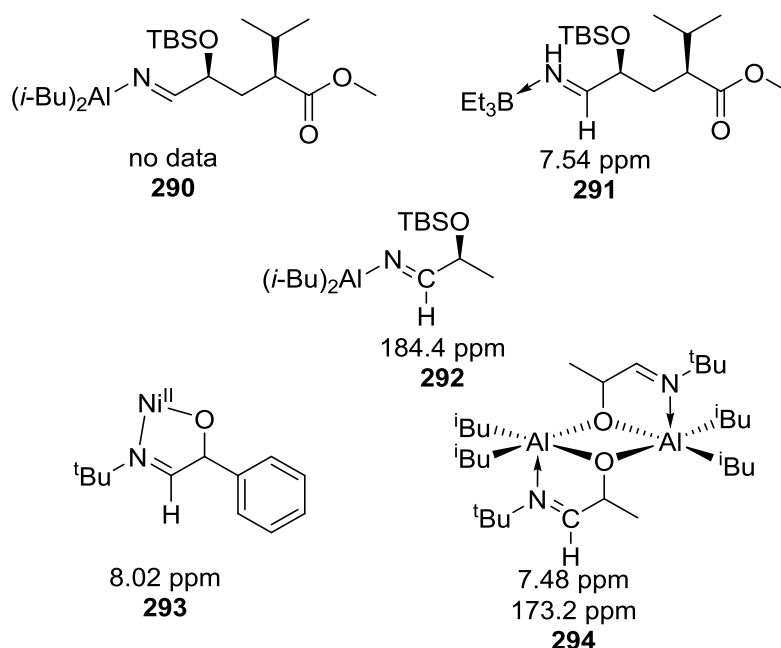
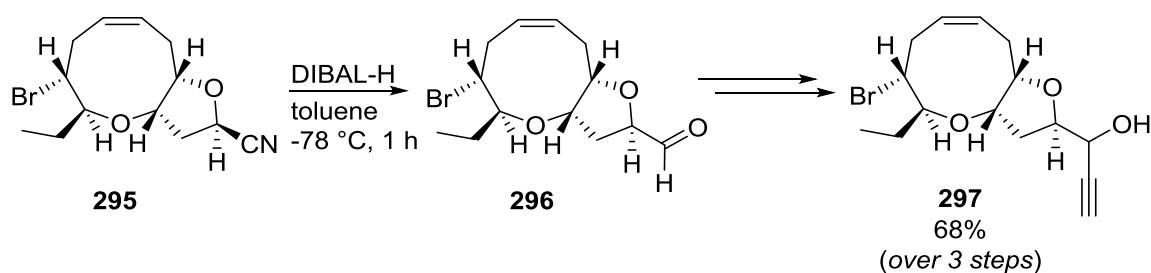


Figure 4.2.4.2: Literature examples of metallated oxazoles.^{73, 89}

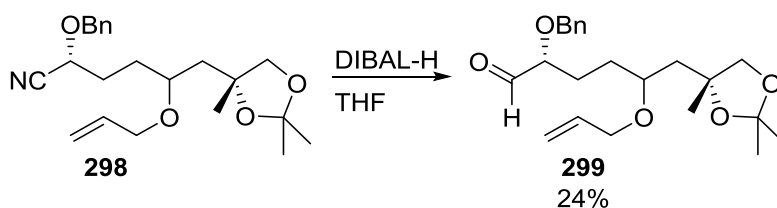
None of the above examples are direct analogues of our proposed side product **289**, nevertheless they show that similar structures are possible. Although none of the procedures used to synthesise the compounds in figure 4.2.4.2 employed acidic work-ups, there is no mention of any attempts to protect them from water (e.g. glove box, anhydrous work-up, etc.) and so it is reasonable to assume that they are fairly stable to hydrolysis. The NMR spectroscopic data, where available, closely matches that seen in side-product **289**.

If aluminium oxazole **289** is indeed the reason for our loss of mass, predicting a mechanism will help to plan ways to prevent its formation. Consultation of the literature reveals a wealth of DIBAL-H reductions of nitriles, and yields of high 80 - 90% are to be expected.⁹⁰ These include the very similar moieties found in other obtusallene natural products, an example is given in scheme 4.2.4.4.



Scheme 4.2.4.4: DIBAL-H reduction of a nitrile, successfully employed in Kim's synthesis of (+)-itomanallene A (**12**).^{53a}

Interestingly, one of the lowest yielding examples that could be found of a DIBAL-H reduction of a nitrile was also the only one containing an allyl ether (scheme 4.2.4.5).⁹¹

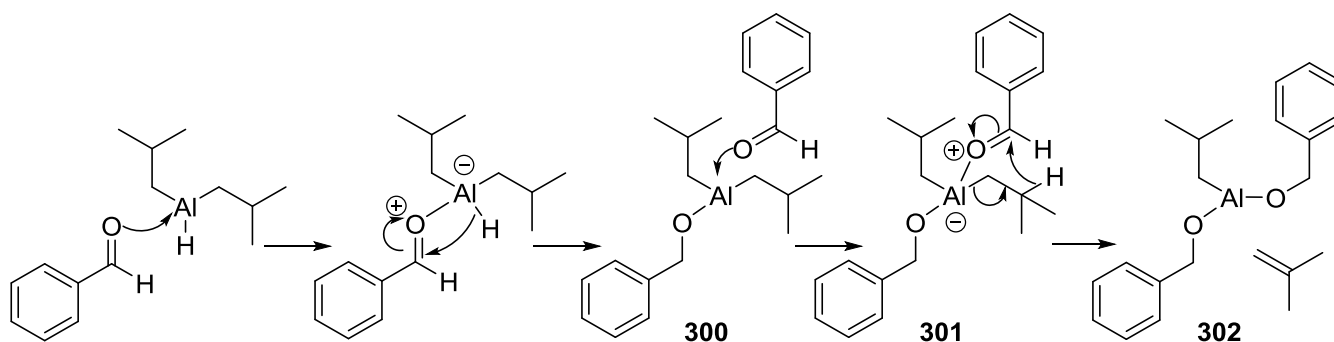


Scheme 4.2.4.5: Literature example of a low yielding DIBAL-H reduction of nitrile **298**.

The authors describe the yield as modest and explain it as being unoptimised. But perhaps it is the presence of the allyl ether that is causing an unexpected side reaction to take place.

It is a common misconception that DIBAL-H reacts with aldehydes and nitriles in a 1 : 1 ratio. Unlike LiAlH_4 , the central metal only has one hydride available for donation. However, with the reagents first use by Ziegler and following investigation by Miller,⁹² it was observed that with certain aromatic aldehydes, one equivalent of DIBAL-H would fully reduce three equivalents of substrate. Effervescence of a gas from these reactions, identified

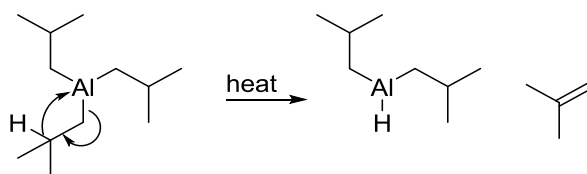
as *tert*butylene, indicated how such super-stoichiometric reactivity was possible (scheme 4.2.4.6).



Scheme 4.2.4.6: β -Hydride elimination from *isobutyl* groups of DIBAL-H, allowing multiple reductions of benzaldehyde.

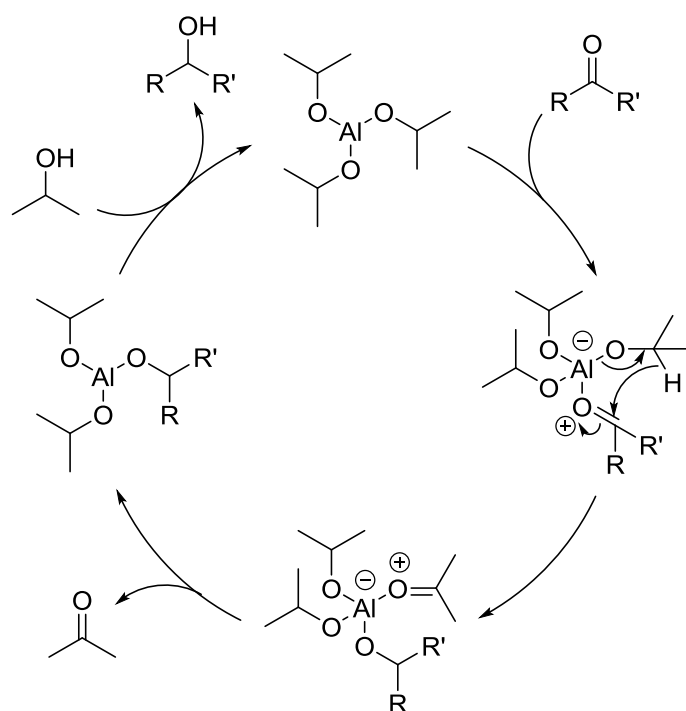
DIBAL-H reductions begin with the coordination of a heteroatom to the aluminium. This imparts a negative charge on the aluminium, making the hydride shift to the carbonyl carbon much more favourable. The resulting aluminium alkoxide **300**, can undergo a second heteroatom coordination. This time however, it is the *isobutyl* hydride that transfers, resulting in an elimination of *tert*butylene from intermediate **301**. The same mechanism can proceed a third time (not shown) before the aluminium trialkoxide is hydrolysed to yield three equivalents of alcohol and aluminium hydroxide.

This β -hydride shift is employed in the synthesis of DIBAL-H, as well as the related Meerwein-Ponndorf-Verley reduction (schemes 4.2.4.7 & 4.2.4.8).⁹³



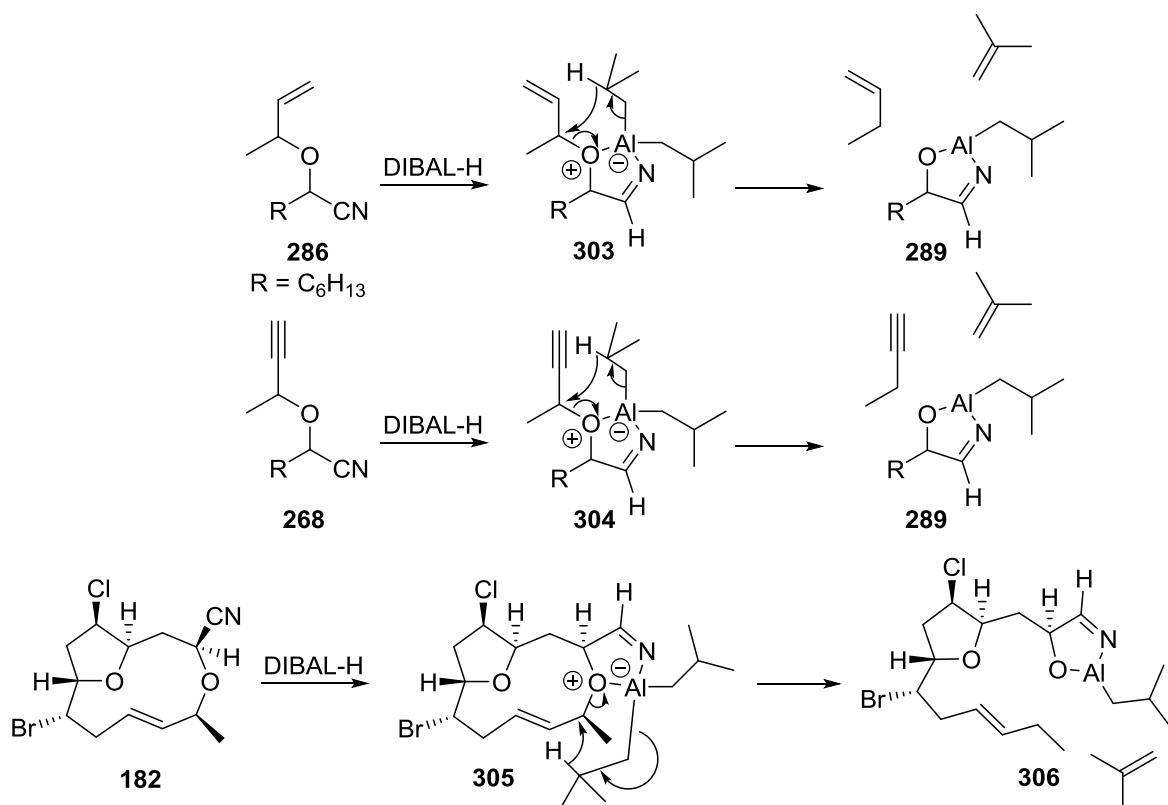
Scheme 4.2.4.7: Synthesis of DIBAL-H from triisobutyl aluminium.

Heating of triisobutyl aluminium results in a β -hydride transfer, elimination of isobutylene and formation of DIBAL-H.⁹⁴



Scheme 4.2.4.8: Catalytic cycle of the Meerwein-Ponndorf-Verley reduction.

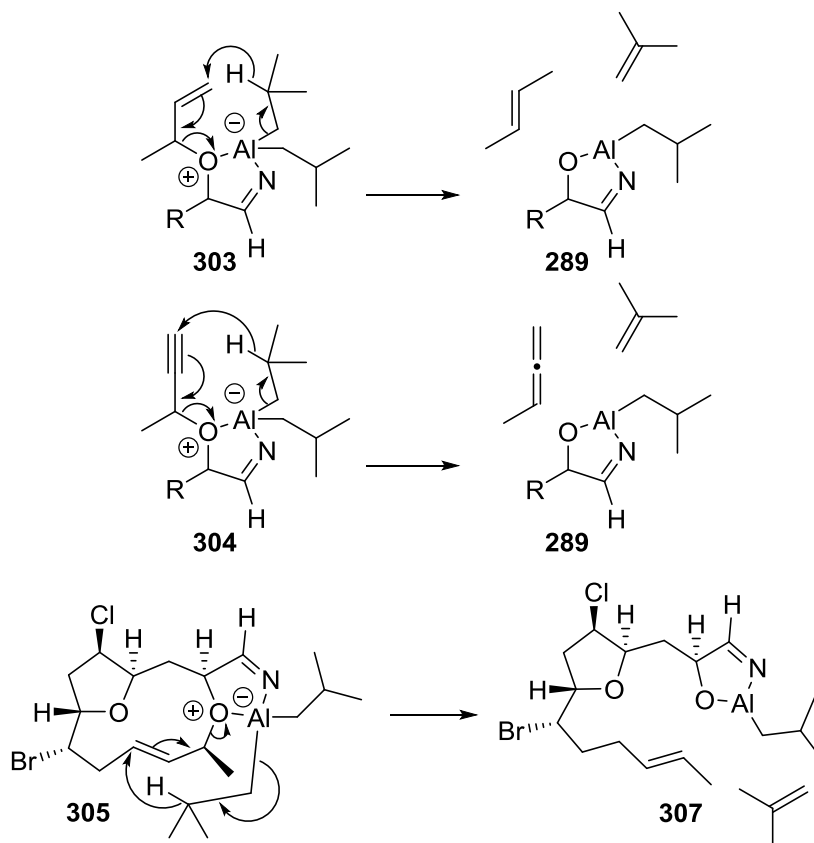
Scheme 4.2.4.8 shows the catalytic cycle of the Meerwein-Ponndorf-Verley reduction employing a similar β -hydride elimination from isopropanol to a ketone.⁹³ Using this information, a possible mechanism for a similar β -hydride shift can be proposed (scheme 4.2.4.9).



Scheme 4.2.4.9: Possible outcomes when treating substrates **286**, **268** & **182** with DIBAL-H.

The reduction of nitriles bearing allylic or propargylic ethers would initially proceed as expected. Coordination of the nitrile to the aluminium and transfer of the metallated hydride may result in intermediates **303**, **304** & **305** with coordination of the ether oxygen to the aluminium. If no further reactivity was possible, these intermediate could be subjected to acidic hydrolysis and the desired aldehydes **287**, **288** & **182** would likely be isolated in satisfactory yields. However, the hydrogen on a DIBAL-H *isobutyl* group may then be appropriately positioned to undergo β -hydride shift, whereby the C-O σ^* bond could undergo S_N2 attack from the *isobutyl* hydrogen, resulting in fragmentation of the compound and generation of *isobutylene* and unsaturated fragments. In the case of model nitrile **286**, 1-butene is the probable liberated product. For alkyne model **268**, this extruded compound is

predicted to methyl 1-butyne. Lastly, for obtusallene system **182**, the molecule undergoes opening of the macrocycle. An S_N2 attack is invoked in scheme 4.2.4.9, although it is certainly possible that a similar fragmentation can be achieved *via* S_N2' attack through the allylic or propargylic π -bonds. The outcome of such an attack is shown in scheme 4.2.4.10.



Scheme 4.2.4.10: Possible alternative fragmentation mechanisms *via* S_N2' hydride attack.

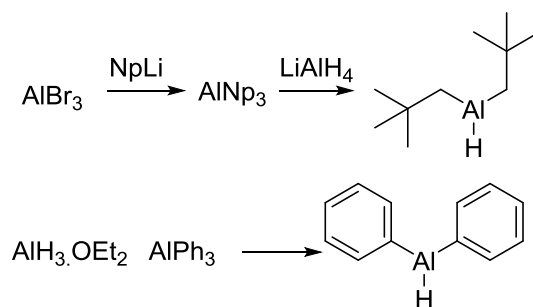
If this was the case, the unsaturated fragments would be 2-butene and methyl allene for substrates **286** & **268** respectively and would result in olefin migration in macrocycle **182**, as shown in scheme 4.2.4.10. This may be used in future studies to distinguish between the two mechanisms. It is known in the literature that allylic groups accelerate the rate of S_N2

attack *via* the electron withdrawing properties of sp^2 carbons,⁹⁵ and such a mechanism gives a 6-membered cyclic intermediate, so we will propose S_N2 to be the most likely.

We can see that some of the mass loss is *via* evolution of fragmented C_4 gases in model systems 286 & 268, but it is also possible that the aluminium oxazoles are water soluble, preventing them being extracted during work up. Alternatively, the acidic work may hydrolyse the metallated species, resulting in α -hydroxy aldehydes that are known to rapidly cyclise and polymerise.⁶⁹ This may be a further reason for the lack of mass recovery.

4.2.5 Alternatives to DIBAL-H Reduction

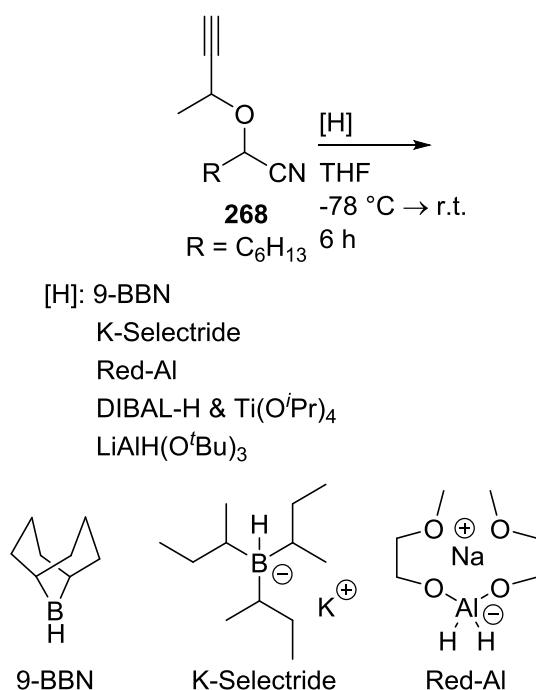
If the β -hydride shift was indeed the source of this problem, this could be ameliorated by employing reducing agents lacking β -hydrogens. Initial thoughts were *dineopentylaluminium hydride* and *diphenylaluminium hydride*.



Scheme 4.2.5.1: Possible routes to alternative aluminium hydrides.

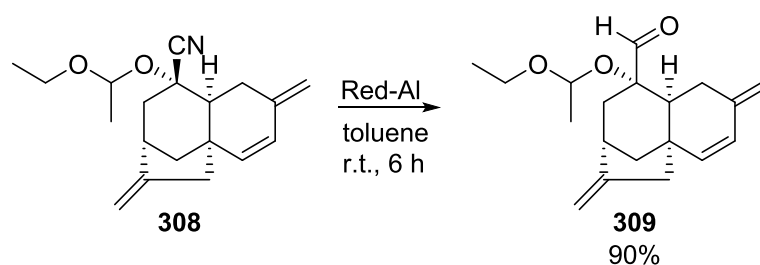
Syntheses for these compounds already exist and are shown in scheme 4.2.5.1,⁹⁶ but the reagents are costly, sensitive to air and water, and the products highly flammable. We did not have the experience or equipment to make these custom reducing reagents. We instead looked to some existing, commercially available reducing agents, the results of

which are shown in scheme 4.2.5.2. Most of the reagents below have β -hydrogens, but it was hoped that the differing sterics and electronics would alter the likelihood of hydride transfer.



Scheme 4.2.5.2: Screening of other reducing agents with nitrile **268**.

Firstly, a K-Selectride reduction was trialled on nitrile **268**. Although not a traditional reagent for nitrile reductions, there exists some literature precedent with high yield.⁹⁷ This reagent and substrate resulted in no reaction however. The similar reagent 9-BBN had no literature precedent for nitrile reductions, but was tested anyway. In this case, trace amounts of aldehyde were seen, accompanied by some olefin peaks, suggesting that hydroboration had taken place. Red-Al had a much greater number of successful nitrile reductions reported in the literature, including in the below reduction of cyanoether **308**, a precursor to platensimycin.⁹⁸

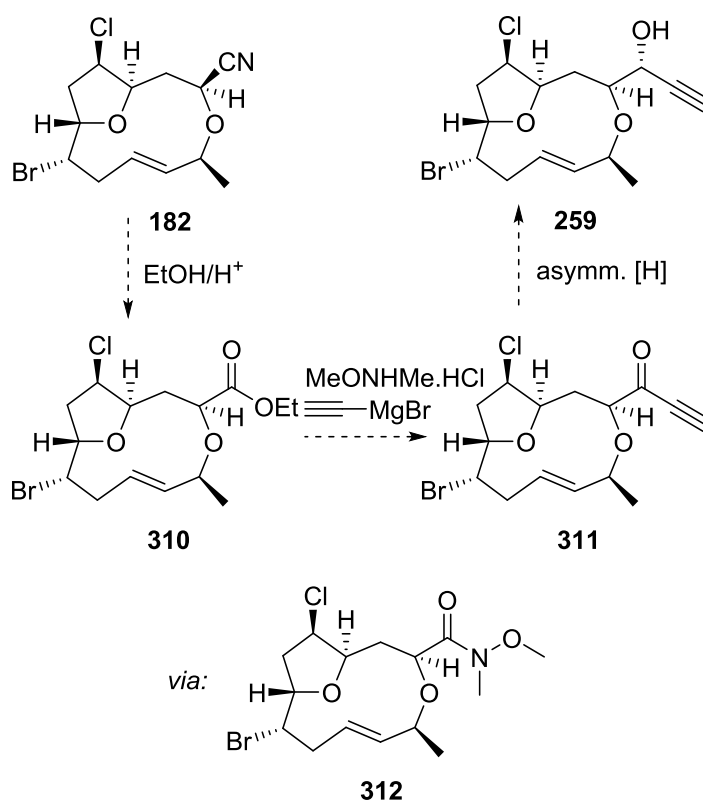


Scheme 4.2.5.3: Successful use of Red-Al in the synthesis of platensimycin analogues.

Unfortunately, Red-Al produced the greatest amount of aluminium oxazole yet seen in any of these reductions. Most likely due to the two β -hydrogens allowing Meerwein-Ponndorf-Verley-type reduction to proceed (scheme 4.2.4.8).

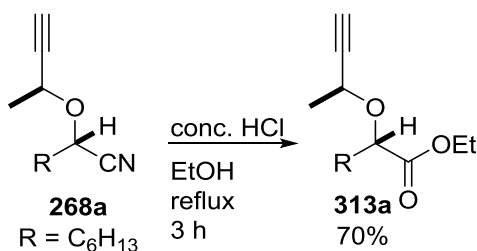
The DIBAL-H reduction of alkyne **268** was repeated with titanium tetraisopropoxide ($\text{Ti}(\text{O}^i\text{Pr})_4$) in an attempt to prevent the chelation of the ether oxygen to the aluminium in intermediate **304**. However, this resulted in very similar ratios of imine-like products as seen without any additive, only a much lower conversion. Lastly, lithium tritertbutoxy aluminium hydride was employed. Having no β -hydrogens, it was hoped that no fragmentation would take place. But after 24 hours and heating to reflux, no reaction was observed.

Reduction of the nitriles was abandoned in favour of different functional group interconversions. Attention was turned to an acid catalysed solvolysis, which could be applied to the nitriles of **182** & **183**, followed by Weinreb amide formation and acetylide addition.



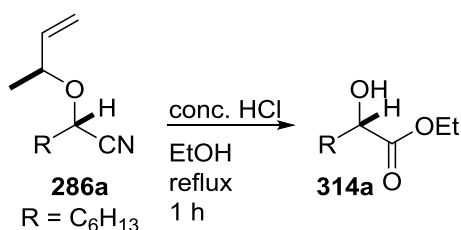
Scheme 4.2.5.4: Proposed ethanolyis and Weinreb amide route of nitrile **182**.

Successful ethanolyis of the nitrile in macrocycle **182**, would give ethyl ester **310**. From here, *N,O*-dimethylhydroxylamine (MeONHMe) could be introduced. The resulting Weinreb amide (**312**) is a necessary intermediate, as chelation of magnesium prevents over addition to a *bis*propargylic alcohol. Procedures were found that employed Grignard reagents as activators for the Weinreb amine, allowing a simultaneous acetylide addition.⁹⁹ This would facilitate direct access to propargyl ketone **311**, where it might be possible to submit to an asymmetric reduction to give propargylic alcohol **259**, with the correct stereochemistry to lead to obtusallene II (**15**).



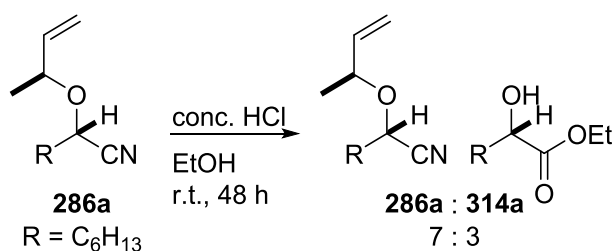
Scheme 4.2.5.5: Ethanolysis of nitrile **268a**.

Alkyne model system **268** (scheme 4.2.5.5) was employed first, due to its observed greater stability than alkene analogue **286**. Refluxing nitrile **268a** in ethanol with hydrochloric acid gave ester **313a** in good yield. The same reaction was attempted with just acetyl chloride in ethanol to generate HCl *in situ*, but the yield was not as high and olefin side products began to dominate. With a promising initial result, the same procedure was applied to alkene **286a** (scheme 4.2.5.6).



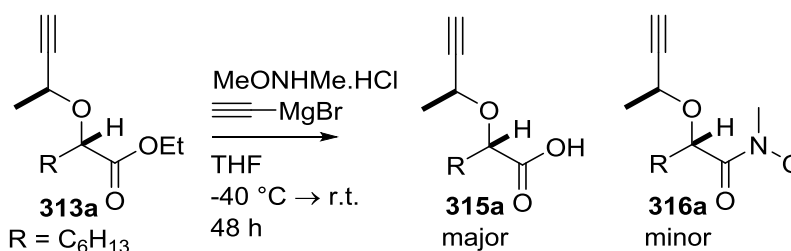
Scheme 4.2.5.6: Ethanolysis of alkene **286a**.

Although under these conditions, the nitrile was successfully converted to the ester, there was simultaneous cleavage of the allyl ether group to give alcohol **314a**. The reaction was repeated at a room temperature for 48 h.



Scheme 4.2.5.7: Ethanolysis of alkene **286a** at room temperature.

Scheme 4.2.5.7 shows that at a lower temperature, the reaction did not go to completion. ^1H NMR spectroscopy of the crude product showed that the only product was again alcohol **314a**. For completion, alkyne **313a** was submitted for the Weinreb ketone synthesis to determine if this would be a valid possibility (scheme 4.2.5.8).

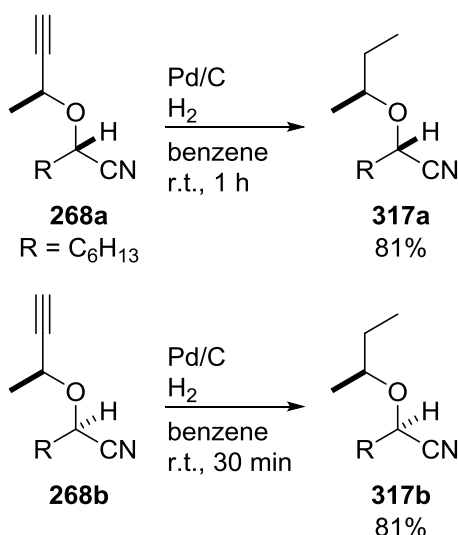


Scheme 4.2.5.8: Attempted Weinreb ketone synthesis of alkyne **313a**.

This reaction produced mostly acid **315a** and but with small amounts of another compound, tentatively assigned as Weinreb amide **316a**. This route was abandoned in favour of attempts to protect the olefin.

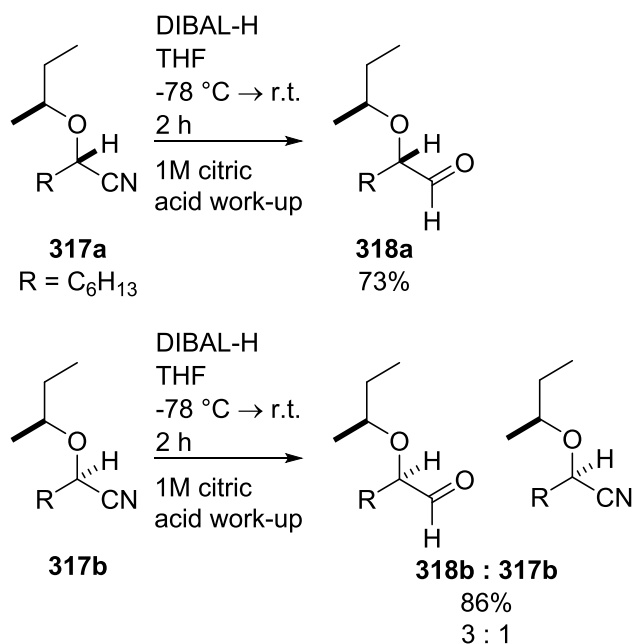
4.2.6 Further Investigation Into the Sensitivity of the Cyanoether Group to DIBAL-H

With all attempts at bypassing the DIBAL-H reduction having failed, methods of minimising the sensitivity of the allyl ether to hydride transfer and fragmentation were sought. Firstly, to get absolute confirmation of the role of this group in the fragmentation, two new model systems were generated. The first of which were the fully hydrogenated compounds **268a** & **268b**.



Scheme 4.2.6.1: Complete hydrogenation of alkynes **268a** & **268b**.

Scheme 4.2.6.1 shows that by removing the quinoline and switching the palladium support to carbon, the alkynes of **268a** & **268b** could be fully reduced to aliphatic compounds **317a** & **317b**. These compounds could be subjected to identical DIBAL-H reduction conditions.

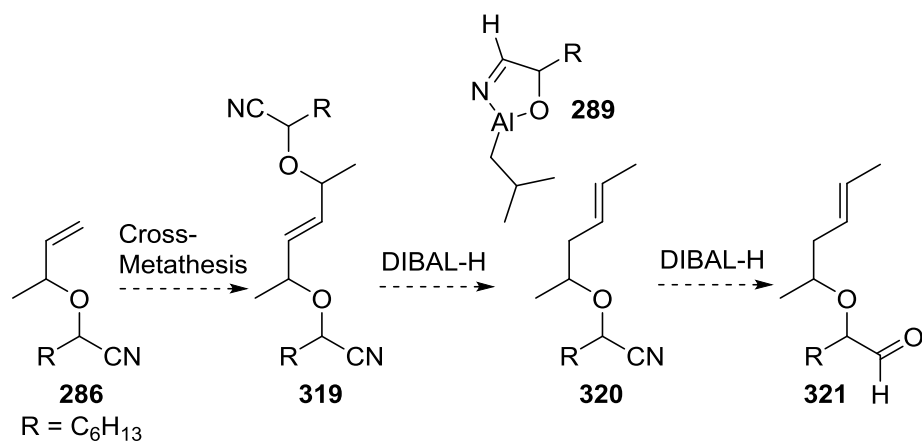


Scheme 4.2.6.2: DIBAL-H reduction of aliphatic nitriles **317a** & **317b**.

Both nitriles **317a** & **317b** were subjected the established DIBAL-H reduction procedure, with a citric acid work-up. The yields given in scheme 4.2.6.2 are based upon the recovered mass and ^1H NMR spectra of the crude materials. Chromatography was not conducted due to the sensitivity of aldehydes **318a** & **318b**. Even so, the crude material was collected in high yield, was very clean and would certainly have been suitable for direct submission to the acetylide addition. There were very minor peaks observed at 7.37 ppm which could be assigned as aluminium imine chelates. When taken with the high mass recovery, it strongly suggests that the lack of an allyl group significantly slowed the rate of direct $\text{S}_{\text{N}}2$ hydride transfer and fragmentation.

Attempts were now made to isolate the products of fragmentation to confirm the mechanism. It had previously been postulated that the products of fragmentation will be low molecular weight olefins, alkynes or allenes (scheme 4.2.4.9) and would be lost to evaporation. The aim was to produce substrates for DIBAL-H reduction that would

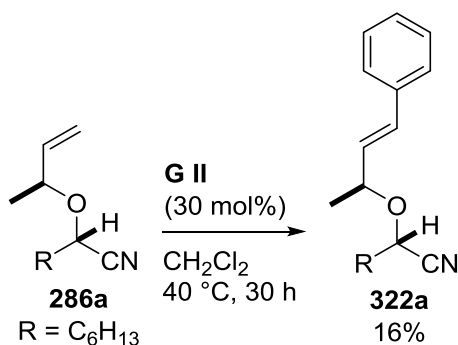
fragment in such a way to allow observation by NMR spectroscopy. The first such substrate and its synthesis is shown in scheme 4.2.6.3.



Scheme 4.2.6.3: Proposed metathesis of olefin **286** and DIBAL-H reduction of dimer **319**.

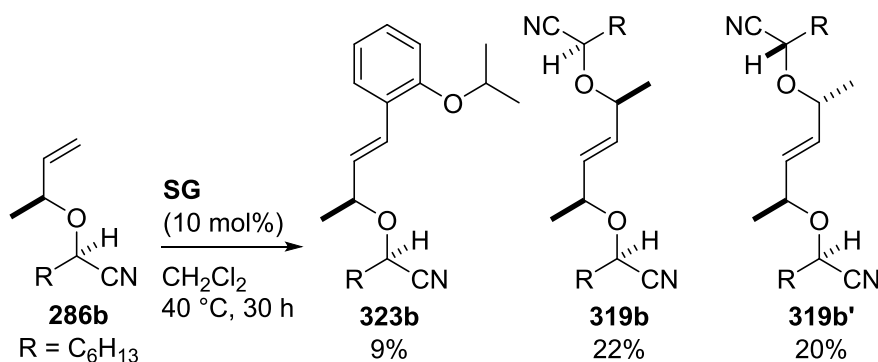
If the undesired reaction pathway was *via* an S_N2' hydride attack to the allyl group, with migration of the olefin, dimer **319** would be an informative substrate. It was reasoned that if dimer **319** was subjected to the DIBAL-H procedure, a single nitrile would first be reduced, possibly resulting in fragmentation to previously proposed aluminium oxazole **289** & homoallylic ether **320**. This new compound would probably not be susceptible to the same fragmentation and, after a reduction of the second nitrile reduction to give aldehyde **321**, could potentially be isolated and characterised.

Accordingly, olefin **286a** was subjected to an cross-metathesis procedure with the full range of Grubbs' catalysts in an attempt to produce dimer **319a**.¹⁰⁰ The only results of interest were with Grubbs' 2nd generation (**G II**) & Stewart-Grubbs' (**SG**) catalysts.¹⁰¹



Scheme 4.2.6.4: Attempted cross-metathesis of olefin **286a** using Grubbs' 2nd generation catalyst.

Treatment with Grubbs' 2nd generation catalyst gave none of the intended dimer **319a**, but instead a small amount of the styrene metathesis compound **322a**, shown in scheme 4.2.6.4. This signifies that the cross-metathesis reaction initiates with a metathesis of the styrene alkylidene present on the catalyst. It would appear that the reaction terminates at this point, as no other products were observed.

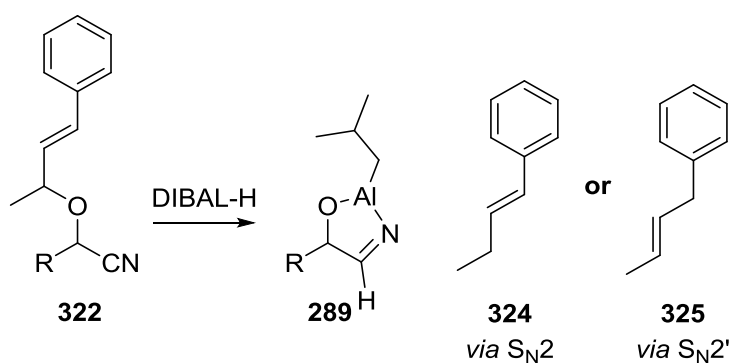


Scheme 4.2.6.5: Attempted RCM dimerisation of olefin **286b** using Stewart-Grubbs' catalyst.

Next, the more active Stewart-Grubbs' catalyst was trialed and the results shown in scheme 4.2.6.5. Again, after prolonged heating of Stewart-Grubbs' catalysts with olefin **286b**, similar aromatic metathesis compound **323b** was observed. Although the desired dimer

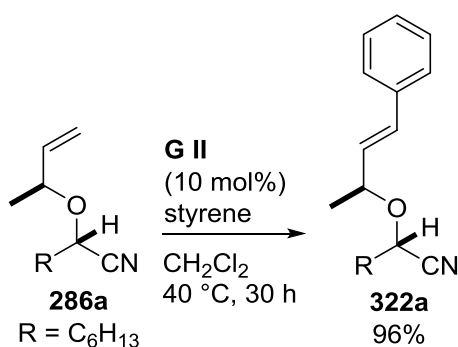
319b was isolated in moderate yield, as the compound now has four stereocentres, it was difficult to assign the ^1H NMR spectra and to assess purity. As before, the relative stereochemistries are arbitrary. If the DIBAL-H reduction was performed, any of the homoallylic products (**321**) could probably not be unambiguously assigned.

Instead, it was decided to repeat the reaction with Grubbs' 2nd generation catalyst with the inclusion of six equivalents of styrene. This would promote the formation of aromatic product **322a**, which would be a more suitable substrate to observe any fragmentation.



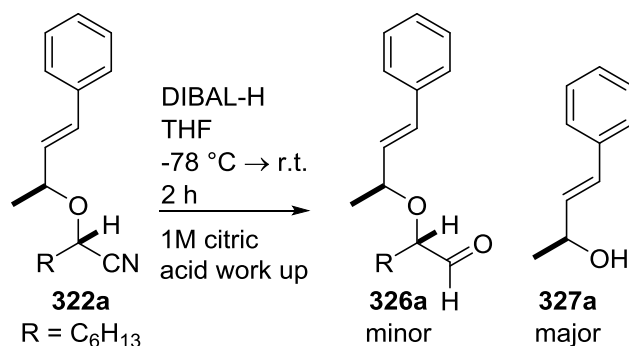
Scheme 4.2.6.6: Fragments proposed to result from the DIBAL-H reduction of nitrile **322**.

The product of fragmentation would be 1-butenylbenzene (**324**) if the mode of rearrangement was *via* $\text{S}_{\text{N}}2$ and 2-butenylbenzene (**325**) if *via* $\text{S}_{\text{N}}2'$ (scheme 4.2.6.6). With both compounds having a boiling point of over 180 °C, they should be possible to isolate and characterise.¹⁰²



Scheme 4.2.6.7: Cross-metathesis of olefin **286a** with **G II** & styrene.

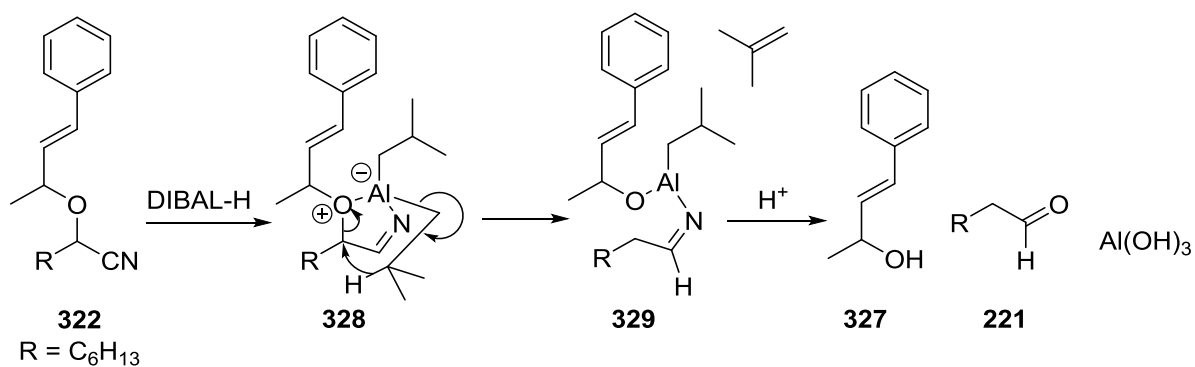
By employing additional styrene in the cross-metathesis (scheme 4.2.6.7), aromatic olefin **322a** was successfully isolated in 96% yield as a single diastereomer and exclusively the *E*-isomer, along with a large amount of 1,2-diphenylethene. Fortunately, they proved to be readily separable and compound **322a** could be submitted to the DIBAL-H reduction.



Scheme 4.2.6.8: Products of the DIBAL-H reduction of aromatic olefin **322a**.

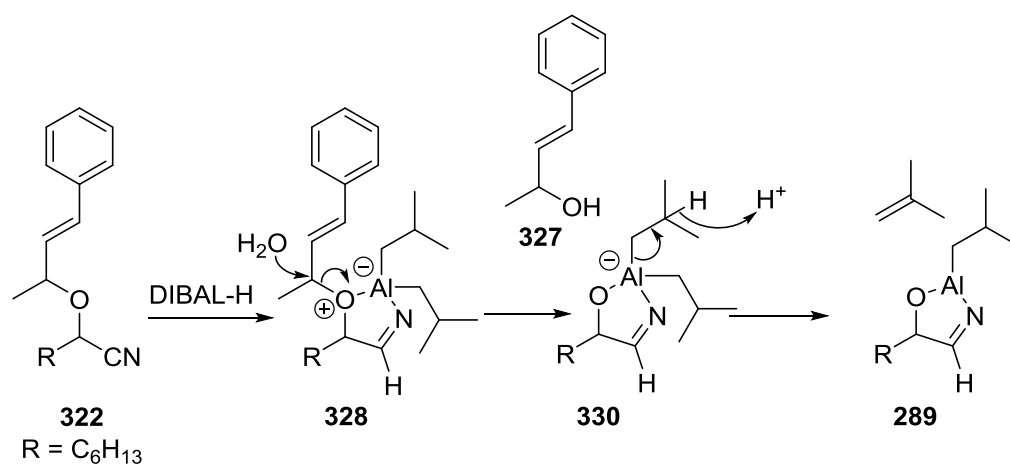
Aromatic olefin **322a** was submitted to the DIBAL-H reduction with an aqueous citric acid work up (scheme 4.2.6.8). At the completion of the reaction, it was found that a trace amount of aldehyde **326a** was produced. The bulk of the crude mixture was aromatic allyl alcohol **327a**, with the data matching perfectly with literature values.¹⁰³ It is possible

that the aromatic group protects the olefin, either sterically or by altering the electronic properties. This could allow a second fragmentation pathway to proceed.



Scheme 4.2.6.9: Alternative fragmentation pathway upon DIBAL-H reduction of aromatic olefin **322**.

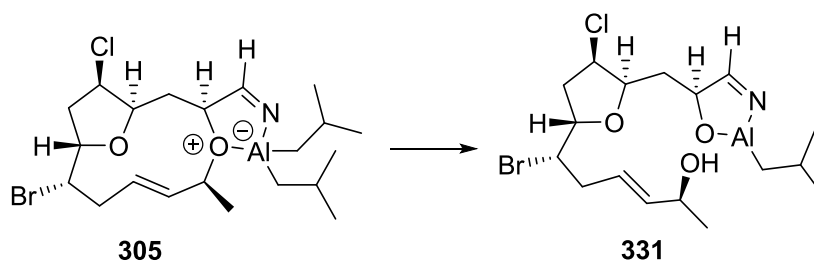
After the formation of aluminium chelate **328**, a second hydride transfer may be possible to the α -carbon. If correct, after work up this would yield allyl alcohol **327** & octaldehyde **221**. However, no octaldehyde (**221**) was observed in the crude ^1H NMR spectrum. It is possible that it may have been lost *in vacuo*, but with a boiling point of 170°C and a tendency for such aldehydes to be visible in trace amounts due to the distinct resonance at 10 ppm, this seems unlikely. An alternative explanation may be that it is the water added during work up that initiates the fragmentation.



Scheme 4.2.6.10: Possible alternative hydrolysis of aluminium chelate **328**.

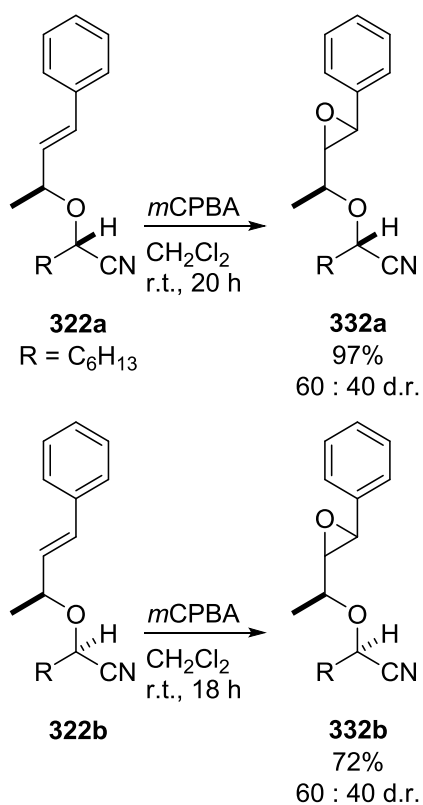
If scheme **4.2.6.10** is correct, the allylic ether carbon is activated enough to make S_N2 attack of water a possibility. This would yield aluminium oxazole **289**, observed in the DIBAL-H reduction of alkyne **268**, as well as the aromatic allyl alcohol **327**, seen in scheme **4.2.6.8**. When considering alkyne and alkene nitriles **268** & **286**, we would expect the side-products of the above reaction to be 3-buten-2-ol or 3-buten-2-ol. Both of these compounds have boiling points of around 100 °C, so may be lost during solvent removal.

If this mechanism is the source of failure in the DIBAL-H reduction of macrocyclic nitriles **182** & **183**, this would make the fragmented aluminium oxazole **331** in scheme **4.2.6.11** our side-product. Although we are not able to positively identify it in any of the crude ¹H NMR spectra.



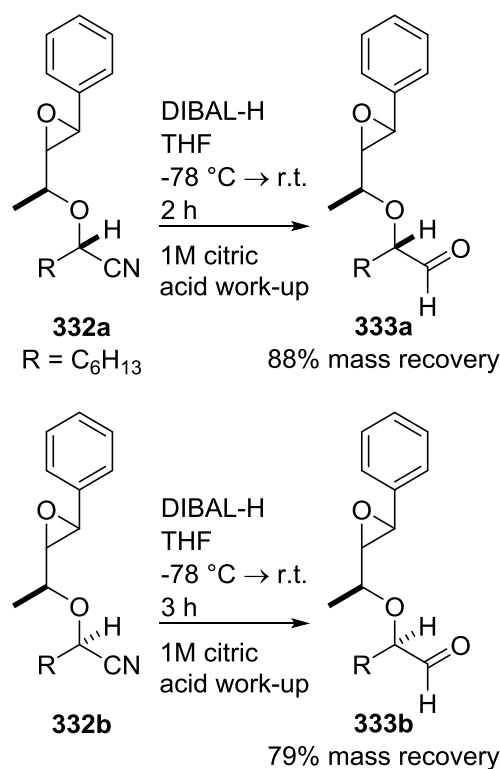
Scheme 4.2.6.11: Fragmented aluminium oxazole **331**, the proposed product upon DIBAL-H reduction of nitriles **182** & **183**.

It was then concluded that the allyl ether group was the cause of the DIBAL-H reduction failure and further work on pursuing this route was abandoned. Aromatic olefin **322** was instead used to investigate a method of protecting the double bond as an epoxide. This route would potentially allow the DIBAL-H reduction to safely proceed in the absence of the sensitive allyl ether group. When applied to the macrocycle of **182** & **183**, it could be followed by derivation to marilzabicycloallene core natural products, or potentially deoxidised to reveal the olefins of obtusallenes II & IV (**15** & **19**) (*vide infra*, sections 4.2.15). Epoxidation was achieved with the use of *m*CPBA.



Scheme 4.2.6.12: Epoxidation of aromatic olefins **322a** & **322b**.

Epoxidation of both olefins **322a** & **322b** with *m*CPBA, as shown in scheme **4.2.6.12**, proceeded in high yield. As new stereocentres had been introduced, the epoxides were collected as mixtures of diastereomers, but could be clearly identified by ^1H NMR spectroscopy. This substrate was subjected to the DIBAL-H reduction procedure, with aqueous citric acid work up (scheme **4.2.6.13**).

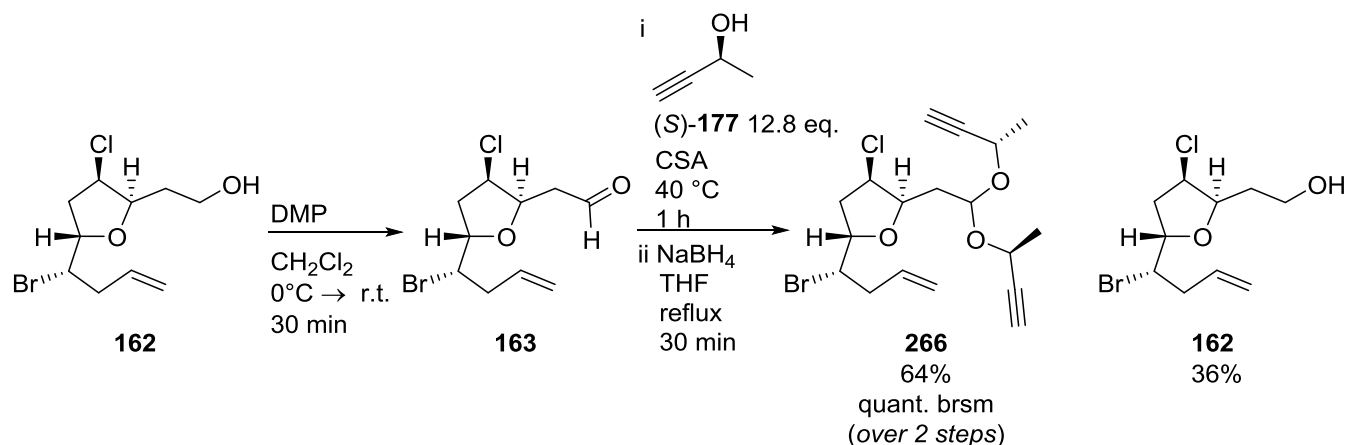


Scheme 4.2.6.13: DIBAL-H reduction of epoxides **332a** & **332b**.

Aldehydes **333a** & **333b** were collected with an excellent mass recovery of 88% and 79% respectively. The material was not chromatographed as similar aldehydes had proven to be sensitive to silica. There was no sign of fragmentation products, such as aluminium oxazoles or epoxy alcohols. With this result, and that of aliphatic substrate **317** (scheme 4.2.6.2), strong evidence had been provided that the allyl group was the issue in this reaction and that removing or masking it would be the solution. This allowed work to start on epoxidising macrocycles **182** & **183** with a view to producing marilzabicycloallenes. The reactions optimised in sections 4.1.1-4.1.3 to progress alcohol **162** to dienes **180** & **181** were applied to the obtusallene system.

4.2.7 Synthesis of Dienes 180 & 181

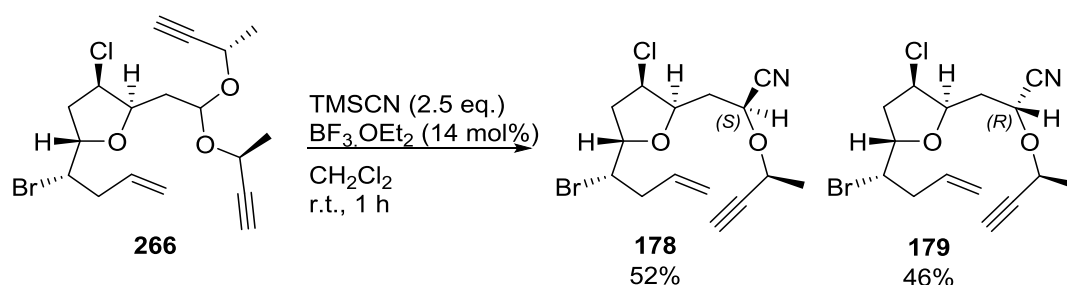
Now that a reliable route to install cyanide, hydrogenate the alkyne had been found and experience with metathesis reactions had been gained, the previously optimised procedures were applied to starting alcohol **162**.



Scheme 4.2.7.1: Dess-Martin oxidation and acetalisation of alcohol **162**.

As shown in scheme **4.2.7.1**, alcohol **162** could be oxidised with DMP and purified by flushing through a silica plug to give a pure product in quantitative yield. Aldehyde **163** was then directly submitted for acetalisation with enantiopure alcohol (S)-**177** and a catalytic quantity of CSA. Quenching with NaBH_4 allowed acetal **266** to be collected in 64% yield, but more importantly, also returned alcohol **162** in a 36% yield, both of which were easily separable. After recycling of alcohol **162**, this meant the two step procedure was essentially quantitative, based on recovered starting material. Although it required multiple repeats of both reactions, the entirety of alcohol **162** was oxidised and acetalised to give 1.69 g (4.17 mmol) of acetal **266**.

The twin alkyne peaks at 2.42 & 2.46 ppm were distinct enough to show that one major diastereomer was present, suggesting that epimerisation of alcohol (*S*)-**177** was not taking place under these acidic conditions. Some very minor peaks were seen in close proximity to the alkyne signals and methyl signals. These are most likely the diastereomeric compound arising from the enantioselective epoxidation of precursor triene **156** (discussed in section 4.2.8). With this early success, the cyanation protocol previously developed was applied to acetal **266**.

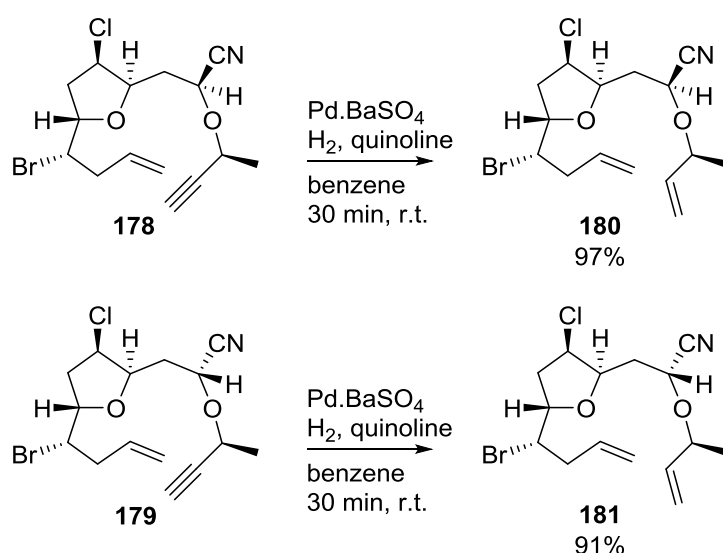


Scheme 4.2.7.2: Cyanation of acetal **266** using TMSCN and BF₃·OEt₂.

Scheme 4.2.7.2 shows that treatment of acetal **266** with TMSCN and BF₃·OEt₂ was successful in replacing one of the ethers with a nitrile group. The stereochemistry at C₄ was assigned by comparison of the NMR spectra with those obtained by Solanki and Bonney.^{42, 48} After multiple repeats of this reaction were performed, it was discovered that the quantity of TMSCN could be halved if the amount of BF₃·OEt₂ was doubled. With these conditions, nitriles **178** & **179** could be produced in a 52% and 46% yield respectively, or 98% combined. As the two previous reactions (scheme 4.2.7.1) were quantitative, this compares very well to Bonney's yield of 23% and 43% for nitriles **178** & **179** from alcohol **266**. More importantly, these optimised reaction were reliable, repeatable and scalable, without risk of generating

the side-products created in the one-pot cyanoetherification (scheme 4.1.1.1). After all of the material produced in the above optimised reactions was combined, a total of 602 mg (1.66 mmol) of **178** and 668 mg (1.85 mmol) of **179** was available for partial hydrogenation to prepare acyclic diene substrates **180** and **181** for optimisation of the RCM reaction. In addition, a further 300 mg (0.827 mmol) of diene **180** was already on hand, as it had been unused and handed down from Bonney's studies.

The alkynes of **178** & **179** were then hydrogenated to prepare the RCM precursors **180** & **181** respectively.



Scheme 4.2.7.3: Hydrogenation of alkynes **178** & **179**.

Replicating Bonney's established conditions of catalytic hydrogenation using palladium on barium sulfate, poisoned with quinoline (scheme 4.2.7.3), pleasingly gave yields above 90% for both dienes **180** & **181**. The only modification to Bonney's procedure was the inclusion of a silica plug work up to remove the catalyst and quinoline, meaning that the product dienes often required no purification. However, it was observed that when

a new batch of Pd.BaSO₄ was used, yields could drop below 70% unless great care was taken by constant monitoring by TLC. The source of yield loss was over-reduction of the C₁₂,C₁₃ olefin, shown in figure 4.2.7.1, which proved to be challenging to remove by column chromatography. This structure of these compounds was assigned based on ¹H NMR spectroscopy. The resonances matched exactly with their diene counterparts, except for those corresponding to the C₁₂,C₁₃ olefin, and newly appearing methylene and methyl peaks. These compounds could be isolated as pure substances, but only as mixtures with their parent dienes, **180** & **181**. The ratio of the two could be calculated by measuring the under integration of the relevant olefin peaks.

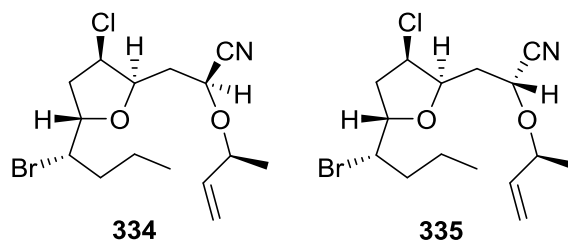


Figure 4.2.7.1: Over hydrogenated side-products **334** & **335**, found after hydrogenation.

Using older catalyst was to our advantage, as presumably the lower activity slowed the reaction sufficiently to prevent over-reduction. It appeared that nitrile **181** was more prone to over-reduction, for reasons unknown. We observed it to have a much larger proportion of the unwanted side-product, and may reflect why Bonney only found 65% yield for this reaction.

4.2.8 Grubbs' RCM of Dienes **180** & **181** to Form Obtusallene Core Macrocycles **182**

& **183**

With both RCM precursors prepared, a trial of the various Grubbs' catalysts was begun.

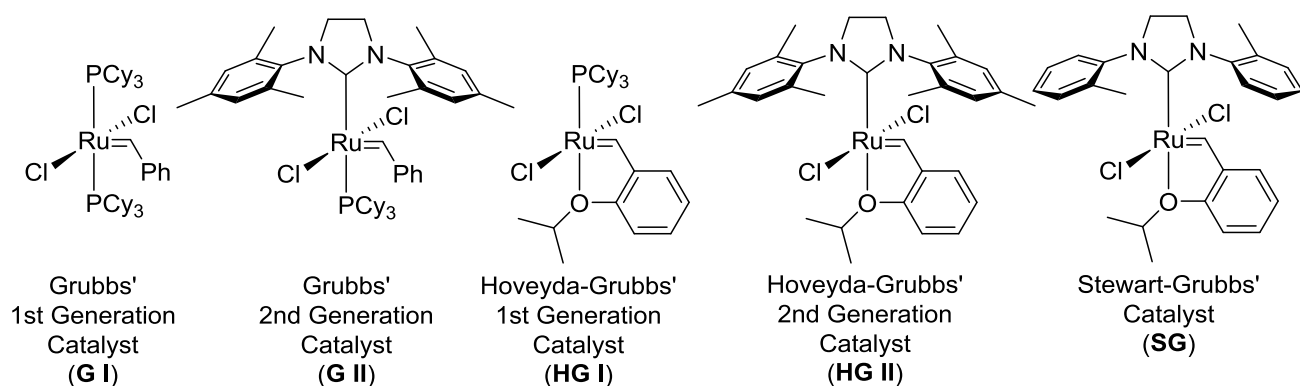
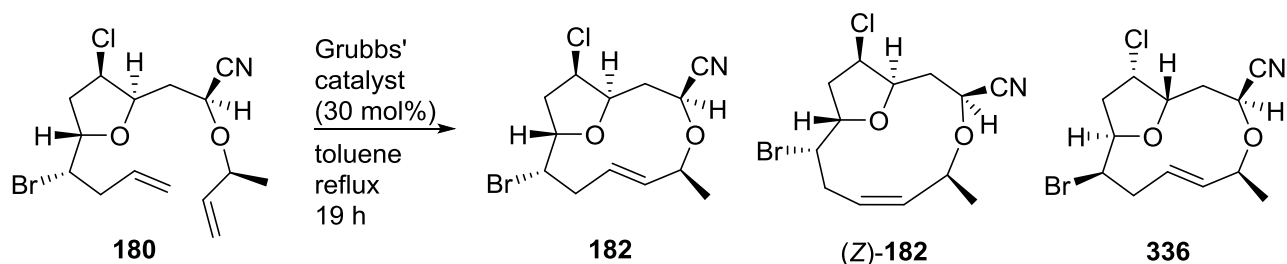


Figure 4.2.8.1: Grubbs' catalysts employed in the RCM of dienes **180** & **181**.

Diene **180** was the first substrate to be investigated. Bonney and Yaqoob had previously attempted cyclisation of this substrate with Stewart Grubbs' & Hoveyda Grubbs' 2nd generation catalysts and found that (*Z*)-**182** predominated (scheme 4.2.8.1), so these catalysts were not considered. In order to encourage macrocyclisation and prevent dimerisation, the concentration was kept very low. The concentration determined by Bonney and Yaqoob was 0.4 mM. For the sake of these test reactions, this equated to the use of 20 mg of diene **180** or **181** in 150 mL of toluene.



Scheme 4.2.8.1: RCM of diene **180** and observed macrocyclic products.

Refluxing diene **180** in toluene with 30 mol% of catalyst gave **182**, (*Z*)-**182** & what was tentatively assigned to be (6,7,9,10)-diastereomeric compound **336** (*vide infra*), as well as some recovered starting material, in varying ratios as shown in table 4.2.8.1. Grubbs' 1st generation catalyst gave a low yield of **182** and an almost equal quantity of (*Z*)-**182**. Hoveyda Grubbs' 1st generation catalyst gave a much more favourable yield of **182**, with small amounts of (*Z*)-**182** & diastereomer **336**.

Catalyst	Yield 182 / %	Yield (<i>Z</i>)- 182 / %	Yield 336 / %	Recovery 180 / %
G I	16	11	6	60
HG I	44	22	5	29

Table 4.2.8.1: Results of the RCM screening of Grubbs' catalysts with diene **182**.

Previously, Bonney had found only an 11% yield using Hoveyda Grubbs' 1st generation catalyst and similar conditions. It was promising to find an initial yield of 44%, but the large amount of (*Z*)-**182** was a concern. Successive attempts would give different ratios of the above compounds. It was reasoned that it may be related to the quantity of water present in the reaction. The toluene used for the above reaction was from the solvent

drying towers, maintained by the technicians at Imperial College. Karl Fischer testing, regularly performed by the technicians, showed the amount of water in toluene to occasionally reach as high as 6 ppm. This is approximately 1 μ L of water present in the volume of toluene employed for the high dilution reaction as performed. Add to this any water present in the substrate and catalyst, and there will be a small, but considerable amount of water in the reaction. To test this hypothesis, the reaction was repeated with the addition of 5 μ L of water, resulting in yields of 28% : 17% : 25% for **182**, (Z)-**182** & recovered **180** respectively.

The reason for such variable results arising from a small inclusion of water is possibly due to the formation of a ruthenium hydride species. These species are often cited as the source of side reactions in Grubbs' catalysed reactions, and the mechanism of formation has been somewhat elucidated.¹⁰⁴ These species are known to form in the presence of protic solvents and give distinct NMR resonances between -6 and -20 ppm.¹⁰⁵ It is possible that trace amounts of water in the toluene were causing the formation of ruthenium hydrides. The catalyst was also refluxed overnight in toluene from the solvent drying towers, in the absence of substrate **180** and the recovered catalyst was submitted for high-field NMR spectroscopy to search for a metal hydride peak. However, nothing was observed.

The recognised method of preventing ruthenium hydrides forming during Grubbs' metathesis reaction is by the addition of 1,4-benzoquinone.¹⁰⁶ However, TLC showed that this compound streaked considerably across the plate, which would make the purification of products and starting materials very difficult when applied to the above reaction.

We instead chose to freshly distil the toluene from sodium and benzophenone and then reflux the solvent for 1 hour on a Dean-Stark apparatus before adding catalyst and

substrate **180**. It was reasoned that this would drive off as much water as possible and reduce the quantity of olefin (Z)-**182** produced.

Catalyst	Yield 182 / %	Yield (Z)- 182 / %	Yield 336 / %	Recovery 180 / %
HG I	55	6	5	15

Table 4.2.8.2: Result of the RCM of substrate **180** with freshly distilled toluene and Dean-Stark apparatus.

Pleasingly, these modifications increased the isolated yield of **182**, but more importantly, decreased the relative amount of geometric isomer (Z)-**182**. Considering the recovery of starting diene **180**, which could be recycled back into subsequent reactions, a yield of 65% b.r.s.m. was observed.

