Studies Towards the Asymmetric Synthesis of Dictyoxetane

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Abstract

The brown alga, *Dictyota dichotoma*, collected from the Indian Ocean has proven to be a prolific source of new diterpenes. The diterpene, dictyoxetane, isolated from the brown alga, is structurally related to the dollabellane class of natural products. Dictyoxetane is the only known natural product having the 2,7-dioxatricyclo[4.2.1.0]nonane ring subunit.

Chapter 1 of this thesis describes the isolation, structure and proposed biosynthesis of dictyoxetane. The methods reported in the literature for the preparation of the dioxatricyclic framework are discussed, which might be applied in a synthesis of dictyoxetane. The Grainger group has previously reported the synthesis of the *trans*-hydrindane core of dictyoxetane starting from a Robinson annulation-derived bicyclic enone. Asymmetric approaches to the starting hydrindanone in this synthesis and the Hajos-Parrish ketone are also presented.

Chapter 2 reports the efforts to address the current limitations of this approach, namely the low-yielding Robinson annulation of an expensive starting material, 2-methylcyclopentanone. An asymmetric synthesis of the *trans*-hydrindane ring system starting from the Hajos-Parrish ketone, involving chemoselective radical-based deoxygenation, is reported.

Studies towards dioxatricyclic ring annulation are described in Chapter 3. A number of strategies such as radical cyclisation, ring-expansion and [4+3] cycloaddition are investigated towards 7-membered ring formation. The Lee [5+2] annulation using allylsilane acetals and

olefin metathesis both provided a way to annulate a 7-membered ring to the hydrindanone system en route to dictyoxetane.

Abbreviations

°C	degrees Celsius
Å	Angstrom (10^{-10} m)
ACCN	1,1'-Azobis(cyclohexanecarbonitrile)
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
ap.	apparent
aq.	aqueous
ASAP	atmospheric solids analysis probe
Ar	aryl
Bn	benzyl
b.p.	boiling point
brsm	based on recovered starting material
br	broad
Bu	butyl
Bz	benzoyl
CAN	ammonium cerium (IV) nitrate
Cat.	catalytic
cm^{-1}	wavenumbers
Conc.	concentrated
Cp	cyclopentadienyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*-*N*-dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
E1cB	elimination unimolecular conjugate base
EI	electron impact ionisation
ee	enantiomeric excess
eq.	equivalent
er	enantiomeric ratio
ES	electrospray ionisation
Et	ethyl
FT-IR	Fourier transform infrared spectroscopy
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
hv	light irradiation
IBX	2-iodoxybenzoic acid
Im	imidazole
i-Pr	isopropyl
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
L	litres
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
µ	micro
M	molar (mol L^{-1})

m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
MHz	megahertz
mL	mililitre
mol	moles
m.p.	melting point
m/*z*	mass/charge
M.S.	molecular sieves
Ms	mesyl (methanesulfonyl)
MVK	methyl vinyl ketone
n-BuLi	*n*-Butyllithium
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
[O]	oxidation
Ph	phenyl
Piv	pivaloyl
ppm	part(s) per million
p	pentet
P	protecting group
pet ether	40-60 °C petroleum ether
PPTS	pyridinium *p*-toluenesulfonate
p-TSA	*para*-toluenesulfonic acid
Py	pyridine
q	quartet

RCM	ring-closing metathesis
R_f	retention factor
rt	room temperature
s	singlet
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet
t-Bu	*tert*-butyl
t.l.c.	thin layer chromatography
TBAF	*tetra*-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
Ts	tosyl (*para*-toluenesulfonyl)
TTMSS	tris(trimethylsilyl)silane
UV	ultraviolet
W	watt
δ	frequency
ν_{max}	frequency
c	concentration
XRD	X-ray diffraction
α	observed optical rotation in degrees

Contents

Chapter one: Introduction

1. Dictyoxetane

1.1. Isolation and structure

The first study of the brown algae *Dictyota dichotoma* (Hudson) Lamourou was undertaken as a survey of marine organisms in 1985 by Pullaiah and co-workers from a sample collected at Krusadai Island in India.[1] This brown algae has been known as a source of a variety of diterpenes and their metabolites.[2] One of these diterpenes is the pentacyclic dictyoxetane **1**, the structure of which belongs to the class of dolabellanes (Figure 1). The structure of dictyoxetane **1** was determined from a colourless crystalline solid by single-crystal X-ray analysis.[1] However, the absolute configuration is yet to be determined.

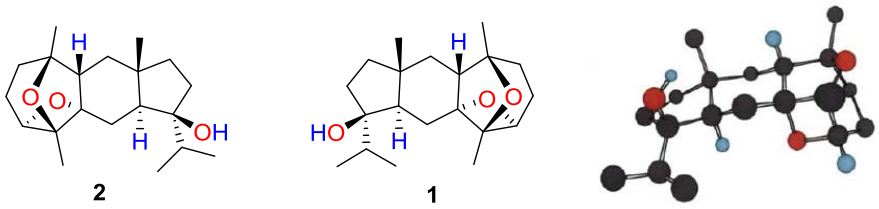


Figure 1. The two possible enantiomers and the crystal structure of dictyoxetane **1**

This unusual diterpene contains a unique dioxatricyclic ring system which has not been found in any other natural products and the biological activity for dictyoxetane has not been reported.

1.2 Dolabellanes

Dolabellanes are known as an important family of natural products isolated from marine and terrestrial sources, such as algae, marine molluscs, moulds, liverworts and higher plants.[3]

They show a wide spectrum of biological activity and also enter the food-chain of marine invertebrates and thus are part of finely balanced marine ecosystems. Therefore, they are worthwhile targets for enantioselective total synthesis due to their biological activity and unsolved supply issue.[4] Notably, dolabellanes isolated from marine animals possess the opposite absolute configuration at 1- and 11-positions compared to dolabellanes found in algae, higher plants or liverworts (Figure 2).[5]

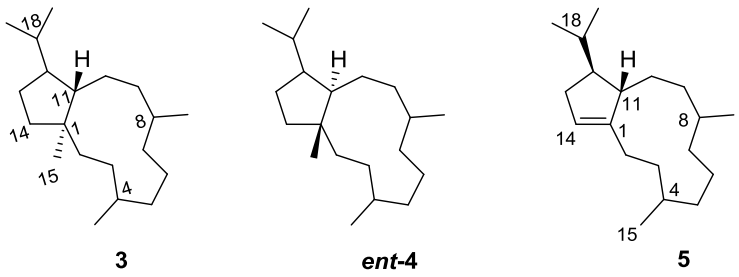


Figure 2. Carbon skeleton of dolabellanes isolated from higher plants, algae **3**, corals, fungi (mould) ***ent*-4** and neodolabellanes **5** isolated from corals

Borschberg (1975) was first to report β-araneosene, the isolated diterpene from the terrestrial mould *Sordaria araneosa* (Figure 3). This bicyclic skeleton was then referred to as "dolabellane" when Faulkner and Ireland isolated a series of related diterpenoids from the sea hare *Dolabella californica* in 1976.[6]

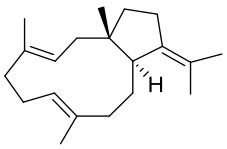
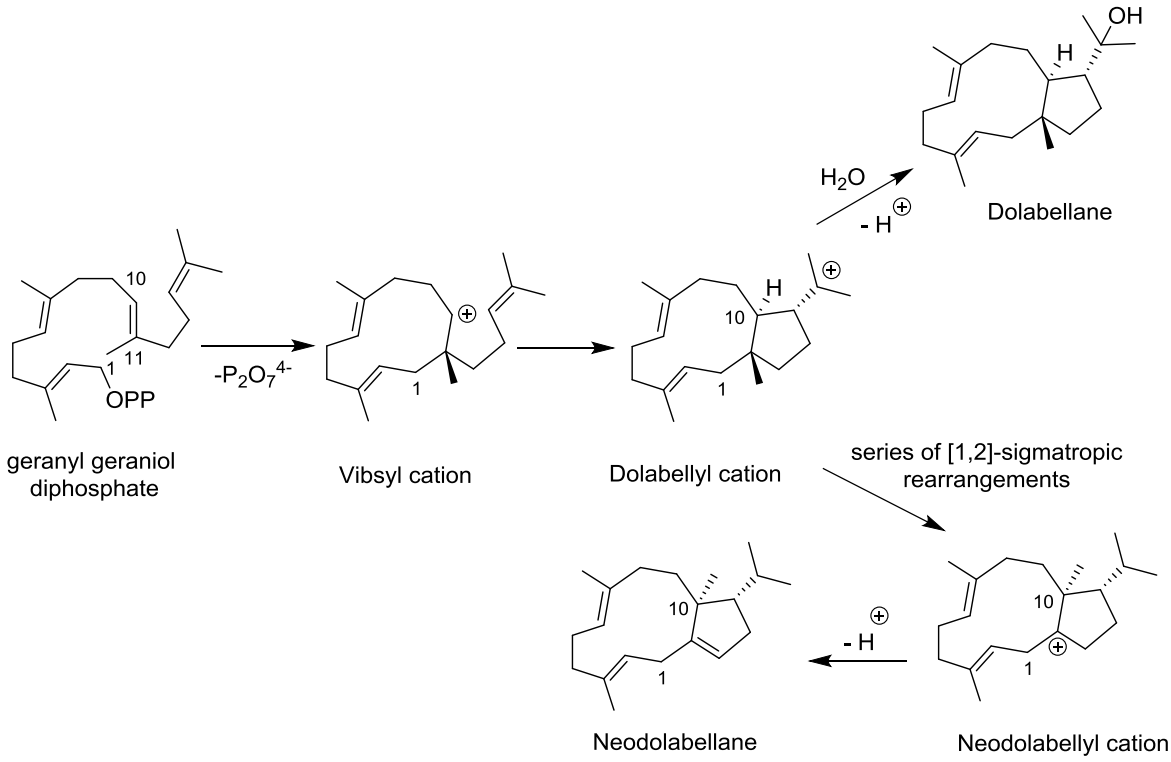


Figure 3. β-araneosene

Rodríguez *et al*. discussed the isolation, total syntheses, biological activity and reactivity of 140 dolabellanes, in a review published in 1998.[7] Depending on their structural features,

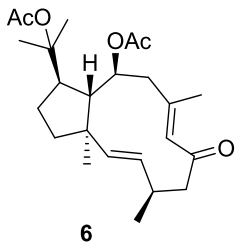
these diterpenes exhibit cytotoxicity against various cancer cell lines and antimicrobial activity against fungi and viruses. The dolabellanes are proposed to be biosynthesised by an anabolic pathway which employs a single achiral substrate, geranyl geraniol diphosphate.[8]

It is assumed that geranyl geraniol diphosphate is initially ionised by an enzymatic, metal ion-initiated process (Scheme 1). The vibsyl cation is the result of first cyclisation, which undergoes a second cyclisation to prepare the dolabellyl cation. Deprotonation or nucleophilic attack by water results in the dolabellane. The dolabellyl cation could also be transformed into the neodolabellyl cation by a series of [1,2]-sigmatropic rearrangements. Subsequently, deprotonation of the neodolabellyl cation affords the neodolabellane.



Scheme 1. Proposed biogenesis to form dolabellane and neodolabellane

Dolabellane studies to date show a wide range of biological activities, such as antifungal activity. The marine sponge *Sigmosceptrella quadrilobata* collected along the coast of the Island Mayotte (Comorian archipelago), has been recognised as a source of the dolabellane **6** (Figure 4).[9] This dolabellane is known to have cytotoxic effects against four cancer cell lines with an IC_{50} between 7.7 and 17.2 µg/mL.

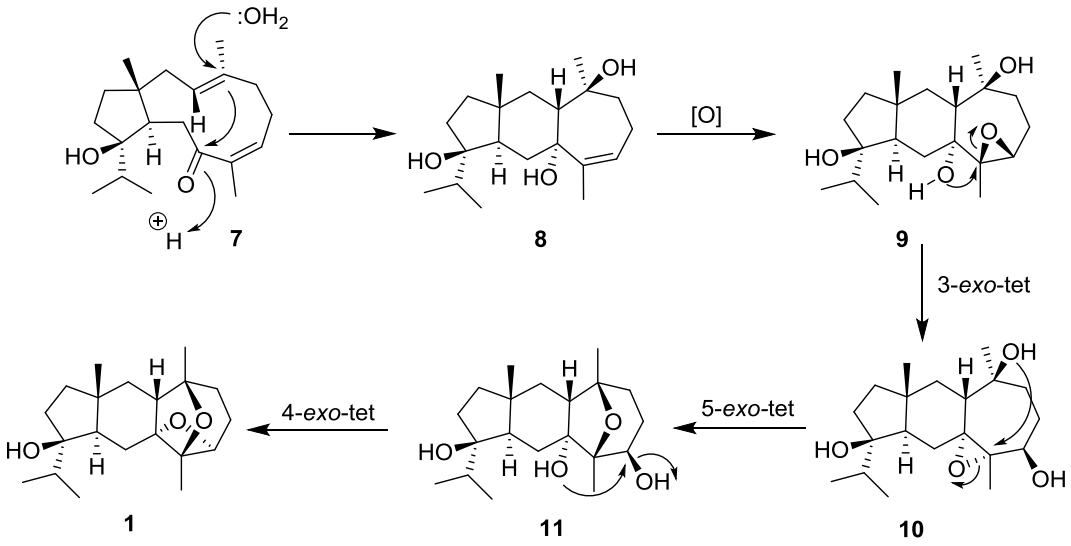


6

Figure 4. Dolabellane **6**

1.3 Synthetic studies towards the dioxatricyclic ring system

In 1995, Hoffmann and co-workers suggested a hypothetical biosynthesis for dictyoxetane **1** (Scheme 2).[10] Dolabellane metabolite **7** is first proposed to undergo a transannular cyclisation. Tricyclic tertiary triol **8** is the result of attack of water from the *exo* face. Stereoselective epoxidation gave epoxide **9**, which was followed by epoxide rearrangement, furnishing a new epoxide **10**. The tetrahydrofuran ring **11** was formed with concomitant epoxide ring opening. Oxetane ring formation *via* a 4-*exo*-tet cyclisation would generate dictyoxetane **1**.



Scheme 2. Proposed biosynthesis of dictyoxetane **1**

Although nothing is known about the biogenetic origin of dictyoxetane, preparation of the dioxatricyclic ring system has been studied and syntheses have been described by three different groups. In 1996, Heathcock and co-workers reported a synthetic approach to the dictyoxetane core structure contained within the heterocycles **12** and **13** (Figure 5).[11] It was proposed that dipolar cycloaddition of a 3-oxidopyrylium salt with an alkene followed by an intramolecular S_N2 displacement furnishes the oxetane ring.[12]

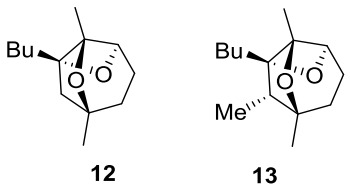
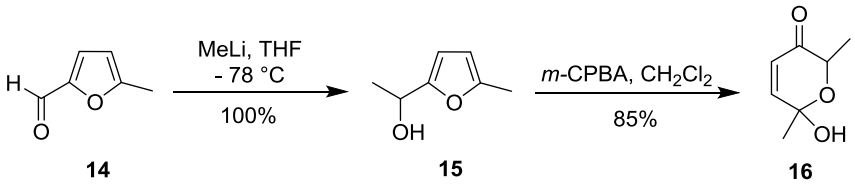


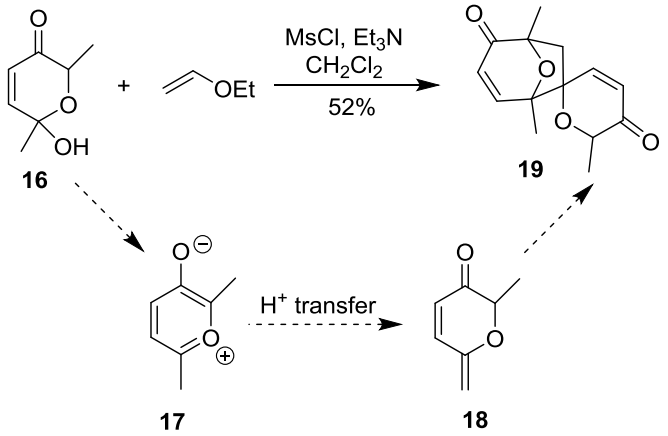
Figure 5. Oxetanes **12** and **13** prepared by Heathcock

Treatment of 5-methylfurfural **14** with MeLi gave 2-furyl carbinol **15**, which was oxidatively rearranged to enone **16** in the presence of *m*-CPBA (Scheme 3).[13]



Scheme 3. Formation of hemiketal **16**

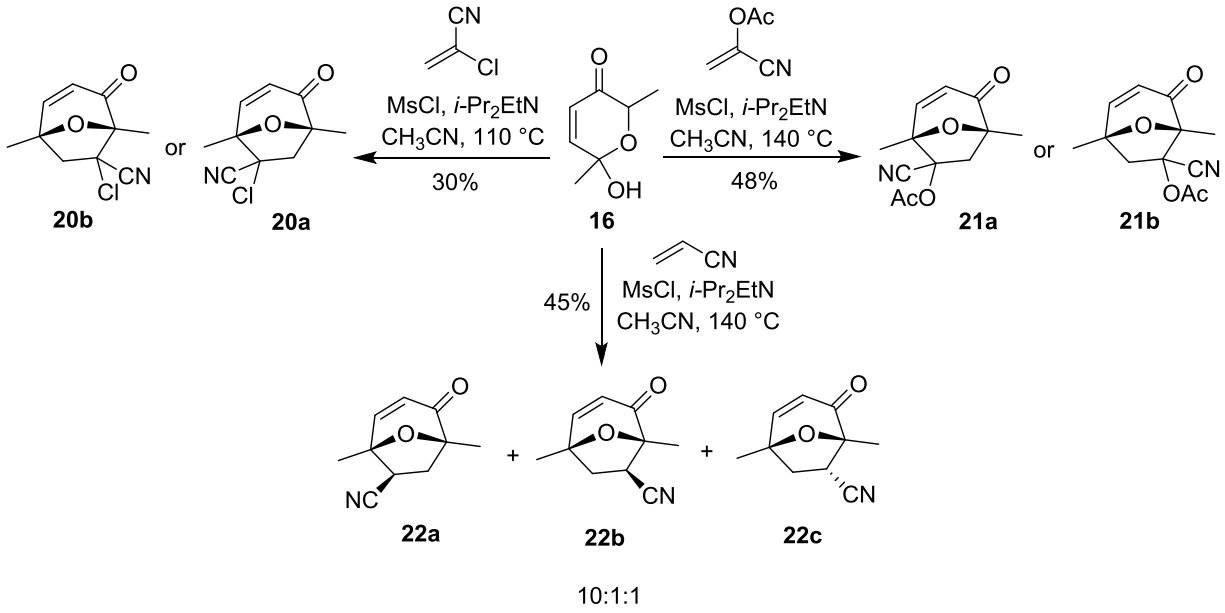
Reaction of hemiketal **16** with methanesulfonyl chloride in the presence of triethylamine gave pyrylium **17** (dipole), which was transformed to dimer **19** in the presence of ethyl vinyl ether as a result of a 1,3-dipolar cycloaddition of ylide **17** with dienone **18**, generated from **17** *via* proton transfer (Scheme 4).[14] The result from this experiment showed that electron-rich dipolarophiles such as ethyl vinyl ether, vinyl acetate and ketene thioacetals were unreactive with **16** with only dimerisation or decomposition observed.



Scheme 4. Formation of dimer **19**

In contrast, more reactive dipolarophiles underwent cycloaddition, leading to a variety of cycloadducts (Scheme 5). An attempted cycloaddition reaction using acrylonitrile as a dipolarophile, provided cycloadducts **22a-c** as a 10:1:1 mixture of diastereomers and regioisomers with no observed dimer formation.[15] α-Acetoxyacrylonitrile and α-

chloroacrylonitrile furnished cycloadducts **20a** or **20b** and **21a** or **21b** respectively in moderate yields as single regioisomers. HMBC NMR analysis confirmed that **20a** and **21a** were the major isomers. The relative stereochemistry was not determined at this stage as the unknown stereocentres would be destroyed upon conversion to a carbonyl.



Scheme 5. Cycloaddition with different dipolarophiles

The observed regiochemistry in **20** and **21** was opposite to that required for dictyoxetane. A three-bond coupling between both methylene protons and the carbonyl carbon showed the cyanoacetal to be distal rather than proximal to the carbonyl (Figure 6).[16]

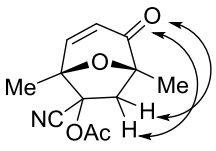
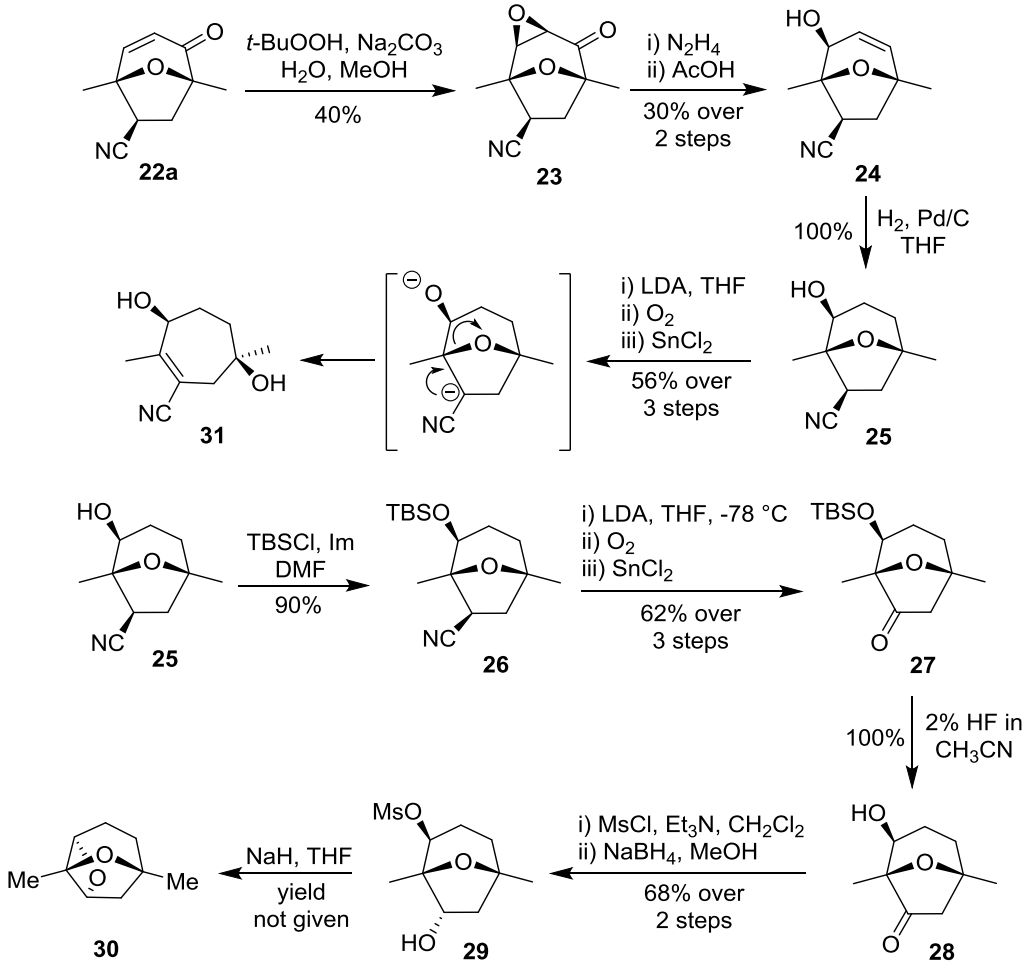


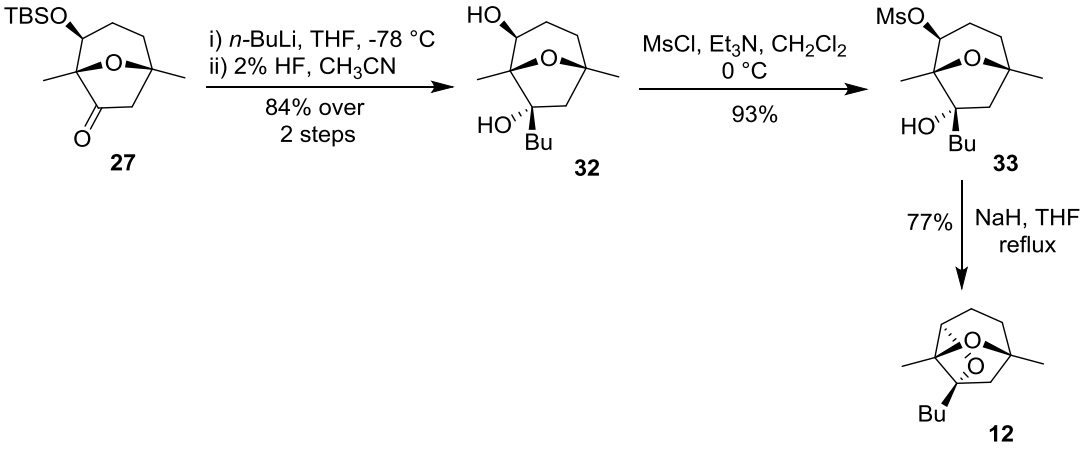
Figure 6. Three-bond coupling between methylene protons and the carbonyl carbon

In order to generate the requisite regiochemistry, Heathcock suggested that **22a** might be employed in Wharton enone transposition (Scheme 6).[16] Stereoselective epoxidation of enone **22a** from the less hindered convex face gave epoxide **23**, which upon consecutive treatment with hydrazine and acetic acid furnished allylic alcohol **24**. Hydrogenation of **24** formed the saturated alcohol **25**, which did not undergo oxidative decyanation as expected but instead furnished cycloheptenol **31**. Alcohol **31** was envisioned to be obtained *via* β-elimination of the intermediate nitrile-stabilised anion. Silyl protection of secondary alcohol **25** gave TBS ether **26** in 90% yield. Deprotonation of nitrile **26** with LDA and oxidation of the resulting anion with oxygen gave ketone **27** after treatment with $SnCl_2$.



Scheme 6. Synthesis of oxetane **30**

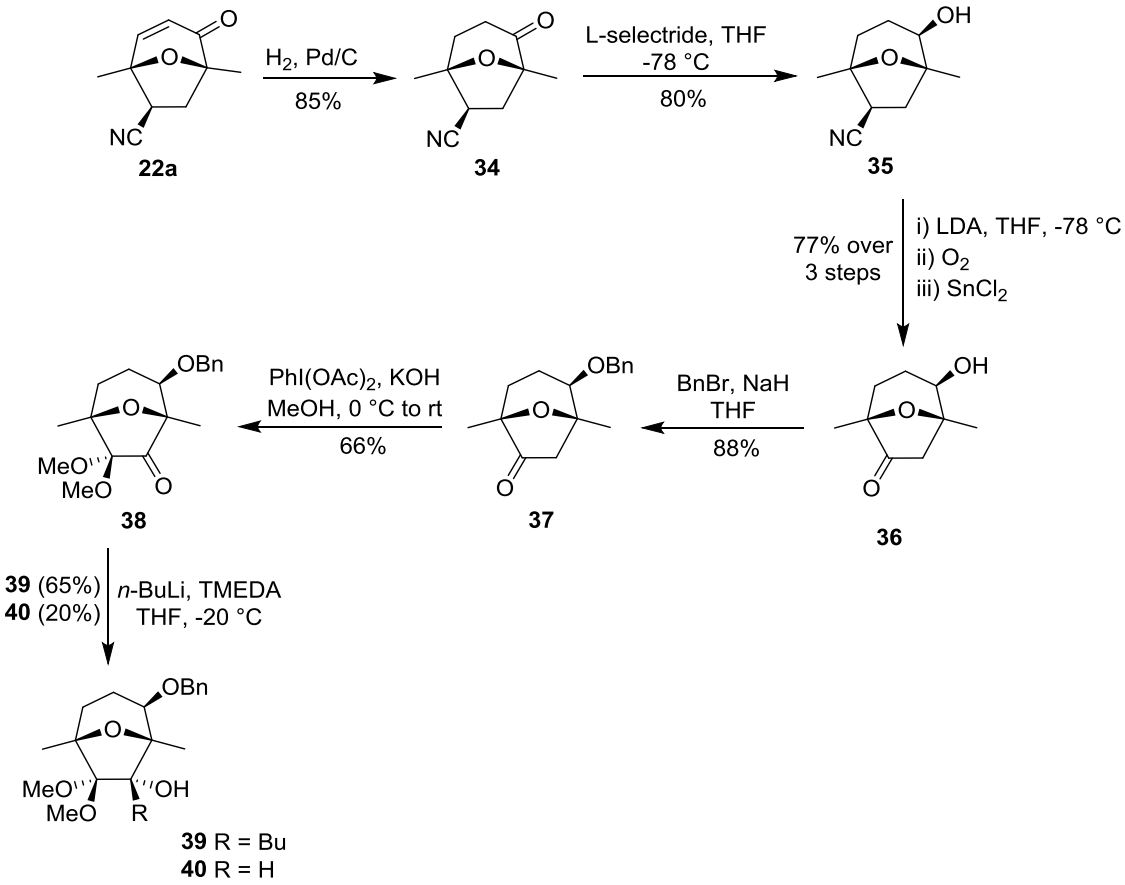
The remaining steps to the oxetane ring required silyl deprotection, mesylation of the alcohol **28** and stereoselective reduction of the resulting keto mesylate from the less hindered convex face to provide *endo* alcohol **29**. The oxetane ring was constructed under basic conditions. Due to the volatile nature of tricycle **30**, Heathcock changed the model system slightly by adding an alkyl substituent to get a heavier analogue so this addition would create a more accurate model system **12**, since the natural product possesses an alkyl substituent at that position (Scheme 7). *n*-BuLi addition to ketone **27** from the less hindered *exo* face gave tertiary alcohol **32** after silyl deprotection. Selective mesylation of the secondary alcohol formed **33** and subsequent cyclisation provided oxetane **12** as a colourless liquid in 77% yield.



Scheme 7. Preparation of butyl oxetane **12**

Despite the additional molecular weight, diether **12** was still volatile but was easier to handle than **30**. Although oxetanes **30** and **12** were successfully synthesised, this approach suffered from several drawbacks. Firstly the epoxidation/Wharton rearrangement was low yielding. Moreover, β-elimination was in competition with the oxidative decyanation. An alternative route to apply carbonyl transposition in the two-carbon bridge, rather than rearranging the

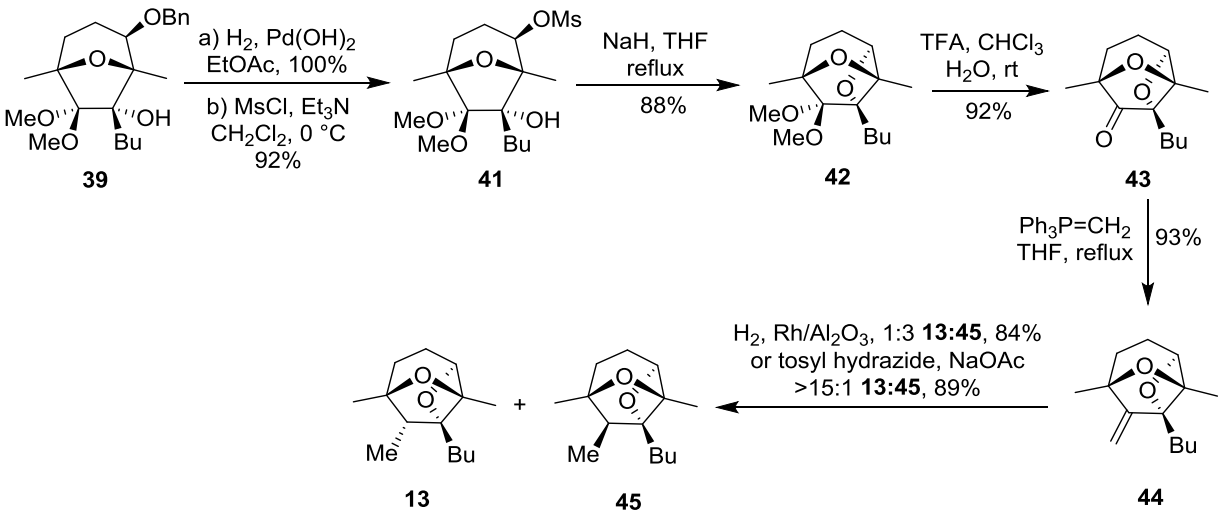
oxygen functionality in the three-carbon bridge was attempted. With this objective, cycloadduct **22a** was converted into hydroxy ketone **36** *via* hydrogenation, stereoselective reduction and oxidative decyanation, giving alcohol **36** which, following benzylation afforded benzyl ether **37** (Scheme 8).[17]



Scheme 8. Transposition of the carbonyl on the 2 carbon bridge

Treating **37** with $PhI(OAc)_2$ in methanolic KOH as an oxidising agent resulted in transformation to the unexpected dimethoxy ketone **38**.[18] Treatment of **38** with butyllithium and TMEDA in THF gave alcohol **39** in 65% yield, accompanied by 20% of the reduction product **40**. Deprotection of benzyl ether **39** followed by mesylation gave **41**, which was directly cyclised to give **42** in high yield (Scheme 9). Under acidic conditions acetal **42** was

hydrolysed to furnish **43**. Wittig olefination of ketone **43** afforded methylene **44**.[19] Attempted hydrogenation of the exocyclic double bond under standard conditions, H_2 over Pd/C, gave a complex mixture of products, which was ascribed to insertion of palladium into the allylic oxetane and subsequent opening of the 4-membered ring. However, the final product from this proposed pathway was not discussed or clarified in the literature.

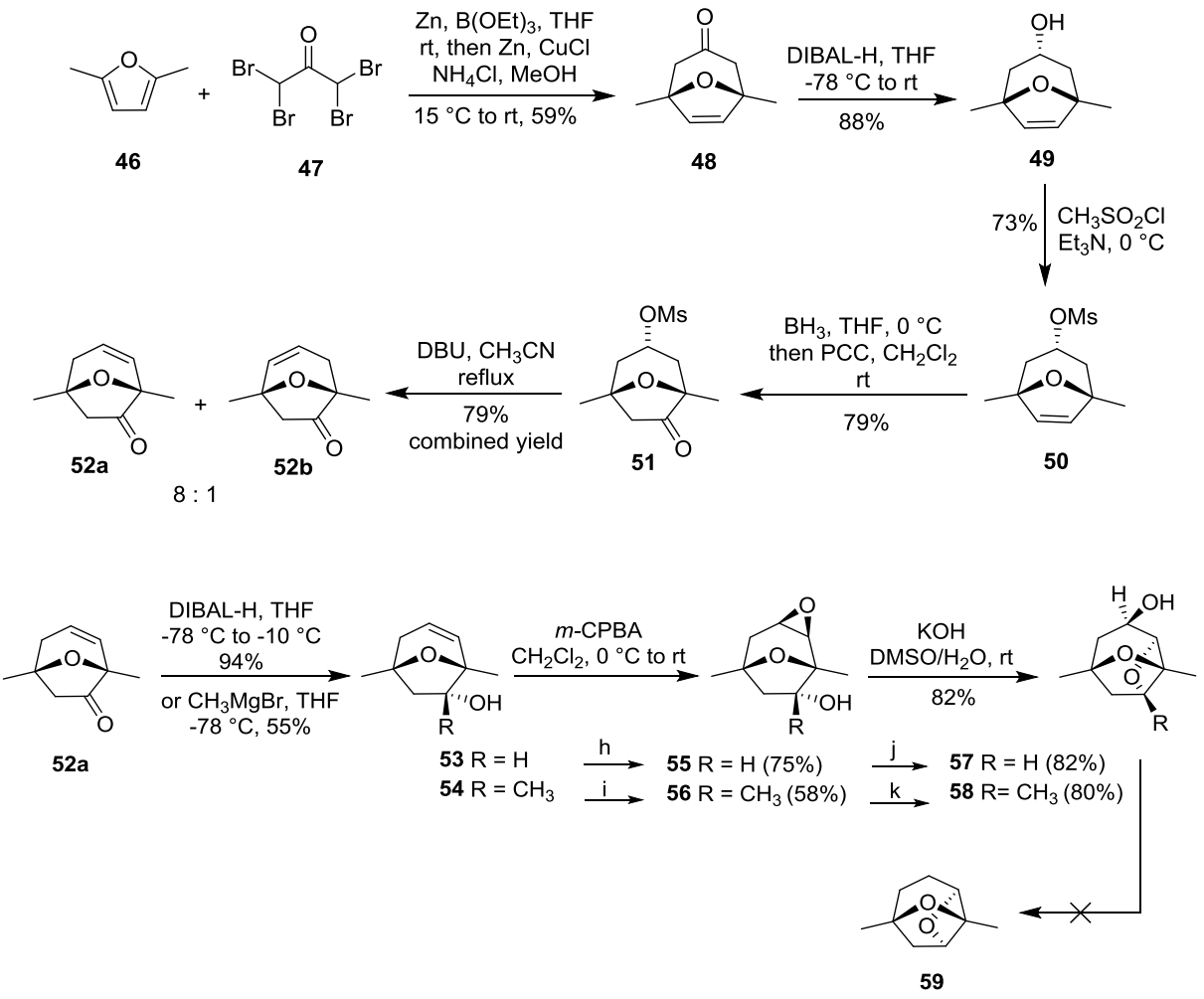


Scheme 9. Synthesis and stability of oxetane **43** to subsequent functional-group transformations

However, a 1:3 mixture of diastereomers **13**:**45** was isolated when the reduction was performed with H_2 over Rh/Al_2O_3.[20] It was speculated that the rhodium catalyst would coordinate to the oxygen of the oxetane in order to direct the hydrogenation from underneath the ring system, producing the *exo* methyl.[10] Hydrogenation of **44** using diimide, which is incapable of oxygen coordination, reversed the facial preference.

Parallel to Heathcock's studies, Reinecke and Hoffmann investigated the possible biosynthetic pathway towards the key oxetane ring by using a stereoelectronically favourable, intramolecular nucleophilic displacement reaction (Scheme 10).[21] 2,5-

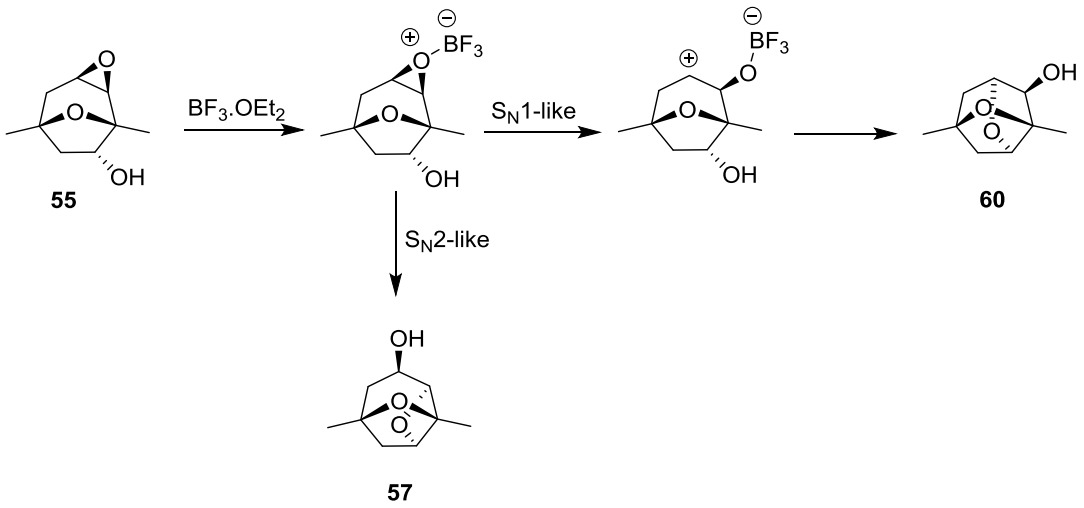
Dimethylfuran **46** and tetrabromoacetone **47** were allowed to react with zinc/copper powder in the presence of triethyl borate as a Lewis acid to undergo cycloaddition reaction. 1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **48** was generated by the triethyl borate method of Hoffmann and Iqbal.[3] Stereoselective reduction of ketoolefin **48** with DIBAL-H gave the unsaturated *endo* alcohol **49.**



Scheme 10. Synthesis of oxetanes **57** and **58**

Mesylation of alcohol **49** was followed by hydroboration/oxidation forming ketomesylate **51** with desymmetrisation of the etheno bridge in bicyclic mesylate **50**. It was proposed that the σ-acceptor effect of the carbonyl group in ketomesylate **51** would control the regiochemistry

of the functionalisation of the three-carbon bridge. Accordingly, a base-mediated elimination furnished ketoolefin **52a** as the major product (**52a**:**52b** 8:1). Stereoselective reduction of the carbonyl group with DIBAL-H gave alcohol **53**. Alternatively, alkylation with CH_3MgBr formed homoallylic alcohol **54**. Again the attack on the bicyclic skeleton occurred from the *exo* face. Epoxidation of the homoallylic alcohol with *m*-CPBA resulted in epoxy alcohols **55** and **56**, which upon treatment with a base transformed to tricyclic oxetanes in very good yields.

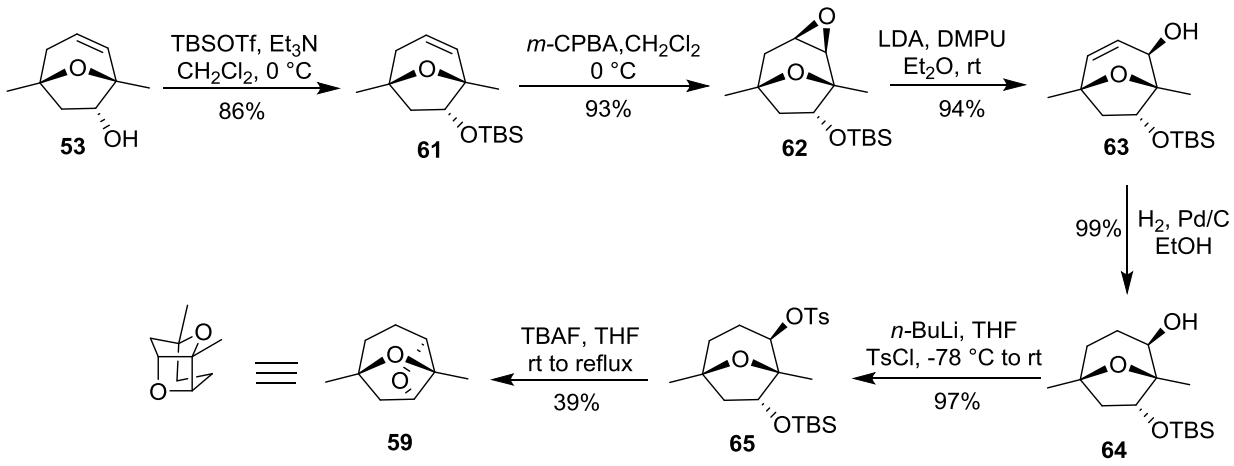


Scheme 11. Formation of oxetanes **57** and **60**

Under basic conditions, hydroxyepoxide **55** was transformed to hydroxyoxetane **57**, in the presence of a catalytic amount of $BF_3.OEt_2$. Isomeric bistetrahydrofuran **60** was also formed (**57:60**, 2:1), presumably *via* an S_N1-like cyclisation (Scheme 11).[22] Attempted hydroxyl group removal was not successful using radical methodology (Scheme 10).

Consequently, Hoffmann *et al.* developed an alternative approach to dioxatricyclic ring **59** (Scheme 12), starting from diastereomerically pure alcohol **53**. Silyl protection of alcohol **53** was followed by epoxidation of **61**, giving *exo*-epoxide **62**, which was converted to allylic

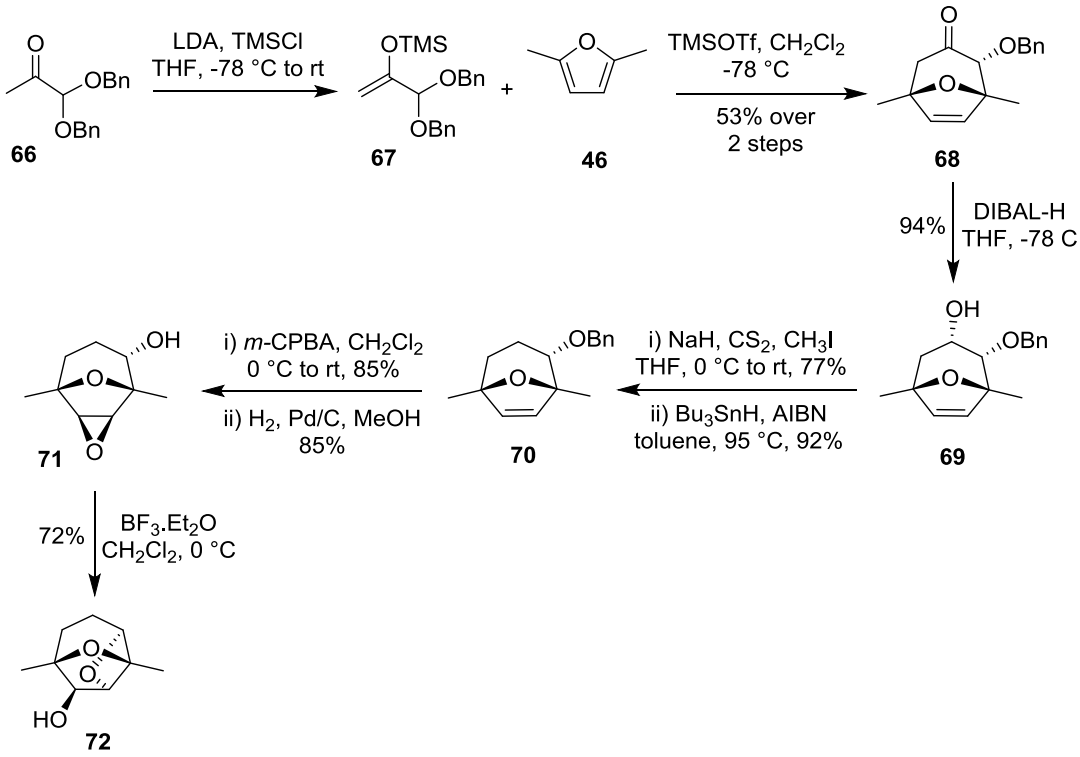
alcohol **63**, under basic conditions. Hydrogenation of the double bond followed by tosylation gave **65** which was converted to oxetane **59** *via* a one-pot TBAF-mediated deprotection and cyclisation.



Scheme 12. Synthesis of oxetane **59**

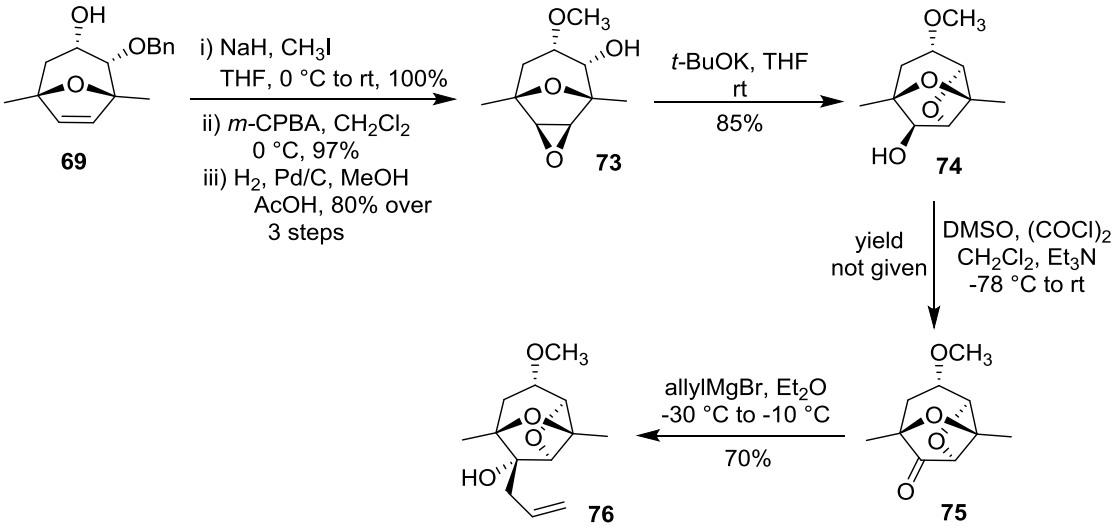
In continuation of this work, Hoffmann (1998) reported progress on the functionalisation of the dioxatricyclic ring system, and investigated the biological activities of these oxetanes.[23]

Initially, α-keto acetal **66** was converted to silyl enol ether **67** (Scheme 13). [4+3] Cycloaddition with 2,5-dimethylfuran **46**[24] in the presence of a catalytic amount of TMSOTf gave adduct **68**.[25] Diastereoselective reduction of the bicyclic adduct **68** provided *endo*-alcohol **69**, which was deoxygenated *via* the Barton-McCombie method, forming oxabicycle **70**. Epoxidation and benzyl ether deprotection furnished **71**. Cyclisation using $BF_3.Et_2O$ as a Lewis acid then furnished tricyclic hydroxy oxetane **72**.[26]



Scheme 13. Synthesis of hydroxy oxetane **72**

Alternatively, *O*-methylation of alcohol **69** was followed by epoxidation and debenzylation to give epoxy alcohol **73** (Scheme 14). Epoxide **73** was converted to alcohol **74** under basic conditions. Keto oxetane **75** was synthesised *via* Swern oxidation. The stereoselective conversion of the ketone into *endo* tertiary homoallylic alcohol **76** showed the stability of the oxetane ring system to Grignard reagents.



Scheme 14. Synthesis of oxygenated oxetanes **74**, **75** and **76**

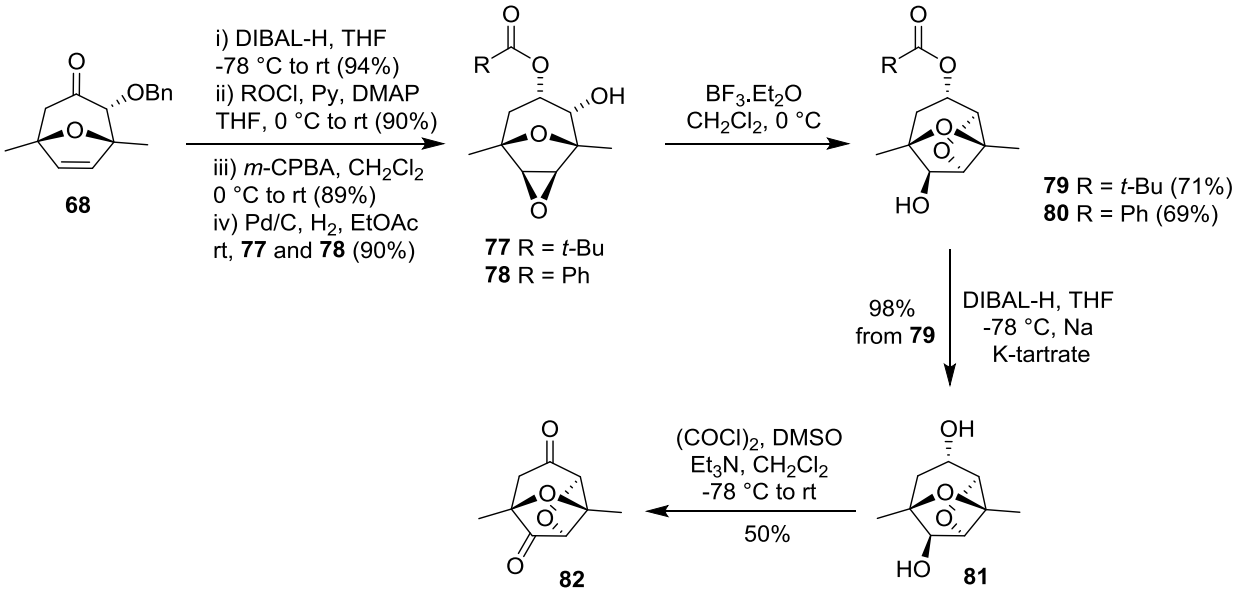
The cytotoxic and cytostatic activities of oxetanes **72**, **74**, **75** and **76** were investigated *in vitro*, through the HMO2 (human gastric carcinoma) and the HEP G2 (human heptocellular carcinoma) cell lines (Table 1).[3] All of the four oxetanes have cytostatic activity. However, the oxetane **75** inhibited cell growth by 68% at 1 µmol/l towards the HMO2 cell line.

Compound	GI_{50}[a] HMO2	HEP G2	TGI[b] HMO2	HEP G2	LC_{50}[c] HMO2	HEP G2
72	4.0	0.1	50	30	>100	>50
74	3.0	<0.1	57	45	>100	>50
75	<0.1	<0.1	72	35	>100	>50
76	<0.1	<0.1	54	30	>100	>50
5-fluorouracil	1.2	0.15	35	50	>50	>50
Cis-platin	0.1	0.5	2.5	30	40	>50

[a] Drug concentration causing 50% growth inhibition. [b] Drug concentration causing 100% growth inhibition.[C] Drug concentration causing 50% reduction of the cells present at time point zero, i. e at 24 h

Table 1. Antitumour activity (µmol/l) measured toward HMO2 and HEP G2 cells

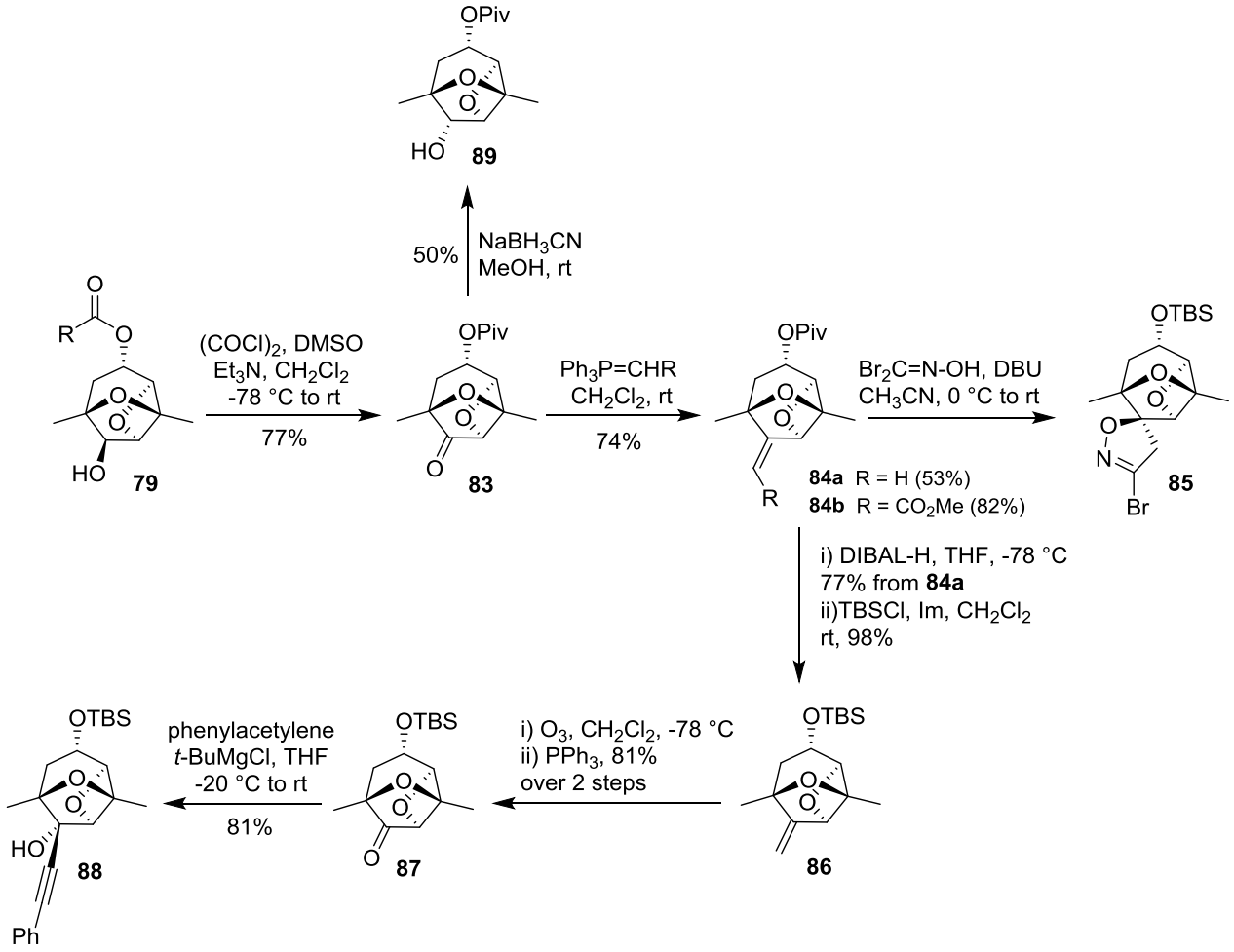
In 2002, in continuation of their previous work, Hoffmann presented progress on the synthesis of dictyoxetane (Scheme 15). Starting from [4+3] cycloadduct *rac*-**68**, ketone reduction, protection and epoxidation provided epoxy alcohols **77** and **78**. Cyclisation under Lewis acid conditions was carried out, after which the ester group on **79** was reductively cleaved to give tricyclic diol **81**.[27] A one-pot double oxidation of diol **81** afforded diketone **82**, which could be used for further transformations on the dioxatricyclic ring system.



Scheme 15. Formation of diketo oxetane **82**

An alternative approach to different substituted oxetanes started with oxidation of alcohol **79** to keto ester **83**, which was stereoselectively reduced to the epimeric alcohol **89** (Scheme 16).[25] Exocyclic olefins **84a** and **84b** were formed *via* Wittig olefination of **83**. Deprotection of **84a**, followed by reprotection and oxidative cleavage afforded protected keto alcohol **87**. Grignard addition to **87** gave **88** with complete stereoselectivity. The exocyclic olefin double bond in **84a** could be employed as a dipolarophile in a nitrile oxide cycloaddition with

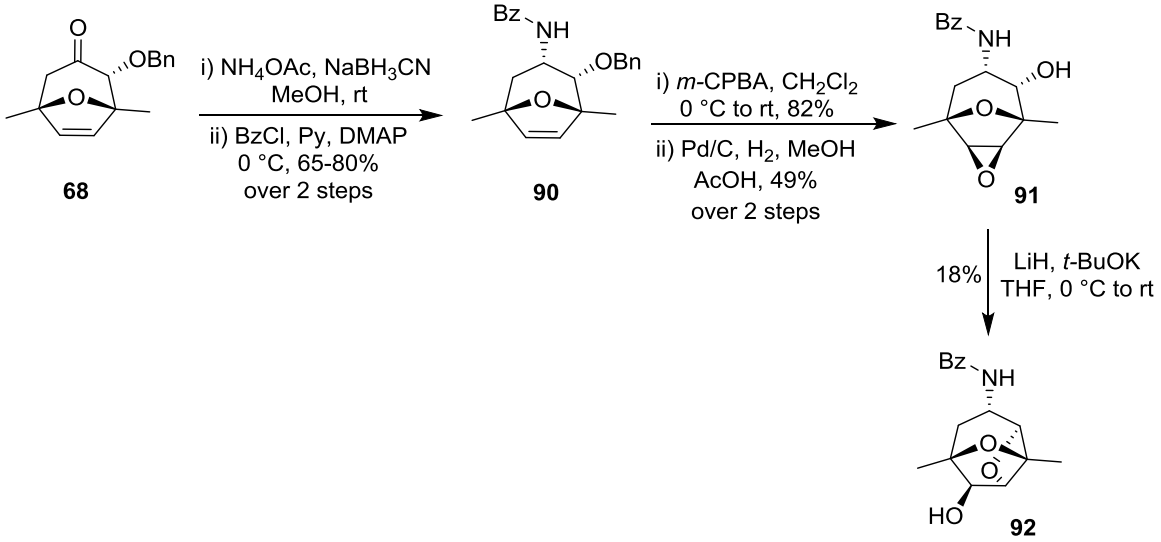
complete π-facial selectivity to form **85**.[26] This showed that the pericyclic reaction and all nucleophilic additions to the carbonyl proceeded selectively from the *exo* face, *trans* to the oxetane oxygen. Pivaloyl protection of the free hydroxyl group is valuable for providing oxetane formation from epoxy alcohols **77** and **78**.



Scheme 16. Preparation of functionalised oxetanes

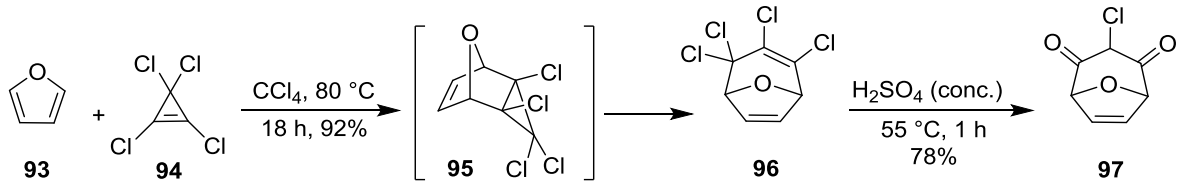
The dioxatricyclic ester *rac*-**84b** possessed cytostatic, but no cytotoxic activity towards tumour cells (cell lines: HepG 7, MCF 7).

Aminated bicyclic olefin **90** was synthesised *via* reductive amination of oxabicyclic ketone **68** followed by protection as an *N*-benzamide.[28] Epoxidation followed by alcohol deprotection gave oxetane precursor **91**, which was cyclised to oxetane **92** after *O*-deprotection (Scheme 17).



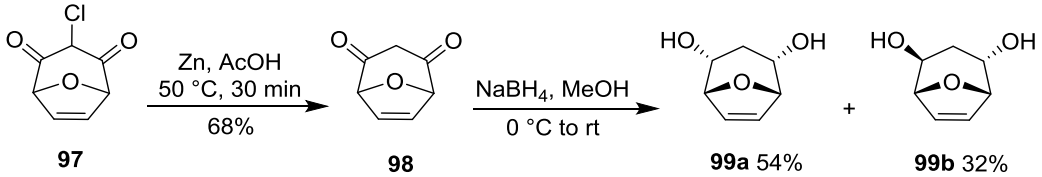
Scheme 17. Amination of oxetane **92**

In 2012, Khlevin *et al*. reported the stereoselective synthesis of the dioxatricyclic ring system starting from Tobey and Law's 1,3-diketone **97** (Scheme 18).[29] Diels-Alder addition of the commercially available tetrachlorocyclopropene **94** to furan **93** led to the formation of tricyclic adduct **95**, which spontaneously rearranged to form the bicyclic product **96**.[30] Acid hydrolysis of adduct **96** gave diketone **97** as the preferential product, which appeared to exist predominantly as a diketone.



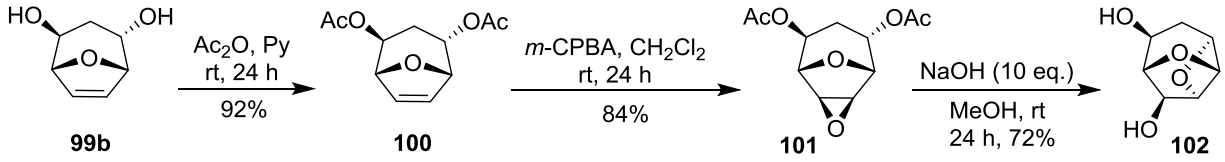
Scheme 18. Synthesis of 8-oxabicyclo[3.2.1]octane core **97**

Due to the presence of the diketone moiety, intermediate **97** was a potentially interesting precursor for the synthesis of bicycle[5.4.0]undecane systems. To synthesise the stereoselective polyhydroxylated cycloheptane derivatives from **97**, reduction of the carbonyl functionalities was required. Due to the high C-H acidity (pK_a ~ 5) in diketone, reduction using complex hydride reagents such as $NaBH_4$ and $LiAlH_4$, suffered from decomposition of the hydrides along with low conversion to diol. Therefore, initially dechlorination of chloro diketone **97** was performed (Scheme 19). Wright and co-workers reported the dechlorination of diketone using zinc under acidic conditions, converting the racemic adduct into a *meso*-compound **98**, which was highly water soluble and readily deprotonated.[31] Upon implementing Wright's conditions, Khlevin achieved the dechloronated diketone which he purified using flash column chromatography. Subsequently, reduction of diketone **98** with $NaBH_4$ in MeOH gave two diastereomeric diols, **99a** and **99b** in 3:2 ratio.



Scheme 19. Reduction of diketone **98**

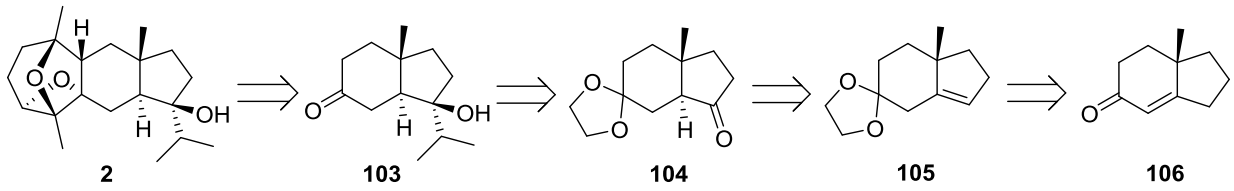
Acetyl protection of the diol **99b** using acetic anhydride in the presence of pyridine gave diacetate **100** which was followed by epoxidation to form epoxide **101** as a single stereoisomer (Scheme 20). Under basic conditions, **101** was converted to tricyclic oxetane diol **102** with a structure similar to the dictyoxetane analogues investigated by Hoffmann.



Scheme 20. Synthesis of oxetane diol **102**

1.4 Synthetic studies towards the *trans*-hydrindane ring system

In 2012, Grainger proposed *trans*-hydrindanone **103** as a potential intermediate in dictyoxetane synthesis.[32] Further retrosynthetic analysis suggested that **103** could be prepared from known enone **106** (Scheme 21).



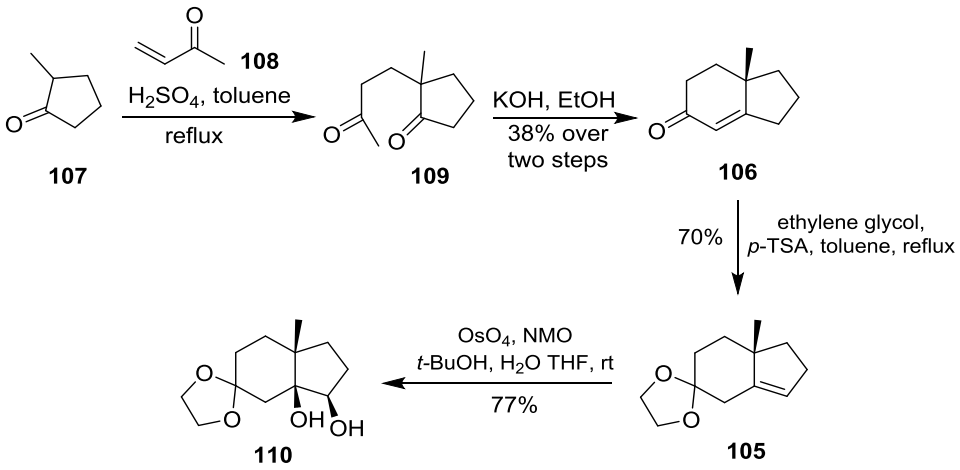
Scheme 21. Retrosynthetic analysis of *trans*-hydrindanone **103**

Initially, the synthesis of enone **106** was performed *via* a two-step Robinson annulation, following Rao's protocol (Scheme 22).[95] Conjugate addition of 2-methylpentanone **107** to MVK **108** under acidic conditions was followed by a base-mediated intramolecular aldol reaction and dehydration, giving cyclohexenone **106** in an improved yield of 38%.

Acetalisation of the α,β-unsaturated carbonyl moiety of **106** using ethylene glycol in the presence of a catalytic amount of *p*-TSA gave acetal **105** in 70% yield with the expected double bond migration as originally reported by Fernholz and Stavely (Scheme 22).[33]

In 1937, Fernholz and Stavely presented the migration of the enone double bond upon acetal formation.[33] The location of the double bond in cyclic systems can be influenced by the strength of an acid. The use of a strong acid such as *p*-TSA ($pK_a < 1$) favours double bond migration whereas an acid of lower acidity ($pK_a \sim 3$) such as acetic acid does not result in double bond migration.

Diol **110** was obtained through dihydroxylation of **105** under Upjohn conditions using OsO_4 in the presence of NMO. The dihydroxylation was completely diastereoselective.

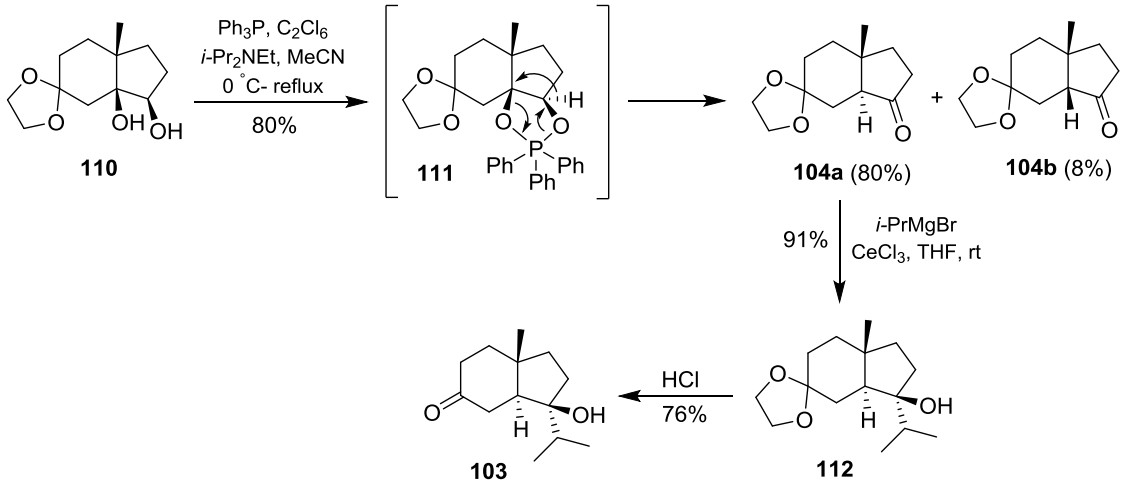


Scheme 22. Diastereoselective synthesis of diol **110**

Treatment of diol **110** with dichlorotriphenylphosphine, generated *in situ* from triphenylphosphine and hexachloroethane, gave cyclic phosphorane **111** as a result of a clean and rapid transformation (Scheme 23).[34] Monitoring the reaction using ^{31}P NMR spectroscopy confirmed the formation of the phosphorane intermediate **111**. Subsequent

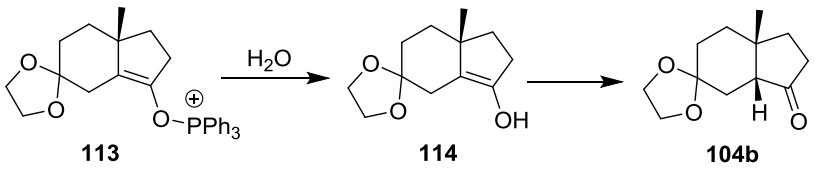
heating gave the *trans*-hydrindanone **104a** in 80% yield *via* a 1,2-hydride migration with the expulsion of $Ph_3P{=}O$.

$CeCl_3$-mediated addition of *i*-PrMgBr to ketone **104a**, *anti* to the methyl group, gave tertiary alcohol **112** in an excellent yield.[35] Acetal hydrolysis of **112** furnished *trans*-hydrindane **103** in 76% yield.



Scheme 23. Stereoselective oxidation-rearrangement approach to *trans*-hydrindane **103**

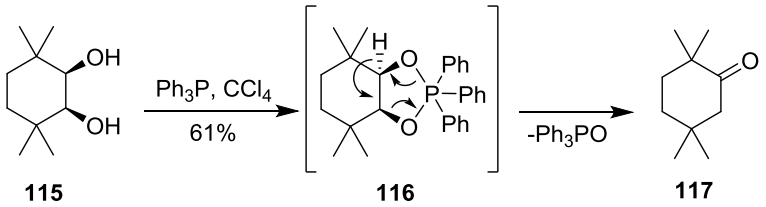
The small amount of *cis*-hydrindanone **104b** is formed by hydrolysis of enol phosphonium **113** to the corresponding enol **114** and subsequent tautomerisation leads to a thermodynamically favoured *cis*-structure **104b** (Scheme 24).



Scheme 24. Formation of *cis*-hydrindanone **104b**

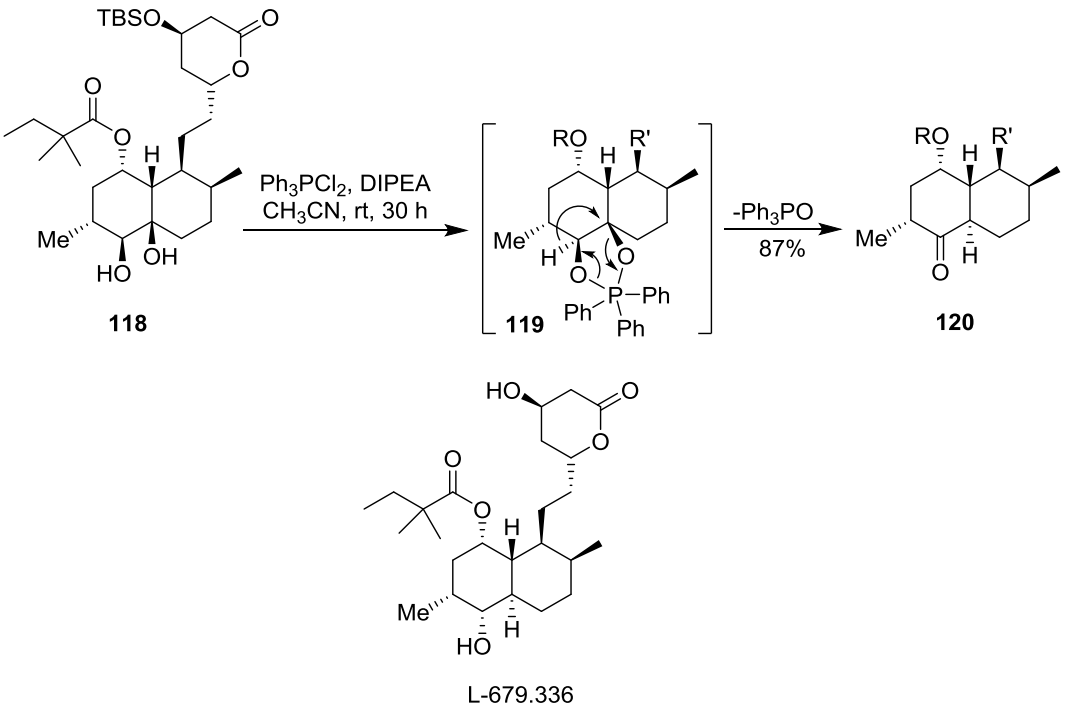
1.4.1 Phosphorane-mediated semipinacol rearrangement

Applequist (1972) reported a semipinacol rearrangement by treating *cis*-diol **115** with PPh_3 in CCl_4, giving cyclic phosphorane **116** (Scheme 25).[36] Though this intermediate was not isolated, 1,2-hydride migration furnished ketone **117**.



Scheme 25. Semipinacol rearrangement to form ketone **117**

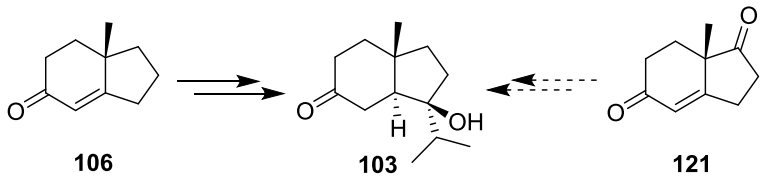
In 1991, Decamp and Mills reported the synthesis of L-679.336, a cholesterol-reducing drug using this type of semipinacol rearrangement (Scheme 26). Diol **118** was transformed into ketone **120** by treating with triphenylphosphine dichloride, formed *in situ* from PPh_3 and hexachloroethane in combination with Hünig's base, furnishing ketone **120** in 87% yield.



Scheme 26. Phosphorus-mediated semipinacol rearrangement

1.5 Asymmetric approaches to hydrindanone and the Hajos-Parrish ketone

Hydrindanone **106** is a key intermediate in the Grainger approach to the *trans*-hydrindane ring system **103** of dictyoxetane (Section 1.4).[32] This section will firstly describe approaches to the preparation of **106** in enantiomerically enriched form, which may be useful in future research directed towards an asymmetric synthesis of the natural product (Scheme 27). The enantioselective synthesis of the Hajos-Parrish ketone **121**, which has not been used in the synthesis of **106** but is a common starting point in the synthesis of steroids and terpenoids and a potential precursor to **106** and/or **103**, is then described.[37]



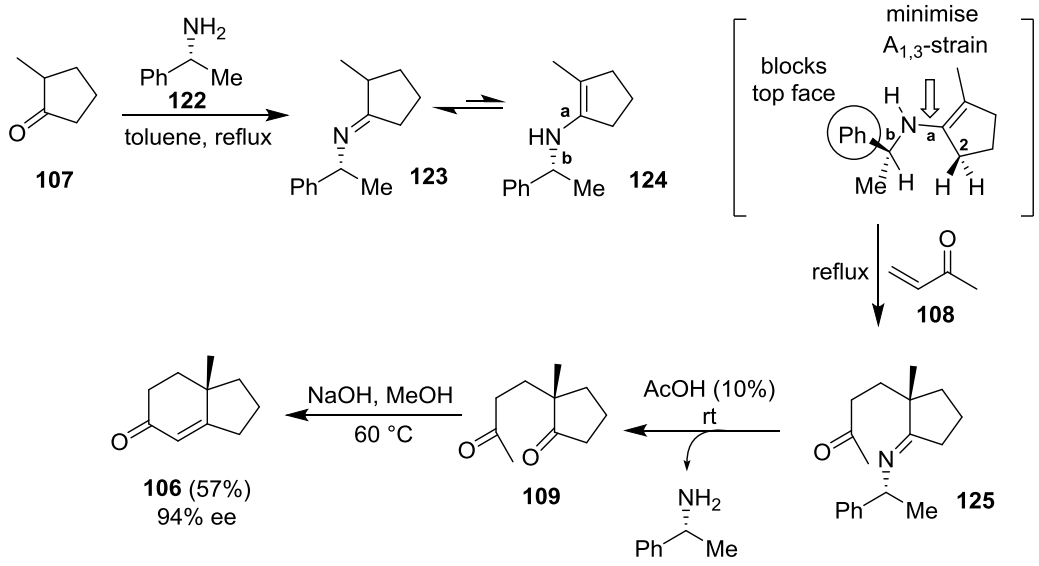
Scheme 27. Two approaches to *trans*-hydrindanone **103**

The mechanism to form the hydrindanone ring system *via* Robinson annulation involves nucleophilic attack of a ketone enolate *via* a Michael reaction on to a vinyl ketone to produce an intermediate Michael adduct which followed by subsequent aldol-ring closure and dehydration forms a bicyclic enone (Section 1.4). Whilst the Robinson annulation has been used extensively in organic synthesis, this approach has some disadvantages in terms of yields, regioselectivity and stereoselectivity. To avoid these limitations, the one-pot Robinson annulation has provided better yields and selectivity.

1.5.1 Asymmetric synthesis of hydrindanone using a chiral auxiliary

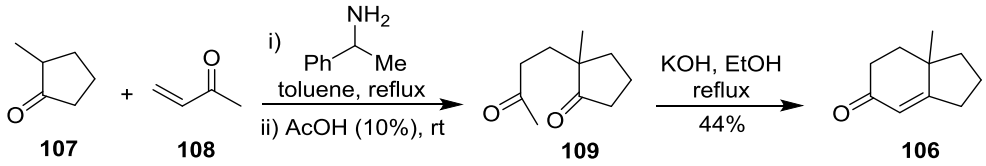
In 1996, Azerad presented the enantioselective synthesis of hydrindanone **106** through a Michael-type alkylation of chiral imines with methyl vinyl ketone (Scheme 28).[38] Condensation of (*R*)-(+)-α-methylbenzylamine **122** with 2-methylcyclopentanone **107** *via* azeotropic removal of water gave ketimine **123** which was first reported by Pfau *et al*. in 1985.[39] (*R*)-(+)-α-Methylbenzylamine **122** is an inexpensive chiral auxiliary amine which can be recovered without any loss of optical purity. To synthesise enone **106**, firstly the Michael addition of enamine **124**, as a reactive nucleophilic species in tautomeric equilibrium with the chiral ketimine **123,** on methyl vinyl ketone **108** led to the adduct **125**. Hydrolysis of **125** with AcOH (10%) furnished diketone **109** which was then converted to enone **106** through

base-induced cyclisation. Although no rationale is provided in the paper, the selective formation of **125** is consistent with a model whereby the conformations about the two C-N bonds are as shown. It is proposed that the phenyl group blocks the top face and also the conformation around bond b is confined to minimise the steric hindrance with the C-2 hydrogens.



Scheme 28. Asymmetric Robinson annulation to form hydrindanone **106**

The desired enone **106** was obtained with 94% ee in 57% overall yield starting from 2-methylcyclopentanone **107**. Repetition of this approach in the Grainger group using racemic *α*-methylbenzylamine led to diketone **109** (Scheme 29). Intramolecular aldol reaction followed by elimination of water in ethanolic KOH gave racemic bicyclic ketone **106** in 44% yield.

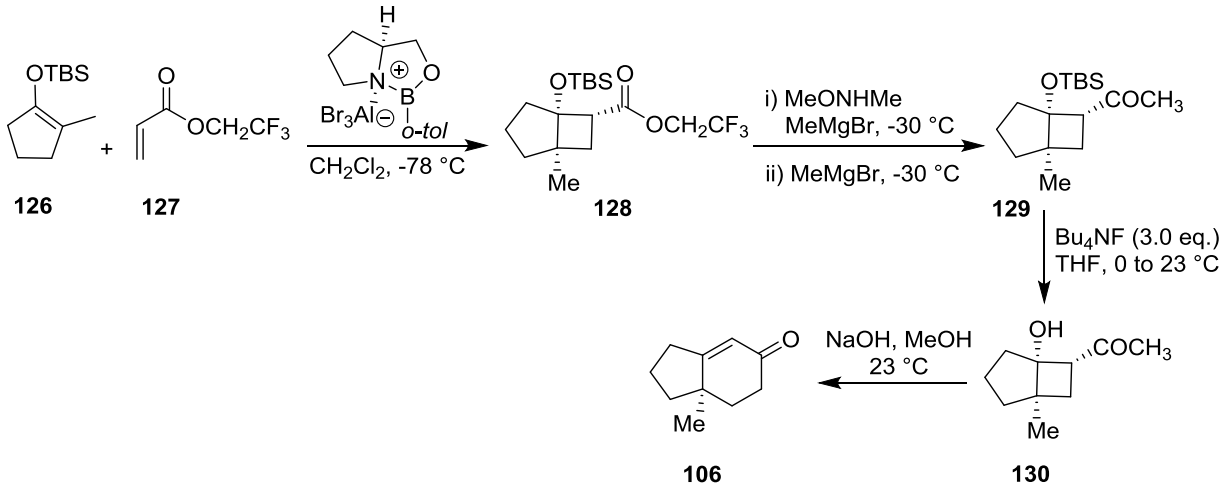


Scheme 29. Preparation of enone **106**

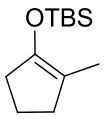
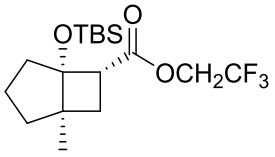
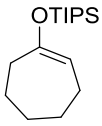
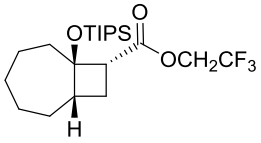
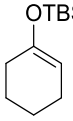
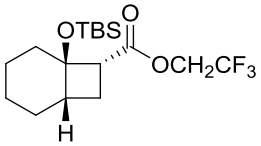
1.5.2 Catalytic asymmetric [2+2]-cycloaddition reaction to form hydrindanone 106

In 2007, Canales and Corey reported a catalytic [2+2]-cycloaddition process starting with silyl enol ether derivatives of various ketones to form bicyclic [2+2]-adducts which could be used as precursors in the synthesis of enantiomerically pure hydrindanones (Scheme 30).[40] The oxazaborolidine-aluminium bromide complex, generated *in situ*, catalysed the reaction of silyl enol ethers and α,β-unsaturated esters to obtain [2+2]-adducts.[41]

The Michael addition of silyl enol ether **126** to trifluoroethyl acrylate **127** led to the bicyclic [2+2]-adduct **128**. Treatment of adduct **128** with the magnesium amide generated *in situ* from *N,O*-dimethylhydroxylamine furnished the Weinreb amide which was followed by Grignard addition of methylmagnesium bromide to form the corresponding methyl ketone **129** through a one-pot process. The enone **106** was formed through desilylation of **129** followed by a base-induced retro aldol-cyclisation sequence. To explore the scope of the reaction, they applied this procedure to the formation of enantiomerically pure enones (Table 2). As shown in Table 2, the selectivity was higher for TIPS-enol ethers than for TBS-enol ethers and in each instance, the *endo* esters predominated.



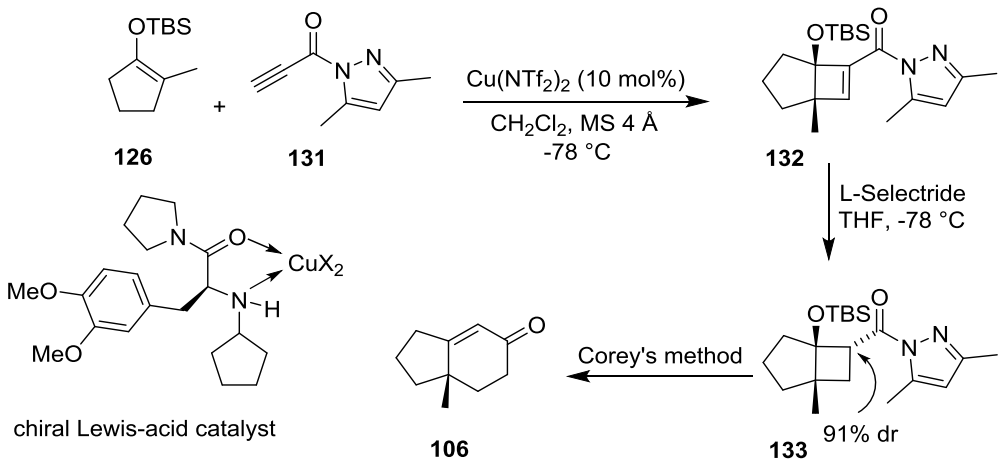
Scheme 30. Enantioselective [2+2] cycloaddition approach to enone **106**

Entry	Enol ether	Product	Time (h)	Yield (*endo*:*exo*)	ee
1		 *exo*	0.5	99 (%) (1:99)	98%
2		 *endo*	4	91 (%) (99:1)	98%
3		 *endo*	6	97 (%) (82:18)	92%

Acrylate to enol ethers with 10 mol% of catalyst in CH_2Cl_2 at -78 °C

Table 2. Enantioselective [2+2]-Cycloaddition

An alternative enantioselective [2+2] cycloaddition reaction with propiolamide derivatives catalysed by a Cu(II)•-3(2-naphthyl)-L-alanine amide complex was reported by Ishihara and Fushimi in 2008 (Scheme 31).[42] The bicyclic [2+2] adduct **133** could act as a very useful chiral intermediate to be transformed into the enantiomerically pure hydrindanone **106**. They proposed that the metal centre of the Cu(II)-complex was key in generating the asymmetric environment to induce the enantioselective reaction. Ishihara presented a stepwise mechanism, through a Michael addition of the propiolamide **131** to the *re*-face of silyl enol ether **126** to afford the intermediate adduct **132** with 73% ee in 80% yield. The Michael reaction was conducted in the presence of 4 Å molecular sieves in order to activate the Cu(II)-complex and also to prevent the hydrolysis of the terminal alkyne functionality. To form the enantiopure hydrindanone **106**, they followed Corey's procedure starting from the intermediate adduct **133**.



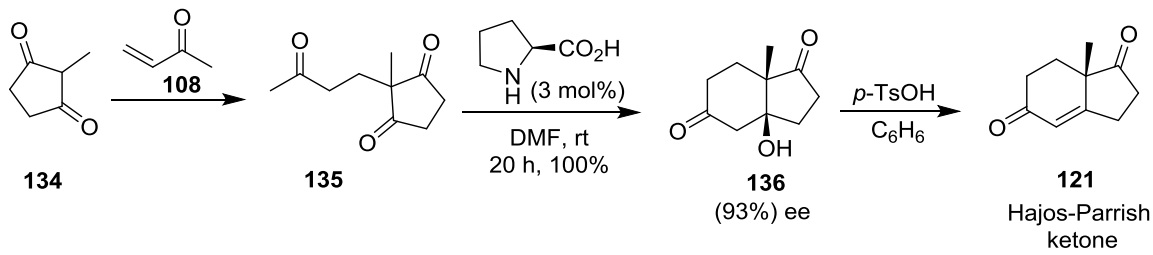
Scheme 31. Enantioselective [2 + 2] cycloaddition to form the hydrindanone **106**

1.5.3 Hajos-Parrish ketone 121

The Hajos-Parrish ketone **121** is an important intermediate in the total synthesis of natural products.[37] In order to synthesise enantiomerically pure compounds, the organocatalysed asymmetric Robinson annulation has been investigated.[43] The original procedure to form the ketone **121** involves the nucleophilic attack of cyclic diketone **134** on to a vinyl ketone **108** to produce the prochiral triketone **135** as an intermediate Michael adduct (Scheme 32).[44] Subsequent intramolecular aldol type ring closure followed by acid-catalysed dehydration affords the annulation product **121**.

1.5.3.1 Proline-catalysed asymmetric synthesis of ketone 121

The enantiopure Hajos-Parrish ketone **121** can be made *via* a proline-catalysed asymmetric Robinson annulation. In the early 1970s, Hajos and Parrish discovered proline to be an effective organocatalyst in asymmetric transformations such as the intramolecular aldol reaction for the synthesis of enone **121**.

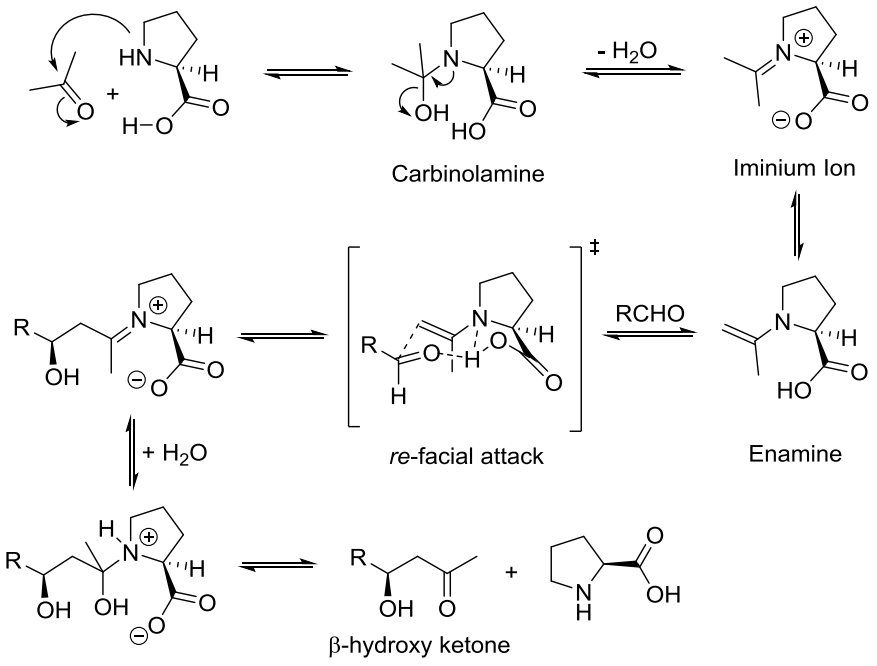


Scheme 32. L-proline-catalysed intramolecular aldol reaction for the synthesis of Hajos-Parrish ketone **121**

Proline, the organocatalyst of this reaction, is a bifunctional secondary pyrrolidine-based amino acid. It is an inexpensive, non-toxic, chiral molecule which is available in both enantiomeric forms. This makes it an important molecule in asymmetric catalysis.

1.5.3.2 Mechanism and computational studies

Despite the fact that the L-proline catalysed intramolecular aldol condensation formed the Hajos-Parrish ketone **121**, debates continued about the mechanism of the reaction. In 1964, Rutter proposed an L-proline-catalysed asymmetric aldol reaction based on aldolase-type approach which involves carbinolamine, iminium ion and enamine-based transformations (Scheme 33).[45] The key intermediate of the intermolecular asymmetric aldol reaction is an enamine formed between L-proline and the corresponding donor substrate.



Scheme 33. Rutter's proposed enamine mechanism of the L-proline-catalysed aldol reaction

To generate the enamine, the pyrrolidine functionality in proline acts as a nucleophile and attacks the carbonyl moiety to yield the carbinolamine, which after dehydration, forms the iminium ion. The enamine attacks the carbonyl functionality of the aldehyde with high enantiofacial selectivity, provided by a highly organised H-bonded framework similar to a chair-like metal-free Zimmerman-Traxler transition state. This proposed mechanism reveals the importance of both a base and an acidic proton in the organocatalyst.

The suggested mechanism by Rutter was considered as an example of a simplified model of a biological system in which L-proline played the role of an enzyme. In 1974, Hajos and Parrish had considered a mechanism for the proline-catalysed asymmetric induction (Figure 7).[44] They believed one of the enantiotopic carbonyl groups in the five-membered ring was activated by proline to give an intermediate carbinolamine followed by the displacement of the proline moiety by nucleophilic attack of the enol from the side chain ketone which led to the cyclisation. This proposed mechanism was rejected by Jung in 1976 because it requires retention of configuration in an S_N2 like process.[46] In 1983, Agami *et al.* proposed a two-proline-molecule mechanism based on observed non-linear effects in asymmetric catalysis.[47] According to Agami, a second proline might be involved in intramolecular proton transfer from the acid to the enamine or in the conversion of the iminium to the enamine. However, a reinvestigation of this result by List and co-workers showed that the non-linear effect was not observed.[45] In 1999, heterogeneous aldolisation on the surface of crystalline proline, based on the solubility problem of proline in organic solvents was proposed by Swaminathan.[48]

In order to obtain insight into how asymmetric catalysis with proline works, Houk *et al*. considered the one-proline enamine model which explained the observed enantioselectivity based on both experimental evidence and computational modelling studies.[49]

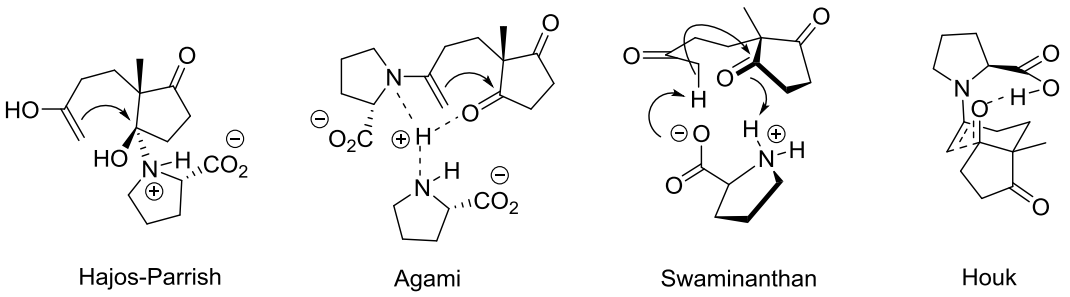


Figure 7. Proposed mechanisms and transition state models for the Hajos-Parrish reaction

This proposed model is the commonly recognised transition state for the Hajos-Parrish reaction. Computational studies revealed the possibility of two chair transition states located for the reaction of the enamine generated from triketones to form (*S*,*S*) and (*R*,*R*)-β-hydroxy ketones (Figure 8).[50] The formation of the (*S*,*S*)-*cis*-β-hydroxy ketone intermediate is preferred over (*R*,*R*)-*trans*-β-hydroxy ketone in primary and secondary amine-catalysed aldol reactions. The more favourable electrostatic interaction between the carbonyl moiety in the five-membered ring and the electron-rich enamine π-bond and also the stability of the *cis*-hydrindanone ring system relative to the *trans*-hydrindanone are the result of this preference. The transition state leading to the (*S*,*S*)- *cis*-β-hydroxy ketone has a lower energy barrier than the (*R*,*R*) one. In the (*R*,*R*) transition state, there is considerable distortion of the iminium double bond away from planarity as a result of an intramolecular hydrogen-bonding interaction of the carboxylic acid group of proline and the forming alkoxide oxygen. Additionally, this large distortion in transition state (*R*,*R*) is a consequence of conformational constraints forced by the hydrindanone ring system.

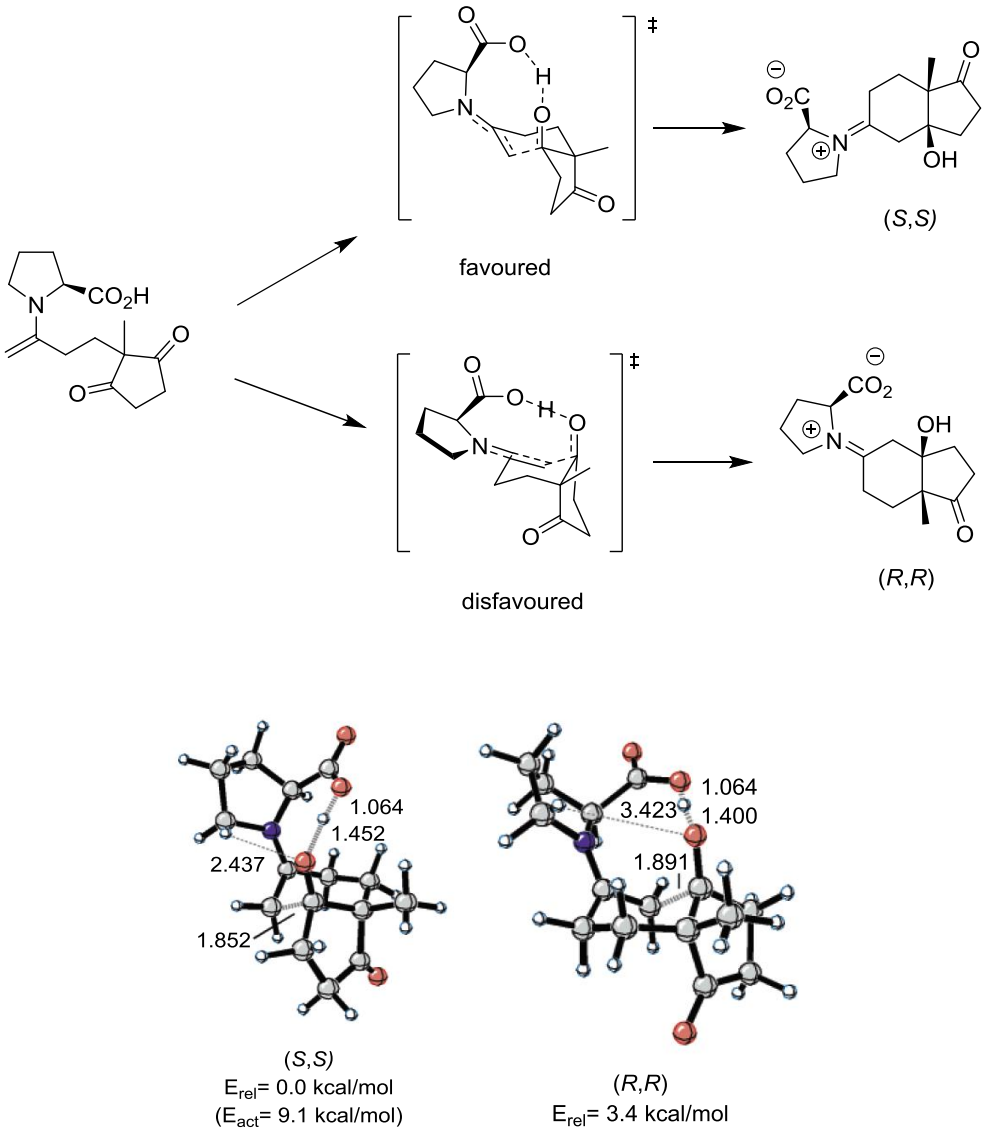
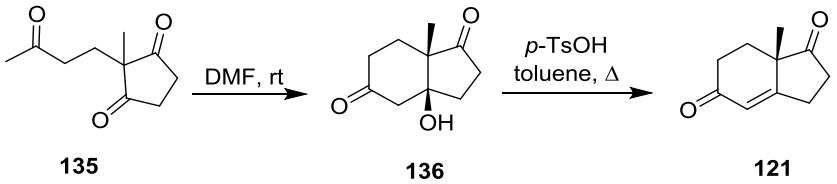


Figure 8. Transition states for the L-proline-catalysed Hajos-Parrish reaction[50]

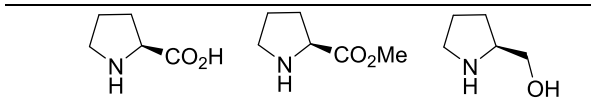
1.5.4 Alternative amine catalysts in asymmetric synthesis of ketone 121

Though L-proline remains the most commonly used catalyst in the intramolecular aldol reaction, this traditional method to cyclic enones still encounters some difficulties in terms of using a high boiling point solvent, long reaction times and multiple recrystallisations to achieve an enantiomerically pure product. In 2004, Hanessian and co-workers investigated

the reactivity of proline derivatives for their ability to catalyse the asymmetric induction.[51] As shown in Table 3,[52] similar results were obtained using *S*-prolinol **138** and *S*-proline methyl ester **137**; both produced the enone **121** in 17% ee. Notably, *cis*-(2*S*,4*S*,4*S*)-4,5-methanoproline **139** in comparison to L-proline showed high enantioselectivity when producing enone **121** in 93% ee and good chemical yield whereas catalysis with *trans*-(2*R*, 4*R*, 5*R*)-methanoproline **140** proceeded at a slower rate, forming the enone **121** with 83% enantiomeric excess. Some highly enantioselective catalysts, with a primary amino moiety, L-phenylalanine **142** and (*S*)-α-methylbenzylamine **141** have been used to form ketone **121** with high chemical yield and 25% and 45% ee respectively.

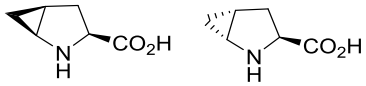


135 **136** **121**

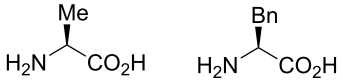


L-proline
93% ee

137 (17%) ee **138** (17%) ee



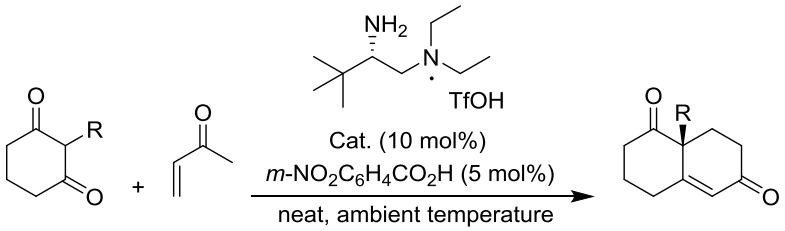
139 (93%) ee **140** (83%) ee



141 (45%) ee **142** (25%) ee

Table 3. Examples of the catalytic asymmetric synthesis of ketone **121**

In 2012, Luo and co-workers presented a simple chiral primary tertiary diamine catalyst derived from an α-amino acid to be an effective catalyst for the Hajos-Parrish reaction (Scheme 34).[43] Additionally, this readily available catalyst is a liquid which allows the reaction to be conducted under solvent-free conditions, resulting in a faster reaction when compared to one conducted in solution.



Scheme 34. Tertiary amine-catalysed asymmetric synthesis

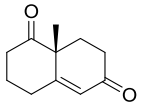
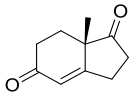
Entry	Product	Time (h)	Yield	ee
1	 Wieland-Miescher ketone	12	95%	92%
2	 Hajos-Parrish ketone	12	95%	96%

Table 4. Asymmetric synthesis of diketones

To investigate the applicability of the primary amine catalyst in the Robinson annulation and to explore the scope and limitations, Luo and co-workers examined the practical use of this catalyst for the Hajos-Parrish and Wieland-Miescher reactions, starting with different triketones as a model to obtain the cyclic enones. They found that this primary amine catalyst in concert with TfOH had good reactivity and high enantioselectivity. They suggested that the addition of a weak *m*-nitrobenzoic acid in the presence of TfOH could significantly

enhance the conversion of the intermediate triketone to the Hajos-Parrish and Wieland-Miescher ketones. As shown in Table 4, this catalyst was applied to the synthesis of ketone **121**, affording an excellent chemical yield and a highly enantiopure ketone.

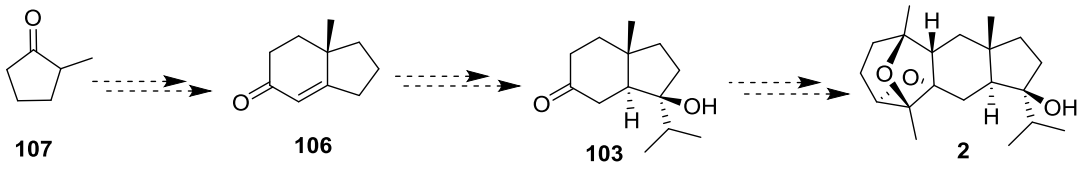
1.6 Summary

Asymmetric approaches to enone **106** are known but there are some limitations such as the cost of the starting material and the low yield for the Robinson annulation. In comparison, the Hajos-Parrish ketone **121** is relatively easy to prepare as a single enantiomer, however it contains additional oxygenation in the cyclopentanone ring which is not required for dictyoxetane synthesis and methodology for the selective deoxygenation of **121** to **106** is currently not known.

1.7 Aims and objectives

The overall aim of this project is the total synthesis of dictyoxetane **2** from the *trans*-hydrindane **103** previously prepared in the Grainger group and to establish the absolute configuration of the natural product through an asymmetric synthesis. At the outset of this project, there were two initial objectives towards this goal.

Firstly, there is a need to improve the synthesis of the *trans*-hydrindane core of dictyoxetane (Scheme 35).



