STUDIES TOWARDS THE TOTAL SYNTHESIS OF PHYLLAEMBLIC ACID

by

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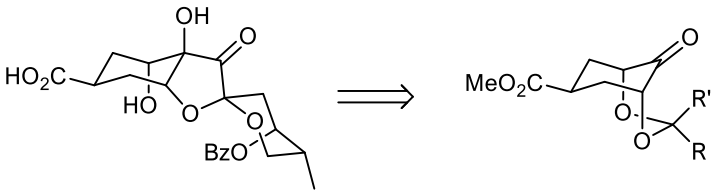
ABSTRACT

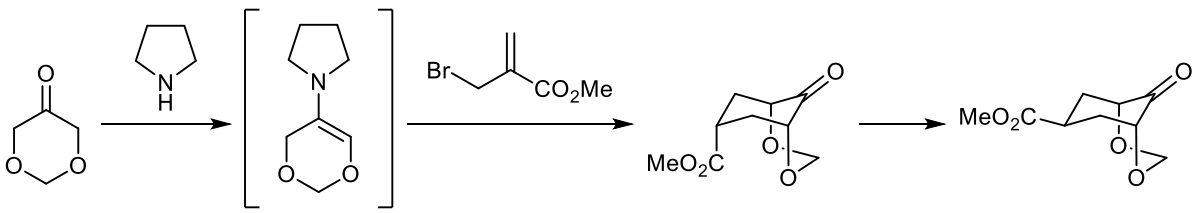
Phyllaemblic acid is a highly oxygenated natural product isolated from the *Phyllanthus emblica* plant. Key structural features include a 6,5-spirocyclic acetal *cis*-fused to a functionalised cyclohexane ring. A total synthesis of phyllaemblic acid has yet to be reported.

The Grainger group approach to phyllaemblic acid takes advantage of a highly stereoselective α,α'-annelation of 1,3-dioxan-5-ones with methyl α-(bromomethyl)acrylate to form *meso* acetal bridged cyclohexanones. However, the ketone functionality in these bicycles showed limited reactivity towards nucleophilic addition. In Chapter 1, synthetic approaches to related natural products are reviewed, along with relevant literature on the π-facial selectivity in nucleophilic additions to carbonyl compounds.



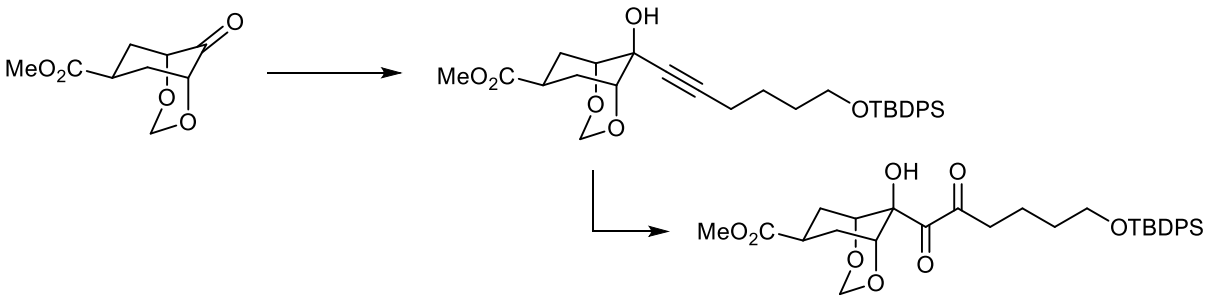
phyllaemblic acid

Chapter 2.1 summarises attempts at preparing a less hindered methylene bridged acetal (R = R' = H) in an attempt to improve the reactivity of the ketone. This bicyclic acetal was prepared by AZADOL / TCCA oxidation of glycerol formal followed by α,α'-annelation. Subsequent base-mediated epimerisation gave the ester stereochemistry required for phyllaemblic acid.



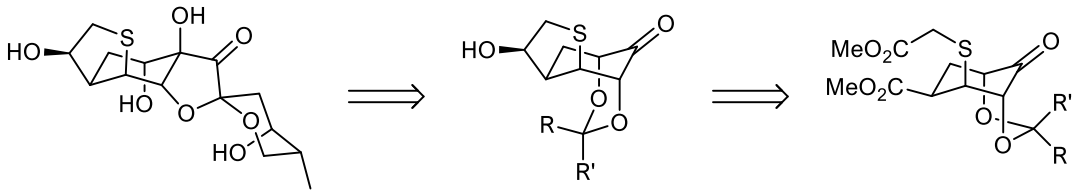
The reactivity of the methylene bridged bicyclic ketone is then examined in Chapter 2.2. Two main methods of introducing the right-hand side fragment on a simplified model system were investigated: Horner-Wadworth-Emmons olefination and acetylide addition.

While both routes resulted in successful C–C bond formation, only the alkyne addition route resulted in the desired stereoselectivity. Synthesis of the right-hand side fragment and future applications to the total synthesis of phyllaemblic acid are also described.



In Chapter 2.3 a Norrish-Yang cyclisation was investigated as an alternative method of C–C bond formation at the carbonyl carbon, but the desired transformation was not successful.

Finally, Chapter 2.4 discusses an approach towards the perhydrobenzothiophene ring system of breynolide, a structurally related natural product *via an* intramolecular Dieckmann cyclisation.



breynolide

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Richard Grainger. Thank you for challenging me with that MSci project back in 4th year, for the opportunity to continue it to a PhD and for your continued guidance and inspiration throughout my time at Birmingham. I appreciate you allowing me my creative freedom even when that meant letting me make some pretty silly mistakes.

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questionable memes kept me going (and I guess your chemistry expertise was useful too). I doubt I'd be the chemist I am today without all of your support over the last 5 years.

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Alice, what can I say? Without you I can say with 100% certainty this thesis would not have been completed. Your emotional support over the last eight years has been invaluable, but in particular these last six months you have kept me sane and motivated to keep going even when all I wanted to do was give up. Thank you for your magical proof-reading skills that helped me turn my jumbled stream of thoughts into something that sounds a lot more "sciencey".

Thanks to Mum and Dad for providing nourishing meals and clean washing when I was tired after a full day at work and a full night writing. These acknowledgements wouldn't be complete without a special mention to Sammy for being the best emotional support pony, mane to cry on and my favourite way to waste time outside of writing.

Finally, thank you to the University of Birmingham and the EPSRC for the financial support.

CONTENTS

ABBREVIATIONS

[O] = oxidation

Ac = acetyl

acac = acetylacetone

aq. = aqueous

ax = axial

AZADOL = 2-azaadamantan-2-ol

b.p. = boiling point

Bn = benzyl

Bz = benzoyl

cat. = catalytic

conc. = concentration

COSY = correlation spectroscopy

d = doublet

d.r. = diastereomeric ratio

DABCO = 1,4-diazabicyclo[2.2.2]octane

dba = dibenzylideneacetone

DBU = 1,8-diazabicyclo[5.4.0] undec-7-ene

DCE = 1,2-dichloroethane

DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL = diisobutylaluminium hydride

DMAP = 4-dimethylaminopyridine

DMDO = dimethyldioxirane

DMF = *N,N*-dimethylformamide

DMSO = dimethylsulfoxide

DTS = diverted total synthesis

EDG = electron donating group

EDTA = ethylenediaminetetracetic acid

eq = equatorial

eq. = equivalents

EWG = electron withdrawing group

FMO = frontier molecular orbital

FPP = Farnesyl pyrophosphate

HBeAg = HBV excreted antigen

HBsAg = HBV surface antigen

HBV = hepatitis B virus

HMBC = heteronuclear multi-bond correlation

HRMS = high resolution mass spectrometry

HSQC = heteronuclear single quantum correlation

HWE = Horner-Wadsworth-Emmons

hv = photon energy

IBX = 2-iodoxybenzoic acid

IC_{50} = half maximal inhibitory concentration

IR = infrared

LCMS = liquid chromatography mass spectrometry

LDA = lithium diisopropylamide

LiHMDS = lithium hexamethyldisilazide

M.S. = molecular sieves

***m*CPBA** = *meta*-chloroperoxybenzoic acid

MeHQ = hydroquinone monomethyl ether

MEM = 2-methoxyethoxymethyl ether

min = minutes

m.p. = melting point

MPM = *para*-methoxyphenylmethyl

MS = mass spectrometry (or spectrum)

NCS = *N*-chlorosuccinimide

NMO = *N*-methylmorpholine *N*-oxide

NMR = nuclear magnetic resonance

nOe = nuclear Overhauser effect

NOESY = nuclear Overhauser effect spectroscopy

Nu = nucleophile

P = protecting group

PCC = pyridinium chlorochromate

ppm = parts per million

***p*TSA** = *para*-toluenesulfonic acid

py = pyridine

RHF = restricted Hartree-Fock

RHS = right-hand side

ROESY = rotating frame Overhauser enhancement spectroscopy

rt = room temperature

s = singlet

sat. = saturated

soln. = solution

SPS = solvent purification system

T.S. = transition state

TBAF = tetra-n-butylammonium fluoride

TBDPS = *tert*-butyldiphenylsilyl

TBHP = *tert*-butyl hydroperoxide

TBS = *tert*-butyldimethylsilyl

TCCA = trichloroisocyanuric acid

temp. = temperature

TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl

TES = triethylsilyl

Tf = trifluoromethanesulfonyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TIPS = triisopropylsilyl

TLC = thin layer chromatography

TMS = trimethylsilyl

TPAP = tetrapropylammonium perruthenate

Tris = tris(hydroxymethyl)aminomethane

UV = ultraviolet

v/v = volume by volume

$\mathbf{\nu_{max}}$ = wavenumber(s)

VT = variable temperature

w/v = weight by volume

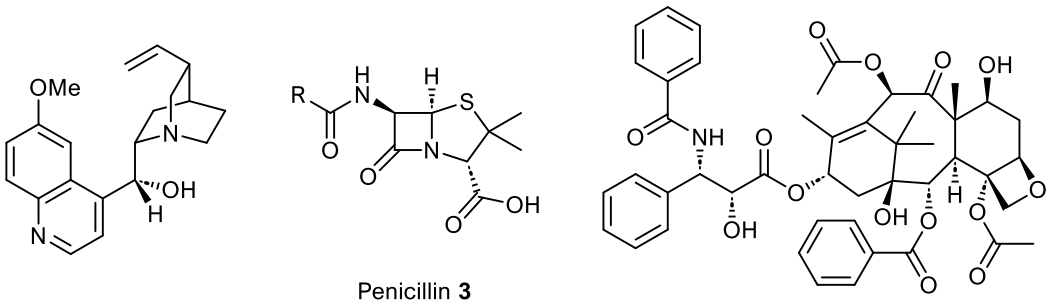
w/w = weight by weight

Δ = heat

CHAPTER 1 – INTRODUCTION

1.1 – NATURAL PRODUCTS IN DRUG DISCOVERY

Natural products are substances that are produced by living organisms including plants, animals and microorganisms. Their use as medicines has been dated back as far as 2100 BC, with records of crude extracts from plant, animal and marine sources being used in traditional medicine.[1] While many traditional medicines have now been shown to have minimal efficacy the active components of several have been isolated in their pure forms and have been validated by modern scientific research. In fact, many of the drugs that are used today are derived from natural products or are inspired by the structure or function of natural products.[2] Notable examples include quinine **2,** an antimalarial first isolated in 1820 from the bark of a cinchona tree; penicillin **3**, an antibiotic originally obtained from *Penicillium* moulds in 1928 by Scottish scientist Alexander Fleming; and paclitaxel **4** (marketed as Taxol), a chemotherapy medication used to treat numerous types of cancer, first isolated from the bark of the Pacific yew (Figure 1.1).[3] All three feature on the World Health Organisation's Model List of Essential Medicines.[4]



Quinine **2**

Penicillin **3**

Paclitaxel **4**

Figure 1.1 *Natural products used in modern medicine*

A 2013 review found that 10% of all approved medicines in the USA are unmodified natural products, with this figure increasing to 38% if medicines derived from natural products are included.[2] Semisynthetic analogues prepared from the naturally occurring compound or fully synthetic derivatives often have improved physicochemical and pharmacokinetic properties relative to the parent compound.[2]

1.1.1 – MODERN DRUG DISCOVERY

Modern drug discovery is driven by the need to quickly screen large numbers of compounds. To achieve this, methods such as high-throughput screening and combinatorial synthesis are required. These techniques depend on robust, reliable reactions with high chemoselectivity and functional group tolerance (Figure 1.2), as well as the commercial availability of reagents.[5] The reliance on these reactions results in compound libraries dominated by sp^2-rich, achiral, aromatic compounds.[6] These flat molecules often exhibit poor physicochemical properties and as a result are much more likely to fail as potential drug candidates.[6]

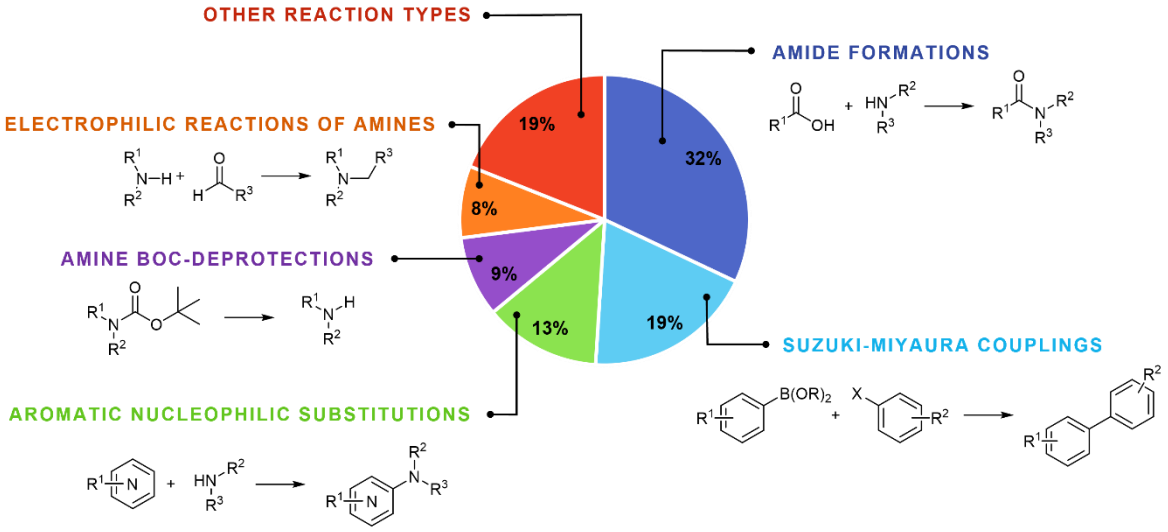


Figure 1.2 *Common chemical reactions in drug discovery and development* [7]

Recently there has been a resurgence of interest in natural products as lead-like compounds for drug discovery as a consequence of the decline in the number of successful drug candidates from alternative methods.[8] When compared with synthetic drug libraries, natural products tend to have a larger number of sp^3 carbon atoms and therefore greater structural diversity.[9] This diversity is necessary to generate effective drug candidates due to the variety of binding sites in druggable protein targets, and it has been shown that compounds with higher degrees of saturation are more likely to succeed in the transition from drug discovery to clinical use.[6,10]

1.1.2 – TOTAL SYNTHESIS IN DRUG DISCOVERY

One of the biggest challenges of using natural products as clinical candidates is maintaining sufficient supply. Often biologically active compounds are produced in such low concentrations that isolation from natural sources is neither practical nor economically viable, so synthesis becomes the only feasible way to produce enough material.

The complex polyketide lactone discodermolide **5** (Figure 1.3) was found to have higher potency towards multi-drug resistant tumours than paclitaxel **4**, but the deep-sea sponge from which it is isolated only contains 0.002% discodermolide by weight. Additionally, the sponge must be harvested at depths greater than 33 m because of the compound's sensitivity to light. Such supply challenges necessitate large scale total synthesis as the only viable source of the quantities required for pre-clinical and clinical studies. Consequently, there have been numerous total syntheses of **5** reported by academic laboratories in an attempt to resolve this supply challenge.[11]

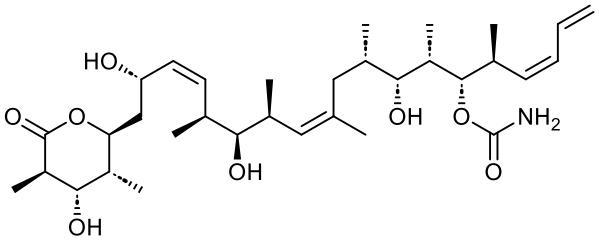


Figure 1.3 *(+)-Discodermolide* ***5***

In 2004, Novartis Pharmaceuticals reported a 64 g-scale synthesis of (+)-discodermolide.[12] This synthesis was a significant achievement in natural product research as it demonstrated the importance of academic synthetic efforts in a clinical context, and confirmed the validity of using total synthesis as a method to access large quantities of a complex natural product.[13]

As well as a means of production, the total synthesis of a natural product can confirm the structure and identify the key steric and electronic features required to ensure optimal

interactions with a specific biological target, known as the pharmacophore.[14] Diverted total synthesis (DTS), a term coined by Danishefsky in 2006, involves the application of this knowledge to synthesise multiple analogues that are less complex than the parent natural product, and therefore easier to produce, while still retaining the required features that give rise to any observed medicinal effects.[15]

A successful example of the DTS approach is the development of anticancer agent eribulin **7** from polyether macrolide halichondrin B **6**, isolated from the marine sponge *Halichondria okadai* (Figure 1.4).[16,17] Halichondrin B **6** was initially chosen for development in 1992 as a result of its anticancer activity, but progress was limited by the low availability of the compound from natural sources. Kishi and co-workers completed the total synthesis of halichondrin B **6** in 1998, which led to the identification of the right-hand half of the molecule as the pharmacophore.[18] This knowledge then led to the development of structurally simplified analogue eribulin **7**, which was found to have greater *in vivo* stability and lower toxicity than halichondrin B, while still showing comparable bioactivity.[17]

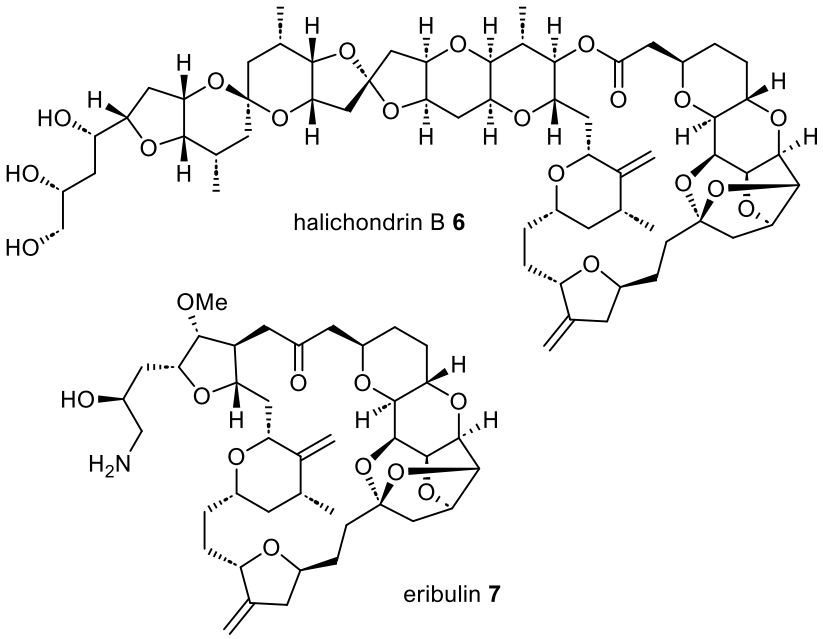


Figure 1.4 *Anticancer agents from Halichondria okadai*

1.1.3 – CONCLUSION

Despite considerable progress in modern drug discovery there are many diseases and conditions for which there are currently no effective treatments. Given their extensive history in drug discovery and vast structural diversity, natural products provide the opportunity to inspire novel drug candidates and continued research into their synthesis is vital in order to harvest their potential.

1.2 – PHYLLAEMBLIC ACID

Phyllanthus emblica, also known as the Indian gooseberry or Malacca tree, is a deciduous tree of the family *Phyllanthaceae* and is widely distributed in areas of Southeast Asia. All parts of the tree are rich in bioactive compounds and its use in traditional medicine has been well documented, but very few of its uses have been validated through clinical research.[19–26]

During their studies on the plant, Zhang *et al.* reported the isolation of a novel highly oxygenated norbisabolane sesquiterpenoid natural product named phyllaemblic acid **1** (Figure 1.5).[27] Although several bisabolane natural products are known, phyllaemblic acid was reported to be the first example of a natural product with a norbisabolane type framework.[27–29]

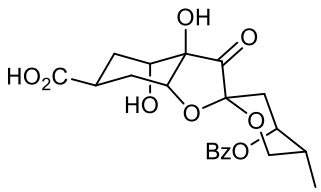


Figure 1.5 *Phyllaemblic acid* ***1***

Phyllaemblic acid **1** contains a 6,5-spirocyclic acetal *cis* fused to a functionalised cyclohexane ring, a framework which can also be found in several other natural products. Assessment of these compounds from a biological standpoint indicates their potential significance, making phyllaemblic acid **1** an appealing candidate for total synthesis. Despite synthetic interest in structurally related compounds, a total synthesis of phyllaemblic acid **1** has not been reported.

1.2.1 – RELATED NATURAL PRODUCTS

Isolated from *Phyllanthus emblica* alongside phyllaemblic acid **1** are its methyl ester **8** and three ester glycosides phyllaemblicins A **11**, B **12** and C **13** (Figure 1.6).[30] Methyl ester **8** and phyllaemblicins B **12** and C **13** were shown to exhibit significant antiviral activity toward coxsackie virus B3 (CVB3),[31] a human pathogen that has been shown to cause cardiac diesease.[32]

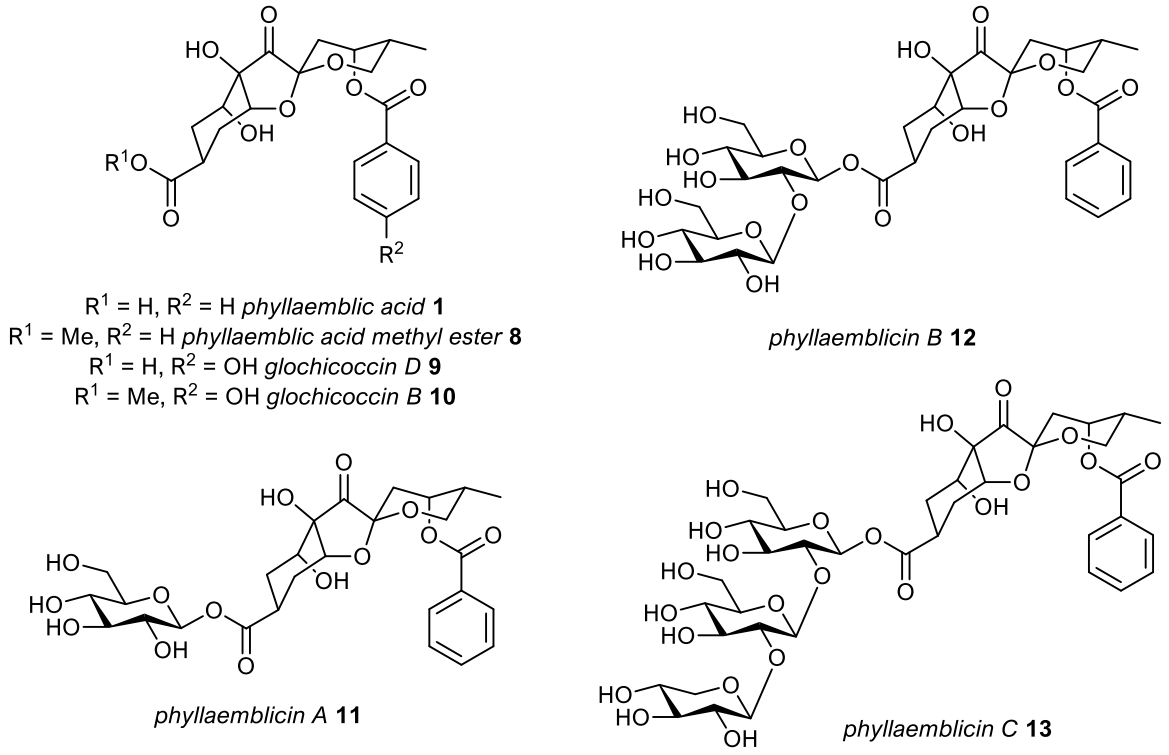


Figure 1.6 *Phyllaemblic acid **1** and related natural products **8** – **13***

The rhizomes of *Glochidion coccineum* were also found to contain both phyllaemblic acid **1** and its methyl ester **8**, as well as structurally related glochicoccin D **9** and B **10** (Figure 1.6). Neither of the glochicoccin compounds showed any antioxidant or cytotoxic effects.[33]

In 2014 Zhang *et al*. isolated eight new highly oxygenated bisabolane sesquiterpenoids from *Phyllanthus emblica*. Phyllaemblicins G6 – G8 **14** – **16** and F **17** are dimeric sesquiterpenoid glycosides with two norbisabolane units connecting through a disaccharide (Figure 1.7).[31,34] These dimers were shown to display anti-viral activities towards hepatitis B virus (HBV) antigens. In particular, phyllaemblicin G6 **14** showed strong inhibition with IC_{50} values of 8.53 μM and 5.68 μM towards the HBV surface antigen (HBsAg) and HBV excreted antigen (HBeAg) secretion respectively.[34]

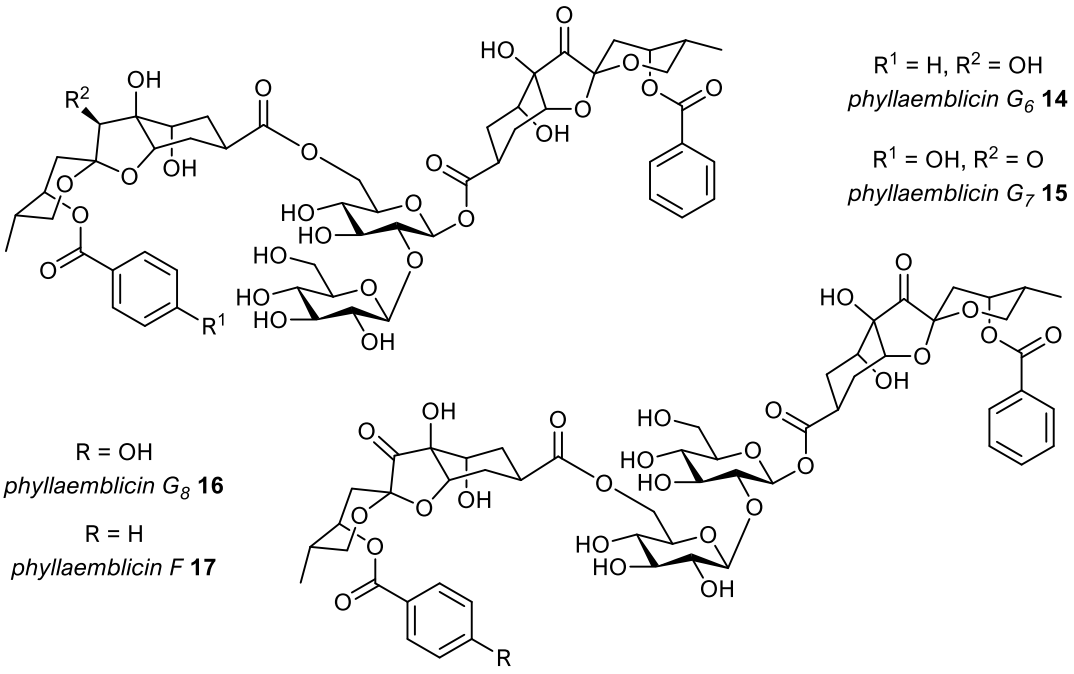
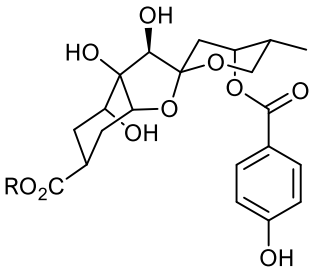
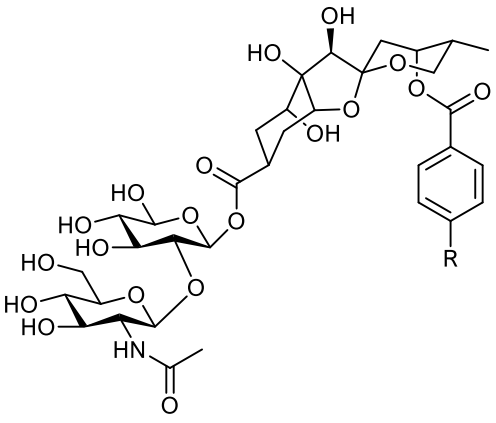


Figure 1.7 *Phyllaemblic acid glycosides* ***14*** *–* ***17***

Phyllanthacidoids (previously reported as phyllanthusols, Figure 1.8) isolated from *Phyllanthus acidus,* another plant of the *Phyllanthus* genus*,* are structurally very similar to phyllaemblic acid, differing only by the presence of an alcohol substituent on the five membered ring of the spiroacetal.[35] A range of these compounds, including phyllanthacidoid acid methyl ester **19**, phyllanthacidoids A **20** and B **21** also showed inhibitory activity against HBV.[36]



R = H *phyllanthacidoid acid* **18**
R = Me *phyllanthacidoid acid methyl ester* **19**



R = OH *phyllanthacidoid A* **20**
R = H *phyllanthacidoid B* **21**

Figure 1.8 *Phyllanthacidoids* ***18*** *–* ***21***

1.2.2 – SYNTHESIS OF 6,5-SPIROACETALS

While a total synthesis of phyllaemblic acid has yet to be reported, there has been significant synthetic interest in structurally related natural products breynolide **22** and phyllanthocin **23**.[37] These natural products share the same 6,5-spirocyclic acetal framework found in phyllaemblic acid (Figure 1.9).

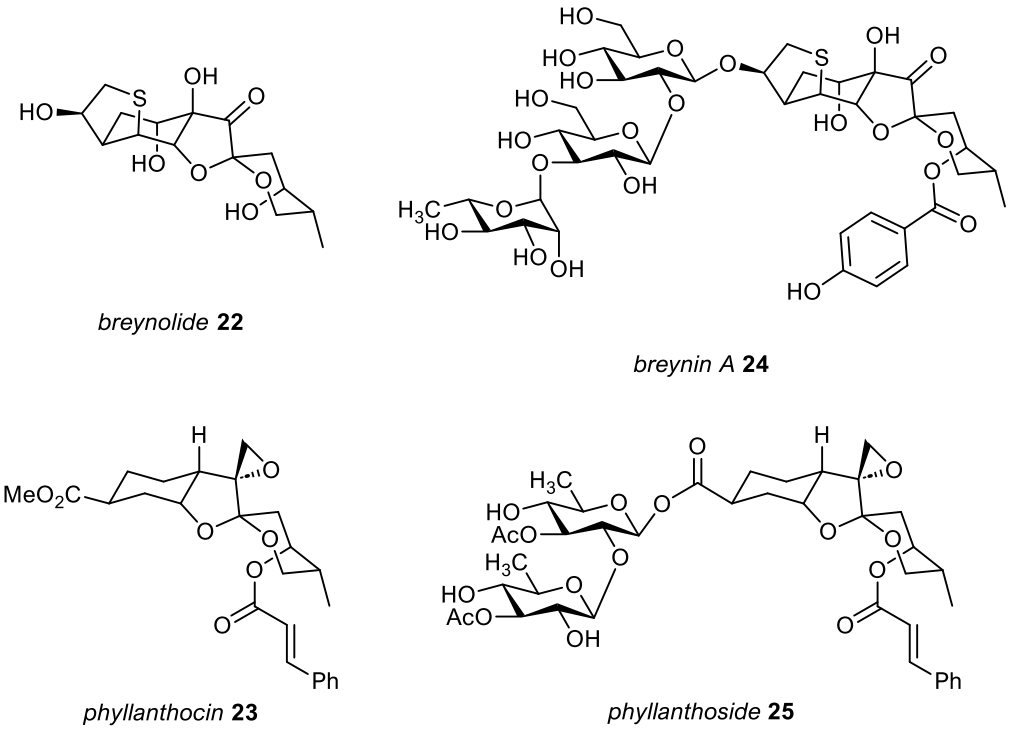


Figure 1.9 *6,5-spiroacetal containing natural products*

Breynolide **22** and phyllanthocin **23**, as well as their respective glycosides breynin A **24** and phyllanthoside **25**, have been isolated from other plants within the *Phyllanthaceae* family.[38,39] These glycosides exhibit important biological activities: phyllanthoside **25** has demonstrated inhibitory effects on several tumour cell lines, while breynin A **24** has displayed significant oral hypocholesterolemic activity in rats.[37]

1.2.2.1 – BIOSYNTHETIC ORIGINS

Sesquiterpenoids are a class of natural products possessing three isoprene-derived units and are derived from farnesyl pyrophosphate (FPP), a biosynthesis precursor that can form various carbon skeletons through cyclisation, oxidation and other functionalisations.[40]

The first reports of the structure of breynolide in 1973 suggested that the C_{15} framework could be constructed biosynthetically from the cyclisation of FPP, followed by rearrangement of the 8–16 bond to 7–16 (Figure 1.10).[41]

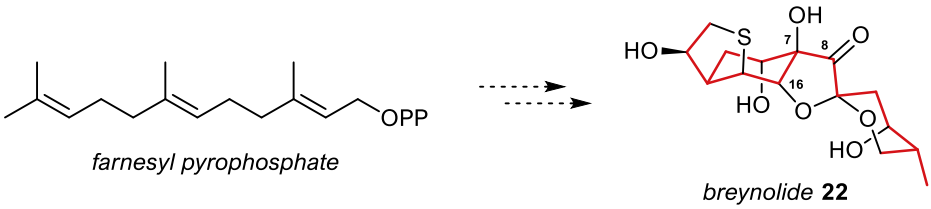


Figure 1.10 *Initially proposed biosynthetic origin of breynolide* ***22***

However the subsequent isolation and characterisation of phyllanthocin **23** in 1977, phyllaemblic acid **1** in 2000 and the other structurally related products discussed in Chapter 1.2.1 give additional clues to the potential biosynthetic origins of these highly oxygenated natural products. For example, phyllanthocin **23** has a bisabolane-type framework, again derived from the cyclisation of FPP (Figure 1.11).[38]

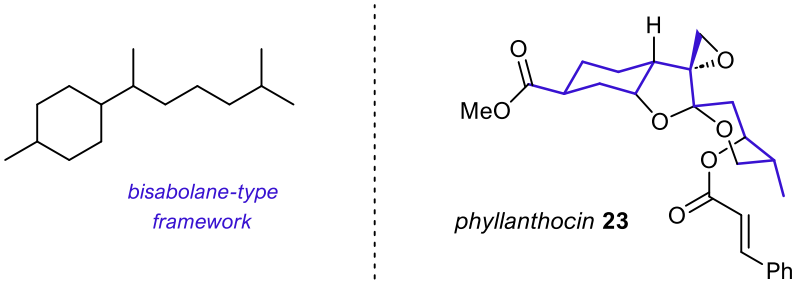


Figure 1.11 *Structures of phyllanthocin* ***22*** *with the norbisabolane framework highlighted*

Phyllaemblic acid **1** shares this carbon framework except with the removal of the central methyl to give a *nor*bisabolane framework.[27] The presence of this framework in both phyllaemblic

acid **1** and breynolide **22** suggests that they may share a biosynthetic origin (Figure 1.12). This would mean that breynolide is also a norsesquiterpenoid, with the additional carbon required to complete the perhydrobenzothiophene ring system being installed *via* a separate process, rather than the FPP cyclisation and rearrangement initially proposed.

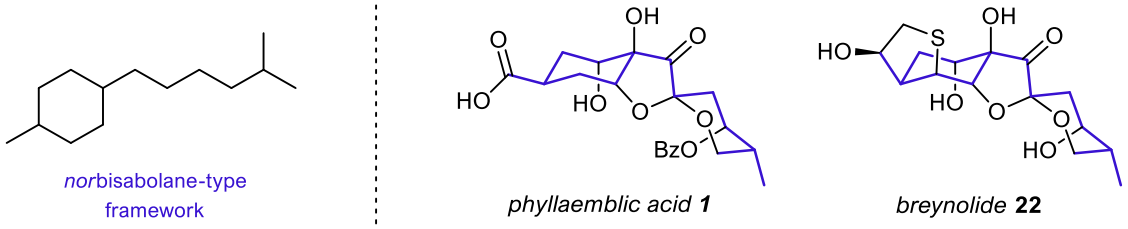


Figure 1.12 *Structures of phyllaemblic acid* ***1*** *and breynolide* ***22*** *with the norbisabolane framework highlighted*

1.2.2.2 – PREVIOUSLY REPORTED SYNTHESES

To date there have been eight reported syntheses of phyllanthocin **23** and three of breynolide **22**.[37] While these syntheses vary largely in strategy, a common feature among them is the formation of the 6,5-spiroacetal under thermodynamic control: spiroacetal configuration **26b** is favoured over **26a** (Figure 1.13) as a result of the anomeric effect and the relative stabilisation provided by having the methyl group equatorial.[37] This strong literature precedent suggests that a similar approach could be applicable to the synthesis of phyllaemblic acid.

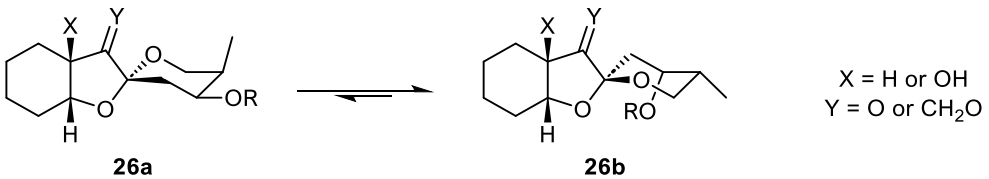
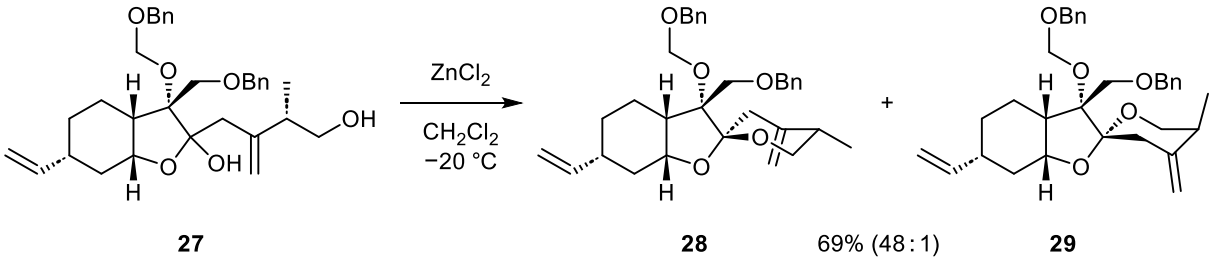


Figure 1.13 *Possible 6,5-spiroacetal configurations in breynolide and phyllanthocin synthesis*

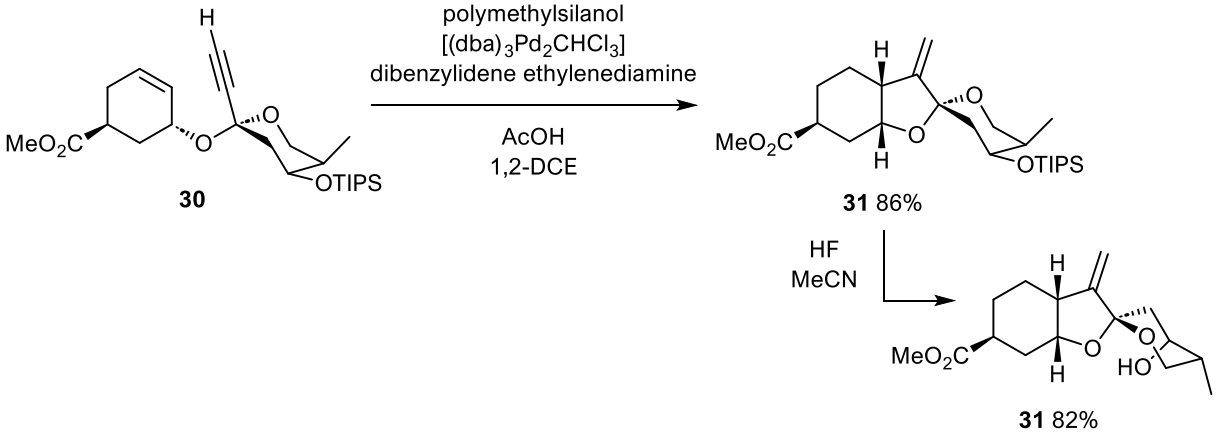
The first synthesis of (+)-phyllanthocin **23** was reported by Collum and co-workers in 1982.[42] Spiroacetalisation of **27** was induced by treatment with a Lewis acid to produce **28** and **29** (48:1) in 69% yield (Scheme 1.1). This is a thermodynamically controlled acetalisation,

confirmed by the observation that identical product distributions could be obtained by resubjecting either of the two spiroacetals **28** or **29** to the reaction conditions.



Scheme 1.1 *Spiroacetal formation in Collum's (+)-phyllanthocin synthesis*

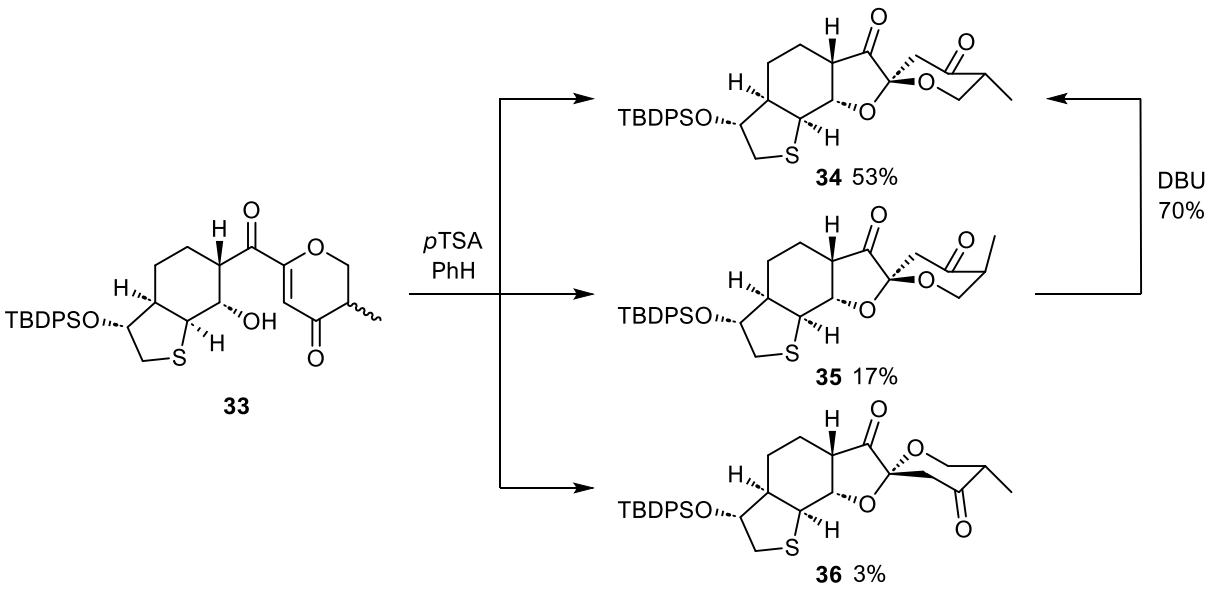
Trost's 1990 synthesis of (±)-phyllanthocin is unique in the sense that the spiroacetal is in place prior to closure of the tetrahydrofuran ring.[43] Palladium-catalysed cycloreduction of **30** generated spiroacetal **31** with the undesired acetal stereochemistry, but subsequent treatment with HF allowed equilibration to the desired thermodynamic product **32** in 82% yield (Scheme 1.2).



Scheme 1.2 *Spiroacetal equilibration in Trost's (±)-phyllanthocin synthesis*

Smith's "stereochemically linear" synthesis of (±)-breynolide uses thermodynamic control to set both the acetal and methyl stereocentres.[44] Racemic enedione **33** was prepared as a mixture of methyl epimers and upon treatment with protic acid generated an 18:6:1 mixture of spiroacetals **34**, **35** and **36** (Scheme 1.3). Treatment of the undesired product **35** with DBU resulted in epimerisation of the methyl group to the more thermodynamically stable equatorial

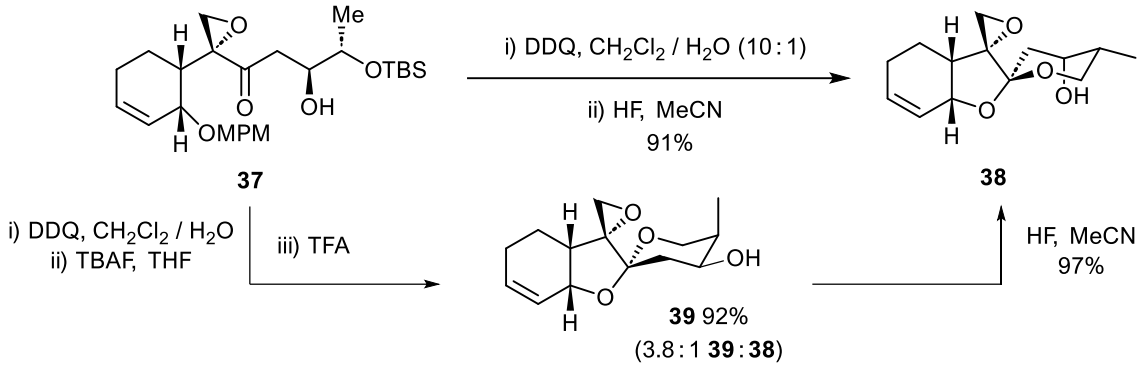
orientation to give an overall conversion to the desired spiroacetal **34** of 77%. A similar approach was also used in the group's 1991 synthesis of (+)-phyllanthocin and Burke's 1999 synthesis of (+)-breynolide.[45,46]



Scheme 1.3 *Spiroacetal formation and equilibration in Smith's (±)-breynolide synthesis*

Both Burke's and Williams' syntheses of (+)-phyllanthocin highlight the importance of carefully selecting the reaction conditions used to induce thermodynamic spiroacetalisation.[47,48]

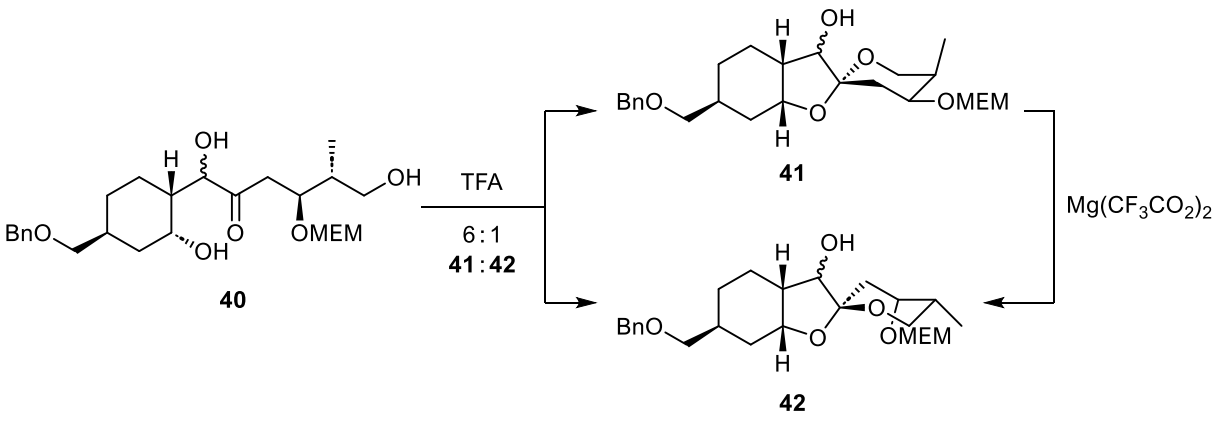
In Burke's synthesis, the MPM ether in **37** was oxidatively cleaved using DDQ and the resulting mixture was treated with 5% aqueous HF to give spiroacetal **38** in 91% yield (Scheme 1.4).[47] These conditions allowed the formation of spiroacetal **38** under thermodynamic control, whereas when the TBS ethers were removed using TBAF in THF followed by treated with TFA, a 3.8:1 mixture of diastereomeric products **39** and **38** was obtained.



Scheme 1.4 *Spiroacetal formation and equilibration in Burke's (+)-phyllanthocin synthesis*

In Williams' synthesis keto triol **40** rapidly formed spiroacetals **41** and **42** in a 6:1 ratio upon treatment with TFA, with the major product **41** possessing the unnatural spiroacetal configuration (Scheme 1.5).[48] A pure sample of correct isomer **42** did not produce the same mixture after resubmission to the reaction conditions so it was concluded that the protic acid induced spiroacetalisation afforded the kinetic product.

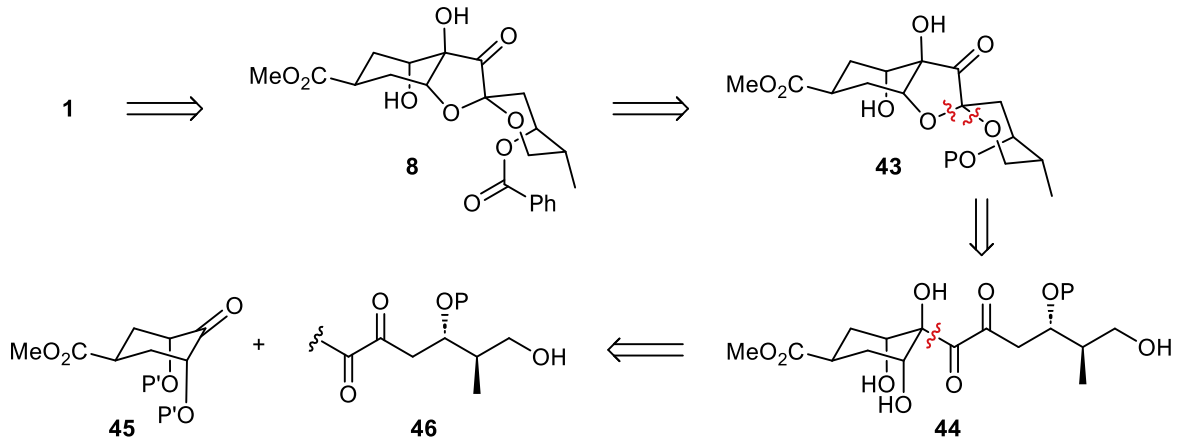
Fortunately, the major product **41** could be isomerised with magnesium trifluoroacetate to give a stable chelation complex, which upon treatment with EDTA yielded spiroacetal **42** with only traces of the undesired spiroacetal configuration **41**.



Scheme 1.5 *Spiroacetal formation and equilibration in Williams' (+)-phyllanthocin synthesis*

1.2.3 – THE GRAINGER GROUP APPROACH

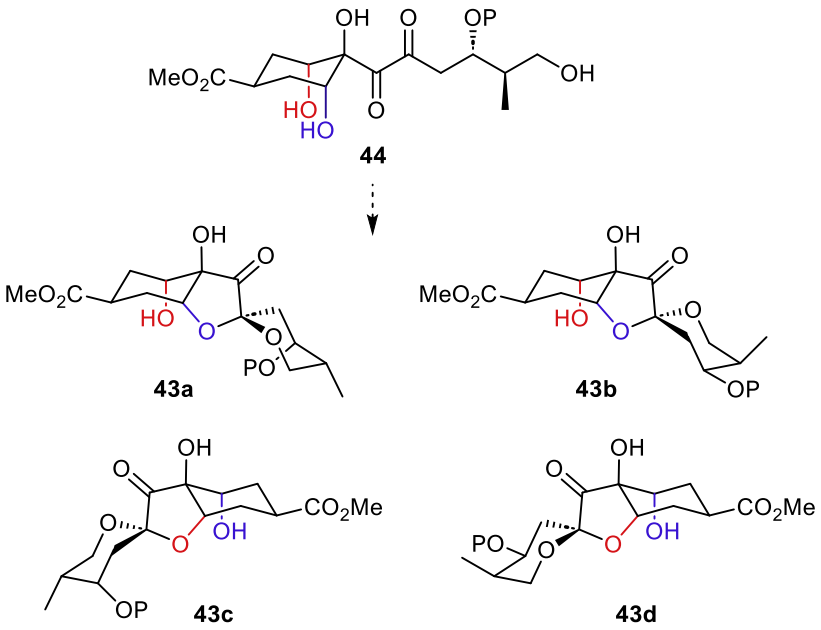
An integral part of the Grainger group strategy towards the synthesis of phyllaemblic acid **1** was the development of a route which takes advantage of the hidden symmetry around the cyclohexane ring.[49] Disconnection of the spiroacetal array in late-stage intermediate **43** to tertiary alcohol **44** unveils this symmetry and allows further disconnection to *meso*-2,4,6,-trisubstituted cyclohexanone **45** and chiral fragment **46** (Scheme 1.6).



Scheme 1.6 *Retrosynthetic analysis of phyllaemblic acid* ***1***

Looking at the synthesis in a forward sense, if facially selective nucleophilic addition to ketone **45** could be achieved, there are a number of ways that a synthetic analogue of chiral fragment **46** could be introduced (discussed in Chapter 1.2.3.3).

While the reported syntheses of breynolide and phyllanthocin set a precedent for the spiroacetalisation step, in phyllaemblic acid there is an additional issue of selectivity: spiroacetalisation could occur from either of the diastereotopic hydroxyl groups to either of the diastereotopic faces of the ketone leading to four potential diastereomers **43a–d** (Scheme 1.7).[50]



Scheme 1.7 *Potential spiroacetalisation products from diketone* ***44***

While the additional hydroxy group in phyllaemblic acid presents a challenge, diastereotopic group selective reactions have been well documented in the field of natural product synthesis, including cases where diastereotopic group selectivity is combined with π-facial selectivity.[51,52] In particular Schreiber's total synthesis of (±)-talaromycin B employed a diastereotopic group selective spiroacetalisation, with the observed selectivity being attributed to the formation of the anomerically stabilised spiroacetal with the substituents orientated equatorially.[53]

For the spiroacetalisation of diketone **44**, the 6-membered ring of the spiroacetal in all four of the products has the ability to adopt two conformations, with the favoured conformation likely being the one where the furanone oxygen is axial (**43a**) as a result of the anomeric effects being maximised (Figure 1.14).

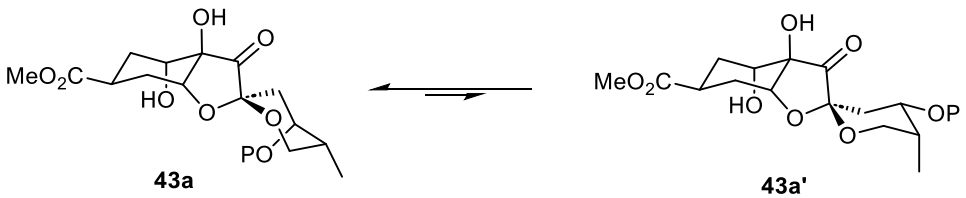
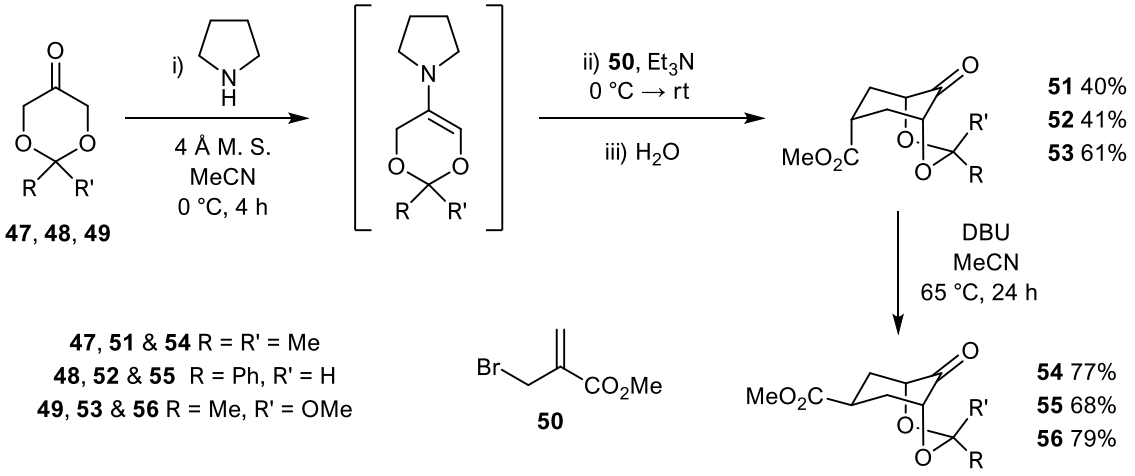


Figure 1.14 *Possible conformations of spiroacetalisation product* ***43a***

Of the four possible products, it is predicted that formation of **43a** should be favoured under thermodynamic control. This is due to the methyl group occupying a more favourable equatorial position, and the acetal C–O dipoles being minimised in this configuration. Additionally, an intramolecular hydrogen bond could occur between the protected hydroxy group and the oxygen in the five-membered ring of the spiroacetal in **43a** which cannot occur in **43a'**. Energy minimisation calculations at the RHF 6-31G* level of theory were performed for benzyl protected **43** (OP = OBn) and spiroacetal **43a** was calculated to be 2.9 kcal mol^{-1} lower in energy than the other equatorial methyl configuration **43c**.[50] Additionally, the fact that this is the stereochemical array found in phyllaemblic acid and many other naturally occurring compounds suggests this is the thermodynamically preferred configuration.[54]

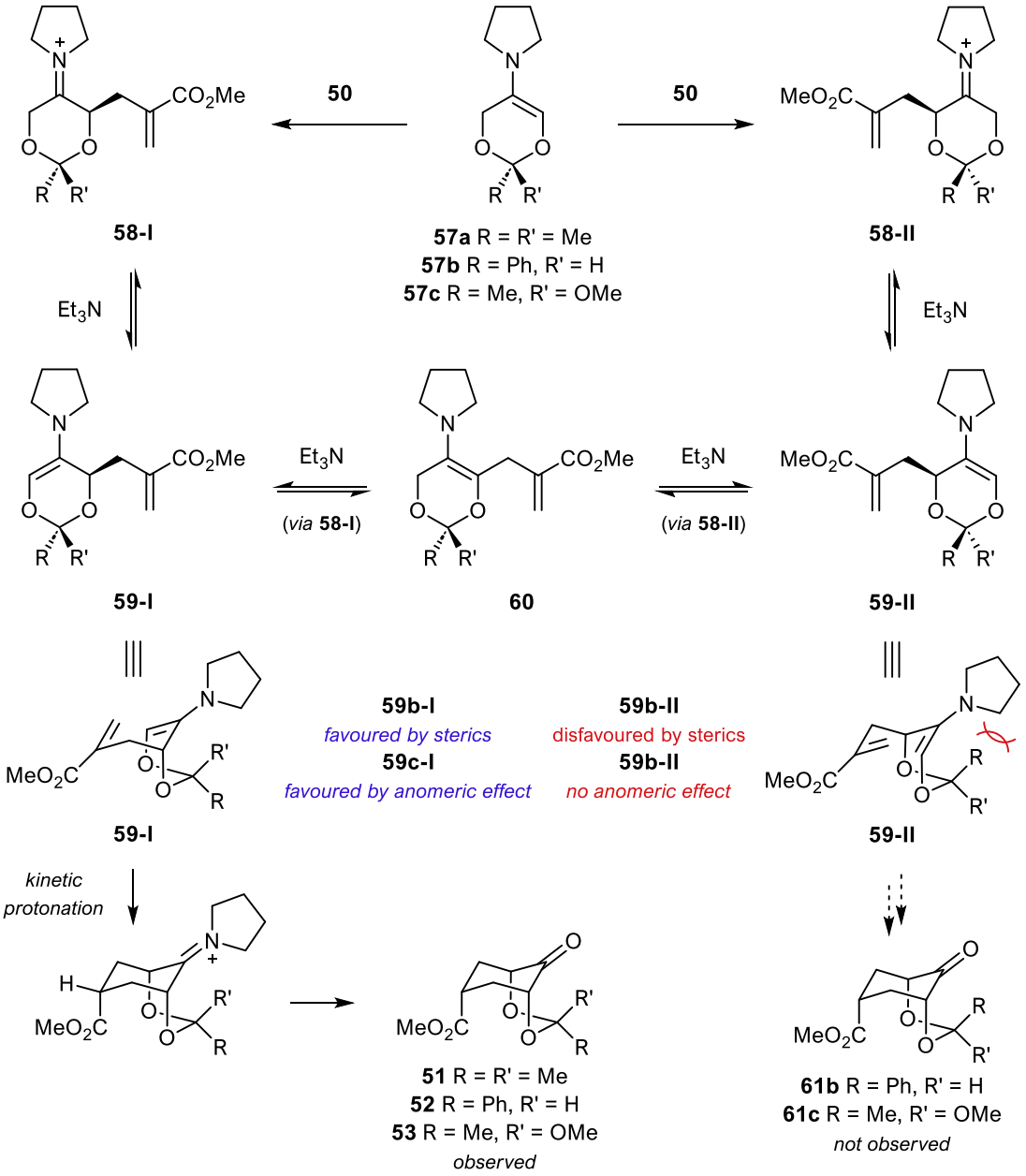
1.2.3.1 – PREVIOUS GROUP WORK

Previous work in the Grainger group used *meso* bicyclic ketones **54**, **55** and **56** as a starting point for phyllaemblic acid synthesis.[49] These ketones were prepared by a stereoselective α,α'-annelation reaction of 1,3-dioxan-5-ones **47**, **48** and **49** with methyl 2-(bromomethyl)acrylate **50** to give axial esters **51, 52** and **53** (Scheme 1.8).[49]



Scheme 1.8 *α,α'-Annelation of 1,3-dioxan-5-ones*

This strategy sets the relative *cis* stereochemistry of the two hydroxyl groups in a single step by tying the two hydroxyl groups together in a ring system through the use of an acetal protecting group. The ester stereochemistry required for phyllaemblic acid was obtained *via* DBU-mediated epimerisation of the stereocentre alpha to the ester group.[49] The stereoselectivity of the α,α'-annelation reaction can be explained by considering the mechanism of the reaction (Scheme 1.9).[49]



Scheme 1.9 *Stereochemical rationale of the α,α'-annelation reaction*

Enamine **57** reacts with bromoacrylate **50** to give a pair of enamines **59-I** and **59-II**, which under basic conditions can readily interconvert *via* iminiums **58-I** and **58-II**. This equilibration allows the more thermodynamically stable enamine to form preferentially.

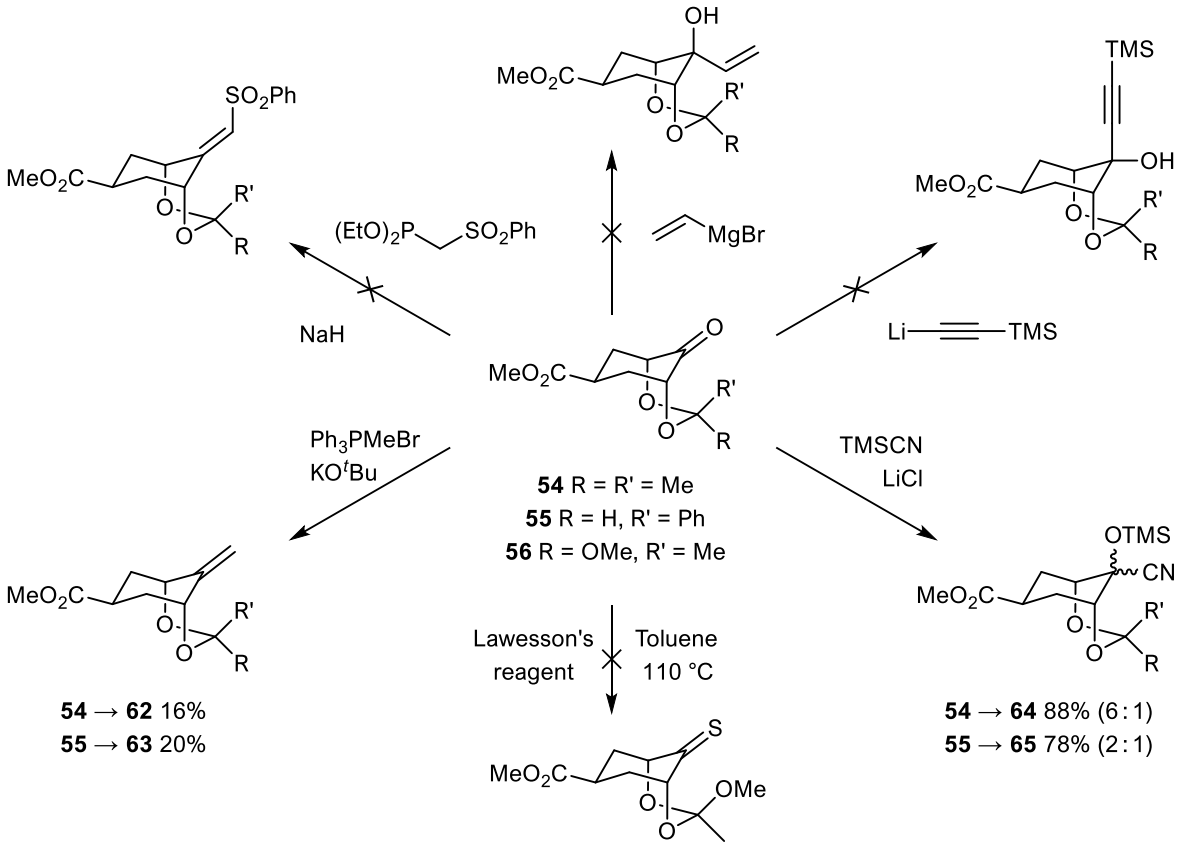
For the benzylidene acetal **57b**, intermediate enamine **59b-I** is lower in energy than alternate enamine **59b-II** where the sterically demanding phenyl group occupies the flagstaff position on the boat conformation. For orthoacetal **59c**, the steric effects are less pronounced and enamine **59c-I** is stabilised as a result of an anomeric effect with the methoxy group, which cannot occur in **59c-II**.

In all cases cyclisation then occurs with kinetic protonation from the less hindered face resulting in an axial ester orientation. Iminium hydrolysis then gives products **51**, **52** and **53** with the observed *syn* relationship between the ester and the alkoxy groups in products **51**, **52** and **53**.

1.2.3.2 – BICYCLIC KETONE REACTIVITY

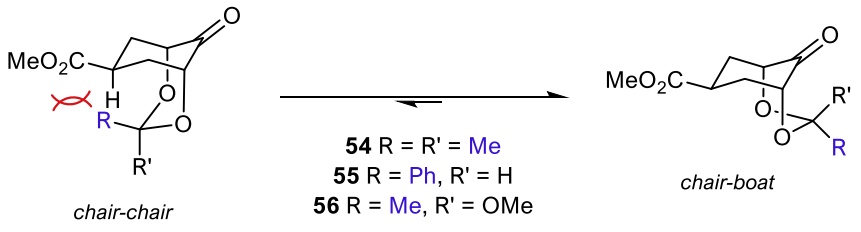
The α,α'-annelation reaction and the following epimerisation successfully installed three out of four stereocentres around the carbocyclic ring but attempts at C–C bond formation at the carbonyl in ketones **54**, **55** and **56** were unsuccessful (Scheme 1.10).[55]

Wittig olefination of **54** and **55** to give alkenes **62** and **63** was partially effective but ultimately was low yielding and further transformation of the products proved difficult. Addition of TMSCN to generate **66** and **67** was achieved in moderate yields but the sense of diastereoselectivity of the reactions could not be determined and the diastereomers could not be separated nor further reacted to progress the synthesis.[50]



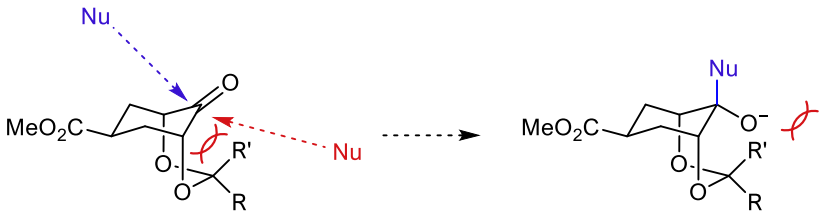
Scheme 1.10 *Attempts at nucleophilic addition into ketones* ***54, 55*** *&* ***56***

The low reactivity of the carbonyl can be partially explained by considering the conformation of bicycles **54**, **55** and **56**. 2D-NMR experiments and X-ray crystallography show all three to adopt a chair-boat conformation as a result of the steric clashes between the axial hydrogen and the acetal substituents which are present in the chair-chair conformation (Scheme 1.11). VT-NMR experiments down to −60 °C showed that the ^{1}H-NMR spectra of ketones **54**, **55** and **56** were near-identical to the spectra recorded at room temperature, which suggests there is no averaging of conformations occurring.[49]



Scheme 1.11 *Conformation of ketones* ***54, 55*** *&* ***56***

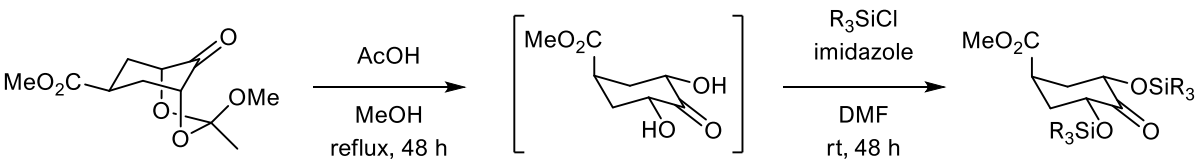
In this chair-boat conformation nucleophilic substitution from the bottom face (equatorial substitution) is blocked by the cyclic acetal protecting group. Reaction from the top face (axial substitution) is less hindered but is likely disfavoured as a result of the steric interactions that develop during the change from an sp^2 to an sp^3 carbon as the tetrahedral intermediate forms, resulting in a high energy transition state (Scheme 1.12).[50]



Scheme 1.12 *Rationale for the low reactivity of ketones* ***54, 55*** *&* ***56***

1.2.3.3 – ALTERNATIVE PROTECTING GROUP STRATEGY

As the poor reactivity of the ketone was attributed to the steric bulk of the acetal blocking nucleophilic addition, an alternative protecting group strategy was attempted. As the relative alcohol stereochemistry had been set, the bulky acetal protecting group was removed in an effort to increase reactivity at the ketone. Unfortunately it was discovered that free diol **66** had poor solubility in most common solvents and therefore the protecting groups that could be installed were limited.[55] Removal of the orthoacetal from **56** followed by silyl reprotection of the alcohols produced monocyclic ketones diol **67** and **68** (Scheme 1.13).

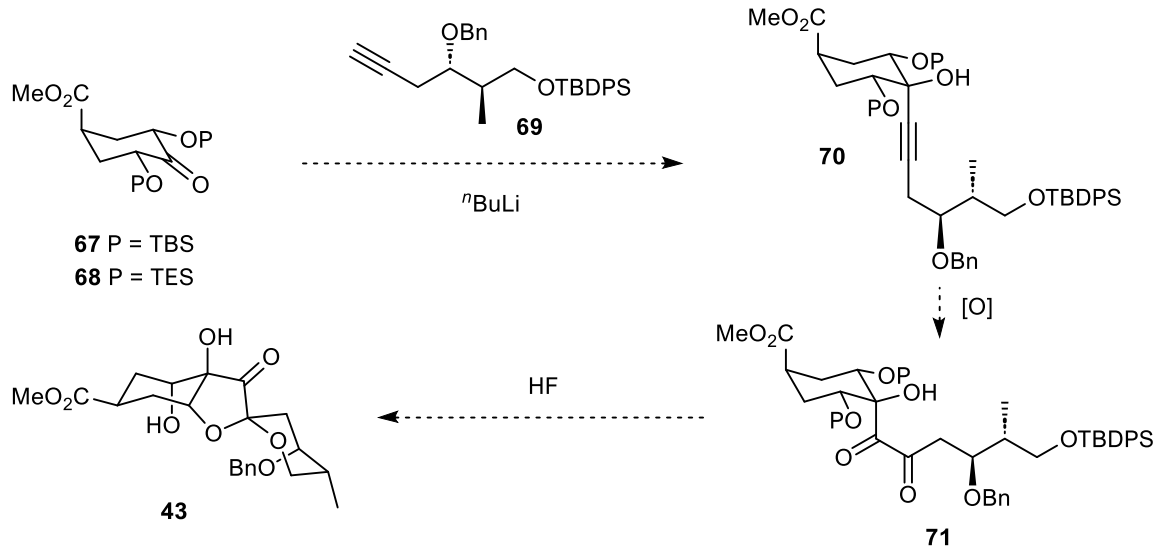


56 **66**

67 R_3 = TBS 83%
68 R_3 = TES 78%

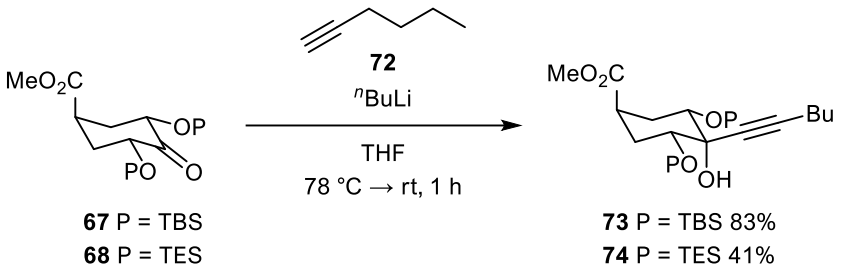
Scheme 1.13 *Silyl protection of ketone* ***56***

With monocyclic ketones **67** and **68** in hand, acetylide addition was attempted. It was envisioned that spiroacetalisation precursor **71** could be accessed directly from propargyl alcohol **70** *via* ruthenium tetroxide oxidation (Scheme 1.14).



Scheme 1.14 *Phyllaemblic acid synthesis from ketone **67** & **68***

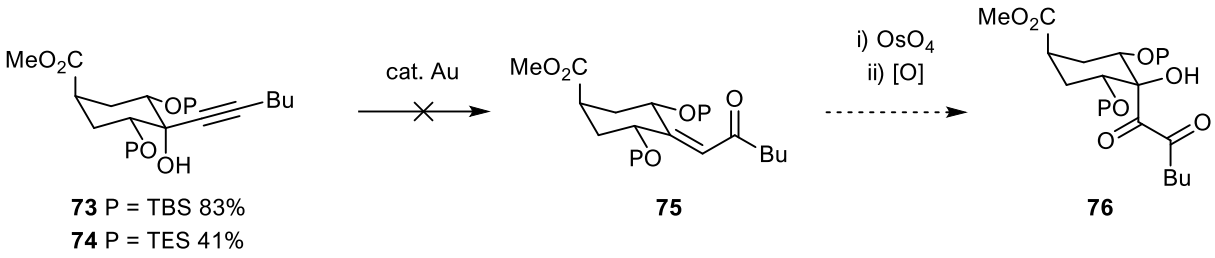
As a test reaction, addition of hexyne **72** to monocyclic ketones **67** and **68** were successful to yield propargyl alcohols **73** and **74** as single stereoisomers, although addition occurred *trans* to the alkoxy substituents.[55]



Scheme 1.15 *Hexyne addition to ketone **67** & **68***

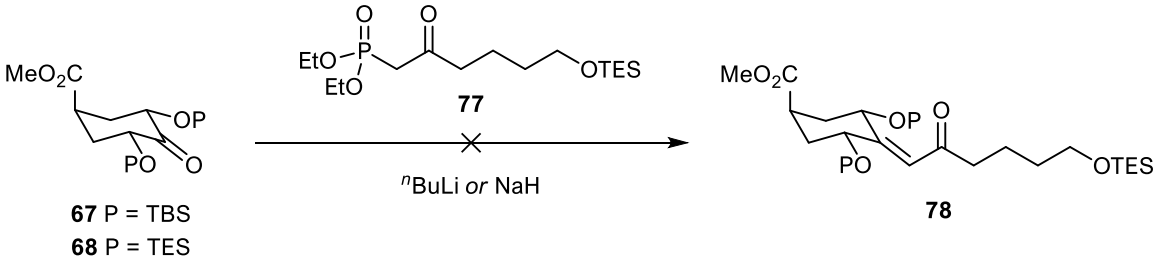
A Meyer-Schuster rearrangement was then attempted to form enone **75** as the reintroduction of an sp^2 centre would remove the incorrect alcohol stereochemistry formed in the previous step. Based on the assumption that additions to enone **75** should show the same π-facial selectivity as ketones **67** and **68**, diketone **76** could then be obtained by dihydroxylation and secondary alcohol oxidation (Scheme 1.16). Unfortunately, for the TES alkyne **74** only traces

of enone were detected by ^{1}H-NMR and no product could be isolated, and for TBS alkyne **73** the desired rearrangement did not occur and no enone was formed.[55]



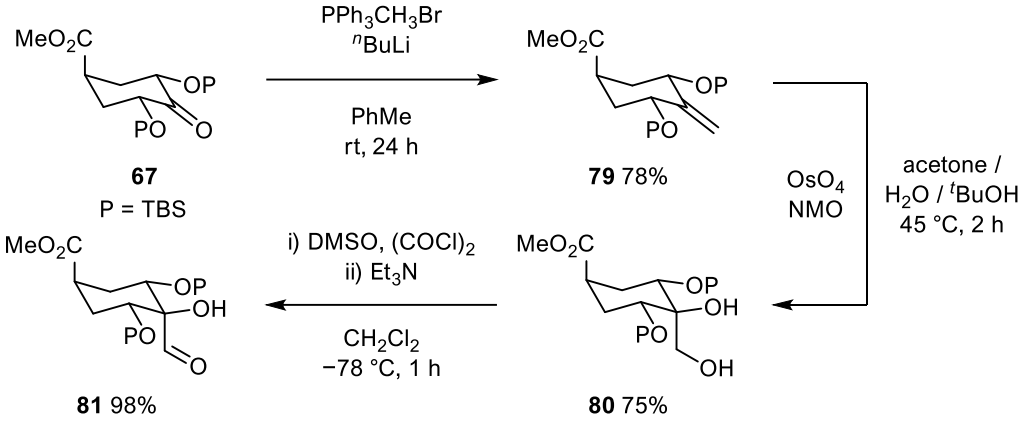
Scheme 1.16 *Meyer-Schuster rearrangement of propargyl alcohol **73** & **74***

As an alternative route to the enone functionality, a Horner-Wadsworth-Emmons olefination was attempted with phosphonate **77** but ultimately failed on both the TES and TBS protected diols.[50,55]



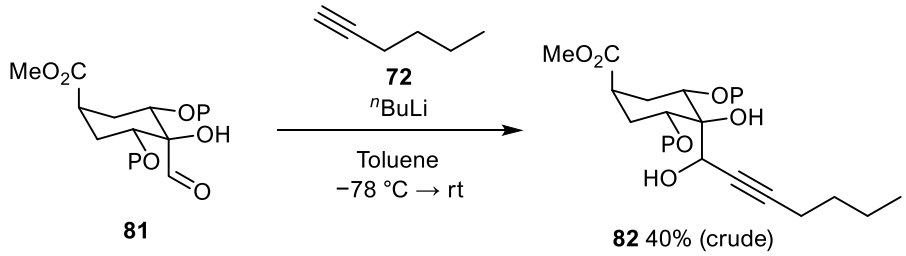
Scheme 1.17 *Horner-Wadsworth-Emmons olefination of monocyclic ketones **67** & **68***

In contrast to the failure of the Horner-Wadsworth-Emmons reaction, Wittig olefination of TBS protected diol **67** was successful to give **79** in 78% yield. Osmium-catalysed dihydroxylation occurred with complete stereocontrol to form **80** as a single stereoisomer which was subsequently oxidised to give meso aldehyde **81** in 98% yield.[50]



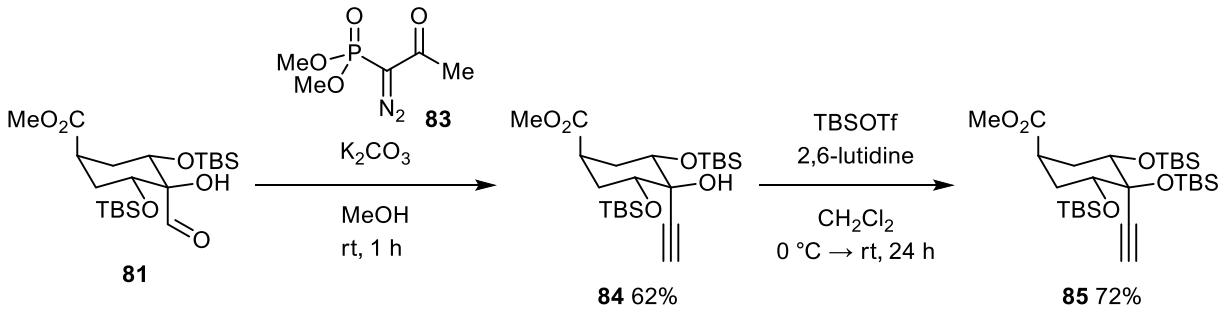
Scheme 1.18 *Homologation of ketone* ***67***

It was hoped that this homologated aldehyde **81** would show increased reactivity in comparison to **67,** but unfortunately hexyne addition was low yielding and product **82** was not able to be fully purified so this route was deemed unviable.[50]



Scheme 1.19 *Hexyne addition to aldehyde* ***81***

Fortunately, aldehyde **81** was able to be successfully homologated with Ohira-Bestmann reagent **83** to give terminal alkyne **84** in 62% yield (Scheme 1.20). Protection of the tertiary alcohol then gave alkyne **85**, with a crystal structure of intermediate **84** confirming the stereochemistry at the tertiary centre (Figure 1.15).