Modification of the conditions showed that the reaction had to be conducted at reflux. The reaction also had to be performed for a long duration to maximise yield, but times longer than 24 hours were detrimental, with an increase in the relative amount of (Z)-**182** and a decrease in recovered **180**. Yields of **182** were quite variable and would range between 20 - 70%, the undesired (Z)-**182** yield would vary between 5 - 20% and diastereomer **336** was more constant with yields of 5 - 7%. Recovery of starting material **180** was similarly changeable at 10 - 50%. It was not immediately obvious why yields were so erratic. Once water content was controlled by distilling toluene and use of a Dean-Stark reflux, the only other variable we could identify to cause a decrease in yield was the quality of the catalyst. Batches of Hoveyda Grubbs' 1st generation catalyst comprised of large, purple crystals gave the best yields, while catalyst in the form of a purple-brown powder gave the worst. Although, ¹H NMR spectral analyses of different batches showed no major differences other

than a small series of three unidentified triplets at 1.4 ppm in the spectra of powdered batches.

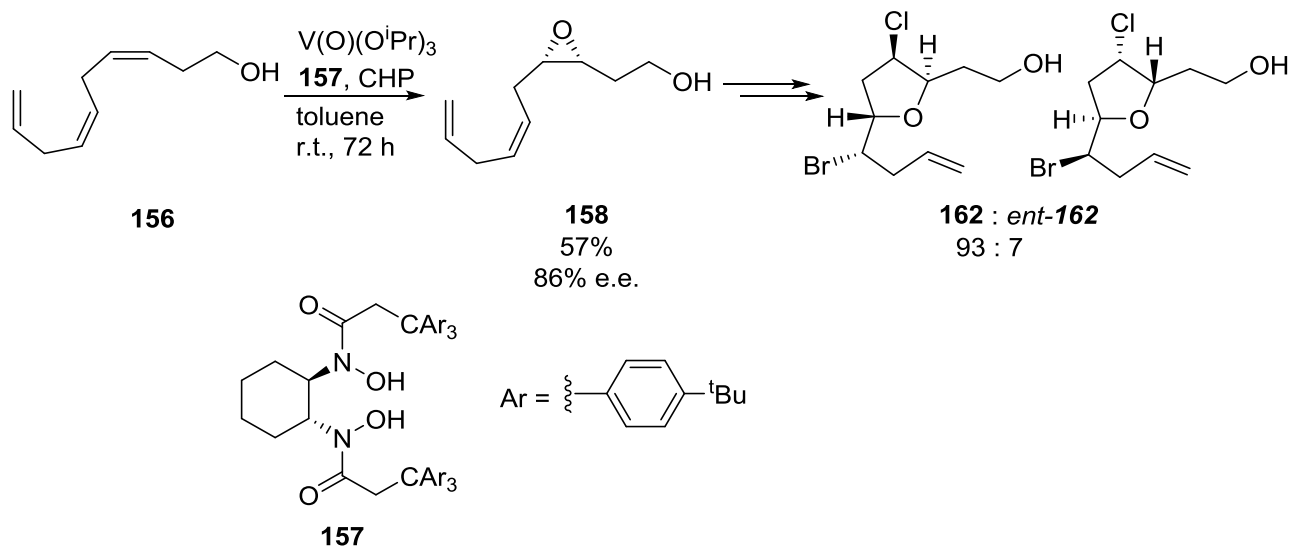
Purification of the catalyst was attempted, based on the original synthesis article.¹⁰⁷ Hoveyda describes column chromatography of the catalyst with a hexane : CH₂Cl₂ system and also its recrystallisation from pentane. However, neither of these procedures could be replicated. Thorough drying of the catalyst using a lyophiliser was also attempted, but yields in subsequent RCM runs were not improved.

Despite these complications, yields of RCM product **182** were deemed sufficiently high and reliable enough to proceed, so the process of processing the remainder of diene **180** was begun. It was quickly found that yields of macrocyclic product **182** rapidly dropped off with reaction scale. Reactions employing a greater than 50 mg scale would suffer deleterious yields, unless catalyst loading was dropped to 10 mol%. Perhaps this is why Bonney observed only 11% recovery of **182**, as his was performed on an 82 mg scale.

In conclusion, it was found that the yield of product **182**, (Z)-**182** and recovery of **180** was highly variable. It appeared to depend on a variety of factors, none of which could be positively identified or completely controlled for, other than the observation that drier solvent generally led to a better result. For this reason, diene **180** was elaborated slowly, in small batches, in order to try and optimise with each successive repeat. Thus, a total of 324 mg (0.968 mmol) of **182** was produced from 47 RCM runs. Compare this to the 71.3 mg predicted from Bonney and Yaqoob's observed yields, it was clear that a significant improvement had been made.

The compound that has been assigned as (6,7,9,10)-diastereomeric compound **336** was only produced in small amounts in each reaction, although quite constant at 5 - 7%. This low yield meant that it had to be isolated and combined with the products of multiple RCM

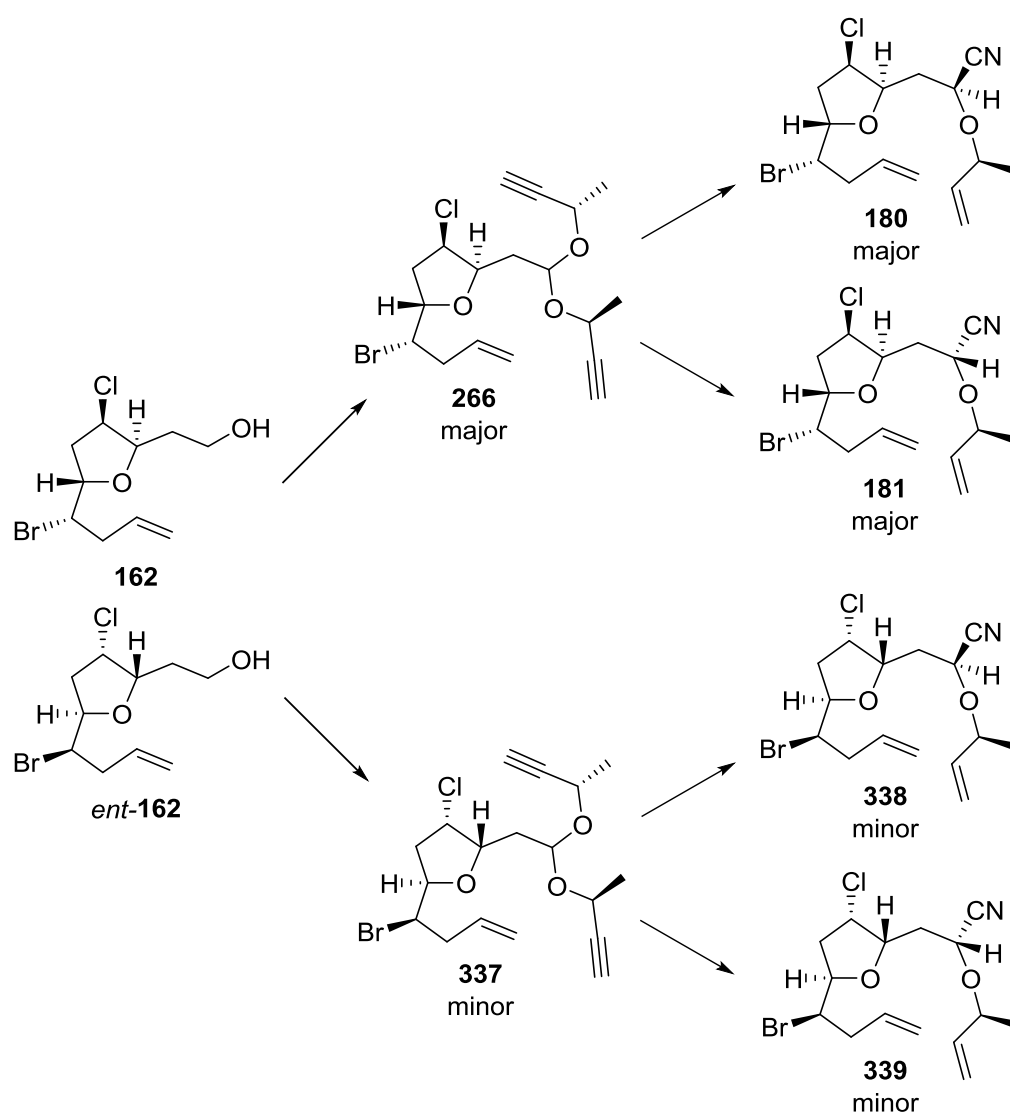
reactions before enough was collected to allow a good spectrum to be collected and analysed. COSY, HSQC & DEPT135 NMR spectroscopy established that the carbon chain was the same 13 carbon contiguous chain, with an identical substitution pattern. In addition, the olefin peaks presented a coupling constant of 15.2 Hz, suggesting the double bond had *E*- geometry. Compare this to the 10.5 Hz coupling constant across the double bond of (*Z*)-**182**. Interestingly, the ^1H NMR resonances of **336** were considerably sharper than that seen for **182**, suggesting that the conformational flexibilities were considerably different between the two compounds. The methyl and methylene resonances were similar between each compound, but the resonances for C₆ & C₉ were shifted by approximately 1 ppm. This suggests that these resonances are key to discerning the identity of the compound. Crystals of sufficient quality for X-ray analysis could not be grown and attempts at mass spectroscopy using chemical ionisation and electron ionisation failed. A likely structure is that which is epimeric at C₆, C₇, C₉ & C₁₀. This compound would originate from the minor enantiomer arising from the epoxidation of triene **156**, before the bromoetherification to form the THF unit of **162**, as well as *ent*-**162**.



Scheme 4.2.8.2: Origin of the minor compound *ent*-**162**.

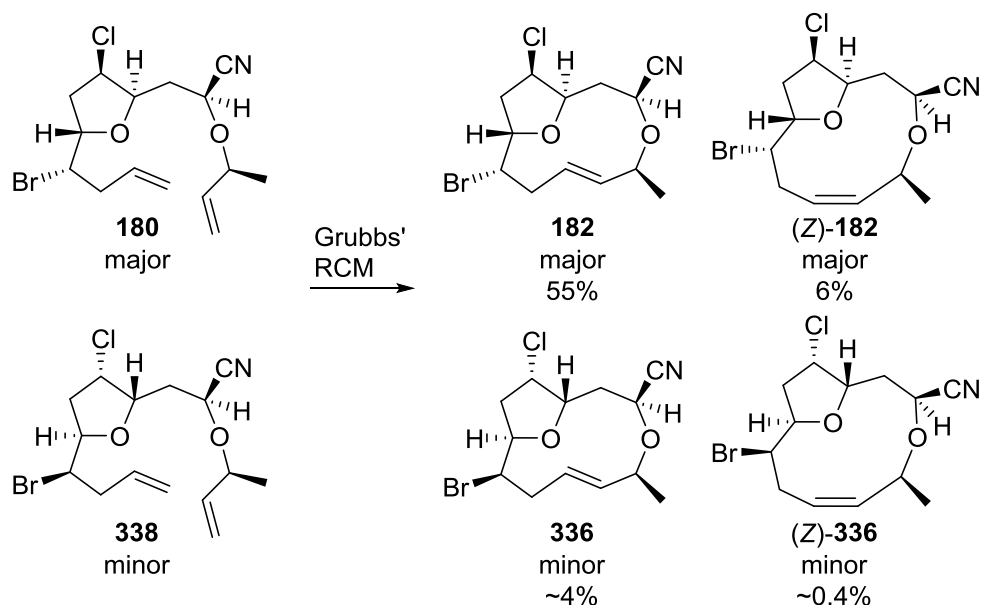
The asymmetric homoallylic epoxidation of triene **156** proceeded with an 86% e.e., as measured by protecting the alcohol as a trityl group and submitting for chiral HPLC.⁴⁸ Presumably, this ratio was constant throughout further reactions up to alcohols **162** & *ent*-**162**, as the two enantiomers would be inseparable by standard column chromatography.

After acetalisation, there would now be a major and minor diastereomer (**266** & **337**), due to the introduction of the fixed stereochemistry of the propargylic ether. Presumably, these diastereomers are still inseparable and unobservable by NMR spectroscopy due to the distance between the propargylic and THF stereocentres. The same will apply after cyanation and hydrogenation to dienes **180** & **181**, each having a corresponding minor (7,8,9,10)-diastereomer, **338** & **339** respectively (scheme 4.2.8.3).



Scheme 4.2.8.3: Major and minor diastereomers arising from the enantiomeric mixture of **162** & *ent*-**162**.

Although these minor diastereomers will only comprise approximately 7% of the mass of the dienes, we must still consider their fate upon RCM.

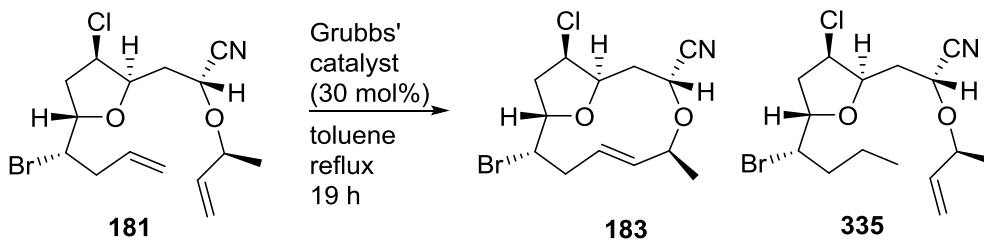


Scheme 4.2.8.4: Major (**182** & (*Z*)-**182**) and minor diastereomers (**336** & (*Z*)-**336**) resulting from the RCM of diastereomeric dienes **180** & **338**.

Based on the observed yields of **182** & (*Z*)-**182**, a prediction of the expected yields of the minor diastereomers, **336** & (*Z*)-**336** can be made (scheme 4.2.8.4). Assuming that the conversion is similar in the major and minor diastereomers, we might expect approximately 4% of the yield to be minor diastereomer **336** and 0.4% to be diastereomer (*Z*)-**336**. Indeed, the observation that a side product comprised between 5 - 7% of the product of these metathesis reactions, strongly supports our hypothesis. The expected yield of 0.4% of (*Z*)-**336** is probably too low to observe, especially on these scales.

Helpfully, starting material **180**, **182**, (*Z*)-**182** & diastereomer **336** could be neatly separated by column chromatography using toluene as eluent. Considering the similarity between each of the products, it is fortunate that they were so easily separable. This highlights the effect of cyclisation, with fixation of dipoles and the resultant large increase in polarity.

Focus then turned to the RCM of diene **181**.



Scheme 4.2.8.5: RCM of diene **181** and observed products.

Catalyst	Yield 183 / %	Yield (Z)-183 / %	Yield 335 / %	Recovery 181 / %
SG	37	0	22	12
G II	20	0	47	0
HG II	54	0	36	0
G I	trace	0	58	37
HG I	trace	0	76	22

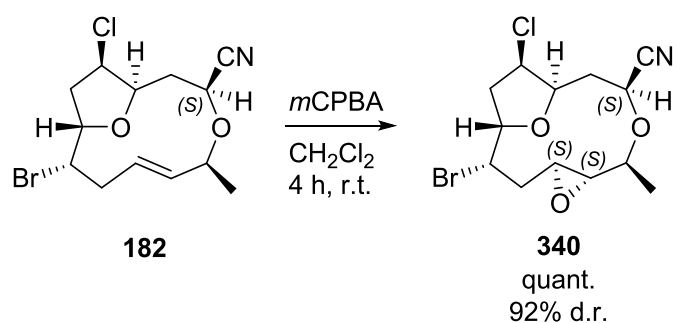
Table 4.2.8.3: Results of the RCM of diene **183** with a range of Grubbs' catalysts.

The results of replicating Bonney's RCM of acyclic diene **181** are presented in table 4.2.8.3. Stewart Grubbs' catalyst showed an improvement of the previously seen yield of 29% with a small amount of recovered starting material. This increase is likely due to the effect of scrupulous drying of the solvent. Both Grubbs' and Hoveyda Grubbs' 1st generation catalysts, gave trace amounts of **183**. Instead, the only product seen was C₁₂,C₁₃-dihydro product **335** in very high yield. These catalysts were accordingly then discounted. Both Grubbs' and Hoveyda Grubbs' 2nd generation catalysts gave high yields of both **183** & C₁₂,C₁₃-dihydro product **335**. Hoveyda Grubbs' 2nd generation catalyst ultimately gave the

highest yield of **183** so this was the catalyst chosen to advance the remainder of the material in small batches. In total, 195 mg (0.582 mmol) of macrocycle **183** was generated from 14 RCM runs, a quantity approximately 40% higher than that expected by Bonney and Yaqoob's work. Interestingly, none of the catalysts in any of the reactions produced the corresponding (Z)-isomer. This shows that minor changes in the conformation of a precursor compound can drastically change its reactivity. In addition, there was no sign of an analogous (6,7,9,10)-diastereomer. We now had suitable quantities of both macrocycles for further studies.

4.2.9 Epoxidation of Macrocyclic Nitrile 182 & Total Synthesis of Marilzabicycloallene C (6)

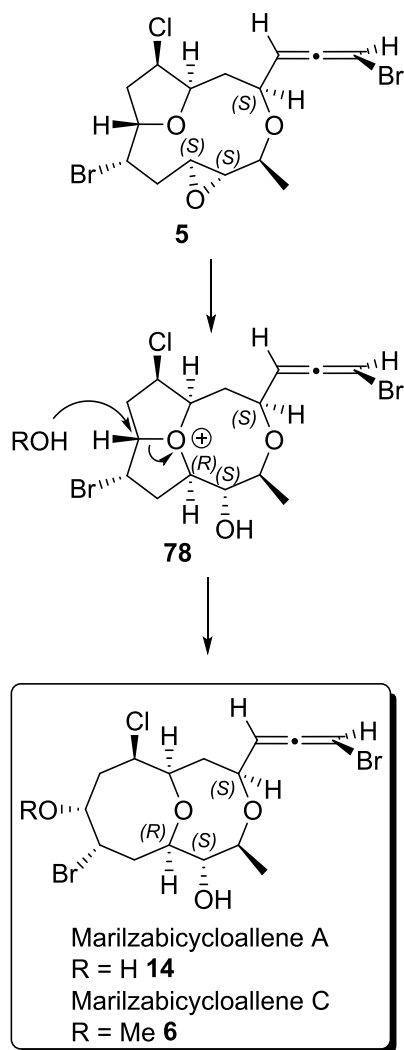
With the entirety of dienes **180** & **181** successfully cyclised, attention turned to their further derivation to obtusallene natural products. Previous work by Yaqoob and Bonney,⁴⁶⁴⁸ as well as that on the model system **286**, showed that direct DIBAL-H reduction of an allylic nitrile would not give sufficient yield to allow completion of a total synthesis. However, with the proof that the olefin could effectively be protected as an epoxide, this alternative method was pursued instead. Macrocycle **182** was investigated first, as the original isolation of marilzabicycloallenes by Norte suggests that only products deriving from epoxidation of one face of the olefin was observed (section 2.3.3).¹² If accurate, this would make the identification of a single product simpler. The epoxidant chosen was *m*CPBA as it had proven to be successful on model substrate **322**.



Scheme 4.2.9.1: Epoxidation of macrocycle **182** with *m*CPBA.

Macrocyclic olefin **182** was treated with *m*CPBA in dichloromethane (scheme 4.2.9.1). Pleasingly, the epoxidation proceeded well and the product epoxide could be isolated in quantitative yield. The structure was identified by the disappearance of the olefin peaks and appearance of distinguishing epoxide peaks at 2.70 and 2.83 ppm, bearing dd and ddd splitting patterns respectively. This was assigned as the (*S,S*)-epoxide of **340**, although definitive confirmation was not possible at this point. Close analysis of the spectrum showed that there was an inseparable impurity, most obviously seen by the second methyl doublet at 1.01 ppm, making up 8% of the mass. Further analysis showed many of the key peaks had counterparts just above the baseline with relative integrals of 8%. This was assigned as the corresponding (*R,R*)-epoxide. Clearly, the epoxidation is highly selective for the *Si*-face of this epimeric nitrile.

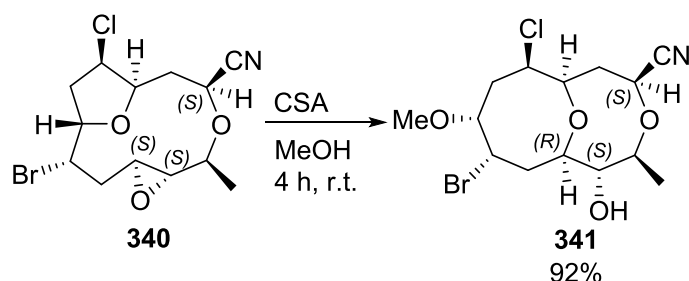
With epoxide **340** in hand, the key transannular oxonium formation - fragmentation reaction that would be essential to the total synthesis of marilzabicycloallenes, was investigated. Two known natural products could potentially derive from this (4*S*,12*S*,13*S*)-macrocycle, marilzabicycloallenes A & C (**14** & **6**)



Scheme 4.2.9.2: Proposed transannular oxonium ion formation - fragmentation reaction to form marilzabicycloallenes A & C (**14** & **6**)

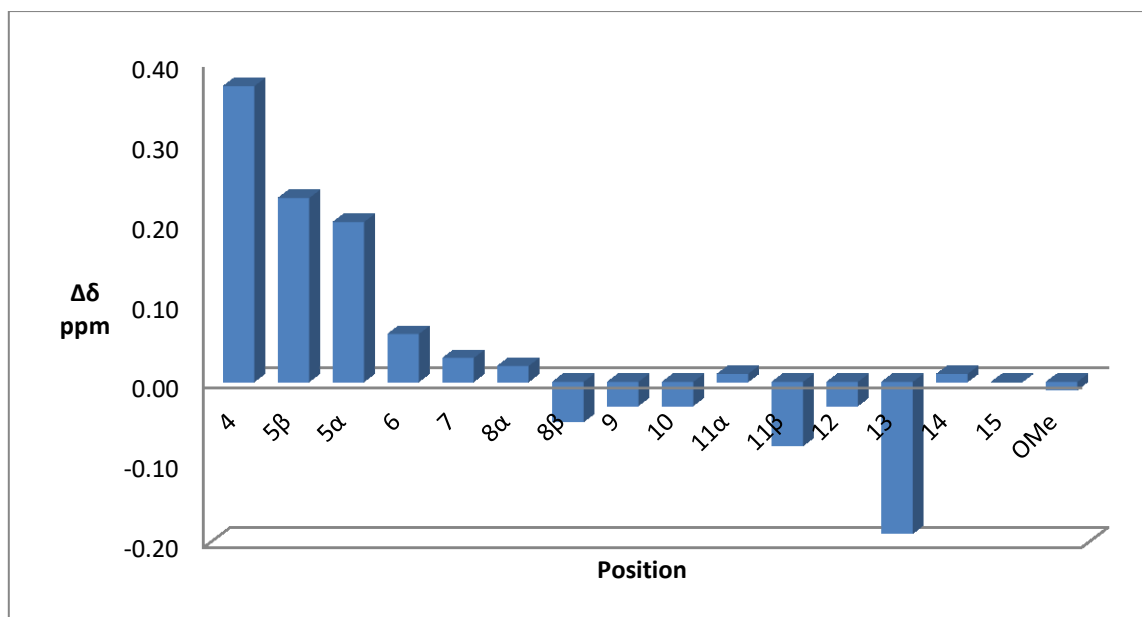
Marilzabicycloallenes A & C (**14** & **6**) show 4*S*,12*R*,13*S* stereochemistry, as C₁₂ is inverted during the opening of the epoxide and formation of the oxonium ion. They differ in the nature of the RO group on C₉, as each is opened by a different nucleophile (scheme 4.2.9.2). This presented a choice of which nucleophile would be investigated and therefore which natural product would be pursued. For reasons of solubility, methanol was chosen as the nucleophile and therefore marilzabicycloallene C (**6**) would be the target. CSA would be

used as the catalyst as the THF motif was shown to be stable to this acid during the acetalisation reaction (scheme 4.2.7.1).



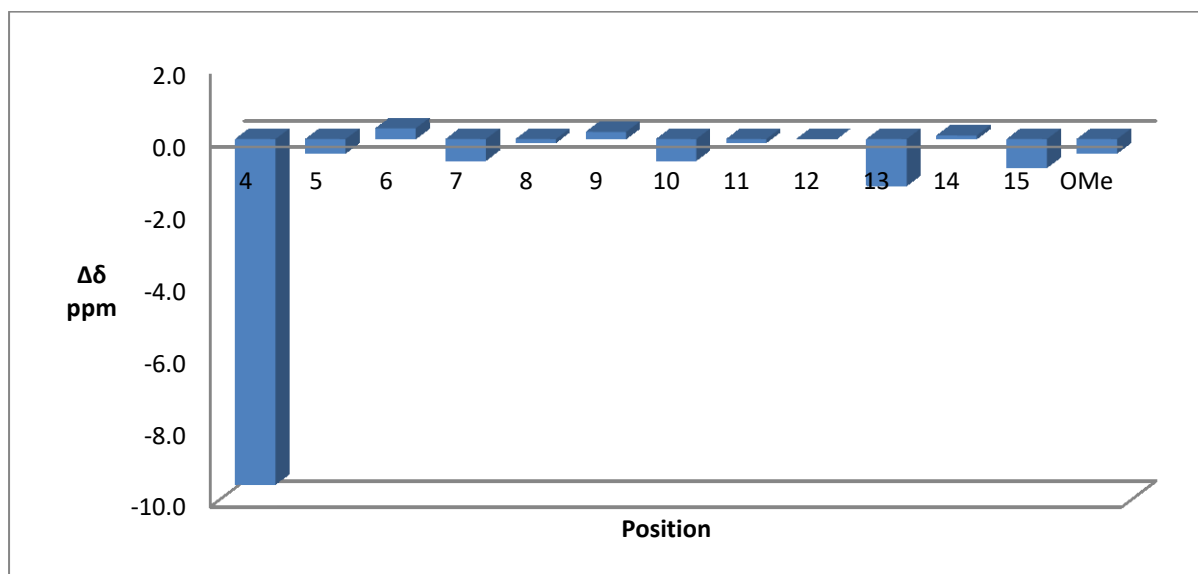
Scheme 4.2.9.3: Successful transannular oxonium ion formation - fragmentation reaction to form marilzabicycloallene C core **341**.

CSA was added to a solution of epoxide **340** in methanol (scheme 4.2.9.3). After work up, the reaction gave a high yield of a white solid, which proved to be insoluble in deuterated chloroform or methanol. However, a 1 : 1 mixture of the two solvents allowed enough to dissolve to record NMR spectra. This data was compared to that reported in the isolation of marilzabicycloallene C (**6**) (see supporting information for detailed data).



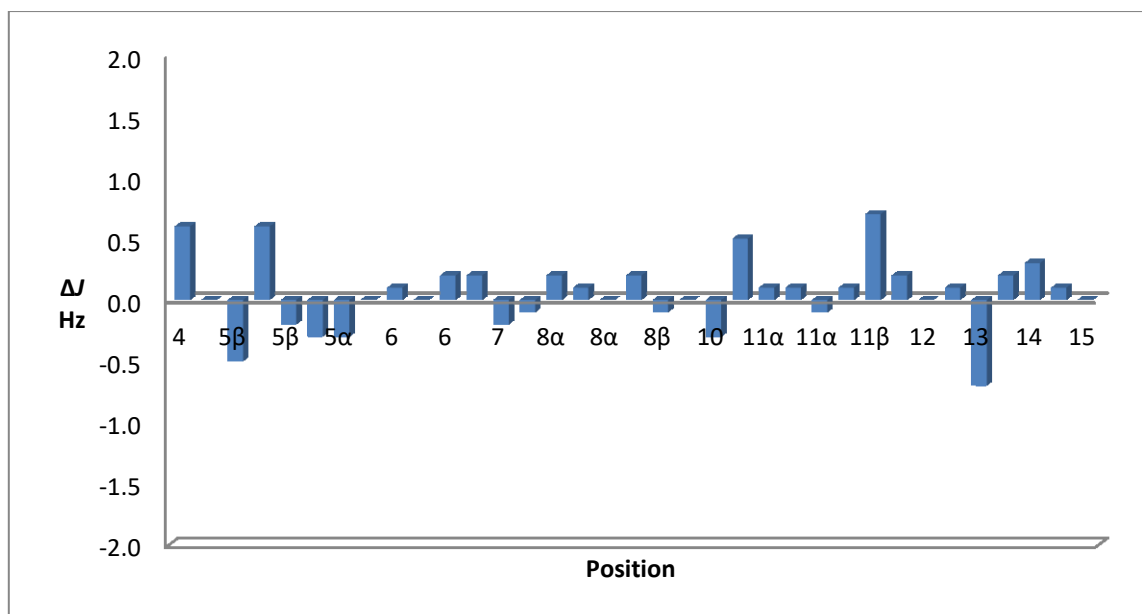
Root-mean-square deviation: 0.13 ppm

Figure 4.2.9.1: Comparison of ^1H NMR spectral data for nitrile **341** and natural marilzabicycloallene **C (6)**.



Root-mean-square deviation: 2.71 ppm

Figure 4.2.9.2: Comparison of ^{13}C NMR spectral data for nitrile **341** and natural marilzabicycloallene **C (6)**.



Root-mean-square deviation: 0.3 Hz

Figure 4.2.9.3: Comparison of ^1H NMR J -values for nitrile **341** and natural marilzabicycloallene **C (6)**.

A full comparison of the spectra was conducted between the molecule isolated and that reported in the literature, to confirm the identity of compound **341**.¹² A couple of considerations must first be made; firstly, the solvent for the NMR experiment was a mixture of CDCl_3 and MeOH-d^4 , so some minor deviation at certain resonances would be expected. Secondly, the synthetic product bears a nitrile, instead of a bromoallene. Thus, as well as the signals for $\text{C}_1\text{-C}_3$ being absent, large deviations in the resonances for C_4 & C_5 are inevitable. Lastly, the resolution of the natural product spectrum appears to be much sharper than that recorded here, despite being run on a higher frequency spectrometer. For this reason, where a natural product peak is noted as a doublet of doublets, we observed a triplet. For the sake of an accurate analysis, these values have been shown in brackets in the supporting information. Similarly, Norte's isolation paper reports coupling constants of ~ 1.0

Hz, whereas only broadened multiplets were observed here. These instances have been recorded in the tables in the supplementary information.

Comparing the ^1H NMR spectral data (figure 4.2.9.1), there is significant correlation although with some notable exceptions. Firstly, the resonances for H_4 , the position bearing the nitrile, show the largest deviation. This is to be expected, as explained above. There is similar deviation about $\text{H}_{5\alpha}$ and $\text{H}_{5\beta}$, for similar reasons, although this is still within ~ 0.20 ppm. The last exception is at H_{13} , which is vicinal to the hydroxyl and will understandably show the greatest shift due to a different solvent system. Root-mean-square (RMS) analysis of all the $\Delta\delta$ values between C_4 and C_{15} gives a value of 0.13 ppm. Omitting C_4 reduces this value further to 0.10 ppm. The most important values in confirming the structure of compound **341** are those corresponding to H_9 & H_{12} . These are the position of new C-O bridging ether bonds and would likely show the largest deviation if the stereochemistry of the compound isolated was different to that of the natural product. They both differ by only -0.03 ppm and so it can be concluded that the stereochemistry at these positions matches marilzabicycloallene **C (6)**.

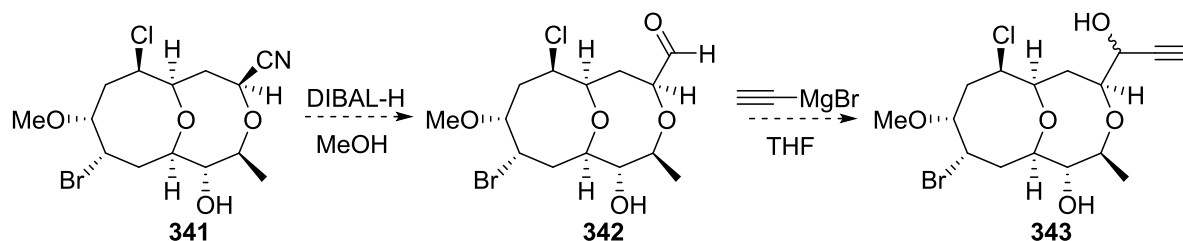
The comparison of the ^{13}C spectra shows even closer correlation (figure 4.2.9.2). Apart from the expected discrepancies at C_4 and C_{13} , there is very little between the chemical shifts of each compound. Again, the peaks corresponding to C_9 & C_{12} match very closely with the natural product data, helping to confirm the structure of **341**. The RMS value for the signals corresponding to all carbons except $\text{C}_1\text{-C}_3$ is 2.71 ppm. Removing C_4 from the analysis gives a much lower value of 0.54 ppm.

Lastly, the coupling constants match well, but do have some variance across the range (figure 4.2.9.3). This is to be expected in a constrained ring system, where minor changes to the relative orientation of protons will have large impact on the observed

coupling constants. However, excluding that of H_4 , the splitting patterns match extremely well. The only concession being the doublet of doublets and triplet issue explained above, which does not detract from the accuracy of the analysis.

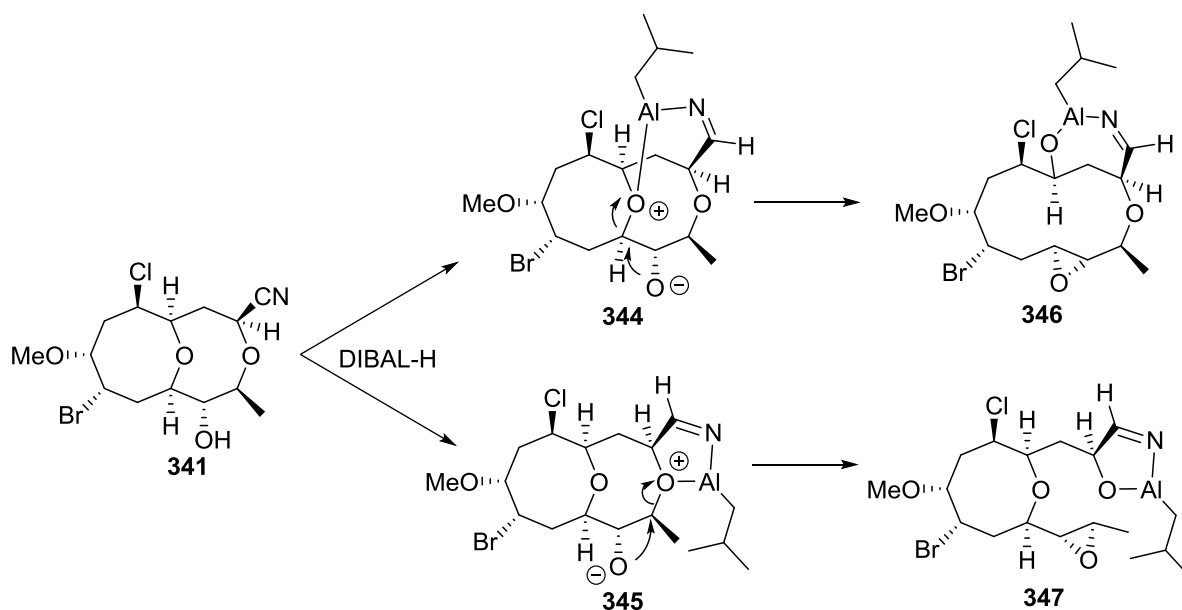
These analyses gives very strong evidence that a successful transannular oxonium formation - fragmentation reaction had been achieved. Very close correlation to the reported spectral data for marilzabicycloallene C (**6**) convincingly suggests that the intended structures and stereochemistries had been installed. Not only this, but strong selectivity for the *Si* face of the olefin of **182** mirrors the lack of isolation of any natural products deriving from the epoxidation of the *Re* face of obtusallene II **15**.

An attempt was made at the DIBAL-H reduction of compound **341**, to determine if it would be an suitable ingress to bromoallene installation.



Scheme 4.2.9.4: Planned DIBAL-H reduction and acetylide addition to marilzabicycloallene C core **341**.

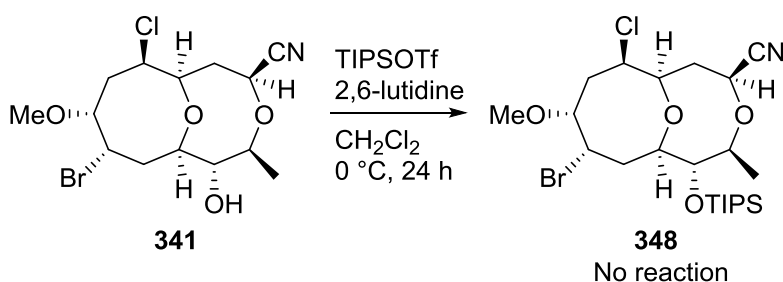
Unfortunately, treatment of **341** with 2.5 equivalents of DIBAL-H gave a mixture of compounds. Some of which contained aldehydes, as determined by ^1H NMR analysis, but no single compound could be identified. A reason for this is proposed in scheme 4.2.9.5.



Scheme 4.2.9.5: Possible outcomes of the DIBAL-H reduction of marilzabicycloallene C core 341.

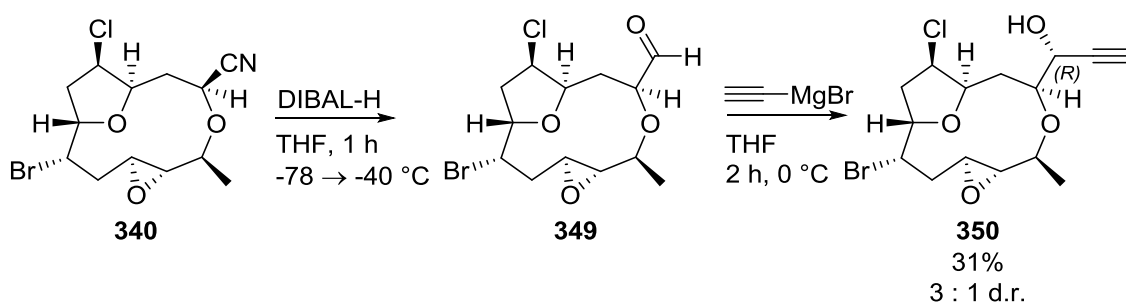
It is possible that the intermediate aluminium-imine is chelated by one of the ether oxygens to form compounds **344** or **345**, allowing the free hydroxyl at C₁₃ to reform an epoxide and fragment the macrocyclic structure and give aluminium oxazoles **346** & **347**. A thorough search of the literature found no DIBAL-H reductions on compounds with similar functionalities.

An attempt was made to protect the alcohol with a suitable group. A bulky *triisopropylsilyl* group was chosen as it would be relatively stable to the subsequent bromoallene installation reactions. Also, it was desirable to use a group that would be removed by TBAF, rather than acid or base which may not have been compatible with the sensitive bromoallene group.



Scheme 4.2.9.6: Attempted silyl protection of compound **341**.

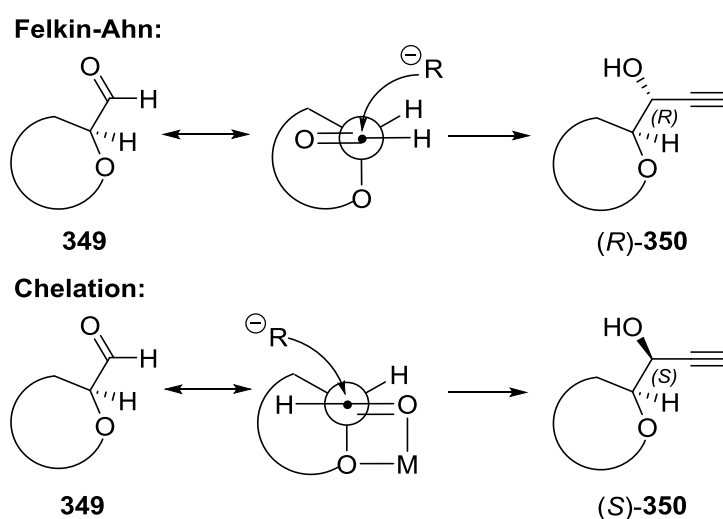
Unfortunately, after prolonged reaction time, there was no evidence of silylation of the alcohol (scheme 4.2.9.6). This route was abandoned in favour of reducing the nitrile of epoxide **340**, which had been shown to proceed well in model system **332** (scheme 4.2.6.13).



Scheme 4.2.9.7: DIBAL-H reduction and subsequent acetylide addition to compound **340**.

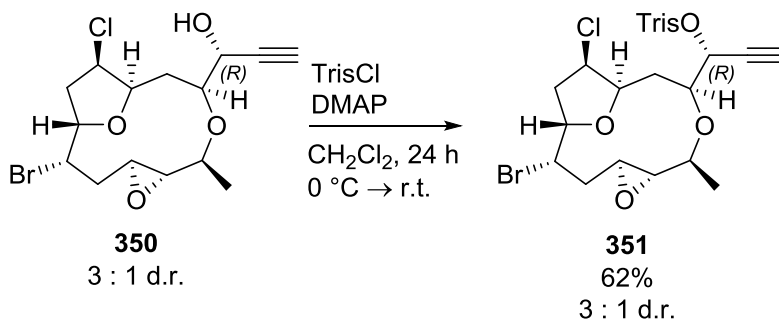
As before, keeping the temperature below -40°C and employing a citric acid work-up allowed aldehyde **349** to be collected in moderate yield and reasonable purity. This was directly treated with ethynylmagnesium bromide giving a 3 : 1 mixture of the propargylic alcohols (**350**) (scheme 4.2.9.7). The major product was assigned as the (*R*)-isomer, although the stereochemistry could not be positively assigned at this point (*vide infra*). This ratio most likely arises from Felkin-Ahn selectivity, shown in scheme 4.2.9.8. Presumably the magnesium bromide cation is not sufficient to effect chelation control.

The two-step yield of 31% does not compare favourably with that seen with epoxy aldehyde **333** (scheme 4.2.6.13). It may be the case that the aromatic group alters the electronic properties sufficiently to change the likelihood of hydride transfer or hydrolysis. In addition, the acetylide addition was not tested with epoxy aldehyde **333**, so perhaps the epoxide is sensitive to nucleophilic substitution and material is lost through that route. Even so, the achieved yield is still much better than the ~10% achieved with macrocyclic olefins **182** & **183** (scheme 4.1.1.3).



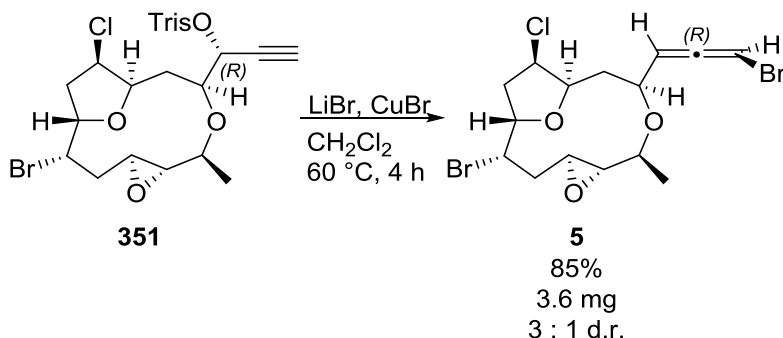
Scheme 4.2.9.8: Felkin-Ahn vs. chelation control in the Grignard addition to aldehyde **349**.

This material was submitted to the established trisylation protocol.^{53a}



Scheme 4.2.9.9: Trisylation of propargylic alcohol **350**.

This reaction proceeded well, giving a 62% yield of the desired product and maintained the 3 : 1 diastereomeric ratio at C₃, as measured by comparison of the alkyne signals. Yields for this reaction often reached >90% in the model system (scheme 3.2.1.2). The decrease in yield may have been due to a transannular oxonium formation - fragmentation reaction, mediated by a chloride nucleophile and any available Lewis acid. Indeed, the crude ¹H NMR spectrum showed traces of other alkyne signals that were removed by column chromatography. It is possible that the conformation of the epoxide and THF motif in the epoxyobtusallene core of **350** is aligned in such a manner that makes it extremely sensitive to rearrangement. This material was quickly submitted to the bromination procedure.



Scheme 4.2.9.10: Successful bromination of trisylate **351** to form 12-epoxyobtusallene II (**5**).

Following the established bromination procedure gave bromoallene bearing compound **5**.^{53a} Again, there was a slight reduction in the expected yield, possibly due to unintended rearrangements facilitated by bromide, but 3.6 mg of material was collected for spectroscopic analysis. The crude ¹H NMR spectrum showed several other bromoallene-like peaks that were removed by chromatography. The diastereomeric purity of the bromoallene followed that of the trisylate and was maintained at 3 : 1. This was measured by the relative integrals of the bromoallene peaks.

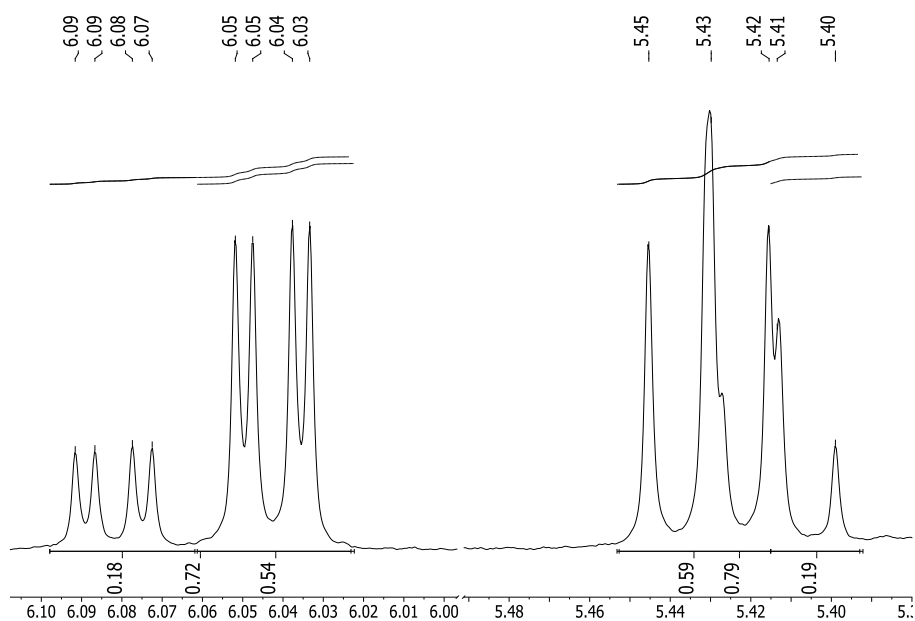


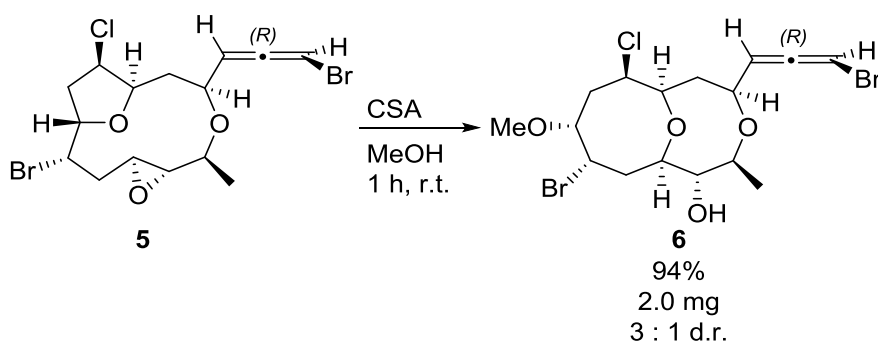
Figure 4.2.9.4: Bromoallene peaks in the ^1H NMR spectrum of 12-epoxyobtusallene II (**5**).

It should be noted that the resonances significantly underintegrate. This is partially due to the isolated nature of the bromoallene protons, allowing limited relaxation pathways. But it is also due to the presence of the corresponding propargylic bromides, observed by alkyne peaks around 2.65 ppm, expected to be produced by double $\text{S}_{\text{N}}2'$ bromination. Interestingly, the peaks deviate from a d.r. of 3 : 1, suggesting there is some equilibration between the two compounds (*vide infra*, scheme 4.2.12.3). Unfortunately, these propargylic bromide compounds were inseparable from the bromoallenes.

Bromoallene **5** bears all the features and stereochemistries necessary to be a real natural product and is Norte's proposed natural intermediate between obtusallene II (**15**) & marilzabicycloallenes A & C (**14** & **6**).¹² However, no such structure has yet been isolated. Conversely, the corresponding 12-epoxyobtusallene IV (**8**) is apparently stable and isolable.^{13g} It is possible that the inherent instability of compound **5** and the specific

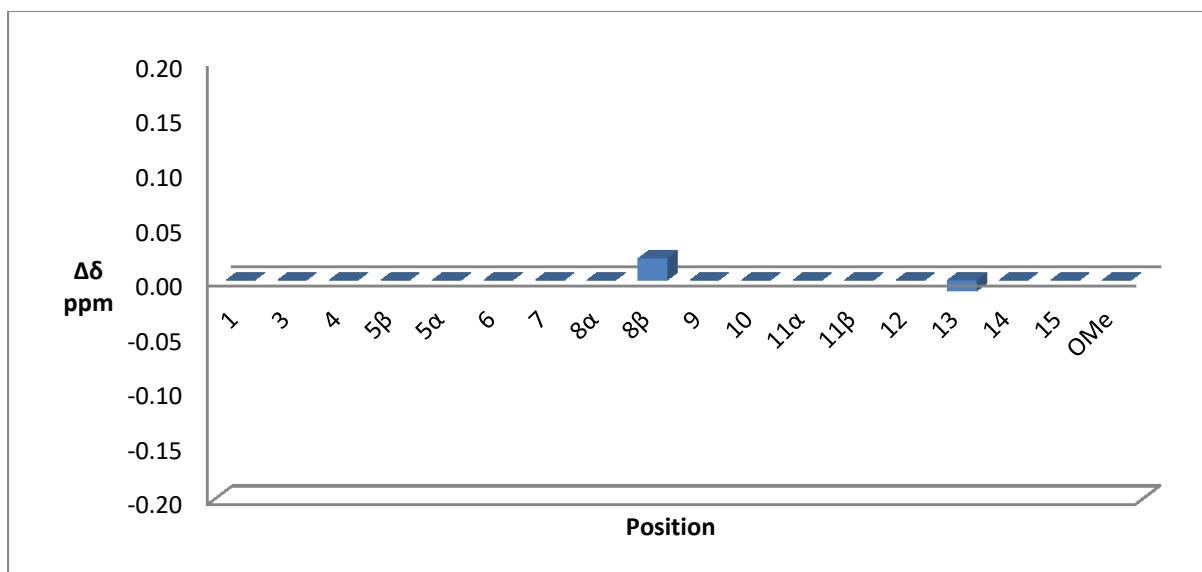
orientation of the THF motif and epoxide, makes it extremely liable to oxonium ion formation and nucleophile trapping, therefore is not possible to isolate under the current extraction procedures. Nonetheless, compound **5** has been pre-emptively named as 12-epoxyobtusallene II, in the event that it is discovered from natural sources in future studies.

With this compound in hand, the established methanol mediated transannular oxonium formation - fragmentation reaction was conducted.



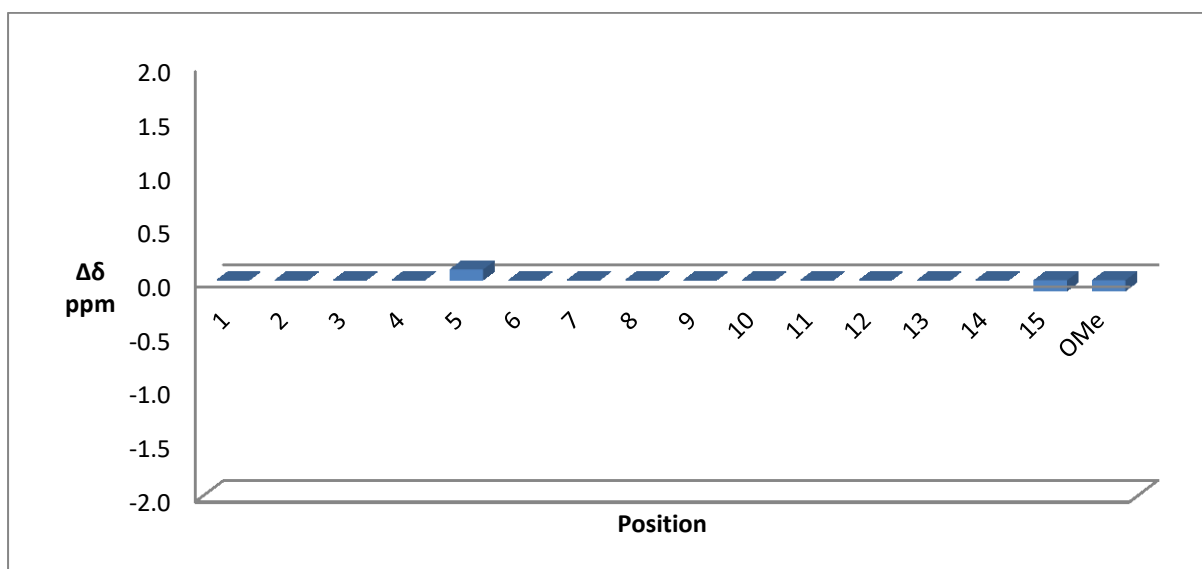
Scheme 4.2.9.11: Transannular oxonium formation - fragmentation of 12-epoxyobtusallene II (**5**) to form marilzabicycloallene C (**6**).

Pleasingly, after treatment with CSA in methanol, the rearrangement proceeded with very high yield and very high regioselectivity. Of the 2.0 mg collected, ^1H NMR spectroscopy gave no evidence of nucleophilic substitution at C₆ or C₁₂. At this point, the stereochemistry at C₉ and C₁₃ could be confirmed by comparing to the data for the natural product (see supplementary information for detailed data).



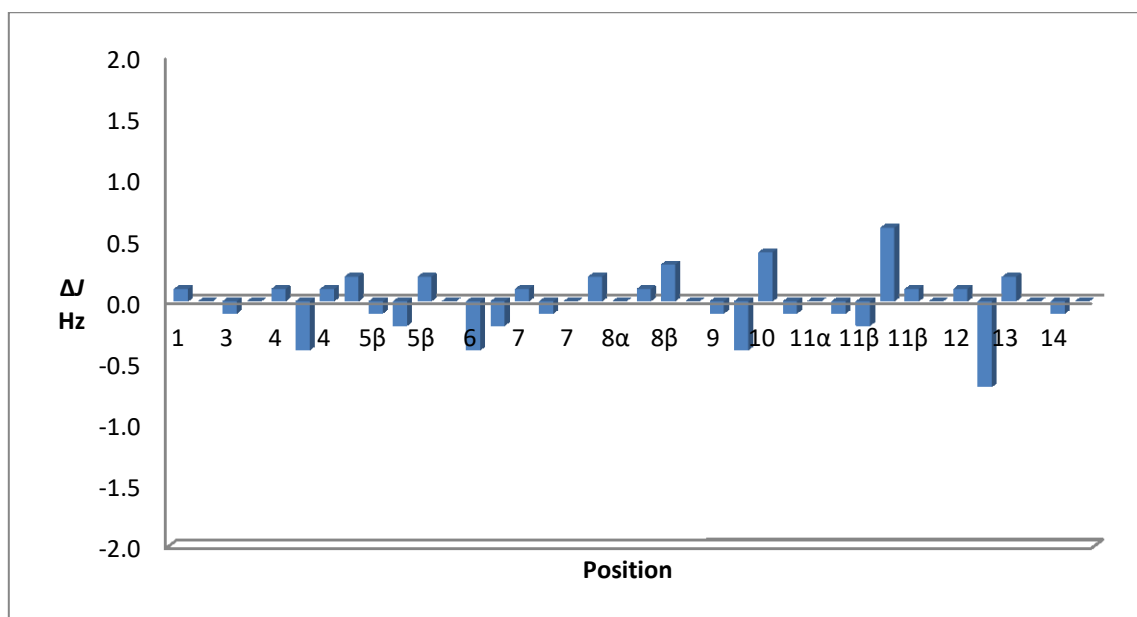
Root-mean-square deviation: 0.01 ppm

Figure 4.2.9.5: Comparison of ^1H NMR spectral data for synthetic and natural marilzabicycloallene C (6).



Root-mean-square deviation: 0.0 ppm

Figure 4.2.9.6: Comparison of ^{13}C NMR spectral data for synthetic and natural marilzabicycloallene C (6).



Root-mean-square deviation: 0.2 Hz

Figure 4.2.9.7: Comparison of ^1H NMR J -values for synthetic and natural marilzabicycloallene C (**6**).

Figures 4.2.9.5 - 4.2.9.7 show that the ^1H and ^{13}C NMR spectral data matches almost perfectly, with RMS values very close to zero. Carbons and protons 1, 2, 3, 4, 6, 9, 12 & 13 all match perfectly with the literature data. These are the important positions in terms of connectivity, so we can conclude that marilzabicycloallene C (**6**) has been successfully synthesised.

The analogous minor diastereomer (S_a)-**6** was also present and could only be distinguished from the major by a few visible peaks. These were compared with the natural product data to prove it was not the intended compound. This is shown in table 4.2.9.1.

Proton	Synthetic (<i>S_a</i>)-6 δ /ppm (500 MHz, CDCl ₃)	Natural (<i>R_a</i>)-6 δ /ppm (600 MHz, CDCl ₃)	$\Delta\delta$ /ppm
1	6.09	6.05	0.04
3	5.40	5.47	-0.07
14	3.45	3.57	-0.12

Table 4.2.9.1: Comparison of ¹H NMR data for synthetic (*S_a*)-6 and natural (*R_a*)-6.

Comparing the visible peaks of the diastereomeric compound present in the sample, it can be seen that the $\Delta\delta$ value is of a significantly larger magnitude. Considering that these compounds only differ by the arrangement of a proton and bromine on the terminal carbon of the allene, this shows the utility of $\Delta\delta$ analysis in unambiguously identifying the natural products that will be produced.

With this data, it had been proven that marilzabicycloallene C (6) had been successfully synthesised, along with the proposed biogenetic precursor 12-epoxyobtusallene II (5). This marked a first for such macrocyclic natural products. In addition, the successful transannular oxonium ion formation - fragmentation reaction on both model **340** & substrate **5**, is consistent with the biogenesis of this class of compounds proposed by Norte.¹² With remarkable regioselectivity, only one side of the epoxide opened to form the oxonium ion and only C₉ was subject to methanolysis. This suggests that the compounds isolated by Norte were not a small selection of the spectrum of natural products formed, but instead, the inherently selected products based on the subtle differences in stereochemistry of the preceding epoxy obtusallenes (**5** & **30**).

Marilzabicycloallene A (**14**), differing by the presence of a hydroxyl at C₉, was considered as a target, but ultimately not pursued. What remained of the 12-epoxyobtusallene II (**5**) sample was employed in attempts at deoxygenation (*vide infra*,

section 4.2.15) as repeating the same transannular oxonium formation - fragmentation reaction with another oxygen nucleophile was not considered to be of merit.

It should be noted at this point that the characterisation of the compounds between epoxide **340** & marilzabicycloallene C (**6**) consisted of only ^1H & ^{13}C NMR, LRMS & HRMS. Other spectroscopic techniques were considered, but ultimately discounted for the following reasons.

IR spectroscopy would have been of limited importance to confirming the identity of the compounds. Attempts to collect IR spectra with similar 1 - 3 mg quantities of other compounds required the full amount to be employed and only resulted in weak signals, barely above the baseline. Recollection of the material was not entirely possible and caused significant contamination. It was felt that any information gained from an IR spectrum was significantly outweighed by the risk of losing the sample and not being able to complete the study.

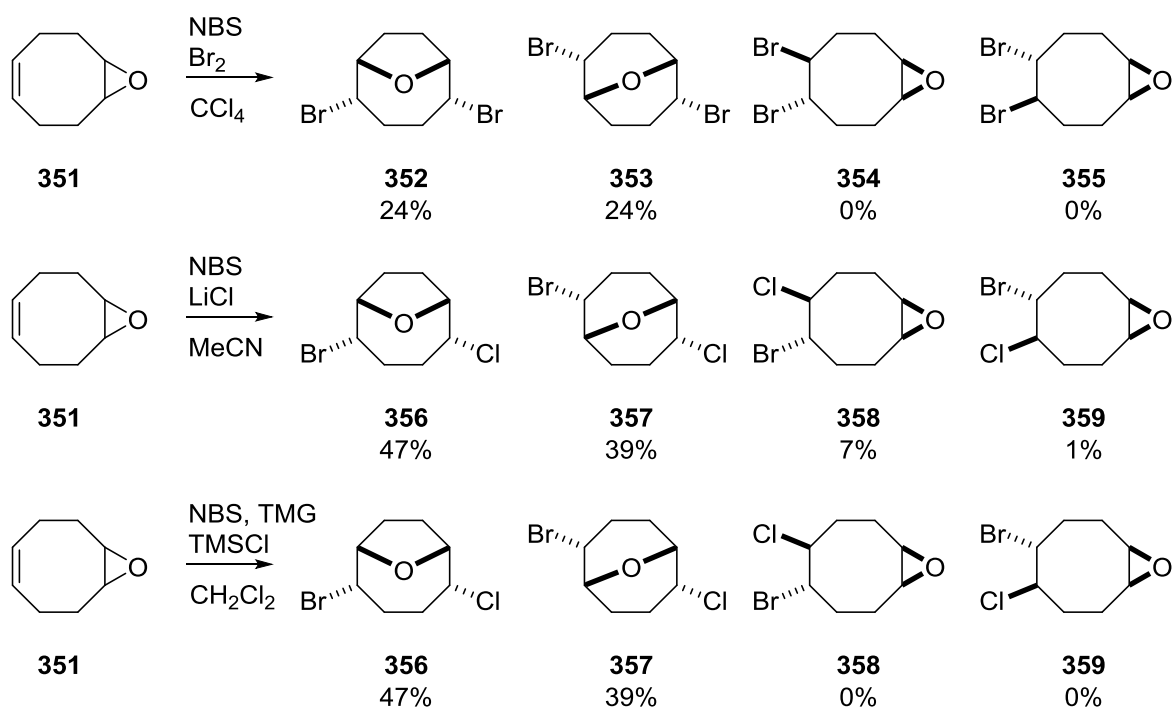
Melting point analysis would not have been beneficial as the intermediates in the bromoallene installation are not known and thus had no comparison. Once the bromoallene was in place and natural products such as marilzabicycloallene C (**6**) had been synthesised, the presence of the diastereomers brought about by the imperfect selectivity of the epoxidation and acetylide addition would make comparison to reported data meaningless. The sensitivity of the obtusallene/marilzabicycloallene systems was also a concern. Heating the samples in air may have resulted in decomposition and prevented any further experimentation taking place.

Optical rotation was not collected as the diastereomeric impurities would certainly alter the optical properties of the samples. In addition, with the quantities available, the measurements would be conducted at very high dilution and incur significantly large errors.

Obviously, there are many different compounds in the obtusallene/marilzabicycloallene manifold and so for a positive identification to be made of a certain compound, the NMR spectral data must be an exact match. Similarly, to that of marilzabicycloallene C (6) (figures 4.2.9.5 - 4.2.9.7), a detailed comparison of ^1H , ^{13}C resonances and J -values was made for each natural product.

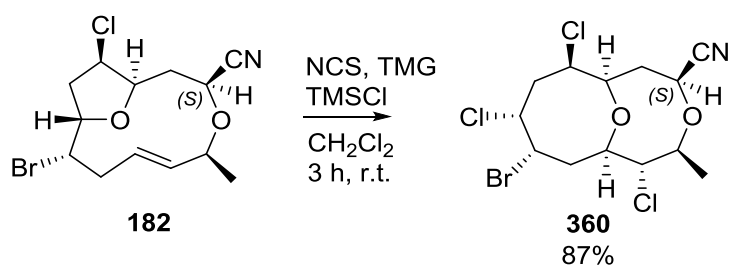
4.2.10 Transannular Dichlorination of Macrocyclic Olefin 182 & the Total Synthesis of Marilzabicycloallene D (7)

Having successfully applied the oxonium formation/fragmentation reaction to elucidate the link between obtusallenes to marilzabicycloallenes, it was now of interest to investigate the fourth member of the marilzabicycloallenes. Marilzabicycloallene D (7) does not fit the pattern of oxygenation at C_9 & C_{13} , instead both of these positions are chlorinated. Presumably, it undergoes a similar transannular -onium ion opening, but such a reaction with chloronium was unknown. In Braddock's investigation into the IBIAERO reaction,²³ a reaction was trialled employing NBS to generate a bromonium ion that subsequently undergoes transannular opening with chloride or bromide, as shown in scheme 4.2.10.1.



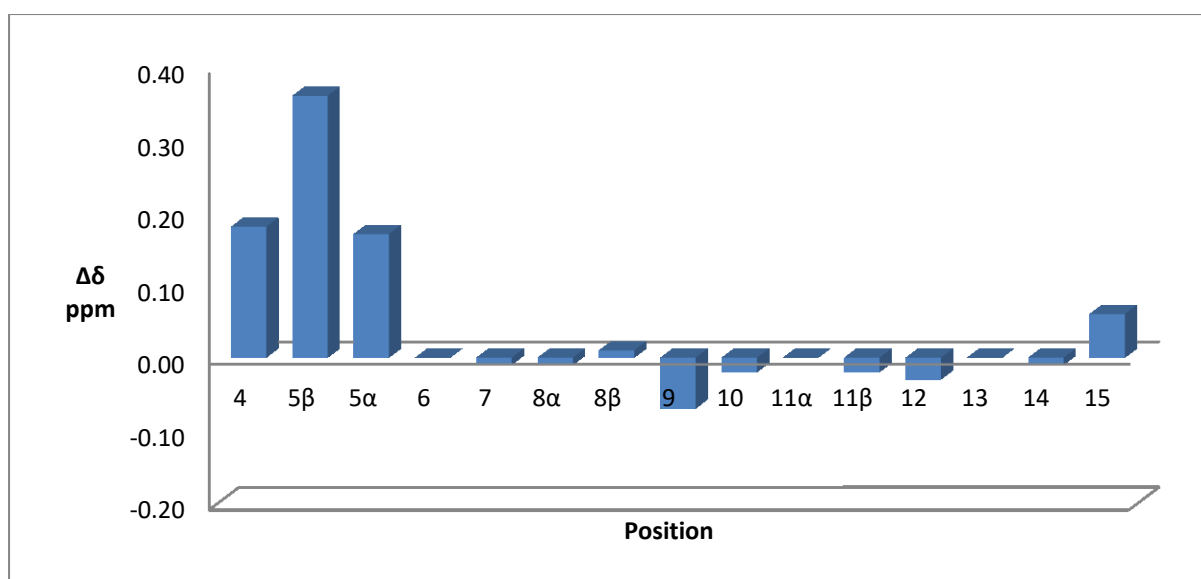
Scheme 4.2.10.1: Transannular bromonium-ion assisted epoxide opening with chloride and bromide.