Scheme 35. Preparation of **103**

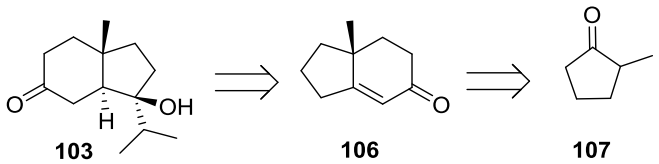
Current limitations of this route are the cost of the starting material 2-methylcyclopentanone **107** and its use in a low-yielding Robinson annulation to form enone **106**. Chapter 2 of this thesis describes approaches to overcoming these limitations, and in particular, the use of the Hajos-Parrish ketone in an asymmetric synthesis of **103**.

The second objective is to develop a synthesis of the dioxatricyclic ring system suitable for use in converting *trans*-hydrindanone **103** to dictyoxetane **2**. To date, no examples have been reported of a dioxatricyclic ring system fused to a cyclohexane ring, as found in dictyoxetane itself. Chapter 3 describes four approaches to this problem using ring-closing metathesis, ring-expansion, [4+3] cycloaddition and a [5+2] annulation as key steps.

Chapter two: Improved synthesis of the *trans*-hydrindane core of dictyoxetane

2.1 Aims and objectives

The potential intermediate in the synthesis of dictyoxetane, *trans*-hydrindanone **103**, was reported by the Grainger group in 2012 starting from enone **106** (Chapter 1, Section 4).[32] However, there are some limitations in this route to enone **103**. The low-yielding Robinson annulation of 2-methylcyclopentanone **107** is a particular limitation of this synthesis and consequently large quantities of **107** would be required for the route to be scaled up (Scheme 36). Although this ketone is commercially available, it is expensive and so the initial objective of this work was to prepare this ketone on large scale. If successful, alternative methods to improve the Robinson annulation would then be investigated.



Scheme 36. Proposed retrosynthesis of *trans*-hydrindane **103**

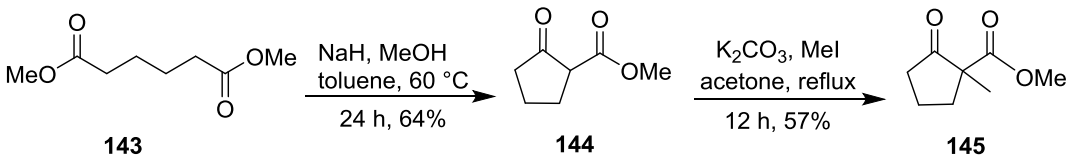
2.2 Results and Discussion

2.2.1 Synthesis of starting materials

2.2.1.1 Synthesis of ketone 107

In 2011, Davies and co-workers described the use of dimethyl adipate **143** in a large-scale Dickmann reaction (Scheme 37).[53] Following Davies's protocol, β-keto ester **144** was successfully prepared in 64% yield on a multigramme-scale (6.0 g), comparable with the yield reported in the literature. The reaction was performed on a large scale (6.0 g); therefore an

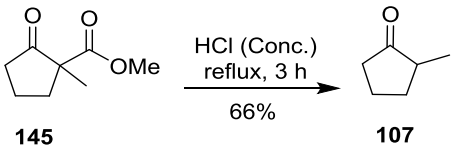
overhead stirrer was needed to obtain a homogenous suspension. Alkylation of **144** with MeI in the presence of K_2CO_3 gave β-keto ester **145** in 88% yield, comparable with the 91% reported in the literature.[53]



143 **144** **145**

Scheme 37. Preparation of β-keto ester **145**

β-Keto ester **145** was subsequently employed in an acid-catalysed hydrolysis-decarboxylation process reported by Rao *et al*. in 1994 to form ketone **107** (Scheme 38).[54] This ketone is a highly volatile compound and required purification through bulb-to-bulb vacuum distillation to afford the product in 66% yield which was lower than the 98% reported in the literature. There were some limitations associated with the scaling up of the reaction to produce **107**, principally that the reaction could not be carried out on scales larger than 6 g.



145 **107**

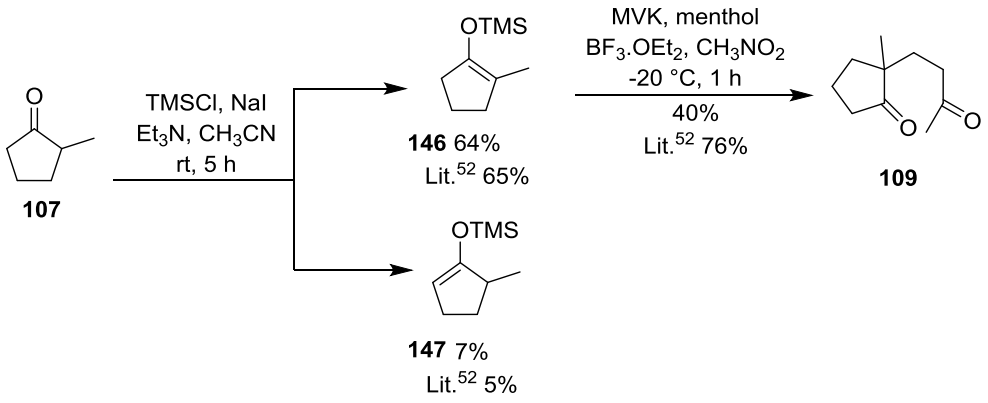
Scheme 38. Synthesis of ketone **107**

2.3 Synthesis of *trans*-hydrindanone 103 starting from ketone 107

To synthesise bicyclic enone **106**, several conditions were investigated. In 1992, Duhamel *et al*. reported the Robinson annulation of **107**, starting from silyl enol ether **146** (Scheme 39).[55] Boron trifluoride-catalysed Michael addition of the silyl enol ether **146** to MVK in the

presence of an alcohol provided diketone **109**. Following the literature procedure, silyl enol ether **146** was first prepared using TMSCl in the presence of NaI. Purification by column chromatography resulted in silyl group hydrolysis; however, distillation gave **146** in 64% yield.

The ^{1}H NMR spectrum of **146** showed the presence of 7% of regioisomer **147**. Subsequent Michael addition of **146** to the reactive electrophile generated from the combination of MVK, menthol and $BF_3.OEt_2$ produced diketone **109** in 40% yield. Monitoring the reaction by t.l.c. indicated hydrolysis of **146** under these conditions. This approach to enone **106** was abandoned due to the volatility of **146** and the relatively low yield of diketone **109**.

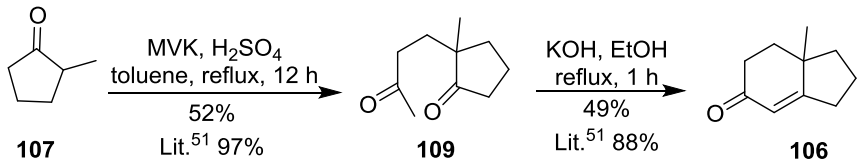


Scheme 39. Synthesis of diketone **109**

In order to overcome the difficulties incurred from the previous route, an alternative route to enone **106** was investigated. The literature presented a two-step Robinson annulation starting from ketone **107** (Scheme 40).[54] The conjugate addition of ketone **107** to MVK under acidic conditions reportedly gave diketone **109** in 97% yield which was then subjected to an aldol reaction without further purification. A base-mediated intramolecular aldol condensation followed by dehydration, gave hydrindanone **106** in an overall 88% yield.

However, previous repetition of this synthesis in the Grainger group had resulted in a yield of 38% for 5,6-fused bicyclic enone **106**.

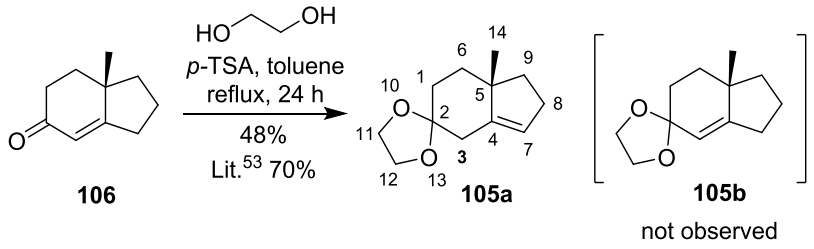
Attempts were made to optimise the Robinson annulation following Rao's conditions. The use of freshly distilled MVK had little effect on the Michael addition to prepare diketone **109**. Monitoring the reaction by t.l.c. always revealed the presence of enone **106** along with diketone **109** after the Michael addition. Therefore, it was decided to remove the solvent and take the crude diketone **109** through to the aldol-dehydration step. Subsequent treatment of **109** with KOH gave cyclohexenone **106** in an improved yield of 49% compared to that previously obtained in the Grainger group.



Scheme 40. Robinson annulation to form hydrindanone **106**

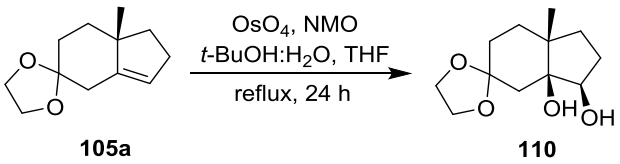
According to the previous work in the group, reacting α-β-unsaturated ketone **106** with 5.54 equivalents of ethylene glycol in the presence of a catalytic amount of *p*-TSA formed the acetal **105a** in 77% yield in which double-bond migration had occurred to the 5-membered ring (Scheme 41).[56] However, repetition of this procedure gave the isolated acetal **105a** in a 48% yield.

^{1}H-^{13}C HMBC analysis of the product showed a correlation between the quaternary carbon of the acetal moiety and the methylene proton at position 3, confirming formation of **105a**. Enone **106** was not fully consumed in the reaction after 24 h, as observed by t.l.c. analysis.



Scheme 41. Acetal formation and alkene migration

Following the literature precedent, dihydroxylation of alkene **105a** was carried out under Upjohn conditions to produce the corresponding diol **110** (Scheme 42).[32] Initially, the reaction was performed at room temperature. Monitoring the reaction by t.l.c. showed only the presence of **105a** after 48 h. Despite this lack of success, it was decided to investigate the effect of temperature on the reaction (Table 5). The results obtained from the temperature screens showed that increasing the temperature from room temperature up to 36 °C and from room temperature to 65 °C gave the desired diol **110** in improved 24% and 57% yields (Entries 2 and 3). Diol **110** was, as expected, obtained as a single diastereoisomer. It is proposed that *syn* dihydroxylation occurs from the less hindered face of the double-bond at the ring junction, on the same side as the methyl group. Alkene **105a** was also not completely consumed.

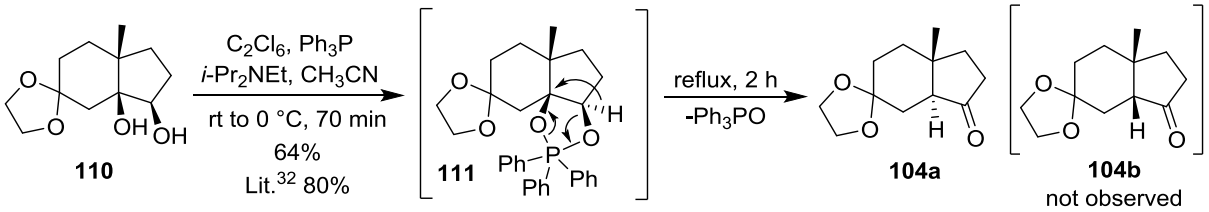


Scheme 42. Dihydroxylation under Upjohn conditions

Entry	Scale (mmol)	Temperature	Time (h)	Yield
1	0.15	rt	48	-
2	1.44	36 °C	72	24%
3	1.48	65 °C	48	57%

Table 5. Attempts to convert alkene **105a** to diol **110**

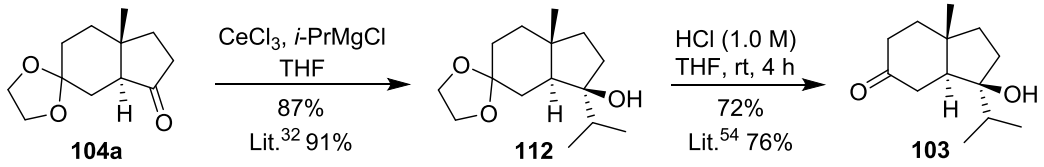
Previous X-ray analysis of a derivative had confirmed the stereochemistry of diol **110**.[32] According to the previous work in the group, diol **110** was employed in a semipinacol-type rearrangement with *in situ*-generated Ph_3PCl_2 giving *trans*-hydrindanone **104a** in 65% yield (Scheme 43), lower than the previously reported 80%. The *cis*-hydrindanone **104b** was not observed.



Scheme 43. Preparation of *trans*-hydrindanone **104a**

Previous research in the group reported that Grignard addition to ketone **104a** in the presence of anhydrous $CeCl_3$ gave the tertiary alcohol **112** in 91% yield (Scheme 44). Unfortunately, repeating this work showed no conversion of the starting material **104a** to **112** by t.l.c. analysis. The effect of temperature and different conditions was therefore investigated, varying from room temperature to 50 °C (Table 6). When the reaction was attempted with 5.0 equivalents of Grignard reagent in the absence of $CeCl_3$, no reaction was observed after 48 h (Table 6, Entry 1). The effect of temperature was investigated, varying from room temperature up to 50 °C, and **112** was isolated in 30% yield while the unreacted

ketone **104a** was recovered in 55 % yield (Entry 2). Use of 10.0 equivalents of the Grignard reagent had a moderate effect on the yield (Entry 3). It was then decided that the commercially available anhydrous $CeCl_3$ might not be of sufficient quality, so anhydrous $CeCl_3$ was prepared from the heptahydrate form by heating *in vacuo*. In practice, 6.0 equivalents of Grignard reagent were mixed with 2.0 equivalents of fresh dehydrated $CeCl_3$ prior to the addition of ketone **104a**. Attempted Grignard addition at 50 °C gave **112** in 58% yield after 48 h (Entry 4). When the reaction was attempted at room temperature in the presence of 3.0 equivalents of Grignard reagent and 2.0 equivalents of freshly dehydrated $CeCl_3$ prior to the addition of ketone **104a**, by generating an organocerium reagent, full conversion of ketone **104a** was observed. The tertiary alcohol **112** was achieved in 87% yield, which is comparable with the 91% yield reported in the literature (Entry 5). It is proposed that the methyl group blocks the top face and the nucleophilic attack to the carbonyl functionality occurs from the lower face of **104a**. Subsequent acetal hydrolysis of **112** afforded the *trans*-hydrindane core of dictyoxetane **103** in 72% yield.[57]



Scheme 44. Synthesis of *trans*-hydrindane **103**

Entry	Reagents	Temperature	Time (h)	Yield
1	*i*-PrMgCl (5.0 eq.)	rt	48	-
2	*i*-PrMgCl (6.0 eq.)	rt to 50 °C	48	30%
3	*i*-PrMgCl (10.0 eq.)	rt to 50 °C	48	45%
4	*i*-PrMgCl (6.0 eq.), $CeCl_3$ (2.0 eq.)	rt to 50 °C	48	58%
5	*i*-PrMgCl (3.0 eq.), $CeCl_3$ (2.0 eq.)	rt	7	87%

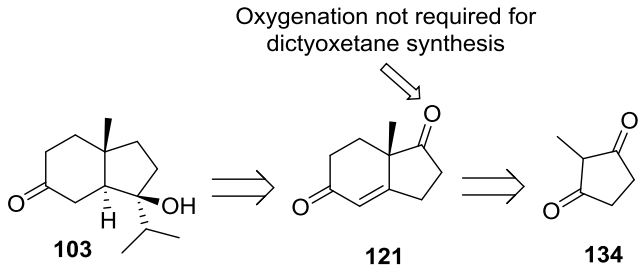
Table 6. Attempted Grignard addition

2.4 Summary

Limitations were encountered in the synthesis of the *trans*-hydrindanone ring system **103** following the previous route established by the Grainger group. Difficulties such as scaling up the formation of 2-methylcyclopentanone **107** and the low yield of Robinson annulation led to an alternative route for the creation of ketone **103** intermediate being devised.

2.5 Alternative approach to *trans*-hydrindane 103 from Hajos-Parrish ketone 121

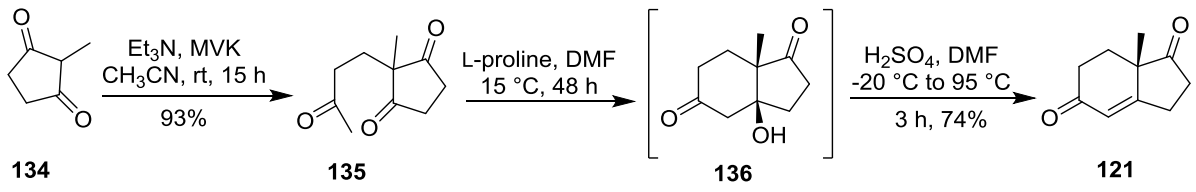
An alternative route to ketone **103** was devised, starting from ketone **121**, to overcome the drawbacks of the former route (Scheme 45). Following this alternative route introduces an unneeded carbonyl functionality in the 5-membered ring of **121**, which would require removal at some stage. However, advantages of this approach include high reported yields for the Robinson annulation and the potential for asymmetric synthesis of *trans*-hydrindane **103**.



Scheme 45. An alternative retrosynthesis of *trans*-hydrindane **103**

2.5.1 Synthesis of Hajos-Parrish ketone 121

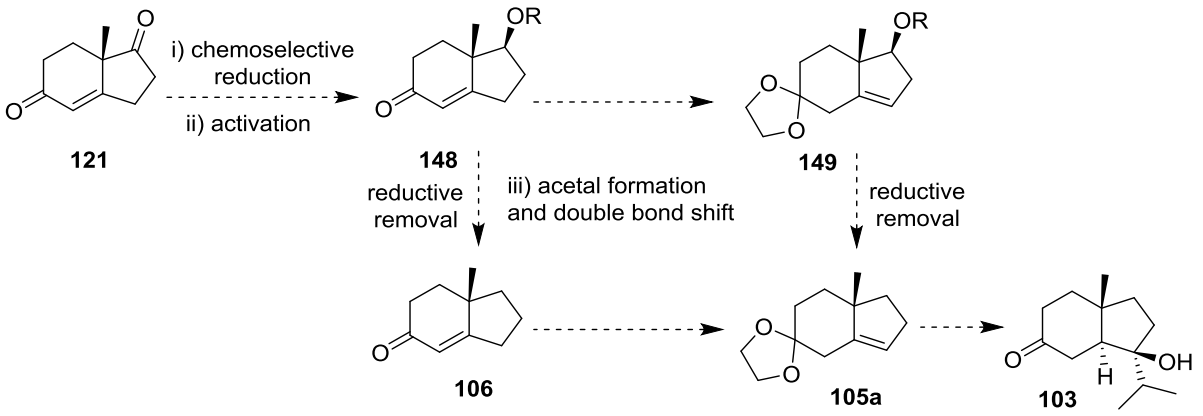
The enone **121** was synthesised *via* an L-proline-catalysed intramolecular aldol reaction and subsequent dehydration as demonstrated by Hajos and Parrish in 1974 (Scheme 46). Triketone **135** was prepared through conjugate addition of diketone **134** to MVK under basic conditions giving the desired porduct in 93% yield. The triketone **135** was subsequently employed in an L-proline-catalysed intramolecular aldol reaction to form the β-hydroxy ketone **136** which was followed by dehydration to access **121** in 74% yield over the two steps.[44] HPLC analysis confirmed that the enantiomeric ratio after recrystallisation of ketone **121** barely increased to 99.71:0.28 (er) from that obtained before recrystallisation, 99.41:0.58 (er), but the yield decreased to 67%. So, it was decided to carry out the procedure without recrystallisation.



Scheme 46. Proline-catalysed intramolecular aldol reaction for the synthesis of the Hajos-Parrish ketone **121**

2.6 Synthetic route to *trans*-hydrindane 103 from ketone 121

The Hajos-Parrish **121** ketone has a carbonyl functionality present in the 5-membered ring which is not required in dictyoxetane **2**. Two different approaches from ketone **121** to enone **103** were envisaged (Scheme 47). Key to these approaches would be the compatibility of the activated alcohol **148** to the acetal formation and double bond shift, or the enone **106** to its reductive removal. Different strategies were considered for the reductive removal of the hydroxyl moiety. A stable activating group which was compatible to migration of the double bond was initially sought which could subsequently be removed by deoxygenation.

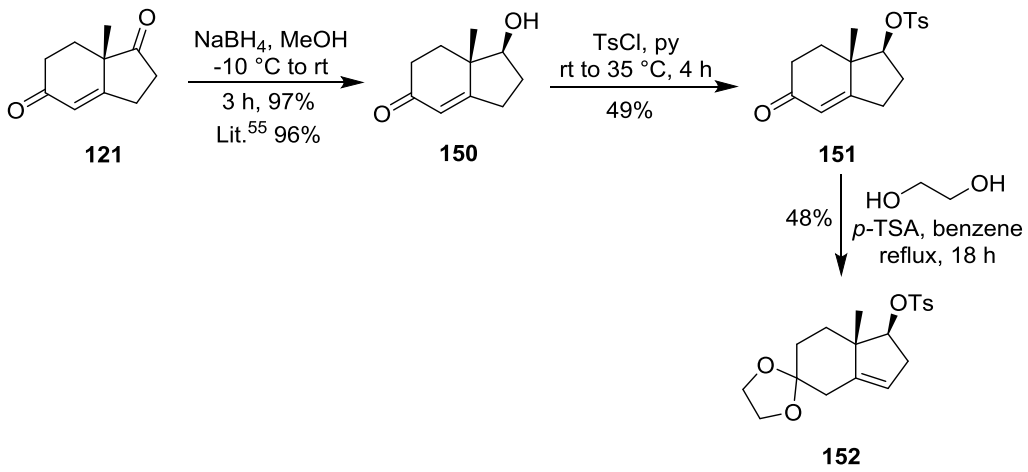


Scheme 47. Proposed deoxygenation to form alkene **103** from ketone **121**

In 1985, Foster and Rees reported the selective reduction of the carbonyl moiety in the 5-membered ring of ketone **121** using $NaBH_4$ to form the alcohol **150** in 96% yield (Scheme 48).[58] Attempted selective reduction using 0.27 equivalents of $NaBH_4$ gave **150** in 97% yield, comparable with the yield reported in the literature. Monitoring the reaction by t.l.c. suggested the presence of a single diastereoisomer which was confirmed by NMR spectroscopy. The stereochemistry at the new alcohol stereocentre was initially assigned

based on literature precedent, and subsequently confirmed by X-ray analysis on a subsequent product.

With alcohol **150** in hand, the use of a tosyl activating group was initially investigated. Treatment of hydroxy enone **150** with 1.6 equivalents of TsCl in pyridine gave **151** in 49% yield after 18 h.[58] Alcohol **150** was also always recovered under these conditions. Following a literature procedure, enone **151** was subjected to acetal formation with ethylene glycol in the presence of a catalytic amount of *p*-TSA giving the novel compound **152** with the expected double bond migration in 48% yield.[56]



Scheme 48. Acetal formation and double-bond migration of tosyl **152**

X-ray analysis of acetal **152** confirmed the stereochemistry of the ketone reduction and the double-bond migration (Figure 9).

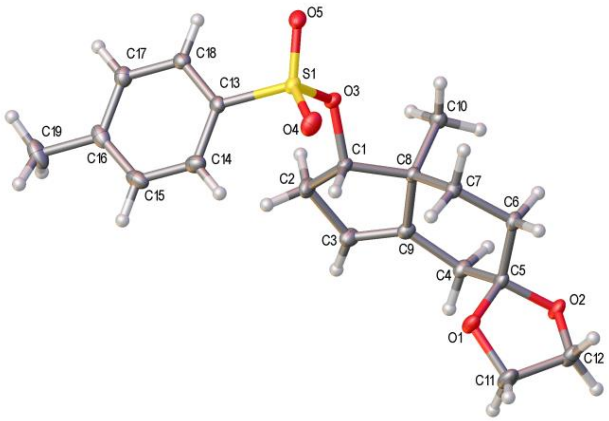
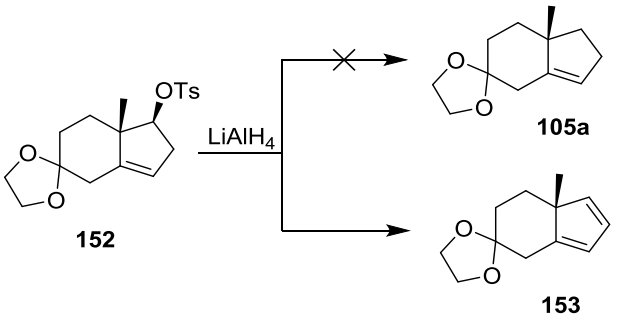


Figure 9. X-ray structure of acetal **152**

The reduction of tosylate **152** was attempted using $LiAlH_4$ as a reducing agent (Scheme 49).[59] Treatment of tosylate **152** with 2.0 equivalents of $LiAlH_4$ gave no reaction in THF after 72 h, as confirmed by t.l.c. analysis (Table 7, Entry 1). Increasing the amount of the reducing agent afforded no improvement and starting material **152** was again recovered (Entry 2). It was decided to investigate the effect of higher boiling point solvents. No reaction occurred when 4.0 equivalents of $LiAlH_4$ were used in refluxing dioxane (Entry 3). Use of diglyme unexpectedly gave the diene **153**, the product of elimination, rather than the desired reduction product **105a**, in 80% yield (Entry 4).

^{1}H NMR spectroscopic analysis of **105a** showed three olefinic protons at 5.28, 6.27 and 6.33 ppm and ^{13}C NMR spectroscopic analysis also confirmed the presence of three C-H signals in the olefinic region.

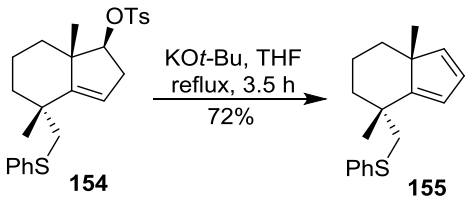


Scheme 49. Failed reduction to alkene **105a**

Entry	Conditions	Yield
1	$LiAlH_4$ (2.0 eq.), THF, reflux, 72 h	-
2	$LiAlH_4$ (4.0 eq.), THF, reflux, 72 h	-
3	$LiAlH_4$ (4.0 eq.), 1,4-dioxane, reflux, 72 h	-
4	$LiAlH_4$ (4.0 eq.), diglyme, reflux, 48 h	**153** (80%)

Table 7. Attempted reduction of **152**

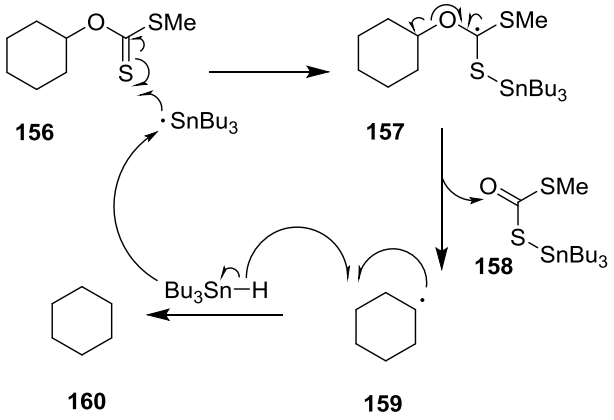
In 1997, Winterfeldt and co-workers reported the elimination of the tosylate **154** under basic conditions to form cyclopentadiene **155** in 72% yield (Scheme 50).[60] Surprisingly, under reductive conditions, the tosylate **154** underwent elimination rather than reduction, although it was not clear what the base was in this case.



Scheme 50. Winterfeldt's elimination of tosylate **155**

Due to the unsuccessful outcome of this reaction, further studies concentrated on radical-mediated reductive removal of secondary alcohol **152**.

Barton and McCombie (1975) were the first to report a radical-mediated removal of alcohols *via* thiocarbonyl intermediates (Scheme 51).[61] According to the classical Barton-McCombie deoxygenation, initiation of the reaction followed by fragmentation gives the secondary carbon-centred radical **159** and the carbonyl by-product **158**. Based on the Barton-McCombie method, tributyltin hydride acts as the hydrogen-atom source and the tributyltin radical, generated from the hydride, serves as the chain carrier. Abstraction of a hydrogen atom by the secondary alkyl radical **159** from tributyltin hydride forms the reduced product **160**.

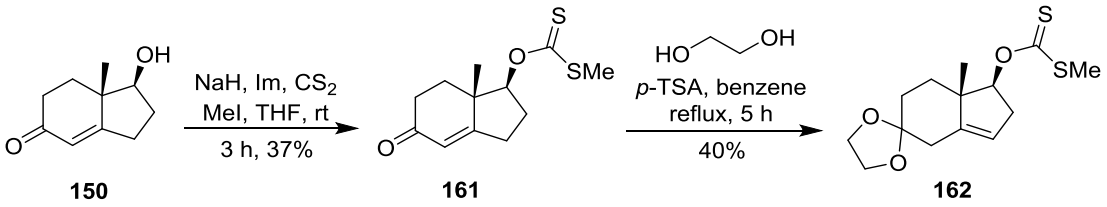


Scheme 51. Barton-McCombie mechanism

Barton and McCombie found that xanthates could be used as convenient precursors for transforming an alcohol into the corresponding alkane. The xanthate **161** was synthesised from nucleophilic addition of secondary alcohol **150** to carbon disulfide followed by methylation, giving **161** in 37% yield while alcohol **150** was recovered in 10% yield (Scheme 52).[62] This result suggests that a significant portion of the alcohol was being consumed in side reactions, indicated by a number of unidentified by-products visible by t.l.c. along with the xanthate **161**. Acetalisation of **161** with ethylene glycol in the presence of catalytic *p*-TSA

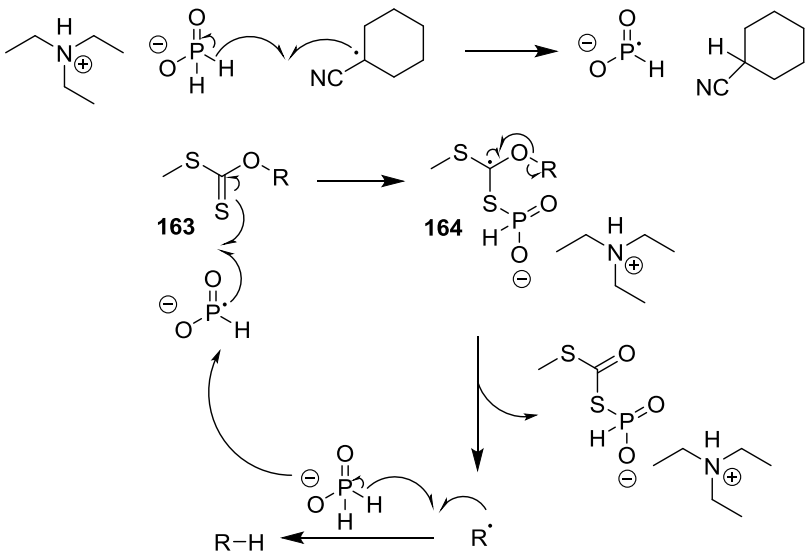
gave the acetal **162** in 40% yield at best. A significant amount of enone **161** was visible by t.l.c. and ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

^{1}H-^{13}C HMBC analysis of **162** indicated the double-bond migration. This result demonstrated the compatibility of the xanthate moiety to the double-bond migration conditions.



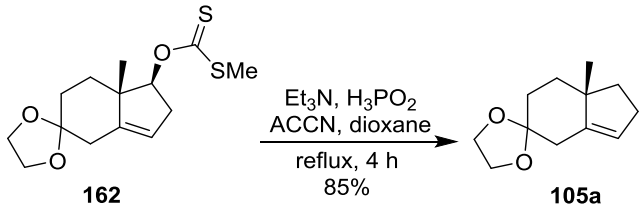
Scheme 52. Acetal protection and double-bond migration of xanthate **161**

Due to the problems associated with the use of the tributyltin hydride, in terms of its toxicity, cost and difficulties encountered in purification, Boivin in 2003 published the successful reductive cleavage of xanthates under tin-free conditions, based on the use of hypophosphorous reagents. The combination of hypophosphorous acid, triethylamine and a radical initiator led to fast and smooth reduction of xanthates.[63] These reactions are initiated with α,α'- azobisisobutyronitrile (AIBN). In practice, it was decided to use ACCN since it is safer and more readily available than AIBN. The mechanism for this reaction is depicted in Scheme 53. In the presence of heat, the ACCN breaks down to generate a carbon-centred radical, which abstracts a hydrogen atom from the hypophosphorous acid-triethylamine salt to facilitate the phosphorous-centred radical anion. This radical anion adds to the xanthate **163** forming the tertiary carbon-centred radical **164**, which fragments to give R• and the phosphorous-containing, water-soluble ammonium salt.



Scheme 53. Mechanism of reduction

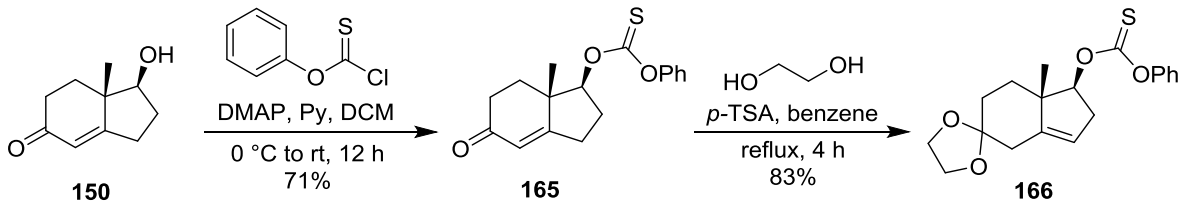
Based on Boivin's conditions, the reductive removal of a xanthate function was attempted by treating xanthate **162** with 5.0 equivalents of aqueous H_3PO_2 and 5.5 equivalents of triethylamine in refluxing dioxane. The reaction was initiated with stoichiometric amounts of ACCN (2.5 eq.) and gave the alkene **105a** in a high 85% yield (Scheme 54).



Scheme 54. Radical-mediated reductive removal of xanthate

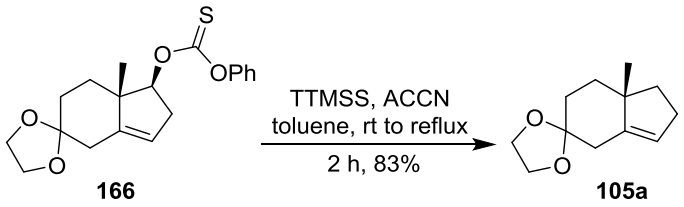
Due to the low yields obtained for xanthate **161** and its subsequent acetalisation, an alternative precursor to the Barton-McCombie reaction was investigated. The thiocarbonyl **165** was easily synthesised from alcohol **150**, in 71% yield (Scheme 55).[64] DMAP was used to make the thionoformate species, a better electrophile for the nucleophilic addition of the alcohol.[64] Following the typical literature procedure, enone **165** was subjected to acetal

formation with ethylene glycol in the presence of a catalytic amount of *p*-TSA giving the novel compound **166** with the concomitant double-bond shift in 83% yield, higher than the 40% obtained with the xanthate functionality.[56]



Scheme 55. Acetal protection and double-bond migration of thiocarbonyl **165**

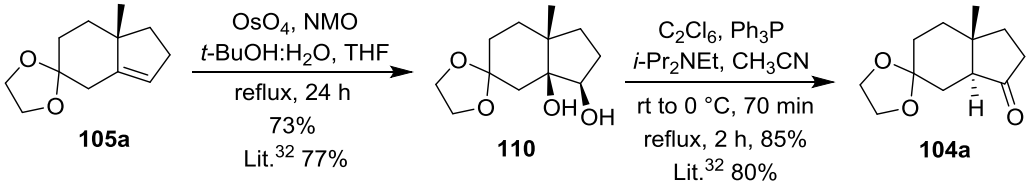
Yorimitsu and Oshima in 2006 published a tin-free radical reduction of the thiocarbonyl moiety using tris(trimethylsilyl)silane as a hydrogen-atom source and ACCN as an initiator.[64] Under these conditions, the reductive removal of the thiocarbonate **166** using stoichiometric amounts of TTMSS and ACCN in refluxing toluene gave alkene **105a** in an 83% yield (Scheme 56).



Scheme 56. Reductive removal of thiocarbonate to alkene **105a**

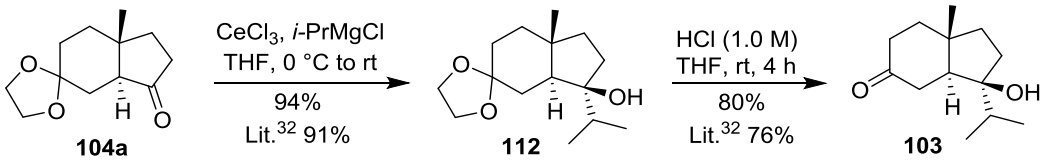
Under improved Upjohn conditions reported for dihydroxylation of alkene **105a** starting from hydrindanone **106**, dihydroxylation of alkene **105a** was carried out to form the corresponding diol **110** in an improved 73% yield (Scheme 57).[32] Treatment of diol **110** with *in situ*-generated Ph_3PCl_2 gave *trans*-hydrindanone **104a** in 85% yield. Use of recrystallised

Ph_3P gave significantly improved yields of ketone **104a**, compared with the commercially supplied material.



Scheme 57. Synthesis of *trans*-hydrindanone **104a**

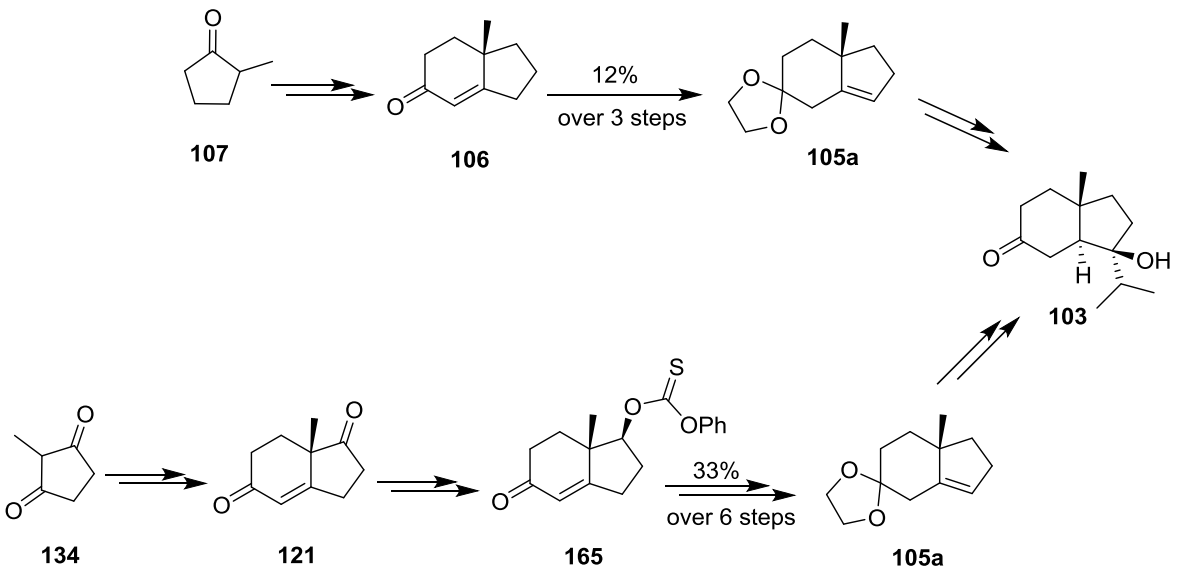
Grignard addition to **104a** in the presence of anhydrous $CeCl_3$ gave full conversion to the tertiary alcohol **112** in 94% yield (Scheme 58). Subsequently, deacetalisation of **112** afforded the *trans*-hydrindane core **103** of dictyoxetane, thus completing the first asymmetric synthesis of this molecule.



Scheme 58. Synthesis of the enantiopure *trans*-hydrindane **103**

2.7 Conclusion

In conclusion, a successful approach to the enantiomerically pure *trans*-hydrindane ring system **103** of dictyoxetane has been developed starting from an L-proline-catalysed asymmetric synthesis of the Hajos-Parrish ketone. This route comprises more steps overall, in comparison to the route starting from ketone **107** (Scheme 59). However by employing this new route better yields and also enantiomerically pure *trans*-hydrindane **103** were achieved.



Scheme 59. Two approaches to *trans*-hydrindanone **103**

Two methods for the tin-free radical-mediated selective deoxygenation of a Hajos-Parrish ketone-derived alcohol *via* thiocarbonyl intermediates have been developed. Both xanthate and thionocarbonate functionalities have been proven to be compatible with acetal formation and double-bond migration.

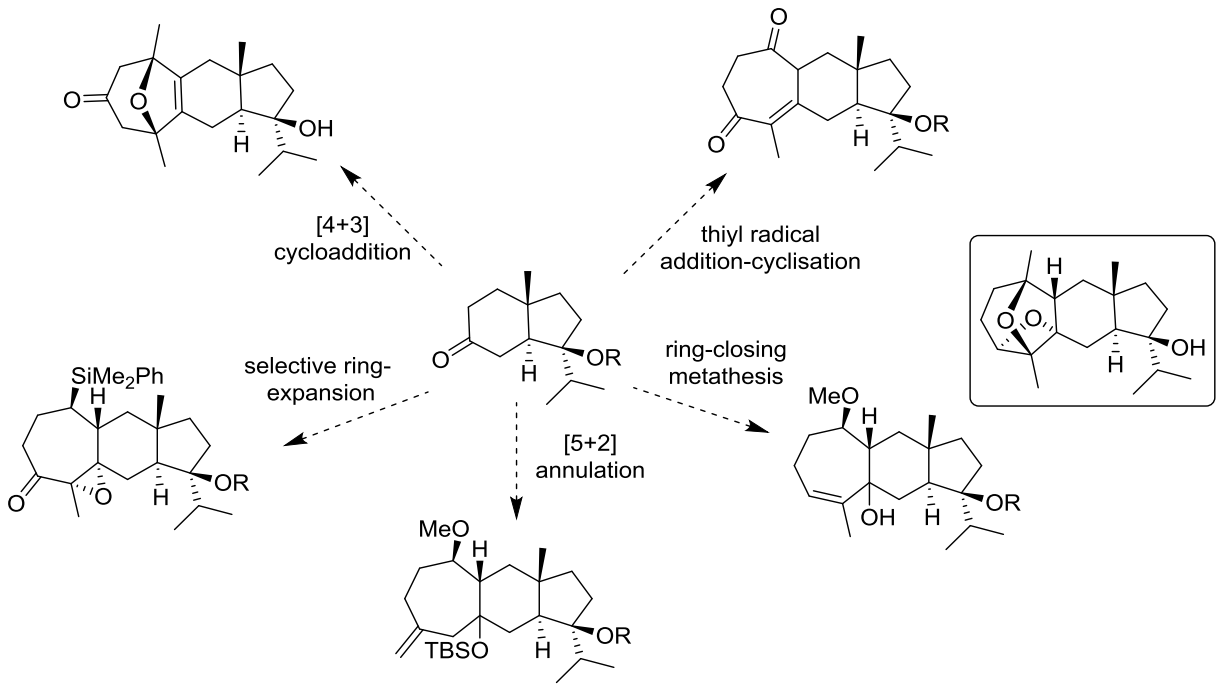
With the *trans*-hydrindanone **103** in hand, Chapter 3 will detail the methodology investigated towards annulation of the dioxatricyclic ring system of the natural product.

Chapter three: Studies towards a new dioxatricyclic ring annulation

3.1 Aims and objectives

With the enantiomerically pure *trans*-hydrindane ring system **103** in hand, the second objective of this project was to investigate a variety of methodologies for 7-membered ring annulation on the cyclohexanone ring. This would allow the methodology to be applied to the synthesis of the dioxatricyclic ring system amenable to use in converting *trans*-hydrindane **103** to dictyoxetane **2**.

To date no examples have been reported of the dioxatricyclic ring system fused to a cyclohexane. In order to synthesise the desired dioxatricyclic subunit of dictyoxetane **2**, five different approaches to form this unique ring system were investigated and are reported in this chapter (Scheme 60).

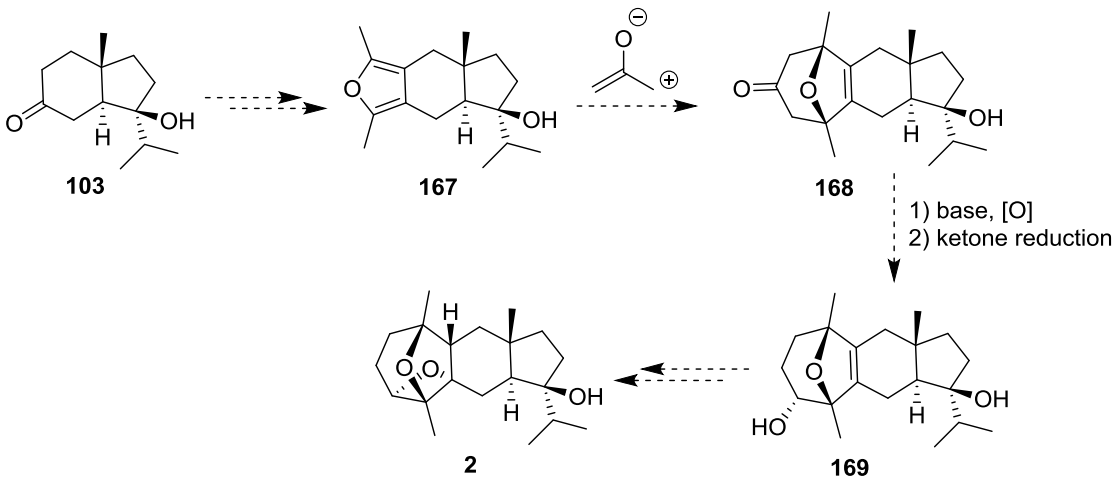


Scheme 60. 5 Approaches to 7-membered ring annulation

3.2 Proposed [4+3] cycloaddition approach to form the dioxatricyclic ring system

3.2.1 Introduction

The [4+3] cycloaddition reaction is an efficient and convergent route to constructing 7-membered rings, which are essential structural subunits in natural products. The proposed synthetic route from *trans*-hydrindane **103** to dictyoxetane **2** is outlined in Scheme 61. Furan annulation of **103** to form **167** was the first to be evaluated. The furan-fused *trans*-hydrindane **167** would undergo selective [4+3] cycloaddition reaction with an oxyallyl cation to form **168**.[28] Regio- and stereoselective α-oxygenation followed by ketone reduction would give alcohol **169**. It was envisioned that dictyoxetane **2** could be prepared from compound **169**.

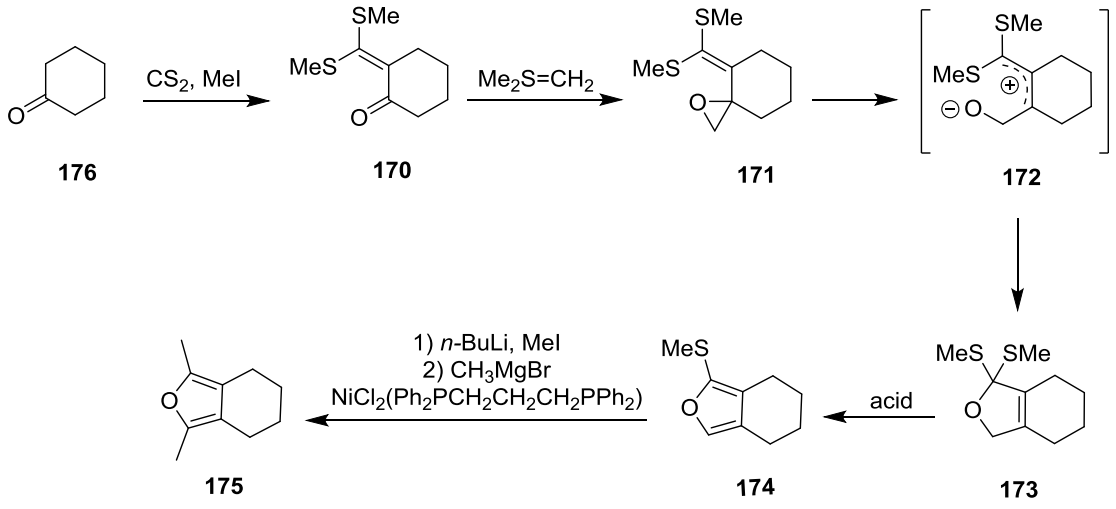


Scheme 61. Proposed synthetic route to dictyoxetane **2**

In order to investigate the possibility of synthesising dictyoxetane **2** *via* a [4+3] cycloaddition reaction, a model system was proposed (Scheme 62). To simplify the stereochemical and

regiochemical issues, the commercially available and inexpensive cyclohexanone **176** was used in place of the *trans*-hydrindanone **103**.

In 1984, Okazaki *et al*. reported the synthesis of tetrasubstituted furan **175** from cyclohexanone **176**.[28] Treating α-oxo ketene dithioacetal **170** with dimethylsulfonium methylide, generated *in situ* from trimethyl sulfonium iodide, initially gave the epoxide **171** followed by conversion into dihydrofuran **173** *via* a zwitterionic intermediate **172**. Acid-mediated elimination of methane-thiol gave furan **174**. The dimethyl-substituted furan **175** was formed by sequential introduction of methyl groups to the 2 position followed by a nickel-catalysed Kumada coupling reaction to methylate at the 5 position of the furan ring.

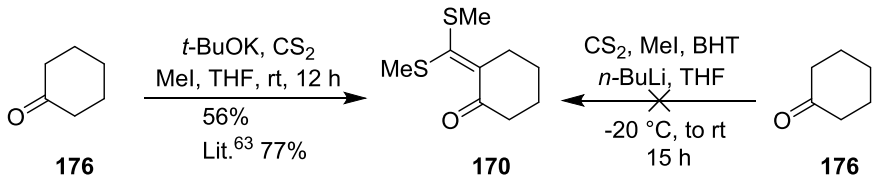


Scheme 62. Okazaki's approach to form tetrasubstituted furan **175**

3.2.2 Results and Discussion

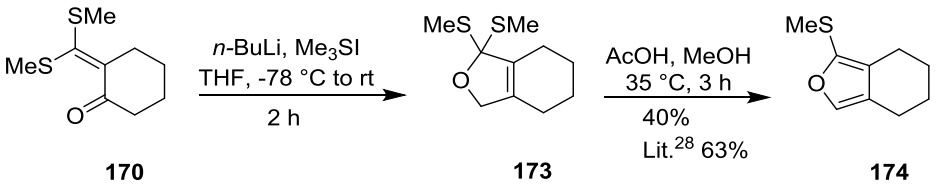
Initial attempts were made to prepare the α-oxo ketene dithioacetal **170** (Scheme 63). Under basic conditions, treatment of ketone **176** with 1.0 equivalent of CS_2 and 2.0 equivalents of MeI furnished the α-oxo ketene dithioacetal **170** in 56% yield, lower than the

77% reported in the literature.[65] Significant amounts of impurities were present, as shown by t.l.c. analysis. An alternative procedure to form **170** involving treating ketone **176** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) and *n*-BuLi at -20 °C gave no reaction.[66]



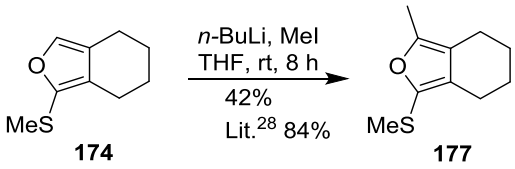
Scheme 63. Formation of α-oxo ketene dithioacetal **170**

With the α-oxo ketene dithioacetal **170** in hand, dihydrofuran **173** formation was attempted (Scheme 64). Purification of compound **173** proved problematic, presumably as a result of its propensity to lose methanethiol, giving 2-(methylthio)furan **174**. Therefore, the crude dihydrofuran **173** was converted to 2-(methylthio)furan **174** in 40% isolated yield over two steps. Impurities were always present in the reaction, as shown by t.l.c. analysis. An alternative method to form 2-(methylthio)furan **174** from **173**, using HCl (2.0 M) in MeOH at 30 °C gave the product **174**, albeit in only 10% isolated yield.



Scheme 64. Synthetic approach to form **174**

2-(Methylthio)furan **174** was subjected to base-mediated methylation with 2.0 equivalents each of *n*-BuLi and MeI in THF, forming **177** in 42% yield (Scheme 65).[28] Some starting material remained along with other unidentified impurities after 8 h.



174 177

Scheme 65. Methylation of **177**

However, due to the overall low yields and difficulties encountered to form tetrasubstituted furan **177**, the dioxatricyclic ring annulation *via* a [4+3] cycloaddition reaction was not attempted.

3.3 Radical cyclisation approach to 7-membered ring annulation

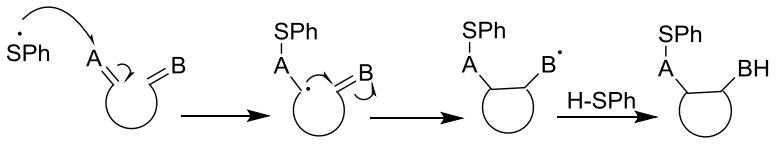
3.3.1 Thiol-mediated intramolecular radical cyclisation

Radical cyclisation is an important method for the synthesis of various cyclic systems *via* intramolecular C-C bond formation. Generally radical reactions are conducted under mild conditions which allow tolerance for sensitive functional groups. To date, most of these reactions have been performed using tin hydride reagents such as tri-*n*-butyltin hydride (*n*-Bu_3SnH) and trimethyltin hydride (Me_3SnH).

However, there are some limitations associated with the use of tin-based radical reagents. Drawbacks include the toxicity of trialkyltin hydrides and difficulties in completely removing tin residues from the reaction mixture. Therefore, the application of tin-based radical reactions has been restricted in the areas of drugs and medicine.

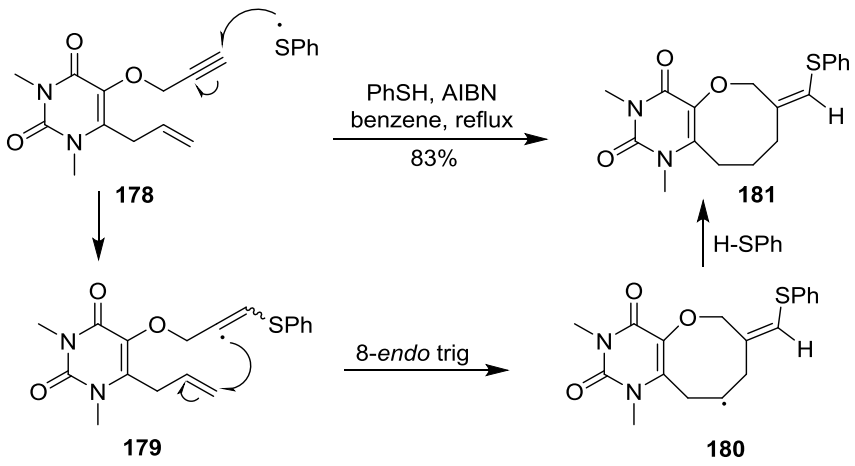
Recently, tin-free methodology based on thiyl radical addition–cyclisation has been developed to construct C-C bonds (Scheme 66).[67] The formation of a carbon-centred radical species generated by the addition of a thiyl radical to an unsaturated bond is the key step in

tin-free radical reactions. The addition of the resulting radical to another multiple bond followed by the abstraction of hydrogen from the thiol furnishes the cyclised product, with regeneration of the thiyl radical.



Scheme 66. Thiol-mediated radical cyclisation approach

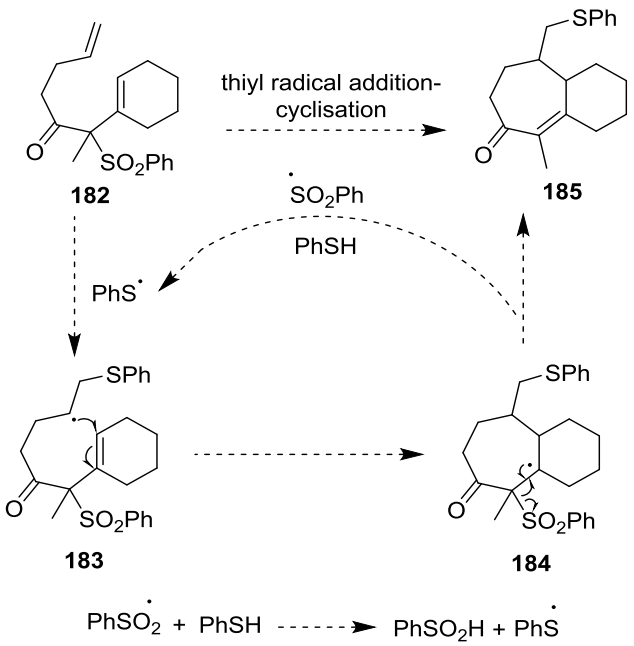
The highly reactive vinyl radical could be generated from the regioselective addition of the thiyl radical at the less hindered position of terminal triple bond. Intramolecular trapping of the vinyl radical intermediate by an adjacent C=C bond would form a carbocyclic ring. Majumdar *et al*. (2007) reported a thiol-mediated regioselective 8-*endo*-trig radical cyclisation (Scheme 67).[68] The thiyl radical, generated from thiophenol and AIBN, was added to the terminal alkyne of enyne **178** to form vinyl radical **179**. Trapping of the intermediary vinyl radical was followed by H-atom abstraction from thiophenol, affording the product **181**.



Scheme 67. Thiyl radical addition-cyclisation to form **181**

3.3.1.1 Proposed approach to 7-membered ring annulation *via* thiyl radical addition-cyclisation

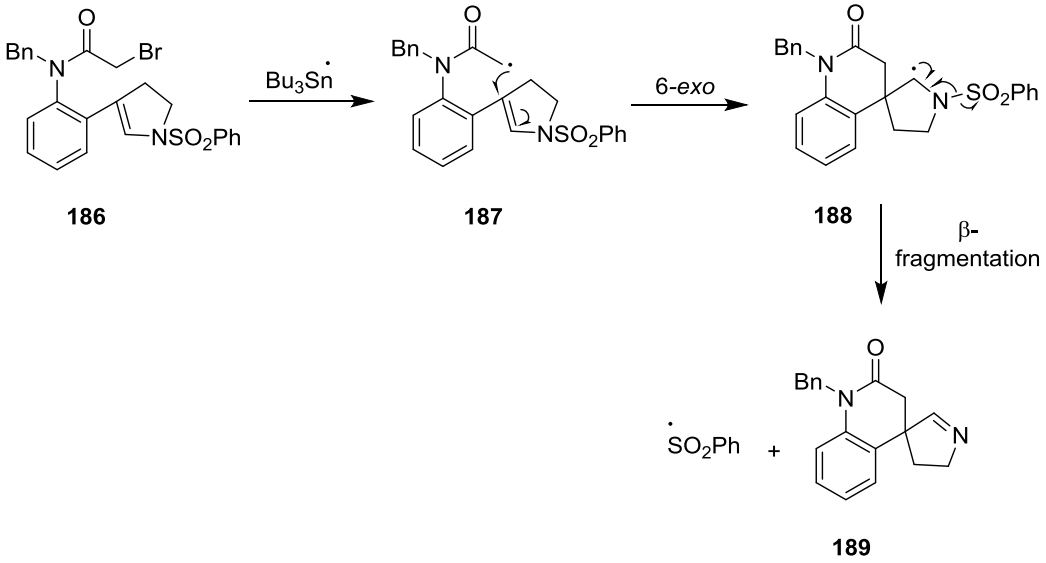
An alternative approach to construct a 7-membered ring on the *trans*-hydrindanone **103** was proposed *via* a thiyl radical addition-cyclisation process (Scheme 68). The proposed mechanism involves the addition of a thiyl radical to the terminus of the double bond in compound **182** to provide alkyl radical species **183**, which could be trapped by the endocyclic double bond to form **184**. β-Sulfonyl radical elimination could form **185** and then re-initiate the catalytic process. Although unprecedented, it was believed that the fragmented β-sulfonyl radical could abstract the hydrogen atom from PhS-H, forming benzenesulfinic acid and the thiyl radical.



Scheme 68. Proposed tandem mechanism for thiyl radical addition-cyclisation-elimination

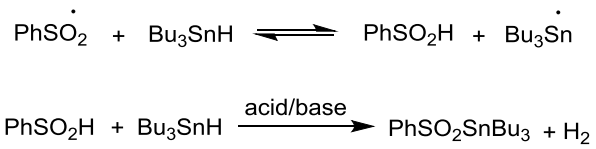
In 2013, Curran and co-workers reported the preparation of imine D **189** *via* cyclisation followed by β-elimination of the sulfonyl radical ($PhSO_2$•) (Scheme 69).[69] Mechanistically, a

tributyltin radical ($Bu_3Sn•$) abstracts bromine from **186** to generate α-amide radical **187**, which undergoes 6-*exo* cyclisation *via* addition to the β-carbon of the ene sulfonamide.



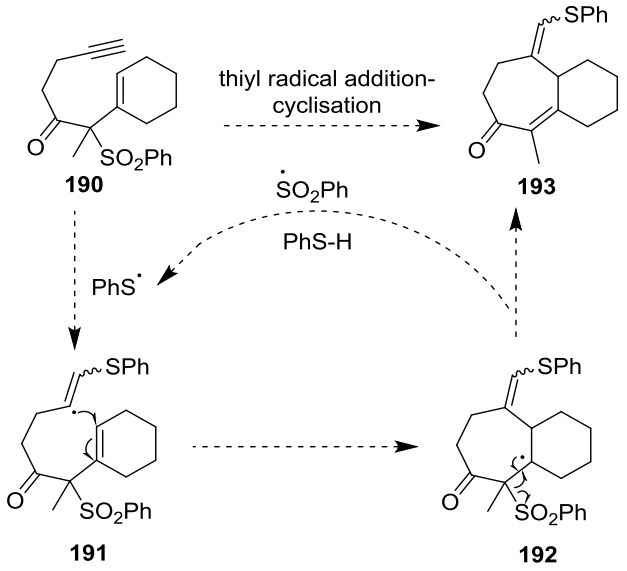
Scheme 69. β-Sulfonyl radical elimination to form **189**

According to Curran, there are two possible subsequent reactions for the generated phenylsulfonyl radical (Scheme 70). A possibility would be the hydrogen-atom abstraction from tin hydride, generating tributyltin radical ($Bu_3Sn•$) and benzenesulfinic acid ($PhSO_2H$). The unstable sulfinic acid could then undergo an acid/base reaction.



Scheme 70. Possible fates of the tin and sulfur reaction components

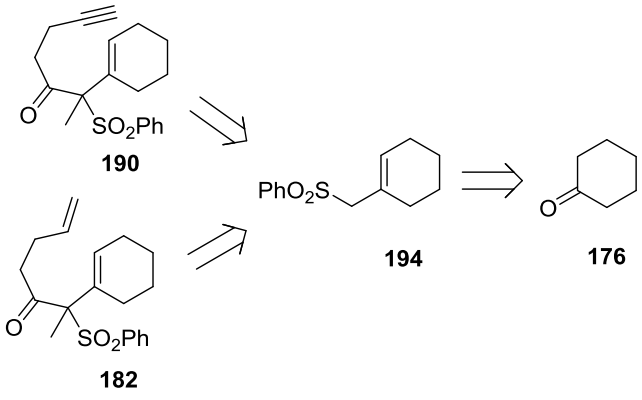
The second approach to 7-membered ring annulation is outlined in Scheme 71. **193** was proposed to furnish *via* thiyl radical addition-cyclisation followed by sulfonyl radical fragmentation.



Scheme 71. Alternative radical reaction to 7-membered ring annulation

As previously described, the addition of the thiyl radical to the terminal triple bond in compound **190** would provide the vinyl radical **191**.[67] This radical could be trapped by an alkene to form **192** along with the sulfonyl radical elimination, forming **193**.

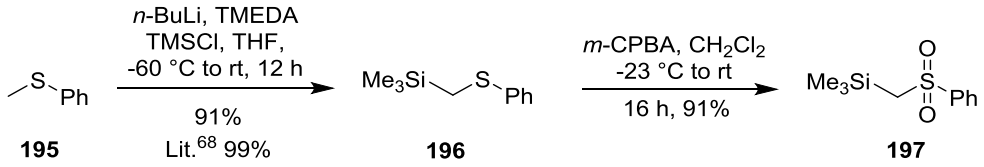
It was proposed that ketones **190** and **182** could be prepared *via* acylation/methylation of allyl sulfone **194**, which could be accessed from cyclohexanone **176** (Scheme 72).



Scheme 72. Proposed approaches to prepare ketones **190** and **182**

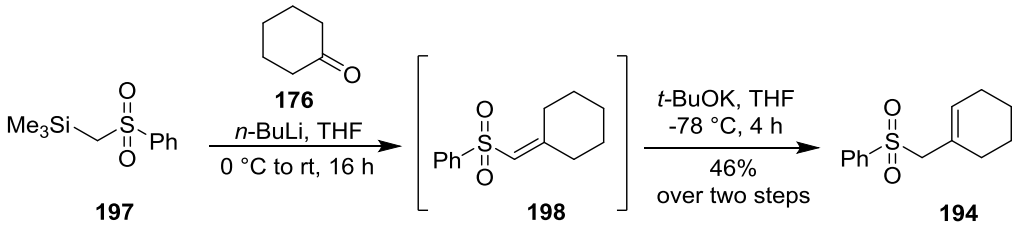
3.3.1.2 Results and Discussion

Initial attempts were made to synthesise the allyl sulfone **194** starting from thioanisole **195**. The α-trimethylsilyl sulfide **196** was synthesised *via* deprotonation of **195** using *n*-BuLi in the presence of freshly distilled TMEDA followed by silylation with TMSCl, giving **196** in an excellent yield, under Ley's conditions (Scheme 73).[70] Oxidation of α-silyl sulfide **196** with 2.5 equivalents of purified *m*-CPBA at -23 °C gave the α-silyl sulfone **197** in 91% yield.[71]



Scheme 73. Preparation of phenyl trimethylsilyl sulfone **197**

The synthesis of vinyl sulfone **198** was attempted starting from α-silyl sulfone **197** (Scheme 74). In 1983, Ley and Simpkins reported a modified Peterson olefination of aldehydes and ketones using **197** to prepare vinyl sulfones.[72] The generated anion from compound **197** reacts with cyclohexanone **176** at -78 °C to form vinyl sulfone **198**. Successful results were achieved using 1,2-dimethoxyethane (DME) as the solvent.



Scheme 74. Synthesis of allyl sulfone **194**

In practice, repetition of the experiment at -78 °C gave no reaction in DME, instead starting material was recovered (Table 8, Entry 1). In order to establish optimum reaction conditions,

the effects of solvent and temperature were examined. Attempted reaction using THF at -78 °C gave the vinyl sulfone **198** in modest yield (Entry 2). Increasing the temperature from -78 °C up to 0 °C furnished the desired product in an improved 74% yield after 16 h (Entry 3). At this stage, there was no evidence of the allyl sulfone **194** by t.l.c. analysis.

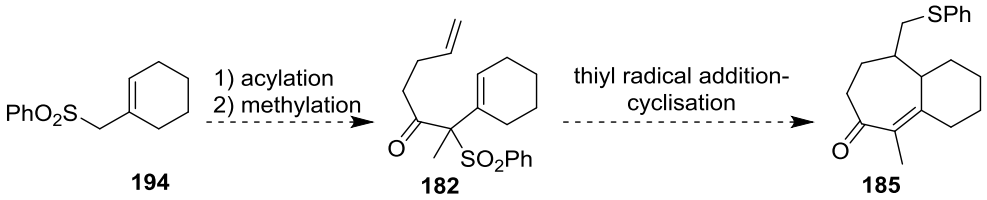
Entry	Solvent	Time	Temperature	Yield (**198**)
1	DME	4 h	-78 °C	-
2	THF	6 h	-78 °C	20%
3	THF	16 h	0 °C to rt	74%

Table 8. Attempted allyl sulfone formation

Allyl sulfones are known to be more thermodynamically stable than their vinylic counterparts. Therefore, the crude reaction mixture of vinyl sulfone **198** was treated with *t*-BuOK at -78 °C in THF, generating the allyl sulfone **194** in 46% yield over the two steps.[73]

^{1}H NMR spectroscopic analysis recorded a new olefinic proton peak at 5.33 ppm and CH_2 protons at 3.67 ppm corresponding to the exocyclic CH_2, confirming the double-bond migration to the β,γ-positions.

With allyl sulfone **194** in hand, various conditions to form ketone **182** were investigated. It was envisaged that the radical precursor **182** would be accessed by acylation of **194** followed by methylation (Scheme 75).



Scheme 75. Initial proposed route to 7-membered ring annulation

Based on the model approach, initial attempts were made to synthesise the β-keto sulfone **200** (Scheme 76). Suitable acylating reagents would be required for these types of transformations. Treatment of allyl sulfone **194** with 1.1 equivalents of 4-pentenoyl chloride **199** in the presence of 1.4 equivalents of *t*-BuOK gave no reaction after 16 h (Table 9, Entry 1).[74] The effect of a stronger base for deprotonation of **194** was therefore investigated.

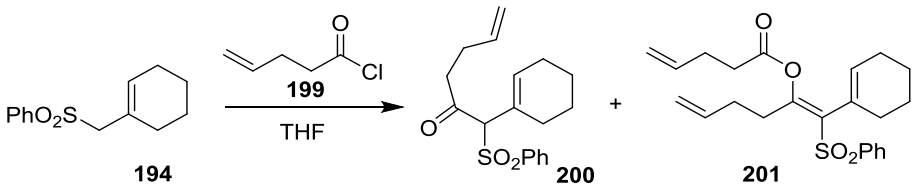
Attempted reaction in the presence of 1.1 equivalents of *n*-BuLi led to the recovery of unreacted starting material, under Savoia's conditions (Entry 2).[75] However, acylation reactions performed using 1.5 and 2.2 equivalents of *n*-BuLi gave β-keto sulfone **200** in 35% and 67% yields, respectively (Entries 3 and 4).

^{1}H-^{13}C HMBC analysis of **200** determined the correlation between the quaternary carbon of the carbonyl moiety and the methine proton α to the sulfone, confirming the formation of an allylic rather than a vinylic sulfone.

Surprisingly, compound **201** was isolated in 20% yield as a by-product when using 2.2 equivalents of *n*-BuLi.

Product **201** was obtained as a single double-bond isomer of undetermined geometry. ^{1}H NMR spectroscopic analysis of **201** showed the appearance of seven proton peaks in the

olefinic region at 4.61, 4.92, 5.63 and 5.88 ppm along with the disappearance of the methine proton adjacent to the sulfone, confirming the formation of **201**.

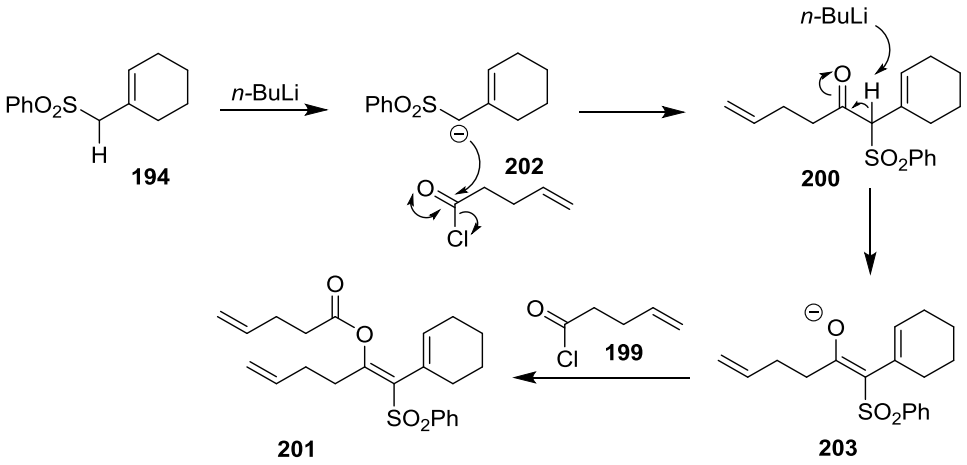


Scheme 76. Acylation of allyl sulfone **194**

Entry	Base	Time	Temperature	Yield (**200**)
1	*t*-BuOK (1.4 eq.)	16 h	-78 °C to rt	-
2	*n*-BuLi (1.1 eq.)	16 h	-78 °C to rt	-
3	*n*-BuLi (1.5 eq.)	16 h	-78 °C to rt	(35%)
4	*n*-BuLi (2.2 eq.)	16 h	-78 °C to rt	(67%) (20%)

Table 9. Attempted acylation reaction

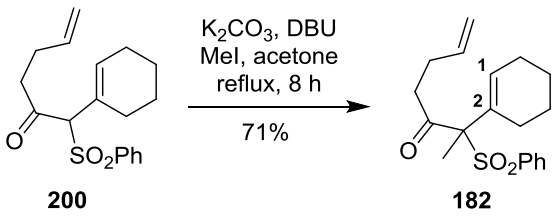
It was thought that the second equivalent of *n*-BuLi could deprotonate the methine proton in compound **200** leading to the formation of anion **203**. As the reaction was performed with 1.5 equivalents of acyl chloride **199**, anion **203** could act as a nucleophile to attack the acyl chloride giving triene **201** (Scheme 77). *O*-acylation of enolates is often observed with acid chlorides. *O*-Acylation of **203** may be further favoured over *C*-acylation because of the hindered nature of the anion at carbon and the formation of the conjugated diene.



Scheme 77. Proposed mechanism to form triene **201**

At this stage, methylation of the β-keto sulfone **200** was performed (Scheme 78).[74] Reacting **200** with MeI using DBU in the presence of K_2CO_3 gave **182** in 71% isolated yield along with the unreacted starting material being recovered after 8 h.

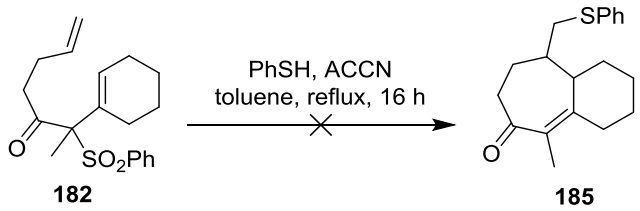
^{1}H NMR spectroscopic analysis indicated a methine proton in the position 1 at 5.42 ppm. ^{1}H-^{13}C HMBC analysis also indicated a correlation between the quaternary carbon of the carbonyl moiety and the methyl protons, confirming the position of methyl moiety in compound **182**.



Scheme 78. Methylation of compound **200**

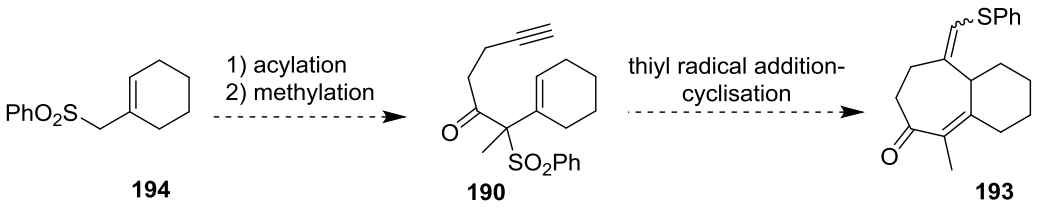
In order to annulate a 7-membered ring, the thiyl radical addition-cyclisation was next attempted (Scheme 79). In practice, treating compound **182** with an equimolar amount of

PhSH and ACCN led to the decomposition of the starting material under thermal conditions. Nothing could be recovered from the attempted radical cyclisation.[76]



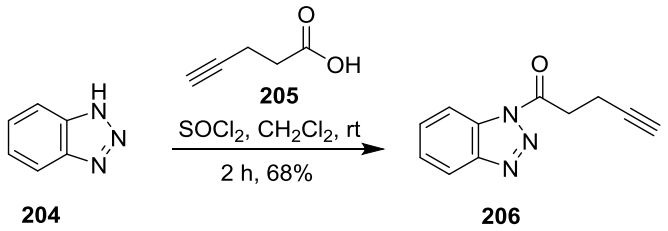
Scheme 79. Attempted radical cyclisation

Following the lack of success to form **185**, an alternative acylating agent with a terminal triple bond was investigated (Scheme 80). It was envisioned that **190** would again be furnished by acylation followed by methylation.



Scheme 80. Alternative approach to 7-membered ring annulation

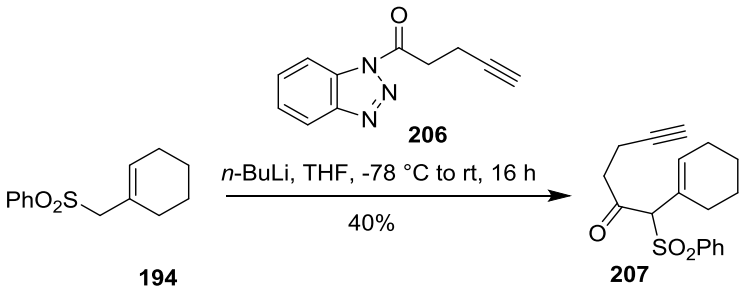
Based on success in ketone acylations in a different part of the project (Section 3.3.6.2), *N*-acylbenzotriazoles were used as acylating agents.[77] The novel *N*-acylbenzotriazole **206** was prepared by treating 4-pentynoic acid **205** with thionyl chloride and benzotriazole **204**, forming **206** in 68% yield (Scheme 81).



Scheme 81. Preparation of *N*-acylbenzotriazole **206**

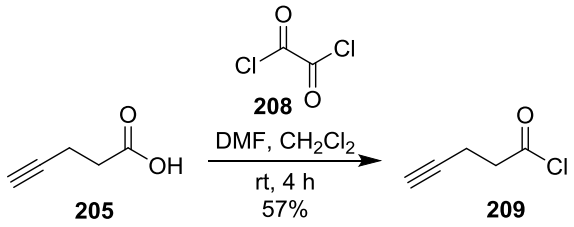
Under the previously optimised conditions for acylation of sulfone **194** using acid chloride, treatment of the allyl sulfone **194** with equimolar *N*-acylbenzotriazole **206** using 2.2 equivalents of *n*-BuLi gave the β-keto sulfone **207** in a modest 40% yield (Scheme 82).[75] The starting material was not fully consumed, as observed by t.l.c. analysis.

The regiochemistry of acylation was again assigned based on ^{1}H NMR and ^{1}H-^{13}C HMBC analyses.



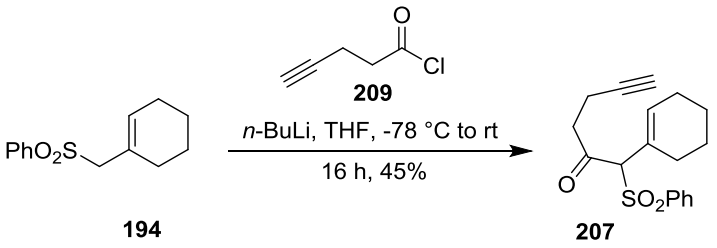
Scheme 82. Acylation of allyl sulfone **194**

Due to the modest yield obtained, attention turned to an alternative acylating agent. 4-Pentynoyl chloride **209** was prepared by treating 4-pentynoic acid **205** with oxalyl chloride **208** in the presence of a catalytic amount of DMF, affording **209** in 57% yield, which was used without further purification (Scheme 83).[78]



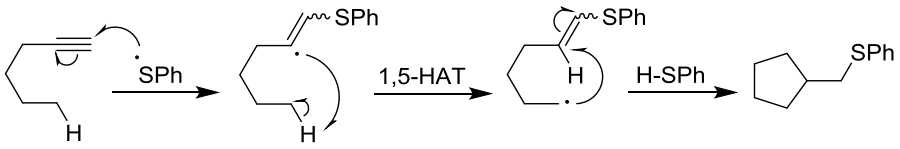
Scheme 83. Acyl chloride formation

Under the same conditions applied to form **200**, acylation of the allyl sulfone **194** using freshly prepared 4-pentynoyl chloride **209** gave compound **207** in 45% yield (Scheme 84).[75]



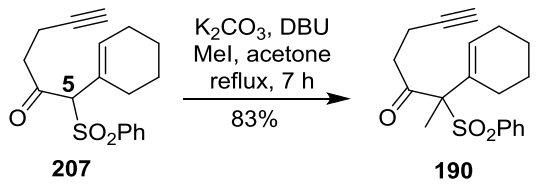
Scheme 84. Preparation of **207**

Vinyl radicals can undergo 1,5-hydrogen atom transfer reactions (Scheme 85).[67] The new radical species formed after translocation can intramolecularly cyclise with an alkene to construct a cyclopentane derivative.



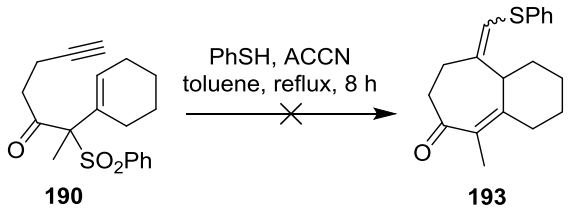
Scheme 85. 1,5-Hydrogen atom transfer

To avoid 1,5-hydrogen atom transfer, methylation of the β-keto sulfone **207** was required prior to the radical reaction. Under basic conditions, methylation of keto sulfone **207** furnished **190** in an excellent 83% yield (Scheme 86).



Scheme 86. Methylation of allyl sulfone **207**

With the radical precursor **190** in hand, the thiol-mediated radical addition-cyclisation was performed (Scheme 87). Reacting **190** with PhSH and ACCN once again led to the decomposition of the starting material.



Scheme 87. Attempted radical cyclisation

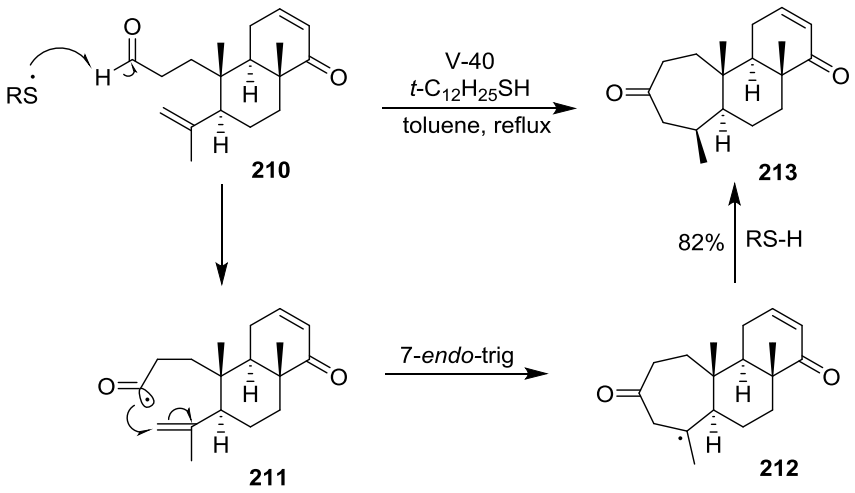
In light of the failure of the vinyl radical cyclisation to furnish a 7-membered ring, an alternative approach through the formation of a reactive acyl radical species was investigated.

3.3.2 Thiol-mediated acyl radical cyclisation of an alkene

Intramolecular addition of acyl radicals to olefins produces cyclic ketones in reasonably good yields. Acyl radicals can be generated through abstraction of a hydrogen atom from an aldehyde using thiyl radicals, and this process can be rendered catalytic in thiol if hydrogen abstraction from the thiol is part of the chain process. In 2005, Tomioka and co-workers

reported a study on the formation of 5- and 6-membered cyclic ketones *via* thiol-catalysed acyl radical cyclisations.[79] They found that the combination of 'odourless' *tert*-dodecanethiol and ACCN or AIBN as initiators could generate the cyclised product.

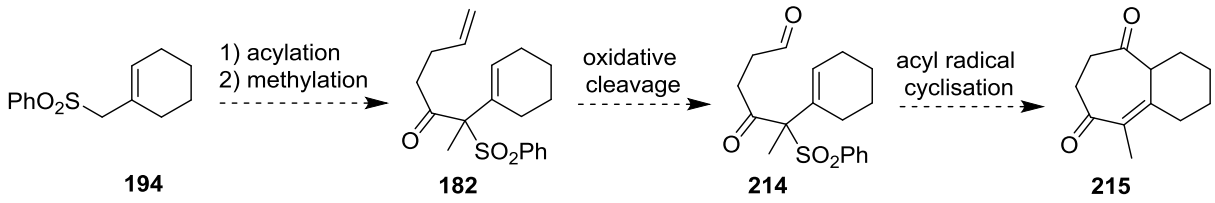
In 2011, Shishido and co-workers reported a study on the total synthesis of Brevione C, employing an acyl radical to form a 7-membered ring system (Scheme 88).[80] The initially generated thiyl radical abstracts the hydrogen atom from the aldehyde **210** to produce the intermediate acyl radical **211**. According to Shishido, the best result was achieved using 3.0 equivalents each of *tert*-dodecanethiol and 1,1'-azobis(cyclohexane-1-carbonitrile) (V-40 initiator). The compound **212** was formed *via* regioselective 7-*endo*-trig cyclisation of the acyl radical onto the exocyclic olefin, followed by stereoselective hydrogen atom abstraction from the thiol giving **213**.



Scheme 88. Preparation of **213** *via* acyl radical cyclisation

3.3.2.1 Proposed approach to 7-membered ring annulation *via* acyl radical cyclisation

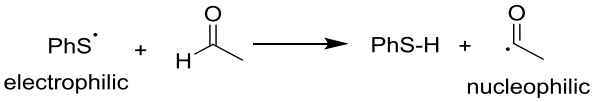
An alternative approach to compound **215** *via* acyl radical cyclisation was proposed (Scheme 89). It was envisaged that **214** would be accessed by oxidative cleavage of terminal olefin **182** to form the aldehyde. Tandem thiyl radical-catalysed acyl radical cyclisation-β-sulfonyl elimination would form cyclised product **215**.



Scheme 89. 7-membered ring annulation *via* acyl radical cyclisation

It was believed that the eliminated sulfonyl radical ($PhSO_2$•) could propagate the chain process, abstracting hydrogen from the aldehyde.

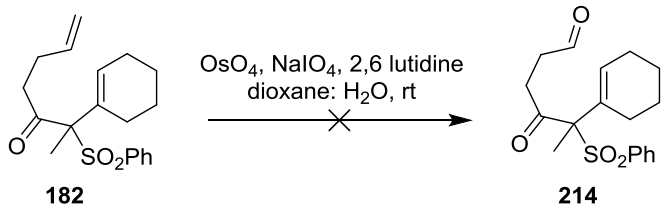
In terms of polarity reversal catalysis (PRC), a polarity-matched pathway is required for the reaction to be successful. Abstraction of a hydrogen atom from an aldehyde by the electrophilic thiyl radical gives thiophenol and the nucleophilic acyl radical (Scheme 90).[81] Due to the stabilisation by resonance of the corresponding thiyl radical, thiophenol is an excellent hydrogen atom donor towards carbon-centred radicals with an S-H bond-dissociation energy (BDE) of 349 kJ mol^{-1}.



Scheme 90. Polar effect in H-atom abstraction

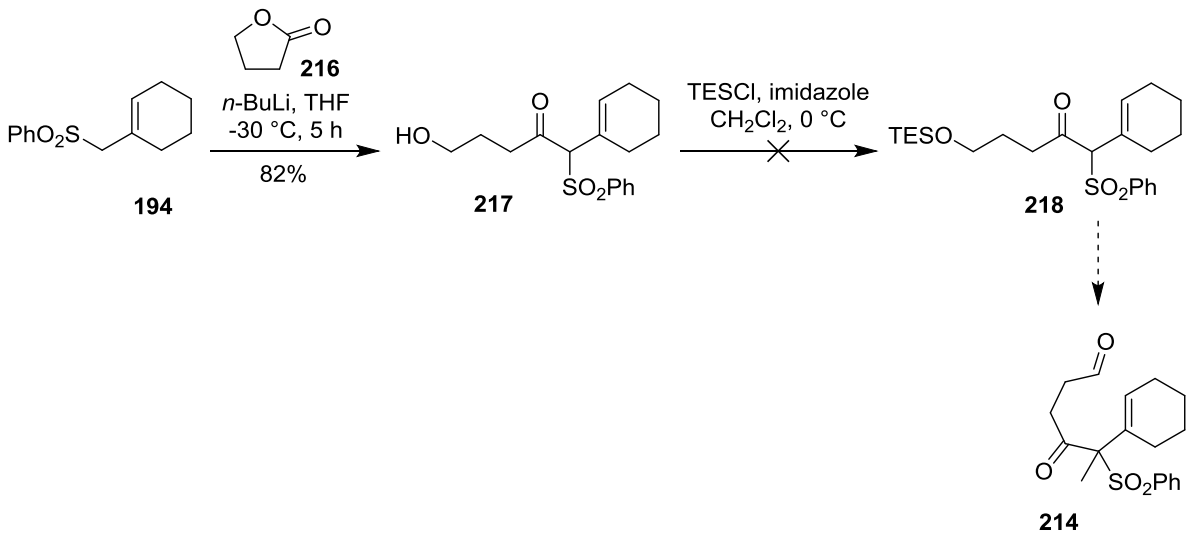
3.3.2.2 Results and Discussion

Treatment of **182** with 2 mol% OsO_4 and 4.0 equivalents of $NaIO_4$ in the presence of 2,6-lutidine led to decomposition of the starting material, as shown by t.l.c analysis (Scheme 91).[82]



Scheme 91. Attempted oxidative-cleavage of alkene **182**

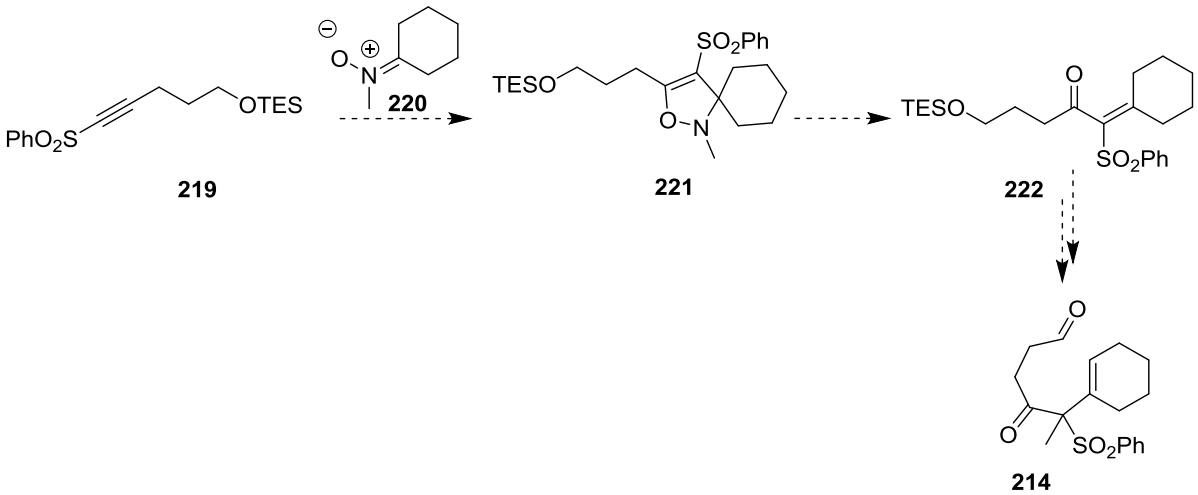
Due to the unsuccessful result obtained for oxidative cleavage of **182**, an alternative route to synthesise **214** was attempted (Scheme 92). Allyl sulfone **194** was subjected to acylation with γ-butyrolactone **216** using *n*-BuLi, giving rise to compound **217** in 82% yield.[75] Attempted TES protection[83] of alcohol **217** did not give the desired product **218**, instead fragmentation of **217** leading to an unidentified product was observed by ^{1}H NMR spectroscopic analysis.



Scheme 92. Alternative proposed route to form **214**

Due to the lack of success in the silylation of **217**, this approach to **214** was abandoned.

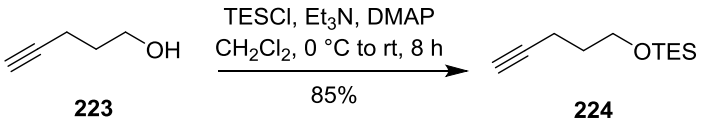
Attention turned to an alternative approach to prepare **214** (Scheme 93). It was envisaged that compound **221** could be accessed *via* a 1,3-dipolar cycloaddition reaction[84] of electron-deficient alkyne **219** and *N*-methylcyclohexylnitrone **220**. Functional group interconversion should then allow access to **214**.



Scheme 93. Alternative approach to form **214**

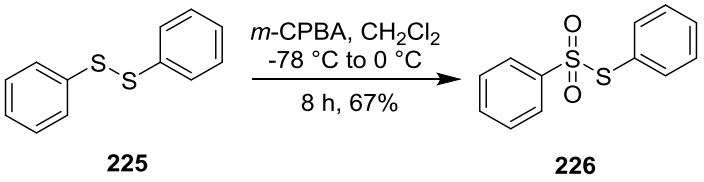
3.3.3 Synthesis of starting materials

The synthesis of the dipolarophile **219** in three steps commenced with the protection of commercially available 4-pentyn-1-ol **223** as its TES ether, giving **224** in 85% isolated yield (Scheme 94).[83]



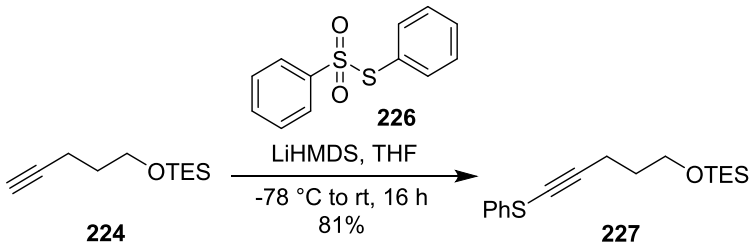
Scheme 94. Silyl protection of alcohol **223**

To perform the addition of phenyl sulfide to the terminal alkyne, first the preparation of thiosulfonate **226** was attempted (Scheme 95).[85] Oxidation of disulfide **225** with stoichiometric *m*-CPBA resulted in S-phenylbenzenethiosulfonate **226** in 67% yield. The starting material was not fully consumed after 8 h, as confirmed by t.l.c. analysis.



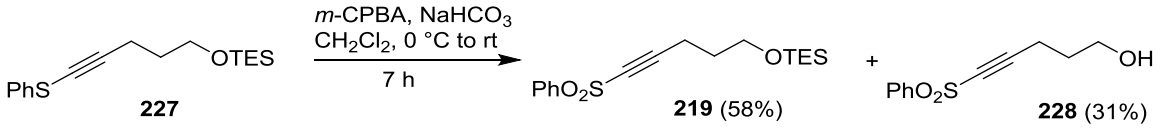
Scheme 95. Oxidation of disulfide **225**

Treatment of the terminal alkyne in **224** with 1.1 equivalents of LiHMDS generated the acetylide anion. The trapping of the resulting anion with thiosulfonate **226** provided the alkynyl sulfide **227** in 81% yield (Scheme 96).[86]



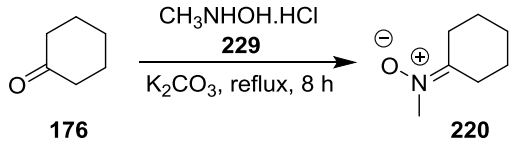
Scheme 96. Synthesis of the alkynyl sulfide **227**

Subsequently, treatment of alkynyl sulfide **227** with purified *m*-CPBA afforded the sulfone **219** in 58% isolated yield, under basic conditions (Scheme 97).[87] The $NaHCO_3$ was added in order to neutralise the benzoic acid generated in the reaction which might hydrolyse the silyl ether. In practice, the desilylated product **228** was also observed in 31% yield, as confirmed by ^1H NMR spectroscopic analysis.



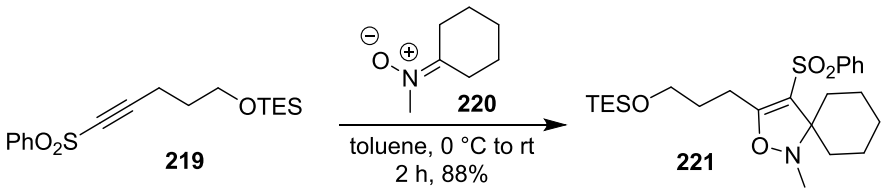
Scheme 97. Oxidation of sulfide to form sulfone **219**

The condensation of cyclohexanone **176** and *N*-methylhydroxylamine hydrochloride **229** in refluxing EtOH gave the nitrone **220** after concentration of the solvent (Scheme 98).[88] Monitoring the reaction by t.l.c. showed the consumption of the starting material after 8 h. Due to the instability of nitrone **220**, it was used immediately in the next step without further purification.



Scheme 98. Synthesis of the nitrone **220**

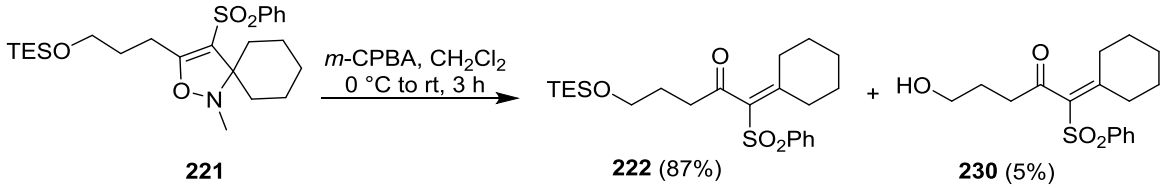
The electron-deficient alkyne **219** was employed in a regiospecific 1,3-dipolar cycloaddition reaction with 2.0 equivalents of nitrone **220** in toluene to give the cycloadduct **221** in 88% yield (Scheme 99).[84] ^{1}H NMR spectroscopic analysis indicated the *N*-methyl protons at 2.51 ppm and ^{13}C NMR spectroscopic analysis also proved the appearance of two quaternary olefinic signals at 114.0 and 167.4 ppm. The regiochemistry of the cyclisation was assigned based on literature precedent.[89]



Scheme 99. 1,3-dipolar cycloaddition reaction to form **221**

The *N*-oxidation of the isoxazoline ring **221** with purified *m*-CPBA, which was followed by spontaneous cheletropic extrusion of nitrosomethane, gave the vinyl sulfone **222** in 87% isolated yield (Scheme 100).[87] The desilylated product **230** was formed as a by-product in 5% yield.

Unfortunately, the vinyl sulfone **222** decomposed on standing, as confirmed by t.l.c. analysis. Thus, it was decided to immediately convert it into the allyl sulfone *via* methylation.

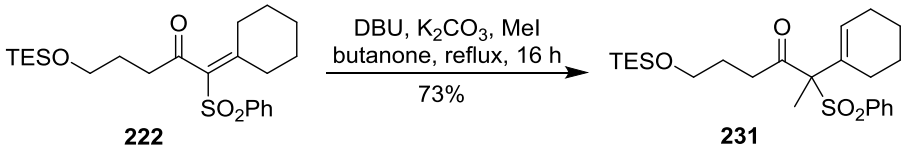


221 **222** (87%) **230** (5%)

Scheme 100. *N*-oxidation of **221** to form **222**

As previously discussed, in order to avoid the competing 1,5-hydrogen atom transfer reaction, alkylation was required prior to radical cyclisation (Scheme 101). Initially, treating **222** with MeI using DBU in the presence of K_2CO_3 gave no reaction with the starting material being recovered.[74] It was decided to probe the effect of a higher boiling point solvent. Therefore, methylation was performed in refluxing butanone, which gave rise to **231** in 73% isolated yield. The remaining unreacted starting material was recovered.

The presence of a CH_3 singlet at 1.79 ppm and olefinic proton at 5.38 ppm in the ^{1}H NMR spectrum of **231**, confirmed the regiochemistry of methylation

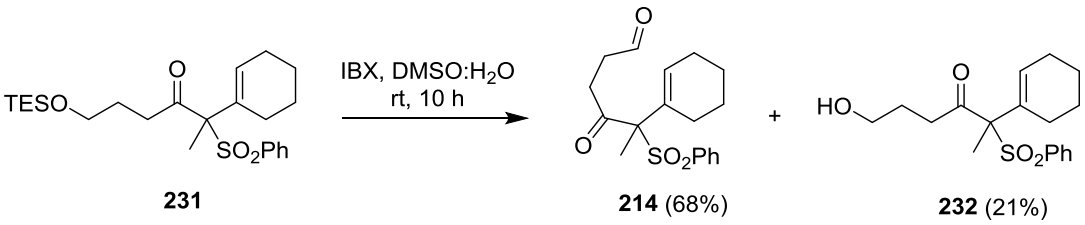


222 **231**

Scheme 101. Methylation of **222**

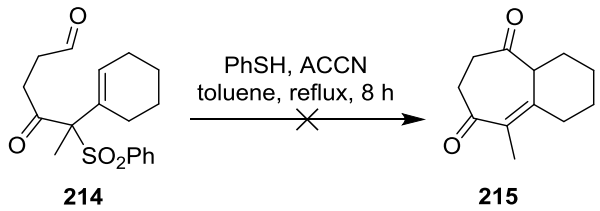
In order to obtain the acyl radical precursor **214**, oxidative removal of the primary silyl ether was investigated. In 2002, Wu *et al*. demonstrated the selective cleavage of TES ethers by *o*-iodoxybenzoic acid (IBX) as an oxidising agent.[90] This procedure could be performed as a direct conversion of TES ethers into the corresponding carbonyl compounds. In practice, treatment of **231** in a homogeneous mixture of solvents with 1.2 equivalents of IBX gave the

corresponding aldehyde **214** in 68% isolated yield (Scheme 102). The alcohol **232** was also isolated in 21% yield without further oxidation to the aldehyde **214** after 10 h.



Scheme 102. Selective oxidation of TES ether to aldehyde **214**

Subsequently, the acyl radical cyclisation to assemble a 7-membered ring system was attempted (Scheme 103).[80] Disappointingly, treating **214** with PhSH in the presence of ACCN, under Shishido's conditions resulted in decomposition of the starting material.

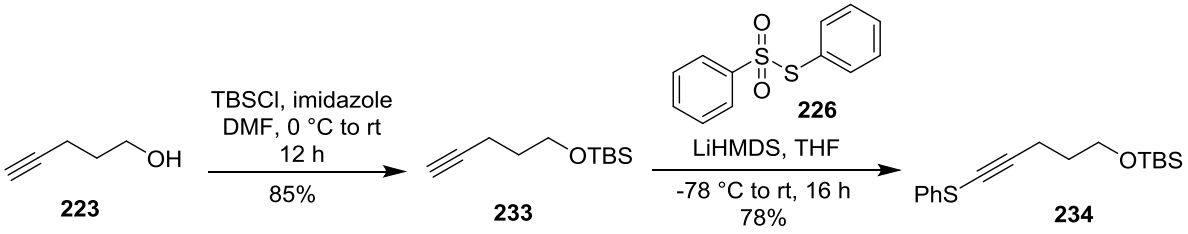


Scheme 103. Attempted acyl radical cyclisation

The instability of intermediate **222** and the observed silyl group deprotection throughout the synthetic approach led to a low overall yield of the desired aldehyde. In order to circumvent this issue, it was decided to repeat the synthesis starting with the protection of 4-pentyn-1-ol **223** as its *tert*-butyldimethylsilyl ether **233** (Scheme 104).[91] Compared to TES ethers, TBS ethers are known to be significantly more stable.

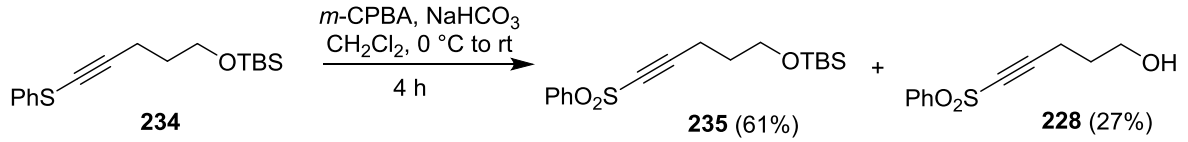
Treatment of the alcohol **223** with TBSCl, using imidazole, furnished the TBS ether **233** in 85% yield. The alkynyl sulfide **234** was synthesised by treating the terminal triple bond **233**

with 1.0 equivalent of LiHMDS and trapping the generated acetylide anion with the thiosulfonate **226** giving **234** in 78% isolated yield.



Scheme 104. Synthesis of alkynyl sulfide **234**

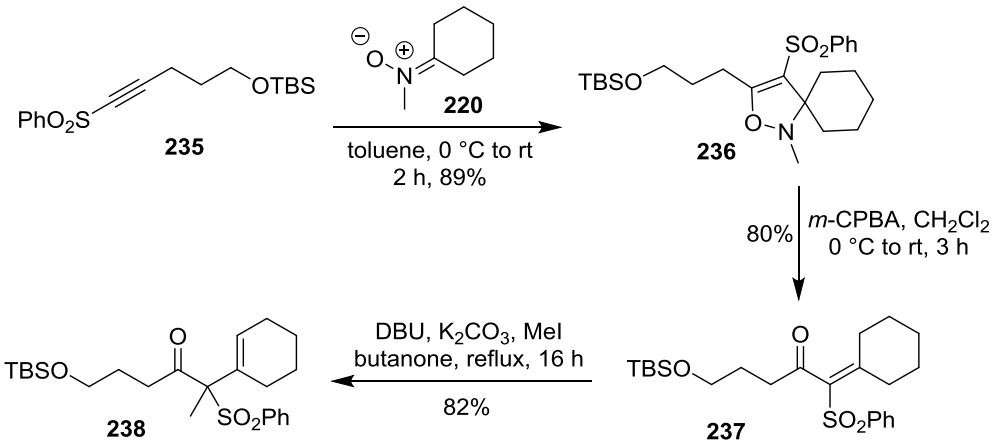
Oxidation of **234** with purified *m*-CPBA gave sulfone **235** in 61% yield (Scheme 105).[87] The desilylated product **228** was also isolated in 27% yield.



Scheme 105. Oxidation to form sulfone **235**

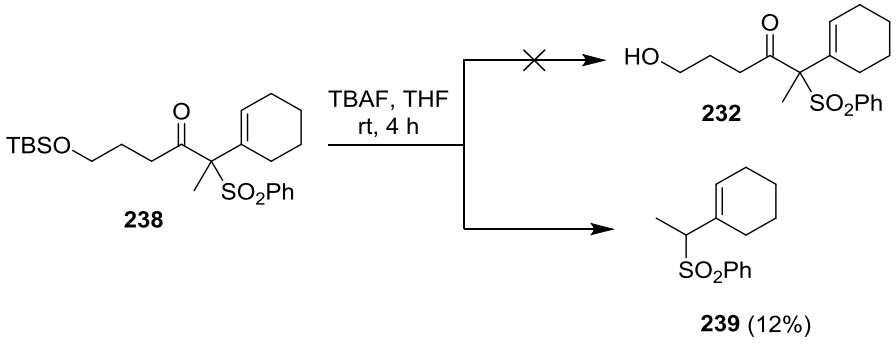
With **235** in hand, a regiospecific 1,3-dipolar cycloaddition reaction using nitrone **220** gave the isoxazoline **236** in 89% yield (Scheme 106).[84] Treatment of isoxazoline **236** with *m*-CPBA gave the substituted vinyl sulfone **237** in 80% yield. In comparison to compound **222**, the TBS ether-protected vinyl sulfone **237** was stable on standing, as shown by t.l.c. analysis.