Scheme 1.20 *Seyferth–Gilbert homologation of aldehyde* ***81***

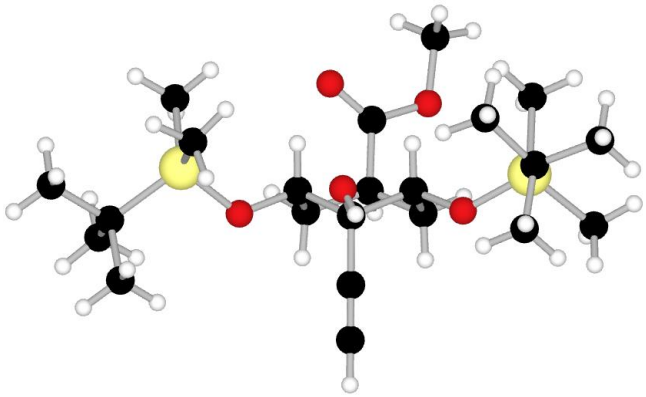
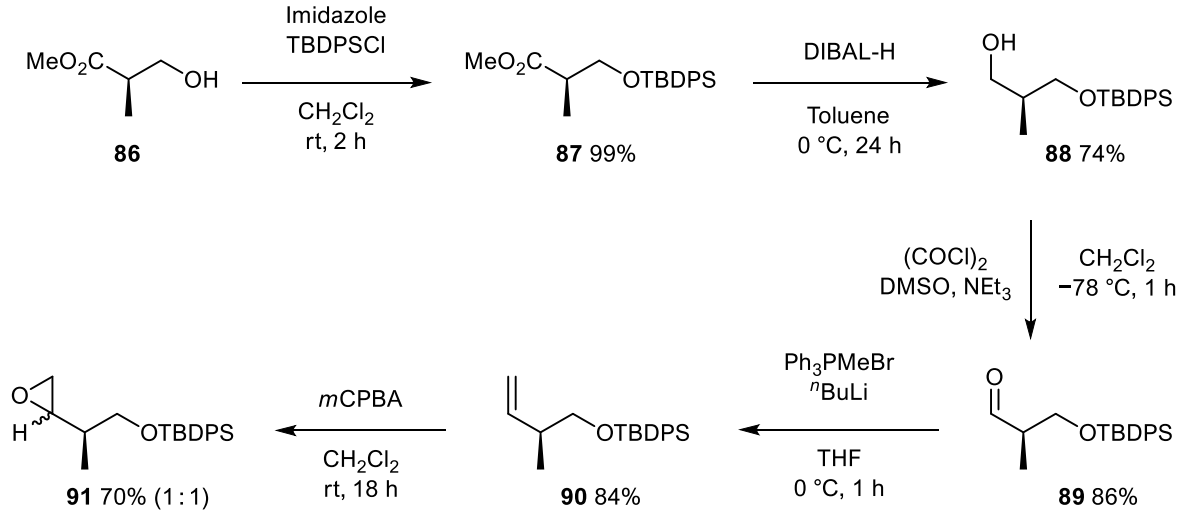


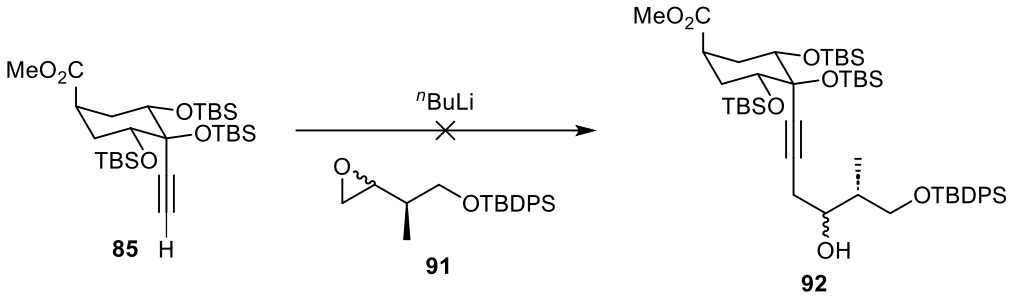
Figure 1.15 *X-ray crystal structures of intermediate alkyne* ***84***

Alkyne **84** possesses the required *trans* relationship between the alkyne and the OTBS groups, meaning an alternative approach to phyllaemblic acid *via* epoxide ring opening was now feasible. Chiral epoxide **91** was prepared as a 1:1 ratio of diastereoisomers in 5 steps from (*R*)-Roche ester **86** (Scheme 1.21).[56]

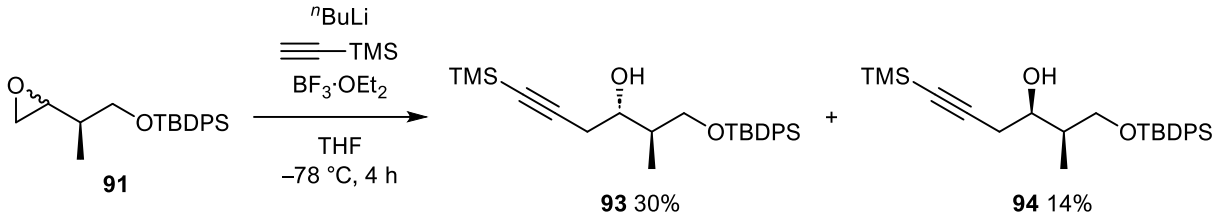


Scheme 1.21 *Synthesis of chiral epoxide* ***91***

Unfortunately, epoxide **91** showed no reactivity towards **85** under a variety of different basic conditions (Scheme 1.22). To confirm that this reactivity was a result of the steric hinderance around the terminal alkyne proton in **85**, epoxide **91** was reacted with TMS acetylene (Scheme 1.23). The epoxide was successfully opened to give a 1:1 mixture of alkynes **93** and **94** (2:1 isolated ratio), therefore this route was abandoned.



Scheme 1.22 *Epoxide ring opening with alkyne* ***85***



Scheme 1.23 *Epoxide ring opening with TMS acetylene*

1.2.4 – CONCLUSION

The reported syntheses of phyllanthocin and breynolide show strong precedent for a thermodynamically controlled spiroacetalisation to be a viable synthetic strategy for phyllaemblic acid but attempts to introduce the diketone moiety to *meso*-2,4,6,-trisubstituted cyclohexanones **54**, **55** and **56** were either unsuccessful or occurred with the incorrect stereochemistry and poor yields. It is likely that the use of the cyclic acetal protecting group is the cause of this poor reactivity, a problem which a successful synthesis of phyllaemblic acid using the α,α'-annelation approach must overcome. While steric interactions undoubtedly play a role in the observed reactivity of *meso*-cyclohexanones **54**, **56**, **67** and **68**, there are other factors that determine both the selectivity and reactivity of nucleophilic additions to carbonyls that also need to be considered.

1.3 – CARBONYL ADDITION REACTIONS

The addition of a nucleophile to a carbonyl compound possessing two different substituents has the possibility to generate two stereoisomeric products depending on the face of addition (Figure 1.16).

Figure 1.16 *Nucleophilic addition to asymmetric ketones*

Asymmetric induction occurs when chiral substituents on the ketone result in the preferential formation of one stereoisomer over the other. Models that can reliably predict this π-facial selectivity are vital in the synthesis of structurally complex molecules such as natural products. Therefore many models, both empirical and theoretical, have been presented in an attempt to describe asymmetric induction at carbonyl carbons during nucleophilic additions.[57]

1.3.1 – ACYCLIC KETONES

The first model for rationalising selectivity in nucleophilic additions to acyclic ketones was put forward by Cram in 1952.[58] In the years that followed alternative models were presented Cornforth,[59] Karabatsos,[60] and Felkin,[61] with each model attempting to address limitations of the last (Figure 1.17). Over time, the models for stereoinduction have evolved into increasingly more sophisticated and accurate tools, with Anh and Eisenstein's additions to Felkin's original model forming the most widely accepted and commonly applied model.[62]

Cram
C–R & C–L eclipsed in T.S.

Karabatsos
C=O & C–M eclipsed in T.S.

Felkin
Staggered T.S.

Cornforth
C–X & C=O dipoles minimised in T.S.

Figure 1.17 *Early models for asymmetric induction in acyclic ketones*

These models all attempt to explain selectivity through comparison of transition state energies and therefore assume Curtin-Hammett kinetics: different conformers of the starting ketone are rapidly interconverting with reaction occurring faster from one conformer.[63] The observed selectivity depends on both the energy barrier between the two conformers and the relative energy of the two transition states (Figure 1.18). Therefore the final product ratio does not always reflect the equilibrium distribution of the starting material.

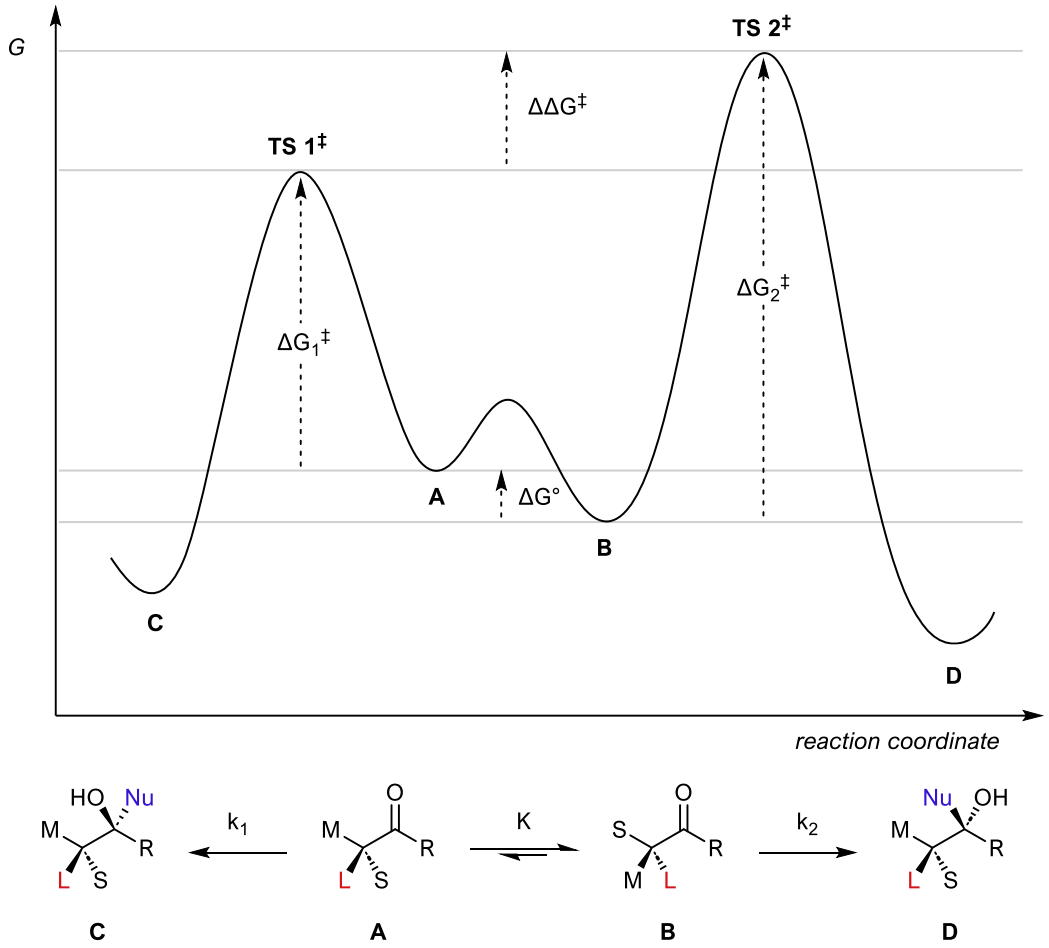


Figure 1.18 *Reaction coordinate free energy profile of a reaction under Curtin-Hammett kinetics: When K >> k_1 and k_2, C:D product ratio is determined by $\Delta\Delta G^{\ddagger}$*

1.3.1.1 – FELKIN-ANH MODEL

Felkin's transition state model is based on the assumption that torsional strain involving partial bonds (i.e. torsional strain in transition states) is larger than torsional strain involving fully

formed bonds (i.e. torsional strain in the starting material).[61] For acyclic carbonyl compounds, this implies that the transition states where the bonds are staggered are the lowest in energy. Consequently, the transition state where the nucleophile adds antiperiplanar to the largest group (L), with the smallest group (S) closest to R, has the least amount of torsional strain, and therefore lowest energy of the six possible staggered transition states (Figure 1.19).

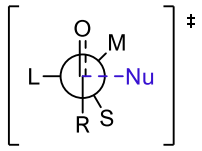


Figure 1.19 *Felkin model*

Computational studies by Anh and Eisenstein modelled hydride additions to ketones and confirmed the Felkin transition states were close to the transition state geometries that were calculated to be lowest in energy, while the Cram and Karabatsos transition states were much higher in energy.[64] Incorporation of the work of Bürgi and Dunitz on carbonyl approach trajectories led to what is now known as the Felkin-Anh model (Figure 1.20).[65,66]

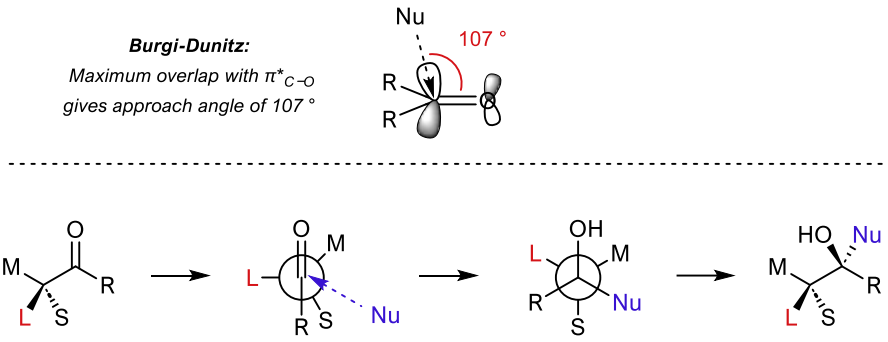


Figure 1.20 *Felkin-Anh model*

The lower energy of the Felkin-Anh transition states is attributed to stabilising hyperconjugative interactions between the σ* antibonding orbital of the C–L bond the σ orbital of the C–Nu bond (Figure 1.21).[64,67] Orbital overlap is maximised and therefore the stabilisation strongest when the nucleophile adds antiperiplanar to the C–L bond.

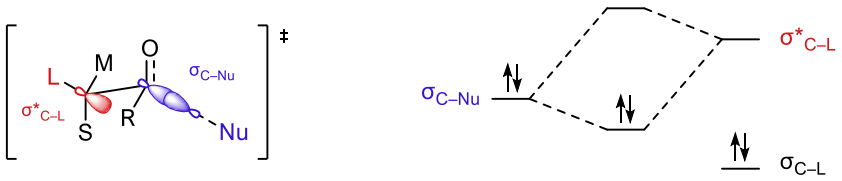


Figure 1.21 *Rationale for Felkin-Anh model*

For ketones bearing an α-heteroatom it is the bond to the polar substituent, C–X, which has the best accepting σ* antibonding orbital. Therefore the greatest transition state stabilisation occurs when C–X is oriented antiperiplanar to the forming C–Nu bond (Figure 1.22).[68]

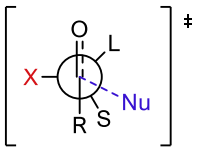


Figure 1.22 *The polar Felkin-Anh model*

1.3.1.2 – POLAR EFFECTS

Before the polar Felkin-Anh model, additions to ketones possessing an electronegative, non-chelating α-substituent were rationalised by a modification of Cram's rule known as the Cornforth model.[59] This model is based on the minimisation of dipoles in the transition state: carbonyl polarisation is easiest when the C=O and C–X dipoles are oriented anti-parallel resulting in a lowering of the transition state energy.[59] In a modern take on the Cornforth model, the Bürgi-Dunitz approach trajectory and the Felkin-Anh staggered transition states are incorporated (Figure 1.23).[69]

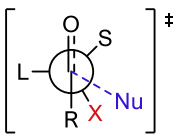


Figure 1.23 *Modern interpretation of the Cornforth model*

While the polar Felkin-Anh model is currently the most widely accepted model for additions to α-heteroatom substituted carbonyls, Evans has reported several examples which are better

accommodated by the Cornforth model.[69,70] While currently there is little experimental evidence for this model, it is likely that the factors stabilising the transition states in these cases are at play in all additions to α-heteroatom substituted carbonyls.[70]

1.3.1.3 – CHELATE CONTROL

If the α or β carbon of a carbonyl substrate has a substituent that can coordinate to metals (e.g. OR, NR_2 or SR), the formation of a chelate ring can have a significant impact on selectivity. This idea of chelation control in ketone additions was first introduced by Cram in 1959.[71]

Selectivity is proposed to occur as a result of coordination between the carbonyl, the donor substituent and the metal restricting C–C bond rotation, resulting in a bias towards the chelated reactant conformer. In the original Cram-Chelate model, the nucleophile was still assumed to add perpendicularly to the carbonyl group and from the least sterically hindered face of the rigid intermediate to give the stereochemical outcome (Figure 1.24).

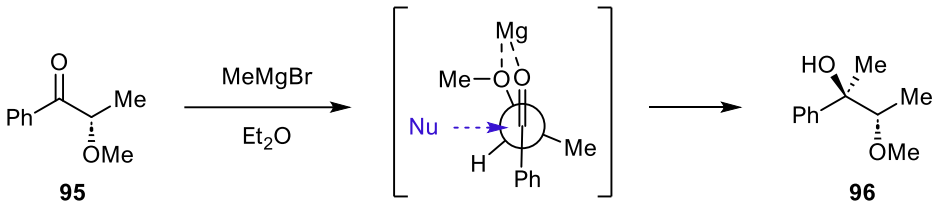
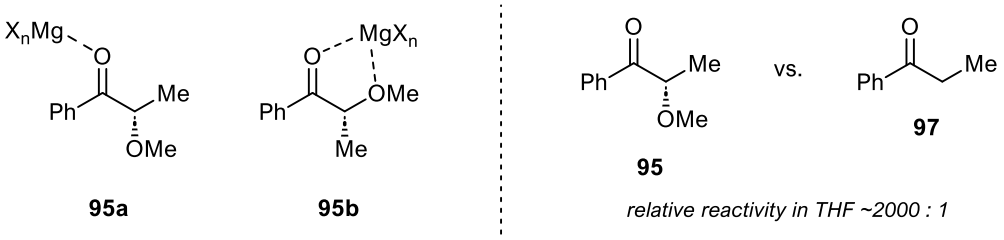


Figure 1.24 *Cram-Chelate model*

More recent studies into the Cram-Chelate effect revealed that chelate **95b** is only a minor component in solvents such as diethyl ether and THF, which are commonly employed for reactions involving organometallics (Figure 1.25).[72] Furthermore, the reaction rates of Me_2Mg additions to various ketones were measured, revealing that ketones containing chelating substituents exhibited reaction rates more than 10^3 times higher than those without (Figure 1.25).[73,74] The supports the assumption that chelate-controlled additions are operating under Curtin−Hammett kinetics: a small proportion of chelated ketone **95b** reacts faster than any other species present.



95a **95b** **95** **97**

relative reactivity in THF ~2000 : 1

Figure 1.25 *Chelate effects involved in nucleophilic additions to* ***95***

1.3.1.4 – STERIC APPROACH CONTROL

For structurally simple acyclic ketones the stereochemical outcomes of nucleophilic additions can be readily explain by considering the stereoelectronic factors discussed above. For reactions of cyclic ketones, steric effects start to become a more dominant factor.[75] The concept of steric approach control predicts selectivity based solely on which face of the carbonyl is least hindered.[76]

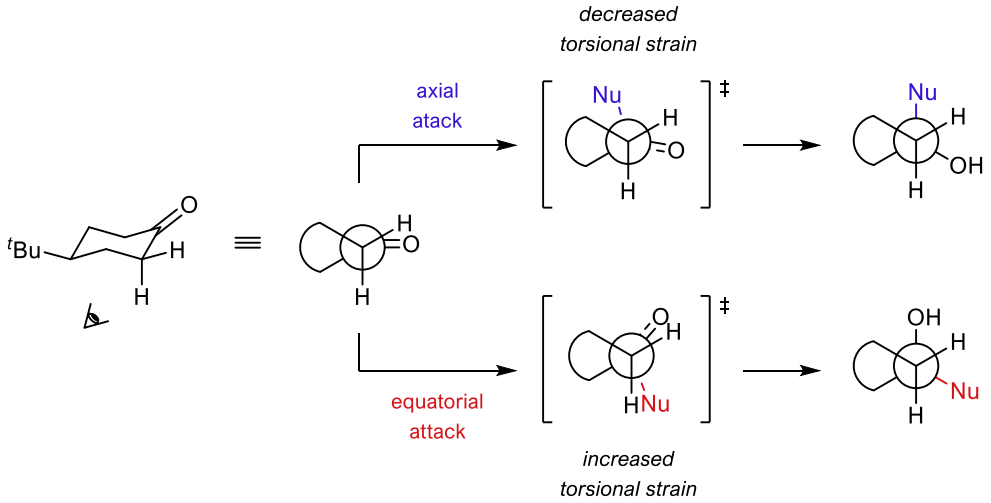
While steric effects are a principal factor in other models, such as determining which face of the ketone is substituted once destabilising interactions in the transition state have been minimised, rationalising additions using the steric approach control model depends only on steric interactions between the ketone and nucleophile to rationalise selectivity.

1.3.2 – CYCLOHEXANONES

Nucleophilic additions to cyclohexanones can proceed *via* either an axial or an equatorial approach trajectory. Based solely on steric approach control, addition from the equatorial face is predicted. This is because for axial addition the required Bürgi–Dunitz approach trajectory is blocked by the 3,5-axial hydrogens. In contrast, the equatorial approach is relatively unhindered (Figure 1.26).[77]

Figure 1.26 *Steric effects determining π-facial selectivity in cyclohexanones*

However, sterics effects alone are not sufficient for predicting nucleophilic additions to cyclohexanones.[78] For equatorial addition there is an increase in torsional strain, a type of intramolecular strain present as a result of non-bonding interactions between two eclipsing bonds, in the transition state compared to the starting ketone (Scheme 1.24). On the other hand, nucleophile addition from the axial face results in a decrease in torsional strain. The observed stereochemical outcome of the addition is therefore determined by the relative impact of both steric and torsional interactions.



Scheme 1.24 *Torsional strain effects determining π-facial selectivity in cyclohexanones*

When the nucleophile is small, such as hydride or acetylide anions, the clash between the nucleophile and the 3,5-axial hydrogens is minimal and therefore in the transition state torsional strain effects dominate, favouring axial substitution.[79] As the size of the nucleophile increases so does the severity of this axial clash and as a result an increased preference for equatorial addition is observed (Figure 1.27).[79] Substitution at the 3 and 5 positions also increases the

severity of these diaxial interactions and results in exclusively equatorial addition, even for hydride addition.

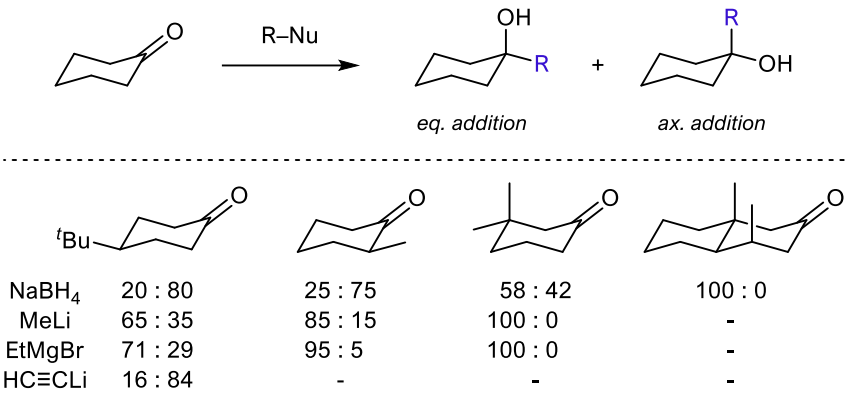


Figure 1.27 *Equatorial : axial ratios of nucleophilic additions to substituted cyclohexanones*

1.3.2.1 – CIEPLAK EFFECT

Conformational restrictions in cyclohexanones mean that a lower energy conformation cannot readily be adopted and as a result the effect of electronegative substituents on π-facial selectivity is less well defined than for acyclic ketones. For conformationally locked cyclic ketones there are many cases where the observed reaction outcomes are inconsistent with those predicted by the Felkin-Anh model.

For example, methyllithium addition to norbornanone **98** results in addition *syn* relative to the ester substituents.[80] Felkin-Anh type analysis would predict that nucleophilic addition occurs *anti* to the ester substituents as a result of stabilisation from the electron withdrawing ester groups making the σ* antibonding orbital of the adjacent C–C bond a better acceptor.[81]

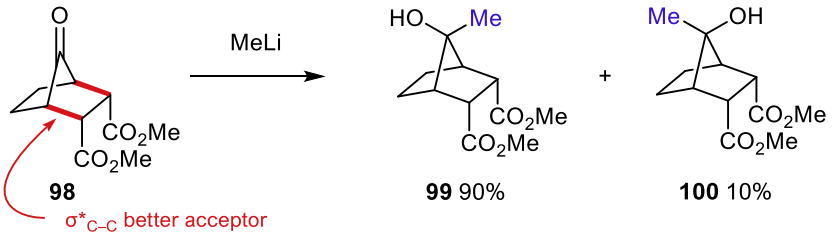


Figure 1.28 *π-facial selectivity of norbornanone* ***98***

As a result of the failure of previous models to predict the observed *syn* selectivity, Cieplak proposed new model for nucleophile addition to cyclohexanones.[82] The model cites hyperconjugation of the forming C–Nu σ* antibonding orbital with geometrically aligned σ orbitals as the interaction which lowers the transition state energy and consequently favours addition from one face over the other (Figure 1.29).[81] The Cieplak effect therefore predicts that the nucleophile adds *anti* to the σ orbital which is the better electron donor, with the electron donating ability of the C–X σ orbital stated as follows: C–S > C–H > C–C > C–N > C–O.[82]

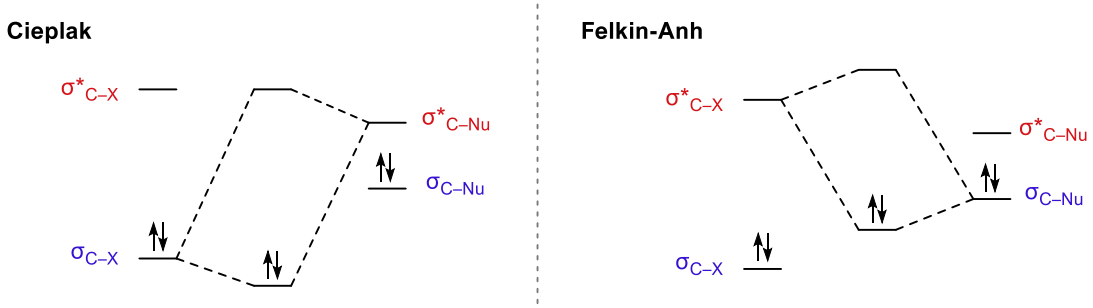


Figure 1.29 *Comparison of hyperconjugation interactions in the Cieplak and Felkin-Anh models*

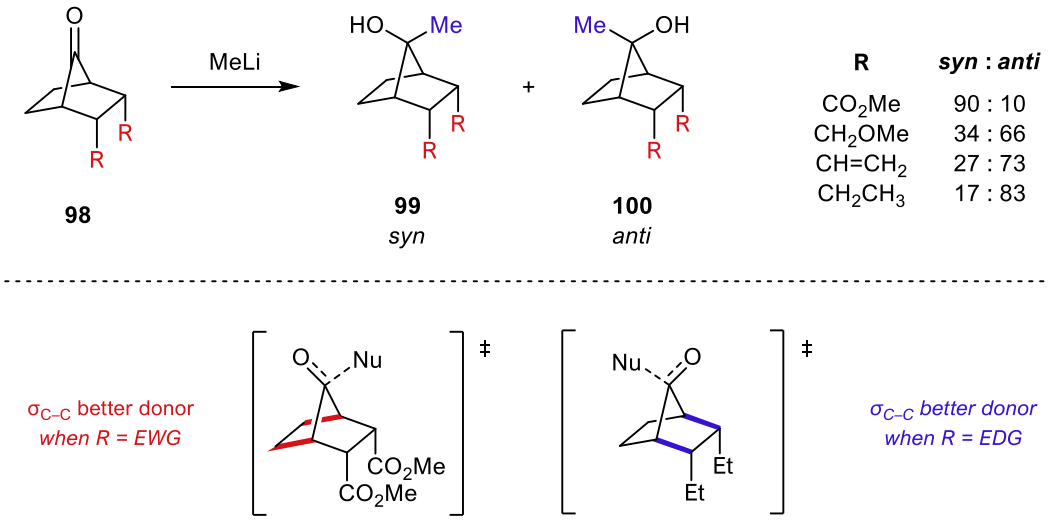
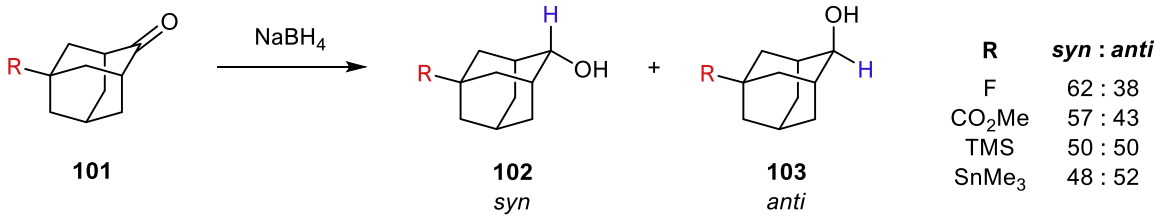


Figure 1.30 *Cieplak's rationale for π-facial selectivity in methylation of substituted norbornanones*

In the above example, the bonds antiperiplanar to the forming C–Nu bond are the cyclohexane C–C bonds, so donation occurs from the C–C σ orbital to the forming C–Nu σ* orbital. The C–C bonds adjacent to the ester substituents are poorer donors so the nucleophile adds *anti* to the

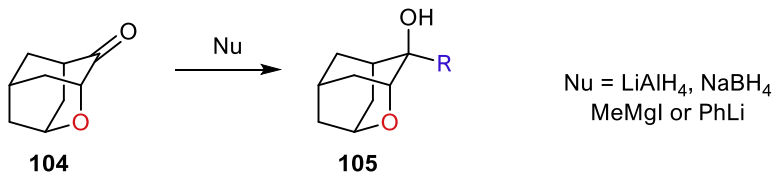
unsubstituted C–C bonds. This gives the opposite prediction to the Felkin-Anh model and is consistent with the observed reaction outcome. As the electron withdrawing nature of R is reduced, the selectivity is reversed (Figure 1.30).[80]

Cieplak's proposal stimulated many experimental and theoretical studies into the effects of electronic substituents on diastereoselectivity in a variety of cyclic ketones.[57,83–91] The addition of nucleophiles to 4-substituted adamantanones **101** provides the most compelling evidence as their symmetrical structure means that steric effects from axial C–H bonds are equal for each approach trajectory.[88] Although the effect is subtle, enhanced *syn* selectivity is observed for electronegative substituents (Scheme 1.25).



Scheme 1.25 *π-facial selectivity of substituted adamantanones*

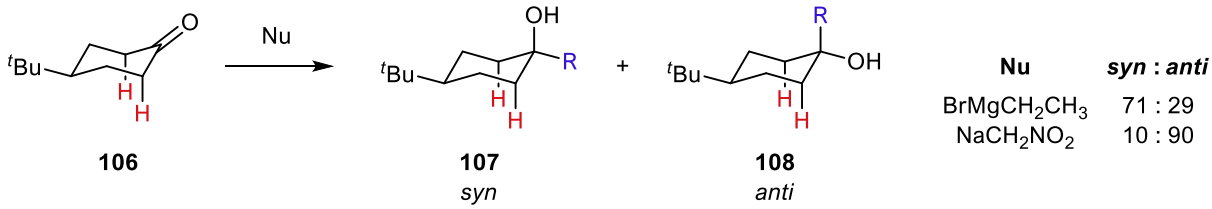
Incorporation of a heteroatom adjacent to the ketone results in a much stronger effect. For alkylation, arylation and reduction of oxa-adamantanone **104** 100% *syn* addition occurs (Scheme 1.26).[92]



Scheme 1.26 *π-facial selectivity of oxa-adamantanone* ***104***

Although consistent with the Cieplak effect, the adamantane framework is no longer symmetrical as the steric effects of an axial C–H and the oxygen lone pair are not equal. The presence of this lone pair also opens up the potential for coordination directed additions (Chapter 1.3.2.2).

The Cieplak effect has also been observed when electron withdrawing groups are present on the nucleophile.[82] In electron-deficient nucleophiles, such as a nitromethane anion, the forming C–Nu σ* orbital is lower in energy and therefore shows greater stabilisation as a result of hyperconjugation with the 2,4-axial C–H σ orbitals, resulting in a preference for axial substitution. In contrast, if the nucleophile is more electron-rich this stabilising effect is less favourable and equatorial addition prevails as a result of steric hinderance from the 3,5-axial C–H bonds (Figure 1.26).[82]



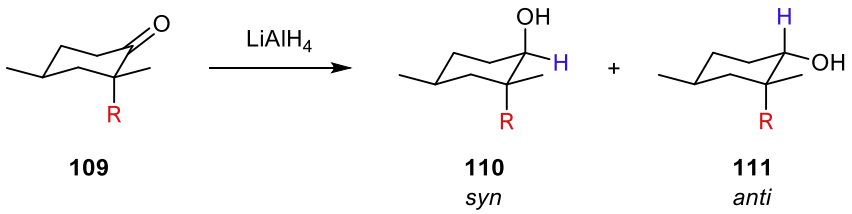
Scheme 1.27 *Effect of nucleophile on π-facial selectivity*

While there is a plethora of examples that appear to support the Cieplak effect, it has attracted criticism due to its unorthodox application of FMO theory.[93]

"Structures are stabilised by stabilizing their highest energy filled states. This is one of the fundamental assumptions in frontier molecular orbital theory. The Cieplak hypothesis is nonsense. Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct." – Prof. David A. Evans.[94]

Another criticism is that the examples which appear to be a manifestation of the Cieplak effect can often be justified by alternative (and more conventional) explanations. In the reduction of trisubstituted cyclohexanone **109**, a small increase in *syn* addition is observed when the axial α-substituent is changed from methyl to methoxy (Scheme 1.28).[95] While this appears to support Cieplak's proposal, the steric effects have not been considered. For a mono-substituted cyclohexane, the energy difference between the conformer where the substituent is axial and when it is equatorial for a certain substituent is known as its A-value.[96]

A-values therefore give a general and easily compared indication of the steric bulk of a substituent. The A values for methyl and methoxy groups are 1.75 kcal mol^{-1} and 0.75 kcal mol^{-1} respectively.[97,98] The equatorial approach in the methoxy substituted cyclohexanone is therefore less hindered which accounts for the slight increase in *syn* selectivity of α-methoxy ketone **109b**.



109

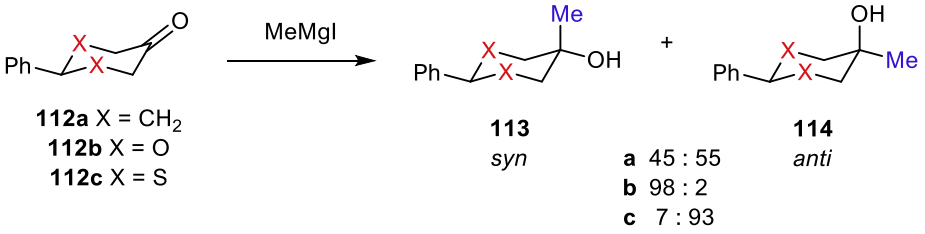
110 *syn*

111 *anti*

R	Yield	*syn* : *anti*
109a Me	85%	5 : 95
109b OMe	66%	13 : 87

Scheme 1.28 *Effect of axial α-methoxy substituent on π-facial selectivity of cyclohexanones*

The additions to 1,3-dioxo and 1,3-dithio analogues of cyclohexanone also appear to exhibit Cieplak type reactivity.[99] 1,3-Dioxan-5-one **112b** shows increased *syn* selectivity compared to cyclohexanone **112a** (C–O bonds are poorer donors than C–H_{ax}) and 1,3-dithian-5-one **112c** shows increased *anti* selectivity (C–S bonds are better donors than C–H_{ax}).[82] Explaining this selectivity based on the Cieplak effect alone ignores the changes in both steric and torsional strain that occur when the methylene unit is replaced with oxygen or sulfur.



112a X = CH_2
112b X = O
112c X = S

113 *syn*

a 45 : 55
b 98 : 2
c 7 : 93

114 *anti*

Scheme 1.29 *Effect of 1,3-heterosubstitution on π-facial selectivity of cyclohexanones*

The absence of the 3,5-axial C–H bonds means that axial addition is no longer disfavoured on steric grounds. Additionally, the C–O bonds in 1,3-dioxan-5-one **112b** are shorter than the C–C bonds in cyclohexanone **112a**. Therefore for equatorial addition, the increase in torsional strain in the transition state becomes more significant, leading to increased preference for axial substitution. Houk, a prominent critic of the Cieplak model, calculated that the increased length

of the C–S bond in 1,3-dithian-5-one **112c** results in the transition state for equatorial addition being free of torsional strain. As a result apparent *anti* addition prevails.[99]

In a similar approach to that of the Cornforth model, Houk attributed the selectivity observed in additions to substituted norbornanones **98** (Figure 1.30) to minimisation of dipoles in the transition state (Figure 1.31).[100]

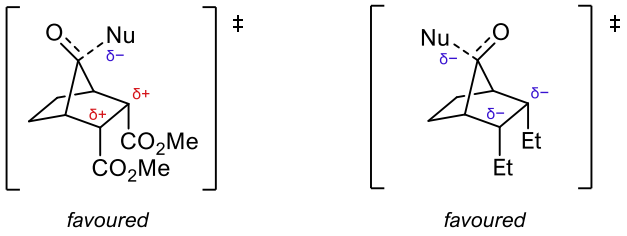
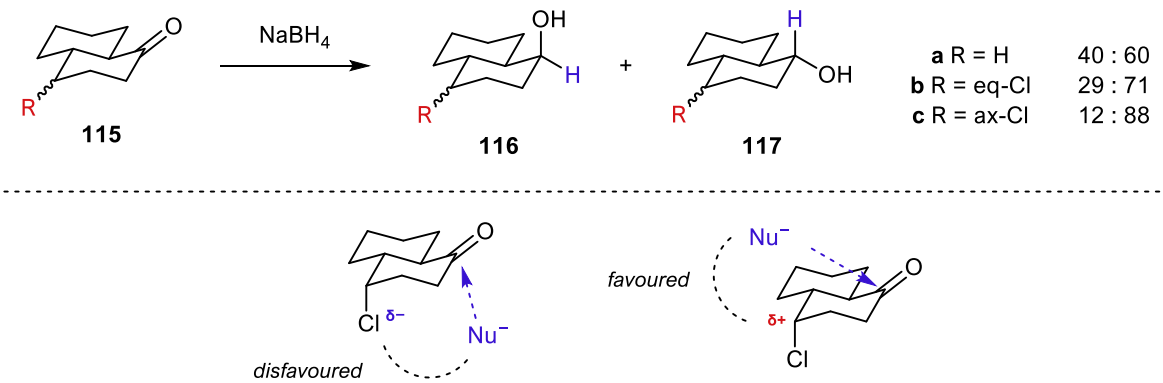


Figure 1.31 *Houk's electrostatic rationale for π-facial selectivity in methylation of substituted norbornanones*

The electrostatic argument can also be used to explain examples where the Cieplak model fails to predict the observed outcome (Scheme 1.30).[100] For additions to substituted *trans*-decalone **115,** the Cieplak effect predicts a greater preference for equatorial substitution for an equatorial Cl substituent than an axial one (antiperiplanar alignment of C–Cl with C-C results in greater stabilisation). In reality, exactly the opposite is observed with **115c** showing even higher selectivity for axial addition than **115b**. Equatorial nucleophile addition is destabilised by a repulsive interaction with the axial chlorine, while addition from the axial face experiences an attractive electrostatic interaction (Scheme 1.30).



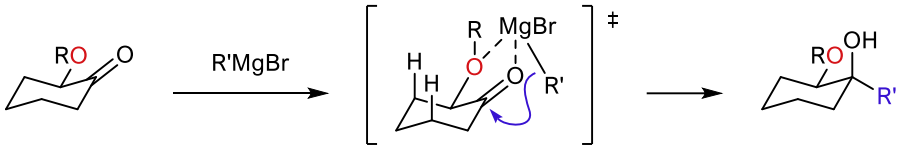
Scheme 1.30 *π-facial selectivity in substituted trans-decalones*

Houk also disputes Cieplak's key assumption that C–H σ orbitals are better electron-donors than C–C.[101] While there are further arguments in support of and against the Cieplak effect based on *ab initio* molecular orbital calculations, they are outside the scope of this review.[92,101–105]

1.3.2.2 – CHELATE CONTROL

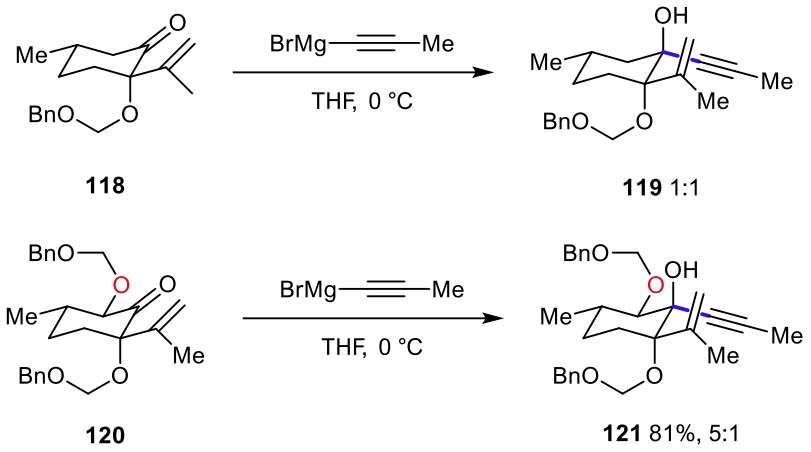
Analysis of additions to substituted cyclic ketones based solely on the Cieplak model is difficult due to the changes in steric effects, torsional strain and electrostatics that are inherent with heteroatom substitution. α-Heteroatom substitution of cyclic ketones also introduces the framework required for chelation-controlled additions. Although cyclohexanones are more conformationally restricted compared to acyclic ketones, the effects of chelation can still be observed.

For cyclohexanones with equatorial α-substituents, Cram-chelate like intermediates can be formed. Here the least hindered face is away from the 3,5-axial hydrogens and equatorial delivery of the nucleophile occurs (Scheme 1.31).[107]



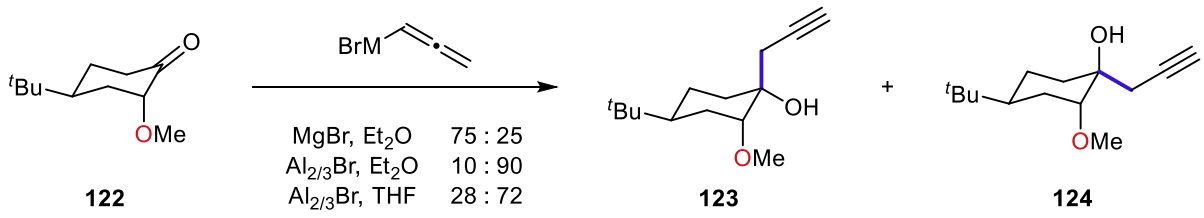
Scheme 1.31 *Chelate control in π-facial selectivity of equatorial α-methoxy substituted cyclohexanones*

Reisman's 15-step synthesis of the complex diterpenoid (+)-ryanodol takes advantage of this equatorial coordination to control the stereochemical outcome of propynyl magnesium bromide addition to cyclohexanone **118** (Scheme 1.32).[108] Typically alkyne nucleophiles are small, and would be expected to favour axial addition (Figure 1.27), but addition resulted in a 1:1 mixture of alcohol stereoisomers **119**.[109] When an α-alkoxy substituent was incorporated in ketone **120**, the equatorial selectivity was increased and tertiary alcohol **121** was formed as a 5:1 ratio diastereomers.



Scheme 1.32 *Effect of chelate control in Reisman's (+)-ryanodol synthesis*

For axial α-substituents, the effect is less clear. When allenylmagnesium bromide was added to methoxycyclohexanone **122** axial addition prevailed which implies little to no chelation to the magnesium occurs (Scheme 1.33).[110] This is likely a consequence of the angle between the two oxygen being too large to form a stable chelate ring. As a result of the lack of chelation, torsional strain controls the reaction selectivity (assuming allenylmagnesium bromide acts a small nucleophile similar to acetylide anions).



Scheme 1.33 *Effect of chelate-control in axial α-methoxy substituted cyclohexanones*

When allenylaluminium bromide is used in place of the Grignard reagent the selectivity is inverted and equatorial addition gives the favoured product. The authors rationalise this based on the ability of aluminium to form stable monodentate complexes with ethers.[111] Addition is then directed from the bottom face of the ketone (Figure 1.32).[112]

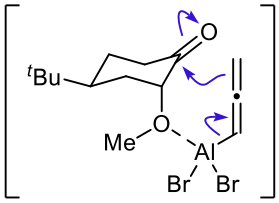
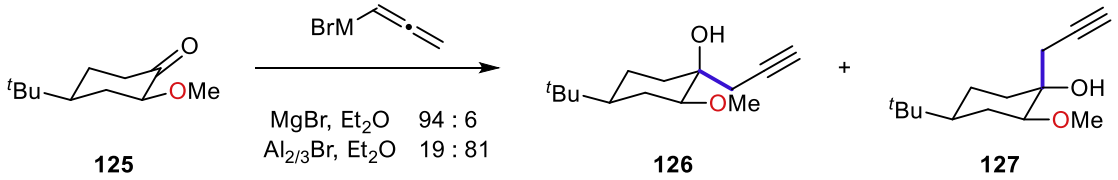


Figure 1.32 *Possible mechanism for chelate-controlled addition of allenylaluminium bromide to ketone* ***122***

Addition of the same reagents to equatorial α-methoxy ketone **125** resulted in 94% equatorial addition for magnesium, and the switch to aluminium only results in a slight decrease in selectivity (Scheme 1.34).[110] This reduction in selectivity is attributed to the inability of aluminium, whose coordination number rarely exceeds four, to stabilise a rigid Cram-like chelate ring resulting in a less rigid transition state.

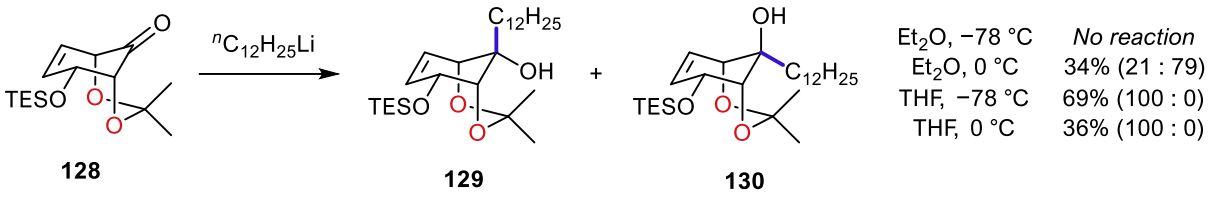


Scheme 1.34 *Effect of chelate-control in equatorial α-methoxy substituted cyclohexanones*

In coordination-controlled ketone additions, the choice of solvent plays a vital role. More strongly coordinating solvents such as THF can disrupt vital interactions leading to a drop in selectivity as a consequence of the lower concentration of the chelated conformation. This effect is demonstrated in the addition of allenylmagnesium bromide to cyclohexanone **122** (Scheme 1.33): when THF is used as the reaction solvent instead of diethyl ether a drop in selectivity from 90:10 to 72:28 is observed.

Takikawa and co-workers reported an unusual solvent effect in their total synthesis of (±)-pseudohygrophorone A[12], in which diastereoselective addition of dodecyllithium to ketone **128** forms a key step.[113,114] When the reaction was performed in diethyl ether the undesired equatorial addition product **130** was formed as the major stereoisomer (Scheme 1.35). This selectivity goes against what would be predicted based on steric hinderance from the acetal.

In contrast, when the addition was performed in THF the stereochemical outcome switched and complete selectivity for the desired axial addition product **129** was observed.



Scheme 1.35 *Solvent effect on π-facial selectivity in Takikawa's pseudohygrophorone A[12] synthesis*

The authors suggest this switch may be a result of the conformational flexibility of bicycle **128** (calculated energy difference of less than 1 kcal mol^{-1} between the pseudo chair-boat and chair-chair conformations) but fail to comment on how this rationalises the observed effect.[113]

One factor that may be at play is coordination from the acetal oxygens resulting in a directing effect, which is then reduced in THF, although the previously discussed examples suggest this is unlikely and doesn't account for such a drastic change in selectivity (Scheme 1.33).

Another factor that needs to be considered in the addition of organometallic regents is their structure, which are often more complex that their chemical formula would suggest.[115] For example, ^{n}BuLi has been shown to be tetrameric (**131**) in diethyl ether, but in THF small amounts of the dimeric species **132** are present (Figure 1.33).[116]

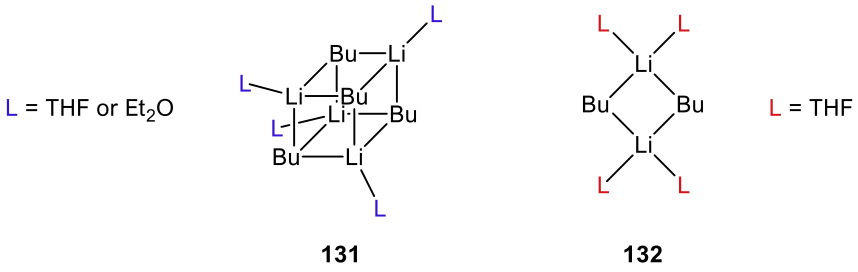
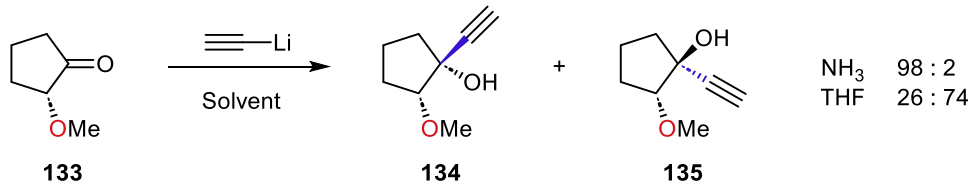


Figure 1.33 *Structures of solvated ^{n}butyllithium aggregates in ethereal solvents*

Studies have shown that the ^{n}BuLi dimer **132** is more than 20000 times more reactive towards carbonyls than the tetrameric species **131**, which may account for the switch in reactivity observed by Takikawa.[117] Dimeric alkyllithiums are also more polarised and therefore would

experience stronger electrostatic repulsion from the axial alkoxy groups resulting in the observed axial addition in THF.[115] This explanation also accounts for the lack of reactivity in diethyl ether at −78 °C.

A similar change in selectivity is also seen in the additions of ethynyllithium to 2-methylcyclopentanone **133** (Scheme 1.36).[118] In liquid ammonia, ethynyllithium is fully dissociated and therefore electrostatic repulsion from the methoxy group results in predominantly *trans* addition.[119] However in THF the ethynyl anion is not dissociated and therefore the stereochemical outcome is controlled by torsional strain effects resulting in only 26% of the *trans* product **135** being formed.[79]



133 **134** **135**

Scheme 1.36 *Effect of solvent on π-facial selectivity in α-methoxy cyclopentanone*

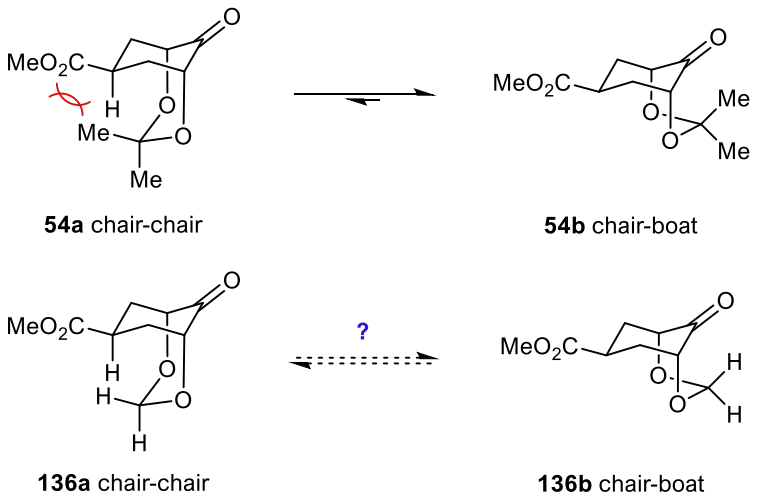
1.3.3 – CONCLUSION

The sheer number of models presented in an attempt to predict π-facial selectivity in carbonyl addition reactions serves as a testament to both the importance of these reactions and the complexity involved in understanding all the various interactions that determine relative transition state stability and ultimately product outcome. In a 1999 review Cieplak himself stated that attributing selectivity to just one or two bonds or local interactions is an oversimplification put forward by organic chemists in the just cause of establishing a predictive rule.[85]

The pioneers of the field have undoubtedly contributed valuable tools for considering carbonyl reactivity, even if their explanatory theories have not held up under the close scrutiny of later investigators.

1.4 – METHYLENE ACETAL HYPOTHESIS

Meso-ketones **54**, **55** and **56** have the relative stereochemistry required for a potential total synthesis of phyllaemblic acid but attempts at carbon-carbon bond formation gave either no reaction or low yields with incorrect stereoselectivity being observed. This poor reactivity was attributed to unfavourable steric interactions in the transition state (Scheme 1.12) leading to the hypothesis that replacing the protecting group with a methylene bridged acetal would alleviate these interactions, thus enhancing the reactivity. The chair-chair conformation of methylene bridged acetal **136** should be more accessible than the equivalent conformation of dimethyl acetal **54** as a result of the reduced steric clash with the axial C-4 H (Scheme 1.37). This ring flip would further alleviate the steric crowding, making the ketone more amenable to nucleophilic substitution from either face.



54a chair-chair **54b** chair-boat

136a chair-chair **136b** chair-boat

Scheme 1.37 *2,4-dioxabicyclo[3.3.1]nonane ring system conformations*

In the absence of steric hinderance from the acetal it is predicted that nucleophilic additions to ketone **136b** should favour addition *cis* to the acetal oxygens, giving the alcohol stereochemistry required for phyllaemblic acid. Based on the Cieplak model addition *cis* to the acetal is predicted as a result of σ_{C-O} being a poorer donor than σ_{C-C}. The absence of axial

hydrogens on the acetal ring means that addition from the lower face (as drawn) would also be the least hindered approach trajectory (Figure 1.34).

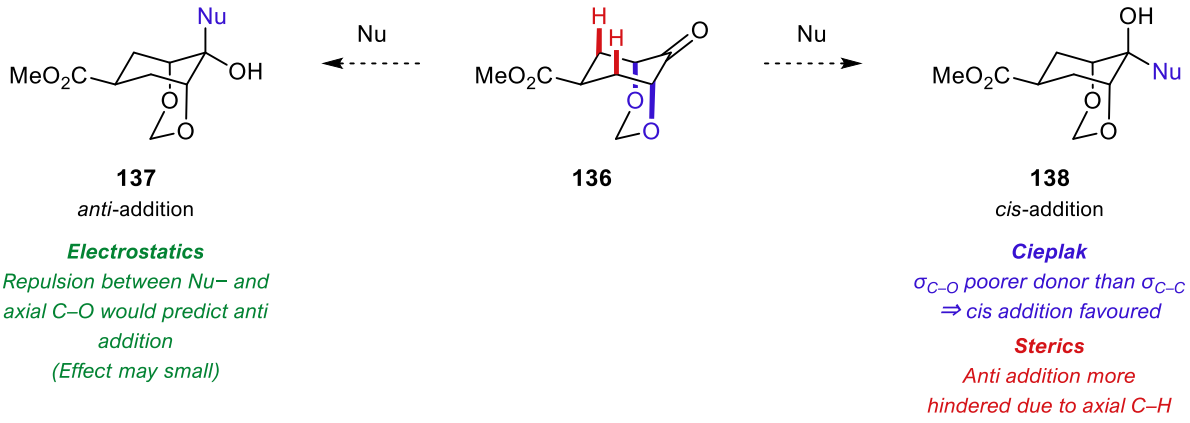
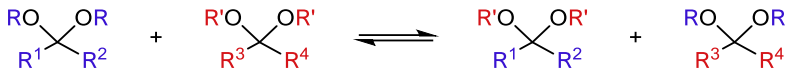


Figure 1.34 *Rationale for predicted π-facial selectivity of bicyclic ketone* ***136***

While the validity of the Cieplak model has been questioned, this system is analogous to the selectivity observed in 1,3-dioxo analogues of cyclohexanone **112** (Scheme 1.29), where *syn* addition was attributed to the decreased steric hinderance and increased torsional strain as a result of shorter C–O bonds disfavouring *anti* addition.[99] Although Cornforth-type analysis of electrostatic repulsion would predict axial addition, examples such as the addition to oxygen substituted adamantanone **104** imply that this repulsion is minor and *syn* addition should still be favoured (Scheme 1.26). The insignificance of electrostatic effects in these 1,3-dioxo systems was also confirmed computationally by Houk.[120]

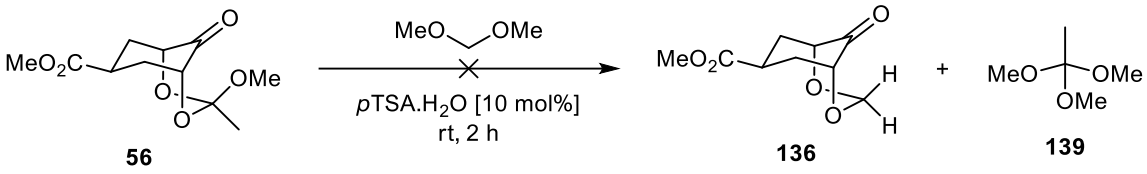
1.4.1 – PREVIOUS SYNTHETIC WORK (ACETAL EXCHANGE ROUTE)

When two distinct acetals react under acidic conditions, an exchange of the alkoxy substituents occurs (Scheme 1.38).[121,122] This reaction can be used to change the acetal protecting group on an alcohol or carbonyl functionality.[123] The formation of the new acetal is a reversible process and the equilibrium can be shifted to the desired product by using a large excess of the exchanging acetal.[124]



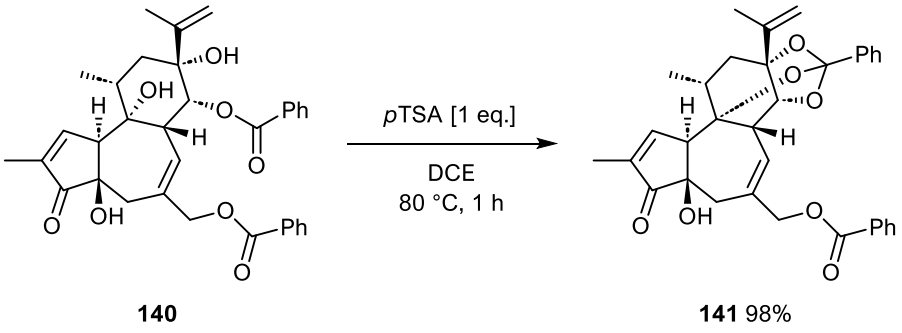
Scheme 1.38 *Acetal exchange reaction*

Previous attempts were made to synthesise methylene bridged acetal **136** *via* an acid-catalysed acetal exchange reaction of bicycle **56** with dimethoxymethane, the dimethyl acetal of formaldehyde (Scheme 1.39).[125] Treatment of **56** with 10 mol% *para*-toluenesulfonic acid monohydrate in neat dimethoxymethane led to the formation of an insoluble precipitate and conversion to the desired acetal **136** was not achieved. As full consumption of starting material was observed this precipitate was attributed to the formation of the diol, which has previously been reported as having low solubility in most common solvents.[55]



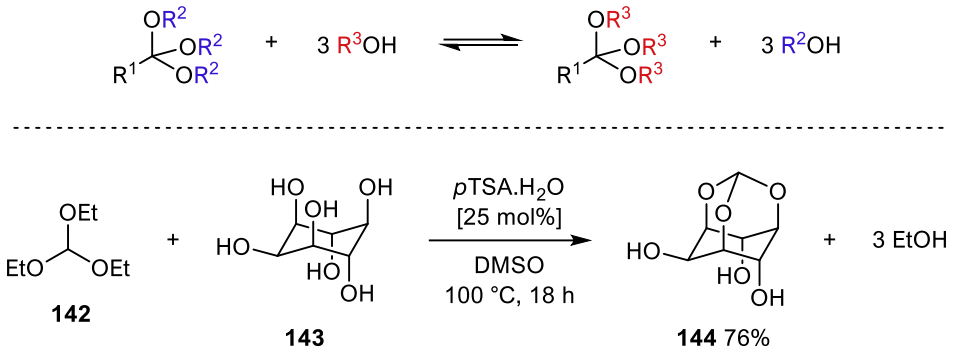
Scheme 1.39 *Atttempted synthesis of methylene acetal* ***136*** *by acetal exchange*

Under similar reaction conditions tricyclic orthoesters can be prepared by intramolecular reaction of an ester with free hydroxyl groups in the same molecule.[126] This method was used by Walpole *et al* in the synthesis of structural analogues of the natural product resiniferatoxin where tricyclic orthoester **141** was formed in near quantitative yield *via* an intramolecular reaction of the ester and the two hydroxy groups in **140** (Scheme 1.40).[127]



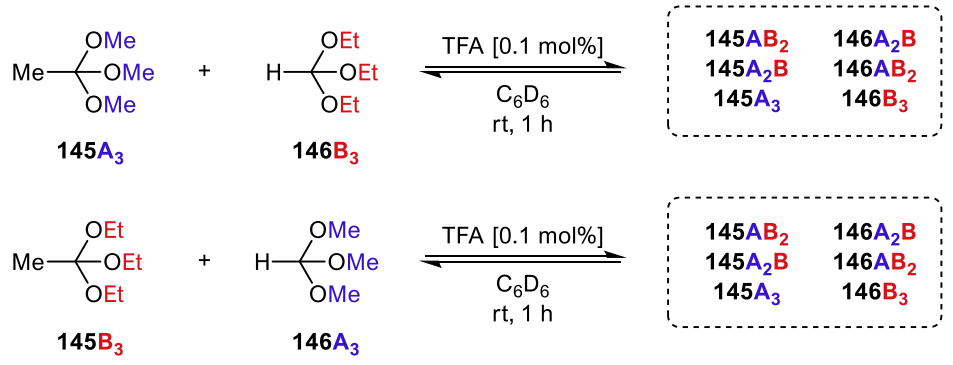
Scheme 1.40 *Intramolecular orthoester formation in resiniferatoxin synthesis*

Similarly to how transesterification of esters with alcohols is a common method of preparing more complex esters, orthoesters can undergo exchange reactions with alcohols to produce other orthoesters (Scheme 1.41).[128–130] The equilibrium is driven in a forwards direction by distillation of the alcohol formed from the reaction and if diols or triols are used, such as the synthesis of orthoester **144** from triethyl orthoformate **142** and myo-inositol **143**, entropy becomes the driving force.[131]



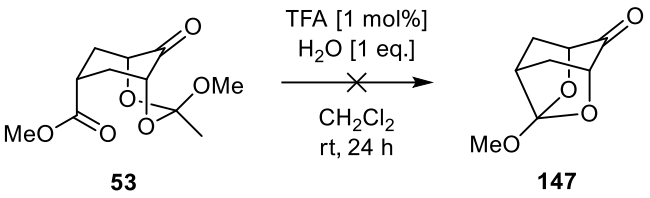
Scheme 1.41 *Orthoester exchange reactions*

Brachvogel *et al.* showed that orthoesters exchange with other orthoesters under acid catalysis.[132] This orthoester metathesis reaction results in 8 different orthoesters in equilibrium (Scheme 1.42). The addition of 1 mol% of water to the reaction mixture resulted in a dramatic increase in the rate of equilibrium. This observation indicates that the reaction is mediated by the free alcohols **A** and **B** generated *in situ* by hydrolysis of the starting orthoesters.



Scheme 1.42 *Brachvogel's orthoester metathesis*

Inspired by these examples, previous work in the group attempted to "tie back" the sterically demanding orthoester in **53** *via* an intramolecular orthoester exchange reaction.[125] It was hoped that this would free up the carbonyl and increase reactivity, but again a similar insoluble precipitate was observed and the desired product **147** was not formed (Scheme 1.43).[125]



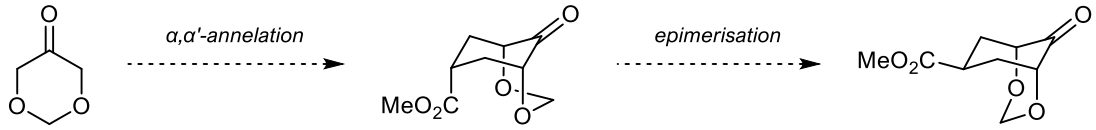
53 **147**

Scheme 1.43 *Attempted intramoleculer orthoester exchange on* ***53***

In summary, acid-catalysed acetal exchange reactions on bicycle **53** failed to provide the less hindered ketones **136** and **147** and this route was abandoned.

1.5 – AIMS & OBJECTIVES

After the failure of the acetal exchange reactions on bicycles **53** and **56**, an alternative route to methylene acetal **136** was planned: annelation of 1,3-dioxan-5-one **148** with acrylate **50** followed by base-mediated epimerisation should give bicyclic ketone **136** (Figure 1.35).



148 **149** **136**

Figure 1.35 *Synthetic route to bicyclic ketone* ***136***

With the overall aim of the present work being the first total synthesis of phyllaemblic acid, the following initial objectives were therefore defined:

1. To prepare 1,3-dioxan-5-one **148** and investigate its reactivity in the α,α'-annelation reaction to prepare key building block **136**.
2. To determine the conformational preferences in oxabicyclic ketones **149** and **136**.
3. To investigate the reactivity and stereoselectivity in addition reactions to ketones **149** and **136.**
4. To prepare RHS chiral fragments suitable for elaboration of **149** and **136** towards phyllaemblic acid.

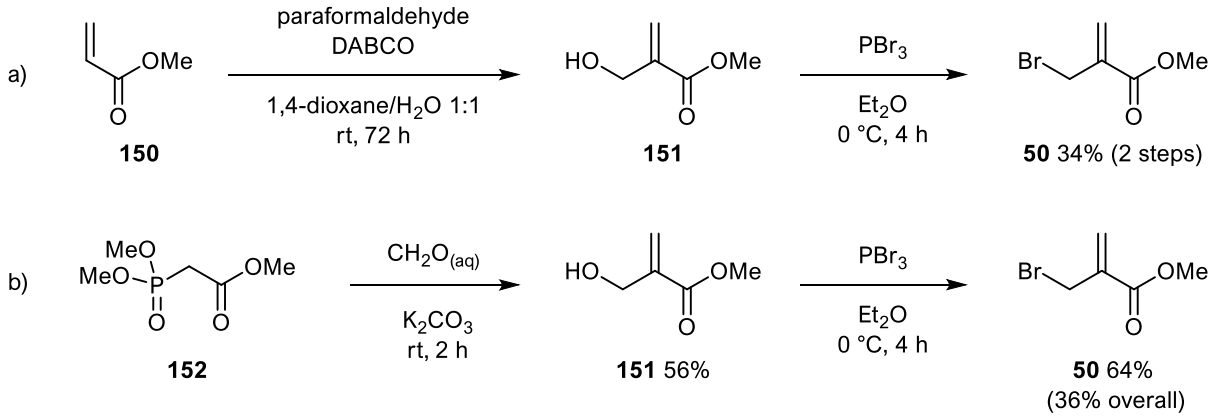
CHAPTER 2 – RESULTS & DISCUSSION

2.1 – SYNTHESIS OF METHYLENE BRIDGED BICYCLIC KETONES

2.1.1 – STARTING MATERIAL SYNTHESIS

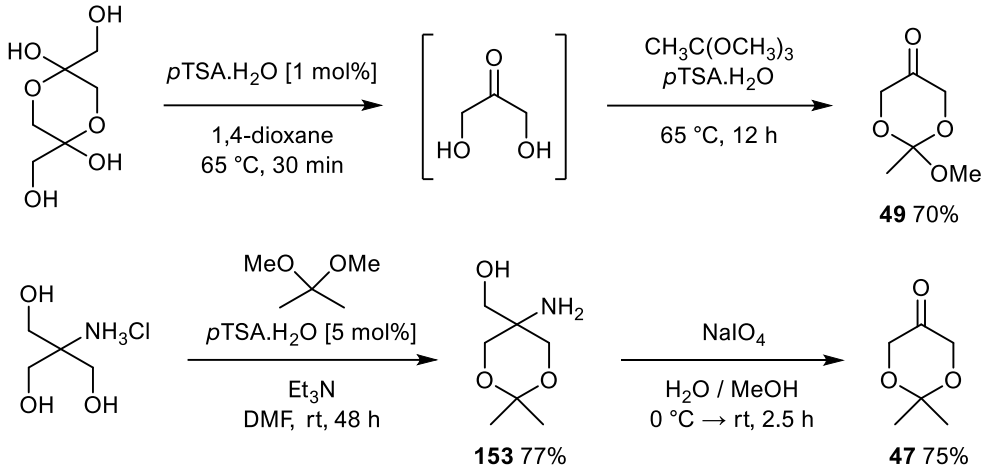
Two methods were used to prepare bromoacrylate **50**: Baylis-Hillman reaction of methyl acrylate **150** (Scheme 2.1a) and Wittig-Horner reaction of trimethyl phosphonoacetate **152** (Scheme 2.1b).[133,134] Bromination of hydroxylate acrylate **151** was achieved using phosphorus tribromide to give bromoacrylate **50** in 64% yield.[134] While both approaches yielded similar overall results the Wittig-Horner route offered greater reliability and scalability, allowing for the preparation of up to 21 g of bromoacrylate **50**.

Activated acrylates are sufficiently reactive to polymerise without the need for an initiator, so it was unsurprising that hydroxyacrylate **151** was found to spontaneously polymerise upon isolation to produce an insoluble polymer-like material.[134–136] Although there are many reported syntheses of **50** in the literature, none advise on how to prevent this polymerisation from occurring. The addition of 1% MeHQ as a radical inhibitor and performing the bromination immediately after purification of alcohol **151** was found to be sufficient to prevent polymerisation.[135] The presence of this radical inhibitor did not appear to have any effect on the subsequent bromination step, and was removed during the distillation of bromoacrylate **50**.



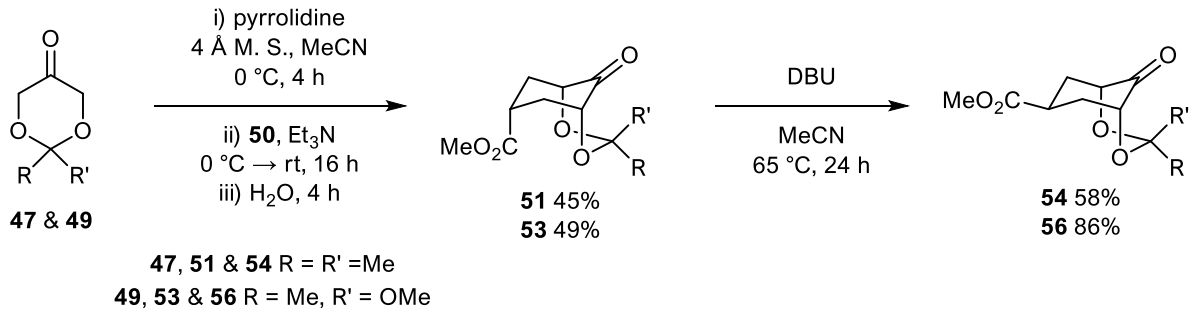
Scheme 2.1 *Synthesis of methyl 2-(bromomethyl)acrylate* ***50***

Acetal exchange of dimeric dihydroxyacetone with trimethyl orthoacetate gave **49** in 70% yield (Scheme 2.2).[137] A similar exchange of Tris HCl with 2,2-dimethoxypropane gave β-amino alcohol **153** and subsequent oxidative cleavage with $NaIO_4$ gave dimethyl dioxanone **47**.[138] Despite significant literature precedence this method initially proved challenging, with an overall yield of only 3% being obtained (literature yields 85 – 92%).[139,140] In both steps the poor yields were due to difficulty replicating the reported workup procedures. In 2020 DeChristopher and co-workers addressed these issues and published an updated method which proved to be more reproducible and allowed the synthesis of β-amino alcohol **153** and dimethyl dioxanone **47** in 77% and 75% yield respectively.[138]



Scheme 2.2 *Synthesis of 2-methoxy-2-methyl-1,3-dioxan-5-one* ***49*** *& 2,2-dimethyl-1,3-dioxan-5-one* ***47***

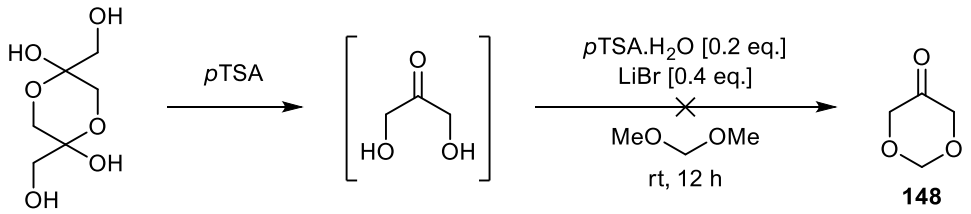
Using the prepared starting materials, the 2,4-dioxabicyclo[3.3.1]nonane ring system was then prepared *via* an α,α'-annelation reaction using previously reported conditions (Scheme 2.3).[49] Condensation of dioxanones **47** and **49** with pyrrolidine formed the corresponding enamines, which upon treatment with triethylamine and methyl 2-(bromomethyl)acrylate **50** gave *meso* ketones **51** and **53** in 45% and 47% yield respectively.[49] Base-mediated epimerisation gave equatorial esters **54** and **56** with the required *anti*-relationship between the ester and alkoxy-substituents.[49]



Scheme 2.3 *α,α'-annelation of 1,3-dioxan-5-ones* ***47*** *&* ***49***

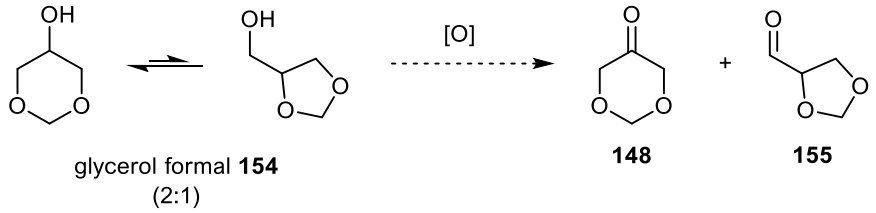
2.1.1.1 – DIOXANONE SYNTHESIS

The first attempt at the synthesis of 1,3-dioxan-5-one **148** was *via* acetal exchange with dihydroxyacetone and dimethoxymethane (Scheme 2.4).[125] Application of the same methodology used for dioxanone **49** (Scheme 2.2), but with dimethoxymethane as the reaction solvent, failed to produce any reaction.[137] Based on literature reports of formaldehyde acetal synthesis from 1,3-diols, addition of lithium bromide was trialled but this resulted in only trace amounts of the desired product being observed in the ^{1}H-NMR of the crude reaction mixture.[141]



Scheme 2.4 *Attempted synthesis of 1,3-dioxan-5-one* ***148*** *via acetal exchange*

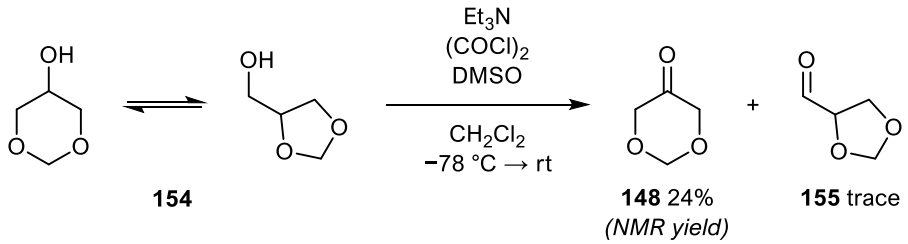
A second route to dioxanone **148** was then attempted based on the oxidation of glycerol formal **154**, a 2:1 mixture of the formaldehyde-derived acetals of glycerol (relative ratio determined by ^{1}H-NMR). If successful, oxidation of this mixture would give the desired dioxanone **148** alongside 1,3-dioxolane-4-carboxaldehyde **155** (Scheme 2.5).



Scheme 2.5 *Proposed oxidation of glycerol formal* ***154***

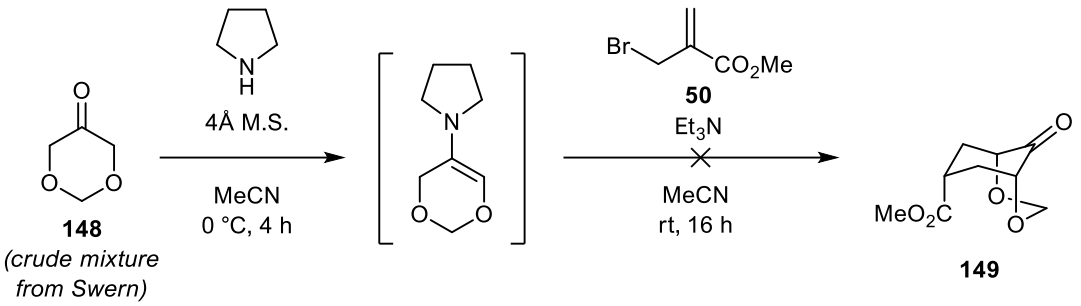
This oxidation proved to be challenging for a number of reasons. The desired product **148** was found to be highly water-soluble so a traditional aqueous workup was not possible. Dioxanone **148** was also found to be sensitive to both acidic conditions and temperature and was also found to degrade during column chromatography (including reverse phase and triethylamine doped-silica). These instabilities meant that purification of dioxanone **148** was limited to low temperature distillation, which when combined with the need to avoid acids and aqueous workups severely limited the available reaction conditions.

The first attempt at glycerol formal oxidation was using modified Swern conditions (Scheme 2.6).[142] The conventional aqueous workup was replaced by the addition of diethyl ether to the reaction followed by filtration of the resulting precipitate. This worked well to produce dioxanone **148** but attempts at separating the product from the excess DMSO in the crude reaction mixture by distillation failed as the boiling points were too close to achieve adequate separation. The yield of dioxanone **148** as a solution in DMSO after distillation was 24% (determined by NMR).[125]



Scheme 2.6 *Swern oxidation of glycerol formal*

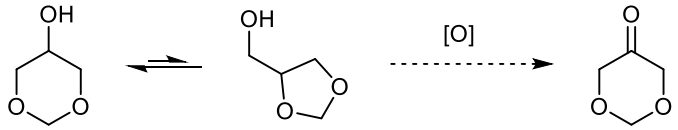
Regardless, the annelation was attempted on contaminated dioxanone **148** with the intent that the DMSO would be removed in the purification of bicycle **149**, but this produced a complex mixture of products, none of which resembled the desired product (Scheme 2.8).[125]



Scheme 2.7 *Attempted α,α'-annelation on crude reaction mixture*

Therefore a variety of oxidation conditions that did not contain acid and could be modified to remove the aqueous workup were then attempted, the results of which are summarised in Table 2.1.

Table 2.1 *Unsuccessful attempts at oxidation of glycerol formal*



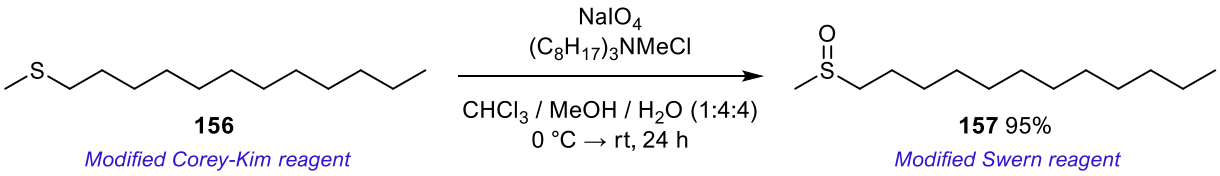
Entry	*Oxidation Conditions*	*Solvent*	*Result*[*]
1	DMSO, $(COCl)_2$, Et_3N	CH_2Cl_2	24% *(contaminated with DMSO)*
2	SMe_2, NCS, Et_3N	CH_2Cl_2	*Oxidation*
3	**157**, $(COCl)_2$, Et_3N	CH_2Cl_2	*Oxidation*
4	**156**, NCS, Et_3N	CH_2Cl_2	*Oxidation*
5	TPAP, NMO	CH_2Cl_2	*No reaction*
6	IBX	DMSO	*No reaction*
7	Ag_2CO_3 / celite	benzene	*No reaction*
8	Dess-Martin Periodinane, $NaHCO_3$ or py	CH_2Cl_2	*Oxidation*
9	PCC	CH_2Cl_2	*Oxidation*

[*] *Success of oxidation determined from detection of product signals in ^{1}H-NMR spectrum of crude reaction mixture. "Oxidation" refers to when product peaks were observed by NMR, but no product could be isolated from the reaction mixture due to difficulty in purification.*

Although successful oxidation to the ketone was achieved in several cases, purification remained the limiting factor in the synthesis of dioxanone **148**. The majority of conditions produced mixtures of volatile products, including aldehyde **155**, which distilled over alongside dioxanone **148** which meant that no clean product could be isolated.