Thus, it had been proven that halides could be appropriate nucleophiles as well as alkoxides and hydroxides. But it was still unknown if a chloronium was a suitable electrophile. By replacing NBS with *N*-chlorosuccinimide (NCS) the question could be answered. The reaction was trialled directly on macrocycle **182** and the source of the chloride nucleophile was chosen to be TMSCl as Braddock's work had shown that this prevented the formation of the 1,2-addition products, **355** & **358**, seen in scheme 4.2.10.1.



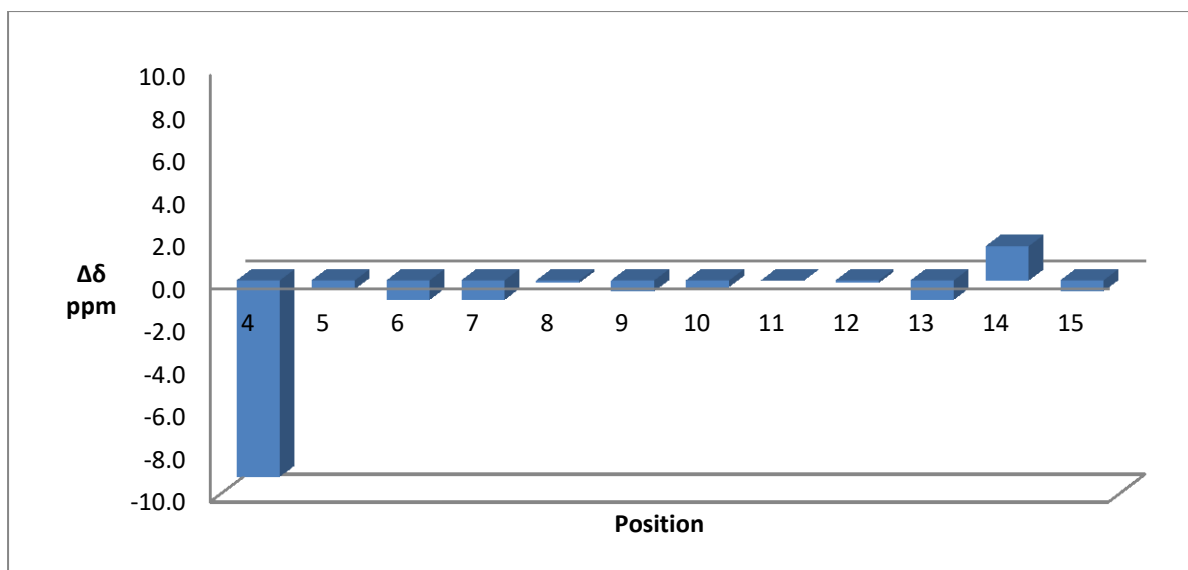
Scheme 4.2.10.2: Successful dichlorination of **182**.

Pleasingly, after stirring macrocycle **182** with NCS and TMSCl for 3 hours, trichloride **360** was collected in high yield. A comparison of the observed NMR spectral data with that of the published literature was conducted.¹²



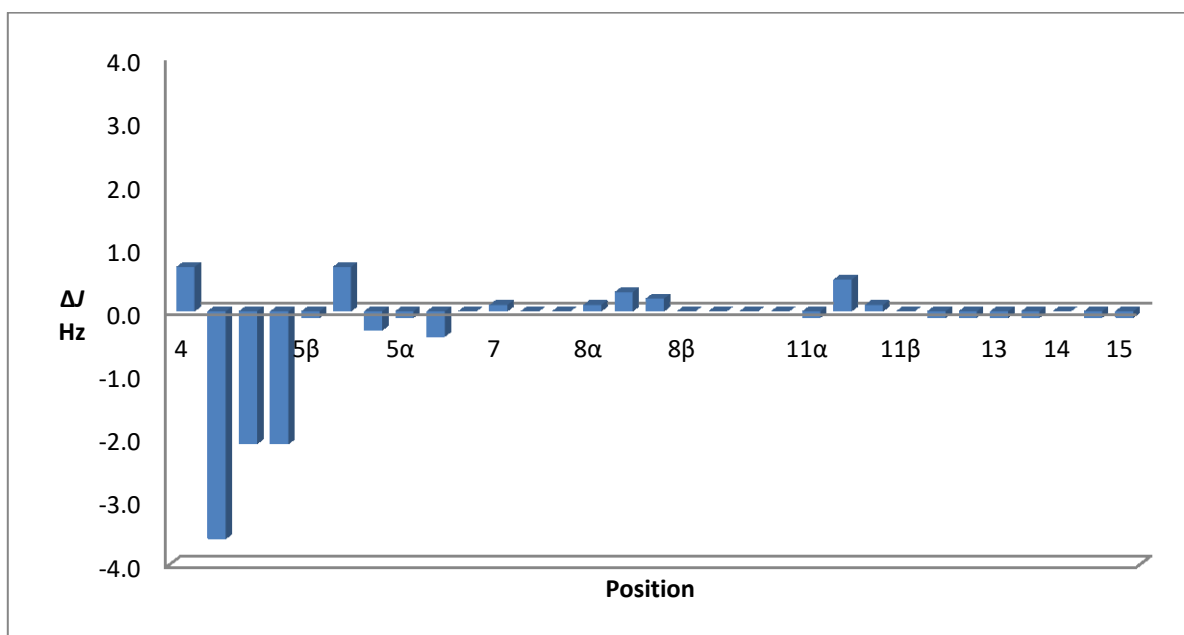
Root-mean-square deviation: 0.12 ppm

Figure 4.2.10.1: Comparison of ^1H NMR spectral data for trichloride **360** with marilzabicycloallene D (**7**).



Root-mean-square deviation: 2.7 ppm

Figure 4.2.10.2: Comparison of ^{13}C NMR spectral data for trichloride **360** with marilzabicycloallene D (**7**).

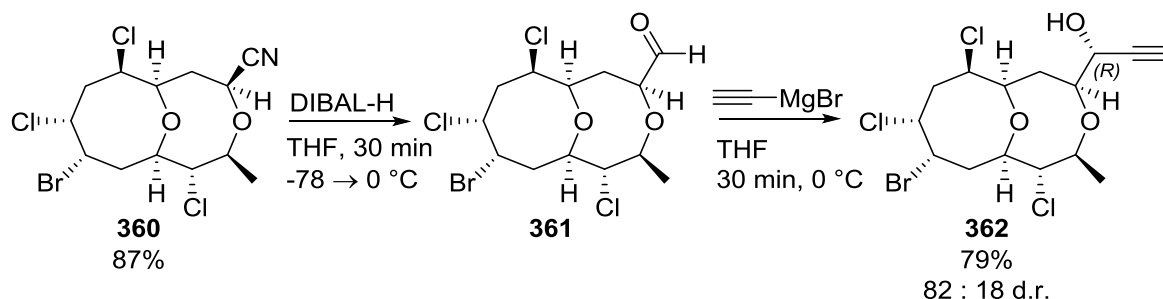


Root-mean-square deviation: 0.9 Hz

Figure 4.2.10.3: Comparison of ^1H NMR J -values for trichloride **360** with marilzabicycloallene D (**7**).

The above figures show that, apart from the large difference in chemical shifts and coupling constants for C₄ & C₅ due to the nitrile group, there was excellent overlap between the two data sets. The key positions of C₆, C₉, C₁₂ & C₁₃, bearing the new chlorides and etheric oxygens showed excellent correlation, meaning there is good probability that the functionality and stereochemistry matches. In addition, there was minimal evidence of the corresponding C₁₂ & C₁₃ diastereomer, meaning that there is high selectivity for electrophilic chlorination of the *Si* face of the olefin in macrocycle **182**.

Having a chloride at the sensitive C₁₃ position instead of an allyl or epoxide group meant that complications were not expected for the following DIBAL-H reduction and acetylide addition (scheme 4.2.10.3).



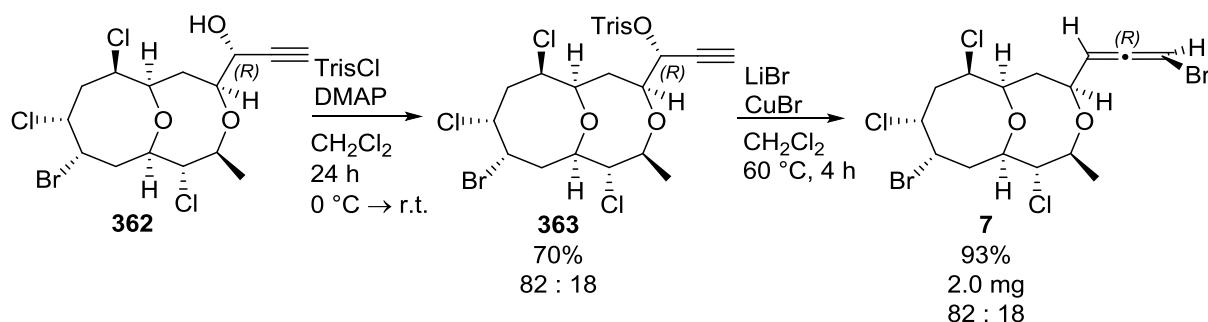
Scheme 4.2.10.3: DIBAL-H reduction and acetylide addition to trichloride nitrile **360**.

Indeed, after treatment of nitrile **360** with DIBAL-H and following addition of ethynylmagnesium bromide, alcohol **362** was isolated in 79% yield and a 82 : 18 diastereomeric ratio at C₃. The stereochemistry of C₃ not able to be assigned at this point and was assumed to be *R*-configured by analogy to the major product observed in the route

towards marilzabicycloallene C (6) (scheme 4.2.9.7). This was confirmed once the bromoallene had been installed (scheme 4.2.10.4).

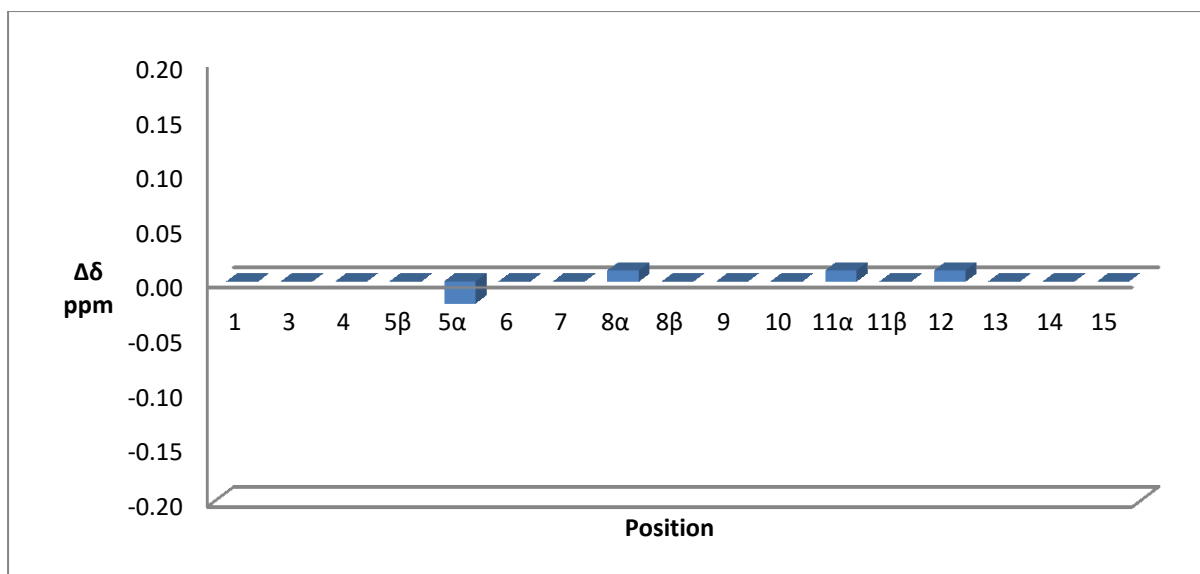
Unlike the olefin of macrocycles **182** & **183**, which can undergo fragmentation and marilzabicycloallene D core **341**, with a free hydroxyl that evidently renders the aluminium-imine chelate unstable, the chloride at C₁₃ of compound **360** adequately protects and prevents any major decomposition pathways upon reaction with DIBAL-H.

Alcohol **362** was carried forward to bromoallene installation *via* trisylation and bromination.



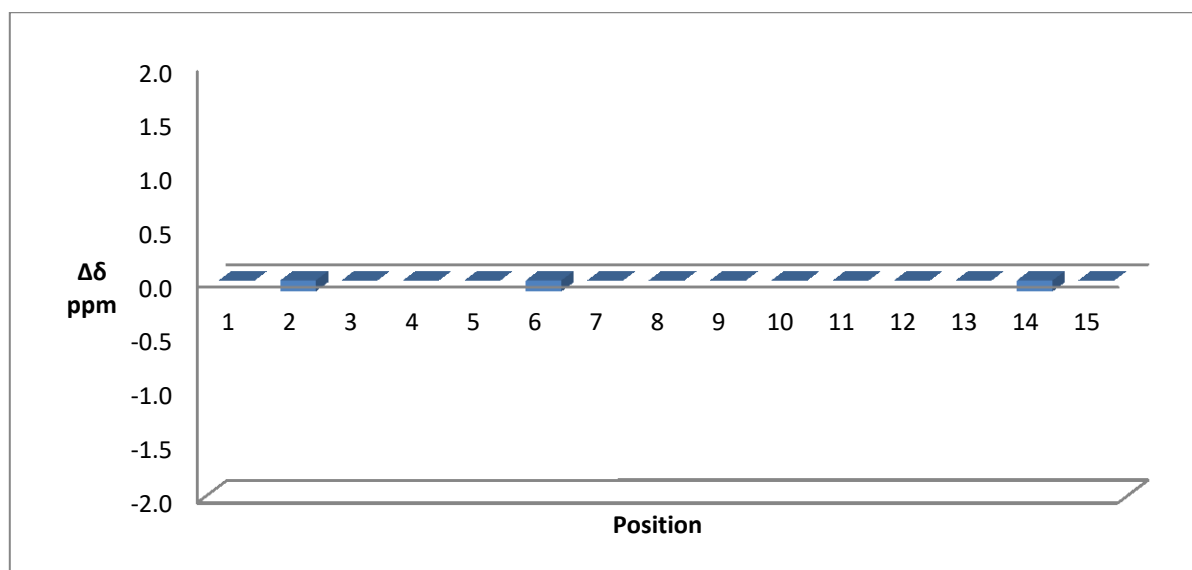
Scheme 4.2.10.4: Trisylation and bromination of alcohol **362** to give marilzabicycloallene D (7).

Trisylate protection of alcohol **362** using TrisCl and DMAP gave a good yield of 70%, with the same 82 : 18 diastereomeric ratio across the bromoallene. Bromination *via* the established LiCuBr₂ procedure produced 2.0 mg of material, in an excellent yield of 93%, maintaining the diastereomeric ratio. The NMR spectral data for this material was compared to that of the natural product, marilzabicycloallene D (7).



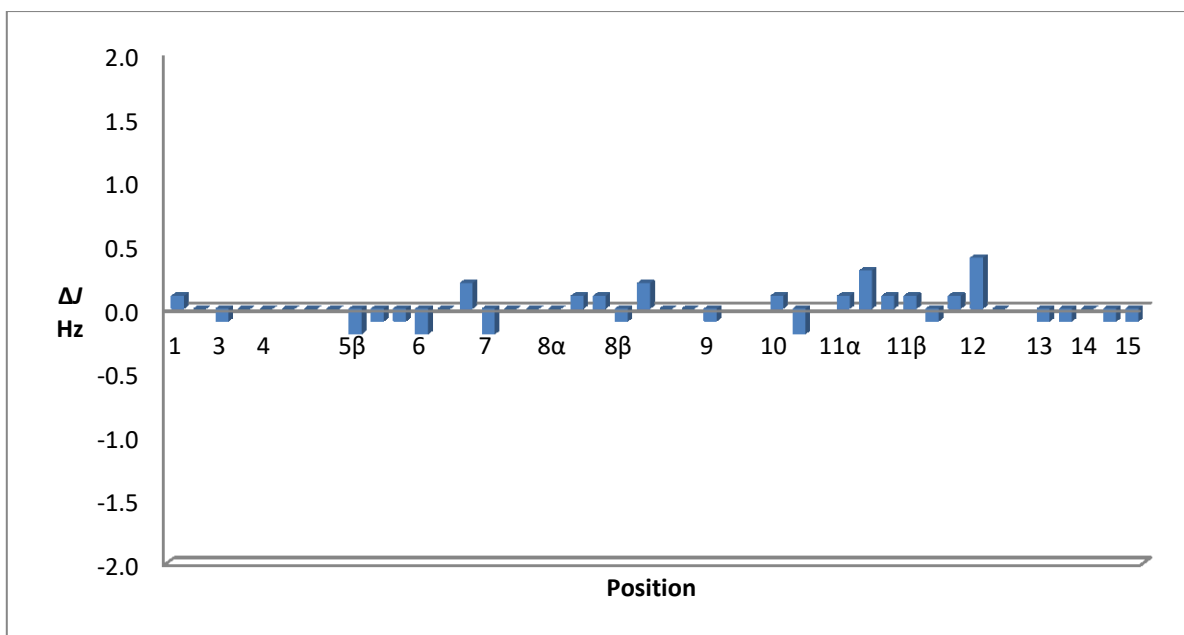
Root-mean-square deviation: 0.01 ppm

Figure 4.2.10.4: Comparison of ^1H NMR spectral data for synthetic and natural marilzabicycloallene D (7).



Root-mean-square deviation: 0.0 ppm

Figure 4.2.10.5: Comparison of ^{13}C NMR spectral data for synthetic and natural marilzabicycloallene D (7).



Root-mean-square deviation: 0.1 Hz

Figure 4.2.10.6: Comparison of ^1H NMR J -values for synthetic and natural marilzabicycloallene D (7).

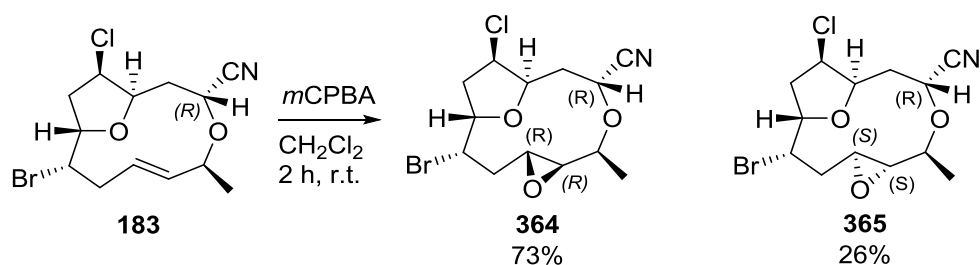
The above figures show that there is excellent overlap of both ^1H & ^{13}C NMR spectral data sets. Most of the ^1H NMR resonances show an identical match and an RMS value of 0.01 ppm. The positions that show minor deviations are those corresponding to C₅, C₈ & C₁₁, which are the conformationally flexible methylenes. The ^{13}C NMR spectra match excellently, with no resonances differing by more than 0.1 ppm and an overall RMS value of 0.0 ppm. Comparison of the J -values also demonstrates very close correlation, except for those of C₅, C₈ & C₁₁, although none of them deviate by more than 0.4 Hz. From this, it can be concluded that marilzabicycloallene D (7) had been successfully synthesised.

With this, it had been demonstrated that chloronium ions are indeed suitable electrophiles and that chloride is a strong enough nucleophile to induce transannular

rearrangement to give marilzabicycloallene cores. As such, strong evidence for the biosynthesis of marilzabicycloallene D (**7**) had been provided.

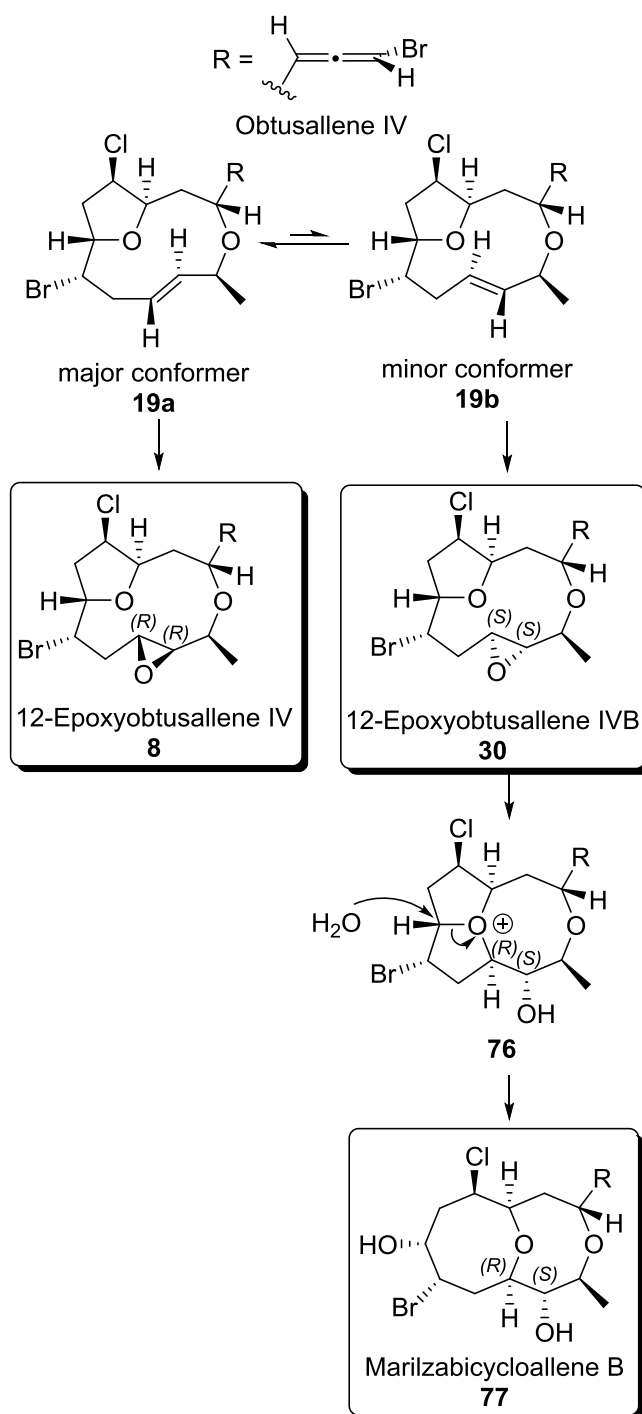
4.2.11 Epoxidation of Macrocyclic Nitrile **183**

With the syntheses of marilzabicycloallenes C & D (**6** & **7**) successful, attention turned to natural products that could be derived from diastereomeric nitrile **183**. This compound was epoxidised in exactly the same manner (scheme 4.2.11.1).



Scheme 4.2.11.1: Epoxidation of macrocycle **183**.

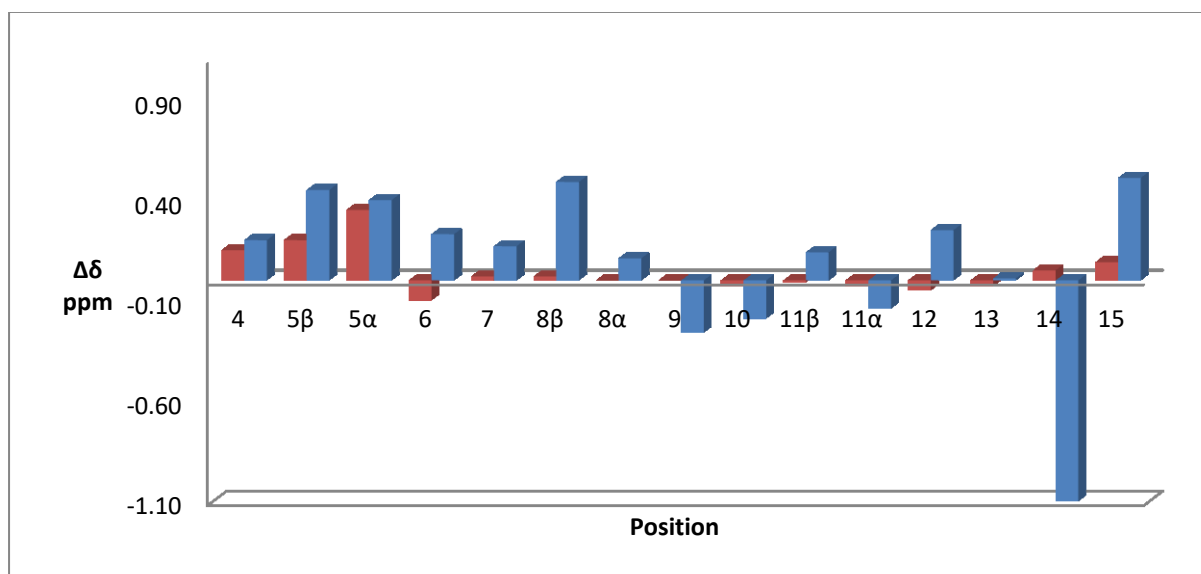
Treatment of olefin **183** with $m\text{CPBA}$ gave a quantitative yield of two epoxides, (*R,R*)-**364** & (*S,S*)-**365**, in an approximate 3 : 1 ratio respectively. Norte and co-workers proposed that due to the slow interconversion of the olefin in obtusallene IV (**19**), two possible epoxides would arise following biological epoxidation.¹²



Scheme 4.2.11.2: Regiochemistry of the epoxidation of obtusallene IV (**19**).

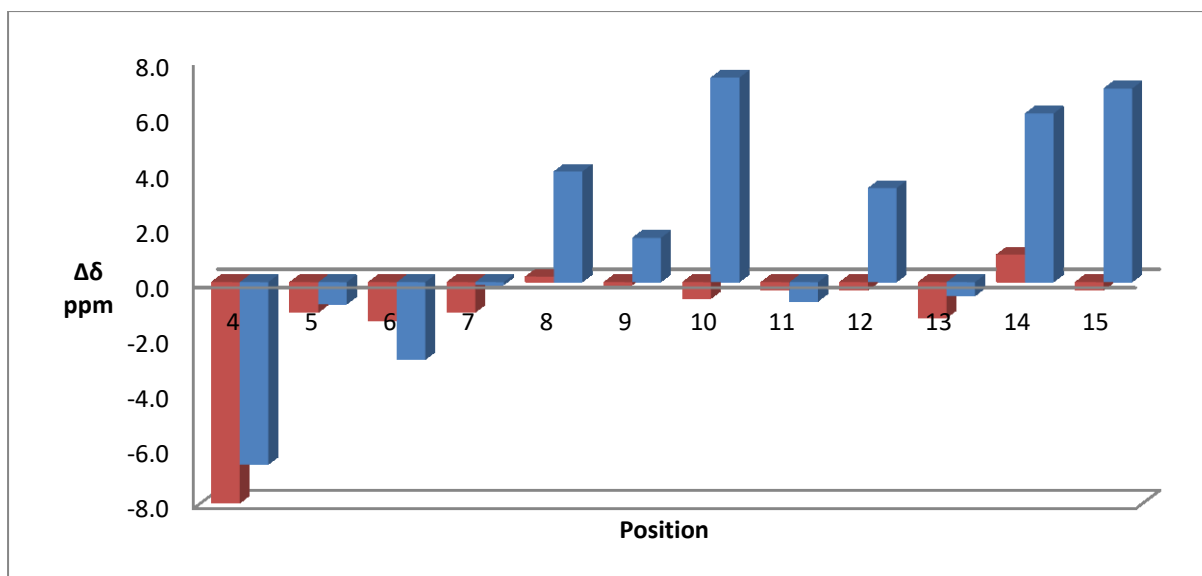
The major conformer **19a** exposes the *Re* face to solvent and thus would give the (*R,R*)-epoxide 12-epoxyobtusallene IV **8**. Conversely, the minor conformer **19b** exposes the *Si* face and would give the (*S,S*)-epoxide 12-epoxyobtusallene IVB (**30**) that can undergo

rearrangement to marilzabicycloallene B (77). These conformers were initially assigned by assuming the major and minor conformers were as predicted by Norte. This assignment was confirmed by comparing the products of epoxidation to the literature data for 12-epoxyobtusallene IV (8).



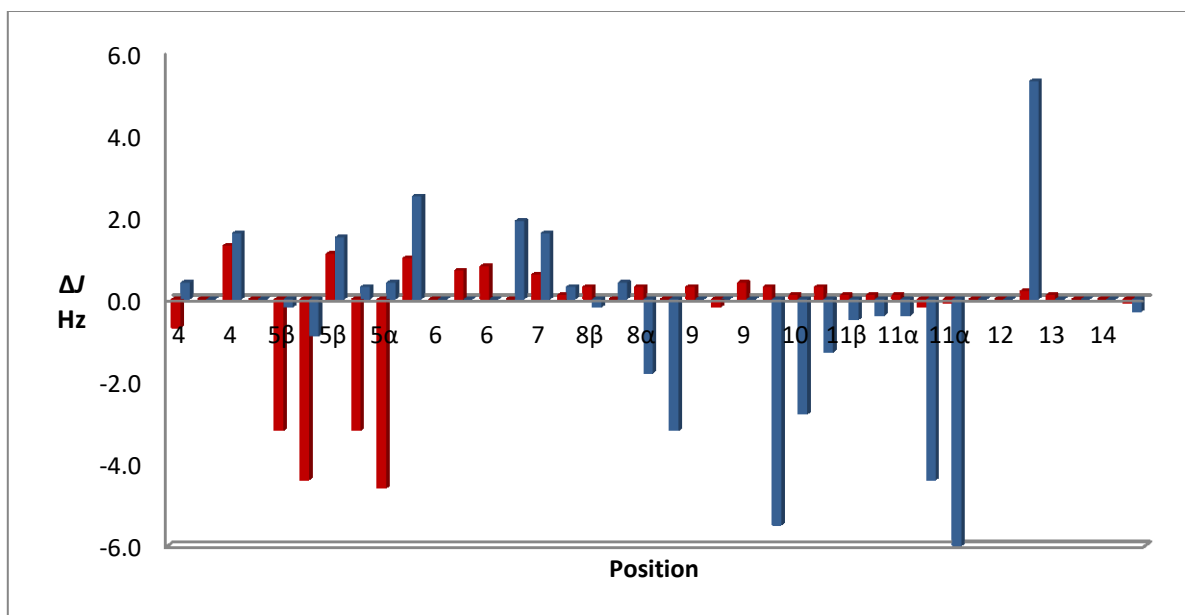
Root-mean-square deviation: 0.12 ppm (red) & 0.40 ppm (blue)

Figure 4.2.11.1: Comparison of ^1H NMR spectral data for epoxide 364 (red) & epoxide 365 (blue) with 12-epoxyobtusallene IV (8).



Root-mean-square deviation: 2.3 ppm (red) & 3.9 ppm (blue)

Figure 4.2.11.2: Comparison of ^{13}C NMR spectral data for epoxide **364** (red) & epoxide **365** (blue) with 12-epoxyobtusallene IV (**8**).



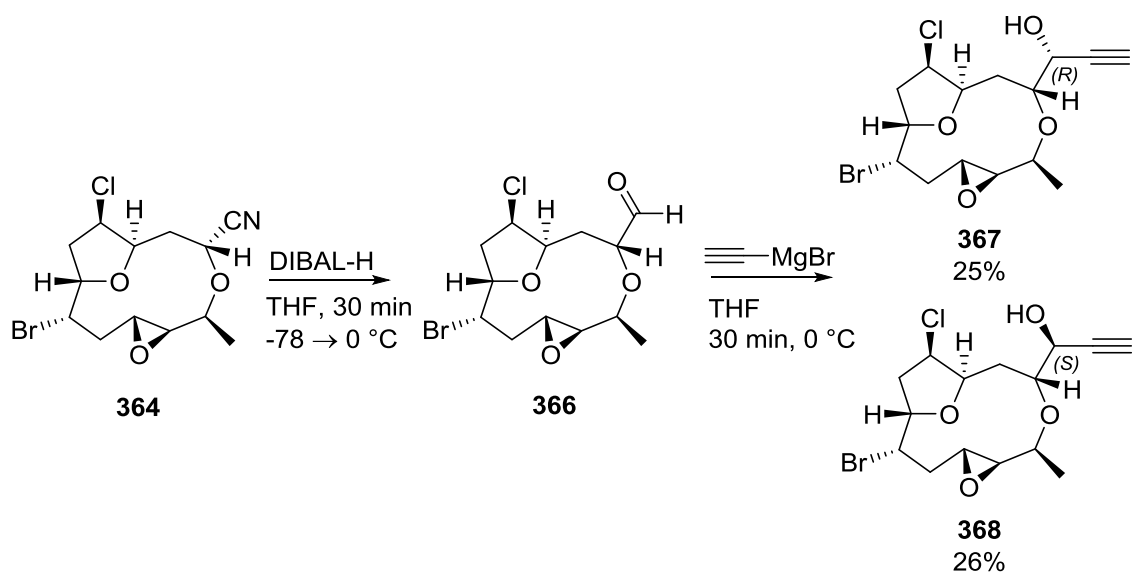
Root-mean-square deviation: 1.3 Hz (red) & 2.1 Hz (blue)

Figure 4.2.11.3: Comparison of ^1H NMR J -values for epoxide **364** (red) & epoxide **365** (blue) with 12-epoxyobtusallene IV (**8**).

All three graphs show that, despite the expected deviations at position 4 & 5, there is excellent overlap between the ^1H & ^{13}C spectra of 12-epoxyobtusallene IV (8) and compound **364** (red). This is especially true between positions H_7 & H_{13} , where the steric and electronic effects of the nitrile are minimal and these protons will more closely resemble those of the natural product **8**, as dictated by the conformation of the epoxide. Conversely, the comparison with compound **365** (blue) shows much larger deviation across the full range of positions. With maximum $\Delta\delta$ values of -1.11 ppm, 7.4 ppm and 5.3 Hz for ^1H , ^{13}C and J respectively, this compound is most likely to bear the opposing (*S,S*)- stereochemistry at the epoxide. A comparison of the RMS values confirms this, as they are significantly lower for compound **364** than **365**. From this, it can be concluded that the synthetic epoxidation mirrors that of the natural and the *Re* face is preferentially favoured. Two synthetic routes could now be followed: towards 12-epoxyobtusallene IV (8) and towards marilzabicycloallene B (77).

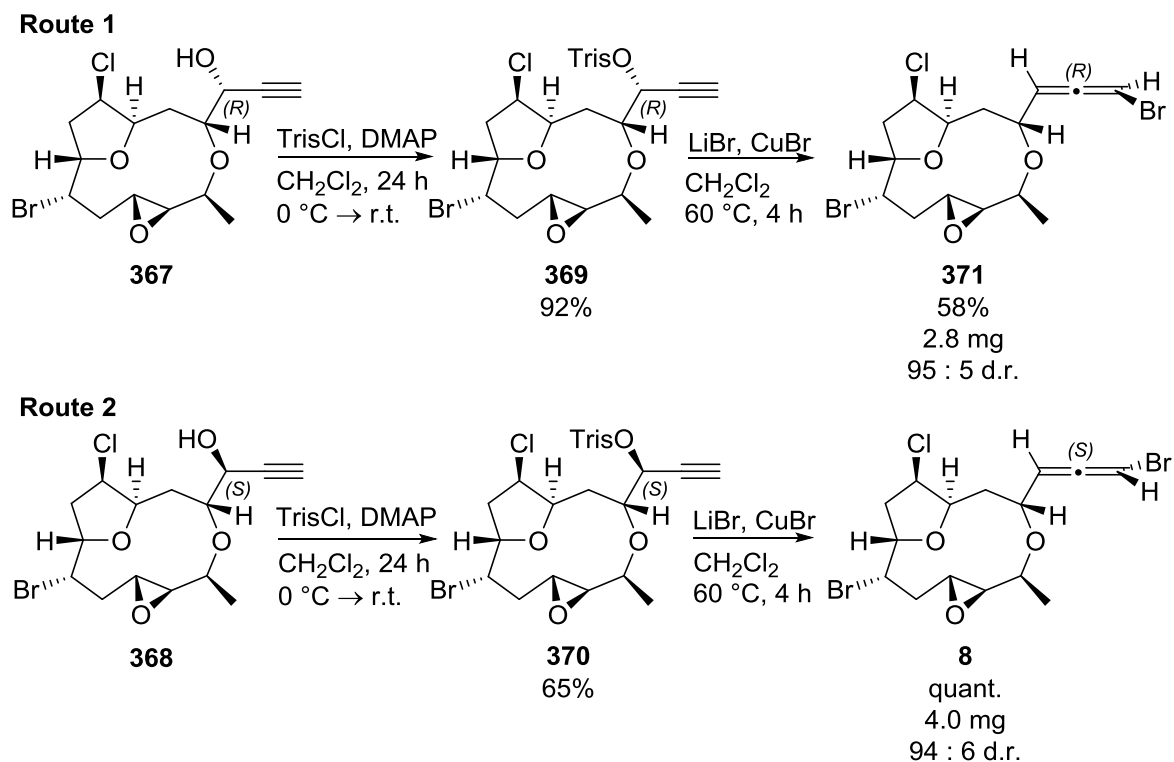
4.2.12 Total Synthesis of 12-Epoxyobtusallene IV (8)

Having concluded that compound **364** corresponded to natural product 12-epoxyobtusallene IV (8), the collected material could be reduced with DIBAL-H and treated to ethynylmagnesium bromide.



Scheme 4.2.12.1: DIBAL-H reduction and acetylide addition to nitrile **364**.

DIBAL-H reduction proceeded well (scheme 4.2.12.1), with aldehyde **366** being collected with good mass recovery and purity. The acetylide addition was achieved with a moderate yield of two propargylic alcohols (**367** & **368**), in an approximately 1 : 1 ratio. Fortunately, the products proved to be separable, meaning that unlike the synthesis of marilzabicycloallenes C & D (sections 4.2.9 & 4.2.10), the material could be carried forward with high diastereomeric purity. There was no unambiguous way at this stage to determine the stereochemistry of propargylic alcohols **367** & **368** and therefore confirm which would lead to the natural product. For this reason, both compounds were carried forward and the stereochemistry retroactively assigned.



Scheme 4.2.12.2: Derivation of propargylic alcohols **367** & **368** into 12-epoxyobtallene IV (**8**) and its C_1 enantiomer **370**.

Trisylation of both alcohols **367** & **368** proceeded very well, with a 92% yield of compound **369** collected and a 65% yield of compound **370**. This loss in yield was due to the reaction not going to completion. Taking into account the recovered material, this reaction can be considered quantitative. Close examination of the baseline showed these compounds to be diastereomerically (and hence enantiomerically) pure. The key peaks at 5.1, 2.3 and 1.0 ppm, corresponding to H_3 , H_1 and H_{15} respectively, are the most distinct and would show the presence of any diastereomeric compounds present (figure 4.2.12.1).

Comparison of the ^3J coupling constants of the H_3 resonances at ~5 ppm for trisylates **369** & **370** was conducted, in a similar manner to Overman's analysis whereby the trisylate with the lowest coupling constant is predicted to correspond to the natural product.^{53b} In this

case, trisylate **369** had a $^3J_{H_3-H_4}$ value of 4.9 Hz, while trisylate **370** showed 2.5 Hz. This analysis predicted that compound **370** bore *S*-stereochemistry at C₃ and thus was the correct diastereomer. This was ultimately proven correct following bromoallene installation.

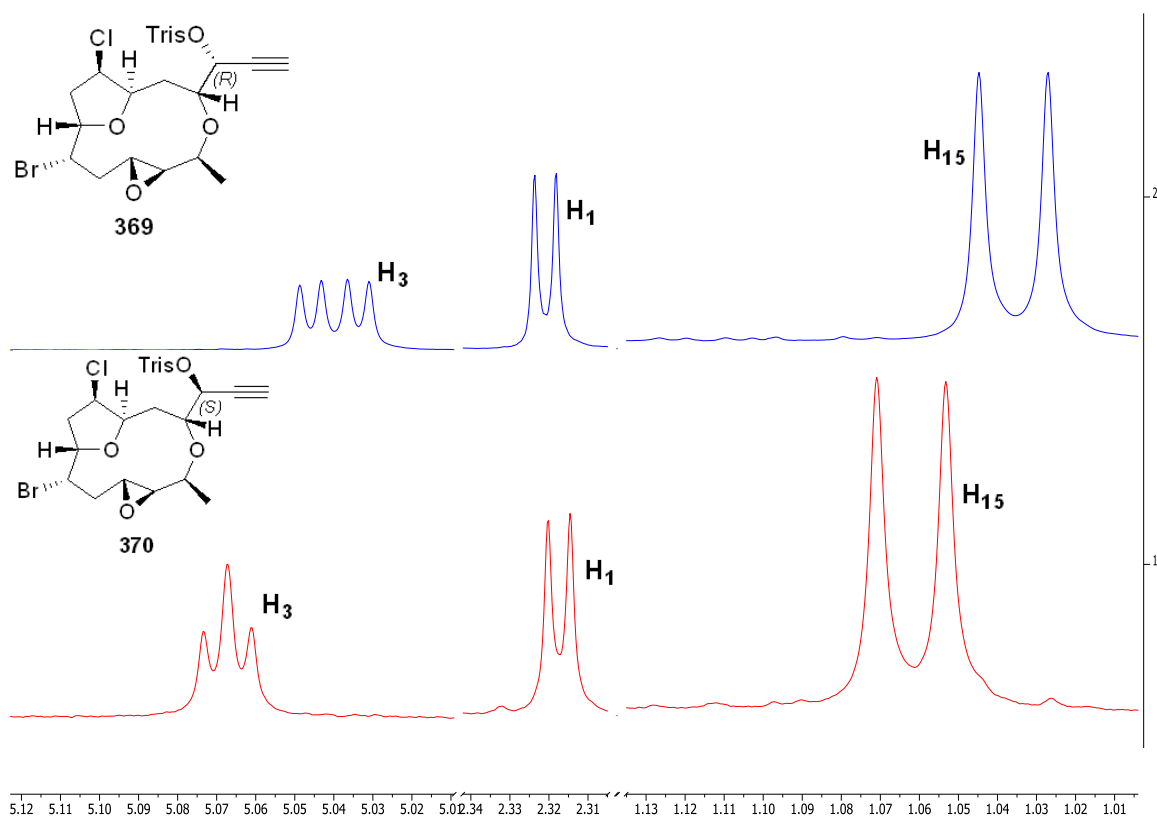
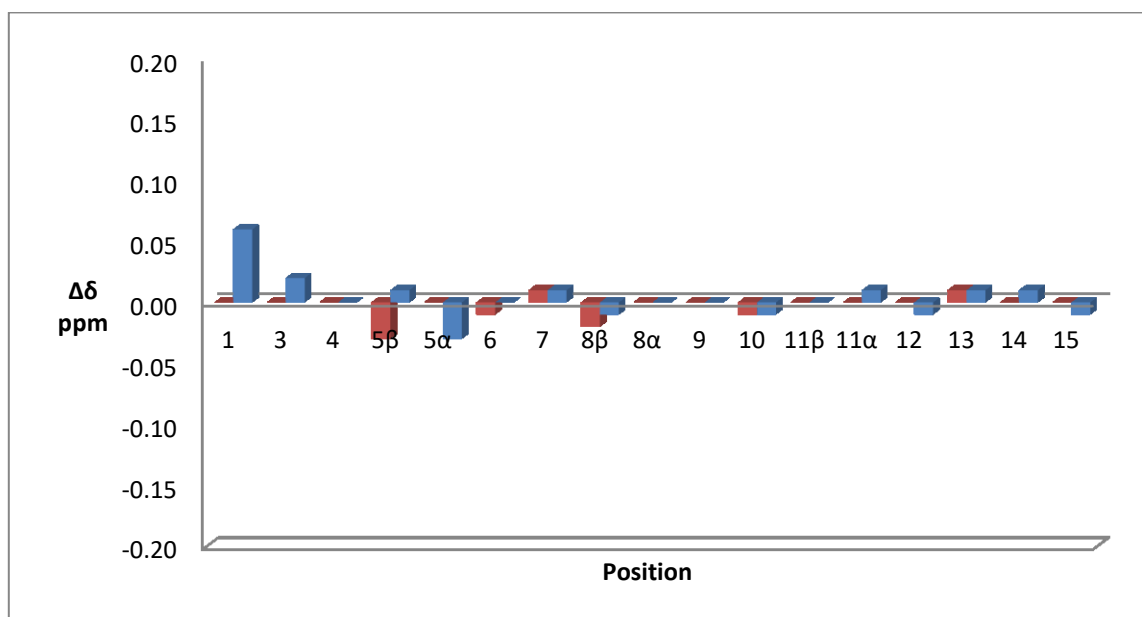


Figure 4.2.12.1: ^1H NMR spectra of trisylates **369** (above) and **370** (below)

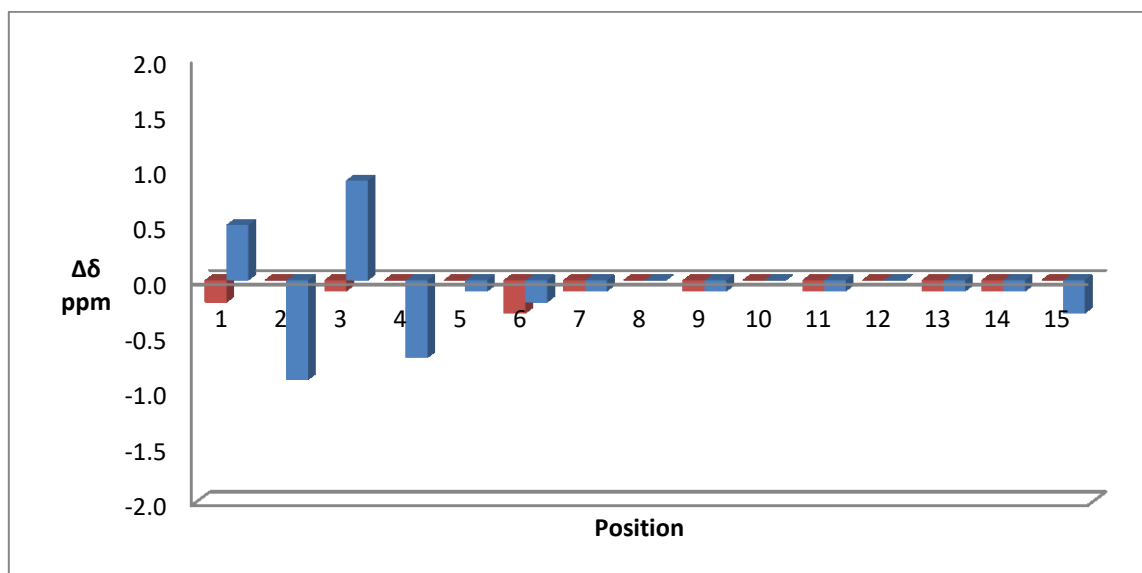
Submitting trisylates **369** & **370** to the bromination procedure gave bromoallenes **371** & **8** in 58% and quantitative yields respectively (scheme 4.2.12.2). This translates to 2.8 mg & 4.0 mg respectively. A further 2.3 mg of bromoallene **8** was prepared in a separate reaction to increase the quality of spectral data. The loss of isolated yield of **371** was due to incomplete reaction and may have been quantitative based on recovered trisylate **369**. Both samples also contained the corresponding propargylic bromides (**29** & **372**, scheme 4.2.12.3),

which were inseparable and unavoidably formed together. Fortunately, the peaks were sharp and distinct enough to allow an $\Delta\delta$ analysis to be conducted.



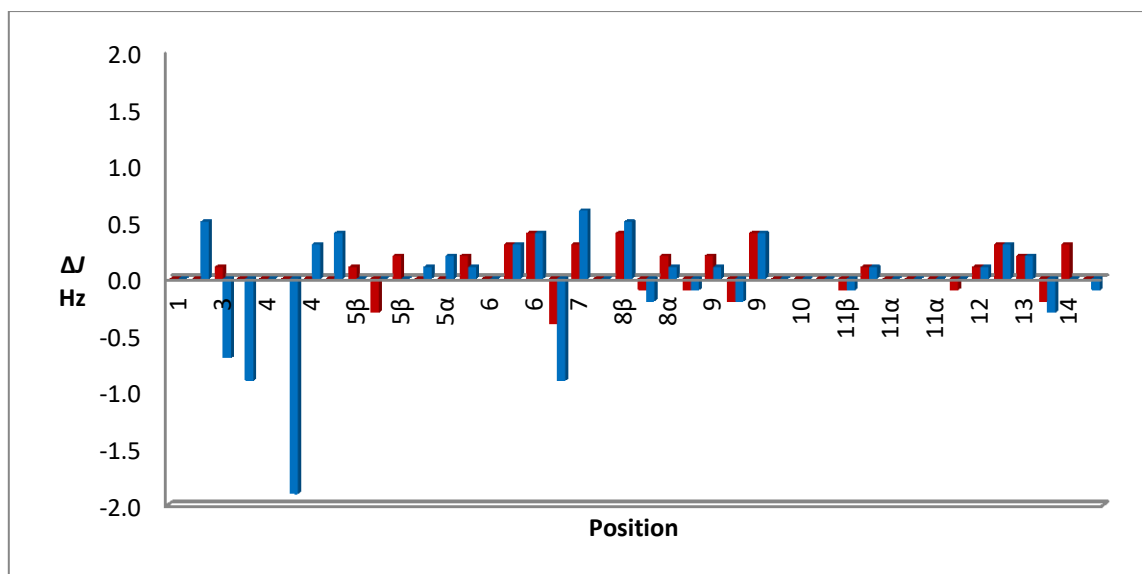
Root-mean-square deviation: 0.01 Hz (red) & 0.02 Hz (blue)

Figure 4.2.12.2: Comparison of ^1H NMR spectral data for synthetic **8** (red) & C₁ epimer **371** (blue) with 12-epoxyobtusallene IV (**8**).



Root-mean-square deviation: 0.11 Hz (red) & 0.41 Hz (blue)

Figure 4.2.12.3: Comparison of ^{13}C NMR spectral data for synthetic **8** (red) & C₁ epimer **371** (blue) with 12-epoxyobtusallene IV (**8**).



Root-mean-square deviation: 0.19 Hz (red) & 0.50 Hz (blue)

Figure 4.2.12.4: Comparison of ^1H NMR J -values for synthetic **8** (red) & C_1 epimer **371** (blue) with 12-epoxyobtusallene IV (**8**).

The above graphs show that the correlation between spectra is much better for the bromoallene (**8**) arising from route 2 in scheme 4.2.12.2 (red). This allows us to retrospectively assign alcohol **368** as having an *S*-configuration and thus the derived bromoallene as 12-epoxyobtusallene IV (**8**). The data for synthetic 12-epoxyobtusallene IV (**8**) matches that reported very closely. There is some discrepancy at certain peaks, especially in the ΔJ analysis, but these are often those resonances showing complex and overlapping multiplets. Norte and co-workers may have interpreted the peaks differently.¹² Even so, the signals match very closely, especially for the peaks corresponding to the bromoallene, which are the most useful in distinguishing compounds **371** & **8**. The data for epimeric compound **371** (blue) also correlates very well along positions $\text{C}_5 - \text{C}_{15}$, but that is to be expected as the macrocyclic stereochemistries are identical. The real differences arise at positions $\text{C}_1 - \text{C}_4$. Only looking at the mismatch for these peaks allows us to discount the product of route 1

(371) as being the natural product. RMS analysis for all three data sets shows that compound 8 has by far the closest correlation.

Interestingly, the ^1H NMR spectra showed that the previously pure compounds now had approximately 5% of the opposing C_1 diastereomer. Figure 4.2.12.5 show that the peaks at 6.1, 5.4, 2.7 and 1.1 ppm, corresponding to C_1 , C_3 , $\text{C}_{1(\text{proparg. brom.})}$ and C_{15} respectively. Each is flanked by peaks representing the minor products in each case and can be directly mapped onto the other spectra.

The presence of the propargylic bromides is expected due to the possibility of double $\text{S}_{\text{N}}2'$ bromination occurring (scheme 4.2.12.3). A bromoallene is a suitable substrate for LiCuBr_2 to substitute a bromine at C_3 . However, the presence of minor diastereomers suggests that the bromination isn't as stereospecific as thought.

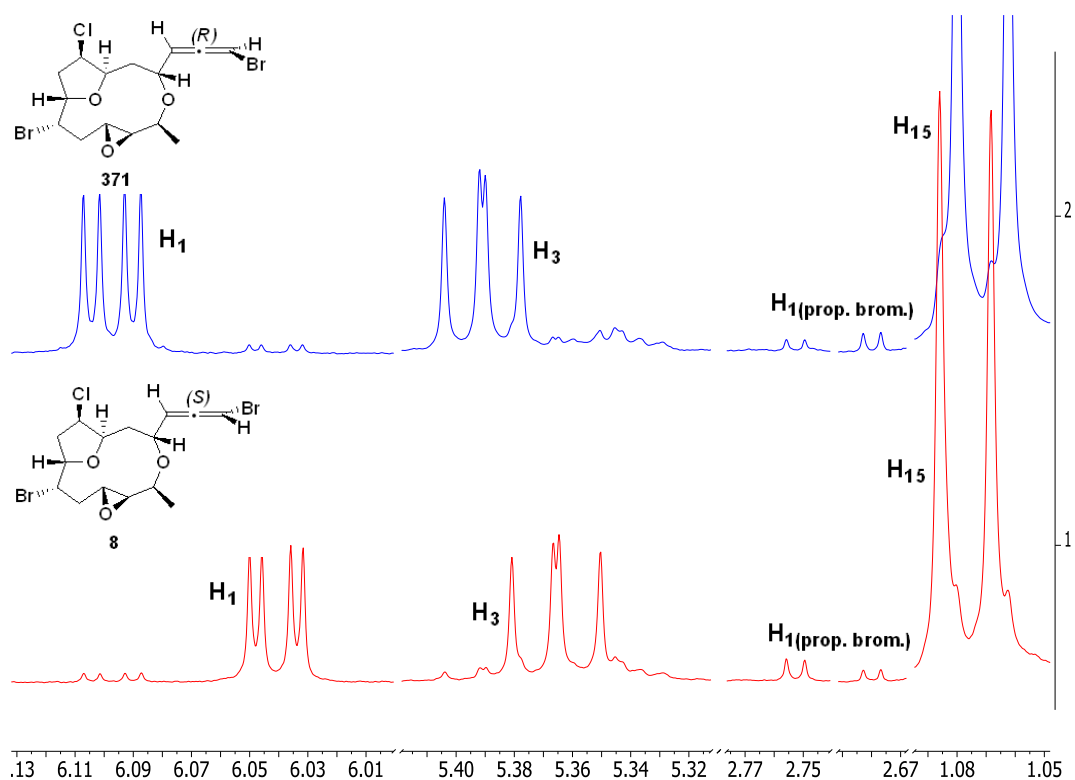
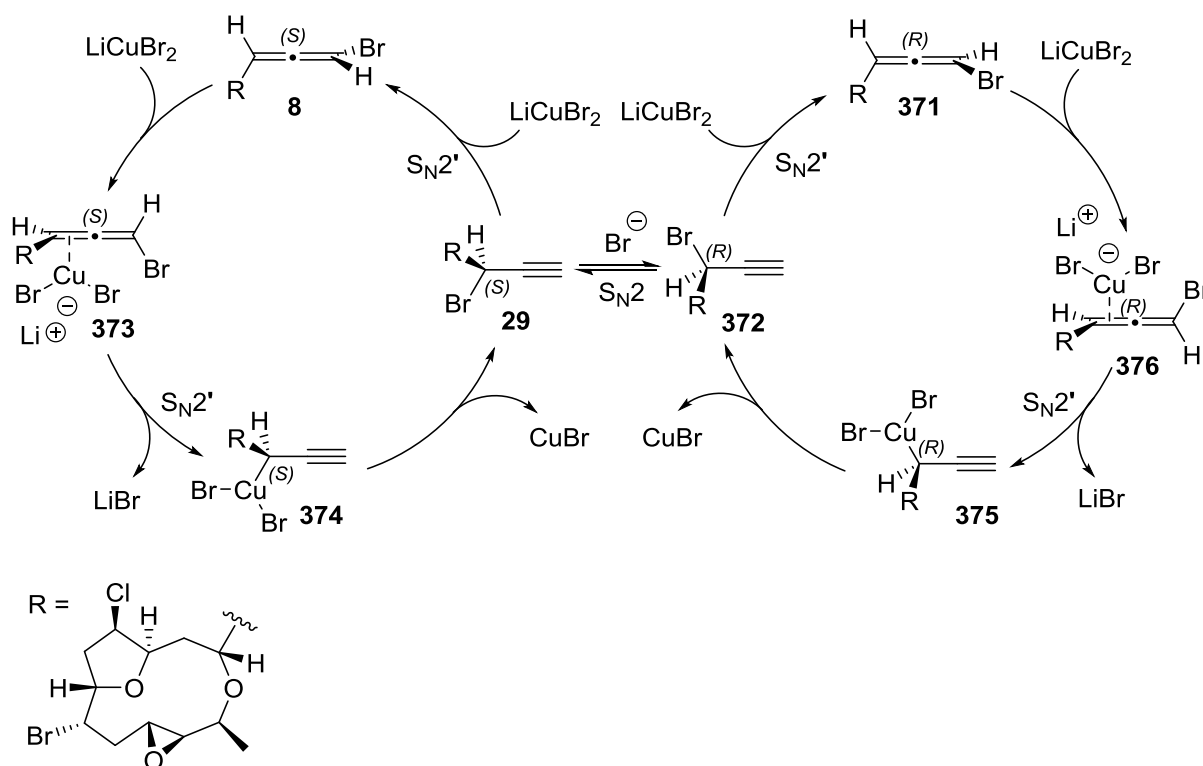


Figure 4.2.12.5: ^1H NMR spectra of bromoallenes 371 (above) and 8 (below).

It is possible that as the propargylic bromides are formed by the previously suggested route (scheme 3.2.1.5, *vide supra*) followed by direct S_N2 substitution by free bromide resulting in racemisation at C₃.^{56b} The resultant compounds can be subjected to a second S_N2' to give the opposing bromoallene. This would explain the decrease in diastereopurity in the products, as well as the roughly similar ratio of propargylic bromides observed in figure 4.2.12.5, as an equilibrium of these compounds would form. A proposed catalytic cycle is shown in scheme 4.2.12.3).



Scheme 4.2.12.3: Possible catalytic cycle resulting in racemisation of bromoallenes/propargylic bromides *via* S_N2.

Interestingly, soon after the completion of the synthesis of 12-epoxyobtusallene IV (8), the latest isolation paper published by Norte and co-workers reported the discovery of marilzanin (29).^{13h}

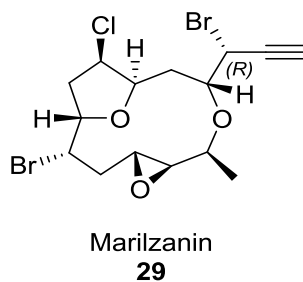
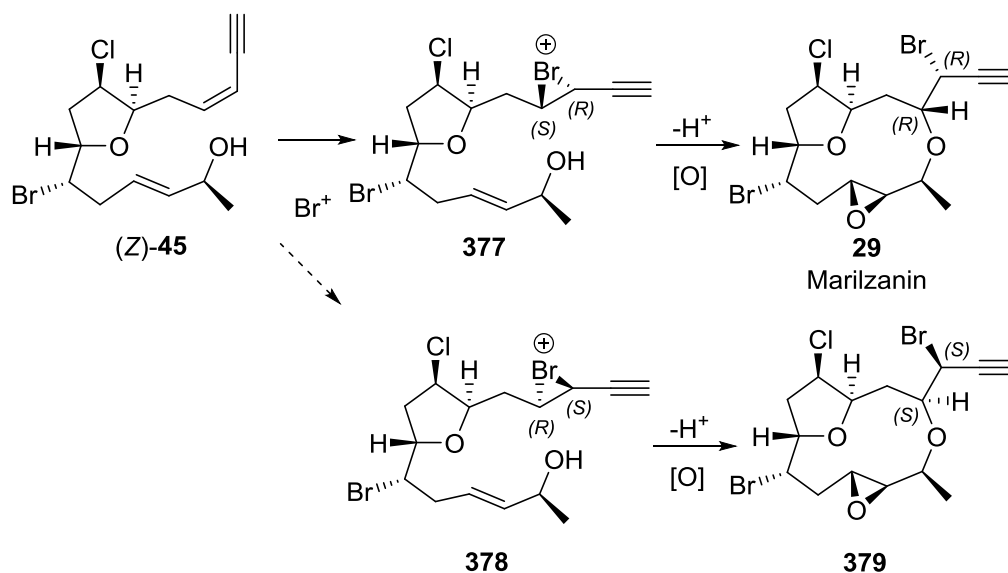


Figure 4.2.12.6: Marilzanin (29), isolated from *Laurencia marilzae*.

Spectral data for this compound contains two key peaks; the H₁ alkyne proton at 2.68 ppm and H₄ at 4.06 ppm with coupling constants of 11.2, 3.9 & 1.8 Hz. Both of these are visible in the spectra of synthetic compounds **371** & **8** (figure 4.2.12.5). Unfortunately, all of the other peaks are obscured by the major products. Although not strong enough to claim a successful total synthesis, we have high confidence that marilzanin (29) is present in both samples, along with its C₃ epimer **372**.

Norte invokes a bromination of the double bond of the enyne of Braddock's macrocyclic ring-closure precursor **45**, followed by S_N2 attack by the free alcohol to simultaneously close the ring and form a propargylic bromide (scheme 4.2.12.4). If this is the case, it might be expected that another natural product would be formed from bromination of the other face of the enyne (**379**). Just as obtusallene II & IV (**15** & **19**) are formed from common precursor **45**, so would marilzanin (29) & compound **379** be co-synthesised.

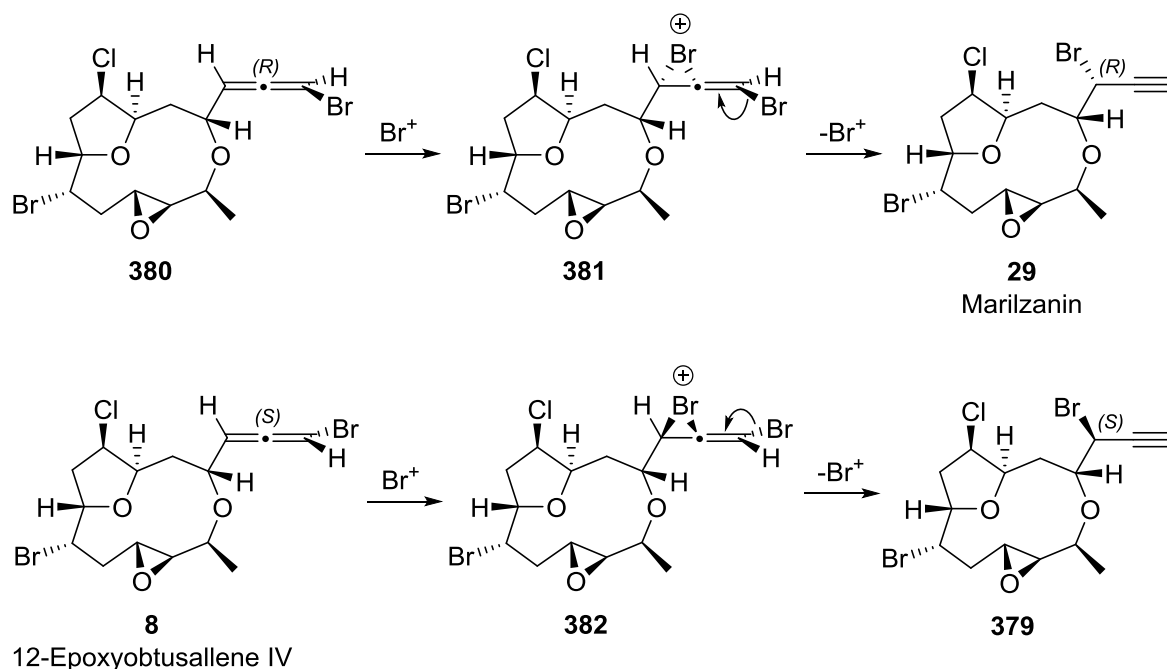
In addition, such a biosynthesis invokes (Z)-**45** as such macrobromooetherification have been shown to proceed in a *syn*-manner. Obtusallene II & IV (**15** & **19**) are expected to be formed from the geometric isomer (E)-**45**.²⁶



Scheme 4.2.12.4: Norte's proposed biogenetic origin of the propargylic bromide of marilzanin (**29**) with a possible side-reaction leading to C₃ epimer **379**.

Compound **379** may therefore represent an undiscovered natural product. An alternative, unconsidered route to these propargylic bromides would be a second electrophilic bromination event on an existing bromoallene, facilitated by vanadium bromoperoxidase. The bromonium ion could be opened by the terminal bromide to give a brominated alkyne (scheme 4.2.12.5). This could be lost as Br^+ to any available nucleophile to yield a propargylic bromide. However, analysis of the mechanism suggests that the opening of (S)-bromoallene of 12-epoxyobtusallene IV (**8**) would result in (S)-propargylic bromide **379**, *via* bromonium ion **381**. The formation of marilzanin (**29**) would require the (R)-

bromoallene of **380**, *via* bromonium ion **381**, which does not represent a known natural product.

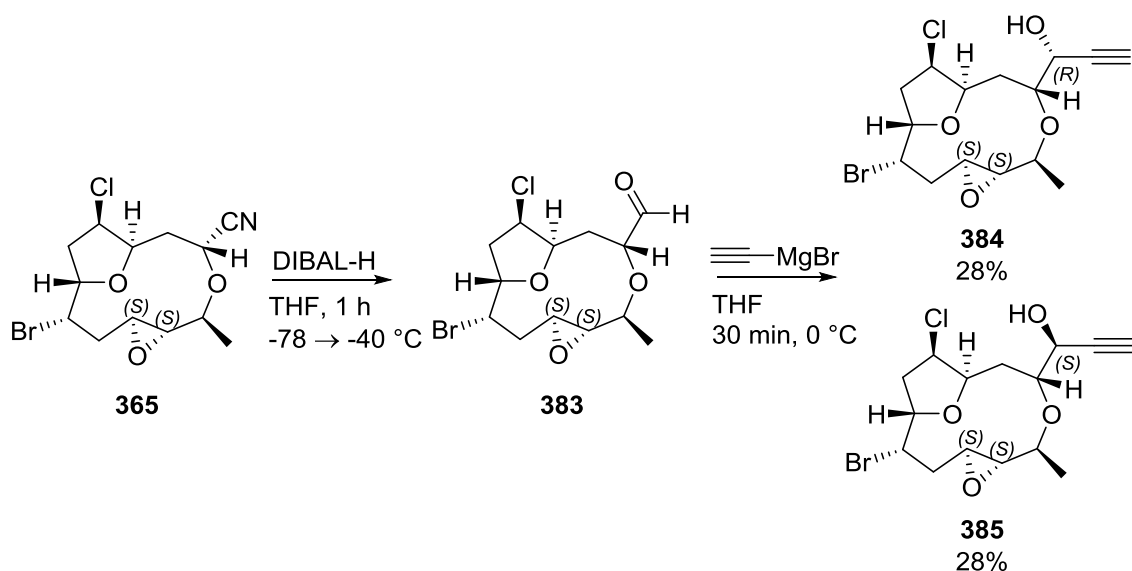


Scheme 4.2.12.5: Possible stereochemical implications of the electrophilic brominations of bromoallenes **380** & **8**.

