Studies towards the Total Synthesis of Phyllaemblic Acid

by

Michael Patrick Kyle

UNIVERSITY OF BIRMINGHAM

A thesis submitted to the

University of Birmingham

for the degree of

DOCTOR OF PHILOSOPHY

School of Chemistry

College of Engineering and Physical Sciences

University of Birmingham

July 2015

Abstract

Phyllaemblic acid is a spirocyclic acetal-containing natural product isolated from *Phyllanthus emblica*. A total synthesis of phyllaemblic acid has yet to be reported. The spirocyclic acetal portion of phyllaemblic acid is structurally similar to that found in the natural products phyllanthocin and breynolide. The introduction of this report discusses the literature methods used in the preparation of these spiroacetals, which might be applied in a synthesis of phyllaemblic acid.

Previous work in the Grainger group has approached the synthesis of phyllaemblic acid through disconnection to a *meso* 4-carbomethoxy-2,6-dihydroxy-substituted cyclohexanone, masked as a dioxabicyclononanone, prepared in turn through an α,α'-annulation reaction of 2-substituted 1,3-dioxan-5-ones with methyl α-bromoacrylate. Epimerisation of the resulting ester gives the stereochemical array found in the carbocyclic ring of phyllaemblic acid.

This project attempted to address the current limitations of this approach, namely the lack of reactivity of the cyclohexanone carbonyl towards intermolecular nucleophilic addition reactions. An approach based on an intramolecular keto-alkyne cyclisation was first investigated, followed by the use of a Meyer-Schuster rearrangement to attempt to overcome the problems encountered in the conversion of the cyclohexanone to an enone. Finally, an approach to the perhydrobenzothiophene ring system found in breynolide using the *meso* 4-carbomethoxy-1,2-dihydroxy-substituted cyclohexanone was investigated.

Acknowledgments

The first thank you obviously needs to go to Dr. Richard Grainger for his help, knowledge and support throughout my PhD. I am truthfully grateful that he gave me this opportunity to fulfil a lifetime ambition (although at the time of writing this I have yet to pass my viva).

When l finished school I left with poor results and the option of going to University seemed to be a very unrealistic dream. So, after going to college and getting the required grades, I want to say thank you to my Mum and James Woodward for persuading me to study Chemistry at undergraduate level.

Thank you to my good friends James Holt, Adam Ross and Sam Kilsby who were my 'study buddies' throughout my undergraduate studies….and my drinking buddies when we weren't studying.

Thank you to Dr. Sandie Dann for your support as my personal tutor; if it wasn't for you my worrying level would have definitely gone too high! Thanks also to all of the organic staff at Loughborough University.

Thank you to my Birmingham based friends Gemma Bullen, Matt Berwick, Rich Myerson, "Ziggy", Jen and James Carr-Smith, Haydn and Maddy Little and Rosie Bamford. You guys have made moving to Birmingham brilliant and I am sure we will be friends for life.

Thank you to the Grainger group past and present: Tom Parsons, Marie Betou, Kevin Munro, Carlotta Figliola, Matt Barrett, Sanaz Ahmadipour and Fatima Khan. With Special Mentions to Tom, Kevin, Rich and not forgetting Dr. Glenn Lees for reading my thesis and general chemistry guidance throughout!

Thank you to my brother and sister: Matthew Kyle and Shannon Kyle - you guys have always been on the end of the phone for me.

Thank you to everybody in the office; sorry I won't be there anymore to help you eat cake!

The biggest thank you has to go to my wonderful wife Danielle Kyle, who has supported me since I was at college right up to this very moment where she will proof read my thesis for spelling mistakes. I could never have got to where I am without you.

A final note and thank you goes to Sean Seamus Kyle F.R.S.C. Unfortunately, you could not see me graduate and I hope this thesis can make you proud. I miss you every day and I plan on using all of my experiences in the past to help students during their school years as I become a teacher. Dad, this is for you.

Contents

Abstract I
Abbreviations VI
Chapter 1 Phyllanthocin, Breynolide and Phyllaemblic acid 1
Introduction 1
Spiroacetalisation in phyllanthocin synthesis 2
Spiroacetalisation in breynolide synthesis 7
Phyllaemblic acid 11
The Grainger group approach: Disconnection of phyllaemblic acid and the α,α'-annulation reaction 15
Conclusions and summary 19
Chapter 2 Intramolecular cyclisation investigation 20
Literature review of carbonyl-alkyne cyclisation reactions 20
Aims and Objectives 32
Results and Discussion 34
Model study for intramolecular studies 34
Attempted annulation reactions 45
A photomediated approach towards C-C bond formation in bicyclic systems 55
Literature review on the Norrish reaction. 55
Results and discussion 59
Photo-activation of bicyclic ketones. 59
Conclusions and summary 62
Chapter 3 Reinvestigation of intermolecular addition on monocyclic ketones 63
Introduction 63
Aims and Objectives 67
Results and Discussion 68
Attempted protection of the diol 68
Reinvestigation of HWE reaction 74
Conclusions and summary 78
Chapter 4 The Meyer-Schuster rearrangement and other alkyne-based routes 80
Introduction 80
Aims and Objectives 81
Results and Discussion 81

Intermolecular addition of an alkyne 81
Attempted rearrangement and formation of enones 87
Spiro epoxide formation 100
Alternative disconnection approach 105
Introduction 105
A new disconnection and approach 106
Results and Discussion 107
Conclusions and summary 115
Chapter 5 Studies towards the tetrahydrothiophene ring in breynolide 117
Introduction 117
Literature review of the synthesis of a tetrahydrothiophene ring 117
Synthesis of 5-membered sulfur heterocycles through thiol conjugate addition and subsequent Dieckmann/ intramolecular aldol 125
Aims and Objectives 128
Results and discussion 131
Conclusions and summary 141
Conclusions and Closing comments 142
Experimental Section 146
Appendices 216
Crystallographic data 216
X-ray for 175 216
X-ray for 177 217
X-ray for 253 218
X-ray for 274 219
X-ray for 300 220
X-ray for 383 221
NMR spectra 222
References 289

Abbreviations

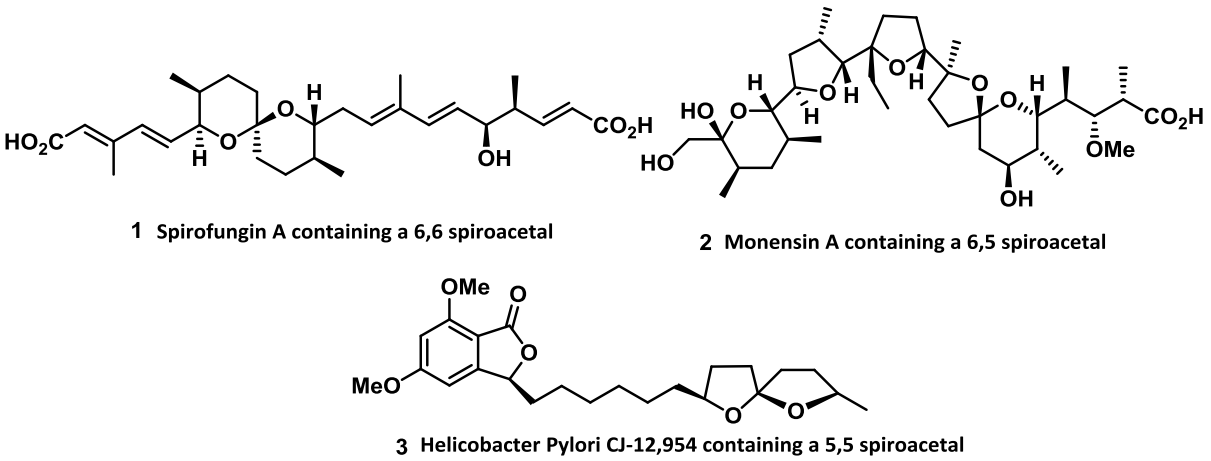
AIBN = 2,2'-azobisisobutyronitrile
app. = apparent
aq. = aqueous
ax = axial
Bn = benzyl
B.p. = boiling point
BRSM = based on recovered starting material
bs = broad singlet
BTMSA = bistrimethylsilylacetylene
CDI = carbonyldiimidazole
cm = centimetre(s)
CSA = camphorsulfonic acid
d = doublet
DABCO = 1,4-diazabicyclo[2.2.2]octane
dba = dibenzylideneacetone
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD = diethyl azodicarboxylate
DIAD = diisopropyl azodicarboxylate
DIBAL = diisobutylaluminium hydride
DIPA = diisopropylamine
DMAP = 4-dimethylaminopyridine
DME = dimethoxyethane
DMF = *N,N*-dimethylformamide
DMTC = dimethylthiocarbamate
eq = equatorial
eq. = equivalent
F/mole = femtomole
g = gram
h = hextet
hr = hour
HMPA = hexamethylphosphoramide
HP = High pressure
HRMS = high resolution mass spectrometry
HWE = Horner-Wadsworth-Emmons
Hz = hertz
^{i}**Pr** = isopropyl
IR = infrared
J = coupling constant (Hz)
LDA = lithium diisopropylamide
LR = Lawesson's reagent
M = molar (mol/L)
m = multiplet
M.p. = melting point
M.S. = molecular sieve
Me = methyl
MEM = methoxyethoxymethyl
mg = miligram
MHz = megahertz
mL = mililitre
mmol = milimole
MP = Medium pressure
MPM = *p*-methoxyphenylmethyl
NBS = *N*-bromosuccinimide
NHC = *N*-heterocyclic carbene
NMO = *N*-Methylmorpholine *N*-Oxide
NMR = nuclear magnetic resonance
NOE = Nuclear Overhauser effect
Non = nonet
Nu = nucleophile
p = pentet
P = protecting group
PFA = paraformaldehyde
Ph = phenyl
PPTS = pyridinium *p*-toluenesulfonate
***p*TSA** = paratoluenesulfonic acid
q = quartet
RBF = round bottom flask
rt = room temperature
s = singlet
SEM = 2-(trimethylsilyl)ethoxymethyl
sept = septet
sm = Starting material
t = triplet
T.L.C. = thin layer chromatography
TBAF = tetra-^{n}butylammonium fluoride
TBS = tertbutyldimethylsilyl
TES = triethylsilane
Tf = trifluoromethanesulfonyl (triflyl)
TFAA = trifluoroacetic anhydride

THF = tetrahydrofuran
TIPS = triisopropylsilyl
TMS = trimethylsilyl
TRIZMA = tris(hydroxymethyl)aminomethane hydrochloride
UV = ultraviolet
W = Watt
Å = angstrom
δ = frequency
ν_{max} = wavenumber(s)
^{o}**C** = degrees Celsius
[O] = oxidation

Chapter 1 Phyllanthocin, Breynolide and Phyllaemblic acid

Introduction

A spiroacetal is a structural subunit found in many naturally occurring molecules including marine, insect and plant derived natural products. Spiroacetals, sometimes described as spiroketals, are defined as cyclic acetals in which two rings are joined by a single atom. This central atom, known as the spiro atom, is flanked by two oxygen atoms that each belong to one of the rings.[1] The most common ring sizes of spiroacetals are 6,6 (eg-**1**), 6,5 (eg-**2**) and 5,5 (eg-**3**)(Figure 1).[2, 3 4]



1 Spirofungin A containing a 6,6 spiroacetal

2 Monensin A containing a 6,5 spiroacetal

3 Helicobacter Pylori CJ-12,954 containing a 5,5 spiroacetal

Figure 1

This review will focus on methods for the formation of 6,5-spiroacetals in the natural products breynolide and phyllanthocin, and the ways that these syntheses may be adapted in studies towards a first total synthesis of phyllaemblic acid.

A key factor that controls the structure and stability of a spiroacetal unit is the formation of either the thermodynamic or kinetic product. Generally, a substituent on a six-membered ring system would be expected to reside in an equatorial position so as to minimise unfavourable 1,3-diaxial interactions (Figure 2).[5] However, an oxygen substituent at the anomeric centre (C_1) of a pyranose ring is found to reside preferentially in an axial rather

than equatorial orientation, despite the unfavourable steric interactions. A stabilising interaction between the pseudo-axial lone pair on oxygen (n) and the σ* antibonding orbital of the C-O bond accounts for this observation. For this interaction to occur, the lone pair on the oxygen must be in an antiperiplanar orientation with respect to the C(1)-O bond.[5]

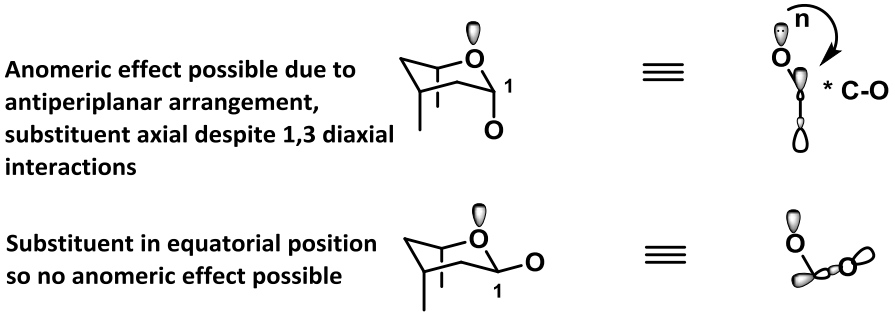


Figure 2

If the anomeric oxygen is in an equatorial position, there is no low-lying acceptor orbital of correct orientation to achieve overlap with the ring oxygen lone pair.

Spiroacetalisation in phyllanthocin synthesis

In 1977 Kupchan *et al.* isolated an extract from *Phyllanthus acumintus*.[6] The extract was found to inhibit growth of the p388 leukaemia system in mice. Subsequent investigation led to the isolation of (+)-phyllanthocin **4** (Figure 3)[6] which possesses a 6,5 spiroacetal unit. To date there have been eight reported total syntheses of phyllanthocin.

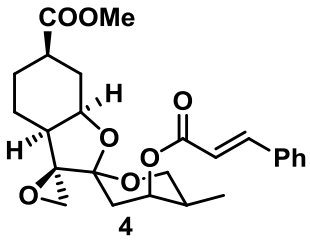
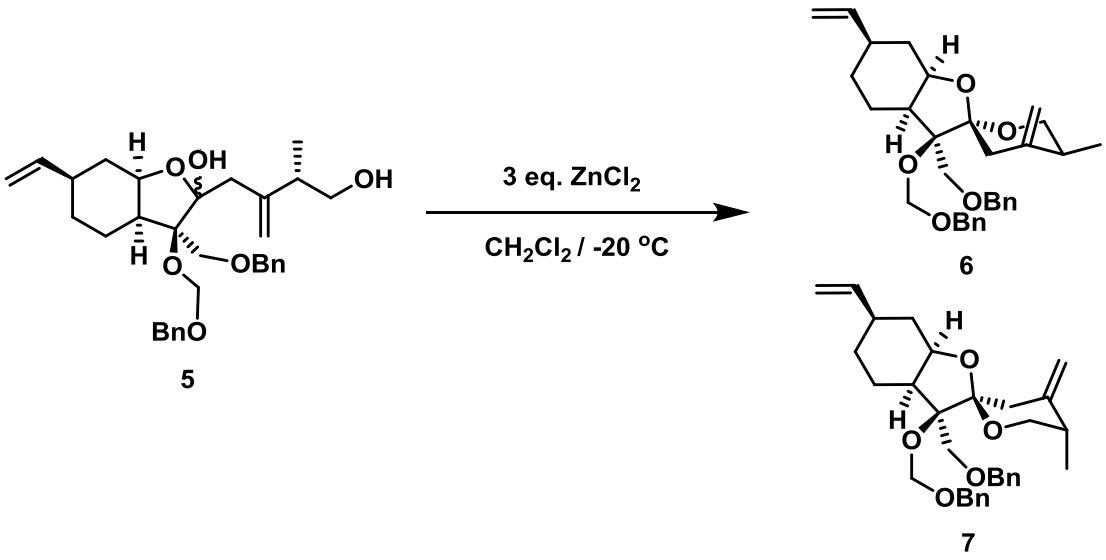


Figure 3

In 1982 the first total synthesis of phyllanthocin was reported by Collum *et al*.[7] The key spiroacetalisation step was initiated by treatment of **5** with $ZnCl_2$ at -20 ^{o}C (Scheme 1).[7] This

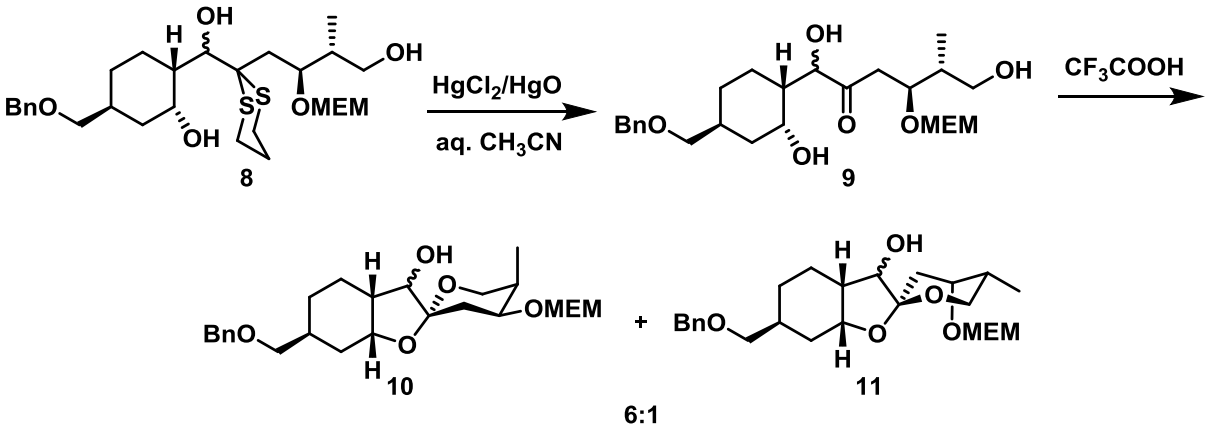
produced two diastereoisomers **6** and **7** in a 48:1 ratio with a 69% combined yield. It was proposed that a thermodynamically driven acetalisation had occurred. Identical product distributions are obtained when re-subjecting **6** and **7** to the reaction conditions. In 1989 Fraser-Reid used a radical cyclisation on an annulated furanose which significantly improved the route towards Collum's key intermediate.[8]



Scheme 1

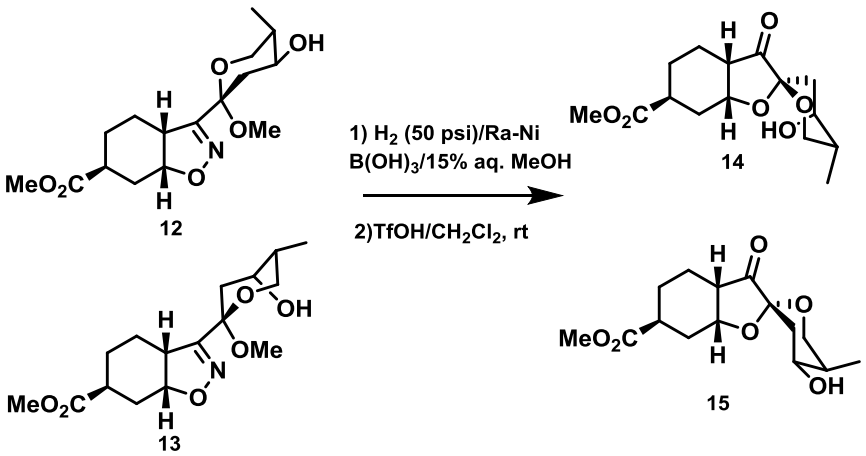
Two years later a second synthesis of (+)-phyllanthocin was successfully completed by Williams *et al*. (Scheme 2).[9] Hydrolysis of the dithiane **8** gave ketone **9**. Upon treatment of spiroacetal precursor **9** with trifluoroacetic acid, spiroacetals **10** and **11** were formed in a 6:1 ratio. Williams reported that the acid promoted cyclisation step had clearly favoured the unnatural configuration of the spiro-centre, therefore concluding that the ring forming step must follow a kinetic pathway. However, it was found that treatment of the major product with certain Lewis acids, such as zinc bromide and stannic chloride, led to facile isomerisation to the desired natural spiroacetal. It was therefore concluded by Williams that

the Lewis acid complexation site may favour certain spiroacetal isomers by providing them with a more stabilised coordination site.[9]



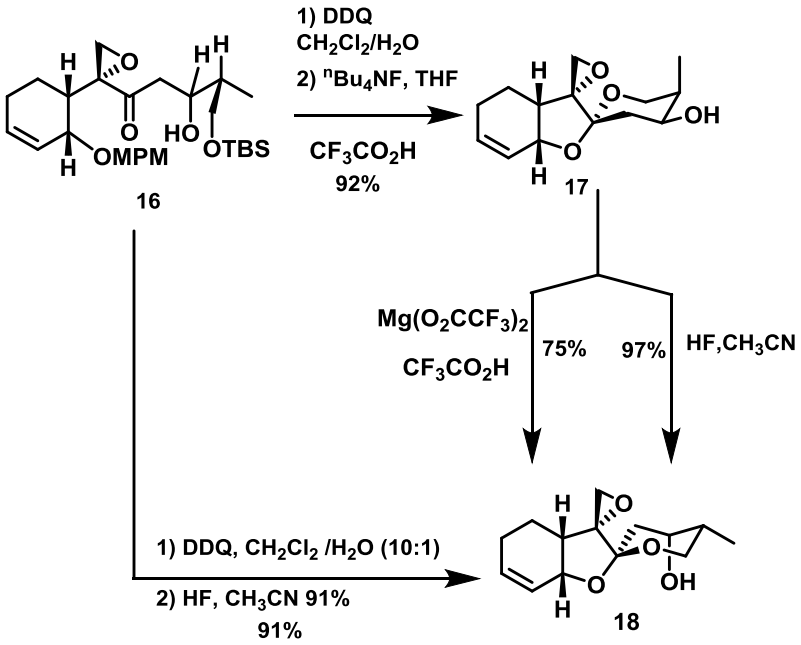
Scheme 2

Martin *et al.* found that hydrogenolysis of a 2.8:1 ratio of **12** and **13** followed by treatment with certain acids gave spiroacetals **14** and **15** (Scheme 3). It was reported that camphorsulfonic acid gave **14** in a moderate yield but trifluoromethanesulfonic acid gave **14** and **15** in a 68% yield in an 18:1 ratio. The spiroacetals **14** and **15** were further subjected to the spiroacetalisation conditions to determine whether an equilibrium existed between the two isomers under the reaction conditions. However, this led to decomposition, suggesting that the β-hydroxy ketone spiroacetalisation is a kinetically driven process.[10]



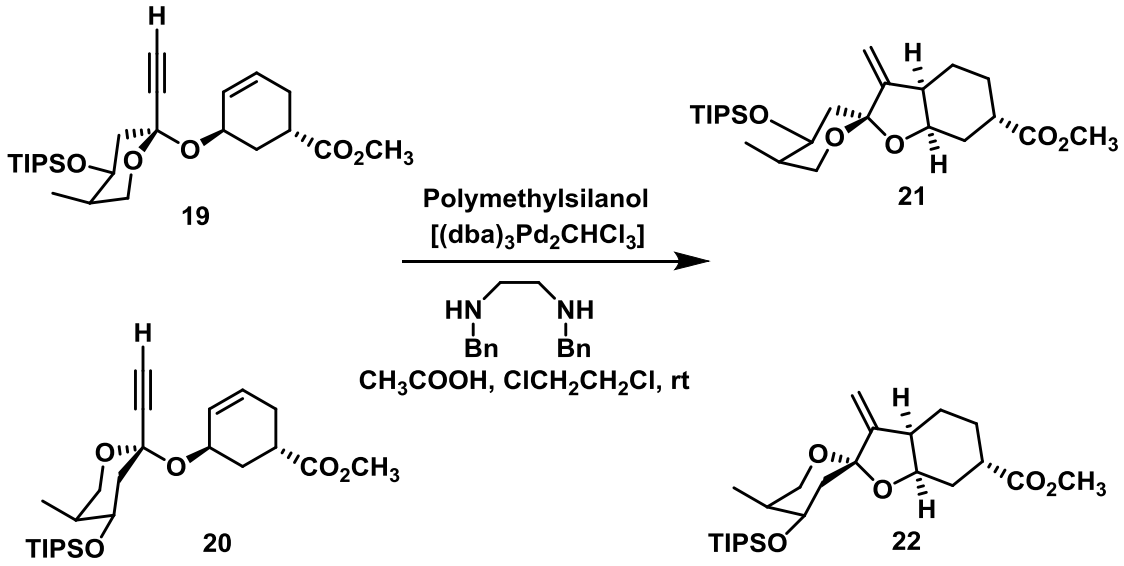
Scheme 3

Burke *et al*. initially encountered problems with the spiroacetalisation step in their synthesis of phyllanthocin.[11] The first spiroacetalisation (Scheme 4)[11] was promoted by oxidative cleavage of the MPM ether in **16** with DDQ. The subsequent mixture of five-membered hemiacetals was treated with $^{n}Bu_4NF$ to cleave the TBS ether followed by trifluoroacetic acid to promote spiroacetalisation. This gave a 3.8:1 mixture of **17** and **18** in an overall yield of 92%. It was found that the unwanted diastereomer **17** was the major product. A variant of Williams' procedure was used to isomerise **17** to **18** in a 75% yield. Subsequently, a more direct method was discovered; cleavage of the TBS ether **16** using 5% aqueous HF in acetonitrile gave the desired spiroacetal **18** directly in a 97% yield.[11]



Scheme 4

Trost *et al*. have reported two approaches to phyllanthocin. The first involved coupling of two racemic starting materials to give a mixture of diastereoisomers **19** and **20** (Scheme 5).[12] The isomers were then subjected to a metal-catalysed reductive cyclisation to afford **21** and **22** in yields of 86% and 78% respectively.[12, 13]



Scheme 5

One year later, Trost reported an asymmetric synthesis of (+)-phyllanthocin.[13] The same reductive cyclisation was used to obtain **21** and **22** in a combined 82% yield. Treatment of **21** under Williams' conditions ($Mg(OCOCF_3)_2$, CF_3CO_2H CH_2Cl_2, rt) gave **22** as a single diastereomer via equilibration to the thermodynamically favoured product.