Inspired by the partially successful Swern conditions (Table 2.1, Entry 1), a Corey-Kim oxidation was attempted as an alternative method of producing the same "activated DMSO" species without requiring the use of DMSO (Table 2.1, Entry 2).[143] Dioxanone **148** was observed in the ^{1}H-NMR of the crude reaction mixture, but no product could be cleanly isolated.

An "odourless" modification of the Swern using dodecyl methyl sulfoxide **157** in place of DMSO was then attempted (Scheme 2.8). It was assumed that sulfoxide **157** would have a higher boiling point than DMSO, therefore making purification of product **148** by distillation a more viable option.[144] Disappointingly, the oxidation of glycerol formal **154** using these conditions failed to replicate the success of the more traditional Swern oxidation and no product formation was detected (Table 2.1, Entry 3). From the same report, a modified Corey-Kim oxidation using long chain sulfide **156** was also attempted (Table 2.1, Entry 4), but only traces of product were observed in the ^{1}H-NMR of the crude reaction mixture.[144]

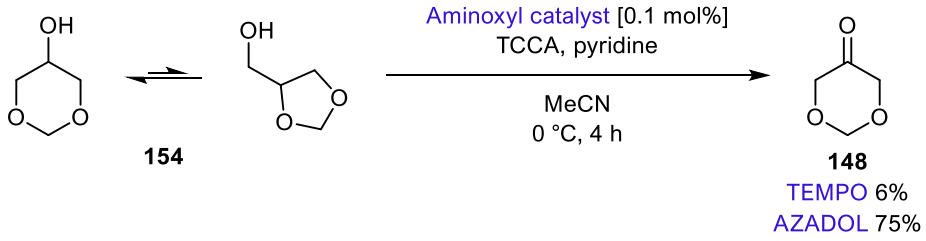


Scheme 2.8 *Synthesis of dodecyl methyl sulfoxide* ***157***

No reaction was observed when glycerol formal **154** was subjected to Ley-Griffith, IBX and Fétizon oxidation conditions (Table 2.1, Entries 5 – 7).[145] Dess–Martin periodinane resulted in successful oxidation, but the acetic acid produced by the reaction caused dioxanone **148** to decompose during distillation, even when base was included to buffer the reaction (Table 2.1,

Entry 8).[145] Oxidation with pyridinium chlorochromate (PCC) showed promise with complete consumption of starting material by ^{1}H-NMR (Table 2.1, Entry 9) but despite multiple distillations, dioxanone **148** could only be isolated alongside significant quantities of an unidentified impurity.[145] As a result of this and the high toxicity associated with chromium-based oxidations, alternative conditions were sought.

Despite being reported as a selective oxidation for primary alcohols, oxidation was attempted using a combination of TEMPO and trichloroisocyanuric acid (TCCA).[146,147] Although the desired oxidation was achieved and the distillation gave clean product, the yield was extremely poor (5%, Scheme 2.9). Encouraged by this partial success, improved aza-adamantane catalyst AZADOL was tried in place of TEMPO.[148] This gave ketone **148** in a much increased 75% yield after extensive optimisation of the distillation conditions, and proved to be reliable up to 20 g scale.[149]



Scheme 2.9 *Succesful synthesis of 1,3-dioxan-5-one* ***148***

The enhanced reactivity of AZADOL over TEMPO towards secondary alcohols is attributed to reduced steric hinderance around the reaction centre (Figure 2.1).[148]

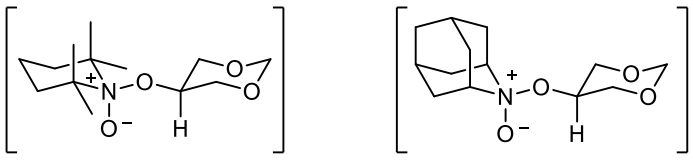
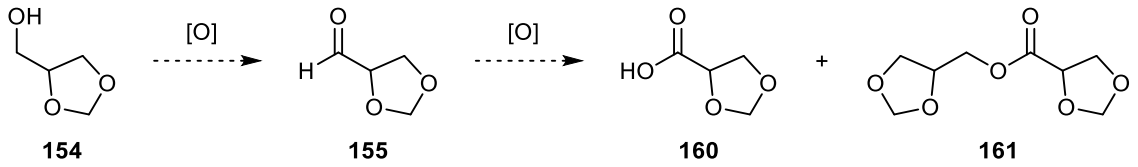


Figure 2.1 *Intermediates in aminoxyl oxidation of 1,3-dioxan-5-one* ***148***

The four flanking methyl groups in TEMPO reduce the ability of more substituted substrates to form the key intermediate **158**. In comparison, the AZADO-derived intermediate **159** is less hindered allowing for a more facile reaction with secondary alcohol substrates such as 1,3-dioxan-5-one **148**.

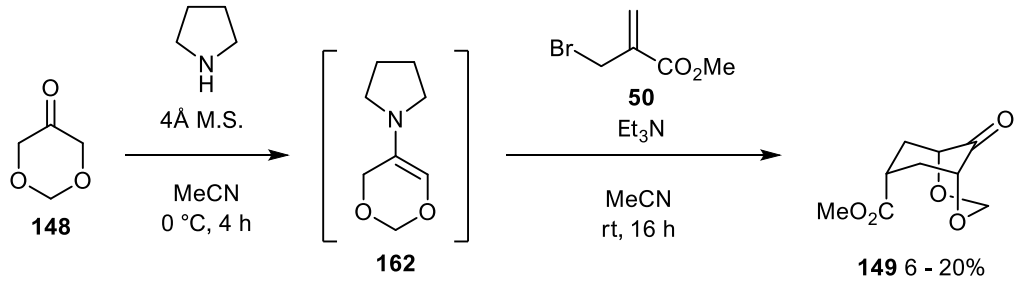
Interestingly, none of the primary alcohol oxidation product **155** was detected when using the AZADOL/TCCA conditions. This was hypothesised to be a result of over oxidation of aldehyde **155** to the corresponding acid **160** and subsequent formation of esters such as **161** (Scheme 2.10). This removal of volatile aldehyde **155** from the crude reaction mixture undoubtedly assisted in achieving clean distillation of **148**.



Scheme 2.10 *Oxidation products from 4-hydroxymethyl-1,3-dioxolane*

2.1.1.2 – ANNELATION REACTION

With dioxanone **148** in hand, attention turned to the synthesis of bicycle **149** *via* the α,α'-annelation reaction with acrylate **50**.[49] Although the reaction was initially successful, the yield was found to be highly variable (6 – 20%) and was much lower than the yields observed for other dioxanones (41 – 61%). Further optimisation was therefore required in order to produce the substantial amounts of starting material needed for a total synthesis.



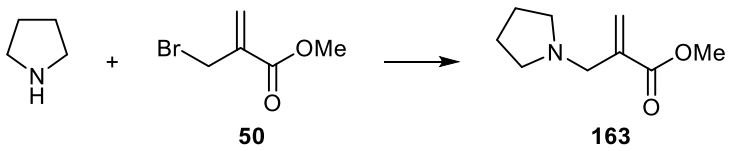
Scheme 2.11 *α,α'-annelation of 1,3-dioxan-5-one **148***

Initially the low yield was thought to be a result of the inability to purify **149** *via* column chromatography. The column was very "streaky" and resulted in co-elution of the product with unwanted side products. At first the streaking was assumed to be a result of the acid-labile acetal interacting with the silica, but the difficulty in purification was not improved when using triethylamine-doped silica or alumina (neutral and basic) columns. Additionally, six-membered methylene acetals have been shown to hydrolyse 10^6 times slower than the equivalent dialkyl acetals and up to 10^9 times slower than orthoacetals. This suggests that methylene acetal **149** should be more stable than both dimethyl acetal **51** and orthoacetal **53**, meaning acid-catalysed hydrolysis is likely not the issue.[150]

In order to evaluate which step of the reaction was causing the low yields, isolation of intermediate enamine **162** was attempted. Despite being successful for other enamine analogues, such as those formed from dioxanones **47** and **48**, enamine **162** was found to be unstable to solvent evaporation and could not be isolated.[50]

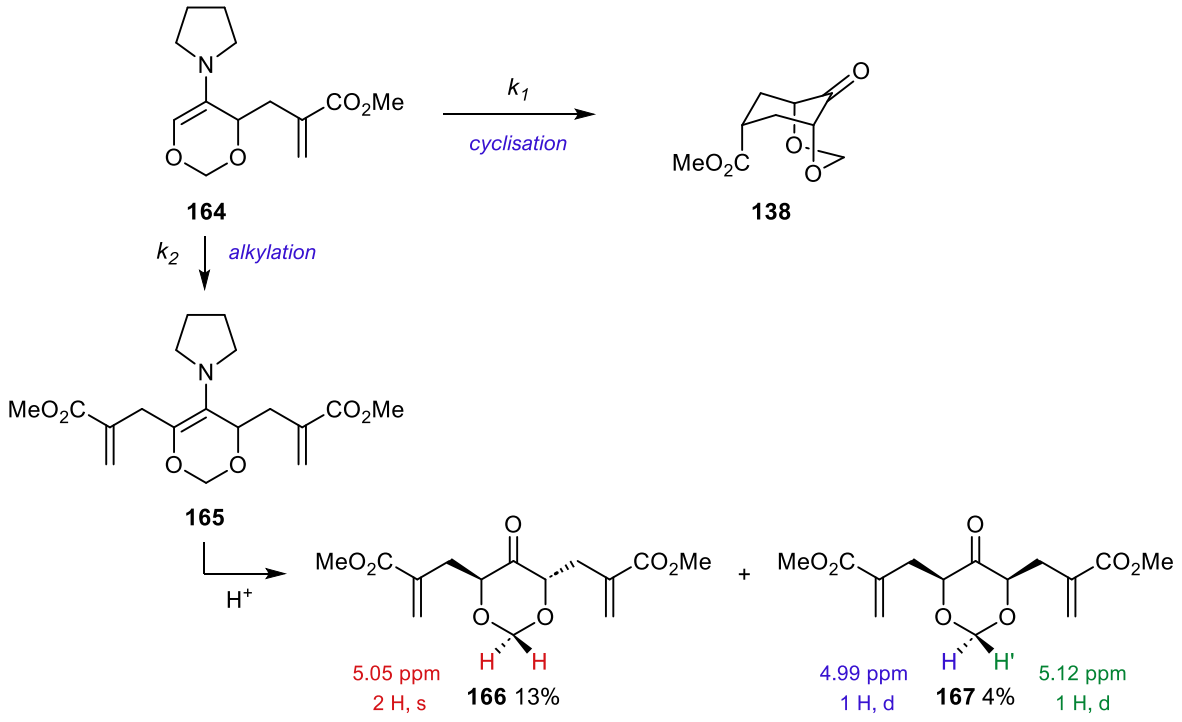
As an alternative method of observing enamine formation the reaction was performed in deuterated acetonitrile and progress monitored *in situ* by ^{1}H-NMR. This revealed that the formation of enamine **162** proceeded quantitatively in under four hours and **162** was stable as long as the reaction temperature was maintained at 0 °C (NMR in Appendix 5.3.1). This result suggested that it was the alkylation / cyclisation step that was causing the low yields of bicycle **149**.

Efforts were made to isolate and characterise the unwanted side products being formed to gain a better understanding of the problem. By comparison of the ^{1}H-NMR spectrum of the crude reaction mixture with the literature the first side product to be identified was acrylate **163**, resulting from conjugate addition of pyrrolidine to bromoacrylate **50** (Scheme 2.12).[151]



Scheme 2.12 *Annelation side product formation*

The formation of **163** reduces the amount of acrylate **50** available for alkylation, so the equivalents of acrylate relative to enamine **162** were increased from 1:1 to 1.3:1. Interestingly this increase resulted in none of the desired product being formed and instead led to the isolation of two additional diastereomeric side products **166** and **167** (Scheme 2.13).



Scheme 2.13 *Dialkylation side product formation*

Dialkylation products **166** and **167** are almost identical by ^{1}H-NMR, with the only major difference being the two acetal signals. *Trans*-product **166** is C_2-symmetric meaning that the acetal protons are equivalent by symmetry and therefore give a 2H singlet in the ^{1}H-NMR spectrum (Scheme 2.13). The *cis* configuration in *meso*-product **167** differentiates the two faces of the cyclohexanone, meaning the acetal protons are no longer equivalent, which results in a pair of 1H doublets being observed (Figure 2.2b). These products were not present in the

^{1}H-NMR of the crude reaction mixture, so it was therefore deduced that they were forming from enamine **165** which was hydrolysing on the column and causing the previously observed streaking in the purification of **149** (Scheme 2.13). To prevent this the crude product was dissolved in dichloromethane and stirred with silica for four hours, followed by evaporation of the solvent to give a "dry-load" for column chromatography. This ensured that enamine **165** was fully hydrolysed prior to purification which resulted in a much cleaner column and increased recovery of ketone **149**.

The formation of these dialkylation side products implies that the rate of cyclisation (Scheme 2.13, k_1) is slow relative to the rate of secondary alkylation (k_2). Double alkylation was not observed in the synthesis of dimethyl acetal **51** and orthoacetal **53** under the standard conditions. This suggests this second intermolecular alkylation to form **165** occurs as a result of decreased steric hinderance in intermediate enamine **164** for the methylene acetal. Several strategies were attempted to reduce the proportion of dialkylated products **166** and **167**, the results of which are summarised in Table 2.2 (key NMR peaks highlighted in Figure 2.2).

Table 2.2 *α,α'-Annelation optimisation*

Entry	*eq.* ***162***	*eq.* ***50***	*Addition Time*	*Conc.*	*Temp.*	*Reaction Time*	*Cyclisation : dialkyation**	*Yield* ***149***
1	1	1	5 min	0.2 M	0 °C → rt	18 h	0.7:1	6%
2	1	1	5 min	0.1 M	0 °C → rt	18 h	0.6:1	9%
3	1.25	1	5 min	0.2 M	0 °C → rt	18 h	4:1	9%
4	1.25	1	1 h	0.2 M	0 °C → rt	18 h	4:1	22%
5	1.25	1	1 h	0.2 M	60 °C	18 h	2:1	19%
6	1.25	1	6 h	0.2 M	0 °C → rt	18 h	2:1	7%
7	1.50	1	1 h	0.2 M	0 °C → rt	18 h	6:1	14%
8	1.75	1	1 h	0.2 M	0 °C → rt	18 h	16:1	30%
9	2	1	1 h	0.2 M	0 °C → rt	18 h	13:1	19%
10	1.50	1	1 h	0.2 M	0 °C → rt	48 h	10:1	33%
11	1.50	1	1 h	0.2 M	0 °C → 40 °C	48 h	30:1	45%

****** Ratio determined by the relative ^{1}H-NMR integrations of the acetal C–H in the cyclised product **149** and the dialkylated products **165**, **166** and **167**.*

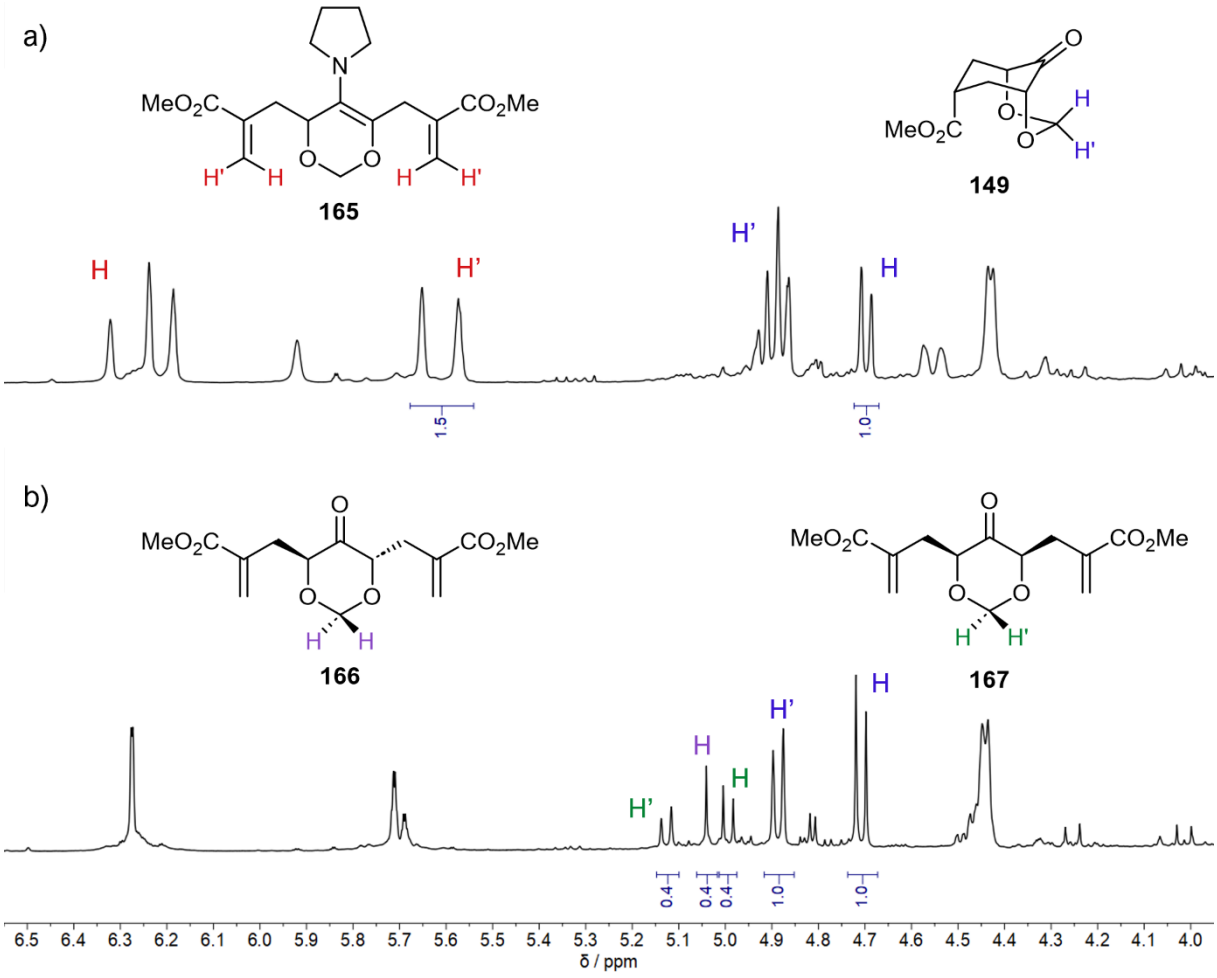


Figure 2.2 *Key ^{1}H-NMR peaks for determining ratio of dialkyation to cyclisation*

Dilution of the reaction in an attempt to favour intramolecular reaction had negligible effect (Table 2.2, Entry 2). Further dilution may have been more effective, but as the step is early in the synthesis and the reaction needs to be performed on a large scale, concentrations of less than 0.1 M were avoided.

Performing the reaction with an excess of enamine **162** (i.e. equal excess of dioxanone **149** and pyrrolidine) showed promise in terms of the ratio between double alkylation and cyclisation (Table 2.2, Entry 3) but the effect on isolated yield was minimal. Slow addition of acrylate **50** to the reaction was then investigated in an attempt to reduce the effective concentration of acrylate and favour cyclisation (Table 2.2, Entries 4 – 6). This showed an increase in yield when

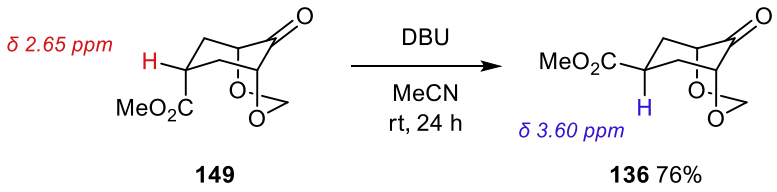
added over one hour, but addition over six hours drastically reduced the yield. Increasing the temperature to 60 °C to favour cyclisation also had a negative effect (Table 2.2, Entry 5).

Using the improved addition time of one hour, further investigation into the enamine equivalents found an optimum ratio of 1.75:1 (Table 2.2, Entries 9 – 11). When the reaction was scaled up, 1.5 equivalents of enamine **164** was found to be sufficient and was more economic in terms of the amount of dioxanone used.

For the reaction time, it was not possible to monitor conversion of enamine to monoalkylated product to cyclised product by TLC so the initial reaction time of 18 hours was set based on success of the previous dioxanone annelations. *In situ* NMR reaction monitoring of the cyclisation step revealed that product formation was slower than anticipated, with enamine being completely consumed after six hours but mono-alkylation signals still being present up to 48 hours into the reaction. In light of these observations the reaction time was increased to 48 hours which increased the yield to 33% (Table 2.2, Entry 10). This result was more consistent in yield with the other annelations so further optimisations were temporarily abandoned in favour of investigations into the reactivity of ketone **136**. Serendipitously the reaction was then performed on a day in the summer where the lab temperature exceeded 35 °C and this gave a further increase in yield from 33% to 45%. Pleasingly this result was repeated when the reaction was performed using a heating mantle to maintain a constant temperature of 40 °C after the addition of acrylate **50** (Table 2.2, Entry 11) to give the final optimised conditions for the annelation of **149**.

Thankfully, optimisation of the epimerisation of axial ester **149** was found to be more straightforward (Scheme 2.14). The reaction was initially performed using the same conditions as the previous epimerisations (65 °C) to give **136** in a disappointing yield of 41% (Scheme 2.14).[49]

The reaction was found to be significantly faster for methylene acetal **149** than for the previous analogues so the reaction was repeated at room temperature. This resulted in a much cleaner reaction and equatorial ester **136** was isolated in 76% yield. This epimerisation was confirmed by a characteristic ^{1}H-NMR shift of the α proton from 2.65 ppm (equatorial C–H in **149**) to 3.60 ppm (axial C–H in **136**).

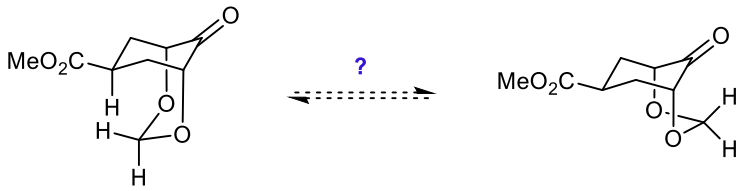


149 **136** 76%

Scheme 2.14 *Epimerisation of axial ester* ***149***

2.1.2 – CONFORMATIONAL ANALYSIS OF BRIDGED BICYCLIC KETONES

Once bicycles **149** and **136** had been synthesised, investigation into their conformational behaviour was undertaken. As discussed in Chapter 1.4 it was hoped that switching the dimethyl acetal in **51** with a methylene acetal would allow ring inversion to occur, alleviating the steric crowding around the ketone, therefore making it more susceptible to nucleophilic addition (Scheme 1.37).



136a chair-chair **136b** chair-boat

Scheme 2.15 *Possible conformations of bicyclic ketone* ***136***

2.1.2.1 – X-RAY CRYSTAL STRUCTURES

X-ray crystal structures of both **149** and **136** were obtained, which showed both the axial ester and the equatorial ester to adopt a chair-boat conformation (Figure 2.3).

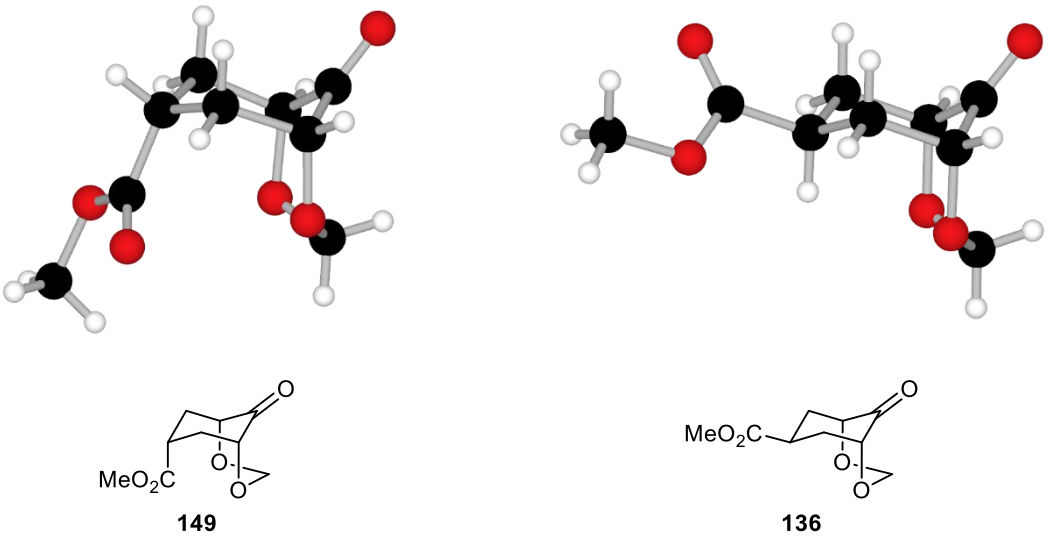


Figure 2.3 *X-ray crystal structures of bicyclic ketones* ***149*** *&* ***136***

Although it was disappointing that the change in acetal did not result in a change in the solid-state conformation, comparison of the crystal structure of methylene acetal **136** with

previously synthesised acetals **54** and **56** shows a clear reduction in steric crowding along the lower face of the ketone (Figure 2.4).[49] As a result, the Bürgi-Dunitz approach angle for bottom face addition is less hindered in methylene acetal **136**.

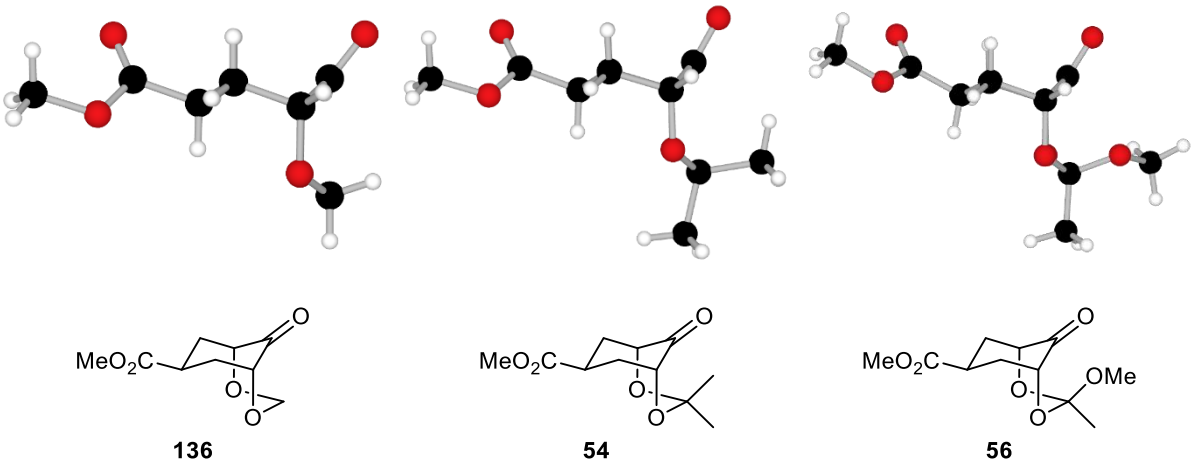


Figure 2.4 *Comparison of the steric crowding around bicyclic ketones*

Additionally, bicycle **136** would be expected to show a smaller barrier to ring inversion as a result of the decreased steric clash between the acetal substituents and the axial C–H in the chair-chair conformation. Therefore the transition state energy for nucleophilic addition should be lower, resulting in a more facile reaction. A similar effect is also observed with axial esters **149** and **51** (Figure 2.5).[49]

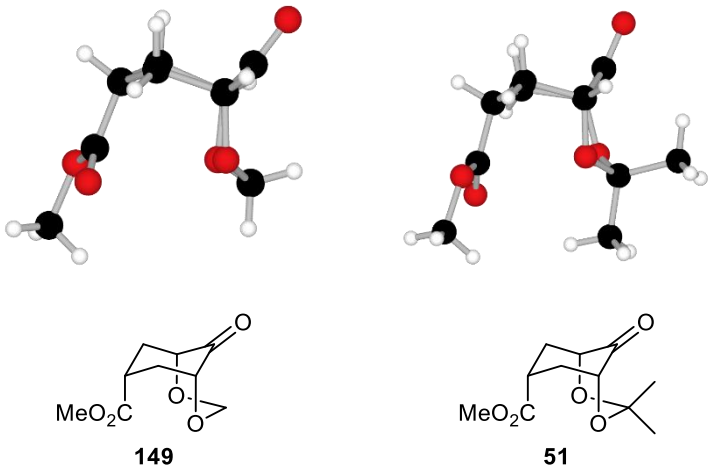
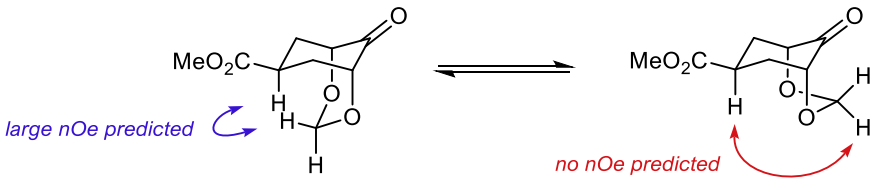


Figure 2.5 *Comparison of the steric crowding around bicyclic ketones*

2.1.2.2 – NMR ANALYSIS

As X-ray analysis only gives information about solid-state conformation, NMR studies were performed to extract information about the solution conformation. It was hoped that if bicyclic ketone **136** adopts a chair-chair conformation in solution, a large nOe would be seen between the acetal C–H and the axial C–H α to the ester (Figure 2.6).



136a *chair-chair* **136b** *chair-boat*

Figure 2.6 *nOe predictions for bicyclic ketone* ***136***

Unfortunately, analysis of the NOESY spectrum of equatorial ester **136** did not provide a clear answer in terms of the in-solution conformation. A small nOe was observed between one of the acetal C–H and the axial α C–H but the magnitude was much smaller than other nOe interactions present, such as that observed between H-3 and H-4_{ax} (Figure 2.7).

As this small magnitude nOe did not provide compelling evidence of the chair-chair conformation, variable temperature NMR experiments were performed in order to further probe the conformation of bicycles **149** and **136**. It was hoped that one of two situations would be observed:

1) At room temperature only the chair-boat conformation is present and heating of the sample provides sufficient energy for ring inversion to occur, causing broadening of the peaks.
2) At room temperature ring inversion occurs faster than the NMR timescale and the NMR spectrum represents an average of the two conformations. Upon cooling, this inversion slows relative to the NMR timescale resulting in broadening of the peaks, and eventually resolution of the peaks into two sets of signals.

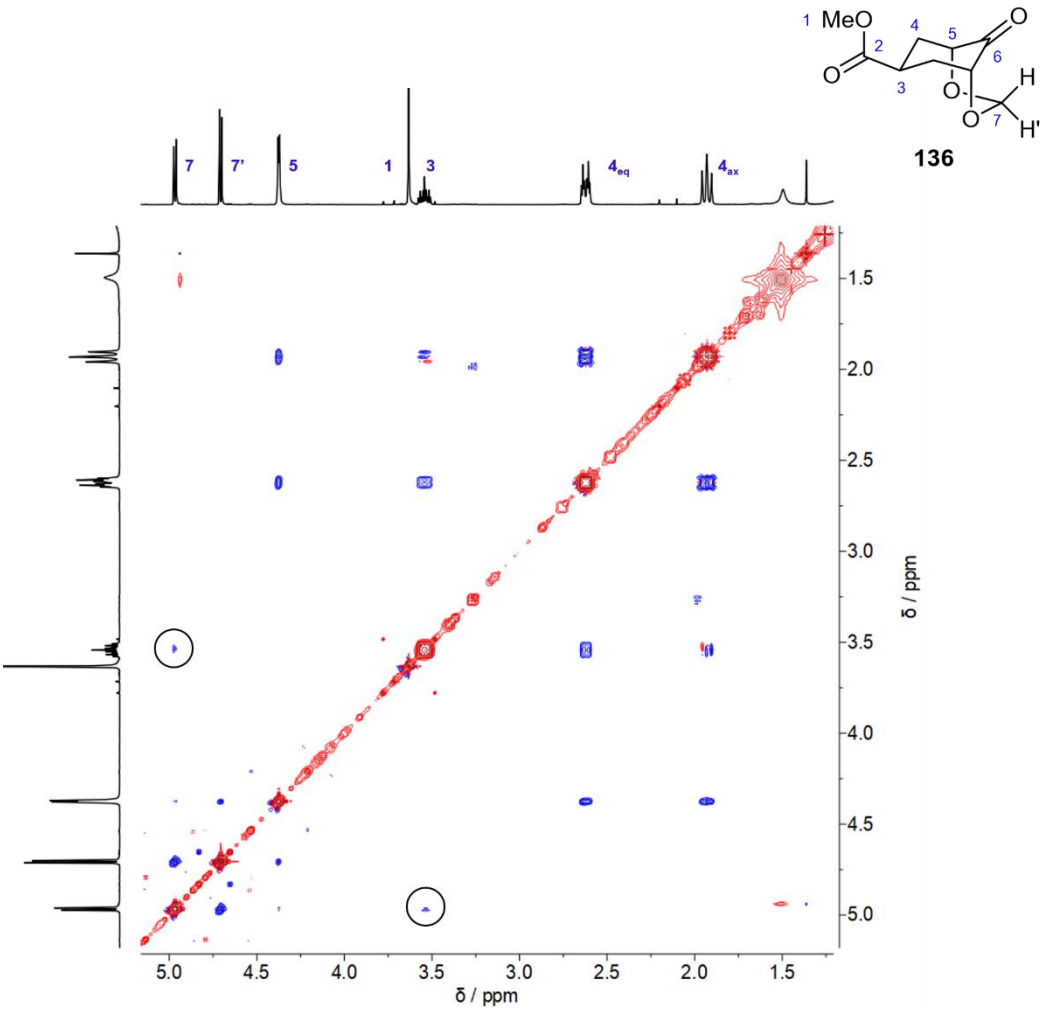
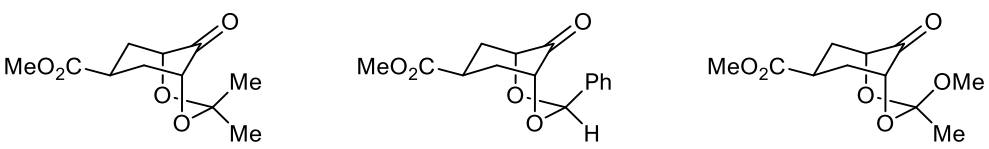


Figure 2.7 *NOESY spectrum of bicyclic ketone* ***136*** *with key nOe circled*

Previous low temperature VT-NMR experiments showed no change for bicyclic ketones **54**, **55** and **56** at low temperatures (Figure 2.8), so high-temperature NMR experiments were performed on methylene acetal **136** first.[49,50] Ramping of the temperature up to 100 °C was shown to have little effect on the ^{1}H-NMR spectra of equatorial ester **136**.



54 **55** **56**

Figure 2.8 *Bicyclic ketones* ***54, 55*** *&* ***56***

On the other hand, gradual cooling of the sample to –30 °C showed some interesting effects, with clear broadening of the peaks being observed at −20 °C (Figure 2.9).* This suggests that ring inversion is occurring at room temperature, with the rate of inversion relative to the NMR timescale slowing as the temperature was dropped. This in turn implies that both the chair-boat and chair-chair conformations of bicyclic ketone **136** are present at room temperature.

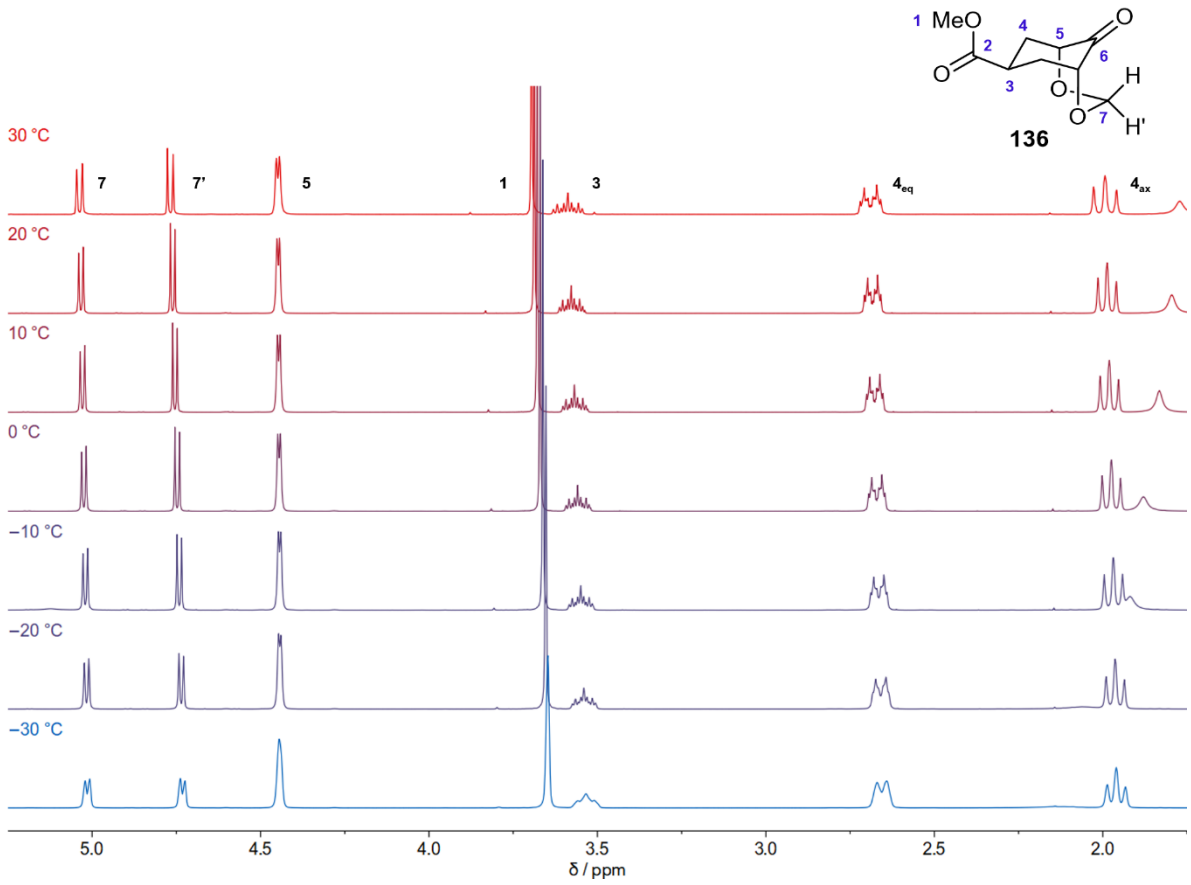


Figure 2.9 *VT-NMR of bicycle* ***136*** *(500 MHz, TCE-d_2)*

While these VT-NMR results seem promising, the observed peak broadening may have been caused by the increased viscosity of TCE-d_2 when measuring spectra at temperatures close to its freezing point of −44 °C. In order to gain a clearer perspective, the experiments would need to be repeated using an NMR solvent with a lower freezing point. Although further low

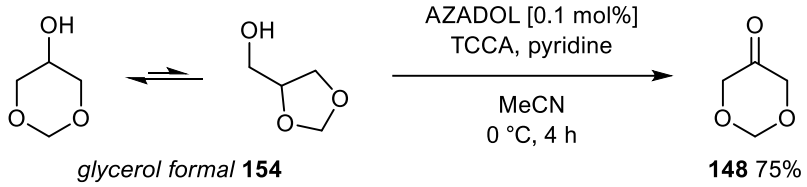
* *Due to a fault with the NMR spectrometer probe, temperatures below −30 °C could not be tested.*

temperature NMR experiments could have helped confirm this hypothesis, the focus remained on the reactivity of these bicycles and is discussed in Chapter 2.2.

2.1.3 – CONCLUSIONS

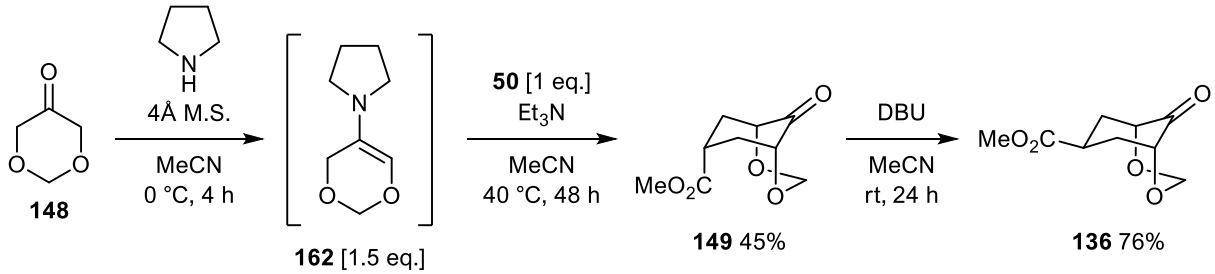
In Chapter 2.1 routes towards bicyclic ketone **136** were investigated to determine if a less bulky acetal could overcome the lack of reactivity of previously investigated ketones towards nucleophilic addition.

Despite frustrating early attempts, methylene dioxanone **148** was successfully synthesised on 20 g scale by the oxidation of glycerol formal **154** using a combination of catalytic AZADOL and TCCA as a stoichiometric oxidant.



Scheme 2.16 *Succesful synthesis of 1,3-dioxan-5-one **148***

Initially the α,α'-annelation proved a little more challenging than previous analogues, with substantial amounts of the dialkylated products being formed, but successful reaction was achieved after re-optimisation of the reaction conditions to give axial ester **149** in 45% yield. Subsequent base-mediated epimerisation gave equatorial ester **136**, with the stereochemical array required for synthesis of phyllaemblic acid.



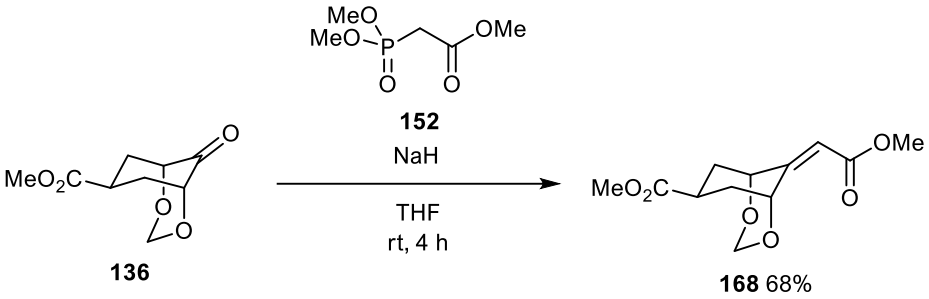
Scheme 2.17 *Synthesis of equatorial ester **136***

The results in Chapter 2.1.2 indicate that ketone **136** should be more susceptible to nucleophilic addition, with π-facial selectivity determined by electronic effects rather than sterics. X-ray analysis of *meso* bicycle **136** showed reduced steric crowding around the ketone in the chair-boat conformation, and low-temperature NMR experiments suggest that the less sterically hindered chair-chair conformation is accessible in solution.

2.2 – REACTIVITY OF METHYLENE BRIDGED BICYCLIC KETONES

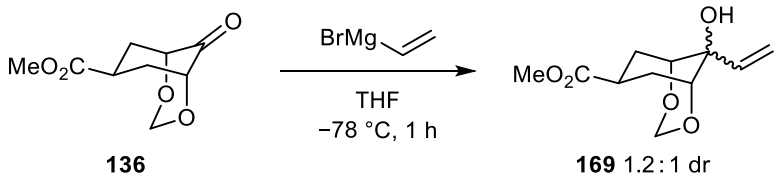
2.2.1 – INTRODUCTION

With the aim of comparing the reactivity of ketone **136** to previously synthesised bicyclic ketones, several test reactions were performed. Firstly a Horner-Wadsworth-Emmons reaction was attempted with trimethyl phosphonoacetate **152**, which was successful to give **168** in 68% yield (Scheme 2.18).[152]



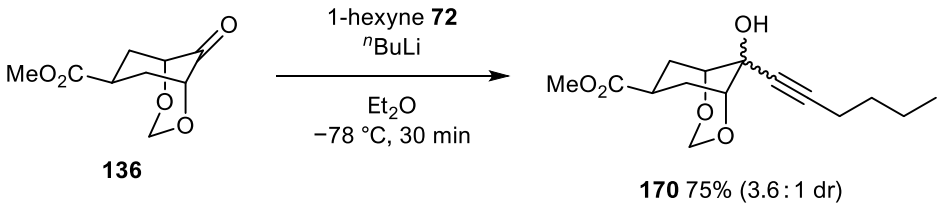
Scheme 2.18 *Horner-Wadsworth-Emmons reaction of ketone* ***136***

Addition of vinylmagnesium bromide was also effective, showing full consumption of starting material to give tertiary alcohol **169** as a 1:1 mixture of diastereomers (Scheme 2.19).



Scheme 2.19 *Grignard addition to ketone* ***136***

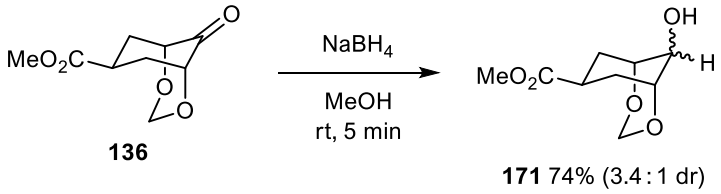
Hexyne addition was attempted using the equatorial selective conditions from Takikawa's pseudohygrophorone synthesis (Scheme 2.20).[113]



Scheme 2.20 *Acetylide addition to ketone* ***136***

Reaction was observed even at −78 °C and propargyl alcohol **170** was isolated in 75% yield as a 3.6:1 mixture of diastereoisomers.

Chemoselective reduction of ketone **136** using sodium borohydride was also attempted, giving secondary alcohol **171** in 74% yield with diastereomeric ratio similar to that of the alkyne addition (Scheme 2.21).

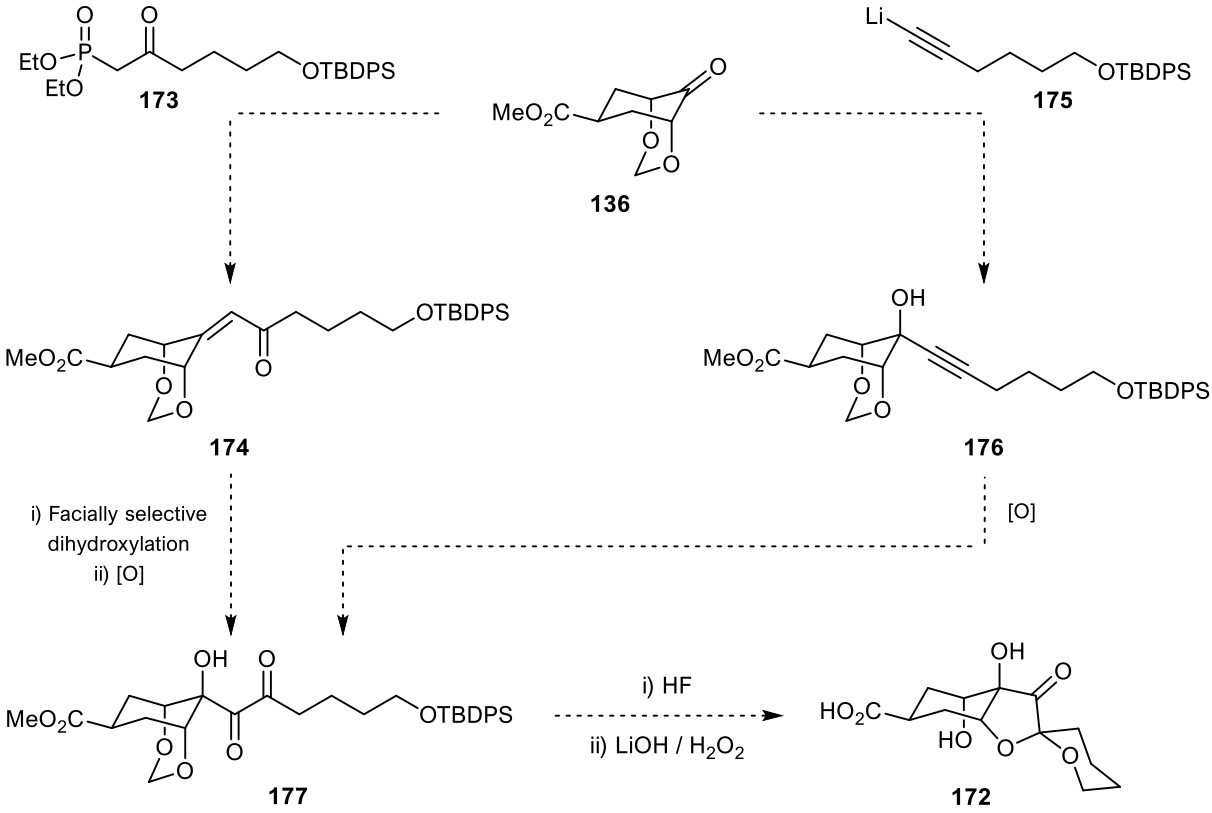


Scheme 2.21 *Reduction of ketone* ***136***

While it was not yet possible to determine the diastereoselectivity of these additions, these test reactions confirm the hypothesis that methylene bridged ketone **136** has much higher reactivity than previous analogues, which all failed to react under similar reaction conditions (Chapter 1.2.3.2). Routes towards installing the diketone component could now be investigated. To assess the feasibility of the total synthesis of phyllaemblic acid **1** from ketone **136** (Figure 2.10), model compound **172** was chosen as the initial target.

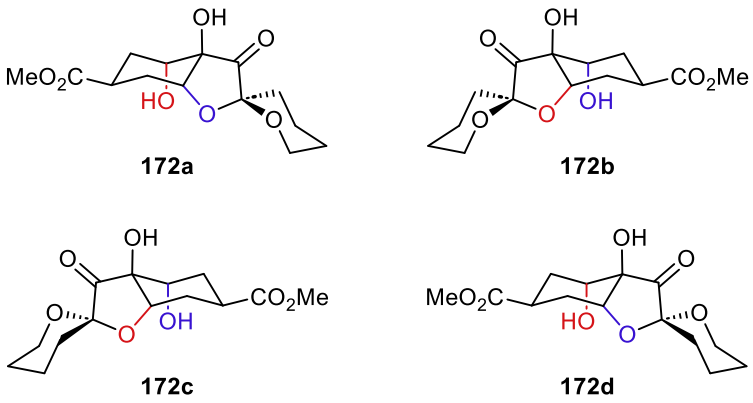
Figure 2.10 *Model compound* ***172***

Based on the successful test reactions two main routes to model compound **172** were investigated: Horner-Wadworth-Emmons olefination followed by enone oxidation; and acetylide addition followed by oxidation to diketone **177** (Scheme 2.22). Spiroacetalisation could then be achieved using Burke's conditions (Scheme 1.4) to give **172**.



Scheme 2.22 *Proposed synthesis of model compound* ***172*** *from ketone* ***136***

Similar to spiroacetal **43** (Figure 1.14) the favoured conformation of model compound **172** is likely the one in which the furanone oxygen is axial as a result of anomeric stabilisation. However as **172** lacks substituents on the six-membered ring of the spiroacetal, both axial hydroxy groups are equally likely to participate to give two pairs of enantiomeric products: **177a**/**177b** and **177c**/**177d** (Scheme 2.23).

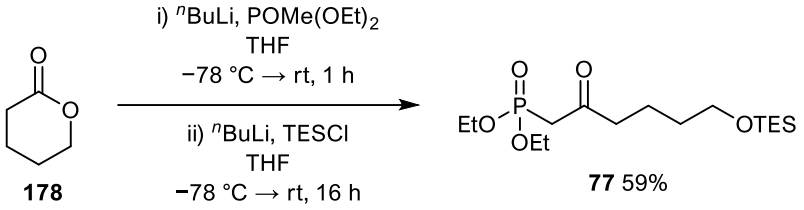


Scheme 2.23 *Potential spiroacetalisation products from diketone* ***177***

2.2.2 – HORNER-WADSWORTH-EMMONS APPROACH

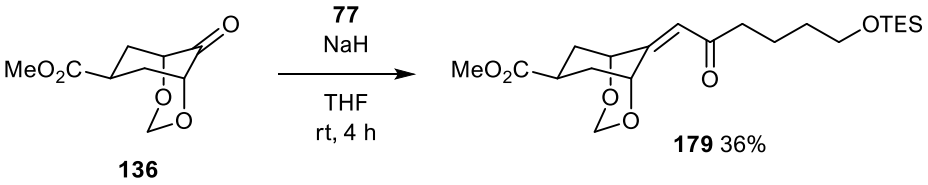
2.2.2.1 – ENONE SYNTHESIS

To test the feasibility of the enone approach towards model compound **172**, phosphonate **77** was synthesised from δ-valerolactone **178** *via* lactone ring-opening and *in situ* TES-protection (Scheme 2.24).[50]



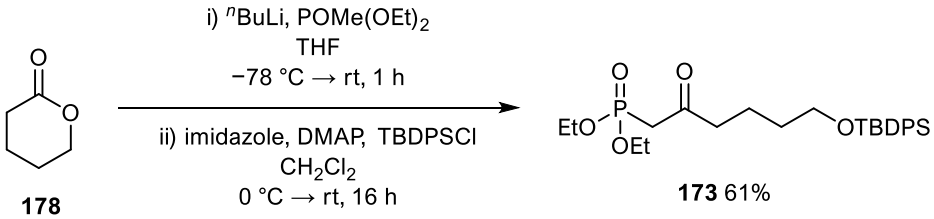
Scheme 2.24 *Synthesis of TES-protected phosphonate* ***77***

Pleasingly the success of the test HWE olefination was repeated when using TES phosphonate **77**, albeit in a disappointing yield of 36% (Scheme 2.25).[152]



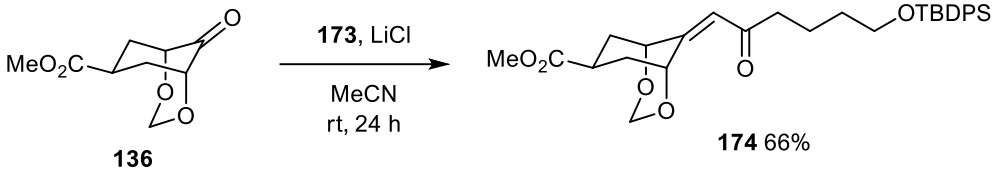
Scheme 2.25 *Synthesis of TES-protected enone* ***179***

When attempting to functionalise enone **179** in later steps the TES-protecting group was found to be labile, so TBDPS phosphonate **173** was prepared as a more stable alternative. The method used to prepare TES-protected phosphonate **77** initially failed, but changing the conditions to a two-step process using standard silyl protecting conditions gave TBDPS-protected phosphonate **173** in 61% yield (Scheme 2.26).



Scheme 2.26 *Synthesis of TBDPS-protected phosphonate* ***173***

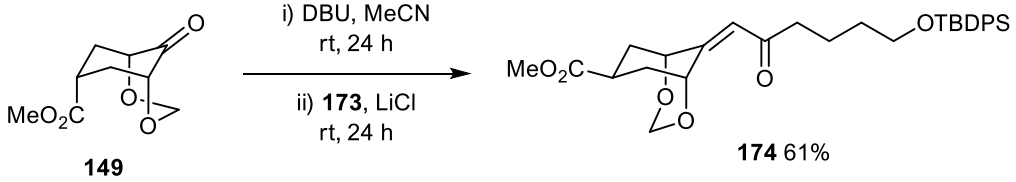
As the yield of TES enone **179** was initially disappointing, alternative milder conditions were considered. The Masamune-Roush conditions of using LiCl and DBU in acetonitrile presented an opportunity to streamline the synthesis as these conditions are near-identical to the conditions used for the epimerisation of axial ester **149**.[153] Firstly these conditions were tested on equatorial ester **136**, giving an improved yield of 66% (Scheme 2.27).



Scheme 2.27 *Synthesis of TBDPS-protected enone* ***174***

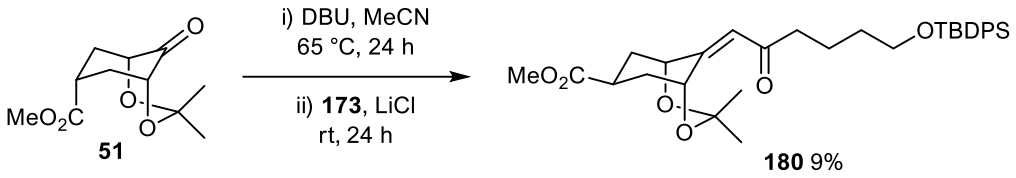
Combining the Masamune-Roush conditions with the epimerisation was then investigated. Initially phosphonate **173** was added at the start, as it was assumed that axial ester **149** would be less reactive towards olefination than equatorial ester **136**. This was not the case and a mixture of ester epimers of enone **174** was isolated.

Delaying the addition of phosphonate **173** until the epimerisation was complete resolved this issue and gave enone **174** in 61% yield *via* a two-step, one-pot process (Scheme 2.28). This was an improvement over the combined yield of the two sperate steps (50%) as well as removing the additional purification step.



Scheme 2.28 *Synthesis of TBDPS-protected enone* ***174*** *via a one-pot epimerisation/HWE*

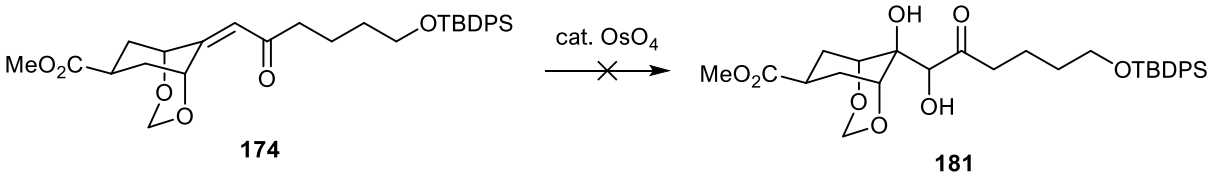
Interestingly these optimised conditions also worked on dimethyl acetal **51,** which previously failed to react in Horner-Wadsworth-Emmons olefination reactions, although the yield was poor.[50]



Scheme 2.29 *Synthesis of dimethyl acetal enone* ***180***

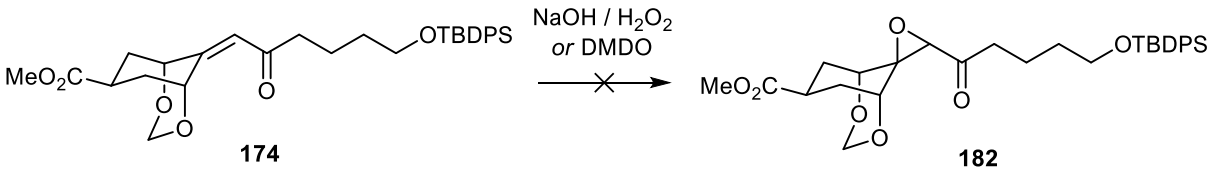
2.2.2.2 – ENONE OXIDATION

With enone **174** in hand, attention turned to the synthesis of spiroacetalisation precursor **177** (Scheme 2.22). Initial attempts at dihydroxylation of enone **174** were unsuccessful, with no reaction being observed using either Upjohn or Sharpless catalytic OsO_4 conditions (generated *in situ* from $K_2[OsO_2(OH)_4]$, Scheme 2.30).



Scheme 2.30 *Attempted dihydroxylation of enone* ***174***

After the failed attempts at dihydroxylation, efforts then turned to the epoxidation of enone **174** (Scheme 2.31). The use of alkaline hydrogen peroxide for the epoxidation of electron deficient alkenes such as enones is well established, but after 24 hours the only observed reaction was partial removal of the TBDPS protecting group.[154]

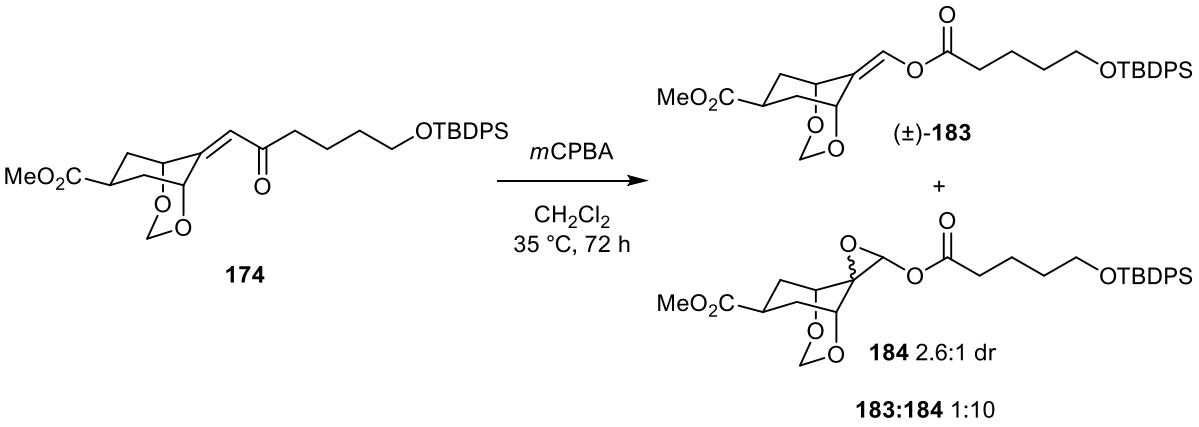


Scheme 2.31 *Attempted epoxidation of enone* ***174***

DMDO has also been reported as a method of epoxidizing enones, but treatment of enone **174** with DMDO failed to produce the desired product.[155] While the reaction outcome was not immediately obvious, there was complete loss of the acetal C-H signals in the ^{1}H-NMR and the

IR spectrum showed a large OH peak which suggests deprotection may have occurred. This is consistent with reports of DMDO-mediated deprotection of benzylidene acetals.[156]

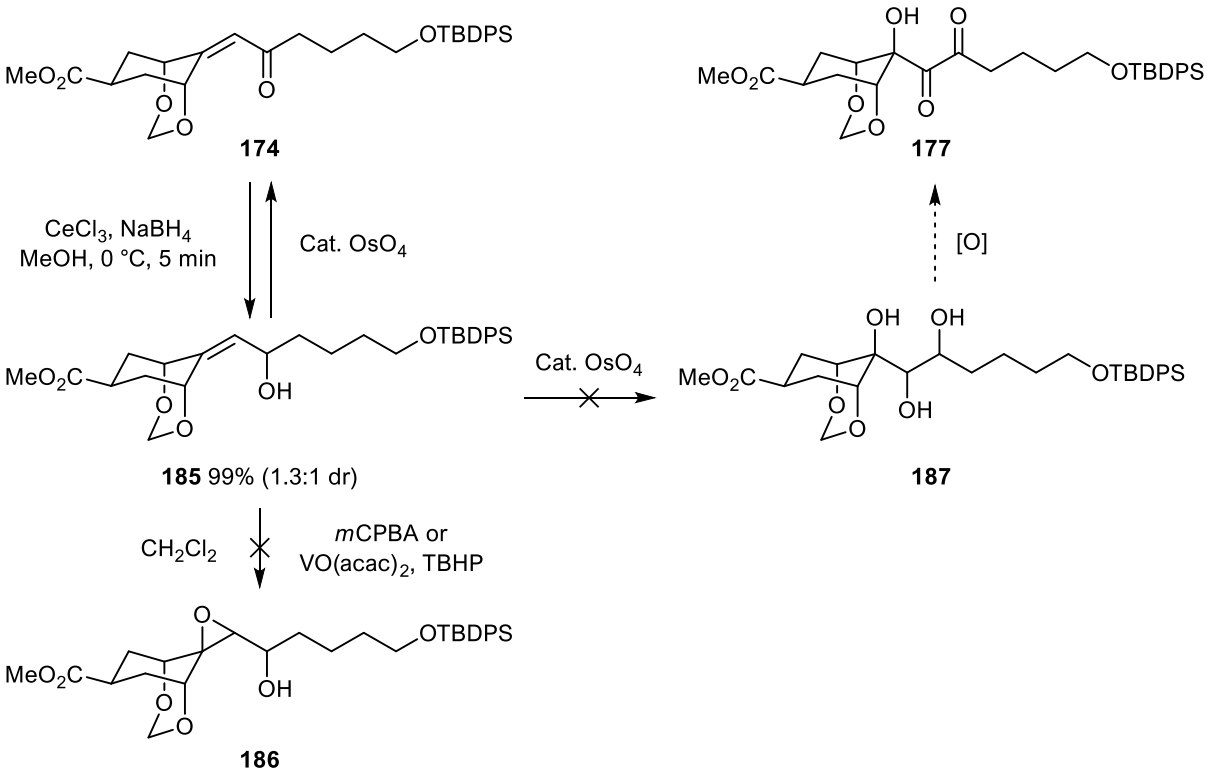
The final attempt at epoxidation of enone **174** was using *m*CPBA, a reagent which typically only reacts with electron rich alkenes, although there are a handful of reported examples where the epoxidation of electron poor enones was successful.[157] Unfortunately this failed to deliver the desired epoxide **182** and only resulted in a mixture of ester **183** and epoxide **184** after 48 hours as a result of a Baeyer-Villiger oxidation followed by partial epoxidation (Scheme 2.32). This transformation was unsurprising, as similar transformations have previously been documented.[158]



Scheme 2.32 *mCPBA induced Baeyer-Villiger oxidation & epoxidation of enone* ***174***

As the functionalisation of electron poor enone **174** was proving difficult, a Luche reduction was performed to form allylic alcohol **185** with the hope that removing the conjugation may increase the reactivity of the C=C bond towards electrophilic oxidations (Scheme 2.33). The Luche reduction occurred in quantitative yield, forming an inseparable 1.3:1 mixture of diastereoisomers (determined by ^{1}H-NMR integration of the acetal protons). As the target compound after dihydroxylation and oxidation was diketone **177**, the formation of alcohol diastereomers at this point was not a concern.

While the Luche reduction was successful, attempts at dihydroxylation only resulted in reoxidation back to enone **174** (Scheme 2.33). Epoxidation attempts using both *m*CPBA and $VO(acac)_2$ / TBHP resulted in consumption of starting material, but epoxide **186** could not be isolated from the reaction mixture despite product mass peaks being detected in the LCMS trace.



Scheme 2.33 *Luche reduction of enone **174** and attempted oxidations*

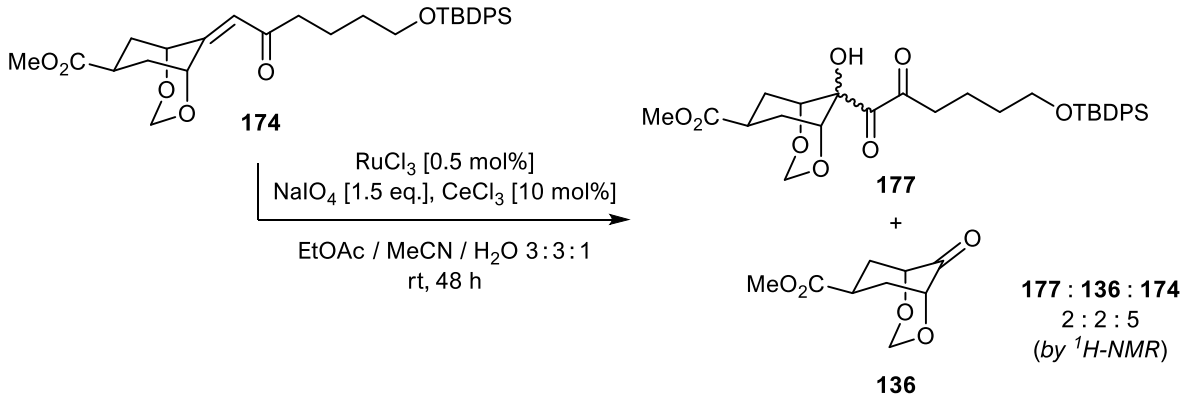
While protection of the alcohol in Luche product **185** may have enabled a successful oxidation, this would have introduced four additional steps to the synthesis (reduction, protection, deprotection and reoxidation) so this idea was disregarded in favour of exploring other oxidation methods.

While osmium tetroxide is the most broadly applied reagent for catalytic dihydroxylations, isoelectronic ruthenium tetroxide has found only limited use for these transformations as its high reactivity tends to result in poor selectivity.[159–161] Ruthenium-catalysed dihydroxylations are also frequently accompanied by undesired side reactions such as fragmentation and

overoxidation of the diol product. The addition of catalytic amounts of $CeCl_3$ has been shown to suppress the rate of these side reactions, allowing for longer reaction times. This in turn allows the dihydroxylation of electron deficient double bonds which could not typically be oxidised under standard conditions.[162]

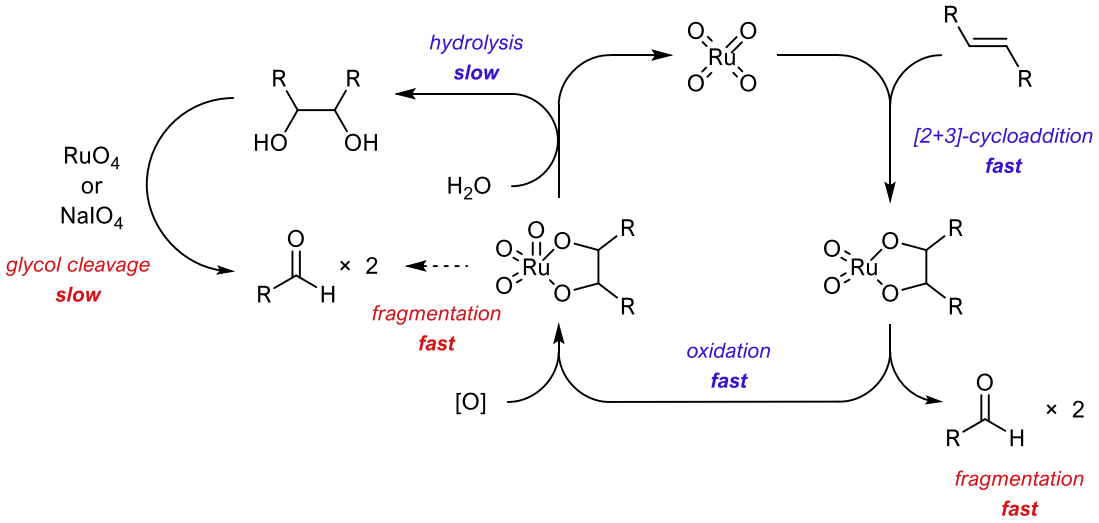
Because the osmium-catalysed dihydroxylation of enone **174** failed and the overoxidation product diketone **177** is ultimately the target compound, RuO_4 was investigated as an alternative method of dihydroxylation.

Literature reaction times for the RuO_4 / $CeCl_3$ bimetallic oxidation system were between 8 and 20 minutes, but application of these conditions to enone **174** produced only trace amounts of product after 24 hours.[162] Increasing the catalyst loading increased the amount of product formation but also resulted in the formation of starting ketone **136** *via* oxidative cleavage (Scheme 2.34).



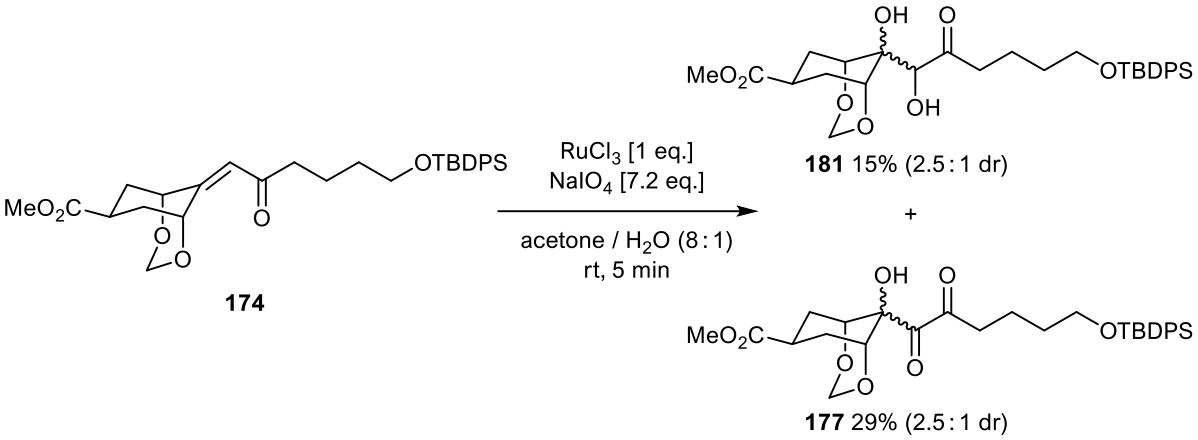
Scheme 2.34 *$RuCl_3$ / $CeCl_3$ / $NaIO_4$ dihydroxylation of enone **174***

This implies that the catalytic turnover rate was slow resulting in an increased amount of electrocyclic fragmentation occurring (Scheme 2.35).[163]



Scheme 2.35 *Proposed mechanism for the formation of dihydroxylation side-products*

In an attempt to counter this, oxidation using stoichiometric amounts of RuO_4 was attempted based on the original dihydroxylation conditions from the steroid literature.[164] This resulted in the successful isolation of diol **181** and overoxidation product **177** alongside unreacted starting material (Scheme 2.36).



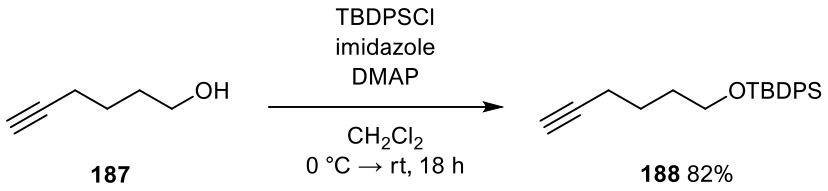
Scheme 2.36 *Stoichiometric RuO_4 dihydroxlayion of enone **174***

Both diketone **177** and hydroxyketone **181** were isolated as a 2.5 : 1 ratio of diastereomers, but the sense of diastereoselectivity could not be determined at this point. Additional equivalents of RuO_4 were added to try and drive the reaction fully to the diketone, but this only resulted in oxidative cleavage back to ketone **136**.

While this oxidation worked on a small scale, the yield of diketone **177** was low (29%) and the results were found to be extremely inconsistent meaning larger quantities could not be prepared. Additionally, the use of stoichiometric amounts of ruthenium is less than ideal for larger scale synthesis, due to both cost and toxicity, so this route was abandoned.

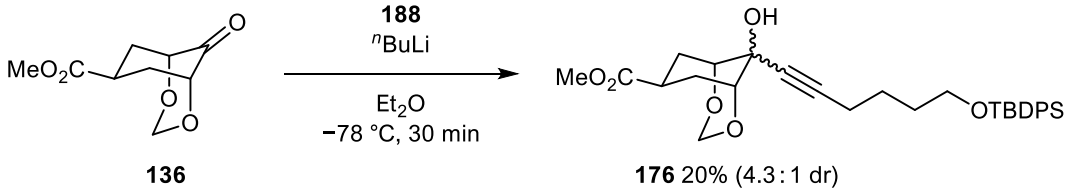
2.2.3 – ACETYLIDE ADDITION

The second route to model compound **172** was *via* acetylide addition and oxidation to spiroacetalisation precursor **177** (Scheme 2.22). To test this route, terminal alkyne **188** was prepared from 5-hexyn-1-ol **187** (Scheme 2.37).



Scheme 2.37 *Synthesis of TBDPS-protected alkyne* ***188***

Addition of lithiated alkyne **188** gave tertiary alcohol **176** in comparable diastereomeric ratio to hexyne addition, although in a lower yield of 20% (Scheme 2.38). While the two diastereomers were not completely separable, the ratio could be enhanced up to ~7:1 through column chromatography.



Scheme 2.38 *Addition of TBDPS-protected alkyne* ***188*** *to ketone* ***136***

The lower yield of TBDPS alkyne **188** compared with hexyne **72** was likely because of instability of the lithiated alkyne formed *in situ*: quenching with D_2O gave highly variable levels of deuterium incorporation, whereas hexyne consistently showed close to complete deuteration.

This instability made it difficult to control the exact stoichiometry of addition, resulting in addition of acetylide to the ester as well as the ketone of bicycle **136** to give **190**, **191**, **192** and **193** as side products (Figure 2.11). Although these products were not directly isolated, they were observed in the LCMS of the crude reaction mixtures and have distinctive sets of acetal C–H signals in the ^{1}H-NMR of the crude reaction mixture.

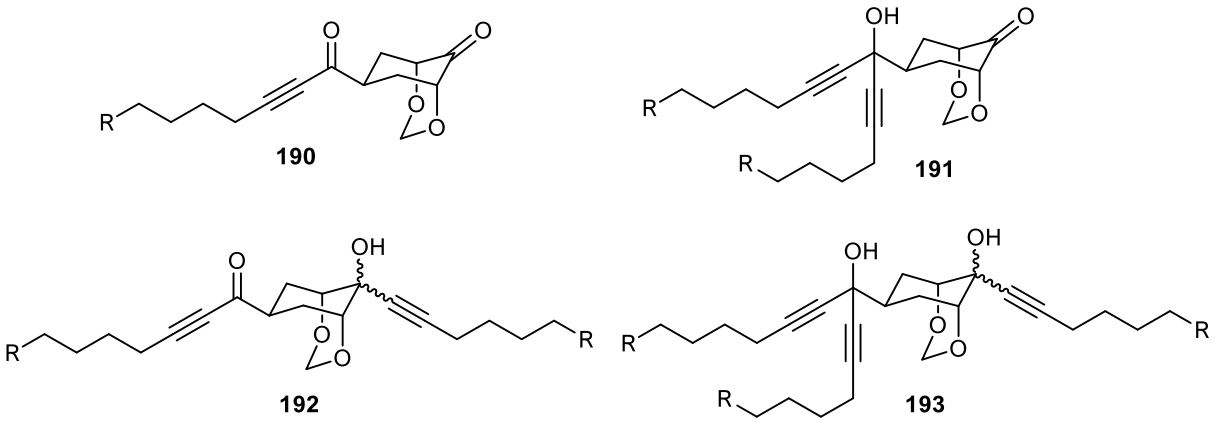


Figure 2.11 *Acetylide addition by-products* ***190*** *–* ***193***

To begin with it was not possible to determine the sense of diastereoselectivity, as key nOe interactions that would help confirm the tertiary alcohol configuration in **176** (such as between acetal C–H and the OH) occurred in regions of the spectra where there were many overlapping signals. Despite this, NOESY analysis did show that both products appear to adopt a chair-chair like conformation, with a large interaction seen between the acetal C–H and the axial α C–H in both products (Figure 2.12).

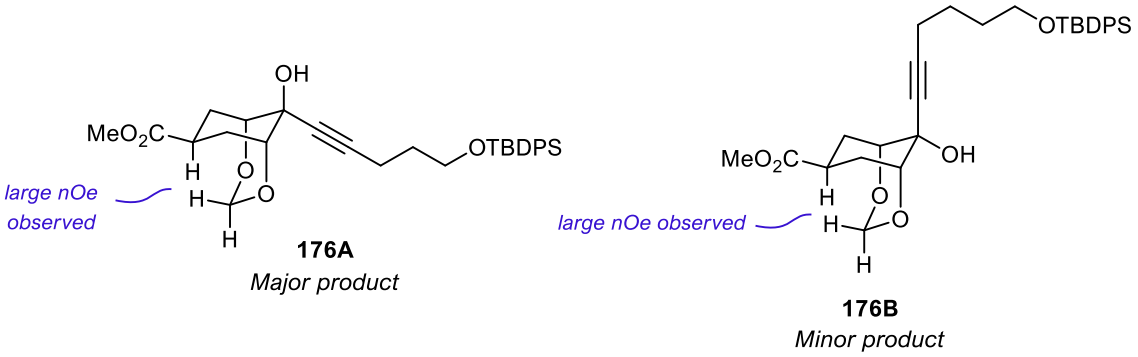


Figure 2.12 *nOe analysis of acetylide addition products* ***176A*** *&* ***176B***

A variety of different conditions were then evaluated with the aim of improving the yield and selectivity of alkyne additions to **136** (Table 2.3).

Table 2.3 *Acetylide addition optimisation*

Entry	*Alkyne*	*Conditions*	*Solvent*	*Temperature*	*Ratio **189**:**190****	*Diastereomer ratio†*
1	**72**	^{n}BuLi	Et_2O	−78 °C	4:1	4:1
2	**188**	^{n}BuLi	Et_2O	−78 °C	8:1†	4:1
3	**72**	^{n}BuLi	Et_2O	−42 °C	2:1	3:1
4	**72**	^{n}BuLi	Et_2O	0 °C	2:1	3:1
5	**72**	^{n}BuLi	THF	−78 °C	**190** only	1:5
6	**72**	^{n}BuLi	Toluene	−78 °C	1:1	2:1
7	**188**	^{n}BuLi, $CeCl_3$	Et_2O	−78 °C	4:1	4:1
8	**72**	EtMgBr	Et_2O	−78 °C	1:2	3:1
9	**188**	KO^{t}Bu (1 eq.)	THF	0 °C	*Degradation*	
10	**188**	KO^{t}Bu (0.2 eq.)	DMSO	23 °C	*No reaction*	
11	**188**	$Zn(OTf)_2$, $^{i}Pr_2NEt$	CH_2Cl_2	23 °C	*No reaction*	

**Ratios estimated based on average of acetal C–H integrals in the ^{1}H-NMR of the crude reaction mixture. Other over addition products were observed in almost all cases, but accurate integration was not possible due to overlapping signals. † Represents best result, ratio was found to be highly variable as a consequence of poor control over reaction stoichiometry.*

Firstly the reaction temperature was increased, but this only resulted in a negligible decrease in the diastereoselectivity and also increased the proportion of ester addition (Table 2.3, Entries 3 and 4).