Marilzabicycloallene C (**6**) had previously been prepared from its 12-epoxyobtusallene II (**5**) precursor. There is only one known marilzabicycloallene derived from an obtusallene IV (**19**) core, marilzabicycloallene B (**77**). (*S,S*)-Epoxide **365** was revisited, to determine if a bromoallene could be installed and rearranged to marilzabicycloallene B (**77**).

4.2.13 Attempt at Synthesis of Marilzabicycloallene B (77)

$\Delta\delta$ analysis and the completion of the synthesis of 12-epoxyobtusallene IV (8) had proved the (*R,R*)-stereochemistry of epoxide **364** (scheme 4.2.11.1). The minor product in this epoxidation, (*S,S*)-epoxide **365**, had the required configuration to be advanced to marilzabicycloallene B (77). Only a small amount of material was available for this attempt, but the relative ease in the synthesis of marilzabicycloallene C (6) & 12-epoxyobtusallene IV (8) suggested little complication.



Scheme 4.2.13.1: DIBAL-H reduction and acetylide addition to nitrile **365**.

Installation of the propargylic alcohol proceeded well, allowing compounds **384** & **385** to be collected in equal 28% yields. Fortunately, the two compounds were separable, allowing individual characterisation. However, it was not possible at any point to positively identify the C₃ stereochemistry. The best attempt that could be made was to compare to the propargylic alcohols produced in the previous section, **367** & **368** (scheme 4.2.12.1). Based on the similar yields and lack of stereoselectivity, it can be inferred that the diastereoiduction

afforded by the macrocycle ether will be the same in both aldehydes, **366** & **383**.

Furthermore, this suggests that the polarity and spectral properties of each pair of propargylic alcohols will be similar.

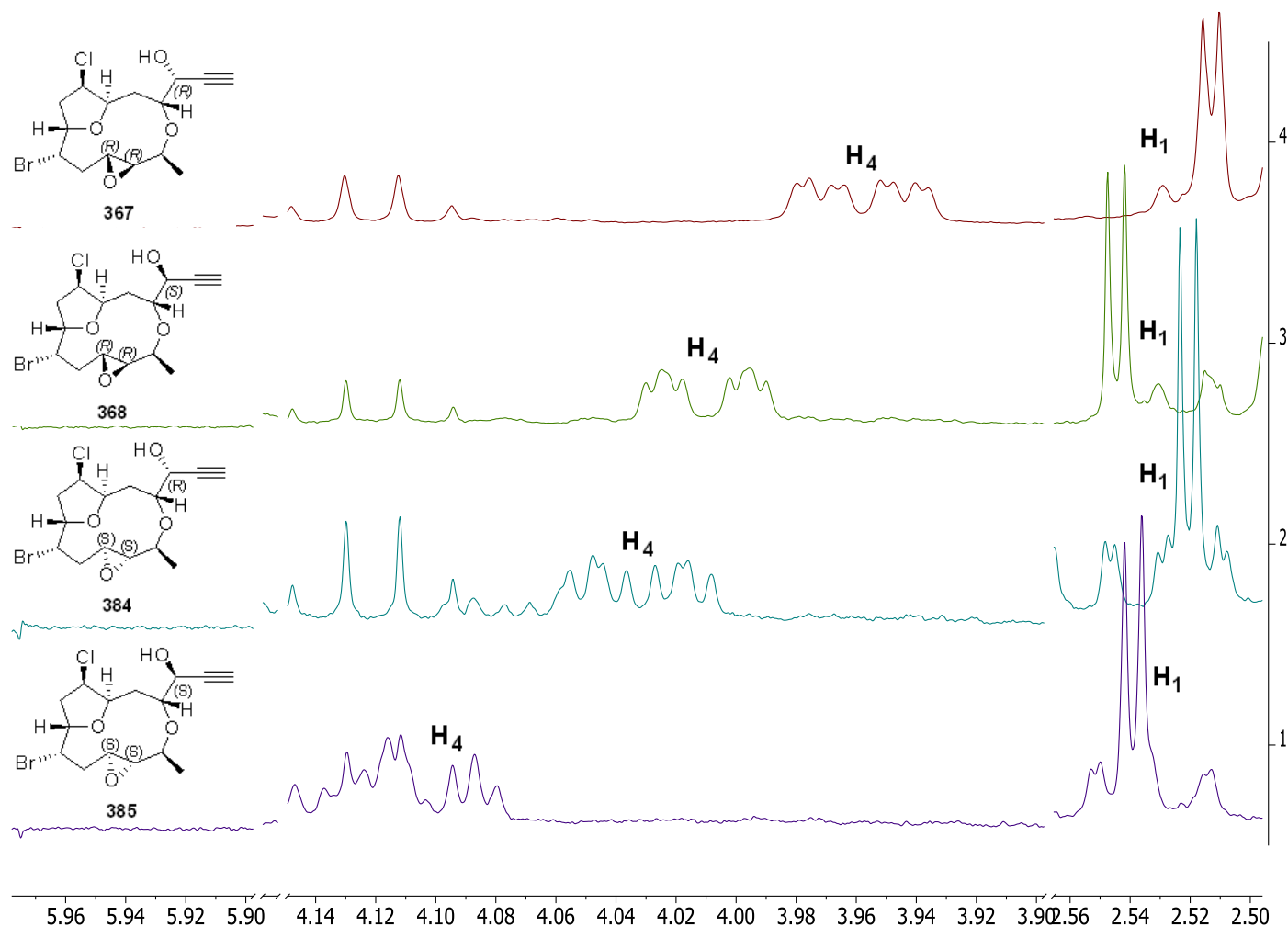


Figure 4.2.13.1: Comparison of the ^1H spectra of propargylic alcohols **367** (red), **368** (green), **384** (blue) & **385** (purple).

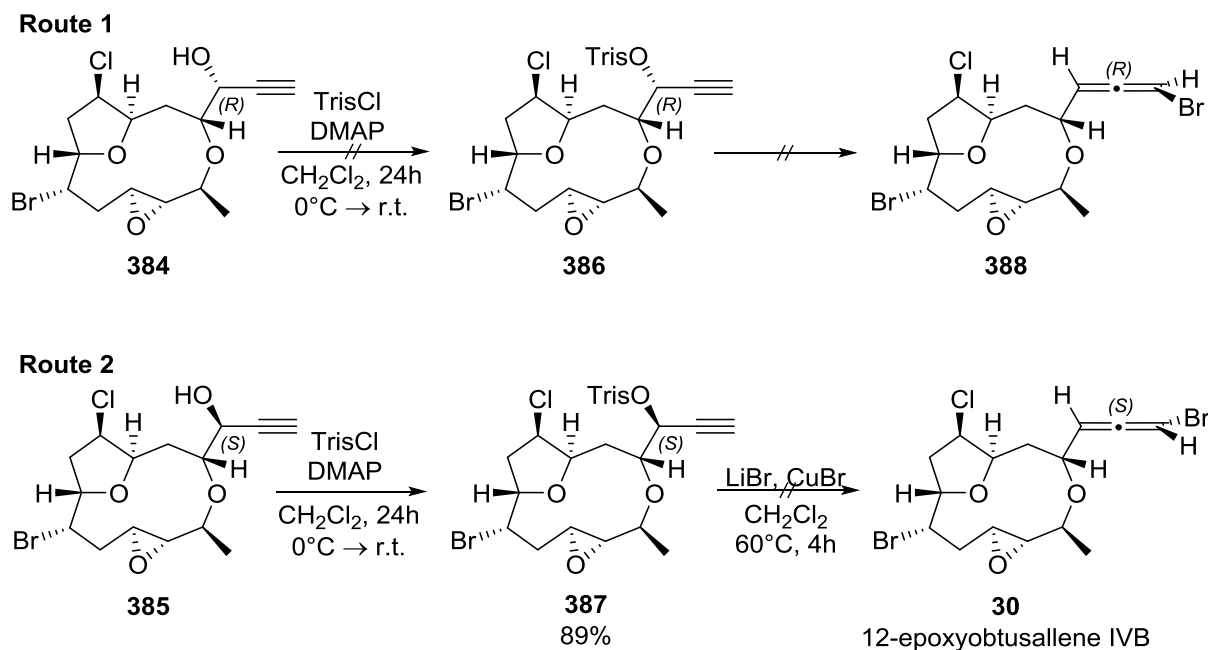
The above spectra show the regions corresponding to the signals for H_1 and H_3 . It can be seen that the alkyne peaks around 2.5 ppm, for the pairs **367** & **384**, and **368** & **385**, show some overlap. Looking at the H_4 peaks around 4.0 ppm, **367** & **384** show clear doublet of

doublet of doublets, while **368** & **385** tend towards a doublet of triplets. Furthermore, compounds **367** & **384** were both the first to elute and **368** & **385** were the last.

Although these assignments are not with complete certainty, compound **384** will be referred as (*R*) and **385** as (*S*).

Interestingly, both compounds showed impurities of about 30% by mass, that were not removed by column chromatography. Comparison of the visible signals to the literature data for marilzabicycloallene B (**77**) showed some strong similarities. The most important of which are at ~4.5 & 3.8 ppm, which bear close resemblance to H₉ and H₁₂ in marilzabicycloallene B (**77**). As these are the protic environments that vary the greatest during the transannular oxonium rearrangement from obtusallene to marilzabicycloallene cores, it is possible that the macrocycle of compounds **384** & **385** readily undergoes rearrangement under the reaction conditions, most likely during the citric acid work-up or during column chromatography.

With only small quantities of two unknown propargylic alcohols, of uncertain purity, attempts were made to trisylate and brominate. Again, these are labelled as route 1 for the (*R*)-alcohol **384** and route 2 for (*S*)-alcohol **385**.



Scheme 4.2.13.2: Attempted trisylations and brominations of propargylic alcohols **384** & **385**.

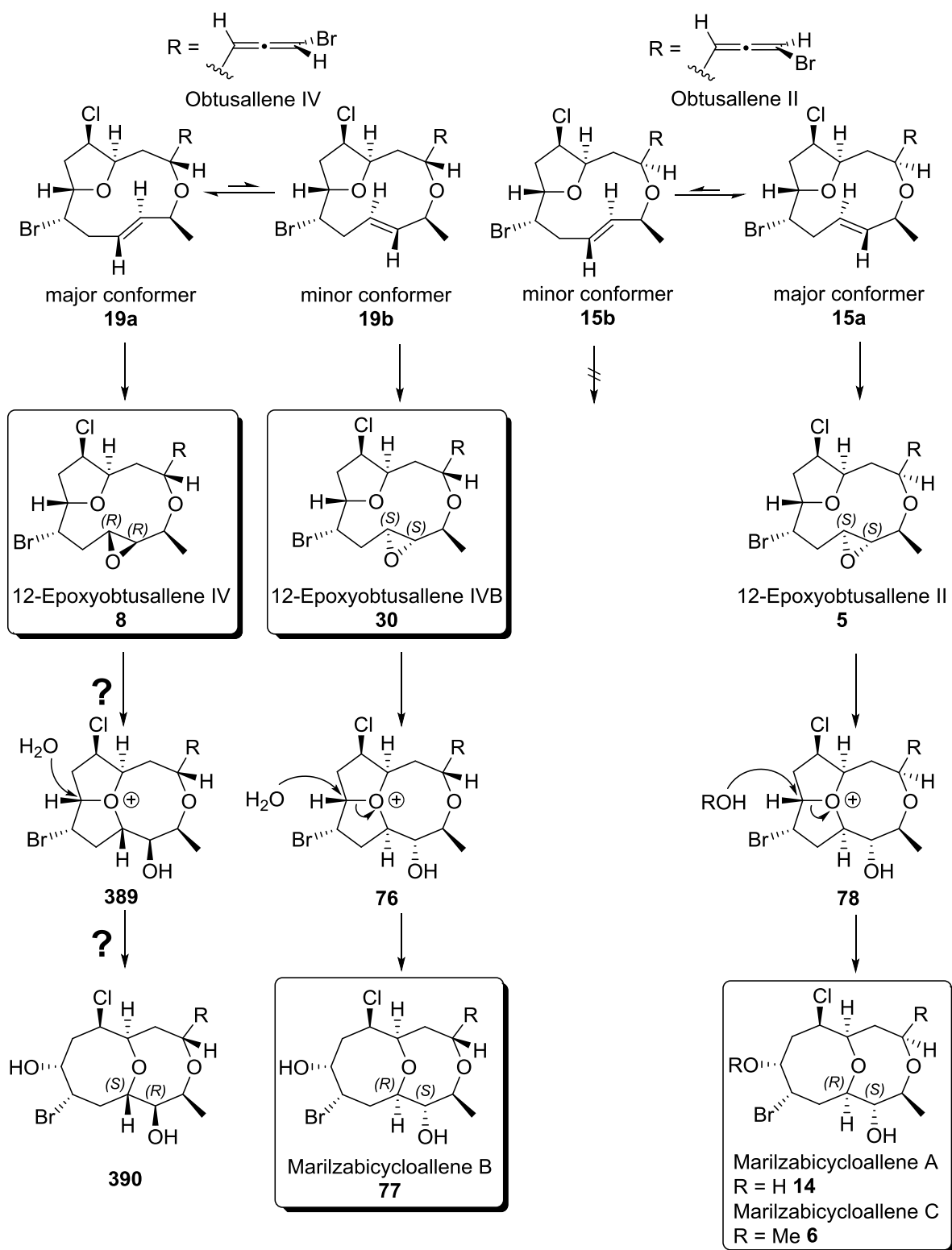
Trisylation of compound **384** gave several products. Counting the alkyne peaks and aromatic peaks suggest that at least four compounds were present. It is possible that one of them is the desired compound **386**, but it is further evidence that the inherent conformation of the (*S,S*)-epoxide **384** promotes transannular oxonium formation and rearrangement, perhaps with chloride as the nucleophile. The compounds were inseparable and with the extremely limited quantities left, the route to bromoallene **388** was abandoned. If the alcohol stereochemistry prediction made earlier was correct, route 2 would be that which lead to natural product 12-epoxyobtusallene IVB (**30**) and then marilzabicycloallene B (**77**).

Route 2 was more successful, with an 89% yield of trisylate **387** collected. Analysis of the $^3J_{\text{H3-H4}}$ coupling constant showed 2.4 Hz, which is within the range expected for the geometry leading to the natural product.^{81a} It still contained a considerable amount of another trisylate, most probably the marilzabicycloallene core observed after the acetylide

addition. The quantity collected was too low to record good quality ^{13}C spectra. A bromination was attempted to determine if 12-epoxyobtusallene IVB (**30**) could be observed in trace amounts. After treating the material to the bromination procedure, a small amount of a mixture of compounds was collected. A trace of a bromoallene peak was seen at 6.04 ppm, which corresponds to that of 12-epoxyobtusallene IVB (**30**),^{13h} but this was far from enough to give a positive identification. This route was also abandoned and further investigation into the complex transannular oxonium ion formation - fragmentation reaction was conducted.

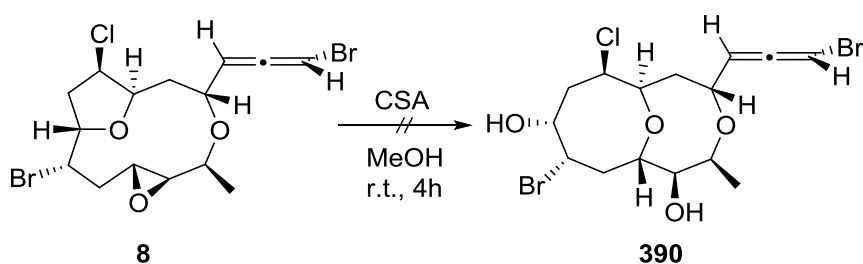
4.2.14 Further Reactivity of 12-Epoxyobtusallene IV (8) & the Total Synthesis of Obtusallene X (9)

Now that an authentic sample of 12-epoxyobtusallene IV (**8**) had been produced, two biosynthetic questions could be investigated. Firstly, according to Norte and co-workers proposed biogenetic scheme,¹² both epoxide **5**, deriving from the major conformer of obtusallene II (**15a**) and **30**, deriving from the minor conformer of obtusallene IV (**19b**) readily undergoes further reaction to marilzabicycloallene cores (scheme 2.3.3.1). Indeed, we were able to prove that 12-epoxyobtusallene II (**5**) was fairly stable, but could be made to yield marilzabicycloallene C (**6**) under acidic solvolysis conditions. 12-Epoxyobtusallene IVB core compound **385** was so sensitive to rearrangement that the installation of the bromoallene, under relatively mild conditions, could not be completed. Why then had no marilzabicycloallene cores such as **390** (scheme 4.2.14.1), deriving from 12-epoxyobtusallene IV (**8**) been isolated?



Scheme 4.2.14.1: Updated biogenesis of marilzabicycloallenes.

Instead of a macrocycle with an (*S*)-configured alcohol at C₁₃ and (*R*)-bridgehead at C₁₂, as seen in all marilzabicycloallenes A - C (**14**, **77** & **6**), a structure such as compound **390** could possibly be produced, with these stereocentres inverted. It is certainly possible that such a marilzabicycloallene exists, but had not been observed or collected in the isolation. With the small quantities of synthetic 12-epoxyobtusallene IV (**8**) available, a test reaction was conducted to attempt to generate this novel core (scheme **4.2.14.2**).



Scheme 4.2.14.2: Attempted transannular oxonium ion formation - rearrangement on 12-epoxyobtusallene IV (**8**).

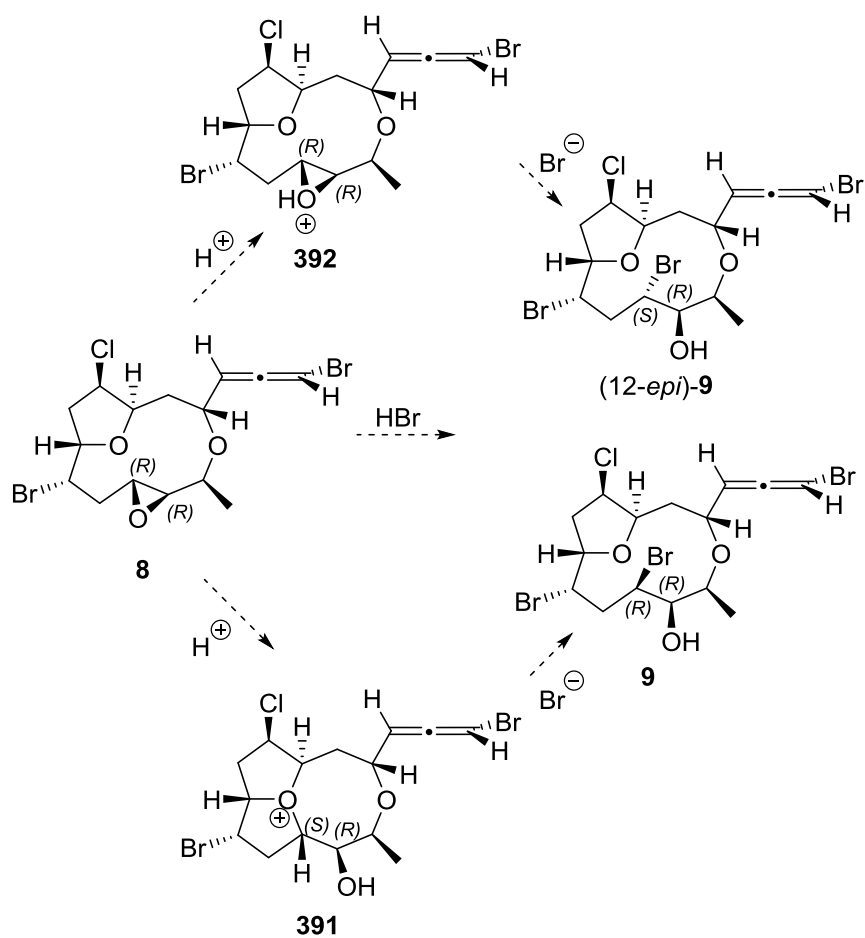
12-Epoxyobtusallene IV (**8**) was submitted to the same transannular oxonium ion - fragmentation reaction with CSA and methanol. After extended reaction time and addition of a total of 50 mol% CSA, there was no evidence of any reaction. The ¹H NMR spectrum of the crude material was identical to the starting material, with no sign of new bromoallenes or C₁₅ methyl groups (the most obvious peaks to observe new compounds). Perhaps with a stronger acid or a higher temperature reaction, a new product may have been formed. But under the conditions used, matching more closely to that expected in a cell, marine or methanolic extraction environment, no reactivity was observed. Comparing to the readiness to rearrange shown by the other compounds in scheme **4.2.14.1**, it can be speculated that the

specific conformation of 12-epoxyobtusallene IV (**8**) is somewhat resistant to either oxonium formation or nucleophilic attack at C₉.

This brings us to the second reactivity question regarding 12-epoxyobtusallene IV (**8**). Obtusallene X (**9**) was discovered in the same isolation as 12-epoxyobtusallene IV (**8**) and ester **27**.^{13g} It is reasonable then to suggest that the three are related.

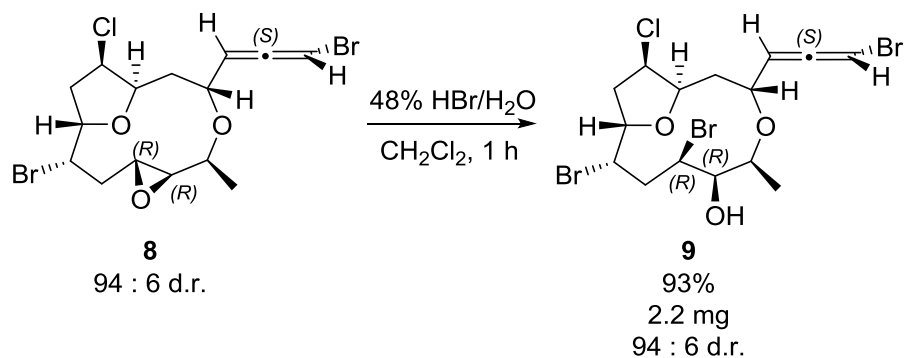
Norte and co-workers assigned compound **9** solely through NMR spectroscopy. TROESY NMR showed correlation between H₄, H₉, H₁₀, H₁₂ & H₁₅ and between H₆, H₇, H₁₃ & H₁₄, suggesting each group of protons is oriented *syn* with respect to each other. This means that C₁₂ and C₁₃ are both (*R*)-configured (scheme **4.2.14.3**). Interestingly, the paper reported two interconverting conformers in an approximately 1 : 1 ratio. The peaks of these apparent conformers made assignment challenging, so the NMR spectroscopic measurement were repeated in C₆D₆ and MeOH-d₄ to resolve the peaks.

The paper made no attempt to suggest a biogenesis, but it is likely that epoxide **8** & bromohydrin **9** are linked by the addition of HBr. Consideration of the stereochemical outcomes of the addition of HBr to 12-epoxyobtusallene IV (**8**) suggests that this mechanism must proceed through oxonium ion **391** with double S_N2 inversion at C₁₂ retaining the (*R*)-stereochemistry, as shown in the lower route in scheme **4.2.14.3**. A direct S_N2 substitution at C₁₂ *via* protonated epoxide **392**, would yield the (12*S*)-bromide (12-*epi*)-**9** of the upper route in scheme **4.2.14.3**.



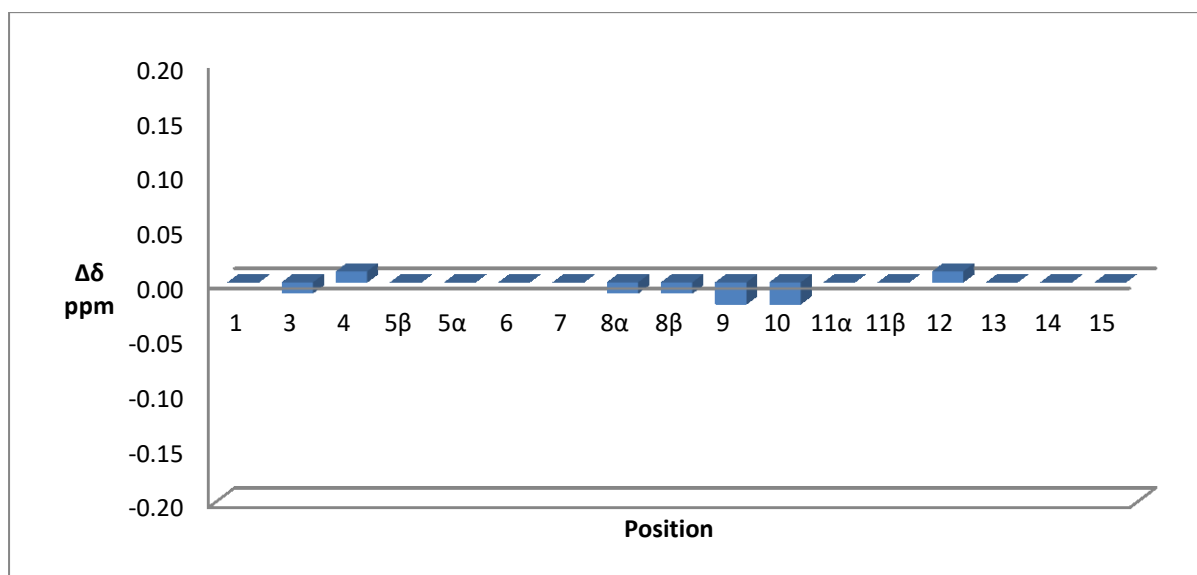
Scheme 4.2.14.3: Stereochemical considerations of the addition of HBr to 12-epoxyobtusallene IV (8).

Recreation of these conditions with a sample of 12-epoxyobtusallene IV (8) and comparison of the product with the natural product data, would confirm which route is correct.



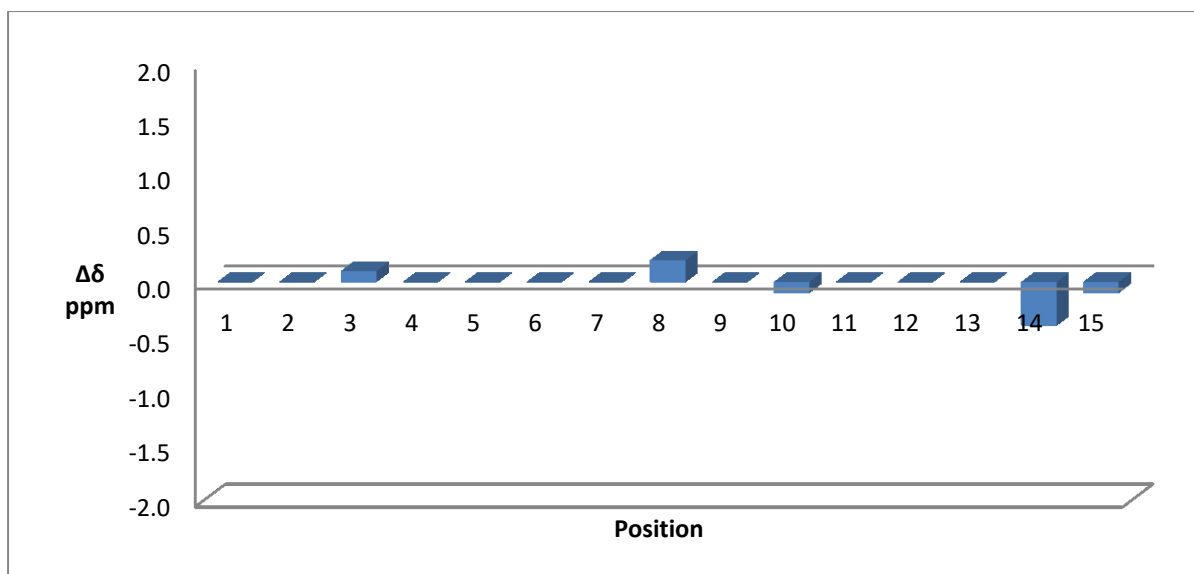
Scheme 4.2.14.4: Successful transannular oxonium ion formation - rearrangement of 12-epoxyobtusallene IV (**8**) to yield obtusallene X (**9**)

12-Epoxyobtusallene IV (**8**) was treated with hydrobromic acid in methylene chloride, which yielded a 2.2 mg of a single product in very high yield. The diastereomeric ratio of 94 : 6 was maintained, as calculated by the H₁ & H₃ bromoallene peaks. Comparison with the literature data for obtusallene X (**9**) showed an excellent match.



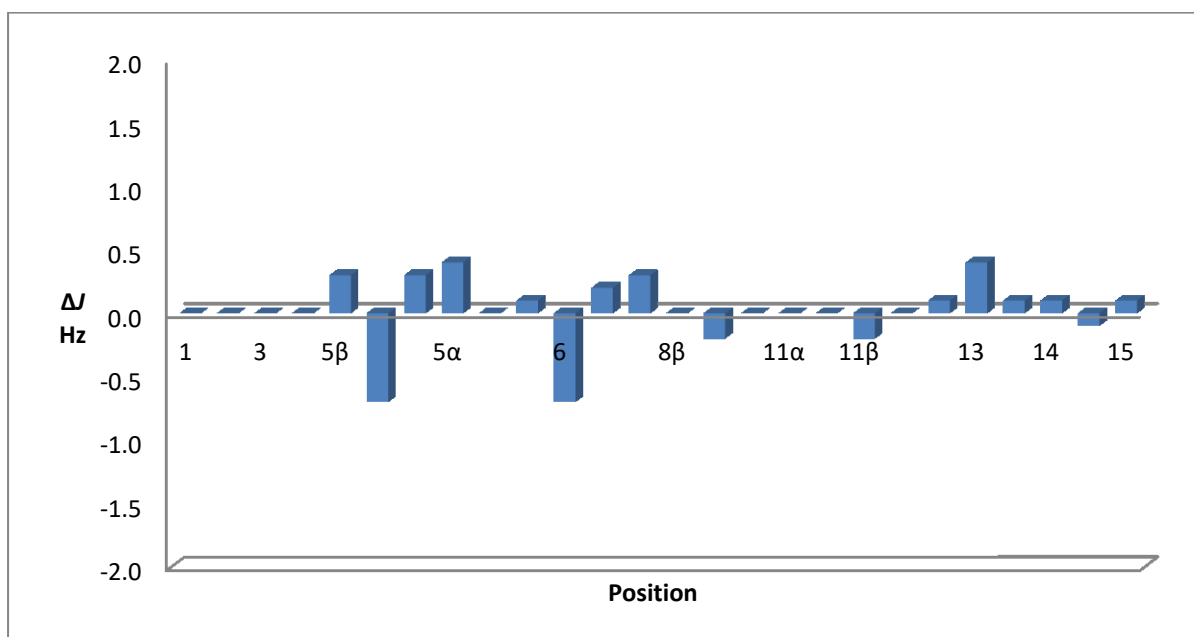
Root-mean-square deviation: 0.01 ppm

Figure 4.2.14.1: Comparison of ¹H NMR spectral data for synthetic and natural obtusallene X (**9**).



Root-mean-square deviation: 0.1 ppm

Figure 4.2.14.2: Comparison of ^{13}C NMR spectral data for synthetic and natural obtusallene X (9).



Root-mean-square deviation: 0.3 Hz

Figure 4.2.14.3: Comparison of ^1H NMR J -values for synthetic and natural obtusallene X (9).

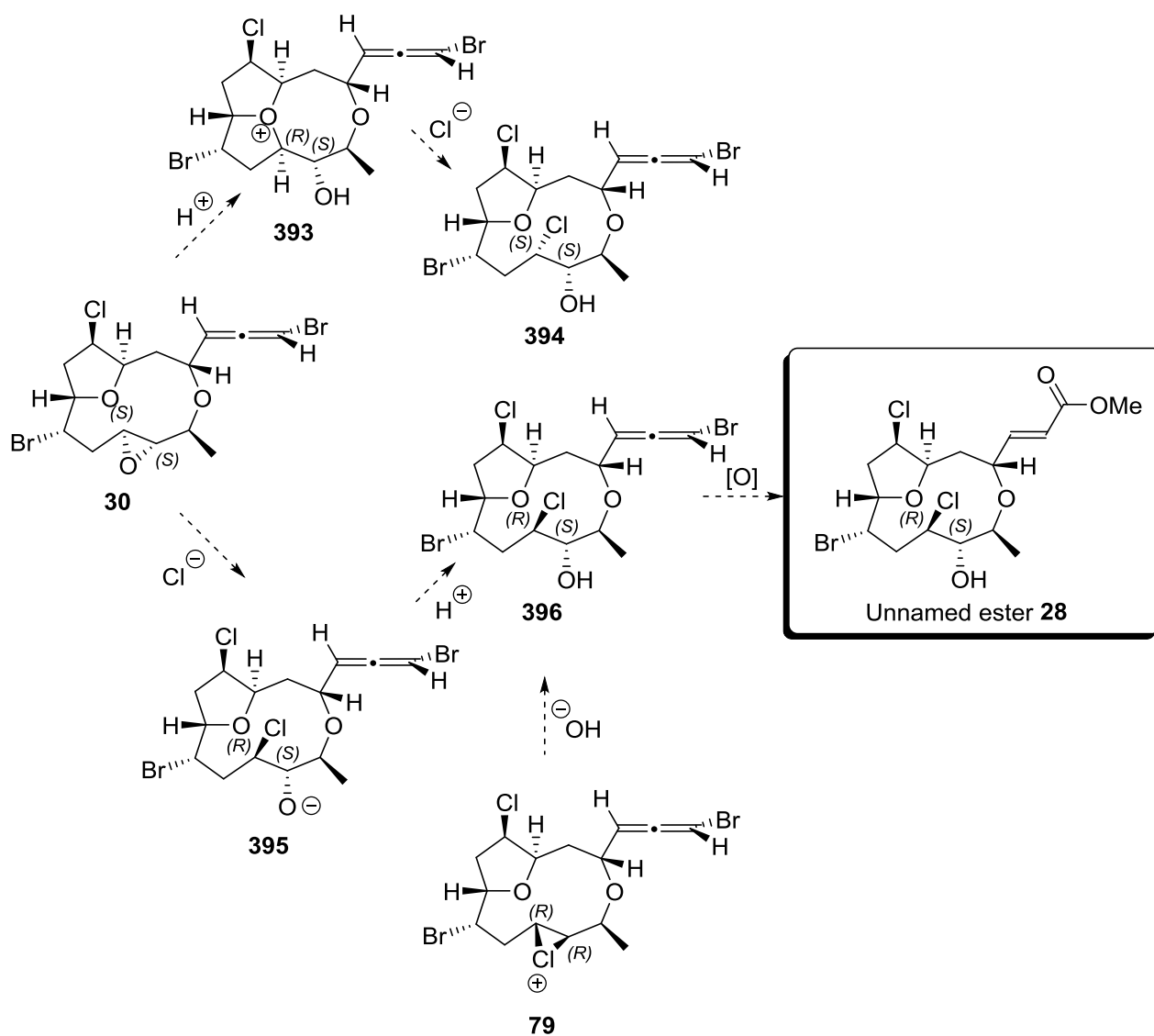
The only discrepancies are found at the signals which Norte and co-workers report as peaks overlapping with the conformer. Interestingly, the spectra for synthetic obtusallene showed none of the extra peaks seen in the isolation paper. This suggests that the signals assigned as a conformer are more likely to be an impurity, possibly another natural product. The paper states that the additional peaks are most divergent between C₁₀ and C₁₅ as this unit undergoes slow rotation, previously seen in other obtusallenes.^{13d, 13f} Based on our observation of sharp signals and no conformational freedom, it seems more likely that Norte isolated a macrocycle bearing the (*S,R*)-bromohydrin of compound (12-*epi*)-**9**, meaning that in biological conditions, both the oxonium ion and direct epoxide opening mechanisms are possible (scheme 4.2.14.3). This raises the question of why this was not observed in the reaction with hydrobromic acid. Perhaps the cell environment has bromide ions in the form of a salt, rather than a protic acid. This may disfavour the formation of oxonium ion **391** and promote a direct substitution of bromide *via* an anionic pathway. Alternatively, the impurity bears an (*S,S*)-bromohydrin, achieved by the stereospecific oxonium ion route, but applied to the epoxide of 12-epoxyobtusallene IVB (**30**).

With RMS values of 0.01 ppm, 0.1 ppm & 0.3 Hz for ¹H, ¹³C and *J*-value analysis, it can be concluded that obtusallene X (**9**) had successfully been synthesised.

In the most recent *Laurencia* isolation,^{13h} several new compounds were discovered, including **28**, bearing an α,β -unsaturated methyl ester and a chlorohydrin. Norte and co-workers propose its precursor to be 12-epoxyobtusallene IVB **30**, with our previously established bromoallene epoxidation mechanism to form one functionality,⁶³ and a transannular oxonium ion formation followed by chloride substitution to form the other. The relative stereochemistry of the chlorohydrin was again deduced by inspection of key correlations in ROESY NMR spectra and without X-ray crystallography to confirm, their

conclusion must be accepted. However, analysis of the stereochemical outcome leads to a conclusion that the double S_N2 inversion resulting from a transannular rearrangement of oxonium ion **393**, which would give 12*S*,13*S* chlorohydrin **394** (scheme 4.2.14.5). This makes the direct substitution of chloride at C₁₂ to open to epoxide of **30** the more probable route. It may be the case that the increased nucleophilicity of chloride promotes this anionic pathway.

An alternative explanation is that chloronium ion formation on the favoured *Re* face of obtusallene IV (**19**), which is an intermediate towards marilzabicycloallene D (**7**), is intercepted by adventitious hydroxide or water. In an aqueous environment, this is likely to happen before the interception of chloride. This give the correct stereochemistry about the chlorohydrin, but given that the molecule must have come into contact with an oxidant to form the α,β -unsaturated methyl ester, the epoxidation route is more probable.



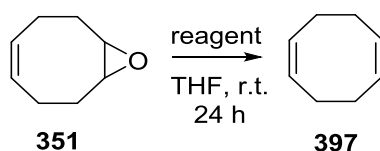
Scheme 4.2.14.5: Possible biogenetic origins of unnamed ester **28**.

It would have been of interest to study such rearrangements further to provide more insight into the biosynthesis of such natural products, but unfortunately a lack of material prohibited such studies.

4.2.15 Attempts at the Deoxygenation of Epoxides with Titanocene(III) Chloride as a Route to Obtusallenes II & IV (15 & 19)

Macrocycles **182** & **183** were successfully epoxidised as a method to bypass the problematic DIBAL-H reduction of allylic ether nitriles and had yielded a range of natural products (sections **4.2.9** & **4.2.11**). Unfortunately, this meant that the original targets, obtusallene II & IV (**15** & **19**), were unattainable. It was apparent that once the epoxy nitriles had been reduced, a method that allowed clean removal of the epoxide oxygen would allow us to rejoin the synthetic route to the macrocyclic olefin natural products, obtusallenes II & IV (**15** & **19**).

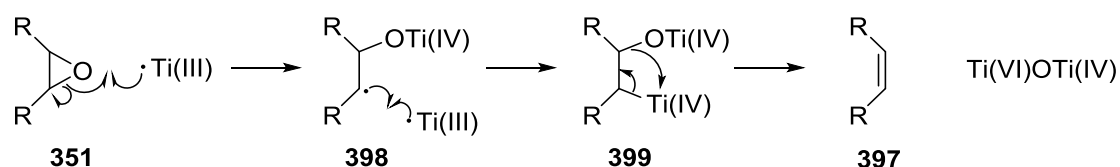
Surprisingly, the literature for such deoxygenations is rather sparse and many of the techniques require access to the rear side of the epoxide to follow a Wittig-type oxaphosphetane decomposition. This is not suitable for the macrocyclic epoxides studied here. Of the remaining *syn*-deoxygenation techniques, a range were trialled with 9-oxabicyclo[6.1.0]non-4-ene (cycloocta-1,5-diene oxide, CODO, **351**). It was reasoned that the ring structure would shield the rear side of the epoxide, if only minimally, to simulate the macrocyclic epoxides of the real system. The results are presented in table **4.2.15.1**.



Entry	Reagent	Result	Ref.
1	$\text{Cp}_2\text{TiCl}_2 + \text{Zn}$	Complex mixture of products	108
2	$\text{Re}(\text{O})\text{Cl}_3(\text{PPh}_3)_2$	Complex mixture of products	109
3	$\text{Re}(\text{O})\text{Cl}_3(\text{PPh}_3)_2 + \text{PPh}_3$	No reaction	109
4	$\text{Mo}(\text{CO})_6$	Complex mixture of products	110
5	Cp_2TiCl	Completion	111

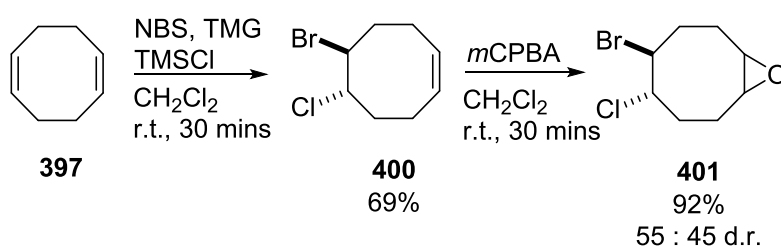
Table 4.2.15.1: Deoxygenation reagents trialled in the deoxygenation of CODO (**351**).

Most of the reagents resulted in an unidentifiable mixture of products, but $\text{Cp}_2\text{Ti(III)Cl}$, prepared separately by reduction with zinc dust, cleanly removed the epoxide oxygen of CODO (**351**). During the initial reduction with zinc, the titanocene(IV) dichloride changes colour from orange-red to lime green as it is reduced to titanocene(III) chloride. After it is added to the epoxide, it rapidly changes to orange as it is oxidised back to titanocene(IV) and subsequently to a bridged Ti(IV) dimeric ether. This species precipitated upon quenching with 1M KH_2PO_4 , as described in the literature,¹¹¹ and could be observed in the crude ^1H NMR spectrum by a prominent peak at 6.29 ppm.¹¹² It was found that 2M HCl was more effective at dissolving and removing this by-product.



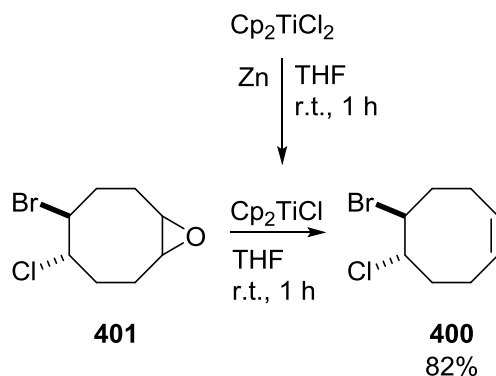
Scheme 4.2.15.1: Mechanism of the titanocene(III) deoxygenation of epoxides.

Unfortunately, the 1,5-cyclooctadiene (**397**) product was too volatile to chromatograph, collect and measure yield. In addition, titanocene(III) monochloride is known to dehalogenate alkyl halides *via* similar single electron processes.¹¹³ In order to increase the boiling point and better simulate the obtusallene macrocycles, 1,5-cyclooctadiene (**397**) was submitted to the brominative chlorination procedure previously developed by the Braddock group (section 4.2.10.1), followed by epoxidation with *m*CPBA.



Scheme 4.2.15.2: Bromochlorination and epoxidation of 1,5-cyclooctadiene (**397**).

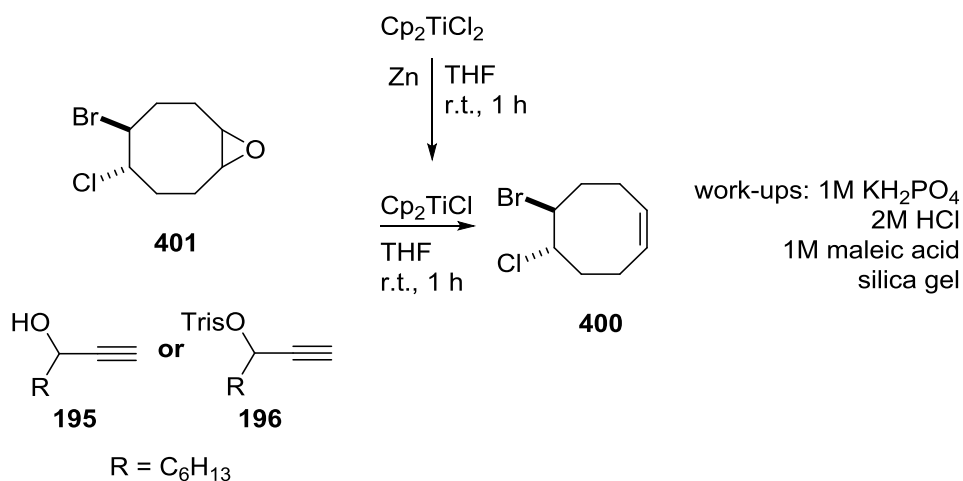
Treatment of 1,5-cyclooctadiene (**397**) with NBS, TMG & TMSCl gave bromochloride **400** in 69% yield. This compound could then be epoxidised with *m*CPBA to yield epoxide **401**, consisting of two diastereomers in a 55 : 45 ratio. These compounds have a sufficiently high boiling point to prevent loss during purification. This new substrate was submitted to the titanocene(III) monochloride deoxygenation (scheme 4.2.15.3).



Scheme 4.2.15.3: Deoxygenation of bromochloro epoxide **401**.

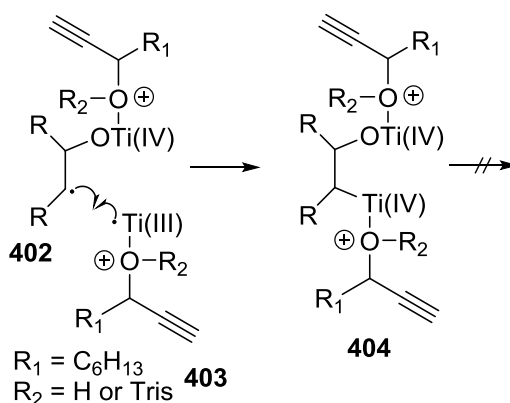
Reducing titanocene(IV) dichloride with zinc, before adding to a solution of epoxide **401** gave very promising initial results. Deoxygenated product **401** was collected in high yield, with no evidence of the halogens being abstracted. It was hoped that this procedure could be applied to one of the obtusallene core macrocyclic epoxides.

In order to determine at which point after the DIBAL-H reduction it was best to apply this deoxygenation, the procedure was repeated in the presence of model propargylic compounds **195** & **196**.



Scheme 4.2.15.4: Deoxygenation of bromochloride epoxide **401** in the presence of propargylic alcohol **195** or propargylic trisylate **196**.

Unfortunately, in all cases and with a range of work-ups, there was significant loss of both the product olefin **400** and propargylic species **195** or **196**. The crude ^1H NMR spectra showed minimal side-products, but upon chromatography, approximately only half of the expected mass of each species was recovered. It was reasoned that the propargylic oxygen of compounds **195** & **196** may have been coordinating to the titanium, interrupting the decomposition pathway that is intended to reveal the olefin. A possible mechanism is given in scheme 4.2.15.5.



Scheme 4.2.15.5: Possible pathway involving coordination of propargylic oxygen to titanium.

It is possible that with an oxygen coordinating to either of the titanium(IV) species **402** or **403**, it interferes with the electronic properties in such a manner to disrupt the decomposition pathway seen in scheme 4.2.15.1. This titanium species (**404**) may now be hydrophilic enough to be lost in the aqueous phase or upon chromatography.

Although disappointing that the reaction was not as successful as the initial results seen in scheme 4.2.15.3, a range of epoxyobtusallene cores were screened to see if even a small yield of a macrocyclic olefin could be generated.

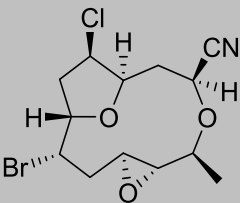
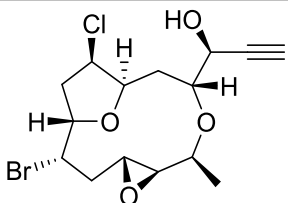
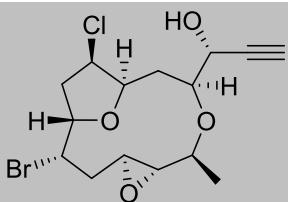
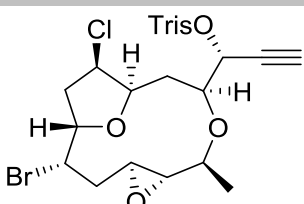
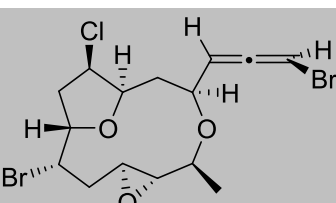
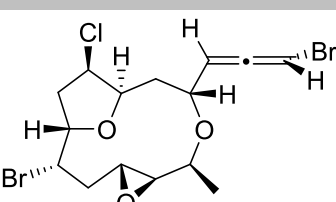
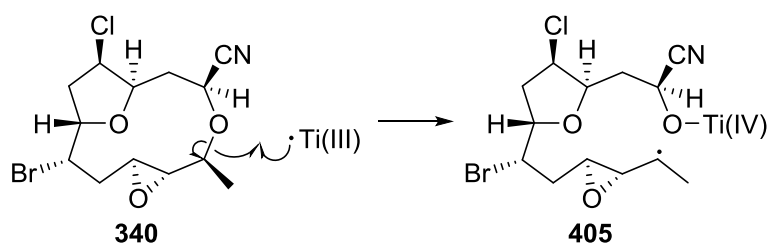
Entry	Substrate	Result
1	 340	Minimal mass recovery, unidentified product.
2	 368	No reaction.
3	 350	Repeat 1: Unidentified products Repeat 2: No reaction.
4	 351	No reaction.
5	 5	Unidentified products, no bromoallene signals present.
6	 8	No reaction.

Table 4.2.15.2: Results of attempted titanocene(III) chloride deoxygenation.

Table 4.2.15.2 summarises the results of applying the titanocene(III) monochloride deoxygenation on a range of obtusallene core macrocyclic epoxides. Unfortunately, none of the attempts were successful. In all cases, the reaction solution rapidly changed from green to orange, suggesting that the titanium was being oxidised, but in the cases where no reaction was observed, this may have been due to oxygen in the reaction despite rigorous attempts to degas the solvents and substrates. In the cases where unidentified products were observed, it may be that the multiple bridging ether oxygens were also susceptible to SET type mechanisms, resulting in ring cleavage and fragmentation.

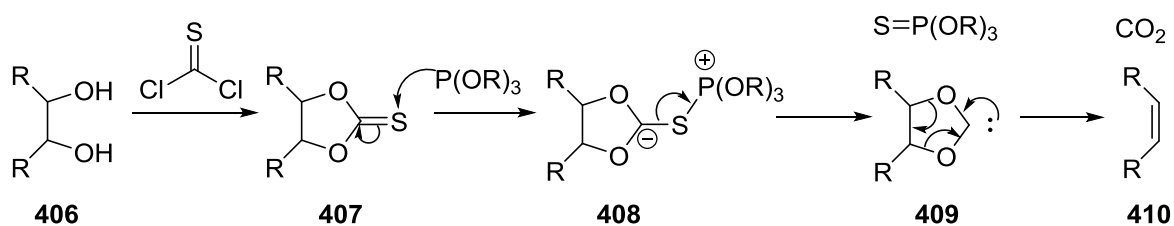


Scheme 4.2.15.6: Possible side reaction between bridging ethers and titanocene(III) chloride.

This method of olefin formation was promising, but ultimately proved to be fruitless.

4.2.16 Attempts at Corey-Winter Olefination as a Route to Obtusallenes II & IV (15 & 19)

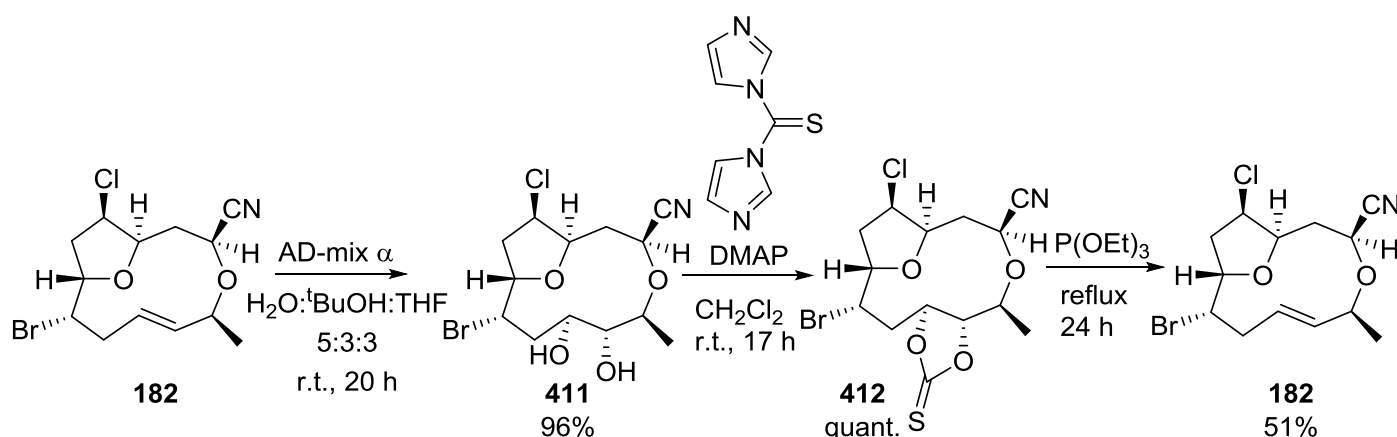
With the deoxygenation route abandoned, work turned towards a Corey-Winter olefination.¹¹⁴ This technique is employed in the conversion of 1,2-diols to olefins *via* an intermediate thiocarbonate.



Scheme 4.2.16.1: Mechanism of the Corey-Winter olefination.

The mechanism of this reaction is given in scheme **4.2.16.1**. A 1,2-diol is treated with thiophosgene to yield a cyclic thiocarbonate. Upon addition of a trialkyl phosphite, the sulfur is abstracted to yield a carbene which decomposes spontaneously to an olefin and carbon dioxide. The utility of this with respect to the obtusallene system is that the stereochemistry of the diol is maintained through to the olefin. If the vulnerable olefins of nitriles **182** & **183** could be dihydroxylated and protected as thiocarbonates, this may be enough to prevent fragmentation during DIBAL-H reduction. The thiocarbonate could be cleanly removed to yield *E*-olefins at an appropriate time in the bromoallene installation.

Test reactions were conducted on nitrile **182** to determine if the necessary steps could be performed on such a delicate and constrained system and the results shown in scheme **4.2.16.2**.



Scheme 4.2.16.2: Successful dihydroxylation and subsequent Corey-Winter olefination of nitrile **182**.

The initial step was a Sharpless asymmetric dihydroxylation of the olefin in **182**.¹¹⁵ The selectivity mnemonic suggested that AD-mix α would be the appropriate reagent,¹¹⁶ but based on what has been previously observed with obtusallene II macrocycle **182**, only one face of the olefin would be exposed to solvent and available for dihydroxylation. This reaction is usually conducted in equal quantities of water and ${}^t\text{BuOH}$, but this solvent mixture did not fully dissolve nitrile **182**. THF was added until the substrate was solvated and then small amounts of water added until the system was monophasic. After 20 hours the reaction was worked up with sodium sulfite to yield a single clean product. ${}^1\text{H}$ NMR analysis showed that the olefin peaks were no longer present and the signals were much sharper, presumably as the conformational freedom of the macrocycle had been modified.

Diol **411** was treated with 1,1'-thiocarbonyldiimidazole, a safer reagent than thiophosgene,¹¹⁷ with DMAP as a base to cleanly produce thiocarbonate **412** in quantitative yield.

This compound could be refluxed in neat triethyl phosphite overnight to complete the olefination and return *E*-olefin **182** in 51% yield. The triethyl phosphite could be removed by forming an azeotropic mixture with toluene and removing *in vacuo* several times. Although this reaction did not go to completion, a high proportion of the starting material was recovered. However, analysis of the ^1H NMR spectrum showed that the thiocarbonate was no longer pure.

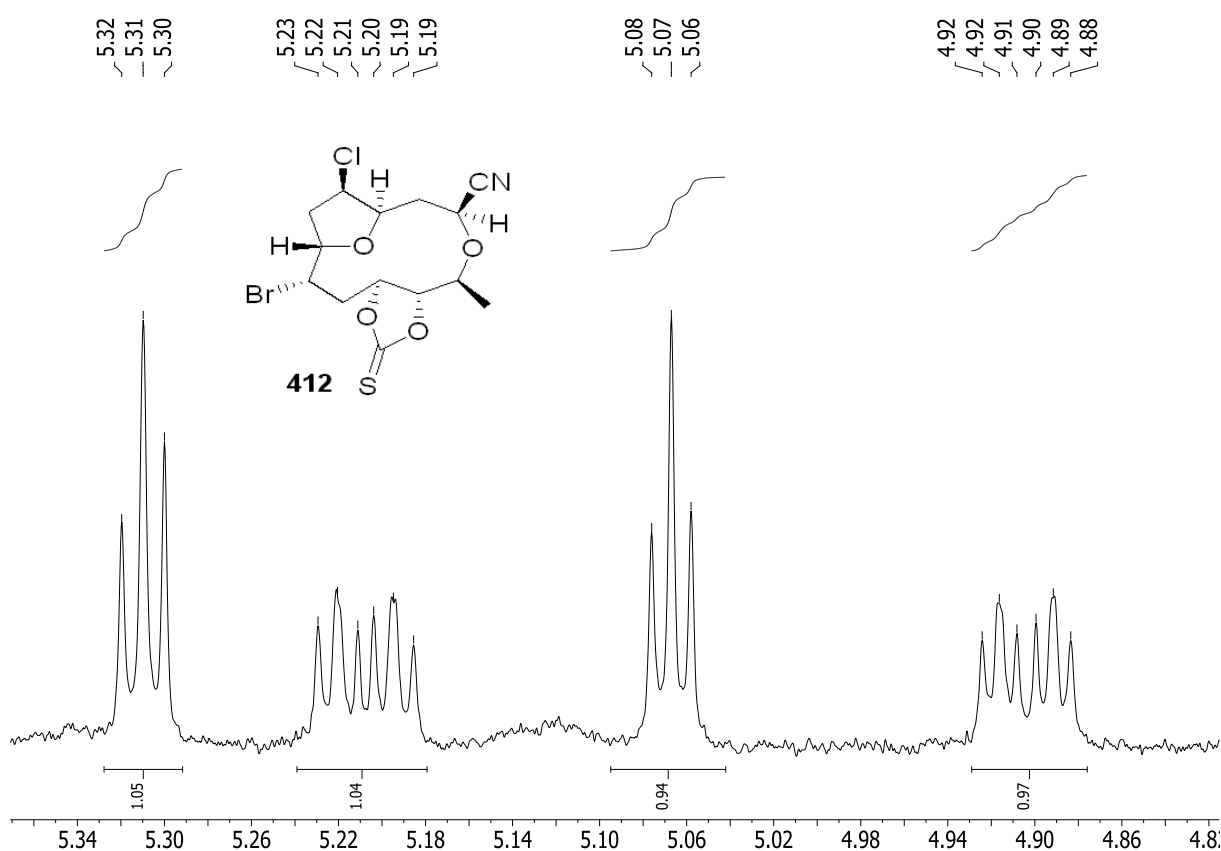
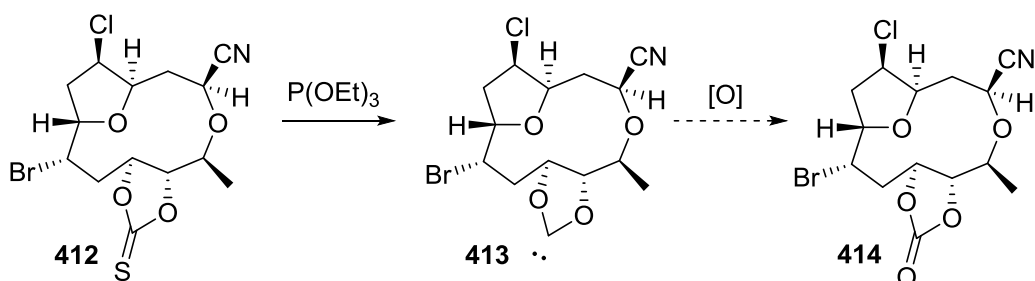


Figure 4.2.16.1: Spectrum of the recovered starting material after Corey-Winter olefination.

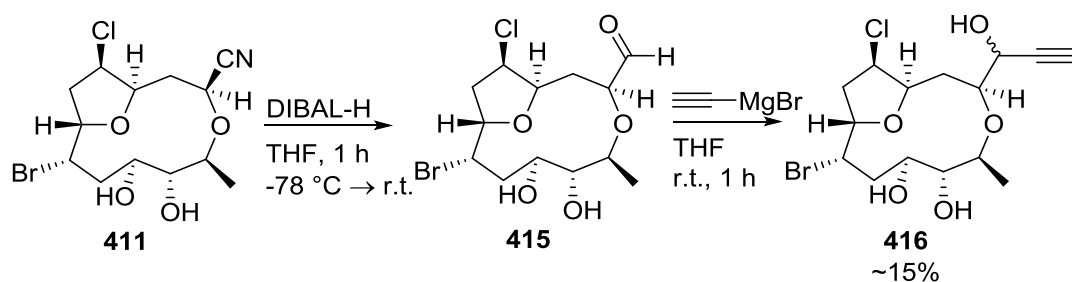
Figure 4.2.16.1 shows the multiplets at 5.31 & 5.20 ppm that represent H_{13} & H_{12} of thiocarbonate **412** respectively. The recovered material spectrum shows very similar multiplets at 5.07 & 4.90 ppm. With very identical coupling constants, it is possible that

during the olefination, the sulfur of the thiocarbonate is successfully abstracted but replaced with an oxygen to form carbonate **414** (shown in scheme 4.2.16.3).



Scheme 4.2.16.3: Possible side reactions in the Corey-Winter olefination.

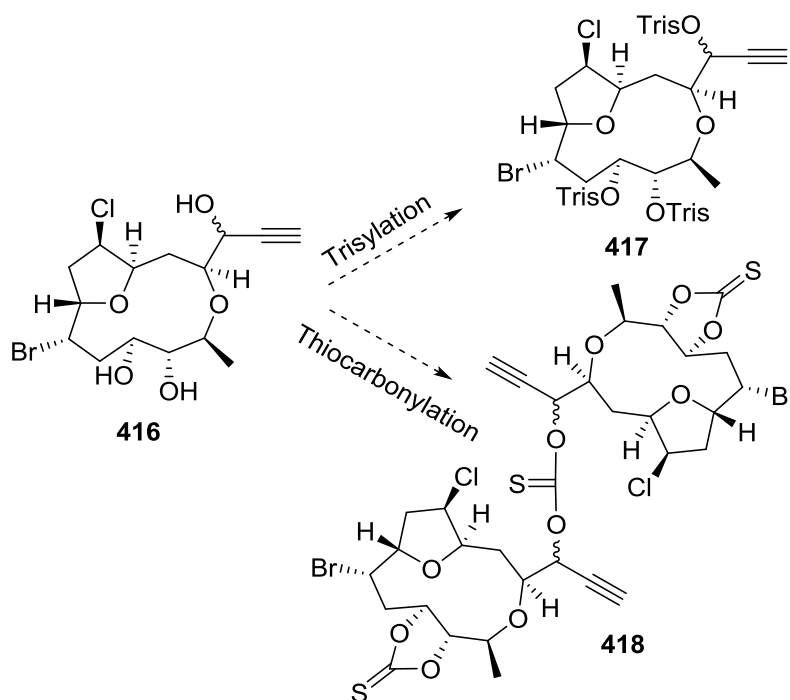
Despite this, the result was still pleasing. Thiocarbonates could be installed and removed efficiently, with no loss of stereochemistry across the olefin. It was now necessary to determine at which point in the bromoallene installation would be the most appropriate time to perform each reaction.



Scheme 4.2.16.4: DIBAL-H reduction and acetylide addition to diol **411**.

The first attempt at adapting these reactions to post-nitrile reduction macrocycles involved diol **411**. As would be expected, many more equivalents of DIBAL-H and ethynylmagnesium bromide were needed to complete the reaction, as two equivalents of

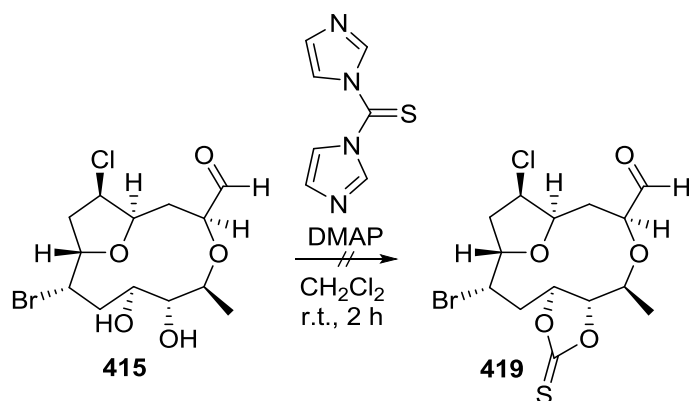
each reagent would be quenched by the diol protons. The success of the nitrile reduction was uncertain, as the material was carried forward as quickly as possible, but a distinct aldehyde peak could be seen in the ^1H NMR spectrum and was assigned to compound **415**. Acetylide addition to aldehyde **415** produced two alkyne containing compounds, as observed in the crude ^1H NMR spectrum. However, column chromatography proved to be very challenging for these triols, with compound **416** being intractable in all solvent systems except pure ethyl acetate. After elution, only one alcohol was isolated in a ~15% yield.



Scheme 4.2.16.5: Possible side reactions involving triol **416**.