Smith *et al*. published their approach to phyllanthocin in 1991.[14] A key premise of their work was that spiroacetal **24** adopts the required configuration at the spiro-centre and would be more stable than the diastereoisomer **23** (Figure 4).[14] By considering the anomeric interactions of the furanone and pyranone oxygens, in conjunction with the rigidity of the perhydrobenzofuranone system, **24** certainly looked to be the more stable isomer. This indeed turned out to be the case; removal of the MEM protecting group from **25** with $ZnCl_2$, followed by the addition of camphorsulfonic acid to induce spiroacetalisation, led to the desired spiroketal **24** in a 71% yield with a ratio of 26:1 over the unwanted diastereoisomer (Scheme 6).

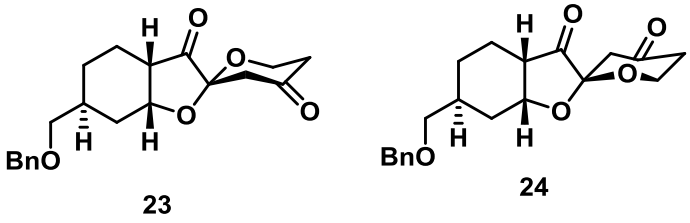
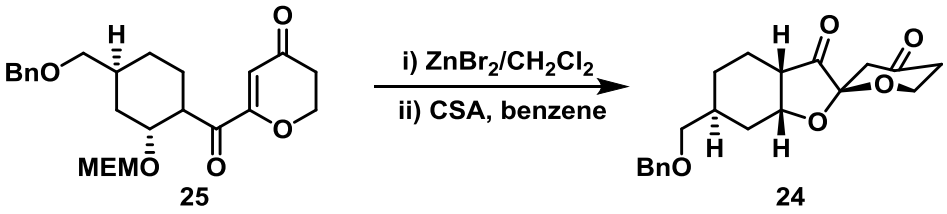
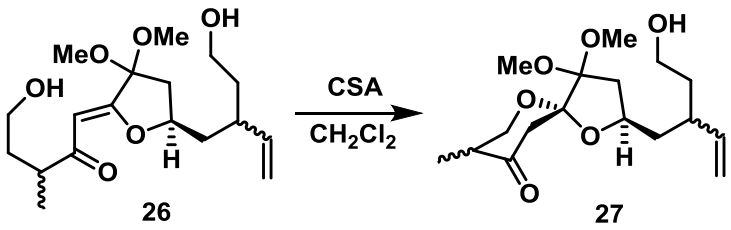


Figure 4



Scheme 6

Ciufolini *et al.* found that spiroacetalisation of **26** gave a mixture of diastereoisomers **27** in a combined 71% yield (Scheme 7). However, the thermodynamic configuration at the spiro-centre was almost exclusively formed. This relative configurational control is probably due to the preference of the tetrahydrofuran to be in the *cis* 2,5-dialkyl arrangement and also to the anomeric effect for the pyranone unit favouring placement of the THF oxygen at the axial position.[15]



Scheme 7

Spiroacetalisation in breynolide synthesis

Breynins A **29** and B **30** are novel glycosides isolated in 1973 from the Taiwanese woody shrub *Breynia officinalis*. The natural products have displayed significant oral hypocholesterolemic activity in rats (Figure 5).[16] Breynogenin **31** and breynolide **28** have been characterised as the aglycon hydrolysis products of breynin A.[17] Breynolide was fully

characterised by Sasaki and Hirata through single crystal X-ray.[16] To date there have been three total syntheses of breynolide and one of breynolide sulfone.

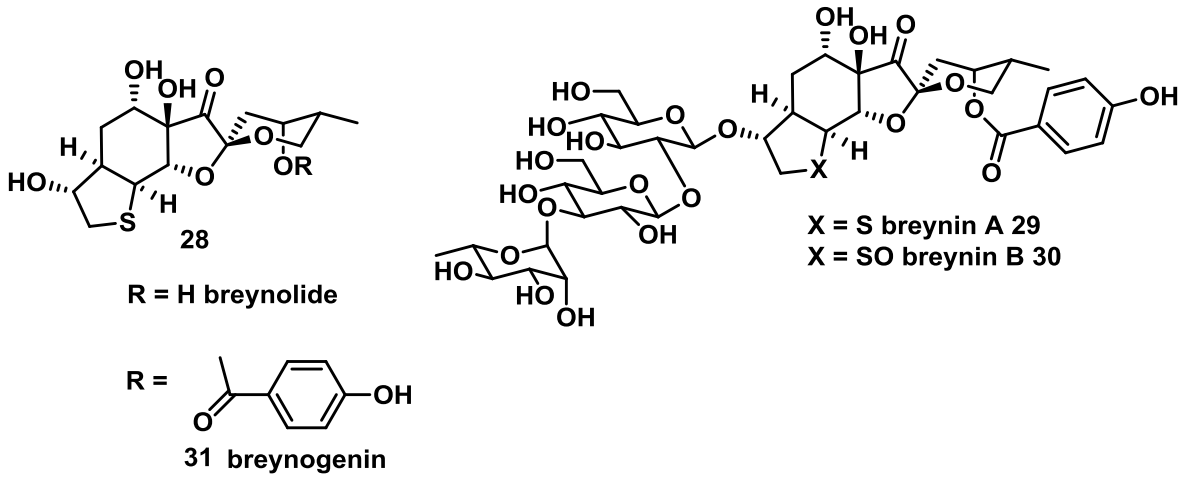
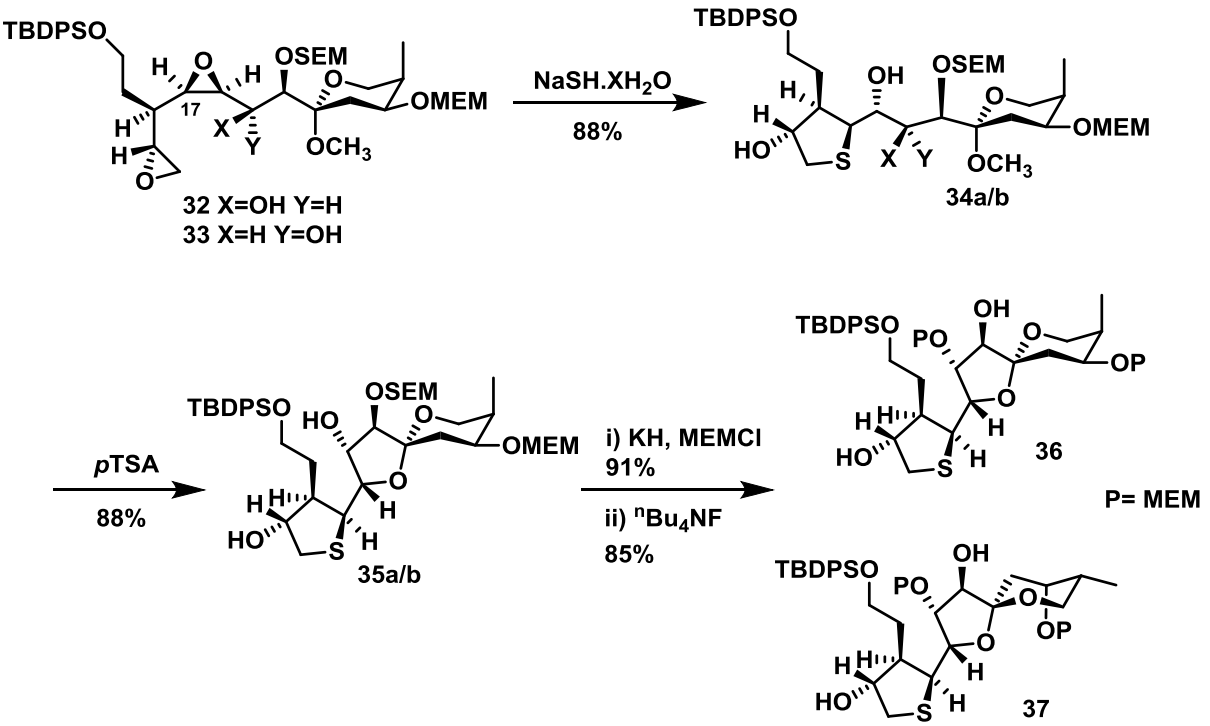


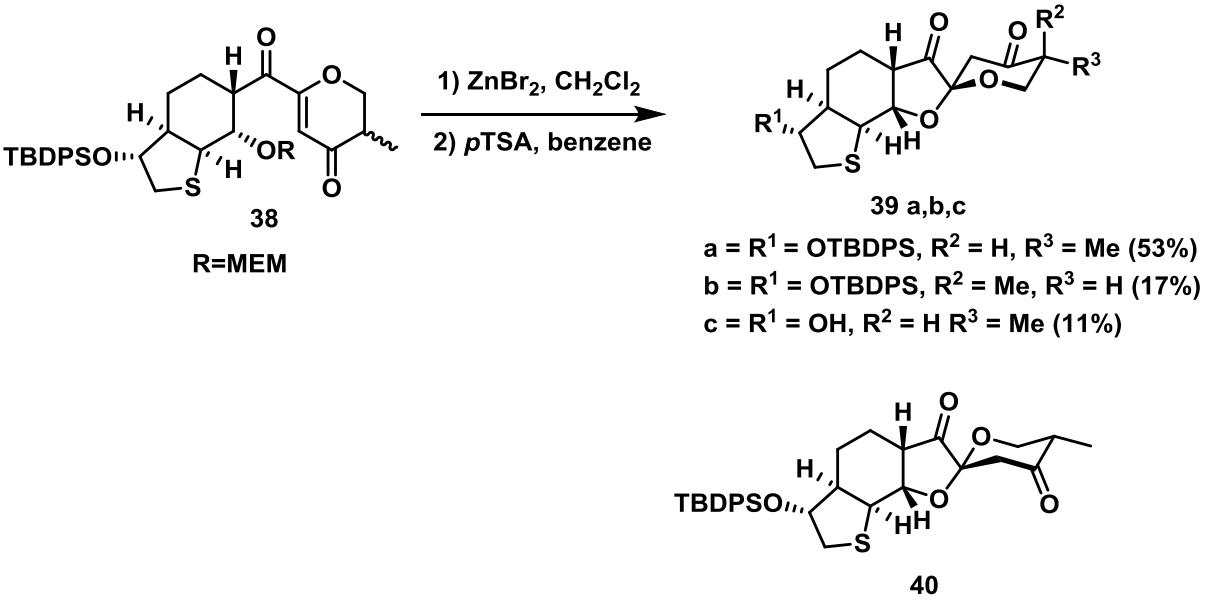
Figure 5

The first synthesis of (+)-breynolide was reported in 1990 by Williams *et al*.[17] Following attack by sodium hydrogen sulfide on the terminal oxirane of a mixture of **32** and **33** in a 75:1 ratio, an intramolecular S_N2 reaction subsequently occurred at C-17 to form the tetrahydrothiophene core in **34a,b**. Treatment of **34a,b** with *p*-toluenesulfonic acid led to a kinetic acetalisation to give **35a,b** which, followed by protection, gave an 85% yield of the diastereoisomers **36** and **37** in a 1:3 ratio (Scheme 8). Both **36** and **37** were each independently converted to breynolide through a subsequent five step sequence.



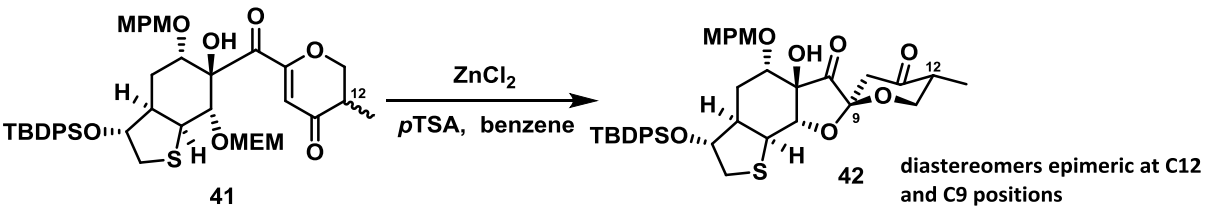
Scheme 8

The second total synthesis of breynolide was reported two years later by Smith *et al*.[18] Intermediate **38** was treated with $ZnBr_2$ to remove the MEM protecting group (Scheme 9). This was followed by treatment with *p*-toluenesulfonic acid to induce equilibration and give the desired spiroacetal configuration **39a** in a 53% yield along with three minor products. Acetal **39b** had the correct configuration at the spiro-centre, whereas **40** did not. Alcohol **39c** was isolated in an 11% yield and was able to be converted to **39a** after silylation. Subjecting **39b** and **40** to the reaction conditions regenerated the original ratio of **39a** and **39b**. Treatment of **39b** with *p*-toluenesulfonic acid equilibrated the axial methyl into the more stable equatorial orientation. These transformations confirmed that cyclisation was thermodynamically controlled.



Scheme 9

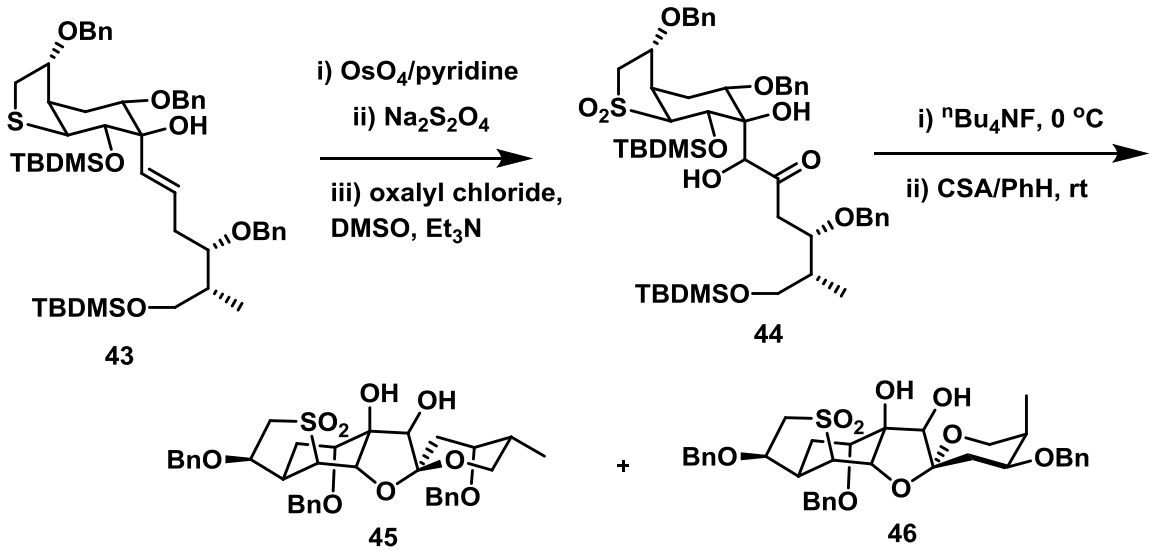
The third, and most recent, synthesis of breynolide was completed in 1998 by Burke *et al*.[19] Their asymmetric synthesis saw the use of the same thermodynamically driven spiroacetalisation employed by Smith *et al*. (Scheme 10). The key spiroacetalisation step started with **41** which was a (1:1) mixture of epimers at C-12. A thermodynamic spiroacetalisation was then attempted which resulted in predominantly the correct stereochemistry at both the C-9 and the C-12 positions. The MEM protecting group was removed with wet $ZnBr_2$ and the crude product was then treated with *p*TSA in benzene for 48 hours which produced a mixture of diastereomeric spiroacetals including **42** in a 68% yield.



Scheme 10

An earlier study is that of the synthesis of breynolide sulfone (Scheme 11).[20] The alkene moiety in **43** was converted to the α-hydroxy ketone **44** using OsO_4 in pyridine, followed by

Swern oxidation. Desilylation followed by treatment with camphorsulfonic acid at rt gave the two spiroacetals **45** and **46** in quantitative yield. Repeated acid-catalysed equilibration using camphorsulfonic acid in refluxing benzene converted **45** to **46** in greater than 95% yield.



Scheme 11

Phyllaemblic acid

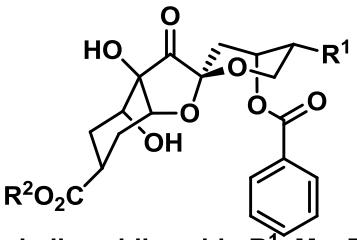
Phyllaemblic acid **47** was isolated along with its methyl ester **48** and three ester glycosides, phyllaemblicins **51**, **52** and **53**, from the roots of *Phyllanthus emblica*. There have been two reports on the uses of *Phyllanthus emblica* extracts which include phyllaemblic acid and its derivatives with regard to its antiviral properties. The roots, bark and leaves have been used for treating eczema, warts, diarrhoea and headaches. The fruit and its juice have been used widely for their biological activities including antibacterial, antioxidant, anti-inflammatory, antitumor and hepatoprotective effects.[21, 22]

Although the biological activity of these natural products makes them attractive targets for synthesis, as yet there have been no reported total syntheses of phyllaemblic acid or any of its derivatives. In contrast, a total of eight syntheses of the structurally related phyllanthocin

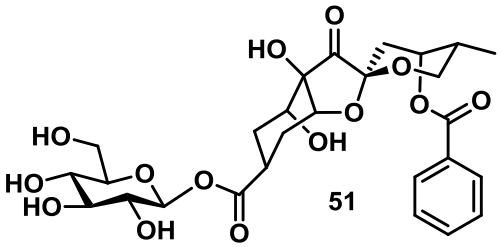
4 and three syntheses of breynolide **28** have been reported. The full structure elucidation of phyllaemblic acid was first published in 2000 by Kouno *et al.*[23, 24]

The rhizomes of a related genus, *Glochiddion coccineum*, were found to contain the structurally similar glochicoccins **49** and **50** (Figure 6).

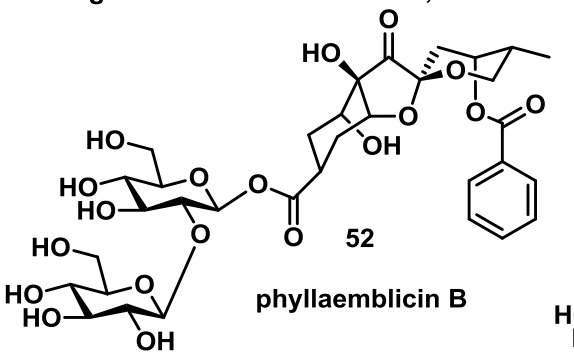
Recently Zhang *et al.*[25] published a further 20 similar structures (**54**-**73**); these were all tested for their antiviral activities against five virus strains: CVB3, hepatitis B virus (HBV), herpes simplex virus type 1 (HSV-1), human enterovirus 71 (EV71) and influenza (H3N2) virus strain. Among these, **55**-**58**, **61**-**63** and **68** all exhibited potential inhibitory activity against hepatitis B virus HBsAG and HBeAg. All of the structures are related to each other by the 6,5 spiroacetal moiety within the molecules.



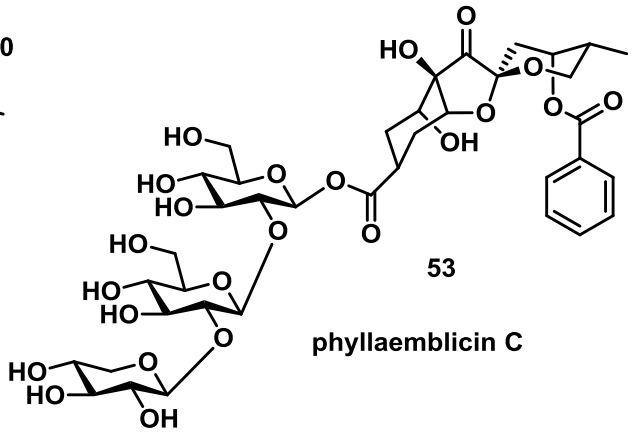
phyllaemblic acid: R^1=Me, R^2=H 47
methyl ester: R^1=Me, R^2=Me 48
glochicoccin D: R^1=OH, R^2=H 49
glochicoccin B: R^1=OH, R^2=Me 50



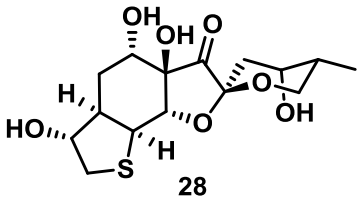
51
phyllaemblicin A



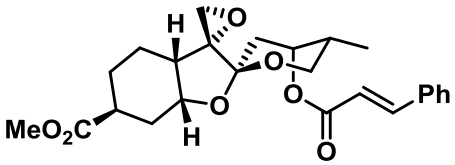
52
phyllaemblicin B



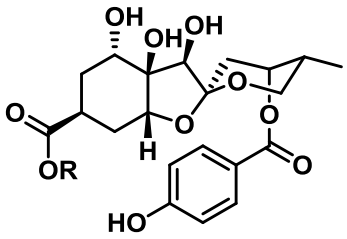
53
phyllaemblicin C



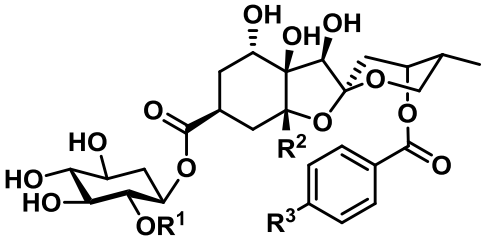
28
breynolide



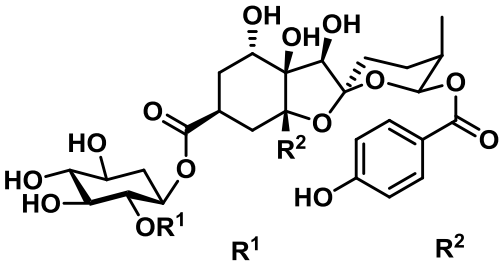
4
phyllanthocin



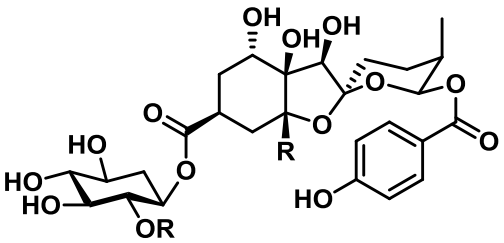
54 R = CH_3 = phyllanthacidoid acid methyl ester
55 R = H = phyllanthacidoid acid



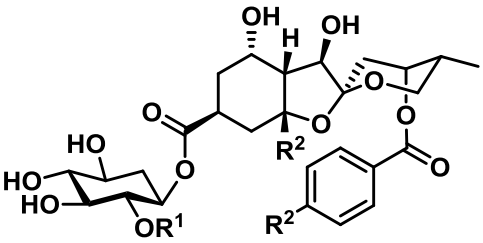
	R^1	R^2	R^3
56	N-Ac-GlcN	H	OH
57	N-Ac-GlcN	H	H
58	Glc	H	H
59	Glc	H	OH
60	H	H	OH
61	N-Ac-GlcN	OH	OH
62	Glc	OH	OH
63	Glc(2-1)Glc	OH	OH
64	Glc	OCH_3	OH
65	N-Ac-GlcN	OCH_3	OH



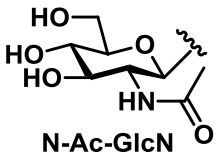
	R^1	R^2
66	N-Ac-GlcN	H
67	Glc	OH
68	N-Ac-GlcN	OCH_3



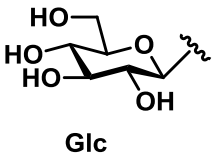
	R
69	N-Ac-GlcN
70	Glc



	R^1	R^2
71	N-Ac-GlcN	H
72	N-Ac-GlcN	OH
73	Glc	OH



N-Ac-GlcN



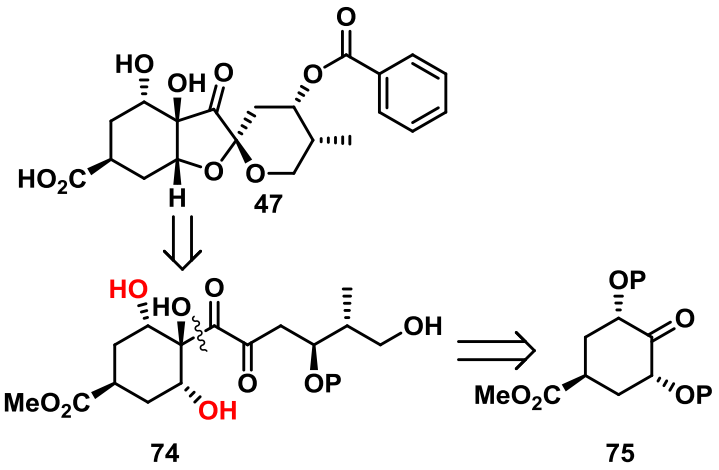
Glc

Figure 6

Various aspects of the reported syntheses of breynolide and phyllanthocin discussed above may prove useful in solving some of the synthetic challenges afforded by phyllaemblic acid. Most notably, the challenging spiroacetal functionality is common to all three natural products and their derivatives.

