Oxonium ions, rearrangements, and natural products



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Abstract

This thesis focuses on the studies of a set of biologically relevant oxonium ions pertinent to the natural product biosynthesis of the red algae of the genus *Laurencia*. The total synthesis of these oxonium ions is reported along with their structural elucidation supported by extensive NMR spectroscopic analysis and DFT computations. The biosynthetic significance of these oxonium ions is demonstrated by their direct derivatisation into 12 natural products, namely (*Z*/*E*)-bromofucins, (*Z*/*E*)-chlorofucins, (*Z*/*E*)-elatenynes, laurendecumenyne B, laurefurenyne E, laurefurenyne F, *ent*-(*Z*/*E*)-laurefucins and *ent*-acetyllaurefucin.

Furthermore, 6 additional natural products are synthesised indirectly from the oxonium ions, namely (*Z*/*E*)-notoryne, laurefurenyne C, laurefurenyne D, *ent*-deacetyllaurencin and *ent*-laurencin. The total synthesis of laurefurenynes C-F also enabled their structural reassignment.

Chapters 1-3 of this thesis introduce the project, provide a brief summary of the chemistry of oxonium ions, and an overview of the proposed biosyntheses of *Laurencia* natural products.

Chapters 4-6 report the total synthesis of the oxonium ions, their characterisation and their direct derivatisation into various natural products.

Chapters 7-8 concerns the total synthesis of *ent*-deacetyllaurencin, *ent*-laurencin and the total synthesis of laurefurenyne C-F and their structural reassignment.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. All DFT computations were performed by Dr Quynh Nguyen under the supervision of Prof. Robert. S. Paton. The authorship of the DFT computations are explicitly stated in the following parts of the thesis, and permission has been obtained from the authors for the use of the DFT computed data in this thesis.

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2. Section **5.2.1**, page 94.
3. Section **5.2.2**, page 101.
4. Section **5.2.2**, page 104.
5. Section **5.2.2**, page 107.
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7. Section **5.2.2**, page 111.
8. Section **6.3**, page 128.
9. Section **6.3**, page 131.
10. Section **6.3**, page 133.
11. Section **12.8**, page 374.

This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

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Selected Abbreviations

Ac	acetyl
Ar	aryl
aq	aqueous
B3LYP	Becke, three-parameter, Lee-Yang-Parr
Bn	benzyl
brsm	based on remaining starting material
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
b.p.	boiling point
cat.	catalytic
conc.	concentrated
COSY	correlation spectroscopy
d	day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DIBAl-H	diisobutylaluminium hydride
DIPA	diisopropylamine

DIPEA	*N*,*N*-diisopropylethylamine, Hünig's base
DMF	dimethyl formamide
DMS	dimethyl sulphide
DMP	Dess–Martin periodinane
DMDO	dimethyldioxirane
DMSO	dimethylsulfoxide
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
EA	ethyl acetate
eq.	equivalent; or equatorial
ESI	electrospray ionisation
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
FC	flash chromatography
GC-MS	gas chromatography–mass spectrometry
hr	hour(s)
HMBC	heteronuclear multiple bond correlation spectroscopy
HMDS	bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide

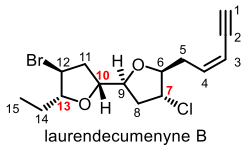
HRMS	high resolution mass spectrometry
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
IBX	2-iodoxybenzoic acid
IPA	isopropyl alcohol
IR	infrared
IS	internal standard
LDA	lithium diisopropylamide
LG	leaving group
M06-2X	Minnesota 06-2X functional
m-CPBA	*meta*-chloroperbenzoic acid
MS	mass spectroscopy, molecular sieves
min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide

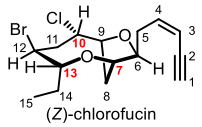
NMI	4-methylimidazole
NOS	*N*-hydroxysuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
MPW	modified Perdew-Wang by Barone and Adamo
Pet. Ether	petroleum ether b.p. 30–40 °C or 40–60 °C
Pet. Ether 30-40	petroleum ether b.p. 30–40 °C
Pet. Ether 40-60	petroleum ether b.p. 40–60 °C
pftb	perfluoro-*tert*-butoxy
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
Piv	pivaloyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
PW91	Perdew-Wang 91
Py	pyridine
R_f	retention factor

ROE	rotating frame nuclear Overhauser effect
ROESY	rotating frame nuclear Overhauser effect spectroscopy
r.t.	room temperature
sat.	saturated
SMD	solvation model based on density
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl or tetramethylsilane (in NMR context)
TOCSY	total correlation spectroscopy
TS	transition state
Ts	4-methylbenzenesulfonyl
TTMSS	tris(trimethylsilyl)silane

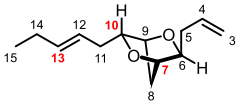
Notes on convention

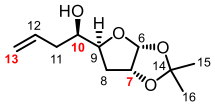
The atom numbering of compounds in this thesis follows the atom numbering of *Laurencia* natural products unless otherwise stated. For example, the atom numbering of the natural products (*Z*)-chlorofucin and laurendecumenyne B is shown as follows:



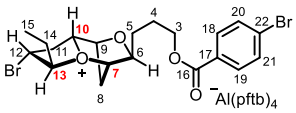


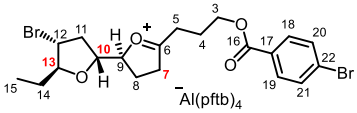
For compounds that are related to the natural products but with less than 15 carbon atoms, the atom numbering is as follows:





For compounds that are related to the natural products but with more than 15 carbon atoms, the atom numbering is as follows:





For compounds that are not related to the natural products, their atom numbering will not follow the rules as stated above.

1 An introduction to the project

1.1 Aims and objectives of the project

This project concerns oxonium ions, rearrangement reactions and natural products. These three branches of chemistry are brought together by the biosynthetic postulates of *Laurencia* natural products that will be introduced in **Chapter 3**.[1–10] The biosynthetic postulates suggest the involvement of complex trialkyloxonium ions **1.1-1.4** in the biosynthesis of a range of natural products of interest (**Figure 1.1**).

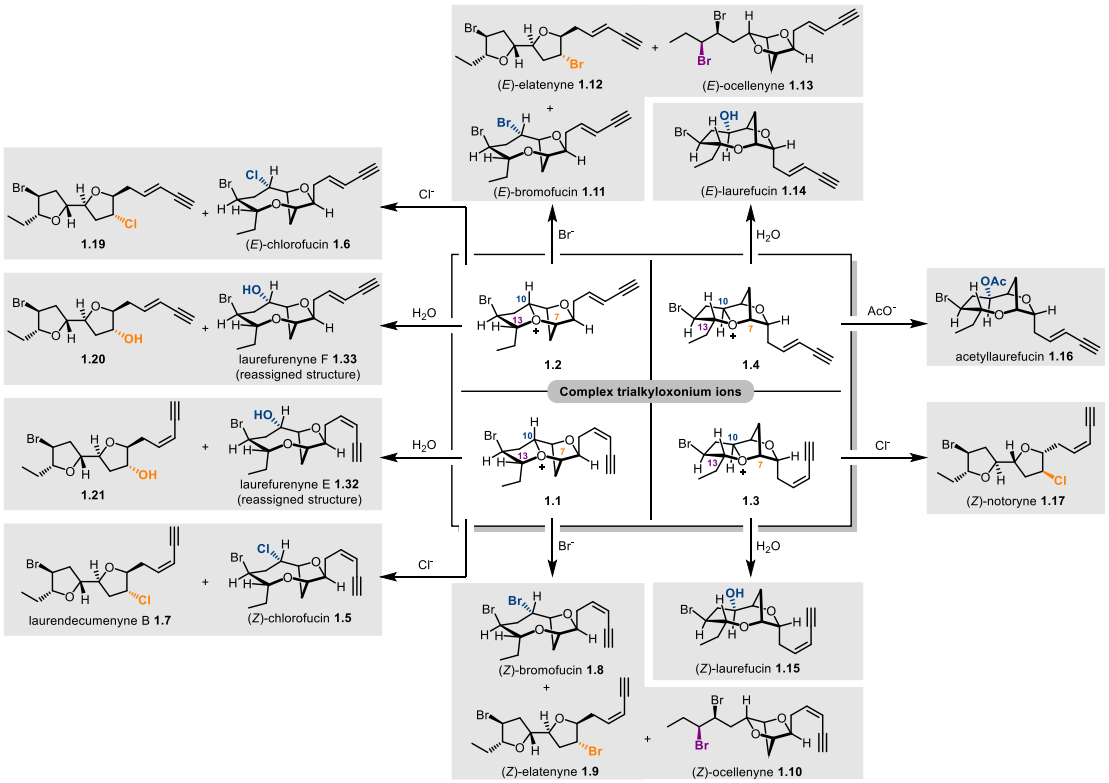


Figure 1.1. The complex trialkyloxonium ions **1.1-1.4**, their respective natural products, and non-natural products **1.19-1.21**.

However, direct evidence for the existence of these trialkyloxonium ions is lacking. Evidence for the existence of these trialkyloxonium ions comes from the structural and stereochemical diversity of the natural products shown above,[9,11–24] along with

biomimetic syntheses of certain membered of these natural products primarily from the Kim group.[4,5,9] The main objective of this project was to synthesise, characterise and study the properties of these trialkyloxonium ions, with the aim of gathering supporting evidence for their participation in *Laurencia* natural product biosynthesis through direct conversion into their respective natural products. If successful, this work would also provide the first direct evidence for the participation of trialkyloxonium ions in biological processes, which is surprising given the hydrolytic instability of the majority of oxonium ions.[25] The chemistry of oxonium ions will be briefly introduced in **Chapter 2**.

In addition to the studies of trialkyloxonium ions, this project also concerns the structural elucidation of the natural products laurefurenynes C-F (**Figure 1.2**).[26] The structures of laurefurenynes A-B **1.22-1.23** have been previously elucidated and reassigned as **1.28-1.29**,[2,3] but the remaining laurefurenynes **1.24-1.27** that are proposed to be biosynthetically related have yet to receive attention. Therefore, the total synthesis of the reassigned structures of laurefurenynes C-F **1.30-1.33** is studied to determine if structural reassignment is necessary for these natural products.

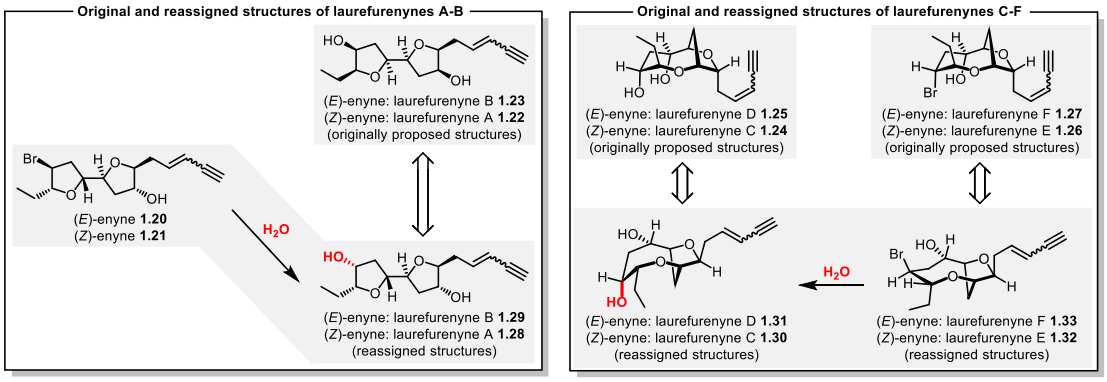


Figure 1.2. The originally proposed and reassigned structures of laurefurenynes A-F.

Finally, the total synthesis of the natural products laurencin **1.39** and deacetyllaurencin **1.38** *via* an unusual retrobiosynthetic approach from (*E*)-prelaurefucin **1.44** or its

structural analogues is reported. Success of this approach allowed synthesis of natural products from both the bromocyclisation phase and the oxonium ion phase of the proposed *Laurencia* natural product biosynthesis (**Figure 1.3**).[1,15]

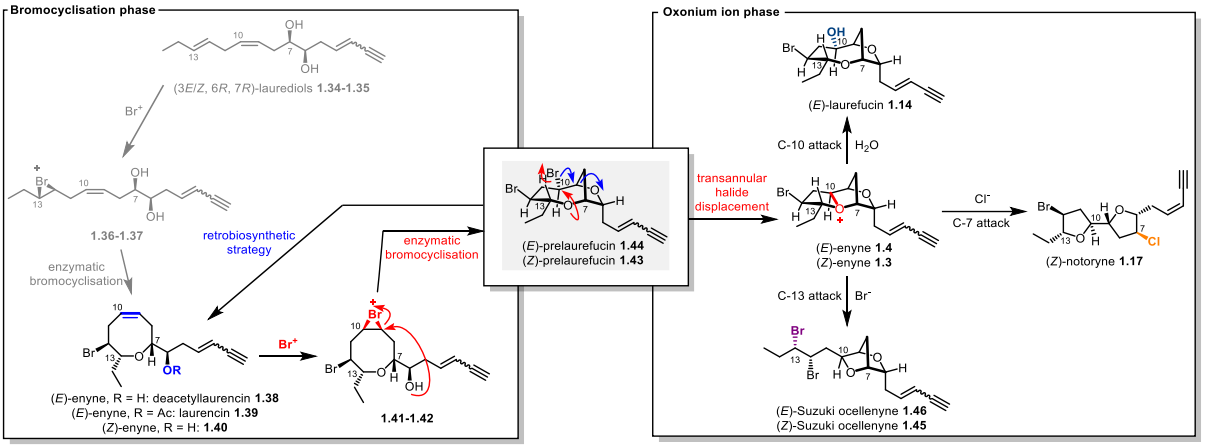


Figure 1.3. The bromocyclisation phase and the oxonium ion phase of *Laurencia* natural product biosynthesis.

2 A brief introduction to oxonium ions

2.1 Purpose of the chapter

The purpose of the chapter is to provide a synopsis of the fundamentals of oxonium ion chemistry. The nomenclature, classification, structures, spectroscopy and selected examples of their synthesis and reactions will be covered. For an extensive collection of examples on reactions that involve oxonium ions, see *Onium Ions* by G. A. Olah *et al*. and references therein.[27]

2.2 Definition and nomenclature of oxonium ions

According to the IUPAC definition of oxonium ions, oxonium ions are defined as "the parent ion H_3O^+ and substitution derivatives thereof".[28] For instance, substitution of all protons with alkyl groups (R) gives R_3O^+ that is a trialkyloxonium ion,[27,29,30] substitution of a proton with a silyl group (R_3Si) gives $R_3SiOH_2^+$ that is a silyloxonium ion,[31,32] and substitution of a proton with a fluorine atom (F) gives FOH_2^+ that is a fluorooxonium ion.[33,34] These examples also illustrate the nomenclature, where the suffix *oxonium ion* is used after naming the ligands attached to the trivalent oxygen except for protons.[27]

The substitution by groups that are divalent or trivalent would yield the structures $R_2C{=}OR^+$ and $RC{\equiv}O^+$ respectively. As suggested by their chemical bonding, substitution of protons by monovalent groups would yield saturated oxonium ions, and substitution by divalent or trivalent groups would yield unsaturated oxonium ions. For the nomenclature of unsaturated oxonium ions, the species $RC{\equiv}O^+$ is named the acyl cation, acylium ion or hydrocarbylidyne oxonium ion as recommended by IUPAC, and the species $R_2C{=}OR^+$ has the IUPAC nomenclature of hydrocarbylidene oxonium

ion.[28,35] For example, the species $CH_3C{\equiv}O^+$ is named acetyl cation, acetylium ion or ethylidyneoxonium ion and the species $(CH_3)_2C{=}OCH_2CH_3^+$ is named ethyl(propan-2-ylidene)oxonium ion. However, less cumbersome aliases for the species $R_2C{=}OR^+$ such as oxocarbenium ion, oxacarbenium ion, oxycarbenium ion and carboxonium ion are often used instead in the literature interchangeably, and it has been suggested that the name "carbonylonium ion" to be used to unify the nomenclature so as to end the confusion brought about by the multiple aliases of the species $R_2C{=}OR^+$.[36] The name "oxocarbenium ion" will be used throughout this thesis to describe the species $R_2C{=}OR^+$.

2.3 Types of oxonium ions

The different types of oxonium ions can be classified as follows (**Figure 2.1**):[27]

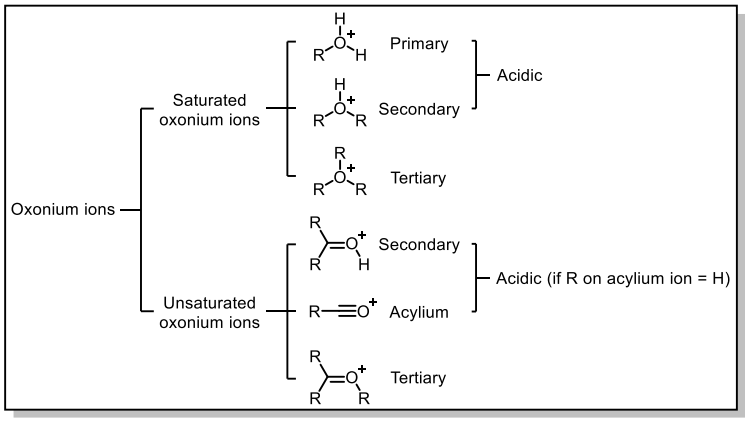


Figure 2.1. Classification of oxonium ions.

Given that oxonium ions can be saturated or unsaturated depending on the valency of their substituents, a further classification can be made based on whether protons are substituents of the trivalent oxygen. These protons are acidic and these oxonium ions are therefore classified as acidic oxonium ions. Both saturated and unsaturated oxonium ions can be acidic.

2.4 Structures of oxonium ions

The structures of saturated oxonium ions are generally pyramidal at the trivalent oxygen as supported by numerous X-ray crystal structures, which suggest that the oxonium oxygens are sp^3 hybridised. These include the hydronium ion **2.1**,[37–41] the methyloxonium ion **2.2**,[42] the dimethyloxonium ion **2.3**,[43] the trimethyloxonium ion **2.4**,[44,45] the 1-oxoniaadamantane **2.5**,[46] the 1,1'-(1,4-butanediyl) bis(tetrahydrofuranium) ion **2.6**,[47] and the oxatriquinane **2.7** (**Figure 2.2**).[48] Pyramidal inversion of trivalent oxygen has also been revealed by NMR spectroscopic studies and computation.[49–51]

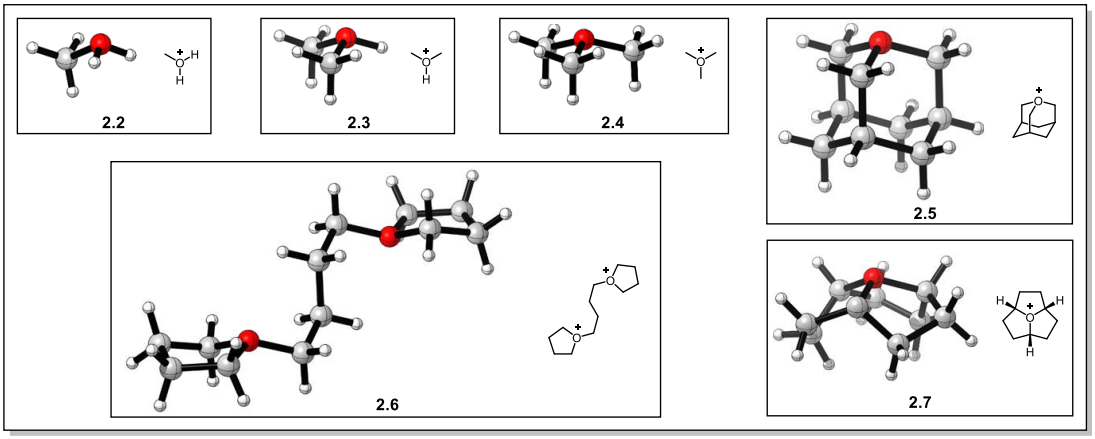


Figure 2.2. X-ray crystal structures of selected saturated oxonium ions (counter anions are omitted).

An exception to this general observation is that the trivalent oxygen of triphenyloxonium ion **2.8** is essentially planar from its X-ray crystal structure analysis (**Figure 2.3**).[52] The observed planarity has been attributed to steric effects caused by the phenyl rings.

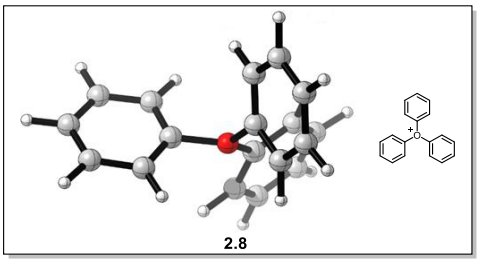


Figure 2.3. X-ray crystal structure of triphenyloxonium ion **2.8** (counter anion is omitted).

The averaged C–O^+ bond lengths of the X-ray crystal structures of the oxonium ions are tabulated below, the computed C–O bond lengths of diethyl (1.425 Å) and diphenyl (1.380 Å) ether are supplied for reference (**Table 2.1**).[53–55]

Compound	Averaged C–O^+ bond lengths/Å	Difference between C–O bond lengths of Et_2O or Ph_2O/Å
2.2	1.450	0.025 (versus Et_2O)
2.3	1.475	0.050 (versus Et_2O)
2.4	1.470	0.045 (versus Et_2O)
2.5	1.510	0.085 (versus Et_2O)
2.6	1.490	0.065 (versus Et_2O)
2.7	1.540	0.115 (versus Et_2O)
2.8	1.473	0.093 (versus Ph_2O)

Table 2.1. Comparison of C–O^+ bond lengths in oxonium ions with C–O bond lengths in ethers.

The difference between the bond lengths of triphenyloxonium ion **2.8** and Ph_2O can be rationalised by invoking weaker electron delocalisation between the oxonium oxygen lone pair of **2.8** with the phenyl π^* orbitals as compared to that in Ph_2O, which lowers the C–O bond order in **2.8**.[52]

The general trend that the C–O^+ bonds of **2.2-2.7** are longer than the C–O bonds in Et_2O can be rationalised by invoking a higher carbocation character of the C–O^+ bonds. However, the rationalisation of the subtle variations in bond lengths for the oxonium ions **2.2-2.7** is not straightforward, and extensive computational studies were performed by Mascal and co-workers to elucidate the factors behind the extraordinary C–O^+ bond length of oxonium ions of the type **2.7**. They proposed that high ring strain of the oxonium ion **2.7** leads to a smaller energy difference between σ^*(C–O^+) and σ(C–O^+) orbitals that translates into a longer C–O^+ bond length.[56]

For the unsaturated oxonium ions, selected X-ray crystal structures are shown as follows (**Figure 2.4**).

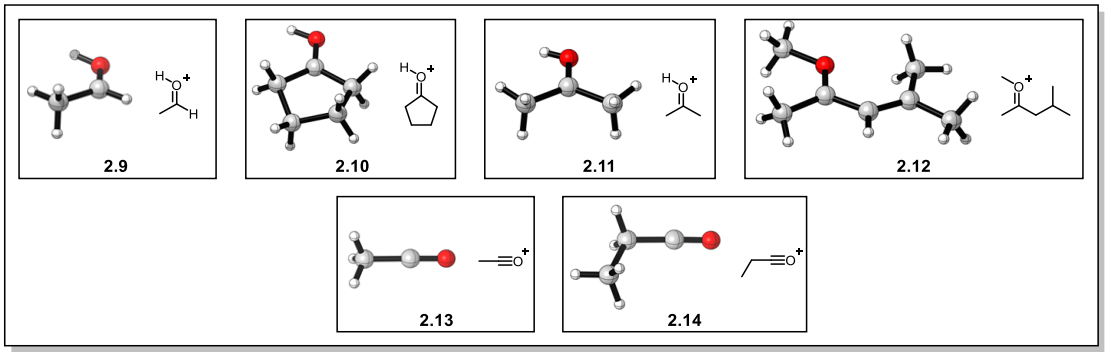


Figure 2.4. X-ray crystal structures of selected unsaturated oxonium ions (counter anions are omitted).

The acylium ions **2.13-2.14** are linear as shown by their X-ray crystal structures,[57–59] which suggest the acylium oxygen atom is sp hybridised. The structures of the oxocarbenium ions **2.9-2.12** suggest that the oxocarbenium ion oxygen is sp^2 hybridised and geometrical isomers are expected with unsymmetrical substrates.[60–64] The *E*-isomer is usually favoured as illustrated in the solution structures of protonated unsymmetrical ketones and aldehydes and the solid state structure of **2.12**.[60,62,63] However, in the case of **2.9**, the *Z*-isomer is observed due to hydrogen bonding of the $H–O^+$ bond of **2.9** with the oxygen of another acetaldehyde molecule in the solid state (**Figure 2.5**).[61]

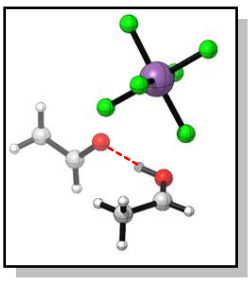


Figure 2.5. Hydrogen bonding of **2.9** with another acetaldehyde molecule in the solid state (red dotted line). The counter anion of **2.9** is SbF_6^-.

The bond lengths of the C=O bonds were found to increase upon the formation of the oxocarbenium ions, however they are still significantly shorter than the average C–O bond length of 1.43 Å that suggest retention of substantial C=O bond character. The bond lengths of the $C_{C=O}$–C bonds were found to decrease instead upon the formation

of the oxocarbenium ions. Bond length data of oxocarbenium ions **2.9-2.11** along with the data of their parent carbonyl compounds (acetaldehyde, cyclopentanone and acetone) **2.15-2.17** are tabulated below (**Table 2.2**).[61,65–67]

	Averaged bond lengths/Å				**Averaged bond lengths/Å**	
Oxocarbenium ions	$C{=}O^+$	$C_{C=O^+}{-}C$ *cis*	$C_{C=O^+}{-}C$ *trans*	**Carbonyl compounds**	C=O	$C_{C=O}{-}C$
2.9	1.239	1.457	-	**2.15**	1.208	1.514
2.10	1.266	1.473	1.469	**2.16**	1.213	1.510
2.11	1.271	1.467	1.459	**2.17**	1.209	1.484

Table 2.2. Comparison of bond lengths between the oxocarbenium ions **2.9-2.11** and their parent carbonyl compounds **2.15-2.17**.

The changes in bond lengths upon oxocarbenium ion formation can be rationalised as follows. The protonation or alkylation of the carbonyl oxygen lone pair lowers their energy, and thus weaken the $n_{C=O}$ to σ^*_{C-C} or σ^*_{C-H} hyperconjugation which results in the observed changes in bond lengths. The asymmetry of the $C_{C=O}{-}C_{cis}$ bonds and the $C_{C=O}{-}C_{trans}$ bonds in the oxocarbenium ions **2.10-2.11** is most likely due to the difference in interaction between lone pairs and $O^+{-}H$ bonds with σ^*_{C-C} orbitals (**Figure 2.6**). The $C{\equiv}O^+$ bond lengths of **2.13-2.14** are around 1.10 Å that are much shorter than the $C{-}O^+$ and $C{=}O^+$ bonds, which can be rationalised by the significant contribution of the triple bond character in their structures.

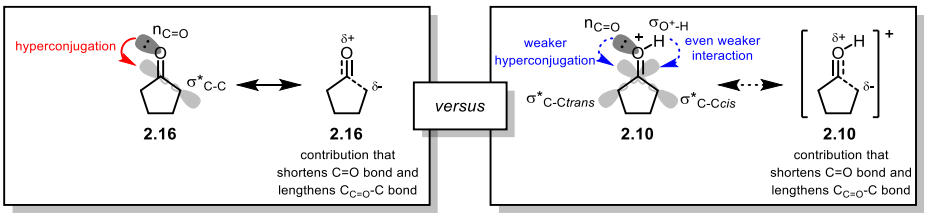


Figure 2.6. Stereochemical model to rationalise the observed changes in bond lengths upon oxocarbenium ion formation using **2.16** and **2.10** as examples.

2.5 Spectroscopy of oxonium ions

The characterisation of oxonium ions are most often carried out by ^{1}H and ^{13}C NMR spectroscopy, and occasionally by ^{17}O NMR spectroscopy, UV, IR and Raman spectroscopy. For saturated oxonium ions, ^{1}H and ^{13}C NMR spectroscopy are the most informative for the purpose of routine characterisation. For trialkyloxonium ions, the formation of the oxonium ions from their ether precursors would generally result in the increase of ^{1}H and ^{13}C NMR chemical shifts of the α-proton and α-carbon by 1.0 and 15.0-20.0 ppm respectively.[27] This change in NMR chemical shift reflects the increase in positive charge from the conversion of a neutral species to a positively charged species. Several well-characterised oxonium ions and their precursors are shown below to illustrate this change in ^{1}H and ^{13}C NMR chemical shifts (**Figure 2.7**).[46,48,68,69]

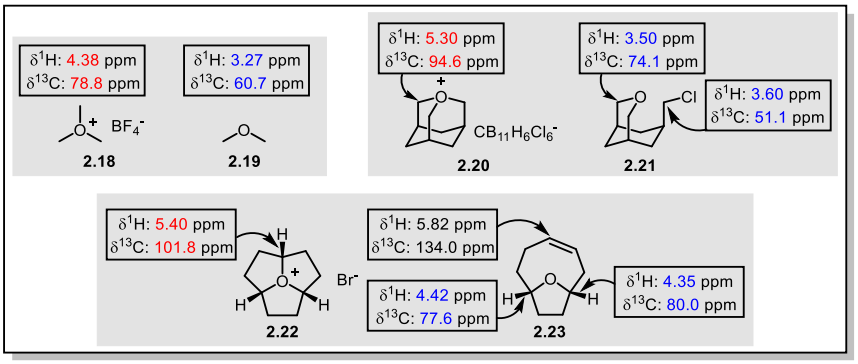


Figure 2.7. Selected examples of well-characterised trialkyloxonium ions and their precursors. The ^{1}H NMR shift of **2.18** was obtained in CD_3CN at 298K, and its ^{13}C NMR shift in CD_2Cl_2/SO_2 at 253K; The ^{1}H and ^{13}C NMR shifts of **2.19** were obtained in CD_2Cl_2 (unspecified acquisition temperature); The ^{1}H and ^{13}C NMR shifts of **2.20** were obtained in SO_2 at 217K with acetone-d_6 as the external standard; The ^{1}H and ^{13}C NMR shifts of **2.21** were obtained in $CDCl_3$ (unspecified acquisition temperature); The ^{1}H and ^{13}C NMR shifts of **2.22** were obtained in CD_3CN (unspecified acquisition temperature); The ^{1}H and ^{13}C NMR shifts of **2.23** were obtained in $CDCl_3$ (unspecified acquisition temperature).

The ^{13}C chemical shifts of the oxonium ions also appear to correlate with their C–O^+ bond lengths, as the order of the oxonium ion carbon ^{13}C chemical shifts of **2.22**, **2.20** and **2.18** mirrors their C–O^+ bond lengths (101.8 ppm/1.540 Å, 94.6 ppm/1.510 Å,

78.8 ppm/1.470 Å). This could be rationalised by a higher carbocation character in the longer bonds.

For the unsaturated oxonium ions, ^{17}O NMR, UV, IR and Raman spectroscopy were also used for their characterisation in addition to ^{1}H and ^{13}C NMR spectroscopy. This was because ^{17}O NMR spectroscopy is sensitive to the π-bond order of oxygen, and thus it could reveal the changes in C–O bond order upon the formation of unsaturated oxonium ions.[70,71] However, the prerequisite for ^{17}O NMR acquisition is the enrichment of the target compound with ^{17}O nuclei, which is not feasible for complex oxonium ions. Therefore, ^{1}H and ^{13}C NMR spectroscopy are still the most convenient method for the characterisation of unsaturated oxonium ions. The ^{1}H and ^{13}C NMR chemical shift of some well-characterised unsaturated oxonium ions are presented below (**Figure 2.8**).[72–75] As for IR and Raman spectroscopy, they are useful to probe the changes in carbonyl stretching frequencies upon the formation of acylium and oxocarbenium ions.[61,76]

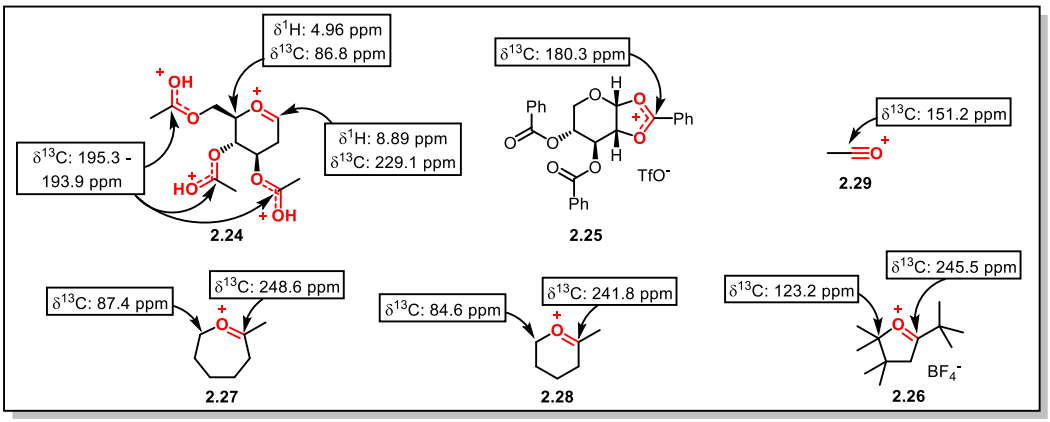


Figure 2.8. Selected ^{1}H and ^{13}C NMR data of unsaturated oxonium ions. The ^{1}H and ^{13}C NMR shifts of **2.24** and **2.29** were obtained in HF/SbF_5 at 233K with acetone-d_6 as the external standard. The ^{1}H and ^{13}C NMR shifts of **2.25** were obtained in CD_2Cl_2 at 195K. The ^{1}H and ^{13}C NMR shifts of **2.26** were obtained in $CDCl_3$ and CD_2Cl_2 respectively (unspecified acquisition temperature). The ^{1}H and ^{13}C NMR shifts of **2.27** and **2.28** were obtained in SO_2ClF at 233K with ^{13}C enriched tetramethylsilane as the external standard.

The ^{13}C chemical shifts of the oxocarbenium ion carbons are dependent on ring sizes and substituents. Except for **2.25** where the positive charge is delocalised onto two oxygen atoms, all the other oxocarbenium ions have their oxocarbenium carbon ^{13}C resonances well above 220 ppm. The ^{13}C NMR resonance of the acetylium ion **2.29** is at 151.2 ppm which is much lower than that in oxocarbenium ions. This is analogous to the difference in ^{13}C NMR resonances of alkenes (~120 ppm) and alkynes (~75 ppm).[77]

2.6 Synthesis of oxonium ions

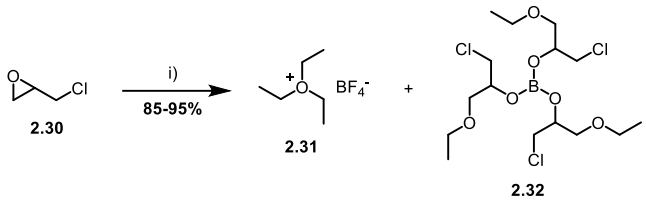
2.6.1 *Synthesis of saturated oxonium ions*

The synthesis of both saturated and unsaturated oxonium ions have been well reviewed and only selected examples will be discussed here to illustrate the key methods for their preparation.[27,78]

Saturated acidic oxonium ions (primary and secondary oxonium ions) can be prepared by the protonation of their parent alcohols and ethers. For instance, H_3O^+ can be prepared by the protonation of H_2O with superacids such as $HSO_3F{\cdot}SbF_5$ and $HF{\cdot}SbF_5$.[79,80] Similarly, the preparation of ROH_2^+ and R_2OH^+ can be achieved in the same way, by protonation of ROH and R_2O with superacids.[81–83]

For saturated non-acidic oxonium ions (tertiary oxonium ions), there are several different methods for their synthesis involving various strategies for alkylation of their parent ethers. The first synthesis of tertiary oxonium ions was reported by Meerwein in 1937, in which the synthesis was achieved by the reaction between $BF_3{\cdot}R_2O$ (R=Me or Et) with epichlorohydrin **2.30** to provide $Me_3O^+BF_4^-$ **2.18** and $Et_3O^+BF_4^-$ **2.31**.[84–87]

These oxonium ions are also known as Meerwein's salts and the synthesis of **2.31** is shown below (**Scheme 2.1**).



Scheme 2.1. Synthesis of **2.31** from **2.30**.

Reagents and conditions: **i)** $BF_3{\cdot}Et_2O$ (1.32 eq.), Et_2O, reflux, 1 hr, *then* r.t., overnight.

The proposed mechanism of the reaction is shown as follows (**Figure 2.9**). The role of epichlorohydrin in this synthesis is to activate R_2O by strain release to form an intermediate oxonium ion **2.34** which subsequently transfers an R group to another molecule of R_2O to form the desired product **2.31** .

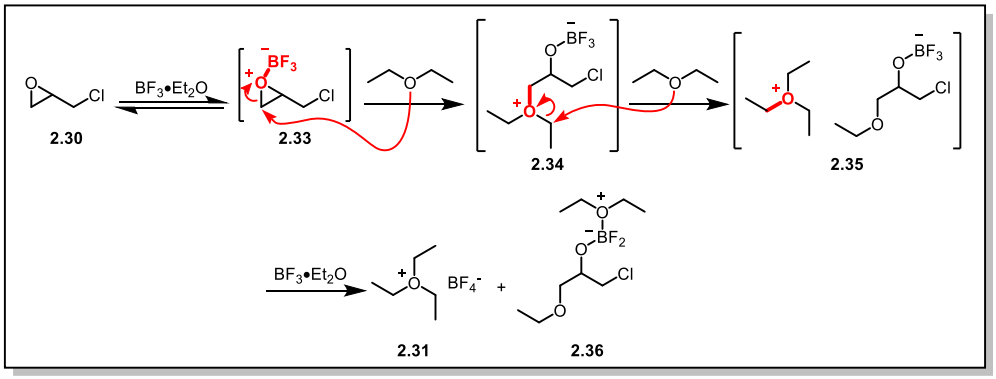
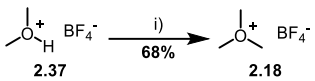


Figure 2.9. Proposed mechanism for the generation of **2.31** in Et_2O from **2.30** and $BF_3{\cdot}Et_2O$.

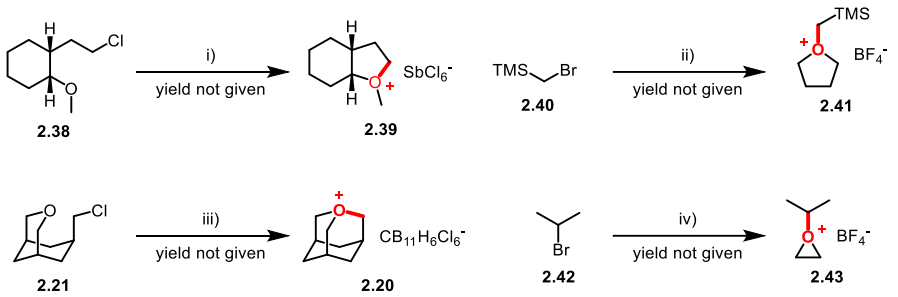
Tertiary oxonium ions can also be generated from the reaction between a primary or a secondary oxonium ion (acidic oxonium ion) with diazoalkane (**Scheme 2.2**).[88–90]



Scheme 2.2. Synthesis of **2.18** from **2.37**.

Reagents and conditions: CH_2N_2, CH_2Cl_2, 40 °C.

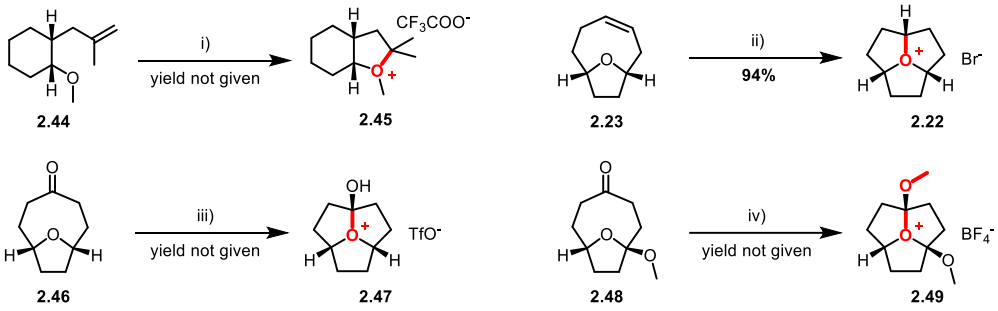
Furthermore, strategies involving the direct activation of leaving groups such as the activation of alkyl halides by halophilic lewis acids ($SbCl_5$), or by a salt metathesis reaction with a source of Ag(I) have also been used for oxonium ion synthesis (**Scheme 2.3**).[29,31,46,50]



Scheme 2.3. Strategies based on leaving group activation and salt metathesis for the generation of tertiary oxonium ions.

Reagents and conditions: **i)** $SbCl_5$. **ii)** $AgBF_4$ (1.0 eq.), THF (1.0 eq.), CH_2Cl_2, r.t., 3 days (exclusion of light). **iii)** $Ag[CB_{11}H_6Cl_6]$ (0.42 eq.), SO_2, -78 °C, *then* -10 °C, 2 hrs. **iv)** $AgBF_4$ (1.0 eq.), ethylene oxide (1.0 eq.), -78 °C, 1 day.

Another strategy that is similar to leaving group activation is the activation of olefins or carbonyl groups by electrophiles followed by intramolecular attack of an ether oxygen onto the incipient carbocation for the synthesis of tertiary oxonium ions (**Scheme 2.4**).[29,48,53,56]



Scheme 2.4. Synthesis of tertiary oxonium ions *via* electrophilic activation of olefins or carbonyl groups.

Reagents and conditions: **i)** CF_3COOH. **ii)** HBr, $CHCl_3$, 10 min. **iii)** TfOH, CD_3CN. **iv)** $Me_3O^+BF_4^-$, CD_3CN, -10 °C to 5 °C, 2 hrs.

Transalkylation strategies have also been realised for the synthesis of oxonium ions. For instance, $Me_3O^+BF_4^-$ **2.18** can be synthesised *via* transalkylation between Me_2O and $Et_3O^+BF_4^-$ **2.31**. The driving force of the reaction is the preferential precipitation of the oxonium ion $Me_3O^+BF_4^-$ **2.18**.[85,87] Transalkylation between different types of oxonium ions is also possible, trimethylorthoformate can be activated by Lewis acids such as $BF_3{\cdot}Et_2O$ to form an oxocarbenium ion that can transfer a methyl group to Me_2O, and thus forming the tertiary oxonium ion $Me_3O^+BF_4^-$ **2.18**.

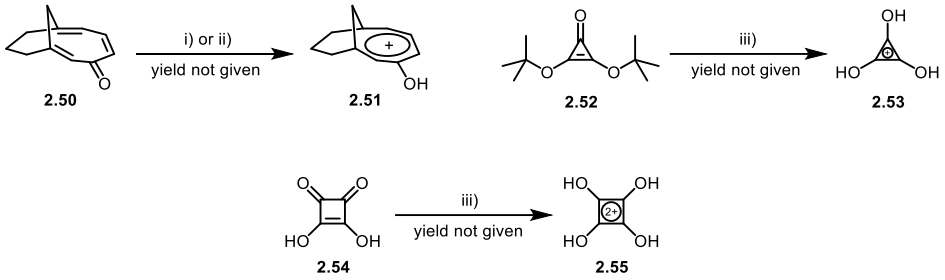
The preparation of dialkylaryl and diarylalkyloxonium ions are however not as straightforward as the preparation of trialkyloxonium ions. For example, the preparation of dimethylphenyloxonium ion requires the use of methyl hexafluoroantimonate to alkylate anisole in SO_2ClF at -120 °C. Dialkylaryloxonium ions are unstable with respect to the conversion to ring-alkylated alkoxybenzenes above -70 °C.[91,92]

The synthesis of triaryloxonium ions was first realised by the reaction of diphenylether with phenyldiazonium tetrafluoroborate but gave a mere 2% yield of the desired product.[93] Triphenyloxonium tetrafluoroborate was found to be very resistant to nucleophilic displacement at the sp^2 oxonium ion carbons.[94]

2.6.2 *Synthesis of unsaturated oxonium ions*

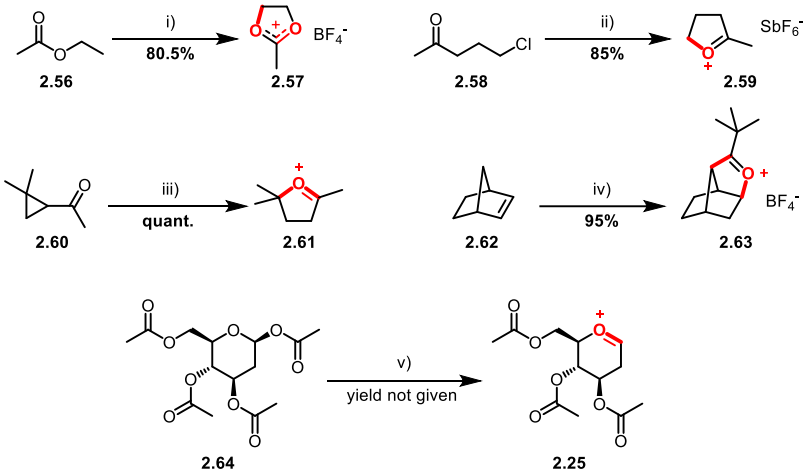
The synthesis of acidic unsaturated oxonium ions can generally be achieved by the protonation of their parent carbonyl compounds by superacids such as HSO_3F-SbF_5 and HF-SbF_5.[61,78,95] However, if the protonated compounds are stabilised by aromaticity, weaker acids such as TFA can also be used.[96,97] Examples include the formation of homoaromatic compound **2.51** and aromatic compounds **2.53** and **2.55** upon protonation of their parent carbonyl compounds are shown below (**Scheme 2.5**).[96–100]

The protonation of CO and CO_2 have also been observed, although the latter only through indirect means.[101–104]



Scheme 2.5. Examples of the preparation of acidic unsaturated oxonium ions.
Reagents and conditions: **i)** TFA. **ii)** $CDCl_3$/TFA. **iii)** HSO_3F-SbF_5, SO_2ClF, -78 °C.

The synthesis of non-acidic unsaturated oxonium ions can be achieved by the protonation of parent vinyl ethers, by hydride abstraction of parent acetals and by alkylation of the parent carbonyl compounds.[105,106] The alkylation can proceed both intermolecularly and intramolecularly. Intermolecular alkylation can be achieved by direct transalkylation with other oxonium ions or with strong alkylating agents such as CH_3F/SbF_5.[70,107] In contrast to intermolecular alkylation, the chemistry of intramolecular alkylation can be more complex and can involve molecular rearrangements for the generation of non-acidic unsaturated oxonium ions.[72,106,108–118] Several examples of these intramolecular alkylations leading to non-acidic unsaturated oxonium ions are displayed below (**Scheme 2.6**).[73,106,110,119,120]



Scheme 2.6. Examples of the preparation of non-acidic unsaturated oxonium ions. Reagents and conditions: **i)** ethylene oxide, BF_3. **ii)** $AgSbF_6$ (1.0 eq.), anhydrous CF_3COOH, 20 °C, 1 hr. **iii)** 90% H_2SO_4, 81 °C. **iv)** *t*-$BuCO^+BF_4^-$, CH_2Cl_2, -50 °C. **v)** HF/SbF_5, -40 °C.

The preparation of the reagent *t*-$BuCO^+BF_4^-$ employed for the transformation of **2.62** to **2.63** is an example of acylium ion synthesis, which can be achieved by the reaction of pivaloyl fluoride with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at -60 °C.[72]

The proposed mechanisms for the generation of **2.57**, **2.61** and **2.63** are as shown below (**Figure 2.10**). The conversion of **2.60** to **2.61** can be categorised as a Cloke-Wilson rearrangement and has been further developed into synthetic methodologies for the synthesis of dihydrofurans.[121,122] Moreover, the Cloke-Wilson rearrangement has also been applied to the total synthesis of natural products such as the total synthesis of norrisolide.[123,124]

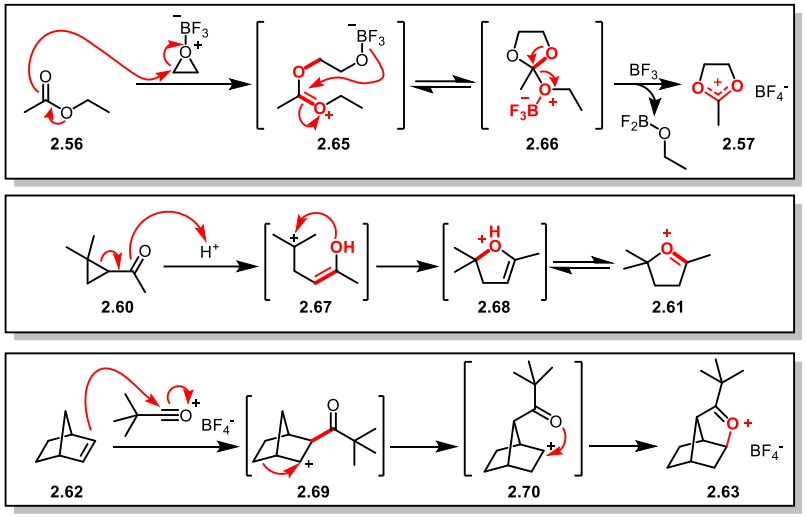


Figure 2.10. Proposed mechanisms for the generation of **2.57**, **2.61** and **2.63**.

2.7 Reactivity of oxonium ions

2.7.1 *Relative acidities of acidic oxonium ions*

As oxonium ions can be categorised as acidic and non-acidic, the discussion of the reactivity of oxonium ions will begin with the introduction of their acidities (for acidic oxonium ions) and relative propensities of alkyl transfers (for non-acidic oxonium ions).

In terms of their acidities, the pK_a values of representative protonated alcohols, ethers, aldehyde, ketones, carboxylic acids, esters, amides and acyl chlorides are tabulated below (**Table 2.3**).[95,125] The pK_a values except that for protonated acyl chlorides and water were determined from the Hammett H_0 acidity function at half protonation, where the condition H_0 = pK_a is satisfied. However, this assumption is only valid if the protonation behaviour of the base obeys the H_0 acidity function. The H_0 acidity function is known not to be universally applicable as it is constructed from data obtained from a series of aniline bases.[126] Other classes of compounds such as amides and alkenes were found to exhibit significant deviations, and the H_A and H_R acidity functions were established to quantify their acidities respectively.[127,128] Despite these limitations, the tabulated pK_a values should still serve as a guideline sufficient for the comparison of the relative acidities of these protonated species. The pK_a values of protonated acyl chlorides were derived from conductometric studies.[129]

Compound class	Representative example	pK_a of protonated compound
Acyl chlorides	Acetyl chloride	-10.9
	Benzoyl chloride	-11.2
Alcohols	Methanol	-2.0
	Phenol	-6.7
Aldehydes	Alkyl aldehydes	ca. -8.0
	Benzaldehyde	-7.1
Amides	Acetamide	ca. 0.0
	Benzamide	ca. -2.0
Carboxylic acids	Acetic acid	-6.1
	Benzoic acid	-7.2
Carboxylic esters	Ethyl acetate	ca. -6.5
	Ethyl benzoate	-7.4
Ethers	Diethyl ether	-3.6
	Tetrahydrofuran	-2.1
	Anisole	-6.5
Ketones	Acetone	-7.2
	Acetophenone	-6.2
Water	Water	-1.7

Table 2.3. Representative pK_a values of some acidic oxonium ions.

The generalisations of the trends of the acidities are considered separately for the aliphatic series and the aromatic series.

For the aliphatic series, the order of compounds in increasing p*K*a is as follows: protonated acyl chlorides, protonated aldehydes, protonated ketones, protonated carboxylic acids and esters, protonated alcohols and esters, protonated water, protonated amides. The low acidity of protonated amides is explained by the high basicity of its conjugate base.[130] The trend of the remaining compounds could be rationalised based on the basicity of their conjugate bases, which are dependent on the differences in hybridisations of the oxygen atoms and the subtle balance of stereoelectronic effects (**Figure 2.11**).

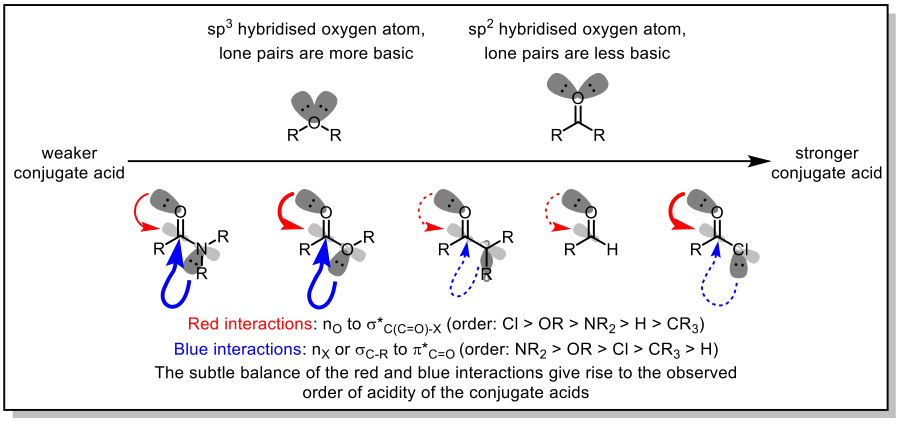


Figure 2.11. Effects of hybridisation and stereoelectronics on the ranking of the pK_as of the acidic oxonium ions. The intensities of arrows reflect the strength of interactions.

The subtle balance of stereoelectronic effects is analogous to the rationalisation of the IR stretching frequencies of C=O bonds of various carbonyl compounds. A study on the basicity of various substituted acetophenones has revealed a good correlation between IR C=O stretching frequencies and their basicity, with a higher stretching frequency corresponding to a lower basicity and thus a stronger conjugate acid.[131] Considering the order of IR C=O stretching frequencies of acyl chlorides (1820-1800 cm^{-1}), aldehydes (1740-1720 cm^{-1}), ketones (1720-1700 cm^{-1}), carboxylic acids (1710-1690 cm^{-1}), esters (1750-1740 cm^{-1}) and amides (1680-1620 cm^{-1}), the order of their IR stretching frequencies roughly reflects the acidity of their conjugate acids except for esters.

For the aromatic series, the p*K*a of protonated aromatic ethers and alcohols are much lower than that of their aliphatic counterparts, most likely because of the reduced basicity of their conjugate bases due to the conjugation of the oxygen lone pairs with the aromatic system.

2.7.2 *Relative alkylating power of non-acidic oxonium ions*

From the studies of the relative acidities of acidic oxonium ions in the previous section, the basicity of the conjugate base plays an important role in the rationalisation of the observed trends of oxonium ions acidities. By extension, the alkylating power of non-acidic unsaturated oxonium ions would be expected to be stronger than that of non-acidic saturated oxonium ions. This order of alkylating power has indeed been established in a study by Jackman and co-workers,[132] in which the methylating power of ketone derived oxocarbenium ion **2.71** was found to be 385 times greater than that of ester derived dioxolenium ion **2.72**, and the methylating power of trimethyloxonium ion **2.72** was found to be 11 times stronger than **2.18** (**Figure 2.12**).

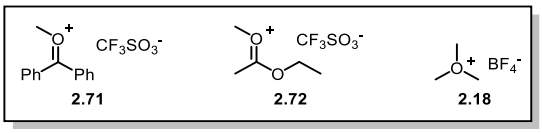
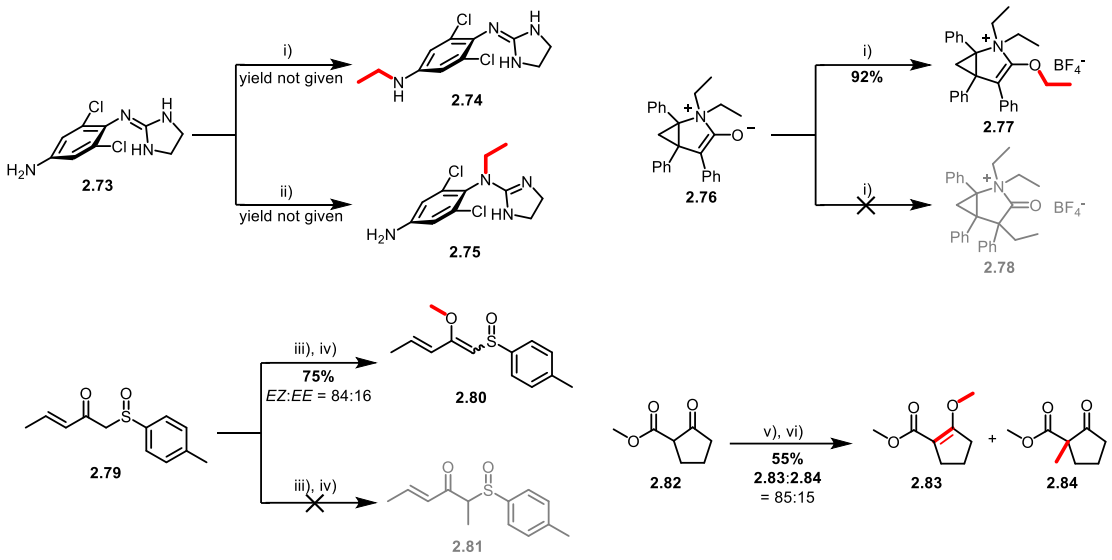


Figure 2.12. Structures of **2.71**, **2.72** and **2.18**.

2.7.3 *Applications of oxonium ions in synthetic chemistry*

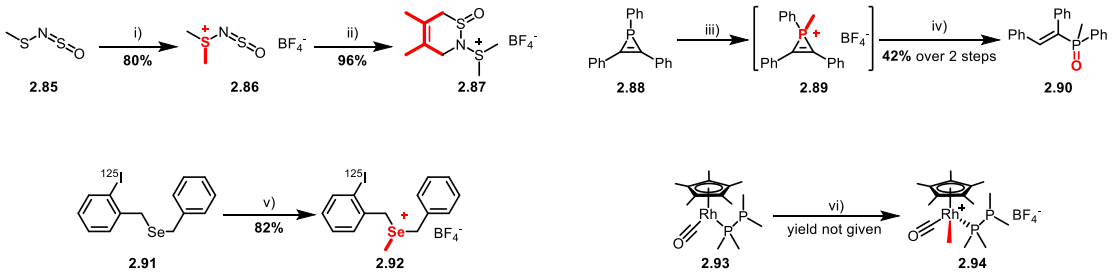
Aside from being invoked as reactive intermediates, oxonium ions also play the role as alkylating agents in synthetic chemistry.[27,61] Trialkyloxonium ions (non-acidic saturated oxonium ions; tertiary oxonium ions) are the most important oxonium ions in this aspect. Trialkyloxonium ions are regarded as "hard electrophiles" in the parlance of the hard-soft acid-base theory, and thus they preferentially alkylate "hard nucleophiles" in the presence of other competing nucleophiles.[27,133–137] Several examples of their alkylation chemistry are illustrated below (**Scheme 2.7**).[27,133,136,138]



Scheme 2.7. Examples of the alkylation chemistry of trialkyloxonium ions.

Reagents and conditions: **i)** $Et_3O^+BF_4^-$. **ii)** EtBr. **iii)** LDA, THF, -30 °C. **iv)** $Me_3O^+BF_4^-$, THF, -30 °C to 20 °C. **v)** KO*t*-Bu, Et_2O, 20 °C, 15 min. **vi)** $Me_3O^+BF_4^-$, HMPA, 25 °C, 3.5 hrs or 90 °C, 0.5 hrs.

Their alkylation chemistry is not limited to *C*-, *N*- and *O*-alkylations, alkylations on other heteroatoms such as sulphur, phosphorous, selenium and transition metals have been demonstrated, in which some cases can lead to further chemical transformations (**Scheme 2.8**).

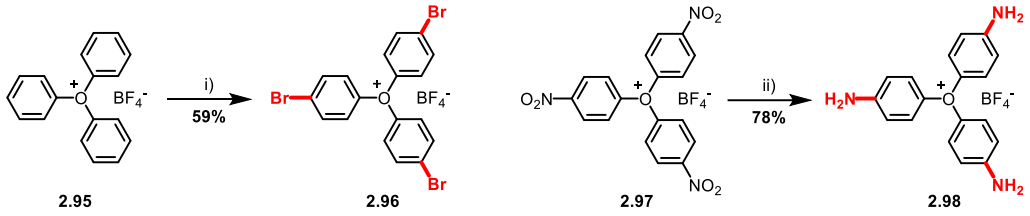


Scheme 2.8. Further examples of the alkylation chemistry of trialkyloxonium ions.

Reagents and conditions: **i)** $Me_3O^+BF_4^-$, neat. **ii)** 2,3-dimethylbuta-1,3-diene, MeCN. **iii)** $Me_3O^+BF_4^-$, CH_2Cl_2, 25 °C, 30 min. **iv)** H_2O, 25 °C. **v)** $Me_3O^+BF_4^-$, CH_2Cl_2, -15 °C, 12 hrs. **vi)** $Me_3O^+BF_4^-$, $MeNO_2$, 2 hrs.

On the other hand, triaryloxonium ions do not transfer their aryl groups readily and it has been shown that triphenyloxonium ions are extremely resistant to nucleophilic attack at the oxonium ion carbons unless boiled in pyridine.[93] They even withstand

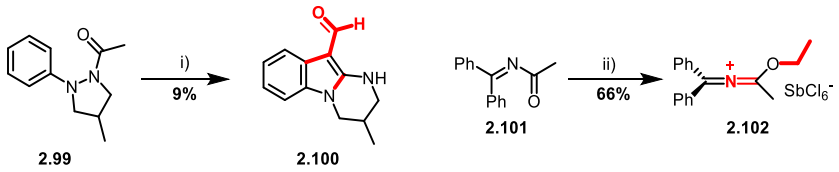
electrophilic bromination and nitro group reductions at the aryl groups without cleavage of the C–O^+ bonds (**Scheme 2.9**).[139,140]



Scheme 2.9. Reactions of triaryloxonium ions.

Reagents and conditions: **i)** $Br_2/AgBF_4$, $MeNO_2$, 20 °C, 3 hrs. **ii)** Sn, conc. HCl, reflux.

Aside from simple alkylation reactions, the alkylation ability of trialkyloxonium ions allows them to activate amides into imino ethers that could engage in further chemical transformations (**Scheme 2.10**).[141,142]



Scheme 2.10. Activation of amides by trialkyloxonium ions.

Reagents and conditions: **i)** $Et_3O^+BF_4^-$, DMF, 150 °C, 18 hrs. **ii)** $Et_3O^+SbCl_6^-$.

A proposed mechanism for the generation of **2.100** from **2.99** is shown below (**Figure 2.13**).

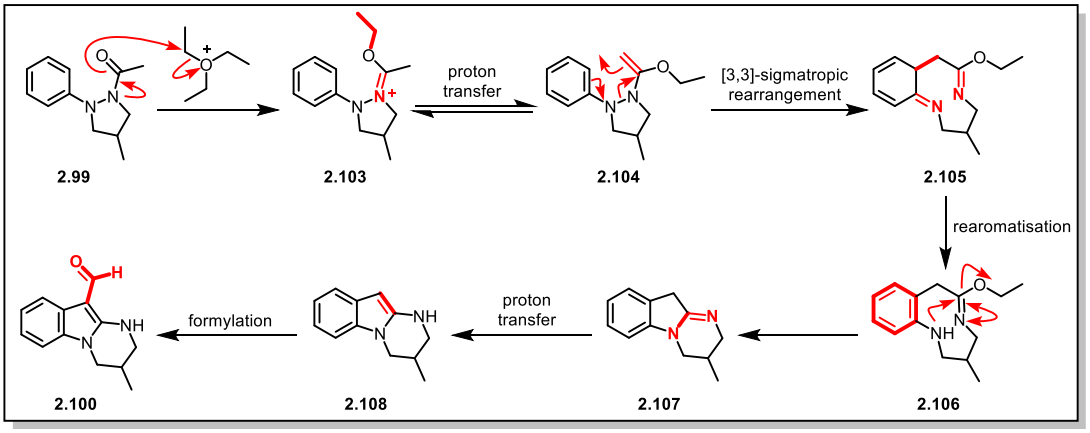
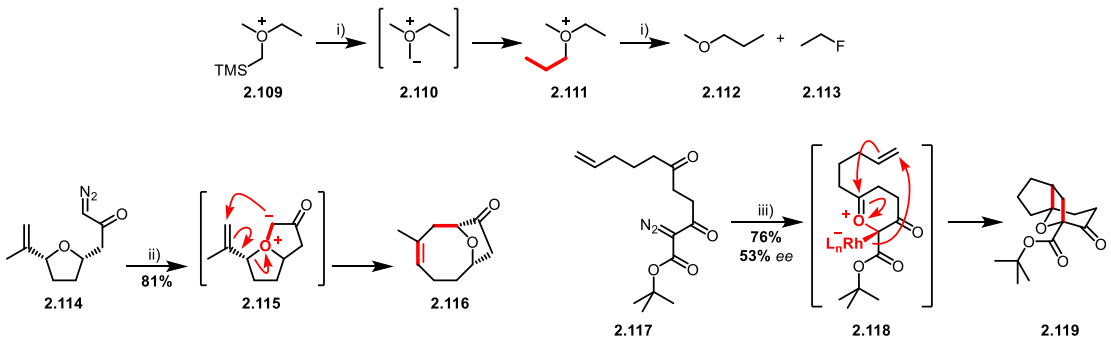


Figure 2.13. Proposed mechanism for the formation of **2.100**.

Oxonium ylides can also be generated from oxonium ions by deprotonation, desilylation or from parent ethers or carbonyl compounds *via* reactions with carbenes. These ylides have been demonstrated to undergo chain homologation, rearrangement and cycloaddition reactions (**Scheme 2.11**).[27,143–147]



Scheme 2.11. Examples of oxonium ylide chemistry.

Reagents and conditions: **i)** CsF. **ii)** $Rh_2(OAc)_4$ (2.0 mol %), CH_2Cl_2, 25 °C, 12 min.

iii) [Rh_2(*S*-DOSP)$_4$] (1.0 mol %), hexane, 28 °C.

3 Oxonium ions and proposed biosynthesis of *Laurencia* natural products

3.1 Purpose of the chapter

The purpose of the chapter is to introduce onium ions in biology and provide a survey of proposed *Laurencia* natural product biosyntheses that involve trialkyloxonium ion intermediates.

3.2 Onium ions in Nature

Nature utilises a range of onium ions to carry out various biological functions.[148] Structurally simple onium ions such as the hydronium ion H_3O^+ and the ammonium ion NH_4^+ transport protons and ammonia molecules in biological systems.[148] More complex onium ions, such as the tetraalkylammonium ions acetylcholine **3.1** and trimethylated lysine **3.2**, are neurotransmitters and epigenetic markers respectively.[149,150] *S*-Adenosylmethionine **3.3**, which is a trialkylsulfonium ion, is involved in processes such as methylation of genetic material, regulation of immune response and amino acid metabolism (**Figure 3.1**).[148,151,152]

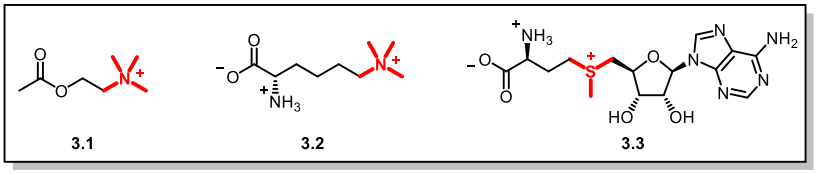


Figure 3.1. Structures of some onium ions in Nature.

3.3 Oxonium ions in Nature

In contrast to tetraalkylammonium ions and trialkylsulfonium ions, trialkyloxonium ions do not seem to participate in biological processes. It has been suggested that Nature

probably chose trialkylsulfonium ions over trialkyloxonium ions because the latter are prone to rapid hydrolysis.[25] The other type of oxonium ion that plays a role in biology is the glycosyl cation, which is a dialkylated unsaturated oxonium ion. An example of a glycosyl cation **2.24** has been reported in HF/SbF_5 superacidic medium.[73]

3.4 Proposed biosynthesis of *Laurencia* natural products by Murai and Suzuki

Interestingly, trialkyloxonium ions **1.3** and **1.4** have been proposed by Murai and Suzuki as key biosynthetic intermediates in the biosynthesis of *Laurencia* natural products (*E*)-laurefucin **1.14**, (*Z*)-notoryne **1.17** and ocellenynes **1.45-1.46**.[1,15] The actual structures of the ocellenynes **1.45-1.46** have not been fully elucidated, and thus they are referred as Suzuki ocellenynes in Murai and Suzuki's biosynthetic postulate (**Figure 3.2**). The significance of the oxonium ion biosynthetic intermediates **1.3-1.4** is that their participation could unify the structural and stereochemical relationship of the isolated natural products. The structural elucidation of the natural products will be discussed in **Chapter 6.1.1**.

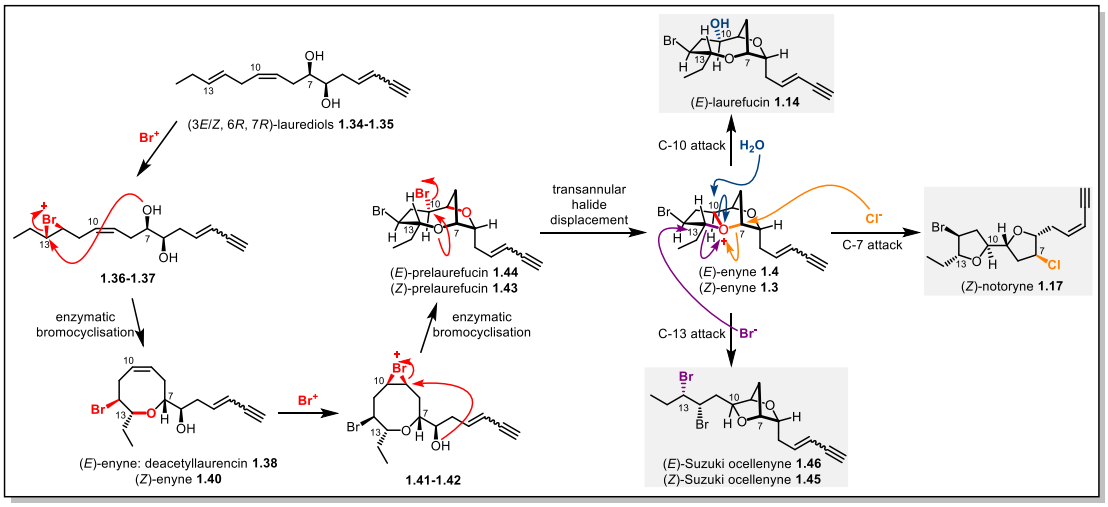


Figure 3.2. Proposed biosynthesis of *Laurencia* natural products *via* **1.3-1.4** by Murai and Suzuki.

The proposed biosynthesis of *Laurencia* natural products by Murai and Suzuki begins with the laurediols **1.34-1.35** which are produced from fatty acid metabolism.[1] The laurediols could then undergo enzymatic bromocyclisation, in which positive bromine Br^+ is proposed to be generated from the enzymatic oxidation of bromide anions Br^- by H_2O_2.[1,153,154] The first bromocyclisation reaction between C_7–OH and C-13 would generate the medium ring ethers **1.38** and **1.40** in which **1.38** is the natural product deacetyllaurencin.[1,23,154] Further bromocyclisation reaction between C_6–OH and C-9 would yield prelaurefucins **1.43-1.44** that could undergo transannular halide displacement to give the trialkyloxonium ions **1.3-1.4**.[1,15] The trialkyloxonium ions possess three electrophilic sites at C-7, C-10 and C-13, which could undergo nucleophilic attack by Cl^-, H_2O and Br^- to generate the natural products (*Z*)-notoryne **1.17**, (*E*)-laurefucin **1.14** and Suzuki ocellenynes **1.45-1.46** respectively.

3.5 Proposed biosynthesis of *Laurencia* natural products by Kim, Burton and Britton

Building on the initial biosynthetic hypothesis as suggested by Murai and Suzuki,[1,15] Kim and Burton proposed the participation of trialkyloxonium ions **1.1** and **1.2** in the biosynthesis of another set of natural products bromofucins **1.8** and **1.11**, chlorofucins **1.5-1.6**, elatenynes **1.9** and **1.12**, laurendecumenyne B **1.7** and ocellenynes **1.10** and **1.13**.[4,9,155] The ocellenynes **1.10** and **1.13** are referred as Burton ocellenynes in the Kim, Burton and Britton biosynthtetic postulate as their structures have not been fully elucidated. Burton and Britton further extended the hypothesis to the natural products laurefurenynes A-F **1.28-1.33**, which could unify the structural and stereochemical relationship of all these natural products (**Figure 3.3**).[2,3] The structural elucidation of the natural products mentioned above will be discussed in **Chapter 6.1.1** and **Chapter 8**.

In contrast to the biosynthetic hypothesis by Murai and Suzuki,[1,15] this proposed biosynthesis of *Laurencia* natural products begins with the laurediols **1.47-1.48** that have the 6*S*, 7*S* configuration. Such variations of laurediol stereochemistry are permitted as the laurediols exist naturally as unequal mixtures of (3*E*/*Z*, 12*E*/*Z*)-(6*R*, 7*R*/6*S*, 7*S*) stereoisomers.[156] The subsequent biosynthetic transformations leading to the trialkyloxonium ions **1.1** and **1.2** are identical to the biosynthetic hypothesis as suggested by Murai and Suzuki.

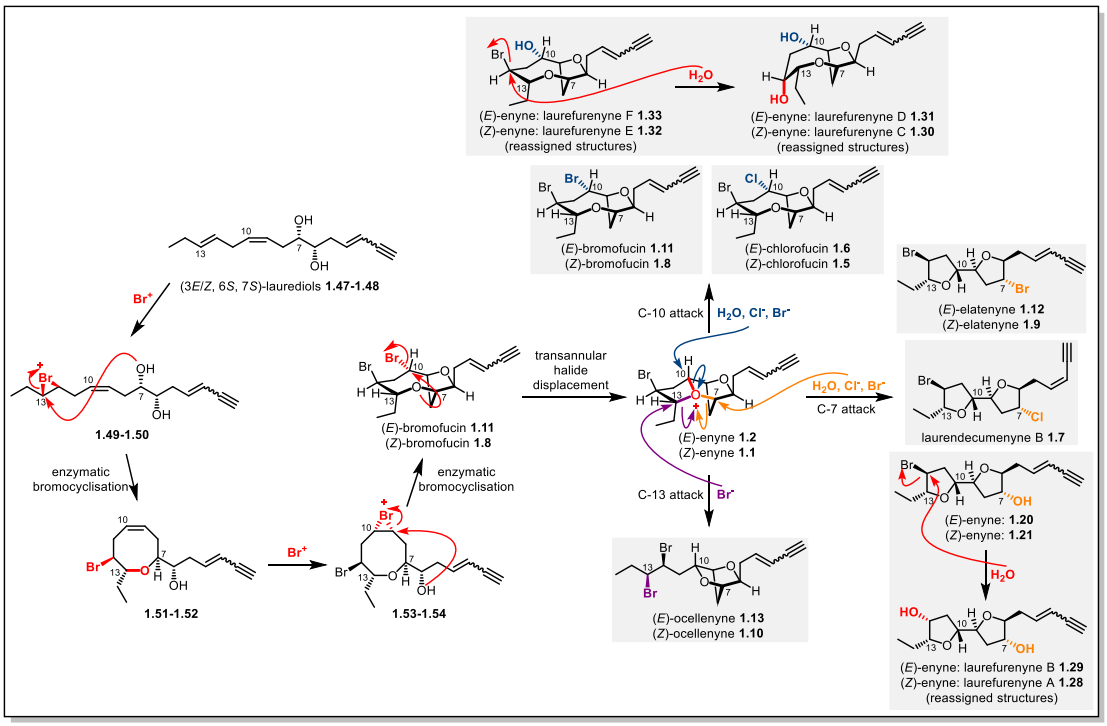


Figure 3.3. Proposed biosynthesis of *Laurencia* natural products *via* **1.1** and **1.2** by Kim, Burton and Britton.

3.6 Proposed biosynthesis of *Laurencia* natural products by Braddock

Considering another set of *Laurencia* natural products, Braddock proposed the following biosynthetic hypothesis involving the participation of a series of trialkyloxonium ions to unify the structural and stereochemical relationship of the obtusallene and marilzabicyclocallene type natural products (**Figure 3.4-3.5**).[157] Some structures of the natural products have been elucidated by X-ray crystallography,[158–162]

NMR spectroscopic analysis,[163] total synthesis,[10,164] and GIAO-based density functional NMR predictions.[165]

In contrast to the biosyntheses proposed by Murai, Suzuki, Kim, Burton and Britton, the biosynthetic postulate suggested by Braddock begins with the epoxides **3.4-3.5** instead of the laurediols **1.34-1.35** and **1.47-1.48**.[157] Formation of the chlorohydrins **3.6-3.7** followed by a series of bromocyclisations would give the cyclic ethers **3.18-3.19**. Subsequent macrocyclisation would give the natural products obtusallene II **3.22** and obtusallene IV **3.23**. The natural products obtusallene II **3.22** and obtusallene IV **3.23** could then generate the rest of the natural products *via* oxonium ion mediated structural rearrangements as displayed in **Figure 3.4-3.5**.[10,157]

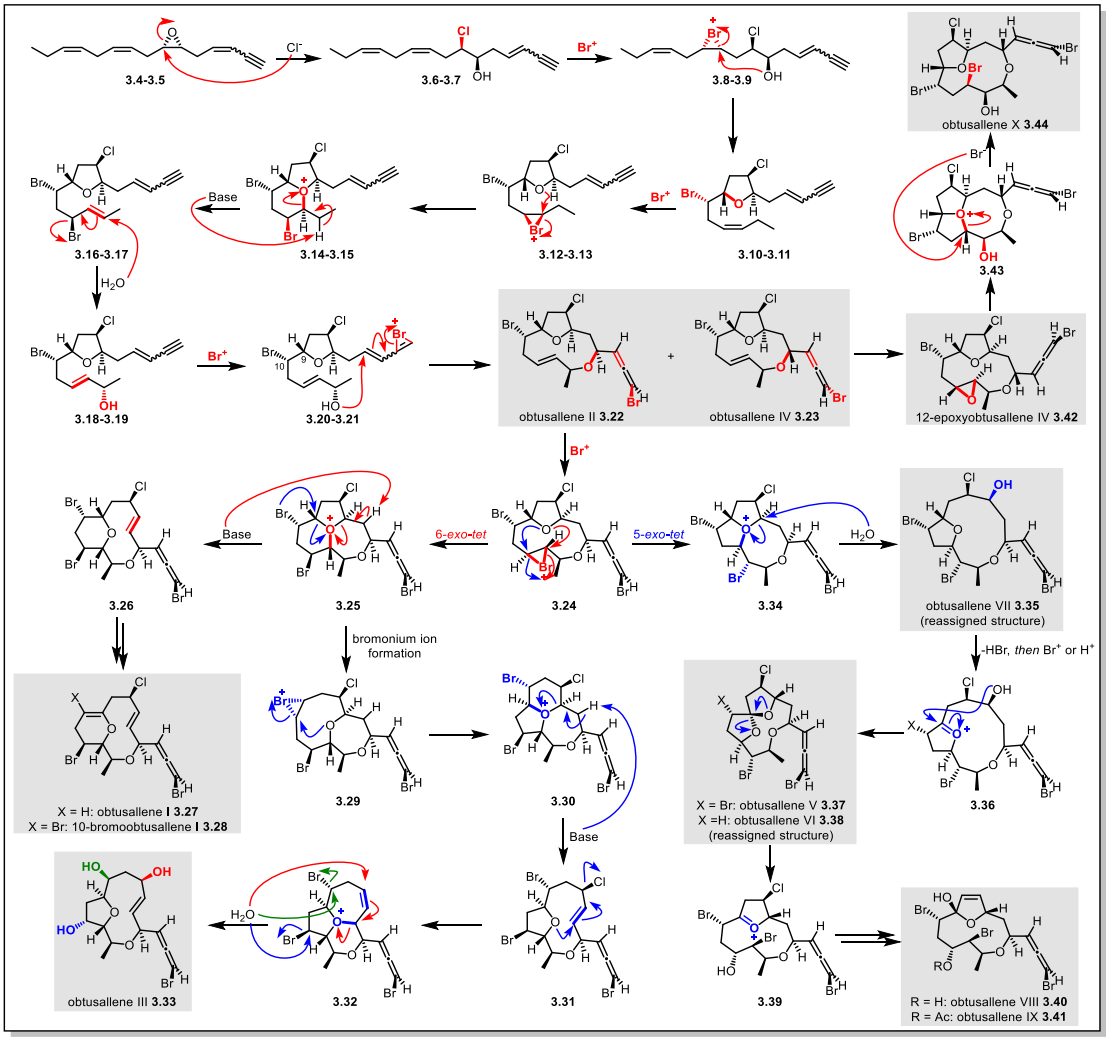


Figure 3.4. Proposed biosynthesis of obtusallene type *Laurencia* natural products by Braddock.

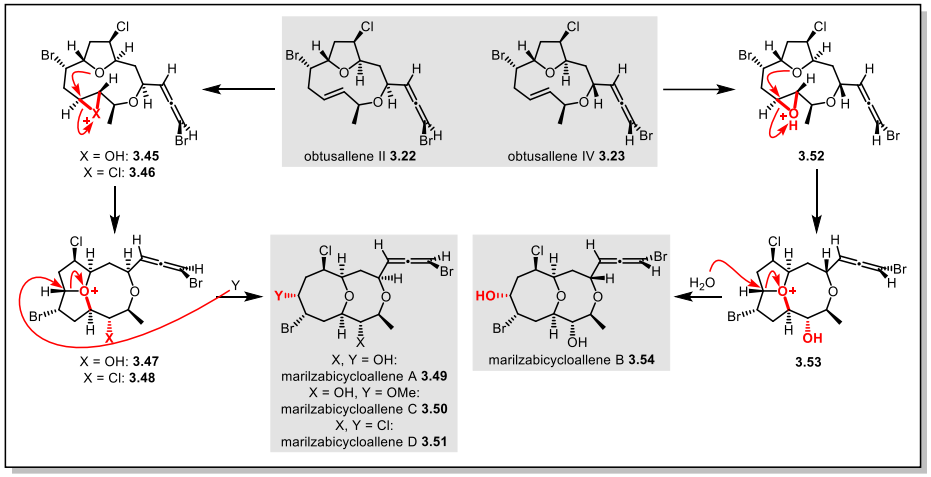


Figure 3.5. Proposed biosynthesis of marilzabicycloallene type *Laurencia* natural products by Braddock.

Braddock also proposed a unifying biosynthesis for the generation of medium ring ether *Laurencia* natural products which are relevant to the biosynthetic postulates described in **Section 3.4** and **3.5**.[6] Braddock proposed the enantiomerically pure epoxide **3.55** as the biosynthetic precursor (**Figure 3.6**).

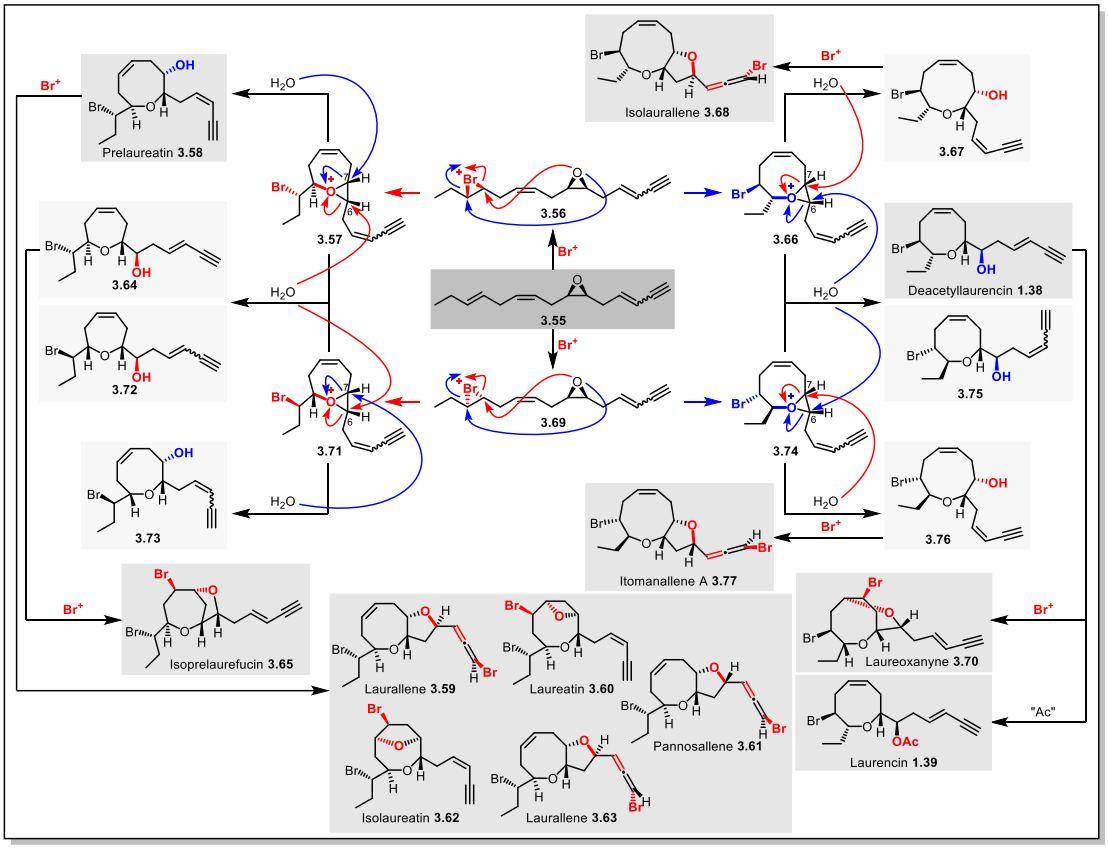


Figure 3.6. Proposed biosynthesis of medium ring ether *Laurencia* natural products by Braddock.

The epoxide **3.55** was proposed to undergo intramolecular bromonium ion assisted epoxide-ring opening to give oxiranium ions **3.57**, **3.71** and **3.66**, **3.74**. Opening of these oxiranium ions by water at C-6 and C-7 would give the 7, 8 and 9-membered ring ether compounds that are either natural products themselves, like deacetyllaurencin **1.38**, or are biosynthetic intermediates that could lead to natural products by further acetylation or intramolecular bromocyclisations.

Similarly, with the epoxide **3.78**, Braddock suggested that opening of the oxiranium ions **3.80**, **3.87** and **3.83**, **3.90** at C-6 and C-7 by chloride anion would give the following medium ring ether natural products (**Figure 3.7**).

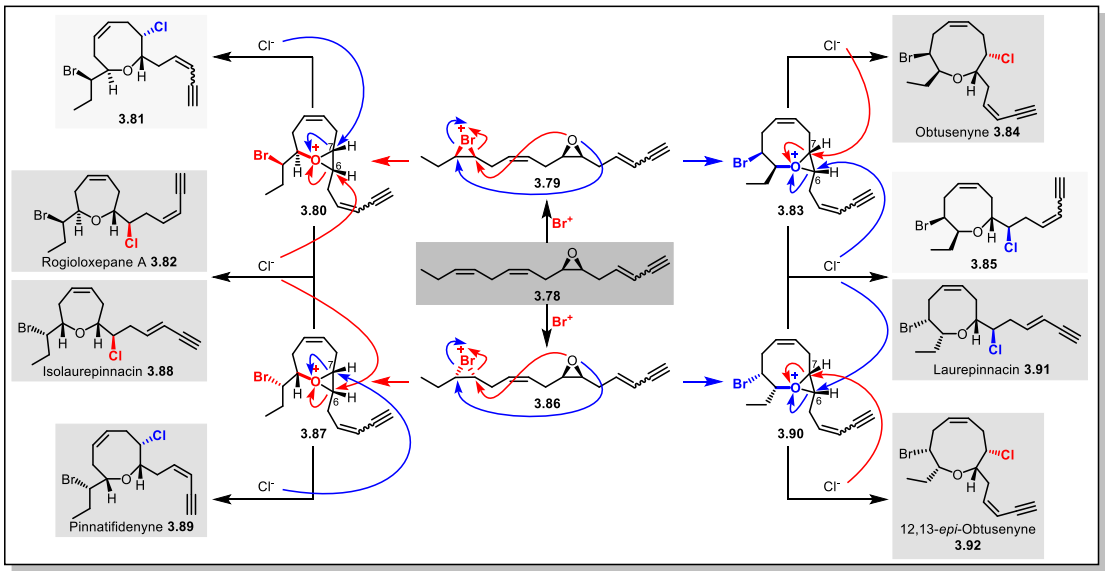


Figure 3.7. Proposed biosynthesis of chlorinated medium ring ether *Laurencia* natural products by Braddock

3.7 Proposed biosynthesis of *Laurencia* natural products by Snyder

Snyder proposed the biosynthesis of *Laurencia* natural products to occur *via* an initial 5-*endo* instead of the 8-*endo* bromoetherification suggested by Murai.[1,7] This suggestion was based on the incredibly low yield (0.015%) of deacetyllaurencin **1.38** obtained from the enzymatic bromocyclisation of laurediol **1.34**,[166] which inspired that

the 8-*endo* bromoetherification could be an unfavourable event even with enzymatic control.[167] After the initial 5-*endo* bromoetherification, another 5-*endo* bromoetherification was proposed to give the oxonium ion **3.95**, which could be quenched by nucleophiles at C-10 to give the medium ring ether **3.96** and further transformed into the natural products (*E*)-laurefucin **1.14** and laureoxanyne **3.70** *via* intramolecular S_N2 reactions (**Figure 3.8**).

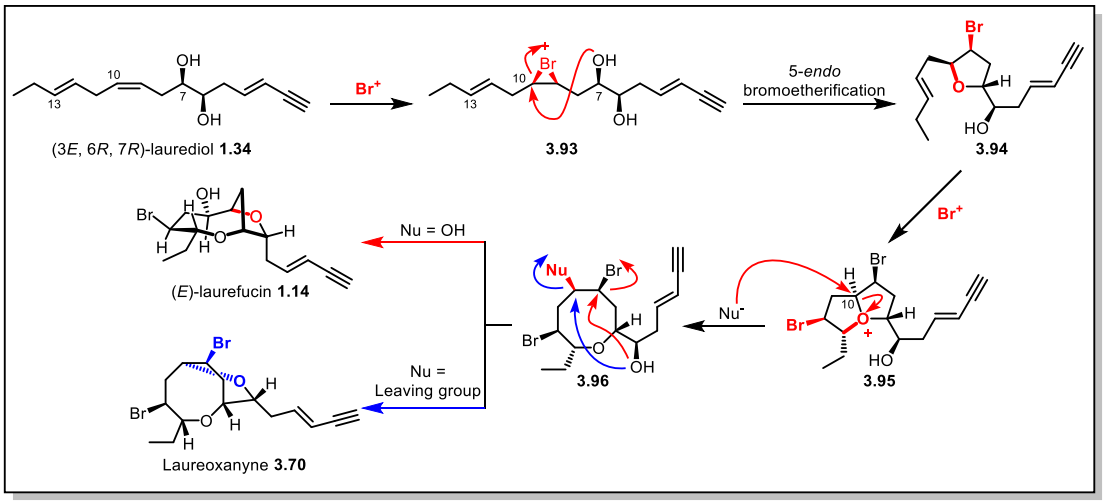


Figure 3.8. Proposed biosynthesis of *Laurencia* natural products by Snyder.

3.8 Proposed biosynthesis of *Laurencia* natural products by Fox

In contrast to the *Laurencia* natural products described above, the natural product laureepoxide **3.102** contains an epoxide rather than a medium ring ether.[168] Fox proposed the biosynthesis of this epoxide natural product *via* a skeletal rearrangement as shown below (**Figure 3.9**).[8]

The authors proposed that the bromonium ion **3.97** could open to form the carbocation **3.98**, which could give the less sterically encumbered oxonium ion **3.101** that could lead to the reported structure of laureepoxide **3.102**.

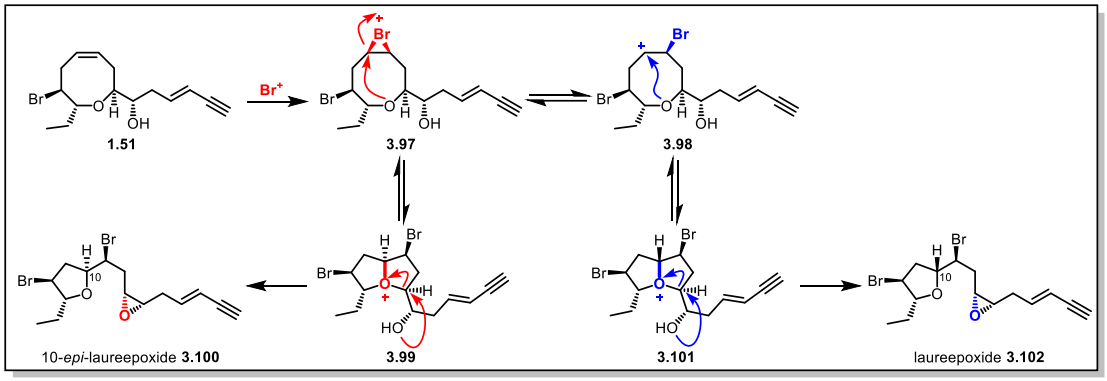
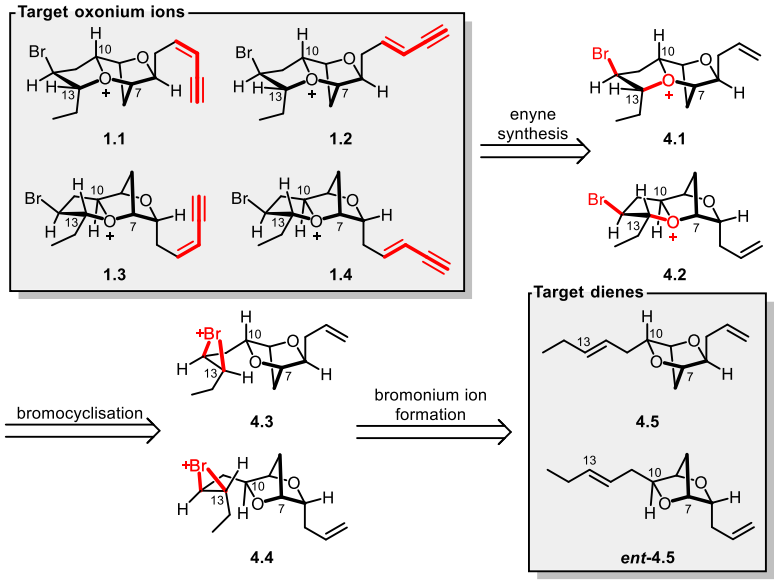


Figure 3.9. Proposed biosynthesis of laureepoxide **3.102** by Fox.

4 The synthesis and studies of a model oxonium ion

4.1 Retrosynthesis of target oxonium ions

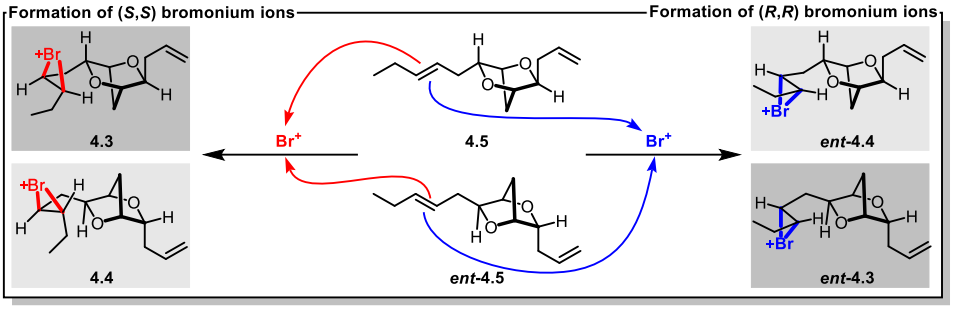
It was envisaged that target oxonium ions **1.1-1.4** could first be simplified to their terminal alkene analogues **4.1-4.2** by disconnection at the enyne C=C bond. The terminal alkenes **4.1-4.2** could then be further simplified to the bromonium ions **4.3-4.4** by disconnection at the C-13–O^+ bond. Subsequent removal of the bromonium ions would suggest the pair of enantiomeric dienes **4.5** and ***ent*-4.5** to be their precursors (**Scheme 4.1**).



Scheme 4.1. Retrosynthetic analysis of oxonium ions **1.1-1.4**.

Facially unselective bromonium ion formation on the more electron rich internal olefin of the pair of enantiomeric dienes **4.5** and ***ent*-4.5** would yield two enantiomeric pairs of bromonium ions **4.3**, ***ent*-4.3** and **4.4**, ***ent*-4.4** (**Scheme 4.2**). Their stereochemical relationship imply that the synthesis of either enantiomer of the dienes **4.5** or ***ent*-4.5** would be sufficient for our studies, as bromonium ions **4.3** and ***ent*-4.4** would be the respective precursors to the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4**. Similarly,

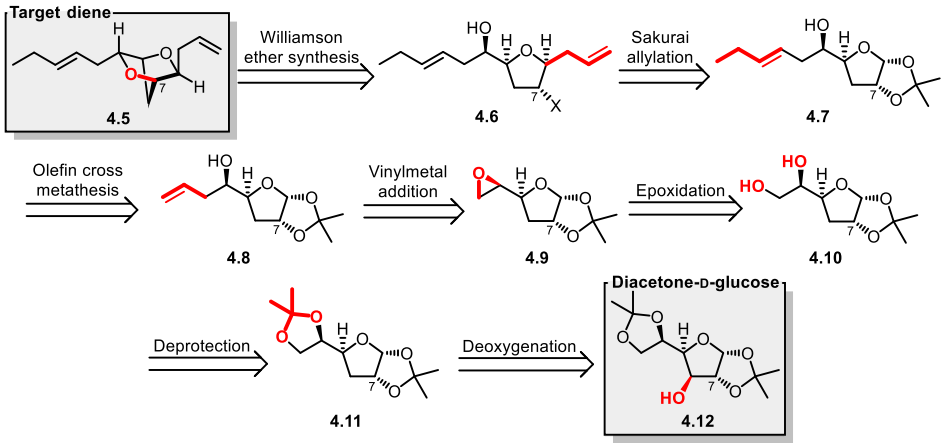
bromonium ions **4.4** and ***ent*-4.3** would be the precursors to the oxonium ions ***ent*-1.1**, ***ent*-1.2** and **1.3**, **1.4**.



Scheme 4.2. Two enantiomeric pairs of bromonium ions.

This analysis would allow facile access to the target oxonium ions and their associated natural products from a single diene precursor. However, one half of the oxonium ions and their associated natural products would be in the unnatural enantiomer series.

The retrosynthetic analysis of **4.5** began with the disconnection of the C-7–O bond in the strained dioxabicyclo[2.2.1] system of **4.5** to generate the 2,3,5-trisubstituted tetrahydrofuran **4.6**, which could be simplified to the fused bicyclic system **4.7** *via* disconnection of the allyl group.[169–173] Further disconnection at the olefin of the fused bicyclic system **4.7** would give **4.8** that could be forged from readily available diacetone-D-glucose **4.12** *via* a well-established sequence of vinylmetal addition, epoxidation, deprotection and deoxygenation reactions (**Scheme 4.3**).[169–171,173–176]

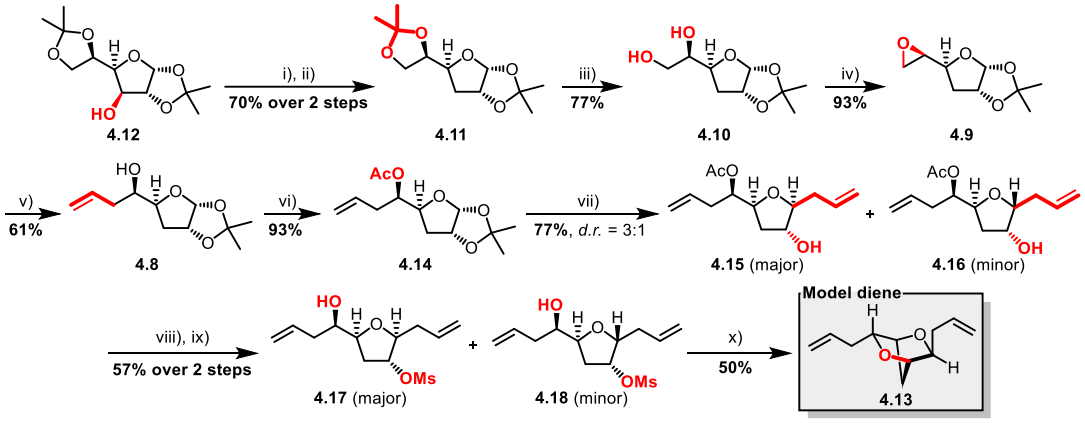


Scheme 4.3. Retrosynthetic analysis of diene **4.5**.

It could be envisaged that the enantiomer ***ent*-4.5** could also be synthesised from diacetone-L-glucose ***ent*-4.12**. However, due to the low commercial availability of diacetone-L-glucose ***ent*-4.12**, the extra steps required for its synthesis from D-glucose,[177] and the low synthetic value concerning the synthesis of ***ent*-4.5** in our studies, its synthesis was not pursued.

4.1.1 *Synthesis of model diene*

Studies of the synthesis of model diene **4.13** were first pursued to probe the viability of the synthesis of the strained dioxabicyclic[2.2.1] scaffold from **4.12** (**Scheme 4.4**).



Scheme 4.4. Synthesis of model diene **4.13**.

Reagents and conditions: **i)** NaH (1.3 eq., 60% suspension in mineral oil), cat. imidazole, CS_2 (3.0 eq.), MeI (1.8 eq.), THF, r.t., 15 min. **ii)** Bu_3SnH (1.6 eq.), toluene, reflux, overnight. **iii)** 75% AcOH in H_2O, r.t., overnight. **iv)** NaH (2.0 eq., 60% suspension in mineral oil), TsCl (1.0 eq.), THF, 0 °C to r.t., overnight. **v)** $CH_2CHMgBr$ (1.9 eq., 1.0 M solution in THF), 10 mol% CuI, THF, -20 °C, 30 min. **vi)** Ac_2O (3.0 eq.), DMAP (3.0 eq.), CH_2Cl_2, r.t., 4 hrs. **vii)** $CH_2CHCH_2SiMe_3$ (5.0 eq.), $BF_3{\cdot}Et_2O$ (3.0 eq), CH_2Cl_2, 0 °C to r.t., overnight. **viii)** MsCl (1.1 eq.), Et_3N (1.1 eq.), CH_2Cl_2, 0 °C to r.t., 30 min. **ix)** K_2CO_3 (2.0 eq.), MeOH/H_2O (5:1), r.t., 36 hrs. **x)** NaH (7.0 eq., 60% suspension in mineral oil), DMF, r.t., overnight. Step **x)** was only carried out with compound **4.17**.

The compound **4.9** was prepared from commercially available **4.12** according to known procedures *via* Barton-McCombie deoxygention, selective acetal hydrolysis and epoxidation.[171,174–176] The epoxide **4.9** was then converted into the homoallylic alcohol **4.8** by a copper-catalysed epoxide opening with vinylmagnesium bromide. The

homoallylic alcohol **4.8** was then converted to its acetate **4.14** and subjected to reaction conditions that promoted a Hosomi-Sakurai allylation and gave **4.15** and **4.16** in a diastereomeric ratio of 3:1 in favour of **4.15**.

The observed diastereomeric ratio was best explained with reference to various observations and models published in literature that suggest both Woerpel's inside attack model and Marrero-Tellado's *exo* facial template model are required to explain the observed stereochemical outcome.[169,171,172,178–181] According to Marrero-Tellado's model, 1,2-*O*-isopropylidene-protected glycofuranosides undergo the Hosomi-Sakurai allylation to give predominantly 1,2-*trans* products because of the *exo* facial template effect enabled by the bicyclic nature of these 1,2-*O*-isopropylidene-protected glycofuranosides (**Figure 4.1**).[180]

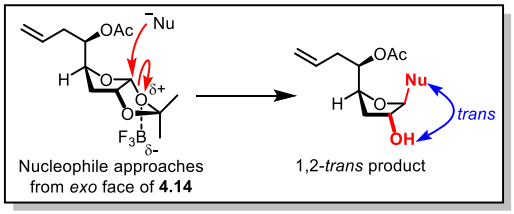


Figure 4.1. Marrero-Tellado's *exo* facial template effect model applied to **4.14** to explain the formation of 1,2-*trans* products from 1,2–O-isopropylidene-protected glycofuranosides.

The 1,2-*trans* selectivity was reported to be independent of the substitution and stereochemistry of existing substituents.[180] However, the 1,2-*trans* selectivity observed with our substrate **4.14** was only modest. In light of the fact that our substrate **4.14** is a 3-deoxy sugar, whereas the substrates employed by Marrero-Tellado bear *tert*-butyldimethylsiloxy groups or acetates at the same position, our substrates could be more activated towards glycosyl cation formation and thus could undergo the Hosomi-Sakurai allylation according to Woerpel's inside attack model *via* a glycosyl cation. In this case, the expected stereochemical outcome of the products would be 1,2-*cis* (**Figure 4.2**).[178,179] As for the substitution pattern at C-4, it was reported by Woerpel

to not significantly influence the stereochemical outcome of the allylation reaction unless the substituents are very sterically hindered.[178]

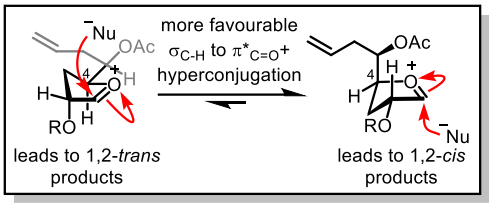


Figure 4.2. Woerpel's inside attack model applied to **4.14** to explain the formation of 1,2-*cis* products.[178,179]

This was further corroborated with another example by Sartillo-Piscil,[172] the substrate **4.19** that was expected to be even more activated towards glycosyl cation formation was found to predominantly provide the 1,2-*cis* product **4.21**, which is expected from a greater contribution of the glycosyl cation intermediate **4.20** (**Figure 4.3**).

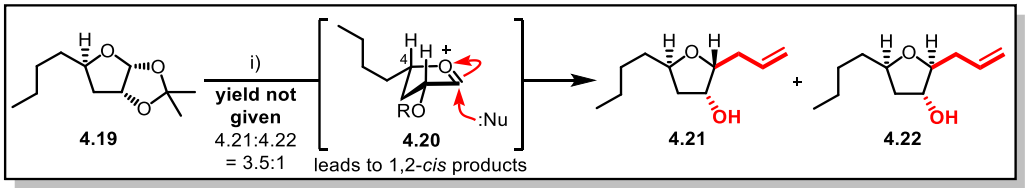


Figure 4.3. The synthesis of 1,2-*cis* product **4.21** as reported by Sartillo-Piscil.[172]
Reagents and conditions: **i)** $CH_2CHCH_2SiMe_3$ (6.0 eq.), $BF_3{\cdot}Et_2O$ (6.0 eq.), CH_2Cl_2, 0 °C, 4 hrs.

Therefore, the observed distribution of 1,2-*trans* and 1,2-*cis* products from the Hosomi-Sakurai allylation of **4.14** would most likely be explained by the simultaneous operation of both the *exo* facial templating mechanism (**Figure 4.1**) and the glycosyl cation mechanism (**Figure 4.2**), but with a slight preference for the *exo* facial templating mechanism as the propensity for **4.14** to form glycosyl cations is not expected to be as high as that of **4.19**.

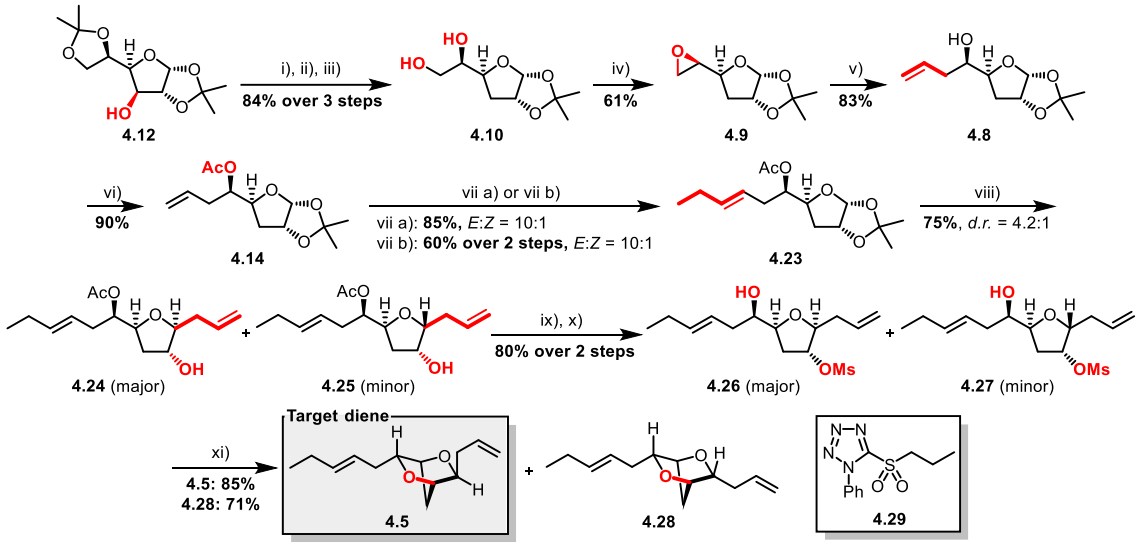
Following the Hosomi-Sakurai allylation, the compounds **4.15** and **4.16** were converted into **4.17** and **4.18** by mesylation of the alcohol and a deprotection of the acetyl group

followed by separation with flash column chromatography. The compound **4.17** was then subjected to conditions as shown above (**Scheme 4.4**) to facilitate an intramolecular etherification to provide the dioxabicyclic[2.2.1] diene **4.13**.

4.1.2 *Synthesis of target diene*

Having synthesised the model diene **4.13**, this synthetic sequence was applied to the synthesis of the target diene **4.5**. A series of optimisations regarding reaction conditions and synthetic operations were carried out along the way to ultimately provide a robust and efficient synthesis of **4.5** in gram scale over a week from diacetone-D-glucose **4.12** (**Scheme 4.5**). The major improvements were to adopt a tin-free deoxygenation protocol using *n*-Bu_4NBH_4 that allowed the first three steps of the synthesis to be telescoped,[182,183] and an intramolecular Mitsunobu reaction for the synthesis of **4.9** that improved reproducibility.

The synthesis of **4.23** could either be achieved by an olefin cross-metathesis reaction between **4.14** and *trans*-3-hexene or a Julia-Kocienski olefination with the reagent **4.29** with the aldehyde derived from **4.14**. The yield obtained from the olefin cross-metathesis reaction was higher than that for the Julia-Kocienski olefination and both reactions gave the same *E*:*Z* ratio as determined by the analysis of their ^{1}H NMR spectra. Although the Julia-Kocienski olefination had a lower reaction yield, it was a more cost-effective method for the large scale synthesis of **4.5** compared to olefin cross-metathesis.



Scheme 4.5. Synthesis of target diene **4.5**.

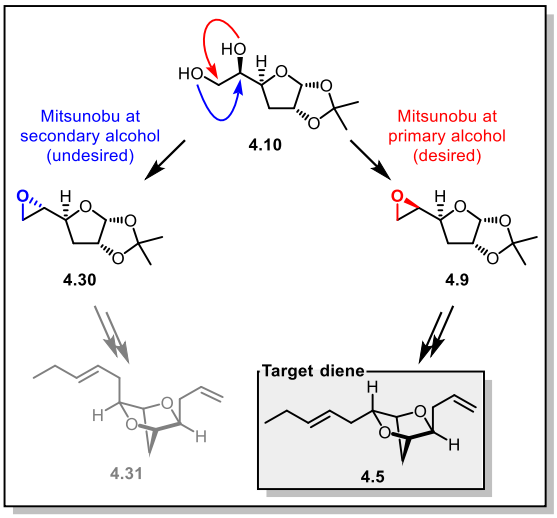
Reagents and conditions: **i)** Tf_2O (1.2 eq.), pyridine (2.2 eq.), CH_2Cl_2, 0 °C, 1 hr. **ii)** *n*-Bu_4BH_4 (3.0 eq.), toluene, 80 °C, overnight. **iii)** 75% AcOH in H_2O, r.t., overnight. **iv)** DEAD (1.2 eq.), PPh_3 (1.2 eq.), toluene, reflux, overnight. **v)** $CH_2CHMgBr$ (1.9 eq., 1.0 M solution in THF), 10 mol% CuI, THF, -20 °C, 1 hr. **vi)** Ac_2O (3.0 eq.), DMAP (3.0 eq.), CH_2Cl_2, r.t., 4 hrs. **vii a)** *trans*-3-hexene (10.0 eq.), Grubb's 2nd generation catalyst (7.5 mol%), CH_2Cl_2, r.t., 2 hrs, then add DMSO, r.t. overnight. **vii b**) cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t., 2 hrs, then **4.29** (0.95 eq.), NaHMDS (1.1 eq., 1.0 M in THF), THF, -78 °C, 40 min. **viii)** $CH_2CHCH_2SiMe_3$ (5.0 eq.), $BF_3{\cdot}Et_2O$ (3.0 eq.), CH_2Cl_2, 0 °C to r.t., overnight. **ix)** MsCl (1.1 eq.), Et_3N (1.1 eq.), CH_2Cl_2, 0 °C to r.t., 30 min. **x)** K_2CO_3 (2.0 eq.), MeOH/H_2O (9:1), r.t., 2 hrs. **xi)** NaH (7.0 eq., 60% suspension in mineral oil), DMF, r.t., overnight.

The strategies for the transformations following the synthesis of **4.23** were analogous to those presented in **Scheme 4.4**. The reaction yields obtained were better and an improvement was observed in the diastereoselectivity of the Hosomi-Sakurai allylation reaction for the synthesis of **4.24** and **4.25**. However, the improvement was only a modest increase from 3:1 to 4.2:1 (**4.24**:**4.25**). This synthetic route therefore allowed the synthesis of **4.5** in 12% overall yield over 11 steps. With 10.0 g of starting material **4.12**, the synthesis could be completed in a week to provide on average 1.0 g of **4.5** for further synthetic studies.

4.1.3 *Structural elucidation of target diene*

The structure of diene **4.5** was confirmed with support from the structural and stereochemical analyses of its precursors, determination of the absolute configurations at secondary alcohol stereocentres by Mosher ester analysis when necessary,[184,185] and comparative NMR studies with its epimer **4.28**.

The analysis began with the determination of the absolute configuration of the secondary alcohol stereocentre of **4.8**. This was deemed necessary as the epoxidation reaction that precedes the synthesis of **4.8** could be stereochemically ambiguous. This was because the Mitsunobu reaction could occur on the secondary alcohol of **4.10** instead of the primary alcohol, and thus providing **4.30** that is an epimer of the desired epoxide **4.9**. The undesired epoxide **4.30** would ultimately provide the species **4.31** (**Scheme 4.6**).



Scheme 4.6. Possible stereochemical outcomes of the stereochemically ambiguous epoxidation reaction of diol **4.10**.

Mosher ester analysis of **4.8** was performed to determine the absolute configuration of the secondary alcohol stereocentre in **4.8**. From the Mosher ester analysis, if the secondary alcohol stereocentre in **4.8** did possess the desired (*R*) configuration, the results as displayed below according to the methods of Hoye and Kakisawa would be expected

(**Figure 4.4**).[184,185] The results of the analysis were in complete agreement with the results as expected for the desired absolute configuration (*see appendix 12.6*).

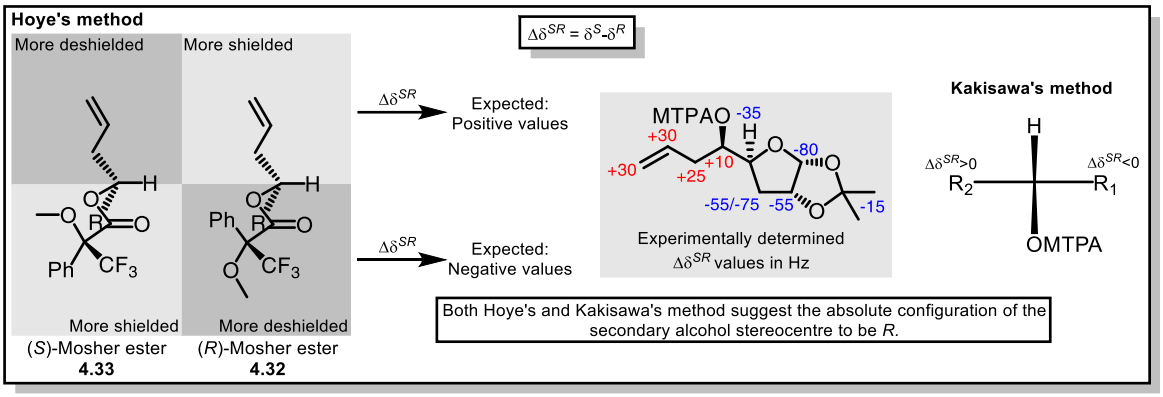


Figure 4.4. Results of Mosher ester analysis of **4.8**.

Next, the relative configurations in **4.26** and **4.27** were determined to assign the 1,2-*trans* and 1,2-*cis* products. The diastereomers **4.26** and **4.27** were separable by column chromatography and were isolated accordingly. The relative configurations of the stereogenic centers of interest were analysed by both 1D NMR ^{1}H-^{1}H nOe experiments and *J*-coupling analysis of their $^{3}J_{HH}$ coupling constants. However, five-membered cyclic systems are conformationally flexible and multiple ring conformations could be populated simultaneously, thus the determination of relative configurations of stereocentres on the ring by *J*-coupling analysis or nuclear Overhauser effect (nOe) may not be conclusive.[186]

The 1D NMR ^{1}H-^{1}H nOe experiments on **4.26** and **4.27** returned inconclusive results. Both **4.26** and **4.27** exhibited ^{1}H-^{1}H nOe correlations between H-6 and H-9, although the nOe correlations in **4.27** were found to be much weaker (**Figure 4.5**). This observation suggests that **4.26** could be the 1,2-*trans* product.

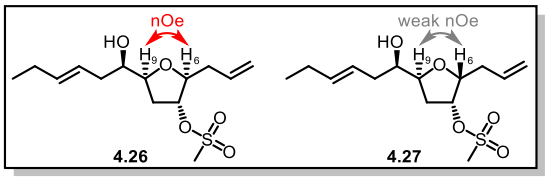


Figure 4.5. ^{1}H-^{1}H nOe correlations between H-6 and H-9 of **4.26** and **4.27** for their structural determination.

The analysis of the $^{3}J_{HH}$ coupling constants of **4.26** and **4.27** was then performed in attempt to discern the 1,2-*trans* and 1,2-*cis* products. The behaviour of $^{3}J_{HH}$ coupling constants of 1,2-*trans* and 1,2-*cis* protons in conformationally flexible tetrahydrofuran systems depends on their range of H–C–C–H dihedral angles. Daranas and co-workers performed molecular dynamics simulations and the results suggest that the dihedral angles adopted by 1,2-*trans* protons is between |60°| and |180°|, whereas the dihedral angles adopted by 1,2-*cis* protons is in the range of +60° to -60°.[186] This implies that only 1,2-*trans* protons can access dihedral angles around 90° which results in small $^{3}J_{HH}$ coupling constants.[187–189] The crucial piece of information in the assignment of **4.26** was therefore the ~2.0 Hz $^{3}J_{HH}$ coupling constant observed between H-6 and H-7. The ~7.0 Hz $^{3}J_{HH}$ coupling constant observed for the same protons in **4.27** was categorised as inconclusive in Daranas' studies as both 1,2-*trans* and 1,2-*cis* protons could exhibit large $^{3}J_{HH}$ coupling constants. However, as both **4.26** and **4.27** have the same molecular connectivity, the 1,2-*cis* product was the only possible assignment for **4.27** (**Figure 4.6**).

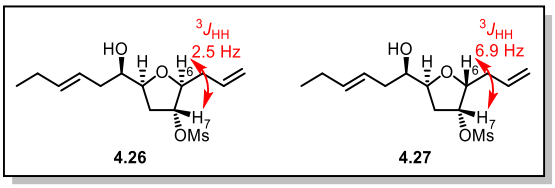


Figure 4.6. $^{3}J_{HH}$ coupling constants for the determination of relative configurations in **4.26** and **4.27**.

Further evidence for the relative configurations of the intermediates **4.26** and **4.27** was obtained from 1D NMR ^{1}H-^{1}H nOe studies of the dienes **4.5** and **4.28**. The results from

all these 1D NMR ^{1}H-^{1}H nOe studies strongly suggest that the assignments for the intermediates **4.26**, **4.27** and the dienes **4.5** and **4.28** are as proposed.

In the 1D NMR ^{1}H-^{1}H nOe experiment of **4.5**, an nOe to H-6 was observed upon irradiation at H-8, which suggested the relative configuration at C-6 as shown below. This was the only piece of evidence for the assignment of the relative stereochemistry of **4.5**, as other modes of irradiation such as at H-11 and H-6 returned inconclusive results (**Figure 4.7**).

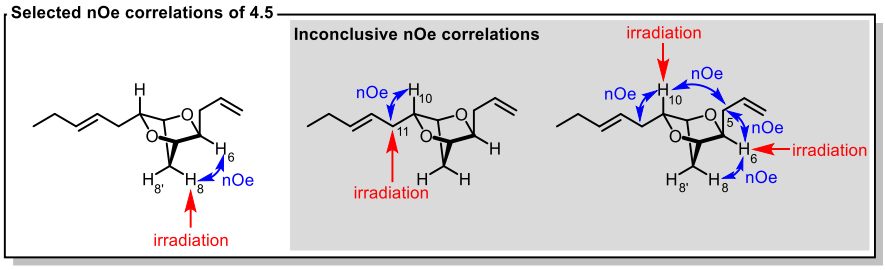


Figure 4.7. ^{1}H-^{1}H nOe correlations of **4.5** for its structural determination.

The 1D NMR ^{1}H-^{1}H nOe experiment of **4.28** demonstrated that upon irradiation at H-8, much stronger nOe correlations were observed at H-11 and H-5 compared to that at H-6 and H-10, suggesting the assignment of **4.28** is as shown (**Figure 4.8**).

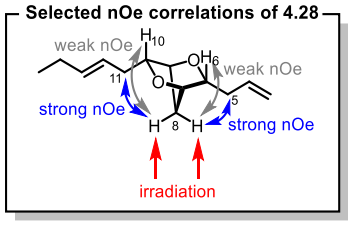
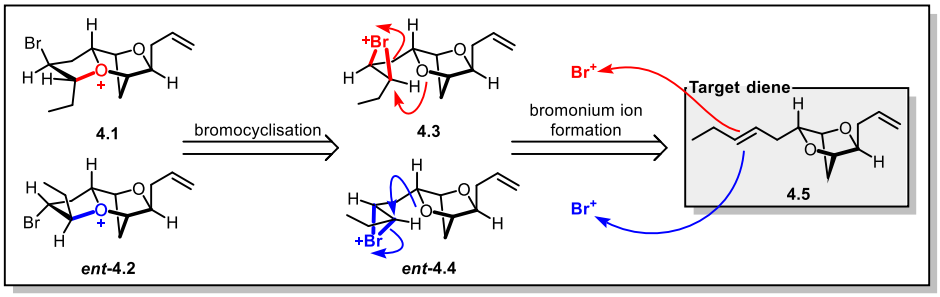


Figure 4.8. ^{1}H-^{1}H nOe correlations of **4.28** for its structural determination.

The development of a robust and efficient synthesis of **4.5** and its structural assignment had therefore been accomplished.

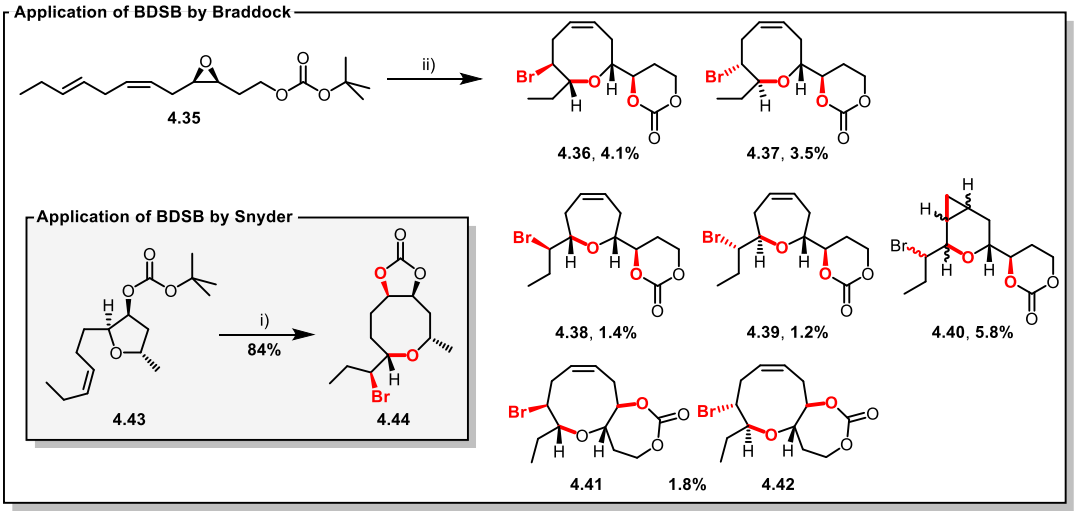
4.2 Studies of oxonium ion generation *via* intramolecular bromocyclisation

Our initial strategy for the generation of oxonium ions **4.1** and ***ent*-4.2** involved the treatment of **4.5** with a source of positive bromine followed by an intramolecular bromocyclisation *via* bromoniums **4.3** and ***ent*-4.4** (**Scheme 4.7**).



Scheme 4.7. Generation of oxonium ions **4.1** and ***ent*-4.2** from **4.5** by an intramolecular bromocyclisation reaction.

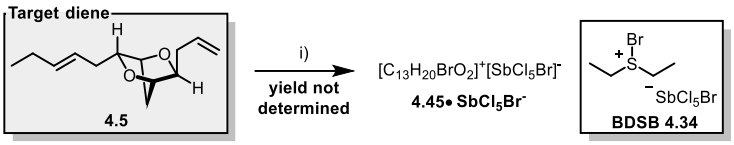
It was envisaged that employing a source of positive bromine that carries weakly coordinating anions would be ideal to realise the desired transformation, as weakly coordination anions are not expected to react with the oxonium ions **4.1** and ***ent*-4.2** and the bromonium ions **4.3** and ***ent*-4.4**. Initial experiments were performed with the BDSB reagent ($Et_2SBr{\cdot}SbCl_5Br$) **4.34**, a reagent popularised by Snyder, as the source of positive bromine.[7,190–192] Snyder and Braddock have previously shown that the BDSB reagent was capable of inducing intramolecular bromocyclisation reactions in substrates **4.43** and **4.35** (**Figure 4.7**).[6,7,190,192]



Scheme 4.8. Application of the BDSB reagent by Snyder and Braddock on **4.43** and **4.35**.
Reagents and conditions: **i)** BDSB (1.2 eq.), $MeNO_2$, -25 °C to 25 °C, 10 mins. **ii)** BDSB, $MeNO_2$, r.t., 1 hr.

However, haloantimonate counter anions can potentially act as a source of halide anions.[190,193] It has also been reported that if the cation of interest is too electrophilic then a haloantimonate counter anion would no longer be considered weakly coordinating.[194]

4.2.1 *Reaction of target diene with BDSB*



Scheme 4.9. Reaction of **4.5** with **4.34** to give the species **4.45**.
Reagents and conditions: **i)** BDSB (1.0 eq.), $EtNO_2$, -78 °C to r.t., 1 hr, then all the volatiles were removed under reduced pressure.

Preliminary experiments were carried out with **4.5** and **4.34** based on the observations that the Meerwein salts $Me_3O^+ \cdot SbCl_6^-$ and $Et_3O^+ \cdot SbCl_6^-$ are commercially available reagents, suggesting that haloantimonate counter anions are compatible with oxonium ions, and to the best of our knowledge no incorporation of Et_2S into cationic species during BDSB-induced bromocyclisations has been reported. Using a modification of

Snyder's reaction condition, namely with $EtNO_2$ as the solvent and a reaction temperature at -78 °C, provided a species that was stable at room temperature (**Scheme 4.9**). Analysis of **4.45** by NMR spectroscopy revealed that none of the expected oxonium ion resonances were observed. High-resolution ESI-MS analysis of **4.45** was inkeeping with species that have the *m/z* values (287.0640 and 289.0619) such as the bromonium ions **4.3** and ***ent*-4.4** or the oxonium ions **4.1** and ***ent*-4.2** (**Figure 4.9**). The exact identity of this species at this stage remains to be elucidated. However, all the available experimental evidence suggest that this species is a precursor to the oxonium ions **4.1** and ***ent*-4.2**. Further experiments were carried out to probe the reactivity and behaviour of this species.

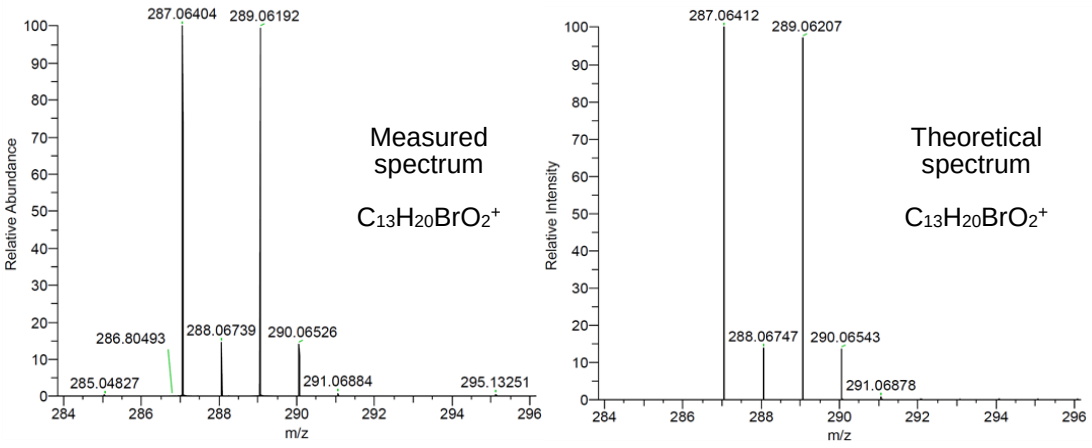
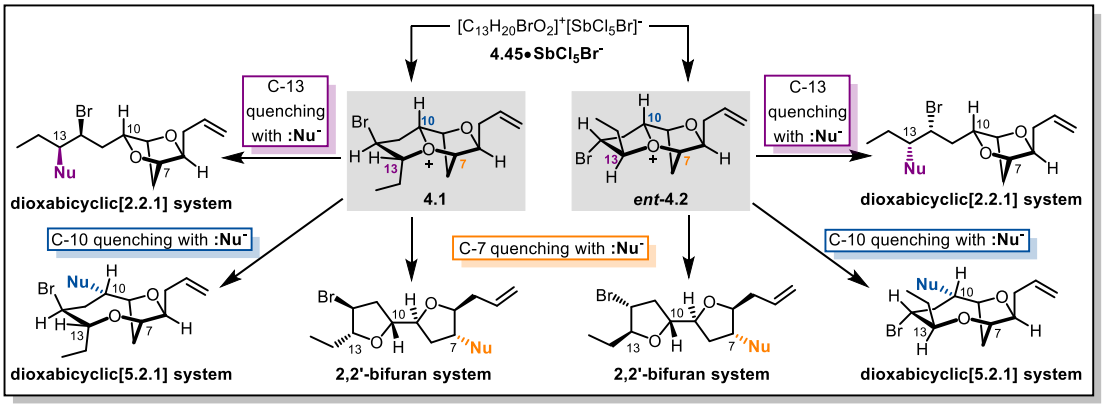


Figure 4.9. Result of high-resolution ESI-MS analysis of **4.45**.

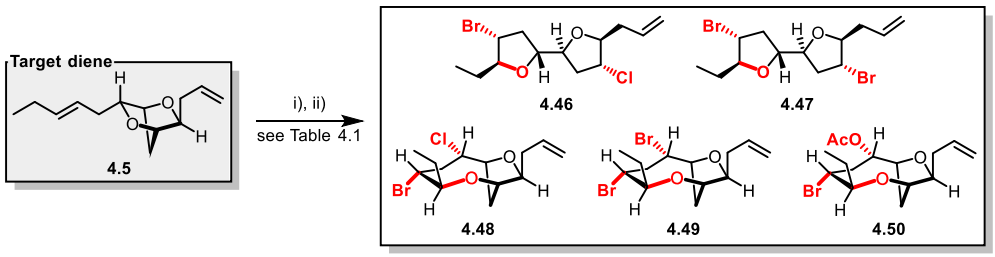
4.2.2 *Probing the behaviour, reactivity and identity of **4.45***

If **4.45** is indeed a precursor to the oxonium ions **4.1** and ***ent*-4.2**, then exposure of **4.45** to nucleophiles will be expected to give products that arise from the nucleophilic opening of the oxonium ions (**Scheme 4.10**).



Scheme 4.10. The possible types of products that could be generated from the nucleophilic opening of oxonium ions **4.1** and ***ent*-4.2** with a generic nucleophile ($:Nu^-$).

The species **4.45** was treated with a range of nucleophiles at different temperatures (**Table 4.1**). The results were surprising, as the major isolable species, the chloride **4.48** obtained from the reactions at room temperature was independent of the type of added nucleophile (**Table 4.1, Column 2**). However, with acetate as the nucleophile and at higher temperatures (50-80 °C), the acetate **4.50** and isomeric chloride **4.46** were obtained (**Table 4.1, Columns 3-4**). The structural elucidation of **4.46, 4.48** and **4.50** will be addressed in **Section 4.2.3**. No reaction was observed when **4.45** was stirred without any added nucleophiles at room temperature overnight. But if the reaction was heated to 50 °C or 80 °C, the isomeric chloride **4.46** was isolated as the major product (**Table 4.1, Entry 1**).



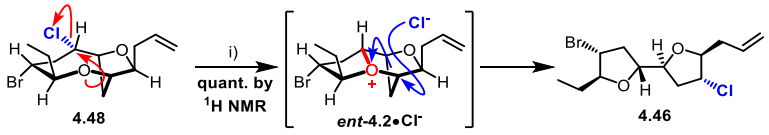
Column / Entry	1	2	3	4
	Nucleophile\T	**20 °C**	**50 °C**	**80 °C**
1	**None**	Insignificant reactivity*	**4.46** (36%) + trace **4.48**	**4.46** (39%) + trace **4.48**
2	***n*-Bu$_4$NF**	**4.48** (10%), incomplete reaction$^{\#}$	**4.48** (12%)	Decomposition
3	***n*-Bu$_4$NCl**	**4.48** (19%), incomplete reaction$^{\#}$	**4.48** (37%) + trace **4.46**	**4.46** (31%) + trace **4.48**
4	***n*-Bu$_4$NBr**	Trace **4.48**	Mixture of **4.46-4.49**	Mixture of **4.46-4.49**
5	***n*-Bu$_4$NI**	**4.48** (21%), incomplete reaction$^{\#}$	**4.48** (32%) + trace **4.46**	**4.46** (32%) + trace **4.48**
6	***n*-Bu$_4$NOAc**	**4.48** (15%), incomplete reaction$^{\#}$	**4.48** (17%) + **4.50** (19%) + trace **4.46**	**4.50** (42%) + trace **4.46** + trace **4.48**

Table 4.1. Results from the reaction of **4.45** with various nucleophiles at different temperatures. Reagents and conditions: **i)** BDSB (1.0 eq.), $EtNO_2$, r.t., 30 min. **ii)** Nucleophile (5.0 eq.), $EtNO_2$, T, overnight. * **4.45** was found to slowly convert to **4.46** if left under ambient conditions for weeks. $^{\#}$ **4.45** is a baseline species on TLC, thus the completion of reaction was determined by the absence of baseline species during TLC analysis.

The generation of alkyl fluorides was found to be unsuccessful that was attributed to the basicity of the fluoride anion that could cause substrate decomposition (**Table 4.1, Entry 2**). Alkyl bromides posed other problems due to the generation of an inseparable mixture of compounds **4.46-4.49** because of spontaneous rearrangement of bromide **4.49** into isomeric bromide **4.47** at room temperature (**Section 4.3**) (**Table 4.1, Entry 4**). As for

the generation of alkyl iodides, the reaction mixture turned brown upon the addition of *n*-Bu_4NI (**Table 4.1, Entry 5**). It has been documented that $SbCl_6^-$ can behave as a weak oxidant that could oxidise iodide to iodine and have itself reduced to $SbCl_4^-$ with the generation of two equivalents of chloride anion.[193] This oxidation process would account for the colour change observed and the isolation of chloride **4.48** instead of the corresponding alkyl iodides.

As chloride **4.48** was shown to be produced first with various added nucleophiles, the production of isomeric chloride **4.46** and acetate **4.50** under these conditions may first involve the transient generation of oxonium ion ***ent*-4.2** from chloride **4.48** *via* transannular chloride displacement followed by quenching with acetate. This would explain why heating must be involved for these transformations as chloride **4.48** would not spontaneously generate oxonium ion ***ent*-4.2** and rearrange into isomeric chloride **4.46** at room temperature overnight. A control experiment was performed to demonstrate that chloride **4.48** can be completely converted to isomeric chloride **4.46** in $EtNO_2$ at 80 °C overnight, implying the participation of the oxonium ion ***ent*-4.2** (**Scheme 4.11**). However, no products arising from the participation of the diastereomeric oxonium ion **4.1** were observed.



Scheme 4.11. The thermal conversion of **4.48** to **4.46**.
Reagents and conditions: **i)** $EtNO_2$, 80 °C, overnight

These experimental observations suggested that **4.45** had a structure that is similar to chloride **4.48**. This was corroborated with comparisons of the ^1H and ^{13}C NMR chemical shifts between **4.45**, diene **4.5**, isomeric chloride **4.46**, chloride **4.48** and acetate **4.50**. Their similarity is reflected by the averaged absolute values of their ^1H and ^{13}C NMR

chemical shift differences with respect to **4.45**, in which the chloride **4.48** was found to have the smallest difference in chemical shifts (**Figure 4.10**, *see appendix 12.1*).

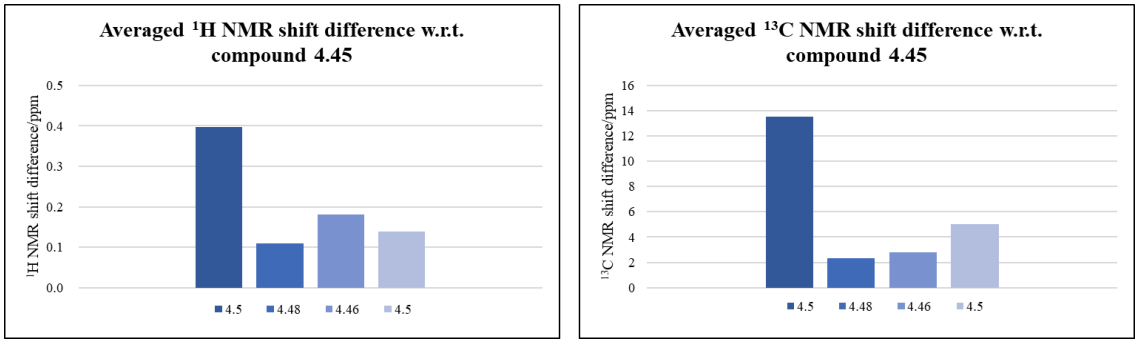
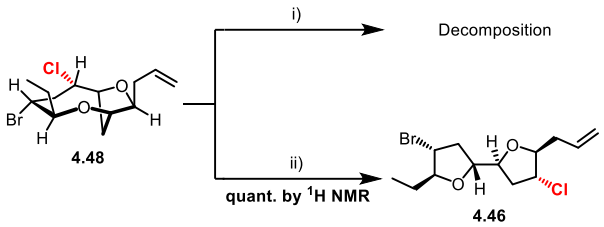


Figure 4.10. Averaged ^{1}H and ^{13}C NMR shift difference of compounds **4.5**, **4.48**, **4.46** and **4.50** with respect to **4.45**.

This structural similarity between **4.45** and chloride **4.48** and the selective generation of chloride **4.48** irrespective of the types of nucleophiles added at room temperature suggested that the C-10 substituent of **4.45** may possess a chloride that is pre-coordinated to C-10. The only chloride species that could play such a role would be the $SbCl_5Br^-$ anion.[190,193]

To further elucidate the identity of **4.45**, two control experiments were performed (**Scheme 4.12**). An equimolar amount of chloride **4.48** and $SbCl_5$ were mixed at 0 °C and warmed to room temperature to probe if it behaved the same as **4.45**. Unfortunately, warming the reaction mixture to room temperature resulted in rapid decomposition into intractable material. However, mixing an equimolar amount of chloride **4.48**, $SbCl_5$ and Et_2S at -78 °C followed by warming to room temperature did not result in rapid decomposition, but a gradual conversion of chloride **4.48** into isomeric chloride **4.46** over the course of 15 days in $CDCl_3$ that resembles the behaviour of **4.45** (**Table 4.1, Entry 1, Column 2**). Monitoring the reaction by ^{1}H NMR spectroscopy did not reveal any resonances that resembled **4.45** over the course of the conversion.



Scheme 4.12. Control experiment to probe the identity of **4.45.**
Reagents and conditions: **i)** $SbCl_5$ (1.0 eq., 1.0 M in CH_2Cl_2), CH_2Cl, 0 °C to r.t. **ii)** $SbCl_5$ (1.0 eq., 0.1 M in CH_2Cl_2), Et_2S (1.0 eq., 0.1 M in CH_2Cl_2), -78 °C to r.t., then $CDCl_3$, r.t., 15 days.

These results suggested that **4.45** is more likely to comprise ***ent*-4.2**, $SbCl_5Br^-$ and Et_2S than just ***ent*-4.2** and $SbCl_5Br^-$, as the absence of Et_2S led to rapid decomposition at room temperature. In addition, the sulfonium ion **4.51** was synthesised independently and did not display the expected reactivity and spectroscopic fingerprints of **4.45** (**Figure 4.11**, *see appendix 12.1*). The elucidation of the identity of **4.45** was not pursued further as it was deemed not crucial to the project at this stage.

Although the exact identity of **4.45** has yet to be established, available experimental observations suggest this unknown compound to potentially bear the structure **4.52** that is analogous to the structure of the organometallic compound **4.53**, in which the SbF_6^- counter anion is coordinated to the electrophilic tungsten centre.[194]

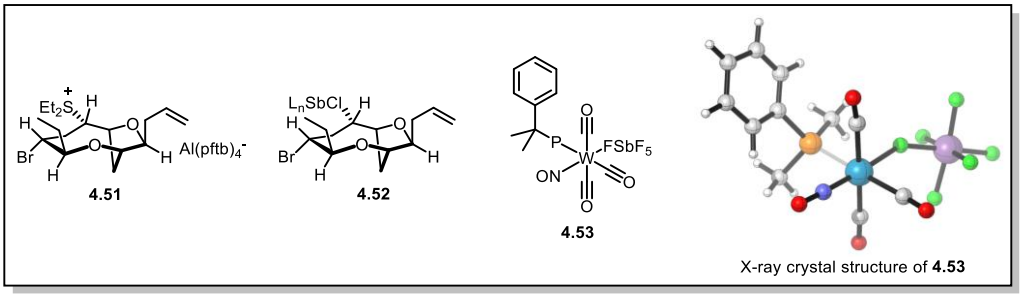


Figure 4.11. Structures of **4.51**, **4.52** and **4.53**.

This mode of coordination would explain the conversion of **4.45** into chloride **4.48** that is irrespective of the identity of added nucleophiles at room temperature. The nature of this reaction is very similar to an acid catalysed hydrolysis of $SbCl_6^-$ into HCl and $SbCl_5OH^-$.[195] Analogously, the Lewis acidic oxonium ion species ***ent*-4.2** could perform

the same function as acid. The added nucleophiles (**Table 4.1**) correspond to water, and chloride **4.48** corresponds to the HCl generated during the hydrolysis (**Figure 4.12**). The absence of bromide incorporation from $SbCl_5Br^-$ could be explained by a statistical preference of Cl coordination to the oxonium ion.

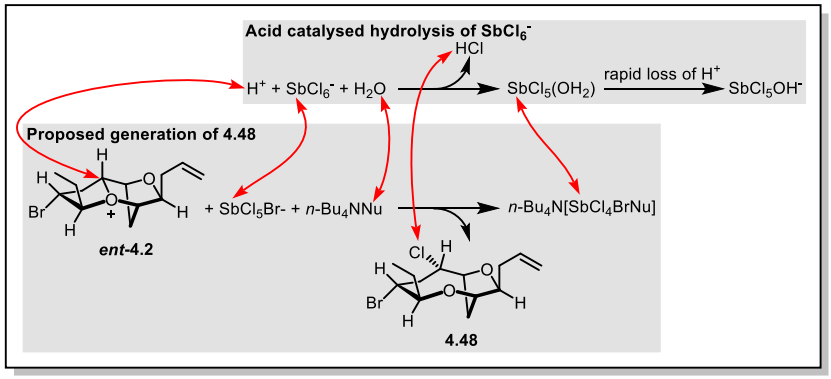
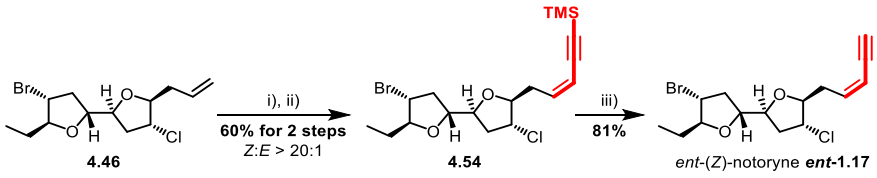


Figure 4.12. Parallelism between acid catalysed hydrolysis of $SbCl_6^-$ and the proposed generation of **4.48**. Red arrows connect analogous species.

4.2.3 *Total synthesis of ent-(Z)-notoryne and ent-(E)-laurefucin*

The structures of **4.46** and **4.50** were confirmed by their conversion into the natural products *ent*-(*Z*)-notoryne ***ent*-1.17** and *ent*-(*E*)-laurefucin ***ent*-1.14** respectively (**Scheme 4.13-4.14**). The structures of (*Z*)-notoryne **1.17** was determined by Suzuki and (*E*)-laurefucin **1.14** by Irie.[5,15,20,21] An X-ray crystal structure of our synthetic *ent*-(*E*)-laurefucin ***ent*-1.14** was obtained to further confirm its structure (**Figure 4.14**).[5,20,21]



Scheme 4.13. Synthesis of *ent*-(*Z*)-notoryne ***ent*-1.17**.

Reagents and conditions: **i)** cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t. **ii)** *tert*-Butyldimethyl(3-(trimethylsilyl)prop-2-yn-1-yl)silane (1.0 eq.), *t*-BuLi (1.0 eq., 1.49 M in pentane), $Ti(Oi\text{-}Pr)_4$ (1.0 eq., 1.0 M in THF), THF, -78 °C then r.t., 1 hr. **iii)** K_2CO_3 (2.0 eq.), MeOH, r.t.

The synthesis of *ent*-(*Z*)-notoryne ***ent*-1.17** began with the Lemieux-Johnson oxidation of the terminal alkene in **4.46**.[196,197] The aldehyde **4.55**, which was not isolated, was converted into **4.54** by the Yamamoto-Peterson reaction (**Figure 4.13**).[198] The TMS-enyne **4.54** was then converted into *ent*-(*Z*)-notoryne ***ent*-1.17** by methanolysis of the TMS protecting group.

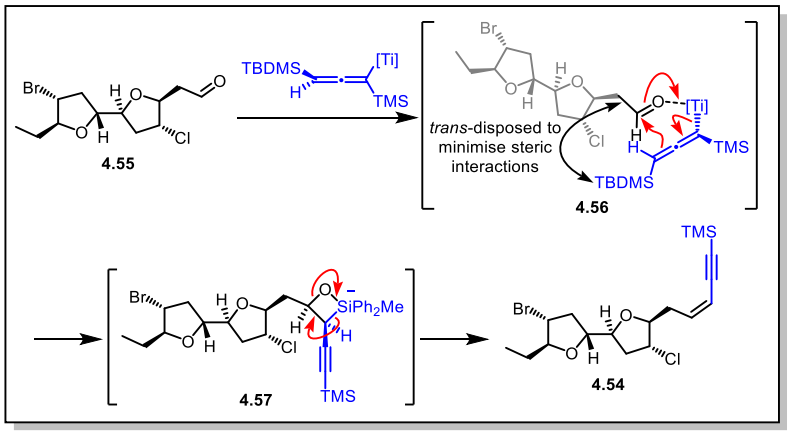
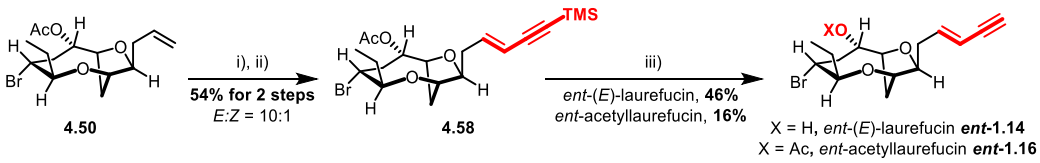


Figure 4.13. Mechanism and stereochemical rationale of the Yamamoto-Peterson reaction.



Scheme 4.14. Synthesis of *ent*-(*E*)-laurefucin ***ent*-1.14** and *ent*-acetyllaurefucin ***ent*-1.16**. Reagents and conditions: **i)** cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t. **ii)** Triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (1.0 eq.), *n*-BuLi (1.0 eq., 2.4 M in hexanes), -78 °C to -0 °C, 2 hrs. **iii)** K_2CO_3 (2.0 eq.), MeOH, r.t.

The synthesis of *ent*-(*E*)-laurefucin ***ent*-1.14** and *ent*-acetyllaurefucin ***ent*-1.16** began with Lemieux-Johnson oxidation of acetate **4.50**,[196,197] the aldehyde generated from the oxidation underwent a Wittig reaction with the semi-stabilised ylide generated from triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide and *n*-BuLi to give the TMS-enyne **4.58**.[199] Methanolysis of the TMS group and partial deprotection of the

acetate group provided *ent*-(*E*)-laurefucin ***ent*-1.14** and *ent*-acetyllaurefucin ***ent*-1.16** that were separated by flash column chromatography.

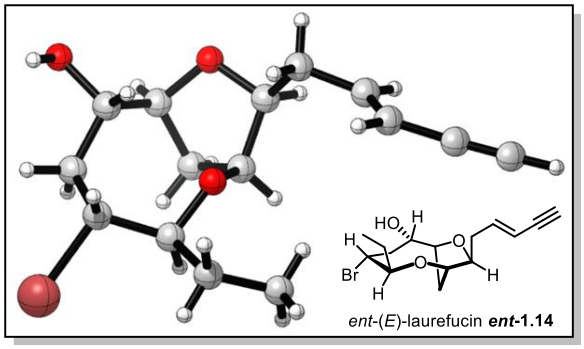
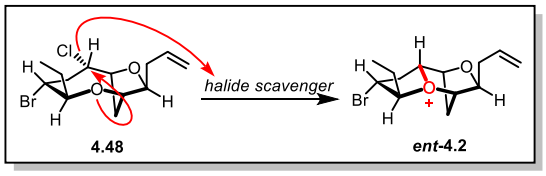


Figure 4.14. X-ray crystal structure of *ent*-(*E*)-laurefucin ***ent*-1.14**.

The bromocyclisation strategy using BDSB implied the participation of the oxonium ion ***ent*-4.2** in the generation of chloride **4.48**, isomeric chloride **4.46** and acetate **4.50**. The synthesis of chloride **4.48** allowed us to study the desired oxonium ion generation reaction using a transannular halide displacement strategy which will be discussed in the next section.

4.3 Studies of oxonium ion generation *via* transannular halide displacement

Following the development of a method to synthesise **4.48**, a transannular halide displacement strategy was postulated for the generation of ***ent*-4.2** from **4.48** (**Scheme 4.15**).



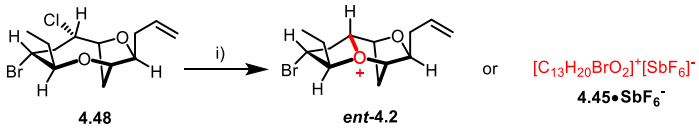
Scheme 4.15. The concept of a transannular halide displacement strategy for the generation of ***ent*-4.2**.

The halide scavenger for this transformation should exhibit the following properties: **1)** It should be easy to obtain or prepare; **2)** it should not interact with ***ent*-4.2** after halide abstraction, nor induce reactions other than the desired transannular halide displacement

with **4.48**; **3)** it should have simple or preferably no ^{1}H and ^{13}C NMR resonances, and the by-products from halide displacement should be easily removed to prevent spectroscopic contamination. Based on these criteria, silver salts that carry weakly coordinating counter anions were selected as suitable candidates.

4.3.1 *Reaction of chloride **4.48** with $AgSbF_6$*

The chloride **4.48** was treated with $AgSbF_6$ in CD_2Cl_2 at room temperature (**Scheme 4.16**), which resulted in immediate precipitation of an insoluble material and the colour of the reaction mixture turned from colourless to red. This was contrary to the observation described in **Scheme 4.12**, as the reaction mixture did not appear to decompose into intractable material at room temperature when SbF_6^- was used as the counter anion.



Scheme 4.16. Reaction of **4.48** with $AgSbF_6$.
Reagents and conditions: $AgSbF_6$ (1.0 eq.), CD_2Cl_2, r.t., then filtered into flame dried Young's NMR tube for NMR analysis.

NMR analysis of the red solution revealed that the product was neither just ***ent*-4.2** nor **4.45**. The ^{1}H NMR spectrum suggested that there was a complicated mixture of species. However, ^{1}H NMR resonances at δ (ppm) = 8.38 (dq, *J* = 15.8, 7.0 Hz, 1H), 6.94 (dt, *J* = 15.6, 1.5 Hz, 1H) and 2.47 (dd, *J* = 6.8, 1.4 Hz, 3H) suggested the presence of a conjugated and electron deficient enone moiety (**Figure 4.15**). The presence of such a moiety implied that the C=C bond in ***ent*-4.2** most likely underwent migration and gave a species such as **4.59** as one of the products.

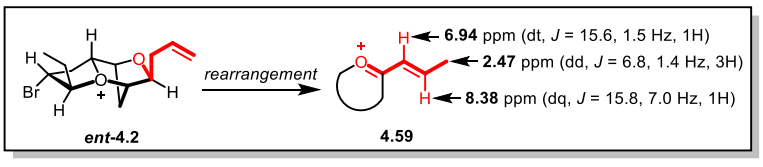
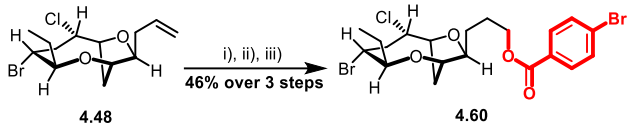


Figure 4.15. The generation of **4.59** from ***ent*-4.2**.

These observations implied that the terminal olefin may be participating in the reaction and hence the chloride **4.48** was modified into **4.60** *via* hydroboration-oxidation followed by ester formation for subsequent studies of the oxonium ion formation reaction (**Scheme 4.17**).



Scheme 4.17. Synthesis of **4.60** from **4.48**.

Reagents and conditions: **i)** 9-BBN (3.0 eq., 0.5 M solution in THF), THF, r.t., overnight. **ii)** 30% aq. H_2O_2 (excess), 15% aq. NaOH (excess), 0 °C to r.t., overnight. **iii)** 4-bromobenzoyl chloride (1.2 eq.), cat. DMAP, Et_3N (1.4 eq.), CH_2Cl_2, r.t., overnight.

Having observed that haloantimonate counter anions may not be spectators in the reaction, the use of other weakly coordinating anions was explored. Potential candidates included Kobayashi's anion $[BAr^F{}_4]^-$, Weller's anion $[BAr^{Cl2}{}_4]^-$, $[B(C_6F_5)_4]^-$, Krossing's anion $[Al(pftb)_4]^-$ (pftb = perfluoro-*tert*-butoxy) and carborane anions $[CB_{11}H_6Cl_6]^-$.[200–205] Krossing's anion $[Al(pftb)_4]^-$ **4.61** was ultimately selected for our studies because of its simple and economical preparation compared to carborane anions, and the absence of phenyl groups compared to $[BAr^F{}_4]^-$ type anions that may form π-complexes with silver cations that could complicate our studies.

4.3.2 *The synthesis of an oxocarbenium ion with $Ag[Al(pftb)_4]\cdot CH_2Cl_2$*

The silver (I) salt of Krossing's anion $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ was synthesised according to the published procedure with a minor modification.[202] During the preparation of $Li[Al(pftb)_4]$, the reaction mixture was heated at 80 °C in toluene overnight but not at reflux to prevent blackening of the reaction mixture. The identity of the anion was confirmed by ESI-MS analysis.

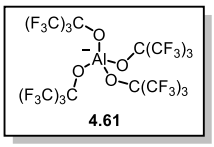
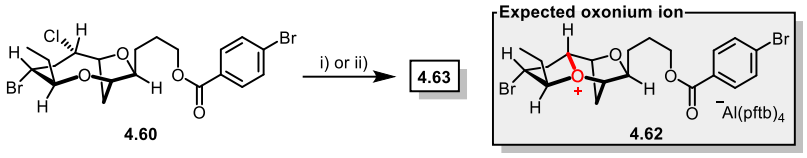


Figure 4.16. Structure of Krossing's anion **4.61.**

Treatment of **4.60** with $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ in CD_2Cl_2 at room temperature induced the precipitation of an insoluble material but the reaction mixture did not turn red as in the case of **4.48**. ^1H NMR analysis of the reaction mixture after cannula filtration revealed a cleaner spectrum compared to that obtained from **4.48** which suggested the formation of a single species **4.63** (**Scheme 4.18**).



Scheme 4.18. Test reaction of **4.60** with $Ag[Al(pftb)_4]\cdot CH_2Cl_2$.
Reagents and conditions: **i)** $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CD_2Cl_2, r.t., then filtered into flame dried Young's NMR tube. **ii)** $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CD_2Cl_2, -78 °C, then filtered into flame dried Young's NMR tube at -78 °C, incubated in freezer at -20 °C overnight.

However, the identity of the new species **4.63** was not clear at this stage as the ^1H NMR spectrum consisted of multiplets that were generally broad and poorly resolved. However, performing the reaction at -78 °C followed by incubation at -20 °C overnight and subsequent NMR spectroscopic analysis at room temperature gave NMR spectra of considerably higher quality.

The analysis of the ^1H-^{13}C HSQC spectrum of **4.23** suggested that the species had 6 CH cross peaks, 7 CH_2 cross peaks and 1 CH_3 cross peak (in total 14 cross peaks), whereas the desired species **4.62** would contain 8 CH cross peaks, 6 CH_2 cross peaks and 1 CH_3 cross peak (in total 15 cross peaks). Moreover, a comparison with the starting material **4.60**, which bears 8 CH cross peaks, 6 CH_2 cross peaks and 1 CH_3 cross peak, also suggested that one cross peak was "missing" in the new species. However, both **4.63** and

4.60 possess 25 protons, and the discrepancy between the number of protons versus the number of carbons combined with the change in the distribution of CH_2 and CH cross peaks suggested that an extra quaternary carbon was present. Expansion of the spectral width of the ^{13}C NMR spectrum from 240 ppm to 300 ppm revealed a signal at 242.4 ppm that corresponded to a quarternary carbon as suggested by DEPT-Q experiment.[73] The molecular connectivity of **4.63** was determined by analysis of ^{1}H-^{1}H COSY correlations that suggested the oxocarbenium ion structure shown below (**Figure 4.17**).