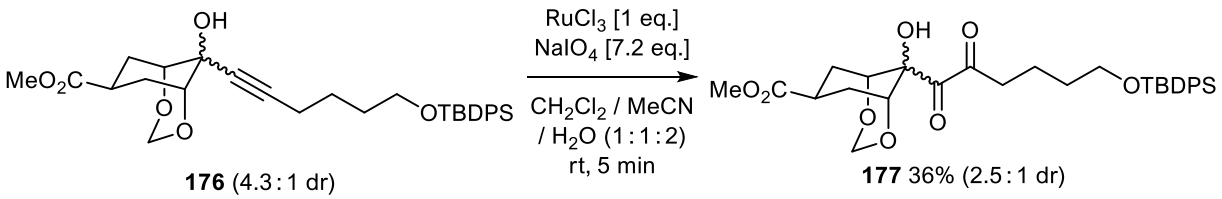
Given the impact solvent can have on π-facial selectivity in nucleophile additions to cyclic ketones (Chapter 1.3.2.2), alternative reaction solvents were tested (Table 2.3, Entries 5 and 6). Replacing Et_2O with THF resulted in a complete inversion of diastereoselectivity, which interestingly mirrors the same switch in selectivity observed in the synthesis of Takikawa's synthesis of pseudohygrophorone (Scheme 1.35).[113] Performing the reaction in toluene resulted in poor selectivity (both chemo and facial).

As it was initially hypothesised that coordination may be a contributing factor to selectivity, different metal bases were tested (Table 2.3, Entries 7 – 11). The less basic organocerium

reagent was prepared by treating the alkynyllithium with $CeCl_3$, but this had little to no effect on the reaction outcome (this was also noted by Takikawa).[113,165] Formation of the alkynyl Grignard using ethylmagnesium bromide had little effect on diastereoselectivity and resulted in a poorly chemoselective reaction, with the major product **190** resulting from addition to the ester only. The use of stoichiometric potassium *tert*-butoxide as the base resulted in an unassignable mixture of products.[166] Catalytic *tert*-butoxide was then tried as a milder alternative, but this failed to produce any reaction.[167] Finally, *in situ* generation of zinc acetylide using $Zn(OTf)_2$ and Hünig's base was attempted, but again only starting materials were recovered.[168]

Based on these failed attempts to improve the addition of hexyne acetylides to ketone **136** it was concluded that the starting conditions (^{n}BuLi, Et_2O, −78 °C) were optimal in terms of both chemo- and diastereoselectivity and attention was turned to the oxidation of the mixture of alkynes **176** to the corresponding diketones **177**.

The use of ruthenium tetroxide was only partially successful due to a rapid oxidative cleavage reaction occurring to reform the original ketone **136**, similar to the side reaction observed during enone dihydroxylation (Scheme 2.36).[55] After just five minutes reaction time a 1:1 mixture of α-hydroxydiketone **177** and ketone **136** was formed (Scheme 2.39). Despite this, diketone **177** was successfully isolated in 36% yield with a diastereomeric ratio of 2.5:1 (starting material 4.3:1).

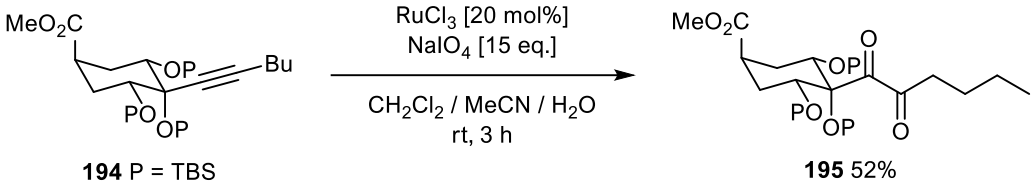


176 (4.3 : 1 dr) **177** 36% (2.5 : 1 dr)

Scheme 2.39 *RuO_4 oxidation of alkyne **176***

Given that formation of starting ketone **136** was also observed as a side reaction in the enone dihydroxylation, the stability of the product to reaction conditions was assessed. Treatment with $NaIO_4$ failed to produce a reaction, but treatment with $RuCl_3$ and $NaIO_4$ resulted in the formation of ketone **136** suggesting the product is unstable to the RuO_4 formed *in situ*. Alkyne oxidation was also attempted using $KMnO_4$ but a significant amount of oxidative cleavage occurred before full consumption of starting material, making it difficult to isolate the desired diketone.

Previous successful alkyne oxidations in the group were performed on a protected tertiary alcohol (Scheme 2.40).[55]

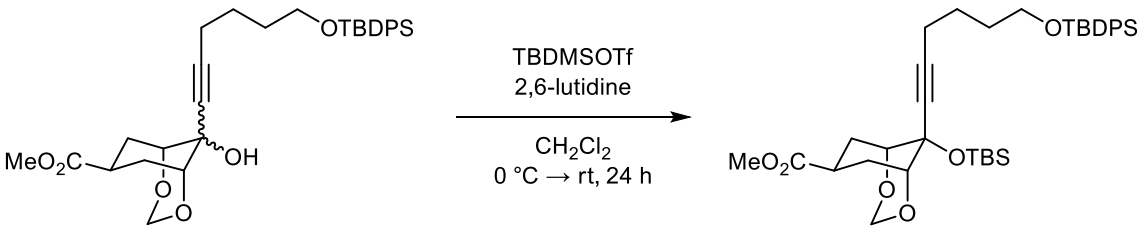


194 P = TBS

195 52%

Scheme 2.40 *RuO_4 oxidation of TBS-protected alkyne **194***

In light of this, attempts were made to protect propargyl alcohol **176** in order to facilitate successful oxidation by suppressing the ability of the starting material to undergo oxidative cleavage (Scheme 2.41). Starting alcohol **176** was used as a 6.5:1 mixture of stereoisomers, so would be expected to give **196** as an equivalent diastereomeric mixture but only one product was isolated upon purification.



176 (6.5:1 dr)

196 5%

Scheme 2.41 *TBS-protection of tertiary alcohol **176***

NOESY experiments (Appendix 5.3.2) provided evidence to suggest the product isolated was the diastereomer arising from axial addition of the alkyne nucleophile. Interaction was seen between one acetal C–H, with the other interacting with both CH_3 environments on the TBS protecting group (Figure 2.13). The latter through space interaction would not be possible if **196** was the opposite diastereomer (axial OTBS), as the acetal and TBS group would be too far apart. The presence of both these interactions also implies rapid conformational switching between the chair-chair and the chair-boat as seen in starting ketone **136**.

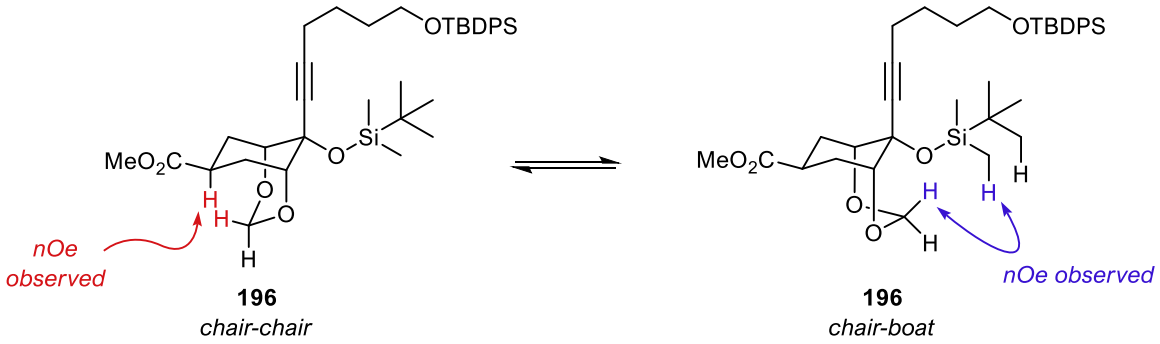
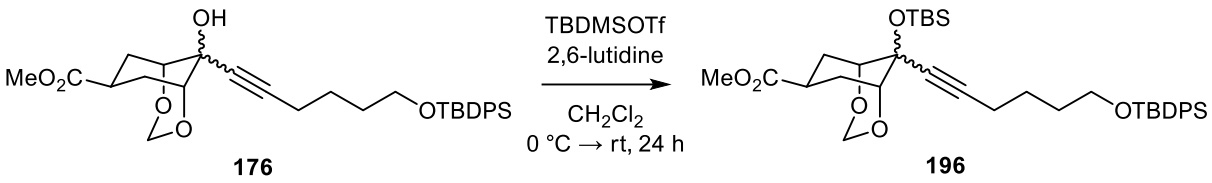


Figure 2.13 *nOe analysis of TBS-protected minor product* ***196***

When comparing the ^{1}H-NMR spectrum of product **196** with that of the reaction mixture it is clear the isolated product was the minor product of the reaction. The major product was not isolated from the column but the crude ^{1}H-NMR spectrum suggests it may be the alternate diastereomer of the isolated product.

The spectrum of this unisolated major product resembles the minor except for one key difference: the uncharacteristically low chemical shift of the methyl CH_3 peak (3.2 ppm compared to the typical 3.6 ppm of the methyl ester). While the cause of this upfield shift is unclear, the ratio of the two products was maintained when the reaction was repeated with a different sample of tertiary alcohol **176** which had been partially purified to have enhanced diastereomeric ratio. This reaction gave the two products in a ratio consistent with that of the starting material (Table 2.4). This further supports the idea that the isolated compound arises from the minor diastereomer of alkyne **176**.

Table 2.4 *Diastereomeric ratios of TBS-protected product* ***196***

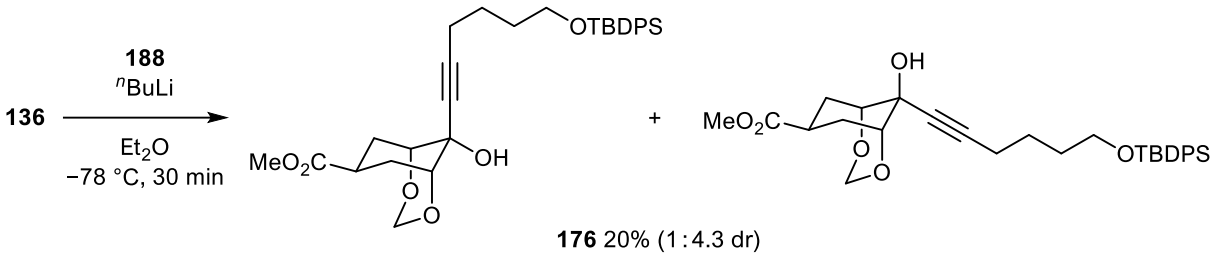


176 **196**

Attempt	*Diastereomeric ratio* ***176****	*Diastereomeric ratio* ***196****
1	6.5:1	4.2:1
2	21:1	15:1

** Determined by integration of acetal C–H signals in ^{1}H-NMR*

Based on the presence of this major product and the nOe interactions observed in the minor product, it was inferred that the selectivity of the initial alkyne addition was 4.3:1 equatorial:axial addition (Scheme 2.42). This is further supported by the selectivity switch between diethyl ether and THF matching the switch in selectivity observed in Takikawa's synthesis of pseudohygrophorone-A[12] (Scheme 1.35).



176 20% (1:4.3 dr)

Scheme 2.42 *Addition of TBDPS-protected alkyne* ***188*** *to ketone* ***136***

While these alkyne addition results were promising, further investigations into isolation of the major product were not able to be conducted due to project time constraints.

2.2.4 – MODEL COMPOUND ROUTE COMPARISON

Once the two diastereomers of diketone **177** prepared by alkyne oxidation had been assigned, the diastereomeric ratio of enone dihydroxylation (Chapter 2.2.2) was then able to be assigned by direct comparison of the ^{1}H-NMR spectra.

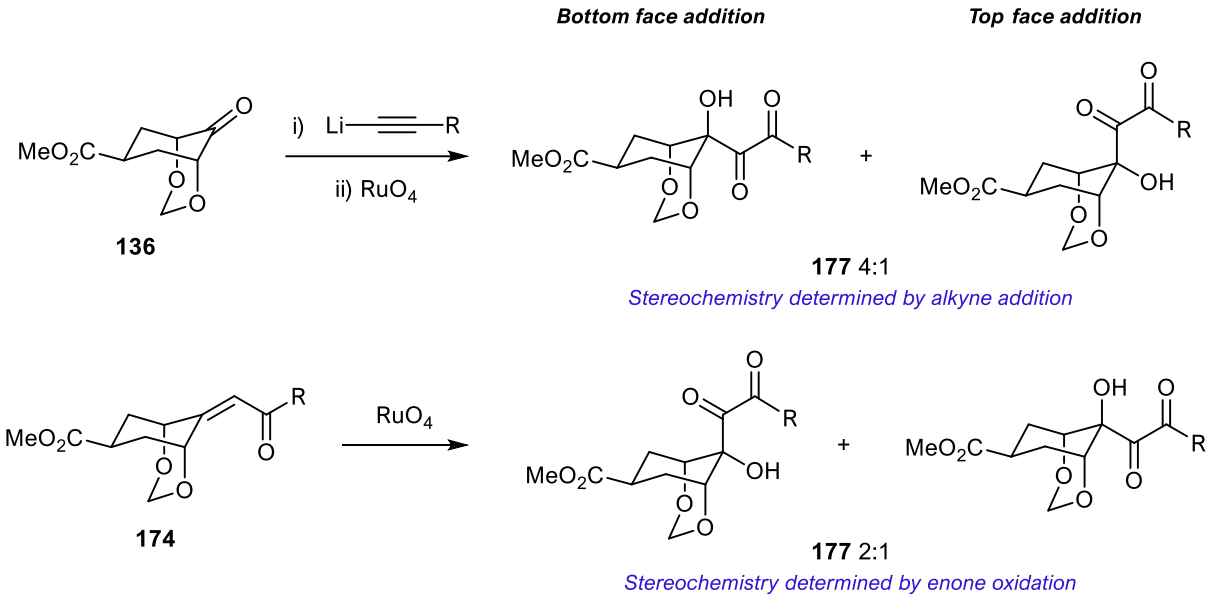


Figure 2.14 *Comparison of diastereoselectivity in the synthesis of diketone* ***177***

This showed that they had opposite diastereoselectivity (Figure 2.14). This means that the major product from the enone route had the incorrect stereochemical array for a total synthesis of phyllaemblic acid, further supporting the decision to abandon this route.

While the two routes give opposite diastereoselectivity, the π-facial selectivity is in fact the same in both (Figure 2.14). In the alkyne route the stereochemistry determining step is the C–C bond formation, which occurs preferentially on the bottom face. On the other hand, in the enone route, the stereochemistry determining step is the C–O bond forming step which again occurs preferentially on the bottom face. This selectivity is consistent with the predictions made in Chapter 1.4 based on the chair-chair conformation.

Given the observed *syn*-selectivity was lower than that observed in related examples (Scheme 1.26 and Scheme 1.29, 100% and 98% respectively), it is likely reaction from the chair-boat conformation is also occurring as this would be expected to favour axial addition due to increased steric hinderance for the desired equatorial addition.

2.2.5 – CONCLUSION

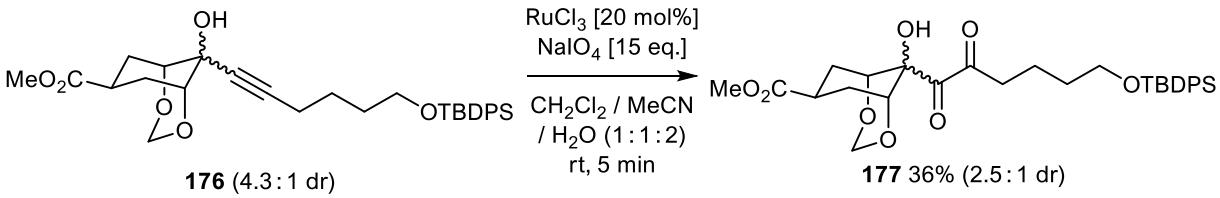
Methylene bridged bicycle **136** offered a significant improvement over previous bicyclic ketones in terms of reactivity towards nucleophiles, and successful reactions were observed with sodium borohydride, Grignard reagents and acetylide anions, as well as under Horner-Wadsworth-Emmons conditions. Based on these successful reactions, the synthesis of model compound **172** was attempted.

Target enone **174** was successfully prepared *via* a Horner-Wadsworth-Emmons olefination, but similar to the ketone in **136**, the reactivity of the enone was low. The only successful oxidation conditions used stoichiometric ruthenium and were not reliable due to the high propensity of the products and / or reaction intermediates to undergo electrocyclic fragmentation reactions.

It is likely that this poor reactivity is a result of the acetal oxygens resulting in an extremely electron poor enone, so the enone route was abandoned and alternative methods of introducing the diketone moiety were investigated.

Addition of TBDPS-protected hexyne **188** gave tertiary alcohol **176** as a 4:1 mixture of diastereoisomers. While absolute proof of the diastereoselectivity was not obtained, the results discussed in Chapter 2.2.3 suggest that these additions occurred with the diastereoselectivity required for the synthesis of phyllaemblic acid (addition *syn* to the acetal). While the cause of this selectivity cannot be proved, the reduction in steric bulk of the acetal undoubtedly plays a part in increasing the reactivity of the ketone, with tertiary products showing clear evidence of the chair-chair conformation, which would not have been possible with the more substituted acetals.

Assuming the tertiary alcohol configuration of alkyne **176** is maintained during oxidation, spiroacetalisation precursor **177** was prepared with the major product having the stereochemical array found in phyllaemblic acid (Scheme 2.43).



Scheme 2.43 *RuO_4 oxidation of alkyne **176***

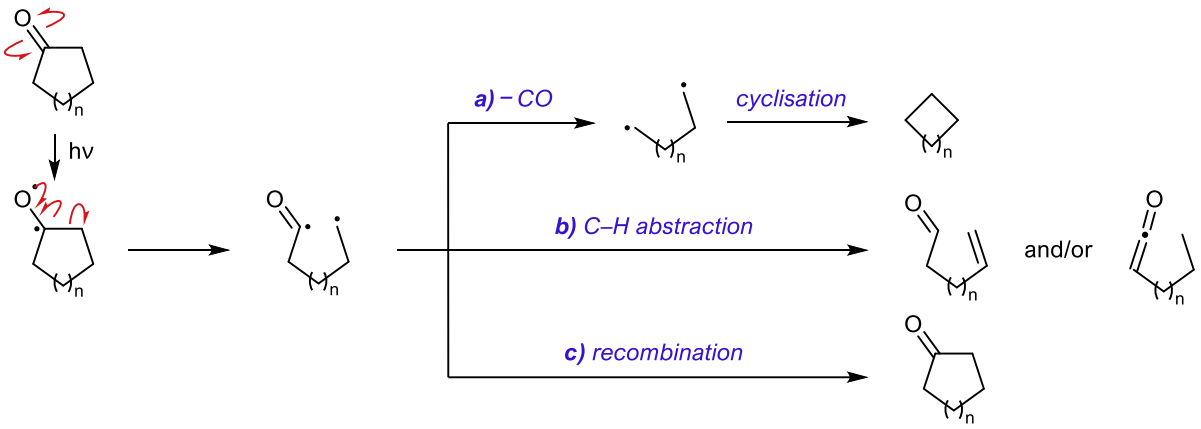
It is clear the alkyne route is better, both in terms of diastereoselectivity and reaction feasibility, and is therefore the best choice for any future work. If the yields of alkyne **176** and diketone **177** could be increased, it would allow for testing of the key spirocyclisation step to form model compound **172** (Scheme 2.22). In the future an alternative protecting group strategy may allow for easier isolation of both alkyne **176** and diketone **177**, as well providing a clearer answer for the stereochemical assignments of the major and minor products.

2.3 – PHOTOMEDIATED APPROACH

2.3.1 – INTRODUCTION

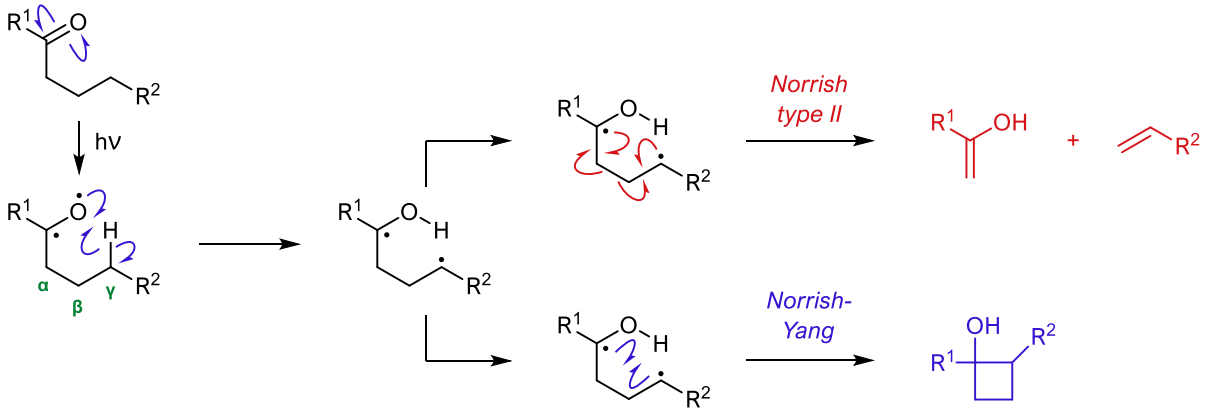
Ketones and aldehydes have long been known to generate diradicals upon photoexcitation.[169] The reactions of these radicals, known as Norrish reactions, are divided into two types based on the outcome of the reaction.[170,171]

In type I Norrish reactions the C–C bond between the carbonyl and α-carbon is homolytically cleaved leading to a pair of radicals (Scheme 2.44).[172] Several reaction pathways are available for the generated radical pair: a) decarbonylation with subsequent cyclisation; b) intramolecular C–H abstraction leading to aldehydes and / or ketenes; and c) recombination.



Scheme 2.44 *Norrish type I reactions*

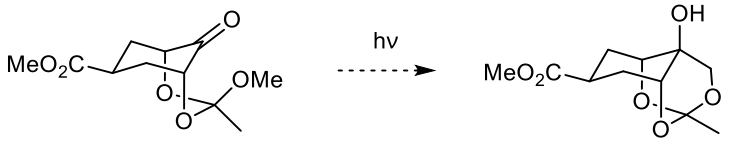
Type II Norrish reactions involve an intramolecular γ-hydrogen abstraction (Scheme 2.45).[172]



Scheme 2.45 *Norrish type II reactions*

The 1,4-diradical that is formed can either undergo fragmentation to produce alkenes and enols or it can recombine to form cyclic alcohols (known as the Norrish−Yang cyclisation).[173]

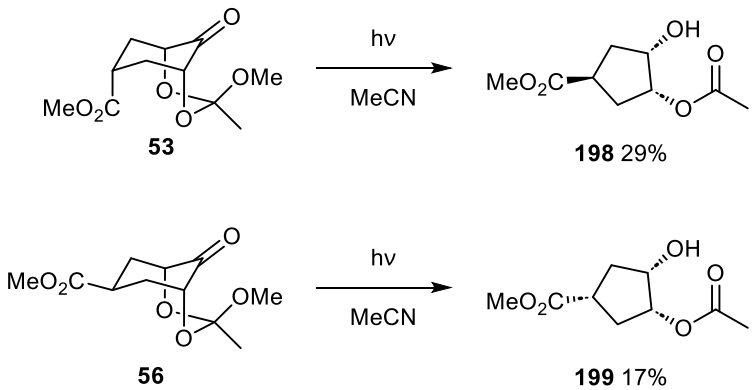
Previous work in the Grainger group attempted a Norrish-Yang type cyclisation using bicyclic ketone **56**. It was thought it may be possible to activate the carbonyl and trigger an intramolecular 1,7 hydrogen atom transfer using the orthoacetal methoxy group (Scheme 2.46). Although less favoured than 1,5 H-atom transfer, successful 1,7 H-atom transfer would have set up the required stereochemistry at the tertiary alcohol.



56 **197**

Scheme 2.46 *Proposed Norrish type II cyclisation of bicyclic ketone* ***56***

Unfortunately, upon photoirradiation there was no evidence of the desired intramolecular reaction. However, interesting stereochemical outcomes were observed in the isolated products (Scheme 2.47). In both cases loss of CO and subsequent cyclisation occurred, indicative of a Norrish type I reaction, but more interestingly epimerisation of the ester appeared to have occurred and the orthoacetal protecting group cleaved. Ultimately, the loss of CO upon irradiation resulted in the decision that a photomediated approach on orthoacetal **56** was not a viable route.[55]



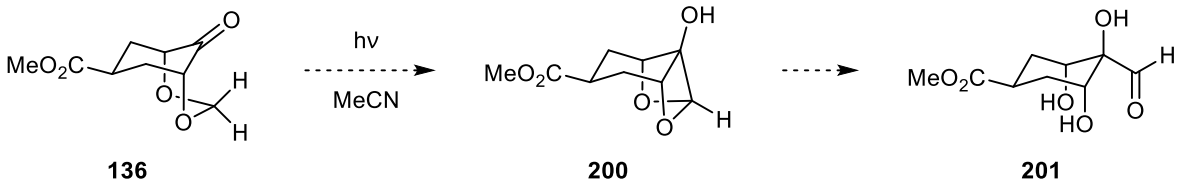
53 **198** 29%

56 **199** 17%

Scheme 2.47 *Attempted photocyclisation of orthoacetals* ***53*** *&* ***56***

2.3.2 – AIM

Although the exact mechanism for the formation of **199** remains unclear, it was hoped that replacing orthoacetal **56** with methylene acetal **136** might affect the reaction outcome. If a type II Norrish-Yang cyclisation could be achieved then the resulting cyclobutanol **200** could be hydrolysed to reveal aldehyde **201** which would function as a handle for further synthesis (Scheme 2.48).

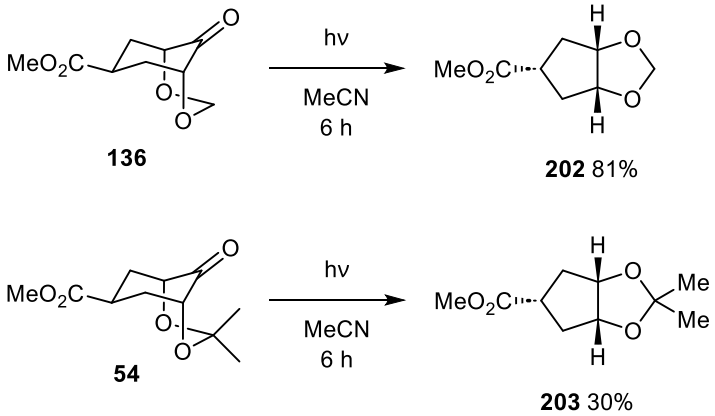


136 **200** **201**

Scheme 2.48 *Proposed Norrish type II cyclisation of bicyclic ketone* ***136***

2.3.3 – RESULTS

Bicyclic ketone **136** was subjected to photoirradiation with a 400 W medium pressure mercury lamp for six hours but as with ketone **56** none of the desired product was observed. Instead the reaction proceeded *via* a Norrish type I pathway with loss of CO to give fused [5.5] bicycle **202** as the product in 81% yield (Scheme 2.49).



136 **202** 81%

54 **203** 30%

Scheme 2.49 *Norrish type I reactions of bicyclic ketones* ***136*** *&* ***54***

The conditions were also tested on dimethyl acetal **54** and the same outcome was observed. With both substrates the reaction proceeded cleanly, but in the case of the dimethyl acetal **54** the reaction proceeded much slower, and only a 30% conversion was achieved in the same time period.

No clear conclusion about the stereochemistry of the ester could be derived from NOESY experiments, but the chemical shift of the α–hydrogen in the ^{1}H-NMR implies a *cis*-relationship between the ester and the acetal (Figure 2.15). This epimerisation is consistent with previously observed results.[55]

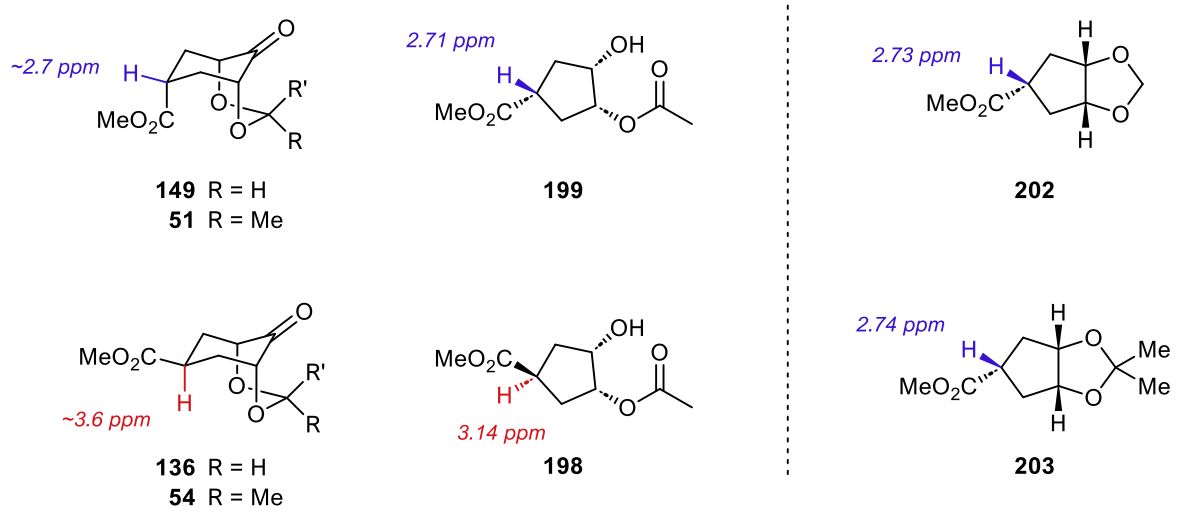
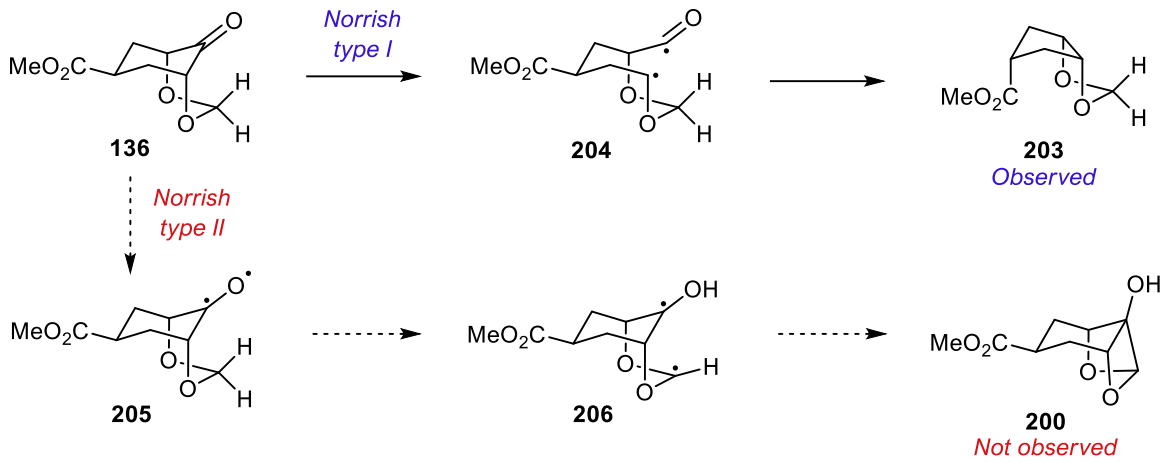


Figure 2.15 *^{1}H-NMR chemical shifts of α–H in various cyclic systems*

For ketone **136** both the type I and the type II pathways generate radicals stabilised by adjacent oxygens, but only type I reactivity is observed (Scheme 2.50). For a successful 1,5 C–H abstraction (type II pathway) the distance between the radical centre and the hydrogen atom should be less 3 Å.[174] The constrained nature of the bicyclic system in **205** means this distance is not readily accessible even in the chair-boat conformation, and the type I pathway prevails.

The epimerisation of the ester is more difficult to explain but may be a result of the low barrier to inversion of alkyl radicals.[175]



Scheme 2.50 *Norrish type I and type II reactions of bicyclic ketone* ***136***

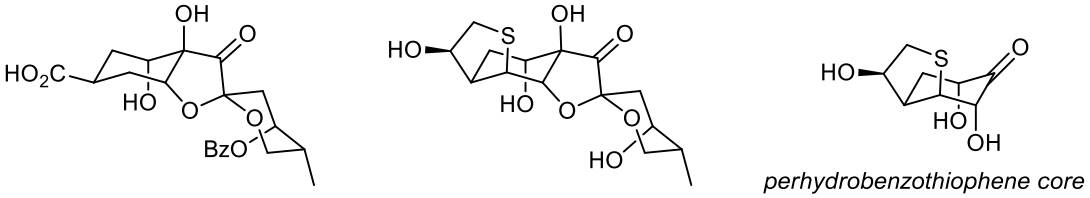
2.3.4 – CONCLUSION

In Chapter 2.3 a Norrish-Yang type intramolecular photocyclisation was investigated as a method of C–C bond formation at the ketone of bicycle **136**. The intended reaction was unsuccessful and resulted in formal loss of CO from the bicyclic system and ester epimerisation to form fused [5.5] bicycle **202.** Therefore the Norrish reaction was abandoned as a potential method of functionalising ketone **136**.

2.4 – BREYNOLIDE TETRAHYDROTHIOPHENE RING SYSTEM

2.4.1 – INTRODUCTION

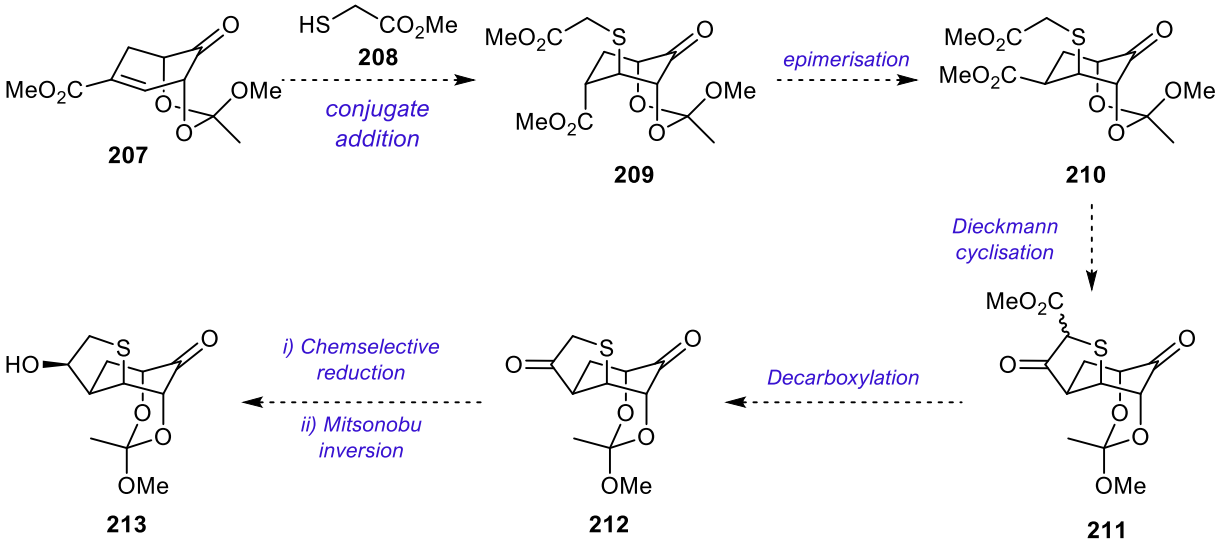
Given their structural similarity, routes described above for phyllaemblic acid **1** could also be applied to the total synthesis of structurally related natural product breynolide **22** (Chapter 1.2.2). While both natural products contain the key 6,5-spiroacetal, the main difference between phyllaemblic acid **1** and breynolide **22** is the presence of the perhydrobenzothiophene ring system (Figure 2.16).



phyllaemblic acid **1** *breynolide* **22** *perhydrobenzothiophene core*

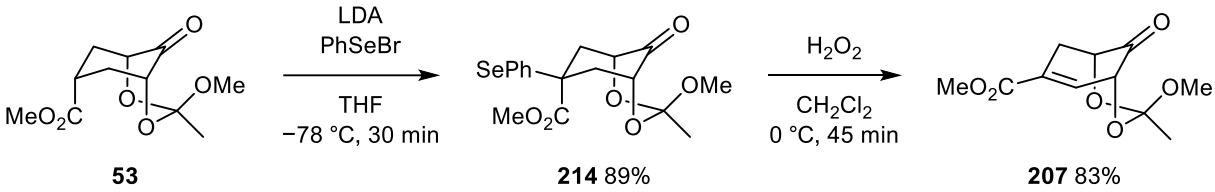
Figure 2.16 *Structure of breynolide's perhydrobenzothiophene core*

It was envisioned that the breynolide ring system could be accessed from α,β-unsaturated ester **207** by thiol conjugate addition and subsequent Dieckmann condensation (Scheme 2.51).



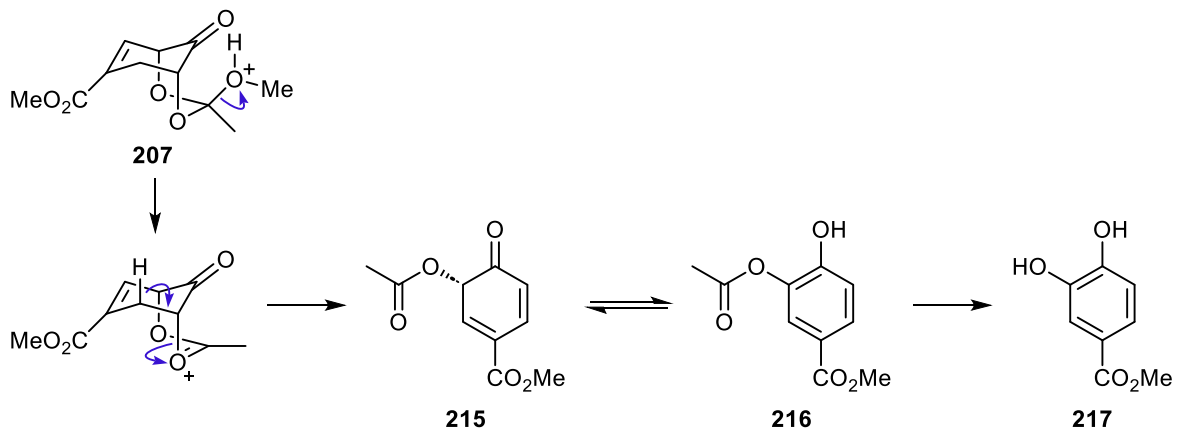
Scheme 2.51 *Proposed synthesis of perhydrobenzothiophene core from α,β-unsaturated ester* ***207***

The enolate of **53** was formed using LDA and quenched with PhSeBr to give selenide **214**. This was then oxidised with hydrogen peroxide to induce selenoxide elimination, giving α,β-unsaturated ester **207** in overall yield of 74% (Scheme 2.52).[55]



Scheme 2.52 *Synthesis of α,β-unsaturated ester* ***207***

α,β-Unsaturated ester **207** was found to be unstable to chromatography and most reaction solvents meaning its synthetic utility was extremely limited.[55] This instability was attributed to the ability of the methoxy substituent in **207** to act as a leaving group. Loss of methanol from orthoacetal **207** results in the formation of ketone **215** which then tautomerises to give phenol **216**. Subsequent loss of acetate accounts for the observed formation of catechol **217** (Scheme 2.53).[55]

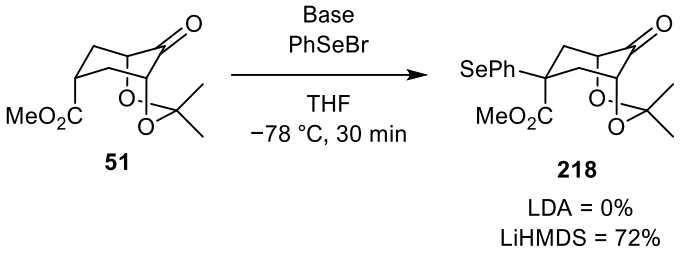


Scheme 2.53 *Decomposition of α,β-unsaturated ester* ***207***

It was envisioned that using dimethyl acetal **51** instead of orthoacetal **53** as the starting point would remove this decomposition pathway and result in a more stable system.

2.4.2 – RESULTS & DISCUSSION

Formation of the enolate of ester **51** was initially attempted using LDA, but this resulted in degradation of the starting material and no product was isolated after quenching with either PhSeBr or D_2O. Switching to LiHMDS as a milder base was more successful to obtain phenyl selenide **218** as a single diastereomer in 72% yield (Scheme 2.54).



Scheme 2.54 *Synthesis of selenide* ***218***

The X-ray crystal structure of selenide **218** confirms the selectivity replicates that of the final step of the annelation: addition of PhSeBr occurs on the opposite face to the acetal, giving axial ester geometry (Figure 2.17).

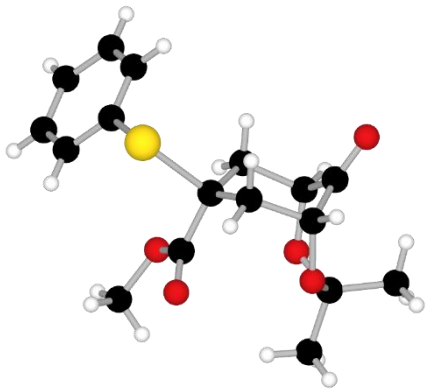
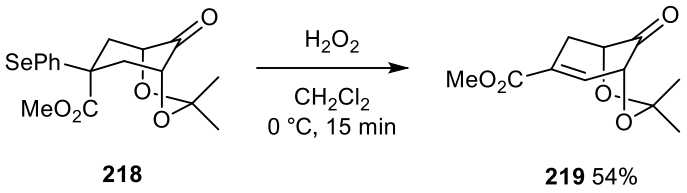


Figure 2.17 *X-ray crystal structure of selenide* ***218***

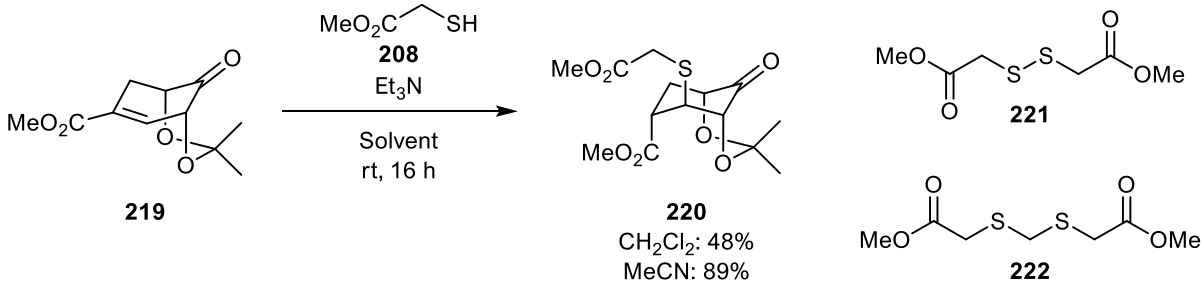
Oxidation of **218** with excess H_2O_2 gave α,β-unsaturated ester **219** in 54% yield (Scheme 2.55). As predicted, **219** proved to be much more stable than **207** allowing for investigation into the Dieckmann cyclisation.



218 **219** 54%

Scheme 2.55 *Synthesis of α,β-unsaturated ester **219***

Addition of methyl thioglycolate **208** initially gave diester **220** as a single diastereomer in 48% yield, but also resulted in a significant amount of side product formation (Scheme 2.56). Notably thiol **208** was observed to react with itself to give disulfide **221** and with the reaction solvent to give thioacetal **222**. Switching the reaction solvent from dichloromethane to acetonitrile resulted in minimal side product formation and increased the yield of diester **220** to 89%.



Scheme 2.56 *Conjugate addition of methyl thioglycolate **208***

Thiolate addition was assumed to have occurred from the top face away from the acetal, and this was confirmed by analysis of the coupling constants in the ^{1}H-NMR spectrum (Figure 2.18). $J_{a\text{-}b}$ is 6.9 Hz which is too small to be the result of axial-axial arrangement (typically J > 10 Hz), meaning H_a must be equatorial. In addition to this, long range "W-coupling" is observed between H_c and H_d (J = 3.0 Hz), confirming that H_c must also be equatorial.

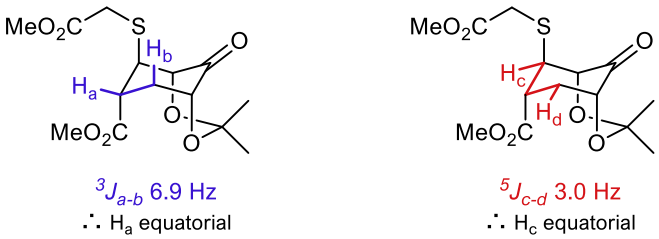
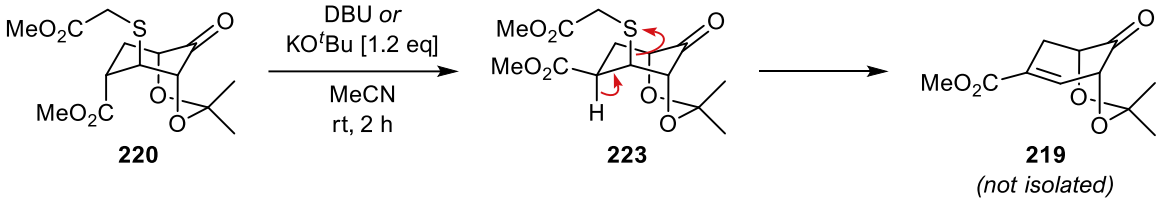


Figure 2.18 *Observed ^{1}H-^{1}H coupling in sulfide **220***

Treatment of diester **220** with base as an attempted epimerisation and Dieckmann cyclisation resulted in the elimination of thiol **208**, reforming starting α,β-unsaturated ester **219**. This is likely a consequence of the antiperiplanar alignment of the acidic proton in equatorial ester **223** with the thiol leaving group favouring E_2 elimination (Scheme 2.57).



Scheme 2.57 *Epimerisation of axial diester* ***220***

2.4.3 – CONCLUSION

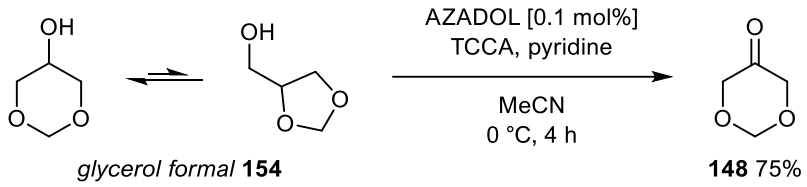
In Chapter 2.4 the suitability of using dimethyl acetal **51** as a building block for the perhydrobenzothiophene core of breynolide **22** was investigated. α,β-Unsaturated ester **219** was successfully prepared in 39% overall yield by selenide formation and H_2O_2-mediated selenoxide elimination. Dimethyl acetal **219** showed vastly improved stability over orthoacetal **207** due to the absence of a leaving group on the acetal.

Conjugate addition of thiol **208** gave sulfide **220** as a single diastereomer but attempts at epimerisation and Dieckmann cyclisation only resulted in elimination of the thiolate to reform starting alkene **219**. It was therefore concluded that α,β-unsaturated ester **219** was unsuitable as a starting point for the synthesis of the perhydrobenzothiophene core of breynolide and the route was therefore abandoned.

CHAPTER 3 – CONCLUSION

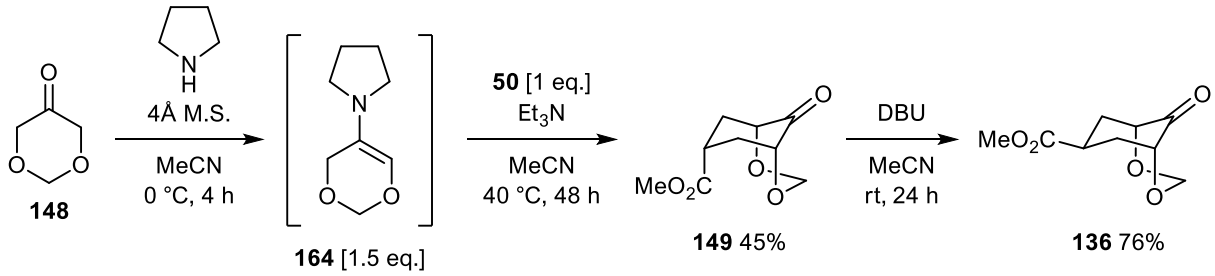
3.1 – SUMMARY

The first objective of the project was to prepare 1,3-dioxan-5-one **148** and investigate its reactivity in the α,α'-annelation reaction to prepare key building block **136**. Synthesis of **149** *via* oxidation of glycerol formal **154** initially proved challenging as a result of difficulties in purification, but AZADOL / TCCA oxidation was successful to give 1,3-dioxan-5-one **148** in 75% yield, 20 g scale (Scheme 3.1).



Scheme 3.1 *Succesful synthesis of 1,3-dioxan-5-one **148***

The α,α'-annelation of dioxanone **148** with bromoacrylate **50** required re-optimisation as a result of increased formation of by-products. However, increasing the equivalents of enamine **164** and running the reaction for 48 hours at 40 °C resulted in the formation of axial ester **149** in 45% yield. Epimerisation was straightforward to yield equatorial ester **136** in 74% yield (Scheme 3.2).



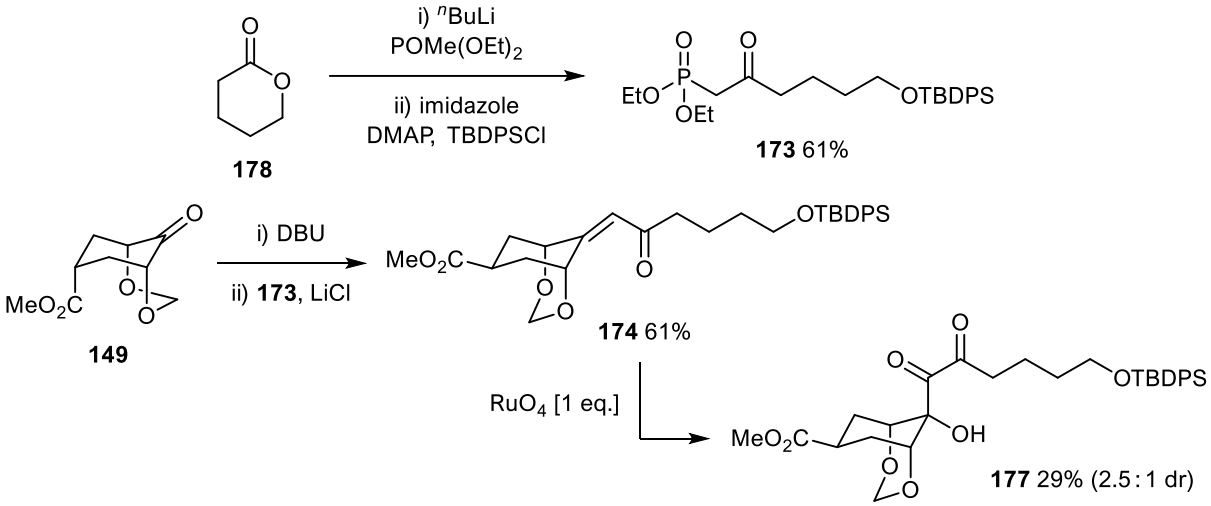
Scheme 3.2 *Synthesis of equatorial ester **136***

The second objective was to determine the conformational preferences of bicyclic ketones **149** and **136**. The X-ray crystal structures showed both to adopt a chair-boat conformation in the solid state, but investigation of the solution conformation was less conclusive. While the nOe experiments did not give clear results, VT-NMR showed signal broadening at lower

temperatures which suggests both conformations are present and interconvert at room temperature.

The third objective was to investigate the reactivity and stereoselectivity in addition reactions to ketones **149** and **136.** Methylene acetal **136** exhibited significantly enhanced reactivity, successfully undergoing reactions with a range of nucleophiles that previous bicyclic ketones were previously unresponsive to. Based on these successful additions, the synthesis of model compound **172** was attempted. Spiroacetalisation precursor **177** was prepared *via* two routes: Horner-Wadsworth-Emmons olefination followed by enone dihydroxylation; and acetylide addition followed by alkyne oxidation.

The first route successfully used a one-pot epimerisation / HWE to prepare enone **174** from **149** but dihydroxylation could only be achieved using stoichiometric ruthenium tetroxide (Scheme 3.3). This oxidation was found to be unreliable and gave the incorrect selectivity for phyllaemblic acid so the HWE route was abandoned in favour of the alkyne addition route.

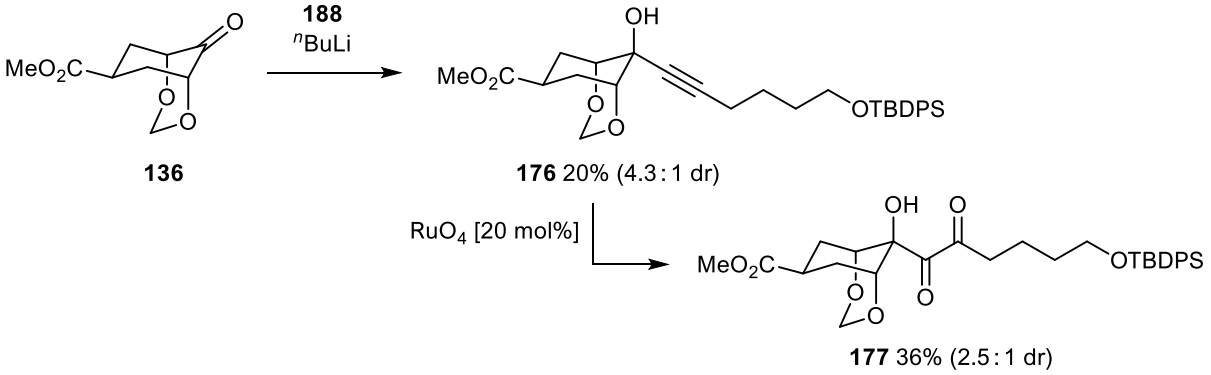


Scheme 3.3 *Synthesis of spiroacetalisation precursor* ***177*** *via HWE olefination*

The alkyne addition route was more successful, with addition of alkyne **188** to ketone **136** resulting in a diastereoselectivity of 4:1. The diastereomers were assigned based on nOe analysis of the TBS protected minor product, which showed the major product to have the

stereochemical array found in phyllaemblic acid (Scheme 3.4). The low yield of tertiary alcohol **176** was assumed to be a result of the instability of the lithium acetylide of **188** as the addition of hexyne occurred with 75% yield. Attempts at further optimising this addition yielded no improvement.

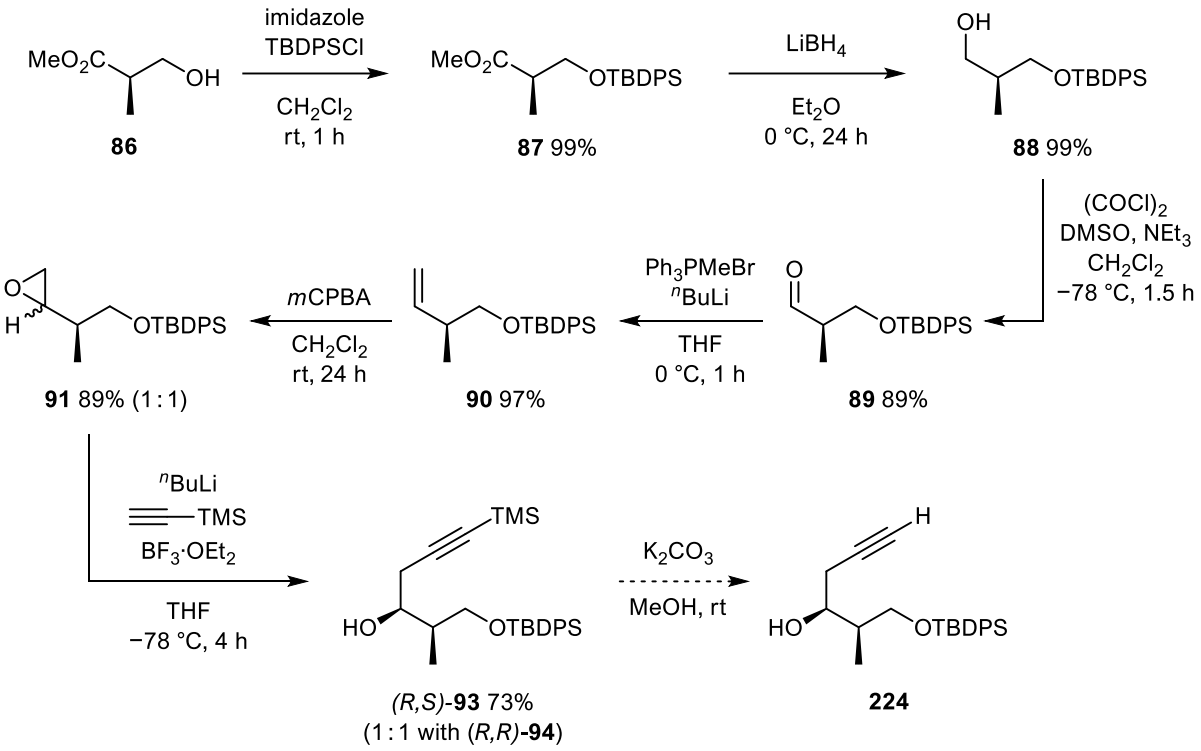
Alkyne oxidation was partially successful to give diketone **177** in 36% yield, but the instability of the product to the reaction conditions resulted in oxidative cleavage to form starting ketone **136**, limiting the feasibility of this reaction.



Scheme 3.4 *Synthesis of spiroacetalisation precursor **177** via alkyne addition*

In Chapter 2.3 C–C formation *via* a photomediated Norrish-Yang cyclisation was attempted as an alternative method of functionalising ketone **136**. Unfortunately, instead of the intended reaction only formal loss of CO occurred so this route was abandoned.

The fourth and final objective of the project was to prepare a RHS chiral fragment suitable for elaboration of **136** towards phyllaemblic acid. As the alkyne addition route to model compound **172** showed the most promise, chiral alkyne **93** was prepared as a separable 1:1 mixture of diastereomers from (*R*)-Roche ester **86** in six steps with an overall yield of 55% (Scheme 3.5). The final TMS deprotection step was not completed due to the addition of achiral alkyne **188** to ketone **136** requiring further optimisation.



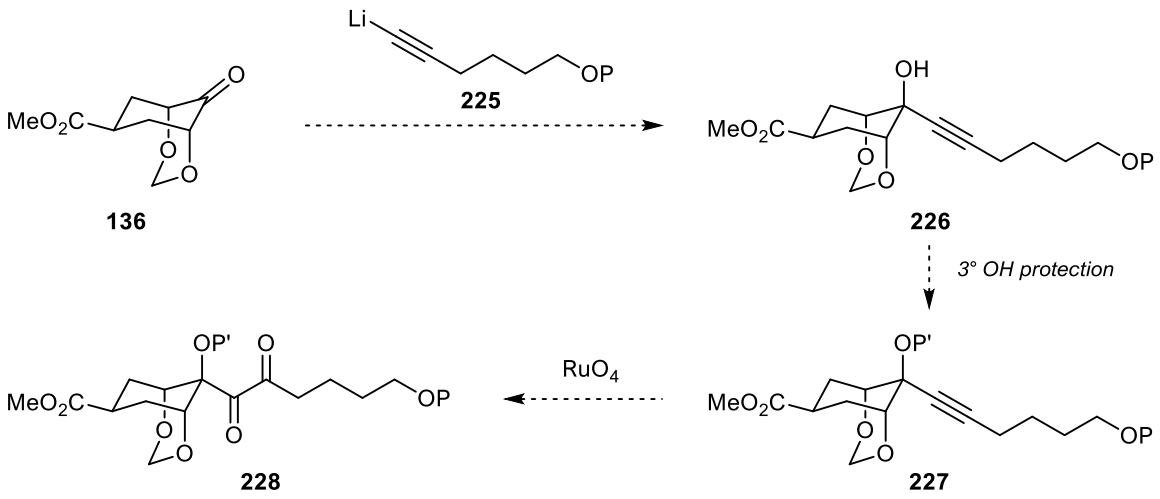
Scheme 3.5 *Synthesis of known alkyne fragment* ***93***

Overall, replacing the acetal in known bicycles **51** and **53** with a smaller methylene acetal successfully increased the reactivity of the carbonyl and allowed nucleophilic addition to occur. This increased reactivity means that a total synthesis of phyllaemblic acid from ketone **136** remains a possibility, but further work must be done to improve the reliability of the alkyne addition route in order for this to be a reality.

In addition to the original project aims, the synthesis of the perhydrobenzothiophene core of breynolide **22** was also investigated. Stable α,β-unsaturated ester **219** was prepared from dimethyl acetal **53** *via* selenide addition and elimination. Methyl thioglycolate was then successfully added to give sulfide **220** but attempts at cyclisation only resulted in elimination so this route was abandoned.

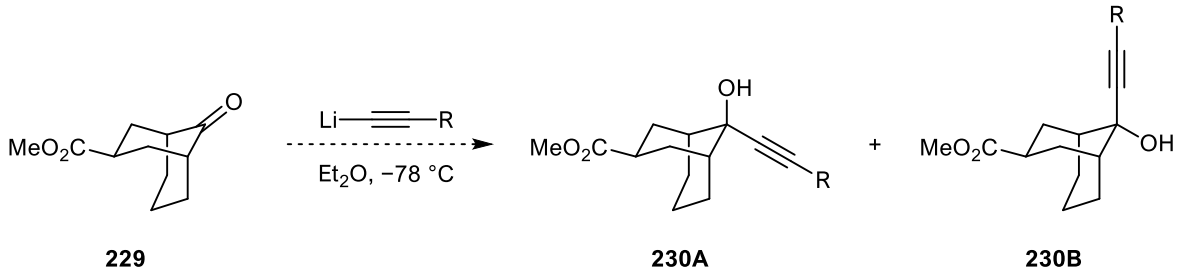
3.2 – FUTURE WORK

Despite the promising alkyne addition results, further improvements need to be made in order to make the total synthesis of phyllaemblic acid **1** viable. Additional work should focus on improving the synthesis of spiroacetalisation precursor **228** *via* alkyne addition and oxidation (Scheme 3.6). Firstly, an alternate alcohol protecting group could improve the stability of alkynyl lithium **225** resulting in higher yield of tertiary alcohol **226**. Secondly, protection of the alcohol should then improve the selectivity of the alkyne oxidation by preventing oxidative cleavage of the product diketone **227** to starting ketone **136**.



Scheme 3.6 *Proposed synthesis of spiroacetalisation precursor* ***228***

As the cause of the observed diastereoselectivity in the alkyne addition step could not be confirmed, further improvements to the diastereomeric ratio of the products may be difficult. Synthesis of cyclohexanone-derived equivalent **229** would provide an interesting comparison, although as discussed in Chapter 1.3.2 (Scheme 1.29) the substitution of oxygen for carbon affects more than one factor involved in determining π-facial selectivity to α-substituted cyclohexanones.

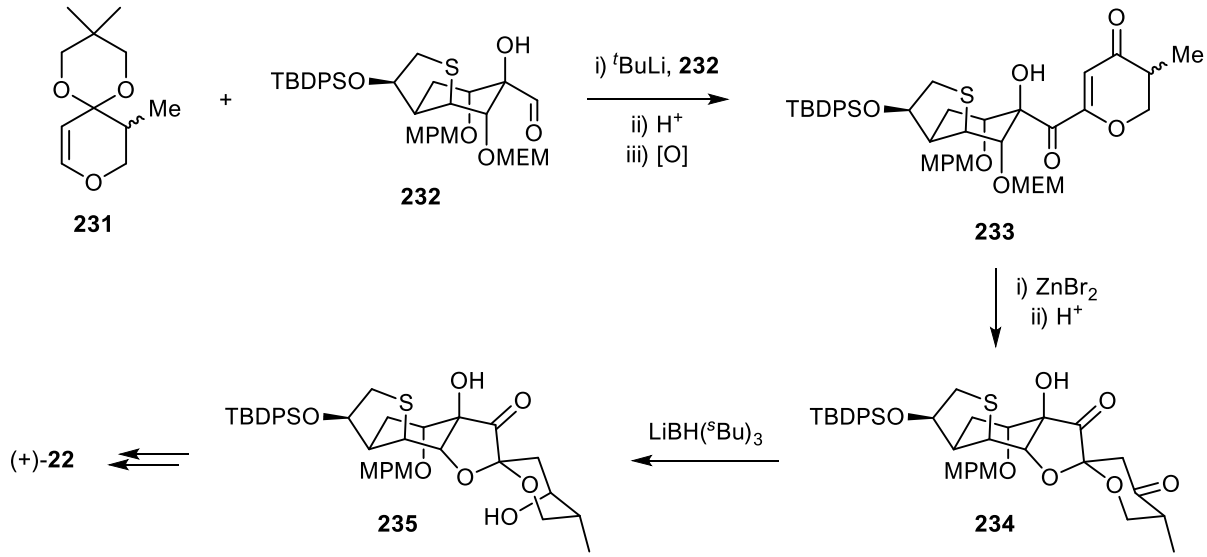


229 **230A** **230B**

Scheme 3.7 *Possible acetylide addition to carbocyclic ketone* ***229***

If the alkyne addition route to phyllaemblic acid could not be improved, or if spiroacetalisation could not be achieved from **228**, an alternative route inspired by the thermodynamically driven strategy employed by Smith and Burke could be tested.[37,44,46]

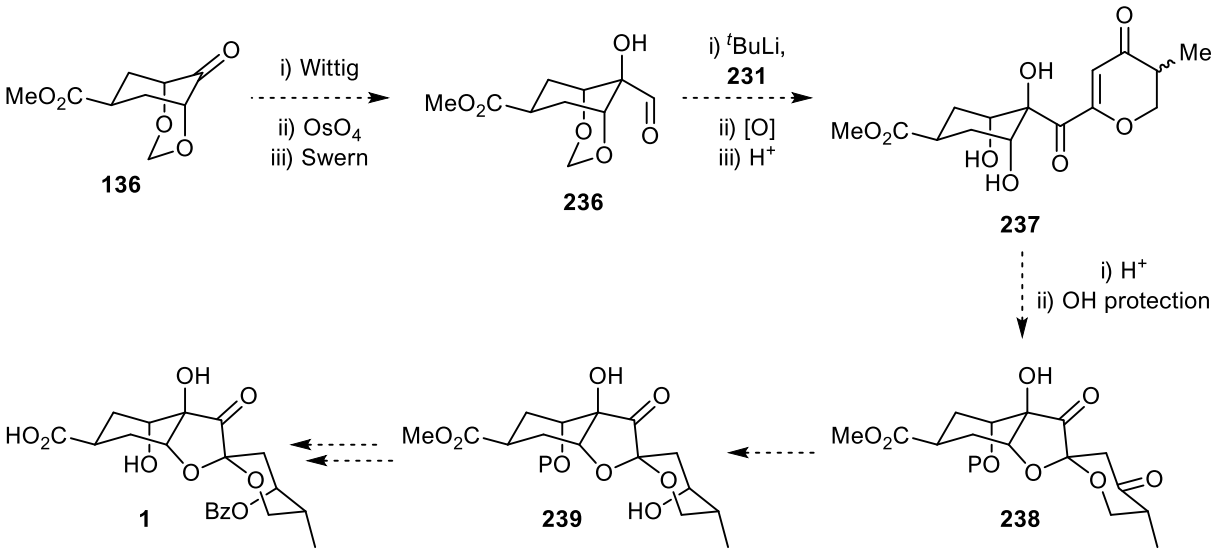
In Burke's synthesis of (+)-breynolide **22**, addition of racemic dihydropyran **231** to aldehyde **232** followed by acetal deprotection and oxidation provided the key intermediate **233**. Upon treatment with acid, intermediate **233** underwent a thermodynamically controlled spiroacetalisation to give ketone **234**. Conversion of (+)-breynolide **22** was then achieved *via* chemo- and stereoselective reduction (Scheme 3.8).



Scheme 3.8 *Burke's synthesis of (+)-breynolide* ***22***

An analogous route could be applied to the synthesis of phyllaemblic acid **1** from bicyclic ketone **136**. Aldehyde **236** could be prepared *via* the Wittig-dihydroxylation-oxidation

sequence used to prepare **81** (Scheme 1.18). Addition of racemic dihydropyran **231**, oxidation and acetal deprotection would then give spiroacetalisation precursor **237**. The examples discussed in Chapter 1.2.2 suggest that it could be possible to achieve the diastereotopic group selective spiroacetalisation to form **238** under thermodynamic control (Scheme 3.9). Phyllaemblic acid **1** could then be accessed from **238** by ketone reduction, protecting group manipulation and ester hydrolysis (as seen above in Scheme 2.22).



Scheme 3.9 *Alternative route to phyllaemblic acid **1** based on Burke's synthesis of breynolide **22***

CHAPTER 4 – EXPERIMENTAL

4.1 – GENERAL EXPERIMENTAL

REAGENTS AND SOLVENTS All solvents and reagents were purchased and used without further purification (unless stated otherwise) from one of the following outlets: Alfa Aesar, Acros Organics, Fisher, Sigma Aldrich, Merck, TCI, Fluorochem or VWR chemicals. *n*-Butyllithium was purchased as a 2.5 M solution in hexane and the solutions titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene, with the measured titre values reported in the individual experimental procedure.[176] Petroleum ether refers to b.p. 40 – 60 °C. Anhydrous solvents were either collected from a PureSolv MD SPS using alumina and silica columns or dried from the bottle *via* activated (300 °C, 6 h, <1 mbar) 4 Å molecular sieves. Any reference to water refers to purified water collected from a PURELAB option-S 7 reverse osmosis water purifier.

REACTION SETUP The following reaction temperatures were achieved *via* the use of the following cooling baths (unless stated otherwise): 0 °C (ice/water), 10 °C (CO_2/1,4-dioxane), −42 °C (CO_2/acetonitrile) and −78 °C (CO_2/acetone) and for reactions above room temperature metal heating blocks were employed and the temperature controlled *via* an external probe. Reactions performed at rt were at an average temperature of 21 °C. Reactions were performed with no effort to exclude air or water unless anhydrous solvents are specified, in which case an Ar atmosphere and flame-dried glassware were used.

CHROMATOGRAPHY Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} (aluminium support) TLC plates. Flash column chromatography was carried out on Aldrich technical grade silica gel, 60 Å, 230 – 400 mesh, 40 – 63 μm particle size. Automated flash column chromatography was performed on a Teledyne ISCO Combi-Flash NextGen 300+ using RediSep Rf Gold Silica columns or Interchim PuriFlash Dry Load Columns.

X-RAY CRYSTALLOGRAPHY Single crystal data were collected by Dr Louise Male on an Agilent Technologies SuperNova diffractometer equipped with a CuKα microfocus X-ray source and an Atlas CCD detector. Structures were solved using Olex2[177] with either the SHELXT[178] or olex2.solve[179] structure solution programs and were refined using SHELXL.[180]

NMR SPECTROSCOPY ^{13}C-NMR are proton decoupled. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated solvents and referenced to the residual solvent peaks.[181,182] Spectra were recorded using Bruker AVIII 300MHz, AVIII 400 MHz, AVANCE NEO 400 MHz and AVANCE NEO 500 MHz NMR spectrometers. JMOD, COSY, HSQC, HMBC, NOESY and ROESY experiments were used to unambiguously assign both ^{1}H-NMR and ^{13}C-NMR spectra. Acrylate olefin protons were assigned based on the additive increments method.[183] NMR spectra were processed using MestReNova 14. Chemical shifts, δ, are reported in ppm and coupling constants, *J*, are measured in Hz. Atom labelling in NMR assignment is arbitrary, and the following abbreviations were used to describe proton environment: eq = equatorial and ax = axial with ′ being used to distinguish non-equivalent but unassignable environments with the same connectivity. The following abbreviations have been used to describe multiplicity: s = singlet, d = doublet, t = triplet, q = quartet and app. = apparent. The term 'stack' is used to describe a region where resonances arising from non-equivalent nuclei are coincident, and multiplet (m) to describe a region where a resonance arises from a single nucleus (or equivalent nuclei) but coupling constants cannot be readily assigned.

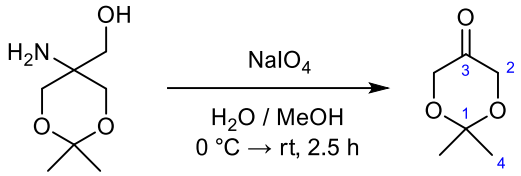
MASS SPECTROMETRY Low- and high-resolution mass spectra were recorded via electrospray (ES), electron impact (EI), chemical ionisation (CI), affinity-purification (AP) or atmospheric solids analysis probe (ASAP) using a Waters Xevo G2-XS, GCT Premier, SQD, Synapt-G2-S or LCT TOF Mass Spectrometer in positive or negative mode (technique and charge detection method stated in each MS report). Liquid chromatography-mass spectrometry analysis was performed using a Waters Xevo-G2-XS with ACQUITY UPLC BEH C18 column, 2.1mm x 100mm, 2.7 µm particle size (raw data was processed and extracted using Xcaliber).

IR SPECTROSCOPY Infrared spectra were recorded neat using a PerkinElmer Spectrum Two FT-IR Spectrometer (with UATR attachment for solid samples).

MELTING POINTS Melting points were determined via a Stuart SMP10 melting point apparatus with a digital temperature reading (1 °C graduations).

4.2 – INDIVIDUAL EXPERIMENTAL PROCEDURES

47 *2,2-Dimethyl-1,3-dioxan-5-one*



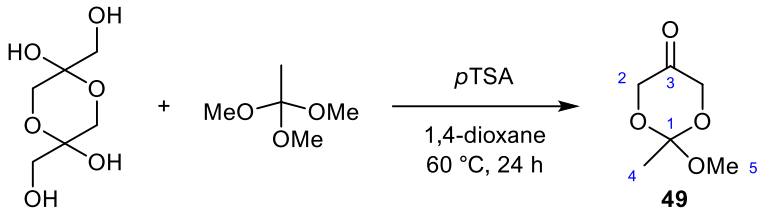
153 **47**

(5-Amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol **153** (4.77 g, 29.6 mmol) was added to a mixture of water (38 mL) and methanol (10 mL) and the resulting solution cooled to 0 °C. A solution of sodium periodate (8.23 g, 38.5 mmol) in water (70 mL) was added dropwise over 90 min, after which time the cooling bath was removed and the reaction allowed to warm to rt. After 2.5 h the reaction mixture was filtered through a pad of celite, rinsed with methanol (3 × 20 mL) and extracted with dichloromethane (7 × 80 mL). The combined organic layers were washed with sodium hydrogen carbonate (5% aq. soln., 100 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure at rt to give **47** as a colourless oil (2.89 g, 75%) of sufficient purity to not require further purification. **R_f:** 0.73 (1:1 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 2989 (CH), 2942 (CH), 1751 (CO); **δ_H (400 MHz, $CDCl_3$):** 4.15 (4 H, s, H-2), 1.45 (6 H, s, H-4); **δ_C (101 MHz, $CDCl_3$):** 208.1 (C, C-3), 100.3 (C, C-1), 67.0 (CH_2, C-2), 23.6 (CH_3, C-4); **LRMS m/z (EI$^+$):** 130.0 ([M]$^+$, 65%), 115.0 ([M − CH_3]$^+$, 100), 100.0 ([M − C_2H_6]$^+$, 85).

A known compound prepared according to a literature procedure.[138] *Analytical data in agreement with literature values.*[50]

49 *2-Methoxy-2-methyl-1,3-dioxan-5-one*

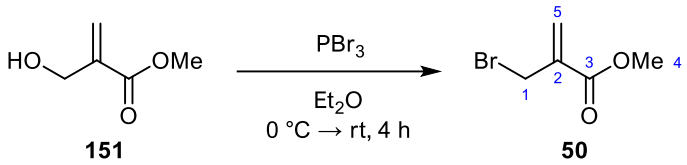


Dimeric dihydroxyacetone (4.09 g, 22.4 mmol) and *p*-toluenesulfonic acid (50 mg, 0.22 mmol, 1 mol%) were added to 1,4-dioxane (200 mL) and the resulting mixture heated to 60 °C. After the dihydroxyacetone had completely dissolved, trimethyl orthoacetate (60.0 mL, 454 mmol) was added. After 24 h the reaction was determined complete by TLC and was allowed to cool to rt, concentrated under reduced pressure and directly purified by distillation (70 °C, 1.0 mbar) to yield dioxanone **49** as a colourless oil (4.53 g, 70%). **R_f:** 0.61 (1:1 petroleum ether:Et_2O, visualised using vanillin / Δ).

ν_{max} / cm^{-1} (neat): 2952 (CH), 2841 (CH), 1740 (CO); **δ_H (400 MHz, $CDCl_3$):** 4.34 (2 H, d, *J* 18.8, H-2), 4.18 (2 H, d, *J* 18.8, H-2′), 3.38 (3 H, s, H-5), 1.58 (3 H, s, H-4); **δ_C (101 MHz, $CDCl_3$):** 204.7 (C, C-3), 112.5 (C, C-1), 67.7 (CH_2, C-2), 51.5 (CH_3, C-5), 20.7 (CH_3, C-4); **LRMS m/z (EI$^+$):** 146.1 ([M]$^+$, 5%), 131.1 ([M − CH_3]$^+$, 100).

A known compound prepared according to a literature procedure.[137] *Analytical data in agreement with literature values.*[55]

***50** Methyl 2-(bromomethyl)acrylate*



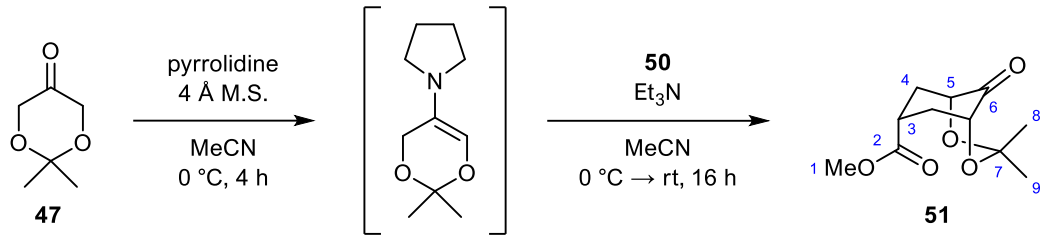
151 **50**

Methyl 2-(hydroxymethyl)acrylate **151** (2.90 g, 25.0 mmol) was dissolved in diethyl ether (32 mL) and the resulting solution cooled to 0 °C. Freshly distilled phosphorus tribromide (1.19 mL, 12.5 mmol) was added dropwise over 5 min after which time the cooling bath was removed and the reaction allowed to warm to rt. After 4 h the reaction was determined complete by TLC and quenched with water (25 mL) and extracted with hexane (3 × 25 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by distillation (100 °C, 55 mbar) to yield acrylate **50** as a colourless oil (2.88 g, 64%). **R_f:** 0.22 (95:5 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 2953 (CH), 1722 (CO), 1632 (CC); **δ_H (400 MHz, $CDCl_3$):** 6.34 (1 H, d, *J* 0.8, H-5$_Z$), 5.96 (1 H, d, *J* 0.8, H-5$_E$), 4.18 (2 H, s, H-1), 3.82 (3 H, s, H-4); **δ_C (101 MHz, $CDCl_3$):** 165.5 (C, C-3), 137.5 (C, C-2), 129.4 (CH_2, C-5), 52.5 (CH_3, C-4), 29.1 (CH_2, C-1); **LRMS m/z (EI$^+$):** 179.9 ([M^{81}Br]$^+$, 63%), 178.0 ([M^{79}Br]$^+$, 65), 148.8 ([M^{81}Br − OCH_3]$^+$, 63), 146.9 ([M^{79}Br − OCH_3]$^+$, 65), 120.8 ([M^{81}Br − CO_2CH_3]$^+$, 62), 118.9 ([M^{79}Br − CO_2CH_3]$^+$, 64), 99.0 ([M − Br]$^+$, 100).

A known compound prepared according to a modified literature procedure.[134] *Analytical data in agreement with literature values.*[55]

51 *Methyl (1R,5S,7r)-3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



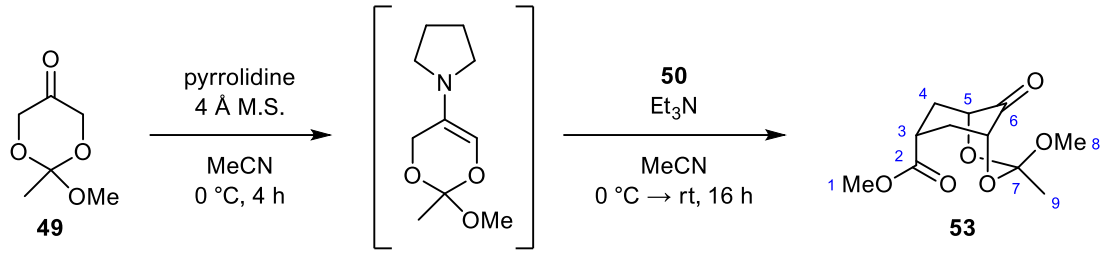
47 **51**

Dioxanone **47** (1.90 g, 14.7 mmol) and activated 4 Å molecular sieves (1.47 g) were added to anhydrous acetonitrile (36 mL) and the resulting mixture cooled to 0 °C. Freshly distilled pyrrolidine (1.20 mL, 14.7 mmol) was added and the reaction was stirred for 4 h, after which time triethylamine (2.10 mL, 14.7 mmol) was added followed by a solution of methyl 2-(bromomethyl)acrylate **50** (2.63 g, 14.7 mmol) in anhydrous acetonitrile (44 mL). The cooling bath was then removed, and the reaction allowed to warm to rt. After 16 h the solution was filtered through a plug of celite and rinsed with acetonitrile (3 × 50 mL). Water (100 mL) was added to the resulting solution and was stirred at room temperature for 4 h. The mixture was then extracted with dichloromethane (3 × 100 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 petroleum ether:Et_2O) to yield bicyclic ketone **51** as a white crystalline solid (1.66 g, 50%). **R_f:** 0.37 (7:3 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

m.p. 67 – 69 °C; **ν_{max} / cm^{-1} (neat):** 2998 (CH), 2953 (CH), 2927 (CH), 1733 (2 × CO); **δ_H (400 MHz, $CDCl_3$):** 4.32 – 4.28 (2 H, m, H-5), 3.78 (3 H, s, H-1), 3.33 – 3.25 (2 H, m, H-4_{eq}), 2.59 (1 H, tt, *J* 7.2, 1.2, H-3), 2.01 (2 H, dd, *J* 13.4, 7.2, H-4_{ax}), 1.39 (3 H, s, H-8 / H-9), 1.37 (3 H, s, H-8 / H-9); **δ_C (101 MHz, $CDCl_3$):** 215.3 (C, C-6), 173.8 (C, C-2), 99.2 (C, C-7), 76.9 (CH, C-5), 52.2 (CH_3, C-1), 38.8 (CH_2, C-4), 34.0 (CH, C-3), 27.9 (CH_3, C-8 / C-9), 24.9 (CH_3, C-8 / C-9); **LRMS m/z (ES$^+$):** 251.1 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{11}H_{16}O_5Na$ 251.0895, found 251.0889.