The Grainger group approach: Disconnection of phyllaemblic acid and the α,α'-annulation reaction

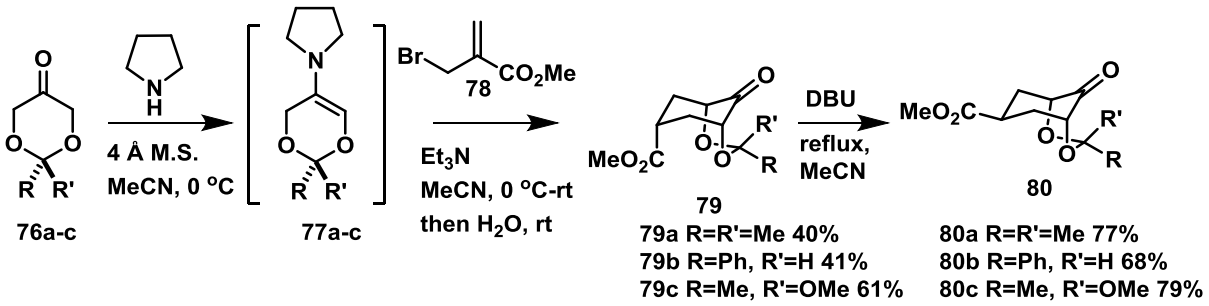
Grainger *et al*. published the first approach towards a synthesis of phyllaemblic acid.[26] Their strategy exploited a hidden symmetry element present in the natural product. The symmetry element can be easily identified after disconnection of the spiroacetal in **47** (Scheme 12).[26] Further disconnection of the carbon chain of **74** leads to the symmetrical *meso* compound **75**.



Scheme 12

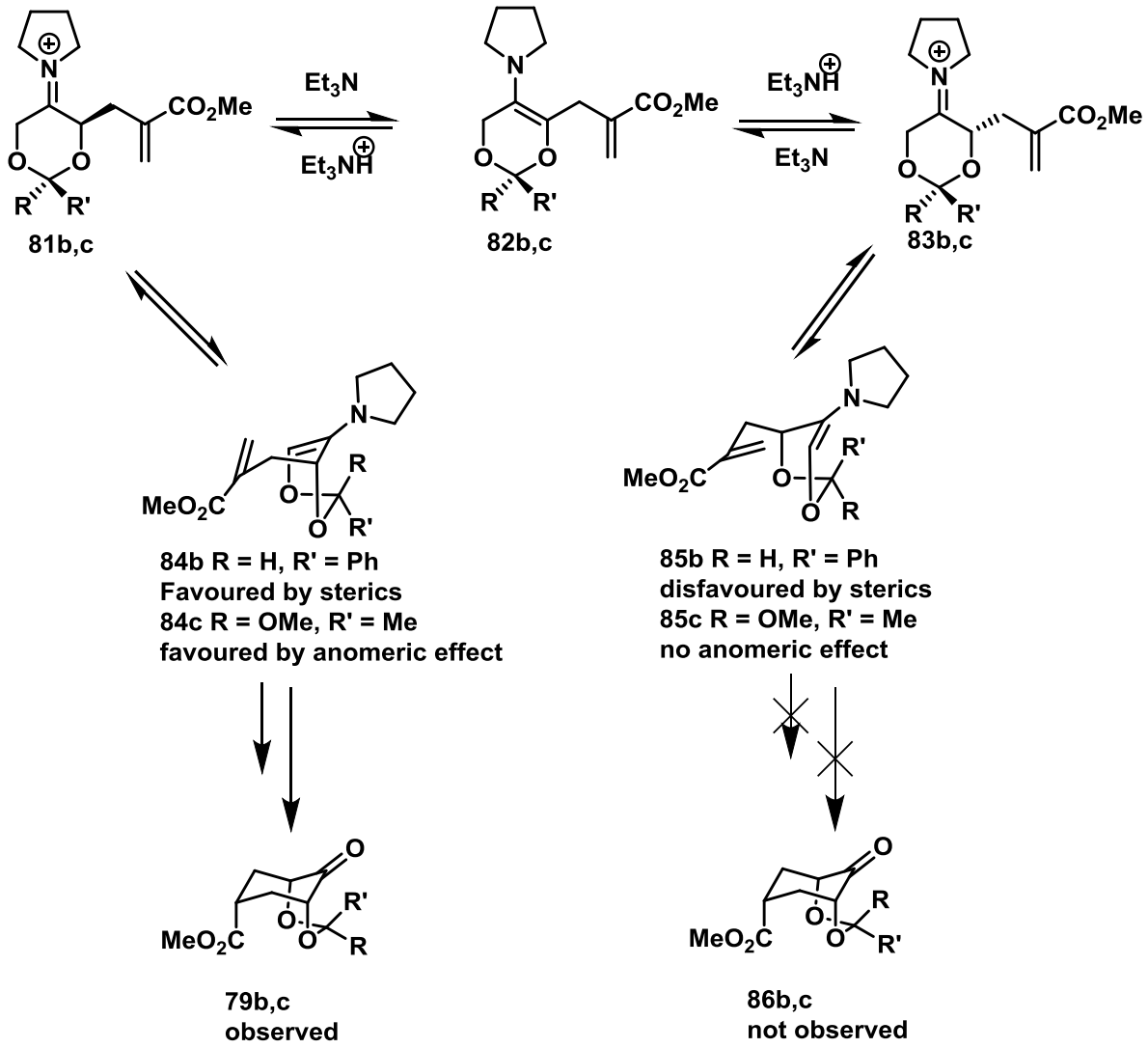
Compound **75** contains three substituents on a cyclohexanone ring, the relative stereochemistry of which must be controlled to give the desired product. The alcohol groups must exhibit *cis* geometry with respect to one another and the ester must be placed on the opposite face to the alcohols. Ideally, all of the stereochemistry should be in place before continuation of the synthesis. The Grainger group achieved this through a stereoselective

α,α'-annulation reaction of a 1,3-dioxan-5-one followed by epimerisation of the resulting ester (Scheme 13).[26]



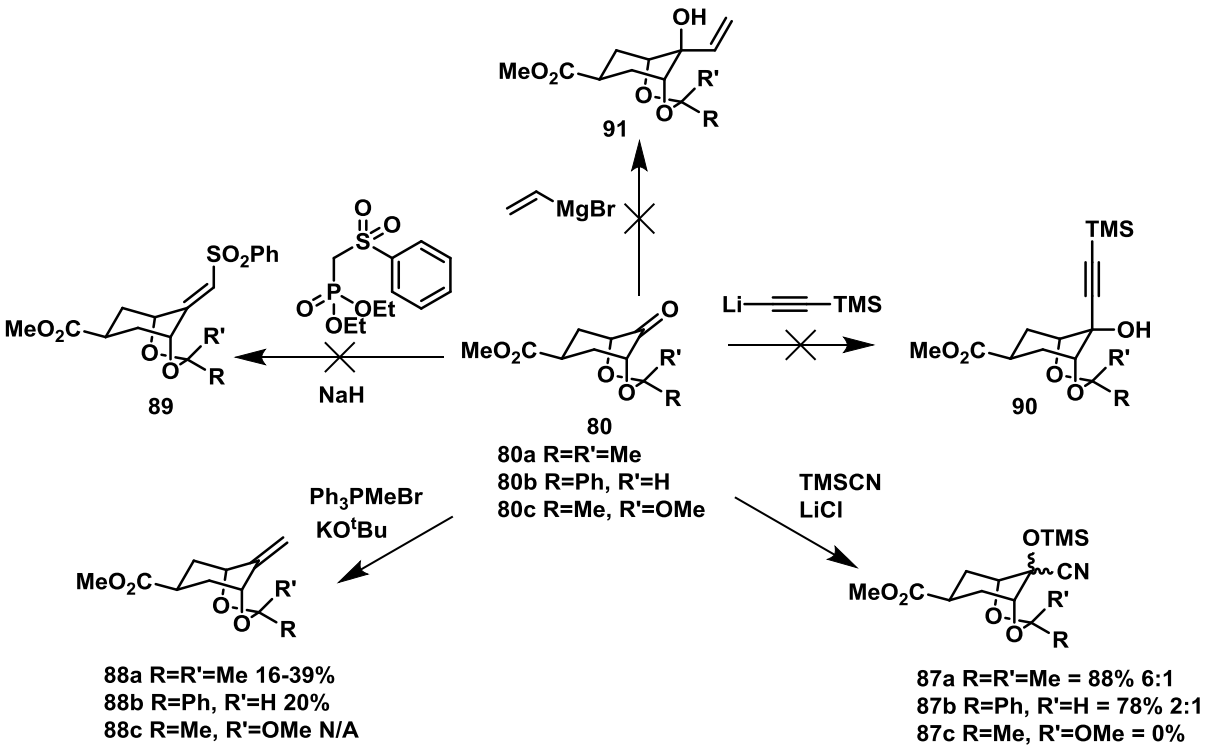
Scheme 13

Condensation of pyrrolidine with 1,3-dioxanone **76** gave **77** which was subsequently treated with **78** and Et_3N. This induced an α,α'-annulation to give **79** which then gives rise to **80** after a separate epimerisation reaction. The stereochemical outcome of this annulation can be rationalised by considering the mechanism (Scheme 14). Allylation of enamines **77b,c** gives rise to two possible iminiums **81b,c** and **83b,c.** These are in equilibrium with each other, via **82b,c**, and with enamines **84b,c** and **85b,c**. For C-C bond formation and cyclisation to occur, the enamines **84b,c** and **85b,c** need to adopt a boat conformation which places the acrylate acceptor in the axial position. This is disfavoured in **85b** due to steric interactions between the flagpole Ph group and the pyrrolidine ring. Removing this steric clash, as in **84b**, results in **79b** being the observed product. The steric interactions in **84c** and **85c** are not as strong but a further anomeric stabilizing effect, only present in **84c**, favours formation of **79c**. Finally, kinetic protonation results in an axially-orientated ester group. This is subsequently converted to the desired thermodynamically favoured equatorial ester via epimerisation using DBU.



Scheme 14

With the successful formation of these bicyclic systems in place, a rapid approach to the natural product was envisaged. Carbon-carbon bond formation was attempted at the bridged ketone on all three bicyclic ketones. However, it was found that intermolecular additions of various nucleophiles gave limited results (Scheme 15).



Scheme 15

It was hoped that nucleophilic addition would lead to the formation of a carbon chain (en route to **74** from **75**, (Scheme 12)). Successful addition of TMSCN proceeded in yields >70% but unfortunately the stereochemistry for the major or minor products **87a**, **87b**, **87c** could not be identified. Further treatment of the product with DIBAL, TBAF, H_2O + MeOH or a Grignard reagent all led to no reaction or degradation of **87a**, **87b**, and **87c**. A simple Wittig reaction was partially successful but low yielding, and again further transformation of the resulting alkenes **88a, 88b** and **88c** was difficult. Horner-Wadsworth-Emmons (HWE), Grignard and acetylide addition to **80** all produced no reaction (**89-91**) and starting material was recovered in each case.

Conclusions and summary

Phyllanthocin and breynolide have been successfully synthesised a number of times by different groups; a review by Smith *et al.*[27] highlights the challenging aspects and retrosynthesis of both phyllanthocin and breynolide. However, from the routes and conditions reviewed it is clear that the spiroacetalisation often gives different results in regards to the thermodynamic or kinetic product. Alternative pathways were discovered even when applying the same conditions used from previous investigations. The reason for this is perhaps summed up best by Williams:[9]

'The Lewis acid complexation site may favour certain spiroacetal isomers by providing them with a more stabilised coordination site'

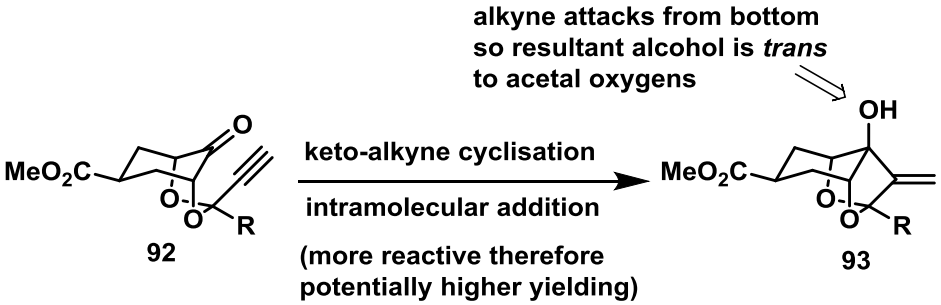
From this quote, and the observations of other researchers, it is concluded that the configurations of stereocentres and the protecting groups used on oxygen functionality of the molecule will play a pivotal role in which spiroacetalisation conditions to use/ will work in future studies.

In an approach towards phyllaemblic acid and related natural products, the Grainger group has so far successfully installed three of the four stereocentres on the cyclohexane ring in the spiroacetalisation precursor **74** (Scheme 12). Further disconnection back to **75** results in a carbonyl ready for intermolecular addition. Unfortunately, nucleophilic attack to this carbonyl has given low yields, and the resultant tertiary alcohol was likely placed *cis* to the oxygens instead of the desired *trans* configuration.

Chapter 2 Intramolecular cyclisation investigation

Literature review of carbonyl-alkyne cyclisation reactions

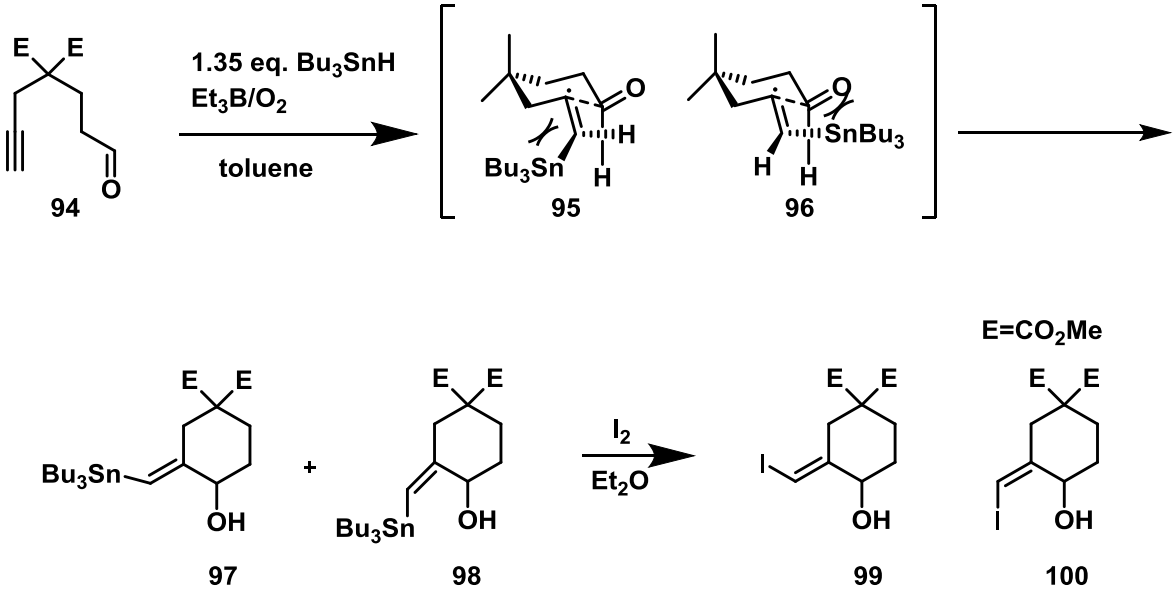
Based on the poor reactivity of the ketone in bicyclic system **80** described in chapter one (Scheme 15), a new approach to C-C bond formation based on an intramolecular keto-alkyne cyclisation was envisaged. This approach aims to overcome the two main problems of low reactivity and incorrect stereochemistry (Scheme 16).



Scheme 16

The key reaction in this new approach is the cyclisation between a carbonyl and alkyne moiety. Below is a review of various procedures for this type of reaction that could be relevant to this work.

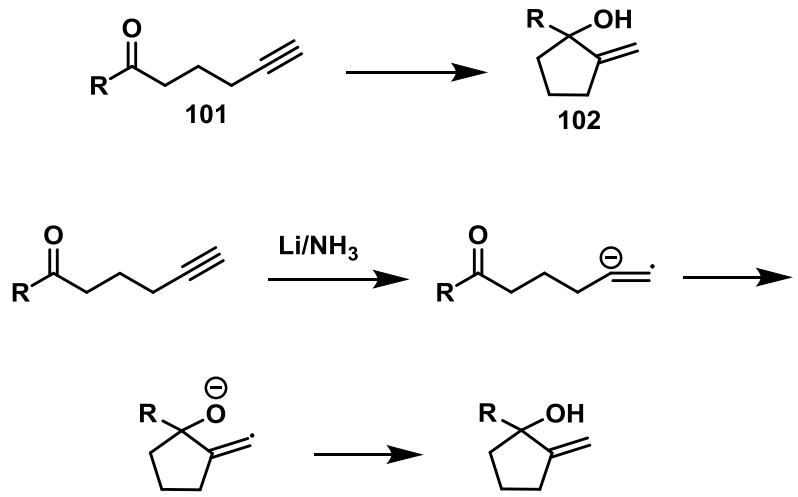
Malacria *et al.* reported a versatile preparation of 2-iodomethylene cycloalkanols (Scheme 17). Cyclisation of **94** was initially attempted under thermal conditions using Bu_3SnH, AIBN and PhH. Under these conditions there was no chemoselectivity in the stannyl radical attack and a complex mixture of products was formed. It was found that running the reaction in the presence of triethylborane at rt gave a clean mixture of vinylstannanes **97** and **98**. These were characterised as the iodo derivatives **99** and **100** in a ratio of 75:25 in an overall yield of 69%, with the major isomer having *E* geometry.



Scheme 17

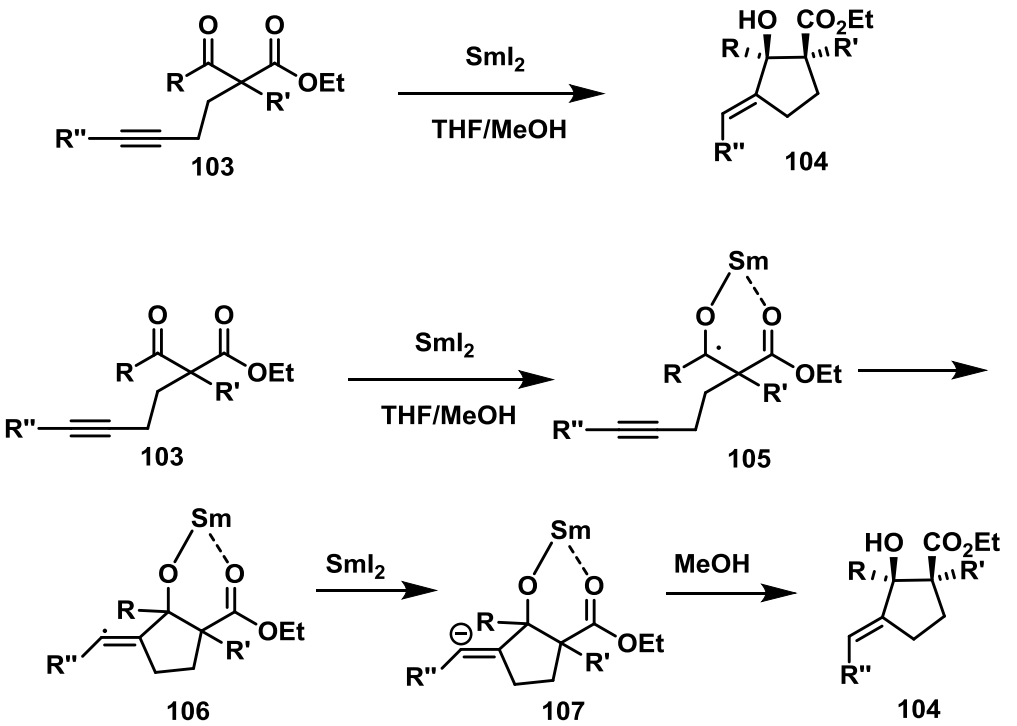
Conversion of vinyl stannanes **97** and **98** to the iodides occurs with retention of stereochemistry. Therefore, the ratio of **99**/**100** directly gives the selectivity of the radical cyclisation. This cyclisation was presumed to occur mainly through the intermediate **95** and not **96**, in which the steric interaction between the stannyl and carbonyl group are minimised. This arrangement could also explain why only moderate stereocontrol is observed, as **95** still suffers from a 1,3-allylic interaction between the stannyl and the developing cyclohexane methylene group.[28-32]

Radical cyclisation can be promoted by the generation of radical anions using dissolving metal conditions. This procedure was developed by Stork *et al.* using ketoalkyne substrates such as **101** (Scheme 18).[33] Treatment of **101** with lithium metal in ammonia gave a mixture of products which could not be purified. However, analysis indicated that **102** was formed in 50% yield based on ^{1}H NMR yields.[33] Other groups have adapted the methodology developed by Stork *et al.* by using other radical anion generators such as sodium naphthalide.[34-37]



Scheme 18

Molander *et al*. used samarium diiodide to carry out an intramolecular reductive coupling reaction on **103** to cyclise to **104** (Scheme 19).[38] High stereoselectivity was achieved when the acetylene bore a terminal TMS group; however, in the investigation that was undertaken only one substrate was found to be reactive (Table 1). Radical formation occurs after addition of SmI_2 to form **105**. A 5-*exo-dig* cyclisation then occurs to give **106**. A further reduction then produces the anion **107** which is protonated to form **104**. From the findings reported, it appears that the presence of an activating group on the alkyne terminus helps to facilitate the cyclisation.[39, 40, 40-42]



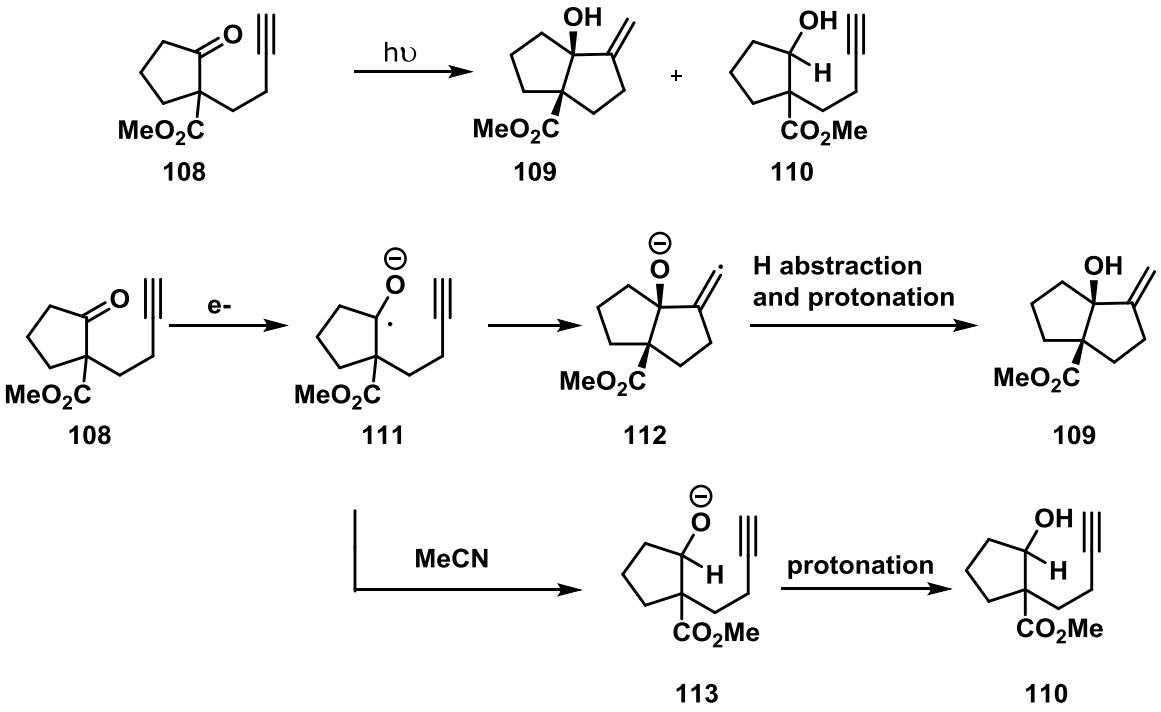
Scheme 19

Entry	R	R'	R''	Yield	Selectivity
1	Me	Me	TMS	51	200:1
2	Me	Me	H	0	N/A
3	Me	Me	CO_2Et	0	N/A