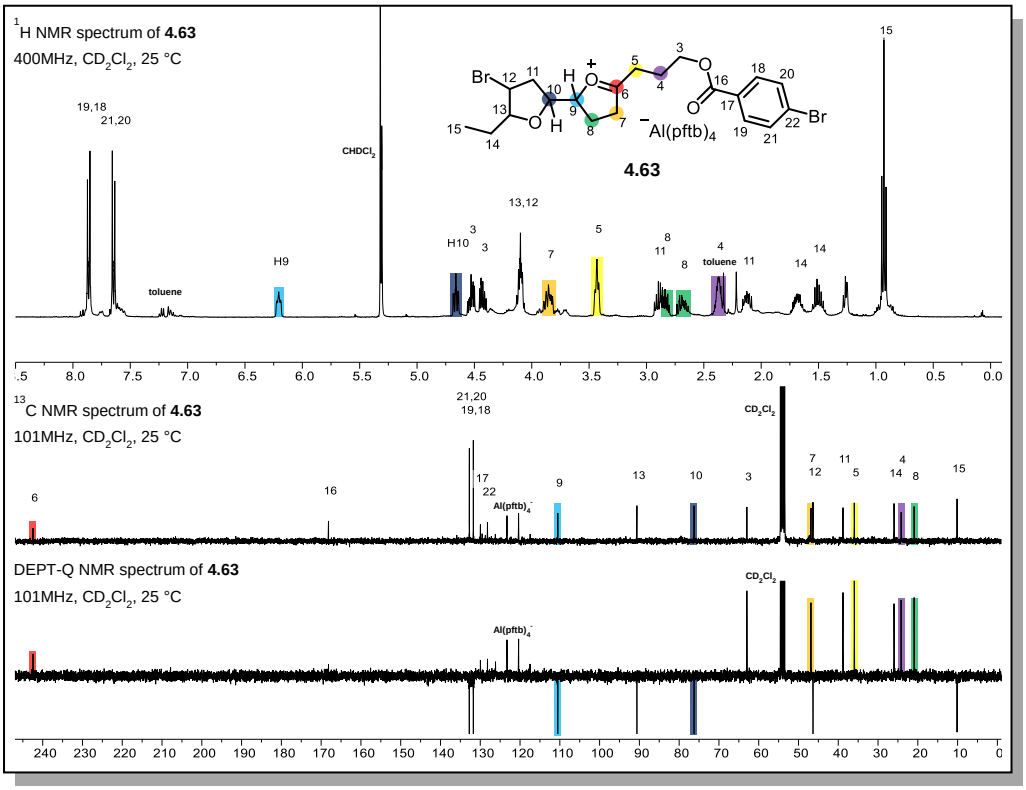


Figure 4.17. Fully assigned ^{1}H (400 MHz, CD_2Cl_2), ^{13}C (101 MHz, CD_2Cl_2) and DEPT-Q (101 MHz, CD_2Cl_2) NMR spectra of **4.63**.

It is noteworthy that the two sets of CH_2 protons adjacent to the oxocarbenium carbon C-6 (H-5s and H-7s) exhibit weak $^{4}J_{HH}$ couplings that are visible in the ^{1}H-^{1}H COSY spectrum, although the $^{4}J_{HH}$ coupling constants could not be readily measured. The ^{1}H and ^{13}C NMR chemical shifts of these two CH_2 groups (3.43/36.1 ppm and 3.85/46.9 ppm) resembles CH_2 groups adjacent to a carbonyl moiety more than CH_2 groups in a tetrahydrofuran skeleton (3.69/68.2 ppm and 1.82/26.0 ppm).[206] In addition, the ^{1}H and

^{13}C NMR resonances of H-9 and C-9 resonate at 6.20 and 110.5 ppm respectively, in keeping with the formation of an oxocarbenium ion.[119]

The crucial piece of evidence that confirmed the structure of **4.63** was provided by the ^{1}H-^{13}C HMBC correlation between C-6 and the surrounding protons. The $^{2}J_{CH}$ and $^{3}J_{CH}$ correlations between C-6 at 242.4 ppm and its coupled protons (H-4s, H-5s, H-7s and H-8s) are shown unambiguously in **Figure 4.18**.

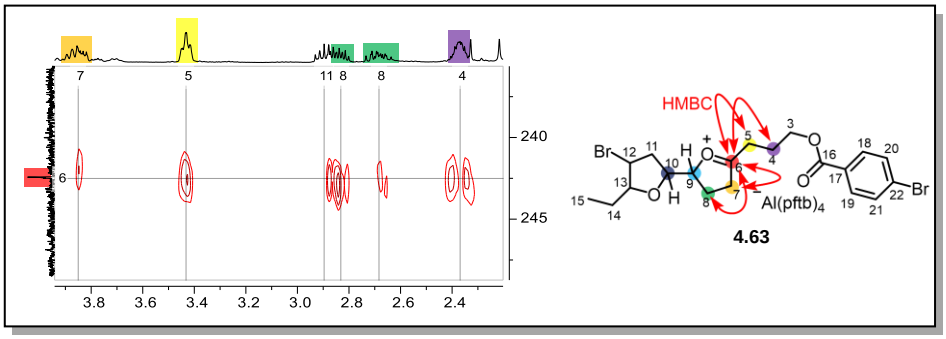


Figure 4.18. An excerpt of the ^{1}H-^{13}C HMBC (400 MHz, 101 MHz, CD_2Cl_2) spectrum of **4.63**.

In the proposed structure of **4.63**, ^{1}H-^{13}C HMBC correlations between H-9 and its surrounding carbons (C-6, C-7, C-8, C-10 and C-11) would be expected but were not observed in the room temperature ^{1}H-^{13}C HMBC spectrum although the expected ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{1}H NOESY correlations were all observed. However, when the ^{1}H-^{13}C HMBC spectrum of **4.63** was acquired at -78 °C, the expected HMBC correlations between H-9 and its adjacent carbons were revealed unambiguously, providing further evidence for the proposed structure of **4.63** (**Figure 4.19**).

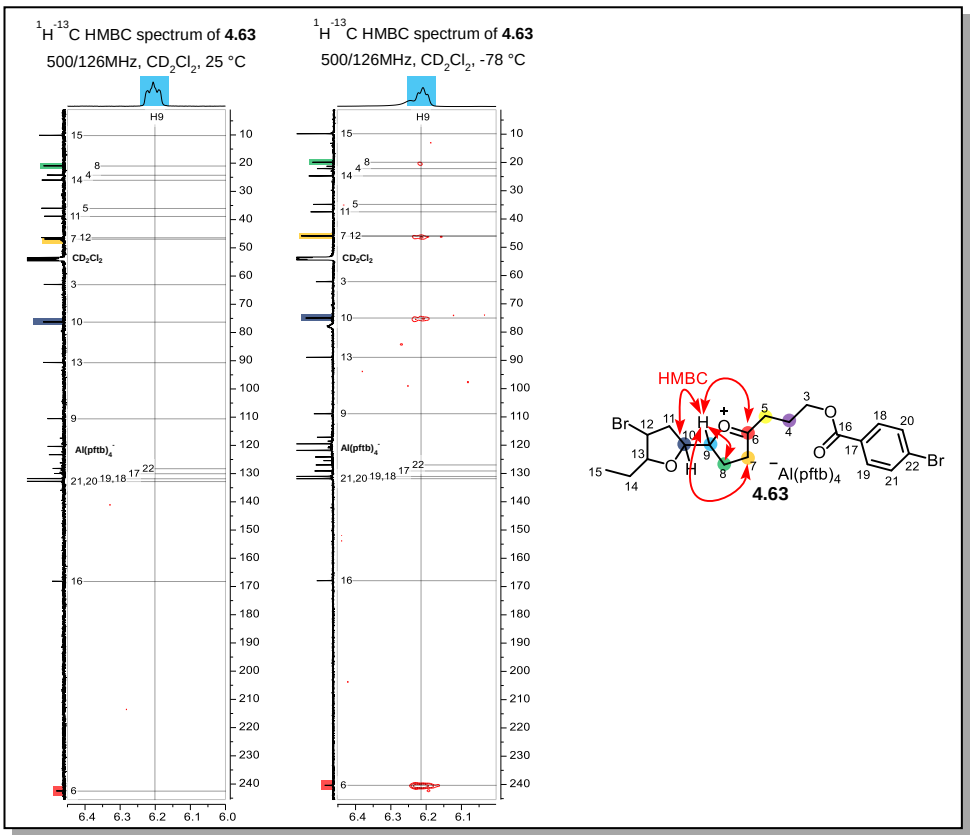
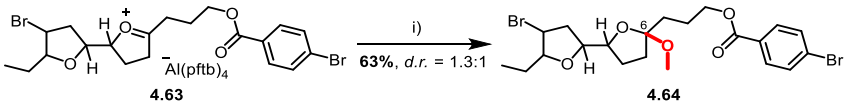


Figure 4.19. Temperature dependence of the ^{1}H-^{13}C HMBC (500 MHz, 126 MHz, CD_2Cl_2) spectrum of **4.63** showing correlations between H-9 and its surronding carbons. Spectrum on the left was acquired at 25 °C, spectrum on the right was acquired at -78 °C.



Scheme 4.19. Acetalisation of **4.63** to generate **4.64**.

Reagents and conditions: **i)** MeOH (excess), $NaHCO_3$ (excess), CD_2Cl_2, r.t., 20 s.

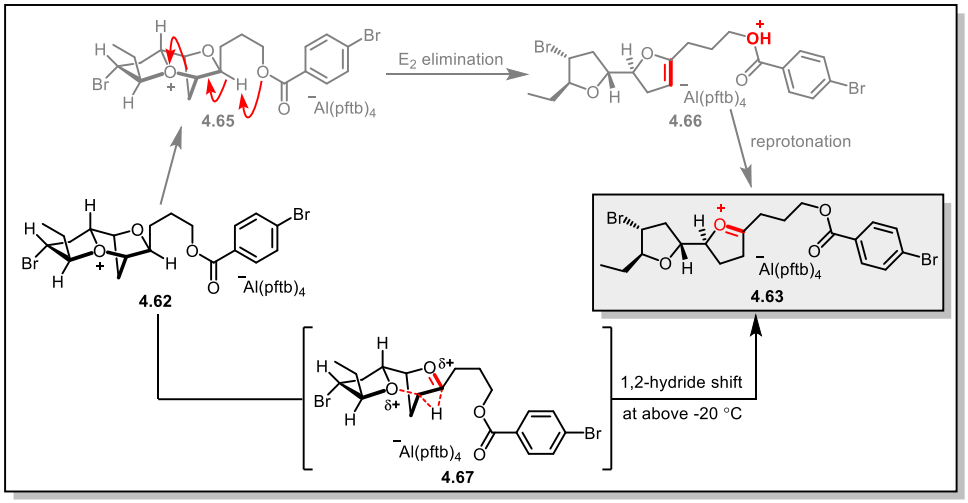
Treatment of **4.63** with excess methanol and $NaHCO_3$ provided acetal **4.64** as a 1.3:1 mixture of epimers. This pair of epimers were inseparable by column chromatography and thus were characterised as a mixture. Their ^{1}H NMR signals exhibited significant overlap especially in the region between 1.61 and 2.23 ppm. Fortunately, it was possible to resolve the overlapped signals and thus assign all the diastereotopic protons and carbons unambiguously with the analysis of their ^{1}H-^{13}C HMBC spectra. The ^{1}H-^{13}C HMBC spectra of **4.64** also exhibited HMBC correlations between C-6 and surrounding

protons that are $^{2}J_{CH}$ and $^{3}J_{CH}$ coupled. The incorporation of the methoxy group at C-6 in **4.64** suggested that this carbon was indeed an electrophilic site in **4.63**.

High-resolution ESI-MS analysis of **4.64** confirmed the existence of $[M+Na]^{+}$ ion as a diagnostic 1:2:1 triplet isotopic pattern for the dibromo compound $C_{21}H_{28}O_5{}^{79}Br_2Na$ / $C_{21}H_{28}O_5{}^{79}Br^{81}BrNa$ / $C_{21}H_{28}O_5{}^{81}Br_2Na$ at *m/z* 541.0195, 543.1074 and 545.0154 respectively (calculated *m/z* 541.0196, 543.0175 and 545.0155). Furthermore, another 1:2:1 triplet signal at *m/z* 487.0115, 489.0094 and 491.0073 was also detected. This was attributed to the generation of the oxocarbenium ion species **4.63** $C_{20}H_{25}O_4{}^{79}Br_2$ / $C_{20}H_{25}O_4{}^{79}Br^{81}Br$ / $C_{20}H_{25}O_4{}^{81}Br_2$ as $[M]^{+}$ in the mass spectrometer (calculated *m/z* 487.0114, 489.0094 and 491.0073).

The structural elucidation of **4.63** by NMR spectroscopy, chemical derivatisation and mass spectrometry has provided strong evidence to support the proposed oxocarbenium structure **4.63**. This species was found to be stable at room temperature inside the flame-dried and argon-filled Young's NMR tube for at least 4 days before significant broadening of ^{1}H NMR signals was observed.

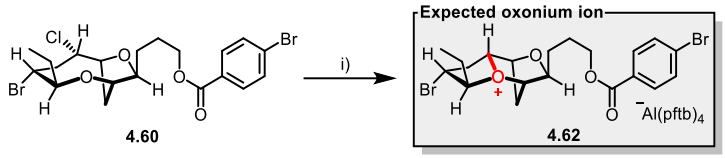
The formation of **4.63** from **4.60** was unexpected. The conservation of both the number of protons and number of carbons suggested that **4.63** was generated by rearrangement of **4.62** *via* a 1,2-hydride shift.[5,207] Another possible mechanism involves an E_2 elimination-reprotonation sequence was deemed unlikely as no appropriate bases were available (**Scheme 4.20**).



Scheme 4.20. Proposed mechanisms for the generation of **4.63** from **4.62** and the proposed stereochemical assignment of **4.63**.

4.3.3 *The synthesis of a model oxonium ion with Ag[Al(pftb)$_4$]·CH$_2$Cl$_2$*

Given the mechanistic proposal above, it was rationalised that the oxonium ion **4.62** could be isolated by keeping both the reaction temperature and the temperature for NMR acquisition below -20 °C to slow down the proposed rearrangement reaction. Treatment of **4.62** with Ag[Al(pftb)$_4$]·CH$_2$Cl$_2$ at -78 °C followed by filtration and NMR acquisition at the same temperature gave a new species that was proposed to be the oxonium ion **4.62** (**Scheme 4.21**).



Scheme 4.21. Test reaction of **4.60** with Ag[Al(pftb)$_4$]·CH$_2$Cl$_2$ for the proposed generation of **4.62**. Reagents and conditions: **i)** Ag[Al(pftb)$_4$]·CH$_2$Cl$_2$ (1.1 eq.), CD$_2$Cl$_2$, -78 °C, 1.5 hrs, then filtered into flame-dried Young's NMR tube at -78 °C with NMR acquisition at -78 °C.

By comparison of the ^{1}H NMR spectra of **4.63**, **4.62** and **4.60** at various temperatures, it was clear that **4.63**, **4.62** and **4.60** were distinct species at -78 °C (**Figure 4.20**). This demonstrated that **4.63** could not be converted into **4.62** by cooling, and the ^{1}H NMR

spectrum of **4.62** was not due to temperature dependence of the ^{1}H NMR spectrum of **4.60**.

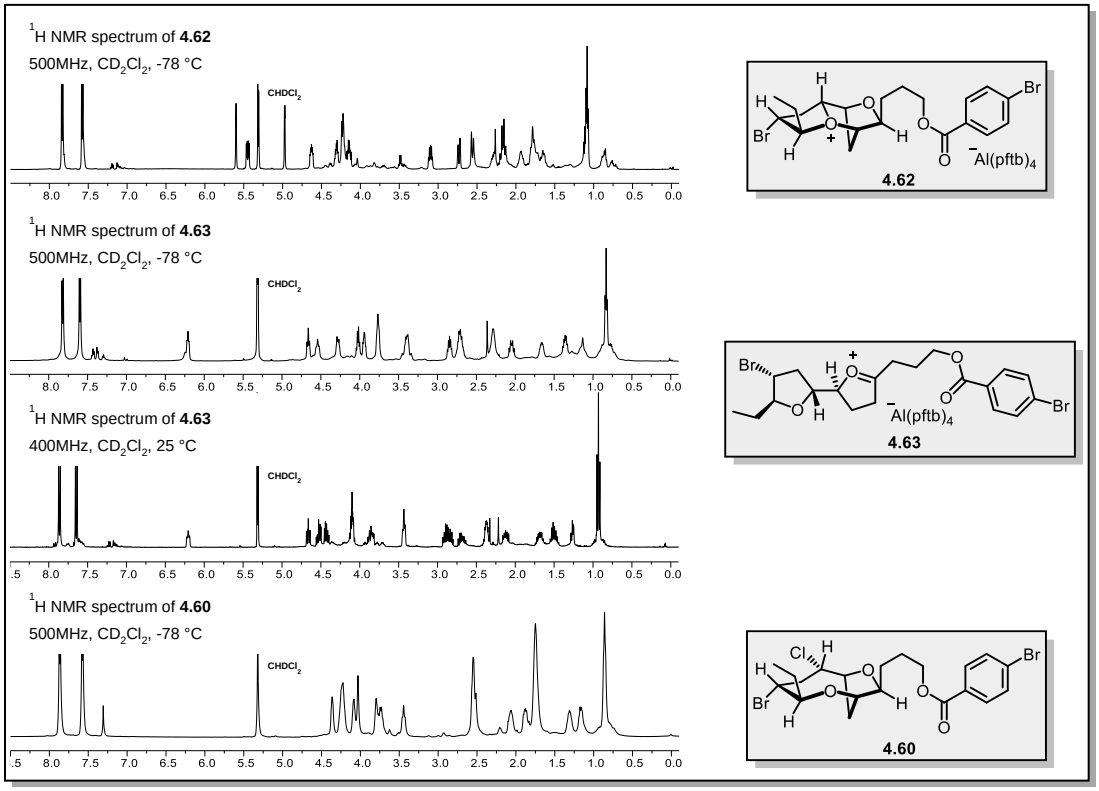


Figure 4.20. Comparison of ^{1}H NMR (500 MHz, CD_2Cl_2) spectra between **4.62**, **4.63** and **4.60** at different temperatures. The broadness of ^{1}H NMR spectra obtained at -78 °C is most likely due to slower molecular tumbling and bond rotations.

The characterisation of **4.62** began with the analysis of its ^{1}H-^{13}C HSQC spectrum. Contrary to the observation in **4.63**, **4.62** did not have any "missing" carbon signals. Thus, both the number of proton and carbon signals in **4.62** were identical with the starting material **4.60**. In addition, the molecular connectivity of **4.62** from the analysis of its ^{1}H-^{1}H COSY correlations suggested the expected connectivity of the proposed oxonium ion **4.62**. The comparison of its ^{1}H and ^{13}C NMR chemical shifts with those of the starting material **4.60** obtained at -78 °C are shown below (**Figure 4.21**).

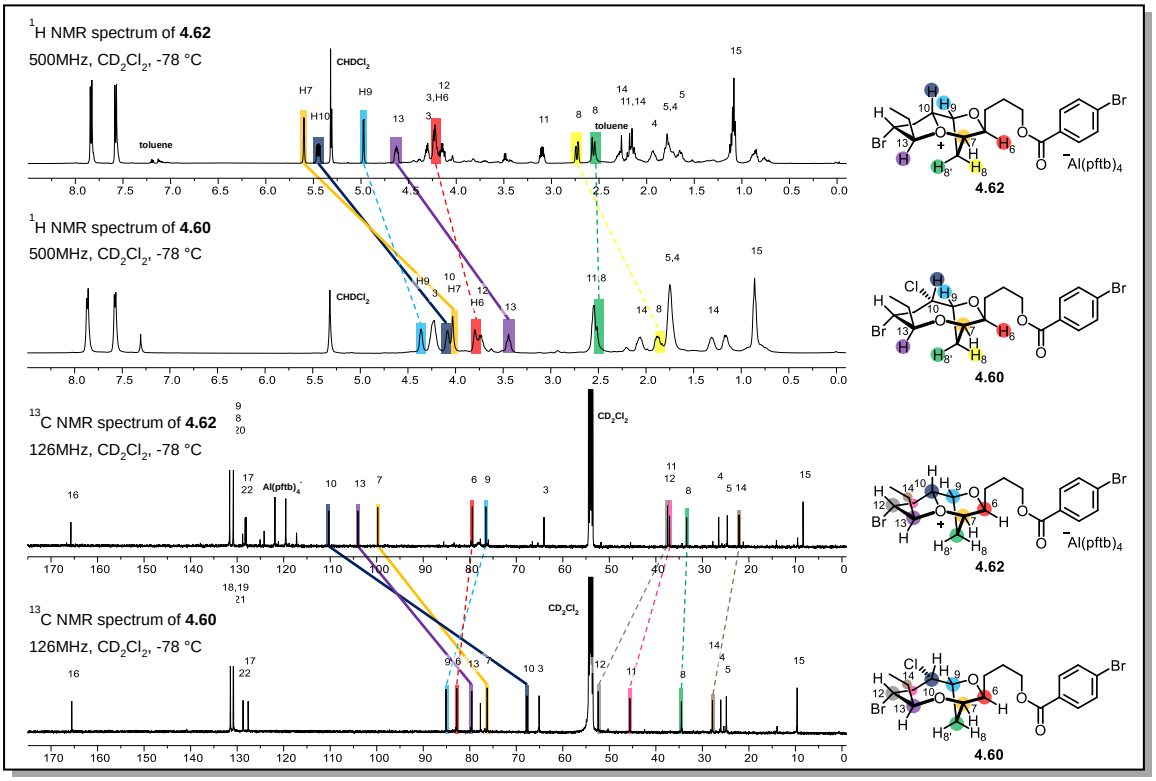


Figure 4.21. ^{1}H and ^{13}C NMR chemical shift comparison between **4.62** and **4.60**.

On formation of the oxonium ion **4.62**, it was found that both ^{1}H and ^{13}C chemical shifts at atoms 7 (orange), 10 (navy) and 13 (purple) increased significantly compared with the chemical shifts of the starting material **4.60**. This increase in chemical shifts imply that these atoms become more electron deficient which are in keeping with the proposed oxonium ion structure of **4.62**. The NMR chemical shifts of **4.62** at these three positions were then compared with the NMR chemical shifts of known tricyclic tertiary oxonium ions, where ^{1}H NMR resonances occur at ca. 5.0 ppm and ^{13}C NMR resonances at ca. 100 ppm (**Section 2.5, Figure 2.7**).[46,48] The experimental data for **4.62** are in agreement with these values, with the ^{1}H NMR resonances of the oxonium ion protons at 4.63-5.60 ppm and ^{13}C NMR resonances of the oxonium ion carbons at 99.8-110.3 ppm. Furthermore, ^{1}H and ^{13}C NMR chemical shifts increase of ca. 1.0-1.5 ppm and 25-40 ppm respectively relative to the starting material are in keeping with the expected increase in chemical shifts upon oxonium ion formation.[27,46,48,53] The ^{1}H chemical shifts of H-6 (red), H-9 (blue) and H-8 (yellow) adjacent to the oxonium ion carbons also increased by ca. 0.5 ppm upon

oxonium ion formation. However, H-8' (green) did not exhibit such an increase in its ^{1}H NMR chemical shift, which was indicative that the increase in ^{1}H NMR chemical shifts of H-6 (red), H-9 (blue) and H-8 (yellow) are due to overlap between their occupied σ_{C-H} orbitals and the vacant $\sigma^{*}_{C-O}{}^{+}$ orbitals of the oxonium ion carbons. On the other hand, the σ_{C-H} orbital of H-8' (green) does not have the correct geometry to overlap with the vacant $\sigma^{*}_{C-O}{}^{+}$ orbital of C-7, and thus its ^{1}H NMR chemical shift did not increase.

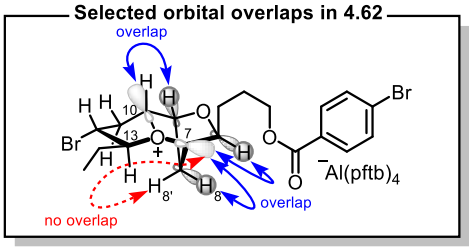


Figure 4.22. Overlap between occupied σ_{C-H} orbitals and vacant $\sigma^{*}_{C-O}{}^{+}$ orbitals in **4.62**.

The ^{13}C NMR chemical shifts of C-6 (red), C-8 (green), C-9 (blue), C-11 (pink), C-12 (grey) and C-14 (brown) decreased upon oxonium ion formation. This general decrease in ^{13}C NMR chemical shift of β-carbons of the trivalent oxygen was also observed in other types of onium ions but no explanations have been proposed (**Figure 4.23**).[46,208–213]

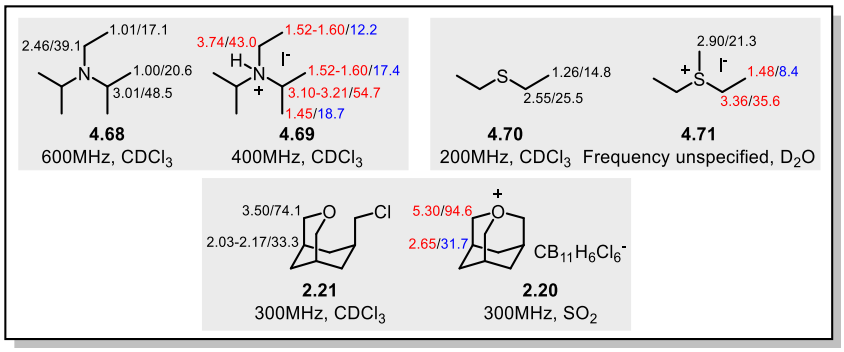


Figure 4.23. Comparison of ^{1}H and ^{13}C NMR resonances of known onium ions with their precursors. Resonances of onium ions in red/blue denotes deshielding/shielding relative to their starting materials respectively.

The connectivity of the proposed oxonium ion **4.62** was fully established by the comparison of its ^{1}H-^{13}C HMBC correlations with that of the starting material **4.60**. The

^{1}H-^{13}C HMBC correlations between H-13/C-7 were observed in both **4.60** and **4.62**. However, ^{1}H-^{13}C HMBC correlations between H-7/C-10 and H-10/C-7 were not observed in **4.60**, which was in contrast to **4.62** that these correlations were observed. Although these two ^{1}H-^{13}C HMBC correlations could operate *via* a $^{4}J_{CH}$ correlation pathway, the proposed structure of the oxonium ion **4.62** does not provide the necessary W-geometry.[214] This suggested the ^{1}H-^{13}C HMBC correlations between atoms 7 and 10 are transannular $^{3}J_{CH}$ correlations, and the simultaneous observation of ^{1}H-^{13}C HMBC correlations between atoms 7, 10 and 13 supports the formation of a trivalent oxygen center as in the proposed structure of oxonium ion **4.62**.

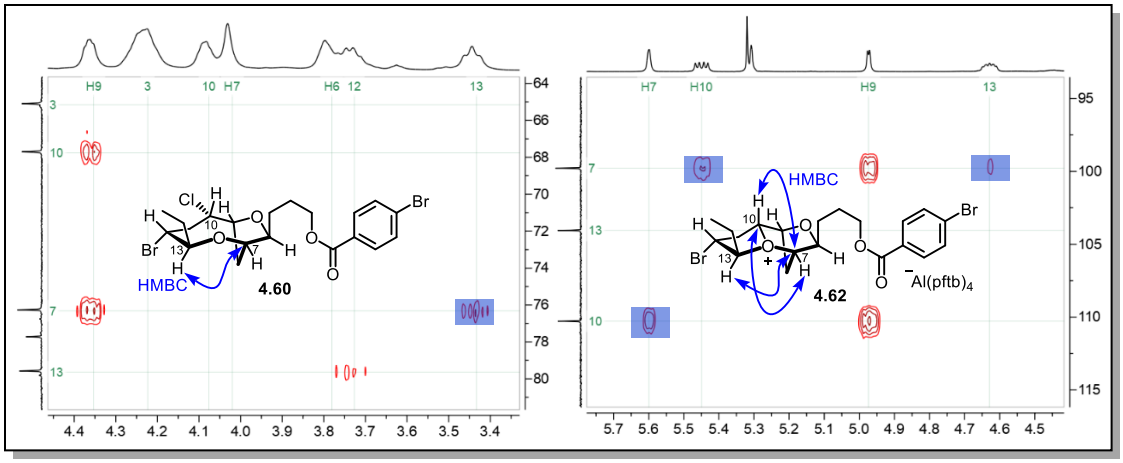
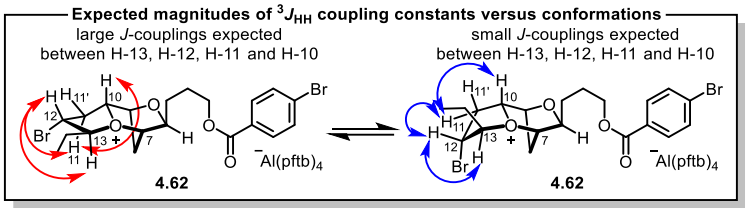


Figure 4.24. Excerpts of ^{1}H-^{13}C HMBC (500 MHz, 126 MHz, CD_2Cl_2) spectra of **4.62** and **4.60** at -78˚C.

Two ring conformers could in theory exist for **4.62** based on ring flipping of the bromine-containing ring, the most populated conformer in the solution state at -78 °C was found based on the analysis of $^{3}J_{HH}$ coupling constants (**Table 4.2**). The experimental $^{3}J_{HH}$ coupling constants were converted into corresponding H–C–C–H dihedral angles using the MestReJ software approximated with the Dìez-Altona-Donders modification of the Karplus equation for the elucidation of the conformation of **4.62** (*see appendix 12.2*).[189]



	$^3J_{HH}$ coupling constants/Hz and dihedral angles/° of 4.62					
Splitting		**H-10**	**H-11**	**H-11'**	**H-12**	**H-13**
dd	**H-10**	-	12.2 (*)	5.6 (37.0)	-	-
ddd	**H-11**	12.2 (*)	-	-	11.3 (163.8)	-
dt	**H-11'**	5.6 (37.0)	-	-	7.1 (36.1)	-
td	**H-12**	-	11.3 (163.8)	7.1 (36.1)	-	10.6 (*)
ddd	**H-13**	-	-	-	10.6 (*)	-

Table 4.2. Two possible conformers of the oxonium ion **4.62** with the extracted $^3J_{HH}$ coupling constants and dihedral angles (in brackets) of the protons of interest. Highlighted entries correspond to diagnostic $^3J_{HH}$ coupling constants. * Denotes dihedral angles that are approximately anti-periplanar as the experimental $^3J_{HH}$ coupling constants were too large for the Dìez-Altona-Donders equation using the chemical groups provided in the MestReJ software.

This analysis suggested the conformation of oxonium ion **4.62** is the one drawn to the left as shown above due to the large *J*-coupling constants observed between H-13 and H-12 and H-11 and H-10. For the other conformer, the corresponding $^3J_{HH}$ coupling constants were expected to be smaller.[189] The observed ^{1}H-^{1}H ROE correlations in **4.62** also support this assignment (**Figure 4.25**).

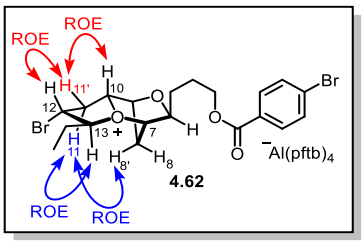


Figure 4.25. ^{1}H-^{1}H ROE correlations of H-11' and H-11 with their surrounding protons.

The overlapping ^{1}H NMR resonances of H-11 and H-14 could be resolved from the analysis of the ^{1}H-^{13}C HSQC spectrum. From the 2D ROESY spectrum of **4.62**, H-11 correlates with H-13 and H-8', and H-11' correlates with H-10 and H-12 (**Figure 4.26**). These ^{1}H-^{1}H ROE correlations are in keeping with the proposed conformation of **4.62**.

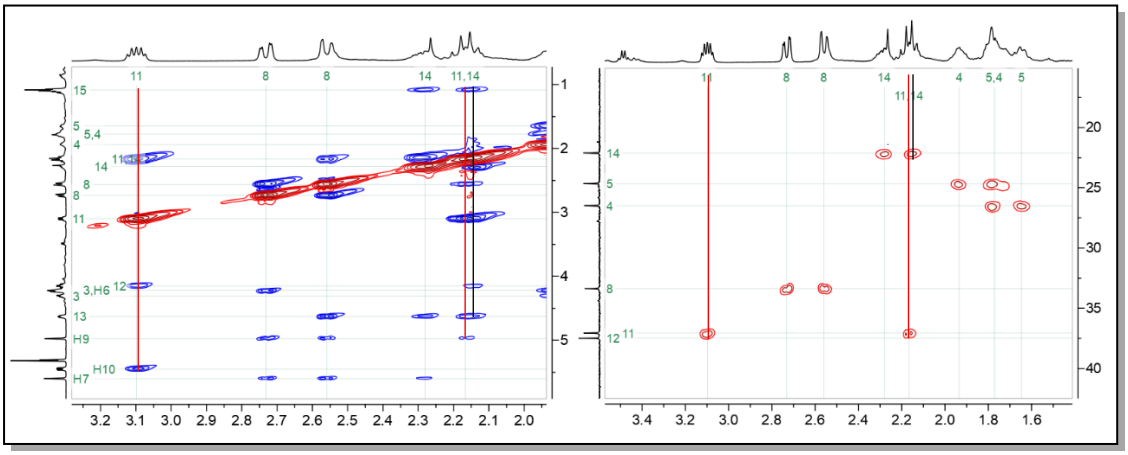
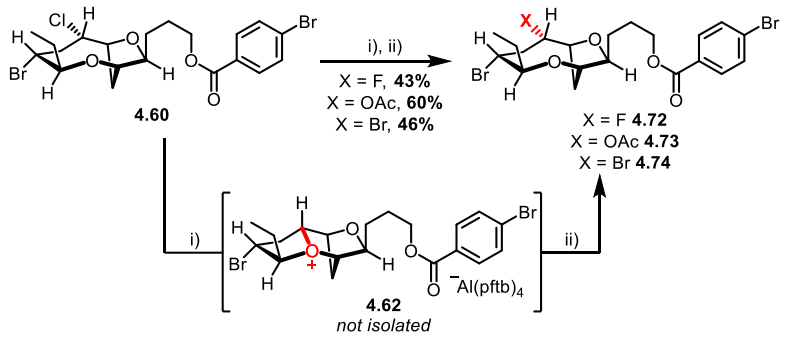


Figure 4.26. Excerpts of ^{1}H-^{1}H ROESY (500 MHz, CD_2Cl_2) spectrum (left) and ^{1}H-^{13}C HSQC (500 MHz, 126 MHz, CD_2Cl_2) spectrum (right) of **4.62**. Black vertical line connects correlations that are related to H-14, red vertical lines connect correlations that are related to H-11 (2.17 ppm) and H-11′ (3.10 ppm).

4.3.4 *Reactivity of model oxonium ion with various nucleophiles*

Having secured evidence for the structure of **4.62**, chemical derivatisation of this species was carried out to probe its reactivity. The oxonium ion **4.62** was synthesised in the same manner as in **Scheme 4.21** but without observing the resultant oxonium ion by NMR spectroscopy. Addition of 5.0 equivalents of various tetrabutylammonium salts to **4.62** at -78 °C followed by warming the reaction mixture to room temperature gave the products **4.72-4.74** (**Scheme 4.22**).



Scheme 4.22. Derivatisation of **4.60** into **4.72-4.74** via **4.62**.

Reagents and conditions: **i)** $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq. for X = F and OAc, 3.0 eq. for X = Br), CH_2Cl_2, -78 °C, 1.5 hrs. If X = Br, then filtered into another round-bottom flask at -78 °C. **ii)** TBAX (5.0 eq., X = F, OAc or Br), CH_2Cl_2, -78 °C, then warmed to r.t.

Under the reaction conditions stated above, the fluoride **4.72**, acetate **4.73** and tribromide **4.74** were synthesised with overall retention of configuration at C-10. The retention of configuration was supported by a comparison of their ^{1}H-^{1}H NOESY spectra with that of **4.60**. For **4.72** and **4.73**, identical and unambiguous nOe correlations between H-10, H-12 and H-5 were observed as in **4.60**. As for **4.74**, the ^{1}H NMR resonance for H-5 unfortunately overlaps with that of H-8 thus rendering the nOe correlation between H-10 and H-5 ambiguous. However, the correlation between H-10 and H-12 is still well resolved (**Figure 4.27**). These results implied a double inversion event had occurred at C-10 and an oxonium ion intermediate **4.62** must be invoked to account for this stereochemical outcome.

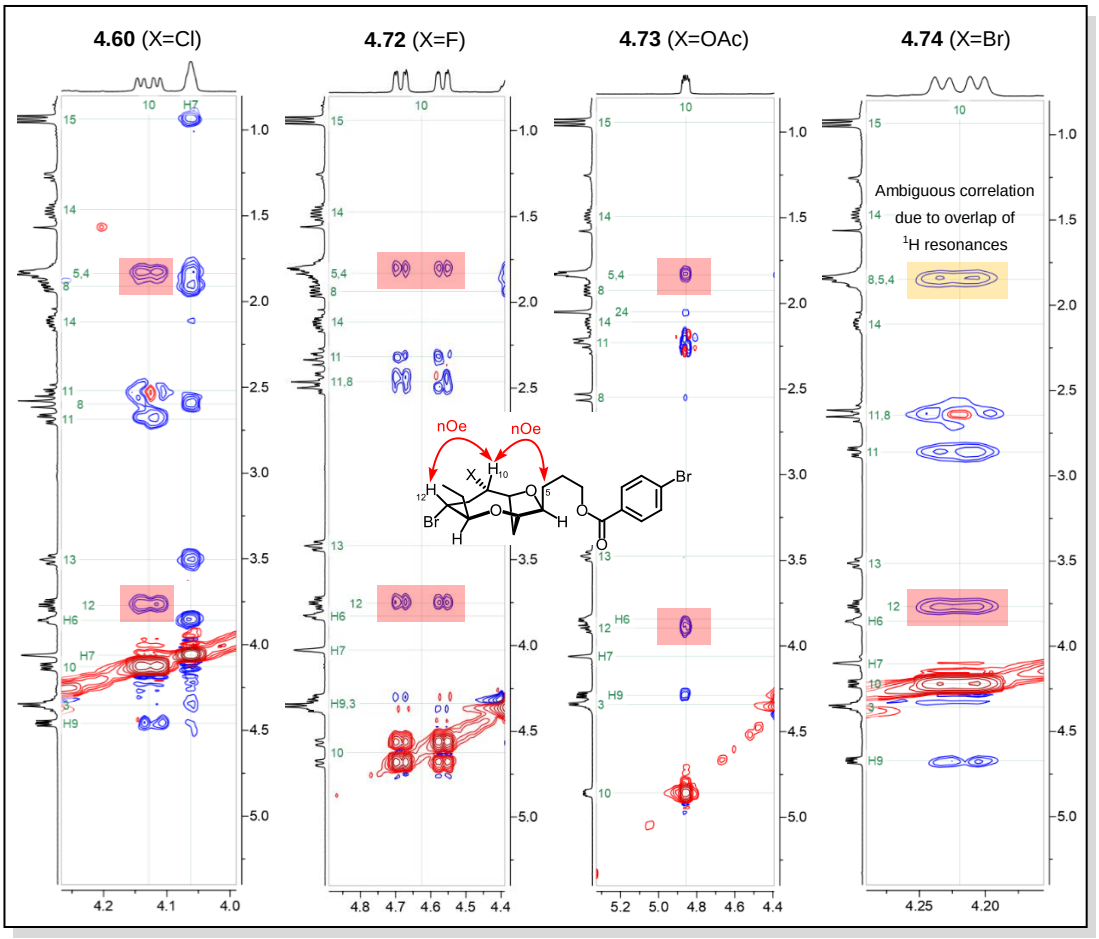
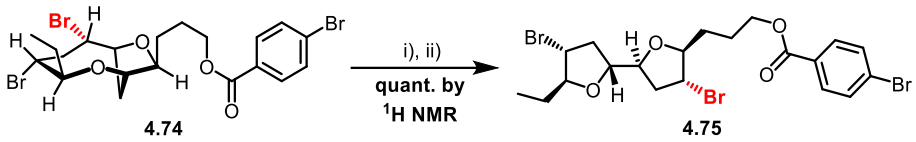


Figure 4.27. Excerpts of ^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$) spectra of **4.60** and **4.72-4.74**.

For the synthesis of tribromide **4.74**, the reaction initially yielded chloride **4.60** instead of the expected **4.74**. Upon the addition of excess tetrabutylammonium bromide, the insoluble AgCl in the reaction mixture redissolved completely. This observation was rationalised by the formation of soluble $[(n\text{-Bu})_4N]^+[AgX_2]^-$ salts, as silver halides are known to form dihaloargentate(I) anions in solutions of high halide concentrations.[215–217] Upon the formation of this complex ion, the soluble dihaloargentate(I) anions may convert the tribromide **4.74** to the chloride **4.60** due to the formation of a stronger C–Cl bond in **4.60**. This led to modifications of reaction conditions to synthesise **4.74**: **1)** Using 3.0 equivalents of the silver salt to ensure complete generation of the oxonium ion **4.62**; **2)** filtration of the reaction mixture into another flame dried flask to remove the insoluble AgCl, thus eliminating potential chloride sources for halide exchange; **3)** addition of 5.0

equivalents of tetrabutylammonium bromide at -78 °C, followed by warming to room temperature. This modification successfully yielded a new species distinct from chloride **4.60**. The tribromide **4.74** rearranged slowly at ambient conditions into compound **4.75** (**Scheme 4.23**). This type of rearrangement has previously been observed by Suzuki and Irie in analogous systems where the rearrangement was performed on silica gel.[15,21] In our system, this rearrangement was incomplete after 7 days at ambient conditions, the sample was then heated to 50 °C for three days to drive the rearrangement to completion.



Scheme 4.23. Conversion of **4.74** to **4.75**. **i)** $CDCl_3$, r.t., 7 days, incomplete conversion. **ii)** $CDCl_3$, 50 °C, 3 days.

The exclusive opening of the oxonium ion at C-10 observed in the reaction between **4.62** and various nucleophiles will be further discussed in **Section 6.3**.

4.3.5 *Thermal sensitivity of model oxonium ion*

The synthesis of **4.62** was based on the hypothesis that it could be thermally unstable towards a 1,2-hydride shift. Variable temperature NMR studies were performed to investigate the rearrangement of **4.62** to **4.63**. The oxonium ion **4.62** began to convert to **4.63** at -33 °C but the rate of the conversion was not appreciable until the sample was further warmed to around 0 °C. The rearrangement was then studied at 5 °C (**Figure 4.28**).

The conversion of **4.62** to **4.63** under these conditions was found to occur smoothly over 6 hours. The variation of the integrals of the two selected ^{1}H NMR signals which correspond to H-9 of both **4.62** and **4.63** with time suggests the rearrangement reaction follows first-order kinetics (**Figure 4.28**). This confirmed our hypothesis that **4.62** is thermally sensitive and could rearrange to **4.63** at a temperature higher than -78 °C.

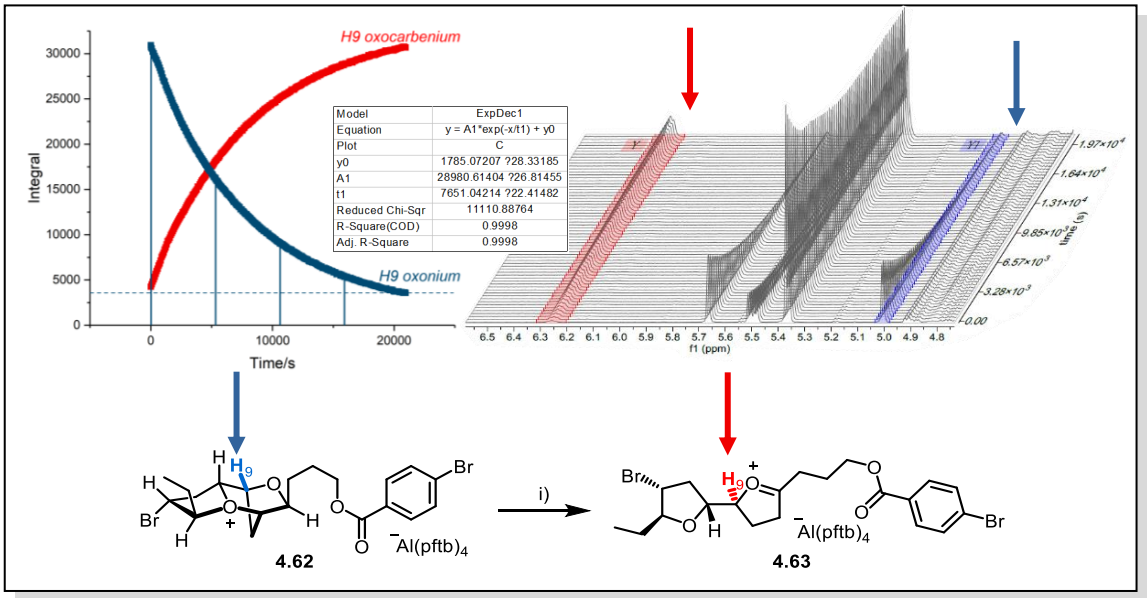


Figure 4.28. Reaction monitoring for the conversion of **4.62** to **4.63**. **i)** CD_2Cl_2, 5 °C, 6 hrs. The average half-life of the conversion is around 5100 seconds (85 minutes, *see appendix 12.5*), with a free energy of activation of 21.2 kcal/mol.

DFT calculations were performed (by Dr Quynh Nguyen and Prof. Rob. S. Paton) to further elucidate the mechanism and free energy of activation of this rearrangement reaction. It was found that the 1,2-hydride shift is a concerted but highly asynchronous process (**Figure 4.29**). The calculated free energy of activation of this process is 20.6 kcal/mol, which is in good agreement with the experimental free energy of activation of 21.2 kcal/mol.

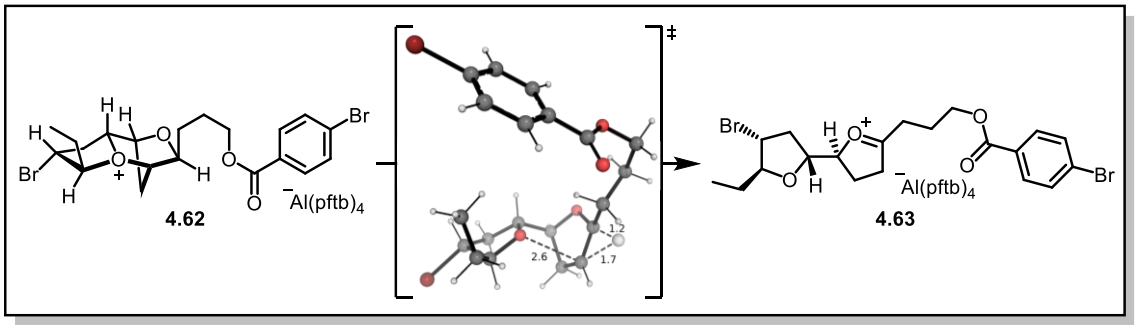


Figure 4.29. DFT calculated transition state of the 1,2-hydride shift process. Transition state structures were calculated from the lowest-energy conformers of **4.62** with M06-2X functional and def2TZVP basis set in CH_2Cl_2.

4.3.6 *Mass spectrometric analysis of oxonium ion precursors*

The oxonium ion precursors **4.60** and **4.72-4.74** were expected to ionise to oxonium ion **4.62** in a mass spectrometer. High-resolution ESI-MS analysis of these oxonium ion precursors were then performed and *m/z* signals that correspond to the oxonium ions were observed. However, these *m/z* signals could also arise from the bromonium ion **4.76** and oxocarbenium ion **4.63** by the rearrangement of the oxonium ion **4.62** (**Figure 4.30**).

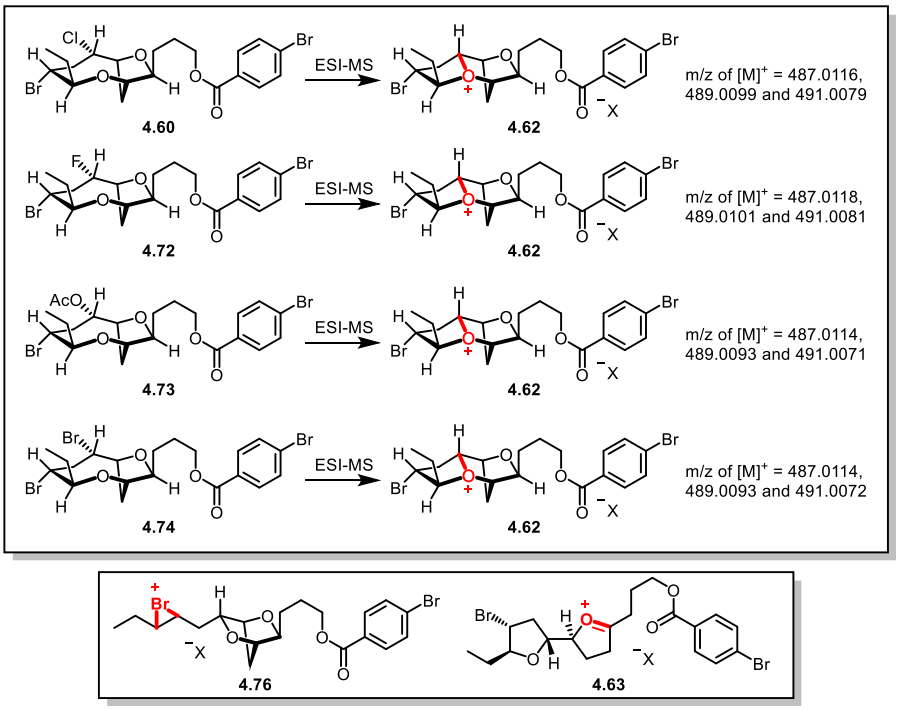


Figure 4.30. The *m/z* signals of the oxonium ion **4.62** from different precursors. The identity of anion X^- is unknown.

4.4 Conclusion

In this chapter, the retrosynthesis of the target oxonium ions **1.1-1.4** which led to the development of a robust synthesis of the diene precursor **4.5** from diacetone-D-glucose **4.12** in 11 steps with an overall yield of 12% has been discussed. Following that, the reactions of **4.5** with BDSB **4.34** have provided insights on the participation of oxonium ion ***ent*-4.2** in the synthesis of **4.46**, **4.48** and **4.50** and the natural products *ent*-(*Z*)-notoryne ***ent*-1.17** and *ent*-(*E*)-laurefucin ***ent*-1.14**. The synthesis of **4.48** has

provided the opportunity to synthesise **4.60** which ultimately led to the synthesis of the oxonium ion **4.62** and the oxocarbenium ion **4.63**. The studies of the reactivity of **4.62** have allowed us to understand the behaviour of this oxonium ion with various nucleophiles and its thermal sensitivity towards rearrangement into **4.63**.

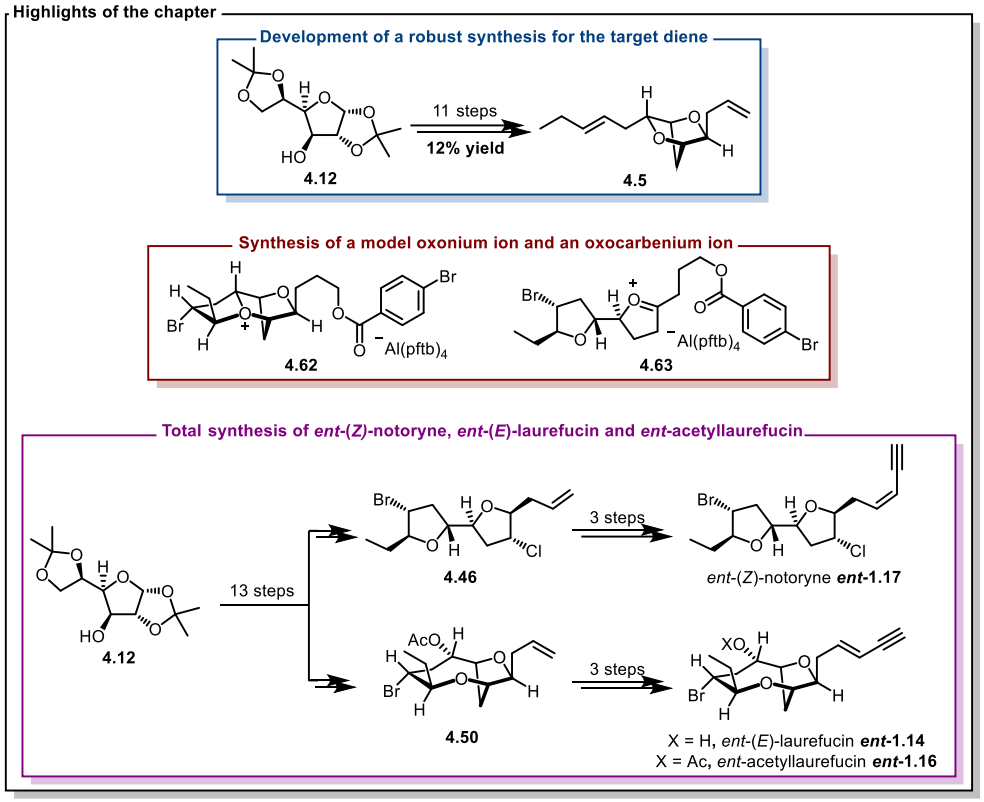


Figure 4.31. Highlights of Chapter 4.

5 The synthesis and studies of biosynthetically relevant oxonium ions

5.1 The development of a unified synthesis of all oxonium ion precursors

This chapter concerns the synthesis and studies of the target oxonium ions **1.1**, **1.2** and ***ent*-1.3, *ent*-1.4**. In **Section 4.3**, it was shown that a transannular halide abstraction strategy was viable for the synthesis of the oxonium ion **4.62** from its precursor **4.60** and it was envisaged that this strategy could also be applied to the synthesis of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** from their precursors **1.5**, **1.6** and ***ent*-5.1**, ***ent*-5.2** respectively (**Figure 5.1**).

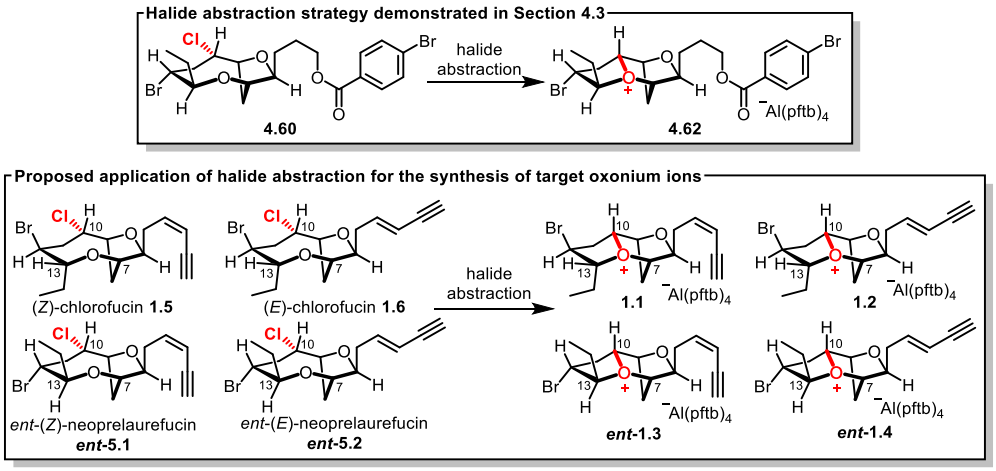


Figure 5.1. Proposed application of the halide abstraction strategy for the synthesis of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** from their respective precursors **1.5**, **1.6** and ***ent*-5.1**, ***ent*-5.2**.

A synthesis of chloride **4.48** that could lead to the synthesis of the *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** was reported in the previous chapter, however, a method for the synthesis of its diastereomer **5.3** that could lead to the chlorofucins **1.5-1.6** required development. The reaction of the diene **4.5** with BDSB **4.34**, which was assumed to be facially unselective, did not give both **4.48** and **5.3** as products. As a facially selective bromonium formation on the diene **4.5** is unlikely,[7] the selective generation of **4.48** is

proposed to arise from the following scenario (**Figure 5.2**). Snyder and co-workers have proposed the BDSB-mediated bromocyclisation of **5.4** involved equilibriation of bromonium ions **5.5** and **5.6** and oxonium ions **5.7** and **5.8**.[7,218–223] It was proposed that the oxonium ion **5.8** may be formed preferentially because its *endo* substituents do not clash with each other, which led to the exclusive formation of product **5.10**. Similarly, the BDSB-mediated bromocyclisation of the diene **4.5** may also involve an equilibrium of bromonium ions ***ent*-4.4** and **4.3** and oxonium ions ***ent*-4.2** and **4.1**, in which the oxonium ion ***ent*-4.2** might be formed preferentially because there is no *syn*-pentane interaction between C-8 and C-14. This might then lead to the exclusive formation of **4.48**.

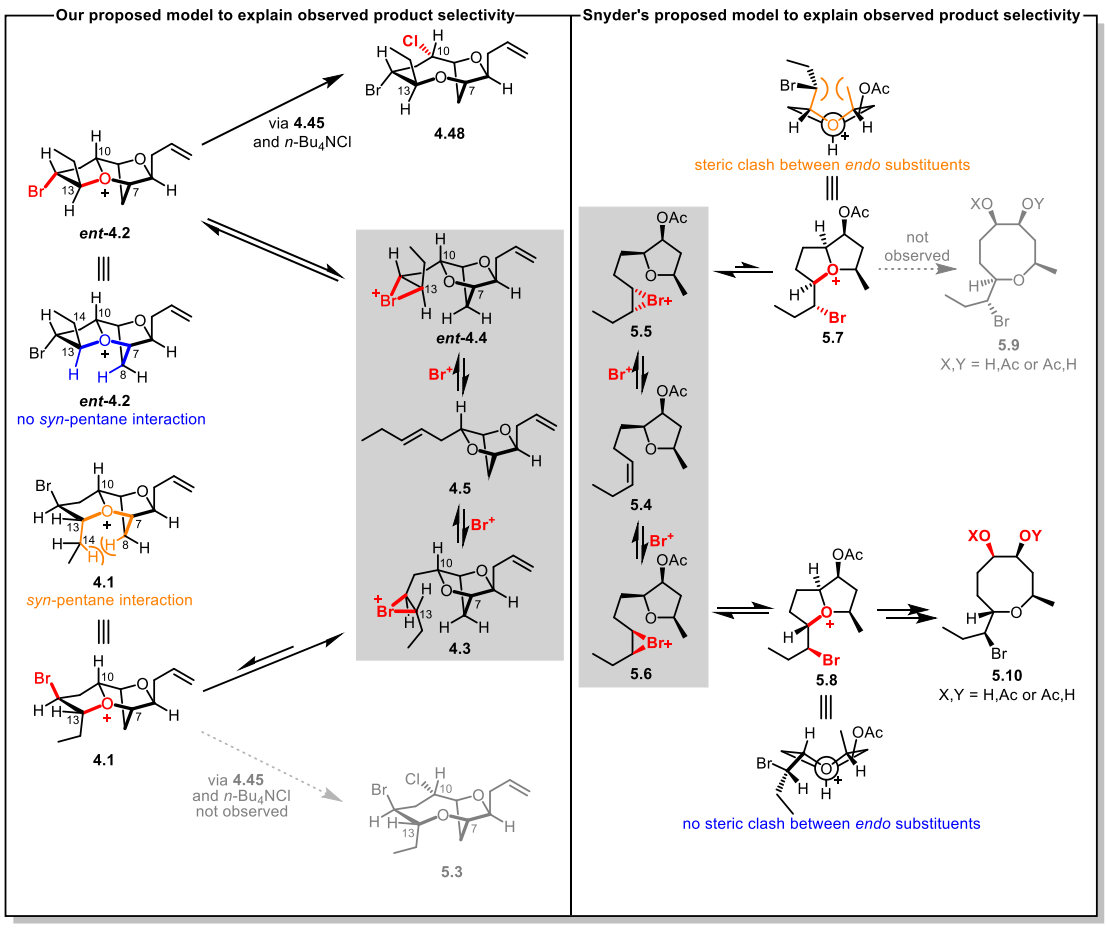


Figure 5.2. Proposed models to explain product selectivity in bromocyclisation reactions mediated by the reagent BDSB **4.34**.

This proposed model could explain the absence of **5.3** as the oxonium ion ***ent*-4.2** may be the only oxonium ion that could react with *n*-Bu_4NCl to provide chloride **4.48**.

As the equilibriation of bromonium ions is enabled by bromonium ion transfer processes,[218–223] a strategy was required for bromonium ion generation under conditions that prohibit bromonium ion transfer to gain access to **5.3**. The development of this strategy began with the regioselective generation of halohydrins **5.15-5.16**. This was built on the hypothesis that upon treatment of the epoxides **5.11-5.12** with metal halides such as $TiCl_4$ or $MgBr_2{\cdot}Et_2O$, chelation between the epoxide oxygen and the ether oxygen of the dioxabicyclic[2.2.1] system should bring about regioselective epoxide opening *via* **5.13-5.14**.[224] The halohydrins **5.15-5.16** could then be converted into the bromomesylates **5.19-5.20**, which are substrates for Braddock's method of enantiopure bromonium ion generation (**Figure 5.3**).[225,226]

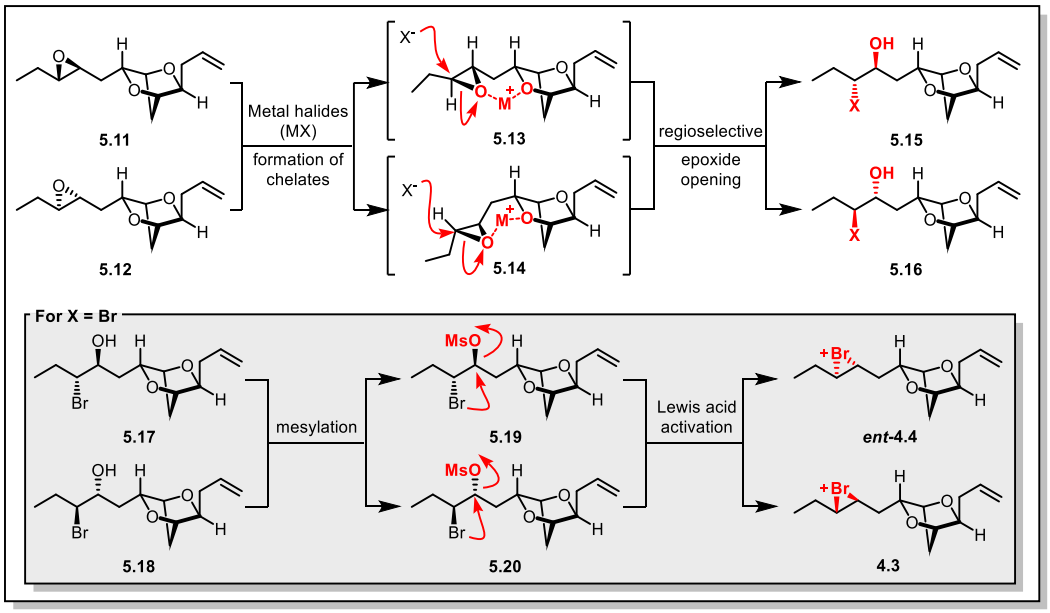
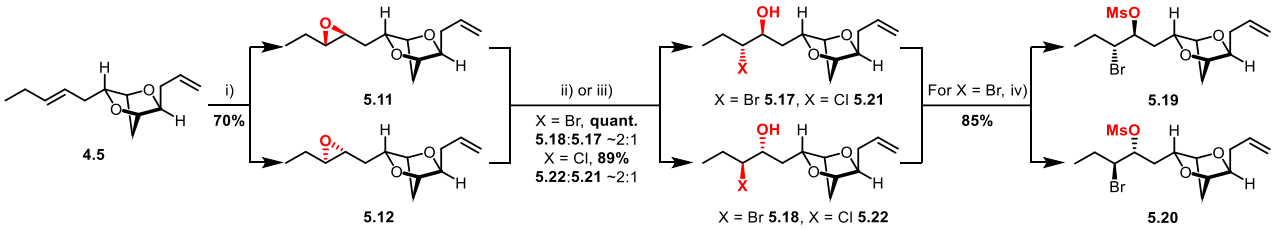


Figure 5.3. Rationale for the regioselective synthesis of halohydrins **5.15-5.16** by chelation-assisted epoxide opening of **5.11-5.12** and the generation of bromonium ions

5.1.1 *Halohydrins as the entry to a unified strategy*

The synthesis of halohydrins **5.15-5.16** commenced with the reaction between a mixture of **5.11-5.12** and $MgBr_2 \cdot Et_2O$ in Et_2O at room temperature. This reaction produced the bromohydrins **5.17-5.18** quantitatively and the bromohydrins were found to be readily separable by column chromatography. This regioselective epoxide opening also allowed the synthesis of the corresponding chlorohydrins **5.21-5.22** with $TiCl_4$ in place of $MgBr_2 \cdot Et_2O$.



Scheme 5.1. Synthesis of bromohydrins **5.17-5.18**, chlorohydrins **5.21-5.22** and bromomesylates **5.19-5.20**.

Reagents and conditions: **i)** *m*-CPBA (1.1 eq.), $CH_2Cl_2/NaHCO_{3(aq)}$, r.t., 1 hr. **ii)** $MgBr_2 \cdot Et_2O$ (2.0 eq.), Et_2O, r.t., 2 hrs. **iii)** $TiCl_4$ (1.1 eq.), CH_2Cl_2, -78 °C to r.t., 30 mins. **iv)** MsCl (1.1 eq.), Et_3N (1.1 eq.), CH_2Cl_2, 0 °C to r.t., 1 hr.

The absolute configurations and thus the diastereomeric ratios of the bromohydrins **5.17-5.18** were determined by Mosher ester analyses of their secondary alcohols with the assumption that the epoxide openings are stereospecific. The (*R*)-Mosher esters **5.23** and (*S*)-Mosher esters **5.24** of **5.17**, and (*R*)-Mosher esters **5.25** and (*S*)-Mosher esters **5.26** of **5.18** were synthesised and analysed according to the procedures of Hoye and Kakisawa.[184,185] The results of the analyses are shown below and the absolute configurations of the secondary alcohol stereocenters of bromohydrins **5.17-5.18** were confirmed to be (*S*) and (*R*) respectively (**Figure 5.4-5.5**). The assignments of the absolute configurations of the chlorohydrins **5.21-5.22** were based on comparison with the bromohydrins **5.17-5.18**.

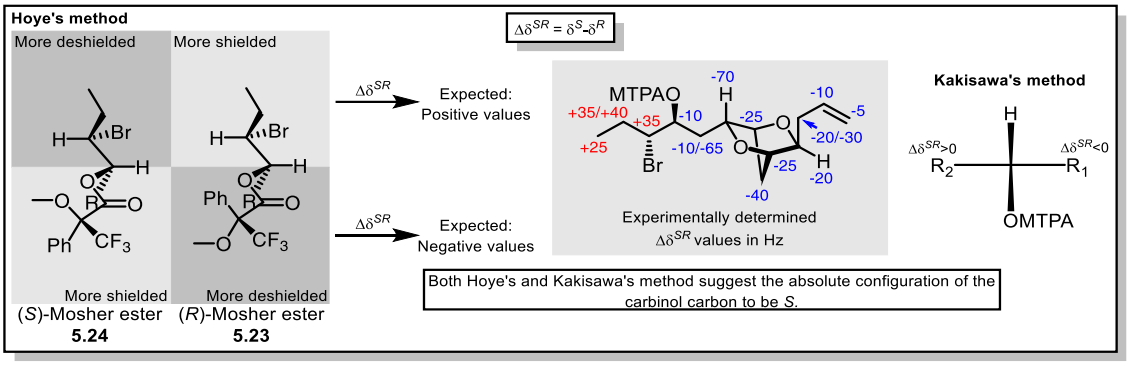


Figure 5.4. Mosher ester analysis of **5.17**.

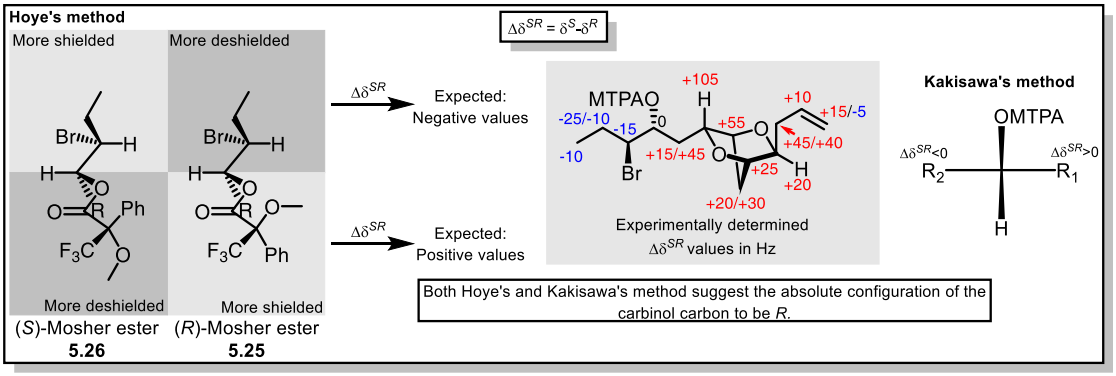
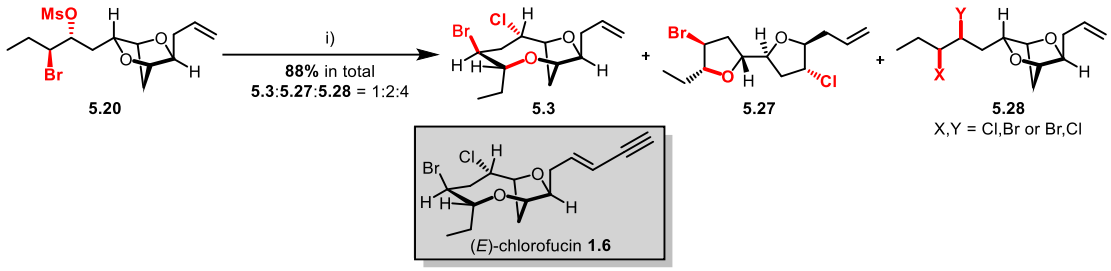


Figure 5.5. Mosher ester analysis of **5.18**.

The bromohydrins **5.17-5.18** were then converted into bromomesylates **5.19-5.20**. Treatment of **5.20** with $TiCl_4$ gave a mixture of isomeric products in ~1:2:4 ratio which were tentatively assigned as [5.2.1]-dioxabicyclic ether **5.3**, 2,2'-bifuran **5.27** and [2.2.1]-dioxabicyclic ether **5.28** respectively (**Scheme 5.2**). A low reaction concentration (0.01 M) was used to reduce the possibility of intermolecular bromonium ion transfer which could complicate the stereochemical outcome of the bromocyclisations as noted above.[7,218–223] It was found that **5.28** could be separated from **5.3** and **5.27**, and **5.28** was found to be a mixture of inseparable isomers that resembled bromomesylate **5.20** according to the analyses of their ^{1}H and ^{13}C NMR spectra. Based on this observation, **5.28** was assigned the structure as shown below with unknown regiochemistry and stereochemistry of the dihalide moiety. The compounds **5.3** and **5.27** were inseparable, but **5.27** had been synthesised previously, and

comparison with the published spectroscopic data confirmed its identity.[9] The identity of **5.3** was deduced by comparison with the spectroscopic data of the natural product (*E*)-chlorofucin **1.6**.[4,11,17]



Scheme 5.2. Reaction of **5.20** under Braddock's reaction conditions.[225,226]
Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), CH_2Cl_2 (0.01 M), -78 °C, 1 hr, then warmed to r.t. and stirred overnight.

The formation of **5.3** and **5.27** strongly suggested that **5.20** was able to form the bromonium ion **4.3** under Braddock's reaction conditions and underwent intramolecular bromocyclisation to form the oxonium ion **4.1**. The oxonium ion **4.1** was transformed to **5.3** *via* a C-10 attack by chloride anion and into **5.27** *via* a C-7 attack by the same nucleophile. The mixture of compounds **5.28** might comprise **5.29**, **5.30** and **5.31**. The compounds **5.29-5.30** could be generated *via* a C-13/C-12 attack by chloride anion on the bromonium ion **4.3**, whereas a C-13 attack by chloride anion onto the oxonium ion **4.1** would generate **5.31** (**Figure 5.6**). These pathways could not be distinguished as **5.28** was generated as an inseparable mixture of products and the elucidation of both the regiochemistry and stereochemistry of the dihalide moiety was not possible.

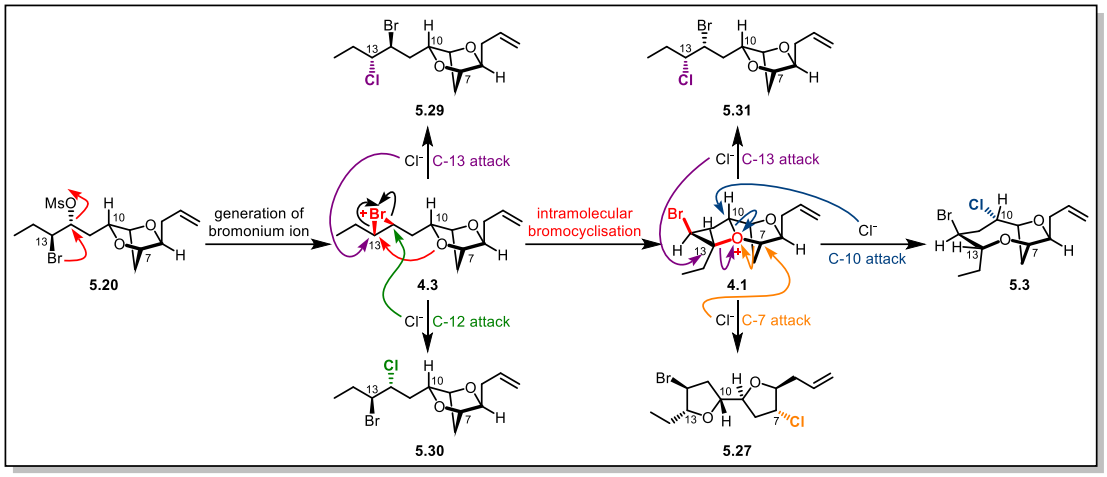
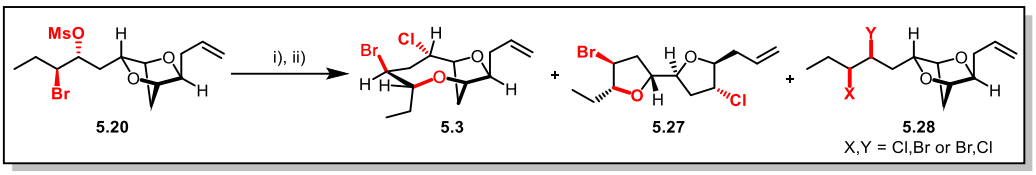


Figure 5.6. Rationalisation of the generation of **5.3**, **5.27** and **5.28** (a mixture of **5.29**-**5.31**) from the reaction of **5.20** with $TiCl_4$.

With these promising results, it was further hypothesised that the addition of an appropriate chloride scavenger to the reaction mixture could prohibit premature nucleophilic opening of the bromonium ion **4.3**, and thus allow the intramolecular bromocyclisation process to prevail to provide **4.1**. Addition of an excess of chloride ion to **4.1** would likely give **5.3** as the major product. This hypothesis was supported by previous studies on the oxonium ion **4.62** as C-10 attack was observed to be the predominant pathway in its reaction with various nucleophiles (**Section 4.3.4**).

The silver compound $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ was selected as the chloride scavenger due to its known compatibility with oxonium ion **4.62**. Treatment of **5.20** with 2.0 equivalents of $TiCl_4$ and 3.0 equivalents of $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ followed by addition of excess *n*-Bu_4NCl gave **5.3** as the major product along with recovered starting material **5.20** (**Table 5.1, Entry 3**).



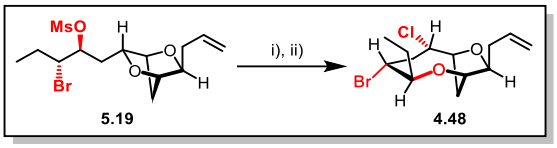
Entry	n	T_1/°C	T_2/°C	Ratio of products			Yield of products	Yield of recovered 5.20
				5.3	5.27	5.28		
1	1	-78	-78 to r.t.	2.5	1.0	1.9	30%	41%
2	2	-78	-78 to r.t.	3.2	1.0	1.6	27%	62%
3	3	-78	-78 to r.t.	5.0	1.0	trace	40%	30%
4	4	-78	-78 to r.t.	2.4	1.0	trace	35%	43%
5	3	-40	-40 to r.t.	1.6	1.0	trace	47%	nil
6	3	-40	-78	9.1	1.0	trace	61%	nil
7	3	-40	-78	7.1	1.0	trace	76%	nil
8	3	-40	-78	7.0	1.0	trace	65%	nil

Table 5.1. Optimisation of reaction conditions for the synthesis of **5.3** from **5.20**.
Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (n eq.), CH_2Cl_2 (0.01 M), T_1, 2 hrs. **ii)** *n*-Bu_4NCl (10.0 eq.), T_2, 1 hr.

Further variations in the equivalents of $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ used did not improve reaction performance (**Table 5.1, Entries 1, 2 and 4**). The reaction also suffered from incomplete conversion. The issue of reaction conversion was overcame by increasing the reaction temperature to -40 °C, just below the temperature where the model oxonium ions was stable to rearrangement. This change of reaction conditions resulted in the complete consumption of starting materials as suggested by TLC analysis and a slight increase in yield was observed. However, the product ratio of **5.3** to **5.27** dropped to 1.6:1. Quenching the reaction at -78 °C instead of at -40 °C boosted the product ratio to 7.0:1 (**Table 5.1, Entries 6-8**).

With the success in the optimisation of the bromocyclisation reaction, the synthesis of chloride **4.48** from **5.19** was studied using the same bromocyclisation reaction. The

synthesis of **4.48** using this protocol would allow the establishment of a unified synthesis of both **5.3** and **4.48**.



Entry	n	T_1/°C	T_2/°C	Yield of 4.48	Yield of recovered 5.19
1	3	-78	-78 to r.t.	57%	nil
2	3	-40	-78 to r.t.	68%	nil

Table 5.2. Optimisation of reaction conditions for the synthesis of **4.48** from **5.19**.
Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (n eq.), CH_2Cl_2 (0.01 M), T_1, 2 hrs. **ii)** *n*-Bu_4NCl (5.0-10.0 eq.), T_2, 1 hr.

Subjecting **5.19** to the reaction conditions described in entry 1 (**Table 5.2**) provided chloride **4.48** under complete conversion as the sole product in 57% yield. Performing the reaction with the optimised condition in entry 2 also generated **4.48** as the only product and with an improved yield of 68%. It was evident at this point that the reactivities of **5.19**-**5.20** toward bromocyclisations are different. Given that the formation of chloride **5.3** from bromomesylate **5.20** required a higher reaction temperature (-40 °C) to achieve complete conversion, while the formation of chloride **4.48** from bromomesylate **5.19** already proceeded smoothly at -78 °C, it seemed that the controlling factors of the observed difference in reactivities lie in the different rates of bromonium ion formation in this case instead of the equilibration of bromonium and oxonium ions as described previously (**Figure 5.2**). This argument was supported by the fact that unconsumed **5.20** was isolated from the reaction mixture (**Table 5.1, Entries 1-4**), which implied that a portion of **5.20** was not consumed over the course of the reaction unless the reaction temperature was increased to -40 °C. A scenario in which bromonium ion formation was faster than oxonium ion generation would not

explain this experimental observation, as the isolation of dihalide **5.28** instead of unconsumed bromomesylate **5.20** would be expected. A model was proposed to explain the experimental observations (**Figure 5.7**).

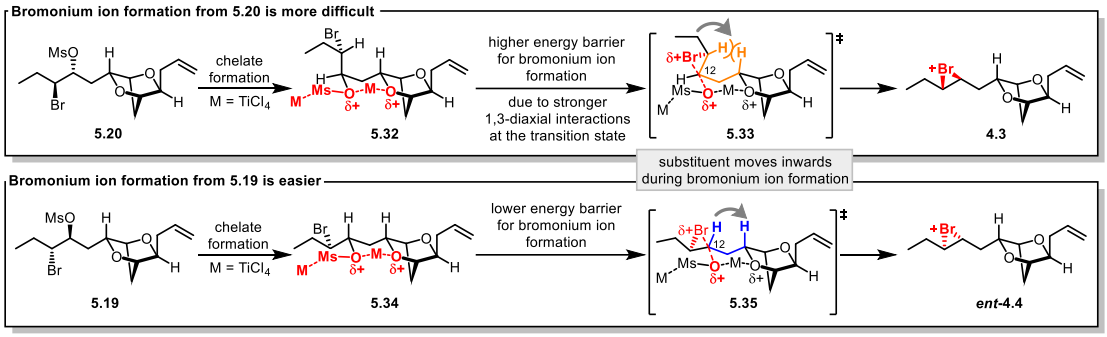


Figure 5.7. Proposed model to explain the higher temperature required for the formation of **4.3** compared to ***ent*-4.4**.

Assuming formation of chelates **5.32** and **5.34** upon addition of $TiCl_4$,[227] the chelates would then undergo bromonium ion formation *via* transition states **5.33** and **5.35**. It was proposed that bromonium ion formation *via* **5.33** would have a higher energetic requirement compared to that *via* **5.35**, as the change of the geometry at C-12 from tetrahedral to trigonal bipyramidal at the transition state of bromonium ion formation would bring the axial substituents at C-12 towards the center of the ring. This would create greater 1,3-diaxial interactions in **5.33** compared to **5.35** as the axial substituent at C-12 of **5.33** is an alkyl group whereas it is a hydrogen in **5.35**.

5.1.2 *A unified synthesis of oxonium ion precursors*

Following the development of a unified synthesis of **5.3** and **4.48**, it was decided to further elaborate **5.3** into chlorofucins **1.5-1.6**, and **4.48** into *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2**. This would allow us to complete the development of a unified synthesis for all the oxonium ion precursors from the diene **4.5** .

For the synthesis of **1.5**, **1.6** and ***ent*-5.1**, ***ent*-5.2** respectively from **5.3** and **4.48**, the (*E*)-enynes were to be installed by a cross metathesis reaction of the terminal olefin with crotonaldehyde followed by a Colvin alkyne synthesis.[2,5] As for the (*Z*)-enynes, they would be installed *via* an oxidative clevage of the terminal olefins followed by a Yamamoto-Peterson enyne synthesis.[9] Alternatively, a Stork-Zhao olefination could be performed to install a (*Z*)-vinyl iodide followed by a Sonogoshira coupling with TMS-acetylene to synthesise the (*Z*)-enynes (**Figure 5.8**).[228] A cross metathesis approach using the enyne **5.36** with the terminal olefins of **5.3** and **4.48** was not pursued as this cross metathesis approach have yet to achieve good levels (>10:1) of *Z*:*E* selectivity in related systems.[4,229]

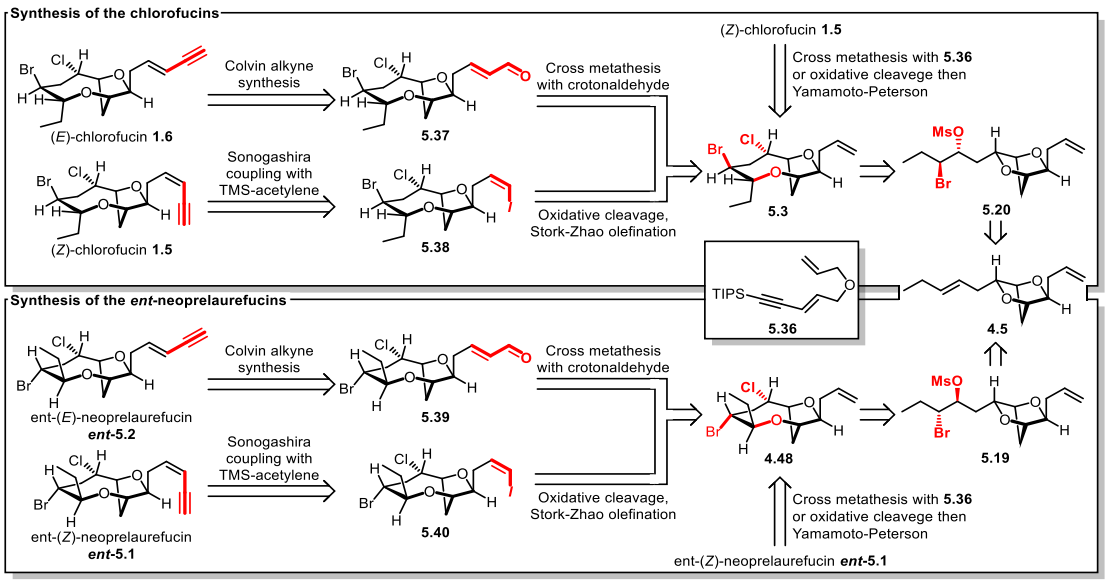
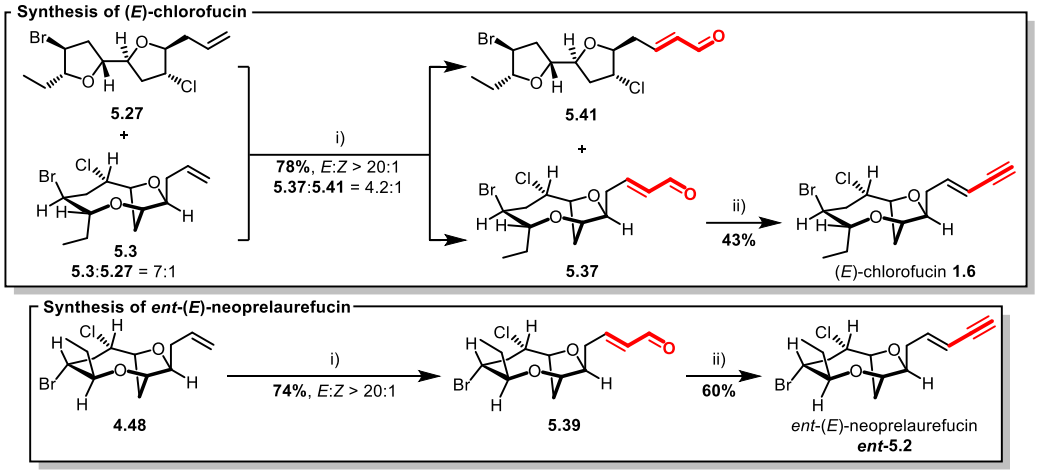


Figure 5.8. Retrosynthetic analysis for the synthesis of chlorofucins **1.5-1.6** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** using various strategies to install the (*E*) and (*Z*)-enynes on **5.3** and **4.48**.

A cross metathesis reaction between **5.3** and **4.48** with crotonaldehyde provided the desired enals **5.37** and **5.39** in good yields with excellent *E*:*Z* ratio. [2,5] The enals **5.37** and **5.39** were then subjected to reaction conditions for the Colvin alkyne synthesis and provided the target oxonium ion precursors (*E*)-chlorofucin **1.6** and *ent*-(*E*)-neoprelaurefucin ***ent*-5.2** in acceptable yields (**Scheme 5.3**).



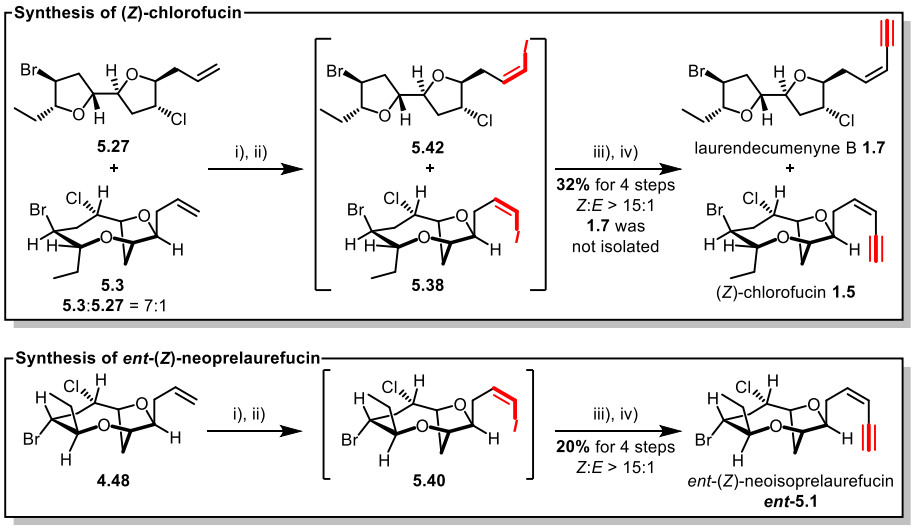
Scheme 5.3. Synthesis of (*E*)-chlorofucin **1.6** and *ent*-(*E*)-neoprelaurefucin ***ent*-5.2** using the strategy of cross metathesis followed by Colvin alkyne synthesis. Reagents and conditions: **i)** crotonaldehyde (10.0 eq.), Grubb's 2nd generation catalyst (10 mol%), CH_2Cl_2, 40 °C, 1 hr. **ii)** $TMSCHN_2$ (1.3-1.5 eq., 2.0 M in Et_2O), *n*-BuLi (1.3-1.5 eq., 2.3 M in hexanes), THF, -78 °C, 1 hr, then 0 °C, 30 mins.

The structure of our synthetic (*E*)-chlorofucin **1.6** was confirmed by comparison with published spectroscopic data (*see appendix 12.4*).[4,11,17]

The change of isomer ratio from 7:1 in the starting materials (**5.3**:**5.27**) to 4.2:1 in the enals (**5.37**:**5.41**) was due to thermal rearrangement of either **5.3** or **5.37** during the cross metathesis reaction in refluxing CH_2Cl_2. This experimental observation will be further discussed in the next section (**Section 5.1.3**).

Following the synthesis of (*E*)-chlorofucin **1.6** and *ent*-(*E*)-neoprelaurefucin ***ent*-5.2**, the synthesis of (*Z*)-chlorofucin **1.5** and *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1** are described below. Their synthesis employed the Stork-Zhao olefination and Sonogashira coupling strategy (**Scheme 5.4**).[228] Much to our surprise, the previous strategy using oxidative cleavage and Yamamoto-Peterson enyne synthesis did not provide **1.5** and ***ent*-5.1**, whereas the same strategy was found to be successfully applied on **4.46** for the total synthesis of *ent*-(*Z*)-notoryne ***ent*-1.17** (**Scheme 4.13**). The oxidative cleavage of **5.3** and **4.48** occurred uneventfully and provided the expected vinyl iodides **5.38** and **5.40**

after Stork-Zhao olefination. However, the vinyl iodides **5.38** and **5.40** were found to be unstable against decomposition and were quickly purified after their synthesis and used immediately without characterisation. The Sonogashira couplings of the vinyl iodides **5.38** and **5.40** with TMS-acetylene occurred smoothly and *in situ* deprotection of the resulting TMS-enynes provided the desired compounds (*Z*)-chlorofucin **1.5** and *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1** in acceptable yields over 4 steps. The identity of our synthetic (*Z*)-chlorofucin **1.5** was again corroborated by comparison with published spectroscopic data (*see appendix 12.4*).[4,19] The natural product laurendecumenyne B **1.7** synthesised using this protocol could not be isolated due to its small quantity. For the synthesis of this natural product, see **Chapter 6**.



Scheme 5.4. Synthesis of **1.5** and ***ent*-5.1** using the strategy of oxidative cleavage, Stork-Zhao olefination followed by a Sonogashira coupling with TMS-acetylene.

Reagents and conditions: **i)** cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t., 1-2 hrs. **ii)** $Ph_3PCH_2I_2$ (3.0 eq.), NaHMDS (3.0 eq., 1.0 M in THF), HMPA (6.0 eq.), THF, -78 °C, 30 mins, then r.t., 1 hr. **iii)** TMS-acetylene (5.0 eq.), CuI (1.0 eq.), $Pd(PPh_3)_4$ (15 mol %), Et_3N, r.t., 1 hr. **iv)** K_2CO_3 (10.0 eq.), MeOH, r.t., 1-2 hrs.

A unified synthesis has been demonstrated for all the oxonium ion precursors chlorofucins **1.5-1.6** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** from diacetone-D-glucose **4.12**. This unified synthesis was enabled by an efficient and

scalable synthesis of the diene **4.5** from diacetone-D-glucose **4.12** in 12% overall yield over 11 steps. A further 6-8 steps of transformations employing a Prilezhaev epoxidation, chelation-assisted regioselective epoxide opening,[224] Braddock's strategy of stereospecific bromonium ion generation,[225,226] transannular functionalisation *via* oxonium ion opening, olefin cross metathesis, Colvin alkyne synthesis or Stork-Zhao olefination and a Sonogashira coupling, gave (*E*)-chlorofucin **1.6** and *ent*-(*E*)-neoprelaurefucin ***ent*-5.2** in 17 steps and (*Z*)-chlorofucin **1.5** and *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1** in 19 steps.

5.1.3 *Attempts to streamline the synthesis of oxonium ion precursors*

Concerning the synthesis of chlorofucins **1.5-1.6** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2**, it appeared that by swapping the steps for the key bromocyclisation reaction with the enyne synthesis could render their synthesis more aesthetically pleasing. As the key bromocyclisation step would increase molecular complexity by the greatest extent and hence appeared the ideal final step of the synthesis (**Figure 5.9**).

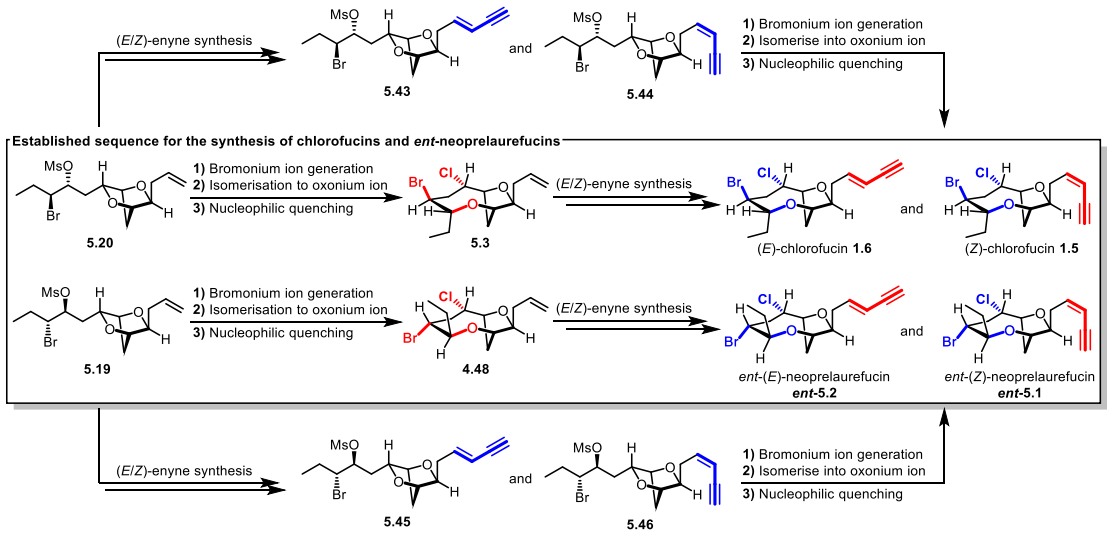
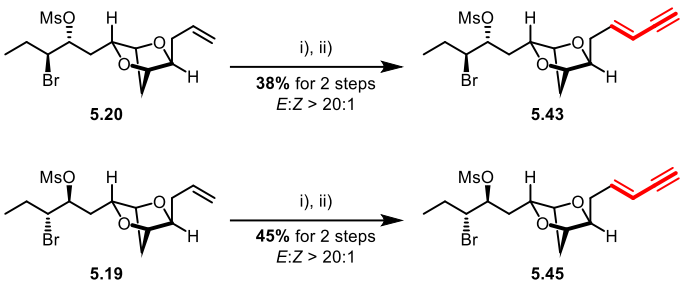


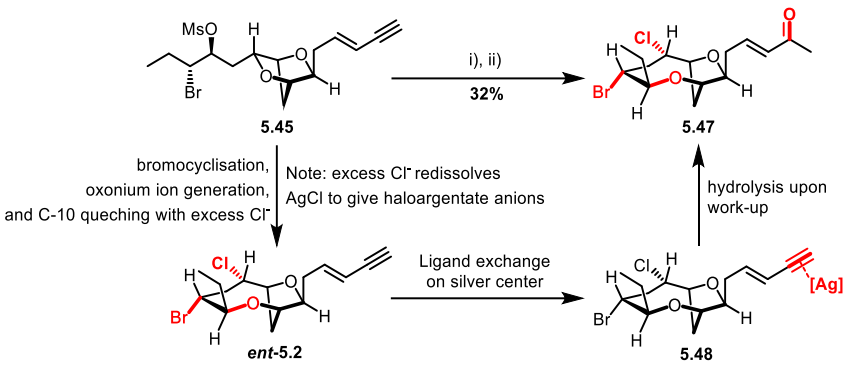
Figure 5.9. Proposed alternative synthetic sequences to synthesise chlorofucins **1.5-1.6** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** from the enynes **5.43-5.46**.

However, the enynes may be activated by the use of excess silver (I) species during the bromocyclisation reaction and hence may undergo further transformations.[230] As for the titanium species, they were not expected to react with the alkyne unless specific ligands were used.[231,232] The (*E*)-enynes **5.43** and **5.45** were synthesised employing established procedures as in the synthesis of (*E*)-chlorofucin **1.6** (**Scheme 5.3**).



Scheme 5.5. The synthesis of enynes **5.43** and **5.45**. Reagents and conditions: **i)** crotonaldehyde (5.0 eq.), Grubb's 2nd generation catalyst (5.0 mol%), CuI (7.5 mol%) Et_2O, r.t., overnight. **ii)** $TMSCHN_2$ (1.3-1.5 eq., 2.0 M in Et_2O), *n*-BuLi (1.3-1.5 eq., 2.3 M in hexanes), THF, -78 °C, 40 mins, then 0 °C, 5 mins.

The enyne **5.45** was then subjected to the established reaction conditions of the bromocyclisation reaction. However, none of the expected product ***ent*-5.2** was observed. Instead, the enone **5.47** was isolated as the major isolable product in 32% yield. This suggested that the enyne moiety was indeed labile under the bromocyclisation conditions. The generation of the enone was proposed to occur *via* silver-mediated hydration of the alkyne, with the proposed reaction mechanism as shown below (**Scheme 5.6**).[215–217,233]



Scheme 5.6. Tandem bromocyclisation-alkyne hydration of enyne **5.45**.

Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (3.0 eq.), CH_2Cl_2 (0.01 M), -40 °C, 2 hrs. **ii)** *n*-Bu_4NCl (5.0-10.0 eq.), -78 °C, 1 hr.

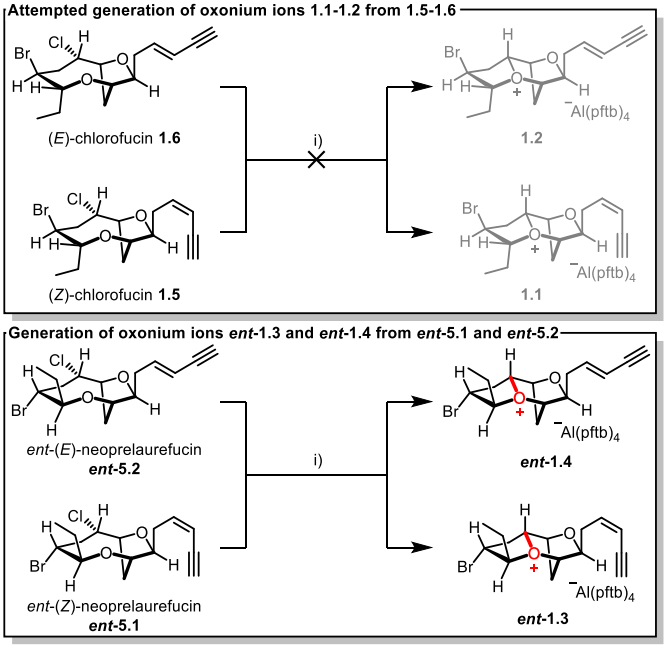
Given that the established procedures for the synthesis of the chlorofucins **1.5-1.6** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** were already sufficient for the realisation of the goals of the project, the bromocyclisations of the enynes **5.43-5.46** were not optimised further.

5.2 Generation of biosynthetically relevant oxonium ions by halide abstraction

Following the successful synthesis of the oxonium ion precursors **1.5-1.6** and ***ent*-5.1**, ***ent*-5.2**, the halide abstraction method demonstrated in **Section 4.3.3** was used to generate the corresponding oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** respectively.

5.2.1 *Different reactivities of oxonium ion precursors*

It was found that the oxonium ion precursors chlorofucins **1.5-1.6** exhibited very different reactivities compared to *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** in terms of their ability to generate oxonium ions. The *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2**, with the same relative configurations as the model oxonium ion precursor **4.60**, generated the desired oxonium ions ***ent*-1.3** and ***ent*-1.4** smoothly at -78 °C on treatment with $Ag[Al(pftb)_4]\cdot CH_2Cl_2$, while the chlorofucins **1.5-1.6** were not reactive under the previously developed halide abstraction conditions at this temperature (**Scheme 5.7**).



Scheme 5.7. Difference in reactivity concerning the generation of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** from their respective precursors **1.5-1.6** and ***ent*-5.1**, ***ent*-5.2**.

Reagents and conditions: **i)** $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CD_2Cl_2, -78 °C, 1.5 hrs, then filter into flame-dried Young's NMR tube at -78 °C and perform NMR acquisition at -78 °C.

By analogy with the X-ray crystallographic structures of the natural products (*E*)-chlorofucin **1.6** and *ent*-(*E*)-laurefucin ***ent*-1.14**,[11,21] the lowest energy conformers of **1.6** and ***ent*-5.2** were assumed to be the structures as shown below (**Figure 5.10**). DFT calculations (performed by Dr Quynh Nguyen and Prof. Robert. S. Paton) suggested that the oxonium ions **1.2** and ***ent*-1.4** would adopt the structure as shown below as their lowest energy conformers (**Figure 5.10**). It was immediately apparent that the lowest energy conformer of oxonium ion precursor ***ent*-5.2** resembles the lowest energy conformer of oxonium ion ***ent*-1.4** and thus the generation of the oxonium ion ***ent*-1.4** from ***ent*-5.2** should be a facile process because of small changes in molecular geometry during the transformation.

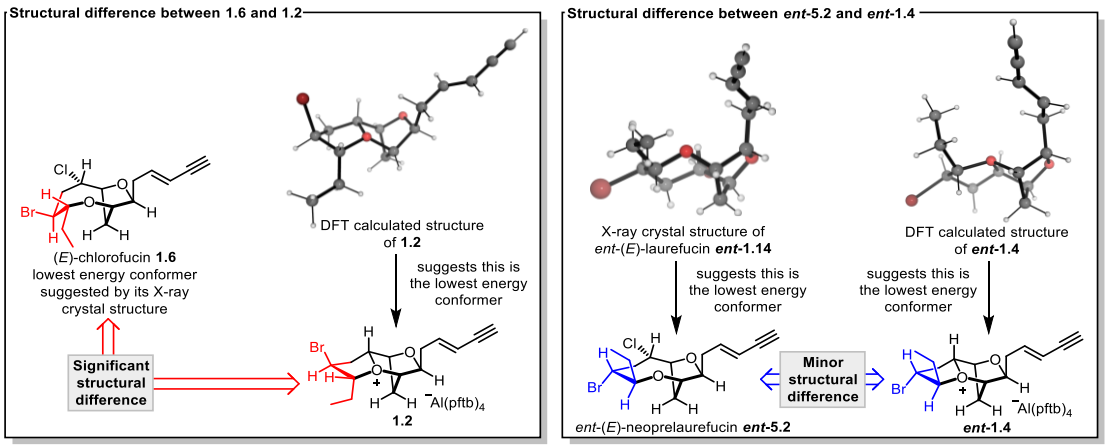


Figure 5.10. Structural differences between the oxonium ions and their precursors as predicted by DFT calculations and analysis of the X-ray crystal structures of related compounds.

Further DFT calculations (performed by Dr Quynh Nguyen and Prof. Robert. S. Paton) suggested, as expected, that the generation of oxonium ion **1.2** required a ring flip of the lowest energy conformer of (*E*)-chlorofucin **1.6** to a higher energy conformer before oxonium ion generation could proceed to produce **1.2** in its lowest energy conformation (**Figure 5.11**). Whereas for the generation of oxonium ion ***ent*-1.4** from *ent*-(*E*)-neoprelaurefucin ***ent*-5.2**, no such ring flip was required (**Figure 5.12**). This was further corroborated by the comparison of overlaid computed, lowest energy

structures of **1.6** and ***ent*-5.2** with their respective reactive conformers which could lead to oxonium ion formation (**Figure 5.13**).

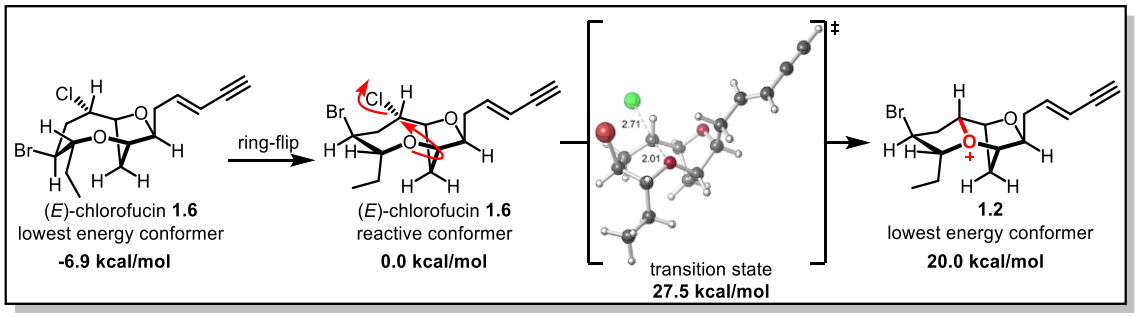


Figure 5.11. DFT calculations for the formation of **1.2** from **1.6**, which suggested the requirement of a ring-flip before oxonium ion formation. Calculations were performed with M06-2X functional and def2TZVP basis set at -78 °C in CH_2Cl_2 (SMD solvation).

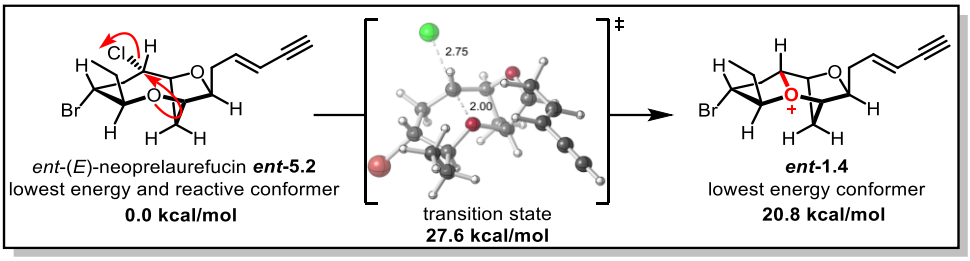


Figure 5.12. DFT calculations for the formation of ***ent*-1.4** from ***ent*-5.2**, which did not suggest the requirement of a ring-flip before oxonium ion formation. Calculations were performed with M06-2X functional and def2TZVP basis set at -78 °C in CH_2Cl_2 (SMD solvation).

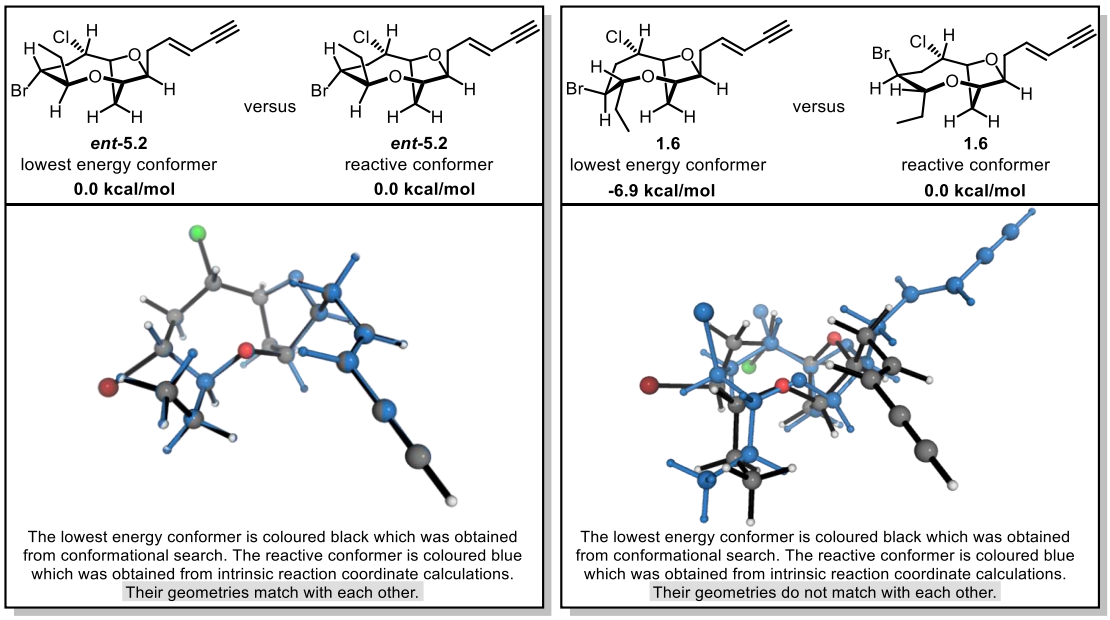


Figure 5.13. Comparison of DFT calculated structures of the lowest energy conformers of **1.6** and ***ent*-5.2** with their reactive conformers.

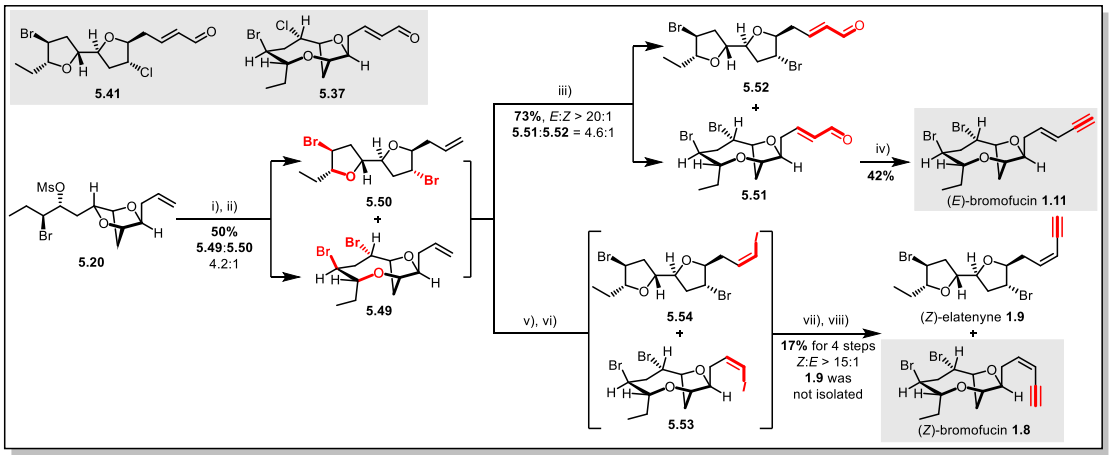
The generation of oxonium ion **1.2** from (*E*)-chlorofucin **1.6** was then attempted at a higher temperature. However, incomplete consumption of **1.6** was observed after 1.5 hours at -40 °C. Further increasing the temperature to -20 °C allowed the complete consumption of **1.6**, yet this also led to complete decomposition. These experimental observations suggested that (*E*)-chlorofucin **1.6** was not a suitable precursor for oxonium ion generation. It was rationalised that having a weaker C–Br bond instead of a C–Cl bond at C-10 should lower the energetic requirement of oxonium ion generation for **1.5-1.6**. The weaker C–Br bond (285 kJ mol^{-1}) compared to the C–Cl bond (327 kJ mol^{-1}) should also be able to compensate for the slightly lower lattice enthalpy of $AgBr_{(s)}$ (900 kJ mol^{-1}) compared to $AgCl_{(s)}$ (916 kJ mol^{-1}).[234]

The bromide analogues bromofucins **1.8** and **1.11** were then synthesied analogously as the corresponding chlorofucins **1.5-1.6** using *n*-Bu_4NBr instead of *n*-Bu_4NCl as the nucleophile in the reaction (**Table 5.1**). This enabled the synthesis of dibromides **5.49-5.50** in 50% yield with an isomer ratio of 3:1 on average. The inseparable mixture of **5.49-5.50** was transformed into the bromofucins **1.8** and **1.11** according to established procedures for (*E*) and (*Z*)-enyne synthesis as employed in the synthesis of **1.5-1.6** with minor modifications (**Scheme 5.8**).

As noted previously (**Scheme 5.3**), the cross metathesis reaction between **5.3** and crotonaldehyde in CH_2Cl_2 led to isomerisation of [5.2.1]-dioxobicyclic ethers **5.3** and **5.37** to 2,2'-bifuran **5.41**. Employing identical conditions for the cross metathesis reaction between **5.49** and crotonaldehyde led to isomerisation as expected. The isomerisation was proposed to involve oxonium ions **4.1** and its corresponding enal, in which competitive opening of these oxonium ions could occur between the dissociable chloride ligand from the Grubb's 2nd generation catalyst and the bromide anion

generated from **5.49** or **5.51** after oxonium ion formation to produce an inseparable mixture of chlorides **5.37**, **5.41** and dibromides **5.51** and **5.52**.

Performing the cross metathesis at room temperature with CuI as a catalyst activator for the Grubb's 2nd generation catalyst did not lead to isomerisation of **5.49** or **5.51**.[235] However, the by-products **5.52** and (*Z*)-elatenyne **1.9** were both contaminated with minute quantities of **5.41** and laurendecumenyne B **1.7**. These minor contaminants most probably originated from the minute quantities of chloride **5.27** produced during the bromocyclisation reaction of **5.20**. It was demonstrated that **5.27** could dominate the production of **5.3** (ratio of **5.27**:**5.3** = 2:1) upon treatment of **5.20** with $TiCl_4$ without any chloride scavenger as shown previously (**Scheme 5.2**). Therefore, it was possible that minute quantities of **5.27** could be produced *via* a background reaction during the synthesis of **5.3** even in the presence of an excess of chloride scavenger.

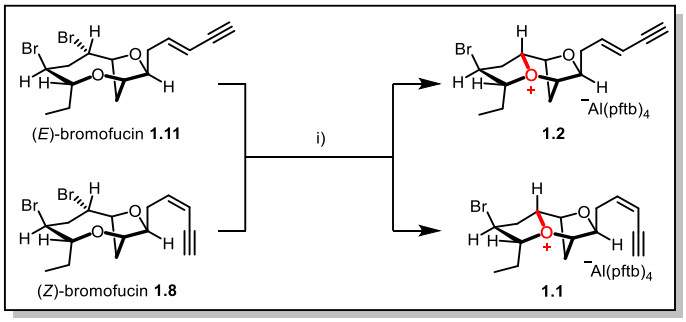


Scheme 5.8. Synthesis of **1.8** and **1.11** from **5.20**.

Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (3.0 eq.), CH_2Cl_2 (0.01 M), -40 °C, 2 hrs. **ii)** *n*-Bu_4NBr (10.0 eq.), -78 °C, 20 min. **iii)** crotonaldehyde (5.0 eq.), Grubb's 2nd generation catalyst (5.0 mol%), CuI (7.5 mol%) Et_2O, r.t., overnight. **iv)** $TMSCHN_2$ (1.3-1.5 eq., 2.0 M in Et_2O), *n*-BuLi (1.3-1.5 eq., 2.3 M in hexanes), THF, -78 °C, 1 hr, then 0 °C, 30 min. **v)** cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t., 1-2 hrs. **vi)** $Ph_3PCH_2I_2$ (3.0 eq.), NaHMDS (3.0 eq., 1.0 M in THF), HMPA (6.0 eq.), THF, -78 °C, 30 min, then r.t., 1 hr. **vii)** TMS acetylene (5.0 eq.), CuI (1.0 eq.), $Pd(PPh_3)_4$ (15 mol %), Et_3N, r.t., 1 hr. **viii)** K_2CO_3 (10.0 eq.), MeOH, r.t., 1-2 hrs.

The structures of our synthetic bromofucins **1.8** and **1.11** were confirmed by comparison with published spectroscopic data of the natural products (*Z*)-bromofucin **1.8** and (*E*)-bromofucin **1.11** respectively (*see appendix 12.4*).[4,24,236]

The generation of the oxonium ions **1.1** and **1.2** was then achieved by employing the conditions as described below (**Scheme 5.9**). Although switching from a C–Cl bond at C-10 to a C–Br bond allowed the generation of the desired oxonium ions **1.1** and **1.2**, the reaction conditions still required a minor modification for the successful generation of **1.1** and **1.2**. Carrying out the reaction at -40 °C was crucial for the generation of **1.1** and **1.2** from bromofucins **1.8** and **1.11**, as insignificant reactivity was observed by performing the reaction at -78 °C. The NMR spectroscopic data of **1.1** and **1.2** were acquired at -78 °C despite the higher reaction temperature required for the generation of these two substrates for easier NMR spectroscopic comparison between the oxonium ions.



Scheme 5.9. Generation of oxonium ions **1.1** and **1.2** from **1.8** and **1.11**.
Reagents and conditions: **i)** Ag[Al(pftb)$_4$]·CH_2Cl_2 (1.1 eq.), CD_2Cl_2, -40 °C, 1.5 hrs, then filter into flame-dried Young's NMR tube at -78 °C and perform NMR acquisition at -78 °C.

5.2.2 *Characterisation of biosynthetically relevant oxonium ions*

This section will focus on the characterisation of the target oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** along with obtaining supporting evidence for their proposed identities. The studies discussed are as follows: **1)** investigations of NMR chemical shift differences between the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** and their respective precursors bromofucins **1.8**, **1.11** and *ent*-neoprelaurefucins ***ent*-5.1**, ***ent*-5.2**; **2)** investigations of NMR chemical shift differences among the oxonium ions themselves; **3)** the differences in ^{1}H-^{13}C HMBC correlations between the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** and their respective precursors **1.8**, **1.11** and ***ent*-5.1**, ***ent*-5.2**; **4)** analysis of $^{3}J_{HH}$ couplings of the oxonium ions to elucidate their preferred conformations in solution; **5)** analysis of DFT calculated oxonium ion NMR chemicals shifts and structures and comparison with our experimental data; **6)** studies of the ionisation behaviour of the oxonium ion precursors by mass spectrometry.

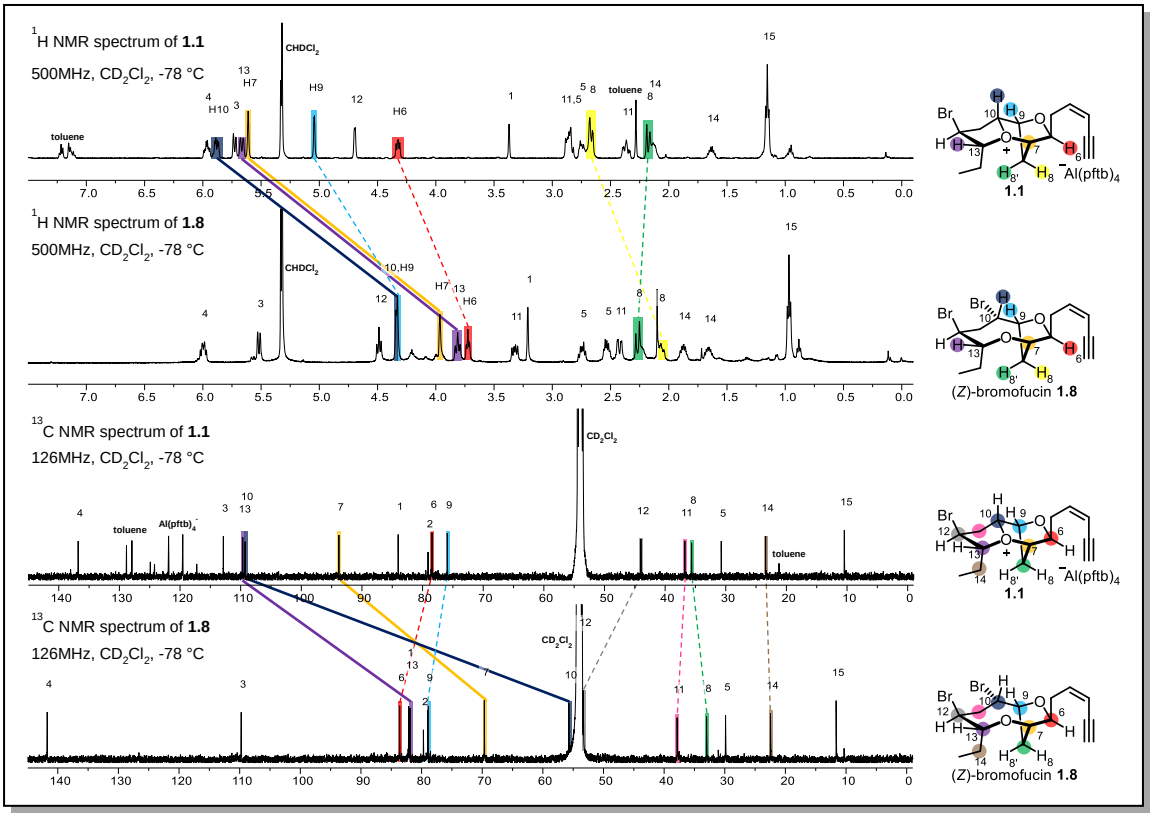


Figure 5.14. ^{1}H and ^{13}C NMR chemical shift comparison between **1.1** and **1.8**.

The analysis of the ^{1}H and ^{13}C NMR chemical shifts of **1.1** and **1.8** is first discussed (**Figure 5.14**). On formation of the oxonium ion **1.1**, it was found that both ^{1}H and ^{13}C chemical shifts at atoms 7 (orange), 10 (navy) and 13 (purple) increased significantly compared with the chemical shifts of the starting material **1.8**. The ^{1}H chemical shift increased by ca. 1.0-1.5 ppm and the ^{13}C chemical shift increased by ca. 25-50 ppm, which is in keeping with the expected increase in chemical shifts upon oxonium ion formation.[27,46,48,53] The ^{1}H chemical shifts of H-6 (red), H-9 (blue) and H-8 (yellow) adjacent to the oxonium ion carbons also increased by ca. 0.5 ppm upon oxonium ion formation. However, H-8' (green) did not exhibit such an increase in its ^{1}H NMR chemical shift, which was indicative that the increase in ^{1}H NMR chemical shifts of H-6 (red), H-9 (blue) and H-8 (yellow) are due to overlap between their occupied σ_{C-H} orbitals and the vacant $\sigma^{*}_{C-O}{}^{+}$ orbitals of the oxonium ion carbons. On the other hand, the σ_{C-H} orbital of H-8' (green) does not have the correct geometry to overlap with the vacant $\sigma^{*}_{C-O}{}^{+}$ orbital of C-7, and thus its ^{1}H NMR chemical shift did not increase (**Figure 5.15**).

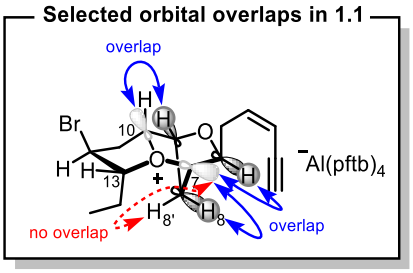


Figure 5.15. Overlap between occupied σ_{C-H} orbitals and vacant $\sigma^{*}_{C-O}{}^{+}$ orbitals in **1.1**.

The ^{13}C NMR chemical shifts of C-6 (red), C-9 (blue), C-11 (pink) and C-12 (grey) decreased upon oxonium ion formation. This general decrease in ^{13}C NMR chemical shift of β-carbons of the trivalent oxygen was also observed in the model oxonium ion **4.62** and other types of onium ions (**Section 4.3.3**). However, the ^{13}C NMR chemical

shift of C-8 (green) and C-14 (brown) slightly increased upon oxonium ion formation, most probably due to the difference in conformation between **1.8** and **1.1** (**Figure 5.11**).

The comparison of ^{1}H and ^{13}C NMR chemical shifts of **1.2** and **1.11** is displayed below (**Figure 5.16**). The variations in chemical shifts are largely analogous to that found in the analysis of **1.1** and **1.11** as they only differ by the enyne geometry. However, the ^{1}H NMR resonances of H-7 (orange) and H-13 (purple) in **1.2** were significantly different to that in **1.1** but not the corresponding ^{13}C NMR resonances (**Figure 5.17**).

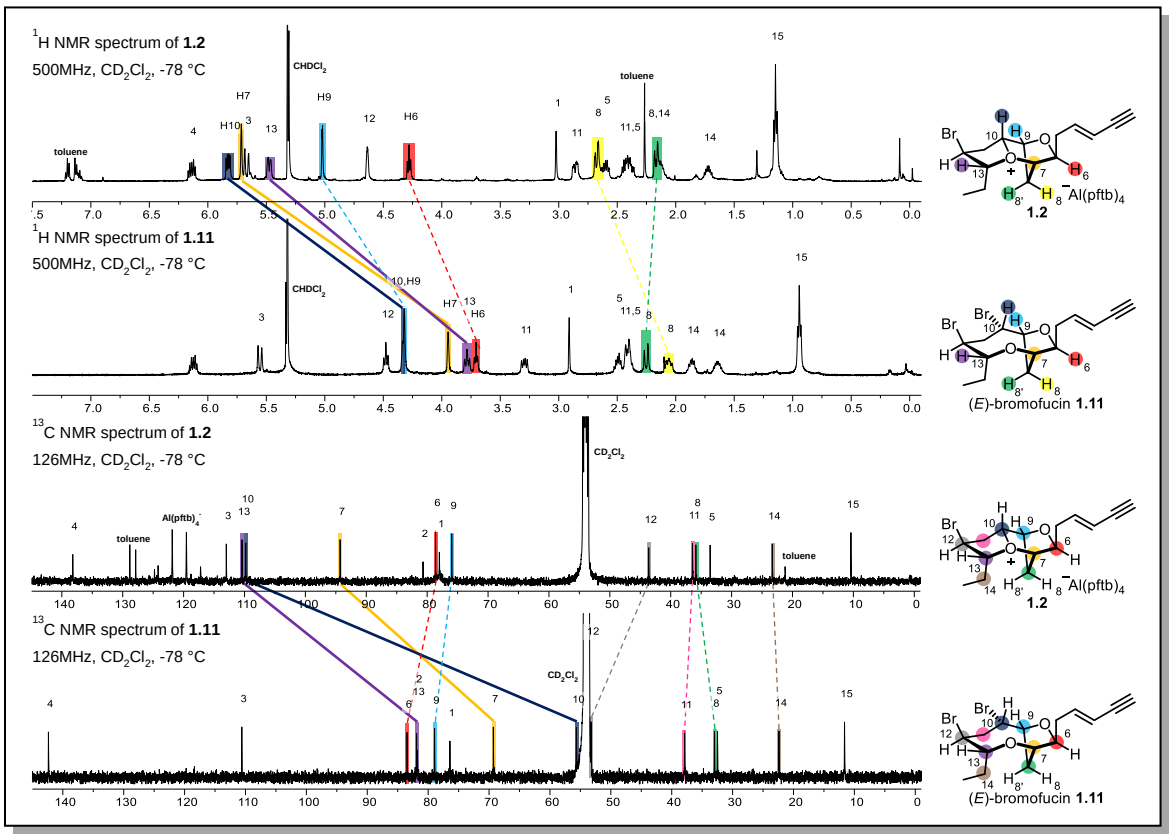


Figure 5.16. ^{1}H and ^{13}C NMR chemical shift comparison between **1.2** and **1.11**.

DFT calculations (performed by Dr Quynh Nguyen and Prof. Robert. S. Paton) suggested that the *Z*-enyne of **1.1** prefers to orient towards and above the oxonium ion, which could potentially influence the ^{1}H chemical shift of H-7 and H-13 through magnetic anisotropy of the acetylene group (**Figure 5.18**).

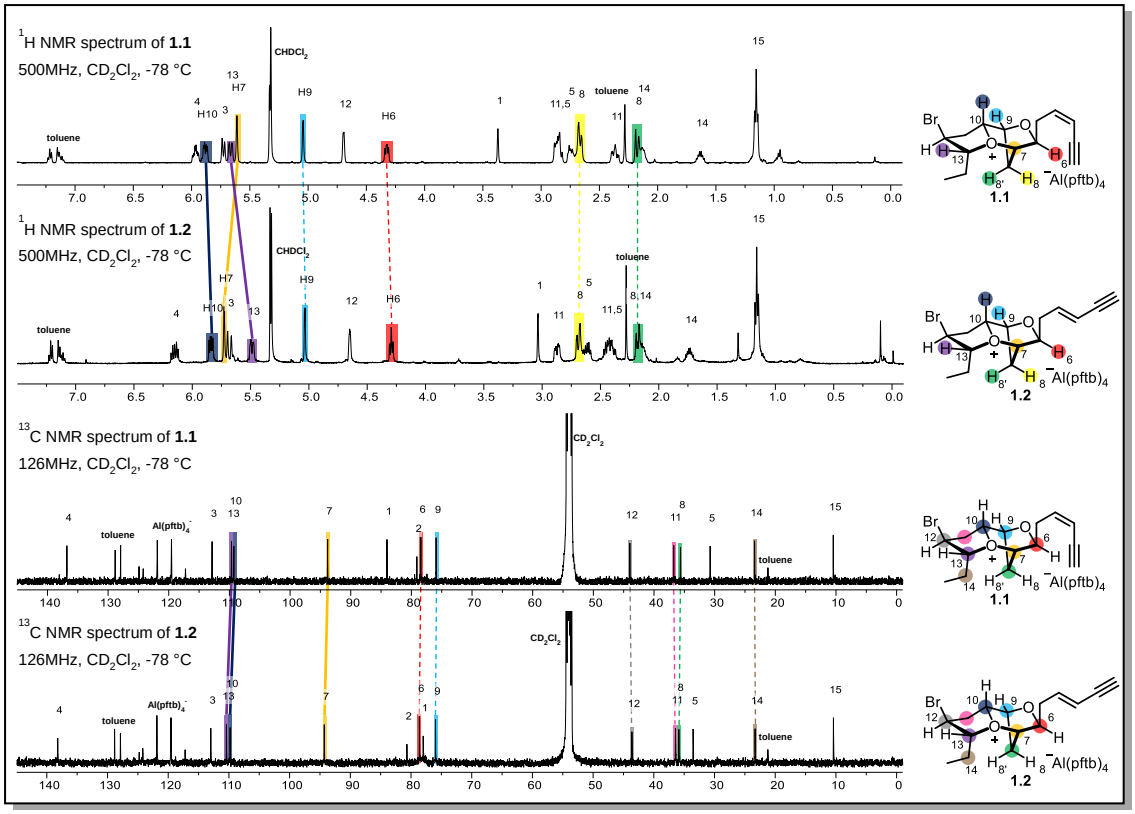


Figure 5.17. ^{1}H and ^{13}C NMR chemical shift comparison between **1.1** and **1.2**.

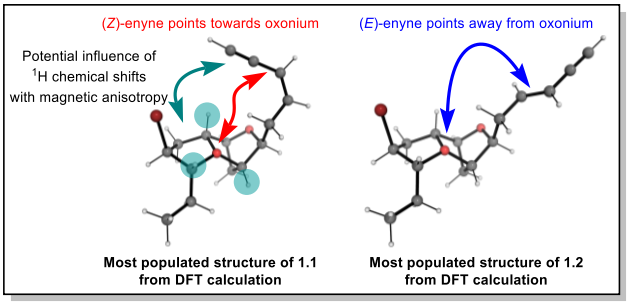


Figure 5.18. The most populated DFT calculated structures of **1.1** and **1.2** from their Boltzmann distributions at -78 °C. The structures of the oxonium ions were optimised in the gas phase employing the B3LYP functional and 6-31+G(d,p) basis set.

The comparison of ^{1}H and ^{13}C NMR chemical shifts between the oxonium ion ***ent*-1.3** and ***ent*-1.4** and their precursors ***ent*-5.1** and ***ent*-5.2** are presented below (**Figure 5.19-5.20**). The variations in chemical shifts are largely analogous to that found in the analysis of the oxonium ions **1.1-1.2** as shown above, with a significant increase in ^{1}H and ^{13}C NMR chemical shifts at atoms 7, 10 and 13 upon oxonium ion formation, along with changes in the ^{1}H chemical shifts of H-6 (red), H-9 (blue) and H-8 (yellow) indicative of overlap between their occupied σ_{C-H} orbitals and vacant $\sigma^*_{C-O}{}^+$ orbitals.

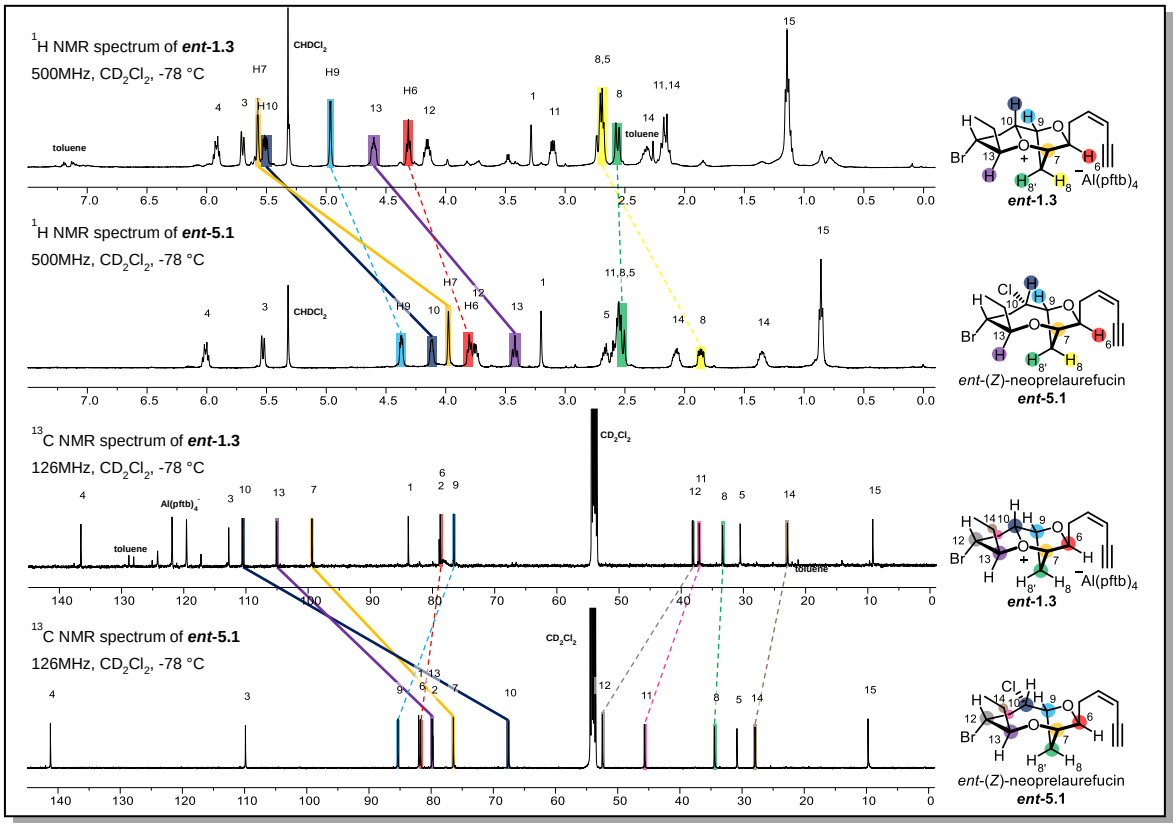


Figure 5.19. ^{1}H and ^{13}C NMR chemical shift comparison between ***ent*-1.3** and ***ent*-5.1**.

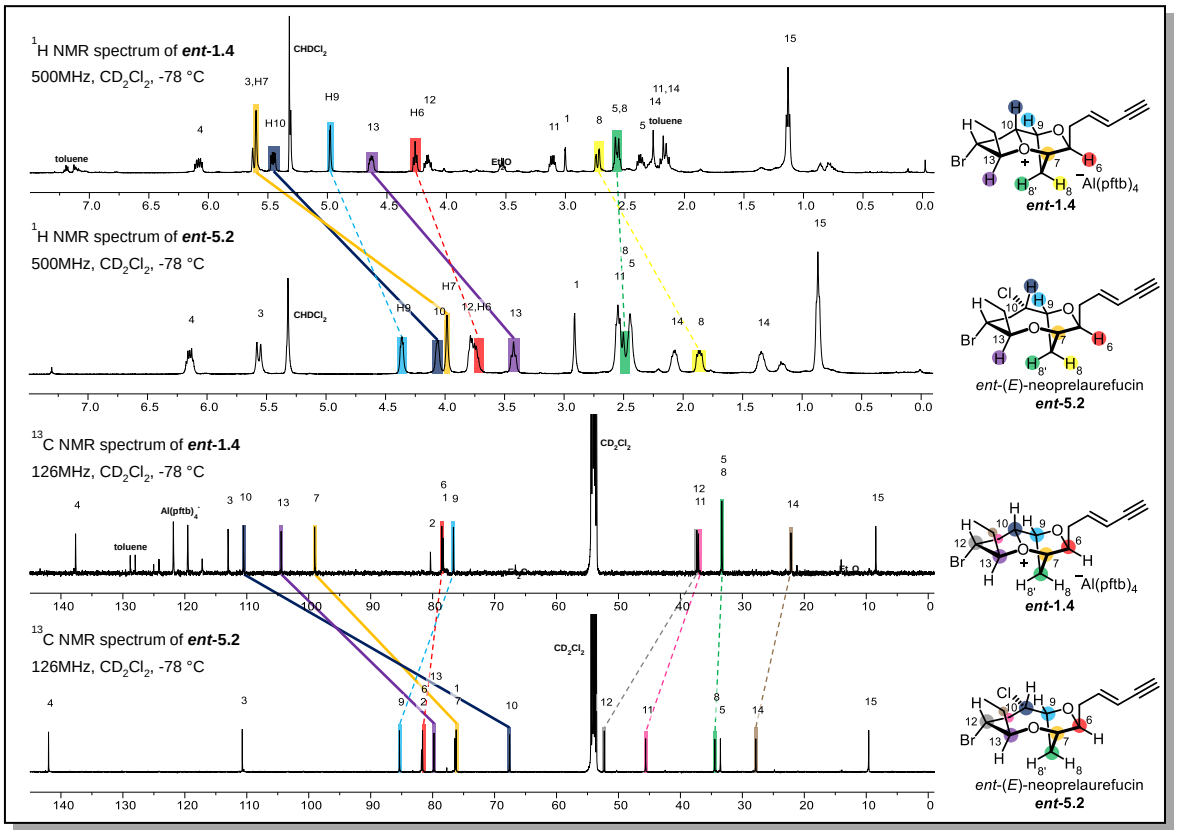


Figure 5.20. ^{1}H and ^{13}C NMR chemical shift comparison between ***ent*-1.4** and ***ent*-5.2**.

A general decrease in ^{13}C NMR chemical shift of the β-carbons C-6 (red), C-8 (green), C-9 (blue), C-11 (pink), C-12 (grey) and C-14 (brown) of the trivalent oxygen was also observed in these two oxonium ions. However, the ^{1}H resonances of H-7 (orange) and H-13 (purple) were not found to be significantly different between oxonium ions ***ent*-1.3** and ***ent*-1.4**. DFT calculations (performed by Dr Quynh Nguyen and Prof. Robert. S. Paton) suggested that the (*Z*)-enyne of ***ent*-1.3**, as opposed to the behaviour of **1.1**, points away from the oxonium ion (**Figure 5.21**).

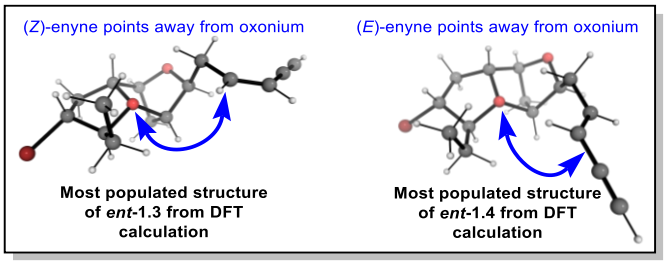


Figure 5.21. The most populated DFT calculated structures of ***ent*-1.3** and ***ent*-1.4** from their Boltzmann distributions at -78 °C. The structures of the oxonium ions were optimised in gas phase employing the B3LYP functional and 6-31+G(d,p) basis set.

Besides chemical shift comparisons, ^{1}H-^{13}C HMBC correlations were also compared between the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** and their respective precursors **1.8**, **1.11** and ***ent*-5.1**, ***ent*-5.2** to elucidate the changes in molecular connectivity after oxonium ion formation (**Figure 5.22-5.23**, **Figure 5.24-5.25**). The correlations of interest were those between H-(7, 10, 13) and C-(7, 10, 13) as oxonium ion formation would theoretically allow the establishment of ^{1}H-^{13}C HMBC correlations through the transannular C–O^{+} bond. However, not every ^{1}H-^{13}C HMBC correlation was visible as the values of $^{3}J_{CH}$ coupling constants depend on a Karplus-like relationship and the intrinsic linewidths of the proton signals;[214,237] a $^{3}J_{CH}$ coupling that is close to 0 Hz or a proton signal that possesses a linewidth broader than the magnitude of its associated $^{3}J_{CH}$ couplings are known to suffer from distortion of lineshape or complete annihilation,[238] leading to no correlation being observed.

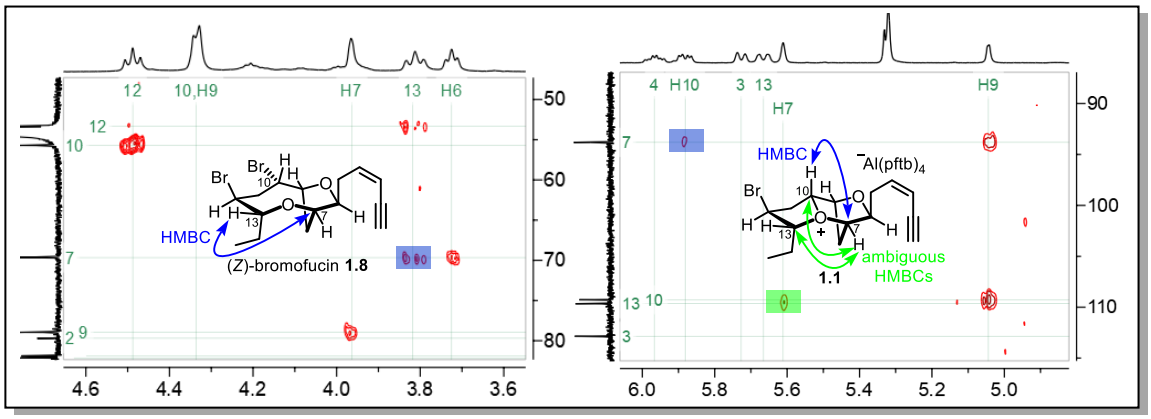


Figure 5.22. Excerpts of ^{1}H-^{13}C HMBC (500 MHz, 126 MHz, CD_2Cl_2) spectra of **1.8** (left) and **1.1** (right) at -78 °C.

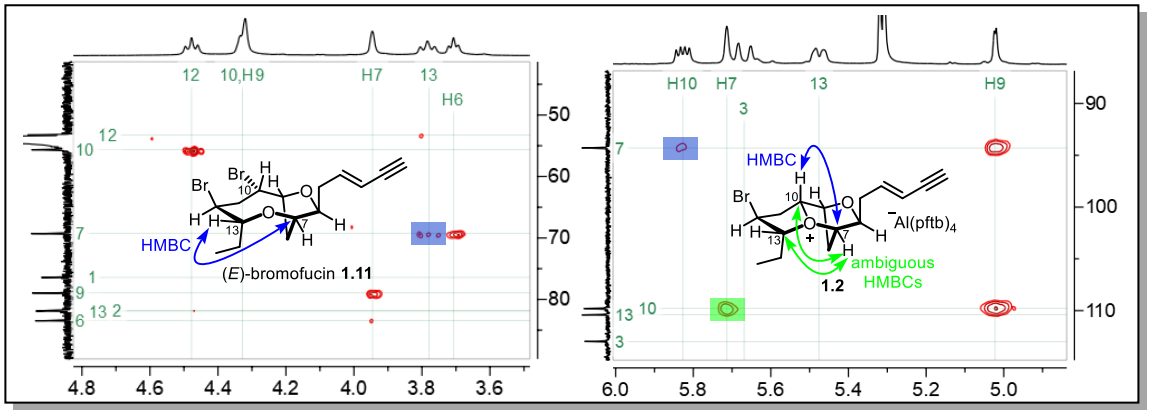


Figure 5.23. Excerpts of ^{1}H-^{13}C HMBC (500 MHz, 126 MHz, CD_2Cl_2) spectra of **1.11** (left) and **1.2** (right) at -78 °C.

The comparative ^{1}H-^{13}C HMBC correlations of **1.1**, **1.2** and **1.8**, **1.11** in **Figure 5.22-5.23** show the changes in ^{1}H-^{13}C HMBC correlations between H-(7, 10, 13) and C-(7, 10, 13) before and after oxonium ion formation. The ^{1}H-^{13}C HMBC correlations between H-13 and C-7 in the starting material **1.8** and **1.11** disappear in the ^{1}H-^{13}C HMBC spectra of **1.1** and **1.2** while new ^{1}H-^{13}C HMBC correlations between H-7 and C-10/C-13 (ambiguous overlap due to small difference in chemical shifts between C-10 and C-13) and that between H-10 and C-7 appear. These changes in ^{1}H-^{13}C HMBC correlations suggest the formation of transannular C–O^{+} bonds in the oxonium ions **1.1** and **1.2**, which allow establishment of $^{3}J_{CH}$ correlations between H-7 and C-10 and that between H-10 and C-7. Without the transannular C–O^{+} bonds, H-7/H-10 must interact

with C-10/C-7 respectively through $^{4}J_{CH}$ pathways that require a crucial W-geometry for orbital interactions, which is lacking in the oxonium ions **1.1** and **1.2**.

These changes in the ^{1}H-^{13}C HMBC correlations between **1.8**, **1.11** and **1.1**, **1.2** suggest a change in molecular connectivity upon oxonium ion formation. However, due to ambiguous correlations between H-7 and C-10/C-13, and the absence of correlations between H-13 and C-7/C-10, the changes in ^{1}H-^{13}C HMBC correlations alone are not conclusive enough to suggest the presence of a trivalent oxygen in oxonium ions **1.1** and **1.2**. However, if the results from ^{1}H and ^{13}C NMR chemical shift comparisons between the precursor **1.8** and **1.11** and the oxonium ions **1.1** and **1.2** are also considered, they provide very strong experimental evidence to support the existence of the oxonium ions **1.1** and **1.2**.

Similarly, the comparative ^{1}H-^{13}C HMBC correlations of oxonium ions ***ent*-1.3**, ***ent*-1.4** and *ent*-neoprelaurefucins ***ent*-5.1**, ***ent*-5.2** show the changes in ^{1}H-^{13}C HMBC correlations between H-(7, 10, 13) and C-(7, 10, 13) before and after oxonium ion formation (**Figure 5.24-5.25**). The ^{1}H-^{13}C HMBC correlations between H-13 and C-7, which are visible in the precursor ***ent*-5.1** and ***ent*-5.2**, remain visible in the ^{1}H-^{13}C HMBC spectra of ***ent*-1.3** and ***ent*-1.4**. In addition, new ^{1}H-^{13}C HMBC correlations between H-7 and C-10 and that between H-10 and C-7 appear.

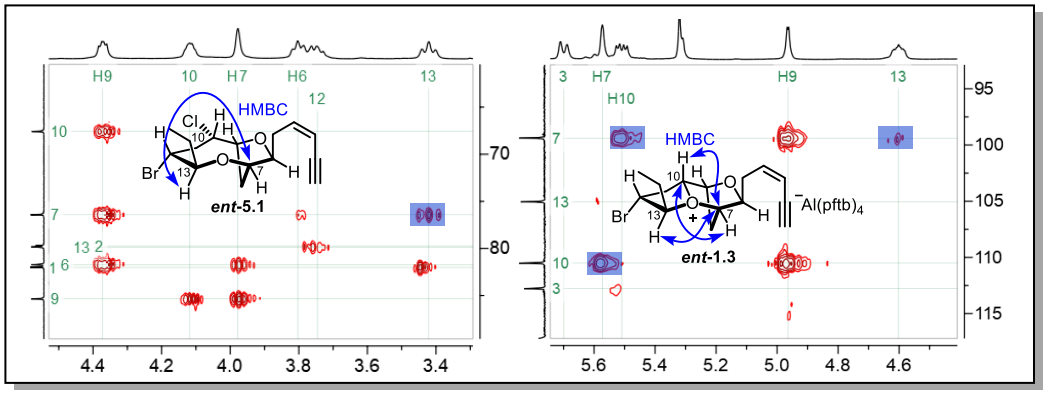


Figure 5.24. Excerpts of ^{1}H-^{13}C HMBC (500 MHz, 126 MHz, CD_2Cl_2) spectra of ***ent*-5.1** (left) and ***ent*-1.3** (right) at -78 °C.

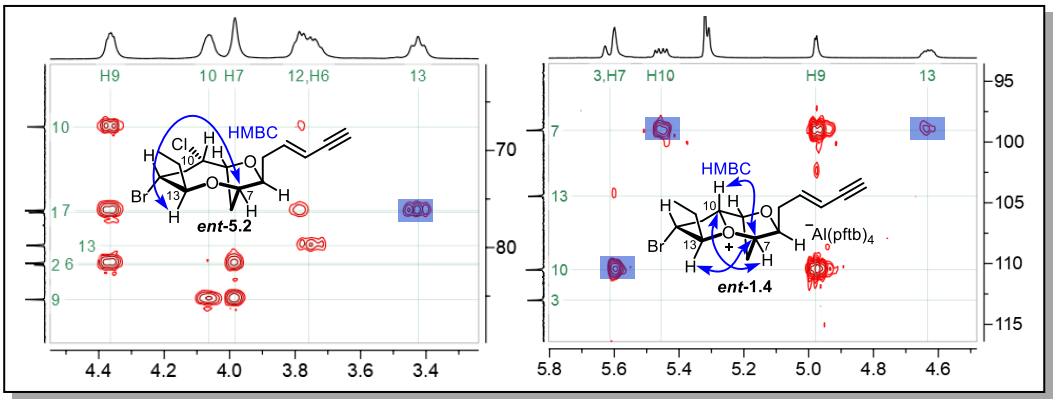


Figure 5.25. Excerpts of ^{1}H-^{13}C HMBC (500 MHz, 126 MHz, CD_2Cl_2) spectra of ***ent*-5.2** (left) and ***ent*-1.4** (right) at -78 °C.

Again, the ^{1}H-^{13}C HMBC correlations between H-7 and C-10 and that between H-10 and C-7 should be $^{3}J_{CH}$ correlations that arise from the establishment of transannular C–O^{+} bonds in the oxonium ions ***ent*-1.3** and ***ent*-1.4**.

The changes in the ^{1}H-^{13}C HMBC correlations between ***ent*-5.1**, ***ent*-5.2** and ***ent*-1.3**, ***ent*-1.4** suggest the presence of a trivalent oxygen atom in the oxonium ions ***ent*-1.3** and ***ent*-1.4** due to the presence of ^{1}H-^{13}C HMBC correlations between H-13 and C-7, H-10 and C-7 and that of H-7 and C-10. These ^{1}H-^{13}C HMBC correlations, considered altogether with the analysis of ^{1}H and ^{13}C chemical shift differences, provide very strong experimental evidence to support the existence of the oxonium ions ***ent*-1.3** and ***ent*-1.4**.

Besides using ^{1}H and ^{13}C chemical shift differences and comparative ^{1}H-^{13}C HMBC correlations to elucidate the identity and the molecular connectivity of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4**, the $^{3}J_{HH}$ couplings of the oxonium ions were also analysed to elucidate their preferred conformations in CD_2Cl_2 at -78°C.

Considering the expected conformations and magnitudes of $^{3}J_{HH}$ coupling constants between H-13, H-12 and H-11′ of the oxonium ions **1.1** and **1.2** (**Figure 5.26**), the experimental and DFT computed (performed by Dr Quynh Nguyen and Prof. Robert.

S. Paton) $^{3}J_{HH}$ coupling constants tabulated in **Table 5.3-5.4** suggest that both oxonium ions **1.1-1.2** should adopt conformations on the right hand side of **Figure 5.26** that have small *J*-coupling constants between H-13 and H-12, H-12 and H-11′. The experimental $^{3}J_{HH}$ constants were also converted into their corresponding dihedral angles by the Dìez-Altona-Donders modification of the Karplus equation using the MestReJ software (*see appendix 12.2*),[189] which were found to be in keeping with the expected conformations.

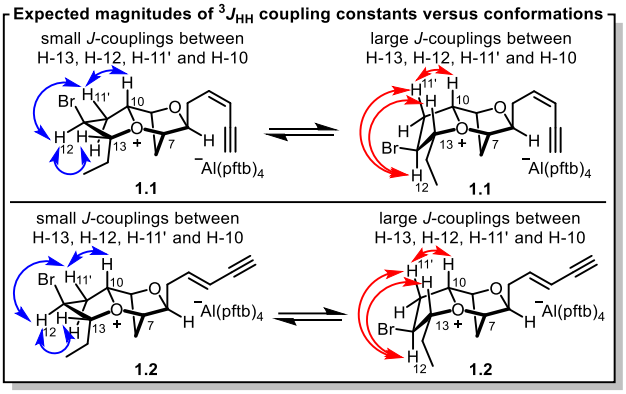


Figure 5.26. Expected conformations and magnitudes of $^{3}J_{HH}$ coupling constants between H-13, H-12 and H-11′ of the oxonium ions **1.1-1.2**.

	$^{3}J_{HH}$ **coupling constants/Hz and dihedral angles/° of 1.1**					
Splitting		**H-10**	**H-11**	**H-11'**	**H-12**	**H-13**
dd	**H-10**	-	**12.0**/13.5 (*)	**5.1**/5.2 (32.3)	-	-
ddd	**H-11**	**12.0**/13.5 (*)	-	-	**4.7**/5.3 (52.7)	-
dd	**H-11'**	**5.1**/5.2 (32.3)	-	-	1.4	-
d	**H-12**	-	**4.7**/5.3 (52.7)	1.4	-	0.5
dd	**H-13**	-	-	-	0.5	-

Table 5.3. Experimental (in bold) and DFT computed $^{3}J_{HH}$ coupling constants of selected protons of the oxonium ion **1.1**. The values in brackets correspond to the dihedral angles between the protons of interest. Highlighted entries correspond to diagnostic $^{3}J_{HH}$ coupling constants. * Denotes dihedral angles that are approximately anti-periplanar as the experimental $^{3}J_{HH}$ coupling constants were too large for the Dìez-Altona-Donders equation using the chemical groups provided in the MestReJ software (*see appendix 12.2*).

	$^3J_{HH}$ coupling constants/Hz and dihedral angles/° of 1.2					
Splitting		**H-10**	**H-11**	**H-11'**	**H-12**	**H-13**
dd	**H-10**	-	**11.3**/13.5 (*)	**5.7**/5.2 (36.3)	-	-
ddd	**H-11**	**11.3**/13.5 (*)	-	-	**5.0**/5.2 (50.9)	-
ddd	**H-11'**	**5.7**/5.2 (36.3)	-	-	**2.3**/1.4 (69.1)	-
ddd	**H-12**	-	**5.0**/5.2 (50.9)	**2.3**/1.4 (69.1)	-	**3.5**/0.5 (57.6)
dt	**H-13**	-	-	-	**3.5**/0.5 (57.6)	-

Table 5.4. Experimental (in bold) and DFT computed $^3J_{HH}$ coupling constants of selected protons of the oxonium ion **1.2**. The values in brackets correspond to the dihedral angles between the protons of interest. Highlighted entries correspond to diagnostic $^3J_{HH}$ coupling constants. * Denotes dihedral angles that are approximately anti-periplanar as the experimental $^3J_{HH}$ coupling constants were too large for the Dìez-Altona-Donders equation using the chemical groups provided in the MestReJ software (*see appendix 12.2*).

As for the oxonium ions ***ent*-1.3** and ***ent*-1.4**, the expected conformations and magnitudes of $^3J_{HH}$ coupling constants between H-13 and H-12, H-12 and H-11 are described below (**Figure 5.27**).

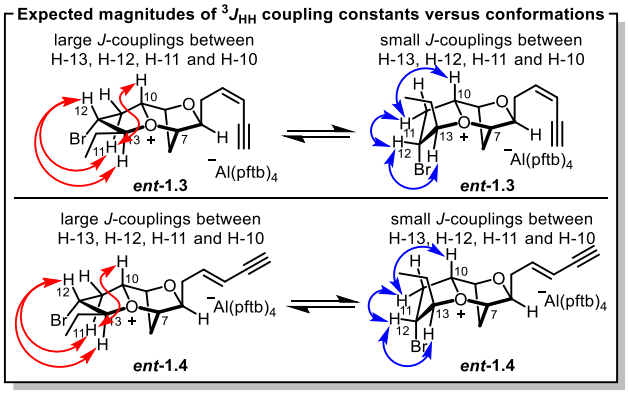


Figure 5.27. Expected conformations and magnitudes of $^3J_{HH}$ coupling constants between H-13, H-12 and H-11 of the oxonium ions ***ent*-1.3** and ***ent*-1.4**.

The experimental and DFT computed (performed by Dr Quynh Nguyen and Prof. Robert. S. Paton) $^3J_{HH}$ coupling constants tabulated in **Table 5.5-5.6** suggest that both

oxonium ions ***ent*-1.3** and ***ent*-1.4** should adopt conformations on the left of **Figure 5.27** that have large *J*-coupling constants between H-13 and H-12, H-12 and H-11. The experimental $^{3}J_{HH}$ constants were also converted into their corresponding dihedral angles by the Dìez-Altona-Donders modification of the Karplus equation using the MestReJ software (*see appendix 12.2*),[189] which were found to be in keeping with the expected conformations.

	$^{3}J_{HH}$ coupling constants/Hz and dihedral angles/° of *ent*-1.3					
Splitting		**H-10**	**H-11**	**H-11'**	**H-12**	**H-13**
dd	**H-10**	-	**12.2**/13.3 (*)	**5.6**/6.3 (29.0)	-	-
ddd	**H-11**	**12.2**/13.3 (*)	-	-	**11.2**/12.7 (162.9)	-
dd	**H-11'**	**5.6**/6.3 (29.0)	-	-	**6.4**/7.2 (40.4)	-
d	**H-12**	-	**11.2**/12.7 (162.9)	**6.4**/7.2 (40.4)	-	**11.2**/11.5 (*)
dd	**H-13**	-	-	-	**11.2**/11.5 (*)	-

Table 5.5. Experimental (in bold) and DFT computed $^{3}J_{HH}$ coupling constants of selected protons of the oxonium ion ***ent*-1.3**. The values in brackets correspond to the dihedral angles between the protons of interest. Highlighted entries correspond to diagnostic $^{3}J_{HH}$ coupling constants. * Denotes dihedral angles that are approximately anti-periplanar as the experimental $^{3}J_{HH}$ coupling constants were too large for the Dìez-Altona-Donders equation using the chemical groups provided in the MestReJ software (*see appendix 12.2*).

The conformations of the four oxonium ions as suggested by this analysis of *J*-coupling constants are also in keeping with their most populated DFT calculated structures (see below).

	$^3J_{HH}$ coupling constants/Hz and dihedral angles/° of *ent*-1.4					
Splitting		**H-10**	**H-11**	**H-11'**	**H-12**	**H-13**
dd	**H-10**	-	**12.2**/13.3 (*)	**5.6**/6.3 (29.0)	-	-
ddd	**H-11**	**12.2**/13.3 (*)	-	-	**11.2**/12.7 (162.9)	-
dd	**H-11'**	**5.6**/6.3 (29.0)	-	-	**6.4**/7.2 (40.4)	-
d	**H-12**	-	**11.2**/12.7 (162.9)	**6.4**/7.2 (40.4)	-	**11.2**/11.5 (*)
dd	**H-13**	-	-	-	**11.2**/11.5 (*)	-

Table 5.6. Experimental (in bold) and DFT computed $^3J_{HH}$ coupling constants of selected protons of the oxonium ion ***ent*-1.4**. The values in brackets correspond to the dihedral angles between the protons of interest. Highlighted entries correspond to diagnostic $^3J_{HH}$ coupling constants. * Denotes dihedral angles that are approximately anti-periplanar as the experimental $^3J_{HH}$ coupling constants were too large for the Dìez-Altona-Donders equation using the chemical groups provided in the MestReJ software (*see appendix 12.2*).