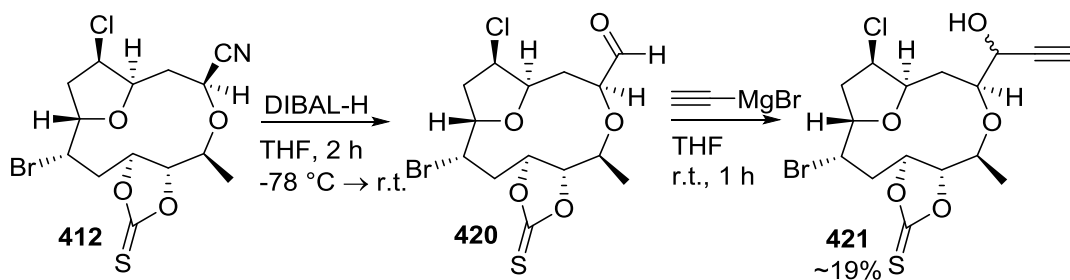
The next steps of this route would have involved either a trisylation or thiocarbonylation, both of which would have had regioselectivity issues due to the multiple hydroxyls. Ultimately, other routes towards a Corey-Winter olefination were explored instead.

The thiocarbonylation was attempted on aldehyde **415**, to avoid the problem of regioselectivity. Furthermore, acetylide addition may have been more successful on thiocarbonate **419**, then diol **415**. The result is shown in scheme 4.2.16.6.



Scheme 4.2.16.6: Thiocarbonylation of aldehyde **415**.

Upon treatment with 1,1'-thiocarbonyldiimidazole and DMAP, a complex mixture of compounds was found, none of which presented an aldehyde resonance in the ^1H NMR spectrum. Instead, it was decided to protect diol **411** as thiocarbonate **412**, before attempting further manipulation (scheme 4.2.16.7).



Scheme 4.2.16.7: DIBAL-H reduction and acetylide addition to thiocarbonate **412**.

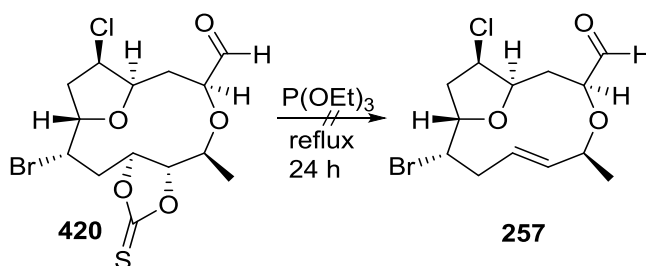
The DIBAL-H reduction of thiocarbonate **412** appeared to proceed well and with good mass recovery. After acetylide addition to resulting aldehyde **420**, an inseparable mixture of propargylic alcohols (**421**) were isolated in low yield. Although it was the most

promising route so far, no further reactions were conducted as the masses of substrate were becoming too small to manipulate and characterise.

Published information about the functional group tolerance of the Corey-Winter olefination is extremely sparse. No literature examples could be found of this reaction being conducted in the presence of free hydroxyl or alkyne functional groups. Although we had shown that alkyl halides were inert to the conditions in scheme 4.2.16.2, there was insufficient material to attempt an optimisation of the subsequent steps. A thorough search of the literature led us to believe that attempting to perform the olefination in the presence of the alkyne in **421** may result in cyclopropanation by addition of the intermediate carbene.¹¹⁸ Alternatively, attempting to trisylate the hydroxyl group of **421**, may have resulted in cleavage of the thiocarbonate, as they are known to be susceptible to halide nucleophiles.¹¹⁹

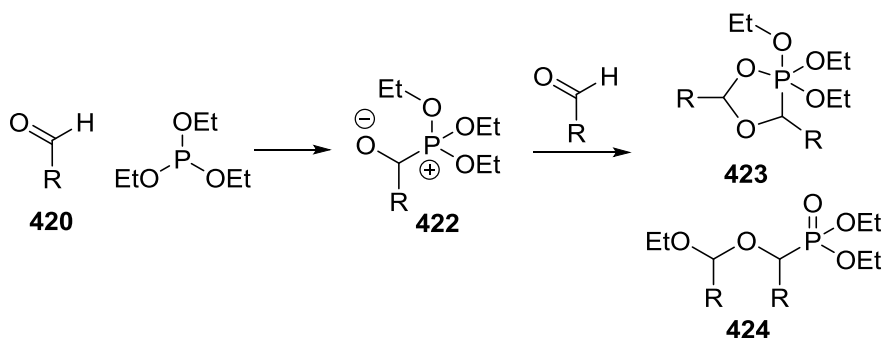
Even if a successful route had been found, there were no longer sufficient amounts of precursor **421** to carry through to a natural product.

As a last attempt, aldehyde **420** was refluxed for 24 hours with triethyl phosphite, but upon isolation, no aldehyde peak was seen in the crude ¹H NMR spectrum.



Scheme 4.2.16.8: Failed attempt at Corey-Winter olefination of aldehyde **420**.

This may be due to an Pudovik-type reaction, whereby the phosphite undergoes addition to the aldehyde to give an oxyanionic intermediate of the form **422**, that can trap a second equivalent of aldehyde to form either cyclic phosphorane **423** or acetal **424** *via* alkyl transfer (shown in scheme **4.2.16.9**).¹²⁰

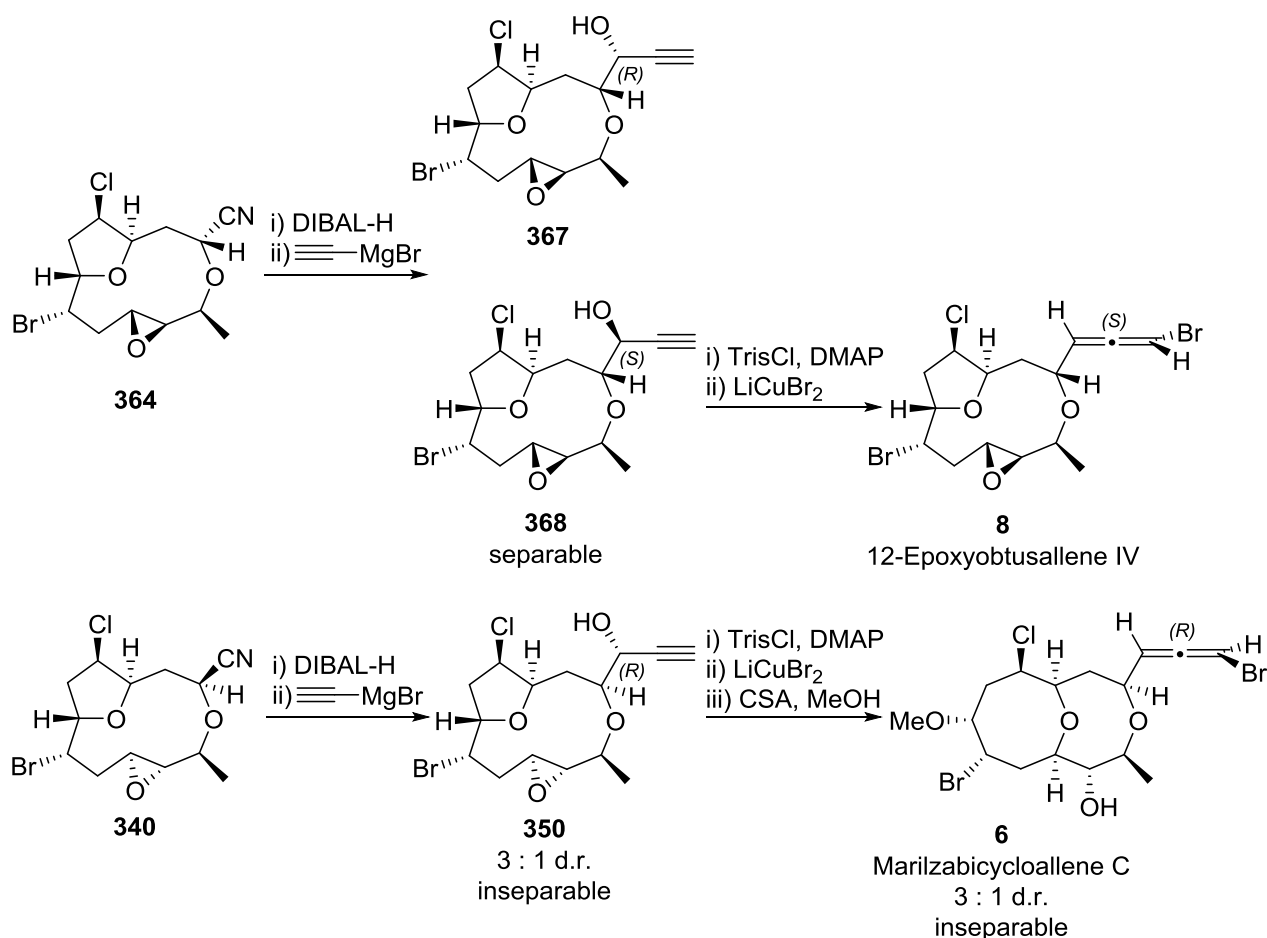


Scheme 4.2.16.9: Pudovik Reaction with aldehyde **420**.

With a lack of promising directions to continue and minimal precursor material available, Corey-Winter olefination and attempts at synthesising obtusallenes II & IV (**15** & **19**), were discarded.

4.2.17 Attempts at Oxidation and Asymmetric Reduction of Propargylic Alcohol **350** to Increase the Diastereopurity of Obtusallene Natural Products

Propargylic alcohols **367** & **368** were easily separable, allowing 12-epoxyobtusallene IV (**8**) to be collected in high diastereopurity after bromoallene installation. Conversely, propargylic alcohol **350** was collected as a mixture of diastereomers, inseparable under a variety of solvent systems. This meant that the derived bromoallene, marilzabicycloallene C (**6**), had a 3 : 1 mixture of diastereomers. This is illustrated in scheme **4.2.17.1**.

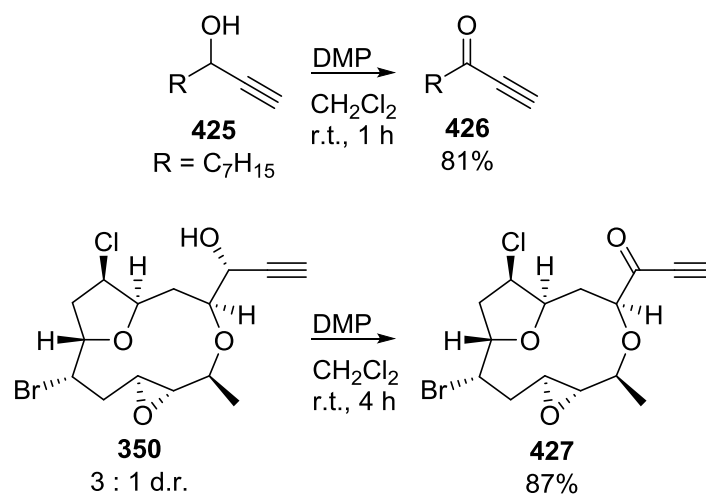


Scheme 4.2.17.1: Propargylic bromides resulting from the DIBAL-H reduction and acetylide addition to nitriles **364** & **340**.

A method was sought to increase the diastereopurity of this mixture of alcohols **350**, not only to improve the quality of the collected spectra, but also to provide a better claim for total synthesis. The method chosen would require an oxidation to a propargylic ketone, followed by an asymmetric reduction using a suitable reducing agent.

Dess-Martin periodinane had previously proven to be an excellent choice for this system, with good tolerance for the halogens. This reagent was chosen to oxidise macrocycle **350**, as well as model system **425**, for test reactions. In this case, the propargylic alcohol

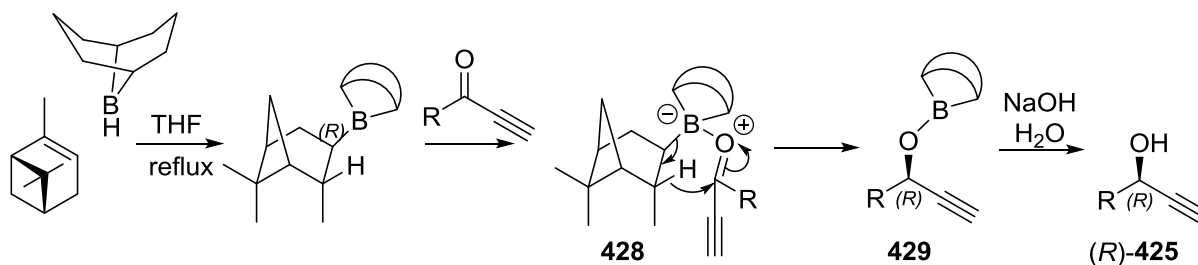
deriving from octaldehyde was used, as the previous model **195** was found to be too volatile once oxidised.



Scheme 4.2.17.2: DMP oxidation of propargylic alcohols **425** & **350**.

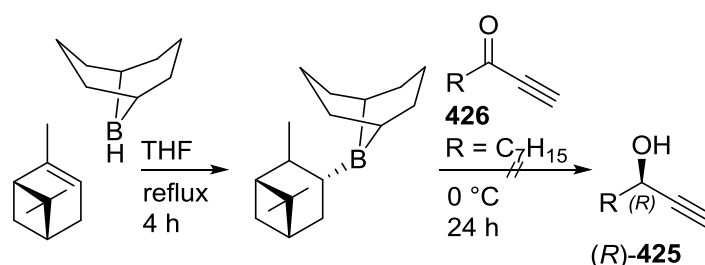
DMP was used to oxidise propargylic alcohols **425** & **350**. Both oxidations in scheme 4.2.17.2 proceeded well with propargylic ketones **426** & **427** being collected in >80% yield.

The first asymmetric reducing agent tested on such propargylic ketones was alpine borane.¹²¹ This technique, often called the Midland reduction, involves generating a chiral borane reducing agent known as alpine borane, using 9-BBN and α -pinene.



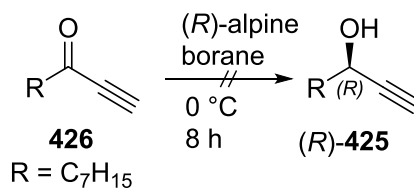
Scheme 4.2.17.3: Generation of (R)-alpine borane and reduction of propargylic ketone **426** to yield (R)-alcohol **425**.

Hydroboration of α -pinene yields an asymmetric borane reagent that, when coordinated with a carbonyl, orients the larger alkyl group away from the bulk of the pinane and cyclooctyl groups (scheme 4.2.17.3). This allows hydride transfer to proceed with high stereoselectivity.¹²² In the above scheme the reagent is derived from (+)- α -pinene which yields (*R*)-alpine borane and thus the (*R*)-propargylic alcohol **425**. The reaction was tested with (*R*)-alpine borane on the model system, both freshly generated and as a commercial solution, to practice the technique.



Scheme 4.2.17.4: Attempted Midland reduction on model propargylic ketone **426**.

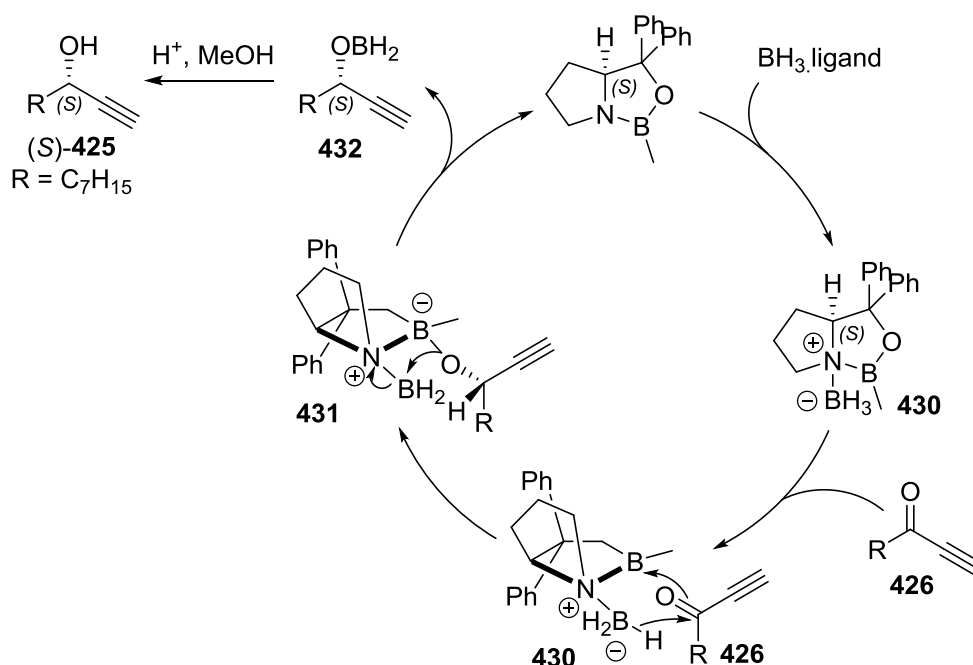
Unfortunately, upon work-up, a mixture of products was formed. The major product was 1,5-cyclooctadiol, but none of the remaining compounds could be identified as a propargylic alcohol by ¹H NMR spectroscopy. The reaction was repeated with a commercially available solution of (*R*)-alpine borane.



Scheme 4.2.17.5: Second attempted Midland reduction of propargylic ketone **426**.

Again, a similar mixture of products was formed and the desired propargylic alcohol was absent. Reasons for these failures are not obvious. The majority of literature Midland reductions are conducted on either silylated or dialkyl alkynes,^{121, 123} but examples of terminal alkynes certainly exist.¹²⁴

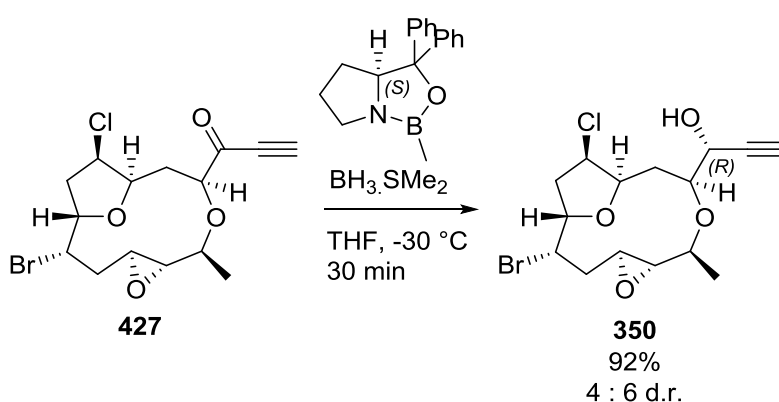
Instead, attention turned to Corey-Bakshi-Shibata (CBS) reduction, which is more suitable for ketones with mismatched alkyl groups.¹²⁵ This technique uses an oxazaborolidine catalyst and a stoichiometric amount of borane in a catalytic cycle shown in scheme 4.2.17.6.



Scheme 4.2.17.6: Catalytic cycle of the CBS reduction.

Coordination of borane to the (S)-configured prolinol nitrogen generates a reducing agent with a large steric bulk on one face. The approach of ketone 426 is directed by the orientation of the larger R-group away from the ring of 430. The coordinated borane of 431 can donate hydride to the carbonyl carbon. Elimination of alkoxyborane species 432 allows the cycle to turnover and an acidic work-up yields an (S)-propargylic alcohol 425.

Literature precedent could be found for very a similar functionality, i.e. propargylic ketones with secondary alkyl or ether groups,¹²⁶ with isolated enantiomeric excesses well above 90%. The procedures described were repeated on propargylic ketone **426**. The reaction was tested with (*S*)-oxazaborolidine catalyst as the corresponding (*R*)-catalyst was not available at the time. If the reaction gave a high excess of (*S*)-**425**, the (*R*)-catalyst would have been obtained and used to achieve the correct diastereomer.

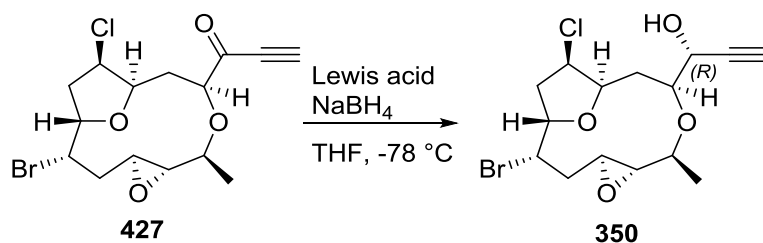


Scheme 4.2.17.7: CBS reduction of propargylic ketone **427**.

Upon isolation it was found that, although high yielding, the ratio of propargylic alcohols was roughly equal, with a slight advantage to the wrong diastereomer, (*S*)-**427**. The reaction was repeated with a much slower rate of addition, in case the borane was reducing the ketone before coordination to the prolinol, but the result was much the same. It is possible that the multiple ether functionalities prevent correct coordination to the correct site and thus renders the reaction less selective.

Although it was previously postulated that the outcome of the acetylide addition was under Felkin-Ahn control, the failure of established asymmetric reduction techniques led us to explore chelation control. The final attempt at producing a diastereo-enriched

propargylic alcohol would be to use Lewis acids and NaBH₄. The final few milligrams of substrate were employed in these attempts.



Scheme 4.2.17.8: Chelation controlled reduction of propargylic ketone **427**

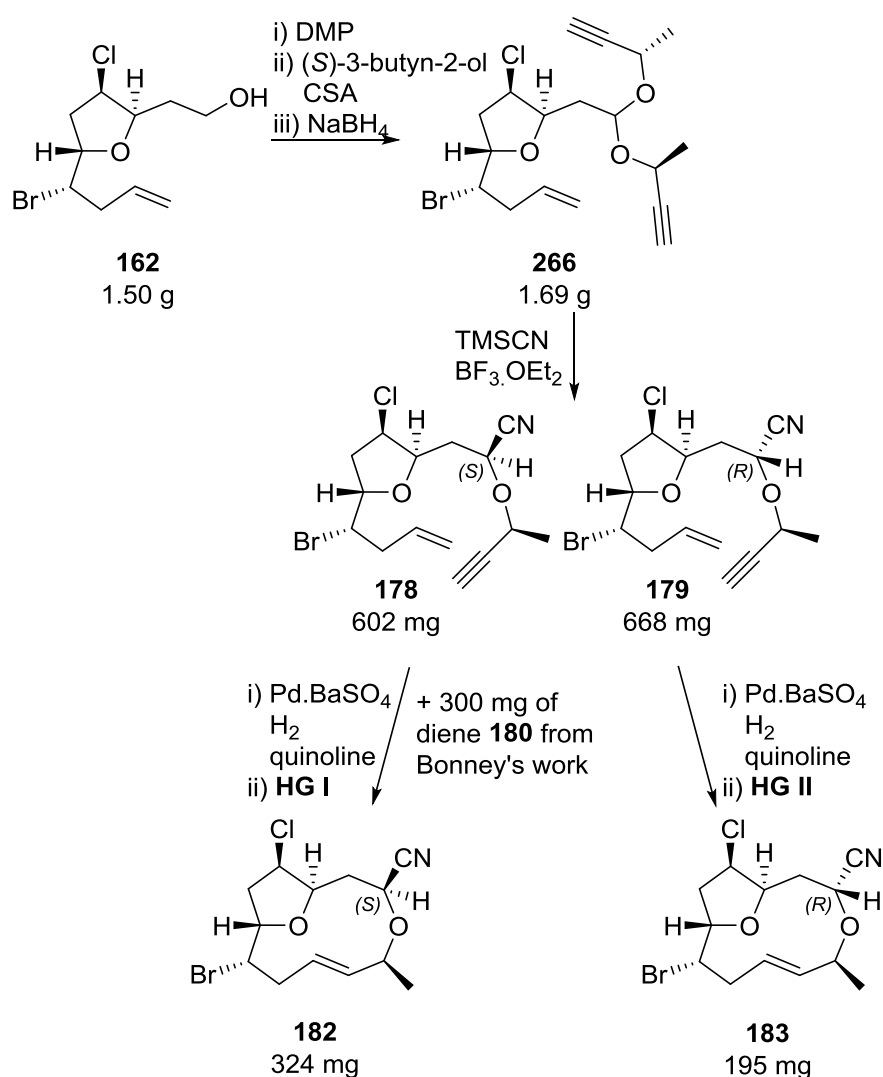
Entry	Lewis acid	Result (<i>R</i> : <i>S</i> -350 d.r.)
1	ZnCl ₂	35 : 65
2	ZnCl ₂	40 : 60
3	Me ₂ AlCl	Mixture of unidentified compounds
4	None	50 : 50

Table 4.2.17.1: Results of chelation controlled reduction of propargylic ketone **427**.

As expected, chelation control did not give the correct diastereomer. The use of zinc chloride as a Lewis acid gave a slight excess of the (*S*)-product, while a reduction with no Lewis acid gave an exactly equal amount of each. It was concluded that nothing could be done to improve the diastereomeric ratio of propargylic alcohol **350**. The 3 : 1 diastereomeric ratio of marilzabicycloallene D (**7**), as shown in section 4.2.10, was not improved upon.

4.2.18 Conclusion

With no further material remaining for experimentation, this study was concluded and the measures of success considered. The initial goal was to progress alcohol **162** towards macrocyclic olefins **182** & **183**. The reactions had already been outlined by Bonney and Yaqoob,^{46, 48} but the expected yields would have given inadequate quantities to conduct further reactions. For each step of the synthesis, the major side products and reasons for yield loss were identified and the yield optimised. The total quantities of each compound produced are shown in scheme 4.2.18.1.



Scheme 4.2.18.1: Successful functionalisation of alcohol **162** to macrocyclic nitriles **182** & **183**.

By splitting the one-pot cyanoetherification into a separate acetal formation and cyanation reactions, and reducing the intermediate aldehyde **163** to back to alcohol **162**, alkynes **178** & **179** could be collected in greater than 90% yield over the three steps. Alkynes **178** & **179** could be partially hydrogenated and resulting macrocycles closed using Grubbs' metathesis to give olefins **182** & **183**. Although these steps were accompanied by major side reactions, forming geometric isomer (Z)-**182** and C₁₂,C₁₃-dihydro compound **335**, the conditions were suitably optimised to collect significant quantities of **182** & **183**. As such, sufficient quantities of precursors to the obtusallene family of natural products had been produced and bromoallene installation could commence.

The objective had been to follow the Overman protocol,^{53b} to affix the bromoallene and generate obtusallenes II & IV (**15** & **19**), before investigating the biosynthesis of other obtusallenes and marilzabicycloallenes. This route required the use of DIBAL-H to reduce the pendant nitrile groups, but it was found that in the presence of allyl ethers, the reaction was very low yielding. Using a model system, some evidence was collected to show the presence of a chelated aluminium imine that was sensitive to fragmentation, either *via* a second hydride transfer or hydrolysis. This proved to an unavoidable barrier to producing obtusallenes II & IV (**15** & **19**), but could be adequately bypassed by protecting the sensitive allyl ether as an epoxide, or conducting a dichlorination/fragmentation to marilzabicycloallene core **360**, with a chloride at C₁₃. Both of these changes allowed DIBAL-H reduction with sufficiently high yield to be followed by bromoallene installation, generating a range of *Laurencia* natural products. The compounds synthesised and their quantities are given in scheme 4.2.18.2.

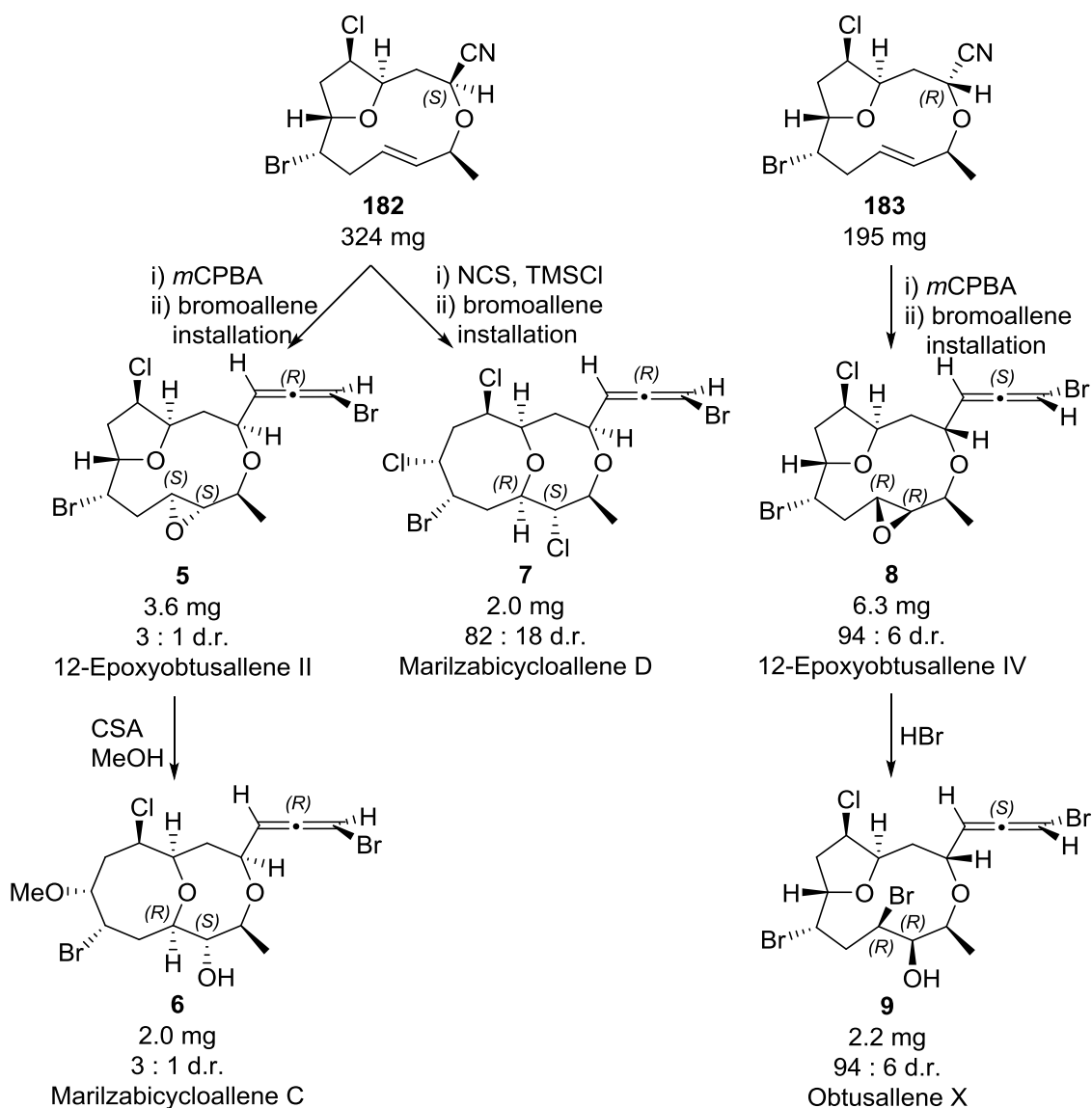


Figure 4.2.18.2: Natural products successfully synthesised from macrocyclic nitriles **182** & **183**.

Following epoxidation and bromoallene installation on **182**, 3.6 mg of the compound that has been named 12-epoxyobtusallene II (**5**) was collected, in a 3 : 1 diastereomeric ratio. Although not a known natural product, it is invoked as an intermediate in Norte's proposed biogenesis of marilzabicycloallene C (**6**), so is likely to exist.¹² Indeed, an acidic methanolysis procedure was designed and employed to yield 2.0 mg of marilzabicycloallene C (**6**), again

in a 3 : 1 ratio. Precursor **182** was also employed in a transannular dichlorination procedure, based on Braddock's previous studies into *Laurencia* natural product biosynthesis.²³ Pleasingly, a trichloride was produced in high yield that could be elaborated to give 2.0 mg of marilzabicycloallene D (**7**) in an 82 : 18 diastereomeric ratio.

Turning to macrocycle **183**, epoxidation resulted in two diastereomeric epoxides, of which the major (*R,R*)-product **364** could be elaborated to give a total of 6.3 mg of 12-epoxyobtusallene IV (**8**), following bromoallene installation. This natural product could be treated with hydrobromic acid to give 2.2 mg of obtusallene X (**9**), in a biomimetic oxonium ion assisted epoxide opening. An attempt was made to affix a bromoallene to the minor (*S,S*)-epoxide **365**, as a route to marilzabicycloallene B (**77**), but the macrocycle appeared to be highly susceptible to rearrangement, obstructing the attempt.

Further investigations were conducted into improving the diastereomeric ratio of 12-epoxyobtusallene II (**5**) and marilzabicycloallene C (**6**), *via* an oxidation of the intermediate propargylic alcohol (**350**) and subsequent asymmetric reduction. However, alpine-borane, CBS and chelation controlled reductions all failed.

Finally, attempts to produce obtusallenes II & IV (**15** & **19**) through titanocene(III) chloride deoxygenation of epoxides or Corey-Winter olefination of diols both failed. The initial targets of the project were missed, but a range of natural products had been produced, each allowing insights into the biosynthesis of these fascinating *Laurencia* metabolites.

5 Experimental

5.1 General Experimental

Experimental Techniques: All reactions were carried out in oven-dried glassware. Air-sensitive reactions were performed under a positive pressure of nitrogen where stated. Reaction temperatures other than room temperature were achieved with a dry-syn and heating mantle, dry ice/acetone bath or dry ice/Et₂O bath. Solvent removal and concentrations were achieved with a rotary evaporator. Column chromatography was performed on Geduran® silica gel, particle size 40-63 µm. Analytical TLC was performed on Kieselgel 60 F254 pre-coated aluminium-backed plates and visualised with either irradiation with UV light (254 or 350 nm) or potassium permanganate/vanillin staining. Brine refers to a saturated aqueous solution of NaCl.

Characterisation: Melting points are uncorrected. Fourier transform infra-red (IR) spectra were recorded neat using an ATR-IR spectrometer. ¹H and ¹³C NMR spectra were recorded on either a Bruker DRX-400 or Bruker AV-400. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the residual solvent peak. ¹H NMR spectra were recorded at 400 MHz. ¹³C NMR spectra were recorded at 100 MHz. ³¹P NMR spectra were recorded at 162 MHz. NMR acquisitions were performed at 298 K. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; qu., quintet; m, multiplet. Low resolution MS (ESI, CI) and HRMS were recorded by the Imperial College Department of Chemistry Mass Spectrometry Service.

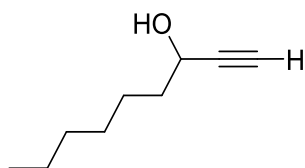
Reagents: DMDO solutions were distilled under reduced pressure from a flask containing NaHCO₃ (2.9 g, 34.5 mmol), oxone™ (6.0 g, 19.5 mmol), acetone (9.56 mL, 130 mmol) and water (12.7 mL) at 0 °C and collected in a receiver flask at -100 °C as adapted from the reported procedure.^{50a} Concentrations were determined by iodometric titration or assumed

to be 0.1 M. Heptaldehyde (**194**), octaldehyde (**221**) and triethylamine were distilled under nitrogen before use, and I₂ was sublimed before use. The molarity of *n*BuLi was determined by titration with menthol and 2,2'-bipyridine in THF directly before use.¹²⁷ LDA was freshly prepared from *n*BuLi and diisopropylamine in THF at -78 °C under N₂. The yellow solution was warmed to 0 °C, stirred for 30 min and used immediately.¹²⁸ All other reagents were obtained from commercial suppliers and used as received.

Solvents: All reactions were carried out in anhydrous solvents, unless used in combination with H₂O. HPLC grade CH₂Cl₂, THF, Et₂O and toluene were dried by passing through a column of alumina beads. CHCl₃ and MeOH were dried over MgSO₄. Extraction solvents and chromatography eluents were used as received. Petroleum ether (40 – 60 °C) and Et₂O were GPR grade. EtOAc and CH₂Cl₂ were GPR or HiPerSolv grade.

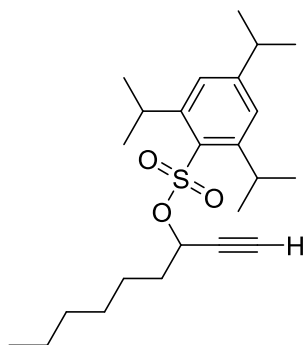
5.2 Procedures and Characterising Data Part I

Non-1-yn-3-ol (**195**)



A solution of heptaldehyde (**194**) (3.00 mL, 21.3 mmol) in THF (43 mL) was added to a stirred solution of ethynylmagnesium bromide in THF (64 mL, 0.5 M, 32.0 mmol) at 0 °C over 20 min. After 1 h, the orange solution was quenched with sat. aq. NH_4Cl solution (8 mL) and the solvent removed *in vacuo* and the residue partitioned between Et₂O (60 mL) and sat. aq. NH_4Cl solution (60 mL). The layers were separated and the organic layer was washed with brine (2 × 60 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to give a brown oil (3.13 g). Column chromatography (petroleum ether : EtOAc 6 : 1) gave title compound **195** (2.35 g, 17.4 mmol, 82%) as a colourless oil; R_f 0.31 (petroleum ether : EtOAc 6 : 1); IR (neat) 3350, 3309, 1038 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 4.34 (td, J = 6.6, 2.0 Hz, 1H, CHOH), 2.43 (d, J = 2.0 Hz, 1H, $\text{C}\equiv\text{CH}$), 2.01 (br. s, 1H, OH), 1.73 - 1.64 (m, 2H, CH_2), 1.46 - 1.38 (m, 2H, CH_2), 1.31 - 1.23 (m, 6H, 3 × CH_2), 0.86 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz; CDCl_3) δ 85.1 ($\text{C}\equiv\text{CH}$), 72.8 ($\text{C}\equiv\text{CH}$), 62.3 (COH), 37.7 (CH_2), 31.7 (CH_2), 28.9 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); MS (CI^+ , NH_3) m/z 158 ($\text{M} + \text{NH}_4$) $^+$; HRMS (CI^+ , NH_3) m/z calcd for $\text{C}_9\text{H}_{20}\text{NO}$ ($\text{M} + \text{NH}_4$) $^+$ 158.1545, found 158.1538.

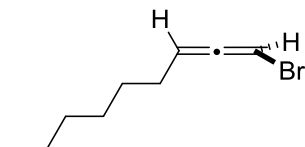
Non-1-yn-3-yl 2,4,6-tris(propan-2-yl)benzene-1-sulphonate (196)



According to the method of Kim,^{53a} to a solution of alcohol **195** (1.10 mg, 7.86 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (2.38 mg, 7.86 mmol) in CH₂Cl₂ (20 mL) followed by a solution of DMAP (960 mg, 7.86 mmol) in CH₂Cl₂ (20 mL). The colourless solution was warmed to room temperature and stirred for 19 h until TLC (petroleum ether : EtOAc 6 : 1) showed completion of the reaction. The solution was passed through a silica plug with Et₂O and the solvent was removed *in vacuo* to give a light yellow oil (3.02 g). Column chromatography (petroleum ether : EtOAc 50 : 1 to 40 : 1) gave the title compound **196** (2.91 g, 7.16 mmol, 91%) as a colourless oil; *R*_f 0.78 (petroleum ether : EtOAc 6 : 1); IR (neat) 3312, 1560, 1463, 1350, 1176, 938 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 7.14 (s, 2H, 2 × Ar-*H*), 5.14 (td, *J* = 6.4, 2.0 Hz, 1H, CHOTris), 4.13 (sept., *J* = 6.8 Hz, 2H, 2 × *ortho*-CH(CH₃)₂), 2.88 (sept., *J* = 6.8 Hz, 1H, *para*-CH(CH₃)₂), 2.26 (d, *J* = 2.0 Hz, 1H, C≡CH), 1.85 - 1.78 (m, 2H, CH₂), 1.48 - 1.40 (m, 2H, CH₂), 1.26 - 1.20 (m, 6H, 3 × CH₂), 1.25 (d, *J* = 7.0 Hz, 6H, *ortho*-CH(CH₃)₂), 1.24 (d, *J* = 7.0 Hz, 6H, *ortho*-CH(CH₃)₂), 1.23 (d, *J* = 7.0 Hz, 6H, *para*-CH(CH₃)₂), 0.85 (t, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 153.6 (*para*-C), 150.6 (2 × *ortho*-C), 130.8 (*ipso*-C), 123.6 (2 × *meta*-C), 79.2 (C≡CH), 75.9 (C≡CH), 70.2 (COTris), 35.7 (CH₂), 34.3 (*para*-CH(CH₃)₂), 31.6 (CH₂), 29.6 (2 × *ortho*-CH(CH₃)₂), 28.6 (CH₂), 24.7 (4 × *ortho*-CH(CH₃)₂), 24.6 (CH₂), 23.6 (2 × *para*-CH(CH₃)₂), 22.5 (CH₂), 14.0 (CH₃); MS (CI⁺,

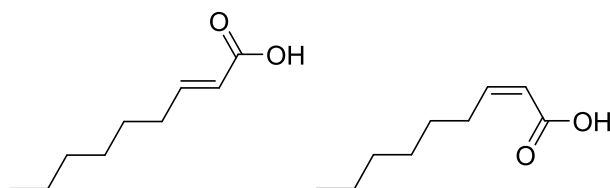
NH₃) m/z 424 (M + NH₄)⁺; HRMS (CI⁺, NH₃) m/z calcd for C₂₄H₄₂NO₃S (M + NH₄)⁺ 424.2885, found 424.2887.

1-Bromonona-1,2-diene (1)



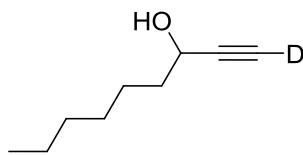
According to the method of Kim,^{53a} LiBr (896 mg, 10.3 mmol) and CuBr (1.48 g, 10.3 mmol) were dissolved in THF (41 mL) and stirred at room temperature for 30 min. The green solution was transferred to a solution of trisylate **196** (1.40 g, 3.44 mmol) in THF (172 mL) and stirred at reflux for 30 min. The solvent was removed *in vacuo* and the brown residue was passed through a short silica plug eluting with petroleum ether. Column chromatography (*n*-hexane) gave the title compound **1** (529 mg, 2.60 mmol, 76%) as a colourless oil: R_f 0.78 (petroleum ether : EtOAc 50 : 1); IR (neat) 3059, 1956, 652 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.91 (dt, J = 5.4, 2.4 Hz, 1H, HC=C=CHBr), 5.38 (app. q., J = 5.4 Hz, 1H, HC=C=CHBr), 2.13 (qd, J = 7.0, 2.4 Hz, 2H, CH₂CH=C), 1.48-1.36 (m, 2H, CH₂), 1.35 – 1.23 (m, 6H, 3 $\times$ CH₂), 0.87 (t, J = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 202.1(C=C=C), 101.1 (HC=C=CHBr), 72.2 (HC=C=CHBr), 31.6 (CH₂), 28.7 (CH₂), 28.3 (CH₂), 28.3 (CH₂), 22.6 (CH₂), 14.1 (CH₃). The molecular ion for this compound could not be observed by electron or chemical ionisation methods.

(E)-Non-2-enoic acid [(E)-2] & (Z)-non-2-enoic acid [(Z)-2]



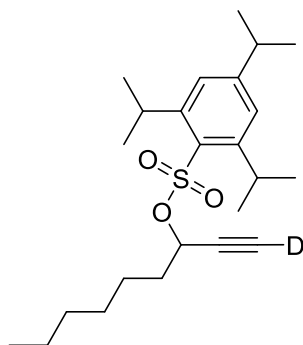
To a stirred solution of 1-bromonona-1,2-diene **1** (100 mg, 0.49 mmol) in acetone (2.0 mL) at -40 °C was added a 0.10 M solution of DMDO in acetone (3.2 mL, 0.32 mmol, 0.66 eq.). The colourless solution was warmed to room temperature and stirred for overnight. The solution was washed with brine (3 × 10mL) and the organic layer dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue extracted with Et₂O (3 × 2 mL) and petroleum ether (3 × 2 mL). The combined organics were evaporated to give a yellow oil. Column chromatography (petroleum ether : EtOAc 4 : 1 to 1 : 2) gave the title compounds (E)-**2** (10 mg, 0.064 mmol, 13%) as a colourless oil: R_f 0.15 (petroleum ether : EtOAc 3 : 1); IR (neat) 3300-2800, 1696, 1650 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.06 (dt, *J* = 15.6, 7.0 Hz, 1H, β-H), 5.80 (dt, *J* = 15.6, 1.5 Hz, 1H, α-H), 2.21 (app. qd, *J* = 7.0, 2.4 Hz, 2H, CH₂CH=CH), 1.46 – 1.40 (m, 2H, CH₂), 1.34 – 1.21 (m, 6H, 3 × CH₂), 0.87 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.8 (CO₂H), 152.5 (β-C), 120.5 (α-C), 32.3 (CH₂), 31.6 (CH₂), 28.8 (CH₂), 27.8 (CH₂), 22.5 (CH₂), 14.0 (CH₃); MS (CI⁺, NH₃) *m/z* 174 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₉H₂₀NO₂ (M + NH₄)⁺ 174.1494, found 174.1494; and (Z)-**2** (12 mg, 0.077 mmol, 15%) as a colourless oil: R_f 0.26 (petroleum ether : EtOAc 3 : 1); IR (neat) 3300-2800, 1696, 1640 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.34 (dt, *J* = 11.5, 7.6 Hz, 1H, β-H), 5.76 (dt, *J* = 11.5, 1.7 Hz, 1H, α-H), 2.64 (app. qd, *J* = 7.6, 1.7 Hz, 2H, CH₂CH=CH), 1.46 – 1.38 (m, 2H, CH₂), 1.35 – 1.22 (m, 6H, 3 × CH₂), 0.86 (t, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.8 (CO₂H), 153.7 (β-C), 118.9 (α-C), 31.6 (CH₂), 29.3 (CH₂), 29.0 (CH₂), 28.9 (CH₂), 22.6 (CH₂), 14.1 (CH₃); MS (CI⁺, NH₃) *m/z* 174 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₉H₂₀NO₂ (M + NH₄)⁺ 174.1494, found 174.1487.

(1-²H)-Non-1-yn-3-ol [(1-²H)-195]



A solution of heptaldehyde (**194**) (2.50 mL, 17.7 mmol) in THF (35.5 mL) was added to a stirred solution of 0.5 M ethynylmagnesium bromide (58.7 mL, 26.6 mmol) at 0 °C under N₂ over 20 min. After 1 h, a solution of *n*BuLi in hexanes (12 mL, 2.21 M, 26.6 mmol) was added dropwise over 5 min. and stirred for an additional 1 h at room temperature. MeOH-d₄ (2.00 mL, 49.2 mmol) was added dropwise to the orange solution before being quenched with sat. aq. NH₄Cl solution (20mL) and the solvent removed *in vacuo*. The resulting brown residue was triturated with Et₂O (2 × 20 mL) and the organic layers were combined and dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give a yellow oil (2.93 g). Column chromatography (petroleum ether : EtOAc 6 : 1) gave the title compound (1-²H)-**195** (2.13 g, 15.1 mmol, 85 %, 70% alkyne deuteration) as a colourless oil [the extent of deuterium incorporation was deduced by inspection of the relative integral (0.30H) for residual non-deuterated alkyne **195** at 2.43 ppm in the ¹H NMR spectrum]; R_f 0.18 (petroleum ether : EtOAc 6 : 1); IR (neat) 3600-3100, 2593cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 4.34 (t, *J* = 6.6, 2.0 Hz, 1H, CHOH), 2.44 (d, *J* = 2.0 Hz, 0.30H, C≡CH), 1.92 (br. s, 1H, OH), 1.72 – 1.65 (m, 2H, CH₂), 1.47 – 1.38 (m, 2H, CH₂), 1.34 – 1.23 (m, 6H, 3 × CH₂), 0.86 (t, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 84.6 (t, *J* = 7.2 Hz, C≡CD), 72.6 (t, *J* = 38.1 Hz, C≡CD), 62.3 (COH), 37.7 (CH₂), 31.7 (CH₂), 28.9 (CH₂), 25.0 (CH₂), 22.6 (CH₂), 14.1 (CH₃); MS (CI⁺, NH₃) *m/z* 160 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₉H₁₉²HNO (M + NH₄)⁺ 160.1335, found 160.1339.

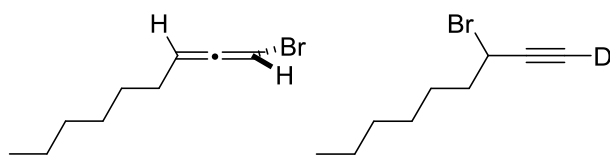
(1-²H)-Non-1-yn-3-yl 2,4,6-tris(propan-2-yl)benzene-1-sulphonate [(1-²H)-196]



According to the method of Kim,^{53a} to a solution of (1-²H)-non-1-yn-3-ol (1-²H)-**195** (1.05 g, 7.42 mmol) in CH₂Cl₂ (18 mL) at 0 °C was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (2.25 g, 5.55 mmol) in CH₂Cl₂ (10 mL), followed by a solution of DMAP (907 mg, 7.42 mmol) in CH₂Cl₂ (10 mL). The colourless solution was warmed to room temperature and stirred for 19 h until TLC (petroleum ether : EtOAc 6 : 1) showed completion. The solution was passed through a silica plug with Et₂O and the solvent was removed *in vacuo* to give a light yellow oil (2.90 g). Column chromatography (petroleum ether : EtOAc 50 : 1 to 6 : 1) gave the title compound (1-²H)-**196** (2.85 g, 6.98 mmol, 94%, 70% deuteration) as a colourless oil [the extent of deuterium incorporation was deduced by inspection of the relative integral (0.30H) for residual non-deuterated alkyne **196** at 2.26 ppm in the ¹H NMR spectrum]; R_f 0.63 (petroleum ether : EtOAc 6 : 1); IR (neat) 3298, 1560, 1463, 1350, 1176, 938 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 7.14 (s, 2H, 2 × Ar-H), 5.14 (t, J = 6.5 Hz, 1H, CHOTris), 4.13 (sept., J = 6.8 Hz, 2H, 2 × *ortho*-CH(CH₃)₂), 2.88 (sept., J = 6.8 Hz, 1H, *para*-CH(CH₃)₂), 2.26 (d, J = 2.0 Hz, 0.30H, C≡CH), 1.86 – 1.79 (m, 2H, CH₂), 1.48 – 1.39 (m, 2H, CH₂), 1.31 – 1.23 (m, 6H, 3 × CH₂), 1.25 (d, J = 6.8 Hz, 6H, *ortho*-CH(CH₃)₂), 1.24 (d, J = 6.8 Hz, 6H, *ortho*-CH(CH₃)₂), 1.23 (d, J = 7.0 Hz, 6H, *para*-CH(CH₃)₂), 0.85 (t, J = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 153.6 (*para*-C), 150.6 (2 × *ortho*-C), 130.8 (*ipso*-C), 123.6 (2 × *meta*-C),

79.2 (C≡CD), 75.9 (C≡CD), 70.2 (COTris), 35.7 (CH₂), 34.3 (*para*-CH(CH₃)₂), 31.6 (CH₂), 29.6 (2 × *ortho*-CH(CH₃)₂), 28.6 (CH₂), 24.7 (4 × *ortho*-CH(CH₃)₂), 24.6 (CH₂), 23.6 (2 × *para*-CH(CH₃)₂), 22.5 (CH₂), 14.0 (CH₃); MS (CI⁺, NH₃) *m/z* 425 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₂₄H₄₁²HNO₃S (M + NH₄)⁺ 425.2943, found 425.2938.

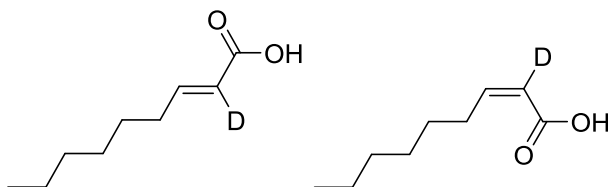
(1-²H)-1-Bromonona-1,2-diene [(1-²H)-1] and 3-bromo-(1-²H)-non-1-yne [(1-²H)-200]



According to the method of Kim,^{53a} LiBr (895 mg, 10.3 mmol) and CuBr (1.48 g, 10.3 mmol) were dissolved in THF (41 mL) and stirred at room temperature for 30 min. The green solution was transferred to a solution of propargylic trisylate (1-²H)-**196** (1.40 g, 3.43 mmol) in THF (172 mL) and stirred at reflux for 30 min. The solvent was removed *in vacuo* and the brown residue was passed through a short silica plug with petroleum ether. The solvent was removed *in vacuo* once more to give a yellow oil (745 mg). Column chromatography (petroleum ether) gave the title compound (1-²H)-**1** (482 mg, 2.36 mmol, 69%, 70% deuteration) as a colourless oil [the deuterium content was deduced by inspection of the integral (0.30H) for the residual non-deuterated allene **1** at 5.91 ppm in the ¹H NMR spectrum; R_f 0.63 (petroleum ether : EtOAc 50 : 1); IR (neat) 1940, 653 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.41 - 5.35 (m, 1H, HC=C=CDBr), 2.13 (q, *J* = 7.0 Hz, 2H, CH₂CH=C), 1.47 - 1.39 (m, 2H, CH₂), 1.35 - 1.24 (m, 6H, 3 × CH₂), 0.87 (t, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 202.0 (HC=C=CDBr), 101.2 (HC=C=CDBr), 72.2 (t, *J* = 33 Hz, HC=C=CDBr), 31.6 (CH₂), 28.7 (CH₂), 28.4 (CH₂), 28.3 (CH₂), 22.6 (CH₂), 14.1 (CH₃); and propargylic bromide (1-²H)-**200** (50 mg, 0.245 mmol, 7%); R_f 0.76 (petroleum ether : EtOAc 50 : 1); IR (neat) 3307,

2594, 1987, 1466, 643 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.45 (t, $J = 6.8$ Hz, 1H, CHBr), 2.62 (d, $J = 2.4$ Hz, 0.30H, $\text{C}\equiv\text{CH}$), 2.02 – 1.95 (m, 2H, CH_2CHBr), 1.55 – 1.46 (m, 2H, CH_2), 1.34 – 1.23 (m, 6H, $3 \times \text{CH}_2$), 0.87 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 82.2 (t, $J = 7.8$ Hz, $\text{C}\equiv\text{CD}$), 74.6 (t, $J = 38$ Hz, $\text{C}\equiv\text{CD}$), 39.5 (CHBr), 36.0 (CH_2), 31.6 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 22.5 (CH_2), 14.0 (CH_3). The molecular ion for these compounds could not be observed by electron or chemical ionisation methods.

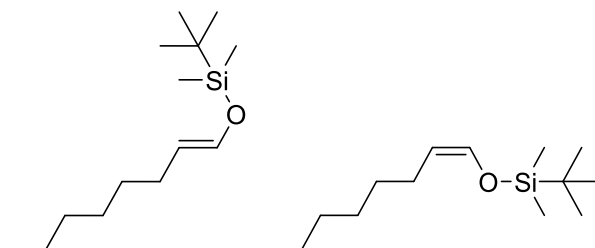
(*E*-2- ^2H)-Non-2-enoic acid [(*E*-2- ^2H)-2] & (*Z*-2- ^2H)-non-2-enoic acid [(*Z*-2- ^2H)-2]



To a stirred solution of (1- ^2H)-1-bromonona-1,2-diene (1- ^2H)-1 (100 mg, 0.834 mmol) in acetone (6.80 mL) at -40 $^{\circ}\text{C}$ was added a 0.10 M solution of DMDO in acetone (5.5 mL, 0.55 mmol, 0.66 eq.). The colourless solution was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue extracted with Et_2O (3×2 mL) and petroleum ether (3×2 mL). The combined organics were evaporated to give a yellow oil. Column chromatography (petroleum ether : EtOAc 4 : 1 to 1 : 2) gave the title compounds (*E*-2- ^2H)-2 (9 mg, 0.057 mmol, 12 %, 65% deuteration) as a colourless oil: R_f 0.17 (petroleum ether : EtOAc 6 : 1); IR (neat) 3300-2800, 1692, 1637 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.10 – 7.02 (m, $\beta\text{-H}$), 2.21 (q, $J = 7.0$ Hz, 2H, $\text{CH}_2\text{CH}=\text{CD}$), 1.49 – 1.40 (m, 2H, CH_2), 1.34 – 1.22 (m, 6H, $3 \times \text{CH}_2$), 0.87 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) 171.2 (CO_2H), 152.3 ($\beta\text{-C}$), 120.4 ($\alpha\text{-C}$), 32.3 (CH_2), 31.6 (CH_2), 28.8 (CH_2), 27.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3); MS (CI^+ , NH_3) m/z 175 ($\text{M} + \text{NH}_4^+$); HRMS (CI^+ , NH_3) m/z calcd for $\text{C}_9\text{H}_{19}^2\text{HNO}_2$ ($\text{M} + \text{NH}_4^+$) 175.1551, found 175.1554; and (*Z*-2- ^2H)-2: R_f 0.26 (petroleum ether : EtOAc 6 : 1); IR

(neat) 3300-2800, 1692, 1633 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.37 – 6.30 (m, $\beta\text{-H}$), 2.64 (q, J = 7.5 Hz, 2H, $\text{CH}_2\text{CH}=\text{CD}$), 1.47 – 1.39 (m, 2H, CH_2), 1.35 – 1.25 (m, 6H, $3 \times \text{CH}_2$), 0.87 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) 170.6 (CO_2H), 153.4 ($\beta\text{-C}$), 118.7 ($\alpha\text{-C}$), 31.6 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3); MS (CI^+ , NH_3) m/z 175 ($\text{M} + \text{NH}_4$) $^+$; HRMS (CI^+ , NH_3) $\text{C}_9\text{H}_{19}^2\text{HNO}_2$ ($\text{M} + \text{NH}_4$) $^+$ 175.1551, found 175.1564; [the deuterium content was deduced by inspection of the integral (0.35H) for the residual non-deuterated α,β -unsaturated carboxylic acids at 5.80 and 5.76 ppm in the ^1H NMR spectrum for *E* and *Z*-5 respectively].

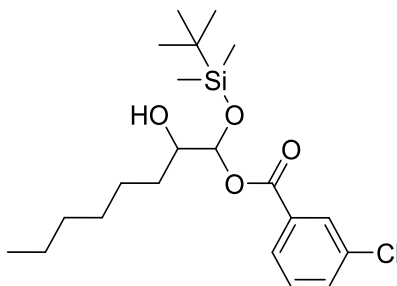
***tert*-Butyldimethyl[(1*E*)-oct-1-en-1-yloxy]silane and *tert*-butyldimethyl[(1*Z*)-oct-1-en-1-yloxy]silane (225)**



According to the method of Taniguchi,¹²⁹ to a solution of octaldehyde (**221**) (900 mg, 1.10 mL, 7.0 mmol) in CH_2Cl_2 (9.6 mL) was added *tert*-butyldimethylsilyl chloride (1.27 g, 8.45 mmol) followed by DBU (1.72 g, 1.69 mL, 11.3 mmol) and stirred for 1.5 h. Water (10 mL) was added to the yellow solution, the layers were separated and the aqueous layer extracted further with Et_2O (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to give the crude product as a yellow oil (2.08 g). Column chromatography (petroleum ether : EtOAc 20 : 1) gave the title compounds (*E*)-**225** & (*Z*)-**225** (1.32 g, 5.46 mmol, 78%) as a colourless oil as an inseparable mixture (2 : 1 respectively); R_f 0.75 (petroleum ether : EtOAc 5 : 1); IR (neat) 3035, 1660, 1254,

1163 cm^{-1} ; (*E*)-**225**: ^1H NMR (400 MHz, CDCl_3) δ 6.20 (dt, $J = 11.9, 1.4$ Hz, 1H, CHOTBS), 4.96 (dt, $J = 11.9, 7.5$ Hz, 1H, CH_2CH), 1.85 (q, $J = 7.5$ Hz, 2H, CH_2CH), 1.34 – 1.20 (m, 8H, $4 \times \text{CH}_2$), 0.90 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.86 (t, $J = 6.8$ Hz, 3H, CH_3), 0.10 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 140.0 (CHOTBS), 111.8 (CH_2CH), 31.7, 30.4, 28.8 & 27.3 ($4 \times \text{CH}_2$), 25.8 ($\text{C}(\text{CH}_3)_3$), 22.7 (CH_2), 18.4 ($\text{C}(\text{CH}_3)_3$), 14.1 (CH_3), -5.2 ($\text{Si}(\text{CH}_3)_2$); (*Z*)-**225**: ^1H NMR (400 MHz, CDCl_3) δ 6.14 (dt, $J = 5.8, 1.4$ Hz 1H, CHOTBS), 4.42 (dt, $J = 6.9, 5.8$ Hz, 1H, CH_2CH), 2.05 (q, $J = 6.9$ Hz, 2H, CH_2CH), 1.34 – 1.20 (m, 8H, $4 \times \text{CH}_2$), 0.90 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.86 (t, $J = 6.8$ Hz, 3H, CH_3), 0.10 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 138.4 (CHOTBS), 110.9 (CH_2CH), 31.8, 30.4, 29.7 & 29.0 ($4 \times \text{CH}_2$), 25.7 ($\text{C}(\text{CH}_3)_3$), 23.6 (CH_2), 18.3 ($\text{C}(\text{CH}_3)_3$), 14.1 (CH_3), -5.4 ($\text{Si}(\text{CH}_3)_2$); MS (CI^+ , NH_3) m/z 243 (M) $^+$; HRMS (CI^+ , NH_3) m/z calcd for $\text{C}_{14}\text{H}_{30}\text{OSi}$ (M) $^+$ 242.2066, found 242.2078.

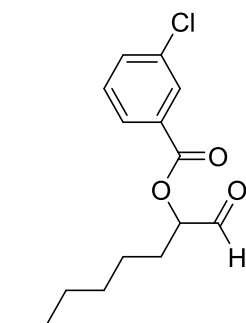
1-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxyoctyl 3-chlorobenzoate (**226**)



According to the method of Hassner,¹³⁰ to a stirred solution of (*E*)- and (*Z*)-**225** (600 mg, 2.47 mmol, 7 : 3) in CHCl_3 (8.4 mL) under N_2 was added *m*CPBA (779 mg, 3.48 mmol) at 0 $^\circ\text{C}$. After 1 h, the colourless solution was transferred to a separating funnel and washed with brine (2×10 mL). The aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to give a white solid (1.30 g, 56 : 44 d.r.) which could be used directly in the subsequent acetylation. Column

chromatography (petroleum ether : EtOAc 15: 1) gave the title compound **226** (903 mg, 2.17 mmol, 88%, 61 : 39 d.r.) as a colourless oil; R_f 0.51 (petroleum ether : EtOAc 3 : 1); IR (neat) 3600-3300, 1726, 1254, 835, 780 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.04 – 7.99 (m, 1H, ArH), 7.96 – 7.91 (m, 1H, ArH), 7.56 – 7.51 (m, 1H, ArH), 7.38 (t, J = 7.9 Hz, 1H, ArH), 6.14 (d, J = 4.0 Hz, 0.61H, CHOTBS), 6.11 (d, J = 3.9 Hz, 0.39H, CHOTBS), 3.73 – 3.66 (m, 1H, CHOH), 2.03 (br. s, 1H, OH), 1.63 – 1.41 (m, 2H, CH_2COH), 1.34 – 1.23 (m, 4H, $2 \times \text{CH}_2$), 0.89 – 0.88 (m, 9H, $\text{C}(\text{CH}_3)_3$), 0.85 (t, J = 6.6 Hz, 3H, CH_3), 0.17 (s, 3H, $\text{Si}(\text{CH}_3)$), 0.07 (s, 1.17H, $\text{Si}(\text{CH}_3)$), 0.06 (s, 1.83H, $\text{Si}(\text{CH}_3)$); ^{13}C NMR (101 MHz, CDCl_3) δ 164.6 & 164.5 (CO_2Ar), 134.7 (C-Cl), 133.4 (*ipso*-C), 131.7 (*para*-C), 129.8 (*ortho* & *meta*-C), 127.9 (*ortho*-C), 94.2 & 93.9 (CHOTBS), 73.7 & 73.5 (CHOH), 31.9, 31.8, 31.3, 29.3 & 29.2 ($3 \times \text{CH}_2$), 25.7 ($\text{C}(\text{CH}_3)_3$), 25.4, 25.3 & 22.6 ($2 \times \text{CH}_2$), 18.0 ($\text{C}(\text{CH}_3)_3$), 14.1 (CH_3), -4.5 & -5.3 ($\text{Si}(\text{CH}_3)_2$); MS (CI^+ , NH_3) m/z 301 ($\text{M} - \text{TBS}$), 276 ($\text{M} - \text{O}_2\text{CAr} + \text{NH}_3$) $^+$, 259 ($\text{M} - \text{O}_2\text{CAr} + \text{H}$) $^+$.

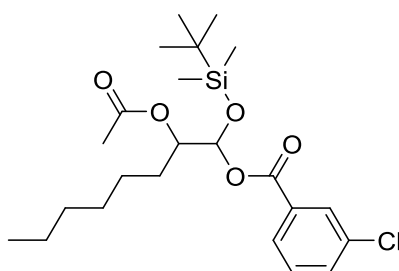
1-Oxoocatan-2-yl 3-chlorobenzoate (**228**)



Column chromatography of crude compound **226** (15.2 g) also gave compound **228** (939 mg, 10%) as a colourless oil, which had not been present in the sample previously; R_f 0.26 (petroleum ether : EtOAc 3 : 1); IR (neat) 3600-3300, 1721, 1251, 745 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.60 (s, 1H, CHO), 8.06 - 8.02 (m, 1H, *ortho*-H), 7.98 - 7.94 (m, 1H, *ortho*-H), 7.58 - 7.54 (m, 1H, *para*-H), 7.40 (t, J = 7.9 Hz, 1H, *meta*-H), 5.22 (dd, J = 8.2, 4.8 Hz, 1H, CHO_2CAr),

2.00 – 1.82 (m, 2H, CH₂), 1.53 – 1.43 (m, 2H, CH₂), 1.39 – 1.25 (m, 6H, 3 × CH₂), 0.87 (t, *J* = 6.8 Hz, 1H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 197.8 (CHO), 164.9 (O₂CAr), 134.7 (C-Cl), 133.5 (*ipso*-C), 130.9 (*para*-C), 129.8 (*ortho* & *meta*-C), 127.9 (*ortho*-C), 79.1 (CHO₂Ar), 31.4 (CH₂), 28.9 (CH₂), 28.7 (CH₂), 24.9 (CH₂), 22.5 (CH₂), 14.0 (CH₃); MS (ES⁺, ToF) *m/z* 282 (M)⁺; HRMS (ES⁺, ToF) *m/z* calcd for C₁₅H₁₉O₃³⁵Cl (M)⁺ 282.1023, found 282.1036.