A known compound prepared according to a literature procedure.[49] *Analytical data in agreement with literature values.*[49]

53 *Methyl (1R,3r,5S,7r)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

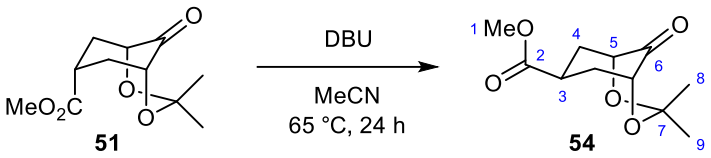


Dioxanone **49** (822 mg, 5.00 mmol) and activated 4 Å molecular sieves (500 mg) were added to anhydrous acetonitrile (12 mL) and the resulting mixture cooled to 0 °C. Freshly distilled pyrrolidine (0.40 mL, 5.0 mmol) was added and the reaction was stirred for 4 h, after which time triethylamine (0.70 mL, 5.0 mmol) was added followed by a solution of methyl 2-(bromomethyl)acrylate **50** (895 mg, 5.00 mmol) in anhydrous acetonitrile (15 mL). The cooling bath was then removed, and the reaction allowed to warm to rt. After 16 h the solution was filtered through a plug of celite and rinsed with acetonitrile (3 × 25 mL). Water (25 mL) was added to the resulting solution and was stirred at room temperature for 4 h. The mixture was then extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 petroleum ether:Et_2O) to yield bicyclic ketone **53** as a white crystalline solid (580 mg, 48%). **R_f:** 0.25 (1:1 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

m.p. 66 – 69 °C; **ν_{max} / cm^{-1} (neat):** 2945 (CH), 2840 (CH), 1732 (2 × CO); **δ_H (400 MHz, $CDCl_3$):** 4.22 – 4.16 (2 H, m, H-5), 3.78 (3 H, s, H-1), 3.28 – 3.20 (2 H, dm, *J* 14.1, H-4$_{eq}$), 3.23 (3 H, s, H-8), 2.64 (1 H, tt, *J* 7.0, 1.4, H-3), 1.99 (2 H, ddd, *J* 14.1, 7.0, 1.0, H-4$_{ax}$), 1.45 (3 H, s, H-9); **δ_C (101 MHz, $CDCl_3$):** 208.1 (C, C-6), 173.7 (C, C-2), 112.1 (C, C-7), 75.3 (CH, C-5), 52.2 (CH_3, C-8), 51.1 (CH_3, C-1), 36.7 (CH_2, C-4), 34.1 (CH, C-3), 19.9 (CH_3, C-9); **LRMS m/z (EI$^+$):** 244.1 ([M]$^+$, 13%), 229.1 ([M − CH_3]$^+$, 100).

A known compound prepared according to a literature procedure.[49] *Analytical data in agreement with literature values.*[49]

54 *Methyl (1R,5S,7s)-3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

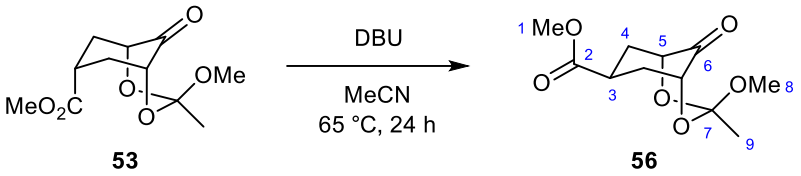


1,8-Diazabicyclo[5.4.0]undec-7-ene (223 mg, 1.49 mmol) and axial ester **51** (340 mg, 1.49 mmol) were added to acetonitrile (15 mL) and the resulting solution was heated to 65 °C. After 24 h the reaction was determined complete by TLC and was allowed to cool to rt, concentrated under reduced pressure to give a residue which was purified by flash column chromatography (3:1 petroleum ether:Et_2O) to yield bicyclic ketone **54** as a white solid (197 mg, 58%). **R_f:** 0.17 (7:3 hexane:EtOAc, visualised using $KMnO_4$ / Δ).

m.p. 80 – 82 °C; **ν_{max} / cm^{-1} (neat):** 2994 (CH), 2963 (CH), 2935 (CH), 1747 (CO_2Me), 1723 (CO); **δ_H (400 MHz, $CDCl_3$):** 4.29 (2 H, d, *J* 3.3, H-5), 3.69 (3 H, s, H-1), 3.57 (1 H, tt, *J* 12.5, 4.6, H-3), 2.70 – 2.54 (2 H, m, H-4_{eq}), 1.95 (2 H, app. t, *J* 13.6, H-4_{ax}), 1.51 (3 H, s, H-8 / H-9), 1.43 (3 H, s, H-8 / H-9); **δ_C (101 MHz, $CDCl_3$):** 214.2 (C, C-6), 174.4 (C, C-2), 98.9 (C, C-7), 76.2 (CH, C-5), 52.2 (CH_3, C-1), 40.5 (CH_2, C-4), 33.3 (CH, C-3), 28.7 (CH_3, C-8 / C-9), 25.2 (CH_3, C-8 / C-9); **LRMS m/z (ASAP$^+$):** 229.1 ([M + H]$^+$, 100%); **HRMS m/z (ASAP$^+$):** calcd. for $C_{11}H_{17}O_5$ 229.1076, found 229.1078.

A known compound prepared according to a literature procedure.[49] *Analytical data in agreement with literature values.*[49]

56 *Methyl (1R,3r,5S,7s)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



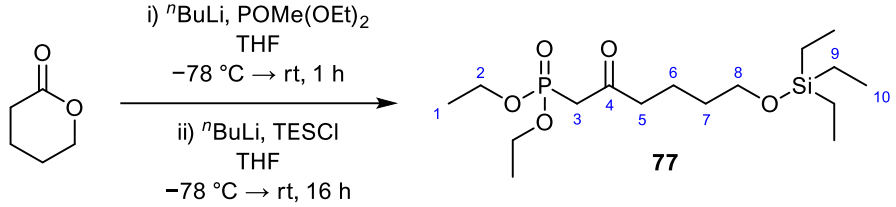
53 **56**

1,8-Diazabicyclo[5.4.0]undec-7-ene (114 mg, 0.750 mmol) and axial ester **53** (182 mg, 0.750 mmol) were added to acetonitrile (6 mL) and the resulting solution was heated to 65 °C. After 24 h the reaction was determined complete by TLC and was allowed to cool to rt, concentrated under reduced pressure to give a residue which was purified by flash column chromatography (3:1 petroleum ether:Et_2O) to yield bicyclic ketone **56** as an off-white solid (156 mg, 85%). **R_f:** 0.52 (1:1 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

m.p. 35 – 37 °C; **ν_{max} / cm^{-1} (neat):** 2952 (CH), 1735 (CO), 1730 (CO); **δ_H (400 MHz, $CDCl_3$):** 4.18 (2 H, d, *J* 3.7, H-5), 3.70 (3 H, s, H-1), 3.45 (1 H, tt, *J* 12.4, 4.6, H-3), 3.26 (3 H, s, H-8), 2.66 – 2.53 (2 H, m, H-4_{eq}), 1.95 (2 H, app. t, *J* 13.6, H-4_{ax}), 1.58 (3 H, s, H-9); **δ_C (101 MHz, $CDCl_3$):** 207.0 (C, C-6), 174.3 (C, C-2), 112.2 (C, C-7), 74.7 (CH, C-5), 52.2 (CH_3, C-8), 51.1 (CH_3, C-1), 38.3 (CH_2, C-4), 33.4 (CH, C-3), 20.2 (CH_3, C-9); **LRMS m/z (ES$^+$):** 245.1 ([M + H]$^+$, 100%), 185.1 ([M − CO_2CH_3]$^+$, 34).

A known compound prepared according to a literature procedure.[49] *Analytical data in agreement with literature values.*[49]

***77** Diethyl (2-oxo-6-((triethylsilyl)oxy)hexyl)phosphonate*

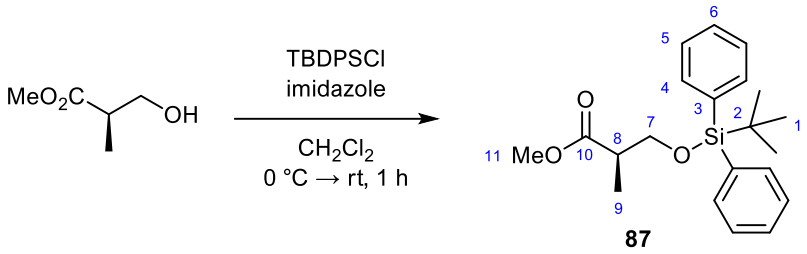


Diethylmethyl phosphonate (1.00 g, 6.58 mmol) was dissolved in anhydrous THF (33 mL) and the resulting solution cooled to −78 °C. *n*-Butyllithium (2.38 M in hexane, 3.10 mL, 6.58 mmol) was added and the reaction stirred for 20 min. δ-Valerolactone (658 mg, 6.58 mmol) was added, the cooling bath removed, and reaction allowed to warm to rt. After 1 h the mixture was cooled to −78 °C, *n*-butyllithium (2.38 M in hexane, 3.10 mL, 6.58 mmol) was added and the reaction stirred for 20 min. Chlorotriethylsilane (990 mg, 6.58 mmol) was then added, the cooling bath removed, and the reaction allowed to warm to rt. After 16 h the reaction was deemed complete by TLC, quenched with ammonium chloride (sat. aq. soln., 30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:EtOAc) to yield phosphonate **77** as a colourless oil (1.43 g, 59%). **R_f:** 0.20 (1:1 hexane:EtOAc, visualised using vanillin / Δ).

ν_{max} / cm^{-1} (neat): 2935 (CH), 2912 (CH), 2876 (CH), 1715 (CO), 1227 (PO); **δ_H (400 MHz, $CDCl_3$):** 4.22 – 4.01 (4 H, m, H-2), 3.60 (2 H, t, *J* 6.4, H-8), 3.06 (2 H, d, $^2J_{P-H}$ 22.8, H-3), 2.64 (2 H, t, *J* 7.2, H-5), 1.76 – 1.45 (4 H, stack, H-6 & H-7), 1.33 (6 H, t, *J* 7.1, H-1), 0.95 (9 H, t, *J* 8.0, H-10), 0.58 (6 H, q, *J* 8.0, H-9); **δ_C (101 MHz, $CDCl_3$):** 202.1 (CH, C-4), 62.7 (CH_2, d, $^2J_{P-C}$ 6.4, C-2), 62.6 (CH_2, C-8), 44.0 (CH_2, C-5), 42.5 (CH_2, d, $^1J_{P-C}$ 127.3, C-3), 32.2 (CH_2, C-7), 20.1 (CH_2, C-6), 16.5 (CH_3, d, $^3J_{P-C}$ 6.3, C-1), 6.9 (CH_2, C-10), 4.5 (CH_2, C-9); **LRMS m/z (ES$^+$):** 367.2 ([M + H]$^+$, 60%); **HRMS m/z (ES$^+$):** calcd. for $C_{16}H_{36}O_5PSi$ 367.2070, found 367.2072.

A known compound prepared according to a literature procedure.[50] *Analytical data in agreement with literature values.*[50]

***87** Methyl (R)-3-((tert-butyldiphenylsilyl)oxy)-2-methylpropanoate*



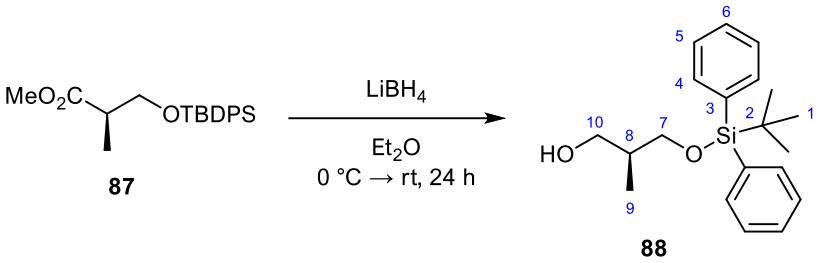
87

(*R*)-3-Hydroxy-2-methylpropionate (250 mg, 2.12 mmol) was dissolved in dichloromethane (11 mL) and the resulting solution cooled to 0 °C. Imidazole (317 mg, 4.65 mmol) and *tert*-butyldiphenylchlorosilane (698 mg, 2.54 mmol) were added, the cooling bath removed, and the reaction allowed to warm to rt. After 1 h the reaction was deemed complete by TLC and was diluted with brine (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (8:2 petroleum ether:Et_2O) to yield ester **87** as a colourless oil (764 mg, 99%). **R_f:** 0.40 (8:2 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 3072 (CH), 2932 (CH), 2858 (CH), 1739 (CH); **δ_H (400 MHz, $CDCl_3$):** 7.69 – 7.61 (4 H, m, H-4), 7.48 – 7.34 (6 H, stack, H-5 & H-6), 3.83 (1 H, dd, *J* 9.7, 6.9, H-7), 3.72 (1 H, dd, *J* 9.7, 5.8, H-7′), 3.68 (3 H, s, H-11), 2.72 (1 H, qdd, *J* 7.1, 6.9, 5.8, H-8), 1.16 (3 H, d, *J* 7.1, H-9), 1.03 (9 H, s, H-1); **δ_C (101 MHz, $CDCl_3$):** 175.5 (C, C-10), 135.7 (CH, C-4), 133.7 (C, C-3), 129.8 (CH, C-6), 127.8 (CH, C-5), 66.1 (CH_2, C-7), 51.7 (CH_3, C-11), 42.5 (CH, C-8), 26.9 (CH_3, C-1), 19.4 (C, C-2), 13.6 (CH_3, C-9); **LRMS m/z (ES$^+$):** 379.2 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{21}H_{28}O_3SiNa$ 379.1705, found 379.1715.

A known compound prepared according to a literature procedure.[56] *Analytical data in agreement with literature values.*[55]

88 *(S)-3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol*

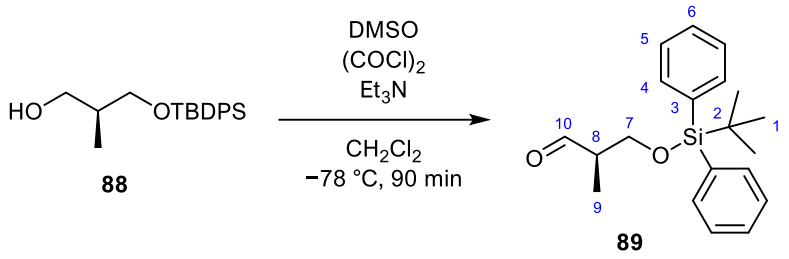


Ester **87** (1.80 g, 5.02 mmol) was dissolved in diethyl ether (25 mL) and the resulting solution cooled to 0 °C. Lithium borohydride (219 mg, 10.0 mmol) was added, the cooling bath removed, and the reaction allowed to warm to rt. After 16 h the reaction was determined complete by TLC, quenched with ammonium chloride (sat. aq. soln., 25 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (8:2 petroleum ether:Et_2O) to yield alcohol **88** as a colourless oil (1.63 g, 99%). **R_f:** 0.14 (8:2 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 3374 (br, OH), 3071 (CH), 2958 (CH), 2930 (CH), 2858 (CH), 1106 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.72 – 7.61 (4 H, m, H-4), 7.51 – 7.33 (6 H, stack, H-5 & H-6), 3.73 (1 H, dd, *J* 10.1, 4.5, H-7), 3.68 (1 H, d, *J* 5.2, H-10), 3.67 (1 H, d, *J* 5.6, H-10′), 3.59 (1 H, dd, *J* 10.1, 7.7, H-7′), 2.50 (1 H, dd, *J* 5.6, 5.2, OH), 2.07 – 1.91 (1 H, m, H-8), 1.06 (9 H, s, H-1), 0.83 (3 H, d, *J* 7.0, H-9); **δ_C (101 MHz, $CDCl_3$):** 135.7 (CH, C-4), 133.3 (C, C-3), 129.9 (CH, C-6), 127.9 (CH, C-5), 68.9 (CH_2, C-7), 67.9 (CH_2, C-10), 37.4 (CH, C-8), 27.0 (CH_3, C-1), 19.3 (C, C-2), 13.3 (CH_3, C-9); **LRMS m/z (ES$^+$):** 351.2 ([M + Na]$^+$, 100%).

A known compound prepared according to a literature procedure.[184] *Analytical data in agreement with literature values.*[55]

89 *(R)-3-((tert-Butyldiphenylsilyl)oxy)-2-methylpropanal*



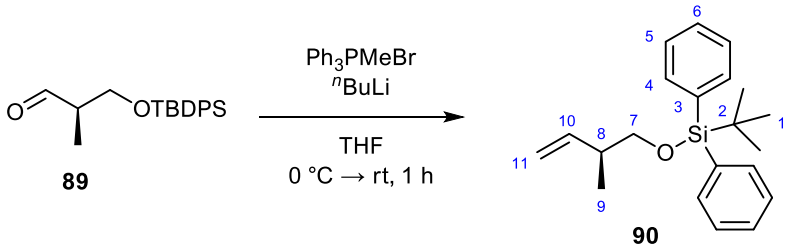
Oxalyl chloride (0.85 mL, 9.9 mmol) was dissolved in anhydrous dichloromethane (5 mL) and the resulting solution cooled to −78 °C. A solution of dimethyl sulfoxide (1.41 mL, 19.8 mmol) in dichloromethane (5 mL) was added and the reaction stirred for 15 min. A solution of alcohol **88** (1.63 g, 4.96 mmol) in dichloromethane (20 mL) was then added dropwise over 5 min and the reaction stirred for 90 min. Triethylamine (5.2 mL, 37 mmol) was added, the cooling bath removed, and the reaction allowed to warm to rt. The reaction was then quenched with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to yield aldehyde **89** as a colourless oil (1.49 g, 89%) of sufficient purity to not require further purification.* **R_f:** 0.44 (9:1 hexane:EtOAc, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 3072 (CH), 2932 (CH), 2858 (CH), 2720 (CH), 1736 (CO), 1106 (CO); **δ_H (400 MHz, $CDCl_3$):** 9.78 (1 H, d, *J* 1.6, H-10), 7.68 – 7.60 (4 H, m, H-4), 7.48 – 7.35 (6 H, stack, H-5 & H-6), 3.90 (1 H, dd, *J* 10.3, 5.0, H-7), 3.84 (1 H, dd, *J* 10.3, 6.4, H-7′), 2.62 – 2.51 (1 H, m, H-8), 1.10 (3 H, d, *J* 7.0, H-9), 1.04 (9 H, s, H-1); **δ_C (101 MHz, $CDCl_3$):** 204.6 (CH, C-10), 135.7 (CH, C-4), 133.3 (C, C-3), 130.0 (CH, C-6), 127.9 (CH, C-5), 64.3 (CH_2, C-7), 49.0 (CH, C-8), 26.9 (CH_3, C-1), 19.4 (C, C-2), 10.4 (CH_3, C-9); **LRMS m/z (ES$^+$):** 365.2 ([M + K]$^+$, 100%).

A known compound prepared according to a literature procedure.[56] *Analytical data in agreement with literature values.*[55]

** Product is unstable to column chromatography.*

90 *(S)-tert-Butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane*

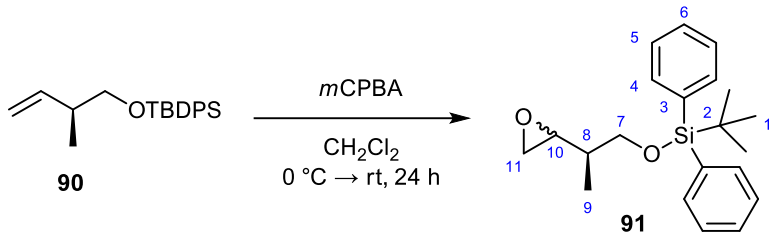


Methyltriphenylphosphonium bromide (1.64 g, 4.60 mmol) was added to anhydrous THF (12 mL) and the resulting suspension cooled to 0 °C. *n*-Butyllithium (2.00 M in hexane, 2.42 mL, 4.60 mmol) was added and the reaction stirred for 20 min. A solution of aldehyde **89** (1.50 g, 4.60 mmol) in THF (12 mL) was added, the cooling bath removed, and the reaction allowed to warm to rt. After 45 min the reaction was quenched with ammonium chloride (sat. aq. soln., 25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (100% hexane) to yield alkene **90** as a colourless oil (726 mg, 97%). **R_f:** 0.68 (95:5 hexane:EtOAc, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 3072 (CH), 2960 (CH), 2931 (CH), 2896 (CH), 2858 (CH), 1106 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.73 – 7.63 (4 H, m, H-4), 7.47 – 7.32 (6 H, stack, H-5 & H-6), 5.80 (1 H, ddd, *J* 17.4, 10.4, 6.9, H-10), 5.03 (1 H, ddd, *J* 17.4, 1.9, 1.4, H-11$_Z$), 4.99 (1 H, ddd, *J* 10.4, 1.9, 1.2, H-11$_E$), 3.57 (1 H, dd, *J* 9.7, 6.2, H-7), 3.49 (1 H, dd, *J* 9.7, 6.7, H-7′), 2.44 – 2.35 (1 H, m, H-8), 1.05 (9 H, s, H-1), 1.03 (3 H, d, *J* 6.8, H-9); **δ_C (101 MHz, $CDCl_3$):** 141.5 (CH, C-10), 135.8 (CH, C-4), 134.1 (C, C-3), 129.7 (CH, C-6), 127.7 (CH, C-5), 114.2 (CH_2, C-11), 68.6 (CH_2, C-7), 40.4 (CH, C-8), 27.0 (CH_3, C-1), 19.5 (C, C-2), 16.3 (CH_3, C-9); **LRMS m/z (Cl$^+$):** 325.2 ([M + H]$^+$, 50%), 309.2 ([M − CH_3]$^+$, 100); **HRMS m/z (Cl$^+$):** calcd. for $C_{21}H_{29}OSi$ 325.1988, found 325.1975.

A known compound prepared according to a literature procedure.[56] *Analytical data in agreement with literature values.*[55]

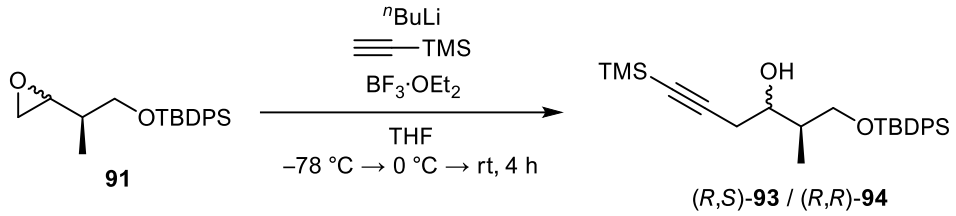
***91** tert-Butyl((2R)-2-(oxiran-2-yl)propoxy)diphenylsilane*



Alkene **90** (752 mg, 2.13 mmol) was dissolved in dichloromethane (10 mL) and the resulting solution cooled to 0 °C. *meta*-Chloroperbenzoic acid (883 mg, 5.12 mmol) was added, the cooling bath removed, and the reaction allowed to warm to rt. After 24 h the reaction was deemed complete by TLC, diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (98:2 petroleum ether:Et_2O) to yield epoxide **91** as a colourless oil (648 mg, 89%, 1.4:1 mixture of diastereoisomers). **R_f:** 0.44 (95:5 hexane:Et_2O, visualised using $KMnO_4$ / Δ). **ν_{max} / cm^{-1} (neat):** 3071 (CH), 2049 (CH), 2960 (CH), 2931 (CH), 2858 (CH), 1106 (CO); **Major isomer δ_H (400 MHz, $CDCl_3$):** 7.72 – 7.61 (4 H, m, H-4), 7.48 – 7.34 (6 H, stack, H-5 & H-6), 3.76 – 3.57 (2 H, m, H-11), 2.85 (1 H, ddd, *J* 6.9, 4.0, 2.7, H-10), 2.77 (1 H, dd, *J* 5.0, 3.9, H-7), 2.60 (1 H, dd, *J* 5.0, 2.8, H-7′), 1.66 – 1.51 (1 H, m, H-8), 1.05 (9 H, s, H-1), 0.99 (3 H, d, *J* 6.8, H-9); **δ_C (101 MHz, $CDCl_3$):** 135.8 (CH, C-4), 133.7 (C, C-3), 129.83 (CH, C-6), 127.83 (CH, C-5), 66.5 (CH_2, C-11), 55.3 (CH, C-10), 47.1 (CH_2, C-7), 39.3 (CH, C-8), 26.9 (CH_3, C-1), 19.4 (C, C-2), 13.5 (CH_3, C-9); **Minor isomer δ_H (400 MHz, $CDCl_3$):** 7.72 – 7.61 (4 H, m, H-4), 7.48 – 7.34 (6 H, stack, H-5 & H-6), 3.76 – 3.57 (2 H, m, H-11), 2.98 (1 H, ddd, *J* 6.9, 4.1, 2.8, H-10), 2.75 (1 H, dd, *J* 5.1, 4.0, H-7), 2.54 (1 H, dd, *J* 5.1, 2.8, H-7′), 1.66 – 1.51 (1 H, m, H-8), 1.06 (9 H, s, H-1), 1.00 (3 H, d, *J* 7.0, H-9); **δ_C (101 MHz, $CDCl_3$):** 135.7 (CH, C-4), 133.8 (C, C-3), 129.76 (CH, C-6), 127.79 (CH, C-5), 66.2 (CH_2, C-11), 54.1 (CH, C-10), 45.9 (CH_2, C-7), 38.7 (CH, C-8), 27.0 (CH_3, C-1), 19.5 (C, C-2), 12.8 (CH_3, C-9); **LRMS m/z (ES$^+$):** 363.2 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{21}H_{28}O_2SiNa$ 363.1756, found 363.1761.

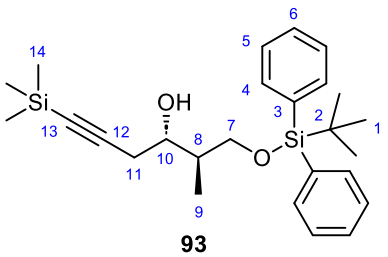
A known compound prepared according to a literature procedure.[56] Analytical data in agreement with literature values.[55] NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7′ & H-11′ resonances used to determine diastereomeric ratio.

93 *(2R,3S)-1-((tert-Butyldiphenylsilyl)oxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol*
& ***94*** *(2R,3R)-1-((tert-Butyldiphenylsilyl)oxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol*



Trimethylsilylacetylene (0.43 mL, 3.1 mmol) was dissolved in anhydrous THF (3.5 mL) and the resulting solution was cooled to –78 °C. *n*-Butyllithium (1.76 M in hexane, 1.52 mL, 2.67 mmol) was added and the reaction stirred for 20 min. The cooling bath was then changed, and the reaction allowed to warm to 0 °C. Boron trifluoride diethyl etherate (0.22 mL, 1.8 mmol) was added followed by a solution of epoxide **91** (302 mg, 0.888 mmol) in THF (3.5 mL), the cooling bath removed, and the reaction allowed to warm to rt. After 1 h the reaction was quenched with ammonium chloride (sat. aq. soln., 10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (99:1 hexane:EtOAc) to yield **93** & **94** as a colourless oil (283 mg, 73%, 1.1:1 mixture of diastereoisomers).

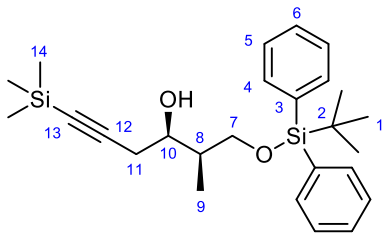
ν_{max} / cm^{-1} (neat): 3454 (br, OH), 3072 (CH), 2960 (CH), 2931 (CH), 2858 (CH), 2175 (CC); **LRMS m/z (AP$^-$):** 473.2 ([M − H]$^-$, 100 %); **HRMS m/z (AP$^-$):** calcd. for $C_{26}H_{37}O_2Si_2$ 437.2332, found 437.2339.



93

R_f: 0.31 (9:1 hexane:Et_2O, visualised using vanillin / Δ); **δ_H (400 MHz, $CDCl_3$):** 7.72 – 7.62 (4 H, m, H-4), 7.49 – 7.34 (6 H, stack, H-5 & H-6), 3.79 (1 H, dd, *J* 10.3, 4.3, H-7), 3.78 – 3.71 (1 H, m, H-10), 3.67 (1 H, dd, *J* 10.3, 6.5, H-7′), 3.45 (1 H, d, *J* 4.1, OH), 2.55 (1 H, dd, *J* 17.0, 4.9, H-11), 2.47 (1 H, dd, *J* 17.0, 6.2, H-11′), 1.96 (1 H, qddd, *J* 7.0, 6.5, 5.9, 4.3, H-8), 1.06 (9 H, s, H-

1), 0.91 (3 H, d, *J* 7.0, H-9), 0.16 (9 H, s, H-14); **δ_C (101 MHz, $CDCl_3$):** 135.7 (CH, C-4), 133.1 (C, C-3), 130.0 (CH, C-6), 127.9 (CH, C-5), 103.8 (C, C-12), 87.1 (C, C-13), 73.8 (CH, C-10), 67.8 (CH_2, C-7), 39.3 (CH, C-8), 27.0 (CH_3, C-1), 26.8 (CH_2, C-11), 19.3 (C, C-2), 13.7 (CH_3, C-9), 0.3 (CH_3, C-14).

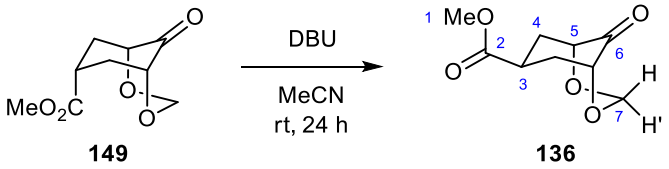


94

R_f: 0.25 (9:1 hexane:Et_2O, visualised using vanillin / Δ); **δ_H (400 MHz, $CDCl_3$):** 7.70 – 7.63 (4 H, m, H-4), 7.48 – 7.35 (6 H, stack, H-5 & H-6), 4.04 (1 H, dddd, *J* 6.9, 6.8, 4.0, 3.4, H-10), 3.76 (1 H, dd, *J* 10.1, 4.2, H-7), 3.68 (1 H, dd, *J* 10.1, 5.4, H-7′), 2.83 (1 H, d, *J* 3.4, OH), 2.50 (1 H, dd, *J* 16.8, 6.8, H-11), 2.42 (1 H, dd, *J* 16.8, 6.9, H-11′), 1.97 – 1.88 (1 H, m, H-8), 1.06 (9 H, s, H-1), 0.97 (3 H, d, *J* 7.1, H-9), 0.14 (9 H, s, H-14); **δ_C (101 MHz, $CDCl_3$):** 135.7 (CH, C-4), 133.2 (C, C-3), 130.0 (CH, C-6), 127.9 (CH, C-5), 103.9 (C, C-12), 86.9 (C, C-13), 72.4 (CH, C-10), 68.4 (CH_2, C-7), 38.4 (CH, C-8), 27.0 (CH_3, C-1), 26.2 (CH_2, C-11), 19.4 (C, C-2), 10.3 (CH_3, C-9), 0.2 (CH_3, C-14).

Known compounds prepared according to a literature procedure.[56] *Analytical data in agreement with literature values.*[55] *NMR assignments of diastereoisomers assigned from small amounts of separated isomers. H-11 & H-11′ resonances used to determine diastereomeric ratio. IR & MS data identical for both isomers.*

136 *Methyl (1R,5S,7s)-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

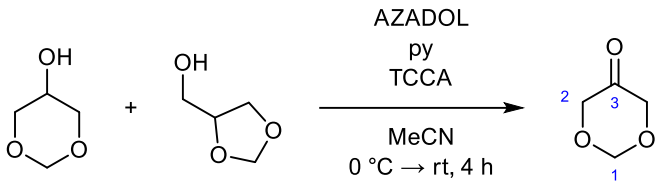


1,8-Diazabicyclo[5.4.0]undec-7-ene (563 mg, 3.70 mmol) and axial ester **149** (740 mg, 3.70 mmol) were added to acetonitrile (15 mL) and the resulting solution was stirred at rt. After 24 h the reaction was determined complete by TLC, concentrated under reduced pressure to give a residue which was purified by flash column chromatography (3:1 hexane:Et_2O) to yield bicyclic ketone **136** as a white solid (559 mg, 76%). **R_f:** 0.42 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

m.p. 65 – 67 °C; **ν_{max} / cm^{-1} (neat):** 2954 (CH), 1753 (CO_2Me), 1733 (CO); **δ_H (400 MHz, $CDCl_3$):** 5.03 (1 H, d, *J* 6.6, H-7′), 4.77 (1 H, d, *J* 6.6, H-7), 4.43 (2 H, d, *J* 3.9, H-5), 3.69 (3 H, s, H-1), 3.60 (1 H, tt, *J* 12.6, 4.6, H-3), 2.73 – 2.63 (2 H, m, H-4_{eq}), 1.99 (2 H, app. t, *J* 13.8, H-4_{ax}); **δ_C (101 MHz, $CDCl_3$):** 211.8 (C, C-6), 174.3 (C, C-2), 90.5 (CH_2, C-7), 80.2 (CH, C-5), 52.2 (CH_3, C-1), 39.7 (CH_2, C-4), 33.0 (CH, C-3); **LRMS m/z (AP$^-$):** 169.0 ([M − OCH_3]$^-$, 100%).

A novel compound prepared according to a modified literature procedure.[49] *HRMS could not be accurately obtained.*

***148** 1,3-Dioxan-5-one*



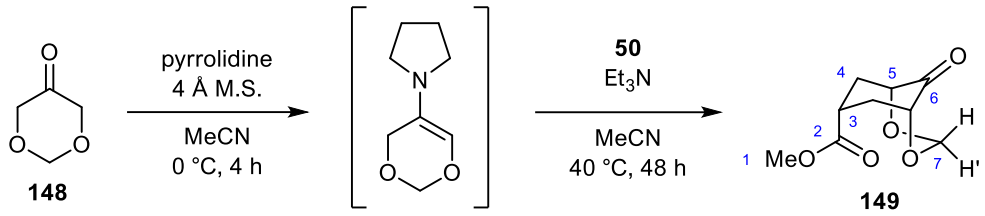
148

Glycerol formal (21.2 mL, 244 mmol), pyridine (24.6 mL, 305 mmol) and 2-azaadamantan-2-ol (38 mg, 0.24 mmol, 0.1 mol%) were dissolved in acetonitrile (80 mL) and the resulting solution cooled to 0 °C using a carefully controlled dry ice / acetone cooling bath. A solution of trichloroisocyanuric acid (23.5 g, 100 mmol) in acetonitrile (80 mL) was added dropwise over 1 h, with the internal reaction temperature maintained between −5 and 5 °C by addition of small amounts dry ice to the cooling bath. The cooling bath was then removed, and the reaction allowed to warm to rt. After 4 h, 2-propanol (3.68 mL, 48.1 mmol) was added and the reaction stirred for a further 20 min, during which time a yellow precipitate formed. The reaction mixture was then filtered through a pad of celite and rinsed with acetonitrile (3 × 100 mL) and the solvents were removed under reduced pressure at rt to give a brown residue which was purified by distillation (30 °C, 3.0 mbar) to yield dioxanone **148** as a white solid (18.7 g, 75%).

m.p. 27 – 30 °C; **ν_{max} / cm^{-1} (neat):** 2867 (CH), 1739 (CO); **δ_H (400 MHz, $CDCl_3$):** 5.01 (2 H, s, H-1). 4.36 (4 H, s, H-2); **δ_C (101 MHz, $CDCl_3$):** 203.8 (C, C-3), 91.6 (CH_2, C-1), 73.5 (CH_2, C-2); **LRMS m/z (EI$^+$):** 102.0 ([M]$^+$, 100%); **HRMS m/z (EI$^+$):** calcd. for $C_4H_6O_3$ 102.0336, found 102.0317.

A known compound prepared according to a literature procedure.[149] *Analytical data in agreement with literature values.*[149]

***149** Methyl (1R,5S,7r)-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



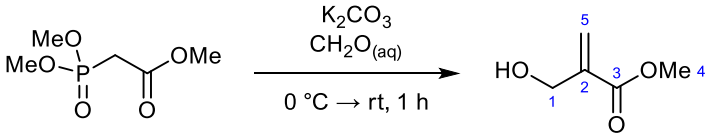
148 **149**

Dioxanone **148** (2.61 g, 25.6 mmol) and activated 4 Å molecular sieves (2.56 g) were added to anhydrous acetonitrile (73 mL) and the resulting mixture cooled to 0 °C. Freshly distilled pyrrolidine (2.10 mL, 25.6 mmol) was added and the reaction was stirred for 4 h, after which time triethylamine (2.38 mL, 17.1 mmol) was added followed by syringe-pump addition of a solution of methyl 2-(bromomethyl)acrylate **50** (3.06 g, 17.1 mmol) in anhydrous acetonitrile (73 mL) over 1 h. The reaction was then heated to 40 °C and stirred for an additional 48 h after which time the solution was filtered through a plug of celite and rinsed with acetonitrile (3 × 100 mL). Water (100 mL) was added to the resulting solution and was stirred at room temperature for 4 h. The acetonitrile was then removed under reduced pressure and the resulting aqueous solution extracted with dichloromethane (20 × 100 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was dissolved in dichloromethane. Silica (~2.5 g) was then added and the mixture stirred for 4 h followed by removal of the solvent under reduced pressure to give a "dry-load" which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield bicyclic ketone **149** as a white crystalline solid (1.52 g, 44%). **R_f:** 0.18 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

m.p. 85 – 88 °C; **ν_{max} / cm^{-1} (neat):** 2952 (CH), 1730 (2 × CO); **δ_H (400 MHz, $CDCl_3$):** 4.90 (1 H, d, *J* 6.5, H-7′), 4.72 (1 H, d, *J* 6.5, H-7), 4.48 – 4.44 (2 H, m, H-5), 3.79 (3 H, s, H-1), 3.38 – 3.29 (2 H, dm, *J* 13.8, H-4_{eq}), 2.65 (1 H, tt, *J* 7.1, 1.2, H-3), 2.04 (2 H, dd, *J* 13.8, 7.1, H-4_{ax}); **δ_C (101 MHz, $CDCl_3$):** 212.8 (C, C-6), 173.8 (C, C-2), 90.6 (CH_2, C-7), 80.9 (CH, C-5), 52.3 (CH_3, C-1), 38.1 (CH_2, C-4), 33.7 (CH, C-3); **LRMS m/z (AP$^-$):** 169.0 ([M − OCH_3]$^-$, 100%).

A novel compound prepared according to a modified literature procedure.[49] *HRMS could not be accurately obtained.*

***151** Methyl 2-(hydroxymethyl)acrylate*



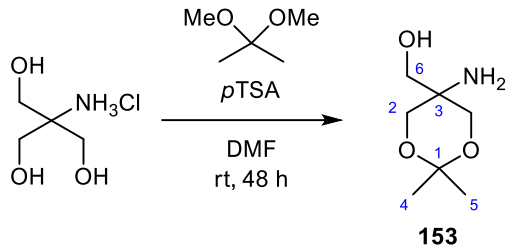
151

Trimethyl phosphonoacetate (10.0 mL, 62.0 mmol) was added to formaldehyde (37% w/v aq. soln., 23.0 mL, 372 mmol) and the resulting mixture was stirred vigorously and cooled to 0 °C. A solution of potassium carbonate (15.0 g, 109 mmol) in water (14 mL) was added dropwise over 30 min, after which time the cooling bath was removed and the reaction allowed to warm to rt. After 1 h the reaction was determined complete by TLC and ammonium chloride (sat. aq. soln., 25 mL) was added slowly. Upon the cessation of effervescence the reaction mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions were washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by distillation (60 °C, 1.3 mbar) to yield acrylate **151** as a colourless oil (4.01 g, 56%). 4-Methoxyphenol (77 mg, 0.62 mmol, 1% w/w) was added to the product to prevent polymerisation.[135] **R_f:** 0.40 (7:3 hexane:EtOAc, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 3422 (br, OH), 2955 (CH), 1714 (CO), 1635 (CC); **δ_H (400 MHz, $CDCl_3$):** 6.26 (1 H, app. q, *J* 0.9, H-5$_Z$), 5.84 (1 H, app. q, *J* 1.3, H-5$_E$), 4.33 (1 H, d, *J* 4.9, H-1), 3.79 (3 H, s, H-4), 2.31 (1 H, t, *J* 5.9, OH); **δ_C (101 MHz, $CDCl_3$):** 166.9 (C, C-3), 139.4 (C, C-2), 126.0 (CH_2, C-5), 62.7 (CH_2, C-1), 52.1 (CH_3, C-4); **LRMS m/z (EI$^+$):** 116.1 ([M]$^+$, 15%), 101.1 ([M − CH_3]$^+$, 37), 99.1 ([M − OH]$^+$, 100).

A known compound prepared according to a modified literature procedure.[134] *Analytical data in agreement with literature values.*[55]

153 *(5-Amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol*



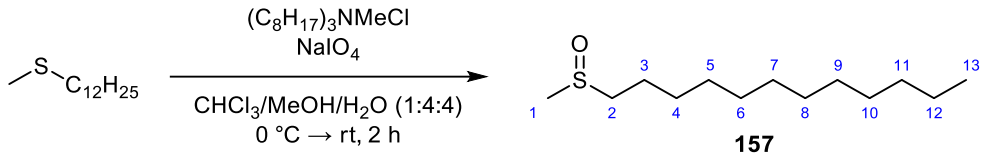
153

2,2-Dimethoxypropane (4.30 mL, 34.9 mmol), 2-amino-2-hydroxymethyl-1,3-propandiol hydrochloride (5.00 g, 31.7 mmol) and *para*-toluenesulfonic acid monohydrate (301 mg, 1.59 mmol, 5 mol%) and were sequentially to *N*,*N*-dimethylformamide (12 mL) and the resulting mixture stirred at rt. After 48 h triethylamine (0.75 mL, 5.4 mmol) was then added and the solvent removed under reduced pressure. The resulting crude gel was sonicated in methanol (50 mL) for 1 h, followed by removal of the solvent under reduced pressure. The resulting residue was suspended in ethyl acetate (45 mL) and triethylamine (7.16 mL, 51.3 mmol) was added and stirred at rt. After 10 min the resulting mixture was filtered through a pad of celite, rinsed with ethyl acetate (3 × 50 mL) and the solvent removed under reduced pressure to yield β-aminoalcohol **153** as a white solid (6.60 g, 77%) of sufficient purity to not require further purification.

ν_{max} / cm^{-1} (neat): 3322 (NH), 3268 (NH), 3150 (br, OH), 2989 (CH), 2955 (CH), 2913 (CH), 2864 (CH); **δ_H (400 MHz, $CDCl_3$):** 3.79 (2 H, d, *J* 11.8, H-2′), 3.52 (2 H, d, *J* 11.8, H-2), 3.49 (2 H, s, H-6), 1.77 (3 H, br, NH_2 & OH), 1.45 (3 H, s, H-4 / H-5), 1.42 (3 H, s, H-4 / H-5); **δ_C (101 MHz, $CDCl_3$):** 98.6 (C, C-1), 67.4 (CH_2, C-2), 65.2 (CH_2, C-6), 50.3 (C, C-3), 25.1 (CH_3, C-4 / C-5), 22.4 (CH_3, C-4 / C-5); **LRMS m/z (ES+):** 162.1 ([M + H]$^+$, 100%), 144.1 ([M − OH]$^+$, 18); **HRMS m/z (ES+):** calcd. for $C_7H_{16}NO_3$ 162.1131, found 162.1130.

A known compound prepared according to a literature procedure.[138] *Analytical data in agreement with literature values.*[50]

***157** 1-(Methylsulfinyl)dodecane*



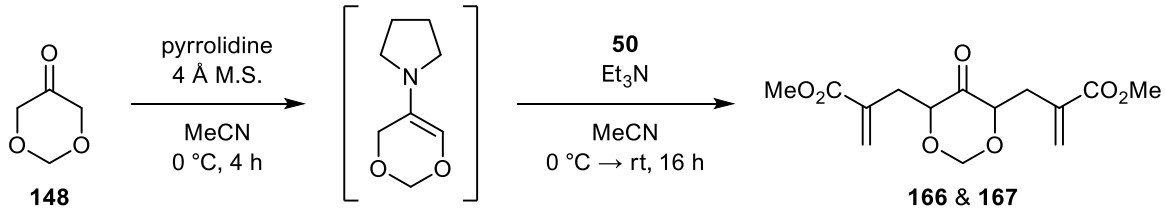
157

Dodecyl methyl sulfide (1.22 mL, 4.62 mmol) was dissolved in a 1:4:4 mixture of chloroform, methanol and water (180 mL) and the resulting solution cooled 0 °C. Trioctylmethylammonium chloride (372 mg, 0.920 mmol) and sodium periodate (5.92 g, 27.7 mmol) were added, the cooling bath removed and the reaction allowed to warm to rt. After 10 min the reaction mixture was then added to water (200 mL) and stirred vigorously at rt. After 2 h the reaction was determined complete by TLC and the reaction mixture was concentrated to half its original volume and extracted with ethyl acetate (3 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (98:2 EtOAc:MeOH) to yield sulfoxide **157** as a white powder (1.02 g, 95%). **R_f:** 0.26 (98:2 EtOAc:MeOH, visualised using $KMnO_4$ / Δ).

m.p. 64 – 66 °C; **ν_{max} / cm^{-1} (neat):** 3000 (CH), 2964 (CH), 2954 (CH), 2915 (CH), 2847 (CH), 1018 (SO); **δ_H (400 MHz, $CDCl_3$):** 2.78 – 2.60 (2 H, m, H-2), 2.56 (3 H, s, H-1), 1.83 – 1.67 (2 H, m, CH_2), 1.55 – 1.15 (18 H, stack, 9 × CH_2), 0.88 (3 H, t, *J* 7.0, H-13); **δ_C (101 MHz, $CDCl_3$):** 55.0 (CH_2, C-2), 38.7 (CH_3, C-1), 32.0 (CH_2), 29.75 (2 × CH_2), 29.68 (CH_2), 29.50 (CH_2), 29.48 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.3 (CH_3, C-13); **LRMS m/z (ES$^+$):** 233.2 ([M]$^+$, 100 %).

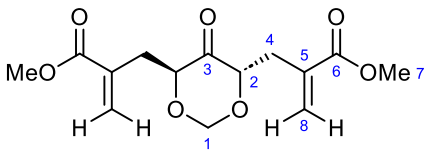
A known compound prepared according to a literature procedure.[144] *Analytical data in agreement with literature values.*[144]

166 *trans-Dimethyl-2,2'-((5-oxo-1,3-dioxane-4,6-diyl)bis(methylene))diacrylate*
*& **167** cis-Dimethyl-2,2'-((5-oxo-1,3-dioxane-4,6-diyl)bis(methylene))diacrylate*



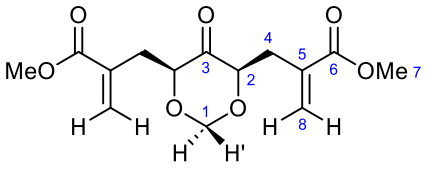
148 **166** & **167**

Dioxanone **148** (1.00 g, 9.79 mmol) and activated 4 Å molecular sieves (979 mg) were added to anhydrous acetonitrile (28 mL) and the resulting mixture cooled to 0 °C. Freshly distilled pyrrolidine (689 mg, 9.79 mmol) was added and the reaction was stirred for 4 h, after which time triethylamine (1.65 mL, 11.7 mmol) was added followed by a solution of methyl 2-(bromomethyl)acrylate **50** (2.09 g, 11.7 mmol) in anhydrous acetonitrile (33 mL). The cooling bath was then removed, and the reaction allowed to warm to rt. After 16 h the solution was filtered through a plug of celite and rinsed with acetonitrile (3 × 500 mL). Water (50 mL) was added to the resulting solution and was stirred at room temperature for 4 h. The acetonitrile was then removed under reduced pressure and the resulting aqueous solution extracted with dichloromethane (10 × 50 mL). The combined organic fractions were stirred over silica for 4 h, then filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield **166** (127 mg, 4%) & **167** (388 mg, 13%) as colourless oils.



166

R_f: 0.33 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ); **δ_H (400 MHz, $CDCl_3$):** 6.29 (2 H, d, *J* 1.1, H-8$_Z$), 5.70 (2 H, app. q, *J* 1.1, 1.0, H-8$_E$), 5.05 (2 H, s, H-1), 4.49 (2 H, dd, *J* 9.7, 4.1, H-2), 3.76 (6 H, s, H-7), 3.00 (2 H, ddd, *J* 14.9, 4.1, 1.0, H-4), 2.61 (2 H, ddd, *J* 14.9, 9.7, 1.0, H-4′); **δ_C (101 MHz, $CDCl_3$):** 206.9 (C, C-3), 167.2 (C, C-6), 135.6 (C, C-5), 128.5 (CH_2, C-8), 89.8 (CH_2, C-1), 78.3 (CH, C-2), 52.2 (CH_3, C-7), 32.4 (CH_2, C-4).

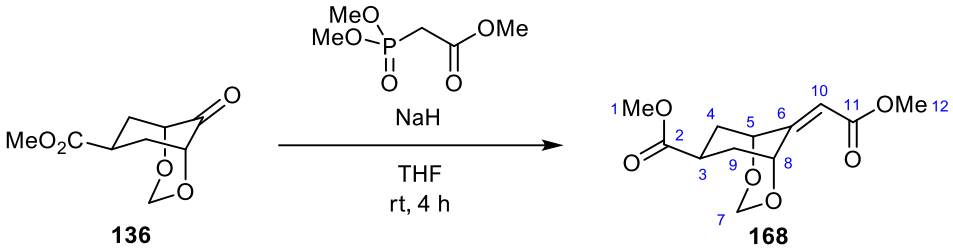


167

R_f: 0.24 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ); **δ_H (400 MHz, $CDCl_3$):** 6.27 (2 H, d, *J* 1.1, H-8_Z), 5.71 (2 H, dd, *J* 1.1, 0.9, H-8_E), 5.12 (1 H, d, *J* 6.5, H-1′), 4.99 (1 H, d, *J* 6.5, H-1), 4.45 (2 H, dd, *J* 9.5, 3.7, H-2), 3.74 (6 H, s, H-7), 3.09 (2 H, ddd, *J* 14.9, 3.7, 0.9, H-4), 2.55 (2 H, ddd, *J* 14.9, 9.5, 0.9, H-4′); **δ_C (101 MHz, $CDCl_3$):** 203.8 (C, C-3), 167.2 (C, C-6), 135.4 (C, C-5), 128.8 (CH_2, C-8), 91.9 (CH_2, C-1), 81.2 (CH, C-2), 52.1 (CH_3, C-7), 32.5 (CH_2, C-4).

*Novel compounds isolated as a by-product from the attempted formation of **149** according to a modified literature procedure.*[49] *Ketone **149** was not formed under these conditions.*

168 *Methyl (1R,5S,7s)-9-(2-methoxy-2-oxoethylidene)-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

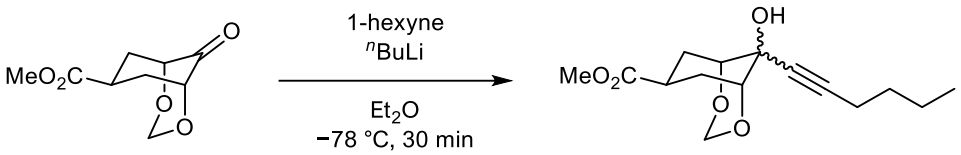


Trimethyl phosphonoacetate (45 mg, 0.25 mmol) was added dropwise over 5 min to a suspension of sodium hydride (50% w/w dispersion in mineral oil, 6 mg, 0.3 mmol) in anhydrous THF (2.5 mL) and the reaction mixture was stirred at rt. After 1 h ketone **136** (50 mg, 0.25 mmol) was added. After 4 h the reaction was determined complete by TLC and the reaction was quenched with water (2.5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (1:1 hexane:Et_2O) to yield enone **168** as a colourless oil (44 mg, 68%). **R_f:** 0.48 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 2953 (CH), 2854 (CH), 1718 (2 × CO), 1669 (CC); **δ_H (400 MHz, $CDCl_3$):** 5.92 – 5.89 (2 H, stack, H-10 & H-8), 4.77 (1 H, d, *J* 5.8, H-7), 4.75 (1 H, d, *J* 5.8, H-7′), 4.65 – 4.59 (1 H, m, H-5), 3.74 (3 H, s, H-12), 3.67 (3 H, s, H-1), 3.47 (1 H, tt, *J* 12.5, 4.7, H-3), 2.53 – 2.42 (2 H, stack, H-4_{eq} & H-9_{eq}), 1.76 (1 H, ddd, *J* 14.3, 12.6, 1.6, H-9_{ax}), 1.70 (1 H, ddd, *J* 14.3, 12.4, 1.8, H-4_{ax}); **δ_C (101 MHz, $CDCl_3$):** 175.5 (C, C-2), 165.2 (C, C-11), 155.7 (C, C-6), 117.0 (CH, C-10), 87.1 (CH_2, C-7), 76.6 (CH_3, C-5), 70.4 (CH_3, C-8), 52.0 (CH_3, C-1), 51.8 (CH_3, C-12), 38.8 (CH_2, C-4), 37.4 (CH_2, C-9), 33.7 (CH, C-3); **LRMS m/z (ES$^+$):** 256.2 ([M]$^+$, 39%).

A novel compound prepared according to a modified literature procedure.[152] *HRMS could not be accurately obtained.*

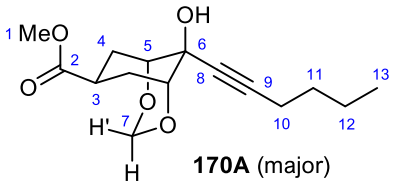
***170A** Methyl (1R,5S,7s,9r)-9-(hex-1-yn-1-yl)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate & **170B** Methyl (1R,5S,7s,9s)-9-(hex-1-yn-1-yl)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



136 **170**

1-Hexyne (23 mg, 0.28 mmol) was dissolved in anhydrous diethyl ether (2.8 mL) and the resulting solution cooled to –78 °C. *n*-Butyllithium (2.38 M in hexane, 0.12 mL, 0.28 mmol) was added and the reaction stirred at –78 °C. After 30 min, the solution of was added to a solution of ketone **136** (46 mg, 0.23 mmol) in diethyl ether (2.3 mL) at –78 °C. After 30 min, the cooling bath was removed and the reaction was allowed to warm to rt, quenched with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic fractions were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:EtOAc) to yield **170** as a colourless oil (49 mg, 75%, 3.6:1 mixture of diastereoisomers). **R_f:** 0.36 (1:1 hexane:Et_2O, visualised using vanillin / Δ).

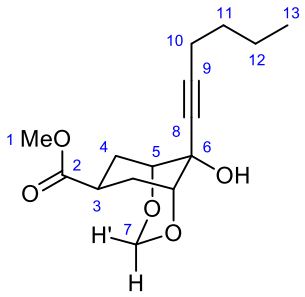
ν_{max} / cm^{-1} (neat): 3409 (br, OH), 2960 (CH), 2931 (CH), 2876 (CH), 1735 (CO); **LRMS m/z (ES$^+$):** 305.1 ([M + Na]$^+$, 53%); **HRMS m/z (ES$^+$):** calcd. for $C_{15}H_{22}O_5Na$ 305.1365, found 305.1369.



170A (major)

δ_H (400 MHz, $CDCl_3$): 5.48 (1 H, d, *J* 5.2, H-7), 5.00 (1 H, d, *J* 5.2, H-7′), 4.19 – 4.13 (2 H, m, H-5), 3.68 (3 H, s, H-1), 3.26 – 3.07 (1 H, m, H-3), 2.55 – 2.05 (6 H, stack, H-4 & H-10), 1.62 – 1.34 (4 H, stack, H-11, H-12 & OH), 0.91 (3 H, t, *J* 7.3, H-13);

δ_C (101 MHz, $CDCl_3$): 175.9 (C, C-2), 87.7 (C, C-9), 85.6 (CH_2, C-7), 82.7 (C, C-8), 74.2 (CH, C-5), 62.7 (C, C-6), 52.0 (CH_3, C-1), 33.5 (CH, C-3), 30.6 (CH_2, C-11), 28.6 (CH_2, C-4), 22.1 (CH_2, C-12), 18.6 (CH_2, C-10), 13.7 (CH_3, C-13).

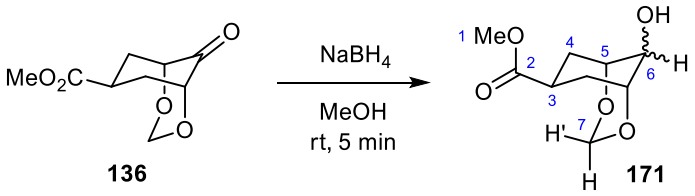


170B (minor)

δ_H (400 MHz, $CDCl_3$): 5.18 (1 H, d, *J* 5.4, H-7'), 5.10 (1 H, d, *J* 5.4, H-7), 4.10 – 4.04 (2 H, m, H-5), 3.70 (3 H, s, H-1), 3.26 – 3.07 (1 H, m, H-3), 2.55 – 2.05 (6 H, stack, H-4 & H-10), 1.62 – 1.34 (5 H, stack, H-11, H-12 & OH), 0.90 (3 H, t, *J* 7.3, H-13); **δ_C (101 MHz, $CDCl_3$):** 175.2 (C, C-2), 87.7 (C, C-9), 86.7 (CH_2, C-7), 82.7 (C, C-8), 74.8 (CH, C-5), 62.7 (C, C-6), 52.2 (CH_3, C-1), 35.3 (CH, C-3), 30.4 (CH_2, C-11), 28.6 (CH_2, C-4), 22.1 (CH_2, C-12), 18.5 (CH_2, C-10), 13.7 (CH_3, C-13).

A novel compound prepared according to a modified literature procedure.[55] *NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7 & H-7' resonances used to determine diastereomeric ratio.*

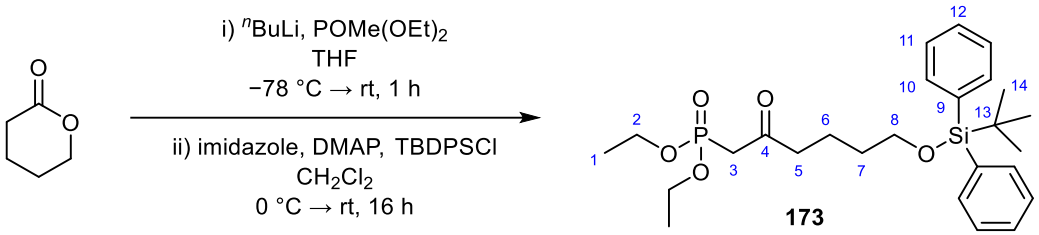
171A *Methyl (1R,5S,7s,9r)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*
& ***171B*** *Methyl (1R,5S,7s,9s)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



Ketone **136** (100 mg, 0.500 mmol) was dissolved in methanol (2.5 mL) and sodium borohydride (21 mg, 0.55 mmol) was added to the resulting solution. After 5 min the reaction was determined complete by TLC and quenched with water (2.5 mL) and extracted with ethyl acetate (3 × 2.5 mL). The combined organic fractions were washed with brine (2.5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (3:1 hexane:EtOAc) to yield alcohol **171** as a white solid (74 mg, 74%, 3.4:1 mixture of diastereoisomers). **R_f:** 0.12 (3:1 hexane:EtOAc, visualised using $KMnO_4$ / Δ); **ν_{max} / cm^{-1} (neat):** 3447 (br, OH), 2931 (CH), 1714 (CO); **LRMS m/z (ASAP$^+$):** 203.1 ([M + H]$^+$, 92 %), 185.1 ([M – OH]$^+$, 100); **HRMS m/z (ASAP$^+$):** calcd. for $C_9H_{15}O_5$ 203.0919, found 203.0921. **Major isomer δ_H (400 MHz, $CDCl_3$):** 5.19 (1 H, d, *J* 5.6, H-7), 4.76 (1 H, d, *J* 5.6, H-7′), 4.55 (1 H, q, *J* 4.8, H-6), 4.33 – 4.28 (2 H, m, H-5), 3.68 (3 H, s, H-1), 3.31 – 3.14 (1 H, m, H-3), 2.21 (1 H, d, *J* 4.8, OH), 2.08 – 1.93 (4 H, m, H-4); **Major isomer δ_C (101 MHz, $CDCl_3$):** 176.6 (C, C-2), 84.8 (CH_2, C-7), 70.7 (CH, C-5), 60.5 (CH, C-6), 51.9 (CH_3, C-1), 33.2 (CH, C-3), 27.8 (CH_2, C-4). **Minor isomer δ_H (400 MHz, $CDCl_3$):** 5.45 (1 H, d, *J* 4.7, H-7), 4.84 (1 H, d, *J* 4.7, H-7′), 4.28 – 4.23 (2 H, m, H-5), 3.75 – 3.71 (1 H, m, H-6), 3.68 (3 H, s, H-1), 3.31 – 3.14 (1 H, m, H-3), 2.65 (1 H, d, *J* 4.6, OH), 2.35 – 2.26 (2 H, m, H-4_{eq}), 1.77 – 1.65 (2 H, m, H-4_{ax}); **Minor isomer δ_C (101 MHz, $CDCl_3$):** 176.6 (C, C-2), 85.4 (CH_2, C-7), 71.7 (CH, C-5), 60.5 (CH, C-6), 52.1 (CH_3, C-1), 33.9 (CH, C-3), 27.8 (CH_2, C-4).

Novel compounds prepared according to a standard procedure.[100] *NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7 & H-7' resonances used to determine diastereomeric ratio.*

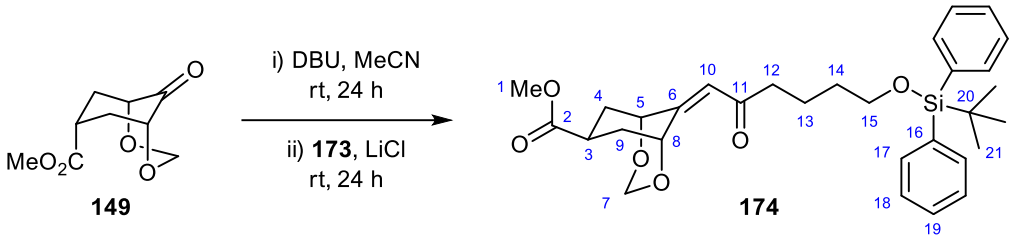
173 *Diethyl (6-((tert-butyldiphenylsilyl)oxy)-2-oxohexyl)phosphonate*



Diethylmethyl phosphonate (2.19 mL, 15.0 mmol) was dissolved in anhydrous THF (30 mL) and the resulting solution cooled to −78 °C. *n*-BuLi (2.00 M in hexane, 7.50 mL, 15.0 mmol) was added and the reaction stirred for 20 min. δ-Valerolactone (1.50 g, 15.0 mmol) was then added, the cooling bath removed, and the reaction allowed to warm to rt. After 1 h the reaction was quenched with ammonium chloride (sat. aq. soln., 30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give the unprotected alcohol as a crude mixture. This crude mixture was then dissolved in dichloromethane (30 mL) and the resulting solution cooled to 0 °C. Imidazole (1.02 g, 15.0 mmol), 4-dimethylaminopyridine (183 mg, 1.50 mmol, 10 mol%) and *tert*-butyl diphenylchlorosilane (3.90 mL, 15.0 mmol) were added, the cooling bath removed, and the reaction allowed to warm to rt. After 16 h the reaction was deemed complete by TLC, diluted with brine and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:EtOAc) to yield phosphonate **173** as a colourless oil (4.48 g, 61%). **R_f:** 0.19 (1:1 hexane:EtOAc, visualised using vanillin / Δ). **ν_{max} / cm^{-1} (neat):** 2932 (CH), 2858 (CH), 1716 (CO), 1253 (PO); **δ_H (400 MHz, $CDCl_3$):** 7.69 – 7.59 (4 H, m, H-10), 7.46 – 7.32 (6 H, stack, H-11 & H-12), 4.20 – 4.06 (4 H, m, H-2), 3.65 (2 H, t, *J* 6.2, H-8), 3.04 (2 H, d, $^2J_{P–H}$ 22.8, H-3), 2.61 (2 H, t, *J* 7.2, H-5), 1.76 – 1.50 (4 H, stack, H-6 & H-7), 1.32 (6 H, t, *J* 7.1, H-1), 1.04 (9 H, s, H-14); **δ_C (101 MHz, $CDCl_3$):** 202.1 (CH, C-4), 135.7 (CH, C-10), 134.1 (C, C-9), 129.7 (CH, C-12), 127.8 (CH, C-11), 63.6 (CH_2, C-8), 62.7 (CH_2, d, $^2J_{P–C}$ 6.3, C-2), 43.9 (CH_2, C-5), 42.5 (CH_2, d, $^1J_{P–H}$ 127.3, C-3), 31.9 (CH_2, C-7), 27.0 (CH_3, C-14), 20.0 (CH_2, C-6), 19.4 (C, C-13) 16.5 (CH_3, d, $^3J_{P–C}$ 6.1, C-1); **LRMS m/z (ES$^+$):** 513.2 ($[M + Na]^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{26}H_{39}O_5PSiNa$ 513.2202, found 513.2213.

A novel compound prepared according to a modified literature procedure.[50]

174 *Methyl (1R,5S,7s)-9-(7-((tert-butyldiphenylsilyl)oxy)-2-oxoheptylidene)-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

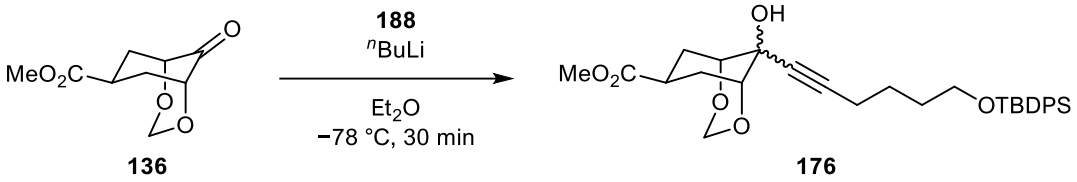


1,8-Diazabicyclo[5.4.0]undec-7-ene (76 mg, 0.50 mmol) and axial ester **149** (100 mg, 0.500 mmol) were added to acetonitrile (5.0 mL) and the resulting solution was stirred at rt. After 24 h the epimerisation was determined complete by TLC and phosphonate **173** (294 mg, 0.600 mmol) and lithium chloride (25 mg, 0.60 mmol) were added, and the reaction stirred at rt. After 24 h the Horner-Wadsworth-Emmons reaction was determined complete by TLC, quenched with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield enone **174** as a colourless oil (176 mg, 61%). **R_f:** 0.41 (1:1 hexane:Et_2O, visualised using vanillin / Δ).

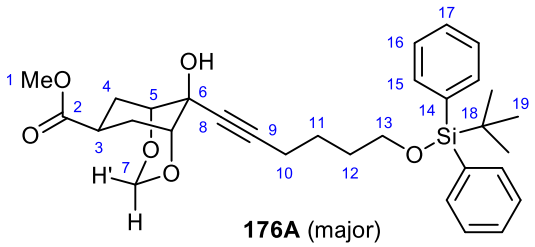
ν_{max} / cm^{-1} (neat): 2930 (CH), 2857 (CH), 1733 (CO_2Me), 1694 (conj. CO), 1641 (CC); **δ_H (500 MHz, TCE-d_2):** 7.67 – 7.61 (4 H, m, H-17), 7.47 – 7.35 (6 H, stack, H-18 & H-19), 6.22 (1 H, s, H-10), 5.80 – 5.73 (1 H, m, H-8), 4.73 (1 H, d, *J* 6.2, H-7), 4.71 (1 H, d, *J* 6.2, H-7′), 4.58 – 4.54 (1 H, m, H-5), 3.69 – 3.62 (5 H, stack, H-1 & H-15), 3.41 (1 H, app. tt, *J* 12.6, 4.6, H-3), 2.60 – 2.40 (4 H, stack, H-4_{eq}, H-9_{eq} & H-12), 1.79 – 1.51 (6 H, stack, H-4_{ax}, H-9_{ax}, H-13 & H-14), 1.02 (9 H, s, H-21); **δ_C (126 MHz, TCE-d_2):** 200.2 (C, C-11), 175.4 (C, C-2), 152.8 (C, C-6), 135.4 (CH, C-17), 133.6 (C, C-16), 129.5 (CH, C-19), 127.6 (CH, C-18), 123.6 (CH, C-10), 86.7 (CH_2, C-7), 76.5 (CH, C-5), 70.3 (CH, C-8), 63.3 (CH_2, C-15), 52.1 (CH_3, C-1), 43.8 (CH_2, C-12), 38.6 (CH_2, C-4), 37.2 (CH_2, C-9), 33.4 (CH, C-3), 31.6 (CH_2, C-14), 26.7 (CH_3, C-21), 20.0 (CH_2, C-13), 19.0 (C, C-20); **LRMS m/z (ES$^+$):** 559.2 ([M + Na]$^+$, 100%), 537.2 ([M + H]$^+$, 42); **HRMS m/z (ES$^+$):** calcd. for $C_{31}H_{41}O_6Si$ 537.2672, found 537.2686.

A novel compound prepared according to a modified literature procedure.[49,153]

176A *Methyl (1R,5S,7s,9r)-9-(6-((tert-butyldiphenylsilyl)oxy)hex-1-yn-1-yl)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate &* ***176B*** *Methyl (1R,5S,7s,9s)-9-(6-((tert-butyldiphenylsilyl)oxy)hex-1-yn-1-yl)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

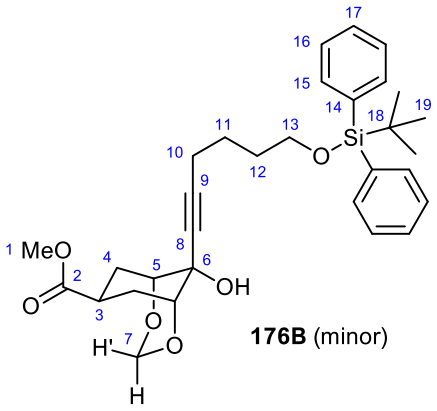


Alkyne **188** (168 mg, 0.500 mmol) was dissolved in anhydrous diethyl ether (2.5 mL) and the resulting solution cooled to –78 °C. *n*-Butyllithium (1.7 M in hexane, 0.32 mL, 0.28 mmol) was added and the reaction stirred at –78 °C. After 30 min, the solution of was added to a solution of ketone **136** (100 mg, 0.500 mmol) in diethyl ether (10 mL) at –78 °C. After 30 min, the cooling bath was removed and the reaction was allowed to warm to rt, quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:EtOAc) to yield **176** as a colourless oil (55 mg, 20%, 4.3:1 mixture of diastereoisomers). **R_f:** 0.31 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ). **ν_{max} / cm^{-1} (neat):** 3425 (br, OH), 2932 (CH), 2858 (CH), 1735 (CO); **δ_C LRMS m/z (ES$^+$):** 559.2 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{31}H_{40}O_6SiNa$ 559.2492, found 559.2506.



δ_H (400 MHz, $CDCl_3$): 7.70 – 7.61 (4 H, m, H-15), 7.46 – 7.34 (6 H, stack, H-16 & H-17), 5.46 (1 H, d, *J* 5.2, H-7), 4.99 (1 H, d, *J* 5.2, H-7′), 4.17 – 4.12 (2 H, m, H-5), 3.72 – 3.61 (5 H, stack, H-1 & H-13), 3.24 – 3.07 (1 H, m, H-3), 2.50 – 2.02 (6 H, stack, H-4 & H-10), 1.73 – 1.54 (5 H, stack, H-11, H-12 & OH), 1.05 (9 H, s, H-19);

δ_C (101 MHz, $CDCl_3$): 175.9 (C, C-2), 135.7 (C, C-15), 134.0 (CH, C-14), 129.7 (C, C-17), 127.8 (C, C-16), 87.4 (C, C-9), 85.6 (CH_2, C-7), 83.0 (C, C-8), 74.1 (CH, C-5), 63.5 (CH_3, C-13), 62.7 (C, C-6), 52.0 (CH_3, C-1), 33.5 (CH, C-3), 31.8 (CH_2, C-11), 28.6 (CH_2, C-4), 27.0 (CH_3, C-19), 25.0 (CH_2, C-12), 19.3 (C, C-18), 18.7 (CH_2, C-10).

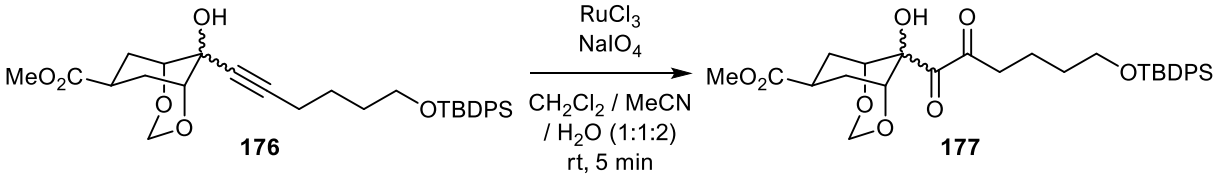


176B (minor)

δ_H (400 MHz, $CDCl_3$): 7.70 – 7.61 (4 H, m, H-15), 7.46 – 7.34 (6 H, stack, H-16 & H-17), 5.16 (1 H, d, *J* 5.3, H-7′), 5.11 (1 H, d, *J* 5.3, H-7), 4.08 – 4.04 (2 H, m, H-5), 3.72 – 3.61 (5 H, stack, H-1 & H-13), 3.24 – 3.07 (1 H, m, H-3), 2.50 – 2.02 (6 H, stack, H-4 & H-10), 1.73 – 1.54 (5 H, stack, H-11, H-12 & OH), 1.05 (9 H, s, H-19); **(101 MHz, $CDCl_3$):** 175.1 (C, C-2), 135.7 (C, C-15), 134.0 (CH, C-14), 129.7 (C, C-17), 127.8 (C, C-16), 87.4 (C, C-9), 86.6 (CH_2, C-7), 83.0 (C, C-8), 74.7 (CH, C-5), 63.4 (CH_3, C-13), 62.7 (C, C-6), 52.1 (CH_3, C-1), 35.2 (CH, C-3), 31.6 (CH_2, C-11), 28.6 (CH_2, C-4), 27.0 (CH_3, C-19), 24.9 (CH_2, C-12), 19.3 (C, C-18), 18.6 (CH_2, C-10).

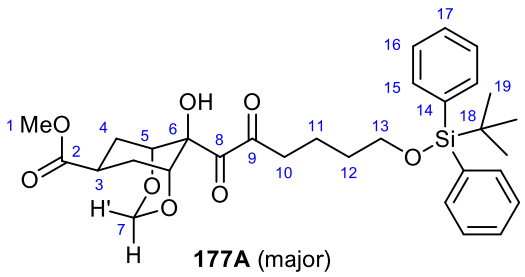
A novel compound prepared according to a modified literature procedure.[55] *NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7 & H-7' resonances used to determine diastereomeric ratio.*

177A *Methyl (1R,5S,7s,9r)-9-(6-((tert-butyldiphenylsilyl)oxy)-2-oxohexanoyl)-9-hydroxy-2,4-dioxabicyclo[3.3.1] nonane-7-carboxylate &* ***177B*** *Methyl (1R,5S,7s,9s)-9-(6-((tert-butyldiphenylsilyl)oxy)-2-oxohexanoyl)-9-hydroxy-2,4-dioxabicyclo[3.3.1] nonane-7-carboxylate*



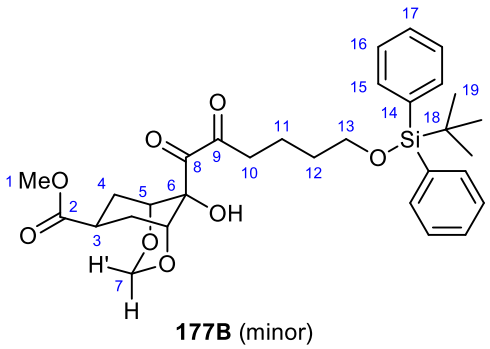
A 4.3:1 mixture of diastereoisomers of alkyne **176** (13.5 mg, 0.0251 mmol) was dissolved in a 1:1 mixture of dichloromethane and acetonitrile (1.50 mL) and a solution of sodium periodate (80.7 mg, 0.377 mmol) in water (1.16 mL) was added. The mixture was stirred vigorously at rt before the addition of ruthenium (III) chloride hydrate (1.04 mg, 5.02 μmol, 20 mol%) as a solution in water (0.34 mL). After 5 min the reaction was determined complete by TLC and filtered through a pad of silica, rinsed with dichloromethane (3 × 10 mL) and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield **177A** & **177B** as a colourless oil (5 mg, 36%, 2.5:1 mixture of diastereoisomers). **R_f:** 0.28 (1:1 hexane:Et_2O, visualised using vanillin / Δ).

ν_{max} / cm^{-1} (neat): 3423 (br, OH), 2930 (CH), 2857 (CH), 1736 (CO), 1714 (2 × CO); **LRMS m/z (ES$^+$):** 591.2 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{31}H_{40}O_8SiNa$ 591.2390, found 591.2408.



δ_H (400 MHz, $CDCl_3$): 7.70 – 7.59 (4 H, m, H-15), 7.49 – 7.30 (6 H, stack, H-16 & H-17), 5.33 (1 H, d, *J* 5.9, H-7′), 5.04 (1 H, d, *J* 5.9, H-7), 4.46 – 4.41 (2 H, m, H-5), 3.74 – 3.62 (5 H, stack, H-1 & H-13), 3.31 – 3.13 (1 H, m, H-3), 2.80 (2 H, t, *J* 7.2, H-10), 2.53 – 2.22 (6 H, stack, H-4 & H-12), 1.80 – 1.52 (3 H, stack, H-11 & OH), 1.04 (9 H, s, H-19); **δ_C (101 MHz, $CDCl_3$):** 203.2 (C, C-9), 196.7 (C, C-8), 174.8 (C, C-2), 135.7 (CH, C-15), 134.0 (C, C-14), 129.7 (CH, C-17), 127.8

(CH, C-16), 87.5 (CH_2, C-7), 75.3 (C, C-6), 70.3 (CH, C-5), 63.4 (CH_2, C-13), 52.3 (CH_3, C-1), 37.5 (CH_2, C-10), 36.1 (CH, C-3), 33.3 (CH_2, C-12), 27.1 (CH_2, C-4), 27.0 (CH_3, C-19), 21.4 (CH_2, C-11), 19.2 (C, C-18).

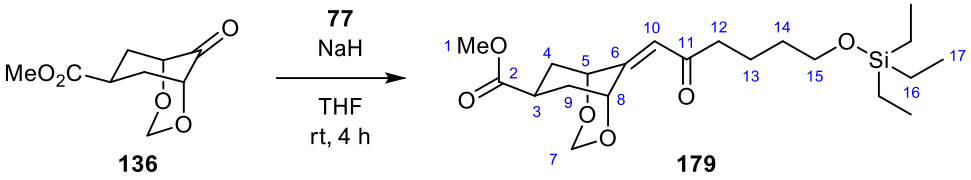


177B (minor)

δ_H (400 MHz, $CDCl_3$): 7.70 – 7.59 (4 H, m, H-15), 7.49 – 7.30 (6 H, stack, H-16 & H-17), 5.33 (1 H, d, *J* 6.2, H-7), 4.71 (1 H, d, *J* 6.2, H-7′), 4.40 – 4.35 (2 H, m, H-5), 3.74 – 3.62 (5 H, stack, H-1 & H-13), 3.31 – 3.13 (1 H, m, H-3), 2.73 (2 H, t, *J* 7.2, H-10), 2.53 – 2.22 (4 H, stack, H-4), 1.80 – 1.52 (5 H, stack, H-11, H-12 & OH), 1.04 (9 H, s, H-19); **δ_C (101 MHz, $CDCl_3$):** 203.2 (C, C-9), 196.7 (C, C-8), 174.6 (C, C-2), 135.7 (CH, C-15), 134.0 (C, C-14), 129.7 (CH, C-17), 127.8 (CH, C-16), 87.2 (CH_2, C-7), 75.3 (C, C-6), 71.4 (CH, C-5), 63.4 (CH_2, C-13), 52.3 (CH_3, C-1), 38.3 (CH_2, C-10), 35.8 (CH, C-3), 31.8 (CH_2, C-12), 30.3 (CH_2, C-4), 27.0 (CH_3, C-19), 19.3 (CH_2, C-11), 19.1 (C, C-18).