DFT calculations of the ^{1}H and ^{13}C NMR chemical shifts of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** were performed (by Dr Quynh Nguyen and Prof. Robert. S. Paton) to add another layer of evidence to support the proposed identities of the oxonium ions. The comparison between the chemical shifts at atoms 7 (orange), 10 (navy) and 13 (purple) are shown below to illustrate the DFT calculated chemical shifts of the oxonium ion carbons and the attached protons are in keeping with experimental values (**Figure 5.28**). However, large mismatch between the experimental and DFT computed ^{13}C chemical shifts at the enyne carbon C-4 and the Br bonded carbon C-12 were observed (*see appendix 12.8*), which was as expected as their computations are known to be computationally challenging.[239,240]

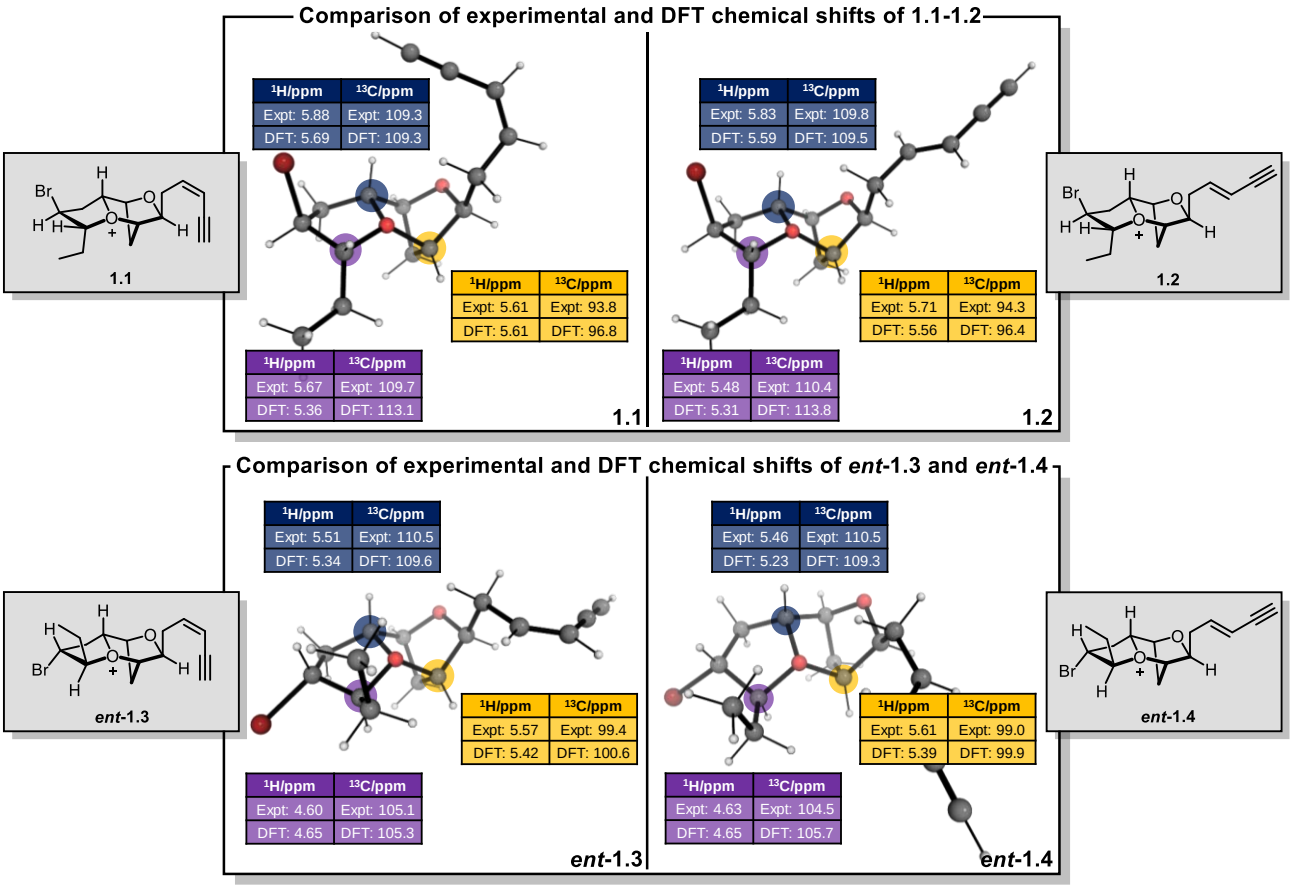


Figure 5.28. Comparison of experimental and computed ^{1}H and ^{13}C NMR chemical shifts of the oxonium ions **1.1-1.2** and ***ent*-1.3**, ***ent*-1.4**. The DFT calculated structures of the oxonium ions shown are the most populated conformers. The DFT calculated structures were optimised in gas phase employing the B3LYP functional and 6-31+G(d,p) basis set, and the calculations of the Boltzmann averaged NMR chemical shifts were performed with the mPW1PW91 functional and 6-311+G(2d,p) basis set with SMD solvation for CH_2Cl_2 on Gaussian 09'.

Finally, mass spectrometric analysis of the oxonium ion precursors bromofucins **1.8** and **1.11** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2** gave *m/z* signals that corresponded to the expected *m/z* signals of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** respectively, which suggested that the oxonium ion precursors ionised *via* transannular halide displacement during the analysis. However, the *m/z* signals observed may be due to rearranged species such as **5.55** and **5.56** that have the same *m/z* signal as the oxonium ions (**Figure 5.29**). This ionisation behaviour of the oxonium

ion precursors further support the ability of them to undergo transannular halide displacement for the formation of oxonium ion species.

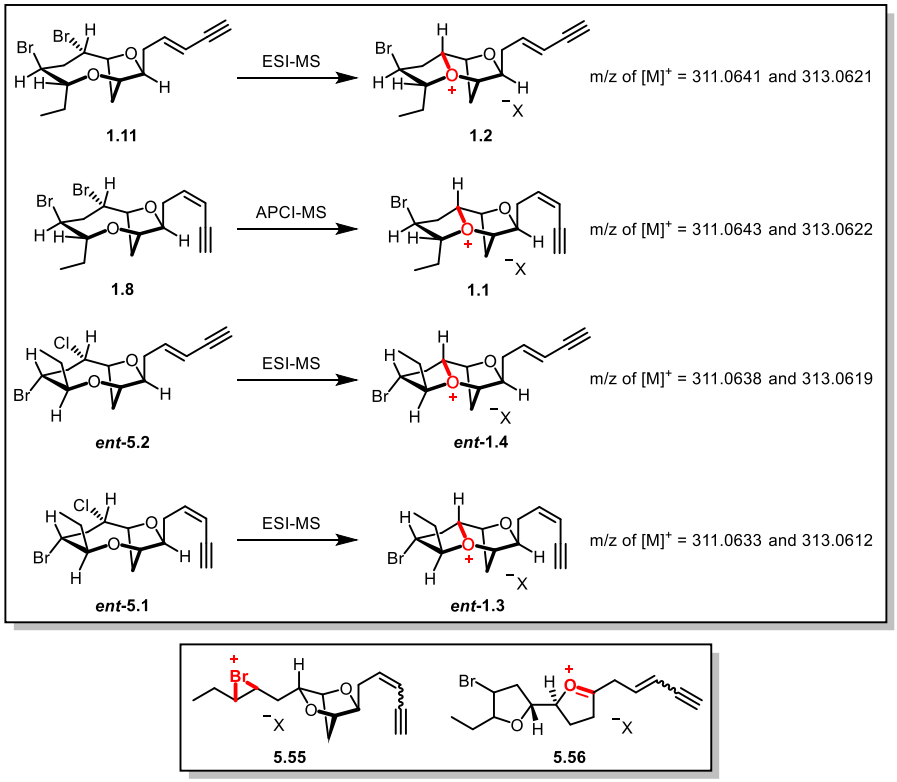


Figure 5.29. The *m/z* signals of the oxonium ions. Note: The identity of the anion X^- is unknown.

5.3 Conclusion

The development of a unified synthesis of all the oxonium ion precursors, the bromofucins **1.8** and **1.11** and *ent*-neoprelaurefucins ***ent*-5.1** and ***ent*-5.2**, has been achieved in 17 and 19 steps respectively. Suitable reaction conditions have also been found for the generation of all the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4**, and they have been characterised by comparative ^{1}H and ^{13}C NMR chemical shifts studies, comparative ^{1}H-^{13}C HMBC correlations, *J*-coupling analysis, DFT computation and mass spectrometric analysis. Strong evidence has been obtained to support the proposed identities of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4**.

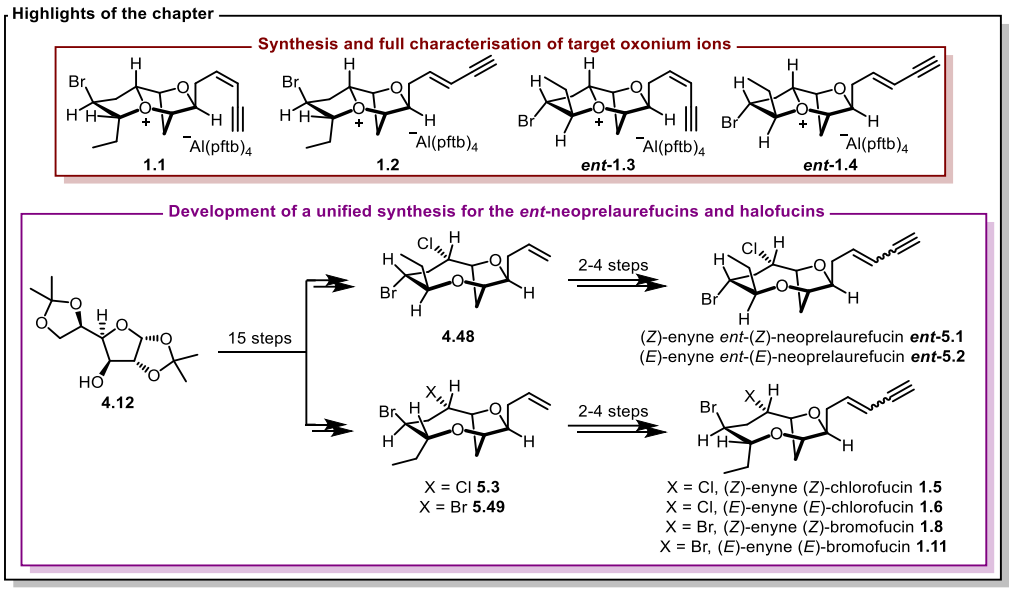


Figure 5.30. Highlights of Chapter 5.

6 Generation of natural products from oxonium ions

This section will focus on the direct derivatisation of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** into various natural products by nucleophilic opening. These processes are our main focus as they are directly related to *Laurencia* natural product biosynthesis (**Chapter 3**).[1,2,4,5,9,15,21]

6.1 A brief introduction to the isolation, structure determination and completed total syntheses of our target *Laurencia* natural products

The direct derivatisaion of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** with various nucleophiles is proposed to generate the 13 natural products as shown below categorised according to their structures (**Figure 6.1**).

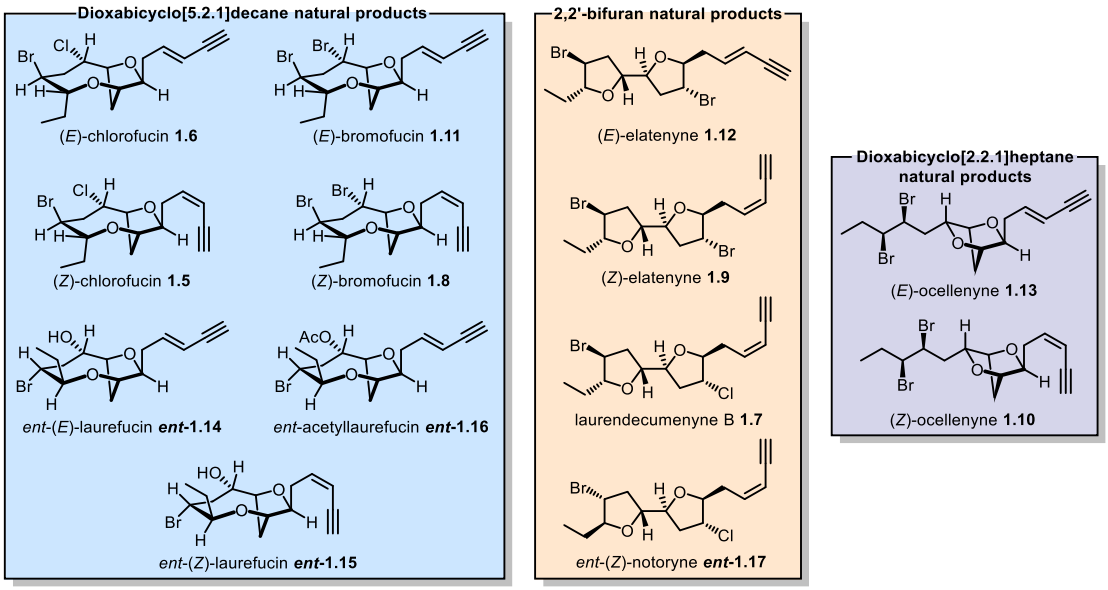


Figure 6.1. Expected natural products from direct derivatisation of oxonium ions.

6.1.1 *Isolation and structure determination of the target natural products*

For dioxabicyclo[5.2.1]decane natural products, (*E*)-chlorofucin **1.6** was first isolated by Fenical and co-workers in 1980, and the structure of the natural product was

established by X-ray crystallography.[11] The same compound was isolated again by Bowden and co-workers in 1993 and they provided full NMR spectroscopic characterisation of the natural product.[17] In 1996, (*E*)-chlorofucin was once again isolated by Suzuki and co-workers.[18] Its geometrical isomer, (*Z*)-chlorofucin **1.5**, was isolated by Suzuki in 2001 and the structural assignment was based on spectroscopic analysis.[19]

The natural product (*E*)-laurefucin **1.14**, which is the natural enantiomer of our target *ent*-(*E*)-laurefucin ***ent*-1.14**, was first isolated by Irie and co-workers in 1972.[20] The compound was initially misassigned as a fused bicyclic compound **6.1** but was reassigned to the bridged bicyclic structure **1.14** by Irie and co-workers in 1973 using X-ray crystallography.[21] The compound was also isolated by Faulkner and co-workers in 1977, Wright and co-workers in 1994 and Davies–Coleman and co-workers in 2005;[22–24] Faulkner also reported the isolation of the geometrical isomer (*Z*)-laurefucin **1.15**. The natural product acetyllaurefucin **1.16** is closely related to the laurefucins **1.14** and **1.15**, and was isolated together with (*E*)-laurefucin **1.14** by Irie and co-workers in 1972,[20] and later by Faulkner and co-workers in 1977.[22] The structural assignment of acetyllaurefucin was based on spectroscopic analysis.

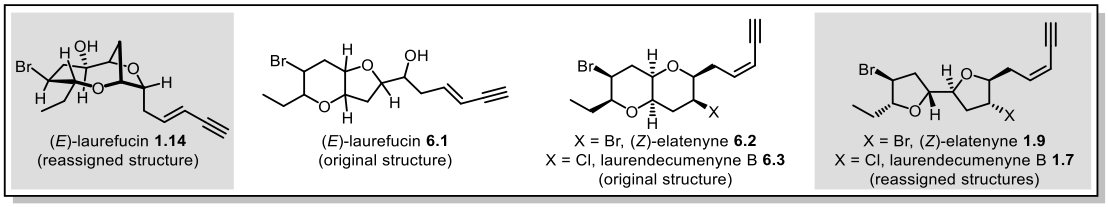


Figure 6.2. Structures of misassigned compounds.

For 2,2'-bifuran natural products, (*Z*)-elatenyne was first isolated by Hall and Reiss in 1986 but was misassigned as a fused bicyclic pyrano[3,2-*b*]pyran **6.2**.[12] The same natural product was isolated by Wang and co-workers in 2007.[14] Burton, Kim and co-workers reassigned the structure of (*Z*)-elatenyne to the 2,2'-bifuran compound **1.9**

by total synthesis and computation.[9,241–243] The geometrical isomer (*E*)-elatenyne was isolated by Erickson and co-workers in 1989, and the structure was confirmed by Burton, Kim and co-workers in 2012.[9] The reassigned structure of (*Z*)-elateyne by Burton, Kim and co-workers was further corroborated by the work of Fujita and co-workers using the crystalline sponge method.[244]

The natural product laurendecumenyne B **1.7** was isolated by Wang and co-workers in 2007.[14] However, the structure was initially misassigned as the fused bicyclic pyrano[3,2-*b*]pyran **6.3**, which was later reassigned and confirmed to be the 2,2'-bifuran structure **1.7** based on the reassignment of (*Z*)-elatenyne by Burton, Kim and co-workers.

(*Z*)-Notoryne **1.17**, the last 2,2'-bifuran natural product in the series, was first isolated by Suzuki and co-workers in 1991.[15] Its structure was determined from extensive degradation studies of the natural product and the authors also provided evidence that notoryne **1.17** is indeed a natural product but not an isolation artefact from the rearrangement of the dioxabicyclo[5.2.1]decane natural products during the isolation process (**Figure 6.3**). Its geometrical isomer (*E*)-notoryne **1.18** has also been proposed as a natural product by Murai.[1]

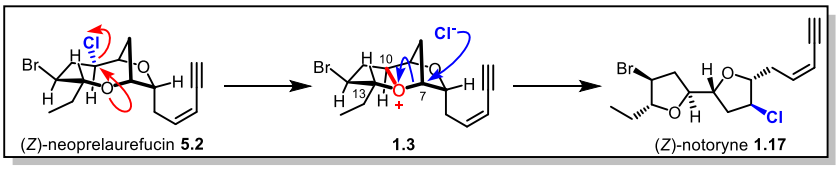


Figure 6.3. Isomerisation of **5.2** to **1.17**.

Lastly, the dioxabicyclic[2.2.1]heptane natural products ocellenynes **1.10**, **1.13** or **1.45, 1.46** were isolated by Scheuer and co-workers in 1981.[16] Their full structures are yet to be determined unambiguously. Kim and co-workers have confirmed the *anti* relationship of the substituents at C-7 and C-10 of the ocellenynes from studies of

model compounds and DFT computations.[155] However, the configurations of the dibromides of the natural product remains to be determined (**Figure 6.4**).

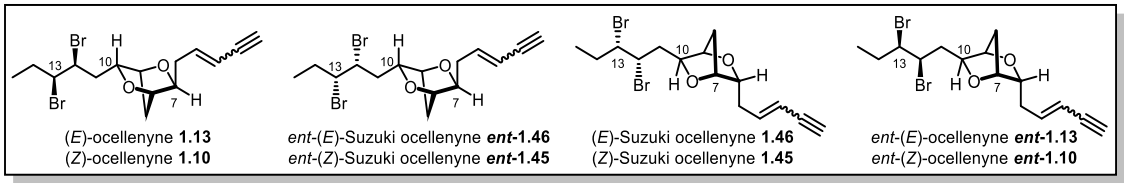


Figure 6.4. Possible structures of the ocellenynes.

6.1.2 *Completed total syntheses of the target natural products in literature*

This section provides a brief summary of the previous total syntheses of the natural products that are pertinent to this project. The first and asymmetric total synthesis of chlorofucins **1.5-1.6** and bromofucins **1.8** and **1.11** was achieved in 14 steps from known allylic alcohol **6.4** by Kim and co-workers in 2018 employing a haloetherification reaction on the substrate **6.5** as the key step to forge the dioxabicyclo[5.2.1]decane scaffold of the natural products (**Figure 6.5**).[4]

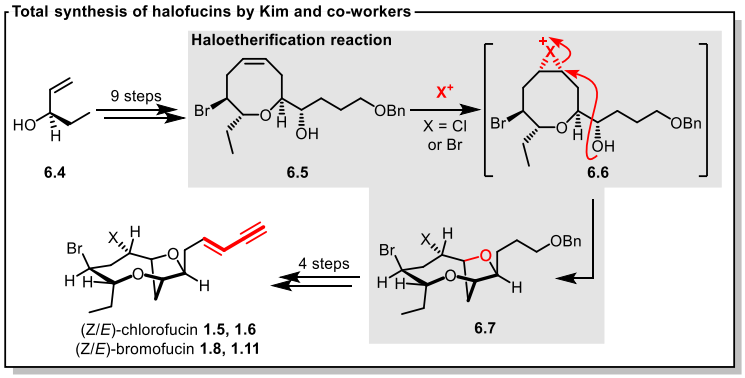


Figure 6.5. Total synthesis of halofucins **1.5-1.6** and **1.8**, **1.11**.

The asymmetric total synthesis of the natural product (*E*)-laurefucin **1.14** was first accomplished by Kim and co-workers in 18 steps from the known oxazolidinone **6.8** in 2008, employing an organoselenium-mediated biomimetic-type intramolecular hydroetherification on the substrate **6.9** as a key step to forge the dioxabicyclo[5.2.1]decane scaffold of the natural product (**Figure 6.6**).[5]

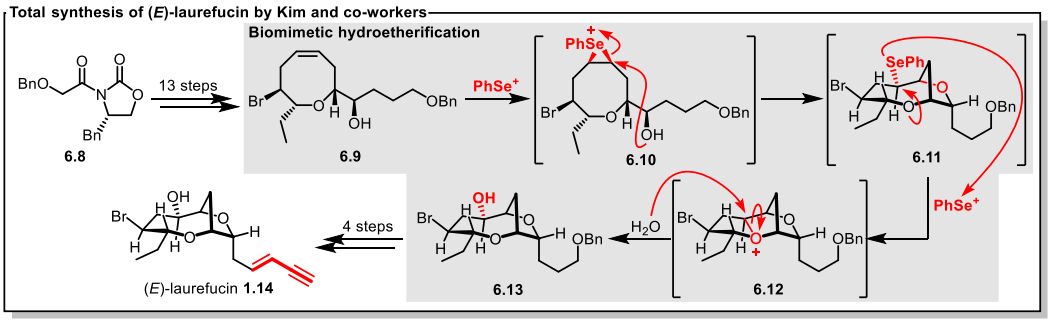


Figure 6.6. Total synthesis of (*E*)-laurefucin **1.14**.

A formal total synthesis of (*E*)-laurefucin **1.14** was accomplished in 13 steps from glyoxal by Snyder and co-workers in 2012. Glyoxal was converted into the known *meso*-diol **6.14** and then a ring-expanding bromoetherification strategy was applied on the substrate **6.15** to forge the dioxabicyclo[5.2.1]decane scaffold of the natural product (**Figure 6.7**).[192]

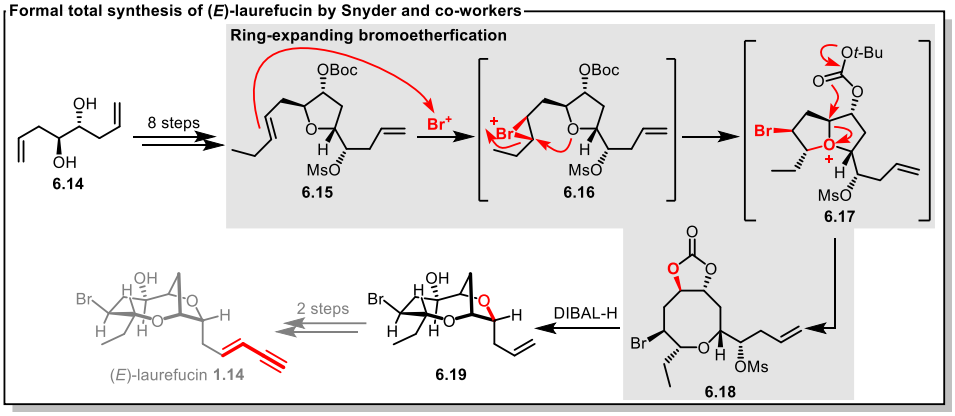


Figure 6.7. Formal total synthesis of (*E*)-laurefucin **1.14**.

The total synthesis of the original structure of (*Z*)-elatenyne **6.2** was accomplished by Burton and co-workers in 17 steps from the bislactone **6.20** in 2006.[241] The synthesis employed a bidirectional strategy which its development was fully reported by Burton and co-workers in 2009.[243] The core pyrano[3.2-*b*]pyran structure **6.24** of the natural product was forged from a Lewis acid mediated rearrangement of the 2,2'-bifuran **6.22** (**Figure 6.8**).

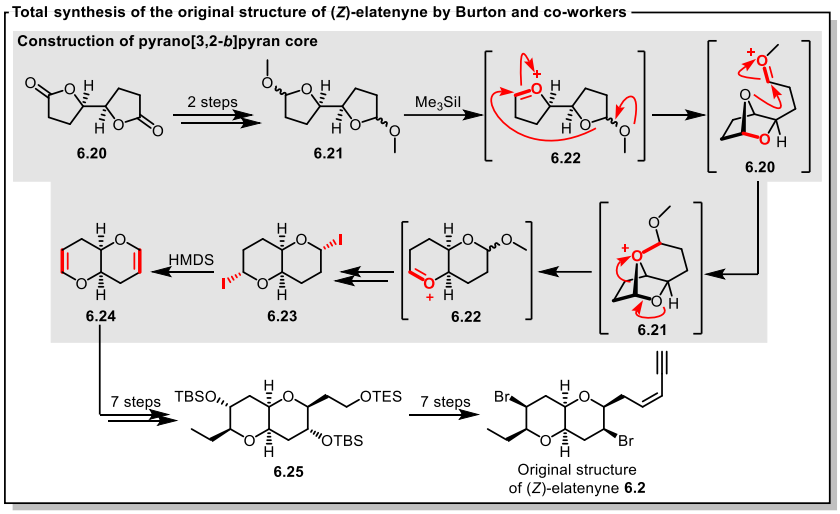


Figure 6.8. Total synthesis of the original structure of (*Z*)-elatenyne **6.2**.

As for the asymmetric total synthesis of both enantiomers of the reassigned structure of (*Z*)-elatenyne, it was reported by Burton (natural enantiomer **1.9** synthesised in 18 steps from the known allylic alcohol **6.26**), Kim (unnatural enantiomer ***ent*-1.9** synthesised in 14 steps from the known allylic alcohol **6.28**) and co-workers in 2012 along with the asymmetric total synthesis of both enantiomers of its geometrical isomer (*E*)-elatenyne (natural enantiomer synthesised in 18 steps by Burton and co-workers from the known allylic alcohol **6.26**, and the unnatural enantiomer synthesised in 14 steps by Kim and co-workers from the known allylic alcohol **6.28**). The total synthesis of the enantiomer of the reassigned structure of laurendecumenyne B ***ent*-1.7** and its geometrical isomer ***ent*-1.19** were also accomplished in 14 steps by Kim and co-workers from **6.28**.[9] Both modular (by Burton and co-workers) and biomimetic (by Kim and co-workers) approaches were demonstrated for the total syntheses of these natural products in their report (**Figure 6.9**).

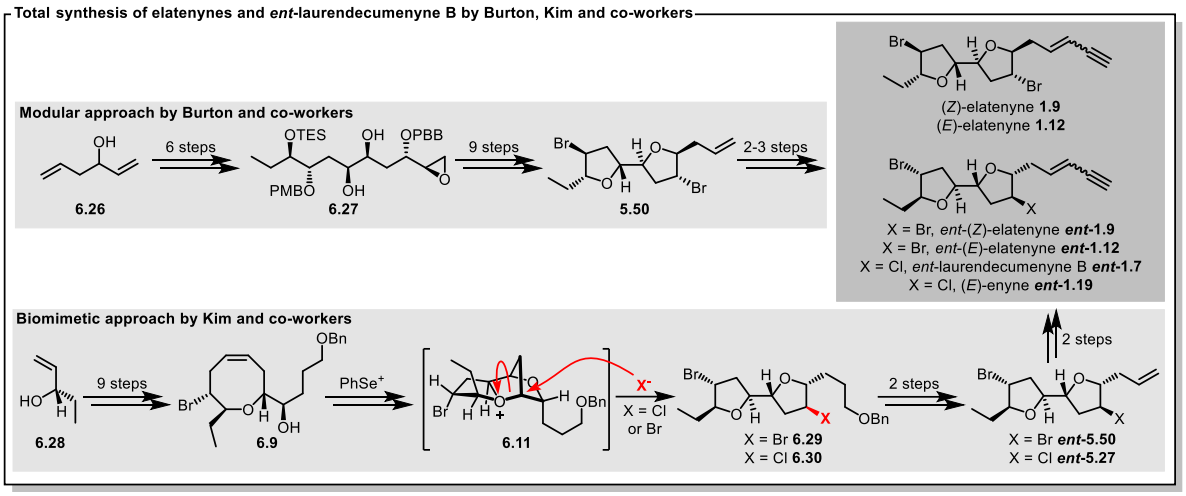


Figure 6.9. Total synthesis of the elatenynes **1.9, 1.12** and ***ent*-1.9, *ent*-1.12** and *ent*-laurendecumenyne B ***ent*-1.7**.

The first and asymmetric total synthesis of (*Z*)-notoryne **1.17** was reported by Ramana and co-workers in 2018.[169] The total synthesis was completed in 14 steps using a chiral pool approach from commercially available diacetone-D-glucose **4.12**.

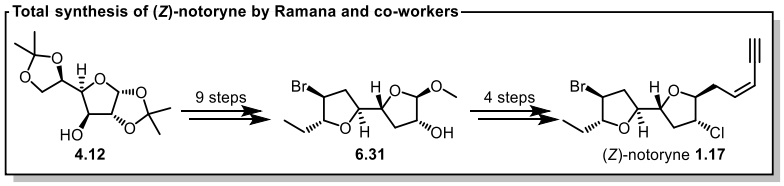


Figure 6.10. Total synthesis of (*Z*)-notoryne **1.17**.

No total synthesis of acetyllaurefucin **1.16**, (*Z*)-laurefucin **1.15** and ocelleynes **1.10**, **1.13** or **1.45**, **1.46** have been reported.

In the following section, the total syntheses of the target natural products except the ocellenynes **1.10**, **1.13** or **1.45**, **1.46** are reported using a single synthetic route. Our total syntheses of the target natural products demonstrate a collective synthesis of *Laurencia* natural products,[245] directly generating 10 out of 13 target natural products by nucleophilic opening of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4**. Further natural products not listed in **Figure 6.1** were also generated by this protocol (see **Chapter 7**), increasing the natural products count to 12 out of 15. Although the total

syntheses were accomplished in 19-21 steps, the step-count to natural products ratio is 1.7.

6.2 Direct derivatisation of oxonium ions into natural products

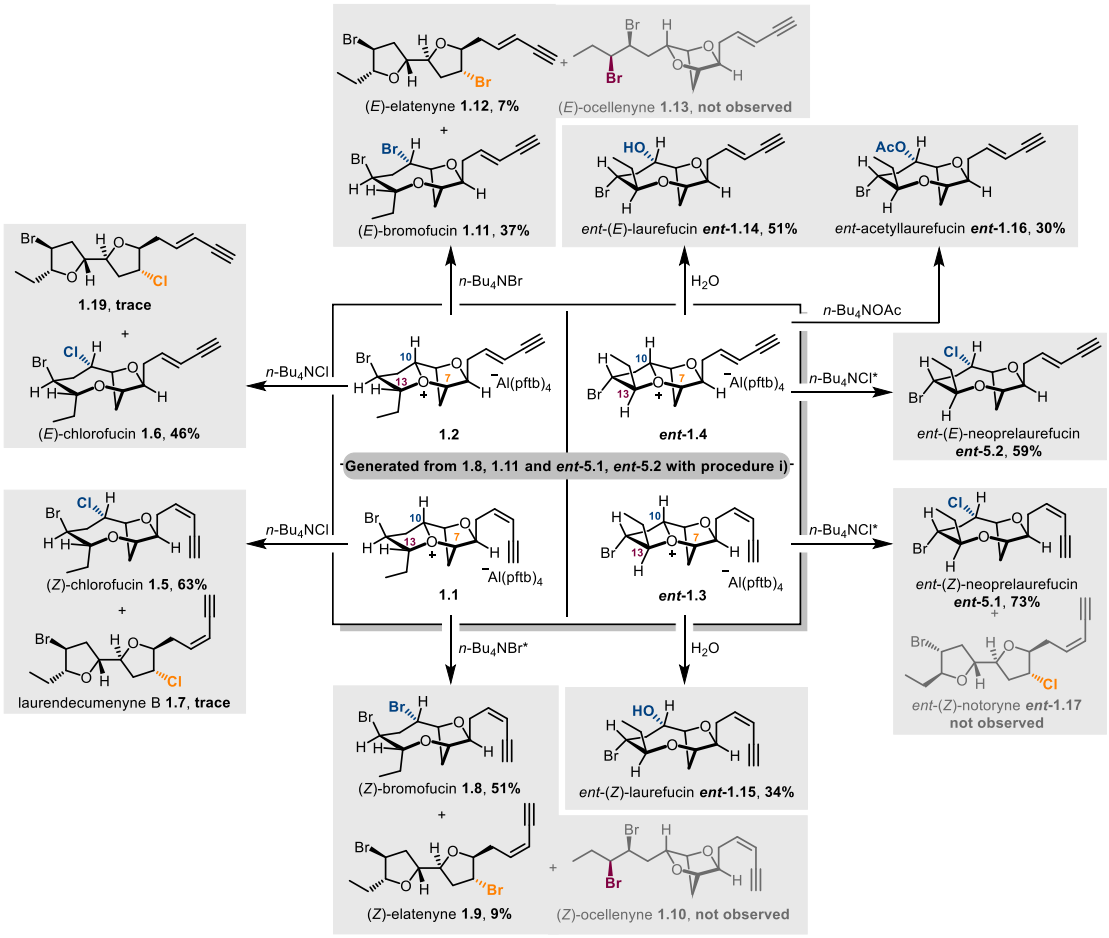


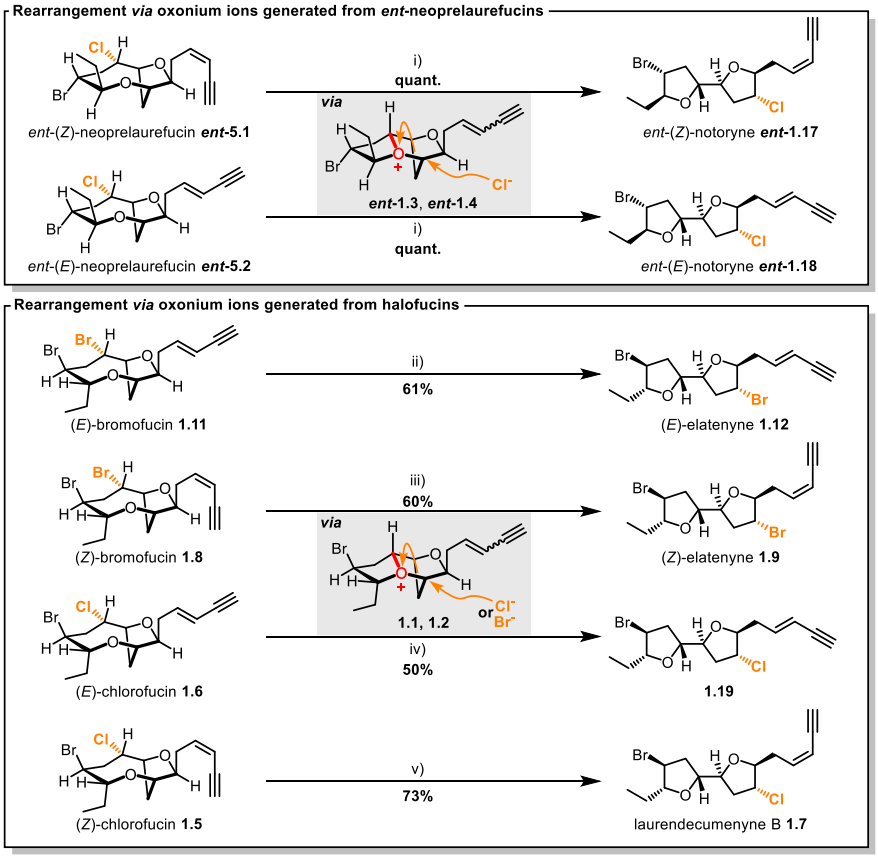
Figure 6.11. Direct derivatisation of oxonium ions **1.1**, **1.2** and ***ent*-1.3, *ent*-1.4** into various natural products by nucleophilic opening.

Reagent and conditions: **i)** (for **1.1**, **1.2**), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CD_2Cl_2, -40 °C, 1.5 hrs, then filter into flame-dried Young's NMR tube at -78 °C and perform NMR acquisition at -78 °C. **ii)** (for ***ent*-1.3**, ***ent*-1.4**), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CD_2Cl_2, -78 °C, 1.5 hrs, then filter into flame-dried Young's NMR tube at -78 °C and perform NMR acquisition at -78 °C. Following procedures **i)** or **ii)**, the NMR samples were warmed to ca. -20 °C - 0 °C, ejected from the spectrometer and incubated at -78 °C in a dry ice-acetone bath, and an excess (5.0-10.0 eq.) of nucleophile as described above was added. The sample was quickly removed from the bath and shaken vigorously, and then returned to the bath and incubated for 15 minutes before gradually warming to room temperature. Entries with an asterisk * did not have the oxonium ions characterised by NMR spectroscopy, and thus the reactions were carried out in CH_2Cl_2, with the reaction progress monitored by TLC analysis and without filtration of $AgCl_{(s)}$.

The nucleophilic opening of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** directly provided 10 out of 13 expected natural products according to the their proposed biosynthesis, and thus provided strong support for the biosynthetic relevance of these oxonium ions in *Laurencia* natural product biosynthesis (**Figure 6.11**).[1,2,4,5,9,15,21] Treatment of oxonium ion **1.1** with *n*-Bu_4NCl provided the natural products (*Z*)-chlorofucin **1.5** in 63% yield and trace laurendecumenyne B **1.7**, and treatment with *n*-Bu_4NBr provided (*Z*)-bromofucin **1.8** in 51% yield and (*Z*)-elatenyne **1.9** in 9% yield. Treatment of oxonium ion **1.2** with *n*-Bu_4NCl provided the natural products (*E*)-chlorofucin **1.6** in 46% yield and trace **1.19**, and treatment with *n*-Bu_4NBr provided (*E*)-bromofucin **1.11** in 37% yield and (*E*)-elatenyne **1.12** in 7% yield. Treatment of oxonium ion ***ent*-1.3** with *n*-Bu_4NCl provided *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1**, which is a putative *Laurencia* metabolite,[4,15] in 73% yield, and treatment with H_2O provided *ent*-(*Z*)-laurefucin ***ent*-1.15** in 34% yield. Treatment of oxonium ion ***ent*-1.4** with *n*-Bu_4NCl provided *ent*-(*E*)-neoprelaurefucin ***ent*-5.2**, which is a putative *Laurencia* metabolite,[4,15] in 59% yield, treatment with H_2O provided *ent*-(*E*)-laurefucin ***ent*-1.14** in 51% yield, and treatment with *n*-Bu_4NOAc provided *ent*-acetyllaurefucin ***ent*-1.16** in 30% yield. The spectroscopic data of all the natural products generated by this method are in keeping with literature data (*see appendix 12.4*).

The reaction conditions of the nucleophilic opening were limited to -78 °C due to the thermal instability of the oxonium ions. The reactivity studies were mostly performed with recycled NMR samples of the oxonium ions, which had to be warmed to ca. -20 °C to 0 °C in the NMR spectrometer for smooth sample ejection. This increase in sample temperature was found to be necessary, as sample ejection at lower temperatures frequently resulted in the sample being frozen in the middle of the bore tube of the NMR spectrometer, and sample retrieval was rendered difficult and complete decomposition of the oxonium ions occured. Due to the operational limitations in

recycling oxonium ion NMR samples, a reduction in reaction efficiency of the nucleophilic opening experiments using these samples was expected. The samples that were ejected successfully were incubated at -78 °C immediately to prevent further decomposition of the oxonium ions, and the nucleophile of choice was then added to the sample at -78 °C for the nucleophilic opening experiments. Alternatively, the oxonium ions could be generated and opened with various nucleophiles without isolation and characterisation by NMR spectroscopy, which were found to give slightly improved yields in some cases. The yield and ratio of isomers generated were determined from their crude ^{1}H NMR spectra.

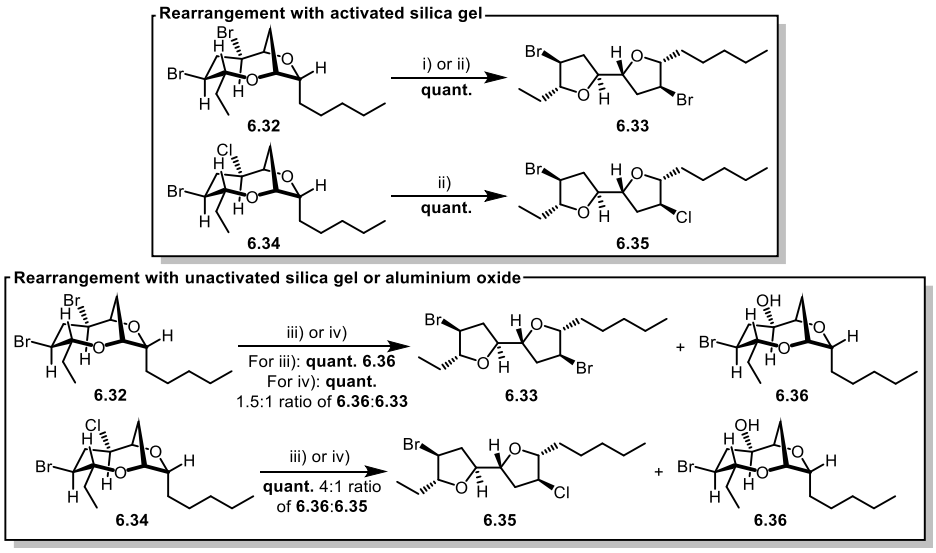


Scheme 6.1. Activated silica-gel mediated rearrangements of dioxabicyclic[5.2.1] type natural products to 2,2'-bifuranyl type natural products.

Reagents and conditions: Activated silica gel (heated to 140 °C under high vacuum for 3 hours) was used for every experiment but was of different batches. The differences in conditions were in reaction times and solvents. **i)** Dry hexanes or Pet.Ether 40-60, 80 °C, overnight. **ii)** Dry hexanes or Pet.Ether 40-60, r.t., 2 days. **iii)** Dry hexanes or Pet.Ether 40-60, r.t., 2 days, then 80 °C, overnight. **iv)** Dry hexanes or Pet.Ether 40-60, 80 °C, 2 days. **v)** Dry $CHCl_3$, 80 °C, 2 days.

For the 3 natural products *ent*-(*Z*)-notoryne ***ent*-1.17**, (*E*)-ocelleyne **1.13** and (*Z*)-ocellenyne **1.10** not generated directly from the opening of oxonium ions, *ent*-(*Z*)-notoryne ***ent*-1.17** was found to be generated from *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1** irreversibly by a rearrangement reaction mediated by activated silica gel as reported by Irie and Suzuki.[15,21] This rearrangement reaction was found to be applicable for (*E*)-bromofucin **1.11**, (*Z*)-bromofucin **1.8**, (*E*)-chlorofucin **1.6**, (*Z*)-chlorofucin **1.5** and *ent*-(*E*)-neoprelaurefucin ***ent*-5.2**, which allowed efficient synthesis of the natural products (*E*)-elatenyne **1.12**, (*Z*)-elatenyne **1.9**, **1.19**, laurendecumenyne B **1.7** and *ent*-(*E*)-notoryne ***ent*-1.18** (**Scheme 6.1**). Hexanes or Pet.Ether 40-60 were chosen as the solvent for these rearrangements because they were first identified as unexpected transformations during chromatographic purification of the compound **6.32** as reported by Irie and co-workers.[21] Activated silica gel was found by Suzuki and co-workers to be essential for the selective transposition of the C-10 substituent of the dioxabicyclic[5.2.1] ethers to the C-7 position of the 2,2'-bifurans in these rearrangements, as the use of unactivated silica gel or aluminium oxide for the rearrangement of the model substrate **6.32** and **6.34** was reported by the same authors to provide the hydrolysis product **6.36** as the major product instead (**Scheme 6.2**).[15]

Futhermore, it was possible to directly monitor the rearrangement of *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1** into *ent*-(*Z*)-notoryne ***ent*-1.17** without the participation of activated silica gel in $CDCl_3$ (**Figure 6.12**). This purely thermal driven rearrangement was complete after 12 days at 80 °C.



Scheme 6.2. Studies of the rearrangements of **6.32** and **6.34** by Irie and Suzuki.[15,21]
Reagents and conditions: **i)** Column chromatography over silicic acid. **ii)** Activated silica gel, hexanes, r.t., 24 hrs. **iii)** Aluminium oxide, hexanes, r.t., 20 hrs. **iv)** Silica gel, hexanes, r.t., 24 hrs.

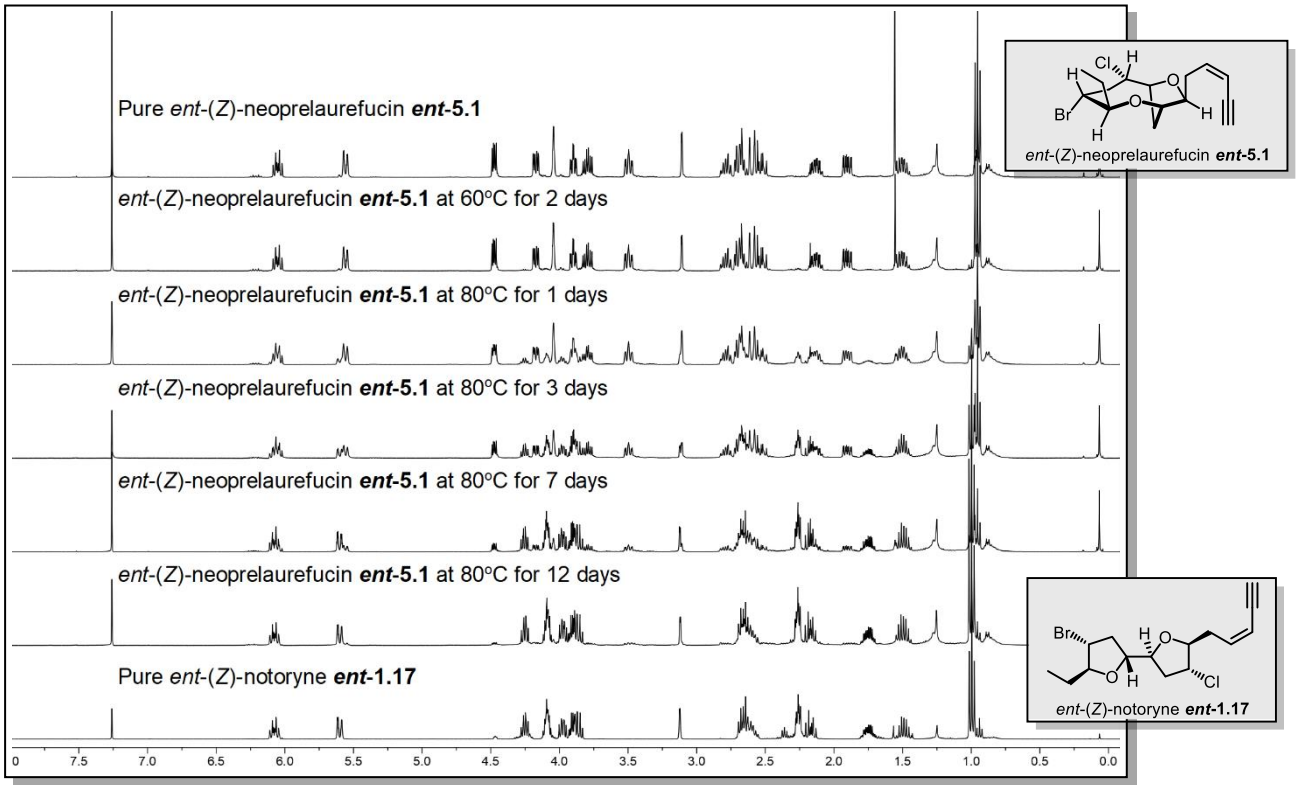


Figure 6.12. Thermal conversion of *ent*-(*Z*)-neoprelaurefucin ***ent*-5.1** to *ent*-(*Z*)-notoryne ***ent*-1.17** in $CDCl_3$ over 12 days.

However, (*E*)-ocelleyne **1.13** and (*Z*)-ocellenyne **1.10** were not obtained either by direct nucleophilic opening of the oxonium ions or by activated silica gel mediated

rearrangements. This observation agrees with results published in related studies, in which nucleophilic opening of related oxonium ions at C-13 would not occur unless C-13 is unsubstituted.[155,246]

6.3 Rationalisation of oxonium ion reactivities in the nucleophilic opening experiments

From the results of the nucleophilic opening experiments described in the previous section, some reactivity trends were observed that could act as the basis for the rationalisation of oxonium ion reactivities in these processes: **1)** nucleophilic opening at C-10 was the predominant pathway for all the oxonium ions; **2)** for oxonium ions **1.1** and **1.2**, nucleophilic opening at C-7 was a minor pathway that was found to be dependent on the identity of the nucleophiles, but this minor pathway was not accessible to oxonium ions ***ent*-1.3** and ***ent*-1.4**; **3)** all products generated from nucleophilic opening at C-10 could be converted to the products from nucleophilic opening at C-7 *via* an activated silica gel mediated rearrangement; **4)** nucleophilic opening at C-13 was not observed for any of the oxonium ions studies.

Considering these trends, the nucleophilic opening of the oxonium ions at C-10 was proposed to be under kinetic control, and nucleophilic opening of the oxonium ions at C-7 would lead to the formation of thermodynamic products. This was because C-10 opening was expected to require the least change in geometry between the products and the oxonium ions, and C-7 opening was expected to benefit from strain release and a substantial increase in entropy due to the formation of highly flexible 2,2'-bifuranyl systems.[9,242] Nucleophilic opening at C-13 could either be a kinetically accessible and reversible pathway as with nucleophilic opening at C-10, or a kinetically inaccessible pathway under the reaction conditions for nucleophilic opening of the oxonium ions. If

the former scenario was true, some C-13 opening products would be observed as intermediate species in a reaction monitoring experiment (**Figure 6.12**). However, no such species was observed and therefore nucleophilic opening at C-13 is more likely a kinetically inaccessible pathway (**Figure 6.13**).

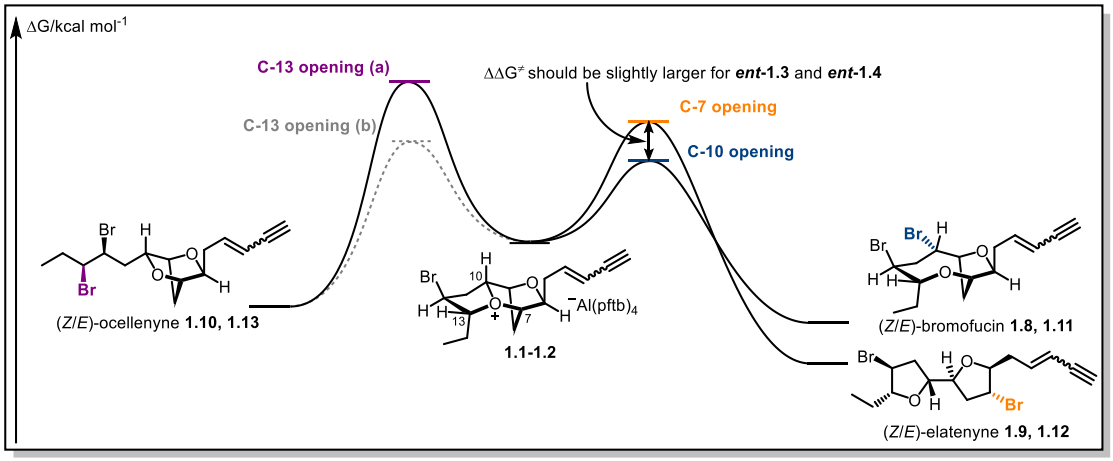


Figure 6.13. A plausible energy profile for the nucleophilic opening of oxonium ions. Pathways for C-7 opening and C-13 opening (a) should be irreversible, whereas pathways for C-10 opening and C-13 opening (b) should be reversible. $\Delta\Delta G^{\ddagger}$ (as shown) should be slightly larger for ***ent*-1.3** and ***ent*-1.4** to account for the absence of their C-7 openings.

Following the establishment of a plausible energy profile (**Figure 6.13**) to account for the experimental observations, DFT calculations (by Dr Quynh Nguyen and Prof. Robert. S. Paton) of the nucleophilic opening reactions were performed to further elucidate the reasons behind the kinetic preference of C-10 opening, the absence of C-13 opening, and the slight difference in C-10 versus C-7 openings of the two sets of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4**.

The investigation began with the analysis of the DFT calculated, Boltzmann weighted ground state bond lengths and selected bond angles of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** (**Figure 6.14-6.15**). The variations in the bond lengths and the selected bond angles of the oxonium ions should provide insights into the relative bond strengths of the oxonium ion C–O^+ bonds and the planarity of the electrophilic oxonium ion carbons C-7, C-10 and C-13 respectively.

Weighted average bond lengths/Å	1.1	1.2	*ent*-1.3	*ent*-1.4
C7-O+	1.53	1.53	1.53	1.53
C10-O+	1.55	1.55	1.56	1.56
C13-O+	1.54	1.54	1.53	1.54

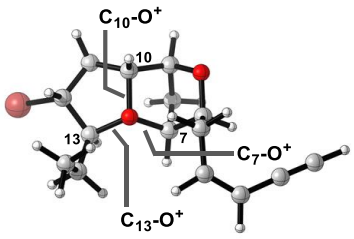


Figure 6.14. Selected weighted average bond lengths of the oxonium ions from their three most populated conformers, as suggested by their Boltzmann distributions at -78 °C. The structures of the oxonium ions were optimised in gas phase employing the B3LYP functional and 6-31+G(d,p) basis set. The DFT calculated structure of ***ent*-1.3** is shown as an example.

Weighted average bond angles/°	1.1	1.2	*ent*-1.3	*ent*-1.4
C6C7C8	102.1	102.1	102.2	101.9
C6C7H7	117.0	117.0	117.7	117.6
H7C7C8	121.8	121.8	121.5	121.8
Sum of angles	340.9	340.9	341.4	341.3
Deviation from planarity (360°)	19.1	19.1	18.6	18.7

Weighted average bond angles/°	1.1	1.2	*ent*-1.3	*ent*-1.4
C9C10C11	122.8	123.0	120.7	120.7
C9C10H10	111.5	111.6	112.0	112.0
H10C10C11	113.0	112.8	114.3	114.3
Sum of angles	347.3	347.3	347.1	346.9
Deviation from planarity (360°)	12.7	12.7	12.9	13.1

Weighted average bond angles/°	1.1	1.2	*ent*-1.3	*ent*-1.4
C12C13C14	115.0	115.0	117.9	118.7
C12C13H13	112.9	112.9	110.5	110.4
H13C13C14	111.0	111.0	111.8	111.7
Sum of angles	338.9	338.9	340.1	340.8
Deviation from planarity (360°)	21.1	21.1	19.9	19.2

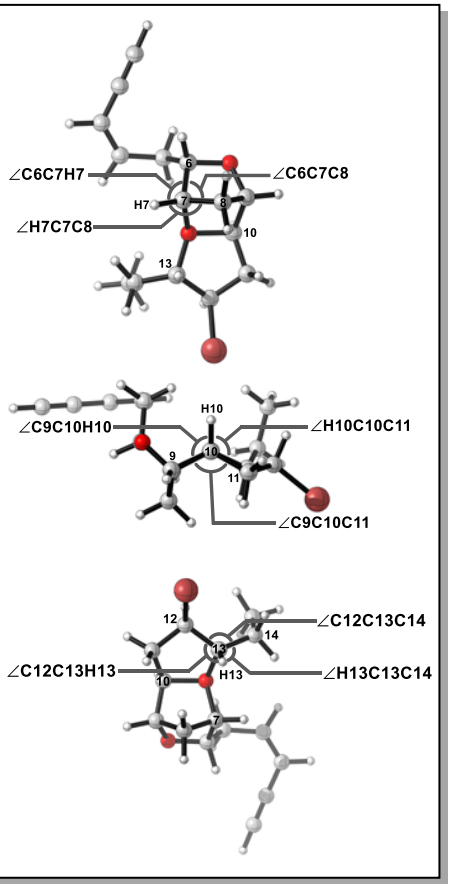


Figure 6.15. Selected weighted average bond angles of the oxonium ions from their three most populated conformers, as suggested by their Boltzmann distributions at -78 °C. The structures of the oxonium ions were optimised in gas phase employing the B3LYP functional and 6-31+G(d,p) basis set. The DFT calculated structure of ***ent*-1.3** at different viewing angles are shown as examples.

The Boltzmann weighted bond lengths of the oxonium ions suggest the C_{10}–O^+ bond is the longest C–O^+ bond in the four oxonium ions (1.55-1.56 Å). The C_7–O^+ and C_{13}–O^+ bonds were found to be shorter than the C_{10}–O^+ bond by 0.01-0.03 Å. The variations of the bond lengths of the C_7–O^+ and C_{13}–O^+ bonds were not able to explain the difference in reactivities between C-7 and C-13 openings, as the C_{13}–O^+ bonds are longer than the C_7–O^+ bonds by 0.01 Å for the oxonium ions **1.1**, **1.2**, and ***ent*-1.4**, but shorter by 0.01 Å for oxonium ion ***ent*-1.3**. The variations in C–O^+ bond lengths could only rationalise the preference for C-10 opening over C-7 and C-13 openings but could not rationalise why C-13 openings were not observed.

The analysis of the planarity of the oxonium ion carbons C-7, C-10 and C-13 by calculating their deviation from planarity was then performed (**Figure 6.15**). The difference between 360° and the sum of angles around the oxonium ion carbons would indicate their degree of planarity. A smaller value would suggest greater planarity, and hence more sp^2-like hybridisation with a higher carbocation character. This might lead to greater reactivity towards nucleophilic attack. The data in **Figure 6.15** suggest that the oxonium ion carbon C-10 is the most planar followed by C-7 and C-13 which have almost identical planarity, again suggesting that C-10 opening should be favoured over C-7 and C-13 openings. However, the difference in the deviation from planarity of C-10 versus that of C-7 in oxonium ions **1.1** and **1.2** is larger than that in oxonium ions ***ent*-1.3** and ***ent*-1.4** (6.4° vs 5.7° respectively). This would suggest C-7 opening is slightly more favoured for ***ent*-1.3** and ***ent*-1.4** compared to that for **1.1** and **1.2**, which is contrary to experimental observations.

Even so, the preference for C-7 over C-13 opening could be rationalised by the combination of the planarity argument with steric considerations. The $\sigma^*_{C–O^+}$ orbital of C-7 is only flanked by two C–H bonds, whereas the $\sigma^*_{C–O^+}$ orbital of C-13 is flanked

by a C–Br bond and a methyl group. Nucleophiles attacking C-7 would therefore experience weaker steric hindrance compared to an attack at C-13.

Given that ground state arguments could not satisfactorily explain the observed behaviours of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** in nucleophilic opening as previously discussed by Braddock and co-workers in related systems,[10] distortion-interaction analyses were performed (by Dr Quynh Nguyen and Prof. Robert. S. Paton) to further elucidate the observed differences in reactivities in the nucleophilic opening of the oxonium ions. The distortion-interaction model is a decomposition of the potential energy surface into two components, a generally destabilising distortion energy (ΔE_{dist}), and a stabilising interaction energy (ΔE_{int}) along the reaction coordinate. The distortion energy is related to the strength of bonds in the reactants that must be broken, flexibility of bond angles that must be deformed and the total number of distortions of this sort that are dependent on the reaction mechanism. The interaction energy is related to the bonding capabilities of the distorted reactants that are dependent on their electronic structures and orientations. The reaction barrier arises when the rate of change of ΔE_{dist} equals the negative of the rate of change of ΔE_{int}, which corresponds to the transition state and the reaction barrier $\Delta E^{\ddagger}$ is then given by $\Delta E_{dist}(TS)+\Delta E_{int}(TS)$ at this point (**Figure 6.16**).[247]

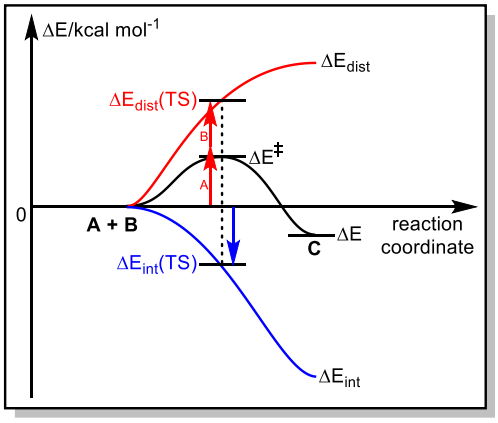


Figure 6.16. Graphical illustration of the distortion-interaction model. The reaction barrier is given by $\Delta E^{\ddagger}=\Delta E_{dist}(TS)+\Delta E_{int}(TS)$ at the transition state.

Two sets of studies using **1.2** and ***ent*-1.4** as model oxonium ions without the inclusion of counter anions were performed. The first set of studies was carried out with water as a neutral nucleophile and the other set with chloride anion as a charged nucleophile to investigate the behaviour of nucleophilic opening of the model oxonium ions under these conditions.

For the first set of studies, the calculations of the transition state energies and structures led to the construction of the following reaction coordinate diagrams (**Figure 6.17-6.18**). The opening of the oxonium ions **1.2** and ***ent*-1.4** by water were found to be endergonic processes because the deprotonation of the products were not included in the calculations. Nevertheless, for the nucleophilic opening of the oxonium ion ***ent*-1.4**, the calculations successfully replicated the experimental result that C-10 opening is predominant. This was rationalised by the distortion-interaction analysis of the nucleophilic opening process in which the interaction energies of C-10 and C-7 opening were found to be similar, but the distortion energy for C-7 opening was found to be greater than that of C-10 opening, hence the observed difference in reactivity.

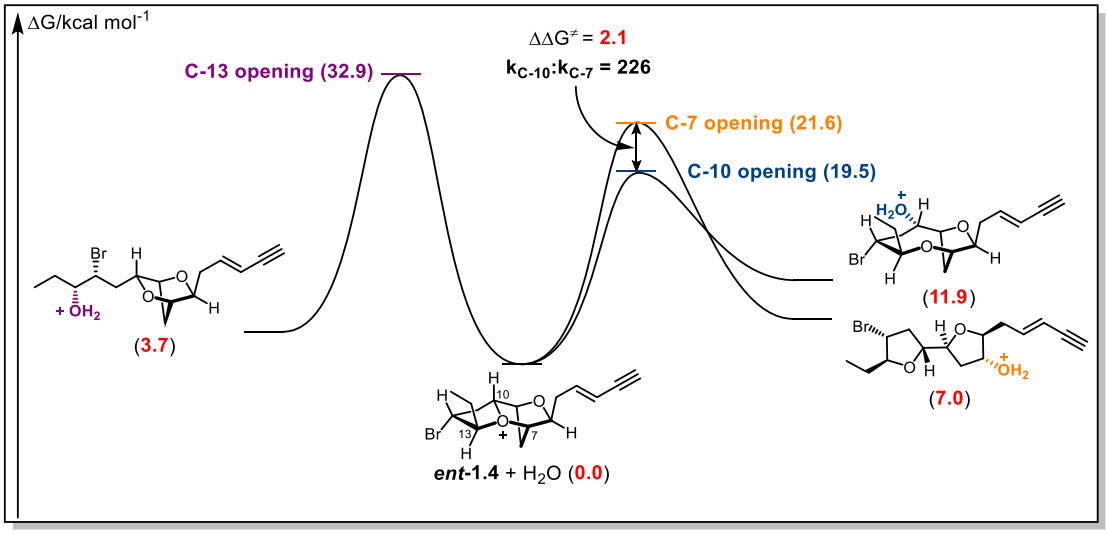


Figure 6.17. Reaction coordinate diagram for the nucleophilic opening of ***ent*-1.4** with H_2O. The most populated conformer of ***ent*-1.4** at 195K in CH_2Cl_2 (SMD solvation) was used for the transition state calculations employing the M06-2X functional and def2TZVP basis set.

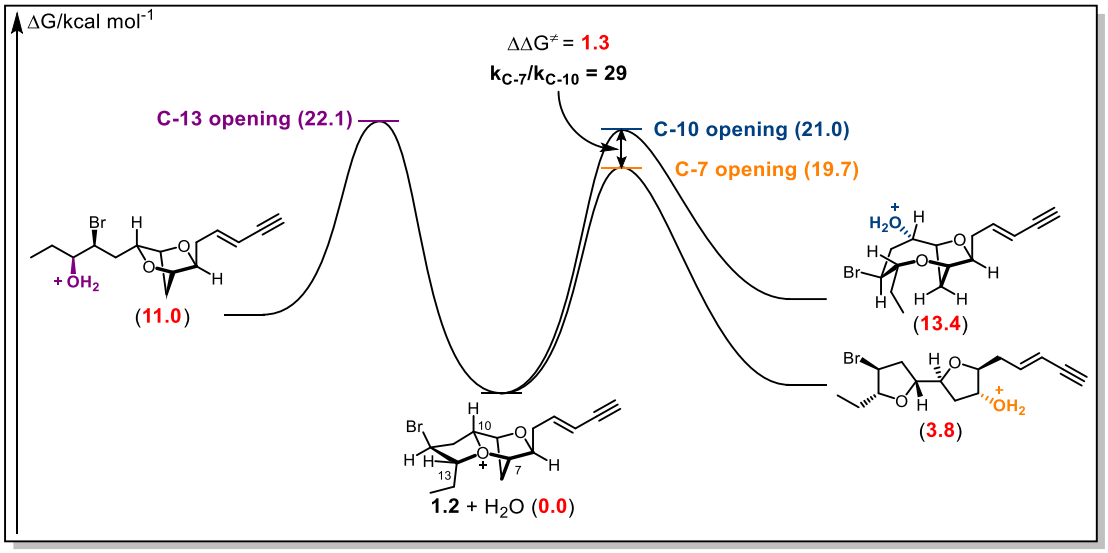


Figure 6.18. Reaction coordinate diagram for the nucleophilic opening of **1.2** with H_2O. The most populated conformer of **1.2** at 195K in CH_2Cl_2 (SMD solvation) was used for the transition state calculations employing the M06-2X functional and def2TZVP basis set.

As for the nucleophilic opening of **1.2**, the calculations did not replicate the experimental results and predicted that C-7 opening would be more favourable instead. This anomaly was attributed to the result that the uncorrected difference in electronic energies (a proxy for enthalpy) of the C-10 and C-7 opening was only 0.2 kcal mol^{-1} more favourable for C-10 opening. It could then be envisaged that a slight change in the entropic contributions in the nucleophilic opening processes could alter the difference in free energies and hence the propensity of C-10 versus C-7 opening.

In light of this anomaly, DFT calculations of the nucleophilic opening using the charged chloride anion as the nucleophile was performed (by Dr Quynh Nguyen and Prof. Robert. S. Paton) and the transition state energies and structures led to the construction of the following reaction coordinate diagrams (**Figure 6.19-6.20**).

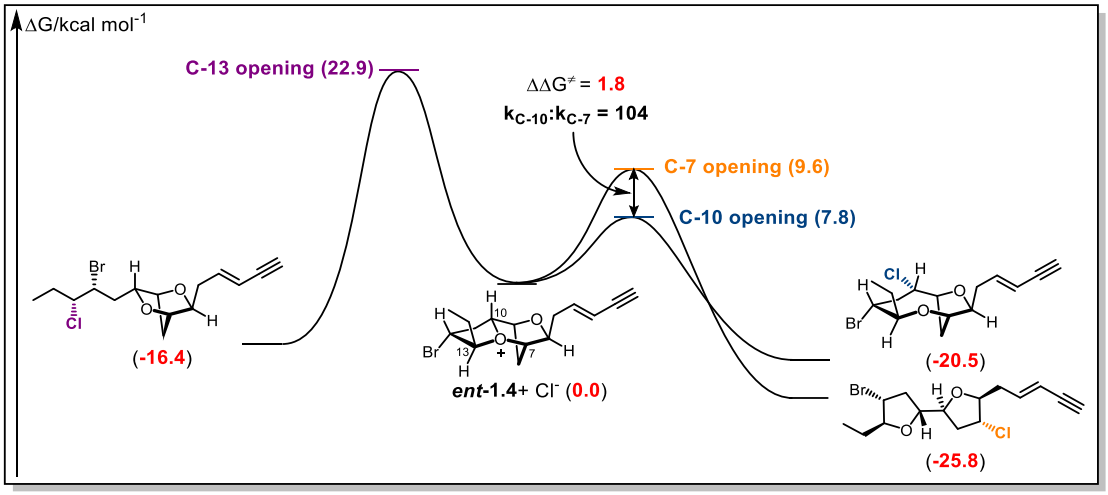


Figure 6.19. Reaction coordinate diagram for the nucleophilic opening of ***ent*-1.4** with Cl^-. The most populated conformer of ***ent*-1.4** at 195K in CH_2Cl_2 (SMD solvation) was used for the transition state calculations employing the M06-2X functional and def2TZVP basis set.

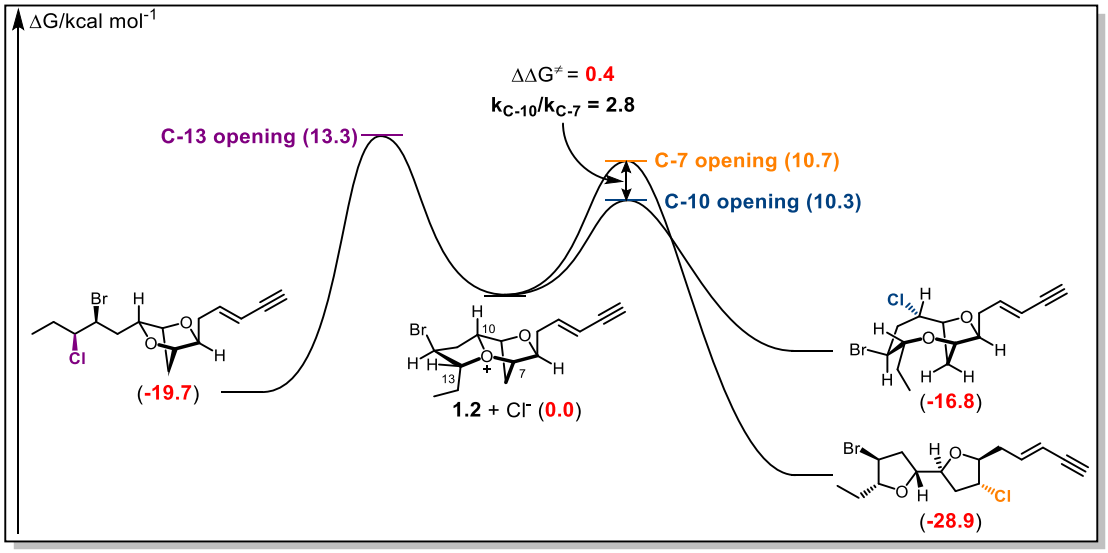


Figure 6.20. Reaction coordinate diagram for the nucleophilic opening of **1.2** with Cl^-. The most populated conformer of ***ent*-1.4** at 195K in CH_2Cl_2 (SMD solvation) was used for the transition state calculations employing the M06-2X functional and def2TZVP basis set.

The openings using chloride anion as the nucleophile were found to be exergonic processes as expected from the combination of two oppositely charged species. The preference for C-10 opening was reproduced in both cases, and a slight leakage to C-7 opening was also predicted in the nucleophilic opening of **1.2** that was in line with experimental observations. The preference for C-10 opening in both cases was due to

the same reason that the distortion energies of C-7 opening were found to be higher than that of C-10 opening, but their interaction energies are similar to one another. The change in the preference of C-10 versus C-7 opening for **1.2** by changing the identity of the nucleophile from water to chloride implied that the preference for these two competing processes could be dependent on the identity of the nucleophiles.

Although the investigations above provided us with insights on the energetic behaviours of the competing C-10 and C-7 opening processes, they did not provide the actual reasons behind these variations in energetic behaviours. In keeping with Braddock and co-worker's conclusion, these oxonium ion opening processes may not have a dominant factor that controls the regioselectivity of the nucleophilic opening processes due to the complexity of the system.[10]

6.4 Conclusion

Substantial evidence has been obtained to support the existence and biosynthetic relevance of oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** in *Laurencia* natural product biosynthesis by their direct derivatisation into 10 out of 13 expected natural products. The reactivities of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** have been studied by distortion-interaction analysis which provided insights for the regioselectivities of the oxonium ion opening processes.

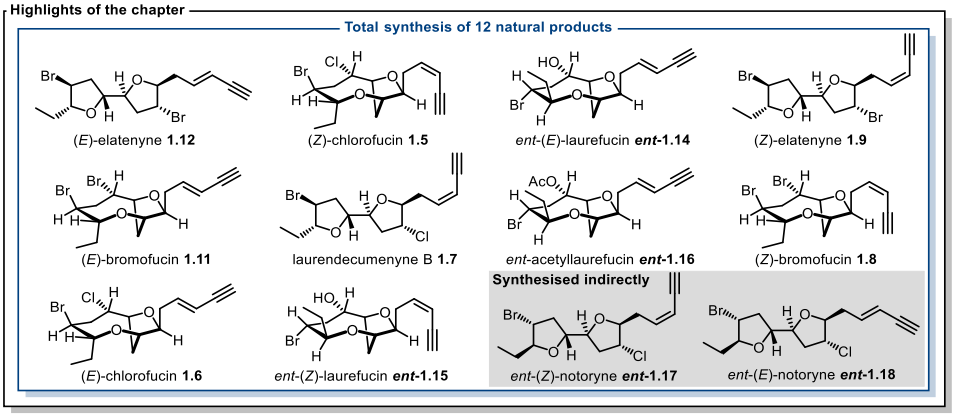


Figure 6.21. Highlights of Chapter 6.

7 A retrobiosynthetic strategy for the total synthesis of *ent*-laurencin

7.1 The retrobiosynthesis idea

The studies described in the previous chapters had focused on oxonium ion formation and derivatisation into natural products that is in the forward direction of the biosynthetic postulate (**Figure 7.1**). Moving one biosynthetic step back from the dibromides **1.8**, **1.11** and **1.43**, **1.44** gives the medium ring ethers **1.38-1.40** and **1.51-1.52**, which allows the synthesis of the natural products deacetyllaurencin **1.38** and laurencin **1.39** by an unusual retrobiosynthetic strategy.

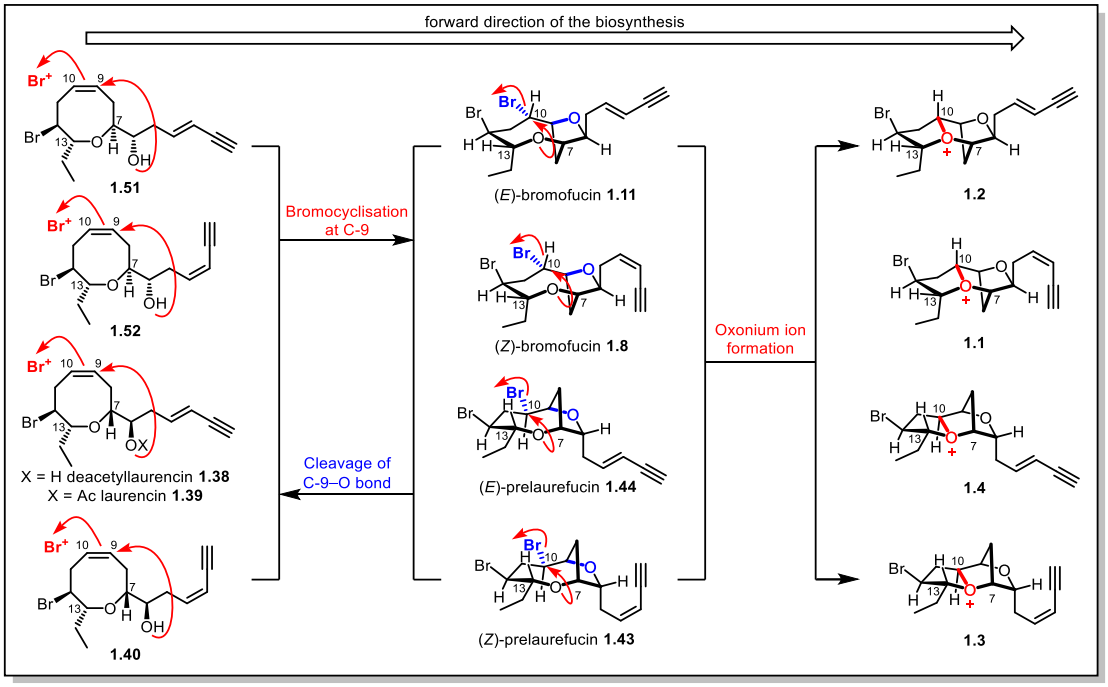
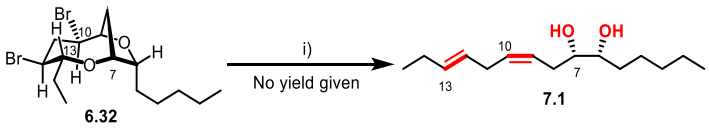


Figure 7.1. A section of the biosynthetic postulate of the *Laurencia* natural products that is related to this project.

The natural product deacetyllaurencin **1.38** was first isolated by Irie and co-workers in 1968,[248] and re-isolated by Wright and co-workers in 1994.[23] Laurencin **1.39** was first

isolated by Irie and co-workers in 1965,[249,250] and its structure was determined unambiguously by X-ray crystallography by Ferguson and co-workers in 1969.[251,252] Laurencin **1.39** has acted as a testbed for the development of synthetic methodologies for the synthesis of medium ring ethers and numerous total syntheses have been reported since its isolation but they will not be reviewed here.[253–262]

Previously, Irie and co-workers treated hexahydroprelaurefucin **6.32** with zinc and acetic acid in ethanol. It resulted in the unselective cleavage of C-9–O and C-13–O bonds to give the diol **7.1**, which demonstrated the possibility to carry out the desired retrobiosynthetic transformation (**Scheme 7.1**).[21]



Scheme 7.1. Conversion of **6.32** to **7.1**. Reagents and conditions: **i)** Zinc and acetic acid, ethanol.

However, the selective conversion of (*E*)-prelaurefucin **1.44** to laurefucin **1.39** would require the development of a method to only activate the C-10–Br bond of (*E*)-prelaurefucin **1.44** to cleave the C-9–O bond. Distinguishing the C-10–Br from the C-12–Br bond was expected to be difficult, and thus it was likely that another substituent would be needed at C-10 to bring about this selective activation. In reality, the synthesis would proceed from the chloride **4.48** which would lead to the synthesis of *ent*-deacetyllaurencin ***ent*-1.38** and *ent*-laurencin ***ent*-1.39** (**Figure 7.2**).

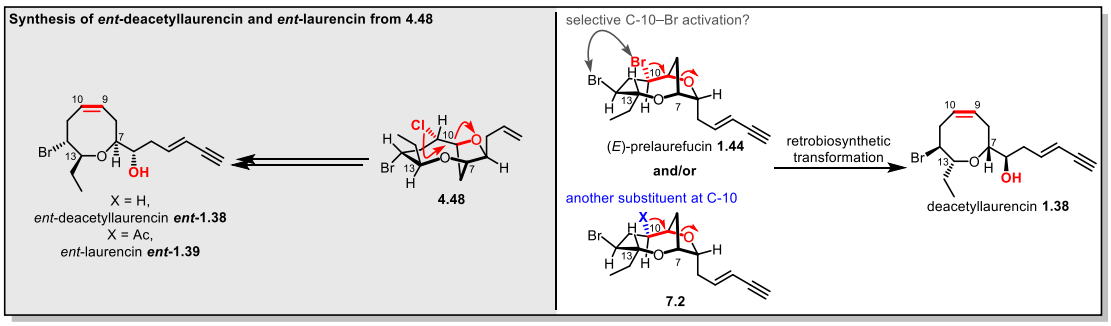


Figure 7.2. Initial strategies for the retrobiosynthetic transformation.

7.2 Sulfone and hydrazine chemistry

The first approach to the synthesis of *ent*-laurencin ***ent*-1.39** was to attach an electron withdrawing group at the C-10 position to enable the regioselective generation of a carbanion to induce the desired C_9–O bond cleavage *via* E_1cb elimination. This electron withdrawing group should be easily removed after the desired transformation and its preparation must also tolerate existing functional groups. Installing a sulfone at the C-10 position of chloride **4.48** should therefore satisfy all these requirements, as a sulfone could significantly acidify α-C–H bonds by the inductive effect,[263] and the vinyl sulfone that is formed after C_9–O cleavage could be removed with sodium dithionite (**Figure 7.3**).[264]

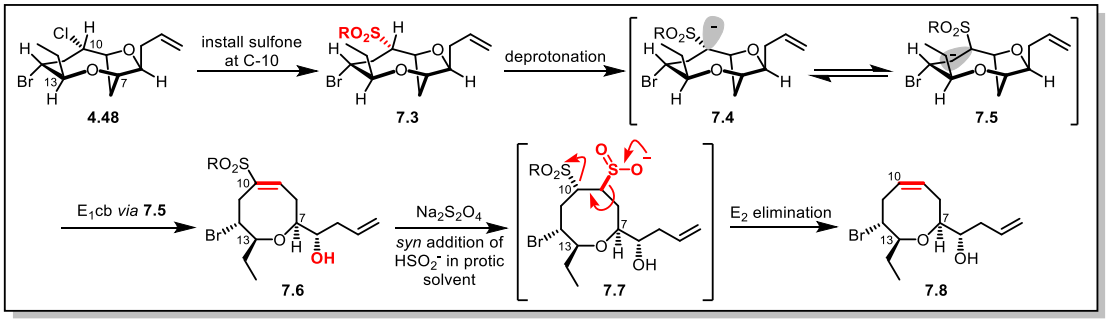
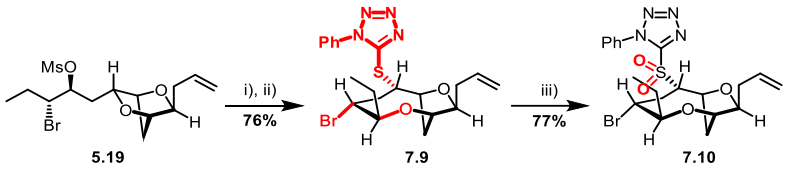


Figure 7.3. Proposed synthesis of **7.8** by sulfone chemistry.

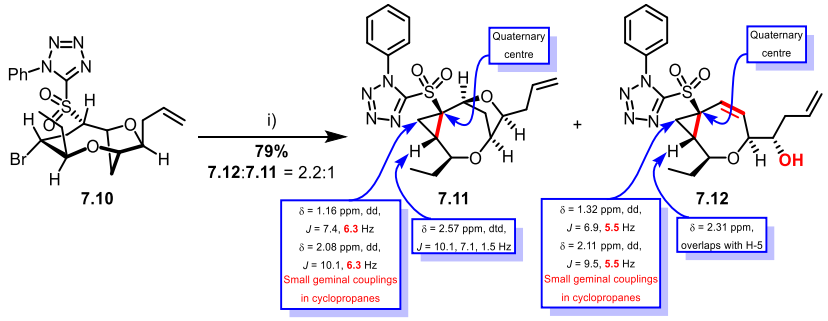
The synthesis of the sulfone was achieved by a modification of the bromocyclisation reaction in the synthesis of **4.48** from **5.19**. Instead of using *n*-Bu_4NCl as the nucleophile to quench the oxonium ion intermediate, 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) was used as the nucleophile to directly give the heteroarylsulfide **7.9** from **5.19**. The heteroarylsulfide **7.9** was then oxidised to the sulfone **7.10**.



Scheme 7.2. Synthesis of **7.10** from **5.19**.

Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (3.0 eq.), CH_2Cl_2 (0.01 M), -40 °C, 2 hrs. **ii)** PTSH (10.0 eq.), -78 °C, 1 hr. **iii)** 30 % aq. H_2O_2, cat. $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$, EtOH, 0 °C to r.t., overnight.

Treatment of the sulfone **7.10** with 1.1 equivalents of NaHMDS in THF at -78 °C did not bring about observable reactivity, but complete conversion of the sulfone **7.10** to a new species was observed on warming the reaction mixture to room temperature as suggested by TLC analysis. Subsequent purification and isolation of this new species revealed that it consisted of two compounds that possess cyclopropyl groups as suggested by extensive spectroscopic analysis (**Scheme 7.3**).



Scheme 7.3. Transformation of **7.10** into **7.11** and **7.12**.

Reagents and conditions: **i)** NaHMDS (1.1 eq., 1.0 M in THF), THF, -78 °C to r.t. 15 mins.

A plausible mechanism for the generation of these two cyclopropanes is shown below (**Figure 7.4**). The generation of compound **7.12** was rationalised through invoking **7.15** as a reaction intermediate. An intramolecular proton transfer in **7.15** would generate the less basic sodiated sulfone **7.16** which could then perform an intramolecular S_N2 reaction, ultimately providing the observed product **7.12**. The driving force for this transformation was most likely due to the difference in the acidity of the O–H bond

(pK_a ~ 30 in DMSO) of the secondary alcohol and the γ-C–H bonds of the vinyl sulfone (estimated pK_a ~ 23 in DMSO).[265]

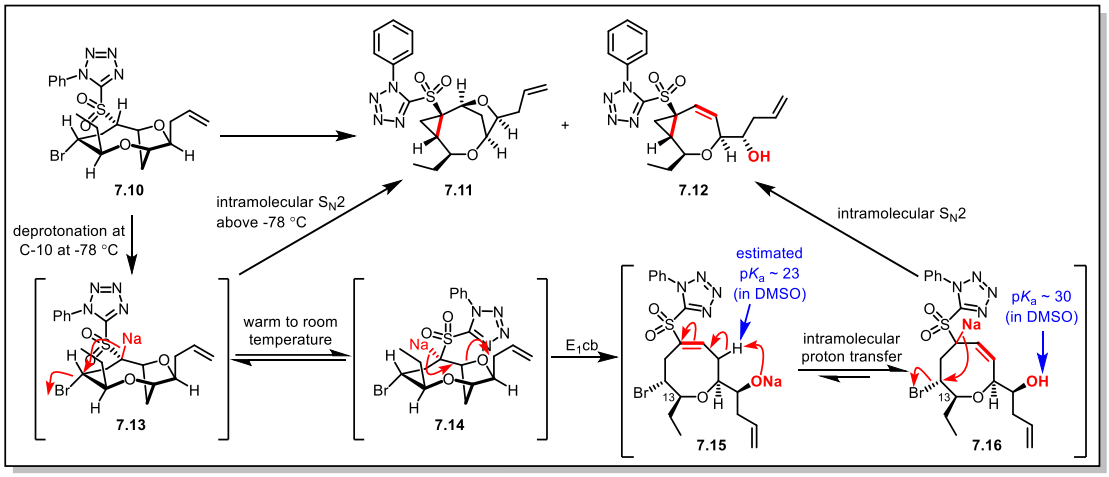


Figure 7.4. A plausible mechanism of the formation of **7.11** and **7.12**.

The formation of **7.12** suggested that the desired E_1cb reaction was possible. To isolate the E_1cb elimination from further transformations, another mode of activation without the participation of acidic vinyl sulfone species was required. The generation of diazene **7.20** from tosylhydrazide **7.17**, and subsequent fragmentation into **7.8** driven by the loss of nitrogen gas was therefore proposed (**Figure 7.5**).

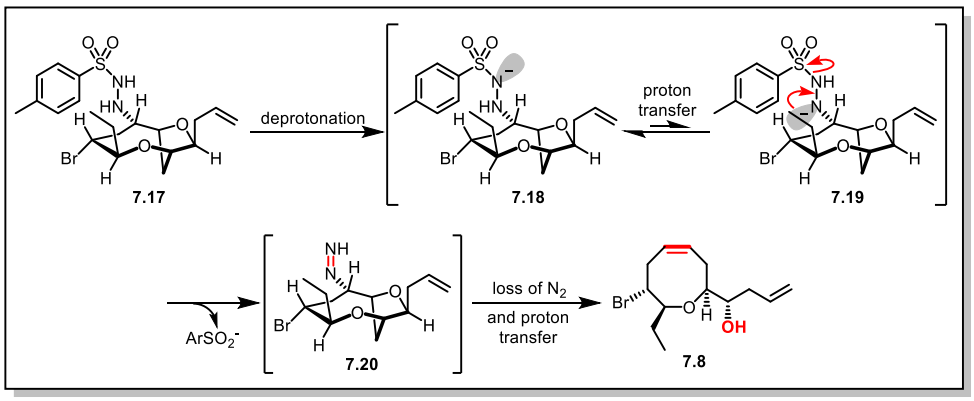
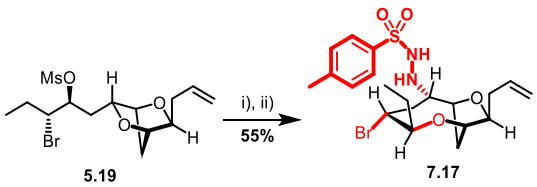


Figure 7.5. Proposed synthesis of **7.8** from **7.17** *via* hydrazine chemistry.

The required tosylhydrazide **7.17** was synthesised from **5.19** using the established bromocyclisation reaction followed by nucleophilic opening with *p*-TsNHNH$_2$ using AgBF$_4$ as an additive (**Scheme 7.4**).

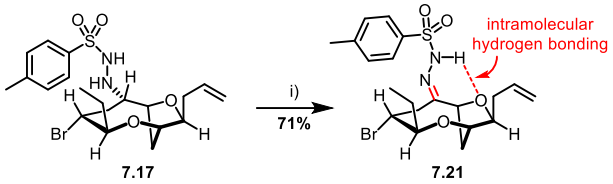


Scheme 7.4. Synthesis of **7.17** from **5.19**.

Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (3.0 eq.), CH_2Cl_2 (0.01 M), -40 °C, 2 hrs. **ii)** *p*-TsNHNH$_2$ (10.0 eq.), $AgBF_4$ (10.0 eq.), -78 °C, 1 hr.

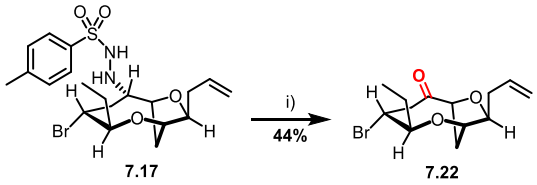
The addition of $AgBF_4$ was essential to the synthesis of **7.17**, otherwise, the chloride **4.48** was obtained as the major product by TLC analysis. This was rationalised based on the difference in bond energies between Ti–Cl bonds (405.4 ± 10.5 kJ mol^{-1}) and Ti–N bonds (476.0 ± 33.0 kJ mol^{-1}),[266] in which the formation of Ti–N bonds at the expense of Ti–Cl bonds was expected to be highly exergonic. The chloride anions displaced from this reaction could therefore compete with *p*-TsNHNH$_2$ for the oxonium ion intermediate and generate **4.48** instead of **7.17** .

Treatment of **7.17** with 1.0 equivalent of NaHMDS surprisingly gave the tosylhydrazone **7.21** as a single geometrical isomer (**Scheme 7.5**). The sulfonamide N–H proton does not appear to undergo exchange with residual H_2O in the sample and thus its NOESY correlations with its surrounding protons in **7.21** were used to determine the geometry of the hydrazone C=N bond. The preferred geometry of the C=N bond may due to favourable intramolecular hydrogen bonding between the N–H bond and the ether oxygen of the dioxabicyclo[2.2.1] system (**Scheme 7.5**).



Scheme 7.5. Generation of **7.21** from **7.17**.
Reagents and conditions: **i)** NaHMDS (1.0 eq., 0.1 M in THF), THF, -78 °C to r.t., 15 mins.

This unexpected generation of hydrazone **7.21** was found to occur only in the presence of atmospheric oxygen. However, the actual mechanism of the oxidation of **7.17** to **7.21** by atmospheric oxygen is unknown. Degassing the solvent and the NaHMDS solution by freeze-pump-thaw technique inhibited the conversion of **7.17** to **7.21**, and further heating of the reaction mixture to 60 °C generated the ketone **7.22** as the only isolable product.



Scheme 7.6. Generation of **7.22** from **7.17** under the exclusion of atmospheric oxygen.
Reagents and conditions: NaHMDS (1.0 eq., 0.1 M in THF), THF, -78 °C to r.t., 1 hr,
then 60 °C, 7 hrs.

Presumably, the ketone **7.22** was formed from the hydrolysis of the imine **7.24** that was generated *via* an E_i elimination through a 4-membered transition state that is analogous to the Cope elimination (5-membered transition state) and Chugaev elimination (6-membered transition state) (**Figure 7.6**).[267]

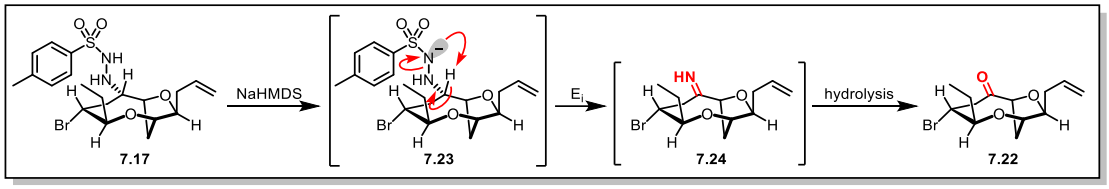


Figure 7.6. Proposed mechanism for the generation of **7.22** via an E_i elimination of **7.17** after deprotonation.

7.3 Kishner-Leonard elimination

In light of the unexpected behaviours of sulfone **7.10** and hydrazine **7.17**, the Kishner-Leonard elimination was employed for the desired C–O bond cleavage,[268,269] again exploiting the loss of nitrogen gas as the thermodynamic driving force for the reaction (**Figure 7.7**).

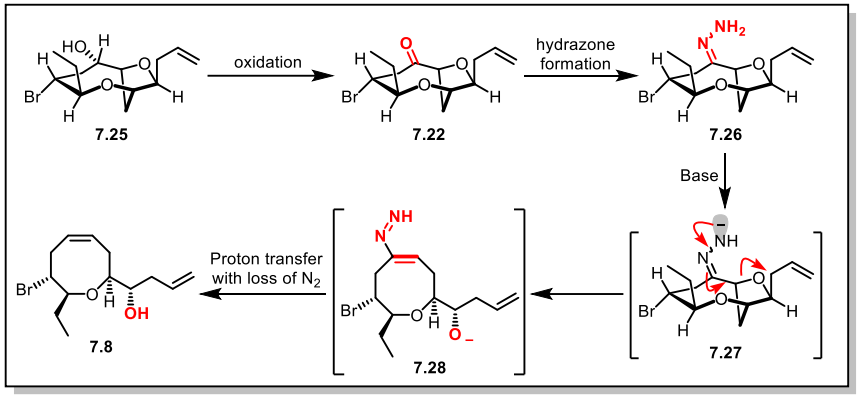
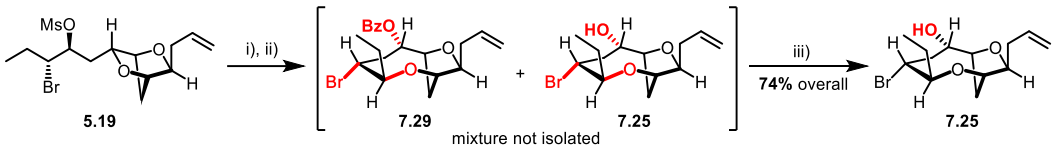


Figure 7.7. Kishner-Leonard elimination of hydrazone **7.26** for the synthesis of **7.8**.

It has been reported that the efficiency of the Kishner-Leonard elimination depends on the properties of the leaving group, in which lower basicity and higher steric bulk of the leaving group promote elimination over normal Wolff-Kishner reduction.[269] It has been demonstrated in Kishner's paper that amide leaving groups such as pyrrolidide anion (pK_{aH} in DMSO ~ 44)[270] was sufficient to undergo competitive Kishner-Leonard elimination over normal Wolff-Kishner reduction.[269]

Considering that the hydrazone **7.26** is eliminating an alkoxide anion (pK_{aH} in DMSO ~ 30), it was expected that the Kishner-Leonard elimination should be significantly favoured over normal Wolff-Kishner reduction. The experiment for the Kishner-Leonard elimination began with the synthesis of **7.25**, which was achieved from **5.19** using the established bromocyclisation reaction followed by nucleophilic opening with AgOBz and then deprotection of the benzoate ester (**Scheme 7.7**).



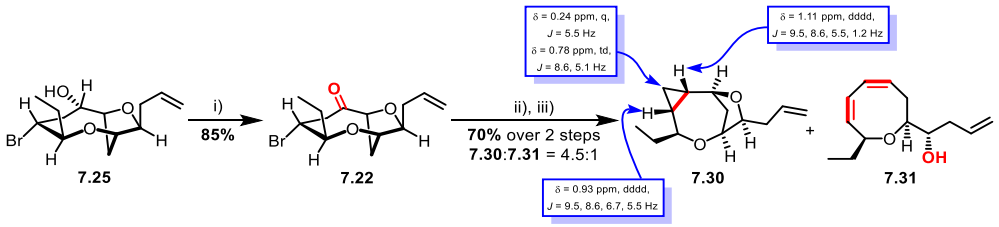
Scheme 7.7. Synthesis of **7.25** from **5.19**.

Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (3.0 eq.), CH_2Cl_2 (0.01 M), -40 °C, 2 hrs. **ii)** AgOBz (10.0 eq.), -78 °C, 1 hr, *then* sat. $NaHCO_{3(aq)}$ followed by excess *n*-Bu_4NI for work-up. **iii)** K_2CO_3 (10.0 eq.), MeOH, 2 hrs.

It was found that a mixture of **7.29** and **7.25** was generated after the first two operations as described in **Scheme 7.7**. Reducing the stirring time of the second step to 0.5 hours resulted in a decrease in the ratio of **7.29**:**7.25**. This implied that AgOBz did not rapidly quench the oxonium ion intermediate in CH_2Cl_2 at -78 °C due to its low solubility, and the source of the hydroxyl group most likely came from the saturated aqueous $NaHCO_3$ solution used in the work-up. However, a direct substitution of AgOBz with saturated aqueous $NaHCO_3$ solution gave the chloride **4.48** as suggested by TLC analysis, with the reason being analogous to the use of excess $AgBF_4$ in the formation of tosylhydrazide **7.17**. In this case, the bond energy of Ti–O bonds (665.0 ± 5.6 kJ mol^{-1}) is much higher than that of Ti–Cl bonds (405.4 ± 10.5 kJ mol^{-1}), and thus an excess of chloride scavenger must be present to sequester chloride anions upon hydrolytic work-up to prevent the formation of **4.48** as the major product. In addition, the use of excess *n*-Bu_4NI after hydrolytic work-up was necessary, most likely to release **7.25** from presumably its Ag(I)-olefin complex, as otherwise only baseline species could be observed by TLC analysis.

The compound **7.25** was oxidised to **7.22** and the Kishner-Leonard elimination was carried out using a literature procedure.[271] The cyclopropane **7.30** was generated as the major product with the diene **7.31** as the minor product (**Scheme 7.8**). The two species

were not separable by flash column chromatography, but their structures were deduced by NMR spectroscopic analysis.



Scheme 7.8. Kishner-Leonard elimination of **7.22**.

Reagents and conditions: **i)** DMP (1.2 eq.), CH_2Cl_2, r.t., 1 hr. **ii)** $NH_2NH_2{\cdot}H_2O$ (2.6 eq.), EtOH, r.t., 2 hrs. **iii)** NaH (3.5 eq.), DMSO, r.t., 1 hr (NaH and DMSO were pre-mixed to form the dimsyl anion).

The simultaneous generation of **7.30** and **7.31** implied that the undesired intramolecular S_N2 cyclopropanation pathway was competing with the desired Kishner-Leonard elimination pathway. In addition, it appeared the Kishner-Leonard elimination product **7.8** reacted further to give **7.31** from the base-mediated elimination of HBr. A plausible mechanism for the generation of **7.30** and **7.31** is suggested as follows (**Figure 7.8**).

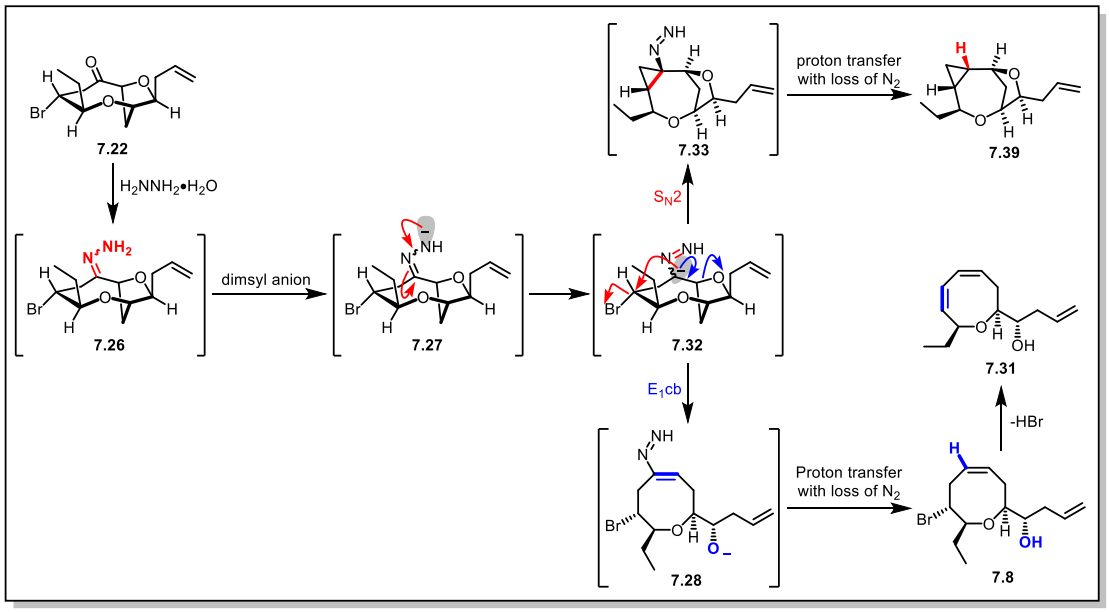
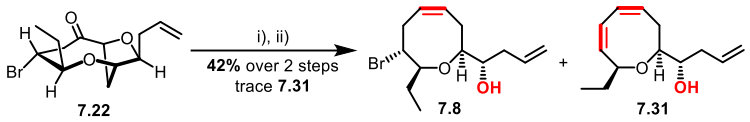


Figure 7.8. Proposed mechanism for the generation of **7.30** and **7.31**.

Furthermore, the direct S_N2 cyclopropanation product **7.30** was the major product under this reaction condition (NaH, DMSO, r.t.), as opposed to the E_1cb-cyclopropanation product **7.12** which was found to be the major product with the sulfone **7.10** as shown

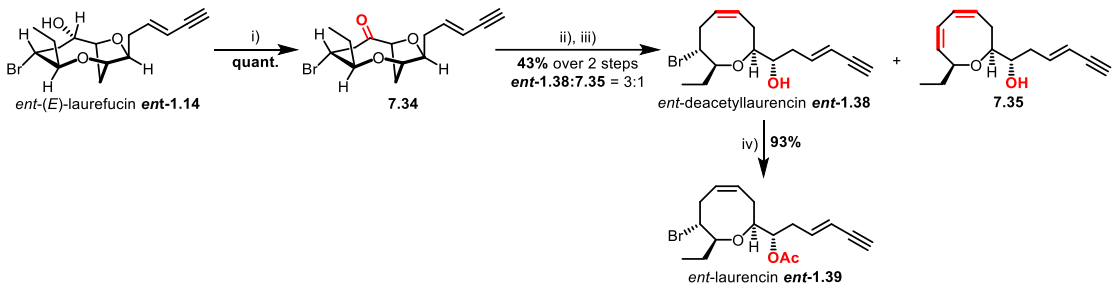
in **Scheme 7.3** (NaHMDS, THF, -78 °C to r.t.). Performing the Kishner-Leonard reduction in THF gave **7.8** as the major product with a trace of **7.31** (**Scheme 7.9**). The exact reason for the switch in selectivity is not clear, however it could be due to the difference in the structure of the carbanion species **7.32** under the two different reaction conditions (i.e. **7.32** may have greater contact-ion pair character in THF, but greater solvent-separated ion pair character in DMSO).



Scheme 7.9. Synthesis of **7.8** from **7.22**.

Reagents and conditions: **i)** $NH_2NH_2{\cdot}H_2O$ (2.6 eq.), EtOH, r.t., 2 hrs. **ii)** NaHMDS (1.1 eq, 0.1 M in THF), THF, -78 °C to r.t. progress monitored by TLC.

This strategy was then applied to *ent*-(*E*)-laurefucin ***ent*-1.14** and the total synthesis of *ent*-laurencin ***ent*-1.39** and *ent*-deacetyllaurencin ***ent*-1.38** was achieved (**Scheme 7.10**). Oxidation of *ent*-(*E*)-laurefucin ***ent*-1.14** with Dess-Martin periodinane provided the ketone **7.34** quantitatively, treatment of ketone **7.34** with $N_2H_4{\cdot}H_2O$ generated the corresponding hydrazone which was not isolated. The hydrazone was treated with two equivalents of NaHMDS to bring about the desired Kishner-Leonard elimination in THF upon warming to room temperature from -78 °C. The extra equivalent of NaHMDS was required to induce Kishner-Leonard elimination as using stoichiometric amount of NaHMDS did not lead to significant reactivity, most probably due to competing acetylene C–H bond deprotonation that was much faster compared to the deprotonation of the hydrazone N–H bond.



Scheme 7.10. Synthesis of *ent*-deacetyllaurencin ***ent*-1.38** and *ent*-laurencin ***ent*-1.39**. Reagents and conditions: **i)** DMP (1.2 eq.), CH_2Cl_2, r.t., 1 hr. **ii)** $NH_2NH_2{\cdot}H_2O$ (2.6 eq.), EtOH, r.t., 2 hrs. **iii)** NaHMDS (2.0 eq, 0.1 M in THF), THF, -78 °C to r.t. progress monitored by TLC **iv)** Ac_2O, DMAP, CH_2Cl_2, r.t., 1 hr.

As expected, the use of two equivalents of base led to the generation of more diene side product **7.35** compared to the results obtained in **Scheme 7.9**.

7.4 Conclusion

In conclusion, an unusual retrobiosynthetic strategy has been developed to gain access to *ent*-laurencin ***ent*-1.39** and *ent*-deacetyllaurencin ***ent*-1.38** from *ent*-(*E*)-laurefucin ***ent*-1.14**.

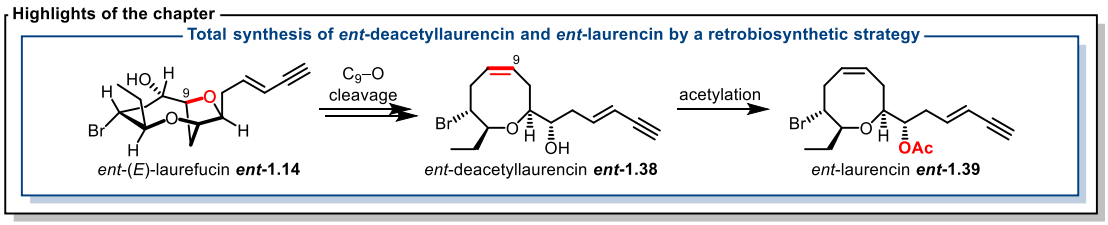


Figure 7.9. Highlights of Chapter 7.

8 Total synthesis of laurefurenynes C-F and their structural reassignment

8.1 Jaspers' biosynthetic hypothesis and structural assignments

The isolation and structural assignments of the natural products laurefurenynes A-F **1.22-1.27** were first reported by Jaspers in 2010.[26] The proposed structures of the natural products are as shown below (**Figure 8.1**).

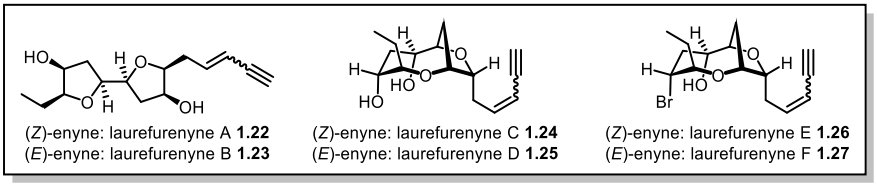


Figure 8.1. Proposed structures of laurefurenynes A-F **1.22-1.27**.

The relative configurations of these six natural products were deduced from analysis of their ^{1}H-^{1}H NOESY correlations, which were corroborated with interatomic distances suggested from molecular modelling using molecular mechanics.[26] However, some of the ^{1}H-^{1}H NOESY correlations were ambiguous due to overlapping ^{1}H NMR resonanes. The structures of laurefurenynes A and B **1.22-1.23** were subsequently reassigned to **1.28-1.29** by Burton and co-workers using total synthesis and DFT computation of NMR chemical shifts.[2] Britton and co-workers also independently reported the reassigned structures of these two natural products, confirming their reassignments.[3]

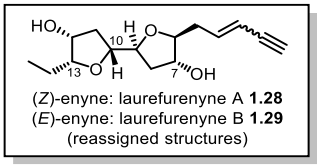


Figure 8.2. Reassigned structures of laurefurenynes A-B **1.28-1.29**.

The structural reassignments of laurefurenynes A and B also suggested that their biosynthesis may involve the oxonium ions **1.1** and **1.2** as biosynthetic intermediates. This suggested that laurefurenynes C-F **1.24-1.27** may also require structural reassignment (**Figure 8.3**).

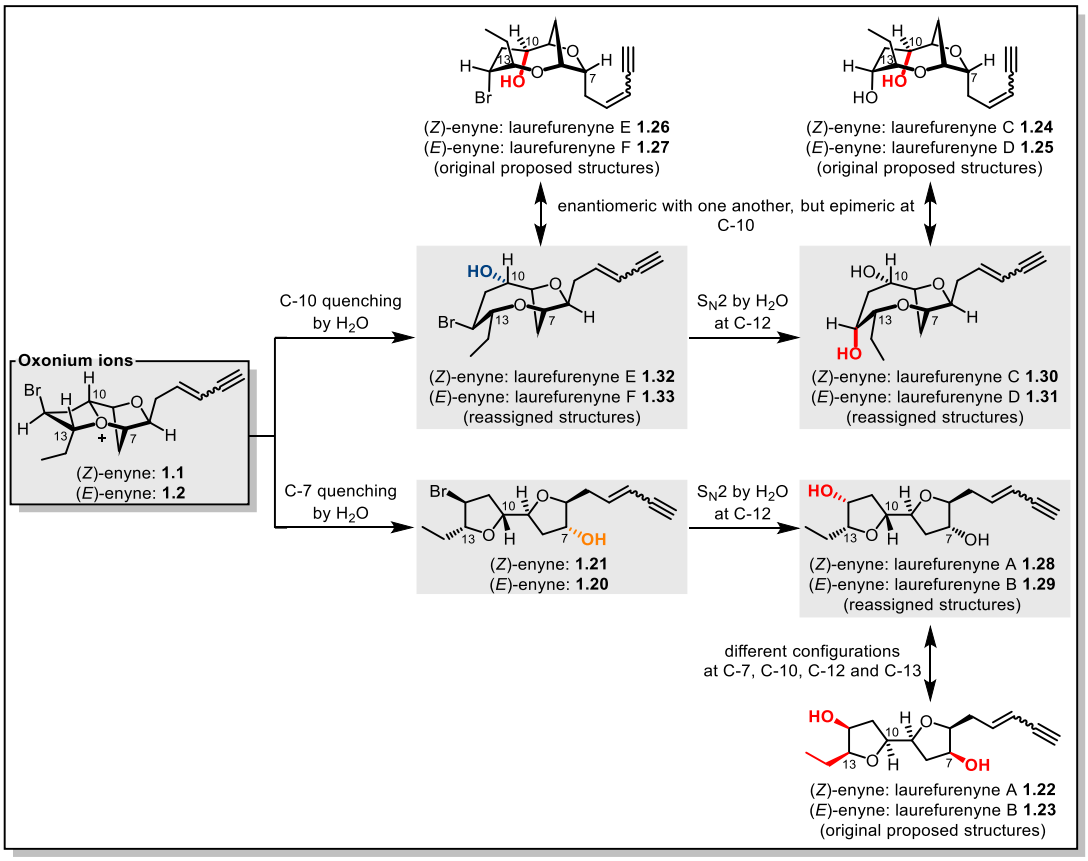


Figure 8.3. Proposed biosynthesis of laurefurenynes A-F from oxonium ions **1.1** and **1.2** and their reassigned structures **1.28-1.33**.

Jaspars also proposed biosynthetic pathways for the biosynthesis of the original structures of laurefurenynes A-F **1.22-1.27**, which involve epoxide or bromonium ion mediated cyclisations of laurediols **8.1** and **8.2** (**Figure 8.4**).

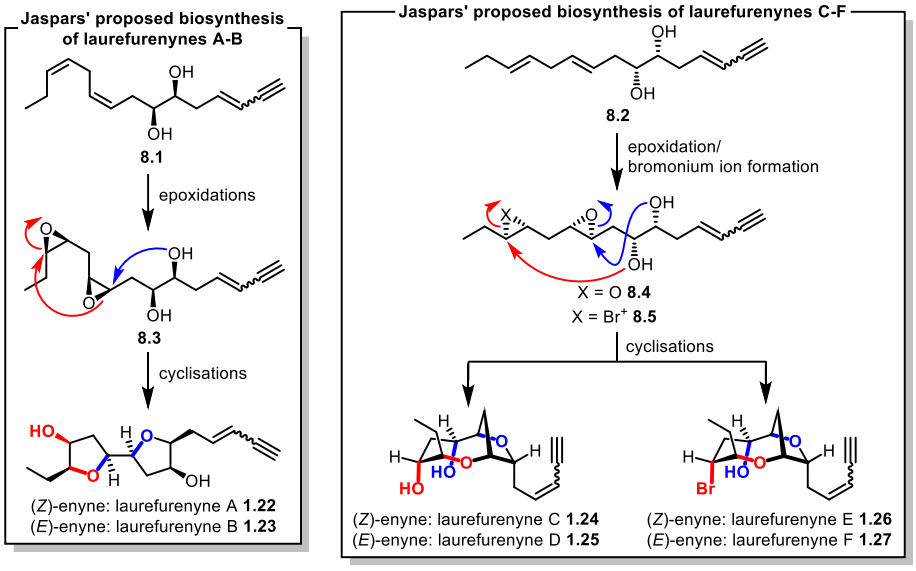
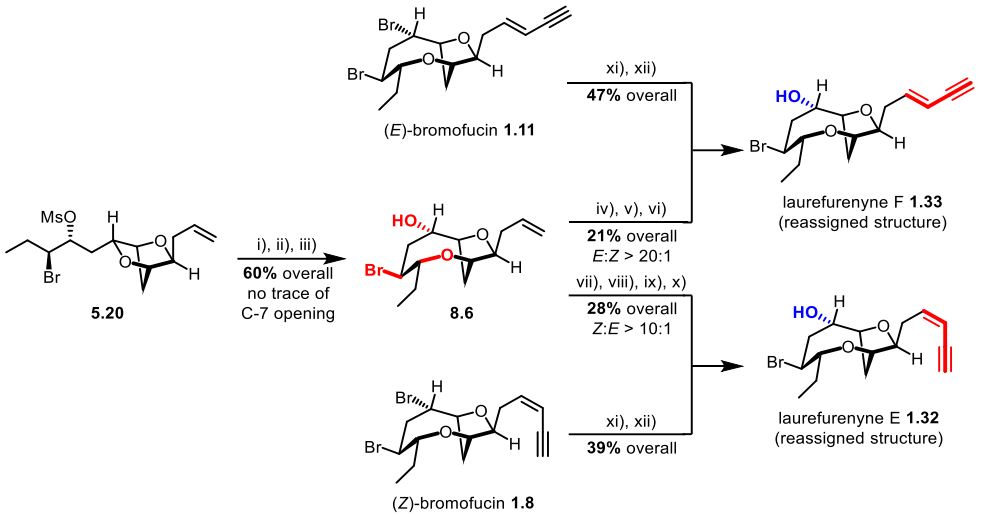


Figure 8.4. Jaspars' proposed biosynthesis of the natural products **1.22-1.27**.

The following sections will describe the total synthesis of the reassigned structures of laurefurenynes C-F **1.30-1.33** and present unambiguous evidence for their structural reassignments.

8.2 Total synthesis of laurefurenynes E-F and their structural reassignment by Mosher ester analysis

The reassigned structures of the natural products laurefurenynes E-F **1.32** and **1.33** were synthesised independently using two protocols. The first protocol relies on the nucleophilic opening of the oxonium ions **1.1** and **1.2** with water at C-10 to directly generate the natural products. The second protocol relies on the direct generation of the core of laurefurenynes E-F **8.6** using the bromocyclisation-nucleophilic quenching strategy as described previously (**Section 7.3**) followed by (*Z*/*E*)-enyne synthesis. The second protocol was developed to provide more material for Mosher ester analysis and to confirm reaction conditions of the (*Z*/*E*)-enyne syntheses would not alter the configurations of the substituents in **8.6**.



Scheme 8.1. Synthesis of laurefurenynes E-F **1.32** and **1.33** from two separate protocols. Reagents and conditions: **i)** $TiCl_4$ (2.0 eq.), $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (3.0 eq.), CH_2Cl_2 (0.01 M), -40 °C, 2 hrs. **ii)** AgOBz (10.0 eq.), -78 °C, 1 hr, *then* sat. $NaHCO_{3(aq)}$ followed by excess TBAI for work-up. **iii)** K_2CO_3 (10.0 eq.), MeOH, 2 hrs. **iv)** Crotonaldehyde (5.0 eq.), Grubb's 2nd generation catalyst (5.0 mol%), CuI (7.5 mol%) Et_2O, r.t., overnight. **v)** $TMSCHN_2$ (1.3-1.5 eq., 2.0 M in Et_2O), *n*-BuLi (1.3-1.5 eq., 2.3 M in hexanes), THF, -78 °C, 1 hr, *then* 0 °C, 30 min. **vi)** K_2CO_3 (10.0 eq.), MeOH, r.t., 1-2 hrs. **vii)** cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t., 1-2 hrs. **viii)** $Ph_3PCH_2I_2$ (3.0 eq.), NaHMDS (3.0 eq., 1.0 M in THF), HMPA (6.0 eq.), THF, -78 °C, 30 min, then r.t., 1 hr. **ix)** TMS acetylene (5.0 eq.), CuI (1.0 eq.), $Pd(PPh_3)_4$ (15 mol %), Et_3N, r.t., 1 hr. **x)** K_2CO_3 (10.0 eq.), MeOH, r.t., 1-2 hrs. **xi)** $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CD_2Cl_2, -40 °C, 1.5 hrs, then filter into flame-dried Young's NMR tube at -78 °C and perform NMR acquisition at -78 °C. **xii)** NMR samples were warmed to ca. -20 °C -0 °C, ejected from the spectrometer and incubated at -78 °C in a dry ice-acetone bath, and excess water was added. The sample was quickly removed from the bath, shaken vigorously and a pinch of $NaHCO_3$ was added. The sample was then returned to the bath and incubated for 15 minutes before gradually warming to room temperature. The steps **xi)** and **xii)** could be performed without NMR analysis and the yields are 69% for **1.33** and 45% for **1.32**.

The spectroscopic data of the laurefurenynes E-F **1.32** and **1.33** synthesised by these two protocols were found to be identical and are in keeping with literature values aside from the specific rotation of laurefurenyne E **1.32**, in which our synthetic samples gave the opposite sign of optical rotation compared to the reported literature value (*see appendix 12.4*).[26] The (*R*)-Mosher esters **8.7** and **8.8** and (*S*)-Mosher esters **8.9** and **8.10** of laurefurenynes E-F were synthesised subsequently and analysed by the method of

Hoye and Kakisawa.[184,185] The results of the Mosher ester analyses are as shown below (**Figure 8.5-8.6**).

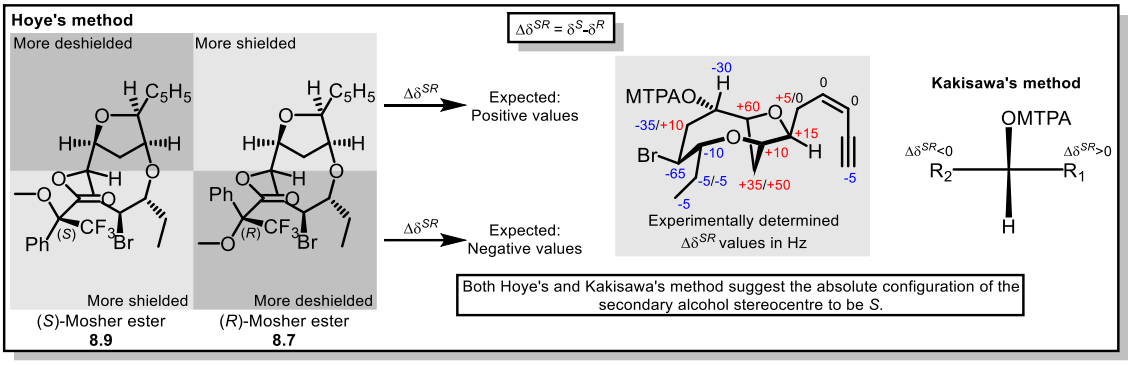


Figure 8.5. Results of Mosher ester analysis of **1.32**.

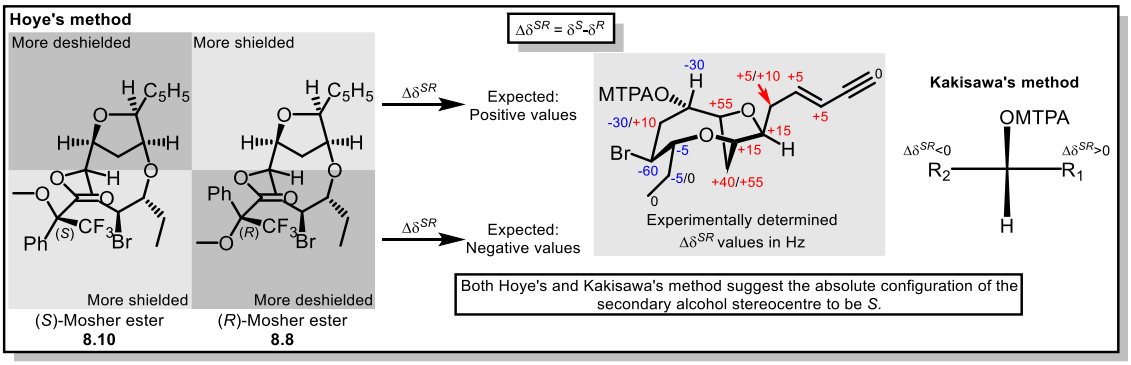


Figure 8.6. Results of Mosher ester analysis of **1.33**.

The Mosher ester analyses suggest the absolute configurations of the secondary alcohols at C-10 of laurefurenynes E-F **1.32** and **1.33** to be (*S*). Given that the absolute configurations of other stereogenic centers are known from the starting material diacetone-D-glucose **4.12** and by analogy with known natural products such as (*Z*/*E*)-bromofucins **1.8** and **1.11** and (*Z*/*E*)-chlorofucins **1.5** and **1.6**, the reassigned structures of laurefurenynes E-F **1.32** and **1.33** are therefore confirmed (**Figure 8.7**).

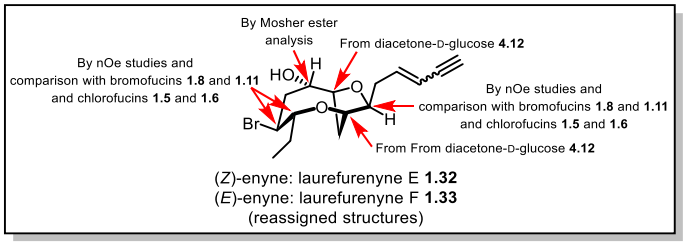


Figure 8.7. Confirmation of the reassignment of the structures of laurefurenynes E-F **1.32** and **1.33**.

8.3 Total synthesis and structural reassignment of laurefurenynes C-D

According to the biosynthetic hypothesis involving the oxonium ions **1.1** and **1.2** (**Figure 8.3**), S_N2 reaction by water at C-12 of the reassigned structures of laurefurenynes E-F **1.32** and **1.33** would yield the reassigned structures of laurefurenynes C-D **1.30** and **1.31** respectively. However, this S_N2 reaction was expected to be challenging because of the effectively neopentyl character of the substrate (**Figure 8.8**).

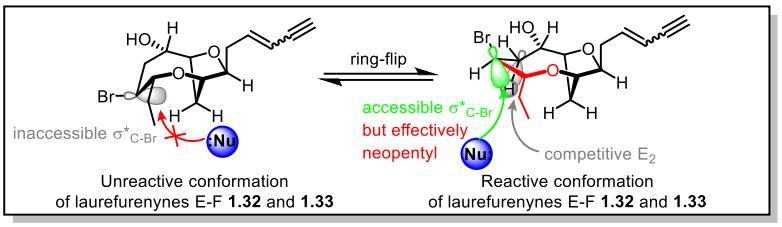
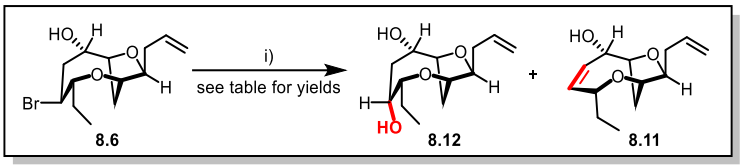


Figure 8.8. S_N2 reaction by a generic nucleophile at C-12 of laurefurenynes E-F **1.32** and **1.33**.

The core of the reassigned structures of laurefurenynes E-F **8.6** was subjected to a variety of oxygen nucleophiles under various reaction conditions that are reported to induce S_N2 reactions at neopentyl centres, but only one reaction condition returned promising results (**Table 8.1**).

The condition described in (**Table 8.1, Entry 1**) was tailored for the inversion of secondary tosylates on cyclic systems derived from steroids and prostaglandins.[272] This condition was also applied to the inversion of an acyclic secondary bromide with

β-oxygen substituents.[273] However, substrate **8.6** which possesses a secondary bromide on a cyclic system with β-oxygen substituents did not react under this condition. Further heating of the reaction mixture to 120 °C resulted in the generation of trace elimination product **8.11**.



Entry	Nucleophile	Equivalents	T/°C	Time/hrs	Additives	Results
1	$NaNO_2$	15	90	12	-	No reaction
2	$NaNO_2$	15	120	36	-	Trace **8.11** was observed
3	LiOAc	15	90	12.	-	No reaction
4	LiOAc	15	120	12	-	Limited conversion, messy crude ^{1}H NMR
5	CsOAc	15	90	36	-	**8.11** in **84%** yield
6	KNO_2	5	r.t.	12	cat. 18-crown-6	No reaction
7	KNO_2	5	90	12	cat. 18-crown-6	Limited conversion
8	KNO_2	5	120	12	cat. 18-crown-6	Decent conversion, messy crude ^{1}H NMR
9	CsTFA	5	120	12	-	**8.12** in **62%** yield, trace **8.11**

Table 8.1. Optimisation of the reaction conditions for the desired S_N2 reaction.
Reagents and conditions: **i)** Nucleophile (x equivalents), additives, DMF, T °C, time.

Standard S_N2 conditions were also attempted although they were not expected to be productive (**Table 8.1, Entries 3-5**). The relatively strongly ion paired LiOAc did not promote significant conversion. On the other hand, the relatively weakly ion paired CsOAc promoted E_2 elimination, generating **8.11** in 84% yield instead of the desired product **8.12**. These experiments suggested weak ion pairing is required for reactivity and the desired S_N2 reaction should be promoted over E_2 elimination with less basic nucleophiles.

Nitrite anion was therefore used again as it is less basic than acetate, and a methodology that employs cat. 18-crown-6 with KNO_2 was reported to invert neopentyl secondary triflates.[274] Unfortunately, such conditions did not promote the desired S_N2 reaction in our system. Another set of condition that employed cesium trifluoroacetate (CsTFA) as the nucleophile also met our criteria for promoting the desired S_N2 reaction.[275] This condition gave the best results and provided **8.12** in synthetically useful yields with only trace **8.11** observed. An X-ray crystal structure of **8.12** was obtained as a proof of its structure and absolute configuration (**Figure 8.9**).

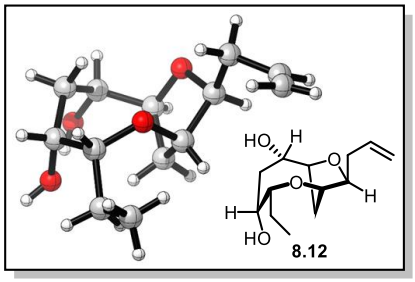
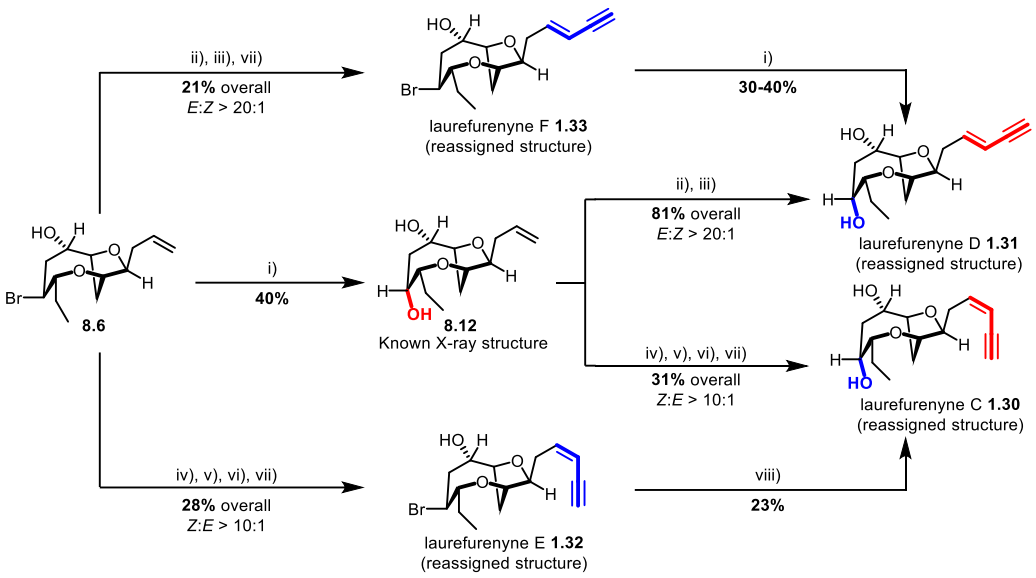


Figure 8.9. X-ray crystal structure of **8.12**.

The synthesis of laurefurenynes C-D **1.30** and **1.31** was then achieved *via* two separate protocols for their structural reassignments (**Scheme 8.2**). The first protocol involves the synthesis of laurefurenynes E-F **1.32** and **1.33** from **8.6** by (*Z*/*E*)-enyne synthesis, followed by an S_N2 reaction with CsTFA to provide laurefurenynes C-D **1.30** and **1.31**. The second protocol involves the generation of diol **8.12** from **8.6** followed by (*Z*/*E*)-enyne synthesis for the synthesis of laurefurenynes C-D **1.30** and **1.31**. The second protocol confirms reaction conditions of the (*Z*/*E*)-enyne syntheses would not alter the configurations of the substituents in diol **8.12**.



Scheme 8.2. Synthesis of laurefurenynes C-D **1.30** and **1.31** using two separate protocols. Reagents and conditions: **i)** CsTFA (5.0 eq.), DMF, 120 °C, 12 hrs. **ii)** crotonaldehyde (5.0 eq.), Grubb's 2nd generation catalyst (5.0 mol%), CuI (7.5 mol%) Et_2O, r.t., overnight. **iii)** $TMSCHN_2$ (1.3-1.5 eq., 2.0 M in Et_2O), *n*-BuLi (1.3-1.5 eq., 2.3 M in hexanes), THF, -78 °C, 1 hr, *then* 0 °C, 30 min, followed by workup using 1.0 M $HCl_{(aq)}$. **iv)** cat. OsO_4, $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), dioxane/H_2O (3:1), r.t., 1-2 hrs. **v)** $Ph_3PCH_2I_2$ (3.0 eq.), NaHMDS (3.0 eq., 1.0 M in THF), HMPA (6.0 eq.), THF, -78 °C, 30 min, then r.t., 1 hr. **vi)** TMS acetylene (5.0 eq.), CuI (1.0 eq.), $Pd(PPh_3)_4$ (15 mol %), Et_3N, r.t., 1 hr. **vii)** K_2CO_3 (10.0 eq.), MeOH, r.t., 1-2 hrs. **viii)** CsTFA (10.0 eq.), DMF, 120 °C, 12 hrs.

The spectroscopic data of the laurefurenynes C-D **1.30** and **1.31** synthesised using these two separate protocols are identical to each other and are in keeping with reported spectroscopic data in literature (*see appendix 12.4*).[26] An X-ray crystal structure of our synthetic natural product laurefurenyne D **1.31** was obtained as a proof of its structure and absolute configuration, which agree unambiguously with our proposed structural reassignment of this natural product (**Figure 8.10**).

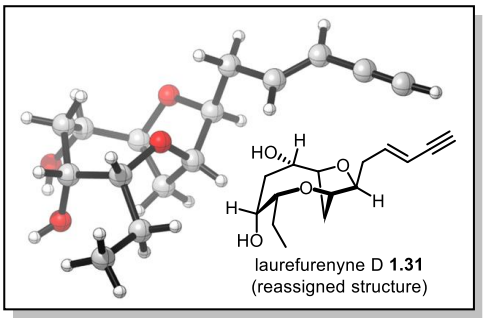
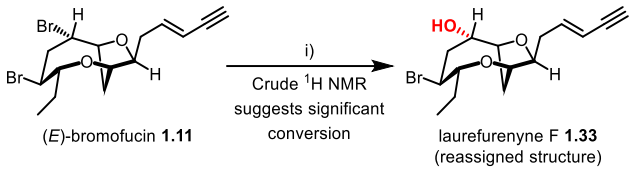


Figure 8.10. X-ray crystal structure of laurefurenyne D **1.31**.

The original structure of the natural product laurefurenyne C **1.24** was reassigned to **1.30** accordingly, as it is just the *Z*-enyne isomer of the natural product laurefurenyne D **1.31**.

The difficulty in performing the desired S_N2 reaction at C-12 of the reassigned structures of laurefurenynes E-F **1.32** and **1.33** raised the question whether laurefurenynes C-D **1.30** and **1.31** are biosynthesised *via* S_N2 reaction by water at C-12 of **1.32** and **1.33** as proposed (**Figure 8.3**). An experiment was performed to study the behaviour of the natural product (*E*)-bromofucin **1.11** under mimicked sea water conditions (**Scheme 8.3**). It was found that under such conditions, the natural product (*E*)-bromofucin **1.11** hydrolysed to the natural product laurefurenyne F **1.33** but not the natural product laurefurenyne D **1.31**.



Scheme 8.3. Conversion of **1.11** into **1.33** under mimicked sea water conditions.
Reagents and conditions: **i)** pH = 7.0 buffer/DMSO (10:1), 28 °C, 5 days.

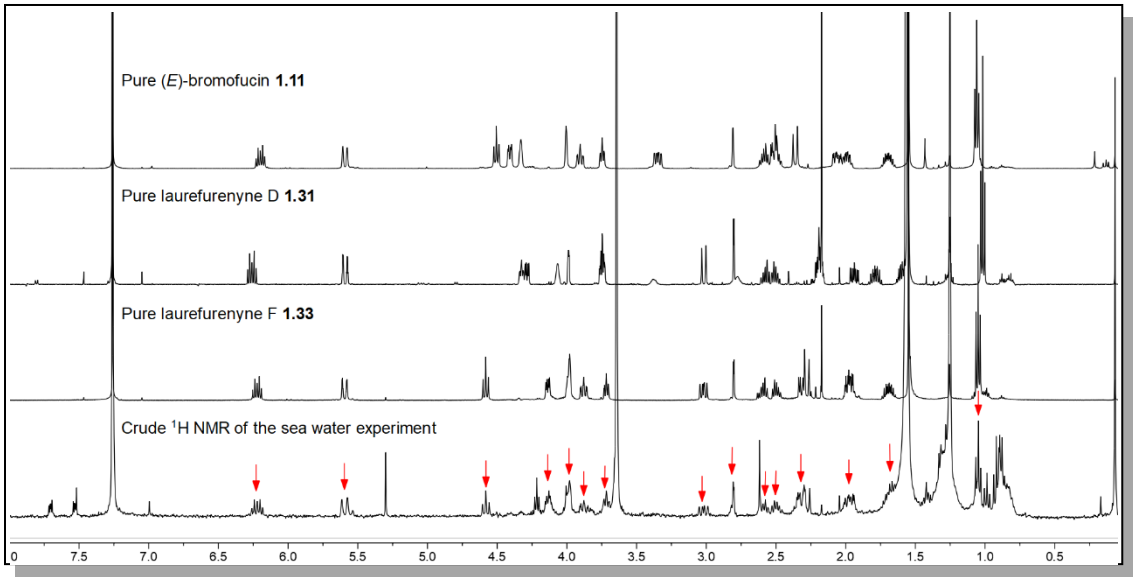


Figure 8.11. Crude ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the sea water experiment compared to the ^{1}H NMR spectrum of pure **1.11**, **1.31** and **1.33** (500 MHz, $CDCl_3$)

This result suggested that the natural products laurefurenynes E-F **1.32** and **1.33** may be hydrolysis products of the natural products (*Z*/*E*)-bromofucins **1.8** and **1.11** *via* the oxonium ions **1.1** and **1.2**, and the natural products laurefurenynes C-D **1.30** and **1.31** may not be biosynthesised *via* the proposed S_N2 reaction at C-12 due to its recalcitrant nature and the absence of such products from the "sea water" experiment. Nevertheless, the synthesis of laurefurenyne F **1.33** in this experiment suggested that oxonium ion intermediate **1.2** was generated and underwent nucleophilic opening at C-10 under buffered aqueous conditions. This provides supporting evidence that the oxonium ion chemistry as proposed in the biosynthesis of *Laurencia* natural products are indeed compatible with aqueous conditions and thus are highly likely to be biosynthetically relevant.

8.4 Conclusion

The first total synthesis of the natural products laurefurenynes C-F **1.30-1.33** and the reassignment of their structures by Mosher ester analyses and X-ray crystallography have been achieved. The direct generation of laurefurenynes E-F **1.32** and **1.33** from the oxonium ions **1.1** and **1.2** increased the number of natural products that could be generated directly from the oxonium ions from 10 out of 13 expected natural products to 12 out of 15 expected natural products.

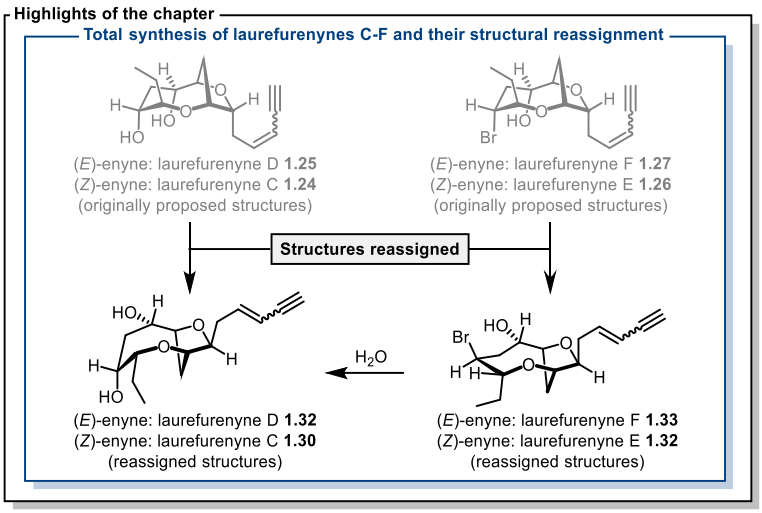


Figure 8.12. Highlights of Chapter 8.

9 Conclusions and future work

9.1 The existence of target oxonium ions

The successful synthesis of the target oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** with extensive spectroscopic analyses corroborated with DFT calculations have provided very strong experimental evidence to support their existence (**Chapter 5**).

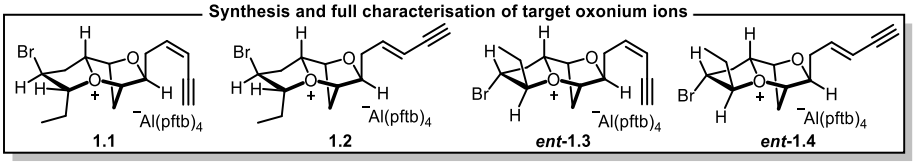


Figure 9.1. Structures of the oxonium ions.

9.2 Competency in the synthesis of natural products

The ability of the oxonium ions **1.1**, **1.2** and ***ent*-1.3**, ***ent*-1.4** to directly generate 12 out of 15 natural products is sufficient to prove their competency in the synthesis of natural products (**Chapter 6** & **8**).

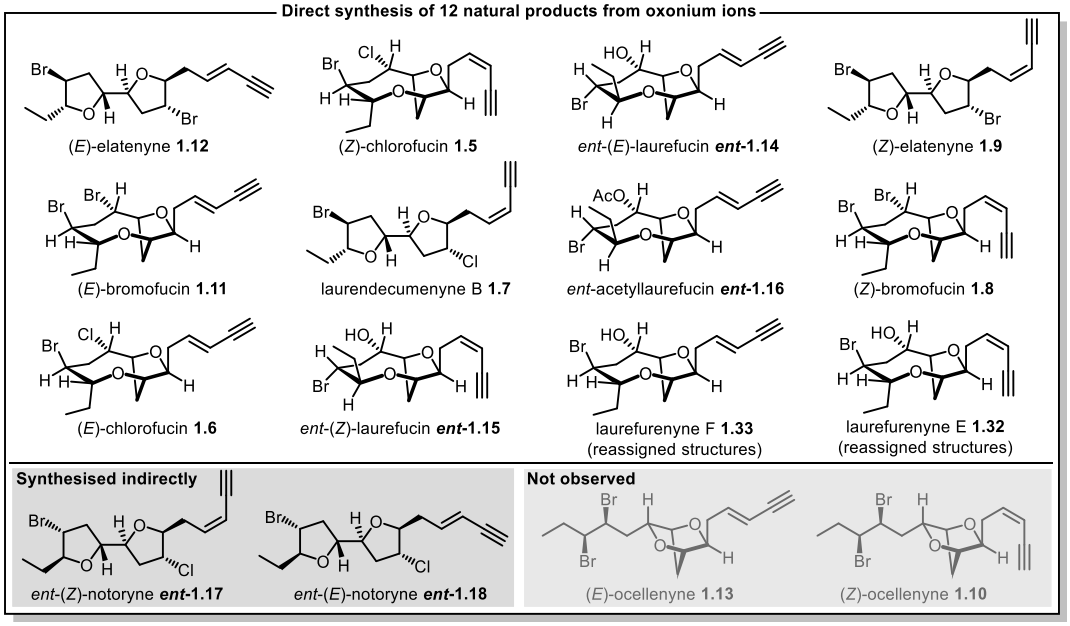


Figure 9.2. Structures of the natural products.

However, the remaining natural products that either had to be generated indirectly, like *ent*-(*Z*/*E*)-notoryne ***ent*-1.17** and ***ent*-1.18**, or were not observed at all, like (*Z*/*E*)-ocellenynes **1.10** and **1.13**, raised questions concerning the proposed biosynthesis, particularly whether the opening of the oxonium ions requires enzymatic intervention.

9.3 Novel retrobiosynthetic strategy for the total synthesis of *ent*-laurencin

The retrobiosynthetic strategy was developed successfully using the Kishner-Leonard elimination to generate *ent*-deacetyllaurencin ***ent*-1.38** and *ent*-laurencin ***ent*-1.39**.

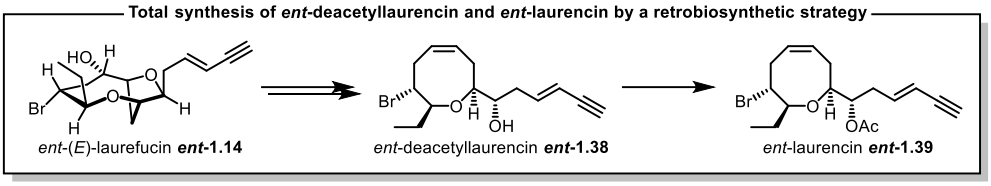


Figure 9.3. Retrobiosynthetic strategy leading to the synthesis of ***ent*-1.38** and ***ent*-1.39**.

9.4 First total synthesis and structural reassignment of laurefurenynes C-F

The total synthesis of laurefurenynes C-F **1.30-1.33** were successful and their structural reassignments were completed using Mosher ester analysis and X-ray crystallography.

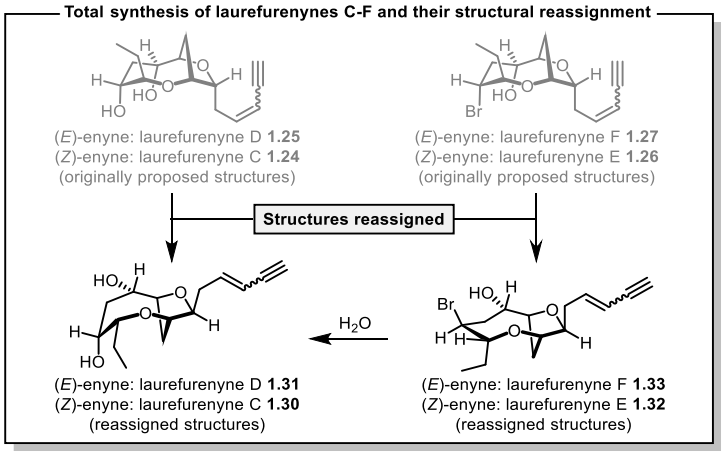


Figure 9.4. Structures of the original and reassigned structures of laurefurenynes C-F.

However, the conversion of laurefurenynes E-F **1.32** and **1.33** into laurefurenynes C-D **1.30** and **1.31** *via* the proposed S_N2 reaction by water at C-12 proved to be a recalcitrant process that requireed the use of harsh reaction conditions. This raised questions concerning their proposed biosynthesis, particularly how the C-12 hydroxyl is installed by biology. Moreover, the direct conversion of laurefurenynes C-D **1.30** and **1.31** into laurefurenynes A-B **1.28** and **1.29** or the conversion of laurefurenynes E-F **1.32** and **1.33** into the precursors of laurefurenynes A-B **1.20** and **1.21** have not been tested. The testing of these transformations would certainly further shed light on the biosynthesis of laurefurenynes A-B **1.28** and **1.29**.

10 Experimental

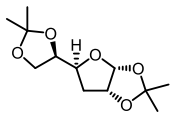
General Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 500 (500/125 MHz) and Bruker AV 400 (400/100 MHz) spectrometer. Proton and carbon chemical shifts are quoted in ppm and referenced to residual protonated solvent. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (double doublet) and so on. Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.1 Hz. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ES). High resolution mass spectra were recorded by the mass spectrometry staff at the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (ES) or a Micromass GCT (FI). *m/z* values are reported in Daltons. High resolution values are calculated to five decimal places from the molecular formula, all found values being within a tolerance of 5.0 ppm. Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer using diamond ATR. Absorption maxima (ν_{max}) are described as strong, medium, weak and broad and are quoted in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 241 polarimeter in a cell of 1.0 dm path length (l). TLC was performed on Merck DC-Alufolien 60 F254 0.2 mm precoated plates and visualised using an acidic vanillin or basic potassium permanganate dip. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography was performed on Merck 60 silica (particle size 40– 63 µm, pore diameter 60 Å) and the solvent system used is recorded in parentheses. All non-aqueous reactions were carried out in flame-dried glassware under an inert atmosphere of argon or nitrogen and employing standard techniques for handling air-sensitive materials. Solvents and commercially available reagents were dried and purified before use, as appropriate. Compounds were named using ChemDraw and the assignments of NMR spectra were done on MestReNova.

10.1 Experimental for Chapter 4

Syntheses of known compounds:

(3a*R*,5*S*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro [2,3-*d*][1,3]dioxole 4.11

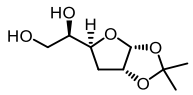


Step 1. *According to the procedures of Roth*[276]: Commercially available diacetone-D-glucose **4.12** (10.0 g, 38.4 mmol) was dissolved in dry THF (150.0 mL) at room temperature, then imidazole (10.0 mg, 0.14 mmol) was added. NaH (2.0 g, 50.0 mmol, 60% suspension in mineral oil) was then added in several portions to the solution and stirring was continued at room temperature for 20 minutes. CS_2 (6.9 mL, 115.0 mmol) was then added to the reaction mixture and stirring was continued for 30 minutes at room temperature, the colour of the reaction mixture darkens to pale reddish-brown after complete addition of CS_2. CH_3I (4.3 mL, 69.1 mmol) was added in one quick injection to the reaction mixture and stirring was continued for 15 minutes at room temperature. TLC analysis at this stage confirmed the complete consumption of starting material. The reaction mixture was quenched with glacial acetic acid (2.0 mL), filtered through a short plug of Celite™, and the residue was washed with isopropanol. The filtrated was concentrated under reduced pressure to give a viscous yellow liquid, then triturated with diethyl ether and filtered. The clear yellow filtrate was then washed with sat. aq. $NaHCO_3$ solution and water three times each, the organic layer was separated and dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a clear viscous yellow oil. The oil then underwent purification by flash column chromatography (20% EA/Pet. Ether 40-60) to give the corresponding xanthate as a clear yellow oil (13.0 g, 37.5 mmol, 97%). R_f = 0.83 (20% EA/Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (t, *J* = 3.2 Hz, 1H), 4.67 (d, *J* = 3.8 Hz, 1H), 4.39 – 4.24 (m, 1H), 4.14 – 4.00 (m, 2H), 2.59 (s, 3H), 1.54 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H). LRMS (ESI) [M+Na$^+$] : *m/z* 373.0. $[\alpha]_D^{25} = -22.4$ (c=0.5, $CHCl_3$). Literature value: $[\alpha]_D^{22} = -23.6$ (c=8.1, $CHCl_3$) .[277] Spectroscopic data are in accordance with literature data.[276,277]

Step 2. *According to the modified procedures of Roth*[276]: A portion of the xanthate (6.45 g, 18.4 mmol) was dissolved in dry toluene (113.0 mL), then Bu_3SnH (8.0 mL, 29.8 mmol) was added to the solution. The reaction mixture was degassed with argon for 30 minutes. Afterwards, the reaction mixture was brought to reflux at 110 °C overnight. TLC analysis was performed at this stage to confirm the completion consumption of starting material. The reaction mixture was then cooled to room temperature and all the

volatiles were evaporated under reduced pressure. The residue was redissolved in ethyl acetate (100.0 mL) and mixed with a sat. aq. KF solution (100.0 mL). The biphasic mixture was stirred vigorously for 1 hour and then filtered through a short plug of Celite™. The organic phase was separated after filtration, dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a colourless oil. The clear oil then underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60 then 10% EA/Pet. Ether 40-60) to give the desired compound **4.11** as a colourless oil (3.24 g, 13.2 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.79 (m, 1H), 4.75 (t, *J* = 4.0 Hz, 1H), 4.19 – 4.05 (m, 3H), 3.87 – 3.76 (m, 1H), 2.18 (dd, *J* = 13.4, 4.0 Hz, 1H), 1.77 (dddd, *J* = 13.5, 10.1, 4.7, 1.2 Hz, 1H), 1.51 (s, 3H), 1.42 (s, 4H), 1.35 (s, 4H), 1.31 (s, 4H). LRMS (ESI [M+H$^+$] : *m/z* 245.0. $[\alpha]_D^{25} = -6.0$ (c=0.5, $CHCl_3$). Literature value: $[\alpha]_D^{22} = -7.6$ (c=0.18, $CHCl_3$) .[277] Spectroscopic data are in accordance with literature data.[276,277]

(*R*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol 4.10

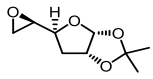


Step 1. *According to the modified procedures of Gruner*[278]: Commercially available diacetone-D-glucose **4.12** (10.0 g, 38.4 mmol) was dissolved in dry CH_2Cl_2 (51.0 mL) and the reaction mixture was cooled to 0 °C. Dry pyridine (6.8 mL, 84.1 mmol) was added followed by the slow addition of triflic anhydride (7.8 mL, 46.3 mmol). The reaction mixture was then stirred at 0 °C for 1 hour. TLC analysis at this stage indicated completion of reaction. The reaction mixture was quenched by the addition of ice water. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated to give the crude triflate as a flaky pale brown solid. The crude triflate was put under high vacuum to remove residual pyridine and was carried forward to the next step.

Step 2. *According to the procedures of Sato*[182]: The crude triflate was dissolved in dry toluene (380.0 mL) and tetrabutylammonium borohydride (*prepared according to the procedures of Brändström*[183]) (29.6 g, 115.2 mmol) was added to the reaction mixture. The reaction mixture was then heated to 80 °C and stirred overnight. TLC analysis at this stage indicated completion of reaction. The reaction mixture was cooled to r.t. and quenched with deionised water. The aqueous layer was then extracted with toluene, the organic layers combined, dried with anhydrous $MgSO_4$ and concentrated to give the crude deoxysugar **4.11**. The crude deoxysugar **4.11** was put under high vacuum to remove residual toluene and was carried forward to the next step.

Step 3. The crude deoxysugar **4.11** was mixed with 75% AcOH in water (112.3 mL glacial acetic acid mixed with 36.1 mL deionised water) and stirred overnight. TLC analysis at this stage indicated completion of reaction. The solvent was removed by azeotropic distillation with toluene to give crude **4.10**. Crude **4.10** then underwent purification by flash column chromatography (50% Acetone/Pet. Ether 40-60) to give **4.10** (6.6 g, 32.3 mmol, 84%) as a colourless oil that solidifies upon prolonged standing. R_f = 0.41 (100% EA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (d, *J* = 3.6 Hz, 1H), 4.76 (t, *J* = 4.2 Hz, 1H), 4.23 (dt, *J* = 10.8, 4.4 Hz, 1H), 3.94 (dq, *J* = 7.8, 3.9 Hz, 1H), 3.72 (ddd, *J* = 10.6, 6.7, 3.6 Hz, 1H), 3.60 (ddd, *J* = 11.1, 6.5, 4.3 Hz, 1H), 2.41 (d, *J* = 4.0 Hz, 1H), 2.14 – 1.98 (m, 2H), 1.85 (ddd, *J* = 13.5, 10.8, 4.8 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H). LRMS (ESI) $[M+Na]^+$: *m/z* 227.1. Melting point: 76-78 °C (lit. 76-78 °C)[279]. $[\alpha]_D^{25} = -8.3$ (c=0.3, $CHCl_3$) . lit. $[\alpha]_D^{21} = -18.0$ (c=1.0, $CHCl_3$) [279]. Spectroscopic and physical data are in accordance with literature data.[279]

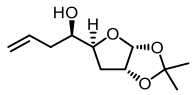
(3a*R*,5*S*,6a*R*)-2,2-Dimethyl-5-((*R*)-oxiran-2-yl)tetrahydrofuro[2,3-*d*][1,3]dioxole 4.9



According to the modified procedures of Hanaya[280]: Compound **4.10** (6.4 g, 31.3 mmol) was mixed with triphenylphosphine (9.9 g, 37.7 mmol) in toluene (200.0 mL). Diethyl azodicarboxylate (5.9 mL, 37.7 mmol) was added to the reaction mixture. The reaction mixture was then heated at 110 °C overnight. All the volatiles were removed under reduced pressure to yield a syrup. The syrup was diluted with diethyl ether (5.0-10.0 mL) and sonicated. The sonication brought about the precipitation of the triphenylphosphine oxide by-product. The mixture was then filtered, the solids were washed with cold diethyl ether and the filtrate was concentrated and underwent purification by flash column chromatography (20% EA/Pet. Ether 40-60) to give the desired compound **4.9** as a colourless oil (4.2 g, 22.5 mmol, 71%). R_f = 0.54 (30% EA/Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, *J* = 3.6 Hz, 1H), 4.74 (dd, *J* = 4.7, 3.8 Hz, 1H), 4.20 (dt, *J* = 10.7, 4.4 Hz, 1H), 3.14 (td, *J* = 4.2, 2.7 Hz, 1H), 2.82 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.60 (dd, *J* = 4.9, 2.6 Hz, 1H), 2.06 (dd, *J* = 13.3, 4.5 Hz, 1H), 1.71 (ddd, *J* = 13.2, 10.6, 4.8 Hz, 1H), 1.49 (s, 3H), 1.31 (s, 3H). LRMS (ESI) $[M+Na^+]$: 209.0. $[\alpha]_D^{25} = -22.2$ (c=1.0, $CHCl_3$) . lit. $[\alpha]_D^{20} = -18.0$ (c=0.1, $CHCl_3$)[281]. Spectroscopic data are in accordance with literature data.[281]

Syntheses of novel compounds:

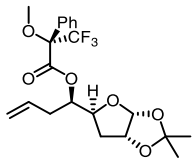
(*R*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-3-en-1-ol 4.8



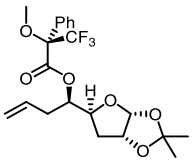
CuI (431.0 mg, 2.3 mmol) was dried under high vacuum, then dry THF (70.0 mL) was added and the reaction mixture was cooled to -20 °C. Vinylmagnesium bromide (1.0 M in THF, 44.0 mL, 44.0 mmol) was then added. Compound **4.9** (4.2 g, 22.5 mmol) was dissolved in dry THF (10.0 mL) and added dropwise. The reaction mixture was stirred at -20 °C for 1 hour, a TLC analysis was performed at this stage to confirm the completion of reaction. The reaction mixture was quenched at -20 °C with sat. aq. NH_4Cl and followed by extraction with ethyl acetate. The organic layer was separated, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a pale yellow oil. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60) to give the desired compound **4.8** (4.2 g, 19.6 mmol, 87%) as a colourless oil. R_f = 0.54 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.78 (m, 2H, CH_2=C**H**CH_2CHOH, C**H**CHCH'HCH), 5.17 – 5.08 (m, 2H, C**H**$_2$=CHCH$_2$CHOH), 4.74 (t, *J* = 4.2 Hz, CHC**H**CH'HCH), 4.20 (dt, *J* = 10.7, 4.1 Hz, CHCHCH'HC**H**), 3.96 (ddd, *J* = 8.6, 5.4, 3.5 Hz, CH_2=CHCH$_2$C**H**OH), 2.26 – 2.13 (m, 2H, CH_2=CHC**H**$_2$CHOH), 1.97 (m, 2H, CH_2=CHCH$_2$CHO**H**, CHCHC**H'**HCH), 1.88 (ddd, *J* = 13.4, 10.6, 4.7 Hz, 1H, CHCHCH'**H**CH), 1.50 (s, 3H, C**H**$_3$CCH$_3$), 1.32 (s, 3H, CH$_3$CC**H**$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2 (CH_2=**C**HCH$_2$CHOH), 118.0 (**C**H$_2$=CHCH$_2$CHOH), 111.4 (CH$_3$**C**CH$_3$), 105.4 (**C**HCHCH'HCH), 80.7 (CH**C**HCH'HCH), 80.6 (CHCHCH'H**C**H), 70.0 (CH_2=CHCH$_2$**C**HOH), 37.5 (CH_2=CH**C**H$_2$CHOH), 31.8 (CHCH**C**H'HCH), 26.9 (**C**H$_3$CCH$_3$), 26.3 (CH$_3$C**C**H$_3$). IR (ν_{max} cm^{-1}): 3476 (O–H stretching, broad), 3077 (alkene sp^2 C–H stretching, weak), 2985-2912 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, weak), 1163 & 1017 (C–O stretching, strong), 915 (vinyl CH=CH$_2$ out of plane wag, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 237.2. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 237.10973, found *m/z* 237.10988 ($C_{11}H_{18}O_4Na$). $[\alpha]_D^{25} = -12.6$ (c=0.5, $CHCl_3$). The absolute configuration of the secondary alcohol in **4.8** was determined by Mosher ester analysis according to the method of Kakisawa/Hoye[184,185]:

Preparation of *S*- and *R*-MTPA esters of **4.8**:

(*R*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-3-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 4.33 and (*R*)-1-((3a*R*,5*S*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-3-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 4.32

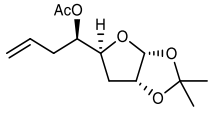


S-MTPA ester **4.33**



R-MTPA ester **4.32**

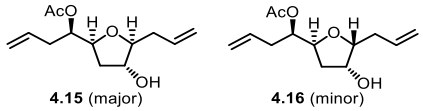
According to the procedures of Hoye[184]: Compound **4.8** (10.0 mg, 47.0 μmol) was transferred to a flame-dried vial. *S*-Mosher acid (34.0 mg, 0.15 mmol) was added followed by dry CH_2Cl_2 (0.7 mL). *N*,*N'*-Dicyclohexylcarbodiimide (30.0 mg, 0.15 mmol) was then added followed by DMAP (8.0 mg, 0.15 mmol). The reaction mixture was stirred overnight at room temperature. TLC analysis at this stage indicated completion of reaction. The reaction mixture was filtered through a short plug of silica gel, the filtrated concentrated and underwent purification by flash column chromatography (10% EA/Pet. Ether 40-60) to give the *S*-MTPA ester **4.33** as a colourless oil (16.8 mg, 37.3 μmol, 79%). R_f = 0.77 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.47 (m, 2H, Ar**H**), 7.47 – 7.31 (m, 3H, Ar**H**), 5.78 (dddd, *J* = 16.7, 10.2, 7.7, 6.3 Hz, 1H, CH_2=C**H**CH_2CHOMTPA), 5.55 (d, *J* = 3.5 Hz, 1H, CHCH'HCHC**H**), 5.49 (dt, *J* = 8.7, 4.6 Hz, 1H, CH_2=CHCH_2C**H**OMTPA), 5.29 – 4.98 (m, 2H, C**H**$_2$=CHCH_2CHOMTPA), 4.57 (t, *J* = 4.2 Hz, 1H, CHCH'HC**H**CH), 4.28 (dt, *J* = 10.7, 4.4 Hz, 1H, C**H**CH'HCHCH), 3.55 (s, 3H, MTPA OC**H**$_3$), 2.53 – 2.28 (m, 2H, CH_2=CHC**H**$_2$CHOMTPA), 1.93 (dd, *J* = 13.3, 4.7 Hz, 1H, CHC**H'**HCHCH), 1.64 (ddd, *J* = 13.3, 10.6, 4.8 Hz, 1H, CHCH'**H**CHCH), 1.47 (s, 3H, C**H**$_3$CCH_3), 1.28 (s, 3H, CH_3CC**H**$_3$). In an entirely analogous fashion, the *R*-MTPA ester **4.32** was prepared from *R*-Mosher acid (17.4 mg, 38.7 μmol, 82%). R_f = 0.77 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.49 (m, 2H, Ar**H**), 7.47 – 7.33 (m, 3H, Ar**H**), 5.80 – 5.58 (m, 2H, CHCH'HCHC**H**, CH_2=C**H**CH_2CHOMTPA), 5.47 (td, *J* = 6.6, 3.6 Hz, 1H, CH_2=CHCH_2C**H**OMTPA), 5.18 – 4.96 (m, 2H, C**H**$_2$=CHCH_2CHOMTPA), 4.67 (t, *J* = 4.1 Hz, 1H, CHCH'HC**H**CH), 4.35 (ddd, *J* = 10.7, 4.6, 3.5 Hz, 1H, C**H**CH'HCHCH), 3.51 (s, 3H, MTPA OC**H**$_3$), 2.38 (tq, *J* = 7.2, 1.3 Hz, 2H, CH_2=CHC**H**$_2$CHOMTPA), 2.04 (dd, *J* = 13.3, 4.6 Hz, 1H, CHC**H'**HCHCH), 1.79 (ddd, *J* = 13.3, 10.7, 4.8 Hz, 1H, CHCH'**H**CHCH), 1.50 (s, 3H, C**H**$_3$CCH_3), 1.31 (s, 3H, CH_3CC**H**$_3$).