Table 1

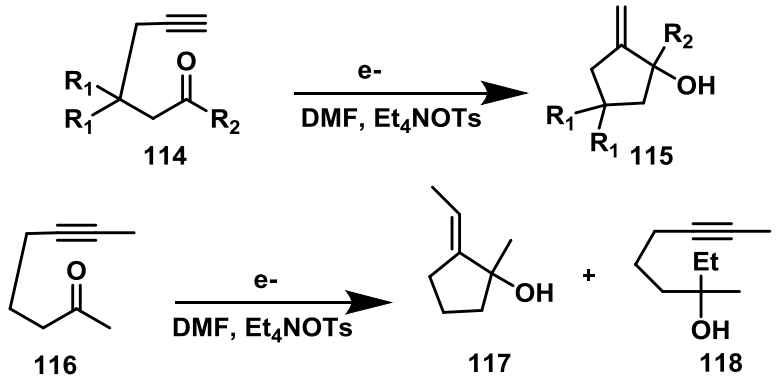
An alternative approach to the radical cyclisation, using photoinitiation, was reported by Cossy *et al*.[43] The group used either neat HMPA or Et_3N in CH_3CN to cyclise acetylenic keto esters **108** through irradiation with UV light to yield **109** and **110** (Scheme 20). Radical anion **111** is formed initially; this undergoes cyclisation via a 5-*exo*-*dig* process to give **112**. Intramolecular cyclisation occurs much more rapidly than H-abstraction from the solvent which would lead to **113**. The reaction has advantages over chemical or electrochemical reduction methods as the procedure can be performed under very mild and homogeneous conditions and no reproducibility issues were observed. When the reaction was carried out

in the presence of HMPA yields of 80% were recorded and with Et_3N/ CH_3CN yields of 86% were obtained.[44-47]



Scheme 20

Electroreduction of **114** was investigated by Shono *et al*. (Scheme 21).[48]



Scheme 21

The electroreduction of **114** at rt was achieved using a carbon electrode, anhydrous DMF as solvent and tetraethylammonium *p*-toluenesulfonate as a supporting electrolyte. A ceramic cylinder was employed as a diaphragm and the electrolysis was continued until 4 F/mole of

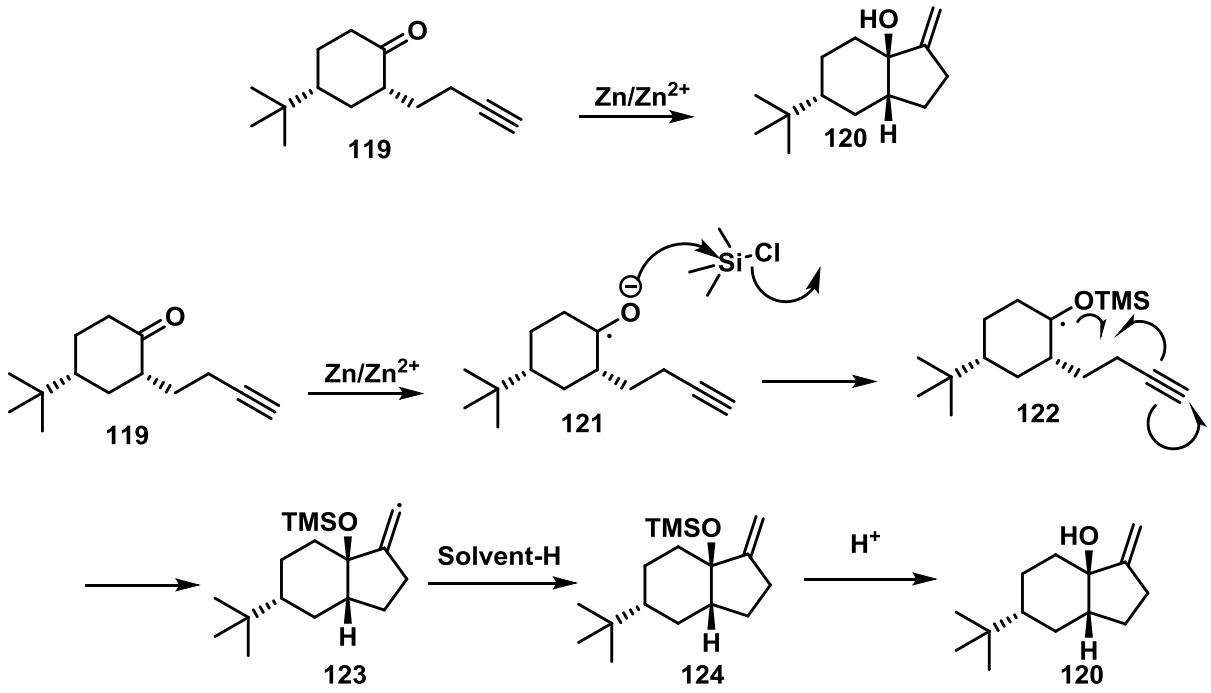
electricity had been used. Various substituents R^1 and R^2 were used and in all cases good yields of the cyclised product **115** were obtained (Table 2).

R^1	R^2	Isolated yield % of 115
H	Me	94
Me	Me	99
Me	Et	95
Me	^{i}Pr	85
Me	^{n}Bu	89

Table 2

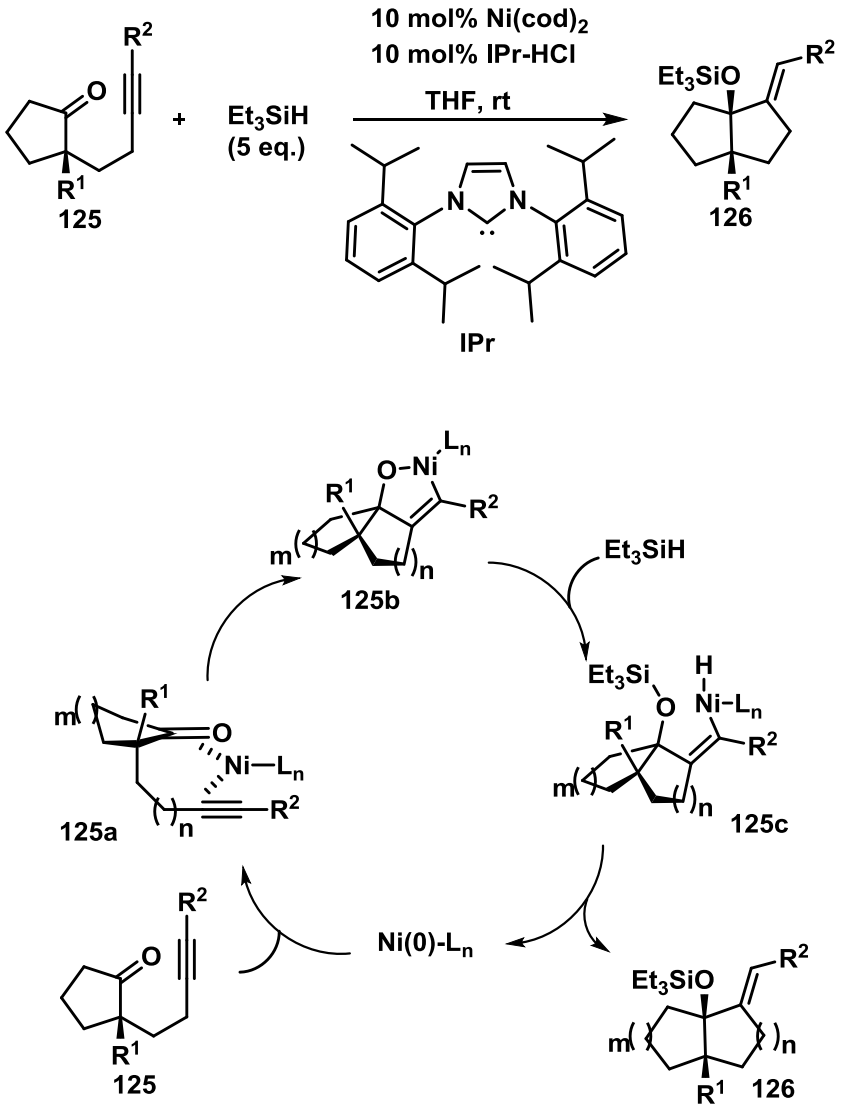
However, when a non-terminal alkyne **116** was used as the substrate, **118** was formed along with desired **117** in 60 and 25% yields respectively. The authors concluded that **118** probably formed through nucleophilic attack of the anionic species generated from **116** on tetraethylammonium tosylate.[49]

Corey *et al*. developed a method for five-membered ring cyclisation involving free radical generation from ketones, such as **119**, followed by addition to a π-bond of the alkyne moiety. The proposed mechanism is outlined below (Scheme 22).[50] Reduction of **119** forms radical anion **121**, which is trapped as the trimethylsilyloxy radical **122**. 5-*exo*-*dig* radical cyclisation gives **123**, which abstracts a hydrogen atom from the solvent to give **124**. The reaction was carried out in the presence of 2,6-lutidine in THF in order to prevent either a zinc chloride or proton-mediated elimination of the tertiary trimethylsilyloxy group. Subsequent deprotection gave alcohol **120** in 74% yield. The group was also successful in forming **110** (Scheme 20) in 77% yield using the TMSCl-Zn-lutidine procedure. A more recent example has been reported by Bertrand and Feray *et al*.[51]



Scheme 22

Sato *et al*. developed a nickel-catalysed cyclisation between an alkyne and a carbonyl using Et_3SiH and an NHC (*N*-heterocyclic carbene) ligand to produce a number of different cyclic compounds (Scheme 23).[52-54]



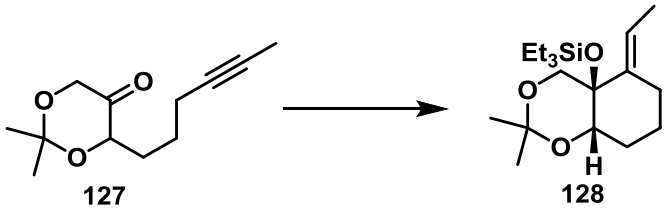
Scheme 23

Treatment of **125** with five equivalents of Et_3SiH in the presence of $Ni(cod)_2$ (10 mol%) and PPh_3 (20 mol%) in THF at rt gave **126** in 44% yield. After screening various conditions, it was found that the NHC ligand IPr gave quantitative yields for the cyclisation when R^2 = Me. The group proposed a catalytic cycle (Scheme 23). Coordination of the alkyne and carbonyl in **125** with a zerovalent nickel complex shown in **125a**, is followed by an oxidative cyclisation to give the oxanickelacycle **125b**. Cleavage of the nickel-oxygen bond by σ-bond metathesis of **125b** with Et_3SiH produces the hydridenickel **125c**. Subsequent reductive elimination from **125c** then gives the cyclised product **126** as a single stereoisomer.

The effect of varying substituents was investigated (Table 3). It should be noted that the presence of a TMS group on the alkyne lowered the yield to 26%, whereas other substituents gave good yields even if they were more sterically demanding (e.g. Ph or CH_2OTBS, entries 3 and 7 in Table 3). Alternative cyclic frameworks were also investigated; the most pertinent being the 1,3-dioxan-5-one **127** which cyclised to give **128** in 99% yield (Scheme 24).

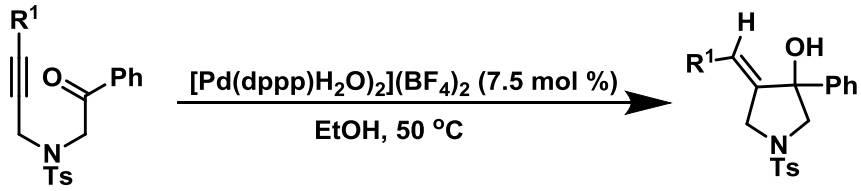
Run	Substrate	Time (hr)	Yield%
1	**125b**: $R^1 = R^2 = H$	0.5	**126b** : 83
2	**125c** : $R^1 = H$ $R^2 = CH_2OTBS$	0.5	**126c** : 99
3	**125d** : $R^1 = H$ $R^2 = Ph$	0.5	**126d** : 97
4	**125e** : $R^1 = H$ $R^2 = CO_2Me$	48	**126e** : 26
5	**125f** : $R^1 = H$ $R^2 = TMS$	40	**126f** : 26
6	**125g**: $R^1 = R^2 = Me$	0.5	**126g** : Quant
7	**125h** : $R^1 = CH_2OTBS$ $R^2 = Me$	0.5	**126h** : 96

Table 3



Scheme 24

As an alternative to nickel, palladium, platinum and rhodium were used by Tsukamoto *et al.*[55], Han and Lu *et al.*[56] Jang *et al.* [57] Tanaka *et al.*[58] and Krische *et al.*[59] The authors all worked on relatively similar substrates with the most pertinent work published by Han and Lu *et al*. (Table 4).

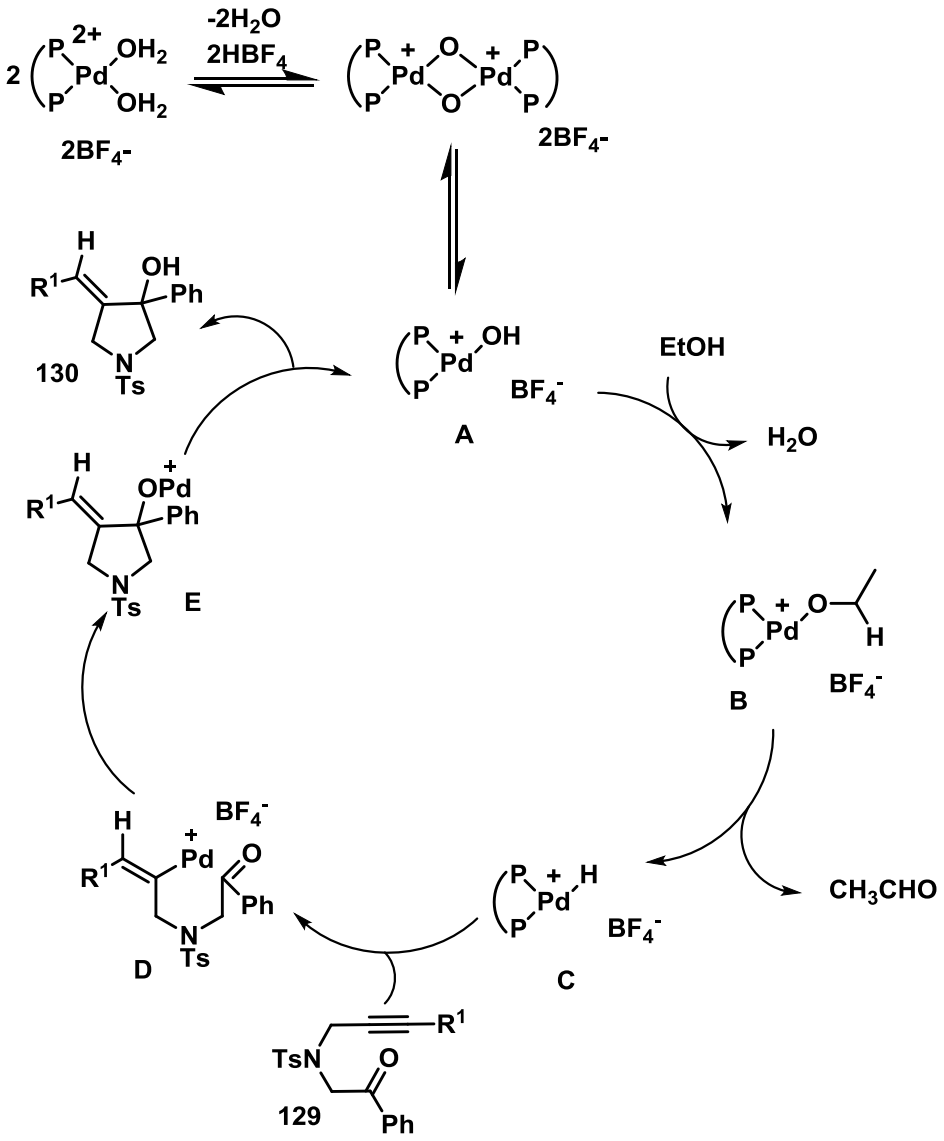


129 130

Entry	Substrate	Time (hr)	Product	Yield
1	**129a** R^1 = Me	24	**130a**	39%
2	**129b** R^1 = Ph	24	**130b**	47%
3	**129c** R^1 = TMS	2	**130c**	65%

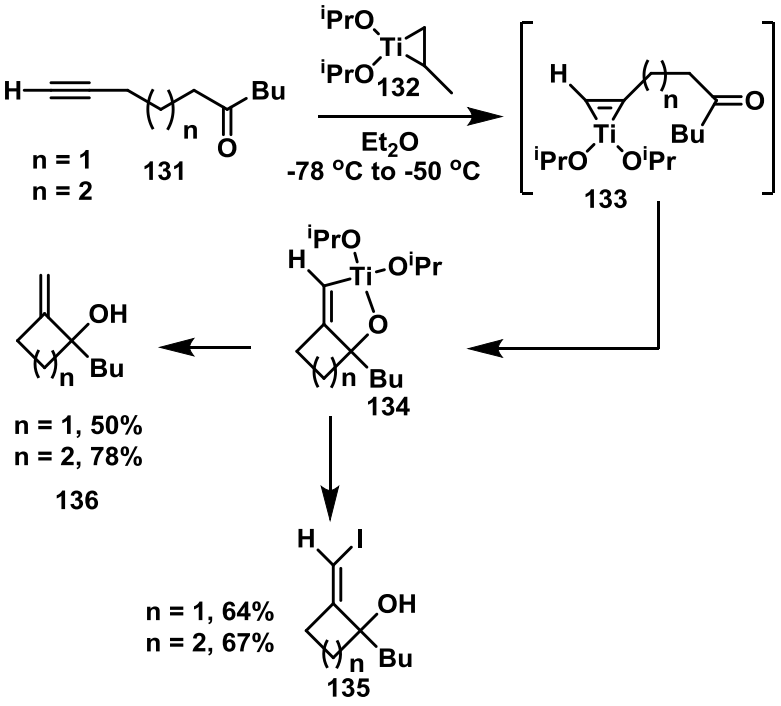
Table 4

The group found that non-terminal alkynes cyclised more efficiently as this suppressed the tendency for dimerisation to occur. When a silicon group was placed on the terminus of the alkyne, a 65% yield was obtained and the reaction time was drastically reduced. A proposed mechanism is given in (Scheme 25). The active catalyst is assumed to be the palladium hydroxo complex **A**. This reacts with ethanol to produce the palladium ethoxide complex **B**, which subsequently generates the palladium hydride complex **C** via β-hydride elimination. Hydropalladation to **129** gives a vinylpalladium intermediate **D**. This is followed by intramolecular cyclisation to the carbonyl group to give **E**. Protonolysis of **E** forms the product and regenerates the palladium (II) catalyst **A** which completes the catalytic pathway.



Scheme 25

Marek *et al*.[60] used a diisopropoxy(η^2-propene)titanium complex **132** to activate an alkyne and perform an intramolecular addition to a ketone to form a variety of cyclic alcohols of different ring sizes (Scheme 26). Both terminal and non-terminal alkynes undergo cyclisation using this method.



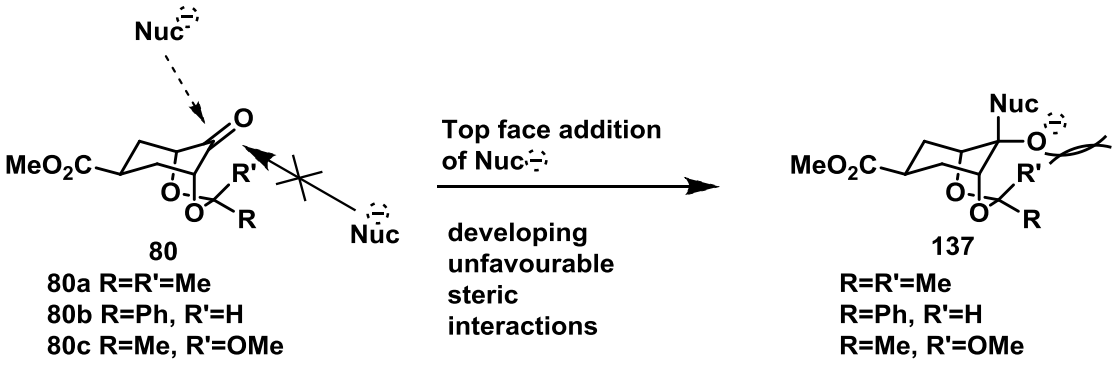
Scheme 26

In the above example (Scheme 26) treatment of **131** with stoichiometric amounts of $Ti(O^iPr)_4$ and 2 eq. of ^{i}PrMgX at -78 ^{o}C leads to the cyclic product **136** after hydrolysis in a 78% yield. Organometallic derivative **134** is presumed to form via the titanacyclopropene derivative **133** although it could not be isolated. The existence of **134** was probed by adding iodine at the end of the reaction. The vinyl iodide **135** was isolated in a 67% yield as a single isomer. Similar examples of keto-alkyne intramolecular cyclisations using a titanium or copper catalyst have been reported.[61 62 63, 64]

In conclusion, a variety of methods are available for the proposed keto-alkyne ring closure outlined in the aims and objectives. It is noted that the presence or absence of large groups on the alkyne terminus may play a role in the cyclisation, and hence access to both terminal and non-terminal alkynes would be advantageous.[65-67]

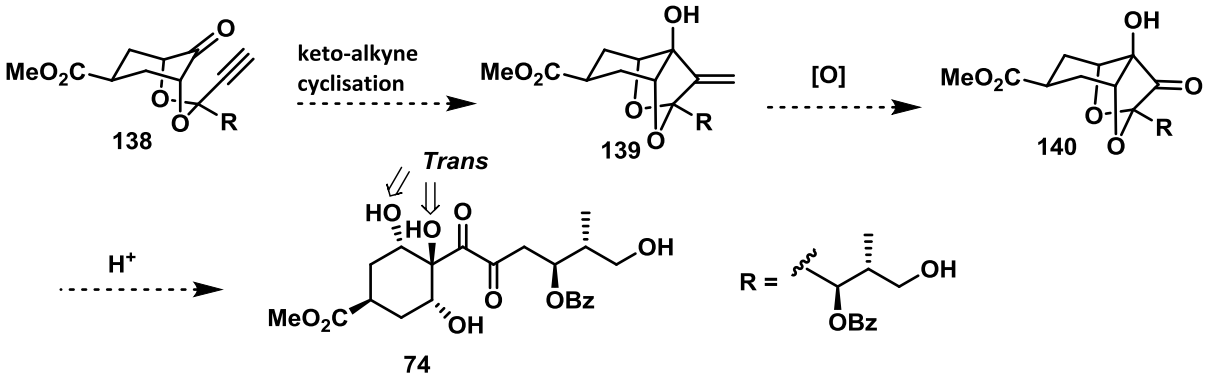
Aims and Objectives

As previously shown in chapter one (Scheme 15), intermolecular nucleophilic addition to **80** has proven to be difficult with very low yields or no reaction often being observed. When sufficient reactivity was obtained, further elaboration was found to be problematic and the route was abandoned. It is assumed that the reason for the lack of reactivity of **80** is due to the acetal blocking the bottom face of the carbonyl. Top face addition is also unfavourable due to developing steric interactions as the carbon changes from being sp^2 to sp^3 hybridised in **137** (Scheme 27).



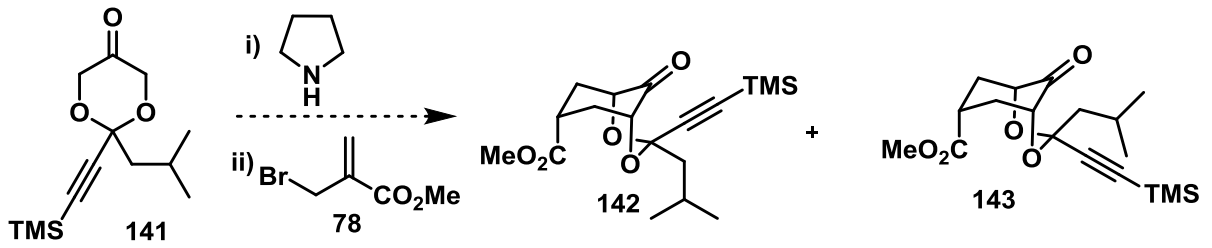
Scheme 27

The initial aim of this project was to investigate a new approach to C-C bond formation at the carbonyl carbon of a bicyclic acetal **138** to form **139**. An oxidative cleavage to form **140** and subsequent removal of the acetal group gives the spiroacetalisation precursor **74**. The compound **138** will be prepared through α,α'-annulation reactions previously developed in the Grainger group.[26] This approach draws on the successful installation of the three stereocentres on the cyclohexane ring already achieved through an α,α'-annulation (Chapter 1, Scheme 13). The tertiary alcohol can then be formed through intramolecular addition, which should both overcome the lack of reactivity of the carbonyl towards intermolecular addition and also control the stereochemistry of the tertiary alcohol to be *trans* to the acetal (Scheme 28).