Treatment of the vinyl sulfone **237** with MeI in the presence of DBU and K_2CO_3 in refluxing butanone gave allyl sulfone **238** in an excellent yield.



Scheme 106. Preparation of allyl sulfone **238**

According to Wu, the oxidative removal of TBS ethers by *o*-iodoxybenzoic acid (IBX) is very slow. TBS ether **238** was therefore subjected to desilylation using 2.0 equivalents of TBAF in THF (Scheme 107).[92] Unfortunately, fragmentation of the starting material was observed at this stage, leading to only 12% recovered allyl sulfone **239**. Analysis of the reaction mixture by t.l.c. showed significant decomposition. This approach to aldehyde **214** therefore had to be abandoned.

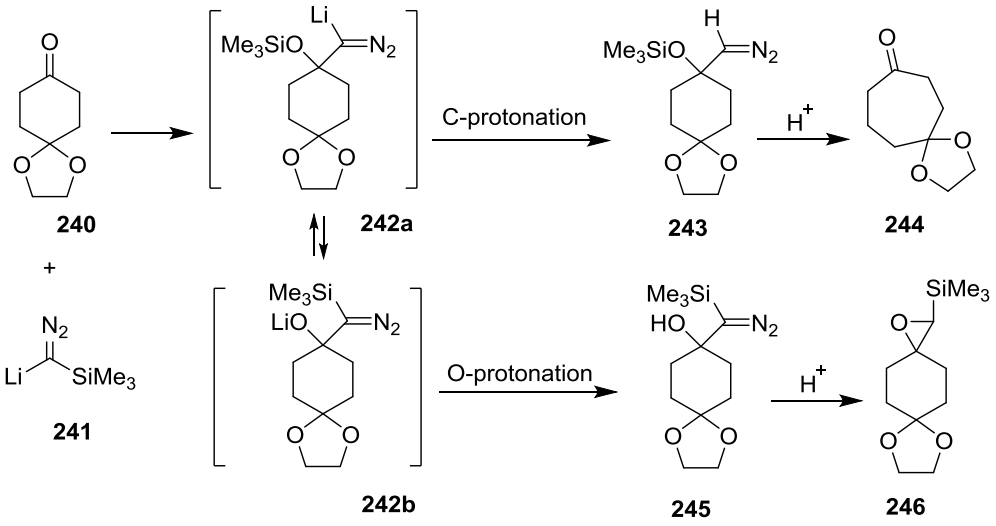


Scheme 107. Attempted desilylation using TBAF

Unfortunately, all attempts to form a 7-membered ring system *via* radical cyclisation proved unsuccessful. Overall the route additionally suffered from instability of some intermediates, notably **202**. The lack of success shifted our focus away from this methodology.

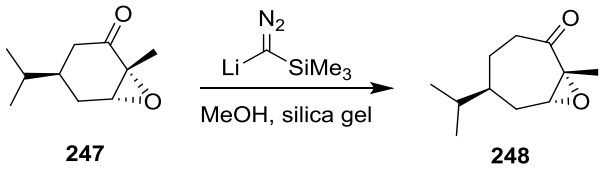
3.3.4 Selective ring-expansion approach to 7-membered ring annulation

Cyclic ketones can undergo ring-expansion through one-carbon insertion between the carbonyl functionality and the α-carbon.[93] In 2012, Lee and co-workers reported an efficient single methylene homologation of a variety of cyclic ketones.[94] Trimethylsilyldiazomethane (TMSD) was deprotonated to its lithiated form (LTMSD) **241** to create a strongly nucleophilic reagent which was added to ketone **240** (Scheme 108). The anionic intermediate **242a** underwent a selective C-protonation with MeOH to generate **243**, which was treated with silica gel to form ketone **244**. The acidity of the proton source plays a key role in the formation of two different products, the epoxide **246** and the ring-expanded ketone **244**. They observed that as the pK_a of the acid increased, formation of the ring-expanded product **244** was enhanced. The epoxide is formed as a by-product, arising from displacement of the nitrogen by the adjacent alcohol.



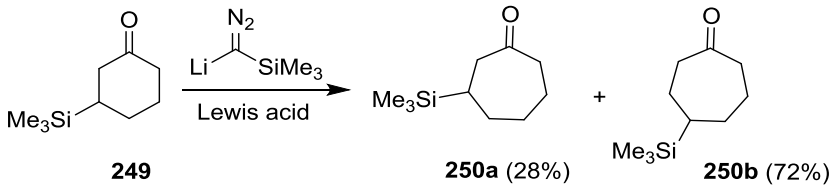
Scheme 108. *C*- versus *O*-protonation and subsequent rearrangement

According to Lee, selective ring-expansion *via* methylene migration proceeds in the presence of an α,β-epoxide (Scheme 109).[94]



Scheme 109. Selective ring-expansion in the presence of an epoxide

In 2004, White *et al*. reported the silicon substituent directing effect on the ring-expansion process.[95] The β-effect of the silicon group is widely used in organic chemistry. Therefore, it was envisioned that the β-carbocation stabilising effect of the silyl moiety could control the selectivity in the migration of the α-carbon in the ring-expansion approach. However, they found that silicon only has a moderate directing effect on the ring expansion of **249**, affording 7-membered rings **250a** and **250b** in a 1.0:2.3 ratio (Scheme 110).

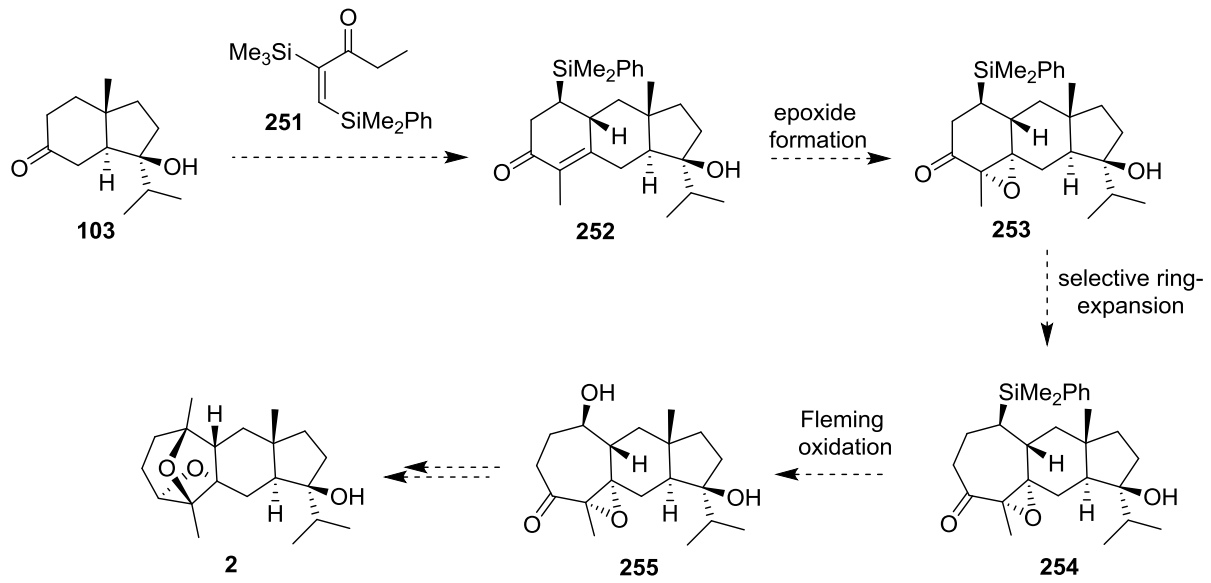


Scheme 110. Ring-expansion of β-silyl cyclohexanone **249**

3.3.4.1 Proposed approach to 7-membered ring annulation *via* selective ring- expansion

An alternative approach to access a 7-membered ring on the *trans*-hydrindanone **103** was proposed *via* a selective ring-expansion process. As depicted in Scheme 111, initially the Robinson annulation with bis-silylated enone **251** was required to introduce the 6-membered enone **252**.

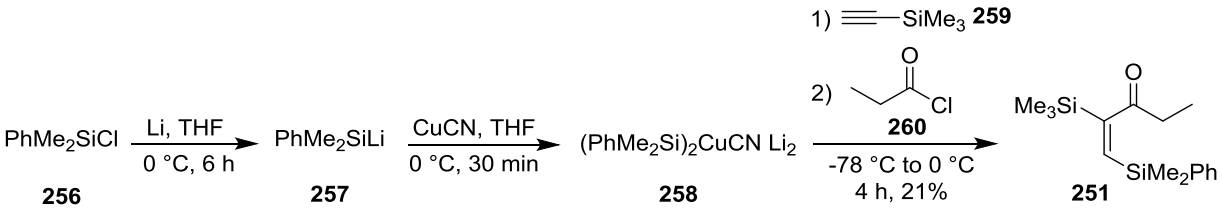
The proposed approach involves epoxide formation to prepare **253** prior to the selective ring-expansion *via* methylene migration to generate ketone **254**. The unmasked hydroxyl group in **255** could then be accessed through Fleming oxidation.



Scheme 111. Proposed regioselective ring-expansion approach to form **254**

3.3.4.2 Results and discussion

In 1992, Fleming *et al*. reported the synthesis of the β-functionalised Michael acceptor **251** starting from phenyldimethylsilyl chloride **256** (Scheme 112). The silyllithium **257** was generated *in situ* from lithiation of silyl chloride **256** followed by treatment with CuCN to form the phenyldimethylsilyl-cuprate reagent **258**.[96] Subsequently, enone **251** was prepared *via* silyl-cupration of the monosilylated acetylene **259** followed by acylation with **260**, giving **251** in a modest yield of 21%. It was thought that the low yield obtained for enone **251** was due to the generation of silicon-containing by-products during the formation of silyllithium **257**.



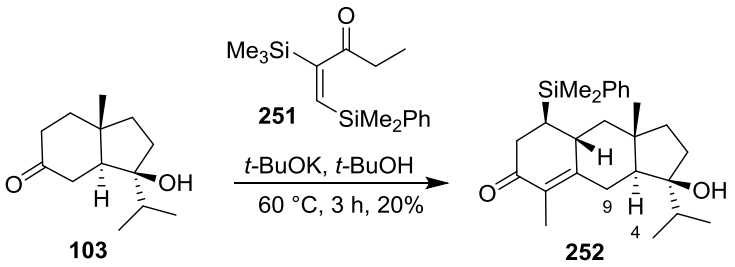
Scheme 112. Preparation of enone **251**

With the bis-silylated enone **251** in hand, the Robinson annulation was attempted to introduce a 6-membered ring (Scheme 113).[97] In the Robinson annulation, it is proposed that the α-silyl group stabilises the enolate produced *via* conjugate addition, increasing the electrophilicity of the double bond. Michael addition of the *trans*-hydrindanone **103** to enone **251** followed by intramolecular aldol condensation formed enone **252** in 20% yield along with the recovery of the starting ketone in 14% yield. Monitoring the reaction by t.l.c. showed decomposition of the starting ketone **103**. Using 2.0 equivalents of the Michael acceptor and an excess of base had little effect on the productivity of the reaction.

^{1}H NMR spectroscopic analysis showed the appearance of a new methyl group at 1.76 ppm and olefinic protons in the aromatic region, confirming the formation of enone **252**. ^{1}H-^{13}C HMBC analysis of **252** indicated the correlation between the proton at the *trans*-ring junction and carbon at position 9, confirming the regiochemistry of the C-C bond formation.

The stereochemistry of the product was not determined, but was assumed as shown. This assumption was drawn from expected addition to the lower face of **103** and from Fleming's observations. The stereochemistry of the silyl functionality is most likely to be *cis* to the bridgehead hydrogen. This was observed by Fleming using cyclohexanone and is possibly thermodynamically controlled.

Attempted Robinson annulation using LDA gave no reaction, with only starting ketone **103** being recovered.

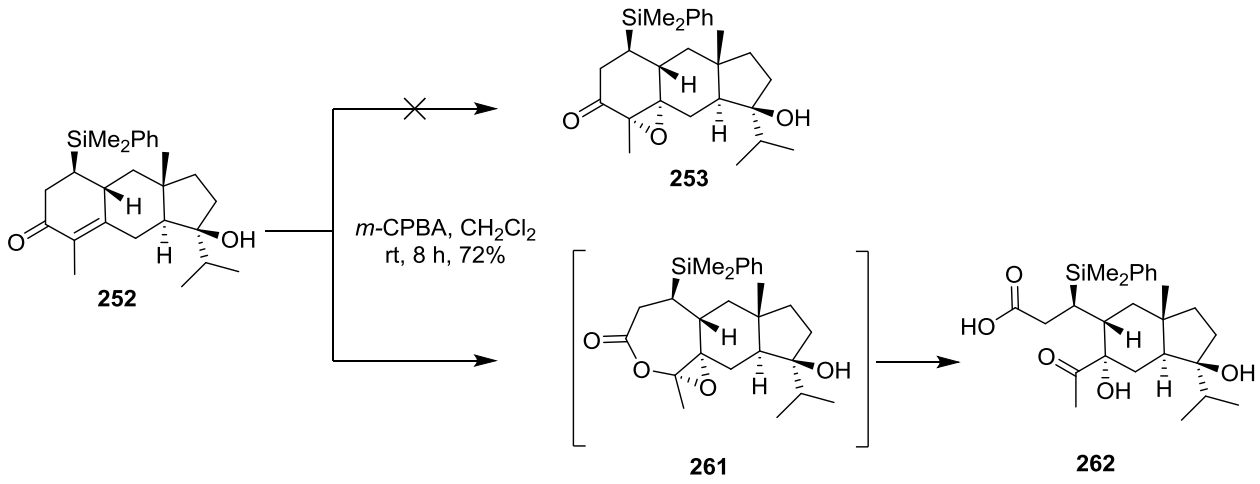


Scheme 113. Robinson annulation to form **252**

Prior to examining the selective ring-expansion approach, it was decided to epoxidise the enone **252**. Treating enone **252** with 1.0 equivalent of purified *m*-CPBA gave no reaction. However, using 2.0 equivalents of *m*-CPBA furnished **262**, the product of epoxidation and Baeyer-Villiger oxidation, in 72% isolated yield (Scheme 114).

^{1}H-^{13}C HMBC analysis of the product indicated no correlation between the quaternary carbon of the carbonyl and the CH_3 protons, confirming the Baeyer-Villiger oxidation along with epoxide formation.

An alternative approach to epoxidation, using $NaOH/H_2O_2$ (30%) instead of *m*-CPBA gave no reaction, with only the starting material recovered after 16 h.[98]



Scheme 114. Attempted epoxide formation

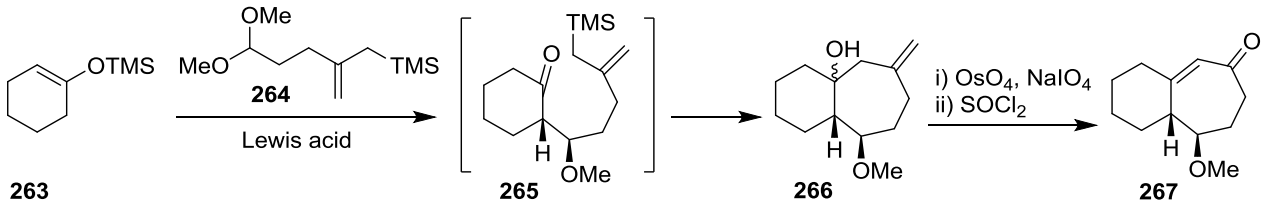
Due to the low yield of the Robinson annulation and the undesired *O*-insertion occurring, this approach was abandoned.

3.3.5 [5+2] annulation reaction to annulate a 7-membered ring

The [5+2] annulation is known to be a useful method in the preparation of fused carbocyclic 7-membered rings. The success in this approach relies on bifunctional annulating reagents containing isolated electrophilic and nucleophilic centres within the same molecule. These two centres are designed to be activated by the same set of conditions.

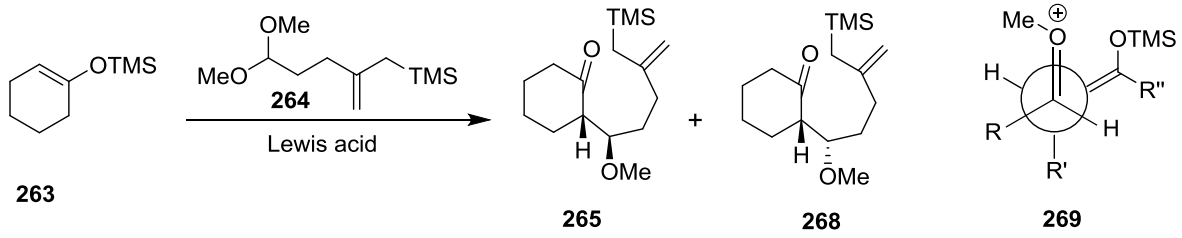
In 1988, Lee *et al*. reported a one-pot [5+2] annulation sequence to prepare 7-membered rings (Scheme 115).[99] Treatment of silyl enol ether **263** with allylsilane acetal **264** in the presence of a Lewis acid gave the intermediate ketone **265**.[100] Intramolecular Lewis acid-induced ring closure afforded the alcohol **266**. Subsequent oxidative cleavage and dehydration gave enone **267** in yields of 62-67%. They found that the stereochemistry of the

first bond-forming reaction was strongly dependent on the Lewis acid or combinations of Lewis acids. The use of $TiCl_4$ or $AlCl_3$ gave excellent selectivity.



Scheme 115. Lee's approach to 7-membered ring annulation

In 1982, Seebach and Goliński suggested the topology of the two approaching reagents, the donor and acceptor π-systems, are in a gauche arrangement (Scheme 116).[101] The chelation of the acetal oxygen and the enol oxygen with Lewis acid, immediately prior to formation of **269**, furnishes the gauche relationship between the enol and the electrophile which results in the formation of isomer **265**.

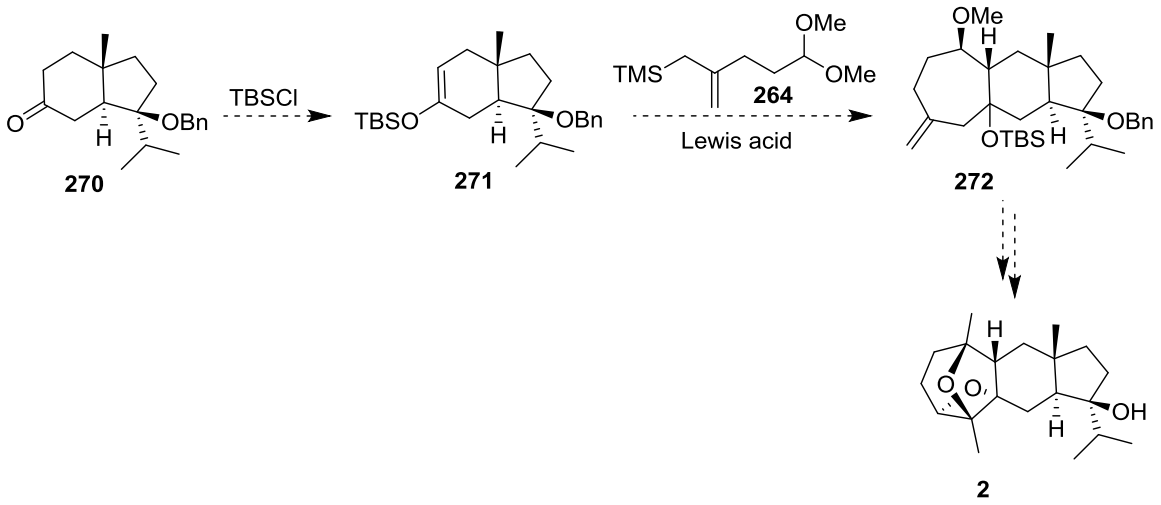


Scheme 116. Two possible isomers of the first C-C bond formation

3.3.5.1 Proposed [5+2] annulation approach to 7-membered ring formation

Based on Lee's protocol, an alternative route to construct a 7-membered ring on the *trans*-hydrindanone **270** *via* a [5+2] annulation reaction was proposed (Scheme 117). In order to examine this approach and successfully annulate a 7-membered ring, firstly synthesis of the

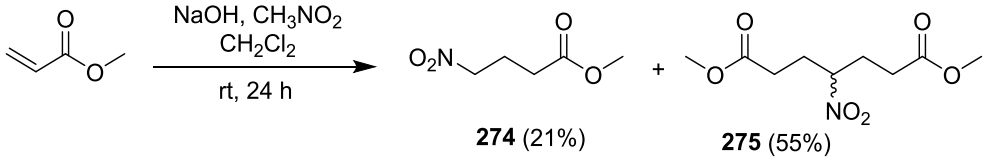
silyl enol ether **271** would be required. The preparation of the tricyclic ring **272** *via* a [5+2] annulation in the presence of Lewis acid would then be evaluated.



Scheme 117. Proposed approach to tricyclic ring **272**

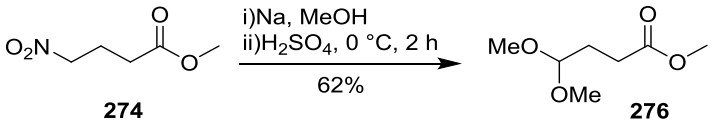
3.3.5.2 Results and Discussion

Initially, it was decided to reinvestigate the Lee [5+2] annulation reaction. In order to repeat the synthesis, the preparation of the allylsilane acetal **264** was first attempted (Scheme 118).[102] The addition of nitromethane to methyl acrylate **273** provided ester **274** along with by-product **275** in 21% and 55% yields, respectively.[103] Monitoring the reaction by t.l.c. showed the presence of the by-product **275** as the major component.



Scheme 118. Synthesis of **274** *via* Michael addition

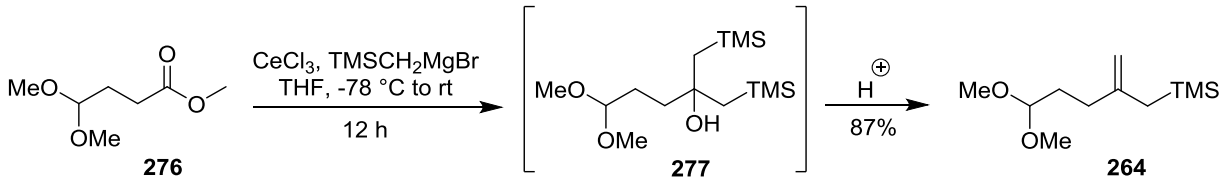
Dimethoxybutanoate **276** was synthesised by treating **274** with *in situ*-generated NaOMe *via* a modified Nef reaction, in 62% isolated yield (Scheme 119).[104] There were some by-products present in the reaction, as observed by t.l.c. analysis. None of these were isolated cleanly.



Scheme 119. Preparation of dimethoxy butanoate **276**

In 1987, Bunnelle and Narayanan reported a synthetic pathway to generate the allylsilane acetal **264** (Scheme 120).[105] Twofold addition of the Grignard reagent to the ester **276** gave the bis(β-silyl) alcohol **277** which by deoxysilylation on silica gel transformed to the allylsilane acetal **264**. It was observed that the enolisation of the intermediate α-silylketone was in competition with the addition of the second equivalent of the Grignard reagent, leading to the low yield for the desired product. They found the enolisation process became slower when the organocerium reagent was used instead of the Grignard reagent, furnishing the allylsilane acetal **264** in an improved yield.

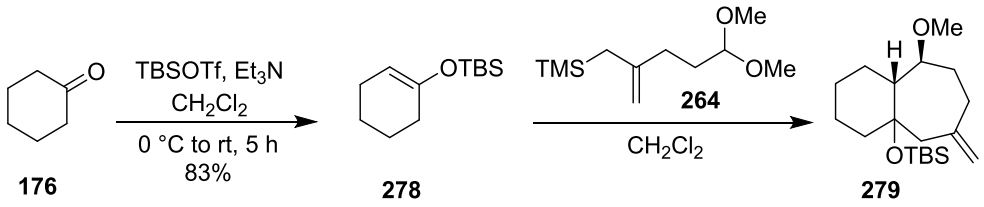
According to the literature procedure, treatment of **276** with a premixed α-silyl Grignard reagent with anhydrous cerium(III) chloride afforded compound **264** in an excellent yield.[100] It should be noted that freshly dehydrated and dried cerium(III) chloride was required for this transformation.



Scheme 120. Preparation of allylsilane acetal **264**

With allylsilane acetal **264** in hand, the reinvestigation of Lee's protocol to annulate a 7-membered ring was attempted. The silyl enol ether **278** was synthesised by treating cyclohexanone **176** with TBSOTf in the presence of Et_3N, giving rise to **278** in 83% isolated yield (Scheme 121).[106]

Silyl enol ether **278** was treated with allylsilane acetal **264** in the presence of sequential addition of TMSOTf and $TiCl_4$, which gave alkene **279** in 12% isolated yield (Table 10, entry 1). It should be noted that using the *tert*-butyldimethylsilyl enol ether of cyclohexanone **176**, rather than the reported trimethylsilyl enol ether, directly gave the annulated product **279**, as a single diastereomer, with the tertiary alcohol in protected form. The starting material **278** was fully consumed in the reaction and significant amounts of by-products were observed by t.l.c. analysis. None of these by-products could be isolated cleanly. Attempts were made to optimise the annulation reaction by examining the effects of various activators.



Scheme 121. [5+2] annulation to form **279**

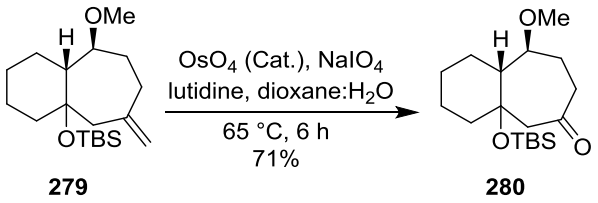
Entry	Lewis acid	Temperature	Time	Yield (**279**)
1	TMSOTf (0.1 eq.), $TiCl_4$ (1.0 eq.)	-78 °C	4 h	12%
2	$AlCl_3$ (3.0 eq.)	-78 °C	4 h	9%
3	$AlCl_3$ (1.0 eq.)	-78 °C	3 h	-
4	TMSOTf (0.1 eq.)	-78 °C to -30 °C	3 h	26%
5	TMSOTf (0.4 eq.)	-78 °C	3 h	13%
6	$TiCl_4$ (0.9 eq.)	-78 °C	3 h	41%
7	$TiCl_4$ (0.4 eq.)	-78 °C	4 h	46%

Table 10. Attempted [5+2] annulation

The [5+2] annulation reaction using 3.0 equivalents of $AlCl_3$ furnished **279** in a low yield (Entry 2). Conversion to cyclohexanone **176** was also observed by t.l.c. analysis. To avoid desilylation, 1.0 equivalent of $AlCl_3$ was used, however this did not give the desired product (Entry 3). Monitoring the reaction by t.l.c. proved the consumption of **278** with conversion to the ketone **176**. It was then decided to test the effect of TMSOTf on the reaction. When 0.1 equivalents or 0.4 equivalents of TMSOTf were used, 7-membered ring annulation was observed in 26% and 13% respectively (Entries 4 and 5). As previously described, a significant portion of the silyl enol ether **278** was being consumed in side reactions, as indicated by t.l.c. analysis. Using a catalytic amount of a strong Lewis acid, $TiCl_4$ furnished compound **279** in improved yields of 41% and 46% respectively (Entries 6 and 7).

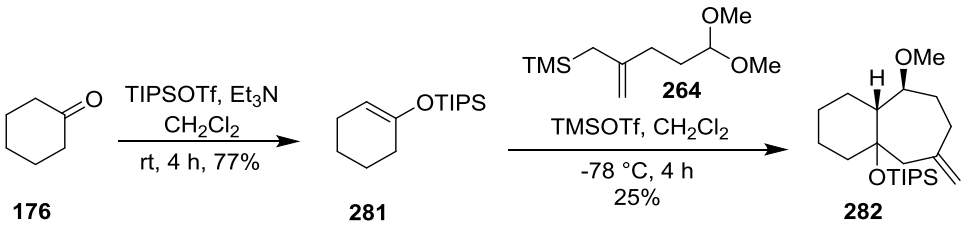
^{1}H NMR spectroscopic analysis of **279** showed the appearance of a signal due to the methine proton at the ring junction at 3.10 ppm adjacent to the methoxy protons peak at 3.33 ppm. ^{13}C NMR spectroscopic analysis indicated the quaternary carbon of the protected tertiary alcohol at 78.3 ppm and the carbon attached to the OMe group at 51.9 ppm.

Oxidative cleavage of alkene **279** in the presence of $OsO_4/NaIO_4$ was performed, giving rise to ketone **280** in 71% isolated yield (Scheme 122).[82] Hydrolysis of the silyl ether was not observed under these conditions.



Scheme 122. Oxidative cleavage of alkene **279** to form **280**

Due to the modest yield obtained for **279**, it was decided to examine the annulation reaction using TIPS enol ether **281** in place of the TBS enol ether **278**. Therefore, the synthesis of the silyl enol ether **281** was performed by treating cyclohexanone **176** with TIPSOTf and Et_3N as base, giving **281** in 77% yield (Scheme 123).[106] The attempted annulation using TMSOTf as an activator gave alkene **282** in 25% isolated yield as a single stereoisomer of undetermined stereochemistry at the tertiary silyl ether. Monitoring the reaction by t.l.c. showed the consumption of the starting material along with the conversion to cyclohexanone **176**. Due to the low yield of **282**, it was decided to use the TBS enol ether in the annulation reaction.

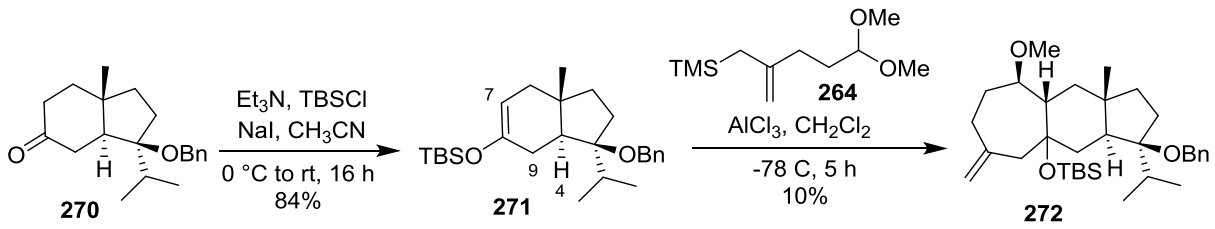


Scheme 123. Attempted [5+2] annulation reaction to form **282**

In order to apply the [5+2] annulation methodology to the *trans*-hydrindanone **270**, initially TBS enol ether formation was undertaken, giving **271** as a single regioisomer in 84% yield

(Scheme 124). ^{1}H-^{13}C HMBC analysis of **271** showed a correlation between the proton at the *trans*-ring junction and carbon at position 9 in the 6-membered ring, confirming the regiochemistry of silyl enol ether formation.

Silyl enol ether **271** was subjected to the annulation reaction using allylsilane acetal **264** in the presence of $AlCl_3$, affording the tricyclic silyl ether **272** as a single stereoisomer in 10% yield. The stereochemistry of the product was not determined, but was assumed as shown based on Seebach's observation. The starting material was fully consumed along with conversion to ketone **270**.



Scheme 124. Preparation of **272** *via* [5+2] annulation

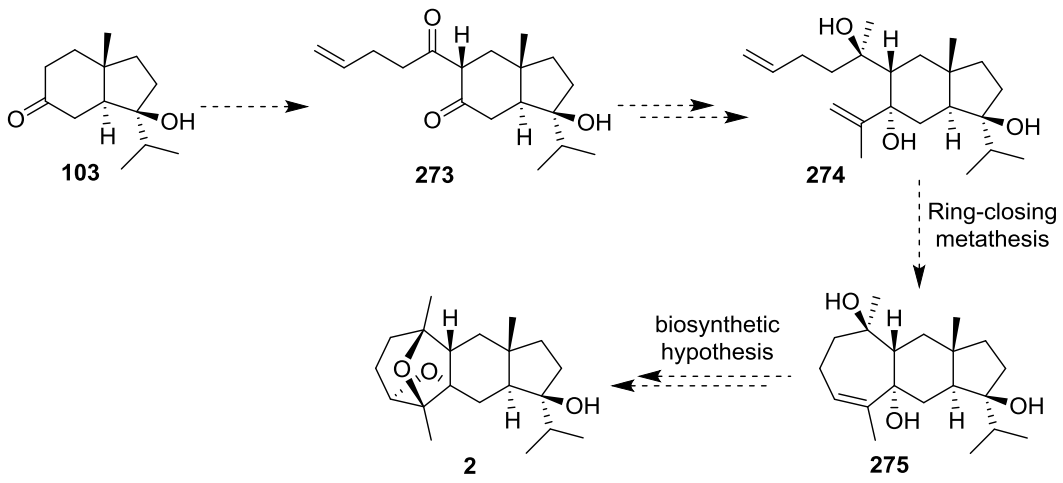
Unfortunately, due to the low yield obtained for the [5+2] annulation reaction, this approach to 7-membered ring formation was abandoned.

3.3.6 Proposed approach to dioxatricyclic ring annulation based on a biosynthetic hypothesis

Based on Hoffmann's biosynthetic hypothesis (Chapter 1, Section 3),[10] a synthetic approach to obtain the tricyclic tertiary triol **275** which is a proposed precursor in the synthesis of dictyoxetane **2** was investigated (Scheme 125).

The synthesis of the 1,3-diketone **273** would be achieved through a Claisen condensation of *trans*-hydrindanone **103**. To achieve the desired stereochemistry at the stereocentre between the two carbonyl groups, epimerisation might be required.

The introduction of the alkyl groups in **274** would require sequential chemoselective and stereoselective addition to both carbonyl moieties in **273**. Literature studies suggested that Grignard reagents could be directly added to 1,3-diketone **273** in the presence of anhydrous $CeCl_3$.[107] It was envisaged that the synthesis of the tricyclic tertiary triol **275** could be obtained through ring-closing-metathesis (Chapter 1, Section 3).



Scheme 125. Proposed approach to biosynthetic precursor **275**

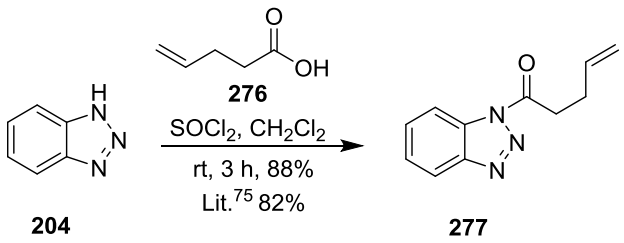
3.3.6.1 Initial approach to 1,3-diketone *via* soft enolisation

In 2007, Coltart and co-workers reported an efficient approach to 1,3-diketone formation *via* a modified Claisen condensation using soft enolisation.[77] Ketones undergo soft enolate formation and acylation under mild conditions. A weak base in concert with a mild Lewis acid effects the deprotonation of ketone reversibly in soft enolisation.[108] In their approach, *N*-acylbenzotriazole is combined with $MgBr_2.OEt_2$ in CH_2Cl_2 prior to the addition of a ketone

and *i*-Pr_2NEt. They suggested that the Lewis acid interacts with the carbonyl oxygen to polarise it and to enhance the acidity of the α-proton which can then be more easily deprotonated in the presence of a weak base.

3.3.6.2 Results and Discussion

Following Coltart's protocol, *N*-acylbenzotriazole **277** was prepared from the acid chloride of 4-pentenoic acid **276** formed with $SOCl_2$, followed by addition of benzotriazole **204**, giving rise to **277** in an excellent 88% yield (Scheme 126).



Scheme 126. Preparation of *N*-acylbenzotriazole **277**

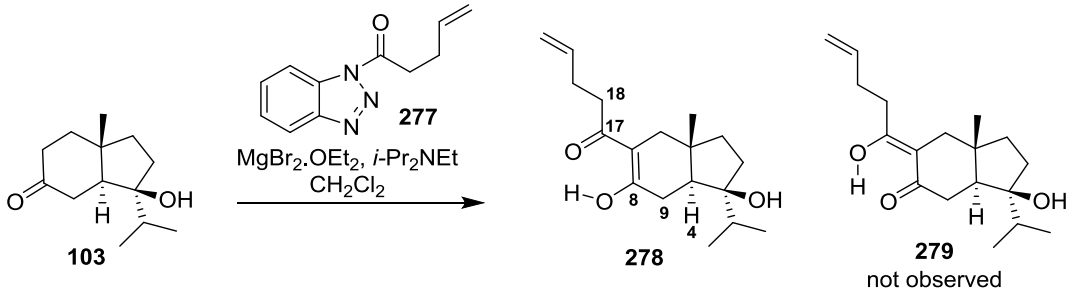
Literature precedent suggested that 1,3-diketone formation could be conducted with reagent-grade CH_2Cl_2 open to air. However, treating ketone **103** with **277** gave no reaction at room temperature with the starting material being recovered (Scheme 127). Monitoring the reaction by t.l.c. showed only the presence of the *trans*-hydrindane **103** after 5 h (Table 11, Entry 1). Increasing the temperature along with the reaction time gave 1,3-diketone **278** in 33% yield after 72 h (Entry 3). Reaction in a microwave at 90 °C led to the desired product in yields of 53% and 64%, achieved after 2 h and 8 h respectively (Entries 4 and 5).

The product **278** was isolated as an enol rather than a 1,3-diketone, as demonstrated by appearance of one quaternary carbonyl carbon and two new alkene carbons in the ^{13}C NMR

spectrum, and as a single regioisomer. The regiochemistry of enol ether formation was determined by ^{1}H- ^{13}C HMBC analysis. The correlation between the carbon at position 9 to the proton at the 4 position at the *trans*-ring junction of *trans*-hydrindane ring and also between the quaternary carbon 8 of the enol and protons at the 9 position, confirmed the regiochemistry of the C-C bond formation.

The relative positions of the C=O and enol was determined by ^{1}H-^{13}C HMBC analysis. No correlation was observed between the quaternary carbonyl carbon and the proton at the 4 position which proved the absence of the carbonyl moiety in the 6-membered ring. Furthermore, the correlation between the quaternary carbon of the carbonyl moiety at position 17 and methylene protons at position 18 demonstrated the position of the enol. Based on NMR spectroscopic analysis, the endocyclic enol **278** is favoured over the exocyclic one **279**.

It should be noted that in a different NMR solvent, a different equilibrium might be observed between the keto and enol form of the product. The enol form is presumably more stable than keto form in the slightly acidic NMR solvent ($CDCl_3$).



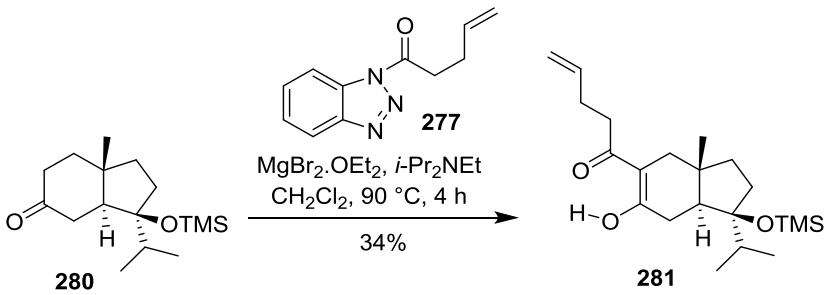
Scheme 127. Claisen condensation through soft enolisation

Entry	Conditions	Yield (**278**)
1	*N*-acylbenzotriazole (1.2 eq.), *i*-Pr_2NEt (3.0 eq.), $MgBr_2.OEt_2$ (2.5 eq.), rt , 5 h	-
2	*N*-acylbenzotriazole (1.2 eq.), *i*-Pr_2NEt (5.0 eq.), $MgBr_2.OEt_2$ (2.5 eq.), rt to reflux, 48 h	-
3	*N*-acylbenzotriazole (1.2 eq.), *i*-Pr_2NEt (3.0 eq.), $MgBr_2.OEt_2$ (2.5 eq.), rt to reflux 72 h	33%
4	*N*-acylbenzotriazole (1.2 eq.), *i*-Pr_2NEt (3.0 eq.), $MgBr_2.OEt_2$ (2.5 eq.), 90 °C (MW), 2 h	53%
5	*N*-acylbenzotriazole (1.2 eq.), *i*-Pr_2NEt (3.0 eq.), $MgBr_2.OEt_2$ (2.5 eq.), 90 °C (MW), 8 h	64%

Table 11. Attempted soft enolisation

Scaling up the reaction in the microwave was the main limitation of this approach to prepare **278**.

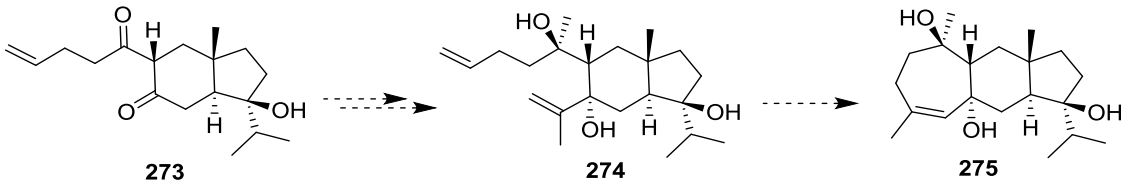
Attempted Claisen reaction on ketone **280** with the silyl-protected tertiary alcohol gave enol **281** in 34% yield, under the same conditions using a microwave reactor (Scheme 128).



Scheme 128. Synthesis of 1,3-diketone **281**

3.3.6.3 Proposed alkylation through Grignard addition

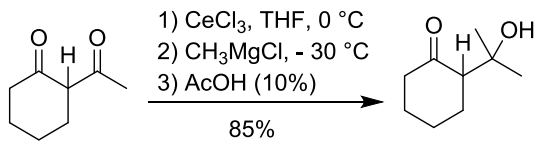
In order to carry out the annulation of the 7-membered carbocyclic ring through ring-closing metathesis (RCM), chemo- and stereoselective Grignard addition to the cyclic carbonyl moiety of 1,3-diketone **273** would be required (Scheme 129). The proposed approach would give the olefinic acyclic compound **274** required for the ring-closing metathesis to form **275**.



273 274 275

Scheme 129. Proposed approach to 7-membered ring formation

In 1993, Bartoli *et al*. reported a chemoselective Grignard addition on 1,3-diketones in the presence of a stoichiometric amount of anhydrous $CeCl_3$ (Scheme 130).[107]

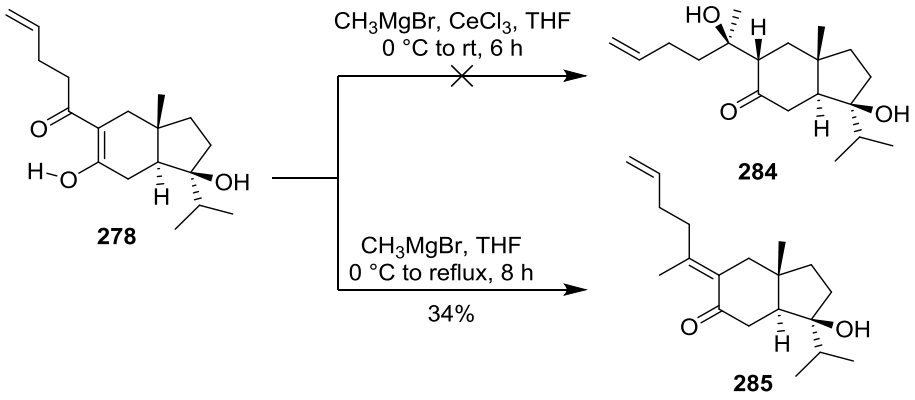


282 283

Scheme 130. Bartoli's Grignard addition to 1,3-diketone **282**

Following Bartoli's conditions, attempted Grignard addition using equimolar amounts of CH_3MgBr and $CeCl_3$ at 0 °C gave no reaction (Scheme 131). Monitoring the reaction by t.l.c. showed the degradation of the starting material along with numerous by-products, none of which could be isolated cleanly. Therefore, it was decided to use a large amount of the Grignard reagent in the absence of $CeCl_3$. The alkylation of **278** was performed with 6.0 equivalents of Grignard reagent, giving the methylated product **285** with further elimination

along with numerous side-reactions occurring. The geometry of the double bond was unidentified. ^{1}H-^{13}C HMBC analysis of **285** showed the correlation between the proton at the *trans*-ring junction and the quaternary carbonyl carbon, confirming the position of double bond.



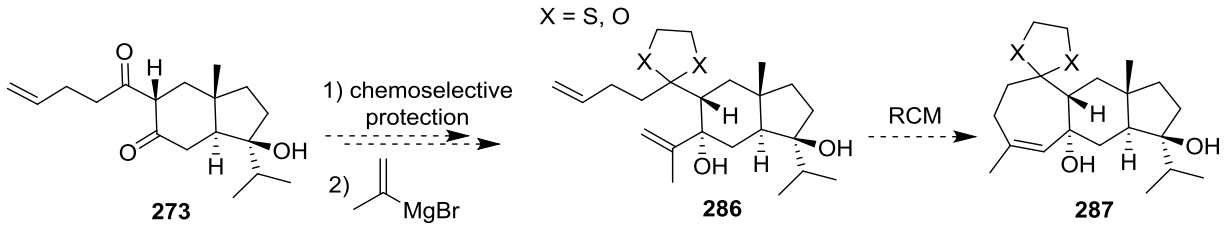
Scheme 131. Attempted Grignard addition

This failure to introduce the methyl functionality through Grignard addition meant alternative approaches to chemoselective protection of one of the carbonyl moieties of 1,3-diketone **273** needed to be investigated.

3.3.6.4 Proposed chemoselective protection of the carbonyl functionality

With the 1,3-diketone **273** in hand, an alternative approach to **287** was considered, based on chemoselective carbonyl protection (Scheme 132). The selective carbonyl protecting group would need to be compatible with ring-closing metathesis. This would allow reaction of a Grignard reagent with the other carbonyl moiety on the 6-membered ring giving the olefinic acyclic compound **286** as a precursor for ring-closing metathesis.[109] Literature studies

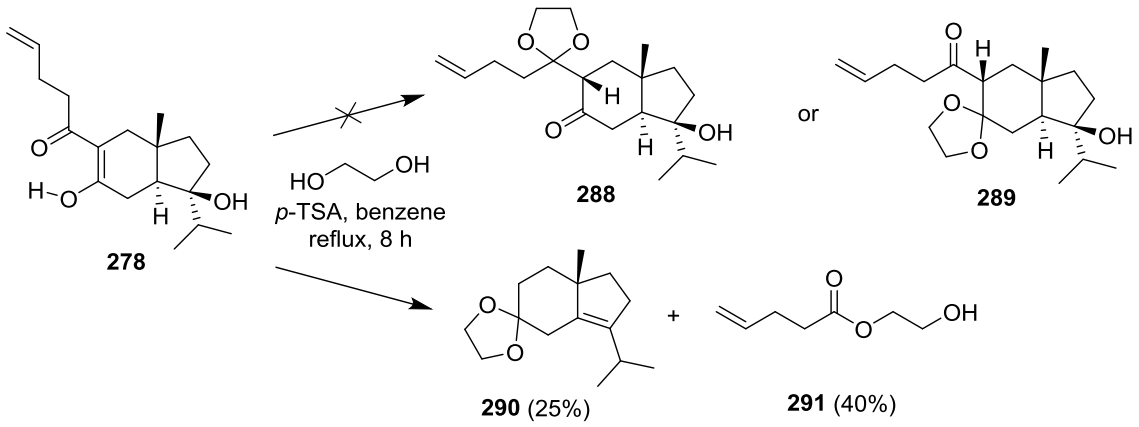
showed that in symmetric 1,3-diketones both carbonyl functionalities could be protected as an acetal.[110] However, in asymmetric 1,3-diketones selective protection of the carbonyl functionality depends on both the protecting group and the reaction conditions. Therefore, the selective protection of the exocyclic carbonyl functionality was proposed.



Scheme 132. Proposed approach to 7-membered ring annulation **287**

Attempted chemoselective acetal protection using ethylene glycol in the presence of a catalytic amount of *p*-TSA furnished acetal **290** along with the retro-Claisen condensation product **291** in 25% and 40% yields respectively (Scheme 133).

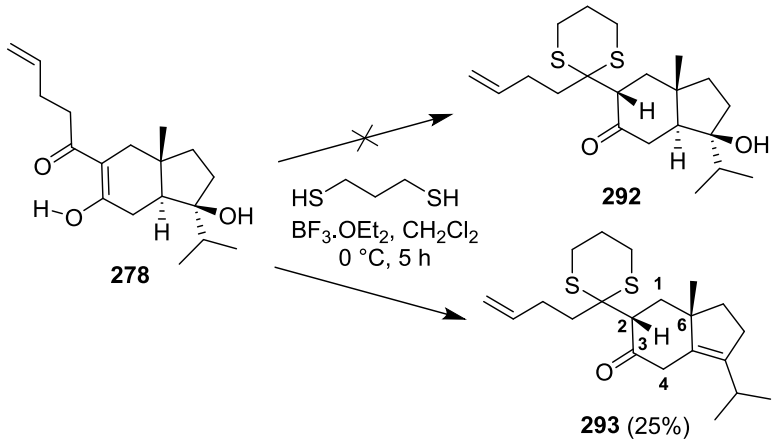
^{1}H NMR spectroscopic analysis revealed the absence of protons in the ethylenic region expected for **288** or **289**, confirming that retro-Claisen reaction had occurred. The ^{13}C NMR spectrum did not show the methine proton which would be expected at the *trans*-ring junction of **288** or **289**. The presence of a new quaternary olefinic carbon at 135.8 ppm suggested elimination of the tertiary alcohol. It was believed that the presence of *p*-TSA led to the elimination product.



Scheme 133. Attempted acetal protection

Due to the problem encountered in the selective acetal protection of **278**, attention was focused on a thioacetal protecting group.

The chemoselective thioacetal protection of one of the ketones was next performed. Treating **278** with 1,3-propanedithiol under mild Lewis acid conditions gave rise to the thioacetal **293** in only 25% isolated yield (Scheme 134).[111] Again elimination of the alcohol occurred. The starting material was not fully consumed, as observed by t.l.c. analysis.



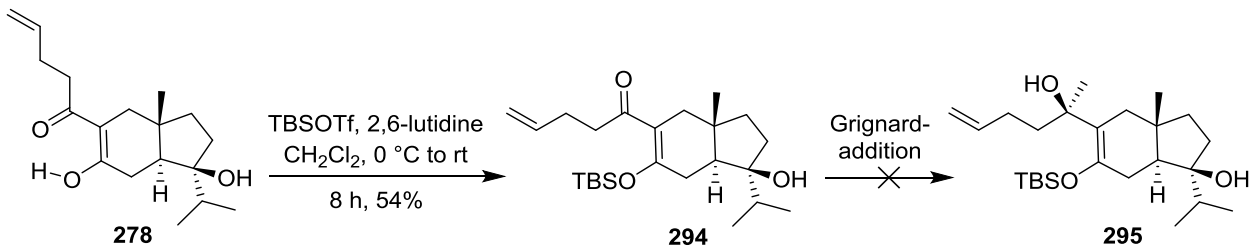
Scheme 134. Attempted thioacetal formation

^{1}H-^{13}C HMBC analysis of **293** showed a correlation between the quaternary carbon of the carbonyl moiety and the protons at the position 4 in the 6-membered ring. Furthermore, the correlation between the quaternary carbon of the thioacetal functionality and methylene protons of the side chain proved the chemoselectivity of the product.

nOe Studies were undertaken to determine the stereochemistry of the product. Irradiation of the methyl group showed an nOe to the proton at position 2 adjacent to the thioacetal on the 6-membered ring. This implies that this hydrogen and the methyl group are *syn* in relation to one another.

Due to the low yield of thioacetal **293** and the elimination of the tertiary alcohol, chemoselective protection of the carbonyl functionality through this approach was abandoned.

An alternative approach to selectively protect one carbonyl moiety of compound **278** was considered using a silyl enol ether (Scheme 135). Regioselective silyl enol ether formation gave **294** by treating enol **278** with TBSOTf in the presence of 2,6-lutidine.[112] The silyl enol ether **294** was isolated in 54% yield along with unreacted starting material being recovered.



Scheme 135. Attempted silyl protection and Grignard addition

X-ray analysis of **294** confirmed the regioselectivity of silyl enol ether formation (Figure 10).

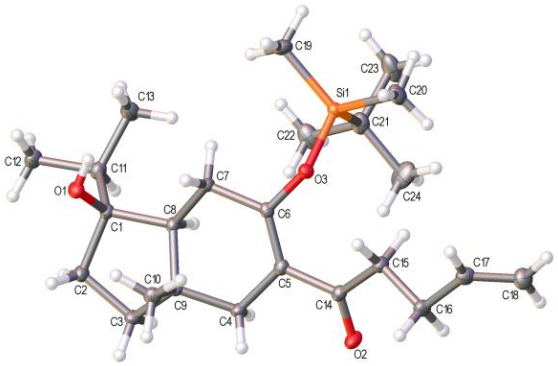
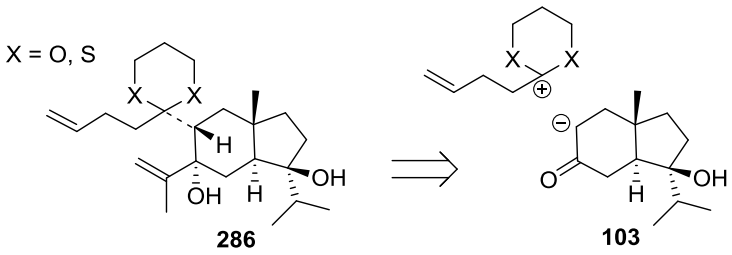


Figure 10. X-ray structure of silyl enol ether **294**

However, attempted Grignard addition to the remaining carbonyl functionality gave no reaction, with unreacted starting material recovered. It was believed that the nucleophilic attack at the carbonyl in the presence of the bulky and robust TBS protecting group is difficult.

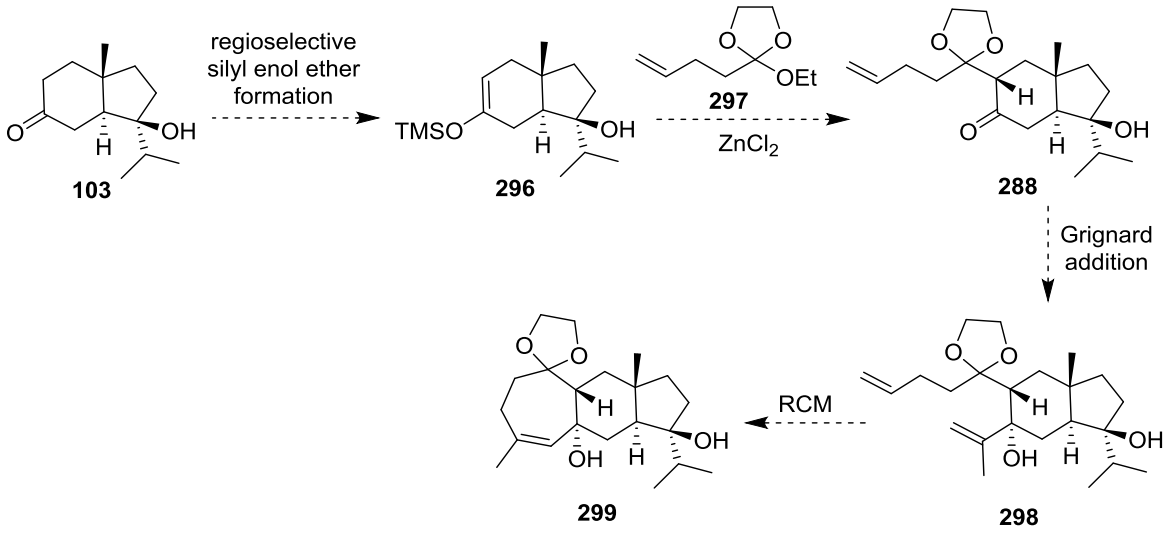
3.3.6.5 Alternative approaches to introducing a protected carbonyl

Due to the unsuccessful results obtained from chemoselective protection of the carbonyl moieties of 1,3-diketone **273**, an alternative approach was proposed. This involved introducing the protected carbonyl to the ring system (Scheme 136).



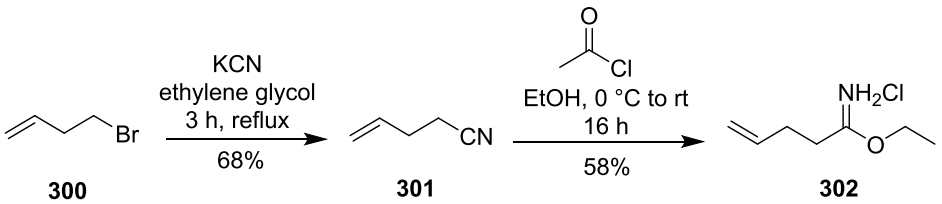
Scheme 136. Proposed approach to introduce a protected carbonyl on **103**

In 1999, Ates and Markó reported the introduction of a protected ketone functionality to silyl enol ether.[113] According to Markó's protocol, the condensation of silyl enol ether **296** with the orthoacetal **297** would lead to β-ketoacetal **288** (Scheme 137).[114]



Scheme 137. Proposed approach to the 7-membered ring *via* introduction of a protected carbonyl

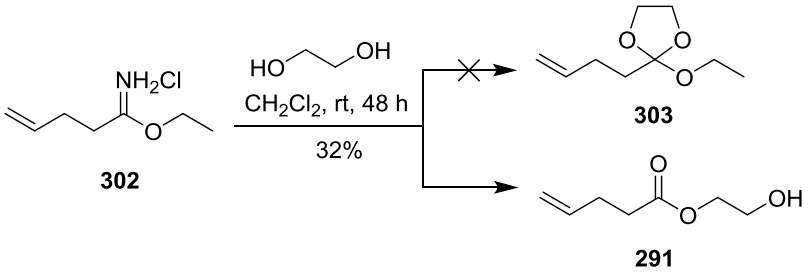
Initially, the synthesis of the requisite annulating agent, orthoacetal **297** was attempted (Scheme 138). Following a literature procedure, treatment of 1-bromo-4-butene **300** with potassium cyanide gave the nitrile **301** in 68% yield.[115] Nitrile **301** was then converted to imidate **302** under classical Pinner conditions.



Scheme 138. Formation of imidate **302**

Treating imidate **302** with ethylene glycol gave ester **291** rather than the desired orthoacetal **303** (Scheme 139).[116] Use of anhydrous ethylene glycol had no effect on the result of this

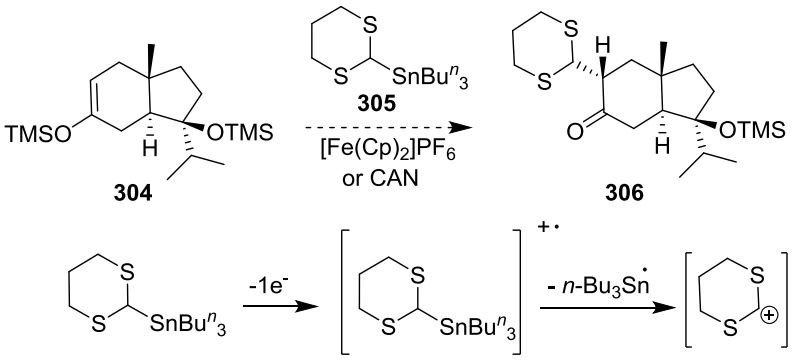
reaction. As imidate **302** is a hygroscopic compound and decomposes easily, there is no further purification reported. It was believed that the dissolved HCl generated in the process of imidate formation was not removed thoroughly from the product **302**, which could drive the reaction to the formation of ester **291**. Even keeping the imidate in a vacuum desiccator over P_2O_5 for several days did not circumvent this issue.



Scheme 139. Attempted formation of orthoacetal **303**

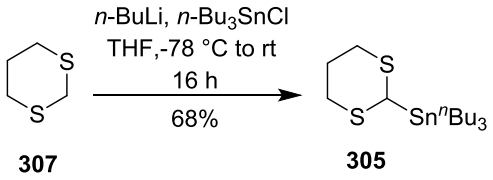
Unfortunately, due to the lack of success in preparing orthoacetal **303**, Markó's approach to C-C bond formation with selective carbonyl protection was not examined. Consequently, attention was turned to alternative approaches.

In 1993, Narasaka *et al*. reported C-C bond formation through nucleophilic addition of silyl enol ethers to the 1,3-dithionyl cation.[117] The cation could be generated *in situ* from single-electron oxidation of 2-tributylstannyl-1,3-dithiane **305** forming the cation radical intermediate which dissociates into a tin radical and the 1,3-dithionyl cation, to form the intermolecular addition product (Scheme 140).



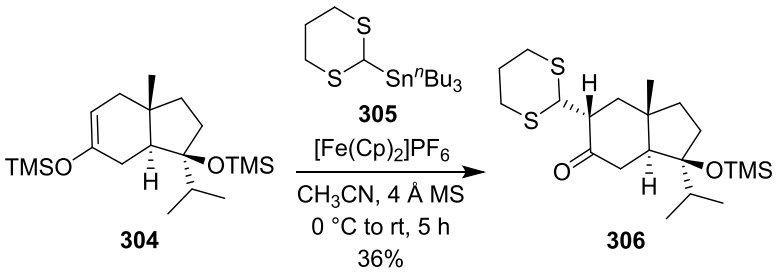
Scheme 140. Narasaka's route to introduce a protected carbonyl

The synthesis of the 1,3-dithian-2-yltin compound **305** was carried out. Treatment of 1,3-dithiane **307** with n-Bu_3SnCl in the presence of n-BuLi gave the 1,3-dithian-2-yltin compound **305** in 68% yield (Scheme 141).[118]



Scheme 141. Synthesis of 2-tributylstannyl-1,3-dithiane **305**

With the 1,3-dithian-2-yltin compound **305** in hand, introducing the protected ketone functionality was attempted under Narasaka's conditions (Scheme 142). Silyl enol ether **304** (Section 3.3.6.6)[119] was treated with 1,3-dithian-2-yltin compound **305** in the presence of equimolar ferrocenium hexafluorophosphate $[Fe(Cp)_2]PF_6$, as an oxidising agent, giving rise to **306** in 36% yield. Yields in this reaction are typically low due to competing desilylation. Monitoring the reaction by t.l.c. confirmed the hydrolysis of the silyl protecting group, resulting in recovery of **103**.



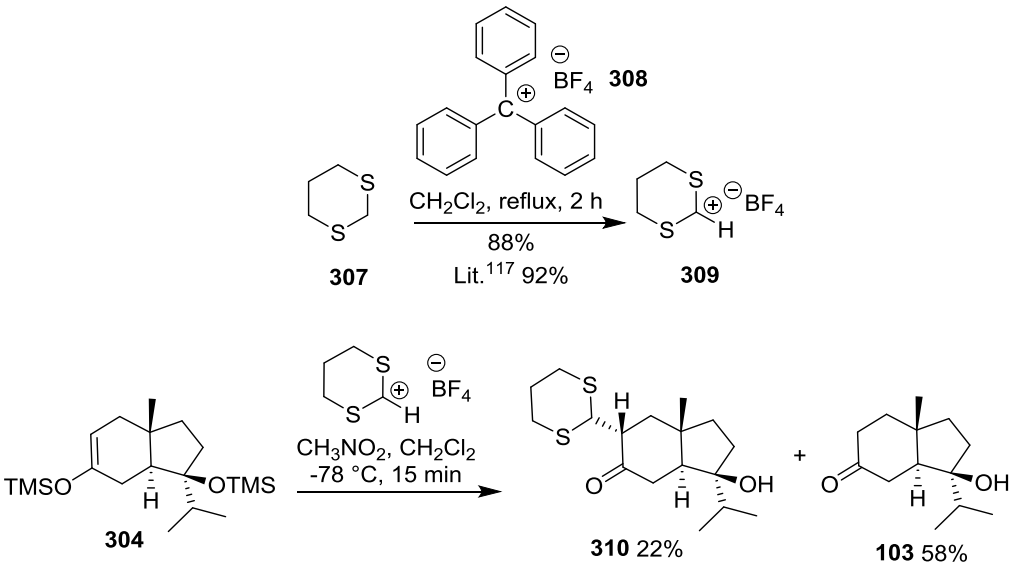
Scheme 142. Introduction of thioacetal protected carbonyl

Under the same conditions, attempted reaction in the presence of ammonium hexanitratocerate(IV) CAN as an oxidising agent did not give the desired product. The removal of silyl protection groups was observed giving *trans*-hydrindanone **103**.

As a result of low yields obtained in introducing a thioacetal-protected carbonyl functionality, attention turned to an alternative route to C-C bond formation. This approach would involve a different method to generate the 1,3-dithionyl cation.

In 1981, Paterson and Lee demonstrated alkylation of silyl enol ethers using the thiocarbocation salt, 1,3-dithienium fluoroborate **309**, to form selectively protected β-dicarbonyl compounds (Scheme 143).[120] 1,3-Dithienium fluoroborate **309** was prepared by hydride abstraction from 1,3-dithiane **307** by trityl fluoroborate **308**. Repetition of this reaction gave compound **309** in 88% yield after trituration.

Based on their protocol, treatment of silyl enol ether **304** with 1,3-dithienium fluoroborate **309** gave the thioacetal **310** in 22% isolated yield along with recovery of **103** in 58% yield. ^{1}H NMR spectroscopic analysis proved the silyl deprotection of the tertiary alcohol.



Scheme 143. Introduction of thioacetal-protected carbonyl

X-ray analysis of the thioacetal **310** confirmed the stereochemistry of the product (Figure 11). Oxidation of one of the sulfur atoms had occurred (in 11% of cases). It is thought that the oxidation of the sulfide to the sulfoxide may have occurred during the growing of the crystals, either by air or as a result of the solvent employed.

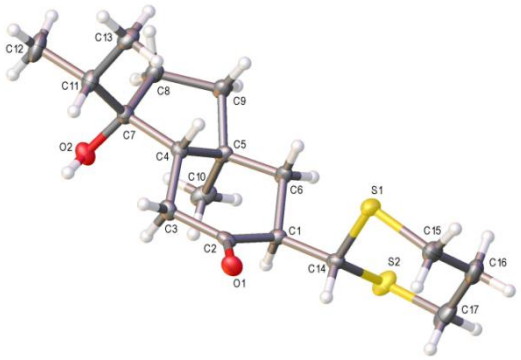
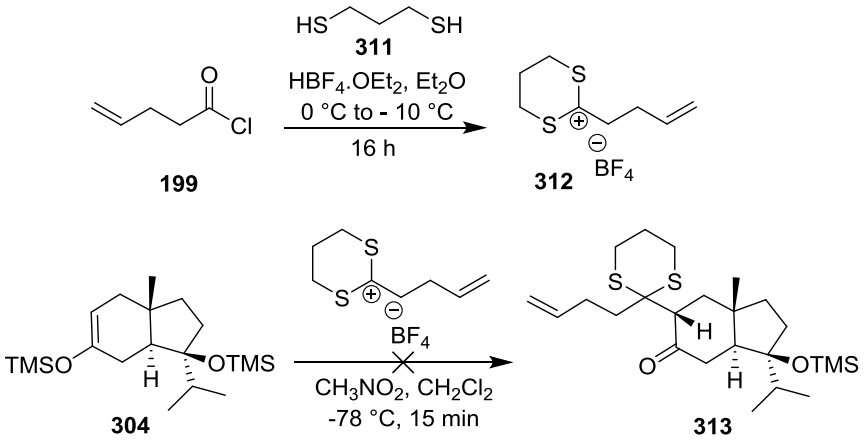


Figure 11. X-ray structure of thioacetal **310**

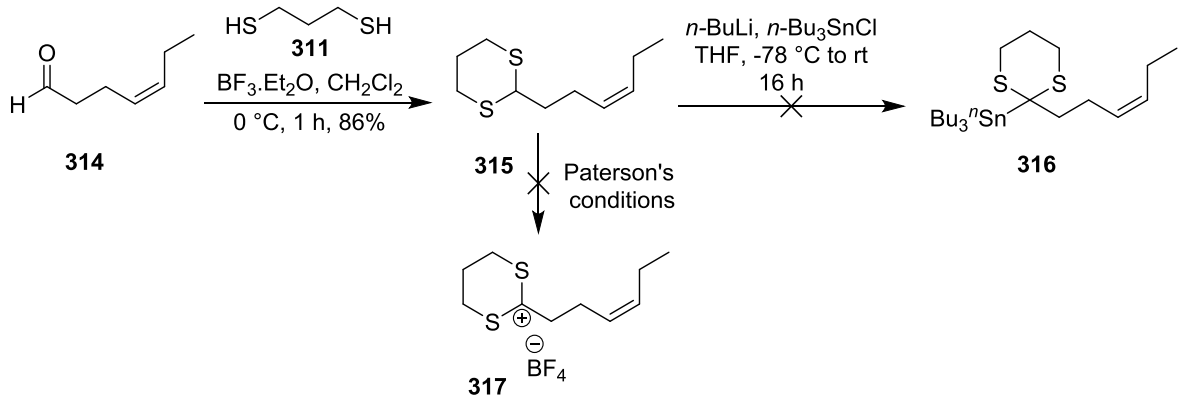
As a consequence of the lack of success in improving the yield of reaction, introducing a more substituted 1,3-dithiane was investigated. Dithianylium tetrafluoroborate **312** was synthesised from acyl chloride **199** in the presence of tetrafluoroboric acid (Scheme 144).[121]

Jung and Bräse reported the purification of **312** by separation; however, it was not possible to separate the product from the solvent. Subsequently, attempted thioacetal formation did not give the desired product **313** but instead ketone **103** was recovered.



Scheme 144. Attempted preparation of **313**

A more substituted 1,3-dithiane **315** was also investigated. Initially, the thioacetal formation was performed by treating the aldehyde **314** with 1,3-propanedithiol **311**, giving **315** in an excellent 86% yield (Scheme 145). However, attempted dithianylium tetrafluoroborate **317** formation was not successful, under Paterson's conditions.[120] Furthermore, attempted 2-tributylstannyl-1,3-dithiane **316** formation gave only recovered starting material.



Scheme 145. Preparation of a more substituted 1,3-dithiane

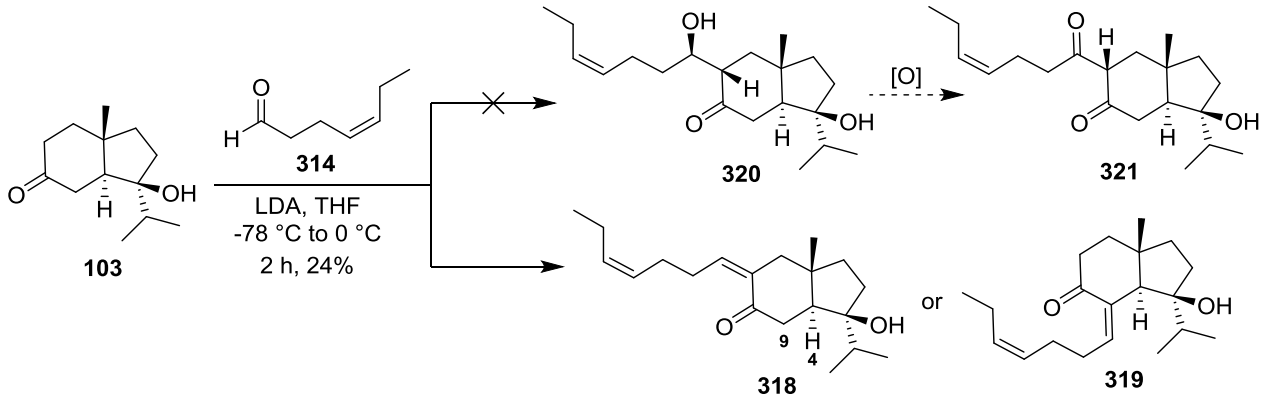
Unfortunately due to the lack of success in introducing a protected carbonyl as a thioacetal, this approach was abandoned.

3.3.6.6 Proposed aldol-oxidation sequence to introduce 1,3-diketone

The aldol reaction has been recognised to be one of the most useful synthetic tools in organic chemistry. It was proposed that an aldol reaction of **103** followed by oxidation could be used to prepare 1,3-diketone **321** (Scheme 146).

According to a literature procedure, the enolate which is generated from **103** in the presence of LDA reacts with *cis*-4-hepten-1-al **314** to furnish the novel α-β-unsaturated ketone **318**, the product of crossed-condensation and dehydration, isolated as a single double bond isomer in 24% yield.[122] The unreacted starting material **103** was recovered.

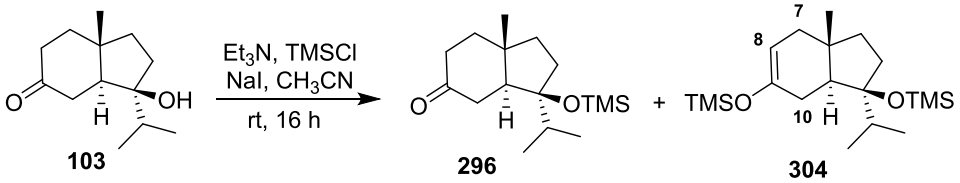
^{1}H NMR spectroscopic analysis indicated a new methine peak in the olefinic region and the ^{13}C NMR spectrum showed three olefinic signals at 128.8, 133.9 and 143.1 ppm which confirmed that dehydration had occurred. The correlation between the proton at the *trans* ring junction and the carbon at position 9 in the 6-membered ring confirmed that the product is **318** rather than **319**, as indicated by ^{1}H-^{13}C HMBC analysis. The geometry of the double bond next to the carbonyl functionality is undetermined.



Scheme 146. Crossed-aldol addition to *trans* hydrindanone **103**

Due to the lack of success in preparing **320**, it was decided to apply the classical Mukaiyama aldol procedure, starting from a silyl enol ether. First, ketone **103** was employed in a silylation reaction to obtain silyl enol ether **296** (Scheme 147).[123] Treating ketone **103** with TMSCl in the presence of NaI and Et_3N at room temperature gave silyl ether **296** along with the bis-silylated product **304** in 35% and 34% yields respectively. The bis-silylated product **304** was obtained as a single regioisomer.

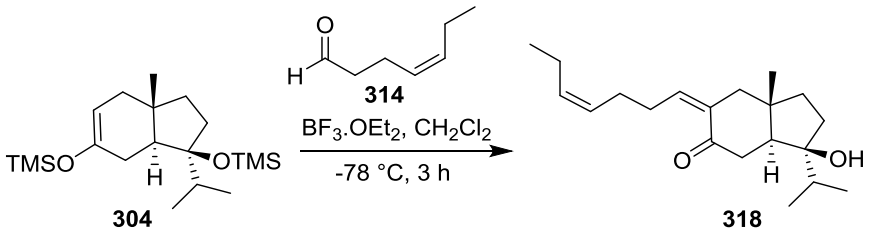
^{1}H-^{13}C HMBC analysis of **304** showed the correlation between the proton at the *trans* ring junction and carbon at the position 10 in the 6-membered ring. Furthermore, the correlation between the olefinic proton at the 8 position and carbon at the 7 position in the 6-membered ring confirmed the regiochemistry of the silyl enol ether formation.



Scheme 147. Silyl enol ether formation

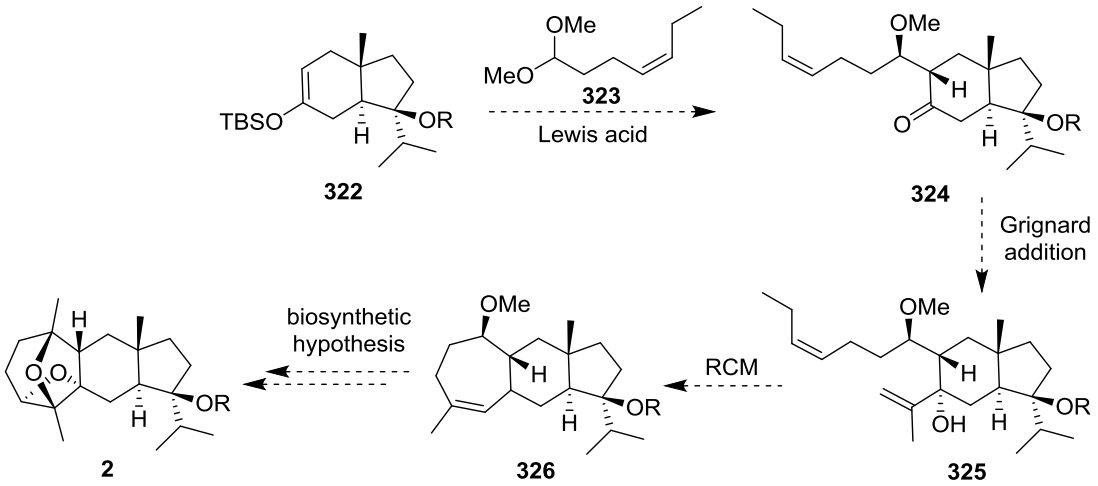
The aldol reaction was then performed under mild conditions, employing $BF_3.OEt_2$ and forming product **318** which was isolated as a single double bond isomer in 28% yield, along with the removal of the silyl protecting group on the tertiary alcohol (Scheme 148).[124] The geometry of the double bond next to the carbonyl functionality was undetermined.

^1H NMR spectroscopic analysis showed silyl ether deprotection and the presence of three methine (C-H) peaks in the olefinic region. The bis-silylated **304** was fully consumed in the reaction with conversion to ketone **103** also observed.



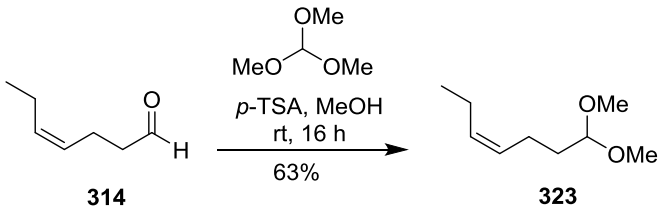
Scheme 148. Mukaiyama aldol reaction

An alternative Mukaiyama aldol-type reaction was also investigated (Scheme 149). In 2012, Hashimoto and co-workers reported a Mukaiyama aldol-type reaction of a silyl enol ether with a dimethyl acetal.[125] They found that TMSOTf would promote the aldol reaction to give the coupling product.



Scheme 149. Proposed approach to form **325**

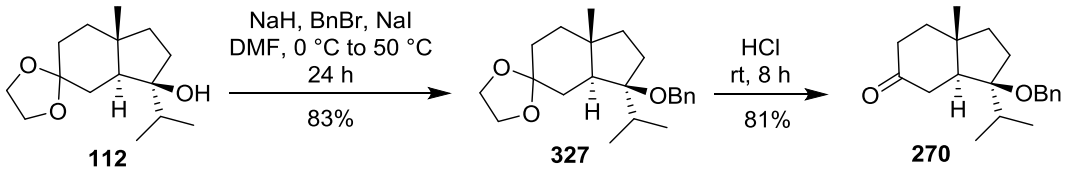
Dimethyl acetal **323** was synthesised by treating aldehyde **314** with MeOH and trimethyl orthoformate in the presence of a catalytic amount of *p*-TSA giving rise to **323** in 63% isolated yield (Scheme 150).[125] The yield was affected by the volatile nature of compound **323** during purification.



Scheme 150. Preparation of dimethyl acetal

As a consequence of the observed elimination of the tertiary alcohol in the presence of Lewis acids, it was decided to protect the tertiary alcohol prior to the Mukaiyama aldol reaction.

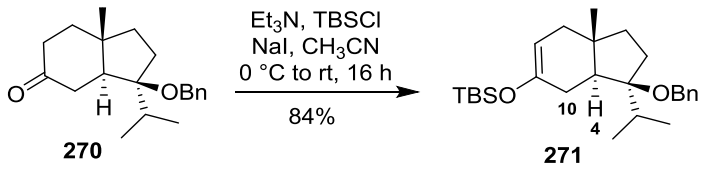
Alcohol **112** was transformed to benzyl ether **327** under basic conditions using benzyl bromide and NaI giving **270** in 83% yield (Scheme 151).[126] Subsequent acetal hydrolysis of **327** gave **270** in 81% yield.



Scheme 151. Synthesis of *trans*-hydrindanone **270** with protected tertiary alcohol

In order to conduct a Mukaiyama aldol-type addition, conversion of the ketone to the silyl enol ether **271** was attempted using TBSCl (Scheme 152). Treatment of ketone **270** with Et_3N and TBSCl in the presence of NaI gave silyl enol ether **271** in 84% yield.[127]

As observed previously, ^{1}H-^{13}C HMBC analysis showed the correlation between the proton at the *trans* ring junction and the carbon at the 10 position in the 6-membered ring, confirming the regiochemistry of the silyl enol ether formation.



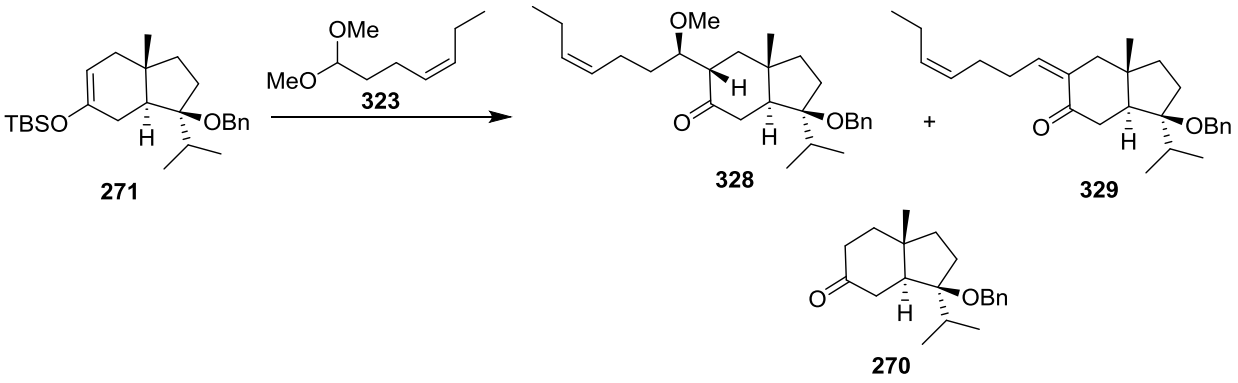
Scheme 152. TBS-enol ether formation

With silyl enol ether **271** in hand, Mukaiyama aldol addition of enol **271** to dimethyl acetal **323** was performed (Scheme 153). According to the literature procedure, coupling silyl enol ether **271** with 1.1 equivalents of dimethyl acetal **323** in the presence of $TiCl_4$ as a Lewis acid

furnished the compound **329** in 70% isolated yield. This compound is the product of elimination of methanol (Table 12, Entry 1).

^{1}H NMR spectroscopic analysis of **329** revealed the disappearance of the methoxy peak and the appearance of a new ethylenic proton at 6.75 ppm. Moreover, the ^{13}C NMR spectrum confirmed a new olefinic quaternary carbon signal at 134.7 ppm. However, the geometry of the double bond was undetermined. It was then decided to examine the reaction in the presence of TMSOTf as a milder Lewis acid. Attempted aldol reaction using 2.0 equivalents of **271** in the presence of 0.1 equivalent of TMSOTf afforded **328** and **329** in yields of 57% and 28% respectively (Entry 2). Subsequently, treating silyl enol ether **271** with an equimolar amount of dimethyl acetal **323** in the presence of a catalytic amount of Lewis acid gave **328** in 66% isolated yield along with elimination of methanol **329** in 21% yield (Entry 3). Monitoring the reaction by t.l.c. showed the presence of a small amount of **270** when the reaction was carried out using TMSOTf.

The products **328** and **329** are obtained as single isomers. The stereochemistry of compound **328** was undetermined but assumed to be as shown, based on the expected addition to lower face of the enol, as observed previously (Section 3.3.5) which was required for the synthesis of dictyoxetane. According to Lee's protocol, the stereoselectivity of the first bond forming reaction is dependent on the coordinating properties of the Lewis acid.



Scheme 153. Mukaiyama aldol addition to enol **271**

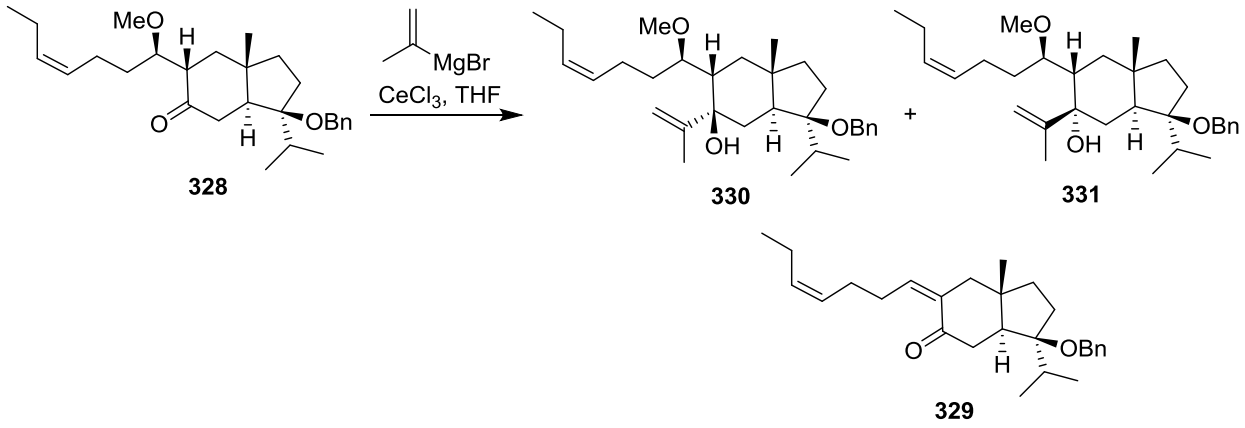
Entry	Reagent	Conditions	Yield
1	1.1 eq.	$TiCl_4$ (1.0 M, 10 mol%), powdered 3 Å MS, CH_2Cl_2, -78 °C, 3 h	**329** 70% **270** 21%
2	2.0 eq.	TMSOTf (10 mol%), powdered 3 Å MS, CH_2Cl_2, -78 °C, 4 h	**328** 57% **329** 28%
3	1.0 eq.	TMSOTf (6 mol%), powdered 3 Å MS, CH_2Cl_2, -78 °C, 4 h	**328** 66% **329** 21%

Table 12. Attempted aldol reaction

To establish the 7-membered carbocyclic ring system, Grignard addition to the remaining carbonyl functionality was required (Scheme 154). Taber *et al*. (2011) reported a procedure for the addition of 2-propenylmagnesium bromide in the presence of anhydrous $CeCl_3$.[109] Under Taber's conditions, treatment of ketone **328** with a Grignard reagent using anhydrous $CeCl_3$ gave no reaction, with starting material being recovered (Table 13, Entry 1). Increasing the reaction temperature from 0 ˚C to reflux gave elimination of the methoxy group giving **329** in 81% yield (Entry 2). Under more forcing conditions, treating ketone **328** with the organocerium(III) reagent at 130 °C in the microwave gave **330** and **331** in 42% yield as an

inseparable mixture of diastereoisomers (Entry 3). The elimination product **329** was also present in the reaction mixture.

Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated the two diastereoisomers formed were present in a 1.6:1 ratio.



Scheme 154. Grignard addition to **328**

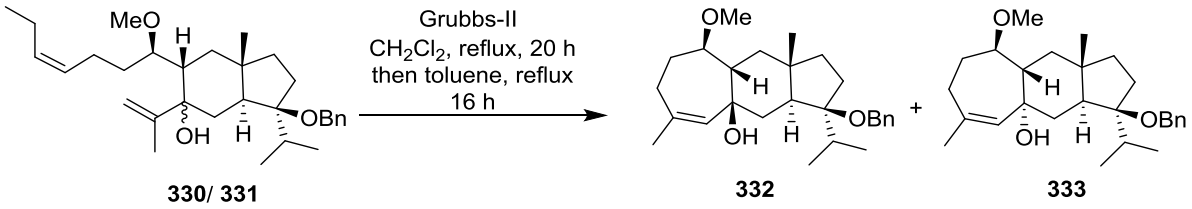
Entry	Conditions	Yield
1	*i*-propenylmagnesium bromide (3.2 eq.), $CeCl_3$ (3.8 eq.), THF, 0 °C to -78 °C, 6 h	-
2	*i*-propenylmagnesium bromide (3.2 eq.), $CeCl_3$ (3.8 eq.), THF, 0 °C to reflux, 16 h	**329** (81%)
3	*i*-propenylmagnesium bromide (3.2 eq.), $CeCl_3$ (3.8 eq.), THF, 0 °C to 130 °C (MW), 8 h	**330** (42%) **331** (36%)

Table 13. Attempted Grignard addition to **328**

3.3.7 Ring-Closing Metathesis

It was envisaged that the olefinic acyclic compounds **330** and **331** would be suitable precursors for 7-membered carbocyclic ring annulation *via* ring-closing metathesis (Scheme

155). Attempted metathesis on the inseparable diastereoisomers **330** and **331** to construct the 7-membered rings **332** and **333** in the presence of 20 mol% of ruthenium catalyst in refluxing CH_2Cl_2 gave no reaction after 20 h.[128] The 7-membered ring system was successfully formed in refluxing toluene, giving two separable diastereomers in 55% and 33% yield. The major product could not be assigned.



330/ 331 **332** **333**

Scheme 155. Ring-closing metathesis to establish 7-membered ring system

3.4 Conclusion and future work

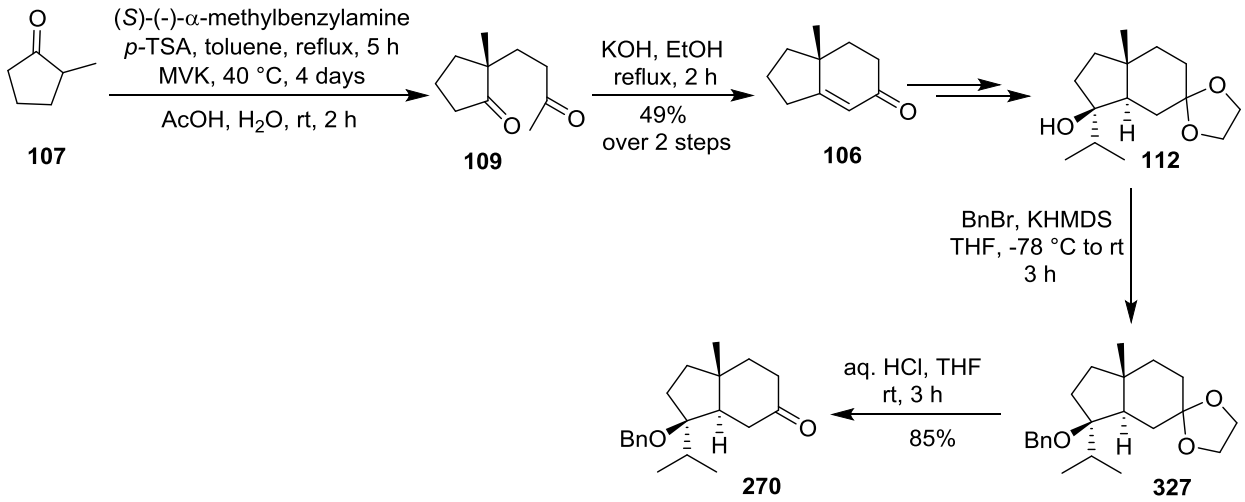
A variety of approaches were examined to annulate a 7-membered ring system. Two successful routes to 7-membered ring annulation on the *trans*-hydrindanone **103** have been developed. The first approach was based on a [5+2] annulation using an allylsilane acetal. It was found that TBS enol ether gives directly the annulated product **272** using TMSOTf as an activator with the tertiary alcohol in protected form. This approach currently suffers from the low yield of **272**, but if this can be overcome, future work will be focused on developing a synthetic route from **272** to the dioxatricyclic ring system of dictyoxetane **2**.

Ring-closing-metathesis offered an alternative route to 7-membered carbocyclic ring annulation, furnishing tricyclic rings **332** and **333**. Further studies to establish the stereochemistry of the major product and to develop a methodology to complete the first synthesis of dictyoxetane will be required.

Chapter four: Addendum

4.1 The Magauer total synthesis of (+)-dictyoxetane

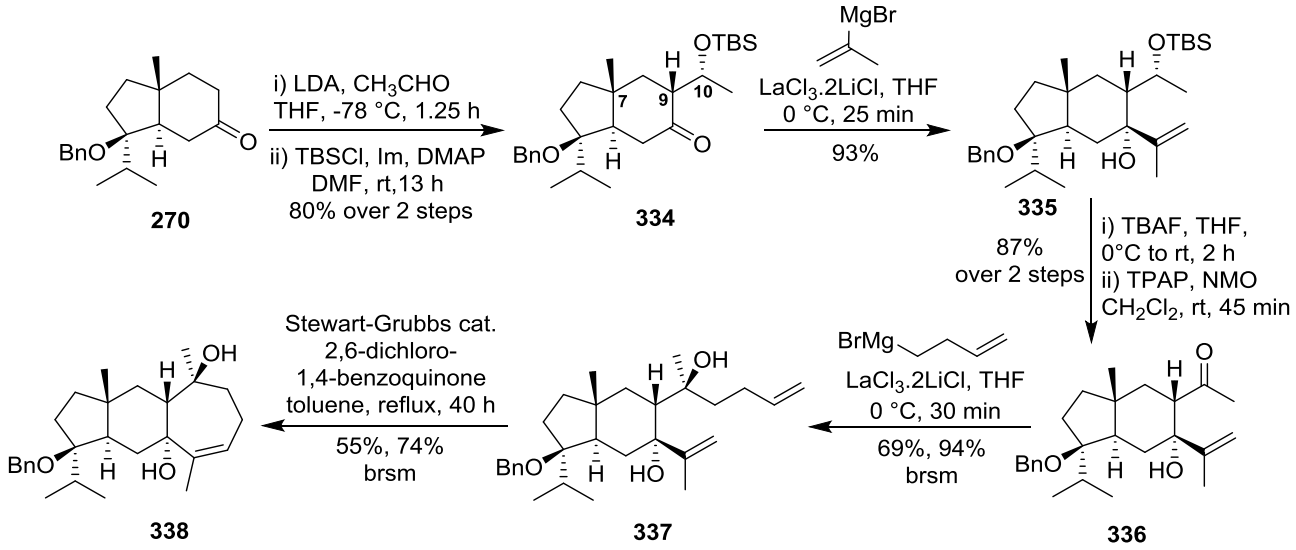
At the outset of this research, a total synthesis of dictyoxetane had not been reported. However, upon completion of the research reported in this thesis and shortly before submission, the first total synthesis of dictyoxetane was reported by Hugelshofer and Magauer in May of 2016.[129] The synthetic approach to the target compound was designed starting from *trans*-hydrindanone **103**, initially reported by the Grainger group in 2012. As previously discussed, hydrindanone **106** plays a key role in the synthesis of ketone **270**. In order to synthesise the enantiomerically enriched enone **106**, (*S*)-(-)-α-methylbenzylamine was used as a chiral auxiliary in the Robinson annulation sequence (Chapter 1, Section 5.1).[39] As previously described (Chapter 2, Section 3), Magauer synthesised *trans*-hydrindanone **270** following the Grainger protocol (Scheme 156). In contrast to the conditions reported in this thesis, benzylation of tertiary alcohol **112** was carried out in the presence of KHMDS in THF, instead of using NaH in DMF.



Scheme 156. Preparation of *trans*-hydrindanone **270**

With *trans*-hydrindanone **270** in hand, regio- and stereoselective aldol reaction with acetaldehyde using LDA gave β-hydroxy ketone which was protected with TBSCl in the presence of imidazole and DMAP, forming silyl ether **334** in 80% yield over two steps (Scheme 157). Due to the stereodiscriminating effect of the quaternary centre attached to the methyl functionality, **334** was formed as a single diastereomer at the stereocentre at position 9 and as a 10:1 mixture at the 10 position. The Grignard addition of *iso*-propenylmagnesium bromide to the cyclic carbonyl functionality, activated by a lanthanide salt, furnished allylic alcohol **335** as a single diastereomer in high yield.[130] Cleavage of the silyl ether using TBAF, followed by Ley-Griffith oxidation, furnished ketone **336** in 87% yield over two steps.[131]

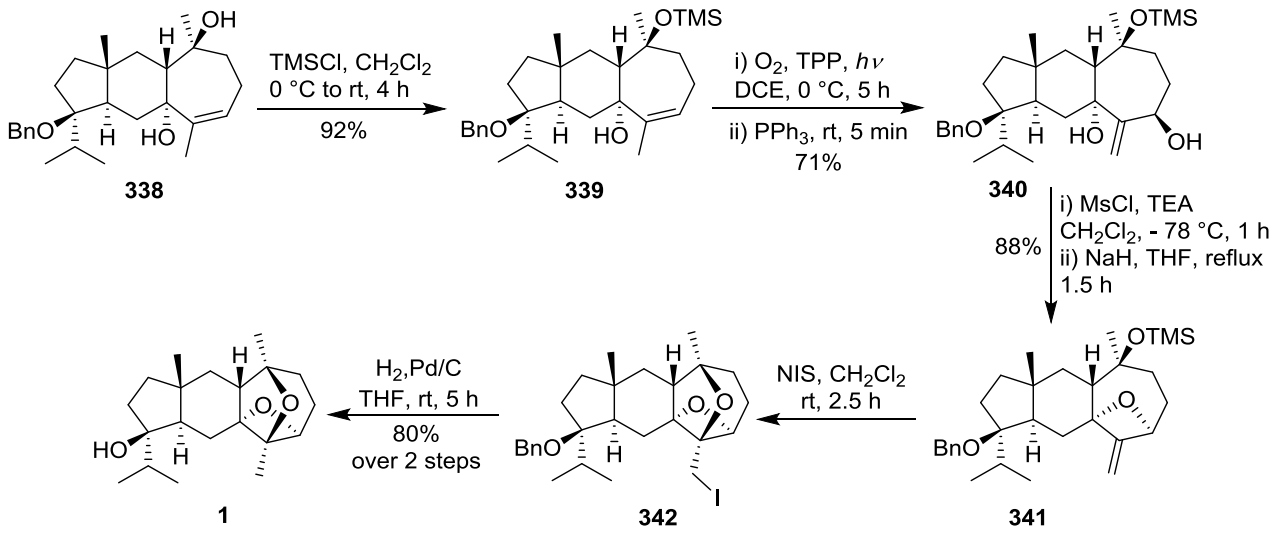
In order to annulate a 7-membered ring, Grignard addition of 3-butenylmagnesium bromide to the β-hydroxy ketone **336**, in the presence of lanthanum(III) chloride complex, afforded the corresponding diene **337** as a single diastereomer (Scheme 157). The synthesis of the tricyclic tertiary diol **338** was obtained *via* ring-closing-metathesis of terminal diene **337**, catalysed by 20 mol% Grubbs (II) in the presence of a benzoquinone derivative.[132] The electron-deficient benzoquinone was used as an additive to suppress the undesirable olefin isomerisation during olefin metathesis.[133]



Scheme 157. Synthetic route to 7-membered ring annulation

In order to synthesise the dioxatricyclic ring system, the oxetane ring was constructed prior to the formation of the tetrahydrofuran ring (Scheme 158). Protection of tertiary alcohol **338** adjacent to the methyl group with *N*-trimethylsilylimidazole at 0 °C gave silyl ether **339** in 92% yield. Photocatalytic oxidation of the silyl ether **339** followed by reduction of the hydroperoxide intermediate with PPh_3 gave allylic alcohol **340** as a single regio- and diastereomer in 71% yield.

Treatment of alcohol **340** with MsCl using TEA afforded an allylic mesylate which was employed in a 4-*exo*-tet cyclisation, under basic conditions in refluxing THF, giving oxetane **341** in 88% yield over two steps. Treatment of **341** with NIS led to 5-*exo*-tet cyclisation with concomitant silyl ether deprotection, giving the tetrahydrofuran of the dioxatricyclic ring system **342**. Subsequently, dictyoxetane **1** was synthesised *via* hydrogenolysis of the benzyl ether, with concomitant dehalogenation of the primary iodide.



Scheme 158. Synthetic approach to dictyoxetane **1**

In summary, the first asymmetric total synthesis of (+)-dictyoxetane **1** was developed by Magauer, building upon the work of Grainger *et al*.

Chapter five: Experimental

5.1 General Experimental

All reagents which were available commercially were purchased from Acros, Alfa Aesar, Fisher Scientific, Fluorochem or Sigma Aldrich. *n*-BuLi was purchased as either a 1.6 M or 2.5 M solution in hexane and was titrated before each use using diphenylacetic acid (DPAA).[134] PPh_3 was purified by recrystallisation from conc. HCl and H_2O. *m*-CPBA was purified by washing with a pH 7 phosphate buffer which was prepared from 0.1 M NaOH (154 mL) and 0.2 M KH_2PO_4 (94 mL), distilled water was added up to 376 mL. A solution of *m*-CPBA (77% w/w, 10 g) in Et_2O (100 mL) was washed with the buffer solution (× 3); the combined organic layers were then dried from $MgSO_4$, filtered and evaporated under reduced pressure to yield pure *m*-CPBA (8.5 g, 85%). MVK was purified by distillation from K_2CO_3. Cyclohexanone was purified by distillation over $MgSO_4$. TMSCl and Et_3N were purified by distillation from CaH_2 under an argon atmosphere. Pyridine was distilled from potassium hydroxide. All reactions in non-aqueous solvents were conducted in flame-dried glassware and under an argon atmosphere with a magnetic stirring device. Volumes of less than 0.2 mL were measured and dispensed with a gastight syringe. Acetone was purified by distillation over 4 Å molecular sieves. The solvents were purified by passing through activated alumina columns and used directly from a Pure Solv-MD solvent purification system and were transferred under argon. All reactions which required heating were conducted using heat-on blocks on stirrer hotplates and the temperature controlled by an external probe. Reactions requiring lower temperatures used the following cooling baths: -78 °C (dry ice/acetone), -15 °C (NaCl/ice/water) and 0 °C (ice/water).

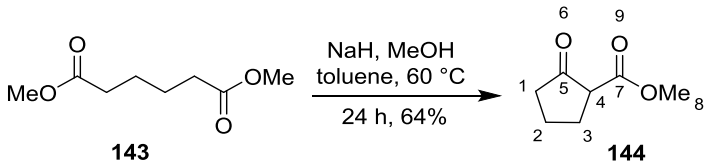
5.2 Analysis

Reactions were followed by thin layer chromatography (TLC) using Merck silica gel 60F254 analytical plates (aluminium support) and were developed using standard visualising agents: Short-wave UV radiation (245 nm), potassium permanganate/Δ, vanillin/Δ and anisaldehyde/Δ. Purification *via* flash column chromatography was conducted using Sigma Aldrich silica gel 60 (0.043-0.063 mm). Infra-red spectra were recorded neat on a Perkin Elmer Spectrum 100 FT-IR spectrometer, only selected absorbencies (ν_{max}) are reported in cm^{-1}. Melting points were recorded using open glass capillaries on a Gallenkamp melting points apparatus and are uncorrected. Optical activities were recorded on polarimeter PolAAr 2001. HPLC was obtained on Agilent (1260 Infinity). MS and HRMS (ESI) were obtained on Waters (Xevo, G2-XS Tof) or Waters Micromass LCT (recorded in the positive mode) using a methanol mobile phase. High resolution (ESI) mass spectra were obtained on either Waters Synapt G2-S or (Xevo, G2-XS Tof) mass spectrometers. High resolution (EI) mass spectra were recorded on a Waters GCT mass spectrometer fitted with a Zebron Capillary GC Column (30 m × 0.25 mm with film thickness of 0.25 μm). HRMS was obtained using a lock-mass to adjust the calibrated mass scale. MS data are reported as (*m/z* (%)) (relative intensity except in cases where only the parent ion is observed). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIII300 (^{1}H, 300 MHz; T = 295 K) and Bruker AVIII400 (1H, 400 MHz; ^{13}C, 101 MHz; T = 295 K) in the solvents indicated. The solvent signals were used as references and the chemical shifts converted to the TMS scale, residual $CHCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm) and C_6D_6 (^{1}H, 7.16 ppm; ^{13}C, 128.0 ppm). Coupling constants (*J*) are reported in Hz. The following abbreviations are used to describe multiplicity in ^{1}H-NMR: m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), br-broad, ap. apparent and in

^{13}C-NMR: C (quaternary), CH (tertiary), CH_2 (secondary) and CH_3 (primary). 1D ^{13}C NMR spectra was recorded using UDEFT or PENDANT pulse sequences from the Bruker standard pulse program library. 2D ^{1}H-^{13}C HSQC, ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMBC NMR spectra were recorded using the Bruker standard pulse program library. Spectra were processed using MestReNova version 10.

5.3 Experimental procedures and analytical data for Chapter two

Methyl-2-oxocyclopentanecarboxylate 144



143 **144**

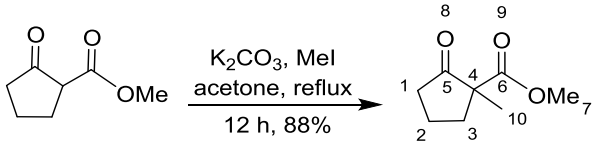
A known compound prepared by a modification of a literature procedure.[53]

A solution of dimethyl adipate **143** (0.34 mL, 2.12 mmol) in MeOH (1.5 mL) was added dropwise over 5 min to a suspension of NaH (60% dispersion in mineral oil, 12.24 g, 340 mmol) in toluene (600 mL) at 60 °C. The reaction mixture was stirred using an overhead stirrer and a reflux condenser. After 30 min, another portion of **143** (34.5 mL, 210 mmol) in toluene (1.2 mL) was added dropwise over 10 min and stirring was continued at 60 °C for 24 h. Upon completion, the solvent was removed *in vacuo*. MeOH (15 mL) and HCl (100 mL of a 1.0 M aq. solution) were added sequentially to the residue and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification *via* bulb-to-bulb distillation under reduced pressure gave **144** as a colourless oil (7.59 g, 64%); b.p. 120 °C (9 mmHg); ν_{max}(neat)/cm^{-1}: 2956 (w), 1752 (s), 1722 (s), 1436 (m), 1110 (s);

δ_H (400 MHz, $CDCl_3$) 1.85 (1H, m, 1H of CH_2), 2.20 (1H, m, 1H of CH_2), 2.34-2.57 (4H, m, 2 × CH_2), 3.16 (1H, t, *J* 9.0 Hz, H-4), 3.79 (3H, s, H-8); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_2, C-3), 27.7 (CH_2, C-2), 38.4 (CH_2, C-1), 52.8 (CH_3, C-8), 55.1 (CH, C-4), 170.1 (C, C-7), 212.4 (C, C-5).[53]

Analytical data in agreement with literature values.