A novel compound prepared according to a modified literature procedure.[185] *NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7 & H-7' resonances used to determine diastereomeric ratio.*

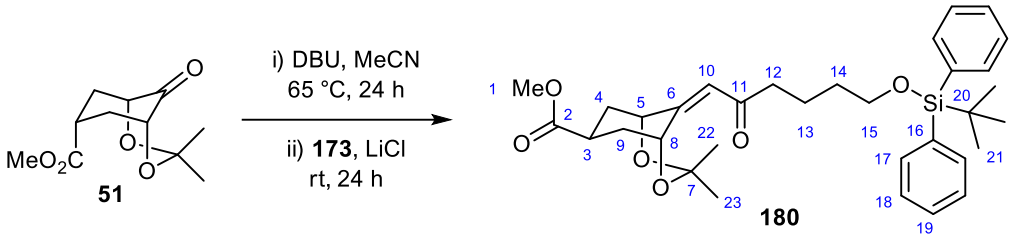
179 *Methyl (1R,5S,7s)-9-(2-oxo-7-((triethylsilyl)oxy)heptylidene)-2,4-dioxabicyclo[3.3.1] nonane-7-carboxylate*



Phosphonate **77** (92 mg, 0.25 mmol) was added dropwise over 5 min to a suspension of sodium hydride (50% w/w dispersion in mineral oil, 6 mg, 0.3 mmol) in anhydrous THF (2.5 mL) and the reaction mixture was stirred at rt. After 1 h ketone **136** (50 mg, 0.25 mmol) was added. After 4 h the reaction was determined complete by TLC and the reaction was quenched with water (2.5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (3:1 hexane:EtOAc) to yield enone **179** as a colourless oil (37 mg, 36%). **R_f:** 0.55 (1:1 petroleum ether:Et_2O, visualised using vanillin / Δ). **ν_{max} / cm^{-1} (neat):** 2953 (CH), 2876 (CH), 1733 (CO_2Me), 1695 (conj. CO), 1641 (CC); **δ_H (400 MHz, $CDCl_3$):** 6.25 (1 H, s, H-10), 5.81 – 5.76 (1 H, m, H-8), 4.74 (2 H, s, H-7), 4.58 – 4.53 (1 H, m, H-5), 3.67 (3 H, s, H-1), 3.61 (2 H, t, *J* 6.3, H-15), 3.46 (1 H, app. tt, *J* 12.5, 4.7, H-3), 2.63 – 2.42 (4 H, stack, H-4_{eq}, H-9_{eq} & H-12), 1.82 – 1.49 (6 H, stack, H-4_{ax}, H-9_{ax}, H-13 & H-14), 0.95 (9 H, t, *J* 7.9, H-17), 0.59 (6 H, q, *J* 7.9, H-16); **δ_C (101 MHz, $CDCl_3$):** 199.9 (C, C-11), 175.6 (C, C-2), 153.5 (C, C-6), 123.7 (CH, C-10), 87.0 (CH_2, C-7), 76.8 (CH, C-5), 70.6 (CH, C-8), 62.6 (CH_2, C-15), 52.0 (CH_3, C-1), 44.1 (CH_2, C-12), 39.1 (CH_2, C-4), 37.7 (CH_2, C-9), 33.8 (CH, C-3), 32.3 (CH_2, C-14), 20.5 (CH_2, C-13), 6.9 (CH_3, C-17), 4.5 (CH_2, C-16); **LRMS m/z (AP$^+$):** 413.2 ([M + Na]$^+$, 14%); **HRMS m/z (AP$^+$):** calcd. for $C_{21}H_{37}O_6Si$ 413.2359, found 413.2353.

A novel compound prepared according to a modified literature procedure.[152]

180 *Methyl (1R,5S,7s)-9-(7-((tert-butyldiphenylsilyl)oxy)-2-oxoheptylidene)-3,3-dimethyl-2,4-dioxabicyclo [3.3.1]nonane-7-carboxylate*

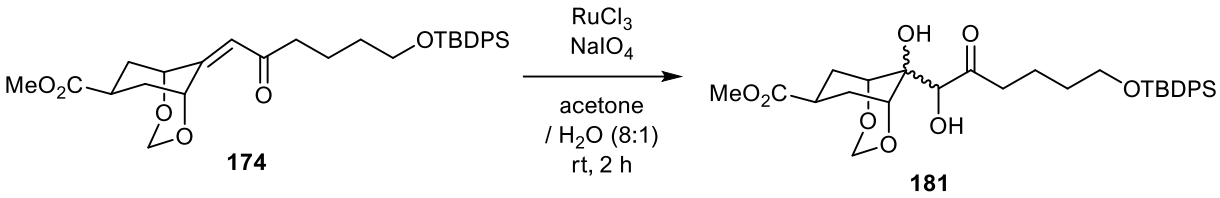


1,8-Diazabicyclo[5.4.0]undec-7-ene (432 mg, 2.84 mmol) and axial ester **51** (530 mg, 2.36 mmol) were added to acetonitrile (10 mL) and the resulting solution was heated to 65 °C. After 24 h the epimerisation was determined complete by TLC and the reaction allowed to cool to rt. Phosphonate **173** (1.39 g, 2.84 mmol) and lithium chloride (50 mg, 2.8 mmol) were added and the reaction stirred at rt. After 24 h the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield enone **180** as a colourless oil (125 mg, 9%). **R_f:** 0.59 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

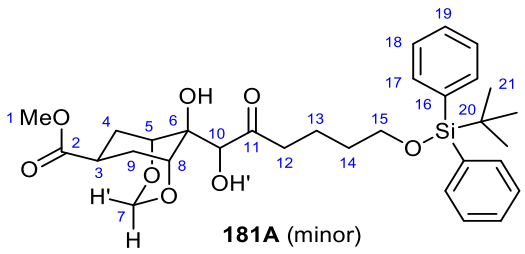
ν_{max} / cm^{-1} (neat): 2932 (CH), 2858 (CH), 1733 (CO_2Me), 1692 (conj. CO), 1636 (CC); **δ_H (400 MHz, $CDCl_3$):** 7.68 – 7.63 (4 H, m, H-17), 7.45 – 7.34 (6 H, stack, H-18 & H-19), 6.16 (1 H, s, H-10), 5.75 – 5.71 (1 H, m, H-8), 4.48 – 4.44 (1 H, m, H-5), 3.70 – 3.64 (5 H, stack, H-1 & H-15), 3.43 (1 H, app. tt, *J* 12.5, 4.8, H-3), 2.58 – 2.38 (4 H, stack, H-4_{eq}, H-9_{eq}, & H-12), 1.83 – 1.52 (6 H, stack, H-4_{ax}, H-9_{ax}, H-13 & H-14), 1.44 (3 H, s, H-23), 1.40 (3 H, s, H-22), 1.05 (9 H, s, H-21); **δ_C (101 MHz, $CDCl_3$):** 200.3 (C, C-11), 175.6 (C, C-2), 157.7 (C, C-6), 135.7 (CH, C-17), 134.0 (C, C-16), 129.7 (CH, C-19), 127.8 (CH, C-18), 119.3 (CH, C-10), 98.0 (CH_2, C-7), 74.0 (C, C-5), 68.0 (CH, C-8), 63.6 (CH_2, C-15), 51.9 (CH_3, C-1), 44.1 (CH_2, C-12), 40.6 (CH, C-4), 39.0 (CH, C-9), 34.3 (CH, C-3), 32.0 (CH_2, C-14), 29.9 (CH_3, C-22), 27.4 (CH_3, C-23), 27.0 (CH_3, C-21), 20.6 (CH_2, C-13), 19.3 (C, C-20); **LRMS m/z (ES$^+$):** 587.3 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{33}H_{44}O_6SiNa$ 587.2805, found 587.2820.

A novel compound prepared according to a modified literature procedure.[49,153]

181A *Methyl (1R,5S,7s-9r)-9-(6-((tert-butyldiphenylsilyl)oxy)-1-hydroxy-2-oxohexyl)-9-hydroxy-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate &* ***181B*** *Methyl (1R,5S,7s,9s)-9-(6-((tert-butyldiphenylsilyl)oxy)-1-hydroxy-2-oxohexyl)-9-hydroxy-2,4-dioxabicyclo[3.3.1] nonane-7-carboxylate*

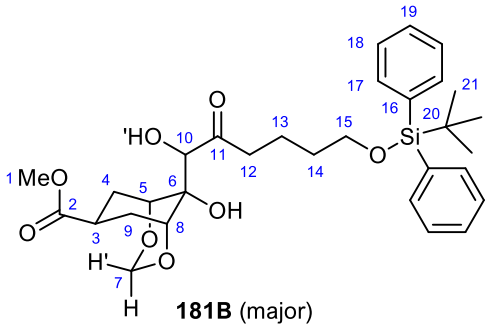


Ruthenium (III) chloride hydrate (23 mg, 0.11 mmol) and sodium periodate (169 mg, 0.790 mmol) were added to a 5:1 mixture of acetone and water (28 mL) and the resulting suspension stirred at rt until the reaction mixture became bright yellow. After 1 h a solution of enone **174** (59 mg, 0.11 mmol) in acetone (16 mL) was added. After 2 h the reaction was deemed complete by TLC and 2-propanol (10 mL) was added. The reaction mixture was extracted with dichloromethane (3 × 25 mL), and the combined organic fractions washed with brine (25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield **177A** & **177B** as a colourless oil (18 mg, 29%, 1:2.5 mixture of diastereoisomers) and **181A** & **181B** as a colourless oil (9 mg, 15%, 1:2.5 mixture of diastereoisomers). **R_f (171):** 0.10 (1:1 hexane:Et_2O, visualised using vanillin / Δ). **ν_{max} / cm^{-1} (neat):** 3453 (br, OH), 2931 (CH), 2859 (CH), 1733 (CO_2Me), 1713 (CO); **LRMS m/z (ES$^+$):** 593.3 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{31}H_{42}O_8SiNa$ 593.2547, found 593.2545.



δ_H (400 MHz, $CDCl_3$): 7.71 – 7.61 (4 H, m, H-17), 7.48 – 7.32 (6 H, stack, H-18 & H-19), 5.43 (1 H, d, *J* 6.2, H-7), 4.94 (1 H, d, *J* 6.9, H-10), 4.87 (1 H, d, *J* 6.2, H-7′), 4.23 – 4.19 (1 H, m, H-5 / H-8), 4.03 – 3.99 (1 H, m, H-5 / H-8), 3.70 (3 H, s, H-1), 3.66 (2 H, t, *J* 6.1, H-15), 3.36 (1 H, d, *J* 6.9, OH′), 3.32 – 3.10 (1 H, m, H-3), 2.94 (1 H, br s, OH), 2.80 – 2.14 (6 H, stack, H-4, H-9 & H-12), 1.78 – 1.50 (4 H, stack, H-13 & H-14), 1.04 (9 H, s, H-21);

δ_C (101 MHz, $CDCl_3$): 213.4 (C, C-11), 175.0 (C, C-2), 135.7 (CH, C-17), 134.0 (C, C-16), 129.7 (CH, C-19), 127.8 (CH, C-18), 87.8 (CH_2, C-7), 74.9 (CH, C-10), 70.7 (CH, C-5 / C-8), 70.4 (CH, C-5 / C-8), 69.7 (C, C-6), 63.5 (CH_2, C-15), 52.3 (CH_3, C-1), 41.6 (CH_2, C-12), 36.6 (CH, C-3), 32.0 (CH_2, C-14), 27.7 (CH_2, C-4 / C-9), 27.3 (CH_2, C-4 / C-9), 27.0 (CH_3, C-21), 20.2 (CH_2, C-13), 19.4 (C, C-20).

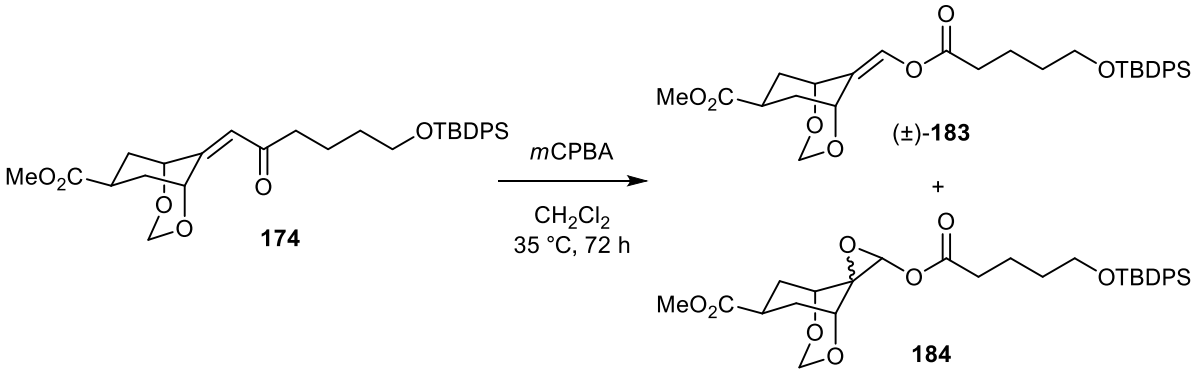


181B (major)

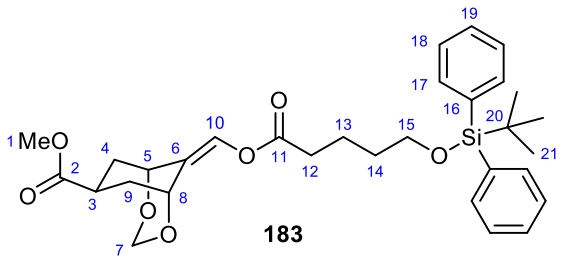
δ_H (400 MHz, $CDCl_3$): 7.71 – 7.61 (4 H, m, H-17), 7.48 – 7.32 (6 H, stack, H-18 & H-19), 5.34 (1 H, d, *J* 6.2, H-7), 4.90 (1 H, d, *J* 6.2, H-7′), 4.18 – 4.02 (3 H, stack, H-5, H-8 & H-10), 3.72 (3 H, s, H-1), 3.66 (2 H, t, *J* 6.1, H-15), 3.56 (1 H, br s, OH), 3.32 – 3.10 (1 H, m, H-3), 3.05 (1 H, d, *J* 9.9, OH′), 2.80 – 2.14 (6 H, stack, H-4, H-9 & H-12), 1.78 – 1.50 (4 H, stack, H-13 & H-14), 1.04 (9 H, s, H-21); **δ_C (101 MHz, $CDCl_3$):** 211.4 (C, C-11), 175.5 (C, C-2), 135.7 (CH, C-17), 134.1 (C, C-16), 129.7 (CH, C-19), 127.8 (CH, C-18), 87.2 (CH_2, C-7), 76.7 (CH, C-10), 72.2 (CH, C-5 / C-8), 72.0 (CH, C-5 / C-8), 71.7 (C, C-6), 63.6 (CH_2, C-15), 52.5 (CH_3, C-1), 39.8 (CH_2, C-12), 36.5 (CH, C-3), 31.9 (CH_2, C-14), 29.9 (CH_2, C-4 / C-9), 29.4 (CH_2, C-4 / C-9), 27.0 (CH_3, C-21), 19.39 (CH_2, C-13), 19.35 (C, C-20).

A novel compound prepared according to a modified literature procedure.[164] *NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7 & H-7′ resonances used to determine diastereomeric ratio.*

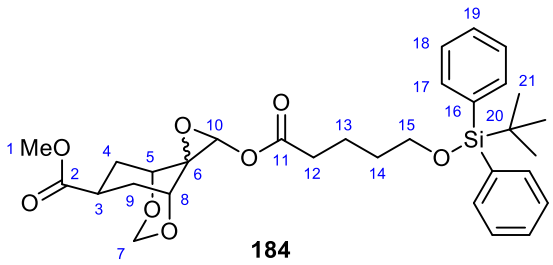
183 *Methyl (1R,5S,7s)-9-(((6-((tert-butyldiphenylsilyl)oxy)hexanoyl)oxy) methylene)-2,4-dioxabicyclo [3.3.1]nonane-7-carboxylate &* ***184*** *Methyl (1R,5S,7s)-3'-((6-((tert-butyldiphenylsilyl)oxy)hexanoyl)oxy)-2,4-dioxaspiro[bicyclo[3.3.1]nonane-9,2'-oxirane]-7-carboxylate*



Enone **174** (50 mg, 0.093 mmol) and *meta*-chloroperbenzoic acid (50 mg, 0.29 mmol) were added to dichloromethane (1.0 mL) and the resulting solution heated to 35 °C. After 72 h the reaction was allowed to cool to rt, diluted with water (1 mL) and extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with sodium hydrogen carbonate (sat. aq. soln., 3 × 5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue that was purified by flash column chromatography (9:1 hexane:EtOAc) to yield **183** & **184** (2.6:1 mixture of diastereoisomers) as colourless oils.*



R_f: 0.56 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ); **δ_H (300 MHz, $CDCl_3$):** 7.69 – 7.62 (4 H, m, H-17), 7.47 – 7.33 (6 H, stack, H-18 & H-19), 7.25 (1 H, s, H-10), 5.19 – 5.11 (1 H, m, H-8), 4.86 (1 H, d, *J* 5.7, H-7), 4.68 (1 H, d, *J* 5.7, H-7′), 4.68 – 4.59 (1 H, m, H-5), 3.72 – 3.64 (5 H, stack, H-1 & H-15), 3.46 (1 H, app. tt, *J* 12.4, 4.6, H-3), 2.50 – 2.27 (4 H, stack, H-4_{eq}, H-9_{eq} & H-12), 1.87 – 1.51 (6 H, stack, H-4_{ax}, H-9_{ax}, H-13 & H-14), 1.05 (9 H, s, H-21); **LRMS m/z (ES^+):** 575.2 ($[M + Na]^+$, 51%); **HRMS m/z (ES^+):** calcd. for $C_{31}H_{40}O_7SiNa$ 575.2441, found 575.2446.

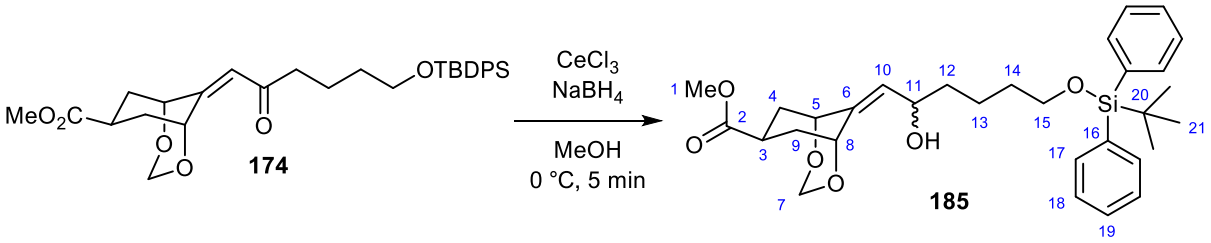


184

R_f: 0.44 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ); **Major isomer δ_H (300 MHz, $CDCl_3$):** 7.70 – 7.62 (4 H, m, H-17), 7.52 – 7.33 (6 H, stack, H-18 & H-19), 5.50 (1 H, s, H-10), 5.23 (1 H, d, *J* 5.8, H-7), 4.80 (1 H, d, *J* 5.8, H-7′), 4.21 – 4.17 (1 H, m, H-8), 3.91 – 3.87 (1 H, m, H-5), 3.70 (3 H, s, H-1), 3.67 (2 H, t, *J* 5.9, H-15), 3.48 – 3.28 (1 H, m, H-3), 2.48 – 2.20 (4 H, stack, H-4_{eq}, H-9_{eq} & H-12), 1.94 – 1.52 (6 H, stack, H-4_{ax}, H-9_{ax}, H-13 & H-14), 1.05 (9 H, s, H-21); **Minor isomer δ_H (300 MHz, $CDCl_3$):** 7.70 – 7.62 (4 H, m, H-17), 7.52 – 7.33 (6 H, stack, H-18 & H-19), 5.60 (1 H, s, H-10), 5.16 (1 H, d, *J* 5.9, H-7), 4.76 (1 H, d, *J* 5.9, H-7′), 4.17 – 4.13 (1 H, m, H-8), 3.87 – 3.83 (1 H, m, H-5), 3.71 (3 H, s, H-1), 3.67 (2 H, t, *J* 5.9, H-15), 3.48 – 3.28 (1 H, m, H-3), 2.48 – 2.20 (4 H, stack, H-4_{eq}, H-9_{eq} & H-12), 1.94 – 1.52 (6 H, stack, H-4_{ax}, H-9_{ax}, H-13 & H-14), 1.05 (9 H, s, H-21); **LRMS m/z (ES^+):** 591.2 ([M + Na]$^+$, 100%); **HRMS m/z (ES^+):** calcd. for $C_{31}H_{40}O_8SiNa$ 591.2390, found 591.2401.

A novel compound prepared according to a modified literature procedure.[56] ** Products unable to be isolated from a mixture of starting material and meta-chlorobenzoic acid so no yield, ^{13}C-NMR or IR could be obtained. MS data was obtained using LCMS. ^{1}H-NMR assigned from mixtures and NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-10 resonance used to determine diastereomeric ratio.*

***185** Methyl (1R,5S,7s)-9-(7-((tert-butyldiphenylsilyl)oxy)-2-hydroxyheptylidene)-2,4-dioxabicyclo[3.3.1] nonane-7-carboxylate*



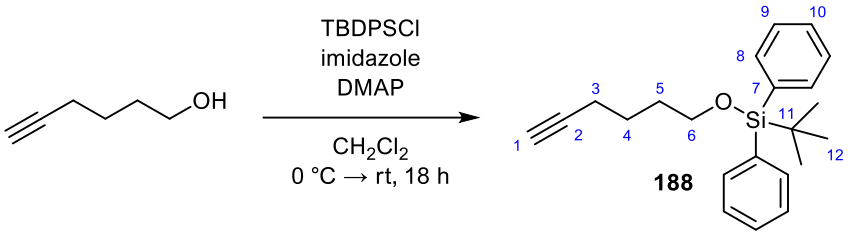
Enone **174** (20 mg, 0.037 mmol) and cerium (III) chloride (21 mg, 0.056 mmol) were added to methanol (0.25 mL) and the resulting mixture cooled to 0 °C. Sodium borohydride (2 mg, 0.04 mmol) was then added and after 5 min the reaction was determined complete by TLC. The reaction was then quenched by adding acetic acid (50% v/v aq. soln.) until the reaction mixture reached neutral pH. Water (1 mL) was added, and the reaction mixture extracted with dichloromethane (3 × 1 mL). The combined organic fractions were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:EtOAc) to yield **185** as a colourless oil (20 mg, 99%, 1.3:1 mixture of diastereoisomers). **R_f:** 0.36 (1:1 hexane:Et_2O, visualised using vanillin / Δ).

ν_{max} / cm^{-1} (neat): 3451 (br, OH), 2930 (CH), 2858 (CH), 1733 (CO); **Major isomer δ_H (400 MHz, $CDCl_3$):** 7.69 – 7.61 (4 H, m, H-17), 7.46 – 7.32 (6 H, stack, H-18 & H-19), 5.55 (1 H, d, *J* 8.7, H-10), 5.03 – 4.99 (1 H, m, H-8), 4.87 (1 H, d, *J* 5.6, H-7), 4.66 (1 H, d, *J* 5.6, H-7′), 4.55 – 4.50 (1 H, m, H-5), 4.40 – 4.27 (1 H, m, H-11), 3.70 – 3.63 (5 H, stack, H-1 & H-15), 3.51 – 3.40 (1 H, m, H-3), 2.44 – 2.32 (2 H, stack, H-4_{eq} & H-9_{eq}), 1.74 – 1.23 (9 H, stack, H-4_{ax}, H-9_{ax}, H-12, H-13, H-14, & OH), 1.04 (9 H, s, H-21); **Minor isomer δ_H (400 MHz, $CDCl_3$):** 7.69 – 7.61 (4 H, m, H-17), 7.46 – 7.32 (6 H, stack, H-18 & H-19), 5.52 (1 H, d, *J* 8.6, H-10), 5.05 – 5.03 (1 H, m, H-8), 4.80 (1 H, d, *J* 5.6, H-7), 4.69 (1 H, d, *J* 5.6, H-7′), 4.55 – 4.50 (1 H, m, H-5), 4.40 – 4.27 (1 H, m, H-11), 3.70 – 3.63 (5 H, stack, H-1 & H-15), 3.51 – 3.40 (1 H, m, H-3), 2.44 – 2.32 (2 H, stack, H-4_{eq} & H-9_{eq}), 1.74 – 1.23 (9 H, stack, H-4_{ax}, H-9_{ax}, H-12, H-13, H-14 & OH), 1.04 (9 H, s, H-21); **Major isomer δ_C (101 MHz, $CDCl_3$):** 175.9 (C, C-2), 135.7 (CH, C-17), 135.3 (C, C-6), 134.1 (C, C-16), 131.4 (CH, C-10), 129.7 (CH, C-19), 127.8 (CH, C-18), 86.2 (CH_2, C-7), 76.3 (CH, C-5), 69.7 (CH, C-8), 67.4 (CH, C-11), 63.7 (CH_2, C-15), 51.9 (CH_3, C-1), 37.7 (CH_2,

C-12), 37.4 (CH_2, C-4), 36.8 (CH_2, C-9), 33.9 (CH, C-3), 32.4 (CH_2, C-14), 27.0 (CH_3, C-21), 21.7 (CH_2, C-13), 19.4 (C, C-20); **Minor isomer δ_C (101 MHz, $CDCl_3$):** 176.0 (C, C-2), 136.4 (C, C-6), 135.7 (CH, C-17), 134.1 (C, C-16), 131.1 (CH, C-10), 129.7 (CH, C-19), 127.8 (CH, C-18), 86.4 (CH_2, C-7), 76.5 (CH, C-5), 70.2 (CH, C-8), 67.5 (CH, C-11), 63.7 (CH_2, C-15), 52.0 (CH_3, C-1), 37.6 (CH_2, C-12), 37.4 (CH_2, C-4), 36.9 (CH_2, C-9), 34.0 (CH, C-3), 32.4 (CH_2, C-14), 27.0 (CH_3, C-21), 21.8 (CH_2, C-13), 19.4 (C, C-20); **LRMS m/z (ES^+):** 561.3 ($[M + Na]^+$, 100%); **HRMS m/z (ES^+):** calcd. for $C_{31}H_{42}O_6SiNa$ 561.2648, found 561.2664.

A novel compound prepared according to a modified literature procedure.[186] *NMR assignments of diastereoisomers assigned from a mixture but listed separately for clarity. H-7 & H-7' resonances used to determine diastereomeric ratio.*

188 *tert-Butyl(hex-5-yn-1-yloxy)diphenylsilane*

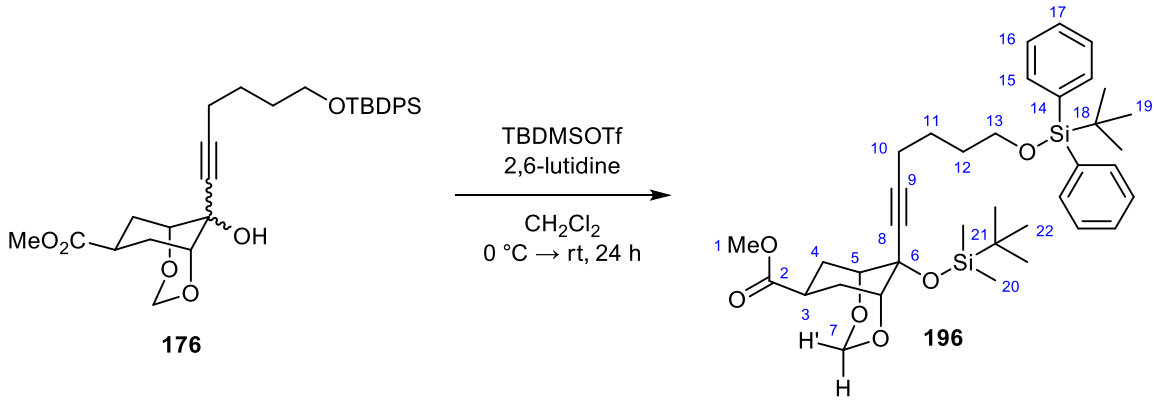


5-Hexyn-1-ol (1.00 g, 10.2 mmol) was dissolved in dichloromethane (40 mL) and the resulting solution cooled to 0 °C. *tert*-Butyldiphenylchlorosilane (3.36 g, 12.2 mmol) and imidazole (124 mg, 1.02 mmol, 10 mol%) were added, the cooling bath removed, and the reaction allowed to warm to rt. After 1 h the reaction was deemed complete by TLC and was quenched with ammonium chloride (sat. aq. soln., 40 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic fractions were washed with brine (40 mL), dried over $MgSO_4$, filtered and solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (95:5 hexane:EtOAc) to yield alkyne **188** as a colourless oil (2.81 g, 82%). **R_f:** 0.51 (98:2 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 3307 (alkyne CH), 3072 (CH), 2932 (CH), 2858 (CH), 1106 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.69 – 7.64 (4 H, m, H-8), 7.47 – 7.34 (6 H, stack, H-9 & H-10), 3.68 (2 H, t, *J* 5.9, H-6), 2.19 (2 H, td, *J* 6.8, 2.7, H-3), 1.94 (1 H, t, *J* 2.7, H-1), 1.73 – 1.58 (4 H, stack, H-4 & H-5), 1.05 (9 H, s, H-12); **δ_C (101 MHz, $CDCl_3$):** 135.7 (CH, C-8), 134.1 (C, C-7), 129.7 (CH, C-10), 127.8 (CH, C-9), 84.7 (C, C-2), 68.4 (CH, C-1), 63.5 (CH_2, C-6), 31.7 (CH_2, C-5), 27.0 (CH_3, C-12), 25.1 (CH_2, C-4), 19.4 (C, C-11), 18.3 (CH_2, C-3); **LRMS m/z (ASAP$^+$):** 337.2 ([M + H]$^+$, 36%); **HRMS m/z (ASAP$^+$):** calcd. for $C_{22}H_{29}O_6Si$ 337.1988, found 337.1998.

A known compound prepared according to a modified literature procedure.[56] *Analytical data in agreement with literature values.*[187]

196 *Methyl-(1R,5S,7s,9s)-9-((tert-butyldimethylsilyl)oxy)-9-(6-((tert-butyldiphenylsilyl)oxy)hex-1-yn-1-yl)-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*

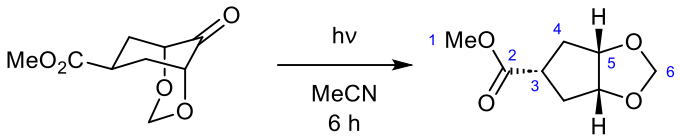


A 6.5:1 mixture of **176A** & **176B** (55 mg, 0.10 mmol) was dissolved in dichloromethane (1 mL) and the resulting solution cooled to 0 °C. 2,6-lutidine (0.24 mL, 2.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.23 mL, 1.0 mmol) were added, the cooling bath removed, and the reaction allowed to warm to rt. After 24 h the reaction was deemed complete by TLC and quenched with ammonium chloride (sat. aq. soln., 1 mL). The reaction mixture was extracted with dichloromethane (3 × 2 mL) and the combined organic fractions were washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (8:2 hexane:EtOAc) to yield **196** as a colourless oil (3 mg, 5%). **R_f:** 0.82 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 2930 (CH), 2858 (CH), 1737 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.68 – 7.63 (4 H, m, H-15), 7.46 – 7.34 (6 H, stack, H-16 & H-17), 5.59 (1 H, d, *J* 3.3, H-7), 4.72 (1 H, d, *J* 3.3, H-7′), 4.14 – 4.06 (2 H, m, H-5), 3.69 – 3.62 (5 H, stack, H-1 & H-13), 3.18 (1 H, tt, *J* 11.7, 5.6, H-3), 2.28 – 2.08 (6 H, stack, H-4 & H-10), 1.69 – 1.59 (4 H, stack, H-11 & H-12), 1.04 (9 H, s, H-19), 0.91 (9 H, s, H-22), 0.21 (6 H, s, H-20); **δ_C (101 MHz, $CDCl_3$):** 176.3 (C, C-2), 135.7 (CH, C-15), 134.0 (C, C-14), 129.7 (CH, C-17), 127.8 (CH, C-16), 91.9 (C, C-9), 85.3 (CH_2, C-7), 79.5 (C, C-8), 75.1 (CH, C-5), 71.2 (C, C-6), 63.3 (CH_2, C-13), 51.8 (CH_3, C-1), 33.4 (CH, C-3), 32.5 (CH_2, C-4), 32.0 (CH_2, C-11), 27.0 (CH_3, C-19), 25.9 (CH_3, C-22), 24.9 (CH_2, C-12), 19.4 (C, C-18), 18.7 (CH_2, C-10), 18.3 (C, C-21), −2.7 (CH_3, C-20); **LRMS m/z (ES$^+$):** 673.4 ([M + Na]$^+$, 62%), 668.4 ([M + NH_4]$^+$, 100); **HRMS m/z (ES$^+$):** calcd. for $C_{37}H_{54}O_6Si_2Na$ 673.3357, found 673.3359.

A novel compound prepared according to a modified literature procedure.[55]

192 *Methyl (3aR,5r,6aS)-tetrahydro-4H-cyclopenta[d][1,3]dioxole-5-carboxylate*



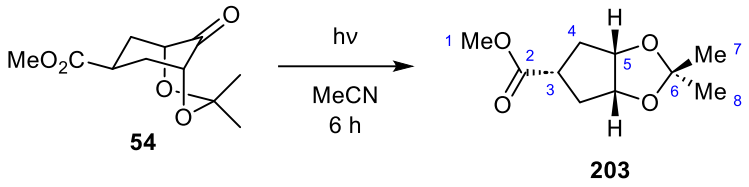
136 **202**

Bicyclic ketone **136** (70 mg, 0.35 mmol) was added to acetonitrile (350 mL) in a Pyrex immersion well photochemical reactor and the resulting solution degassed using argon for 15 minutes. The reaction mixture was then irradiated with a 400 W medium pressure mercury lamp. After 6 h the reaction was determined complete by ^{1}H-NMR analysis of the reaction mixture and the solvents removed under reduced pressure to yield **202** as a colourless oil (49 mg, 81%) of sufficient purity to not require further purification. **R_f:** 0.29 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 2952 (CH), 2842 (CH), 2763 (CH), 1728 (CO); **δ_H (400 MHz, $CDCl_3$):** 4.96 (1 H, s, H-6), 4.82 (1 H, s, H-6′), 4.58 – 4.49 (2 H, m, H-5), 3.69 (3 H, s, H-1), 2.73 (1 H, tt, *J* 7.8, 6.1, H-3), 2.26 (2 H, dddd, *J* 14.6, 6.2, 2.2, 1.0, H-4), 2.08 – 2.01 (2 H, m, H-4′); **δ_C (101 MHz, $CDCl_3$):** 174.2 (C, C-2), 94.3 (CH_2, C-6), 80.2 (CH, C-5), 51.7 (CH_3, C-1), 41.4 (CH, C-3), 34.1 (CH_2, C-4); **LRMS m/z (ES$^+$):** 195.1 ([M + Na]$^+$, 100%), 141.1 ([M − CH_3]$^+$, 92); **HRMS m/z (ES$^+$):** calcd. for $C_8H_{12}O_4Na$ 195.0633, found 195.0633.

A novel compound prepared according to a modified literature procedure.[55]

***203** Methyl (3aR,5r,6aS)-2,2'-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxole-5-carboxylate*



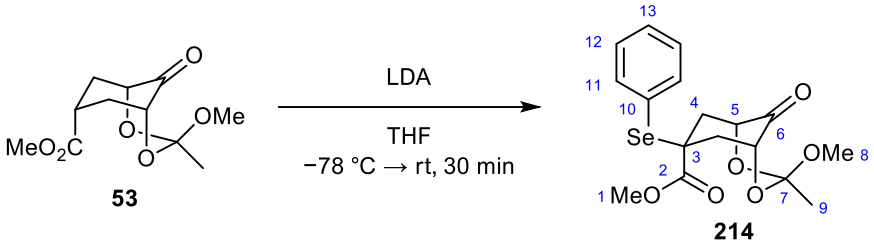
54 **203**

Bicyclic ketone **54** (75 mg, 0.33 mmol) was added to acetonitrile (300 mL) in a Pyrex immersion well photochemical reactor and the resulting solution degassed using argon for 15 minutes. The reaction mixture was then irradiated with a 400 W medium pressure mercury lamp. After 6 h the reaction was determined complete by ^{1}H-NMR analysis of the reaction mixture and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (1:1 hexane:Et_2O) to yield **203** as a colourless oil (20 mg, 30%). **R_f:** 0.33 (1:1 hexane:Et_2O, visualised using $KMnO_4$ / Δ).

ν_{max} / cm^{-1} (neat): 2985 (CH), 2939 (CH), 1732 (CO); **δ_H (400 MHz, $CDCl_3$):** 4.59 – 4.53 (2 H, m, H-5), 3.63 (3 H, s, H-1), 2.74 (1 H, tt, *J* 8.0, 3.3, H-3), 2.40 (2 H, dd, *J* 14.2, 3.3, H-4), 1.80 (2 H, dddd, *J* 14.5, 8.0, 4.3, 1.7, H-4′), 1.31 (3 H, s, H-7/8), 1.20 (3 H, s, H-7/8); **δ_C (101 MHz, $CDCl_3$):** 174.4 (C, C-2), 110.3 (C, C-6), 80.5 (CH, C-5), 51.8 (CH_3, C-1), 42.4 (CH, C-3), 34.9 (CH_2, C-4), 25.9 (CH_3, C-7/8), 24.0 (CH_3, C-7/8); **LRMS m/z (ES$^+$):** 223.1 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{10}H_{16}O_4Na$ 223.0946, found 223.0951.

A novel compound prepared according to a modified literature procedure.[55]

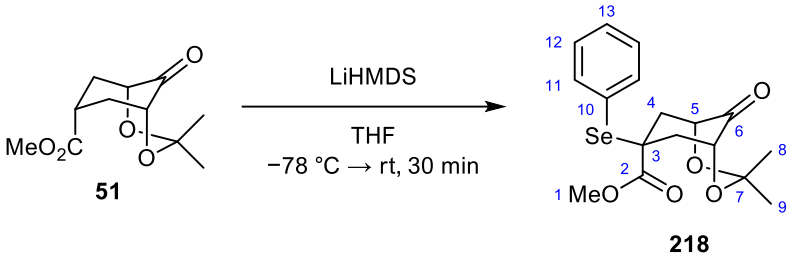
214 *Methyl (1R,3r,5S,7s)-3-methoxy-3-methyl-9-oxo-7-(phenylselanyl)-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



Diisopropylamine (15 mg, 0.15 mmol) was added to anhydrous THF (0.50 mL) and the resulting solution cooled to −78 °C. *n*-Butyllithium (1.5 M in hexanes, 0.10 mL, 0.15 mmol) was added and stirred for 20 min. A solution of ester **53** (49 mg, 0.20 mmol) in THF (0.50 mL) was added and the resulting mixture stirred for a further 20 min, after which time a solution of phenylselenyl bromide (71 mg, 0.30 mmol) in THF (0.50 mL) was added dropwise over 15 min. After a further 15 min the cooling bath was removed and the reaction allowed to warm to rt, quenched with brine (2 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified recrystallisation from methanol to yield selenide **214** as a white solid (34 mg, 72%). **R_f:** 0.47 (1:1 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ). **m.p.** 76 – 79 °C; **ν_{max} / cm^{-1} (neat):** 2947 (CH), 1750 (CO_2Me), 1726 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.58 – 7.52 (2 H, m, H-12), 7.45 – 7.39 (1 H, m, H-13), 7.35 – 7.29 (2 H, m, H-11), 4.14 – 4.08 (2 H, m, H-5), 3.66 (3 H, s, H-1), 3.41 – 3.33 (2 H, dm, *J* 14.7, H-4$_{eq}$), 3.18 (3 H, s, H-8), 2.23 (2 H, app. dt, *J* 14.7, 3.0, H-4$_{ax}$), 1.38 (3 H, s, H-9); **δ_C (101 MHz, $CDCl_3$):** 207.0 (C, C-6), 172.4 (C, C-2), 138.2 (CH, C-12), 130.1 (CH, C-13), 129.1 (CH, C-11), 126.3 (C, C-10), 112.1 (C, C-7), 75.1 (CH, C-5), 52.2 (CH_3, C-1), 51.1 (CH_3, C-8), 44.03 (CH_2, C-4), 43.96 (C, C-3), 19.8 (CH_3, C-9); **LRMS m/z (ES$^+$):** 403.1 ([M^{82}Se + H]$^+$, 20%), 402.1 ([M^{81}Se + H]$^+$, 20), 401.1 ([M^{80}Se + H]$^+$, 100), 400.1 ([M^{79}Se + H]$^+$, 6), 399.1 ([M^{78}Se + H]$^+$, 47), 398.1 ([M^{77}Se + H]$^+$, 20), 397.1 ([M^{76}Se + H]$^+$, 20); **HRMS m/z (ES$^+$):** calcd. for $C_{17}H_{21}O_6{}^{76}Se$ 397.0530, found 397.0541.

A known compound prepared according to a literature procedure.[55] *Analytical data in agreement with literature values.*[55]

218 *Methyl (1R,5S,7s)-3,3-dimethyl-9-oxo-7-(phenylselanyl)-2,4-dioxabicyclo[3.3.1] nonane-7-carboxylate*



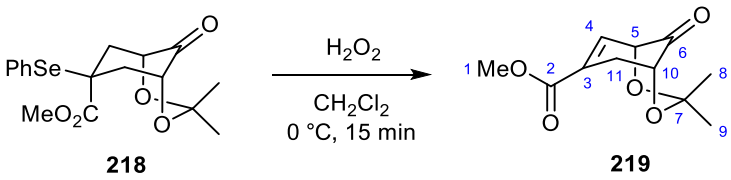
Ester **51** (1.65 g, 7.25 mmol) was added to anhydrous THF (36 mL) the resulting solution cooled to −78 °C. Lithium hexamethyldisilazide (1.30 M in THF, 8.40 mL, 10.9 mmol) was added and the mixture was stirred for 30 min, after which time a solution of phenylselenyl bromide (2.57 g, 10.9 mmol) in THF (36 mL) was added dropwise over 15 min. After a further 15 min the cooling bath was removed and the reaction allowed to warm to rt, quenched with brine (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified recrystallisation from methanol to yield selenide **218** as a white solid (1.99 g, 72%). **R_f:** 0.31 (7:3 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

m.p. 109 – 111 °C; **ν_{max} / cm^{-1} (neat):** 2988 (CH), 2935 (CH), 1748 (CO_2Me), 1718 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.57 – 7.52 (2 H, m, H-12), 7.45 – 7.38 (1 H, m, H-13), 7.36 – 7.29 (2 H, m, H-11), 4.26 – 4.21 (2 H, m, H-5), 3.67 (3 H, s, H-1), 3.48 – 3.40 (2 H, dm, *J* 14.7, H-4_{eq}), 2.26 (2 H, app. dt, *J* 14.7, 3.0, H-4_{ax}), 1.36 (3 H, d, *J* 0.8, H-8 / H-9), 1.31 (3 H, d, *J* 0.8, H-8 / H-9); **δ_C (101 MHz, $CDCl_3$):** 214.3 (C, C-6), 172.4 (C, C-2), 138.2 (CH, C-12), 130.1 (CH, C-13), 129.1 (CH, C-11), 126.4 (C, C-10), 99.4 (C, C-7), 76.8 (CH, C-5), 52.2 (CH_3, C-1), 46.1 (CH_2, C-4), 44.2 (C, C-3), 27.7 (CH_3, C-8 / C-9), 24.9 (CH_3, C-8 / C-9); **LRMS m/z (ASAP$^+$):** 387.1 ([M^{82}Se + H]$^+$, 20%), 386.1 ([M^{81}Se + H]$^+$, 21), 385.1 ([M^{80}Se + H]$^+$, 100), 384.1 ([M^{79}Se + H]$^+$, 28), 383.1 ([M^{78}Se + H]$^+$, 47), 382.1 ([M^{77}Se + H]$^+$, 24), 381.1 ([M^{76}Se + H]$^+$, 20);

HRMS m/z (ASAP$^+$): calcd. for $C_{17}H_{21}O_5{}^{76}Se$ 381.0581, found 381.0592.

A novel compound prepared according to a modified literature procedure.[188]

219 *(±)-(1R,5S)Methyl-3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]non-6-ene-7-carboxylate*

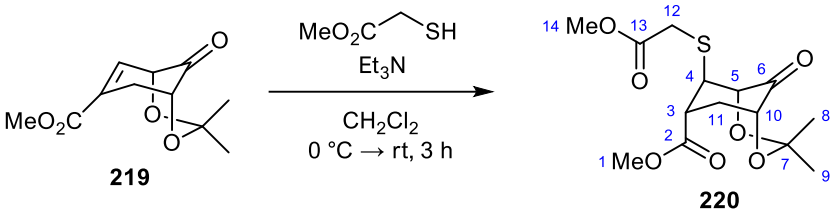


218 **219**

Phenyl selenide **218** (488 mg, 1.27 mmol) was dissolved in dichloromethane (6.2 mL) and the resulting solution was cooled to 0 °C. Hydrogen peroxide (60% w/w aq. soln., 0.29 mL, 5.1 mmol) was then added and the mixture was stirred at 0 °C. After 15 min the reaction was determined complete by TLC and was quenched with sodium thiosulfate (sat. aq. soln., 10 mL). The mixture was then extracted with dichloromethane (3 × 10 mL) dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a residue which was purified by flash column chromatography (7:3 petroleum ether:Et_2O) to yield unsaturated ester **219** as a white solid (248 mg, 86%). **R_f:** 0.45 (7:3 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ). **m.p.** 61 – 62 °C; **ν_{max} / cm^{-1} (neat):** 2996 (CH), 2954 (CH), 1747 (CO_2Me), 1718 (CO); **δ_H (400 MHz, $CDCl_3$):** 7.05 (1 H, dd, *J* 6.0, 2.6, H-4), 4.44 (1 H, app. dt, *J* 3.5, 2.2, H-10), 4.25 (1 H, dd, *J* 6.0, 2.2, H-5), 3.78 (3 H, s, H-1), 3.28 (1 H, dd, *J* 18.2, 3.5, H-11), 2.78 (1 H, app. dt, *J* 18.3, 2.6, H-11′), 1.45 (3 H, s, H-8 / H-9), 1.44 (3 H, s, H-8 / H-9); **δ_C (101 MHz, $CDCl_3$):** 211.8 (C, C-6), 166.3 (C, C-2), 138.2 (CH, C-4), 131.1 (C, C-3), 99.3 (C, C-7), 74.8 (CH, C-10), 69.6 (CH, C-5), 52.5 (CH_3, C-1), 39.5 (CH_2, C-11), 29.2 (CH_3, C-8 / C-9), 26.0 (CH_3, C-8 / C-9); **LRMS m/z (ES$^+$):** 249.1 ([M + Na]$^+$, 29%); **HRMS m/z (ES$^+$):** calcd. for $C_{11}H_{14}O_5Na$ 249.0739, found 249.0742.

A novel compound prepared according to a modified literature procedure.[188]

220 *(±)-Methyl (1R,5R,6R,7R)-6-((2-methoxy-2-oxoethyl)thio)-3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate*



219 **220**

Ester **219** (100 mg, 0.440 mmol) was dissolved in acetonitrile (4.4 mL) and the resulting solution cooled to 0 °C. Triethylamine (0.31 mL, 2.2 mmol) and methyl mercaptoacetate (0.20 mL, 2.2 mmol) were added, the cooling bath removed, and the resulting solution was allowed to warm to rt. After 3 h the reaction was determined complete by TLC and concentrated under reduced pressure to give a residue which was purified by flash column chromatography (1:1 petroleum ether:Et_2O) to yield sulfide **220** as a white solid (131 mg, 89%). **R_f:** 0.26 (1:1 petroleum ether:Et_2O, visualised using $KMnO_4$ / Δ).

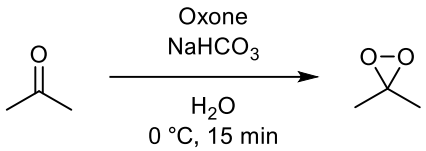
m.p. 95 – 97 °C; **ν_{max} / cm^{-1} (neat):** 2994 (CH), 2951 (CH), 1730 (2 × CO); **δ_H (400 MHz, $CDCl_3$):** 4.60 (1 H, ddd, *J* 4.1, 3.0, 1.3, H-4), 4.30 (1 H, dd, *J* 4.1, 2.5, H-5), 4.25 (1 H, ddd, *J* 4.5, 2.5, 1.8, H-10), 3.78 (3 H, s, H-1), 3.73 (3 H, s, H-14), 3.35 (1 H, d, *J* 15.2, H-12), 3.28 (1 H, d, *J* 15.2, H-12′), 3.16 (1 H, dddd, *J* 15.1, 4.5, 3.0, 1.4, H-11$_{eq}$), 2.77 (1 H, ddd, *J* 6.9, 1.4, 1.3, H-3), 2.20 (1 H, ddd, *J* 15.1, 6.9, 1.8, H-11$_{ax}$), 1.40 (3 H, s, H-8), 1.34 (3 H, s, H-9); **δ_C (101 MHz, $CDCl_3$):** 210.5 (C, C-6), 172.1 (C, C-2), 170.2 (C, C-13), 100.0 (C, C-7), 78.5 (CH, C-5), 76.2 (CH, C-10), 52.9 (CH_3, C-14), 52.5 (CH_3, C-1), 52.4 (CH, C-4), 41.3 (CH, C-3), 35.1 (CH_2, C-11), 34.0 (CH_2, C-12), 27.9 (CH_3, C-9), 25.4 (CH_3, C-8); **LRMS m/z (ES$^+$):** 256.2 ([M + Na]$^+$, 100%); **HRMS m/z (ES$^+$):** calcd. for $C_{14}H_{20}O_7SNa$ 355.0827, found 355.0818.

A novel compound prepared according to a modified literature procedure.[189]

CHAPTER 5 – APPENDICES

5.1 – DIMETHYLDIOXIRANE SYNTHESIS

5.1.1 – SYNTHESIS



Sodium hydrogencarbonate (24 g, 0.29 mol) was added to a mixture of water (20 mL) and acetone (30 mL) in a 1 L round-bottomed flask, and the resulting suspension was cooled to 0 °C and stirred for 20 min. Oxone (25 g, 0.040 mol) was added and the reaction stirred vigorously for a further 15 min, after which time the reaction flask was attached to a rotary evaporator fitted with a 250 mL bump guard, and with the bath at room temperature. The bump guard was cooled using acetone / CO_2 (Figure 5.1) and a vacuum of 205 mbar was applied *via* a diaphragm pump with a built-in vacuum regulator. During this process, the flask is rotated vigorously (200 rpm) to prevent bumping of the slurry into the bump trap. After 15 min, the bath temperature was raised to 40 °C over the course of 10 min. Once the bath reached 40 °C, the vacuum was released and the flask raised from the water bath. The pale-yellow acetone DMDO solution was decanted into a graduated cylinder to measure the total volume of the solution and then dried over Na_2SO_4. The solution was then filtered and titrated (Appendix 5.1.2) to give dimethyldioxirane as a pale-yellow solution in acetone (71 mM, 27 mL, 5%). The DMDO solution was used immediately following titration.

Known compound prepared according to an Org. Synth. procedure.[190]

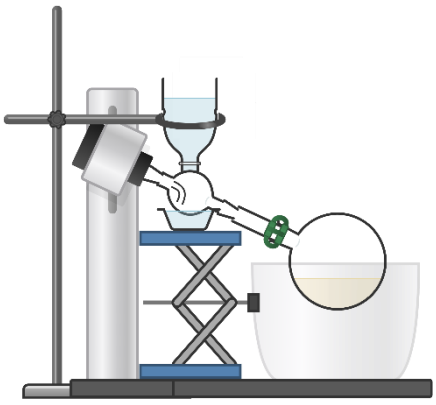
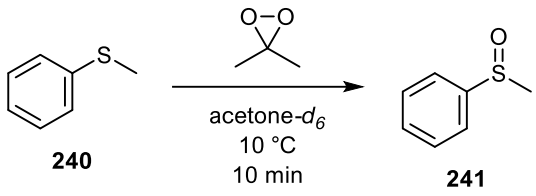


Figure 5.1

5.1.2 – TITRATION



A solution of thioanisole **240** (52 mg, 0.42 mmol) in acetone-d_6 (0.60 mL, 0.70 M) was cooled to 10 °C. A solution of dimethyldioxirane in acetone (3.0 mL, unknown concentration) was added and the reaction stirred for 10 min after which time an 0.65 mL aliquot of the reaction mixture was added directly to an NMR tube. Analysis of the signal integration of the phenyl protons of sulfoxide **241** (δ 7.7 – 7.5 ppm) against the phenyl protons of thioanisole **240** (δ 7.3 – 7.1 ppm) in the ^{1}H-NMR spectrum allows for determination of the ratio of oxidized product to excess thioanisole (Figure 5.2).* From this, the concentration of the DMDO solution was calculated.

Performed according to the procedure of Adam et al.[190,191] **No evidence of overoxidation to sulfone observed: 7.95 – 7.87 (2 H, m), 7.71 – 7.61 (2 H, m), 7.59 – 7.52 (1 H, m), 3.02 (3 H, s).*[192]

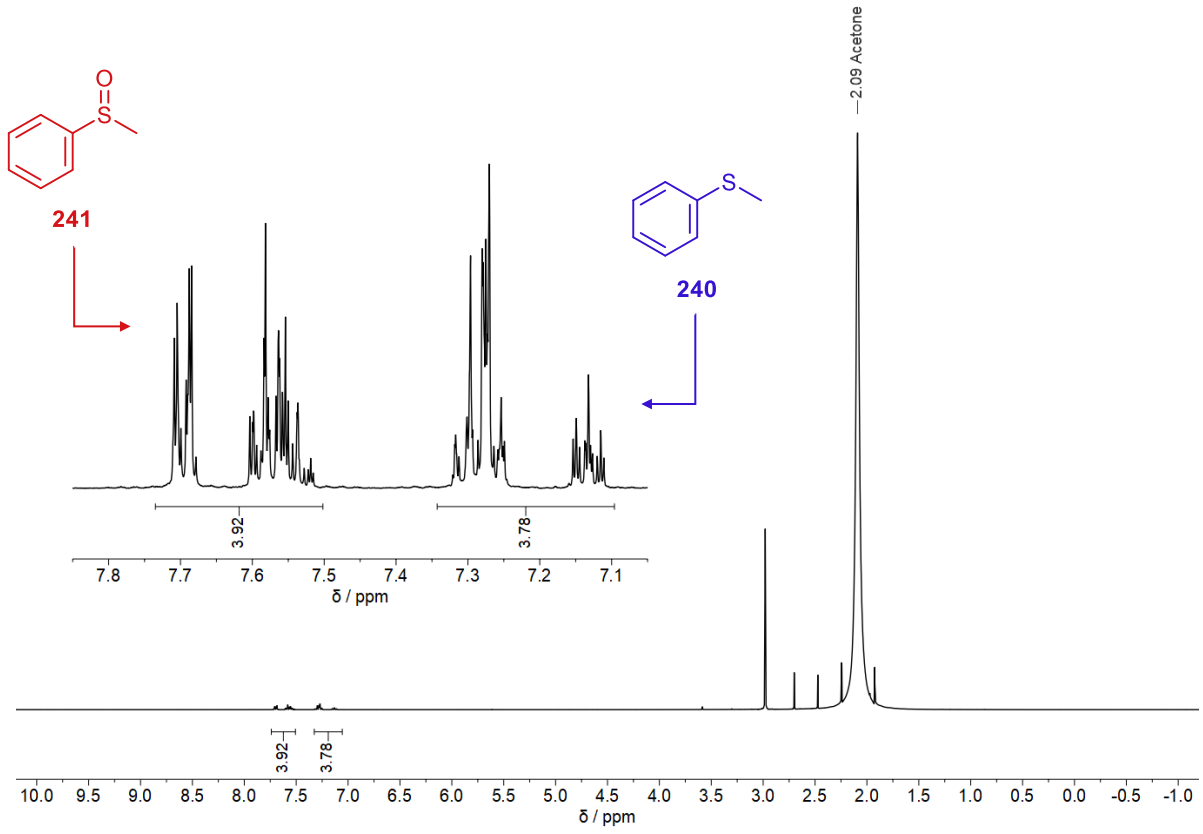
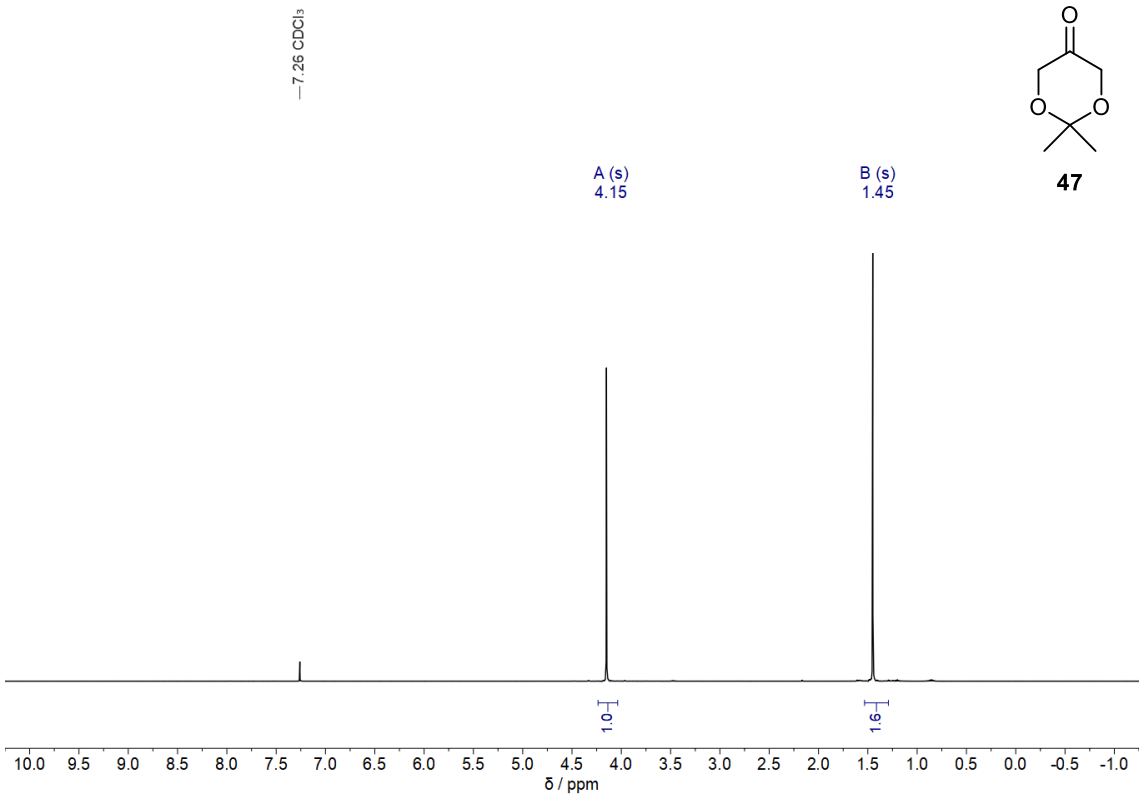


Figure 5.2 *^{1}H-NMR titration of DMDO*

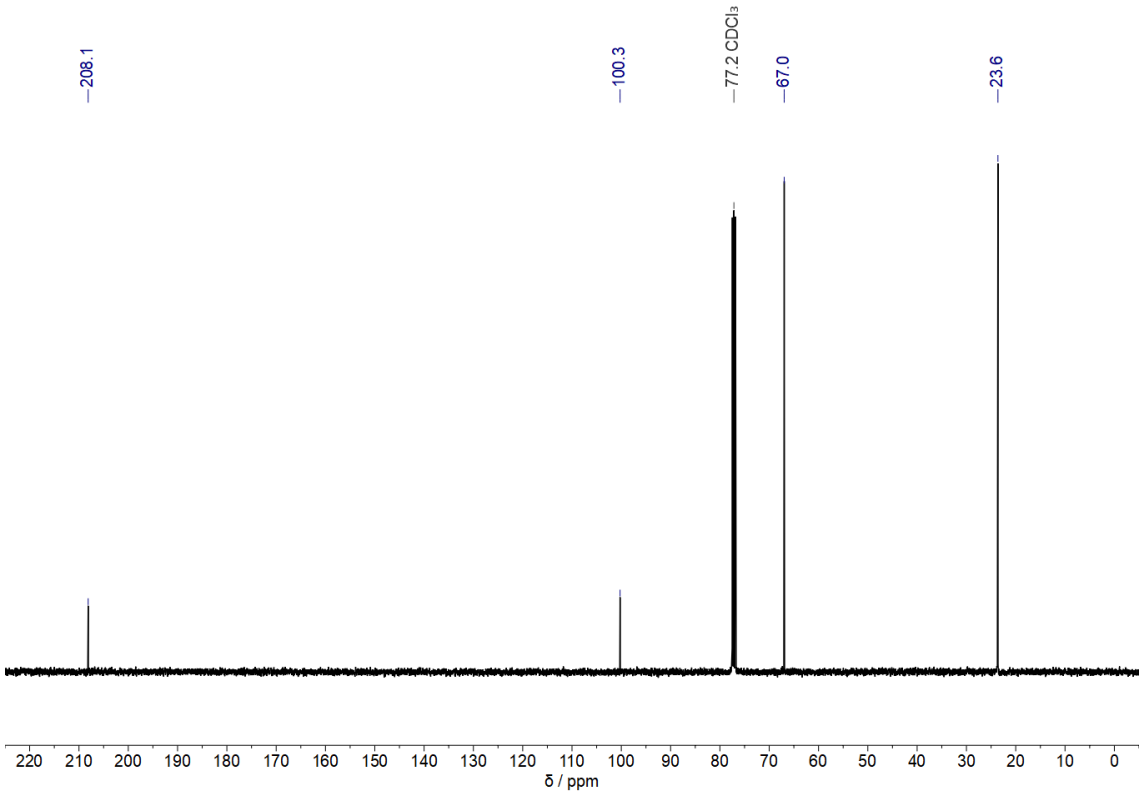
5.2 – 1D NMR SPECTRA

^{1}H-NMR spectrum of **47** in $CDCl_3$ (400 MHz, 298 K)

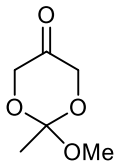


47

^{13}C-NMR spectrum of **47** in $CDCl_3$ (101 MHz, 298 K)

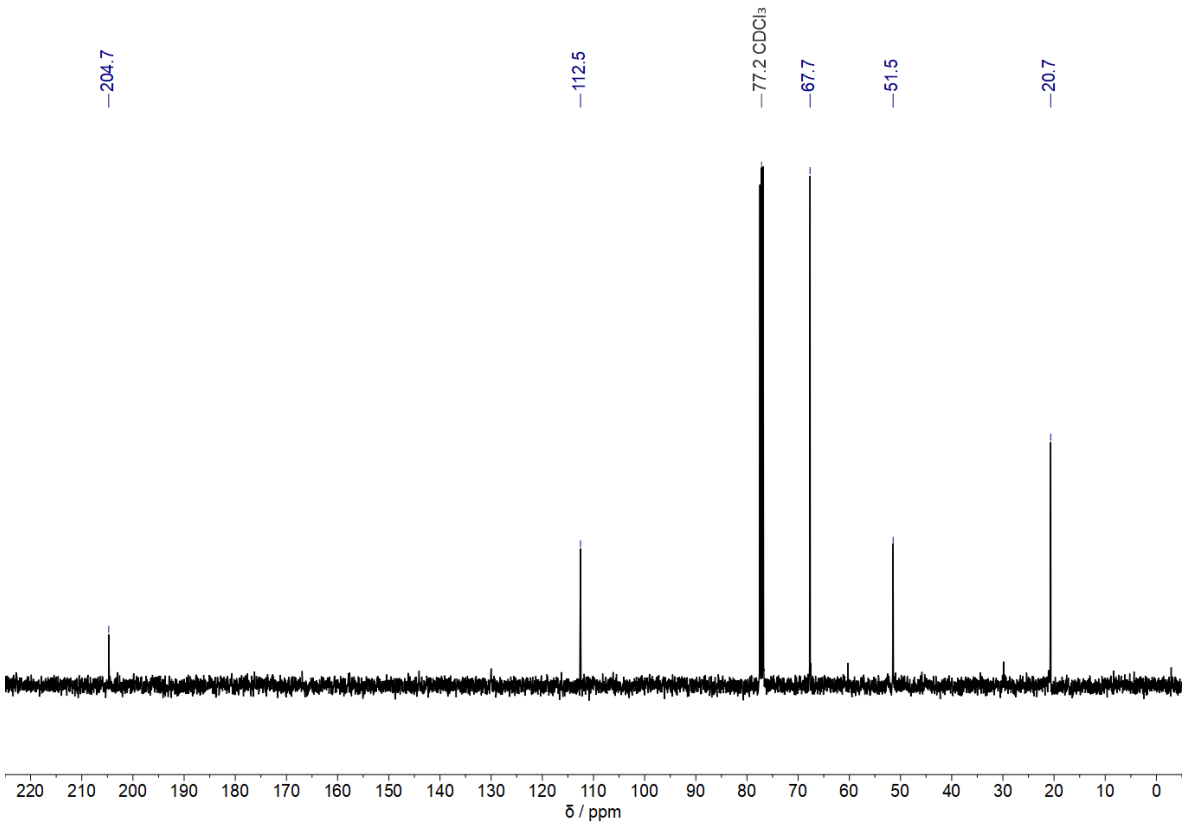


^{1}H-NMR spectrum of **49** in $CDCl_3$ (400 MHz, 296 K)

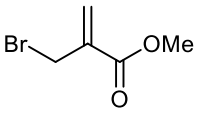


49

^{13}C-NMR spectrum of **49** in $CDCl_3$ (101 MHz, 295 K)



^{1}H-NMR spectrum of **50** in $CDCl_3$ (400 MHz, 298 K)



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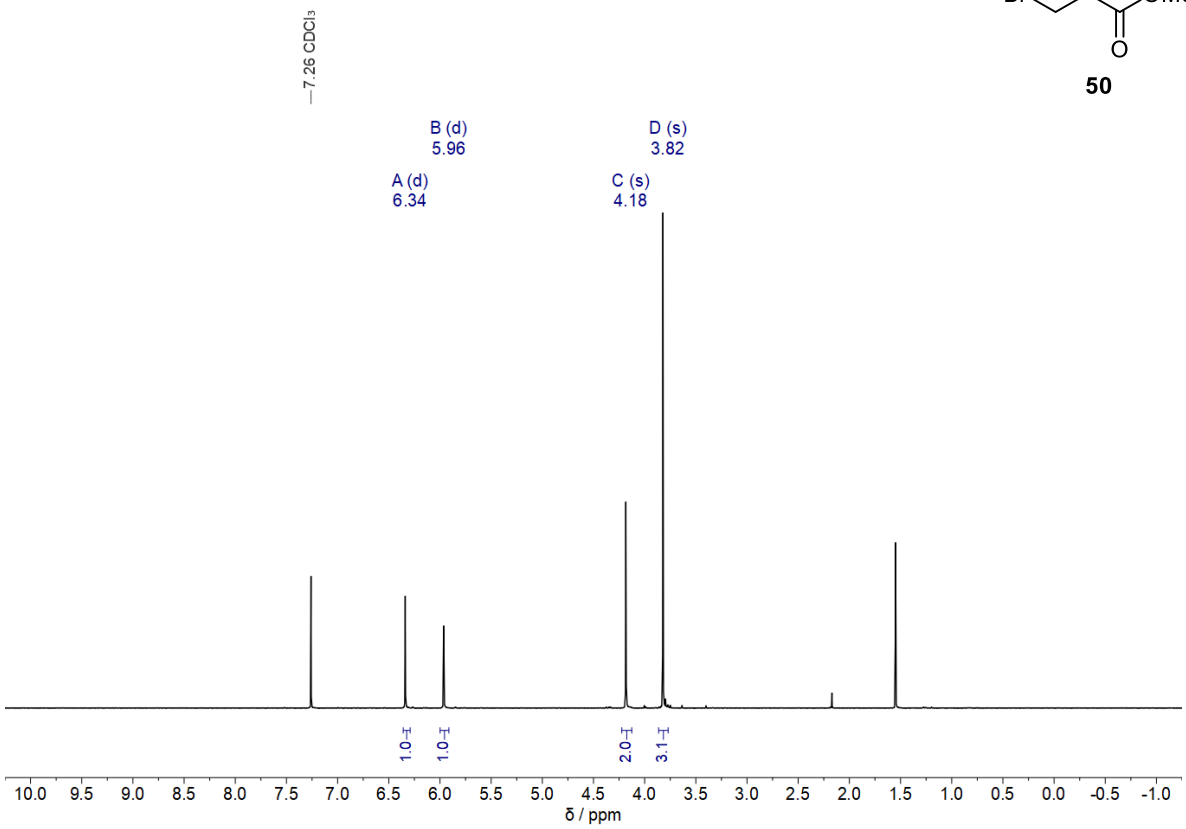
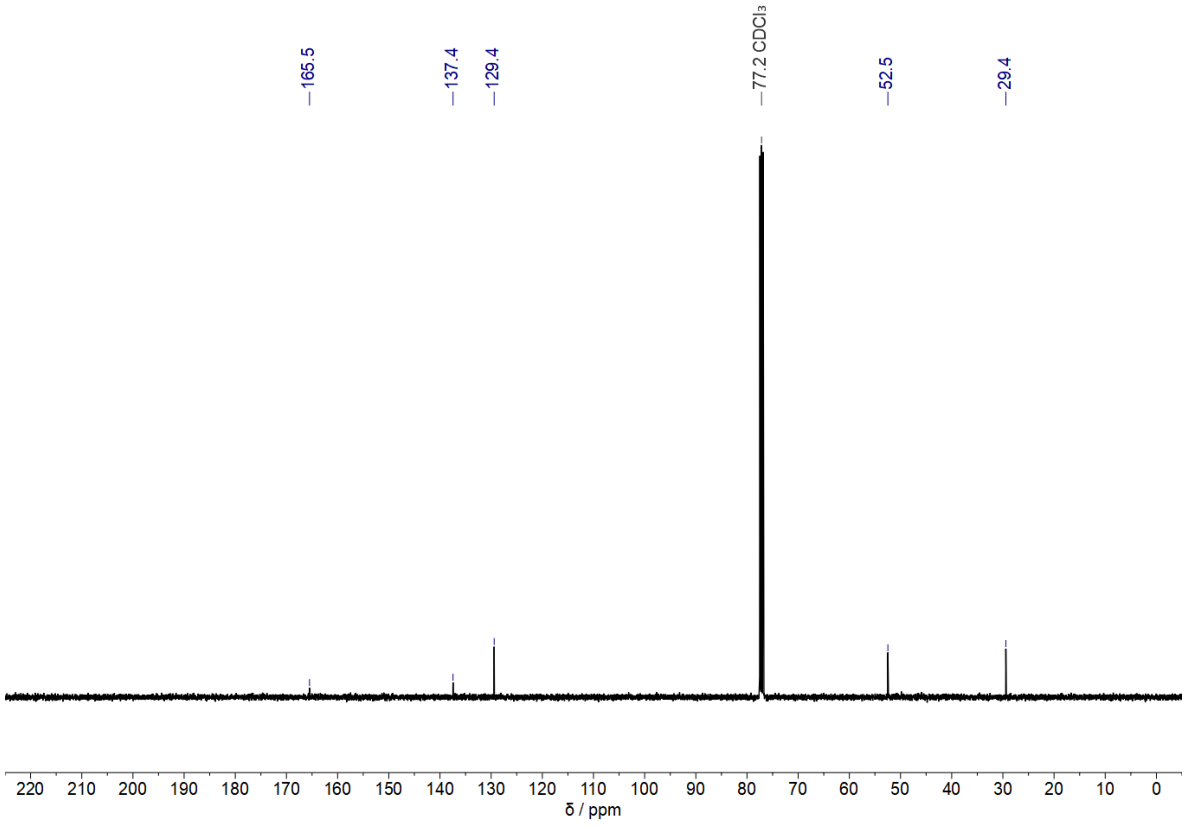
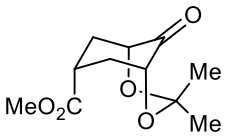


^{13}C-NMR spectrum of **50** in $CDCl_3$ (101 MHz, 298 K)

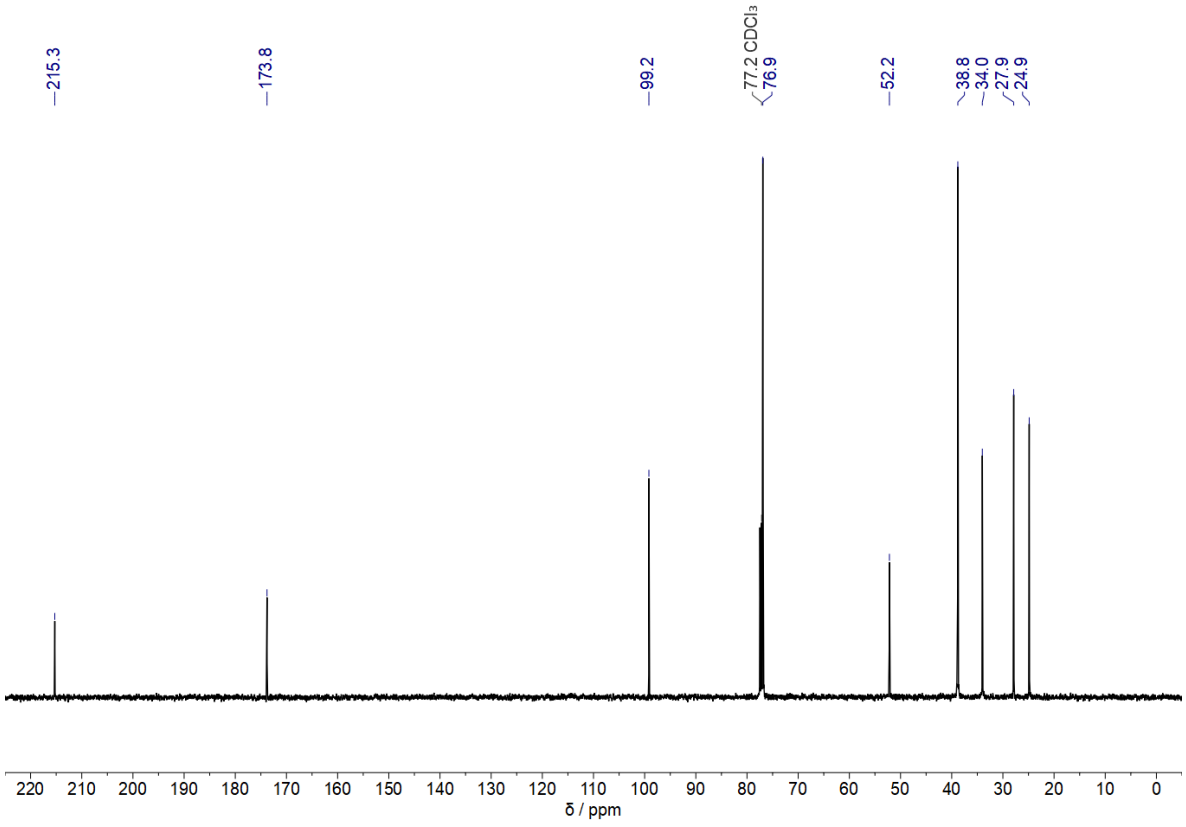


^{1}H-NMR spectrum of **51** in $CDCl_3$ (400 MHz, 294 K)

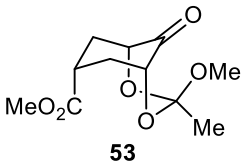


51

^{13}C-NMR spectrum of **51** in $CDCl_3$ (101 MHz, 295 K)

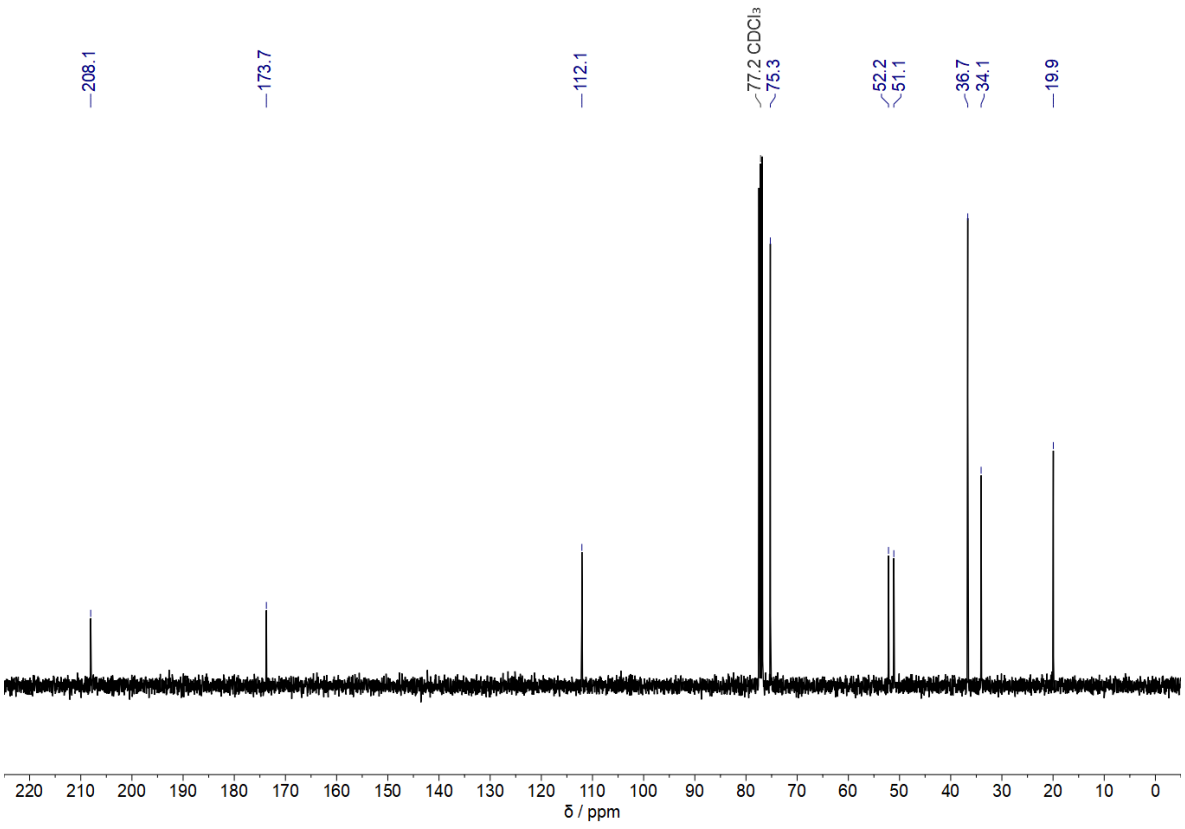


^{1}H-NMR spectrum of **53** in $CDCl_3$ (400 MHz, 295 K)

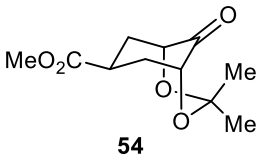


53

^{13}C-NMR spectrum of **53** in $CDCl_3$ (101 MHz, 296 K)

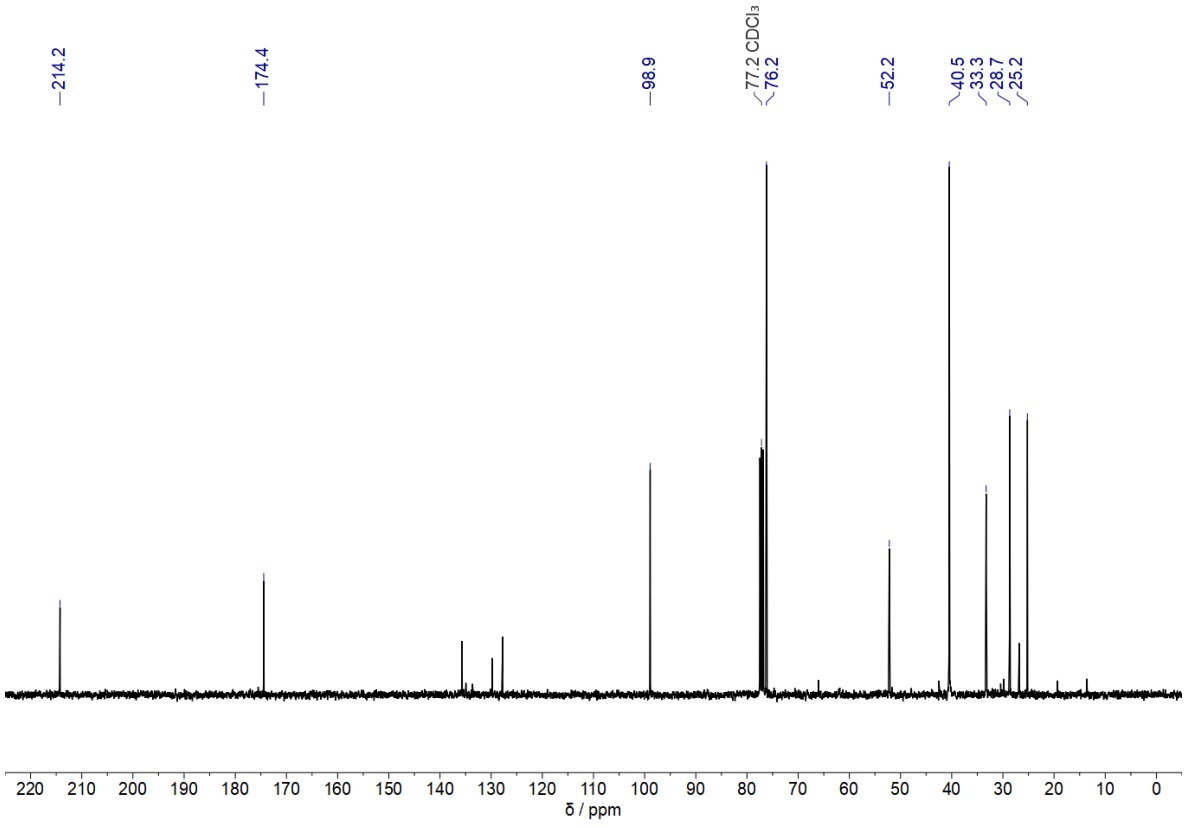


^{1}H-NMR spectrum of **54** in $CDCl_3$ (300 MHz, 300 K)