(*R*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-3-en-1-yl acetate 4.14

Compound **4.8** (4.0 g, 18.7 mmol) was mixed with DMAP (7.1 g, 58.1 mmol) in dry CH_2Cl_2 (125.0 mL) at room temperature. Acetic anhydride (5.5 mL, 58.1 mmol) was added subsequently. The reaction mixture was stirred at room temperature for 2 hours. TLC analysis was performed at this stage to confirm the completion of reaction. The reaction was quenched with sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated and dried with anhydrous $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (15% EA/Pet. Ether 40-60) to give the desired compound **4.14** as a colourless oil (4.3 g, 16.8 mmol, 90%). R_f = 0.63 (20% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, *J* = 3.6 Hz, 1H, C**H**CHCH'HCH), 5.74 (dt, *J* = 10.2, 7.4, 6.7 Hz, 1H, CH_2=C**H**CH'HCHOAc), 5.14 – 5.03 (m, 3H, CH_2=CHCH'HC**H**OAc, C**H**$_2$=CHCH'HCHOAc), 4.71 (dd, *J* = 4.7, 3.8 Hz, 1H, CHC**H**CH'HCH), 4.24 (dt, *J* = 10.2, 4.9 Hz, 1H, CHCHCH'HC**H**), 2.42 (dddt, *J* = 14.2, 6.2, 4.7, 1.4 Hz, 1H, CH_2=CHC**H'**HCHOAc), 2.33 (dtt, *J* = 14.5, 7.7, 1.2 Hz, 1H, CH_2=CHCH'**H**CHOAc), 2.07 (dd, *J* = 13.3, 4.5 Hz, 1H, CHCHC**H'**HCH), 2.04 (s, 3H, OAc C**H**$_3$), 1.75 (ddd, *J* = 13.4, 10.7, 4.8 Hz, 1H, CHCHCH'**H**CH), 1.50 (s, 3H, C**H**$_3$CCH$_3$), 1.31 (s, 3H, CH$_3$CC**H**$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4 (OAc **C**=O), 133.3 (CH_2=**C**HCH'HCHOAc), 118.1 (**C**H_2=CHCH'HCHOAc), 111.4 (CH$_3$**C**CH$_3$), 105.6 (**C**HCHCH'HCH), 80.3 (CH**C**HCH'HCH), 78.5 (CHCHCH'H**C**H), 72.9 (CH_2=CHCH'H**C**HOAc), 35.9 (CH_2=CH**C**H'HCHOAc), 34.8 (CHCH**C**H'HCH), 26.9 (**C**H$_3$CCH$_3$), 26.3 (CH$_3$C**C**H$_3$), 21.2 (OAc **C**H$_3$). IR (ν_{max} cm^{-1}): 3080 (alkene sp^2 C–H stretching, weak), 2986-2938 (alkane sp^3 C–H stretching, broad), 1740 (ester C=O stretching, strong), 1643 & 1435 (alkene C=C stretching, weak), 1231 (C–O stretching, strong), 939 (vinyl CH=CH_2 out of plane wag, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 279.2. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 257.13835, found *m/z* 257.13864 ($C_{13}H_{21}O_5$). $[\alpha]_D^{25} = -6.0$ (c=0.20, $CHCl_3$).

(*R*)-1-((2*S*,4*R*,5*S*)-5-Allyl-4-hydroxytetrahydrofuran-2-yl)but-3-en-1-yl acetate 4.15 and (*R*)-1-((2*S*,4*R*,5*R*)-5-allyl-4-hydroxytetrahydrofuran-2-yl)but-3-en-1-yl acetate 4.16

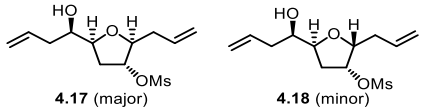


4.15 (major) **4.16** (minor)

The compound **4.14** (0.6 g, 2.3 mmol) was dissolved in dry CH_2Cl_2 (39.0 mL) and the reaction mixture was cooled to 0 °C. Allyltrimethylsilane (1.8 mL, 11.6 mmol) was added to the reaction mixture and stirring was continued for 15 minutes at 0 °C. $BF_3{\cdot}Et_2O$ (0.9 mL, 7.0 mmol) was added at 0 °C and the reaction was warmed to room temperature afterwards and stirred overnight. TLC analysis was performed at this stage to confirm the complete consumption of starting materials. The reaction was quenched by sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated and dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (15% EA/Pet. Ether 40-60) for the isolation of **4.15** (0.14 g, 0.58 mmol, 25%) and a mixture of **4.15** and **4.16** (0.29 g, 1.21 mmol, 53%) (**4.16** was not characterised at this stage as it could not be separated from **4.15**) both as colourless oils (0.43 g, 1.79 mmol, 78% for 2 steps in total, d.r. (**4.15**:**4.16**) = 3:1). R_f for **4.15** = 0.37 (20% EA/Pet. Ether 40-60); R_f for **4.16** = 0.46 (20% EA/Pet. Ether 40-60). Characterisation for **4.15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.69 (m, 2H, $CH_2C\mathbf{H}CH'HCHOAc$, $OCHCH_2C\mathbf{H}CH_2$), 5.14 – 5.01 (m, 5H, $CH_2CHCH'HC\mathbf{H}OAc$, $C\mathbf{H}_2CHCH'HCHOAc$, $OCHCH_2CHC\mathbf{H}_2$), 4.19 (ddd, *J* = 9.1, 6.3, 4.9 Hz, 1H, $C\mathbf{H}CH'HCHOH$), 4.11 (dt, *J* = 6.1, 3.0 Hz, 1H, $CHCH'HC\mathbf{H}OH$), 3.81 (td, *J* = 6.5, 3.1 Hz, 1H, $OC\mathbf{H}CH_2CHCH_2$), 2.38 (dddt, *J* = 14.4, 6.4, 4.9, 1.4 Hz, 1H, $CH_2CHC\mathbf{H'}HCHOAc$), 2.30 (m, 2H, $OCHC\mathbf{H}_2CHCH_2$), 2.21 (dddt, *J* = 14.2, 9.7, 6.9, 1.3 Hz, 1H, $CH_2CHCH'\mathbf{H}CHOAc$), 2.04 (s, 3H, OAc $C\mathbf{H}_3$), 2.00 (ddd, *J* = 13.2, 9.1, 6.2 Hz, 1H, $CHC\mathbf{H'}HCHOH$), 1.87 (ddd, *J* = 13.1, 6.3, 2.9 Hz, 1H, $CHCH'\mathbf{H}CHOH$), 1.74 (s, 1H, $CHCH'HCHO\mathbf{H}$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (OAc **C**=O), 134.1 ($CH_2\mathbf{C}HCH'HCHOAc$), 133.5 ($OCHCH_2\mathbf{C}HCH_2$), 118.0 ($\mathbf{C}H_2CHCH'HCHOAc$), 117.8 ($OCHCH_2CH\mathbf{C}H_2$), 85.9 ($O\mathbf{C}HCH_2CHCH_2$), 78.6 ($\mathbf{C}HCH'HCHOH$), 75.2 ($CHCH'H\mathbf{C}HOH$), 73.7 ($CH_2CHCH'H\mathbf{C}HOAc$), 38.6 ($OCH\mathbf{C}H_2CHCH_2$), 36.0 ($CH\mathbf{C}H'HCHOH$), 35.7 ($CH_2CH\mathbf{C}H'HCHOAc$), 21.3 (OAc $\mathbf{C}H_3$). IR (ν_{max} cm^{-1}): 3420 (O–H stretching, broad), 3078 (alkene sp^2 stretching, weak), 2980-2910 (alkane sp^3 C–H stretchings, broad), 1740 (ester C=O stretching, strong), 1643 (alkene C=C stretching, medium), 1235 & 1026 (C–O stretchings, strong), 915 (vinyl CH_2 out of plane wag, strong). LRMS (ESI) [M+Na+]: *m/z* 263.0. HRMS (ESI) [M+Na$^+$]: calculated for *m/z*

263.12538, found *m/z* 263.12537 ($C_{13}H_{20}O_4Na$). $[\alpha]_D^{25} = -10.0$ (c=0.20, $CHCl_3$)

(2*S*,3*R*,5*S*)-2-Allyl-5-((*R*)-1-hydroxybut-3-en-1-yl)tetrahydrofuran-3-yl methanesulfonate 4.17 and (2*R*,3*R*,5*S*)-2-allyl-5-((*R*)-1-hydroxybut-3-en-1-yl)tetrahydrofuran-3-yl methanesulfonate 4.18

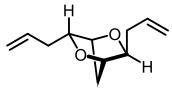


A mixture of **4.15** and **4.16** (0.29 g, 1.21 mmol) was dissolved in dry CH_2Cl_2 (4.7 mL) and the reaction mixture was cooled to 0 °C. Et_3N (0.85 mL, 1.33 mmol) was then added followed by MsCl (0.10 mL, 1.33 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirring was continued for 30 minutes. TLC analysis was performed at this stage to confirm the complete consumption of starting materials. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2, the organic layer was separated and dried with anhydrous $MgSO_4$. The residue was purified by column chromatography (10% EA/Pet. Ether 40-60) to give an inseparable mixture of the mesylated acetates (0.27g, 0.85 mmol, 70%). The two components in the mixture were not isolated and characterised but ^{1}H NMR and LRMS of the mixture were obtained to confirm the existence of the mesylated acetates. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.65 (m, 3H), 5.22 – 5.00 (m, 10H), 4.92 (dt, *J* = 6.0, 2.3 Hz, 1H), 4.30 (dt, *J* = 9.2, 6.2 Hz, 1H), 4.18 (dt, *J* = 10.4, 5.4 Hz, 1H), 4.11 (td, *J* = 6.3, 2.5 Hz, 1H), 4.00 (td, *J* = 7.0, 3.0 Hz, 1H), 3.05 (s, 3H), 3.03 (s, 3H), 2.52 – 2.26 (m, 8H), 2.25 – 2.06 (m, 3H), 2.05 (s, 3H), 2.04 (s, 3H). LRMS (ESI) [M+Na^+] : *m/z* 341.1.

The mesylated acetates (0.27 g, 0.85 mmol) were dissolved in MeOH (4.2 mL). K_2CO_3 (0.23 g, 1.68 mmol) was dissolved in H_2O (0.84 mL) and was added to the solution of the mesylated acetates. The reaction mixture was stirred at room temperature for 36 hours. TLC analysis was performed at this stage to confirm the complete consumption of starting materials. All volatiles were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 and extracted with water. The organic layer was separated and dried with $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography (20% EA/Pet. Ether 40-60 then 30% EA/Pet. Ether 40-60) to achieve the separation and isolation of **4.17** (0.11 g, 0.40 mmol, 47%) and **4.18** (81.0 mg, 0.30 mol, 35%) respectively as colourless oils (0.19 g, 0.70 mmol, 82% in total). Characterisation of **4.17**: R_f = 0.47 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.72 (m, 2H, $CH_2C\mathbf{H}CH_2CHOH$, $OCHCH_2C\mathbf{H}CH_2$), 5.21 – 5.07 (m, 4H, $C\mathbf{H}_2CHCH_2CHOH$, $OCHCH_2CHC\mathbf{H}_2$), 4.94 (dt, *J* = 6.1, 2.1 Hz, 1H, CHCH'HC**H**OMs), 4.16 (td, *J* = 6.4, 2.5 Hz, 1H, $OC\mathbf{H}CH_2CHCH_2$), 4.10 (ddd, *J* = 10.1, 5.4, 3.5 Hz, 1H, C**H**CH'HCHOMs), 3.90 (td, *J* = 6.7, 3.5 Hz, 1H,

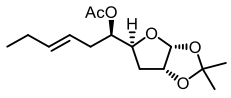
$CH_2CHCH_2C\mathbf{H}OH$), 3.03 (s, 3H, OMs $C\mathbf{H}_3$), 2.38 – 2.33 (m, 2H, $OCHC\mathbf{H}_2CHCH_2$), 2.26 – 2.16 (m, 3H, $CHC\mathbf{H}$'HCHOMs, $CH_2CHC\mathbf{H}_2CHOH$), 2.09 (ddd, *J* = 14.1, 5.6, 1.8 Hz, 1H, CHCH'**H**CHOMs), 1.87 (s, 1H, $CH_2CHCH_2CHO\mathbf{H}$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.1 ($CH_2\mathbf{C}HCH_2CHOH$), 133.1 ($OCHCH_2\mathbf{C}HCH_2$), 118.9 ($\mathbf{C}H_2CHCH_2CHOH$), 118.1 ($OCHCH_2CH\mathbf{C}H_2$), 83.8 (CHCH'H**C**HOMs), 83.1 ($O\mathbf{C}HCH_2CHCH_2$), 81.1 (**C**HCH'HCHOMs), 70.3 ($CH_2CHCH_2\mathbf{C}HOH$), 38.8 (OMs $\mathbf{C}H_3$), 37.9 ($CH_2CH\mathbf{C}H_2CHOH$), 37.4 ($OCH\mathbf{C}H_2CHCH_2$), 31.8 (CH**C**H'HCHOMs). IR (ν_{max} cm^{-1}): 3541 (O–H stretching, broad), 3078 (alkene sp^2 C–H stretching, weak), 2979-2907 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, weak), 1334 (sulfone antisymmetric stretching, strong), 1170 (sulfone symmetric stretching, strong), 1072 (C–O stretching, strong), 901 (vinyl CH_2 out of plane wagging, strong). LRMS (ESI) [M+Na^+]: *m/z* 299.0. HRMS (ESI) [M+Na^+]: calculated for *m/z* 299.09237, found *m/z* 299.09232 ($C_{12}H_{20}O_5Na^{32}S$). $[\alpha]_D^{25} = -21.0$ (c=0.20, $CHCl_3$) . Characterisation of **4.18**: R_f = 0.34 (30% EA/ Pet.Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.74 (m, 2H, $CH_2C\mathbf{H}CH$'HCHOH, $OCHCH'HC\mathbf{H}CH_2$), 5.21 (dt, *J* = 5.3, 2.6 Hz, 1H, $CHCH_2C\mathbf{H}OMs$), 5.21 – 5.08 (m, 4H, $C\mathbf{H}_2CHCH'HCHOH$, $OCHCH'HCHC\mathbf{H}_2$), 4.21 (ddd, *J* = 9.0, 6.8, 3.8 Hz, 1H, $C\mathbf{H}CH_2CHOMs$), 4.10 (td, *J* = 7.0, 3.2 Hz, 1H, $OC\mathbf{H}CH'HCHCH_2$), 3.91 (dt, *J* = 8.6, 4.4 Hz, 1H, $CH_2CHCH'HC\mathbf{H}OH$), 3.05 (s, 3H, OMs $C\mathbf{H}_3$), 2.46 (dddt, *J* = 14.3, 10.2, 7.0, 1.5 Hz, 1H, $OCHC\mathbf{H}'HCHCH_2$), 2.40 (dddt, *J* = 14.6, 9.4, 6.7, 1.4 Hz, 1H, $OCHCH'\mathbf{H}CHCH_2$), 2.34 – 2.27 (m, 2H, $CHC\mathbf{H}_2CHOMs$), 2.22 (dddt, *J* = 14.3, 6.3, 4.8, 1.3 Hz, 1H, $CH_2CHC\mathbf{H}'HCHOH$), 2.14 (dddt, *J* = 14.3, 8.5, 7.3, 1.2 Hz, 1H, $CH_2CHCH'\mathbf{H}CHOH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.1 ($CH_2\mathbf{C}HCH'HCHOH$), 133.8 ($OCHCH'H\mathbf{C}HCH_2$), 118.3 ($\mathbf{C}H_2CHCH'HCHOH$), 118.0 ($OCHCH'HCH\mathbf{C}H_2$), 82.2 ($CHCH_2\mathbf{C}HOMs$), 81.5 ($O\mathbf{C}HCH'HCHCH_2$), 80.0 ($\mathbf{C}HCH_2CHOMs$), 71.3 ($CH_2CHCH'H\mathbf{C}HOH$), 38.8 (OMs $\mathbf{C}H_3$), 37.5 ($CH_2CH\mathbf{C}H'HCHOH$), 34.1 ($OCH\mathbf{C}H'HCHCH_2$), 33.3 ($CH\mathbf{C}H_2CHOMs$). IR (ν_{max} cm^{-1}): 3541 (O–H stretching, broad), 3078 (alkene sp^2 C–H stretching, weak), 2979-2907 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, weak), 1334 (sulfone antisymmetric stretching, strong), 1170 (sulfone symmetric stretching, strong), 1072 (C–O stretching, strong), 901 (vinyl CH_2 out of plane wagging, strong). LRMS (ESI) [M+Na^+]: *m/z* 299.0. HRMS (ESI) [M+Na^+]: calculated for *m/z* 299.09237, found *m/z* 299.09235 ($C_{12}H_{20}O_5Na^{32}S$). $[\alpha]_D^{25} = -52.0$ (c=0.20, $CHCl_3$).

(1*S*,3*R*,4*S*,6*S*)-3,6-Diallyl-2,5-dioxabicyclo[2.2.1]heptane 4.13



The compound **4.17** (90.0 mg, 0.33 mmol) was dissolved in dry DMF (1.5 mL). NaH (0.1 g, 2.3 mmol, 60% suspension in mineral oil) was mixed with dry DMF (1.5 mL). The DMF solution of **4.17** was added dropwise to the NaH slurry at room temperature and stirred overnight. TLC analysis was performed at this stage to confirm the completion consumption of starting materials. The reaction was quenched with water at 0 °C then extracted with Pet. Ether 40-60. The petroleum ether layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography (5% EA/Pet. Ether 40-60) to give the desired compound **4.13** (30.0 mg, 0.17 mmol, 50%) as a volatile colourless oil. R_f = 0.69 (20% EA/Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.66 (m, 2H, $CH_2C\mathbf{H}CH'HCHO$, $CHCH_2C\mathbf{H}CH_2$), 5.18 – 5.03 (m, 4H, $C\mathbf{H}_2CHCH'HCHO$, $CHCH_2CHC\mathbf{H}_2$), 4.36 (d, *J* = 2.4 Hz, 1H, $C\mathbf{H}CH_2CHO$), 4.27 (d, *J* = 2.3 Hz, 1H, $CHCH_2C\mathbf{H}O$), 3.89 (t, *J* = 7.2 Hz, 1H, $CH_2CHCH'HC\mathbf{H}O$), 3.85 (td, *J* = 7.1, 1.1 Hz, 1H, $C\mathbf{H}CH_2CHCH_2$), 2.47 – 2.28 (m, 2H, $CHC\mathbf{H}_2CHCH_2$), 2.14 (dtt, *J* = 13.2, 6.6, 1.5 Hz, 1H, $CH_2CHC\mathbf{H'}HCHO$), 2.02 (dtt, *J* = 14.6, 7.5, 1.3 Hz, 1H, $CH_2CHCH'\mathbf{H}CHO$), 1.93 – 1.83 (m, 2H, $CHC\mathbf{H}_2CHO$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6 ($CHCH_2\mathbf{C}HCH_2$), 133.6 ($CH_2\mathbf{C}HCH'HCHO$), 117.6 ($CHCH_2CH\mathbf{C}H_2$), 117.4 ($\mathbf{C}H_2CHCH'HCHO$), 83.6 ($CH_2CHCH'H\mathbf{C}HO$), 82.3 ($\mathbf{C}HCH_2CHCH_2$), 79.4 ($CHCH_2\mathbf{C}HO$), 77.2 ($\mathbf{C}HCH_2CHO$), 38.7 ($CH_2CH\mathbf{C}H'HCHO$), 35.4 ($CH\mathbf{C}H_2CHCH_2$), 34.8 ($CH\mathbf{C}H_2CHO$). IR (ν_{max} cm^{-1}): 3078 & 3001 (alkene sp^2 C–H stretching, weak), 2970-2902 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1078 & 1051 (C–O stretchings, strong), 951 & 912 (vinyl CH_2 out of plane wag, strong). LRMS (ESI) [M+Na$^+$]: *m/z* 203.1. HRMS (ESI) [M+Na$^+$]: calculated for *m/z* 203.10425, found *m/z* 203.10440 ($C_{11}H_{16}O_2Na$). $[\alpha]_D^{25} = +88.3$ (c=0.30, $CHCl_3$).

(*R*,*E*)-1-((3a*R*,5*S*,6a*R*)-2,2-Dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)hex-3-en-1-yl acetate 4.23



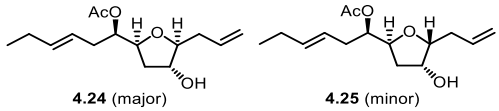
By olefin cross metathesis: Compound **4.14** (1.6 g, 6.2 mmol) was dissolved in dry CH_2Cl_2 (66.0 mL) followed by the addition of *trans*-3–Hexene (8.5 mL, 62.0 mmol). The solution was degassed with argon for 30 minutes. Grubb's 2nd generation catalyst (390.0 mg, 0.46 mmol) was then added, and the reaction mixture was stirred at room

temperature for 2 hours. TLC analysis was performed at this stage to confirm the completion of reaction. DMSO (2.4 mL) was added to the reaction mixture and stirred overnight. All volatiles were removed under reduced pressure and the deep brown residue was purified by column chromatography (5% EA/Pet. Ether 40-60 then 10% EA/Pet. Ether 40-60) to give the desired compound **4.23** (1.7 g, 97%, *E:Z* = 10:1 inseparable mixture, *E*:*Z* ratio determined by examining alkene C–H resonances on ^{1}H NMR at 5.53, 5.32 ppm (*E* isomer) and 5.47, 5.27 (*Z* isomer) respectively) as a colourless oil.

By Julia-Kocienski Olefination: Compound **4.14** (2.5 g, 9.7 mmol) was dissolved in a 3:1 mixture of dioxane/water (97.0 mL) at room temperature. 2,6-lutidine (2.2 mL, 19.0 mmol) was added followed by a solution of 2.5% OsO_4 in ^{t}BuOH (0.5 mL). $NaIO_4$ (8.1 g, 38.1 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. TLC analysis at this stage confirmed the completion of reaction. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated to give the crude aldehyde as a brown oil. The crude aldehyde was put under high vacuum to remove residual 2,6-lutidine and dioxane. Sulfone **4.29** (2.3 g, 9.2 mmol) was dissolved in dry THF (87.0 mL) and the reaction mixture was cooled to -78 °C. NaHMDS (1.0 M in THF, 10.7 mL, 10.7 mmol) was then added, in which the reaction mixture turned from colourless to bright yellow. The crude aldehyde was then dissolved in dry THF (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred at -78 °C for 40 minutes, in which a TLC analysis at this stage indicated completion of reaction. The reaction mixture was then quenched with sat. aq. NH_4Cl, warmed to room temperature and extracted with ethyl acetate. The organic layers were combined, dried with anhydrous $MgSO_4$, concentrated and then underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60 then 10% EA/Pet. Ether 40-60) to give the desired compound **4.23** (1.9 g, 68%, *E:Z* = 10:1 inseperable mixture, *E*:*Z* ratio determined by examining alkene C–H resonances on ^{1}H NMR at 5.53, 5.32 ppm (*E* isomer) and 5.47, 5.27 (*Z* isomer) respectively) as a colourless oil. R_f = 0.64 (20% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, *J* = 3.6 Hz, 1H, C**H**CHCH'HCH), 5.53 (dtt, *J* = 15.5, 6.6, 1.4 Hz, 1H, CH_3CH_2C**H**=CHCH'HCHOAc), 5.32 (dddd, *J* = 14.0, 6.7, 4.1, 1.5 Hz, 1H, CH_3CH_2CH=C**H**CH'HCHOAc), 5.04 (dt, *J* = 7.6, 5.1 Hz, 1H, CH_3CH_2CH=CHCH'HC**H**OAc), 4.71 (dd, *J* = 4.8, 3.7 Hz, 1H, CHC**H**CH'HCH), 4.24 (dt, *J* = 10.7, 4.8 Hz, 1H, CHCHCH'HC**H**), 2.40 – 2.29 (m, 1H, CH_3CH_2CH=CHC**H'**HCHOAc), 2.25 (dtd, *J* = 14.2, 7.6, 1.1 Hz, 1H, CH_3CH_2CH=CHCH'**H**CHOAc), 2.09 – 2.05 (m, 1H, CHCHC**H'**HCH), 2.03 (s, 3H, OAc C**H**$_3$), 1.98 (m, 2H, CH_3C**H**$_2$CH=CHCH'HCHOAc), 1.76 (ddd, *J* = 13.4, 10.7, 4.8 Hz, 1H, CHCHCH'**H**CH), 1.49 (s, 3H, C**H**$_3$CCH$_3$), 1.31 (s, 3H, CH_3CC**H**$_3$), 0.94 (t, *J*

= 7.4 Hz, 3H, C**H**$_3$CH$_2$CH=CHCH'HCHOAc). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4 (OAc **C**=O), 136.0 (CH$_3$CH$_2$**C**H=CHCH'HCHOAc), 123.4 (CH$_3$CH$_2$CH=**C**HCH'HCHOAc), 111.3 (CH$_3$**C**CH$_3$), 105.6 (**C**HCHCH'HCH), 80.3 (CH**C**HCH'HCH), 78.4 (CHCHCH'H**C**H), 73.2 (CH$_3$CH$_2$CH=CHCH'H**C**HOAc), 34.7 (CH$_3$CH$_2$CH=CH**C**H'HCHOAc), 34.6 (CHCH**C**H'HCH), 26.9 (**C**H$_3$CCH$_3$), 26.3 (CH$_3$C**C**H$_3$), 25.7 (CH$_3$**C**H$_2$CH=CHCH'HCHOAc), 21.2 (OAc **C**H$_3$), 13.9 (**C**H$_3$CH$_2$CH=CHCH'HCHOAc). IR (ν_{max} cm^{-1}): 3021 (alkene sp^2 C–H stretching, weak), 2988-2898 (alkane sp^3 C–H stretching, broad), 1741 (ester C=O stretching, strong), 1163 (C–O stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 307.2. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 285.16965, found *m/z* 285.16975 (C$_{15}$H$_{25}$O$_5$). $[\alpha]_D^{25} = -8.7$ (c=0.30, $CHCl_3$).

(*R*,*E*)-1-((2*S*,4*R*,5*S*)-5-Allyl-4-hydroxytetrahydrofuran-2-yl)hex-3-en-1-yl acetate 4.24 and
(*R*,*E*)-1-((2*S*,4*R*,5*R*)-5-allyl-4-hydroxytetrahydrofuran-2-yl)hex-3-en-1-yl acetate 4.25

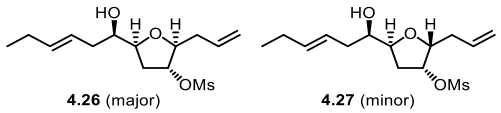


4.24 (major) **4.25** (minor)

Compound **4.23** (1.66 g, 5.84 mmol) was dissolved in dry CH_2Cl_2 (100.0 mL) and the reaction mixture was cooled to 0 °C. Allyltrimethylsilane (4.6 mL, 28.9 mmol) was added followed by $BF_3{\cdot}Et_2O$ (2.2 mL, 17.9 mmol). The reaction mixture was warmed to room temperature and stirred overnight. TLC analysis at this stage have indicated completion of reaction. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were combined, dried with anhydrous $MgSO_4$, concentrated and underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 to 50% EA/Pet. Ether 40-60) to give the compounds **4.24** and **4.25** as a difficult-to-separate 4.2:1 epimeric mixture in the form of a colourless oil, where each epimer is an inseparable 10:1 mixture of *E*:*Z* geometrical isomers (1.35 g, 5.03 mmol, 86%). Characterisation of **4.24**: R_f = 0.33 (20% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 17.0, 10.2, 7.4, 6.5 Hz, 1H, CHCH$_2$C**H**=CH$_2$), 5.53 (dtt, *J* = 15.4, 6.4, 1.4 Hz, 1H, CH$_3$CH$_2$C**H**=CHCH$_2$CHOAc), 5.33 (dtt, *J* = 15.5, 7.1, 1.5 Hz, 1H, CH$_3$CH$_2$CH=C**H**CH$_2$CHOAc), 5.14 – 5.06 (m, 2H, CHCH$_2$CH=C**H**$_2$), 5.01 (dt, *J* = 7.8, 5.0 Hz, 1H, CH$_3$CH$_2$CH=CHCH$_2$C**H**OAc), 4.19 (ddd, *J* = 9.0, 6.3, 4.6 Hz, 1H, C**H**CH'HCHOH), 4.11 (dt, *J* = 6.1, 3.0 Hz, 1H, CHCH'HC**H**OH), 3.81 (td, *J* = 6.5, 3.1 Hz, 1H, C**H**CH$_2$CH=CH$_2$), 2.34 – 2.14 (m, 4H, CH$_3$CH$_2$CH=CHC**H**$_2$CHOAc, CHC**H**$_2$CH=CH$_2$), 2.04 (s, 3H, OAc CH$_3$), 2.03 – 1.95 (m, 3H, CHC**H'**HCHOH, CH$_3$C**H**$_2$CH=CHCH$_2$CHOAc), 1.86 (ddd, *J* = 13.2, 6.4, 3.0

Hz, 1H, CHCH'**H**CHOH), 1.67 (s, 1H, CHCH'HCHO**H**), 0.94 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH$_2$CH=CHCH$_2$CHOAc). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (OAc **C**=O), 135.8 (CH_3CH_2**C**H=CHCH$_2$CHOAc), 134.2 (CHCH$_2$**C**H=CH$_2$), 123.6 (CH_3CH_2CH=**C**HCH$_2$CHOAc), 117.7 (CHCH$_2$CH=**C**H$_2$), 85.9 (**C**HCH$_2$CH=CH$_2$), 78.6 (**C**HCH'HCHOH), 75.3 (CHCH'H**C**HOH), 74.1 (CH_3CH_2CH=CHCH$_2$**C**HOAc), 38.6 (CH**C**H$_2$CH=CH$_2$), 35.8 (CH**C**H'HCHOH), 34.5 (CH_3CH_2CH=CH**C**H$_2$CHOAc), 25.7 (CH_3**C**H$_2$CH=CHCH$_2$CHOAc), 21.3 (OAc **C**H$_3$), 13.9 (**C**H$_3$CH$_2$CH=CHCH$_2$CHOAc). IR (ν_{max} cm^{-1}): 3436 (O–H stretching, broad), 3077 (alkene sp^2 C–H stretching, weak), 2962-2910 (alkane sp^3 C–H stretchings, broad), 1740 (ester C=O stretching, strong), 1235 (C–O stretching, strong), 968 (*trans*-alkene C–H out of plane deformation, strong), 916 (vinyl CH$_2$ out of plane wag, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 291.2. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 291.15668, found *m/z* 291.15665 ($C_{15}H_{24}O_4Na$). $[\alpha]_D^{25} = +23.5$ (c=0.20, $CHCl_3$). Characterisation of **4.25**: R_f = 0.39 (20% EA/ Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 16.6, 10.3, 7.5, 6.3 Hz, 1H, CHCH'HC**H**=CH'H), 5.52 (dtt, *J* = 15.2, 6.3, 1.3 Hz, 1H, CH_3CH_2C**H**=CHCH'HCHOAc), 5.32 (dtt, *J* = 15.5, 7.0, 1.6 Hz, 1H, CH_3CH_2CH=C**H**CH'HCHOAc), 5.16 (dq, *J* = 17.2, 1.6 Hz, 1H, CHCH'HCH=C**H'**H), 5.08 (dq, *J* = 10.3, 1.4 Hz, 1H, CHCH'HCH=CH'**H**), 4.99 (dt, *J* = 7.7, 5.2 Hz, 1H, CH_3CH_2CH=CHCH'HC**H**OAc), 4.31 – 4.25 (m, 2H, CHCH$_2$C**H**OH, C**H**CH$_2$CHOH), 3.85 (ddd, *J* = 7.7, 6.6, 2.8 Hz, 1H, C**H**CH'HCH=CH'H), 2.46 (dtt, *J* = 14.5, 6.5, 1.6 Hz, 1H, CHC**H'**HCH=CH'H), 2.37 (dtt, *J* = 14.2, 7.5, 1.2 Hz, 1H, CHCH'**H**CH=CH'H), 2.30 (dddt, *J* = 14.3, 6.4, 5.3, 1.2 Hz, 1H, CH_3CH_2CH=CHC**H'**HCHOAc), 2.24 (dddt, *J* = 15.6, 7.8, 6.6, 1.3 Hz, 1H, CH_3CH_2CH=CHCH'**H**CHOAc), 2.05 – 2.01 (m, 5H, OAc C**H**$_3$, CHC**H**$_2$CHOH), 2.01 – 1.94 (m, 2H, CH_3C**H**$_2$CH=CHCH'HCHOAc), 1.64 (s, 1H, CHCH$_2$CHO**H**), 0.94 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH$_2$CH=CHCH'HCHOAc). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (OAc **C**=O), 135.7 (CH_3CH_2**C**H=CHCH'HCHOAc), 134.6 (CHCH'H**C**H=CH'H), 123.6 (CH_3CH_2CH=**C**HCH'HCHOAc), 117.3 (CHCH'HCH=**C**H'H), 82.4 (**C**HCH'HCH=CH'H), 77.8 (CHCH$_2$**C**HOH), 74.9 (CH_3CH_2CH=CHCH'H**C**HOAc), 73.0 (**C**HCH$_2$CHOH), 36.9 (CH**C**H$_2$CHOH), 34.4 (CH_3CH_2CH=CH**C**H'HCHOAc), 33.8 (CH**C**H'HCH=CH'H), 25.7 (CH_3**C**H$_2$CH=CHCH'HCHOAc), 21.3 (OAc **C**H$_3$), 13.9 (**C**H$_3$CH$_2$CH=CHCH'HCHOAc). IR (ν_{max} cm^{-1}): 3449 (O–H stretching, broad), 3077 (alkene sp^2 C–H stretching, weak), 2961-2874 (alkane sp^3 C–H stretchings, broad), 1739 (ester C=O stretching, strong), 1235 (C–O stretching, strong), 967 (*trans*-alkene C–H out of plane deformation, strong), 915 (vinyl CH$_2$ out of plane wag, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 291.2. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 291.15668, found *m/z* 291.15662 ($C_{15}H_{24}O_4Na$). $[\alpha]_D^{25} = -5.0$ (c=0.20, $CHCl_3$).

(2*S*,3*R*,5*S*)-2-Allyl-5-((*R*,*E*)-1-hydroxyhex-3-en-1-yl)tetrahydrofuran-3-yl methane sulfonate 4.26 and (2*R*,3*R*,5*S*)-2-allyl-5-((*R*,*E*)-1-hydroxyhex-3-en-1-yl)tetrahydrofuran-3-yl methanesulfonate 4.27

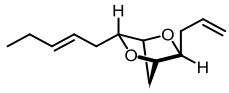


4.26 (major) **4.27** (minor)

A mixture of compounds **4.24** and **4.25** (1.35 g, 5.03 mmol) was dissolved in dry CH_2Cl_2 (22.0 mL) and the reaction mixture was cooled to 0 °C. Et_3N (0.76 mL, 5.51 mmol) was added followed by MsCl (0.42 mL, 5.51 mmol). The reaction mixture was then warmed to room temperature and stirring was continued for 1 hour. TLC analysis at this stage indicated completion of reaction. The reaction was then quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted with CH_2Cl_2 for three times. The organic layers were then combined, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The concentrate was then dissolved in a mixture of MeOH (22.0 mL) and water (2.5 mL). K_2CO_3 (1.40 g, 10.1 mmol) was then added and the reaction mixture was stirring was continued for 2 hours. TLC analysis at this stage indicated completion of reaction. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried with anhydrous $MgSO_4$, concentrated and underwent purification by flash column chromatography (20% EA/ Pet. Ether 40-60 to 30% EA/Pet. Ether 40-60) to give compounds **4.26** and **4.27** respectively as a colourless oil (1.14 g, 3.77 mmol, 75%) and a white solid (0.23 g, 0.76 mmol, 15%). Please note several fractions which contained both epimers were discarded. Characterisation of **4.26**: R_f = 0.49 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, $CHCH_2C\mathbf{H}=CH_2$), 5.59 (dtt, *J* = 15.3, 6.2, 1.4 Hz, 1H, $CH_3CH_2C\mathbf{H}=CHCH_2CHOH$), 5.40 (dtt, *J* = 15.6, 7.1, 1.6 Hz, 1H, $CH_3CH_2CH=C\mathbf{H}CH_2CHOH$), 5.22 – 5.12 (m, 2H, $CHCH_2CH=C\mathbf{H}_2$), 4.94 (dt, *J* = 6.3, 2.2 Hz, 1H, CHCH'HC**H**OMs), 4.15 (td, *J* = 6.4, 2.5 Hz, 1H, $C\mathbf{H}CH_2CH=CH_2$), 4.10 (ddd, *J* = 9.7, 5.6, 3.6 Hz, 1H, C**H**CH'HCHOMs), 3.84 (td, *J* = 6.7, 3.6 Hz, 1H, $CH_3CH_2CH=CHCH_2C\mathbf{H}OH$), 3.03 (s, 3H, OMs $C\mathbf{H}_3$), 2.36 (td, *J* = 7.1, 1.3 Hz, 2H, $CHC\mathbf{H}_2CH=CH_2$), 2.26 – 2.15 (m, 1H, CHC**H'**HCHOMs), 2.16 – 2.07 (m, 3H, CHCH'**H**CHOMs, $CH_3CH_2CH=CHC\mathbf{H}_2CHOH$), 2.07 – 2.00 (m, 2H, $CH_3C\mathbf{H}_2CH=CHCH_2CHOH$), 1.78 (s, 1H, $CH_3CH_2CH=CHCH_2CHO\mathbf{H}$), 0.98 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H}_3CH_2CH=CHCH_2CHOH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1 ($CH_3CH_2\mathbf{C}H=CHCH_2CHOH$), 133.2 ($CHCH_2\mathbf{C}H=CH_2$), 124.0 ($CH_3CH_2CH=\mathbf{C}HCH_2CHOH$), 118.8 ($CHCH_2CH=\mathbf{C}H_2$), 83.8 (CHCH'H**C**HOMs), 83.1 (**C**$HCH_2CH=CH_2$), 81.1 (**C**HCH'HCHOMs), 70.8 ($CH_3CH_2CH=CHCH_2\mathbf{C}HOH$), 38.8 (OMs **C**$H_3$), 37.9 ($CH\mathbf{C}H_2CH=CH_2$), 36.3 ($CH_3\mathbf{C}H_2CH=CHCH_2CHOH$), 31.9

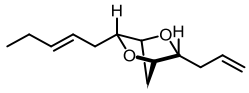
($CH_3CH_2CH=CH\mathbf{C}H_2CHOH$), 25.7 ($CH\mathbf{C}H'HCHOMs$), 13.8 ($\mathbf{C}H_3CH_2CH=CHCH_2CHOH$). IR ($\nu_{max}$ cm^{-1}): 3457 (O–H stretching, broad), 3078 (alkene sp^2 C–H stretching, weak), 2962-2875 (alkane sp^3 C–H stretching, broad), 1643 (*trans*-alkene C=C stretching, weak), 1336 (sulfone antisymmetric stretching, strong), 1243 (C–O stretching, strong), 1172 (sulfone symmetric stretching, strong), 970 (*trans*-alkene C–H out of plane deformation, strong), 909 (vinyl CH_2 out of plane wag, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 327.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 327.12367, found *m/z* 327.12364 ($C_{14}H_{24}O_5Na^{32}S$). $[\alpha]_D^{25} = -36.0$ (c=0.30, $CHCl_3$) . Characterisation of **4.27**: R_f = 0.35 (30% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, $CHCH'HC\mathbf{H}=CH'H$), 5.59 (dtt, *J* = 15.3, 6.4, 1.3 Hz, 1H, $CH_3CH_2C\mathbf{H}=CHCH'HCHOH$), 5.39 (dtt, *J* = 15.5, 7.1, 1.5 Hz, 1H, $CH_3CH_2CH=C\mathbf{H}CH'HCHOH$), 5.21 (dt, *J* = 5.3, 2.6 Hz, 1H, $CHCH_2C\mathbf{H}OMs$), 5.17 (dq, *J* = 17.2, 1.6 Hz, 1H, $CHCH'HCH=C\mathbf{H'}H$), 5.12 (dq, *J* = 10.2, 1.4 Hz, 1H, $CHCH'HCH=CH'\mathbf{H}$), 4.24 – 4.16 (m, 1H, $C\mathbf{H}CH_2CHOMs$), 4.09 (ddd, *J* = 7.4, 6.5, 3.2 Hz, 1H, $C\mathbf{H}CH'HCH=CH'H$), 3.84 (dt, *J* = 8.6, 4.6 Hz, 1H, $CH_3CH_2CH=CHCH'HC\mathbf{H}OH$), 3.05 (s, 3H, OMs $C\mathbf{H}_3$), 2.52 – 2.42 (m, 1H, $CHC\mathbf{H'}HCH=CH'H$), 2.45 – 2.35 (m, 1H, $CHCH'\mathbf{H}CH=CH'H$), 2.37 – 2.25 (m, 2H, $CHC\mathbf{H}_2CHOMs$), 2.21 – 2.11 (m, 1H, $CH_3CH_2CH=CHC\mathbf{H'}HCHOH$), 2.13 – 1.98 (m, 3H, $CH_3CH_2CH=CHCH'\mathbf{H}CHOH$, $CH_3C\mathbf{H}_2CH=CHCH'HCHOH$), 1.72 (s, 1H, $CH_3CH_2CH=CHCH'HCHO\mathbf{H}$), 0.98 (t, *J* = 7.5 Hz, 3H, $C\mathbf{H}_3CH_2CH=CHCH'HCHOH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4 ($CH_3CH_2\mathbf{C}H=CHCH'HCHOH$), 133.8 ($CHCH'H\mathbf{C}H=CH'H$), 124.0 ($CH_3CH_2CH=\mathbf{C}HCH'HCHOH$), 117.9 ($CHCH'HCH=\mathbf{C}H'H$), 82.2 ($CHCH_2\mathbf{C}HOMs$), 81.5 ($\mathbf{C}HCH_2CHOMs$), 80.0 ($\mathbf{C}HCH'HCH=CH'H$), 71.7 ($CH_3CH_2CH=CHCH'H\mathbf{C}HOH$), 38.8 (OMs $\mathbf{C}H_3$), 36.4 ($CH_3CH_2CH=CH\mathbf{C}H'HCHOH$), 34.1 ($CH\mathbf{C}H'HCH=CH'H$), 33.4 ($CH\mathbf{C}H_2CHOMs$), 25.8 ($CH_3\mathbf{C}H_2CH=CHCH'HCHOH$), 13.9 ($\mathbf{C}H_3CH_2CH=CHCH'HCHOH$). IR ($\nu_{max}$ cm^{-1}): 3455 (O–H stretching, broad), 3078 (alkene sp^2 C–H stretching, weak), 2962-2860 (alkane sp^3 C–H stretching, broad), 1643 (*trans*-alkene C=C stretching, weak), 1336 (sulfone antisymmetric stretching, strong), 1243 (C–O stretching, strong), 1172 (sulfone symmetric stretching, strong), 969 (*trans*-alkene C–H out of plane deformation, strong), 910 (vinyl CH_2 out of plane wag, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 327.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 327.12367, found *m/z* 327.12370 ($C_{14}H_{24}O_5Na^{32}S$). Melting Point: 52 °C-54 °C. $[\alpha]_D^{25} = -15.3$ (c=0.30, $CHCl_3$).

(1*S*,3*S*,4*S*,6*R*)-3-Allyl-6-((*E*)-pent-2-en-1-yl)-2,5-dioxabicyclo[2.2.1]heptane 4.5



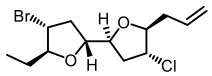
NaH (60% dispersion in mineral oil, 1.00 g, 25.0 mmol) was suspended in dry DMF (110.0 mL). Compound **4.26** (1.10 g, 3.62 mmol) was dissolved in dry DMF (10.0 mL) and added to the NaH suspension dropwise at room temperature. The reaction mixture was stirred overnight. TLC analysis at this stage indicated the completion of reaction. The reaction mixture was cooled to 0 °C and excess NaH was quenched with the dropwise addition of water. The reaction mixture was further diluted with water after quenching and extracted with Pet. Ether 40-60. The organic layers were combined, dried with anhydrous $MgSO_4$, concentrated and underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60 to 10% EA/Pet. Ether 40-60) to give the desired compound **4.5** as a colourless oil (0.70 g, 3.37 mmol, 93%). R_f = 0.74 (30% EA/Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H, $CHCH_2C\mathbf{H}$=CH'H), 5.52 (dt, *J* = 15.4, 6.4 Hz, 1H, $CH_3CH_2C\mathbf{H}$=CHCH'HCH), 5.32 (dtd, *J* = 15.3, 7.7, 1.6 Hz, 1H, CH_3CH_2CH=C**H**CH'HCH), 5.14 (dt, *J* = 17.2, 1.8 Hz, 1H, $CHCH_2CH$=C**H'**H), 5.07 (dt, *J* = 9.9, 1.5 Hz, 1H, $CHCH_2CH$=CH'**H**), 4.34 (d, *J* = 2.4 Hz, 1H, OC**H**CH_2CHO), 4.26 (d, *J* = 2.3 Hz, 1H, OCHCH$_2$C**H**O), 3.84 (m, 2H, C**H**CH_2CH=CH'H, CH_3CH_2CH=CHCH'HC**H**), 2.45 – 2.29 (m, 2H, CHC**H**$_2$CH=CH'H), 2.14 – 2.06 (m, 1H, CH_3CH_2CH=CHC**H'**HCH), 2.05 – 1.96 (m, 2H, $CH_3C\mathbf{H}_2CH$=CHCH'HCH), 1.95 – 1.82 (m, 3H, OCHC**H**$_2$CHO, CH_3CH_2CH=CHCH'**H**CH), 0.96 (t, *J* = 7.4 Hz, 3H, C**H**$_3CH_2CH$=CHCH'HCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 ($CH_3CH_2\mathbf{C}H$=CHCH'HCH), 134.7 ($CHCH_2\mathbf{C}H$=CH'H), 123.7 (CH_3CH_2CH=**C**HCH'HCH), 117.4 ($CHCH_2CH$=**C**H'H), 84.3 (CH_3CH_2CH=CHCH'H**C**H), 82.3 (**C**HCH_2CH=CH'H), 79.3 (OCHCH$_2$**C**HO), 77.1 (O**C**HCH_2CHO), 37.5 (CH_3CH_2CH=CH**C**H'HCH), 35.4 (CH**C**H_2CH=CH'H), 34.7 (OCH**C**H_2CHO), 25.7 ($CH_3\mathbf{C}H_2CH$=CHCH'HCH), 13.8 (**C**H_3CH_2CH=CHCH'HCH). IR (ν_{max} cm^{-1}): 3078 (alkene sp^2 C–H stretchings, weak), 2962-2875 (alkane sp^3 C–H stretchings, broad), 1641 (alkene C=C stretchings, medium), 1077 (C–O stretchings, strong), 917 (alkene C=CH$_2$ out of plane wag, strong). LRMS (ESI) [M+H]$^+$: *m/z* 209.2. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 209.15361, found *m/z* 209.15379 ($C_{13}H_{21}O_2$). $[\alpha]_D^{25} = +70.3$ (c=0.30, $CHCl_3$) .The relative configuration of **4.5** was confirmed by comparative 1D nOe studies with its epimer **4.28**.

(1*S*,3*R*,4*S*,6*R*)-3-Allyl-6-((*E*)-pent-2-en-1-yl)-2,5-dioxabicyclo[2.2.1]heptane 4.28



Compound **4.28** was synthesised from compound **4.27** (70.0 mg, 0.23 mmol) in an entirely analogous fashion as that for the synthesis of compound **4.5** from compound **4.26**. Crude compound **4.28** was purified by column chromatography (5% EA/Pet. Ether 40-60) to give the desired compound **4.28** (34.2 mg, 0.16 mmol, 71%) as a pale yellow oil. R_f = 0.74 (30% EA/Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.1, 10.3, 6.9 Hz, 1H, CHCH'HC**H**=CH_2), 5.52 (dtt, *J* = 15.2, 6.2, 1.3 Hz, 1H, CH_3CH_2C**H**=CHCH'HCH), 5.33 (dddt, *J* = 15.5, 7.9, 6.3, 1.6 Hz, 1H, CH_3CH_2CH=C**H**CH'HCH), 5.12 – 5.03 (m, 2H, CHCH'HCH=C**H**$_2$), 4.28 (m, 2H, OC**H**CH_2CHO, OCHCH_2C**H**O), 3.89 (t, *J* = 7.2 Hz, 1H, C**H**CH'HCH=CH_2), 3.85 (t, *J* = 7.2 Hz, 1H, CH_3CH_2CH=CHCH'HC**H**), 2.18 – 2.06 (m, 2H, CH_3CH_2CH=CHC**H'**HCH, CHC**H'**HCH=CH_2), 2.06 – 1.97 (m, 3H, CH_3C**H**$_2$CH=CHCH'HCH, CHCH'**H**CH=CH_2), 1.97 – 1.86 (m, 1H, CH_3CH_2CH=CHCH'**H**CH), 1.71 (d, *J* = 1.5 Hz, 2H, OCHC**H**$_2$CHO), 0.96 (t, *J* = 7.5 Hz, 3H, C**H**$_3CH_2CH$=CHCH'HCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (CH_3CH_2**C**H=CHCH'HCH), 133.7 (CHCH'H**C**H=CH_2), 123.7 (CH_3CH_2CH=**C**HCH'HCH), 117.5 (CHCH'HCH=**C**H_2), 83.3 (CH_3CH_2CH=CHCH'H**C**H), 82.6 (**C**HCH'HCH=CH_2), 78.7 (O**C**HCH_2CHO, OCHCH_2**C**HO), 38.5 (CH**C**H'HCH=CH_2), 37.2 (CH_3CH_2CH=CH**C**H'HCH), 30.9 (OCH**C**H_2CHO), 25.7 (CH_3**C**H_2CH=CHCH'HCH), 13.8 (**C**H_3CH_2CH=CHCH'HCH). IR (ν_{max} cm^{-1}): 3078 (alkene sp^2 C–H stretchings, weak), 2964-2904 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretchings, medium), 1070-1051 (C–O stretchings, strong), 912 (vinyl CH_2 out of plane wag, strong). LRMS (ESI) [M+H]$^+$: *m/z* 209.2. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 209.15361, found *m/z* 209.15384 ($C_{13}H_{21}O_2$). $[\alpha]_D^{25} = +127.2$ (c=0.5, $CHCl_3$).

(2*S*,2'*R*,4*R*,4'*R*,5*S*,5'*S*)-5-Allyl-4'-bromo-4-chloro-5'-ethyloctahydro-2,2'-bifuran, 4.46



Representative procedure A: Without nucleophiles at 80 °C.

Compound **4.5** (30.0 mg, 0.14 mmol) was dissolved in dry $EtNO_2$ (1.4 mL) and BDSB (75.2 mg, 0.14 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes, then all volatiles were removed under high vacuum. The residue was

redissolved in $EtNO_2$ (1.4 mL) and stirred overnight at the designated temperature. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (10% EA/ Pet. Ether 40-60) to give the desired compound **4.46** (18.0 mg, 0.06 mmol, 39% for 2 steps) as a yellow oil.

Representative procedure B: With nucleophile (Cl^-) at 80 °C.

Compound **4.5** (30.0 mg, 0.14 mmol) was dissolved in dry $EtNO_2$ (1.4 mL) and BDSB (75.2 mg, 0.14 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes, then all volatiles were removed under high vacuum. The residue was redissolved in $EtNO_2$ (1.4 mL) and TBACl (200.0 mg, 0.72 mmol) was added, then stirred overnight at the designated temperature. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (10% EA/Pet. Ether 40-60) to give the desired compound **4.46** (14.5 mg, 0.05 mmol, 31% for 2 steps) as a yellow oil.

By thermal rearrangement from 4.48:

Compound **4.48** (5.0 mg, 16.0 μmol) was dissolved in $EtNO_2$ (0.16 mL) and heated to 80 °C overnight. NMR analysis of the reaction mixture revealed quantitative conversion into **4.46**.

By $SbCl_5$/Et_2S mediated rearrangement from 4.48:

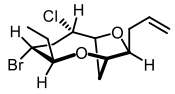
Compound **4.48** (3.0 mg, 9.6 μmol) was dissolved in CH_2Cl_2 (0.5 mL) at -78 °C, Et_2S (0.1 mL, 10.0 μmol, 0.1M solution in CH_2Cl_2) was added followed by $SbCl_5$ (0.1 mL, 10.0 μmol, 0.1M solution in CH_2Cl_2). The reaction mixture was then warmed to room temperature, all volatiles were removed and the residue was dissolved in $CDCl_3$. NMR monitoring of the reaction mixture revealed quantitative conversion into **4.46** over 15 days

Characterisation data for 4.46:

R_f = 0.86 (20% EA/ Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, C**H**=CH_2), 5.16 – 5.08 (m, 2H, CH=C**H**$_2$), 4.23 (td, *J* = 7.2, 5.5 Hz, 1H, ClCHCH_2C**H**), 4.06 – 4.01 (m, 2H, ClC**H**CHO and ClCHC**H**O), 3.95 (ddd, *J* = 8.2, 6.8, 5.5 Hz, 1H, BrCHCH'HC**H**), 3.91 (td, *J* = 7.5, 4.0 Hz, 1H, CH_3CH'HC**H**), 3.86 (dt, *J* = 8.8, 7.3 Hz, 1H, BrC**H**), 2.65 (dt, *J* = 13.1, 6.9 Hz, 1H, BrCHC**H'**HCH), 2.42 – 2.28 (m, 2H, C**H**$_2$CH=CH_2), 2.26 – 2.21 (m, 2H, ClCHC**H**$_2$), 2.17 (dt, *J* = 13.1, 8.4 Hz, 1H, BrCHCH'**H**CH), 1.75 (dqd, *J* = 13.9, 7.5, 4.0 Hz, 1H, CH_3C**H'**HCH), 1.49

(dt, *J* = 14.0, 7.3 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 0.99 (t, *J* = 7.5 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.5 ($\mathbf{C}H=CH_2$), 118.2 ($CH=\mathbf{C}H_2$), 87.3 ($CH_3CH'H\mathbf{C}H$), 86.5 ($ClCHC\mathbf{H}O$), 80.1 ($ClCHCH_2\mathbf{C}H$), 79.0 ($BrCHCH'H\mathbf{C}H$), 59.1 (Cl–CH), 47.5 (Br–CH), 39.4 ($BrCH\mathbf{C}H'HCH$), 38.2 ($ClCH\mathbf{C}H_2CH$), 38.0 ($\mathbf{C}H_2CH=CH_2$), 25.6 ($CH_3\mathbf{C}H'HCH$), 10.2 ($\mathbf{C}H_3CH'HCH$). IR (ν_{max} cm^{-1}): 3078 (alkene sp^2 C–H stretching, weak), 2965-2878 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1065 (ether C–O–C antisymmetric stretching, strong), 918 (terminal alkene $CH=CH_2$ out-of-plane deformation/wagging, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 345.0, 347.0 and 349.0. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 345.02276, 347.02038 and 349.01759, found *m/z* 345.02274, 347.02069 and 349.01774 ($C_{13}H_{20}O_2{}^{79}Br^{35}ClNa$, $C_{13}H_{20}O_2{}^{79}Br^{37}ClNa$/$C_{13}H_{20}O_2{}^{81}Br^{35}ClNa$ and $C_{13}H_{20}O_2{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = -50.6$ (c=0.53, $CHCl_3$).

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-6-chloro-3-ethyl-2,8-dioxabicyclo[5.2.1] decane 4.48

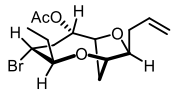


Representative procedure with nucleophile (Cl^-) at 50 °C.

Compound **4.5** (30.0 mg, 0.14 mmol) was dissolved in dry $EtNO_2$ (1.4 mL) and BDSB (75.2 mg, 0.14 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes, then all volatiles were removed under high vacuum. The residue was redissolved in $EtNO_2$ (1.4 mL) and TBACl (200 mg, 0.72 mmol) was added, then stirred overnight at the designated temperature. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (10% EA/ Pet. Ether 40-60) to give the desired compound **4.48** (17.0 mg, 0.05 mmol, 37% for 2 steps) as a yellow oil. R_f = 0.77 (20% EA/ Pet. Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, $C\mathbf{H}=CH'H$), 5.14 (dq, *J* = 17.2, 1.6 Hz, 1H, $CH=C\mathbf{H}'H$), 5.07 (ddt, *J* = 10.2, 2.0, 1.1 Hz, 1H, $CH=CH'\mathbf{H}$), 4.46 (dd, *J* = 7.7, 4.2 Hz, 1H, $ClCHC\mathbf{H}$), 4.15 (ddd, *J* = 10.6, 4.2, 1.1 Hz, 1H, $ClC\mathbf{H}$), 4.04 (td, *J* = 2.3, 1.2 Hz, 1H, $ClCHCHCH'HC\mathbf{H}$), 3.84 (td, *J* = 7.4, 2.4 Hz, 1H, $ClCHCHCH'HCHC\mathbf{H}$), 3.79 (dt, *J* = 10.9, 5.4 Hz, 1H, $BrC\mathbf{H}$), 3.49 (ddd, *J* = 10.8, 8.8, 2.5 Hz, 1H, $BrCHC\mathbf{H}$), 2.69 (ddd, *J* = 15.4, 5.0, 1.1 Hz, 1H, $BrCHC\mathbf{H}'H$), 2.61 – 2.56 (m, 1H, $ClCHCHC\mathbf{H}'HCH$), 2.56 – 2.49 (m, 1H, $BrCHCH'\mathbf{H}$), 2.45 (tt, *J* = 7.2, 1.2 Hz, 2H, $OCHC\mathbf{H}_2CH=CH'H$), 2.12 (dqd, *J* = 14.8, 7.4, 2.5 Hz, 1H, $CH_3C\mathbf{H}'H$), 1.89 (ddd, *J* = 14.3, 7.7, 2.3 Hz, 1H, $ClCHCHCH'\mathbf{H}CH$),

1.49 (ddq, *J* = 14.3, 8.7, 7.3 Hz, 1H, CH_3CH'**H**), 0.95 (t, *J* = 7.3 Hz, 3H, C**H**$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4 (**C**H=CH'H), 117.6 (CH=**C**H'H), 85.2 (ClCH**C**H), 83.4 (O**C**HCH$_2$CH=CH'H), 80.5 (BrCH**C**H), 76.7 (ClCHCHCH'H**C**H), 66.7 (Cl**C**H), 52.0 (Br**C**H), 45.4 (BrCH**C**H'H), 34.4 (ClCHCH**C**H'HCH), 34.3 (OCH**C**H$_2$CH=CH'H), 28.2 (CH_3**C**H'H), 9.6 (**C**H$_3$). IR (ν_{max} cm^{-1}): 3077 (alkene sp^2 C–H stretching, weak), 2964-2876 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1062 (ether C–O–C antisymmetric stretching, strong), 917 (terminal alkene CH=CH$_2$ out-of-plane deformation/wagging, strong). HRMS (CI) [M+H]$^+$: calculated for *m/z* 323.0408, 325.0388 and 327.0358, found *m/z* 323.0401, 325.0382 and 327.0363 ($C_{13}H_{21}O_2{}^{79}Br^{35}Cl$, $C_{13}H_{21}O_2{}^{79}Br^{37}Cl$/$C_{13}H_{21}O_2{}^{81}Br^{35}Cl$ and $C_{13}H_{21}O_2{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = +54.2$ (c=0.30, $CHCl_3$).

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-yl acetate 4.50

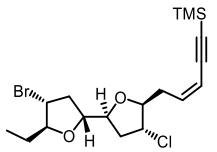


Representative procedure with nucleophile (OAc$^-$) at 80 °C.

Compound **4.5** (30.0 mg, 0.14 mmol) was dissolved in dry $EtNO_2$ (1.4 mL) and BDSB (75.2 mg, 0.14 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes, then all volatiles were removed under high vacuum. The residue was redissolved in $EtNO_2$ (1.4 mL) and TBAOAc (217 mg, 0.72 mmol) was added, then stirred overnight at the designated temperature. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (10% EA/Pet. Ether 40-60 first to remove non-polar species then 30% EA/Pet. Ether 40-60) to give the desired compound (21.0 mg, 0.06 mmol, 42% for 2 steps) as a colourless oil. R_f = 0.66 (20% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.3, 10.2, 7.0 Hz, 1H, C**H**=CH'H), 5.13 (dq, *J* = 17.2, 1.5 Hz, 1H, CH=C**H'**H), 5.05 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, CH=CH'**H**), 4.86 (ddd, *J* = 8.9, 4.1, 2.2 Hz, 1H, AcOC**H**), 4.29 (dd, *J* = 7.7, 4.1 Hz, 1H, AcOCHC**H**), 4.04 (td, *J* = 2.4, 1.2 Hz, 1H, AcOCHCHCH'HC**H**), 3.91 (td, *J* = 10.3, 5.4 Hz, 1H, BrC**H**), 3.82 (ddd, *J* = 7.9, 6.7, 2.4 Hz, 1H, OC**H**CH$_2$CH=CH'H), 3.46 (ddd, *J* = 10.8, 8.9, 2.5 Hz, 1H, CH_3CH_2C**H**), 2.53 (dd, *J* = 14.2, 1.2 Hz, 1H, AcOCHCHC**H'**HCH), 2.52 – 2.36 (m, 2H, OCHC**H**$_2$CH=CH'H), 2.30 – 2.18 (m, 2H, BrCHC**H**$_2$), 2.12 (ddd, *J* = 14.0, 7.4, 2.5 Hz, 1H, CH_3C**H**$_2$), 2.04 (s, 3H, Acetyl C**H**$_3$), 1.91 (ddd, *J* = 14.3, 7.8, 2.3 Hz, 1H, AcOCHCHCH'**H**CH), 1.51 (ddq, *J* = 14.4, 8.9, 7.2 Hz, 1H, CH_3C**H**$_2$), 0.96 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH$_2$). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 170.6 (Acetyl **C**=O), 134.6 (**C**H=CH'H), 117.4 (CH=**C**H'H), 83.3 (O**C**HCH$_2$CH=CH'H), 80.8 (AcO**C**H), 80.6 (CH_3CH_2**C**H), 80.3 (AcOCH**C**H), 76.8 (AcOCHCHCH'H**C**H), 51.7 (Br**C**H), 41.6 (BrCH**C**H$_2$), 34.3 (OCH**C**H$_2$CH=CH'H), 33.5 (AcOCHCH**C**H'HCH), 28.1 (CH_3**C**H$_2$), 21.6 (Acetyl **C**H$_3$), 9.8 (**C**H$_3$CH$_2$). IR (ν_{max} cm^{-1}): 3077 (alkene sp^2 C–H stretching, weak), 2964-2878 (alkane sp^3 C–H stretchings, broad), 1729 (ester C=O stretching, strong), 1642 (alkene C=C stretching, medium), 1238 (ester and ether C–O–C stretching, strong), 1065 (ether C–O–C antisymmetric stretching, strong), 916 (terminal alkene CH=CH$_2$ out-of-plane deformation/wagging, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 369.0 and 371.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 369.06719 and 371.06515, found *m/z* 369.06718 and 371.06499 ($C_{15}H_{23}O_4{}^{79}BrNa$, and $C_{15}H_{23}O_4{}^{81}BrNa$). $[\alpha]_D^{25} = +115.0$ (c=0.36, $CHCl_3$)

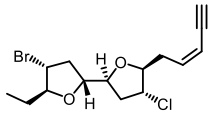
((*Z*)-5-((2*S*,2'*R*,4*R*,4'*R*,5*S*,5'*S*)-4'-Bromo-4-chloro-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)trimethylsilane 4.54



Compound **4.46** (53.5 mg, 0.17 mmol) was dissolved in a solution of 3:1 dioxane:H_2O (1.7 mL) at room temperature. Then 2,6-lutidine (38.0 µL, 0.33 mmol) was added followed by 2.5% OsO_4 in *t*-BuOH (13.0 µL). $NaIO_4$ (139.0 mg, 0.65 mmol) was added and the reaction mixture was stirred at room temperature until completion. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material (Product R_f = 0.26 (10% EA/Pet. Ether 40-60)). The reaction mixture was diluted with H_2O then extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated. Residual volatiles from the concentrated residue were removed under high vacuum for 1 hour and the residue was taken directly to the next step of the synthesis. *tert*-Butyldimethyl(3-(trimethylsilyl)prop-2-yn-1-yl)silane (113.0 mg, 0.50 mmol) was dissolved in dry THF (1.0 mL) and the reaction mixture was cooled to -78 ºC. Then *t*-BuLi (1.49 M, 0.33 mL, 0.50 mmol, concentration obtained from titration against a known standard of diphenylacetic acid) was added and stirring was continued for 1 hour at -78 ºC. $Ti(OiPr)_4$ (0.15 mL, 0.50 mmol) was dissolved in dry THF (0.5 mL) and added dropwise to the lithiated silane solution prepared above at -78 ºC and stirring was continued for 10 minutes. A portion of this solution (1.3 mL) was removed by syringe and then the concentrated residue above was dissolved in dry THF (0.5 mL, then 0.5 mL rinse) and added to the reaction mixture at -78 ºC and stirring was continued for 30 minutes. The reaction mixture was then warmed to room temperature and stirring was continued for a further 30 minutes. A

TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction mixture was quenched with aqueous HCl (0.1 M) and extracted with diethyl ether. The organic layer was separated, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (3% diethyl ether/Pet. Ether 40-60) to give the desired compound (42.0 mg, 0.10 mmol, *Z:E* > 20:1 (inseparable geometrical isomers), 60% for 2 steps) as a colourless oil. R_f = 0.69 (10% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (dt, *J* = 10.9, 7.5 Hz, 1H, CH'HC**H**=CH), 5.63 (dd, *J* = 10.9, 1.4 Hz, 1H, CH'HCH=C**H**), 4.25 (td, *J* = 7.2, 5.5 Hz, 1H, ClCHCHOC**H**), 4.13 – 4.08 (m, 2H, ClC**H** and ClCHC**H**), 3.97 (ddd, *J* = 8.2, 6.7, 5.5 Hz, 1H, BrCHCHOC**H**), 3.91 (td, *J* = 7.5, 4.0 Hz, 1H, BrCHC**H**), 3.86 (dt, *J* = 8.9, 7.3 Hz, 1H, BrC**H**), 2.70 – 2.62 (m, 2H, BrCHC**H'**H and C**H'**HCH=CH), 2.58 (dddd, *J* = 10.7, 7.3, 5.6, 1.3 Hz, 1H, CH'**H**CH=CH), 2.25 (dd, *J* = 7.3, 5.2 Hz, 2H, ClCHC$\mathbf{H}_2$), 2.18 (dt, *J* = 13.1, 8.4 Hz, 1H, BrCHCH'**H**), 1.75 (dqt, *J* = 15.2, 7.7, 4.2 Hz, 1H, CH_3C**H'**H), 1.49 (dp, *J* = 14.6, 7.4 Hz, 1H, CH_3CH'**H**), 0.99 (t, *J* = 7.4 Hz, 3H, C$\mathbf{H}_3$CH'H), 0.20 (s, 8H, Si(C$\mathbf{H}_3$)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3 (CH'H**C**H=CH), 112.4 (CH'HCH=**C**H), 101.6 (**C**≡CSi(CH_3)$_3$), 100.0 (C≡**C**Si(CH_3)$_3$), 87.3 (BrCH**C**H), 86.5 (ClCH**C**H), 80.3 (ClCHCHO**C**H), 79.1 (BrCHCHO**C**H), 59.4 (Cl**C**H), 47.5 (Br**C**H), 39.5 (BrCH**C**H'H), 38.3 (ClCH**C**H_2), 34.6 (**C**H'HCH=CH), 25.6 (CH_3**C**H'H), 10.2 (**C**H_3CH'H), 0.1 (Si(**C**H_3)$_3$). IR (ν_{max} cm^{-1}): 3027 (alkene sp^2 C–H stretching, weak), 2962-2879 (alkane sp^3 C–H stretchings, broad), 2149 (alkyne C≡C stretching, weak), 1250 (ether C–O–C stretching, strong), 1067 (ether C–O–C antisymmetric stretching, strong), 843 (Si–CH_3 rocking, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 441.1, 443.1 and 445.1. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 441.06227, 443.06022 and 445.05726, found *m/z* 441.06227, 443.05987 and 445.05708 ($C_{18}H_{28}O_2{}^{79}Br^{35}ClNaSi$, $C_{18}H_{28}O_2{}^{81}Br^{35}ClNaSi$/$C_{18}H_{28}O_2{}^{79}Br^{37}ClNaSi$ and $C_{18}H_{28}O_2{}^{81}Br^{37}ClNaSi$). $[\alpha]_D^{25} = -28.3$ (c=0.60, $CHCl_3$)

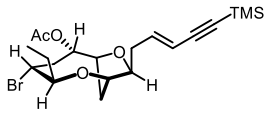
(2*R*,2'*S*,4*R*,4'*R*,5*S*,5'*S*)-4-Bromo-4'-chloro-5-ethyl-5'-((*Z*)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran, *ent*-(*Z*)-notoryne *ent*-1.17



Compound **4.54** (21.0 mg, 0.05 mmol) was dissolved in MeOH (2.5 mL), then K_2CO_3 (14 mg, 0.10 mmol) was added. The reaction mixture was stirred at room temperature until completion. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material. All volatiles were evaporated under reduced pressure, the residue dissolved in 5% Diethyl ether/Pet. Ether 40-60 and purified by column chromatography (5% Diethyl ether/Pet. Ether 40-60) to give the desired

compound (14.0 mg, 0.04 mmol, *Z:E* > 20:1 (inseparable geometrical isomers), 81%) as a colourless oil. R_f = 0.49 (10% Diethyl ether/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (dtd, *J* = 10.9, 7.5, 0.9 Hz, 1H, CH'HC**H**=CH), 5.60 (ddt, *J* = 10.9, 2.6, 1.4 Hz, 1H, CH'HCH=C**H**), 4.25 (td, *J* = 7.3, 5.6 Hz, 1H, ClCHCHOC**H**), 4.13 – 4.04 (m, 2H, ClC**H** and ClCHC**H**OCH), 3.97 (ddd, *J* = 8.3, 6.8, 5.6 Hz, 1H, BrCHCHOC**H**), 3.91 (td, *J* = 7.5, 3.9 Hz, 1H, BrCHC**H**), 3.86 (dt, *J* = 8.8, 7.3 Hz, 1H, BrC**H**), 3.12 (dd, *J* = 2.3, 0.9 Hz, 1H, C≡C**H**), 2.70 – 2.63 (m, 2H, BrCHC**H'**H, C**H'**HCH=CH), 2.59 (dddd, *J* = 14.6, 7.4, 6.0, 1.4 Hz, 1H, CH'**H**CH=CH), 2.26 (ddd, *J* = 7.0, 5.3, 2.9 Hz, 2H, ClCHC**H**$_2$), 2.17 (dt, *J* = 13.1, 8.5 Hz, 1H, BrCHCH'**H**), 1.75 (dqd, *J* = 14.0, 7.6, 4.0 Hz, 1H, CH_3C**H'**H), 1.49 (dp, *J* = 14.6, 7.4 Hz, 1H, CH_3CH'**H**), 1.00 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1 (CH'H**C**H=CH), 111.2 (CH'HCH=**C**H), 87.3 (BrCH**C**HOCH), 86.3 (ClCH**C**HOCH), 82.5 (**C**≡CH and C≡**C**H), 80.3 (ClCHCHO**C**H), 79.1 (BrCHCHO**C**H), 59.4 (Cl**C**H), 47.5 (Br**C**H), 39.5 (BrCH**C**H'H), 38.3 (ClCH**C**H_2), 34.6 (**C**H'HCH=CH), 25.6 (CH_3**C**H'H), 10.2. (**C**H_3CH'H). IR (ν_{max} cm^{-1}): 3293 (alkyne sp C–H stretching, strong), 3030 (alkene sp^2 C–H stretching, weak), 2965-2878 (alkane sp^3 C–H stretchings, broad), 2096 (alkyne C≡C stretching, weak), 1250 (ether C–O–C stretching, medium), 1069 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 369.0, 371.0 and 373.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 369.02274, 371.02069 and 373.01774, found *m/z* 369.02282, 371.02055 and 373.01772 ($C_{15}H_{20}O_2{}^{79}Br^{35}ClNa$, $C_{15}H_{20}O_2{}^{81}Br^{35}ClNa$ / $C_{15}H_{20}O_2{}^{79}Br^{37}ClNa$ and $C_{15}H_{20}O_2{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = -32.0$ (c=1.30, $CHCl_3$) . Literature value of enantiomer: $[\alpha]_D^{25} = +36.4$ (c=0.80, $CHCl_3$) ,[169] $[\alpha]_D = +40.3$ (c=1.03, $CHCl_3$) .[15] Spectroscopic data are in accordance with literature data.[15,169]

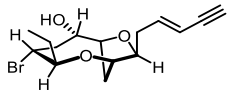
(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1]decan-6-yl acetate 4.58



Compound **4.50** (32.0 mg, 0.09 mmol) was dissolved in a solution of 3:1 dioxane:H_2O (0.92 mL) at room temperature. Then 2,6-lutidine (21.0 µL, 0.18 mmol) was added followed by 2.5% OsO_4 in *t*-BuOH (10.0 µL). $NaIO_4$ (77.0 mg, 0.36 mmol) was added and the reaction mixture was stirred at room temperature until completion. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material (Product R_f = 0.47 (50% EA/Pet. Ether 40-60)). The reaction mixture was diluted with H_2O then extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated. Residual volatiles from the concentrated residue

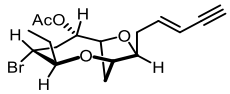
were removed under high vacuum for 1 hour and the residue was taken directly to the next step of the synthesis. Triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (91.0 mg, 0.24 mmol) was dissolved in dry THF (2 mL) and the reaction mixture was cooled to -78 °C. *n*-BuLi (0.1 mL, 0.24 mmol, 2.4 M) was added. The ylide solution was then warmed to -40 °C and stirring was continued for 30 minutes after which it was gradually warmed to -30 °C. The reaction mixture was then cooled to -78 °C again. The concentrated residue was dissolved in dry THF (1.1 mL) and the reaction mixture was cooled to -78 °C, then a portion of the ylide solution (0.76 mL) was added to the reaction mixture. The reaction mixture was warmed to 0 ºC over 2 hours. TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction was quenched with sat. aq. NH_4Cl solution and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (30% EA/Pet. Ether 40-60) to give the desired compound (22.0 mg, 0.05 mmol, *E:Z* = 10:1 (inseparable geometrical isomers), 54% for 2 steps) as a colourless oil. R_f = 0.83 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (dt, *J* = 15.9, 7.4 Hz, 1H, CH_2C**H**=CH), 5.60 (dt, *J* = 15.9, 1.5 Hz, 1H, CH_2CH=C**H**), 4.83 (ddd, *J* = 8.9, 4.1, 2.2 Hz, 1H, AcOC**H**), 4.28 (dd, *J* = 7.7, 4.1 Hz, 1H, AcOCHC**H**), 4.05 (td, *J* = 2.3, 1.2 Hz, 1H, AcOCHCHCH'HC**H**), 3.89 (td, *J* = 10.3, 5.9 Hz, 1H, BrC**H**), 3.80 (td, *J* = 7.3, 2.4 Hz, 1H, OC**H**CH_2CH=CH), 3.46 (ddd, *J* = 8.8, 5.9, 2.4 Hz, 1H, BrCHC**H**), 2.53 (d, *J* = 14.6 Hz, 1H, AcOCHCHC**H'**HCH), 2.51 – 2.43 (m, 2H, C$\mathbf{H}_2$CH=CH), 2.26 – 2.19 (m, 2H, AcOCHC$\mathbf{H}_2$), 2.12 (dqd, *J* = 14.6, 7.4, 2.4 Hz, 1H, CH_3C**H'**H), 2.04 (s, 3H, Acetyl C$\mathbf{H}_3$), 1.90 (ddd, *J* = 14.2, 7.9, 2.3 Hz, 1H, AcOCHCHCH'**H**CH), 1.51 (ddq, *J* = 14.3, 8.8, 7.2 Hz, 1H, CH_3CH'**H**), 0.97 (t, *J* = 7.4 Hz, 3H, C$\mathbf{H}_3$CH'H), 0.16 (s, 9H, Si(C$\mathbf{H}_3$)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (Acetyl **C**=O), 141.3 (CH_2**C**H=CH), 112.5 (CH_2CH=**C**H), 103.8 (**C**≡CTMS), 93.6 (C≡**C**TMS), 82.7 (O**C**HCH_2CH=CH), 80.7 (BrCH**C**H), 80.5 (AcO**C**H), 80.4 (AcOCH**C**H), 76.8 (AcOCHCHCH'H**C**H), 51.5 (Br**C**H), 41.7 (BrCH**C**H_2), 33.7 (**C**H_2CH=CH), 33.5 (AcOCHCH**C**H'HCH), 28.1 (CH_3**C**H'H), 21.6 (Acetyl **C**H_3), 9.8 (**C**H_3CH'H), 0.1 (Si(**C**H_3)$_3$). IR (ν_{max} cm^{-1}): 3007 (alkene sp^2 C–H stretching, weak), 2961-2878 (alkane sp^3 C–H stretchings, broad), 2130 (alkyne C≡C stretching, weak), 1732 (ester C=O stretching, strong), 1238 (ester and ether C–O–C stretching, strong), 1070 (ether C–O–C antisymmetric stretching, strong), 841 (Si–CH_3 rocking, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 465.1 and 467.1 HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 465.10672 and 467.10467, found *m/z* 465.10658 and 467.10449 ($C_{20}H_{31}O_4{}^{79}$BrNaSi and $C_{20}H_{31}O_4{}^{81}$BrNaSi). $[\alpha]_D^{25} = +99.0$ (c=0.44, $CHCl_3$).

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-ol, *ent*-(*E*)-laurefucin *ent*-1.14



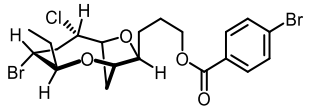
Compound **4.58** (22.0 mg, 0.05 mmol) was dissolved in MeOH (5.0 mL) then K_2CO_3 (14.0 mg, 0.10 mmol) was added. The reaction mixture was then stirred at room temperature overnight. TLC analysis was performed at this stage to confirm the complete consumption of the starting material. All volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (25% EA/Pet. Ether 40-60) to give the desired compound ***ent*-1.14** (7.6 mg, 0.02 mmol, *E:Z*=10:1, 46%) along with *ent*-acetyllaurefucin ***ent*-1.16** (2.9 mg, 7.8 µmol, *E:Z* = 10:1, 16%) as colourless oils. R_f = 0.40 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, C_6D_6) δ 6.23 (dt, *J* = 16.0, 7.3 Hz, 1H, CH'HC**H**=CH), 5.53 (dq, *J* = 16.0, 1.7 Hz, 1H, CH'HCH=C**H**), 4.00 (dd, *J* = 8.0, 3.7 Hz, 1H, HOCHC**H**), 3.61 (dd, *J* = 9.6, 3.7 Hz, 1H, HOC**H**), 3.39 (td, *J* = 10.4, 4.7 Hz, 1H, BrC**H**), 3.32 (td, *J* = 7.2, 2.4 Hz, 1H, OC**H**CH'HCH=CH), 3.21 (d, *J* = 2.8 Hz, 1H, HOCHCHCH'HC**H**), 3.03 (ddd, *J* = 10.4, 9.0, 2.5 Hz, 1H, CH_3CH'HC**H**), 2.56 (d, *J* = 2.2 Hz, 1H, C≡C**H**), 2.35 (dtd, *J* = 13.8, 6.9, 1.6 Hz, 1H, C**H'**HCH=CH), 2.26 (dtd, *J* = 13.9, 7.7, 1.4 Hz, CH'**H**CH=CH), 2.12 (ddd, *J* = 15.0, 4.7, 1.2 Hz, 1H, HOCHC**H'**H), 2.01 – 1.91 (m, 2H, HOCHCH'**H** and CH_3C**H'**H), 1.81 (d, *J* = 14.4 Hz, 1H, HOCHCHC**H'**H), 1.26 (ddq, *J* = 14.3, 8.8, 7.2 Hz, 1H, CH_3CH'**H**), 1.09 (ddd, *J* = 14.4, 8.1, 2.5 Hz, 1H, HOCHCHCH'**H**), 0.76 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'H), 0.50 (s, 1H, O**H**). ^{13}C NMR (126 MHz, C_6D_6) δ 142.6 (CH'H**C**H=CH), 111.5 (CH'HCH=**C**H), 84.0 (HOCH**C**H), 82.5 (**C**≡CH), 82.2 (O**C**HCH'HCH=CH), 80.1 (CH_3CH'H**C**H), 78.0 (HO**C**H), 77.0 (C≡**C**H), 76.9 (HOCHCHCH'H**C**H), 53.3 (Br**C**H), 43.5 (HOCH**C**H'H), 33.9 (**C**H'HCH=CH), 33.1 (HOCHCH**C**H'HCH), 28.4 (CH_3**C**H'H), 9.7 (**C**H_3CH'H). IR (ν_{max} cm^{-1}): 3405 (O–H stretchings, broad), 3294 (alkyne sp C–H stretching, strong), 3008 (alkene sp^2 C–H stretching, weak), 2918-2853 (alkane sp^3 C–H stretchings, broad), 2095 (alkyne C≡C stretching, very weak), 1261 (ether C–O–C stretching, strong), 1065 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 351.1 and 353.1. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 351.05663 and 353.05458, found *m/z* 351.05656 and 353.05458 ($C_{15}H_{21}O_3{}^{79}$BrNa and $C_{15}H_{21}O_3{}^{81}$BrNa). $[\alpha]_D^{25} = +42.0$ (c=0.57, $CHCl_3$). Literature values of enantiomer: $[\alpha]_D^{25} = -77.3$ (c=0.21, $CHCl_3$)[5] and $[\alpha]_D = -80.0$ (conc. and solvent not given).[20] Spectroscopic data are in accordance with literature data.[5,20]

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-yl acetate, *ent*-acetyllaurefucin *ent*-1.16



Compound **4.58** (22.0 mg, 0.05 mmol) was dissolved in MeOH (5.0 mL) then K_2CO_3 (14.0 mg, 0.10 mmol) was added. The reaction mixture was then stirred at room temperature for one overnight. A TLC analysis was performed at this stage to confirm the complete consumption of the starting material. All volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (25% EA/Pet. Ether 40-60) to give the desired compound ***ent*-1.16** (2.9 mg, 7.8 μmol, *E:Z* = 10:1, 16%) along with *ent*-(*E*)-laurefucin ***ent*-1.14** (7.6 mg, 0.02 mmol, *E:Z*=10:1, 46%) as colourless oils. R_f = 0.80 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, C_6D_6) δ 6.14 (dt, *J* = 16.0, 7.5 Hz, 1H, CH_2C**H**=CH), 5.46 (dq, *J* = 16.0, 1.7 Hz, 1H, CH_2CH=C**H**), 5.01 (dd, *J* = 9.9, 4.1 Hz, 1H, AcOC**H**), 4.14 (dd, *J* = 7.8, 4.1 Hz, 1H, AcOCHC**H**), 3.81 (td, *J* = 10.8, 4.8 Hz, 1H, BrC**H**), 3.32 (td, *J* = 7.3, 2.4 Hz, 1H, OC**H**CH_2CH=CH), 3.21 (d, *J* = 2.5 Hz, 1H, AcOCHCHCH'HC**H**), 3.02 (ddd, *J* = 11.0, 7.2, 2.6 Hz, 1H, BrCHC**H**), 2.53 (d, *J* = 2.2 Hz, 1H, C≡C**H**), 2.34 – 2.30 (m, 2H, C**H**$_2$CH=CH), 2.27 (dd, *J* = 14.7, 4.9 Hz, 1H, AcOCHC**H**'H), 2.04 (dt, *J* = 14.8, 10.6 Hz, 1H, AcOCHCH'**H**), 1.96 (dqd, *J* = 14.9, 7.5, 2.6 Hz, 1H, CH_3C**H'**H), 1.80 (d, *J* = 14.3 Hz, 1H, AcOCHCHC**H'**HCH), 1.59 (s, 2H, Acetyl C**H**$_3$), 1.22 (ddq, *J* = 14.4, 9.0, 7.2 Hz, 1H, CH_3CH'**H**), 1.09 (ddd, *J* = 14.3, 7.8, 2.3 Hz, 1H, AcOCHCHCH'**H**CH), 0.74 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8 (Acetyl **C**=O), 142.2 (CH_2**C**H=CH), 111.7 (CH_2CH=**C**H), 82.5 (**C**≡CH), 82.3 (O**C**HCH_2CH=CH), 80.7 (AcO**C**H), 80.5 (BrCH**C**H), 80.3 (AcOCH**C**H), 77.0 (C≡**C**H), 76.8 (AcOCHCHCH'H**C**H), 52.1 (Br**C**H), 42.0 (AcOCH**C**H'H), 33.8 (**C**H_2CH=CH), 33.2 (AcOCHCH**C**H'HCH), 28.1 (Acetyl **C**H_3), 20.8 (CH_3**C**H'H), 9.7 (**C**H_3CH'H). IR (ν_{max} cm^{-1}): 3289 (alkyne sp C–H stretching, strong), 3011 (alkene sp^2 C–H stretching, weak), 2919-2852 (alkane sp^3 C–H stretchings, broad), 2100 (alkyne C≡C stretching, weak), 1730 (ester C=O stretching, strong), 1241 (ester and ether C–O–C stretching, strong), 1071 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 393.1 and 395.1. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 393.06719 and 395.06515, found *m/z* 393.06710 and 395.06510 ($C_{17}H_{23}O_4{}^{79}$BrNa and $C_{17}H_{23}O_4{}^{81}$BrNa). $[\alpha]_D^{25} = +107.0$ (c=0.28, $CHCl_3$) . Literature value of enantiomer: $[\alpha]_D = -126.5$ (conc. and solvent not given).[20] Spectroscopic data are in accordance with literature data.[20]

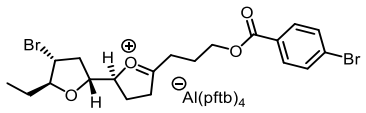
3-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-9-yl)propyl 4-bromobenzoate 4.60



Compound **4.48** (16.0 mg, 0.05 mmol) was mixed with a solution of 0.5 M 9-BBN in THF (0.3 mL) and stirred overnight. Then 15% NaOH (0.17 mL) and 30% H_2O_2 (0.20 mL) were added at 0 °C and stirring was continued for overnight. The reaction mixture was quenched with sat. $Na_2S_2O_3$ and extracted with EA. The organic layer was separated, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (30% Acetone/Pet. Ether 40-60) to remove the majority of the 1,4-cyclooctanediol by-product, which proved difficult-to-separate from the desired primary alcohol. This residue was then dissolved in dry CH_2Cl_2 (0.83 mL), then Et_3N (10 μL, 0.07 mmol) was added followed by DMAP (1 mg, 2.5 μmol) and 4-bromobenzoyl chloride (12.0 mg, 0.06 mmol) and stirred overnight. TLC analysis was performed at this stage to confirm the complete consumption of the starting material. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (10% EA/Pet. Ether 40-60) to give the desired compound as a colourless oil (12.0 mg, 0.02 mmol, 46% over 3 steps). R_f = 0.77 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H, Ar**H**), 7.63 – 7.53 (m, 2H, Ar**H**), 4.46 (dd, *J* = 7.7, 4.3 Hz, 1H, ClCHC**H**O), 4.41 – 4.29 (m, 2H, ArCOOC**H**$_2$), 4.13 (ddd, *J* = 10.6, 4.3, 1.2 Hz, 1H, ClC**H**CHO), 4.06 (td, *J* = 2.4, 1.2 Hz, 1H, ClCHCHCH'HC**H**), 3.86 (td, *J* = 6.7, 2.4 Hz, 1H, ArCOOCH$_2$CH$_2$CH$_2$C**H**), 3.77 (td, *J* = 10.8, 5.1 Hz, 1H, BrC**H**), 3.50 (ddd, *J* = 10.8, 8.7, 2.6 Hz, 1H, CH$_3$CH'HC**H**), 2.68 (ddd, *J* = 15.4, 5.0, 1.1 Hz, 1H, BrCHC**H'**H), 2.60 (dd, *J* = 14.3, 1.1 Hz, 1H, ClCHCHC**H'**HCH), 2.53 (dt, *J* = 15.4, 10.8 Hz, 1H, BrCHCH'**H**), 2.12 (dqd, *J* = 14.8, 7.4, 2.5 Hz, 1H, CH$_3$C**H'**HCH), 1.91 (ddd, *J* = 14.3, 7.7, 2.2 Hz, 1H, ClCHCHCH'**H**CH), 1.88 – 1.78 (m, 4H, 3, ArCOOCH$_2$C**H**$_2$C**H**$_2$CH), 1.47 (ddq, *J* = 14.3, 8.7, 7.2 Hz, 1H, CH$_3$CH'**H**CH), 0.93 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (Ar**C**OO), 131.8 (Ar**C**H), 131.2 (Ar**C**H), 129.4 (Ar**C**Br), 128.2 (Ar**C**), 85.1 (ClCH**C**H), 83.4 (ArCOOCH$_2$CH$_2$CH$_2$**C**H), 80.4 (CH$_3$CH'H**C**H), 77.0 (ClCHCHCH'H**C**H), 66.6 (Cl**C**H), 65.2 (ArCOO**C**H$_2$), 51.9 (Br**C**H), 45.4 (BrCH**C**H'H), 34.5 (ClCHCH**C**H'HCH), 28.2 (CH$_3$**C**H'HCH), 26.4 (ArCOOCH$_2$**C**H$_2$CH$_2$CH), 25.6 (ArCOOCH$_2$CH$_2$**C**H$_2$CH), 9.7 (**C**H$_3$CH'HCH). **NMR data at -78 °C in CD_2Cl_2**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.90 – 7.81 (m, 2H, Ar**H**), 7.61 – 7.50 (m, 2H, Ar**H**), 4.36 (dd, *J* = 7.6, 4.3 Hz, 1H, ClCHC**H**O), 4.23 (m, 2H,

OCHCH$_2$CH$_2$C**H**$_2$OCOAr), 4.09 (q, *J* = 5.4 Hz, 1H, ClC**H**CHO), 4.03 (s, 1H, OC**H**CH'HCHO), 3.79 (t, *J* = 7.7 Hz, 1H, OC**H**CH$_2$CH$_2$CH$_2$OCOAr), 3.74 (q, *J* = 9.4 Hz, 1H, BrC**H**CH$_2$), 3.44 (t, *J* = 10.0 Hz, 1H, CH$_3$CH'HC**H**), 2.64 – 2.44 (m, 3H, BrCHC**H**$_2$, OCHC**H'**HCHO), 2.07 (dq, *J* = 15.0, 7.3 Hz, 1H, CH$_3$C**H'**HCH), 1.88 (dd, *J* = 14.3, 7.5 Hz, 1H, OCHCH'**H**CHO), 1.80 – 1.69 (m, 4H, OCHC**H**$_2$C**H**$_2$CH$_2$OCOAr), 1.31 (dt, *J* = 15.3, 7.5 Hz, 1H, CH$_3$CH'**H**CH), 0.86 (t, *J* = 7.2 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 165.5 (**C**=O), 131.5 (Ar**C**H), 130.8 (Ar**C**H), 128.7 (Ar**C**Br), 127.6 (Ar**C**), 85.1 (ClCH**C**HO), 82.8 (O**C**HCH$_2$CH$_2$CH$_2$OCOAr), 79.6 (CH$_3$CH'H**C**H), 76.3 (O**C**HCH'HCHO), 67.7 (Cl**C**HCHO), 65.1 (OCHCH$_2$CH$_2$**C**H$_2$OCOAr), 52.4 (Br**C**HCH$_2$), 45.6 (BrCH**C**H$_2$), 34.5 (OCH**C**H'HCHO), 27.8 (CH$_3$**C**H'HCH), 26.0 (OCHCH$_2$**C**H$_2$CH$_2$OCOAr), 24.9 (OCH**C**H$_2$CH$_2$CH$_2$OCOAr), 9.6 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 2962-2874 (alkane sp^3 C–H stretchings, broad), 1719 (conjugated ester C=O stretching, strong), 1271 (ester and ether C–O–C stretching, strong), 1065 (ether C–O–C antisymmetric stretching, strong), 849 (aromatic *para*-disubstituted C–H out of plane deformation, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 545.0, 547.0 and 549.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 544.9703, 546.96799 and 548.96594, found *m/z* 544.97010, 546.96783 and 548.96544 ($C_{20}H_{25}O_4{}^{79}Br_2{}^{35}ClNa$, $C_{20}H_{25}O_4{}^{79}Br^{81}Br^{35}ClNa$/ $C_{20}H_{25}O_4{}^{81}Br_2{}^{35}ClNa$/ $C_{20}H_{25}O_4{}^{79}Br^{81}Br^{37}ClNa$ and $C_{20}H_{25}O_4{}^{81}Br_2{}^{37}ClNa$). $[\alpha]_D^{25} = +25.6$ (c=0.37, $CHCl_3$).

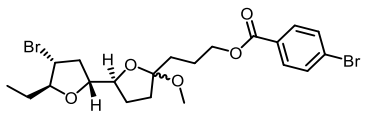
(*S*)-2-((2*R*,4*R*,5*S*)-4-Bromo-5-ethyltetrahydrofuran-2-yl)-5-(3-((4-bromobenzoyl) oxy)propyl)-3,4-dihydro-2*H*-furan-1-ium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate 4.63



Compound **4.60** (14.0 mg, 26.9 μmol) was dissolved in CD_2Cl_2 (0.30 mL) and the reaction mixture was cooled to -78 °C. AgAl(pftb)$_4$·CH_2Cl_2 (35.0 mg, 30.2 μmol) was weighed in a N_2 filled glove bag and dissolved in CD_2Cl_2 (0.30 mL). The suspension of AgAl(pftb)$_4$·CH_2Cl_2 in CD_2Cl_2 was then added to the cold solution of compound **4.60**. The reaction mixture was stirred at -78 °C for 1.5 hr, then filtered into a flame dried and argon filled Young's NMR tube at -78 °C, in which the solution was pale yellow/straw coloured. The sample was then stored in a freezer at -20 °C overnight, in which the colour of the solution changed from pale yellow/straw to red/reddish brown. The sample was then taken for NMR analysis at 25 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.88 – 7.84 (m, 2H, Ar**H**), 7.67 – 7.63 (m, 2H, Ar**H**), 6.20 (td, *J* = 6.3, 2.9 Hz, 1H, OCHC**H**O$^+$), 4.66 (ddd, *J* = 9.4, 7.3, 2.3 Hz, 1H, OC**H**CHO$^+$), 4.53 (ddd, *J* = 12.0, 7.1, 4.9 Hz, 1H, CH$_2$CH$_2$C**H'**HOCOAr), 4.43 (ddd, *J* = 11.9, 6.1, 4.9 Hz, 1H,

$CH_2CH_2CH'\mathbf{H}OCOAr$), 4.13 – 4.06 (m, 2H, BrC**H** and $CH_3CH'HC\mathbf{H}$), 3.91 – 3.80 (m, 2H, $O^+CHCH'HC\mathbf{H}_2$), 3.48 – 3.39 (m, 2H, $C\mathbf{H}_2CH_2CH'HOCOAr$), 2.94 – 2.87 (m, 1H, BrCHC**H'**H), 2.89 – 2.78 (m, 1H, $O^+CHC\mathbf{H'}CH$), 2.69 (dtd, *J* = 13.3, 9.3, 7.2 Hz, 1H, $O^+CHCH'C\mathbf{H}$), 2.41 – 2.33 (m, 2H, $CH_2C\mathbf{H}_2CH'HOCOAr$), 2.12 (ddd, *J* = 13.7, 9.0, 7.3 Hz, 1H, BrCHCH'**H**), 1.67 (dqd, *J* = 15.2, 7.5, 4.7 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 1.51 (dqd, *J* = 14.4, 7.2, 3.4 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 0.93 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 242.4 (O^+=**C**), 168.2 (O=**C**), 132.7 (Ar**C**H), 131.7 (Ar**C**H), 130.0 (Ar**C**), 128.2 (Ar**C**Br), 126.2 (**C**F_3), 123.3 (**C**F_3), 120.4 (**C**F_3), 117.5 (**C**F_3), 110.5 (OCH**C**HO^+), 90.6 ($CH_3CH'H\mathbf{C}H$), 76.3 (O**C**$HCHO^+$), 63.0 ($CH_2CH_2\mathbf{C}H'HOCOAr$), 46.9 ($O^+CHCH'H\mathbf{C}H_2$), 46.4 (Br**C**H), 38.8 (BrCH**C**H'CH), 36.0 (**C**$H_2CH_2CH'HOCOAr$), 26.0 ($CH_3\mathbf{C}H'HCH$), 24.2 ($CH_2\mathbf{C}H_2CH'HOCOAr$), 20.9 ($O^+CH\mathbf{C}H'HCH_2$), 10.1 (**C**$H_3CH'HCH$). **NMR data at -78 °C in CD_2Cl_2**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.84 – 7.80 (m, 2H, Ar**H**), 7.62 – 7.57 (m, 2H, Ar**H**), 6.21 (dt, *J* = 6.7, 3.5 Hz, 1H, OCHC**H**O^+), 4.66 (ddd, *J* = 7.6, 7.2, 3.7 Hz, 1H, OC**H**CHO^+), 4.58 – 4.50 (m, 1H, $CH_2CH_2C\mathbf{H'}HOCOAr$), 4.32 – 4.25 (m, 1H, $CH_2CH_2CH'\mathbf{H}OCOAr$), 4.02 (q, *J* = 7.5 Hz, 1H, BrC**H**CH'H), 3.94 (td, *J* = 11.8, 10.6, 7.4 Hz, 1H, $CH_3CH'HC\mathbf{H}$), 3.79 – 3.72 (m, 2H, $O^+CHCH_2C\mathbf{H}_2$), 3.47 – 3.32 (m, 2H, $C\mathbf{H}_2CH_2CH'HOCOAr$), 2.85 (dt, *J* = 13.8, 7.4 Hz, 1H, BrCHC**H'**H), 2.76 – 2.65 (m, 2H, $O^+CHC\mathbf{H}_2CH_2$), 2.34 – 2.22 (m, 2H, $CH_2C\mathbf{H}_2CH'HOCOAr$), 2.05 (dt, *J* = 13.8, 7.6 Hz, 1H, BrCHCH'**H**), 1.66 (ddq, *J* = 14.2, 10.6, 6.5 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 1.35 (ddq, *J* = 14.4, 11.8, 7.2 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 0.83 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 240.3 (O^+=**C**), 167.9 (O=**C**), 131.8 (Ar**C**H), 131.1 (Ar**C**H), 129.1 (Ar**C**), 127.0 (Ar**C**Br), 124.2 (**C**F_3), 121.9 (**C**F_3), 119.5 (**C**F_3), 117.2 (**C**F_3), 108.9 (OCH**C**HO^+), 88.9 ($CH_3CH'H\mathbf{C}H$), 75.0 (O**C**$HCHO^+$), 62.2 ($CH_2CH_2\mathbf{C}H'HOCOAr$), 46.1 ($O^+CHCH_2\mathbf{C}H_2$), 46.0 (Br**C**HCH'H), 37.5 (BrCH**C**H'H), 34.8 (**C**$H_2CH_2CH'HOCOAr$), 24.8 ($CH_3\mathbf{C}H'HCH$), 22.2 ($CH_2\mathbf{C}H_2CH'HOCOAr$), 19.9 ($O^+CH\mathbf{C}H_2CH_2$), 9.8 (**C**$H_3CH'HCH$). HRMS (ESI) $[M]^+$: calculated for *m/z* 487.01141, 489.00936 and 491.00732, found *m/z* 487.01149, 489.00936 and 491.00728 ($C_{20}H_{25}O_4{}^{79}Br_2$, $C_{20}H_{25}O_4{}^{79}Br^{81}Br$ and $C_{20}H_{25}O_4{}^{81}Br_2$).

3-((2*S*,2'*R*,4'*R*,5'*S*)-4'-Bromo-5'-ethyl-5-methoxyoctahydro-[2,2'-bifuran]-5-yl) propyl 4-bromobenzoate 4.64

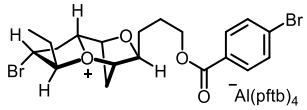


Compound **4.60** (14.0 mg, 26.9 μmol) was dissolved in CD_2Cl_2 (0.30 mL) and the reaction mixture was cooled to -78 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (35.0 mg, 30.2 μmol) was weighed in a N_2 filled glove bag and dissolved in CD_2Cl_2 (0.30 mL). The suspension

of $AgAl(pftb)_4 \cdot CH_2Cl_2$ in CD_2Cl_2 was then added to the cold solution of compound **4.60**. The reaction mixture was stirred at -78 °C for 1.5 hr, then filtered into a flame dried and argon filled Young's NMR tube at -78 °C. The sample was then stored in a freezer at -20 °C overnight then taken for NMR analysis at 25 °C. After the analysis, an excess of MeOH (2.0 mL) was added to the reaction mixture in the Young's NMR tube, in which the red/reddish brown solution was decolourised instantaneously, the solution was then shaken for 20 seconds. An excess of $NaHCO_3$ was then added to neutralise the acid in the reaction mixture. The crude mixture was concentrated under reduced pressure and mixed with minimum volume of 10% EA/Pet. Ether 40-60. The suspension was then loaded on a column and underwent purification by flash chromatography (20% EA/Pet. Ether) to give compound **4.64** (9.0 mg, 17.3 μmol, 1.3:1 mixture of epimers, 64%) as a colourless oil. R_f = 0.61 (20% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.82 (m, 2H, Ar**H**, both epimers), 7.63 – 7.53 (m, 2H, Ar**H**, both epimers), 4.39 – 4.30 (m, 2H, CH'HCH$_2$C**H**$_2$OCOAr, both epimers), 4.17 – 4.10 (m, 1H, OCHC**H**OCOCH$_3$, both epimers), 3.98 – 3.90 (m, 2H, CH$_3$CH'HC**H** and OC**H**CHOCOCH$_3$, both epimers), 3.90 – 3.84 (m, 1H, BrC**H**, both epimers), 3.24 – 3.17 (m, 3H, OCHCHOCOC**H**$_3$, both epimers), 2.73 – 2.58 (m, 1H, BrCHC**H'**H, both epimers), 2.30 (dt, *J* = 13.3, 8.3 Hz, 0.5H, BrCHCH'**H**, minor epimer), 2.22 – 2.13 (m, 1H, BrCHCH'**H** and OCHC**H'**HCH'H, major epimer), 2.11 – 2.00 (m, 1H, OCHC**H'**HCH'H and OCHCH'HC**H'**H, minor epimer; **C**H'HCH$_2$CH$_2$OCOAr, both epimers), 1.99 – 1.88 (m, 1H, OCHCH'**H**CH'H, minor epimer; OCHCH'HC**H'**H, major epimer), 1.86 – 1.73 (m, 1H, OCHCH'**H**CH'H, major epimer; OCHCH'HCH'**H** and C**H'**HCH$_2$CH$_2$OCOAr, both epimers), 1.73 – 1.61 (m, 1H, CH$_3$C**H'**HCH and CH'**H**CH$_2$CH$_2$OCOAr, both epimers), 1.50 (dt, *J* = 14.5, 7.3 Hz, 1H, CH$_3$CH'**H**CH, both epimers), 1.02 – 0.95 (m, 3H, C**H**$_3$CH'HCH, both epimers). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (**C**=O, both epimers), 131.9 (Ar**C**H, both epimers), 131.2 (Ar**C**H, both epimers), 129.4 (Ar**C**, both epimers) 128.2 (Ar**C**Br, both epimers), 109.7 (OCHCHO**C**OCH$_3$, both epimers), 87.2 (CH$_3$CH'H**C**H, major epimer), 86.9 (CH$_3$CH'H**C**H, minor epimer), 82.9 (OCH**C**HOCOCH$_3$, minor epimer), 80.8 (OCH**C**HOCOCH$_3$, major epimer), 80.2 (O**C**HCHOCOCH$_3$, minor epimer), 79.4 (O**C**HCHOCOCH$_3$, major epimer), 65.3 (CH'HCH$_2$**C**H$_2$OCOAr, both epimers), 48.5 (OCHCHOCO**C**H$_3$, minor epimer), 48.4 (OCHCHOCO**C**H$_3$, major epimer), 47.9 (Br**C**H, minor epimer), 47.8 (Br**C**H, major epimer), 39.7 (BrCH**C**H'H, minor epimer), 39.5 (BrCH**C**H'H, major epimer), 36.2 (OCHCH'H**C**H'H, minor epimer), 35.0 (OCHCH'H**C**H'H, major epimer), 31.5 (**C**H'HCH$_2$CH$_2$OCOAr, minor epimer), 31.0 (**C**H'HCH$_2$CH$_2$OCOAr, major epimer), 28.1 (OCH**C**H'HCH'H, minor epimer), 26.8 (OCH**C**H'HCH'H, major epimer), 25.6 (CH$_3$**C**H'HCH, both epimers), 24.3 (CH'H**C**H$_2$CH$_2$OCOAr, both epimers), 10.1 (**C**H$_3$CH'HCH, major epimer), 10.0

(**C**H_3CH'HCH, minor epimer). IR (ν_{max} cm^{-1}): 2960-2853 (alkane sp^3 C–H stretching, broad), 1721 (ester C=O stretching, strong), 1591 (aromatic C=C stretching, medium), 1272 (ester and ether C–O–C stretching, strong), 1115, 1103, 1069, 1038, 1012 (ether C–O–C stretchings, strong), 757 (aromatic *para*-disubstituted C–H out of plane deformation, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 541.0, 543.1 and 545.0. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 541.01957, 543.01752 and 545.01548, found *m/z* 541.01952, 543.10737 and 545.01536. ($C_{21}H_{28}O_5{}^{79}Br_2Na$, $C_{21}H_{28}O_5{}^{79}Br^{81}BrNa$ and $C_{21}H_{28}O_5{}^{81}Br_2Na$).

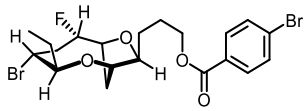
(1*S*,3*S*,4*S*,6*S*,7*R*,8a*R*)-7-Bromo-3-(3-((4-bromobenzoyl)oxy)propyl)-6-ethyl hexahydro-1*H*-1,4-methanofuro[1,2-a][1,4]dioxin-5-ium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate 4.62



Compound **4.60** (10.4 mg, 20.0 μmol) was dissolved in CD_2Cl_2 (0.30 mL) and the reaction mixture was cooled to -78 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (25.0 mg, 21.6 μmol) was weighed in a nitrogen filled glove bag and dissolved in CD_2Cl_2 (0.30 mL). The suspension of $AgAl(pftb)_4{\cdot}CH_2Cl_2$ in CD_2Cl_2 was then added to the cold solution of compound **4.60**. The reaction mixture was stirred at -78 °C for 1.5 hr, then filtered into a flame dried and argon filled Young's NMR tube at -78 °C, in which the solution was pale yellow/straw coloured. The sample was then taken for NMR analysis at -78 °C. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.87 – 7.78 (m, 2H, Ar**H**), 7.60 – 7.54 (m, 2H, Ar**H**), 5.60 (d, *J* = 2.4 Hz, 1H, O^+C**H**CH'HCHO), 5.45 (dd, *J* = 12.2, 5.6 Hz, 1H, O^+C**H**CH'HCHBr), 4.97 (d, *J* = 3.0 Hz, 1H, O^+CHCH'HC**H**O), 4.63 (ddd, *J* = 11.3, 5.9, 3.6 Hz, 1H, CH_3CH'HC**H**O^+), 4.31 (dt, *J* = 11.1, 5.5 Hz, 1H, OCHCH'HCH'HC**H'**HOCOAr), 4.22 (td, *J* = 9.1, 7.9, 2.7 Hz, 2H, OCHCH'HCH'HCH'**H**OCOAr and OC**H**CH'HCH'HCH'HOCOAr), 4.15 (td, *J* = 11.3, 6.4 Hz, 1H, O^+CHCH'HC**H**Br), 3.10 (dt, *J* = 12.7, 6.0 Hz, 1H, O^+CHC**H'**HCHBr), 2.73 (dd, *J* = 13.5, 3.3 Hz, 1H, O^+CHC**H'**HCHO), 2.56 (dd, *J* = 13.4, 2.6 Hz, 1H, O^+CHCH'**H**CHO), 2.33 – 2.25 (m, 1H, CH_3C**H'**HCHO^+), 2.22 – 2.11 (m, 2H, O^+CHCH'**H**CHBr and CH_3CH'**H**CHO^+), 1.98 – 1.89 (m, 1H, OCHCH'HC**H'**HCH'HOCOAr), 1.85 – 1.72 (m, 2H, OCHC**H'**HCH'HCH'HOCOAr and OCHCH'HCH'**H**CH'HOCOAr), 1.69 – 1.61 (m, 1H, OCHCH'**H**CH'HCH'HOCOAr), 1.08 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHO^+). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 165.7 (**C**=O), 131.6 (Ar**C**H), 130.8 (Ar**C**H), 128.3 (Ar**C**Br), 128.1 (Ar**C**), 124.2 (**C**F_3), 121.9 (**C**F_3), 119.5 (**C**F_3), 117.2 (**C**F_3), 110.3 (O^+**C**HCH'HCHBr), 104.0 (CH_3CH'H**C**HO^+), 99.8 (O^+**C**HCH'HCHO), 79.4

(O**C**HCH'HCH'HCH'HOCOAr), 76.5 (O^+CHCH'H**C**HO), 64.0 (OCHCH'HCH'H**C**H'HOCOAr), 37.5 (O^+CHCH'H**C**HBr), 37.1 (O^+CH**C**H'HCHBr), 33.4 (O^+CH**C**H'HCHO), 26.5 (OCHCH'H**C**H'HCH'HOCOAr), 24.6 (OCH**C**H'HCH'HCH'HOCOAr), 22.1 (CH_3**C**H'HCHO$^+$), 8.4 (**C**H_3CH'HCHO$^+$).

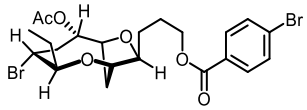
3-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-6-fluoro-2,8-dioxabicyclo[5.2.1]decan-9-yl)propyl 4-bromobenzoate 4.72



Compound **4.60** (16.5 mg, 31.7 μmol) was dissolved in CH_2Cl_2 (0.50 mL) and the reaction mixture was cooled to -78 °C. $AgAl(pftb)_4 \cdot CH_2Cl_2$ (40.6 mg, 35.0 μmol) was weighed in a nitrogen filled glove bag and dissolved in CH_2Cl_2 (0.50 mL). The suspension of $AgAl(pftb)_4 \cdot CH_2Cl_2$ in CH_2Cl_2 was then added to the cold solution of compound **4.60**. The reaction mixture was stirred at -78 °C for 1.5 hr, then TBAF solution (1.0 M in THF) (0.16 mL, 0.16 mmol) was added and the reaction mixture warmed to room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (20% EA/Pet. Ether) to give the desired compound **4.72** as a colourless oil (7.0 mg, 13.9 μmol, 43%). R_f = 0.49 (10% EA/ Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 2H, Ar**H**), 7.62 – 7.54 (m, 2H, Ar**H**), 4.63 (dddd, *J* = 47.9, 10.9, 2.9, 1.3 Hz, 1H, FC**H**), 4.41 – 4.26 (m, 3H, FCHC**H**O, OCHCHCH$_2$CH$_2$C**H**$_2$OCOAr), 4.03 (td, *J* = 3.4, 1.9 Hz, 1H, OC**H**CHCH$_2$CH$_2$CH$_2$OCOAr), 3.83 (td, *J* = 6.8, 2.4 Hz, 1H, OCHC**H**CH$_2$CH$_2$CH$_2$OCOAr), 3.75 (td, *J* = 11.1, 5.2 Hz, 1H, BrC**H**), 3.42 (ddd, *J* = 10.7, 8.6, 2.6 Hz, 1H, CH$_3$CH'HC**H**), 2.55 – 2.39 (m, 2H, FCHC**H'**H, OCHC**H'**HCHO), 2.32 (dt, *J* = 14.9, 11.4 Hz, 1H, FCHCH'**H**), 2.11 (dtd, *J* = 14.7, 7.4, 2.6 Hz, 1H, CH$_3$C**H'**HCH), 1.94 (ddd, *J* = 14.2, 7.8, 2.2 Hz, 1H, OCHCH'**H**CHO), 1.92 – 1.73 (m, 4H, OCHCHCH$_2$C**H**$_2$C**H**$_2$OCOAr), 1.48 (ddq, *J* = 14.3, 8.6, 7.3 Hz, 1H, CH$_3$CH'**H**CH), 0.94 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (**C**=O), 131.8 (Ar**C**), 131.2 (Ar**C**), 129.4 (Ar**C**Br), 128.2 (Ar**C**), 99.8 (d, *J* = 170.9 Hz, F**C**H), 82.9 (OCH**C**HCH$_2$CH$_2$CH$_2$OCOAr), 81.6 (d, *J* = 32.4 Hz, FCH**C**HO), 80.3 (CH$_3$CH'H**C**H), 76.9 (O**C**HCHCH$_2$CH$_2$CH$_2$OCOAr), 65.2 (OCHCHCH$_2$CH$_2$**C**H$_2$OCOAr), 50.6 (d, *J* = 10.5 Hz, Br**C**H), 42.43 (d, *J* = 26.8 Hz, FCH**C**H'H), 33.83 (d, *J* = 7.0 Hz, OCH**C**H'HCHO), 27.9 (CH$_3$**C**H'HCH), 26.4 (OCHCHCH$_2$**C**H$_2$CH$_2$OCOAr), 25.7 (OCHCH**C**H$_2$CH$_2$CH$_2$OCOAr), 9.6 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 2963-2875 (alkane sp^3 C–H stretching, broad), 1719 (ester C=O stretching, strong), 1590 (aromatic C=C stretching, medium), 1270 (ester

and ether C–O–C stretching, strong), 1241 (C-F stretching, strong), 1067 (ether C–O–C antisymmetric stretching, strong), 757 (aromatic *para*-disubstituted C–H out of plane deformation, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 529.0, 531.0 and 533.0. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 528.99958, 530.99754 and 532.99549, found *m/z* 528.99958, 530.99741 and 532.99516. ($C_{20}H_{25}O_4{}^{79}Br_2FNa$, $C_{20}H_{25}O_4{}^{79}Br^{81}BrFNa$ and $C_{20}H_{25}O_4{}^{81}Br_2FNa$). $[\alpha]_D^{25} = +28.6$ (c=0.70, $CHCl_3$).

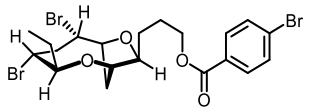
3-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-6-acetoxy-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-9-yl)propyl 4-bromobenzoate 4.73



Compound **4.60** (18.3 mg, 35.1 μmol) was dissolved in CH_2Cl_2 (0.50 mL) and the reaction mixture was cooled to -78 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (45.0 mg, 38.8 μmol) was weighed in a nitrogen filled glove bag and dissolved in CH_2Cl_2 (0.50 mL). The suspension of $AgAl(pftb)_4{\cdot}CH_2Cl_2$ in CH_2Cl_2 was then added to the cold solution of compound **4.60**. The reaction mixture was stirred at -78 °C for 1.5 hr, then TBAOAc (53.0 mg, 175 μmol) was added and the reaction mixture warmed to room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60) to give the desired compound **4.73** as a colourless oil (11.4 mg, 20.9 μmol, 60%). R_f = 0.34 (10% EA/Pet. Ether 40-60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H, Ar**H**), 7.61 – 7.53 (m, 2H, Ar**H**), 4.86 (ddd, *J* = 8.6, 4.0, 2.3 Hz, 1H, AcOC**H**), 4.38 – 4.31 (m, 2H, OCHCHCH$_2$CH$_2$C**H**$_2$OCOAr), 4.29 (dd, *J* = 7.8, 4.1 Hz, 1H, AcOCHC**H**O), 4.06 (td, *J* = 2.3, 1.1 Hz, 1H, OCHC**H**CH$_2$CH$_2$CH$_2$OCOAr), 3.89 (dt, *J* = 10.3, 5.2 Hz, 1H, BrC**H**), 3.84 (dd, *J* = 6.1, 3.6 Hz, 1H, OC**H**CHCH$_2$CH$_2$CH$_2$OCOAr), 3.47 (ddd, *J* = 10.7, 8.8, 2.6 Hz, 1H, CH$_3$CH'HC**H**), 2.55 (d, *J* = 14.2 Hz, 1H, OCHC**H'**HCHO), 2.30 – 2.18 (m, 2H, AcOCHC**H**$_2$CH), 2.11 (dqd, *J* = 14.7, 7.4, 2.5 Hz, 1H, CH$_3$C**H'**HCH), 2.05 (s, 3H, **C**H$_3$C=O), 1.92 (ddd, *J* = 14.2, 7.8, 2.3 Hz, 1H, OCHCH'**H**CHO), 1.88 – 1.77 (m, 4H, OCHCHC**H**$_2$C**H**$_2$CH$_2$OCOAr), 1.49 (ddq, *J* = 14.3, 8.7, 7.2 Hz, 1H, CH$_3$CH'**H**CH), 0.94 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (CH$_3$**C**=O), 166.0 (**C**=O), 131.8 (Ar**C**H), 131.2 (Ar**C**H), 129.4 (Ar**C**Br), 128.1 (Ar**C**), 83.3 (OCH**C**HCH$_2$CH$_2$CH$_2$OCOAr), 80.7 (AcO**C**H), 80.5 (CH$_3$CH'H**C**H), 80.2 (AcOCH**C**HO), 77.0 (O**C**HCHCH$_2$CH$_2$CH$_2$OCOAr), 65.2 (OCHCHCH$_2$CH$_2$**C**H$_2$OCOAr), 51.6 (Br**C**H), 41.6 (AcOCH**C**H$_2$CH), 33.6 (OCH**C**H'HCHO), 28.1 (CH$_3$**C**H'HCH), 26.3 (OCHCHCH$_2$**C**H$_2$CH$_2$OCOAr), 25.7 (OCHCH**C**H$_2$CH$_2$CH$_2$OCOAr), 21.6 (**C**H$_3$C=O), 9.8 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}):

2963-2875 (alkane sp^3 C–H stretching, broad), 1719 (ester C=O stretching, strong), 1590 (aromatic C=C stretching, medium), 1285 (ester and ether C–O–C stretching, strong), 1067 (ether C–O–C antisymmetric stretching, strong), 757 (aromatic *para*-disubstituted C–H out of plane deformation, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 569.0, 571.0 and 573.0. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 569.01448, 571.01244 and 573.01039, found *m/z* 569.01462, 571.01239 and 573.01018. ($C_{22}H_{28}O_6{}^{79}Br_2Na$, $C_{22}H_{28}O_6{}^{79}Br^{81}BrNa$ and $C_{22}H_{28}O_6{}^{81}Br_2Na$). $[\alpha]_D^{25} = +57.3$ (c=1.20, $CHCl_3$).

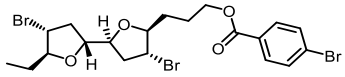
3-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4,6-Dibromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-9-yl)propyl 4-bromobenzoate 4.74



Compound **4.60** (22.0 mg, 42.2 μmol) was dissolved in CH_2Cl_2 (0.50 mL) and the reaction mixture was cooled to -78 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (147.0 mg, 0.127 mmol) was weighed in a nitrogen filled glove bag and dissolved in CH_2Cl_2 (0.50 mL). The suspension of $AgAl(pftb)_4{\cdot}CH_2Cl_2$ in CH_2Cl_2 was then added to the cold solution of compound **4.60**. The reaction mixture was stirred at -78 °C for 1.5 hr, then filtered with a filter cannula into a flame dried 10 mL round bottom flask at -78 °C under nitrogen. To the filtrate was added TBAB (68.0 mg, 0.211 mmol) and the reaction mixture warmed to room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (20% EA/Pet. Ether 40-60) to give the desired compound **4.74** as a colourless oil (11.0 mg, 19.5 μmol, 46%). R_f = 0.71 (30% EA/Pet. Ether 40-60, same R_f as the starting material). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 2H, Ar**H**), 7.62 – 7.54 (m, 2H, Ar**H**), 4.67 (dd, *J* = 7.7, 4.4 Hz, 1H, BrCHC**H**O), 4.36 (m, *J* = 4.8 Hz, 2H, OCHCH$_2$CH$_2$C**H**$_2$OCOAr), 4.22 (dd, *J* = 10.7, 4.5 Hz, 1H, BrC**H**CHO), 4.10 (d, *J* = 2.8 Hz, 1H, OC**H**CH'HCHO), 3.85 (td, *J* = 6.6, 2.4 Hz, 1H, OC**H**CH$_2$CH$_2$CH$_2$OCOAr), 3.77 (td, *J* = 10.8, 5.0 Hz, 1H, BrC**H**CH'H), 3.51 (ddd, *J* = 10.8, 8.6, 2.6 Hz, 1H, CH$_3$CH'HC**H**), 2.86 (dd, *J* = 15.5, 5.0 Hz, 1H, BrCHC**H'**H), 2.71 – 2.55 (m, 2H, BrCHCH'**H** and OCHC**H'**HCHO), 2.11 (dqd, *J* = 14.7, 7.4, 2.5 Hz, 1H, CH$_3$C**H'**HCH), 1.85 (m, 5H, OCHCH'**H**CHO and OCHC**H**$_2$C**H**$_2$CH$_2$OCOAr), 1.47 (dp, *J* = 14.7, 7.5 Hz, 1H, CH$_3$CH'**H**CH), 0.93 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (**C**=O), 131.8 (Ar**C**H), 131.2 (Ar**C**H), 129.4 (Ar**C**Br), 128.2 (Ar**C**), 85.8 (BrCH**C**HO), 83.4 (O**C**HCH$_2$CH$_2$CH$_2$OCOAr), 80.5 (CH$_3$CH'H**C**H), 77.0 (O**C**HCH'HCHO), 65.2 (OCHCH$_2$CH$_2$**C**H$_2$OCOAr), 58.1 (Br**C**HCHO), 52.1 (Br**C**HCH'H), 46.2 (BrCH**C**H'H), 34.8 (OCH**C**H'HCHO), 28.2 (CH$_3$**C**H'HCH), 26.4

(OCHCH$_2$**C**H$_2$CH$_2$OCOAr), 25.6 (OCH**C**H$_2$CH$_2$CH$_2$OCOAr), 9.7 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 2961-2875 (alkane sp^3 C–H stretching, broad), 1719 (ester C=O stretching, strong), 1591 (aromatic C=C stretching, medium), 1272 (ester and ether C–O–C stretching, strong), 1066 (ether C–O–C antisymmetric stretching, strong), 757 (aromatic *para*-disubstituted C–H out of plane deformation, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 588.9, 590.9, 592.9 and 594.9. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 588.91952, 590.91747, 592.91543 and 594.91338, found *m/z* 588.91900, 590.91767, 592.91540 and 594.91326. ($C_{20}H_{25}O_4{}^{79}Br_3Na$, $C_{20}H_{25}O_4{}^{79}Br_2{}^{81}BrNa$, $C_{20}H_{25}O_4{}^{79}Br{}^{81}Br_2Na$ and $C_{20}H_{25}O_4{}^{81}Br_3Na$). $[\alpha]_D^{25} = +19.5$ (c=1.10, $CHCl_3$).

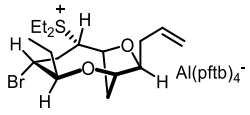
3-((2*S*,2'*R*,4*R*,4'*R*,5*S*,5'*S*)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)propyl 4-bromobenzoate 4.75



Compound **4.74** (11.0 mg, 19.5 μmol) in $CDCl_3$ in an NMR tube was kept under ambient conditions for 7 days, in which at this point its ^{1}H NMR spectrum was acquired and suggested incomplete conversion to compound **4.75**. The sample was then heated to 50 °C for three days in which its ^{1}H NMR spectrum was acquired again and at this point suggested quantitative and clean conversion to compound **4.75**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.81 (m, 2H, Ar**H**), 7.66 – 7.48 (m, 2H, Ar**H**), 4.35 (t, *J* = 6.4 Hz, 2H, OCHCH'HCH'HC**H**$_2$OCOAr), 4.22 (td, *J* = 7.0, 5.4 Hz, 1H, BrCHCH$_2$C**H**), 4.09 (ddd, *J* = 8.3, 6.0, 3.9 Hz, 1H, OC**H**CH'HCH'HCH$_2$OCOAr), 3.99 – 3.90 (m, 2H, BrC**H**CH$_2$CH, CH$_3$CH'HCHBrCHCH'HC**H**), 3.90 (td, *J* = 7.5, 4.0 Hz, 1H, CH$_3$CH'HC**H**BrCHCH'HCH), 3.86 (dt, *J* = 8.6, 7.3 Hz, 1H, CH$_3$CH'HCHBrC**H**CH'HCH), 2.65 (dt, *J* = 13.6, 7.0 Hz, 1H, CH$_3$CH'HCHBrCHC**H'**HCH), 2.43 – 2.30 (m, 2H, BrCHC**H**$_2$CH), 2.15 (dt, *J* = 13.2, 8.4 Hz, 1H, CH$_3$CH'HCHBrCHCH'**H**CH), 2.01 – 1.91 (m, 1H, OCHCH'HC**H'**HCH$_2$OCOAr), 1.93 – 1.79 (m, 2H, OCHC**H'**HCH'HCH$_2$OCOAr and OCHCH'HCH'**H**CH$_2$OCOAr), 1.73 (dqd, *J* = 15.0, 7.5, 4.0 Hz, 1H, CH$_3$C**H'**HCHBrCHCH'HCH), 1.62 (dtd, *J* = 12.7, 9.9, 5.3 Hz, 1H, OCHCH'**H** CH'HCH$_2$OCOAr), 1.48 (dp, *J* = 14.6, 7.3 Hz, 1H, CH$_3$CH'**H**CHBrCHCH'HCH), 0.99 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCHBrCHCH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (**C**=O), 131.9 (Ar**C**H), 131.3 (Ar**C**H), 129.4 (Ar**C**), 128.2 (Ar**C**Br), 87.4 (CH$_3$CH'H**C**HBrCHCH'HCH), 86.9 (O**C**HCH'HCH'HCH$_2$OCOAr), 80.2 (BrCHCH$_2$**C**H), 79.0 (CH$_3$CH**'**HCHBrCHCH'H**C**H), 65.1 (OCHCH'HCH'H**C**H$_2$OCOAr), 48.9 (Br**C**HCH$_2$CH), 47.4 (CH$_3$CH'HCHBr**C**HCH'HCH), 39.5 (CH$_3$CH'HCHBrCH**C**H'HCH), 38.7 (BrCH**C**H$_2$CH), 30.1 (OCH**C**H'HCH'HCH$_2$OCOAr), 25.6

(CH_3**C**H'HCHBrCHCH'HCH), 25.3 (OCHCH'H**C**H'HCH_2OCOAr), 10.2 (**C**H_3CH'HCHBrCH CH'HCH). IR (ν_{max} cm^{-1}): 2962-2877 (alkane sp^3 C–H stretching, broad), 1719 (ester C=O stretching, strong), 1591 (aromatic C=C stretching, medium), 1271 (ester and ether C–O–C stretching, strong), 1068 (ether C–O–C antisymmetric stretching, strong), 757 (aromatic *para*-disubstituted C–H out of plane deformation, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 588.9, 590.9, 592.9 and 594.9. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 588.91952, 590.91747, 592.91543 and 594.91338, found *m/z* 588.91984, 590.91733, 592.91515 and 594.91253. ($C_{20}H_{25}O_4{}^{79}Br_3Na$, $C_{20}H_{25}O_4{}^{79}Br_2{}^{81}BrNa$, $C_{20}H_{25}O_4{}^{79}Br{}^{81}Br_2Na$ and $C_{20}H_{25}O_4{}^{81}Br_3Na$). $[\alpha]_D^{25} = -28.7$ (c=0.71, $CHCl_3$).

((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-yl) diethylsulfonium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate 4.51



Compound **4.48** (6.0 mg, 17.0 μmol) was dissolved in CH_2Cl_2 (0.5 mL) at -78 °C. $AgAl(pftb)_4 \cdot CH_2Cl_2$ (22.0 mg, 19.0 μmol) was weighed in a nitrogen filled glove bag and dissolved in CH_2Cl_2 (0.5 mL). The suspension of $AgAl(pftb)_4 \cdot CH_2Cl_2$ in CH_2Cl_2 was then added to the cold solution of compound **4.48**. The reaction mixture was stirred at -78 °C for 1.5 hrs, then filtered into a flame dried round bottom flask at -78 °C. A solution of Et_2S (0.19 mL, 19 μmol, 0.1 M in CH_2Cl_2) was added at -78 °C and the reaction mixture was warmed to room temperature. All volatiles were removed under reduced pressure and the residue was dissolved in $CDCl_3$ for NMR analysis at 25 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, OCHCH_2C**H**CH_2), 5.22 – 5.05 (m, 2H, OCHCH_2CHC**H**$_2$), 4.35 (dd, *J* = 7.3, 5.2 Hz, 1H, (CH_3CH_2)$_2$S$^+$CHC**H**CH'HCH), 4.18 (q, *J* = 1.8 Hz, 1H, (CH_3CH_2)$_2$S$^+$CHCHCH'HC**H**), 3.99 (td, *J* = 7.3, 2.3 Hz, 1H, OC**H**CH_2CHCH_2), 3.76 (dd, *J* = 9.9, 5.2 Hz, 1H, (CH_3CH_2)$_2$S$^+$C**H**CHCH'HCH), 3.70 (td, *J* = 11.2, 10.8, 4.9 Hz, 1H, CH_3CH'HCHC**H**BrCH'H), 3.63 (ddd, *J* = 10.6, 8.6, 2.4 Hz, 1H, CH_3CH'HC**H**CHBrCH'H), 3.43 – 3.34 (m, 1H, (CH_3C**H**$_2$)$_2$S$^+$CHCHCH'HCH), 3.33 – 3.26 (m, 1H, (CH_3C**H**$_2$)$_2$S$^+$CHCHCH'HCH), 3.22 (dtd, *J* = 13.9, 7.4, 1.2 Hz, 2H, (CH_3C**H**$_2$)$_2$S$^+$CHCHCH'HCH), 2.64 (dd, *J* = 14.7, 1.4 Hz, 1H, (CH_3CH_2)$_2$S$^+$CHCHC**H'**HCH), 2.50 – 2.38 (m, 3H, OCHC**H**$_2$CHCH_2, CH_3CH'HCHCHBrC**H'**H), 2.31 (dd, *J* = 15.4, 4.9 Hz, 1H, CH_3CH'HCHCHBrCH'**H**), 2.20 (dd, *J* = 7.6, 2.3 Hz, 1H, CH_3C**H'**HCHCHBrCH'H), 2.19 – 2.13 (m, 1H, (CH_3CH_2)$_2$S$^+$CHCHCH'**H**CH), 1.65 – 1.54 (m, 6H, (C**H**$_3$CH$_2$)$_2$S$^+$CHCHCH'HCH),

1.56 – 1.49 (m, 1H, CH_3CH'**H**$CHCHBrCH'H$), 0.99 (t, *J* = 7.3 Hz, 3H, C**H**$_3CH'HCHCHBrCH'H$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.9 ($OCHCH_2$**C**HCH_2), 118.4 ($OCHCH_2CH$**C**H_2), 84.6 (O**C**HCH_2CHCH_2), 81.5 ($CH_3CH'H$**C**$HCHBrCH'H$), 76.7 (($CH_3CH_2)_2S^+CHCHCH'H$**C**H), 75.6 (($CH_3CH_2)_2S^+CH$**C**$HCH'HCH$), 59.7 (($CH_3CH_2)_2S^+$**C**$HCHCH'HCH$), 49.0 ($CH_3CH'HCH$**C**$HBrCH'H$), 37.5 $CH_3CH'HCHCHBr$**C**$H'H$), 34.8 (($CH_3CH_2)_2S^+CHCH$**C**$H'HCH$), 33.9 (OCH**C**H_2CHCH_2), 33.2 ((CH_3**C**$H_2)_2S^+CHCHCH'HCH$), 31.3 ((CH_3**C**$H_2)_2S^+CHCHCH'HCH$), 28.0 (CH_3**C**$H'HCHCHBrCH'H$), 9.5 ((**C**$H_3CH_2)_2S^+CHCHCH'HCH$), 9.4 ((**C**$H_3CH_2)_2S^+CHCHCH'HCH$), 9.4 (**C**$H_3CH'HCHCHBrCH'H$).

10.2 Experimental for Chapters 5 and 6

The compounds **5.11** and **5.12** were not characterised due to extensive overlapping of resonances in their NMR spectra. However, their ^{1}H and ^{13}C NMR spectra were compared to that of **4.5** to prove the consumption of the internal alkene and the formation of the epoxide.

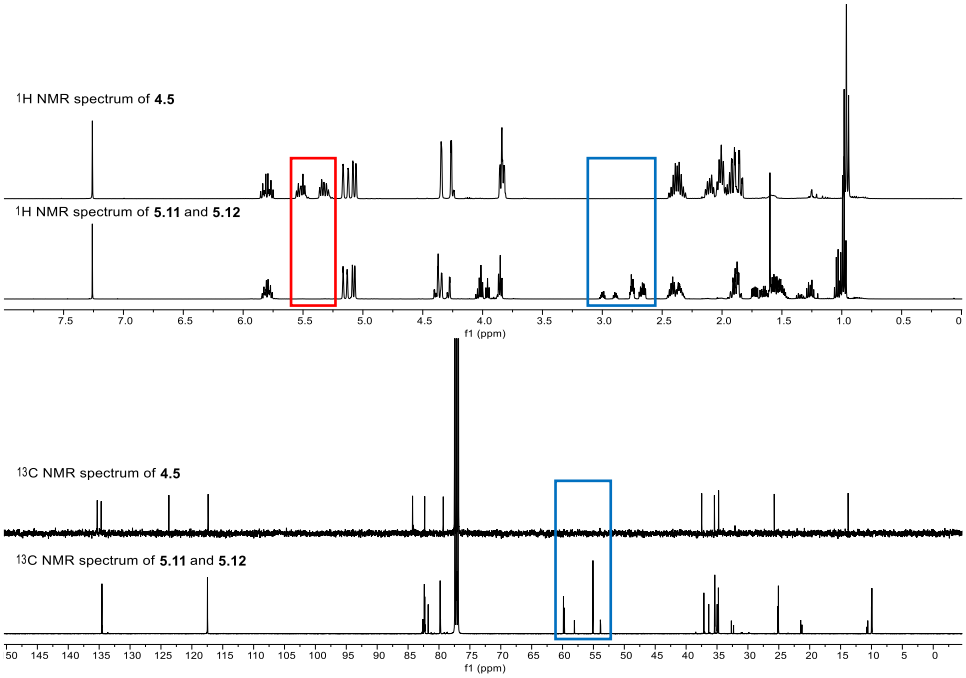
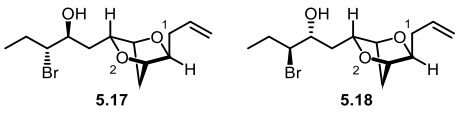


Figure 10.1. Comparison of ^{1}H and ^{13}C NMR spectra (400 MHz, $CDCl_3$) between **4.5**, **5.11** and **5.12.**

(2*R*,3*S*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromopentan-2-ol 5.18 and (2*S*,3*R*)-1-((1*S*,3*R*,4*S*,6*S*)-6-allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromopentan-2-ol 5.17



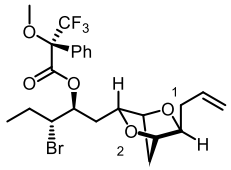
Compound **4.5** (100.0 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and a 0.5 M solution of aqueous $NaHCO_3$ was added (1.7 mL). *m*-CPBA (91.5 mg, 0.53 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. TLC analysis at this stage indicated significant consumption of starting material. *This reaction is best carried out in a 100.0 mg scale with respect to compound* **4.5** *for optimal yields. The quantity of m-CPBA should not exceed 1.1 equivalents.* The reaction mixture was then diluted with CH_2Cl_2, the organic layer was separated, washed with 1M aq. NaOH then water. The organic layers were then combined, dried with anhydrous $MgSO_4$ and concentrated. The crude was then purified by a quick flash column chromatography to yield an inseparable mixture of epoxides (62.0 mg, 0.28 mmol, 70% b.r.s.m.) where the consumption of the internal alkene was confirmed by ^{1}H NMR

analysis and was carried forward to the next step. R_f = 0.33 (20% EA/Pet. Ether 40-60). The mixture of epoxides (150.0 mg, 0.67 mmol) was dissolved in dry Et_2O (13.4 mL) and $MgBr_2{\cdot}Et_2O$ (346.0 mg, 1.34 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. TLC analysis (20% EA/CH_2Cl_2) at this stage indicated completion of reaction. All volatiles were then removed by a dry stream of nitrogen, the resulting white crusty solid was then redissolved in 10% EA/CH_2Cl_2 and underwent purification by flash column chromatography (20% EA/CH_2Cl_2) to give two separable bromohydrins **5.18** (130.0 mg, 0.43 mmol, 64%) and **5.17** (66.0 mg, 0.22 mmol, 32%) respectively. Characterisation data for **5.18**: R_f = 0.51 (20% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, OCHCH'HC**H**=CH'H), 5.15 (dq, *J* = 17.2, 1.7 Hz, 1H, OCHCH'HCH=C**H'**H), 5.08 (ddd, *J* = 10.1, 2.2, 1.2 Hz, 1H, OCHCH'HCH=CH'**H**), 4.36 (d, *J* = 1.7 Hz, 1H, O_2C**H**CH_2CHO_1), 4.34 (q, *J* = 2.1, 1.5 Hz, 1H, O_2CHCH_2C**H**O_1), 4.13 (dd, *J* = 9.3, 4.6 Hz, 1H, CH_3CH'HCHBrCHOHCH'HC**H**), 4.06 (dtd, *J* = 5.5, 4.3, 2.9 Hz, 1H, CH_3CH'HC**H**BrCHOHCH'HCH), 3.92 – 3.82 (m, 2H, CH_3CH'HCHBrC**H**OHCH'HCH and OC**H**CH'HCH=CH'H), 2.50 (d, *J* = 7.2 Hz, 1H, CH_3CH'HCHBrCHO**H**CH'HCH), 2.42 (dt, *J* = 14.1, 7.0 Hz, 1H, OCHC**H'**HCH=CH'H), 2.34 (dt, *J* = 14.1, 7.1 Hz, 1H, OCHCH'**H**CH=CH'H), 1.95 (dqd, *J* = 14.7, 7.3, 3.2 Hz, 1H, CH_3C**H'**HCHBrCHOHCH'HCH), 1.91 (t, *J* = 1.6 Hz, 2H, O_2CHC**H**$_2CHO_1$), 1.81 (ddq, *J* = 14.7, 9.8, 7.3 Hz, 1H, CH_3CH'**H**CHBrCHOHCH'HCH), 1.71 (ddd, *J* = 14.2, 9.5, 4.6 Hz, 1H, CH_3CH'HCHBrCHOHC**H'**HCH), 1.49 (ddd, *J* = 14.2, 9.3, 2.6 Hz, 1H, CH_3CH'HCHBrCHOHCH'**H**CH), 1.08 (t, *J* = 7.2 Hz, 3H, C**H**$_3$CH'HCHBrCHOHCH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5 (OCHCH'H**C**H=CH'H), 117.5 (OCHCH'HCH=**C**H'H), 82.4 (O**C**HCH'HCH=CH'H), 81.9 (CH_3CH'HCHBrCHOHCH'H**C**H), 80.2 (O_2CHCH_2**C**HO_1), 77.3 (O_2**C**HCH_2CHO_1), 71.7 (CH_3CH'HCHBr**C**HOHCH'HCH), 65.3 (CH_3CH'H**C**HBrCHOHCH'HCH), 37.0 (CH_3CH'HCHBrCHOH**C**H'HCH), 35.3 (OCH**C**H'HCH=CH'H), 35.0 (O_2CH**C**H_2CHO_1), 27.2 (CH_3**C**H'HCHBrCHOHCH'HCH), 12.6 (**C**H_3CH'HCHBrCHOHCH'HCH). IR (ν_{max} cm^{-1}): 3426 (O–H stretching, broad), 3077 (alkene sp^2 C–H stretching, weak), 3000-2921 (aliphatic sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1055 (ether C–O–C antisymmetric stretching, strong), 649 (C–Br stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 305.1 and 307.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 305.07468 and 307.07264, found *m/z* 305.07480 and 307.07273. ($C_{13}H_{22}O_3{}^{79}Br$ and $C_{13}H_{22}O_3{}^{81}Br$). $[\alpha]_D^{25} = +95.0$ (c=0.40, $CHCl_3$). Characterisation data for **5.17**: R_f = 0.60 (20% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H, OCHCH'HC**H**=CH'H), 5.14 (dq, *J* = 17.1, 1.6 Hz, 1H, OCHCH'HCH=C**H'**H),

5.08 (dq, *J* = 10.2, 1.3 Hz, 1H, OCHCH'HCH=CH'**H**), 4.41 (d, *J* = 2.5 Hz, 1H, $O_2C\mathbf{H}CH_2CHO_1$), 4.25 (d, *J* = 2.4 Hz, 1H, $O_2CHCH_2C\mathbf{H}O_1$), 4.13 (dd, *J* = 10.5, 3.6 Hz, 1H, $CH_3CH'HCHBrCHOHCH'HC\mathbf{H}$), 3.93 (m, 1H, $CH_3CH'HC\mathbf{H}BrCHOHCH'HCH$), 3.89 (m, 1H, $CH_3CH'HCHBrC\mathbf{H}OHCH'HCH$), 3.86 (m, 1H, $OC\mathbf{H}CH'HCH=CH'H$), 3.69 (d, *J* = 2.1 Hz, 1H, $CH_3CH'HCHBrCHO\mathbf{H}CH'HCH$), 2.42 (dtt, *J* = 14.0, 7.0, 1.4 Hz, 1H, OCHC**H'**HCH=CH'H), 2.34 (dtt, *J* = 14.1, 7.2, 1.3 Hz, 1H, OCHCH'**H**CH=CH'H), 1.98 – 1.90 (m, 3H, $O_2CHC\mathbf{H}_2CHO_1$ and $CH_3C\mathbf{H'}HCHBrCHOHCH'HCH$), 1.84 (ddd, *J* = 14.0, 3.7, 1.8 Hz, 1H, $CH_3CH'HCHBrCHOHC\mathbf{H'}HCH$), 1.78 (dqd, *J* = 14.7, 7.3, 1.9 Hz, 1H, $CH_3CH'\mathbf{H}CHBrCHOHCH'HCH$), 1.42 (dt, *J* = 14.0, 10.5 Hz, 1H, $CH_3CH'HCHBrCHOHCH'\mathbf{H}CH$), 1.07 (t, *J* = 7.2 Hz, 3H, $C\mathbf{H}_3CH'HCHBrCHOHCH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3 ($OCHCH'H\mathbf{C}H=CH'H$), 117.7 ($OCHCH'HCH=\mathbf{C}H'H$), 84.7 ($CH_3CH'HCHBrCHOHCH'H\mathbf{C}H$), 82.4 ($O\mathbf{C}HCH'HCH=CH'H$), 79.8 ($O_2CHCH_2\mathbf{C}HO_1$), 77.7 ($O_2\mathbf{C}HCH_2CHO_1$), 73.8 ($CH_3CH'HCHBr\mathbf{C}HOHCH'HCH$), 63.9 ($CH_3CH'H\mathbf{C}HBrCHOHCH'HCH$), 36.9 ($CH_3CH'HCHBrCHOH\mathbf{C}H'HCH$), 35.2 ($O_2CH\mathbf{C}H_2CHO_1$), 35.2 ($OCH\mathbf{C}H'HCH=CH'H$), 27.4 ($CH_3\mathbf{C}H'HCHBrCHOHCH'HCH$), 12.4 ($\mathbf{C}H_3CH'HCHBrCHOHCH'HCH$). IR ($\nu_{max}$ cm^{-1}): 3439 (O–H stretching, broad), 3077 (alkene sp^2 C–H stretching, weak), 2967-2920 (aliphatic sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1056 (ether C–O–C antisymmetric stretching, strong), 647 (C–Br stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 305.1 and 307.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 305.07468 and 307.07264, found *m/z* 305.07487 and 307.07279. ($C_{13}H_{22}O_3{}^{79}Br$ and $C_{13}H_{22}O_3{}^{81}Br$). $[\alpha]_D^{25} = +76.9$ (c=1.52, $CHCl_3$). The regiochemistry of epoxide opening was determined by ^1H-^{13}C HMBC analyses. The absolute stereochemistry of the secondary alcohols of **5.18** and **5.17** were determined by Mosher ester analysis according to the method of Kakisawa/Hoye[184,185]. The absolute configuration of the secondary bromides of **5.18** and **5.17** were assigned from the assumption that the epoxide openings are stereospecific.

Preparation of *S*- and *R*-Mosher esters **5.24** and **5.23** of **5.17**:

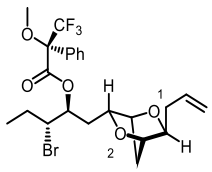
(2*S*,3*R*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromo pentan-2-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*S*-Mosher ester 5.24)



By the method of Hoye[184]: Compound **5.17** (6.7 mg, 22.0 μmol) was mixed with *S*-Mosher acid (12.0 mg, 50.0 μmol) in dry CH_2Cl_2 (0.4 mL). Dicyclohexylcarbodiimide (10.0 mg, 50 μmol) was added followed by DMAP (6.0 mg, 50 μmol). The reaction mixture was stirred overnight. The reaction mixture was filtered, the crude was concentrated and underwent purification by flash column chromatography (50% Et_2O/Pet. Ether 40-60) to give the desired compound *S*-Mosher ester **5.24** as a colourless oil (8.2 mg, 16.7 μmol, 71%). R_f: 0.34 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (m, 2H, Ar**H**), 7.44 – 7.38 (m, 3H, Ar**H**), 5.76 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H, OCHCH'HC**H**=CH'H), 5.27 (dt, *J* = 7.7, 4.3 Hz, 1H, CH_3CH'HCHBrC**H**O(MTPA)CH'HCH), 5.11 (dq, *J* = 17.2, 1.6 Hz, 1H, OCHCH'HCH=C**H'**H), 5.07 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, OCHCH'HCH=CH'**H**), 4.24 (d, *J* = 2.5 Hz, 1H, O_2C**H**CH_2CHO_1), 4.19 (d, *J* = 2.2 Hz, 1H, O_2CHCH_2C**H**O_1), 4.16 (dt, *J* = 9.8, 3.9 Hz, 1H, CH_3CH'HC**H**BrCHO(MTPA)CH'HCH), 3.80 (td, *J* = 7.1, 1.1 Hz, 1H, OC**H**CH'HCH=CH'H), 3.75 (t, *J* = 7.1 Hz, 1H, CH_3CH'HCHBrCHO(MTPA)CH'HC**H**), 3.60 (s, 3H, MTPA COC**H**$_3$), 2.32 (dtt, *J* = 13.9, 7.0, 1.4 Hz, 1H, OCHC**H'**HCH=CH'H), 2.21 (dtt, *J* = 14.1, 7.2, 1.3 Hz, 1H, OCHCH'**H**CH=CH'H), 1.89 – 1.82 (m, 2H, CH_3CH'HCHBrCHO(MTPA)C**H'**HCH and CH_3C**H'**HCHBrCHO(MTPA)CH'HCH), 1.82 – 1.76 (m, 2H, OCHC**H**$_2$CHO), 1.73 (ddd, *J* = 14.6, 9.0, 6.4 Hz, 1H, CH_3CH'**H**CHBrCHO(MTPA)CH'HCH), 1.65 (ddd, *J* = 14.8, 6.8, 4.3 Hz, 1H, CH_3CH'HCHBrCHO(MTPA)CH'**H**CH), 1.07 (t, *J* = 7.2 Hz, 3H, C**H**$_3$CH'HCHBrCHO(MTPA)CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1 (MTPA **C**=O), 134.4 (OCHCH'H**C**H=CH'H), 132.0 (MTPA Ar**C**), 129.8 (MTPA Ar**C**H), 128.6 (MTPA Ar**C**H), 127.6 (MTPA Ar**C**H), 126.8 (MTPA **C**F_3), 124.5 (MTPA **C**F_3), 122.3 (MTPA **C**F_3), 120.0 (MTPA **C**F_3), 117.5 (OCHCH'HCH=**C**H'H), 85.1 (MTPA **C**OCH_3), 84.9 (MTPA **C**OCH_3), 84.6 (MTPA **C**OCH_3), 84.4 (MTPA **C**OCH_3), 82.3 (O**C**HCH'HCH=CH'H), 80.6 (CH_3CH'HCHBrCHO(MTPA)CH'H**C**H), 79.5 (O_2CHCH_2**C**HO_1), 77.1 (O_2**C**HCH_2CHO_1), 75.8 (CH_3CH'HCHBr**C**HO(MTPA)CH'HCH), 57.9 (CH_3CH'H**C**HBrCHO(MTPA)CH'HCH), 55.9 (MTPA CO**C**H_3), 35.3 (OCH**C**H'HCH=CH'H), 35.0 (CH_3CH'HCHBrCHO(MTPA)**C**H'HCH), 34.8

($O_2CH\mathbf{C}H_2CHO_1$), 27.4 ($CH_3\mathbf{C}H'HCHBrCHO(MTPA)CH'HCH$), 12.4 ($\mathbf{C}H_3CH'HCHBrCHO(MTPA)CH'HCH$). IR ($\nu_{max}$ cm^{-1}): 3076 (alkene sp^2 C–H stretching, weak), 2973-2851 (aliphatic sp^3 C–H stretchings, broad), 1747 (ester C=O stretching, strong), 1642 (alkene C=C stretching, weak), 1495 (phenyl ring stretching, weak), 1167 (C-F stretching, strong), 1080 (ether C–O–C antisymmetric stretching, strong), 719 (monosubstituted benzene C–H out of plane deformation, strong), 648 (C–Br stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 521.1 and 523.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 521.11450 and 523.11245, found *m/z* 521.11414 and 523.11193. ($C_{23}H_{29}O_5{}^{79}BrF_3$ and $C_{23}H_{29}O_5{}^{81}BrF_3$). $[\alpha]_D^{25} = +11.5$ (c=0.87, $CHCl_3$).

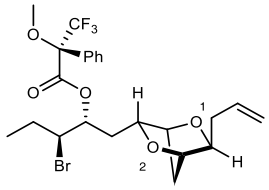
(2*S*,3*R*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromo pentan-2-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*R*-Mosher ester 5.23)



By the method of Hoye[184]: Compound **5.17** (6.2 mg, 20.3 μmol) was mixed with *R*-Mosher acid (12.0 mg, 50.0 μmol) in dry CH_2Cl_2 (0.4 mL). Dicyclohexylcarbodiimide (10.0 mg, 50 μmol) was added followed by DMAP (6.0 mg, 50 μmol). The reaction mixture was stirred overnight. The reaction mixture was filtered, the crude was concentrated and underwent purification by flash column chromatography (50% Et_2O/Pet. Ether 40-60) to give the desired compound *R*-Mosher ester **5.23** as a colourless oil (8.4 mg, 16.1 μmol, 81%). R_f: 0.34 (30% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H, Ar**H**), 7.44 – 7.37 (m, 13H, Ar**H**), 5.78 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H, OCHCH'HC**H**=CH'H), 5.29 (dt, *J* = 7.5, 4.6 Hz, 1H, $CH_3CH'HCHBrC\mathbf{H}O(MTPA)CH'HCH$), 5.12 (dq, *J* = 17.2, 1.6 Hz, 1H, OCHCH'HCH=C**H'**H), 5.08 (ddt, *J* = 10.2, 2.0, 1.1 Hz, 1H, OCHCH'HCH=CH'**H**), 4.31 (d, *J* = 2.8 Hz, 1H, $O_2C\mathbf{H}CH_2CHO_1$), 4.24 (d, *J* = 2.1 Hz, 1H, $O_2CHCH_2C\mathbf{H}O_1$), 4.09 (ddd, *J* = 9.6, 5.1, 3.5 Hz, 1H, $CH_3CH'HC\mathbf{H}BrCHO(MTPA)CH'HCH$), 3.89 (dd, *J* = 7.7, 6.3 Hz, 1H, $CH_3CH'HCHBrCHO(MTPA)CH'HC\mathbf{H}$), 3.84 (td, *J* = 7.2, 1.1 Hz, 1H, OC**H**CH'HCH=CH'H), 3.56 (s, 3H, MTPA $COC\mathbf{H}_3$), 2.36 (dtt, *J* = 13.9, 6.9, 1.4 Hz, 1H, OCHC**H'**HCH=CH'H), 2.27 (dtt, *J* = 14.1, 7.2, 1.3 Hz, 1H, OCHCH'**H**CH=CH'H), 1.94 – 1.84 (m, 3H, $CH_3CH'HCHBrCHO(MTPA)C\mathbf{H}'HCH$ and $O_2CHC\mathbf{H}_2CHO_1$), 1.84 – 1.73 (m, 2H, $CH_3CH'HCHBrCHO(MTPA)CH'\mathbf{H}CH$ and $CH_3C\mathbf{H}'HCHBrCHO(MTPA)CH'HCH$), 1.65 (ddq, *J* = 14.5, 9.7, 7.3 Hz, 1H, $CH_3CH'\mathbf{H}CHBrCHO(MTPA)CH'HCH$), 1.02 (t, *J* = 7.2 Hz, 3H, $C\mathbf{H}_3CH'HCHBrCHO(MTPA)CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (MTPA

C=O), 134.4 (OCHCH'H**C**H=CH'H), 131.9 (MTPA Ar**C**), 129.8 (MTPA Ar**C**H), 128.6 (MTPA Ar**C**H), 127.7 (MTPA Ar**C**H), 126.8 (MTPA **C**F_3), 124.5 (MTPA **C**F_3), 122.2 (MTPA **C**F_3), 119.9 (MTPA **C**F_3), 117.5 (OCHCH'HCH=**C**H'H), 85.1 (MTPA **C**OCH_3), 84.9 (MTPA **C**OCH_3), 84.6 (MTPA **C**OCH_3), 84.4 (MTPA **C**OCH_3), 82.4 (O**C**HCH'HCH=CH'H), 80.9 (CH_3CH'HCHBrCHO(MTPA)CH'H**C**H), 79.6 (O_2CHCH$_2$**C**HO_1), 77.1 (O_2**C**HCH$_2$CHO_1), 75.9 (CH_3CH'HCHBr**C**HO(MTPA)CH'HCH), 57.5 (CH_3CH'H**C**HBrCHO(MTPA)CH'HCH), 55.7 (MTPA CO**C**H_3), 35.4 (CH_3CH'HCHBrCHO(MTPA)**C**H'HCH), 35.3 (OCH**C**H'HCH=CH'H), 34.9 (O_2CH**C**H$_2$CHO_1), 27.2 (CH_3**C**H'HCHBrCHO(MTPA)CH'HCH), 12.2 (**C**H_3CH'HCHBrCHO(MTPA)CH'HCH). IR (ν_{max} cm^{-1}): 3075 (alkene sp^2 C–H stretching, weak), 2974-2852 (aliphatic sp^3 C–H stretchings, broad), 1749 (ester C=O stretching, strong), 1642 (alkene C=C stretching, weak), 1497 (phenyl ring stretching, weak), 1170 (C-F stretching, strong), 1081 (ether C–O–C antisymmetric stretching, strong), 720 (monosubstituted benzene C–H out of plane deformation, strong), 651 (C–Br stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 521.1 and 523.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 521.11450 and 523.11245, found *m/z* 521.11414 and 523.11193. ($C_{23}H_{29}O_5{}^{79}BrF_3$ and $C_{23}H_{29}O_5{}^{81}BrF_3$). $[\alpha]_D^{25} = +40.5$ (c=1.11, $CHCl_3$).