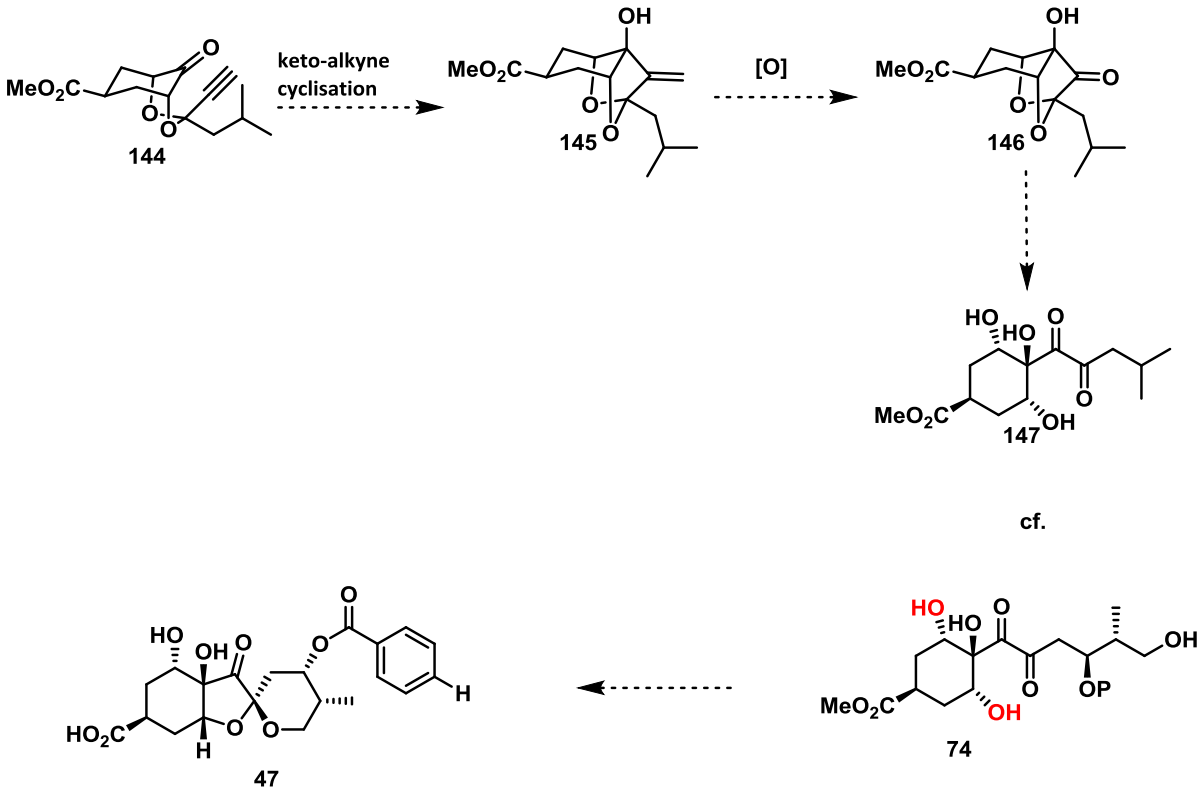
Scheme 28

In a model study, dioxanone **141** will be subjected to an α,α'-annulation reaction; this could result in formation of either of the diastereoisomers **142** or **143** (Scheme 29). Previous work in the group has shown that the larger group at the acetal centre resides in a pseudo-equatorial position on the boat conformation adopted by the dioxanone ring, with the smaller group in the flagstaff position (Scheme 13 and 14). Based on this precedent, it is expected that **142** would be the favoured diastereoisomer. If this is indeed the case, then the carbonyl and alkyne should be favourably orientated in space to undergo an intramolecular keto-alkyne cyclisation reaction (Scheme 30).



Scheme 29

If the cyclisation of **144** proves successful, then subsequent oxidative cleavage of the alkene in **145** would give ketone **146**. Acetal cleavage would then reveal the hydroxyl groups in **147**, analogous to the diastereotopic alcohols found in **74**, as required in the synthesis of phyllaemblic acid **47**.



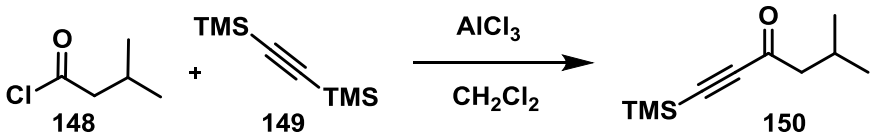
Scheme 30

Results and Discussion

Model study for intramolecular studies

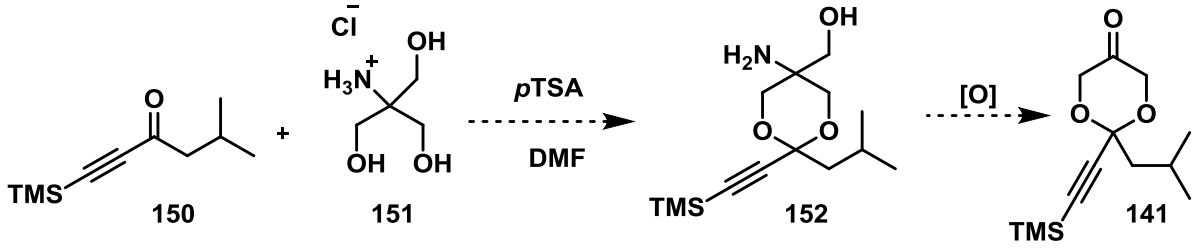
Compound **141** has been assessed as a suitable dioxanone for an α,α'-annulation reaction[26] (Scheme 29), potentially providing a substrate **142** on which to test the desired keto-alkyne cyclisation reaction.

In order to obtain the substituted 1,3-dioxan-5-one **141**, 5-methyl-1-(trimethylsilyl)hex-1-yn-3-one **150** was first synthesised (Scheme 31).[68] Reaction with one equivalent each of isovaleryl chloride **148**, BTMSA **149** and $AlCl_3$ in CH_2Cl_2 at 0 ^{o}C followed by warming to rt gave the desired product **150** in 98% yield.



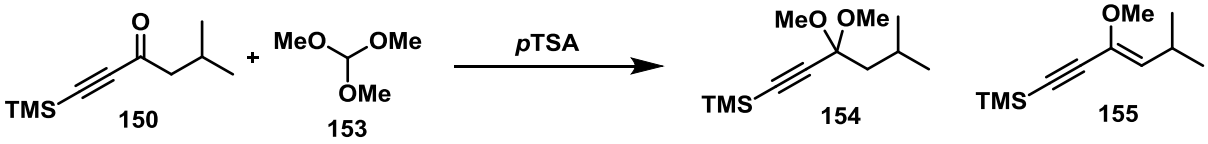
Scheme 31

TRIZMA **151** was expected to undergo acetalisation with **150** to form **152** (Scheme 32). Acetal **152** would then be subjected to an oxidative cleavage to form **141**. Forbes *et al*. had used TRIZMA in their synthesis of 1,3-dioxan-5-ones, though they had first activated the carbonyl moiety by converting it to a dimethyl acetal.[69] Initial attempts to form an acetal directly from **150** with TRIZMA proved problematic, possibly due to the low reactivity of the ketone. Therefore, a variation of Forbes' procedure was investigated.



Scheme 32

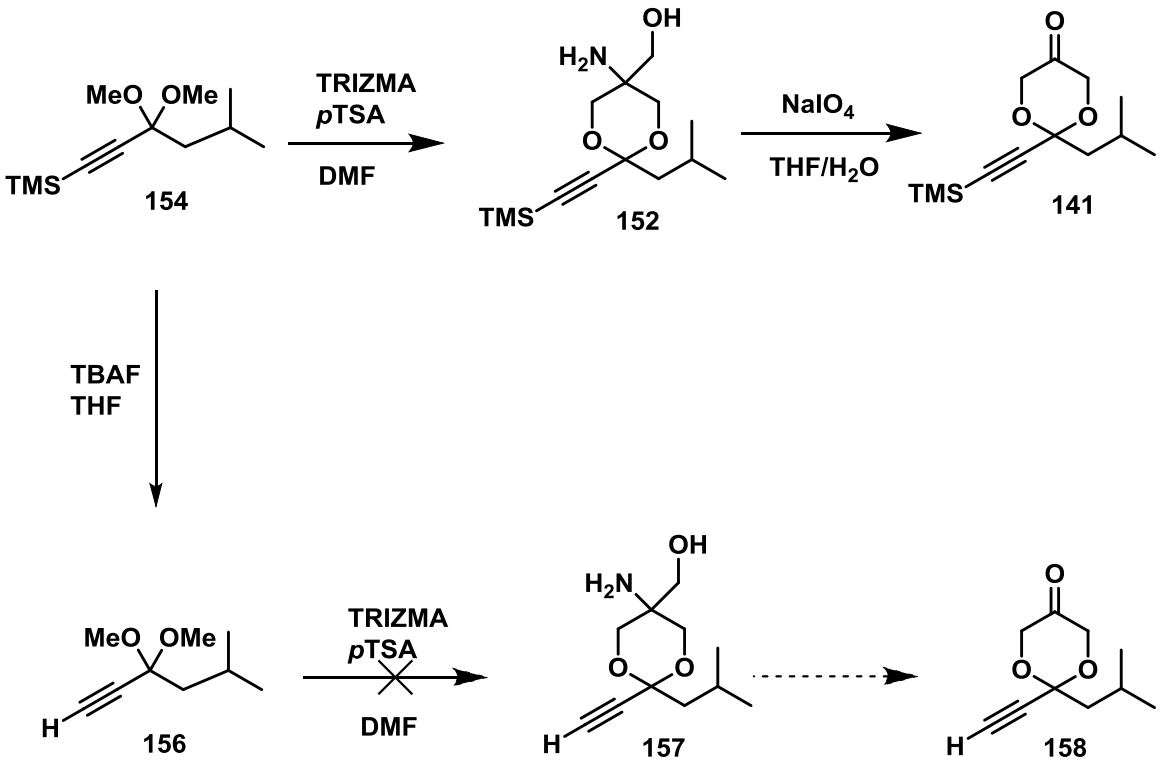
Attempts were made to activate the ketone functionality of **150** by acetalisation via reaction with trimethyl orthoformate and *p*TSA in MeOH to form **153**. The reaction gave two major products and some unreacted starting material which could only be partially purified by column chromatography. Small amounts of each compound were isolated for characterisation; the compounds isolated were found to be ketone **150**, the desired dimethyl acetal **154** and the enol ether **155** (Scheme 33).



Scheme 33

Further attempts to improve the purification of the products from this reaction were unsuccessful. As all three compounds isolated from the reaction mixture could potentially lead to the desired product **141**, it was decided to use the partially purified material directly in the next step of the reaction sequence.

Attempts were made to react the partially purified dimethylacetal **154** with TRIZMA to form acetal **152**, followed directly by oxidative cleavage with $NaIO_4$ to form **141** (Scheme 34). Following literature precedent, the crude amino alcohol **152** was used in the subsequent oxidation.[69] However, the desired compound **141** was obtained in a consistently low yield, typically less than 6% over two steps. The TMS group was removed from **154** with TBAF to give **156** in 47% yield. It was hoped that this would lead, by analogy, to **158**; however, the acetalisation with TRIZMA and **156** to give **157** was also unsuccessful.



Scheme 34

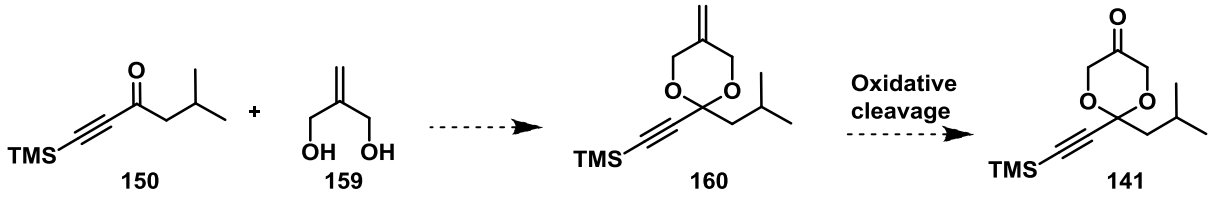
Due to the oxidative cleavage of TRIZMA acetals being a known procedure, it was assumed that the poor yields of **141** were due to the problematic formation of **152**. Attempts were made to try to isolate the amino alcohol **152** but this proved troublesome. Analysis of the ^{1}H NMR of the crude reaction mixture, before and after workup, showed the presence of large quantities of impurities which obscured the product resonances. Monitoring the reaction by T.L.C. also proved difficult, as although dimethylacetal **154** looked as though it was being consumed, the consumption of TRIZMA and product formation were difficult to follow as both were very polar. Eventually it was found that the T.L.C. eluent CMAW (chloroform 65%: methanol 20%: acetic acid 10%: water 5%) would move TRIZMA and **152** off the baseline. Once suitable conditions had been found to enable T.L.C analysis of the reaction, various conditions were tested in an attempt to improve the efficiency of formation of **141** (Table 5). Various solvents, temperatures and extended reaction times did not improve the efficiency of the reaction and so this approach was abandoned.

sm mmol	eq. TRIZMA	Solvent	Temp	Time	Comments	Yield of 141
150 1.37	1.2	toluene	reflux	24 hr	A	-
150 1.37	1.2	benzene	reflux	24 hr	A	-
150 0.437	1	DMF	65 ^{o}C	2 days	B	-
154 4.07	1.1	DMF	65 ^{o}C	20 hr	C	3%
154 24.02	1.1	DMF	65 ^{o}C	20 hr	C	6%
154 2.18	1	DMF	65 ^{o}C	2 hr	D	-
154 37.9	1	DMF	65 ^{o}C	2 days	E	2%
154 0.437	2	DMF	65 ^{o}C- rt	24 hr	F	-
154 0.437	5	DMF	reflux	24 hr	H	-
156 0.640	1	DMF	65 ^{o}C	24 hr	-	-
156 2.56	1	DMF	reflux	24 hr	-	-

Table 5

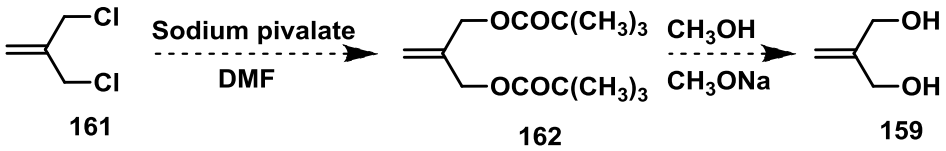
(A) Dean Stark setup, (B) DMF at 65^{o}C dissolves TRIZMA, (C) after 20 hours $NaIO_4$ cleavage undertaken, (D) attempted to isolate **152**, (E) after 2 days $NaIO_4$ cleavage undertaken, (F) after 18 hr rt 1 eq. of TRIZMA added; after 12 hr 1 eq. of TRIZMA added, (H) 5 eq. of TRIZMA added.

An alternative strategy to form **141** via oxidative cleavage of alkene **160** was proposed (Scheme 35). 2-Methylene-1,3-propane diol **159** was identified as a suitable precursor to acetal **160**.



Scheme 35

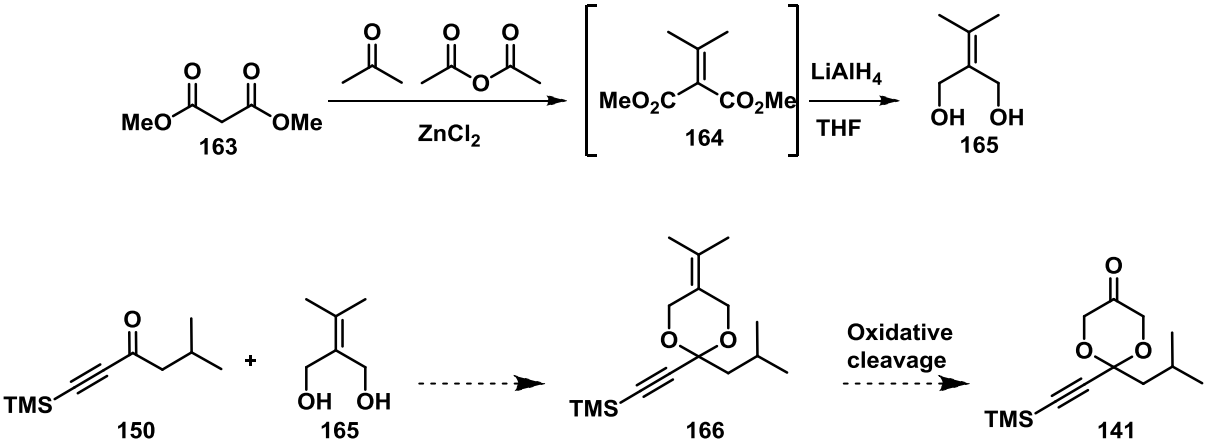
1,3-Dichloro-2-methylenepropane **161** has been reported to undergo substitution with sodium pivalate to give **162**, followed by methanolysis to obtain the desired diol **159** (Scheme 36).[70] However, the diol proved difficult to obtain via this route. DMF was used as the solvent but this led to problems during the work up; diol **159** could not be distilled away from the DMF. Extraction using brine and Et_2O led to the diol preferentially residing in the aqueous layer. Distillation was attempted but unfortunately the diol was unable to be obtained.



Scheme 36

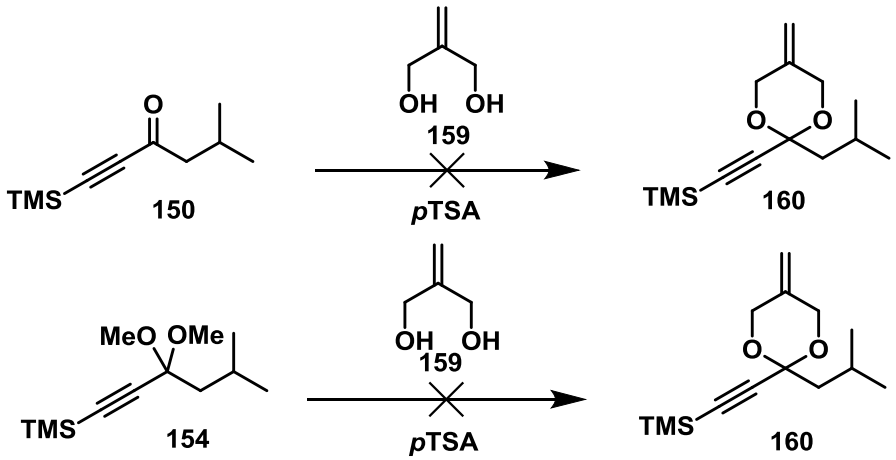
In order to overcome the problems caused by the use of DMF, diol **165** was synthesised via known literature procedures (Scheme 37).[71, 72] This would have enabled access to acetal **166** which after an oxidative cleavage would have led to the desired acetal **141**. Refluxing dimethylmalonate, acetone and acetic anhydride in the presence of $ZnCl_2$ gave **164** which was subsequently reduced to afford the diol **165**. The literature reported a yield of 30% for **165**, however, yields of <1% were recorded. This appeared to be due to 1,4-hydride addition

occurring in competition with ester reduction. This approach was abandoned due to the very low efficiency of this reaction.



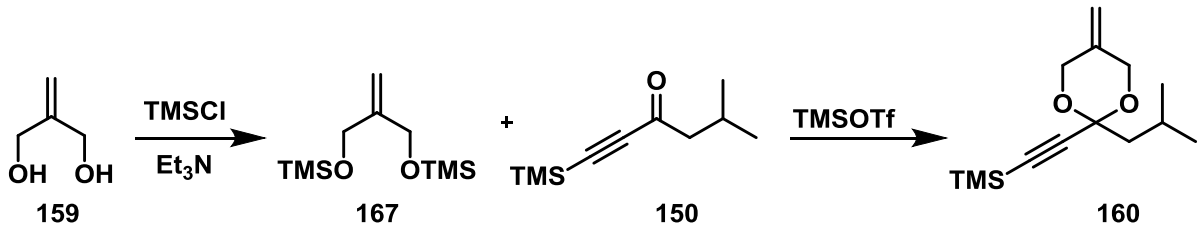
Scheme 37

Diol **159** is commercially available, albeit expensive. Since there were problems with synthesising it effectively, it was decided to purchase the diol and use it directly in the acetalisation reactions.



Scheme 38

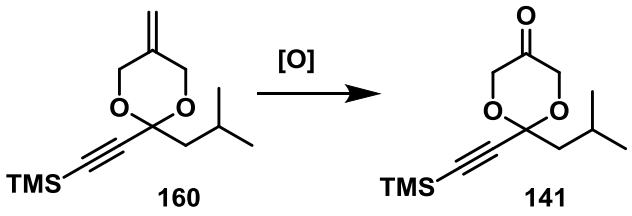
Treatment of ketone **150** with diol **159** and catalytic amounts of *p*TSA proved to be fruitless and no reaction was observed (Scheme 38). Acetalisation using diol **159** and dimethyl acetal **154** was also undertaken but again no reaction was observed. Therefore, attention turned to the use of a variation of a literature procedure reported by Noyori *et al*. (Scheme 39).[73]



Scheme 39

The first step was conversion of **159** to the bis-TMS-ether **167**. This was successfully achieved by reacting diol **159** with 2.1 eq. of TMSCl and Et_3N in CH_2Cl_2 using the method of Veyrieres *et al.*[74] This reaction gave **167** in yields greater than 95%. ^1H NMR analysis indicated that the protected diol **167** was pure; however, T.L.C. analysis showed impurities present. Repeated washings of the product with water and brine gave **167** as a clear oil in 91% yield. However, when **167** was reacted with **150** under literature conditions,[73] no trace of **160** was obtained. Subsequent investigation found that addition of **167** and **150** to a solution of catalytic TMSOTf in CH_2Cl_2 at 0 ^oC and subsequent warming to rt, gave the desired acetal **160** in a yield of 89%.

Attention now turned to the conversion of the alkene moiety in **160** to a carbonyl in order to obtain the desired compound **141** (Scheme 40). Ozonolysis was initially chosen as the preferred technique for this conversion.



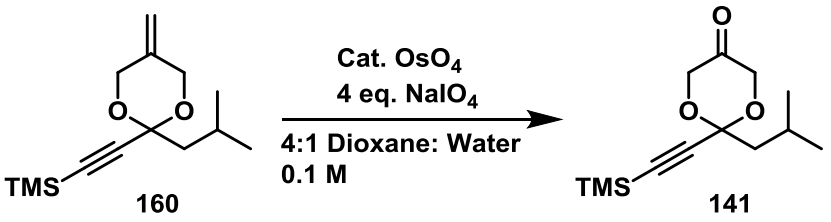
Scheme 40

Ozonolysis was initially attempted using CH_2Cl_2/MeOH as the solvent with O_3 bubbled through the reaction mixture until a colour change from colourless to blue occurred. The reaction was quenched with dimethyl sulfide and concentrated under reduced pressure.

Column chromatography produced the desired compound **141** in 27% yield with no other material being isolated. It was thought that the moderate yield may be due to some hydrolysis of the acetal group. To minimise this problem, the same reaction was run in the presence of ten equivalents of sodium bicarbonate. This produced a mixture of products, including some material from which the TMS group had been removed. The reaction was repeated in the absence of sodium bicarbonate and a mixture of products was again observed. ^{1}H NMR analysis indicated that once again the TMS group had been removed, despite the absence of sodium bicarbonate.

The use of OsO_4 with $NaIO_4$ has received wide attention for the conversion of alkenes to aldehydes and ketones. The Johnson-Lemieux oxidation has been used since 1957,[75] however, the reaction often only produces moderate yields of between 60-65%. A number of years later Jin *et al.*[76] reported an increase in yield by the addition of 2,6-lutidine. This suppressed alpha-hydroxy ketone by-product formation and increased the yield to around 90%.

Initial attempts to affect Johnson-Lemieux oxidation on compound **160** were focused on using both the traditional method and the 2,6-lutidine method (Scheme 41). As **160** contains a terminal alkene, α-hydroxy ketone by-product formation would not be an issue; however, α-hydroxy aldehyde may still form and hence 2,6-lutidine was used in some reactions to observe its effect (Table 6).