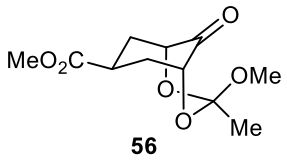


54

^{13}C-NMR spectrum of **54** in $CDCl_3$ (101 MHz, 295 K)

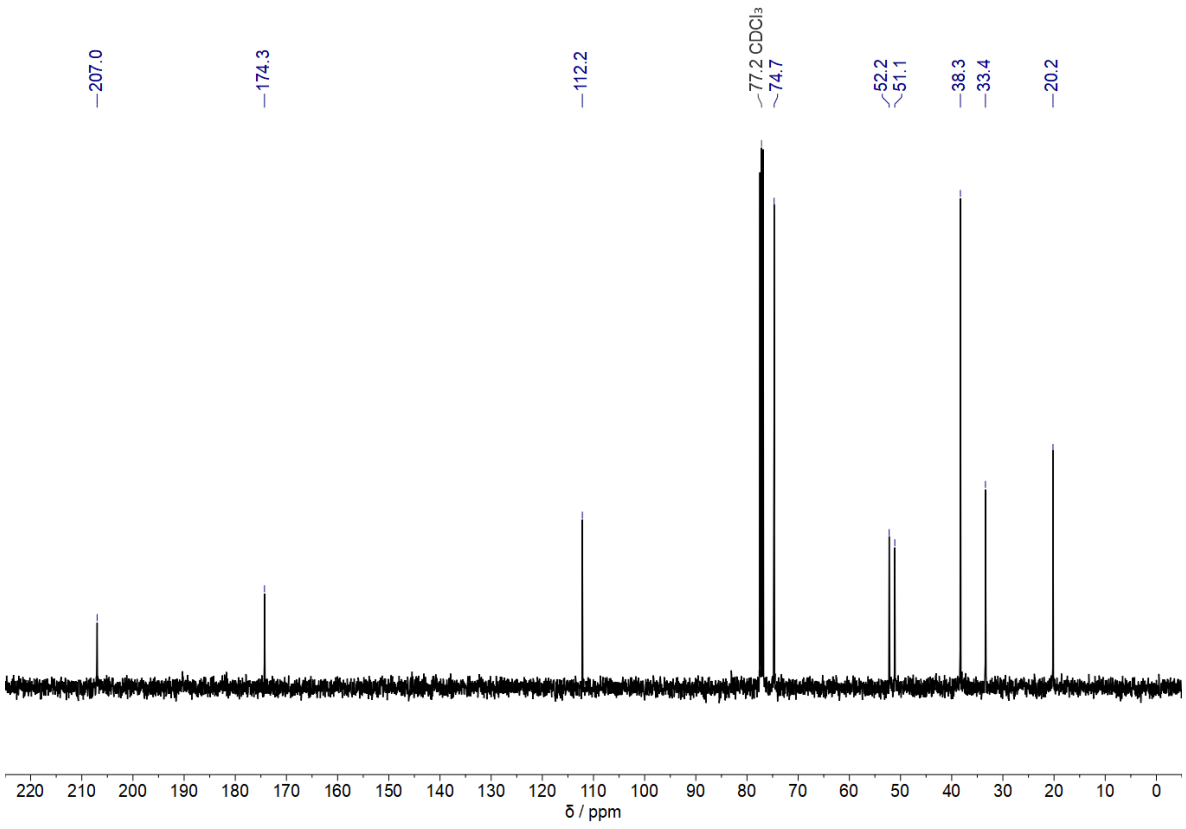


^{1}H-NMR spectrum of **56** in $CDCl_3$ (400 MHz, 296 K)

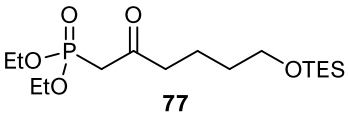


56

^{13}C-NMR spectrum of **56** in $CDCl_3$ (101 MHz, 296 K)

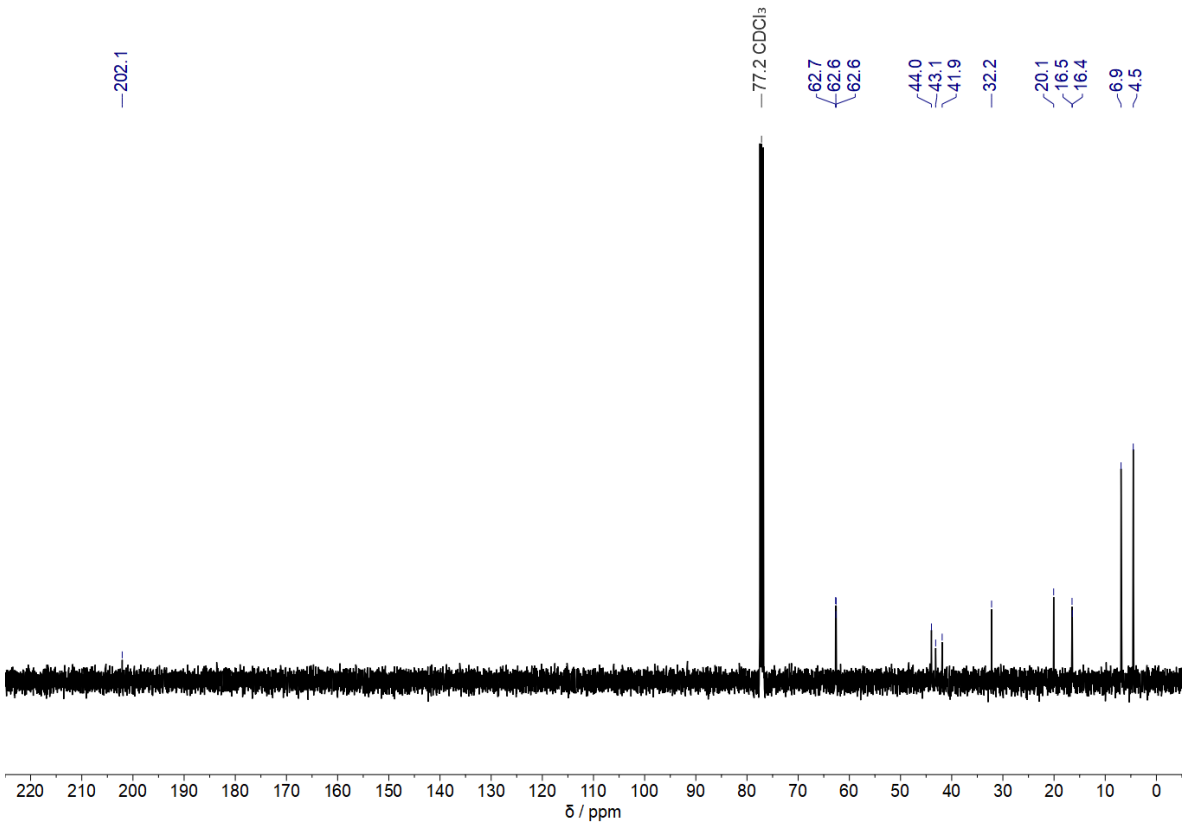


^{1}H-NMR spectrum of **77** in $CDCl_3$ (400 MHz, 298 K)

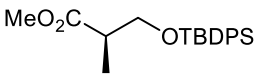


77

^{13}C-NMR spectrum of **77** in $CDCl_3$ (101 MHz, 298 K)



^{1}H-NMR spectrum of **87** in $CDCl_3$ (400 MHz, 298 K)



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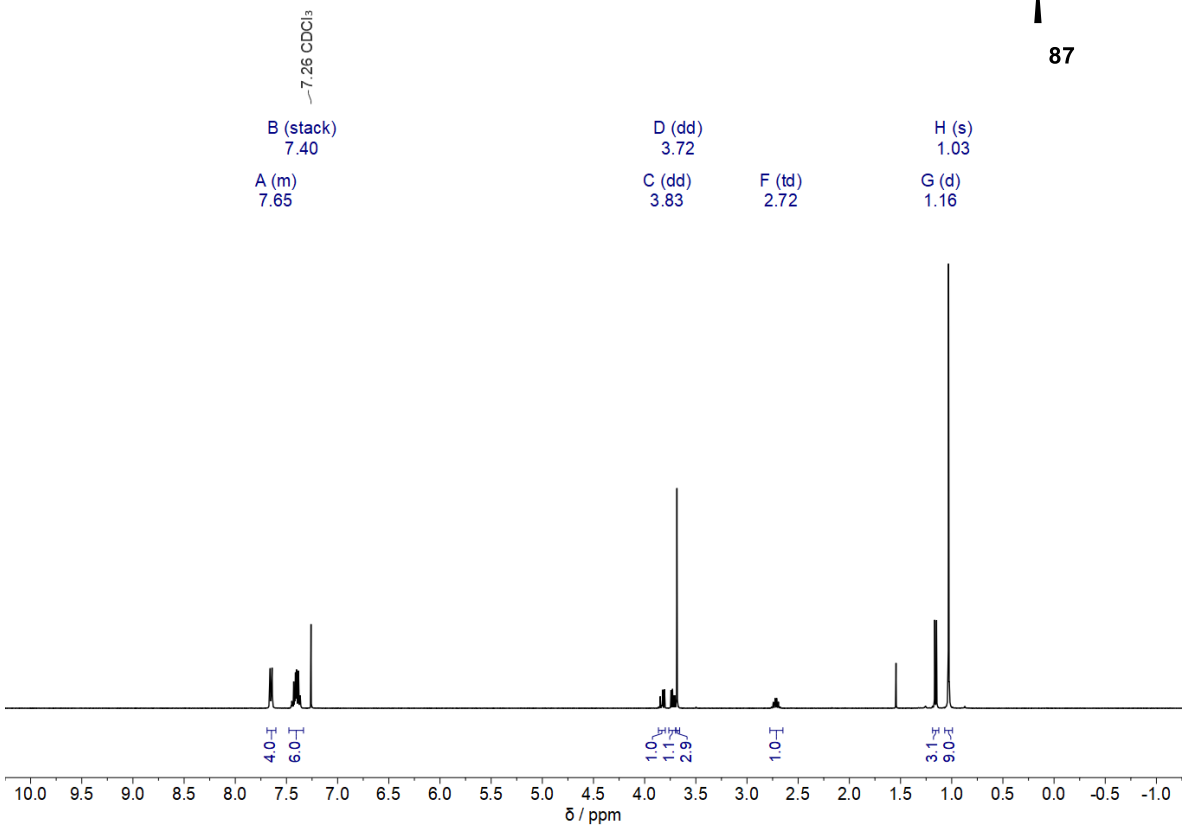
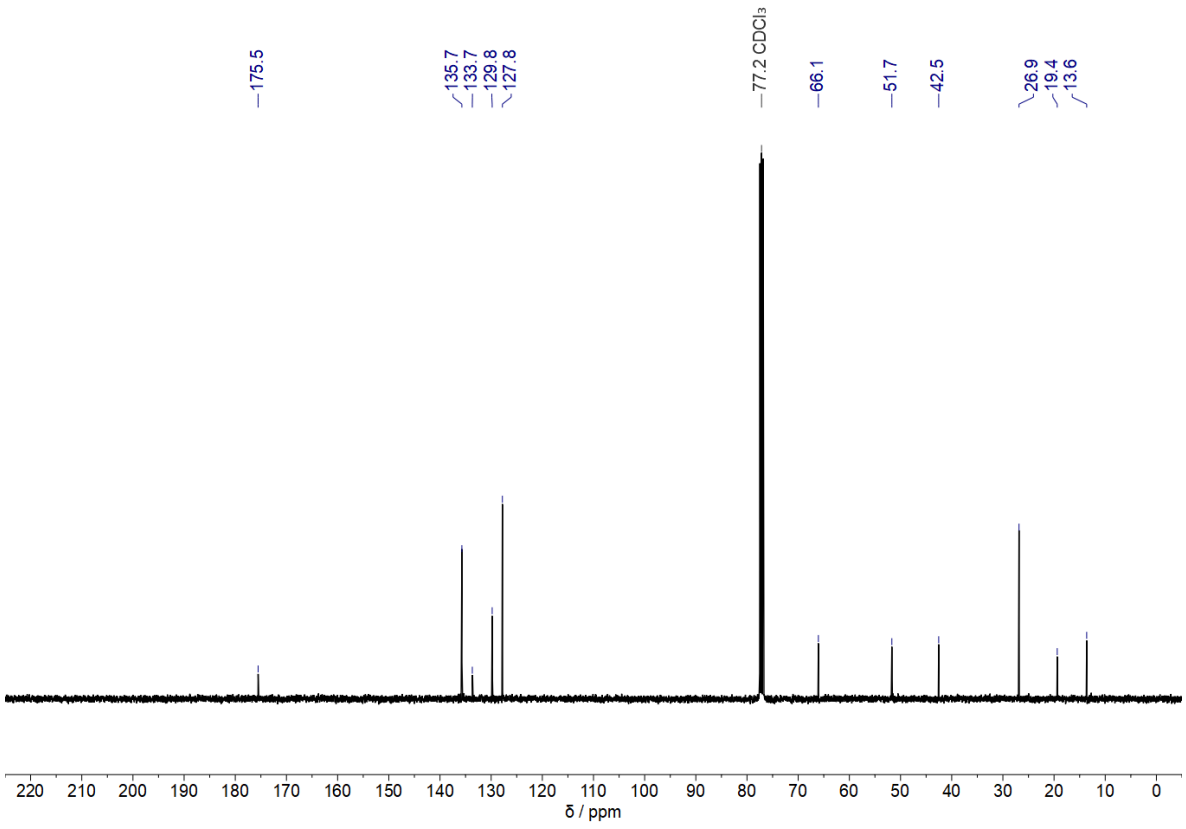
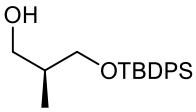


^{13}C-NMR spectrum of **87** in $CDCl_3$ (101 MHz, 298 K)



^{1}H-NMR spectrum of **88** in $CDCl_3$ (400 MHz, 298 K)



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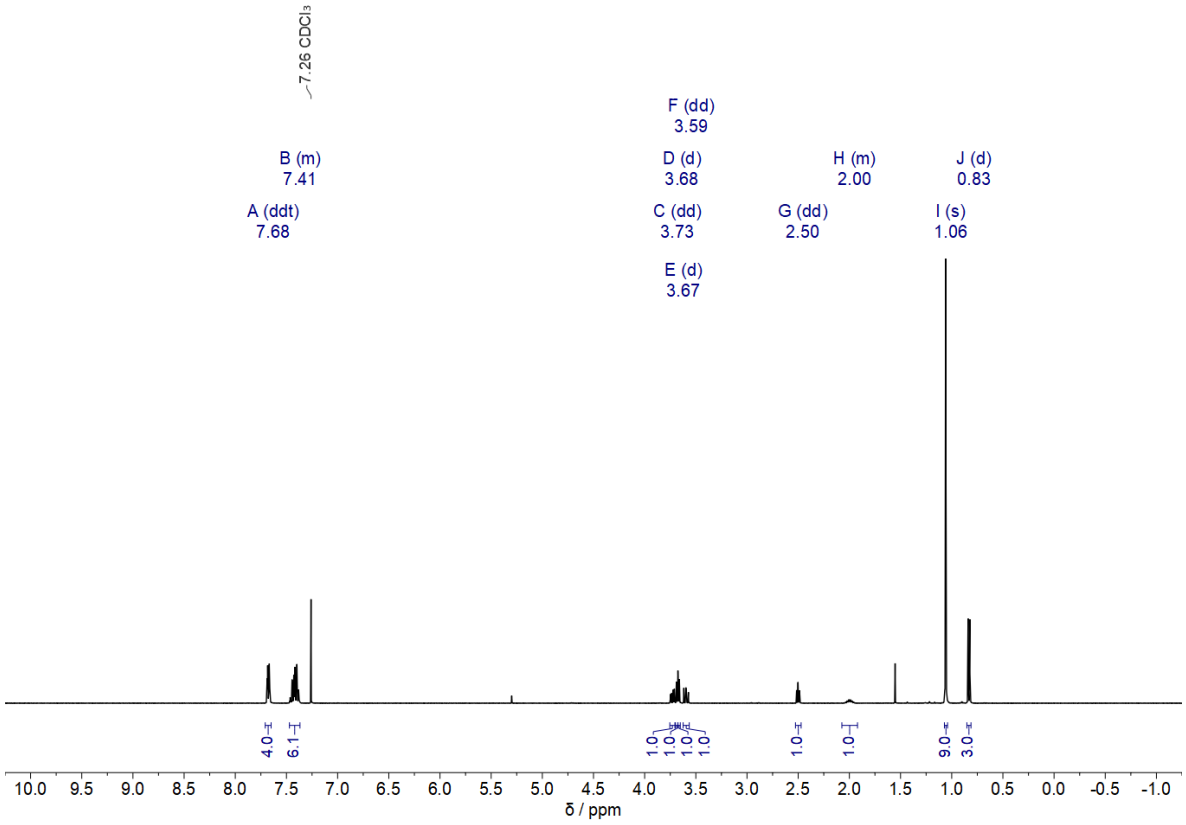
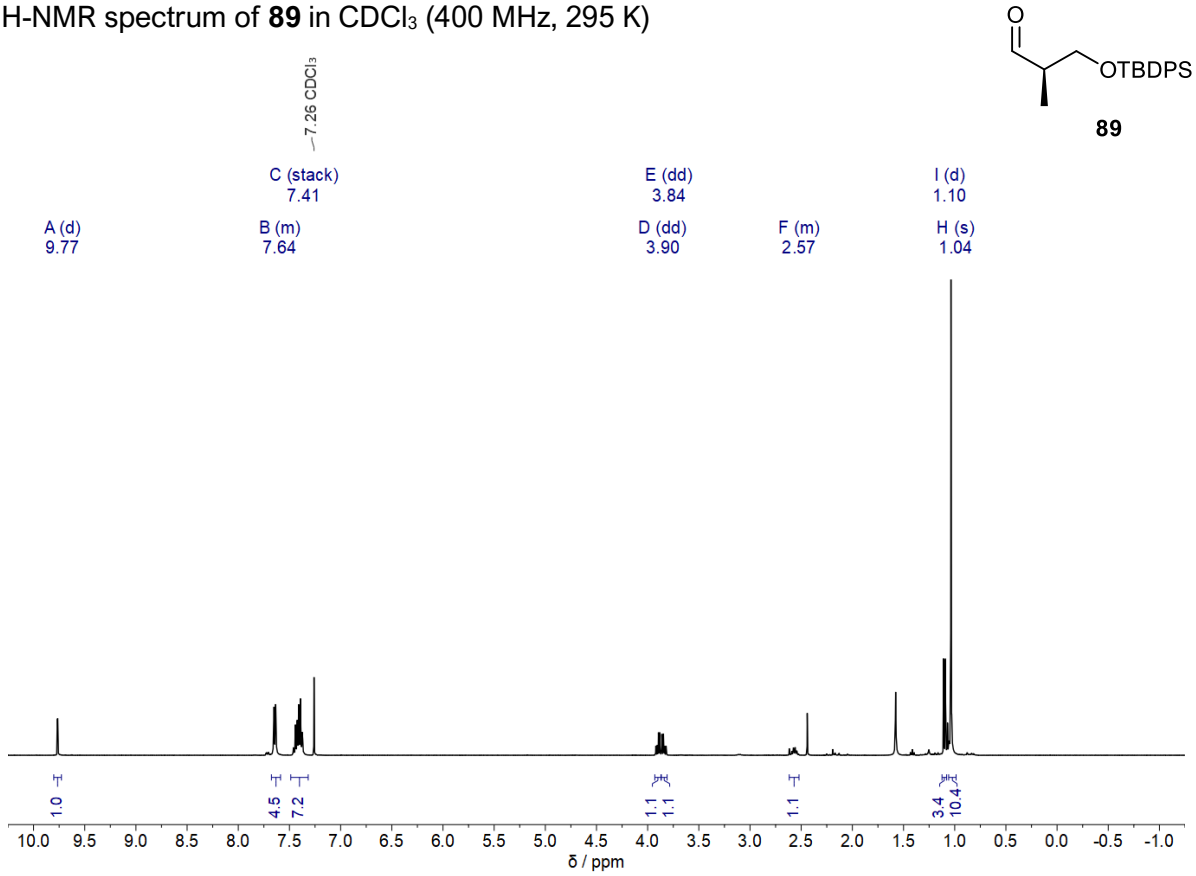
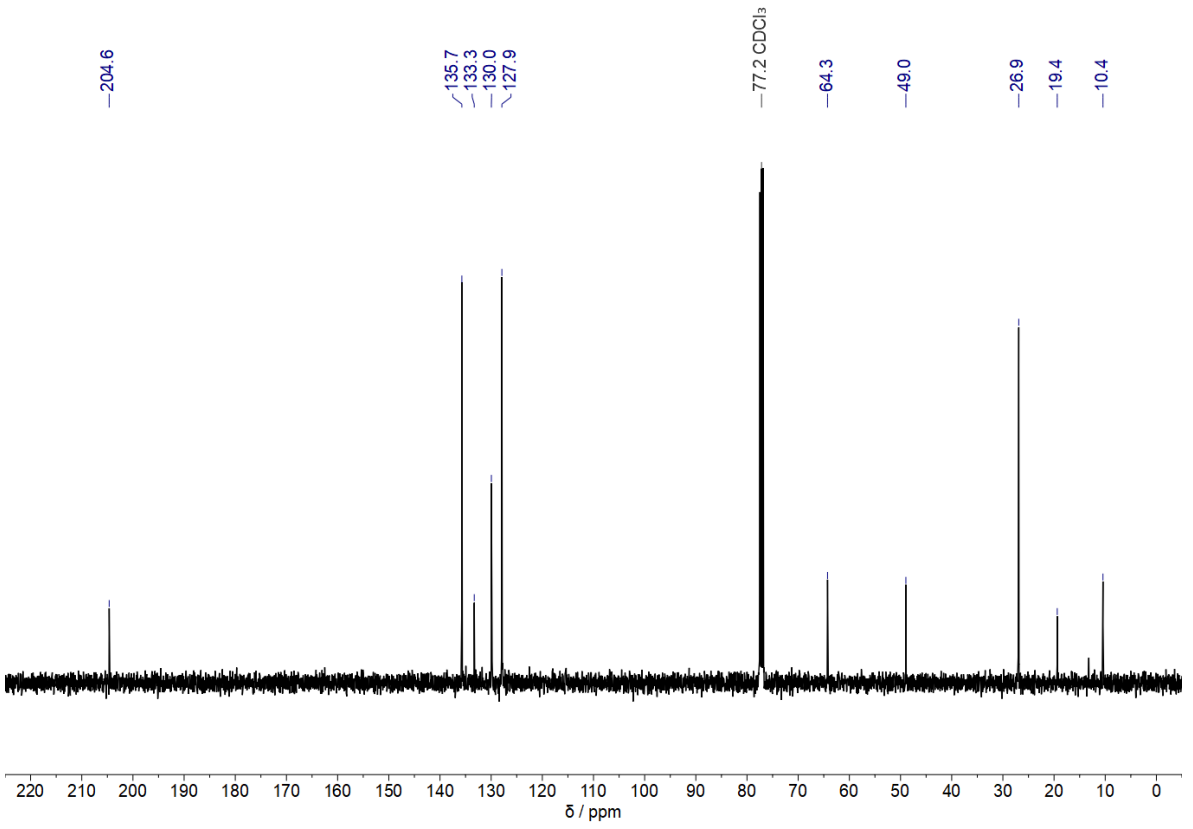
^{13}C-NMR spectrum of **88** in $CDCl_3$ (101 MHz, 298 K)



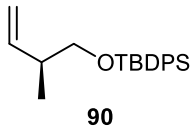
^{1}H-NMR spectrum of **89** in $CDCl_3$ (400 MHz, 295 K)



^{13}C-NMR spectrum of **89** in $CDCl_3$ (101 MHz, 296 K)

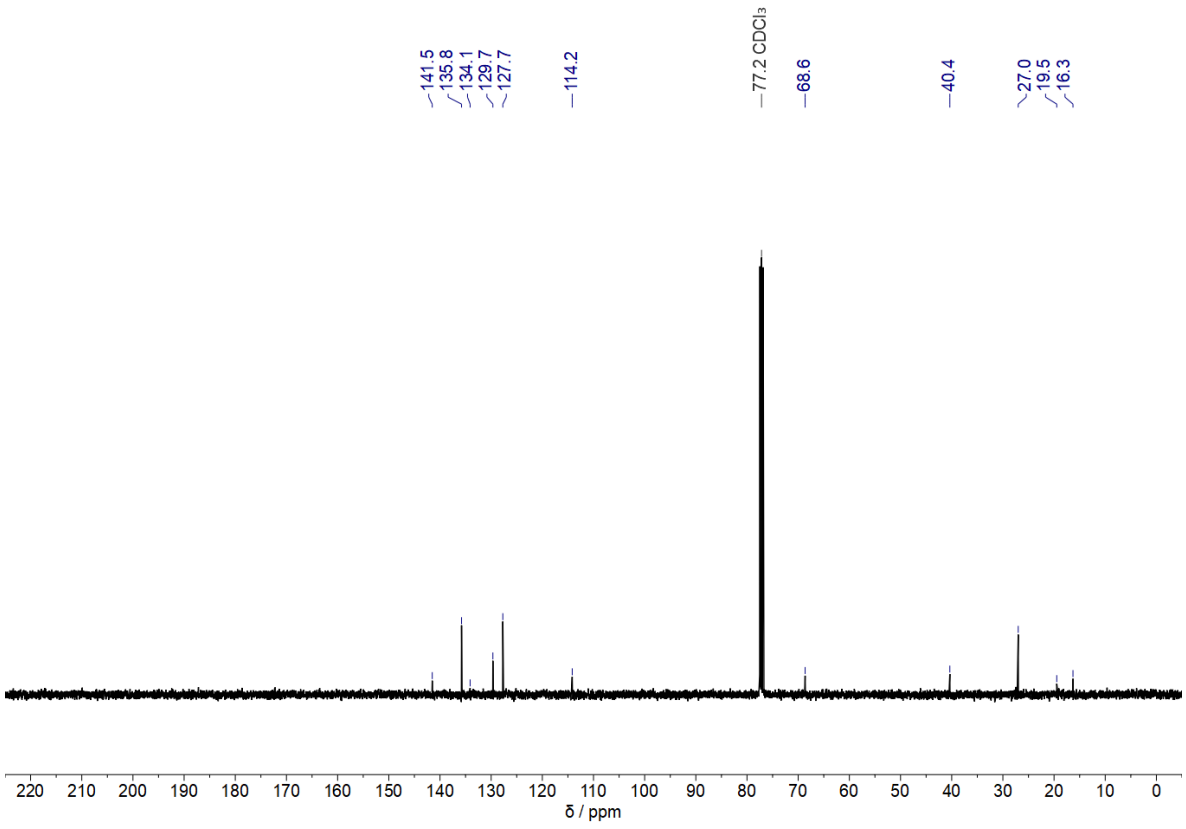


^{1}H-NMR spectrum of **90** in $CDCl_3$ (400 MHz, 298 K)

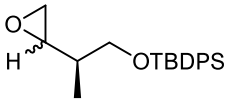


90

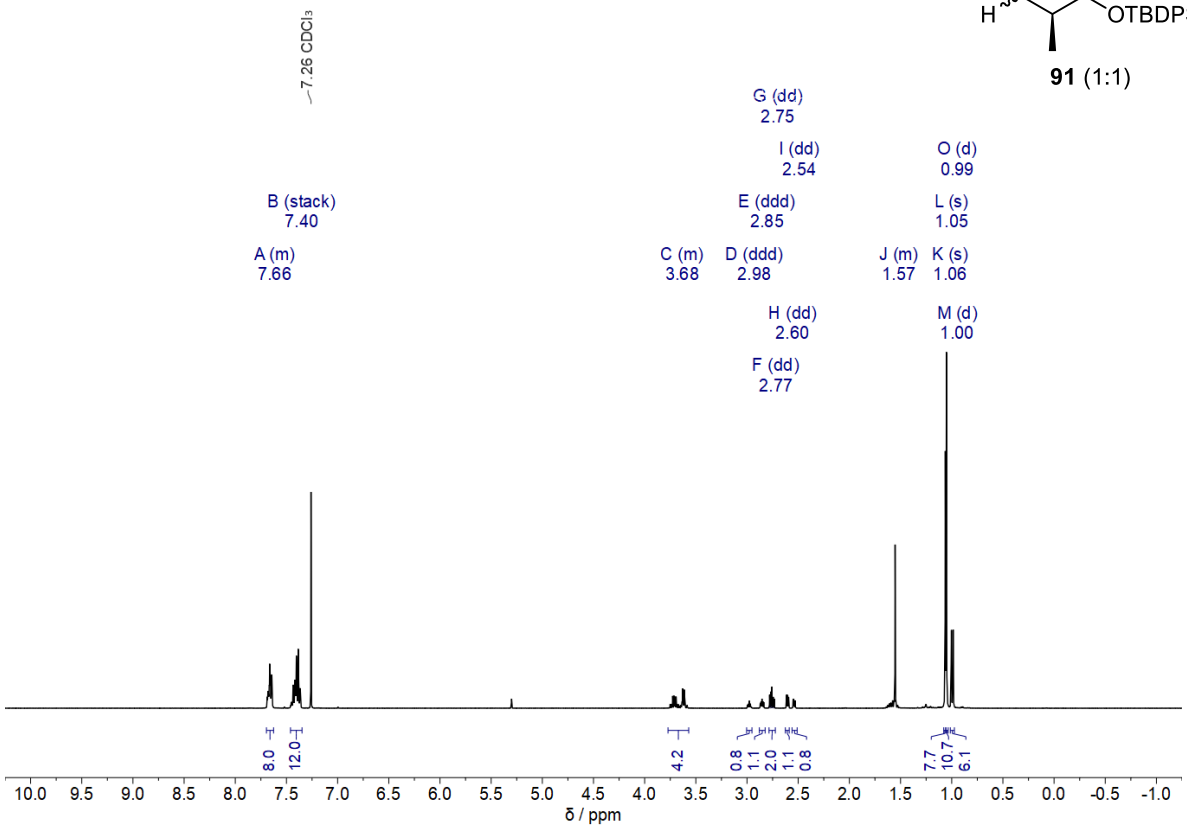
^{13}C-NMR spectrum of **90** in $CDCl_3$ (101 MHz, 298 K)



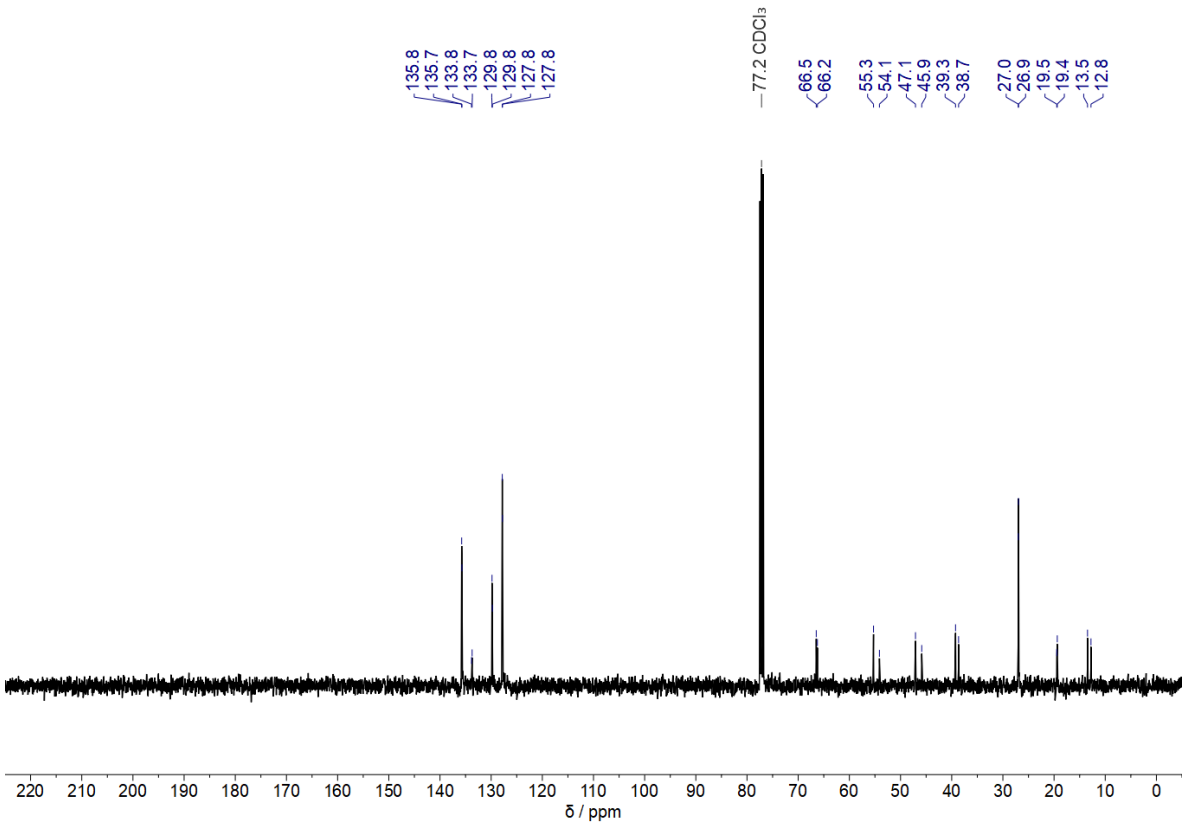
^{1}H-NMR spectrum of **91** in $CDCl_3$ (400 MHz, 294 K)



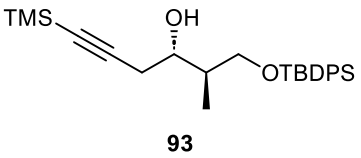
91 (1:1)



^{13}C-NMR spectrum of **91** in $CDCl_3$ (101 MHz, 295 K)

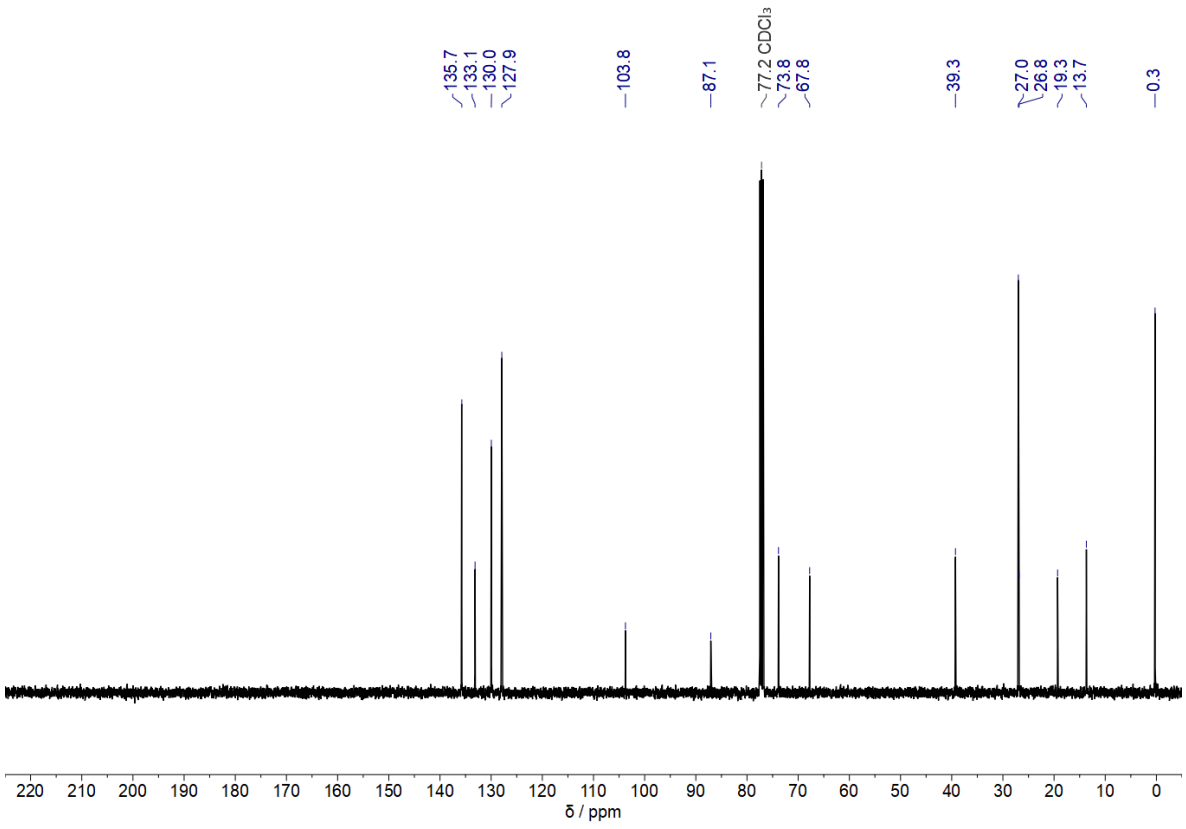


^{1}H-NMR spectrum of **93** in $CDCl_3$ (400 MHz, 298 K)

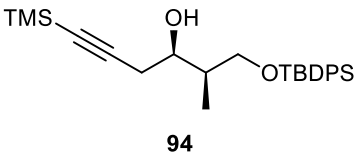


93

^{13}C-NMR spectrum of **93** in $CDCl_3$ (101 MHz, 298 K)

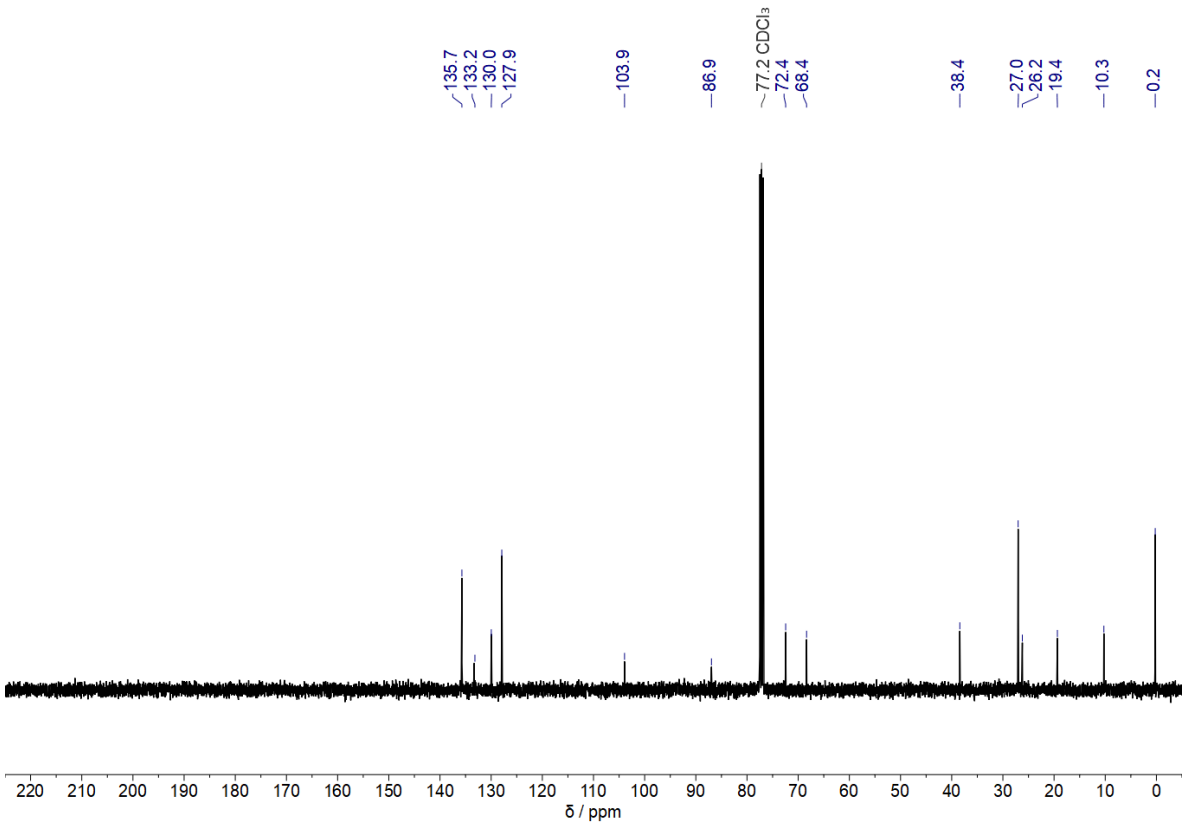


^{1}H-NMR spectrum of **94** in $CDCl_3$ (400 MHz, 298 K)

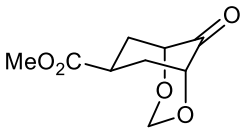


94

^{13}C-NMR spectrum of **94** in $CDCl_3$ (101 MHz, 298 K)

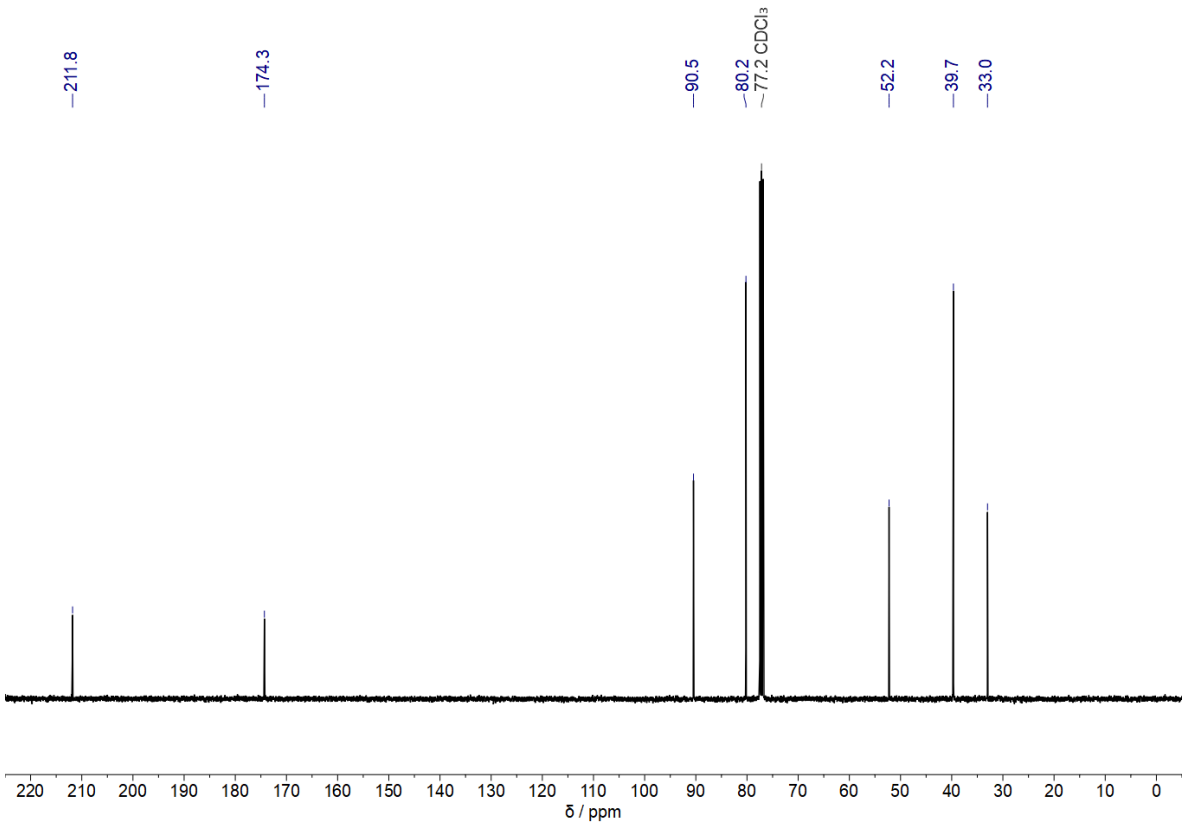


^{1}H-NMR spectrum of **136** in $CDCl_3$ (400 MHz, 298 K)

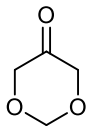


136

^{13}C-NMR spectrum of **136** in $CDCl_3$ (101 MHz, 298 K)

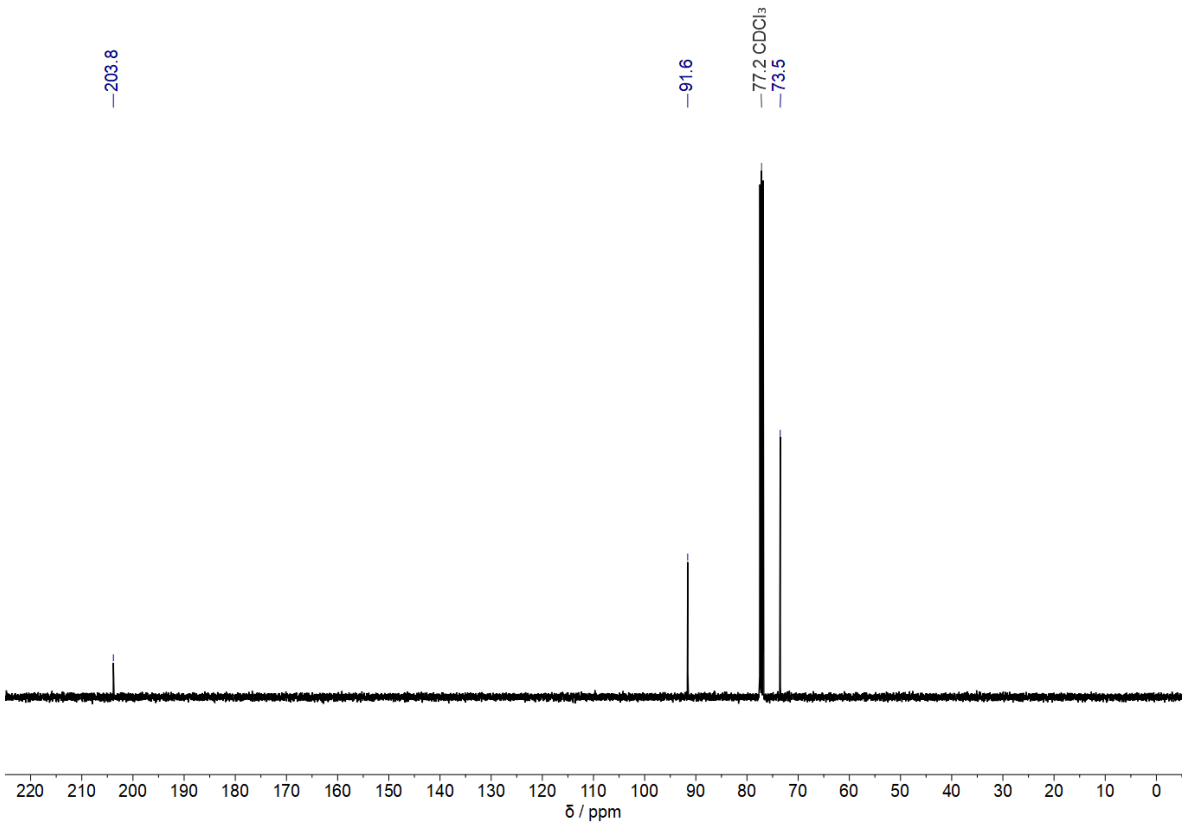


^{1}H-NMR spectrum of **148** in $CDCl_3$ (400 MHz, 295 K)

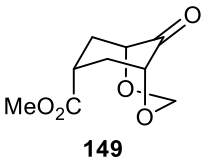


148

^{13}C-NMR spectrum of **148** in $CDCl_3$ (101 MHz, 298 K)

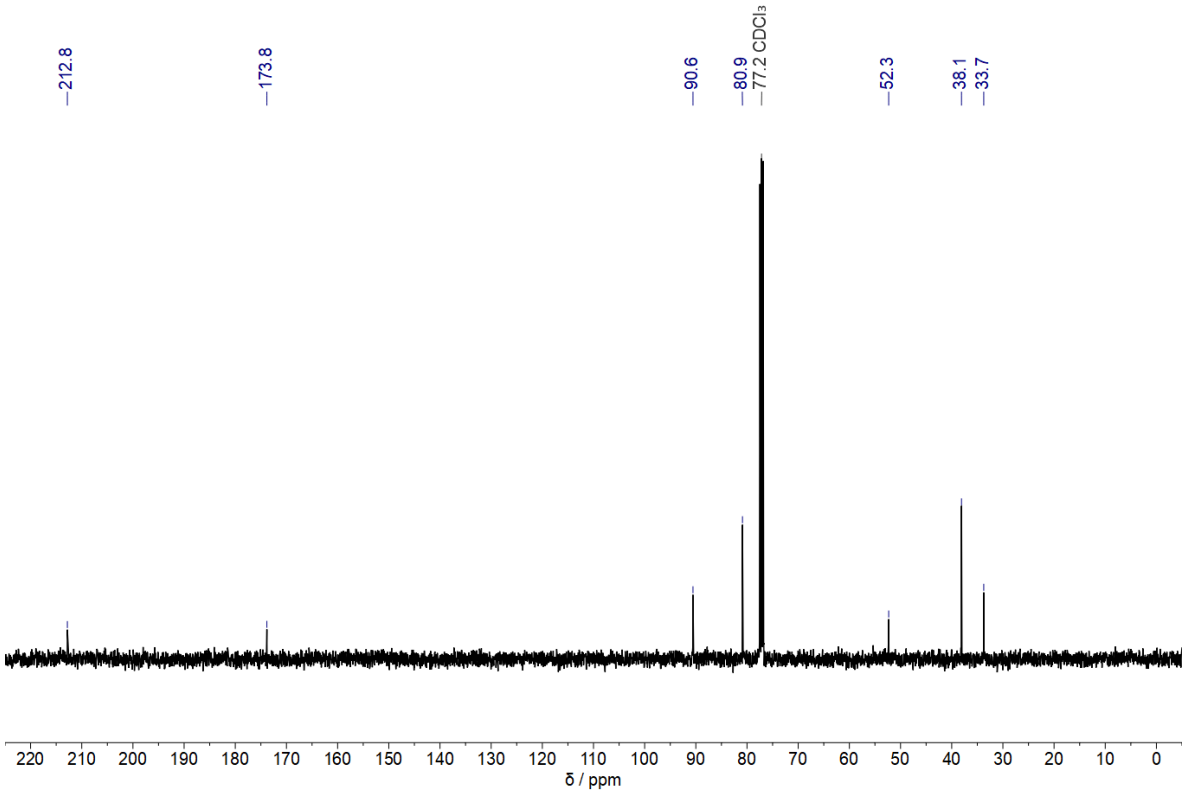


^{1}H-NMR spectrum of **149** in $CDCl_3$ (400 MHz, 295 K)

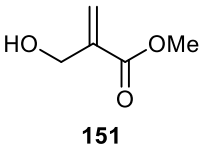


149

^{13}C-NMR spectrum of **149** in $CDCl_3$ (101 MHz, 295 K)

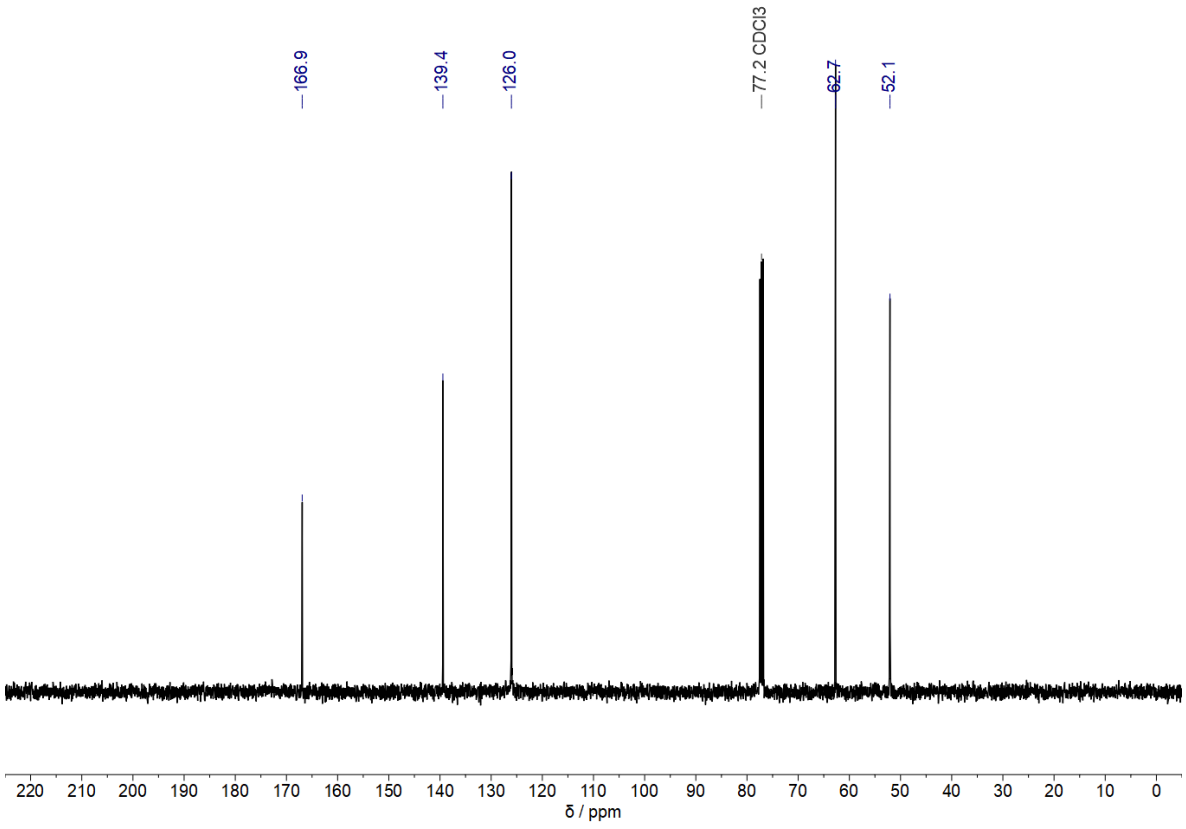


^{1}H-NMR spectrum of **151** in $CDCl_3$ (400 MHz, 296 K)

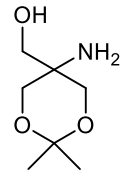


151

^{13}C-NMR spectrum of **151** in $CDCl_3$ (101 MHz, 296 K)

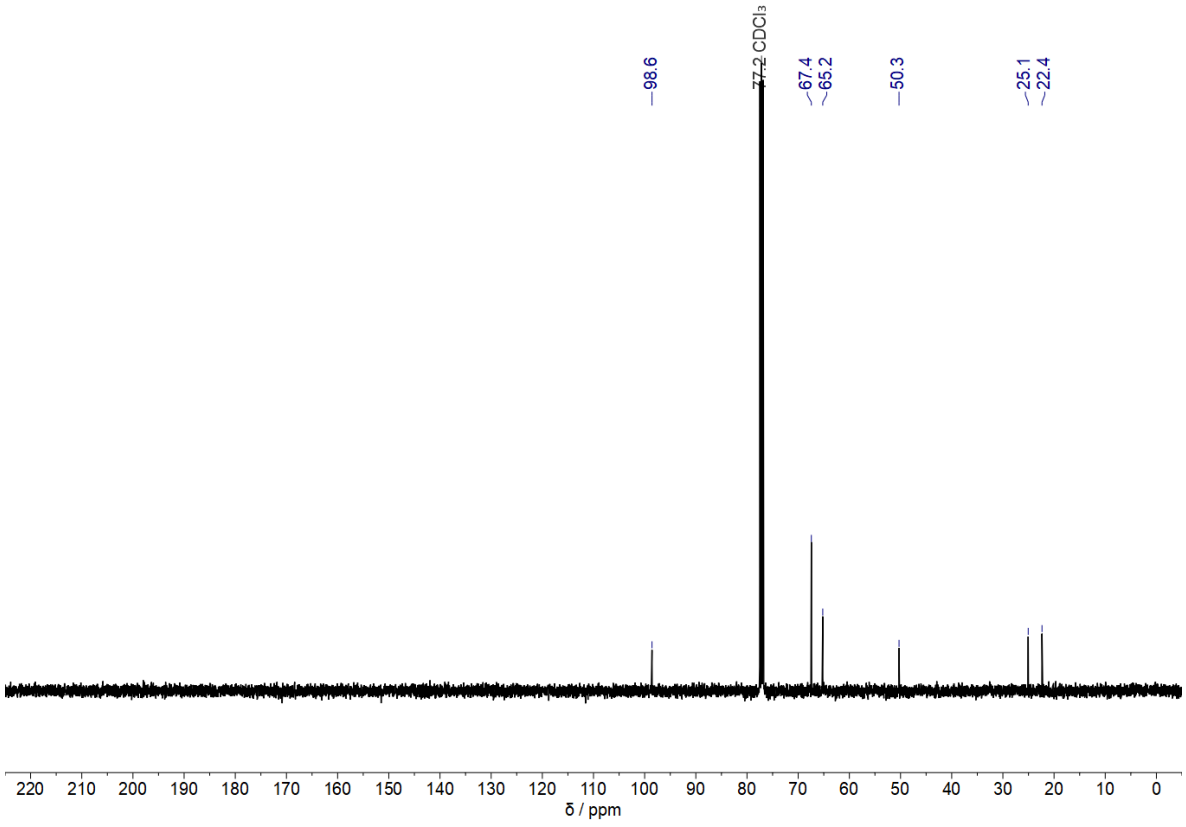


^{1}H-NMR spectrum of **153** in $CDCl_3$ (400 MHz, 298 K)

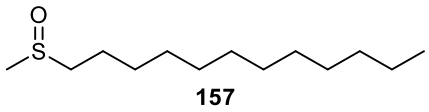


153

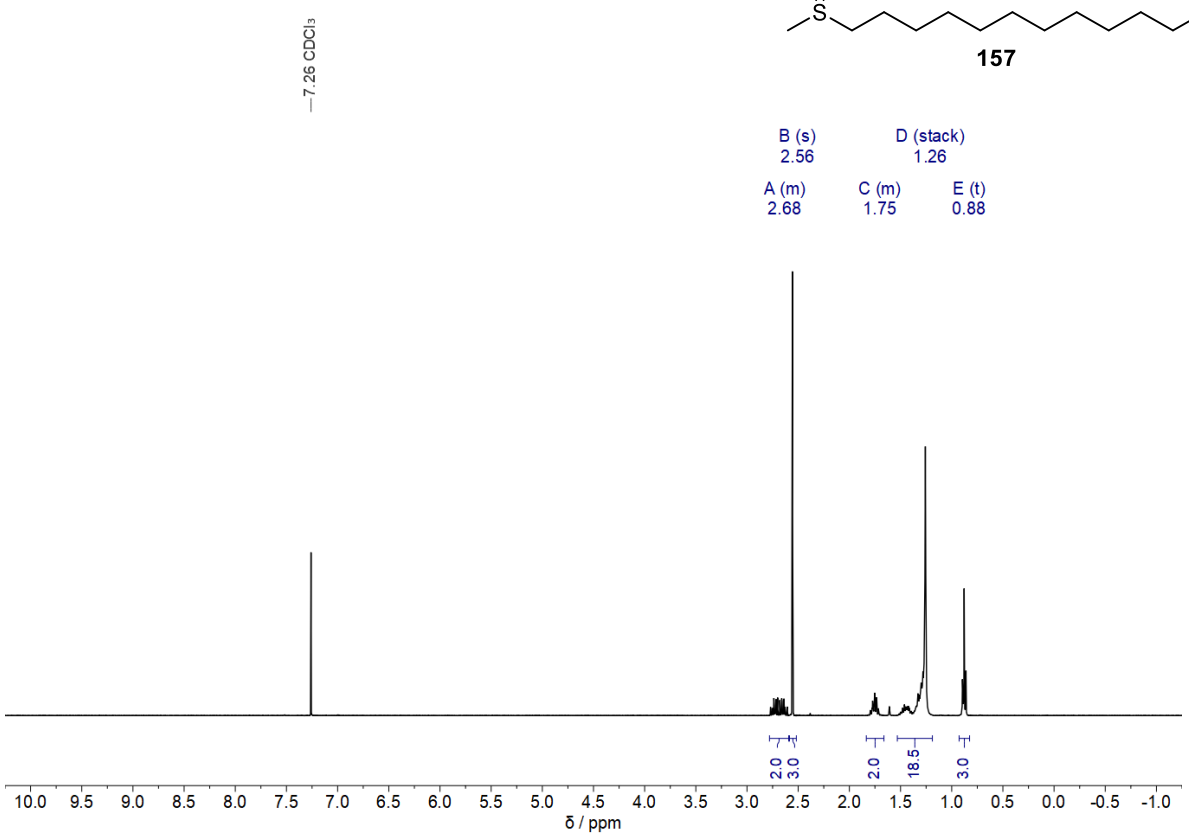
^{13}C-NMR spectrum of **153** in $CDCl_3$ (101 MHz, 298 K)



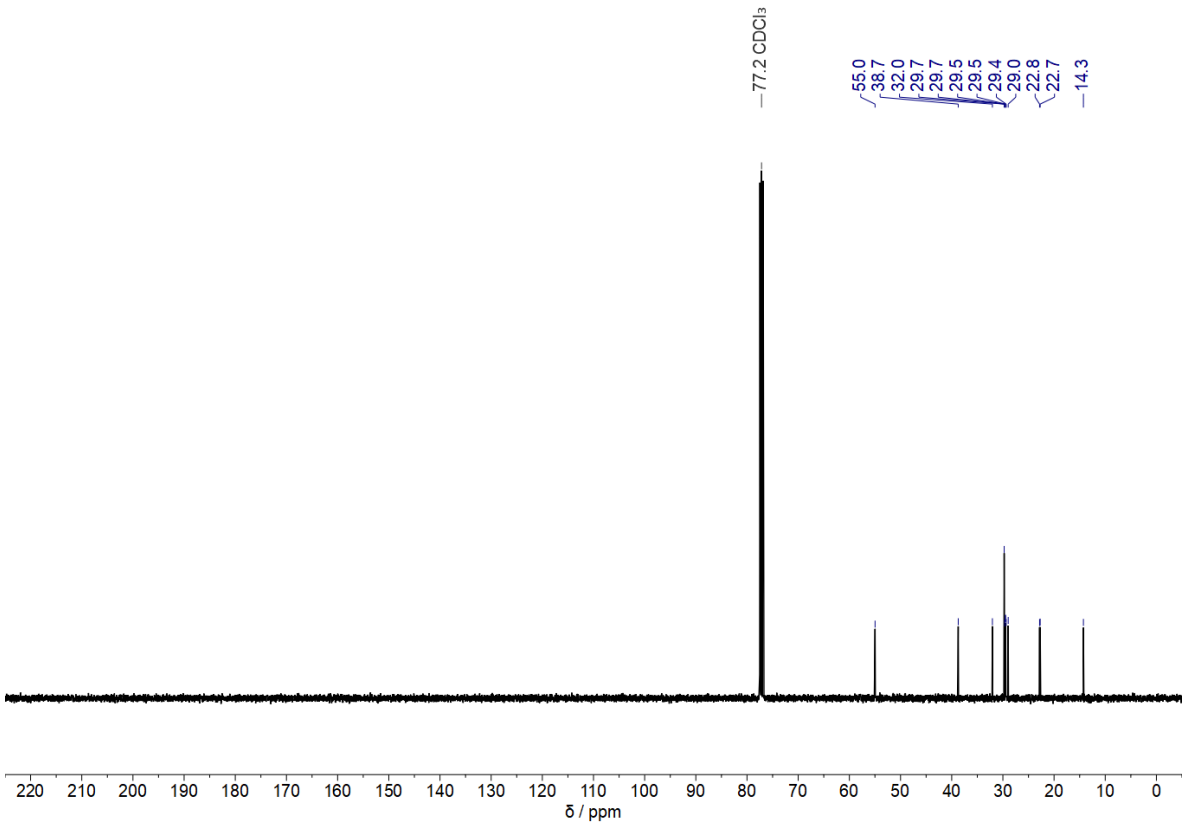
^{1}H-NMR spectrum of **157** in $CDCl_3$ (400 MHz, 298 K)



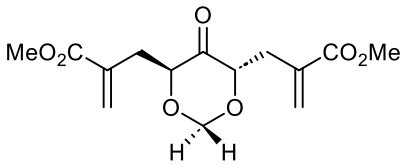
157



^{13}C-NMR spectrum of **157** in $CDCl_3$ (101 MHz, 298 K)

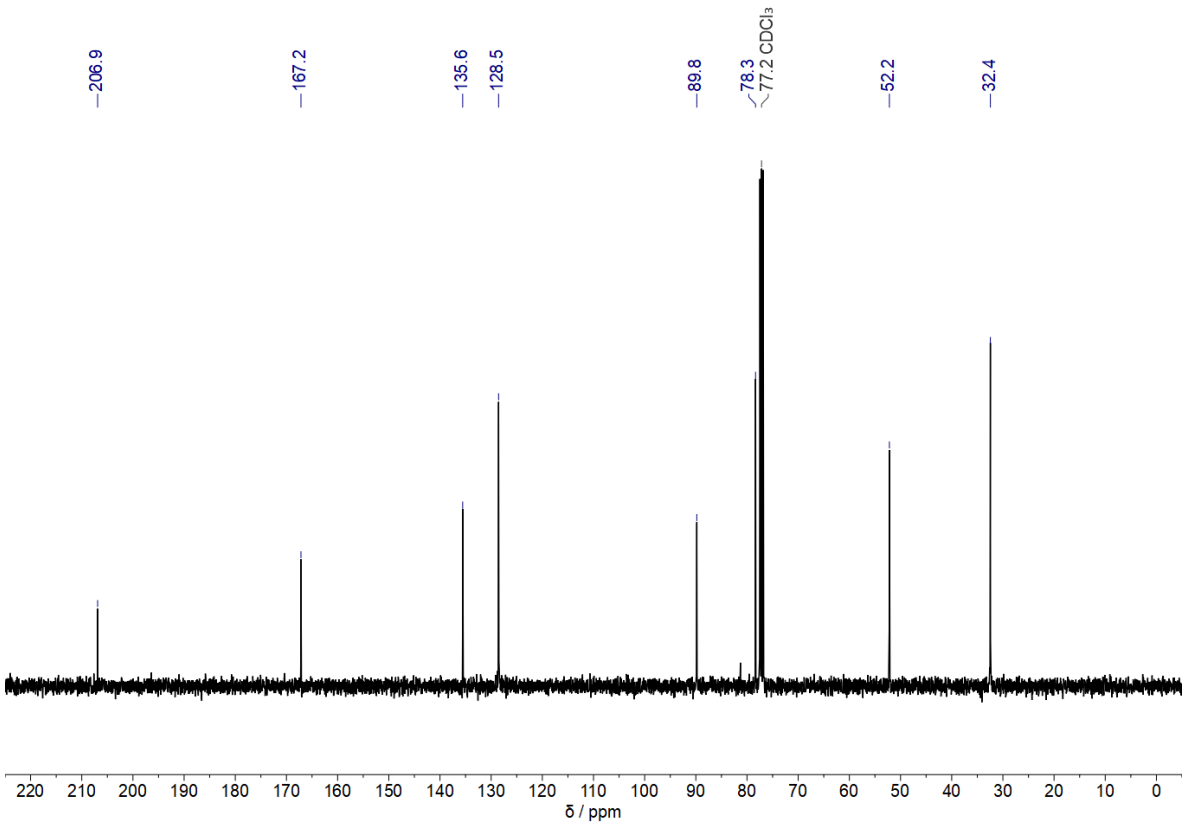


^{1}H-NMR spectrum of **166** in $CDCl_3$ (400 MHz, 295 K)

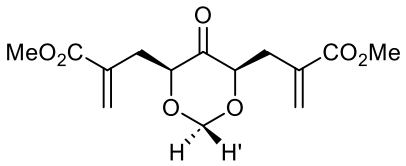


166

^{13}C-NMR spectrum of **166** in $CDCl_3$ (101 MHz, 295 K)

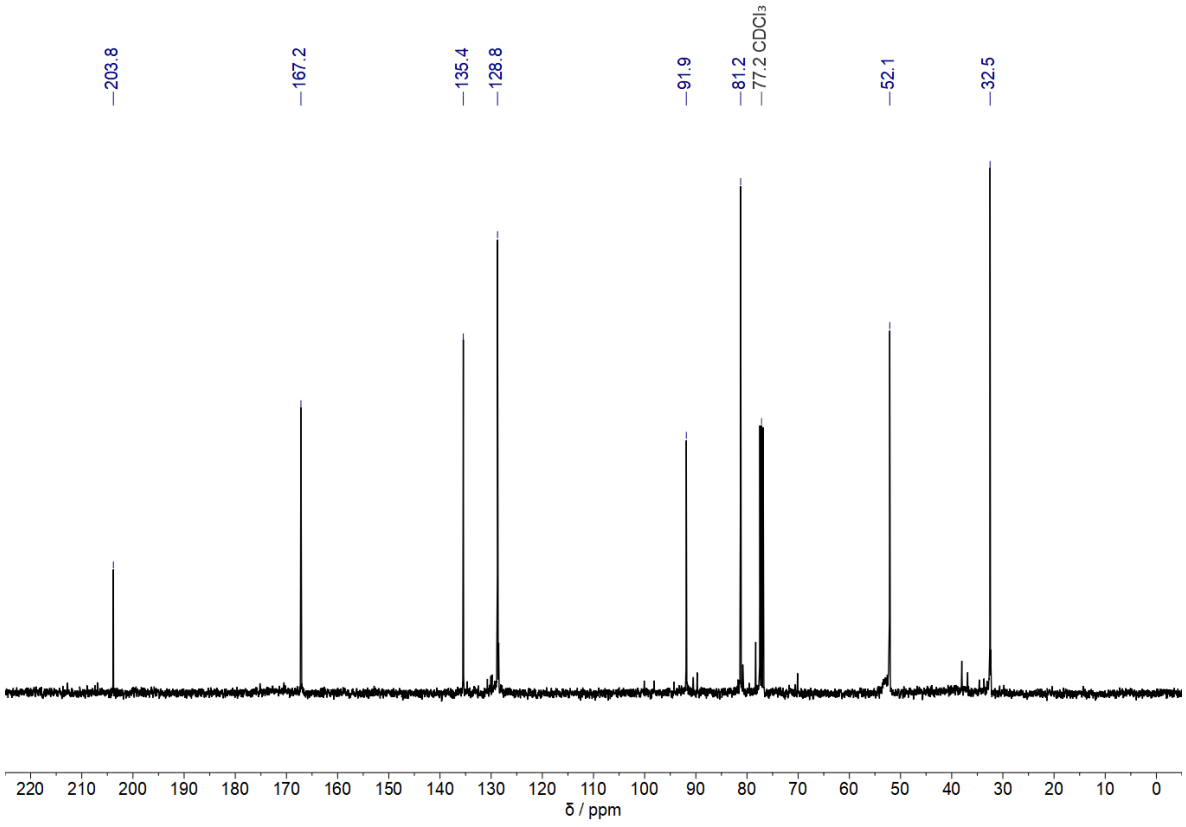


^{1}H-NMR spectrum of **167** in $CDCl_3$ (400 MHz, 295 K)

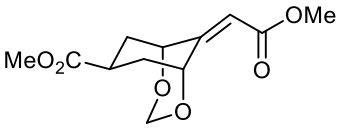


167

^{13}C-NMR spectrum of **167** in $CDCl_3$ (101 MHz, 295 K)

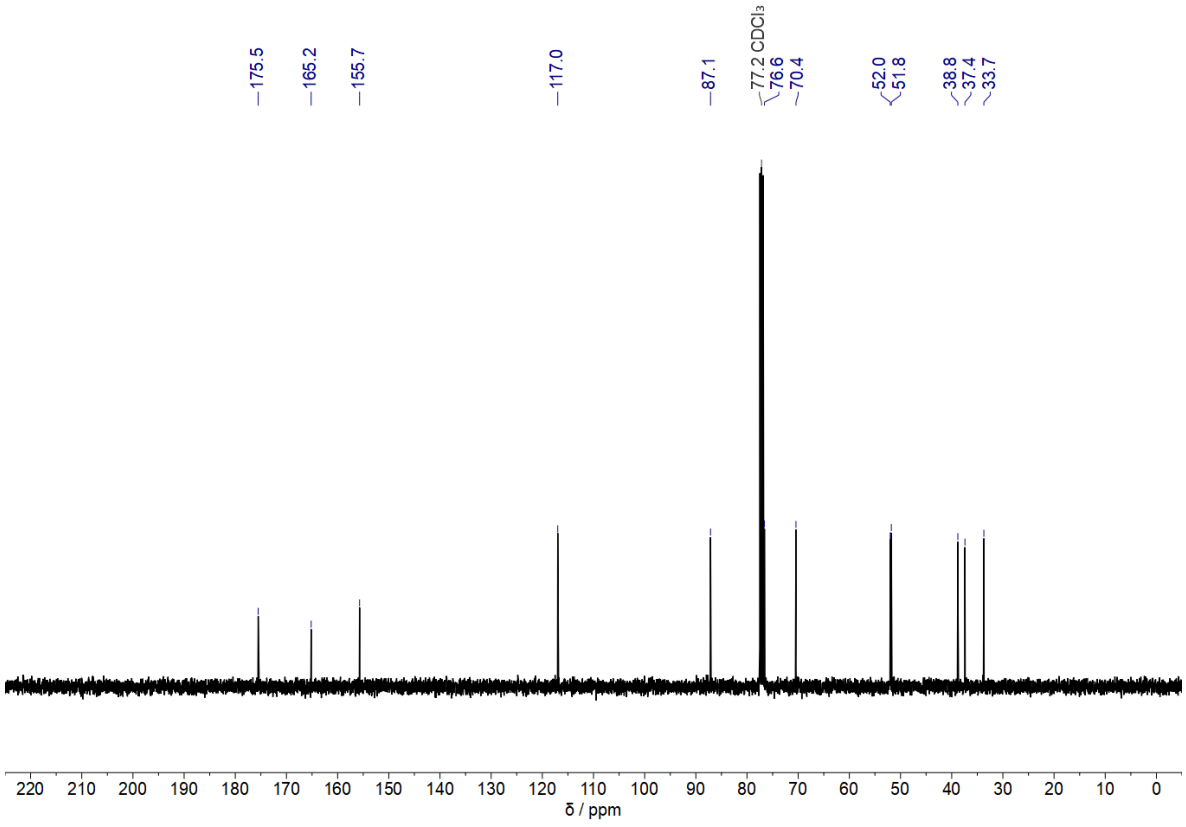


^{1}H-NMR spectrum of **168** in $CDCl_3$ (400 MHz, 298 K)

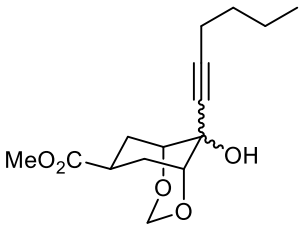


168

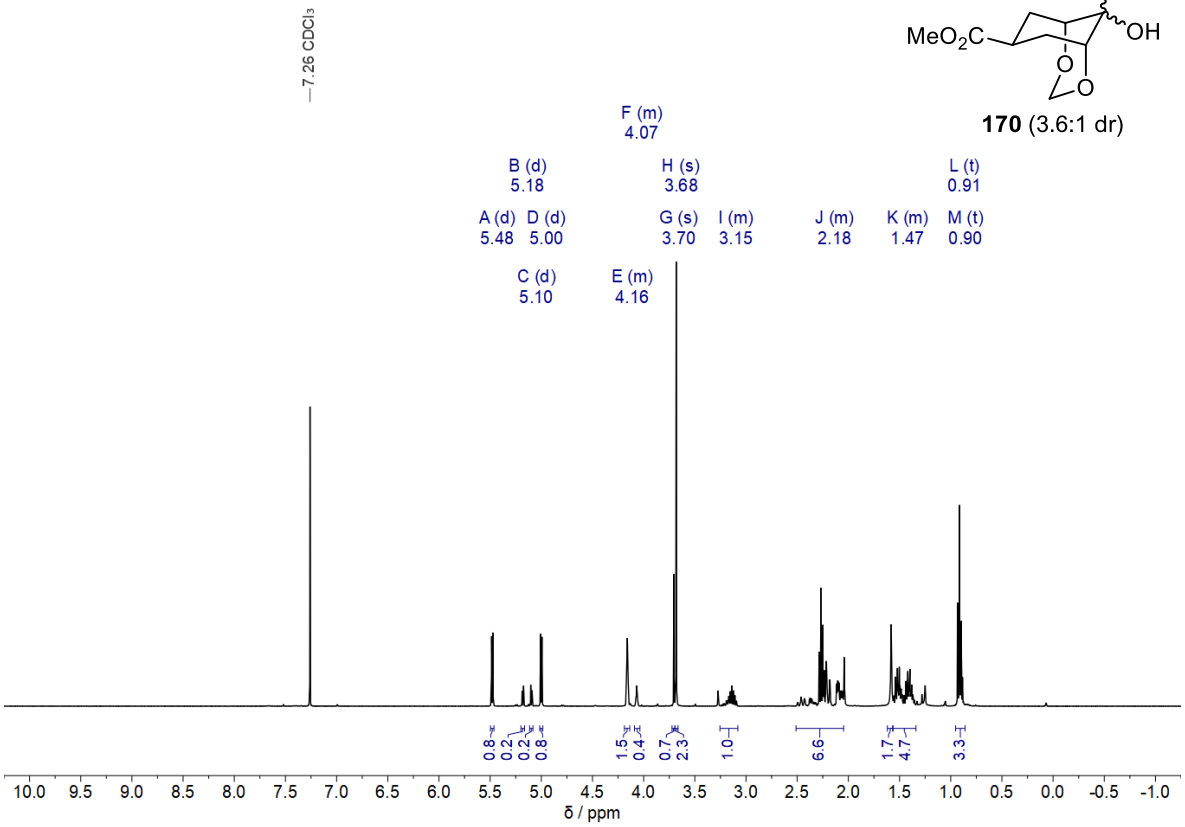
^{13}C-NMR spectrum of **168** in $CDCl_3$ (101 MHz, 298 K)



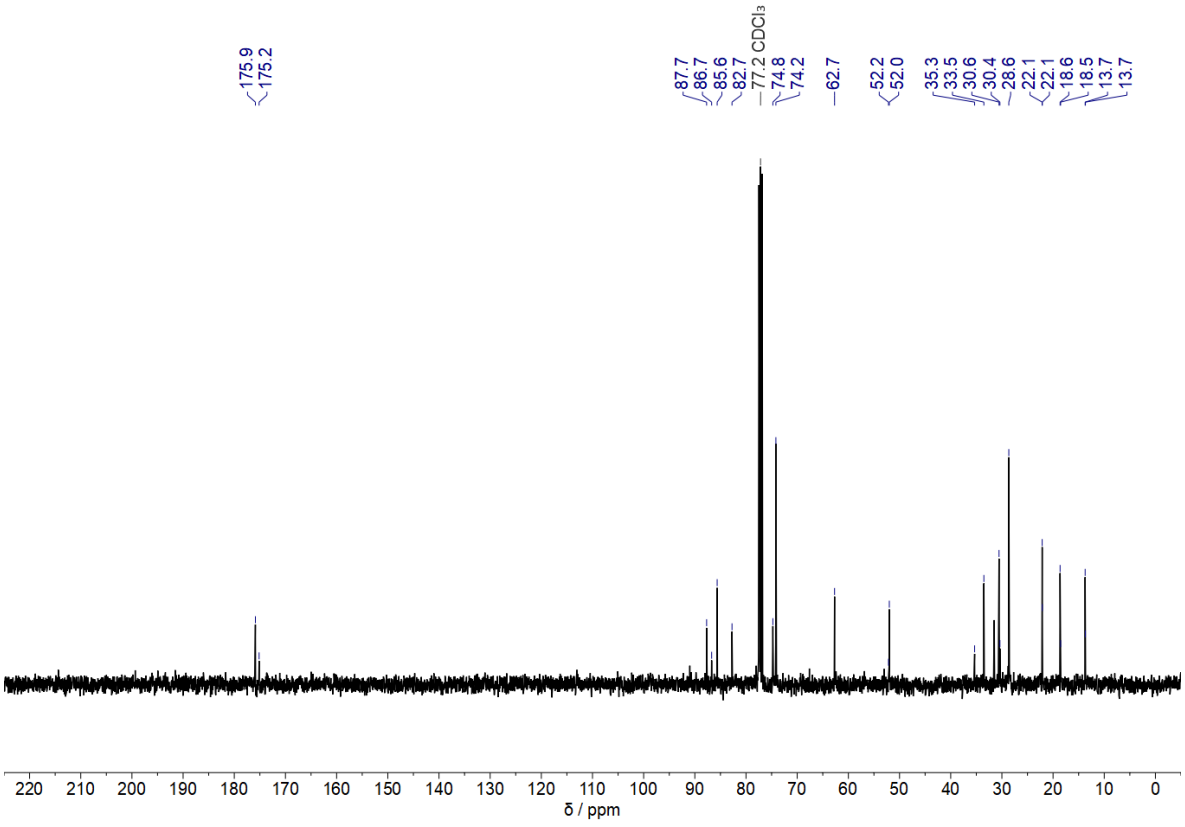
^{1}H-NMR spectrum of **170** in $CDCl_3$ (400 MHz, 295 K)



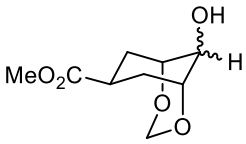
170 (3.6:1 dr)



^{13}C-NMR spectrum of **170** in $CDCl_3$ (101 MHz, 295 K)