Preparation of *S*- and *R*-Mosher esters **5.26** and **5.25** of **5.18**:

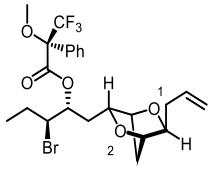


(2*R*,3*S*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromo pentan-2-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*S*-Mosher ester 5.26)

By the method of Hoye[184]: Compound **5.18** (5.0 mg, 16.0 μmol) was mixed with *S*-Mosher acid (12.0 mg, 50.0 μmol) in dry CH_2Cl_2 (0.4 mL). Dicyclohexylcarbodiimide (10.0 mg, 50 μmol) was added followed by DMAP (6.0 mg, 50 μmol). The reaction mixture was stirred overnight. The reaction mixture was filtered, the crude was concentrated and underwent purification by flash column chromatography (40% Et_2O/Pet. Ether 40-60) to give the desired compound *S*-Mosher ester **5.26** as a colourless oil (5.0 mg, 9.6 μmol, 60%). R_f: 0.63 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H, Ar**H**), 7.48 – 7.36 (m, 3H, Ar**H**), 5.78 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, OCHCH'HC**H**=CH'H), 5.24 (dt, *J* = 9.7, 3.2 Hz, 1H, CH_3CH'HCHBrC**H**O(MTPA)CH'HCH), 5.12 (dd, *J* = 17.1, 1.8 Hz, 1H, OCHCH'HCH=C**H'**H), 5.08 (dd, *J* = 10.3, 1.9 Hz, 1H, OCHCH'HCH=CH'**H**), 4.36 (d, *J* = 2.4 Hz, 1H, O_2C**H**CH'HCHO_1), 4.28 – 4.23 (m, 1H,

$CH_3CH'HC\mathbf{H}BrCHO(MTPA)CH'HCH$), 4.24 (d, *J* = 2.1 Hz, 1H, $O_2CHCH'HC\mathbf{H}O_1$), 3.87 (dd, *J* = 9.6, 3.9 Hz, 1H, $CH_3CH'HCHBrCHO(MTPA)CH'HC\mathbf{H}$), 3.83 (dd, *J* = 7.2, 1.1 Hz, 1H, $OC\mathbf{H}CH'HCH{=}CH'H$), 3.57 (s, 3H, MTPA $COC\mathbf{H}_3$), 2.35 (dt, *J* = 14.1, 7.1 Hz, 1H, $OCHC\mathbf{H'}HCH{=}CH'H$), 2.33 – 2.21 (m, 1H, $OCHCH'\mathbf{H}CH{=}CH'H$), 1.95 (td, *J* = 9.9, 4.9 Hz, 1H, $CH_3CH'HCHBrCHO(MTPA)C\mathbf{H'}HCH$), 1.89 (dd, *J* = 10.3, 2.4 Hz, 1H, $O_2CHC\mathbf{H'}HCHO_1$), 1.88 – 1.79 (m, 2H, $CH_3C\mathbf{H'}HCHBrCHO(MTPA)CH'HCH$, $O_2CHCH'\mathbf{H}CHO_1$), 1.75 – 1.64 (m, 1H, $CH_3CH'\mathbf{H}CHBrCHO(MTPA)CH'HCH$), 1.48 (ddd, *J* = 14.5, 9.7, 3.0 Hz, 1H, $CH_3CH'HCHBrCHO(MTPA)CH'\mathbf{H}CH$), 1.07 (t, *J* = 7.2 Hz, 3H, $C\mathbf{H}_3CH'HCHBrCHO(MTPA)CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (MTPA **C**=O), 134.4 ($OCHCH'H\mathbf{C}H{=}CH'H$), 132.0 (MTPA Ar**C**), 129.8 (MTPA Ar**C**H), 128.6 (MTPA Ar**C**H), 127.7 (MTPA Ar**C**H), 117.6 ($OCHCH'HCH{=}\mathbf{C}H'H$), 84.8 (MTPA $\mathbf{C}OCH_3$), 82.3 ($O\mathbf{C}HCH'HCH{=}CH'H$), 80.0 ($O_2CHCH'H\mathbf{C}HO_1$), 79.8 ($CH_3CH'HCHBrCHO(MTPA)CH'H\mathbf{C}H$), 77.2 ($O_2\mathbf{C}HCH'HCHO_1$), 75.1 ($CH_3CH'HCHBr\mathbf{C}HO(MTPA)CH'HCH$), 58.2 ($CH_3CH'H\mathbf{C}HBrCHO(MTPA)CH'HCH$), 55.7 (MTPA $CO\mathbf{C}H_3$), 35.3 ($O\mathbf{C}HCH'HCH{=}CH'H$), 35.0 ($O_2CH\mathbf{C}H'HCHO_1$), 34.4 ($CH_3CH'HCHBrCHO(MTPA)\mathbf{C}H'HCH$), 28.1 ($CH_3\mathbf{C}H'HCHBrCHO(MTPA)CH'HCH$), 12.5 ($\mathbf{C}H_3CH'HCHBrCHO(MTPA)CH'HCH$). IR ($\nu_{max}$ cm^{-1}): 3075 (alkene sp^2 C–H stretching, weak), 2971 (aliphatic sp^3 C–H stretchings, broad), 1747 (ester C=O stretching, strong), 1642 (alkene C=C stretching, weak), 1497 (phenyl ring stretching, weak), 1168 (C-F stretching, strong), 1080 (ether C–O–C antisymmetric stretching, strong), 720 (monosubstituted benzene C–H out of plane deformation, strong), 647 (C–Br stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 521.1 and 523.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 521.11450 and 523.11245, found *m/z* 521.11463 and 523.11244. ($C_{23}H_{29}O_5{}^{79}BrF_3$ and $C_{23}H_{29}O_5{}^{81}BrF_3$). $[\alpha]_D^{25} = +67.0$ (c=0.50, $CHCl_3$).

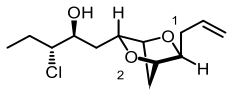
(2*R*,3*S*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromo pentan-2-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (*R*-Mosher ester 5.25)



By the method of Hoye[184]: Compound **5.18** (5.0 mg, 16.0 μmol) was mixed with *R*-Mosher acid (12.0 mg, 50.0 μmol) in dry CH_2Cl_2 (0.4 mL). Dicyclohexylcarbodiimide (10.0 mg, 50 μmol) was added followed by DMAP (6.0 mg, 50 μmol). The reaction

mixture was stirred overnight. The reaction mixture was filtered, the crude was concentrated and underwent purification by flash column chromatography (40% Et_2O/Pet. Ether 40-60) to give the desired compound *R*-Mosher ester **5.25** as a colourless oil (4.7 mg, 9.0 μmol, 56%). R_f: 0.63 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.50 (m, 2H, Ar**H**), 7.44 – 7.32 (m, 3H, Ar**H**), 5.76 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H, OCHCH'HC**H**=CH_2), 5.24 (dt, *J* = 9.9, 2.8 Hz, 1H, CH_3CH'HCHBrC**H**O(MTPA)CH'HCH), 5.15 – 5.03 (m, 2H, OCHCH'HCH=C**H**$_2$), 4.31 (d, *J* = 2.5 Hz, 1H, O_2CHCH'HC**H**O_1), 4.28 (ddd, *J* = 9.8, 4.3, 2.9 Hz, 1H, CH_3CH'HC**H**BrCHO(MTPA)CH'HCH), 4.13 (d, *J* = 2.2 Hz, 1H, O_2C**H**CH'HCHO_1), 3.79 (td, *J* = 7.1, 1.1 Hz, 1H, OC**H**CH'HCH=CH_2), 3.66 (dd, *J* = 10.2, 3.5 Hz, 1H, CH_3CH'HCHBrCHO(MTPA)CH'HC**H**), 3.64 (s, 3H, MTPA COC**H**$_3$), 2.32 – 2.21 (m, 1H, OCHC**H'**HCH=CH_2), 2.24 – 2.14 (m, 1H, OCHCH'**H**CH=CH_2), 1.96 – 1.89 (m, 1H, CH_3CH'HCHBrCHO(MTPA)C**H'**HCH), 1.92 – 1.85 (m, 1H, CH_3C**H'**HCHBrCHO(MTPA)CH'HCH), 1.88 – 1.81 (m, 1H, O_2CHC**H'**HCHO_1), 1.81 – 1.74 (m, 1H, O_2CHCH'**H**CHO_1), 1.77 – 1.69 (m, 1H, CH_3CH'**H**CHBrCHO(MTPA)CH'HCH), 1.44 – 1.33 (m, 1H, CH_3CH'HCHBrCHO(MTPA)CH'**H**CH), 1.09 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHBrCHO(MTPA)CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4 (MTPA **C**=O), 134.5 (OCHCH'H**C**H=CH_2), 132.2 (MTPA Ar**C**), 129.9 (MTPA Ar**C**H), 128.7 (MTPA Ar**C**H), 127.4 (MTPA Ar**C**H), 117.5 (OCHCH'HCH=**C**H_2), 82.3 (O**C**HCH'HCH=CH_2), 79.9 (MTPA **C**OCH_3), 79.9 (O_2CHCH'H**C**HO_1), 79.5 (CH_3CH'HCHBrCHO(MTPA)CH'H**C**H), 77.3 (O_2**C**HCH'HCHO_1), 75.1 (CH_3CH'HCHBr**C**HO(MTPA)CH'HCH), 59.0 (CH_3CH'H**C**HBrCHO(MTPA)CH'HCH), 56.0 (MTPA CO**C**H_3), 35.2 (OCH**C**H'HCH=CH_2), 35.0 (O_2CH**C**H'HCHO_1), 34.4 (CH_3CH'HCHBrCHO(MTPA)**C**H'HCH), 28.3 (CH_3**C**H'HCHBrCHO(MTPA)CH'HCH), 12.6 (**C**H_3CH'HCHBrCHO(MTPA)CH'HCH). IR (ν_{max} cm^{-1}): 3076 (alkene sp^2 C–H stretching, weak), 2971-2852 (aliphatic sp^3 C–H stretchings, broad), 1748 (ester C=O stretching, strong), 1642 (alkene C=C stretching, weak), 1495 (phenyl ring stretching, weak), 1169 (C-F stretching, strong), 1081 (ether C–O–C antisymmetric stretching, strong), 720 (monosubstituted benzene C–H out of plane deformation, strong), 651 (C–Br stretching, strong). LRMS (ESI) [M+H]$^+$: *m/z* 521.1 and 523.1. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 521.11450 and 523.11245, found *m/z* 521.11440 and 523.11227. ($C_{23}H_{29}O_5{}^{79}BrF_3$ and $C_{23}H_{29}O_5{}^{81}BrF_3$). $[\alpha]_D^{25} = +101.5$ (c=0.47, $CHCl_3$).

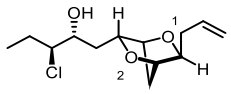
(2*S*,3*R*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-chloro pentan-2-ol 5.21



Compounds **5.11** and **5.12** (18.5 mg, 83.6 μmol) was dissolved in dry CH_2Cl_2 (1.6 mL) and the reaction mixture was cooled to -78˚C. A 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (90 μL, 90.0 μmol) was added and the reaction mixture was stirred at -78 °C for 1 hour, then warmed to room temperature and stirring was continued for 30 minutes. The reaction mixture was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (20% EA/CH_2Cl_2) to give the desired compounds **5.21** (6.0 mg, 23.1 μmol, 29%), **5.22** (7.4 mg, 28.5 μmol, 36%) and a mixture of **5.21** and **5.22** (4.9 mg, 18.8 μmol, 24%) as colourless oils. The ratio of **5.22**:**5.21** is ~ 2:1. Characterisation data for **5.21**: R_f = 0.46 (50% EA/Pet. Ether 40-60. Note: Same R_f as starting material). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H, OCHCH'HC**H**CH'H), 5.15 (dq, *J* = 17.1, 1.6 Hz, 1H, OCHCH'HCHC**H'**H), 5.08 (ddt, *J* = 10.2, 2.0, 1.1 Hz, 1H, OCHCH'HCHCH'**H**), 4.41 (d, *J* = 2.6 Hz, 1H, O_2C**H**CH'HCHO$_1$), 4.25 (d, *J* = 2.4 Hz, 1H, O_2CHCH'HC**H**O$_1$), 4.13 (dd, *J* = 10.6, 3.5 Hz, 1H, CH_3CH'HCHClCHOHCH'HC**H**), 3.91 (ddt, *J* = 9.9, 5.8, 2.0 Hz, 1H, CH_3CH'HCHClC**H**OHCH'HCH), 3.87 (td, *J* = 7.2, 1.1 Hz, 1H, OC**H**CH'HCHCH'H), 3.76 (ddd, *J* = 9.2, 5.8, 3.3 Hz, 1H, CH_3CH'HC**H**ClCHOHCH'HCH), 3.70 (d, *J* = 2.1 Hz, 1H, CH_3CH'HCHClCHO**H**CH'HCH), 2.43 (dtt, *J* = 14.0, 6.9, 1.4 Hz, 1H, OCHC**H'**HCHCH'H), 2.35 (dtt, *J* = 14.1, 7.2, 1.3 Hz, 1H, OCHCH'**H**CHCH'H), 1.98 (dd, *J* = 10.4, 2.6 Hz, 1H, O_2CHC**H'**HCHO$_1$), 1.94 – 1.89 (m, 2H, O_2CHCH'**H**CHO$_1$ and CH_3C**H'**HCHClCHOHCH'HCH), 1.84 (ddd, *J* = 14.1, 3.6, 2.0 Hz, 1H, CH_3CH'HCHClCHOHC**H'**HCH), 1.67 (ddq, *J* = 14.5, 9.3, 7.2 Hz, 1H, CH_3CH'**H**CHClCHOHCH'HCH), 1.39 (dt, *J* = 14.2, 10.3 Hz, 1H, CH_3CH'HCHClCHOHCH'**H**CH), 1.06 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHClCHOHCH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3 (OCHCH'H**C**HCH'H), 117.7 (OCHCH'HCH**C**H'H), 84.9 (CH_3CH'HCHClCHOHCH'H**C**H), 82.4 (O**C**HCH'HCHCH'H), 79.9 (O_2CHCH'H**C**HO$_1$), 77.7 (O_2**C**HCH'HCHO$_1$), 74.0 (CH_3CH'HCHCl**C**HOHCH'HCH), 68.6 (CH_3CH'H**C**HClCHOHCH'HCH), 36.0 (CH_3CH'HCHClCHOH**C**H'HCH), 35.3 (OCH**C**H'HCHCH'H), 35.2 (O_2CH**C**H'HCHO$_1$), 26.9 (CH_3**C**H'HCHClCHOHCH'HCH), 11.1 (**C**H$_3$CH'HCHClCHOHCH'HCH). IR (ν_{max} cm^{-1}): 3435 (O–H stretching, broad), 3078 (alkene sp^2 C–H stretching, weak), 3000-2879 (aliphatic sp^3 C–H stretchings, broad),

1642 (alkene C=C stretching, medium), 1058 (ether C–O–C antisymmetric stretching, strong), 807 (C–Cl stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 261.1 and 263.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 261.12520 and 263.12225, found *m/z* 261.12540 and 263.12240. ($C_{13}H_{22}O_3{}^{35}Cl$ and $C_{13}H_{22}O_3{}^{37}Cl$). $[\alpha]_D^{25} = +67.6$ (c=0.58, $CHCl_3$).

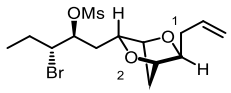
(2*R*,3*S*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-chloro pentan-2-ol 5.22



Compound **5.11** and **5.12** (18.5 mg, 83.6 μmol) was dissolved in dry CH_2Cl_2 (1.6 mL) and the reaction mixture was cooled to -78˚C. A 1M solution of $TiCl_4$ in CH_2Cl_2 (90 μL, 90.0 μmol) was added and the reaction mixture was stirred at -78 °C for 1 hour, then warmed to room temperature and stirring was continued for 30 minutes. The reaction mixture was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (20% EA/CH_2Cl_2) to give the desired compounds **5.21** (6.0 mg, 23.1 μmol, 29%), **5.22** (7.4 mg, 28.5 μmol, 36%) and a mixture of **5.21** and **5.22** (4.9 mg, 18.8 μmol, 24%) as colourless oils. The ratio of **5.22**:**5.21** is ~ 2:1. Characterisation data for **5.22**: R_f = 0.40 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H, OCHCH'HC**H**CH'H), 5.15 (dt, *J* = 17.2, 1.7 Hz, 1H, OCHCH'HCHC**H'**H), 5.08 (dp, *J* = 10.2, 1.3 Hz, 1H, OCHCH'HCHCH'**H**), 4.36 (d, *J* = 1.9 Hz, 1H, O_2C**H**CH_2CHO_1), 4.33 (t, *J* = 1.4 Hz, 1H, O_2CHCH_2C**H**O_1), 4.13 (dd, *J* = 9.3, 4.6 Hz, 1H, CH_3CH'HCHClCHOHCH'HC**H**), 3.92 – 3.83 (m, 3H, CH_3CH'HCHClC**H**OHCH'HCH, CH_3CH'HC**H**ClCHOHCH'HCH and OC**H**CH'HCHCH'H), 2.55 (d, *J* = 6.9 Hz, 1H, CH_3CH'HCHClCHO**H**CH'HCH), 2.42 (dtt, *J* = 14.0, 7.0, 1.4 Hz, 1H, OCHC**H'**HCHCH'H), 2.34 (dtt, *J* = 14.0, 7.2, 1.3 Hz, 1H, OCHCH'**H**CHCH'H), 1.94 – 1.88 (m, 3H, O_2CHC**H**$_2CHO_1$ and CH_3C**H'**HCHClCHOHCH'HCH), 1.72 – 1.65 (m, 2H, CH_3CH'HCHClCHOHC**H'**HCH and CH_3CH'**H**CHClCHOHCH'HCH), 1.47 (ddd, *J* = 14.0, 9.3, 2.3 Hz, 1H, CH_3CH'HCHClCHOHCH'**H**CH), 1.07 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHClCHOHCH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.5 (OCHCH'H**C**HCH'H), 117.5 (OCHCH'HCH**C**H'H), 82.4 (O**C**HCH'HCHCH'H), 82.0 (CH_3CH'HCHClCHOHCH'H**C**H), 80.2 (O_2CHCH_2**C**HO_1), 77.3 (O_2**C**HCH_2CHO_1), 71.8 (CH_3CH'HCHCl**C**HOHCH'HCH), 69.4 (CH_3CH'H**C**HClCHOHCH'HCH), 36.1 (CH_3CH'HCHClCHOH**C**H'HCH), 35.3

(OCH**C**H'HCHCH'H), 35.0 ($O_2CH\mathbf{C}H_2CHO_1$), 26.6 ($CH_3\mathbf{C}H$'HCHClCHOHCH'HCH), 11.3 ($\mathbf{C}H_3$CH'HCHClCHOHCH'HCH). IR (ν_{max} cm^{-1}): 3427 (O–H stretching, broad), 3078 (alkene sp^2 C–H stretching, weak), 2968-2923 (aliphatic sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1057 (ether C–O–C antisymmetric stretching, strong), 814 (C–Cl stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 261.1 and 263.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 261.12520 and 263.12225, found *m/z* 261.12541 and 263.12242. ($C_{13}H_{22}O_3{}^{35}Cl$ and $C_{13}H_{22}O_3{}^{37}Cl$). $[\alpha]_D^{25} = +104.9$ (c=0.51, $CHCl_3$).

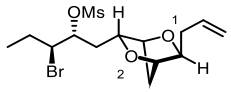
(2*S*,3*R*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromo pentan-2-yl methanesulfonate 5.19



Compound **5.17** (56 mg, 0.18 mmol) was dissolved in dry CH_2Cl_2 (2.0 mL) and the reaction mixture was cooled to 0 °C. To this solution was added Et_3N (26 µL, 0.20 mmol), then MsCl (16 µL, 0.20 mmol) and gradually warmed to room temperature. The reaction was stirred at room temperature until completion, then quenched by sat. $NaHCO_{3(aq)}$, extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (40% EA/Pet. Ether 40-60) to give the desired compound **5.19** as a colourless oil (60 mg, 0.16 mmol, 86%). R_f = 0.26 (30% EA/Pet. Ether 40-60, Note: More polar than starting material). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H, OCHCH'HC**H**=CH'H), 5.14 (dq, *J* = 17.2, 1.7 Hz, 1H, OCHCH'HCH=C**H'**H), 5.12 – 5.05 (m, 1H, OCHCH'HCH=CH'**H**), 4.88 (dt, *J* = 6.5, 5.1 Hz, 1H, CH_3CH'HCHBrC**H**OMsCH_2CH), 4.37 (d, *J* = 1.5 Hz, 1H, $O_2C\mathbf{H}CH_2CHO_1$), 4.27 (d, *J* = 1.8 Hz, 1H, $O_2CHCH_2C\mathbf{H}O_1$), 4.20 (ddd, *J* = 10.3, 4.7, 3.4 Hz, 1H, CH_3CH'HC**H**BrCHOMsCH_2CH), 3.96 (dd, *J* = 8.7, 5.2 Hz, 1H, CH_3CH'HCHBrCHOMs$CH_2C\mathbf{H}$), 3.86 (td, *J* = 7.1, 1.1 Hz, 1H, OC**H**CH'HCH=CH'H), 3.13 (s, 3H, OMs C$\mathbf{H}_3$), 2.40 (dt, *J* = 13.8, 6.9 Hz, 1H, OCHC**H'**HCH=CH'H), 2.31 (dt, *J* = 14.2, 7.2 Hz, 1H, OCHCH'**H**CH=CH'H), 2.01 – 1.82 (m, 5H, $O_2CHC\mathbf{H}_2CHO_1$, CH_3CH'HCHBrCHOMsC$\mathbf{H}_2$CH, $CH_3C\mathbf{H}$'HCHBrCHOMsCH_2CH), 1.76 (dtd, *J* = 14.6, 7.3, 3.2 Hz, 1H, CH_3CH'**H**CHBrCHOMsCH_2CH), 1.11 (t, *J* = 7.2 Hz, 3H, C$\mathbf{H}_3$CH'HCHBrCHOMsCH_2CH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.3 (OCHCH'H**C**H=CH'H), 117.6 (OCHCH'HCH=**C**H'H), 82.4 (O**C**HCH'HCH=CH'H), 81.3 (CH_3CH'HCHBr**C**HOMsCH_2CH), 80.8 (CH_3CH'HCHBrCHOMs$CH_2\mathbf{C}$H), 79.8 ($O_2CHCH_2\mathbf{C}HO_1$), 77.3 ($O_2\mathbf{C}HCH_2CHO_1$), 58.5 (CH_3CH'H**C**HBrCHOMsCH_2CH), 39.1 (OMs **C**H_3), 36.3 (CH_3CH'HCHBrCHOMs**C**H_2CH), 35.4

(OCH**C**H'HCH=CH'H), 35.0 ($O_2CH\mathbf{C}H_2CHO_1$), 27.4 ($CH_3\mathbf{C}H'HCHBrCHOMsCH_2CH$), 12.5 ($\mathbf{C}H_3CH'HCHBrCHOMsCH_2CH$). IR ($\nu_{max}$ cm^{-1}): 3077 (alkene sp^2 C–H stretching, weak), 3010-2936 (aliphatic sp^3 C–H stretchings, broad), 1641 (alkene C=C stretching, weak), 1354 (SO_2 antisymmetric stretching, strong), 1172 (SO_2 symmetric stretching, strong), 1080 (ether C–O–C antisymmetric stretching, strong), 915 (vinyl CH_2 out of plane wagging, strong), 650 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 383.1 and 385.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 383.05223 and 385.05019, found *m/z* 383.05197 and 385.04996. ($C_{14}H_{24}O_5{}^{79}Br^{32}S$ and $C_{14}H_{24}O_5{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +53.5$ (c=1.14, $CHCl_3$).

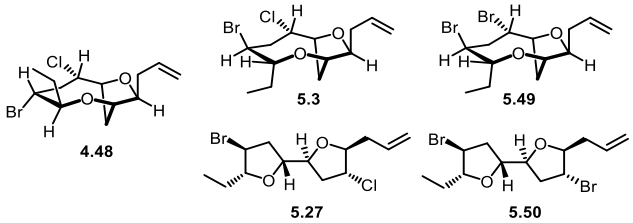
(2*R*,3*S*)-1-((1*S*,3*R*,4*S*,6*S*)-6-Allyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-3-bromo pentan-2-yl methanesulfonate 5.20



Compound **5.18** (150 mg, 0.49 mmol) was dissolved in dry CH_2Cl_2 (5.0 mL) and the reaction mixture was cooled to 0 °C. To this solution was added Et_3N (76 µL, 0.55 mmol), then MsCl (42 µL, 0.55 mmol) and gradually warmed to room temperature. The reaction was stirred at room temperature until completion, then quenched by sat. aq. $NaHCO_3$, extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (20% EA/Pet. Ether 40-60) to give the desired compound **5.18** as a colourless oil (160 mg, 0.42 mmol, 85%). R_f = 0.66 (20% EA/Pet. Ether 40-60, Note: Less polar than starting material). ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.2, 10.4, 7.0 Hz, 1H, OCHCH'HC**H**=CH_2), 5.16 – 5.04 (m, 2H, OCHCH'HCH=C**H**$_2$), 4.81 (dt, *J* = 9.9, 3.0 Hz, 1H, $CH_3CH'HCHBrC\mathbf{H}OMsCH'HCH$), 4.39 (d, *J* = 2.5 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 4.33 – 4.25 (m, 2H, $CH_3CH'HC\mathbf{H}BrCHOMsCH'HCH$ and $O_2CHCH'HC\mathbf{H}O_1$), 3.96 (dd, *J* = 10.4, 3.3 Hz, 1H, $CH_3CH'HCHBrCHOMsCH'HC\mathbf{H}$), 3.90 – 3.83 (m, 1H, OC**H**CH'HCH=CH_2), 3.15 (s, 3H, OMs C**H**$_3$), 2.38 (dt, *J* = 13.8, 6.8 Hz, 1H, OCHC**H'**HCH=CH_2), 2.26 (dt, *J* = 14.3, 7.3 Hz, 1H, OCHCH'**H**CH=CH_2), 1.99 (ddd, *J* = 14.7, 9.9, 3.3 Hz, 1H, $CH_3CH'HCHBrCHOMsC\mathbf{H'}HCH$), 1.93 (dd, *J* = 10.4, 2.4 Hz, 1H, $O_2CHC\mathbf{H'}HCHO_1$), 1.89 – 1.81 (m, 2H, $O_2CHCH'\mathbf{H}CHO_1$ and $CH_3C\mathbf{H'}HCHBrCHOMsCH'HCH$), 1.72 (dqd, *J* = 14.6, 7.2, 2.8 Hz, 1H, $CH_3CH'\mathbf{H}CHBrCHOMsCH'HCH$), 1.44 (ddd, *J* = 14.6, 10.4, 2.8 Hz, 1H, $CH_3CH'HCHBrCHOMsC\mathbf{H'}HCH$), 1.09 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHBrCHOMsCH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.2 (OCHCH'H**C**H=CH_2), 117.7 (OCHCH'HCH=**C**H$_2$), 82.3 (O**C**HCH'HCH=CH_2), 80.0 ($CH_3CH'HCHBr\mathbf{C}HOMsCH'HCH$), 79.9 ($O_2CHCH'H\mathbf{C}HO_1$), 79.5 ($CH_3CH'HCHBrCHOMsCH'H\mathbf{C}H$), 77.4 ($O_2\mathbf{C}HCH'HCHO_1$), 60.2

($CH_3CH'H\mathbf{C}HBrCHOMsCH'HCH$), 38.7 (OMs $\mathbf{C}H_3$), 35.5 ($OCH\mathbf{C}H'HCH{=}CH_2$), 35.2 ($O_2CH\mathbf{C}H'HCHO_1$), 35.0 ($CH_3CH'HCHBrCHOMs\mathbf{C}H'HCH$), 28.3 ($CH_3\mathbf{C}H'HCHBrCHOMsCH'HCH$), 12.6 ($\mathbf{C}H_3CH'HCHBrCHOMsCH'HCH$). IR ($\nu_{max}$ cm^{-1}): 3077 (alkene sp^2 C–H stretching, weak), 3004-2880 (aliphatic sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, weak), 1358 (SO_2 antisymmetric stretching, strong), 1174 (SO_2 symmetric stretching, strong), 1077 (ether C–O–C antisymmetric stretching, strong), 919 (vinyl CH_2 out of plane wagging, strong), 650 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 383.1 and 385.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 383.05223 and 385.05019, found *m/z* 383.05234 and 385.05019. ($C_{14}H_{24}O_5{}^{79}Br{}^{32}S$ and $C_{14}H_{24}O_5{}^{81}Br{}^{32}S$). $[\alpha]_D^{25} = +84.4$ (c=0.63, $CHCl_3$).

General procedures for the synthesis of compounds 4.48, 5.3, 5.27, 5.49 and 5.50.



Compound **5.17** or **5.18** (25.0 mg, 65.0 μmol) was dissolved in dry CH_2Cl_2 (6.5 mL) and the reaction mixture was cooled to -40 °C. A solution of $TiCl_4$ (0.5 M in CH_2Cl_2, 0.26 mL, 0.13 mmol) was introduced by a quick injection (where the solution changes from colourless to bright yellow) immediately followed by another quick injection of a solution of $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (226.0 mg in 1.0 mL CH_2Cl_2, 0.20 mmol) (where the solution changes from bright yellow to bright orange). The reaction mixture was vigorously stirred at -40 °C for 2 hours. The reaction mixture was then cooled to -78 °C, where the desired quenching reagent was added to achieve the synthesis of compounds **4.48, 5.3, 5.27, 5.49** and **5.50** according to the table below (**Table 10.1**). Please note the reaction is best carried out at 25.0 mg scale with respect to compounds **5.17** and **5.18** for optimal yields and isomer ratio.

Desired species	Quenching reagent	Equivalents	Stirring time
5.49, 5.50	*n*-Bu_4NBr	10.0	20 minutes
5.3, 5.27	*n*-Bu_4NCl	10.0	1 hour
4.48	*n*-Bu_4NCl	10.0	1 hour

Table 10.1. Quenching conditions for the synthesis of compounds **4.48**, **5.3**, **5.27**, **5.49** and **5.50**.

The stirring time for the synthesis of compounds **5.49** and **5.50** was designed to be shorter to prevent potential bromide/chloride exchange in compound **5.49** as such exchange was observed in related studies. However, it was later revealed that such exchange is less efficient with compound **5.49**. Nevertheless, the quenching was found

to be completed in 20 minutes by TLC analyses thus the stirring time as reported. For the case of quenching with tetrabutylammonium chloride, the quenching was also found to completed within 1 hour by TLC analyses, however there was no concern of bromide/chloride exchange thus having a stirring time of 1 hour at -78 °C was inconsequential.

The reaction mixture was removed from the dry ice/acetone bath and then quenched with sat. aq. $NaHCO_3$ (where the reaction mixture was decolourised) and additional deionised water was added to thaw the reaction mixture. The aqueous layer was then extracted with CH_2Cl_2, the organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (10% EA/Pet. Ether 40-60 for all cases) to give the results tabulated below (**Table 10.2**). Although compounds **5.3, 5.27, 5.49** and **5.50** were not characterised as they were found to be inseparable from each other, their crude ^{1}H NMR spectra were obtained and compared with the natural products (*E*/*Z*)-bromofucin **1.11** and **1.8**, (*E*/*Z*)-elatenyne **1.12** and **1.9**, (*E*/*Z*)-chlorofucin **1.6** and **1.5** and lauredecumenyne B **1.7** and its *E*-isomer **1.19** to demonstrate their spectroscopic similarities and thus assignment of product ratios (**Figure 10.2-10.3**).

Desired species	**R_f value**	**Eluent system for TLC**	**Yield**	**Isomer ratio** (determined by ^{1}H NMR)	**Characterised or carried forward to next step**
5.49, 5.50	0.77	20% EA/ Pet. Ether 40-60	50%	3:1 (**5.49:5.50**, inseparable)	Carried forward to next step
5.3, 5.27	0.77	20% EA/ Pet. Ether 40-60	70%	7:1 (**5.3**:**5.27**, inseparable)	Carried forward to next step
4.48	0.71	20% EA/ Pet. Ether 40-60	68%	**4.48** exclusive	Characterised

Table 10.2. Experimental results for the synthesis of compounds **4.48, 5.3, 5.27, 5.49 and 5.50**.

Determination of isomer ratio (5.49:5.50 and 5.3:5.27) by ^{1}H NMR:

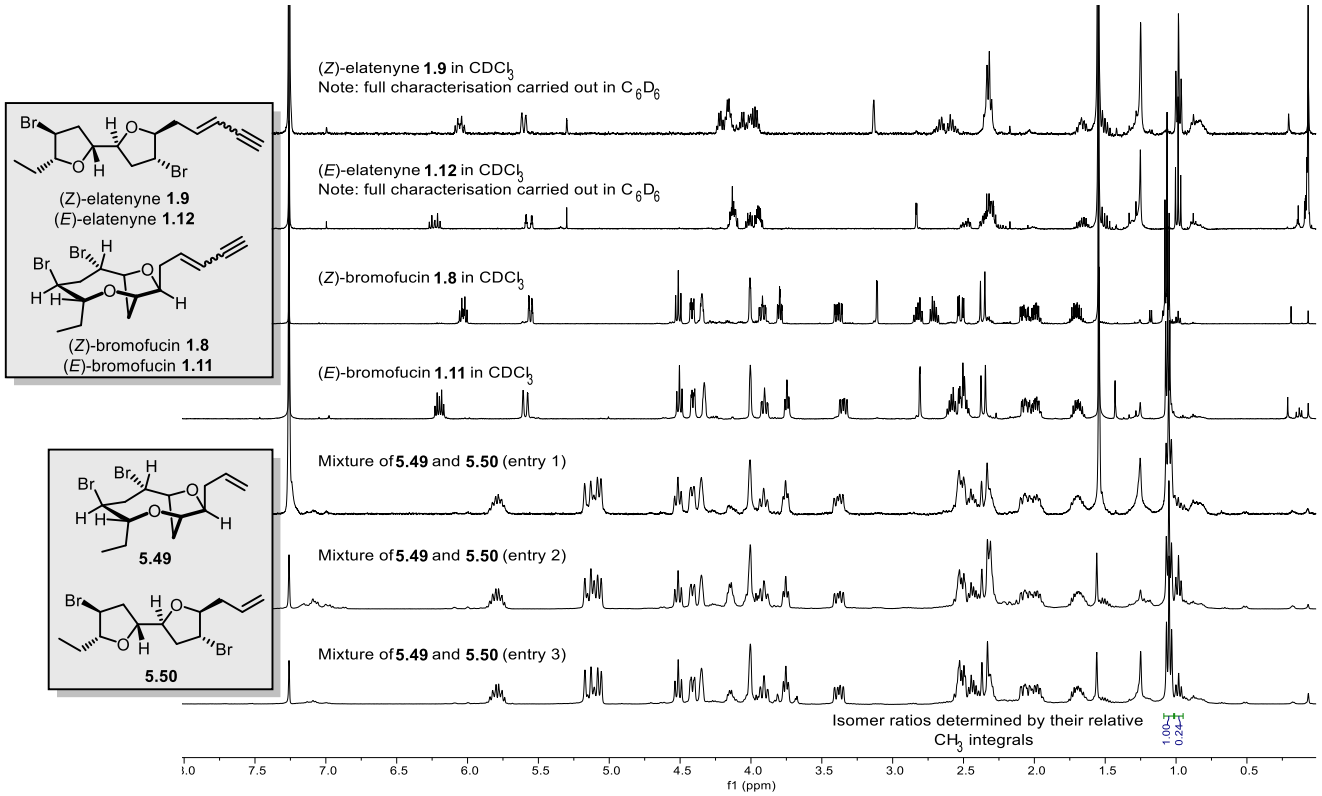


Figure 10.2. Determination of the **5.49**:**5.50** ratio by relative CH_3 integrals**.**

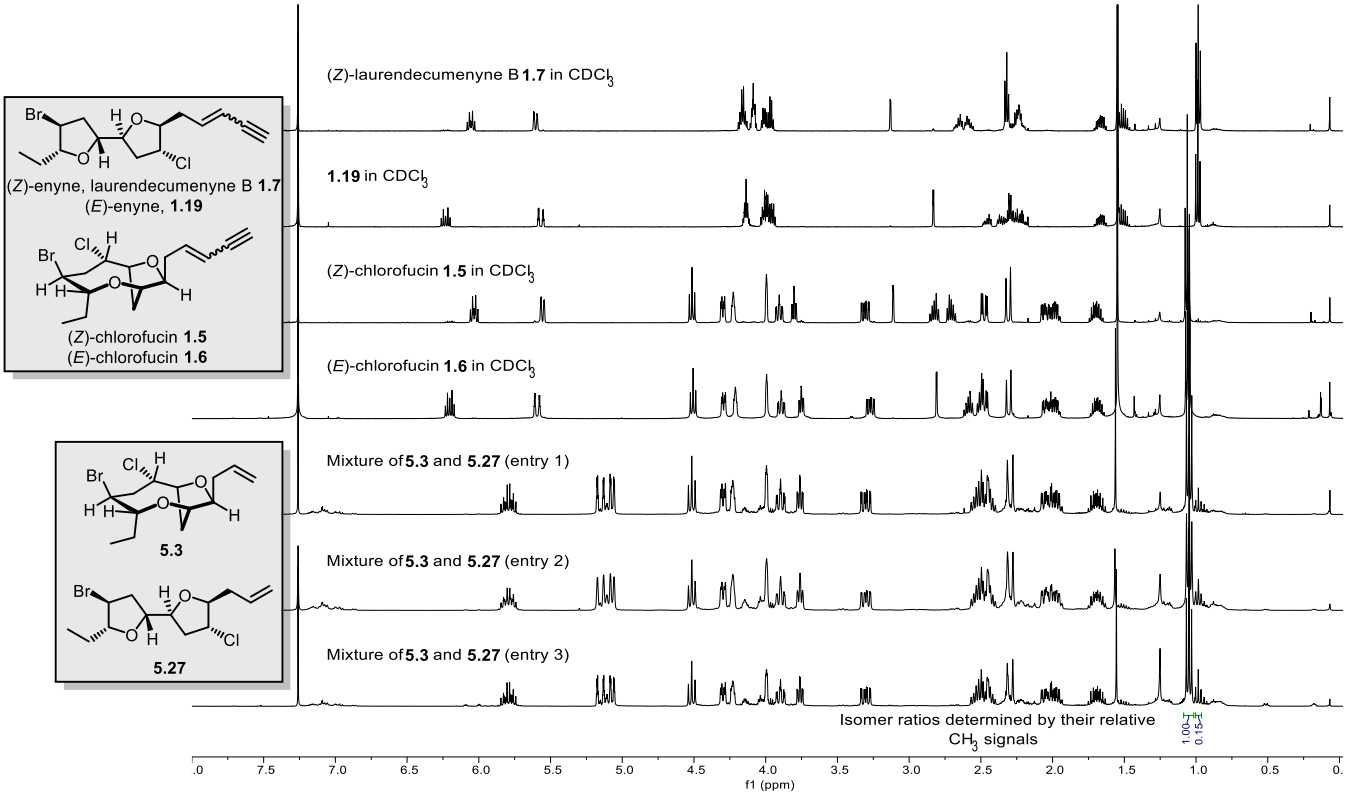
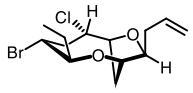


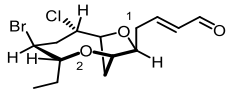
Figure 10.3. Determination of the **5.3**:**5.27** ratio by relative CH_3 integrals.

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-6-chloro-3-ethyl-2,8-dioxabicyclo [5.2.1]decane 4.48



This compound was synthesised using the general procedures as described above. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, C**H**=CH'H), 5.14 (dq, *J* = 17.2, 1.6 Hz, 1H, CH=C**H'**H), 5.07 (ddt, *J* = 10.2, 2.0, 1.1 Hz, 1H, CH=CH'**H**), 4.46 (dd, *J* = 7.7, 4.2 Hz, 1H, ClCHC**H**), 4.15 (ddd, *J* = 10.6, 4.2, 1.1 Hz, 1H, ClC**H**), 4.04 (td, *J* = 2.3, 1.2 Hz, 1H, ClCHCHCH'HC**H**), 3.84 (td, *J* = 7.4, 2.4 Hz, 1H, ClCHCHCH'HCHC**H**), 3.79 (dt, *J* = 10.9, 5.4 Hz, 1H, BrC**H**), 3.49 (ddd, *J* = 10.8, 8.8, 2.5 Hz, 1H, BrCHC**H**), 2.69 (ddd, *J* = 15.4, 5.0, 1.1 Hz, 1H, BrCHC**H'**H), 2.61 – 2.56 (m, 1H, ClCHCHC**H'**HCH), 2.56 – 2.49 (m, 1H, BrCHCH'**H**), 2.45 (tt, *J* = 7.2, 1.2 Hz, 2H, OCHC**H**$_2$CH=CH'H), 2.12 (dqd, *J* = 14.8, 7.4, 2.5 Hz, 1H, CH_3C**H'**H), 1.89 (ddd, *J* = 14.3, 7.7, 2.3 Hz, 1H, ClCHCHCH'**H**CH), 1.49 (ddq, *J* = 14.3, 8.7, 7.3 Hz, 1H, CH_3CH'**H**), 0.95 (t, *J* = 7.3 Hz, 3H, C**H**$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4 (**C**H=CH'H), 117.6 (CH=**C**H'H), 85.2 (ClCH**C**H), 83.4 (O**C**HCH$_2$CH=CH'H), 80.5 (BrCH**C**H), 76.7 (ClCHCHCH'H**C**H), 66.7 (Cl**C**H), 52.0 (Br**C**H), 45.4 (BrCH**C**H'H), 34.4 (ClCHCH**C**H'HCH), 34.3 (OCH**C**H$_2$CH=CH'H), 28.2 (CH_3**C**H'H), 9.6 (**C**H$_3$). IR (ν_{max} cm^{-1}): 3077 (alkene sp^2 C–H stretching, weak), 2964-2876 (alkane sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1062 (ether C–O–C antisymmetric stretching, strong), 917 (terminal alkene CH=CH$_2$ out–Of-plane deformation/wagging, strong). LRMS (ESI) no ionization. HRMS (CI) [M+H$^+$]: calculated for *m/z* 323.0408, 325.0388 and 327.0358, found *m/z* 323.0401, 325.0382 and 327.0363 ($C_{13}H_{21}O_2{}^{79}Br^{35}Cl$, $C_{13}H_{21}O_2{}^{79}Br^{37}Cl$/$C_{13}H_{21}O_2{}^{81}Br^{35}Cl$ and $C_{13}H_{21}O_2{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = +54.2$ (c=0.30, $CHCl_3$).

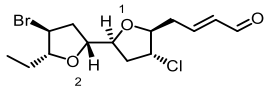
(*E*)-4-((1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-2,8-dioxabicyclo[5.2.1] decan-9-yl)but-2-enal 5.37



By the method of Kim[4]: A mixture of **5.3** and **5.27** (8.0 mg, 25.0 μmol, **5.3**:**5.27** ~ 7:1) was dissolved in CH_2Cl_2 (0.5 mL) and degassed with argon, then crotonaldehyde (predominantly *trans*) (21 μL, 0.25 mmol) was added followed by 2nd Generation Grubb's catalyst (2.0 mg, 2.5 μmol). An exhaust needle was installed, and the reaction mixture was then heated to 40 °C for 1.5 hours. A TLC analysis at this stage confirmed the complete consumption of starting materials. The reaction mixture was then cooled to room temperature and a few drops of DMSO was added and stirred open to air

overnight. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 to 50% EA/Pet. Ether 40-60) to give the compounds **5.37** (5.5 mg, 15.6 μmol, 63%, *E:Z* > 20:1) and **5.41** (1.3 mg, 3.8 μmol, 15%, *E:Z* > 20:1) as colourless oils. Characterisation data for **5.37**: R_f = 0.56 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H, $OCHCH_2CHCHC\mathbf{H}O$), 6.85 (dt, *J* = 15.7, 7.1 Hz, 1H, $OCHCH_2C\mathbf{H}CHCHO$), 6.22 (ddt, *J* = 15.7, 7.9, 1.5 Hz, 1H, $OCHCH_2CHC\mathbf{H}CHO$), 4.51 (t, *J* = 9.3 Hz, 1H, $BrC\mathbf{H}CH'HCHCl$), 4.32 (dd, *J* = 9.6, 3.6 Hz, 1H, $O_2CHCH'HC\mathbf{H}O_1$), 4.22 (p, *J* = 2.6 Hz, 1H, $BrCHCH'HC\mathbf{H}Cl$), 4.03 (t, *J* = 2.6 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 3.94 – 3.89 (m, 1H, $CH_3CH'HC\mathbf{H}$), 3.88 (ddd, *J* = 7.7, 6.1, 1.9 Hz, 1H, $OC\mathbf{H}CH_2CHCHCHO$), 3.26 (ddd, *J* = 15.5, 9.1, 2.3 Hz, 1H, $BrCHC\mathbf{H'}HCHCl$), 2.89 – 2.65 (m, 2H, $OCHC\mathbf{H}_2CHCHCHO$), 2.49 (dd, *J* = 15.5, 4.8 Hz, 1H, $BrCHCH'\mathbf{H}CHCl$), 2.35 (d, *J* = 15.6 Hz, 1H, $O_2CHC\mathbf{H'}HCHO_1$), 2.09 (ddd, *J* = 15.7, 9.6, 3.4 Hz, 1H, $O_2CHCH'\mathbf{H}CHO_1$), 2.00 (dqd, *J* = 15.1, 7.6, 2.7 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 1.70 (ddq, *J* = 14.3, 11.2, 7.1 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 1.05 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9 ($OCHCH_2CHCH\mathbf{C}HO$), 154.3 ($OCHCH_2\mathbf{C}HCHCHO$), 134.9 ($OCHCH_2CH\mathbf{C}HCHO$), 83.3 ($O\mathbf{C}HCH_2CHCHCHO$), 83.2 ($CH_3CH'H\mathbf{C}H$), 79.5 ($O_2CHCH'H\mathbf{C}HO_1$), 70.3 ($O_2\mathbf{C}HCH'HCHO_1$), 61.1 ($BrCHCH'H\mathbf{C}HCl$), 51.3 ($Br\mathbf{C}HCH'HCHCl$), 38.4 ($BrCH\mathbf{C}H'HCHCl$), 33.3 ($O_2CH\mathbf{C}H'HCHO_1$), 32.6 ($OCH\mathbf{C}H_2CHCHCHO$), 23.1 ($CH_3\mathbf{C}H'HCH$), 11.9 ($\mathbf{C}H_3CH'HCH$). IR (ν_{max} cm^{-1}): 2964-2931 (aliphatic sp^3 C–H stretchings, broad), 2735 (overtone of aldehyde C–H bending, weak), 1687 (conjugated C=O stretching, strong), 1063 (ether C–O–C antisymmetric stretching, strong), 801 (C–Cl stretching, medium), 666 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 351.0, 353.0 and 355.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 351.03681, 353.03476 and 355.03181, found *m/z* 351.03565, 353.03341 and 355.03053. ($C_{14}H_{21}O_3{}^{79}Br^{35}Cl$, $C_{14}H_{21}O_3{}^{81}Br^{35}Cl/C_{14}H_{21}O_3{}^{79}Br^{37}Cl$ and $C_{14}H_{21}O_3{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = -26.2$ (c=0.55, $CHCl_3$). Literature value: $[\alpha]_D^{25} = -31.7$ (c=0.59, $CHCl_3$).[4] Spectroscopic data are in accordance with literature data.[4]

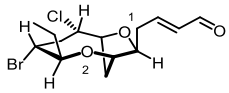
(*E*)-4-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4'-Bromo-4-chloro-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)but-2-enal 5.41



This compound was synthesized employing the same method as the synthesis of compound **5.37** which is as shown above. Characterisation data for **5.41**: R_f = 0.71 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, *J* = 7.8 Hz, 1H, $OCHCH'HCHCHC\mathbf{H}O$), 6.85 (dt, *J* = 15.7, 7.0 Hz, 1H, $OCHCH'HC\mathbf{H}CHCHO$), 6.21

(ddt, *J* = 15.7, 7.9, 1.5 Hz, 1H, OCHCH'HCHC**H**CHO), 4.22 – 4.12 (m, 2H, O_2C**H**CHO_1 and O_2CHC**H**O_1), 4.09 – 4.00 (m, 2H, C**H**CHBrCH'H and C**H**CHClCH'H), 4.00 – 3.91 (m, 2H, CHC**H**BrCH'H and CHC**H**ClCH'H), 2.71 (dddd, *J* = 16.7, 6.7, 4.7, 1.5 Hz, 1H, OCHC**H'**HCHCHCHO), 2.62 – 2.50 (m, 1H, OCHCH'**H**CHCHCHO), 2.37 – 2.27 (m, 2H, CHCHBrC**H'**H and CHCHClC**H'**H), 2.27 – 2.19 (m, 2H, CHCHBrCH'**H** and CHCHClCH'**H**), 1.66 (dqd, *J* = 14.9, 7.5, 5.0 Hz, 1H, CH_3C**H'**H), 1.50 (dp, *J* = 14.7, 7.4 Hz, 1H, CH_3CH'**H**), 0.98 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.8 (OCHCH'HCHCH**C**HO), 152.7 (OCHCH'H**C**HCHCHO), 135.3 (OCHCH'HCH**C**HCHO), 88.9 (**C**HCHBrCH'H), 85.1 (**C**HCHClCH'H), 79.7 (O_2CH**C**HO_1), 79.1 (O_2**C**$HCHO_1$), 58.8 (CH**C**HClCH'H), 48.7 (CH**C**HBrCH'H), 39.1 (CHCHBr**C**H'H), 37.6 (CHCHCl**C**H'H), 36.4 (OCH**C**H'HCHCHCHO), 26.9 (CH_3**C**H'H), 10.2 (**C**H_3CH'H). IR (ν_{max} cm^{-1}): 2965-2878 (aliphatic sp^3 C–H stretchings, broad), 2739 (overtone of aldehyde C–H bending, weak), 1689 (conjugated C=O stretching, strong), 1065 (ether C–O–C antisymmetric stretching, strong), 794 (C–Cl stretching, medium). LRMS (ESI) [M+Na]$^+$: *m/z* 373.0, 375.0 and 377.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 373.01766, 375.01561 and 377.01266, found *m/z* 373.01768, 375.01533 and 377.01262. ($C_{14}H_{20}O_3{}^{79}Br^{35}ClNa$, $C_{14}H_{20}O_3{}^{81}Br^{35}ClNa$/$C_{14}H_{20}O_3{}^{79}Br^{37}ClNa$ and $C_{14}H_{20}O_3{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = -26.7$ (c=0.30, $CHCl_3$).

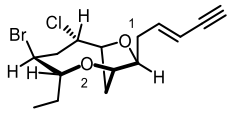
(*E*)-4-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-2,8-dioxabicyclo[5.2.1] decan-9-yl)but-2-enal 5.39



By the method of Kim[4]: Compound **4.48** (106 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (6.6 mL) and degassed with argon for 30 minutes. Crotonaldehyde (0.27 mL, 3.30 mmol) was added followed by Grubb's 2nd generation catalyst (28.0 mg, 0.03 mmol). The reaction mixture was heated to 40 °C for 1.5 hours. TLC analysis at this stage confirmed the complete consumption of starting materials. The reaction mixture was cooled to room temperature and DMSO (0.18 mL) was added. The reaction mixture was stirred at room temperature overnight and then all volatiles were evaporated under reduced pressure. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 40-60 to 50% EA/Pet. Ether 40-60 40-60) to give the desired compound **5.39** as a colourless oil (86.0 mg, 0.24 mmol, 74% *E*:*Z* > 20:1). R_f = 0.54 (50% EA/Pet. Ether 40-60 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.9 Hz, 1H, OCHCH_2CH=CHC**H**O), 6.87 (ddd, *J* = 15.6, 7.7, 6.5 Hz, 1H, OCHCH_2C**H**=CHCHO), 6.21 (ddt, *J* = 15.7, 7.9, 1.5 Hz, 1H, OCHCH_2CH=C**H**CHO), 4.50 (dd, *J* = 7.7, 4.2 Hz, 1H, ClCHC**H**O), 4.13 (ddd, *J* = 10.6, 4.3, 1.2 Hz, 1H,

ClC**H**CHO), 4.08 (td, *J* = 2.4, 1.2 Hz, 1H, O_2C**H**CH'HCHO$_1$), 3.96 (td, *J* = 7.0, 2.4 Hz, 1H, OC**H**CH_2CH=CHCHO), 3.79 (td, *J* = 10.8, 5.0 Hz, 1H, BrC**H**CH'H), 3.52 (ddd, *J* = 10.8, 8.8, 2.5 Hz, 1H, CH_3CH'HC**H**), 2.76 (dddd, *J* = 15.5, 7.7, 6.4, 1.6 Hz, 1H, BrCHC**H'**H), 2.73 – 2.67 (m, 2H, OCHC**H**$_2$CH=CHCHO), 2.63 (d, *J* = 14.4 Hz, 1H, O_2CHC**H'**HCHO$_1$), 2.55 (dt, *J* = 15.4, 10.8 Hz, 1H, BrCHCH'**H**), 2.14 (dqd, *J* = 14.8, 7.4, 2.6 Hz, 1H, CH_3C**H'**HCH), 1.94 (ddd, *J* = 14.5, 7.8, 2.3 Hz, 1H, O_2CHCH'**H**CHO$_1$), 1.50 (ddq, *J* = 14.3, 8.7, 7.2 Hz, 1H, CH_3CH'**H**CH), 0.94 (t, *J* = 7.3 Hz, 4H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9 (**C**=O), 154.1 (OCHCH$_2$**C**H=CHCHO), 134.9 (OCHCH$_2$CH=**C**HCHO), 85.5 (ClCH**C**HO), 81.9 (O**C**HCH$_2$CH=CHCHO), 80.7 (CH_3CH'H**C**H), 77.1 (O_2**C**HCH'HCHO$_1$), 66.3 (Cl**C**HCHO), 51.6 (Br**C**HCH'H), 45.4 (BrCH**C**H'H), 34.4 (O_2CH**C**H'HCHO$_1$), 33.5 (OCH**C**H$_2$CH=CHCHO), 28.2 (CH_3**C**H'HCH), 9.7 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 2964-2876 (alkane sp^3 C–H stretching, broad), 2739 (aldehyde C–H stretching, weak), 1690 (conjugated aldehyde C=O stretch, strong), 1065 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+MeOH+Na]$^+$: *m/z* 405.0, 407.0 and 409.0. HRMS (ESI) [M+MeOH+Na]$^+$: calculated for *m/z* 405.04387, 407.04182 and 409.03887, found *m/z* 405.04390, 407.04158 and 409.03887. ($C_{15}H_{24}O_4{}^{79}Br^{35}ClNa$, $C_{15}H_{24}O_4{}^{81}Br^{35}ClNa$/ $C_{15}H_{24}O_4{}^{79}Br^{37}ClNa$ and $C_{15}H_{24}O_4{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = +29.5$ (c=0.50, $CHCl_3$).

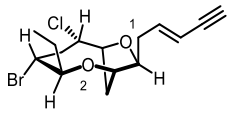
(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1]decane, (*E*)-chlorofucin, 1.6



According to the modified procedures of Kim[4]: $TMSCHN_2$ (2.0 M in diethyl ether, 80 µL, 0.14 mmol) was dissolved in dry THF (1.0 mL) at -78 °C. A solution of *n*-BuLi (2.35M in THF, 60 µL, 0.14 mmol) was added to the $TMSCHN_2$ solution dropwise and stirring was continued for 30 minutes. A portion of this solution (0.3 mL) was transferred by syringe in one quick injection to a solution of compound **5.37** (5.0 mg, 14.0 µmol) in dry THF (0.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 hour then warmed to 0 °C and stirring was continued for 30 minutes. The reaction was quenched with sat. aq. NH_4Cl, extracted with diethyl ether, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (3% Et_2O/Pet. Ether 40-60 to 5% Et_2O/Pet. Ether 40-60) to give the desired compound **1.6** as a pale yellow oil (2.1 mg, 6.0 µmol, 43%, *E:Z* > 20:1). R_f = 0.74 (30%EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 15.3, 7.4 Hz, 1H, OCHCH'HC**H**CHCCH), 5.59 (dq, *J* = 16.0, 1.7 Hz, 1H,

OCHCH'HCHC**H**CCH), 4.51 (t, *J* = 9.3 Hz, 1H, BrC**H**CH'HCHCl), 4.29 (dd, *J* = 9.6, 3.7 Hz, 1H, O_2CHCH'HC**H**O_1), 4.24 – 4.16 (m, 1H, BrCHCH'HC**H**Cl), 4.02 – 3.94 (m, 1H, O_2C**H**CH'HCHO_1), 3.89 (ddd, *J* = 11.8, 9.5, 2.6 Hz, 1H, CH_3CH'HC**H**), 3.75 (td, *J* = 7.1, 1.9 Hz, 1H, OC**H**CH'HCHCHCCH), 3.27 (ddd, *J* = 15.5, 9.1, 2.3 Hz, 1H, BrCHC**H'**HCHCl), 2.81 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHCC**H**), 2.59 (dtd, *J* = 15.0, 7.5, 1.5 Hz, 1H, OCHC**H'**HCHCHCCH), 2.54 – 2.43 (m, 2H, BrCHCH'**H**CHCl and OCHCH'**H**CHCHCCH), 2.31 (d, *J* = 15.6 Hz, 1H, O_2CHC**H'**HCHO_1), 2.04 (ddd, *J* = 15.8, 9.7, 3.5 Hz, 1H, O_2CHCH'**H**CHO_1), 1.98 (dqd, *J* = 15.1, 7.5, 4.9 Hz, 1H, CH_3C**H'**HCH), 1.69 (ddq, *J* = 14.2, 11.3, 7.1 Hz, 1H, CH_3CH'**H**CH), 1.06 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (OCHCH'H**C**HCHCCH), 111.5 (OCHCH'HCH**C**HCCH), 84.1 (O**C**HCH'HCHCHCCH), 83.2 (CH_3CH'H**C**H), 82.3 (OCHCH'HCHCH**C**CH), 79.4 (O_2CHCH'H**C**HO_1), 76.6 (OCHCH'HCHCHCC**H**), 69.9 (O_2**C**HCH'HCHO_1), 61.3 (BrCHCH'H**C**HCl), 51.6 (Br**C**HCH'HCHCl), 38.4 (BrCH**C**H'HCHCl), 33.3 (O_2CH**C**H'HCHO_1), 32.7 (OCH**C**H'HCHCHCCH), 23.1 (CH_3**C**H'HCH), 11.9 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3294 (acetylene C–H stretching, strong), 3018 (alkene sp^2 C–H stretching, weak), 2964-2859 (aliphatic sp^3 C–H stretchings, broad), 2102 (acetylene C≡C stretching, weak), 1062 (ether C–O–C antisymmetric stretching, strong), 800 (C–Cl stretching, medium), 665 (C–Br stretching, medium). LRMS (ESI) [M+H]$^+$: *m/z* 347.0 and 349.0. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 347.04080 and 349.03875, found *m/z* 347.04084 and 349.03851. ($C_{15}H_{21}O_2{}^{79}Br^{35}Cl$ and $C_{14}H_{21}O_3{}^{81}Br^{35}Cl$/$C_{14}H_{21}O_3{}^{79}Br^{37}Cl$). $[\alpha]_D^{25} = +9.5$ (c=0.21, $CHCl_3$) . lit. $[\alpha]_D^{25} = +11.6$ (c=0.42, $CHCl_3$)[4] and $[\alpha]_D^{25} = +12.0$ (c=1.4, $CHCl_3$).[11] Spectroscopic data are in accordance with literature data[4,11].

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decane *ent*-5.2

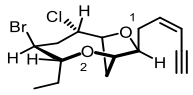


According to the modified procedures of Kim[4]: $TMSCHN_2$ (0.12 mL, 0.24 mmol, 2.0 M solution in Et_2O) was mixed with dry THF (1.0 mL) at -78 °C. *n*-BuLi (0.10 mL, 0.24 mmol, 2.3 M solution in hexanes) was then added and stirring was continued for 30 minutes. Compound **S21** (51.0 mg, 0.14 mmol) was dissolved in dry THF (2.0 mL) and the reaction mixture was cooled to -78 °C, in which the preformed $TMSCLiN_2$ solution was then added rapidly. The reaction mixture was stirred at -78 °C for 1 hour, then warmed to 0 °C and stirring was continued for 30 minutes. TLC analysis at this stage showed complete consumption of starting material. The reaction was then

quenched with sat. aq. NH_4Cl solution and extracted with Et_2O. The organic layer was separated, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting yellow crude oil then underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60 to 10% EA/Pet. Ether 40-60) to give the desired compound ***ent*-5.2** as a pale oil (30.0 mg, 86.5 μmol, 60%, *E:Z* > 20:1). R_f = 0.54 (20% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (dt, *J* = 16.1, 7.4 Hz, 1H, OCHCH$_2$C**H**=CHCCH), 5.58 (dq, *J* = 15.9, 1.7 Hz, 1H, OCHCH$_2$CH=C**H**CCH), 4.47 (dd, *J* = 7.7, 4.2 Hz, 1H, ClCHC**H**O), 4.12 (ddd, *J* = 10.5, 4.2, 1.1 Hz, 1H, ClC**H**CHO), 4.05 (td, *J* = 2.4, 1.2 Hz, 1H, O$_2$C**H**CH'HCHO$_1$), 3.84 (td, *J* = 7.3, 2.4 Hz, 1H, OC**H**CH$_2$CH=CHCCH), 3.79 (td, *J* = 10.8, 5.0 Hz, 1H, BrC**H**CH'H), 3.50 (ddd, *J* = 10.8, 8.7, 2.5 Hz, 1H, CH$_3$CH'HC**H**), 2.81 (d, *J* = 2.3 Hz, 1H, OCHCH$_2$CH=CHCC**H**), 2.69 (ddd, *J* = 15.5, 4.9, 1.1 Hz, 1H, BrCHC**H'**H), 2.59 (d, *J* = 14.4 Hz, 1H, O$_2$CHC**H'**HCHO$_1$), 2.57 – 2.48 (m, 3H, BrCHCH'**H** and OCHC**H**$_2$CH=CHCCH), 2.13 (dqd, *J* = 14.8, 7.0, 2.1 Hz, 1H, CH$_3$C**H'**HCH), 1.90 (ddd, *J* = 14.4, 7.8, 2.3 Hz, 1H, O$_2$CHCH'**H**CHO$_1$), 1.50 (ddq, *J* = 14.3, 8.7, 7.4 Hz, 1H, CH$_3$CH'**H**CH), 0.96 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 (OCHCH$_2$**C**H=CHCCH), 111.6 (OCHCH$_2$CH=**C**HCCH), 85.3 (ClCH**C**HO), 82.7 (O**C**HCH$_2$CH=CHCCH), 82.2 (OCHCH$_2$CH=CH**C**CH), 80.6 (CH$_3$CH'H**C**H), 76.8 (O$_2$**C**HCH'HCHO$_1$), 76.6 (OCHCH$_2$CH=CHC**C**H), 66.5 (Cl**C**HCHO), 51.8 (Br**C**HCH'H), 45.4 (BrCH**C**H'H), 34.4 (O$_2$CH**C**H'HCHO$_1$), 33.6 (OCH**C**H$_2$CH=CHCCH), 28.2 (CH$_3$**C**H'HCH), 9.7 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 3291 (acetylene sp C–H stretching, strong), 3007 (alkene sp^2 C–H stretching, medium), 2964-2851 (aliphatic sp^3 C–H stretchings, broad), 2120 (acetylene C≡C stretching, weak), 1063 (ether C–O–C antisymmetric stretching, strong), 667 (C–Cl stretching, strong). LRMS (ESI) [M+H]$^+$: *m/z* 347.0, 349.0 and 351.0. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 347.04080, 349.03875 and 351.03580, found *m/z* 347.04073, 349.03843 and 351.03564. ($C_{15}H_{20}O_2{}^{79}Br^{35}Cl$, $C_{15}H_{20}O_2{}^{81}Br^{35}Cl$ / $C_{15}H_{20}O_2{}^{79}Br^{37}Cl$ and $C_{15}H_{20}O_2{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = +62.7$ (c=0.50, $CHCl_3$). **NMR data at -78 °C in CD_2Cl_2**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.14 (dt, *J* = 15.3, 7.5 Hz, 1H, OCHCH$_2$C**H**=CHCCH), 5.57 (d, *J* = 15.9 Hz, 1H, OCHCH$_2$CH=C**H**CCH), 4.36 (dd, *J* = 7.6, 4.3 Hz, 1H, ClCHC**H**O), 4.06 (dt, *J* = 8.2, 4.0 Hz, 1H, ClC**H**CHO), 3.98 (s, 1H, O$_2$C**H**CH'HCHO$_1$), 3.83 – 3.69 (m, 2H, BrC**H**CH'H and OC**H**CH$_2$CH=CHCCH), 3.42 (t, *J* = 9.9 Hz, 1H, CH$_3$CH'HC**H**), 2.91 (s, 1H, OCHCH$_2$CH=CHCC**H**), 2.55 (m, 2H, BrCHC**H'H**), 2.50 (d, *J* = 14.1 Hz, 1H, O$_2$CHC**H'**HCHO$_1$), 2.48 – 2.40 (m, 2H, OCHC**H**$_2$CH=CHCCH), 2.07 (dt, *J* = 14.8, 7.3 Hz, 1H, CH$_3$C**H'**HCH), 1.86 (dd, *J* = 14.4, 7.5 Hz, 1H, O$_2$CHCH'**H**CHO$_1$), 1.34 (dq, *J* = 14.8, 7.4 Hz, 1H, CH$_3$CH'**H**CH), 0.87 (t, *J* = 7.2 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 142.0 (OCHCH$_2$**C**H=CHCCH), 110.7 (OCHCH$_2$CH=**C**HCCH), 85.4 (ClCH**C**HO), 81.8

(OCHCH$_2$CH=CH**C**CH), 81.6 (O**C**HCH$_2$CH=CHCCH), 79.8 (CH$_3$CH'H**C**H), 76.4 (OCHCH$_2$CH=CHC**C**H), 76.2 (O$_2$**C**HCH'HCHO$_1$), 67.6 (Cl**C**HCHO), 52.3 (Br**C**HCH'H), 45.6 (BrCH**C**H'H), 34.4 (O$_2$CH**C**H'HCHO$_1$), 33.5 (OCH**C**H$_2$CH=CHCCH), 27.8 (CH$_3$**C**H'HCH), 9.6 (**C**H$_3$CH'HCH).

(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1]decane, (*Z*)-chlorofucin 1.5



According to the procedures of Shirokane[228]: Compound **5.3** and **5.27** (23.7 mg, 74.0 µmol, isomeric ratio ~7:1) was dissolved in 3:1 dioxane:H$_2$O (1.3 mL), then 2,6-lutidine (17.0 µL, 0.14 mmol) was added followed by a solution of 2.5% OsO$_4$ in *t*-BuOH (17.0 µL). NaIO$_4$ (62.0 mg, 0.29 mmol) was then added and the reaction mixture was stirring was continued for 1-2 hours. A TLC analysis at this stage showed complete consumption of starting material. The reaction mixture was then diluted with CH$_2$Cl$_2$ and H$_2$O followed by extraction with CH$_2$Cl$_2$. The organic layer was separated, dried with MgSO$_4$ and concentrated to give a crude brown oil. This crude brown oil was dried under high vacuum while the procedures below were carried out.

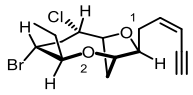
Ph$_3$PCH$_2$I$_2$ (117.0 mg, 0.22 mmol) was suspended in dry THF (3.0 mL) at room temperature and a solution of NaHMDS (0.21 mL, 1.0M solution in THF) was added. The reaction mixture was stirred at room temperature for 15 minutes in which the colour of the solution changed from bright yellow to deep orange. This solution was then cooled to -78 °C and HMPA (78.0 µL, 0.45 mmol) was added and stirring was continued for 15 minutes. The dried crude brown oil was then dissolved in dry THF (0.7 mL) and added to the reaction mixture. The reaction mixture was stirred at -78 °C for 30 minutes then room temperature for 1 hour. A TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH$_4$Cl and extracted with ethyl acetate. The organic layer was separated, dried with MgSO$_4$ and concentrated. The crude mixture quickly underwent purification by flash column chromatography (5% EA/Pentane), product R_f = 0.51 (10% EA/Pet. Ether 40-60). The purified vinyl iodide was then quickly used for the following transformations due to its instability.

The vinyl iodide (18.9 mg, 42.0 µmol) was dissolved in dry Et$_3$N (2.1 mL), then trimethylsilylacetylene (30.0 µL, 0.21 mmol) was added followed by CuI (8.0 mg, 42.0 µmol). The mixture was then degassed with dry argon for 15 minutes. Pd(PPh$_3$)$_4$ (7.3 mg, 6.3 µmol) was then added and the reaction mixture was stirred at room temperature with exclusion of light for 1 hour. A TLC analysis at this stage showed the complete

consumption of starting material. K_2CO_3 (58.0 mg, 0.42 mmol) and MeOH (2.1 mL) were added to the reaction mixture and stirring was continued for 1-2 hours until completion. The reaction mixture was then diluted with H_2O and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$, filtered through a short plug of silica and concentrated. The resulting pale brown crude oil then underwent purification by flash column chromatography twice (5% Et_2O/Pet. Ether 40-60 to remove minor impurities), (50% $CHCl_3$/Pet. Ether 40-60 + 1% EA to separate (*Z*)-chlorofucin **1.5** from laurendecumenyne B **1.7**) to give the desired compound **1.5** as a colourless oil (8.1 mg, 23.3 μmol, 32% over 4 steps, *Z:E* > 15:1). **The laurendecumenyne B 1.7 generated by this method was not isolated.** R_f (**1.5**) = 0.51 (10% EA/Pet. Ether 40-60 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dtd, *J* = 11.0, 7.6, 0.9 Hz, 1H, OCHCH'HC**H**CHCCH), 5.56 (ddt, *J* = 10.9, 2.6, 1.4 Hz, 1H, OCHCH'HCHC**H**CCH), 4.51 (t, *J* = 9.3 Hz, 1H, BrC**H**CH'HCHCl), 4.30 (dd, *J* = 9.6, 3.6 Hz, 1H, O_2CHCH'HC**H**O_1), 4.26 – 4.17 (m, 1H, BrCHCH'HC**H**Cl), 3.99 (t, *J* = 2.6 Hz, 1H, O_2C**H**CH'HCHO_1), 3.91 (ddd, *J* = 11.8, 9.6, 2.7 Hz, 1H, CH_3CH'HC**H**), 3.80 (td, *J* = 7.1, 1.9 Hz, 1H, OC**H**CH'HCHCHCCH), 3.31 (ddd, *J* = 15.5, 9.1, 2.2 Hz, 1H, BrCHC**H'**HCHCl), 3.11 (d, *J* = 2.3 Hz, 1H, OCHCH'HCHCHCC**H**), 2.82 (dtd, *J* = 13.9, 7.6, 1.4 Hz, 1H, OCHC**H'**HCHCHCCH), 2.71 (dtd, *J* = 14.0, 7.2, 1.3 Hz, 1H, OCHCH'**H**CHCHCCH), 2.48 (dd, *J* = 15.5, 4.8 Hz, 1H, BrCHCH'**H**CHCl), 2.31 (d, *J* = 15.5 Hz, 1H, O_2CHC**H'**HCHO_1), 2.05 (ddd, *J* = 15.4, 9.6, 3.3 Hz, 1H, O_2CHCH'**H**CHO_1), 1.98 (dqd, *J* = 15.1, 7.6, 2.6 Hz, 1H, CH_3C**H'**HCH), 1.70 (ddq, *J* = 14.2, 11.2, 7.1 Hz, 1H, CH_3CH'**H**CH), 1.06 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3 (OCHCH'H**C**HCHCCH), 110.6 (OCHCH'HCH**C**HCCH), 84.2 (O**C**HCH'HCHCHCCH), 83.0 (CH_3CH'H**C**H), 82.2 (OCHCH'HCHCHC**C**H), 80.2 (OCHCH'HCHCH**C**CH), 79.4 (O_2CHCH'H**C**HO_1), 70.2 (O_2**C**HCH'HCHO_1), 61.4 (BrCHCH'H**C**HCl), 51.7 (Br**C**HCH'HCHCl), 38.4 (BrCH**C**H'HCHCl), 33.4 (O_2CH**C**H'HCHO_1), 30.2 (OCH**C**H'HCHCHCCH), 23.1 (CH_3**C**H'HCH), 11.9 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3293 (acetylene sp C–H stretching, medium), 2964-2877 (aliphatic sp^3 C–H stretchings, broad), 2097 (acetylene C≡C stretching, weak), 1062 (ether C–O–C antisymmetric stretching, strong), 740 (C–Cl stretching, medium), 667 (C–Br stretching, medium). HRMS (APCI) [M+H]$^+$: calculated for *m/z* 347.04080, 349.03875 and 351.03580, found *m/z* 347.04080, 349.03851 and 351.03573. ($C_{15}H_{21}O_2{}^{79}Br^{35}Cl$, $C_{15}H_{21}O_2{}^{79}Br^{37}Cl$/$C_{15}H_{21}O_2{}^{81}Br^{35}Cl$ and $C_{15}H_{21}O_2{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = -12.4$ (c=0.37, $CHCl_3$), lit. $[\alpha]_D^{25} = -14.3$ ($c = 0.63, CHCl_3$)[4] and $[\alpha]_D^{25} = -11.3$ ($c = 0.58, CHCl_3$).[19] Spectroscopic data are in accordance with literature data[4,19].

(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-

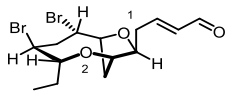
dioxabicyclo[5.2.1]decane *ent*-5.1



According to the procedures of Shirokane[228]: Compound **4.48** (95.0 mg, 0.30 mmol) was dissolved in a 3:1 solution of 1,4-dioxane and water (3.0 mL). 2,6-lutidine (67.0 µL, 0.58 mmol) was added followed by a solution of 2.5% OsO_4 in *t*-BuOH (25.0 µL). $NaIO_4$ (248.0 mg, 1.16 mmol) was then added and the reaction mixture was stirred at room temperature until completion. The reaction mixture was then diluted with water and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$, concentrated and the crude aldehyde dried under high-vacuum. $Ph_3PCH_2I_2$ (469.0 mg, 0.89 mmol) was dissolved in dry THF (6.0 mL) at room temperature followed by the addition of a 1M solution of NaHMDS in THF (0.83 mL, 0.83 mmol) and stirring was continued for 15 minutes. The solution was then cooled to -78 °C and HMPA (0.31 mL, 1.80 mmol) was added and stirring was continued for 15 minutes. The dried crude aldehyde was dissolved in THF (9.0 mL), added to the solution of the Wittig reagent at -78 °C and stirring was continued for 30 minutes at this temperature. The reaction mixture was then warmed to room temperature and stirring was continued for 1 hour. A TLC analysis at this stage revealed the complete consumption of starting material. The reaction mixture was quenched by sat. aq. NH_4Cl, extracted with EtOAc, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude vinyl iodide was then quickly underwent purification by flash column chromatography to remove any impurities. The vinyl iodide was not characterized as it was found to decompose slowly overnight. The purified vinyl iodide (54.0 mg, 0.12 mmol) was dissolved in dry Et_3N (6.0 mL) at room temperature and TMS acetylene (83.0 µL, 0.60 mmol) was added followed by CuI (23.0 mg, 0.12 mmol). The reaction mixture was degassed with argon for 15 minutes. $Pd(PPh_3)_4$ (21.0 mg, 18.0 µmmol) was then added and the reaction mixture stirring was continued for 1 hours with the exclusion of light. TLC analysis at this stage revealed the complete consumption of starting material. To the reaction mixture was then added K_2CO_3 (166.0 mg, 1.2 mmol) and MeOH (5.5 mL) and stirred until completion. The reaction mixture was quenched by H_2O, extracted with EtOAc, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60) to give the desired compound ***ent*-5.1** as a colourless oil (20.0 mg, 57.6 µmol, 20% over 4 steps, *Z*:*E* > 15:1). R_f = 0.49 (10% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (dtd, *J* = 10.9, 7.5, 0.9 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.56 (ddt, *J* = 10.9, 2.5, 1.4 Hz, 1H, OCHCH'HCH=C**H**CCH), 4.47 (dd, *J* = 7.7, 4.3 Hz, 1H, O_2CHCH'HC**H**O_1), 4.17 (ddd, *J* = 10.6, 4.3, 1.2 Hz, 1H, ClC**H**CH'HCHBr), 4.04 (td, *J* = 2.3, 1.2 Hz, 1H, O_2C**H**CH'HCHO_1), 3.90 (td, *J* = 7.4, 2.4 Hz, 1H,

OC**H**CH'HCH=CHCCH), 3.80 (td, *J* = 10.8, 5.0 Hz, 1H, ClCHCH'HC**H**Br), 3.50 (ddd, *J* = 10.8, 8.9, 2.5 Hz, 1H, CH_3CH'HC**H**), 3.11 (dd, *J* = 2.2, 0.9 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.79 (dtd, *J* = 14.2, 7.2, 1.7 Hz, 1H, OCHC**H'**HCH=CHCCH), 2.73 – 2.64 (m, 2H, ClCHC**H'**HCHBr, OCHCH'**H**CH=CHCCH), 2.60 (d, *J* = 14.4 Hz, 1H, O_2CHC**H'**HCHO$_1$), 2.54 (dt, *J* = 15.4, 10.8 Hz, 1H, ClCHCH'**H**CHBr), 2.13 (dqd, *J* = 14.8, 7.4, 2.5 Hz, 1H, CH_3C**H'**HCH), 1.90 (ddd, *J* = 14.4, 7.7, 2.3 Hz, 1H, O_2CHCH'**H**CHO$_1$), 1.50 (ddq, *J* = 14.3, 8.8, 7.2 Hz, 1H, CH_3CH'**H**CH), 0.96 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (OCHCH'H**C**H=CHCCH), 110.6 (OCHCH'HCH=**C**HCCH), 85.3 (O_2CHCH'H**C**HO$_1$), 82.7 (O**C**HCH'HCH=CHCCH), 82.2 (OCHCH'HCH=CHC**C**H), 80.6 (CH_3CH'H**C**H), 80.2 (OCHCH'HCH=CH**C**CH), 77.0 (O_2**C**HCH'HCHO$_1$, 66.5 (Cl**C**HCH'HCHBr), 52.0 (ClCHCH'H**C**HBr), 45.4 (ClCH**C**H'HCHBr), 34.4 (O_2CH**C**H'HCHO$_1$), 31.0 (OCH**C**H'HCH=CHCCH), 28.2 (CH_3**C**H'HCH), 9.8 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3293 (acetylene sp C–H stretching, strong), 3011 (alkene sp^2 C–H stretching, medium), 2918-2876 (aliphatic sp^3 C–H stretchings, broad), 2097 (acetylene C≡C stretching, weak), 1065 (ether C–O–C antisymmetric stretching, strong), 667 (C–Cl stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 369.0, 371.0 and 373.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 369.0233, 371.0211 and 373.0189, found *m/z* 369.0229, 371.0205 and 373.0181. ($C_{15}H_{20}O_2{}^{79}Br^{35}ClNa$, $C_{15}H_{20}O_2{}^{81}Br^{35}ClNa$ / $C_{15}H_{20}O_2{}^{79}Br^{37}ClNa$ and $C_{15}H_{21}O_2{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = +44.3$ (c=0.70, $CHCl_3$). **NMR data at -78 °C in CD_2Cl_2**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.01 (dt, *J* = 11.0, 7.6 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.53 (dd, *J* = 10.8, 1.6 Hz, 1H, OCHCH'HCH=C**H**CCH), 4.37 (dd, *J* = 7.4, 4.3 Hz, 1H, O_2CHCH'HC**H**O$_1$), 4.12 (dt, *J* = 8.4, 4.3 Hz, 1H, ClC**H**CH_2CHBr), 3.98 (s, 1H, O_2C**H**CH'HCHO$_1$), 3.80 (m, 1H, OC**H**CH'HCH=CHCCH), 3.75 (t, *J* = 10.3, 7.3 Hz, 1H, ClCHCH_2C**H**Br), 3.42 (td, *J* = 10.6, 1.4 Hz, 1H, CH_3CH'HC**H**), 3.20 (d, *J* = 2.2 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.67 (dt, *J* = 14.1, 7.1 Hz, 1H, OCHC**H'**HCH=CHCCH), 2.64 – 2.47 (m, 4H, ClCHC**H**$_2$CHBr, O_2CHC**H'**HCHO$_1$ and OCHCH'**H**CH=CHCCH), 2.07 (dqd, *J* = 13.5, 7.5, 1.6 Hz, 1H, CH_3C**H'**HCH), 1.86 (ddd, *J* = 14.2, 7.4, 1.4 Hz, 1H, O_2CHCH'**H**CHO$_1$), 1.35 (ddq, *J* = 13.9, 9.6, 7.2 Hz, 1H, CH_3CH'**H**CH), 0.86 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 141.2 (OCHCH'H**C**H=CHCCH), 109.9 (OCHCH'HCH=**C**HCCH), 85.4 (O_2CHCH'H**C**HO$_1$), 82.0 (OCHCH'HCH=CHC**C**H), 81.7 (O**C**HCH'HCH=CHCCH), 79.8 (CH_3CH'H**C**H), 79.7 (OCHCH'HCH=CH**C**CH), 76.4 (O_2**C**HCH'HCHO$_1$), 67.6 (Cl**C**HCH_2CHBr), 52.5 (ClCHCH_2**C**HBr), 45.7 (ClCH**C**H_2CHBr), 34.4 (O_2CH**C**H'HCHO$_1$), 30.8 (OCH**C**H'HCH=CHCCH), 27.9 (CH_3**C**H'HCH), 9.7 (**C**H_3CH'HCH)

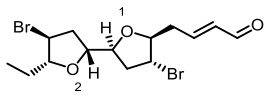
(*E*)-4-((1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4,6-Dibromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-9-yl)but-2-enal 5.51



According to the procedures of Voigtritter[235]: To a mixture of **5.49** and **5.50** (7.2 mg, 0.02 mmol, **5.49**:**5.50** ~ 4:1) was added dry Et_2O (1.0 mL) and degassed with dry Argon for 15 minutes. Crotonaldehyde (10.0 µL, 0.10 mmol) was added followed by 2nd Generation Grubb's catalyst (1.0 mg, 1.00 µmol) and CuI (0.3 mg, 1.50 µmol). The reaction mixture was then stirred at room temperature overnight with an exhaust needle. TLC at this stage showed complete consumption of starting materials. The volatiles were removed and the resulting brown crude oil then underwent purification by flash column chromatography (40% Et_2O/Pet. Ether 40-60 to 60% Et_2O/Pet. Ether 40-60) to give the desired compound **5.51** as a pale green oil (4.8 mg, 12.0 µmol, 60%, *E:Z* > 20:1). The enal **5.52** arising from **5.50** was also isolated however was found to be contaminated with slight **5.41** which was inseparable from **5.52** (1.0 mg, 2.6 µmol, 13%, *E:Z* > 20:1). R_f = 0.58 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.9 Hz, 1H, $OCHCH_2CHCHC\mathbf{H}O$), 6.85 (dt, *J* = 15.7, 7.1 Hz, 1H, $OCHCH_2C\mathbf{H}CHCHO$), 6.22 (ddt, *J* = 15.7, 7.8, 1.5 Hz, 1H, $OCHCH_2CHC\mathbf{H}CHO$), 4.51 (t, *J* = 9.2 Hz, 1H, $BrC\mathbf{H}CHCH'HCH_3$), 4.44 (dd, *J* = 9.6, 3.6 Hz, 1H, $O_2CHCH'HC\mathbf{H}O_1$), 4.37 – 4.28 (m, 1H, $CH'HC\mathbf{H}Br$), 4.04 (t, *J* = 2.6 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 3.92 (ddd, *J* = 11.8, 9.5, 2.7 Hz, 1H, $BrCHC\mathbf{H}CH'HCH_3$), 3.87 (ddd, *J* = 7.7, 6.1, 1.9 Hz, 1H, $OC\mathbf{H}CH_2CHCHCHO$), 3.34 (ddd, *J* = 15.8, 8.9, 2.4 Hz, 1H, $C\mathbf{H}'HCHBr$), 2.85 – 2.68 (m, 2H, $OCHC\mathbf{H}_2CHCHCHO$), 2.54 (dd, *J* = 15.8, 4.7 Hz, 1H, $CH'\mathbf{H}CHBr$), 2.40 (d, *J* = 15.6 Hz, 1H, $O_2CHC\mathbf{H}'HCHO_1$), 2.11 (ddd, *J* = 15.6, 9.6, 3.4 Hz, 1H, $O_2CHCH'\mathbf{H}CHO_1$), 2.01 (dqd, *J* = 15.2, 7.6, 2.7 Hz, 1H, $BrCHCHC\mathbf{H}'HCH_3$), 1.70 (ddq, *J* = 14.2, 11.3, 7.1 Hz, 1H, $BrCHCHCH'\mathbf{H}CH_3$), 1.05 (t, *J* = 7.3 Hz, 3H, $BrCHCHCH'HC\mathbf{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9 ($OCHCH_2CHCH\mathbf{C}HO$), 154.3 ($OCHCH_2\mathbf{C}HCHCHO$), 134.9 ($OCHCH_2CH\mathbf{C}HCHO$), 83.6 ($O\mathbf{C}HCH_2CHCHCHO$), 83.1 ($BrCH\mathbf{C}HCH'HCH_3$), 79.9 ($O_2CHCH'H\mathbf{C}HO_1$), 70.3 ($O_2\mathbf{C}HCH'HCHO_1$), 55.0 ($CH'H\mathbf{C}HBr$), 52.7 ($Br\mathbf{C}HCHCH'HCH_3$), 38.7 ($\mathbf{C}H'HCHBr$), 33.7 ($O_2CH\mathbf{C}H'HCHO_1$), 32.6 ($OCH\mathbf{C}H_2CHCHCHO$), 23.1 ($BrCHCH\mathbf{C}H'HCH_3$), 11.9 ($BrCHCHCH'H\mathbf{C}H_3$). IR (ν_{max} cm^{-1}): 2964-2876 (aliphatic sp^3 C–H stretchings, broad), 2736 (overtone of aldehyde C–H bending, weak), 1688 (conjugated C=O stretching, strong), 1061 (ether C–O–C antisymmetric stretching, strong), 645 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 395.0, 397.0 and 399.0. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 394.98520, 396.98315 and 398.98110,

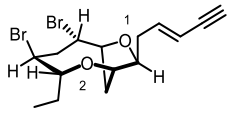
found *m/z* 394.98531, 396.98317 and 398.98115. ($C_{14}H_{21}O_3{}^{79}Br_2$, $C_{14}H_{21}O_3{}^{79}Br^{81}Br$/$C_{14}H_{21}O_3{}^{81}Br^{79}Br$ and $C_{14}H_{21}O_3{}^{81}Br_2$). $[\alpha]_D^{25} = -27.3$ (c=0.37, $CHCl_3$). Literature value: $[\alpha]_D^{25} = -40.2$ (c=0.64, $CHCl_3$)[4]. Spectroscopic data are in accordance with literature data.[4]

(*E*)-4-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)but-2-enal 5.52



This compound was synthesised employing the same method as the synthesis of compound **5.51** which is as shown above. Characterisation data for **5.52**: R_f = 0.69 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, *J* = 7.9 Hz, 1H, OCHCH'HCH=CHC**H**O), 6.86 (dt, *J* = 15.7, 7.0 Hz, 1H, OCHCH'HC**H**=CHCHO), 6.21 (ddt, *J* = 15.7, 7.9, 1.4 Hz, 1H, OCHCH'HCH=C**H**CHO), 4.21 – 4.16 (m, 2H, O_2C**H**CHO$_1$, OC**H**CH'HCH=CHCHO), 4.16 – 4.13 (m, 1H, O_2CHC**H**O$_1$), 4.03 (dt, *J* = 7.2, 5.3 Hz, 1H, CH_3CH'HC**H**CHBrCH'H), 3.97 – 3.93 (m, 1H, CH_3CH'HCHC**H**BrCH'H), 3.93 – 3.90 (m, 1H, CH'HC**H**Br), 2.74 (dddd, *J* = 15.2, 6.9, 4.4, 1.4 Hz, 1H, OCHC**H'**HCH=CHCHO), 2.55 (dtd, *J* = 15.0, 7.3, 1.4 Hz, 1H, OCHCH'**H**CH=CHCHO), 2.45 – 2.37 (m, 1H, C**H'**HCHBr), 2.37 – 2.32 (m, 2H, CH'**H**CHBr), 2.32 – 2.27 (m, 1H, CH_3CH'HCHCHBrC**H'**H), 2.23 (dt, *J* = 13.6, 7.5 Hz, 1H, CH_3CH'HCHCHBrCH'**H**), 1.66 (dqd, *J* = 14.8, 7.4, 5.3 Hz, 1H, CH_3C**H'**HCHCHBrCH'H), 1.49 (dq, *J* = 13.9, 7.5 Hz, 1H, CH_3CH'**H**CHCHBrCH'H), 0.98 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCHCHBrCH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.8 (OCHCH'HCH=CH**C**HO), 152.7 (OCHCH'H**C**H=CHCHO), 135.3 (OCHCH'HCH=**C**HCHO), 89.0 (CH_3CH'H**C**HCHBrCH'H), 85.3 (O**C**HCH'HCH=CHCHO), 79.9 (O_2CH**C**HO$_1$), 79.1 (O_2**C**HCHO$_1$), 48.7 (CH_3CH'HCH**C**HBrCH'H), 47.6 (CH'H**C**HBr), 39.1 (CH_3CH'HCHCHBr**C**H'H), 38.1 (**C**H'HCHBr), 36.2 (OCH**C**H'HCH=CHCHO), 26.9 (CH_3**C**H'HCHCHBrCH'H), 10.2 (**C**H_3CH'HCHCHBrCH'H). IR (ν_{max} cm^{-1}): 2963-2876 (aliphatic sp^3 C–H stretchings, broad), 2739 (overtone of aldehyde C–H bending, weak), 1689 (conjugated C=O stretching, strong), 1063 (ether C–O–C antisymmetric stretching, strong), 699 (C–Br stretching, medium). LRMS (ESI) [M+MeOH+Na]$^+$: *m/z* 449.0, 451.0 and 453.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 416.96714, 418.96509 and 420.96305, found *m/z* 416.96686, 418.96516 and 420.96310. ($C_{14}H_{20}O_3{}^{79}Br_2Na$, $C_{14}H_{20}O_3{}^{79}Br^{81}BrNa$/$C_{14}H_{20}O_3{}^{81}Br^{79}BrNa$ and $C_{14}H_{20}O_3{}^{81}Br_2Na$). $[\alpha]_D^{25} = -31.0$ (c=0.20, $CHCl_3$).

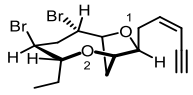
(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4,6-Dibromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decane, (*E*)-bromofucin 1.11



According to the modified procedures of Kim[4]: $TMSCHN_2$ (80.0 µL, 0.16 mmol, 2.0 M solution in Et_2O) was mixed with dry THF (1.0 mL) at -78 °C. *n*-BuLi (70 µL, 0.16 mmol, 2.3 M solution in hexanes) was then added and stirring was continued for 30 minutes. Compound **5.51** (6.2 mg, 16.0 µmol) was dissolved in dry THF (0.5 mL) and the reaction mixture was cooled to -78 °C, in which a portion of the preformed $TMSCLiN_2$ solution (0.35 mL) was then added rapidly. The reaction mixture was stirred at -78 °C for 1 hour, then warmed to 0 °C and stirring was continued for 30 minutes. TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH_4Cl solution and extracted with Et_2O. The organic layer was separated, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting yellow crude oil then underwent purification by flash column chromatography (3% Et_2O/Pet. Ether 40-60 to 5% Et_2O/Pet. Ether 40-60) to give the desired compound **1.11** as a colourless oil (2.6 mg, 6.7 µmol, 42%, *E:Z* > 20:1). R_f = 0.74 (20% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 15.4, 7.4 Hz, 1H, OCHCH'HC**H**CHCCH), 5.59 (dq, *J* = 16.1, 1.6 Hz, 1H, OCHCH'HCHC**H**CCH), 4.51 (t, *J* = 9.2 Hz, 1H, BrC**H**CHCH'HCH_3), 4.41 (dd, *J* = 9.6, 3.6 Hz, 1H, O_2CHCH'HC**H**O_1), 4.33 (q, *J* = 2.6 Hz, 1H, CH'HC**H**Br), 4.01 (t, *J* = 2.6 Hz, 1H, O_2C**H**CH'$HCHO_1$), 3.90 (ddd, *J* = 11.7, 9.5, 2.6 Hz, 1H, BrCHC**H**CH'HCH_3), 3.75 (td, *J* = 7.0, 1.8 Hz, 1H, OC**H**CH'HCHCHCCH), 3.35 (ddd, *J* = 15.7, 8.9, 2.4 Hz, 1H, C**H'**HCHBr), 2.81 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHCC**H**), 2.59 (ddd, *J* = 14.1, 7.9, 6.5 Hz, 1H, OCHC**H'**HCHCHCCH), 2.56 – 2.41 (m, 2H, CH'**H**CHBr, OCHCH'**H**CHCHCCH), 2.36 (d, *J* = 15.5 Hz, 1H, O_2CHC**H'**$HCHO_1$), 2.06 (ddd, *J* = 15.7, 9.7, 3.5 Hz, 1H, O_2CHCH'**H**CHO_1), 1.99 (dqd, *J* = 15.2, 7.7, 3.7 Hz, 1H, BrCHCHC**H'**HCH_3), 1.69 (ddq, *J* = 14.3, 11.3, 7.1 Hz, 1H, BrCHCHCH'**H**CH_3), 1.06 (t, *J* = 7.3 Hz, 3H, BrCHCHCH'HC**H**$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9 (OCHCH'H**C**HCHCCH), 111.5 (OCHCH'HCH**C**HCCH), 84.4 (O**C**HCH'HCHCHCCH), 83.0 (BrCH**C**HCH'HCH_3), 82.3 (OCHCH'HCHCH**C**CH), 79.7 (O_2CHCH'H**C**HO_1), 76.6 (OCHCH'HCHCHC**C**H), 69.9 (O_2**C**HCH'$HCHO_1$), 55.3 (CH'H**C**HBr), 53.0 (Br**C**HCHCH'HCH_3), 38.7 (**C**H'HCHBr), 33.7 (O_2CH**C**H'$HCHO_1$), 32.7 (OCH**C**H'HCHCHCCH), 23.1 (BrCHCH**C**H'HCH_3), 11.9 (BrCHCHCH'H**C**H_3). IR (ν_{max} cm^{-1}): 3293 (acetylene sp C–H stretching, medium), 2853-2963 (aliphatic sp^3 C–H stretchings, broad), 2103 (acetylene C≡C stretching, weak), 1059 (ether C–O–C antisymmetric stretching, strong), 646 (C–Br stretching,

medium). LRMS (ESI) $[M+H]^+$: *m/z* 391.0, 393.0 and 395.0. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 390.99028, 392.98824 and 394.98619, found *m/z* 390.99025, 392.98820 and 394.98614. ($C_{15}H_{21}O_2{}^{79}Br_2$, $C_{15}H_{21}O_2{}^{79}Br^{81}Br$/$C_{15}H_{21}O_2{}^{81}Br^{79}Br$ and $C_{15}H_{21}O_2{}^{81}Br_2$). $[\alpha]_D^{25} = +1.4$ (c=0.35, $CHCl_3$). Literature values: $[\alpha]_D^{24} = +2.9$ ($c = 0.35, CHCl_3$), $[\alpha]_D^{25} = +1.7$ ($c = 0.018, CHCl_3$) .[4,236] Spectroscopic data are in accordance with literature data[4,236]. **NMR data at -78 °C in CD_2Cl_2:** ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.12 (dt, *J* = 15.3, 7.5 Hz, 1H, OCHCH'HC**H**CHCCH), 5.56 (dd, *J* = 15.9, 2.4 Hz, 1H, OCHCH'HCHC**H**CCH), 4.48 (t, *J* = 9.2 Hz, 1H, BrC**H**CHCH'HCH$_3$), 4.37 – 4.27 (m, 2H, CH'HC**H**Br, O_2CHCH'HC**H**O_1), 3.99 – 3.89 (m, 1H, O_2C**H**CH'HCHO_1), 3.83 – 3.74 (m, 1H, BrCHC**H**CH'HCH$_3$), 3.71 (t, *J* = 7.2 Hz, 1H, OC**H**CH'HCHCHCCH), 3.29 (dd, *J* = 15.8, 8.8 Hz, 1H, C**H'**HCHBr), 2.91 (d, *J* = 2.4 Hz, 1H, OCHCH'HCHCHCC**H**), 2.50 (dt, *J* = 14.1, 7.1 Hz, 1H, OCHC**H'**HCHCHCCH), 2.41 (dd, *J* = 14.0, 6.9 Hz, 2H, CH'**H**CHBr, OCHCH'**H**CHCHCCH), 2.29 – 2.21 (m, 1H, O_2CHC**H'**HCHO_1), 2.06 (dd, *J* = 15.4, 9.9 Hz, 1H, O_2CHCH'**H**CHO_1), 1.87 (dq, *J* = 15.0, 7.7 Hz, 1H, BrCHCHC**H'**HCH$_3$), 1.64 (tq, *J* = 14.0, 7.0 Hz, 1H, BrCHCHCH'**H**CH$_3$), 0.94 (t, *J* = 7.3 Hz, 3H, BrCHCHCH'HC**H**$_3$). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 142.4 (OCHCH'H**C**HCHCCH), 110.6 (OCHCH'HCH**C**HCCH), 83.5 (O**C**HCH'HCHCHCCH), 81.9 (BrCH**C**HCH'HCH$_3$), 81.8 (OCHCH'HCHCH**C**CH), 79.0 (O_2CHCH'H**C**HO_1), 76.4 (OCHCH'HCHCHC**C**H), 69.3 (O_2**C**HCH'HCHO_1), 55.6 (CH'H**C**HBr), 53.2 (Br**C**HCHCH'HCH$_3$), 37.9 (**C**H'HCHBr), 33.0 (O_2CH**C**H'HCHO_1), 32.5 (OCH**C**H'HCHCHCCH), 22.4 (BrCHCH**C**H'HCH$_3$), 11.6 (BrCHCHCH'H**C**H$_3$).

(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4,6-Dibromo-3-ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decane, (*Z*)-bromofucin 1.8



According to the procedures of Shirokane[228]: To a mixture of **5.49** and **5.50** (24.0 mg, 65.0 μmol, isomeric ratio ~4:1) was dissolved in 3:1 dioxane:H_2O (1.1 mL), then 2,6-lutidine (15.0 μL, 0.13 mmol) was added followed by a solution of 2.5% OsO_4 in *t*-BuOH (15.0 μL). $NaIO_4$ (55.0 mg, 0.26 mmol) was then added and the reaction mixture was stirring was continued for 1-2 hours. A TLC analysis at this stage showed complete consumption of starting material. The reaction mixture was then diluted with CH_2Cl_2 and H_2O followed by extraction with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated to give a crude brown oil. This crude brown oil was dried under high vacuum while the procedures below were carried out.

$Ph_3PCH_2I_2$ (103.4 mg, 0.20 mmol) was suspended in dry THF (2.5 mL) at room

temperature and a solution of NaHMDS (0.18 mL, 1.0M solution in THF) was added. The reaction mixture was stirred at room temperature for 15 minutes in which the colour of the solution changed from bright yellow to deep orange. This solution was then cooled to -78 °C and HMPA (70.0 μL mL, 0.40 mmol) was added and stirring was continued for 15 minutes. The dried crude brown oil was then dissolved in dry THF (1.0 mL) and added to the reaction mixture. The reaction mixture was stirred at -78 °C for 30 minutes then room temperature for 1 hour. A TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude mixture quickly underwent purification by flash column chromatography (5% EA/Pentane), product R_f = 0.30 (10% EA/Pet. Ether 40-60). The purified vinyl iodide was then quickly used for the following transformations due to its instability.

The vinyl iodide (16.1 mg, 33.0 μmol) was dissolved in dry Et_3N (1.7 mL), then trimethylsilylacetylene (23.0 μL, 0.17 mmol) was added followed by CuI (6.3 mg, 33.0 μmol). The mixture was then degassed with dry argon for 15 minutes. $Pd(PPh_3)_4$ (6.0 mg, 5.0 μmol) was then added and the reaction mixture was stirred at room temperature with exclusion of light for 1 hour. A TLC analysis at this stage showed the complete consumption of starting material. K_2CO_3 (46.0 mg, 0.33 mmol) and MeOH (1.7 mL) were added to the reaction mixture and stirring was continued for 1-2 hours until completion. The reaction mixture was then diluted with H_2O and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$, filtered through a short plug of silica and concentrated. The resulting pale brown crude oil then underwent purification by flash column chromatography twice (5% Et_2O/Pet. Ether 40-60 to remove minor impurities), (0.5% EA/CH_2Cl_2 to separate **1.8** from **1.9**) to give the desired compound **1.8** as a colourless oil (4.0 mg, 10.3 μmol, 17% over 4 steps, *Z:E* > 15:1). **The (*Z*)-elatenyne 1.9 generated by this method was not isolated**. R_f (**1.9**) = 0.74 (0.5% EA/CH_2Cl_2). R_f (**1.8**) = 0.68 (0.5% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dtd, *J* = 10.8, 7.5, 0.9 Hz, 1H, OCHCH'HC**H**CHCCH), 5.56 (ddt, *J* = 10.9, 2.5, 1.4 Hz, 1H, OCHCH'HCHC**H**CCH), 4.51 (t, *J* = 9.2 Hz, 1H, CH_3CH'HCHC**H**Br), 4.42 (dd, *J* = 9.6, 3.6 Hz, 1H, O_2CHCH'HC**H**O_1), 4.37 – 4.31 (m, 1H, CH'HC**H**Br), 4.01 (t, *J* = 2.7 Hz, 1H, O_2C**H**CH'HCHO_1), 3.92 (ddd, *J* = 11.8, 9.5, 2.6 Hz, 1H, CH_3CH'HC**H**CHBr), 3.80 (td, *J* = 7.1, 1.9 Hz, 1H, OC**H**CH'HCHCHCCH), 3.38 (ddd, *J* = 15.8, 8.9, 2.3 Hz, 1H, C**H'**HCHBr), 3.11 (dd, *J* = 2.5, 0.9 Hz, 1H, OCHCH'HCHCHCC**H**), 2.82 (dtd, *J* = 13.9, 7.5, 1.4 Hz, 1H, OCHC**H'**HCHCHCCH), 2.71 (dtd, *J* = 14.1, 7.1, 1.4 Hz, 1H, OCHCH'**H**CHCHCCH), 2.52 (dd, *J* = 15.8, 4.8 Hz, 1H, CH'**H**CHBr), 2.37 (d, *J* = 15.5 Hz, 1H, O_2CHC**H'**HCHO_1), 2.07 (ddd, *J* = 15.4, 9.6, 3.3 Hz, 1H, O_2CHCH'**H**CHO_1), 1.99 (dqd, *J* = 15.1, 7.6, 2.6 Hz, 1H,

$CH_3C\mathbf{H'}HCHCHBr$), 1.70 (ddq, *J* = 14.3, 11.4, 7.1 Hz, 1H, $CH_3CH'\mathbf{H}CHCHBr$), 1.06 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCHCHBr$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3 ($OCHCH'\mathbf{H}CHCHCCH$), 110.6 ($OCHCH'HCH\mathbf{C}HCCH$), 84.4 ($O\mathbf{C}HCH'HCHCHCCH$), 82.9 ($CH_3CH'H\mathbf{C}HCHBr$), 82.2 ($OCHCH'HCHCHC\mathbf{C}H$), 80.2 ($OCHCH'HCHCH\mathbf{C}CH$), 79.7 ($O_2CHCH'H\mathbf{C}HO_1$), 70.2 ($O_2\mathbf{C}HCH'HCHO_1$), 55.5 ($CH'H\mathbf{C}HBr$), 53.2 ($CH_3CH'HCH\mathbf{C}HBr$), 38.7 ($\mathbf{C}H'HCHBr$), 33.7 ($O_2CH\mathbf{C}H'HCHO_1$), 30.2 ($OCH\mathbf{C}H'HCHCHCCH$), 23.2 ($CH_3\mathbf{C}H'HCHCHBr$), 11.9 ($\mathbf{C}H_3CH'HCHCHBr$). IR (ν_{max} cm^{-1}): 3292 (acetylene sp C–H stretching, medium), 2964-2853 (aliphatic sp^3 C–H stretchings, broad), 2096 (acetylene C≡C stretching, weak), 1058 (ether C–O–C antisymmetric stretching, strong), 645 (C–Br stretching, medium). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 390.99028, 392.98824 and 394.98619, found *m/z* 390.99037, 392.98824 and 394.98634. ($C_{15}H_{21}O_2{}^{79}Br_2$, $C_{15}H_{21}O_2{}^{79}Br^{81}Br$/$C_{15}H_{21}O_2{}^{81}Br^{79}Br$ and $C_{15}H_{21}O_2{}^{81}Br_2$). $[\alpha]_D^{25} = -10.0$ (c=0.10, $CHCl_3$). Literature values:$[\alpha]_D^{25} = -5.2$ ($c = 0.09, CHCl_3$) [4] and $[\alpha]_D^{24} = -0.5$ ($c = 0.25, CHCl_3$).[24] Spectroscopic data are in accordance with literature data.[4,24] **NMR data at -78 °C in CD_2Cl_2:** ^1H NMR (500 MHz, CD_2Cl_2) δ 6.00 (dt, *J* = 11.0, 7.8 Hz, 1H, $OCHCH'HC\mathbf{H}CHCCH$), 5.52 (d, *J* = 11.1 Hz, 1H, $OCHCH'HCHC\mathbf{H}CCH$), 4.49 (t, *J* = 9.2 Hz, 1H, $CH_3CH'HCHC\mathbf{H}Br$), 4.34 (d, *J* = 7.0 Hz, 2H, $CH'HC\mathbf{H}Br$, $O_2CHCH'HC\mathbf{H}O_1$), 3.96 (d, *J* = 2.6 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 3.81 (t, *J* = 10.1 Hz, 1H, $CH_3CH'HC\mathbf{H}CHBr$), 3.72 (t, *J* = 7.3 Hz, 1H, $OC\mathbf{H}CH'HCHCHCCH$), 3.32 (dd, *J* = 15.8, 8.8 Hz, 1H, $C\mathbf{H'}HCHBr$), 3.21 (d, *J* = 2.4 Hz, 1H, $OCHCH'HCHCHCC\mathbf{H}$), 2.74 (dt, *J* = 15.4, 8.1 Hz, 1H, $OCHC\mathbf{H'}HCHCHCCH$), 2.53 (dt, *J* = 12.5, 5.9 Hz, 1H, $OCHCH'\mathbf{H}CHCHCCH$), 2.42 (dd, *J* = 15.6, 4.3 Hz, 1H, $CH'\mathbf{H}CHBr$), 2.27 (d, *J* = 15.6 Hz, 1H, $O_2CHC\mathbf{H'}HCHO_1$), 2.10 – 2.02 (m, 1H, $O_2CHCH'\mathbf{H}CHO_1$), 1.88 (dd, *J* = 14.7, 7.7 Hz, 1H, $CH_3C\mathbf{H'}HCHCHBr$), 1.66 (ddd, *J* = 14.6, 11.9, 6.9 Hz, 1H, $CH_3CH'\mathbf{H}CHCHBr$), 0.97 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCHCHBr$). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 141.7 ($OCHCH'H\mathbf{C}HCHCCH$), 109.7 ($OCHCH'HCH\mathbf{C}HCCH$), 83.6 ($O\mathbf{C}HCH'HCHCHCCH$), 82.1 ($OCHCH'HCHCHC\mathbf{C}H$), 81.9 ($CH_3CH'H\mathbf{C}HCHBr$), 79.7 ($OCHCH'HCHCH\mathbf{C}CH$), 79.0 ($O_2CHCH'H\mathbf{C}HO_1$), 69.7 ($O_2\mathbf{C}HCH'HCHO_1$), 55.7 ($CH'H\mathbf{C}HBr$), 53.3 ($CH_3CH'HCH\mathbf{C}HBr$), 37.9 ($\mathbf{C}H'HCHBr$), 33.0 ($O_2CH\mathbf{C}H'HCHO_1$), 29.9 ($OCH\mathbf{C}H'HCHCHCCH$), 22.5 ($CH_3\mathbf{C}H'HCHCHBr$), 11.6 ($\mathbf{C}H_3CH'HCHCHBr$).

General procedures for the synthesis of oxonium ions 1.1 and 1.2:

Compound **1.8** or **1.11** (5.0 mg, 13.0 μmol) was dissolved in dry CD_2Cl_2 (0.3 mL) at -40 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (16.2 mg, 14.0 μmol) was weighed in a nitrogen filled

glove bag and dissolved in dry CD_2Cl_2 (0.3 mL) and then added to the solution of the starting material. The reaction mixture was stirring was continued for 15 minutes at -40 °C in which precipitation of a brown substance was observed. The reaction mixture was then continued to stir at this temperature for 1 hour. An optional TLC analysis could be carried out at this point to confirm if the starting material was completely consumed. The reaction mixture was then cooled to -78 °C and equilibrated for 30 minutes. The reaction mixture was then filtered at -78 °C into a flame dried and argon filled Young's NMR tube for subsequent NMR analyses at -78 °C (**Figure 10.4**). The colour of the filtrate could range from pale yellow to pale pink.

General procedures for the synthesis of oxonium ions *ent*-1.3 *and ent*-1.4:
Compound ***ent*-5.1** or ***ent*-5.2** (6.7 mg, 19.3 μmol) was dissolved in dry CD_2Cl_2 (0.30 mL) and the reaction mixture was cooled to -78 °C. $AgAl(pftb)_4 \cdot CH_2Cl_2$ (25.0 mg, 21.6 μmol) was weighed in a nitrogen filled glove bag and dissolved in dry CD_2Cl_2 (0.3 mL) and then added to the solution of the starting material. The reaction mixture was stirred at -78 °C for 1.5 hr in which precipitation of a brown substance was observed. An optional TLC analysis could be carried out at this point to confirm if the starting material was completely consumed. The reaction mixture was then filtered at -78 °C into a flame dried and argon filled Young's NMR tube for subsequent NMR analyses at -78 °C (**Figure 10.4**). The colour of the filtrate could range from pale yellow to pale pink.

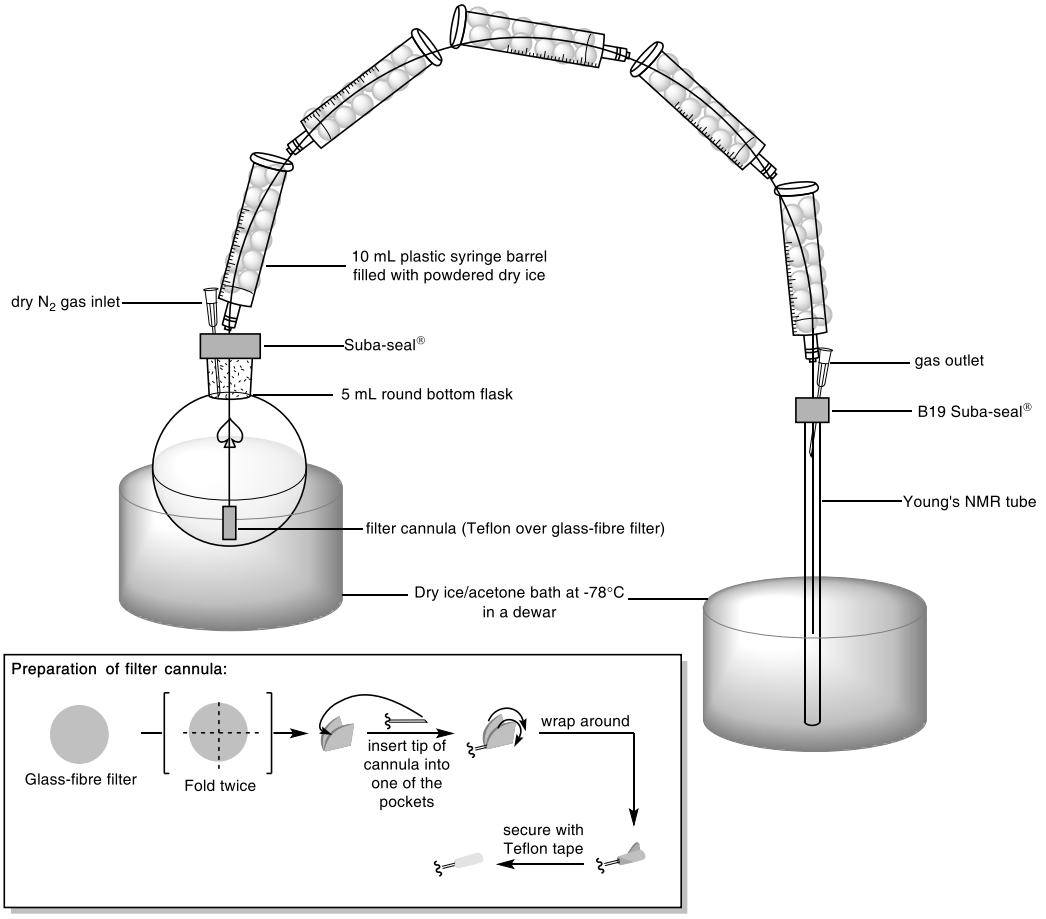
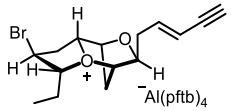


Figure 10.4. Experimental setup for filtration at -78 °C.

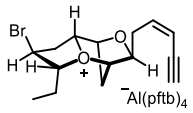
(1*S*,3*S*,4*S*,6*R*,7*S*,8a*R*)-7-Bromo-6-ethyl-3-((*E*)-pent-2-en-4-yn-1-yl)hexahydro-1*H*-1,4-methanofuro[1,2-a][1,4]dioxin-5-ium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate 1.2



This compound was synthesised according to the general procedures as described above. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.14 (dt, *J* = 15.2, 7.3 Hz, 1H, OCHCH'HC**H**CHCCH), 5.83 (dd, *J* = 11.3, 5.7 Hz, 1H, BrCHCH'HC**H**O$^+$), 5.71 (s, 1H, O$^+$C**H**CH'HCHO), 5.67 (dd, *J* = 15.9, 2.2 Hz, 1H, OCHCH'HCHC**H**CCH), 5.48 (dt, *J* = 11.7, 3.5 Hz, 1H, CH_3CH'HC**H**O$^+$), 5.02 (d, *J* = 3.0 Hz, 1H, O$^+$CHCH'HC**H**O), 4.64 (ddd, *J* = 5.0, 3.5, 2.3 Hz, 1H, BrC**H**CH'HCHO$^+$), 4.28 (t, *J* = 7.4 Hz, 1H, OC**H**CH'HCHCHCCH), 3.02 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHCC**H**), 2.86 (ddd, *J* = 14.9, 5.8, 2.6 Hz, 1H, BrCHC**H'**HCHO$^+$), 2.68 (dd, *J* = 13.3, 3.2 Hz, 1H, O$^+$CHC**H'**HCHO), 2.60 (dt, *J* = 14.8, 7.4 Hz, 1H, OCHC**H'**HCHCHCCH), 2.48 – 2.34 (m, 2H, BrCHCH'**H**CHO$^+$, OCHCH'**H**CHCHCCH), 2.20 – 2.08 (m, 2H, O$^+$CHCH'**H**CHO, CH_3C**H'**HCHO$^+$),

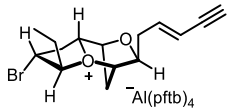
1.72 (ddq, *J* = 13.9, 11.7, 7.1 Hz, 1H, $CH_3CH'\mathbf{H}CHO^+$), 1.15 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCHO^+$). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 138.2 (OCHCH'H**C**HCHCCH), 113.0 (OCHCH'HCH**C**HCCH), 110.4 ($CH_3CH'H\mathbf{C}HO^+$), 109.8 ($BrCHCH'H\mathbf{C}HO^+$), 94.3 ($O^+\mathbf{C}HCH'HCHO$), 80.7 (OCHCH'HCHCH**C**CH), 78.6 (O**C**HCH'HCHCHCCH), 78.0 (OCHCH'HCHCHC**C**H), 76.0 ($O^+CHCH'H\mathbf{C}HO$), 43.6 ($Br\mathbf{C}HCH'HCHO^+$), 36.4 ($BrCH\mathbf{C}H'HCHO^+$), 35.9 ($O^+CH\mathbf{C}H'HCHO$), 33.5 (OCH**C**H'HCHCHCCH), 23.3 ($CH_3\mathbf{C}H'HCHO^+$), 10.4 ($\mathbf{C}H_3CH'HCHO^+$).

(1*S*,3*S*,4*S*,6*R*,7*S*,8a*R*)-7-Bromo-6-ethyl-3-((*Z*)-pent-2-en-4-yn-1-yl)hexahydro-1*H*-1,4-methanofuro[1,2-a][1,4]dioxin-5-ium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate 1.1



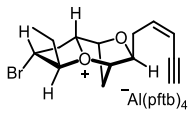
This compound was synthesised according to the general procedures as described above. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.97 (td, *J* = 10.5, 5.0 Hz, 1H, OCHCH'HC**H**CHCCH), 5.88 (dd, *J* = 12.0, 5.1 Hz, 1H, BrCHCH'HC**H**O^+), 5.73 (d, *J* = 10.7 Hz, 1H, OCHCH'HCHC**H**CCH), 5.67 (dd, *J* = 12.8, 3.3 Hz, 1H, $CH_3CH'HC\mathbf{H}O^+$), 5.61 (s, 1H, $O^+C\mathbf{H}CH'HCHO$), 5.04 (d, *J* = 3.0 Hz, 1H, $O^+CHCH'HC\mathbf{H}O$), 4.70 (d, *J* = 4.5 Hz, 1H, $BrC\mathbf{H}CH'HCHO^+$), 4.33 (dd, *J* = 9.8, 6.2 Hz, 1H, OC**H**CH'HCHCHCCH), 3.37 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHCC**H**), 2.86 (ddd, *J* = 19.2, 11.4, 8.0 Hz, 2H, BrCHC**H'**$HCHO^+$, OCHC**H'**HCHCHCCH), 2.75 (dd, *J* = 13.3, 6.9 Hz, 1H, OCHCH'**H**CHCHCCH), 2.67 (dd, *J* = 13.1, 3.1 Hz, 1H, $O^+CHC\mathbf{H'}HCHO$), 2.36 (ddd, *J* = 15.2, 12.0, 4.7 Hz, 1H, $BrCHCH'\mathbf{H}CHO^+$), 2.18 (d, *J* = 13.6 Hz, 1H, $O^+CHCH'\mathbf{H}CHO$), 2.16 – 2.09 (m, 1H, $CH_3C\mathbf{H'}HCHO^+$), 1.63 (dq, *J* = 13.0, 6.7 Hz, 1H, $CH_3CH'\mathbf{H}CHO^+$), 1.15 (t, *J* = 7.2 Hz, 3H, $C\mathbf{H}_3CH'HCHO^+$). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 136.8 (OCHCH'H**C**HCHCCH), 112.9 (OCHCH'HCH**C**HCCH), 109.7 ($CH_3CH'H\mathbf{C}HO^+$), 109.3 ($BrCHCH'H\mathbf{C}HO^+$), 93.8 ($O^+\mathbf{C}HCH'HCHO$), 84.0 (OCHCH'HCHCHC**C**H), 79.1 (OCHCH'HCHCH**C**CH), 78.4 (O**C**HCH'HCHCHCCH), 75.9 ($O^+CHCH'H\mathbf{C}HO$), 44.0 ($Br\mathbf{C}HCH'HCHO^+$), 36.7 ($BrCH\mathbf{C}H'HCHO^+$), 35.6 ($O^+CH\mathbf{C}H'HCHO$), 30.7 (OCH**C**H'HCHCHCCH), 23.4 ($CH_3\mathbf{C}H'HCHO^+$), 10.4 ($\mathbf{C}H_3CH'HCHO^+$).

(1*S*,3*S*,4*S*,6*S*,7*R*,8a*R*)-7-Bromo-6-ethyl-3-((*E*)-pent-2-en-4-yn-1-yl)hexahydro-1*H*-1,4-methanofuro[1,2-*a*][1,4]dioxin-5-ium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate *ent*-1.4



This compound was synthesised according to the general procedures as described above. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.08 (ddd, *J* = 15.1, 8.3, 6.1 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.65 – 5.56 (m, 2H, OCHCH'HCH=C**H**CCH and O^{+}C**H**CH'HCHO), 5.46 (dd, *J* = 12.2, 5.6 Hz, 1H, O^{+}C**H**CH'HCHBr), 4.98 (d, *J* = 3.1 Hz, 1H, O^{+}CHCH'HC**H**O), 4.63 (ddd, *J* = 11.2, 5.8, 3.5 Hz, 1H, CH_3CH'HC**H**), 4.26 (t, *J* = 7.4 Hz, 1H, OC**H**CH'HCH=CHCCH), 4.16 (td, *J* = 11.2, 6.4 Hz, 1H, O^{+}CHCH'HC**H**Br), 3.11 (dt, *J* = 12.7, 6.0 Hz, 1H, O^{+}CHC**H'**HCHBr), 3.00 (d, *J* = 2.3 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.73 (dd, *J* = 13.6, 3.3 Hz, 1H, O^{+}CHC**H'**HCHO), 2.62 – 2.51 (m, 2H, OCHC**H'**HCH=CHCCH and O^{+}CHCH'**H**CHO), 2.37 (dt, *J* = 14.9, 7.6 Hz, 1H, OCHCH'**H**CH=CHCCH), 2.32 – 2.23 (m, 1H, CH_3C**H'**HCH), 2.23 – 2.11 (m, 2H, O^{+}CHCH'**H**CHBr and CH_3CH'**H**CH), 1.13 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 137.6 (OCHCH'H**C**H=CHCCH), 124.2 (**C**F_3), 121.9 (**C**F_3), 119.5 (**C**F_3), 117.2 (**C**F_3), 113.0 (OCHCH'HCH=**C**HCCH), 110.5 (O^{+}**C**HCH'HCHBr), 104.5 (CH_3CH'H**C**H), 99.0 (O^{+}**C**HCH'HCHO), 80.4 (OCHCH'HCH=CH**C**CH), 78.5 (O**C**HCH'HCH=CHCCH), 78.3 (OCHCH'HCH=CHC**C**H), 76.6 (O^{+}CHCH'H**C**HO), 37.4 (O^{+}CHCH'H**C**HBr), 37.1 (O^{+}CH**C**H'HCHBr), 33.3 (OCH**C**H'HCH=CHCCH and O^{+}CH**C**H'HCHO), 22.2 (CH_3**C**H'HCH), 8.5 (**C**H_3CH'HCH).

(1*S*,3*S*,4*S*,6*S*,7*R*,8a*R*)-7-Bromo-6-ethyl-3-((*Z*)-pent-2-en-4-yn-1-yl)hexahydro-1*H*-1,4-methanofuro[1,2-a][1,4]dioxin-5-ium tetrakis((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)aluminate *ent*-1.3



This compound was synthesised according to the general procedures as described above. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.92 (dt, *J* = 10.8, 7.2 Hz, 1H, OCHCH_2C**H**=CHCCH), 5.70 (dd, *J* = 11.2, 2.3 Hz, 1H, OCHCH_2CH=C**H**CCH), 5.57 (d, *J* = 2.2 Hz, 1H, O^{+}C**H**CH'HCHO), 5.51 (dd, *J* = 12.2, 5.6 Hz, 1H, O^{+}C**H**CH'HCHBr), 4.96 (d, *J* = 3.2 Hz, 1H, O^{+}CHCH'HC**H**O), 4.60 (ddd, *J* = 11.2, 7.1, 3.2 Hz, 1H, CH_3CH'HC**H**), 4.31 (t, *J* = 7.6 Hz, 1H, OC**H**CH_2CH=CHCCH), 4.15 (td, *J* = 11.2, 6.4 Hz, 1H, O^{+}CHCH'HC**H**Br), 3.28 (d, *J* = 2.4 Hz, 1H, OCHCH_2CH=CHCC**H**), 3.10 (dt, *J* = 12.8,

6.0 Hz, 1H, $O^+CHC\mathbf{H'}HCHBr$), 2.76 – 2.65 (m, 3H, $O^+CHC\mathbf{H'}HCHO$ and $OCHC\mathbf{H}_2CH{=}CHCCH$), 2.56 (dd, *J* = 13.7, 2.9 Hz, 1H, $O^+CHCH'\mathbf{H}CHO$), 2.32 (ddq, *J* = 12.8, 8.3, 5.2, 4.2 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 2.22 – 2.10 (m, 2H, $O^+CHCH'\mathbf{H}CHBr$, $CH_3CH'\mathbf{H}CH$), 1.14 (t, *J* = 7.4 Hz, 4H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 136.5 ($OCHCH_2\mathbf{C}H{=}CHCCH$), 124.2 ($\mathbf{C}F_3$), 121.9 ($\mathbf{C}F_3$), 119.6 ($\mathbf{C}F_3$), 117.2 ($\mathbf{C}F_3$), 112.8 ($OCHCH_2CH{=}\mathbf{C}HCCH$)), 110.5 ($O^+\mathbf{C}HCH'HCHBr$), 105.1 ($CH_3CH'H\mathbf{C}H$), 99.4 ($O^+\mathbf{C}HCH'HCHO$), 83.9 ($OCHCH_2CH{=}CHC\mathbf{C}H$), 78.9 ($OCHCH_2CH{=}CH\mathbf{C}CH$), 78.7 ($O\mathbf{C}HCH_2CH{=}CHCCH$), 76.6 ($O^+CHCH'H\mathbf{C}HO$), 38.1 ($O^+CHCH'H\mathbf{C}HBr$), 37.1 ($O^+CH\mathbf{C}H'HCHBr$), 33.4 ($O^+CH\mathbf{C}H'HCHO$), 30.5 ($OCH\mathbf{C}H_2CH{=}CHCCH$), 22.9 ($CH_3\mathbf{C}H'HCH$), 9.2 ($\mathbf{C}H_3CH'HCH$).

General procedures for the derivatisation of oxonium ions 1.1, 1.2 and *ent*-1.3, *ent*-1.4 from NMR samples:

The oxonium ion NMR sample which was equilibrated at -78 °C in the NMR spectrometer was warmed gradually to -20 °C at a gas flow rate of 650 litres per hour (usually takes ~5 – 10 minutes). As the sample temperature approaches -20 °C, an attempt was made to eject the sample. The ejection may not be successful if the sample was still frozen in the spectrometer. If this was the case, the spectrometer temperature would be further raised to 0 °C, keeping the gas flow rate at 650 litres per hour. This further warming ensures successful ejection but is expected to deteriorate sample quality significantly. Once ejected, the sample was quickly transferred to a dry ice bath and the reaction mixture was cooled to -78 °C to prevent further deterioration of sample quality. The recycled sample was then treated with 5-10 equivalents of the nucleophile of choice as shown below (**Table 10.3**). An immediate colour change should be visible upon the addition of nucleophiles, with a change from pale pink to pale yellow the most common. The reaction mixture in the Young's NMR tube was then removed from the dry ice bath and quickly shaken vigorously and then immediately incubated in the dry ice bath for 15 minutes and warmed to room temperature. In the case where water was chosen to be the nucleophile, a pinch of $NaHCO_3$ was added right after the introduction of water to neutralise the acids generated. As the reaction mixture is warmed to room temperature, the reaction was worked up using general procedures (extracted with CH_2Cl_2/water, organic layer was separated, dried with $MgSO_4$ and concentrated). The crude was then redissolved with ethyl acetate and a minimum volume of pentane was added to precipitate ionic impurities. The mixture was then filtered through a short plug of silica gel to remove the precipitate. The filtrate was then concentrated and dried under high vacuum. A crude ^1H NMR was then acquired for the determination of any isomer ratios if applicable. The compounds of interest were then purified according to the conditions tabulated below and isolated as a mixture of isomers for yield

determination (**Table 10.3**).

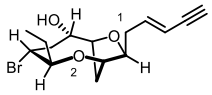
General procedures for the derivatisation of oxonium ions 1.1, 1.2 and *ent*-1.3, *ent*-1.4 without involving NMR analysis of the oxonium ions.

The procedures for the generation of the oxonium ions from compounds **1.8** and **1.11** and ***ent*-5.1** and ***ent*-5.2** are the same as that of the procedures involving NMR analysis except the solvent used was dry CH_2Cl_2 and cryogenic filtration was found to be not necessary for the case of halide nucleophiles. The quenching was performed by the direct addition of 5-10 eq. of desired nucleophiles in the reaction mixture at -78 °C, stirring was continued for 15 minutes, warmed to room temperature and worked up using general procedures (extracted with CH_2Cl_2/water, organic layer was separated, dried with $MgSO_4$ and concentrated). In the case where oxygen nucleophiles were used without cryogenic filtration, an extra step of adding excess tetrabutylammonium iodide to the quenched solution was required as it was found that the TLC profile of these experiments generated an intense baseline spot before the addition of tetrabutylammonium iodide. The baseline spot was released after the addition of tetrabutylammonium iodide and the R_f of the released spot corresponded to the R_f of the desired compound. It was rationalised that silver-olefin complexes might have formed under these conditions that required excess halides to decomplex the olefin from silver species. This was supported by the observation that when excess halide nucleophiles were used, no such baseline species were generated during TLC analysis. The crude was then redissolved with ethyl acetate and a minimum volume of pentane was added to precipitate ionic impurities. The mixture was then filtered through a short plug of silica gel to remove the precipitate. The filtrate was then concentrated and dried under high vacuum. A crude ^1H NMR was then acquired for the determination of any isomer ratios if applicable. The compounds of interest were then purified according to the conditions tabulated below and isolated as a mixture of isomers for yield determination (**Table 10.3**).

Oxonium ion	Nucleophile (5-10 eq.)	Isomer ratio	Yield	Eluent system	With filtration
1.2	*n*-Bu_4NBr	5.6:1 (**1.11**:**1.12**)	43%	5% EA/Pet. Ether 40-60	Yes
1.2	*n*-Bu_4NCl	Trace **1.19**	46%	5% EA/Pet. Ether 40-60	Yes
1.1	*n*-Bu_4NBr	5.6:1 (**1.8**:**1.9**)	60%	5% EA/Pet. Ether 40-60	No
1.1	*n*-Bu_4NCl	Trace **1.7**	63%	5% EA/Pet. Ether 40-60	Yes
***ent*-1.4**	*n*-Bu_4NOAc	***ent*-1.16** exclusive	31%	30% EA/Pet. Ether 40-60	Yes
***ent*-1.4**	*n*-Bu_4NCl	***ent*-5.2** exclusive	59%	10% EA/Pet. Ether 40-60	No
***ent*-1.4**	H_2O	***ent*-1.14** exclusive	51%	50% EA/Pet. Ether 40-60	Yes
***ent*-1.3**	*n*-Bu_4NCl	***ent*-5.1** exclusive	73%	10% EA/Pet. Ether 40-60	No
***ent*-1.3**	H_2O	***ent*-1.15** exclusive	34%	50% EA/Pet. Ether 40-60	Yes

Table 10.3. Quenching conditions, experimental results and purification conditions for oxonium ion quenching experiments.

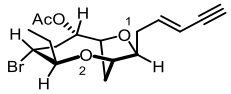
(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1] decan-6-ol, *ent*-(*E*)-laurefucin *ent*-1.14



This compound was synthesised according to the general procedures from ***ent*-5.2** (8.2 mg, 23.6 μmol) as described above as a white solid (4.0 mg, 12.1 μmol, 51%). $R_f = 0.31$ (50% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, C_6D_6) δ 6.23 (dt, $J = 16.1$, 7.4 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.53 (dq, $J = 15.9$, 1.7 Hz, 1H, OCHCH'HCH=C**H**CCH), 4.00 (dd, $J = 8.0$, 3.7 Hz, 1H, HOCHC**H**O), 3.61 (q, $J = 4.2$ Hz, HOC**H**CHO), 3.39 (td, J = 10.3, 4.7 Hz, 1H, BrC**H**CH'H), 3.32 (td, J = 7.2, 2.4 Hz, 1H, OC**H**CH'HCH=CHCCH), 3.21 (dt, $J = 3.3$, 1.5 Hz, 1H, O_2C**H**CH'HCHO$_1$), 3.03 (ddd, J = 10.5, 8.9, 2.5 Hz, 1H, CH_3CH'HC**H**), 2.56 (d, J = 2.2 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.35 (dtd, J = 13.8, 6.9, 1.7 Hz, 1H,

OCHC**H'**HCH=CHCCH), 2.26 (dtd, *J* = 13.9, 7.7, 1.5 Hz, 1H, OCHCH'**H**CH=CHCCH), 2.12 (ddd, *J* = 15.0, 4.7, 1.2 Hz, 1H, BrCHC**H'**H), 2.01 – 1.90 (m, 2H, BrCHCH'**H** and CH_3C**H'**HCH), 1.81 (d, *J* = 14.4 Hz, 1H, O_2CHC**H'**$HCHO_1$), 1.64 (d, *J* = 3.9 Hz, 1H, O**H**), 1.25 (ddq, *J* = 14.3, 9.0, 7.3 Hz, 1H, CH_3CH'**H**CH), 1.09 (ddd, *J* = 14.4, 8.1, 2.4 Hz, 1H, O_2CHCH'**H**CHO_1), 0.76 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, C_6D_6) δ 142.6 (OCHCH'H**C**H=CHCCH), 111.5 (OCHCH'HCH=**C**HCCH), 83.9 (HOCH**C**HO), 82.5 (OCHCH'HCH=CH**C**CH), 82.2 (O**C**HCH'HCH=CHCCH), 80.1 (CH_3CH'H**C**H), 78.0 (HO**C**HCHO), 77.0 (OCHCH'HCH=CHC**C**H), 76.9 (O_2**C**$HCH'HCHO_1$), 53.3 (Br**C**HCH'H), 43.6 (BrCH**C**H'H), 33.9 (OCH**C**H'HCH=CHCCH), 33.1 (O_2CH**C**$H'HCHO_1$), 28.4 (CH_3**C**H'HCH), 9.7 (**C**$H_3CH'HCH$). IR (ν_{max} cm^{-1}): 3405 (O–H stretchings, broad), 3294 (alkyne sp C–H stretching, strong), 3008 (alkene sp^2 C–H stretching, weak), 2918-2853 (alkane sp^3 C–H stretchings, broad), 2095 (alkyne C≡C stretching, very weak), 1261 (ether C–O–C stretching, strong), 1065 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 351.1 and 353.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 351.05663 and 353.05458, found *m/z* 351.05656 and 353.05458 ($C_{15}H_{21}O_3{}^{79}BrNa$ and $C_{15}H_{21}O_3{}^{81}BrNa$). $[\alpha]_D^{25} = +72.2$ (c=0.27, $CHCl_3$). Literature values of enantiomer: $[\alpha]_D^{25} = -77.3$ (c=0.21, $CHCl_3$) [5] and $[\alpha]_D = -80.0$ (conc. and solvent unspecified) .[20] Melting point: 104-105 °C. lit. 105-106 °C[5]/107-108 °C.[20] Spectroscopic data are in accordance with literature data.[5,20]

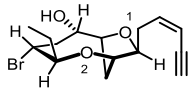
(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1] decan-6-yl acetate, *ent*-acetyllaurefucin *ent*-1.16



This compound was synthesised according to the general procedures from ***ent*-5.2** (10.0 mg, 28.8 μmol) as described above as a colourless oil (3.4 mg, 9.2 μmol, 31%). R_f = 0.60 (30% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, C_6D_6) δ 6.14 (dt, *J* = 15.9, 7.3 Hz, 1H, $OCHCH_2C$**H**=CHCCH), 5.46 (dq, *J* = 16.0, 1.7 Hz, 1H, $OCHCH_2CH=C$**H**CCH), 5.01 (ddd, *J* = 10.0, 4.1, 1.0 Hz, 1H, AcOC**H**CHO), 4.14 (dd, *J* = 7.8, 4.1 Hz, 1H, AcOCHC**H**O), 3.81 (td, *J* = 10.8, 4.8 Hz, 1H, BrC**H**CH'H), 3.32 (ddd, *J* = 7.8, 6.7, 2.4 Hz, 1H, OC**H**CH_2CH=CHCCH), 3.21 (q, *J* = 1.9 Hz, 1H, O_2C**H**$CH'HCHO_1$), 3.02 (ddd, *J* = 10.8, 8.8, 2.4 Hz, 1H, $CH_3CH'HC$**H**), 2.53 (d, *J* = 2.2 Hz, 1H, $OCHCH_2CH=CHCC$**H**), 2.32 (m, 2H, OCHC**H**$_2$CH=CHCCH), 2.26 (dd, *J* = 14.7, 4.9 Hz, 1H, BrCHC**H'**H), 2.04 (ddd, *J* = 14.8, 11.2, 10.0 Hz, 1H, BrCHCH'**H**), 1.96 (dqd, *J* = 14.8, 7.4, 2.5 Hz, 1H, CH_3C**H'**HCH), 1.80 (d, *J* = 14.3 Hz, 1H, O_2CHC**H'**$HCHO_1$), 1.59 (s, 3H, C**H**$_3$C=O), 1.22 (ddq, *J* = 14.3, 9.1, 7.3 Hz, 1H,

$CH_3CH'\mathbf{H}CH$), 1.10 (ddd, *J* = 14.2, 7.8, 2.3 Hz, 1H, $O_2CHCH'\mathbf{H}CHO_1$), 0.74 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8 ($CH_3\mathbf{C}$=O), 142.2 ($OCHCH_2\mathbf{C}H$=CHCCH), 111.7 ($OCHCH_2CH$=$\mathbf{C}$HCCH), 82.5 ($OCHCH_2CH$=CH$\mathbf{C}$CH), 82.3 (O$\mathbf{C}$HCH$_2$CH=CHCCH), 80.7 (AcO$\mathbf{C}$HCHO), 80.5 ($CH_3CH'H\mathbf{C}H$), 80.3 ($O_2CHCH'H\mathbf{C}HO_1$), 77.0 ($OCHCH_2CH$=CHC$\mathbf{C}$H), 76.8 ($O_2\mathbf{C}HCH'HCHO_1$), 52.1 (Br$\mathbf{C}$HCH'H), 41.8 (BrCH$\mathbf{C}$H'H), 33.8 (OCH$\mathbf{C}$H$_2$CH=CHCCH), 33.2 ($O_2CH\mathbf{C}H'HCHO_1$), 28.1 ($CH_3\mathbf{C}H'HCH$), 20.8 ($\mathbf{C}H_3C$=O), 9.7 ($\mathbf{C}H_3CH'HCH$). ^1H NMR (500 MHz, CCl_4) δ 6.11 (dt, *J* = 15.4, 7.3 Hz, 1H), 5.49 (dd, *J* = 16.0, 2.0 Hz, 1H), 4.68 (dt, *J* = 7.2, 4.2 Hz, 1H), 4.14 (dd, *J* = 7.9, 4.3 Hz, 1H), 4.02 (d, *J* = 2.8 Hz, 1H), 3.90 – 3.67 (m, 2H), 3.42 (td, *J* = 9.6, 2.4 Hz, 1H), 2.62 (d, *J* = 2.5 Hz, 1H), 2.59 – 2.36 (m, 3H), 2.21 – 2.10 (m, 3H), 2.01 (s, 2H), 1.83 (ddd, *J* = 14.1, 7.8, 2.5 Hz, 1H), 1.51 (ddq, *J* = 14.4, 12.5, 7.4 Hz, 1H), 0.99 (t, *J* = 7.3 Hz, 3H). IR (ν_{max} cm^{-1}): 3289 (alkyne sp C–H stretching, strong), 3011 (alkene sp^2 C–H stretching, weak), 2919-2852 (alkane sp^3 C–H stretchings, broad), 2100 (alkyne C≡C stretching, weak), 1730 (ester C=O stretching, strong), 1241 (ester and ether C–O–C stretching, strong), 1071 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 393.1 and 395.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 393.06719 and 395.06515, found *m/z* 393.06710 and 395.06510 ($C_{17}H_{23}O_4{}^{79}BrNa$ and $C_{17}H_{23}O_4{}^{81}BrNa$). $[\alpha]_D^{25} = +114.5$ (c=0.34, $CHCl_3$). Literature value of enantiomer: $[\alpha]_D = -126.5$ (conc. and solvent unspecified) .[20] Spectroscopic data are in accordance with literature data.[20]

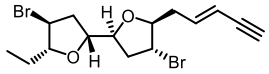
(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-ol, *ent*-(*Z*)-laurefucin *ent*-1.15



This compound was synthesised according to the general procedures from ***ent*-1.3** (6.4 mg, 18.0 μmol) as described above as a colourless oil (2.0 mg, 6.1 μmol, 34%). R_f = 0.40 (50% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, C_6D_6) δ 5.94 (dt, *J* = 10.9, 7.4 Hz, 1H, OCHCH'HC$\mathbf{H}$CHCCH), 5.45 (dq, *J* = 10.9, 1.6 Hz, 1H, OCHCH'HCHC$\mathbf{H}$CCH), 4.04 (dd, *J* = 8.0, 3.8 Hz, 1H, $O_2CHCH'HC\mathbf{H}O_1$), 3.68 (d, *J* = 9.1 Hz, 1H, BrCHCH'HC$\mathbf{H}$OH), 3.54 (td, *J* = 7.2, 2.3 Hz, 1H, OC$\mathbf{H}$CH'HCHCHCCH), 3.42 (td, *J* = 10.3, 4.6 Hz, 1H, BrC$\mathbf{H}$CH'HCHOH), 3.31 (q, *J* = 2.0 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 3.08 (ddd, *J* = 10.5, 8.9, 2.5 Hz, 1H, $CH_3CH'HC\mathbf{H}$), 2.88 (dtd, *J* = 14.4, 7.4, 1.6 Hz, 1H, OCHC$\mathbf{H}$'HCHCHCCH), 2.78 (d, *J* = 2.3 Hz, 1H, OCHCH'HCHCHCC$\mathbf{H}$), 2.73 (dtd, *J* = 14.4, 7.4, 1.6 Hz, 1H, OCHCH'$\mathbf{H}$CHCHCCH), 2.14 (dd, *J* = 14.8, 4.6 Hz, 1H, BrCHC$\mathbf{H}$'HCHOH), 2.03 – 1.91 (m, 2H,

BrCHCH'**H**CHOH, CH_3C**H'**HCH), 1.86 (d, *J* = 14.4 Hz, 1H, O_2CHC**H'**$HCHO_1$), 1.53 (d, *J* = 4.2 Hz, 1H, BrCHCH'HCHO**H**), 1.33 (ddq, *J* = 14.2, 8.9, 7.3 Hz, 1H, CH_3CH'**H**CH), 1.13 (ddd, *J* = 14.4, 8.1, 2.5 Hz, 1H, O_2CHCH'**H**CHO_1), 0.78 (t, *J* = 7.3 Hz, 3H, C**H**$_3CH'HCH$). ^{13}C NMR (126 MHz, C_6D_6) δ 142.1 (OCHCH'H**C**HCHCCH), 110.3 (OCHCH'HCH**C**HCCH), 83.8 ($O_2CHCH'HCHO_1$), 82.5 (OCHCH'HCHCHC**C**H), 82.3 (O**C**HCH'HCHCHCCH), 80.5 (OCHCH'HCHCH**C**CH), 80.1 ($CH_3CH'HCH$), 77.9 (BrCHCH'H**C**HOH), 77.3 (O_2**C**$HCH'HCHO_1$), 53.5 (Br**C**HCH'HCHOH), 43.4 (BrCH**C**H'HCHOH), 33.1 (O_2CH**C**$H'HCHO_1$), 31.5 (OCH**C**H'HCHCHCCH), 28.5 (CH_3**C**H'HCH), 9.8 (**C**$H_3CH'HCH$). IR (ν_{max} cm^{-1}): 3398 (O–H stretchings, broad), 3294 (acetylene sp C–H stretching, medium), 2922 (aliphatic sp^3 C–H stretchings, broad), 2097 (acetylene C≡C stretching, weak), 1066 (ether C–O–C antisymmetric stretching, strong), 631 (C–Br stretching, medium). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 329.07468 and 331.07264, found *m/z* 329.07399 and 331.07198. ($C_{15}H_{22}O_3{}^{79}Br$ and $C_{15}H_{22}O_3{}^{81}Br$). $[\alpha]_D^{25} = +27.3$ (c=0.10, $CHCl_3$).

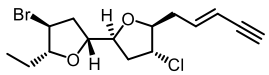
(2*R*,2'*S*,4*S*,4'*R*,5*R*,5'*S*)-4,4'-Dibromo-5-ethyl-5'-((*E*)-pent-2-en-4-yn-1-yl)octa hydro-2,2'-bifuran, (*E*)-elatenyne 1.12



Compound **1.11** (3.6 mg, 9.2 μmol) was dissolved in dry Pet. Ether 40-60 (2.0 mL) and a pinch of activated silica gel (~20.0 mg) was added. The reaction flask was closed with a brand-new Suba-Seal® septum and stirred at room temperature for 2 overnights. A crude NMR was taken to confirm the completion of the reaction. The reaction was stopped at this stage and all volatiles were removed. The crude mixture then underwent purification by flash column chromatography (0.5% EA/CH_2Cl_2) to give the desired compound **1.12** as a colourless oil (2.2 mg, 5.6 μmol, 61%). R_f = 0.67 (1% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ 6.12 (dt, *J* = 16.1, 7.2 Hz, 1H, BrCHCHCH'HC**H**CHCCH), 5.36 (dq, *J* = 16.0, 1.7 Hz, 1H, BrCHCHCH'HCHC**H**CCH), 3.91 – 3.87 (m, 1H, $CH_3CH'HC$**H**), 3.87 – 3.84 (m, 1H, BrCHC**H**CH'HCHCHCCH), 3.82 – 3.78 (m, 1H, BrCHCH'HC**H**CHCH'H), 3.78 – 3.73 (m, 1H, BrCHCH'HCHC**H**CH'H), 3.48 (dt, *J* = 7.6, 5.3 Hz, 1H, BrC**H**CH'HCHCHCH'H), 3.44 (dt, *J* = 7.5, 5.6 Hz, 1H, BrC**H**CHCH'HCHCHCCH), 2.54 (d, *J* = 2.2 Hz, 1H, BrCHCHCH'HCHCHCC**H**), 2.02 – 1.96 (m, 2H, BrCHC**H'**HCHCHCH'H, BrCHCHC**H'**HCHCHCCH), 1.95 – 1.91 (m, 1H, BrCHCH'HCHCHC**H'**H), 1.88 – 1.84 (m, 1H, BrCHCH'HCHCHCH'**H**), 1.84 – 1.81 (m, 1H, BrCHCHCH'**H**CHCHCCH), 1.81 – 1.77 (m, 1H, BrCHCH'**H**CHCHCH'H), 1.43 – 1.32 (m, 1H, CH_3C**H'**HCH), 1.28 – 1.12 (m, 1H, CH_3CH'**H**CH), 0.82 (t, *J* = 7.4

Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, C_6D_6) δ 140.9 (BrCHCHCH'H**C**HCHCCH), 112.2 (BrCHCHCH'HCH**C**HCCH), 88.7 (CH_3CH'H**C**H), 86.0 (BrCH**C**HCH'HCHCHCCH), 82.2 (BrCHCHCH'HCHCH**C**CH), 79.9 (BrCHCH'HCH**C**HCH'H), 79.4 (BrCHCH'H**C**HCHCH'H), 77.4 (BrCHCHCH'HCHCHC**C**H), 49.2 (Br**C**HCH'HCHCHCH'H), 48.4 (Br**C**HCHCH'HCHCHCCH), 39.3 (BrCH**C**H'HCHCHCH'H), 38.8 (BrCHCH'HCHCH**C**H'H), 36.6 (BrCHCH**C**H'HCHCHCCH), 26.8 (CH_3**C**H'HCH), 10.2 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3294 (acetylene sp C–H stretching, medium), 2852-2962 (aliphatic sp^3 C–H stretchings, broad), 2103 (acetylene C≡C stretching, weak), 1064 (ether C–O–C antisymmetric stretching, strong), 642 (C–Br stretching, medium). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 390.99028, 392.98824 and 394.98619, found *m/z* 390.99006, 392.98802 and 394.98604. ($C_{15}H_{21}O_2{}^{79}Br_2$, $C_{15}H_{21}O_2{}^{79}Br^{81}Br$/ $C_{15}H_{21}O_2{}^{81}Br^{79}Br$ and $C_{15}H_{21}O_2{}^{81}Br_2$). $[\alpha]_D^{25} = -24.6$ (c=0.13, CH_2Cl_2). Literature value: $[\alpha]_D^{25} = -33.0$ (c=0.09, CH_2Cl_2)[9] and Literature value of enantiomer: $[\alpha]_D^{25} = +29.5$ (c=0.35, CH_2Cl_2).[9] Spectroscopic data are in accordance with literature data.[9,13]

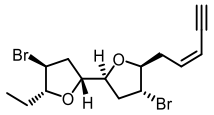
(2*R*,2'*S*,4*S*,4'*R*,5*R*,5'*S*)-4-Bromo-4'-chloro-5-ethyl-5'-((*E*)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran 1.19



Compound **1.6** (3.0 mg, 8.6 μmol) was dissolved in dry hexane (1.5 mL) and a pinch of activated silica gel (~20.0 mg) was added. The reaction flask was closed with a brand-new Suba-Seal® septum and stirred at 80 °C for 2 overnights. A crude NMR was taken to confirm the completion of the reaction. The reaction was stopped at this stage and all volatiles were removed. The crude mixture then underwent purification by flash column chromatography (50% CH_2Cl_2/Pentane) to give the desired compound **1.19** as a colourless oil (1.5 mg, 4.3 μmol, 50%). R_f = 0.42 (50% CH_2Cl_2/Pentane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 15.7, 7.2 Hz, 1H, OCHCH'HC**H**CHCCH), 5.57 (ddt, *J* = 16.0, 2.3, 1.5 Hz, 1H, OCHCH'HCHC**H**CCH), 4.19 – 4.09 (m, 2H, OC**H**CH_2CHBr, OC**H**CH_2CHCl), 4.04 – 3.99 (m, 2H, CH_3CH'HC**H**, OC**H**CH'HCHCHCCH), 4.00 – 3.97 (m, 1H, OCHCH_2C**H**Cl), 3.97 – 3.93 (m, 1H, OCHCH_2C**H**Br), 2.83 (dd, *J* = 2.3, 0.6 Hz, 1H, OCHCH'HCHCHCC**H**), 2.46 (dddd, *J* = 13.8, 6.8, 4.8, 1.6 Hz, 1H, OCHC**H'**HCHCHCCH), 2.36 (dddd, *J* = 13.1, 6.8, 5.7, 1.6 Hz, 1H, OCHCH'**H**CHCHCCH), 2.33 – 2.27 (m, 2H, OCHC**H**$_2$CHBr), 2.27 – 2.17 (m, 2H, OCHC**H**$_2$CHCl), 1.67 (dqd, *J* = 14.0, 7.5, 5.0 Hz, 1H, CH_3C**H'**HCH), 1.50 (dp, *J* = 13.9, 7.4 Hz, 1H, CH_3CH'**H**CH), 0.99 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8 (OCHCH'H**C**HCHCCH), 112.0 (OCHCH'HCH**C**HCCH),

88.9 ($CH_3CH'H\mathbf{C}H$), 85.9 ($O\mathbf{C}HCH'HCHCHCCH$), 82.0 ($OCHCH'HCHCH\mathbf{C}CH$), 79.6 ($O\mathbf{C}HCH_2CHCl$), 79.3 ($O\mathbf{C}HCH_2CHBr$), 77.4 ($OCHCH'HCHCHC\mathbf{C}H$), 58.9 ($OCHCH_2\mathbf{C}HCl$), 48.9 ($OCHCH_2\mathbf{C}HBr$), 39.0 ($OCH\mathbf{C}H_2CHBr$), 38.1 ($OCH\mathbf{C}H_2CHCl$), 36.9 ($OCH\mathbf{C}H'HCHCHCCH$), 26.9 ($CH_3\mathbf{C}H'HCH$), 10.2 ($\mathbf{C}H_3CH'HCH$). IR (ν_{max} cm^{-1}): 3295 (acetylene sp C–H stretching, medium), 2852-2963 (aliphatic sp^3 C–H stretchings, broad), 2103 (acetylene C≡C stretching, weak), 1067 (ether C–O–C antisymmetric stretching, strong), 796 (C–Cl stretching, medium), 640 (C–Br stretching, medium). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 347.04080, 349.03875 and 351.03580, found *m/z* 347.04077, 349.03852 and 351.03588. ($C_{15}H_{21}O_2{}^{79}Br^{35}Cl$, $C_{15}H_{21}O_2{}^{79}Br^{37}Cl$/ $C_{15}H_{21}O_2{}^{81}Br^{35}Cl$ and $C_{15}H_{21}O_2{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = -35.2$ (c=0.10, CH_2Cl_2) . Literature value of enantiomer: $[\alpha]_D^{25} = +28.8$ (c=0.57, CH_2Cl_2).[9] Spectroscopic data are in accordance with literature data.[9]

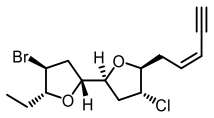
(2*R*,2'*S*,4*S*,4'*R*,5*R*,5'*S*)-4,4'-Dibromo-5-ethyl-5'-((*Z*)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran, (*Z*)-elatenyne 1.9



Compound **1.8** (2.5 mg, 6.4 μmol) was dissolved in dry Pet. Ether 40-60 (2.0 mL) and a pinch of activated silica gel (~20.0 mg) was added. The reaction flask was closed with a brand-new Suba-Seal® septum and stirred at room temperature for 2 overnights. A crude NMR was taken to probe if the reaction was complete, yet the conversion was only at 50%. The reaction mixture was then stirred at 80 °C for 1 extra overnight for completion. The reaction was stopped at this stage and all volatiles were removed. The crude mixture then underwent purification by flash column chromatography (0.5% EA/CH_2Cl_2) to give the desired compound **1.9** as a colourless oil (1.5 mg, 3.8 μmol, 60%). R_f = 0.68 (2% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ 5.72 (dt, *J* = 10.7, 7.4 Hz, 1H, BrCHCHCH'HC**H**CHCCH), 5.37 (dq, *J* = 10.9, 1.6 Hz, 1H, BrCHCHCH'HCHC**H**CCH), 4.07 (dt, *J* = 6.8, 5.3 Hz, 1H, BrCHC**H**CH'HCHCHCCH), 3.91 (dt, *J* = 7.9, 5.2 Hz, 1H, $CH_3CH'HC\mathbf{H}$), 3.90 – 3.83 (m, 2H, BrCHCH'HC**H**CHCH'H, BrCHCH'HCHC**H**CH'H), 3.67 (dt, *J* = 7.3, 5.0 Hz, 1H, BrC**H**CHCH'HCHCHCCH), 3.53 (dt, *J* = 7.6, 5.4 Hz, 1H, BrC**H**CH'HCHCHCH'H), 2.76 (d, *J* = 2.3 Hz, 1H, BrCHCHCH'HCHCHCC**H**), 2.51 (dddd, *J* = 14.5, 7.2, 5.4, 1.4 Hz, 1H, BrCHCHC**H'**HCHCHCCH), 2.41 (dddd, *J* = 14.5, 7.4, 5.3, 1.6 Hz, 1H, BrCHCHCH'**H**CHCHCCH), 2.09 – 2.04 (m, 1H, BrCHC**H'**HCHCHCH'H), 2.04 – 1.99 (m, 1H, BrCHCH'HCHCHC**H'**H), 1.95 – 1.91 (m, 1H, BrCHCH'HCHCHCH'**H**), 1.91 – 1.87 (m, 1H, BrCHCH'**H**CHCHCH'H), 1.38 (dqd, *J* = 14.8, 7.4, 4.6 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 1.23 (dp, *J* = 14.8, 7.9, 7.4 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 0.81 (t, *J* = 7.4 Hz,

3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, C_6D_6) δ 140.2 (BrCHCHCH'H**C**HCHCCH), 111.2 (BrCHCHCH'HCH**C**HCCH), 88.7 (CH_3CH'H**C**H), 86.5 (BrCH**C**HCH'HCHCHCCH), 82.9 (BrCHCHCH'HCHCHC**C**H), 80.2 (BrCHCHCH'HCHCH**C**CH), 80.1 (BrCHCH'HCH**C**HCH'H), 79.6 (BrCHCH'H**C**HCHCH'H), 49.3 (Br**C**HCH'HCHCHCH'H), 49.0 (Br**C**HCHCH'HCHCHCCH), 39.4 (BrCH**C**H'HCHCHCH'H), 39.1 (BrCHCH'HCHCH**C**H'H), 34.7 (BrCHCH**C**H'HCHCHCCH), 26.8 (CH_3**C**H'HCH), 10.2 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3294 (acetylene sp C–H stretching, medium), 2852-2962 (aliphatic sp^3 C–H stretchings, broad), 2097 (acetylene C≡C stretching, weak), 1068 (ether C–O–C antisymmetric stretching, strong. HRMS (APCI) $[M+H]^+$: calculated for *m/z* 390.99028, 392.98824 and 394.98619, found *m/z* 390.99039, 392.98837 and 394.98638. ($C_{15}H_{21}O_2{}^{79}Br_2$, $C_{15}H_{21}O_2{}^{79}Br^{81}Br$/ $C_{15}H_{21}O_2{}^{81}Br^{79}Br$ and $C_{15}H_{21}O_2{}^{81}Br_2$). $[\alpha]_D^{25} = -2.1$ (c=0.14, $CHCl_3$). Literature value: $[\alpha]_D^{25} = -4.0$ ($c = 0.25, CHCl_3$).[9] Spectroscopic data are in accordance with literature data.[9,12]

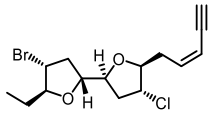
(2*R*,2'*S*,4*S*,4'*R*,5*R*,5'*S*)-4-Bromo-4'-chloro-5-ethyl-5'-((*Z*)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran, laurendecumenyne B 1.7



Compound **1.5** (3.7 mg, 10.7 μmol) was dissolved in dry $CHCl_3$ (1.0 mL) and a pinch of activated silica gel (~20.0 mg) was added. The reaction flask was closed with a brand-new Suba-Seal® septum and stirred at 80 °C for 1 overnight. A crude NMR was taken to confirm the completion of the reaction. The reaction was stopped at this stage and all volatiles were removed. The crude mixture then underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60) to give the desired compound **1.7** as a colourless oil (2.7 mg, 7.8 μmol, 73%). R_f = 0.51 (10% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (dtd, *J* = 11.0, 7.5, 1.0 Hz, 1H, ClCHCHCH'HC**H**CHCCH), 5.60 (ddt, *J* = 10.8, 2.5, 1.4 Hz, 1H, ClCHCHCH'HCHC**H**CCH), 4.21 – 4.11 (m, 2H, BrCHCH$_2$C**H**CHCH$_2$, BrCHCH$_2$CHC**H**CH$_2$), 4.13 – 4.07 (m, 1H, ClCHC**H**CH'HCHCHCCH), 4.11 – 4.05 (m, 1H, ClC**H**CHCH'HCHCHCCH), 4.01 (dt, *J* = 7.3, 5.1 Hz, 1H, CH_3CH'HC**H**), 3.96 (q, *J* = 5.9 Hz, 1H, BrC**H**CH$_2$CHCHCH$_2$), 3.13 (dd, *J* = 2.3, 0.9 Hz, 1H, ClCHCHCH'HCHCHCC**H**), 2.66 (dddd, *J* = 14.5, 7.5, 5.5, 1.4 Hz, 1H, ClCHCHC**H'**HCHCHCCH), 2.58 (dddd, *J* = 14.5, 7.5, 5.5, 1.4 Hz, 1H, ClCHCHCH'**H**CHCHCCH), 2.32 (t, *J* = 6.3 Hz, 2H, BrCHC**H**$_2$CHCHCH$_2$), 2.28 – 2.20 (m, 2H, BrCHCH$_2$CHCHC**H**$_2$), 1.66 (dqd, *J* = 15.0, 7.5, 4.9 Hz, 1H, CH_3C**H'**HCH), 1.51 (dp, *J* = 13.8, 7.3 Hz, 1H, CH_3CH'**H**CH), 0.99 (t, *J* = 7.4 Hz, 3H,

C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0 (ClCHCHCH'H**C**HCHCCH), 111.3 (ClCHCHCH'HCH**C**HCCH), 88.9 (CH_3CH'H**C**H), 86.4 (ClCH**C**HCH'HCHCHCCH), 82.5 (ClCHCHCH'HCHCHC**C**H), 80.1 (ClCHCHCH'HCHCH**C**CH), 79.8 (BrCHCH$_2$CH**C**HCH$_2$), 79.4 (BrCHCH$_2$**C**HCHCH$_2$), 59.5 (Cl**C**HCHCH'HCHCHCCH), 49.0 (Br**C**HCH$_2$CHCHCH$_2$), 39.0 (BrCH**C**H$_2$CHCHCH$_2$), 38.4 (BrCHCH$_2$CHCH**C**H$_2$), 34.7 (ClCHCH**C**H'HCHCHCCH), 26.9 (CH_3**C**H'HCH), 10.2 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 3293 (acetylene sp C–H stretching, medium), 2964-2878 (aliphatic sp^3 C–H stretchings, broad), 1073 (ether C–O–C antisymmetric stretching, strong), 799 (C–Cl stretching, medium), 646 (C–Br stretching, medium). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 347.04080, 349.03875 and 351.03580, found *m/z* 347.04044, 349.03809 and 351.03540. ($C_{15}H_{21}O_2{}^{79}Br^{35}Cl$, $C_{15}H_{21}O_2{}^{79}Br^{37}Cl$/ $C_{15}H_{21}O_2{}^{81}Br^{35}Cl$ and $C_{15}H_{21}O_2{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = -8.7$ (c=0.10, CH_2Cl_2) . Literature value of enantiomer: $[\alpha]_D^{25} = -9.1$ (c=1.05, CH_2Cl_2).[9] Spectroscopic data are in accordance with literature except for the specific rotation.[9,14]

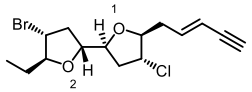
(2*R*,2'*S*,4*R*,4'*R*,5*S*,5'*S*)-4-Bromo-4'-chloro-5-ethyl-5'-((*Z*)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran, *ent*-(*Z*)-notoryne *ent*-1.17



Compound ***ent*-5.1** (1.0 mg, 2.9 μmol) was dissolved in dry hexanes (1.0 mL) and a pinch of activated silica gel (~20.0 mg) was added. The reaction flask was closed with a brand-new Suba-Seal® septum and stirred at 80 °C for 1 overnight. A crude NMR was taken to confirm the completion of the reaction. The reaction was stopped at this stage and all volatiles were removed. The crude mixture then underwent purification by flash column chromatography (5% EA/Pentane) to give the desired compound ***ent*-1.17** as a colourless oil (1.0 mg, 2.9 μmol, 100%). R_f = 0.50 (10% EA/Pet. Ether 40-60). Alternatively, compound ***ent*-5.1** (3.0 mg, 8.6 μmol) was dissolved in $CDCl_3$ (0.6 mL) and heated to 60 °C for 2 overnights, in which no reaction was observed. The sample was then heated to 80 °C for 12 overnights in which a complete conversion from ***ent*-5.1** to ***ent*-1.17** was followed and observed by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (dtd, *J* = 10.9, 7.5, 0.9 Hz, 1H, CH'HC**H**=CH), 5.60 (ddt, *J* = 10.9, 2.6, 1.4 Hz, 1H, CH'HCH=C**H**), 4.25 (td, *J* = 7.3, 5.6 Hz, 1H, ClCHCHOC**H**), 4.13 – 4.04 (m, 2H, ClC**H** and ClCHC**H**OCH), 3.97 (ddd, *J* = 8.3, 6.8, 5.6 Hz, 1H, BrCHCHOC**H**), 3.91 (td, *J* = 7.5, 3.9 Hz, 1H, BrCHC**H**), 3.86 (dt, *J* = 8.8, 7.3 Hz, 1H, BrC**H**), 3.12 (dd, *J* = 2.3, 0.9 Hz, 1H, C≡C**H**), 2.70 – 2.63 (m, 2H, BrCHC**H'**H, C**H'**HCH=CH), 2.59 (dddd, *J* = 14.6, 7.4, 6.0, 1.4 Hz, 1H, CH'**H**CH=CH), 2.26 (ddd, *J* = 7.0, 5.3, 2.9 Hz, 2H,

ClCHC**H**$_2$), 2.17 (dt, *J* = 13.1, 8.5 Hz, 1H, BrCHCH'**H**), 1.75 (dqd, *J* = 14.0, 7.6, 4.0 Hz, 1H, CH_3C**H'**H), 1.49 (dp, *J* = 14.6, 7.4 Hz, 1H, CH_3CH'**H**), 1.00 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1 (CH'H**C**H=CH), 111.2 (CH'HCH=**C**H), 87.3 (BrCH**C**HOCH), 86.3 (ClCH**C**HOCH), 82.5 (C≡**C**H), 80.3 (ClCHCHO**C**H), 80.1 (**C**≡CH), 79.1 (BrCHCHO**C**H), 59.4 (Cl**C**H), 47.5 (Br**C**H), 39.5 (BrCH**C**H'H), 38.3 (ClCH**C**H$_2$), 34.6 (**C**H'HCH=CH), 25.6 (CH_3**C**H'H), 10.2. (**C**H_3CH'H). IR (ν_{max} cm^{-1}): 3293 (alkyne sp C–H stretching, strong), 3030 (alkene sp^2 C–H stretching, weak), 2965-2878 (alkane sp^3 C–H stretchings, broad), 2096 (alkyne C≡C stretching, weak), 1250 (ether C–O–C stretching, medium), 1069 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 369.0, 371.0 and 373.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 369.02274, 371.02069 and 373.01774, found *m/z* 369.02282, 371.02055 and 373.01772 ($C_{15}H_{20}O_2{}^{79}Br^{35}ClNa$, $C_{15}H_{20}O_2{}^{81}Br^{35}ClNa$ / $C_{15}H_{20}O_2{}^{79}Br^{37}ClNa$ and $C_{15}H_{20}O_2{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = -47.2$ (c=0.30, $CHCl_3$) . Literature value of enantiomer: $[\alpha]_D^{25} = +36.4$ (c=0.80, $CHCl_3$) ,[169] $[\alpha]_D = +40.3$ (c=1.03, $CHCl_3$) .[15] Spectroscopic data are in accordance with literature data.[15,169]

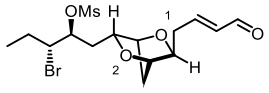
(2*R*,2'*S*,4*R*,4'*R*,5*S*,5'*S*)-4-Bromo-4'-chloro-5-ethyl-5'-((*E*)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran *ent*-(*E*)-notoryne *ent*-1.18



Compound ***ent*-5.2** (3.4 mg, 9.8 μmol) was mixed with a pinch of activated silica gel (heated to 140 °C under high vacuum for 3 hours for activation) and dry hexane and heated to 80 °C overnight in a reaction flask closed with a brand-new Suba-Seal® septum. All volatiles were then evaporated and the residue underwent purification by flash column chromatography (5% EA/Pet. Ether) to give the desired compound ***ent*-1.18** as a colourless oil (3.4 mg, 9.8 μmol, quantitative, *E:Z* > 20:1). R_f = 0.50 (10% EA/Pet. Ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 15.9, 7.2 Hz, 1H, OCHCH'HC**H**CHCCH), 5.57 (dq, *J* = 16.0, 1.7 Hz, 1H, OCHCH'HCHC**H**CCH), 4.22 (td, *J* = 7.1, 5.4 Hz, 1H, O_2CHC**H**O_1), 4.03 – 4.00 (m, 1H, OC**H**CH'HCHCHCCH), 4.00 – 3.97 (m, 1H, ClC**H**CH_2), 3.97 – 3.93 (m, 1H, O_2C**H**CHO_1), 3.91 (td, *J* = 7.4, 3.9 Hz, 1H, C**H**CHBrCH'H), 3.87 (dt, *J* = 8.6, 7.2 Hz, 1H, CHC**H**BrCH'H), 2.83 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHCC**H**), 2.66 (dt, *J* = 13.4, 6.9 Hz, 1H, CHCHBrC**H'**H), 2.47 (dddd, *J* = 13.9, 6.9, 5.0, 1.6 Hz, 1H, OCHC**H'**HCHCHCCH), 2.37 (dddd, *J* = 14.9, 7.5, 6.1, 1.5 Hz, 1H, OCHCH'**H**CHCHCCH), 2.32 – 2.20 (m, 2H, ClCHC**H**$_2$), 2.14 (dt, *J* = 13.1, 8.4 Hz, 1H, CHCHBrCH'**H**), 1.75 (dqd, *J* = 14.0, 7.6, 4.0 Hz, 1H, CH_3C**H'**H), 1.49 (dp, *J* = 14.0, 7.4 Hz, 1H, CH_3CH'**H**), 1.00 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9 (OCHCH'H**C**HCHCCH), 112.0

(OCHCH'HCH**C**HCCH), 87.4 (**C**HCHBrCH'H), 85.9 (O**C**HCH'HCHCHCCH), 82.0 (OCHCH'HCHCH**C**CH), 80.2 (O_2CH**C**HO_1), 79.0 (O_2**C**$HCHO_1$), 76.9 (OCHCH'HCHCHC**C**H), 58.8 (Cl**C**HCH_2), 47.4 (CH**C**HBrCH'H), 39.5 (CHCHBr**C**H'H), 38.0 (ClCH**C**H_2), 36.8 (OCH**C**H'HCHCHCCH), 25.6 (CH_3**C**H'H), 10.2 (**C**H_3CH'H). IR (ν_{max} cm^{-1}): 3294 (acetylene C–H stretching, strong), 2963-2877 (aliphatic sp^3 C–H stretchings, broad), 1683 (alkene C=C stretching, medium), 1066 (ether C–O–C antisymmetric stretching, strong), 799 (C–Cl stretching, strong), 642 (C–Br stretching, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 369.0, 371.0 and 373.0. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 369.02274, 371.02069 and 373.01774, found *m/z* 369.02276, 371.02050 and 373.01774. ($C_{15}H_{20}O_2{}^{79}Br^{35}ClNa$, $C_{14}H_{20}O_3{}^{81}Br^{35}ClNa$ /$C_{14}H_{20}O_3{}^{79}Br^{37}ClNa$ and $C_{14}H_{20}O_3{}^{81}Br^{37}ClNa$). $[\alpha]_D^{25} = -27.9$ (c=0.34, $CHCl_3$).