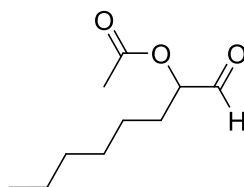
1-[(*tert*-Butyldimethylsilyl)oxy]-1-[(3-chlorophenyl)carbonyloxy-2-yl acetate (227**)**



To a stirred solution of alcohol **226** (4.48 g, 10.8 mmol, 56 : 44 d.r.) in Et₂O (112.5mL) at room temperature was added Ac₂O (2.34 g, 2.16 mL, 22.9 mmol), Et₃N (3.13 g, 4.31mL, 30.9 mmol) and DMAP (35.5 mg, 0.29 mmol) at room temperature. After 4 h, the colourless solution was quenched with MeOH and stirred for a further 10 min. The solution was transferred to a separating funnel and washed successively with sat. aq. NaHCO₃ solution (2 × 50 mL), 1M HCl (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give the title compound **227** (4.89 g, 10.7 mmol, 99%, 56 : 44 d.r.) as a colourless oil; *R*_f 0.68 (petroleum ether : EtOAc 10 : 1); IR (neat) 3600-3300, 1729, 1230, 835, 781 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.97 (m, 1H, ArH), 7.93 – 7.87 (m, 1H, ArH), 7.54 - 7.49 (m, 1H, ArH), 7.40 – 7.34 (m, 1H, ArH), 6.28 (d, *J* = 3.5 Hz, 0.44H, CHOTBS), 6.20 (d, *J* = 5.0 Hz, 0.56H, CHOTBS), 5.05 (ddd, *J* = 8.8, 5.0, 3.7 Hz, 0.56H, CHOAc), 4.96 (dt, *J* = 9.5, 3.5 Hz, 0.54H, CHOAc), 2.02 (s, 1.32H, O₂CCH₃), 1.96 (s, 1.68H, O₂CCH₃), 1.80 – 1.60 (m, 2H, CH₂), 1.40 – 1.20 (m, 8H, 4 × CH₂), 0.87 (s, 9H, C(CH₃)₃), 0.85 (t, *J* = 6.6 Hz, 3H, CH₃), 0.15

(m, 3H, Si(CH₃)), 0.05 (m, 3H, Si(CH₃)); ¹³C NMR (101 MHz, CDCl₃) δ 170.6 & 170.2 (O₂CCH₃), 164.3 (O₂CCH₃), 134.7 & 134.7 (C-Cl), 133.3 & 133.3 (*ipso*-C), 131.8 & 131.6 (*para*-C), 129.8 (*ortho* & *meta*-C), 127.9 (*ortho*-C), 92.1 & 91.5 (CHOTBS), 74.5 & 74.3 (CHOAc), 31.7, 29.1, 29.0, 29.0 & 27.4 (3 × CH₂), 25.6 (C(CH₃)₃), 25.3, 24.9 & 22.6 (2 × CH₂), 21.0 & 20.9 (CO₂CH₃), 17.9, (C(CH₃)₃), 14.1 (CH₃), -4.5, -4.6 & -5.3 (Si(CH₃)₂); MS (ES⁺, TOF) *m/z* 479 (M + Na)⁺; HRMS (ES⁺, ToF) *m/z* calcd for C₂₃H₃₇O₅³⁵ClSiNa (M + Na)⁺ 479.1995, found 479.1995.

1-Oxo-octan-2-yl acetate (197)

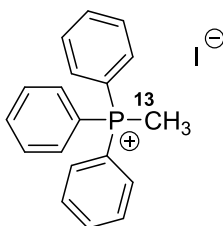


According to a modified method of Fraser-Reid,¹³¹ to a stirred solution of acetate **227** (4.79 g, 10.5 mmol) in THF (144 mL) was added AcOH (5.26 mL, 91.9 mmol) and a solution of TBAF in THF (26.2 mL, 1M, 26.2 mmol). The colourless solution was stirred at room temperature for 90 min before being transferred to a separating funnel and washed successively with sat. aq. NaHCO₃ solution (2 × 100 mL) and 1M HCl (2 × 100 mL). The aqueous layers were extracted with Et₂O (2 × 50 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over Na₂SO₄ and the solvent removed *in vacuo* to give the crude product (2.12 g). Column chromatography (petroleum ether : EtOAc 5: 1) gave the title compound **197** (1.29 g, 6.93 mmol, 66%); R_f 0.38 (petroleum ether : EtOAc 5 : 1); IR (neat) 1738, 1231 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H, CHO), 4.95 (dd, *J* = 8.6, 4.7 Hz, 1H, CHOAc), 2.14 (s, 3H, O₂CCH₃), 1.99 – 1.56 (m, 2H, CH₃), 1.44 – 1.32 (m, 2H, CH₂), 1.26 (m, 6H, 3 × CH₂), 0.85 (t, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 198.4 (CHO), 170.6 (O₂CCH₃), 78.4

(CHOAc), 31.5 (CH₂), 28.9 (CH₂), 28.6 (CH₂), 24.9 (CH₂), 22.5 (CH₂), 20.6 (O₂CCH₃), 14.0 (CH₃).

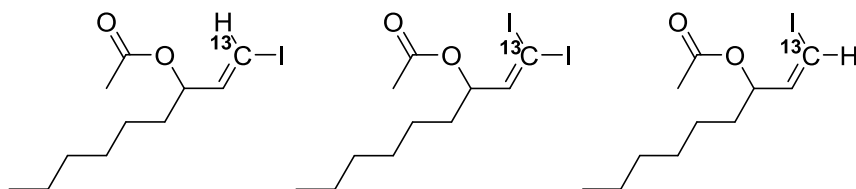
The molecular ion for this compounds could not be observed by electron or electrospray ionisation methods.

(¹³C)-Methyltriphenylphosphonium iodide [(¹³C)-198]



According to a modified method of Sato,¹³² to a solution of PPh₃ (1.84 g, 7.00 mmol) in THF (10 mL) in a Schlenk tube was added ¹³MeI (99 atom % ¹³C, 0.440 mL, 7.00 mmol) dropwise with minimal stirring. A white precipitate formed immediately. After stirring overnight, the solvent was removed *via* cannula and passed through filter paper into a Buchner funnel. The white crystals were washed with THF (3 × 5 mL) and the solvent again removed *via* cannula to give the phosphonium salt (¹³C)-**198**. [the extent of ¹³C incorporation was deduced by inspection of the relative integral (0.03H, 3H) for residual non-labeled phosphonium salt **198** at 2.20 ppm in the ¹H NMR spectrum]: m.p. 174-175 °C (lit.¹³³ 176 °C); IR (neat) 3017, 2919, 1586, 1490, 1440, 999, 752, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00 – 7.50 (m, 15H, 15 × Ar-H), 3.20 (dd, *J* = 135.1, 13.2 Hz, 3H, ¹³CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 135.2 (d, *J* = 2.6 Hz, (3 × *para*-C), 133.4 (d, *J* = 10.8 Hz, 6 × *meta*-H), 130.5 (d, *J* = 12.9 Hz, 6 × *ortho*-H), 119.0 (d, *J* = 89.4 Hz, 3 × *ipso*-H), 11.6 (d, *J* = 57.0 Hz, ¹³CH₃); ³¹P NMR (162 MHz, CDCl₃) δ 21.57 (d, *J* = 56.8 Hz, 1P). MS (ES⁺, ToF) *m/z* 278 (M – I)⁺; HRMS (ES⁺, ToF) *m/z* calcd for C₁₈¹³CH₃³¹P (M – I)⁺ 278.1180, found 278.1191.

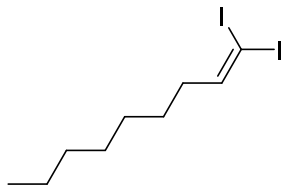
(*E*-1-¹³C)-1-Iodonon-1-en-3-yl acetate [(*E*-1-¹³C)-199], (1-¹³C)-1,1-diiodonon-1-en-3-yl acetate [(1-¹³C)-234] & (*Z*-1-¹³C)-1-iodonon-1-en-3-yl acetate [(*Z*-1-¹³C)-199]



According to a modified method of Curran,¹³⁴ to a stirred solution of (¹³C)-**198** (2.70 g, 6.63 mmol) in THF (14.2 mL) at 0 °C was added *n*BuLi in hexanes (3.00 mL, 2.21 M, 6.63 mmol) at 0 °C. After 10 min, the orange solution was transferred by cannula to a stirred solution of I₂ (1.68 g, 6.63 mmol) in THF (21.5 mL) at -78 °C over 30 min. The resulting brown suspension was stirred for 30 min, then a solution of sodium hexamethyldisilazane (3.6 mL, 1.0 M, 3.6 mmol) was added dropwise over 15 min. The resulting red suspension was stirred at -78 °C for 30 min, then -20 °C for 15 min, re-cooled to -78 °C and a solution of aldehyde **197** (1.06 g, 5.69 mmol) in THF (5.69 mL) was added dropwise over 30 min. The orange suspension was stirred at -78 °C for 30 min, then -20 °C for 1 h and finally room temperature for 1 h. TLC (petroleum ether : EtOAc 5 : 1) of the yellow suspension showed that no aldehyde **197** remained. The reaction mixture was passed through a short silica plug with petroleum ether : EtOAc 5 : 1 and the solvent removed *in vacuo* to give the crude product (1.15 g) as a yellow oil. Column chromatography (petroleum ether : EtOAc 50 : 1) gave a 2 : 3 : 5 mixture of iodoalkene acetates (*E*-1-¹³C)-**199** : (*Z*-1-¹³C)-**199** : (1-¹³C)-**234** (705 mg, 1.87 mmol, 33%) as a colourless oil, which could be subsequently deprotected as a mixture. Separation of (*E*-1-¹³C)-**199** and (*Z*-1-¹³C)-**199** geometrical isomers from each other, but not diiodide (1-¹³C)-**234** from either was possible by careful column chromatography. Each compound was formed as 99% 1-¹³C atom [the extent of ¹³C incorporation at the 1-position was deduced by

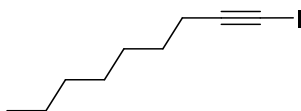
inspection of their ^1H NMR and ^{13}C NMR spectra]. (*E*-1- ^{13}C)-**199** (99% 1- ^{13}C atom) as a colourless oil; R_f 0.58 (petroleum ether : EtOAc 10 : 1); IR (neat) 1738, 1590 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.39 (ddd, $^1J_{\text{CH}} = 190.4$ Hz, $J = 15.6, 0.9$ Hz, 1H, ^{13}CHI), 6.45 (ddd, $^2J_{\text{CC}} = 7.0$ Hz, $J = 15.6, 7.0$ Hz, 1H, $\text{CH}=\text{CH}^{13}\text{CHI}$), 5.15 (app. qu., $J = 6.9$ Hz, 1H, CHOAc), 2.04 (s, 3H, O_2CCH_3), 1.70 – 1.50 (m, 2H, CH_2), 1.40 – 1.20 (m, 8H, $4 \times \text{CH}_2$), 0.86 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.3 (O_2CCH_3), 144.0 (d, $^1J_{\text{CC}} = 76.1$ Hz, $\text{CH}=\text{CH}^{13}\text{CHI}$), 79.8 (^{13}CHI), 75.7 (CHOAc), 33.7 (CH_2), 31.6 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 22.6 (CH_2), 21.2 (O_2CCH_3), 14.1 (CH_3); (1- ^{13}C)-**234** (99% 1- ^{13}C atom) as a colourless oil; R_f 0.56 (petroleum ether : EtOAc 10 : 1); IR (neat) 1738, 1575 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.98 (d, $J = 7.6$ Hz, 1H, $\text{CH}=\text{Cl}_2$), 5.11-4.98 (m, 1H, CHOAc), 2.03 (s, 3H, O_2CCH_2), 1.75 – 1.55 (m, 2H, CH_2), 1.40 – 1.20 (m, 8H, $4 \times \text{CH}_2$), 0.87 (t, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 167.0 (O_2CCH_3), 150.7 (d, $^1J_{\text{CC}} = 75.7$ Hz, $\text{CH}=\text{CH}^{13}\text{Cl}_2$), 79.3 (CHOAc), 33.4 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 24.6 (CH_2), 22.6 (CH_2), 21.0 (O_2CCH_3), 14.1 ($^{13}\text{Cl}_2$ & CH_3); (*Z*-1- ^{13}C)-**199** (99% 1- ^{13}C atom) as a colourless oil; R_f 0.53 (petroleum ether : EtOAc 10 : 1); IR (neat) 1737, 1594 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.42 (ddd, $^1J_{\text{CH}} = 184.6$ Hz, $J = 8.0, 0.9$ Hz, 1H, ^{13}CHI), 6.20 (ddd, $^2J_{\text{CH}} = 15.5$, $J = 8.0, 7.8$ Hz, 1H, $\text{CH}=\text{CH}^{13}\text{CHI}$), 5.40 (app. qu., $J = 6.6$ Hz, 1H, CHOAc), 2.03 (s, 3H, O_2CCH_3), 1.75 – 1.55 (m, 2H, CH_2), 1.35 – 1.20 (m, 8H, $4 \times \text{CH}_2$), 0.87 (t, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.1 (O_2CCH_3), 139.8 (d, $^1J_{\text{CC}} = 76.0$ Hz, $\text{CH}=\text{CH}^{13}\text{CHI}$), 83.6 (^{13}CHI), 79.3 (CHOAc), 33.4 (CH_2), 32.9 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 24.7 (CH_2), 21.1 (O_2CCH_3), 14.1 (CH_3).

1,1-Diiodonon-1-ene (238)



To a stirred solution of PPh_3 (1.15 g, 4.38 mmol), iodoform (1.65 g, 4.19 mmol) and $t\text{BuOK}$ (449 mg, 4.00 mmol) in THF (20 mL) at room temperature was added octaldehyde (**221**) (0.313 mL, 0.257 mg, 2.00 mmol). After 1 h, the dark red solution was quenched with brine (20 mL) and extracted with Et_2O (2×20 mL). The organic layers were dried over Na_2SO_4 , filtered and the solvent removed *in vacuo* to give a viscous red oil (2.27 g). Column chromatography (petroleum ether : EtOAc 25 : 1) gave title compound **238** (540 mg, 1.42 mmol, 71%) as a light pink oil; R_f 0.70 (petroleum ether : EtOAc 10 : 1); IR (neat) 1457, 713 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.92 (t, $J = 7.0$ Hz, 1H, $\text{CH}=\text{Cl}_2$), 1.90 (q, $J = 7.0$ Hz, 2H, CH_2CH), 1.45 – 1.35 (m, 2H, CH_2), 1.33 – 1.20 (m, 8H, $4 \times \text{CH}_2$), 0.90 – 0.84 (m, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 153.4 ($\text{CH}=\text{Cl}_2$), 39.6, 31.7, 29.1, 29.0, 27.4 & 22.7 ($5 \times \text{CH}_2$), 14.1 (CH_3), 11.3 ($\text{CH}=\text{Cl}_2$); MS (CI, NH_3) m/z 124 ($\text{M} - \text{I}_2$) $^+$.

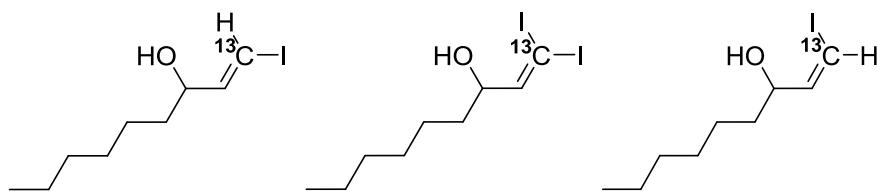
1-Iodonon-1-yne (240)



To neat 1,1-diiodonon-1-ene **238** (100 mg, 0.265 mmol) was added a 3% solution of K_2CO_3 in MeOH (3.60 mL, 0.781 mmol) and the cloudy mixture stirred at room temperature overnight. The reaction was quenched with sat. aq. NH_4Cl solution (5 mL) and extracted

with Et₂O (2 × 10 mL) and petroleum ether (2 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give a yellow oil (43 mg). Column chromatography (petroleum ether) gave title compound **240** (25 mg, 0.100 mmol, 38%); R_f 0.80 (petroleum ether : EtOAc 50 : 1); IR (neat) 1465, 723 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.33 (t, *J* = 7.1 Hz, 2H, CH₂≡CI), 1.53 – 1.45 (m, 2H, CH₂), 1.39 – 1.18 (m, 8H, 4 × CH₂), 0.86 (d, *J* = 7.2 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 94.88 (C≡CI), 31.69 (CHC≡CI), 28.83, 28.75, 28.50, 22.62 & 20.82 (5 × CH₂), 14.07 (CH₃), -7.73 (CI); MS (EI⁺) *m/z* 250 (M)⁺.

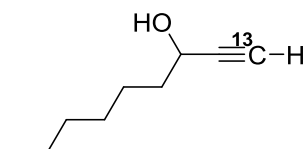
(*E*-1-¹³C)-1-Iodonon-1-en-3-ol [(*E*-1-¹³C)-241], (1-¹³C)-1,1-diiodonon-1-en-3-ol [(1-¹³C)-242] & (*Z*-1-¹³C)-1-iodonon-1-en-3-ol [(*Z*-1-¹³C)-241]



According to a modified procedure,¹³⁵ to a 2 : 3 : 5 mixture of acetates (*E*-1-¹³C)-**199** : (*Z*-1-¹³C)-**199** : (1-¹³C)-**234** (691 mg, 1.82 mmol) was added a 3% solution of K₂CO₃ in MeOH (27.3 mL, 5.92 mmol) and the cloudy mixture stirred at room temperature for 18 h. The reaction was quenched with sat. aq. NH₄Cl solution (10 mL) and extracted with Et₂O (3 × 30 mL). The organic layers were dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give a colourless as a 2 : 3 : 5 mixture of alcohols (*E*-1-¹³C)-**241** : (*Z*-1-¹³C)-**241** : (1-¹³C)-**242** (666 mg, 86% purity, 1.72 mmol, 94%) which could be used directly in the subsequent dehydrohalogenation. Column chromatography of a small quantity of the mixture (petroleum ether : EtOAc 10 : 1) separated iodide (*Z*-1-¹³C)-**241** from a mixture of iodide (*E*-1-¹³C)-**241** and diiodide (1-¹³C)-**242** to give each as colourless oils with 99% 1-¹³C atom [the ¹³C content at the 1-position was deduced by inspection of their ¹H NMR and ¹³C NMR

spectra]. (*E*-1-¹³C)-**241**: (99% 1-¹³C atom); *R*_f 0.36 (petroleum ether : EtOAc 5 : 1); IR (neat) 3600-3100, 1587 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 6.56 (dd, *J* = 14.6, 6.5 Hz, 1H, CH=¹³CHI), 6.33 (ddd, ¹*J*_{CH} = 194.7, *J* = 14.6, 1.2 Hz, 1H, CH=¹³CHI), 4.07 (app. qu., *J* = 6.5 Hz, 1H, CHOH), 1.80 – 1.60 (br. s, 1H, OH), 1.61 – 1.48 (m, 2H, CH₂), 1.40 – 1.20 (m, 8H, 4 × CH₂), 0.86 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 148.7 (d, ¹*J*_{CC} = 75.4 Hz, CH=¹³CHI), 77.1 (¹³CHI), 74.7 (CHOH), 36.6 (CH₂), 31.7 (CH₂), 29.1 (CH₂), 25.1 (CH₂), 22.6 (CH₂), 14.1 (CH₃); (1-¹³C)-**242**: (99% 1-¹³C atom); *R*_f 0.36 (petroleum ether : EtOAc 5 : 1); IR (neat) 3600-3100, 1566, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.01 (d, *J* = 7.8 Hz, 1H, CH=¹³Cl₂), 4.01 (app. qu., *J* = 7.4 Hz, 1H, CHOH), 1.80 – 1.60 (br. s, 1H, OH), 1.61 – 1.48 (m, 2H, CH₂), 1.40 – 1.20 (m, 8H, 4 × CH₂), 0.87 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 154.7 (d, ¹*J*_{CC} = 75.0 Hz, CH=¹³CHI), 78.0 (CHOH), 35.4 (CH₂), 31.7 (CH₂), 29.2 (CH₂), 24.9 (CH₂), 22.6 (CH₂), 14.1 (CH₃), 12.3 (¹³CHI); (*Z*-1-¹³C)-**241**: (99% 1-¹³C atom); *R*_f 0.30 (petroleum ether : EtOAc 5 : 1); IR (neat) 3600-3100, 1592 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 6.30 (ddd, ¹*J*_{CH} = 193.8, *J* = 7.6, 0.9 Hz, 1H, CH=¹³CHI), 6.22 (app. q., *J* = 7.8 Hz, 1H, CH=¹³CHI), 4.38 (app. qu., *J* = 6.7 Hz, 1H, CHOH), 1.75 – 1.65 (br. s, 1H, OH), 1.64 – 1.51 (m, 2H, CH₂), 1.40 – 1.20 (m, 8H, 4 × CH₂), 0.87 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 143.4 (d, ¹*J*_{CC} = 74.7 Hz, CH=¹³CHI), 82.3 (¹³CHI), 74.4 (CHOH), 35.9 (CH₂), 31.8 (CH₂), 29.2 (CH₂), 24.9 (CH₂), 22.6 (CH₂), 14.1 (CH₃).

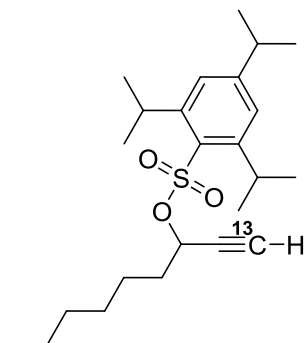
(1-¹³C)-Non-1-yn-3-ol [(1-¹³C)-195]



To a mixture of 2 : 3 : 5 mixture of alcohols (*E*-1-¹³C)-**241** : (*Z*-1-¹³C)-**241** : (1-¹³C)-**242** (533 mg, 1.60 mmol) in THF (8 mL) at -78 °C was added a solution of LDA in THF (8.7 mL, 0.63 M,

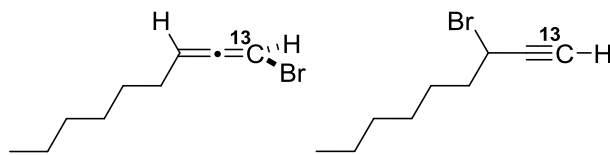
5.48 mmol) and the colourless solution was stirred for 2 h. A further quantity of LDA in THF (0.64 mL, 0.63 M, 0.403 mmol) was added and stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL), dried over Na_2SO_4 , filtered and the solvent removed *in vacuo* to give a yellow oil (506 mg). A smaller scale reaction using 0.23 mmol of the 2 : 3 : 5 mixture of alcohols was also conducted under the same conditions and combined with the previous. Column chromatography of the combined crude reaction mixtures (petroleum ether : EtOAc 7 : 1) gave the title compound (1- ^{13}C)-**195** (207 mg, 1.47 mmol, 80%, 96% 1- ^{13}C , 4% 2- ^{13}C atom) as a colourless oil [the ^{13}C content at the 1- and 2-positions was deduced by inspection of their ^1H NMR and ^{13}C NMR spectra]: R_f 0.30 (petroleum ether : EtOAc 5 : 1); IR (neat) 3600-3100, 3294, 1036 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 4.38 – 4.31 (m, 1H, CHOH), 2.43 (dt, $^1J_{\text{CH}} = 249.9$ Hz, $J = 1.6$ Hz, 1H, $\text{C}\equiv^{13}\text{CH}$), 1.93 – 1.81 (br. s, 1H, OH), 1.75 – 1.65 (m, 2H, CH_2), 1.48 – 1.39 (m, 2H, CH_2), 1.34 – 1.23 (m, 6H, 3 x CH_2), 0.86 (t, $J = 6.7$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz; CDCl_3) δ 85.1 (d, $^1J_{\text{CC}} = 169$ Hz, $\text{C}\equiv^{13}\text{CH}$), 72.8 ($\text{C}\equiv^{13}\text{CH}$), 62.3 (d, $^2J_{\text{CC}} = 11.4$ Hz, COH), 37.7 (CH_2), 31.7 (CH_2), 28.9 (CH_2), 25.0, 22.6 (CH_2), 14.1 (CH_3).

(1- ^{13}C)-Non-1-yn-3-yl 2,4,6-tris(propan-2-yl)benzene-1-sulphonate [(1- ^{13}C)-196]



According to the method of Kim,^{53a} to a solution of alcohol (1-¹³C)-**195** (207 mg, 1.47 mmol, 96% 1-¹³C, 4% 2-¹³C atom) in CH₂Cl₂ (4.0 mL) at 0 °C was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (444 mg, 1.47 mmol) and DMAP (179 mg, 1.47 mmol) in CH₂Cl₂ (7.0 mL). The colourless solution was warmed to room temperature and stirred for 24 h until TLC (petroleum ether : EtOAc 6 : 1) showed completion. The solution was passed through a silica plug with Et₂O and the solvent was removed *in vacuo* to give a light yellow oil (553 mg). Column chromatography (petroleum ether : EtOAc 1 : 0 to 50 : 1) gave title compound **195** (501 mg, 1.23 mmol, 84%, 96% 1-¹³C, 4% 2-¹³C atom) [the ¹³C content at the 1- and 2-positions was deduced by inspection of their ¹H NMR and ¹³C NMR spectra]: R_f 0.56 (petroleum ether : EtOAc 6 : 1); IR (neat) 3298, 1600, 1463, 1350, 1177, 937 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 7.14 (s, 2H, 2 × Ar-H), 5.17 – 5.11 (m, 1H, CHOTris), 4.13 (sept., *J* = 6.8 Hz, 2H, 2 × *ortho*-CH(CH₃)₂), 2.88 (sept., *J* = 6.8 Hz, 1H, *para*-CH(CH₃)₂), 2.26 (dd, ¹*J*_{CH} = 252.7, *J* = 2.0 Hz, 1H, C≡¹³CH), 1.86 – 1.78 (m, 2H, CH₂), 1.48 – 1.39 (m, 2H, CH₂), 1.31 – 1.23 (m, 6H, 3 × CH₂), 1.25 (d, *J* = 7.0 Hz, 6H, *ortho*-CH(CH₃)₂), 1.24 (d, *J* = 7.0 Hz, 6H, *ortho*-CH(CH₃)₂), 1.23 (d, *J* = 7.0 Hz, 6H, *para*-CH(CH₃)₂), 0.85 (t, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz; CDCl₃) δ 153.6 (*para*-C), 150.6 (2 × *ortho*-C), 130.9 (*ipso*-C), 123.6 (2 × *meta*-C), 79.4 (d, ¹*J*_{CC} = 176.1 Hz, C≡¹³CH), 75.9 (C≡¹³CH), 70.2 (d, ²*J*_{CC} = 12.5 Hz, COTris), 35.7 (CH₂), 34.3 (*para*-CH(CH₃)₂), 31.6 (CH₂), 29.6 (2 × *ortho*-CH(CH₃)₂), 28.6 (CH₂), 24.7 (2 × *ortho*-CH(CH₃)₂), 24.7 (2 × *ortho*-CH(CH₃)₂), 24.6 (CH₂), 23.6 (2 × *para*-CH(CH₃)₂), 22.5 (CH₂), 14.0 (CH₃); MS (ESI) *m/z* 430 (M + Na)⁺; HRMS (ESI) *m/z* calcd for C₂₃(¹³C)H₃₈O₃NaS (M + Na)⁺ 430.2467, found 430.2468.

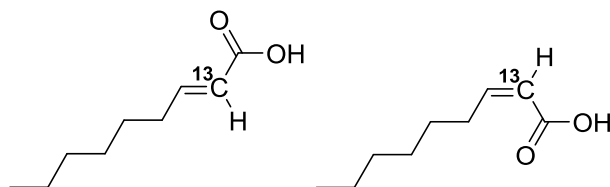
(1-¹³C)-1-Bromonona-1,2-diene [(1-¹³C)-1] and (1-¹³C)-3-bromonon-1-yne [(1-¹³C)-200]



According to the method of Kim,^{53a} LiBr (319 mg, 3.68 mmol) and CuBr (528 mg, 3.68 mmol) dissolved in THF (14.7 mL) and stirred at room temperature for 30 min. The green solution was transferred to a solution of propargylic trisylate (1-¹³C)-**196** (500 mg, 1.23 mmol) in THF (62 mL) and stirred at reflux for 30 min. The solvent was removed *in vacuo* and the brown residue was passed through a short silica plug with petroleum ether. The solvent was removed *in vacuo* once more to give a colourless oil (190 mg). Column chromatography (petroleum ether) gave title compound (1-¹³C)-**1** (145 mg, 0.710 mmol, 58%, 96% 1-¹³C, 4% 2-¹³C atom) as a colourless oil; *R*_f 0.65 (petroleum ether : EtOAc 50 : 1); IR (neat) 1945, 1189, 635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.90 (ddt, ¹*J*_{CH} = 211.9, *J* = 5.6, 2.3 Hz, 1H, HC=C=¹³CHBr), 5.38 (ddt, *J* = 8.8, 6.8, 5.8 Hz, 1H, HC=C=¹³CHBr), 2.13 (dq, *J* = 7.0, 2.4 Hz, 2H, CH₂CH=¹³C), 1.47 – 1.39 (m, 2H, CH₂), 1.35 – 1.22 (m, 6H, 3 × CH₂), 0.87 (t, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 202.1 (d, ¹*J*_{CC} = 115.7 Hz, HC=C=¹³CHBr), 101.1 (d, ²*J*_{CC} = 8.9 Hz, HC=C=¹³CHBr), 72.1 (HC=C=¹³CHBr), 31.6 (CH₂), 28.7 (CH₂), 28.3 (CH₂), 28.3 (CH₂), 22.6 (CH₂), 14.1 (CH₃); and propargylic bromide (1-¹³C)-**200** (14 mg, 0.069 mmol, 6%, 96% 1-¹³C, 4% 2-¹³C atom); *R*_f 0.76 (petroleum ether : EtOAc 50 : 1); IR (neat) 3289, 1466, 635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.45 (ddt, *J* = 6.8, 4.3, 2.5 Hz, 1H, ¹³CHBr), 2.62 (dd, *J* = 253, 2.4 Hz, 1H, C≡¹³CH), 2.02 – 1.96 (m, 2H, CH₂CHBr), 1.55 – 1.46 (m, 2H, CH₂), 1.34 – 1.23 (m, 6H, 3 × CH₂), 0.87 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 82.7 (6, *J* = 178 Hz, C≡¹³CH), 74.8 (C≡¹³CH), 39.5 (CHBr), 36.0, 31.6, 28.4, 27.2 & 22.5 (5 × CH₂), 14.0 (CH₃). The molecular ions for these compounds could not be observed by electron, chemical or electrospray

ionisation methods; [the ^{13}C content at the 1- and 2-positions was deduced by inspection of their ^1H NMR and ^{13}C NMR spectra].

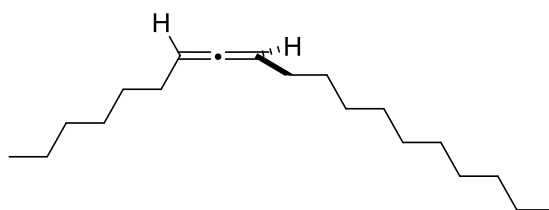
(*E*-2- ^{13}C)-Non-2-enoic acid [(*E*-2- ^{13}C)-2] & (*Z*-2- ^{13}C)-non-2-enoic acid [(*Z*-2- ^{13}C)-2]



To a stirred solution of bromoallene (1- ^{13}C)-1 (92 mg, 0.451 mmol) in acetone (2 mL) at $-40\text{ }^{\circ}\text{C}$ was added a 0.10 M solution of DMDO in acetone (3.00 mL, 0.300 mmol, 0.66 eq.). The colourless solution was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue extracted with Et₂O (3 $\times$ 2 mL) and petroleum ether (3 $\times$ 2 mL). The solvent was removed *in vacuo* once more to give a colourless oil (98 mg). Column chromatography (petroleum ether : EtOAc 4 : 1 to 1 : 2) gave (*E*-2- ^{13}C)-2 (10 mg, 0.064 mmol, 14 %, 96% 1- ^{13}C , 4% 2- ^{13}C atom) as a colourless oil: R_f 0.14 (petroleum ether : EtOAc 6 : 1); IR (neat) 3300-2800, 1692, 1627 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.06 (ddt, J = 15.6, 7.0, 1.8 Hz, 1H, β -H), 5.78 (ddt, $^1J_{\text{CH}}$ = 163, J = 15.6, 1.5 Hz, 1H, α -H), 2.21 (ddq, J = 6.8, 6.0, 1.5 Hz, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 1.48 – 1.40 (m, 2H, CH_2), 1.32 – 1.22 (m, 6H, 3 $\times$ CH_2), 0.87 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 170.8 (d, J = 74.2 Hz, CO_2H), 152.4 (d, $^1J_{\text{CC}}$ = 69.7 Hz, β -C), 120.3 (α - ^{13}C), 32.3 (CH_2), 31.6 (CH_2), 28.8 (CH_2), 27.8 (CH_2), 22.5 (CH_2), 14.1 (CH_3); MS (CI^+ , NH_3) m/z 175 ($\text{M} + \text{NH}_4$) $^+$; HRMS (CI^+ , NH_3) m/z calcd for $\text{C}_8(^{13}\text{C})\text{H}_{22}\text{NO}_2$ ($\text{M} + \text{NH}_4$) $^+$ 175.1527, found 175.1527; and (*Z*-2- ^{13}C)-2 (10 mg, 0.064 mmol, 14 %, 96% 1- ^{13}C , 4% 2- ^{13}C atom): R_f 0.20 (petroleum ether : EtOAc 6 : 1); IR (neat) 3300-2800, 1694, 1615 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.33 (dt, J = 11.4, 7.5 Hz, 1H, β -H), 5.75 (ddt, $^1J_{\text{CH}}$ = 163.2, J = 11.5, 1.7 Hz, 1H, α -H), 2.64 (ddq, J = 7.1, 5.6, 1.7 Hz, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 1.47 – 1.37 (m, 2H, CH_2),

1.34 – 1.23 (m, 6H, 3 × CH₂), 0.86 (t, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.3 (d, *J* = 70.8 Hz, CO₂H), 153.5 (d, *J* = 69.3 Hz, β-C), 118.6 (α-C), 31.6 (CH₂), 29.7 (CH₂), 29.2 (CH₂), 28.9 (CH₂), 22.6 (CH₂), 14.1 (CH₃); MS (CI⁺, NH₃) *m/z* 175 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₈(¹³C)H₂₂NO₂ (M + NH₄)⁺ 175.1527, found 175.1526. [The ¹³C content at the 1- and 2-positions was deduced by inspection of their ¹H NMR and ¹³C NMR spectra].

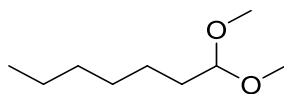
Nonadeca-7,8-diene (249)



According to the method of Moreau,⁸⁰ a solution of trisylate **196** (203 mg, 0.500 mmol) and CuBr (7.2 mg, 0.050 mmol) dissolved in THF (0.5 mL) was added dropwise to a 1.0 M solution of decylmagnesium bromide (0.62 mL, 0.62 mmol) at room temperature. The yellow solution was stirred for 90 min until TLC (hexane : EtOAc 50 : 1) shows completion of the reaction. The reaction was passed through a short silica plug, eluting with hexane. The solvent was removed *in vacuo* to give a yellow oil (190 mg). Column chromatography (hexane) gave title compound **249** (100 mg, 0.378 mmol, 76%) as a colourless oil: *R_f* 0.64 (hexane : EtOAc 50 : 1); ¹H NMR (400 MHz, CDCl₃) δ 5.04 (p, *J* = 4.8 Hz, 2H, HC=C=CH), 1.95 (dt, *J* = 12.3, 6.0 Hz, 4H, 2 × CH₂), 1.42 – 1.32 (m, 4H, 2 × CH₂), 1.32 – 1.21 (m, 20H, 10 × CH₂), 0.89 – 0.83 (m, 6H, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 203.8 (HC=C=CH), 90.9 (HC=C=CH), 31.9, 31.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.2, 29.1, 29.0, 28.8, 22.7 & 22.7 (14 × CH₂), 14.1 (2 × CH₃); HRMS (EI⁺, TOF) *m/z* calcd for C₁₉H₃₆ (M)⁺ 264.2817, found 264.2809.

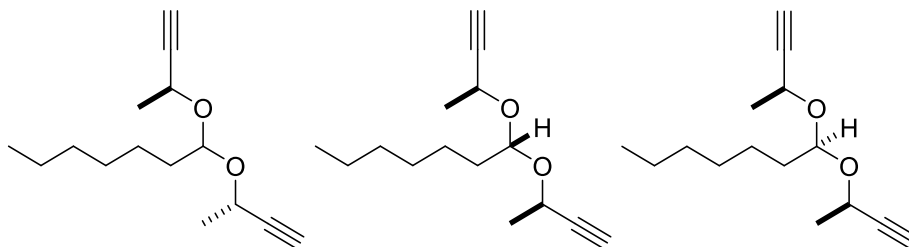
5.3 Procedures and Characterising Data Part II

1,1-Dimethoxyheptane (274)



According to the procedure of Frisch,⁸⁵ to a solution of heptaldehyde (**194**) (1.00 mL, 7.15 mmol) in methanol (10.0 mL) at 0°C, was added CH(OMe)₃ (1.57 mL, 14.4 mmol), followed by *p*-toluenesulfonic acid monohydrate (111 mg, 0.478 mmol). The colourless solution was stirred for a 5 h until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NaHCO₃ (10 mL), extracted with CH₂Cl₂ (3 × 30 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give an yellow oil (950 mg). Column chromatography (hexane : EtOAc 19 : 1) gave a acetal **274** (907 mg, 5.66 mmol, 79%) as a colourless oil: R_f 0.75 (hexane : EtOAc 19 : 1); IR (neat) 2926, 1462, 1124, 1056 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.35 (t, *J* = 5.8 Hz, 1H, CH(OCH₃)₂), 3.30 (s, 6H, 2 × OCH₃), 1.63 – 1.53 (m, 2H, CH₂), 1.37 – 1.22 (m, 8H, 4 × CH₂), 0.87 (t, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 104.6 (CH(OCH₃)₂), 52.6 (2 × OCH₃), 32.5 (CH₂), 31.8 (CH₂), 29.2 (CH₂), 24.6 (CH₂), 22.6 (CH₂), 14.1 (CH₃); MS (CI⁺, NH₃) *m/z* 159 (M - H)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₉H₁₉O₂ (M - H)⁺ 159.1385, found 159.1381.

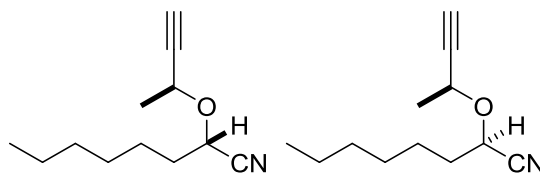
1,1-Bis[(2S*)-but-3-yn-2-yloxy]heptane (**267A**), (1r*)-1-[(2R*)-but-yn-2-yloxy]-1-[(2S*)-but-yn-2-yloxy]heptane (**267B**) & (1s*)-1-[(2R*)-but-yn-2-yloxy]-1-[(2S*)-but-yn-2-yloxy]heptane (**267C**)



To a solution of heptaldehyde (**194**) (2.10 mL, 15.0 mmol) in (±)-3-butyn-2-ol (15.1 mL, 192 mmol) was added CSA (111 mg, 0.478 mmol). The yellow solution was heated to 40 °C and stirred for 1 h. The reaction was diluted with THF (60 mL), quenched with NaBH₄ (3.55 g, 15.0 mmol) and stirred for a further 30 mins. Water (40 mL) was added to the cloudy mixture and stirred for 30 mins, before the mixture was extracted with CH₂Cl₂ (3 × 30 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give an yellow oil (3.83 g). Column chromatography (hexane : EtOAc 9 : 1) gave a 52 : 35 : 13 mixture of acetals **267A**, **267B** & **267C** (2.39 g, 10.1 mmol, 67%) as a colourless oil: R_f 0.51 (hexane : EtOAc 9 : 1); IR (neat) 3311, 2926, 1737, 1372, 1089 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.97 (t, *J* = 5.5 Hz, 0.35H, **267B**-CHO₂), 4.92 (dd, *J* = 6.3, 4.8 Hz, 0.52H, **267A**-CHO₂), 4.71 (t, *J* = 5.7 Hz, 0.13H, **267C**-CHO₂), 4.58 (qd, *J* = 6.7, 2.0 Hz, 0.52H, **267A**-CHCH₃), 4.51 (td, *J* = 6.7, 2.1 Hz, 0.70H, 2 × **267B**-CHCH₃), 4.47 (qd, *J* = 6.6, 2.0 Hz, 0.26H, 2 × **267C**-CHCH₃), 4.34 (qd, *J* = 6.6, 2.1 Hz, 0.52H, **267A**-CHCH₃), 2.43 (d, *J* = 2.0 Hz, 0.47H, **267A**-C≡CH), 2.41 (d, *J* = 2.1 Hz, 0.24H, 2 × **267C**-C≡CH), 2.40 (d, *J* = 2.0 Hz, 0.63H, 2 × **267B**-C≡CH), 2.37 (d, *J* = 2.0 Hz, 0.47H, **267A**-C≡CH), 1.74 – 1.61 (m, 2H, CH₂), 1.47 – 1.43 (m, 6H, CHCH₃), 1.44 – 1.33 (m, 2H, CH₂), 1.34 – 1.23 (m, 6H, CH₂), 0.88 (t, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 101.1, 100.7 & 100.7 (CHO₂), 84.7, 84.5, 84.1 & 84.1 (C≡CH), 72.6, 72.5, 72.5 & 72.2 (C≡CH), 61.5, 61.3, 60.8 &

60.5 (CHCH₃), 34.5, 34.2, 31.7, 31.6, 29.1, 29.0, 24.7, 24.3, 22.8, 22.6 & 22.6 (CH₂), 22.3 22.1 & 22.0 (CHCH₃), 14.1 & 14.0 (CH₃); MS (CI⁺, NH₃) *m/z* 254 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₁₂H₂₃N₂O (M + NH₄)⁺ 254.2120, found 254.2110; and heptanol (**284**) (528 mg, 4.54 mmol, 30%) as a colourless oil.

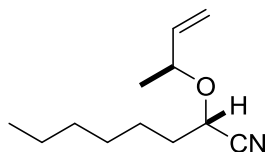
2-(But-3-yn-2-yloxy)octanenitrile (**268a/b**)



According to a modified procedure,⁸⁸ to a solution of acetals **267A-C** (500 mg, 2.12 mmol) in CH₂Cl₂ (3.0 mL) was added TMS-CN (1.33 mL, 10.6 mmol) and BF₃.OEt₂ (18.5 μL, 0.150 mmol) and the yellow solution stirred for 2 h. A further quantity of TMS-CN (1.33 mL, 10.6 mmol) and BF₃.OEt₂ (18.5 μL, 0.150 mmol) was added and stirred for a further 1 h until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NH₄Cl (5 mL) and stirred for an additional 10 min. The mixture was extracted with CH₂Cl₂ (3 × 10 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give an orange oil (536 mg). Column chromatography (hexane : EtOAc 25 : 1) gave the title compound **268a** (196 mg, 1.01 mmol, 48%) as a colourless oil: R_f 0.37 (hexane : EtOAc 4 : 1); IR (neat) 3298, 2929, 1459, 1097 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.52 (t, *J* = 6.6 Hz, 1H, CHCN), 4.45 (qd, *J* = 6.6, 2.0 Hz, 1H, CHCH₃), 2.49 (d, *J* = 2.0 Hz, 1H, C≡CH), 1.90 – 1.79 (m, 2H, CH₂), 1.49 (d, *J* = 6.6 Hz, 4H, CHCH₃), 1.54 – 1.45 (m, 2H, CH₂), 1.38 – 1.25 (m, 6H, 3 × CH₂) 0.89 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 118.3 (CN), 81.7 (C≡CH), 74.7 (C≡CH), 66.3 (CHCH₃), 64.8 (CHCN), 33.4 (CH₂), 31.5 (CH₂), 28.6 (CH₂), 24.6 (CH₂), 22.5 (CH₂), 21.7 (CH₃), 14.0 (CH₃) MS (CI⁺, NH₃) *m/z* 211 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd

for $C_{12}H_{23}N_2O$ ($M + NH_4$)⁺ 211.1810, found 211.1804; and **268b** (186 mg, 0.963 mmol, 46%) as a colourless oil: R_f 0.27 (hexane : EtOAc 4 : 1); IR (neat) 3293, 2930, 1458, 1096 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (qd, J = 6.6, 2.1 Hz, 1H, $CHCH_3$), 4.30 (t, J = 6.6 Hz, 1H, $CHCN$), 2.56 (d, J = 2.1 Hz, 1H, $C\equiv CH$), 1.86 – 1.79 (m, 2H, CH_2), 1.49 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.54 – 1.41 (m, 2H, CH_2), 1.39 – 1.23 (m, 6H, $3 \times CH_2$), 0.88 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 118.9 (CN), 81.7 ($C\equiv CH$), 75.1 ($C\equiv CH$), 66.4 ($CHCH_3$), 66.1 ($CHCN$), 33.7 (CH_2), 31.5 (CH_2), 28.6 (CH_2), 24.6 (CH_2), 22.5 (CH_2), 21.7 (CH_3), 14.0 (CH_3); MS (CI^+ , NH_3) m/z 211 ($M + NH_4$)⁺; HRMS (CI^+ , NH_3) m/z calcd for $C_{12}H_{23}N_2O$ ($M + NH_4$)⁺ 211.1810, found 211.1804.

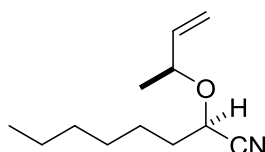
2-(But-3-en-2-yloxy)octanenitrile (286a)



According to the procedure of Bonney,⁴⁸ to a solution of alkyne **268a** (32 mg, 0.17 mmol) and quinoline (33 μ L, 0.279 mmol) in benzene (4.0 mL) was added 5% Pd.BaSO₄ (17.0 mg, 0.0080 mmol) and the flask flushed with hydrogen. A positive pressure of hydrogen was maintained with rapid stirring for 1 h until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The mixture was passed through a silica plug, eluting with EtOAc. The solvent was removed and the yellow oil redissolved in Et₂O (5 mL) and washed successively with 2M HCl (3×3 mL) and brine (3 mL). The solvent was removed *in vacuo* to give olefin **286a** (33.0 mg, 0.17 mmol, quant.) as a colourless oil: R_f 0.42 (hexane : EtOAc 9 : 1); IR (neat) 2929, 1461, 1376, 1085 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (ddd, J = 17.4, 10.1, 8.2 Hz, 1H, $CH=CH_2$), 5.30 (d, J = 16.0 Hz, 1H, $CH=CH_2$), 5.26 (dd, J = 10.4, 1.0 Hz, 1H, $CH=CH_2$), 4.16 (t, J = 6.7 Hz, 1H, $CHCN$), 4.11 (q, J = 6.7 Hz, 1H, $CHCH_3$), 1.84 – 1.76 (m, 2H, CH_2), 1.50 – 1.42 (m,

2H, CH₂), 1.36 – 1.23 (m, 6H, 3 × CH₂), 1.29 (d, *J* = 6.4 Hz, 3H, CHCH₃), 0.88 (t, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 138.0 (C=CH₂), 118.9 (C=CH₂), 118.8 (CN), 76.9 (CHCH₃), 65.6 (CHCN), 33.6 (CH₂), 31.5 (CH₂), 28.7 (CH₂), 24.8 (CH₂), 22.5 (CH₂), 21.4 (CHCH₃), 14.0 (CH₃).

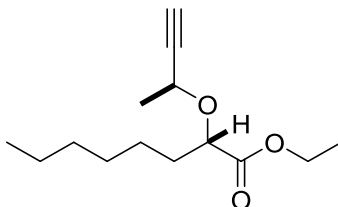
2-(But-3-en-2-yloxy)octanenitrile (286b)



According to the procedure of Bonney,⁴⁸ to a solution of alkyne **268b** (109 mg, 0.564 mmol) and quinoline (116 μL, 0.980 mmol) in benzene (14 mL) was added 5% Pd.BaSO₄ (59.6 mg, 0.0282) and the flask flushed with hydrogen. A positive pressure of hydrogen was maintained with rapid stirring for 1 h until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The mixture was passed through a silica plug, eluting with EtOAc. The solvent was removed and the yellow oil redissolved in Et₂O (10 mL) and washed successively with 2M HCl (3 × 10 mL) and brine (10 mL). The solvent was removed *in vacuo* to give olefin **286b** (110 mg, 0.16 mmol, quant.) as a colourless oil: *R*_f 0.34 (hexane : EtOAc 9 : 1); IR (neat) 2929, 1461, 1376, 1085 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.87 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1H, CH=CH₂), 5.28 (dt, *J* = 17.2, 1.2 Hz, 1H, CH=CH₂), 5.21 (dt, *J* = 10.4, 1.2 Hz, 1H, CH=CH₂), 4.12 (t, *J* = 6.6 Hz, 1H, CHCN), 4.06 (qt, *J* = 6.6, 0.9 Hz, 1H, CHCH₃), 1.86 – 1.77 (m, 2H, CH₂), 1.52 – 1.43 (m, 2H, CH₂), 1.37 – 1.24 (m, 6H, 3 × CH₂), 1.27 (d, *J* = 6.3 Hz, 3H, CHCH₃), 0.89 (t, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 138.8 (C=CH₂), 119.3 (CN), 117.0 (C=CH₂), 78.0 (CHCH₃), 66.5 (CHCN), 34.0 (CH₂), 31.5 (CH₂), 28.7 (CH₂), 24.7 (CH₂), 22.5 (CH₂), 20.2

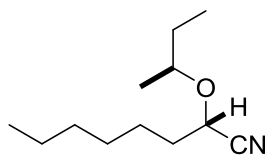
(CHCH₃), 14.0 (CH₃); MS (CI⁺, NH₃) *m/z* 213 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₁₂H₂₅N₂O (M + NH₄)⁺ 213.1967, found 213.1965.

Ethyl 2-(but-3-yn-2-yloxy)octanoate (313a)



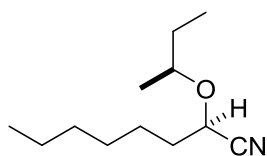
To a solution of alkyne **268a** (26.5 mg, 0.137 mmol) in ethanol (400 μ L) was added conc. HCl (600 mg) and the flask heated to reflux for 1 h until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was neutralised with 2M NaOH (5 mL) and extracted with CH₂Cl₂ (3 $\times$ 3 mL). The solvent was removed *in vacuo* to give a yellow oil. Column chromatography (hexane : EtOAc 9 : 1) gave the title compound **313a** (23.1 mg, 0.0961 mmol, 70%) as a colourless oil: R_f 0.36 (hexane : EtOAc 9 : 1); ¹H NMR (400 MHz, CDCl₃) δ 4.28 (qd, *J* = 6.6, 2.1 Hz, 1H, CHCH₃), 4.20 (q, *J* = 7.1 Hz, 1H, OCH₂), 3.99 (t, *J* = 6.4 Hz, 1H, CHCO₂), 2.40 (d, *J* = 2.1 Hz, 1H, C $\equiv$ CH), 1.74 – 1.67 (m, 2H, CH₂), 1.46 (d, *J* = 6.6 Hz, 3H, CHCH₃), 1.32 – 1.21 (m, 11H, 4 $\times$ CH₂ & OCH₂CH₃), 0.86 (t, *J* = 6.7 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 173.0 (CO₂Et), 83.4 (C $\equiv$ CH), 76.1 (C $\equiv$ CH), 73.2 (OCH₂CH₃), 64.4 (CHCO₂), 60.7 (CHCH₃), 33.0 (CH₂), 31.6 (CH₂), 28.9 (CH₂), 25.2 (CH₂), 22.6 (CH₂), 22.1 (CH₂), 14.3 (CH₂CH₃), 14.1 (CH₃).

2-(Butan-2-yloxy)octanenitrile (317a)



According to a modified procedure,¹³⁶ to a solution of alkyne **268a** (50 mg, 0.26 mmol) in benzene (6.5 mL) was added 10% Pd/C (27.5 mg, 0.0259) and the flask flushed with hydrogen. A positive pressure of hydrogen was maintained with rapid stirring for 1 h until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The mixture was passed through a silica plug, eluting with EtOAc. The solvent was removed *in vacuo* to give title compound **317a** (41.7 mg, 0.211 mmol, 81%) as a colourless oil: R_f 0.51 (hexane : EtOAc 9 : 1); ^1H NMR (400 MHz, CDCl_3) δ 4.12 (t, J = 6.6 Hz, 1H, CHCN), 3.61 (h, J = 6.1 Hz, 1H, CHCH_3), 1.84 – 1.76 (m, 2H, CH_2), 1.64 – 1.48 (m, 2H, CH_2), 1.52 – 1.39 (m, 2H, CH_2), 1.38 – 1.24 (m, 6H, $3 \times \text{CH}_2$), 1.24 (d, J = 6.3 Hz, 3H, CHCH_3), 0.88 (t, J = 7.4 Hz, 3H, CH_3), 0.88 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 119.6 (CN), 77.9 (CHCH_3), 67.0 (CHCN), 34.1 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 24.8 (CH_2), 22.5 (CH_2), 19.6 (CHCH_3), 14.0 (CH_3), 9.2 (CH_3).

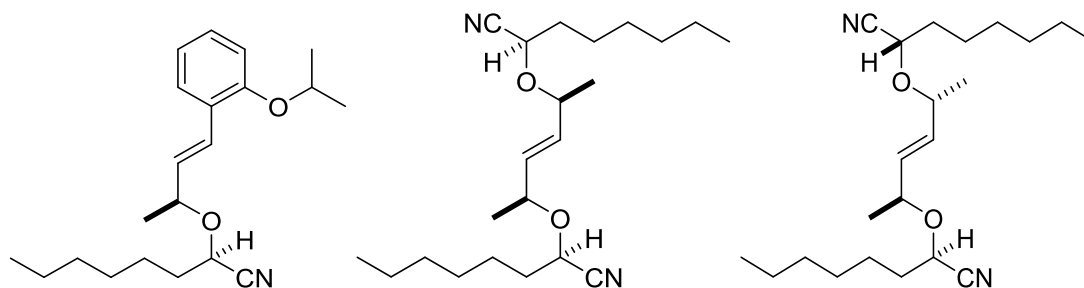
2-(Butan-2-yloxy)octanenitrile (317b)



According to a modified procedure,¹³⁶ to a solution of alkyne **268b** (20 mg, 0.10 mmol) in benzene (2.6 mL) was added 10% Pd/C (11 mg, 0.010) and the flask flushed with hydrogen. A positive pressure of hydrogen was maintained with rapid stirring for 30 min until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The mixture was passed through a silica plug, eluting with EtOAc. The solvent was removed *in vacuo* to give title compound

317b (16.0 mg, 0.0811 mmol, 81%) as a colourless oil: R_f 0.49 (hexane : EtOAc 9 : 1); IR (neat) 2929, 1461, 1379, 1090 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.18 (t, J = 6.5 Hz, 1H, CHCN), 3.61 (h, J = 6.0 Hz, 1H, CHCH_3), 1.84 – 1.78 (m, 2H, CH_2), 1.62 – 1.51 (m, 2H, CH_2), 1.51 – 1.43 (m, 2H, CH_2), 1.37 – 1.25 (m, 6H, $3 \times \text{CH}_2$), 1.13 (d, J = 6.1 Hz, 3H, CHCH_3), 0.95 (t, J = 7.4 Hz, 3H, CH_3), 0.89 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 119.2 (CN), 76.9 (CHCH_3), 66.4 (CHCN), 34.0 (CH_2), 31.6 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 24.8 (CH_2), 22.5 (CH_2), 18.3 (CHCH_3), 14.0 (CH_3), 9.8 (CH_3); MS (CI^+ , NH_3) m/z 215 ($\text{M} + \text{NH}_4^+$); HRMS (CI^+ , NH_3) m/z calcd for $\text{C}_{12}\text{H}_{27}\text{N}_2\text{O}$ ($\text{M} + \text{NH}_4^+$) 215.2123, found 215.2121.

2-[[*(3E)*-4-[2-(Propan-2-yloxy)phenyl]but-3-en-2-yl]oxy]octanenitrile (**323b**), (*2R*)-2-[[*(2S^*,3E,5S^*)*-5-[[*(1R^*)*-1-cyanoheptyl]oxy]hex-3-en-2-yl]oxy]octanenitrile (**319b**) & (*2S^**)-2-[[*(2R^*,3E,5S^*)*-5-[[*(1R^*)*-1-cyanoheptyl]oxy]hex-3-en-2-yl]oxy]octanenitrile (**319b'**)

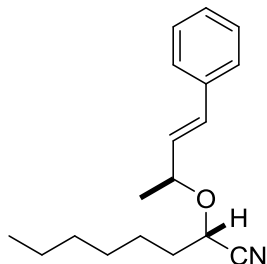


According to the procedure of Somfai,¹⁰⁰ to a solution of olefin **286b** (20 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added Stewart-Grubbs catalyst (5.8 mg, 0.010 mmol) and the green solution stirred at room temperature for 1 h. The reaction was then heated to 40°C and stirred for 30 h. The solvent was removed *in vacuo* to give a green tar (71 mg). Column chromatography (hexane : toluene 1 : 2) gave title compound **323b** (3.1 mg, 0.0094 mmol, 9%) as a colourless oil: R_f 0.46 (hexane : toluene 1 : 1); IR (neat) 2925, 1671, 1454, 1241 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, J = 7.7, 1.7 Hz, 1H, *meta*-Ar), 7.20 (ddd, J = 8.2, 7.3, 1.7 Hz,

^1H , *ortho*-Ar), 6.97 – 6.86 (m, 3H, *meta*-Ar, *para*-Ar & CH=CHAr), 6.19 (dd, J = 16.1, 7.8 Hz, 1H, CH=CHAr), 4.54 (hept, J = 6.0 Hz, 1H, CH(CH₃)₂), 4.25 (dq, J = 7.0, 6.3, 0.8 Hz, 1H, CHCH₃), 4.16 (t, J = 6.6 Hz, 1H, CHCN), 1.88 – 1.80 (m, 2H, CH₂), 1.53 – 1.45 (m, 2H, CH₂), 1.39 – 1.35 (m, 9H, 3 × CH₃), 1.37 – 1.21 (m, 6H, 3 × CH₂), 0.89 (t, J = 7.0 Hz, 3H, CH₃); ^{13}C NMR (101 MHz, CDCl₃) δ 132.4 (*ipso*-Ar), 130.1 (CH=CHAr), 128.9 (*ortho*-Ar), 127.6 (*meta*-Ar), 127.2 (*para*-Ar), 123.2 (*ortho*-Ar), 120.8 (*meta*-Ar), 119.6 (CN), 114.2 (CH=CHAr), 78.5 (CHCH₃), 70.9 (CH(CH₃)₂), 66.3 (CHCN), 34.0 (CH₂), 31.6 (CH₂), 28.7 (CH₂), 24.7 (CH₂), 22.5 (CH₂), 22.2 (CH(CH₃)₂), 20.9 (CHCH₃), 14.0 (CH₃); MS (CI⁺, NH₃) m/z 330 (M + H)⁺; HRMS (CI⁺, NH₃) m/z calcd for C₂₁H₃₂NO₂ (M + H)⁺ 330.2433, found 330.2439; dimer **319b** (3.9 mg, 0.011 mmol, 22%) as a white solid: R_f 0.26 (hexane : toluene 1 : 1); IR (neat) 2927, 1678, 1458, 1376, 1089 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 5.81 (dd, J = 4.5, 2.3 Hz, 2H, CH=CH), 4.16 (t, J = 6.7 Hz, 2H, 2 × CHCN), 4.10 (qdd, J = 6.5, 4.5, 2.4 Hz, 2H, 2 × CHCH₃), 1.84 – 1.77 (m, 4H, 4 × CH₂), 1.51 – 1.41 (m, 2H, 2 × CH₂), 1.37 – 1.24 (m, 12H, 6 × CH₂), 1.28 (d, J = 6.4 Hz, 6H, 2 × CH₃), 0.88 (t, J = 6.9 Hz, 6H, 2 × CH₃); ^{13}C NMR (101 MHz, CDCl₃) δ 134.1 (CH=CH), 120.2 (2 × CN), 78.0 (2 × CHCH₃), 67.3 (2 × CHCN), 34.2 (2 × CH₂), 31.5 (2 × CH₂), 28.6 (2 × CH₂), 24.7 (2 × CH₂), 22.5 (2 × CH₂), 20.9 (2 × CHCH₃), 14.0 (2 × CH₃); HRMS (CI⁺, NH₃) m/z calcd for C₂₄H₄₁N₃O₂Na (M + CH₃CN + Na)⁺ 426.3096, found 426.3099; and diastereomeric dimer **319b'** (3.7 mg, 0.010 mmol, 20%) as a colourless oil: R_f 0.18 (hexane : toluene 1 : 1); IR (neat) 2927, 1678, 1459, 1377 1088 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 5.74 (dd, J = 4.4, 2.2 Hz, 2H, CH=CH), 4.13 – 4.04 (m, 4H, 2 × CHCN & 2 × CHCH₃), 1.85 – 1.78 (m, 4H, 2 × CH₂), 1.52 – 1.41 (m, 4H, 2 × CH₂), 1.32 (d, J = 6.3 Hz, 6H, 2 × CH₃), 1.37 – 1.25 (m, 12H, 6 × CH₂), 0.89 (t, J = 7.0 Hz, 6H, 2 × CH₃); ^{13}C NMR (101 MHz, CDCl₃) δ 133.6 (CH=CHAr), 119.5 (2 × CN), 77.7 (2 × CHCH₃), 66.8 (2 × CHCN), 34.1 (2 × CH₂), 31.5 (2 × CH₂), 28.7 (2 × CH₂), 24.7 (2 × CH₂), 22.5 (2

$\times \text{CH}_2$), 20.4 ($2 \times \text{CHCH}_3$), 14.0 ($2 \times \text{CH}_3$); HRMS (CI^+ , NH_3) m/z calcd for $\text{C}_{24}\text{H}_{41}\text{N}_3\text{O}_2\text{Na}$ ($\text{M} + \text{CH}_3\text{CN} + \text{Na}$)⁺ 426.3096, found 426.3101.

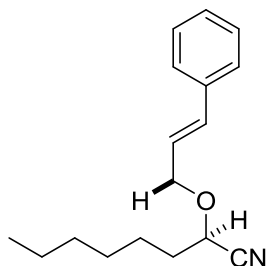
2-[[*(3E)*-4-Phenylbut-3-en-2-yl]oxy]octanenitrile (**322a**)



According to a modified procedure,¹³⁷ to a solution of olefin **286a** (42 mg, 0.22 mmol) and styrene (49 μL , 0.43 mmol) in CH_2Cl_2 (5 mL) was added Grubbs 2nd generation catalyst (18.3 mg, 0.0216 mmol) and the brown solution stirred at 40°C for 3 h. A further quantity of styrene (49 μL , 0.43 mmol) and the reaction stirred for a further 18 h. A final quantity of styrene (49 μL , 0.43 mmol) and the reaction stirred for a further 2 h. A small spatula of silica was added to the reaction, filtered and the solvent removed *in vacuo* to give brown crystals (139 mg). Column chromatography (hexane : EtOAc 20 : 1) gave title compound **322a** (25 mg, 0.090 mmol, 41%) as white crystals: R_f 0.53 (hexane : toluene 1 : 2); IR (neat) 3029, 2927, 1677, 1456, 1086 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.38 (m, 2H, *ortho*-Ar), 7.37 – 7.31 (m, 2H, *meta*-Ar), 7.31 – 7.25 (m, 1H, *para*-Ar), 6.63 (d, J = 15.9 Hz, 1H, $\text{CH}=\text{CHAr}$), 5.96 (dd, J = 15.9, 8.6 Hz, 1H, $\text{CH}=\text{CHAr}$), 4.32 (dq, J = 8.6, 6.3 Hz, 1H, CHCH_3), 4.21 (t, J = 6.6 Hz, 1H, CHCN), 1.85 – 1.78 (m, 2H, CH_2), 1.51 – 1.42 (m, 2H, CH_2), 1.39 (d, J = 6.3 Hz, 3H, CHCH_3), 1.35 – 1.23 (m, 6H, $3 \times \text{CH}_2$), 0.86 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 135.8 (*ipso*-Ar), 134.0 ($\text{CH}=\text{CHAr}$), 128.9 (*para*-Ar), 128.7 ($2 \times$ *meta*-Ar), 128.3 ($\text{CH}=\text{CHAr}$), 126.7 ($2 \times$ *ortho*-Ar), 119.2 (CN), 76.6 (CHCH_3), 65.6 (CHCN), 33.6 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 24.8

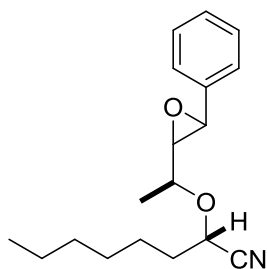
(CH₂), 22.5 (CH₂), 21.7 (CHCH₃), 14.0 (CH₃); MS (CI⁺, NH₃) *m/z* 289 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₁₈H₂₉N₂O (M + NH₄)⁺ 289.2280, found 289.2274.

2-[[*(3E)*-4-Phenylbut-3-en-2-yl]oxy]octanenitrile (**322b**)



According to a modified procedure,¹³⁷ to a solution of olefin **286b** (20 mg, 0.10 mmol) and styrene (49 μ L, 0.43 mmol) in CH₂Cl₂ (2.5 mL) was added Grubbs 2nd generation catalyst (8.7 mg, 0.010 mmol) and the brown solution stirred at 40 °C for 3 h. A further quantity of styrene (49 μ L, 0.43 mmol) and the reaction stirred for a further 18 h. A small spatula of silica was added to the reaction, filtered and the solvent removed *in vacuo* to give a white oily solid (113 mg). Column chromatography (hexane : toluene 1 : 1) gave title compound **322b** (26 mg, 0.096 mmol, 96%) as white crystals: R_f 0.15 (hexane : toluene 1 : 1); IR (neat) 2927, 1731, 1455, 1082 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.40 (m, 2H, *ortho*-Ar), 7.36 – 7.31 (m, 2H, *meta*-Ar), 7.28 - 7.23 (m, 1H, *para*-Ar), 6.60 (d, *J* = 15.9 Hz, 1H, CH=CHAr), 6.21 (dd, *J* = 15.9, 7.5 Hz, 1H, CH=CHAr), 4.25 (dq, *J* = 7.3, 6.2, 1.0 Hz, 1H, CHCH₃), 4.16 (t, *J* = 6.6 Hz, 1H, CHCN), 1.89 – 1.81 (m, 2H, CH₂), 1.54 – 1.46 (m, 2H, CH₂), 1.37 (d, *J* = 6.3 Hz, 3H, CHCH₃), 1.35 – 1.24 (m, 6H, 3 $\times$ CH₂), 0.89 (t, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 136.2 (*ipso*-Ar), 132.2 (CH=CHAr), 130.1 (*para*-Ar), 128.6 (2 $\times$ *meta*-Ar), 128.0 (CH=CHAr), 126.7 (2 $\times$ *ortho*-Ar), 119.5 (CN), 77.8 (CHCH₃), 66.5 (CHCN), 34.0 (CH₂), 31.6 (CH₂), 28.7 (CH₂), 24.8 (CH₂), 22.5 (CH₂), 20.7 (CHCH₃), 14.0 (CH₃); MS (CI⁺, NH₃) *m/z* 289 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₁₈H₂₉N₂O (M + NH₄)⁺ 289.2280, found 289.2277.