Scheme 41

Entry	sm mmol	Temp	Time	2,6-Lutidine	Yield
1	0.4	50 °C	1 hr	No	62%
2	0.4	50 °C	1 hr	No	49%
3	1.2	60 °C	2.5 hr	No	50%
4	4.0	50 °C	24 hr	No	sm only
5	1.0	60 °C	12 hr	No	19%
6	1.2	60 °C	12 hr	No	sm only
7	0.4	50 °C	12 hr	2 eq.	-[a]
8	0.4	rt	24 hr	2 eq.	-[b]
9	0.4	reflux	12 hr	No	sm only
10	0.4	25-50 °C	12 hr	No	33%
11	0.4	50 °C	4 hr	No	47%
12	1.2	60 °C	4 hr	No	32%
13	4.8	50 °C	4 hr	No	63% BRSM
14	4.8	50 °C	4 hr	No	50% BRSM
15	5.2	50 °C	4 hr	No	46% BRSM
16	4.0	50 °C	4 hr	No	61% BRSM
17	4.4	50 °C	4 hr	No	53%
18	8.0	60 °C	4 hr	No	59%
19	5.1	50 °C	4 hr	No	53%

Table 6

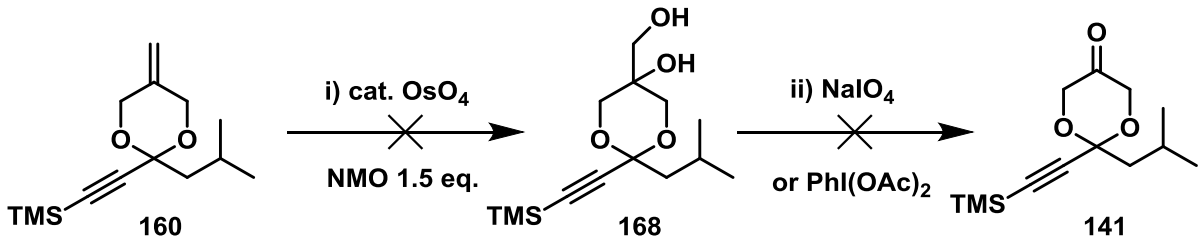
[a]Acetal cleaved. [b]No reaction, no recovered sm, (For entries 13-19, any solid material was filtered off before a basic work up)

The reaction was first attempted for one hour at 50 °C (entries 1-2). This gave yields of **141** in 62% and 49% respectively. However, starting material **160** was present in both reactions.

Increasing the reaction time to 2.5 hours showed no improvement, giving **141** in a 50% yield with **160** still present (entry 3). The reaction time was increased to between twelve and twenty four hours to attempt to increase the yield of **141** (entries 4-7). T.L.C. analysis showed that, once again, **160** remained present in the reaction. In some cases the yield was dramatically decreased (entry 5) and the acetal was cleaved (entry 7). The effect of temperature was investigated, varying from rt to reflux (entries 8-10). The entries showed that increasing temperature made no difference as **160** was observed and a low yield was obtained in entry 10. Throughout this investigation, inconsistent results were obtained with the yield ranging from 0-63%. The addition of 2,6-lutidine proved not to be beneficial to the reaction (entries 7, 8). To date, it has been found that four hours at 50 ^{o}C, followed by a careful work up and filtration step to remove any solid material, will give consistent yields of between 50-60% (entries 13-19).

The reactions in Table 6 produced a variety of yields and on occasion inconsistent results (entry 12). Therefore, alternative solvents and oxidising agents were investigated in an attempt to improve the yield of **141** (Table 7). The Upjohn dihydroxylation was developed in 1976 as a way to form 1,2-diols.[77] The method employs cat. OsO_4 and NMO in mixed solvent systems such as 5:5:2 acetone: water: ^{t}BuOH or 10:1 acetone: water. This chemistry has led to a two-step procedure for the oxidative cleavage of alkenes, via formation of the corresponding diol, followed by addition of a second oxidant.[78] This approach was investigated using various conditions. Treatment of alkene **160** with osmium tetroxide gave complete consumption of starting material by T.L.C. analysis. However, after $NaIO_4$ was added no material could be isolated. A different solvent system was used along with stoichiometric 2,6-lutidine. Starting material **160** was again consumed but upon addition of

$NaIO_4$ acetal cleavage occurred (entry 2). As the diol **168** appeared to be formed, and there was no trace of starting material, an attempt was made to isolate it. Unfortunately, it was not possible to recover any product (entry 3). An alternative method developed by Nicolaou *et al.*[79] uses $PhI(OAc)_2$ instead of $NaIO_4$. This work showed promising results for the formation of ketones from 1,2-diols. Unfortunately, when applied to **160**, only degraded material was obtained (entries 4 and 5).



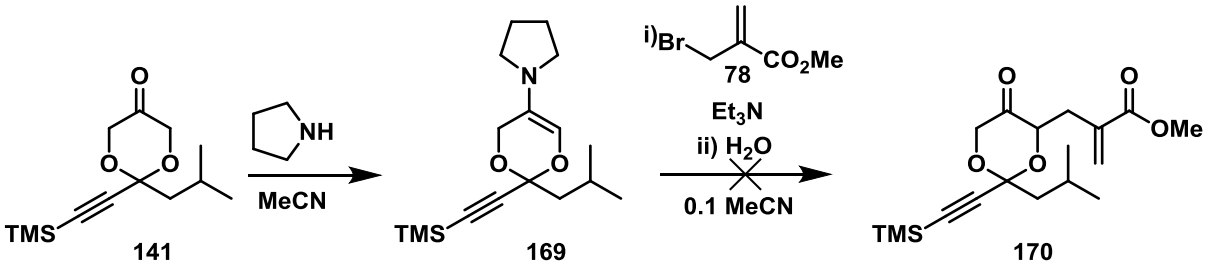
Entry	sm mmol	Solvent	Temp[d]	Time 1	Time 2	2,6-lutidine	Step 2 Oxidant	Result
1	0.396	acetone: H_2O: ^tBuOH 5:5:2	60 °C	[a]	12 hr	No	$NaIO_4$ 4 eq.	degraded material
2	0.396	acetone: water 10:1	50 °C	[a]	2 days	Yes	$NaIO_4$ 4 eq.	degraded material
3	0.396	acetone: water 10:1	50 °C	3 hr	-	Yes	-[b]	no recovery
4	0.396	acetone: water 10:1	50 °C	[a]	2 days	Yes	$PhI(OAc)_2$ 1.5 eq.	degraded material
5	3.96	acetone: water 10:1	50 °C	[c]	12 hr	Yes	$PhI(OAc)_2$ 1.5 eq.	degraded material

Table 7

[a] Reactions monitored by T.L.C. until sm was consumed then continued to step 2. [b] Attempted to isolate diol instead of proceeding with oxidative cleavage. [c] Reaction proceeded after sm was almost completely consumed. [d] Temperature was maintained throughout step 1 and 2.

Attempted annulation reactions

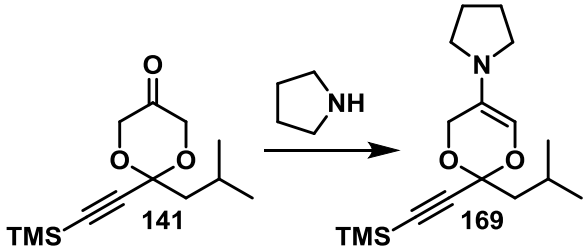
Although the yields of **141** obtained via the Lemieux-type approach were not ideal, sufficient material was obtained to enable investigation of the α,α'-annulation reaction. The methodology initially used was the same as for the formation of **80** (Scheme 13). However, the first attempt at this reaction gave a complex mixture of products. ^{1}H NMR analysis of the crude reaction mixture suggested that the starting material **141** had been consumed, with the appearance of new alkene resonances. From this data it was tentatively concluded that after formation of **169** monosubstitution had occurred to give **170** (Scheme 42). Unfortunately, **170** could not be isolated and mass spectrometric analysis gave no evidence for or against the proposed structure. With this in mind, the reaction was repeated and subjected to reflux overnight. It was assumed that if monosubstitution had occurred, then the higher temperature may provide the energy needed to complete the annulation. The ^{1}H NMR spectrum of the crude reaction mixture suggested formation of a new product with large amounts of impurities. Due to the difficulty in assigning the structures of the products, and the problems when trying to follow the reaction, it was decided to make sure the first step of the reaction sequence was proceeding.



Scheme 42

The formation of enamine **169** is key for the successful annulation reaction to occur (Chapter 1, Scheme 29). As there was no evidence of an annulation occurring under standard

conditions, further investigation was undertaken to determine whether the condensation of pyrrolidine with **141** was taking place (Table 8).



Entry	sm mmol	Pyrrolidine eq.	Toluene conc.	Temp	Time	Yield
1	0.2	1	0.1	rt	12 hr	-[a]
2	0.2	1	0.1	rt-50 °C	48 hr	-[b]
3	0.2	2	0.1	50 °C	72 hr	-[c]
4	0.4	4	0.1	50 °C	72 hr	68%
5	1.0	4	0.5	50 °C	24 hr	60%

Table 8

[a]CSA used which promoted acetal cleavage. [b] Enamine observed by ^{1}H NMR, no reaction until temp increased to 50 °C. [c] Enamine observed by ^{1}H NMR, 1 eq. of pyrrolidine added after 48 hr.

Traditional enamine formation using pyrrolidine often uses toluene as a solvent with catalytic *p*TSA at rt.[80] Due to the presence of an acid sensitive acetal, the slightly milder acid CSA was used instead (entry 1). This unfortunately resulted in acetal cleavage. The use of 1 eq. of pyrrolidine at rt gave no reaction, as shown by ^{1}H NMR analysis of the crude reaction mixture. The reaction temperature was increased to 50 °C and after 48 hours enamine **169** had started to form (entry 2). The reaction was then left for 72 hours at 50 °C. ^{1}H NMR analysis of the crude reaction mixture showed enamine formation along with starting material in an approximate ratio of 50:50. Another 1 eq. of pyrrolidine was added and ^{1}H NMR now showed that the desired enamine **169** was the major product (entry 3). The

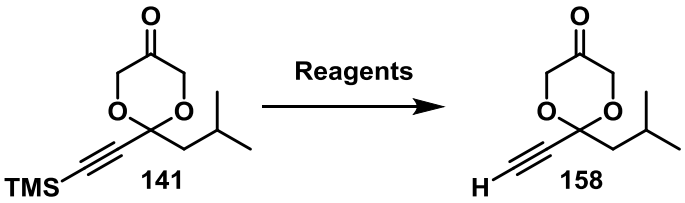
reaction was set up on slightly larger scale with 4 eq. of pyrrolidine in an attempt to fully convert all of the starting material. After 72 hours enamine **169** was isolated in a yield of 68% (entry 4). The solution concentration of **141** was increased to 0.5 M to increase reaction rate; after 24 hours **169** was isolated in a 60% yield (entry 5).

After formation of **169** was confirmed, the annulation reaction was attempted to form **142** (Scheme 29). 1 eq. of Et_3N and methyl bromomethylacrylate were added to a solution of **169** in MeCN and the reagents subjected to the same conditions previously investigated.[26] ^1H NMR of the crude material showed that the methyl bromomethylacrylate and **169** had been consumed. Purification of the crude material proved problematic as there were multiple components of very similar polarity that could not be separated. The ^1H NMR data from the crude material showed the presence of resonances corresponding to new alkene group(s). It was assumed from this that the alkylation step had worked; however, cyclisation was not proceeding to completion.

It was thought that the presence of the TMS group may be interfering in the intramolecular addition, preventing the second ring from forming. In order to test this theory, it was decided to remove the TMS group.

As **141** contains an acid sensitive acetal, it was decided to use MeOH and K_2CO_3 at 0 ^oC to remove the TMS group. The deprotection initially worked well with 2 eq. of K_2CO_3 (Table 9) (entries 1, 2, 4 and 5), although leaving the reaction to warm above 0 ^oC led to degradation (entry 3). Scaling the reaction required increased reaction times which then led to problems; **158** was observed by T.L.C. but by-products rapidly formed leading to degraded material (entries 6-8). TBAF was used as an alternative but this also resulted in degradation (entry 9).

The amount of K_2CO_3 was reduced in an attempt to control the rate of the reaction and prevent degradation (entries 10-12). With careful monitoring of reaction progress, followed by rapid workup, yields of 70% were obtained. However, consistent results were still difficult to obtain. Therefore, silyl deprotection was attempted at various points along the four step synthesis of **141**.

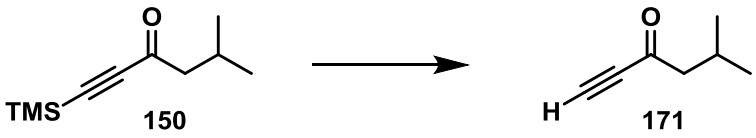


Entry	sm mmol	Solvent ratio 4:1	Reagent eq.	Time	Yield
1	0.4	MeOH:H_2O	K_2CO_3 2 eq.	30 Min	42%
2	0.4	MeOH:H_2O	K_2CO_3 2 eq.	15 Min	77%
3	0.4	MeOH:H_2O	K_2CO_3 2 eq.	30 Min	-[a]
4	1.0	MeOH:H_2O	K_2CO_3 2 eq.	30 Min	76%
5	1.0	MeOH:H_2O	K_2CO_3 2 eq.	1 hr	80%
6	1.7	MeOH:H_2O	K_2CO_3 2 eq.	3.5 hr	-[b]
7	2.0	MeOH:H_2O	K_2CO_3 2 eq.	3.5 hr	-[b]
8	2.0	MeOH:H_2O	K_2CO_3 2 eq.	1 hr	-[b]
9	0.2	THF 0.1 M	TBAF 1.2 eq.	-	-[c]
10	1.0	MeOH:H_2O	K_2CO_3 1 eq.	45 Min	78%
11	2.2	MeOH:H_2O	K_2CO_3 1 eq.	50 Min	51%
12	3.0	MeOH:H_2O	K_2CO_3 1 eq.	1 hr	59%

Table 9

[a] Reaction failed when temp increased above 0 ^oC. [b] Scaling the reaction led to degradation. [c] Reaction monitored by T.L.C., degradation observed immediately, no product ever formed.

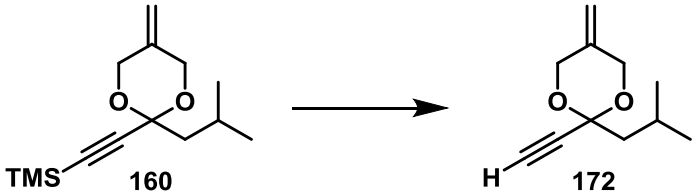
A few different conditions were attempted for the removal of the TMS group in **150** (Table 10). All conditions used showed good results via T.L.C. analysis; however, the main issue was the high volatility of the product **171**.



Entry	sm mmol	Reagent	Solvent	Yield
1	2.7	K_2CO_3 2 eq.	MeOH/H_2O	-
2	1.3	NaF 1 eq.	Ether: water with 0.1 eq. NBu_4Cl	-
3	1.4	TBAF 1.2 eq.	THF	-

Table 10

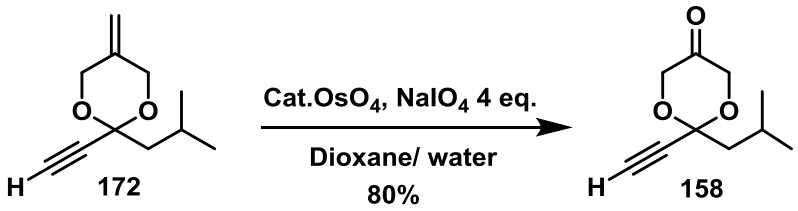
Due to the difficulty in isolating the ketone **171**, it was decided to remove the TMS group after the Noyori acetalisation. The procedure for TMS removal from **160** proceeded smoothly and reproducible results were now obtainable, with yields around 80% (Table 11).



Entry	sm mmol	Reagent	Solvent	Yield
1	0.54	K_2CO_3 1 eq.	MeOH/H_2O	66%
2	2.0	K_2CO_3 1 eq.	MeOH/H_2O	80%
3	2.5	K_2CO_3 1 eq.	MeOH/H_2O	79%

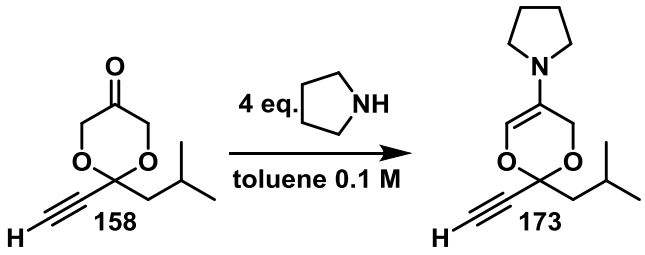
Table 11

Subsequent oxidation of the alkene **172** to give **158** also proved to be relatively straightforward with reproducible yields of around 80% (Scheme 43).



Scheme 43

Attention then turned to the formation of the enamine **173**. The same conditions employed previously for the formation of enamine **169** were initially investigated (Table 12). After monitoring the crude reaction mixture by ^{1}H NMR it was found that **173** was forming (entry 1). The reaction was scaled up and left for 12 hours at 50 ^{o}C leading to enamine **173** being isolated in a 92% yield (entry 2). It was found that **173** formed faster than the previous enamine **169** when heated at 50 ^{o}C. Subsequent investigation showed that the yield of **173** was not significantly impacted when carrying out the reaction at rt (entries 3-6).

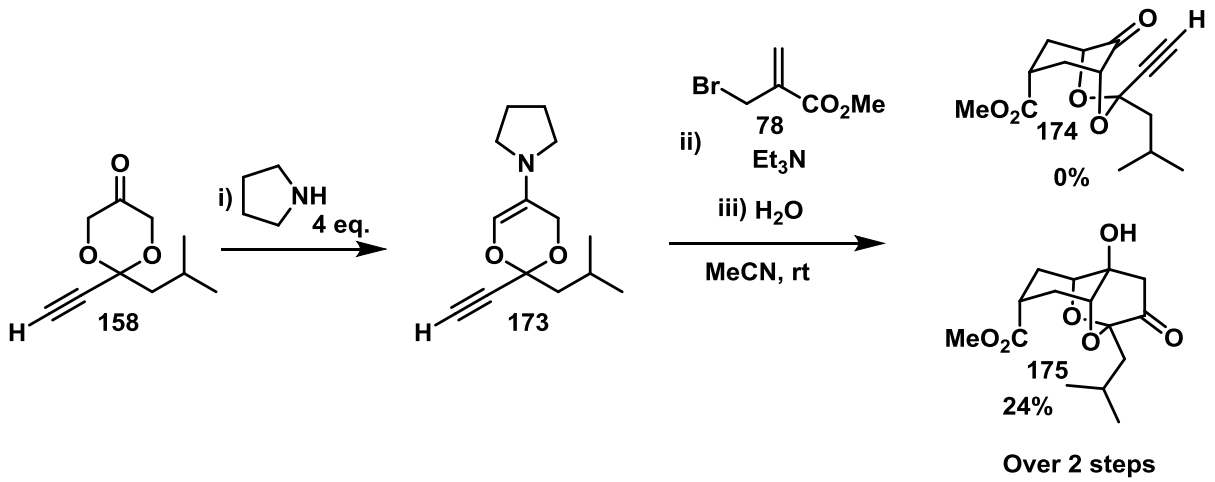


Entry	sm mmol	Time	Temp	Yield
1	0.4	12 hr	50 ^{o}C	-[a]
2	0.5	12 hr	50 ^{o}C	92%
3	0.9	2 days	rt	86%
4	0.8	12 hr	rt	88%
5	0.8	12 hr	rt	69%
6	3.4	12 hr	rt	88%

Table 12

[a] Enamine formation observed by crude NMR.

With successful formation of enamine **173** in hand, the annulation reaction was attempted. As stated earlier, annulation of **169** was studied first; however, no product formation was observed under any of the conditions tested.



Scheme 44

Alkyne **158** reacted fully, but the product obtained was not the expected annulation compound **174**. Instead compound **175** was isolated from a complex reaction mixture in modest yield. The structure of **175** was additionally proven by X-ray crystallography (Figure 7).

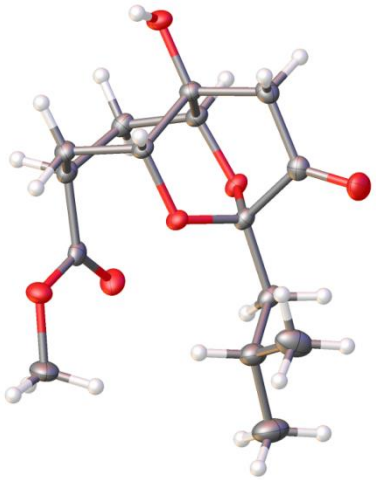
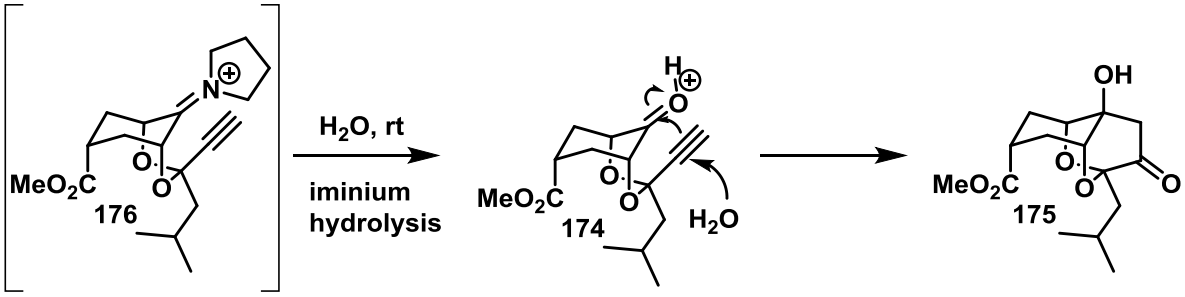


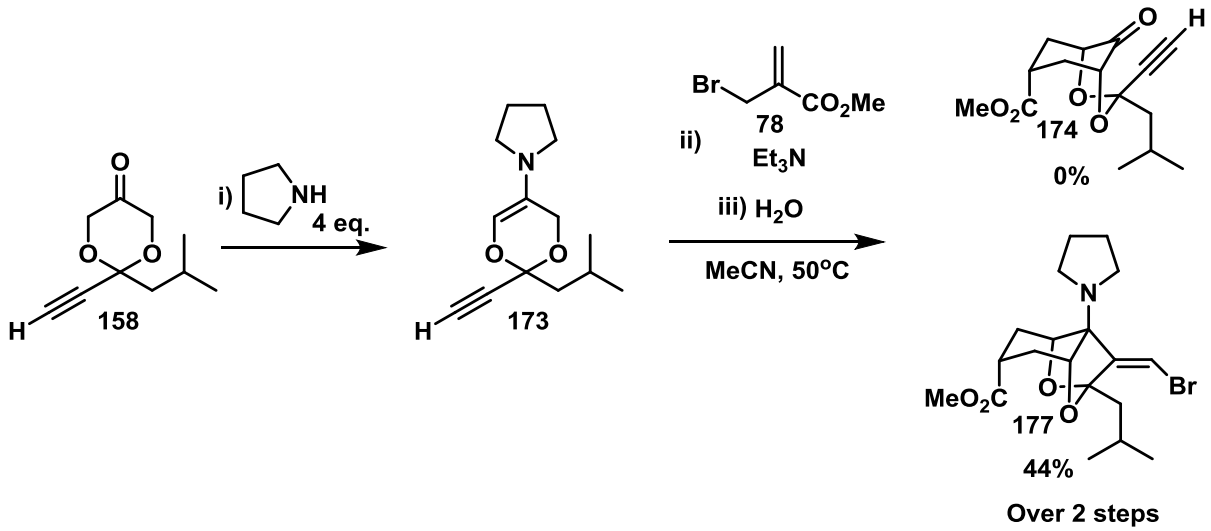
Figure 7 Crystal structure of molecule 1 of 175 with ellipsoids drawn at the 50% probability level. The structure contains three crystallographically-independent molecules.

Based on the formation of **175**, it was concluded that α,α'-annulation to form **176** had taken place. After iminium hydrolysis of **176** to form **174** it is proposed that the resultant carbonyl and alkyne are in such close proximity that they undergo *in situ* cyclisation to form **175** (Scheme 45). What remains unclear is how stepwise or concerted the reaction is.



Scheme 45

Before the structure was confirmed to be that of **175**, the structure was tentatively assigned to be that of **174**. When running the reaction it was noted by T.L.C. analysis that degradation was occurring. It was assumed that this was the main reason low yields were being obtained. In order to reduce reaction times and hopefully minimise degradation, the temperature was raised to 50 ^{o}C. Again, none of the desired alkyne **174** was obtained, but instead the vinyl bromide **177** had formed (Scheme 46).



Scheme 46

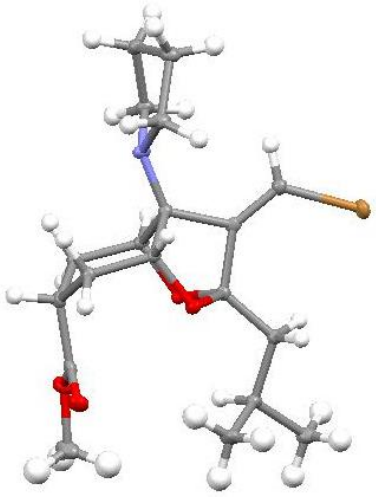
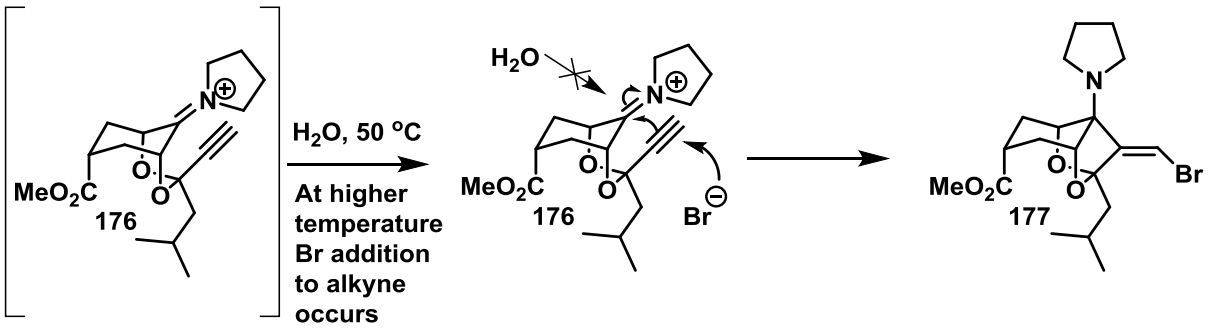


Figure 8 Crystal structure of 177 with ellipsoids drawn at the 50% probability level.