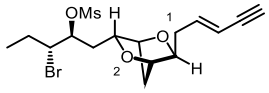
(2*S*,3*R*)-3-Bromo-1-((1*S*,3*R*,4*S*,6*S*)-6-((*E*)-4-oxobut-2-en-1-yl)-2,5-dioxabicyclo[2.2.1] heptan-3-yl)pentan-2-yl methanesulfonate 5.60



According to the procedures of Voigtritter[235]: Compound **5.17** (14.5 mg, 38.0 μmol) was dissolved in dry Et_2O (2.0 mL) and degassed with dry argon for 15 minutes. Crotonaldehyde (16.0 μL, 0.19 mmol) was then added followed by 2nd Generation Grubb's catalyst (1.6 mg, 1.9 μmol) and CuI (0.6 mg, 2.9 μmol). The reaction mixture was stirred overnight with an exhaust needle. A TLC analysis was performed at this stage to confirm the complete consumption of starting materials. All volatiles were removed and the brown crude oil then underwent purification by flash column chromatography (60% EA/Pet. Ether 40-60 to 100% EA) to give the desired compound **5.60** as a pale green oil (12.3 mg, 30.0 μmol, 79%, *E:Z* > 20:1). R_f = 0.59 (100% EA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H, OCHCH'HCHCHC**H**O), 6.86 (dt, *J* = 15.7, 7.0 Hz, 1H, OCHCH'HC**H**CHCHO), 6.21 (ddd, *J* = 15.8, 7.8, 1.6 Hz, 1H, OCHCH'HCHC**H**CHO), 4.87 (q, *J* = 5.3 Hz, 1H, CH_3CH'HCHBrC**H**OMsCH'HCHO), 4.40 (s, 1H, O_2CHCH_2C**H**O_1), 4.33 (d, *J* = 1.8 Hz, 1H, O_2C**H**CH_2CHO_1), 4.19 (ddd, *J* = 10.1, 4.9, 3.4 Hz, 1H, CH_3CH'HC**H**BrCHOMsCH'HCHO), 4.02 – 3.96 (m, 2H, CH_3CH'HCHBrCHOMsCH'HC**H**O, H6), 3.13 (s, 3H, OMs C**H**$_3$), 2.69 (dddd, *J* = 14.6, 8.0, 6.5, 1.6 Hz, 1H, OCHC**H'**HCHCHCHO), 2.58 (dddd, *J* = 14.8, 7.3, 5.8, 1.3 Hz, 1H, OCHCH'**H**CHCHCHO), 2.01 – 1.91 (m, 4H, O_2CHC**H**$_2CHO_1$, CH_3CH'HCHBrCHOMsC**H'**HCHO, CH_3C**H'**HCHBrCHOMsCH'HCHO), 1.87 (dt, *J* = 14.9, 5.4 Hz, 1H, CH_3CH'HCHBrCHOMsCH'**H**CHO), 1.77 (ddq, *J* = 14.7, 10.3, 7.4 Hz, 1H, CH_3CH'**H**CHBrCHOMsCH'HCHO), 1.11 (t, *J* = 7.2 Hz, 3H, CH_3C**H'**HCHBrCHOMsCH'HCHO). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9

(OCHCH'HCHCH**C**HO), 153.9 (OCHCH'H**C**HCHCHO), 135.0 (OCHCH'HCH**C**HCHO), 81.1 (O**C**HCH'HCHCHCHO), 80.9 (CH_3CH'HCHBrCHOMsCH'H**C**HO), 80.9 (CH_3CH'HCHBr**C**HOMsCH'HCHO), 80.0 (O_2**C**HCH$_2$CHO$_1$), 77.5 (O_2CHCH$_2$**C**HO$_1$), 58.2 (CH_3CH'H**C**HBrCHOMsCH'HCHO), 39.1 (OMs **C**H$_3$), 36.3 (CH_3CH'HCHBrCHOMs**C**H'HCHO), 35.0 (O_2CH**C**H$_2$CHO$_1$), 34.5 (OCH**C**H'HCHCHCHO), 27.4 (CH_3**C**H'HCHBrCHOMsCH'HCHO), 12.5 (**C**H$_3$CH'H CHBrCHOMsCH'HCHO). IR (ν_{max} cm^{-1}): 2881-2969 (aliphatic sp^3 C–H stretchings, broad), 2741 (overtone of aldehyde C–H bending, weak), 1684 (conjugated C=O stretching, strong), 1353 (SO_2 antisymmetric stretching, strong), 1172 (SO_2 symmetric stretching, strong), 1072 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 411.0 and 413.0. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 411.04715 and 413.04510, found *m/z* 411.04689, and 413.04477. ($C_{15}H_{24}O_6{}^{79}Br^{32}S$ and $C_{15}H_{24}O_6{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +60.1$ (c=1.10, $CHCl_3$).

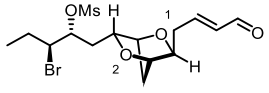
(2*S*,3*R*)-3-Bromo-1-((1*S*,3*R*,4*S*,6*S*)-6-((*E*)-pent-2-en-4-yn-1-yl)-2,5-dioxabicyclo[2.2.1] heptan-3-yl)pentan-2-yl methanesulfonate 5.45



According to the modified procedures of Kim[5]: $TMSCHN_2$ (0.12 mL, 0.23 mmol, 2.0M solution in Et_2O) was mixed with dry THF (1.0 mL) at -78 °C. *n*-BuLi (0.1 mL, 0.23 mmol, 2.3M solution in hexanes) was then added and stirring was continued for 30 minutes. Compound **5.60** (9.3 mg, 23.0 μmol) was dissolved in dry THF (0.96 mL) and the reaction mixture was cooled to -78˚C, in which a portion of the preformed $TMSCLiN_2$ solution (0.24 mL) was then added rapidly. The reaction mixture was stirred at -78 °C for 40 minutes, then warmed to 0 °C and stirring was continued for 5 minutes. TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH_4Cl solution and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting yellow crude oil then underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60) to give the desired compound **5.45** as a pale yellow oil (5.3 mg, 13.0 μmol, 57%, *E:Z* > 20:1). R_f = 0.71 (100% EA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 16.1, 7.3 Hz, 1H, OCHCH'HC**H**CHCCH), 5.58 (dq, *J* = 16.0, 1.7 Hz, 1H, OCHCH'HCHC**H**CCH), 4.87 (dt, *J* = 6.5, 5.2 Hz, 1H, CH_3CH'HCHBrC**H**OMsCH'HCHO), 4.37 (d, *J* = 1.8 Hz, 1H, O_2C**H**CH$_2$CHO$_1$), 4.28 (d, *J* = 1.6 Hz, 1H, O_2CHCH$_2$C**H**O$_1$), 4.19 (ddd, *J* = 10.2, 4.8, 3.4 Hz, 1H, CH_3CH'HC**H**BrCHOMsCH'HCHO), 3.96 (dd, *J* = 8.6, 5.2 Hz, 1H,

$CH_3CH'HCHBrCHOMsCH'HC\mathbf{H}O$), 3.85 (td, *J* = 7.1, 1.1 Hz, 1H, $OC\mathbf{H}CH'HCHCHCCH$), 3.13 (s, 3H, OMs $C\mathbf{H}_3$), 2.81 (d, *J* = 2.2 Hz, 1H, $OCHCH'HCHCHCC\mathbf{H}$), 2.47 (dtd, *J* = 14.0, 7.0, 1.6 Hz, 1H, $OCHC\mathbf{H}'HCHCHCCH$), 2.37 (dtd, *J* = 14.2, 7.5, 1.5 Hz, 1H, $OCHCH'\mathbf{H}CHCHCCH$), 1.98 – 1.93 (m, 2H, $CH_3CH'HCHBrCHOMsC\mathbf{H}'HCHO$, $CH_3C\mathbf{H}'HCHBrCHOMsCH'HCHO$), 1.92 – 1.90 (m, 2H, $O_2CHC\mathbf{H}_2CHO_1$), 1.86 (dt, *J* = 14.9, 5.4 Hz, 1H, $CH_3CH'HCHBrCHOMsCH'\mathbf{H}CHO$), 1.76 (ddq, *J* = 14.5, 10.2, 7.2 Hz, 1H, $CH_3CH'\mathbf{H}CHBrCHOMsCH'HCHO$), 1.11 (t, *J* = 7.2 Hz, 3H, $C\mathbf{H}_3CH'HCHBrCHOMsCH'HCHO$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 ($OCHCH'H\mathbf{C}HCHCCH$), 111.6 ($OCHCH'HCH\mathbf{C}HCCH$), 82.2 ($OCHCH'HCHCH\mathbf{C}CH$), 81.7 ($O\mathbf{C}HCH'HCHCHCCH$), 81.2 ($CH_3CH'HCHBr\mathbf{C}HOMsCH'HCHO$), 80.8 ($CH_3CH'HCHBrCHOMsCH'H\mathbf{C}HO$), 79.9 ($O_2CHCH_2\mathbf{C}HO_1$), 77.3 ($O_2\mathbf{C}HCH_2CHO_1$), 76.7 ($OCHCH'HCHCHC\mathbf{C}H$), 58.4 ($CH_3CH'H\mathbf{C}HBrCHOMsCH'HCHO$), 39.1 (OMs $\mathbf{C}H_3$), 36.3 ($CH_3CH'HCHBrCHOMs\mathbf{C}H'HCHO$), 34.9 ($O_2CH\mathbf{C}H_2CHO_1$), 34.6 ($OCH\mathbf{C}H'HCHCHCCH$), 27.4 ($CH_3\mathbf{C}H'HCHBrCHOMsCH'HCHO$), 12.5 ($\mathbf{C}H_3CH'HCHBrCHOMsCH'HCHO$). IR ($\nu_{max}$ cm^{-1}): 3286 (acetylene sp C–H stretching, medium), 2850-2969 (aliphatic sp^3 C–H stretchings, broad), 2101 (acetylene C≡C stretching, weak), 1353 (SO_2 antisymmetric stretching, strong), 1172 (SO_2 symmetric stretching, strong), 1059 (ether C–O–C antisymmetric stretching, strong), 633 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 407.1 and 409.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 407.05223 and 409.05019, found *m/z* 407.05264 and 409.05055. ($C_{16}H_{24}O_5{}^{79}Br^{32}S$ and $C_{16}H_{24}O_5{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +51.2$ (c=0.25, $CHCl_3$).

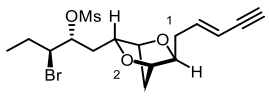
(2*R*,3*S*)-3-Bromo-1-((1*S*,3*R*,4*S*,6*S*)-6-((*E*)-4-oxobut-2-en-1-yl)-2,5-dioxabicyclo[2.2.1] heptan-3-yl)pentan-2-yl methanesulfonate 5.61



According to the procedures of Voigtritter[235]: Compound **5.18** (20.0 mg, 52.0 μmol) was dissolved in dry Et_2O (2.6 mL) and degassed with dry argon for 15 minutes. Crotonaldehyde (22.0 μL, 0.26 mmol) was then added followed by 2nd Generation Grubb's catalyst (2.2 mg, 2.6 μmol) and CuI (0.7 mg, 3.7 μmol). The reaction mixture was stirred overnight with an exhaust needle. A TLC analysis was performed at this stage to confirm the complete consumption of starting materials. All volatiles were removed and the brown crude oil then underwent purification by flash column chromatography (60% EA/Pet. Ether 40-60 to 100% EA) to give the desired compound **5.61** as a pale green oil (15.9 mg, 38.8 μmol, 75%, *E:Z* > 20:1). R_f = 0.57 (100% EA).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 7.8 Hz, 1H, OCHCH'HCHCHC**H**O), 6.86 (dt, *J* = 15.6, 7.0 Hz, 1H, OCHCH'HC**H**CHCHO), 6.20 (dd, *J* = 15.7, 7.8 Hz, 1H, OCHCH'HCHC**H**CHO), 4.86 (dt, *J* = 9.8, 2.9 Hz, 1H, CH_3CH'HCHBrC**H**OMsCH'HCHO), 4.41 (d, *J* = 2.5 Hz, 1H, O_2C**H**CH'HCHO$_1$), 4.33 (d, *J* = 2.3 Hz, 1H, O_2CHCH'HC**H**O$_1$), 4.27 (dt, *J* = 10.0, 3.7 Hz, 1H, CH_3CH'HC**H**BrCHOMsCH'HCHO), 4.04 – 3.93 (m, 2H, CH_3CH'HCHBrCHOMsCH'HC**H**O, OC**H**CH'HCHCHCHO), 3.14 (s, 3H, OMs C**H**$_3$), 2.67 (dddd, *J* = 14.6, 8.1, 6.5, 1.6 Hz, 1H, OCHC**H'**HCHCHCHO), 2.56 (dddd, *J* = 14.9, 7.4, 5.8, 1.4 Hz, 1H, OCHCH'**H**CHCHCHO), 2.01 – 1.93 (m, 2H, O_2CHC**H'**HCHO$_1$, CH_3CH'HCHBrCHOMsC**H'**HCHO), 1.91 – 1.82 (m, 2H, O_2CHCH'**H**CHO$_1$, CH_3C**H'**HCHBrCHOMsCH'HCHO), 1.73 (dqd, *J* = 14.6, 7.3, 2.9 Hz, 1H, CH_3CH'**H**CHBrCHOMsCH'HCHO), 1.46 (ddd, *J* = 14.5, 10.3, 2.7 Hz, 1H, CH_3CH'HCHBrCHOMsCH'**H**CHO), 1.10 (t, *J* = 7.2 Hz, 3H, C**H**$_3$CH'HCHBrCHOMs CH'HCHO). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9 (OCHCH'HCHCH**C**HO), 153.9 (OCHCH'H**C**HCHCHO), 135.0 (OCHCH'HCH**C**HCHO), 81.0 (O**C**HCH'HCHCHCHO), 80.0 (O_2CHCH'H**C**HO$_1$), 79.8 (CH_3CH'HCHBrCHOMsCH'H**C**HO), 79.5 (CH_3CH'HCHBr**C**HOMsCH'HCHO), 77.6 (O_2**C**HCH'HCHO$_1$), 59.9 (CH_3CH'H**C**HBrCHOMsCH'HCHO), 38.9 (OMs **C**H$_3$), 35.2 (CH_3CH'HCHBrCHOMs**C**H'HCHO), 35.2 (O_2CH**C**H'HCHO$_1$), 34.5 (OCH**C**H'HCHCHCHO), 28.2 (CH_3**C**H'HCHBrCHOMsCH'HCHO), 12.6 (**C**H$_3$CH'HCHBrCHOMsCH'HCHO). IR (ν_{max} cm^{-1}): 2852-2969 (aliphatic sp^3 C–H stretchings, broad), 2740 (overtone of aldehyde C–H bending, weak), 1685 (conjugated C=O stretching, strong), 1355 (SO_2 antisymmetric stretching, strong), 1173 (SO_2 symmetric stretching, strong), 1071 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+H]$^+$: *m/z* 411.0 and 413.0. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 411.04715 and 413.04510, found *m/z* 411.04714, and 413.04496. ($C_{15}H_{24}O_6{}^{79}Br^{32}S$ and $C_{15}H_{24}O_6{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +111.0$ (c=0.25, $CHCl_3$).

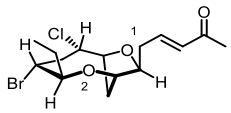
(2*R*,3*S*)-3-Bromo-1-((1*S*,3*R*,4*S*,6*S*)-6-((*E*)-pent-2-en-4-yn-1-yl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)pentan-2-yl methanesulfonate 5.43



According to the modified procedures of Kim[5]: $TMSCHN_2$ (0.17 mL, 0.33 mmol, 2.0M solution in Et_2O) was mixed with dry THF (1.0 mL) at -78 °C. *n*-BuLi (0.14 mL, 0.33 mmol, 2.3M solution in hexanes) was then added and stirring was continued for 30 minutes. Compound **5.61** (13.4 mg, 33.0 μmol) was dissolved in dry THF (1.44 mL) and the reaction mixture was cooled to -78 °C, in which a portion of the preformed

$TMSCLiN_2$ solution (0.26 mL) was then added rapidly. The reaction mixture was stirred at -78 °C for 40 minutes, then warmed to 0 °C and stirring was continued for 5 minutes. TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH_4Cl solution and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting yellow crude oil then underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60) to give the desired compound **5.43** as a pale yellow oil (6.8 mg, 16.7 μmol, 51%, *E:Z* > 20:1). R_f = 0.74 (100% EA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (dt, *J* = 15.3, 7.4 Hz, 1H, OCHCH'HC**H**CHCCH), 5.56 (dq, *J* = 15.9, 1.7 Hz, 1H, OCHCH'HCHC**H**CCH), 4.82 (dt, *J* = 9.8, 3.0 Hz, 1H, CH_3CH'HCHBrC**H**OMsCH'HCHO), 4.38 (d, *J* = 2.6 Hz, 1H, O_2C**H**CH'HCHO$_1$), 4.33 – 4.22 (m, 2H, CH_3CH'HC**H**BrCHOMsCH'HCHO, O_2CHCH'HC**H**O$_1$), 3.96 (dd, *J* = 10.3, 3.3 Hz, 1H, CH_3CH'HCHBrCHOMsCH'HC**H**O), 3.86 (td, *J* = 7.1, 1.1 Hz, 1H, OC**H**CH'HCHCHCCH), 3.14 (s, 3H, OMs C**H**$_3$), 2.81 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHCC**H**), 2.45 (dtd, *J* = 14.0, 7.0, 1.6 Hz, 1H, OCHC**H'**HCHCHCCH), 2.33 (dtd, *J* = 14.0, 7.0, 1.6 Hz, 1H, OCHCH'**H**CHCHCCH), 1.98 (ddd, *J* = 14.5, 9.8, 3.3 Hz, 1H, CH_3CH'HCHBrCHOMsC**H'**HCHO), 1.93 (dd, *J* = 10.4, 2.5 Hz, 1H, O_2CHC**H'**HCHO$_1$), 1.91 – 1.80 (m, 2H, O_2CHCH'**H**CHO$_1$, CH_3C**H'**HCHBrCHOMsCH'HCHO), 1.73 (dqd, *J* = 14.6, 8.0, 7.3, 2.8 Hz, 1H, CH_3CH'**H**CHBrCHOMsCH'HCHO), 1.44 (ddd, *J* = 14.5, 10.3, 2.9 Hz, 1H, CH_3CH'HCHBrCHOMsCH'**H**CHO), 1.09 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHBrCHOMsCH'HCHO). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6 (OCHCH'H**C**HCHCCH), 111.7 (OCHCH'HCH**C**HCCH), 82.1 (OCHCH'HCHCH**C**CH), 81.7 (O**C**HCH'HCHCHCCH), 79.9 (O_2CHCH'H**C**HO$_1$), 79.8 (CH_3CH'HCHBr**C**HOMsCH'HCHO), 79.6 (CH_3CH'HCHBrCHOMsCH'H**C**HO), 77.4 (O_2**C**HCH'HCHO$_1$), 76.7 (OCHCH'HCHCHC**C**H), 60.1 (CH_3CH'H**C**HBrCHOMsCH'HCHO), 38.8 (OMs **C**H$_3$), 35.1 (O_2CH**C**H'HCHO$_1$), 35.1 (CH_3CH'HCHBrCHOMs**C**H'HCHO), 34.7 (OCH**C**H'HCHCHCCH), 28.3 (CH_3**C**H'HCHBrCHOMsCH'HCHO), 12.6 (**C**H_3CH'HCHBrCHOMsCH'HCHO). IR (ν_{max} cm^{-1}): 3285 (acetylene sp C–H stretching, medium), 2880-2969 (aliphatic sp^3 C–H stretchings, broad), 2102 (acetylene C≡C stretching, weak), 1356 (SO_2 antisymmetric stretching, strong), 1174 (SO_2 symmetric stretching, strong), 1073 (ether C–O–C antisymmetric stretching, strong), 645 (C–Br stretching, medium). LRMS (ESI) [M+H]$^+$: *m/z* 407.1 and 409.1. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 407.05223 and 409.05019, found *m/z* 407.05244 and 409.05032. ($C_{16}H_{24}O_5{}^{79}Br^{32}S$ and $C_{16}H_{24}O_5{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +57.9$ (c=0.68, $CHCl_3$).

(*E*)-5-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-4-Bromo-6-chloro-3-ethyl-2,8-dioxabicyclo[5.2.1] decan-9-yl) pent-3-en-2-one 5.47

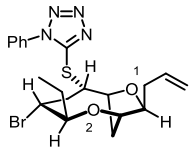


Compound **5.45** (5.3 mg, 13.0 μmol) was dissolved in dry CH_2Cl_2 (1.0 mL) and the reaction mixture was cooled to -40 °C. A solution of 0.5M $TiCl_4$ in CH_2Cl_2 (52.0 μL, 26.0 μmol) was added followed by an immediate addition of a solution of $AgAl(pftb)_4 \cdot CH_2Cl_2$ (45.0 mg, 39 μmol) in CH_2Cl_2 (0.3 mL). The reaction mixture was stirred at -40˚C for 2 hours then cooled to -78 °C. Tetrabutylammonium chloride (36.0 mg, 0.13 mmol) was then added and stirred at -78 °C for 1 hour. A TLC analysis at this stage have not been able to confirm the completion of reaction as the product was found to possess the same R_f value as the starting material. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 to 50% EA/Pet. Ether 40-60) to give the desired compound **5.47** as a colourless oil (1.5 mg, 4.1 μmol, 32%, *E:Z* > 20:1). R_f = 0.52 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (ddd, *J* = 16.0, 7.7, 6.6 Hz, 1H, $OCHCH_2C\mathbf{H}CHCOCH_3$), 6.17 (dt, *J* = 16.0, 1.5 Hz, 1H, $OCHCH_2CHC\mathbf{H}COCH_3$), 4.49 (dd, *J* = 7.7, 4.2 Hz, 1H, $O_2CHCH'HC\mathbf{H}O_1$), 4.13 (ddd, *J* = 10.6, 4.2, 1.1 Hz, 1H, $BrCHCH'HC\mathbf{H}Cl$), 4.07 (td, *J* = 2.4, 1.2 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 3.93 (td, *J* = 7.1, 2.4 Hz, 1H, $OC\mathbf{H}CH_2CHCHCOCH_3$), 3.79 (td, *J* = 10.8, 5.0 Hz, 1H, $BrC\mathbf{H}CH'HCHCl$), 3.51 (ddd, *J* = 10.8, 8.9, 2.5 Hz, 1H, $CH_3CH'HC\mathbf{H}$), 2.70 (ddd, *J* = 15.2, 4.9, 1.0 Hz, 1H, $BrCHC\mathbf{H'}HCHCl$), 2.68 – 2.49 (m, 4H, $BrCHCH'\mathbf{H}CHCl$, $O_2CHC\mathbf{H'}HCHO_1$, $OCHC\mathbf{H}_2CHCHCOCH_3$), 2.25 (s, 3H, $OCHCH_2CHCHCOC\mathbf{H}_3$), 2.14 (dqd, *J* = 14.7, 7.3, 2.5 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 1.93 (ddd, *J* = 14.4, 7.8, 2.3 Hz, 1H, $O_2CHCH'\mathbf{H}CHO_1$), 1.49 (ddq, *J* = 14.4, 8.9, 7.3 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 0.95 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5 ($OCHCH_2CHCH\mathbf{C}OCH_3$), 143.7 ($OCHCH_2\mathbf{C}HCHCOCH_3$), 133.4 ($OCHCH_2CH\mathbf{C}HCOCH_3$), 85.4 ($O_2CHCH'H\mathbf{C}HO_1$), 82.2 ($O\mathbf{C}HCH_2CHCHCOCH_3$), 80.7 ($CH_3CH'H\mathbf{C}H$), 76.6 ($O_2\mathbf{C}HCH'HCHO_1$), 66.4 ($BrCHCH'H\mathbf{C}HCl$), 51.7 ($Br\mathbf{C}HCH'HCHCl$), 45.4 ($BrCH\mathbf{C}H'HCHCl$), 34.4 ($O_2CH\mathbf{C}H'HCHO_1$), 33.3 ($OCH\mathbf{C}H_2CHCHCOCH_3$), 28.2 ($CH_3\mathbf{C}H'HCH$), 27.1 ($OCHCH_2CHCHCO\mathbf{C}H_3$), 9.7 ($\mathbf{C}H_3CH'HCH$). IR ($\nu_{max}$ cm^{-1}): 2852-2962 (aliphatic sp^3 C–H stretchings, broad), 1697 (conjugated C=O stretching, strong), 1259 (ether C–O–C stretching, strong), 1062 (ether C–O–C antisymmetric stretching, strong), 800 (C–Cl stretching, strong), 666 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 365.1, 367.0 and 369.0. HRMS (ESI)

$[M+H]^+$: calculated for *m/z* 365.05136, 367.04931 and 369.04636, found *m/z* 365.05158, 367.04932 and 369.04651. ($C_{15}H_{23}O_3{}^{79}Br^{35}Cl$, $C_{15}H_{23}O_3{}^{79}Br^{37}Cl$/ $C_{15}H_{23}O_3{}^{81}Br^{35}Cl$ and $C_{15}H_{23}O_3{}^{81}Br^{37}Cl$). $[\alpha]_D^{25} = +13.3$ (c=0.15, $CHCl_3$).

10.3 Experimental for Chapter 7

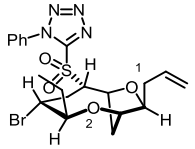
5-(((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-yl)thio)-1-phenyl-1*H*-tetrazole 7.9



Compound **5.19** (25.0 mg, 65.0 μmol) was dissolved in dry CH_2Cl_2 (6.5 mL) and the reaction mixture was cooled to -40 °C. $TiCl_4$ (0.26 mL, 0.5 M in CH_2Cl_2, 195.0 μmol) was added followed by a solution of $AgAl(pftb)_4 \cdot CH_2Cl_2$ (226.0 mg, 130.0 μmol, in 1.0 mL CH_2Cl_2) immediately. The reaction mixture was stirred at -40 °C for 2 hours, then cooled to -78 °C. PTSH (1-phenyl-1*H*-tetrazole-5-thiol) (116.0 mg, 0.65 mmol) was added to the reaction mixture and stirring was continued for 1 hour. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ then warmed to r.t. The quenched reaction mixture was then extracted with CH_2Cl_2, the organic layers combined and dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60) to give the desired compound **7.9** as a white foam (23.0 mg, 49.4 μmol, 76%). R_f = 0.60 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.48 (m, 5H, Ar**H**), 5.80 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H, OCHCH'HC**H**=CH'H), 5.14 (dq, *J* = 17.1, 1.6 Hz, 1H, OCHCH'HCH=C**H'**H), 5.06 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, OCHCH'HCH=CH'**H**), 4.32 (dd, *J* = 7.5, 5.7 Hz, 1H, O_2CHCH'HC**H**O_1), 4.11 (h, *J* = 1.1 Hz, 1H, O_2C**H**CH'HCHO_1), 4.06 (td, *J* = 10.3, 6.3 Hz, 1H, BrC**H**CH_2CHSAr), 4.00 (t, *J* = 7.3 Hz, 1H, BrCHCH_2C**H**SAr), 3.88 (ddd, *J* = 8.6, 6.4, 2.5 Hz, 1H, OC**H**CH'HCH=CH'H), 3.58 (ddd, *J* = 10.8, 9.0, 2.5 Hz, 1H, CH_3CH'HC**H**), 2.76 – 2.65 (m, 3H, O_2CHC**H'**HCHO_1, BrCHC**H**$_2$CHSAr), 2.55 – 2.48 (m, 1H, OCHC**H'**HCH=CH'H), 2.48 – 2.41 (m, 1H, OCHCH'**H**CH=CH'H), 2.17 (dqd, *J* = 14.8, 7.5, 2.5 Hz, 1H, CH_3C**H'**HCH), 1.96 (ddd, *J* = 14.3, 7.5, 2.3 Hz, 1H, O_2CHCH'**H**CHO_1), 1.57 (ddd, *J* = 14.0, 9.0, 7.1 Hz, 1H, CH_3CH'**H**CH), 0.98 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9 (tetrazole **C**), 134.3 (OCHCH'H**C**H=CH'H), 133.8 (Ar**C**), 130.2 (Ar**C**), 129.9 (Ar**C**), 123.9 (Ar**C**), 117.6 (OCHCH'HCH=**C**H'H), 83.8 (O**C**HCH'HCH=CH'H), 81.1 (CH_3CH'H**C**H), 80.4 (O_2CHCH'H**C**HO_1), 77.0 (O_2**C**HCH'HCHO_1), 55.5 (BrCHCH_2**C**HSAr), 53.3 (Br**C**HCH_2CHSAr), 34.5 (BrCH**C**H_2CHSAr), 34.4 (O_2CH**C**H'HCHO_1, OCH**C**H'HCH=CH'H), 28.4 (CH_3**C**H'HCH), 9.8 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3009-2876 (aliphatic sp^3 C–H stretchings, broad), 1642 (C=C stretching, medium), 1597 (tetrazole C=C and C=N stretchings, medium), 1499 (tetrazole C=N and N=N stretchings, strong), 1061 (ether C–O–C antisymmetric stretching, strong), 756 (monosubstituted benzene C–H out of plane deformation, strong), 693 (C–Br stretching,

medium). LRMS (ESI) $[M+H]^+$: *m/z* 465.1 and 467.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 465.09544 and 467.09339, found *m/z* 465.09492 and 467.09270. ($C_{20}H_{26}O_2N_4{}^{79}Br^{32}S$ and $C_{20}H_{26}O_2N_4{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +84.4$ (c=0.32, $CHCl_3$).

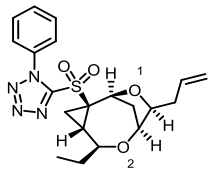
5-(((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-yl)sulfonyl)-1-phenyl-1*H*-tetrazole 7.10



Compound **7.9** (20.0 mg, 43.0 μmol) was dissolved in EtOH (0.4 mL) and the reaction mixture was cooled to 0 °C. A solution of 30% aq. H_2O_2 (40 μL) was mixed with $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (8.0 mg, 6.5 μmol) and the reaction mixture was cooled to 0 °C. The solution containing compound **7.9** was then mixed with the oxidant solution at 0 °C and then gradually warmed to r.t. and stirred overnight. TLC analyses have revealed that the reaction was not complete, thus a further addition of 30% aq. H_2O_2 (40 μL) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (8.0 mg, 6.5 μmol) as an oxidant solution at 0 °C was performed. The reaction was stirred at r.t. for a further 7 hours where TLC analysis indicated completion of the reaction. The reaction mixture was diluted with ethyl acetate, then the organic layer was separated, washed with sat. aq. $Na_2S_2O_3$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60) to give the desired compound **7.10** as a crispy white foam (16.4 mg, 33.0 μmol, 77%). R_f = 0.7 (50% EA/Pet. Ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H, Ar**H**), 7.65 – 7.62 (m, 1H, Ar**H**), 7.62 – 7.57 (m, 2H, Ar**H**), 5.73 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H, $OCHCH_2C\mathbf{H}$=CH'H), 5.12 (dq, *J* = 17.1, 1.6 Hz, 1H, $OCHCH_2CH$=C**H'**H), 5.07 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, $OCHCH_2CH$=CH'**H**), 4.79 (dd, *J* = 7.4, 5.3 Hz, 1H, $O_2CHCH'HC\mathbf{H}O_1$), 4.08 (q, *J* = 1.9 Hz, 1H, $O_2C\mathbf{H}CH'HCHO_1$), 3.91 – 3.78 (m, 3H, $BrCHCH'HC\mathbf{H}SO_2Ar$, $BrC\mathbf{H}CH'HCHSO_2Ar$, $OC\mathbf{H}CH_2CH$=CH'H), 3.56 (ddd, *J* = 10.8, 8.7, 2.5 Hz, 1H, $CH_3CH'HC\mathbf{H}$), 2.80 (dd, *J* = 15.5, 4.7 Hz, 1H, $BrCHC\mathbf{H'}HCHSO_2Ar$), 2.61 (d, *J* = 14.4 Hz, 1H, $O_2CHC\mathbf{H'}HCHO_1$), 2.42 – 2.37 (m, 2H, $OCHC\mathbf{H}_2CH$=CH'H), 2.33 (ddd, *J* = 15.4, 12.0, 9.7 Hz, 1H, $BrCHC\mathbf{H'}HCHSO_2Ar$), 2.16 (dqd, *J* = 14.0, 7.3, 2.5 Hz, 1H, $CH_3C\mathbf{H'}HCH$), 2.04 (ddd, *J* = 14.4, 7.7, 2.1 Hz, 1H, $O_2CHCH'\mathbf{H}CHO_1$), 1.61 – 1.55 (m, 1H, $CH_3CH'\mathbf{H}CH$), 0.97 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7 (tetrazole **C**), 133.8 ($OCHCH_2\mathbf{C}H$=CH'H), 133.1 (Ar**C**), 131.7 (Ar**C**), 129.7 (Ar**C**), 125.8 (Ar**C**), 117.9 ($OCHCH_2CH$=**C**H'H), 84.0 ($O\mathbf{C}HCH_2CH$=CH'H), 81.2 ($CH_3CH'H\mathbf{C}H$), 76.8 ($O_2\mathbf{C}HCH'HCHO_1$), 75.3 ($BrCHCH'H\mathbf{C}HSO_2Ar$), 73.5 ($O_2CHCH'H\mathbf{C}HO_1$), 51.4 ($Br\mathbf{C}HCH'HCHSO_2Ar$), 35.0 ($BrCH\mathbf{C}H'HCHSO_2Ar$), 34.1

(O_2CH**C**$H'HCHO_1$, OCH**C**$H_2CH{=}CH'H$), 28.2 (CH_3**C**$H'HCH$), 9.6 (**C**$H_3CH'HCH$). IR (ν_{max} cm^{-1}): 2961-2853 (aliphatic sp^3 C–H stretchings, broad), 1642 (C=C stretching, medium), 1595 (tetrazole C=C and C=N stretchings, medium), 1497 (tetrazole C=N and N=N stretchings, strong), 1346 (sulfone SO_2 antisymmetric stretching, strong), 1152 (sulfone SO_2 symmetric stretching, strong), 1063 (ether C–O–C antisymmetric stretching, strong), 760 (monosubstituted benzene C–H out of plane deformation, strong), 689 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 497.1 and 499.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 497.08527 and 499.08322, found *m/z* 497.08535 and 499.08308. ($C_{20}H_{26}O_4N_4{}^{79}Br{}^{32}S$ and $C_{20}H_{26}O_4N_4{}^{81}Br{}^{32}S$). $[\alpha]_D^{25} = +36.0$ (c=0.20, $CHCl_3$).

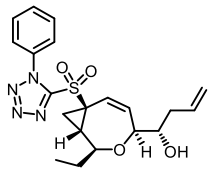
5-(((1*S*,2*R*,4*S*,5*R*,7*S*,8*S*)-8-Allyl-5-ethyl-6,9-dioxatricyclo[5.2.1.0^{2,4}]decan-2-yl)sulfonyl)-1-phenyl-1*H*-tetrazole 7.11



Compound **7.10** (6.5 mg, 13.0 μmol) was dissolved in dry THF (0.2 mL) and the reaction mixture was cooled to -78 °C. NaHMDS (0.14 mL, 0.1 M in THF, 14.0 μmol) was added at -78 °C where the solution turned from colourless to bright yellow. The reaction mixture was then gradually warmed to r.t. and the solution decolourised and became cloudy over 15 minutes. TLC analysis at this point indicated completion of reaction. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 to 50% EA/Pet. Ether 40-60) to give a mixture of **7.11** and **7.12**. This mixture underwent further purification by flash column chromatography (5% EA/DCM to 10% EA/DCM) to give **7.11** as a colourless oil (1.7 mg, 4.1 μmol, 31%). R_f = 0.57 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.66 (m, 2H, Ar**H**), 7.63 – 7.50 (m, 3H, Ar**H**), 5.53 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1H, OCHCH'HC**H**=CH'H), 5.23 (dd, *J* = 8.0, 1.5 Hz, 1H, $O_2CHCH'HC$**H**O_1), 5.00 (dq, *J* = 17.2, 1.6 Hz, 1H, OCHCH'HCH=C**H'**H), 4.95 (ddt, *J* = 10.3, 2.1, 1.1 Hz, 1H, OCHCH'HCH=CH'**H**), 4.15 (q, *J* = 1.9, 1.3 Hz, 1H, O_2C**H**$CH'HCHO_1$), 3.63 (ddd, *J* = 8.4, 6.1, 2.1 Hz, 1H, OC**H**CH'HCH=CH'H), 3.44 (q, *J* = 6.5 Hz, 1H, CH_3CH_2C**H**), 2.57 (dtd, *J* = 10.1, 7.1, 1.5 Hz, 1H, C**H**$CH'HCSO_2Ar$), 2.12 (d, *J* = 15.1 Hz, 1H, O_2CHC**H'**$HCHO_1$), 2.08 (dd, *J* = 10.1, 6.3 Hz, 1H, CHC**H'**$HCSO_2Ar$), 2.02 – 1.98 (m, 1H, OCHC**H'**HCH=CH'H), 1.97 – 1.91 (m, 1H, O_2CHCH'**H**CHO_1), 1.90 – 1.79 (m, 2H, CH_3C**H**$_2CH$), 1.60 (dt, *J* = 14.0, 6.8 Hz, 1H, OCHCH'**H**CH=CH'H), 1.16 (dd, *J* = 7.4, 6.3 Hz, 1H,

CHCH'**H**CSO$_2$Ar), 1.05 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH$_2$CH). ^{13}C NMR (126 MHz, CDCl$_3$) δ 155.1 (tetrazole **C**), 134.1 (Ar**C**), 134.0 (OCHCH'H**C**H=CH'H), 131.1 (Ar**C**), 129.1 (Ar**C**), 126.8 (Ar**C**), 117.5 (OCHCH'HCH=**C**H'H), 85.7 (O**C**HCH'HCH=CH'H), 76.5 (O$_2$CHCH'H**C**HO$_1$), 75.5 (O$_2$**C**HCH'HCHO$_1$), 73.7 (CH$_3$CH$_2$**C**H), 50.0 (CHCH'H**C**SO$_2$Ar), 32.3 (OCH**C**H'HCH=CH'H), 31.8 (O$_2$CH**C**H'HCHO$_1$), 31.5 (**C**HCH'HCSO$_2$Ar), 30.3 (CH$_3$**C**H$_2$CH), 15.6 (CH**C**H'HCSO$_2$Ar), 10.1 (**C**H$_3$CH$_2$CH). IR (ν_{max} cm^{-1}): 2962-2852 (aliphatic sp^3 C–H stretchings, broad), 1641 (C=C stretching, weak), 1596 (tetrazole C=C and C=N stretchings, weak), 1497 (tetrazole C=N and N=N stretchings, strong), 1348 (sulfone SO$_2$ antisymmetric stretching, strong), 1180 (sulfone SO$_2$ symmetric stretching, strong), 1051 (ether C–O–C antisymmetric stretching, strong), 761 (monosubstituted benzene C–H out of plane deformation, strong). LRMS (ESI) [M+H]$^+$: *m/z* 417.2. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 417.15910, found *m/z* 417.15919. (C$_{20}$H$_{25}$O$_4$N$_4$^{32}S). $[\alpha]_D^{25} = +107$ (c=0.10, $CHCl_3$).

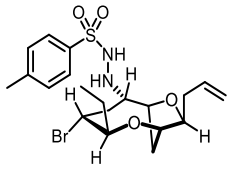
(*S*)-1-((1*S*,2*S*,4*S*,7*S*)-2-Ethyl-7-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)-3-oxabicyclo[5.1.0] oct-5-en-4-yl)but-3-en-1-ol 7.12



Compound **7.10** (6.5 mg, 13.0 μmol) was dissolved in dry THF (0.2 mL) and the reaction mixture was cooled to -78 °C. NaHMDS (0.14 mL, 0.1 M in THF, 14.0 μmol) was added at -78 °C where the solution turned from colourless to bright yellow. The reaction mixture was then gradually warmed to r.t. and the solution decolourised and became cloudy over 15 minutes. TLC analysis at this point indicated completion of reaction. The reaction mixture was quenched with sat. aq. NH$_4$Cl and extracted with ethyl acetate. The organic layer was dried with MgSO$_4$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 to 50% EA/Pet. Ether 40-60) to give a mixture of **7.11** and **7.12.** This mixture underwent further purification by flash column chromatography (5% EA/DCM to 10% EA/DCM) to give **7.12** as a colourless oil (3.2 mg, 7.7 μmol, 59%). R_f = 0.57 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 – 7.64 (m, 2H, Ar**H**), 7.63 – 7.60 (m, 1H, Ar**H**), 7.59 – 7.54 (m, 2H, Ar**H**), 6.08 (ddd, *J* = 11.8, 2.0, 1.3 Hz, 1H, OCHCH=C**H**), 5.80 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H, CHOHCH$_2$C**H**=CH$_2$), 5.62 (dd, *J* = 11.8, 2.6 Hz, 1H, OCHC**H**=CH), 5.14 – 5.07 (m, 2H, CHOHCH$_2$CH=C**H**$_2$), 4.10 (dt, *J* = 3.1, 2.3 Hz, 1H, OC**H**CH=CH), 3.51 (qd, *J* = 6.4, 3.2 Hz, 1H, C**H**OHCH$_2$CH=CH$_2$), 2.92 (ddd, *J* = 9.2, 7.4, 5.8 Hz, 1H, CH$_3$CH$_2$C**H**), 2.35 – 2.27 (m, 3H, CHOHC**H**$_2$CH=CH$_2$, C**H**CH'HCSO$_2$Ar), 2.15 (d, *J* = 6.1 Hz, 1H,

CHO**H**$CH_2CH{=}CH_2$), 2.11 (dd, *J* = 9.5, 5.5 Hz, 1H, CHC**H'**$HCSO_2Ar$), 1.72 – 1.65 (m, 2H, $CH_3C\mathbf{H}_2CH$), 1.32 (dd, *J* = 6.9, 5.5 Hz, 1H, CHCH'**H**CSO_2Ar, 0.97 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H}_3CH_2CH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1 (tetrazole **C**), 137.6 (OCH**C**H=CH), 134.5 ($CHOHCH_2\mathbf{C}H{=}CH_2$), 133.4 (Ar**C**), 131.5 (Ar**C**), 129.3 (Ar**C**), 126.5 (Ar**C**), 120.8 (OCHCH=**C**H), 118.1 ($CHOHCH_2CH{=}\mathbf{C}H_2$), 83.7 (O**C**HCH=CH), 81.3 ($CH_3CH_2\mathbf{C}H$), 72.6 (**C**$HOHCH_2CH{=}CH_2$), 44.3 (CHCH'H**C**SO_2Ar), 38.0 ($CHOH\mathbf{C}H_2CH{=}CH_2$), 32.9 (**C**HCH'$HCSO_2Ar$), 29.1 ($CH_3\mathbf{C}H_2CH$), 22.7 (CH**C**H'$HCSO_2Ar$), 10.2 (**C**$H_3CH_2CH$). IR ($\nu_{max}$ cm^{-1}): 3563-3466 (O–H stretching, broad), 2964-2853 (aliphatic sp^3 C–H stretchings, broad), 1641 (C=C stretching, weak), 1595 (tetrazole C=C and C=N stretchings, weak), 1498 (tetrazole C=N and N=N stretchings, strong), 1348 (sulfone SO_2 antisymmetric stretching, strong), 1168 (sulfone SO_2 symmetric stretching, strong), 1049 (ether C–O–C antisymmetric stretching, strong), 761 (monosubstituted benzene C–H out of plane deformation, strong). LRMS (ESI) $[M+H]^+$: *m/z* 417.2. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 417.15910, found *m/z* 417.15918. ($C_{20}H_{25}O_4N_4{}^{32}S$). $[\alpha]_D^{25} = +36.5$ (c=0.26, $CHCl_3$).

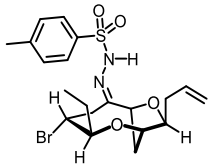
_N'_-((1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-yl)-4-methylbenzenesulfonohydrazide 7.17



The compound **5.19** (25.0 mg, 65.0 μmol) was dissolved in CH_2Cl_2 (6.5 mL) and the reaction mixture was cooled to -40 °C. A solution of $TiCl_4$ in CH_2Cl_2 (0.5 M, 0.26 mL, 0.13 mmol) was then added, quickly followed by $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (226.0 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) and stirred at -40 °C for 2 hours. The reaction mixture was then cooled to -78 °C, $TsNHNH_2$ (121.0 mg, 0.65 mmol) was added with $AgBF_4$ (128.0 mg, 0.65 mmol) and stirred at this temperature for 1 hour. TLC analysis at this stage indicated complete consumption of starting material. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and excess TBAI. The aqueous layer was extracted with CH_2Cl_2, and all the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 to 50% EA/Pet. Ether 40-60) to give the compound **7.17** as a white opaque oil (17.0 mg, 36.0 μmol, 55%). R_f = 0.34 (50% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.73 (m, 2H, Ar C–H), 7.40 – 7.29 (m, 2H, Ar C–H), 5.97 (s, 1H, $ArSO_2N\mathbf{H}NHCHCHCH'HCH$), 5.79 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, $OCHCH_2C\mathbf{H}CH'H$), 5.14 (dq, *J* = 17.2, 1.6 Hz, 1H, $OCHCH_2CHC\mathbf{H'}H$), 5.08 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H, $OCHCH_2CHCH'\mathbf{H}$), 3.97 (td, *J* = 2.4, 1.2 Hz, 1H,

$ArSO_2NHNHCHCHCH'HC\mathbf{H}$), 3.88 – 3.82 (m, 1H, $ArSO_2NHNHCHC\mathbf{H}CH'HCH$), 3.79 (td, *J* = 7.3, 2.5 Hz, 1H, $OC\mathbf{H}CH_2CHCH'H$), 3.41 (ddd, *J* = 10.8, 8.5, 2.5 Hz, 1H, $CH_3CH'HC\mathbf{H}CHBrCH'H$), 3.32 (s, 1H, $CH_3CH'HCHC\mathbf{H}BrCH'H$), 2.90 (dd, *J* = 9.5, 4.7 Hz, 1H, $ArSO_2NHNHC\mathbf{H}CHCH'HCH$), 2.44 (s, 3H, Ar $C\mathbf{H}_3$), 2.41 (d, *J* = 14.5 Hz, 1H, $ArSO_2NHNHCHCHC\mathbf{H'}HCH$), 2.34 (tt, *J* = 7.1, 1.3 Hz, 2H, $OCHC\mathbf{H}_2CHCH'H$), 2.22 (dd, *J* = 15.0, 4.7 Hz, 1H, $CH_3CH'HCHCHBrC\mathbf{H'}H$), 2.05 (dqd, *J* = 14.7, 7.4, 2.3 Hz, 1H, $CH_3C\mathbf{H'}HCHCHBrCH'H$), 1.85 – 1.76 (m, 2H, $ArSO_2NHNHCHCHCH'\mathbf{H}CH$, $CH_3CH'HCHCHBrCH'\mathbf{H}$), 1.38 (ddq, *J* = 14.7, 8.5, 7.3 Hz, 1H, $CH_3CH'\mathbf{H}CHCHBrCH'H$), 0.89 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH'HCHCHBrCH'H$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3 (Ar $\mathbf{C}H_3$), 135.5 (Ar $\mathbf{C}$-SO_2), 134.6 ($OCHCH_2\mathbf{C}HCH'H$), 129.8 (Ar **C**–H), 128.5 (Ar **C**–H), 117.4 ($OCHCH_2CH\mathbf{C}H'H$), 83.5 ($O\mathbf{C}HCH_2CHCH'H$), 80.7 ($ArSO_2NHNHCH\mathbf{C}HCH'HCH$), 80.5 ($CH_3CH'H\mathbf{C}HCHBrCH'H$), 76.9 ($ArSO_2NHNHCHCHCH'H\mathbf{C}H$), 67.3 ($ArSO_2NHNH\mathbf{C}HCHCH'HCH$), 53.1 ($CH_3CH'HCH\mathbf{C}HBrCH'H$), 39.2 ($CH_3CH'HCHCHBr\mathbf{C}H'H$), 34.5 ($OCH\mathbf{C}H_2CHCH'H$), 33.9 ($ArSO_2NHNHCHCH\mathbf{C}H'HCH$), 28.3 ($CH_3\mathbf{C}H'HCHCHBrCH'H$), 21.7 (Ar $\mathbf{C}H_3$), 9.6 ($\mathbf{C}H_3CH'HCHCHBrCH'H$). IR ($\nu_{max}$ cm^{-1}): 3252 (N–H stretching, broad), 2961-2855 (aliphatic sp^3 C–H stretchings, broad), 1663 (N–H distortion, medium), 1642 (C=C stretching, medium), 1328 (SO_2 antisymmetric stretching, strong), 1160 (SO_2 symmetric stretching, strong), 1092 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+Na]^+$: *m/z* 495.1 and 497.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 495.09236 and 497.09032, found *m/z* 495.09231 and 497.09014 ($C_{20}H_{29}O_4N_2{}^{79}BrNa^{32}S$ and $C_{20}H_{29}O_4N_2{}^{81}BrNa^{32}S$). $[\alpha]_D^{25} = +37.2$ (c=0.10, $CHCl_3$).

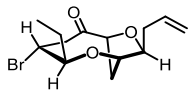
N'-((1*S*,3*S*,4*R*,7*S*,9*S*,*Z*)-9-allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-ylidene)-4-methylbenzenesulfonohydrazide 7.21



The compound **7.17** (7.8 mg, 17.0 μmol) was dissolved in THF (1.5 mL) at -78 °C, then a solution of NaHMDS (0.1 M in THF, 0.18 mL, 18.0 μmol) was added and stirring was continued for 15 minutes at -78 °C. The reaction mixture was warmed to room temperature afterwards. TLC at this stage indicated the complete consumption of starting materials. The reaction mixture was quenched with sat. aq. NH_4Cl, the aqueous layer was extract with ethyl acetate and all the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60) to give the compound **7.21** as a thick

colourless oil (5.6 mg, 12.0 μmol, 71%). R_f = 0.63 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H, $ArSO_2N$**H**N=CCHCH'HCH), 7.88 – 7.70 (m, 2H, Ar C–H), 7.42 – 7.27 (m, 2H, Ar C–H), 5.64 (ddt, *J* = 17.0, 10.3, 7.4, 6.7 Hz, 1H, OCHCH'HC**H**CH_2), 5.10 – 4.95 (m, 2H, OCHCH'HCHC**H**$_2$), 4.79 (d, *J* = 7.3 Hz, 1H, $ArSO_2NHN$=CC**H**CH'HCH), 4.02 (q, *J* = 1.9 Hz, 1H, $ArSO_2NHN$=CCHCH'HC**H**), 3.79 (ddd, *J* = 7.8, 6.7, 2.3 Hz, 1H, OC**H**CH'HCHCH_2), 3.54 (td, *J* = 10.8, 4.5 Hz, 1H, CH_3CH'HCHC**H**BrCH'H), 3.47 (ddd, *J* = 10.4, 7.3, 2.5 Hz, 1H, CH_3CH'HC**H**CHBrCH'H), 2.98 (dd, *J* = 13.7, 4.4 Hz, 1H, CH_3CH'HCHCHBrC**H'**H), 2.66 (dd, *J* = 14.1, 1.4 Hz, 1H, $ArSO_2NHN$=CCHC**H'**HCH), 2.60 (dd, *J* = 13.7, 11.4 Hz, 1H, CH_3CH'HCHCHBrCH'**H**), 2.41 (s, 3H, Ar C**H**$_3$), 2.07 (dt, *J* = 14.0, 7.8, 6.7 Hz, 1H, OCHC**H'**HCHCH_2), 2.02 – 1.91 (m, 2H, $ArSO_2NHN$=CCHCH'**H**CH, CH_3C**H'**HCHCHBrCH'H), 1.87 (dt, *J* = 14.0, 7.4, 6.7 Hz, 1H, OCHCH'**H**CHCH_2), 1.44 (dp, *J* = 14.5, 7.3 Hz, 1H, CH_3CH'**H**CHCHBrCH'H), 0.81 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHCHBrCH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3 ($ArSO_2NHN$=**C**CHCH'HCH), 143.8 (Ar CH_3–C), 136.2 (Ar **C**-SO_2), 133.5 (OCHCH'H**C**HCH_2), 129.4 (Ar **C**–H), 127.9 (Ar **C**–H), 117.9 (OCHCH'HCH**C**H_2), 83.2 (O**C**HCH'HCHCH_2), 80.8 (CH_3CH'H**C**HCHBrCH'H), 76.6 ($ArSO_2NHN$=CCHCH'H**C**H), 75.9 ($ArSO_2NHN$=C**C**HCH'HCH), 53.5 (CH_3CH'HCH**C**HBrCH'H), 43.6 (CH_3CH'HCHCHBr**C**H'H), 34.2 ($ArSO_2NHN$=CCH**C**H'HCH), 33.3 (OCH**C**H'HCHCH_2), 27.4 (CH_3**C**H'HCHCHBrCH'H), 21.7 (Ar **C**H_3–C), 8.8 (**C**H_3CH'HCHCHBrCH'H). IR (ν_{max} cm^{-1}): 3184 (N–H stretching, broad), 2953-2854 (aliphatic sp^3 C–H stretchings, broad), 1731 (C=N stretching, unusually high wavenumber, strong; the corresponding ketone **7.22** C=O stretching is at 1713 cm^{-1}), 1644 (C=C stretching, medium), 1376 (SO_2 antisymmetric stretching, strong), 1168 (SO_2 symmetric stretching, strong), 1094 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+H]$^+$: *m/z* 471.1 and 473.1. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 471.09477 and 473.09272, found *m/z* 471.09499 and 473.09273 ($C_{20}H_{28}O_4N_2{}^{79}Br^{32}S$ and $C_{20}H_{28}O_4N_2{}^{81}Br^{32}S$). $[\alpha]_D^{25} = +21.7$ (c=0.30, $CHCl_3$).

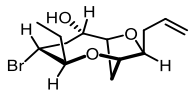
(1*S*,3*S*,4*R*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-one 7.22



The compound **7.25** (10.0 mg, 33.0 μmol) was dissolved in CH_2Cl_2 (0.7 mL) at room temperature. Dess-Martin periodinane (17.0 mg, 39.0 μmol) was added and the reaction mixture stirring was continued for 1 hour. TLC analysis at this stage indicated the complete consumption of starting material. The reaction mixture was quenched with

sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60) to give the compound **7.22** as a colourless oil (8.5 mg, 28.0 μmol, 85%). R_f = 0.57 (10% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, OCHCH'HC**H**CH'H), 5.14 (dq, *J* = 17.2, 1.6 Hz, 1H, OCHCH'HCHC**H'**H), 5.07 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, OCHCH'HCHCH'**H**), 4.26 (d, *J* = 7.1 Hz, 1H, O=CC**H**CH'HCH), 4.19 (q, *J* = 1.9 Hz, 1H, O=CCHCH'HC**H**), 3.98 (ddd, *J* = 11.4, 10.3, 5.2 Hz, 1H, CH_3CH'HCHC**H**BrCH'H), 3.92 (ddd, *J* = 8.7, 6.3, 2.4 Hz, 1H, OC**H**CH'HCHCH'H), 3.58 (ddd, *J* = 10.7, 8.4, 2.6 Hz, 1H, CH_3CH'HC**H**CHBrCH'H), 3.00 (t, *J* = 11.5 Hz, 1H, CH_3CH'HCHCHBrC**H'**H), 2.95 – 2.85 (m, 2H, O=CCHC**H'**HCH, CH_3CH'HCHCHBrCH'**H**), 2.53 – 2.44 (m, 1H, OCHC**H'**HCHCH'H), 2.40 (dddt, *J* = 13.8, 8.6, 7.4, 1.2 Hz, 1H, OCHCH'**H**CHCH'H), 2.15 – 2.06 (m, 2H, O=CCHCH'**H**CH, CH_3C**H'**HCHCHBrCH'H), 1.55 – 1.48 (m, 1H, CH_3CH'**H**CHCHBrCH'H), 0.96 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCHCHBrCH'H). 13C NMR (126 MHz, $CDCl_3$) δ 206.5 (O=**C**CHCH'HCH), 134.2 (OCHCH'H**C**HCH'H), 117.7 (OCHCH'HCH**C**H'H), 83.2 (O**C**HCH'HCHCH'H), 81.2 (CH_3CH'H**C**HCHBrCH'H), 79.9 (O=C**C**HCH'HCH), 77.1 (O=CCHCH'H**C**H), 51.7 (CH_3CH'HCH**C**HBrCH'H), 46.8 (CH_3CH'HCHCHBr**C**H'H), 34.6 (O=CCH**C**H'HCH), 33.9 (OCH**C**H'HCHCH'H), 27.0 (CH_3**C**H'HCHCHBrCH'H), 9.6 (**C**H_3CH'HCHCHBrCH'H). IR (ν_{max} cm^{-1}): 2963-2921 (aliphatic sp^3 C–H stretchings, broad), 1713 (ketone C=O stretching, strong), 1641 (C=C stretching, medium), 1080 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 325.0 and 327.0. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 325.04098 and 327.03893, found *m/z* 325.04102 and 327.03891 ($C_{13}H_{19}O_3{}^{79}BrNa$ and $C_{13}H_{19}O_3{}^{81}BrNa$). $[\alpha]_D^{25} = +10.0$ (c=0.30, $CHCl_3$).

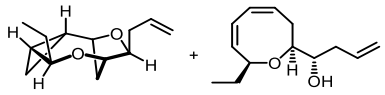
(1*S*,3*S*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-ol 7.25



The compound **5.19** (55.0 mg, 0.147 mmol) was dissolved in CH_2Cl_2 (12.0 mL) and the reaction mixture was cooled to -40 °C. A solution of $TiCl_4$ in CH_2Cl_2 (0.5 M, 0.58 mL, 0.288 mmol) was then added, quickly followed by $AgAl(pftb)_4 \cdot CH_2Cl_2$ (501.0 mg, 0.432 mmol) in CH_2Cl_2 (2.0 mL) and stirred at -40 °C for 2 hours. The reaction mixture was then cooled to -78 °C, AgOBz (315.0 mg, 1.44 mmol) was added and stirred at this temperature for 1 hour. TLC analysis at this stage indicated complete consumption of

starting material. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and excess TBAI. The aqueous layer was extracted with CH_2Cl_2, and all the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and filtered through a plug of silica gel (50% EA/Pet. Ether 40-60) to give a mixture of **7.29** and **7.25**. The mixture was dissolved in MeOH (5.0 mL) and K_2CO_3 (203.0 mg, 1.47 mmol) was added and stirring was continued for 2 hours. TLC analysis at this stage indicated complete consumption of starting material. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60) to give the compound **7.25** as a colourless oil (33.4 mg, 0.109 mmol, 74%). R_f = 0.31 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, OCHCH$_2$C**H**CH'H), 5.14 (dq, *J* = 17.2, 1.6 Hz, 1H, OCHCH$_2$CHC**H'**H), 5.06 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H, OCHCH$_2$CHCH'**H**), 4.18 (dd, *J* = 8.0, 3.8 Hz, 1H, CHOHC**H**CH'HCH), 4.03 (td, *J* = 2.4, 1.1 Hz, 1H, CHOHCHCH'HC**H**), 3.96 (dt, *J* = 9.0, 4.1 Hz, 1H, C**H**OHCHCH'HCH), 3.87 – 3.84 (m, 1H, CH$_3$CH'HCHC**H**BrCH'H), 3.84 – 3.79 (m, 1H, OC**H**CH$_2$CHCH'H), 3.50 (td, *J* = 9.4, 2.6 Hz, 1H, CH$_3$CH'HC**H**CHBrCH'H), 2.52 (d, *J* = 14.4 Hz, 1H, CHOHCHC**H'**HCH), 2.48 – 2.34 (m, 4H, CHO**H**CHCH'HCH, OCHC**H**$_2$CHCH'H, CH$_3$CH'HCHCHBrC**H'**H), 2.27 (dt, *J* = 15.1, 9.8 Hz, 1H, CH$_3$CH'HCHCHBrCH'**H**), 2.09 (dqd, *J* = 14.7, 7.4, 2.6 Hz, 1H, CH$_3$C**H'**HCHCHBrCH'H), 1.89 (ddd, *J* = 14.3, 8.0, 2.5 Hz, 1H, CHOHCHCH'**H**CH), 1.48 (ddq, *J* = 14.3, 9.0, 7.3 Hz, 1H, CH$_3$CH'**H**CHCHBrCH'H), 0.95 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCHCHBrCH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.7 (OCHCH$_2$**C**HCH'H), 117.4 (OCHCH$_2$CH**C**H'H), 83.7 (CHOH**C**HCH'HCH), 83.4 (O**C**HCH$_2$CHCH'H), 80.4 (CH$_3$CH'H**C**HCHBrCH'H), 77.9 (**C**HOHCHCH'HCH), 76.8 (CHOHCHCH'H**C**H), 53.1 (CH$_3$CH'HCH**C**HBrCH'H), 42.2 (CH$_3$CH'HCHCHBr**C**H'H), 34.3 (OCH**C**H$_2$CHCH'H), 33.3 (CHOHCH**C**H'HCH), 28.3 (CH$_3$**C**H'HCHCHBrCH'H), 9.8 (**C**H$_3$CH'HCHCHBrCH'H). IR (ν_{max} cm^{-1}): 3394 (O–H stretching, broad), 2961-2918 (aliphatic sp^3 C–H stretchings, broad), 1642 (C=C stretching, medium), 1100 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 327.1 and 329.1. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 327.05663 and 329.05458, found *m/z* 327.05666 and 329.05462 ($C_{13}H_{21}O_3{}^{79}BrNa$ and $C_{13}H_{21}O_3{}^{81}BrNa$). $[\alpha]_D^{25} = +46.7$ (c=0.60, $CHCl_3$).

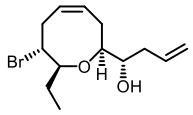
(1*S*,2*S*,4*R*,5*S*,7*S*,8*S*)-8-Allyl-5-ethyl-6,9-dioxatricyclo[5.2.1.0^{2,4}]decane 7.30 and (*S*)-1-((2*S*,4*Z*,6*Z*,8*S*)-8-ethyl-3,8-dihydro-2*H*-oxocin-2-yl)but-3-en-1-ol 7.31



The compound **7.22** (6.0 mg, 20.0 μmol) was dissolved in EtOH (0.4 mL) and a solution of $N_2H_4{\cdot}H_2O$ in EtOH (1.0 M, 51.0 μL, 51.0 μmol) was added. The reaction mixture was stirred at room temperature till reaction completion as suggested by TLC analysis. All volatiles were removed under reduced pressure to yield the crude hydrazone. In parallel with the preparation of the hydrazone, DMSO (4.0 mL) was mixed with NaH (27.0 mg, 0.7 mmol) and heated to 60 °C for 3 hours. The resulting dimsyl anion solution was cooled to room temperature. The crude hydrazone was then mixed with the dimsyl anion solution (0.44 mL) at room temperature and stirring was continued for 1 hour, in which effervescence was observed upon addition of the dimsyl anion solution. TLC analysis at this stage indicated the complete consumption of starting materials. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (15% EA/Pet. Ether 40-60) to give an inseparable mixture of compounds **7.30** and **7.31** as a colourless oil (2.5 mg, 12.0 μmol, 60%, **7.30**:**7.31** = 4.5:1). R_f = 0.69 (30% EA/Pet. Ether 40-60). NMR characterisation for **7.30**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 – 5.85 (m, 1H, OCHCH'HC**H**CH'H), 5.15 (d, *J* = 17.2 Hz, 1H, OCHCH'HCHC**H'**H), 5.05 (d, *J* = 10.2 Hz, 1H, OCHCH'HCHCH'**H**), 4.73 (d, *J* = 7.4 Hz, 1H, CHC**H**CH'HCH), 4.25 (t, *J* = 3.8 Hz, 1H, CHCHCH'HC**H**), 3.82 (td, *J* = 7.0, 3.3 Hz, 1H, OC**H**CH'HCHCH'H), 3.35 (q, *J* = 6.7 Hz, 1H, CH_3CH_2C**H**CHCH'H), 2.60 – 2.53 (m, 1H, OCHC**H'**HCHCH'H), 2.47 (dt, *J* = 14.5, 7.6 Hz, 1H, OCHCH'**H**CHCH'H), 2.05 (d, *J* = 14.5 Hz, 1H, CHCHC**H'**HCH), 1.75 – 1.61 (m, 3H, CHCHCH'**H**CH, CH_3C**H**$_2$CHCHCH'H), 1.11 (q, *J* = 8.4 Hz, 1H, C**H**CHCH'HCH), 0.95 (m, 4H, CH_3CH_2CHC**H**CH'H, C**H**$_3CH_2CHCHCH$'H), 0.78 (td, *J* = 8.6, 5.1 Hz, 1H, CH_3CH_2CHCHC**H'**H), 0.24 (q, *J* = 5.5 Hz, 1H, $CH_3CH_2CHCHCH$'**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2 (OCHCH'H**C**HCH'H), 116.5 (OCHCH'HCH**C**H'H), 84.7 (O**C**HCH'HCHCH'H), 78.8 (CH**C**HCH'HCH), 76.8 (CHCHCH'H**C**H), 76.4 (CH_3CH_2**C**HCHCH'H), 35.6 (OCH**C**H'HCHCH'H), 30.4 (CH_3**C**$H_2CHCHCH$'H), 30.2 (CHCH**C**H'HCH), 22.8 (CH_3CH_2CH**C**HCH'H), 20.9 (**C**HCHCH'HCH), 10.4 (**C**$H_3CH_2CHCHCH$'H), 9.0 (CH_3CH_2CHCH**C**H'H). NMR characterisation for **7.31**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (dd, *J* = 11.1, 3.4 Hz, 1H, CHCHC**H**CHCH'H), 6.02 – 5.96 (m, 1H, CHC**H**CHCHCH'H), 5.96 – 5.85 (m, 1H, OCHCHOHCH'HC**H**CH'H), 5.79 (q, *J* = 8.9 Hz, 1H, CHCHCHC**H**CH'H), 5.51 (dd,

J = 11.1, 6.9 Hz, 1H, C**H**CHCHCHCH'H), 5.15 (d, *J* = 17.2 Hz, 1H, OCHCHOHCH'HCHC**H'**H), 5.10 (d, *J* = 11.3 Hz, 1H, OCHCHOHCH'HCHCH'**H**), 3.56 (p, *J* = 5.4, 4.7 Hz, 1H, OCHC**H**OHCH'HCHCH'H), 3.50 (q, *J* = 6.4 Hz, 1H, CH_3CH_2C**H**), 3.01 (t, *J* = 6.4 Hz, 1H, OC**H**CHOHCH'HCHCH'H), 2.60 – 2.53 (m, 2H, OCHCHO**H**CH'HCHCH'H, CHCHCHCHC**H'**H), 2.47 (dt, *J* = 14.5, 7.6 Hz, 1H, OCHCHOHC**H'**HCHCH'H), 2.32 (dt, *J* = 14.3, 7.4 Hz, 1H, OCHCHOHCH'**H**CHCH'H), 1.95 (dt, *J* = 14.4, 7.4 Hz, 1H, CHCHCHCHCH'**H**), 1.75 – 1.61 (m, 2H, CH_3C**H**$_2$CH), 0.95 (m, 3H, C**H**$_3CH_2CH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2 (OCHCHOHCH'H**C**HCH'H), 133.1 (**C**HCHCHCHCH'H), 129.4 (CHCHCH**C**HCH'H), 129.0 (CHCH**C**HCHCH'H), 127.5 (CH**C**HCHCHCH'H), 117.4 (OCHCHOHCH'HCH**C**H'H), 78.2 (CH_3CH_2**C**H), 76.7 (O**C**HCHOHCH'HCHCH'H), 74.1 (OCH**C**HOHCH'HCHCH'H), 38.3 (OCHCHOH**C**H'HCHCH'H), 32.6 (CHCHCHCH**C**H'H), 30.3(CH_3**C**H_2CH), 9.0 (**C**H_3CH_2CH). LRMS (ESI) $[M+Na]^+$: *m/z* 231.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 231.13555, found *m/z* 231.13576 ($C_{13}H_{20}O_2Na$).

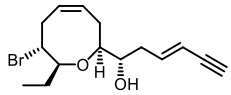
(*S*)-1-((2*S*,7*R*,8*S*,*Z*)-7-Bromo-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)but-3-en-1-ol 7.8



The compound **7.22** (10.5 mg, 35.0 μmol) was dissolved in EtOH (0.7 mL) at room temperature. A solution of $N_2H_4{\cdot}H_2O$ in EtOH (1.0 M, 90.0 μL, 90.0 μmol) was added. The reaction mixture was stirred at room temperature till reaction completion as suggested by TLC analysis. All volatiles were removed under reduced pressure to yield the crude hydrazone. The crude hydrazone was dissolved in THF (1.0 mL) and the reaction mixture was cooled to -78 °C, a solution of NaHMDS in THF (0.1 M, 0.39 mL, 39.0 μmol) was added and gradually warmed to room temperature. Effervescence was observed during the warming of the reaction mixture. TLC analysis at this stage indicated the complete consumption of starting materials. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (3% EA/CH_2Cl_2 to 5% EA/CH_2Cl_2) to give the compound **7.8** as a colourless oil (4.2 mg, 14.5 μmol, 42%), with trace **7.31** that was discarded after column chromatography. R_f = 0.60 (5% EA/CH_2Cl_2). ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.05 – 5.93 (m, 1H, BrCHCH'HCHC**H**CH'H), 5.93 – 5.84 (m, 2H, OCHCHOHCH'HC**H**CH_2, BrCHCH'HC**H**CHCH'H), 5.24 – 5.02 (m, 2H, OCHCHOHCH'HCHC**H**$_2$), 4.09 (dt, *J* = 10.2, 3.4 Hz, 1H, BrC**H**CH'HCHCHCH'H),

3.57 – 3.54 (m, 1H, OCHC**H**OHCH'HCHCH$_2$), 3.54 – 3.51 (m, 1H, CH$_3$CH'HC**H**), 3.24 (dd, *J* = 10.6, 5.6 Hz, 1H, OC**H**CHOHCH'HCHCH$_2$), 3.17 (ddd, *J* = 13.9, 9.3, 3.5 Hz, 1H, BrCHC**H'**HCHCHCH'H), 2.48 (ddd, *J* = 14.0, 6.2, 3.3 Hz, 1H, BrCHCH'**H**CHCHCH'H), 2.46 – 2.41 (m, 2H, OCHCHO**H**CH'HCHCH$_2$, BrCHCH'HCHCHC**H'**H), 2.41 – 2.36 (m, 1H, OCHCHOHC**H'**HCHCH$_2$), 2.24 (dtd, *J* = 14.2, 7.8, 1.3 Hz, 1H, OCHCHOHCH'**H**CHCH$_2$), 2.14 (dd, *J* = 14.3, 8.4 Hz, 1H, BrCHCH'HCHCHCH'**H**), 1.98 (dqd, *J* = 14.9, 7.4, 2.5 Hz, 1H, CH$_3$C**H'**HCH), 1.64 (dp, *J* = 14.6, 7.4 Hz, 1H, CH$_3$CH'**H**CH), 0.98 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (176 MHz, $CDCl_3$) δ 134.8 (OCHCHOHCH'H**C**HCH$_2$), 129.8 (BrCHCH'HCH**C**HCH'H), 128.8 (BrCHCH'H**C**HCHCH'H), 117.7 (OCHCHOHCH'HCH**C**H$_2$), 83.9 (O**C**HCHOHCH'HCHCH$_2$), 83.8 (CH$_3$CH'H**C**H), 73.6 (OCH**C**HOHCH'HCHCH$_2$), 55.9 (Br**C**HCH'HCHCHCH'H), 38.2 (OCHCHOH**C**H'HCHCH$_2$), 32.5 BrCH**C**H'HCHCHCH'H), 30.8 BrCHCH'HCHCH**C**H'H), 25.8 (CH$_3$**C**H'HCH), 9.3 (**C**H$_3$CH'HCH). IR (ν_{max} cm^{-1}): 3446 (O–H stretching, broad), 2962-2923 (aliphatic sp^3 C–H stretchings, broad), 1641 (C=C stretching, medium), 1064 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M–Br+Na]$^+$: *m/z* 231.1. HRMS (ESI) [M–Br+Na]$^+$: calculated for *m/z* 231.13555, found *m/z* 231.13573 ($C_{13}H_{20}O_2Na$). $[\alpha]_D^{25} = -11.2$ (c=0.42, $CHCl_3$).

(*S*,*E*)-1-((2*S*,7*R*,8*S*,*Z*)-7-Bromo-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)hex-3-en-5-yn-1-ol *ent*-deacetyllaurencin *ent*-1.38

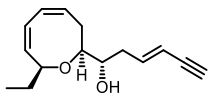


The compound **7.34** (9.9 mg, 30.3 μmol) was dissolved in EtOH (0.55 mL) at room temperature. A solution of $N_2H_4{\cdot}H_2O$ in EtOH (1.0 M, 80.0 μL, 80.0 μmol) was added. The reaction mixture was stirred at room temperature till reaction completion as suggested by TLC analysis. All volatiles were removed under reduced pressure to yield the crude hydrazone. The crude hydrazone was dissolved in THF (1.0 mL) and the reaction mixture was cooled to -78 °C, a solution of NaHMDS in THF (0.1 M, 0.66 mL, 66.0 μmol) was added and gradually warmed to room temperature. Effervescence was observed during the warming of the reaction mixture. TLC analysis at this stage indicated the complete consumption of starting materials. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (1% EA/CH_2Cl_2 to 2% EA/CH_2Cl_2) to give a separable mixture of the compound ***ent*-1.38** (3.0 mg, 9.6 μmol, 32%) and **7.35** (0.8 mg, 3.4 μmol, 11%) as a colourless oils. R_f for ***ent*-1.38** = 0.71 (3% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 15.2, 7.2 Hz, 1H,

OCHCHOHCH'HC**H**CHC≡CH), 5.96 (dt, *J* = 10.6, 7.7 Hz, 1H, BrCHCH'HCHC**H**CH'H), 5.93 – 5.84 (m, 1H, BrCHCH'HC**H**CHCH'H), 5.57 (dq, *J* = 16.0, 1.8 Hz, 1H, OCHCHOHCH'HCHC**H**C≡CH), 4.08 (dt, *J* = 10.0, 3.5 Hz, 1H, BrC**H**CH'HCHCHCH'H), 3.58 – 3.54 (m, 1H, OCHC**H**OHCH'HCHCHC≡CH), 3.54 – 3.50 (m, 1H, CH_3CH'HC**H**), 3.22 (ddd, *J* = 10.5, 5.8, 1.3 Hz, 1H, OC**H**CHOHCH'HCHCHC≡CH), 3.15 (ddd, *J* = 13.1, 9.0, 3.6 Hz, 1H, BrCHC**H'**HCHCHCH'H), 2.83 (d, *J* = 2.3 Hz, 1H, OCHCHOHCH'HCHCHC≡C**H**), 2.48 (ddd, *J* = 14.0, 6.0, 3.2 Hz, 1H, BrCHCH'**H**CHCHCH'H), 2.43 (d, *J* = 4.5 Hz, 1H, OCHCHO**H**CH'HCHCHC≡CH), 2.45 – 2.38 (m, 2H, OCHCHOHC**H'**HCHCHC≡CH, BrCHCH'HCHCHC**H'**H), 2.35 – 2.26 (m, 1H, OCHCHOHCH'**H**CHCHC≡CH), 2.11 (ddd, *J* = 14.3, 8.2, 1.4 Hz, 1H, BrCHCH'HCHCHCH'**H**), 1.97 (dqd, *J* = 14.9, 7.5, 2.8 Hz, 1H, CH_3C**H'**HCH), 1.64 (dp, *J* = 14.4, 7.2 Hz, 1H, CH_3CH'**H**CH), 0.97 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3 (OCHCHOHCH'H**C**HCHC≡CH), 129.6 (BrCHCH'HCH**C**HCH'H), 128.9 (BrCHCH'H**C**HCHCH'H), 111.4 (OCHCHOHCH'HCH**C**HC≡CH), 83.8 (CH_3CH'H**C**H), 83.7 (O**C**HCHOHCH'HCHCHC≡CH), 82.2 (OCHCHOHCH'HCHCH**C**≡CH), 76.6 (OCHCHOHCH'HCHCHC≡**C**H), 73.5 (OCH**C**HOHCH'HCHCHC≡CH), 55.6 (Br**C**HCH'HCHCHCH'H), 37.4 (OCHCHOH**C**H'HCHCHC≡CH), 32.5 (BrCH**C**H'HCHCHCH'H), 30.8 (BrCHCH'HCHCH**C**H'H), 25.8 (CH_3**C**H'HCH), 9.2 (**C**H_3CH'HCH). ^{1}H NMR (500 MHz, C_6D_6) δ 6.33 (dt, *J* = 16.1, 7.2 Hz, 1H, OCHCHOHCH'HC**H**CHC≡CH), 5.85 (ddd, *J* = 10.6, 9.4, 6.2 Hz, 1H, BrCHCH'HCHC**H**CH'H), 5.63 (dt, *J* = 10.6, 7.8 Hz, 1H, BrCHCH'HC**H**CHCH'H), 5.45 (dq, *J* = 16.0, 1.8 Hz, 1H, OCHCHOHCH'HCHC**H**C≡CH), 3.75 (dt, *J* = 10.0, 3.4 Hz, 1H, BrC**H**CH'HCHCHCH'H), 3.31 (ddd, *J* = 9.8, 6.9, 2.7 Hz, 1H, CH_3CH'HC**H**), 3.16 (dq, *J* = 9.2, 4.8 Hz, 1H, OCHC**H**OHCH'HCHCHC≡CH), 2.85 (ddd, *J* = 13.5, 9.4, 3.6 Hz, 1H, BrCHC**H'**HCHCHCH'H), 2.74 (ddd, *J* = 10.6, 5.3, 1.4 Hz, 1H, OC**H**CHOHCH'HCHCHC≡CH), 2.57 (d, *J* = 2.3 Hz, 1H, OCHCHOHCH'HCHCHC≡C**H**), 2.24 (ddd, *J* = 14.0, 6.2, 3.2 Hz, 1H, BrCHCH'**H**CHCHCH'H), 2.12 – 2.04 (m, 1H, BrCHCH'HCHCHC**H'**H), 2.01 (dddt, *J* = 14.8, 7.1, 4.0, 1.8 Hz, 1H, OCHCHOHC**H'**HCHCHC≡CH), 1.92 (dtd, *J* = 14.7, 7.7, 1.6 Hz, 1H, OCHCHOHCH'**H**CHCHC≡CH), 1.86 (d, *J* = 5.0 Hz, 1H, OCHCHO**H**CH'HCHCHC≡CH), 1.81 (dqd, *J* = 14.9, 7.4, 2.7 Hz, 1H, CH_3C**H'**HCH), 1.64 (ddd, *J* = 14.3, 8.5, 1.3 Hz, 1H, BrCHCH'HCHCHCH'**H**), 1.42 (dqd, *J* = 14.9, 7.4, 6.9 Hz, 1H, CH_3CH'**H**CH), 0.77 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, C_6D_6) δ 142.8 (OCHCHOHCH'H**C**HCHC≡CH), 129.9 (BrCHCH'HCH**C**HCH'H), 128.6 (BrCHCH'H**C**HCHCH'H), 111.5 (OCHCHOHCH'HCH**C**HC≡CH), 83.7 (O**C**HCHOHCH'HCHCHC≡CH), 83.6

($CH_3CH'HC\mathbf{H}$), 83.6 (O**C**HCHOHCH'HCHCHC≡CH), 82.5 (OCHCHOHCH'HCHCH**C**≡CH), 77.1 (OCHCHOHCH'HCHCHC≡**C**H), 73.3 (OCH**C**HOHCH'HCHCHC≡CH), 56.1 (Br**C**HCH'HCHCHCH'H), 37.2 (OCHCHOH**C**H'HCHCHC≡CH), 32.5 (BrCH**C**H'HCHCHCH'H), 30.4 (BrCHCH'HCHCH**C**H'H), 26.0 (CH_3**C**H'HCH), 9.1 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3441 (O–H stretching , broad), 3293 (acetylene C–H stretching, medium), 2922 (aliphatic sp^3 C–H stretchings, broad), 2103 (C≡C stretching, weak), 1668 (C=C stretching, medium), 1059 (ether C–O–C antisymmetric stretching, strong). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 313.08087 and 315.07882, found *m/z* 313.07988 and 315.07777 ($C_{15}H_{22}O_2{}^{79}Br$ and $C_{15}H_{22}O_2{}^{81}Br$). $[\alpha]_D^{25} = -34.7$ (c=0.05, $CHCl_3$). Literature value of enantiomer: $[\alpha]_D^{17} = +46.1$ ($c = 1.15, CHCl_3$).[249] Spectroscopic data are in accordance with literature data.[23,249]

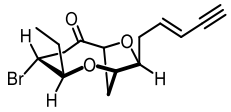
(*S*,*E*)-1-((2*S*,4*Z*,6*Z*,8*S*)-8-Ethyl-3,8-dihydro-2*H*-oxocin-2-yl)hex-3-en-5-yn-1-ol 7.35



This compound was obtained as a side product in the synthesis of *ent*-deacetyllaurencin ***ent*-1.38** and thus share the same experimental procedure (*see above*). The compound **7.35** was isolated as a colourless oil (0.8 mg, 3.4 μmol, 11%). R_f for **7.35** = 0.54 (3% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 16.2, 7.2 Hz, 1H, OCHCHOHCH'HC**H**CHC≡CH), 6.10 (dd, *J* = 10.8, 3.8 Hz, 1H, CHCHC**H**CHCH'H), 5.99 (dd, *J* = 11.2, 3.5 Hz, 1H, CHC**H**CHCHCH'H), 5.79 (dt, *J* = 10.8, 8.3 Hz, 1H, CHCHCHC**H**CH'H), 5.57 (dq, *J* = 16.0, 1.8 Hz, 1H, OCHCHOHCH'HCHC**H**C≡CH), 5.51 (dd, *J* = 11.1, 6.9 Hz, 1H, C**H**CHCHCHCH'H), 3.57 (dq, *J* = 7.4, 5.0 Hz, 1H, OCHC**H**OHCH'HCHCHC≡CH), 3.54 – 3.46 (m, 1H, $CH_3CH'HC\mathbf{H}$), 2.99 (ddd, *J* = 7.1, 5.5, 1.8 Hz, 1H, OC**H**CHOHCH'HCHCHC≡CH), 2.82 (d, *J* = 2.3 Hz, 1H, OCHCHOHCH'HCHCHC≡C**H**), 2.52 (d, *J* = 5.0 Hz, 1H, OCHCHO**H**CH'HCHCHC≡CH), 2.52 – 2.49 (m, 1H, CHCHCHCHC**H'**H), 2.49 – 2.46 (m, 1H, OCHCHOHC**H'**HCHCHC≡CH), 2.39 (dtd, *J* = 14.7, 7.4, 1.4 Hz, 1H, OCHCHOHCH'**H**CHCHC≡CH), 1.94 (dt, *J* = 14.4, 7.7 Hz, 1H, CHCHCHCHCH'**H**), 1.68 (dq, *J* = 15.1, 7.5 Hz, 1H, CH_3C**H'**HCH), 1.63 – 1.58 (m, 1H, CH_3CH'**H**CH), 0.93 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7 (OCHCHOHCH'H**C**HCHC≡CH), 133.0 (**C**HCHCHCHCH'H), 129.3 (CHCHCH**C**HCH'H), 129.2 (CHCH**C**HCHCH'H), 127.6 (CH**C**HCHCHCH'H), 111.1 (OCHCHOHCH'HCH**C**HC≡CH), 82.4 (OCHCHOHCH'HCHCH**C**≡CH), 78.1 ($CH_3CH'H\mathbf{C}H$), 76.6 (O**C**HCHOHCH'HCHCHC≡CH), 76.4

(OCHCHOHCH'HCHCHC≡**C**H), 74.0 (OCH**C**HOHCH'HCHCHC≡CH), 37.6 (OCHCHOH**C**H'HCHCHC≡CH), 32.7 (CHCHCHCH**C**H'H), 30.2 (CH_3**C**H'HCH), 10.3 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3454 (O–H stretching , broad), 3310 (acetylene C–H stretching, medium), 2960-2853 (aliphatic sp^3 C–H stretchings, broad), 2103 (C≡C stretching, weak), 1667 (C=C stretching, medium), 1063 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 233.2. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 233.15361, found *m/z* 233.15371 ($C_{15}H_{21}O_2$). $[\alpha]_D^{25} = +56.3$ (c=0.08, $CHCl_3$).

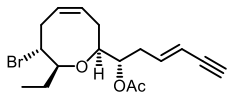
(1*S*,3*S*,4*R*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((E)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-one 7.34



The compound *ent*-(*E*)-laurefucin ***ent*-1.14** (10.0 mg, 30.3 μmol) was dissolved in CH_2Cl_2 (2.0 mL) at room temperature. Dess-Martin periodinane (15.0 mg, 35.3 μmol) was added and stirred at room temperature until completion. TLC analysis at this stage indicated complete consumption of starting materials. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 and the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (30% EA/CH_2Cl_2) to give the compound **7.34** as a colourless oil (9.9 mg, 30.3 μmol, 100%). R_f = 0.71 (50% EA/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (dt, *J* = 15.3, 7.4 Hz, 1H, OCHCH'HC**H**CHC≡CH), 5.57 (dd, *J* = 15.3, 1.2 Hz, 1H, OCHCH'HCHC**H**C≡CH), 4.26 (d, *J* = 7.1 Hz, 1H, O=CC**H**CH'HCH), 4.19 (s, 1H, O=CCHCH'HC**H**), 3.97 (td, *J* = 11.0, 5.3 Hz, 1H, CH_3CH'HCHC**H**BrCH'H), 3.92 (ddd, *J* = 8.7, 6.3, 2.4 Hz, 1H, OC**H**CH'HCHCHC≡CH), 3.59 (ddd, *J* = 10.7, 8.9, 2.5 Hz, 1H, CH_3CH'HC**H**CHBrCH'H), 3.01 (t, *J* = 11.6 Hz, 1H, CH_3CH'HCHCHBrC**H'**H), 2.96 – 2.91 (m, 1H, O=CCHC**H'**HCH), 2.91 – 2.85 (m, 1H, CH_3CH'HCHCHBrCH'**H**), 2.80 (d, *J* = 2.2 Hz, 1H, OCHCH'HCHCHC≡C**H**), 2.54 (dt, *J* = 13.0, 6.3 Hz, 1H, OCHC**H'**HCHCHC≡CH), 2.45 (dt, *J* = 14.3, 8.1 Hz, 1H, OCHCH'**H**CHCHC≡CH), 2.16 – 2.07 (m, 2H, O=CCHCH'**H**CH, CH_3C**H'**HCHCHBrCH'H), 1.53 – 1.49 (m, 1H, CH_3CH'**H**CHCHBrCH'H), 0.97 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCHCHBrCH'H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3 (O=**C**CHCH'HCH), 141.5 (OCHCH'H**C**HCHC≡CH), 111.7 (OCHCH'HCH**C**HC≡CH), 82.4 (O**C**HCH'HCHCHC≡CH), 82.2 (OCHCH'HCHCH**C**≡CH), 81.4 (CH_3CH'H**C**HCHBrCH'H), 80.0 (O=C**C**HCH'HCH), 77.1 (O=CCHCH'H**C**H), 76.6 (OCHCH'HCHCHC≡**C**H), 51.5

($CH_3CH'HCH\mathbf{C}HBrCH'H$), 46.8 ($CH_3CH'HCHCHBr\mathbf{C}H'H$), 34.6 (O=CCH**C**H'HCH), 33.2 (OCH**C**H'HCHCHC≡CH), 27.0 ($CH_3\mathbf{C}H'HCHCHBrCH'H$), 9.6 ($\mathbf{C}H_3CH'HCHCHBrCH'H$). IR ($\nu_{max}$ cm^{-1}): 3290 (acetylene C–H stretching, medium), 2920-2853 (aliphatic sp^3 C–H stretchings, broad), 2101 (C≡C stretching, weak), 1713 (ketone C=O stretching, strong), 1632 (C=C stretching, medium), 1061 (ether C–O–C antisymmetric stretching, strong). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 327.05903 and 329.05699, found *m/z* 327.05922 and 329.05725 ($C_{15}H_{21}O_2$). $[\alpha]_D^{25} = +22.0$ (c=0.15, $CHCl_3$).

(*S*,*E*)-1-((2*S*,7*R*,8*S*,*Z*)-7-Bromo-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl)hex-3-en-5-yn-1-yl acetate *ent*-laurencin *ent*-1.39

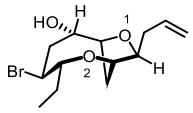


The compound ***ent*-1.38** (2.5 mg, 8.0 μmol) was dissolved in CH_2Cl_2 (0.8 mL) at room temperature and then DMAP (3.0 mg, 25.0 μmol) was added followed by a solution of Ac_2O in CH_2Cl_2 (0.1 M, 0.25 mL, 25.0 μmol). The reaction mixture was stirred at room temperature for 1 hour, in which TLC analysis at this stage indicated the completion consumption of starting materials. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (5% EA/Pet. Ether 40-60 to 10% EA/Pet. Ether 40-60) to give the compound ***ent*-1.39** as a colourless oil (2.6 mg, 7.3 μmol, 91%). R_f = 0.42 (10% EA/Pet. Ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (dt, *J* = 15.2, 7.3 Hz, 1H, OCHCHOAcCH'HC**H**CHC≡CH), 5.97 – 5.91 (m, 1H, BrCHCH'HCHC**H**CH'H), 5.91 – 5.85 (m, 1H, BrCHCH'HC**H**CHCH'H), 5.53 (dq, *J* = 15.9, 1.7 Hz, 1H, OCHCHOAcCH'HCHC**H**C≡CH), 5.00 (dt, *J* = 8.7, 4.3 Hz, 1H, OCHC**H**OAcCH'HCHCHC≡CH), 4.07 (dt, *J* = 10.0, 3.4 Hz, 1H, BrC**H**CH'HCHCHCH'H), 3.43 (ddd, *J* = 9.8, 7.2, 2.6 Hz, 1H, $CH_3CH'HC\mathbf{H}$), 3.39 (dd, *J* = 10.6, 4.6 Hz, 1H, OC**H**CHOAcCH'HCHCHC≡CH), 3.15 (ddd, *J* = 13.8, 8.5, 3.6 Hz, 1H, BrCHC**H'**HCHCHCH'H), 2.82 (d, *J* = 2.2 Hz, 1H, OCHCHOAcCH'HCHCHC≡C**H**), 2.55 – 2.49 (m, 1H, OCHCHOAcC**H'**HCHCHC≡CH), 2.49 – 2.44 (m, 1H, BrCHCH'**H**CHCHCH'H), 2.44 – 2.39 (m, 1H, OCHCHOAcCH'**H**CHCHC≡CH), 2.39 – 2.30 (m, 1H, BrCHCH'HCHCHC**H'**H), 2.12 – 2.03 (m, 4H, BrCHCH'HCHCHCH'**H**, OAc C$\mathbf{H}_3$), 1.95 (dqd, *J* = 14.8, 7.5, 2.6 Hz, 1H, $CH_3C\mathbf{H}'HCH$), 1.59 (dp, *J* = 14.8, 7.4 Hz, 1H, $CH_3CH'\mathbf{H}CH$), 0.98 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H}_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (OAc **C**=O), 141.3 (OCHCHOAcCH'H**C**HCHC≡CH), 129.4

(BrCHCH'HCH**C**HCH'H), 129.1 (BrCHCH'H**C**HCHCH'H), 111.8 (OCHCHOAcCH'HCH**C**HC≡CH), 84.7 (CH_3CH'H**C**H), 82.0 (OCHCHOAcCH'HCHCH**C**≡CH), 81.5 (O**C**HCHOAcCH'HCHCHC≡CH), 77.0 (OCHCHOAcCH'HCHCHC≡**C**H), 74.2 (OCH**C**HOAcCH'HCHCHC≡CH), 56.1 (Br**C**HCH'HCHCHCH'H), 34.0 (OCHCHOAc**C**H'HCHCHC≡CH), 32.4 (BrCH**C**H'HCHCHCH'H), 29.8 (BrCHCH'HCHCH**C**H'H), 25.9 (CH_3**C**H'HCH), 21.2 (OAc **C**H_3), 9.5 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3291 (acetylene C–H stretching, medium), 2961-2922 (aliphatic sp^3 C–H stretchings, broad), 1739 (ester C=O stretching, strong), 1632 (C=C stretching, medium), 1071 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 355.1 and 357.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 355.09033 and 357.08829, found *m/z* 355.09027 and 357.08815 ($C_{17}H_{24}O_3{}^{79}Br$ and $C_{17}H_{24}O_3{}^{81}Br$). $[\alpha]_D^{25} = -61.0$ (c=0.10, $CHCl_3$). Literature values of enantiomer: $[\alpha]_D^{20} = +70.0$ ($c = 0.05, CHCl_3$) ,[255] $[\alpha]_D^{25} = +69.0$ (c=1.00, $CHCl_3$) ,[260] $[\alpha]_D^{24} = +68.2$ (c=0.35, $CHCl_3$) ,[259] $[\alpha]_D^{25} = +72.5$ (c=0.17, $CHCl_3$) ,[257] $[\alpha]_D^{27} = +70.2$ (c=1.00, $CHCl_3$) ,[249] $[\alpha]_D^{24} = +69.6$ (c=0.26, $CHCl_3$) ,[261] $[\alpha]_D^{24} = +51.7$ ($CHCl_3$); the low value of the specific rotation was attributed to minor contamination by the *cis* enyne diastereomer of laurencin.[258] Spectroscopic data are in accordance with literature data.[249,250,261,262,253–260]

10.4 Experimental for Chapter 8

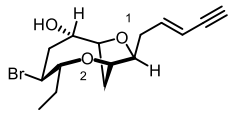
(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-9-Allyl-4-bromo-3-ethyl-2,8-dioxabicyclo[5.2.1]decan-6-ol 8.6



Compound **5.20** (25.0 mg, 65.0 μmol) was dissolved in dry CH_2Cl_2 (6.5 mL) and the reaction mixture was cooled to -40 °C. $TiCl_4$ (0.26 mL, 0.5 M in CH_2Cl_2, 195.0 μmol) was added followed by a solution of $AgAl(pftb)_4 \cdot CH_2Cl_2$ (226.0 mg, 130.0 μmol, in 1.0 mL CH_2Cl_2) immediately. The reaction mixture was stirred at -40°C for 2 hours, then cooled to -78°C. AgOBz (149.0 mg, 0.65 mmol) was added to the reaction mixture and stirring was continued for 1 hour. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, warmed to r.t. and excess TBAI was added. The quenched reaction mixture was then extracted with CH_2Cl_2, the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and filtered through a plug of silica gel (50% EA/Pet. Ether 40-60) to give a mixture of **8.6** and its benzoate ester. The mixture was dissolved in MeOH (2.2 mL) and K_2CO_3 (90.0 mg, 0.65 mmol) was added and stirring was continued for 2 hours. TLC analysis at this stage indicated complete consumption of starting material. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (40% EA/ Pet. Ether 40-60) to give the compound **8.6** as a colourless oil, which sometimes would solidify upon standing (12.6 mg, 41.2 μmol, 63%). R_f = 0.40 (40% EA/ Pet.Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H, OCHCH'HC**H**=CH'H), 5.15 (dq, *J* = 17.2, 1.5 Hz, 1H, OCHCH'HCH=C**H'**H), 5.06 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H, OCHCH'HCH=CH'**H**), 4.59 (t, *J* = 9.5 Hz, 1H, BrC**H**CH'HCHOH), 4.14 (ddd, *J* = 9.7, 3.2, 2.0 Hz, 1H, O_2CHCH'HC**H**O_1), 4.02 – 3.99 (m, 1H, BrCHCH'HC**H**OH), 3.98 (t, *J* = 2.5 Hz, 1H, O_2C**H**CH'HCHO_1), 3.89 (ddd, *J* = 11.8, 9.5, 2.6 Hz, 1H, CH_3CH'HC**H**), 3.72 (td, *J* = 7.1, 1.9 Hz, 1H, OC**H**CH'HCH=CH'H), 3.05 (ddd, *J* = 15.2, 9.7, 1.8 Hz, 1H, BrCHC**H'**HCHOH), 2.54 (dt, *J* = 14.1, 7.1 Hz, 1H, OCHC**H'**HCH=CH'H), 2.44 (dt, *J* = 13.9, 7.1 Hz, 1H, OCHCH'**H**CH=CH'H), 2.31 (dd, *J* = 15.2, 5.2 Hz, 1H, BrCHCH'**H**CHOH), 2.27 (d, *J* = 15.3 Hz, 1H, O_2CHC**H'**HCHO_1), 2.02 – 1.94 (m, 2H, O_2CHCH'**H**CHO_1, CH_3C**H'**HCH), 1.70 (ddq, *J* = 14.2, 11.3, 7.1 Hz, 1H, CH_3CH'**H**CH), 1.04 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9 (OCHCH'H**C**H=CH'H), 117.3 (OCHCH'HCH=**C**H'H), 84.1 (O**C**HCH'HCH=CH'H), 83.4 (CH_3CH'H**C**H), 78.8 (O_2CHCH'H**C**HO_1), 70.6 (BrCHCH'HC**H**OH), 70.0 (O_2**C**HCH'HCHO_1), 52.0 (Br**C**HCH'HCHOH), 38.9 (BrCH**C**H'HCHOH), 33.5 (OCH**C**H'HCH=CH'H), 33.2

(O_2CH**C**H'HCHO_1), 23.2 (CH_3**C**H'HCH), 11.9 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3409 (O–H stretching, broad), 3077 (alkene sp^2 =C–H stretching, weak), 2964-2931 (aliphatic sp^3 C–H stretchings, broad), 1642 (C=C stretching, medium), 1041 (ether C–O–C antisymmetric stretching, strong), 656 (C–Br stretching, medium). LRMS (ESI) $[M+Na]^+$: *m/z* 327.1 and 329.1. HRMS (ESI) $[M+Na]^+$: calculated for *m/z* 327.05663 and 329.05458, found *m/z* 327.05671 and 329.05469. ($C_{13}H_{21}O_3{}^{79}BrNa$ and $C_{13}H_{21}O_3{}^{81}BrNa$). $[\alpha]_D^{25} = +3.5$ (c=0.20, $CHCl_3$).

(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-ol, laurefurenyne F 1.33



Synthesis from recycled NMR sample:

Compound **1.11** (5.0 mg, 13.0 μmol) was dissolved in dry CD_2Cl_2 (0.3 mL) and the reaction mixture was cooled to -40 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (16.2 mg, 14.0 μmol) in dry CD_2Cl_2 (0.3 mL) was then added at -40 °C. The reaction mixture was stirring was continued for 15 minutes at -40 °C in which precipitation of a brown substance was observed. The reaction mixture was then continued to stir at this temperature for 1 hour. An optional TLC analysis could be carried out at this point to confirm if the starting material is completely consumed. The reaction mixture was then cooled to -78°C and equilibrated for 30 minutes. The reaction mixture was then filtered at -78°C into a flame dried and argon filled Young's NMR tube for subsequent NMR analyses. The colour of the filtrate could range from pale yellow to pale pink. After the analysis, the NMR sample was warmed to ca. -20 °C -0 °C, ejected from the spectrometer and incubated at -78 °C in a dry ice-acetone bath, and an excess of water was added. The sample was quickly removed from the bath, shaken vigorously and a pinch of $NaHCO_3$ was added. The sample was then returned to the bath and incubated for 15 minutes before gradually warming to room temperature. The reaction mixture was extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (10% EA/CH_2Cl_2 then 20% EA/CH_2Cl_2) to give the desired compound **1.33** as a colourless oil (2.0 mg, 6.2 μmol, 47%).

Synthesis without NMR analysis:

Compound **1.11** (3.8 mg, 9.7 μmol) was dissolved in dry CH_2Cl_2 (1.5 mL) and the reaction mixture was cooled to -40 °C. $AgAl(pftb)_4{\cdot}CH_2Cl_2$ (12.4 mg, 11.0 μmol) in dry CH_2Cl_2 (0.5 mL) was then added at -40 °C. A precipitation of a brown substance was observed. The reaction was stirred at -40 °C for 1 hour, then cooled to -78 °C and excess

H_2O was added followed by a pinch of $NaHCO_3$. The reaction mixture was then warmed to room temperature and excess tetrabutylammonium iodide was added to the reaction mixture, in which the colour of the organic layer changed from pale purple to pale yellow. The reaction mixture was extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography twice (50% EA/Pet.Ether 40-60 to remove tetrabutylammonium salts) then (20% EA/CH_2Cl_2 to separate the desired product from other minor impurities) to give the desired compound **1.33** as a colourless oil (2.2 mg, 6.7 μmol, 69%).

Synthesis from 8.6:

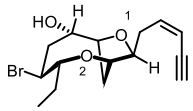
According to the procedures of Voigtritter[235]: The compound **8.6** (18.0 mg, 59.0 μmol) was dissolved in Et_2O (3.0 mL) and degassed with Argon. Crotonaldehyde (24.0 μL, 0.30 mmol) was added. Grubb's 2nd generation catalyst (2.5 mg, 3.0 μmol) was added, followed by CuI (0.8 mg, 4.4 μmol) and then stirred at room temperature overnight. TLC analysis at this stage confirmed the complete consumption of starting materials. All volatiles were then removed under reduced pressure, and the residue then underwent purification by flash column chromatography (50% EA/ Pet. Ether 40-60, 70% EA/ Pet. Ether 40-60 then 100% EA) to give the enal (14.0 mg, 41.9 μmol, 71%) which was carried forward immediately to the next step.

According to the procedures of Kim[5]: A solution of $TMSCHN_2$ in Et_2O (2.0M, 0.21 mL, 0.42 mmol) was added to a solution of LDA (0.5M, 0.84 mL, 0.42 mmol) at -78 °C dropwise. The enal (14.0 mg, 41.9 μmol) was then dissolved in THF (1.0 mL) and added to the $TMSCLiN_2$ solution at -78 °C dropwise. The reaction mixture was stirred at -78 °C for 1 hour then 0 °C for 1 hour. TLC analysis at this stage confirmed the complete consumption of starting materials. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O. The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated, diluted with 10% EA/Pet. Ether 40-60 and then filtered through a short plug of silica gel. The filtrate was concentrated and dissolved in MeOH (1.0 mL) and K_2CO_3 (4.0 mg, 32.0 μmol) was added and the reaction mixture was stirring was continued for 1-2 hours at room temperature. TLC analysis at this stage indicated complete consumption of starting materials. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography twice (50% EA/Pet.Ether) to give the desired compound **1.33** as a colourless oil (4.0 mg, 12.2 μmol, 29%, *E*:*Z* > 20:1).

Characterisation data of **1.33**: R_f = 0.40 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dt, *J* = 15.4, 7.4 Hz, 1H, OCHCH'HC**H**CHCCH), 5.60 (dq, *J* = 16.0, 1.7 Hz, 1H, OCHCH'HCHC**H**CCH), 4.58 (t, *J* = 9.6 Hz, 1H, BrC**H**CH'HCHOH), 4.14

(ddd, *J* = 9.7, 3.2, 2.1 Hz, 1H, $O_2CHCH'HCHO_1$), 4.02 – 3.94 (m, 2H, BrCHCH'HCHOH, $O_2CHCH'HCHO_1$), 3.88 (ddd, *J* = 11.8, 9.6, 2.6 Hz, 1H, $CH_3CH'HCH$), 3.72 (td, *J* = 7.2, 1.9 Hz, 1H, OCHCH'HCHCHCCH), 3.02 (ddd, *J* = 15.3, 9.7, 1.7 Hz, 1H, BrCHCH'HCHOH), 2.80 (d, *J* = 2.3 Hz, 1H, OCHCH'HCHCHCCH), 2.59 (dtd, *J* = 15.1, 7.5, 1.5 Hz, 1H, OCHCH'HCHCHCCH), 2.50 (dtd, *J* = 15.1, 7.5, 1.5 Hz, 1H, OCHCH'HCHCHCCH), 2.32 (dd, *J* = 15.2, 5.6 Hz, 1H, BrCHCH'HCHOH), 2.28 (d, *J* = 15.7 Hz, 1H, $O_2CHCH'HCHO_1$), 2.03 – 1.91 (m, 2H, $O_2CHCH'HCHO_1$, $CH_3CH'HCH$), 1.69 (ddq, *J* = 14.2, 11.4, 7.1 Hz, 1H, $CH_3CH'HCH$), 1.05 (t, *J* = 7.3 Hz, 3H, $CH_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3 (OCHCH'HCHCHCCH), 111.3 (OCHCH'HCHCHCCH), 83.5 ($CH_3CH'HCH$), 83.4 (OCHCH'HCHCHCCH), 82.4 (OCHCH'HCHCHCCH), 78.8 ($O_2CHCH'HCHO_1$), 76.4 (OCHCH'HCHCHCCH), 70.5 (BrCHCH'HCHOH), 70.1 ($O_2CHCH'HCHO_1$), 51.8 (BrCHCH'HCHOH), 38.9 (BrCHCH'HCHOH), 33.1 ($O_2CHCH'HCHO_1$), 32.8 (OCHCH'HCHCHCCH), 23.2 ($CH_3CH'HCH$), 11.9 ($CH_3CH'HCH$). IR (ν_{max} cm^{-1}): 3403 (O–H stretchings, broad), 3292 (acetylene sp C–H stretching, medium), 2964-2878 (aliphatic sp^3 C–H stretchings, broad), 2102 (acetylene C ≡ C stretching, weak), 1064 (ether C–O–C antisymmetric stretching, strong), 651 (C–Br stretching, medium). LRMS (ESI) $[M+H]^+$: *m/z* 329.1 and 331.1. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 329.07468 and 331.07264, found *m/z* 329.07477 and 331.07268. ($C_{15}H_{22}O_3{}^{79}Br$ and $C_{15}H_{22}O_3{}^{81}Br$). $[\alpha]_D^{25} = +17.5$ (c=0.12, MeOH), lit. $[\alpha]_D^{25} = +17.0$ ($c = 0.10$, MeOH).[26] Spectroscopic data are in accordance with literature data.[26]

(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*Z*)-p*ent*-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-ol, laurefurenyne E 1.32



Synthesis from recycled NMR sample:

Compound **1.8** (3.0 mg, 7.8 µmol) was dissolved in dry CD_2Cl_2 (0.3 mL) and the reaction mixture was cooled to -40 °C. $AgAl(pftb)_4 \cdot CH_2Cl_2$ (10.0 mg, 8.6 µmol) in dry CD_2Cl_2 (0.3 mL) was then added at -40 °C. The reaction mixture was stirring was continued for 15 minutes at -40 °C in which precipitation of a brown substance was observed. The reaction mixture was then continued to stir at this temperature for 1 hour. An optional TLC analysis could be carried out at this point to confirm if the starting material is completely consumed. The reaction mixture was then cooled to -78 °C and equilibrated for 30 minutes. The reaction mixture was then filtered at -78 °C into a flame dried and argon filled Young's NMR tube for subsequent NMR analyses. The

colour of the filtrate could range from pale yellow to pale pink. After the analysis, the NMR sample was warmed to ca. -20 °C -0 °C, ejected from the spectrometer and incubated at -78 °C in a dry ice-acetone bath, and an excess of water was added. The sample was quickly removed from the bath, shaken vigorously and a pinch of $NaHCO_3$ was added. The sample was then returned to the bath and incubated for 15 minutes before gradually warming to room temperature. The reaction mixture was extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography twice (50% EA/Pet. Ether 40-60) then (20% EA/CH_2Cl_2) to give the desired compound **1.32** as a colourless oil (1.0 mg, 3.0 μmol, 39%).

Synthesis without NMR analysis:

Compound **1.8** (11.3 mg, 29.0 μmol) was dissolved in dry CH_2Cl_2 (2.5 mL) and the reaction mixture was cooled to -40 °C. $AgAl(pftb)_4 \cdot CH_2Cl_2$ (37.1 mg, 32.0 μmol) in dry CH_2Cl_2 (1.5 mL) was then added at -40 °C. A precipitation of a brown substance was observed. The reaction was stirred at -40 °C for 1 hour, then cooled to -78 °C and excess H_2O was added followed by a pinch of $NaHCO_3$. The reaction mixture was then warmed to room temperature and excess tetrabutylammonium iodide was added to the reaction mixture, in which the colour of the organic layer changed from pale purple to pale yellow. The reaction mixture was extracted with CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (30% EA/Pet. Ether 40-60 then 50% EA/Pet. Ether 40-60) to recover unconsumed **1.8** (4.0 mg, 10.2 μmol, 35%) and give the desired compound **1.32** as a colourless oil (2.8 mg, 8.5 μmol, 45% brsm).

Synthesis from 8.6:

According to the procedures of Shirokane[228]: Compound **8.6** (20.0 mg, 66.0 μmol) was dissolved in 3:1 dioxane:H_2O (1.1 mL), then 2,6-lutidine (15.0 μL, 0.13 mmol) was added followed by a solution of 2.5% OsO_4 in *t*-BuOH (15.0 μL). $NaIO_4$ (55.0 mg, 0.26 mmol) was then added and the reaction mixture was stirring was continued for 1-2 hours. A TLC analysis at this stage showed complete consumption of starting material. The reaction mixture was then diluted with CH_2Cl_2 and H_2O followed by extraction with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated to give a crude brown oil. This crude brown oil was dried under high vacuum while the procedures below were carried out.

$Ph_3PCH_2I_2$ (140.0 mg, 0.26 mmol) was suspended in dry THF (2.5 mL) at room temperature and a solution of NaHMDS (0.24 mL, 1.0M solution in THF) was added. The reaction mixture was stirred at room temperature for 15 minutes in which the colour of the solution changed from bright yellow to deep orange. This solution was then cooled to -78 °C and HMPA (95.0 μL, 0.53 mmol) was added and stirring was continued

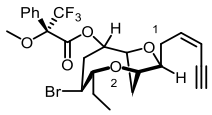
for 15 minutes. The dried crude brown oil was then dissolved in dry THF (1.0 mL) and added to the reaction mixture. The reaction mixture was stirred at -78 °C for 30 minutes then room temperature for 1 hour. A TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude mixture quickly underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60), product $R_f = 0.40$ (50% EA/Pet. Ether 40-60). The purified vinyl iodide was then quickly used for the following transformations due to its instability.

The vinyl iodide (9.8 mg, 23.0 μmol) was dissolved in dry Et_3N (1.2 mL), then trimethylsilylacetylene (16.0 μL, 11.4 μmol) was added followed by CuI (4.4 mg, 23.0 μmol). The mixture was then degassed with dry argon for 15 minutes. $Pd(PPh_3)_4$ (4.0 mg, 3.5 μmol) was then added and the reaction mixture was stirred at room temperature with exclusion of light for 1 hour. A TLC analysis at this stage showed the complete consumption of starting material. K_2CO_3 (32.0 mg, 0.23 mmol) and MeOH (1.2 mL) were added to the reaction mixture and stirring was continued for 1-2 hours until completion. The reaction mixture was then diluted with H_2O and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$, filtered through a short plug of silica and concentrated. The resulting pale brown crude oil then underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60) to give the desired compound **1.32** as a colourless oil (7.5 mg, 22.8 μmol, 35% over 4 steps, *Z:E* > 15:1).

Characterisation data of **1.32**: $R_f = 0.35$ (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (dtd, *J* = 10.8, 7.7, 0.8 Hz, 1H, OCHCH'HC**H**CHCCH), 5.55 (ddt, *J* = 10.9, 2.6, 1.4 Hz, 1H, OCHCH'HCHC**H**CCH), 4.59 (t, *J* = 9.6 Hz, 1H, BrC**H**CH'HCHOH), 4.15 (dd, *J* = 9.7, 4.0 Hz, 1H, O_2CHCH'HC**H**O_1), 4.01 (s, 1H, BrCHCH'HC**H**OH), 3.99 – 3.97 (m, 1H, O_2C**H**CH'HCHO_1), 3.90 (ddd, *J* = 11.7, 9.5, 2.6 Hz, 1H, CH_3CH'HC**H**), 3.77 (td, *J* = 7.1, 1.9 Hz, 1H, OC**H**CH'HCHCHCCH), 3.10 (dd, *J* = 2.4, 0.8 Hz, 1H, OCHCH'HCHCHCC**H**), 3.06 (ddd, *J* = 15.3, 9.7, 1.8 Hz, 1H, BrCHC**H'**HCHOH), 2.83 (dtd, *J* = 13.8, 7.0, 1.2 Hz, 1H, OCHC**H'**HCHCHCCH), 2.71 (dtd, *J* = 13.8, 7.0, 1.2 Hz, 1H, OCHCH'**H**CHCHCCH), 2.33 (dd, *J* = 15.2, 5.2 Hz, 1H, BrCHCH'**H**CHOH), 2.28 (d, *J* = 15.6 Hz, 1H, O_2CHC**H'**HCHO_1), 2.03 – 1.92 (m, 2H, O_2CHCH'**H**CHO_1, CH_3C**H'**HCH), 1.70 (ddq, *J* = 14.2, 11.2, 7.1 Hz, 1H, CH_3CH'**H**CH), 1.06 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 (OCHCH'H**C**HCHCCH), 110.4 (OCHCH'HCH**C**HCCH), 83.4 (CH_3CH'H**C**H), 83.4 (O**C**HCH'HCHCHCCH), 82.1 (OCHCH'HCHCHC**C**H), 80.3 (OCHCH'HCHCH**C**CH), 78.8 (O_2CHCH'H**C**HO_1), 70.6 (BrCHCH'H**C**HOH), 70.3 (O_2**C**HCH'HCHO_1), 52.0 (Br**C**HCH'HCHOH), 38.9 (BrCH**C**H'HCHOH), 33.2

(O_2CH**C**H'HCHO_1), 30.3 (OCH**C**H'HCHCHCCH), 23.2 (CH_3**C**H'HCH), 12.0 (**C**H_3CH'HCH). IR (ν_{max} cm^{-1}): 3412 (O–H stretchings, broad), 3292 (acetylene sp C–H stretching, medium), 2964-2903 (aliphatic sp^3 C–H stretchings, broad), 2096 (acetylene C ≡ C stretching, weak), 1064 (ether C–O–C antisymmetric stretching, strong), 651 (C–Br stretching, medium). HRMS (APCI) $[M+H]^+$: calculated for *m/z* 329.07468 and 331.07264, found *m/z* 329.07431 and 331.07227. ($C_{15}H_{22}O_3{}^{79}Br$ and $C_{15}H_{22}O_3{}^{81}Br$). $[\alpha]_D^{25} = -4.7$ (c=0.17, MeOH, $Z:E = 7.8:1$), $[\alpha]_D^{25} = -5.9$ (c=0.10, MeOH, $Z:E > 15:1$). Literature value: $[\alpha]_D^{25} = +11.0$ ($c = 0.10$, MeOH).[26] NMR spectroscopic data are in accordance with literature data.[26]

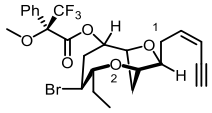
(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8.9



According to the procedures of Hoye[184]: Compound **1.32** (2.0 mg, 6.1 μmol) was mixed with (*S*)-Mosher Acid (4.3 mg, 18.2 μmol) and dissolved in dry CH_2Cl_2 (1.0 mL). *N*,*N*'-Dicyclohexylcarbodiimide (3.8 mg, 18.2 μmol) was added followed by DMAP (2.2 mg, 18.2 μmol). The reaction mixture was stirred at r.t. overnight and filtered through a plug of silica to remove any insoluble matter. The filtrate was concentrated and underwent purification by flash column chromatography (10% EA/Pet.Ether 40-60) to give the desired compound **8.9** as a colourless oil (1.2 mg, 2.2 μmol, 36%). R_f = 0.65 (20% EA/Pet.Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H, Ar**H**), 7.45 – 7.36 (m, 3H, Ar**H**), 6.04 (ddd, *J* = 10.5, 7.7, 6.8 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.56 (ddt, *J* = 10.8, 2.4, 1.3 Hz, 1H, OCHCH'HCH=C**H**CCH), 5.30 – 5.20 (m, 1H, BrCHCH'HC**H**OMTPA), 4.19 (dd, *J* = 9.4, 4.0 Hz, 1H, $O_2CHCH'HCHO_1$), 4.15 (t, *J* = 9.9 Hz, 1H, BrC**H**CH'HCHOMTPA), 3.99 (t, *J* = 2.6 Hz, 1H, O_2C**H**CH'HCHO_1), 3.87 (ddd, *J* = 11.9, 9.6, 2.6 Hz, 1H, $CH_3CH'HC$**H**), 3.78 (td, *J* = 7.1, 1.8 Hz, 1H, OC**H**CH'HCH=CHCCH), 3.55 (s, 3H, MTPA –OCH_3), 3.17 – 3.05 (m, 2H, BrCHC**H'**HCHOMTPA, OCHCH'HCH=CHCC**H**), 2.88 – 2.79 (m, 1H, OCHC**H'**HCH=CHCCH), 2.75 – 2.68 (m, 1H, OCHCH'**H**CH=CHCCH), 2.52 (dd, *J* = 15.7, 5.1 Hz, 1H, BrCHCH'**H**CHOMTPA), 2.15 (d, *J* = 15.5 Hz, 1H, O_2CHC**H'**HCHO_1), 2.01 (ddd, *J* = 15.5, 9.5, 3.3 Hz, 1H, O_2CHCH'**H**CHO_1), 1.90 (dqd, *J* = 15.3, 7.6, 2.5 Hz, 1H, CH_3C**H'**HCH), 1.61 (ddd, *J* = 14.6, 11.3, 7.2 Hz, 1H, CH_3CH'**H**CH), 1.03 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1 (MTPA **C**=O), 141.3 (OCHCH'H**C**H=CHCCH), 132.2 (Ar**C**), 129.9 (Ar**C**), 128.7 (Ar**C**), 127.5 (Ar**C**), 110.6 (OCHCH'HCH=**C**HCCH), 85.2 (MTPA **C**CF_3), 85.0

(MTPA **C**CF_3), 84.8 (MTPA **C**CF_3), 84.5 (MTPA **C**CF_3), 83.8 (O**C**HCH'HCH=CHCCH), 83.3 (CH_3CH'H**C**H), 82.2 (OCHCH'HCH=CHC**C**H), 80.2 (OCHCH'HCH=CH**C**CH), 76.1 (O_2CHCH'H**C**HO_1), 74.7 (BrCHCH'H**C**HOMTPA), 70.3 (O_2**C**HCH'HCHO_1), 55.6 (MTPA –O**C**H_3), 51.1 (Br**C**HCH'HCHOMTPA), 35.8 (BrCH**C**H'HCHOMTPA), 33.8 (O_2CH**C**H'HCHO_1), 30.1 (OCH**C**H'HCH=CHCCH), 23.1 (CH_3**C**H'HCH), 11.9 (**C**H_3CH'HCH).

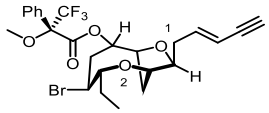
(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8.7



According to the procedures of Hoye[184]: Compound **1.32** (2.0 mg, 6.1 μmol) was mixed with (*R*)-Mosher Acid (4.3 mg, 18.2 μmol) and dissolved in dry CH_2Cl_2 (1.0 mL). *N*,*N*'-Dicyclohexylcarbodiimide (3.8 mg, 18.2 μmol) was added followed by DMAP (2.2 mg, 18.2 μmol). The reaction mixture was stirred at r.t. overnight and filtered through a plug of silica to remove any insoluble matter. The filtrate was concentrated and underwent purification by flash column chromatography (10% EA/Pet.Ether 40-60) to give the desired compound **8.7** as a colourless oil (1.5 mg, 2.8 μmol, 45%). R_f = 0.65 (20% EA/Pet.Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H, Ar**H**), 7.46 – 7.38 (m, 3H, Ar**H**), 6.04 (dtd, *J* = 10.7, 7.4, 0.7 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.56 (ddt, *J* = 10.9, 2.5, 1.3 Hz, 1H, OCHCH'HCH=C**H**CCH), 5.32 (t, *J* = 4.7 Hz, 1H, BrCHCH'HC**H**OMTPA), 4.28 (t, *J* = 9.6 Hz, 1H, BrC**H**CH'HCHOMTPA), 4.07 (dd, *J* = 9.5, 4.0 Hz, 1H, O_2CHCH'HC**H**O_1), 3.97 (t, *J* = 2.6 Hz, 1H, O_2C**H**CH'HCHO_1), 3.89 (ddd, *J* = 11.8, 9.6, 2.6 Hz, 1H, CH_3CH'HC**H**), 3.75 (td, *J* = 7.1, 1.8 Hz, 1H, OC**H**CH'HCH=CHCCH), 3.56 (s, 3H, MTPA –OC**H**$_3$), 3.17 (ddd, *J* = 15.8, 9.7, 1.9 Hz, 1H, BrCHC**H'**HCHOMTPA), 3.11 (dd, *J* = 2.2, 0.9 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.83 (dtd, *J* = 14.1, 7.7, 1.1 Hz, 1H, OCHC**H'**HCH=CHCCH), 2.71 (dtd, *J* = 13.9, 7.4, 1.2 Hz, 1H, OCHCH'**H**CH=CHCCH), 2.50 (dd, *J* = 15.7, 5.2 Hz, 1H, BrCHCH'**H**CHOMTPA), 2.08 (d, *J* = 15.6 Hz, 1H, O_2CHC**H'**HCHO_1), 1.97 – 1.85 (m, 2H, O_2CHCH'**H**CHO_1, CH_3C**H'**HCH), 1.62 (ddd, *J* = 14.5, 11.3, 7.2 Hz, 1H, CH_3CH'**H**CH), 1.04 (t, *J* = 7.3 Hz, 3H, CH_3C**H'**HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1 (MTPA **C**=O), 141.3 (OCHCH'H**C**H=CHCCH), 132.2 (Ar**C**), 129.9 (Ar**C**), 128.8 (Ar**C**), 127.5 (Ar**C**), 110.6 (OCHCH'HCH=**C**HCCH), 83.7 (O**C**HCH'HCH=CHCCH), 83.3 (CH_3CH'H**C**H), 82.2 (OCHCH'HCH=CHC**C**H), 80.2 (OCHCH'HCH=CH**C**CH), 75.8 (O_2CHCH'H**C**HO_1), 74.1 (BrCHCH'H**C**HOMTPA), 70.3 (O_2**C**HCH'HCHO_1), 55.7 (MTPA –O**C**H_3), 51.4 (Br**C**HCH'HCHOMTPA), 36.2

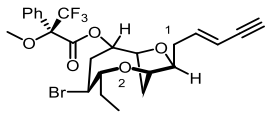
(BrCH**C**H'HCHOMTPA), 33.6 (O_2CH**C**H'HCHO_1), 30.1 (OCH**C**H'HCH=CHCCH), 23.1 (CH_3**C**H'HCH), 11.9 (**C**H_3CH'HCH).

(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8.10



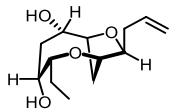
According to the procedures of Hoye[184]: Compound **1.33** (2.0 mg, 6.1 μmol) was mixed with (*S*)-Mosher Acid (4.3 mg, 18.2 μmol) and dissolved in dry CH_2Cl_2 (1.0 mL). *N*,*N*'-Dicyclohexylcarbodiimide (3.8 mg, 18.2 μmol) was added followed by DMAP (2.2 mg, 18.2 μmol). The reaction mixture was stirred at r.t. overnight and filtered through a plug of silica to remove any insoluble matter. The filtrate was concentrated and underwent purification by flash column chromatography (10% EA/Pet.Ether 40-60) to give the desired compound **8.10** as a colourless oil (2.2 mg, 4.0 μmol, 66%). R_f = 0.56 (20% EA/Pet.Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H, Ar**H**), 7.46 – 7.39 (m, 3H, Ar**H**), 6.20 (dt, *J* = 15.4, 7.4 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.59 (dq, *J* = 15.7, 1.5 Hz, 1H, OCHCH'HCH=C**H**CCH), 5.31 (t, *J* = 3.4 Hz, 1H, BrCHCH'HC**H**OMTPA), 4.27 (t, *J* = 9.6 Hz, 1H, BrC**H**CH'HCHOMTPA), 4.07 (dd, *J* = 9.6, 4.1 Hz, 1H, O_2CHCH'HC**H**O_1), 3.99 – 3.94 (m, 1H, O_2C**H**CH'HCHO_1), 3.87 (ddd, *J* = 11.8, 9.8, 2.6 Hz, 1H, CH_3CH'HC**H**), 3.70 (td, *J* = 7.4, 1.8 Hz, 1H, OC**H**CH'HCH=CHCCH), 3.56 (d, *J* = 1.2 Hz, 3H, MTPA –OC**H**$_3$), 3.13 (ddd, *J* = 15.8, 9.6, 1.8 Hz, 1H, BrCHC**H'**HCHOMTPA), 2.81 (d, *J* = 2.2 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.58 (dtd, *J* = 15.0, 7.4, 1.3 Hz, 1H, OCHC**H'**HCH=CHCCH), 2.54 – 2.46 (m, 2H, BrCHCH'**H**CHOMTPA, OCHCH'**H**CH=CHCCH), 2.07 (d, *J* = 15.6 Hz, 1H, O_2CHC**H'**HCHO_1), 1.95 – 1.86 (m, 2H, O_2CHCH'**H**CHO_1, CH_3C**H'**HCH), 1.61 (ddd, *J* = 14.6, 11.4, 7.2 Hz, 1H, CH_3CH'**H**CH), 1.03 (t, *J* = 7.3 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1 (MTPA **C**=O), 141.9 (OCHCH'H**C**H=CHCCH), 132.1 (Ar**C**), 129.9 (Ar**C**), 128.8 (Ar**C**), 127.5 (Ar**C**), 111.5 (OCHCH'HCH=**C**HCCH), 83.7 (O**C**HCH'HCH=CHCCH), 83.4 (CH_3CH'H**C**H), 82.3 (OCHCH'HCH=CH**C**CH), 76.6 (OCHCH'HCH=CHC**C**H), 75.8 (O_2CHCH'H**C**HO_1), 74.1 (BrCHCH'H**C**HOMTPA), 70.0 (O_2**C**HCH'HCHO_1), 55.7 (MTPA –O**C**H$_3$), 51.2 (Br**C**HCH'HCHOMTPA), 36.2 (BrCH**C**H'HCHOMTPA), 33.6 (O_2CH**C**H'HCHO_1), 32.6 (OCH**C**H'HCH=CHCCH), 23.0 (CH_3**C**H'HCH), 11.8 (**C**H_3CH'HCH).

(1*S*,3*R*,4*S*,6*S*,7*S*,9*S*)-4-Bromo-3-ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo [5.2.1]decan-6-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8.8



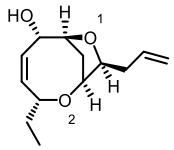
According to the procedures of Hoye[184]: Compound **1.33** (2.0 mg, 6.1 μmol) was mixed with (*R*)-Mosher Acid (4.3 mg, 18.2 μmol) and dissolved in dry CH_2Cl_2 (1.0 mL). *N*,*N*'-Dicyclohexylcarbodiimide (3.8 mg, 18.2 μmol) was added followed by DMAP (2.2 mg, 18.2 μmol). The reaction mixture was stirred at r.t. overnight and filtered through a plug of silica to remove any insoluble matter. The filtrate was concentrated and underwent purification by flash column chromatography (10% EA/Pet.Ether 40-60) to give the desired compound **8.8** as a colourless oil (1.4 mg, 2.6 μmol, 42%). R_f = 0.67 (20% EA/Pet.Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.8, 2.9 Hz, 2H, Ar**H**), 7.47 – 7.38 (m, 3H, Ar**H**), 6.20 (dt, *J* = 15.4, 7.4 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.59 (dt, *J* = 15.9, 1.8 Hz, 1H, OCHCH'HCH=C**H**CCH), 5.30 (d, *J* = 4.5 Hz, 1H, BrCHCH'HC**H**OMTPA), 4.27 (t, *J* = 9.6 Hz, 1H, BrC**H**CH'HCHOMTPA), 4.07 (dd, *J* = 9.5, 4.1 Hz, 1H, O_2CHCH'HC**H**O_1), 3.96 (d, *J* = 3.1 Hz, 1H, O_2C**H**CH'HCHO_1), 3.87 (td, *J* = 10.5, 9.4, 2.5 Hz, 1H, CH_3CH'HC**H**), 3.70 (t, *J* = 7.0 Hz, 1H, OC**H**CH'HCH=CHCCH), 3.56 (d, *J* = 1.1 Hz, 3H, OMTPA –OC**H**$_3$), 3.13 (ddd, *J* = 15.8, 9.7, 1.8 Hz, 1H, BrCHC**H'**HCHOMTPA), 2.81 (d, *J* = 2.2 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.62 – 2.54 (m, 1H, OCHC**H'**HCH=CHCCH), 2.50 (ddd, *J* = 16.3, 10.4, 6.0 Hz, 2H, BrCHCH'**H**CHOMTPA, OCHCH'**H**CH=CHCCH), 2.07 (d, *J* = 15.6 Hz, 1H, O_2CHC**H'**HCHO_1), 1.95 – 1.82 (m, 2H, O_2CHCH'**H**CHO_1, CH_3C**H'**HCH), 1.61 (ddd, *J* = 14.6, 11.4, 7.2 Hz, 1H, CH_3CH'**H**CH), 1.03 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1 (MTPA **C**=O), 141.9 (OCHCH'H**C**H=CHCCH), 132.2 (Ar**C**), 129.9 (Ar**C**), 128.8 (Ar**C**), 127.5 (Ar**C**), 126.9 (MTPA **C**F_3), 124.6 (MTPA **C**F_3), 122.3 (MTPA **C**F_3), 120.0 (MTPA **C**F_3), 111.5 (OCHCH'HCH=**C**HCCH), 85.2 (MTPA **C**CF_3), 85.0 (MTPA **C**CF_3), 84.8 (MTPA **C**CF_3), 84.5 (MTPA **C**CF_3), 83.7 (O**C**HCH'HCH=CHCCH), 83.5 (CH_3CH'H**C**H), 82.3 (OCHCH'HCH=CH**C**CH), 76.6 (OCHCH'HCH=CHC**C**H), 76.1 (O_2CHCH'H**C**HCHO_1), 74.6 (BrCHCH'H**C**HOMTPA), 70.0 (O_2**C**HCH'HCHO_1), 55.6 (MTPA O**C**H$_3$), 50.9 (Br**C**HCH'HCHOMTPA), 35.8 (BrCH**C**H'HCHOMTPA), 33.7 (O_2CH**C**H'HCHO_1), 32.6 (OCH**C**H'HCH=CHCCH), 23.0 (CH_3**C**H'HCH), 11.8 (**C**H_3CH'HCH).

(1*S*,3*R*,4*R*,6*S*,7*S*,9*S*)-9-Allyl-3-ethyl-2,8-dioxabicyclo[5.2.1]decane-4,6-diol 8.12



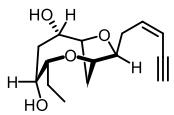
The compound **8.6** (3.0 mg, 10.0 μmol) was dissolved in DMF (0.1 mL) and caesium trifluoroacetate (12.3 mg, 50.0 μmol) was added. The reaction was then stirred at 120 °C overnight. TLC analysis at this stage indicated complete consumption of starting materials. The reaction was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (100% EA) to give the desired compound **8.12** as a white solid (1.5 mg, 6.2 μmol, 62%). R_f = 0.31 (100% EA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, OCHCH'HC**H**CH'H), 5.15 (dq, *J* = 17.1, 1.6 Hz, 1H, OCHCH'HCHC**H'**H), 5.07 (ddt, *J* = 10.3, 2.3, 1.2 Hz, 1H, OCHCH'HCHCH'**H**), 4.30 (ddd, *J* = 8.4, 3.5, 1.4 Hz, 1H, OHCHC**H**CH'HCH), 4.27 (ddd, *J* = 7.0, 5.2, 2.7 Hz, 1H, CH_3CH'HCHC**H**OHCH$_2$), 4.09 (q, *J* = 3.9 Hz, 1H, OHC**H**CHCH'HCH), 4.02 (dd, *J* = 4.1, 2.1 Hz, 1H, OHCHCHCH'HC**H**), 3.79 (dt, *J* = 8.5, 4.9 Hz, 1H, CH_3CH'HC**H**CHOHCH$_2$), 3.76 (td, *J* = 7.1, 2.1 Hz, 1H, OC**H**CH'HCHCH'H), 3.29 (s, 1H, O**H**CHCHCH'HCH), 2.97 (d, *J* = 15.1 Hz, 1H, OHCHCHC**H'**HCH), 2.74 (s, 1H, CH_3CH'HCHCHO**H**CH$_2$), 2.53 (dt, *J* = 13.9, 6.9 Hz, 1H, OCHC**H'**HCHCH'H), 2.46 (dt, *J* = 14.0, 7.1 Hz, 1H, OCHCH'**H**CHCH'H), 2.24 – 2.17 (m, 2H, CH_3CH'HCHCHOHC**H**$_2$), 1.96 (ddd, *J* = 14.4, 10.0, 4.0 Hz, 1H, OHCHCHCH'**H**CH), 1.77 (ddq, *J* = 14.6, 9.2, 7.3 Hz, 1H, CH_3C**H'**HCHCHOHCH$_2$), 1.60 (dqd, *J* = 14.7, 7.3, 2.1 Hz, 1H, CH_3CH'**H**CHCHOHCH$_2$), 1.01 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCHCHOHCH$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.2 (OCHCH'H**C**HCH'H), 117.1 (OCHCH'HCH**C**H'H), 83.9 (O**C**HCH'HCHCH'H), 79.7 (OHCH**C**HCH'HCH), 79.2 (CH_3CH'H**C**HCHOHCH$_2$), 73.5 (OH**C**HCHCH'HCH), 73.0 (CH_3CH'HCH**C**HOHCH$_2$), 71.0 (OHCHCHCH'H**C**H), 33.8 (OCH**C**H'HCHCH'H), 32.1 (OHCHCH**C**H'HCH), 31.1 (CH_3CH'HCHCHOH**C**H$_2$), 23.4 (CH_3**C**H'HCHCHOHCH$_2$), 11.4 (**C**H$_3$CH'HCHCHOHCH$_2$). IR (ν_{max} cm^{-1}): 3336 (O–H stretchings, broad), 2963-2857 (aliphatic sp^3 C–H stretchings, broad), 1642 (alkene C=C stretching, medium), 1078 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+H]$^+$: 243.2. HRMS (ESI) [M+H]$^+$: calculated for *m/z* 243.15909, found *m/z* 243.15933. ($C_{13}H_{23}O_4$). $[\alpha]_D^{25} = +27.0$ (c=0.10, $CHCl_3$). Melting point: 118.4 °C.

(1*S*,3*R*,6*S*,7*S*,9*S*,*Z*)-9-Allyl-3-ethyl-2,8-dioxabicyclo[5.2.1]dec-4-en-6-ol 8.11



Compound **8.6** (5.0 mg, 16.0 μmol) was dissolved in DMF (0.8 mL). CsOAc (47.0 mg, 0.25 mmol) was added and the reaction mixture was stirred at 90˚C overnight. TLC analysis suggested that the reaction was complete. Crude NMR analysis revealed that the major product is the elimination product **8.11**. The crude mixture then underwent purification by flash column chromatography (50% EA/CH_2Cl_2) to give the desired compound **8.11** in moderate purity (3.0 mg, 13.3 μmol, 84%). R_f = 0.40 (50% EA/Pet. Ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 17.3, 10.2, 7.0 Hz, 1H, $OCHCH_2C$**H**=CH'H), 5.60 – 5.51 (m, 2H, C**H**=C**H**CHOH), 5.17 (dq, *J* = 17.2, 1.6 Hz, 1H, $OCHCH_2CH$=C**H'**H), 5.09 (ddt, *J* = 10.1, 2.1, 1.1 Hz, 1H, $OCHCH_2CH$=CH'**H**), 4.82 (s, 1H, CH=CHC**H**OH), 4.29 – 4.23 (m, 2H, $CH_3CH'HC$**H**, $O_2CHCH'HC$**H**O_1), 4.16 (dd, *J* = 4.5, 2.8 Hz, 1H, O_2C**H**$CH'HCHO_1$), 3.78 (td, *J* = 7.2, 2.8 Hz, 1H, OC**H**CH_2CH=CH'H), 2.63 (dt, *J* = 14.1, 0.9 Hz, 1H, O_2CHC**H'**$HCHO_1$), 2.48 (m, 2H, $OCHC$**H**$_2CH$=CH'H), 1.97 (d, *J* = 4.4 Hz, 1H, CH=CHCHO**H**), 1.94 (dt, *J* = 8.7, 4.8 Hz, 1H, O_2CHCH'**H**CHO_1), 1.74 (dt, *J* = 13.8, 7.4 Hz, 1H, CH_3C**H'**HCH), 1.53 – 1.48 (m, 1H, CH_3CH'**H**CH), 0.94 (t, *J* = 7.4 Hz, 3H, C**H**$_3CH'HCH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0 ($OCHCH_2$**C**H=CH'H), 133.5 (**C**H=**C**HCHOH), 117.3 ($OCHCH_2CH$=**C**H'H), 84.8 ($O_2CHCH'H$**C**HO_1), 83.4 (O**C**HCH_2CH=CH'H), 76.7 (CH=CH**C**HOH), 75.4 (O_2**C**$HCH'HCHO_1$), 75.0 ($CH_3CH'H$**C**H), 34.2 (O_2CH**C**$H'HCHO_1$), 33.7 (OCH**C**H_2CH=CH'H), 27.8 (CH_3**C**H'HCH), 10.4 (**C**$H_3CH'HCH$). IR (ν_{max} cm^{-1}): 3413 (O–H stretching, broad), 2930 (aliphatic sp^3 C–H stretchings, broad), 1642 (C=C stretching, medium), 1045 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 247.1. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 247.13047, found *m/z* 247.13046. ($C_{13}H_{20}O_3Na$). $[\alpha]_D^{25} = -10.0$ (c=0.10, $CHCl_3$).

(1*S*,3*R*,4*R*,6*S*,7*S*,9*S*)-3-Ethyl-9-((*Z*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1] decane-4,6-diol laurefurenyne C 1.30



Synthesis from 1.32:

The compound laurefurenyne E **1.32** (4.0 mg, 12.0 μmol) was dissolved in DMF (0.12 mL), and caesium trifluoroacetate (30.0 mg, 0.12 mmol) was added. The reaction

mixture was then stirred at 120 °C for 12 hours. TLC analysis at this stage indicated the complete consumption of starting material. The reaction mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with ethyl acetate and all the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60 then 100% EA) to give the desired compound **1.30** as a colourless oil (0.8 mg, 2.8 μmol, 23%).

Synthesis from 8.12:

According to the procedures of Shirokane[228]: Compound **8.12** (3.0 mg, 12.0 μmol) was dissolved in 3:1 dioxane:H_2O (0.2 mL), then 2,6-lutidine (3.0 μL, 24.0 μmol) was added followed by a solution of 2.5% OsO_4 in *t*-BuOH (3.0 μL). $NaIO_4$ (10.0 mg, 47.0 μmol) was then added and the reaction mixture was stirring was continued for 1-2 hours. A TLC analysis at this stage showed complete consumption of starting material. The reaction mixture was then diluted with CH_2Cl_2 and H_2O followed by extraction with CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$ and concentrated to give a crude brown oil. This crude brown oil was dried under high vacuum while the procedures below were carried out.

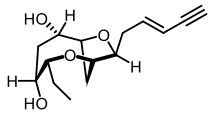
$Ph_3PCH_2I_2$ (32.0 mg, 60.0 μmol) was suspended in dry THF (0.3 mL) at room temperature and a solution of NaHMDS (55.0 μL, 1.0M solution in THF) was added. The reaction mixture was stirred at room temperature for 15 minutes in which the colour of the solution changed from bright yellow to deep orange. This solution was then cooled to -78 °C and HMPA (21.0 μL, 0.12 mmol) was added and stirring was continued for 15 minutes. The dried crude brown oil was then dissolved in dry THF (0.3 mL) and added to the reaction mixture. The reaction mixture was stirred at -78 °C for 30 minutes then room temperature for 1 hour. A TLC analysis at this stage showed complete consumption of starting material. The reaction was then quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and concentrated. The crude mixture quickly underwent purification by flash column chromatography (70% EA/Pet. Ether 40-60 then 100% EA), product R_f = 0.40 (100% EA). The purified vinyl iodide was then quickly used for the following transformations due to its instability.

The vinyl iodide (1.5 mg, 4.1 μmol) was dissolved in dry Et_3N (0.3 mL), then trimethylsilylacetylene (3.0 μL, 20.0 μmol) was added followed by CuI (0.8 mg, 4.1 μmol). The mixture was then degassed with dry argon for 15 minutes. $Pd(PPh_3)_4$ (0.7 mg, 0.61 μmol) was then added and the reaction mixture was stirred at room temperature with exclusion of light for 1 hour. A TLC analysis at this stage showed the complete consumption of starting material. K_2CO_3 (6.0 mg, 41.0 μmol) and MeOH (0.3 mL) were added to the reaction mixture and stirring was continued for 1-2 hours until

completion. The reaction mixture was then diluted with H_2O and extracted with ethyl acetate. The organic layer was separated, dried with $MgSO_4$, filtered through a short plug of silica and concentrated. The resulting pale brown crude oil then underwent purification by flash column chromatography (100% EA) to give the desired compound **1.30** as a colourless oil (1.0 mg, 3.8 μmol, 32% over 4 steps, *Z:E* > 15:1).

Characterisation of **1.30**: R_f = 0.40 (100% EA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (dt, *J* = 10.9, 7.4 Hz, 1H, OCHCH'HC**H**CHC≡CH), 5.55 (dd, *J* = 10.8, 2.1 Hz, 1H, OCHCH'HCHC**H**C≡CH), 4.32 – 4.29 (m, 1H, OHCHC**H**CH'HCH), 4.29 – 4.27 (m, 1H, CH_3CH'HCHC**H**OHCH_2), 4.09 (s, 1H, OHC**H**CHCH'HCH), 4.02 (t, *J* = 3.1 Hz, 1H, OHCHCHCH'HC**H**), 3.84 – 3.80 (m, 1H, CH_3CH'HC**H**CHOHCH_2), 3.80 – 3.77 (m, 1H, OC**H**CH'HCHCHC≡CH), 3.32 (d, *J* = 8.2 Hz, 1H, O**H**CHCHCH'HCH), 3.10 (d, *J* = 2.3 Hz, 1H, OCHCH'HCHCHC≡C**H**), 2.98 (d, *J* = 15.0 Hz, 1H, OHCHCHC**H'**HCH), 2.85 (dt, *J* = 14.3, 7.2 Hz, 1H, OCHC**H'**HCHCHC≡CH), 2.76 – 2.67 (m, 2H, CH_3CH'HCHCHO**H**CH_2, OCHC**H'**HCHCHC≡CH), 2.29 – 2.14 (m, 2H, CH_3CH'HCHCHOHC**H**$_2$), 1.96 (ddd, *J* = 14.5, 10.0, 4.0 Hz, 1H, OHCHCHC**H'**HCH), 1.78 (dp, *J* = 14.7, 8.5, 7.4 Hz, 1H, CH_3C**H'**HCHCHOHCH_2), 1.64 – 1.59 (m, 1H, CH_3CH'**H**CHCHOHCH_2), 1.02 (t, *J* = 7.4 Hz, 3H, C**H**$_3$CH'HCHCHOHCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (OCHCH'H**C**HCHC≡CH), 110.2 (OCHCH'HCH**C**HC≡CH), 83.2 (O**C**HCH'HCHCHC≡CH), 82.0 (OCHCH'HCHCHC≡**C**H), 80.3 (OCHCH'HCHCH**C**≡CH), 79.7 (OHCH**C**HCH'HCH), 79.2 (CH_3CH'H**C**HCHOHCH_2), 73.5 (OH**C**HCHCH'HCH), 72.9 (CH_3CH'HCH**C**HOHCH_2), 71.2 (OHCHCHCH'H**C**H), 32.1 (OHCHCH**C**H'HCH), 31.0 (CH_3CH'HCHCHOH**C**H_2), 30.5 (OCH**C**H'HCHCHC≡CH), 23.3 (CH_3**C**H'HCHCHOHCH_2), 11.4 (**C**H_3CH'HCHCHOHCH_2). IR (ν_{max} cm^{-1}): 3350 (O–H stretching , broad), 3291 (acetylene C–H stretching, medium), 2963-2854 (aliphatic sp^3 C–H stretchings, broad), 2096 (C≡C stretching, weak), 1668 (C=C stretching, medium), 1084 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) [M+Na]$^+$: *m/z* 289.1. HRMS (ESI) [M+Na]$^+$: calculated for *m/z* 289.14103, found *m/z* 289.14105 ($C_{15}H_{22}O_4Na$). $[\alpha]_D^{25} = +10.8$ (c=0.13, MeOH) . Literature value: $[\alpha]_D^{25} = +20.0$ (c=0.10, MeOH) .[26] Spectroscopic data are in accordance with literature data.[26]

(1*S*,3*R*,4*R*,6*S*,7*S*,9*S*)-3-Ethyl-9-((*E*)-pent-2-en-4-yn-1-yl)-2,8-dioxabicyclo[5.2.1] decane-4,6-diol laurefurenyne D 1.31



Synthesis from 1.33:

The compound laurefurenyne F **1.33** (4.0 mg, 12.0 μmol) was dissolved in DMF (0.12 mL), and caesium trifluoroacetate (15.0 mg, 60.0 μmol) was added. The reaction mixture was then stirred at 120 °C for 12 hours. TLC analysis at this stage indicated the complete consumption of starting material. The reaction mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with ethyl acetate and all the organic layers were combined and dried with $MgSO_4$. The crude was concentrated and underwent purification by flash column chromatography (50% EA/Pet. Ether 40-60 then 100% EA) to give the desired compound **1.31** as a colourless oil (1.2 mg, 4.5 μmol, 38%). The compound was crystallised by slow diffusion of pentane into a solution of **1.31** in ethyl acetate for X-ray crystallographic analysis.

Synthesis from 8.12:

According to the procedures of Shepherd[2]: The compound **8.12** (3.0 mg, 12.0 μmol) was dissolved in CH_2Cl_2 (0.4 mL) and degassed with argon. Crotonaldehyde (10.0 μL, 0.12 mmol) was added followed by Grubb's 2nd generation catalyst (0.5 mg, 0.6 μmol). The reaction mixture was then stirred at 40 °C for 1 hour. TLC analysis at this stage confirmed the complete consumption of starting materials. DMSO (0.1 mL) was added and stirred open to air overnight. All volatiles were then removed under reduced pressure, and the residue quickly underwent purification by flash column chromatography (100% EA) to give the enal (3.4 mg, 12.0 μmol, quant.) which was carried forward immediately to the next step.

According to the procedures of Kim[5]: A solution of $TMSCHN_2$ in Et_2O (2.0M, 60.0 μL, 0.12 mmol) was added to a solution of LDA (0.5M, 0.24 mL, 0.12 mmol) at -78 °C dropwise. The enal (3.4 mg, 12.0 μmol) was then dissolved in THF (0.3 mL) and added to the $TMSCLiN_2$ solution at -78 °C dropwise. The reaction mixture was stirred at -78 °C for 1 hour then 0 °C for 1 hour. TLC analysis at this stage confirmed the complete consumption of starting materials. The reaction mixture was quenched with aq. HCl (1.0M) and extracted with ethyl acetate. The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated. The crude then underwent purification by flash column chromatography (50% EA/Pet.Ether 40-60 then 100% EA) to give the desired compound **1.31** as a colourless oil (2.6 mg, 9.8 μmol, 81%, *E*:*Z* > 20:1).

Characterisation of **1.31**: R_f = 0.43 (100% EA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (dt, *J* = 15.3, 7.4 Hz, 1H, OCHCH'HC**H**=CHCCH), 5.59 (dq, *J* = 15.9, 1.7 Hz, 1H,

OCHCH'HCH=C**H**CCH), 4.32 (ddd, *J* = 7.3, 5.5, 1.7 Hz, 1H, $CH_3CH'HCHC\mathbf{H}OH$), 4.29 (dd, *J* = 9.6, 4.0 Hz, 1H, $CH_2CHOHC\mathbf{H}CH'HCH$), 4.07 (s, 1H, $CH_2C\mathbf{H}OHCHCH'HCH$), 3.99 (dd, *J* = 3.7, 2.0 Hz, 1H, $CH_2CHOHCHCH'HC\mathbf{H}$), 3.79 – 3.68 (m, 2H, OC**H**CH'HCH=CHCCH, $CH_3CH'HC\mathbf{H}CHOH$), 3.37 (s, 1H, $CH_2CHO\mathbf{H}CHCH'HCH$), 3.02 (d, *J* = 15.0 Hz, 1H, $CH_2CHOHCHC\mathbf{H'}HCH$), 2.80 (d, *J* = 2.2 Hz, 1H, OCHCH'HCH=CHCC**H**), 2.77 (s, 1H, $CH_3CH'HCHCHO\mathbf{H}$), 2.58 (dtd, *J* = 14.7, 7.4, 1.5 Hz, 1H, OCHC**H'**HCH=CHCCH), 2.50 (dtd, *J* = 14.9, 7.4, 1.1 Hz, 1H, OCHCH'**H**CH=CHCCH), 2.25 – 2.14 (m, 2H, $C\mathbf{H}_2CHOHCHCH'HCH$), 1.94 (ddd, *J* = 14.3, 9.9, 3.8 Hz, 1H, $CH_2CHOHCHCH'\mathbf{H}CH$), 1.79 (ddq, *J* = 14.6, 9.5, 7.3 Hz, 1H, $CH_3C\mathbf{H'}HCHCHOH$), 1.60 (ddd, *J* = 14.5, 7.5, 2.3 Hz, 1H, $CH_3CH'\mathbf{H}CHCHOH$), 1.02 (t, *J* = 7.4 Hz, 3H, $C\mathbf{H}_3CH'HCHCHOH$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7 ($OCHCH'H\mathbf{C}H=CHCCH$), 111.1 ($OCHCH'HCH=\mathbf{C}HCCH$), 83.2 ($O\mathbf{C}HCH'HCH=CHCCH$), 82.4 ($OCHCH'HCH=CH\mathbf{C}CH$), 79.9 ($CH_2CHOH\mathbf{C}HCH'HCH$), 79.5 ($CH_3CH'H\mathbf{C}HCHOH$), 76.4 ($OCHCH'HCH=CHC\mathbf{C}H$), 73.6 ($CH_2\mathbf{C}HOHCHCH'HCH$), 73.2 ($CH_3CH'HCH\mathbf{C}HOH$), 70.4 ($CH_2CHOHCHCH'H\mathbf{C}H$), 33.0 ($OCH\mathbf{C}H'HCH=CHCCH$), 31.9 ($CH_2CHOHCH\mathbf{C}H'HCH$), 30.2 ($\mathbf{C}H_2CHOHCHCH'HCH$), 22.6 ($CH_3\mathbf{C}H'HCHCHOH$), 11.5 ($\mathbf{C}H_3CH'HCHCHOH$). IR ($\nu_{max}$ cm^{-1}): 3291 (O–H stretching overlapped with acetylene sp C–H stretching, broad), 2921 (aliphatic sp^3 C–H stretchings, broad), 2100 (acetylene C≡C stretching, weak), 1664 (C=C stretching, medium), 1084 (ether C–O–C antisymmetric stretching, strong). LRMS (ESI) $[M+H]^+$: *m/z* 267.2. HRMS (ESI) $[M+H]^+$: calculated for *m/z* 267.15909, found *m/z* 267.15919 ($C_{15}H_{23}O_4$). $[\alpha]_D^{25} = +14.0$ (c=0.10, MeOH) . Literature value: $[\alpha]_D^{25} = +32.0\ (c = 0.10, \mathrm{MeOH})$.[26] Spectroscopic data are in accordance with literature data.[26]

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12 Appendix

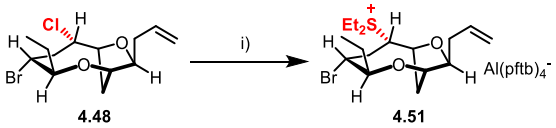
12.1 Attempts on the structural elucidation of 4.45

12.1.1 *Calculations of the NMR chemical shift differences between **4.45** and **4.5**, **4.48**, **4.46** and **4.50***

	4.45/ppm		4.45-4.5/ppm		4.5/ppm		4.45-4.48/ppm		4.48/ppm		4.45-4.46/ppm		4.46/ppm		4.45-4.50/ppm		4.50/ppm	
Atom No.	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**
3	5.11	118.1	0.0	0.7	5.11	117.4	0.0	0.7	5.12	117.4	0.0	0.6	5.10	117.5	0.0	-0.1	5.12	118.2
4	5.74	133.7	-0.1	-1.6	5.80	135.3	-0.1	-0.7	5.80	134.4	0.0	-0.9	5.79	134.6	-0.1	0.2	5.82	133.5
5	2.43	34.2	0.1	-3.3	2.37	37.5	0.0	-0.2	2.45	34.4	0.0	-0.1	2.44	34.3	0.2	-4.0	2.20	38.2
6	3.94	84.3	0.1	0.0	3.84	84.3	0.1	0.9	3.84	83.4	0.1	1.0	3.82	83.3	-0.1	-2.2	4.04	86.5
7	4.15	76.8	-0.2	-2.5	4.34	79.3	0.1	-0.1	4.03	76.9	0.1	0.0	4.04	76.8	0.1	17.7	4.04	59.1
8	2.47	35.3	0.6	0.6	1.88	34.7	0.2	0.8	2.24	34.5	0.3	1.8	2.22	33.5	0.1	-2.7	2.35	38.0
9	4.58	75.9	0.3	-6.4	4.26	82.3	0.1	-9.2	4.45	85.1	0.3	-4.4	4.29	80.3	0.4	-4.2	4.23	80.1
10	3.85	59.3	0.0	-25.0	3.84	84.3	-0.3	-7.1	4.14	66.4	-1.0	-21.5	4.86	80.8	-0.1	-19.7	3.96	79.0
11	2.48	37.7	0.4	2.3	2.10	35.4	-0.1	-7.7	2.58	45.4	0.3	-3.9	2.21	41.6	0.1	-1.7	2.41	39.4
12	3.94	50.6	-1.4	-73.1	5.32	123.7	0.2	-1.2	3.78	51.8	0.0	-1.1	3.91	51.7	0.1	3.1	3.86	47.5
13	3.63	81.2	-1.9	-53.5	5.52	134.7	0.2	0.9	3.48	80.3	0.2	0.6	3.46	80.6	-0.3	-6.1	3.90	87.3
14	1.83	28.0	-0.2	2.3	2.01	25.7	0.0	-0.2	1.80	28.2	0.0	-0.1	1.82	28.1	0.2	2.4	1.62	25.6
15	0.97	9.6	0.0	-4.2	0.96	13.8	0.0	-0.1	0.95	9.7	0.0	-0.2	0.96	9.8	0.0	-0.6	0.99	10.2
Average of absolute value			0.4	13.5			0.1	2.3			0.2	2.8			0.1	5.0		

Table 12.1. NMR chemical shifts of the titled compounds, their differences with each other, and the average of the absolute values of the differences.