Methyl-1- methyl-2-oxocyclopentanecarboxylate 145



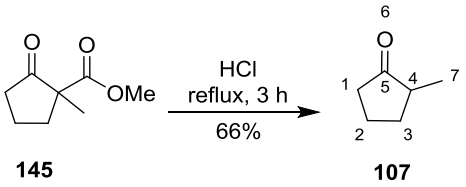
144 **145**

A known compound prepared by a modification of a literature procedure.[53]

A mixture of **144** (7.6 g, 53.39 mmol), K_2CO_3 (18.1 g, 131 mmol) and MeI (8.1 mL, 131 mmol) in anhydrous acetone (100 ml) was heated at reflux for 12 h before being cooled to rt. The solvent was removed *in vacuo* and the residue was taken up Et_2O (180 mL) and washed sequentially with H_2O (170 mL) and HCl (2 x 170 mL of a 1.0 M aq. solution). The organic extract was washed with brine (170 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification *via* bulb-to-bulb distillation gave the *title compound* **145** as a colourless oil (7.3 g, 88%); b.p. 120-125 °C (10 mmHg); ν_{max}(neat)/cm^{-1}: 2956 (w), 1753 (s), 1723 (s), 1150 (m), 729 (s); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, H-10), 1.74-1.94 (2H, m, H-2), 2.03-2.09 (1H, m, 1H of CH_2), 2.30-2.32 (1H, m, 1H of CH_2), 2.34-2.40 (2H, m, CH_2), 3.67 (3H, s, H-7); δ_C (100 MHz, $CDCl_3$) 19.6 (CH_3, C-10), 19.7 (CH_2), 36.2 (CH_2), 37.8 (CH_2), 52.6 (CH_3, C-7), 56.0 (C, C-4), 172.7 (C, C-6), 215.7 (C, C-5).

Analytical data in agreement with literature values.[53]

2-Methylcyclopentanone 107



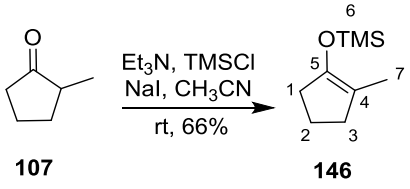
145 **107**

A known compound prepared according to a literature procedure.[54]

A two-phase reaction mixture of **145** (12.72 g, 81.44 mmol) and conc. HCl (30 mL) was heated under reflux for 3 h before being cooled to rt. The reaction mixture was diluted with ice-cold water (70 mL) and extracted with Et_2O (6 × 60 mL). The combined organic extracts were washed with $NaHCO_3$ (30 mL of a saturated aq. solution), brine (30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent, purification through bulb-to-bulb distillation gave **107** as a colourless liquid (5.25 g, 66%); b.p. 84-88 °C (11 mmHg); ν_{max}(neat)/cm^{-1}: 2985 (w), 1740 (s), 834 (m); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 7.0 Hz, H-7), 1.48-1.50 (1H, m, 1H of CH_2), 1.81-1.83 (1H, m, 1H of CH_2), 2.12-2.19 (3H, m, H-3 and H-4), 2.31-2.39 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3, C-7), 20.5 (CH_2), 31.8 (CH_2), 37.5 (CH_2), 43.9 (CH, C-4), 221.8 (C, C-5).

Analytical data in agreement with literature values.[50]

2-Methyl-1-trimethylsiloxycyclopent-1-ene 146



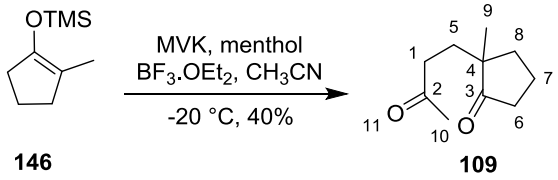
107 **146**

A known compound prepared according to the literature procedure.[55]

A solution of NaI (2.61 g, 17.43 mmol) in CH_3CN (4 mL) was added dropwise over 5 min to a mixture of 2-methylcyclopentanone **107** (1.38 g, 14.06 mmol), Et_3N (2.21 mL, 17.43 mmol) and TMSCl (2.21 mL, 17.43 mmol) in CH_3CN (10 mL) at rt and stirred for 3 h. The reaction mixture was stirred for 3 h before being filtered. The filtrate was washed with pentane (20 mL) and the acetonitrile phase was extracted with pentane (6 x 10 mL). The pentane extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification through bulb-to-bulb distillation gave the *title compound* **146** as a colourless liquid (1.6 g, 66%); R_f 0.52 (pet ether/Et_2O 8:2); b.p. 60 °C (10 mmHg); ν_{max}(neat)/cm^{-1}: 1690 (w), 1480 (m), 1356 (s); δ_H (400 MHz, C_6D_6) 0.17 (9H, s, Si(CH_3)$_3$), 1.52 (3H, s, CCH_3), 1.57-1.84 (2H, m, CH_2), 2.15-2.31 (4H, m, 2 × CH_2); δ_C (100 MHz, C_6D_6) 3.9 (CH_3, (CH_3)$_3$Si), 17.2 (CH_2), 19.1 (CH_3, CH_3C=), 32.0 (CH_2), 34.8 (CH_2, 2 × CH_2), 104.1 (C, C=C), 175.4 (C, C=O).

Analytical data in agreement with literature values.[51]

2-Methyl-2-(3-oxobutyl)cyclopentanone 109



146 **109**

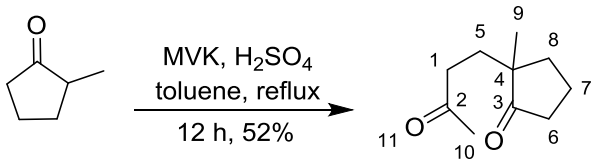
A known compound prepared according to the literature procedure.[55]

Method A

A solution of MVK (1.6 mL, 19.24 mmol) in CH_3NO_2 (15 mL) was added to a stirred solution of silyl enol ether **146** (4.3 g, 25.5 mmol) in CH_3NO_2 (20 mL) at -20 °C. A solution of BF_3.OEt_2 (0.64 mL, 5.19 mmol) and menthol (3.0 g, 19.24 mmol) in $MeNO_2$ (5 mL) added dropwise

over 5 min and stirred for 2 h at -20 °C before being warmed to 0 °C. The reaction mixture was quenched with $NaHCO_3$ (25 mL of a saturated aq. solution) and diluted with H_2O (25 mL). After extraction with CH_2Cl_2 (4 x 15 mL), the combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (pet ether/Et_2O 7:3) gave the diketone **109** as a colourless oil (1.7 g, 40%). R_f 0.25 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2960 (w), 1731 (s), 1713 (s), 1163 (m); δ_H(400 MHz, $CDCl_3$) 1.11 (3H, s, H-9), 1.89 (2H, t, *J* 7.2 Hz, C*H*$_2$), 2.10 (3H, s, H-10), 2.23-2.31 (2H, m, C*H*$_2$), 2.45 (2H, t, *J* 7.2 Hz, C*H*$_2$), 2.68-2.92 (4H, m, 2 × C*H*$_2$); δ_C(100 MHz, $CDCl_3$) 19.2 (CH_3, C-9), 22.2 (CH_2), 30.6 (CH_3, C-10), 30.7 (CH_2), 31.4 (CH_2), 34.5 (CH_2), 37.2 (CH_2), 48.1 (C, C-4), 209.1 (C, C-2), 222.6 (C, C-3).

Method B



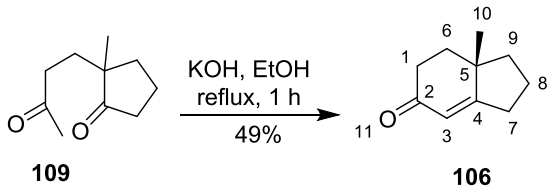
107 **109**

A solution of **107** (4.75 g, 48.40 mmol), MVK (4.03 mL, 48.40 mmol) and conc. H_2SO_4 (2-4 drops) in toluene (30 mL) was heated at reflux for 12 h before being cooled to rt slowly. The reaction mixture was washed with ice-cold water (20 mL) and $NaHCO_3$ (20 mL of a saturated aq. solution). The organic extract was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **109** as a colourless oil (4.24 g, 52%). R_f 0.25 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2960 (w), 1731 (s), 1713 (s), 1163 (m); δ_H(400 MHz, $CDCl_3$) 1.11 (3H, s, H-9), 1.89 (2H, t, *J* 7.2 Hz, C*H*$_2$), 2.10 (3H, s, H-10), 2.23-2.31 (2H, m, C*H*$_2$), 2.45 (2H, t, *J* 7.2 Hz, C*H*$_2$), 2.68-2.92 (4H, m, 2 × C*H*$_2$); δ_C(100

MHz, $CDCl_3$) 19.2 (CH_3, C-9), 22.2 (CH_2), 30.6 (CH_3, C-10), 30.7 (CH_2), 31.4 (CH_2), 34.5 (CH_2), 37.2 (CH_2), 48.1 (C, C-4), 209.1 (C, C-2), 222.6 (C, C-3).

Analytical data in agreement with literature values.[54]

(±)-7a-Methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one 106



109 **106**

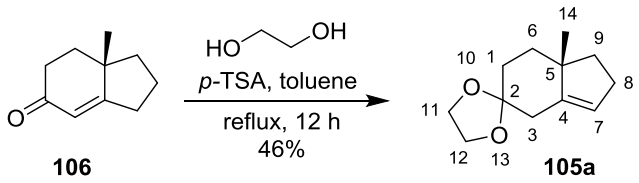
A known compound prepared according to a literature procedure.[54]

A solution of KOH (2.0 g, 35.6 mmol) in EtOH (15 mL) was stirred at rt for 30 min before being added to **109** (0.95 g, 5.64 mmol) in EtOH (6 mL). The resultant reaction mixture was heated under reflux for 1 h after which time the cooled reaction mixture was neutralized, then acidified using AcOH to achieve pH = 6. The solvent was removed under reduced pressure and the residue was partitioned between Et_2O (20 mL) and ice-cold water (20 mL). The aqueous layer was further extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with H_2O (20 mL), $NaHCO_3$ (20 mL of a saturated aq. solution), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **106** as a yellow oil (0.42 g, 49%). R_f 0.44 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2959 (w), 1655 (s), 1453 (m), 1109 (m); δ_H(400 MHz, $CDCl_3$) 1.14 (3H, s, H-10), 1.47 (1H, td, *J* 11.8 and 8.4 Hz, 1H of H-6), 1.74-1.96 (4H, m, H-7 and H-9), 2.03 (1H, ddd, *J* 13.0, 5.3 and 2.0 Hz, 1H of CH_2), 2.35-2.40 (1H, m, 1H of CH_2), 2.45-2.59 (2H, m, CH_2), 2.70-2.73 (1H, m, 1H of CH_2), 5.75 (1H, s, H-3); δ_C(100 MHz, $CDCl_3$) 21.5

(CH_2), 22.8 (CH_3, C-10), 31.1 (CH_2), 34.2 (CH_2), 36.4 (CH_2), 41.2 (CH_2), 43.1 (C, C-5), 121.7 (CH, C-3), 179.2 (C, C-4), 199.6 (C, C-2).

Analytical data in agreement with literature values.[50]

(±)-7a-methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolane] 105a



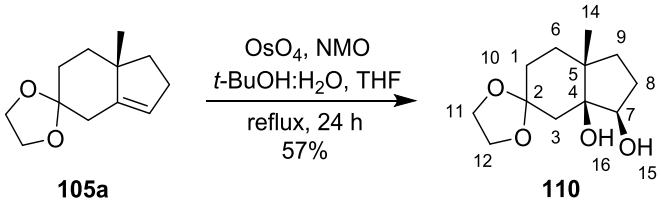
A known compound prepared according to a literature procedure.[56]

Ethylene glycol (0.97 mL, 17.3 mmol) and *p*-TSA (60 mg, 0.31 mmol) were added sequentially to a stirred solution of enone **106** (0.47 g, 3.12 mmol) in toluene (10 mL) and the reaction mixture was heated at reflux under a Dean-Stark apparatus. After 12 h, the reaction mixture was cooled to rt and the solvent removed under reduced pressure. The residue was dissolved in Et_2O (10 mL), H_2O (10 mL) was added and the aqueous layer extracted with Et_2O (2 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) afforded **105a** as a pale yellow oil (0.28 g, 46%). R_f 0.53 (pet ether/Et_2O 6:4); ν_{max}(neat)/cm^{-1}: 2940 (w), 1088 (s), 1019 (m), 946 (m); δ_H(400 MHz, $CDCl_3$) 1.06 (3H, s, H-14), 1.51-1.54 (1H, m, 1H of H-1), 1.64-1.74 (3H, m, 1H of H-9, 1H of H-1 and 1H of H-6), 1.76-1.93 (2H, m, 1H of H-6 and 1H of H-9), 2.24-2.38 (3H, m, H-8 and 1H of H-3), 2.44 (1H, dd, *J* 13.4 and 2.3 Hz, 1H of H-3), 3.92-3.99 (4H, m, H-11 and H-12), 5.30 (1H, d, *J* 2.0 Hz, H-7); δ_C(100 MHz, $CDCl_3$) 22.6

(CH_3), 30.8 (CH_2), 32.1 (CH_2), 36.5 (CH_2), 38.0 (CH_2), 40.6 (CH_2), 45.4 (C, C-5), 64.5 (CH_2, C-11), 64.6 (CH_2, C-12), 110.2 (C, C-2), 122.9 (CH, C-7), 146.7 (C, C-4).

Analytical data in agreement with literature values.[52]

(3*R*, 3a*S*, 7a*S*)-7a-Methylhexahydrospiro[indene-5,2'-[1,3]dioxolane]-3,3a(4*H*)-diol 110



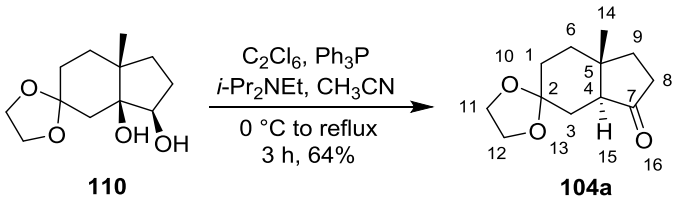
A known compound prepared by a modification of a literature procedure.[32]

OsO_4 (2 µL of a 4 wt % aq. solution) was added to a stirred solution of NMO (0.18 g, 1.58 mmol) and alkene **105a** (280 mg, 1.44 mmol) in THF (1.4 mL) and *t*-BuOH/H_2O (5 mL:0.5 mL). The reaction was heated at reflux for 24 h. Sodium metabisulfite (160 mg, 0.84 mmol) was added as one portion and the reaction mixture was stirred for a further 1 h before being diluted with EtOAc (8 mL), then the resulting mixture was washed with HCl (8 mL of a 1.0 M aq. solution) and brine (2 x 8 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 3:7) gave diol **110** as a white solid (185 mg, 57%); m.p. 80-84 °C; $[\alpha]_D^{25}$= +30° ($CHCl_3$, *c* 0.15); R_f 0.11 (per ether/Et_2O 6:4); ν_{max}(neat)/cm^{-1}: 3436 (br), 3375 (br), 2944 (w), 1091 (m); δ_H(400 MHz, $CDCl_3$) 1.09 (3H, s, H-14), 1.43-1.54 (5H, m, 2 × CH_2 and 1H of CH_2), 1.57-1.72 (4H, m, 2 × CH_2), 2.04-2.1 (1H, m, 1H of CH_2), 2.43 (1H, s, H-15), 2.65 (1H, s, H-16), 3.76-3.89 (4H, m, H-11 and H-12), 4.19 (1H, dd, *J* 8.2, 4.1 Hz, H-7); δ_C(100 MHz, $CDCl_3$) 21.4 (CH_3), 28.5 (CH_2), 30.2

(CH_2), 32.3 (CH_2), 33.7 (CH_2), 40.1 (CH_2), 42.2 (C, C-5), 64.1 (CH_2, C-11), 64.3 (CH_2, C-12), 76.5 (CH, C-7), 81.3 (C, C-4), 108.8 (C, C-2).

Analytical data in agreement with literature values.[31]

(3a*S*, 7a*S*)-7a-Methylhexahydrospirol[[1,3]dioxolane-2,5'-inden]-3(2*H*)-one 104a



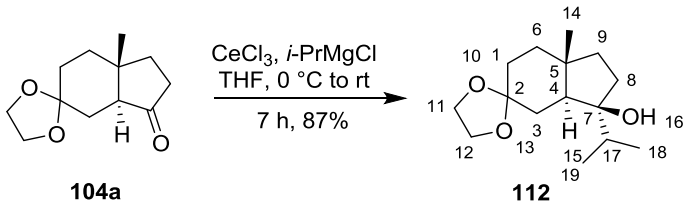
A known compound prepared according to a literature procedure.[32]

Hexachloroethane (67 mg, 0.28 mmol) was added to a solution of Ph_3P (75 mg, 0.28 mmol) in CH_3CN (5 mL). After 20 min at rt, *i*-Pr_2NEt (10 µL, 0.75 mm) was added as one portion and the reaction mixture cooled to 0 °C before a solution of diol **110** (30 mg, 0.13 mmol) in CH_3CN (3 mL) was added dropwise over 5 min. After 50 min, the reaction mixture was heated under reflux for 2 h before being allowed to cool to rt slowly. The resulting mixture was diluted with Et_2O (15 mL), washed with H_2O (2 × 15 mL) and the combined aqueous layers were extracted with Et_2O (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (pet ether/Et_2O 6:4) to give **104a** as a clear oil (18 mg, 64%), which solidified on standing to give a white solid. $[\alpha]_D^{25}$= +104° ($CHCl_3$, *c* 1.12); R_f 0.26 (pet ether/Et_2O 1:1); m.p. 62-65 °C; ν_{max}(neat)/cm^{-1}: 2934 (w), 1728 (s), 1260 (m): δ_H(400 MHz, $CDCl_3$) 0.67 (3H, s, H-14), 1.46 (1H, ap. t, *J* 12.9 Hz, 1H of C*H*$_2$), 1.55-1.69 (4H, m, 2 × C*H*$_2$), 1.71-1.87 (2H, m, 1H of C*H*$_2$ and 1H of C*H*$_2$), 1.95 (1H, dt, *J* 13.3 and 2.6 Hz, 1H of C*H*$_2$), 2.15-2.41 (3H, m, H-15 and C*H*$_2$), 3.81-

4.10 (4H, m, H-11 and H-12); δ_C(100 MHz, $CDCl_3$) 16.6 (CH_3, C-14), 29.5 (CH_2), 31.3 (CH_2), 35.0 (CH_2), 36.2 (CH_2), 36.3 (CH_2), 38.4 (C, C-5), 57.6 (CH, C-4), 64.0 (CH_2, C-11), 64.3 (CH_2, C-12), 109.3 (C, C-2), 216.1 (C, C-7).

Analytical data in agreement with literature values.[31]

(3*S*, 3a*S*, 7a*S*)-3-*iso*-Propyl-7a-methyloctahydrospiro-[[1,3]dioxolane-2,5'-inden]-3-ol 112



Preparation of anhydrous $CeCl_3$

A two-neck flame dried flask was charged with powdered cerium(III) chloride heptahydrate ($CaCl_3.7H_2O$, 10 g, 0.027 mol) then attached to a vacuum pump. The flask was held under vacuum and heated gradually to 90 °C over 30 min. Heating at 90-100 °C was continued for 2 h with intermittent shaking. After 2 h, the system was filled with argon and cooled to rt. The containing of the flask was transferred to a mortar and pulverised quickly with a pestle under the flow of argon through a funnel. The white powder and a magnetic stirrer bar were placed in the original flask and heating introduced gradually to 90 °C over 30 min under reduced pressure. The flask was heated at 90-100 °C for 1.5 h with intermittent shaking giving cerium(III) chloride monohydrate ($CeCl_3.H_2O$) which was gradually heated to 165 °C over 30 min under reduced pressure without stirring. A fine, white powder of anhydrous cerium(III) chloride was generated after heating continued for 16 h with gentle stirring

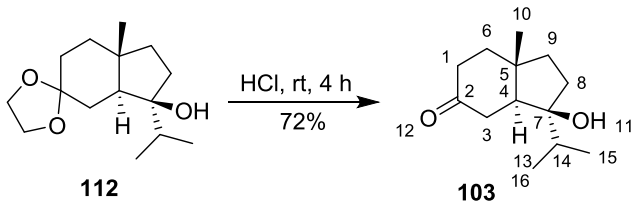
before being cooled to rt. Argon was introduced to the flask and the resulting anhydrous cerium(III) chloride was transferred to a vial and kept in a desiccator after flushing with argon.

A known compound prepared by a modification of a literature procedure.[35]

THF (14 mL) was added at rt to the vigorously stirred anhydrous $CeCl_3$ (1.2 g, 4.85 mmol) to form a uniform white suspension which was stirred for 2 h. The resultant suspension was cooled to 0 °C and *i*-PrMgCl (3.63 mL of a 2.0 M soln. in THF, 7.26 mmol) was added dropwise over 10 min to form an off-white suspension. The resulting suspension was stirred for 1 h when **104a** (0.51 g, 2.42 mmol) in THF (25 mL) was added dropwise over 5 min and the reaction mixture was warmed gradually to rt. After 6 h, the reaction mixture was cooled to 0 °C, quenched with H_2O (15 mL) and extracted with Et_2O (2 × 15 mL). The organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (hexane/EtOAc 6:4) gave **112** as a clear colourless oil (0.54 g, 87%). $[\alpha]_D^{25}$= + 8° ($CHCl_3$, *c* 1.0); R_f 0.24 (hexane/EtOAc 1:1); ν_{max}(neat)/cm^{-1}: 3500 (br), 2944 (w), 2875 (w), 1087 (s), 945 (m); δ_H(400 MHz, C_6D_6) 0.41 (1H, br s, H-16), 0.62, 0.65 (6H, 2 × d, *J* 6.8 Hz, H-18 and H-19), 1.02 (1H, br q, *J* 10.2 Hz, 1H of C*H*$_2$), 1.11 (3H, s, H-14), 1.38 (1H, septet, *J* 7.0 Hz, H-17), 1.45-1.53 (4H, m, 2 × C*H*$_2$), 1.65-1.73 (3H, m, C*H*$_2$ and H-15), 1.77-1.96 (2H, m, C*H*$_2$), 2.21 (1H, m, 1H of C*H*$_2$), 3.51-3.62 (4H, m, H-11 and H-12); δ_C(100 MHz, C_6D_6) 17.2 (CH_3, C-14), 17.9 (CH_3, C-18), 18.2 (CH_3, C-19), 36.8 (CH_2), 37.6 (CH_2), 38.2 (CH_2), 38.8 (CH_2), 38.9 (CH_2), 41.8 (CH, C-17), 43.2 (C, C-5), 52.4 (CH, C-4), 64.2 (CH_2, C-11), 64.4 (CH_2, C-12), 83.2 (C, C-7), 110.2 (C, C-2).

Analytical data in agreement with literature values.[34]

(3*S*, 3a*S*, 7a*S*)-3-Hydroxy-3-*iso*-propyl-7a-methylhexahydro-1*H*-inden-5(6*H*)-one 103

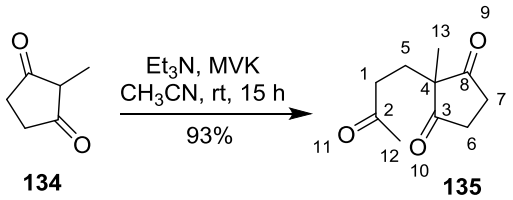


A known compound prepared according to a literature procedure.[32]

A solution of acetal **112** (70 mg, 0.27 mmol) in THF (1.5 mL) was treated with HCl (2.5 mL of a 1.0 M aq. solution). The reaction mixture was stirred at rt for 4 h. Upon completion, the resulting mixture was quenched with $NaHCO_3$ (5 mL of a saturated aq. solution) and extracted with Et_2O (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (hexane/EtOAc 7:3) to yield **103** as a clear colourless oil (45 mg, 72%). $[\alpha]_D^{25}$= +151° ($CHCl_3$, *c* 0.5); R_f 0.43 (hexane/EtOAc 1:1); ν_{max}(neat)/cm^{-1}: 3496 (br), 2937 (w), 1704 (s), 945 (s); δ_H(400 MHz, C_6D_6) 0.41 (1H, br s, H-11), 0.61, 0.64 (6H, 2 × d, *J* 6.8 Hz, H-15 and H-16), 0.81 (1H, br q, *J* 11.2 Hz, 1H of H-9), 1.03 (3H, s, H-10), 1.11 (1H, td, *J* 11.4 and 6.5 Hz, 1H of H-6), 1.26 (1H, septet, *J* 6.8 Hz, H-14), 1.34 (1H, dd, *J* 12.5 and 5.9 Hz, H-13), 1.41-1.47 (2H, m, C*H*$_2$), 1.62 (1H, ddd, *J* 14.2, 11.1 and 9.6 Hz, 1H of H-8), 1.74 (1H, ddd, *J* 14.2, 9.5 and 1.2 Hz, 1H of H-8), 2.11-2.21 (2H, m, C*H*$_2$), 2.28-2.35 (2H, m, C*H*$_2$); δ_C(100 MHz, C_6D_6) 17.4 (CH_3, C-10), 18.0 (CH_3, C-15), 18.2 (CH_3, C-16), 37.1 (CH_2), 37.3 (CH_2), 37.6 (CH_2), 38.1 (CH_2), 39.1 (C, C-5), 39.3 (CH_2), 41.2 (CH, C-14), 52.8 (CH, C-4), 82.8 (C, C-7), 209.6 (C, C-2).

Analytical data in agreement with literature values.[31]

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione 135

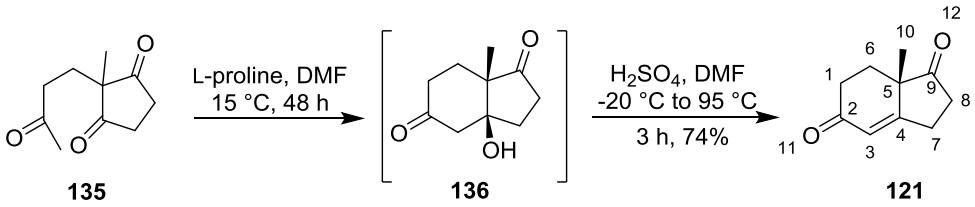


A known compound prepared according to a literature procedure.[135]

Triethylamine (13.15 mL, 93.6 mmol) and methyl vinyl ketone (2.67 mL, 32.1 mmol) were sequentially added to a solution of dione **134** (3.0 g, 26.7 mmol) in CH_3CN (50 mL). The reaction mixture was stirred for 15 h at rt, then the solvent was removed under reduced pressure and purified directly by column chromatography (hexane/EtOAc 6:4) to afford triketone **135** as an orange oil (4.54 g, 93%). R_f 0.46 (hexane/EtOAc 4:6); ν_{max}(neat)/cm^{-1}: 2976 (w), 1731 (s), 1660 (s), 1647 (s), 1163 (m); δ_H(400 MHz, $CDCl_3$) 1.09 (3H, s, H-13), 1.87 (2H, t, *J* 6.4 Hz, CH_2), 2.08 (3H, s, H-12), 2.44 (2H, t, *J* 7.2 Hz, CH_2), 2.68-2.89 (4H, m, 2 × CH_2); δ_C(100 MHz, $CDCl_3$) 18.9 (CH_3, C-13), 27.6 (CH_2), 29.8 (CH_3, C-12), 34.5 (CH_2), 34.9 (CH_2), 37.2 (CH_2), 51.2 (C, C-4), 207.7 (C, *C*=O), 215.6 (C, *C*=O), 215.9 (C, *C*=O).

Analytical data in agreement with literature values.[136]

(*S*)-7a-Methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5 (6*H*)-dione 121



A known compound prepared by a modification of a literature procedure.[43]

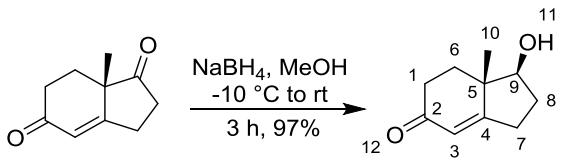
A solution of L-proline (0.11 g, 0.11 mmol) in DMF (35 mL) was degassed by alternative evacuation and refilling of the flask with argon and the system was shielded from light with aluminum foil and stirred for 1 h at rt. A solution of **135** (6.0 g, 34.84 mmol) in DMF (10 mL) was added to the flask containing L-proline and DMF and degassed for 10 min. The resultant reaction mixture was stirred for 48 h at 15 °C. Upon formation of **136**, the mixture was heated to 95 °C whilst maintaining stirring. DMF (10 mL) was added to another flask and cooled to -20 °C which followed by addition of conc. H_2SO_4 (0.5 mL) portion-wise over 10 min at a rate to maintain -20 °C. When the temperature of the flask containing **136** reached 75 °C, a (4 mL) aliquot of the conc. H_2SO_4 in DMF solution was added in one portion and the mixture heated to 95 °C and stirred for 1 h before the addition of (6.5 mL) of the conc. H_2SO_4 solution was again added as one portion and the reaction monitored *via* t.l.c. After 3 h, the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 mL), washed with H_2SO_4 (25 mL of a 2.0 M aq. solution) and brine (25 mL). Each aqueous wash was extracted with CH_2Cl_2 (25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give an oily, brown semi-solid. Purification by column chromatography (hexane/EtOAc 3:7) gave **95** as a yellow solid (4.15 g, 74%) which was subjected to bulb-to-bulb distillation (0.1 mmHg) to give **121** (3.86 g) as a pale yellow solid which was taken up in Et_2O (20 mL) at reflux. The solution was heated at reflux to the point of turbidity with hexane, once the formation of crystals was observed the mixture was allowed to rest at rt for 2 h and then subsequently cooled to 17 °C for 30 min. After filtration a white solid was collected and dried under reduced pressure. $[\alpha]_D^{25}$= +332.8° (toluene, *c* 1.0). R_f 0.46 (hexane/EtOAc 2:8); ν_{max}(neat)/cm^{-1}: 2956 (w), 2941 (w), 1742 (s), 1660 (s), 1145 (s); m.p. 57-60 °C; δ_H(400 MHz, $CDCl_3$) 1.31 (3H, s, H-10), 1.84 (1H, td, *J* 13.7

and 5.6 Hz, 1H of CH_2), 2.10 (1H, ddd, *J* 13.7, 5.1 and 2.3 Hz, 1H of CH_2), 2.38-2.54 (3H, m, CH_2 and 1H of CH_2), 2.70-2.83 (2H, m, CH_2), 2.94 (1H, m, 1H of CH_2), 5.96 (1H, t, *J* 2.0 Hz, H-3); δ_C(100 MHz, $CDCl_3$) 21.0 (CH_3, C-10), 27.2 (CH_2), 29.6 (CH_2), 33.3 (CH_2), 36.3 (CH_2), 49.1 (C, C-5), 123.9 (CH, C-3), 170.2 (C, C-4), 198.3 (C, *C*=O), 216.7 (C, *C*=O).

Before recrystallisation: 99.41:0.58 er as determined by HPLC analysis [Daicel Chiralpak AD, H_2O:MeCN, 85:15, 1.0 mL/min, λ 210 nm, t(minor) = 12.9 min, t(major) = 17.8 min]. After recrystallisation: 99.71:0.28 er, H_2O:MeCN, 85:15, 1.0 mL/min, λ 210 nm, t(minor) = 12.96 min, t(major) = 17.85 min].

Analytical data in agreement with literature values.[42]

(1*S*, 7a*S*)-1-Hydroxy-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one 150



121 **150**

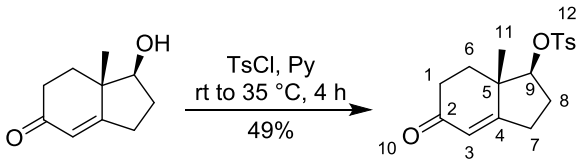
A known compound prepared according to a literature procedure.[58]

A solution of $NaBH_4$ (0.27 g, 7.28 mmol) in MeOH (4 mL) was added dropwise over 5 min to a solution of **121** (4.43 g, 26.97 mmol) in MeOH (30 mL) at -10 °C before being warmed to rt. The reaction mixture was stirred for 3 h before being cooled to -10 °C at which point the pH was adjusted to between 5-7 with HCl (8 mL of a 2.0 M aq. solution). The solvent was removed under reduced pressure and the aqueous residue was extracted with EtOAc (2 × 15 mL), and the organic extracts washed with $NaHCO_3$ (15 mL of a saturated aq. solution), H_2O (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by

column chromatography (hexane/EtOAc 4:6) gave **150** as a pale yellow oil (4.22 g, 97%). $[\alpha]_D^{25}$= +80° ($CHCl_3$, *c* 1.0); R_f 0.15 (hexane/EtOAc 1:1); ν_{max}(neat)/cm^{-1}: 3392 (br), 2943 (w), 2865 (w), 1644 (s); δ_H(400 MHz, C_6D_6) 0.77 (3H, s, H-10), 1.19-1.77 (3H, m, CH_2 and 1H of CH_2), 1.80-2.28 (3H, m, CH_2 and 1H of CH_2), 2.13 (1H, m, 1H of CH_2), 2.36 (1H, m, 1H of CH_2), 3.31 (1H, dd, *J* 10.2 and 7.6 Hz, H-9), 5.73 (1H, t, *J* 2.0 Hz, H-3); δ_C(100 MHz, C_6D_6) 15.53 (CH_3, C-10), 26.7 (CH_2), 29.9 (CH_2), 34.2 (CH_2), 35.0 (CH_2), 45.7 (C, C-5), 124.2 (CH, C-3), 173.8 (C, C-4), 197.4 (C, C-2).

Analytical data in agreement with literature values.[137]

(±)-(1*S*, 7a*S*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl 4-methylbenzenesulfonate 151



150 **151**

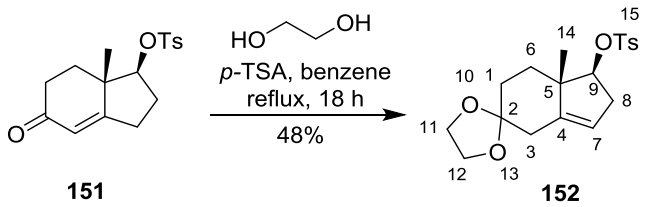
A known compound prepared by a modification of a literature procedure.[58]

TsCl (7.9 g, 41.83 mmol) was added to a solution of **150** (4.15 g, 24.90 mmol) in pyridine (35 mL) at rt. The reaction mixture was heated to 35 °C for 4 h. Upon completion, the solvent was removed *in vacuo* and the residue was quenched with H_2O (10 mL) and extracted with Et_2O (3 × 25 mL). The organic extracts were washed with HCl (20 mL of a 2.0 M aq. solution), $NaHCO_3$ (15 mL of a saturated aq. solution), brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (hexane/EtOAc 8:2) gave **151** as a white solid (3.81 g, 49%). R_f 0.26 (hexane/EtOAc 1:1); ν_{max}(neat)/cm^{-1}:

2958 (w), 2945 (w), 1659 (s), 1171 (s), 984 (s); m.p. 102-107 °C; δ_H(400 MHz, $CDCl_3$) 0.97 (3H, s, H-11), 1.04 (1H, td, *J* 13.7 and 5.1 Hz, 1H of H-6), 1.37-1.53 (3H, m, CH_2 and 1H of H-6), 1.72-1.89 (3H, m, CH_2 and 1H of CH_2), 2.52 (3H, s, CH_3CAr), 2.66 (1H, m, 1H of CH_2), 4.34 (1H, dd, *J* 9.9 and 8.0 Hz, H-7), 5.71 (1H, s, H-3), 7.29 (2H, d, *J* 8.0 Hz, 2 × C*H*Ar), 7.73 (2H, d, *J* 8.2 Hz, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 16.1 (CH_3, C-11), 21.4 (CH_3, *C*H_3CAr), 26.0 (CH_2), 26.4 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 44.5 (C, C-5), 87.2 (CH, C-9), 123.8 (CH, C-3), 127.6 (2 × CH, *C*HAr), 129.7 (2 × CH, C*H*Ar), 133.5 (C, *C*Ar), 144.8 (C, *C*Ar), 170.4 (C, C-4), 197.9 (C, *C*=O).

Analytical data in agreement with literature values.[55]

(±)-(1*S*, 7a*S*)-7a-Methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolan]-1-yl 4-methylbenzenesulfonate 152



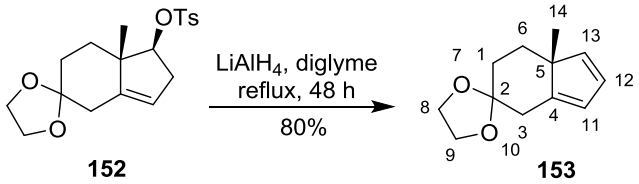
151 **152**

A novel compound prepared by a modification of a literature procedure.[56]

Ethylene glycol (0.61 mL, 11.08 mmol) and *p*-TSA (40 mg, 0.20 mmol) were sequentially added to a solution of enone **151** (0.67g, 2.09 mmol) in benzene (25 mL) and the reaction mixture was heated at reflux under a Dean-Stark apparatus. After 18 h, the reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL), H_2O (10 mL) was added and aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet

ether/Et_2O 6:4) to afford **152** as a white solid (0.28 g, 48%). R_f 0.39 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2958 (w), 2945 (w), 1357 (m), 1093 (s), 983 (s); m.p. 106-110 °C; δ_H(400 MHz, $CDCl_3$) 1.07 (3H, s, H-14), 1.36 (1H, ddd, *J* 14.5, 13.9 and 4.5 Hz, 1H of H-6), 1.59-1.68 (2H, m, 1H of H-6 and 1H of H-5), 1.76 (1H, ddd, *J* 14.1, 13.4 and 4.5 Hz, 1H of H-1), 2.32-2.38 (2H, m, C*H*$_2$), 2.40-2.46 (2H, m, C*H*$_2$), 2.51 (3H, s, C*H*$_3$CAr), 3.86-3.97 (4H, m, H-11 and H-12), 4.62 (1H, t, *J* 8.3 Hz, H-9), 5.16 (1H, d, *J* 1.4 Hz, H-7), 7.31 (2H, d, *J* 8.1 Hz, 2 × C*H*Ar), 7.78 (2H, d, *J* 8.3 Hz, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 15.8 (CH_3, C-14), 21.6 (CH_3, *C*H_3CAr), 20.8 (CH_2), 35.1 (CH_2), 36.5 (CH_2), 36.7 (CH_2), 46.2 (C, C-5), 64.3 (CH_2, C-11), 64.6 (CH_2, C-12), 89.3 (CH, C-9), 108.7 (C, C-2), 118.4 (CH, C-7), 127.8 (2 × CH, *C*HAr), 129.7 (2 × CH, *C*HAr), 140.3 (C, CH_3*C*Ar), 144.6 (C, C-4), 144.8 (C, *C*Ar); *m/z* HRMS (ES^+) found 365.1427 $[M+H]^+$ $C_{19}H_{25}O_5S$ requires 365.1423; (ES^+) 365.1 ($[M+H]^+$, 100%).

(±)-(*R*)-7a-Methyl-4,6,7,7a-tetrahydrospiro[indene-5,2'-[1,3]dioxolane] 153

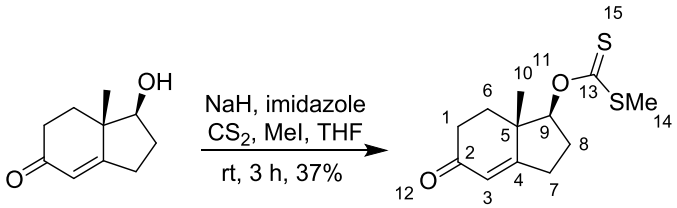


A novel compound prepared according to a literature procedure.[59]

$LiAlH_4$ (0.34 g, 8.96 mmol) was added to a stirred solution of acetal **152** (1.63 g, 4.48 mmol) in diglyme (20 mL). The reaction mixture was heated under reflux for 48 h after which time, the solvent was removed under reduced pressure and the residue was purified by column chromatography (pet ether/Et_2O 6:4) to give **153** as a colourless oil (0.70 g, 80%). R_f 0.55 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2951 (w), 2880 (w), 1088 (s); δ_H(400 MHz, $CDCl_3$) 1.08 (3H, s, H-14), 1.14 (1H, m, 1H of C*H*$_2$), 1.60 (1H, m, 1H of C*H*$_2$), 1.79-1.88 (2H, m, C*H*$_2$), 2.48 (1H,

dd, *J* 13.3 and 1.6 Hz, 1H of H-3), 2.63 (1H, dd, *J* 13.3 and 2.5 Hz, 1H of H-3), 3.84-4.05 (4H, m, H-8 and H-9), 5.28 (1H, s, H-11), 6.27 (1H, dd, *J* 5.3 and 1.8 Hz, C*H*=), 6.33 (1H, dd, *J* 5.3 and 1.1 Hz, C*H*=); δ_C(100 MHz, $CDCl_3$) 18.3 (CH_3), 30.8 (CH_2), 31.7 (CH_2), 37.1 (CH_2), 52.3 (C, C-14), 64.8 (CH_2, C-8), 65.0 (CH_2, C-9), 111.5 (C, C-2), 123.1 (CH, *C*H=), 129.1 (CH, *C*H=), 145.4 (CH, *C*H=), 153.7 (C, C-4); *m/z* HRMS (ES^+) found 193.1226 $[M+H]^+$ $C_{12}H_{17}O_2$ requires 193.1229; (ES^+) 193.0 ($[M+H]^+$, 100%).

(±)-(1*S*, 7a*S*)-7a-Methyl-7,7a-dihydro-1-*S*-methyldithiocarbonate-5(6*H*)-indanone 161



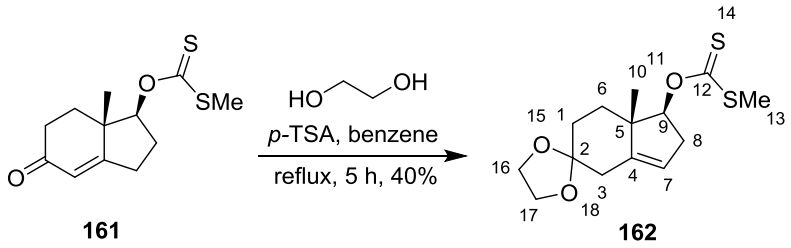
150 **161**

A novel compound prepared according to a literature procedure.[62]

Imidazole (0.44 mg, 6.6 µmol), NaH (60% dispersion in mineral oil, 0.1 g, 2.8 mmol), CS_2 (0.33 mL, 5.58 mmol) and MeI (0.19 mL, 3.16 mmol) were sequentially added to a solution of enone **150** (0.31 g, 1.86 mmol) in THF (20 mL). The reaction mixture was stirred for 3 h at rt. Upon completion, the solvent was removed under reduced pressure and the residue was quenched with $NaHCO_3$ solution (8 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **161** as a yellow oil (0.18 g, 37%). R_f 0.38 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2924 (w), 1667 (s), 1194 (s), 1067 (s), 1044 (s); δ_H(400 MHz, $CDCl_3$) 1.30 (3H,

s, H-10), 1.71-1.86 (4H, m, 2 × CH_2), 2.32-2.39 (2H, m, CH_2), 2.41-2.54 (2H, m, CH_2), 2.58 (3H, s, H-14), 5.61 (1H, m, H-9), 5.83 (1H, s, H-3); δ_C(100 MHz, $CDCl_3$) 18.0 (CH_3, C-10), 19.8 (CH_3, C-14), 26.4 (CH_2), 27.4 (CH_2), 33.8 (CH_2), 35.0 (CH_2), 44.5 (C, C-5), 90.3 (CH, C-9), 124.2 (CH, C-3), 170.4 (C, C-2), 198.9 (C, C-2), 215.0 (C, C-13); *m/z* HRMS (ES^+) found 279.0483 $[M+Na]^+$ $C_{12}H_{16}O_2S_2Na$ requires 279.0489; (ES^+) 279.0 ($[M+Na]^+$, 90%).

(±)-*S*-Methyl O-((1*S*, 7a*S*)-7a-methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolan]-1-yl) carbonodithioate 162



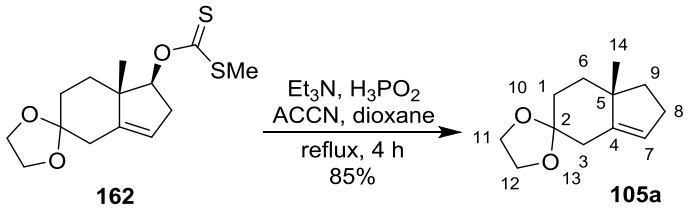
161 162

A novel compound prepared according to a literature procedure.[32]

Ethylene glycol (0.58 mL, 10.27 mmol) and *p*-TSA (34 mg, 0.018 mmol) were sequentially added to a solution of **161** (0.22 g, 0.9 mmol) in benzene (20 mL) and the reaction mixture was heated to reflux under a Dean-Stark apparatus. After 5 h, the reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL), H_2O (8 mL) was added and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with $NaHCO_3$ (10 mL of a saturated aq. solution), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 8:2) to afford **162** as a pale yellow solid (0.11 g, 40%). R_f 0.51 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2952 (w), 2930 (w), 1215 (s), 1063 (s); m.p. 45-50 °C; δ_H(400 MHz, $CDCl_3$) 1.14 (3H, s, H-10), 1.67-1.91 (4H,

m, 2 × CH_2), 2.34-2.45 (3H, m, CH_2 and 1H of CH_2), 2.55 (3H, s, H-13), 2.93 (1H, m, 1H of CH_2), 3.92-3.98 (4H, m, H-16 and H-17), 5.21 (1H, d, *J* 1.8 Hz, H-7), 5.86 (1H, t, *J* 7.7 Hz, H-9); δ_C(100 MHz, $CDCl_3$) 17.2 (CH_3, C-10), 19.6 (CH_3, C-13), 31.8 (CH_2), 36.2 (CH_2), 36.7 (CH_2), 37.3 (CH_2), 48.1 (C, C-5), 65.1 (CH_2, C-16), 65.4 (CH_2, C-17), 91.8 (CH, C-9), 109.2 (C, C-2), 119.6 (CH, C-7), 145.5 (C, C-4), 216.2 (C, C-12); *m/z* HRMS (ES^+) found 301.0934 $[M+H]^+$ $C_{14}H_{21}O_3S_2$ requires 301.0932; (ES^+) 301.0 ($[M+H]^+$, 100%).

(±)-7a-Methyl-1,2, 4,6,7,7a-hexahydrospiro[[1,3]dioxolane-2,5'-indene] 105a



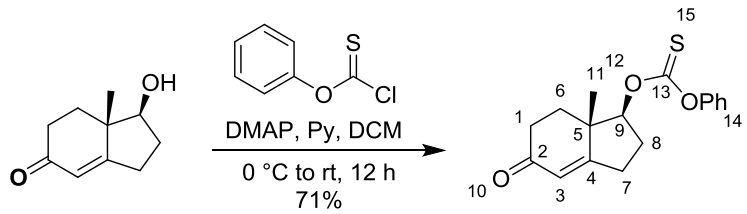
A known compound prepared by a modification of a literature procedure.[63]

A solution of dithiocarbamate **162** (20 mg, 0.06 mmol), Et_3N (51.2 µL, 0.36 mmol) and H_3PO_2 (48 µL of a 50 wt% in aq. solution, 0.63 mmol) in dioxane (3 mL) was heated under reflux for 20 min after which time, a solution of ACCN (36 mg, 0.15 mmol) in dioxane was added portion-wise and the reaction mixture was heated to reflux for 4 h. An additional portion of ACCN was added if required, typically after 30 min of reflux. Upon completion, the reaction mixture was cooled, diluted with EtOAc (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pet ether/Et_2O 8:2) gave **105a** as a pale yellow oil (10 mg, 85%). R_f 0.53 (pet ether/Et_2O 6:4); ν_{max}(neat)/cm^{-1}: 2940 (w), 1088 (s), 1019 (m), 946 (m); δ_H(400

MHz, $CDCl_3$) 1.06 (3H, s, H-14), 1.51 (1H, td, *J* 13.4 and 4.1 Hz, 1H of H-6), 1.64-1.74 (3H, m, 1H of H-5, 1H of H-1 and 1H of H-6), 1.76-1.93 (2H, m, 1H of H-1 and 1H of H-9), 2.24-2.38 (3H, m, H-8 and 1H of H-3), 2.44 (1H, dd, *J* 13.4 and 2.3 Hz, 1H of H-3), 3.92-3.99 (4H, m, H-11 and H-12), 5.30 (1H, d, *J* 2.0 Hz, H-7); δ_C(100 MHz, $CDCl_3$) 22.6 (CH_3, C-14), 30.8 (CH_2), 32.1 (CH_2), 36.5 (CH_2), 38.0 (CH_2), 40.6 (CH_2), 45.4 (C, C-5), 64.5 (CH_2, C-11), 64.7 (CH_2, C-12), 110.2 (C, C-2), 122.9 (CH, C-7), 146.7 (C, C-4).

Analytical data in agreement with literature values.[129]

O-((1*S*, 7a*S*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl)O-phenyl carbonothioate 165



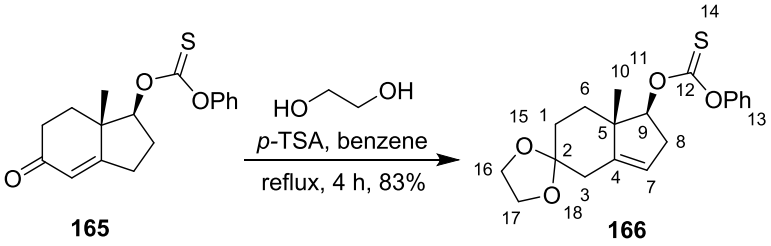
150 **165**

A novel compound prepared according to a literature procedure.[64]

Pyridine (2.7 mL, 33.38 mmol) and DMAP (0.11 g, 0.9 mmol) were sequentially added to a stirred solution of **150** (1.5 g, 9.02 mmol) in DCM (25 mL). The flask was immersed in an ice-bath and *O*-phenyl chlorothionoformate (1.38 mL, 9.92 mmol) was added dropwise over 5 min at 0 °C. After 12 h at rt, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL), washed with H_2O (15 mL) and extracted with EtOAc (2 × 20 mL). The organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave **165** as a yellow oil (1.94 g, 71%) which solidified on standing to give a

yellow solid. $[\alpha]_D^{25}$= -51° ($CHCl_3$, *c* 1.0); R_f 0.34 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2935 (w), 1663 (s), 1486 (m), 1200 (s), 778 (m); m.p. 54-57 °C; δ_H(400 MHz, $CDCl_3$) 1.29 (3H, s, H-11), 1.94-2.07 (2H, m, CH_2), 2.21 (1H, m, 1H of CH_2), 2.38-2.62 (4H, m, 2 × CH_2), 2.86 (1H, m, 1H of CH_2), 5.32 (1H, m, H-9), 5.85 (1H, s, H-3), 7.09-7.14 (2H, m, 2 × C*H*Ar), 7.31 (1H, t, *J* 12.0 Hz, C*H*Ar), 7.43-7.51 (2H, m, 2 × C*H*Ar); δ_C (100 MHz, $CDCl_3$) 17.8 (CH_3, C-11), 26.1 (CH_2), 27.2 (CH_2), 33.7 (CH_2), 34.9 (CH_2), 45.8 (C, C-5), 90.0 (CH, C-9), 122.5 (CH, *C*HAr), 124.5 (2 × CH, *C*HAr), 127.4 (CH, C-3), 130.3 (2 × CH, C*H*Ar), 154.0 (C, *C*Ar), 172.3 (C, C-4), 193.3 (C, C-13), 199.1 (C, C-2); *m/z* HRMS (ES^+) found 303.1046 ($[M+H]^+$, 79%) $C_{17}H_{19}O_3S$ requires 303.1055; (ES^+) 303.1 ($[M+H]^+$, 79%).

O-((1*S*, 7a*S*)-7a-Methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolan]-1-yl) O-phenyl carbonothioate 166



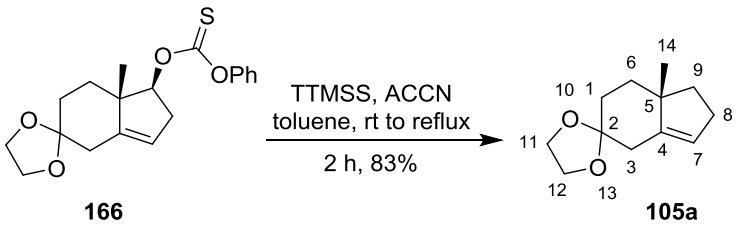
165 **166**

A novel compound prepared according to a literature procedure.[32]

Ethylene glycol (2.86 mL, 51.28 mmol) and *p*-TSA (0.12 g, 0.64 mmol) were sequentially added to a solution of thionocarbonate **165** (1.94 g, 6.41 mmol) in benzene (15 mL) and the reaction mixture was heated to reflux under a Dean-Stark apparatus. After 4 h, the reaction mixture was cooled to rt and the solvent removed under reduced pressure. The residue was dissolved in Et_2O (10 mL), washed with H_2O (8 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over

$MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **166** as a white solid (1.85 g, 83%). $[\alpha]_D^{25}$= -128° ($CHCl_3$, *c* 1.0); R_f 0.44 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2962 (w), 2936 (w), 2884 (w), 1489 (m), 1260 (s), 1196 (s), 1016 (s), 880 (s); m.p. 84-87 °C; δ_H(400 MHz, $CDCl_3$) 1.14 (3H, s, H-10) 1.62-1.69 (2H, m, C*H*$_2$), 1.73-1.90 (2H, m, C*H*$_2$), 2.33-2.37 (2H, m, C*H*$_2$), 2.40 (1H, m, 1H of C*H*$_2$), 2.90 (1H, m, 1H of C*H*$_2$), 3.68-3.87 (4H, m, H-16 and H-17), 5.28 (1H, dd, *J* 14.1 and 10.0 Hz, H-7), 5.57 (1H, t, *J* 8.0 Hz, H-9), 7.07-7.17 (2H, m, 2 × C*H*Ar), 7.29 (1H, m, C*H*Ar), 7.35-7.46 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 16.2 (CH_3, C-10), 31.1 (CH_2), 35.1 (CH_2), 35.8 (CH_2), 36.5 (CH_2), 47.2 (C, C-5), 64.5 (CH_2, C-16), 64.8 (CH_2, C-17), 91.8 (CH, C-9), 108.9 (C, C-2), 118.2 (CH, C-7), 121.8 (CH, *C*HAr), 126.4 (2 × CH, *C*HAr), 129.4 (2 × CH, *C*HAr), 144.4 (C, C-4, 153.1 (C, *C*Ar), 195.4 (C, C-12); *m/z* HRMS (ES^+) found 369.1145 $[M+Na]^+$ $C_{19}H_{22}O_4NaS$ requires 369.1137; (ES^+) 369.0 ($[M+Na]^+$, 100%).

(*S*)-7a-Methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolane] 105a



A known compound prepared by a modification of a literature procedure.[64]

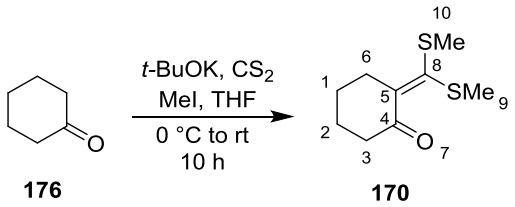
TTMSS (1.36 mL, 4.37 mmol) was added to a solution of ACCN (1.07 g, 4.37 mmol) in toluene (24 mL) at rt followed by the addition of thionocarbonate **166** (1.27 g, 3.66 mmol) in toluene (4 mL). The resultant solution was degassed for 10 min by alternative evacuation and refilling with argon before being heated at reflux for 2 h. Upon completion, the solvent was removed

in vacuo and the residue was dissolved in Et_2O (20 mL), washed with H_2O (15 mL) and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) afforded **105a** as a pale yellow oil (0.58 g, 81%). $[\alpha]_D^{25}$= +31.5° ($CHCl_3$, *c* 1.5); R_f 0.53 (pet ether/Et_2O 6:4); ν_{max}(neat)/cm^{-1}: 2940 (w), 1088 (s), 1019 (m), 946 (m); δ_H(400 MHz, $CDCl_3$) 1.07 (3H, s, H-14), 1.54 (1H, td, *J* 13.4 and 4.1 Hz, 1H of H-6), 1.62-1.71 (3H, m, 1H of H-9, 1H of H-1 and 1H of H-6), 1.76-1.91 (2H, m, 1H of H-1 and 1H of H-9), 2.22-2.33 (3H, m, H-1 and 1H of H-3), 2.45 (1H, dd, *J* 13.4 and 2.3 Hz, 1H of H-3), 3.90-3.98 (4H, m, H-11 and H-12), 5.34 (1H, d, *J* 2.0 Hz, H-7); δ_C(100 MHz, $CDCl_3$) 22.4 (CH_3), 30.3 (CH_2), 32.3 (CH_2), 36.7 (CH_2), 38.2 (CH_2), 40.7 (CH_2), 45.5 (C, C-5), 64.5 (CH_2, C-11), 64.6 (CH_2, C-12), 110.6 (C, C-2), 123.9 (CH, C-7), 146.9 (C, C-4).

Analytical data in agreement with literature values.[32]

5.4 Experimental procedures and analytical data for Chapter three

2-(Bis(methylthio)methylene)cyclohexan-1-one 170



176 **170**

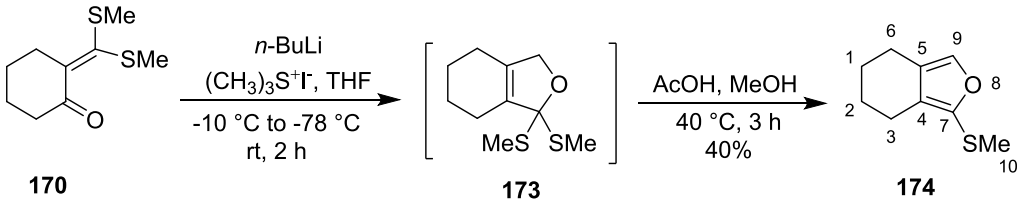
A known compound prepared according to a literature procedure.[65]

t-BuOK (1.14 g, 10.18 mmol) was added to a stirred solution of **176** (0.5 g, 5.09 mmol) in THF (15 mL) at rt. After 15 min, CS_2 (0.3 mL, 5.09 mmol) was added dropwise over 5 min at -20

°C, taking caution not to allow the mixture to heat excessively. MeI (0.63 mL, 10.18 mmol) was added in a similar fashion before being warmed to rt gradually. After 10 h, the reaction mixture was quenched with ice-cold water (15 mL), extracted with Et_2O (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/EtOAc 8:2) gave **170** as a yellow oil (0.58 g, 56%). R_f 0.42 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2922 (w), 1687 (s), 1474 (s), 1265 (s); δ_H(400 MHz, $CDCl_3$) 1.75-1.96 (4H, m, 2 × CH_2), 2.35, 2.37 (6H, 2 × s, H-9 and H-10), 2.50 (2H, dd, *J* 9.1 and 4.4 Hz, CH_2), 2.86-2.93 (2H, m, CH_2); δ_C(100 MHz, $CDCl_3$) 18.3 (CH_3, C-9), 18.5 (CH_3, C-10), 24.4 (CH_2), 24.7 (CH_2), 33.6 (CH_2), 41.6 (CH_2), 138.2 (C, C-5), 151.2 (C, C-8), 199.1 (C, C-4); *m/z* HRMS (EI^+) found 202.0484 $[M]^+$ $C_9H_{14}S_2O$ requires 202.0486; (EI^+) 202.0 ($[M]^+$, 89%).

Analytical data in agreement with literature values.[28]

1-(Methylthio)-4,5,6,7-tetrahydroisobenzofuran 174



170 **173** **174**

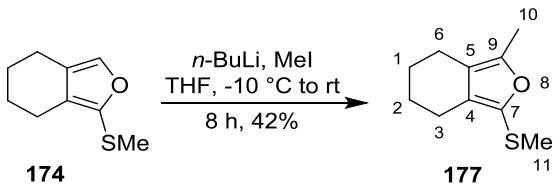
A known compound prepared according to a literature procedure.[28]

n-BuLi (0.65 mL of a 1.8 M soln. in hexane, 1.17 mmol) was added dropwise over 5 min to a solution of trimethylsulfonium iodide (0.24 g, 1.17 mmol) in THF (0.2 mL) at -10 °C. The reaction mixture was stirred for 15 min before being cooled to -78 °C. A solution of **170** (0.2 g, 0.98 mmol) in THF (4 mL) was added portion-wise, after which the ice-bath was removed and the reaction mixture stirred at rt for 2 h. The reaction mixture was quenched with H_2O

(5 mL) and extracted with Et_2O (2 × 25 mL). The organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting crude yellow oil **173** was dissolved in MeOH (10 mL) and acetic acid (12 mL of a 10% aq. solution) was added. The reaction mixture was heated at 35 °C for 3 h, then neutralised with Na_2CO_3 (15 mL of a saturated aq. solution) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **174** as a pale yellow oil (0.65 g, 40%). R_f 0.68 (pet ether/Et_2O 6:4); ν_{max}(neat)/cm^{-1}: 2922 (w), 1656 (m), 1418 (s), 933 (m); δ_H(400 MHz, $CDCl_3$) 1.60-1.71 (4H, m, 2 × CH_2), 2.26 (3H, s, H-10), 2.43-2.51 (4H, m, 2 × CH_2), 7.17 (1H, br s, H-9); δ_C(100 MHz, $CDCl_3$) 18.7 (CH_3, C-10), 20.2 (CH_2), 21.2 (CH_2), 23.2 (CH_2), 23.4 (CH_2), 121.1 (C, CH_2*C*=), 124.7 (C, CH_2*C*=), 139.7 (CH, C-9), 140.3 (C, C-7); *m*/*z* HRMS (EI^+) found 168.0617 $[M]^+$ $C_9H_{12}SO$ requires 168.0609; (EI^+) 168.0 ($[M]^+$, 100%).

Analytical data in agreement with literature values.[27]

1-Methyl-3-(methylthio)-4,5,6,7-tetrahydroisobenzofuran 177



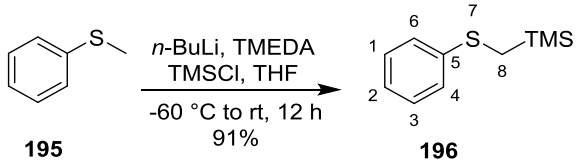
A known compound prepared by a modification of a literature procedure.[27]

n-Buli (0.21 mL of a 1.8 M soln. in hexane, 0.4 mmol) was added dropwise over 5 min to a solution of **174** (44 mg, 0.26 mmol) in THF (2.5 mL) at -10 °C. After 30 min, MeI (24 µL, 0.40

mmol) was added and the cooling was removed. The reaction mixture was stirred at rt for 2 h before being quenched with H_2O (8 mL) and extracted with Et_2O (2 × 8 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **177** as a colourless oil (20 mg, 42%). R_f 0.62 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2923 (w), 2855 (w), 1439 (s), 1246 (m), 966 (s); δ_H(400 MHz, $CDCl_3$) 1.65-1.72 (4H, m, 2 × CH_2), 2.19 (3H, s, H-10), 2.29 (3H, s, H-11), 2.38-2.45 (2H, m, CH_2), 2.47-2.84 (2H, m, CH_2); δ_C(100 MHz, $CDCl_3$) 12.2 (CH_3), 19.7 (CH_3), 20.7 (CH_2), 21.6 (CH_2), 23.4 (CH_2), 23.5 (CH_2), 117.8 (C, C-5), 128.2 (C, C-4), 137.4 (C, C-7), 148.4 (C, C-9); *m/z* HRMS (EI^+) found 182.0760 $[M]^+$ $C_{10}H_{14}OS$ requires 182.0765; (EI^+) 182.0 ($[M]^+$, 84%).

Analytical data in agreement with literature values.[27]

(Phenylsulfanyl-methyl)trimethylsilane 196



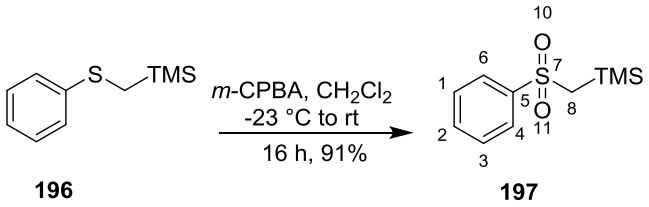
A known compound prepared according to a literature procedure.[70]

n-BuLi (15 mL of a 1.6 M in soln. in hexane, 24.15 mmol) was added dropwise over 10 min to a mixture of thioanisol **195** (1.9 mL, 16.10 mmol) and TMEDA (2.47 mL, 16.42 mmol) in THF (14 mL) at -40 °C. The resulting pale yellow solution was stirred for 1 h at -40 °C and then cooled to -60 °C. TMSCl (3.3 mL, 25.76 mmol) in THF (1.0 mL) was added in one portion, then stirred for 30 min at -60 °C before being warmed slowly to rt. After 12 h, the reaction mixture was quenched with NH_4Cl (15 mL of a saturated aq. solution) and extracted with

Et_2O (2 × 10 mL). The organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **196** as a colourless liquid (2.90 g, 91%). R_f 0.62 (pet ether/Et_2O 7:3); ν_{max}(neat)/cm^{-1}: 2955 (w), 1479 (m), 1249 (s), 845 (s); δ_H(400 MHz, $CDCl_3$) 0.19 (9H, s, Si(C*H*$_3$)$_3$), 2.18 (2H, s, H-8), 7.10 (1H, m, C*H*Ar), 7.24-7.31 (4H, m, 4 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -1.7 (CH_3, Si(*C*H_3)$_3$), 18.3 (CH_2), 124.4 (2 × CH, *C*HAr), 125.8 (2 × CH, *C*HAr), 128.6 (CH, *C*HAr), 140.5 (C, *C*Ar).

Analytical data in agreement with literature values.[70]

(Phenylsulfonyl-methyl)trimethylsilane 197



196 **197**

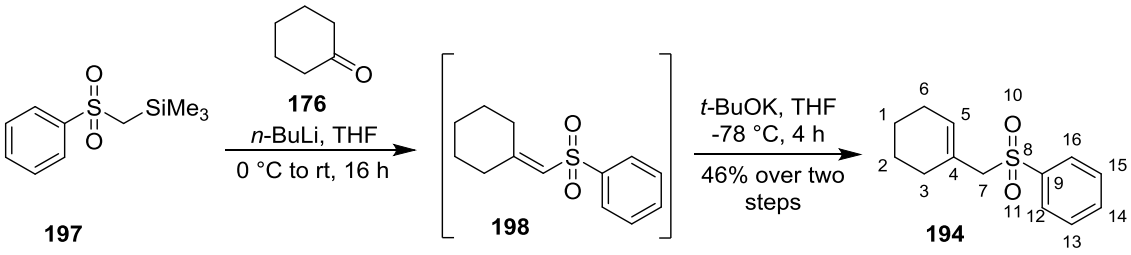
A known compound prepared according to the literature procedure.[71]

196 (1.0 g, 5.09 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 1 h to a mixture of purified *m*-CPBA (2.1 g, 12.72 mmol) in CH_2Cl_2 (45 mL) at -23 °C before being warmed to rt. After 16 h, the reaction mixture was quenched with $NaHCO_3$ (2 × 20 mL of a saturated aq. solution) and the organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) yielded **197** as a white solid (1.06 g, 91%); m.p. 71-76 °C; R_f 0.37 (pet ether/Et_2O 7:3); ν_{max}(neat)/cm^{-1}: 2931 (w), 2860 (w), 1447 (m), 1303 (s), 1141 (s), 746 (s); δ_H(400 MHz, $CDCl_3$) 0.30 (9H, s, Si(C*H*$_3$)$_3$), 2.81 (2H, s, C*H*$_2$), 7.21 (1H, m, C*H*Ar), 7.28-7.34 (4H, m, 4 × C*H*Ar);

δ_C(100 MHz, $CDCl_3$) -0.2 (CH_3, Si(CH_3)$_3$), 48.9 (CH_2), 127.5 (2 × CH, *C*HAr), 129.8 (CH, *C*HAr), 129.7 (2 × CH, *C*HAr), 130.5 (C, *C*Ar).

Analytical data in agreement with literature values.[71]

(Cyclohex-1-enyl)methyl phenyl sulfone 194



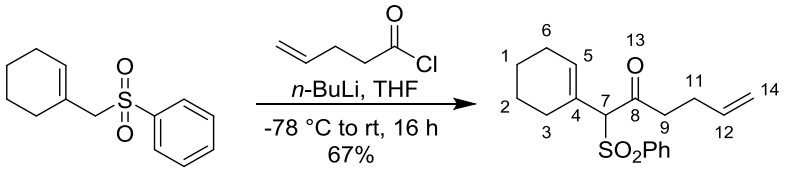
A known compound prepared by a modification of the literature procedure.[72]

n-BuLi (2.0 mL of a 2.3 M soln. in hexane, 4.64 mmol) was added dropwise over 10 min to a solution of **197** (1.06 g, 4.64 mmol) in THF (23 mL) at 0 °C. After 30 min at 0 °C, cyclohexanone **176** (0.45 mL, 4.64 mmol) was added slowly over 5 min and the reaction mixture was immediately allowed to warm to rt. After 16 h, the reaction mixture was quenched with NH_4Cl (15 mL of a saturated aq. solution) and extracted with Et_2O (2 × 20 mL). The organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting colourless oil **198** (0.64 g) in THF (9 mL) was treated with *t*-BuOK (0.30 g, 2.70 mmol) at -78 °C and stirred for 4 h before being quenched with H_2O (10 mL) and extracted with Et_2O (2 × 10 mL). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **194** as a white solid (0.51 g, 46% over 2 steps); m.p. 68-73 °C. R_f 0.37 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2937 (w), 2861 (w), 1447 (m), 1297 (s), 1082 (s), 742(s); δ_H(400 MHz, $CDCl_3$) 1.46-1.61 (4H,

m, 2 × CH_2), 1.88-1.95 (2H, m, CH_2), 2.04-2.06 (2H, m, CH_2), 3.67 (2H, s, H-7), 5.33 (1H, tt, *J* 3.8 and 1.7 Hz, H-5), 7.52-7.58 (2H, m, 2 × C*H*Ar), 7.71 (1H, m, C*H*Ar), 7.84-7.87 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 21.5 (CH_2), 22.6 (CH_2), 25.5 (CH_2), 28.6 (CH_2), 64.8 (CH_2), 126.1 (C, C-4), 128.5 (2 × CH, *C*HAr), 128.8 (2 × CH, *C*HAr), 132.9 (CH, C-5), 133.5 (CH, *C*HAr), 138.2 (C, *C*Ar); *m/z* HRMS (ES^+) found 259.0770 $[M+Na]^+$ $C_{13}H_{16}O_2NaS$ requires 259.0769; (ES^+) 259.0 ($[M+Na]^+$, 100%).

Analytical data in agreement with literature values.[72]

1-(cyclohex-1-enyl)-1-(phenyl sulfonyl)hex-5-en-2-one 200



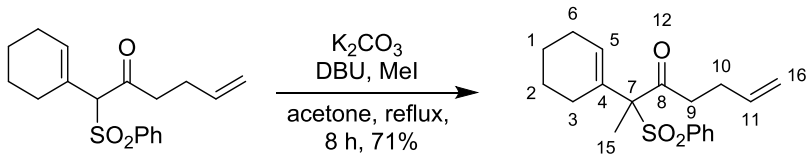
194 **200**

A novel compound prepared according to a literature procedure.[73]

n-BuLi (0.57 mL of a 1.6 M soln. in hexane, 0.92 mmol) was added dropwise over 10 min to a solution of allyl sulfone **194** (0.1 g, 0.42 mmol) in THF (1.6 mL) at -78 °C. After 30 min at -78 °C, a solution of 4-pentenoyl chloride (74 µL, 0.63 mmol) in THF (0.5 mL) was added over 5 min and the reaction mixture was stirred for 15 min before being warmed to rt. After 16 h, the reaction mixture was washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **200** as a colourless oil (90 mg, 67%). R_f 0.39 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 2858 (w), 1721 (s), 1447 (m), 1305 (s), 1141 (s); δ_H(400 MHz, $CDCl_3$) 1.47-1.62 (4H, m, 2 × CH_2), 1.92-1.99 (2H, m, CH_2), 2.03-2.09 (2H, m, CH_2), 2.26-2.32 (2H, m, CH_2), 2.64 (2H,

td, *J* 7.3 and 2.6 Hz, H-11), 4.54 (1H, s, H-7), 4.98 (1H, dd, *J* 10.2 and 1.7 Hz, 1H of H-14), 5.06 (1H, dd, *J* 16.8 and 1.7 Hz, 1H of H-14), 5.61 (1H, tt, *J* 3.7 and 1.7 Hz, H-5), 5.73 (1H, ddt, *J* 16.8, 10.2 and 6.5 Hz, H-12), 7.52-7.61 (2H, m, 2 × C*H*Ar), 7.58 (1H, m, C*H*Ar), 7.88-8.04 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 21.3 (CH_2), 22.7 (CH_2), 25.7 (CH_2), 27.2 (CH_2), 28.6 (CH_2), 42.8 (CH_2), 80.2 (CH, C-7), 115.4 (CH_2, C-14), 125.9 (C, C-4), 129.9 (2 × CH, *C*HAr), 133.8 (2 × CH, *C*HAr), 134.2 (C, *C*Ar), 134.5 (CH, *C*HAr), 136.1 (CH, C-5), 137.4 (CH, C-12), 199.1 (C, C-8); *m/z* HRMS (ES^+) found 341.1191 $[M+Na]^+$ $C_{18}H_{22}O_3NaS$ requires 341.1187; (ES^+) 341.1 ($[M+Na]^+$, 100%).

2-(Cyclohex-1-en-1-yl)-2-(phenylsulfonyl)hept-6-en-3-one 182



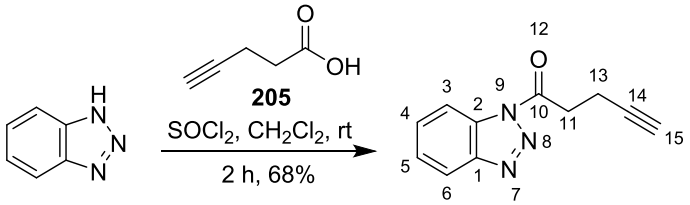
200 **182**

A novel compound prepared according to a literature procedure.[74]

A mixture of **200** (70 mg, 0.21 mmol), K_2CO_3 (26 mg, 0.19 mmol), DBU (57 µL, 0.38 mmol) and MeI (0.13 mL, 2.1 mmol) in anhydrous acetone (4.0 mL) was heated under reflux. After 8 h, the reaction mixture was cooled to rt and washed with brine (4 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave the *title compound* **182** as a colourless oil (50 mg, 71%). R_f 0.42 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 1716 (s), 1446 (m), 1301 (s), 1139 (s); δ_H(400 MHz, $CDCl_3$) 1.48-1.70 (4H, m, 2 × CH_2), 1.78 (3H, s, H-15), 1.90-1.97 (2H, m, CH_2), 1.99-2.14 (2H, m, CH_2), 2.21-2.34 (2H, m, CH_2), 2.58 (2H, ddd, *J* 7.9, 6.6 and 3.1 Hz, H-9), 5.01 (1H, dd, *J*

16.9 and 1.6 Hz, 1H of H-16), 5.37 (1H, dd, *J* 10.2 and 1.6 Hz, 1H of H-16), 5.42 (1H, m, H-5), 5.74 (1H, ddt, *J* 16.9, 10.2 and 6.7 Hz, H-11), 7.46 (1H, m, C*H*Ar), 7.49-7.56 (4H, m, 4 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 16.3 (CH_3), 22.1 (CH_2), 23.6 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 28.5 (CH_2), 39.5 (CH_2), 82.3 (C, C-7), 116.4 (CH_2, C-16), 125.6 (CH, C-5), 128.6 (2 × CH, *C*HAr), 129.7 (CH, *C*HAr), 132.2 (2 × CH, *C*HAr), 134.2 (CH, C-11), 134.9 (C, *C*Ar), 136.6 (C, C-4), 204.3 (C, C-8). Parent ion could not be observed in MS (ES^+).

1-(1H-1,2,3-Benzotriazole-1-yl)-pentynone 206

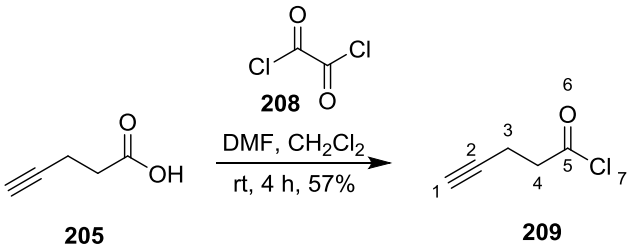


A novel compound prepared according to a literature procedure.[77]

$SOCl_2$ (0.15 mL, 2.03 mmol) was added to a stirred solution of204**5** (0.58 g, 2.88 mmol) in CH_2Cl_2 (15 mL) at rt. The reaction mixture was stirred for 30 min before 4-pentynoic acid **205** (0.20 g, 2.03 mmol) was added in one portion and stirring was continued for 2 h. The resulting suspension was filtered and washed with NaOH (3 × 10 mL of a 2.0 M aq. solution), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **206** as a white solid (0.28 g, 68%); m.p. 70-74 °C. R_f 0.38 (pet ether/Et_2O 7:3); ν_{max}(neat)/cm^{-1}: 3289 (s), 2921 (w), 1721 (s), 747 (s); δ_H(400 MHz, $CDCl_3$) 2.04 (1H, t, *J* 2.6 Hz, H-15), 2.82 (2H, td, *J* 7.2 and 2.6 Hz, CH_2), 3.71 (2H, t, *J* 7.2 Hz, CH_2), 7.53 (1H, m, C*H*Ar), 7.68 (1H, ddd, *J* 8.2, 7.1 and 1.0 Hz, C*H*Ar), 8.14 (1H, dt, *J* 8.3, 1.0 Hz, C*H*Ar), 8.31 (1H, dt, *J* 8.3 and 1.0 Hz, C*H*Ar); δ_C(100 MHz, $CDCl_3$) 13.9 (CH_2), 34.8 (CH_2,

H-11), 69.3 (CH, C-15), 81.6 (C, C-14), 114.3 (CH, *C*HAr), 120.2 (CH, *C*HAr), 126.1 (CH, *C*HAr), 130.3 (CH, *C*HAr), 135.8 (C, *C*Ar), 145.2 (C*, C*Ar), 171.8 (C, C-10); *m/z* HRMS (EI^+) found 199.0747 $[M]^+$ $C_{11}H_9N_3O$ requires 199.0746; (EI^+) 199.0 ($[M]^+$, 11%).

4-Pentynoyl chloride 209



205 209

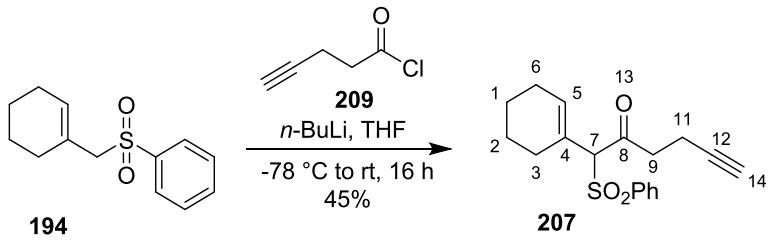
A known compound prepared according to a literature procedure.[78]

DMF (2-4 drops, cat.) and oxalyl chloride **208** (0.22 mL, 2.68 mmol) were sequentially added to a solution of **205** (160 mg, 1.34 mmol) in CH_2Cl_2 (6 mL) at rt. After 4 h, the solvent was removed under reduced pressure to give **209** as a yellow oil (90 mg, 57%) which was used without purification. ν_{max}(neat)/cm^{-1}: 3310 (s), 2125 (w), 1780 (s); δ_H(300 MHz, $CDCl_3$); 2.04 (1H, t, *J* 2.7 Hz, H-1), 2.57 (2H, td, *J* 7.1 and 2.7 Hz, CH_2), 3.14 (2H, t, *J* 7.1 Hz, H-5); δ_C(100 MHz, $CDCl_3$) 14.7 (CH_2), 45.6 (CH_2), 70.3 (CH, C-1), 80.4 (C, C-2), 172.2 (C, C-5).

Analytical data in agreement with literature values.[78]

1-(Cyclohex-1-enyl)-1-(phenyl sulfonyl)hex-5-n-2-one 207

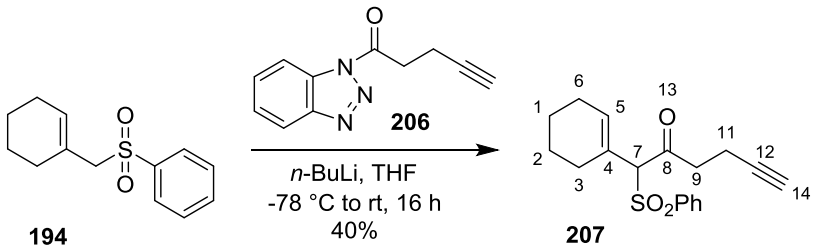
Method A



A novel compound prepared according to a literature procedure.[75]

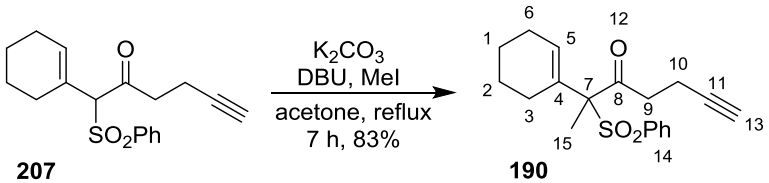
n-BuLi (0.92 mL of a 1.5 M soln. in hexane, 1.4 mmol) was added dropwise over 10 min to a solution of allyl sulfone **194** (150 mg, 0.63 mmol) in THF (2.5 mL) at -78 °C. After 30 min at -78 °C, a solution of 4-pentynoyl chloride **209** (110 mg, 0.95 mmol) in THF (0.6 mL) was added over 5 min and the reaction was stirred for 15 min before being warmed to rt. After 16 h, the reaction mixture was quenched with NH_4Cl (8 mL of a saturated aq. solution) and extracted with Et_2O (2 × 15 mL). The organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **207** as a pale yellow solid (90 mg, 45%).

Method B



n-BuLi (0.28 mL of a 1.6 M soln. in hexane, 0.46 mmol) was added dropwise over 10 min to a solution of allyl sulfone **194** (50 mg, 0.21 mmol) in THF (1 mL) at -78 °C and stirred for 30 min at -78 °C. A solution of **206** (46 mg, 0.23 mmol) in THF (0.5 mL) was added over 5 min, then stirred for 15 min before being warmed to rt. After 16 h, the reaction mixture was washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **207** as a pale yellow solid (27 mg, 40%); m.p. 81-84 °C. R_f 0.32 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3310 (s), 2928 (w), 1724 (s), 1447 (m), 1306 (s), 1150 (s); δ_H(400 MHz, $CDCl_3$) 1.47-1.62 (4H, m, 2 × C*H*$_2$), 1.92 (1H, t, *J* 2.7 Hz, H-14), 1.94-202 (2H, m, C*H*$_2$), 2.04-2.09 (2H, m, C*H*$_2$), 2.43 (2H, td, *J* 7.2 and 2.6 Hz, H-11), 2.81 (2H, t, *J* 7.2 Hz, H-9), 4.55 (1H, s, H-7), 5.62 (1H, tt, *J* 3.7 and 1.7 Hz, H-5), 7.53-7.68 (2H, m, 2 × C*H*Ar), 7.62 (1H, m, C*H*Ar), 7.85-7.89 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 12.9 (CH_2), 21.4 (CH_2), 22.4 (CH_2), 25.5 (CH_2), 28.3 (CH_2), 42.6 (CH_2), 68.8 (CH, C-14), 80.9 (CH, C-7), 82.2 (C, C-12), 125.8 (C, C-4), 128.6 (CH, 2 × *C*HAr), 129.8 (CH, 2 × *C*HAr), 134.2 (CH, C*H*Ar), 135.0 (CH, C-5), 137.1 (C, *C*Ar), 198.2 (C, C-8); *m*/*z* HRMS (AP^+) found 317.1214 $[M]^+$ $C_{18}H_{21}O_3S$ requires 317.1211; (AP^+) 317.1 ($[M]^+$, 100%).

2-(Cyclohex-1-en-1-yl)-2-(phenylsulfonyl)hept-6-yn-3-one 190



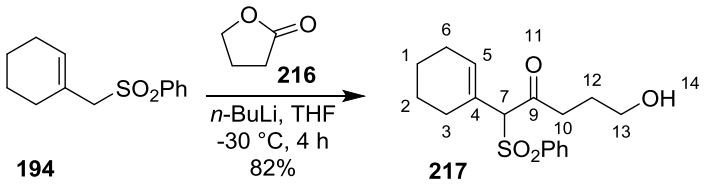
207 **190**

A novel compound prepared according to a literature procedure.[74]

A mixture of **207** (150 mg, 0.47 mmol), K_2CO_3 (65 mg, 0.47 mmol), DBU (0.12 mL, 0.84 mmol) and MeI (0.3 mL, 4.7 mmol) in anhydrous acetone (8.0 mL) was heated under reflux for 7 h

before being cooled to rt. The reaction mixture was washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave the *title compound* **19** as a pale yellow solid **0** (130 mg, 83%); m.p. 91-95 °C. R_f 0.29 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3276 (m), 2929 (w), 2859 (w), 1717 (s), 1446 (m), 1299 (s), 1137 (s), 688 (s); δ_H(400 MHz, $CDCl_3$) 1.49-1.71 (4H, m, 2 × C*H*$_2$), 1.79 (3H, s, H-15), 1.91 (1H, t, *J* 2.7 Hz, H-13), 1.90-1.97 (2H, m, C*H*$_2$), 2.11-2.18 (2H, m, C*H*$_2$), 2.46 (2H, td, *J* 7.2 and 2.6 Hz, H-10) 2.79 (2H, t, *J* 7.2 Hz, H-9), 5.38 (1H, m, H-5), 7.45 (1H, m, C*H*Ar), 7.58-7.65 (4H, m, 4 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 13.5 (CH_2), 16.1 (CH_3), 21.3 (CH_2), 22.8 (CH_2), 26.1 (CH_2), 26.4 (CH_2), 38.8 (CH_2, C-9), 69.4 (CH, C-13), 81.7 (C, C-11), 83.1 (C, C-7), 128.3 (2 × CH, *C*HAr), 131.8 (2 × CH, *C*HAr), 133.9 (CH, *C*HAr), 134.5 (CH, C-5), 136.9 (C, *C*Ar), 141.6 (C, C-4), 202.6 (C, C-8); *m/z* HRMS (ES^+) found 353.1184 $[M+Na]^+$ $C_{19}H_{22}O_3NaS$ requires 353.1187; (ES^+) 353.1 ($[M+Na]^+$, 88%).

1-(Cyclohex-1-en-1-yl)-5-hydroxy-1-(phenylsulfonyl)pentan-2-one 217

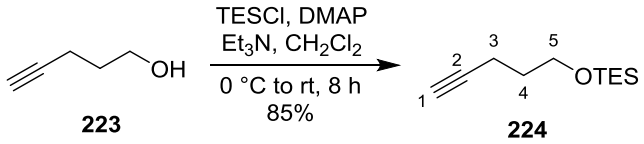


A novel compound prepared by a modification of a literature procedure.[75]

n-BuLi (0.62 mL of a 1.5 M soln. in hexane, 0.93 mmol) was added dropwise over 20 min to a solution of **194** (0.1 g, 0.12 mmol) in THF (1.5 mL) at -30 °C. The reaction mixture was stirred for 30 min before a solution of lactone **216** (32 µL, 0.42 mmol) in THF (0.5 mL) was added dropwise over 5 min. The reaction mixture was stirred at -30 °C for 4 h before being quenched with NH_4Cl (4 mL of a saturated aq. solution) and extracted with Et_2O (2 × 4 mL).

The combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 3:7) to afford **217** as a clear colourless oil (100 mg, 82%). R_f 0.21 (pet ether/Et_2O 3:7); ν_{max}(neat)/cm^{-1}: 3390 (br), 2932 (w), 1720 (s), 1447 (m), 1307 (s), 1145 (s), 589 (s); δ_H(300 MHz, $CDCl_3$) 1.45-1.49 (4H, m, 2 × CH_2), 1.76-1.81 (2H, m, CH_2), 1.89-1.94 (2H, m, CH_2), 2.10-2.14 (2H, m, CH_2), 2.93 (2H, t, *J* 7.8 Hz, H-10), 3.46 (2H, t, *J* 7.0 Hz, H-13), 4.32 (1H, s, H-7), 5.50 (1H, dt, *J* 3.9 and 2.0 Hz, H-5), 7.42-7.56 (3H, m, 3 × C*H*Ar), 7.79-7.84 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 21.1 (CH_2), 22.5 (CH_2), 25.6 (CH_2), 28.4 (CH_2), 38.7 (CH_2), 40.1 (CH_2), 61.4 (CH_2), 80.7 (CH, C-7), 127.3 (CH, C-5), 128.3 (2 × CH, *C*HAr), 129.7 (2 × CH, *C*HAr), 133.7 (CH, *C*HAr), 134.0 (C, *C*Ar), 134.3 (C, C-4), 204.2 (C, C-9); *m/z* HRMS (ES^+) found 345.1138 $[M+Na]^+$ $C_{17}H_{22}O_4SNa$ requires 345.1136; (ES^+) 345.1 ($[M+Na]^+$, 100%).

Triethyl(pent-4-yn-1-yloxy)silane 224



223 **224**

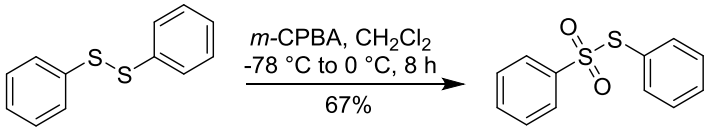
A known compound prepared according to a literature procedure.[83]

TESCl (0.80 mL, 4.75 mmol) was added in a one portion to a solution of 4-pentyn-1-ol **223** (0.4 g, 4.75 mmol), DMAP (0.11 g, 0.95 mmol) and Et_3N (1.33 mL, 9.5 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After 8 h at rt, the reaction mixture filtered through celite pad, quenched with H_2O (6 mL), washed with brine (6 mL), dried over $MgSO_4$, filtered and evaporated to 2/3 of solvent under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) afforded **224** (0.8 g, 85%). R_f 0.68 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2954 (w), 2876 (w),

1103 (s), 739 (s); δ_H(400 MHz, $CDCl_3$) 0.65 (6H, quin., *J* 7.9 Hz, Si(CH_2)$_3$), 0.95 (9H, t, *J* 7.9 Hz, (CH_3)$_3$), 1.74 (2H, tt, *J* 7.1 and 6.1 Hz, H-4), 1.95 (1H, t, *J* 2.7 Hz, H-1), 2.30 (2H, td, *J* 7.1 and 2.7 Hz, H-3), 3.63 (2H, t, *J* 6.1 Hz, H-5); δ_C(100 MHz, $CDCl_3$) 5.5 (6 × CH_2, Si(CH_2)$_3$), 7.6 (3 × CH_3, Si(CH_2)$_3$(CH_3)$_3$), 16.0 (CH_2), 32.7 (CH_2), 62.3 (CH_2), 69.4 (CH, C-1), 85.4 (C, C-2).

Analytical data in agreement with literature values.

S-phenylbenzenethiosulfonate 226



225 **226**

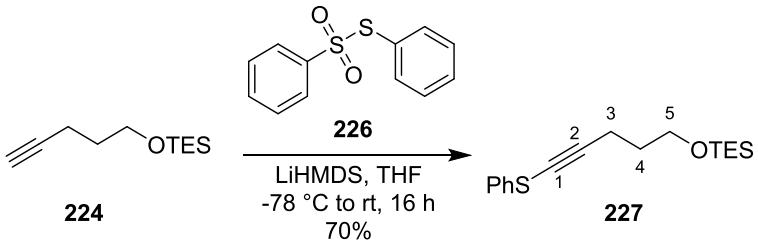
A known compound prepared according to a literature procedure.[85]

A solution of *m*-CPBA (2.37 g, 13.74 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min to a solution of phenyl disulfide **225** (1.5 g, 6.87 mmol) in CH_2Cl_2 (60 mL) at -78 °C and stirred for 3 h before being warmed to rt. After 6 h, the reaction mixture was quenched with $NaHCO_3$ (2 × 15 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **226** as a pale yellow solid (1.16 g, 67%); m.p. 39-43 °C. R_f 0.34 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3065 (w), 1324 (m), 1143 (s); δ_H(400 MHz, $CDCl_3$) 7.30-7.36 (4H, m), 7.39-7.49 (3H, m), 7.54-7.59 (3H, m); δ_C(100 MHz, $CDCl_3$) 127.5 (CHAr), 127.9 (2 × CHAr), 128.7 (2 × CHAr), 129.2 (2 × CHAr), 131.4 (2 × CHAr), 133.6 (C, *C*Ar), 136.5 (CHAr), 142.6 (C, *C*Ar); *m*/*z*

HRMS (ES^+) found 273.0022 $[M+Na]^+$ $C_{12}H_{10}O_2NaS_2$ requires 273.0020; (ES^+) 273.0 ($[M+Na]^+$, 100%).

Analytical data in agreement with literature values.

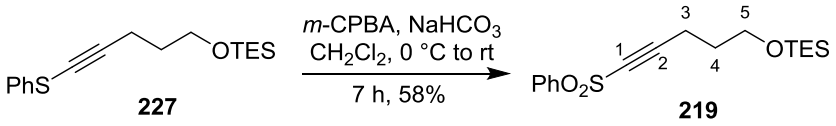
Triethyl((5-(phenylthio)pent-4-yn-1-yl)oxy)silane 227



A novel compound prepared according to a literature procedure.[86]

LiHMDS (0.8 mL of a 1.0 M soln. in THF, 0.8 mmol) was added dropwise over 5 min to a solution of **224** (0.16 g, 0.8 mmol) in THF (3 mL) at -78 °C and stirred for 1 h. A solution of **226** (0.18 g, 0.72 mmol) in THF (1.0 mL) was added dropwise over 5 min and allowed to warm slowly to rt. After 16 h, the reaction mixture was quenched with NH_4Cl (8 mL of a saturated aq. solution) and extracted with Et_2O (2 × 10 mL). The organic extracts were washed with brine (8 mL), dried $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) gave **227** as a yellow oil (0.17 g, 70%). R_f 0.62 (pet ether/Et_2O 8:2); ν_{max}(neat)/cm^{-1}: 2952 (w), 2875 (w), 1101 (s), 734 (s); δ_H(400 MHz, $CDCl_3$) 0.58 (6H, quin., *J* 7.9 Hz, $Si(CH_2)_3$), 0.93 (9H, t, *J* 8.0 Hz, $Si(CH_2)_3(CH_3)_3$), 1.71-1.79 (2H, m, CH_2), 2.21 (2H, td, *J* 7.1 and 2.7 Hz, CH_2), 2.52 (2H, t, *J* 7.1 Hz, CH_2), 3.67 (2H, t, *J* 6.1 Hz, CH_2), 7.18 (1H, m, CHAr), 7.22-7.37 (4H, m, 4 × CHAr); δ_C(100 MHz, $CDCl_3$) 4.5 (3 × CH_2, $Si(CH_2)_3$), 7.9 (3 × CH_3, $Si(CH_2)_3(CH_3)_3$), 16.8 (CH_2), 31.8 (CH_2), 61.4 (CH_2), 64.8 (C, C≡), 84.4 (C, ≡C), 125.9 (2 × CH, CHAr), 126.2 (CH, CHAr), 129.1 (2 × CH, CHAr), 133.8 (C, CAr).

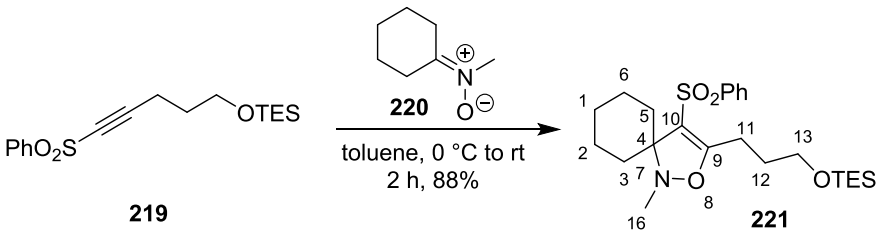
Triethyl((5-phenylsulfonyl)pent-4-yn-1-yl)oxy)silane 219



A novel compound prepared according to a literature procedure.[87]

$NaHCO_3$ (87 mg, 1.04 mmol) and purified *m*-CPBA (180 mg, 1.04 mmol) were added sequentially to a solution of **227** (160 mg, 0.52 mmol) in CH_2Cl_2 (5.2 mL) at 0 °C before being warmed to rt. After 7 h, the reaction mixture was washed with H_2O (5 mL) and organic extract was quenched with $NaHCO_3$ (2 × 10 mL of a saturated aq. solution). The organic extracts were washed with brine (8 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave **219** as a colourless oil (75 mg, 58%). R_f 0.45 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2954 (w), 2201 (s), 1327 (s), 1160 (s), 1090 (s), 727 (s); δ_H(400 MHz, $CDCl_3$) 0.59 (6H, quin., *J* 8.0 Hz, Si(CH_2)$_3$), 0.95 (9H, t, *J* 7.9 Hz, (CH_3)$_3$), 1.78 (2H, tt, *J* 7.1 and 5.8 Hz, H-4), 2.51 (2H, t, *J* 7.1 Hz, CH_2), 3.63 (2H, t, *J* 5.8 Hz, CH_2), 7.68-7.60 (2H, m, C*H*Ar), 7.72 (1H, m, C*H*Ar), 8.04-8.12 (2H, m, C*H*Ar); δ_C(100 MHz, $CDCl_3$) 4.7 (3 × CH_2, Si(*C*H_2)$_3$), 7.1 (3 × CH_3, Si(CH_2)$_3$(CH_3)$_3$), 15.9 (CH_2), 30.5 (CH_2), 61.0 (CH_2), 78.5 (C, ≡*C*), 97.8 (C, ≡*C*), 127.6 (2 × CH, *C*HAr), 129.7 (2 × CH, *C*HAr), 134.3 (CH, *C*HAr), 142.4 (C, *C*Ar); *m*/*z* HRMS (ES^+) found 361.1272 $[M+Na]^+$ $C_{17}H_{26}O_3SiNaS$ requires 361.1270; (ES^+) 361.1 ($[M+Na]^+$, 100%).

1-Methyl-4-(phenylsulfonyl)-3-)3-((triethylsilyl)oxy)propyl)-2-oxa-1-azaspiro[4.5]dec-3-ene 221



Preparation of *N*-methylcyclohexylnitrone **220**[88]

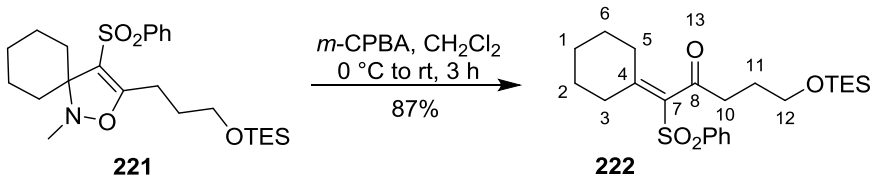
A mixture of cyclohexanone (0.3 mL, 3.05 mmol), *N*-methylhydroxylamine hydrochloride (0.32 g, 3.87 mmol) and K_2CO_3 (0.53 g, 3.87 mmol) in EtOH (10 mL) was refluxed for 8 h. The reaction mixture was filtered and filtrate concentrated under reduced pressure, leaving **220** as an unstable yellow liquid which was used immediately in the next step.

A novel compound prepared by a modification of a literature procedure.[84]

219 (120 mg, 0.35 mmol) was added dropwise over 5 min to a solution of nitrone **220** (89 mg, 0.7 mmol) in toluene (0.36 mL) at 0 °C. The reaction mixture was stirred an additional 20 min at 0 °C before being warmed to rt. After 2 h, the solvent was removed under reduced pressure and the resulting dark coloured oil was purified by column chromatography (pet ether/Et_2O 6:4) to give **221** as a colourless oil (100 mg, 88%). R_f 0.51 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2933 (w), 2875 (w), 1619 (s), 1151 (s), 722(s); δ_H(400 MHz, $CDCl_3$) 0.63 (6H, quin., *J* 8.0 Hz, Si(C*H*$_2$)$_3$), 0.98 (9H, t, *J* 7.9 Hz, (C*H*$_3$)$_3$), 1.06-1.12 (2H, m, C*H*$_2$), 1.45-1.54 (4H, m, 2 × C*H*$_2$), 1.46-1.59 (4H, m, 2 × C*H*$_2$), 1.83-1.97 (2H, m, C*H*$_2$), 2.51 (3H, s, H-16), 2.82-2.98 (2H, m, C*H*$_2$), 3.73 (2H, t, *J* 5.8 Hz, C*H*$_2$), 7.34-7.42 (3H, m, 3 × C*H*Ar), 7.81-7.93 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 6.2 (3 × CH_2, Si(*C*H$_2$)$_3$), 7.2 (3 × CH_3, (*C*H$_3$)$_3$), 22.4 (CH_2), 24.8 (CH_2), 29.6 (CH_2), 36.4 (CH_2), 39.1 (CH_3, C-16), 60.5 (CH_2), 72.2 (C, C-4), 114.0 (C, C-10), 126.6 (2 ×

CH, *C*HAr), 128.8 (2 × CH, *C*HAr), 142.9 (C, *C*Ar), 132.7 (CH, *C*HAr), 167.4 (C, C-9); *m/z* HRMS (ES^+) found 488.2261 $[M+Na]^+$ $C_{24}H_{39}O_4SiNaSN$ requires 488.2267; (ES^+) 488.2 ($[M+Na]^+$, 100%).

1-Cyclohexylidene-1-(phenylsulfonyl)-5-((triethylsilyl)oxy)pentan-2-one 222



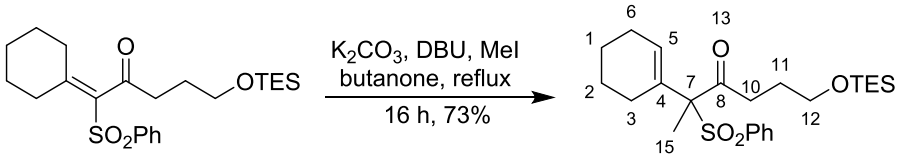
221 **222**

A novel compound prepared according to a literature procedure.[87]

Purified *m*-CPBA (54 mg, 0.31 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise over 5 min to a solution of **221** (100 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C before being warmed to rt. After 3 h, the reaction mixture was quenched with $NaHCO_3$ (5 mL of a saturated aq. solution) and the organic extract washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **222** as a colourless oil (80 mg, 87%). R_f 0.34 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2935 (w), 2875 (w), 1702 (s), 1446 (m), 1147(s), 724 (s); δ_H(400 MHz, $CDCl_3$) 0.61 (6H, quin., *J* 6.8 Hz, Si(CH_2)$_3$), 0.97 (9H, t, *J* 7.9 Hz, Si(CH_2)$_3$(CH_3)$_3$), 1.42-1.58 (4H, m, 2 × CH_2), 1.59-1.68 (2H, m, CH_2), 1.88-1.97 (2H, m, CH_2), 2.10 (2H, t, *J* 6.2 Hz, CH_2), 2.50 (2H, t, *J* 5.6 Hz, CH_2), 2.94 (2H, t, *J* 7.2 Hz, H-10), 3.69 (2H, t, *J* 6.2 Hz, H-12), 7.24 (2H, m, 2 × C*H*Ar), 7.32 (1H, m, C*H*Ar), 7.66 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 4.2 (3 × CH_2, Si(*C*H_2)$_3$), 6.9 (3 × CH_3, Si(CH_2)$_3$(*C*H_3)$_3$), 25.6 (CH_2), 26.4 (CH_2), 27.2 (CH_2), 28.2 (CH_2), 30.6 (CH_2), 34.1 (CH_2), 42.3 (CH_2), 61.4 (CH_2), 127.9 (2 × CH, *C*HAr), 129.1 (2 × CH, *C*HAr), 133.2 (CH, *C*HAr), 137.5 (C, C-7), 142.3 (C, *C*Ar),

157.7 (C, C-4), 202.1 (C, C-8); *m/z* HRMS (ES^+) found 459.1998 $[M+Na]^+$ $C_{23}H_{36}O_4SiNaS$ requires 459.2001; (ES^+) 459.1 ($[M+Na]^+$, 81%).

2-(Cyclohex-1-en-1-yl)-2-(phenylsulfonyl)-6-((triethylsilyl)oxy)hexan-3-one 231

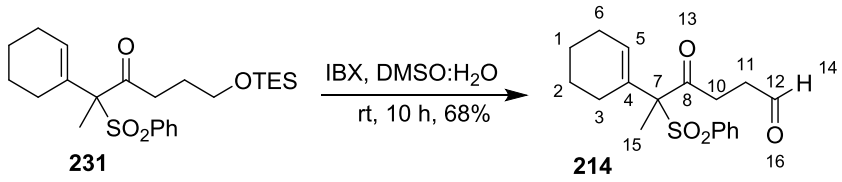


222 **231**

A novel compound prepared according to a literature procedure.[74]

A mixture of **222** (80 mg, 0.18 mmol), K_2CO_3 (25 mg, 0.18 mmol), DBU (50 µL, 0.32 mmol) and MeI (0.11 mL, 1.8 mmol) in butanone (4 mL) was heated under reflux. After 16 h, the reaction mixture was cooled to rt and washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave the *title compound* **231** as a colourless oil (60 mg, 73%). R_f 0.29 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2933 (w), 2875 (w), 1717 (s), 1447 (m), 1301 (s), 1139 (s), 726 (s); δ_H(400 MHz, $CDCl_3$) 0.56 (6H, quin., *J* 8.0 Hz, $Si(CH_2)_3$), 0.92 (9H, t, *J* 7.9 Hz, $Si(CH_2)_3(CH_3)_3$), 1.57-1.72 (4H, m, 2 × CH_2), 1.79 (3H, s, H-15), 1.80-1.86 (2H, m, CH_2), 1.96-1.99 (2H, m, CH_2), 2.03-2.12 (2H, m, CH_2), 2.51-2.60 (2H, m, CH_2), 3.57 (2H, t, *J* 6.4 Hz, CH_2), 5.38 (1H, m, H-5), 7.46-7.51 (2H, m, 2 × CHAr), 7.58 (1H, m, CHAr), 7.92-7.97 (2H, m, 2 × CHAr); δ_C(100 MHz, $CDCl_3$) 4.8 (3 × CH_2, $Si(CH_2)_3$), 7.2 (3 × CH_3, $Si(CH_2)_3(CH_3)_3$), 16.1 (CH_2), 22.6 (CH_2), 25.6 (CH_2), 26.8 (CH_2), 28.4 (CH_2), 35.6 (CH_2), 61.3 (CH_2), 80.6 (C, C-7), 127.6 (2 × CH, CHAr), 128.2 (2 × CH, CHAr), 129.7 (CH, CHAr), 134.2 (C, CAr), 136.6 (C, C-4), 204.3 (C, C-8); *m/z* HRMS (ES^+) found 473.2148 ($[M+Na]^+$, 58%) $C_{24}H_{38}O_4SiNaS$ requires 473.2158; (ES^+) 473.1 ($[M+Na]^+$, 58%).