The structure of **177** was conclusively proven by X-ray crystallography (Figure 8). Interestingly this time a five-membered ring has formed instead of the six-membered ring in **175**. The formation of **177** again proves that an annulation has taken place. The ^{1}H NMR taken of the product **177** had multiple multiplets and the majority of the coupling constants could not be resolved. When looking at the crystal structure this is perhaps unsurprising as the chair is quite twisted hence reducing the symmetry in the molecule.

When thinking about the mechanism for the product formation it is again assumed that the alkyne is in close proximity to the iminium (Scheme 47). However, as this reaction is run at 50 ^{o}C as opposed to room temperature, it is proposed that the water quench of iminium **176** does not take place. Due to the higher temperature the system now has enough energy for a resultant bromide to form the observed vinyl bromide.



Scheme 47

At first glance it may seem that the tricyclic systems obtained (**175, 177**) can be utilised in a synthesis of phyllaemblic acid. However, after further consideration of the precursor **74** needed for spiroacetalisation it becomes apparent that taking these systems on further would be problematic (Figure 9).

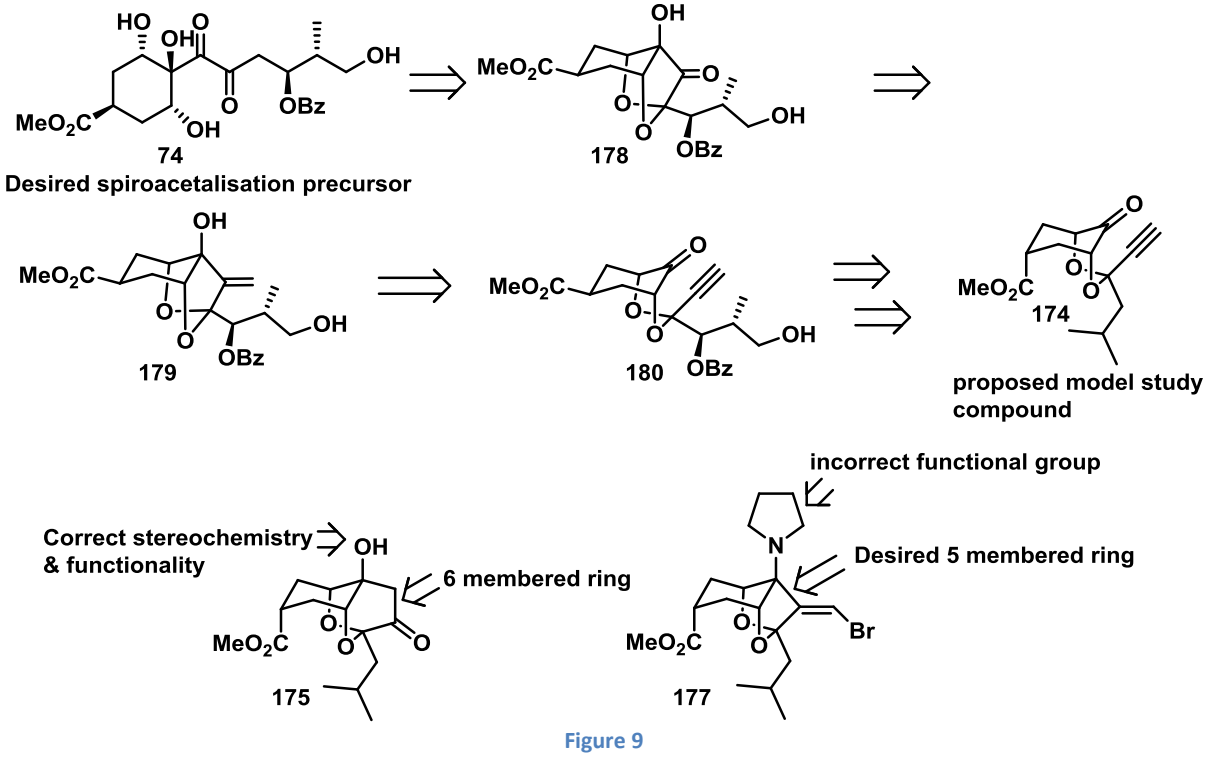


Figure 9

In the first case, product **175** has the correct stereochemistry and functionality; however, a six-membered ring was obtained where a five needs to be present in order to obtain the alpha-hydroxyketone moiety in **74**. In the case of the reaction run at 50°C, product **177** has the five-membered ring system; however, a pyrrolidine ring now resides in place of the

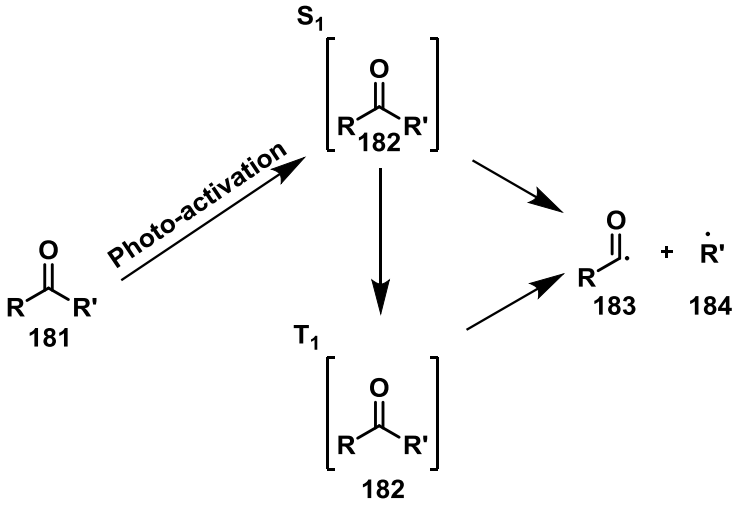
alcohol. This would be very difficult to functionalise further, therefore it was concluded that the keto-alkyne cyclisation was not a viable pathway towards the total synthesis of phyllaemblic acid.

An extensive search of the literature was conducted in the hope that this novel approach to these interesting tricyclic systems can be used in target synthesis. However, to date there has been no natural product or organic analogue identified that could benefit from the products formed by this apparent proximity effect.

A photomediated approach towards C-C bond formation in bicyclic systems

Literature review on the Norrish reaction.

Norrish *et al.*[81] were the first to report details of the photo-activation of carbonyl compounds which results in either Norrish type 1 (Scheme 48) or type 2 (Scheme 49) reaction pathways.

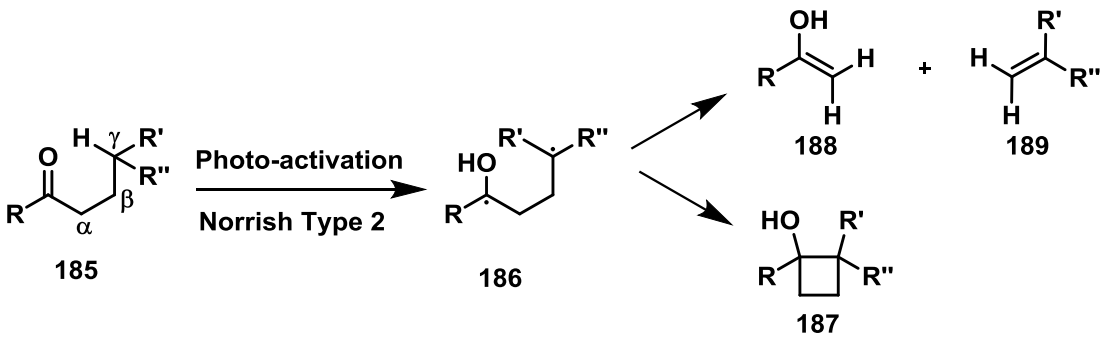


Scheme 48

The Norrish type 1 reaction is the homolysis of a ketone **181** resulting in two radical fragments **183** and **184**. The carbonyl group is excited to a photochemical singlet state. Through intersystem crossing (ISC) a triplet state can also be formed. After cleavage from

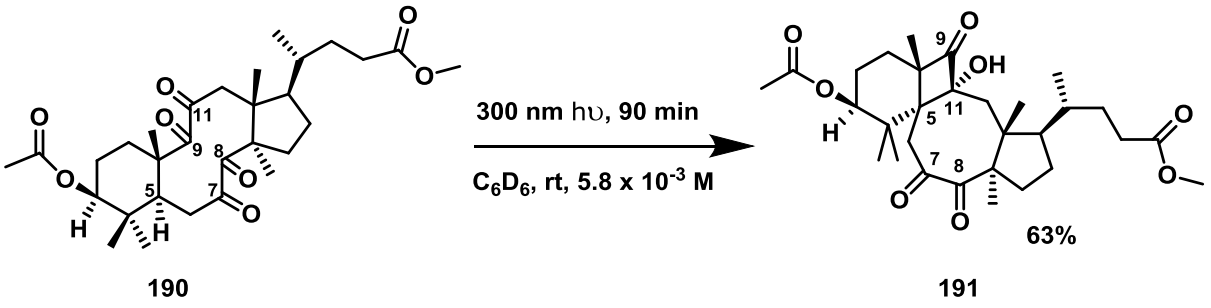
either the singlet or the triplet state, the two radical fragments **183** and **184** are obtained. Once the radicals have formed several reaction pathways are available. These include: recombination, with the formation of a new C-C bond and loss of CO; recombination, resulting in racemisation on the alpha substituent; the formation of an aldehyde and an alkene or the formation of a ketene and an alkane.

The Norrish type 2 reaction has the same principle as a type 1. However, after photo activation of **185** and hydrogen abstraction to give **186**, a secondary reaction can occur known as a Norrish-Yang reaction. This results when 1,5-hydrogen abstraction occurs from the gamma position, leading to a diradical species forming and recombining to give a cyclobutane ring **187**. An alternative pathway would result in the formation of **188** and **189**; however, the abstraction of a gamma proton would normally be the preferred route.



Scheme 49

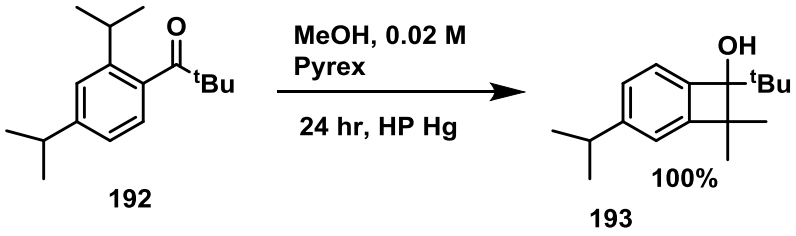
The Norrish-Yang cyclisation has been utilised in several natural product syntheses. Tochtrop *et al.*[82] irradiated **190** to create the four-membered ring in **191** in their approach towards bryonolic acid (Scheme 50).



190 191

Scheme 50

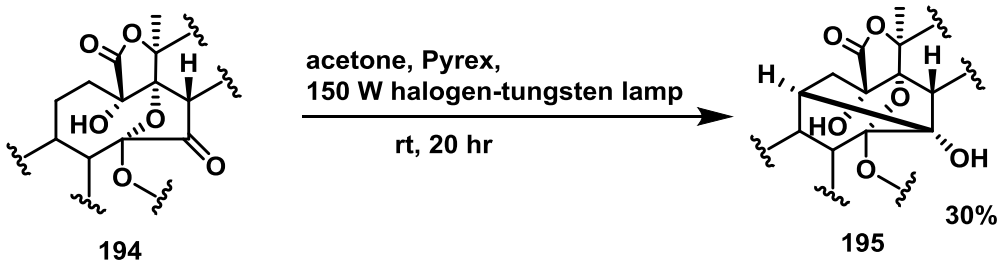
Whilst creating analogues for a methodology study Yoshioka *et al.*[83] also used the Norrish-Yang reaction on **192** to form a cyclobutane fused to an aromatic ring in **193** (Scheme 51).



192 193

Scheme 51

Kawai *et al.*[84] utilised a Norrish pathway in their novel synthesis of physalin-R. Interestingly, the photo-activation of **194** led to the formation of a six-membered ring **195** rather than a four-membered ring. This is possibly due to the bridged ether which shuts down the classic Norrish-Yang mechanism (Scheme 52).

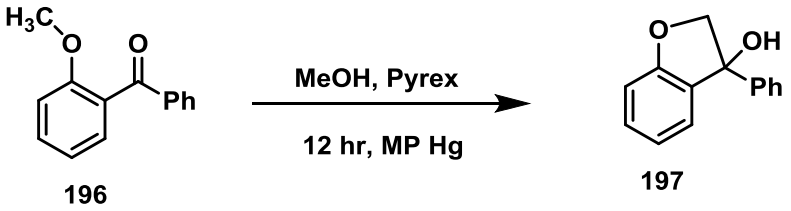


194 195

Scheme 52

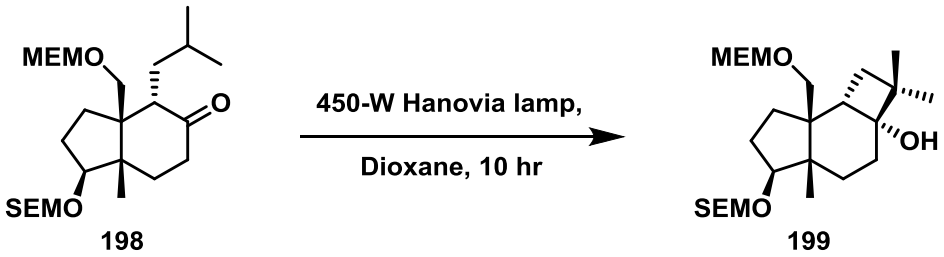
Wanger *et al.*[85] reported the photo-cyclisation of o-alkoxy phenyl ketones. The work detailed the successful cyclisation of several analogues resulting in the formation of five-membered rings. What is particularly interesting about this work is that after photo-activation of the

carbonyl in **196**, hydrogen is abstracted from a methoxy group. The resultant radical subsequently cyclises to give the product **197** (Scheme 53).



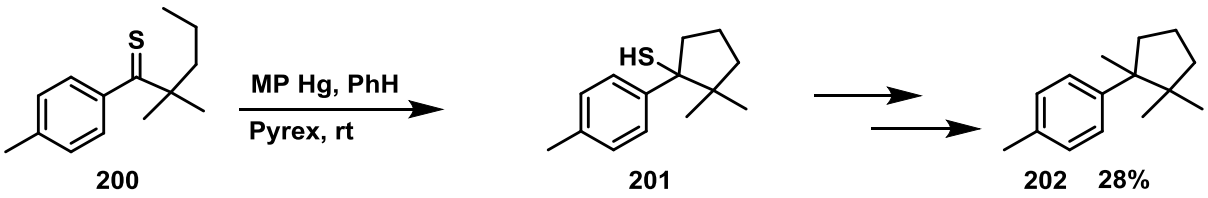
Scheme 53

Paquette *et al.*[86] used the Norrish type 2 cyclisation to successfully synthesise the natural products punctatin A and D. The key step in their approach was to take the cyclic ketone **198** and irradiate with a 450-W Hanovia lamp for 10 h; which gave the cyclobutyl alcohol **199** in 62% yield (Scheme 54).



Scheme 54

Mayo *et al.*[87] synthesised cuparene **203** using a photochemical method to form the five-membered ring[88]. This is a particularly interesting reaction as the Norrish-Yang cyclisation was undertaken on thioketone **200**. It was found that reaction of thioketones are dependent on the excitation wavelength and therefore afford a five-membered ring **201** even with the presence of a gamma hydrogen. This eventually led to the natural product **202** (Scheme 55).



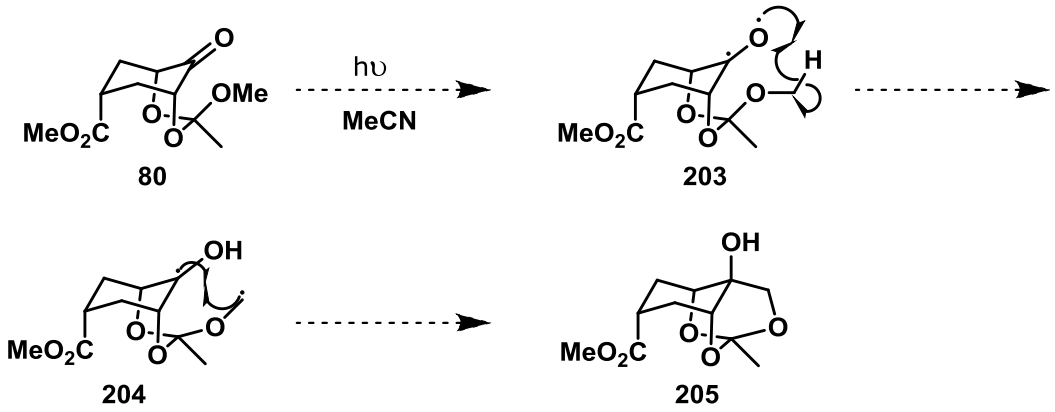
Scheme 55

Results and discussion

Photo-activation of bicyclic ketones.

Bicyclic ketones **79** and **80** were easily obtainable and it was thought that it may be possible to activate the carbonyl and trigger a cyclisation using the methoxy attached to the orthoacetal.

Looking at the bicyclic ketone **79**, diradical formation and subsequent 1,7- hydrogen abstraction in **203** could set up a C-C bond formation process to occur through the recombination of the primary and tertiary radical in **204**. This would then set up the required stereochemistry at the tertiary alcohol needed to continue investigations to functionalise **205** (Scheme 56).



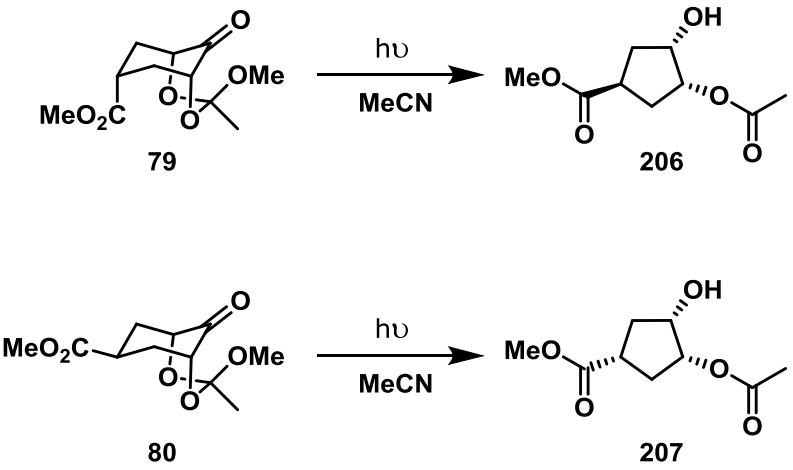
Scheme 56

It was decided to subject both the bicyclic ketones **79** and **80** to photo irradiation (Table 13).

Entry	Bicyclic ketone	Solvent	Reaction vessel	Yield
1	**79**	MeCN	Pyrex	29% of **206**
2	**79**	MeCN	quartz	degradation
3	**79**	MeOH	Pyrex	degradation
4	**80**	MeCN	Pyrex	17% of **207**

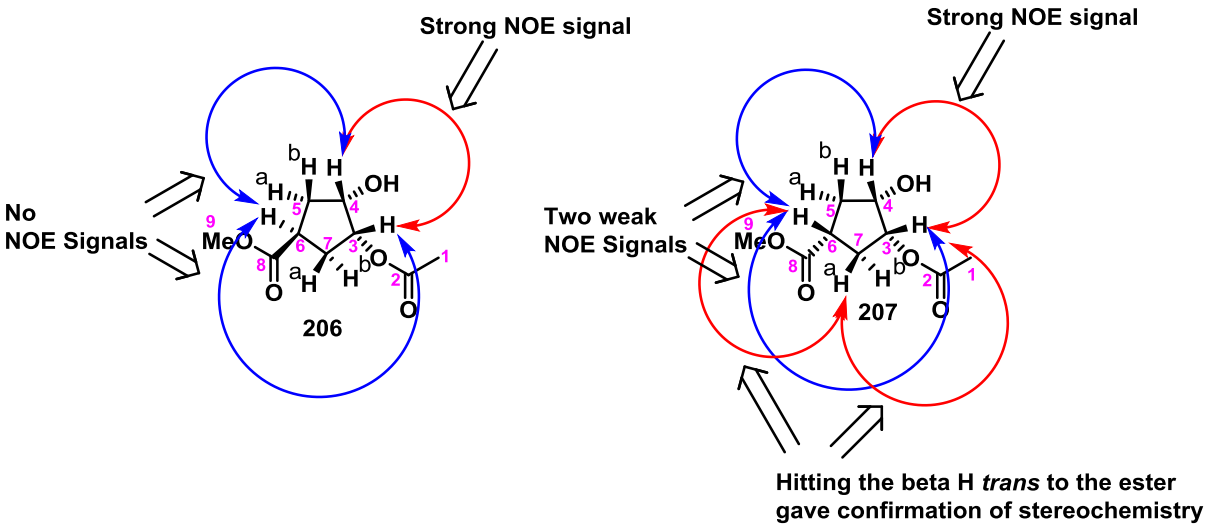
Table 13

Unfortunately, there was no evidence of the desired intramolecular reaction. However, major products **206**, **207** were isolated with interesting stereochemical outcomes (Scheme 57).



Scheme 57

Red- Strong NOE
Blue- Weak/ no NOE signal



Scheme 58

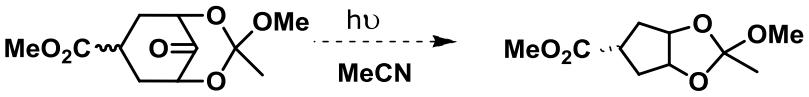
In the first example (Scheme 58) the stereochemistry of **206** was easy to identify from NOE analysis. The hydrogen on carbon 4 was clearly *cis* to the hydrogen on carbon 3 as demonstrated by a strong NOE between them. Irradiating these hydrogens led to no signal

observed for the hydrogen on carbon 6. This clearly indicates that the ester is *trans* to the alcohol and the acetate.

The stereochemistry of **207** was slightly harder to confirm. Again a strong NOE signal was found between the two hydrogens on carbons 4 and 3. However, these hydrogens gave a very weak NOE to the hydrogen attached to carbon 6. Confirmation of the stereochemistry was completed by irradiation of Ha on carbon 7. Ha also showed a strong NOE to the hydrogen on carbon 6. This gave clear evidence that the ester was *cis* to the alcohol and acetate.

The photochemical decomposition of cyclic ketones to cyclic alkanes is a known procedure in the literature. This phenomenon was first documented by Norrish *et al.* and further investigated by Benson *et al.*[89]

However, the loss of CO presents several problems for a mechanistic explanation for the observed products (Scheme 57). Assuming loss of CO occurs through photolysis, the remaining di radical species would then ring close to give a five-membered ring (Scheme 59). This process was first reported by Blacet *et al.*[90] who observed cyclohexanone decomposing to cyclopentane under photochemical conditions.



79/80 **206b/207b**

Scheme 59

Looking at the molecules **206b**/**207b** it is difficult to envisage how cleavage of the acetal occurs. The reaction was performed in Pyrex glassware, so no further part of the molecule should be photo-activated. The position of the ester further adds to the complexity of the

unknown reaction pathway. In both cases the ester appears to have undergone an epimerisation which under the reaction conditions should not occur. To date the mechanistic pathway of these unusual reactions remains unclear. The loss of CO from **79**/**80** resulted in the decision that a photo mediated approach on the bicyclic system was not a viable route towards the natural product.