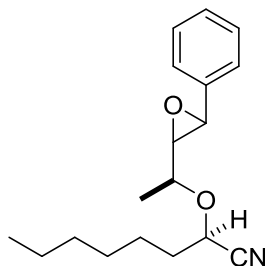
2-[1-(3-Phenyloxiran-2-yl)ethoxy]octanenitrile (**332a**)



To a solution of olefin **322a** (14.5 mg, 0.0534 mmol) in CH₂Cl₂ (200 μ L) was added *m*CPBA (18.4 mg, 75%, 0.0800 mmol) and the colourless solution stirred at room temperature for 20 h until TLC (hexane : toluene 1 : 2) showed completion of the reaction. The reaction was quenched with 20% Na₂SO₃ (1 mL) and stirred for 30 mins, before the mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give an colourless oil (25 mg). Column chromatography (hexane : toluene 1 : 2) gave a 60 : 40 mixture of epoxides **332a** (14.9 mg, 0.0518 mmol, 97%) as a colourless oil: *R*_f 0.43 (hexane : toluene 1 : 2); ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.30 (m, 3H, 3 $\times$ Ar-*H*), 7.29 – 7.23 (m, 2H, 2 $\times$ Ar-*H*), 4.68 (t, *J* = 6.6 Hz, 0.40H, minor CHCN), 4.42 (t, *J* = 6.6 Hz, 0.60H, major CHCN), 3.94 (qd, *J* = 6.5, 3.9 Hz, 0.60H, major CHCH₃), 3.90 (d, *J* = 2.0 Hz, 0.60H, major CHOAr), 3.65 (d, *J* = 2.1 Hz, 0.40H, minor CHOAr), 3.59 (dq, *J* = 7.5, 6.6 Hz, 0.40H, minor CHCH₃), 3.01 (dd, *J* = 7.6, 2.1 Hz, 0.40H, minor CHO), 2.97 (dd, *J* = 3.9, 2.1 Hz, 0.60H, major CHO), 1.94 – 1.76 (m, 2H, CH₂), 1.58 – 1.40 (m, 2H, CH₂), 1.37 (d, *J* = 6.5 Hz, 1.80H, major CHCH₃), 1.35 (d, *J* = 6.6 Hz, 1.20H, minor CHCH₃), 1.33 – 1.24 (m, 6H, 3 $\times$ CH₂), 0.90 (t, *J* = 7.1 Hz, 1.20H, minor CH₃), 0.87 (t, *J* = 7.0 Hz, 1.80H, major CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 136.6 (major *ipso*-Ar), 136.2 (minor *ipso*-Ar), 128.6 (*para*-Ar), 128.5 (2 $\times$ minor *meta*-Ar), 128.4 (2 $\times$ major *meta*-Ar), 125.6 (2 $\times$ minor *ortho*-Ar), 125.5 (2 $\times$ major *ortho*-Ar), 118.9 (minor CN), 118.8 (major CN), 76.8 (minor CHCH₃), 73.2 (major CHCH₃), 68.4 (major CHOAr), 67.8 (minor CHOAr), 65.2 (minor CHCN), 64.2 (major CHCN), 55.9 (major CHO), 54.8 (minor CHO), 33.9 (minor CH₂),

33.7 (major CH₂), 31.6 (minor CH₂), 31.5 (major CH₂), 28.7 (minor CH₂), 28.6 (major CH₂), 24.7 (minor CH₂), 24.7 (major CH₂), 22.5 (minor CH₂), 22.5 (major CH₂), 18.0 (major CHCH₃), 17.7 (minor CHCH₃), 14.0 (minor CH₃), 14.0 (major CH₃).

2-[1-(3-Phenyloxiran-2-yl)ethoxy]octanenitrile (**332b**)



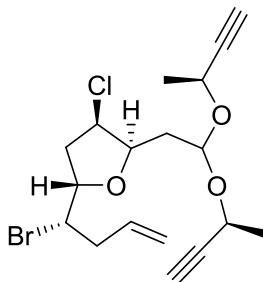
To a solution of olefin **322b** (13 mg, 0.048 mmol) in CH₂Cl₂ (200 μL) was added *m*CPBA (12.4 mg, 75%, 0.0539 mmol) and the colourless solution stirred at room temperature for 18 h until TLC (hexane : toluene 1 : 2) showed completion of the reaction. The reaction was quenched with 10% Na₂SO₃ (1 mL) and stirred for 30 mins, before the mixture was extracted with CH₂Cl₂ (3 × 3 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give an colourless oil (14 mg). Column chromatography (hexane : toluene 1 : 2) gave a 60 : 40 mixture of epoxides **332b** (10.0 mg, 0.0348 mmol, 72%) as a colourless oil: R_f 0.28 (hexane : toluene 1 : 2); IR (neat) 2928, 1605, 1461, 1094 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.24 (m, 5H, 5 × Ar-H), 4.70 (t, *J* = 6.6 Hz, 0.40H, minor CHCN), 4.44 (t, *J* = 6.6 Hz, 0.60H, major CHCN), 3.97 (qd, *J* = 6.5, 4.0 Hz, 0.60H, major CHCH₃), 3.92 (d, *J* = 2.0 Hz, 0.60H, major CHOAr), 3.67 (d, *J* = 2.1 Hz, 0.40H, minor CHOAr), 3.62 (dq, *J* = 7.6, 6.5 Hz, 0.40H, minor CHCH₃), 3.03 (dd, *J* = 7.6, 2.1 Hz, 0.40H, minor CHO), 3.00 (dd, *J* = 3.9, 2.1 Hz, 0.60H, major CHO), 1.97 – 1.79 (m, 2H, CH₂), 1.61 – 1.45 (m, 2H, CH₂), 1.40 (d, *J* = 6.5 Hz, 1.80H, major CHCH₃), 1.37 (d, *J* = 6.6 Hz, 1.20H, minor CHCH₃), 1.42 – 1.26 (m, 6H, 3 × CH₂), 0.93 (t, *J* = 6.8 Hz, 1.20H, minor CH₃), 0.89 (t, *J* = 7.0 Hz, 1.80H, major CH₃); ¹³C NMR (101 MHz, CDCl₃) δ

136.6 (major *ipso*-Ar), 136.2 (minor *ipso*-Ar), 128.6 (*para*-Ar), 128.5 (2 × minor *meta*-Ar), 128.4 (2 × major *meta*-Ar), 125.6 (2 × minor *ortho*-Ar), 125.5 (2 × major *ortho*-Ar), 118.9 (minor CN), 118.8 (major CN), 76.8 (minor CHCH₃), 73.2 (major CHCH₃), 68.4 (major CHOAr), 67.8 (minor CHOAr), 65.2 (minor CHCN), 64.2 (major CHCN), 55.9 (major CHO), 54.8 (minor CHO), 33.9 (minor CH₂), 33.7 (major CH₂), 31.6 (minor CH₂), 31.5 (major CH₂), 28.7 (minor CH₂), 28.6 (major CH₂), 24.7 (minor CH₂), 24.7 (major CH₂), 22.5 (minor CH₂), 22.5 (major CH₂), 18.0 (major CHCH₃), 17.7 (minor CHCH₃), 14.0 (minor CH₃), 14.0 (major CH₃); MS (CI⁺, NH₃) *m/z* 305 (M + NH₄)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₁₈H₂₉N₂O₂ (M + NH₄)⁺ 305.2229, found 305.2221.

General Procedure for the DIBAL-H Reduction of Nitriles:

To solutions of nitriles **268a/b**, **286a/b**, **317a/b**, **322a/b** & **332a/b** (5.0 - 40 mg) in THF (0.1 M) at -78°C was added DIBAL-H (0.86M, 1.5 eq.) dropwise. The colourless solutions were warmed to room temperature and stirred for 30 min - 3 hours until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was quenched with 1M citric acid (1 mL) and stirred for 15 mins. The mixture was extracted with CH₂Cl₂ (3 × 3 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give the crude products. No further purification was performed.

(2*R*,3*R*,5*S*)-2-{2,2-Bis[(2*S*)-but-3-yn-2-yloxy]ethyl}-5-[(1*S*)-1-bromobut-3-en-1-yl]-3-chlorooxolane (266)

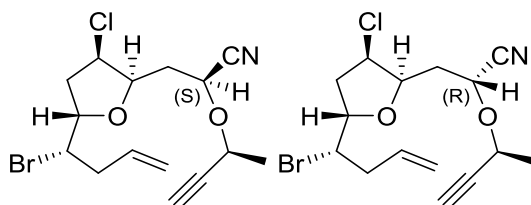


To a stirred solution of alcohol **162** (495 mg, 1.75 mmol) in CH₂Cl₂ (7 mL) at 0 °C was added Dess-Martin periodinane (1.48 g, 75% active, 2.62 mmol, 1.5 eq.). The white suspension was allowed to warm to room temperature and stirred for 30 min until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The mixture was passed through a silica plug, eluting with *n*-hexane : EtOAc 2 : 1 and the solvent was removed *in vacuo* to give a light yellow oil (498 mg). This material was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **163** (498 mg) in (2*S*)-but-3-yn-2-ol (1.75 mL, 22.3 mmol) at room temperature was added CSA (51.9 mg, 0.223 mmol, 0.13 eq.) and the yellow solution was heated to 40 °C. After 1 h, NaBH₄ (704 mg, 1.74 mmol) was added, followed by THF (3 mL). After a further 30 min at 40 °C, water (5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 5 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give a colourless oil (699 mg). Column chromatography (*n*-hexane : EtOAc 4 : 1) gave the title compound **266** (450 mg, 1.11 mmol, 64% over two steps, quant. brsm) as a colourless oil: *R*_f 0.61 (*n*-hexane : EtOAc 2 : 1); IR (neat) 3296, 2924, 1736, 1091, 1040 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 5.87 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H, CH₂=CH), 5.21 – 5.13 (m, 2H, CH₂=CH), 5.09 (t, *J* = 5.8 Hz, 1H, CH(OR)₂), 4.63 (qd, *J* = 6.5, 1.8 Hz, 1H, CHCH₃), 4.57 (dd, *J* = 4.7, 2.9 Hz, 1H, CHCl), 4.51 – 4.40 (m, 2H, CHOCHBr, CHCH₃), 4.29 (td, *J* = 6.8, 2.8 Hz, 1H,

CHOCHCl), 4.01 (ddd, $J = 8.6, 5.4, 3.1$ Hz, 1H, CHBr), 2.72 (ddd, $J = 9.7, 7.7, 6.4$ Hz, 2H, CH_2CHBr), 2.54 (ddd, $J = 14.3, 9.7, 4.8$ Hz, 1H, CH_2CHCl), 2.46 (d, $J = 2.0$ Hz, 1H, $\text{C}\equiv\text{CH}$), 2.42 (d, $J = 2.0$ Hz, 1H, $\text{C}\equiv\text{CH}$), 2.36 (dd, $J = 13.6, 5.9$ Hz, 1H, CH_2CHCl), 2.18 (ddd, $J = 13.6, 7.3, 6.1$ Hz, 1H, $\text{CH}_2\text{CH(OR)}_2$), 2.02 (dt, $J = 13.8, 6.1$ Hz, 1H, $\text{CH}_2\text{CH(OR)}_2$), 1.46 (d, $J = 5.7$ Hz, 3H, Me), 1.45 (d, $J = 5.5$ Hz, 3H, Me); ^{13}C NMR (101 MHz, CDCl_3) δ 134.8 ($\text{CH}_2=\text{CH}$), 118.1 ($\text{CH}_2=\text{CH}$), 98.1 (CH(OR)_2), 84.2 ($\text{C}\equiv\text{CH}$), 84.0 ($\text{C}\equiv\text{CH}$), 79.3 (CHOCHBr), 78.6 (CHOCHCl), 73.0 ($\text{C}\equiv\text{CH}$), 72.9 ($\text{C}\equiv\text{CH}$), 62.8 (CHCH_3), 62.3 (CHCH_3), 61.7 (CHCl), 58.0 (CHBr), 41.1 (CH_2CHCl), 40.0 (CH_2CHBr), 36.7 ($\text{CH}_2\text{CH(OR)}_2$), 22.6 (CH_3), 22.0 (CH_3); MS (ES^+ , TOF) 425 ($\text{M} + \text{Na}$) $^+$; HRMS (ES^+ , TOF) m/z calcd for $\text{C}_{18}\text{H}_{24}\text{O}_3\text{Na}^{35}\text{Cl}^{79}\text{Br}$ ($\text{M} + \text{Na}$) $^+$ 425.0495, found 425.0509; and starting alcohol **162** (180 mg, 0.635 mmol, 36%) as a colourless oil: ^1H NMR (400 MHz; CDCl_3) δ 5.86 (ddt, $J = 17.1, 10.3, 6.9$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.20 – 5.13 (m, 2H, $\text{CH}_2=\text{CH}$), 4.54 (dd, $J = 4.7, 2.7$ Hz, 1H, CHCl), 4.46 (ddd, $J = 9.5, 6.3, 3.2$ Hz, 1H, CHOCHBr), 4.37 (ddd, $J = 8.5, 4.5, 3.0$ Hz, 1H, CHOCHCl), 4.02 (ddd, $J = 8.6, 5.8, 3.2$ Hz, 1H, CHBr), 3.82 (t, $J = 5.7$ Hz, 2H CH_2OH), 2.77 – 2.65 (m, 2H, CH_2CHBr), 2.53 (ddd, $J = 14.3, 9.5, 5.0$ Hz, 1H, CH_2CHCl), 2.38 (ddd, $J = 13.9, 6.2, 1.1$ Hz, 1H, CH_2CHCl), 2.08 (ddt, $J = 14.6, 8.6, 5.8$ Hz, 1H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.92 – 1.83 (m, 1H, $\text{CH}_2\text{CH}_2\text{OH}$); ^{13}C NMR (101 MHz; CDCl_3) δ 134.7 ($\text{CH}_2=\text{CH}$), 118.0 ($\text{CH}_2=\text{CH}$), 82.2 (CHClCHO), 78.8 (CHBrCHO), 63.0 (CHCl), 60.7 (CHOH), 57.8 (CHBr), 41.0 (CH_2CHCl), 40.1 (CH_2CHBr), 34.0 ($\text{CH}_2\text{CH}_2\text{OH}$).

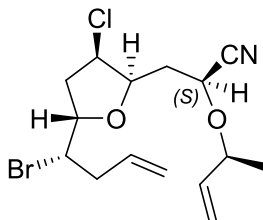
(2S)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolane-2-yl]-2-[(2S)-but-3-yn-2-yloxy]propanenitrile (178) & (2R)-3-[(2R,3R,5S)-5-[(1S)-1-bromobut-3-en-1-yl]-3-chlorooxolane-2-yl]-2-[(2S)-but-3-yn-2-yloxy]propanenitrile (179)



According to a modified procedure of Utimoto,⁸⁸ to a stirred solution of acetal **266** (280 mg, 0.694 mmol) in CH_2Cl_2 (1.0 mL) at room temperature was added trimethylsilyl cyanide (217 μL , 1.73 mmol, 2.5 eq.) and $\text{BF}_3\cdot\text{OEt}_2$ (12 μL , 0.097 mmol, 0.14 eq.). The orange solution was stirred for 2 h until TLC (*n*-hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was quenched with water (1 mL) and stirred for a further 15 min. The mixture was extracted with CH_2Cl_2 (3 $\times$ 3 mL), dried over Na_2SO_4 , filtered and the solvent removed *in vacuo* to give an orange oil (350 mg). Column chromatography (*n*-hexane : EtOAc 9 : 1) gave **178** (130 mg, 0.360 mmol, 52%) as a colourless oil: R_f 0.29 (*n*-hexane : EtOAc 9 : 1); ^1H NMR (400 MHz, CDCl_3) δ 5.86 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H, $\text{CH}_2=\text{CH}$), 5.22 – 5.12 (m, 2H, $\text{CH}_2=\text{CH}$), 4.73 (t, J = 7.0 Hz, 1H, CHCN), 4.58 – 4.54 (m, 1H, CHCl), 4.48 (m, 2H, CHOCHBr , CHCH_3), 4.41 (ddd, J = 8.2, 5.5, 3.0 Hz, 1H, CHOCHCl), 4.01 (ddd, J = 8.6, 5.8, 3.0 Hz, 1H, CHBr), 2.73 (ddd, J = 8.1, 6.3, 4.9 Hz, 2H, CH_2CHBr), 2.58 (ddd, J = 14.3, 9.5, 4.9 Hz, 1H, CHCH_2Cl), 2.55 (d, J = 2.0 Hz, 1H, $\text{C}\equiv\text{CH}$), 2.44 – 2.33 (m, 2H, CH_2CHCl , CH_2CHCN), 2.18 (ddd, J = 13.8, 7.2, 5.6 Hz, 1H, CH_2CHCN), 1.50 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 134.6 ($\text{CH}=\text{CH}_2$), 118.2 ($\text{CH}=\text{CH}_2$), 117.6 (CN), 81.4 ($\text{C}\equiv\text{CH}$), 78.8 (CHOCHBr), 78.6 (CHOCHCl), 75.1 ($\text{C}\equiv\text{CH}$), 65.0 (CHCH_3), 64.0 (CHCN), 62.1 (CHCl), 57.4 (CHBr), 40.9 (CH_2CHCl), 39.9 (CH_2CHBr), 35.4 (CH_2CHCN), 21.7 (CH_3); and **179** (116 mg, 0.321 mmol,

46%) as a colourless oil: R_f 0.22 (*n*-hexane : EtOAc 9 : 1); ^1H NMR (400 MHz, CDCl_3) δ 5.93 – 5.75 (m, 1H, $\text{CH}_2=\text{CH}$), 5.25 – 5.08 (m, 2H, $\text{CH}_2=\text{CH}$), 4.59 – 4.31 (m, 5H, CHCN , CHCl , CHCH_3 , CHOCHBr , CHOCHCl), 3.99 (td, $J = 7.1, 2.7$ Hz, 1H, CHBr), 2.72 (td, $J = 7.1, 1.5$ Hz, 2H, CH_2CHBr), 2.63 – 2.52 (m, 1H, CH_2CHCl) 2.60 (d, $J = 2.2$ Hz, 1H, $\text{C}\equiv\text{CH}$), 2.38 (dd, $J = 14.0, 6.3$ Hz, 1H, CH_2CHCl), 2.30 – 2.09 (m, 2H, CH_2CHCN), 1.49 (dd, $J = 6.6, 1.4$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 134.5 ($\text{CH}=\text{CH}_2$), 118.7 (CN), 118.4 ($\text{CH}=\text{CH}_2$), 81.6 ($\text{C}\equiv\text{CH}$), 78.4 (CHClCHO), 77.7 (CHBrCHO), 75.3 ($\text{C}\equiv\text{CH}$), 67.3 (CHCH_3), 63.9 (CHCN), 62.3 (CHCl), 58.3 (CHBr), 41.6 (CH_2CHCl), 40.7 (CHCHBr), 36.7 (CH_2CHCN), 21.7 (CH_3); all other data were collected by Solanki and Bonney.{Solanki, 2009 #78}{Bonney, 2011 #100}

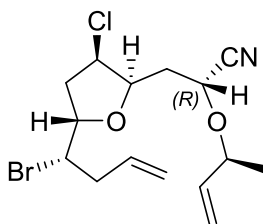
(2S)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolan-2-yl]-2-[(2S)-but-3-en-2-yloxy]propanenitrile (180)



To a solution of nitrile **178** (140 mg, 0.388 mmol) and quinoline (79.8 μL , 0.675 mmol) in benzene (9.70 mL) was added 5% Pd.BaSO_4 (41.3 mg, 0.0194 mmol, 5 mol%). The flask was then flushed with hydrogen and the atmosphere maintained with hydrogen filled balloons. The black suspension was stirred vigorously for 30 min until TLC (*n*-hexane : EtOAc 3 : 1) showed completion of the reaction. The reaction mixture was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a yellow oil (170 mg). Column chromatography (*n*-hexane : EtOAc 10 : 1) gave the diene **180** (136.5 mg, 0.376 mmol, 97%) as a colourless oil: R_f 0.57 (*n*-hexane : EtOAc 3 : 1); ^1H NMR (400 MHz,

CDCl₃) δ 5.85 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H, CH=CH₂), 5.61 (ddd, J = 17.5, 10.1, 8.2 Hz, 1H, CH=CH₂), 5.36 – 5.26 (m, 2H, CH=CH₂), 5.18 – 5.12 (m, 2H, CH=CH₂), 4.50 (dd, J = 4.8, 3.2 Hz, 1H, CHCN), 4.43 (ddd, J = 9.5, 6.2, 3.1 Hz, 1H, CHCl), 4.40 – 4.33 (m, 2H, CHOCHBr, CHOCHCl), 4.14 (p, J = 6.4 Hz, 1H, CHCH₃), 4.00 (ddd, J = 8.6, 5.7, 3.0 Hz, 1H, CHBr), 2.70 (q, J = 7.4, 6.7 Hz, 2H, CH₂CHBr), 2.55 (ddd, J = 14.2, 9.5, 4.9 Hz, 1H, CH₂CHCl), 2.36 (dd, J = 13.9, 6.2 Hz, 1H, CH₂CHCl), 2.27 (dt, J = 14.0, 7.0 Hz, 1H, CH₂CHCN), 2.13 (ddd, J = 13.6, 7.8, 5.0 Hz, 1H, CH₂CHCN), 1.30 (d, J = 6.3 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 137.6 (CH=CH₂), 134.6 (CH=CH₂), 119.2 (CH=CH₂), 118.2 (CN), 118.2 (CH=CH₂), 78.9 (CHBrCHO), 78.8 (CHClCHO), 77.2 (CHCH₃), 63.4 (CHCN), 62.4 (CHCl), 57.3 (CHBr), 40.9 (CH₂CHCl), 39.9 (CH₂CHBr), 35.6 (CH₂CHCN), 21.3 (CH₃); all other data were collected by Solanki and Bonney.{Solanki, 2009 #78}{Bonney, 2011 #100}

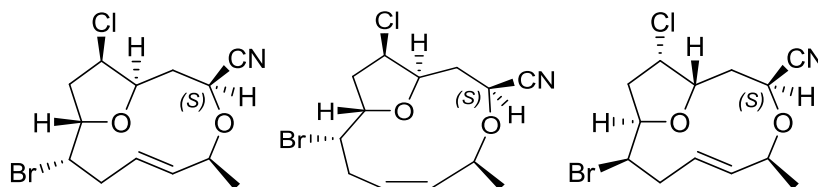
(2R)-3-[(2R,3R,5S)-5-[(1S)-1-Bromobut-3-en-1-yl]-3-chlorooxolan-2-yl]-2-[(2S)-but-3-en-2-yloxy]propanenitrile (181)



To a solution of nitrile **179** (102 mg, 0.283 mmol) and quinoline (58.1 μ L, 0.492 mmol) in benzene (7.00 mL) was added 5% Pd.BaSO₄ (30.0 mg, 0.0141 mmol, 5 mol%). The flask was then flushed with hydrogen and the atmosphere maintained with hydrogen filled balloons. The black suspension was stirred vigorously for 30 min until TLC (*n*-hexane : EtOAc 3 : 1) showed completion of the reaction. The reaction mixture was passed through a plug of silica, eluting with EtOAc. The solvent was removed *in vacuo* to give a yellow oil (162 mg).

The oil was redissolved in EtOAc (~5 mL) and washed with 1M HCl (3 × 3 mL). The solvent was removed *in vacuo* again to give a yellow oil (111 mg). Column chromatography (*n*-hexane : EtOAc 10 : 1) gave the diene **181** (93.0 mg, 0.256 mmol, 91%) as a colourless oil: *R*_f 0.35 (*n*-hexane : EtOAc 3 : 1); ¹H NMR (400 MHz, CDCl₃) δ 5.93 – 5.81 (m, 2H, CH=CH₂), 5.34 – 5.21 (m, 2H, CH=CH₂), 5.20 – 5.13 (m, 2H, CH=CH₂), 4.49 (dd, *J* = 4.9, 2.9 Hz, 1H, CHCl), 4.45 – 4.34 (m, 3H, CHCN, CHOCHBr, CHOCHCl), 4.13 (dq, *J* = 14.3, 7.1, 6.7 Hz, 1H, CHCH₃), 4.00 (td, *J* = 7.1, 2.7 Hz, 1H, CHBr), 2.73 (tt, *J* = 7.1, 1.3 Hz, 2H, CH₂CHBr), 2.59 (ddd, *J* = 14.2, 9.5, 4.9 Hz, 1H, CH₂CHCl), 2.39 (dd, *J* = 13.9, 6.3 Hz, 1H, CH₂CHCl), 2.22 (ddd, *J* = 14.2, 9.7, 3.2 Hz, 1H, CH₂CHCN), 2.16 – 2.08 (m, 1H, CH₂CHCN), 1.30 (d, *J* = 6.3 Hz, 1H, CH₃), ¹³C NMR (101 MHz, CDCl₃) δ 138.7 (CH=CH₂), 134.5 (CH=CH₂), 119.2 (CN), 118.3 (CH=CH₂), 117.4 (CH=CH₂), 79.0 (CHBrCHO), 78.9 (CHClCHO), 78.4 (CHCH₃), 63.4 (CHCN), 62.4 (CHCl), 58.2 (CHBr), 41.6 (CH₂CHCl), 40.7 (CH₂CHBr), 36.8 (CH₂CHCN), 20.2 (CH₃); all other data were collected by Solanki and Bonney.{Solanki, 2009 #78}{Bonney, 2011 #100}

(1*R*,3*S*,5*S*,6*E*,9*S*,10*S*,12*R*)-9-Bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridec-6-ene-3-carbonitrile (182), (1*S*,3*S*,5*S*,6*E*,9*R*,10*R*,12*S*)-9-bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridec-6-ene-3-carbonitrile [(*Z*)-182] & (1*R*,3*S*,5*S*,6*Z*,9*S*,10*S*,12*R*)-9-bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridec-6-ene-3-carbonitrile (336)

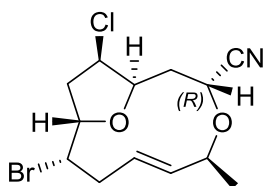


Toluene (160 – 400 mL) was refluxed in Dean-Stark apparatus for 1 h. The flask was removed from the hot plate and allowed to cool before diene **180** (20 – 50 mg, 0.0551 – 0.138 mmol) and Hoveyda-Grubbs I catalyst (3.3 – 8.3 mg, 10 mol%) was added. The flask was

covered with aluminium foil and the orange solution was returned to reflux for 17 – 24 h. The flask was removed from the hot plate and allowed to cool before di(ethylene glycol) vinyl ether (6 – 15 μ L) was added. The solvent was removed *in vacuo* to give a brown oil. Column chromatography (toluene) gave the *E*-macrocycle **182** (17 – 55%) as white crystals: R_f 0.13 (toluene); ^1H NMR (400 MHz, 298 K, CDCl_3) δ 6.03 – 5.87 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 5.68 – 5.30 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 4.59 – 4.47 (m, 1H, CHCN , CHCl), 4.42 (td, J = 4.9, 2.3 Hz, 1H, CHBr), 4.03 (dq, J = 8.7, 6.3 Hz, 1H, CHCH_3), 2.90 – 2.64 (m, 2H, CH_2CHBr), 2.46 – 2.33 (m, 1H, CH_2CHCl), 2.30 – 2.11 (m, 3H, CH_2CHCl , CH_2CHCN), 1.33 (d, J = 6.3 Hz, 3H, CH_3); ^1H NMR (400 MHz, 323 K, CDCl_3) δ 5.95 (dt, J = 14.5, 7.0 Hz, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 5.55 (dd, J = 15.4, 9.3 Hz, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 4.52 (dd, J = 6.5, 4.9 Hz, 1H, CHCl), 4.48 (t, J = 4.6 Hz, 1H, CHCN), 4.41 (td, J = 4.9, 2.3 Hz, 1H, CHBr), 4.28 – 4.12 (m, 2H, CHOCHBr , CHOCHCl), 4.02 (dq, J = 8.7, 6.4 Hz, 1H, CHCH_3), 2.77 (dd, J = 7.7, 4.2 Hz, 2H, CH_2CHBr), 2.41 (ddd, J = 13.7, 9.5, 6.5 Hz, 1H, CH_2CHBr), 2.29 – 2.19 (m, 2H, CH_2CHBr , CH_2CHCN), 2.15 (ddd, J = 15.3, 4.9, 2.7 Hz, 1H, CH_2CHCN), 1.33 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, 323 K, CDCl_3) δ 133.1 ($\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 130.6 ($\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 119.3 (CN), 81.0 (CHBrCHO), 79.1 (CHBrCHO), 76.4 (CHCH_3), 66.9 (CHCN), 59.9 (CHCl), 51.4 (CHBr), 41.6 (CH_2CHCl), 40.4 (CH_2CHCN), 38.3 (CH_2CHBr), 21.1 (CH_3); diastereomeric macrocycle **336** (8 – 12%): R_f 0.17 (toluene); ^1H NMR (500 MHz, CDCl_3) δ 5.69 (ddd, J = 15.2, 10.7, 2.5 Hz, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 5.26 (ddd, J = 15.2, 9.4, 2.1 Hz, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 4.73 (dt, J = 9.4, 6.7 Hz, 1H, CHOCHBr), 4.45 (dt, J = 12.3, 5.4, 4.0 Hz, 1H, CHBr), 4.40 (dd, J = 4.3, 2.0 Hz, 1H, CHCl), 4.23 – 4.19 (m, 1H, CHCN), 3.92 (td, J = 6.4, 2.1 Hz, 1H, CHOCHCl), 3.80 (dq, J = 9.6, 6.3 Hz, 1H, CHCH_3), 2.85 (ddd, J = 14.8, 6.1, 2.5 Hz, 1H, CH_2CHBr), 2.46 (dd, J = 14.5, 7.2 Hz, 1H, CH_2CHBr), 2.44 – 2.39 (m, 1H, CH_2CHCl), 2.36 (ddd, J = 14.3, 9.4, 4.5 Hz, 1H, CH_2CHCl), 1.95 – 1.92 (m, 2H, CH_2CHCN), 1.31 (d, J = 6.3 Hz,

3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 132.0 (CH₂CH=CHCHCH₃), 130.9 (CN), 129.0 (CH₂CH=CHCHCH₃), 81.1 (CHCH₃), 78.4 (CHBrCHO), 75.3 (CHClCHO), 64.8 (CHCN), 61.5 (CHCl), 49.2 (CHBr), 38.7 (CH₂CHCl), 37.2 (CH₂CHBr), 36.8 (CH₂CHCN), 21.1 (CH₃); and Z-macrocyclic (Z)-**182** (10 - 15%): R_f 0.22 (toluene); ¹H NMR (400 MHz, CDCl₃) δ 5.58 (dd, J = 10.9, 9.1 Hz, 1H, CH₂CH=CHCHCH₃), 5.51 (td, J = 10.5, 6.1 Hz, 1H, CH₂CH=CHCHCH₃), 4.60 (dq, J = 8.9, 6.2 Hz, 1H, CHCH₃), 4.47 (dt, J = 11.5, 5.7 Hz, 1H, CHOCHCl), 4.40 (dt, J = 10.1, 6.8 Hz, 1H, CHCl), 4.33 (t, J = 8.0 Hz, 1H, CHOCHBr), 4.22 (d, J = 9.2 Hz, 1H, CHCN), 3.98 (ddd, J = 12.5, 3.6, 1.3 Hz, 1H, CHBr), 3.15 (td, J = 12.7, 10.5 Hz, 1H, CH₂CHCl), 2.57 (dtd, J = 13.4, 7.2, 3.7 Hz, 2H, CH₂CHBr), 2.37 (ddd, J = 15.4, 11.4, 9.5 Hz, 1H, CH₂CHCl), 2.15 – 2.04 (m, 2H, CH₂CHCN), 1.38 (d, J = 6.1 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 135.4 (CH₂CH=CHCHCH₃), 128.4 (CH₂CH=CHCHCH₃), 119.6 (CN), 77.9 (CHClCHO), 73.6 (CHCH₃), 73.5 (CHClCHO), 65.0 (CHCN), 55.6 (CHCl), 53.9 (CHBr), 38.2 (CH₂CHCl), 35.4 (CH₂CHCN), 35.0 (CH₂CHBr), 19.8 (CH₃); all other data were collected by Solanki and Bonney.[Solanki, 2009 #78]{Bonney, 2011 #100}

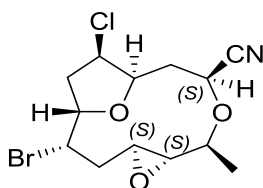
(1R,3R,5S,6E,9S,10S,12R)-9-Bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridec-6-ene-3-carbonitrile (183)



Toluene (160 - 400 mL) was refluxed in Dean-Stark apparatus for 1 h. The flask was removed from the hot plate and allowed to cool before diene **181** (20 - 50 mg, 0.055 - 0.14 mmol) and Hoveyda-Grubbs II catalyst (3.3 – 8.6 mg, 10 mol%) was added. The flask was covered with aluminium foil and the orange solution was returned to reflux for 17 – 24 h. The flask was

removed from the hot plate and allowed to cool before di(ethylene glycol) vinyl ether (6 – 15 μ L) was added. The solvent was removed *in vacuo* to give a brown oil. Column chromatography (toluene) gave the *E*-macrocycle **183** (35 – 54%) as white crystals: R_f 0.13 (toluene); ^1H NMR (400 MHz, CDCl_3) δ 5.90 – 5.77 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 5.72 – 5.59 (m, 1H, $\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 4.72 (td, $J = 8.1, 5.4$ Hz, 1H, CHOCHBr), 4.54 – 4.44 (m, 2H, CHCH_3 , CHBr), 4.43 – 4.38 (m, 1H, CHCl), 4.37 – 4.29 (m, 1H, CHCN), 3.92 – 3.77 (m, 1H, CHOCHCl), 2.93 – 2.84 (m, 1H, CH_2CHBr), 2.55 – 2.35 (m, 3H, CH_2CHBr , $2 \times \text{CH}_2\text{CHCl}$), 1.95 – 1.89 (m, 2H, CH_2CHCN), 1.42 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 130.1 ($\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 128.3 ($\text{CH}_2\text{CH}=\text{CHCHCH}_3$), 119.6 (CN), 78.3 (CHOCHBr), 75.3 (CHOCHBr), 71.8 (CHCH_3), 61.4 (CHCl), 56.5 (CHCN), 49.2 (CHBr), 38.8 (CH_2CHCl), 37.6 (CH_2CHBr), 36.3 (CH_2CHCN), 13.5 (CH_3); all other data were collected by Solanki and Bonney.[Solanki, 2009 #78]{Bonney, 2011 #100}

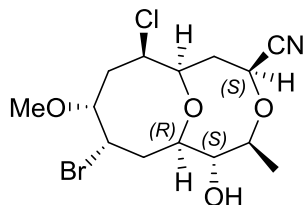
(1*S*,2*S*,4*S*,6*S*,7*S*,9*S*,11*R*,12*R*)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane-9-carbonitrile (340)



To a solution of *E*-macrocycle **182** (22.5 mg, 0.0672 mmol) in CH_2Cl_2 (400 μ L) was added *m*CPBA (23.2 mg, 75%, 0.101 mmol). The colourless solution was stirred for 2 h until TLC (*n*-hexane : EtOAc 4 : 1) showed completion of the reaction. The reaction was quenched with 20% Na_2SO_3 (1 mL) and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3×3 mL), the organic layers washed with sat. aq. NaHCO_3 (2×3 mL), dried over Na_2SO_4 , filtered and the solvent removed *in vacuo* to give a colourless oil (26.2 mg). Column

chromatography (*n*-hexane : EtOAc 4 : 1) gave epoxide **340** (22.8 mg, 0.0439 mmol, 97%) as a colourless oil: *R*_f 0.15 (*n*-hexane : EtOAc 4 : 1); IR (neat) 2926, 1673, 1260, 1090, 927 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.51 (dd, *J* = 5.1, 3.0 Hz, 1H, CHOCHBr), 4.42 (dt, *J* = 11.0, 3.2 Hz, 1H, CHOCHCl), 4.37 – 4.32 (m, 3H, CHBr, CHCl, CHCN), 3.36 (dt, *J* = 9.4, 2.1 Hz, 1H, CH₂CHO), 3.22 (dq, *J* = 8.4, 6.4 Hz, 1H, CHCH₃), 2.84 (ddd, *J* = 14.6, 4.5, 2.0 Hz, 1H, CH₂CHBr), 2.76 – 2.67 (m, 2H, CHCH₃CHO, CH₂CHCl), 2.50 (ddd, *J* = 14.8, 11.1, 8.9 Hz, 1H, CH₂CHCN), 2.42 (dd, *J* = 14.2, 6.4 Hz, 1H, CH₂CHCl), 2.00 (ddd, *J* = 14.7, 3.4, 0.9 Hz, 1H, CH₂CHCN), 1.67 (ddd, *J* = 14.7, 9.4, 2.5 Hz, 1H, CH₂CHBr), 1.42 (d, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 119.1 (CN), 82.7 (CHCH₃), 81.5 (CHClCHO), 79.2 (CHBr), 69.6 (CHCN), 62.5 (CHCH₃CHO), 61.5 (CHOCHBr), 58.5 (CH₂CHO), 55.1 (CHCl), 42.8 (CH₂CHCl), 39.9 (CH₂CHBr), 37.0 (CH₂CHCN), 19.7 (CH₃); MS (CI⁺, NH₃) *m/z* 350 (M + H)⁺; HRMS (CI⁺, NH₃) *m/z* calcd for C₁₃H₁₈NO₃³⁵Cl⁷⁹Br (M + H)⁺ 350.0159, found 350.0161; with 8% of the mass believed to be the epimeric epoxide, calculated by comparison of the integral of the methyl protons.

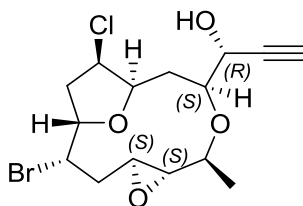
(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-12-chloro-6-hydroxy-10-methoxy-5-methyl-4,13-dioxabicyclo[5.5.1]tridecan-3-carbonitrile (341)



To a solution of epoxide **340** (5.0 mg, 0.014 mmol) in MeOH (200 μL) was added CSA (0.33 mg, 0.0014 mmol) and the cloudy suspension stirred for 2 h. A further quantity of CSA was added (0.33 mg, 0.0014 mmol) and stirring continued for 2 h until TLC (*n*-hexane : EtOAc 2 :

1) showed completion of the reaction. Water (1 mL) was added to the reaction mixture and extracted with CH₂Cl₂ (3 × 3 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give a white solid (4.6 mg). Column chromatography (*n*-hexane : EtOAc 2 : 1) gave compound **341** (5.0 mg, 0.0439 mmol, 93%) as a colourless oil: R_f 0.08 (*n*-hexane : EtOAc 2 : 1); [α]_D -0.09 (*c* 0.24, MeOH : CHCl₃ 1 : 1); IR 3357, 2923, 1641, 1082 cm⁻¹; ¹H NMR (400 MHz, CD₃OD : CDCl₃ 1 : 1) δ 4.82 (t, *J* = 3.8 Hz, 1H, CHBr), 4.70 (dd, *J* = 11.9, 2.0 Hz, 1H, CHCN), 4.21 (dt, *J* = 5.9, 1.7 Hz, 1H, CHCl), 4.03 (d, *J* = 7.1 Hz, 1H, CHOMe), 3.95 (dt, *J* = 11.0, 1.9 Hz, 1H, CHOCHCl), 3.71 (t, *J* = 10.0 Hz, 1H, CHOCHBr), 3.58 (dq, *J* = 9.3, 6.3 Hz, 1H, CHCH₃), 3.36 (s, 3H, OCH₃), 3.07 (t, *J* = 9.2 Hz, 1H, CHOH), 2.92 (ddd, *J* = 16.2, 7.2, 1.8 Hz, 1H, CH₂CHCl), 2.60 (ddd, *J* = 15.2, 4.2, 1.3 Hz, 1H, CH₂CHBr), 2.36 (ddd, *J* = 14.3, 11.9, 10.7 Hz, 1H, CH₂CHCN), 2.19 (ddd, *J* = 15.2, 10.7, 3.5 Hz, 1H, CH₂CHBr), 2.12 (dd, *J* = 16.2, 5.6 Hz, 1H, CH₂CHCl), 1.69 (dt, *J* = 14.5, 1.7 Hz, 1H, CH₂CHCN), 1.35 (d, *J* = 6.2 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CD₃OD : CDCl₃ 1 : 1) δ 118.3 (CN), 86.8 (CHCH₃), 85.4 (CHOCHCl), 84.5 (CHOCHBr), 79.2 (CHOMe), 73.4 (CHOH), 71.5 (CHCN), 63.3 (CHCl), 60.4 (CHBr), 55.7 (OCH₃), 42.1 (CH₂CHBr), 40.3 (CH₂CHCl), 38.3 (CH₂CHCN), 19.8 (CH₃); HRMS (ES⁻, TOF) *m/z* calcd for C₁₄H₂₀NO₄³⁵Cl⁷⁹Br (M + H)⁺ 380.0264, found 380.0302.

(1R)-1-[(1S,2S,4S,6S,7S,9S,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (350)



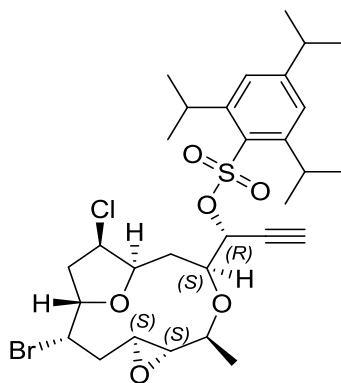
To a stirred solution of nitrile **340** (21.0 mg, 0.0599 mmol) at in THF (300 μ L) at -78 °C was added DIBAL-H in THF (105 μ L, 0.86 M, 0.0898 mmol) and the colourless solution warmed to -40 °C. After 30 min, a further aliquot of DIBAL-H in THF (105 μ L, 0.86 M, 0.0898 mmol) was added and stirred for an additional 30 min until TLC (*n*-hexane : EtOAc 1 : 1) showed completion of the reaction. The reaction was quenched with a 1M aqueous citric acid solution (1 mL) and stirred for 15 minutes. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), the organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a white solid (10.5 mg). This material was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **349** (10.5 mg) in THF (300 μ L) at 0 °C was added ethynylmagnesium bromide in THF (89 μ L, 0.5 M, 0.0447 mmol) and the yellow solution stirred for 30 min. A second aliquot of ethynylmagnesium bromide in THF (100 μ L, 0.5 M, 0.0500 mmol) was added and stirred for an additional 1 h. A third aliquot of ethynylmagnesium bromide in THF (100 μ L, 0.5 M, 0.0500 mmol) was added and stirred for an additional 30 min until TLC (*n*-hexane : EtOAc 1 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NH₄Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), the organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow oil (12.4 mg). Column chromatography (toluene : MeCN 9 : 1) gave title compound **350** (7.0 mg, 0.018 mmol, 31%, 3 : 1 d.r.) as a colourless oil: *R*_f 0.09 (toluene : MeCN 9 : 1); ¹H NMR (400 MHz, CDCl₃) δ 4.51 (dd, *J* = 5.3, 3.0 Hz, 1H, CHOCHBr), 4.45 – 4.35 (m, 3H, CHBr, CHOCHCl, CHCl), 4.32 (td, *J* = 4.7, 2.2 Hz, 0.77H, CHCOH major product), 4.19 (ddd, *J* = 7.1, 4.7, 2.2 Hz, 0.23H, CHCOH, minor product), 3.72 (dd, *J* = 8.3, 4.7 Hz, 0.25H, CHOH minor product), 3.67 (dd, *J* = 8.1, 4.8 Hz, 0.75H, CHOH major product), 3.43 (dt, *J* = 9.3, 2.1 Hz, 1H, CH₂CHO), 3.32 (dq, *J* = 8.2, 6.4 Hz, 0.25H, CHCH₃

minor product), 3.24 (dq, $J = 8.4, 6.4$ Hz, 0.76H, CHCH_3 major product), 2.84 (ddd, $J = 14.6, 4.8, 2.0$ Hz, 1H, CH_2CHBr), 2.77 (dd, $J = 8.3, 2.3$ Hz, 1H, CHCH_3CHO), 2.74 (ddd, $J = 13.8, 8.4, 5.1$ Hz, 1H, CH_2CHCl), 2.49 (d, $J = 2.2$ Hz, 0.61H, $\text{C}\equiv\text{CH}$ major product), 2.47 (d, $J = 2.2$ Hz, 0.20H, $\text{C}\equiv\text{CH}$ minor product), 2.41 (dd, $J = 14.1, 6.5$ Hz, 1H, CH_2CHCl), 2.23 (d, $J = 4.7$ Hz, 0.67H, OH), 2.05 (ddd, $J = 14.6, 11.0, 8.1$ Hz, 1H, CH_2CHOH), 1.92 (dd, $J = 14.3, 2.7$ Hz, 0.75H, CH_2CHCOH major product), 1.77 (dd, $J = 14.6, 2.6$ Hz, 0.24H, CH_2CHCOH minor product), 1.70 (ddd, $J = 14.6, 9.3, 2.3$ Hz, 1H, CH_2CHBr), 1.42 (d, $J = 6.4$ Hz, 0.73H, CH_3 minor product), 1.40 (d, $J = 6.4$ Hz, 2.27H, CH_3 major product); ^{13}C NMR (101 MHz, CDCl_3) δ 84.7 (CHOH), 83.0 (CHBr), 81.4 (CHCH_3), 79.1 (CHClCHO), 77.2 ($\text{C}\equiv\text{CH}$), 74.6 ($\text{C}\equiv\text{CH}$), 65.9 (CHCOH), 63.4 (CHCH_3CHO), 62.4 (CHBrCHO), 58.9 (CH_2CHO), 55.6 (CHCl), 42.8 (CH_2CHCl), 39.9 (CH_2CHBr), 32.9 (CH_2CHCOH), 20.5 (CH_3); HRMS (ES^+) m/z calcd for $\text{C}_{15}\text{H}_{21}\text{O}_4^{35}\text{Cl}^{79}\text{Br}$ ($\text{M} + \text{H}$) $^+$ 379.0307, found 379.0306; with 8% of the mass believed to be the epimeric epoxide, calculated by comparison of the integral of the methyl protons.

(1R)-1-[(1S,2S,4S,6S,7S,9S,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-

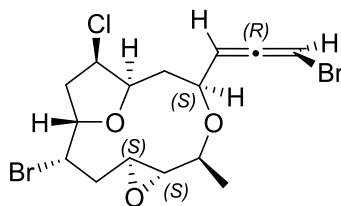
trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-yl 2,4,6-tris(propan-2-yl)benzene-1-sulfonate (351)



To a stirred solution of alcohol **350** (5.9 mg, 0.016 mmol, 3 : 1 d.r.) in CH₂Cl₂ (200 µL) was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride and DMAP in CH₂Cl₂ (253 µL, 0.0613 M, 0.0155 mmol of each). The colourless solution was stirred for 17 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (6.2 mg). Column chromatography (*n*-hexane : EtOAc 25 : 1) gave title compound **351** (6.2 mg, 0.0096 mmol, 62%, 3 : 1 d.r.) as a white solid: R_f 0.43 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 7.17 (s, 2H, ArH), 5.03 (dd, *J* = 4.7, 2.2 Hz, 0.75H, CHOTris major product), 5.01 (dd, *J* = 5.7, 2.2 Hz, 0.25H, CHOTris minor product), 4.49 (dd, *J* = 5.1, 2.8 Hz, 1H, CHOCHBr), 4.40 – 4.32 (m, 3H, CHOCHCl, CHCl, CHBr), 4.13 (hept, *J* = 6.7 Hz, 2H, CH(CH₃)₂), 3.83 (dd, *J* = 7.9, 4.7 Hz, 0.75H, CHCOTris major product), 3.79 (dd, *J* = 7.9, 5.9 Hz, 0.25H, CHCOTris minor product), 3.39 (dt, *J* = 9.4, 2.2 Hz, 1H, CH₂CHO), 3.21 (dq, *J* = 7.9, 6.3 Hz, 0.75H, CHCH₃ major product), 3.16 (dq, *J* = 7.8, 6.3 Hz, 0.25H, CHCH₃ minor product), 2.91 (hept, *J* = 7.4 Hz, 1H, CH(CH₃)₂), 2.82 (ddd, *J* = 14.7, 4.7, 2.0 Hz, 1H, CH₂CHBr), 2.76 – 2.68 (m, 2H, CH₂CHCl, CHCH₃CHO), 2.39 (dd, *J* = 14.1, 6.4 Hz, 1H, CH₂CHCl), 2.32 (d, *J* = 2.2 Hz, 0.76H, C≡CH major product), 2.26 (d, *J* = 2.2 Hz, 0.25H, C≡CH minor product), 2.13 – 2.03 (m, 1H, CH₂CHCOTris), 1.87 (dd, *J* = 14.4, 2.8 Hz, 0.25H, CH₂CHCOTris minor product), 1.81 (dd, *J* = 14.5, 2.9 Hz, 0.75H, CH₂CHCOTris major product), 1.66 (ddd, *J* = 14.6, 9.4, 2.3 Hz, 1H, CH₂CHBr), 1.36 (d, *J* = 6.4 Hz, 0.73H, CH₃ minor product), 1.30 – 1.23 (m, 18H, 6 × CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 174.8 (*ipso*Ar), 154.0 (*para*Ar), 150.9 (*ortho*Ar), 123.7 (*meta*Ar), 83.0 (CHCOTris), 82.5 (CHBr), 81.9 (CHCH₃), 79.1 (CHClCHO), 77.2 (C≡CH), 76.9 (C≡CH), 72.2 (CHOTris), 63.3 (CHCH₃CHO), 62.2 (CHBrCHO), 58.8 (CH₂CHO), 55.5 (CHCl), 42.8 (CH₂CHCl), 40.0 (CH₂CHBr), 34.3

(CH(CH₃)₂), 33.7 (CH₂CHCOTris), 29.7 (CH(CH₃)₂), 24.8 (CH(CH₃)₂), 24.7 (CH(CH₃)₂), 24.6 (CH(CH₃)₂), 23.6 (CH(CH₃)₂), 19.7 (CH₃).

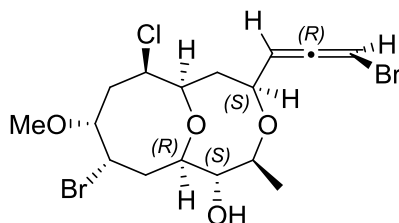
(1*S*,2*S*,4*S*,6*S*,7*S*,9*S*,11*R*,12*R*)-2-Bromo-9-[(*R*)-3-bromopropa-1,2-dien-1-yl]-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane, 12-epoxyobtusallene II (5)



LiBr (11.4 mg, 0.131 mmol) and CuBr (18.8 mg, 0.131 mmol) were dissolved in CH₂Cl₂ (1.2 mL). The mixture was stirred at room temperature for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of trisylate **351** (6.2 mg, 0.0096 mmol, 3 : 1 d.r.) in CH₂Cl₂ (300 µL) was added the LiCuBr₂ solution (265 µL, 0.109 M, 0.0289 mmol). The green solution was heated to 60 °C and stirred for 4h, until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (4.8 mg). Column chromatography (toluene to toluene : MeCN 50 : 1) gave title compound **5** (3.6 mg, 0.0096 mmol, 85%, 3 : 1 d.r.) as a white solid: R_f 0.52 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 6.08 (dd, *J* = 5.7, 2.0 Hz, 0.18H, HC=CBrH minor product), 6.04 (dd, *J* = 5.7, 1.7 Hz, 0.54H, HC=CBrH major product), 5.43 (t, *J* = 5.9 Hz, 0.60H, HC=CBrH major product), 5.41 (t, *J* = 5.8 Hz, 0.20H HC=CBrH minor product), 4.53 (dd, *J* = 5.5, 3.1 Hz, 0.24H CHCl minor product), 4.50 (dd, *J* = 5.3, 3.0 Hz, 0.76H CHCl major product), 4.46 – 4.32 (m, 3H, CHOCHBr, CHOCHCl, CHBr), 4.18 (ddd, *J* = 7.9, 6.0, 1.7 Hz, 0.75H, CHCH=CBr major product), 4.13 (td, *J* = 6.8, 2.1 Hz, 0.25H, CHCH=CBr

minor product), 3.43 (dt, $J = 9.4, 2.2$ Hz, 1H, CH_2CHO), 3.17 – 3.07 (m, 1H, CHCH_3), 2.83 (ddd, $J = 14.5, 4.8, 1.9$ Hz, 1H, CH_2CHBr), 2.79 – 2.71 (m, 2H, CHCH_3CHO , CH_2CHCl), 2.42 (ddd, $J = 14.1, 6.6, 0.7$ Hz, 1H, CH_2CHCl), 2.24 – 2.15 (m, 1H, $\text{CH}_2\text{CHCH}=\text{CHBr}$), 1.75 – 1.65 (m, 2H, $\text{CH}_2\text{CHCH}=\text{CHBr}$, CH_2CHBr), 1.38 (d, $J = 6.3$ Hz, 0.75H, CH_3 minor product), 1.37 (d, $J = 6.4$ Hz, 2.25H, CH_3 major product); ^{13}C NMR (101 MHz, CDCl_3) δ 200.7 ($\text{CH}=\text{C}=\text{CHBr}$), 103.1 ($\text{CH}=\text{C}=\text{CHBr}$), 82.7 (CHClCHO), 81.0 (CHCH_3), 79.9 ($\text{CHCH}=\text{C}=\text{CHBr}$), 79.1 (CHBrCHO), 73.7 ($\text{CH}=\text{C}=\text{CHBr}$), 63.5 (CHCH_3CHO), 62.3 (CHCl), 58.7 (CH_2CHO), 56.0 (CHBr), 42.8 (CH_2CHCl), 39.8 (CH_2CHBr), 37.1 ($\text{CH}_2\text{CHCH}=\text{C}=\text{CHBr}$), 20.3 (CH_3); MS (ES^+ , TOF) m/z 440.9 ($\text{M} + \text{H}^+$); HRMS (ES^+ , TOF) m/z calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{ClBr}_2$ ($\text{M} + \text{H}^+$) 440.9468, found 440.9458; 15% of the mass believed to be the corresponding propargylic bromides in a 3 : 2 d.r., calculated by comparison of the integral of the methyl protons. The observable peaks are given here: ^1H NMR (400 MHz, CDCl_3) δ 5.03 (td, $J = 4.5, 2.2$ Hz, 0.13H HCBBr), 3.85 – 3.77 (m, 0.30H, $\text{CHCHBr}\equiv\text{CH}$), 3.34 – 3.20 (m, 0.30H, CHCH_3 , CH_2CHO), 2.66 (d, $J = 2.4$ Hz, 0.06H, $\text{CHBr}\equiv\text{CH}$), 2.65 (d, $J = 2.4$ Hz, 0.09H, $\text{CHBr}\equiv\text{CH}$), 1.43 (d, $J = 6.3$ Hz, 0.20H, CH_3), 1.43 (d, $J = 6.4$ Hz, 0.30H, CH_3).

(1R,2S,3S,5S,7R,8R,10R,11S)-11-Bromo-5-[(R)-3-bromopropa-1,2-dien-1-yl]-8-chloro-10-methoxy-3-methyl-4,13-dioxabicyclo[5.5.1]tridecan-2-ol, marilzabicycloallene C (6)

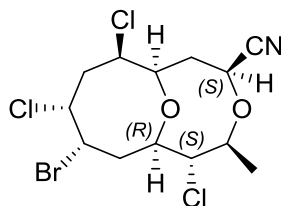


To a sample of epoxide **5** (2.0 mg, 0.0045 mmols) was added a solution of CSA in MeOH (100 μL , 0.0043 μM , 0.00043 mmols) and the suspension stirred for 1 h. An additional aliquot of

CSA in MeOH (100 μ L, 0.0043 μ M, 0.00043 mmols) was added and stirring resumed for 1h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NaHCO₃ (1 mL) and stirred for 5 min. The mixture was partitioned between water (1 mL) and CH₂Cl₂ (3 mL), separated and extracted further with CH₂Cl₂ (2 $\times$ 3 mL). The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a white solid (2.5 mg). Column chromatography (*n*-hexane : EtOAc 4 : 1 to 2 : 1) gave title compound **6** (2.0 mg, 0.042 mmol, 94%, 3 : 1 d.r.) as a white solid: R_f 0.19 (*n*-hexane : EtOAc 2 : 1; ¹H NMR (500 MHz, CDCl₃) δ 6.09 (dd, *J* = 5.7, 2.2 Hz, 0.18H, HC $\equiv$ CHBr minor product), 6.05 (dd, *J* = 5.7, 2.1 Hz, 0.54H, HC $\equiv$ CHBr major product), 5.47 (t, *J* = 5.5 Hz, 0.60H, HC $\equiv$ CBrH major product), 5.40 (t, *J* = 5.3 Hz, 0.20H, HC $\equiv$ CBrH minor product), 4.85 (t, *J* = 3.9 Hz, 1H, CHBr), 4.33 (ddt, *J* = 9.6, 5.0, 2.2 Hz, 1H, CHCH $\equiv$ CHBr), 4.18 (dt, *J* = 5.7, 1.9 Hz, 1H, CHCl), 4.06 (d, *J* = 7.2 Hz, 1H, CHOMe), 3.89 (dt, *J* = 10.9, 1.7 Hz, 1H, CHOCHCl), 3.74 (t, *J* = 9.9 Hz, 1H, CHOCHBr), 3.57 (dq, *J* = 9.0, 6.1 Hz, 1H, CHCH₃), 3.37 (s, 3H, OCH₃), 3.25 (td, *J* = 9.2, 5.6 Hz, 1H, CHOH), 2.90 (ddd, *J* = 16.1, 7.1, 1.9 Hz, 1H, CH₂CHCl), 2.59 (ddd, *J* = 15.0, 4.1, 1.3 Hz, 1H, CH₂CHBr), 2.27 (ddd, *J* = 15.6, 10.8, 3.6 Hz, 1H, CH₂CHBr), 2.19 (dd, *J* = 16.5, 10.6 Hz, 1H, CH₂CHCl), 2.13 (dt, *J* = 14.5, 10.9 Hz, 1H, CH₂CHCH $\equiv$ CHBr), 1.52 – 1.46 (m, 1H, CH₂CHCH $\equiv$ CHBr), 1.36 (d, *J* = 6.2 Hz, 0.75H, CH₃ minor product), 1.35 (d, *J* = 6.2 Hz, 2.25H, CH₃ major product); ¹³C NMR (126 MHz, CDCl₃) δ 200.9 (CH=C=CHBr), 103.2 (CH=C=CHBr), 86.7 (CHOCHCl), 85.1 (CHCH₃), 84.5 (CHOCHBr), 81.1 (CHCH=C=CHBr), 79.0 (CHOMe), 74.7 (CHOH), 74.1 (CH=C=CHBr), 63.9 (CHCl), 61.0 (CHBr), 56.0 (OCH₃), 42.2 (CH₂CHBr), 40.4 (CH₂CHCl), 38.8 (CH₂CHCH=C=CHBr), 20.5 (CH₃); HRMS (ES⁺, TOF) *m/z* calcd for C₁₇H₂₄O₆ClBr₂ (M + CHO₂)⁺ 516.9628, found 516.9639; with 6% of the mass believed to be the corresponding propargylic bromides in a 5 : 1 d.r., calculated by comparison to the integral of the alkyne protons. The observable peaks are given here: ¹H NMR (500 MHz,

CDCl₃) δ 2.70 (d, J = 2.5 Hz, 0.05H), 2.67 (d, J = 2.5 Hz, 0.01H); HRMS (ES⁻, TOF) m/z calcd for C₁₇H₂₄O₆³⁵Cl⁷⁹Br₂ (M + CHO₂)⁻ 516.9628, found 516.9639.

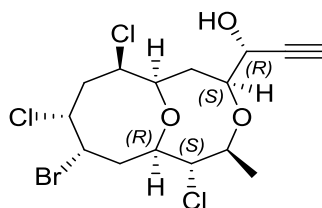
(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-6,10,12-trichloro-5-methyl-4,13-dioxabicyclo[5.5.1]tridecane-3-carbonitrile (360)



To a solution of (*E*)-olefin **182** (10.0 mg, 0.0299 mmol) in CH₂Cl₂ (360 μ L) was added TMG (0.1 μ L, 0.000797 mmol), TMSCl (4.2 μ L, 0.033 mmol) and NCS (8.0 mg, 0.060 mmol). The colourless solution was stirred for 3 h until TLC (*n*-hexane : EtOAc 4 : 1) showed completion of the reaction. The reaction was quenched with 10% Na₂SO₃ (1 mL) and stirred for an additional 5 min. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give a colourless oil (18.0 mg). Column chromatography (*n*-hexane : EtOAc 10 : 1) gave trichloride **360** (10.6 mg, 0.0261 mmol, 87%) as a colourless oil: *R*_f 0.22 (*n*-hexane : EtOAc 4 : 1); IR (neat) 2930, 1677, 1143 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.98 – 4.92 (m, 2H, 9-CHCl & CHBr), 4.53 (dd, J = 11.9, 1.9 Hz, 1H, CHCN), 4.05 (dt, J = 5.5, 1.9 Hz, 1H, 7-CHCl), 3.98 – 3.88 (m, 2H, 12-CHOCHCl & 6-CHOCHCl), 3.74 (dq, J = 9.6, 6.1 Hz, 1H, CHCH₃), 3.51 (t, J = 9.7 Hz, 1H, 13-CHCl), 3.23 (ddd, J = 16.5, 8.1, 2.1 Hz, 1H, CH₂CHCl), 2.78 (ddd, J = 15.0, 4.7, 1.3 Hz, 1H, CH₂CHBr), 2.63 (ddt, J = 16.4, 5.4, 1.1 Hz, 1H, CH₂CHCl), 2.54 (ddd, J = 14.6, 11.9, 10.9 Hz, 1H, CH₂CHCN), 2.33 (ddd, J = 15.1, 10.4, 3.1 Hz, 1H, CH₂CHBr), 1.69 (dt, J = 14.6, 1.7 Hz, 1H, CH₂CHCN), 1.52 (d, J = 6.1 Hz, 1H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 117.4 (CN), 86.7 (CHCH₃), 85.3 (6-

CHOCHCl), 84.2 (12-CHOCHCl), 71.9 (CHCN), 62.6 (CHBr), 62.5 (7-CHCl), 62.1 (13-CHCl), 59.6 (9-CHCl), 45.1 (CH₂CHCl), 44.1 (CH₂CHBr), 37.9 (CH₂CHCN), 21.9 (CH₃); HRMS (ES, TOF) *m/z* calcd for C₁₄H₁₈NO₄Cl₃Br (M + HCO₂)⁻ 447.9485, found 447.9480.

(1R)-[(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-6,10,12-trichloro-5-methyl-4,13-dioxabicyclo[5.5.1]tridecan-3-yl]prop-2-yn-1-ol (362)

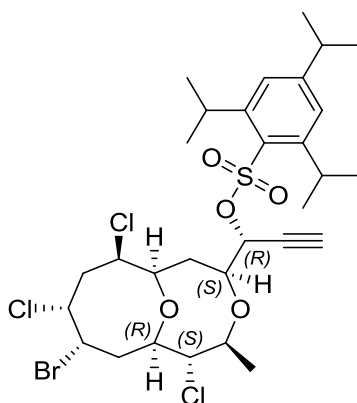


To a stirred solution of nitrile **360** (5.0 mg, 0.012 mmol) at in THF (200 μ L) at -78°C was added DIBAL-H in THF (22 μ L, 0.86 M, 0.019 mmol), the colourless solution warmed to room temperature and stirred for 30 min until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The reaction was quenched with a 1M aqueous citric acid solution (2 mL) and stirred for 10 minutes. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), the organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a cloudy oil (7.5 mg). This material was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **361** (7.5 mg) in THF (150 μ L) at 0 °C was added ethynylmagnesium bromide in THF (37 μ L, 0.5 M, 0.019 mmol) and the yellow solution stirred for 30 min until TLC (*n*-hexane : EtOAc 1 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NH₄Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), the organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow oil (5.2 mg). Column chromatography (*n*-hexane : EtOAc 1

: 1) gave title compound **362** (4.2 mg, 0.0097 mmol, 79%, 82 : 18 d.r.) as a colourless oil: R_f 0.52 (*n*-hexane : EtOAc 1 : 1); ^1H NMR (400 MHz, CDCl_3) δ 5.05 – 4.97 (m, 2H, 9-CHCl & CHBr), 4.30 (dd, J = 4.9, 2.2 Hz, 0.82H, CHCOH major product), 4.17 (dd, J = 5.7, 1.7 Hz, 0.18H, CHCOH minor product), 4.11 – 4.08 (m, 1H, 7-CHCl), 4.05 – 3.93 (m, 2H, 12-CHOCHCl & 6-CHOCHCl), 3.85 – 3.74 (m, 2H, CHCH₃ & CHOH), 3.58 (t, J = 9.7 Hz, 1H, 13-CHCl), 3.28 (ddd, J = 16.4, 8.0, 2.0 Hz, 1H, CH₂CHCl), 2.82 (ddd, J = 15.1, 4.7, 1.3 Hz, 1H, CH₂CHBr), 2.65 (ddt, J = 16.4, 5.4, 1.2 Hz, 1H, CH₂CHCl), 2.53 (d, J = 2.2 Hz, 1H, C $\equiv$ CH), 2.37 (ddd, J = 15.2, 10.4, 3.2 Hz, 1H, CH₂CHBr), 2.20 (dt, J = 14.5, 11.2 Hz, 1H, CH₂CHCOH), 1.76 – 1.67 (m, 1H, CH₂CHCOH), 1.54 (d, J = 6.1 Hz, 1H, CH₃); ^{13}C NMR (101 MHz, CDCl_3) δ 86.8 (CHCH₃), 86.2 (CHOH), 85.2 (6-CHOCHCl), 84.0 (12-CHOCHCl), 75.3 (C $\equiv$ CH), 74.8 (C $\equiv$ CH), 68.2 (CHCOH), 63.5 (7-CHCl), 63.0 (9-CHCl), 63.0 (13-CHCl), 60.1 (CHBr), 45.3 (CH₂CHCl), 44.3 (CH₂CHBr), 38.8 (CH₂CHCOH), 22.1 (CH₃).