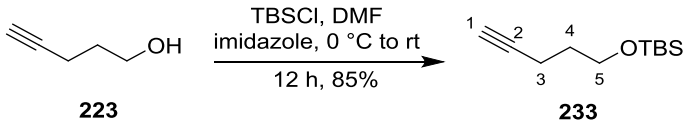
5-(Cyclohex-1-en-1-yl)-4- oxo-5-(phenylsulfonyl)hexenal 214



A novel compound prepared according to a literature procedure.[90]

IBX (13 mg, 0.048 mmol) was added to a solution of **231** (20 mg, 0.04 mmol) in DMSO:H_2O (0.22 mL/4 µL). The reaction mixture was stirred at rt for 10 h before being diluted with Et_2O (4 mL). H_2O (5 mL) was added and the aqueous layer extracted with Et_2O (3 × 5 mL). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 4:6) gave the *title compound* **214** as a colourless oil (10 mg, 68%). R_f 0.14 (pet ether/Et_2O 2:8); ν_{max}(neat)/cm^{-1}: 2929 (w), 2858 (w), 1712 (s), 1446 (m), 1298 (s), 1137 (s), 689 (s); δ_H(400 MHz, $CDCl_3$) 1.51-1.73 (4H, m, 2 × C*H*$_2$), 1.81 (3H, s, H-15), 1.94-2.03 (2H, m, C*H*$_2$), 2.09-2.16 (2H, m, C*H*$_2$), 2.73 (2H, t, *J* 5.7 Hz, C*H*$_2$), 2.84-2.92 (2H, m, C*H*$_2$), 5.40 (1H, tt, *J* 3.9 and 1.6 Hz, H-5), 7.44-7.51 (2H, m, 2 × C*H*Ar), 7.62 (1H, m, *C*HAr), 7.90-7.94 (2H, m, 2 × *C*HAr), 9.72 (1H, s, H-14); δ_C(100 MHz, $CDCl_3$) 16.8 (CH_3), 21.3 (CH_2), 22.8 (CH_2), 25.7 (CH_2), 25.9 (CH_2), 31.9 (CH_2), 37.2 (CH_2), 88.3 (C, C-7), 127.9 (2 × CH, *CHAr*), 131.3 (2 × CH, *C*HAr), 133.5 (CH, *C*HAr), 134.1 (CH, C-5), 199.7 (C, C-8), 201.3 (C, C-12); *m*/*z* HRMS (ES^+) found 357.1136 ($[M+Na]^+$, 71%) $C_{18}H_{22}O_4NaS$ requires 357.1137; (ES^+) 357.1 ($[M+Na]^+$, 71%).

tert-Butyldimethyl(pent-4-yn-1-yloxy)silane 233



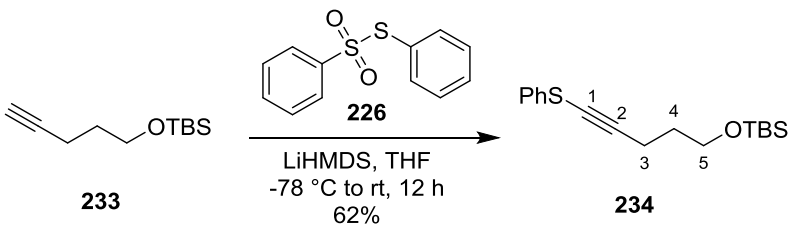
223 **233**

A known compound prepared according to the literature procedure.[83]

A solution of TBSCl (0.37 g, 2.49 mmol) in dry DMF (2 mL) was added dropwise over 10 min to a solution of **223** (0.2 g, 2.37 mmol) and imidazole (0.4 g, 5.92 mmol) in dry DMF (4 mL) at 0 °C. The reaction mixture was stirred at rt for 12 h before H_2O (10 mL) was added and the resulting mixture extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **233** as a colourless oil (0.4 g, 85%). R_f 0.71 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2954 (w), 1254 (s), 1102 (s), 831 (s), 774 (s); δ_H(400 MHz, $CDCl_3$) 0.06 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.69-1.76 (2H, m, H-4), 1.93 (1H, t, *J* 2.7 Hz, H-1), 2.26 (2H, td, *J* 7.1 and 2.7 Hz, H-3), 3.68-3.71 (2H, ap. t, *J* 6.0 Hz, H-5); δ_C(100 MHz, $CDCl_3$) -4.8 (2 × CH_3, Si(*C*H_3)$_2$), 15.3 (CH_2, C-3), 26.3 (3 × CH_3, SiC(*C*H_3)$_3$), 31.9 (CH_2, C-4), 61.8 (CH_2, C-5), 68.6 (CH, C-1), 84.7 (C, C-2).

Analytical data in agreement with literature values.[83]

tert-Butyldimethyl((5-(phenylthio)pent-4-yn-1-yl)oxy)silane 234

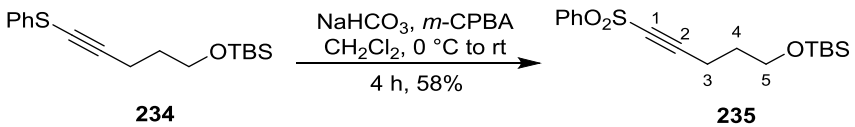


233 **234**

A novel compound prepared according to a literature procedure.[86]

LiHMDS (1.26 mL of a 1.0 M soln. in THF, 1.26 mmol) was added dropwise over 5 min to a stirred solution of **233** (SM) (0.25 g, 1.26 mmol) in THF (6 mL) at -78 °C. The resulting reaction mixture was stirred at -78 °C for 1 h, then a solution of **226** (0.29 g, 1.13 mmol) in THF (2 mL) was added dropwise over 5 min before being warmed gradually to rt. After 12 h, the reaction mixture was quenched with NH_4Cl (10 mL of a saturated aq. solution) and extracted with Et_2O (2 × 10 mL). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) gave **234** as a pale yellow oil (0.24 g, 62%). R_f 0.57 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2952 (w), 2855(w), 1254 (s), 1104 (s), 834 (s); δ_H(400 MHz, $CDCl_3$) 0.06 (6H, s, Si(CH_3)$_2$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.76-1.85 (2H, m, H-4), 2.54 (2H, t, *J* 7.0 Hz, H-3), 3.72 (2H, t, *J* 6.0 Hz, H-5), 7.21 (1H, m, C*H*Ar), 7.28-7.43 (4H, m, 4 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -5.4 (2 × CH_3, Si(*C*H_3)$_2$), 16.6 (CH_2, C-3), 25.7 (3 × CH_3, SiC(*C*H_3)$_3$), 31.3 (C, Si*C*(CH$_3$)$_3$), 31.5 (CH_2, C-4), 61.3 (CH_2, C-5), 64.6 (C, *C*≡), 99.3 (C, ≡*C*), 125.6 (2 × CH, *C*HAr), 125.9 (CH, *C*HAr), 128.8 (2 × CH, *C*HAr), 133.5 (C, *C*Ar); *m*/*z* HRMS (ES^+) found 329.1369 $[M+Na]^+$ $C_{17}H_{26}OSNaSi$ requires 329.1371; (ES^+) 329.1 ($[M+Na]^+$, 100%).

tert-Butyldimethyl((5-(phenylsulfonyl)pent-4-yn-1-yl)oxy)silane 235

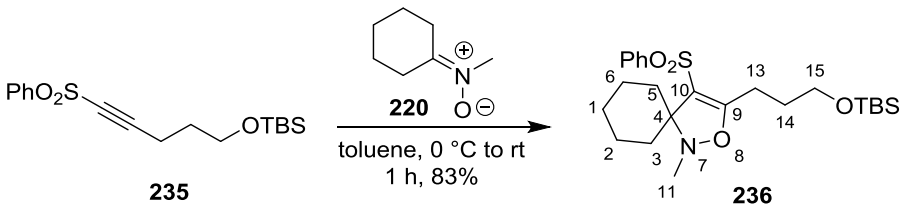


234 **235**

A novel compound prepared according to a literature procedure.[87]

$NaHCO_3$ (0.11 g, 1.42 mmol) and purified *m*-CPBA (0.24 g, 1.42 mmol) were added to a solution of **234** (0.22 g, 0.71 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The reaction mixture was stirred for 4 h at rt. Upon completion, the crude mixture was quenched with $NaHCO_3$ (2 × 8 mL of a saturated aq. solution) and extracted with EtOAc (20 mL). The organic extract was washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **235** as a colourless oil (0.14 g, 58%). R_f 0.44 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2954 (w), 2857 (w), 2201 (s), 1159 (s), 1089 (s), 832 (s); δ_H(400 MHz, $CDCl_3$) 0.01 (6H, s, Si(CH_3)$_2$), 0.85 (9H, s, SiC(CH_3)$_3$), 1.74 (2H, tt, *J* 7.1 and 5.8 Hz, H-4), 2.48 (2H, t, *J* 7.1 Hz, H-3), 3.61 (2H, t, *J* 5.8 Hz, H-5), 7.55 (1H, m, C*H*Ar), 7.64-7.70 (2H, m, 2 × C*H*Ar), 7.99 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -5.6 (2 × CH_3, Si(*C*H_3)$_2$), 15.3 (CH_2, C-3), 25.6 (3 × CH_3, SiC(*C*H_3)$_3$), 29.8 (CH_2), 29.5 (C, *C*(CH$_3$)$_3$), 60.6 (CH_2, C-5), 78.0 (C, *C*≡), 97.3 (C, ≡*C*), 127.0 (2 × CH, *C*HAr), 129.0 (2 × CH, *C*HAr), 133.8 (CH, *C*HAr), 141.8 (C, *C*Ar); *m*/*z* HRMS (ES^+) found 361.1271 $[M+Na]^+$ $C_{17}H_{26}O_3SNaSi$ requires 361.1270.

3-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-methyl-4-(phenylsulfonyl)-2-oxa-1-azaspiro[4.5]dec-3-ene 236

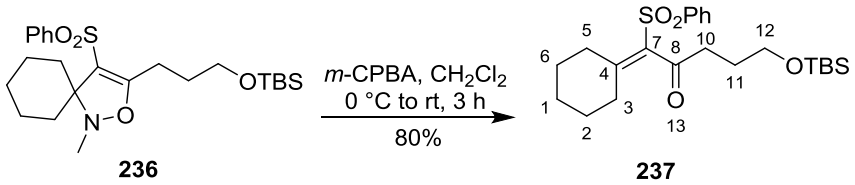


A novel compound prepared by a modification of a literature procedure.[84]

235 (140 mg, 0.41 mmol) was added dropwise over 5 min to a solution of nitrone **220** (66 mg, 0.52 mmol) in toluene (0.27 mL) at 0 °C and stirred for 20 min before being warmed to

rt. After 1 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography (pet ether/Et_2O 7:3) to give **236** as a colourless oil (160 mg, 83%). R_f 0.54 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 2857 (w), 1619 (s), 1151 (s), 1101 (s), 834 (s); δ_H(400 MHz, $CDCl_3$) 0.07 (6H, s, Si(CH_3)$_2$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.16-1.21 (2H, m, CH_2), 1.40-1.52 (4H, m, 2 × CH_2), 1.54-1.68 (4H, m, 2 × CH_2), 1.81-1.86 (2H, m, CH_2), 2.77-2.85 (2H, m, CH_2), 3.17 (3H, s, H-11), 3.69 (2H, t, *J* 6.3 Hz, CH_2), 7.46-7.61 (3H, m, 3 × C*H*Ar), 7.82-7.91 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -5.4 (2 × CH_3, Si(*C*H_3)$_2$), 18.5 (CH_2), 22.6 (CH_2), 22.9 (CH_2), 24.8 (CH_2), 25.7 (3 × CH_3, SiC(*C*H_3)$_3$), 28.0 (CH_2), 30.0 (C, Si*C*(CH$_3$)$_3$), 32.6 (CH_2), 39.0 (CH_3, C-11), 47.3 (CH_2), 62.1 (CH_2), 72.1 (C), 112.9 (C, *C*=) 126.6 (2 × CH, *C*HAr), 128.8 (2 × CH, *C*HAr), 132.5 (CH, *C*HAr), 143.4 (C, *C*Ar), 168.2 (C, *C*=); *m/z* HRMS (ES^+) found 488.2274 $[M+Na]^+$ $C_{24}H_{39}NO_4SNaSi$ requires 488.2267; (ES^+) 488.2 ($[M+Na]^+$, 100%).

5-((*tert*-Butyldimethylsilyl)oxy)-1-cyclohexylidene-1-(phenylsulfonyl)pentan-2-one 237



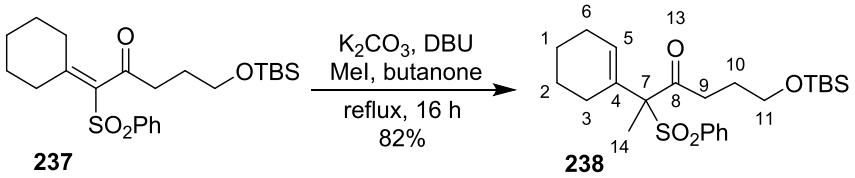
236 **237**

A novel compound prepared according to a literature procedure.[87]

Purified *m*-CPBA (88 mg, 0.51 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise over 5 min to a solution of **236** (160 mg, 0.34 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h, quenched with $NaHCO_3$ (6 mL of a saturated aq. solution) and extracted with DCM (2 × 6 mL). The combined organic extracts were washed with brine (6 mL), dried

over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **237** as a colourless oil (120 mg, 80%). R_f 0.42 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 2857 (w), 1700 (s), 1300(s), 1141 (s), 834 (s); δ_H(400 MHz, $CDCl_3$) 0.05 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.38-1.66 (6H, m, 3 × CH_2), 1.85-1.94 (2H, m, H-11), 2.08 (2H, t, *J* 6.3 Hz, CH_2), 2.56 (2H, t, *J* 5.9 Hz, CH_2), 2.92 (2H, t, *J* 7.2 Hz, H-10), 3.68 (2H, t, *J* 6.1 Hz, H-12), 7.50-7.62 (3H, m, 3 × C*H*Ar), 7.93-7.96 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -4.8 (2 × CH_3, Si(*C*H_3)$_2$), 25.9 (CH_2), 26.3 (3 × CH_3, SiC(*C*H_3)$_3$), 26.9 (CH_2), 27.7 (CH_2), 28.1 (CH_2), 28.6 (C, Si*C*(CH$_3$)$_3$), 31.0 (CH_2), 34.4 (CH_2), 43.0 (CH_2, C-10), 62.2 (CH_2, C-12), 127.8 (2 × CH, *C*HAr), 129.5 (2 × CH, *C*HAr), 133.6 (CH, *C*HAr), 138.1 (C), 143.2 (C), 158.0 (C), 202.6 (C, C-8); *m/z* HRMS (ES^+) found 459.2003 $[M+Na]^+$ $C_{23}H_{36}O_4SNaSi$ requires 459.2001; (ES^+) 459.1 ($[M+Na]^+$, 100%).

6-((*tert*-Butyldimethylsilyl)oxy)-2-(cyclohex-1-en-1-yl)-2-(phenylsulfonyl)hexan-3-one 238

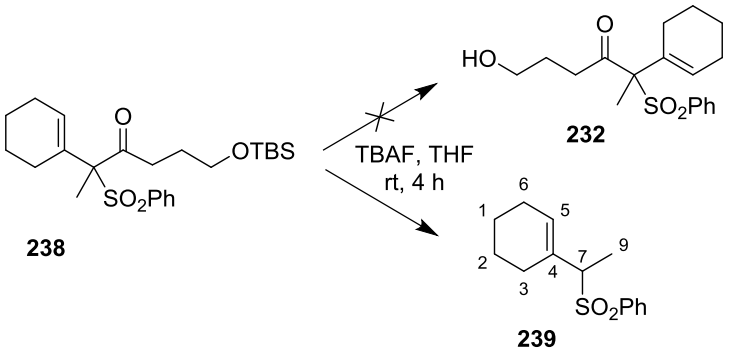


A novel compound prepared according to a literature procedure.[74]

A mixture of **237** (120 mg, 0.27 mmol), K_2CO_3 (37 mg, 0.27 mmol), DBU (73 µL, 0.48 mmol) and MeI (0.2 mL, 2.7 mmol) in butanone (6 mL) was heated under reflux for 16 h. The reaction mixture was cooled to rt and washed with brine (8 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave the *title compound* **238** as a colourless oil (100 mg, 82%). R_f 0.49 (pet

ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2934 (w), 1715 (s), 1446 (m), 1138 (s), 726 (s); δ_H(400 MHz, $CDCl_3$) 0.01 (6H, s, Si(CH_3)$_2$), 0.86 (9H, s, SiC(CH_3)$_3$), 1.50-1.59 (4H, m, 2 × CH_2), 1.60-1.73 (2H, m, CH_2), 1.79 (3H, s, H-14), 1.93-2.16 (4H, m, 2 × CH_2), 2.49-2.64 (2H, m, CH_2), 3.51-3.59 (2H, m, CH_2), 5.38 (1H, t, *J* 3.8 Hz, H-5), 7.45-7.61 (3H, m, 3 × C*H*Ar), 7.92-7.96 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -3.2 (2 × CH_3, Si(CH_3)$_2$), 16.8 (CH_3, C-14), 21.8 (CH_2), 22.7 (CH_2), 26.3 (3 × CH_3, SiC(CH_3)$_3$), 23.3 (CH_2), 26.2 (CH_2), 26.9 (CH_2), 27.4 (C, Si*C*(CH_3)$_3$), 36.2 (CH_2), 62.1 (CH_2), 89.5 (C), 118.5 (CH, C-5), 128.3 (2 × CH, *C*HAr), 131.8 (2 × CH, *C*HAr), 134.1 (CH, *C*HAr), 133.8 (C), 142.3 (C), 201.4 (C, C-8); *m/z* HRMS (ES^+) found 473.2162 $[M+Na]^+$ $C_{24}H_{38}O_4SNaSi$ requires 473.2158; (ES^+) 473.2 ($[M+Na]^+$, 100%).

1-(Cyclohexen-1-yl)-1-(phenylsulfonyl)ethane 239



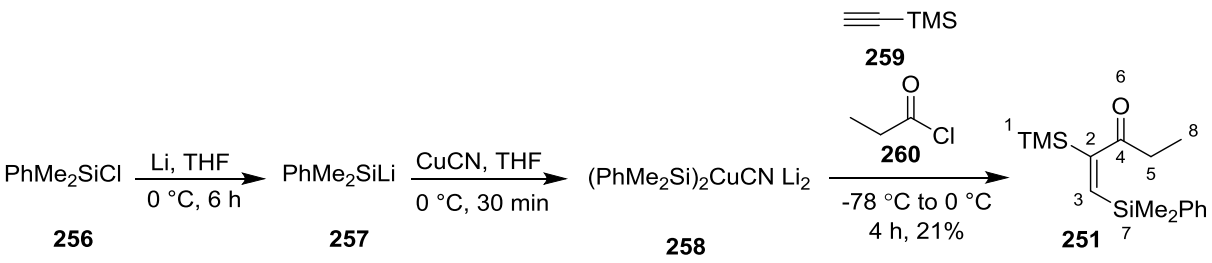
A known compound prepared by modification of a literature procedure.[92]

TBAF (0.26 mL of a 1.0 M soln. in THF, 0.26 mmol) was added to a solution of **238** (60 mg, 0.13 mmol) in THF (5 mL) and the reaction mixture was stirred at rt for 4 h. Upon completion, the solvent was removed under reduced pressure, then the residue was dissolved in DCM (5 mL), quenched with NH_4Cl (5 mL of a saturated aq. solution) and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic extracts were

washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **239** as a colourless oil (40 mg, 12%). R_f 0.58 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2930 (w), 2858 (w), 1446 (m), 1302 (s), 1141 (s), 1084 (s), 727 (s); δ_H(300 MHz, $CDCl_3$) 1.48 (3H, d, *J* 7.2 Hz, H-9), 1.50-1.58 (4H, m, 2 × C*H*$_2$), 1.85-2.09 (4H, m, 2 × C*H*$_2$), 3.57 (1H, q, *J* 7.2 Hz, H-7), 5.39 (1H, td, *J* 3.8 and 1.9 Hz, H-5), 7.46-7.65 (3H, m, 3 × C*H*Ar), 7.79-7.89 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 12.2 (CH_3), 21.7 (CH_2), 22.6 (CH_2), 25.5 (CH_2), 26.4 (CH_2), 67.6 (CH, C-7), 128.5 (CH, C-5), 129.1 (2 × CH, *C*HAr), 130.9 (2 × CH, *C*HAr), 131.2 (CH, *C*HAr), 133.3 (C), 137.4 (C).

Analytical data in agreement with literature values. [138]

(*E*)-4-Trimethylsilyl-5-dimethyl(phenyl)silylpent-4-en-3-one 251



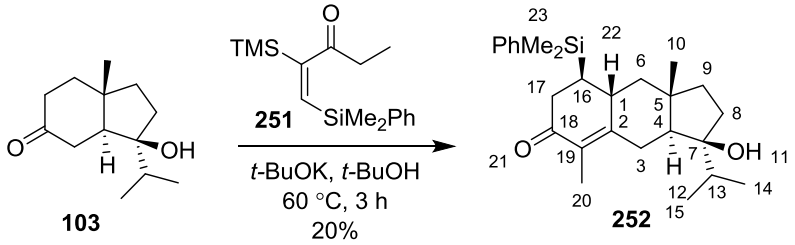
A known compound prepared according to the literature procedure.[97]

Freshly cut lithium metal pieces (49 mg, 7.00 mmol) were washed once with THF (10 mL) with the help of syringe. $PhMe_2SiCl$ **256** (500 mg, 2.92 mmol) was added dropwise over 5 min to a suspension of Li in THF (3.8 mL) at 0 °C and stirred for 6 h until a consistent red solution was formed. The resulting $PhMe_2SiLi$ **257** (0.5 mL of a 0.6 M soln. in THF, 0.33 mmol) was added to a slurry solution of CuCN (56 mg, 0.66 mmol) in THF (0.72 mL) at 0 °C and stirred for 30 min before being cooled to -78 °C. Trimethylsilylacetylene **259** (91 µL, 0.66

mmol) was added to the reaction mixture at -78 °C followed by the addition of **260**. After 30 min, the reaction mixture was gradually warmed to 0 °C and stirred for 4 h before being quenched with NH_4Cl (10 mL of a saturated aq. solution) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) afforded **251** as a colourless oil (180 mg, 21%). R_f 0.54 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2956 (w), 1684 (s), 1247(s), 1114 (m), 824 (s), 696 (s); δ_H(400 MHz, $CDCl_3$) 0.15 (9H, s, Si(C*H*$_3$)$_3$), 0.35 (6H, s, Si(C*H*$_3$)$_2$Ph), 0.87 (3H, t, *J* 7.2 Hz, H-8), 2.30 (2H, q, *J* 7.2 Hz, H-5), 6.34 (1H, s, H-3), 7.32-7.37 (3H, m, 3 × C*H*Ar), 7.47-7.54 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -1.7 (3 × CH_3, Si(*C*H_3)$_3$), -1.5 (2 × CH_3, Si(*C*H_3)$_2$Ph), 6.9 (CH_3, C-8), 36.6 (CH_2), 127.2 (2 × CH, *C*HAr), 128.8 (CH, *C*HAr), 133.7 (2 × CH, *C*HAr), 138.0 (C, Si*C*Ar), 143.3 (CH, C-3), 169.4 (C, C-2), 211.4 (C, C-4); *m/z* HRMS (EI^+) found 290.1526 $[M]^+$ $C_{16}H_{26}OSi_2$ requires 290.1522; (EI^+) 290.1 ($[M]^+$, 46%).

Analytical data in agreement with literature values.[96]

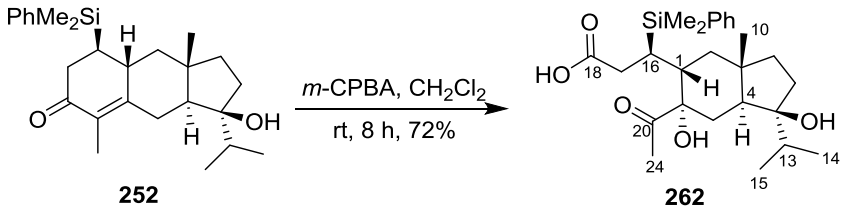
(±)-(3*S*, 3a*S*, 8*R*, 8a*R*, 9a*S*)-5, 9a-Dimethyl-8-(dimethyl(phenyl)silyl)-3-hydroxy-3-*iso*-propyl-1, 2, 3, 3a, 4, 7, 8, 8a, 9, 9a-decahydro-6*H*-cyclopenta[*b*]naphthal-4a-en-6-one 252



A novel compound prepared by a modification of a literature procedure.[97]

103 (40 mg, 0.19 mmol) and **251** (81 mg, 0.28 mmol) in *t*-BuOH (90 μL) were added to a stirred solution of *t*-BuOK (74 mg, 0.66 mmol) in *t*-BuOH (0.5 mL) at 60 °C. After 3 h, the reaction mixture was cooled to rt and extracted with Et_2O (2 × 4 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (pet ether/Et_2O 7:3) to afford **252** as a colourless oil (16 mg, 20%). R_f 0.49 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2954 (w), 1650 (s), 1247 (s), 1112 (s), 830 (s); δ_H(400 MHz, $CDCl_3$) 0.32, 0.34 (6H, 2 × s, Si(C*H*$_3$)$_2$Ph), 0.89, 0.95 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 1.01 (3H, s, H-10), 1.25-1.36 (2H, m, 1H of C*H*$_2$ and H-12), 1.54-1.59 (3H, m, C*H*$_2$ and H-13), 1.67-1.72 (3H, m, C*H*$_2$ and H-16), 1.76 (3H, s, H-20), 1.82 (1H, dd, *J* 12.4 and 5.1 Hz, H-22), 1.95-2.04 (2H, m, C*H*$_2$), 2.42 (1H, dd, *J* 15.7 and 4.3 Hz, 1H of C*H*$_2$), 2.52 (1H, m, 1H of C*H*$_2$), 2.69 (1H, dd, *J* 14.5 and 3.0 Hz, 1H of C*H*$_2$), 7.37-7.32 (3H, m, C*H*Ar), 7.48-7.46 (2H, m, C*H*Ar); δ_C(100 MHz, $CDCl_3$) -3.5 (CH_3, Si(*C*H_3)$_2$Ph), -3.0 (CH_3, Si(*C*H_3)$_2$Ph), 10.9 (CH_3, C-20), 17.2 (CH_3), 18.0 (CH_3), 18.5 (CH_3), 27.1 (CH_2), 27.3 (CH, C-16), 36.6 (CH_2), 36.8 (CH, C-1), 37.3 (CH, C-13), 38.1 (CH_2), 39.0 (CH_2), 41.6 (C, C-16), 49.0 (CH_2), 53.2 (CH, C-4), 83.0 (C, C-7), 127.7 (2 × CH, *C*HAr), 129.0 (CH, *C*HAr), 131.0 (C, C-19), 133.6 (2 × CH, *C*HAr), 137.2 (C, *C*Ar), 160.1 (C, C-2), 199.4 (C, C-18); *m*/*z* HRMS (ES^+) found 433.2535 $[M+Na]^+$ $C_{26}H_{38}O_2SiNa$ requires 433.2539; (ES^+) 433.2 ($[M+Na]^+$, 68%).

(*R*)-3-((1*S*, 3a*S*, 5*R*, 6*S*, 7a*S*)-6-acetyl-1,6-dihydroxy-1-*iso*-propyl-3a-methyloctahydro-1*H*-inden-5-yl)-3-(dimethyl(phenyl)silyl)propanoic acid 262

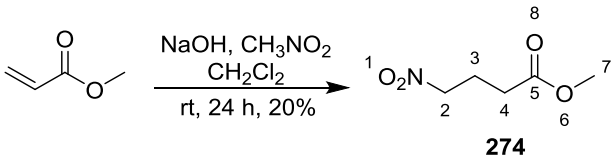


A novel compound prepared by a modification of a literature procedure.[139]

252 (40 mg, 0.09 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise over 5 min at rt to a solution of purified *m*-CPBA (33 mg, 0.19 mmol) in CH_2Cl_2 (0.5 mL). After 8 h, the reaction mixture was quenched with $NaHCO_3$ (2 mL of a saturated aq. solution), washed with brine (3 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave **262** as a pale yellow oil (30 mg, 72%). R_f 0.45 (pet ether/Et_2O 3:7); ν_{max}(neat)/cm^{-1}: 3325 (br), 2924 (w), 1695 (s), 1303 (s), 1262 (s), 750 (m); δ_H(400 MHz, $CDCl_3$) 0.34, 0.35 (6H, 2 × s, Si(CH_3)$_2$), 0.89, 0.95 (6H, 2 × d, *J* 6.9 Hz, H-14 and H-15), 1.01 (3H, s, H-10), 1.12 (1H, m, 1H of CH_2), 1.25-1.36 (4H, m, H-1, H-16 and CH_2), 1.58 (1H, m, 1H of CH_2), 1.71 (1H, m, H-13), 1.76 (3H, s, H-24), 1.82 (1H, dd, *J* 12.4 and 5.0 Hz, 1H of CH_2), 2.04 (2H, m, CH_2), 2.21 (1H, dd, *J* 15.7 and 4.2 Hz, 1H of CH_2), 2.52 (1H, m, 1H of CH_2), 2.69 (1H, dd, *J* 14.4 and 3.0 Hz, 1H of CH_2), 7.31-7.35 (3H, m, 3 × C*H*Ar), 7.42-7.49 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -2.8, -2.4 (2 × CH_3, Si(*C*H_3)$_2$), 11.5 (CH_3, C-24), 17.9 (CH_3, C-14), 18.6 (CH_3, C-15), 19.3 (CH_3, C-10), 27.8 (CH, C-16), 28.0 (CH_2), 37.2 (CH_2), 37.5 (CH_2), 37.8 (CH_2), 39.1 (CH, C-1), 39.6 (CH, C-13), 42.2 (C), 49.7 (CH_2), 53.9 (CH, C-4), 79.1 (C), 83.5 (C), 85.1 (C), 128.3 (3 × CH, *C*HAr), 129.6 (2 × CH, *C*HAr), 129.8 (C, *C*Ar), 160.1 (C, C-18), 200.2 (C,

C-20); *m/z* HRMS (ES^+) found 465.2438 $[M+Na]^+$ $C_{26}H_{38}O_4SiNa$ requires 465.2437; (ES^+) 465.2 ($[M+Na]^+$, 64%).

Methyl 4-nitrobutanoate 274



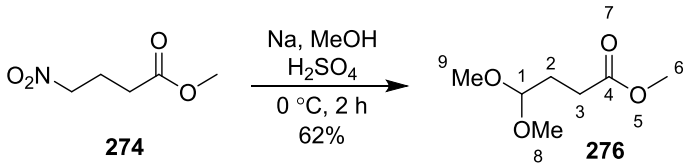
274

A known compound prepared according to a literature procedure.[103]

NaOH (10 mL of a 0.6 M aq. solution) was added dropwise over 5 min to a solution of CH_3NO_2 (2.8 mL, 52.2 mmol) and methyl acrylate (4.7 mL, 52.2 mmol) in CH_2Cl_2 (10 mL) at rt. The reaction mixture was stirred for 24 h after which there was a separation in the layers. The organic layer was washed with H_2O (2 × 20 mL), dried $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 6:4) to give **274** as a colourless liquid (1.42 g, 20%). R_f 0.37 (pet ether/Et_2O 3:7); ν_{max}(neat)/cm^{-1}: 2956 (w), 1731 (s), 1548 (s), 1171 (s); δ_H(400 MHz, $CDCl_3$) 2.18-2.26 (2H, quin., *J* 6.8 Hz, H-3), 2.38 (2H, t, *J* 7.2 Hz, H-2), 3.61 (3H, s, H-7), 4.39 (2H, t, *J* 6.7 Hz, H-4); δ_C(100 MHz, $CDCl_3$) 22.1 (CH_2, C-3), 29.9 (CH_2, C-2), 51.6 (CH_3), 74.0 (CH_2, C-4), 172.1 (C, C-5).

Analytical data in agreement with literature values.[103]

Methyl-4,4-dimethoxybutanoate 276



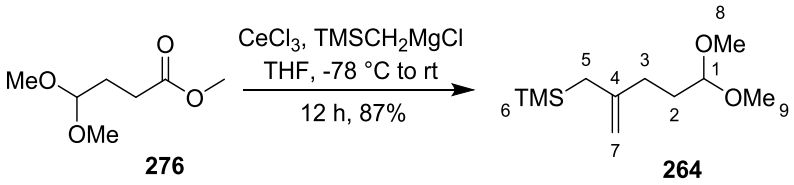
274 **276**

A known compound prepared according to a literature procedure.[104]

Freshly cut metal Na (0.64 g, 28 mmol) was dissolved in MeOH (25 mL) at 0 °C during 30 min. **274** (2.06 g, 14 mmol) was added dropwise over 30 min to a solution of freshly prepared NaOMe at 0 °C. The resulting mixture was added at 0 °C to another flask equipped with a mixture of MeOH (22 mL) and H_2SO_4 (4.1 mL of a 18.0 M, 77 mmol). After 1 h at 0 °C, the reaction mixture was poured into a 1:1 mixture of DCM:H_2O (25 mL/25 mL). The aqueous layer was extracted with DCM (2 × 20 mL) and the combined organic extracts were washed with NaOH (15 mL of a 1% aq. solution), dried over $MgSO_2$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 6:4) gave **276** as a colourless oil (1.42 g, 62%). R_f 0.38 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2952 (w), 2833 (w), 1736 (s), 1123 (s), 1059 (s); δ_H(400 MHz, $CDCl_3$) 1.93 (2H, td, *J* 7.5 and 5.6 Hz, H-3), 2.38 (2H, t, *J* 7.5 Hz, H-2), 3.33 (6H, s, H-8 and H-9), 3.68 (3H, s, H-6), 4.40 (1H, t, *J* 5.6 Hz, H-1); δ_C(100 MHz, $CDCl_3$) 28.2 (CH_2, C-2), 29.5 (CH_2, C-3), 52.0 (CH_3, C-6), 53.6 (2 × CH_3, C-8 and C-9), 104.1 (CH, C-*1*), 174.1 (C, C-5); *m/z* HRMS (ES^+) found 185.0792 $[M+Na]^+$ $C_7H_{14}O_4Na$ requires 185.0790; (ES^+) 185.0 ($[M+Na]^+$, 100%).

Analytical data in agreement with literature values.[104]

(5,5-Dimethoxy-2-methylenepentyl)trimethylsilane 264



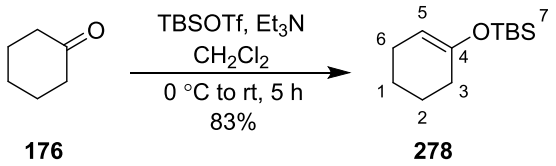
A known compound prepared according to a literature procedure.[100]

THF (46 mL) was added at rt to the vigorously stirred anhydrous $CeCl_3$ (4.55 g, 18.5 mmol) to form a uniform white suspension which was stirred for 2 h. The suspension was cooled to -

78 °C and $TMSCH_2MgCl$ (18.5 mL of a 1.0 M soln. in THF, 18.5 mmol) was added dropwise over 20 min to form an off-white suspension. The resulting suspension was stirred for 1 h when **276** (0.50 g, 3.0 mmol) in THF (2 mL) was added dropwise over 5 min and the reaction mixture was warmed gradually to rt. After 8 h, the reaction mixture was cooled to 0 °C and quenched with HCl (25 mL of a 1.0 M aq. solution). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with $NaHCO_3$ (20 mL of a saturated aq. solution), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude bis(β-silyl) alcohol (0.84 g) was dissolved in DCM (10 mL) and silica gel (0.5 g, ~150 mesh Å) was added. The mixture was stirred at rt for 20 min. The silica gel was filtered off and thoroughly washed with DCM (3 × 15 mL), then the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 1:1) to give **264** as a colourless liquid (0.58 g, 87%). R_f 0.51 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2953 (w), 1633 (w), 1247 (s), 1126 (s), 1057 (s), 840 (s); δ_H(400 MHz, $CDCl_3$) 0.02 (9H, s, Si(CH_3)$_3$), 1.53 (2H, s, H-5), 1.71-1.78 (2H, m, H-2), 2.02 (2H, dd, *J* 9.6 and 6.2 Hz, H-3), 3.32 (6H, s, H-8 and H-9), 4.38 (1H, t, *J* 5.7 Hz, H-1), 4.53 (1H, s, 1H of H-7), 4.60 (1H, s, 1H of H-7); δ_C(100 MHz, $CDCl_3$) -0.8 (3 × CH_3, Si(CH_3)$_3$), 27.4 (CH_2, C-5), 31.1 (CH_2, C-2), 33.4 (CH_2, C-3), 53.1 (2 × CH_3, C-8 and C-9) 104.6 (CH, C-1), 107.4 (CH_2, C-7), 147.3 (C, C-4).

Analytical data in agreement with literature values.[100]

tert-Butyl(cyclohex-1-en-1-yloxy)dimethylsilane 278



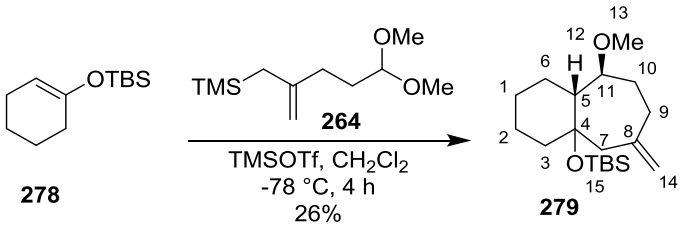
176 **278**

A known compound prepared according to a literature procedure.[106]

TBSOTf (1.87 mL, 8.1 mmol) and Et_3N (2.28 mL, 16.2 mmol) were sequentially added to a solution of cyclohexanone **176** (0.2 g, 2.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 5 h at rt, the reaction mixture was quenched with $NaHCO_3$ (10 mL of a saturated aq. solution) and EtOAc (15 mL) was added. The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) gave **278** as a colourless oil (0.36 g, 83%). R_f 0.68 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 2858 (w), 1669 (m), 1193 (s), 890 (s), 835 (s); δ_H(400 MHz, $CDCl_3$) 0.12 (6H, s, Si(CH_3)$_2$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.47-1.53 (2H, m, CH_2), 1.61-1.69 (2H, m, CH_2), 1.97-2.02 (4H, m, 2 × CH_2), 4.86 (1H, m, H-5); δ_C(100 MHz, $CDCl_3$) -3.91 (2 × CH_3, Si(*C*H_3)$_2$), 22.8 (CH_2), 23.6 (CH_2), 24.3 (3 × CH_3, SiC(*C*H_3)$_3$), 26.1 (CH_2), 30.3 (CH_2), 104.8 (CH, C-5), 150.9 (C, C-4).

Analytical data in agreement with literature values.[127]

(±)-(((9*S*, 9a*R*)-9-Methoxy-6-methylenedecahydro-4a*H*-benzo[7]annulen-4a-yl)oxy)-(*tert*-butyl)dimethylsilane 279

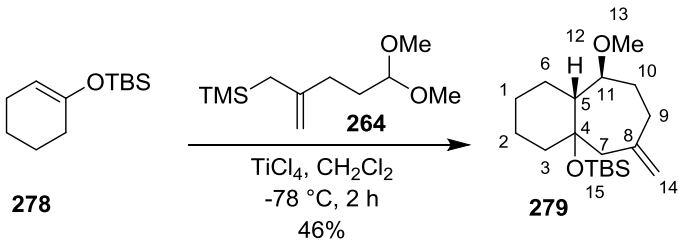


Method A

A novel compound prepared by a modification of a literature procedure.[102]

TMSOTf (47 µL, 0.047 mmol) was added dropwise over 10 min to a solution of **278** (100 mg, 0.47 mmol) and **264** (110 mg, 0.51 mmol) in CH_2Cl_2 (9.4 mL) in the presence of pulverized 3 Å molecular sieves at -78 °C. After 2 h at - 78 °C, the reaction mixture was warmed to -30 °C, quenched with $NaHCO_3$ (5 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (2 × 8 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) gave **279** as a colourless oil (40 mg, 26%). R_f 0.67 (pet ether/Et_2O 7:3).

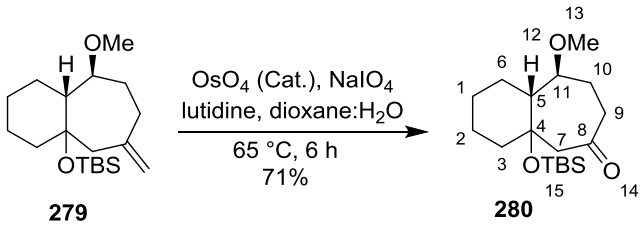
Method B



$TiCl_4$ (0.25 mL of a 1.0 M soln. in CH_2Cl_2, 0.25 mmol) was added dropwise over 10 min to a solution of **278** (60 mg, 0.28 mmol) and **264** (67 mg, 0.31 mmol) in CH_2Cl_2 (5.6 mL) in the presence of pulverized 3 Å molecular sieves at -78 °C. After 5 h at -78 °C, the reaction mixture was warmed to -30 °C, quenched with $NaHCO_3$ (4 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (2 × 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) gave **279** as a colourless oil (38 mg, 46%). R_f 0.55 (pet ether/Et_2O 1:1).

Analytical data for **279**; ν_{max}(neat)/cm^{-1}: 2928 (w), 2856 (w), 1641 (w), 1251 (m), 1085 (s), 1028 (s), 833 (s); δ_H(400 MHz, $CDCl_3$) 0.16 (6H, s, Si(CH_3)$_2$), 0.95 (9H, s, SiC(CH_3)$_3$), 1.15 (1H, m, 1H of CH_2), 1.32-1.55 (4H, m, 2 × CH_2), 1.58-1.80 (4H, m, 2 × CH_2), 1.88 (1H, m, 1H of CH_2), 1.99 (1H, ddd, *J* 12.4, 11.1 and 3.3 Hz, H-12), 2.25 (1H, m, 1H of CH_2), 2.30 (1H, d, *J* 13.4 Hz, 1H of H-7), 2.51 (1H, ddd, *J* 12.8, 11.1 and 3.2 Hz, 1H of CH_2), 2.65 (1H, d, *J* 13.5 Hz, 1H of H-7), 3.10 (1H, ddd, *J* 8.5, 4.8 and 3.5 Hz, H-11), 3.33 (3H, s, H-13), 4.71 (1H, s, 1H of H-14), 4.77 (1H, s, 1H of H-14); δ_C(100 MHz, $CDCl_3$) 0.1 (CH_3, Si(*C*H_3)$_2$), 0.3 (CH_3, Si(*C*H_3)$_2$), 24.2 (CH_2), 27.1 (CH_2), 27.5 (CH_2), 28.1 (3 × CH_3, SiC(*C*H_3)$_3$), 29.6 (CH_2), 31.3 (C, Si*C*(CH_3)$_3$), 31.7 (CH_2), 42.3 (CH_2), 51.9 (CH, C-5), 53.2 (CH_2, C-7), 59.0 (CH_3, C-13), 78.3 (C, C-4), 84.9 (CH, C-11), 112.8 (CH_2, C-14), 143.3 (C, C-8); *m/z* HRMS (EI^+) found 324.2487 $[M]^+$ $C_{19}H_{36}O_2Si$ requires 324.2485; (EI^+) 324.2 ($[M]^+$, 100%).

(±)-(9*S*, 9a*R*)-4a-((*tert*-Butyldimethylsilyl)oxy)-9-methoxydecahydro-6*H*-benzo[7]annulen-6-one 280

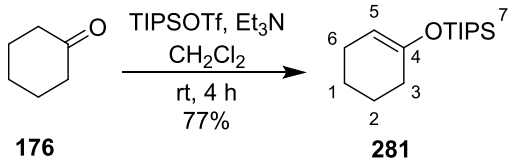


A novel compound prepared by a modification of a literature procedure.[82]

OsO_4 (2-3 drops of a 4 wt% aq. solution), $NaIO_4$ (0.36 g, 1.72 mmol) and lutidine (0.1 mL, 0.86 mmol) were added to a solution of **279** (0.14 g, 0.43 mmol) in a 3:1 mixture of dioxane and H_2O (4.3 mL). The reaction mixture was stirred at 65 °C for 6 h. The crude reaction mixture was filtered to remove the precipitate and quenched with $Na_2S_2O_5$ (6 mL of a saturated aq. solution), the resulting mixture was then washed with $NaHCO_3$ (3 × 10 mL of a 0.1 M aq. solution), extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **280** as a colourless oil (100 mg, 71%). R_f 0.37 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 2856 (w), 1703 (s), 1254 (m), 1025 (s), 833 (s); δ_H(400 MHz, $CDCl_3$) 0.05, 0.14 (6H, 2 × s, Si(C*H*$_3$)$_2$), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 1.16 (1H, dt, *J* 13.1 and 3.7 Hz, 1H of C*H*$_2$), 1.21-139 (5H, m, 2 × C*H*$_2$ and H-12), 1.41 (1H, m, 1H of C*H*$_2$), 1.58 (1H, m, 1H of C*H*$_2$), 1.68 (1H, m, 1H of C*H*$_2$), 1.84 (1H, m, 1H of C*H*$_2$), 2.37 (1H, ddd, *J* 11.6, 9.5 and 2.7 Hz, 1H of C*H*$_2$), 2.53 (1H, ddd, *J* 11.6, 9.8 and 2.3 Hz, 1H of C*H*$_2$), 2.62 (1H, d, *J* 14.5 Hz, 1H of H-7), 2.89 (1H, d, *J* 14.5 Hz, 1H of H-7), 3.12 (1H, ddd, *J* 9.3, 7.1 and 3.2 Hz, 1H of C*H*$_2$), 3.33 (3H, s, H-13); δ_C(100 MHz, $CDCl_3$) -0.29 (2 × CH_3, Si(*C*H$_3$)$_2$), 20.6 (CH_2), 23.9 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 28.3 (3 × CH_3, SiC(*C*H$_3$)$_3$), 29.8 (C, Si*C*(CH$_3$)$_3$), 40.5 (CH_2), 43.3 (CH_2), 55.0 (CH, C-5), 58.9 (CH_3, C-13), 60.3

(CH_2, C-7), 76.3 (C, C-4), 85.1 (CH, C-11), 212.8 (C, C-8); *m/z* HRMS (ES^+) found 349.2176 $[M+Na]^+$ $C_{18}H_{34}O_3SiNa$ requires 349.2175; (ES^+) 349.2 ($[M+Na]^+$, 78%).

(cyclohex-1-en-1-yloxy)tri-*iso*-propylsilane 281



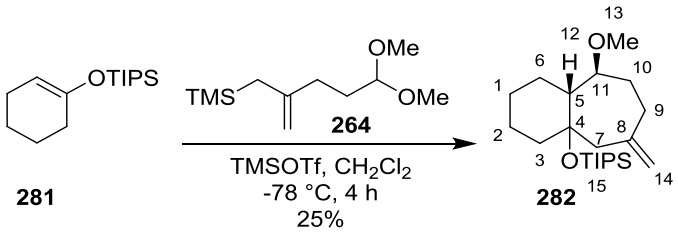
176 **281**

A known compound prepared according to the literature procedure.[106]

TIPSOTf (0.65 mL, 2.43 mmol) was added to a solution of cyclohexanone **176** (0.20 g, 2.03 mmol) and TEA (0.51 mL, 3.65 mmol) in CH_2Cl_2 (6 mL) at rt. The reaction mixture was stirred for 4 h before being diluted with DCM (6 mL) and washed with $NaHCO_3$ (10 mL of a saturated aq. solution). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pet ether/Et_2O 9:1) afforded **281** as a colourless oil (0.40 g, 77%). R_f 0.71 (pet ether/Et_2O 7:3); ν_{max}(neat)/cm^{-1}: 2928 (w), 2866 (w), 1668 (m), 1192 (s), 882 (s); δ_H(300 MHz, $CDCl_3$) 1.06 (18H, d, *J* 5.2 Hz, $Si(CH)_3(CH_3)_6$), 1.12-1.15 (3H, m, $Si(CH)_3$), 1.42-1.53 (2H, m, CH_2), 1.59-1.69 (2H, m, CH_2), 1.94-2.08 (4H, m, 2 × CH_2), 4.86 (1H, m, H-5); δ_C(100 MHz, $CDCl_3$) 12.6 (6 × CH_3, $Si(CH)_3(CH_3)_6$), 18.4 (CH_2), 22.4 (3 × CH, $Si(CH)_3$), 23.3 (CH_2), 23.9 (CH_2), 30.0 (CH_2), 104.4 (CH, C-5), 151.2 (C, C-4).

Analytical data in agreement with literature values.[140]

(±)-(((9*S*, 9a*R*)-9-Methoxy-6-methylenedecahydro-4a*H*-benzo[7]annulen-4a-yl)oxy) tri-*iso*-propylsilane 282

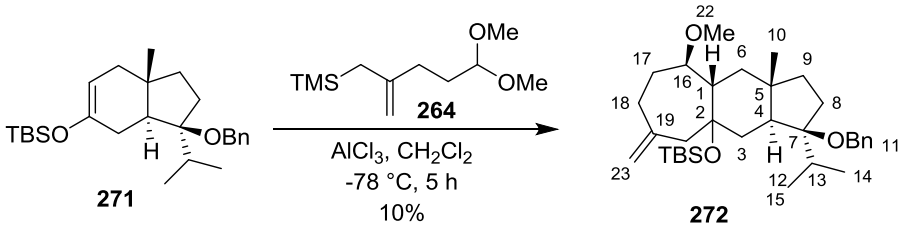


A novel compound prepared by a modification of a literature procedure.[100]

TMSOTf (17 µL, 78 mmol) was added dropwise over 5 min to a solution of **281** (100 mg, 390 mmol) and **264** (93 mg, 430 mmol) in CH_2Cl_2 (7.8 mL) at -78 °C. After 4 h at -78 °C, the reaction mixture was warmed to -30 °C, quenched with $NaHCO_3$ (6 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (2 × 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) afforded **282** as a colourless oil (35 mg, 25%). R_f 0.60 (pet ether/Et_2O 7:3); ν_{max}(neat)/cm^{-1}: 2929 (w), 2865 (w), 1641 (w), 1125 (m), 1085 (s), 1030 (s), 881 (s); δ_H(400 MHz, $CDCl_3$) 1.10 (18H, s, Si(CH)$_3$(C*H*$_3$)$_6$), 1.12-1.14 (3H, m, Si(C*H*)$_3$(CH$_3$)$_6$), 1.32-1.52 (4H, m, 2 × C*H*$_2$), 1.58-1.75 (4H, m, 2 × C*H*$_2$), 1.81-1.89 (2H, m, C*H*$_2$), 2.02 (1H, ddd, *J* 12.2, 10.8 and 4.1 Hz, H-12), 2.21 (1H, m, 1H of C*H*$_2$), 2.29 (1H, d, *J* 13.0 Hz, 1H of H-7), 2.48 (1H, ddd, *J* 12.6, 10.7 and 3.8 Hz, 1H of C*H*$_2$), 2.65 (1H, d, *J* 12.9 Hz, 1H of H-7), 3.19 (1H, dt, *J* 8.6 and 4.2 Hz, H-11), 3.29 (3H, s, H-13), 4.68 (1H, s, 1H of H-14), 4.74 (1H, s, 1H of H-14); δ_C(100 MHz, $CDCl_3$) 14.6 (CH_2), 19.1 (6 × CH_3, Si(CH)$_3$(*C*H$_3$)$_6$), 22.6 (CH_2), 24.9 (CH_2), 26.1 (CH_2), 28.9 (CH_2), 30.5 (C, Si*C*(CH$_3$)$_3$), 40.3 (CH_2), 50.3 (CH_2), 51.9 (CH, C-5), 57.7 (CH_3, C-13),

76.9 (C, C-4), 82.3 (CH, C-11), 111.6 (CH_2, C-14), 146.5 (C, C-8); *m/z* HRMS (EI^+) found 366.2942 $[M]^+$ $C_{22}H_{42}O_2Si$ requires 366.2954; (EI^+) 366.2 ($[M]^+$, 68%).

(±)-(((3*S*, 3a*S*, 9*R*, 9a*S*, 10a*S*)-3-(Benzyloxy)-3-*iso*-propyl-9-methoxy-10a-methyl-6-methylenedodecahydrocyclohepta[*f*]inden-4a(1*H*)-yl)oxy)(*tert*-butyl)dimethylsilane 272

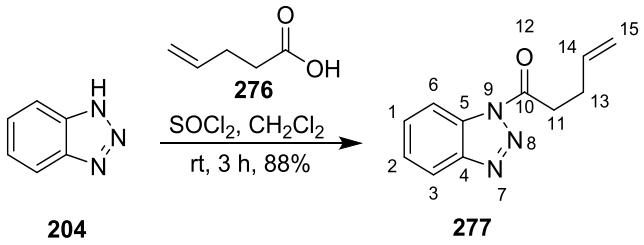


A novel compound prepared by a modification of a literature procedure.[100]

A solution of **271** (74 mg, 0.17 mmol) and **264** (110 mg, 0.53 mmol) in CH_2Cl_2 (3 mL) was added to a suspension of $AlCl_3$ (7.2 mg, 0.05 mmol) in CH_2Cl_2 (4 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 5 h, then quenched with $NaHCO_3$ (5 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 9:1) to afford **272** as a translucent semi-solid (10 mg, 10%). R_f 0.63 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2929 (w), 2856 (w), 1086 (s), 1026 (s), 832 (s); δ_H(400 MHz, $CDCl_3$) 0.17, 0.21 (6H, s, Si(CH_3)$_2$), 0.92 (3H, s, H-10), 0.94 (9H, s, SiC(CH_3)$_3$), 0.99, 1.01 (6H, 2 × d, *J* 2.2 Hz, CH(CH_3)$_2$), 1.21-1.36 (2H, m, H-12 and 1H of CH_2), 1.62-1.90 (3H, m, H-13, H-1 and 1H of CH_2), 2.04-2.21 (6H, m, 3 × CH_2), 2.24-2.35 (4H, m, 2 × CH_2), 2.51 (1H, ddd, *J* 12.5, 11.8 and 3.5 Hz, 1H of CH_2), 2.76 (1H, d, *J* 13.1 Hz, 1H of CH_2), 3.15 (1H, dt, *J* 9.0 and 3.6 Hz, H-16), 3.28 (3H, s, H-22), 4.43 (2H, s, CArCH_2O), 4.72 (1H, s, 1H

of H-23), 4.77 (1H, s, H-23), 7.23 (1H, m, C*H*Ar), 7.27-7.38 (4H, m, 4 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) -1.0 (CH_3, Si(*C*H_3)), -0.3 (CH_3, Si(*C*H_3)), 18.6 (CH_3, C-14), 18.9 (CH_3, C-15), 19.3 (CH_3, C-10), 26.9 (3 × CH_3, SiC(*C*H_3)$_3$), 27.8 (CH_2), 30.1 (CH_2), 33.3 (CH_2), 39.4 (C, Si*C*(CH$_3$)$_3$), 39.8 (CH_2), 40.5 (CH_2), 41.4 (C, C-12), 42.3 (CH_2), 44.8 (CH), 47.1 (CH), 50.9 (CH_2), 57.5 (CH_3, C-22), 63.0 (CH_2, ArC*C*H_2O), 78.5 (C, C-2), 89.2 (C, C-7), 111.2 (CH_2, C-23), 126.8 (2 × CH, *C*HAr), 127.0 (CH, *C*HAr), 128.5 (2 × CH, *C*HAr), 140.7 (C, *C*Ar), 146.9 (C, C-19); *m/z* HRMS (ES^+) found 549.3743 ([M+Na]$^+$, 67%) $C_{33}H_{54}O_3NaSi$ requires 549.3740; (ES^+) 549.3 ([M+Na]$^+$, 67%).

1-(1*H*-1,2,3-Benzotriazole-1-yl)-pentenone 277



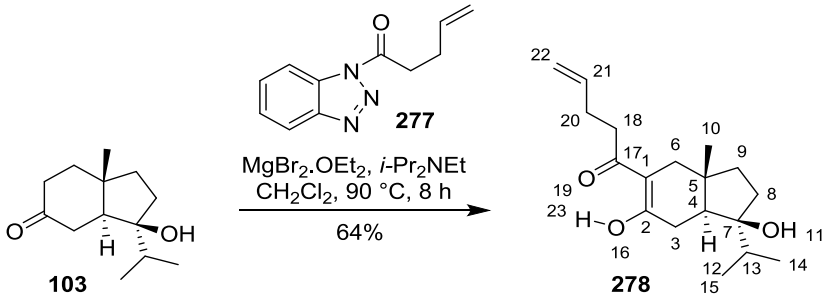
A known compound prepared according to a literature procedure.[77]

$SOCl_2$ (0.36 mL, 4.93 mmol) was added to a stirred solution of **204** (2.40 g, 20.14 mmol) in CH_2Cl_2 (25 mL) at rt. After 30 min, 4-pentenoic acid **276** (0.51 mL, 5 mmol) was added in one portion and stirring was continued for 2 h. The resulting suspension was filtered, washed with NaOH (3 × 20 mL of a 2.0 M aq. solution), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a light-yellow oil. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **277** as a colourless oil (0.89 g, 88%). R_f 0.42 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3080 (w), 2920 (w), 1737 (s), 1378 (s), 957 (s); δ_H(400 MHz, $CDCl_3$) 2.64 (2H, q, *J* 7.0 Hz, H-13), 3.54 (2H, t, *J* 7.4 Hz, H-11), 5.13 (1H, dd, *J* 10.2 and 1.3 Hz, E-H of H-15), 5.21 (1H, dd, *J* 16.8 and 1.3 Hz, Z-H of H-15), 5.96 (1H, ddt, *J* 16.8, 10.2 and 6.5 Hz, H-14),

7.51-7.66 (2H, m, 2 × C*H*Ar), 8.11-8.24 (2H, m, 2 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 28.3 (CH_2), 34.9 (CH_2), 114.5 (CH, *C*HAr), 116.4 (CH_2, C-15), 120.3 (CH, *C*HAr), 126.3 (CH, *C*HAr), 130.5 (CH, *C*HAr), 131.2 (C, *C*Ar), 136.2 (CH, C-14), 146.3 (C, *C*Ar), 172.0 (C, C-10); *m/z* HRMS (EI^+) found 201.0899 $[M]^+$ $C_{11}H_{11}N_3O$ requires 201.0902; (EI^+) 201.0 ($[M]^+$, 100%).

Analytical data in agreement with literature values.[108]

(±)-(3*R*, 3a*R*, 7a*R*, *Z*)-3-Hydroxy-6-(1-hydroxypent-4-en-1-ylidene)-3-*iso*-propyl-7a-methyloctahydro-5*H*-inden-5-one 278

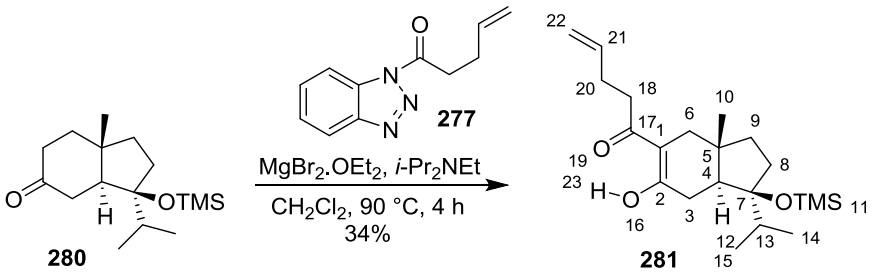


A novel compound prepared according to a literature procedure.[77]

103 (0.17 g, 0.8 mmol) Was added dropwise over 5 min to a mixture of **277** (0.19 g, 0.96 mmol), $MgBr_2.OEt_2$ (0.51 g, 2.0 mmol) and *i*-Pr_2NEt (0.41 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) at rt. The resulting suspension changed from colourless to yellow while *i*-Pr_2NEt was added. The reaction mixture was heated at 90 °C in the microwave for 8 h, by which time a solution had formed. After being cooled to rt, the reaction mixture was quenched with HCl (10 mL of a 10% aq. solution) and stirring was continued at rt for 5 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **278** as a single enol

regioisomer (0.15 g, 64%) and in the form of a yellow oil. R_f 0.22 (pet ether/Et_2O 3:1); ν_{max}(neat)/cm^{-1}: 3464 (br), 2934 (w), 2871 (w), 1698 (s), 1013 (s), 911(s); δ_H(400 MHz, $CDCl_3$) 0.92, 0.94 (6H, 2 × d, *J* 5.7 Hz, H-14 and H-15), 1.01 (3H, s, H-10), 1.29 (1H, m, 1H of CH_2), 1.58 (1H, dd, *J* 13.1 and 5.1 Hz, H-12), 1.69 (1H, m, 1H of CH_2), 1.75-1.83 (2H, m, CH_2), 2.03-2.18 (2H, m, H-13 and 1H of CH_2), 2.27-2.42 (4H, m, 2 × CH_2), 2.44-2.57 (3H, m, CH_2 and 1H of CH_2), 4.97 (1H, dd, *J* 16.7 and 1.8 Hz, 1H of H-22), 5.07 (1H, dd, *J* 10.4 and 1.8 Hz, 1H of H-22), 5.86 (1H, ddt, *J* 16.7, 10.4 and 6.4 Hz, H-21); δ_C(100 MHz, $CDCl_3$) 17.4 (CH_3), 17.9 (CH_3), 18.7 (CH_3), 28.7 (CH_2), 30.4 (CH_2), 36.6 (CH, C-13), 37.9 (CH_2), 38.2 (CH_2), 39.3 (CH_2), 40.8 (CH_2), 41.3 (C, C-5), 48.2 (CH, C-4), 82.8 (C, C-7), 106.2 (C, C-1), 115.6 (CH_2, C-22), 137.7 (CH, C-21), 184.1 (C, C-17), 200.5 (C, C-2); *m/z* HRMS (ES^+) found 293.2112 $[M]^+$ $C_{18}H_{29}O_3$ requires 293.2117; (ES^+) 293.2 ($[M]^+$, 100%).

(±)-(3*R*, 3a*R*, 7a*R*, *Z*)-6-(1-Hydroxypent-4-en-1-ylidene)-3-*iso*-propyl-7a-methyl-3-((trimethylsilyl)oxy)octahydro-5*H*-inden-5-one 281

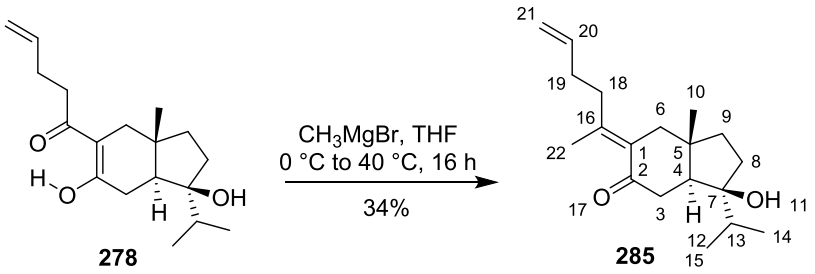


A novel compound prepared according to a literature procedure.[77]

280 (45 mg, 0.16 mmol) Was added dropwise over 5 min to a mixture of **277** (38 mg, 0.19 mmol), $MgBr_2.OEt_2$ (100 mg, 0.40 mmol) and *i*-Pr_2NEt (84 µL, 0.48 mmol) in CH_2Cl_2 (3 mL) at rt. The resulting suspension changed from colourless to yellow while *i*-Pr_2NEt was added. The reaction mixture heated at 90 °C in the microwave for 4 h, by which time a solution had

formed. After being cooled to rt, the reaction mixture was quenched with HCl (5 mL of a 10% aq. solution) and stirring continued at rt for 5 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) gave **281** as a single enol regioisomer and in the form of a colourless oil (20 mg, 34%). R_f 0.70 (pet ether/Et_2O 6:4); ν_{max}(neat)/cm^{-1}: 3336 (br), 2974 (w), 2889 (w), 1653 (s), 1045 (s), 879 (m); δ_H(400 MHz, $CDCl_3$) 0.14 (9H, s, Si(C*H*$_3$)$_3$), 0.90, 0.92 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 0.96 (3H, s, H-10), 1.21 (1H, br q, *J* 8.8 Hz, 1H of C*H*$_2$), 1.42 (1H, dd, *J* 12.8 and 5.2 Hz, H-12), 1.88 (1H, septet, *J* 6.8 Hz, H-13), 2.03 (1H, m, 1H of C*H*$_2$), 2.12 (2H, d, *J* 6.5 Hz, H-6), 2.14 (1H, d, *J* 6.9 Hz, 1H of C*H*$_2$), 2.39 (2H, ap. t, *J* 7.2 Hz, H-20), 2.27 (2H, ddd, *J* 12.8, 8.6 and 5.2 Hz, H-18), 2.47 (1H, d, *J* 6.9 Hz, 1H of C*H*$_2$), 2.54-2.62 (2H, m, C*H*$_2$), 5.05 (1H, dd, *J* 10.1 and 1.6 Hz, 1H of H-22), 5.10 (1H, dd, *J* 16.7 and 1.6 Hz, 1H of H-22), 5.85 (1H, ddt, *J* 16.7, 10.1 and 6.4 Hz, H-21); δ_C(100 MHz, $CDCl_3$) 2.3 (3 × CH_3, Si(*C*H$_3$)$_3$), 18.2 (2 × CH_3, C-14 and C-15), 18.5 (CH_3, C-10), 28.2 (CH_2), 31.8 (CH_2), 36.1 (CH_2), 38.8 (CH_2), 39.3 (CH, C-13), 39.7 (CH_2), 40.0 (CH_2), 40.7 (C, C-5), 45.6 (CH, C-4), 85.9 (C, C-7), 105.7 (C, C-1), 115.1 (CH_2, C-22), 137.3 (CH, C-21), 185.2 (C, C-17), 199.6 (C, C-2); *m*/*z* HRMS (ES^+) found 365.2499 $[M+H]^+$ $C_{21}H_{37}O_3Si$ requires 365.2512.

(3*R*, 3a*R*, 7a*R*, *E*)-6-(Hex-5-en-2-ylidene)-3-hydroxy-3-*iso*-propyl-7a-methyloctahydro-5*H*-inden-5-one 285

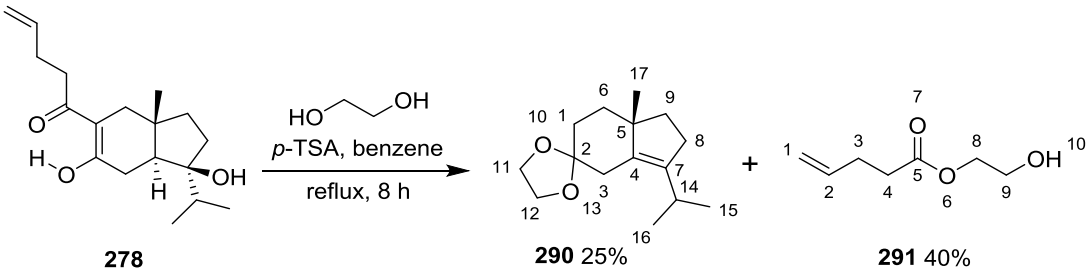


A novel compound prepared by a modification of a literature procedure.[107]

Methyl magnesium bromide (0.3 mL of a 2.0 M soln. in THF, 0.6 mmol) was added dropwise over 5 min to a stirred solution of **278** (30 mg, 0.1 mmol) in THF (1 mL) at 0 °C. The reaction mixture was heated to 40 °C for 16 h. After being cooled to rt, the resulting mixture was diluted with Et_2O (5 mL), quenched with H_2O (4 mL) and the aqueous layer was extracted with Et_2O (2 × 4 mL). The combined organic extracts were dried over $MgSO_4$, filtered, evaporated under reduced pressure and the residue purified by column chromatography (pet ether/Et_2O 6:4) to afford **285** as a colourless oil (10 mg, 34%) with an undetermined geometry of the double bond. R_f 0.28 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3464 (br), 2934 (w), 2871 (w), 1698 (s), 1367 (s), 1001 (m), 911 (s); δ_H(400 MHz, $CDCl_3$) 0.92, 0.94 (6H, 2 × d, *J* 4.8 Hz, CH(C*H*$_3$)$_2$), 1.06 (3H, s, C*H*$_3$), 1.17-1.25 (2H, m, C*H*$_2$), 1.56-1.68 (2H, m, CH_2), 1.76 (3H, s, C-22), 1.78-1.85 (2H, m, C-12 ,C-13), 2.07-2.14 (2H, m, C*H*$_2$), 2.22-2.28 (2H, m, C*H*$_2$), 2.29-2.44 (2H, m, C*H*$_2$), 2.47-2.58 (2H, m, C*H*$_2$), 5.06 (1H, dd, *J* 1.4, 10.1 Hz, 1H of C-21), 5.13 (1H, dd, *J* 1.4, 16.9 Hz, 1H of C-21), 5.84 (1H, ddt, *J* 6.7, 10.1 and 16.9 Hz, C-20); δ_C(100 MHz, $CDCl_3$) 17.4 (CH_3, C-14), 18.0 (CH_3, C-15), 20.9 (CH_3, C-22), 32.9 (CH_2), 36.2 (CH_2), 37.4 (CH, C-13), 38.0 (CH_2), 39.1 (CH_2), 39.3 (C, C-5), 41.8 (CH_2), 42.0 (CH_2), 50.3 (CH, C-4), 83.2 (C, C-7),

115.3 (CH_2, C-21), 131.3 (C, C-1), 149 (C, C-16), 138.5 (CH, C-20), 197.6 (C, C-2); *m/z* HRMS (ES^+) found 331.2243 $[M.H_2O+Na]^+$ $C_{19}H_{32}O_3Na$ requires 331.2249; (ES^+) 331.21 ($[M.H_2O + Na]^+$, 100%).

(±)-(*R*)-3-*iso*-Propyl-7a-methyl-1,2,4,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolane] 290 and 2-Hydroxyethyl-4-pentenoate 291



278 **290** 25% **291** 40%

Novel compounds prepared by a modification of a literature procedure.[32]

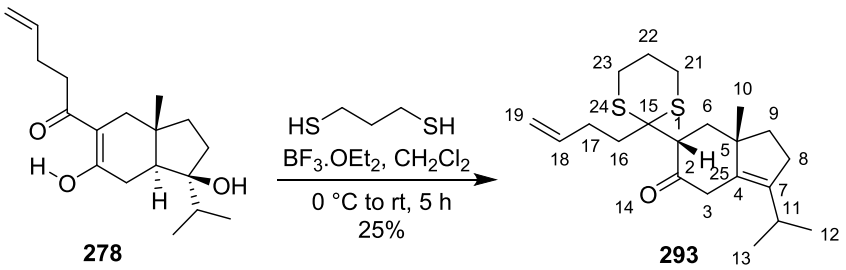
Ethylene glycol (0.28 mL, 5.1 mmol) and *p*-TSA (8 mg, 0.045 mmol) were sequentially added to a stirred solution of **278** (150 mg, 0.51 mmol) in benzene (4.5 mL) at rt and the reaction mixture was heated under refluxed for 8 h using a Dean-Stark apparatus. Upon completion, the solvent was removed *in vacuo* and the residue dissolved in Et_2O (10 mL), H_2O (8 mL) was added and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (10 mL of a saturated aq. solution), brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **290** as a yellow oil (30 mg, 25%) followed by **291** (30 mg, 40%) as a colourless oil.

Analytical data for **290**; R_f 0.58 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2953 (w), 2870 (w), 1084 (s), 945 (m); δ_H(400 MHz, $CDCl_3$) 0.92, 0.94 (6H, 2 × d, *J* 6.9 Hz, H-15 and H-16), 1.01

(3H, s, H-17), 1.49-1.56 (2H, m, CH_2), 1.60-1.75 (3H, m, CH_2 and 1H of CH_2), 1.83 (1H, m, 1H of CH_2), 2.12 (1H, ddd, *J* 14.1, 4.3 and 2.3 Hz, 1H of CH_2), 2.23-2.35 (2H, m, CH_2), 2.49 (1H, dd, *J* 14.4 and 2.5 Hz, 1H of H-3), 2.60 (1H, septet, *J* 6.9 Hz, H-14), 3.90-4.02 (4H, m, H-11 and H-12); δ_H(100 MHz, $CDCl_3$) 21.6 (CH_3, C-15), 22.1 (CH_3, C-16), 22.7 (CH_3, C-17), 26.8 (CH, C-14), 29.4 (CH_2), 32.3 (CH_2), 33.5 (CH_2), 37.9 (CH_2), 39.2 (CH_2), 46.5 (C, C-5), 64.6 (CH_2, C-11), 64.9 (CH_2, C-12), 110.3 (C, C-2), 135.8 (C, C-4), 140.2 (C, C-7); *m/z* HRMS (ES^+) found 259.1671 $[M+Na]^+$ $C_{15}H_{24}O_2Na$ requires 259.1674; (ES^+) 259.1 ($[M+Na]^+$, 100%).

Analytical data for **291**; R_f 0.21 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3445 (br), 2978 (w), 1736 (s), 1176(s); δ_H(400 MHz, $CDCl_3$) 2.35-2.41 (2H, m, H-3), 2.44-2.49 (2H, m, H-4), 3.81 (2H, t, *J* 4.5 Hz, CH_2), 4.22 (2H, ap t, *J* 4.6 Hz, CH_2), 5.04 (1H, dd, *J* 10.2 and 1.2 Hz, 1H of H-1), 5.13 (1H, dd, *J* 16.8 and 1.2 Hz, 1H of H-1), 5.82 (1H, ddt, *J* 16.8, 10.2 and 6.2 Hz, H-2); δ_C(100 MHz, $CDCl_3$) 28.9 (CH_2, C-4), 33.5 (CH_2, C-3), 61.3 (CH_2), 66.1 (CH_2), 115.8 (CH_2, C-1), 136.7 (CH, C-2), 173.5 (C, C-5); *m/z* HRMS (AP^+) found 145.0870 $[M+H]^+$ $C_7H_{13}O_3$ requires 145.0865; (AP^+) 145.0 ($[M+H]^+$, 100%).

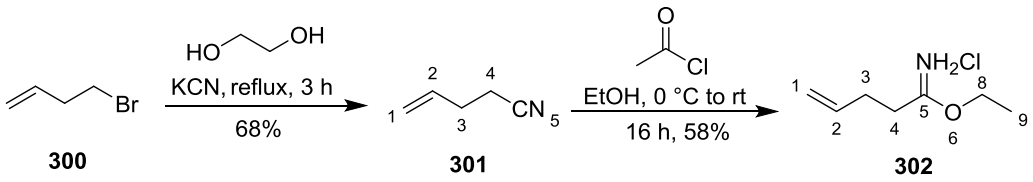
(±)-(6*S*, 7a*R*)-6-(2-(But-3-en-1-yl)-1,3-dithian-2-yl)-3-*iso*-propyl-7a-methyl-1,2,4,6,7,7a-hexahydro-5*H*-inden-5-one 293



A novel compound prepared according to a literature procedure.[111]

$BF_3.OEt_2$ (8.02 µL, 0.065 mmol) was added to a solution of **278** (40 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 10 min at 0 °C, 1,3-propanedithiol (6.5 µL, 0.065 mmol) was added dropwise over 5 min and the resulting mixture was stirred for 5 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (2 mL of a saturated aq. solution) and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed with NaOH (8 mL of a 0.1 M aq. solution), brine (8 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **293** as a pale yellow oil (12 mg, 25%). R_f 0.62 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2954 (w), 2865 (w), 1714 (s), 908 (s); δ_H(500 MHz, $CDCl_3$) 0.94, 1.02 (6H, 2 × d, *J* 6.8 Hz, H-12 and H-13), 0.98 (3H, s, H-10), 1.43 (1H, dd, *J* 13.4 and 3.2 Hz, 1H of H-6), 1.58 (1H, m, 1H of H-9), 1.73 (1H, ddd, *J* 12.5, 6.1 and 3.4 Hz, 1H of H-9), 1.81-1.88 (2H, m, H-22), 2.15 (1H, t, *J* 13.4 Hz, 1H of H-6), 2.22-2.32 (3H, m, 1H of H-3 and H-8), 2.37 (2H, ap. t, *J* 16.3 Hz, H-17), 2.62-2.68 (2H, m, 1H of H-23 and H-11), 2.70-2.84 (3H, m, 1H of H-23 and H-16), 3.05-3.15 (3H, m, H-1 and H-21), 3.43 (1H, d, *J* 14.0 Hz, 1H of H-3), 5.05 (1H, dd, *J* 10.2 and 1.6 Hz, 1H of H-19), 5.12 (1H, dd, *J* 16.8 and 1.6 Hz, 1H of H-19), 5.85 (1H, ddt, *J* 16.8, 10.2 and 6.4 Hz, H-18); δ_C(100 MHz, $CDCl_3$) 21.2 (2 × CH_3, C-12 and C-13), 23.0 (CH_3), 25.4 (CH_2, C-22), 25.6 (CH_2, C-21), 26.4 (CH_2, C-23), 26.8 (CH, C-11), 27.7 (CH_2, C-17), 28.2 (CH_2, C-8), 36.6 (CH_2, C-3), 39.1 (CH_2, C-9), 39.3 (CH_2, C-6), 44.4 (CH_2, C-16), 46.0 (C, C-5), 52.3 (C, C-15), 56.8 (CH, C-1), 115.0 (CH_2, C-19), 132.7 (C, C-4), 137.4 (CH, C-18), 141.7 (C, C-7), 209.5 (C, C-2); *m/z* HRMS (ES^+) found 365.1962 $[M]^+$ $C_{21}H_{33}OS_2$ requires 365.1973; (ES^+) 365.1 ($[M]^+$, 100%).

Ethylhex-5-enimidate hydrochloride 302



300 **301** **302**

Known compounds prepared by a modification of a literature procedure.[115]

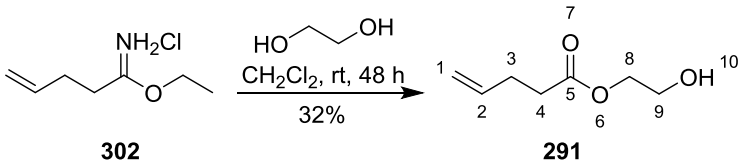
Potassium cyanide (1.0 g, 15.35 mmol) was added to a stirred solution of 1-bromo-4-butene **300** (1.4 mL, 13.81 mmol) in ethylene glycol (10 mL). The reaction mixture was heated under reflux for 3 h before being cooled to rt. The resultant brown solution was diluted with Et_2O (20 mL), washed with H_2O (20 mL) and extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and followed by removal of the solvent at atmosphere pressure. Purification *via* bulb-to-bulb distillation at atmosphere pressure gave the *title compound* **301** as a colourless liquid (0.85 g, 68%); b.p. 144-145 °C; ν_{max}(neat)/cm^{-1}: 3110 (br), 3030 (w), 2960 (w), 2880 (w), 1460 (m); δ_H(400 MHz, $CDCl_3$) 2.21-2.74 (4H, m, 2 × CH_2), 5.35 (1H, dd, *J* 10.2 and 1.6 Hz, 1H of H-1), 5.42 (1H, dd, *J* 16.7 and 1.6 Hz, 1H of H-1), 5.62 (1H, ddt, *J* 16.7, 10.2 and 6.5 Hz, H-2); δ_C(100 MHz, $CDCl_3$) 17.2 (CH_2), 29.5 (CH_2), 117.8 (CH_2, C-1), 119.2 (C, C-5), 134.4 (CH, C-2).

Acetyl chloride (1.0 mL, 14.72 mmol) was added dropwise (strongly exothermic reaction) over 5 min to the solution of nitrile **301** (0.15 g, 1.84 mmol) in EtOH (1.3 mL, 22.0 mmol) at 0 °C. The internal pressure was reduced time to time by piercing the septum with a needle. After 16 h at rt, the system was opened and the mixture was vigorously stirred for 30 min to remove dissolved HCl. The solvent evaporated under reduced pressure to give a viscous gel which was washed with Et_2O (3 × 4 mL) to remove any trace of HCl and dried under reduced

pressure for several hours (< 1 mbar) to afford **302** as a white solid (0.18 g, 58%); m.p. 98-104 °C; ν_{max}(neat)/cm^{-1}: 3368 (br), 2938 (br), 1642 (m), 1444 (m), 1390 (s); δ_H(400 MHz, CD_3CN) 1.39 (3H, t, *J* 6.7 Hz, H-9) 2.44 (2H, q, *J* 7.0 Hz, H-3), 2.78 (2H, t, *J* 7.3 Hz, H-4), 4.47 (2H, q, *J* 6.8 Hz, H-8), 5.12 (1H, dd, *J* 10.2 and 1.6 Hz, 1H of H-1), 5.22 (1H, dd, *J* 16.8 and 1.6 Hz, 1H of H-1), 5.83 (1H, ddt, *J* 16.8, 10.2 and 6.4 Hz, H-2); δ_C(100 MHz, CD_3CN) 14.6 (CH_3), 30.7 (CH_2, C-3), 33.8 (CH_2, C-4), 71.9 (CH_2, C-8), 118.0 (CH_2, C-1), 136.7 (CH, C-2), 180.3 (C, C-5).

Analytical data in agreement with literature values.[115]

2-Hydroxyethyl-4-pentenoate 291



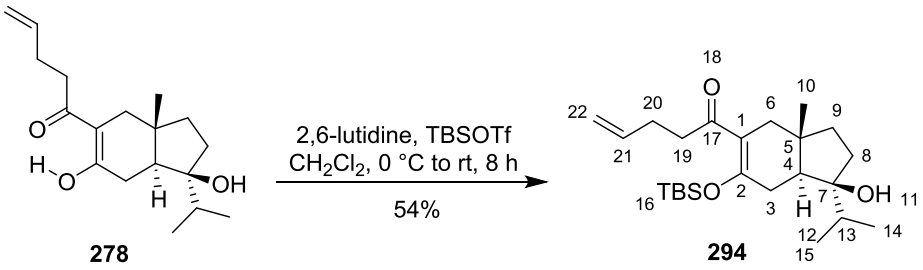
302 **291**

A novel compound prepared according to a literature procedure.[116]

Ethylene glycol (0.1 mL, 1.77 mmol) was added to a solution of imidate **302** (0.32 g, 1.95 mmol) in CH_2Cl_2 (4 mL) at rt. The reaction mixture was stirred at rt for 2 day after which time, the resultant mixture was filtered through celite pad to remove insoluble materials, which was washed several times with CH_2Cl_2. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (pet ether/Et_2O 6:4) to yield **291** as a colourless oil (0.11 g, 32%). R_f 0.22 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3445 (br), 2978 (w), 1736 (s), 1176(s); δ_H(400 MHz, $CDCl_3$) 2.35-2.41 (2H, m, H-3), 2.44-2.49 (2H, m, H-4), 3.81 (2H, t, *J* 4.5 Hz, C*H*$_2$), 4.22 (2H, ap. t, *J* 4.6 Hz, C*H*$_2$), 5.04 (1H, dd, *J* 10.2 and 1.2 Hz, 1H of H-1), 5.12 (1H, dd, *J* 16.8 and 1.2 Hz, 1H of H-1), 5.82 (1H, ddt, *J* 16.8, 10.2 and 6.2

Hz, H-2); δ_C(100 MHz, $CDCl_3$) 28.9 (CH_2, C-4), 33.5 (CH_2, C-3), 61.3 (CH_2), 66.1 (CH_2), 115.8 (CH_2, C-1), 136.7 (CH, C-2), 173.5 (C, C-5); *m/z* HRMS (AP^+) found 145.0870 $[M+H]^+$ $C_7H_{13}O_3$ requires 145.0865; (AP^+) 145.0 ($[M+H]^+$, 100%).

(±)-1-((1*R*, 3a*R*, 7a*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-1-*iso*-propyl-3a-methyl-2, 3, 3a, 4, 7, 7a-hexahydro-1*H*-inden-5-yl)pent-4-en-1-one 294



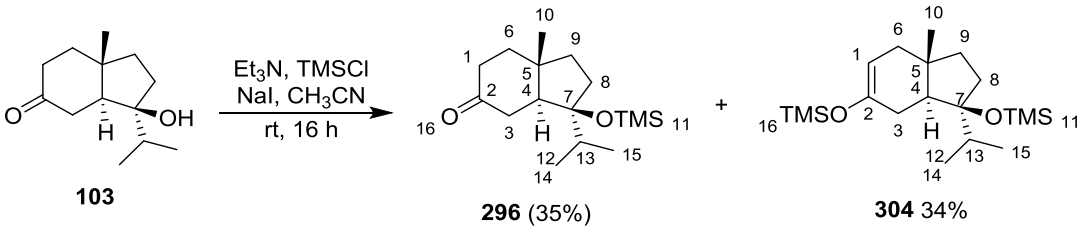
A novel compound prepared according to a literature procedure.[112]

2,6-lutidine (0.23 ml, 2.04 mmol) and TBSOTf (0.23 ml, 1.02 mmol) were sequentially added to a solution of **278** (0.20 g, 0.68 mmol) in CH_2Cl_2 (7 mL) at 0 °C and the reaction mixture was stirred for 15 min at 0 °C before being warmed to rt. After 8 h, the reaction mixture was quenched with saturated NH_4Cl (8 mL of a saturated aq. solution) and extracted with Et_2O (2 × 8 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **294** as a white solid (150 mg, 54%). R_f 0.46 (pet ether/Et_2O 1:1); m.p. 61-65 °C; ν_{max}(neat)/cm^{-1}: 2955 (w), 2859 (w), 1637 (s), 1256 (s), 1148 (m), 837 (s); δ_H(400 MHz, $CDCl_3$) 0.22, 0.24 (6H, 2 × s, Si(CH_3)$_2$), 0.91, 0.92 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 0.94 (3H, s, H-10), 0.96 (9H, s, (CH_3)$_3$CSi), 1.51 (1H, dd, *J* 12.4 and 5.2 Hz, H-12), 1.64-1.79 (3H, m, CH_2, H-13), 1.93 (2H, m, CH_2), 2.03-2.12 (3H, m, CH_2 and 1H of CH_2), 2.22-2.41 (3H, m, CH_2, 1H of CH_2), 2.86 (2H, t, *J* 7.8 Hz, H-3), 4.90 (1H, dd, *J* 10.2 and 2.0 Hz, 1H of H-

22), 5.04 (1H, dd, *J* 16.9 and 2.0 Hz, 1H of H-22), 5.83 (1H, ddt, *J* 16.9, 10.2 and 6.6 Hz, H-21); δ_C (100 MHz, $CDCl_3$) -2.9 (CH_3, Si*C*H_3), -2.6 (CH_3, Si*C*H_3), 17.2 (CH_3, C-14), 18.1 (CH_3, C-15), 18.7 (CH_3, C-10), 26.2 (3 × CH_3, SiC(*C*H_3)$_3$), 28.8 (CH_2), 30.7 (CH_2), 29.0 (CH_2), 37.9 (CH, C-12), 38.9 (C, C-5), 39.2 (CH_2), 39.9 (CH_2), 43.1 (CH_2), 49.7 (CH, C-13), 82.8 (C, C-7), 114.7 (CH_2, C-22), 117.3 (C, C-1), 138.3 (CH, C-21), 159.4 (C, C-2), 210 (C, C-17); *m/z* HRMS (ES^+) found 429.2804 $[M+Na]^+$ $C_{24}H_{42}O_3NaSi$ requires 429.2801; (ES^+) 429.2 ($[M+Na]^+$, 89%).

(±)-(3*R*, 3a*R*, 7a*R*)-3-*iso*-propyl-7a-methyl-3-((trimethylsilyl)oxy)octahydro-5*H*-inden-5-one 296 and (±)-(((3*R*, 3a*R*, 7a*R*)-1-*iso*-propyl-3a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1,6-diyl)bis(oxy))bis(trimethylsilane) 304

Method A

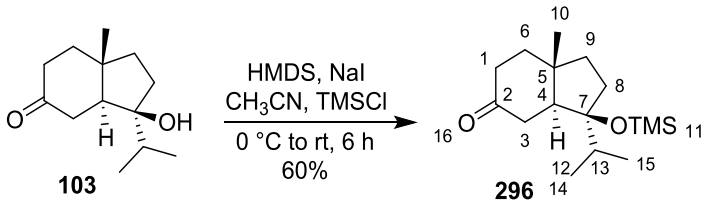


Novel compounds prepared according to a literature procedure.[119]

Triethylamine (1 mL, 7.28 mmol), TMSCl (0.93 mL, 7.28 mmol) and NaI (1.0 g, 7.28 mmol) were sequentially added to a solution of **103** (0.22 g, 1.04 mmol) in CH_3CN (12 mL) at rt. Upon addition of NaI, the solution immediately became cloudy. After 16 h at rt, the reaction mixture was diluted with EtOAc (12 mL) and washed with $NaHCO_3$ (10 mL of a saturated aq. solution). The organic extract was washed with brine (12 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O

9:1) gave **296** as a colourless oil (0.13 g, 35%) followed by **304** as a clear colourless oil (0.10 g, 34%).

Method B



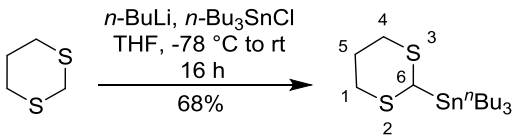
HMDS (0.98 mL, 4.70 mmol) and NaI (0.75 g, 5.05 mmol) were sequentially added to the solution of **103** (0.10 g, 0.47 mmol) in CH_3CN (12 mL) at rt. The reaction mixture was cooled to 0 °C and TMSCl (0.3 mL, 2.35 mmol) was added dropwise over 5 min before being allowed to warm to rt slowly. After 6 h, the reaction mixture was quenched with NH_4Cl (10 mL of a saturated aq. solution) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and purified by column chromatography (pet ether/Et_2O 9:1) to give **296** as a colourless oil (0.1 g, 60%).

Analytical data for **296**: R_f 0.55 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2957 (w), 2833 (w), 1655 (s), 1249 (m), 882 (s); δ_H(400 MHz, $CDCl_3$) 0.12 (9H, s, Si(CH_3)$_3$), 0.87, 0.89 (6H, 2 × d, *J* 4.2 Hz, H-14 and H-15), 1.16 (3H, s, H-10), 1.12 (1H, m, 1H of CH_2), 1.54 (1H, dd, *J* 12.5 and 6.3 Hz, H-12), 1.60-1.69 (2H, m, 1H of CH_2 and H-13), 1.79-1.88 (2H, m, CH_2), 2.06-2.11 (2H, m, CH_2), 2.29-2.37 (2H, m, CH_2), 2.42 (1H, m, 1H of CH_2), 2.53 (1H, m, 1H of CH_2); δ_C(100 MHz, $CDCl_3$) 2.5 (3 × CH_3, Si(*C*H$_3$)$_3$), 18.4 (2 × CH_3, C-14 and C-15), 37.2 (CH_3, C-10), 37.6 (CH_2), 39.1 (CH_2), 40.2 (CH, C-13), 40.6 (CH_2), 41.5 (CH_2), 41.6 (CH_2), 50.2 (CH, C-4), 86.3 (C, C-7),

214.0 (C, C-2); *m*/*z* HRMS (ES^+) found 193.1595 $[M+H-H_2O-TMS]^+$ $C_{13}H_{21}O$ requires 193.1592; (ES^+) 193.1 ($[M+H-H_2O-TMS]^+$, 100%).

Analytical data for **304**: R_f 0.63 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2958 (w), 1249 (m), 1073 (m), 834 (s); δ_H(500 MHz, $CDCl_3$) 0.11 (9H, s, COSi(C*H*$_3$)$_3$), 0.19 (9H, s, =COSi(C*H*$_3$)$_3$), 0.86, 0.89 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 0.95 (3H, s, H-10), 1.06 (1H, br q, *J* 11.7 Hz, 1H of H-8), 1.49 (1H, dd, *J* 12.1 and 4.9 Hz, H-12), 1.58 (1H, ddd, *J* 12.0, 6.5 and 2.1 Hz, 1H of H-8), 1.77-1.84 (4H, m, H-6, 1H of H-3 and H-13), 1.93-1.98 (2H, m, H-9), 2.22 (1H, m, 1H of H-3), 4.75 (1H, dd, *J* 4.8 and 2.0 Hz, H-1); δ_C(100 MHz, $CDCl_3$) 0.5 (3 × CH_3, (*C*H_3)$_3$SiOCCH), 2.5 (3 × CH_3, (*C*H_3)$_3$SiOC=), 18.7 (2 × CH_3, C-14 and C-15), 18.9 (CH_3, C-10), 30.7 (CH_2, C-3), 38.6 (CH_2, C-6), 39.4 (CH, C-13), 39.8 (CH_2, C-8), 40.3 (C, C-4), 40.5 (CH_2, C-9), 48.4 (CH, C-5), 86.4 (C, C-7), 103.8 (CH, C-1), 151.9 (C, C-2); *m*/*z* HRMS (ES^+) found 233.2150 $[M-2 \times TMS+Na]^+$ $C_{13}H_{22}O_2Na$ requires 354.68 $C_{19}H_{38}O_2Si_2$; (ES^+) 233.2 ($[M-2 \times TMS+Na]^+$, 100%).

(1,3)-Dithian-2-yl)tri-n-butyltin 305



307 **305**

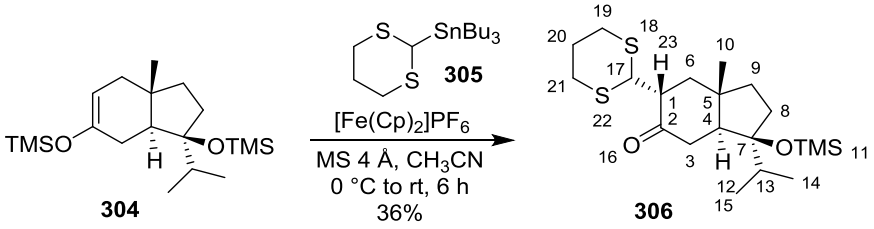
A known compound prepared by a modification of the literature procedure.[118]

A solution of *n*-BuLi (0.36 mL of a 2.5 M soln. in hexane, 0.90 mmol) was added dropwise over 10 min to a solution of 1,3-dithiane **307** (0.1 g, 0.83 mmol) in THF (2 mL) at -78 °C. The reaction mixture was stirred for 3 h before being allowed to warm to 0 °C, then once again cooled to -78 °C. Tri-*n*-butyltin chloride (0.51 mL, 3.32 mmol) was added gradually over 20 min at -78 °C and the ice bath was removed. After 16 h at rt, the reaction mixture was

quenched by addition of crushed solid carbon dioxide (Ca. 0.2 g) followed by gradual addition of H_2O (8 mL). Most of the THF was removed *in vacuo* and the remaining aqueous suspension extracted with DCM (3 × 10 mL). The organic extracts were washed with K_2CO_3 (10 mL of a 5% aq. solution), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **305** as a colourless oil (0.23 g, 68%). R_f 0.78 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2956 (s), 2923 (s), 2853 (m), 1463 (m); δ_H(400 MHz, $CDCl_3$) 0.92 (9H, t, *J* 7.3 Hz, 3 × C*H*$_3$), 1.06 (6H, ap. t, *J* 8.0 Hz, Sn(C*H*$_2$)$_3$), 1.35 (6H, sextet, *J* 12.2 Hz, 3 × CH_3C*H*$_2$), 1.56-1.60 (6H, m, 3 × $SnCH_2$C*H*$_2$), 2.09-2.22 (2H, m, H-6), 2.57-2.66 (2H, m, H-1), 2.87-2.96 (2H, m, H-5), 4.02 (1H, s, H-3); δ_c(100 MHz, $CDCl_3$) 9.7 (3 × CH_2, Sn*C*H$_2$), 14.1 (3 × CH_3), 27.1 (CH_2, C-6), 27.2 (CH, C-3), 27.7 (3 × CH_2, *C*H$_2$CH$_3$), 29.3 (3 × CH_2, $SnCH_2$*C*H$_2$), 32.7 (2 × CH_2, C-1 and C-5).

Analytical data in agreement with literature values.[118]

(±)-(3*R*, 3a*R*, 6*S*, 7a*R*)-6-(1,3-Dithian-2-yl)-3-*iso*-propyl-7a-methyl-3-((trimethylsilyl)oxy)octahydro-5*H*-inden-5-one 306

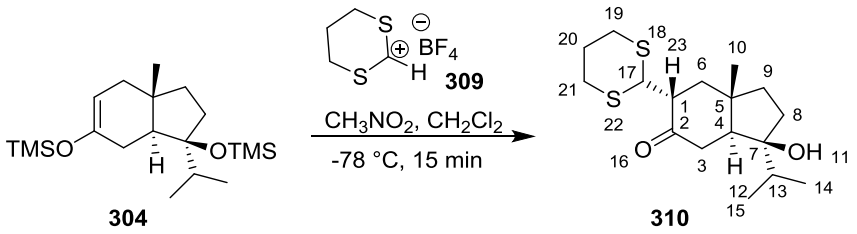


A novel compound prepared by a modification of a literature procedure.[117]

2-Tributylstannyl-1,3-dithiane **305** (85 mg, 0.21 mmol) in CH_3CN (2.1 mL) and **304** (50 mg, 0.14 mmol) were added sequentially to a solution of ferrocenium hexafluorophosphate (70 mg, 0.21 mmol) in CH_3CN (1.0 mL) including suspended molecular sieves 4 Å (100 mg) at 0 °C.

After being stirred for 5 h at rt, the reaction mixture was quenched with $NaHCO_3$ (2 mL of a saturated aq. solution) and insoluble materials were removed by filtration through a celite pad, which was washed several times with DCM. The organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **306** as a colourless oil (20 mg, 36%). R_f 0.46 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2955 (w), 2926 (w), 1704 (s), 1249 (m), 1072 (s), 835 (s); δ_H(400 MHz, $CDCl_3$) 0.12 (9H, s, Si(C*H*$_3$)$_3$), 0.86, 0.88 (6H, 2 × d, *J* 7.3 Hz, H-14 and H-15), 1.12 (3H, s, H-10), 1.22 (1H, m, 1H of C*H*$_2$), 1.57-1.71 (3H, m, C*H*$_2$ and H-12), 1.74-1.87 (3H, m, H-13 and C*H*$_2$), 2.03-2.11 (4H, m, H-19 and H-21), 2.40 (1H, dd, *J* 17.3 and 4.5 Hz, 1H of C*H*$_2$), 2.54 (1H, dd, *J* 17.3 and 3.6 Hz, 1H of C*H*$_2$), 2.70 (1H, ddd, *J* 11.3, 7.3 and 3.2 Hz, H-23), 2.89-3.02 (3H, m, 1H of C*H*$_2$ and C*H*$_2$), 4.86 (1H, d, *J* 3.2 Hz, H-17); δ_C(100 MHz, $CDCl_3$) 2.3 (3 × CH_3, Si(*C*H_3)$_2$), 18.1 (CH_3, C-14), 18.2 (CH_3, C-15), 25.5 (CH_2), 30.6 (CH_2), 31.4 (CH, C-13), 38.8 (2 × CH_2, C-19 and C-21), 39.7 (CH_2), 40.3 (CH_2), 40.8 (C, C-5), 41.3 (CH_2), 48.9 (CH, C-4), 49.4 (CH, C-17), 50.5 (CH, C-1), 86.2 (C, C-7), 207.2 (C, C-2); *m/z* HRMS (ES^+) found 423.1812 $[M+Na]^+$ $C_{20}H_{36}O_2S_2NaSi$ requires 423.1824; (ES^+) 423.1 ($[M+Na]^+$, 100%).

(±)-(3*R*, 3a*R*, 6*S*, 7a*R*)-6-(1,3-Dithian-2-yl)-3-hydroxy-3-*iso*-propyl-7a-methyloctahydro-5*H*-inden-5-one 310



Preparation of 1,3-dithienium tetrafluoroborate **309** [121]

Trityl fluoroborate **308** (0.27 g, 0.83 mmol) was added to a solution of 1,3-dithiane **307** (0.10 g, 0.83 mmol) in DCM (3 mL) and the reaction mixture heated under reflux. After 2 h, most of the solvent was removed under reduced pressure followed by trituration with cold Et_2O (2 × 6 mL) and drying *in vacuo* for several hours to give **309** as a yellow solid (0.15 g, 88%).

A novel compound prepared according to a literature procedure.[120]

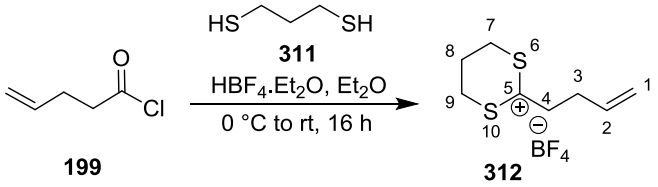
A solution of 1,3-dithienium fluoroborate **309** (28 mg, 0.14 mmol) in dry CH_3NO_2 (0.1 mL) was added dropwise over 5 min to a stirred solution of **304** (50 mg, 0.14 mmol) in DCM (0.7 mL) at -78 °C. After 15 min, the reaction mixture was allowed to warm to rt, washed with $NaHCO_3$ (2 mL of a saturated aq. solution) and extracted with Et_2O (4 mL). The organic extract was washed with brine (2 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) gave **310** as a pale yellow oil (10 mg, 22%).

Analytical data for 1,3-dithienium tetrafluoroborate **309**: m.p. 186-189 °C; δ_H(300 MHz, DMSO) 1.68-1.79 (2H, m, $SCH_2C\mathit{H}_2$), 2.56-2.71 (4H, m, 2 × $SC\mathit{H}_2$); δ_C(100 MHz, DMSO) 16.5 (CH_2, $SCH_2\mathit{C}H_2$), 25.6 (2 × CH_2, $S\mathit{C}H_2$), 46.2 (CH).

Analytical data for **310**: R_f 0.52 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3497 (br), 2955 (w), 2861 (w), 1700 (s), 1136 (m); δ_H(400 MHz, $CDCl_3$) 0.90, 0.94 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 1.18 (1H, m, 1H of $C\mathit{H}_2$), 1.24 (3H, s, H-10), 1.56 (1H, td, *J* 12.8 and 5.7 Hz, 1H of $C\mathit{H}_2$), 1.63-1.72 (4H, m, 2 × $C\mathit{H}_2$), 1.80-1.91 (3H, m, H-12 and $C\mathit{H}_2$), 2.04-2.18 (2H, m, $C\mathit{H}_2$), 2.43-2.56 (4H, m, H-21 and H-19), 2.74 (1H, ddd, *J* 12.5, 6.5 and 3.2 Hz, H-23), 2.88 (1H, m, H-13), 4.87 (1H, d, *J* 3.2 Hz, H-17); δ_C(100 MHz, $CDCl_3$) 17.9 (CH_3, C-10), 18.6 (CH_3, C-14), 18.9 (CH_3, C-15), 32.1 (CH_2), 37.7 (CH_2), 37.9 (CH_2), 38.3 (CH, C-13), 38.5 (CH_2), 39.8 (CH_2), 41.2 (CH_2),

41.9 (C, C-5), 49.3 (CH_2), 51.3 (CH, C-1), 52.1 (CH, C-17), 52.5 (CH, C-4), 83.7 (C, C-7), 213.1 (C, C-2); *m/z* HRMS (ES^+) found 351.1430 $[M+Na]^+$ $C_{17}H_{28}O_2S_2Na$ requires 351.1428; (ES^+) 351.1 ($[M+Na]^+$, 100%).

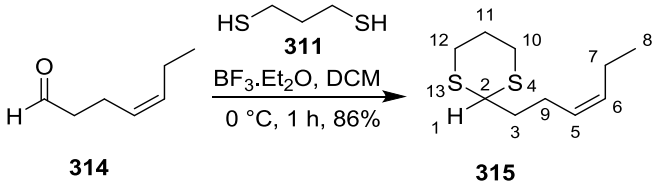
2-(But-3-en-1-yl)-1,3-dithian-2-ylium tetrafluoroborate 312



A novel compound prepared by a modification of the literature procedure.[121]

1,3-propanedithiol **311** (84 µl, 0.84 mmol) and $HBF_4.Et_2O$ (0.34 mL, 2.52 mmol) were added to a solution of **199** (0.1 mL, 0.84 mmol) in Et_2O (0.4 mL) at 0 °C. After 1 h at rt, the reaction mixture was kept in the freezer for 16 h; ν_{max}(neat)/cm^{-1}: 2988 (w), 1389 (w), 1019 (m), 895 (m); δ_H(400 MHz, CD_3CN) 2.32-2.38 (2H, m, H-8), 2.58 (2H, ddd, *J* 14.4, 4.7 and 3.5 Hz, H-3), 3.30 (2H, t, *J* 7.4 Hz, H-4), 3.58 (4H, dd, *J* 6.7 and 4.6 Hz, H-7 and H-9), 5.18 (1H, dd, *J* 10.2 and 1.6 Hz, 1H of H-1), 5.22 (1H, dd, *J* 17.6 and 1.6 Hz, 1H of H-2), 5.83 (1H, ddt, *J* 17.6, 10.2 and 6.8 Hz, H-2); δ_c(100 MHz, CD_3CN) 16.6 (CH_2, C-8), 33.5 (2 × CH_2, C-7 and C-9), 35.5 (CH_2, C-3), 45.7 (CH_2, C-4), 118.5 (CH_2, C-1), 135.1 (CH, C-2); *m/z* HRMS (ES^+) found 173.0463 $[M-BF_4^-]^+$ $C_8H_{13}S_2$ requires 173.0459.