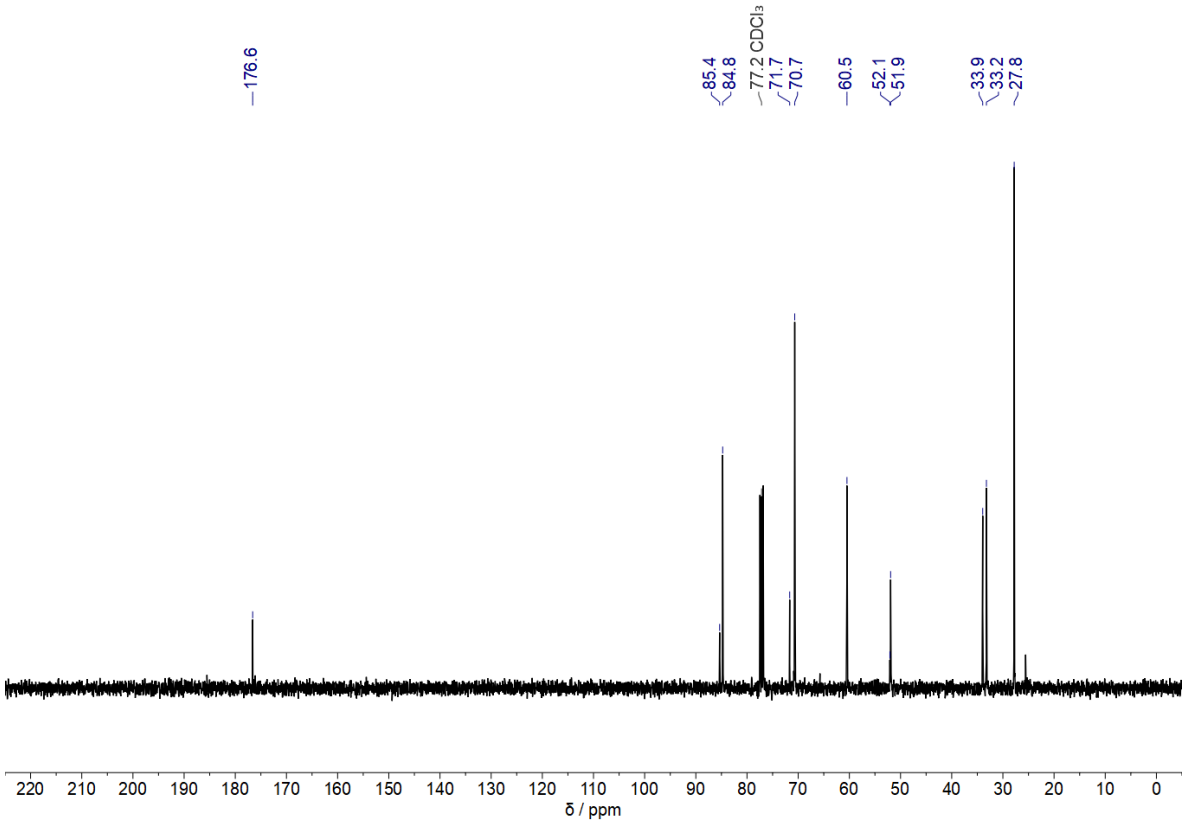


^{1}H-NMR spectrum of **171** in $CDCl_3$ (400 MHz, 296 K)

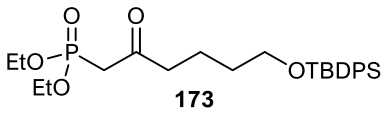


171 (3.4:1 dr)

^{13}C-NMR spectrum of **171** in $CDCl_3$ (101 MHz, 296 K)

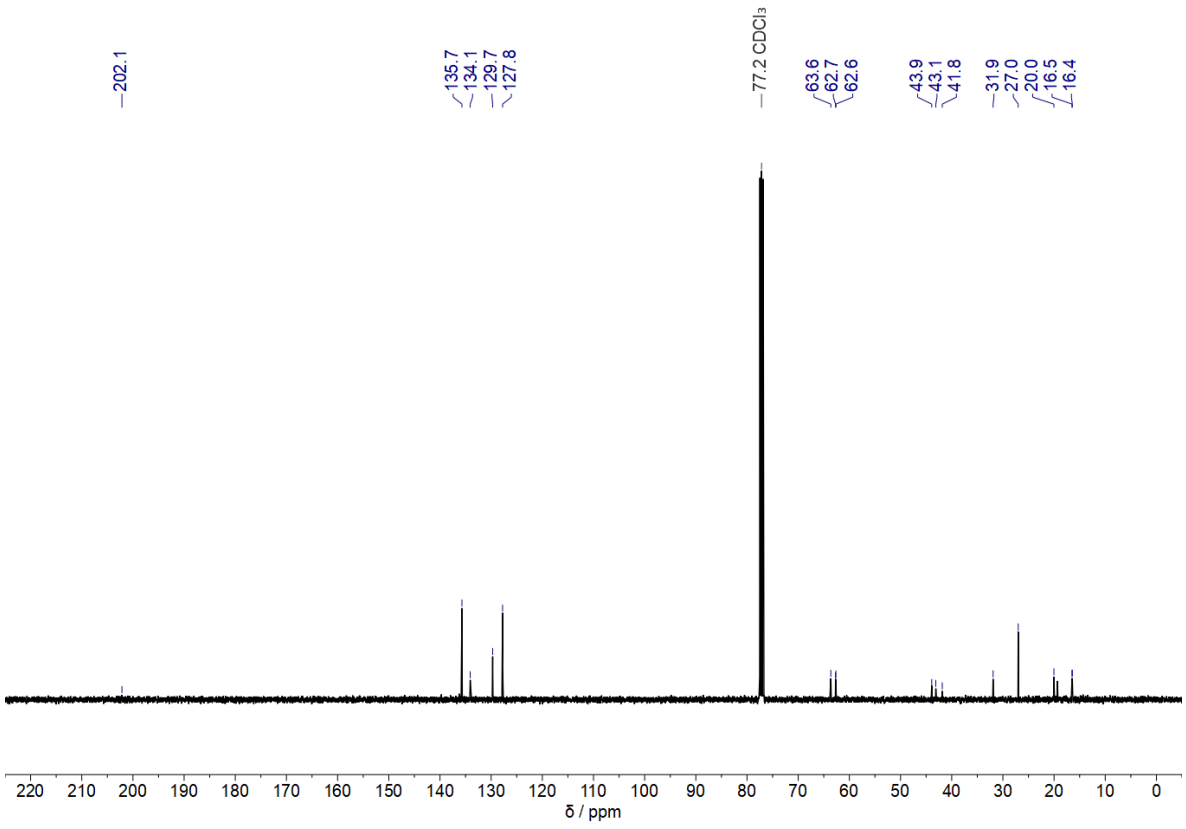


^{1}H-NMR spectrum of **173** in $CDCl_3$ (400 MHz, 298 K)

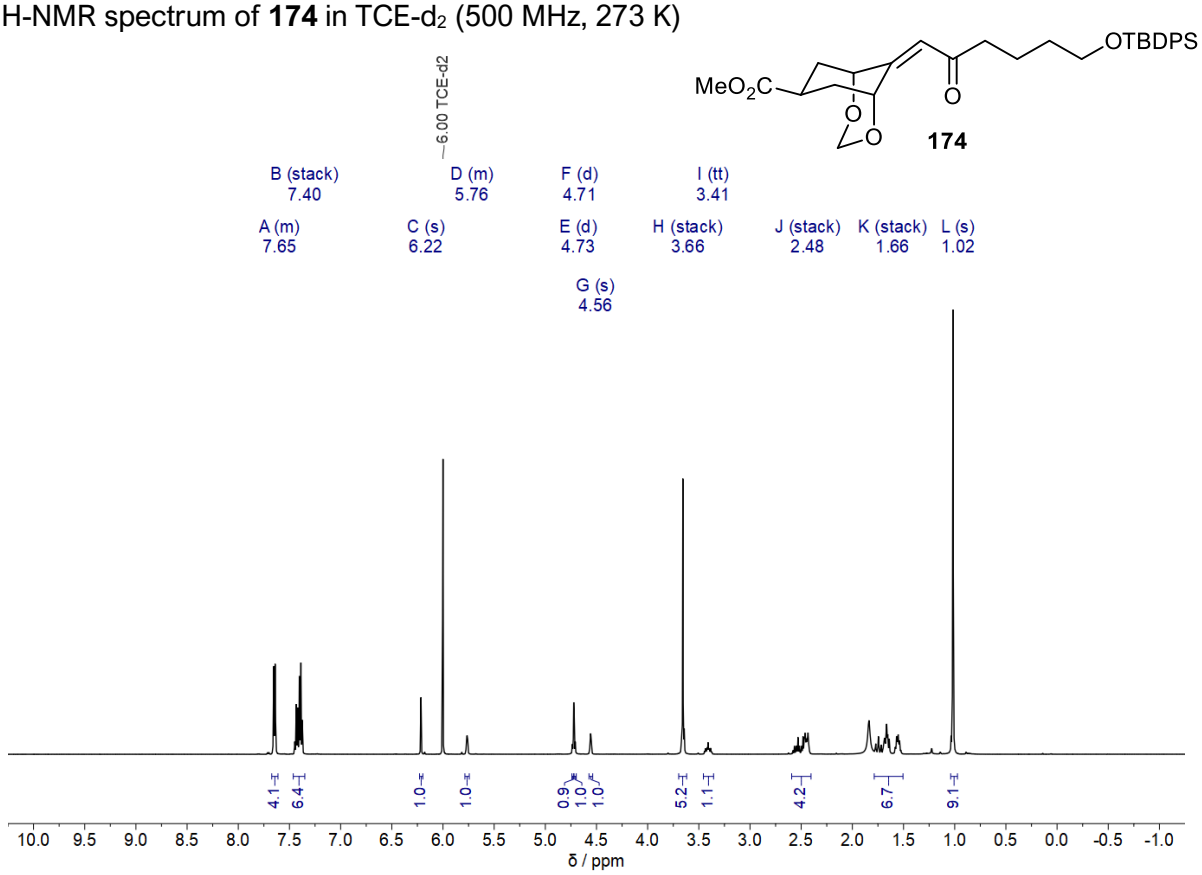


173

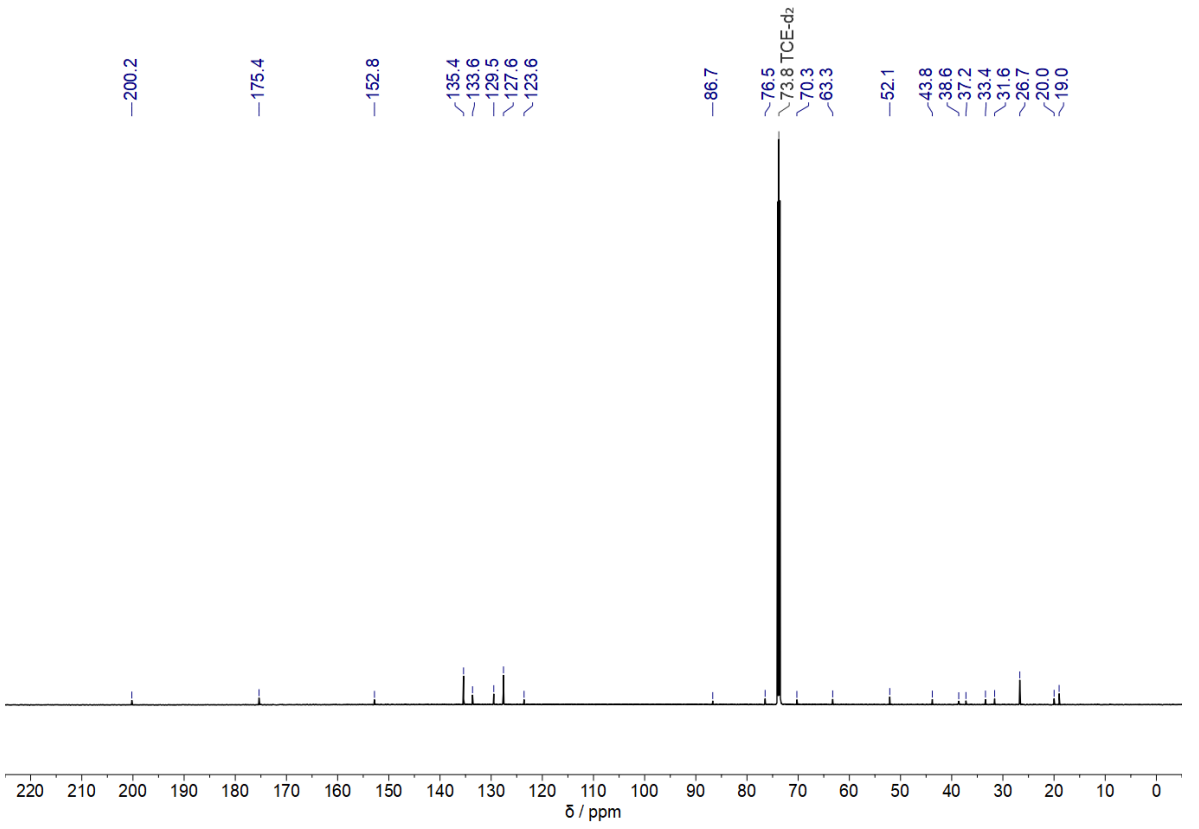
^{13}C-NMR spectrum of **173** in $CDCl_3$ (101 MHz, 298 K)



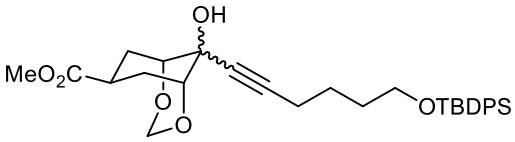
^{1}H-NMR spectrum of **174** in TCE-d_2 (500 MHz, 273 K)



^{13}C-NMR spectrum of **174** in TCE-d_2 (126 MHz, 273 K)

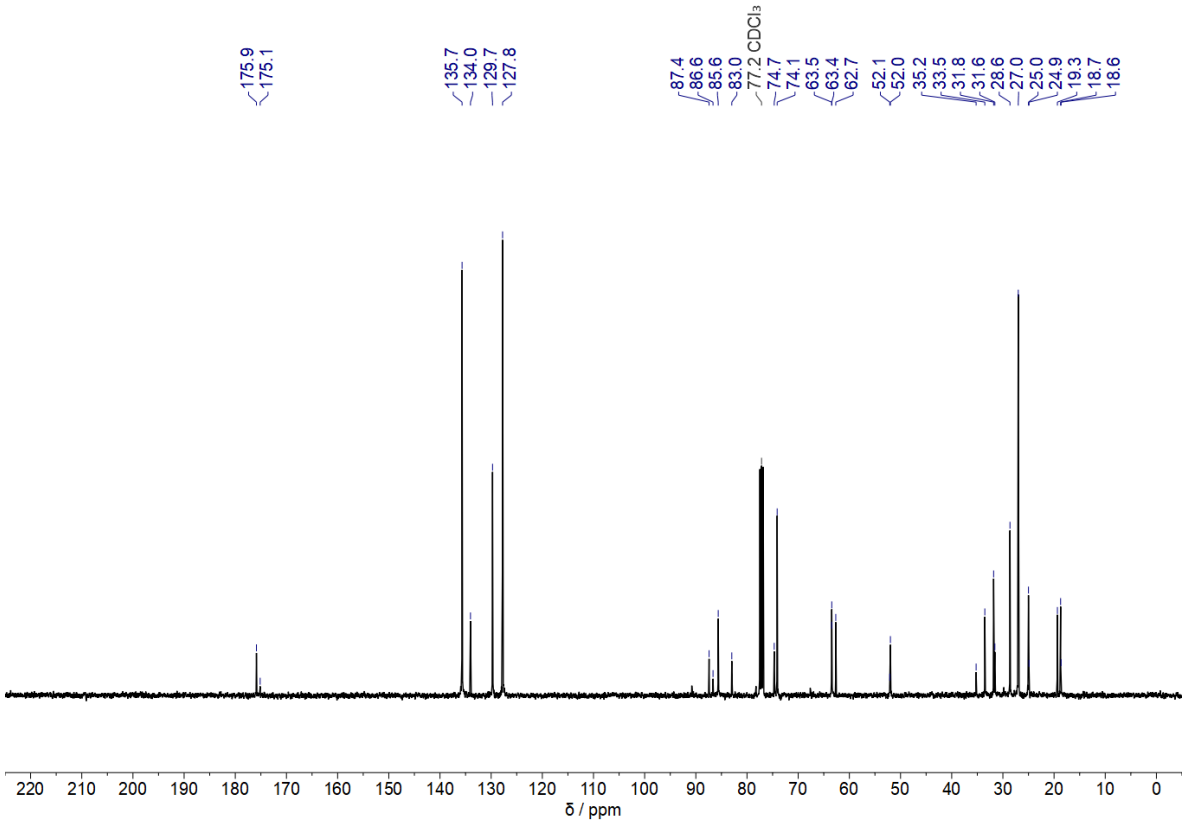


^{1}H-NMR spectrum of **176** in $CDCl_3$ (400 MHz, 295 K)

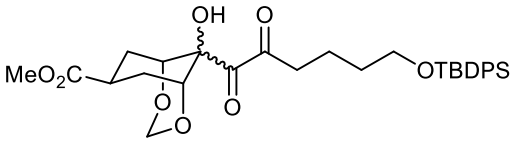


176 (4.3:1 dr)

^{13}C-NMR spectrum of **176** in $CDCl_3$ (101 MHz, 296 K)

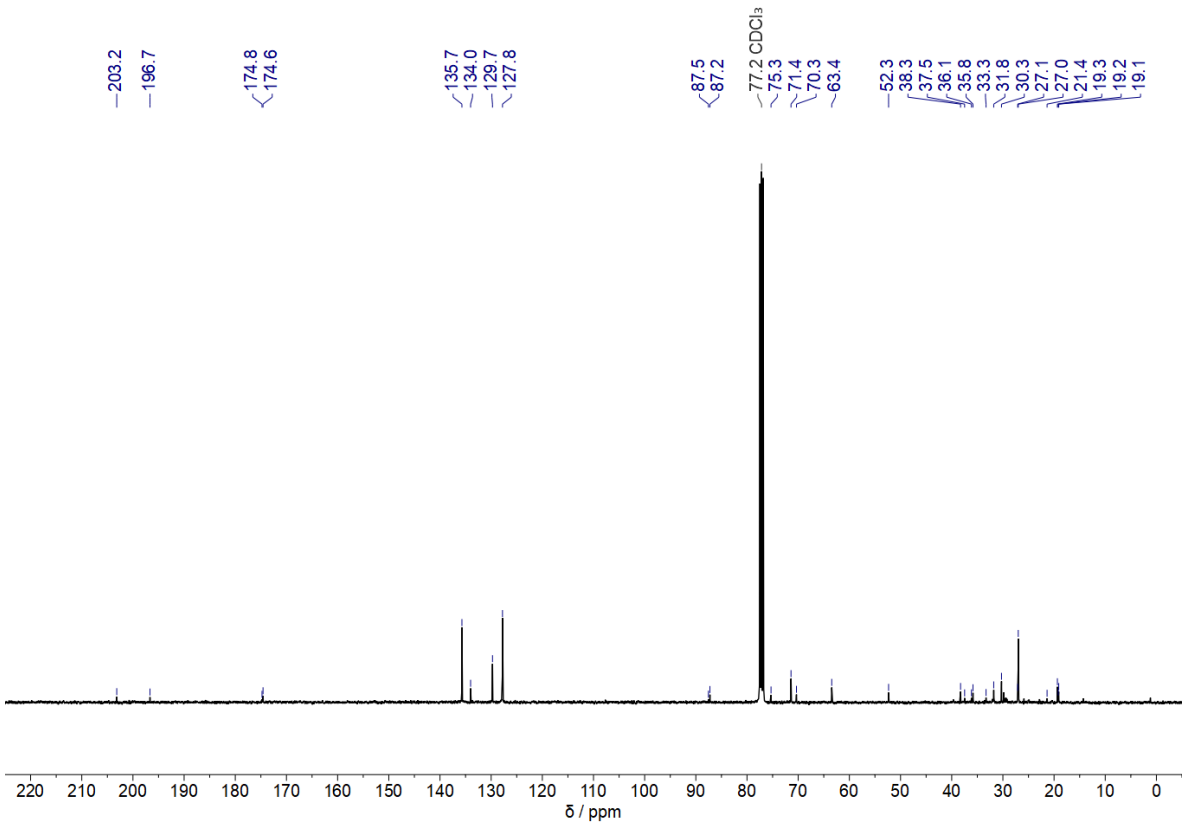


^{1}H-NMR spectrum of **177** in $CDCl_3$ (300 MHz, 300 K)

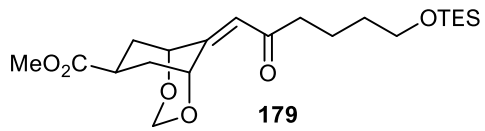


177 (2.5:1 dr)

^{13}C-NMR spectrum of **177** in $CDCl_3$ (101 MHz, 295 K)

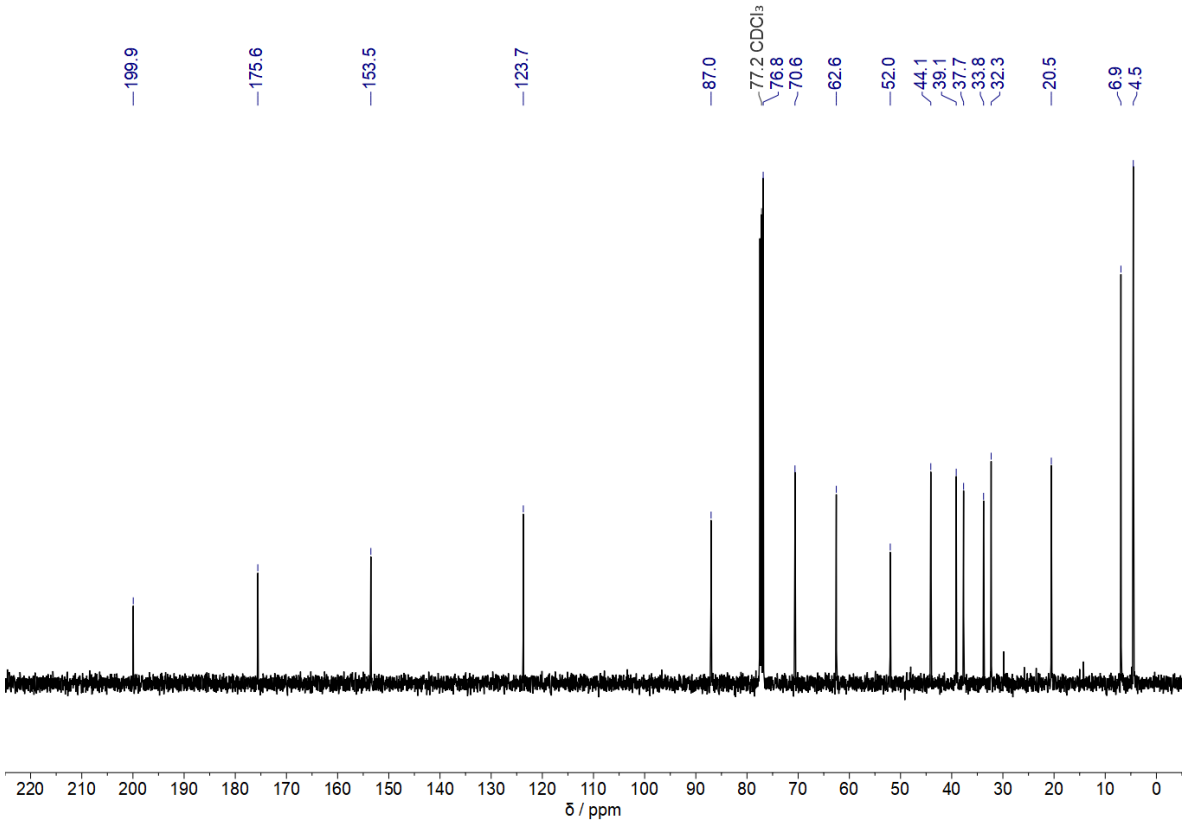


^{1}H-NMR spectrum of **179** in $CDCl_3$ (400 MHz, 295 K)

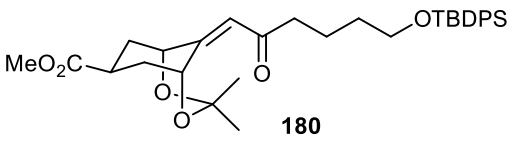


179

^{13}C-NMR spectrum of **179** in $CDCl_3$ (101 MHz, 295 K)

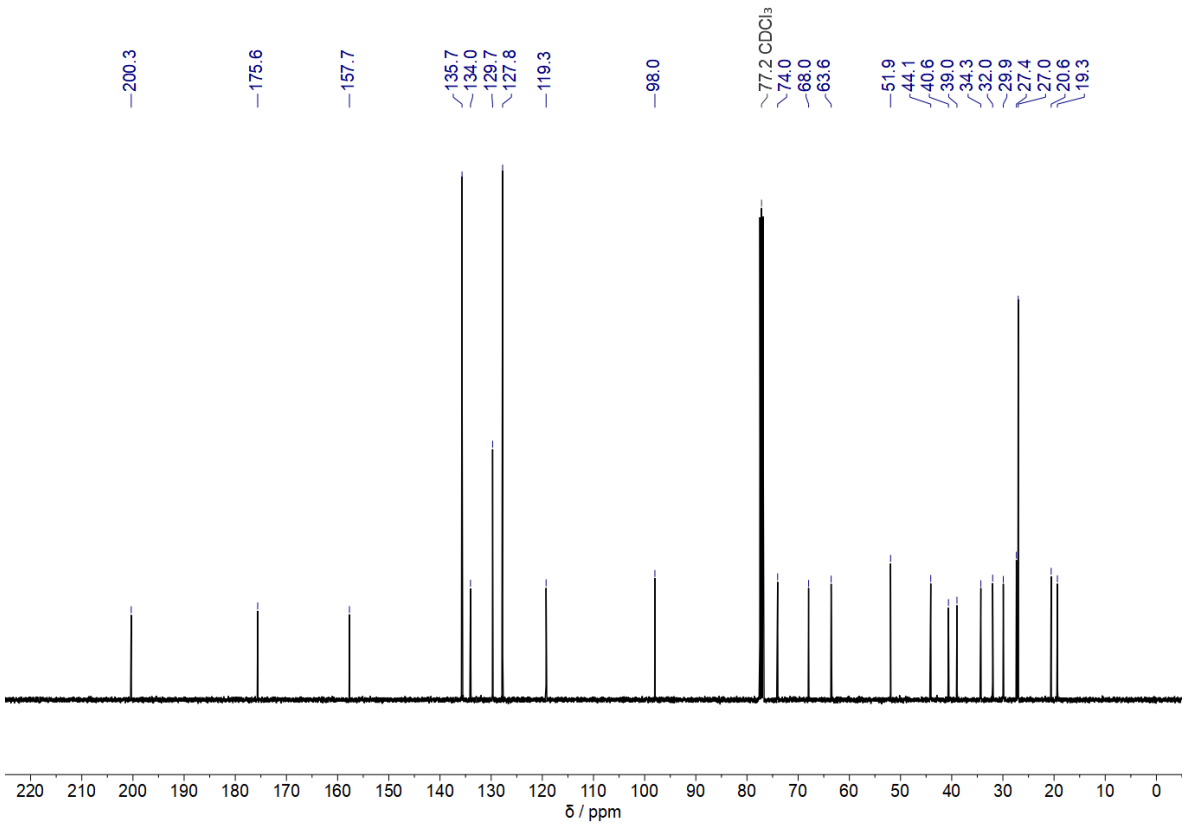


^{1}H-NMR spectrum of **180** in $CDCl_3$ (400 MHz, 298 K)

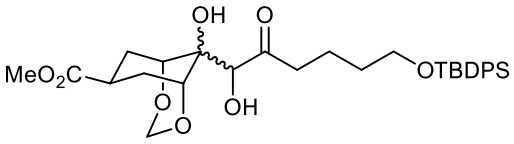


180

^{13}C-NMR spectrum of **180** in $CDCl_3$ (101 MHz, 298 K)

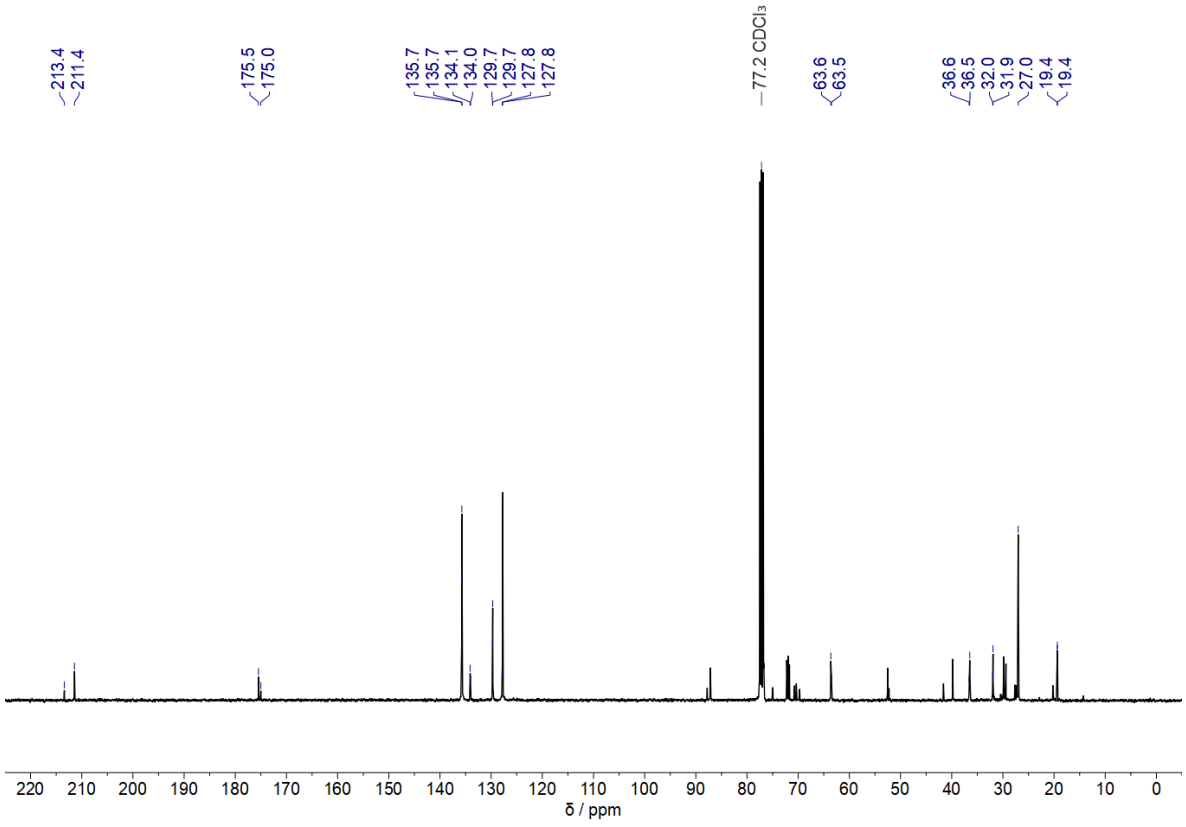


^{1}H-NMR spectrum of **181** in $CDCl_3$ (300 MHz, 300 K)

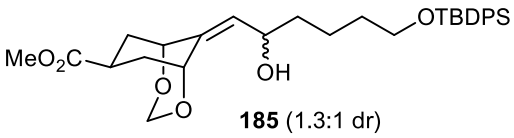


181 (2.5:1 dr)

^{13}C-NMR spectrum of **181** in $CDCl_3$ (101 MHz, 296 K)

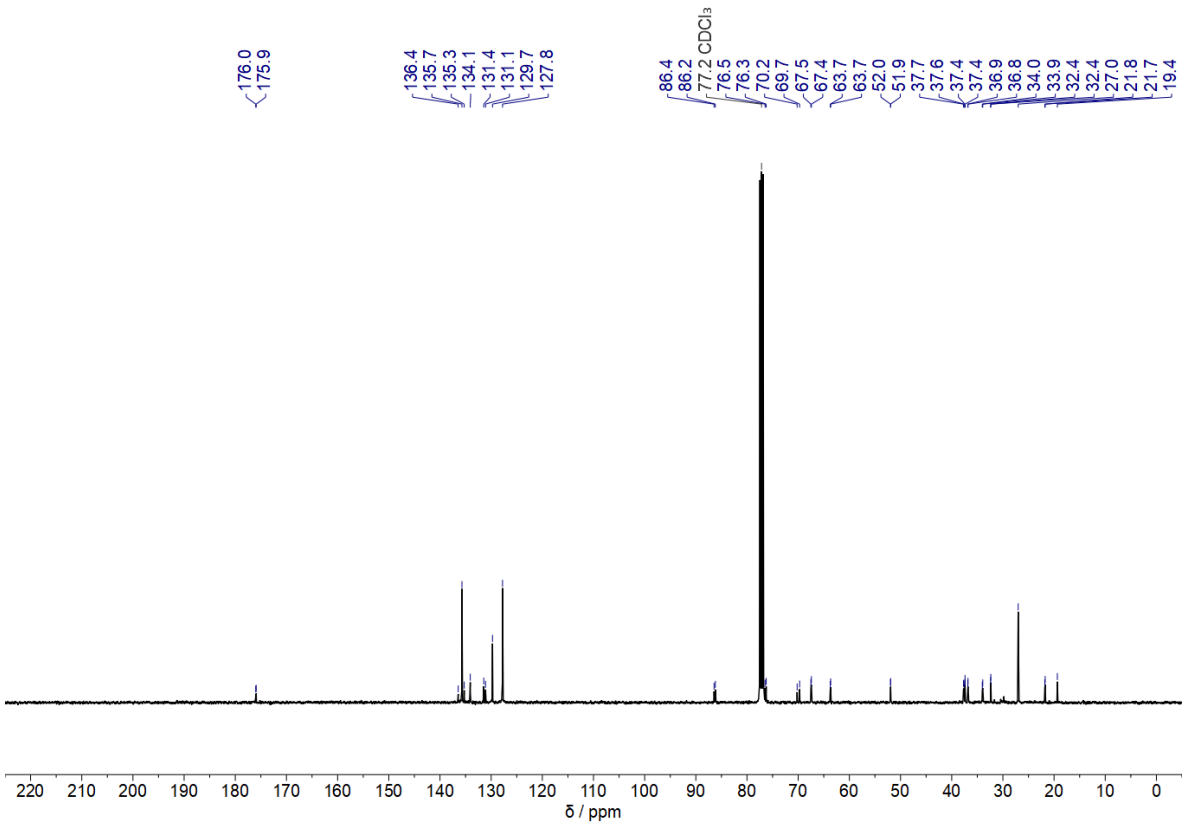


^{1}H-NMR spectrum of **185** in $CDCl_3$ (400 MHz, 298 K)

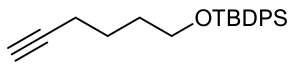


185 (1.3:1 dr)

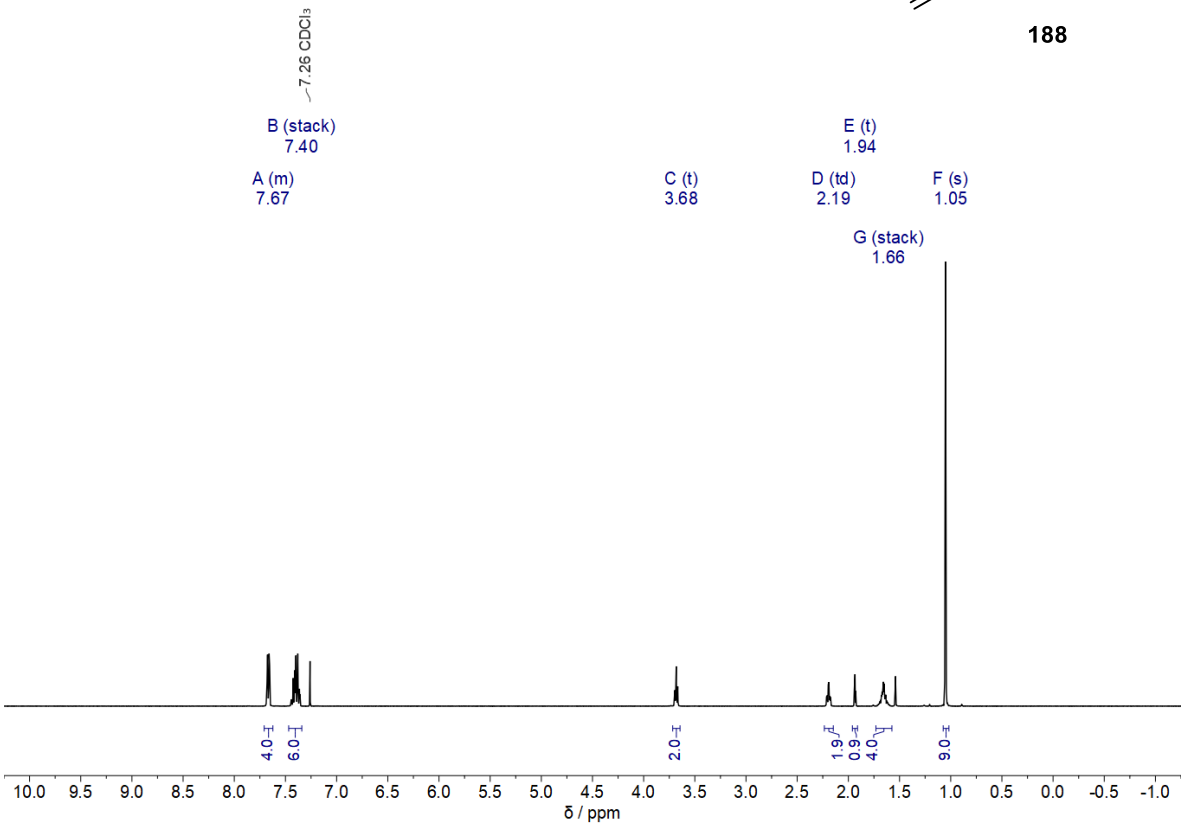
^{13}C-NMR spectrum of **185** in $CDCl_3$ (101 MHz, 296 K)



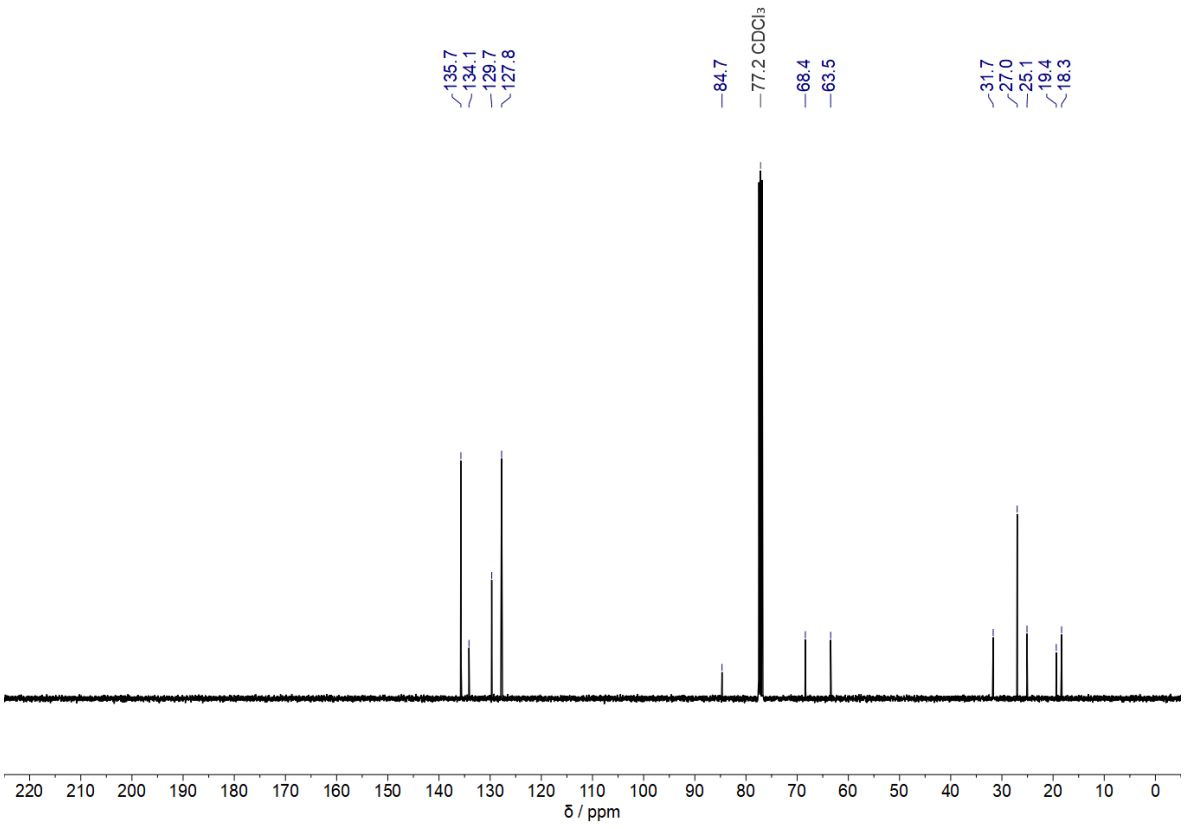
^{1}H-NMR spectrum of **188** in $CDCl_3$ (400 MHz, 298 K)

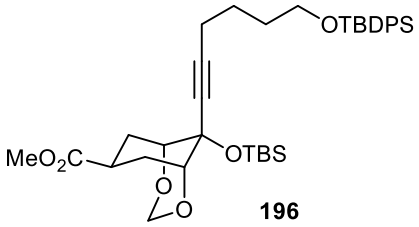


188

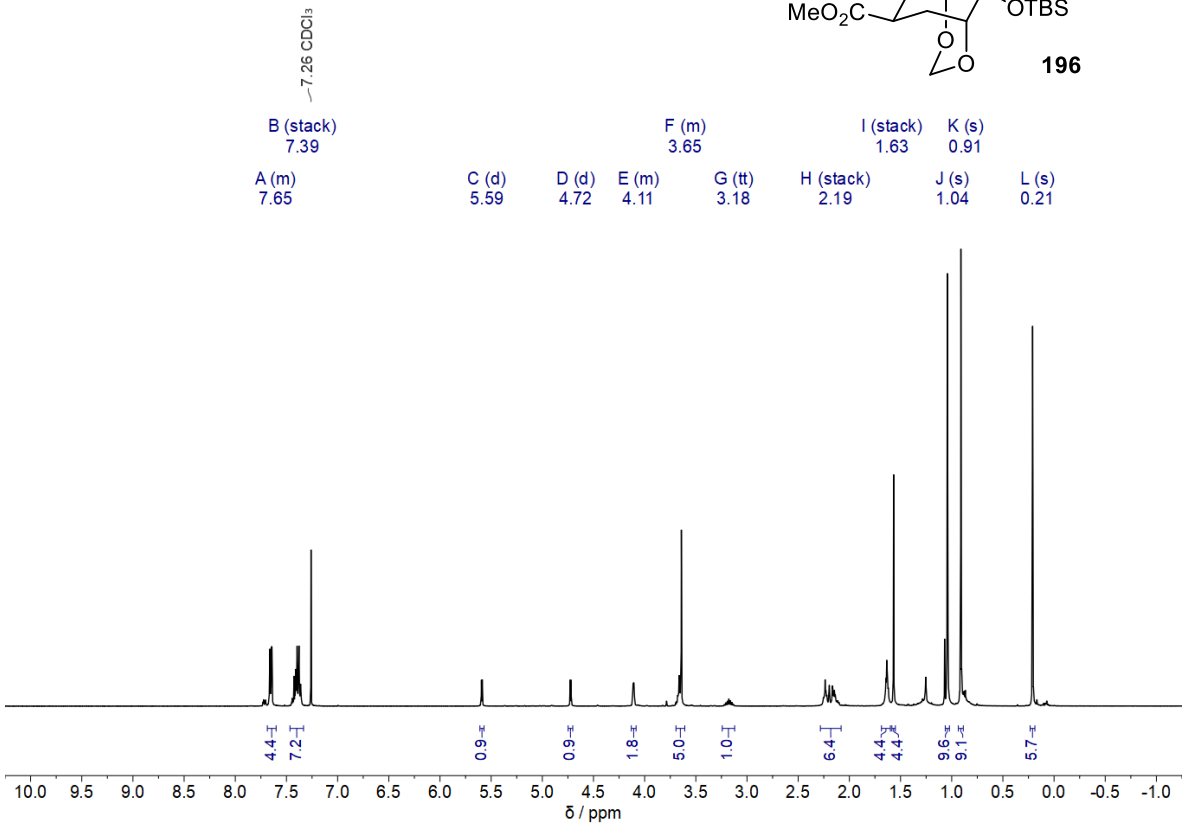


^{13}C-NMR spectrum of **188** in $CDCl_3$ (101 MHz, 298 K)

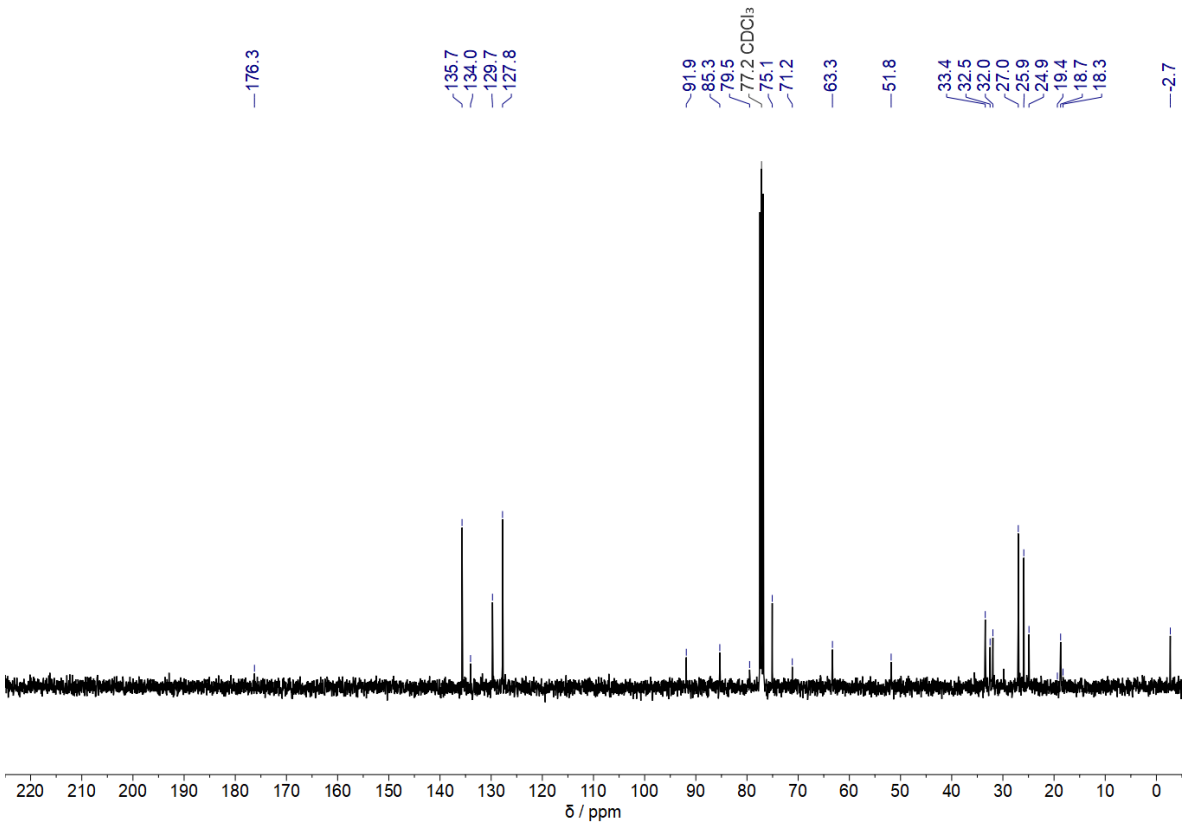




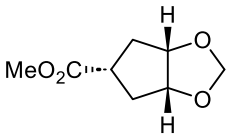
^{1}H-NMR spectrum of **196** in $CDCl_3$ (400 MHz, 295 K)



^{13}C-NMR spectrum of **196** in $CDCl_3$ (101 MHz, 295 K)

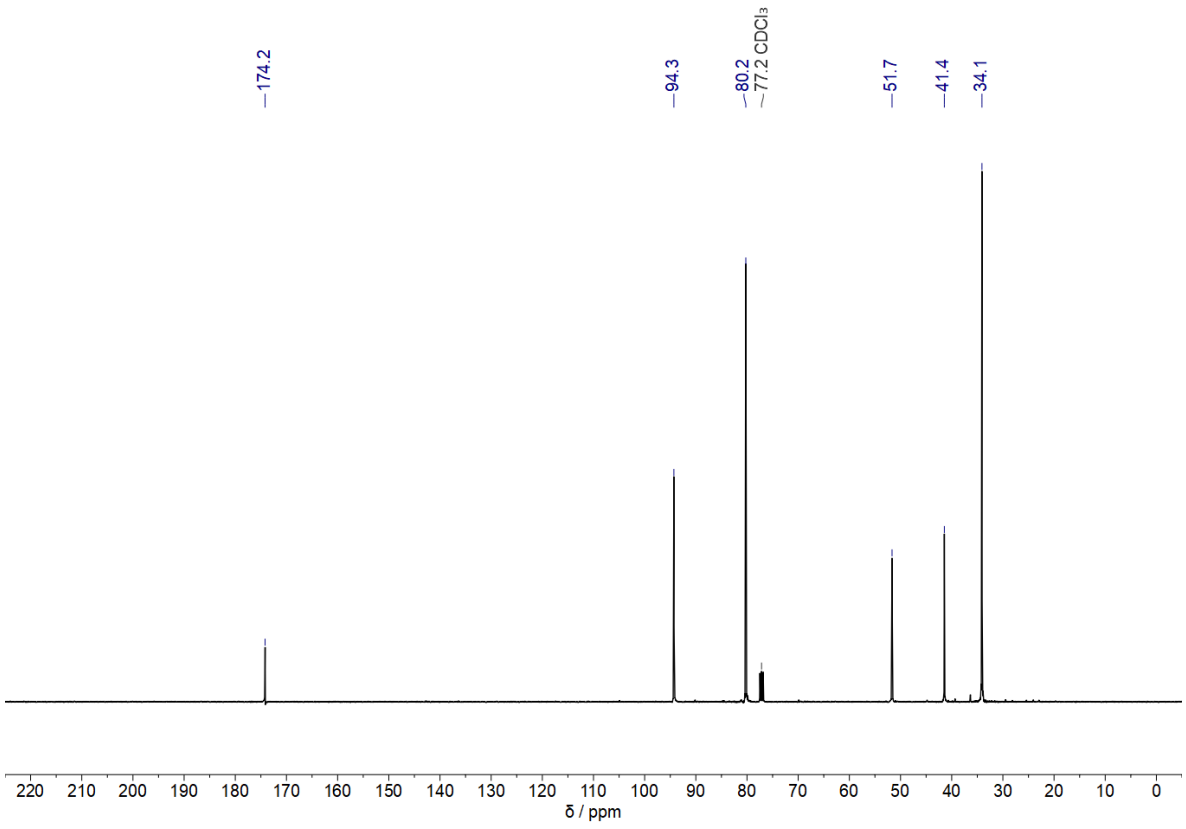


^{1}H-NMR spectrum of **202** in $CDCl_3$ (400 MHz, 295 K)

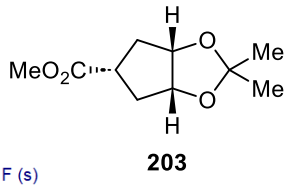


202

^{13}C-NMR spectrum of **202** in $CDCl_3$ (101 MHz, 295 K)

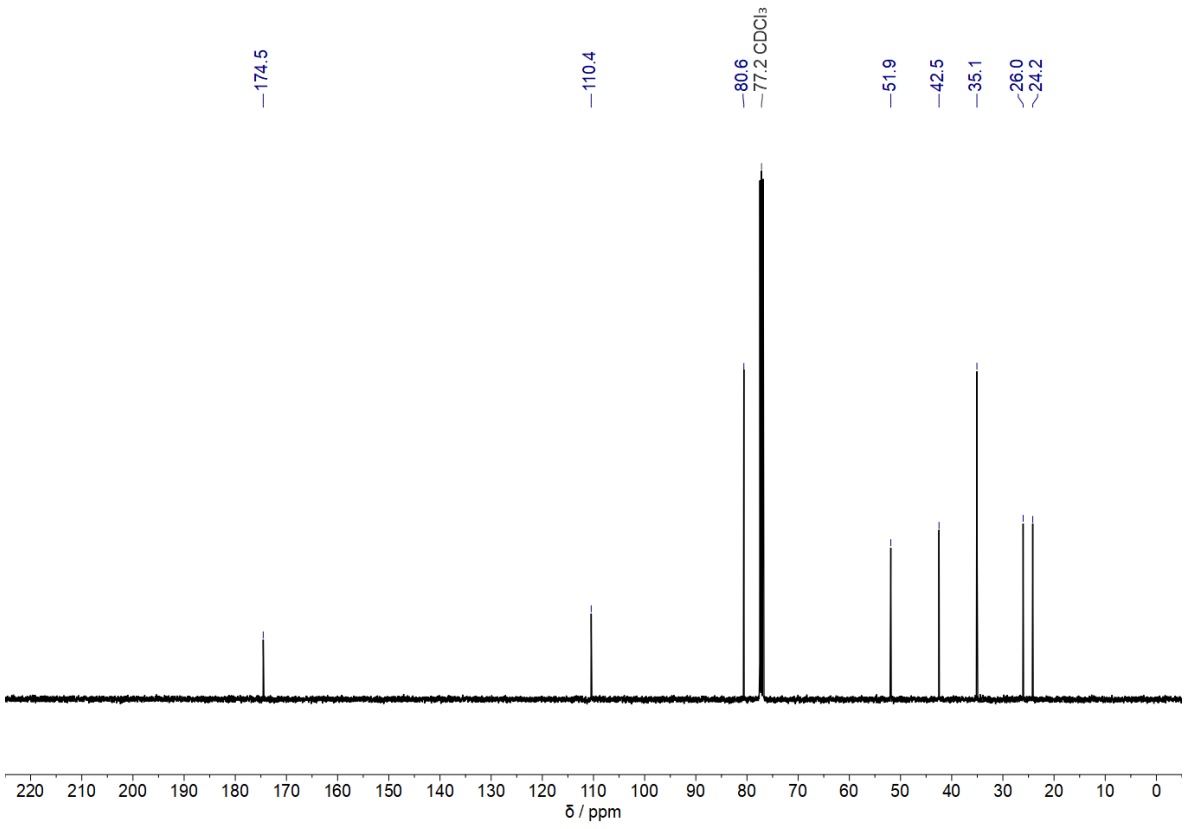


^{1}H-NMR spectrum of **203** in $CDCl_3$ (400 MHz, 298 K)

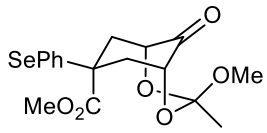


203

^{13}C-NMR spectrum of **203** in $CDCl_3$ (101 MHz, 298 K)

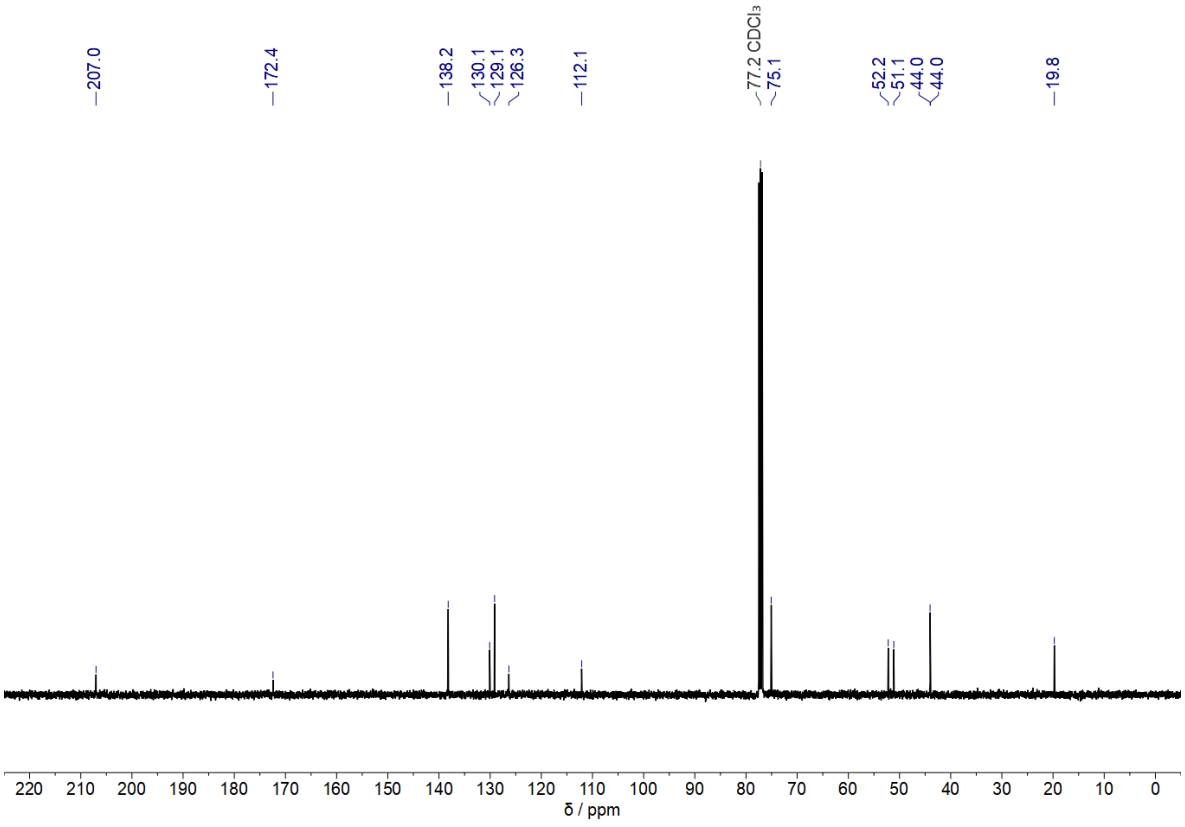


^{1}H-NMR spectrum of **214** in $CDCl_3$ (400 MHz, 298 K)

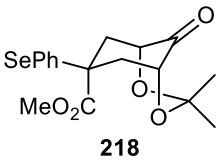


214

^{13}C-NMR spectrum of **214** in $CDCl_3$ (101 MHz, 298 K)

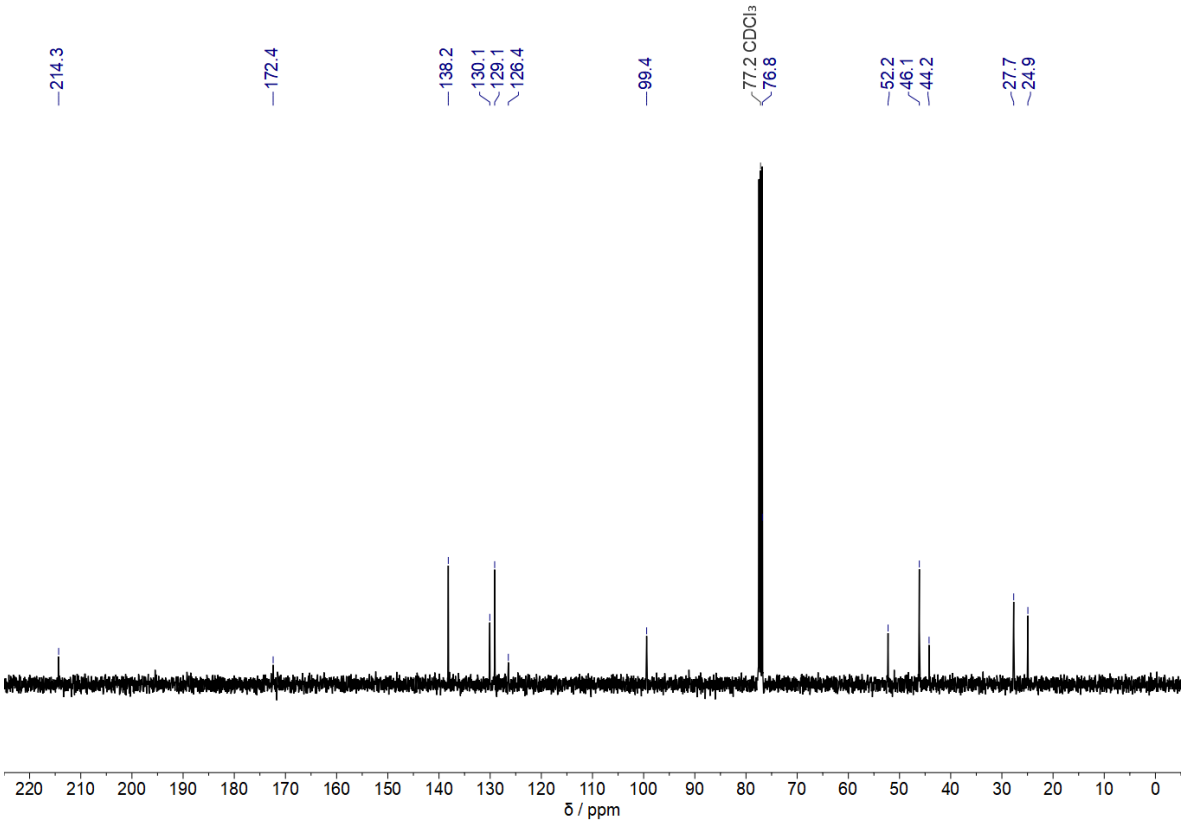


^{1}H-NMR spectrum of **218** in $CDCl_3$ (400 MHz, 294 K)

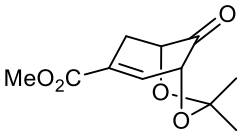


218

^{13}C-NMR spectrum of **218** in $CDCl_3$ (101 MHz, 295 K)

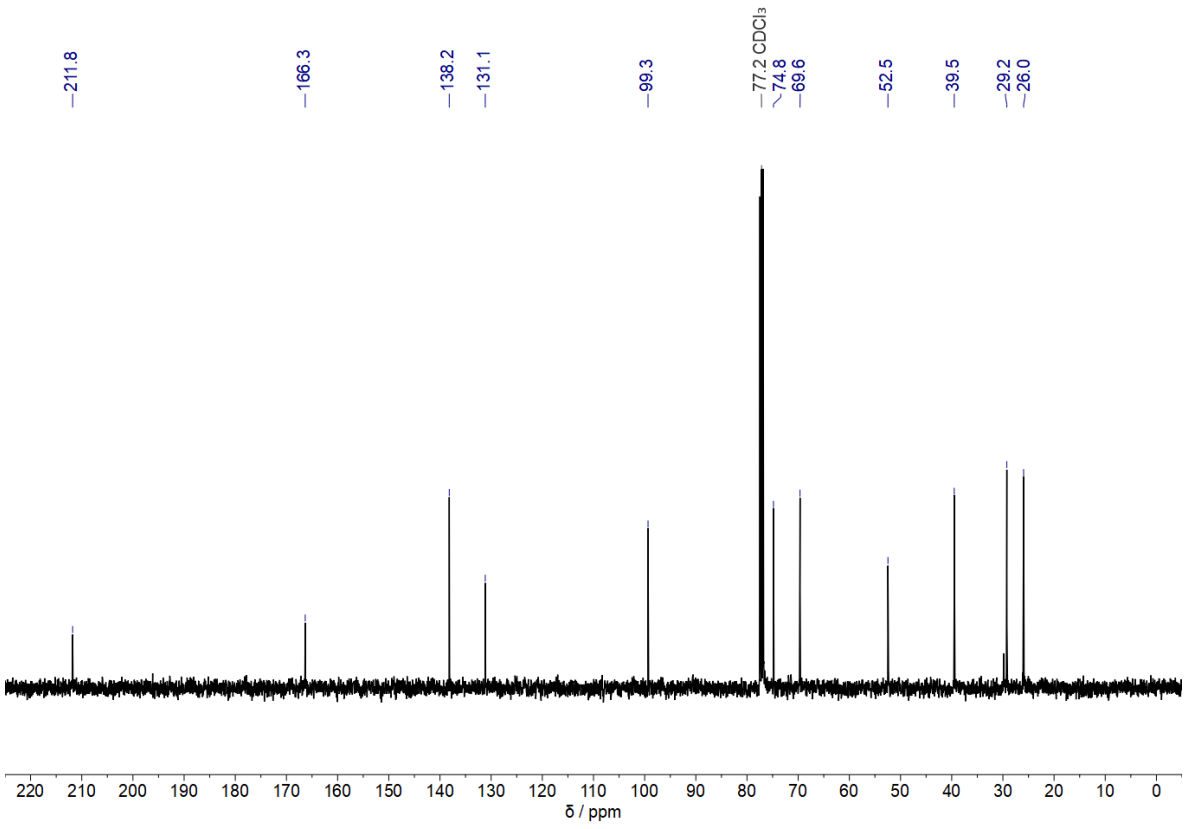


^{1}H-NMR spectrum of **219** in $CDCl_3$ (400 MHz, 295 K)

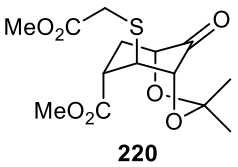


219

^{13}C-NMR spectrum of **219** in $CDCl_3$ (101 MHz, 295 K)

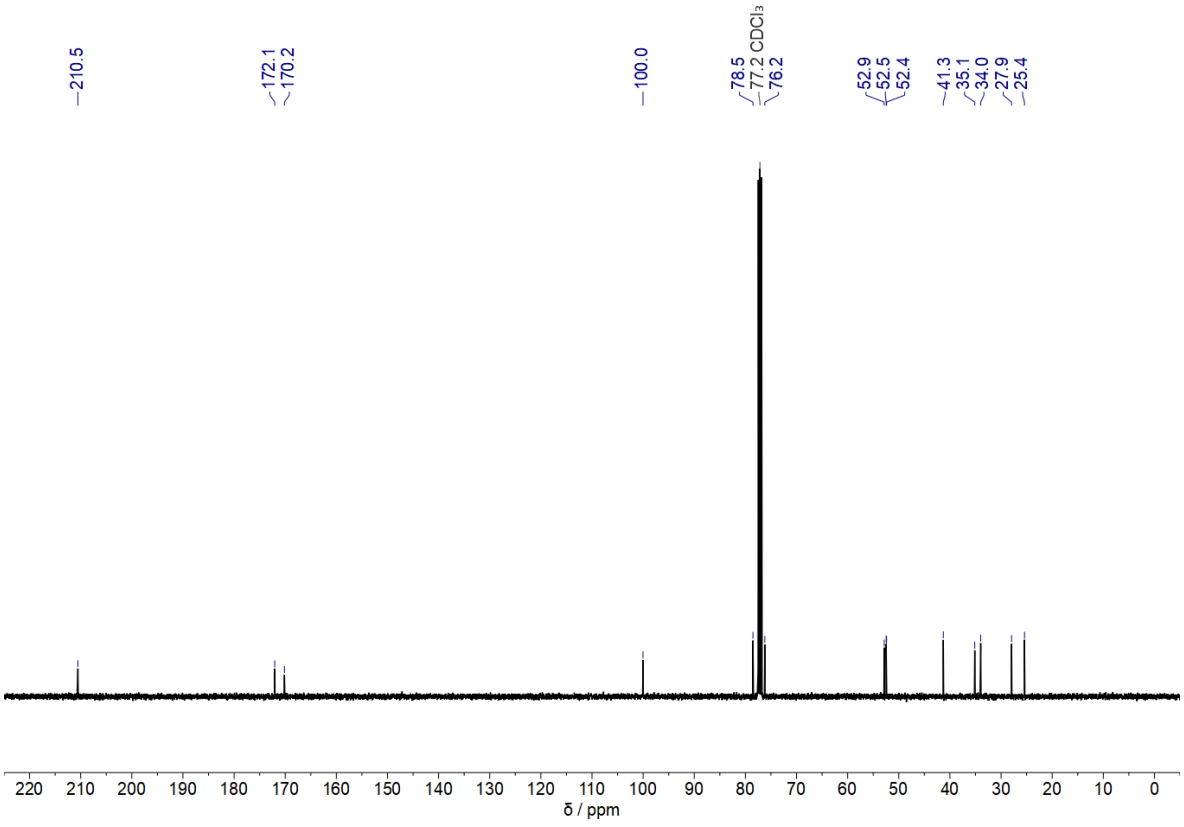


^{1}H-NMR spectrum of **220** in $CDCl_3$ (400 MHz, 294 K)



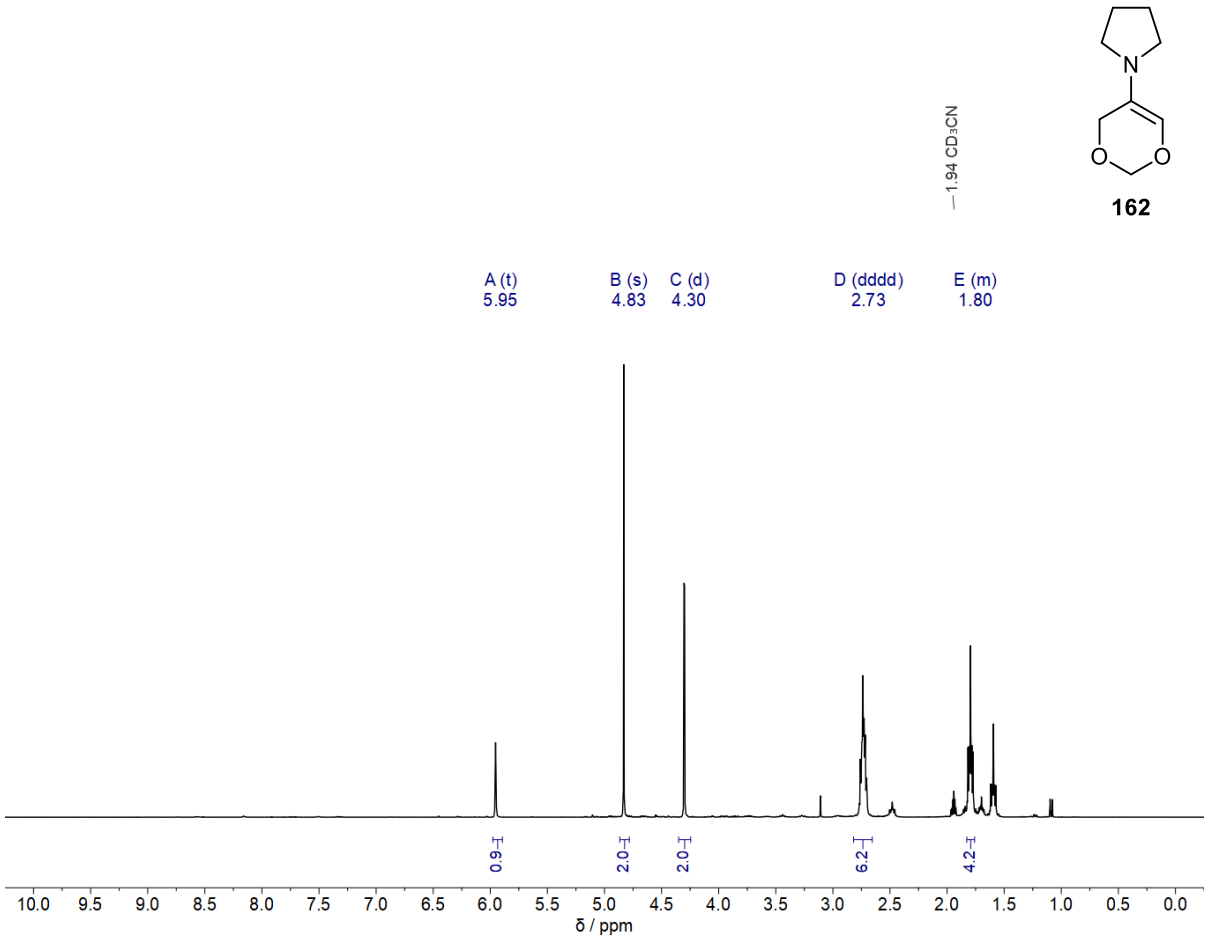
220

^{13}C-NMR spectrum of **220** in $CDCl_3$ (101 MHz, 298 K)

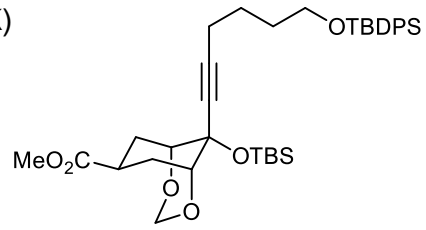


5.3 – ADDITIONAL NMR SPECTRA

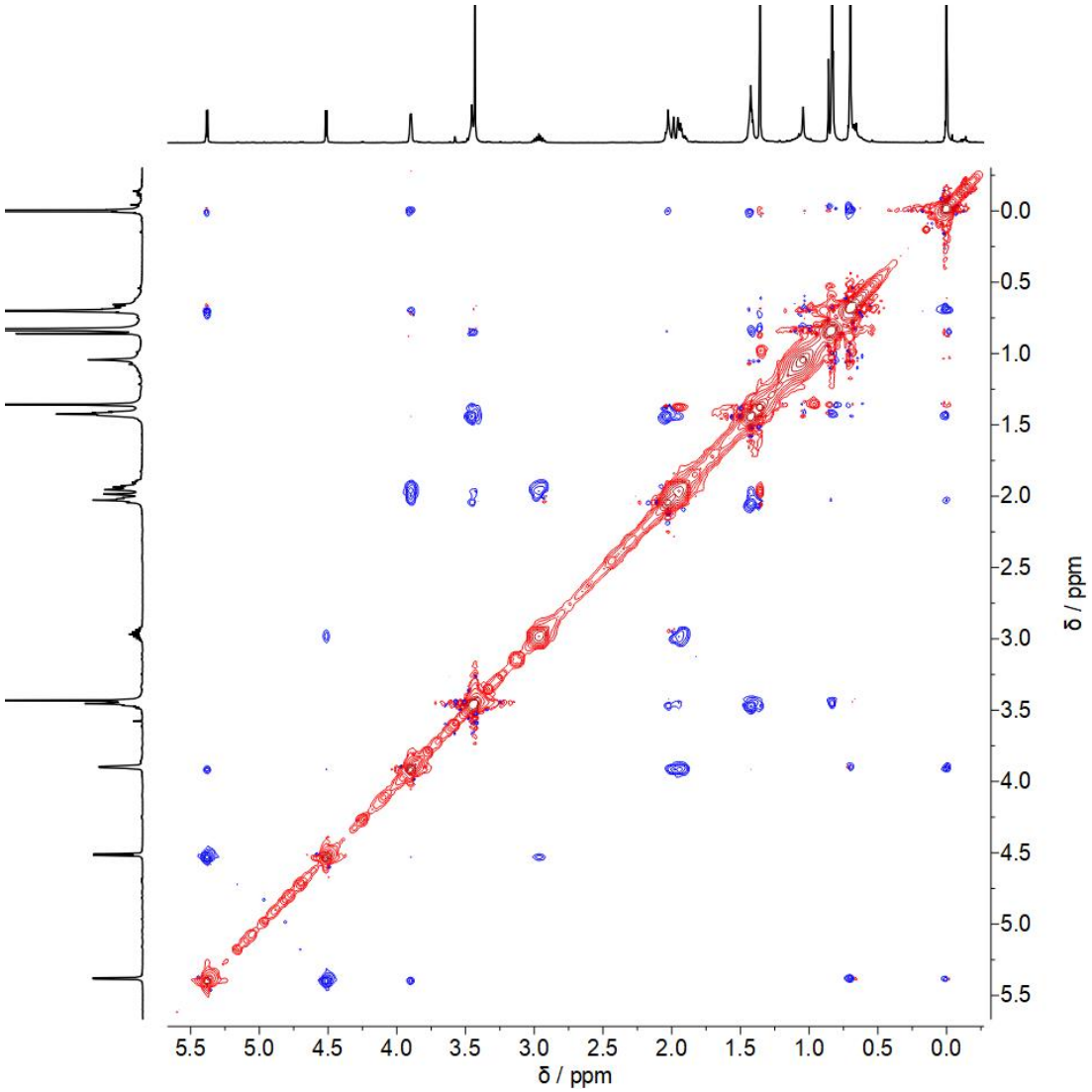
5.3.1 – ^{1}H-NMR spectrum of pyrrolidine enamine **162** in CD_3CN (300 MHz, 293 K)



5.3.2 – NOESY spectrum of **196** in $CDCl_3$ (400 MHz, 295 K)



196



5.4 – CRYSTALLOGRAPHIC DATA

*X-ray analysis of **136** - Crystallised from slow evaporation of $CDCl_3$ solution.*

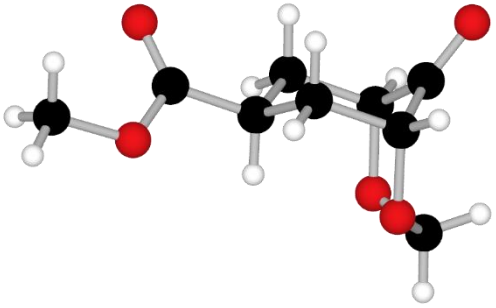


Table 5.1** Crystal data and structure refinement for **136

Empirical formula	$C_9H_{12}O_5$
Formula weight	200.19
Temperature / K	99.9(3)
Crystal system	monoclinic
Space group	$P2_1/n$
a / Å	5.9337(4)
b / Å	16.8591(11)
c / Å	9.4086(6)
α / °	90
β / °	102.834(7)
γ / °	90
Volume / Å^3	917.69(11)
Z	4
ρ_{calc} / g cm^{-3}	1.449
μ / mm^{-1}	1.019
F(000)	424.0
Crystal size / mm^3	0.294 × 0.171 × 0.13
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection / °	10.494 to 146.166
Index ranges	−4 ≤ h ≤ 7, −19 ≤ k ≤ 20, −11 ≤ l ≤ 11
Reflections collected	3478
Independent reflections	1773 [R_{int} = 0.0174, R_{sigma} = 0.0202]
Data/restraints/parameters	1773/0/128
Goodness-of-fit on F^2	1.111
Final R indexes [I>=2σ (I)]	R_1 = 0.0368, wR_2 = 0.0955
Final R indexes [all data]	R_1 = 0.0395, wR_2 = 0.0982
Largest diff. peak/hole / e Å^{-3}	0.31/−0.33

*X-ray analysis of **149** - Crystallised from slow evaporation of $CDCl_3$ solution.*

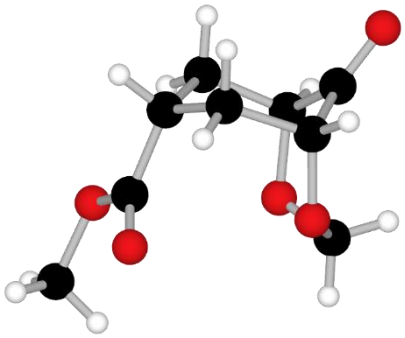


Table 5.2** Crystal data and structure refinement for **149

Empirical formula	$C_9H_{12}O_5$
Formula weight	200.19
Temperature / K	100.01(10)
Crystal system	triclinic
Space group	P-1
a / Å	6.3628(3)
b / Å	6.7155(3)
c / Å	12.3065(5)
α / °	76.145(4)
β / °	89.709(4)
γ / °	61.739(5)
Volume / Å^3	446.07(4)
Z	2
ρ_{calc} / g cm^{-3}	1.490
μ / mm^{-1}	1.048
F(000)	212.0
Crystal size / mm^3	0.257 × 0.087 × 0.029
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection / °	7.458 to 146.164
Index ranges	−7 ≤ h ≤ 7, −7 ≤ k ≤ 8, −15 ≤ l ≤ 15
Reflections collected	6223
Independent reflections	1747 [R_{int} = 0.0252, R_{sigma} = 0.0168]
Data/restraints/parameters	1747/0/128
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0477, wR_2 = 0.1294
Final R indexes [all data]	R_1 = 0.0489, wR_2 = 0.1317
Largest diff. peak/hole / e Å^{-3}	0.32/−0.20

*X-ray analysis of **218** - Crystallised from slow evaporation of hexane and ethyl acetate solution.*

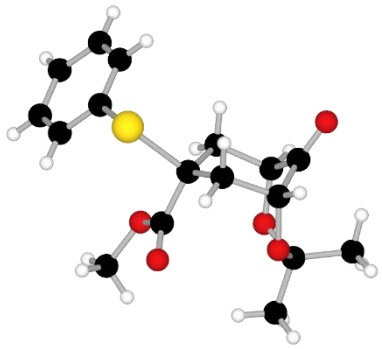


Table 5.3** Crystal data and structure refinement for **218

Empirical formula	$C_{17}H_{20}O_5Se$
Formula weight	383.29
Temperature / K	100.01(10)
Crystal system	monoclinic
Space group	Ia
a / Å	9.5667(3)
b / Å	10.3537(3)
c / Å	16.9432(6)
α / °	90
β / °	103.790(4)
γ / °	90
Volume / Å^3	1629.86(9)
Z	4
ρ_{calc} / g cm^{-3}	1.562
μ / mm^{-1}	3.328
F(000)	784.0
Crystal size / mm^3	0.254 × 0.068 × 0.047
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection / °	10.094 to 145.198
Index ranges	−10 ≤ h ≤ 11, −12 ≤ k ≤ 8, −18 ≤ l ≤ 20
Reflections collected	3107
Independent reflections	1982 [R_{int} = 0.0183, R_{sigma} = 0.0276]
Data/restraints/parameters	1982/2/211
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0238, wR_2 = 0.0612
Final R indexes [all data]	R_1 = 0.0243, wR_2 = 0.0619
Largest diff. peak/hole / e Å^{-3}	0.33/−0.52

CHAPTER 6 – BIBLIOGRAPHY

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