12.1.2 *Synthesis of the sulfonium ion **4.51***



Scheme 12.1. Generation of the sulfonium ion **4.51**.

Reagents and conditions: **i)** $Ag[Al(pftb)_4]\cdot CH_2Cl_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 1.5 hrs, then filtered into flame-dried round bottom flask at -78 °C, then Et_2S (1.1 eq.) was added and warmed to r.t., followed by NMR acquisition in $CDCl_3$ at 25 °C.

The sulfonium ion **4.51** was synthesised from **4.48** *via* formation of the corresponding oxonium ion and its quenching by Et_2S. Comparison of its ^{1}H and ^{13}C chemical shifts with **4.48** is shown below (**Figure 12.1**). The ^{1}H and ^{13}C NMR chemical shifts of atoms 7 and 13 did not change drastically as compared with the oxonium ions. The ^{1}H and ^{13}C NMR chemical shifts at atom 10 did not become more deshielded but were found to be shielded by 0.5 ppm/7.0 ppm respectively upon formation of the sulfonium ion. However, if the ^{1}H and ^{13}C chemical shifts of the ethyl groups (atoms 16-19) of the sulfonium ions are compared with the ^{1}H and ^{13}C chemical shifts of diethyl sulfide (**Figure 4.24**), the ^{1}H and ^{13}C chemical shifts of the α-C–Hs are deshielded by 0.75 ppm/6.8 ppm respectively, whereas the ^{1}H and ^{13}C chemical shifts of the β-C–Hs are deshielded by 0.33 ppm and shielded by 5.4 ppm respectively as expected from the

formation of a sulfonium ion (**Figure 12.1**).

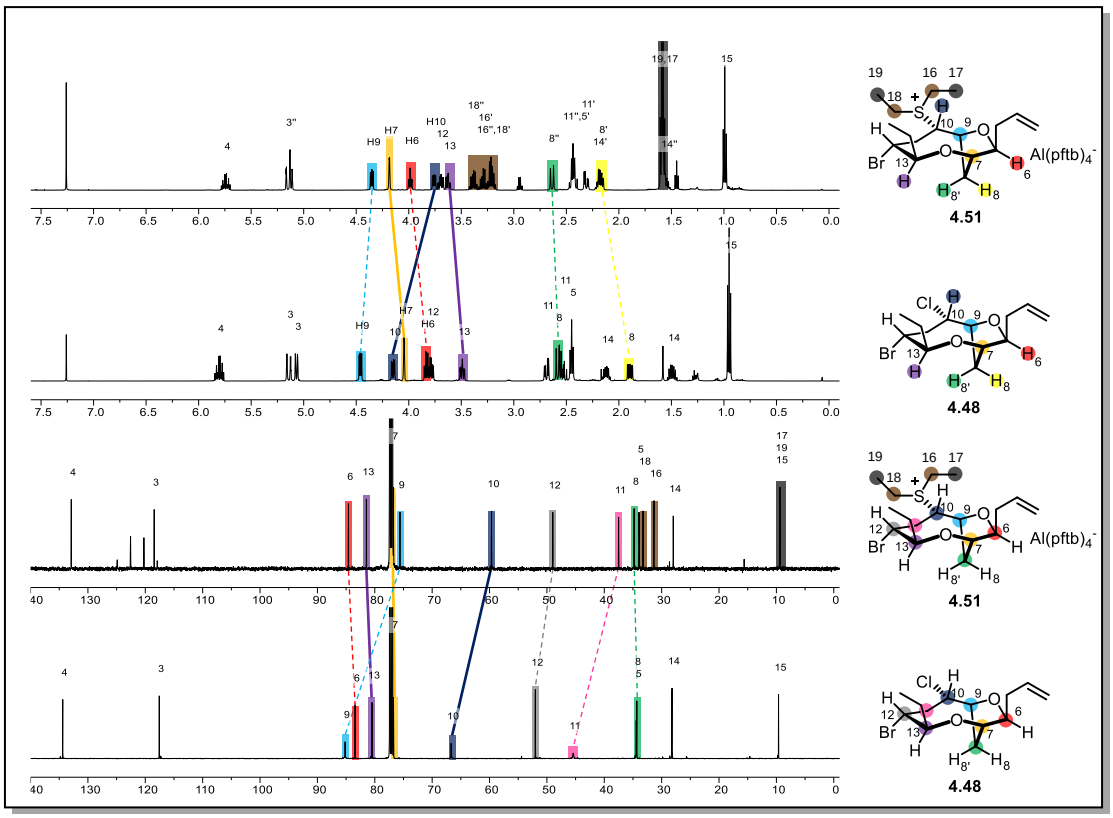


Figure 12.1. ^{1}H and ^{13}C NMR chemical shift comparison between **4.51** and **4.48**.

The formation of the sulfonium ion is further supported by the ^{1}H-^{13}C HMBC correlations between atoms 10, 16 and 18 (**Figure 12.2**).

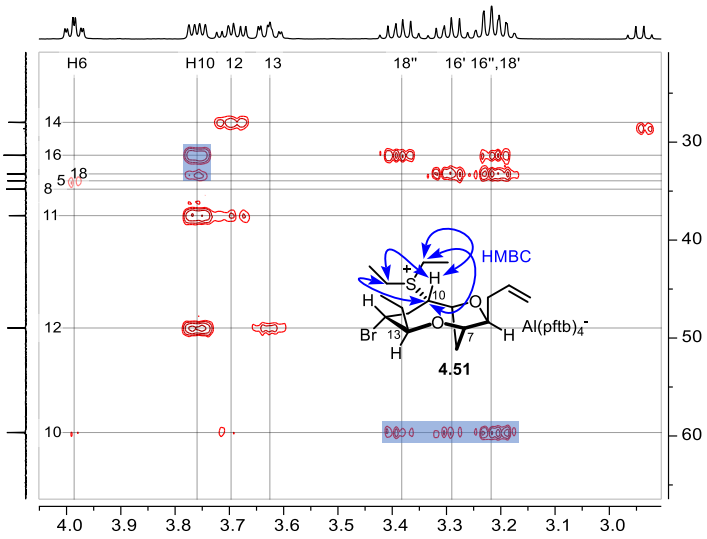


Figure 12.2. ^{1}H-^{13}C HMBC correlation between atoms 10, 16 and 18 in **4.51**.

However, the comparison of the ^{1}H and ^{13}C chemical shifts of **4.51** and **4.45** as if they are both sulfonium ions revealed that they are not identical (**Figure 12.3**).

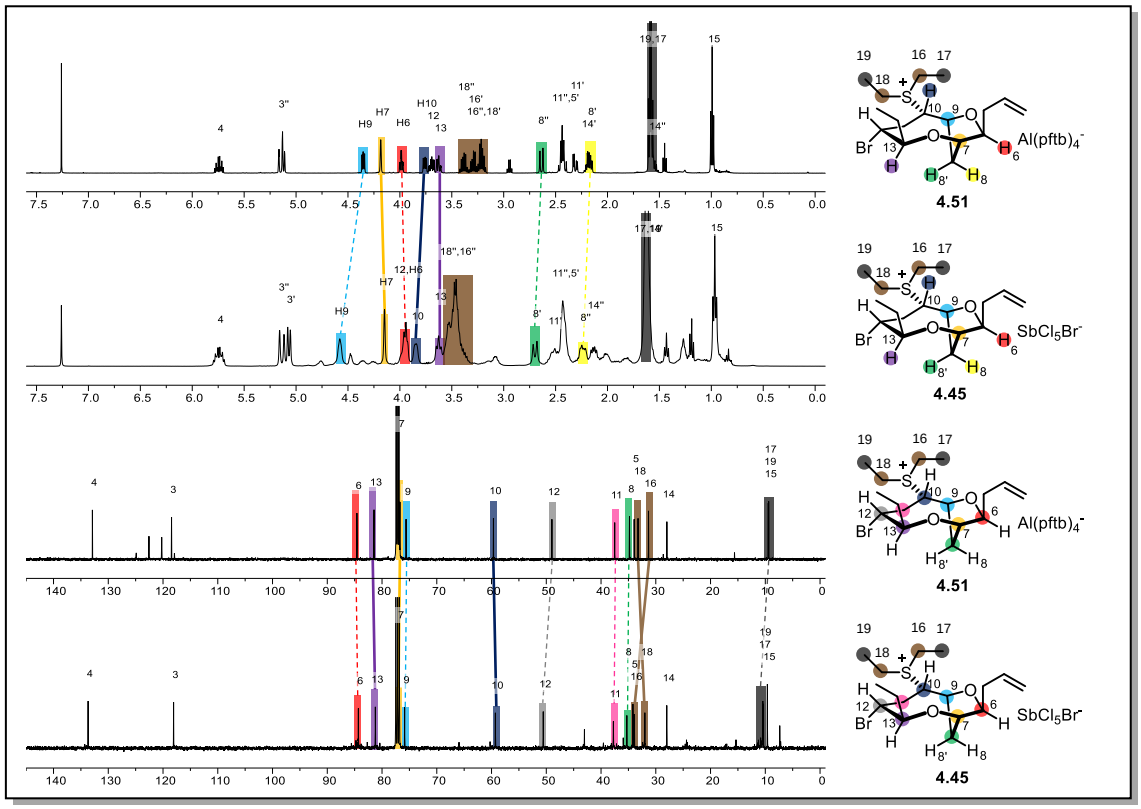


Figure 12.3. ^{1}H and ^{13}C NMR chemical shift comparison between **4.51** and **4.45**. Note: The assignments for atoms 16 and 18 are interchangeable in **4.45**.

12.2 Usage of the MestReJ software

The MestReJ software was obtained as a freeware from Mestrelab Research at http://mestrelab.com/software/freeware/.[189] The Dìez-Altona-Donders (DAD) equation (cross terms) was used for all the dihedral angles predictions from experimental $^{3}J_{HH}$ coupling constants as suggested by the authors, however with the following caveats.

> *The most precise of these equations, the DAD cross-terms (eq 9), is directly applicable, with a σ deviation of 0.31 Hz, to those fragments CHS_1S_2–CHS_3S_4 with substituents of known λ parameters. Otherwise, the λ parameters may be determined from appropriate J^M couplings to methyl groups by means of eq 7 or, when this approach is not possible, λ parameters from similar substituents may be used. The equation does not account explicitly for the effect upon J of changes in the bond angles HCC. Therefore, the predicted J values can show large deviations from the experimental ones for strained cyclic compounds, when substantial deviations of HCC angles from tetrahedral value occur, i.e., three- and four membered rings and multicycles. In five-membered rings, large deviations appear when the contribution to J from the Barfield effect is important. –Navarro-Vázquez and co-workers*

The chemical groups are assigned as follows for the prediction of the dihedral angles (**Figure 12.4**).

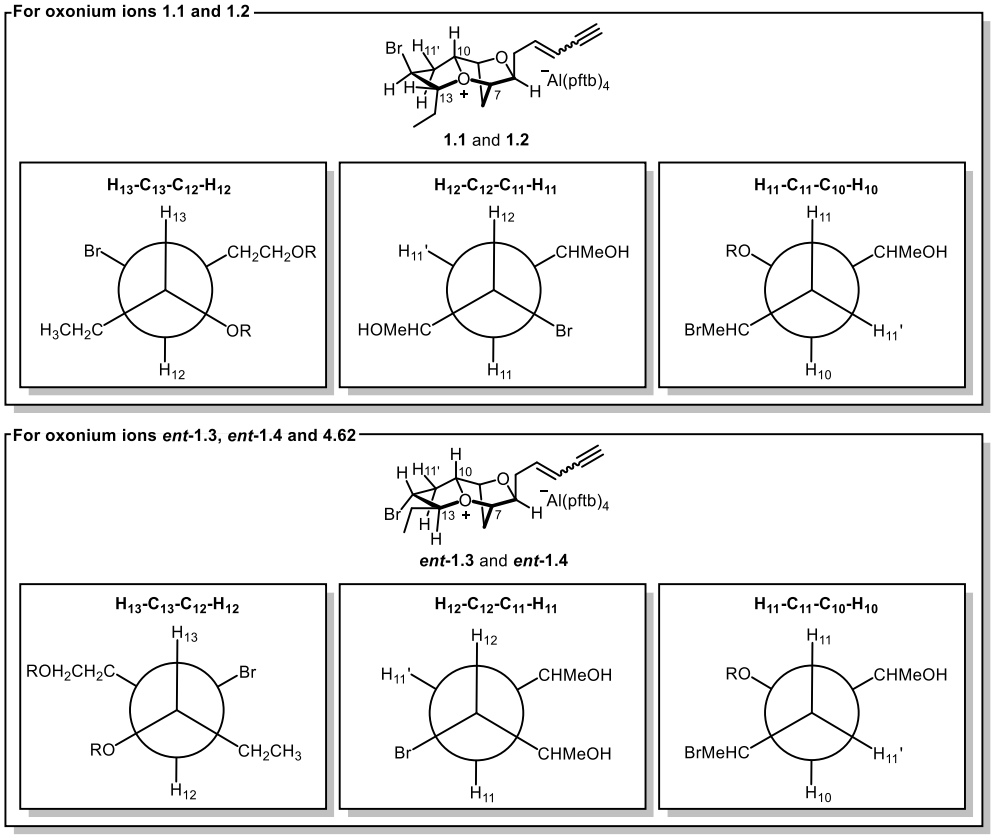


Figure 12.4. Assignment of chemical groups in the MestReJ software.

12.3 NMR spectra of the oxonium ions 4.62, 1.1, 1.2, *ent*-1.3, *ent*-1.4 and the oxocarbenium ion 4.63

This section presents the completely assigned NMR spectra of the oxonium ions **4.62**, **1.1**, **1.2**, ***ent*-1.3**, ***ent*-1.4** and oxocarbenium ion **4.63** synthesised in this project.

12.3.1 *NMR spectra of the oxonium ion **4.62** (500 MHz, CD_2Cl_2, -78 °C)*

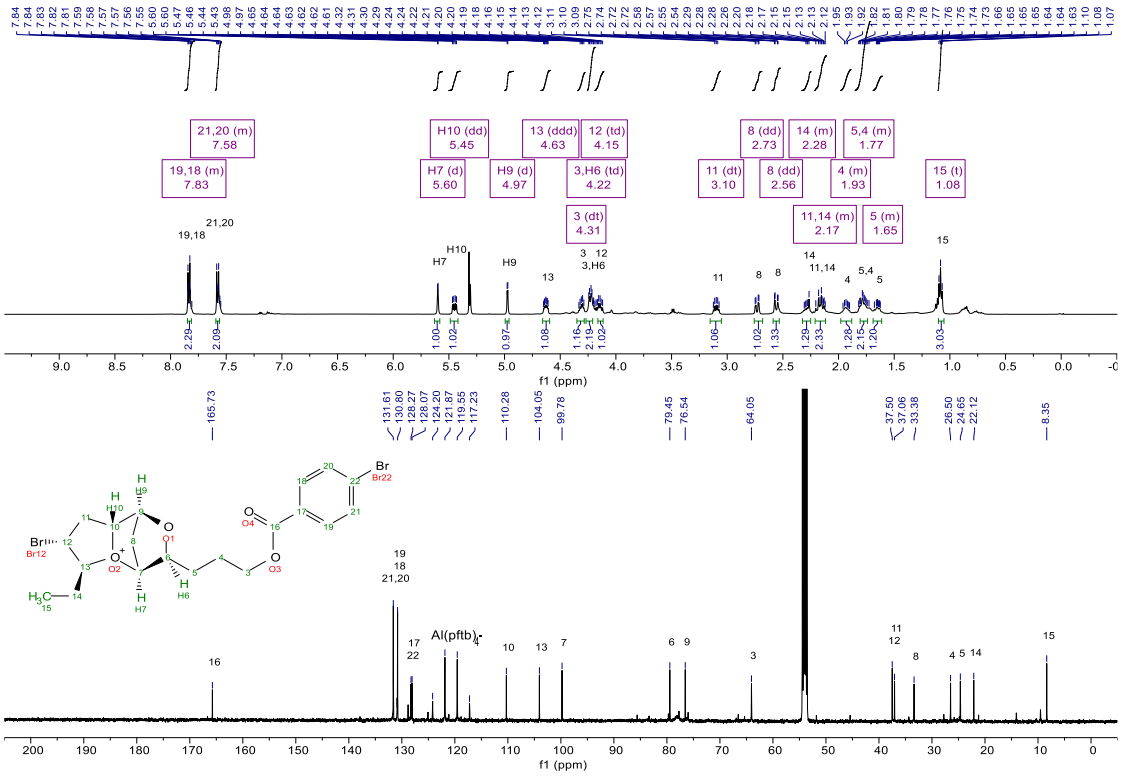
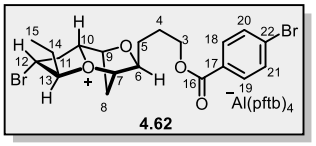


Figure 12.5. ^{1}H and ^{13}C NMR spectra of **4.62**.



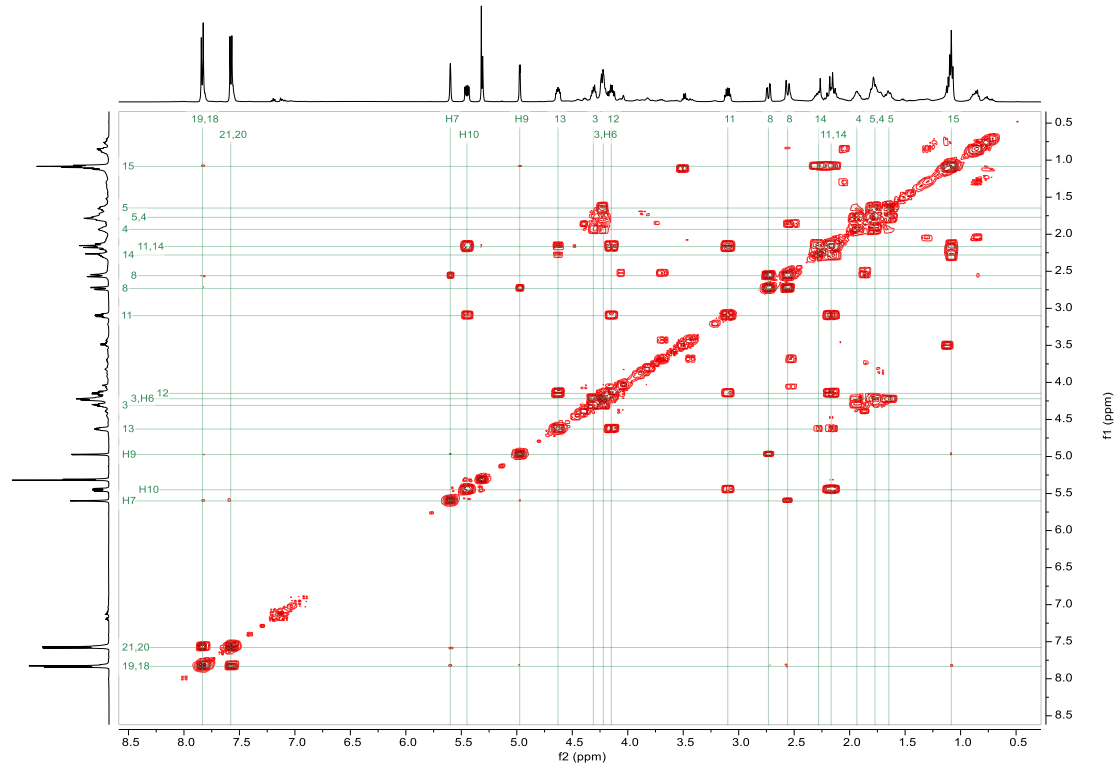
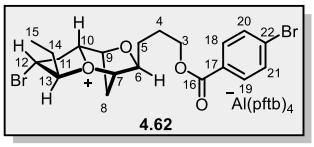


Figure 12.6. ^{1}H-^{1}H COSY spectrum of **4.62**.



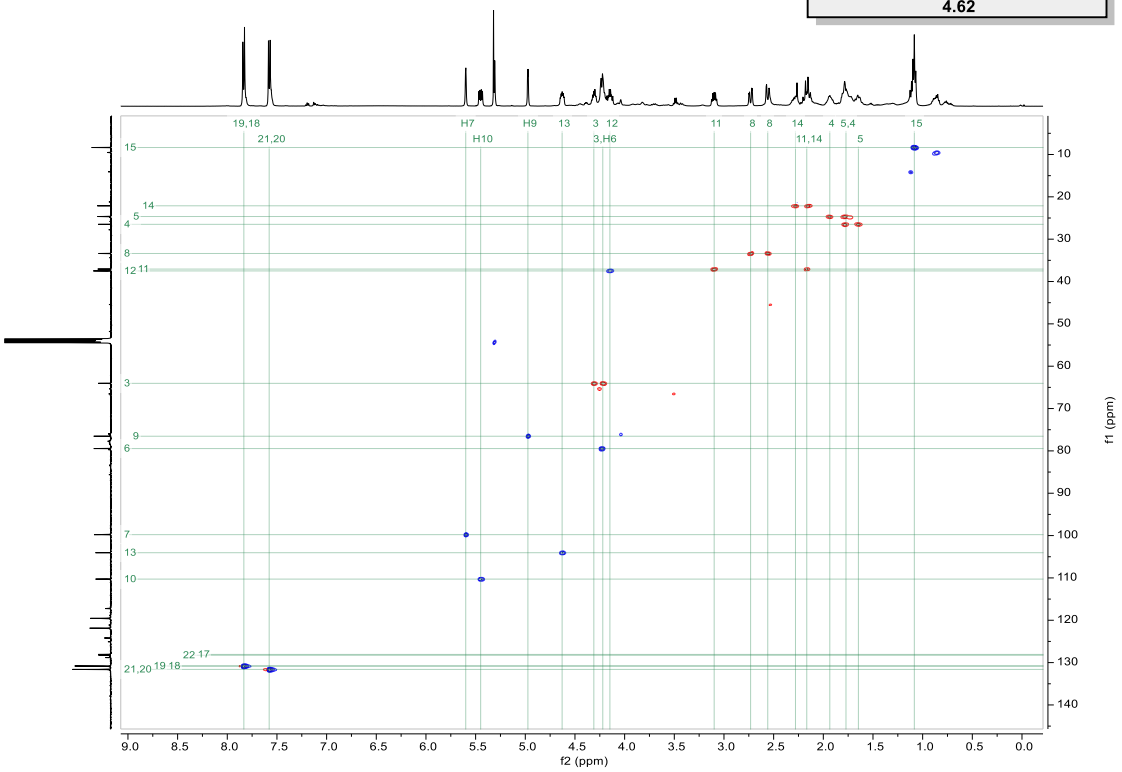


Figure 12.7. ^{1}H-^{13}C edited–HSQC spectrum of **4.62**.

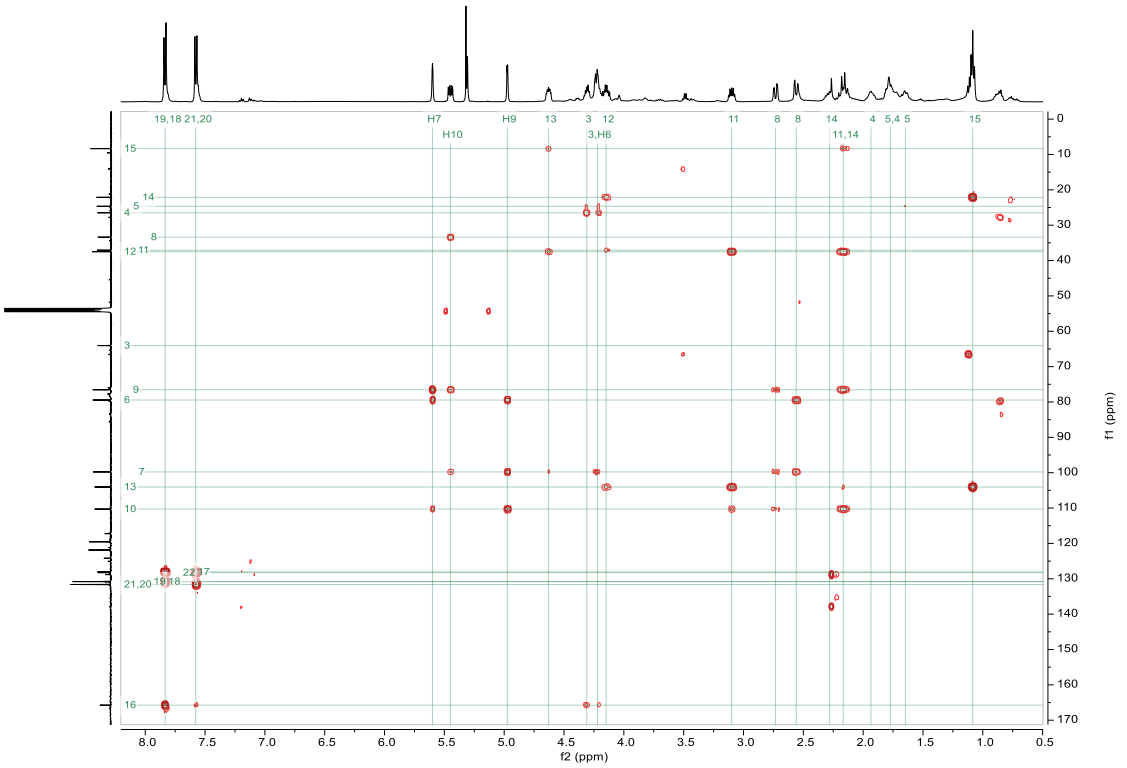
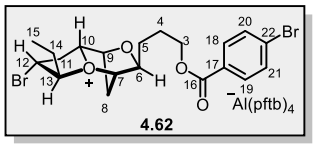


Figure 12.8. ^{1}H-^{13}C HMBC spectrum of **4.62**.



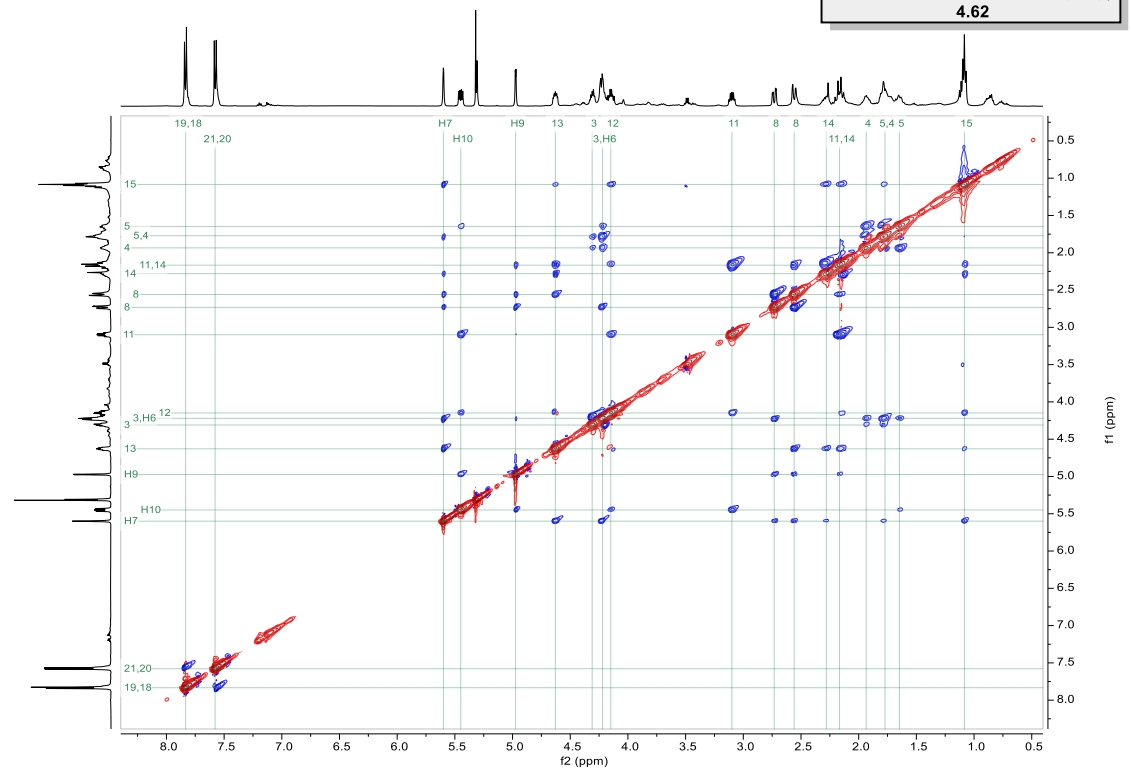


Figure 12.9. ^{1}H-^{1}H ROESY spectrum of **4.62**.

12.3.2 *NMR spectra of the oxonium ion **1.1** (500 MHz, CD_2Cl_2, -78 °C)*

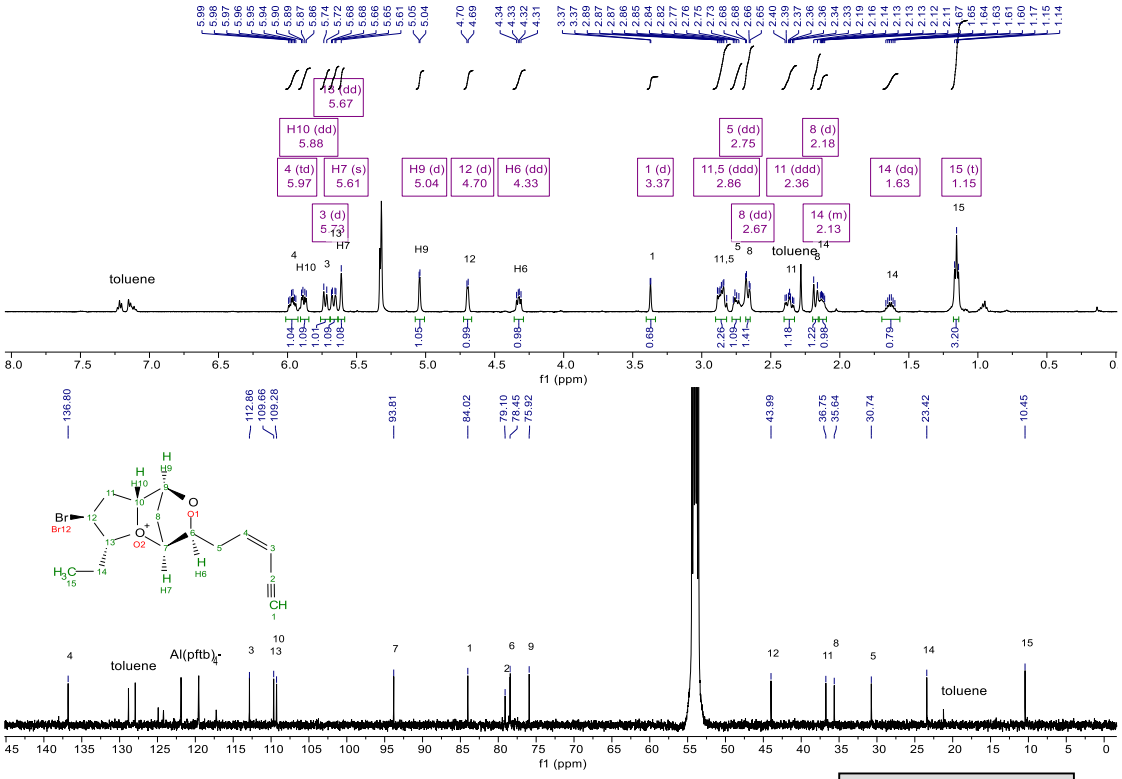


Figure 12.10. ^{1}H and ^{13}C NMR spectra of **1.1**.

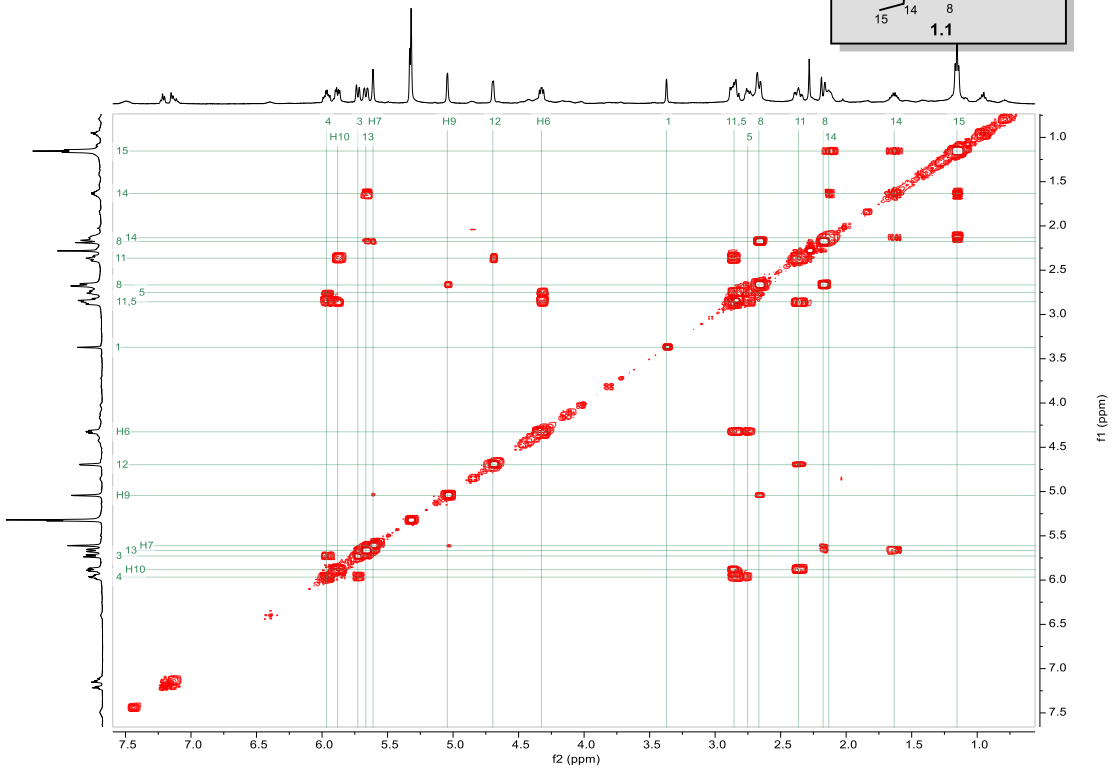


Figure 12.11. ^{1}H-^{1}H COSY spectrum of **1.1**.

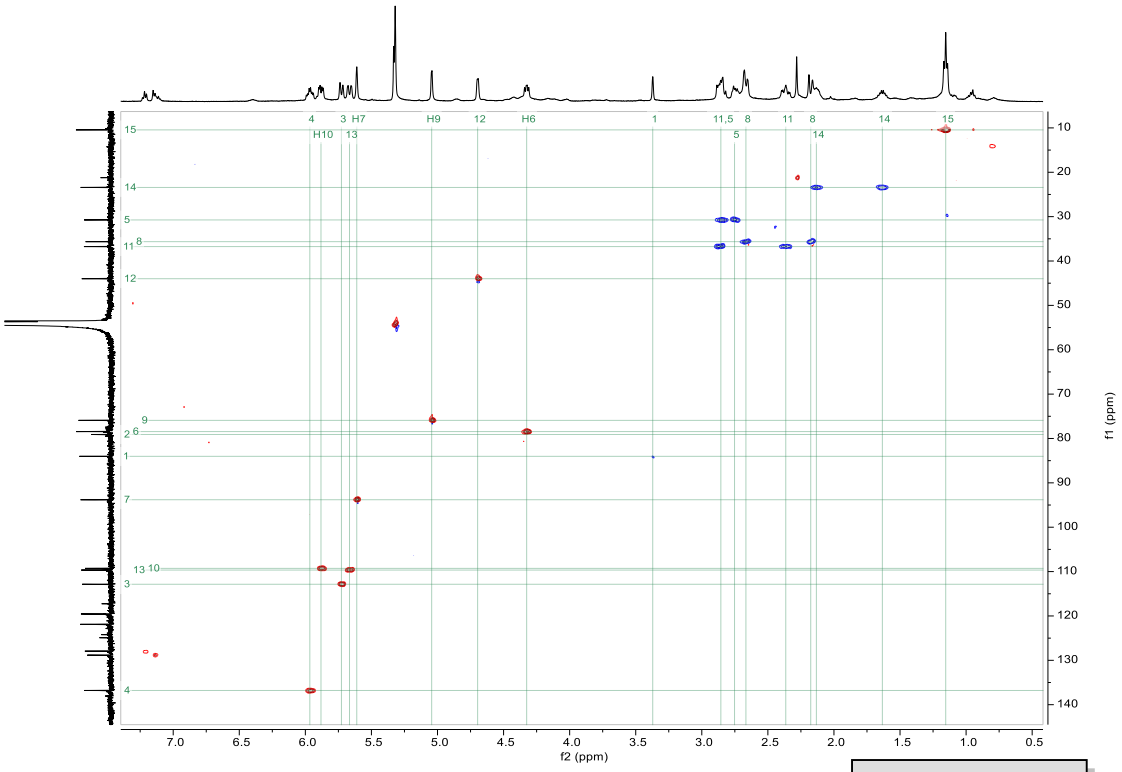
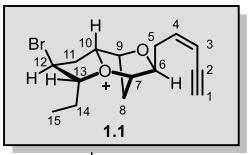


Figure 12.12. ^{1}H-^{13}C edited–HSQC spectrum of **1.1**.



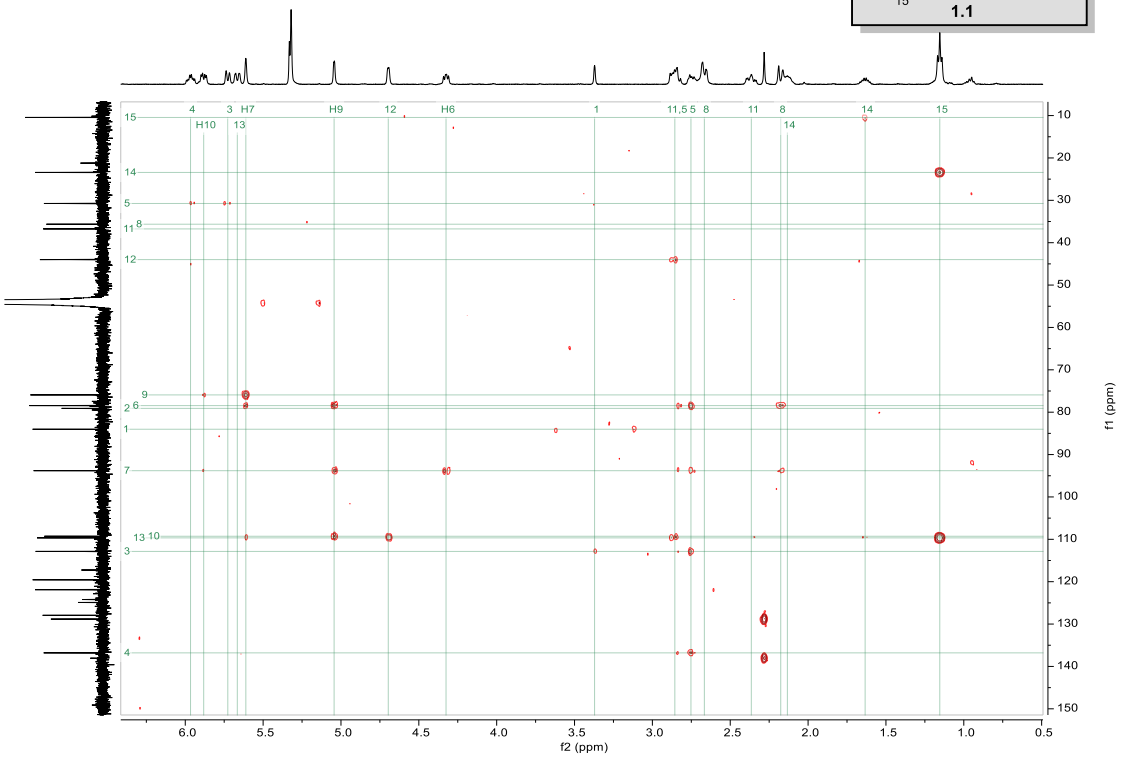


Figure 12.13. ^{1}H-^{13}C HMBC spectrum of **1.1**.

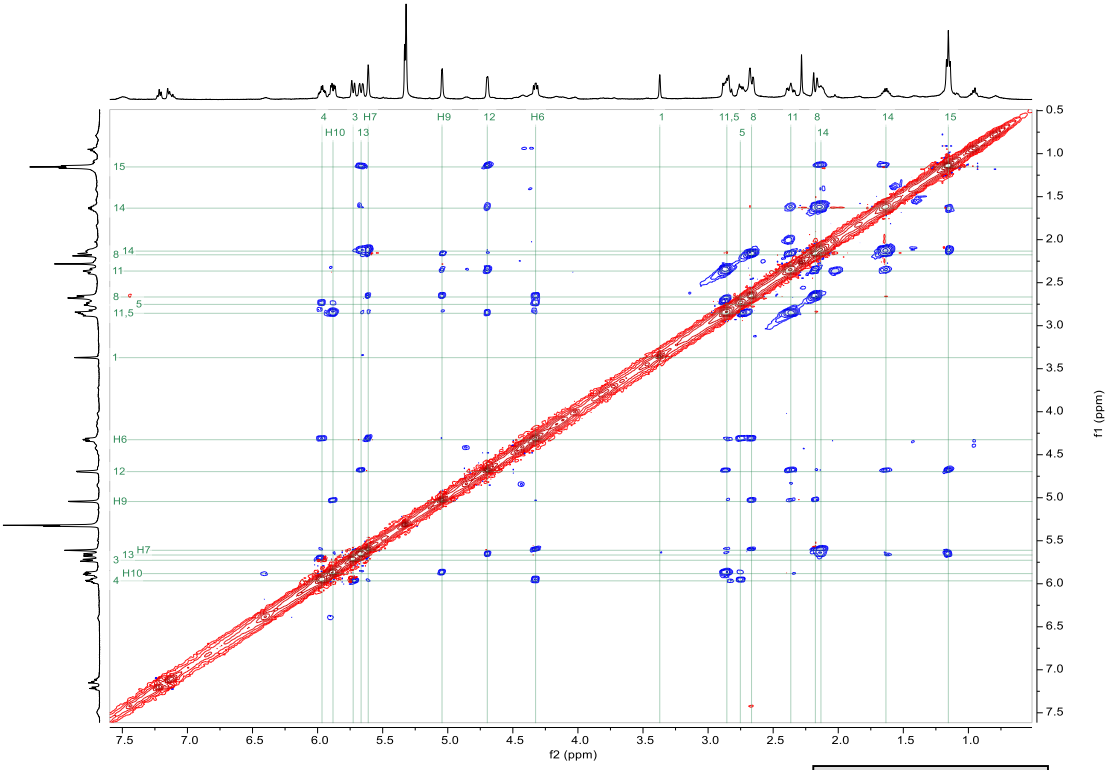


Figure 12.14. ^{1}H-^{1}H ROESY spectrum of **1.1**.

12.3.3 *NMR spectra of the oxonium ion **1.2** (500 MHz, CD_2Cl_2, -78 °C)*

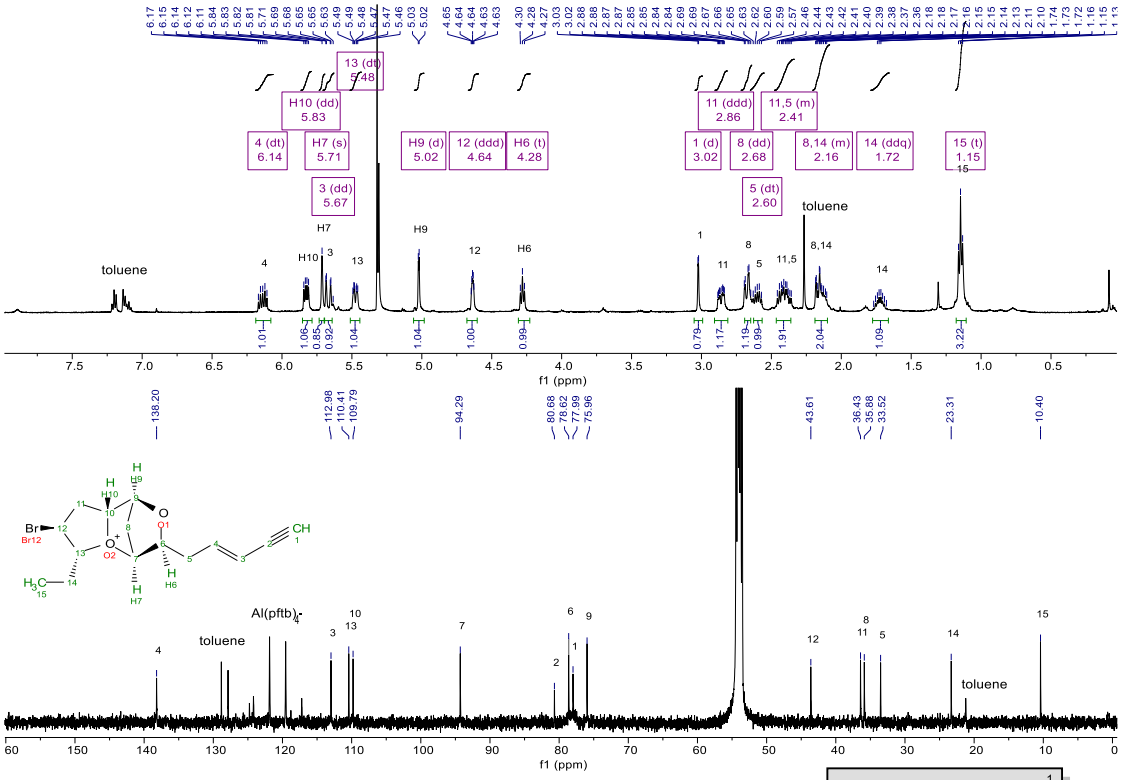


Figure 12.15. ^{1}H and ^{13}C NMR spectra of **1.2**.

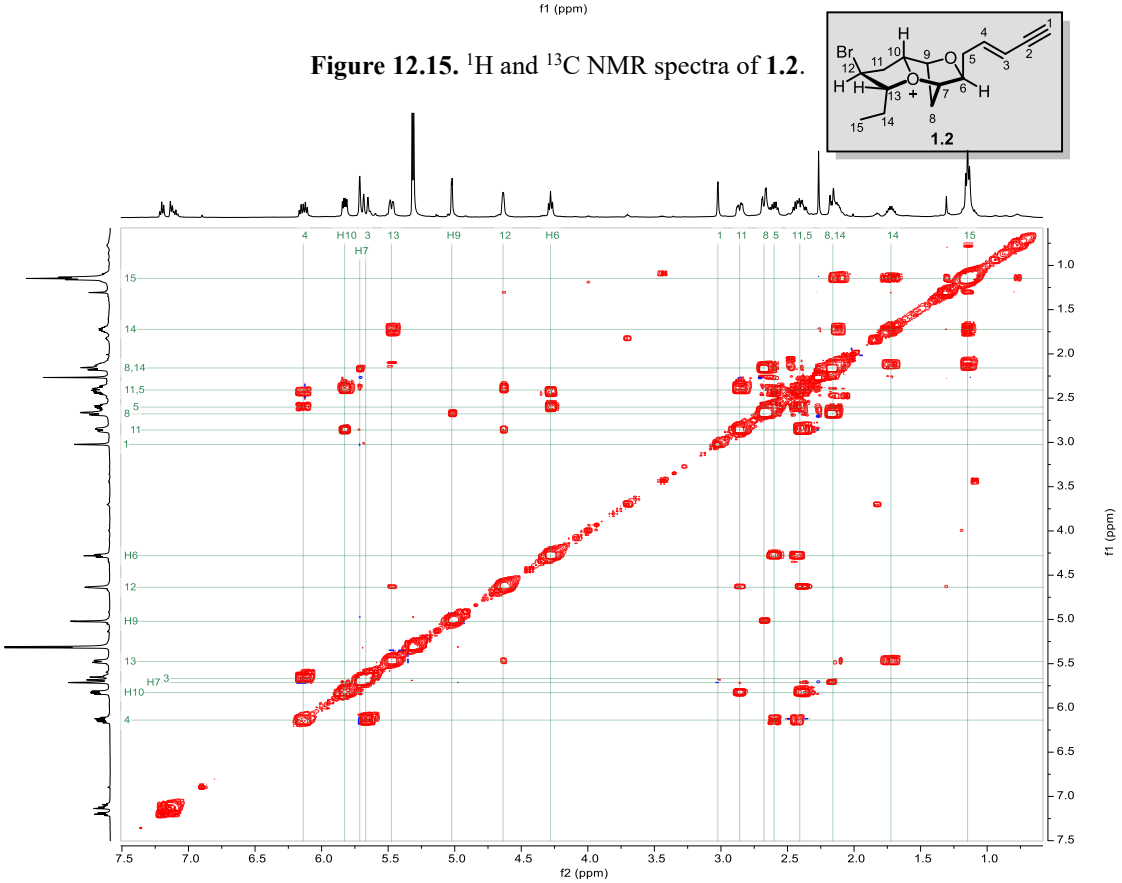


Figure 12.16. ^{1}H-^{1}H COSY spectra of **1.2**.

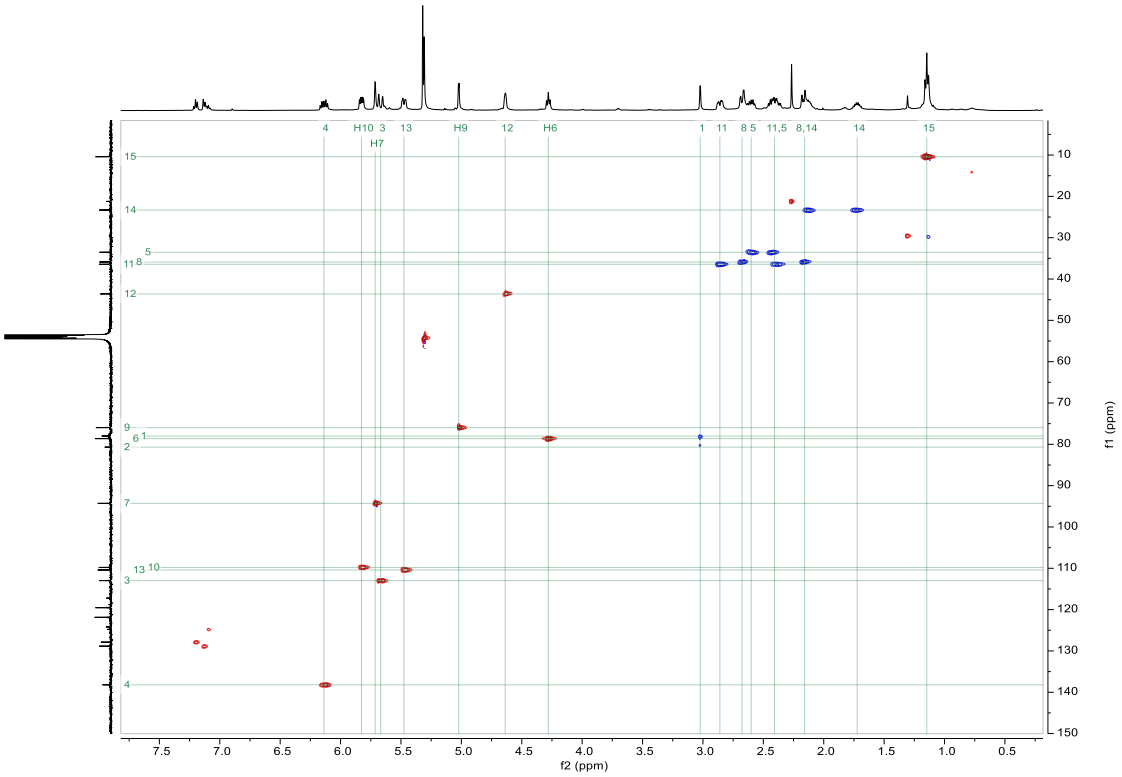
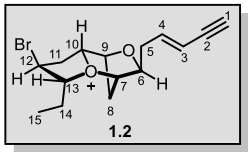


Figure 12.17. ^{1}H-^{13}C edited–HSQC spectra of **1.2**.



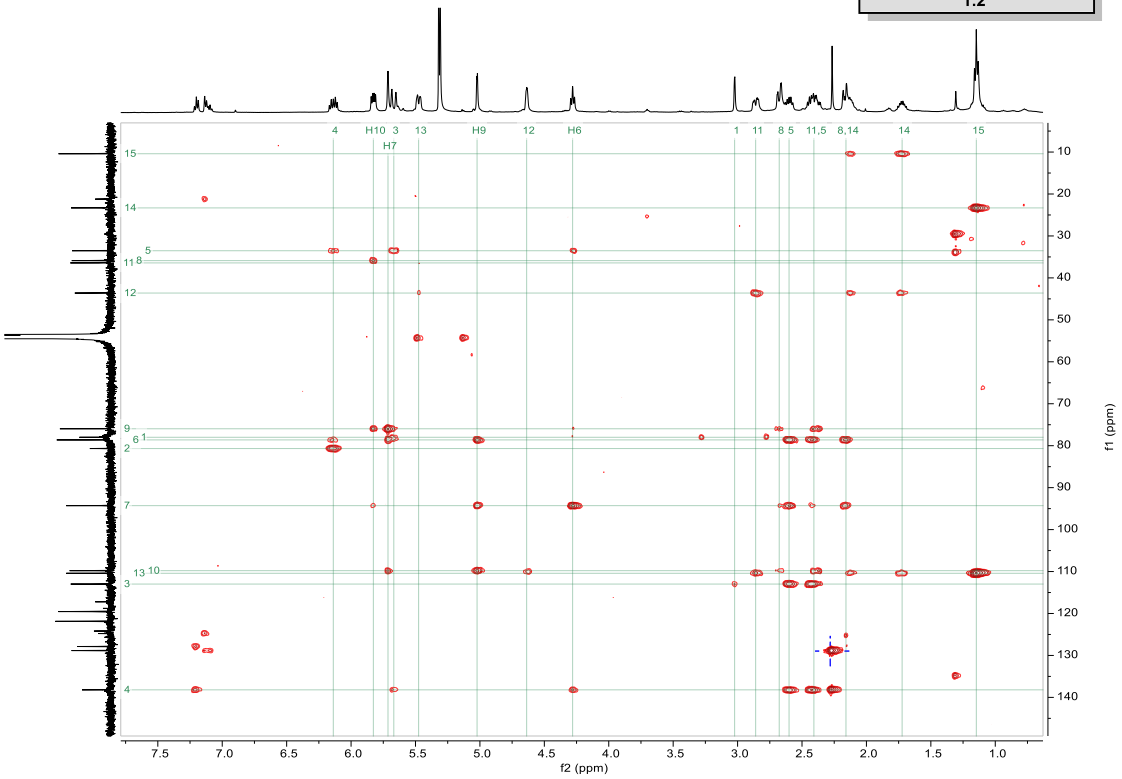


Figure 12.18. ^{1}H-^{13}C HMBC spectra of **1.2**.

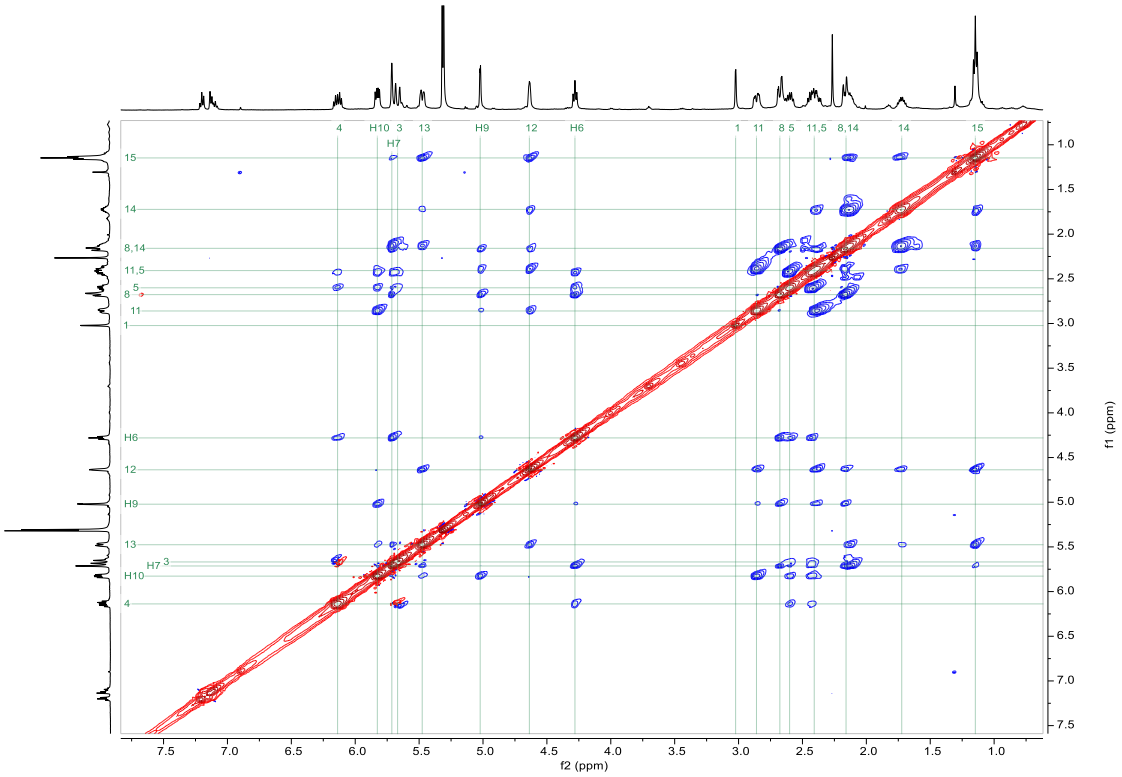
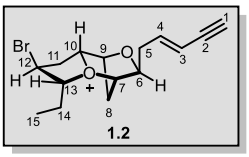


Figure 12.19. ^{1}H-^{1}H ROESY spectra of **1.2**.



12.3.4 *NMR spectra of the oxonium ion **ent-1.3** (500 MHz, CD_2Cl_2, -78 °C)*

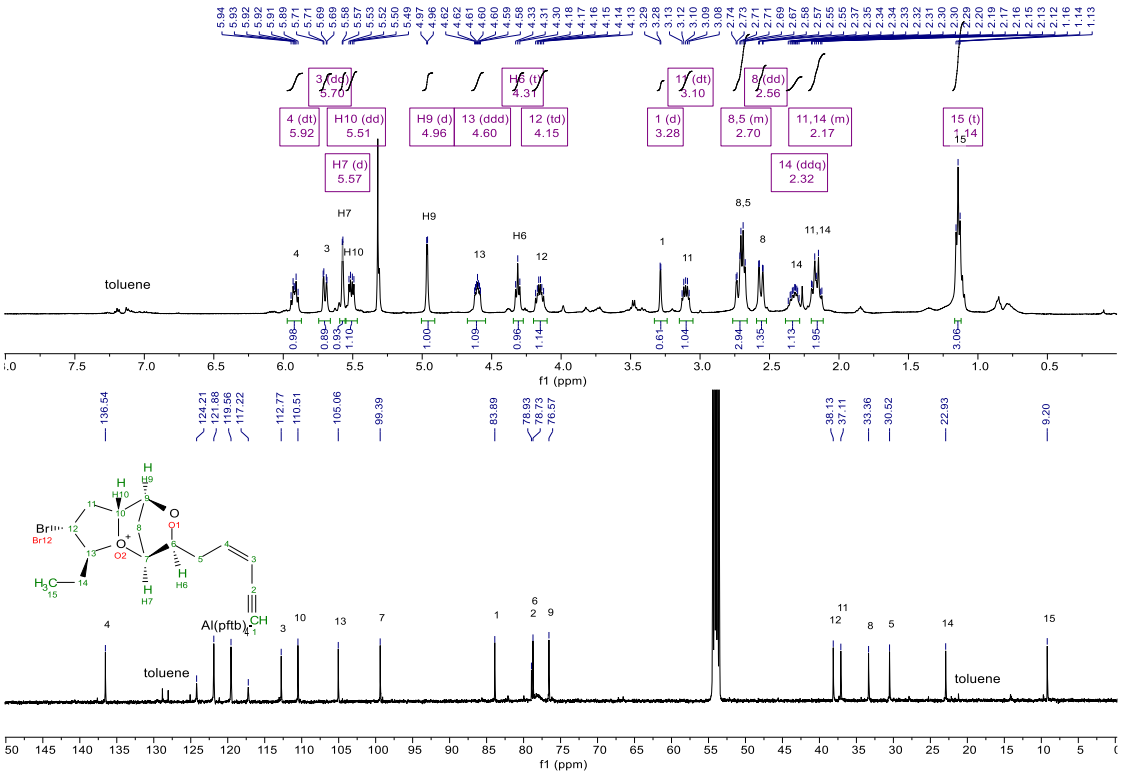


Figure 12.20. ^{1}H and ^{13}C NMR spectra of ***ent*-1.3**.

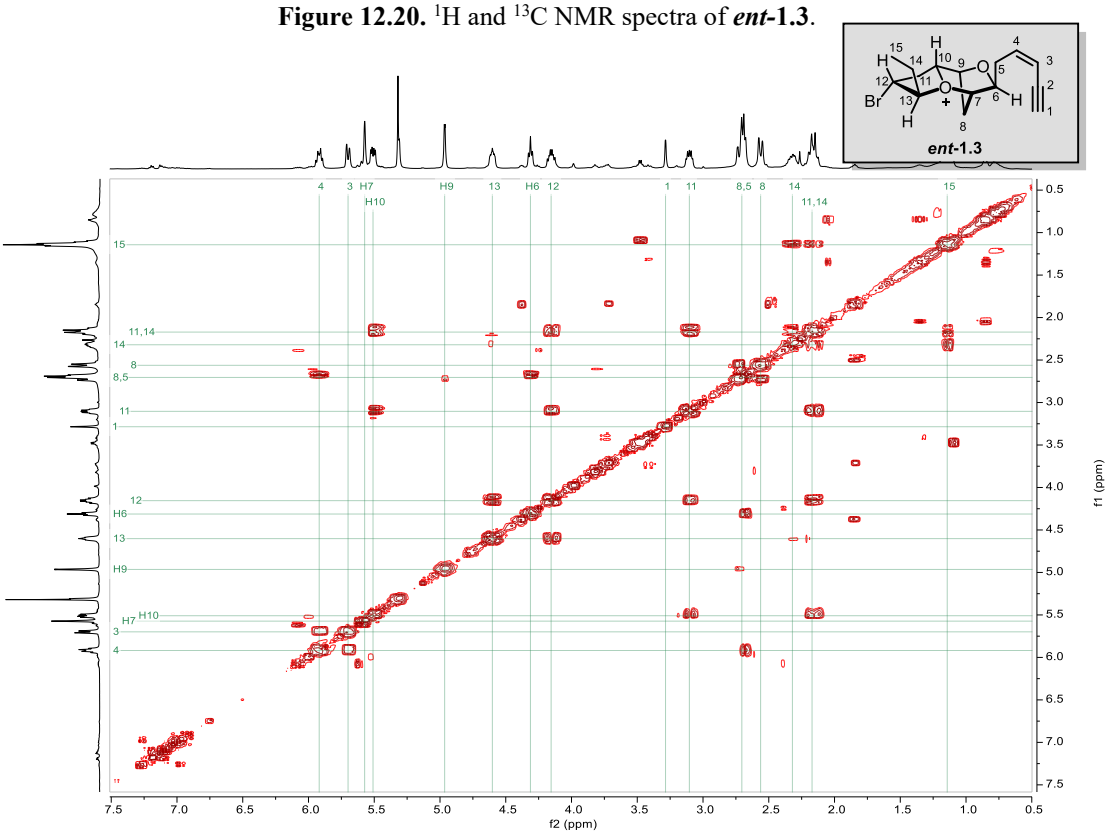


Figure 12.21. ^{1}H-^{1}H COSY spectra of ***ent*-1.3**.

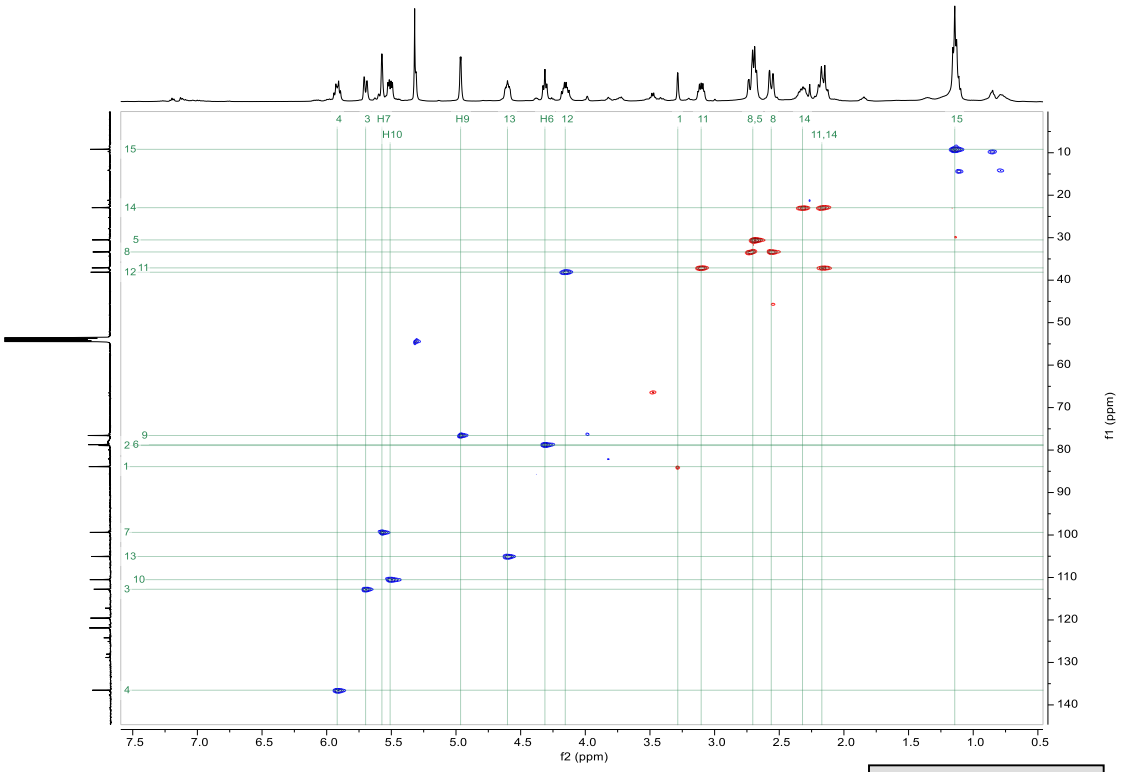
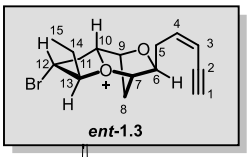


Figure 12.22. ^{1}H-^{13}C edited–HSQC spectra of ***ent*-1.3**.



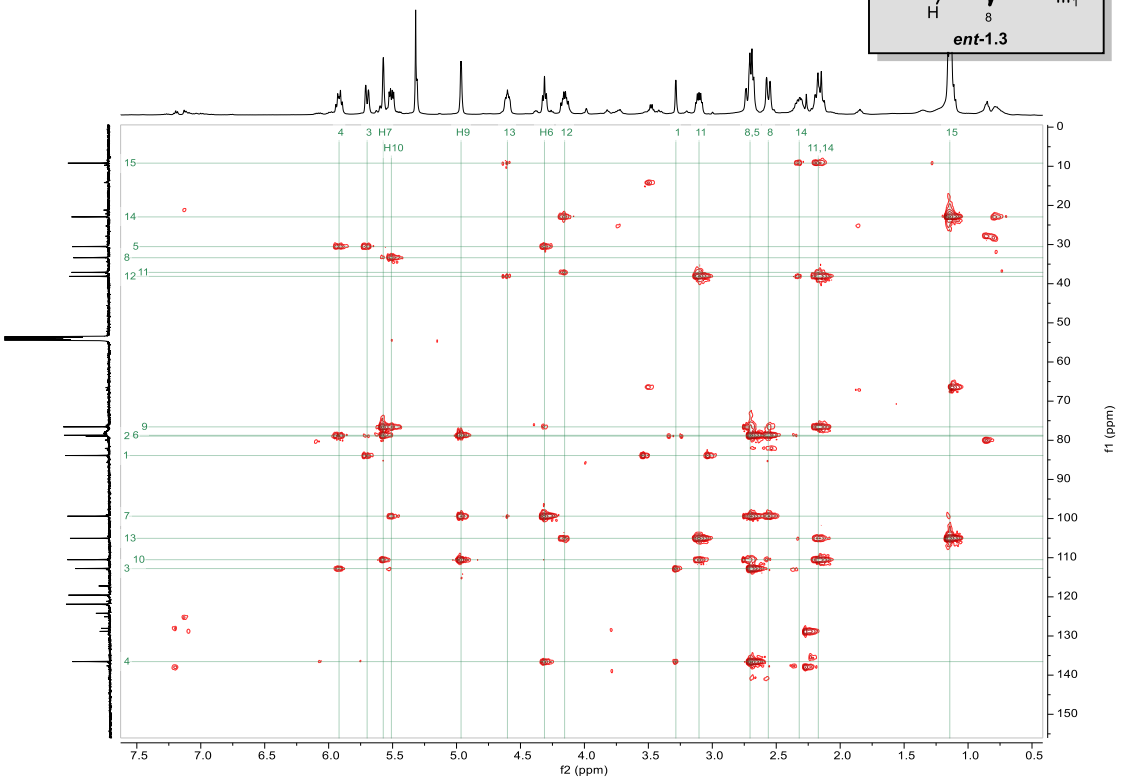


Figure 12.23. ^{1}H-^{13}C HMBC spectra of ***ent*-1.3**.

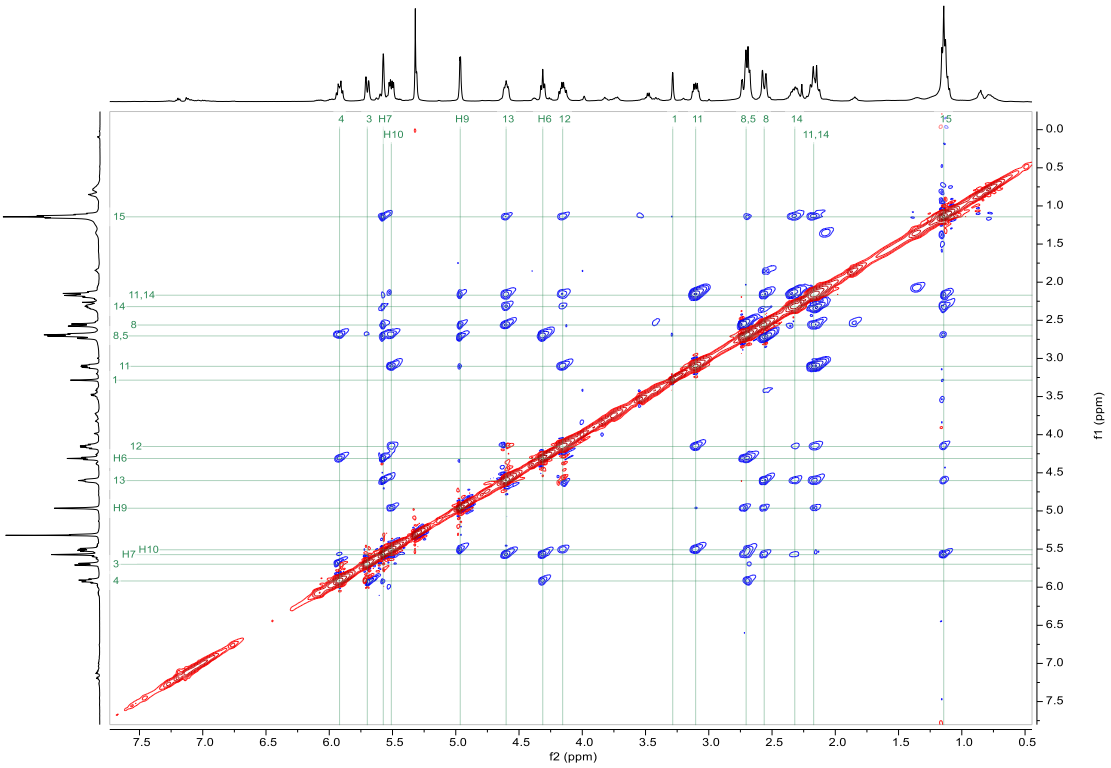
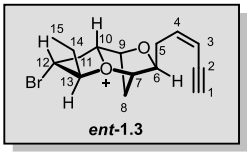


Figure 12.24. ^{1}H-^{1}H ROESY spectra of ***ent*-1.3**.



12.3.5 *NMR spectra of the oxonium ion **ent-1.4** (500 MHz, CD_2Cl_2, -78 °C)*

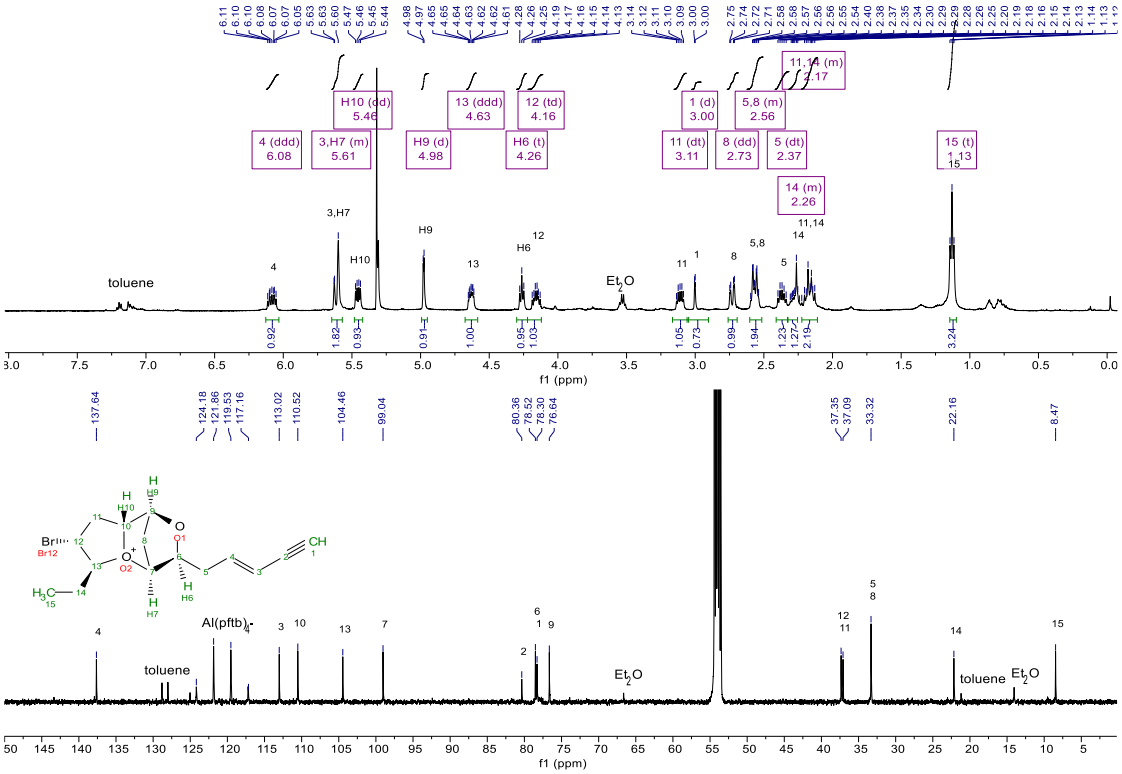


Figure 12.25. ^{1}H and ^{13}C NMR spectra of ***ent*-1.4**.

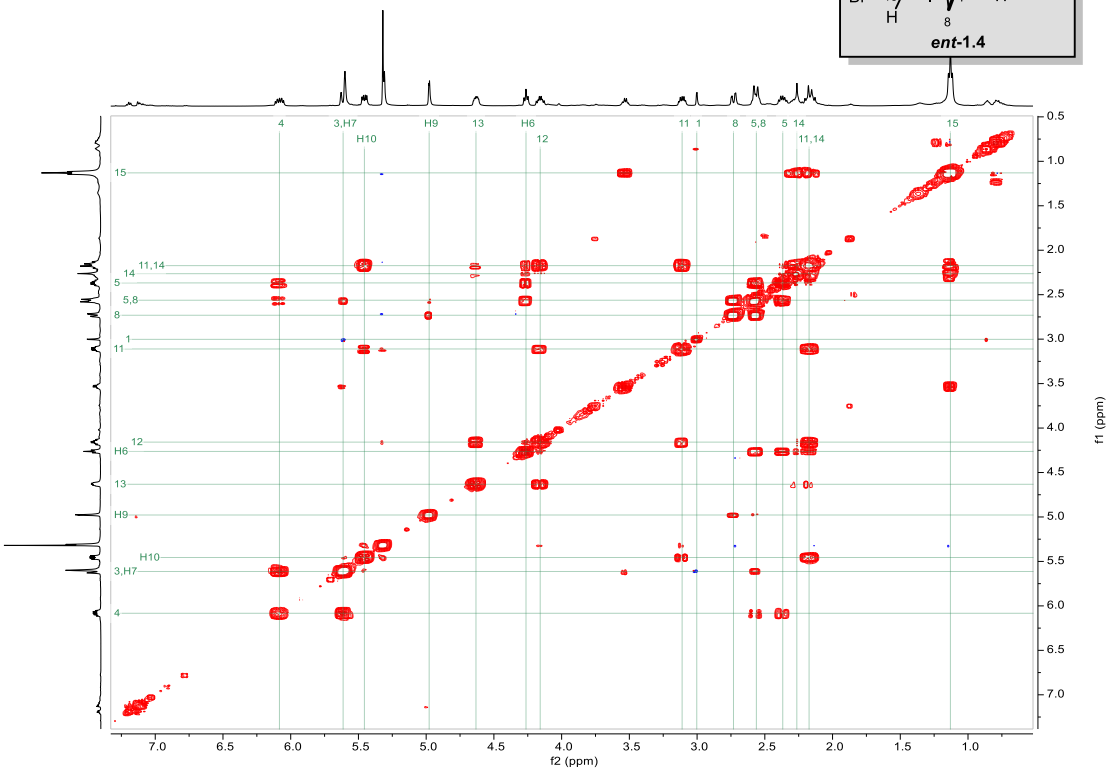


Figure 12.26. ^{1}H-^{1}H COSY spectra of ***ent*-1.4**.

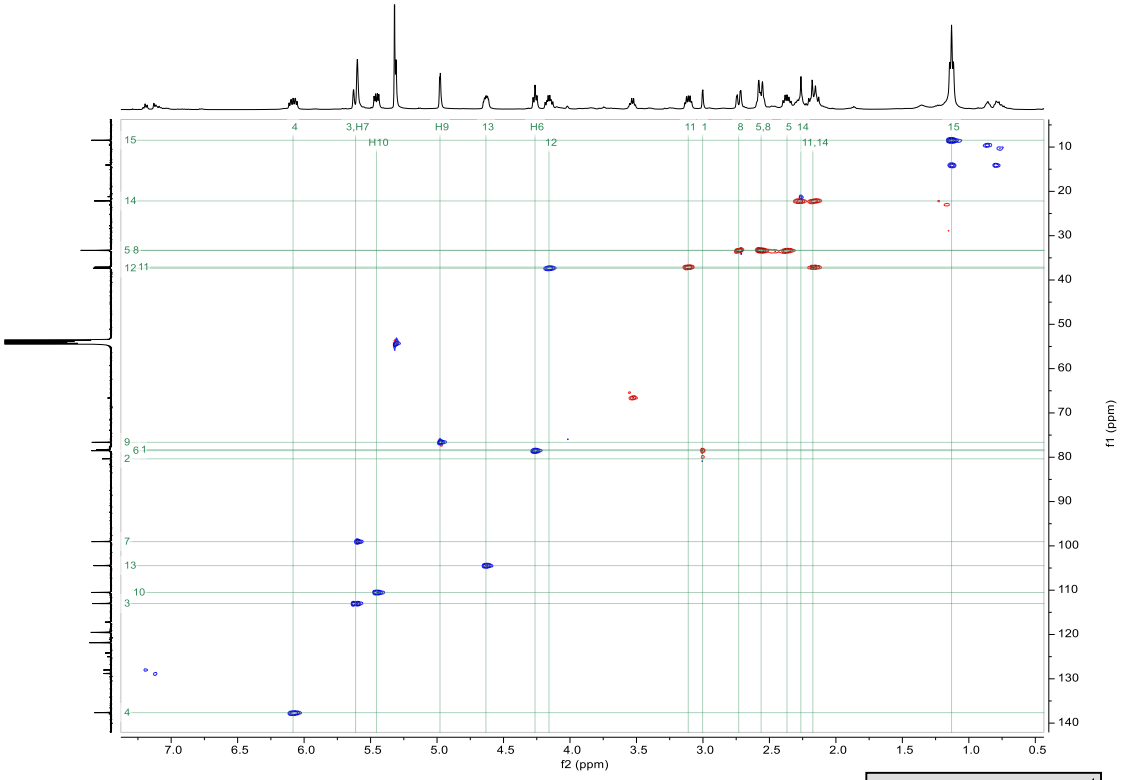
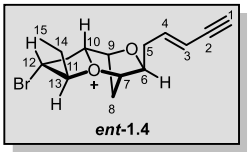


Figure 12.27. ^{1}H-^{13}C edited–HSQC spectra of ***ent*-1.4**.



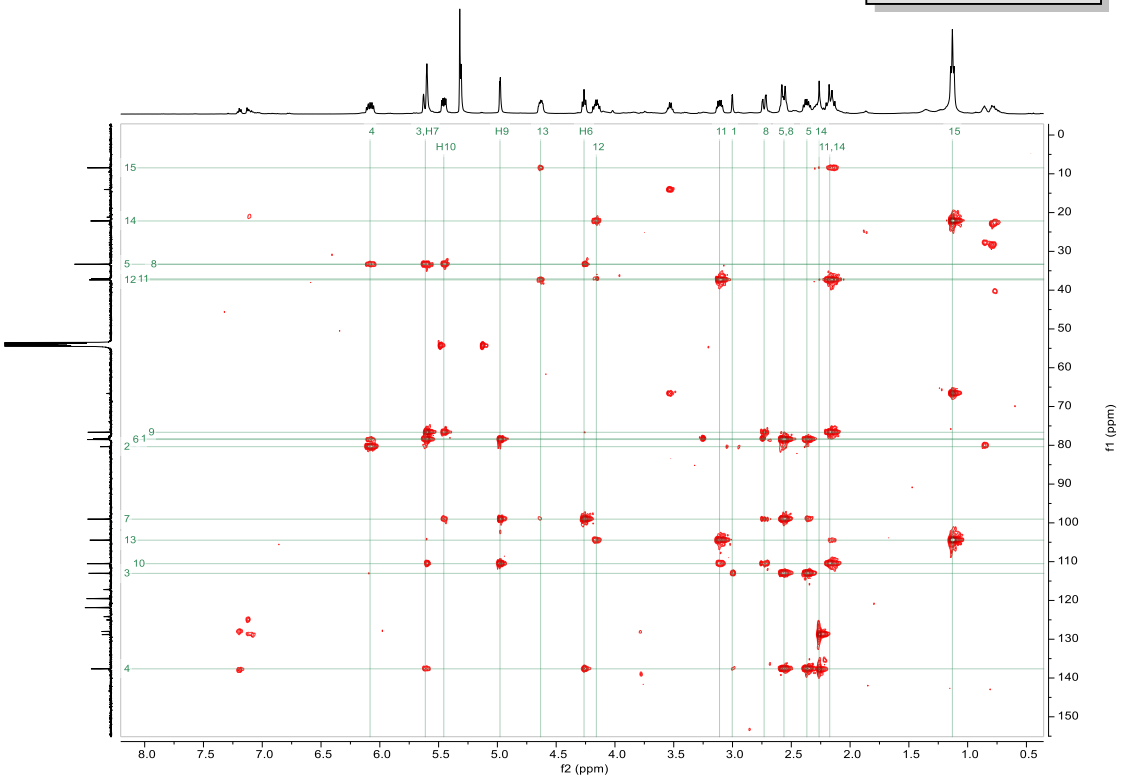


Figure 12.28. ^{1}H-^{13}C HMBC spectra of ***ent*-1.4**.

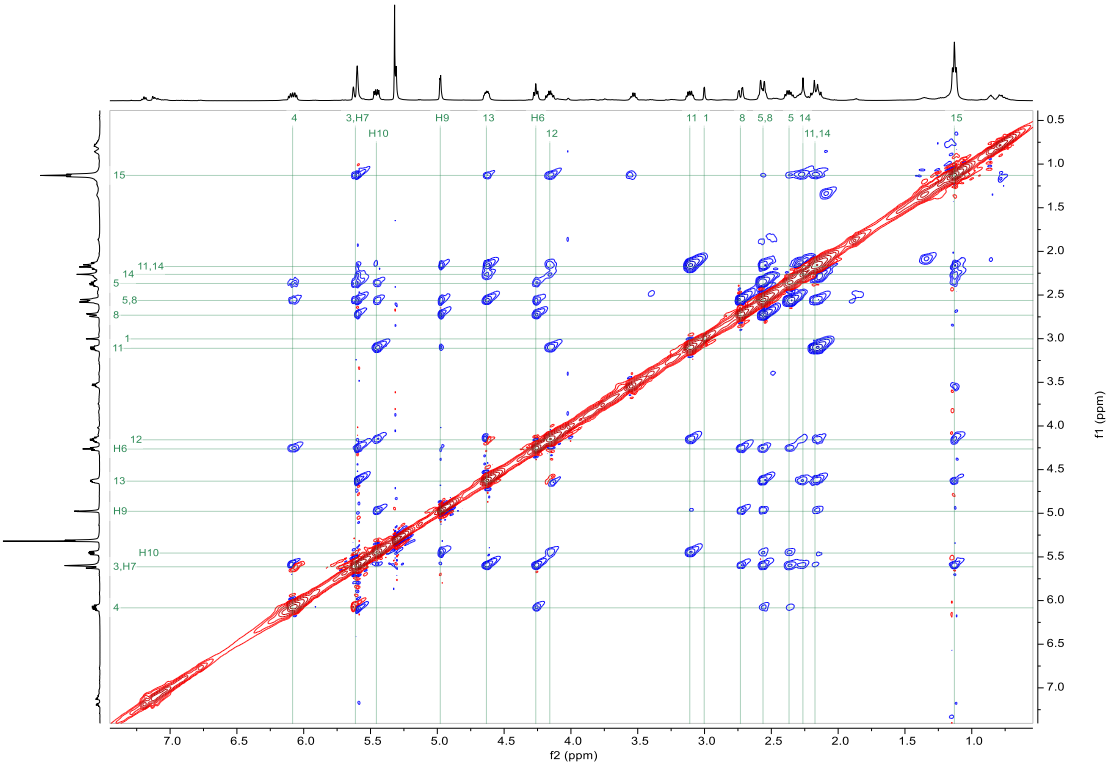
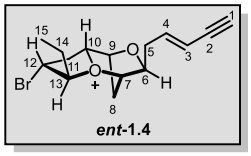


Figure 12.29. ^{1}H-^{1}H ROESY spectra of ***ent*-1.4**.



12.3.6 *NMR spectra of the oxocarbenium ion **4.63** (400 MHz, CD_2Cl_2, 25 °C)*

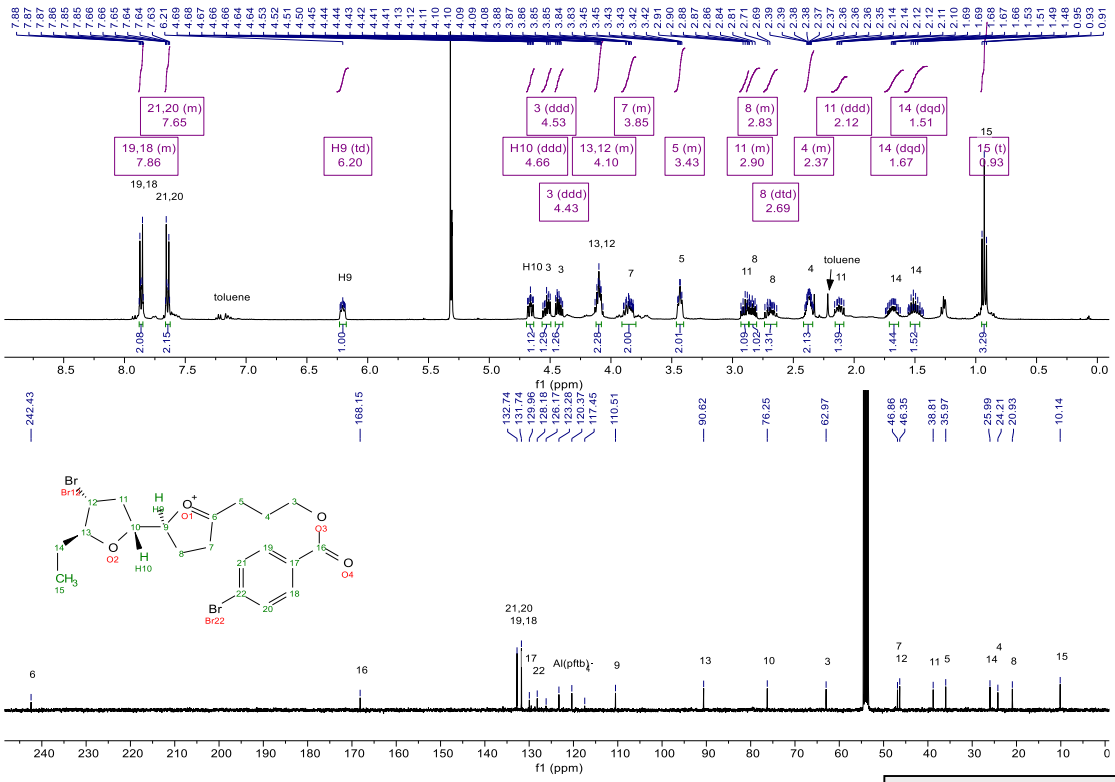


Figure 12.30. ^{1}H and ^{13}C NMR spectra of **4.63** at 25 °C.

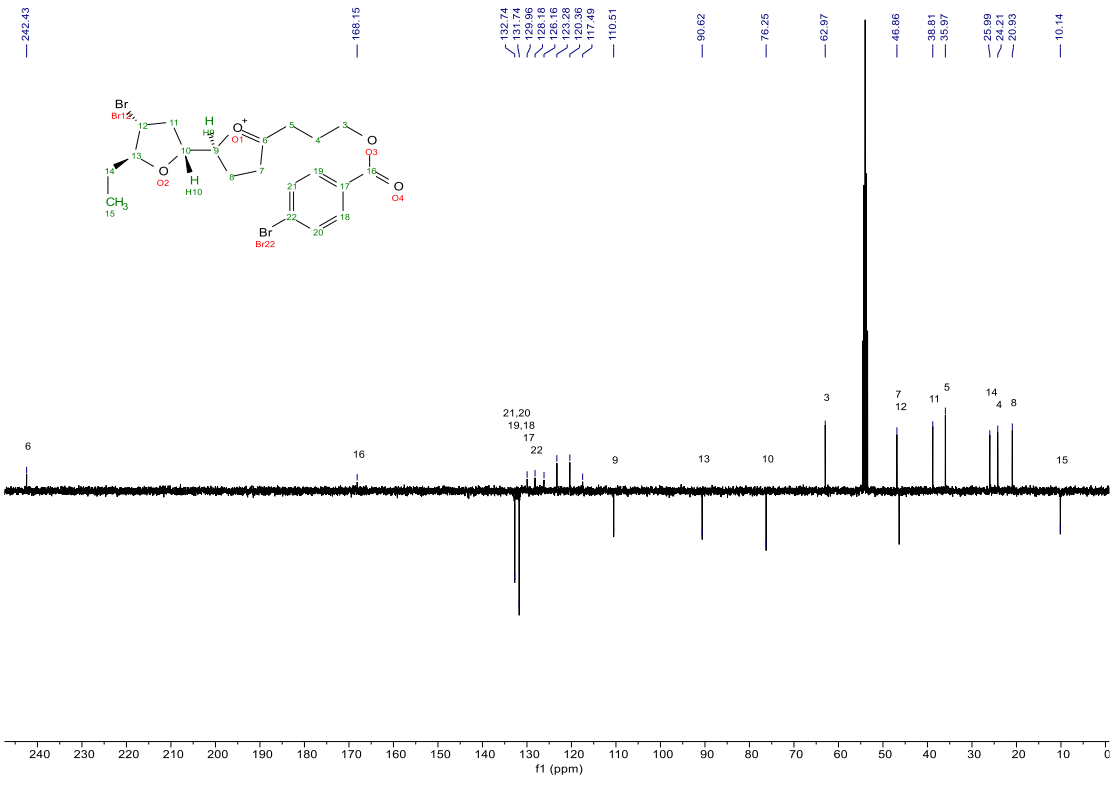


Figure 12.31. DEPT-Q spectra of **4.63** at 25 °C.

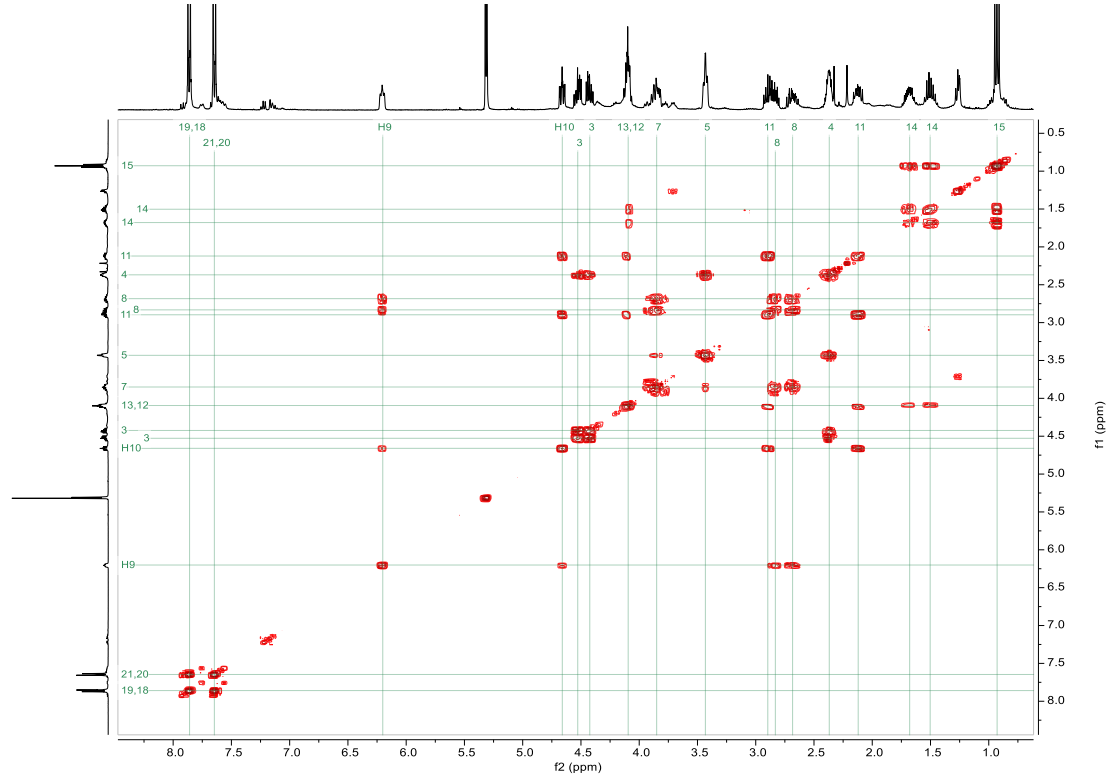
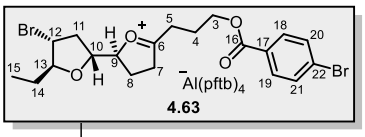


Figure 12.32. ^{1}H-^{1}H COSY spectrum of **4.63** at 25 °C.



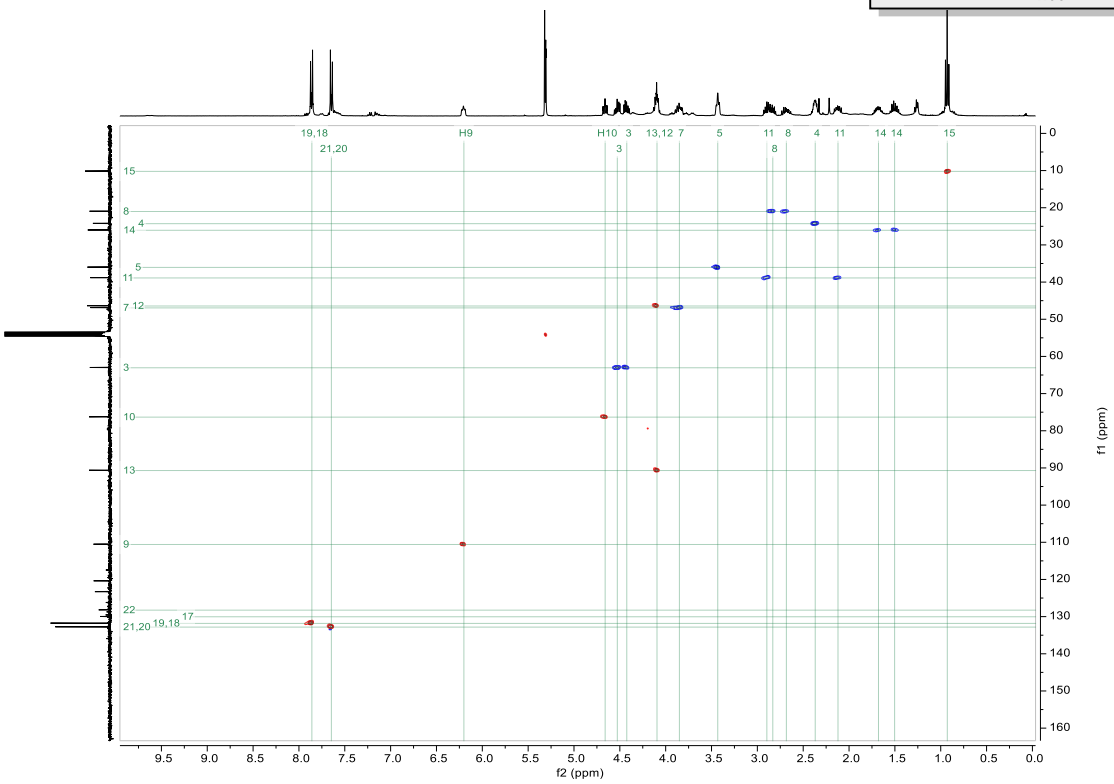


Figure 12.33. ^{1}H-^{13}C edited HSQC spectrum of **4.63** at 25 °C.

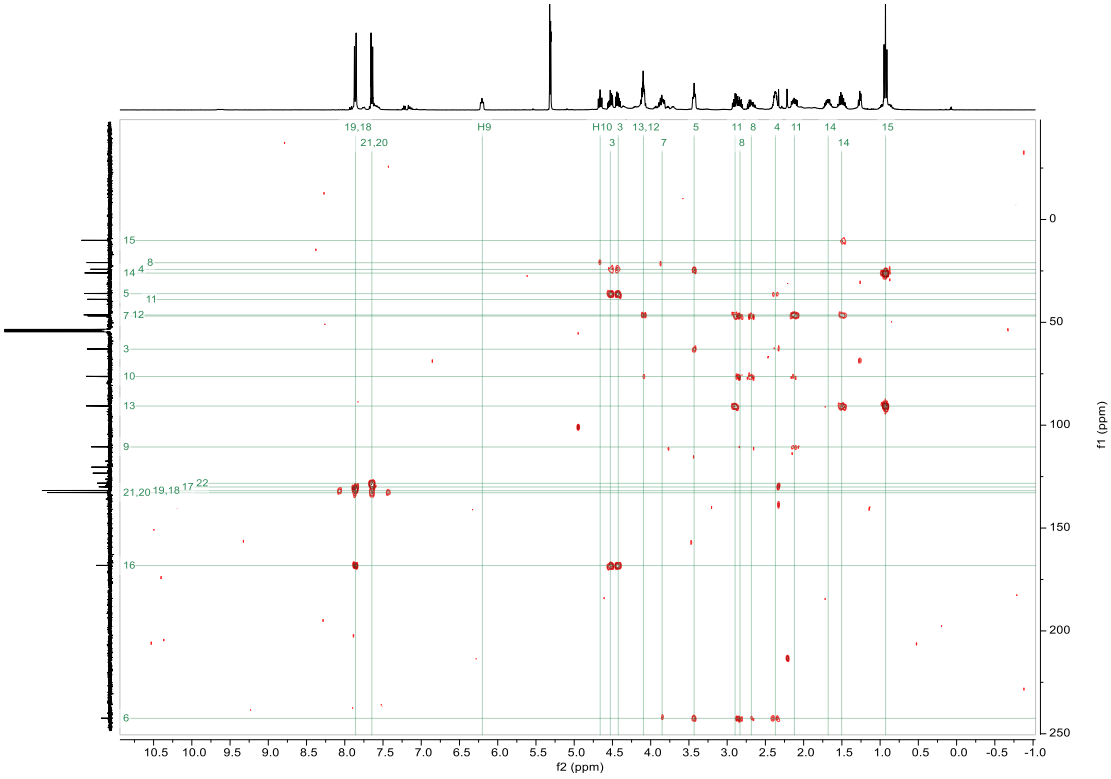
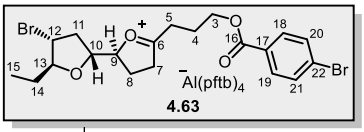


Figure 12.34. ^{1}H-^{13}C HMBC spectrum of **4.63** at 25 °C.



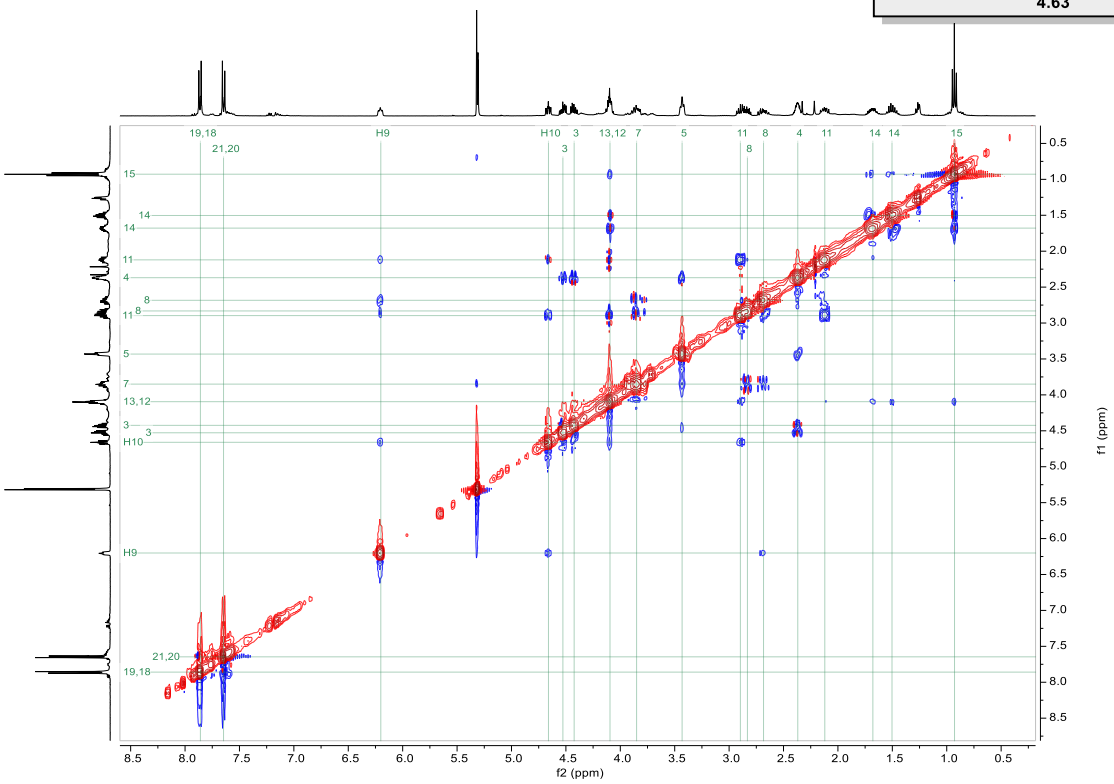


Figure 12.35. ^{1}H-^{1}H NOESY spectrum of **4.63** at 25 °C.

12.3.7 *NMR spectra of the oxocarbenium ion **4.63** (400 MHz, CD_2Cl_2, -78 °C)*

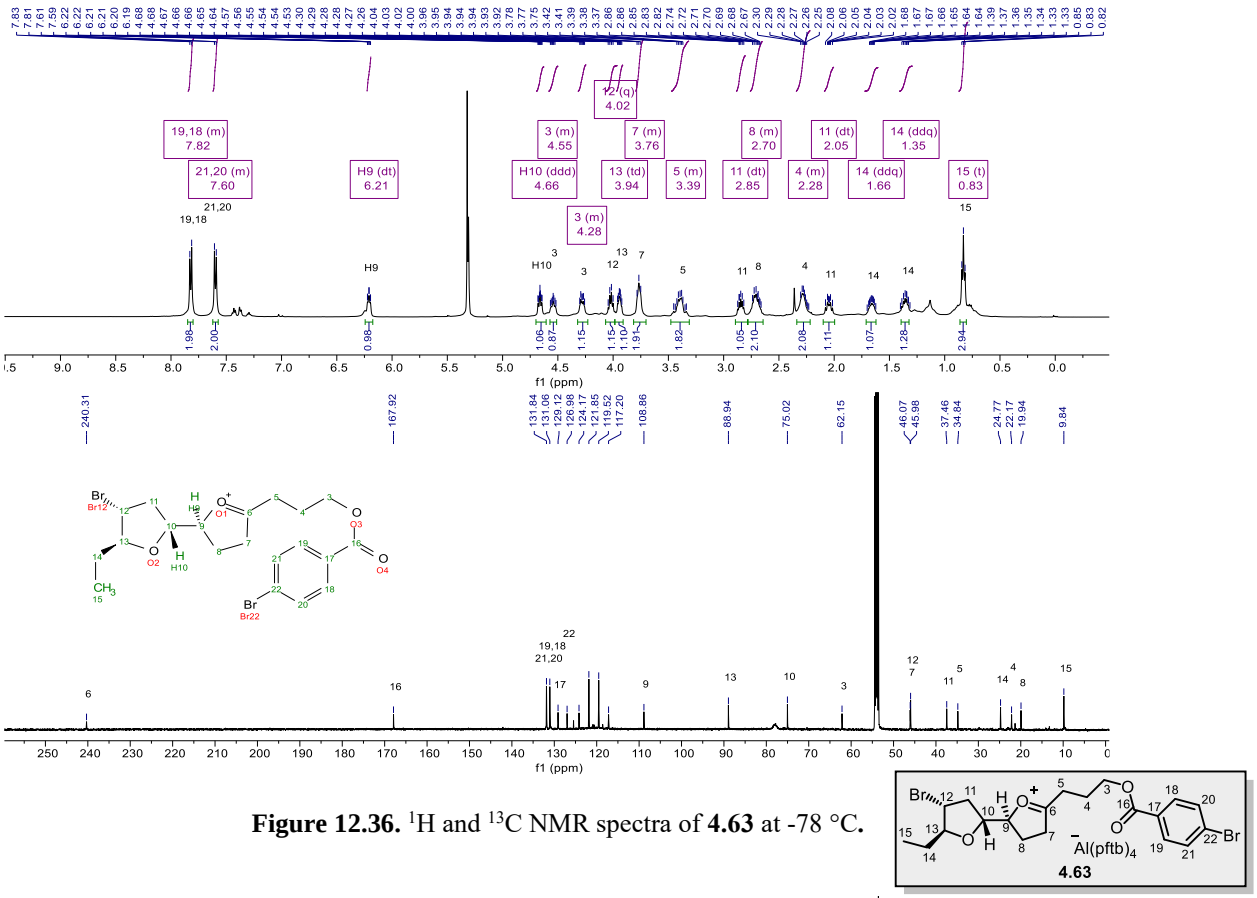


Figure 12.36. ^{1}H and ^{13}C NMR spectra of **4.63** at -78 °C.

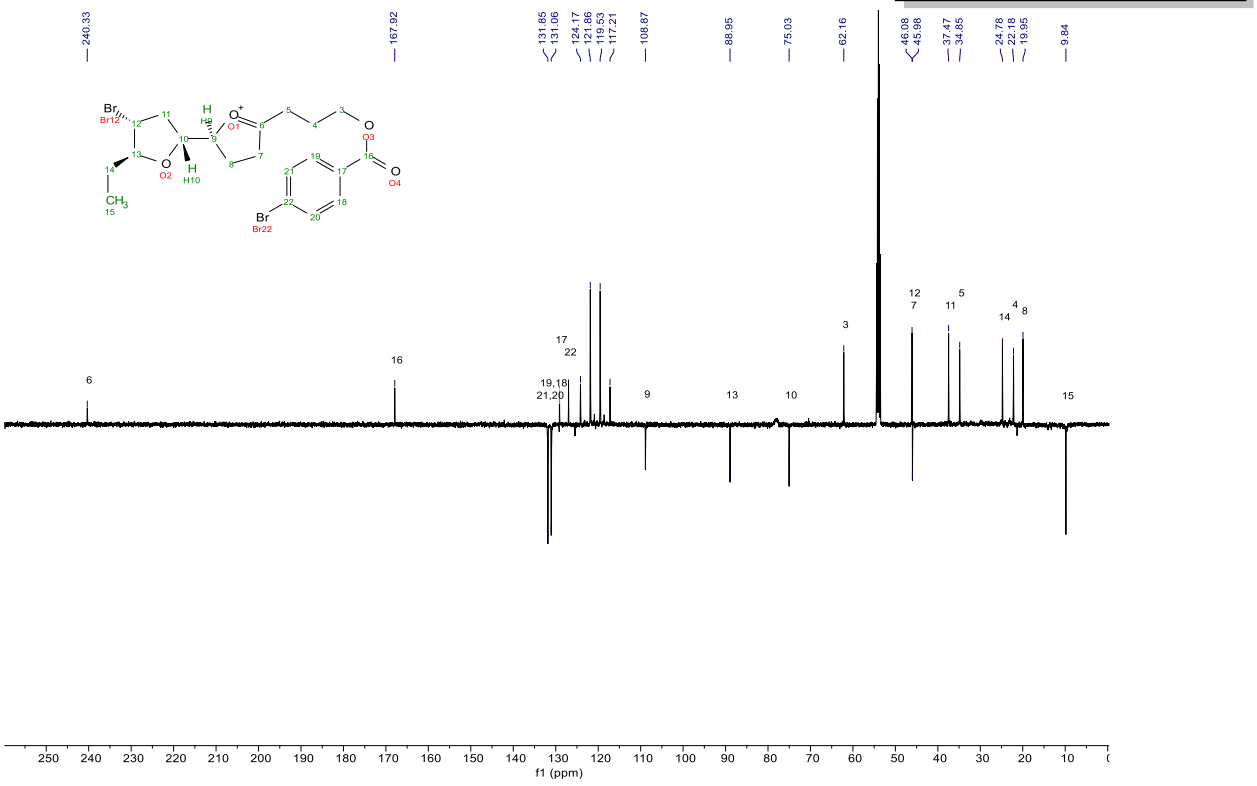


Figure 12.37. DEPT-Q spectrum of **4.63** at -78 °C.

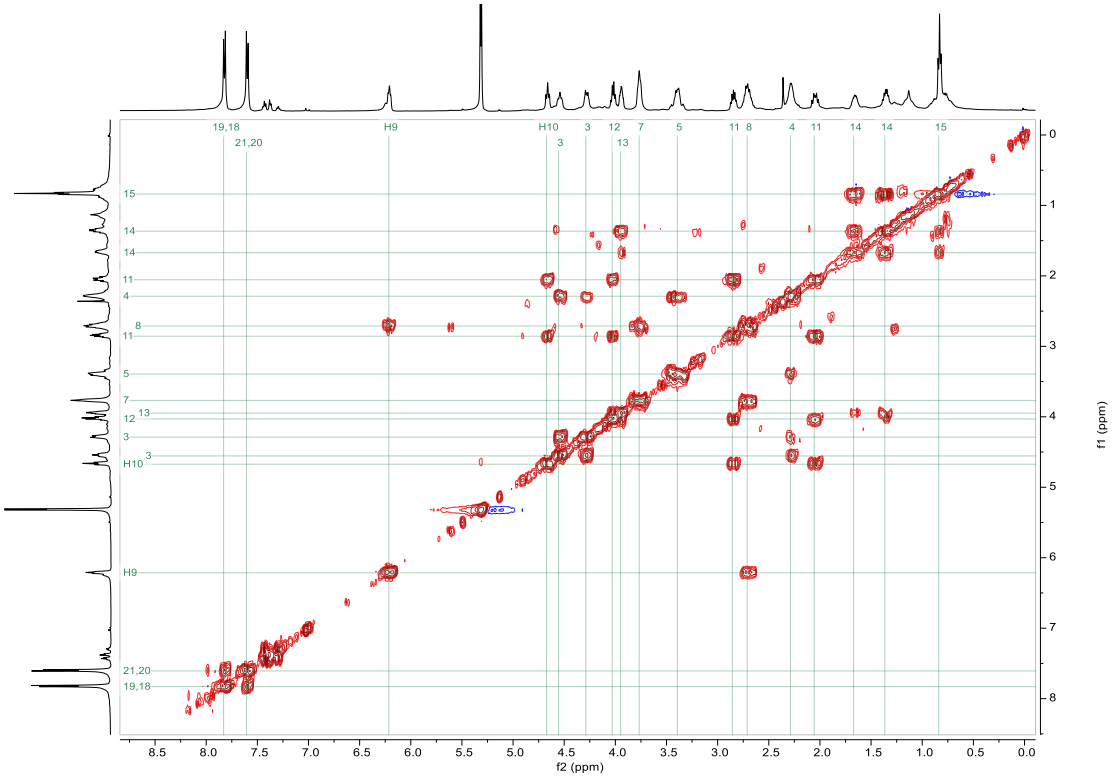
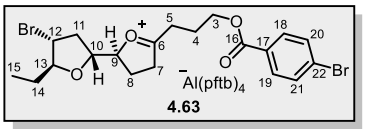


Figure 12.38. ^{1}H-^{1}H COSY spectrum of **4.63** at -78 °C.



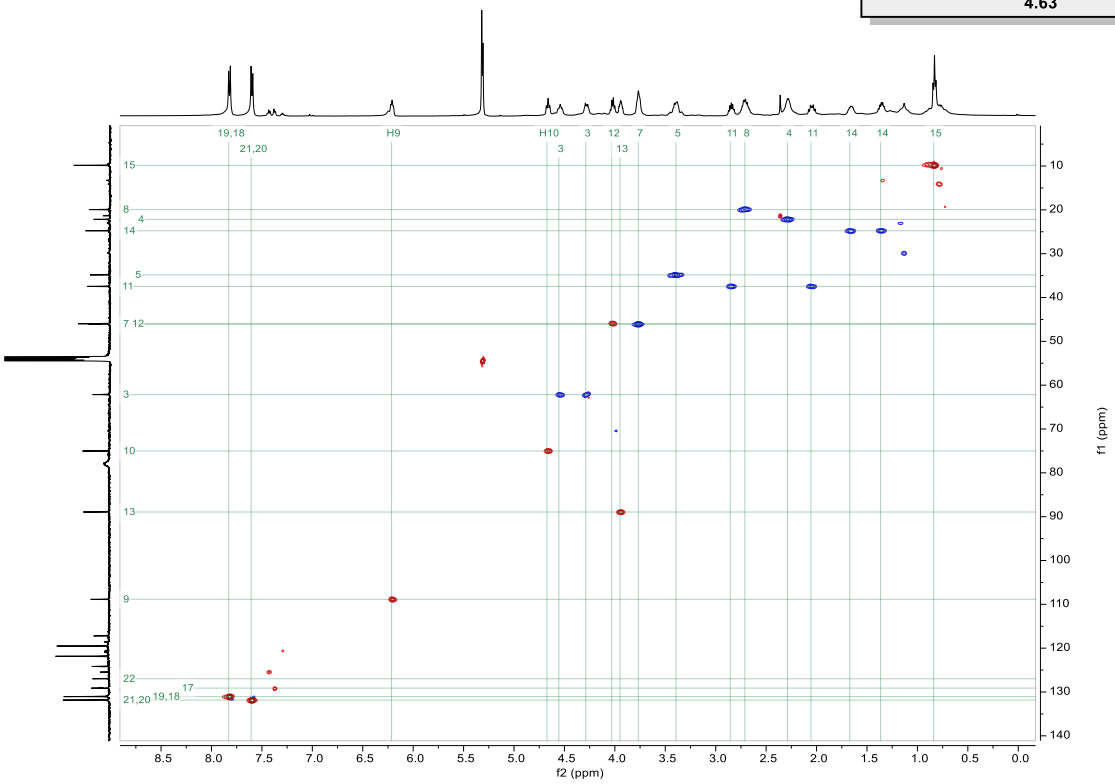
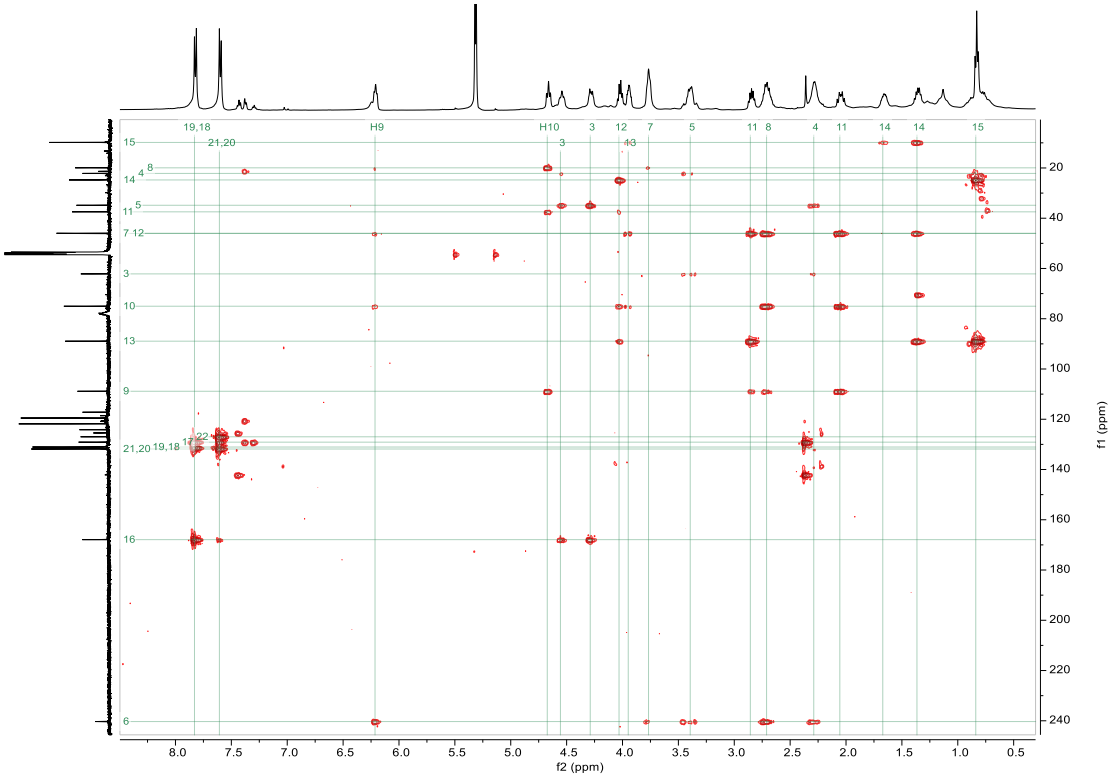


Figure 12.39. ^{1}H-^{13}C edited–HSQC spectrum of **4.63** at 78 °C.



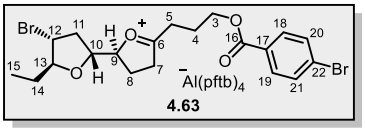


Figure 12.40. ^{1}H-^{13}C HMBC spectrum of **4.63** at -78 °C.

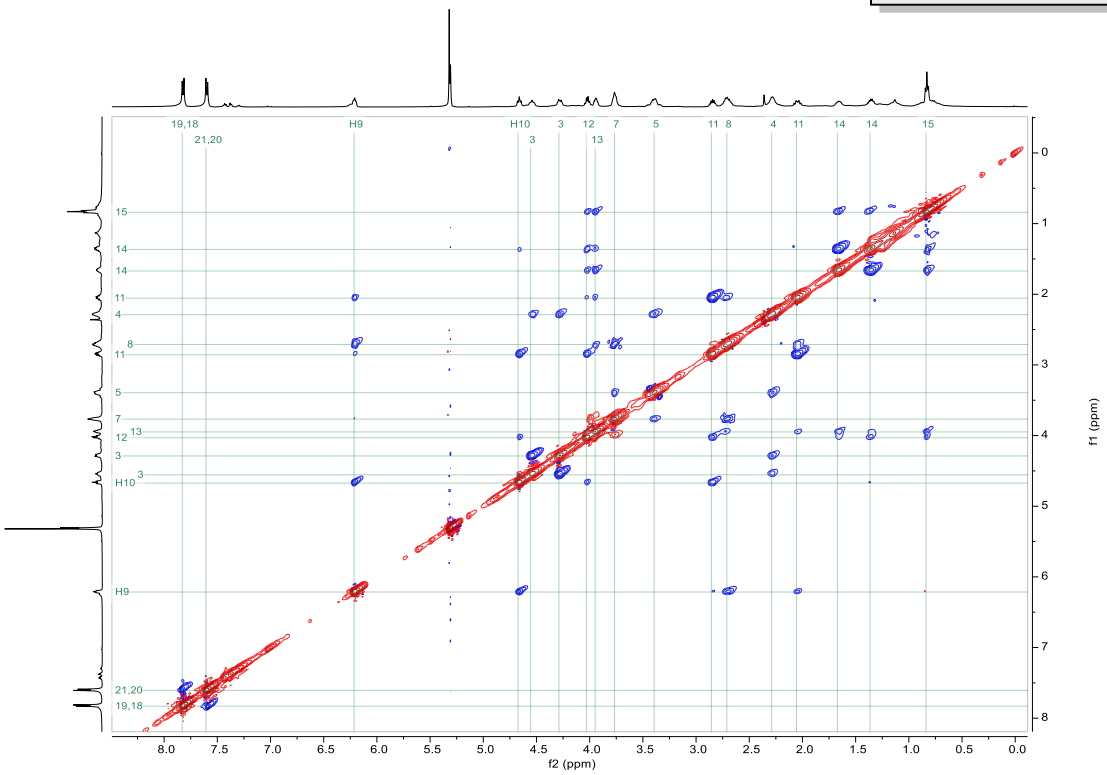


Figure 12.41. ^{1}H-^{1}H ROESY spectrum of **4.63** at -78 °C.

12.4 NMR spectra of all synthesised natural products and comparison of their spectroscopic data with literature

12.4.1 *ent-(Z)-notoryne* ***ent-1.17*** *(500 MHz, $CDCl_3$, 25 °C)*

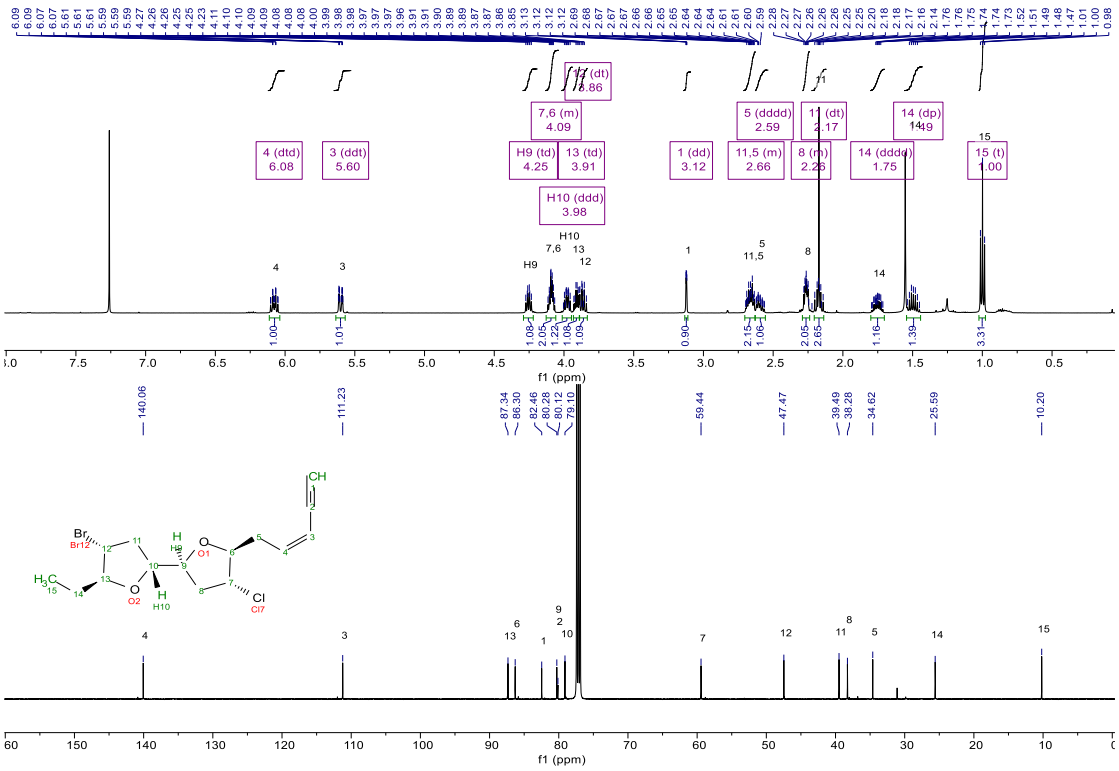


Figure 12.42. ^{1}H and ^{13}C NMR spectra of *ent*-(*Z*)-notoryne.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic *ent*-(*Z*)-notoryne ***ent*-1.17**	25	589	0.30	$CHCl_3$	-47.2
Literature synthetic (*Z*)-notoryne[169] **1.17**	25	589	0.80	$CHCl_3$	+36.4
Natural (*Z*)-notoryne[15] **1.17**	25	589	1.03	$CHCl_3$	+40.3

Table 12.2. Comparison of specific rotations of *ent*-(*Z*)-notoryne with natural (*Z*)-notoryne and literature synthetic (*Z*)-notoryne.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic *ent*-(*Z*)-notoryne						Natural (*Z*)-notoryne						Literature synthetic (*Z*)-notoryne		
	500/126 MHz, $CDCl_3$						400/101 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	3.12	dd, 2.2, 0.9	82.5	-0.01	0.4	**1**	3.13	dd, 2.4, 0.8	82.1	0.00	0.2	**1**	3.13	d, 1.9	82.3
2			80.1	-	0.3	**2**			79.8	-	0.2	**2**			80.0
3	5.60	ddt, 10.9, 2.6, 1.5	111.2	0.00	0.4	**3**	5.60	dddd, 10.8, 2.4, 1.3, 1.3	110.8	0.00	0.3	**3**	5.60	ddd, 11.0, 3.3, 1.4	111.1
4	6.08	dtd, 10.9, 7.5, 1.0	140.1	0.00	0.6	**4**	6.08	dddd, 10.8, 7.3, 7.3, 0.8	139.5	0.00	0.4	**4**	6.08	dt, 11.0, 7.6	139.9
5	2.59	dddd, 14.6, 7.5, 6.1, 1.4	34.6	0.00	0.3	**5**	2.59	dddd, 14.8, 7.3, 7.0, 1.3	34.3	0.01	0.2	**5**	2.60	dddd, 13.0, 6.9, 6.1, 1.2	34.5
5'	2.66	m		-0.01		**5'**	2.67	m		0.00		**5'**	2.67	m	
6	4.09	m	86.3	-0.01	0.4	**6**	4.10	m	**85.9**	0.00	0.3	**6**	4.10	m	86.2
7	4.09	m	59.4	-0.01	0.3	**7**	4.10	m	59.1	0.00	0.2	**7**	4.10	m	59.3
8	2.26	m	38.3	-0.04	0.3	**8**	2.30	m	**38.0**	0.00	0.2	**8**	2.30	m	38.2
9	4.25	td, 7.2, 5.6	80.3	-0.01	0.4	**9**	4.26	ddd, 7.3, 7.3, 5.5	**79.9**	0.00	0.2	**9**	4.26	dt, 7.3, 5.9	80.1
10	3.98	ddd, 8.3, 6.7, 5.5	79.1	0.00	0.3	**10**	3.98	ddd, 8.3, 6.8, 5.5	**78.8**	0.00	0.2	**10**	3.98	ddd, 8.1, 6.5, 5.7	79.0
11	2.17	dt, 13.1, 8.5	39.5	0.00	0.2	**11**	2.17	ddd, 13.2, 8.3, 8.3	**39.3**	0.00	0.1	**11**	2.17	dt, 13.2, 8.5	39.4
11'	2.66	m		0.00		**11'**	2.66	ddd, 13.2, 6.8, 6.8		0.02		**11'**	2.68	m	
12	3.86	dt, 8.7, 7.3	47.5	0.00	0.3	**12**	3.86	ddd, 8.3, 7.3, 6.8	47.2	0.01	0.1	**12**	3.87	dt, 8.3, 7.3	47.3
13	3.91	td, 7.5, 3.9	87.3	0.00	0.3	**13**	3.91	ddd, 7.3, 7.2, 3.9	**87.0**	0.01	0.2	**13**	3.92	td, 7.5, 3.9	87.2
14	1.49	dp, 14.7, 7.4	25.6	0.00	0.2	**14**	1.49	dqd, 14.3, 7.3, 7.2	25.4	0.02	0.1	**14**	1.51	dq, 14.3, 7.3	25.5
14'	1.75	dddd, 15.0, 7.5, 6.5, 4.0		-0.01		**14'**	1.76	dqd, 14.3, 7.3, 3.9		0.00		**14'**	1.76	dqd, 14.3, 7.3, 3.8	
15	1.00	t, 7.5	10.2	0.00	0.2	**15**	1.00	t, 7.3	10.0	0.01	0.0	**15**	1.01	t, 7.3	10.0
				-0.01	0.3		**Mean**			0.00	0.2				
				0.01	0.1		**Standard deviation**			0.01	0.1				
						Red values indicate ambiguous assignments									

Table 12.3. Comparison of ^{1}H and ^{13}C NMR chemical shifts of *ent*-(*Z*)-notoryne with natural (*Z*)-notoryne[169] and literature synthetic (Z)-notoryne.[15]

12.4.2 *ent-(E)-notoryne* ***ent-1.18*** *(500 MHz, $CDCl_3$, 25 °C)*

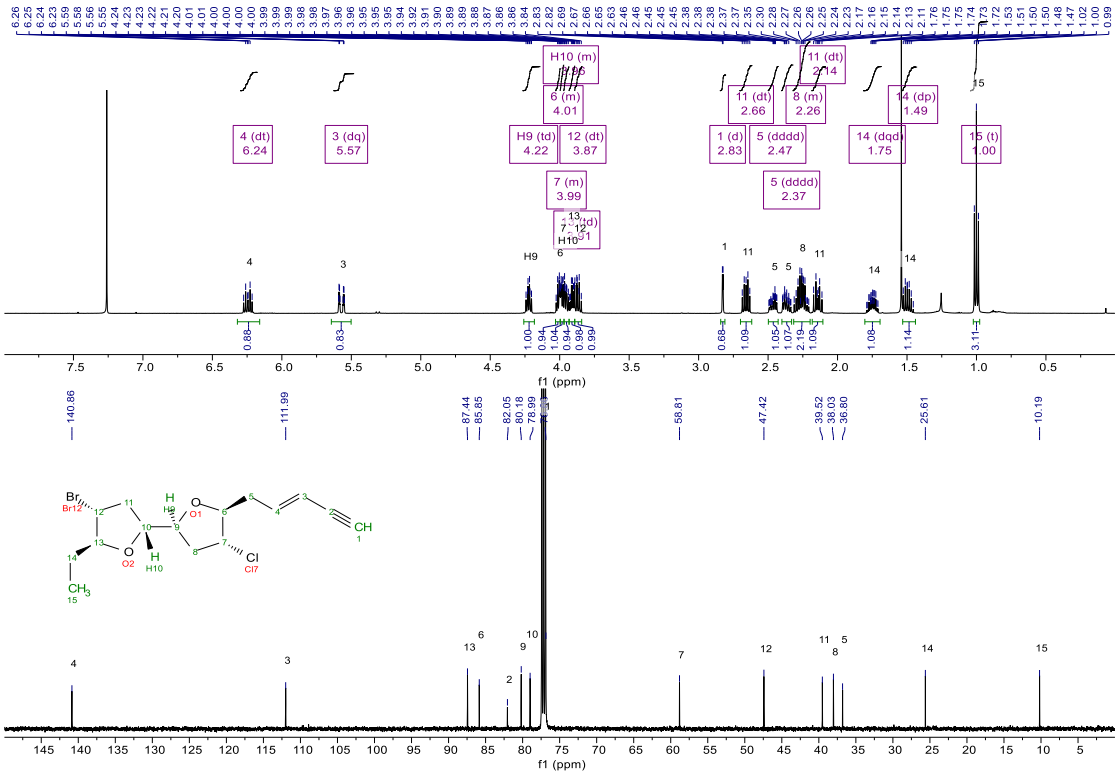


Figure 12.43. ^{1}H and ^{13}C NMR spectra of *ent*-(*E*)-notoryne.

The natural product (*E*)-notoryne has been reported by Murai and co-workers to be a natural product, however no spectroscopic data was provided.[282]

12.4.3 *ent-(E)-laurefucin* ***ent-1.14*** *(500 MHz, C_6D_6, 25 °C)*

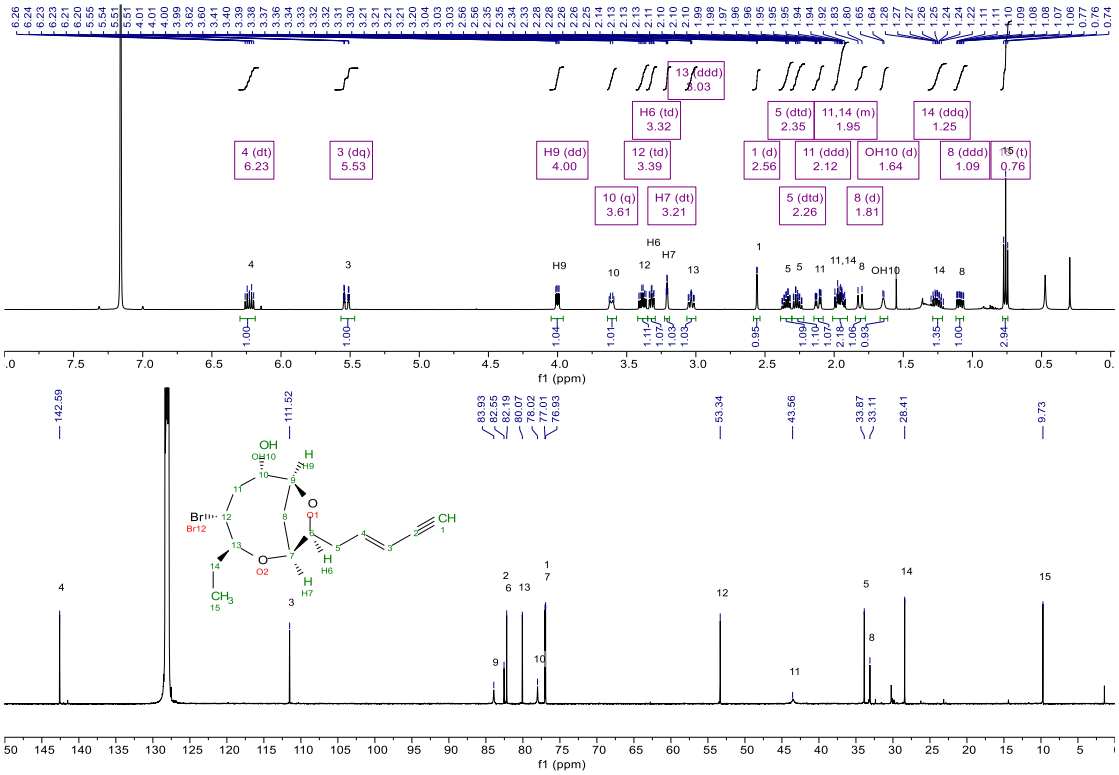


Figure 12.44. ^{1}H and ^{13}C NMR spectra of *ent*-(*E*)-laurefucin.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic *ent*-(*E*)-laurefucin ***ent*-1.14**	25	589	0.27	$CHCl_3$	+72.2
Literature synthetic (*E*)-laurefucin[5] **1.14**	25	589	0.21	$CHCl_3$	-77.3
Natural (*E*)-laurefucin[20] **1.14**	-	589	-	-	-80.0

Table 12.4. Comparison of specific rotations of *ent*-(*E*)-laurefucin with natural (*E*)-laurefucin and literature synthetic (*E*)-laurefucin.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic *ent*-(*E*)-laurefucin						Natural (*E*)-laurefucin						Literature synthetic (*E*)-laurefucin		
	500/126 MHz, C_6D_6						300/76 MHz, C_6D_6						400/101 MHz, C_6D_6		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.56	d, 2.2	77.0	-0.07	0.1	**1**	2.63	d, 2.3	76.9	-0.03	0.1	**1**	2.60	d, 2.0	77.0
2			82.6	-	0.1	**2**			82.5	-	0.0	**2**			82.5
3	5.53	dq, 15.9, 1.7	111.5	-0.04	0.0	**3**	5.57	dddd, 15.8, 3.8, 2.3, 1.5	111.5	0.00	0.0	**3**	5.57	dd, 16.0, 1.8	111.5
4	6.23	dt, 16.1, 7.4	142.6	-0.03	0.1	**4**	6.26	ddd, 15.8, 7.4, 7.3	142.5	0.01	0.0	**4**	6.27	ddd, 15.4, 7.4, 7.4	142.5
5	2.26	dtd, 13.9, 7.6, 1.5	33.9	-	0.1	**5**	2.36	m	33.8	-	0.0	**5**	2.35	m	33.8
5'	2.35	dtd, 13.8, 6.9, 1.7				**5'**						**5'**			
6	3.32	td, 7.1, 2.4	82.2	-0.06	0.0	**6**	3.38	ddd, 7.3, 7.1, 2.4	82.2	-0.02	-0.1	**6**	3.36	ddd, 7.4, 7.4, 2.2	82.1
7	3.21	dt, 3.3, 1.5	76.9	-0.06	0.0	**7**	3.27	ddd, 2.4, 2.3, 1.1	76.9	-0.05	-0.1	**7**	3.22	s	76.8
8	1.09	ddd, 14.4, 8.1, 2.4	33.1	-0.07	-0.1	**8**	1.16	ddd, 14.2, 8.0, 2.3	33.2	-0.04	-0.1	**8**	1.12	ddd, 14.3, 8.0, 2.2	33.1
8'	1.81	d, 14.4		-0.07		**8'**	1.88	d, 14.2		-0.04		**8'**	1.84	d, 14.4	
9	4.00	dd, 8.0, 3.7	83.9	-0.09	-0.4	**9**	4.09	dd, 8.0, 3.6	84.3	-0.03	-0.1	**9**	4.06	dd, 7.9, 3.6	84.2
10	3.61	q, 4.1	78.0	-0.11	0.0	**10**	3.72	ddd, 9.8, 3.6, 1.3	78.0	-0.05	0.1	**10**	3.67	dd, 9.5, 3.1	78.1
11	1.95	m	43.5	-0.09	-0.2	**11**	2.04	m	43.7	-0.01	0.0	**11**	2.03	m	43.7
11'	2.12	ddd, 15.0, 4.7, 1.2		-0.14	0.0	**11'**	2.26	ddd, 14.7, 4.7, 1.3		-0.07	0.0	**11'**	2.19	dd, 14.8, 4.6	
12	3.39	td, 10.4, 4.7	53.3	-0.11	0.1	**12**	3.50	ddd, 10.6, 10.4, 4.7	53.2	-0.06	0.1	**12**	3.44	ddd, 10.5, 10.5, 4.7	53.3
13	3.03	ddd, 10.5, 8.9, 2.6	80.1	-0.06	0.0	**13**	3.09	ddd, 10.6, 8.9, 2.7	80.1	-0.03	-0.1	**13**	3.06	ddd, 10.7, 10.7, 2.1	80.0
14	1.25	ddq, 14.3, 9.0, 7.3	28.4	-0.07	0.1	**14**	1.32	m	28.3	-0.02	0.1	**14**	1.30	m	28.4
14'	1.95	m		-0.06		**14'**	2.01	m		0.02		**14'**	2.03	m	
15	0.76	t, 7.4	9.7	-0.05	0.1	**15**	0.81	dd, 7.4, 7.4	9.6	-0.01	0.1	**15**	0.80	dd, 7.3, 7.3	9.7
				-0.07	0.0		**Mean**			-0.03	0.0				
				0.03	0.1		**Standard deviation**			0.02	0.1				

Table 12.5. Comparison of ^{1}H and ^{13}C NMR chemical shifts of *ent*-(*E*)-laurefucin with natural (*E*)-laurefucin[23] and literature synthetic (*E*)-laurefucin.[5]

12.4.4 *ent-(Z)-laurefucin* ***ent-1.15*** *(500 MHz, C_6D_6, 25 °C)*

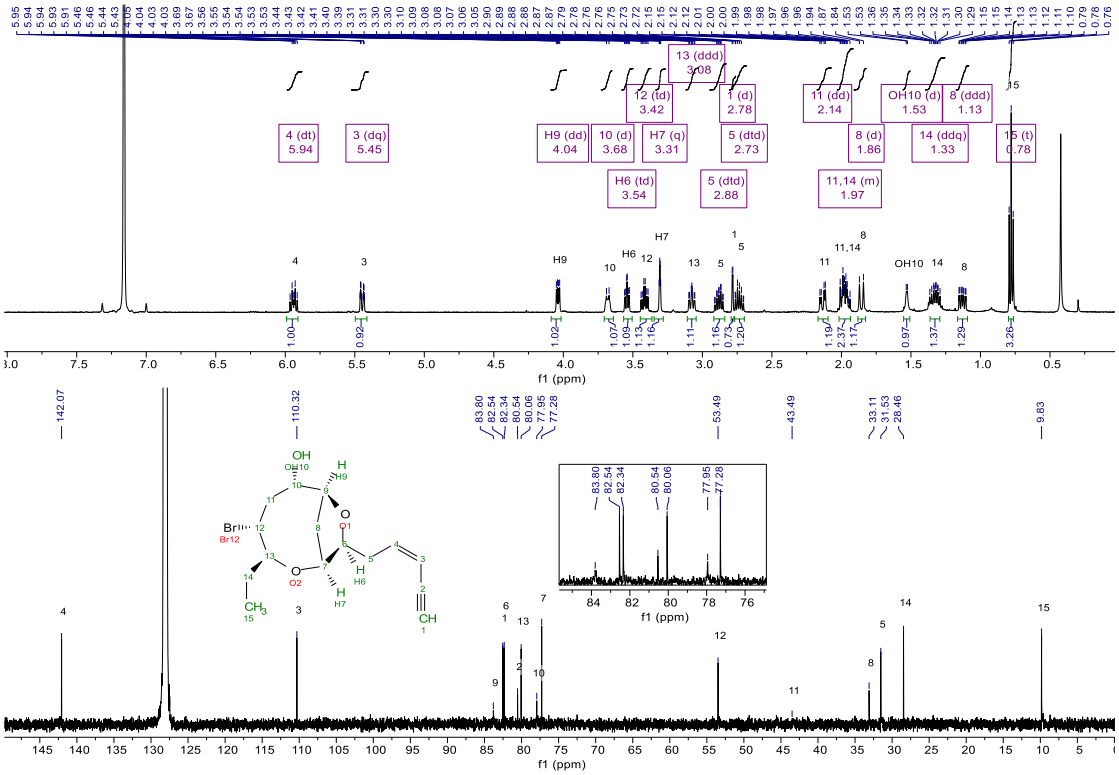


Figure 12.45. ^{1}H and ^{13}C NMR spectra of *ent*-(*Z*)-laurefucin.