(*Z*)-2-(Hex-3-en-1-yl)-1,3-dithiane 315

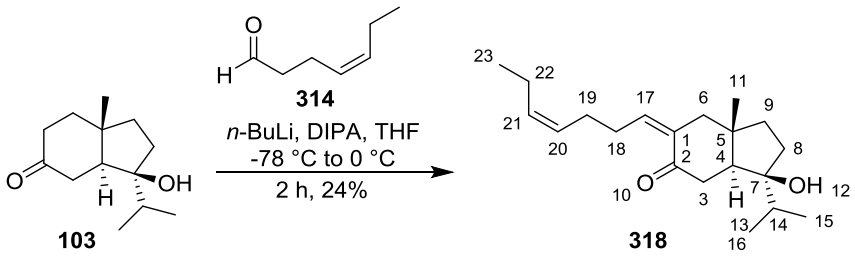


A novel compound prepared according to a literature procedure.[111]

1,3-propane dithiol **311** (44 µL, 0.44 mmol) was added to a stirred solution of **314** (52 µL, 0.40 mmol) in DCM (0.4 mL) at rt. The reaction mixture was cooled to 0 °C before a solution of $BF_3.Et_2O$ (24.6 µL, 0.2 mmol) was added dropwise over 5 min. After 1 h at 0 °C, the reaction mixture was allowed to warm to rt, quenched with $NaHCO_3$ (4 mL of a saturated aq. solution) and extracted with DCM (3 × 4 mL). The combined organic extracts were washed with NaOH (4 mL of a 0.1 M aq. solution), brine (4 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave **315** as a colourless oil (70 mg, 86%). R_f 0.68 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2965 (w), 1639 (m), 1276 (m), 854 (s); δ_H(400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.5 Hz, H-8), 1.75-1.83 (2H, m, C*H*$_2$), 2.02-2.11 (2H, m, C*H*$_2$), 2.25-2.41 (4H, m, 2 × C*H*$_2$), 2.72-2.87 (4H, m, H-10 and H-12), 4.03 (1H, t, *J* 7.1 Hz, H-1), 5.31 (1H, m, C*H*=), 5.42 (1H, m, C*H*=); δ_C(100 MHz, $CDCl_3$) 14.8 (CH_3), 21.1 (CH_2), 24.6 (CH_2), 26.5 (CH_2), 30.8 (2 × CH_2, C-10 and C-12), 35.8 (CH_2), 47.3 (CH, C-2), 127.6 (CH, *C*H=), 133.6 (CH, *C*H=); *m*/*z* HRMS (EI^+) found 202.0853 $[M]^+$ $C_{10}H_{18}S_2$ requires 202.0850; (EI^+) 202.0 ($[M]^+$, 80%).

(±)-(3*R*, 3a*R*, 7a*R*, *Z*)-6-((*Z*)-Hept-4-en-1-ylidene)-3-hydroxy-3-*iso*-propyl-7a-methyloctahydro-5*H*-inden-5-one 318

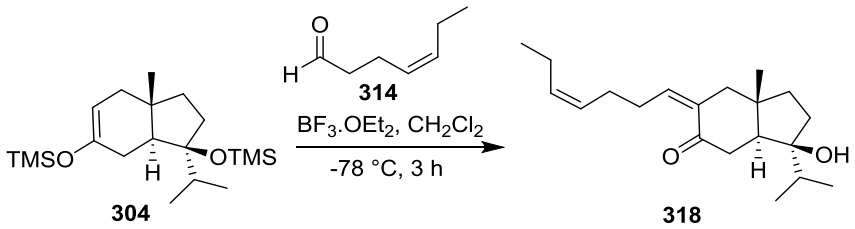
Method A



A novel compound prepared according to a literature procedure.[122]

A solution of **103** (57 mg, 0.27 mmol) in THF (0.54 mL) was added to a solution of LDA obtained at -78 °C from DIPA (25 µL, 0.27 mmol) and *n*-BuLi (0.11 mL of a 2.5 M soln. in hexane, 0.28 mmol) in THF (0.38 mL). After 30 min at -78 °C, a solution of *cis*-4-hepten-1-al **314** (42 µL, 0.32 mmol) in THF (0.45 mL) was added and the reaction mixture was stirred for 2 h before being warmed to 0 °C slowly. The reaction mixture was quenched with NH_4Cl (4 mL of a saturated aq. solution) and extracted with Et_2O (2 × 8mL). The combined organic extracts were washed with H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **318** as a colourless oil (20 mg, 24%) with an undetermined geometry of the double bond next to the carbonyl functionality.

Method B [124]

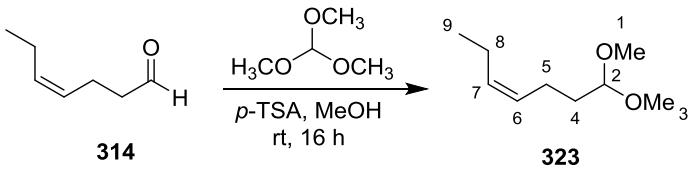


A solution of **304** (50 mg, 0.14 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise over 2 min to a mixture of aldehyde **314** and $BF_3.OEt_2$ in CH_2Cl_2 (3 mL) at -78 °C and stirred for 3 h before being warmed to rt slowly. The reaction mixture was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 7:3) afforded **318** as a colourless oil (13 mg, 30%) with an undetermined geometry of the double bond next to the carbonyl functionality.

Analytical data for **318**: R_f 0.42 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3491 (br), 2958 (w), 2874 (w), 1678 (s), 1455 (m), 1139 (s); δ_H(400 MHz, $CDCl_3$) 0.93, 0.95 (6H, 2 × d, *J* 4.8 Hz, H-15 and H-16), 0.97 (3H, t, *J* 5.6 Hz, H-23) 1.05 (3H, s, H-11), 1.30 (1H, dd, *J* 12.1 and 5.8 Hz, 1H of C*H*$_2$), 1.71 (1H, septet, *J* 6.8 Hz, H-14), 1.74 (2H, quin., *J* 6.9 Hz, H-22), 1.75-1.87 (3H, m, H-13 and 1H of C*H*$_2$), 1.99-2.03 (4H, m, 2 × C*H*$_2$), 2.09-2.20 (4H, m, 2 × C*H*$_2$), 2.61-2.69 (2H, m, C*H*$_2$), 5.32-5.42 (2H, m, H-20 and H-21), 6.78 (1H, ap. t, *J* 7.2 Hz, H-17); δ_C(100 MHz, $CDCl_3$) 15.4 (CH_3, C-23), 18.5 (CH_3, C-15), 18.7 (CH_3, C-C-16), 20.4 (CH_3, C-11), 21.7 (CH_2, C-22), 27.1 (CH_2), 29.4 (CH_2), 38.1 (CH_2), 38.9 (CH_2), 39.1 (CH, C-14), 40.4 (CH_2), 42.1 (CH_2), 42.3 (C, C-5), 50.6 (CH, C-4), 84.4 (C, C-7), 128.8 (CH, C-20), 133.9 (CH, C-21), 135.8 (C, C-1), 143.1 (CH, C-

17), 202.1 (C, C-2); *m/z* HRMS (ES^+) found 327.2305 $[M+Na]^+$ $C_{20}H_{32}O_2Na$ requires 327.2300; (ES^+) 327.1 ($[M+Na]^+$, 100%).

(4*Z*)-1,1-Dimethoxy-4-heptene 323



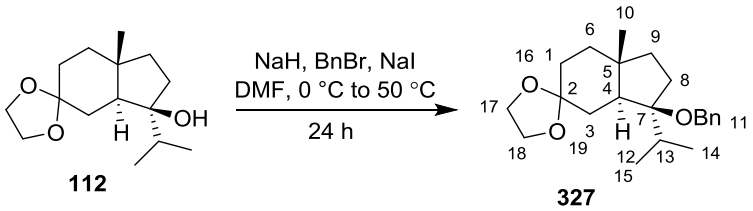
314 **323**

A known compound prepared according to a literature procedure.[125]

Trimethyl orthoformate (0.48 mL, 4.45 mmol) and *p*-TSA (15.2 mg, 0.08 mmol) were added to a solution of **314** (100 mg, 0.89 mmol) in MeOH (0.6 mL). The reaction mixture was stirred at rt for 16 h. $NaHCO_3$ (4 mL of a saturated aq. solution) and DCM (10 mL) were added, the layers were separated and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 7:3) to give **323** as a colourless oil (900 mg, 63%). R_f 0.67 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2959 (w), 2829 (w), 1703 (s), 1123 (s), 1060 (s); δ_H(400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.5 Hz, H-9), 1.58-1.65 (2H, m, H-4), 1.97-2.10 (4H, m, 2 × C*H*$_2$), 3.29 (6H, s, H-1 and H-3), 4.34 (1H, t, *J* 5.8 Hz, H-2), 5.24-5.40 (2H, m, H-6 and H-7); δ_C(100 MHz, $CDCl_3$) 14.7 (CH_3, C-9), 20.9 (CH_2), 22.8 (CH_2), 32.9 (CH_2), 53.1 (2 × CH_3, C-1 and C-3), 104.5 (CH, C-2), 128.5 (CH, =CH), 132.8 (CH, =CH).

Analytical data in agreement with literature values.[125]

(3*S*, 3a*S*, 7a*S*)-3-Benzyloxy-3-*iso*-propyl-7a-methyloctahydrospire-[[1,3]dioxolane- 2,5-inden]-3-ol 327

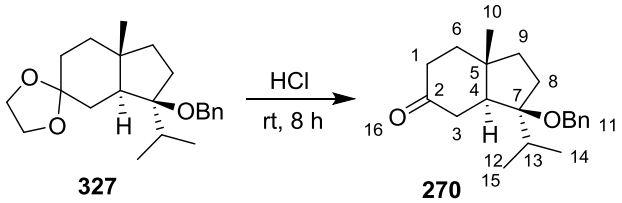


A novel compound prepared by a modification of a literature procedure.[126]

NaH (60% dispersion in mineral oil, 67.5 mg, 1.76 mmol) was added to a solution of **112** (300 mg, 1.18 mmol) in DMF (4 mL) at 0 °C and the reaction mixture was stirred at rt for 1 h. Benzyl bromide (0.24 mL, 2.0 mmol) and NaI (88.0 mg, 0.59 mmol) were added sequentially to the reaction mixture at 0 °C and the resulting mixture was heated at 50 °C. After 24 h, the reaction mixture was diluted with EtOAc (5 mL), quenched with H_2O (8 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 9:1) afforded **327** as a white solid (340 mg, 83%); m.p. 69-75 °C. $[\alpha]_D^{25}$= -49° ($CHCl_3$, *c* 1.5); R_f 0.64 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2947 (w), 2869 (w), 1457 (m), 1081 (s), 738 (s); δ_H(400 MHz, $CDCl_3$) 0.89, 0.91 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 1.01 (3H, s, H-10), 1.09 (1H, m, 1H of C*H*$_2$), 1.36 (1H, td, *J* 13.3 and 4.6 Hz, 1H of C*H*$_2$), 1.56-1.60 (3H, m, C*H*$_2$ and 1H of C*H*$_2$), 1.71-1.88 (5H, m, H-12 and 2 × C*H*$_2$), 2.10 (1H, m, 1H of C*H*$_2$), 2.21 (1H, septet, *J* 6.8 Hz, H-13), 3.89-3.93 (4H, m, H-17 and H-18), 4.37 (2H, s, OC*H*$_2$CAr), 7.13-7.36 (5H, m, 5 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 18.0 (2 × CH_3, C-14 and C-15), 18.3 (CH_3, C-10), 31.6 (CH_2), 32.8 (CH, C-13), 33.6 (CH_2), 34.2 (CH_2), 36.7 (CH_2), 39.3 (CH_2), 40.0 (C, C-5), 48.2 (CH, C-4), 62.3 (CH_2, O*C*H$_2$CAr), 64.1 (CH_2, C-17), 64.2 (CH_2, C-18), 87.4 (C,

C-7), 110.9 (C, C-2), 126.5 (2 × CH, *C*HAr), 126.6 (CH, *C*HAr), 128.0 (2 × CH, *C*HAr), 140.2 (C, *C*Ar); *m/z* HRMS (ES^+) found 367.2245 $[M+Na]^+$ $C_{22}H_{32}O_3Na$ requires 367.2249; (ES^+) 367.2 ($[M+Na]^+$, 86%).[129]

(3*S*, 3a*S*, 7a*S*)-3-Benzyloxy-3-*iso*-propyl-7a-methyloctahydro-5*H*-inden-5-one 270

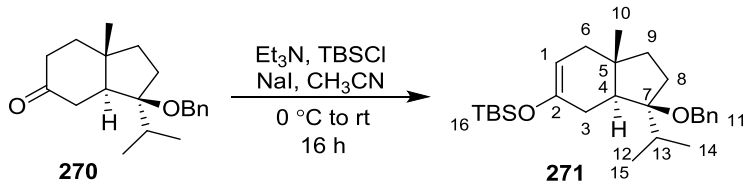


A novel compound prepared by a modification of a literature procedure.[32]

HCl (12 mL of a 1.0 M aq. solution) was added to a solution of acetal **327** (0.34 g, 0.98 mmol) in THF (20 mL). The reaction mixture was stirred at rt for 8 h, then the resulting solution was quenched with $NaHCO_3$ (20 mL of a saturated aq. solution) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 7:3) to give **270** as a white solid (0.26 g, 77%); m.p. 68-71 °C. $[\alpha]_D^{25}$= -18.7° ($CHCl_3$, *c* 2.0); R_f 0.42 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2944 (w), 2864 (w), 1704 (s), 1454 (w), 1047 (s), 698 (s); δ_H(400 MHz, $CDCl_3$) 0.86, 0.89 (6H, 2 × d, *J* 6.8 Hz, H-14 and H-15), 1.15 (3H, s, H-10), 1.20 (1H, br q, *J* 10.7 Hz, 1H of CH_2), 1.51 (1H, td, *J* 12.6 and 6.2 Hz, 1H of CH_2), 1.65 (1H, dd, *J* 11.9 and 7.8 Hz, 1H of CH_2), 1.74-1.89 (3H, m, H-12 and CH_2), 2.16-2.46 (5H, m, 2 × CH_2 and H-13), 2.71 (1H, dd, *J* 16.2 and 14.4 Hz, 1H of CH_2), 4.36 (2H, s, OCH_2CAr), 7.19 (1H, m, C*H*Ar), 7.26-7.29 (4H, m, 4 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 17.8 (CH_3, C-10), 18.5 (2 × CH_3, C-14 and C-15), 33.3 (CH, C-13), 35.3 (CH_2), 37.5 (CH_2), 38.0 (CH_2),

40.2 (CH_2), 41.8 (CH_2), 42.1 (C, C-5), 49.9 (*C*H, C-4), 62.9 (*C*H_2, O*C*H_2CAr), 87.6 (C, C-7), 127.1 (2 × CH, *C*HAr), 127.3 (CH, *C*HAr), 128.6 (2 × CH, *C*HAr), 140.1 (C, *C*Ar), 213.9 (C, C-2); *m/z* HRMS (ES^+) found 323.1985 $[M+Na]^+$ $C_{20}H_{28}O_2Na$ requires 323.1987; (ES^+) 323.1 ($[M+Na]^+$, 85%).

(±)-(((3*S*, 3a*S*, 7a*S*)-3-Benzyloxy-3-*iso*-propyl-7a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl)oxy)(*tert*-butyl)dimethylsilane 271

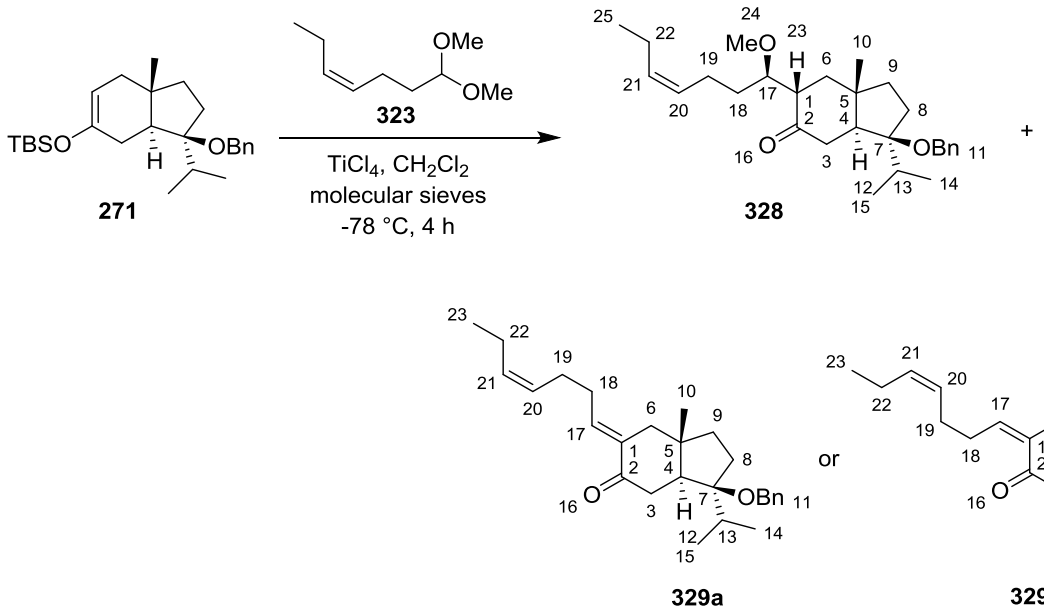


A novel compound prepared by a modification of a literature procedure.[127]

Triethylamine (84 µL, 0.60 mmol), TBSCl (90 mg, 0.60 mmol) and NaI (90 mg, 0.60 mmol) were sequentially added to a solution of **270** (120 mg, 0.40 mmol) in CH_3CN (0.8 mL) at 0 °C. The reaction mixture was stirred at rt for 16 h, then quenched with $NaHCO_3$ (4 mL of a saturated aq. solution) and extracted with Et_2O (2 × 5 mL). The combined organic extracts was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 9:1) to give **271** as a pale yellow oil (140 mg, 84%). R_f 0.64 (pet ether/EtO_2 1:1); ν_{max}(neat)/cm^{-1}: 2940 (w), 2894 (w), 2865 (w), 1705 (s), 1047 (m), 698 (s); δ_H(400 MHz, $CDCl_3$) 0.13, 0.14 (6H, 2 × s, Si(C*H*$_3$)$_2$), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.94, 0.97 (6H, 2 × d, *J* 1.9 Hz, H-14 and H-15, 1.02 (3H, s, H-10), 1.22 (1H, m, 1H of C*H*$_2$), 1.60-1.76 (2H, m, 1H of C*H*$_2$ and H-12), 1.79-2.03 (4H, m, 2 × C*H*$_2$), 2.20 (1H, m, 1H of C*H*$_2$), 2.27 (1H, septet, *J* 6.9 Hz, H-13), 2.47 (1H, m, 1H of C*H*$_2$), 4.44 (2H, s, OC*H*$_2$CAr), 4.78 (1H, dt, *J* 5.8 and 2.4 Hz, H-1), 7.21-7.38 (5H, m, C*H*Ar); δ_C(100 MHz,

$CDCl_3$) -3.9 (CH_3, Si(CH_3)), -3.7 (CH_3, Si(CH_3)), 18.0 (CH_3), 18.6 (CH_3), 19.2 (CH_3), 26.2 (3 × CH_3, SiC(CH_3)$_3$), 30.7 (CH_2), 32.1 (C, SiC(CH_3)$_3$), 33.6 (CH, C-13), 35.5 (CH_2), 39.0 (CH_2), 40.3 (CH_2), 41.0 (C, C-5), 47.4 (CH, C-4), 62.8 (CH_2, ArCCH$_2$O), 87.6 (C, C-7), 103.8 (CH, C-1), 127.0 (2 × CH, CHAr), 127.3 (CH, CHAr), 128.5 (2 × CH, CHAr), 140.7 (C, CAr), 152.0 (C, C-2); *m*/*z* LRMS (ES^+) found 323.3 ([M-TMS+Na]$^+$, 71%) $C_{20}H_{28}O_2$ requires 372.62.

(±)-(3*S*, 3a*S*, 6*S*, 7a*S*)-3-(Benzyloxy)-3-*iso*-propyl-6-((*S*, *Z*)-1-methoxyhept-4-en-1-yl)-7a-methyloctahydro-5*H*-inden-5-one 328 and (±)-(3*S*, 3a*S*, 7a*S*, *E*)-3-(Benzyloxy)-6-((*Z*)-hept-4-en-1-ylidene)-3-*iso*-propyl-7a-methyloctahydro-5*H*-inden-5-one 329



Novel compounds prepared according to a literature procedure.[125]

$TiCl_4$ (3.6 µL of a 1.0 M soln. in CH_2Cl_2, 3.6 µmol) was added dropwise over 10 min to a solution of **323** (30 mg, 0.07 mmol) and **271** (12 mg, 0.07 mmol) in CH_2Cl_2 (1.3 mL) in the

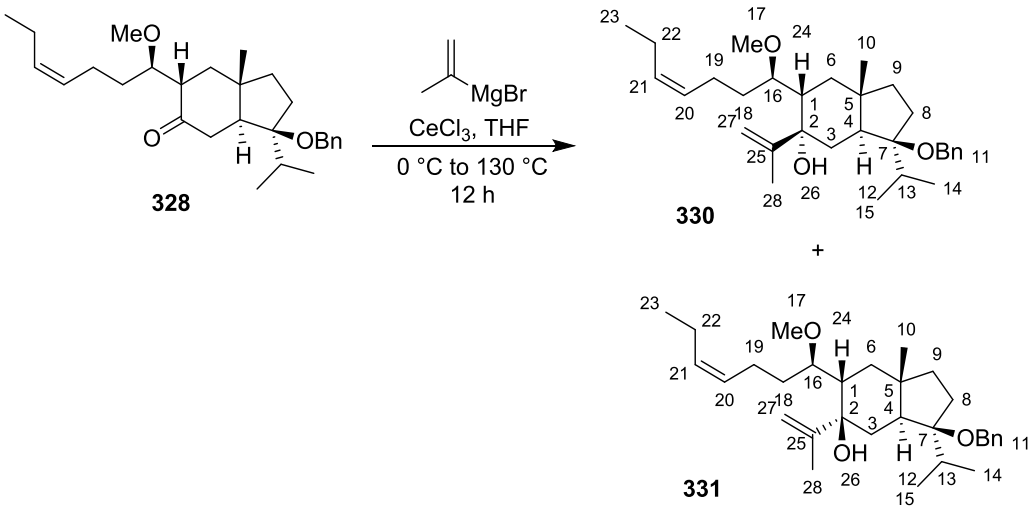
presence of pulverized 3 Å molecular sieves at -78 °C. The reaction mixture was stirred at -78 °C for 4 h, quenched with $NaHCO_3$ (4 mL of a saturated aq. solution) and filtered through a celite pad. The filtrate was extracted with CH_2Cl_2 (3 × 8 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (pet ether/Et_2O 8:2) to give **328** as a colourless oil (20 mg, 70%) followed by **329a** or **329b** as a colourless oil (6 mg, 21%).

Analytical data for **328**: R_f 0.65 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2960 (m), 2834 (m), 1710 (s), 1455 (m), 1087 (s), 1064 (s); δ_H(400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 6.8 Hz, H-25), 0.89, 0.94 (6H, 2 × d, *J* 2.7 Hz, H-14 and H-15), 1.09 (3H, s, H-10), 1.19-1.39 (2H, m, C*H*$_2$), 1.56-1.72 (3H, m, C*H*$_2$ and H-13), 1.76-1.89 (3H, m, H-12 and C*H*$_2$), 1.93-2.03 (4H, m, 2 × C*H*$_2$), 2.17-2.32 (3H, m, H-23 and C*H*$_2$), 2.48 (1H, m, 1H of C*H*$_2$), 2.68 (1H, m, 1H of C*H*$_2$), 3.26 (3H, s, H-24), 3.91 (1H, td, *J* 7.2 and 2.4 Hz, H-17), 4.37 (2H, s, OC*H*$_2$CAr), 5.22-5.39 (2H, m, H-20 and H-21), 7.19-7.29 (5H, m, 5 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 14.1 (CH_3, C-25), 17.5 (CH_3, C-14), 17.9 (CH_3, C-15), 18.4 (CH_3, C-10), 20.3 (CH_2), 23.5 (CH_2), 31.5 (CH_2), 32.6 (CH_2), 34.4 (CH_2), 35.3 (CH, C-13), 36.1 (CH_2), 39.9 (CH_2), 40.8 (CH_2), 41.3 (CH_2), 41.3 (C, C-5), 47.9 (CH, C-12), 49.0 (CH, C-1), 58.2 (CH_3, C-24), 62.2 (CH_2, O*C*H_2CAr), 78.8 (CH, C-17), 87.3 (C, C-7), 126.4 (2 × CH, *C*HAr), 126.5 (2 × CH, *C*HAr), 128.0 (CH, *C*HAr), 132.0 (2 × CH, C-20 and C-21), 139.5 (C, *C*Ar), 212.8 (C, C-2); *m*/*z* HRMS (ES^+) found 449.3031 $[M+Na]^+$ $C_{28}H_{42}O_3Na$ requires 449.3032; (ES^+) 449.3 ($[M+Na]^+$, 100%)

Analytical data for **329a** or **329b** with an undetermined geometry of the double bond: R_f 0.48 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 2957 (m), 2928 (m), 1684 (s), 1063 (s), 696 (s); δ_H(400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.8 Hz, H-23), 0.97, 0.99 (6H, 2 × d, *J* 2.7 Hz, H-14 and H-15), 1.01

(3H, s, H-10), 1.21-1.34 (2H, m, CH_2), 1.74 (1H, dd, *J* 11.8 and 7.6 Hz, H-12), 1.89-1.95 (4H, m, 2 × CH_2), 1.97-2.04 (2H, m, CH_2), 2.09-2.33 (4H, m, 2 × CH_2), 2.51 (1H, m, 1H of CH_2), 2.86 (1H, m, 1H of CH_2), 4.42 (2H, s, CH_2OCAr), 5.27-5.43 (2H, m, H-20 and H-21), 6.75 (1H, m, H-17), 7.19-7.35 (5H, m, 5 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 14.1 (CH_3, C-23), 17.3 (CH_3, C-14), 17.8 (CH_3, C-15), 19.0 (CH_3, C-10), 25.7 (CH_2), 28.1 (CH_2), 29.5 (CH_2), 30.1 (CH_2), 32.7 (CH_2), 34.7 (CH, C-13) , 38.5 (C, C-5), 40.0 (CH_2), 40.3 (CH_2), 46.0 (CH, C-12), 62.3 (CH_2, O*C*H_2CAr), 87.3 (C, C-7), 126.4 (2 × CH, *C*HAr), 126.6 (2 × CH, *C*HAr), 126.8 (CH, *C*HAr), 132.6 (CH, C-20), 132.9 (CH, C-21), 134.7(C, C-1), 139.5 (CH, C-17), 141.6 (C, *C*Ar), 201.5 (C, C-2); *m*/*z* HRMS (ES^+) found 417.2774 $[M+Na]^+$ $C_{27}H_{38}O_2Na$ requires 417.2770; (ES^+) 417.2 ($[M+Na]^+$, 81%).

(±)-(3*S*, 3a*S*, 5*S*, 6*S*, 7a*S*)-3-(Benzyloxy)-3-*iso*-propyl-6-((*R*,*Z*)-1-methoxyhept-4-en-1-yl)-7a-methyl-5-(prop-1-en-2-yl)octahydro-1*H*-inden-5-ol 330 and (±)-(3*S*, 3a*S*, 5*R*, 6*S*, 7a*S*)-3-(Benzyloxy)-3-*iso*-propyl-6-((*R*,*Z*)-1-methoxyhept-4-en-1-yl)-7a-methyl-5-(prop-1-en-2-yl)octahydro-1*H*-inden-5-ol 331

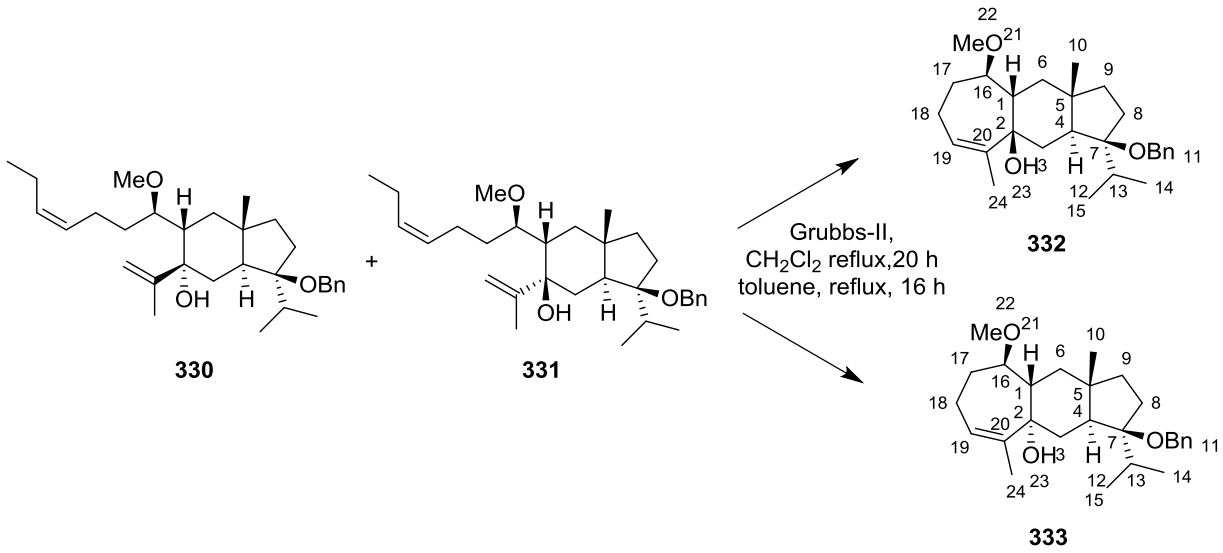


Novel compounds prepared by a modification of a literature procedure.[109]

THF (0.5 mL) was added to the vigorously stirred anhydrous $CeCl_3$ (100 mg, 0.26 mmol) to form a uniform milky suspension which was stirred for 2 h at rt. The suspension was cooled to 0 °C and *iso*-propenylmagnesium bromide (1.2 mL, 0.35 mmol) was added dropwise over 15 min to form an off-white suspension. The resulting suspension was stirred for 1 h when **328** (50 mg, 0.11 mmol) in THF (1.2 mL) was added dropwise over 5 min followed by heating at 130 °C in the microwave for 8 h. The reaction mixture was quenched with NH_4Cl (4 mL of a 5% aq. solution) and extracted with Et_2O (3 × 5 mL). The organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether/Et_2O 8:2) gave a mixture of inseparable diastereoisomers **330** and **331** as a colourless oil (22 mg, 42%). R_f 0.64 (pet ether/Et_2O 1:1); ^1H NMR indicates that two diastereomers exist in 1.6:1 ratio. The data for the major diastereoisomer is reported. ν_{max}(neat)/cm^{-1}: 3447 (br), 2935 (w), 1454 (s), 1386 (s), 1080 (s); δ_H(400 MHz, $CDCl_3$) 1.06 (3H, t, *J* 6.8 Hz, H-23), 1.14, 1.17 (6H, 2 × d, *J* 2.7 Hz, H-14 and H-15), 1.20 (3H, s, H-10), 1.31-1.38 (4H, m, 2 × C*H*$_2$), 1.50-1.75 (3H, m, H-13 and C*H*$_2$), 1.89 (3H, s, H-28), 2.04-2.20 (4H, m, 2 × C*H*$_2$), 2.21-2.34 (3H, m, C*H* and C*H*$_2$), 2.35-2.46 (2H, m, C*H*$_2$), 3.27 (1H, ddd, *J* 8.1. 4.2 and 2.3 Hz, H-24), 3.43 (3H, s, H-17), 3.61 (1H, ddd, *J* 10.2, 4.4 and 1.9 Hz, H-16), 4.55 (2H, s, OC*H*$_2$CAr), 4.81 (1H, d, *J* 2.2 Hz, 1H of H-27), 5.06 (1H, d, *J* 2.2 Hz, 1H of H-27), 5.39-5.54 (2H, m, H-20 and H-21), 7.34-7.49 (5H, m, 5 × C*H*Ar); δ_C(100 MHz, $CDCl_3$) 13.9 (CH_3), 14.3 (CH_3, C-23), 17.8 (CH_3), 18.0 (CH_3), 18.3 (CH_3), 20.1 (CH_2), 22.7 (CH_2), 23.7 (CH_2), 28.7 (CH_2), 32.0 (CH_2), 32.2 (CH, *C*H(CH_3)$_2$), 33.2 (CH_2), 33.6 (CH_2), 41.1 (C, C-5), 41.4 (CH, C-1), 44.3 (CH, C-12), 55.6 (CH_3, C-17), 62.3 (CH_2, O*C*H$_2$CAr), 84.9 (CH, C-16), 87.9 (C, C-2), 110.2 (CH_2, C-27), 126.1 (CH, *C*HAr), 126.2 (2 × CH, *C*HAr), 127.4 (2 × CH, *C*HAr), 131.4, 132.0 (2 ×

CH, C-20 and C-21), 141.0 (C, *C*Ar), 151.9 (C, C-25); *m*/*z* HRMS (ES^+) found 491.3494 $[M+Na]^+$ $C_{31}H_{48}O_3Na$ requires 491.3501; (ES^+) 491.3 ($[M+Na]^+$, 100%).

(±)-(3*S*, 3a*S*, 4a*R*, 9*R*, 9a*S*, 10a*S*)-3-(Benzyloxy)-3-*iso*-propyl-9-methoxy-5,10a-dimethyl-2,3,3a,4,7,8,9,9a,10,10a-decahydrocyclohepta[*f*]inden-4a(1*H*)-ol 332 and (±)-(3*S*, 3a*S*, 4a*S*, 9*R*, 9a*S*, 10a*S*)-3-(Benzyloxy)-3-*iso*-propyl-9-methoxy-5,10a-dimethyl-2,3,3a,4,7,8,9,9a,10,10a-decahydrocyclohepta[*f*]inden-4a(1*H*)-ol 333



Novel compounds prepared by a modification of a literature procedure.[128]

A solution of Grubbs-II catalyst (3.7 mg, 4.4 µmol) in CH_2Cl_2 (0.2 mL) was added dropwise over 10 min to a stirred solution of a mixture of diastereomers **330** and **331** (21 mg, 40 µmol) in CH_2Cl_2 (2.0 mL) under reflux. The reaction mixture was heated at reflux for 20 h before being cooled to rt. The solvent was removed under reduced pressure and replaced with toluene (2.5 mL) and the resulting mixture was stirred at 90 °C for 16 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (pet ether/Et_2O 8:2)

to afford **332** as a translucent semi-solid (10 mg, 55%) followed by **333** as a colourless oil (6.0 mg, 33%).

Analytical data for major diastereoisomer **333**; $[\alpha]_D^{25}$= -33.8° (chloroform, *c* 1.0); R_f 0.63 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3496 (br), 2927 (w), 1454 (m), 1086 (s), 729 (s), 695 (s); δ_H(400 MHz, $CDCl_3$) 1.01, 1.03 (6H, 2 × d, *J* 6.4 Hz, H-14 and H-15), 1.05 (3H, s, H-10), 1.11 (1H, s, OH), 1.23 (1H, m, 1H of C*H*$_2$), 1.54-1.68 (3H, m, C*H*$_2$ and 1H of C*H*$_2$), 1.76 (3H, s, H-24), 1.72-1.76 (3H, m, H-21 and 2 × H-6), 1.84 (1H, dd, *J* 5.8 and 12.3 Hz, H-12), 1.87-1.96 (2H, m, C*H*$_2$), 2.17 (1H, m, 1H of H-18), 2.28 (1H, septet, *J* 6.8 Hz, H-13), 2.60 (1H, m, 1H of H-18), 3.31 (3H, s, H-22), 3.42 (1H, m, H-16), 4.41 (2H, s, CArC*H*$_2$O), 5.43 (1H, dd, *J* 2.8 and 1.6 Hz, H-19), 7.22 (1H, m, C*H*Ar), 7.29-7.35 (4H, m, C*H*Ar); δ_C(100 MHz, $CDCl_3$) 17.8 (CH_3), 18.4 (CH_3), 18.6 (CH_3), 19.1 (CH_3), 32.8 (CH_2), 33.0 (CH, C-13), 33.5 (C, C-5), 33.7 (CH_2), 33.9 (CH_2), 37.3 (CH_2), 40.6 (CH_2), 42.0 (CH_2), 44.6 (CH, C-4), 45.3 (CH, C-1), 56.9 (CH_3, C-22), 62.7 (CH_2, CAr*C*H_2O), 73.6 (C, C-2), 76.5 (CH, C-16), 88.2 (C, C-7), 122.9 (CH, C-19), 126.6 (2 × CH, *C*HAr), 126.9 (CH, *C*HAr), 128.4 (2 × CH, *C*HAr), 139.2 (C, C-20), 140.3 (C, *C*Ar); *m/z* HRMS (ES^+) found 435.2874 $[M+Na]^+$ $C_{27}H_{40}O_3Na$ requires 435.2875; (ES^+) 435.2 $[M+Na]^+$, 100%).

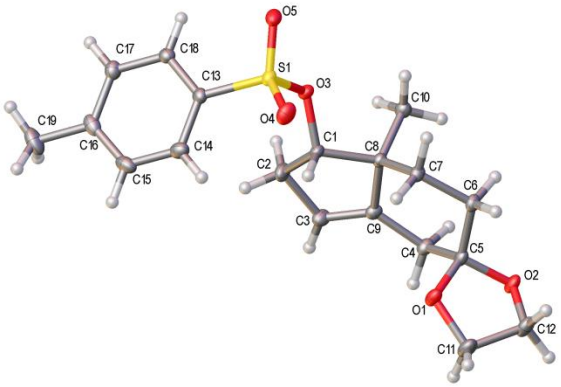
Analytical data for minor diastereoisomer **332**; $[\alpha]_D^{25}$= -23.1° (chloroform, *c* 1.0); R_f 0.47 (pet ether/Et_2O 1:1); ν_{max}(neat)/cm^{-1}: 3472 (br), 2925 (w), 1453 (m), 1087 (s), 1055 (s), 730 (s), 695 (s); δ_H(400 MHz, $CDCl_3$) 0.99, 1.01 (6H, 2 × d, *J* 4.0 Hz, H-14 and H-15), 1.05 (3H, s, H-10), 1.12 (1H, s, OH), 1.25 (1H, m, 1H of C*H*$_2$), 1.59-1.70 (3H, m, C*H*$_2$ and 1H of C*H*$_2$), 1.73 (3H, s, H-24), 1.74-1.81 (3H, m, H-21 and 2 × H-6), 1.84-1.93 (2H, m, H-3), 1.97 (1H, dd, *J* 5.7 and 12.3 Hz, H-12), 2.21 (1H, m, 1H of H-18), 2.30 (1H, septet, *J* 6.8 Hz, H-13), 2.60 (1H, m, H-18), 3.35 (3H, s, H-22), 3.38 (1H, m, H-16), 4.43 (2H, s, CArC*H*$_2$O), 5.40 (1H, dd, *J* 2.8 and 1.6 Hz, H-

19), 7.22 (1H, m, C*H*Ar), 7.29-7.35 (4H, m, C*H*Ar); δ_C(100 MHz, $CDCl_3$) 17.8 (CH_3), 18.4 (CH_3), 18.6 (CH_3), 19.1 (CH_3), 32.8 (CH_2), 33.0 (CH, C-13), 33.5 (C, C-5), 33.7 (CH_2), 33.9 (CH_2), 37.3 (CH_2), 40.6 (CH_2), 42.0 (CH_2), 44.6 (CH, C-4), 45.3 (CH, C-1), 56.9 (CH_3, C-22), 62.7 (CH_2, CAr*C*H_2O), 73.6 (C, C-2), 76.5 (CH, C-16), 88.2 (C, C-7), 122.9 (CH, C-19), 126.6 (2 × CH, *C*HAr), 126.9 (CH, *C*HAr), 128.4 (2 × CH, *C*HAr), 139.2 (C, C-20), 140.3 (C, *C*Ar); *m/z* HRMS (ES^+) found 435.2854 $[M+Na]^+$ $C_{27}H_{40}O_3Na$ requires 435.2875; (ES^+) 435.2 ($[M+Na]^+$, 60%).

Appendices

Appendix A

Crystal data and structure refinement for SA-152.

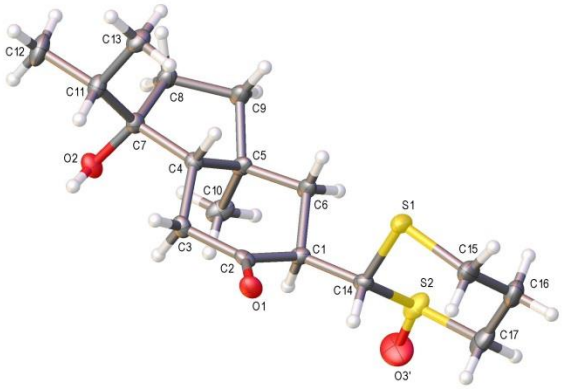


Crystal obtained from slow evaporation of CH_2Cl_2/hexane (1:1)

Identification code	SA-152	
Empirical formula	$C_{19}H_{24}O_5S$	
Formula weight	364.44	
Temperature	100.00(10) K	
Wavelength	1.5418 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 27.0507(2) Å	α= 90°.
	b = 5.81680(10) Å	β= 106.5740(10)°.
	c = 23.3541(2) Å	γ = 90°.
Volume	3522.05(7) $Å^3$	
Z	8	
Density (calculated)	1.375 Mg/m^3	
Absorption coefficient	1.866 mm^{-1}	
F(000)	1552	
Crystal size	0.200 x 0.110 x 0.090 mm^3	
Theta range for data collection	3.409 to 73.956°.	
Index ranges	-33<=h<=33, -7<=k<=7, -29<=l<=29	
Reflections collected	59850	
Independent reflections	3572 [R(int) = 0.0266]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	1.00000 and 0.68543
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3572 / 0 / 228
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0297, wR2 = 0.0792
R indices (all data)	R1 = 0.0302, wR2 = 0.0797
Extinction coefficient	n/a
Largest diff. peak and hole	0.451 and -0.414 e.$Å^{-3}$

Crystal data and structure refinement for SA-310

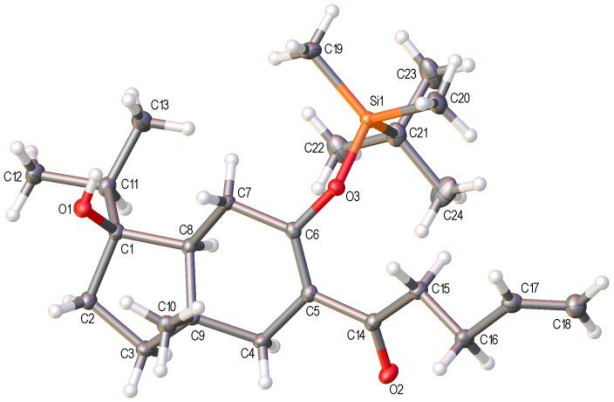


Crystal obtained from slow evaporation of CH_2Cl_2/hexane (1:1)

Identification code	SA6-310
Empirical formula	$C_{17}H_{28}O_{2.11}S_2$
Formula weight	330.27
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	11.7260(2)
b/Å	6.36011(12)
c/Å	11.7706(2)
α/°	90
β/°	91.5160(17)
γ/°	90
Volume/$Å^3$	877.52(3)
Z	2
$\rho_{calc}g/cm^3$	1.250
μ/mm^{-1}	0.307
F(000)	358.0
Crystal size/mm^3	0.309 × 0.1298 × 0.0918
Radiation	MoKα (λ = 0.71073)
2Θ range for data	4.84 to

collection/°	52.728
Index ranges	-14 ≤ h ≤ 14, -7 ≤ k ≤ 7, -14 ≤ l ≤ 14
Reflections collected	18073
Independent reflections	3569 [R_{int} = 0.0331, R_{sigma} = 0.0260]
Data/restraints/parameters	3569/1/207
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0293, wR_2 = 0.0684
Final R indexes [all data]	R_1 = 0.0317, wR_2 = 0.0699
Largest diff. peak/hole / e $Å^{-3}$	0.27/-0.17
Flack parameter	-0.02(2)

Crystal data and structure refinement for SA-294

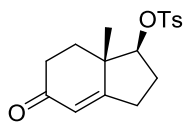


Crystal obtained from slow evaporation of CH_2Cl_2/hexane (1:1)

Identification code	SA-294
Empirical formula	$C_{24}H_{42}O_3Si$
Formula weight	406.66
Temperature/K	99.98(14)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.93099(14)
b/Å	13.9060(3)
c/Å	21.5613(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2377.97(7)
Z	4
ρ_{calc}g/cm^3	1.136
μ/mm^{-1}	1.021
F(000)	896.0
Crystal size/mm^3	0.1635 × 0.1413 × 0.0436
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.564 to 148.744
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 16, -26 ≤ l ≤ 26
Reflections collected	9002
Independent reflections	4701 [R_{int} = 0.0224, R_{sigma} = 0.0305]

Data/restraints/parameters	4701/0/265
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0278, wR_2 = 0.0681
Final R indexes [all data]	R_1 = 0.0297, wR_2 = 0.0696
Largest diff. peak/hole / e $Å^{-3}$	0.25/-0.23
Flack parameter	0.010(11)

Appendix B



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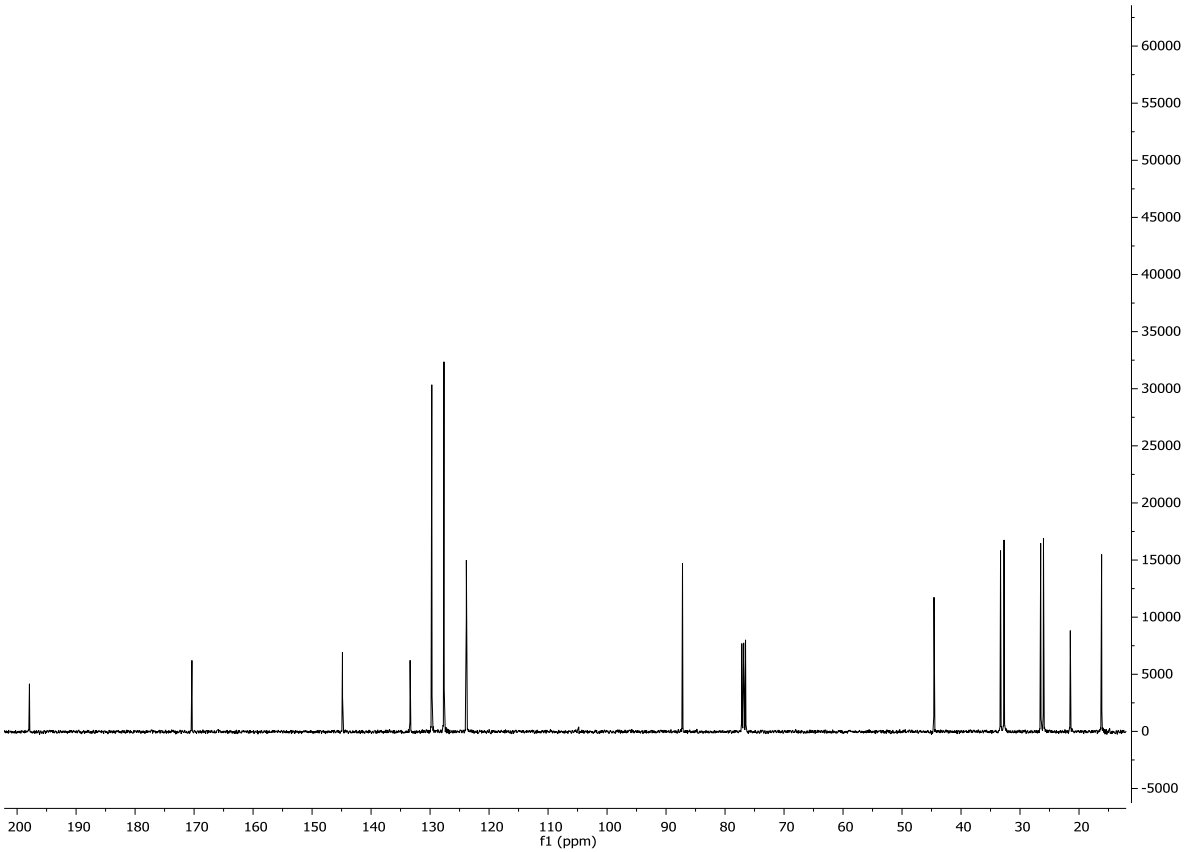

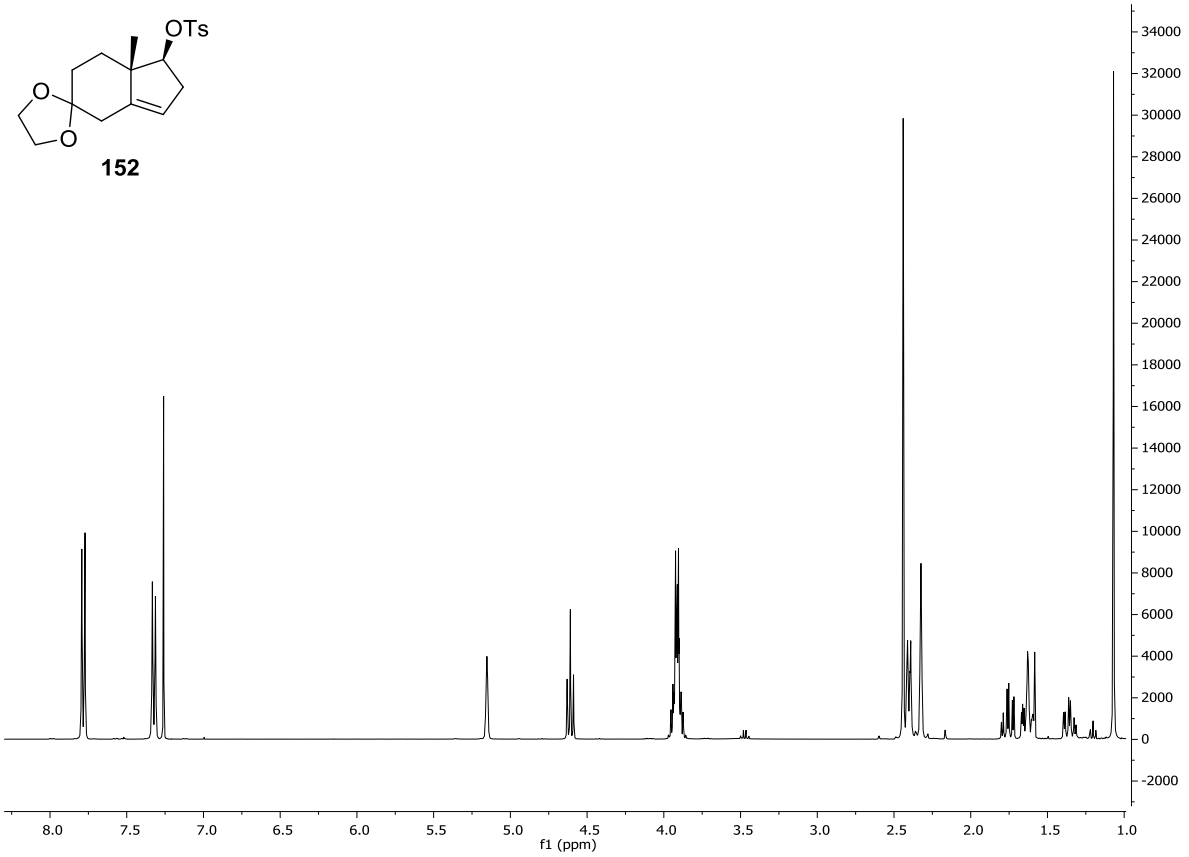
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152
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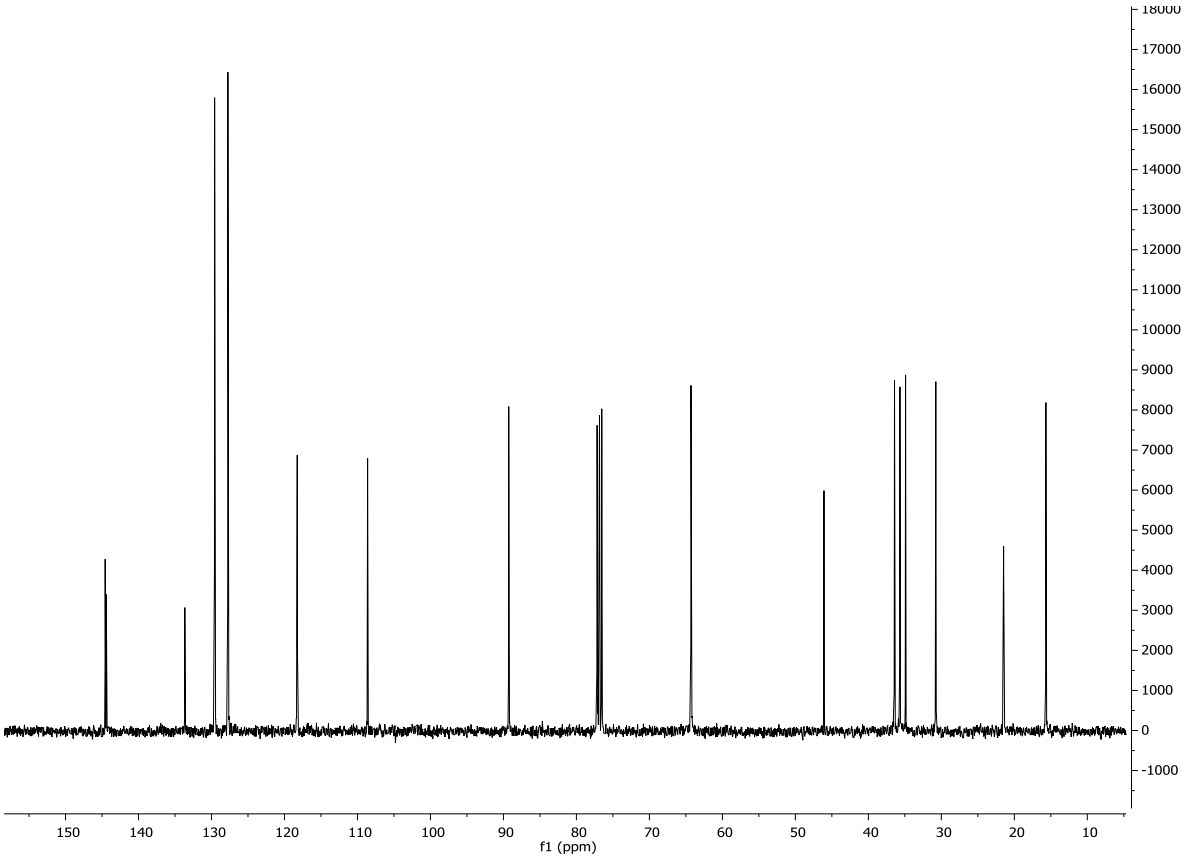
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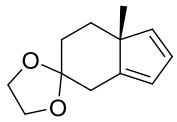

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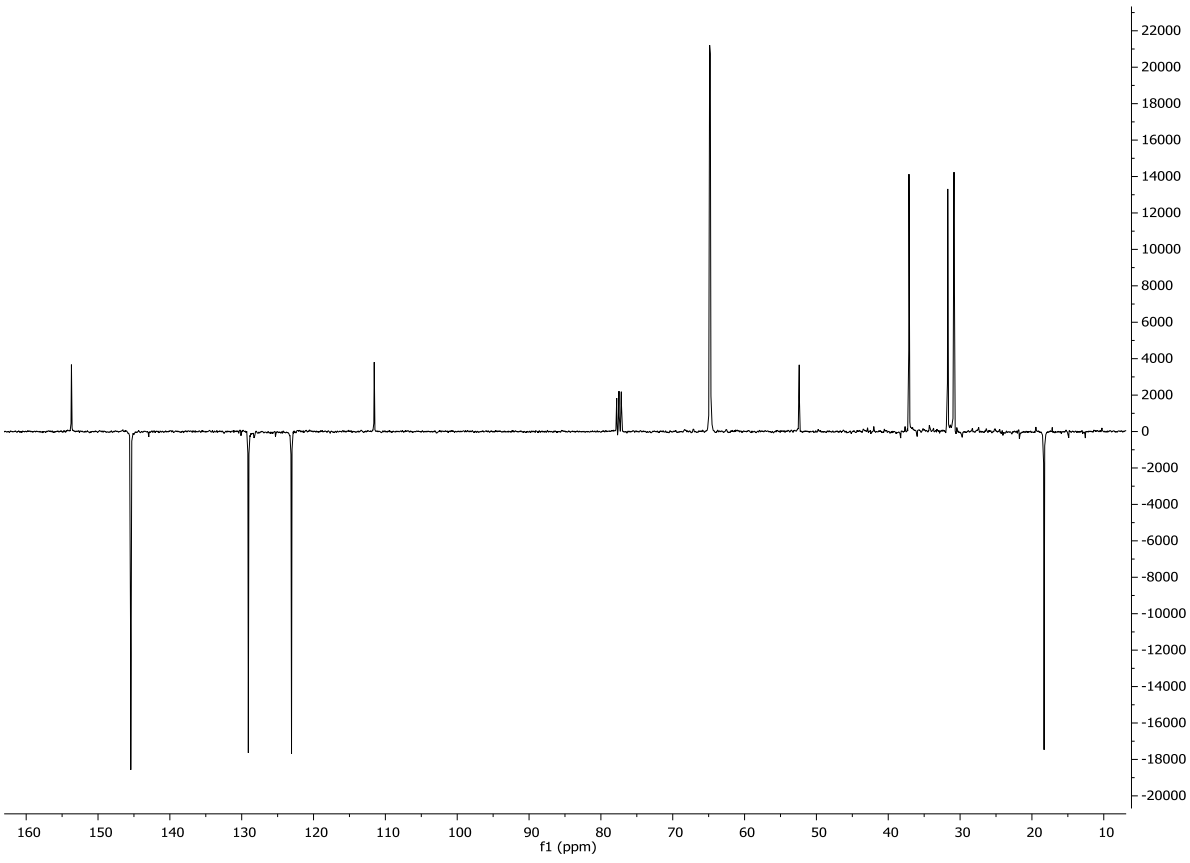
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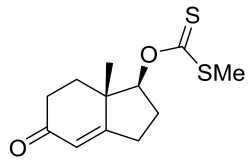
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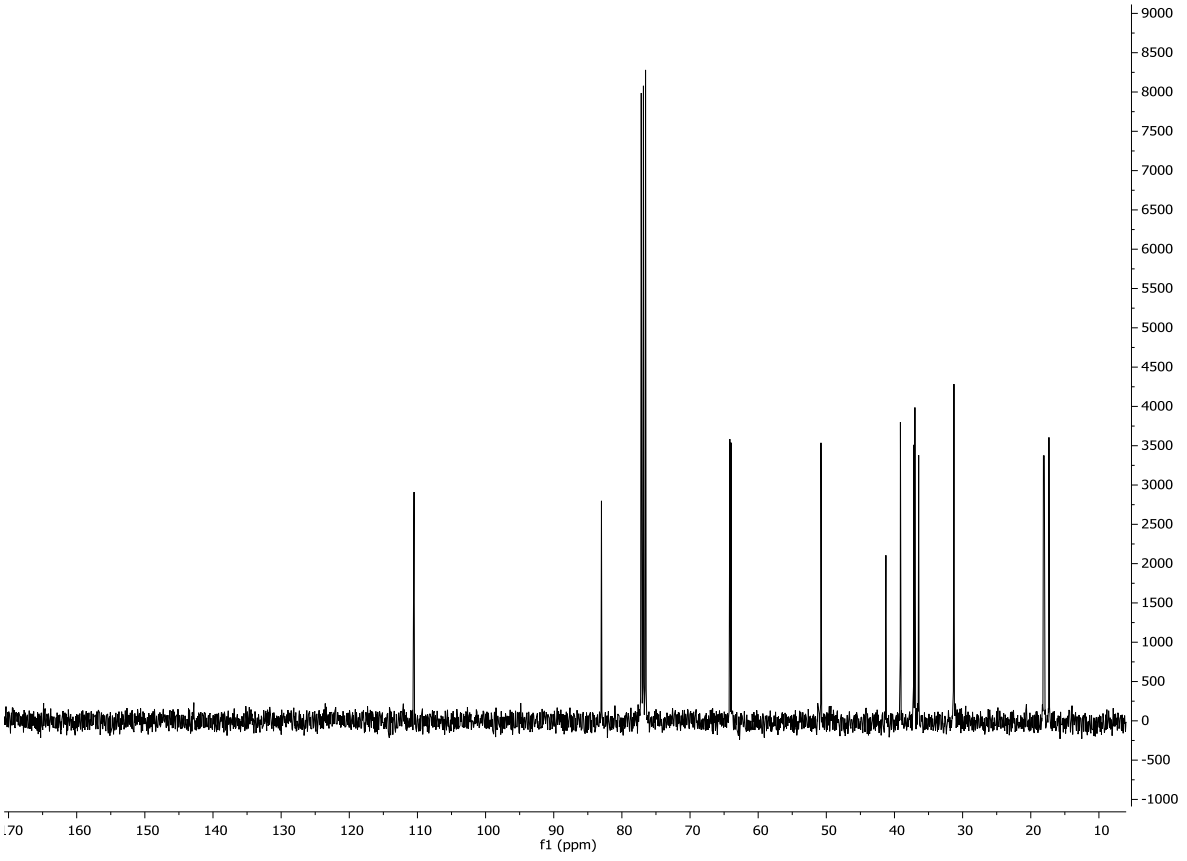
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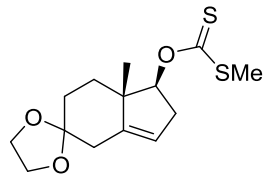
f1 (ppm)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O
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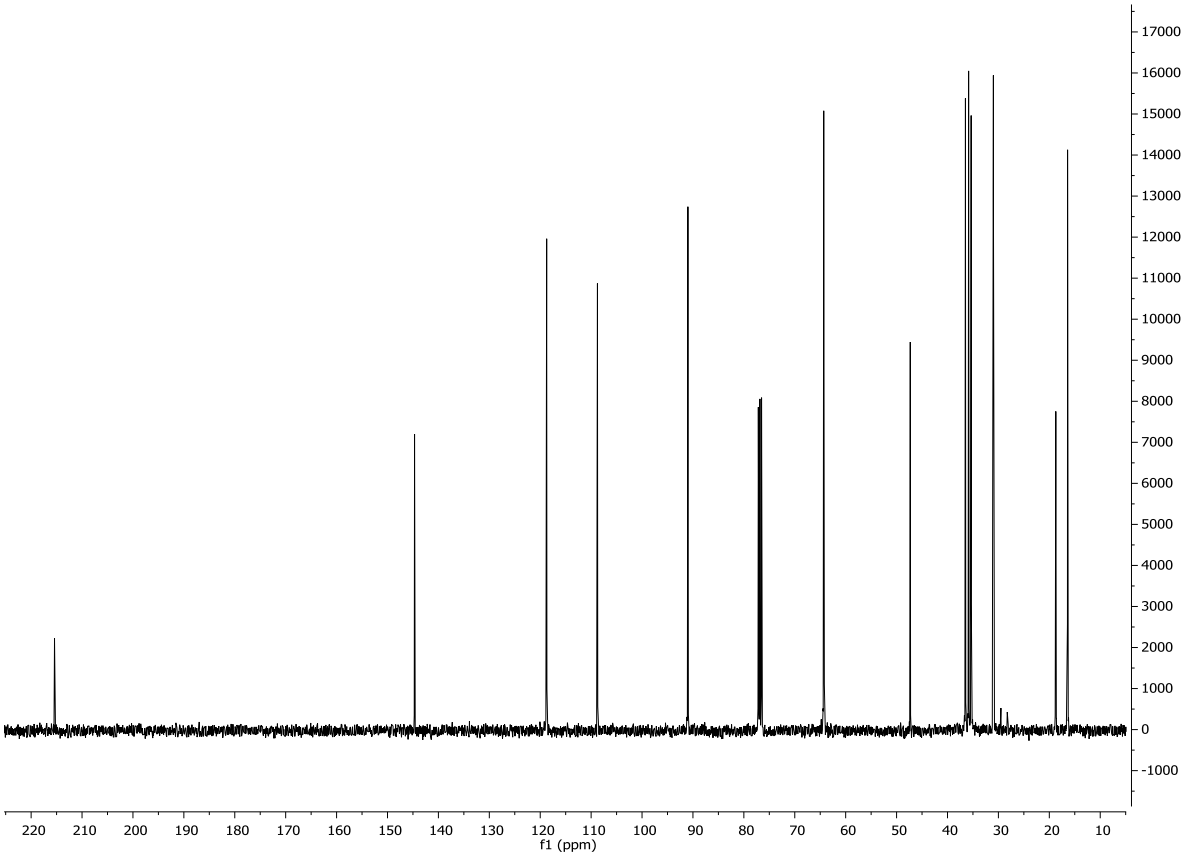
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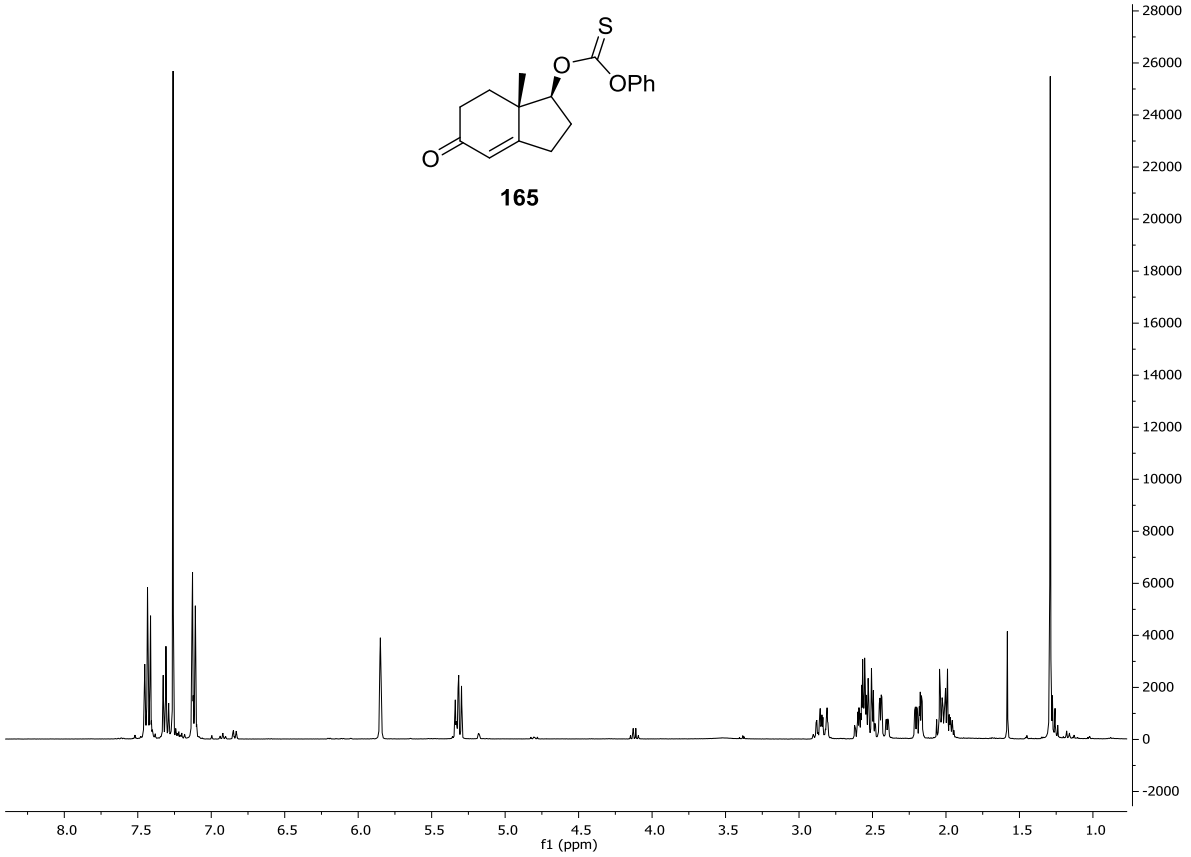
10
f1 (ppm)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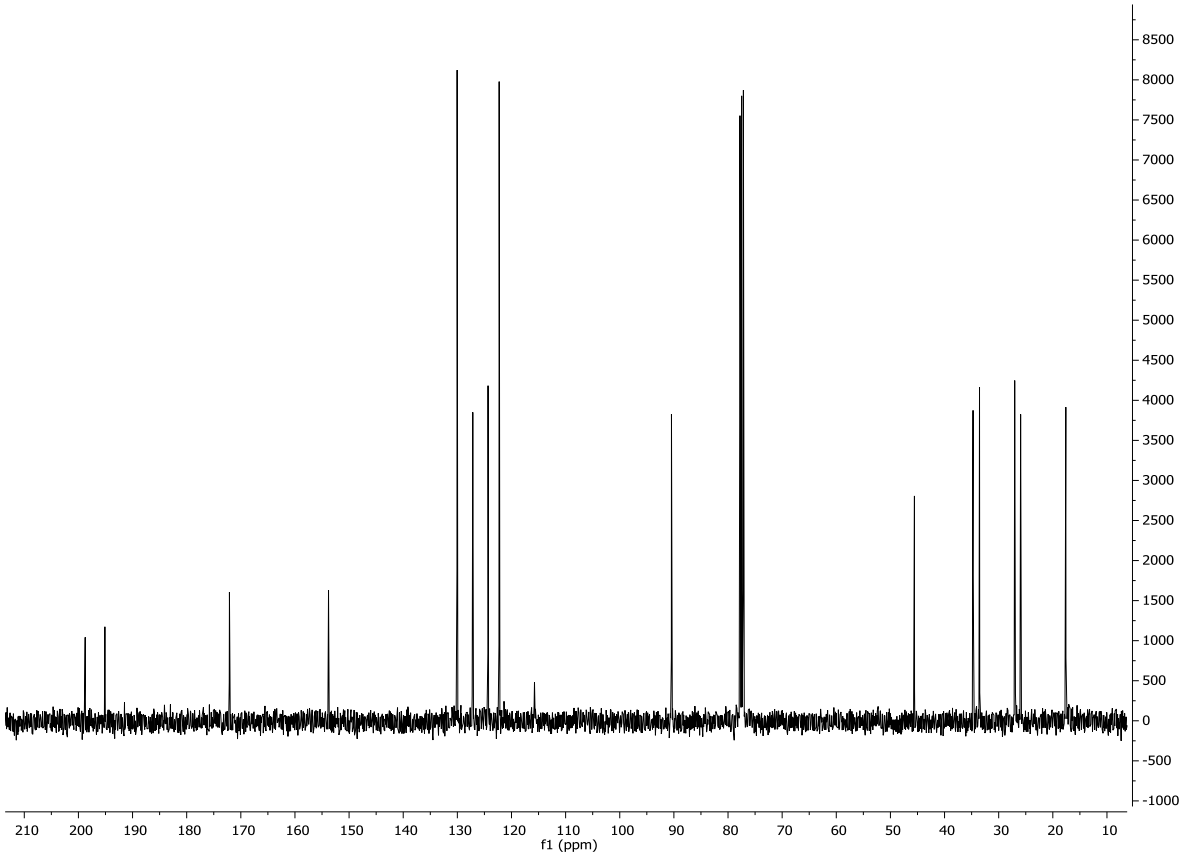
1.0
f1 (ppm)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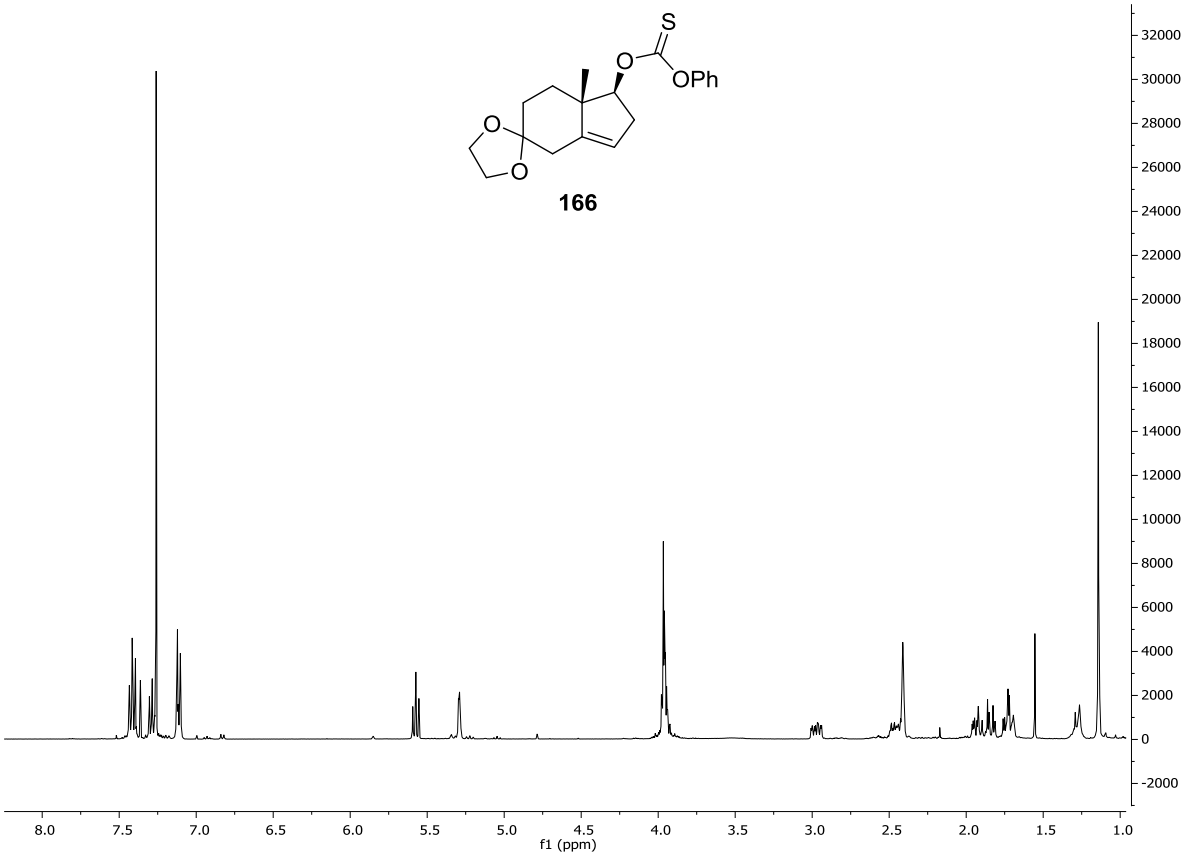
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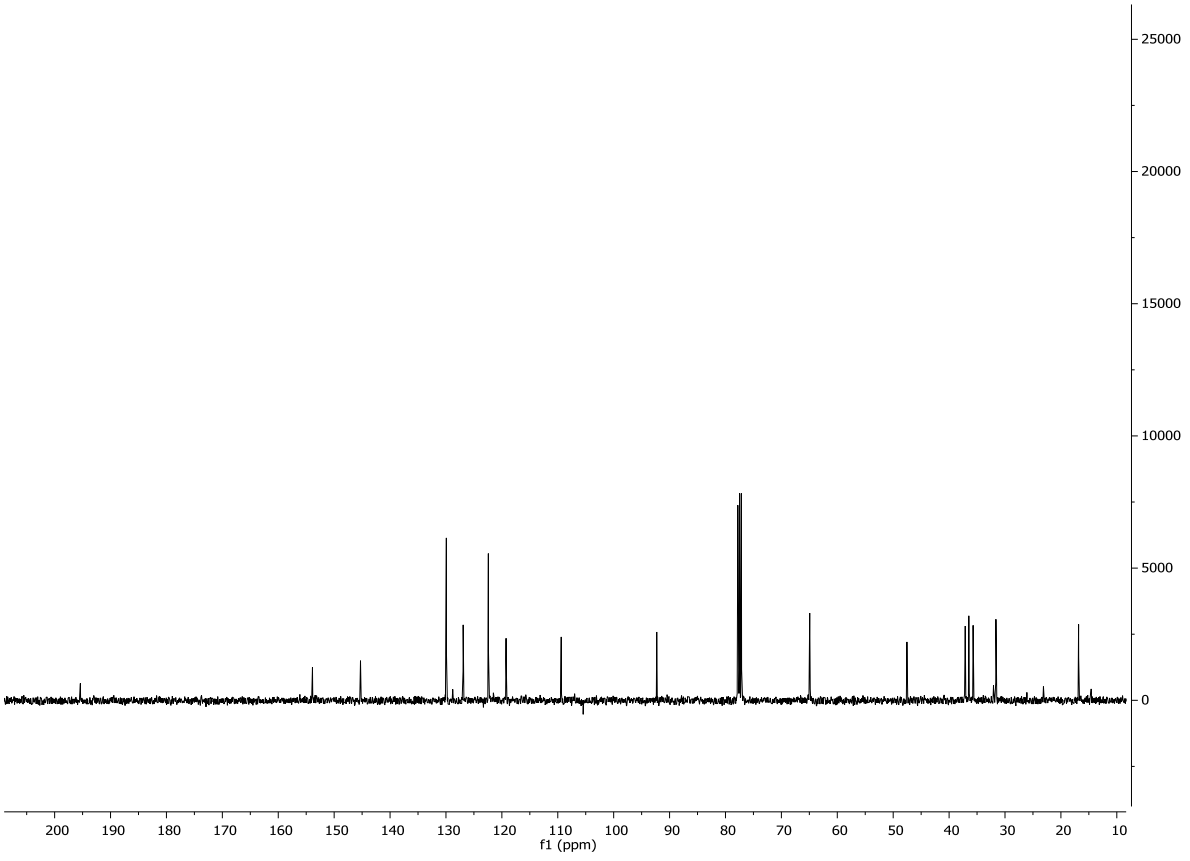
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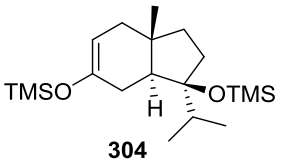
f1 (ppm)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15000
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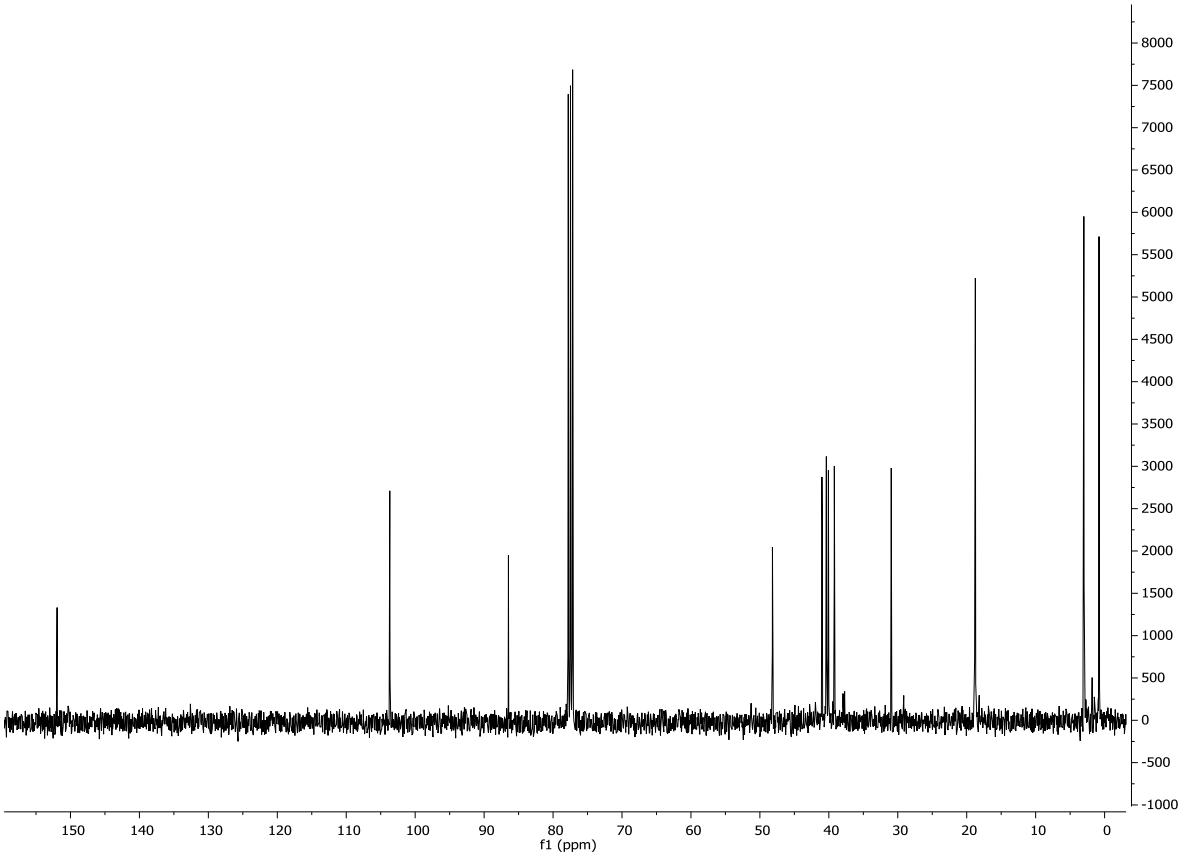
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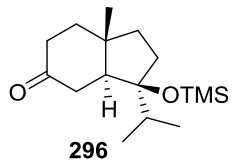
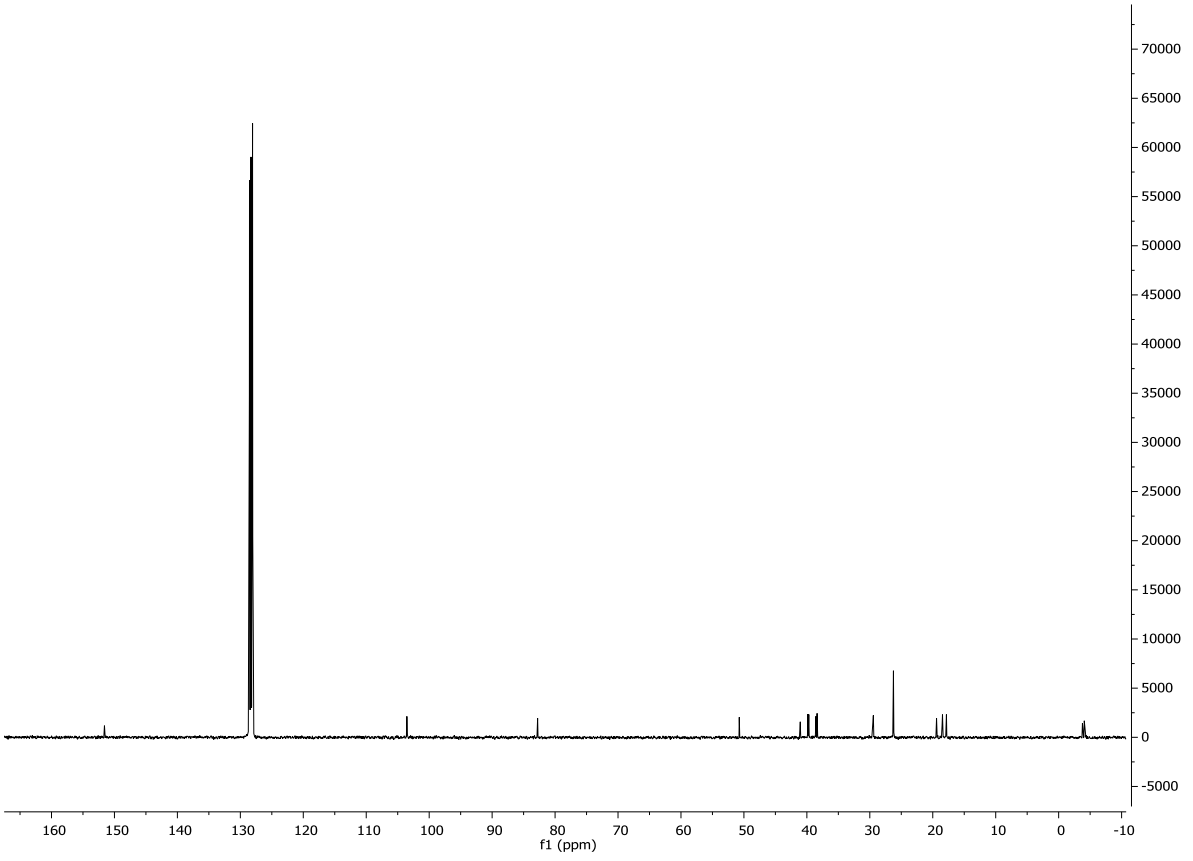
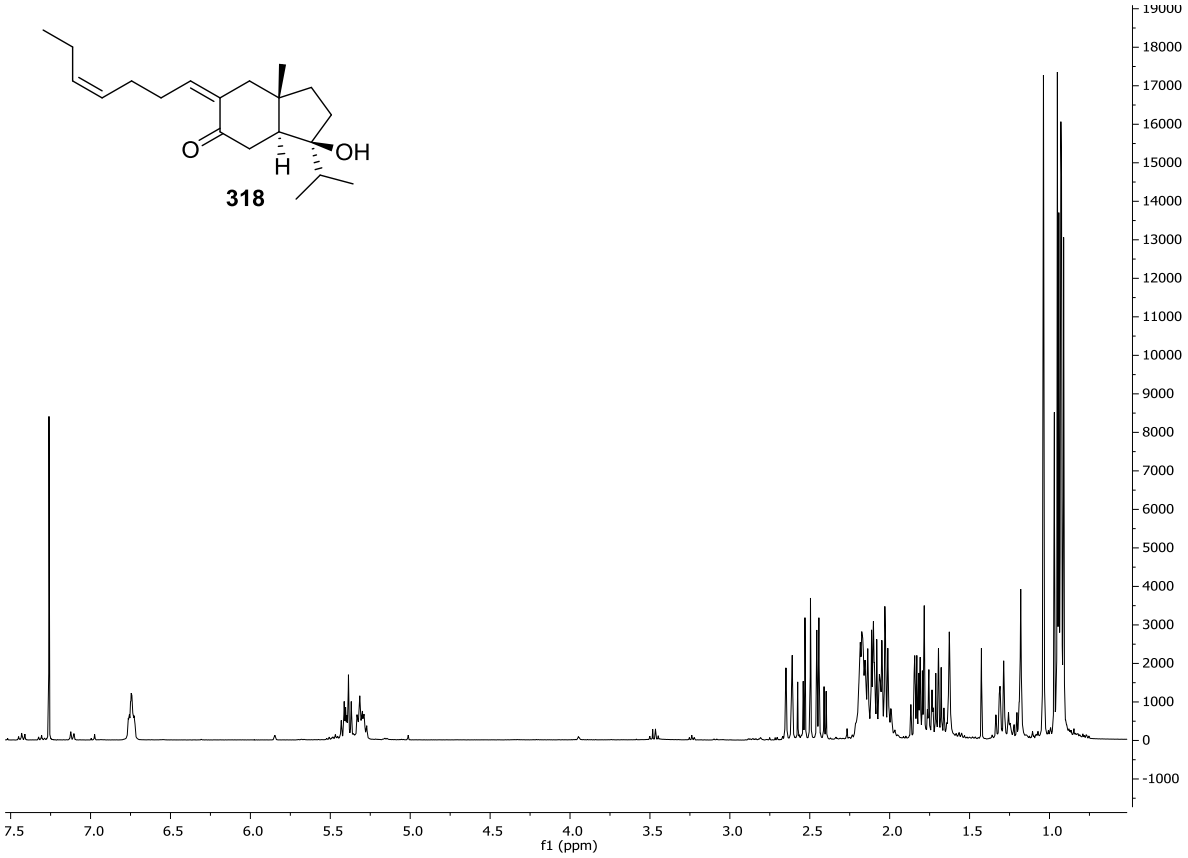
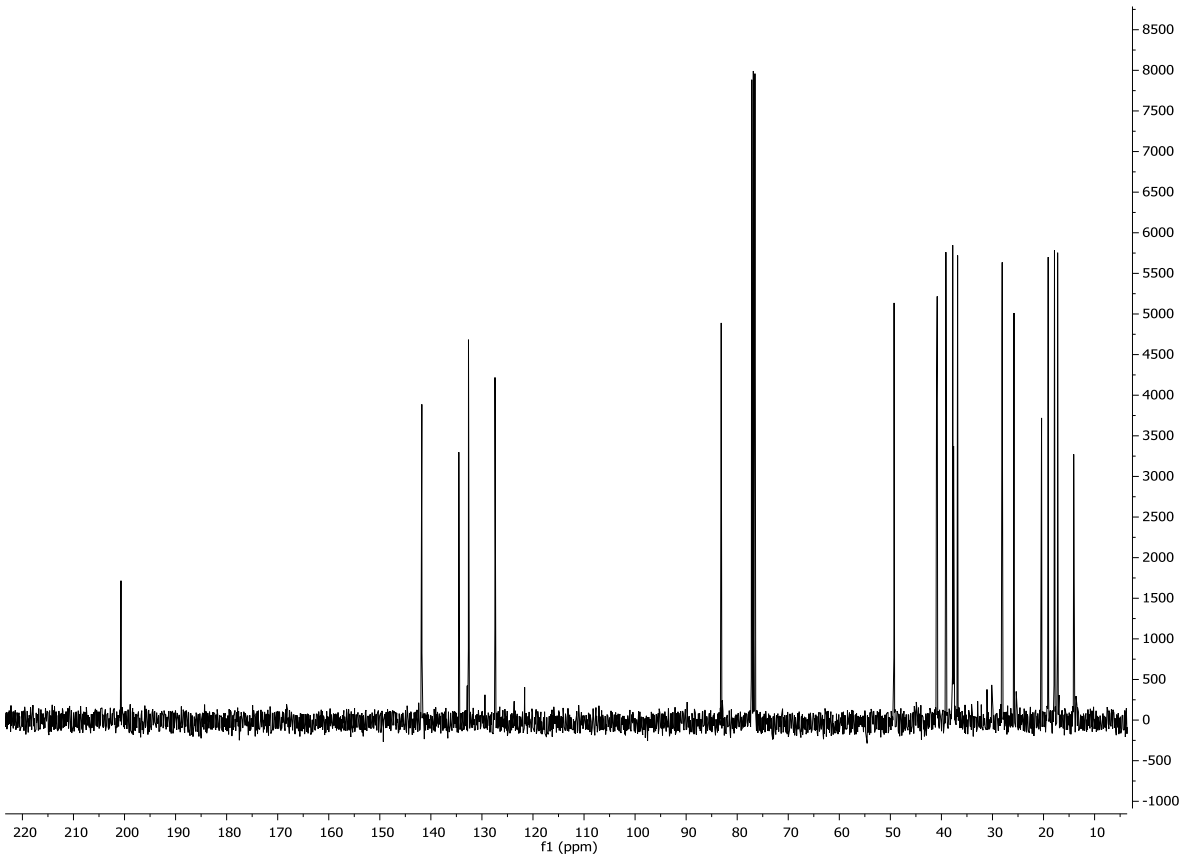
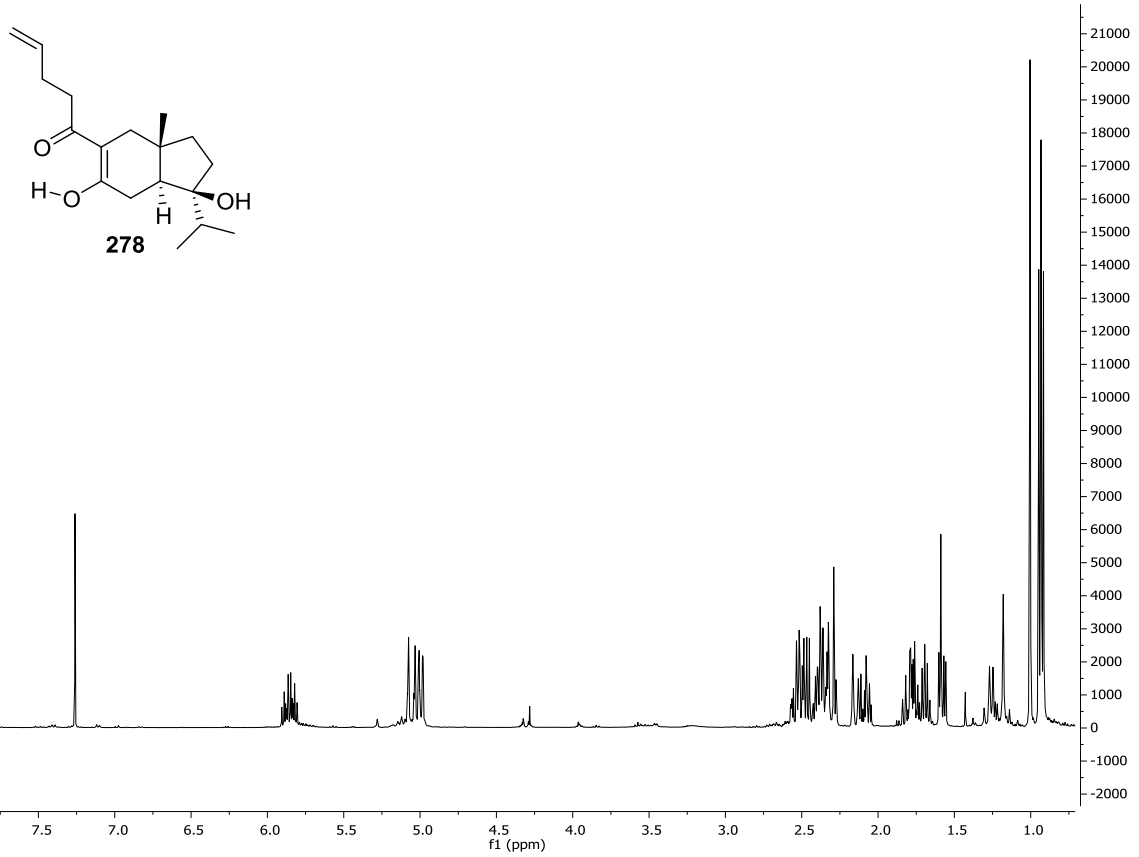


296

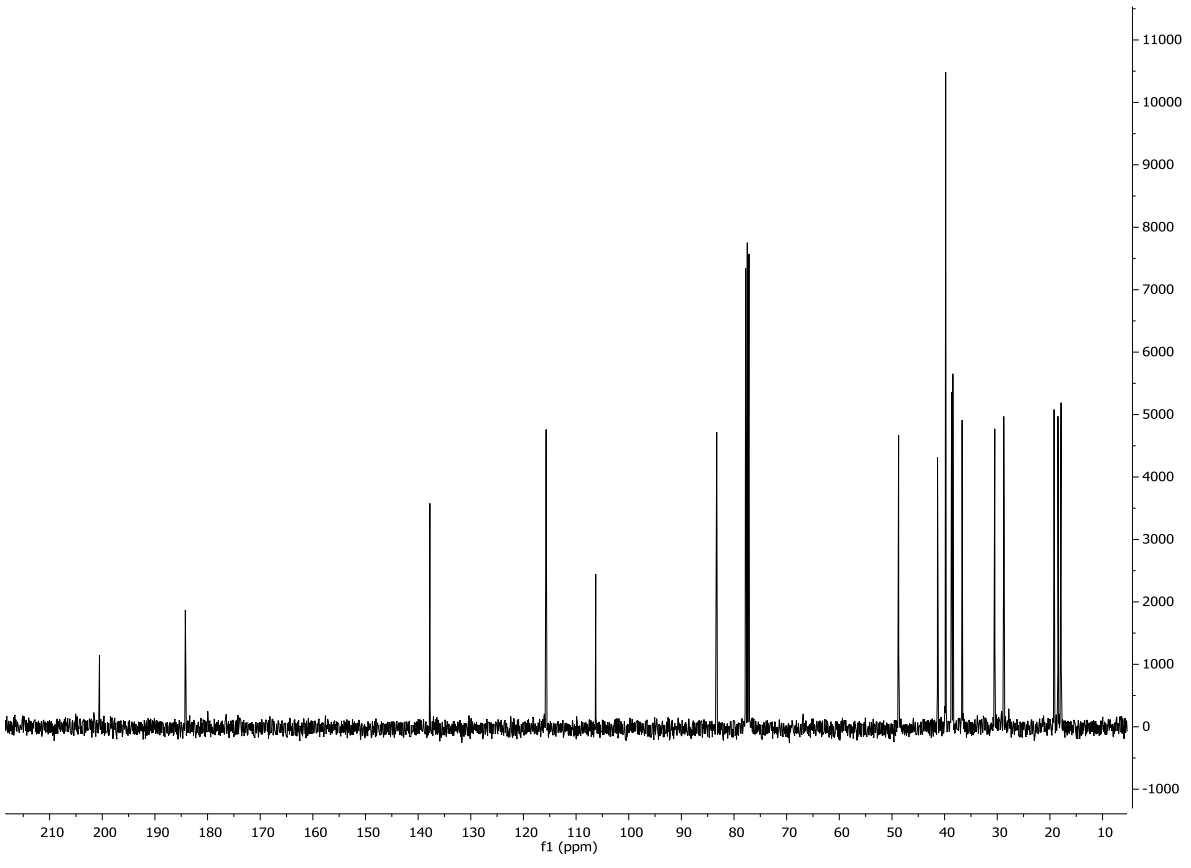


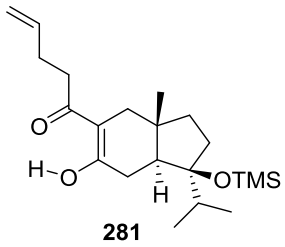

O
H
OH
318
f1 (ppm)


f1 (ppm)



278




O
H
O
H
OTMS

281

110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
13.5
13.0
12.5
12.0
11.5
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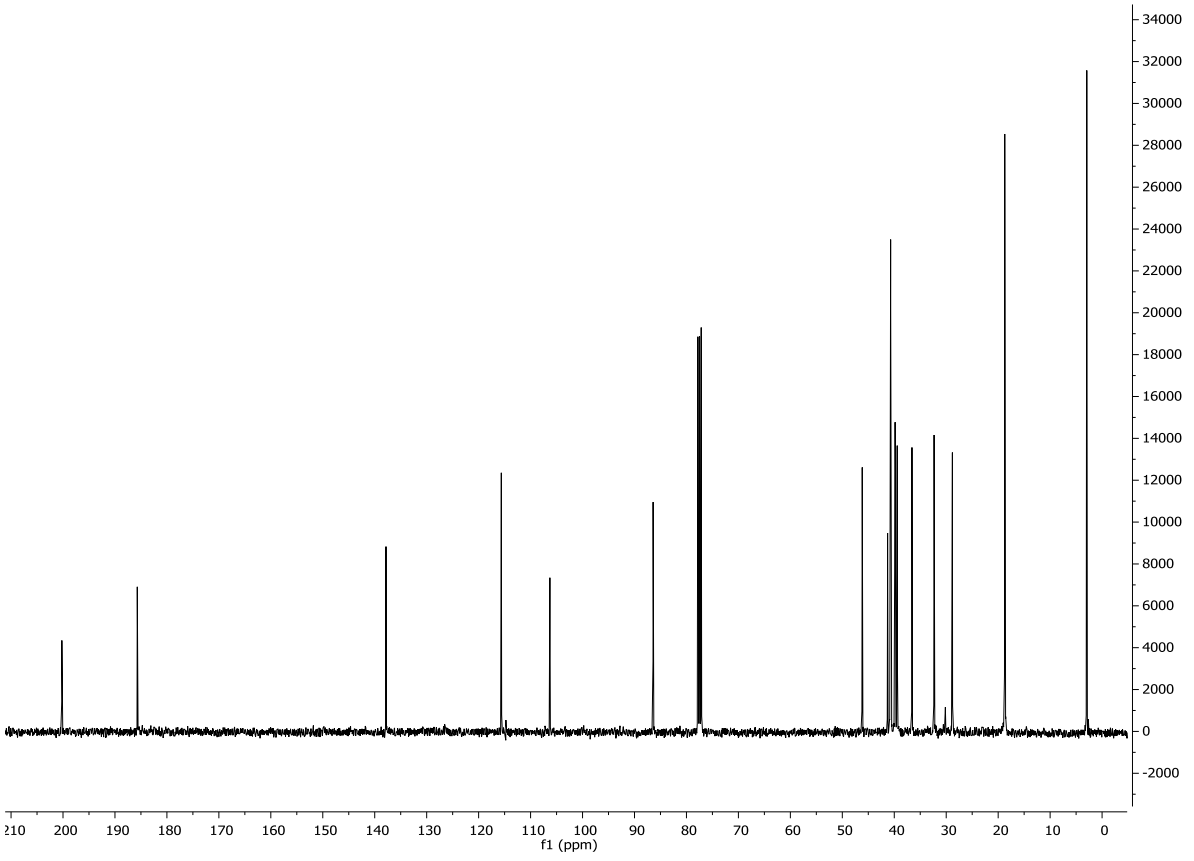
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)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32000
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20000
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12000
10000
8000
6000
4000
2000
0
-2000
210
200
190
180
170
160
150
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130
120
110
100
90
80
70
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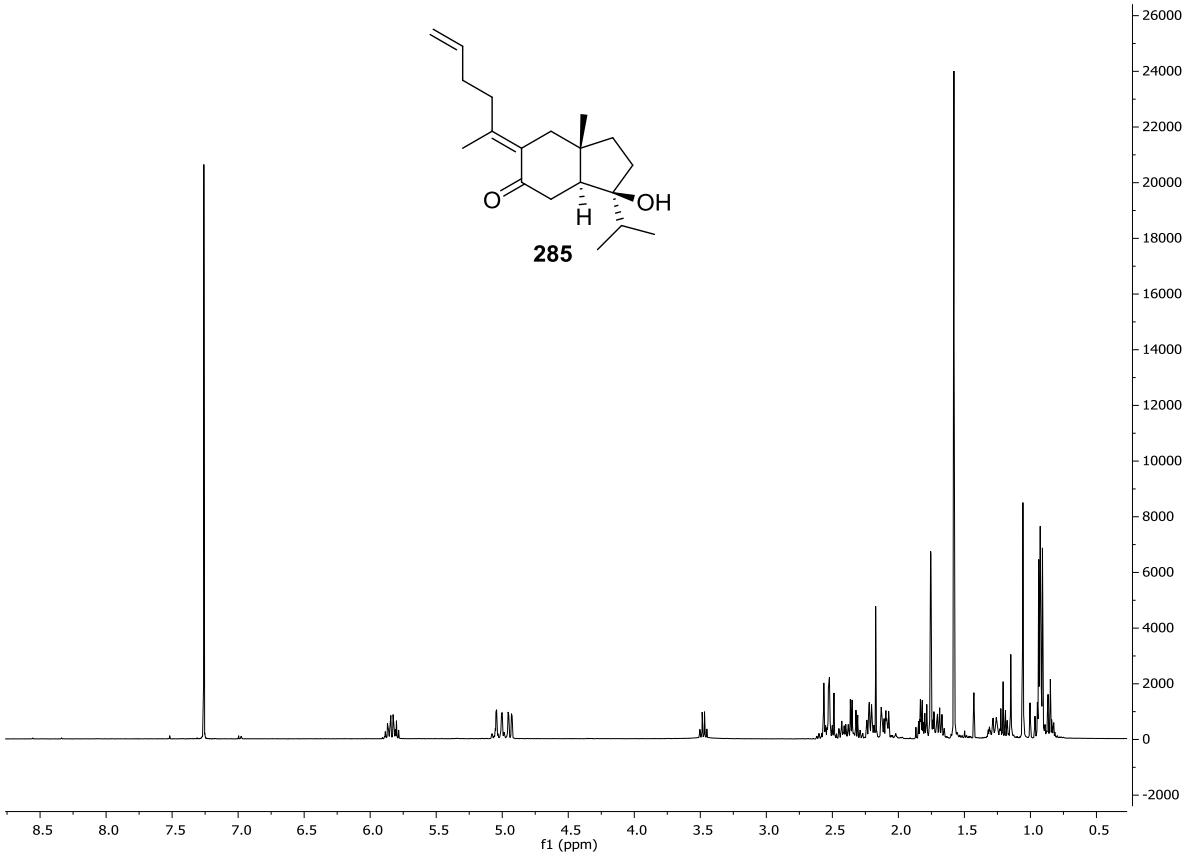
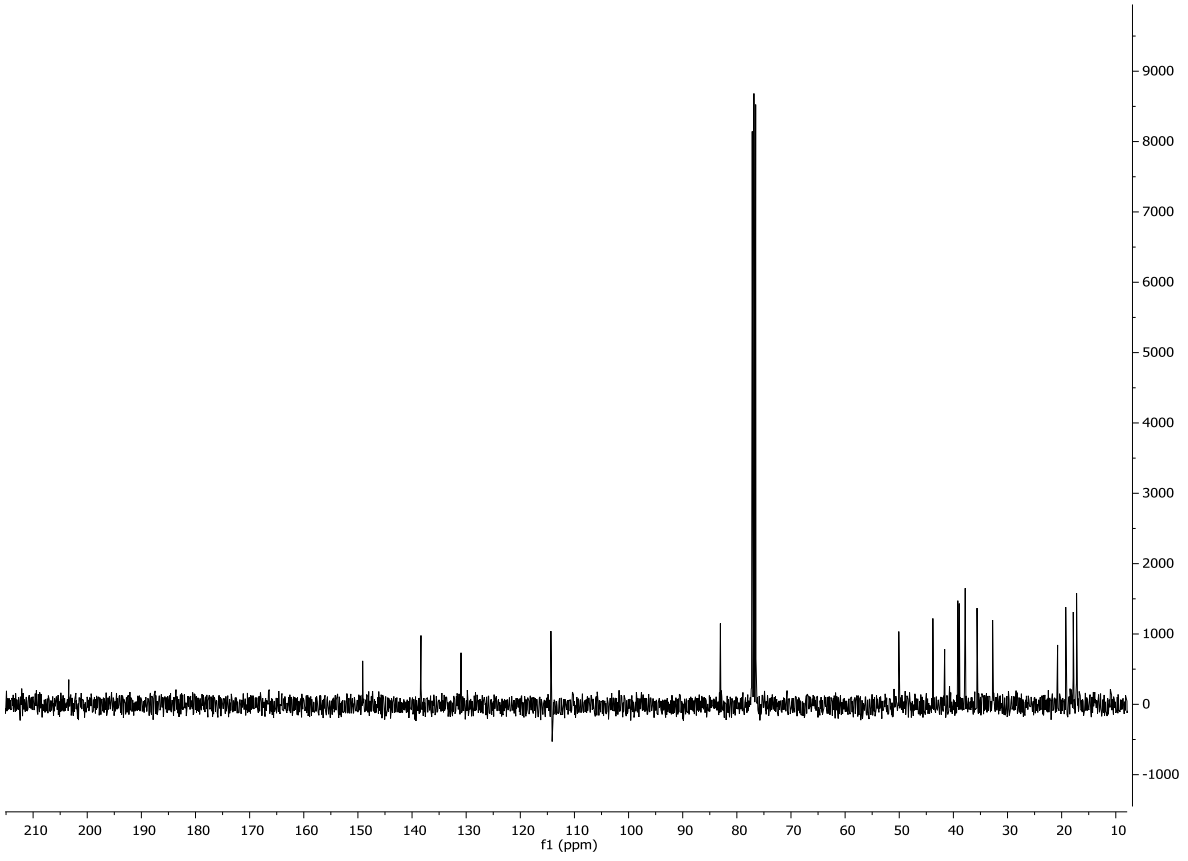
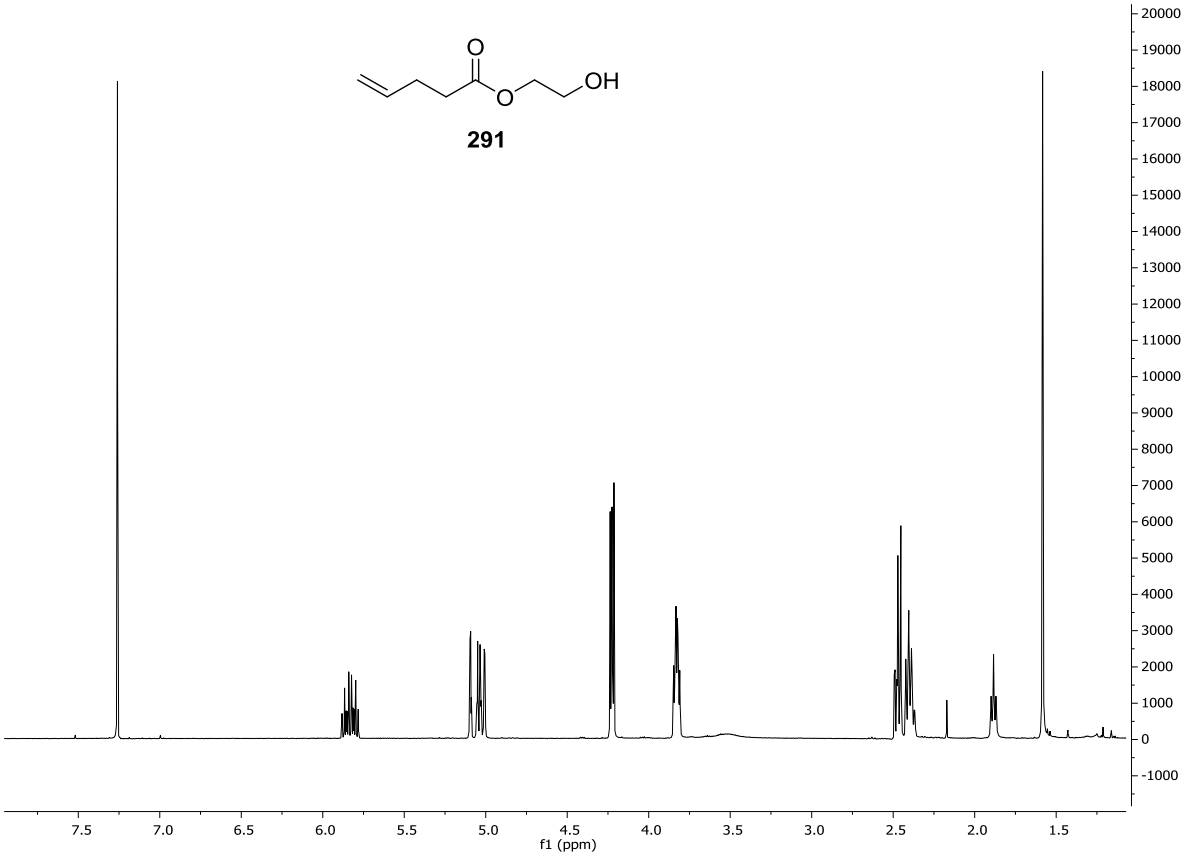
50
40
30
20
10
0
f1 (ppm)