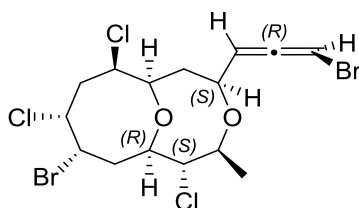
(1R)-1-[(1R,3S,5S,6S,7R,9S,10R,12R)-9-Bromo-6,10,12-trichloro-5-methyl-4,13-dioxabicyclo[5.5.1]tridecan-3-yl]prop-2-yn-1-yl 2,4,6-tris(isopropyl)benzene-1-sulfonate
(**363**)



To a stirred solution of alcohol **362** (2.5 mg, 0.0061 mmol, 82 : 18 d.r.) in CH_2Cl_2 (100 μL) was added a solution of 2,4,6-tris(isopropyl)benzenesulfonyl chloride and DMAP in CH_2Cl_2 (100

μL , 0.061 M, 0.0061 mmol of each). The colourless solution was stirred for 17 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (6.2 mg). Column chromatography (*n*-hexane : EtOAc 25 : 1) gave title compound **363** (3.0 mg, 0.0043 mmol, 70%, 82 : 18 d.r.) as a white solid: R_f 0.43 (*n*-hexane : EtOAc 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 7.20 (s, 2H, Ar-*H*), 5.04 (dd, J = 6.2, 2.3 Hz, 0.18H, CHOTris minor product), 5.02 – 4.96 (m, 2.72H, 9-CHCl, CHBr & CHOTris major product), 4.14 (hept, J = 6.5 Hz, 2H, $\text{CH}(\text{CH}_3)_2$), 4.06 (dt, J = 5.3, 1.9 Hz, 1H, 7-CHCl), 4.03 – 4.00 (m, 1H, CHCOTris), 3.99 – 3.96 (m, 1H, 12-CHOCHCl), 3.93 (dt, J = 11.1, 1.6 Hz, 1H, 6-CHOCHCl), 3.78 (q, J = 6.1 Hz, 0.18H, CHCH_3 minor product), 3.75 (q, J = 6.1 Hz, 0.82H, CHCH_3 major product), 3.54 (t, J = 9.7 Hz, 0.20H, 13-CHCl minor product), 3.52 (t, J = 9.7 Hz, 0.80H, 13-CHCl major product), 3.26 (ddd, J = 16.3, 8.3, 2.1 Hz, 1H, CH_2CHCl), 2.94 (hept, J = 6.8 Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 2.80 (ddd, J = 15.1, 4.8, 1.5 Hz, 1H, CH_2CHBr), 2.64 (ddt, J = 16.2, 5.3, 1.0 Hz, 1H, CH_2CHCl), 2.35 (ddd, J = 15.1, 10.4, 2.9 Hz, 1H, CH_2CHBr), 2.33 (d, J = 2.2 Hz, 0.79H, $\text{C}\equiv\text{CH}$ major product), 2.30 (d, J = 2.2 Hz, 0.18H, $\text{C}\equiv\text{CH}$ minor product), 2.17 (dt, J = 14.3, 11.1 Hz, 1H, $\text{CH}_2\text{CHCOTris}$), 1.70 – 1.61 (m, 1H, $\text{CH}_2\text{CHCOTris}$), 1.50 (d, J = 6.1 Hz, 0.54H, CH_3 minor product), 1.45 (d, J = 6.1 Hz, 2.55H, CH_3 major product), 1.33 – 1.26 (m, 18H, $3 \times \text{CH}(\text{CH}_3)_2$); ^{13}C NMR (101 MHz, CDCl_3) δ 156.0 (*para*Ar), 150.9 (*ortho*Ar), 123.7 (*meta*Ar), 110.0 (*ipso*Ar), 85.9 (CHCOTris), 85.3 (CHBr), 84.4 (CHCH_3), 83.8 (6-CHOCHCl), 77.2 ($\text{C}\equiv\text{CH}$), 76.3 ($\text{C}\equiv\text{CH}$), 71.6 (CHOTris), 63.3 (13-CHCl), 63.0 (9-CHCl), 62.9 (12-CHOCHCl), 60.7 (7-CHCl), 45.5 (CH_2CHCl), 40.2 (CH_2CHBr), 34.6 ($\text{CH}_2\text{CHCOTris}$), 34.3 ($\text{CH}(\text{CH}_3)_2$), 33.2 ($\text{CH}(\text{CH}_3)_2$), 24.8 ($\text{CH}(\text{CH}_3)_2$), 24.7 ($\text{CH}(\text{CH}_3)_2$), 23.6 ($\text{CH}(\text{CH}_3)_2$), 21.5 (CH_3).

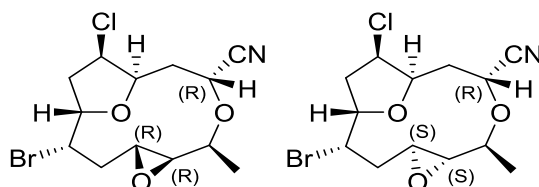
(1R,2S,3S,5S,7R,8R,10R,11S)-11-Bromo-5-[(R_a)-3-bromopropa-1,2-dien-1-yl]-2,8,10-trichloro-3-methyl-4,13-dioxabicyclo[5.5.1]tridecane, marilzabicycloallene D (7)



LiBr (25 mg, 0.29 mmol) and CuBr (42 mg, 0.29 mmol) were dissolved in CH₂Cl₂ (1.0 mL). The mixture was stirred at room temperature for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of trisylate **363** (3.0 mg, 0.0043 mmols, 82 : 18 d.r.) in CH₂Cl₂ (100 µL) was added the LiCuBr₂ solution (80 µL, 0.29 M, 0.023 mmol). The green solution stirred for 1h at room temperature then heated to 60 °C for 2 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give title compound **7** white solid (2.0 mg, 0.0040 mmol, 93%, 82 : 18 d.r.) as a white solid: R_f 0.63 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 6.10 (dd, *J* = 5.7, 2.2 Hz, 0.11H, HCBr minor bromoallene), 6.07 (dd, *J* = 5.7, 2.1 Hz, 0.52H, HCBr major bromoallene), 5.43 (t, *J* = 5.5 Hz, 0.61H, HC=CBrH major bromoallene), 5.38 (t, *J* = 5.3 Hz, 0.15H, HC=CBrH minor bromoallene), 5.01 (d, *J* = 7.7 Hz, 1H, 9-CHCl), 4.96 (dd, *J* = 4.3, 3.0 Hz, 1H, CHBr), 4.35 (ddt, *J* = 11.2, 5.5, 2.1 Hz, 1H, CHCH=CBr), 4.06 (dt, *J* = 5.2, 1.9 Hz, 1H, 7-CHCl), 3.97 (dd, *J* = 10.3, 9.8, 1.2 Hz, 1H, 12-CHOCHCl), 3.93 (dt, *J* = 11.0, 1.9 Hz, 1H, 6-CHOCHCl), 3.75 (dq, *J* = 9.8, 6.1 Hz, 1H, CHCH₃), 3.51 (t, *J* = 9.7 Hz, 1H, 13-CHCl), 3.25 (ddd, *J* = 16.4, 7.9, 2.0 Hz, 1H, CH₂CHCl), 2.79 (ddd, *J* = 15.2, 4.5, 1.3 Hz, 1H, CH₂CHBr), 2.62 (ddt, *J* = 16.3, 5.6, 1.1 Hz, 1H, CH₂CHCl), 2.35 (ddd, *J* = 15.2, 10.4, 3.3 Hz, 1H, CH₂CHBr), 2.18 (dt, *J* = 14.5, 11.1 Hz, 1H, CH₂CHCN), 1.52 – 1.48 (m, 1H, CH₂CHCN), 1.47 (d, *J* = 6.2 Hz, 0.57H, CH₃ minor product),

1.46 (d, $J = 6.1$ Hz, 2.51H, CH_3 major product); ^{13}C NMR (126 MHz, CDCl_3) δ 200.9 ($\text{CH}=\text{C}=\text{CHBr}$), 102.7 ($\text{CH}=\text{C}=\text{CHBr}$), 86.1 (6- CHOCHCl), 85.0 (CHCH_3), 84.3 (12- CHOCHCl), 81.1 ($\text{CHCH}=\text{C}=\text{CHBr}$), 74.3 ($\text{CH}=\text{C}=\text{CHBr}$), 63.4 (7- CHCl), 63.0 (13- CHCl), 62.9 (CHBr), 60.1 (9- CHCl), 45.2 (CH_2CHCl), 44.1 (CH_2CHBr), 38.3 ($\text{CH}_2\text{CHCH}=\text{C}=\text{CHBr}$), 22.4 (CH_3); HRMS (ES^+ , TOF) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{O}_2\text{Cl}_2\text{Br}_2$ ($\text{M} - \text{Cl}$) $^+$ 458.9129, found 459.9131; with 8% of the mass believed to be the corresponding propargylic bromides in a 1 : 1 d.r., calculated by comparison to the integral of the alkyne protons. The observable peaks are given here: ^1H NMR (400 MHz, CDCl_3) δ 2.70 (d, $J = 2.5$ Hz, 0.05H), 2.68 (d, $J = 2.4$ Hz, 0.05H).

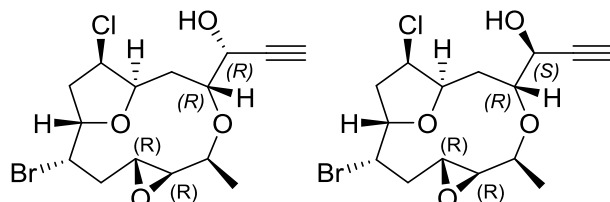
(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane-9-carbonitrile (364) and (1S,2S,4S,6S,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane-9-carbonitrile (365)



To a solution of *E*-macrocycle **182** (25.0 mg, 0.0747 mmol) in CH_2Cl_2 (830 μL) was added mCPBA (25.8 mg, 75%, 0.112 mmol). The colourless solution was stirred for 2 h until TLC (*n*-hexane : Et_2O 2 : 1) showed completion of the reaction. The reaction was quenched with 10% Na_2SO_3 (1 mL) and stirred for an additional 5 min. The mixture was extracted with CH_2Cl_2 (3 $\times$ 3 mL), the organic layers washed with sat. aq. NaHCO_3 (2 $\times$ 5 mL), dried over Na_2SO_4 , filtered and the solvent removed *in vacuo* to give a cloudy oil (37.8 mg). Column chromatography (*n*-hexane : Et_2O 2 : 1) gave major epoxide **364** (19.0 mg, 0.0542 mmol, 73%) as a colourless oil: R_f 0.17 (*n*-hexane : EtOAc 2 : 1); IR 2926, 1681, 1262, 1090, 927 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.76 (dt, $J = 9.8, 6.3$ Hz, 1H, CHOCHBr), 4.60 (dd, $J = 10.3, 3.1$ Hz,

^1H , CHCN), 4.63 – 4.56 (m, 1H, CHCH_3), 4.47 (ddd, $J = 13.0, 6.0, 3.2$ Hz, 1H, CHBr), 4.43 (ddd, $J = 4.4, 2.4, 1\text{Hz}$, 1H, CHCl), 4.17 (dt, $J = 10.8, 2.6$ Hz, 1H, CHOCHCl), 3.13 (dd, $J = 8.7, 2.1$ Hz, 1H, CH_2CHO), 3.00 (dd, $J = 3.6, 2.2$ Hz, 1H, CHCH_3CHO), 2.63 (dd, $J = 15.1, 3.0$ Hz, 1H, CH_2CHBr), 2.52 (dd, $J = 14.5, 6.8$ Hz, 1H, CH_2CHCl), 2.43 (ddd, $J = 14.4, 9.8, 4.4$ Hz, 1H, CH_2CHCl), 2.09 (ddd, $J = 10.6, 6.4, 2.9$ Hz, 2H, CH_2CHCN), 1.86 (ddd, $J = 15.1, 12.5, 8.6$ Hz, 1H, CH_2CHBr), 1.17 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 119.1 (CN), 77.8 (CHClCHO), 77.7 (CHBrCHO), 73.2 (CHCH_3), 61.0 (CHCl), 60.3 (CHCH_3CHO), 58.1 (CHCN), 53.6 (CH_2CHO), 46.3 (CHBr), 39.2 (CH_2CHCl), 36.6 (CH_2CHCN), 35.5 (CH_2CHBr), 9.9 (CH_3); HRMS (ES^+ , TOF) m/z calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3^{35}\text{Cl}^{79}\text{Br}$ ($\text{M} + \text{H}$) $^+$ 350.0153, found 350.0152; and minor epoxide **365** (6.8 mg, 0.0194 mmol, 26%) as a colourless oil: R_f 0.16 (n -hexane : EtOAc 2 : 1); IR 2926, 1671, 1263, 1087, 948 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.65 (dd, $J = 11.4, 3.4$ Hz, 1H, CHCN), 4.58 (dd, $J = 6.3, 3.4$ Hz, 1H, CHCl), 4.54 – 4.45 (m, 2H, CHOCHCl & CHOCHBr), 4.31 (ddd, $J = 7.2, 3.1, 1.6$ Hz, 1H, CHBr), 3.48 – 3.38 (m, 2H, CHCH_3 & CH_2CHO), 3.04 (dd, $J = 8.7, 2.1$ Hz, 1H, CHCH_3CHO), 2.99 (dt, $J = 14.7, 6.3$ Hz, 1H, CH_2CHCl), 2.78 (ddd, $J = 14.5, 7.2, 2.5$ Hz, 1H, CH_2CHBr), 2.54 (ddd, $J = 14.8, 7.7, 1.2$ Hz, 1H, CH_2CHCl), 2.34 (ddd, $J = 13.6, 9.9, 3.3$ Hz, 1H, CH_2CHCN), 2.14 (ddd, $J = 14.1, 11.4, 4.4$ Hz, 1H, CH_2CHCN), 1.75 (ddd, $J = 14.6, 8.3, 1.6$ Hz, 1H, CH_2CHBr), 1.59 (d, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 125.5 (CN), 79.4 (CHBrCHO), 78.3 (CHCH_3), 76.4 (CHClCHO), 62.0 (CHCl), 61.1 (CHCH_3CHO), 59.8 (CHCN), 57.3 (CH_2CHO), 54.3 (CHBr), 43.0 (CH_2CHCl), 36.9 (CH_2CHCN), 35.1 (CH_2CHBr), 17.2 (CH_3); HRMS (ES^+ , TOF) m/z calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3^{35}\text{Cl}^{79}\text{Br}$ ($\text{M} + \text{H}$) $^+$ 350.0153, found 350.0147.

(1R)-1-[(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (367) and (1S)-1-[(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (368)

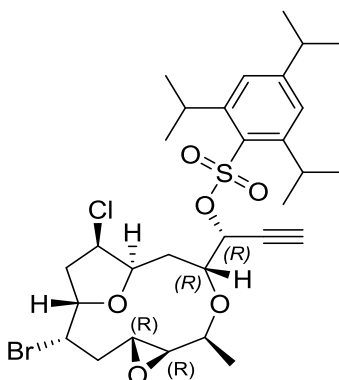


To a stirred solution of nitrile **364** (6.8 mg, 0.019 mmol) at in THF (300 μ L) at -78 $^{\circ}$ C was added DIBAL-H in THF (34 μ L, 0.86 M, 0.029 mmol) and the colourless solution warmed to 0 $^{\circ}$ C and stirred for 30 min until TLC (toluene : MeCN 9 : 1) showed completion of the reaction. The reaction was quenched with a 1M aqueous citric acid solution (1 mL) and stirred for 15 minutes. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), the organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a white solid (6.8 mg). This material was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **366** (6.8 mg) in THF (200 μ L) at 0 $^{\circ}$ C was added ethynylmagnesium bromide in THF (57 μ L, 0.5 M, 0.029 mmol) and the yellow solution stirred for 30 min until TLC (*n*-hexane : EtOAc 1 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NH₄Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH₂Cl₂ (3 $\times$ 3 mL), the organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow oil (10.8 mg). Column chromatography (*n*-hexane : EtOAc 2 : 1) gave compound **367** (1.8, 0.0047 mg, 25%) as a colourless oil: R_f 0.12 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 4.78 (dt, *J* = 9.6, 6.5 Hz, 1H, CHOCHBr), 4.56 (qd, *J* = 7.2, 3.2 Hz, 1H, CHCH₃), 4.49 (ddd, *J* = 12.8, 5.7, 2.9 Hz, 1H, CHBr), 4.43 (dd, *J* = 4.2, 2.4 Hz, 1H,

CHCl), 4.28 – 4.22 (m, 2H, CHOH & CHOCHCl), 3.96 (ddd, $J = 11.2, 4.7, 1.8$ Hz, 1H, CHCOH), 3.14 (dd, $J = 8.8, 2.2$ Hz, 1H, CH₂CHO), 3.09 (t, $J = 3.2, 2.3$ Hz, 1H, CHCH₃CHO), 2.63 (dd, $J = 14.9, 2.9$ Hz, 1H, CH₂CHBr), 2.51 (d, $J = 2.2$ Hz, 1H, C≡CH), 2.50 (dd, $J = 11.8, 6.9$ Hz, 1H, CH₂CHCl), 2.43 (td, $J = 9.8, 4.8$ Hz, 1H, CH₂CHCl), 2.23 (d, $J = 6.0$ Hz, 1H, OH), 2.02 (ddd, $J = 13.5, 10.8, 1.9$ Hz, 1H, CH₂CHCOH), 1.89 (ddd, $J = 15.4, 12.9, 9.1$ Hz, 1H, CH₂CHBr), 1.80 (ddd, $J = 13.7, 11.2, 2.1$ Hz, 1H, CH₂CHCOH), 1.12 (d, $J = 7.1$ Hz, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 82.3 (C≡CH), 78.8 (CHClCHO), 78.0 (CHBrCHO), 74.7 (C≡CH), 72.3 (CHCH₃), 70.3 (CHCOH), 65.6 (CHOH), 62.5 (CHCl), 61.5 (CHCH₃CHO), 54.3 (CH₂CHO), 46.9 (CHBr), 38.8 (CH₂CHCl), 35.4 (CH₂CHBr), 33.1 (CH₂CHCOH), 10.5 (CH₃); and compound **368** (1.9 mg, 0.0050 mmol, 26%) as a colourless oil: R_f 0.07 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 4.78 (dt, $J = 9.7, 6.3$ Hz, 1H, CHOCHBr), 4.58 (qd, $J = 7.3, 3.3$ Hz, 1H, CHCH₃), 4.49 (ddd, $J = 12.6, 5.6, 2.9$ Hz, 1H, CHBr), 4.43 (dd, $J = 4.3, 2.1$ Hz, 1H, CHCl), 4.38 (ddd, $J = 5.4, 3.1, 2.3$ Hz, 1H, CHOH), 4.24 (dt, $J = 10.9, 2.2$ Hz, 1H, CHOCHCl), 4.01 (dt, $J = 11.3, 2.6$ Hz, 1H, CHCOH), 3.14 (dd, $J = 8.8, 2.2$ Hz, 1H, CH₂CHO), 3.09 (dd, $J = 3.3, 2.3$ Hz, 1H, CHCH₃CHO), 2.63 (dd, $J = 14.9, 2.9$ Hz, 1H, CH₂CHBr), 2.54 (d, $J = 2.2$ Hz, 1H, C≡CH), 2.50 (dd, $J = 14.4, 6.8$ Hz, 1H, CH₂CHCl), 2.43 (ddd, $J = 14.3, 9.6, 4.4$ Hz, 1H, CH₂CHCl), 2.24 (d, $J = 5.5$ Hz, 1H, OH), 1.99 (ddd, $J = 14.2, 10.9, 1.9$ Hz, 1H, CH₂CHCOH), 1.92 – 1.81 (m, 2H, CH₂CHBr & CH₂CHCOH), 1.08 (d, $J = 7.1$ Hz, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 81.1 (C≡CH), 79.0 (CHClCHO), 78.0 (CHBrCHO), 75.3 (C≡CH), 72.3 (CHCH₃), 70.6 (CHCOH), 66.0 (CHOH), 62.4 (CHCl), 61.5 (CHCH₃CHO), 54.2 (CH₂CHO), 46.9 (CHBr), 38.9 (CH₂CHCl), 35.4 (CH₂CHBr), 32.1 (CH₂CHCOH), 10.5 (CH₃); HRMS (ES⁺, TOF) m/z calcd for C₁₅H₂₁O₄³⁵Cl⁷⁹Br (M + H)⁺ 379.0312, found 379.0316;

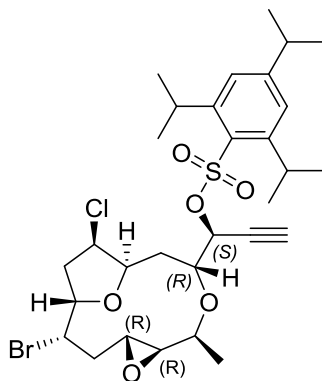
(1R)-1-[(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-yl 2,4,6-tris(isopropyl)benzene-1-sulfonate (369)



To a sample tube containing alcohol **367** (4.6 mg, 0.012 mmol) was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride and DMAP in CH₂Cl₂ (400 μL, 0.038 M, 0.015 mmol of each). The colourless solution was stirred for 20 h, a further aliquot of 2,4,6-triisopropylbenzenesulfonyl chloride and DMAP in CH₂Cl₂ (200 μL, 0.038 M, 0.0076 mmol of each) and stirring resumed for 4 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (12.6 mg). Column chromatography (*n*-hexane : EtOAc 7 : 1) gave title compound **369** (7.2 mg, 0.011 mmol, 92%) as a white solid: *R*_f 0.50 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 7.17 (s, 2H, ArH), 5.04 (dd, *J* = 4.9, 2.2 Hz, 1H, CHOTris), 4.75 (dt, *J* = 9.7, 6.5 Hz, 1H, CHOCHBr), 4.54 (qd, *J* = 7.1, 3.4 Hz, 1H, CHCH₃), 4.47 (ddd, *J* = 12.7, 5.7, 2.9 Hz, 1H, CHBr), 4.40 (dd, *J* = 3.9, 2.3 Hz, 1H, CHCl), 4.22 (dt, *J* = 11.1, 2.2 Hz, 1H, CHOCHCl), 4.16 – 4.07 (m, 3H, CH(CH₃)₂ & CHCOTris), 3.11 (dd, *J* = 8.8, 2.2 Hz, 1H, CH₂CHO), 3.03 (dd, *J* = 3.5, 2.2 Hz, 1H, CHCH₃CHO), 2.91 (hept, *J* = 6.8 Hz, 1H, CH(CH₃)₂), 2.62 (dd, *J* = 14.9, 2.9 Hz, 1H, CH₂CHBr), 2.49 (dd, *J* = 14.4, 6.9 Hz, 1H, CH₂CHCl), 2.41 (ddd, *J* = 14.3, 9.7, 4.4 Hz, 1H, CH₂CHCl), 2.32

(d, $J = 2.2$ Hz, 1H, $\text{C}\equiv\text{CH}$), 2.02 (ddd, $J = 13.0, 11.0, 1.7$ Hz, 1H, $\text{CH}_2\text{CHCOTris}$), 1.86 (td, $J = 14.9, 12.9, 8.9$ Hz, 1H, CH_2CHBr), 1.80 (ddd, $J = 14.3, 11.3, 1.8$ Hz, 1H, $\text{CH}_2\text{CHCOTris}$), 1.34 – 1.19 (m, 18H, $6 \times \text{CH}_3$), 1.04 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 154.0 (*para*Ar), 150.9 (*ortho*Ar), 123.7 (*meta*Ar), 110.0 (*ipso*Ar), 78.6 (CHClCHO), 77.8 (CHBrCHO), 77.2 ($\text{C}\equiv\text{CH}$), 76.5 ($\text{C}\equiv\text{CH}$), 72.6 (CHCH_3), 71.1 (CHOTris), 68.8 (CHCOTris), 62.1 (CHCl), 61.2 (CHCH_3CHO), 54.1 (CH_2CHO), 46.9 (CHBr), 38.9 (CH_2CHCl), 35.5 (CH_2CHBr), 34.3 ($\text{CH}(\text{CH}_3)_2$), 32.1 ($\text{CH}_2\text{CHCOTris}$), 29.7 ($\text{CH}(\text{CH}_3)_2$), 24.7 ($\text{CH}(\text{CH}_3)_2$), 24.7 ($\text{CH}(\text{CH}_3)_2$), 23.6 ($\text{CH}(\text{CH}_3)_2$), 9.8 (CH_3).

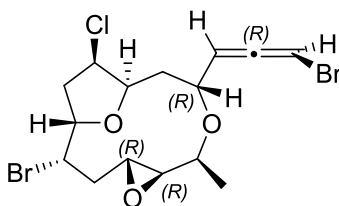
(1S)-1-[(1S,2S,4R,6R,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-yl 2,4,6-tris(isopropyl)benzene-1-sulfonate (370)



To a sample tube containing alcohol **368** (5.0 mg, 0.013 mmol) was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride and DMAP in CH_2Cl_2 (440 μL , 0.038 M, 0.017 mmol of each). The colourless solution was stirred for 20 h, a further aliquot of 2,4,6-triisopropylbenzenesulfonyl chloride and DMAP in CH_2Cl_2 (200 μL , 0.038 M, 0.0076 mmol of each) and stirring resumed for 4 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc

2 : 1. The solvent was removed *in vacuo* to give a white solid (12.6 mg). Column chromatography (*n*-hexane : EtOAc 7 : 1) gave title compound **370** (5.5 mg, 0.0085 mmol, 65%) as a white solid: *R*_f 0.58 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 7.16 (s, 2H, *ArH*), 5.07 (t, *J* = 2.5 Hz, 1H, *CHOTris*), 4.76 (dt, *J* = 9.7, 6.3 Hz, 1H, *CHOCHBr*), 4.51 – 4.44 (m, 2H, *CHCH*₃ & *CHBr*), 4.39 (dd, *J* = 4.1, 2.2 Hz, 1H, *CHCl*), 4.22 (dt, *J* = 11.0, 2.2 Hz, 1H, *CHOCHCl*), 4.18 – 4.10 (m, 3H, *CH(CH*₃)₂ & *CHCOTris*), 3.11 (dd, *J* = 8.8, 2.2 Hz, 1H, *CH₂CHO*), 3.04 (dd, *J* = 3.1, 2.3 Hz, 1H, *CHCH₃CHO*), 2.90 (hept, *J* = 7.3 Hz, 1H, *CH(CH*₃)₂), 2.62 (dd, *J* = 14.8, 2.9 Hz, 1H, *CH₂CHBr*), 2.49 (dd, *J* = 14.5, 6.9 Hz, 1H, *CH₂CHCl*), 2.42 (ddd, *J* = 14.3, 9.6, 4.4 Hz, 1H, *CH₂CHCl*), 2.32 (d, *J* = 2.3 Hz, 1H, *C≡CH*), 1.93 (ddd, *J* = 12.6, 10.8, 1.7 Hz, 1H *CH₂CHCOTris*), 1.87 (ddd, *J* = 14.7, 9.2, 3.6 Hz, 1H), 1.80 (ddd, *J* = 13.6, 10.1, 2.0 Hz, 2H, *CH₂CHBr*), 1.32 – 1.21 (m, 18H, 6 × *CH*₃), 1.06 (d, *J* = 7.0 Hz, 3H, *CH*₃); ¹³C NMR (101 MHz, CDCl₃) δ 153.9 (*paraAr*), 150.8 (*orthoAr*), 123.6 (*metaAr*), 110.0 (*ipsoAr*), 78.6 (*CHClCHO*), 78.0 (*C≡CH*), 77.9 (*CHBrCHO*), 77.2 (*C≡CH*), 72.9 (*CHCH*₃), 72.4 (*CHOTris*), 69.9 (*CHCOTris*), 62.2 (*CHCl*), 61.4 (*CHCH₃CHO*), 54.1 (*CH₂CHO*), 46.8 (*CHBr*), 38.9 (*CH₂CHCl*), 35.4 (*CH₂CHBr*), 34.3 (*CH(CH*₃)₂), 32.9 (*CH₂CHCOTris*), 29.7 (*CH(CH*₃)₂), 24.8 (*CH(CH*₃)₂), 24.6 (*CH(CH*₃)₂), 23.6 (*CH(CH*₃)₂), 23.6 (*CH(CH*₃)₂), 10.2 (*CH*₃); HRMS (ES⁺, TOF) *m/z* calcd for C₃₀H₄₃O₆S³⁵Cl⁷⁹Br (M + H)⁺ 645.1652, found 645.1659.

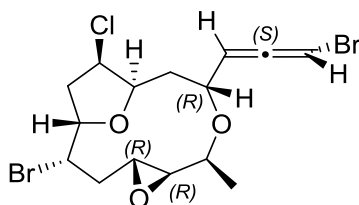
(1*S*,2*S*,4*R*,6*R*,7*S*,9*R*,11*R*,12*R*)-2-Bromo-9-[(*R_a*)-3-bromopropa-1,2-dien-1-yl]-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane (371)



LiBr (11.4 mg, 0.131 mmol) and CuBr (18.8 mg, 0.131 mmol) were dissolved in CH₂Cl₂ (1.20 mL). The mixture was stirred at room temperature for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of trisylate **369** (7.0 mg, 0.011 mmol) in CH₂Cl₂ (300 μL) was added the LiCuBr₂ solution (300 μL, 0.109 M, 0.0327 mmol). The green solution was heated to 60 °C and stirred for 4 h, until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (4.2 mg). Column chromatography (toluene) gave title compound **371** (2.8 mg, 0.0063 mmol, 58%, 95 : 5 d.r.) as a white solid: *R_f* 0.52 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 6.10 (dd, *J* = 5.7, 2.2 Hz, 1H, HC=CBrH), 5.39 (dd, *J* = 5.7, 4.8 Hz, 1H, HC=CBrH), 4.76 (dt, *J* = 9.6, 6.3 Hz, 1H, CHOCHBr), 4.55 (dd, *J* = 6.8, 3.4 Hz, 1H, CHCH₃), 4.51 – 4.47 (m, 1H, CHBr), 4.45 (dt, *J* = 4.5, 2.1 Hz, 1H, CHCH=CCHBr), 4.42 (dd, *J* = 3.5, 2.4 Hz, 1H, CHCl), 4.27 (dt, *J* = 10.8, 2.2 Hz, 1H, CHOCHCl), 3.17 (dd, *J* = 8.7, 2.2 Hz, 1H, CH₂CHO), 3.04 (dd, *J* = 3.7, 2.3 Hz, 1H, CHCH₃CHO), 2.64 (dd, *J* = 14.9, 3.0 Hz, 1H, CH₂CHBr), 2.49 (dd, *J* = 14.4, 7.0 Hz, 1H, CH₂CHCl), 2.43 (ddd, *J* = 14.2, 9.6, 4.3 Hz, 1H, CH₂CHCl), 1.95 – 1.84 (m, 2H, CH₂CHCH=CCHBr & CH₂CHBr), 1.71 (ddd, *J* = 13.9, 11.2, 2.0 Hz, 1H, CH₂CHCH=CCHBr), 1.07 (d, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 200.2 (CH=C=CHBr), 104.3 (CH=C=CHBr), 79.0 (CHClCHO), 77.7 (CHBrCHO), 74.6 (CH=C=CHBr), 72.1 (CHCH₃), 65.7

(CHCH=C=CHBr), 62.0 (CHCl), 61.5 (CHCH₃CHO), 53.9 (CH₂CHO), 46.9 (CHBr), 39.0 (CH₂CHCl), 37.6 (CH₂CHCH=C=CHBr), 35.7 (CH₂CHBr), 9.9 (CH₃); HRMS (ES⁺, TOF) *m/z* calcd for C₁₅H₂₀O₃³⁵Cl⁷⁹Br₂ (M + H)⁺ 440.9468, found 440.9476; with 8% of the mass believed to be the corresponding propargylic bromides in a 2 : 1 d.r., calculated by comparison of the integral of the methyl protons. The observable peaks are given here: ¹H NMR (400 MHz, CDCl₃) δ 2.75 (d, *J* = 2.5 Hz, 0.03H, C≡CH minor propargylic bromide), 2.68 (d, *J* = 2.4 Hz, 0.06H, C≡CH major propargylic bromide), 1.09 (d, *J* = 6.8 Hz, 0.32H, CH₃); There was insufficient material to record a melting point or rotation to compare with the literature values.

(1*S*,2*S*,4*R*,6*R*,7*S*,9*R*,11*R*,12*R*)-2-Bromo-9-[(*S*_a)-3-bromopropa-1,2-dien-1-yl]-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecane, 12-epoxyobtusallene IV (8)

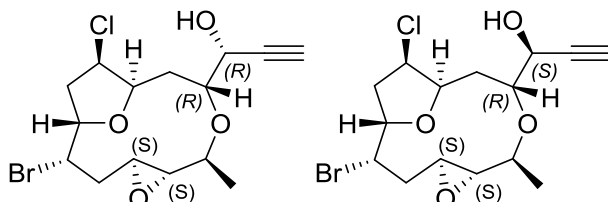


LiBr (11.4 mg, 0.131 mmol) and CuBr (18.8 mg, 0.131 mmol) were dissolved in CH₂Cl₂ (1.20 mL). The mixture was stirred at room temperature for 1 h, during which time the salts dissolved and turned bright green. To a stirred solution of trisylate **370** (5.5 mg, 0.0085 mmol) in CH₂Cl₂ (300 μL) was added the LiCuBr₂ solution (235 μL, 0.109 M, 0.0256 mmol). The green solution was heated to 60 °C and stirred for 2.5 h, until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (3.3 mg). Column chromatography (toluene) gave title compound **8** (3.8 mg, 0.0085 mmol,

quant. , 94 : 6 d.r.) as a white solid: R_f 0.52 (*n*-hexane : EtOAc 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 6.04 (dd, J = 5.7, 1.7 Hz, 1H, $\text{HC}=\text{CBrH}$), 5.37 (dd, J = 6.5, 5.7 Hz, 1H, $\text{HC}=\text{CBrH}$), 4.76 (dt, J = 9.7, 6.3 Hz, 1H, CHOCHBr), 4.54 (qd, J = 6.9, 3.7 Hz, 1H, CHCH_3), 4.49 (ddd, J = 12.7, 5.9, 2.9 Hz, 1H, CHBr), 4.45 (ddt, J = 11.0, 6.4, 1.8, 1.7 Hz, 1H, $\text{CHCH}=\text{CHBr}$), 4.42 (dd, J = 4.0, 2.1 Hz, 1H, CHCl), 4.26 (dt, J = 10.8, 2.2 Hz, 1H, CHOCHCl), 3.18 (dd, J = 8.6, 2.2 Hz, 1H, CH_2CHO), 3.04 (dd, J = 3.7, 2.3 Hz, 1H, CHCH_3CHO), 2.64 (dd, J = 14.9, 3.0 Hz, 1H, CH_2CHBr), 2.48 (dd, J = 14.4, 6.9 Hz, 1H, CH_2CHCl), 2.43 (ddd, J = 14.3, 9.7, 4.3 Hz, 1H, CH_2CHBr), 1.89 (ddd, J = 15.0, 12.7, 8.7 Hz, 1H, $\text{CH}_2\text{CHCH}=\text{CHBr}$), 1.86 (ddd, J = 13.9, 10.5, 2.0 Hz, 1H, CH_2CHBr), 1.74 (ddd, J = 13.8, 11.0, 2.1 Hz, 1H, $\text{CH}_2\text{CHCH}=\text{CHBr}$), 1.08 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 201.0 ($\text{CH}=\text{C}=\text{CHBr}$), 103.3 ($\text{CH}=\text{C}=\text{CHBr}$), 78.9 (CHClCHO), 77.7 (CHBrCHO), 73.9 ($\text{CH}=\text{C}=\text{CHBr}$), 72.1 (CHCH_3), 66.4 ($\text{CHCH}=\text{C}=\text{CHBr}$), 62.0 (CHCl), 61.5 (CHCH_3CHO), 53.9 (CH_2CHO), 46.9 (CHBr), 39.0 (CH_2CHCl), 37.7 ($\text{CH}_2\text{CHCH}=\text{C}=\text{CHBr}$), 35.7 (CH_2CHBr), 10.2 (CH_3); HRMS (ES^+ , TOF) m/z calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3^{35}\text{Cl}^{79}\text{Br}_2$ ($\text{M} + \text{H}$) $^+$ 440.9468, found 440.9464. with 8% of the mass believed to be the corresponding propargylic bromides in a 2 : 1 d.r., calculated by comparison of the integral of the methyl protons. The observable peaks are given here: ^1H NMR (400 MHz, CDCl_3) δ 2.75 (d, J = 2.5 Hz, 0.06H), 2.68 (d, J = 2.4 Hz, 0.03H). There was insufficient material to record a melting point or rotation to compare with the literature values.

(1R)-1-[(1S,2S,4S,6S,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (384) &

(1S)-1-[(1S,2S,4S,6S,7S,9R,11R,12R)-2-bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-ol (385)



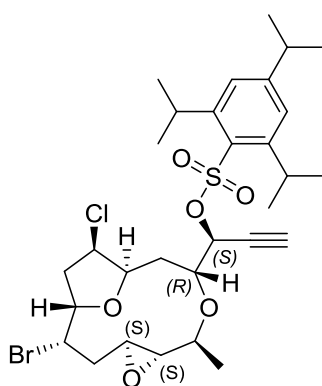
To a stirred solution of nitrile **365** (7.2 mg, 0.021 mmol) at in THF (300 μ L) at -78°C was added DIBAL-H in THF (36 μ L, 0.86 M, 0.0308 mmol) and the colourless solution warmed to -40°C . After 30 min, a further aliquot of DIBAL-H in THF (36 μ L, 0.86 M, 0.0308 mmol) was added and stirred for an additional 30 min until TLC (toluene : acetonitrile 9 : 1) showed completion of the reaction. The reaction was quenched with a 1M aqueous citric acid solution (1 mL) and stirred for 15 minutes. The mixture was extracted with CH_2Cl_2 (3×3 mL), the organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a white solid (8.8 mg). This material was carried through to the next step without further purification.

To a stirred solution of crude aldehyde **383** (14.0 mg) in THF (300 μ L) at 0°C was added ethynylmagnesium bromide in THF (117 μ L, 0.5 M, 0.0585 mmol) and the yellow solution stirred for 30 min until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NH_4Cl (1 mL) and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3×3 mL), the organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow oil (6.2 mg). ^1H NMR showed the presence of two alkynes in 1 : 1 ratio. Careful column chromatography (*n*-hexane : EtOAc 3 : 1) gave compound **384**

(2.2 mg, 0.0058 mmol, 28%) as a colourless oil: R_f 0.09 (*n*-hexane : EtOAc 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 4.66 (ddd, J = 8.0, 6.1, 3.8 Hz, 1H, CHOCHBr), 4.57 (ddd, J = 6.1, 3.1, 1.1 Hz, 1H, CHCl), 4.51 – 4.46 (m, 1H, CHOH), 4.38 (dt, J = 10.7, 3.1 Hz, 1H, CHOCHCl), 4.25 (ddd, J = 10.2, 3.8, 1.9 Hz, 1H, CHBr), 4.03 (ddd, J = 11.3, 4.6, 3.2 Hz, 1H, CHCOH), 3.43 (d, J = 2.2 Hz, 1H,), 3.41 (d, J = 2.2 Hz, 1H, CH_2CHO), 3.34 (dq, J = 8.7, 6.4 Hz, 1H, CHCH_3), 3.17 (td, J = 4.1, 2.2 Hz, 1H, CHCH_3CHO), 2.83 (dt, J = 14.8, 6.2 Hz, 1H, CH_2CHCl), 2.66 (ddd, J = 15.6, 10.1, 3.7 Hz, 1H, CH_2CHBr), 2.54 (ddd, J = 15.0, 7.9, 1.2 Hz, 1H, CH_2CHCl), 2.52 (d, J = 2.2 Hz, 1H, $\text{C}\equiv\text{CH}$), 2.23 (ddd, J = 16.9, 3.8, 1.6 Hz, 1H, CH_2CHCl), 2.16 (ddd, J = 13.9, 10.8, 3.0 Hz, 1H, CH_2CHCOH), 1.91 (ddd, J = 14.1, 11.3, 2.9 Hz, 1H, CH_2CHCOH), 1.46 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 82.1 ($\text{C}\equiv\text{CH}$), 79.1 (CHClCHO), 78.1 (CHBrCHO), 76.4 (CHCH_3), 75.0 ($\text{C}\equiv\text{CH}$), 71.1 (CHCOH), 65.6 (CHOH), 62.6 (CHCl), 61.9 (CH_2CHO), 60.1 (CHCH_3CHO), 50.1 (CHBr), 40.2 (CH_2CHCl), 34.7 (CH_2CHBr), 31.7 (CH_2CHCOH), 18.1 (CH_3); and compound **385** (2.2 mg, 0.0058 mmol, 28%) as a colourless oil: R_f 0.05 (*n*-hexane : EtOAc 2 : 1); with 31% of the mass believed to be the corresponding marilzabicycloallene core structure; and compound **385** (2.2 mg, 0.0058 mmol, 28%) as a colourless oil: R_f 0.05 (*n*-hexane : EtOAc 2 : 1); ^1H NMR (400 MHz, CDCl_3) δ 4.65 (td, J = 8.0, 6.3, 3.8 Hz, 1H, CHCl), 4.58 (dt, J = 5.4, 2.4 Hz, 2H, CHOCHBr & CHOH), 4.34 (dt, J = 10.7, 3.2 Hz, 1H, CHBr), 4.27 (ddd, J = 9.7, 3.8, 1.9 Hz, 1H, CHOCHCl), 4.10 (dt, J = 11.5, 3.0 Hz, 1H, CHCOH), 3.40 – 3.28 (m, 2H, CHCH_3 & CHCH_3CHO), 3.20 (ddd, J = 5.3, 3.6, 2.0 Hz, 1H, CH_2CHO), 2.86 (dt, J = 15.0, 6.2 Hz, 1H, CH_2CHCl), 2.69 (ddd, J = 15.4, 9.8, 3.6 Hz, 1H, CH_2CHBr), 2.54 (ddd, J = 14.7, 8.0, 1.0 Hz, 1H, CH_2CHCl), 2.54 (d, J = 2.3 Hz, 1H, $\text{C}\equiv\text{CH}$), 2.28 (d, J = 3.4 Hz, 1H, OH), 2.24 – 2.14 (m, 2H, CH_2CHBr & CH_2CHCOH), 1.98 (ddd, J = 14.5, 11.5, 3.0 Hz, 1H, CH_2CHCOH), 1.44 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 80.4 ($\text{C}\equiv\text{CH}$), 79.1 (CHCl), 77.8 (CHBr), 76.4 (CHCH_3), 75.5 ($\text{C}\equiv\text{CH}$), 72.2 (CHCOH), 65.3 (CHOH), 62.7 (CHBrCHO), 60.2

(CHCH₃CHO), 57.4 (CH₂CHO), 50.8 (CHClCHO), 40.7 (CH₂CHCl), 34.9 (CH₂CHBr), 30.0 (CH₂CHCOH), 18.0 (CH₃); with 29% of the mass believed to be the corresponding marilzabicycloallene core structure.

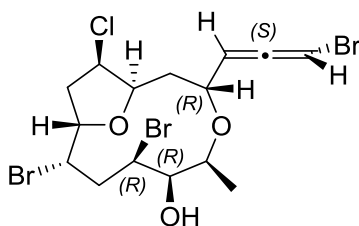
(1S)-1-[(1S,2S,4S,6S,7S,9R,11R,12R)-2-Bromo-12-chloro-7-methyl-5,8,14-trioxatricyclo[9.2.1.0^{4,6}]tetradecan-9-yl]prop-2-yn-1-yl 2,4,6-tris(propan-2-yl)benzene-1-sulfonate (387)



To a sample tube containing alcohol **385** (2.2 mg, 0.0058 mmol) was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride and DMAP in CH₂Cl₂ (200 μL, 0.038 M, 0.0058 mmol of each). The colourless solution was stirred for 20 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The solution was passed through a plug of silica, eluting with *n*-hexane : EtOAc 2 : 1. The solvent was removed *in vacuo* to give a white solid (3.9 mg). Column chromatography (*n*-hexane : EtOAc 10 : 1) gave title compound **387** (3.3 mg, 0.0051 mmol, 89%) as a white solid: *R*_f 0.47 (*n*-hexane : EtOAc 2 : 1); ¹H NMR (400 MHz, CDCl₃) δ 7.16 (s, 2H, ArH), 5.25 (t, *J* = 2.3 Hz, 1H, CHOTris), 4.62 (ddd, *J* = 8.1, 5.7, 3.8 Hz, 1H, CHOCHBr), 4.56 (ddd, *J* = 6.3, 3.2, 0.9 Hz, 1H, CHCl), 4.37 (dt, *J* = 10.6, 3.2 Hz, 1H, CHOCHCl), 4.25 (ddd, *J* = 9.4, 3.6, 1.6 Hz, 1H, CHBr), 4.19 – 4.10 (m, 3H, CHCOTris & CH(CH₃)₂), 3.29 (dd, *J* = 8.7, 2.1 Hz, 1H, CHCH₃CHO), 3.24 (p, *J* = 8.0, 6.3 Hz, 1H, CH(CH₃)₂),

3.18 (dt, $J = 5.4, 3.3$ Hz, 1H, CH_2CHO), 2.90 (hept, $J = 7.1$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 2.87 (dt, $J = 14.9, 6.1$ Hz, 1H, CH_2CHCl), 2.66 (ddd, $J = 15.4, 9.7, 3.6$ Hz, 1H, CH_2CHBr), 2.53 (ddd, $J = 15.0, 8.1, 1.5$ Hz, 1H, CH_2CHCl), 2.40 (d, $J = 2.3$ Hz, 1H, $\text{C}\equiv\text{CH}$), 2.17 (ddd, $J = 13.6, 11.0, 3.2$ Hz, 1H, $\text{CH}_2\text{CHCOTris}$), 2.10 (ddd, $J = 15.3, 5.2, 1.4$ Hz, 1H, CH_2CHBr), 1.91 (ddd, $J = 14.5, 11.6, 3.2$ Hz, 1H, $\text{CH}_2\text{CHCOTris}$), 1.37 (d, $J = 6.5$ Hz, 3H, CH_3), 1.30 – 1.24 (m, 18H, $6 \times \text{CH}_3$); There was insufficient material to record a clear ^{13}C NMR spectrum.

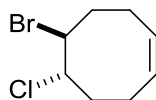
(1R,3R,5S,6R,7R,9S,10S,12R)-7,9-Dibromo-3-[(*S*)-3-bromopropa-1,2-dien-1-yl]-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridecan-6-ol, obtusallene X (9)



To a sample of 12-epoxyobtusallene IV **8** (2.0 mg, 0.0043 mmol) in dichloromethane (200 μL) was added hydrobromic acid in water (0.97 μL , 48%, 0.0086 mmol) and stirred in the dark for 1 h until TLC (*n*-hexane : EtOAc 2 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. NaHCO_3 (1 mL) and stirred for 5 min. The mixture was partitioned between water (1 mL) and CH_2Cl_2 (3 mL), separated and extracted further with CH_2Cl_2 (2×3 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a colourless oil (4.1 mg). Column chromatography (*n*-hexane : EtOAc 6 : 1) gave title compound **9** (2.2 mg, 0.042 mmol, 93%) as a colourless oil: R_f 0.33 (*n*-hexane : EtOAc 2 : 1); ^1H NMR (500 MHz, CDCl_3) δ 6.03 (dd, $J = 5.6, 0.9$ Hz, 1H, HCBBr), 5.73 (dd, $J = 8.9, 5.6$ Hz, 1H, $\text{HC}=\text{CBrH}$), 4.62 – 4.53 (m, 3H, $\text{CHCH}=\text{CHBr}$, CHCl , CHBrCHOH), 4.48 – 4.42 (m, 2H, CHOCHBr , CHBr), 4.39 (dt, $J = 11.3, 5.0, 4.1$ Hz, 1H, CHOCHCl), 4.18 (qd, $J = 6.6,$

3.2 Hz, 1H, CHCH₃), 3.92 (d, *J* = 3.4 Hz, 1H, OH), 3.69 (dd, *J* = 6.5, 3.4 Hz, 1H, CHBrCHOH), 2.87 (dd, *J* = 15.5, 12.1 Hz, 1H, CH₂CHBr), 2.65 (ddd, *J* = 15.3, 9.3, 2.4 Hz, 1H, CH₂CHBr), 2.53 (ddd, *J* = 13.7, 9.6, 7.6 Hz, 1H, CH₂CHCl), 2.37 (ddd, *J* = 14.7, 11.3, 2.1 Hz, 1H, CH₂CHCH=CHBr), 2.25 (ddd, *J* = 13.7, 5.5, 0.9 Hz, 1H, CH₂CHCl), 1.72 (ddd, *J* = 14.8, 7.3, 3.9 Hz, 1H, CH₂CHCH=CHBr), 1.36 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 202.2 (CH=C=CHBr), 100.0 (CH=C=CHBr), 76.5 (CHOH), 76.4 (CHOCHCl), 74.2 (CHOCHBr), 73.5 (CH=C=CHBr), 72.6 (CHCH₃), 70.4 (CHCH=C=CHBr), 59.7 (CHCl), 58.1 (CHBrCOH), 48.5 (CHBr), 43.6 (CH₂CHBr), 41.3 (CH₂CHCl), 35.3 (CH₂CHCH=C=CHBr), 13.0 (CH₃); HRMS (ES⁺, TOF) *m/z* calcd for C₁₅H₂₁O₃³⁵Cl⁷⁹Br₃ (M + H)⁺ 520.8724, found 520.8724.

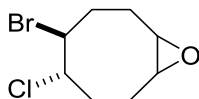
(1*Z*,5*S,6*S**)-5-Bromo-6-chlorocyclooct-1-ene (400)**



According to a modified procedure,²³ to a solution of 1,5-cyclooctadiene (**397**) (882mg, 8.15 mmols) in CH₂Cl₂ (101 mL) was added 1,1,3,3-tetramethylguanidine (10.2 μL, 0.0815 mmols), trimethylsilyl chloride (1.03 mL, 8.15 mmols) and *N*-bromosuccinimide (1.45 g, 8.15 mmols) and the colourless solution stirred at room temperature in the dark for 30 mins, until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was quenched with 20% Na₂SO₃ (50 mL) and stirred for 10 min. The mixture extracted with CH₂Cl₂ (3 × 50 mL) and washed with brine (100 mL). The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow oil (1.87 g). Column chromatography (hexane : EtOAc 25 : 1) gave title compound **400** (1.26 g, 5.63 mmols, 69%) as a colourless oil: *R*_f 0.52 (hexane : EtOAc 1 : 1); IR (neat) 2929.8, 1713.8, 1439.8, 735.4 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.69 – 5.58 (m, 2H), 4.59 – 4.48 (m, 2H), 2.74 – 2.56 (m, 4H), 2.30 – 2.17 (m, 3H), 2.15 – 2.07 (m, 1H);

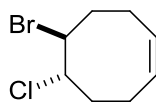
^{13}C NMR (101 MHz, CDCl_3) δ 128.8, 128.2, 66.7, 59.5, 35.0, 34.4, 25.2, 24.1; MS: no mol. ion seen in EI^+ or CI^+ modes.

(4*S,5*S**)-4-Bromo-5-chlorooxabicyclo[6.1.0]nonane (**401**)**



To a sample of olefin **400** (840 mg, 3.76 mmols) in CH_2Cl_2 (9.4 mL) was added *m*CPBA (1.30 g, 75%, 5.64 mmols) and the suspension stirred at room temperature for 30 mins, until TLC (hexane : EtOAc 9 : 1) showed completion of the reaction. The reaction was quenched with 20% Na_2SO_3 (10 mL) and stirred for 10 min. The mixture extracted with CH_2Cl_2 (3×10 mL) and washed with brine (20 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give a white solid (1.05 g). Column chromatography (hexane : EtOAc 9 : 1) gave an inseparable mixture of two epimeric epoxides **401** (833 mg, 3.48 mmols, 92%, 55 : 45 d.r.) as white crystals: R_f 0.22 (hexane : EtOAc 1 : 1); IR (neat) 2928.5, 1717.4, 1438.6, 1024.6, 735.6 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.79 – 4.57 (m, 2H), 3.18 (ddt, J = 16.5, 10.5, 3.9 Hz, 1H), 3.09 (dq, J = 9.7, 4.7 Hz, 1H), 2.76 – 2.54 (m, 2H), 2.33 – 2.03 (m, 4H), 1.75 – 1.59 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 61.8, 60.5, 56.1, 55.9, 54.9, 54.6, 54.0, 52.2, 31.9, 31.2, 29.9, 29.2, 24.4, 24.1, 23.6, 22.6; MS (ES^+ , TOF) m/z 238 (M^+); HRMS (ES^+ , TOF) m/z calcd for $\text{C}_8\text{H}_{12}\text{OClBr}$ (M^+) 237.9760, found 237.9749.

(1Z,5S*,6S*)-5-Bromo-6-chlorocyclooct-1-ene (400)



To a sample of freshly activated zinc (72.0 mg, 1.10 mmols) and titanocene dichloride (91.4 mg, 0.367 mmols) was added THF (1.6 mL). The mixture immediately turned green and was stirred for 1 hour. The green solution was transferred to a flask containing epoxide **401** (40 mg, 0.167 mmols) using a syringe fitted with a cotton wool filter. The reaction was stirred for 5 minutes, over which time the colour changed to orange. The reaction was quenched with sat. aq. NaH_2PO_4 (2 mL), forming an orange precipitate. The mixture was partitioned between water (4 mL) and CH_2Cl_2 (3 mL), separated and extracted further with CH_2Cl_2 (2×3 mL). The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to give an orange solid (22.1 mg). Column chromatography (hexane : EtOAc 20 : 1) gave title compound **400** (30.7 mg, 0.137 mmols, 82%) as a colourless oil.

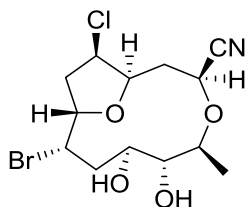
General Procedure for the Deoxygenation of Macrocyclic Epoxides:

Zinc dust was activated before use by adding to 2M HCl and sonicating for 3 minutes. The grey mixture was filtered and washed successively with water, acetone, ethanol and diethyl ether. The grey solid was dried overnight at 120°C under high vacuum, to yield a fine, light grey powder.

To a sample of freshly activated zinc (72.0 mg, 1.10 mmols) and titanocene dichloride (91.4 mg, 0.367 mmols) was added THF (1.6 mL). The mixture immediately turned green and was stirred for 1 hour. A portion of the green titanocene solution (2.2 eq.) was transferred to a flask containing a macrocyclic epoxide (**340**, **368**, **350**, **351**, **5**, or **8**) and stirred for 5 minutes, over which time the colour changed to orange. The reaction was quenched with sat. aq.

NaH₂PO₄ (1 mL), forming an orange precipitate. The mixture was partitioned between water (1 mL) and CH₂Cl₂ (3 mL), separated and extracted further with CH₂Cl₂ (2 × 3 mL). The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give an orange solid. ¹H NMR of the crude material showed no reaction had occurred in the case of **368**, **350**, **351** & **8** and loss of the nitrile and bromoallene groups in **340** & **5**.

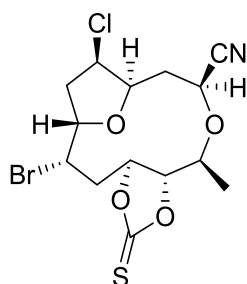
(1R,3S,5S,6S,7S,9S,10S,12R)-9-Bromo-12-chloro-6,7-dihydroxy-5-methyl-4,13-dioxabicyclo[8.2.1]tridecane-3-carbonitrile (411**)**



To a mixture of *E*-macrocycle **182** (10.0 mg, 0.0300 mmols) and AD-mix- α (209 mg) was added a water (400 μ L), ^tBuOH (400 μ L) and THF (400 μ L). After 2h, further portions of water (600 μ L), ^tBuOH (200 μ L) and THF (200 μ L) were added until the orange solution was monophasic. The reaction was stirred at room temperature for 20 h until TLC (hexane : EtOAc 1 : 1) showed completion of the reaction. The reaction was quenched with sat. aq. Na₂SO₃ (1 mL) and stirred for 5 min. The mixture was partitioned between water (1 mL) and CH₂Cl₂ (3 mL), separated and extracted further with CH₂Cl₂ (2 × 3 mL). The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow solid (30.9 mg). Column chromatography (hexane : EtOAc 1 : 1) gave title compound **411** (10.6 mg, 0.042 mmols, 96%) as a colourless oil: R_f 0.21 (hexane : EtOAc 1 : 1); ¹H NMR (400 MHz, CDCl₃) δ 4.59 (ddd, *J* = 9.2, 6.6, 2.7 Hz, 1H, CHCl), 4.49 (ddd, *J* = 11.1, 6.6, 4.1 Hz, 1H, CHOCHCl), 4.40

(ddd, $J = 12.1, 4.9, 2.3$ Hz, 1H, CHBr), 4.22 (ddd, $J = 9.8, 5.5, 2.3$ Hz, 1H, CHOCHBr), 4.16 (dd, $J = 9.5, 0.8$ Hz, 1H, CHCN), 4.09 (qd, $J = 6.5, 1.6$ Hz, 1H, CHCH₃), 3.88 (ddt, $J = 8.4, 5.2, 2.5$ Hz, 1H, CH₂CHOH), 3.24 (ddd, $J = 9.0, 8.2, 1.8$ Hz, 1H, CHOHCHCH₃), 2.63 (dt, $J = 13.4, 9.5$ Hz, 1H, CH₂CHCl), 2.57 (dd, $J = 11.6, 9.5$ Hz, 1H, CH₂CHCN), 2.53 (dd, $J = 2.6, 1.2$ Hz, 1H, OH), 2.41 (dddd, $J = 13.2, 12.2, 2.3, 1.1$ Hz, 1H), 2.25 (dt, $J = 14.6, 5.2$ Hz, 1H, CH₂CHBr), 2.13 (ddd, $J = 13.6, 5.5, 2.7$ Hz, 1H, CH₂CHBr), 2.04 (d, $J = 1.6$ Hz, 1H, OH), 2.01 (dd, $J = 11.3, 4.2$ Hz, 1H, CH₂CHCN), 1.47 (d, $J = 6.4$ Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 119.2 (CN), 78.4 (CHOCHCl), 77.6 (CHOHCHCH₃), 77.1 (CHCH₃), 73.6 (CHOCHBr), 69.8 (CH₂CHOH), 65.8 (CHCN), 57.6 (CHCl), 51.0 (CHBr), 41.5 (CH₂CHCl), 40.7 (CH₂CHBr), 35.1 (CH₂CHCN), 16.2 (CH₃); MS (ES⁻, TOF) m/z 368 (M)⁻; HRMS (ES⁻, TOF) m/z calcd for C₁₄H₂₀NO₆ClBr (M + HCO₂)⁻ 412.0163, found 412.0171.

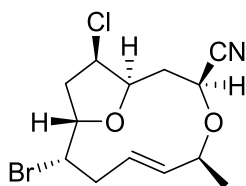
(1*S*,2*S*,4*S*,8*S*,9*S*,11*S*,13*R*,14*R*)-2-Bromo-14-chloro-9-methyl-6-sulfanylidene-5,7,10,16-tetraoxatricyclo[11.2.1.0^{4,8}]hexadecane-11-carbonitrile (412)



According to a modified procedure,¹¹⁷ to a sample of diol **411** (3.8 mg, 0.010 mmols) was added a solution of DMAP and 1,1'-thiocarbonyldiimidazole in CH₂Cl₂ (300 μ L, 0.0047 mmols DMAP & 0.019 mmols 1,1'-thiocarbonyldiimidazole) and the yellow solution stirred at room temperature for 17 h until TLC (hexane : EtOAc 1 : 1) showed completion of the reaction. The reaction was quenched with 1M NH₄Cl (1 mL) and stirred for 5 min. The

mixture was partitioned between water (1 mL) and CH₂Cl₂ (3 mL), separated and extracted further with CH₂Cl₂ (2 × 3 mL). The organic layer was dried over Na₂SO₄ and the solvent removed *in vacuo* to give a yellow oil (6.3 mg). Column chromatography (hexane : EtOAc 3 : 1) gave title compound **412** (4.1 mg, 0.0010 mmols, quant.) as a white solid: R_f 0.59 (hexane : EtOAc 1 : 1); ¹H NMR (400 MHz, CDCl₃) δ 5.31 (t, *J* = 4.0 Hz, 1H, CH₂CHOC=S), 5.21 (dt, *J* = 10.3, 3.7 Hz, 1H, CHCHOC=S), 4.48 – 4.32 (m, 5H, CHOCHCl, CHCl, CHBr, CHOCHBr & CHCN), 4.12 (qd, *J* = 6.6, 3.6 Hz, 1H, CHCH₃), 2.87 (ddd, *J* = 15.4, 6.1, 3.1 Hz, 1H, CH₂CHBr), 2.68 – 2.56 (m, 2H, CH₂CHBr & CH₂CHCl), 2.41 – 2.29 (m, 2H, CH₂CHCl & CH₂CHCN), 2.07 (dd, *J* = 14.8, 3.3 Hz, 1H, CH₂CHCN), 1.32 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 190.2 (C=S), 117.6 (CN), 83.7 (CHCHOC=S), 80.3 (CHOCHCl), 80.2 (CH₂CHOC=S), 76.0 (CHOCHBr), 74.7 (CHCH₃), 66.9 (CHCN), 58.8 (CHCl), 52.2 (CHBr), 41.1 (CH₂CHCl), 40.3 (CH₂CHBr), 34.4 (CH₂CHCN), 14.5(CH₃); MS (ES⁺, TOF) *m/z* 454 (M + HCO₂); HRMS (ES⁺, TOF) *m/z* calcd for C₁₅H₁₈NO₆SClBr (M + HCO₂)⁺ 453.9727, found 453.9722.

(1R,3S,5S,6E,9S,10S,12R)-9-Bromo-12-chloro-5-methyl-4,13-dioxabicyclo[8.2.1]tridec-6-ene-3-carbonitrile (182)



According to a modified procedure of Corey and Winter,¹¹⁴ to a sample of thiocarbonate **412** (3.6 mg, 0.0088 mmols) was added triethyl phosphite (400 μL, 2.33 mmols) and the colourless solution heated to reflux for 24 h. Toluene was added (4 mL) to form an azeotropic mixture and the solvents removed *in vacuo*. This process was repeated three times to give a white solid (4.4 mg). Column chromatography (hexane : EtOAc 2 : 1) gave title

compound **182** (1.5 mg, 0.0045 mmols, 51%) as a white solid along with starting thiocarbonate **412** (1.7 mg, 0.0042 mmols, 48%).

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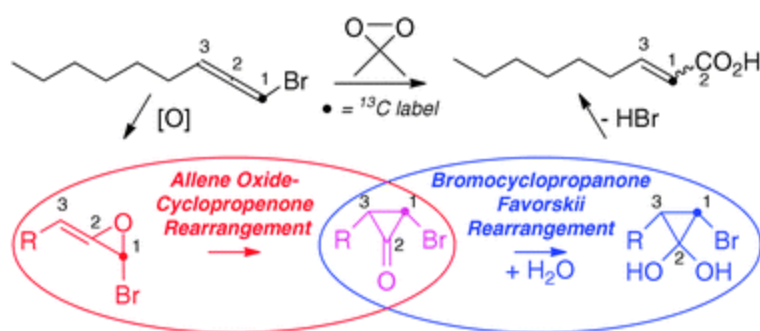
7 Appendices

7.1 Published Manuscript - Epoxidation of bromoallenes connects red algae metabolites by an intersecting bromoallene oxide - Favorskii manifold

D. Christopher Braddock, James Clarke & Henry S. Rzepa

Chem. Commun., **2013**, 49, 11176-11178

DMDO epoxidation of bromoallenes gives directly α,β -unsaturated carboxylic acids under the reaction conditions. Calculated (ω B97XD/6-311G(d,p)/SCRF = acetone) potential energy surfaces and ^2H - and ^{13}C -labeling experiments are consistent with bromoallene oxide intermediates which spontaneously rearrange *via* a bromocyclopropanone in an intersecting bromoallene oxide – Favorskii manifold.



7.2 Unpublished Manuscript - Epimeric Face-Selective Oxidations and Diastereodivergent Transannular Oxonium Ion Formation-Fragmentations: Computational Modelling & Total Syntheses of 12-Epoxyobtusallene IV, 12-Epoxyobtusallene II, Obtusallene X, Marilzabicycloallene C and Marilzabicycloallene D

James Clarke, Karl J. Bonney, Muhammad Yaqoob, Savade Solanki, Henry S. Rzepa,

Andrew J. P. White, David S. Millan & D. Christopher Braddock

J. Org. Chem., **2016**, *81*, 9539-9552

The total synthesis of 12-epoxyobtusallene IV, 12-epoxyobtusallene II, obtusallene X, marilzabicycloallene C and marilzabicycloallene D as halogenated C₁₅-acetogenin twelve-membered bicyclic and tricyclic ether bromoallene-containing marine metabolites from *Laurencia* species are described. Two enantiomerically pure C₄-epimeric dioxabicyclo[8.2.1]tridecenes were synthesised by *E*-selective ring-closing metathesis where their absolute stereochemistry was previously set *via* catalytic asymmetric homoallylic epoxidation and elaborated via regioselective epoxide-ring opening and diastereoselective bromoetherification. Epimeric face-selective oxidation of their ^{12,13} olefins followed by bromoallene installation allowed access to the oppositely configured 12,13-epoxides of 12-epoxyobtusallene II & 12-epoxyobtusallene IV. Subsequent exploration of their putative biomimetic oxonium ion formation-fragmentations reactions revealed diastereodivergent pathways

giving marilzabicycloallene **C** and obtusallene **X** respectively. The original configurations of the substrates evidently control oxonium ion formation and their subsequent preferred mode of fragmentation by nucleophilic attack at C₉ or C₁₂. Quantum modelling of this stereoselectivity at the ©B97X-D/Def2-TZVPPD/SCRF=methanol level revealed that in addition to direction resulting from hydrogen bonding, the dipole moment of the ion-pair transition state is an important factor. Marilzabicycloallene **D** as a pentahalogenated twelve-membered bicyclic ether bromoallene was synthesised by a face-selective chloronium ion initiated oxonium ion formation-fragmentation process followed by subsequent bromoallene installation.