The natural product (*Z*)-laurefucin **1.15** has been reported by Faulkner and co-workers to be a natural product, however no spectroscopic data was provided.[22]

12.4.5 *(Z)-chlorofucin **1.5** (500 MHz, $CDCl_3$, 25 °C)*

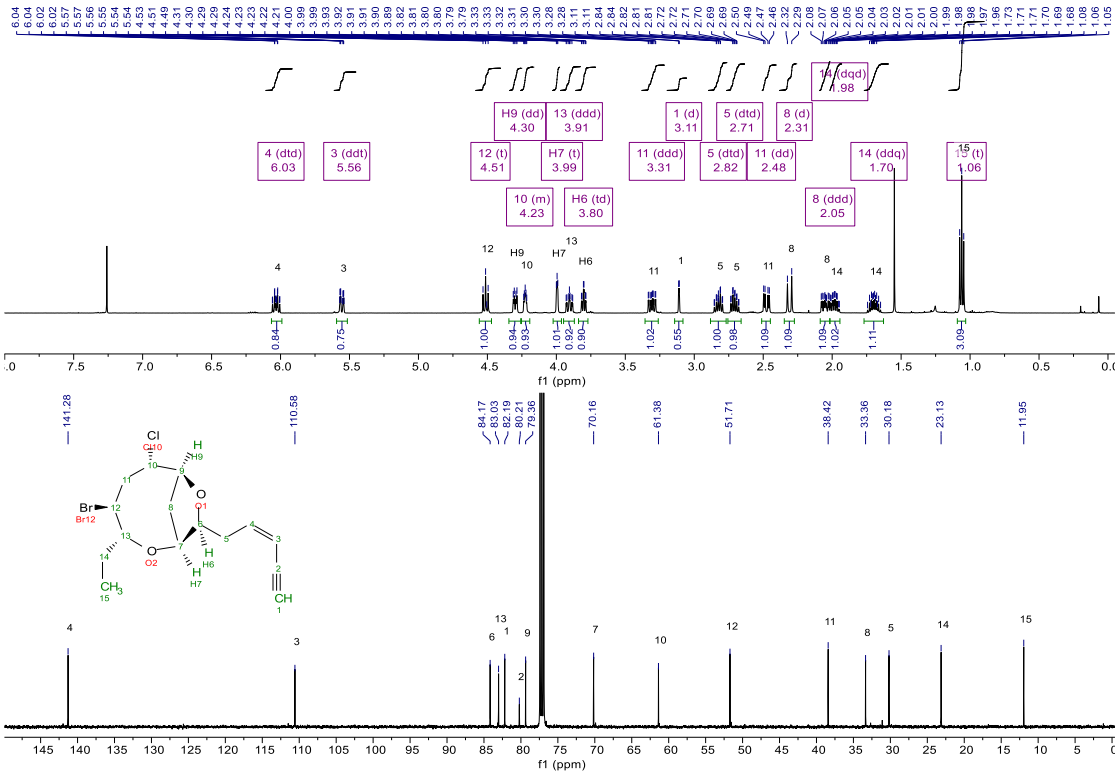


Figure 12.46. ^{1}H and ^{13}C NMR spectra of (*Z*)-chlorofucin.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic (*Z*)-chlorofucin **1.5**	25	589	0.37	$CHCl_3$	-12.4
Literature synthetic (*Z*)-chlorofucin[4] **1.5**	25	589	0.63	$CHCl_3$	-14.3
Natural (*Z*)-chlorofucin[19] **1.5**	24	589	0.58	$CHCl_3$	-11.3

Table 12.6. Comparison of specific rotations of (*Z*)-chlorofucin with natural (*Z*)-chlorofucin and literature synthetic (*Z*)-chlorofucin.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic (*Z*)-chlorofucin						Natural (*Z*)-chlorofucin						Literature synthetic (*Z*)-chlorofucin		
	500/126 MHz, $CDCl_3$						400/101 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	3.11	d, 2.3	82.2	0.00	0.1	**1**	3.11	d, 2.0	82.1	0.00	-0.1	**1**	3.11	d, 1.7	82.0
2			80.2	-	0.1	**2**			80.1	-	0.0	**2**			80.1
3	5.56	ddt, 10.9, 2.6, 1.4	110.6	-0.01	0.1	**3**	5.57	dd, 10.7, 2.0	110.5	-0.01	-0.1	**3**	5.56	d, 10.8	110.4
4	6.03	dtd, 11.0, 7.6, 0.9	141.3	0.01	0.1	**4**	6.02	ddd, 10.7, 7.3, 7.3	141.2	0.01	-0.1	**4**	6.03	ddd, 10.7, 7.5, 7.5	141.1
5	2.71	dtd, 14.0, 7.2, 1.3	30.2	-0.01	0.1	**5**	2.72	ddd, 7.3, 6.8, 6.3	30.1	0.01	-0.1	**5**	2.71	ddd, 14.1, 7.2, 7.2	30.0
5'	2.82	dtd, 13.9, 7.6, 1.4		0.01		**5'**	2.81	ddd, 7.3, 6.8, 6.3		-0.02		**5'**	2.83	ddd, 14.6, 7.6, 7.6	
6	3.80	td, 7.1, 1.9	84.2	0.00	0.1	**6**	3.80	ddd, 7.3, 6.8, 2.0	84.1	0.00	-0.1	**6**	3.80	ddd, 7.1, 7.1, 1.5	84.0
7	3.99	t, 2.6	70.2	-0.01	0.1	**7**	4.00	m	70.1	0.00	-0.1	**7**	4.00	br	70.0
8	2.05	ddd, 15.4, 9.6, 3.3	33.4	-0.02	0.1	**8**	2.07	ddd, 6.3, 4.9, 3.4	33.3	-0.02	-0.1	**8**	2.05	ddd, 15.4, 9.6, 3.3	33.2
8'	2.31	d, 15.5		-0.02		**8'**	2.33	m		-0.02		**8'**	2.31	d, 15.6	
9	4.30	dd, 9.6, 3.6	79.4	-0.01	0.1	**9**	4.31	ddd, 5.9, 4.9, 3.0	79.3	-0.01	-0.1	**9**	4.30	dd, 9.6, 3.5	79.2
10	4.23	m	61.4	0.01	0.1	**10**	4.22	ddd, 10.4, 5.4, 4.9	61.3	0.01	-0.1	**10**	4.23	br	61.2
11	2.48	dd, 15.5, 4.8	38.4	-0.02	0.0	**11**	2.50	ddd, 10.4, 4.9, 4.4	38.4	-0.02	-0.1	**11**	2.48	dd, 15.5, 4.8	38.3
11'	3.31	ddd, 15.5, 9.1, 2.2		0.02		**11'**	3.29	ddd, 9.3, 6.8, 4.4		0.01		**11'**	3.30	ddd, 15.5, 9.1, 2.1	
12	4.51	t, 9.3	51.7	0.00	0.1	**12**	4.51	dd, 9.3, 9.3	51.6	0.01	-0.1	**12**	4.52	dd, 9.3, 9.3	51.5
13	3.91	ddd, 11.8, 9.6, 2.7	83.0	-0.08	0.0	**13**	3.99	ddd, 9.3, 4.4, 3.0	83.0	-0.08	-0.1	**13**	3.91	ddd, 11.6,11.6, 2.5	82.9
14	1.70	ddq, 14.2, 11.2, 7.1	23.1	-0.02	0.0	**14**	1.72	dqd, 11.8, 7.8, 3.0	23.1	-0.02	-0.1	**14**	1.70	m	23.0
14'	1.98	dqd, 15.1, 7.6, 2.6		-0.01		**14'**	1.99	dqd, 11.8, 7.8, 4.4		-0.01		**14'**	1.98	dddd, 10.1, 7.5, 7.5, 2.6	
15	1.06	t, 7.4	12.0	0.00	0.1	**15**	1.06	dd, 7.8, 7.8	11.9	0.00	-0.1	**15**	1.06	dd, 7.4, 7.4	11.8
				-0.01	0.1		**Mean**			-0.01	-0.1				
				0.02	0.0		**Standard deviation**			0.02	0.0				

Table 12.7. Comparison of ^{1}H and ^{13}C NMR chemical shifts of (*Z*)-chlorofucin with natural (*Z*)-chlorofucin[19] and literature synthetic (*Z*)-chlorofucin.[4]

12.4.6 *(E)-chlorofucin **1.6** (500 MHz, $CDCl_3$, 25 °C)*

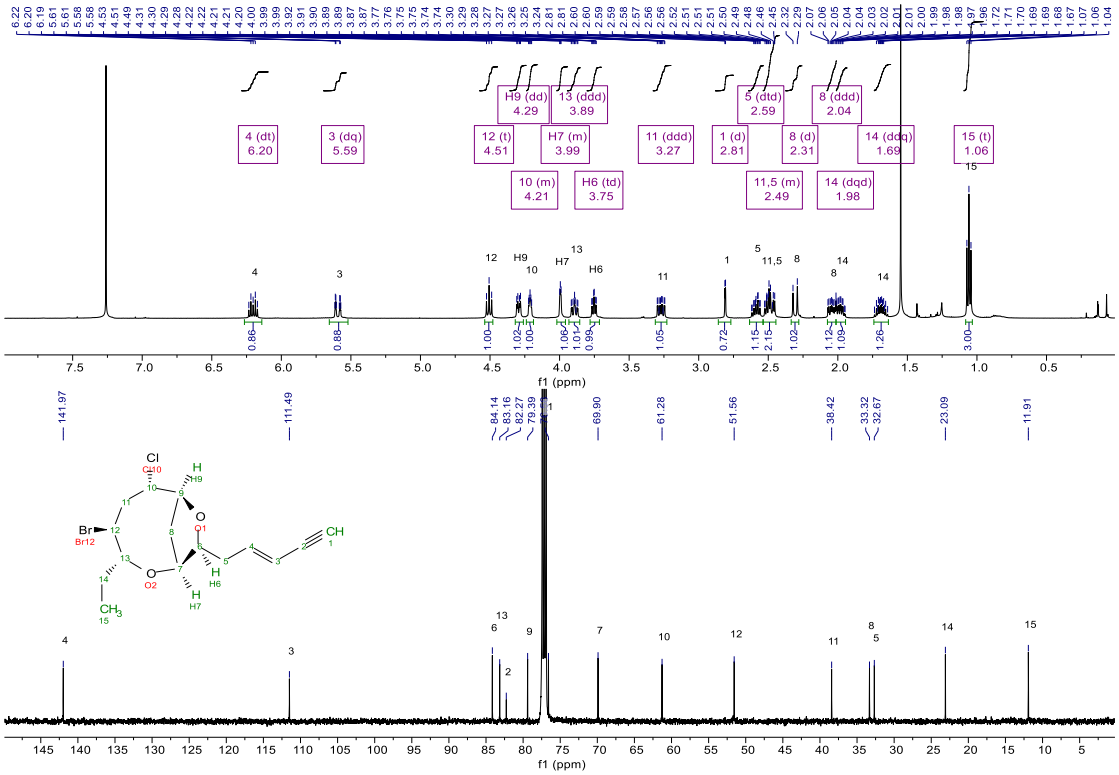


Figure 12.47. ^{1}H and ^{13}C NMR spectra of (*E*)-chlorofucin.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic (*E*)-chlorofucin **1.6**	25	589	0.21	$CHCl_3$	+9.5
Literature synthetic (*E*)-chlorofucin[4] **1.6**	25	589	0.42	$CHCl_3$	+11.6
Natural (*E*)-chlorofucin[11] **1.6**	24	589	1.40	$CHCl_3$	+12.0

Table 12.8. Comparison of specific rotations of (*E*)-chlorofucin with natural (*E*)-chlorofucin and literature synthetic (*E*)-chlorofucin.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic (*E*)-chlorofucin						Natural (*E*)-chlorofucin						Literature synthetic (*E*)-chlorofucin		
	500/126 MHz, $CDCl_3$						300/76 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.81	d, 2.2	76.6	0.01	0.2	**1**	2.80	d, 2.0	76.4	0.01	0.0	**1**	2.81	d, 1.9	76.4
2			82.3	-	0.1	**2**			82.2	-	-0.1	**2**			82.1
3	5.59	dq, 16.0, 1.7	111.5	0.01	0.2	**3**	5.58	ddd, 15.5, 3.5, 2.0	111.3	0.01	0.0	**3**	5.59	dd, 16.0, 1.3	111.3
4	6.20	dt, 15.3, 7.4	142.0	0.00	0.2	**4**	6.20	ddd, 15.5, 7.9, 7.4	141.8	0.00	0.0	**4**	6.20	ddd, 15.4, 7.4, 7.4	141.8
5	2.49	m	32.7	-0.06	0.2	**5**	2.55	m	32.5	-	0.0	**5**	2.54	m	32.5
5'	2.59	dtd, 15.0, 7.5, 1.5		0.01		**5'**	2.58	m				**5'**		m	
6	3.75	td, 7.1, 1.9	84.1	0.00	0.1	**6**	3.75	ddd, 7.2, 7.1, 1.7	84.0	0.00	0.0	**6**	3.75	ddd, 7.4, 7.4, 1.3	84.0
7	3.99	m	69.9	0.00	0.2	**7**	3.99	br	69.7	0.00	0.1	**7**	3.99	br	69.8
8	2.04	ddd, 15.8, 9.7, 3.5	33.3	-0.01	0.1	**8**	2.05	ddd, 15.6, 9.5, 3.4	33.2	-0.01	0.0	**8**	2.04	ddd, 15.3, 9.6, 3.3	33.2
8'	2.31	d, 15.6		-0.04		**8'**	2.35	d, 15.6		-0.04		**8'**	2.31	d, 15.6	
9	4.29	dd, 9.6, 3.7	79.4	0.01	0.2	**9**	4.28	dd, 9.5, 3.5	79.2	0.01	0.0	**9**	4.29	dd, 9.6, 3.5	79.2
10	4.21	m	61.3	0.01	0.3	**10**	4.20	br	61.0	0.01	0.1	**10**	4.21	br	61.1
11	2.49	m	38.4	-0.01	0.1	**11**	2.50	m	38.3	0.04	0.0	**11**	2.54	m	38.3
11'	3.27	ddd, 15.5, 9.1, 2.3		0.00		**11'**	3.27	ddd, 15.8, 9.0, 2.3		0.00		**11'**	3.27	ddd, 15.5, 9.1, 2.0	
12	4.51	t, 9.3	51.6	0.01	0.2	**12**	4.50	t, 9.7	51.4	0.01	0.0	**12**	4.51	dd, 9.3, 9.3	51.4
13	3.89	ddd, 11.8, 9.5, 2.6	83.2	0.00	0.2	**13**	3.89	ddd, 11.7, 9.7, 2.6	83.0	0.00	0.0	**13**	3.89	ddd, 11.6, 11.6, 2.4	83.0
14	1.69	ddq, 14.2, 11.3, 7.1	23.1	0.04	0.2	**14**	1.65	ddq, 14.7, 11.7, 7.4	22.9	0.04	0.0	**14**	1.69	m	22.9
14'	1.98	dqd, 15.1, 7.5, 4.9		-0.02		**14'**	2.00	ddq, 14.7, 7.4, 2.6		-0.02		**14'**	1.98	ddd, 10.0, 7.6, 2.5	
15	1.06	t, 7.3	11.9	0.01	0.2	**15**	1.05	t, 7.4	11.7	0.01	0.0	**15**	1.06	dd, 7.3, 7.3	11.7
				0.00	0.2		**Mean**			0.00	0.0				
				0.02	0.1		**Standard deviation**			0.02	0.0				

Table 12.9. Comparison of ^{1}H and ^{13}C NMR chemical shifts of (*E*)-chlorofucin with natural (*E*)-chlorofucin[11] and literature synthetic (*E*)-chlorofucin.[4]

12.4.7 *(Z)-bromofucin **1.8** (500 MHz, $CDCl_3$, 25 °C)*

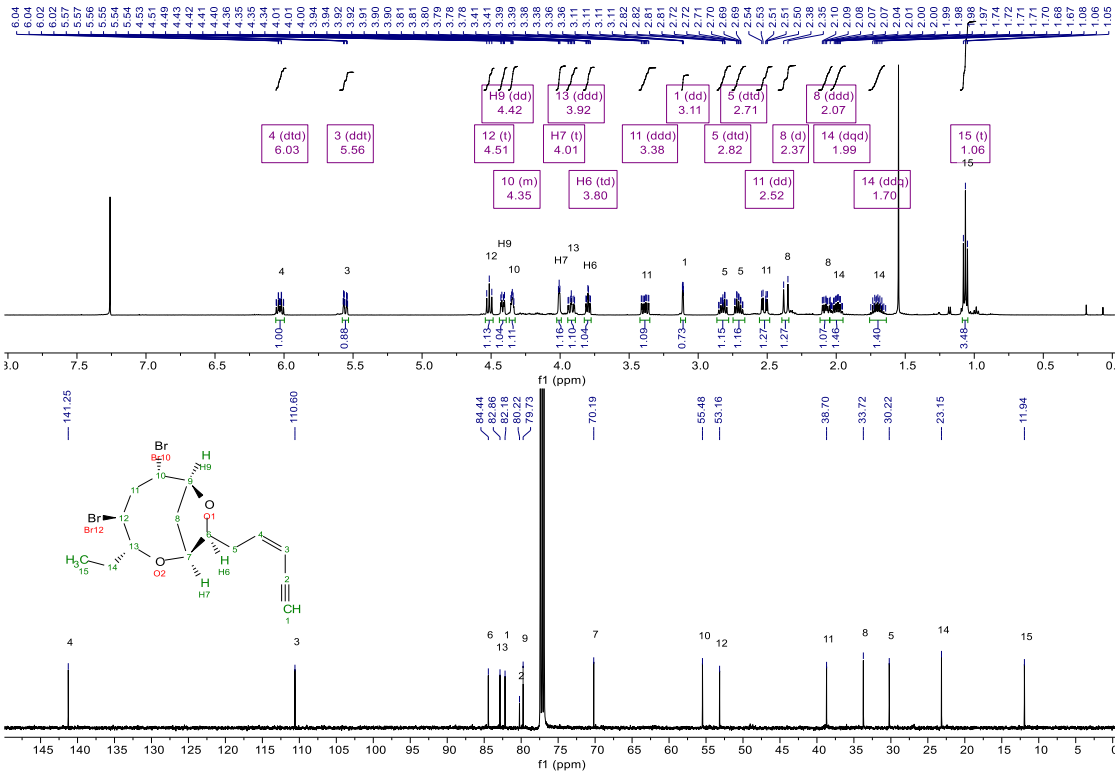


Figure 12.48. ^{1}H and ^{13}C NMR spectra of (*Z*)-bromofucin.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic (*Z*)-bromofucin **1.8**	25	589	0.10	$CHCl_3$	-10.0
Literature synthetic (*Z*)-bromofucin[4] **1.8**	25	589	0.09	$CHCl_3$	-5.2
Natural (*Z*)-bromofucin[24] **1.8**	24	589	0.25	$CHCl_3$	-0.5

Table 12.10. Comparison of specific rotations of (*Z*)-bromofucin with natural (*Z*)-bromofucin and literature synthetic (*Z*)-bromofucin.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic (*Z*)-bromofucin						Natural (*Z*)-bromofucin						Literature synthetic (*Z*)-bromofucin		
	500/126 MHz, $CDCl_3$						300/76 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	3.11	dd, 2.5, 0.9	82.2	0.01	0.2	**1**	3.10	d, 1.0	82.0	0.01	0.0	**1**	3.11	d, 1.6	82.0
2			80.2	-	0.2	**2**			80.0	-	0.1	**2**			80.1
3	5.56	ddt, 10.9, 2.5, 1.4	110.6	0.02	0.2	**3**	5.54	d, 10.0	110.4	0.02	0.0	**3**	5.56	d, 10.9	110.4
4	6.03	dtd, 10.8, 7.5, 0.9	141.3	0.01	0.2	**4**	6.02	ddd, 10.0, 7.0, 8.0	141.1	0.01	0.0	**4**	6.03	ddd, 10.8, 7.7, 7.7	141.1
5	2.71	dtd, 14.1, 7.1, 1.4	30.2	0.01	0.1	**5**	2.70	ddd, 16.0, 8.0, 7.0	30.1	0.01	0.0	**5**	2.71	ddd, 14.1, 7.2, 7.2	30.1
5'	2.82	dtd, 13.9, 7.5, 1.4		0.01		**5'**	2.81	ddd, 16.0, 8.0, 7.0		0.01		**5'**	2.82	ddd, 14.6, 7.6, 7.6	
6	3.80	td, 7.1, 1.9	84.4	0.01	0.1	**6**	3.79	ddd, 8.0, 7.0, 1.0	84.3	0.01	0.0	**6**	3.80	ddd, 7.1, 7.1, 1.6	84.3
7	4.01	t, 2.7	70.2	0.01	0.1	**7**	4.00	br	70.1	0.01	-0.1	**7**	4.01	br	70.0
8	2.07	ddd, 15.4, 9.6, 3.3	33.7	0.01	0.1	**8**	2.06	m	33.6	0.01	0.0	**8**	2.07	ddd, 15.3, 9.7, 3.3	33.6
8'	2.37	d, 15.5		0.03		**8'**	2.34	d, 16.0		0.03		**8'**	2.37	d, 15.5	
9	4.42	dd, 9.6, 3.6	79.7	0.02	0.1	**9**	4.40	dd, 10.0, 3.0	79.6	0.02	0.0	**9**	4.42	dd, 9.6, 3.3	79.6
10	4.35	m	55.5	0.01	0.2	**10**	4.34	br	55.3	0.01	0.0	**10**	4.35	br	55.3
11	2.52	dd, 15.8, 4.8	38.7	0.01	0.1	**11**	2.51	dd, 16.0, 5.0	38.6	0.01	-0.1	**11**	2.52	dd, 15.8, 4.7	38.5
11'	3.38	ddd, 15.8, 8.9, 2.3		0.01		**11'**	3.37	ddd, 16.0, 9.0, 2.0		0.02		**11'**	3.39	ddd, 15.8, 8.9, 2.2	
12	4.51	t, 9.2	53.2	0.01	0.2	**12**	4.50	dd, 10.0, 9.0	53.0	0.01	0.0	**12**	4.51	dd, 9.2, 9.2	53.0
13	3.92	ddd, 11.8, 9.5, 2.6	82.9	0.01	0.2	**13**	3.91	ddd, 12.0, 10.0, 3.0	82.7	0.01	0.0	**13**	3.92	ddd, 11.6, 11.6, 2.4	82.7
14	1.70	ddq, 14.3, 11.4, 7.1	23.2	0.05	0.2	**14**	1.65	m	23.0	0.06	0.0	**14**	1.71	m	23.0
14'	1.99	dqd, 15.1, 7.6, 2.6		0.00		**14'**	1.99	m		0.01		**14'**	2.00	dddd, 10.1, 7.6, 7.6, 2.5	
15	1.06	t, 7.3	11.9	0.00	0.1	**15**	1.06	t, 7.0	11.8	0.01	0.0	**15**	1.07	dd, 7.3, 7.3	11.8
				0.01	0.2		**Mean**			0.02	0.0				
				0.01	0.1		**Standard deviation**			0.01	0.0				

Table 12.11. Comparison of ^{1}H and ^{13}C NMR chemical shifts of (*Z*)-bromofucin with natural (*Z*)-bromofucin[24] and literature synthetic (*Z*)-bromofucin.[4]

12.4.8 *(E)-bromofucin **1.11** (500 MHz, $CDCl_3$, 25 °C)*

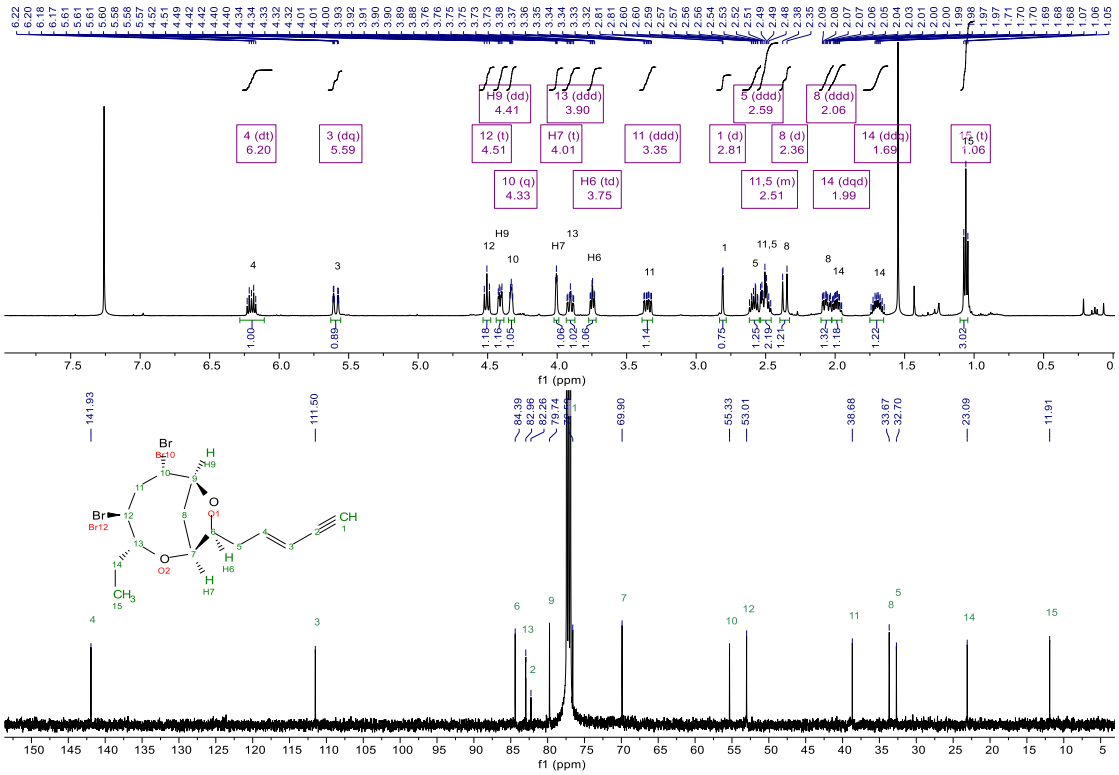


Figure 12.49. ^{1}H and ^{13}C NMR spectra of (*E*)-bromofucin.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic (*E*)-bromofucin **1.11**	25	589	0.35	$CHCl_3$	+1.4
Literature synthetic (*E*)-bromofucin[4] **1.8**	24	589	0.35	$CHCl_3$	+2.9
Natural (*E*)-bromofucin[236] **1.8**	25	589	0.018 (unit not given)	$CHCl_3$	+1.7

Table 12.12. Comparison of specific rotations of (*E*)-bromofucin with natural (*E*)-bromofucin and literature synthetic (*E*)-bromofucin.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic (*E*)-bromofucin						Natural (*E*)-bromofucin						Literature synthetic (*E*)-bromofucin		
	500/126 MHz, $CDCl_3$						300/76 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.81	d, 2.2	76.6	0.00	0.2	**1**	2.81	d, 2.0	76.4	0.00	0.0	**1**	2.81	d, 1.9	76.4
2			82.3	-	0.2	**2**			82.1	-	0.0	**2**			82.1
3	5.59	dq, 16.1, 1.6	111.5	0.01	0.1	**3**	5.58	ddd, 16.0, 4.0, 2.0	111.4	0.01	0.0	**3**	5.59	d, 16.0	111.4
4	6.20	dt, 15.4, 7.4	141.9	0.00	0.1	**4**	6.20	ddd, 16.0, 8.0, 7.0	141.8	0.00	0.0	**4**	6.20	ddd, 15.3, 7.5, 7.5	141.8
5	2.51	m	32.7	-	0.2	**5**	2.53	m	32.5	-	0.0	**5**	2.51	m	32.5
5'	2.59	ddd, 14.1, 7.9, 6.5				**5'**						**5'**	2.59	ddd, 14.7, 7.5, 7.5	
6	3.75	td, 7.0, 1.8	84.4	0.01	0.1	**6**	3.74	ddd, 7.0, 7.0, 2.0	84.3	0.01	0.0	**6**	3.75	ddd, 7.2, 7.2, 1.5	84.3
7	4.01	t, 2.6	69.9	0.01	0.1	**7**	4.00	br	69.8	0.01	0.0	**7**	4.01	br	69.8
8	2.06	ddd, 15.7, 9.7, 3.5	33.7	0.00	0.2	**8**	2.06	ddd, 16.0, 10.0, 3.0	33.5	0.00	0.0	**8**	2.06	ddd, 15.3, 9.7, 3.2	33.5
8'	2.36	d, 15.5		0.00		**8'**	2.36	d, 16.0		0.00		**8'**	2.36	d, 15.6	
9	4.41	dd, 9.6, 3.6	79.7	0.01	0.1	**9**	4.40	dd, 10.0, 4.0	79.6	0.01	0.0	**9**	4.41	dd, 9.6, 3.3	79.6
10	4.33	q, 2.6	55.3	0.00	0.1	**10**	4.33	br	55.2	0.00	0.0	**10**	4.33	br	55.2
11	2.51	m	38.7	-0.02	0.2	**11**	2.53	m	38.5	-0.02	0.0	**11**	2.51	m	38.5
11'	3.35	ddd, 15.7, 8.9, 2.4		0.01		**11'**	3.34	ddd, 16.0, 9.0, 2.0		0.01		**11'**	3.35	ddd, 15.8, 8.9, 2.2	
12	4.51	t, 9.2	53.0	0.01	0.3	**12**	4.50	dd, 10.0, 9.0	52.7	0.01	0.2	**12**	4.51	dd, 9.2, 9.2	52.9
13	3.90	ddd, 11.7, 9.5, 2.6	83.0	0.01	0.2	**13**	3.89	ddd, 12.0, 10.0, 3.0	82.8	0.02	0.0	**13**	3.91	ddd, 11.5, 11.5, 2.4	82.8
14	1.69	ddq, 14.3, 11.3, 7.1	23.1	0.01	0.1	**14**	1.68	ddq, 15.0, 12.0, 7.0	23.0	0.02	0.0	**14**	1.70	m	23.0
14'	1.99	dqd, 15.2, 7.7, 3.7		0.00		**14'**	1.99	ddq, 15.0, 7.0, 3.0		0.00		**14'**	1.99	ddd, 14.7, 7.5, 2.5	
15	1.06	t, 7.3	11.9	0.00	0.1	**15**	1.06	t, 7.0	11.8	0.00	-0.1	**15**	1.06	dd, 7.3, 7.3	11.7
				0.00	0.2		**Mean**			0.00	0.0				
				0.01	0.1		**Standard deviation**			0.01	0.1				

Table 12.13. Comparison of ^{1}H and ^{13}C NMR chemical shifts of (*E*)-bromofucin with natural (*E*)-bromofucin[6] and literature synthetic (*E*)-bromofucin.[4]

12.4.9 *laurendecumenyne B **1.7** (500 MHz, $CDCl_3$, 25 °C)*

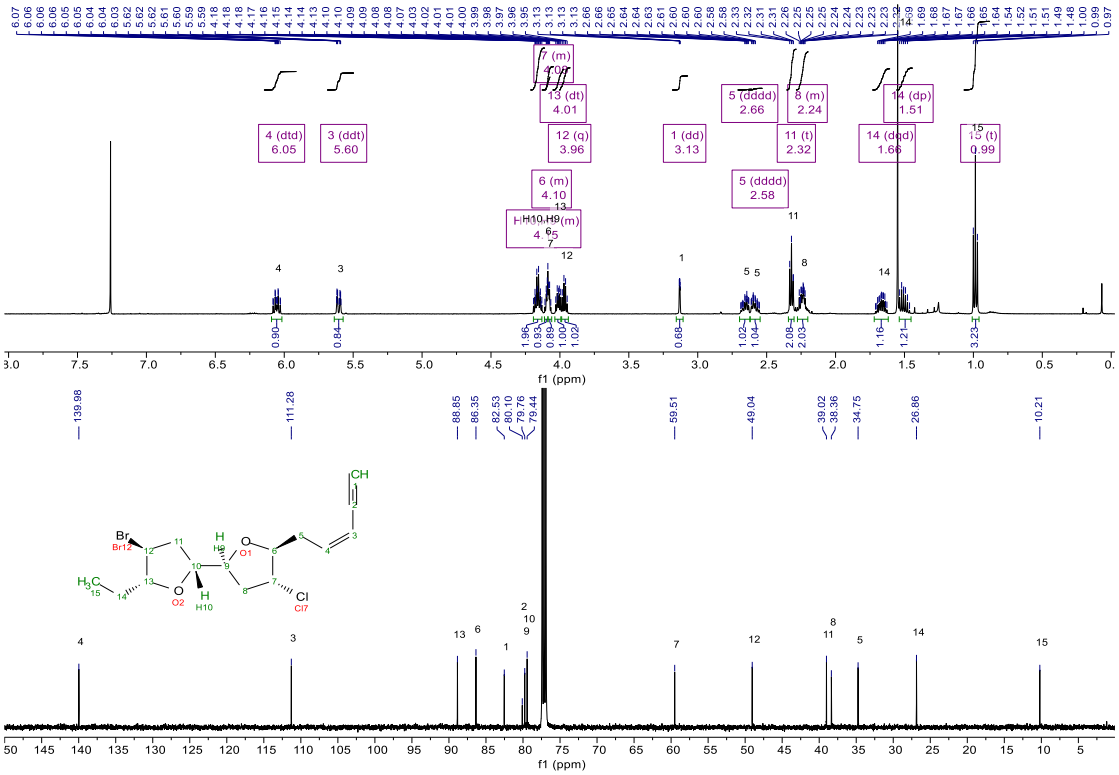


Figure 12.50. ^{1}H and ^{13}C NMR spectra of laurendecumenyne B.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic laurendecumenyne B **1.7**	25	589	0.10	CH_2Cl_2	-8.7
Literature synthetic *ent*-laurendecumenyne B[9] ***ent*-1.7**	25	589	1.05	CH_2Cl_2	-9.1
Natural laurendecumenyne B[14] **1.7**	-	-	-	-	-

Table 12.14. Comparison of specific rotations of laurendecumenyne B with literature synthetic *ent*-laurendecumenyne B. The reported specific rotation of *ent*-laurendecumenyne B has the same sign as the specific rotation of synthetic laurendecumenyne B.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic laurendecumenyne B						Natural laurendecumenyne B						Lit. synthetic *ent*-laurendecumenyne B		
	500/126 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$						500/126 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	3.13	dd, 2.3, 0.9	82.5	0.00	0.1	**1**	3.13	br	82.4	0.00	0.0	**1**	3.13	d, 1.8	82.4
2			80.1	-	0.1	**2**			80.0	-	-0.1	**2**			79.9
3	5.60	ddt, 10.8, 2.5, 1.4	111.3	0.00	0.2	**3**	5.60	d, 10.9	111.1	0.00	0.0	**3**	5.60	ddd, 10.9, 1.6, 1.6	111.1
4	6.05	dtd, 11.0, 7.5, 1.0	140.0	0.00	0.2	**4**	6.05	dt, 10.9, 7.5	139.8	0.00	0.0	**4**	6.05	dddd, 10.8, 7.4, 7.4, 0.5	139.8
5	2.58	dddd, 14.5, 7.5, 5.5, 1.4	34.8	-0.01	0.2	**5**	2.59	m	34.6	-0.01	0.0	**5**	2.58	m	34.6
5'	2.66	dddd, 14.5, 7.5, 5.5, 1.4		0.01		**5'**	2.65			0.00		**5'**	2.65	m	
6	4.10	m	86.4	0.03	0.2	**6**	4.07	m	86.2	0.01	0.0	**6**	4.08		86.2
7	4.08	m	59.5	0.01	0.2	**7**	4.07	m	59.3	0.01	0.0	**7**	4.08		59.3
8	2.24	m	38.4	0.01	0.1	**8**	2.23	m	38.3	-	-0.1	**8**	2.24	m	38.2
8'	2.24	m		-0.08		**8'**	2.32	m				**8'**			
9	4.15	m	79.8	0.00	0.2	**9**	4.15	m	79.6	0.00	0.0	**9**	4.15		79.6
10	4.15	m	79.4	0.00	0.1	**10**	4.15	m	79.3	0.00	0.0	**10**	4.15		79.3
11	2.32	t, 6.3	39.0	0.00	0.0	**11**	2.32	m	39.0	0.00	-0.1	**11**	2.32	m	38.9
11'						**11'**						**11'**			
12	3.96	q, 5.9	49.0	-0.01	0.2	**12**	3.97	m	48.8	-0.01	0.1	**12**	3.96	ddd, 17.7, 11.9, 6.0	48.9
13	4.01	dt, 7.3, 5.1	88.9	0.01	0.2	**13**	4.00	m	88.7	0.00	0.0	**13**	4.00	ddd, 7.3, 5.3, 5.3	88.7
14	1.51	dp, 13.8, 7.3	26.9	0.01	0.2	**14**	1.50	m	26.7	0.00	0.0	**14**	1.50	m	26.7
14'	1.66	dqd, 15.0, 7.5, 4.9		0.00		**14'**	1.66	m		0.00		**14'**	1.66	m	
15	0.99	t, 7.4	10.2	0.01	0.2	**15**	0.98	t, 7.4	10.0	0.00	0.0	**15**	0.98	dd, 7.5, 7.5	10.0
				0.00	0.2		**Mean**			0.00	0.0				
				0.02	0.1		**Standard deviation**			0.01	0.1				

Table 12.15. Comparison of ^{1}H and ^{13}C NMR chemical shifts of laurendecumenyne B with natural laurendecumenyne B[22] and literature synthetic *ent*-laurendecumenyne B.[9]

12.4.10 *(Z)-elatenyne **1.9** (500 MHz, C_6D_6, 25 °C)*

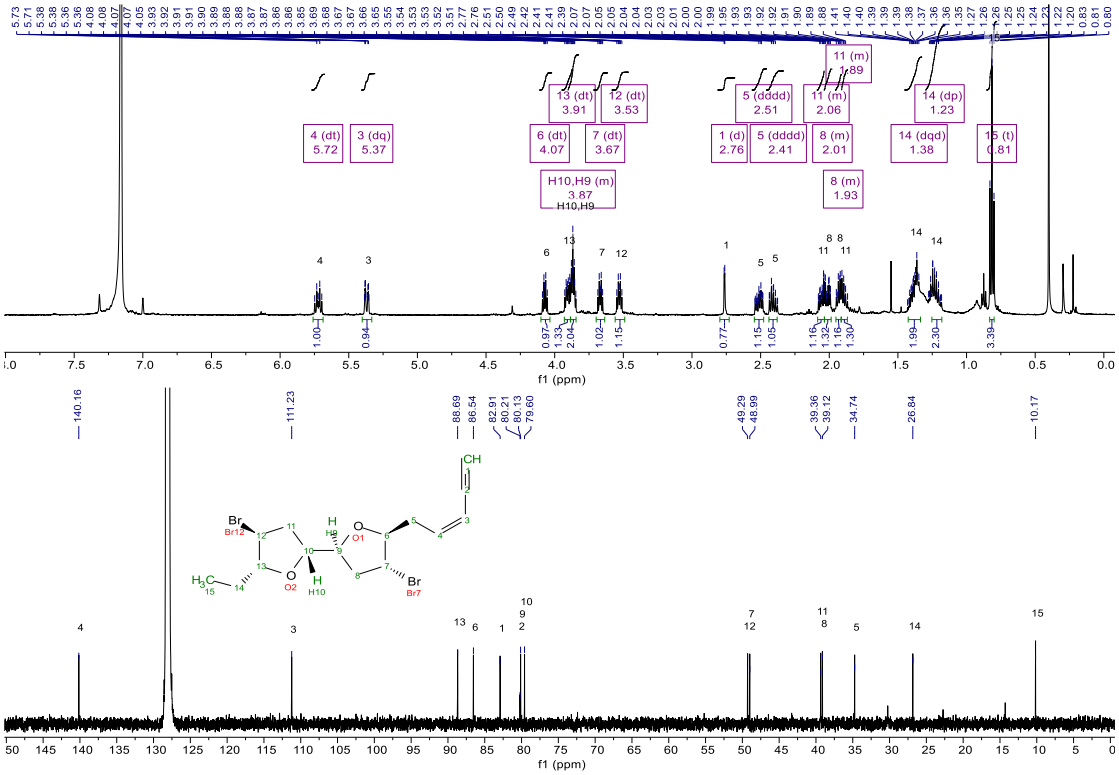


Figure 12.51. ^{1}H and ^{13}C NMR spectra of (*Z*)-elatenyne.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic (*Z*)-elatenyne **1.9**	25	589	0.14	$CHCl_3$	-2.1
Literature synthetic (*Z*)-elatenyne[9] **1.9**	25	589	0.25	$CHCl_3$	-4.0
Natural (*Z*)-elatenyne[12] **1.9**	25	589	1.40	CH_2Cl_2	+16.8

Table 12.16. Comparison of specific rotations of (*Z*)-elatenyne with natural (*Z*)-elatenyne and literature synthetic (*Z*)-elatenyne.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic (*Z*)-elatenyne						Natural (*Z*)-elatenyne						Literature synthetic (*Z*)-elatenyne		
	500/126 MHz, C_6D_6						500/126 MHz, C_6D_6						500/126 MHz, C_6D_6		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.76	d, 2.3	82.9	-0.01	0.0	**1**	2.77	d, 1.8	82.9	-0.01	0.0	**1**	2.76	m	82.9
2			80.2	-	0.0	**2**			80.2	-	0.0	**2**			80.2
3	5.37	dq, 10.9, 1.6	111.2	0.01	0.0	**3**	5.36	dd, 11.0, 1.8	111.2	0.01	0.0	**3**	5.37	ddt, 11.0, 2.2, 1.3	111.2
4	5.72	dt, 10.7, 7.4	140.2	0.00	0.1	**4**	5.72	dt, 11.0, 7.5	140.1	0.00	0.1	**4**	5.72	ddt, 11.0, 0.6, 7.6	140.2
5	2.41	dddd, 14.5, 7.4, 5.3, 1.6	34.7	0.00	0.0	**5**	2.41	ddd, 14.5, 7.5, 7.5	34.7	0.00	0.0	**5**	2.41	m	34.7
5'	2.51	dddd, 14.5, 7.2, 5.4, 1.4		0.02		**5'**	2.49	ddd, 14.5, 6.5, 6.5		-0.02		**5'**	2.51	m	
6	4.07	dt, 6.8, 5.3	86.5	0.01	0.0	**6**	4.06	dt, 5.5, 5.5	86.5	0.01	0.0	**6**	4.07	dt, 6.6, 5.4	86.5
7	3.67	dt, 7.3, 5.0	49.0	0.01	0.1	**7**	3.66	dt, 7.5, 5.5	48.9	0.01	0.1	**7**	3.67	dt, 7.3, 5.0	49.0
8	1.93	m	39.1	0.02	0.0	**8**	1.91	ddd, 6.3, 4.9, 3.4	39.1	0.00	0.0	**8**	1.91	m	39.1
8'	2.01	m		0.10		**8'**	**1.91**	m		0.12		**8'**	2.03	m	
9	3.87	m	80.1	0.01	0.0	**9**	3.86	m	80.1	0.03	0.0	**9**	3.89	m	80.1
10	3.87	m	79.6	0.01	0.1	**10**	3.86	m	79.5	0.03	0.1	**10**	3.89	m	79.6
11	1.89	m	39.4	-0.09	0.1	**11**	**1.98**	m	39.3	-0.07	0.1	**11**	1.91	m	39.4
11'	2.06	m		0.03		**11'**	2.03	m		0.00		**11'**	2.03	m	
12	3.53	dt, 7.6, 5.4	49.3	0.00	0.1	**12**	3.53	dt, 7.0, 5.5	49.2	0.00	0.1	**12**	3.53	dt, 7.6, 5.4	49.3
13	3.91	dt, 7.9, 5.2	88.7	0.02	0.1	**13**	3.89	dt, 7.5, 5.0	88.6	0.00	0.1	**13**	3.89	m	88.7
14	1.23	dp, 14.8, 7.9, 7.4	26.8	0.00	0.0	**14**	1.23	ddq, 14.0, 7.5, 7.5	26.8	0.01	0.0	**14**	1.24	m	26.8
14'	1.38	dqd, 14.8, 7.4, 4.6		0.01		**14'**	1.37	ddq, 14.0, 7.5, 5.0		0.02		**14'**	1.39	m	
15	0.81	t, 7.4	10.2	0.00	0.1	**15**	0.81	t, 7.5	10.1	0.01	0.1	**15**	0.82	t, 7.6	10.2
				0.01	0.0		**Mean**			0.01	0.0				
				0.03	0.1		**Standard deviation**			0.04	0.1				
						Red values indicate ambiguous assignments									

Table 12.17. Comparison of ^{1}H and ^{13}C NMR chemical shifts of (*Z*)-elatenyne with natural (*Z*)-elatenyne[20] and literature synthetic (*Z*)-elatenyne.[4]

12.4.11 *(E)-elatenyne **1.12** (500 MHz, C_6D_6, 25 °C)*

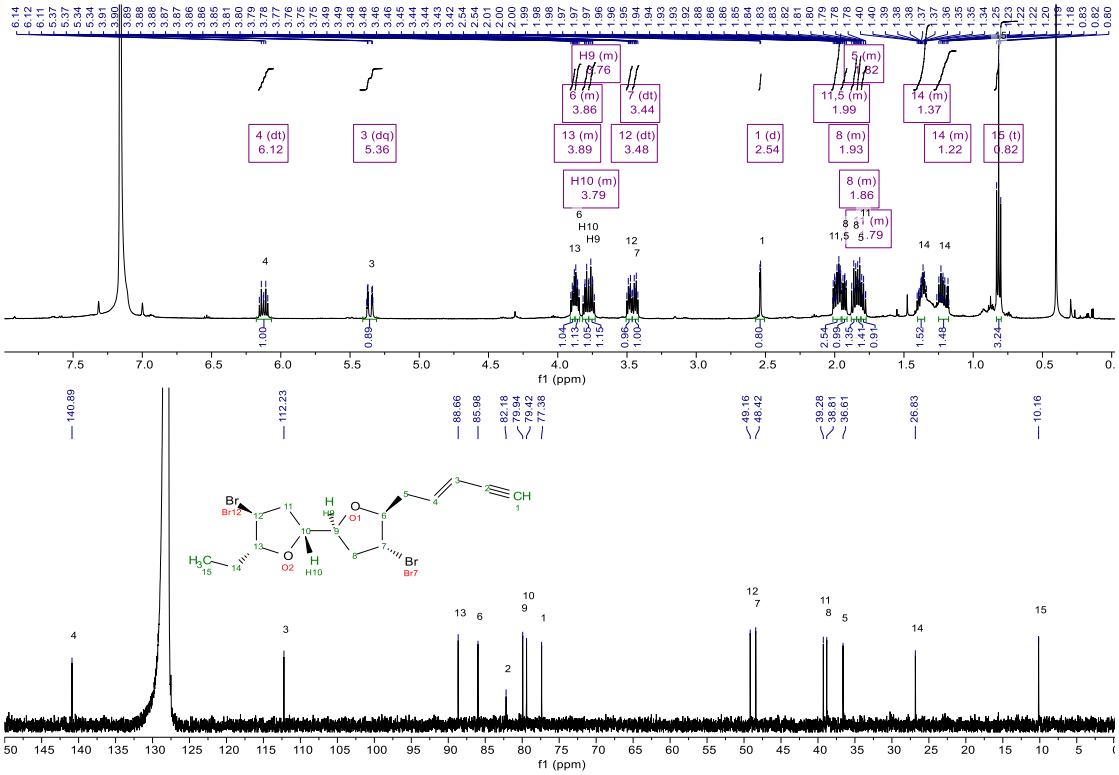


Figure 12.52. ^{1}H and ^{13}C NMR spectra of (*E*)-elatenyne.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic (*E*)-elatenyne **1.12**	25	589	0.13	CH_2Cl_2	-24.6
Literature synthetic (*E*)-elatenyne[9] **1.12**	25	589	0.09	CH_2Cl_2	-33.0
Literature synthetic *ent*-(*E*)-elatenyne[9] ***ent*-1.12**	25	589	0.35	CH_2Cl_2	+29.5

Table 12.18. Comparison of specific rotations of (*E*)-elatenyne with literature synthetic (*E*)-elatenyne and literature synthetic *ent*-(*E*)-elatenyne.

Comparison of ^{1}H and ^{13}C chemical shifts															
	Synthetic (*E*)-elatenyne						Natural (*E*)-elatenyne						Literature synthetic (*E*)-elatenyne		
	500/126 MHz, C_6D_6						400/101 MHz, C_6D_6						500/126 MHz, C_6D_6		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**Δδ^{1}H**	**Δδ^{13}C**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**Δδ^{1}H**	**Δδ^{13}C**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.54	d, 2.2	77.4	0.00	0.1	**1**	2.54	dddd, 2.3, 0.9, 0.8, 0.8	77.3	0.00	0.0	**1**	2.54	m	77.3
2			82.2	-	0.1	**2**			82.1	-	0.0	**2**			82.1
3	5.35	dq, 16.0, 1.7	111.2	0.00	-1.0	**3**	5.35	dddd, 16.0, 2.3, 1.5, 1.5	112.2	0.00	0.0	**3**	5.35	ddt, 16.1, 2.2, 1.6	112.2
4	6.12	dt, 16.1, 7.2	140.9	0.01	0.1	**4**	6.11	dddd, 16.0, 7.2, 7.0, 0.9	140.8	0.01	0.0	**4**	6.12	dt, 16.1, 7.3	140.8
5	1.82	m	36.6	-0.01	0.0	**5**	1.83	dddd, 14.9, 7.3, 7.0, 1.5, 0.	36.6	-0.01	0.0	**5**	1.84	m	36.6
5'	1.99	m		0.00		**5'**	1.99	dddd, 14.9, 7.2, 4.7, 1.5, 0.		0.03		**5'**	1.96	m	
6	3.86	m	86.0	0.00	0.1	**6**	3.86	dddd, 7.3, 5.8, 4.7, 0.6	85.9	0.02	2.7	**6**	3.88	m	**88.6**
7	3.44	dt, 7.5, 5.6	48.4	0.00	0.1	**7**	3.44	dddd, 7.5, 5.8, 5.4, 0.6	48.3	0.00	0.1	**7**	3.44	dt, 7.6, 5.7	48.4
8	1.86	m	38.8	0.02	0.0	**8**	1.84	dddd, 13.8, 7.5, 6.8, 0.6	38.8	0.00	0.0	**8**	1.84	m	38.8
8'	1.93	m		-0.01		**8'**	1.94	ddd, 13.8, 6.9, 5.4		0.02		**8'**	1.96	m	
9	3.76	m	79.9	0.01	0.0	**9**	3.75	dddd, 7.0, 6.9, 6.8, 0.6	79.9	0.03	0.0	**9**	3.78	m	79.9
10	3.79	m	79.4	0.00	0.0	**10**	3.79	dddd, 7.1, 7.0, 6.8, 0.6	79.4	-0.01	0.0	**10**	3.78	m	79.4
11	1.79	m	39.3	-0.01	0.1	**11**	1.80	dddd, 13.8, 7.6, 7.1, 0.7	39.2	0.04	0.0	**11**	1.84	m	39.2
11'	1.99	m		0.01		**11'**	1.98	ddd, 13.8, 6.8, 5.0		-0.02		**11'**	1.96	m	
12	3.48	dt, 7.6, 5.3	49.2	0.00	0.1	**12**	3.48	dddd, 7.6, 5.9, 5.0, 0.6	49.1	0.00	0.0	**12**	3.48	dt, 7.6, 5.4	49.1
13	3.89	m	88.7	0.01	0.1	**13**	3.88	dddd, 7.6, 5.9, 4.6, 0.7	88.6	0.00	-2.7	**13**	3.88	m	**85.9**
14	1.22	m	26.8	0.01	0.0	**14**	1.21	ddd, 13.8, 7.6, 7.4	26.8	0.01	0.0	**14**	1.22	m	26.8
14'	1.37	m		0.00		**14'**	1.37	ddd, 13.8, 7.5, 4.6		0.01		**14'**	1.38	m	
15	0.82	t, 7.4	10.2	0.02	0.1	**15**	0.80	dd, 7.5, 7.4	10.1	0.02	0.0	**15**	0.82	t, 7.6	10.1
				0.00	0.0		**Mean**			0.01	0.0				
				0.01	0.3		**Standard deviation**			0.02	1.0				
												Red values indicate ambiguous assignments			

Table 12.19. Comparison of ^{1}H and ^{13}C NMR chemical shifts of (*E*)-elatenyne with natural (*E*)-elatenyne[21] and literature synthetic (*E*)-elatenyne.[4]

12.4.12 *ent-acetyllaurefucin* ***ent-1.16*** *(500 MHz, C_6D_6 and CCl_4 25 °C)*

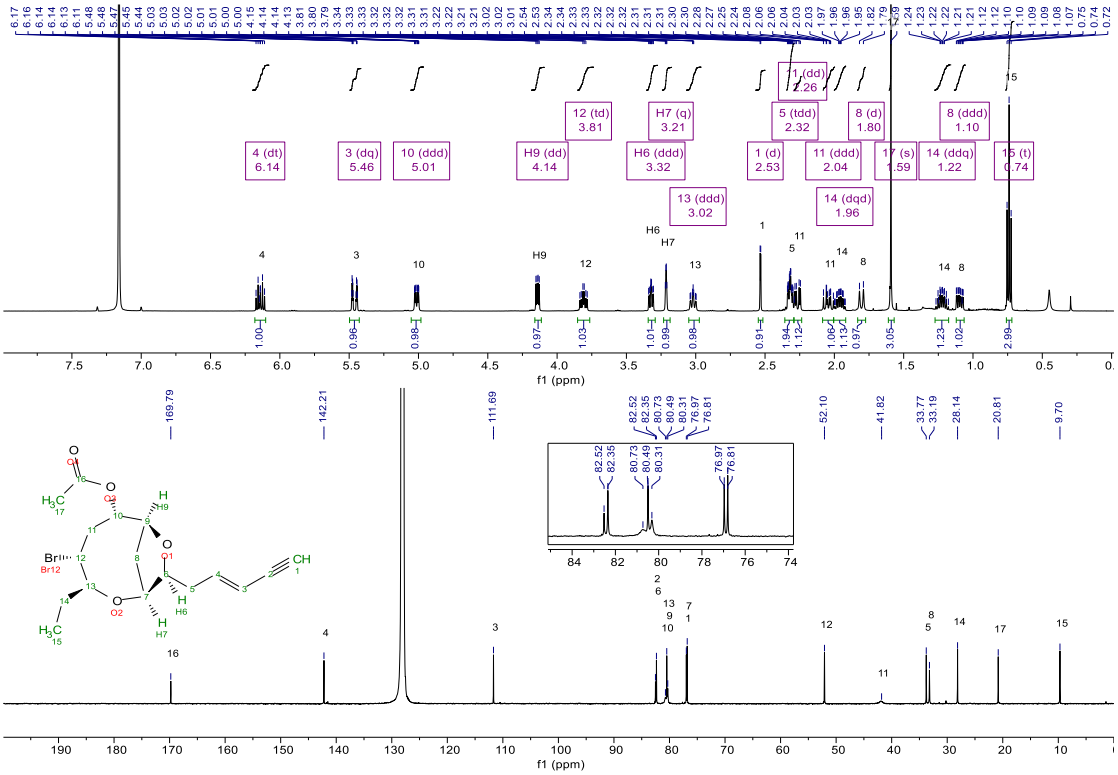


Figure 12.53. ^{1}H and ^{13}C NMR spectra of *ent*-acetyllaurefucin in $CDCl_3$.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic *ent*-acetyllaurefucin ***ent*-1.16**	25	589	0.34	$CHCl_3$	+114.5
Natural acetyllaurefucin[20] ***ent*-1.16**	-	589	-	-	-126.5

Table 12.20. Comparison of specific rotations *ent*-acetyllaurefucin with natural acetyllaurefucin.

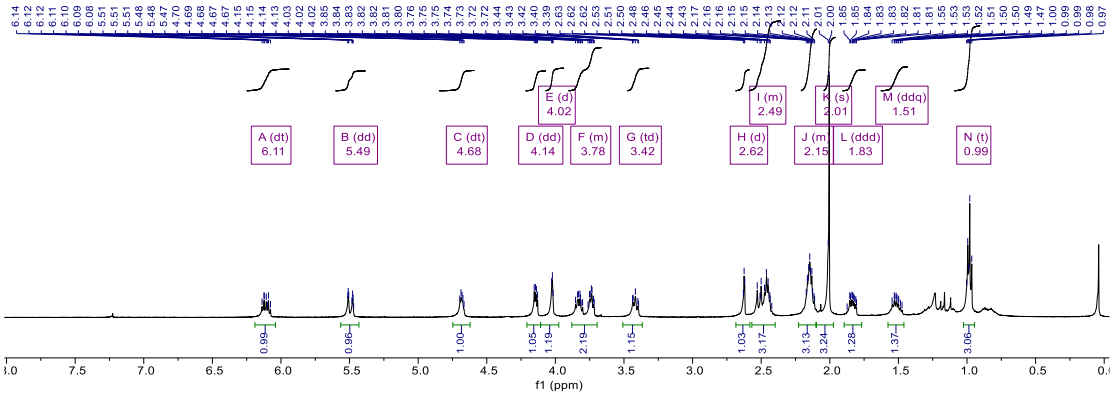


Figure 12.54. ^{1}H NMR spectra of *ent*-acetyllaurefucin in CCl_4.

Comparison of ^{1}H chemical shifts							
Synthetic *ent*-acetyllaurefucin				Natural acetyllaurefucin			
500 MHz, CCl_4				Frequency not given, CCl_4			
^{1}H/ppm	**Integral**	**Multiplicity/Hz**	**$\Delta\delta^{1}$H**	**τ/ppm**	**^{1}H/ppm**	**Integral**	**Multiplicity/Hz**
0.98	3	t, 7.3	0.00	9.02	0.98	3	t, 7.0
1.51	1	ddq, 14.4, 12.5, 7.4	-				
1.83	1	ddd, 14.2, 7.9, 2.4	-				
2.01	3	s	0.00	7.99	2.01	3	s
2.15	3	m	-				
2.46	3	m	-				
2.62	1	d, 2.5	-0.06	7.32	2.68	1	d, 2.5
3.41	1	td, 9.6, 2.4	-0.04	6.55	3.45	1	td, 9.0, 2.0
3.78	2	m	0.01	6.23	3.77	2	m
4.02	1	d, 3.0	-0.02	5.96	4.04	1	s
4.14	1	dd, 7.7, 4.3	-0.02	5.84	4.16	1	dd, 7.0, 4.0
4.68	1	dt, 7.3, 4.2	-0.04	5.28	4.72	1	dt, 5.0, 4.0
5.49	1	dd, 16.0, 2.0	-0.02	4.49	5.51	1	d, 16.0
6.11	1	dt, 15.4, 7.4	-0.02	3.87	6.13	1	dt, 16.0, 7.0
Mean			-0.02				
Standard deviation			0.02				

Table 12.21. Comparison of ^{1}H NMR chemical shifts of *ent*-acetyllaurefucin with natural acetyllaurefucin.[20]

12.4.13 *ent-deacetyllaurencin* ***ent-1.38*** *(500 MHz, $CDCl_3$ and C_6D_6, 25 °C)*

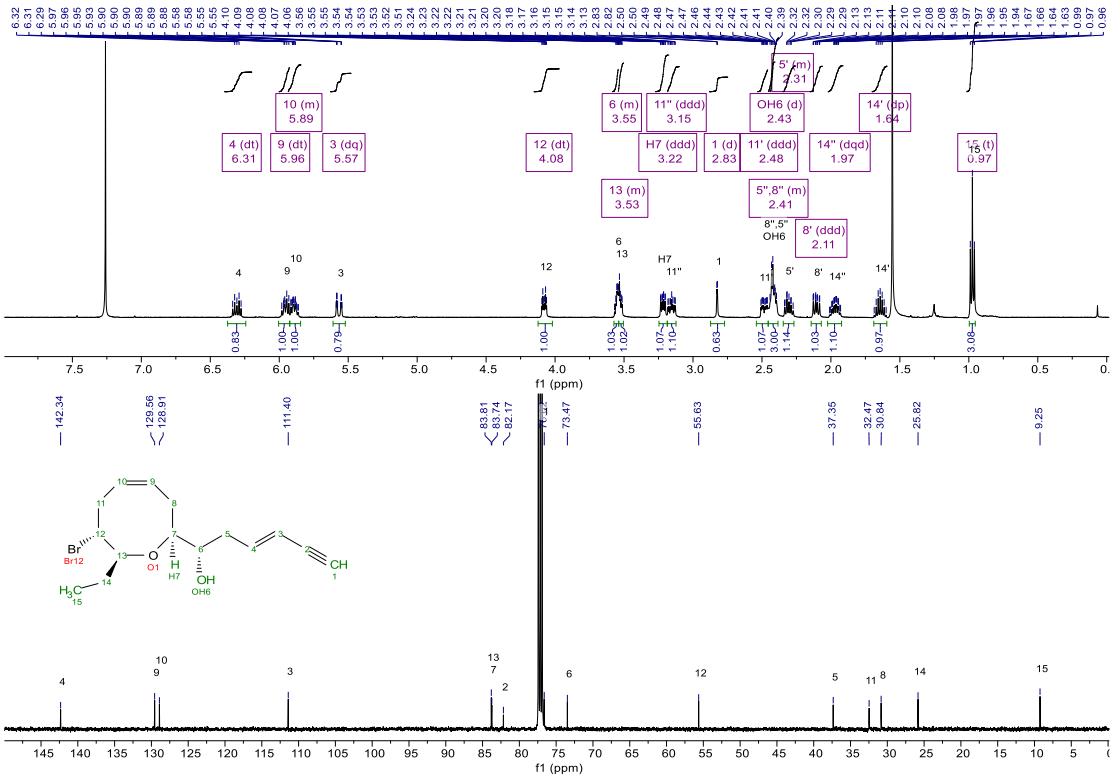


Figure 12.55. ^{1}H and ^{13}C NMR spectra of *ent*-deacetyllaurencin in $CDCl_3$.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic *ent*-deacetyllaurencin ***ent*-1.38**	25	589	0.05	$CHCl_3$	-34.7
Natural deacetyllaurencin[249] **1.38**	17	589	1.15	$CHCl_3$	+46.1

Table 12.22. Comparison of specific rotations of *ent*-deacetyllaurencin with natural deacetyllaurencin.

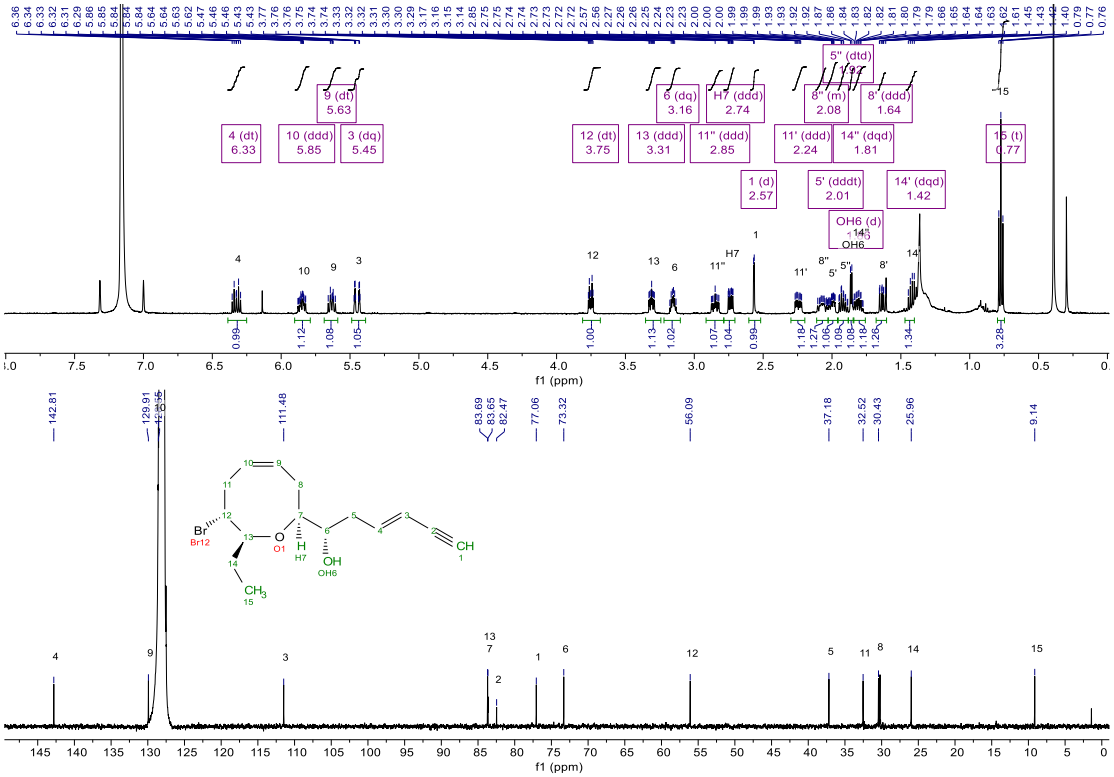


Figure 12.56. ^{1}H and ^{13}C NMR spectra of *ent*-deacetyllaurencin in C_6D_6**.**

Comparison of ^{1}H and ^{13}C chemical shifts									
	Synthetic *ent*-deacetyllaurencin						Natural deacetyllaurencin		
	500/126 MHz, C_6D_6						300/76 MHz, C_6D_6		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**Δδ^{1}H**	**Δδ^{13}C**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.57	d, 2.3	77.1	-0.04	0.1	**1**	2.61	dd, 2.3, 0.6	77.0
2	-	-	82.5	-	0.1	**2**	-	-	82.4
3	5.45	dq, 16.0, 1.8	111.5	-0.04	0.1	**3**	5.49	dddd, 16.0, 2.3, 1.6, 1.6	111.4
4	6.33	dt, 16.1, 7.2	142.8	-0.03	0.1	**4**	6.36	dddd, 16.0, 7.4, 7.3, 0.6	142.7
5	1.92	dtd, 14.7, 7.7, 1.6	37.2	-	0.1	**5**	1.97	m	37.1
5'	2.01	dddt, 14.8, 7.1, 4.0, 1.8				**5'**			
6	3.16	dq, 9.2, 4.8	73.3	-0.04	0.0	**6**	3.20	ddd, 7.8, 5.3, 4.2	73.3
7	2.74	ddd, 10.6, 5.3, 1.4	83.7	-0.04	0.1	**7**	2.78	ddd, 10.5, 5.3, 1.4	83.6
8	1.64	ddd, 14.3, 8.5, 1.3	30.4	-0.03	0.0	**8**	1.67	ddd, 14.2, 8.5, 1.4	30.4
8'	2.08	m		-0.04		**8'**	2.12	m	
9	5.63	dt, 10.6, 7.8	129.9	-0.04	0.0	**9**	5.67	dddd, 10.6, 8.2, 6.9, 1.0	129.9
10	5.85	ddd, 10.6, 8.4, 6.2	128.6	-0.04	0.0	**10**	5.89	dddd, 10.6, 9.4, 6.3, 2.0	128.6
11	2.24	ddd, 14.0, 6.2, 3.2	32.5	-0.05	0.0	**11**	2.29	ddd, 14.0, 6.3, 3.3	32.5
11'	2.85	ddd, 13.5, 9.4, 3.6		-0.04		**11'**	2.89	dddd, 14.0, 9.4, 3.7, 1.0	
12	3.75	dt, 10.0, 3.4	56.1	-0.05	0.1	**12**	3.80	ddd, 10.0, 3.7, 3.3	56.0
13	3.31	ddd, 9.8, 6.9, 2.7	83.7	-0.04	0.1	**13**	3.35	ddd, 10.0, 6.9, 2.7	83.6
14	1.42	dqd, 14.9, 7.4, 6.9	26.0	-0.04	0.1	**14**	1.46	m	25.9
14'	1.81	dqd, 14.9, 7.4, 2.7		-0.03		**14'**	1.84	m	
15	0.77	t, 7.4	9.1	-0.05	0.0	**15**	0.82	dd, 7.4, 7.4	9.1
OH6	1.86	d, 5.0	-	-	-	**OH6**	-	-	-
	Mean			-0.04	0.1				
	Standard deviation			0.01	0.1				

Table 12.23. Comparison of ^{1}H and ^{13}C NMR chemical shifts of *ent*-deacetyllaurencin and natural deacetyllaurencin.[23]

12.4.14 *ent-laurencin* ***ent-1.39*** *(500 MHz, $CDCl_3$, 25 °C)*

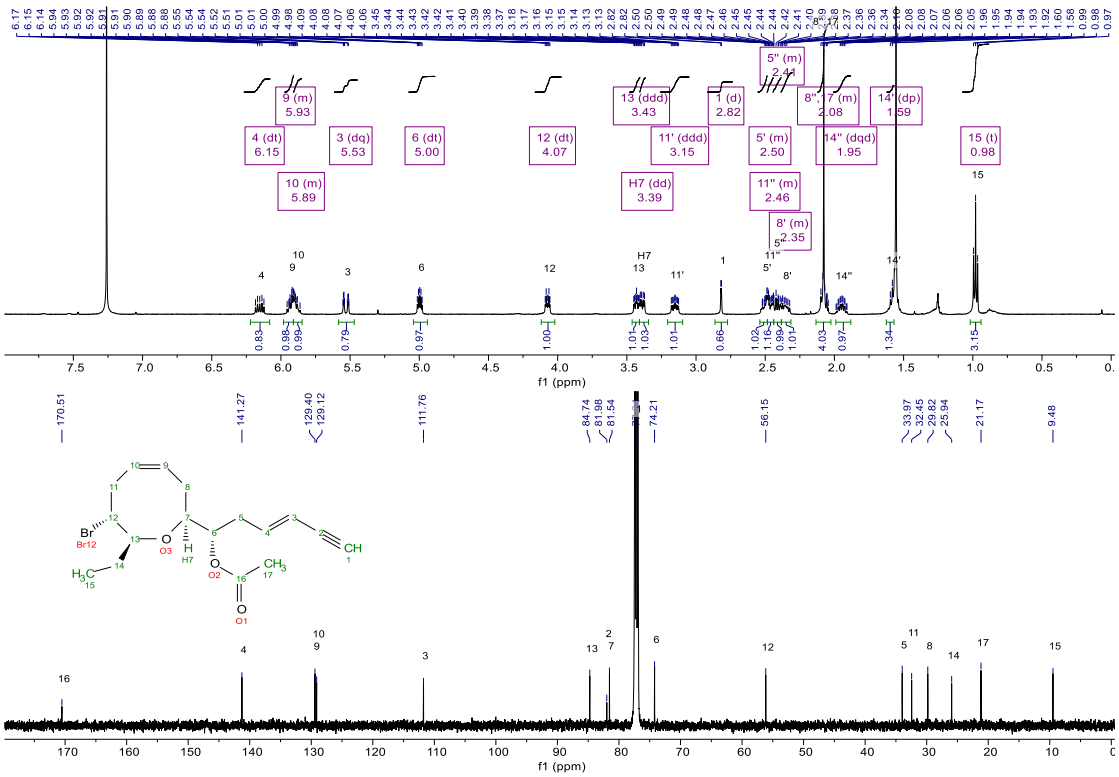


Figure 12.57. ^{1}H and ^{13}C NMR spectra of *ent*-laurencin.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic *ent*-laurencin ***ent*-1.39**	25	589	0.10	$CHCl_3$	-61.0
Literature synthetic laurencin[255]* **1.39**	20	589	0.05	$CHCl_3$	+70.0
Natural laurencin[249,250] **1.39**	17	589	1.00	$CHCl_3$	+70.2

Table 12.24. Comparison of specific rotations of *ent*-laurencin, natural laurencin and literature synthetic laurencin.

* Specific rotation data of other synthetic laurencin (not listed here) are available in their respective publications.[253,254,257–262]

Comparison of ^{1}H and ^{13}C chemical shifts														
	Synthetic *ent*-laurencin 500/126 MHz, $CDCl_3$					Literature synthetic laurencin 500/62.5 MHz, $CDCl_3$					Natural laurencin 300/76 MHz, $CDCl_3$			
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.82	d, 2.2	77.0	0.00	0.3	**1**	2.82	d, 1.5	76.7	0.01	-	**1**	2.83	d, 2.0	-
2			82.0	0.00	0.2	**2**			81.8	0.00	-	**2**			-
3	5.53	dq, 15.9, 1.7	111.8	0.00	0.2	**3**	5.53	dd, 16.0, 1.5	111.6	-0.01	-	**3**	5.52	d, 15.0	-
4	6.15	dt, 15.2, 7.3	141.3	-0.01	0.2	**4**	6.16	dt, 16.0, 7.2	141.1	-0.01	-	**4**	6.15	dt, 15.0, 7.0	-
5	2.41	m	34.0	-	0.2	**5**	2.43	m	33.8	-	-	**5**	2.40	-	-
5'	2.50	m				**5'**						**5'**			
6	5.00	dt, 8.7, 4.3	74.2	0.00	0.1	**6**	5.00	dt, 8.7, 4.4	74.1	-0.02	-	**6**	4.98	dt, 8.0, 5.0	-
7	3.39	dd, 10.6, 4.6	81.5	0.00	0.1	**7**	3.39	dd, 10.5, 4.4	81.4	0.01	-	**7**	3.40	d, 5.0	-
8	2.08	m	29.8	0.00	0.1	**8**	2.08	m	29.7	0.12	-	**8**	2.20	-	-
8'	2.35	m		-0.08		**8'**	2.43	m		-0.03		**8'**	2.40	-	
9	5.93	m	129.4	-	0.2	**9**	5.91	m	129.2	-	-	**9**	5.90	m	-
10	5.89	m	129.1		0.1	**10**			129.0		-	**10**	5.90	m	-
11	2.46	m	32.5	0.03	0.2	**11**	2.43	m	32.3	-0.03	-	**11**	2.40	-	-
11'	3.15	ddd, 13.8, 8.5, 3.6		-0.01		**11'**	3.16	ddd, 14.0, 8.5, 3.4		0.04		**11'**	3.20	-	
12	4.07	dt, 10.0, 3.4	56.2	0.00	0.2	**12**	4.07	dt, 9.9, 3.4	56.0	0.00	-	**12**	4.07	dt, 9.0, 3.0	-
13	3.43	ddd, 9.8, 7.2, 2.6	84.7	0.00	0.1	**13**	3.43	ddd, 9.9, 7.4, 2.6	84.6	-0.03	-	**13**	3.40	ddd, 9.0, 7.0, 3.0	-
14	1.59	dp, 14.8, 7.4	25.9	0.02	0.1	**14**	1.57	dq, 14.4, 7.4	25.8	-0.01	-	**14**	1.56	-	-
14'	1.95	dqd, 14.8, 7.4, 2.6		0.00		**14'**	1.95	ddq, 14.4, 7.4, 2.6		0.02		**14'**	1.97	-	
15	0.98	t, 7.4	9.5	0.00	0.2	**15**	0.98	t, 7.4	9.3	0.00	-	**15**	0.98	t, 7.0	-
Ac	2.08	s	21.2	0.00	0.2	**Ac**	2.08	s	21.0	-0.05	-	**Ac**	2.03	s	-
Ac CO			170.5	0.00	0.2	**Ac CO**			170.3	0.00	-	**Ac CO**			-
				0.00	0.2			**Mean**		0.00					
				0.02	0.1			**Standard deviation**		0.04					

Table 12.25. Comparison of ^{1}H and ^{13}C NMR chemical shifts of *ent*-laurencin with natural laurencin[249,250] and literature synthetic laurencin.[255]

NMR spectroscopic data of other synthetic laurencin (not listed here) are available in their respective publications.[253,254,257–262]

12.4.15 *laurefurenyne C **1.30** (500 MHz, $CDCl_3$, 25 °C)*

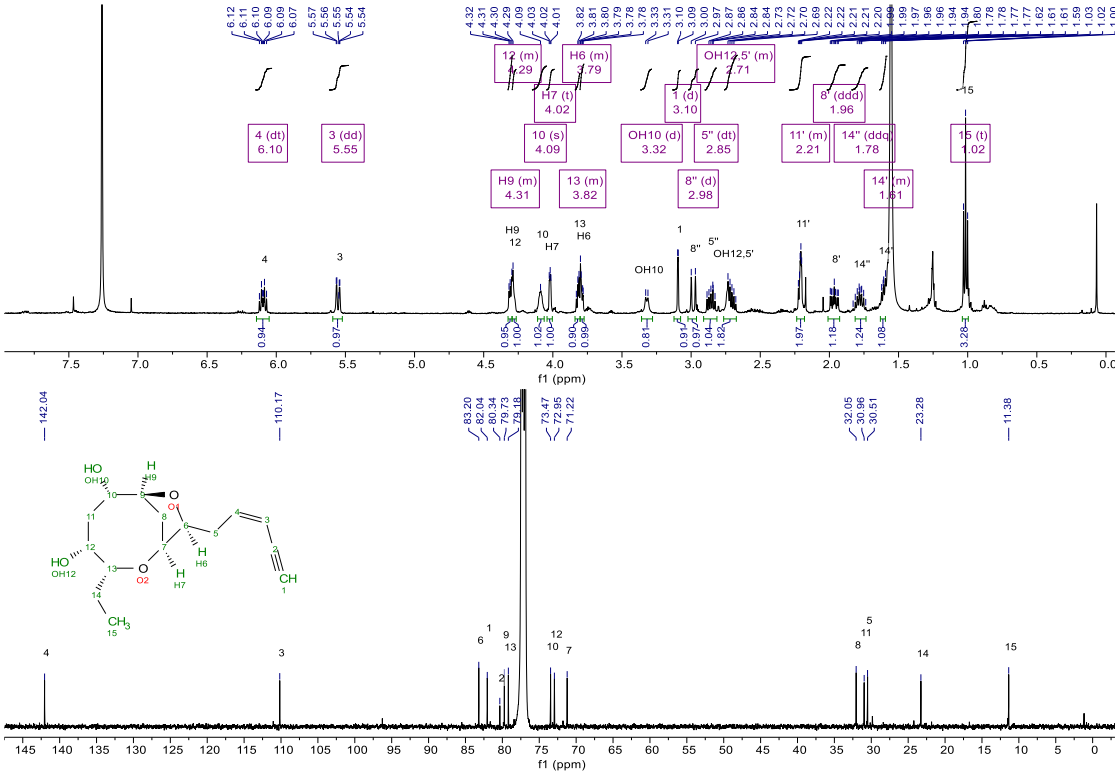


Figure 12.58. ^{1}H and ^{13}C NMR spectra of laurefurenyne C.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic laurefurenyne C **1.30**	25	589	0.13	MeOH	+10.8
Natural laurefurenyne C[26] **1.30**	17	589	0.10	MeOH	+20.0

Table 12.26. Comparison of specific rotations of laurefurenyne C and natural laurefurenyne C.

Comparison of ^{1}H and ^{13}C chemical shifts									
	Synthetic laurefurenyne C						Natural laurefurenyne C		
	500/126 MHz, $CDCl_3$						400/101 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	3.10	d, 2.3	82.0	0.01	0.1	**1**	3.09	d, 2.1	81.9
2			80.3	-	-	**2**			-
3	5.55	dd, 10.8, 2.1	110.2	0.00	0.2	**3**	5.55	dd, 11.2, 2.1	110.0
4	6.10	dt, 10.9, 7.4	142.0	0.02	0.2	**4**	6.08	11.2, 8.0	141.8
5	2.71	m	30.5	0.02	0.1	**5**	2.69	m	30.4
5'	2.85	dt, 14.3, 7.2		0.00		**5'**	2.85	m	
6	3.79	m	83.2	0.01	0.2	**6**	3.78	m	83.0
7	4.02	t, 3.1	71.2	0.00	0.2	**7**	4.02	m	71.0
8	1.96	ddd, 14.5, 10.0, 4.0	32.1	0.00	0.1	**8**	1.96	m	32.0
8'	2.98	d, 15.0		0.00		**8'**	2.98	d, 15.2	
9	4.31	m	79.7	0.01	0.2	**9**	4.30	m	79.5
10	4.09	s	73.5	0.00	0.2	**10**	4.09	m	73.3
11	2.21	m	31.0	0.00	0.2	**11**	2.21	br	30.8
11'						**11'**			
12	4.29	m	73.0	0.00	0.2	**12**	4.29	m	72.8
13	3.82	m	79.2	0.01	0.3	**13**	3.81	m	78.9
14	1.61	m	23.3	0.04	0.2	**14**	1.57	m	23.1
14'	1.78	ddq, 14.7, 8.5, 7.4		0.04		**14'**	1.74	m	
15	1.02	t, 7.4	11.4	0.01	0.1	**15**	1.01	t, 7.5	11.3
OH10	3.32	d, 8.2	-	-0.02	-	**OH10**	3.34	br	-
OH12	2.71	m	-	-0.01	-	**OH12**	2.72	br	-
	Mean			0.01	0.2				
	Standard deviation			0.01	0.1				

Table 12.27. Comparison of ^{1}H and ^{13}C NMR chemical shifts of laurefurenyne C with natural laurefurenyne C.[26]

12.4.16 *laurefurenyne D **1.31** (500 MHz, $CDCl_3$, 25 °C)*

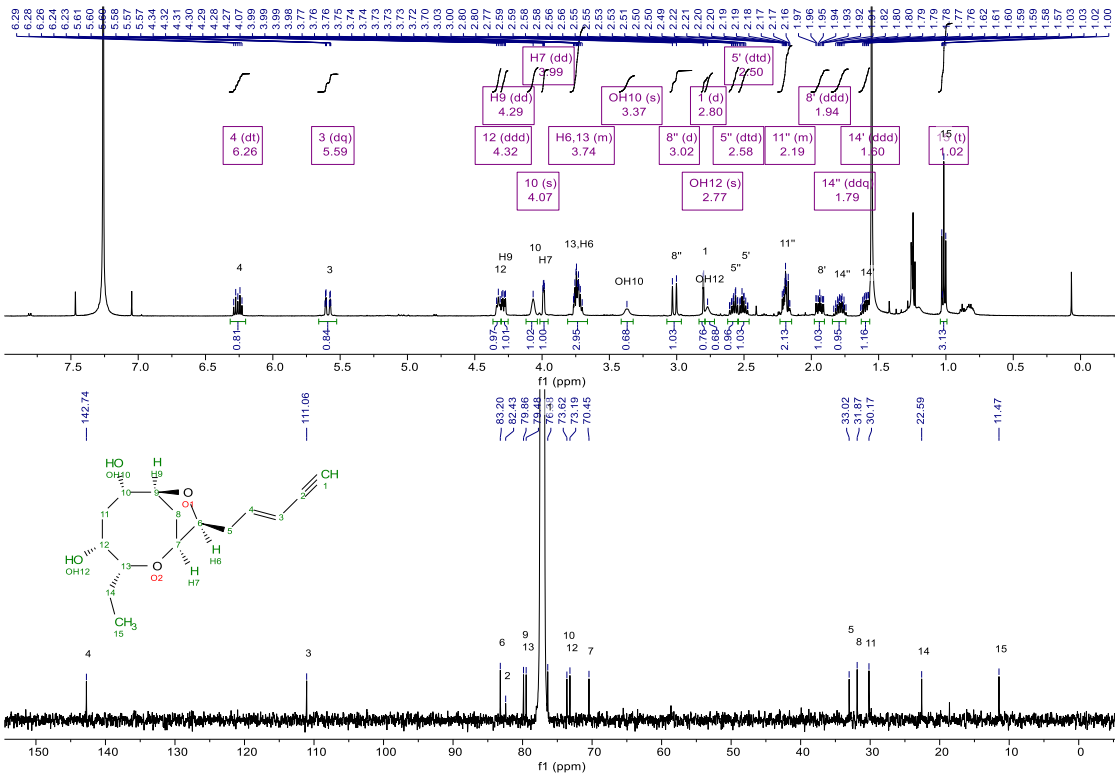


Figure 12.59. ^{1}H and ^{13}C NMR spectra of laurefurenyne D.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic laurefurenyne D **1.31**	25	589	0.10	MeOH	+14.0
Natural laurefurenyne D[26] **1.31**	17	589	0.10	MeOH	+32.0

Table 12.28. Comparison of specific rotations of laurefurenyne D with natural laurefurenyne D.

Comparison of ^{1}H and ^{13}C chemical shifts									
	Synthetic laurefurenyne D						Natural laurefurenyne D		
	500/126 MHz, $CDCl_3$						400/101 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.80	d, 2.2	76.4	0.04	0.2	**1**	2.76	d, 1.6	76.2
2			82.4	-	0.2	**2**			82.2
3	5.59	dq, 15.9, 1.7	111.1	0.00	0.3	**3**	5.59	dd, 16.0, 1.6	110.8
4	6.26	dt, 15.3, 7.4	142.7	0.00	0.2	**4**	6.26	dt, 16.0, 7.5	142.5
5	2.50	dtd, 14.9, 7.4, 1.1	33.0	-	0.2	**5**	2.54	m	32.8
5'	2.58	dtd, 14.7, 7.4, 1.5				**5'**			
6	3.74	m	83.2	0.01	0.3	**6**	3.73	m	82.9
7	3.99	dd, 3.7, 2.0	70.5	0.00	0.3	**7**	3.99	dd, 3.6, 2.0	70.2
8	1.94	ddd, 14.3, 9.9, 3.8	31.9	0.01	0.2	**8**	1.93	m	31.7
8'	3.02	d, 15.0		0.00		**8'**	3.02	d, 16.2	
9	4.29	dd, 9.6, 4.0	79.9	0.00	0.2	**9**	4.29	dd, 9.8, 3.9	79.7
10	4.07	s	73.6	0.00	0.2	**10**	4.07	m	73.4
11	2.19	m	30.2	-0.01	0.5	**11**	2.20	m	29.7
11'						**11'**			
12	4.32	ddd, 7.3, 5.5, 1.7	73.2	0.02	0.1	**12**	4.30	m	73.1
13	3.74	m	79.5	-0.02	0.2	**13**	3.76	m	79.3
14	1.60	ddd, 14.5, 7.5, 2.3	22.6	0.03	0.3	**14**	1.57	m	22.3
14'	1.79	ddq, 14.6, 9.5, 7.3		0.02		**14'**	1.77	m	
15	1.02	t, 7.4	11.5	0.04	0.1	**15**	0.98	t, 7.5	11.4
OH10	3.37	s	-	0.00	-	**OH10**	3.37	br	-
OH12	2.77	s	-	-0.03	-	**OH12**	2.80	br	-
	Mean			0.01	0.2				
	Standard deviation			0.02	0.1				

Table 12.29. Comparison of ^{1}H and ^{13}C NMR chemical shifts of laurefurenyne D with natural laurefurenyne D.[26]

12.4.17 *laurefurenyne E **1.32** (500 MHz, $CDCl_3$, 25 °C)*

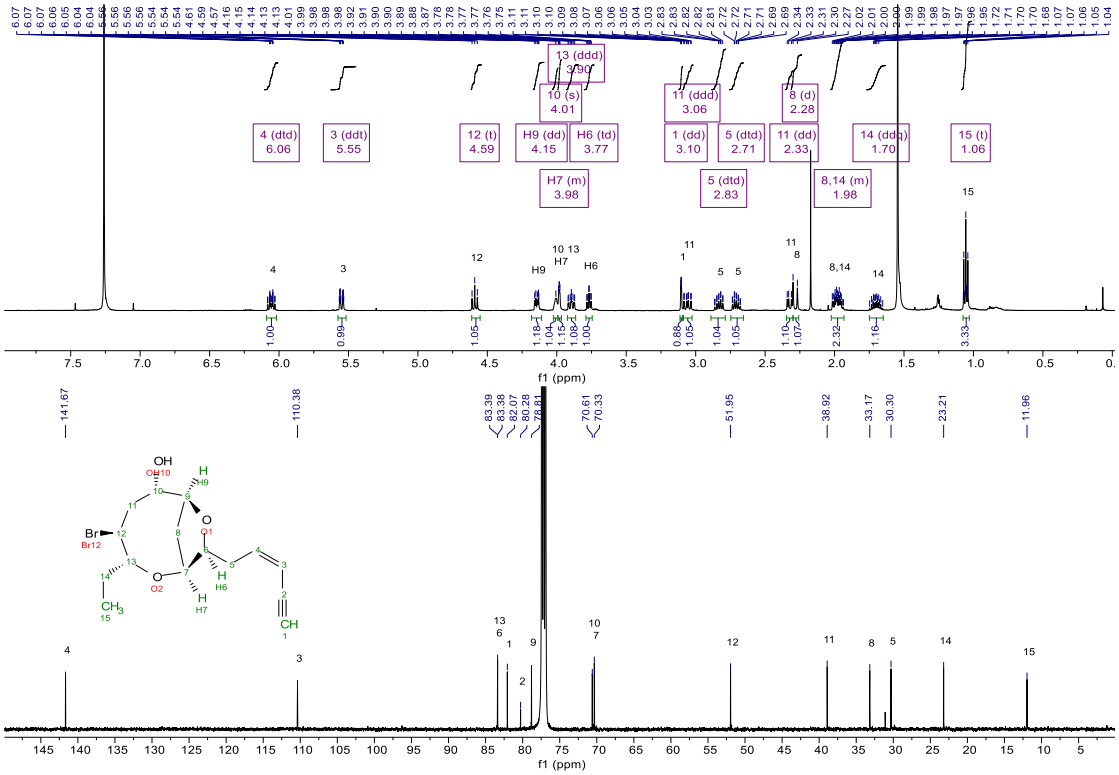


Figure 12.60. ^{1}H and ^{13}C NMR spectra of laurefurenyne E.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic laurefurenyne E **1.32**	25	589	0.17	MeOH	-4.7 (*Z*:*E* = 7.8:1)
Synthetic laurefurenyne E **1.32**	25	589	0.10	MeOH	-5.9 (*Z*:*E* > 15:1)
Natural laurefurenyne E[26] **1.32**	25	589	0.10	MeOH	+11.0

Table 12.30. Comparison of specific rotations of laurefurenyne D with natural laurefurenyne E.

Comparison of ^{1}H and ^{13}C chemical shifts									
	Synthetic laurefurenyne E						Natural laurefurenyne E		
	500/126 MHz, $CDCl_3$						400/101 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	3.10	dd, 2.4, 0.8	82.1	0.03	0.4	**1**	3.07	d, 2.0	81.7
2			80.3	-	-0.4	**2**			80.7
3	5.55	ddt, 10.9, 2.5, 1.4	110.4	0.04	0.2	**3**	5.51	dd, 10.9, 2.0	110.2
4	6.06	dtd, 10.8, 7.3, 0.8	141.7	0.05	0.2	**4**	6.01	dt, 10.9, 7.8	141.5
5	2.71	dtd, 13.8, 7.0, 1.2	30.3	0.03	0.2	**5**	2.68	m	30.1
5'	2.83	dtd, 13.8, 7.0, 1.2		0.04		**5'**	2.79	m	
6	3.77	td, 7.1, 1.9	83.4	0.05	0.2	**6**	3.72	ddd, 8.8, 7.1, 2.0	83.2
7	3.98	m	70.3	0.04	0.1	**7**	3.94	m	70.2
8	1.98	m	33.2	0.06	0.1	**8**	1.92	m	33.1
8'	2.28	d, 15.6		0.04		**8'**	2.24	d, 15.9	
9	4.15	dd, 9.7, 4.0	78.8	0.05	0.2	**9**	4.10	dd, 9.6, 4.0	78.6
10	4.01	s	70.6	0.05	0.1	**10**	3.96	m	70.5
11	2.33	dd, 15.2, 5.2	38.9	0.05	0.1	**11**	2.28	dd, 15.2, 5.1	38.8
11'	3.06	ddd, 15.3, 9.7, 1.8		0.05		**11'**	3.01	dddd, 15.3, 11.3, 9.7, 1.8	
12	4.59	t, 9.6	52.0	0.04	0.2	**12**	4.55	t, 9.6	51.8
13	3.90	ddd, 11.7, 9.5, 2.6	83.4	0.04	0.2	**13**	3.86	ddd, 11.8, 9.6, 2.8	83.2
14	1.70	ddq, 14.2, 11.2, 7.1	23.3	0.04	0.2	**14**	1.66	m	23.1
14'	1.98	m		0.05		**14'**	1.93	m	
15	1.06	t, 7.4	12.0	0.04	0.2	**15**	1.02	t, 7.2	11.8
OH10	-	-	-	-	-	**OH10**	-	-	-
	Mean			0.04	0.1				
	Standard deviation			0.01	0.2				

Table 12.31. Comparison of ^{1}H and ^{13}C NMR chemical shifts of laurefurenyne E with natural laurefurenyne E.[26]

12.4.18 *laurefurenyne F **1.33** (500 MHz, $CDCl_3$, 25 °C)*

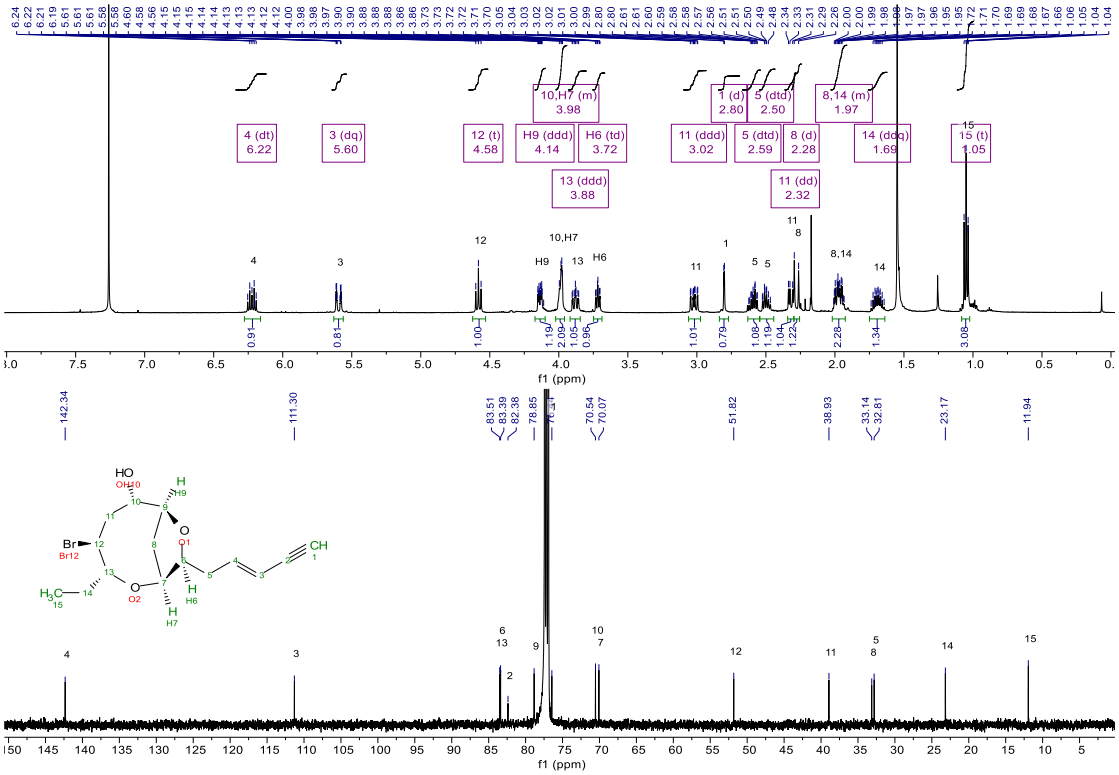


Figure 12.61. ^{1}H and ^{13}C NMR spectra of laurefurenyne F.

Comparison of specific rotations					
Natural Product	**T/°C**	**λ /nm**	**c (g/100 mL)**	**Solvent**	**Measured specific rotation**
Synthetic laurefurenyne F **1.33**	25	589	0.12	MeOH	+17.5
Natural laurefurenyne F[26] **1.33**	25	589	0.10	MeOH	+17.0

Table 12.32. Comparison of specific rotations of laurefurenyne F and natural laurefurenyne F.

Comparison of ^{1}H and ^{13}C chemical shifts									
	Synthetic laurefurenyne F						Natural laurefurenyne F		
	500/126 MHz, $CDCl_3$						400/101 MHz, $CDCl_3$		
Atom No.	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**	**$\Delta\delta^{1}H$**	**$\Delta\delta^{13}C$**	**Atom No.**	**^{1}H/ppm**	**Multiplicity/Hz**	**^{13}C/ppm**
1	2.80	d, 2.3	76.4	0.01	-0.2	**1**	2.79	d, 1.7	76.6
2	-	-	82.4	-	-	**2**	-	-	**81.8**
3	5.60	dq, 16.0, 1.7	111.3	0.05	0.0	**3**	5.55	dd, 15.9, 1.7	111.3
4	6.22	dt, 15.4, 7.4	142.3	0.04	0.2	**4**	6.18	dt, 15.9, 7.5	142.1
5	2.50	dtd, 15.1, 7.5, 1.5	32.8	0.05	0.0	**5**	2.45	m	32.8
5'	2.59	dtd, 15.1, 7.5, 1.5		0.03		**5'**	2.56	m	
6	3.72	td, 7.6, 1.9	83.4	0.05	0.0	**6**	3.67	ddd, 8.6, 7.3, 2.1	83.4
7	3.98	m	70.0	0.04	-0.1	**7**	3.94	m	70.1
8	1.97	m	33.1	0.05	-0.1	**8**	1.92	m	33.2
8'	2.28	d, 15.7		0.04		**8'**	2.24	d, 16.1	
9	4.14	ddd, 9.7, 3.2, 2.1	78.9	0.04	0.0	**9**	4.10	dd, 9.6, 3.9	**78.9**
10	3.98	m	70.5	0.02	0.0	**10**	3.96	m	70.5
11	2.32	dd, 15.2, 5.6	39.0	0.04	0.1	**11**	2.28	dd, 15.1, 5.0	38.9
11'	3.02	ddd, 15.3, 9.7, 1.7		0.04		**11'**	2.98	dddd, 15.4, 11.2, 9.8, 1.8	
12	4.58	t, 9.6	51.8	0.04	0.0	**12**	4.54	t, 9.6	51.8
13	3.88	ddd, 11.8, 9.6, 2.6	83.5	0.04	0.0	**13**	3.84	ddd, 13.5, 9.6, 2.4	83.5
14	1.69	ddq, 14.2, 11.4, 7.1	23.2	0.04	0.0	**14**	1.65	m	23.2
14'	1.97	m		0.01		**14'**	1.96	m	
15	1.05	t, 7.3	11.9	0.04	0.0	**15**	1.01	t, 7.2	11.9
OH10	-	-	-	-	-	**OH10**	-	-	-
	Mean			0.04	0.0				
	Standard deviation			0.01	0.1				
						Blue value indicates corrected chemical shift			
						Red value indicates ambiguous assignment			

Table 12.33. Comparison of ^{1}H and ^{13}C NMR chemical shifts of laurefurenyne F with natural laurefurenyne F.[26] The ^{13}C chemical shift of C-9 of natural laurefurenyne F was corrected from 78.4 ppm to 78.9 ppm from the original ^{13}C NMR spectrum supplied by Prof. Marcel Jaspars.

12.5 Kinetics of the oxonium-oxocarbenium ion conversion

The oxonium ion **4.62** was generated according to the procedure as described in the experimental at -78 °C. It was then warmed to 5 °C in an NMR spectrometer and a series of ^{1}H NMR spectrum was acquired to monitor its conversion to the oxocarbenium ion **4.63**. An initial NMR experiment was performed to test the viability of this reaction monitoring experiment. This was followed by two additional experiments performed under similar reaction conditions for the extraction of the kinetic parameters of the oxonium-oxocarbenium ion conversion, and the corresponding plots are shown below (**Figure 12.62**).

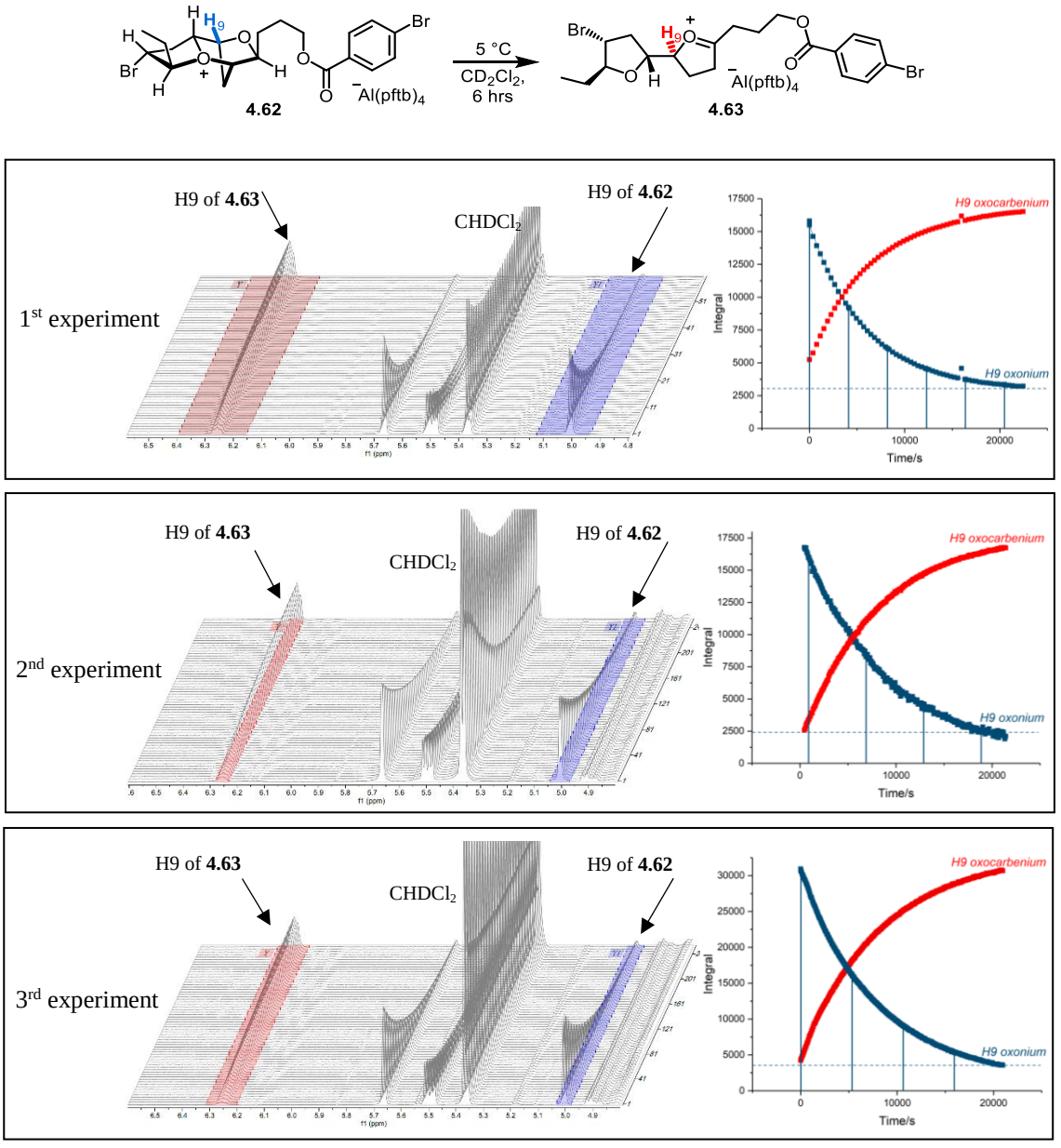


Figure 12.62. Kinetic data for the rearrangement of **4.62** to **4.63**.

The data of the best fit curves for the first-order decay of the integral of H9 oxonium signal over time for each of the experiments are displayed below (**Figure 12.63**):

1st experiment

Model	ExpDec1
Equation	y = A1*exp(-x/t1) + y0
Plot	B
y0	2968.91569 ?38.18776
A1	12551.75127 ?55.87498
t1	5908.32424 ?69.66074
Reduced Chi-Sqr	12738.61301
R-Square(COD)	0.99889
Adj. R-Square	0.99886

2nd experiment

Model	ExpDec1
Equation	y = A1*exp(-x/t1) + y0
Plot	B
y0	624.65851 ?47.68087
A1	17048.32286 ?40.3495
t1	8641.03531 ?69.36512
Reduced Chi-Sqr	21094.05076
R-Square(COD)	0.99876
Adj. R-Square	0.99875

3rd experiment

Model	ExpDec1
Equation	y = A1*exp(-x/t1) + y0
Plot	C
y0	1785.07207 ?28.33185
A1	28980.61404 ?26.81455
t1	7651.04214 ?22.41482
Reduced Chi-Sqr	11110.88764
R-Square(COD)	0.9998
Adj. R-Square	0.9998

Figure 12.63. Data of the best fit curves for the first-order decay of the integral of H9 resonance of **4.62** over time for each of the experiments.

Using the data from these experiments, the half-life of the rearrangement of **4.62** to **4.63** at 5 °C in CD_2Cl_2 and the free energy of activation of the rearrangement are calculated as follows:

$$\text{By } t_{\frac{1}{2}} = \frac{ln2}{k} \text{ and the Eyring equation } k = \frac{k_B T}{h} e^{\frac{-\Delta G^{\ddagger}}{RT}},$$

$$\text{the half-life } t_{\frac{1}{2}} \text{ and Gibbs energy of activation } \Delta G^{\ddagger}$$

$$\text{of each set of data are as follows:}$$

$$t_{\frac{1}{2}_{1st\ experiment}} = 4095.3\ s;\ \Delta G^{\ddagger} = 21.031\ kcal\ mol^{-1}$$

$$t_{\frac{1}{2}_{2nd\ experiment}} = 5989.5\ s;\ \Delta G^{\ddagger} = 21.241\ kcal\ mol^{-1}$$

$$t_{\frac{1}{2}_{3rd\ experiment}} = 5303.2\ s;\ \Delta G^{\ddagger} = 21.174\ kcal\ mol^{-1}$$

$$\text{Average half-life of the rearrangement:}$$

$$\frac{4095.3 + 5989.5 + 5303.2}{3} = 5129.3\ s$$

$$\text{Uncertainty: } \sqrt{\frac{(5129.3 - 4095.3)^2 + (5129.3 - 5985.5)^2 + (5129.3 - 5303.2)^2}{3}} = 781.6\ s$$

$$\text{Average Gibbs energy of activation of the rearrangement:}$$

$$\frac{21.031 + 21.241 + 21.174}{3} = 21.149\ kcal\ mol^{-1}$$

$$\text{Uncertainty: } \sqrt{\frac{(21.149 - 21.031)^2 + (21.149 - 21.241)^2 + (21.149 - 21.174)^2}{3}} = 0.088\ kcal\ mol^{-1}$$

12.6 Data for Mosher ester analyses

Atom No.	δ *S*-ester/ppm	δ *R*-ester/ppm	$\Delta\delta^{SR}$/ppm	$\Delta\delta^{SR}$/Hz
8	5.14	5.08	+0.06	+30
7	5.77	5.71	+0.06	+30
6	2.43	2.38	+0.05	+25
5	5.49	5.47	+0.02	+10
4	4.28	4.35	-0.07	-35
3'	1.93	2.04	-0.11	-55
3	1.64	1.79	-0.15	-75
2	4.56	4.67	-0.11	-55
1	5.55	5.71	-0.16	-80
10	1.47	1.50	-0.03	-15
11	1.28	1.31	-0.03	-15

$$\Delta\delta^{SR}=\delta^{S}-\delta^{R}$$

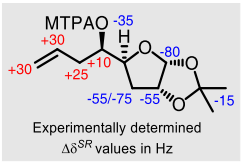


Table 12.34. ^{1}H NMR chemical shifts and $\Delta\delta^{SR}$ data for Mosher ester analysis of **4.8**.

Atom No.	δ *S*-ester/ppm	δ *R*-ester/ppm	$\Delta\delta^{SR}$/ppm	$\Delta\delta^{SR}$/Hz
15	1.07	1.02	+0.05	+25
14'	1.85	1.78	+0.07	+35
14	1.73	1.65	+0.08	+40
13	4.16	4.09	+0.07	+35
12	5.27	5.29	-0.02	-10
11'	1.85	1.87	-0.02	-10
11	1.65	1.78	-0.13	-65
10	3.75	3.89	-0.14	-70
9	4.19	4.24	-0.05	-25
8'	1.79	1.87	-0.08	-40
8	1.79	1.87	-0.08	-40
7	4.24	4.31	-0.07	-35
6	3.80	3.84	-0.04	-20
5'	2.32	2.36	-0.04	-20
5	2.21	2.27	-0.06	-30
4	5.76	5.78	-0.02	-10
3'	5.11	5.12	-0.01	-5
3	5.07	5.08	-0.01	-5

$$\Delta\delta^{SR}=\delta^{S}-\delta^{R}$$

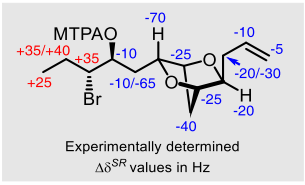


Table 12.35. ^{1}H NMR chemical shifts and $\Delta\delta^{SR}$ data for Mosher ester analysis of **5.17**.

Atom No.	δ *S*-ester/ppm	δ *R*-ester/ppm	$\Delta\delta^{SR}$/ppm	$\Delta\delta^{SR}$/Hz
15	1.07	1.09	-0.02	-10
14'	1.83	1.88	-0.05	-25
14	1.71	1.73	-0.02	-10
13	4.25	4.28	-0.03	-15
12	5.24	5.24	0.00	0
11'	1.95	1.92	+0.03	+15
11	1.48	1.39	+0.09	+45
10	3.87	3.66	+0.21	+105
9	4.24	4.13	+0.11	+55
8'	1.89	1.85	+0.04	+20
8	1.83	1.77	+0.06	+30
7	4.36	4.31	+0.05	+25
6	3.83	3.79	+0.04	+20
5'	2.35	2.26	+0.09	+45
5	2.27	2.19	+0.08	+40
4	5.78	5.76	+0.02	+10
3'	5.12	5.09	+0.03	+15
3	5.08	5.09	-0.01	-5

$$\Delta\delta^{SR}=\delta^{S}-\delta^{R}$$

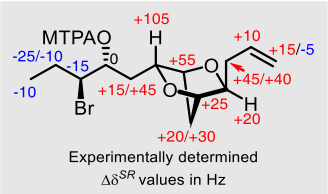


Table 12.36. ^{1}H NMR chemical shifts and $\Delta\delta^{SR}$ data for Mosher ester analysis of **5.18**.

Atom No.	δ *S*-ester/ppm	δ *R*-ester/ppm	$\Delta\delta^{SR}$/ppm	$\Delta\delta^{SR}$/Hz
15	1.03	1.04	-0.01	-5
14'	1.90	1.91	-0.01	-5
14	1.61	1.62	-0.01	-5
13	3.87	3.89	-0.02	-10
12	4.15	4.28	-0.13	-65
11'	3.10	3.17	-0.07	-35
11	2.52	2.50	+0.02	+10
10	5.26	5.32	-0.06	-30
9	4.19	4.07	+0.12	+60
8'	2.15	2.08	+0.07	+35
8	2.01	1.91	+0.10	+50
7	3.99	3.97	+0.02	+10
6	3.78	3.75	+0.03	+15
5'	2.83	2.82	+0.01	+5
5	2.71	2.71	0.00	0
4	6.04	6.04	0.00	0
3	5.56	5.56	0.00	0
2			0.00	0
1	3.10	3.11	-0.01	-5

$$\Delta\delta^{SR}{=}\delta^{S}\text{-}\delta^{R}$$

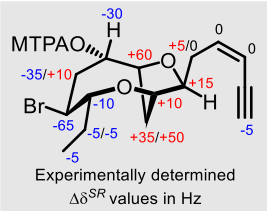


Table 12.37. ^{1}H NMR chemical shifts and $\Delta\delta^{SR}$ data for Mosher ester analysis of **1.32**.

Atom No.	δ *S*-ester/ppm	δ *R*-ester/ppm	$\Delta\delta^{SR}$/ppm	$\Delta\delta^{SR}$/Hz
15	1.03	1.03	0.00	0
14'	1.89	1.90	-0.01	-5
14	1.61	1.61	0.00	0
13	3.86	3.87	-0.01	-5
12	4.15	4.27	-0.12	-60
11'	3.07	3.13	-0.06	-30
11	2.52	2.50	+0.02	+10
10	5.24	5.30	-0.06	-30
9	4.18	4.07	+0.11	+55
8'	2.15	2.07	+0.08	+40
8	2.01	1.90	+0.11	+55
7	3.99	3.96	+0.03	+15
6	3.73	3.70	+0.03	+15
5'	2.58	2.57	+0.01	+5
5	2.52	2.50	+0.02	+10
4	6.21	6.20	+0.01	+5
3	5.60	5.59	+0.01	+5
2			0.00	0
1	2.81	2.81	0.00	0

$$\Delta\delta^{SR}{=}\delta^{S}\text{-}\delta^{R}$$

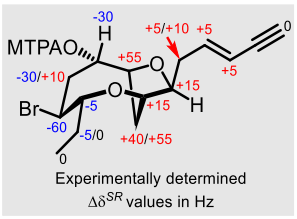


Table 12.38. ^{1}H NMR chemical shifts and $\Delta\delta^{SR}$ data for Mosher ester analysis of **1.33**.

12.7 1D NMR ^{1}H-^{1}H nOe experiments

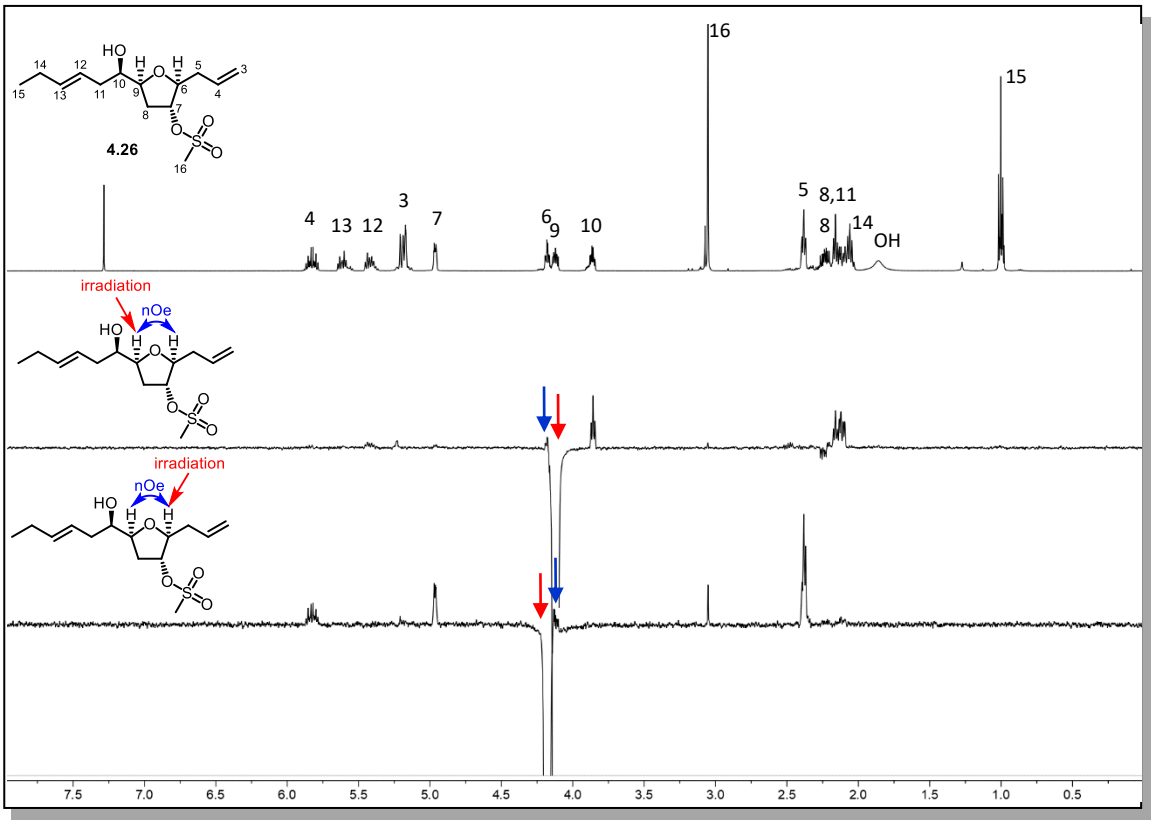


Figure 12.64. 1D nOe (500 MHz, $CDCl_3$) studies of **4.26** for the determination of its structure.

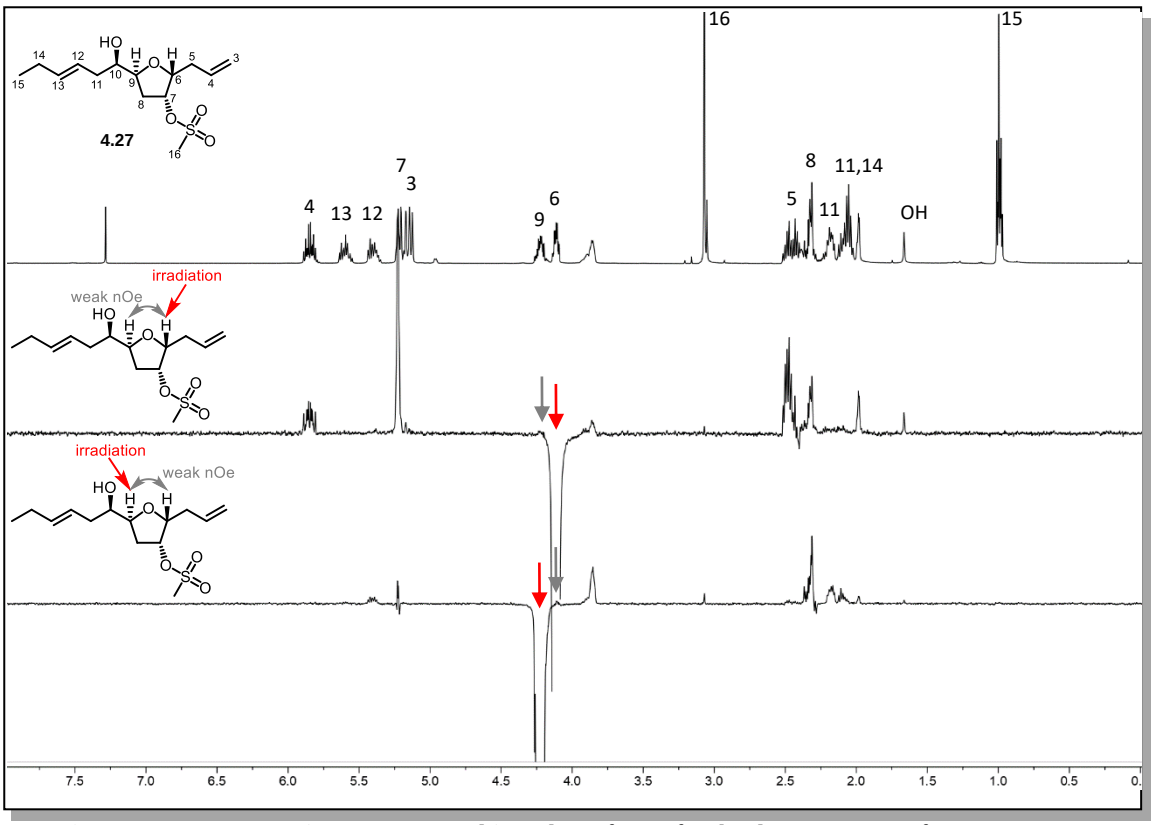


Figure 12.65. 1D nOe (500 MHz, $CDCl_3$) studies of **4.27** for the determination of its structure.

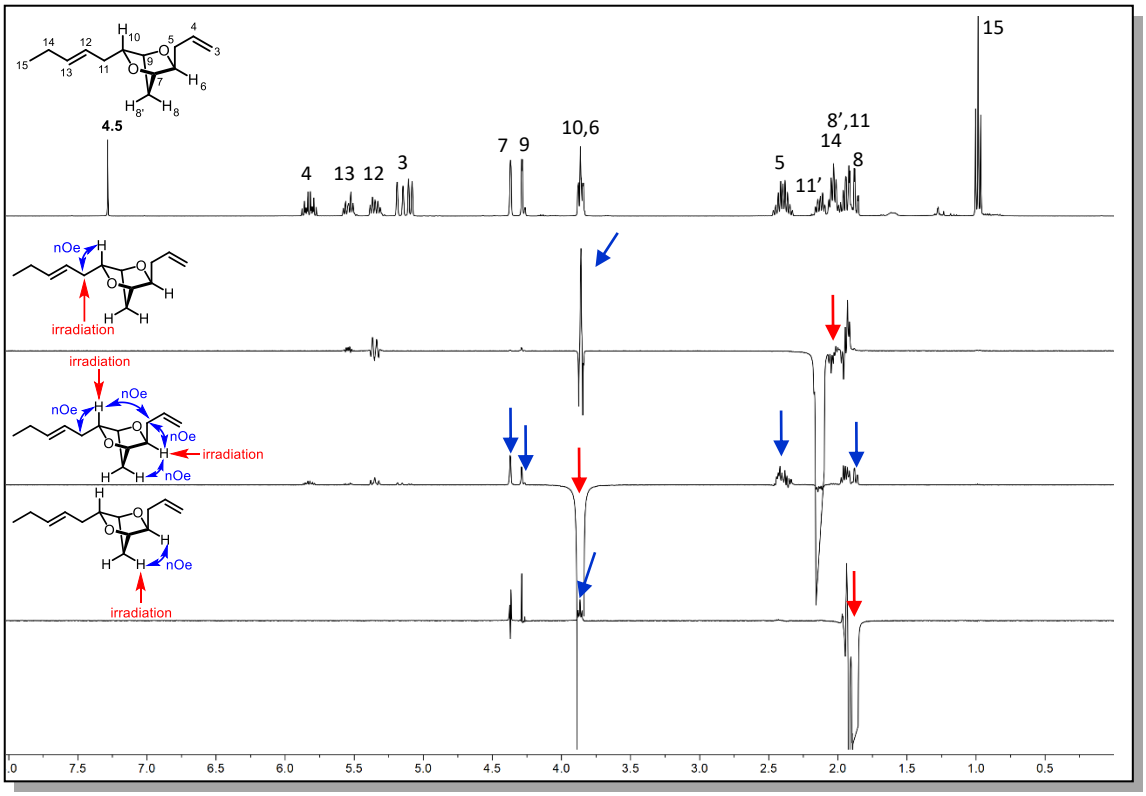


Figure 12.66. 1D nOe (500 MHz, $CDCl_3$) studies of **4.5** for the determination of its structure.

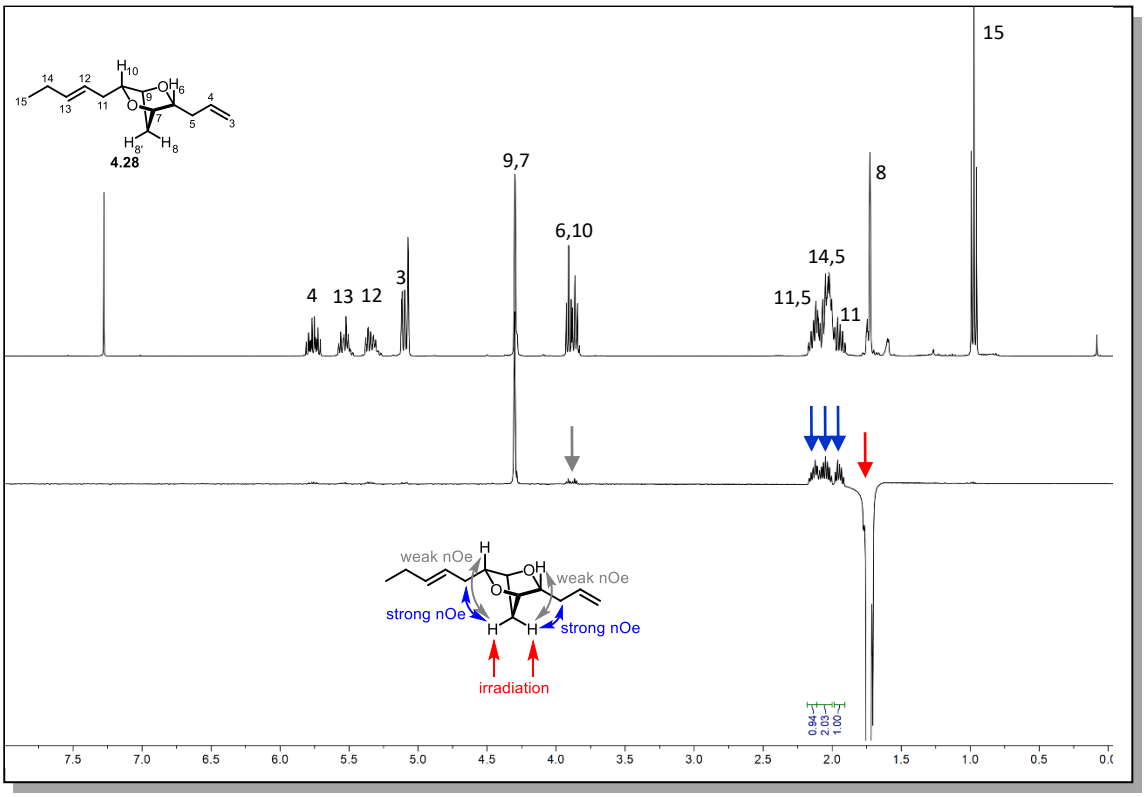
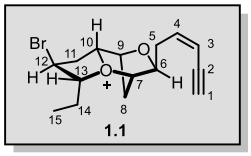


Figure 12.67. 1D nOe (500 MHz, $CDCl_3$) studies of **4.28** for the determination of its structure.

12.8 Experimental vs DFT calculated chemical shifts of oxonium ions

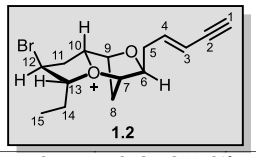
All DFT computations were performed by Dr Quynh Nguyen under the supervision of Prof. Robert. S. Paton.



Experimental vs DFT calculated ^{1}H shifts of 1.1			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	3.37	3.52	0.15
2			0.00
3	5.73	5.88	0.15
4	5.97	6.51	0.54
5	2.75	2.80	0.05
5'	2.86	2.92	0.06
6	4.33	4.23	-0.10
7	5.61	5.61	0.00
8	2.18	2.36	0.18
8'	2.67	2.50	-0.17
9	5.04	4.72	-0.32
10	5.88	5.69	-0.19
11	2.36	2.58	0.22
11'	2.86	2.58	-0.28
12	4.70	4.74	0.04
13	5.67	5.36	-0.31
14	1.63	1.82	0.19
14'	2.13	2.27	0.14
15	1.15	1.15	0.00

Experimental vs DFT calculated ^{13}C shifts of 1.1			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	84.0	87.2	3.2
2	79.1	80.2	1.1
3	112.9	112.2	-0.7
4	136.8	146.8	10.0
5	30.7	33.5	2.8
6	78.5	81.1	2.6
7	93.8	96.8	3.0
8	35.6	36.8	1.2
9	75.9	77.5	1.6
10	109.3	109.3	0.0
11	36.8	38.6	1.8
12	44.0	61.3	17.3
13	109.7	113.1	3.4
14	23.4	25.0	1.6
15	10.5	10.4	-0.1

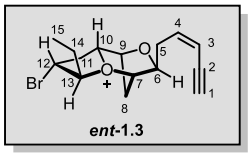
Table 12.39. Experimental vs DFT calculated chemical shifts of **1.1**.



Experimental vs DFT calculated ^{1}H shifts of 1.2			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	3.02	3.19	0.17
2			0.00
3	5.67	5.89	0.22
4	6.14	6.65	0.51
5	2.41	2.57	0.16
5'	2.60	2.60	0.00
6	4.28	4.15	-0.13
7	5.71	5.56	-0.15
8	2.16	2.39	0.23
8'	2.68	2.50	-0.18
9	5.02	4.72	-0.30
10	5.83	5.59	-0.24
11	2.41	2.56	0.15
11'	2.86	2.57	-0.29
12	4.64	4.76	0.12
13	5.48	5.31	-0.17
14	1.72	1.81	0.09
14'	2.16	2.25	0.09
15	1.15	1.14	-0.01

Experimental vs DFT calculated ^{13}C shifts of 1.2			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	78.0	81.6	3.6
2	80.7	81.6	0.9
3	113.0	112.3	-0.7
4	138.2	148.1	9.9
5	33.5	36.9	3.4
6	78.6	81.8	3.2
7	94.3	96.4	2.1
8	35.9	36.7	0.8
9	76.0	77.3	1.3
10	109.8	109.5	-0.3
11	36.4	38.7	2.3
12	43.6	61.6	18.0
13	110.4	113.8	3.4
14	23.3	25.2	1.9
15	10.4	10.4	0.0

Table 12.40. Experimental vs DFT calculated chemical shifts of **1.2**.

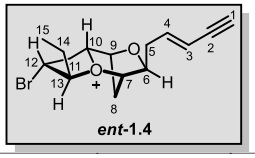


Experimental vs DFT calculated ^{1}H shifts of *ent* -1.3			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	3.28	3.56	0.28
2			0.00
3	5.70	5.88	0.18
4	5.92	6.42	0.50
5	2.70	2.77	0.07
5'	2.70	2.77	0.07
6	4.31	4.26	-0.05
7	5.57	5.42	-0.15
8	2.56	2.56	0.00
8'	2.70	2.66	-0.04
9	4.96	4.63	-0.33
10	5.51	5.34	-0.17
11	2.17	2.17	0.00
11'	3.10	2.94	-0.16
12	4.15	4.23	0.08
13	4.60	4.65	0.05
14	2.17	2.20	0.03
14'	2.32	2.23	-0.09
15	1.14	1.19	0.05

Experimental vs DFT calculated ^{13}C shifts of *ent* -1.3			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	83.9	87.9	4.0
2	78.9	80.3	1.4
3	112.8	112.7	-0.1
4	136.5	145.6	9.1
5	30.5	32.6	2.1
6	78.7	80.9	2.2
7	99.4	100.6	1.2
8	33.4	34.3	0.9
9	76.6	78.1	1.5
10	110.5	109.6	-0.9
11	37.1	39.0	1.9
12	38.1	54.3	16.2
13	105.1	105.3	0.2
14	22.9	24.6	1.7
15	9.2	8.0	-1.2

Table 12.41. Experimental vs DFT calculated chemical shifts of ***ent*-1.3**.

Experimental vs DFT calculated ^{1}H shifts of *ent* -1.4			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	3.00	3.22	0.22
2			0.00
3	5.61	5.86	0.25
4	6.08	6.49	0.41
5	2.37	2.49	0.12
5'	2.56	2.72	0.16
6	4.26	4.23	-0.03
7	5.61	5.39	-0.22
8	2.56	2.58	0.02
8'	2.73	2.67	-0.06
9	4.98	4.63	-0.35
10	5.46	5.23	-0.23
11	2.17	2.16	-0.01
11'	3.11	2.94	-0.17
12	4.16	4.22	0.06
13	4.63	4.65	0.02
14	2.17	2.19	0.02
14'	2.26	2.20	-0.06
15	1.13	1.16	0.03



***ent*-1.4**

Experimental vs DFT calculated ^{13}C shifts of *ent*- 1.4			
Atom No.	**Experimental/ppm**	**Calculated/ppm**	**Calc-Expt/ppm**
1	78.3	82.0	3.7
2	80.4	81.3	0.9
3	113.0	112.4	-0.6
4	137.6	146.9	9.3
5	33.3	35.8	2.5
6	78.5	80.6	2.1
7	99.0	99.9	0.9
8	33.3	34.4	1.1
9	76.6	78.3	1.7
10	110.5	109.3	-1.2
11	37.1	39.3	2.2
12	37.4	54.0	16.6
13	104.5	105.7	1.2
14	22.2	24.5	2.3
15	8.5	8.0	-0.5

Table 12.42. Experimental vs DFT calculated chemical shifts of ***ent*-1.4**.

12.9 X-ray crystallographic data

12.9.1 *X-ray crystallographic data for **ent-1.14***

Table 1. Crystal data and structure refinement for 6960.

Identification code	6960	
Empirical formula	C15 H21 Br1 O3	
Formula weight	329.23	
Temperature	250 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.3606(3) Å	α= 90°.
	b = 13.1527(7) Å	β= 90°.
	c = 14.3775(10) Å	γ = 90°.
Volume	1581.01(15) Å^3	
Z	4	
Density (calculated)	1.383 Mg/m^3	
Absorption coefficient	3.561 mm^{-1}	
F(000)	679.996	
Crystal size	0.28 x 0.08 x 0.02 mm^3	
Theta range for data collection	4.556 to 76.390°.	
Index ranges	-7<=h<=10, -16<=k<=11, -17<=l<=17	
Reflections collected	8437	
Independent reflections	3256 [R(int) = 0.041]	
Completeness to theta = 74.098°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.93 and 0.50	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3256 / 670 / 274	
Goodness-of-fit on F^2	1.0121	
Final R indices [I>2sigma(I)]	R1 = 0.0431, wR2 = 0.1030	
R indices (all data)	R1 = 0.0592, wR2 = 0.1267	
Absolute structure parameter	-0.04(3)	
Largest diff. peak and hole	0.23 and -0.30 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6960. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-2183(3)	6223(2)	5365(2)	71
O(2)	698(3)	5422(2)	6361(2)	73
O(3)	-365(3)	8322(2)	5253(2)	73
C(1)	-465(16)	866(7)	5356(11)	109
C(2)	-430(7)	1758(5)	5295(5)	97
C(3)	-304(6)	2825(5)	5143(8)	97
C(4)	-1452(7)	3460(4)	5145(7)	91
C(5)	-1342(10)	4546(5)	4921(4)	85
C(6)	-1884(5)	5198(2)	5705(3)	76
C(7)	-947(5)	5341(3)	6603(3)	71
C(8)	-1626(4)	6334(3)	6954(3)	67
C(9)	-1627(4)	6950(2)	6053(3)	61
C(10)	1(4)	7400(2)	5750(2)	61
Br(1)	3959(4)	7249(3)	7604(2)	125
C(11)	1251(7)	7626(3)	6524(5)	72
C(12)	2417(6)	6739(3)	6728(2)	83
C(13)	1731(6)	5753(5)	7090(4)	92
C(14)	3029(7)	4888(6)	7061(9)	108
C(15)	2324(9)	3893(6)	7308(8)	116
C(101)	-966(12)	828(8)	5396(11)	91
C(102)	-1001(7)	1693(5)	5173(7)	90
C(103)	-1194(11)	2724(5)	4871(6)	87
C(104)	-552(11)	3521(5)	5250(7)	87
C(105)	-850(12)	4622(6)	4973(6)	82
Br(101)	3705(5)	7510(4)	7766(3)	104
C(111)	1077(10)	7679(5)	6539(6)	63
C(112)	2347(9)	6915(4)	6741(3)	74
C(113)	1822(8)	5825(6)	7015(6)	73
C(114)	3299(10)	5166(7)	7263(13)	87
C(115)	2809(13)	4203(10)	7711(12)	100

Table 3. Bond lengths [Å] and angles [°] for 6960.

O(1)-C(6)	1.456(4)	Br(1)-C(12)	1.924(4)
O(1)-C(9)	1.453(4)	C(11)-C(12)	1.549(6)
O(2)-C(7)	1.422(5)	C(11)-H(111)	0.950
O(2)-C(13)	1.4262(19)	C(11)-H(112)	0.950
O(2)-C(7)	1.422(5)	C(12)-C(13)	1.510(6)
O(2)-C(113)	1.4310(19)	C(12)-H(121)	0.950
O(3)-C(10)	1.441(4)	C(13)-C(14)	1.573(7)
O(3)-H(31)	0.946	C(13)-H(131)	0.950
C(1)-C(2)	1.176(8)	C(14)-C(15)	1.478(7)
C(1)-H(11)	0.950	C(14)-H(141)	0.950
C(2)-C(3)	1.424(7)	C(14)-H(142)	0.950
C(3)-C(4)	1.272(7)	C(15)-H(151)	0.950
C(3)-H(32)	0.954	C(15)-H(152)	0.950
C(4)-C(5)	1.468(7)	C(15)-H(153)	0.950
C(4)-H(41)	0.950	C(101)-C(102)	1.182(8)
C(5)-C(6)	1.487(7)	C(101)-H(1011)	0.950
C(5)-H(51)	0.950	C(102)-C(103)	1.434(7)
C(5)-H(52)	0.950	C(103)-C(104)	1.298(8)
C(6)-C(7)	1.522(6)	C(103)-H(1031)	0.950
C(6)-H(61)	0.950	C(104)-C(105)	1.522(7)
C(6)-C(7)	1.522(6)	C(104)-H(1041)	0.950
C(6)-C(105)	1.558(7)	C(105)-H(1051)	0.950
C(6)-H(62)	0.950	C(105)-H(1052)	0.950
C(7)-C(8)	1.510(5)	Br(101)-C(112)	2.018(6)
C(7)-H(71)	0.950	C(111)-C(112)	1.490(7)
C(8)-C(9)	1.529(5)	C(111)-H(1111)	0.950
C(8)-H(81)	0.950	C(111)-H(1112)	0.950
C(8)-H(82)	0.950	C(112)-C(113)	1.551(7)
C(9)-C(10)	1.546(4)	C(112)-H(1121)	0.950
C(9)-H(91)	0.950	C(113)-C(114)	1.550(8)
C(10)-C(11)	1.556(6)	C(113)-H(1131)	0.950
C(10)-H(101)	0.950	C(114)-C(115)	1.479(9)
C(10)-C(111)	1.493(6)	C(114)-H(1141)	0.950
C(10)-H(102)	0.948	C(114)-H(1142)	0.950

Br(1)-C(12)-C(13)	109.15(9)	C(6)-C(105)-H(1052)	108.7	C(115)-H(1151)	0.950	O(2)-C(7)-C(8)	112.4(3)	
C(1)-C(12)-H(121)	103.9	C(104)-C(105)-H(1052)	108.7	C(115)-H(1152)	0.950	C(6)-C(7)-H(71)	111.8	
Br(1)-C(12)-H(121)	109.2	H(1051)-C(105)-H(1052)	109.5	C(115)-H(1153)	0.950	O(2)-C(7)-H(71)	111.8	
C(13)-C(12)-H(121)	109.5	C(10)-C(111)-C(112)	114.34(10)			C(8)-C(7)-H(71)	111.6	
C(12)-C(13)-O(2)	103.8(4)	C(10)-C(111)-H(1111)	114.4	C(6)-O(1)-C(9)	109.0(3)	C(7)-C(8)-C(9)	100.1(3)	
C(12)-C(13)-C(14)	110.48(9)	C(112)-C(111)-H(1111)	112.2	C(7)-O(2)-C(13)	115.4(4)	C(7)-C(8)-H(81)	111.6	
O(2)-C(13)-C(14)	100.3(5)	C(10)-C(111)-H(1112)	101.0	C(7)-O(2)-C(113)	120.1(5)	C(9)-C(8)-H(81)	111.5	
C(12)-C(13)-H(131)	115.3	C(112)-C(111)-H(1112)	104.2	C(10)-O(3)-H(31)	97.7	C(7)-C(8)-H(82)	112.0	
O(2)-C(13)-H(131)	112.7	H(1111)-C(111)-H(1112)	109.5	C(2)-C(1)-H(11)	178.9	C(9)-C(8)-H(82)	111.9	
C(14)-C(13)-H(131)	113.0	C(111)-C(112)-Br(101)	106.41(10)	C(1)-C(2)-C(3)	174.59(10)	H(81)-C(8)-H(82)	109.5	
C(13)-C(14)-C(15)	111.04(10)	C(111)-C(112)-C(113)	118.13(10)	C(2)-C(3)-C(4)	126.20(10)	C(8)-C(9)-O(1)	103.2(3)	
C(13)-C(14)-H(141)	107.0	Br(101)-C(112)-C(113)	109.43(10)	C(2)-C(3)-H(32)	116.9	C(8)-C(9)-C(10)	116.2(3)	
C(15)-C(14)-H(141)	109.9	C(111)-C(112)-H(1121)	112.1	C(4)-C(3)-H(32)	116.9	O(1)-C(9)-C(10)	109.9(3)	
C(13)-C(14)-H(142)	108.9	Br(101)-C(112)-H(1121)	106.2	C(3)-C(4)-C(5)	126.23(10)	C(8)-C(9)-H(91)	109.1	
C(15)-C(14)-H(142)	110.5	C(113)-C(112)-H(1121)	104.0	C(3)-C(4)-H(41)	116.7	O(1)-C(9)-H(91)	109.1	
H(141)-C(14)-H(142)	109.5	C(112)-C(113)-O(2)	111.2(5)	C(5)-C(4)-H(41)	117.1	C(10)-C(9)-H(91)	109.1	
C(14)-C(15)-H(151)	107.4	C(112)-C(113)-C(114)	110.52(10)	C(4)-C(5)-C(6)	112.08(10)	C(9)-C(10)-O(3)	105.9(2)	
C(14)-C(15)-H(152)	110.8	O(2)-C(113)-C(114)	117.9(8)	C(4)-C(5)-H(51)	108.9	C(9)-C(10)-C(111)	117.6(4)	
H(151)-C(15)-H(152)	109.5	C(112)-C(113)-H(1131)	104.2	C(6)-C(5)-H(51)	108.9	O(3)-C(10)-C(111)	109.7(3)	
C(14)-C(15)-H(153)	110.1	O(2)-C(113)-H(1131)	107.4	C(4)-C(5)-H(52)	108.7	C(9)-C(10)-H(101)	108.4	
H(151)-C(15)-H(153)	109.5	C(114)-C(113)-H(1131)	104.6	C(6)-C(5)-H(52)	108.7	O(3)-C(10)-H(101)	108.4	
H(152)-C(15)-H(153)	109.5	C(113)-C(114)-C(115)	111.02(10)	H(51)-C(5)-H(52)	109.5	C(111)-C(10)-H(101)	106.5	
C(102)-C(101)-H(1011)	178.5	C(113)-C(114)-H(1141)	116.0	C(5)-C(6)-O(1)	109.4(4)	C(9)-C(10)-O(3)	105.9(2)	
C(101)-C(102)-C(103)	174.57(10)	C(115)-C(114)-H(1141)	106.4	C(5)-C(6)-C(7)	123.9(5)	C(9)-C(10)-C(111)	114.2(5)	
C(102)-C(103)-C(104)	126.22(10)	C(113)-C(114)-H(1142)	105.7	O(1)-C(6)-C(7)	105.0(3)	O(3)-C(10)-C(111)	107.3(4)	
C(102)-C(103)-H(1031)	116.8	C(115)-C(114)-H(1142)	108.0	C(5)-C(6)-H(61)	105.9	C(9)-C(10)-H(102)	108.6	
C(104)-C(103)-H(1031)	116.9	H(1141)-C(114)-H(1142)	109.5	O(1)-C(6)-H(61)	105.7	O(3)-C(10)-H(102)	108.5	
C(103)-C(104)-C(105)	126.26(10)	C(114)-C(115)-H(1151)	113.3	C(7)-C(6)-H(61)	105.7	C(111)-C(10)-H(102)	112.0	
C(103)-C(104)-H(1041)	116.9	C(114)-C(115)-H(1152)	108.3	O(1)-C(6)-C(7)	105.0(3)	C(10)-C(11)-C(12)	114.44(9)	
C(105)-C(104)-H(1041)	116.8	H(151)-C(115)-H(1152)	109.5	O(1)-C(6)-C(105)	108.6(4)	C(10)-C(11)-H(111)	114.2	
C(6)-C(105)-C(104)	112.18(10)	C(114)-C(115)-H(1153)	106.7	C(7)-C(6)-C(105)	110.3(5)	C(12)-C(11)-H(111)	111.1	
C(6)-C(105)-H(1051)	108.8	H(1151)-C(115)-H(1153)	109.5	O(1)-C(6)-H(62)	110.9	C(10)-C(11)-H(112)	102.6	
C(104)-C(105)-H(1051)	109.0	H(1152)-C(115)-H(1153)	109.5	C(7)-C(6)-H(62)	110.9	C(12)-C(11)-H(112)	104.0	
				C(105)-C(6)-H(62)	111.0	H(111)-C(11)-H(112)	109.5	
Symmetry transformations used to generate equivalent atoms:				C(6)-C(7)-O(2)	107.4(3)	C(11)-C(12)-Br(1)	106.43(9)	
				C(6)-C(7)-C(8)	101.4(3)	C(11)-C(12)-C(13)	118.25(9)	

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for 6960. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	71(1)	54(1)	88(2)	4(1)	-18(1)	-3(1)
O(2)	61(1)	73(1)	84(2)	13(1)	9(1)	14(1)
O(3)	74(2)	57(1)	87(2)	14(1)	-2(1)	3(1)
C(1)	119(5)	82(4)	127(6)	0(5)	54(5)	24(4)
C(2)	102(4)	75(3)	115(5)	3(4)	37(4)	13(4)
C(3)	95(4)	78(4)	117(5)	0(4)	14(4)	8(4)
C(4)	91(4)	63(3)	120(5)	-11(4)	2(4)	-2(3)
C(5)	92(4)	61(3)	101(4)	-4(3)	0(4)	-8(3)
C(6)	86(2)	53(2)	90(3)	4(2)	-5(2)	-8(2)
C(7)	66(2)	64(2)	83(2)	16(2)	4(2)	3(2)
C(8)	52(2)	71(2)	77(2)	6(2)	7(2)	6(1)
C(9)	50(2)	53(2)	79(2)	3(2)	-4(2)	0(1)
C(10)	55(2)	56(2)	72(2)	5(2)	-4(1)	1(1)
Br(1)	52(1)	209(2)	115(2)	-19(1)	-16(1)	-5(1)
C(11)	55(3)	83(4)	79(4)	3(4)	0(3)	-5(3)
C(12)	47(3)	114(4)	86(4)	8(3)	-2(3)	7(3)
C(13)	63(3)	112(4)	100(5)	33(4)	-2(4)	19(3)
C(14)	71(3)	120(4)	135(5)	42(4)	-10(4)	18(3)
C(15)	87(4)	111(5)	151(6)	48(5)	-5(5)	31(4)
C(101)	96(5)	68(4)	108(6)	1(5)	38(5)	8(4)
C(102)	102(4)	66(4)	104(5)	1(4)	21(5)	12(4)
C(103)	96(4)	67(4)	99(5)	1(4)	14(4)	1(4)
C(104)	98(4)	57(3)	106(5)	-7(4)	-1(5)	7(4)
C(105)	93(4)	55(4)	98(5)	-2(4)	-8(4)	-3(4)
Br(101)	63(2)	164(2)	84(1)	8(2)	-18(1)	-25(2)
C(111)	41(3)	79(5)	69(5)	12(5)	-1(4)	-16(4)
C(112)	49(4)	101(4)	72(4)	18(4)	5(4)	-9(4)
C(113)	44(4)	103(5)	73(5)	28(5)	20(4)	4(4)
C(114)	59(4)	106(5)	97(5)	21(5)	7(5)	13(4)
C(115)	78(5)	111(6)	112(6)	27(6)	9(5)	17(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x 10^3$) for 6960.

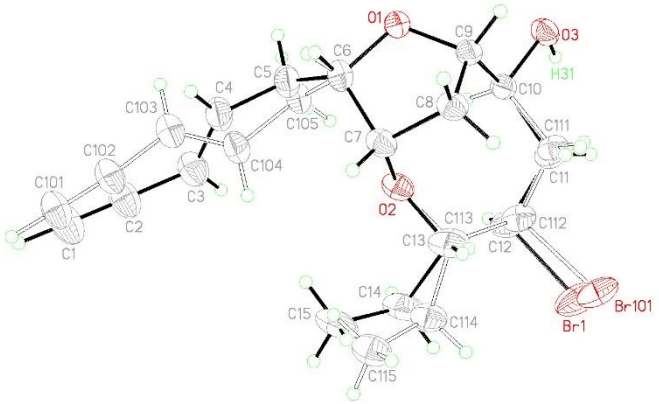
	x	y	z	U(eq)
H(11)	-501	145	5393	130
H(31)	684	8473	5050	88
H(32)	733	3083	4999	115
H(41)	-2476	3206	5314	108
H(51)	-261	4708	4778	102
H(52)	-1995	4682	4395	102
H(61)	-2898	4939	5886	92
H(62)	-2860	4850	5818	92
H(71)	-1131	4802	7029	85
H(81)	-956	6633	7412	80
H(82)	-2674	6254	7199	80
H(91)	-2387	7485	6105	73
H(101)	494	6937	5331	73
H(102)	496	6939	5334	73
H(111)	1813	8248	6444	74
H(112)	607	7666	7068	74
H(121)	2930	6621	6148	80
H(131)	1201	5798	7673	107
H(141)	3832	5065	7500	151
H(142)	3484	4865	6456	151
H(151)	3161	3404	7292	158
H(152)	1871	3912	7913	158
H(153)	1523	3712	6869	158
H(1011)	-968	134	5581	108
H(1031)	-1884	2836	4356	103
H(1041)	183	3407	5743	104
H(1051)	149	4960	4912	98
H(1052)	-1394	4632	4394	98
H(1111)	533	7891	7085	69
H(1112)	1639	8239	6280	69

Table 6. Hydrogen bonds for 6960 [Å and °].

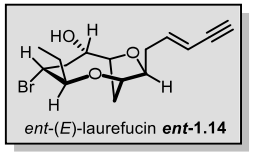
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(1)-H(11)...O(3)#1	0.95	2.41	3.351(10)	171
C(101)-H(11)...O(3)#1	0.98	2.41	3.341(10)	159
O(3)-H(31)...O(1)#2	0.95	1.92	2.868(10)	180
C(12)-H(121)...O(3)#2	0.95	2.47	3.399(10)	166
C(112)-H(121)...O(3)#2	1.06	2.47	3.461(10)	156
C(1)-H(1011)...O(3)#1	1.10	2.48	3.351(10)	135
C(101)-H(1011)...O(3)#1	0.95	2.48	3.341(10)	150
C(12)-H(1121)...O(3)#2	0.90	2.52	3.399(10)	169
C(112)-H(1121)...O(3)#2	0.95	2.52	3.461(10)	173
H(1121)	3041	6815	6226	91
H(1131)	1275	5911	7589	75
H(1141)	4061	5471	7666	110
H(1142)	3793	5005	6687	110
H(1151)	3674	3748	7812	160
H(1152)	2316	4359	8288	160
H(1153)	2048	3894	7309	160

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z #2 x+1/2,-y+3/2,-z+1



Displacement ellipsoids drawn at 20% probability for clarity.



ent-(*E*)-laurefucin ***ent*-1.14**

12.9.2 *X-ray crystallographic data for **8.11***

Table 1. Crystal data and structure refinement for 6955.

Identification code	6955	
Empirical formula	C13 H22 O4	
Formula weight	242.32	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.9422(2) Å	α= 90°.
	b = 7.6020(2) Å	β= 101.005(2)°.
	c = 14.7513(4) Å	γ = 90°.
Volume	654.10(3) Å^3	
Z	2	
Density (calculated)	1.230 Mg/m^3	
Absorption coefficient	0.734 mm^{-1}	
F(000)	264	
Crystal size	0.10 x 0.08 x 0.06 mm^3	
Theta range for data collection	6.112 to 76.695°.	
Index ranges	-7<=h<=7, -9<=k<=9, -18<=l<=18	
Reflections collected	13847	
Independent reflections	2731 [R(int) = 0.079]	
Completeness to theta = 75.161°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.96 and 0.60	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2730 / 5 / 182	
Goodness-of-fit on F^2	1.001.5	
Final R indices [I>2sigma(I)]	R1 = 0.0575, wR2 = 0.1495	
R indices (all data)	R1 = 0.0586, wR2 = 0.1537	
Absolute structure parameter	-0.01(9)	
Largest diff. peak and hole	0.41 and -0.37 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 6955. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(6)	3921(4)	2241(3)	3692(1)	41
C(7)	3714(3)	3924(3)	3116(1)	34
C(8)	1236(3)	3749(3)	2607(1)	35
C(9)	1018(3)	1768(3)	2411(1)	36
C(10)	1171(3)	1187(3)	1430(1)	33
C(11)	3233(3)	1786(3)	1023(1)	30
C(12)	3520(3)	3766(3)	871(1)	32
C(13)	5135(3)	4681(3)	1686(1)	32
C(14)	4688(4)	6658(3)	1762(2)	44
C(15)	6638(5)	7580(3)	2414(3)	63
O(1)	2833(3)	941(2)	3052(1)	41
O(2)	5389(2)	3770(2)	2545(1)	30
O(17)	1300(2)	4581(2)	616(1)	38
O(16)	-946(2)	1696(2)	831(1)	40
C(103)	8782(11)	2979(9)	5530(5)	50
C(3)	8819(11)	3623(13)	5172(6)	62
C(4)	7001(9)	2619(7)	5023(3)	46
C(104)	7844(7)	3138(6)	4651(4)	37
C(5)	6324(4)	1643(3)	4119(2)	48

Table 3. Bond lengths [Å] and angles [°] for 6955.

C(6)-C(7)	1.527(3)						
C(6)-O(1)	1.433(3)	C(103)-H(1032)	0.933				
C(6)-C(5)	1.517(3)	C(3)-C(4)	1.307(11)				
C(6)-H(61)	0.998	C(3)-H(32)	0.932				
C(7)-C(8)	1.526(2)	C(3)-H(31)	0.933				
C(7)-O(2)	1.427(2)	C(4)-C(5)	1.512(5)				
C(7)-H(71)	0.967	C(4)-H(41)	0.935				
C(8)-C(9)	1.534(3)	C(104)-C(5)	1.566(5)				
C(8)-H(82)	0.956	C(104)-H(1041)	0.941				
C(8)-H(81)	0.965	C(5)-H(52)	0.973				
C(9)-C(10)	1.533(3)	C(5)-H(54)	0.982				
C(9)-O(1)	1.437(2)	C(5)-H(53)	0.974				
C(9)-H(91)	0.992	C(5)-H(51)	0.974				
C(10)-C(11)	1.532(2)						
C(10)-O(16)	1.445(2)	C(7)-C(6)-O(1)	103.51(15)				
C(10)-H(101)	0.964	C(7)-C(6)-C(5)	116.87(19)				
C(11)-C(12)	1.537(3)	O(1)-C(6)-C(5)	109.70(18)				
C(11)-H(111)	0.965	C(7)-C(6)-H(61)	109.7				
C(11)-H(112)	0.962	O(1)-C(6)-H(61)	107.0				
C(12)-C(13)	1.552(2)	C(5)-C(6)-H(61)	109.5				
C(12)-O(17)	1.441(2)	C(6)-C(7)-C(8)	99.70(16)				
C(12)-H(121)	0.957	C(6)-C(7)-O(2)	105.59(15)				
C(13)-C(14)	1.534(3)	C(8)-C(7)-O(2)	114.75(14)				
C(13)-O(2)	1.426(2)	C(6)-C(7)-H(71)	113.1				
C(13)-H(131)	0.967	C(8)-C(7)-H(71)	112.5				
C(14)-C(15)	1.527(3)	O(2)-C(7)-H(71)	110.6				
C(14)-H(142)	0.963	C(7)-C(8)-C(9)	102.53(15)				
C(14)-H(141)	0.965	C(7)-C(8)-H(82)	110.1				
C(15)-H(151)	0.950	C(9)-C(8)-H(82)	109.4				
C(15)-H(152)	0.946	C(7)-C(8)-H(81)	113.4				
C(15)-H(153)	0.953	C(9)-C(8)-H(81)	112.3				
O(17)-H(171)	0.805(18)	H(82)-C(8)-H(81)	109.0				
O(16)-H(161)	0.812(18)	C(8)-C(9)-C(10)	116.29(16)				
C(103)-C(104)	1.315(9)	C(8)-C(9)-O(1)	106.27(15)				
C(103)-H(1031)	0.930	C(10)-C(9)-O(1)	108.80(15)				
C(8)-C(9)-H(91)	109.6	C(14)-C(15)-H(152)	108.3				
C(10)-C(9)-H(91)	109.0	H(151)-C(15)-H(152)	109.5				
O(1)-C(9)-H(91)	106.4	C(14)-C(15)-H(153)	110.8				
C(9)-C(10)-C(11)	118.71(15)	H(151)-C(15)-H(153)	107.9				
C(9)-C(10)-O(16)	107.37(14)	H(152)-C(15)-H(153)	109.6				
C(11)-C(10)-O(16)	110.40(15)	C(9)-O(1)-C(6)	108.58(16)				
C(9)-C(10)-H(101)	106.9	C(7)-O(2)-C(13)	121.17(13)				
C(11)-C(10)-H(101)	105.9	C(12)-O(17)-H(171)	120(3)				
O(16)-C(10)-H(101)	106.9	C(10)-O(16)-H(161)	111(2)				
C(10)-C(11)-C(12)	117.88(14)	C(104)-C(103)-H(1031)	120.2				
C(10)-C(11)-H(111)	107.0	C(104)-C(103)-H(1032)	119.3				
C(12)-C(11)-H(111)	109.2	H(1031)-C(103)-H(1032)	120.5				
C(10)-C(11)-H(112)	107.0	C(4)-C(3)-H(32)	120.6				
C(12)-C(11)-H(112)	105.1	C(4)-C(3)-H(31)	121.9				
H(111)-C(11)-H(112)	110.6	H(32)-C(3)-H(31)	117.5				
C(11)-C(12)-C(13)	113.28(14)	C(3)-C(4)-C(5)	120.5(6)				
C(11)-C(12)-O(17)	109.77(14)	C(3)-C(4)-H(41)	119.8				
C(13)-C(12)-O(17)	114.17(15)	C(5)-C(4)-H(41)	119.7				
C(11)-C(12)-H(121)	107.2	C(103)-C(104)-C(5)	121.5(5)				
C(13)-C(12)-H(121)	104.3	C(103)-C(104)-H(1041)	118.7				
O(17)-C(12)-H(121)	107.5	C(5)-C(104)-H(1041)	119.8				
C(12)-C(13)-C(14)	113.93(16)	C(6)-C(5)-C(4)	106.9(2)				
C(12)-C(13)-O(2)	114.53(15)	C(6)-C(5)-H(52)	108.0				
C(14)-C(13)-O(2)	113.67(17)	C(4)-C(5)-H(52)	108.9				
C(12)-C(13)-H(131)	103.8	C(6)-C(5)-H(54)	111.0				
C(14)-C(13)-H(131)	105.2	C(4)-C(5)-H(54)	113.1				
O(2)-C(13)-H(131)	104.1	H(52)-C(5)-H(54)	108.8				
C(13)-C(14)-C(15)	111.98(17)	C(6)-C(5)-C(104)	113.4(2)				
C(13)-C(14)-H(142)	110.3	C(6)-C(5)-H(53)	109.0				
C(15)-C(14)-H(142)	108.2	C(104)-C(5)-H(53)	110.0				
C(13)-C(14)-H(141)	109.3	C(6)-C(5)-H(51)	107.6				
C(15)-C(14)-H(141)	108.9	C(104)-C(5)-H(51)	107.6				
H(142)-C(14)-H(141)	108.1	H(53)-C(5)-H(51)	109.1				
C(14)-C(15)-H(151)	110.7						

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for 6955. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(6)	43(1)	52(1)	31(1)	-1(1)	11(1)	5(1)
C(7)	28(1)	39(1)	34(1)	-7(1)	6(1)	4(1)
C(8)	23(1)	46(1)	38(1)	-8(1)	11(1)	4(1)
C(9)	29(1)	43(1)	40(1)	-2(1)	14(1)	-5(1)
C(10)	26(1)	35(1)	39(1)	-6(1)	8(1)	-2(1)
C(11)	25(1)	33(1)	33(1)	-5(1)	7(1)	3(1)
C(12)	24(1)	37(1)	35(1)	4(1)	11(1)	6(1)
C(13)	23(1)	30(1)	45(1)	2(1)	9(1)	1(1)
C(14)	34(1)	30(1)	65(1)	2(1)	5(1)	1(1)
C(15)	53(1)	31(1)	98(2)	-11(1)	-5(1)	-5(1)
O(1)	43(1)	42(1)	39(1)	5(1)	10(1)	-4(1)
O(2)	21(1)	31(1)	37(1)	-1(1)	5(1)	4(1)
O(17)	29(1)	43(1)	40(1)	9(1)	1(1)	7(1)
O(16)	24(1)	49(1)	47(1)	-11(1)	4(1)	-1(1)
C(103)	49(3)	60(3)	40(3)	1(2)	5(2)	-6(3)
C(3)	45(3)	86(6)	57(4)	-25(4)	11(3)	0(3)
C(4)	50(3)	59(3)	28(2)	6(2)	6(2)	14(2)
C(104)	32(2)	43(2)	37(3)	3(2)	11(2)	1(2)
C(5)	53(1)	47(1)	39(1)	-3(1)	-4(1)	15(1)

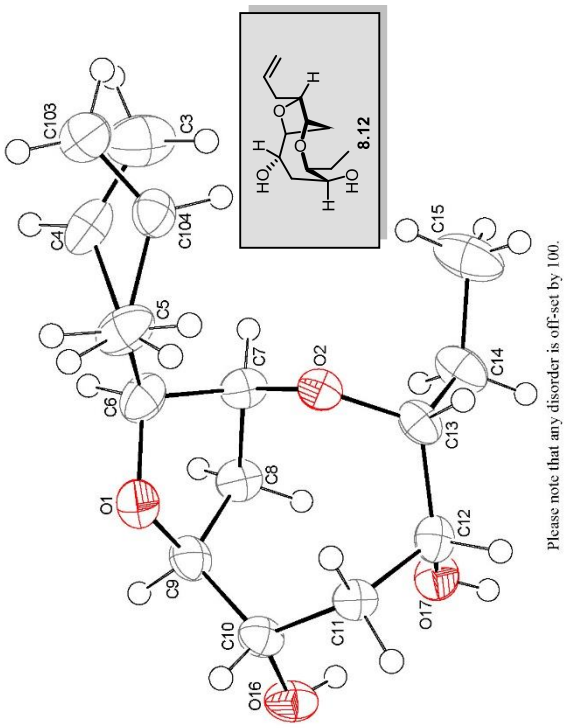
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x 10^3$) for 6955.

	x	y	z	U(eq)
H(61)	2984	2351	4183	50
H(71)	3968	4979	3488	40
H(82)	212	4080	3005	41
H(81)	896	4443	2050	41
H(91)	-438	1327	2562	44
H(101)	1217	-81	1433	40
H(111)	4588	1342	1425	36
H(112)	3065	1267	419	35
H(121)	4287	3892	360	39
H(131)	6631	4597	1522	39
H(142)	4520	7206	1164	53
H(141)	3282	6830	1986	51
H(151)	6241	8763	2518	95
H(152)	7954	7560	2141	95
H(153)	6964	6999	2997	95
H(1031)	9581	3916	5846	60
H(1032)	8642	1917	5831	60
H(32)	9366	4090	5756	75
H(31)	9615	3903	4703	75
H(41)	6108	2506	5478	55
H(1041)	8067	4190	4344	44
H(52)	6266	390	4246	57
H(54)	7387	1839	3694	57
H(53)	6225	659	4533	57
H(51)	7062	1249	3620	56
H(171)	1030(60)	5220(40)	172(17)	57(2)
H(161)	-920(60)	2720(30)	680(20)	60(2)

Table 6. Hydrogen bonds for 6955 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(8)-H(81)...O(17)	0.96	2.18	3.013(5)	144
O(17)-H(171)...C(10)#1	0.805	2.581	3.326(5)	155(3)
O(17)-H(171)...O(16)#1	0.805	1.851	2.648(5)	170(4)
O(16)-H(161)...O(17)	0.812	1.946	2.618(5)	140(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x,y+1/2,-z



12.9.3 *X-ray crystallographic data for **1.31***

Table 1. Crystal data and structure refinement for 6993.

Identification code	6993	
Empirical formula	C15 H22 O4	
Formula weight	266.34	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 5.8853(2) Å	α= 90°.
	b = 7.6219(2) Å	β= 97.424(3)°.
	c = 16.1377(4) Å	γ = 90°.
Volume	717.82(4) Å³	
Z	2	
Density (calculated)	1.232 Mg/m³	
Absorption coefficient	0.719 mm⁻¹	
F(000)	287.998	
Crystal size	0.31 x 0.20 x 0.01 mm³	
Theta range for data collection	5.529 to 76.168°.	
Index ranges	-7<=h<=6, -9<=k<=9, -20<=l<=20	
Reflections collected	11890	
Independent reflections	2974 [R(int) = 0.051]	
Completeness to theta = 74.645°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.53	
Refinement method	Full-matrix least-squares on F²	
Data / restraints / parameters	2971 / 1 / 173	
Goodness-of-fit on F²	1.0016	
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.1151	
R indices (all data)	R1 = 0.0458, wR2 = 0.1175	
Absolute structure parameter	-0.07(9)	
Largest diff. peak and hole	0.30 and -0.17 e.Å⁻³	

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for 6993. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4568(5)	5000(4)	6193(2)	52
C(2)	3606(4)	4243(3)	5610(2)	45
C(3)	2320(4)	3314(3)	4931(2)	44
C(4)	1568(4)	4022(3)	4206(1)	39
C(5)	159(4)	3069(3)	3502(1)	37
C(6)	-2106(3)	4006(3)	3228(1)	32
C(7)	-1958(3)	5879(3)	2904(1)	28
C(8)	-4346(3)	6086(3)	2429(1)	28
C(9)	-4799(3)	4279(3)	2029(1)	29
C(10)	-4387(3)	4063(3)	1115(1)	28
C(11)	-2146(3)	4719(2)	830(1)	27
C(12)	-1610(3)	6687(2)	913(1)	26
C(13)	-76(3)	7133(2)	1747(1)	26
C(14)	-255(3)	9018(3)	2052(1)	31
C(15)	700(4)	10320(3)	1472(2)	41
O(16)	-6318(2)	4820(2)	585(1)	31
O(17)	-3705(2)	7702(2)	767(1)	29
O(21)	-3323(3)	3067(2)	2530(1)	35
O(22)	-171(2)	5843(2)	2385(1)	27

Table 3. Bond lengths [Å] and angles [°] for 6993.

C(1)-C(2)	1.184(4)	C(14)-C(15)	1.521(3)
C(1)-H(11)	0.924	C(14)-H(141)	0.970
C(2)-C(3)	1.436(3)	C(14)-H(142)	0.946
C(3)-C(4)	1.313(3)	C(15)-H(152)	0.971
C(3)-H(31)	0.966	C(15)-H(151)	0.959
C(4)-C(5)	1.504(3)	C(15)-H(153)	0.985
C(4)-H(41)	0.950	O(16)-H(161)	0.810
C(5)-C(6)	1.526(3)	O(17)-H(171)	0.822
C(5)-H(51)	0.970		
C(5)-H(52)	0.982	C(2)-C(1)-H(11)	174.9
C(6)-C(7)	1.527(3)	C(1)-C(2)-C(3)	176.5(3)
C(6)-O(21)	1.444(2)	C(2)-C(3)-C(4)	124.2(2)
C(6)-H(61)	0.984	C(2)-C(3)-H(31)	117.5
C(7)-C(8)	1.519(2)	C(4)-C(3)-H(31)	118.3
C(7)-O(22)	1.426(2)	C(3)-C(4)-C(5)	124.4(2)
C(7)-H(71)	0.942	C(3)-C(4)-H(41)	118.2
C(8)-C(9)	1.530(3)	C(5)-C(4)-H(41)	117.4
C(8)-H(82)	0.976	C(4)-C(5)-C(6)	111.61(18)
C(8)-H(81)	0.951	C(4)-C(5)-H(51)	110.3
C(9)-C(10)	1.534(3)	C(6)-C(5)-H(51)	109.7
C(9)-O(21)	1.442(2)	C(4)-C(5)-H(52)	108.4
C(9)-H(91)	0.963	C(6)-C(5)-H(52)	107.2
C(10)-C(11)	1.535(2)	H(51)-C(5)-H(52)	109.6
C(10)-O(16)	1.450(2)	C(5)-C(6)-C(7)	116.73(17)
C(10)-H(101)	0.969	C(5)-C(6)-O(21)	108.70(16)
C(11)-C(12)	1.535(2)	C(7)-C(6)-O(21)	103.89(14)
C(11)-H(112)	0.960	C(5)-C(6)-H(61)	109.1
C(11)-H(111)	0.957	C(7)-C(6)-H(61)	109.3
C(12)-C(13)	1.558(2)	O(21)-C(6)-H(61)	108.7
C(12)-O(17)	1.449(2)	C(6)-C(7)-C(8)	100.34(15)
C(12)-H(121)	0.977	C(6)-C(7)-O(22)	105.22(15)
C(13)-C(14)	1.527(2)	C(8)-C(7)-O(22)	114.25(14)
C(13)-O(22)	1.430(2)	C(6)-C(7)-H(71)	110.7
C(13)-H(131)	0.990	C(8)-C(7)-H(71)	112.7
O(22)-C(7)-H(71)	112.6	C(13)-C(12)-O(17)	114.19(14)
C(7)-C(8)-C(9)	102.63(15)	C(11)-C(12)-H(121)	104.4
C(7)-C(8)-H(82)	108.5	C(13)-C(12)-H(121)	107.1
C(9)-C(8)-H(82)	109.1	O(17)-C(12)-H(121)	108.1
C(7)-C(8)-H(81)	113.0	C(12)-C(13)-C(14)	115.31(14)
C(9)-C(8)-H(81)	111.8	C(12)-C(13)-O(22)	113.57(14)
H(82)-C(8)-H(81)	111.4	C(14)-C(13)-O(22)	113.83(15)
C(8)-C(9)-C(10)	117.52(16)	C(12)-C(13)-H(131)	104.5
C(8)-C(9)-O(21)	106.27(14)	C(14)-C(13)-H(131)	104.5
C(10)-C(9)-O(21)	108.19(15)	O(22)-C(13)-H(131)	103.4
C(8)-C(9)-H(91)	108.5	C(13)-C(14)-C(15)	111.68(16)
C(10)-C(9)-H(91)	106.9	C(13)-C(14)-H(141)	107.3
O(21)-C(9)-H(91)	109.3	C(15)-C(14)-H(141)	109.5
C(9)-C(10)-C(11)	120.06(15)	C(13)-C(14)-H(142)	110.2
C(9)-C(10)-O(16)	108.35(14)	C(15)-C(14)-H(142)	110.7
C(11)-C(10)-O(16)	109.41(15)	H(141)-C(14)-H(142)	107.3
C(9)-C(10)-H(101)	105.1	C(14)-C(15)-H(152)	108.4
C(11)-C(10)-H(101)	106.6	C(14)-C(15)-H(151)	106.9
O(16)-C(10)-H(101)	106.4	H(152)-C(15)-H(151)	108.8
C(10)-C(11)-C(12)	117.85(15)	C(14)-C(15)-H(153)	112.5
C(10)-C(11)-H(112)	108.9	H(152)-C(15)-H(153)	110.5
C(12)-C(11)-H(112)	108.5	H(151)-C(15)-H(153)	109.6
C(10)-C(11)-H(111)	105.0	C(10)-O(16)-H(161)	106.3
C(12)-C(11)-H(111)	105.8	C(12)-O(17)-H(171)	110.8
H(112)-C(11)-H(111)	110.6	C(6)-O(21)-C(9)	108.80(14)
C(11)-C(12)-C(13)	112.21(14)	C(13)-O(22)-C(7)	120.63(13)
C(11)-C(12)-O(17)	110.28(14)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for 6993. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	60(2)	45(1)	46(1)	1(1)	-9(1)	-5(1)
C(2)	49(1)	43(1)	41(1)	3(1)	-1(1)	1(1)
C(3)	53(1)	39(1)	41(1)	2(1)	1(1)	-1(1)
C(4)	38(1)	35(1)	44(1)	4(1)	1(1)	3(1)
C(5)	44(1)	34(1)	33(1)	4(1)	-1(1)	8(1)
C(6)	37(1)	31(1)	26(1)	2(1)	1(1)	0(1)
C(7)	26(1)	30(1)	26(1)	-2(1)	-1(1)	2(1)
C(8)	23(1)	32(1)	28(1)	-2(1)	1(1)	1(1)
C(9)	25(1)	30(1)	31(1)	1(1)	-1(1)	-2(1)
C(10)	27(1)	23(1)	31(1)	-1(1)	-2(1)	-1(1)
C(11)	26(1)	25(1)	28(1)	-2(1)	0(1)	2(1)
C(12)	22(1)	25(1)	30(1)	0(1)	1(1)	1(1)
C(13)	19(1)	24(1)	34(1)	-2(1)	0(1)	0(1)
C(14)	32(1)	26(1)	36(1)	-4(1)	-1(1)	0(1)
C(15)	50(1)	26(1)	47(1)	0(1)	3(1)	-6(1)
O(16)	25(1)	32(1)	33(1)	-4(1)	-4(1)	-1(1)
O(17)	24(1)	27(1)	33(1)	5(1)	-4(1)	4(1)
O(21)	42(1)	28(1)	32(1)	4(1)	-3(1)	-3(1)
O(22)	23(1)	27(1)	31(1)	1(1)	-2(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x 10^3$) for 6993.

	x	y	z	U(eq)
H(31)	1987	2092	5017	53
H(41)	1945	5212	4114	47
H(51)	-138	1876	3666	45
H(52)	1017	3053	3019	46
H(61)	-3038	3995	3693	37
H(71)	-1663	6676	3351	32
H(82)	-5420	6283	2832	33
H(81)	-4440	6994	2022	33
H(91)	-6373	3968	2056	34
H(101)	-4450	2810	1013	32
H(112)	-888	4079	1125	31
H(111)	-2290	4467	245	30
H(121)	-705	6933	460	30
H(131)	1513	7033	1612	29
H(141)	620	9090	2603	37
H(142)	-1795	9289	2111	38
H(152)	732	11473	1729	61
H(151)	2244	9964	1428	63
H(153)	-191	10347	912	61
H(171)	-3705	8333	354	42
H(161)	-6023	5850	537	47
H(11)	5294	5505	6677	62

Table 6. Hydrogen bonds for 6993 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(8)-H(81)...O(17)	0.95	2.19	3.019(3)	145
O(17)-H(171)...C(10)#1	0.82	2.55	3.268(3)	147
O(17)-H(171)...O(16)#1	0.82	1.89	2.716(3)	179
O(16)-H(161)...O(17)	0.81	1.96	2.676(3)	146

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y+1/2,-z