O
H
OH
285
f1 (ppm)


f1 (ppm)


O
O
OH
291
20000
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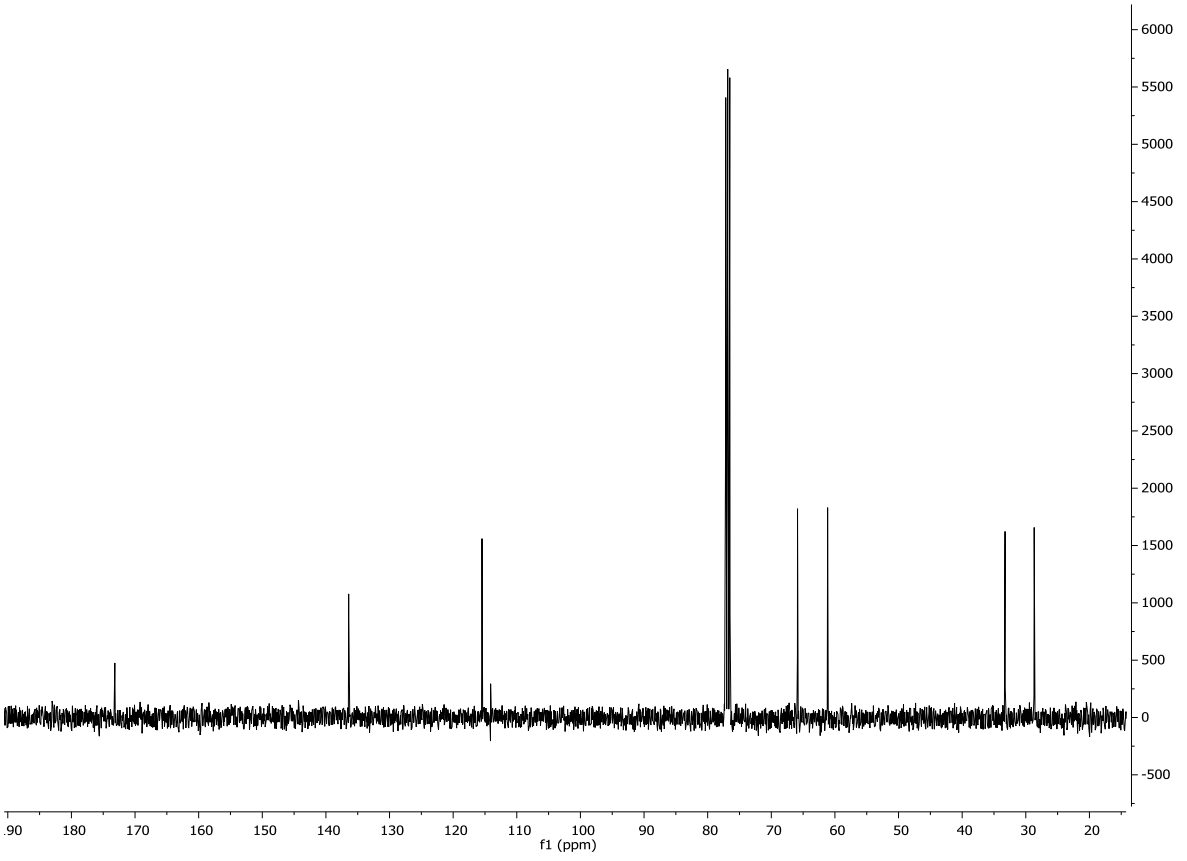
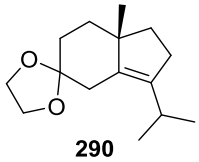
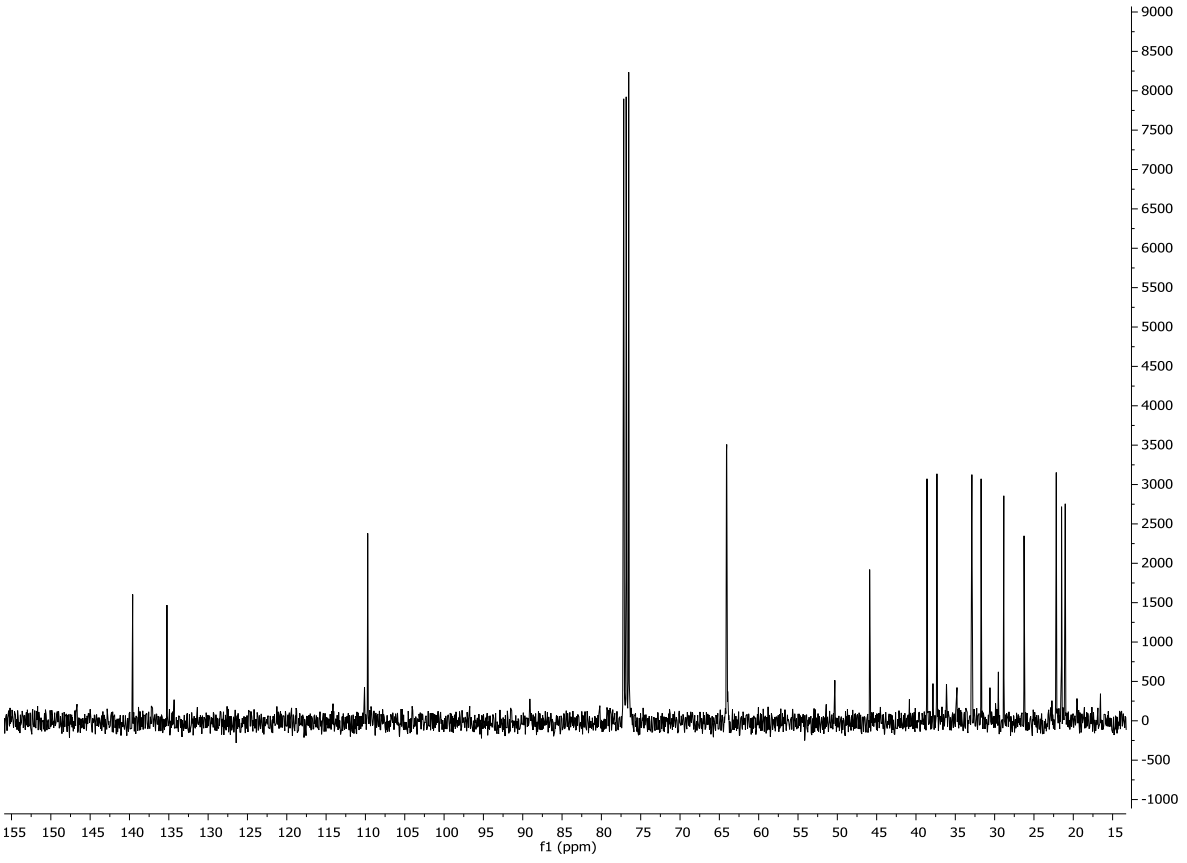
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)



290

34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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7500
7000
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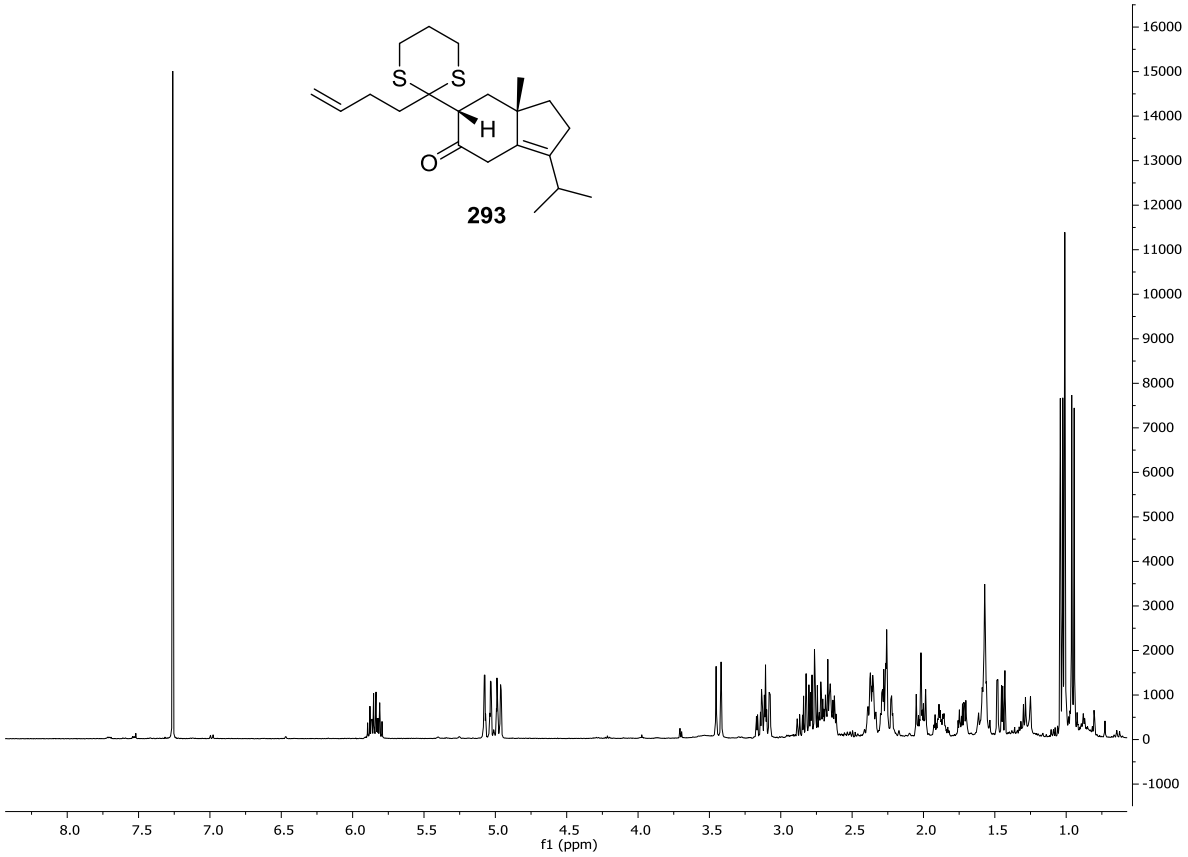
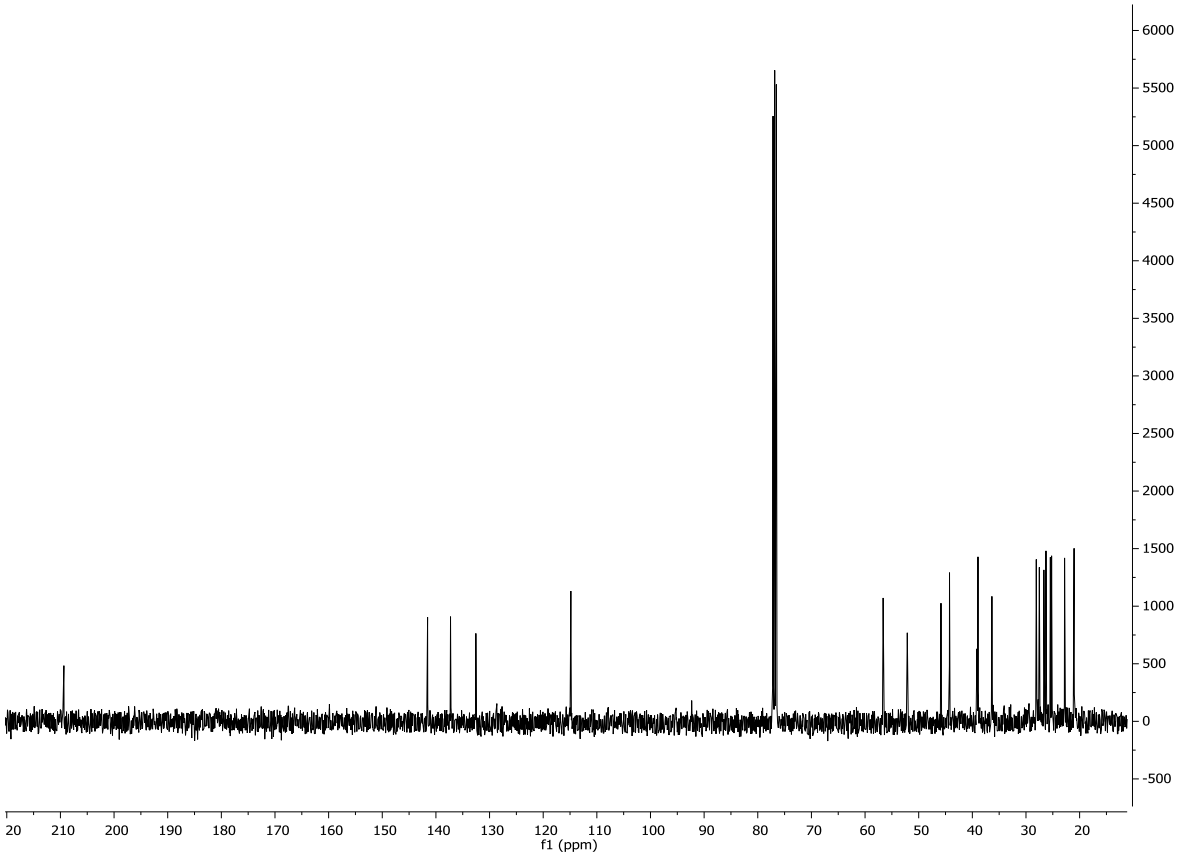
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)


S
S
H
O
293
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
20
210
200
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170
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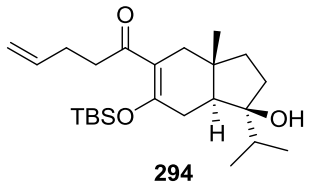
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


O
TBSO
H
OH

294

70000
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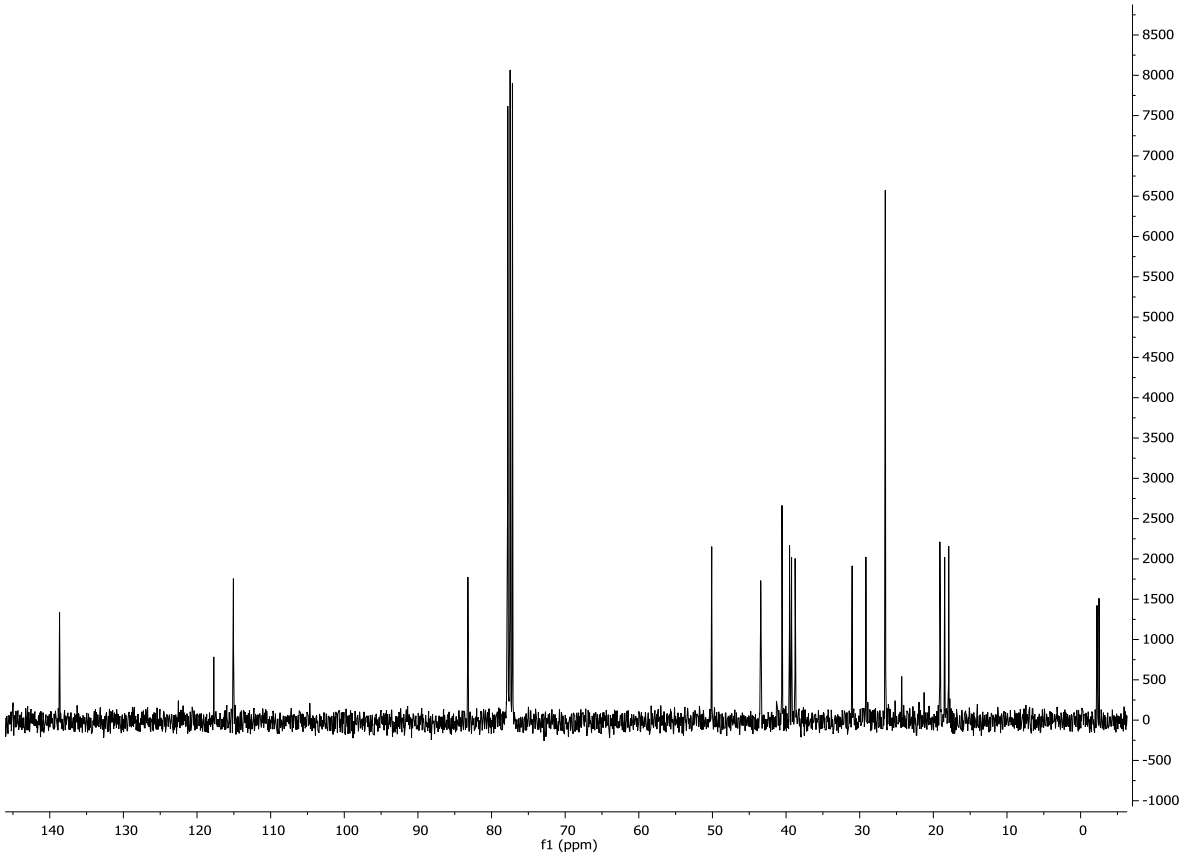
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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7000
6500
6000
5500
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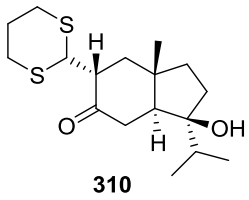
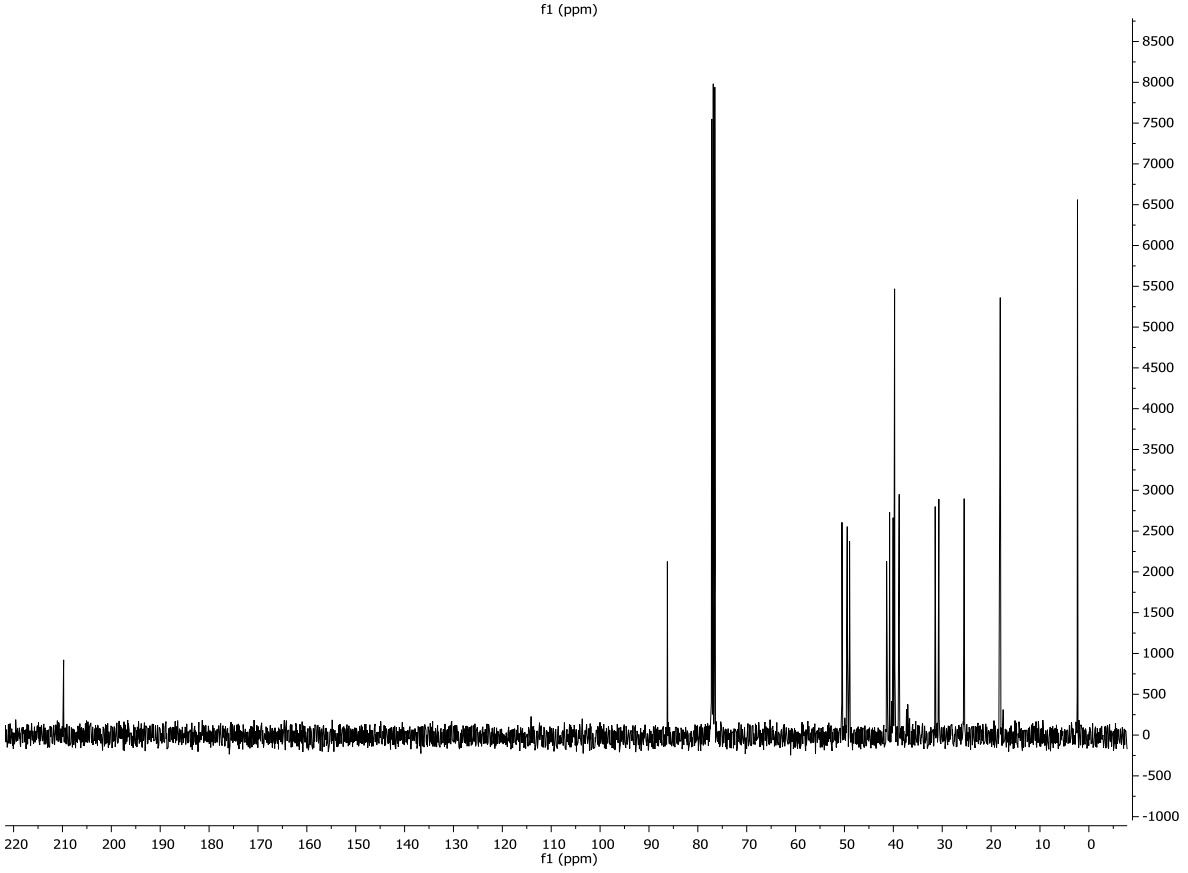
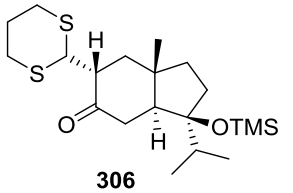
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



310




S
H
S
O
H
OTMS

306

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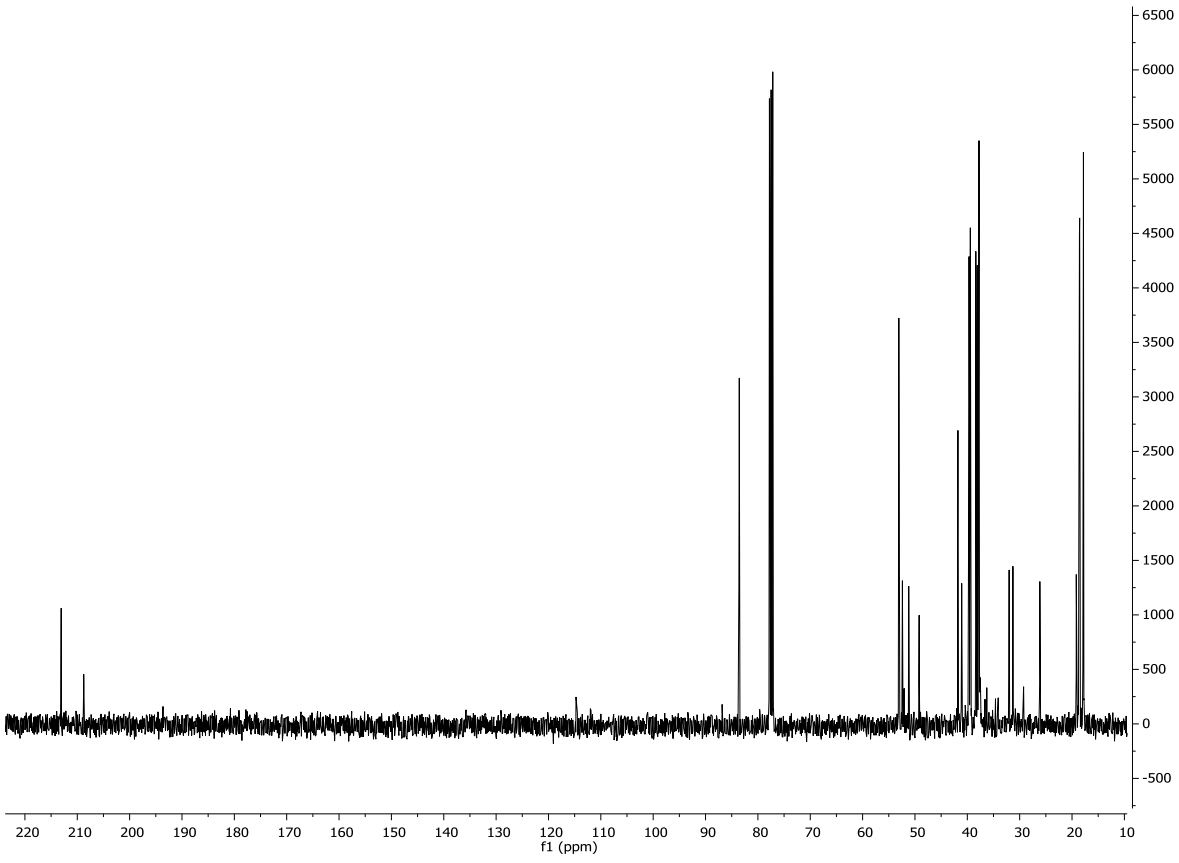
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
220
210
200
190
180
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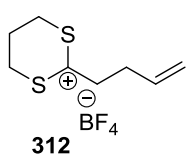
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


S
S
BF4

312

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14000
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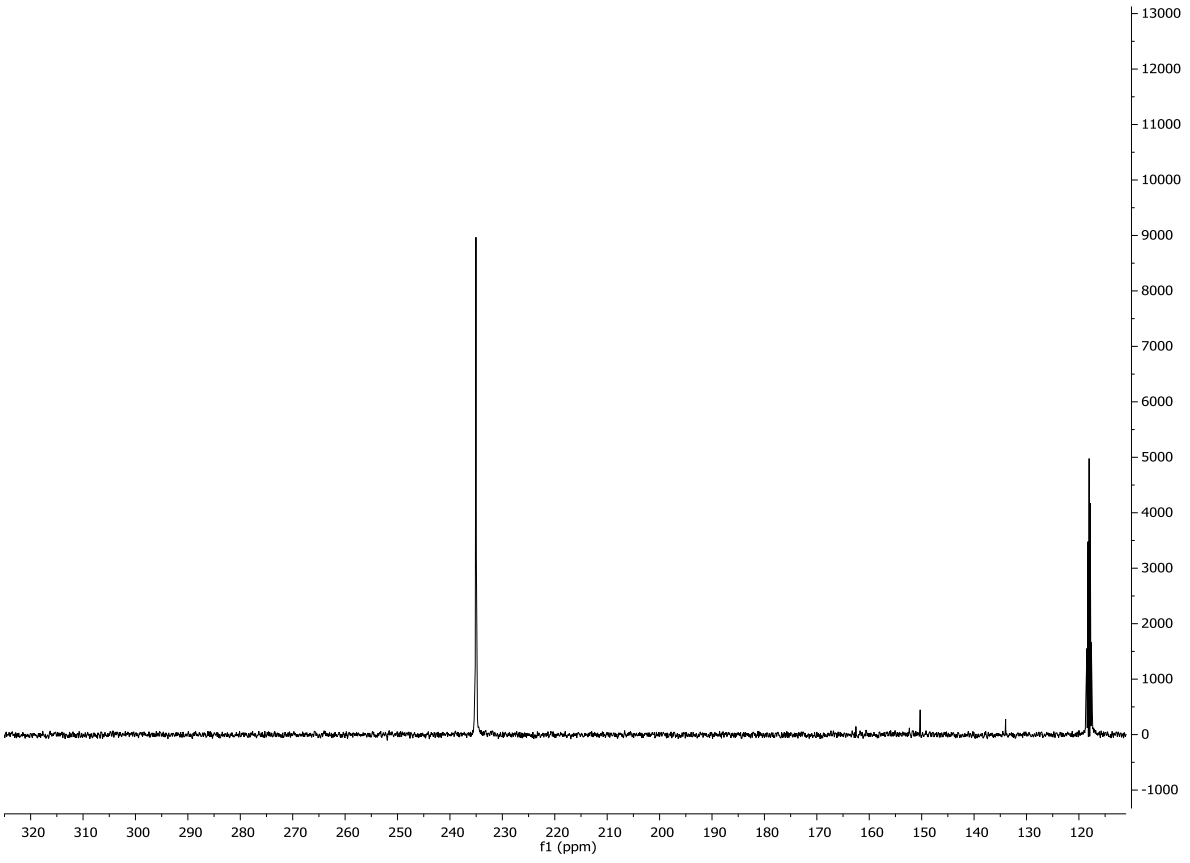
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)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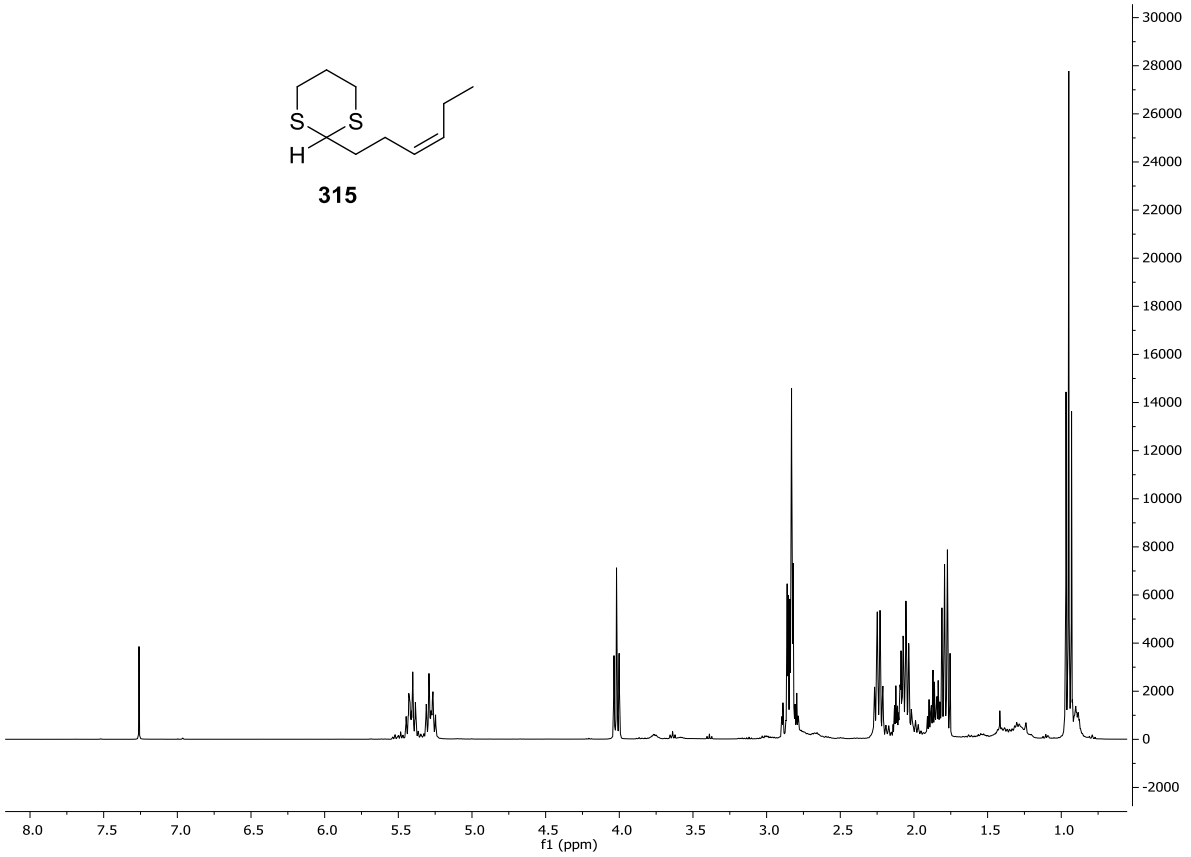
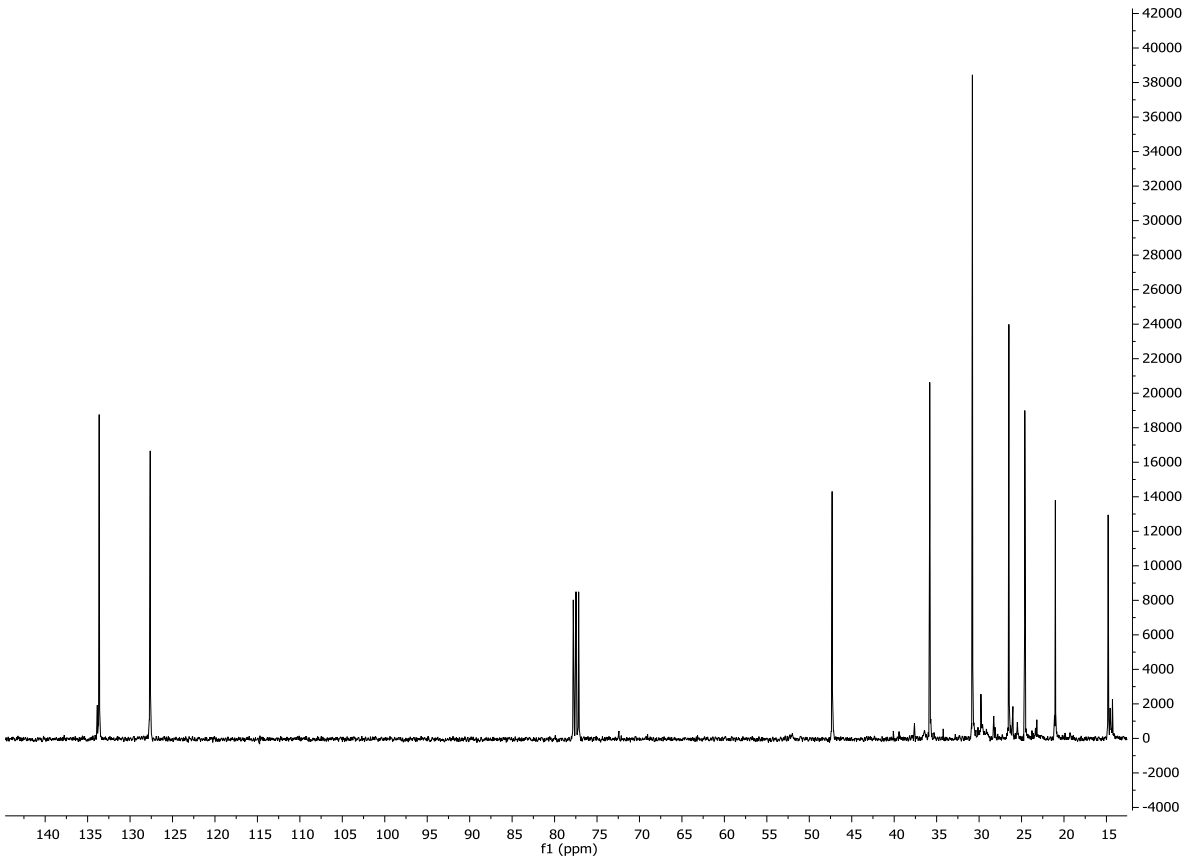
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
320 310 300 290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120
f1 (ppm)


S
S
H
315
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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38000
36000
34000
32000
30000
28000
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24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
140
135
130
125
120
115
110
105
100
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90
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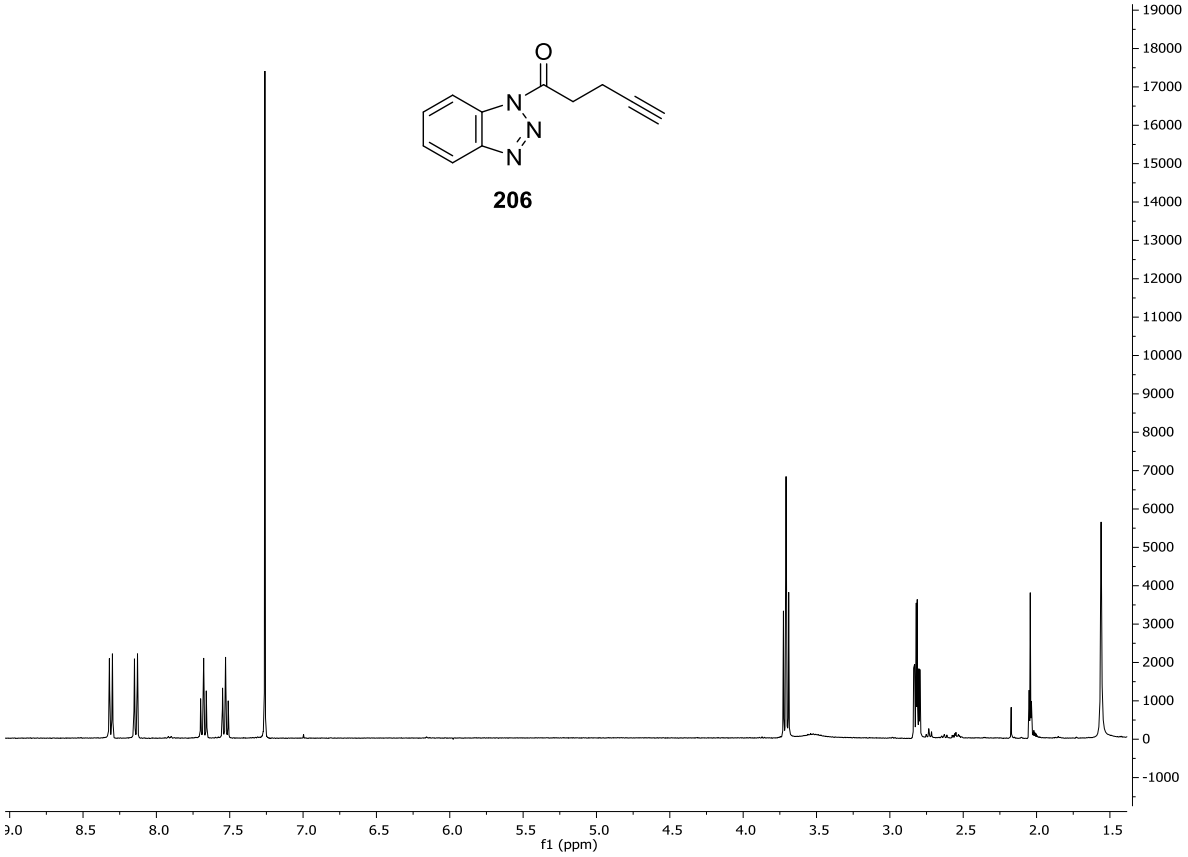
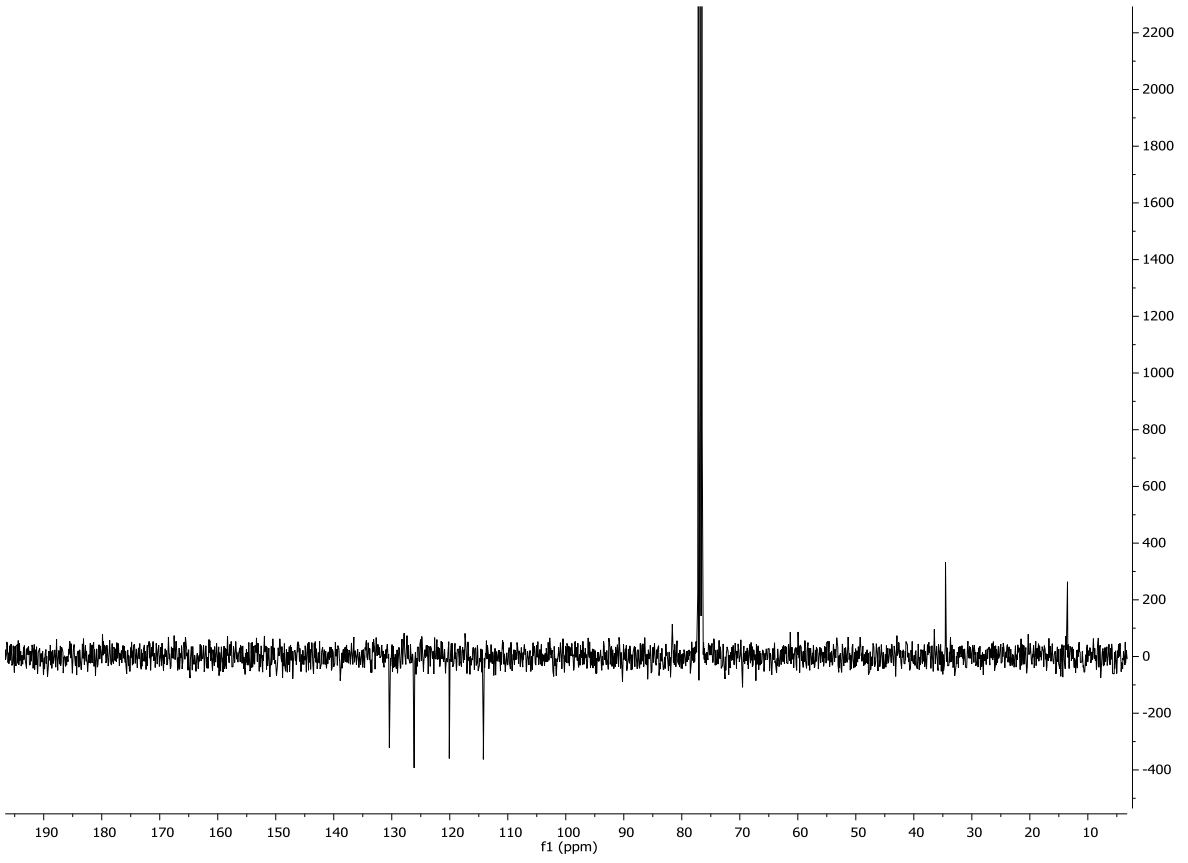
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)


O
N
N
N
206
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)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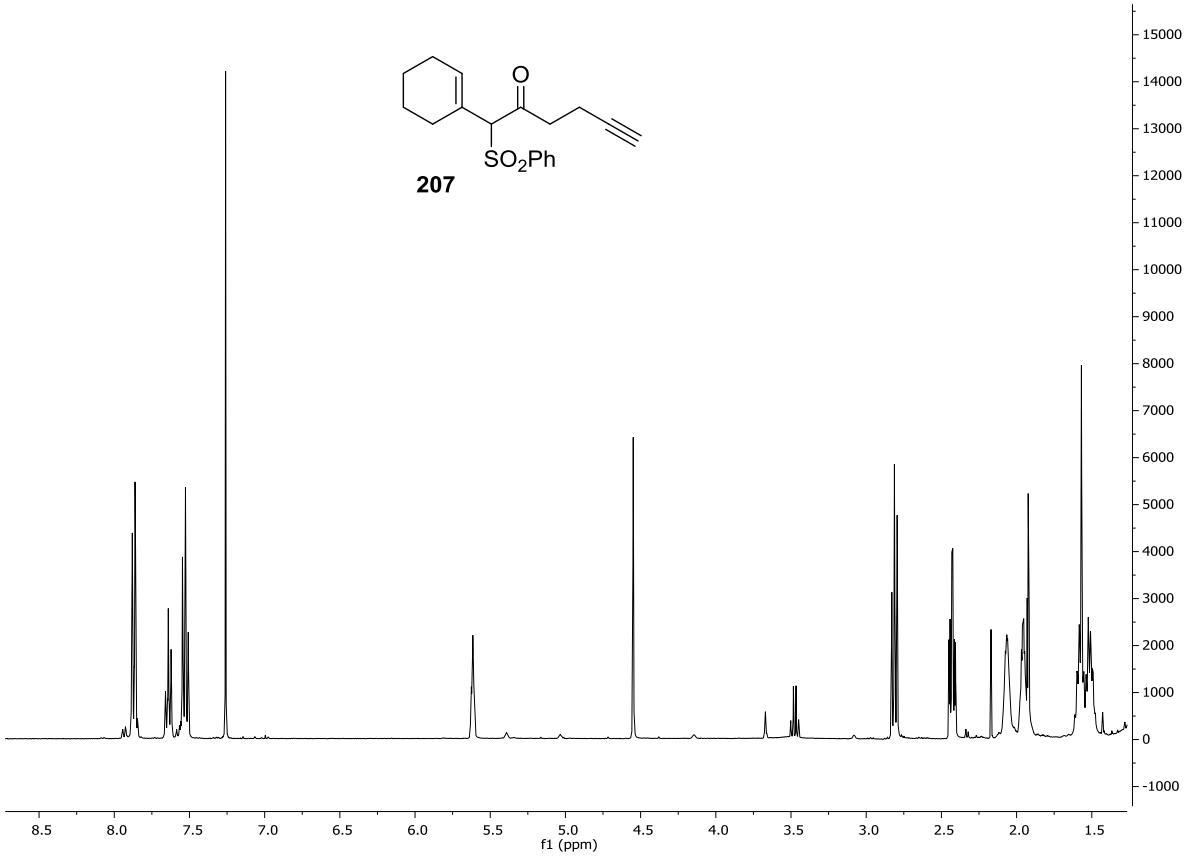
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
SO2Ph
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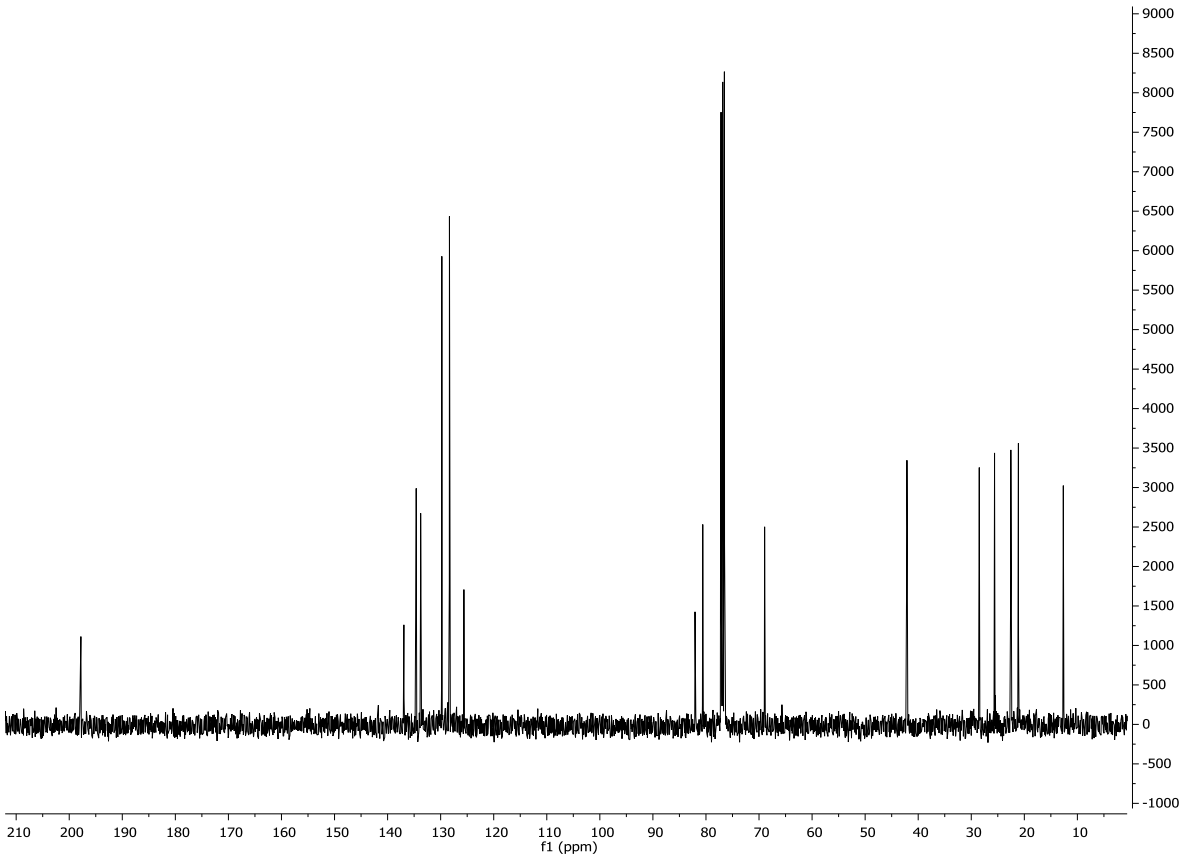
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


9000
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7500
7000
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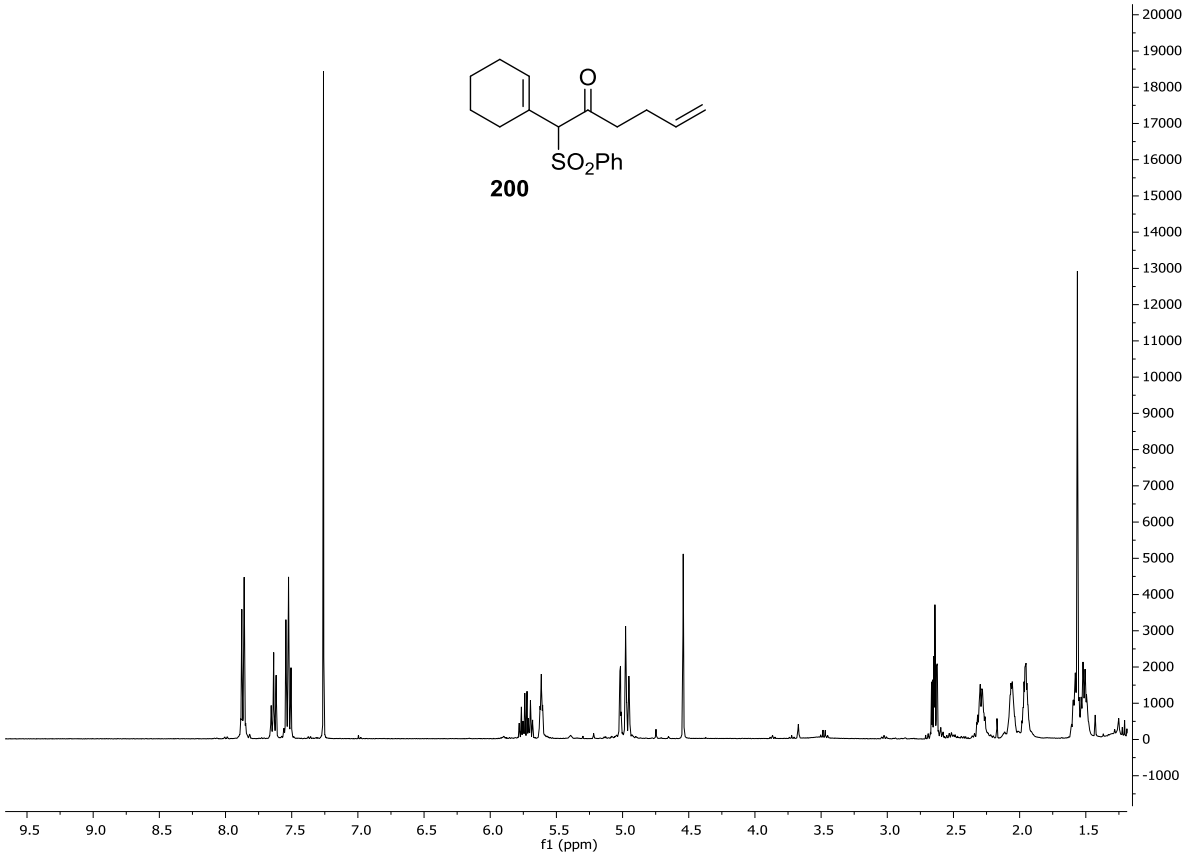
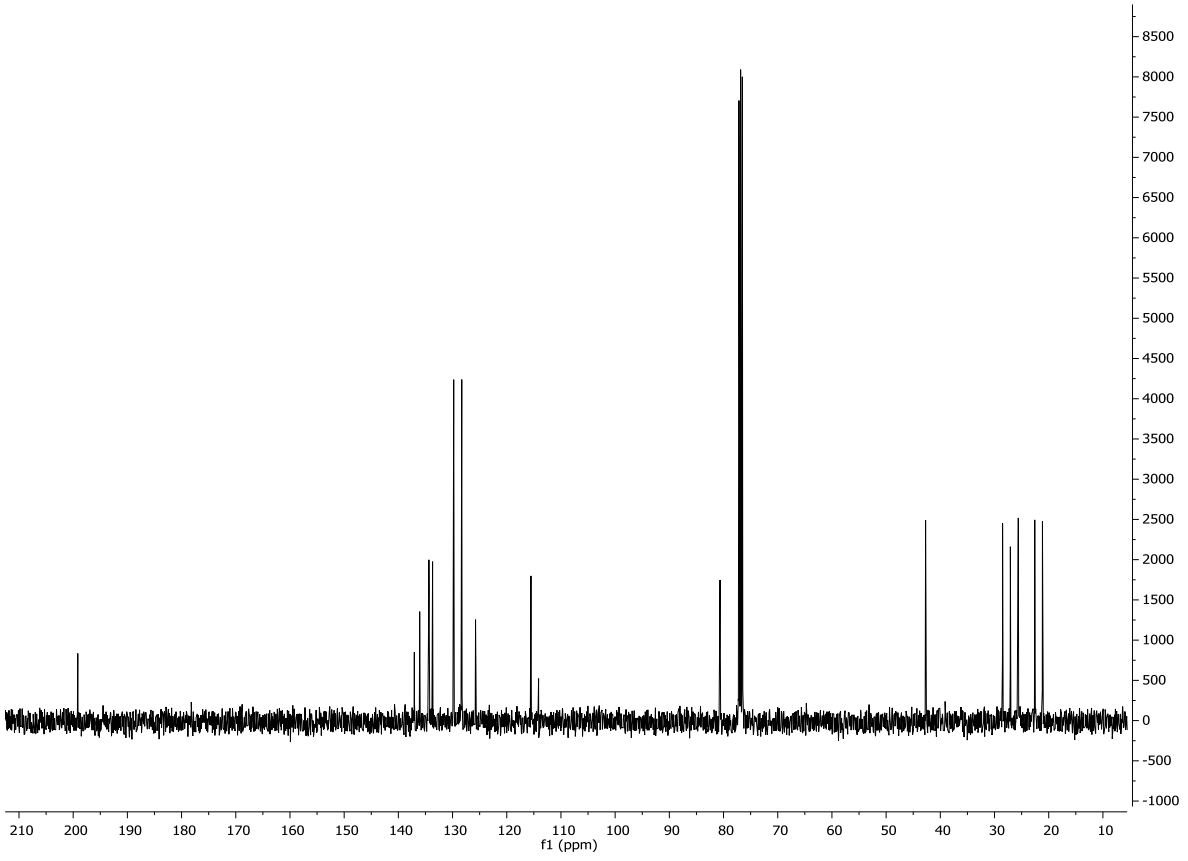
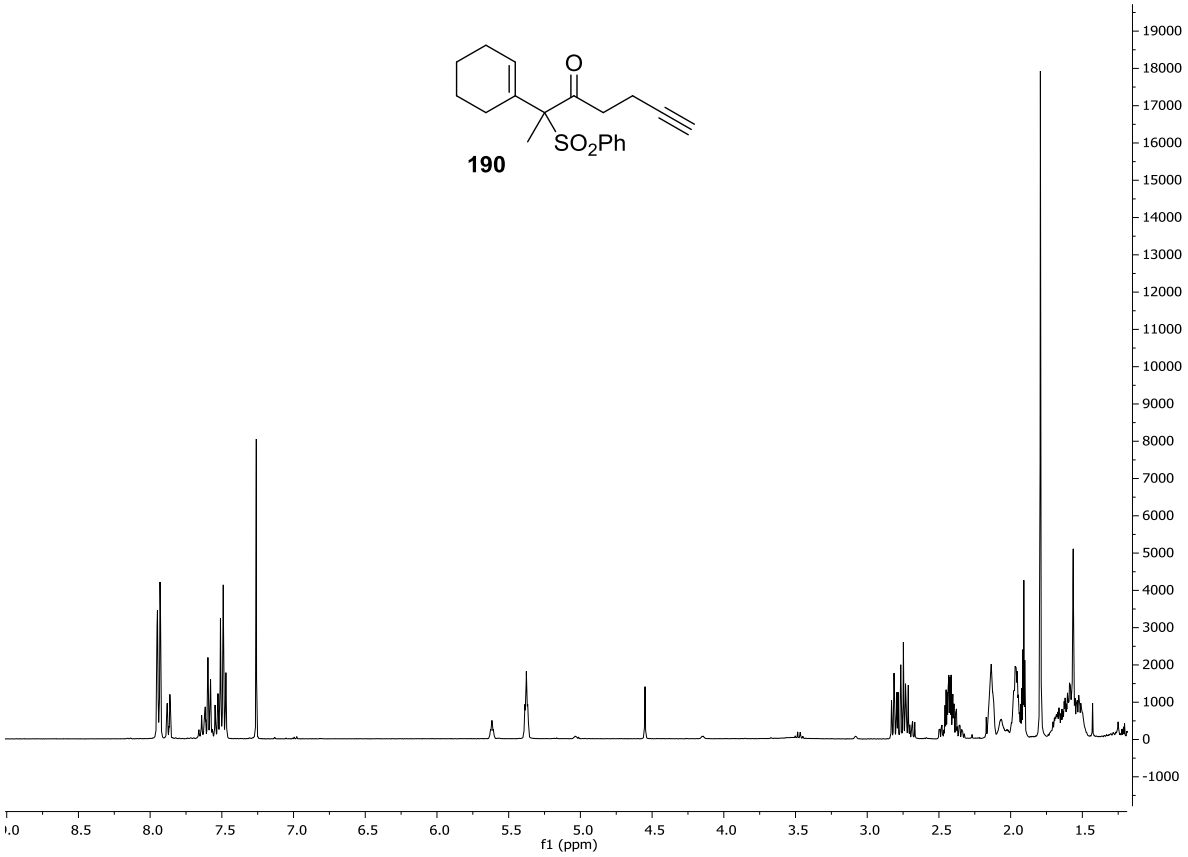
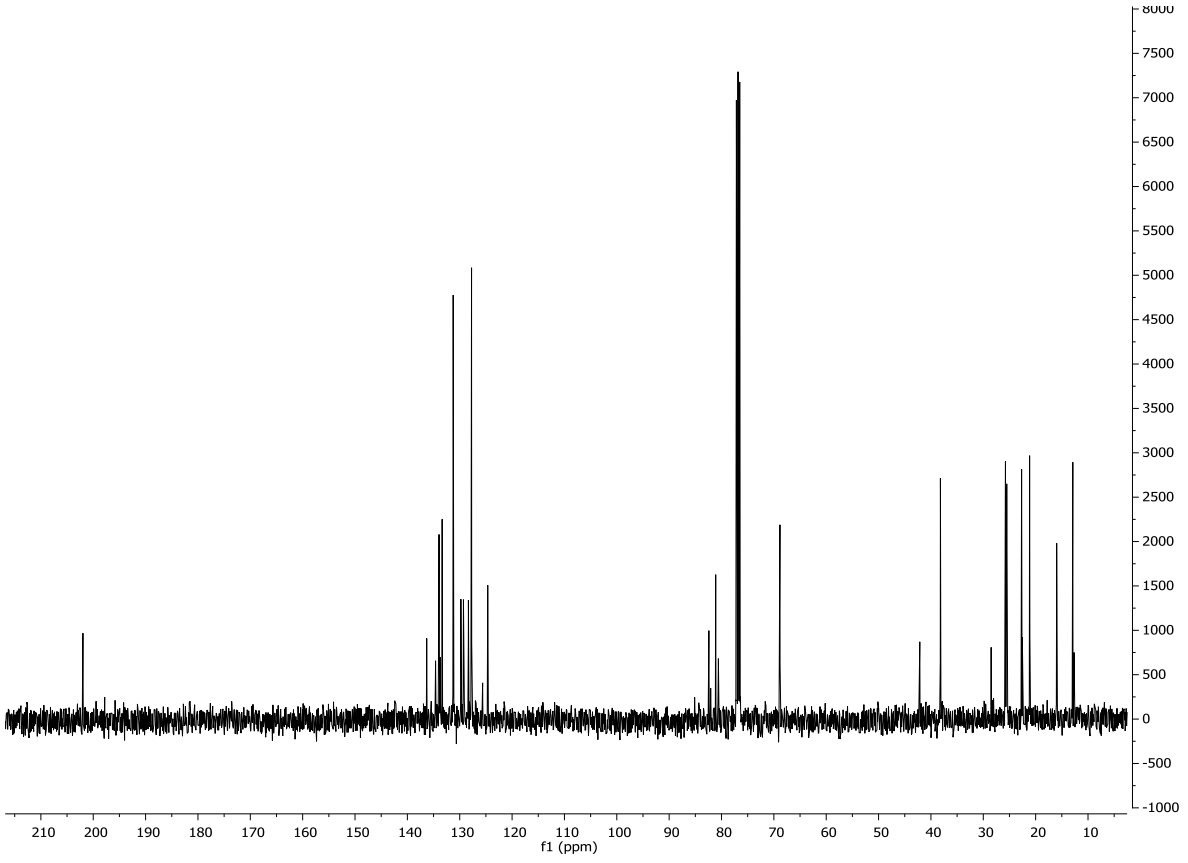
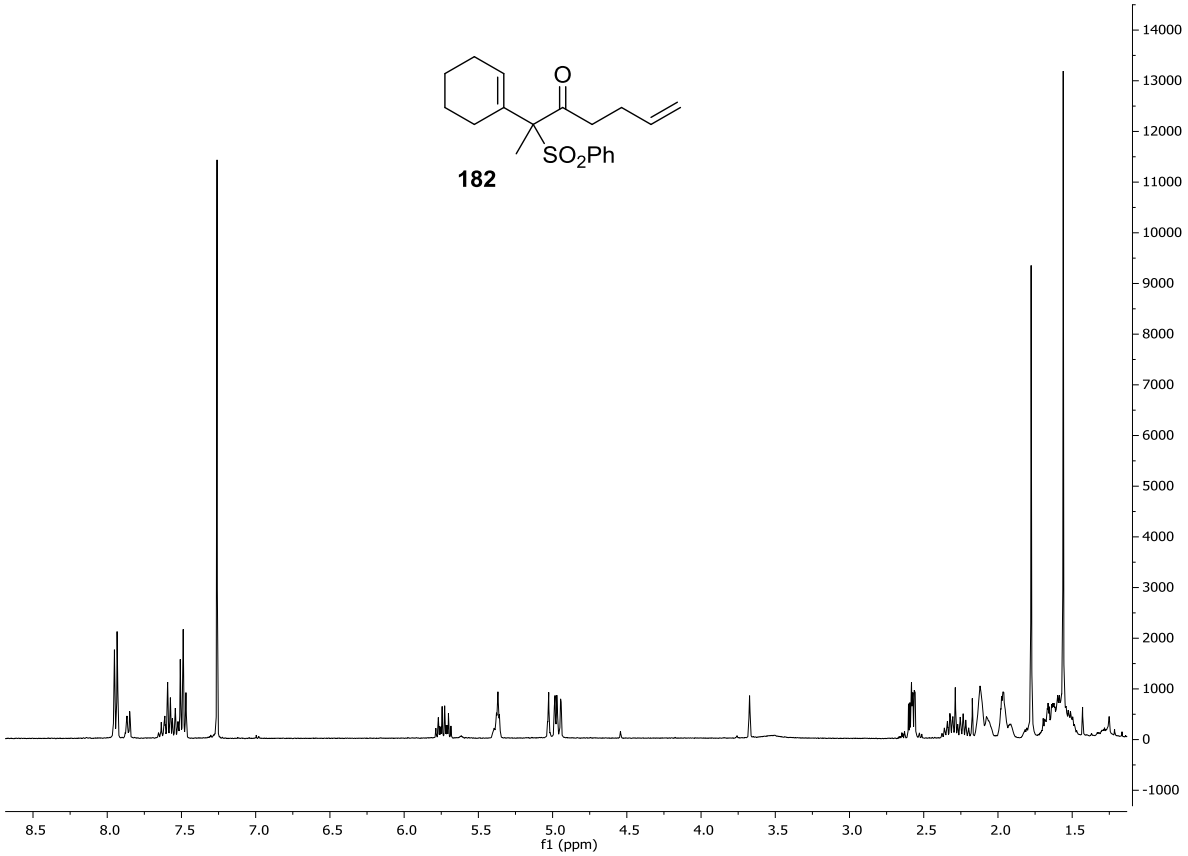
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

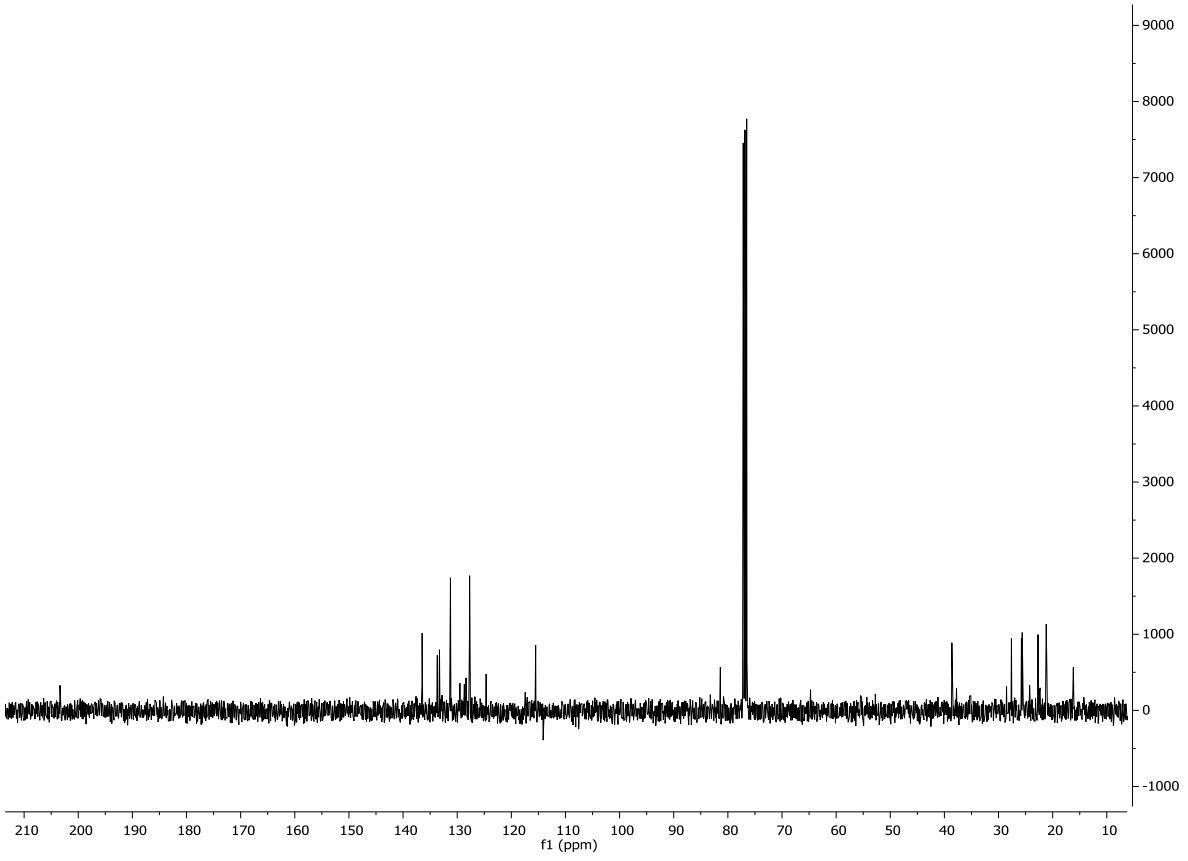

O
SO2Ph
200
f1 (ppm)

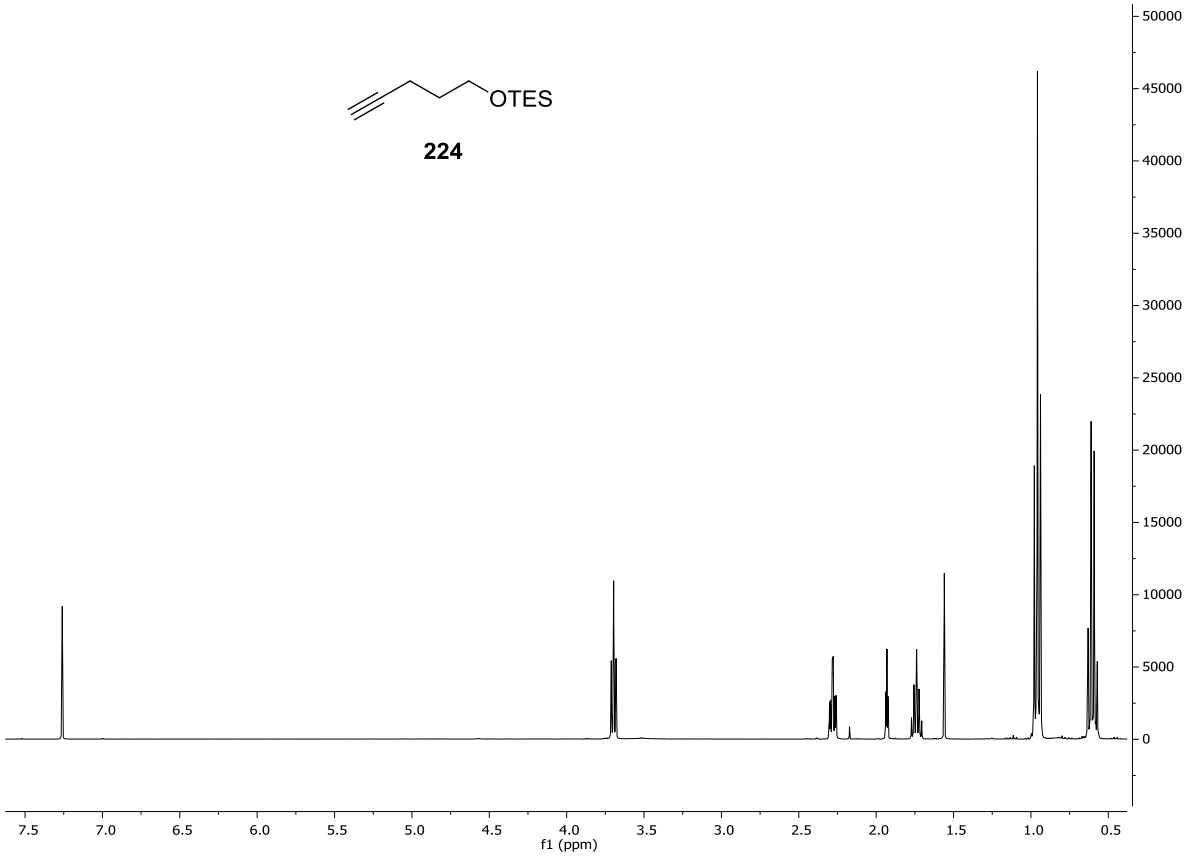

f1 (ppm)

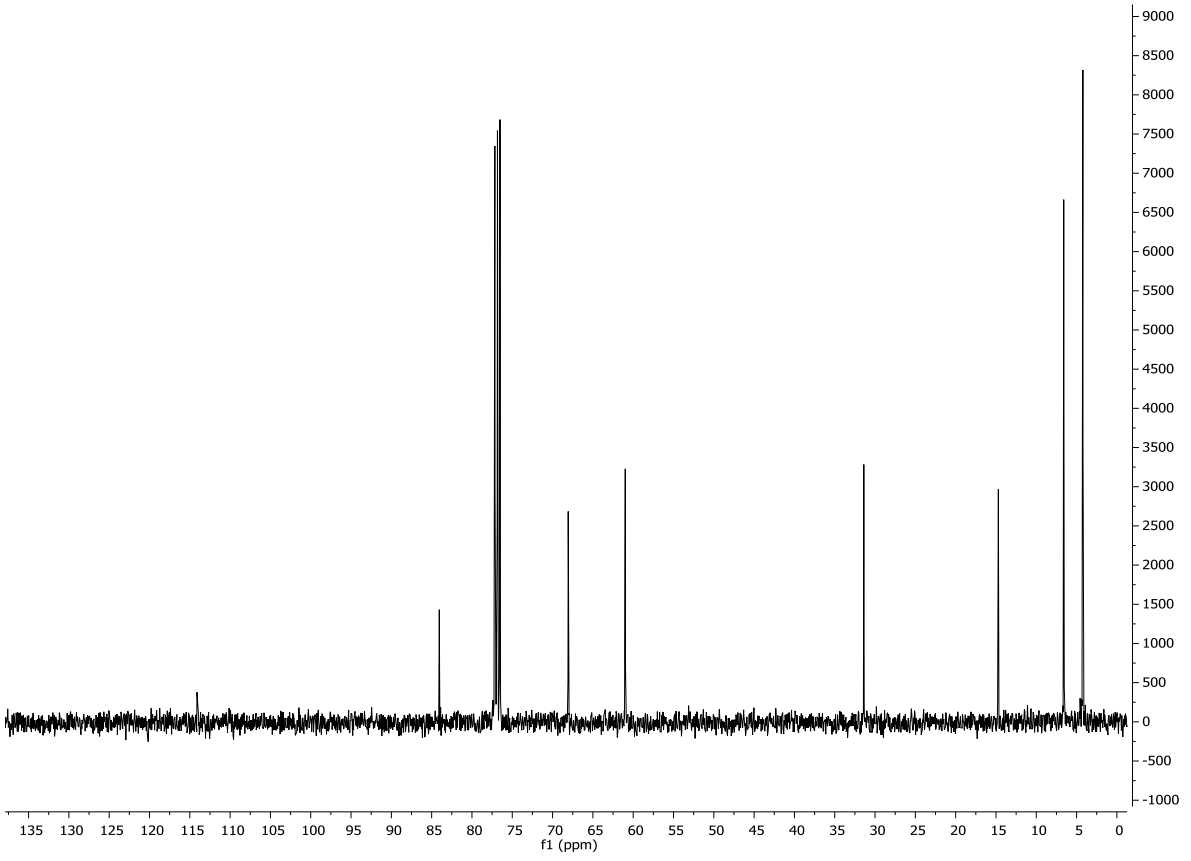

O
SO2Ph
190
f1 (ppm)

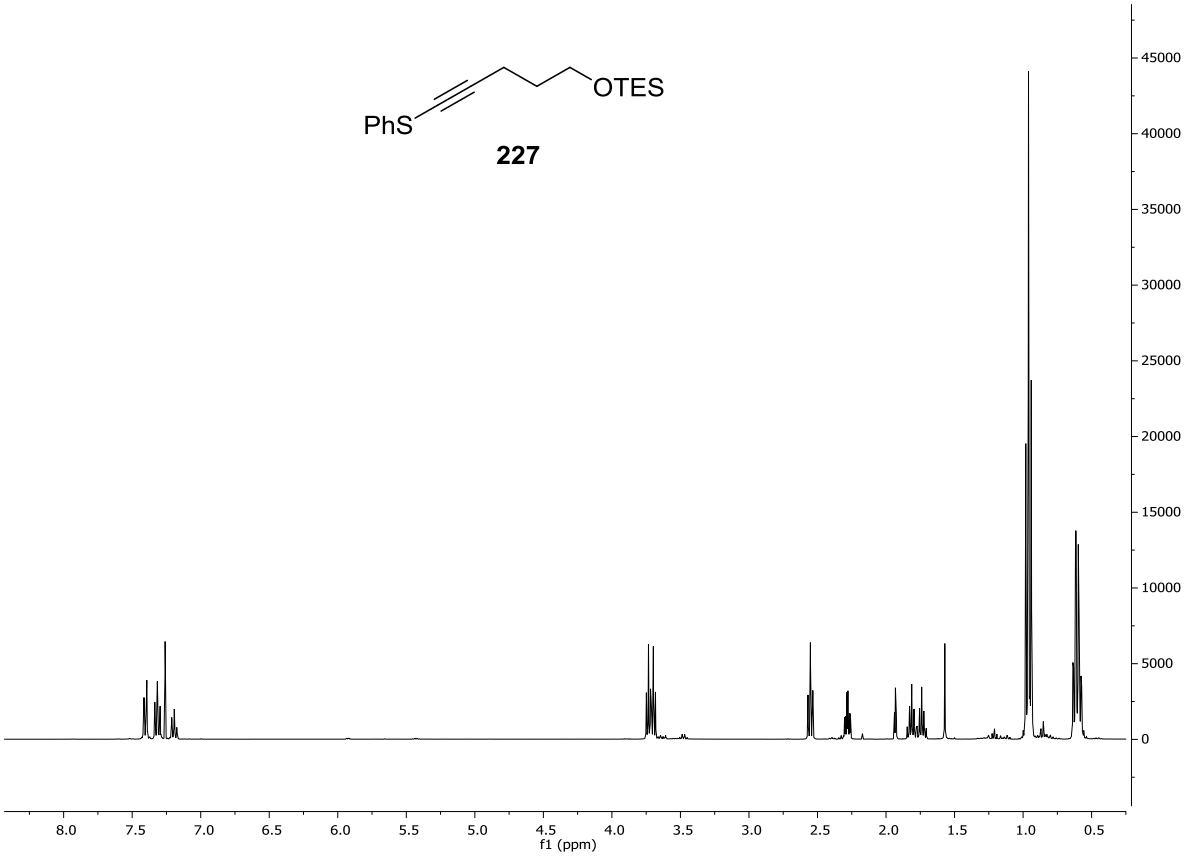

f1 (ppm)


O
SO2Ph
182
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

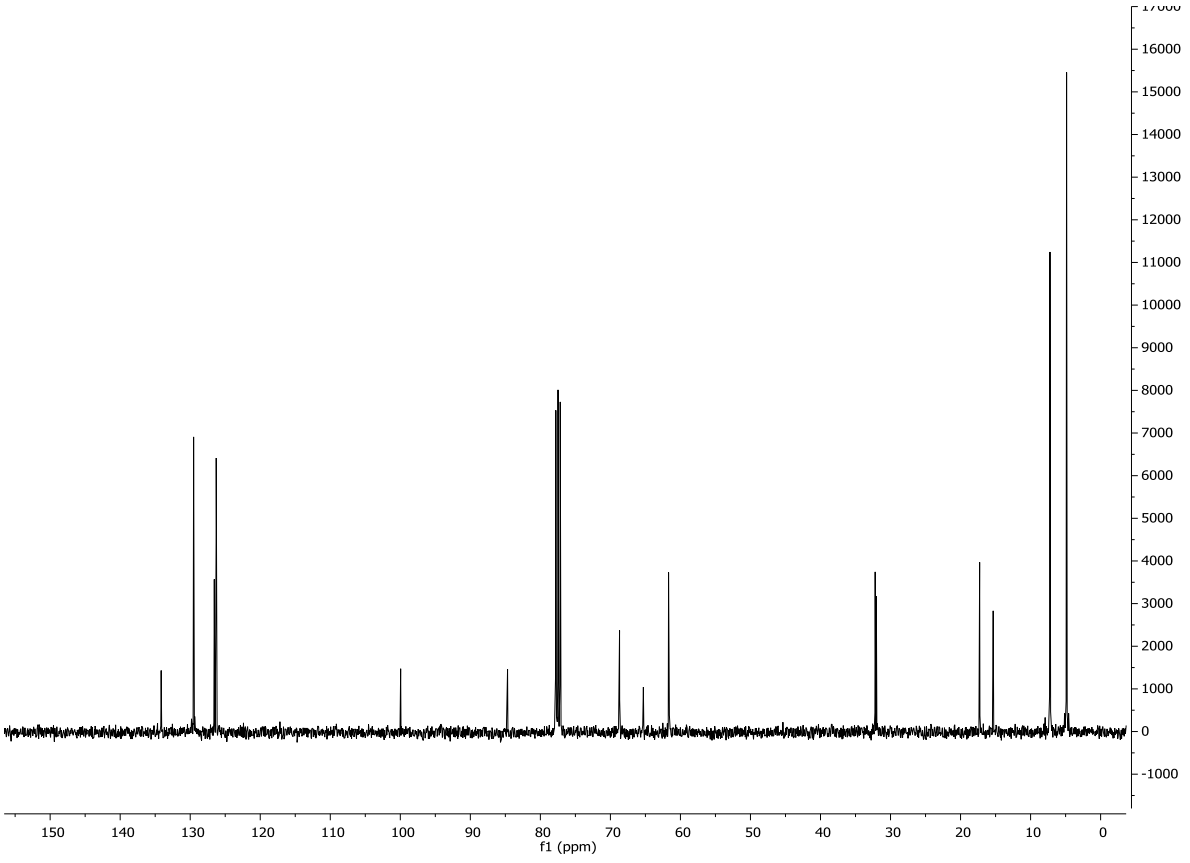

9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

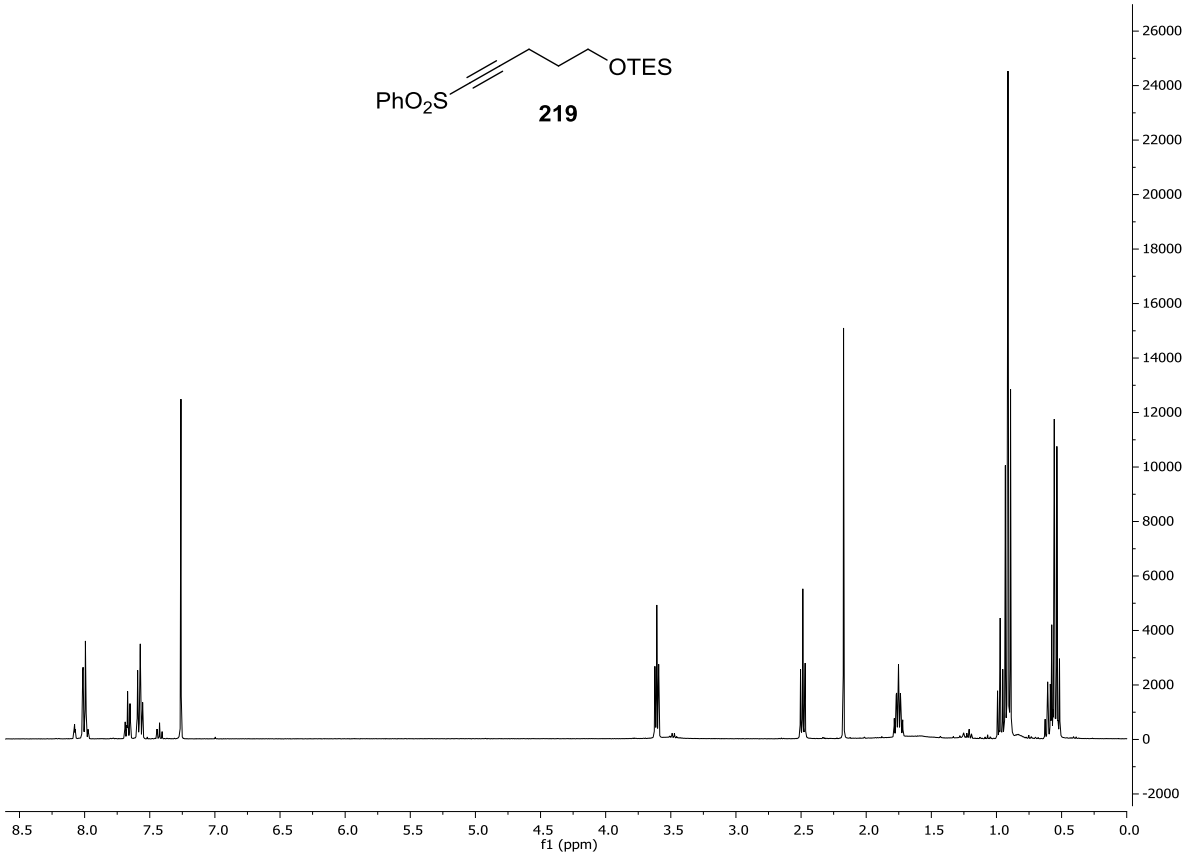

OTES
224
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

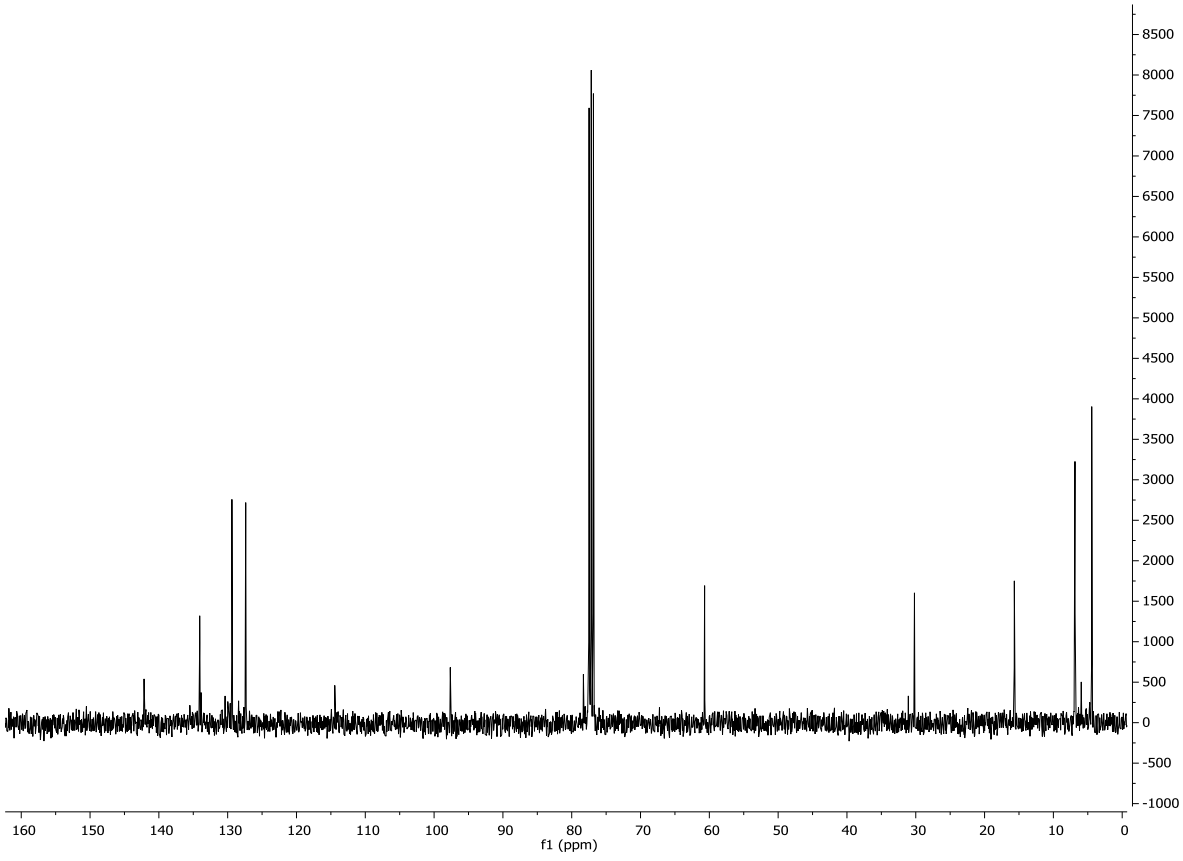

9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)

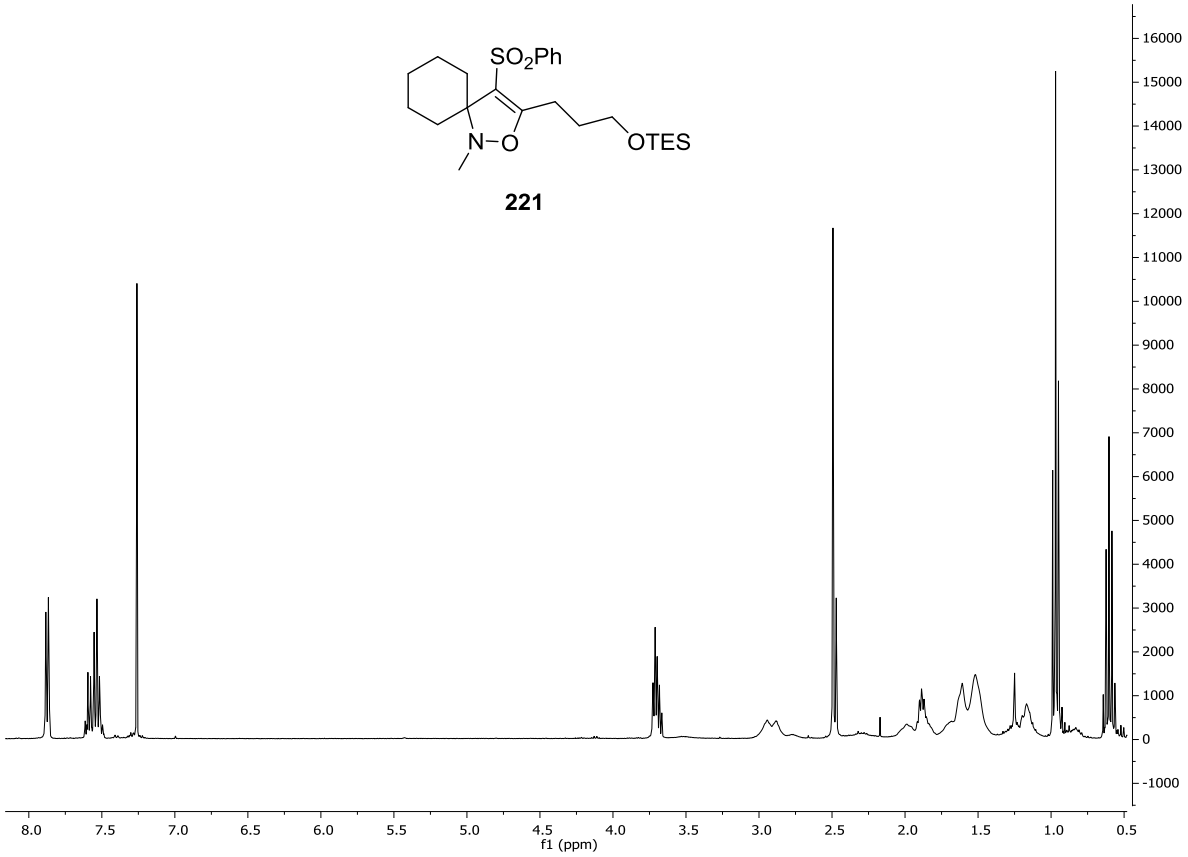

PhS
OTES
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

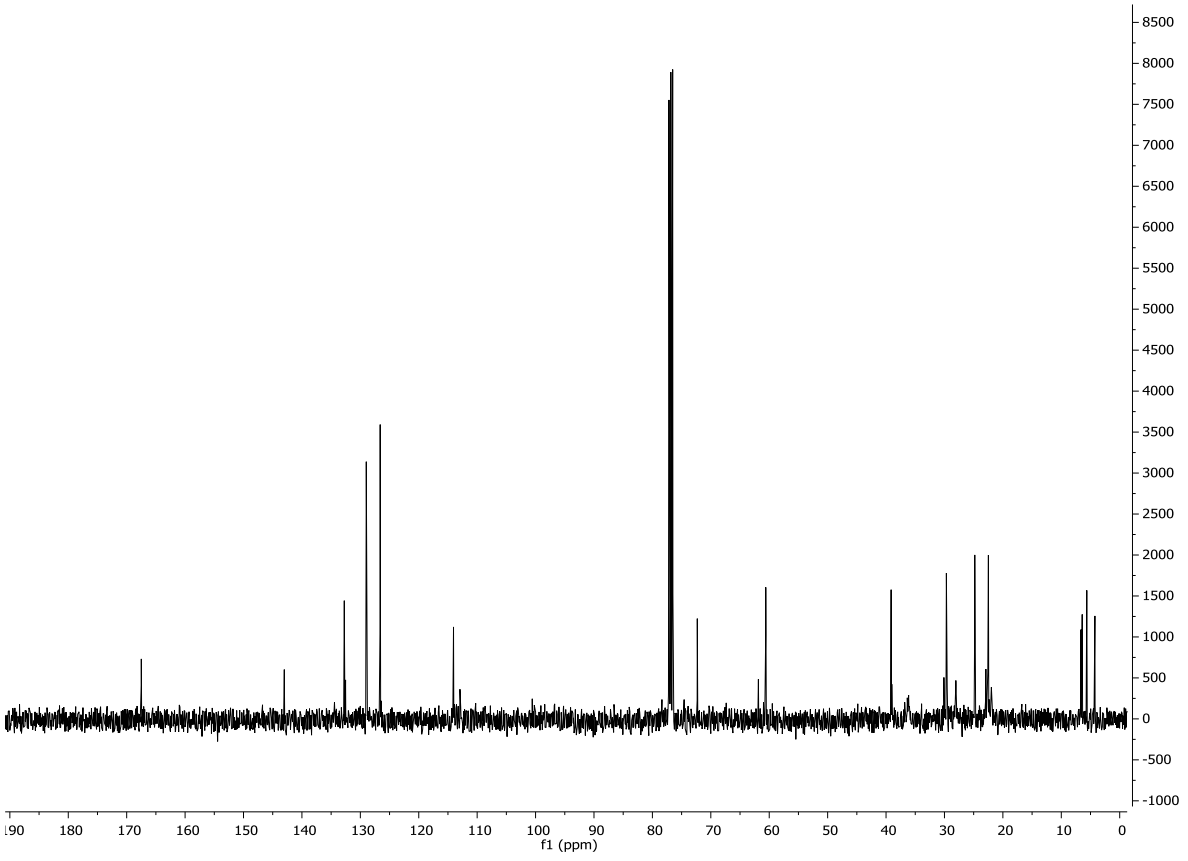
227

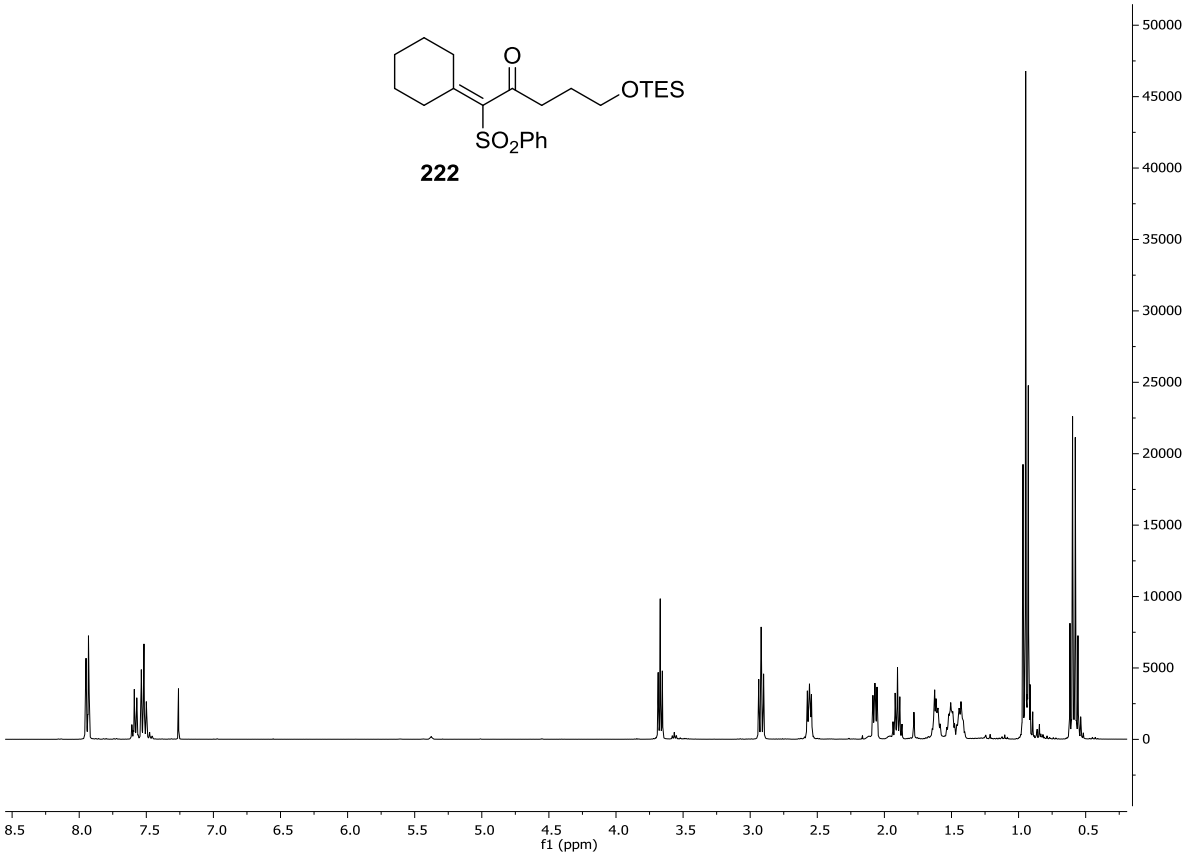

16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

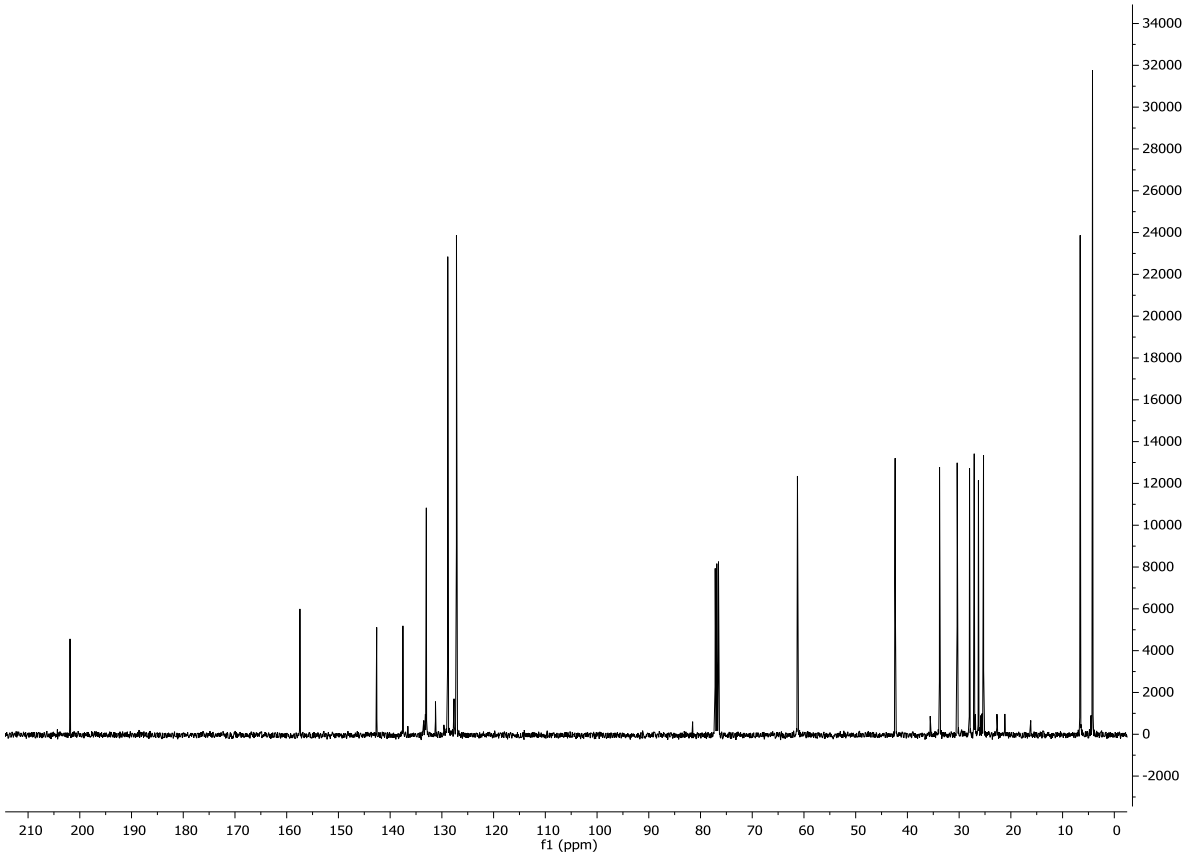

PhO2S
OTES
219
f1 (ppm)

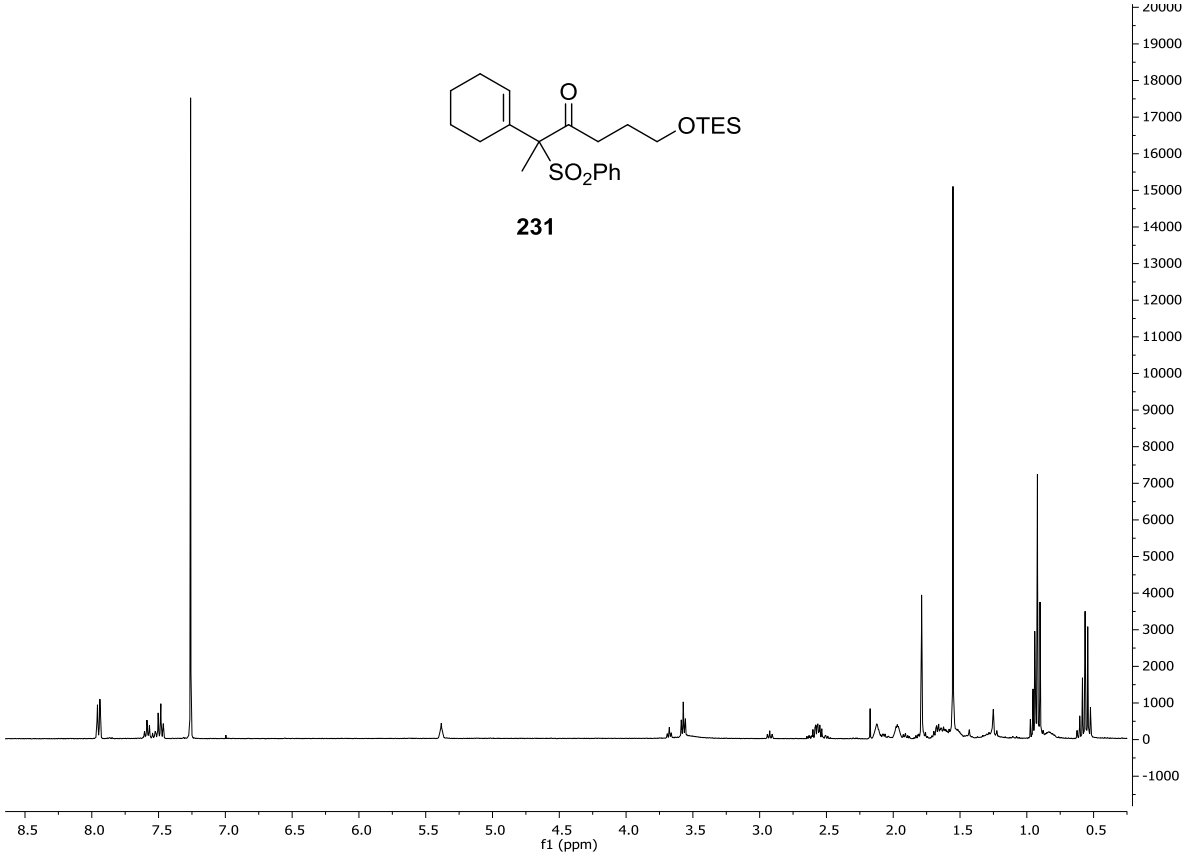

f1 (ppm)

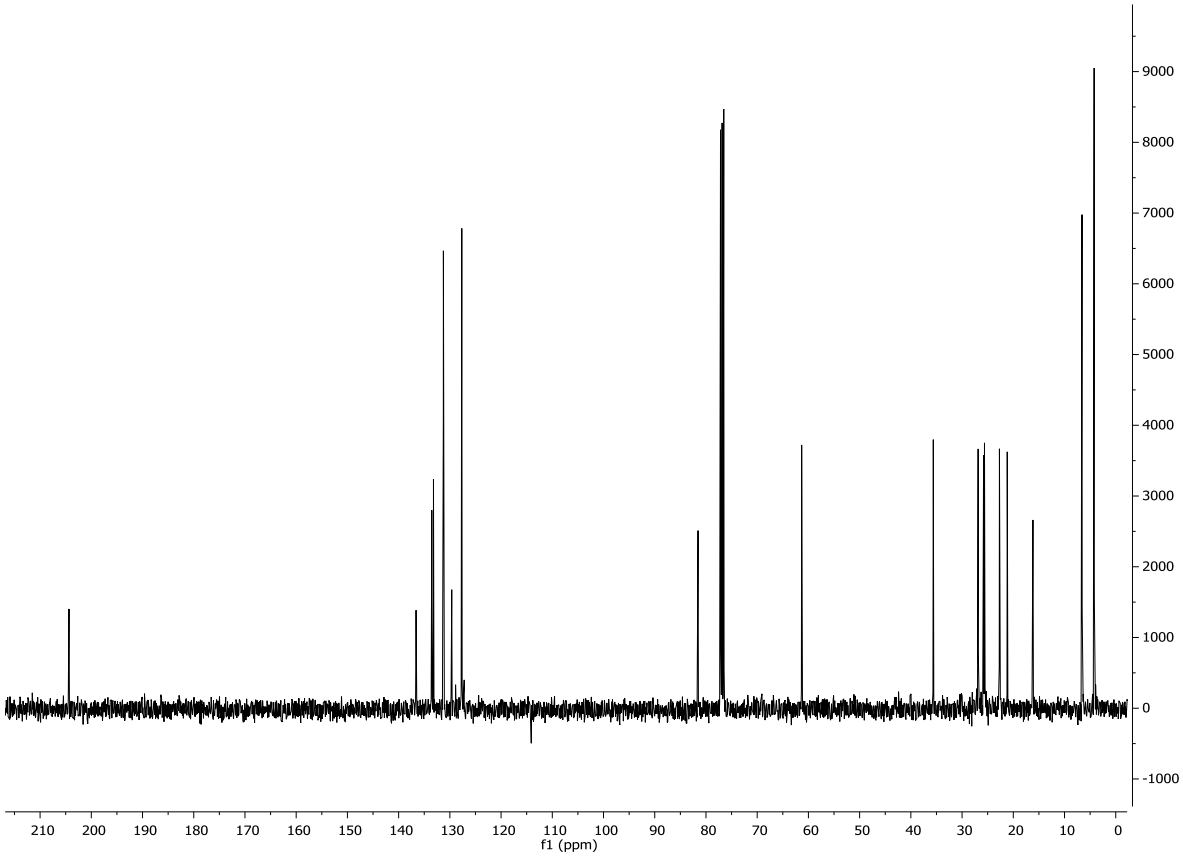

SO2Ph
N−O
OTES
221
f1 (ppm)

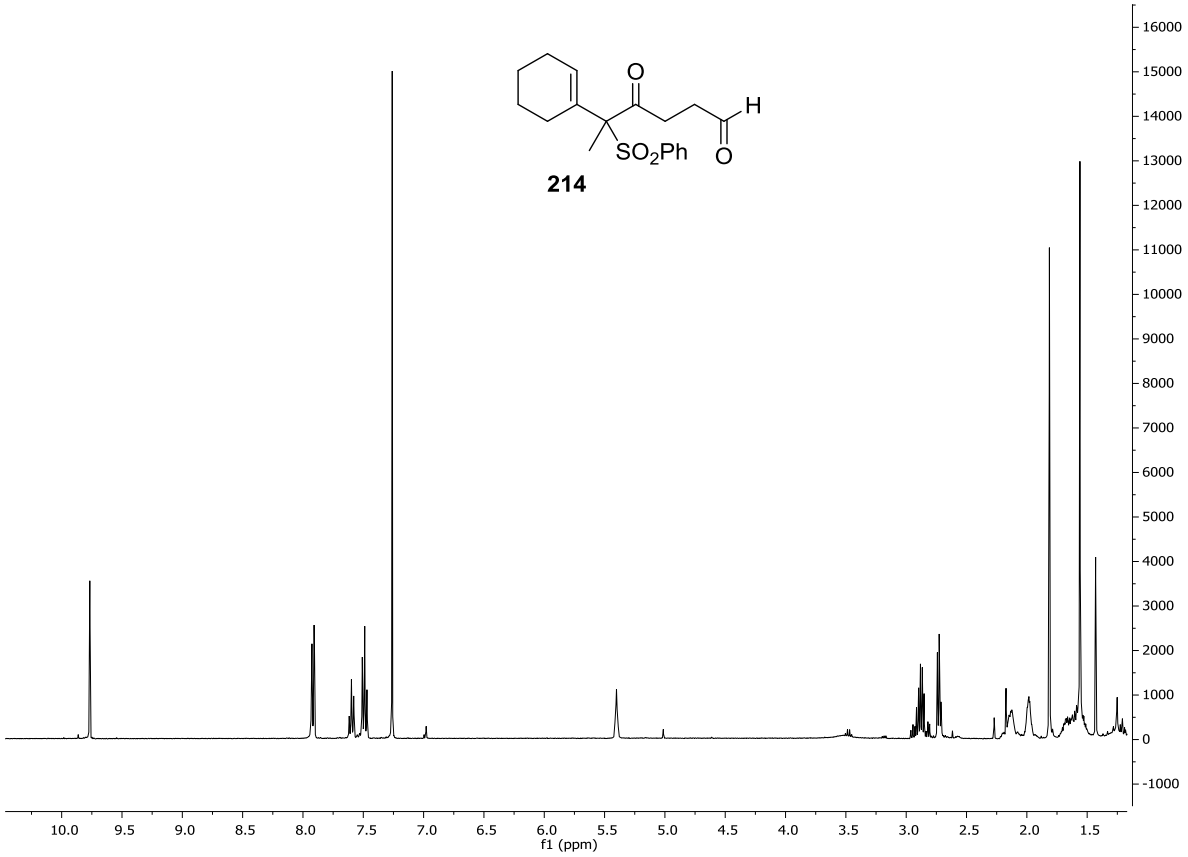

f1 (ppm)

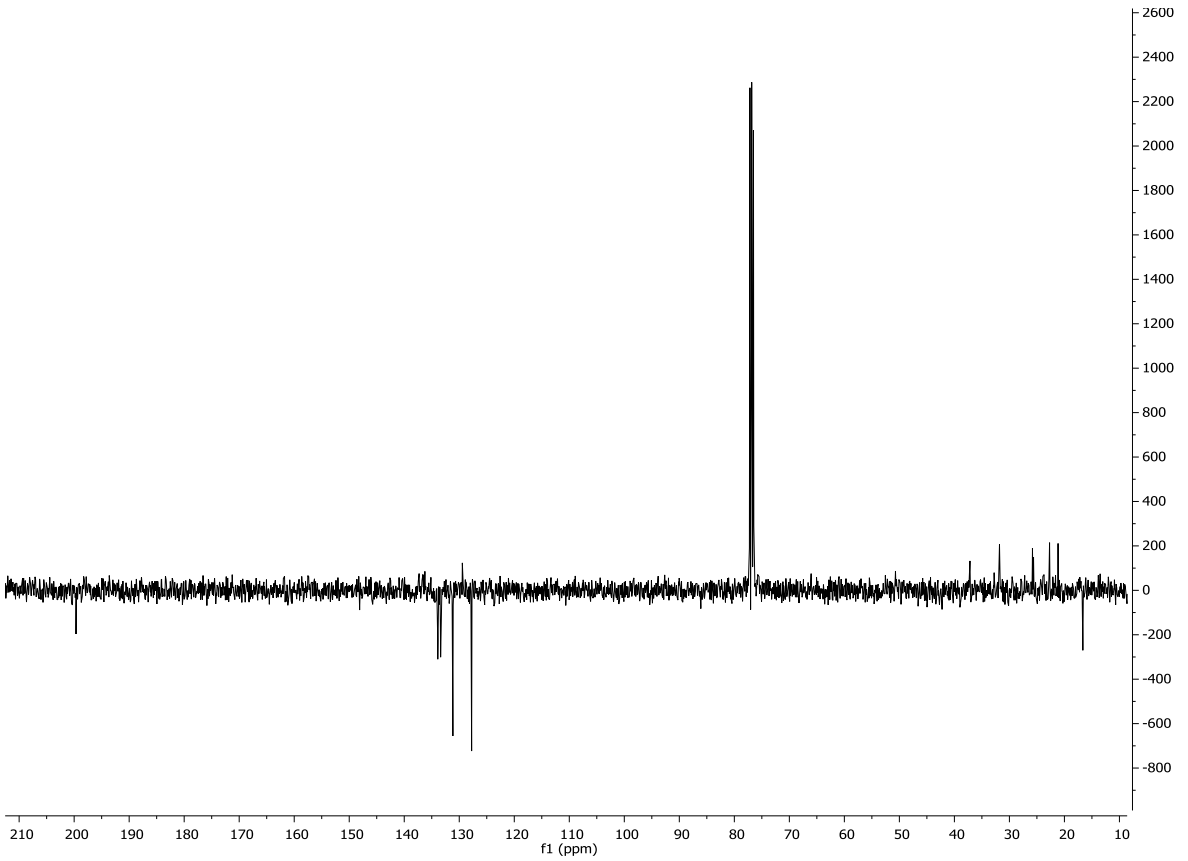

O
OTES
SO2Ph
222
f1 (ppm)

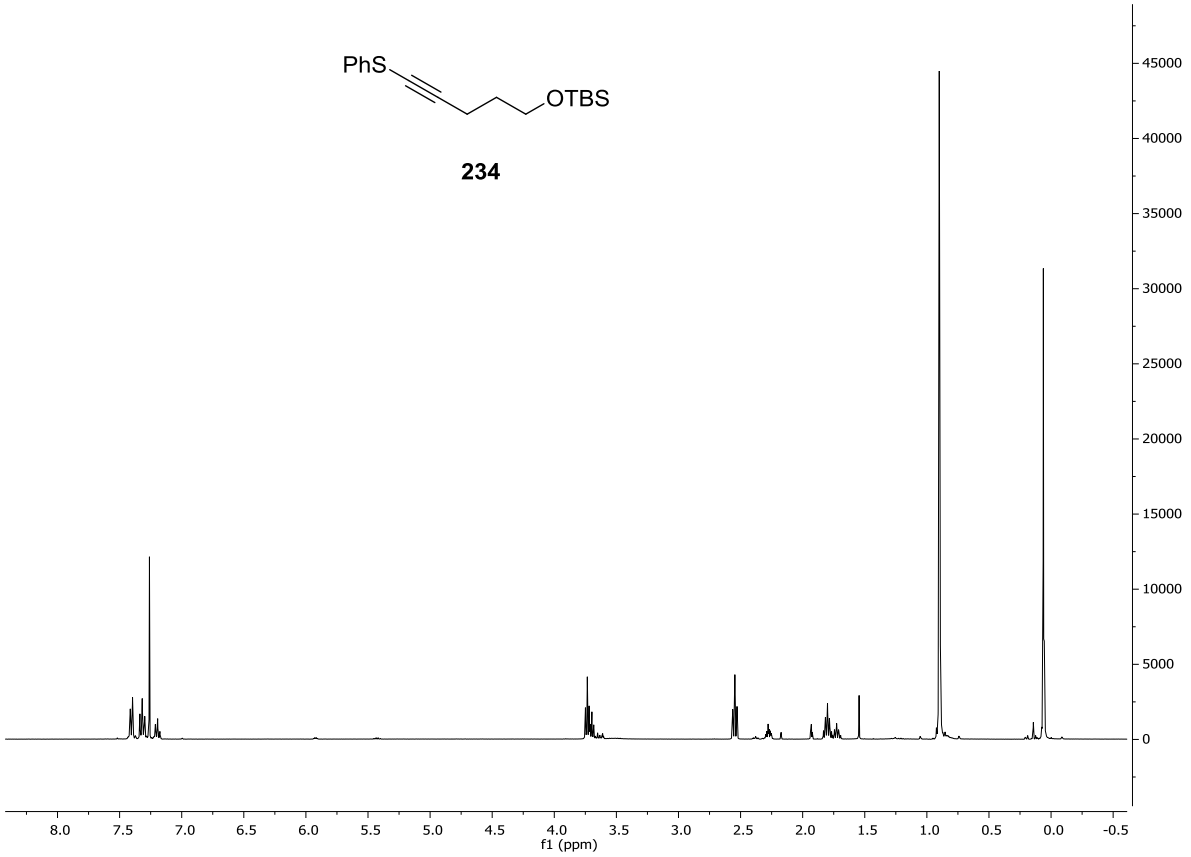

f1 (ppm)

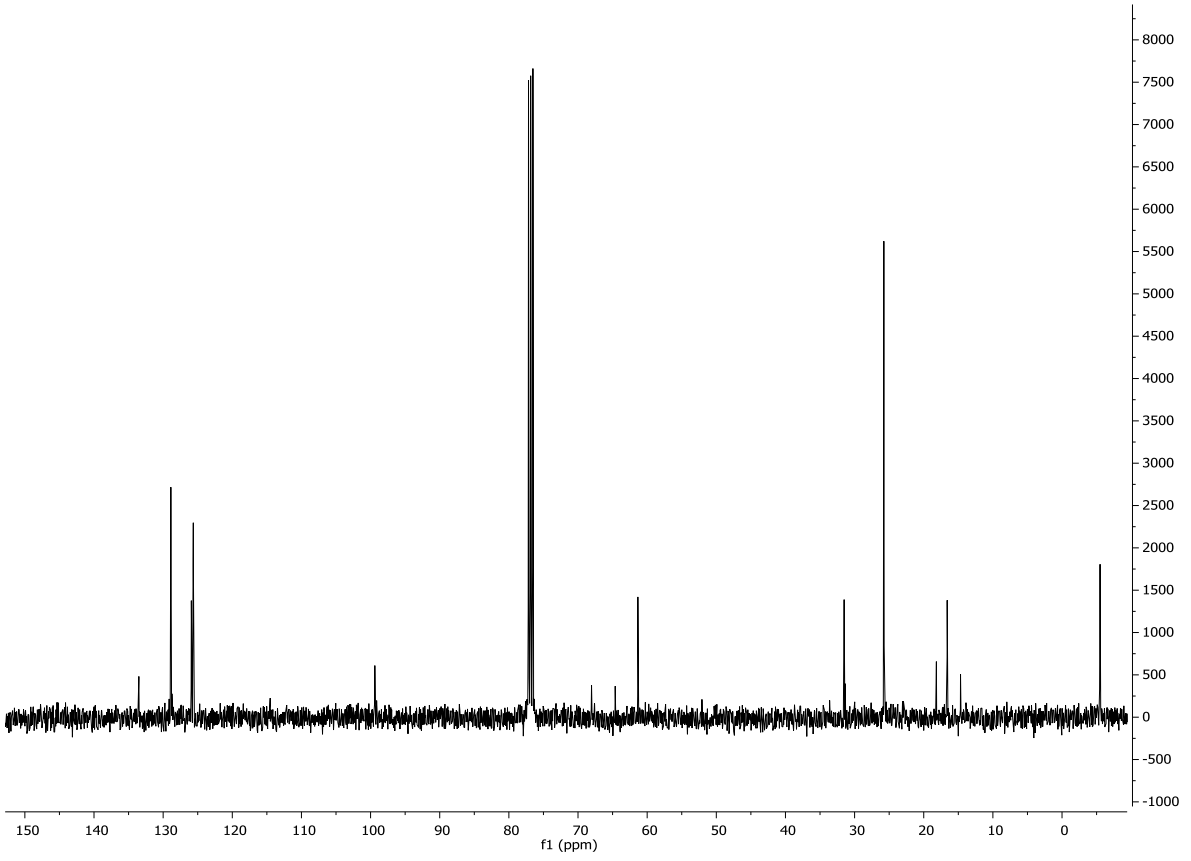

O
OTES
SO2Ph
231
f1 (ppm)

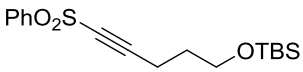

f1 (ppm)


O
H
SO2Ph
O
214
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)


2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
-800
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

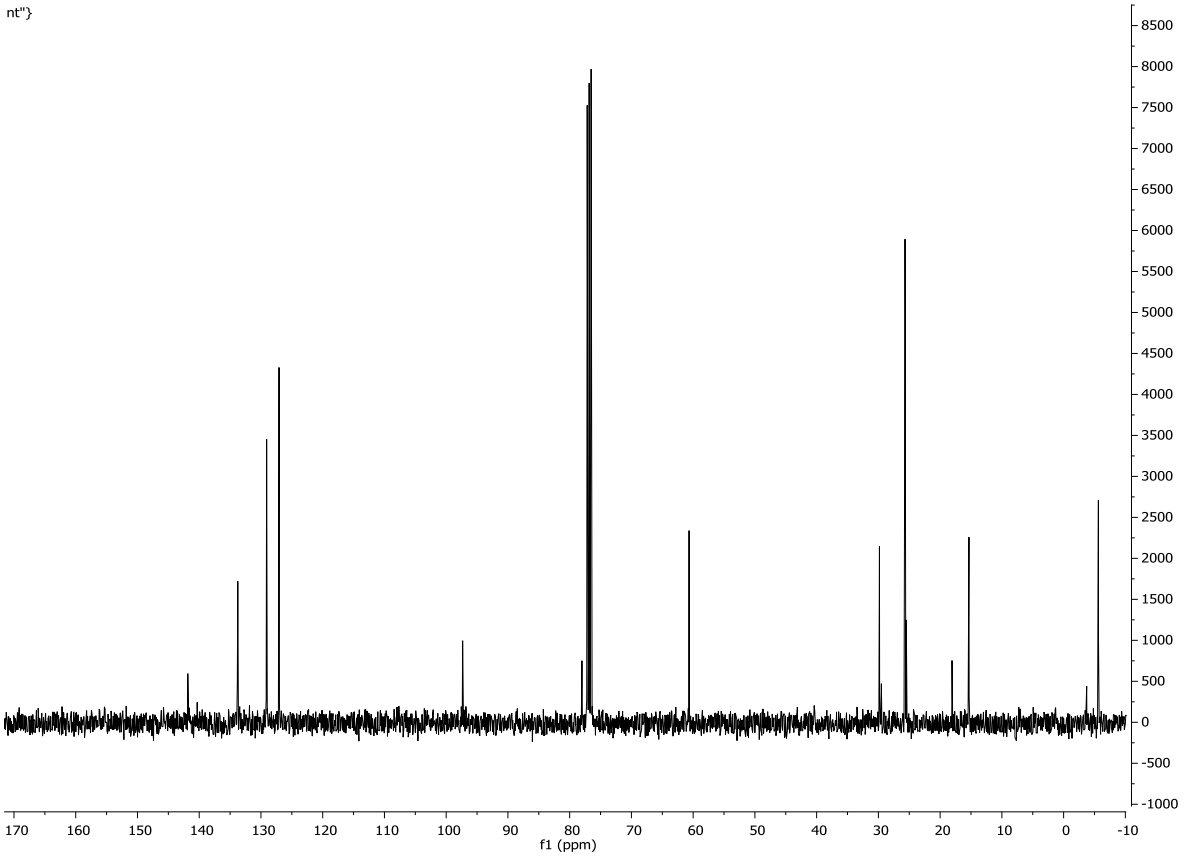

PhS
OTBS
234
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

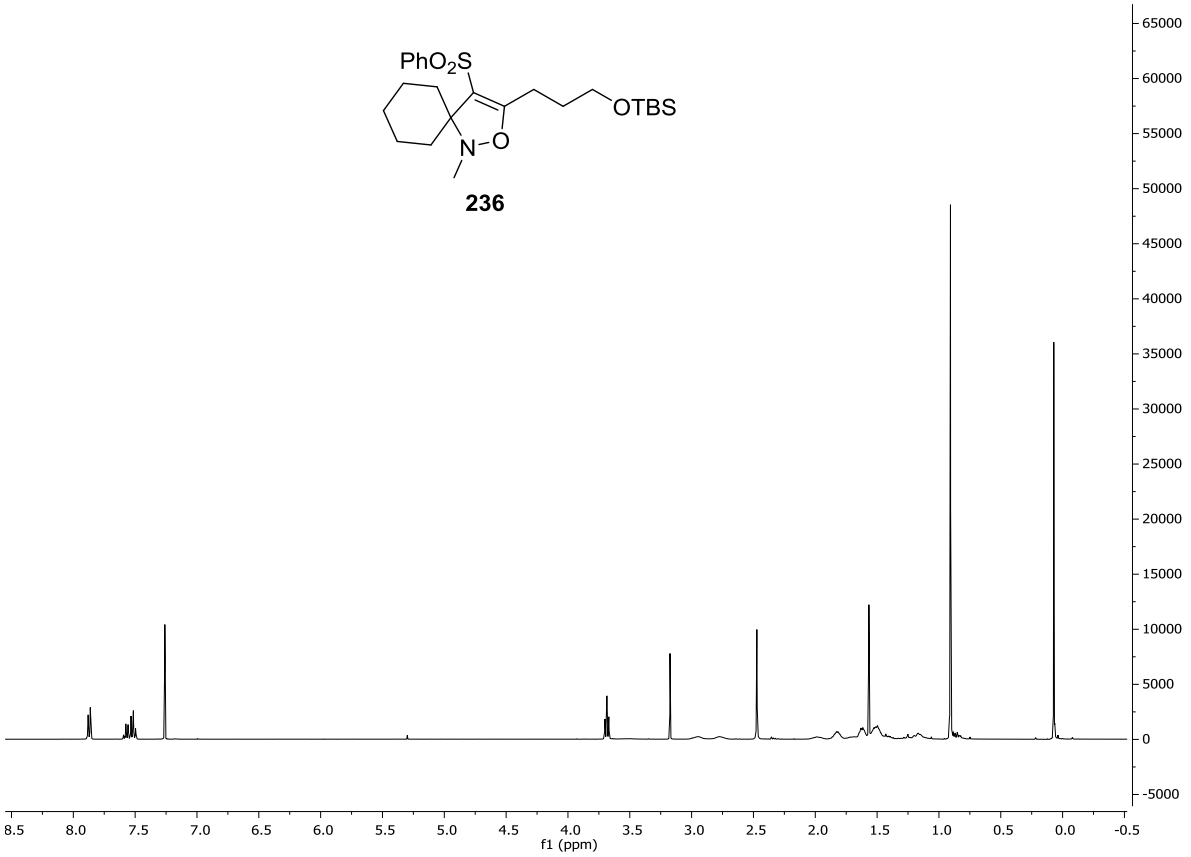

8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


PhO2S
OTBS

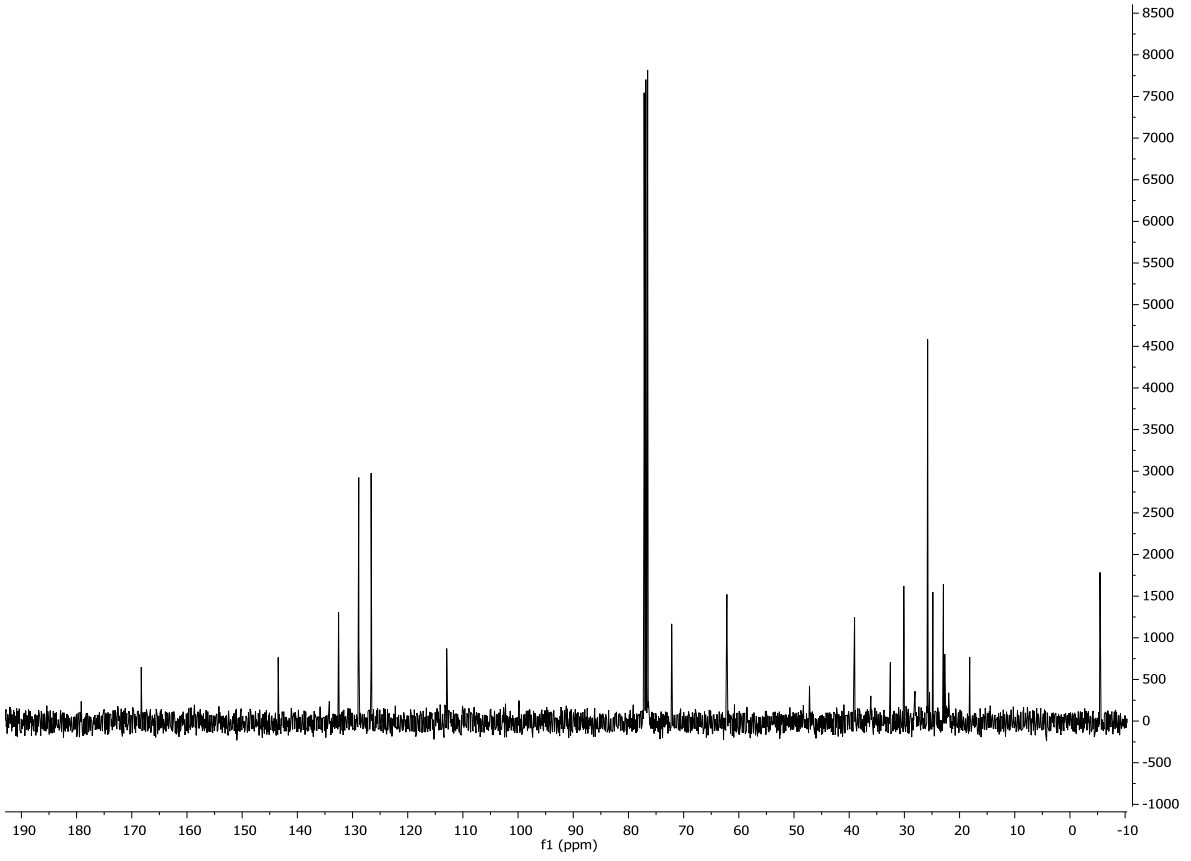
235

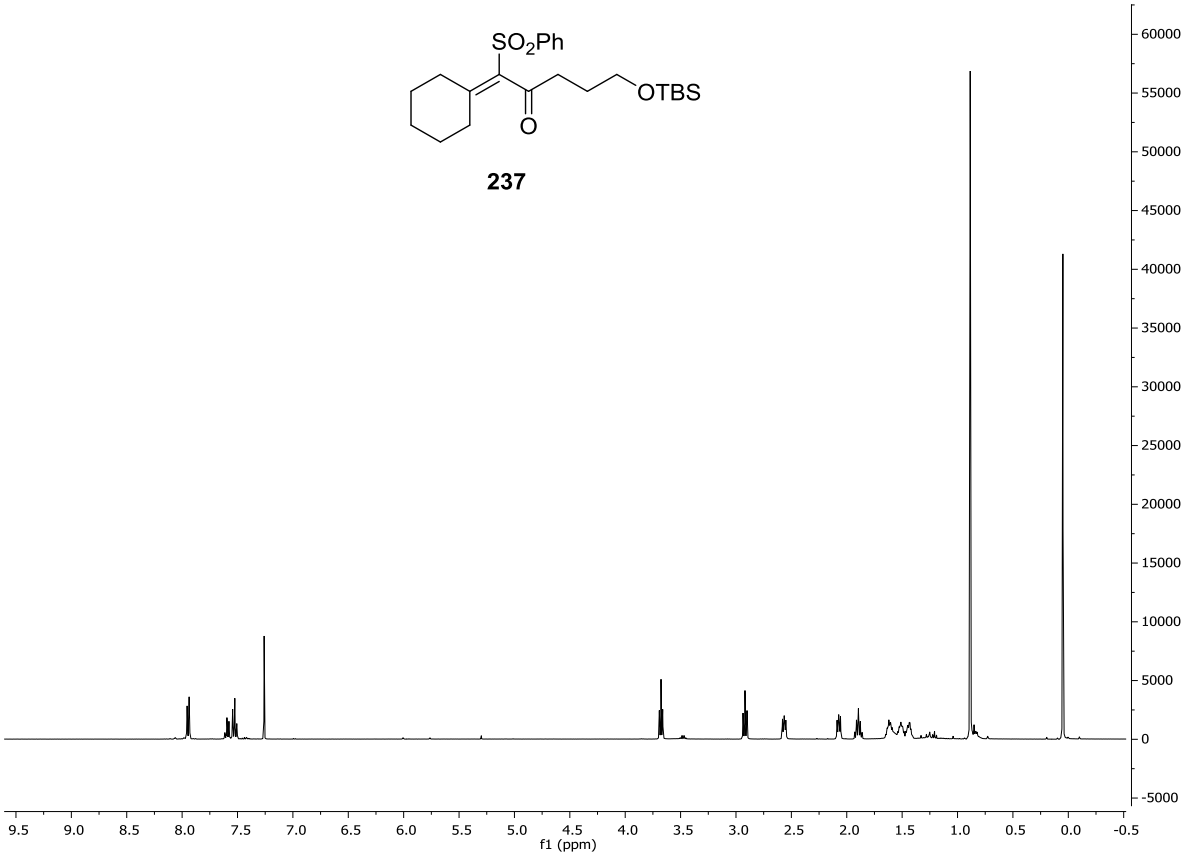
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


nt"}
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

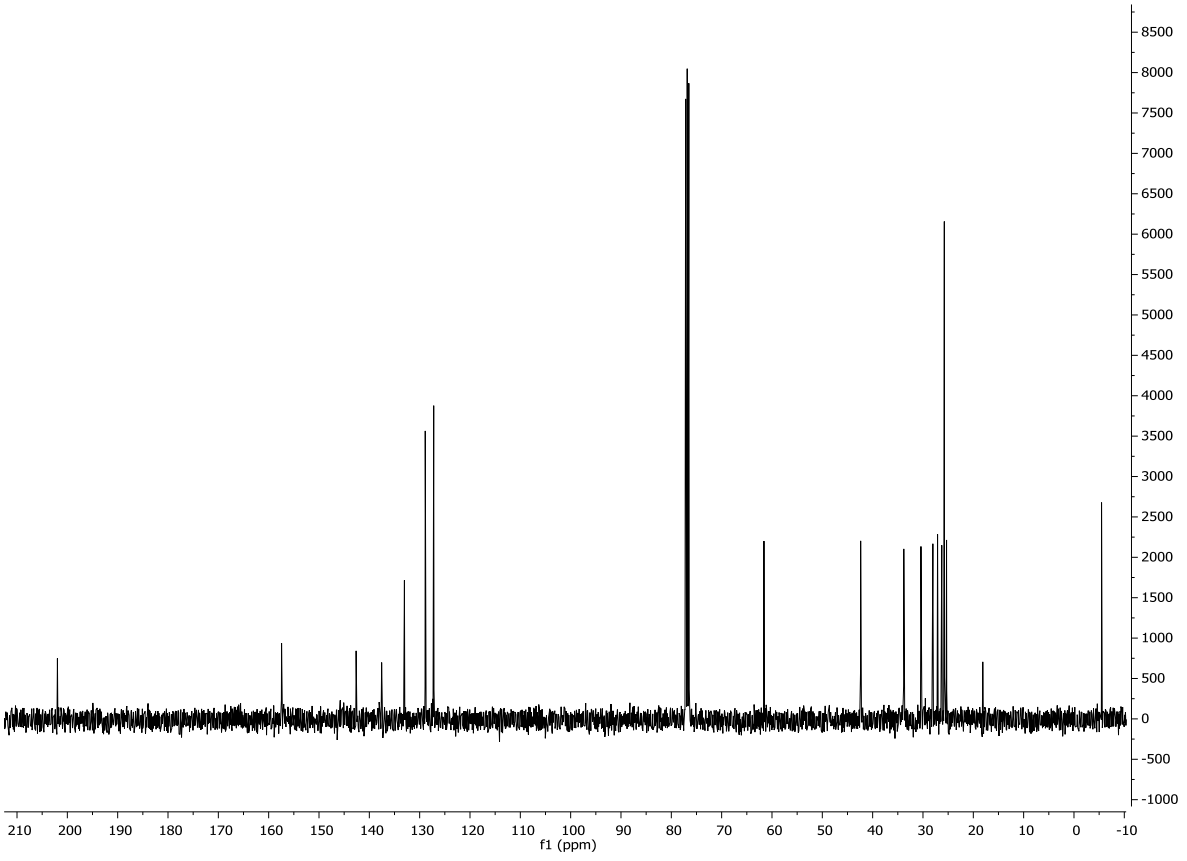


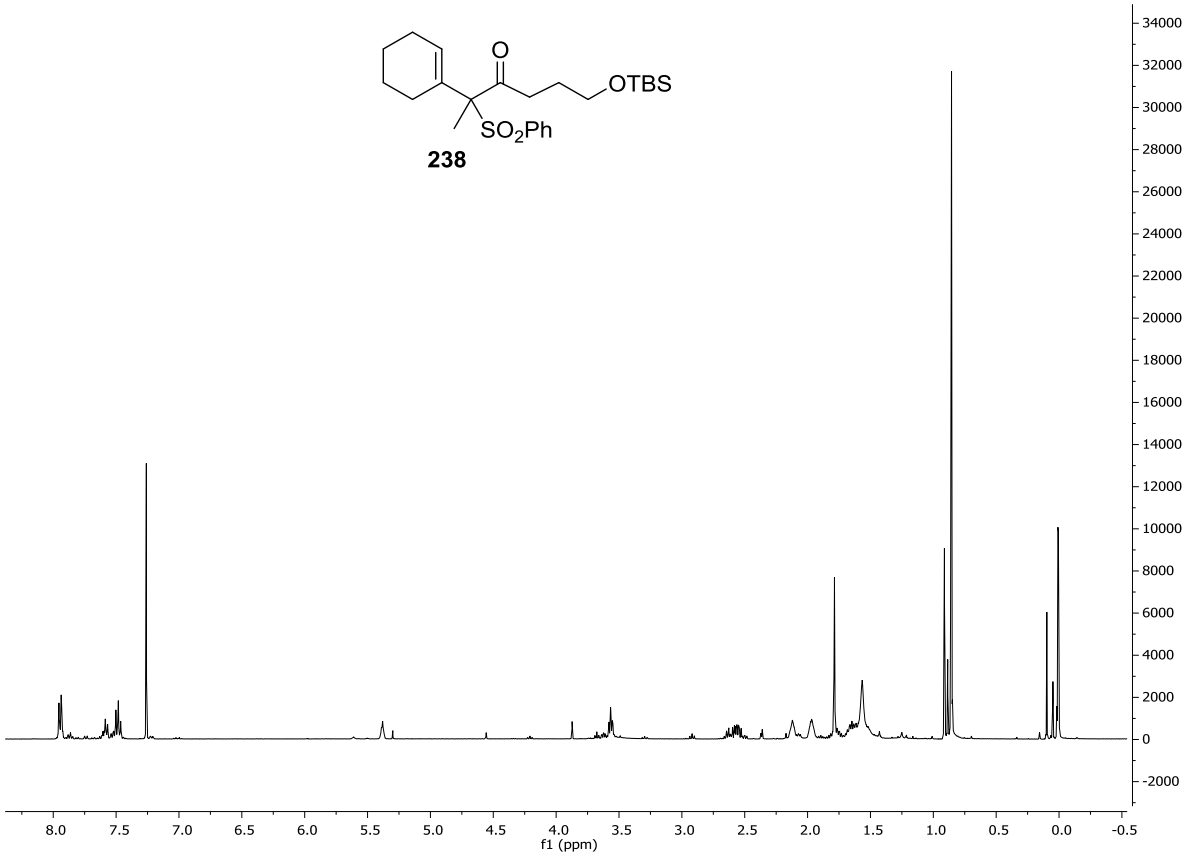
236

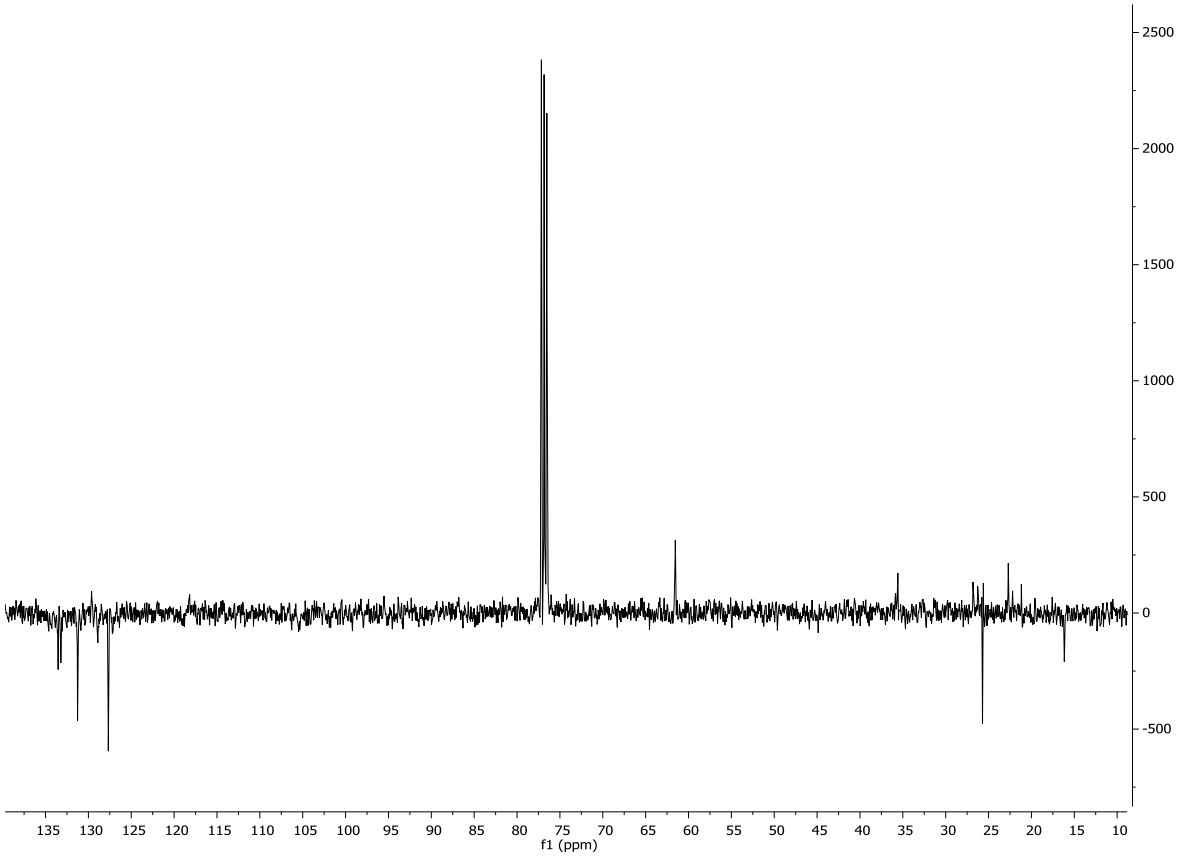


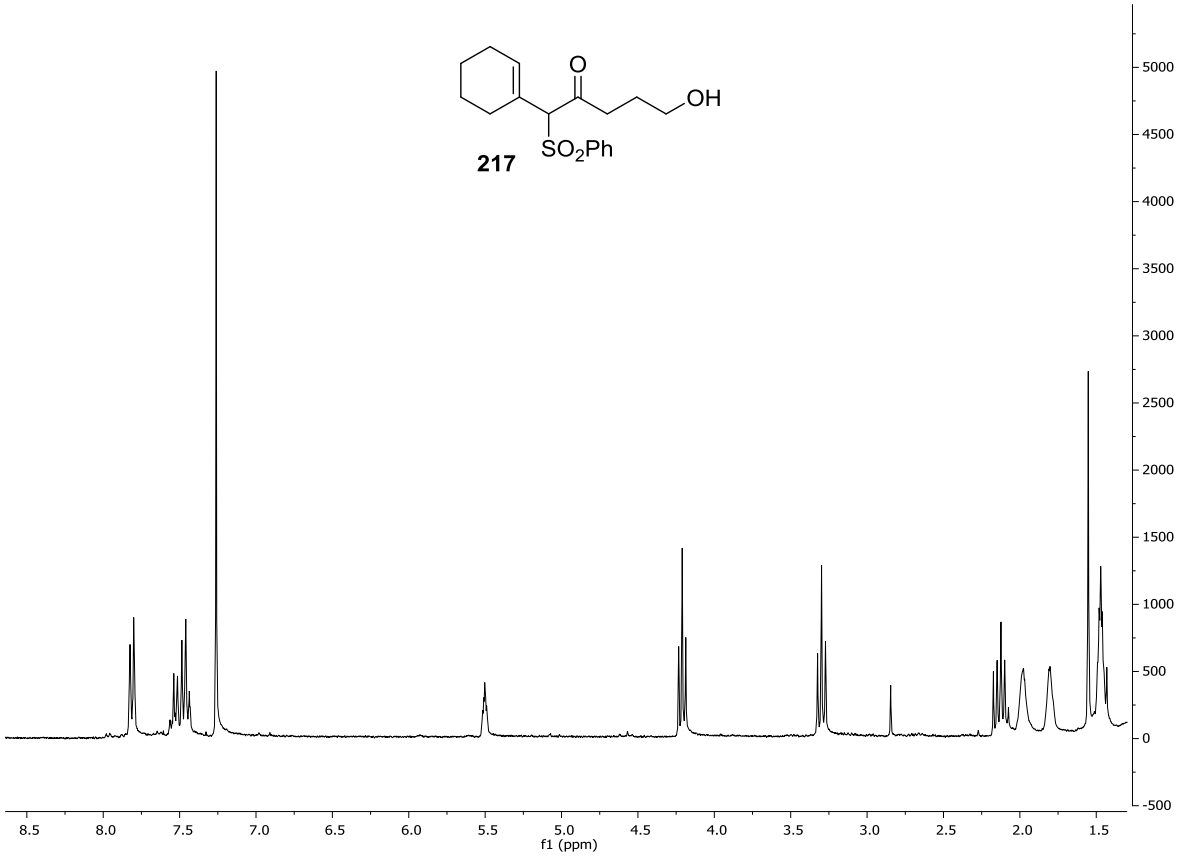

SO2Ph
OTBS
O
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

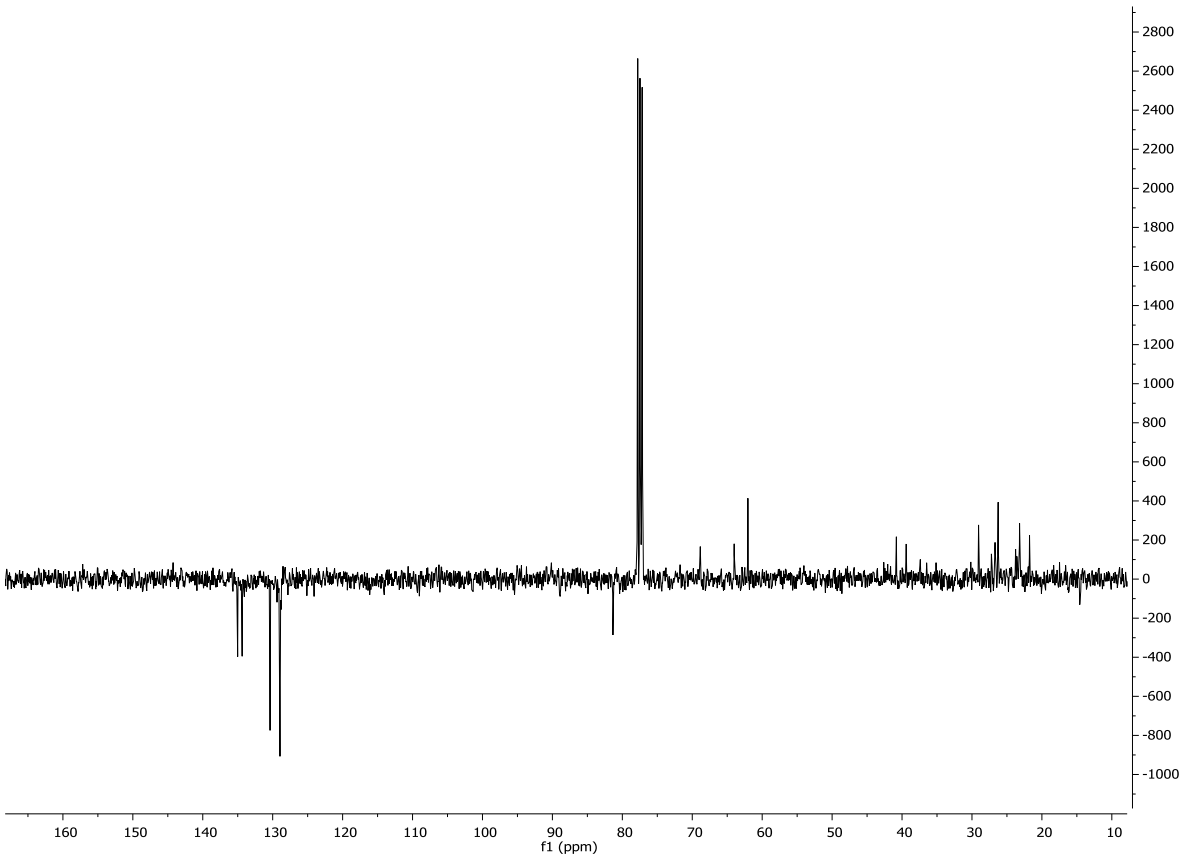
237

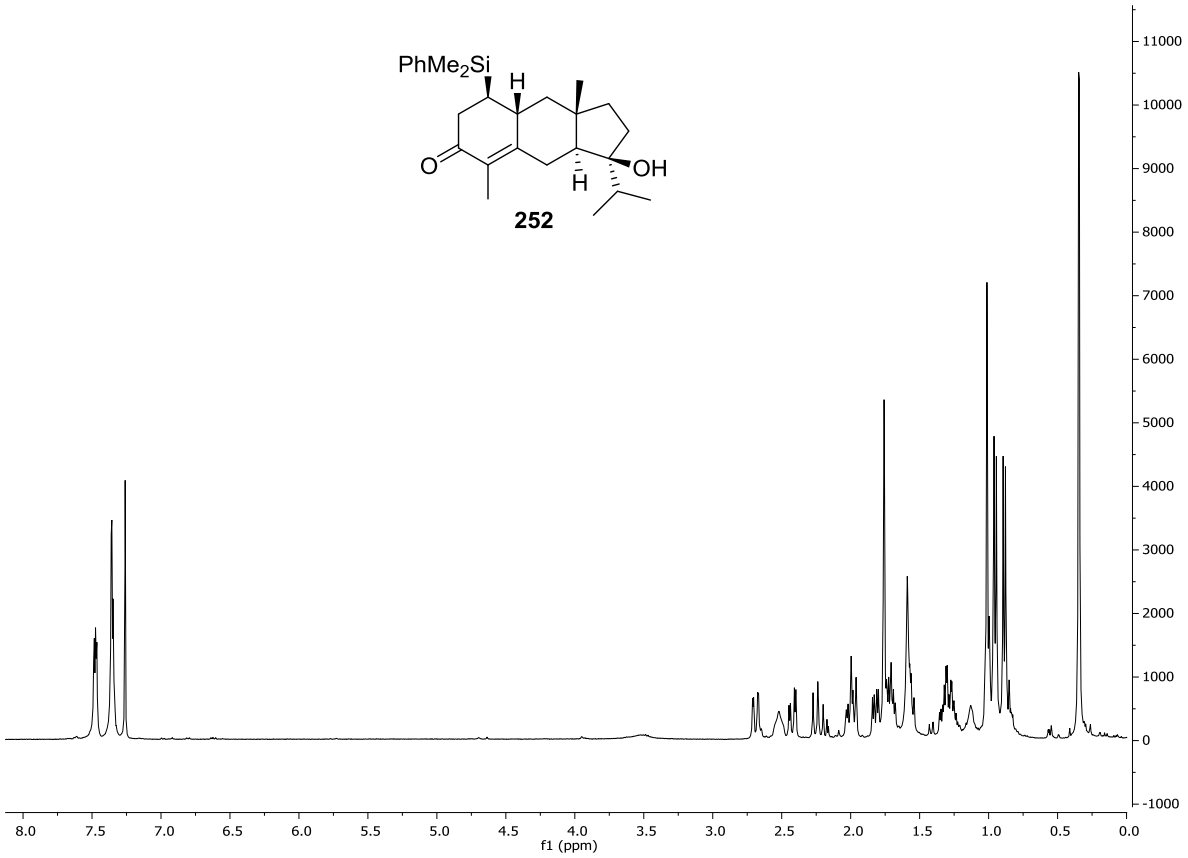

8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

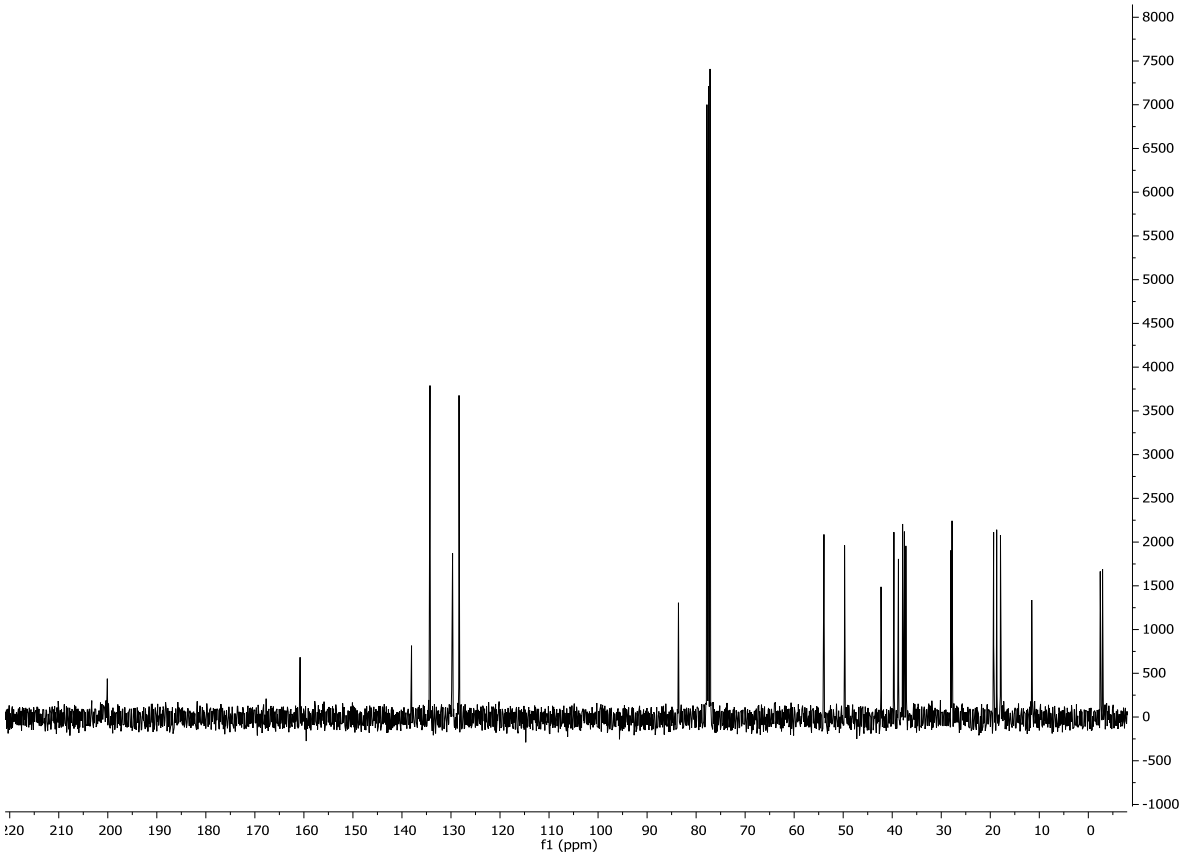

O
OTBS
SO2Ph
238
f1 (ppm)

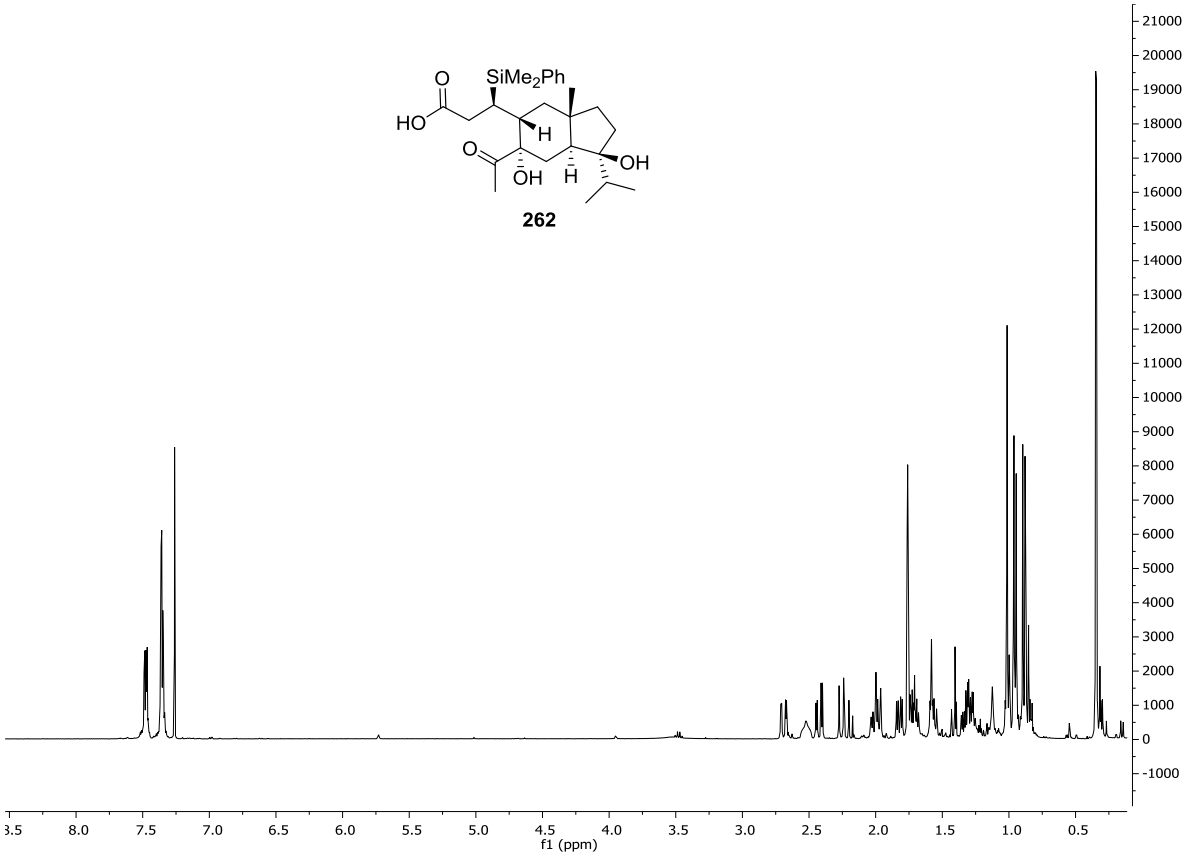

f1 (ppm)

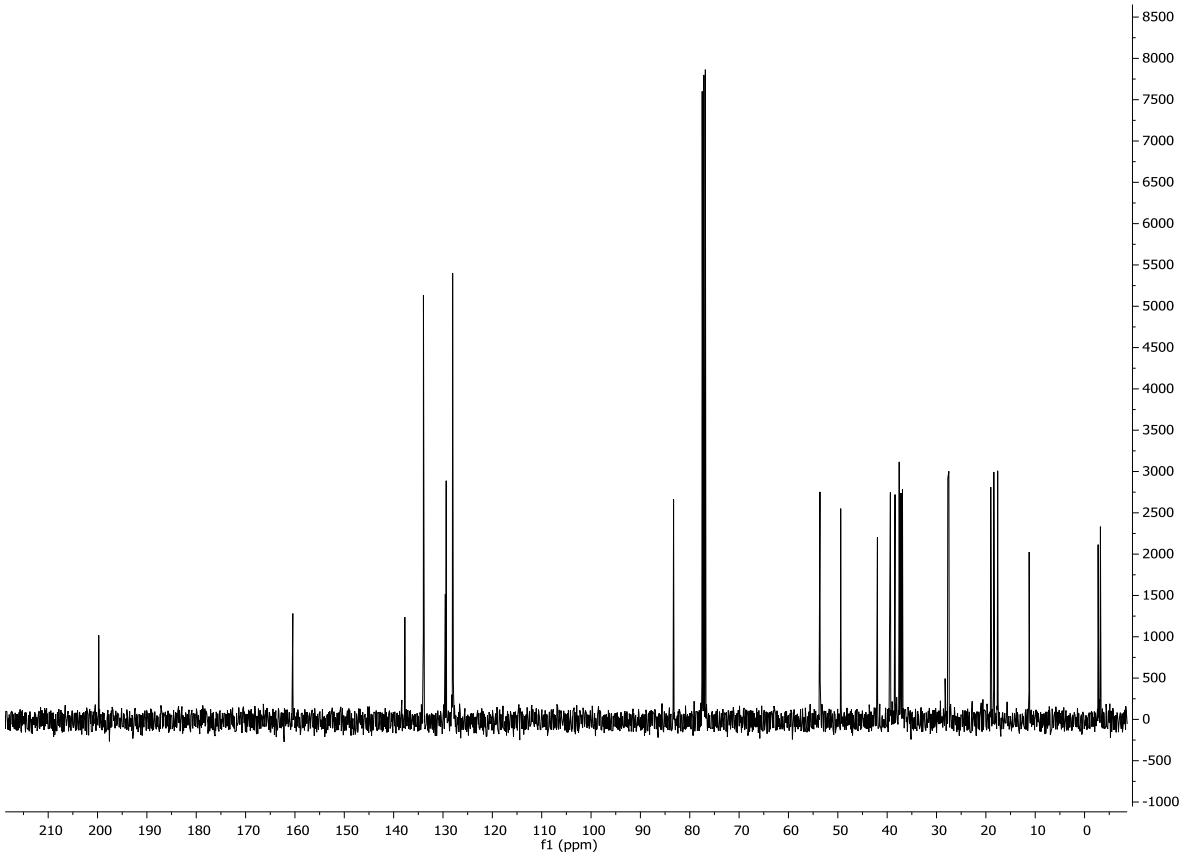

O
OH
SO2Ph
217
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

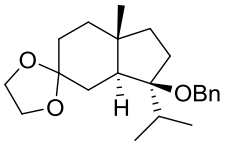

2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
-800
-1000
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


PhMe2Si
H
O
OH
H
252
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

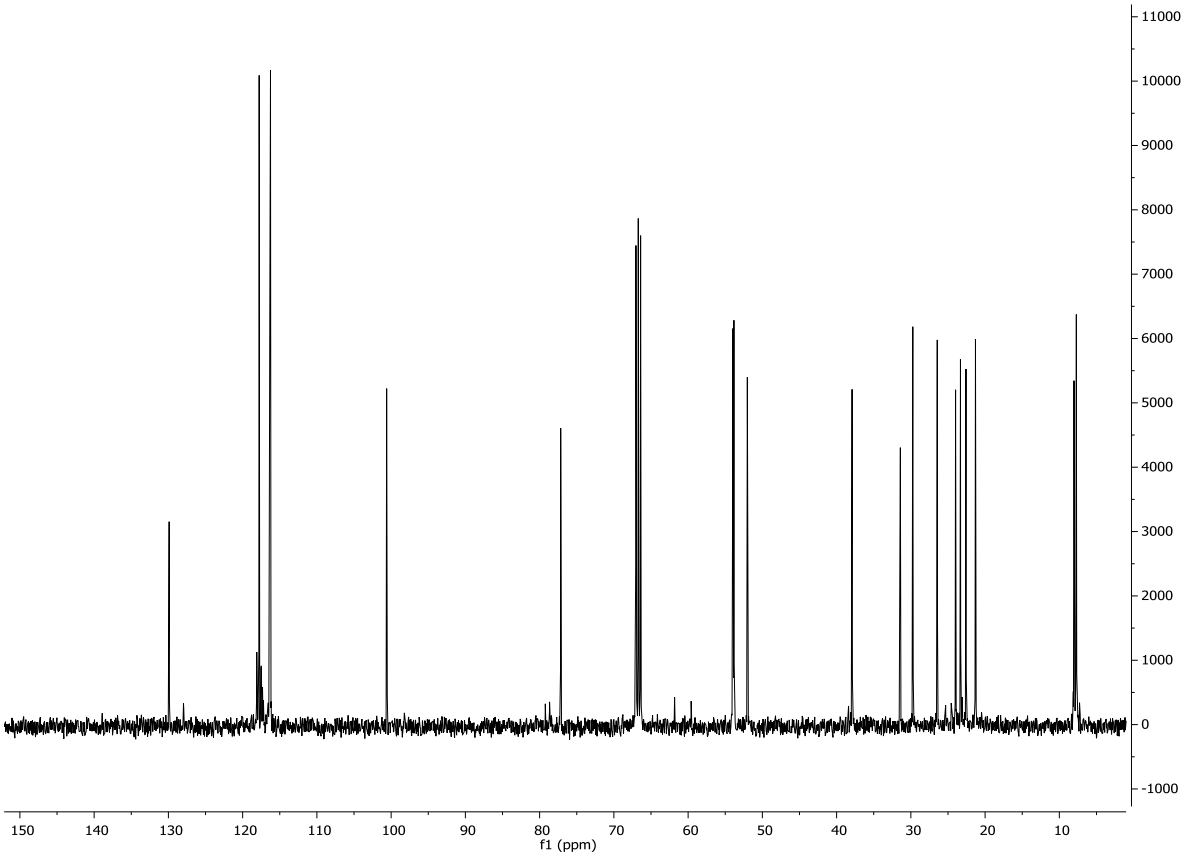

O
SiMe2Ph
HO
H
O
OH
H
OH
262
f1 (ppm)

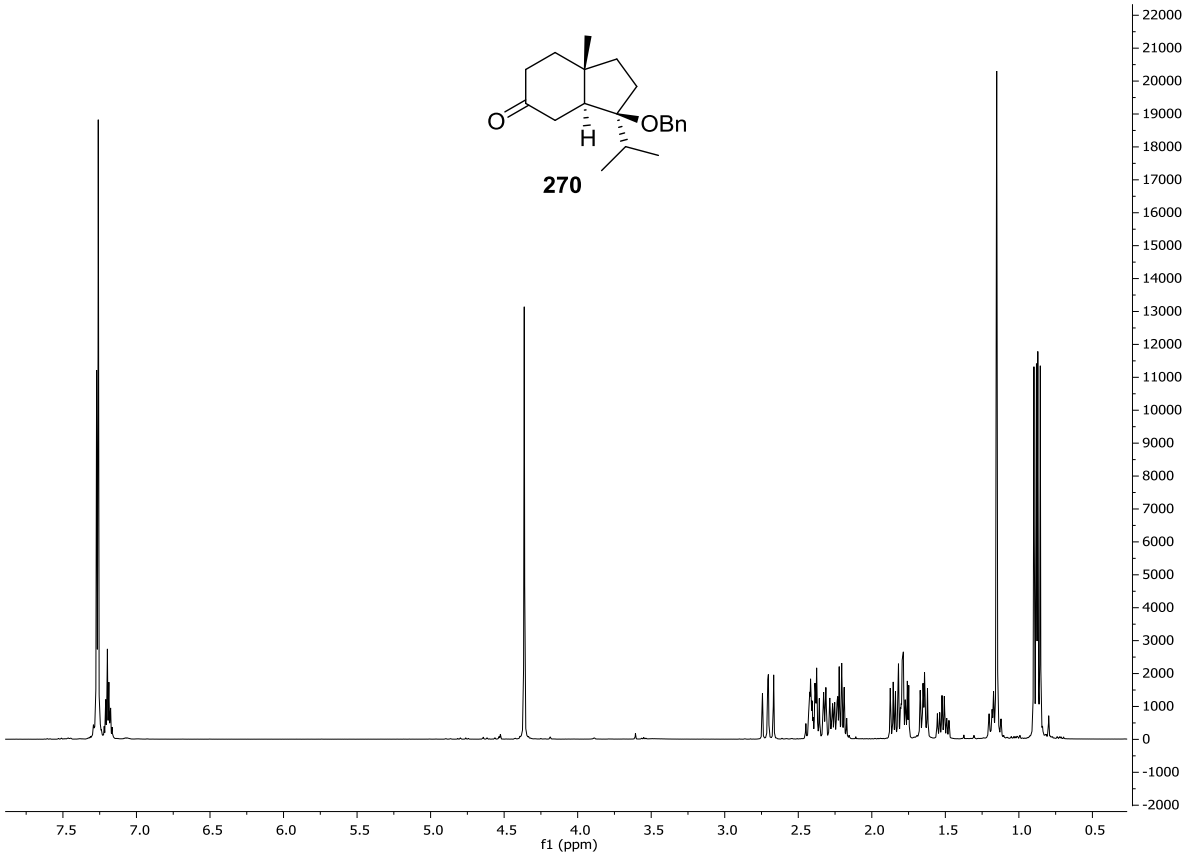

f1 (ppm)

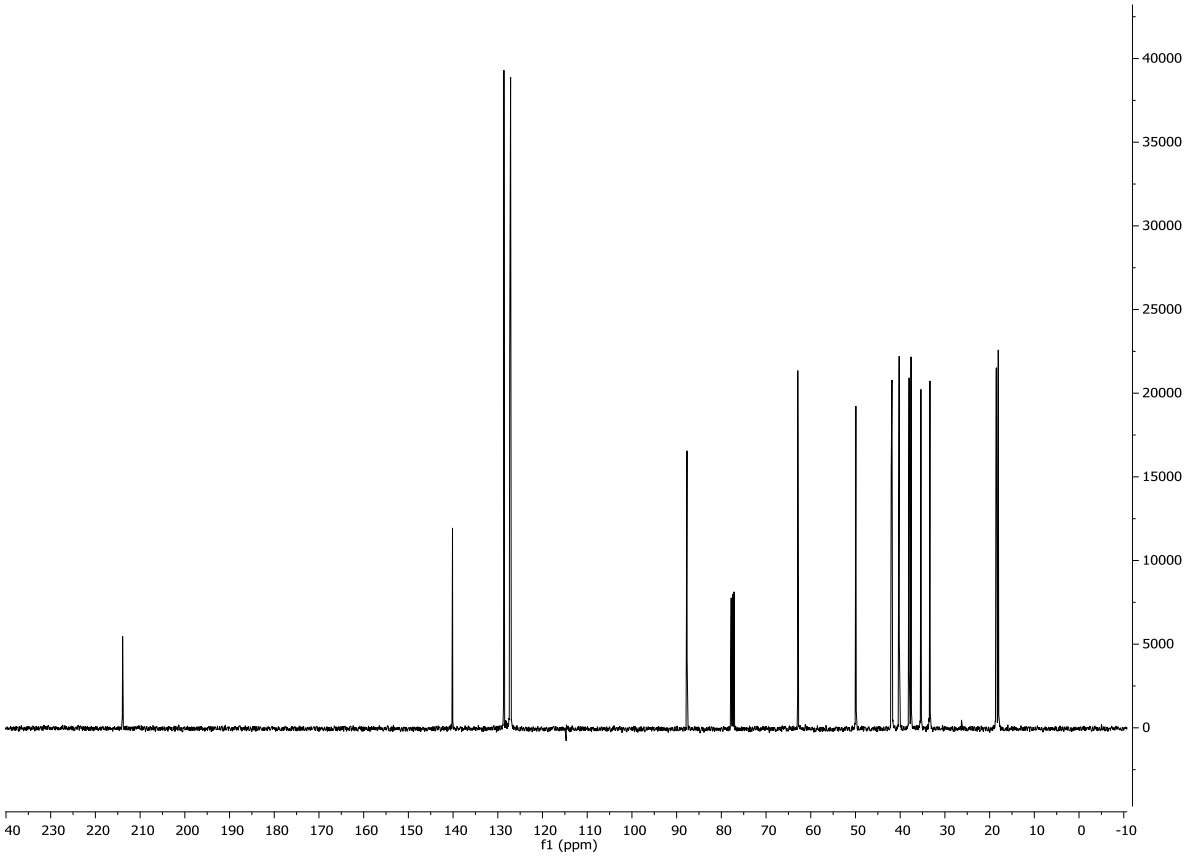

O
O
H
OBn

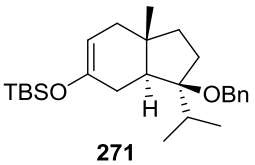
327

18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

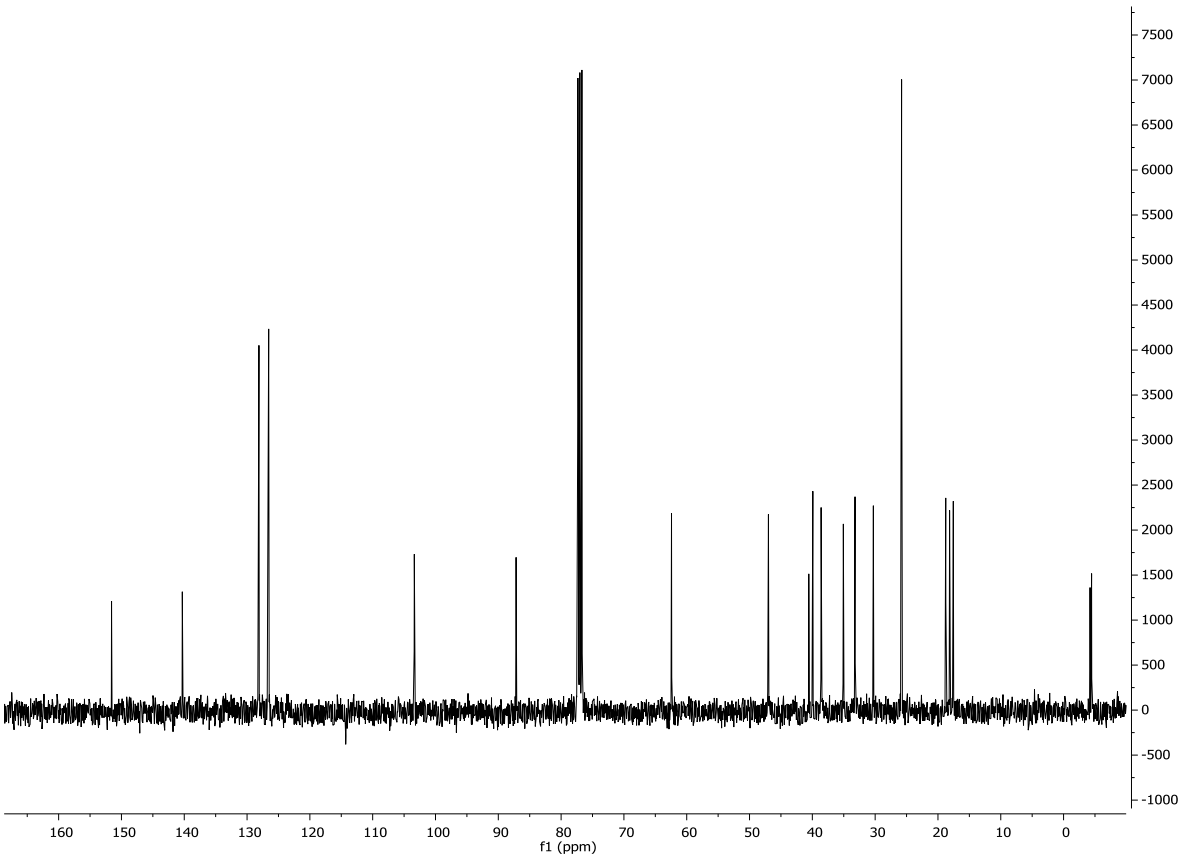

O
H
OBn
270
f1 (ppm)


f1 (ppm)


TBSO
H
OBn

271

50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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7000
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6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
160
150
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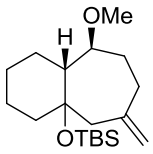
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OMe
H
OTBS

279

85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
7.5
7.0
6.5
6.0
5.5
5.0
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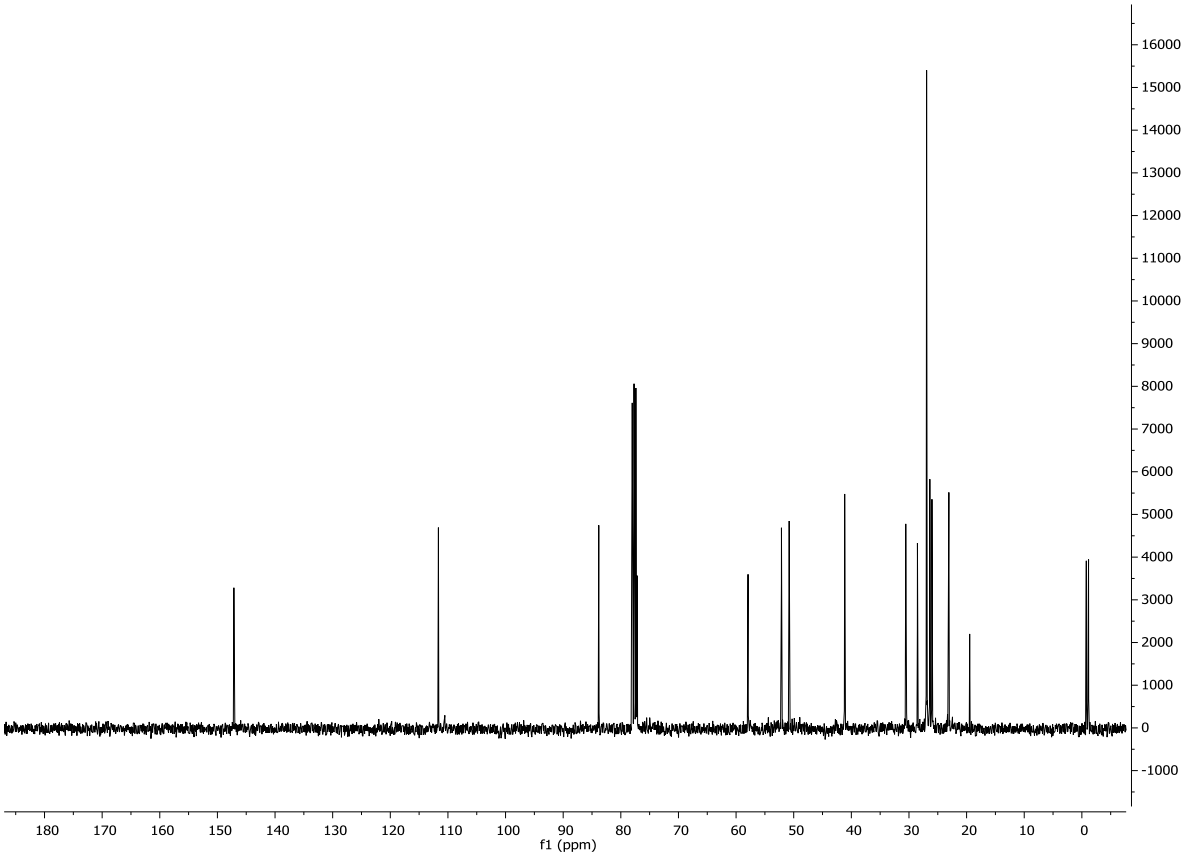
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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13000
12000
11000
10000
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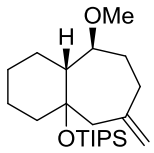
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OMe
H
OTIPS

282

120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
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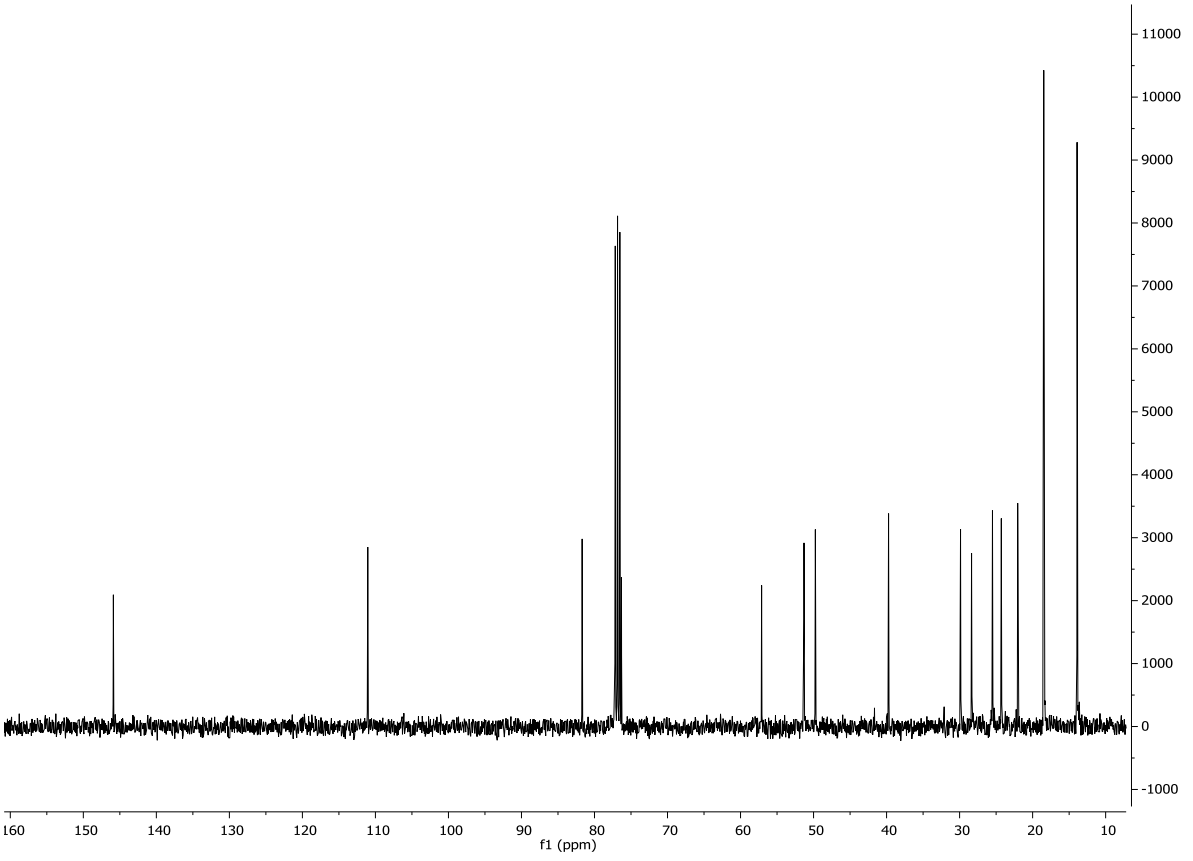
1.5
1.0
0.5
f1 (ppm)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9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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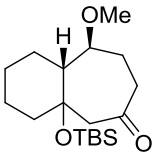
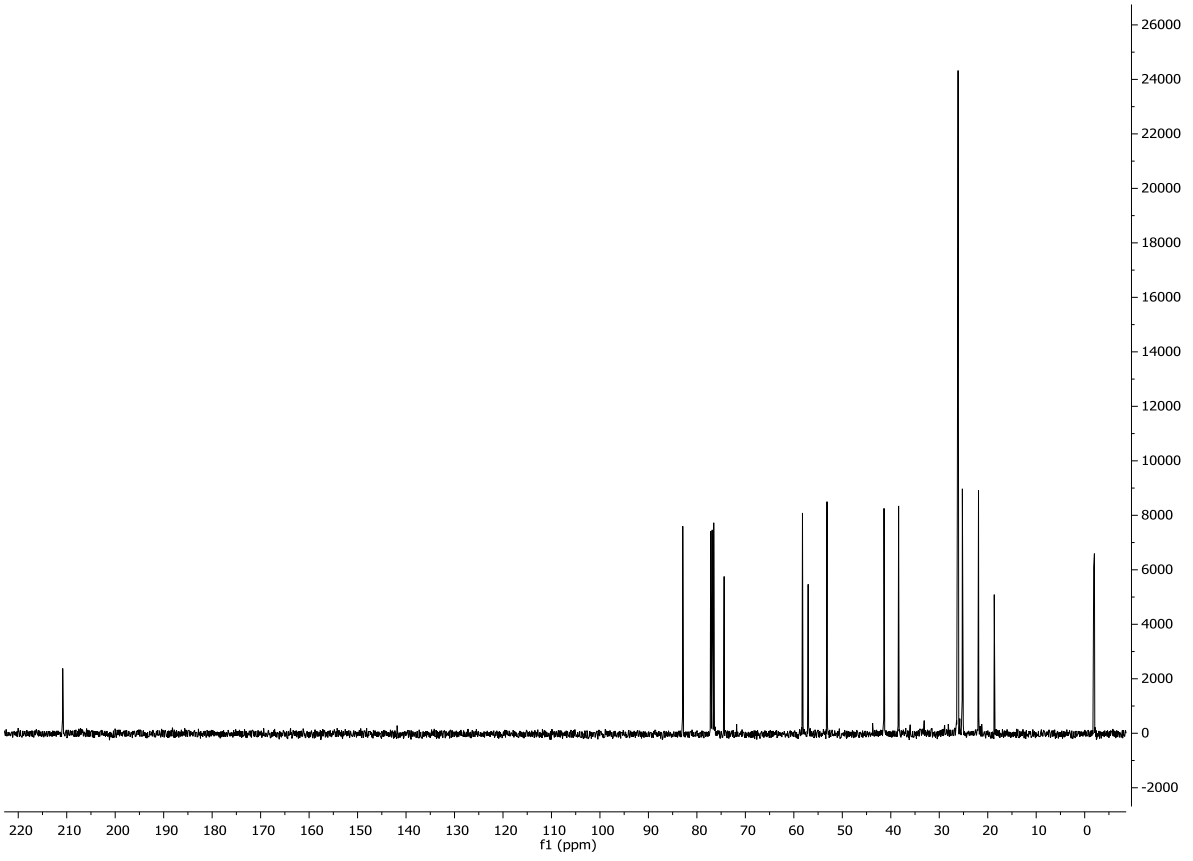
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OMe
H
OTBS
O

280

110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
220
210
200
190
180
170
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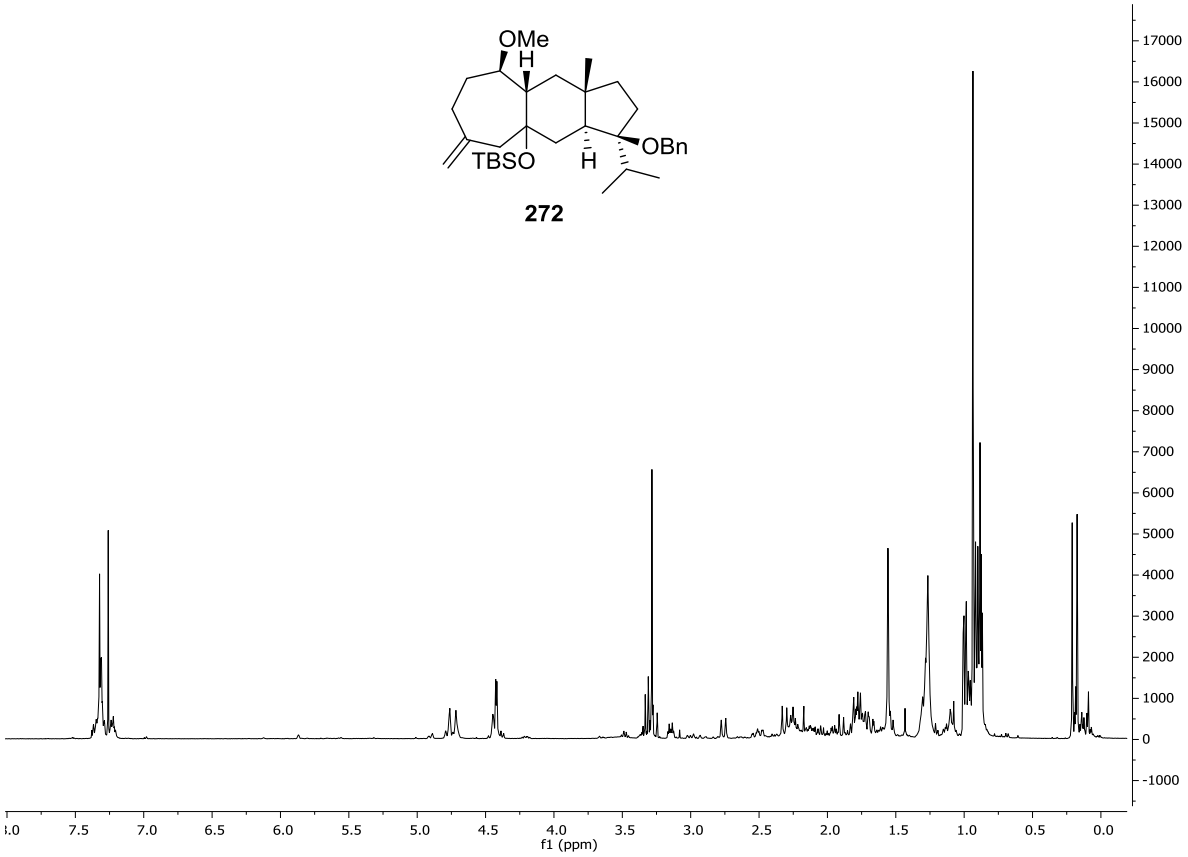
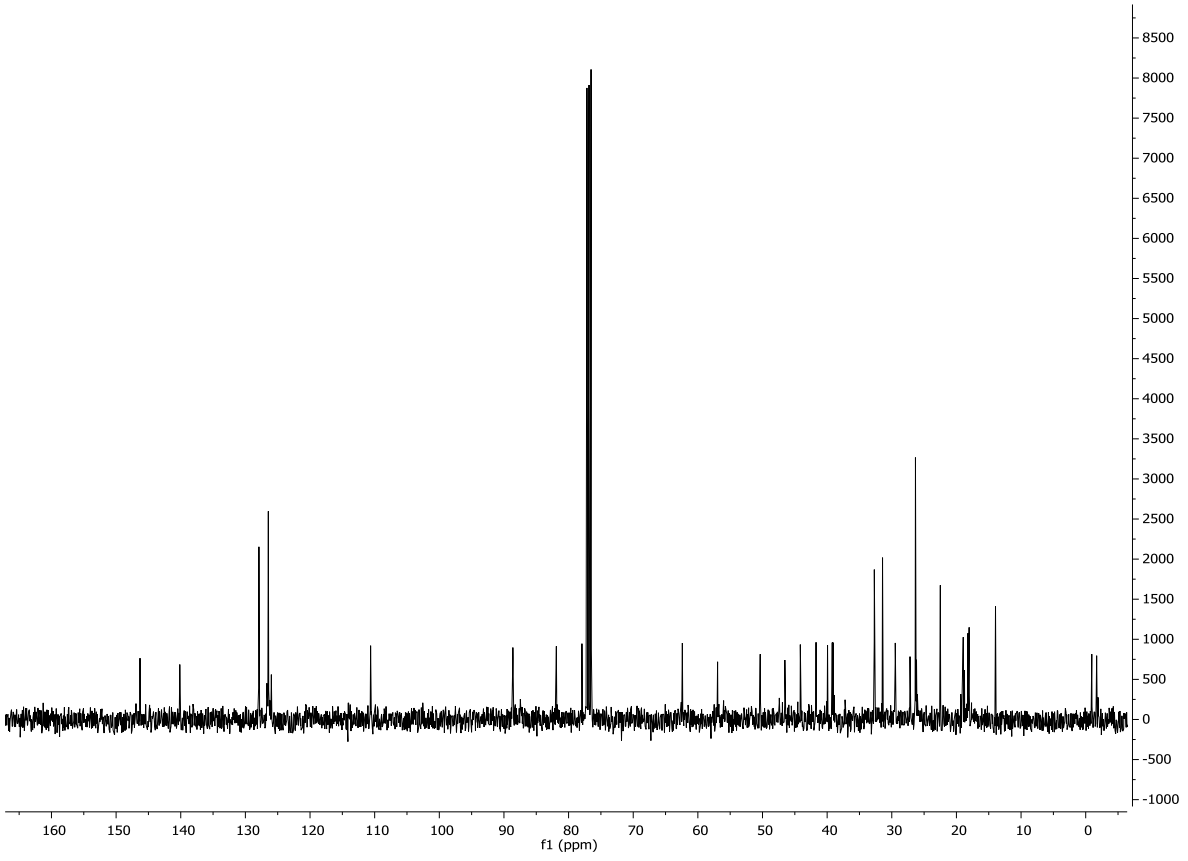
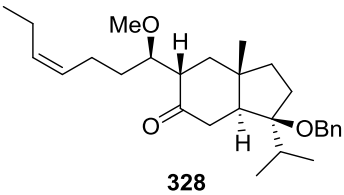
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

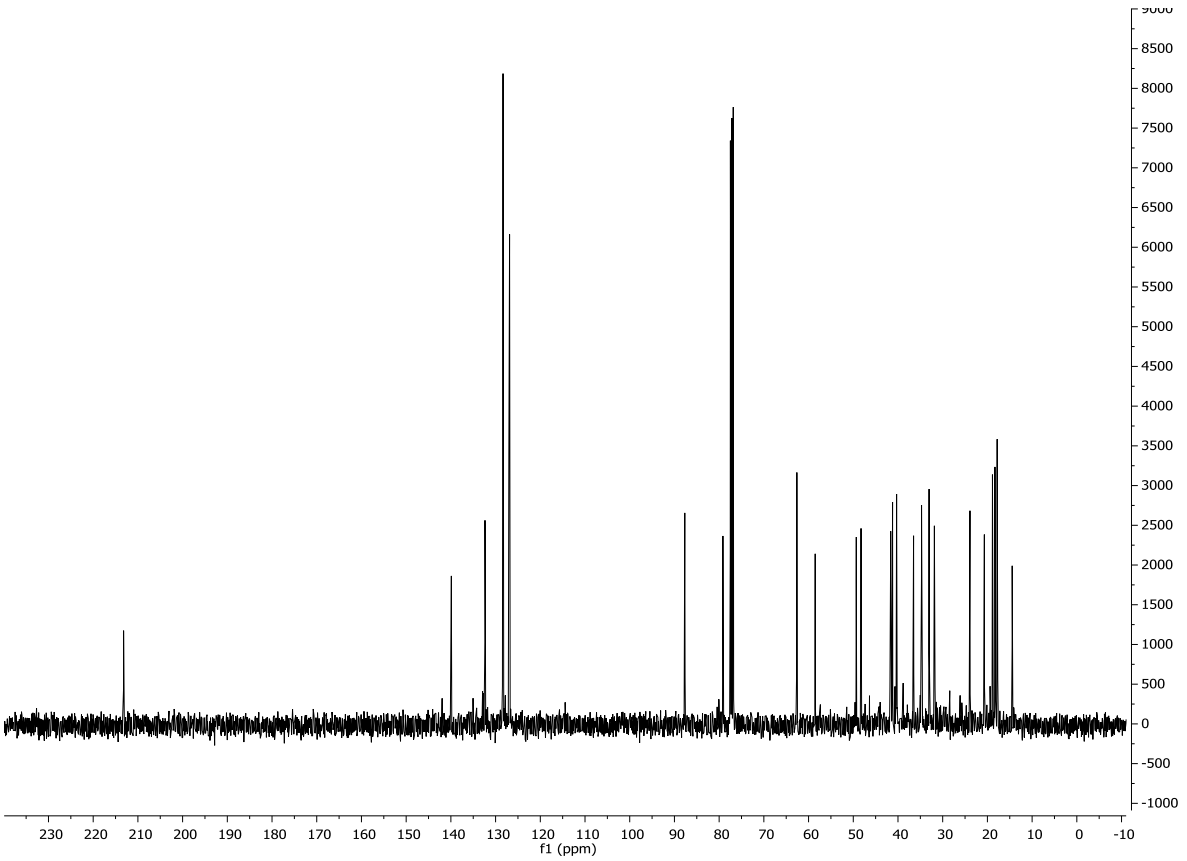


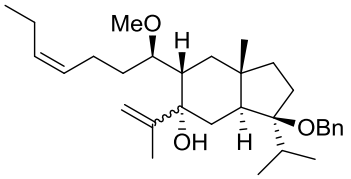
272





328




MeO
H
OH
H
OBn

330

15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
7.5
7.0
6.5
6.0
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5.0
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4.0
3.5
3.0
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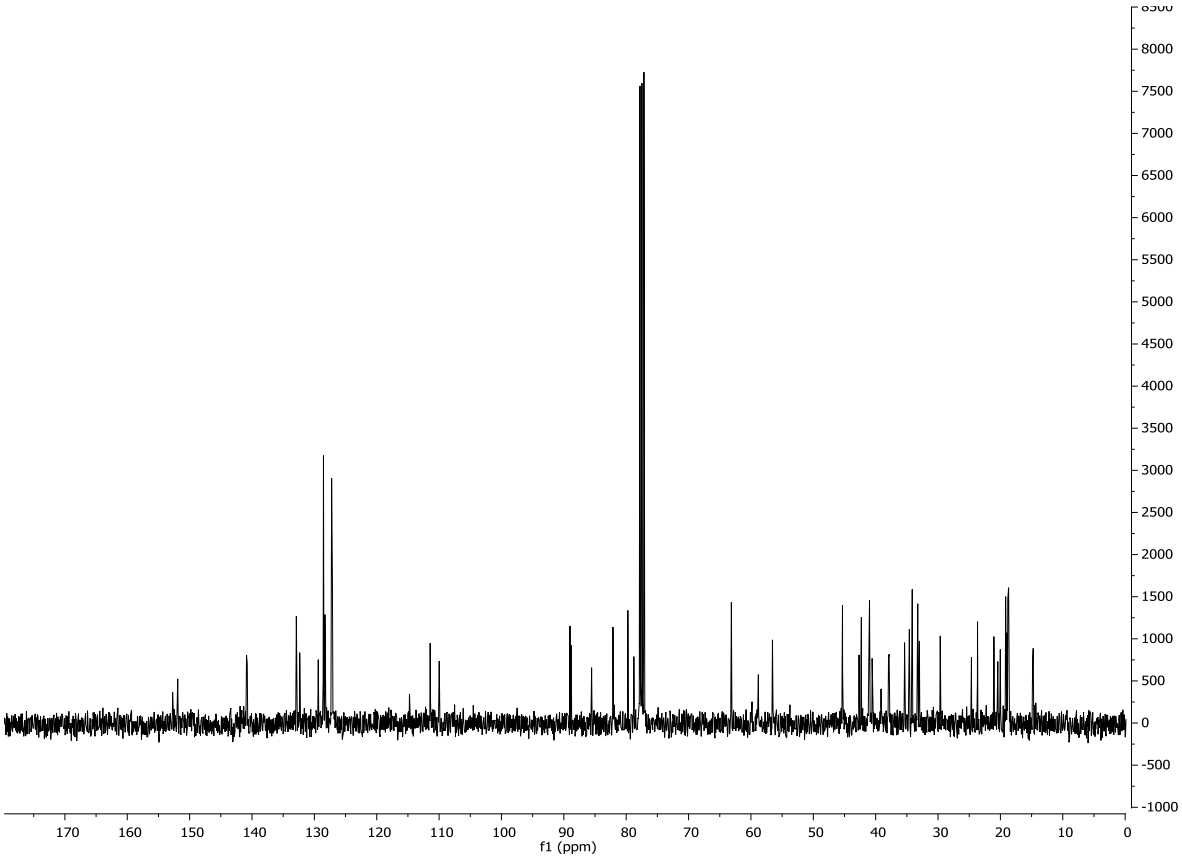
1.5
1.0
0.5
f1 (ppm)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-500
-1000
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70
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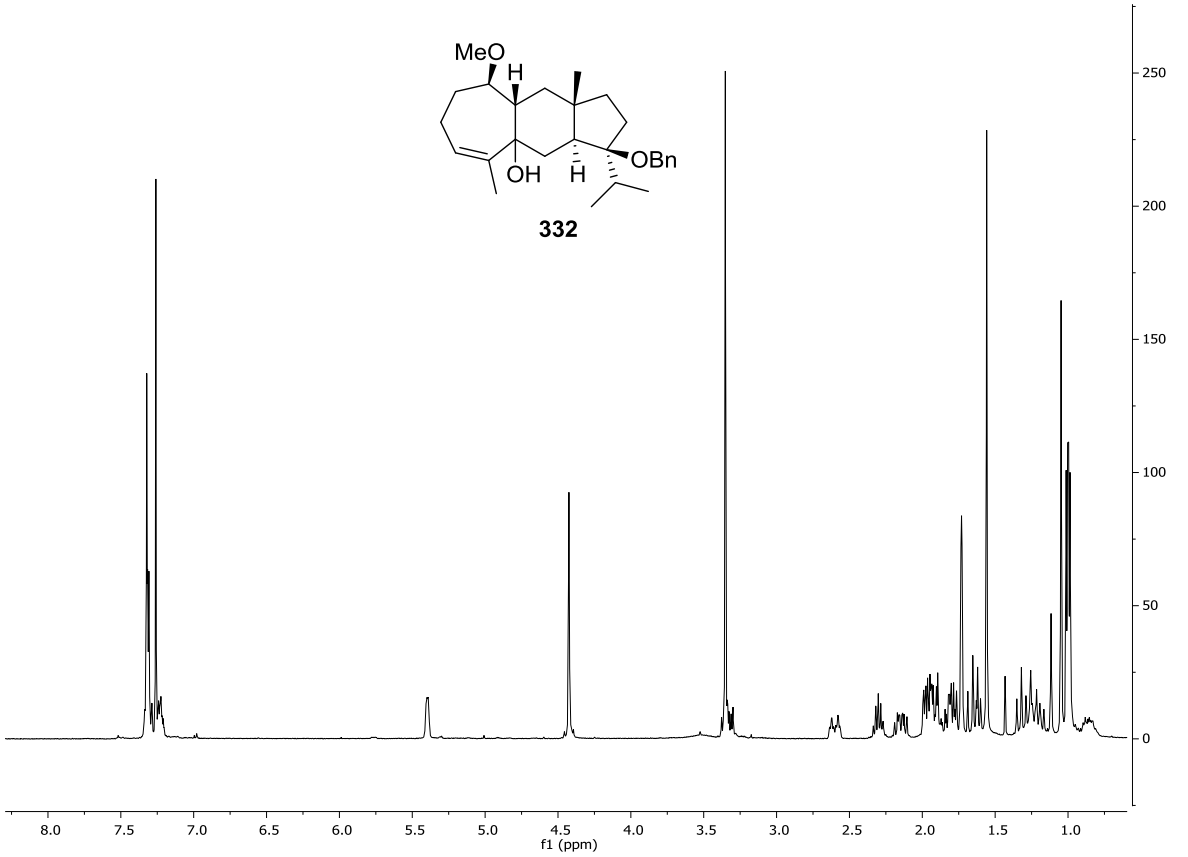
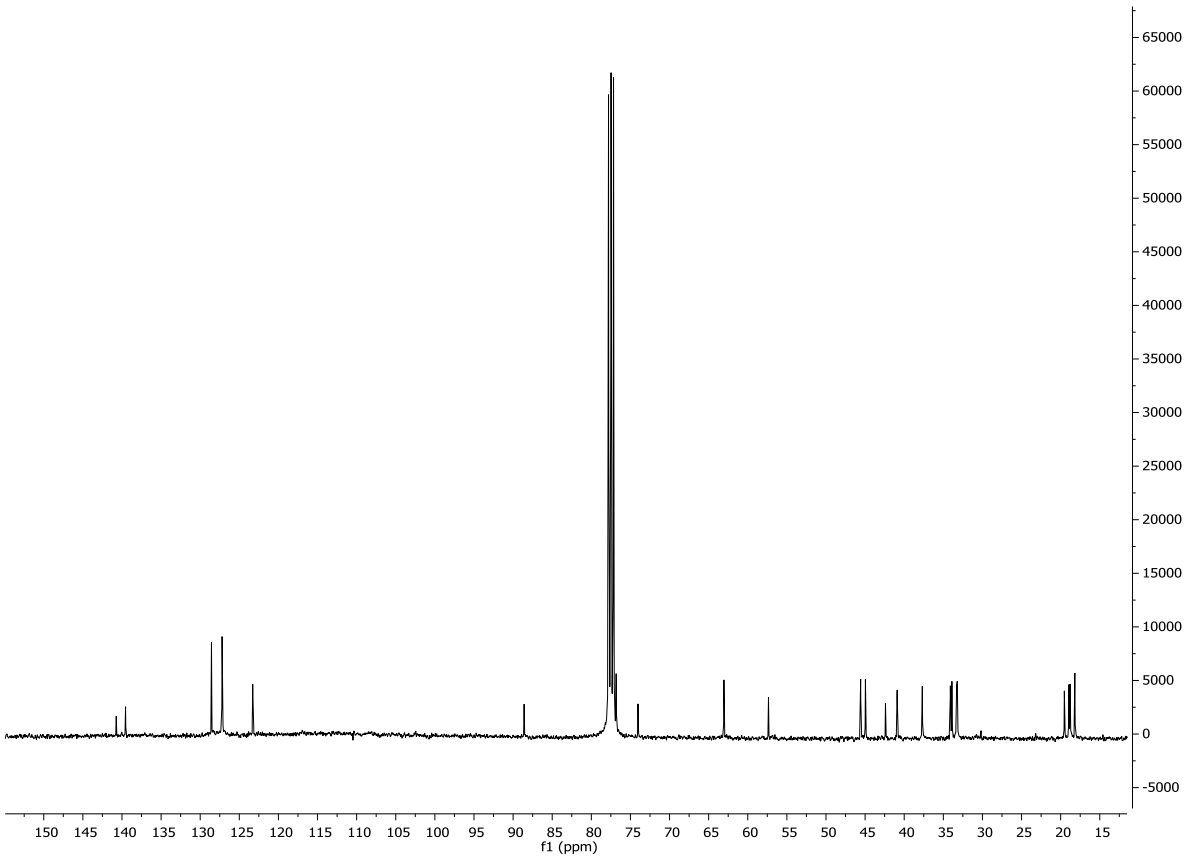
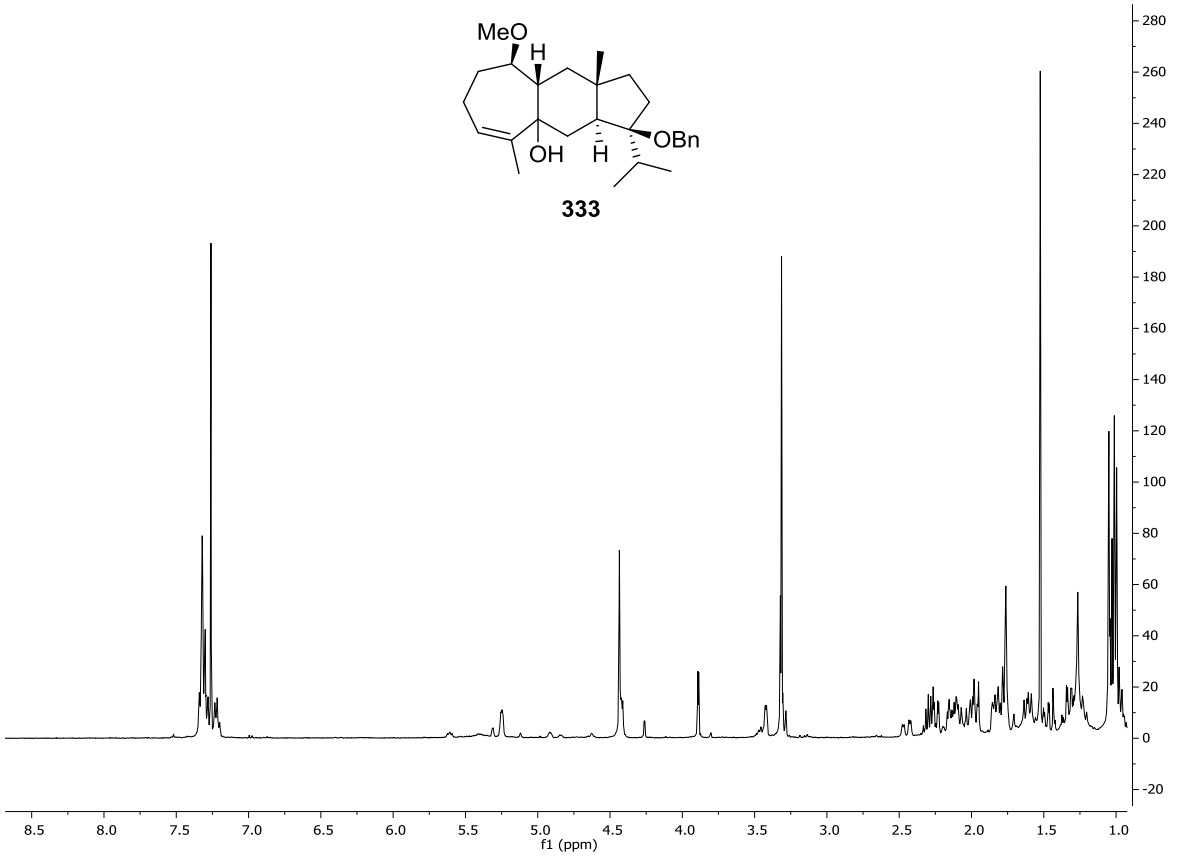
50
40
30
20
10
0
f1 (ppm)

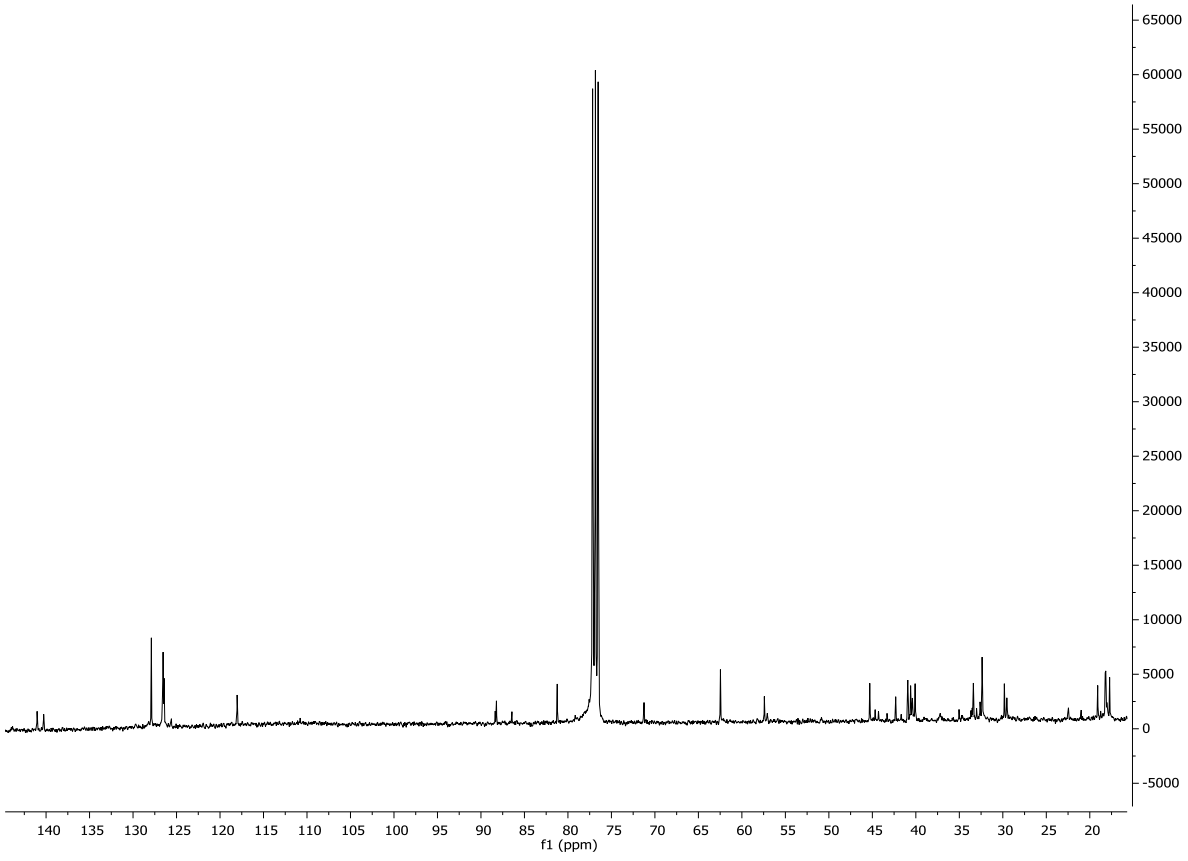


332





333



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2237.
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