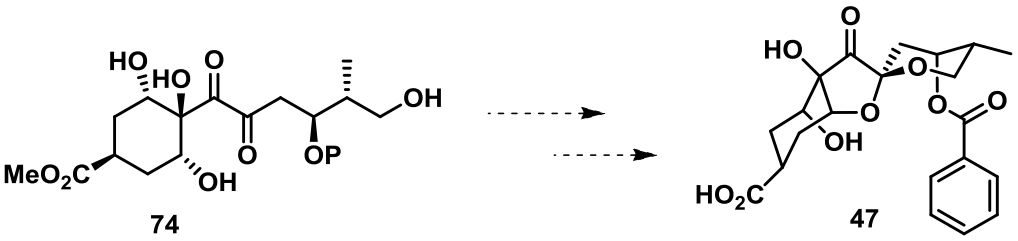
Conclusions and summary

In chapter two, two routes have been investigated in order to determine if an intramolecular addition reaction could overcome the lack of reactivity of the ketone **80** towards intermolecular addition and lead to the correct stereochemical array shown in **74** (Scheme 12). The first investigation focused on a proposed keto-alkyne cyclisation. This work led to the synthesis of novel 1,3-dioxanones **141** and **158** which were subjected to α,α'-annulation reactions. Keto-alkyne cyclisation studies were unable to be attempted due to the formation of tricyclic systems **174** and **175**. The mechanistic pathway for their formation is not fully known; however, the close proximity of an alkyne to a reactive electrophilic carbon is thought to attribute to the observed reactivity. Ultimately, this led to the conclusion that an intramolecular keto-alkyne cyclisation is not a viable pathway towards phyllaemblic acid. A new intramolecular addition was attempted using the readily available bicyclic ketones **79** and **80**. The proposed cyclisation reaction used light to initiate an excited carbonyl to then abstract a hydrogen and ring close. This investigation was based on literature precedent set by Norrish and Wanger. Unfortunately, this led to the formal loss of CO from the bicyclic system to form **206/207**. Although there is literature precedent for the formal loss of CO, the mechanistic pathway for the subsequent epimerisation and removal of the orthoacetal still remains unclear.

Chapter 3 Reinvestigation of intermolecular addition on monocyclic ketones

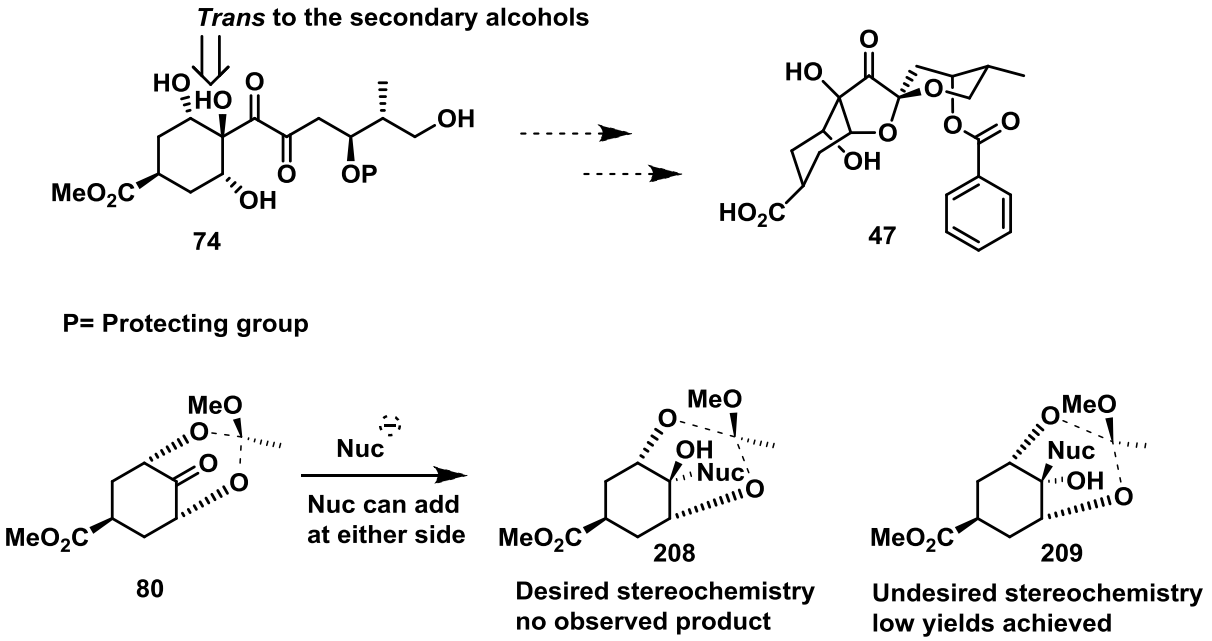
Introduction

The Grainger group approach to phyllaemblic acid, as discussed in chapter two, requires the spiroacetalisation precursor **74** to be synthesised with all six stereocentres set (Scheme 60).



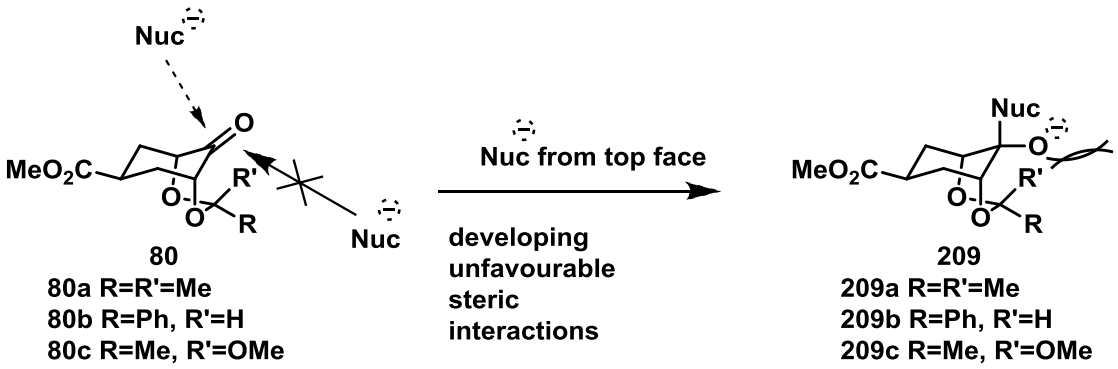
Scheme 60

In the approaches investigated so far, three of the stereocentres on the cyclohexane ring have been set by the α,α'-annulation reaction followed by epimerisation. The resulting ketone **80** was found to be unreactive to a variety of nucleophiles. When reaction had occurred, it had proceeded in low yield with the undesired stereochemistry required for the natural product; the tertiary alcohol is *cis* to the oxygen atoms **209** and not in the required *trans* configuration **208** (Scheme 61).



Scheme 61

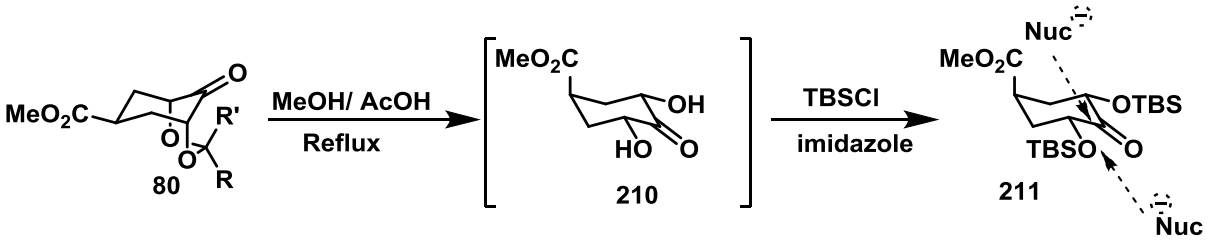
It was thought that the reason for the low reactivity of **80** and the observed undesired stereochemistry was due to nucleophilic addition occurring at the more accessible top face. This leads to a developing steric clash with the flagpole R′ group due to the boat chair conformation adopted by the bicyclic ring (Scheme 62).



Scheme 62

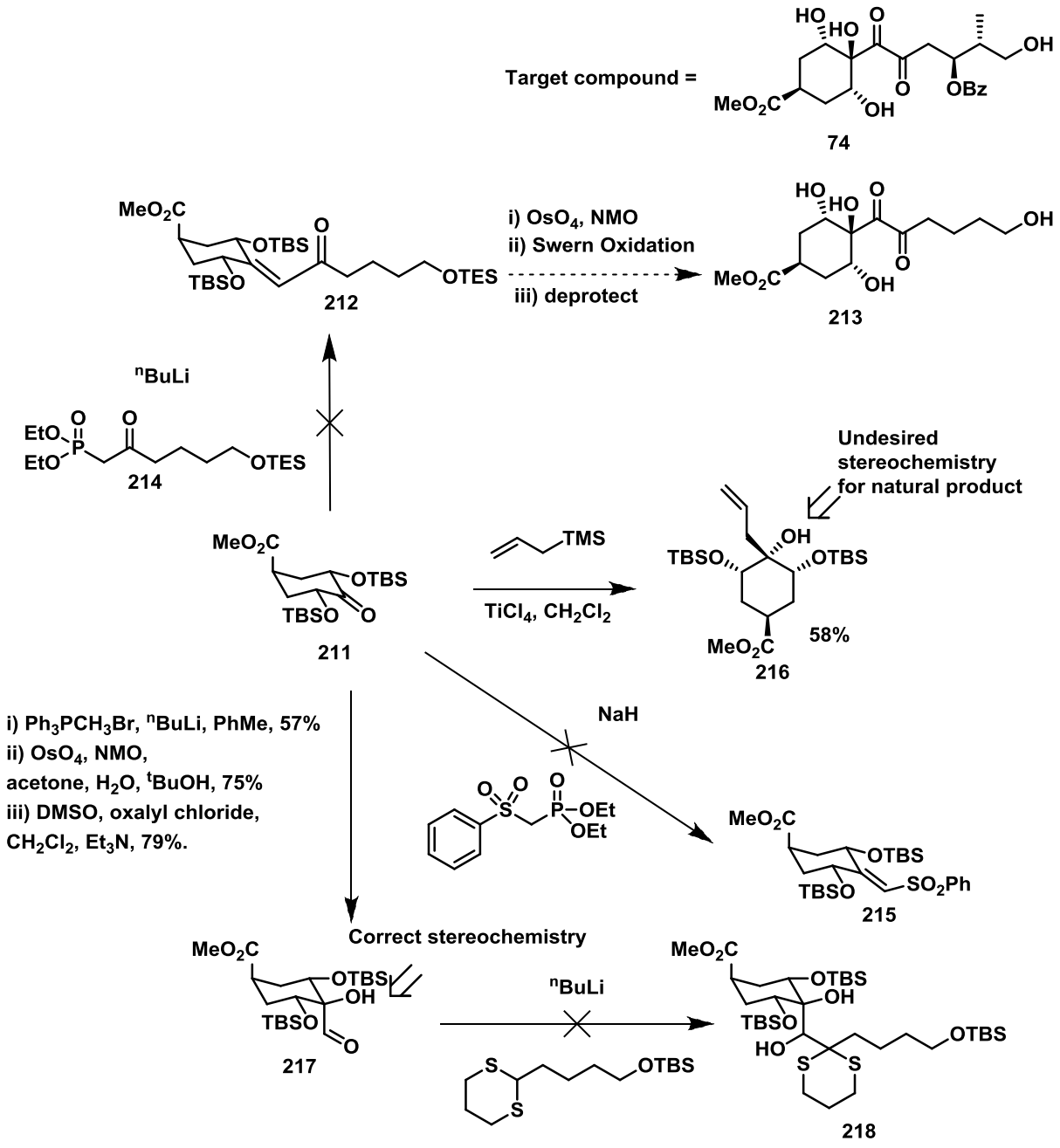
Previous work in the group sought to overcome the low reactivity of ketone **80**. Acetal deprotection gave **210** and was followed by reprotection to produce the bis-TBS ether **211**. It was hoped that the transformation of the ketone **80** from a constrained bicyclic structure

to a more flexible monocyclic form would facilitate nucleophilic attack and increase reactivity (Scheme 63).



Scheme 63

Unfortunately, poor reactivity of the ketone in **211** was again observed and further functionalisation of the products was problematic (Scheme 64).



Scheme 64

The ideal transformation would have been the HWE from the monocyclic ketone **211** to produce **212**. If this reaction had occurred, adding further functionality to phosphonate **214** would have led to the spiroacetalisation precursor **74** in two steps. Unfortunately, the HWE was extensively investigated and could not be achieved on **211**[91]**,** presumably due to low reactivity of the ketone (Scheme 64).

Reaction with a more reactive phosphonate was examined to give **215**. It was proposed that the vinyl sulfone could eventually lead to an α-hydroxy aldehyde, but again no reaction was observed (Scheme 64).

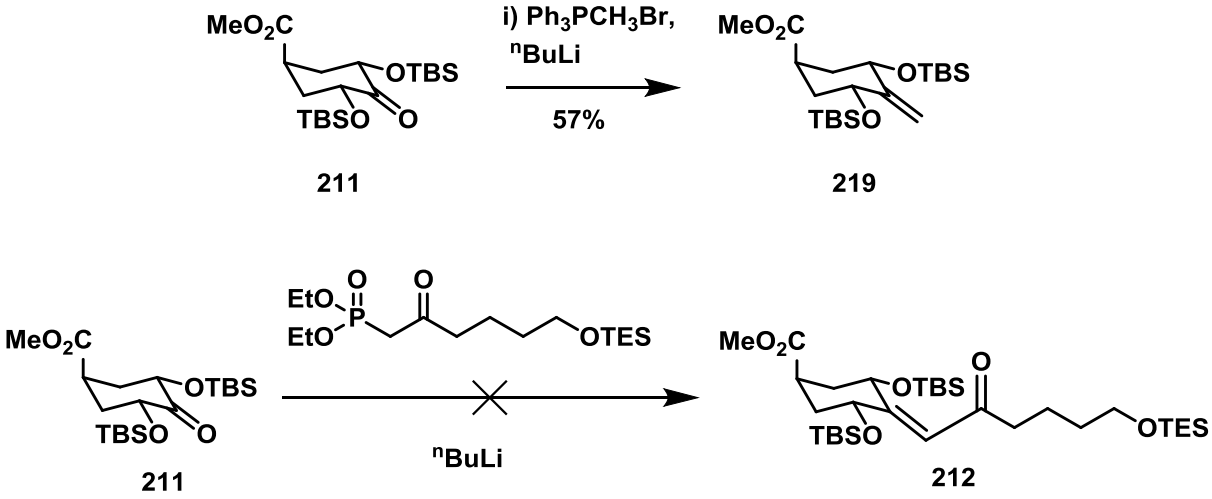
A Sakurai reaction was successfully carried out on **211** to produce **216** in 58% yield. However, top face addition occurred, resulting in the undesired stereochemistry i.e. OH *cis* to the OTBS groups (Scheme 64). This was presumably due to the steric bulk of the OTBS groups flanking the ketone.

Finally, aldehyde **217** was formed from **211** in good overall yield. This was achieved by a simple Wittig reaction, followed by dihydroxylation. This set up the required stereochemistry, i.e. the tertiary OH is *trans* to the OTBS groups. Swern oxidation of the primary alcohol gave aldehyde **217** (Scheme 64).[91]

Unfortunately, further transformation of the aldehyde **217** was found to be difficult. Addition of a dithiane anion would have potentially led to a system **218** where spiroacetalisation studies could be investigated. However, the aldehyde proved to be unreactive to this type of chemistry (Scheme 64).[91]

Aims and Objectives

Previous investigations found that a methylene could be introduced into **211** in moderate yield via a Wittig reaction to form **219**. Based on this observation, it was postulated that the issue of no reactivity towards HWE was due to the large TBS protecting groups flanking either side of the carbonyl in **211**. This caused the carbonyl to be sterically hindered and hence prevented the formation of **212** (Scheme 65).



Scheme 65

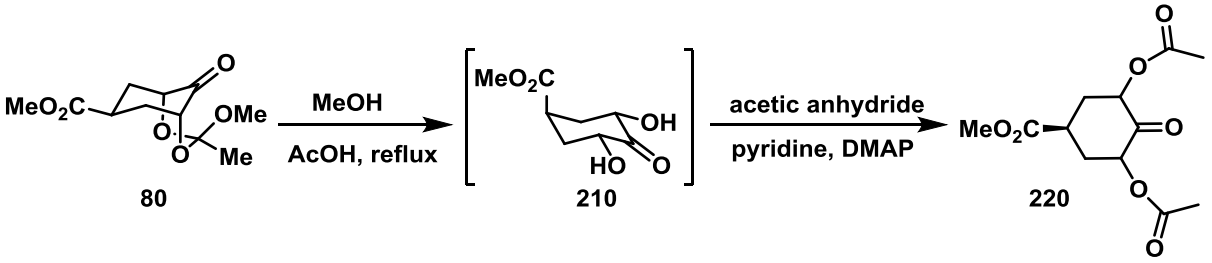
Despite these unpromising prior results, it was decided to reinvestigate intermolecular additions on a monocyclic system. Specifically focusing on the HWE, it was postulated that using a different protecting group would allow the desired transformation to take place.

Results and Discussion

Attempted protection of the diol

The ideal protecting group would be electron-withdrawing and small in size as this would reduce the steric hindrance and increase the reactivity of the ketone towards the desired HWE reaction.

A simple acyl group was chosen as the ideal candidate to meet both of these criteria and form **220** (Scheme 66).



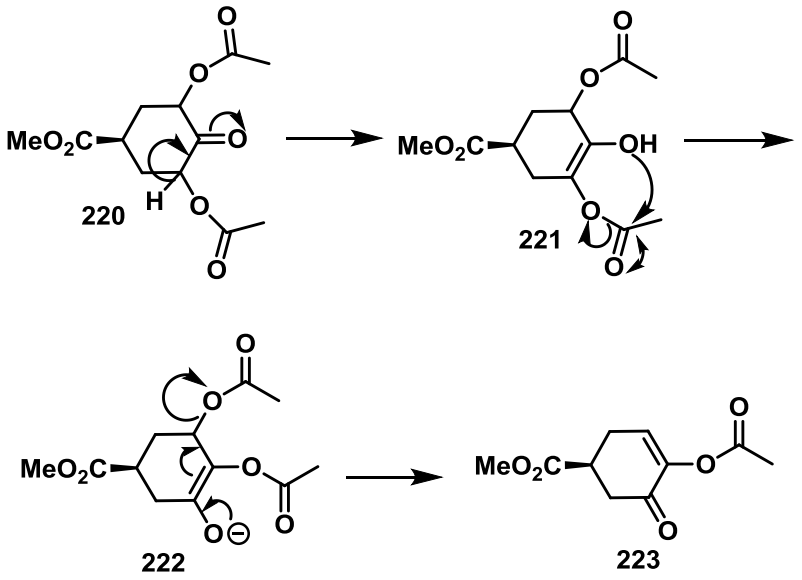
Scheme 66

Entry	Ac_2O	Pyridine	Et_3N	DMAP	Acetyl Chloride	Temp	Solvent	Yield
1	2.2 eq.	×	2.2 eq.	10 mol%	×	reflux	CH_2Cl_2	-
2	×	×	2.0 eq.	×	2.0	rt-reflux	THF	-
3	3 eq.	✓	×	×	×	rt-reflux	pyridine	-
4	4.4 eq.	✓	×	10 mol%	×	rt	pyridine	46% **223**

Table 14

However, installing acyl groups proved to be problematic (Table 14) and monitoring the reaction proved difficult, as the diol that is formed *in situ* was not able to be visualised in a wide variety of T.L.C. stains. Neither product nor starting material could be isolated in entries 1-3.

Successful formation of **220** was achieved in (entry 4); however, the acyl groups were found to migrate *in situ* which led to the isolation of **223** in 46% yield. It is proposed that enol formation occurs to form **221** which then initiates an acyl group transfer **222**. Elimination of the acetate group then forms the conjugated ketone **223** (Scheme 67). The migration of acyl groups and elimination of acetate groups is well known[92-94] but no related examples for comparison to the system below could be found.

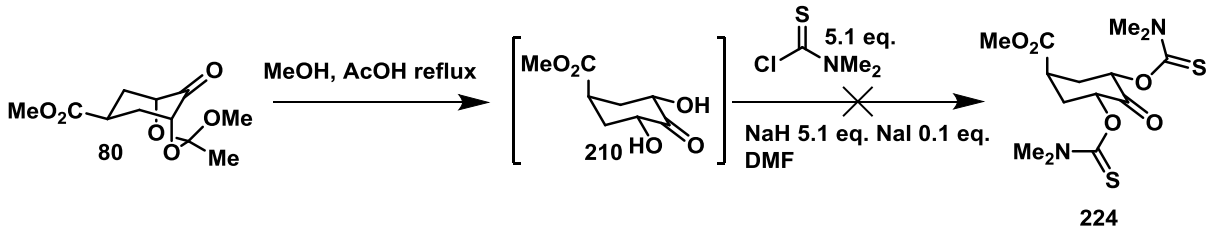


Scheme 67

After the unsuccessful attempt at installation of the acyl groups, attention turned to a variety of different protecting groups that were expected to be compatible with a subsequent HWE reaction.

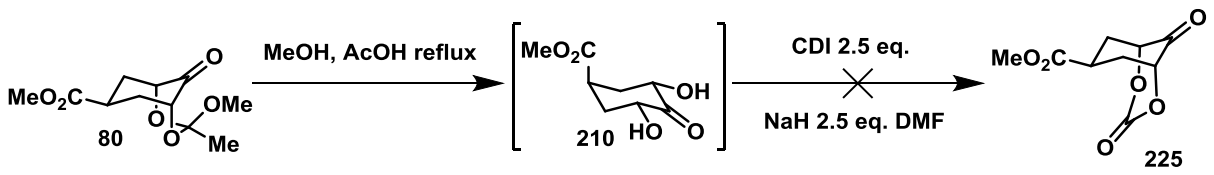
Dimethylthiocarbamate (DMTC) is a relatively unusual protecting group but Falck *et al.*[95] showed it to be stable to a wide variety of conditions and reagents. The DMTCs can be removed with $NaIO_4$ or H_2O_2 in the presence of other common alcohol protecting groups. It would be ideally suited as a protecting group for the alcohol functionalities of **210** as it is small and electron-withdrawing, which should favour a subsequent HWE reaction. The literature method for DMTC protection uses a 5 mmol solution in THF with 5.1 eq. of NaH and 0.1 eq. of NaI. It was expected that the THF used could be switched to DMF, without compromising the installation of the DMTC group, in order to aid solubility of diol **210**. Even with the diol fully dissolved in DMF, the conditions used still resulted in no formation of **224**. The inability to follow the reaction made it difficult to identify reasons as to why no reaction

was observed (Scheme 68). Frustratingly, isolation of starting material was also problematic as diol **210** was largely lost during aqueous work-up.



Scheme 68

Carbonyldiimidazole with NaH in DMF was used to try and form the bicyclic system **225**. It was hoped that the installation of another carbonyl would lead to a dipole interaction pushing the two carbonyls away from each other and providing more space for a nucleophile to attack. Unfortunately, no material could be isolated from this reaction. As with the DMTC protection, monitoring the reaction was difficult and it was assumed that no reaction was taking place (Scheme 69). Again, starting material was largely lost during aqueous work-up.

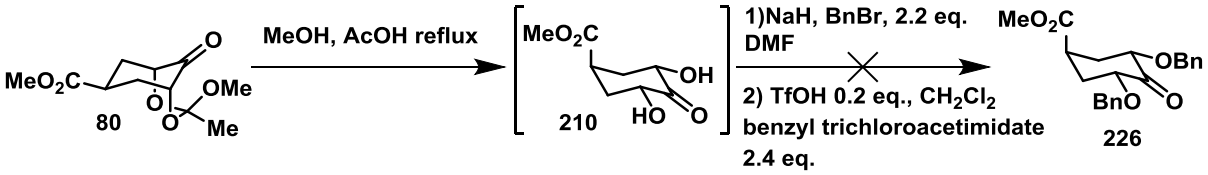


Scheme 69

Although not particularly small or electron-withdrawing, the use of benzyl groups were investigated as it was hoped that they would orientate in a conformation to open up the carbonyl for nucleophilic addition **226**. There are two main sets of conditions to try when attempting a benzyl protection.[96, 97] The first uses a base such as NaH and benzyl bromide; this was ideally suited for our system as DMF is often used as the solvent. Unfortunately, were unable to protect the diol to give **226** using basic conditions. Again, problems with monitoring the reaction persisted so an attempt was made to obtain ^{1}H NMR of the crude

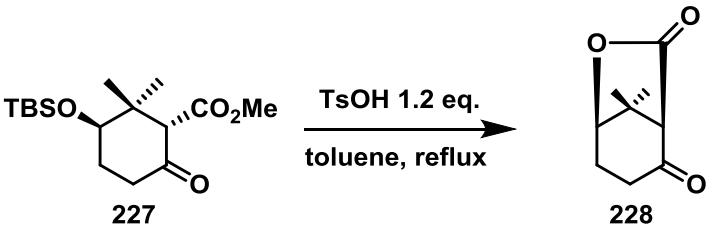
reaction mixture. The data obtained from the crude ^{1}H NMR showed no evidence of product formation or remaining starting material and the spectrum contained multiple resonances indicating a complex mixture of products. This may indicate that compound **210** is unstable to strongly basic conditions, decomposing in various ways such as ester hydrolysis or elimination to give an α,β-unsaturated ketone. Attempts were made to obtain a ^{1}H NMR of the crude diol before investigating various reaction conditions; however, the data obtained for the diol was consistently poor in quality. This meant that NMR spectroscopy could not be used to monitor the reaction and it is unclear why basic benzylation conditions were unsuccessful.

The second route uses benzyl trichloroacetimidate in the presence of an acid; unfortunately, this method cannot be performed in DMF. Despite the very low solubility of **210** in alternative solvents, acidic benzylation in CH_2Cl_2 was attempted. However, presumably due to this poor solubility, no reaction occurred (Scheme 70).



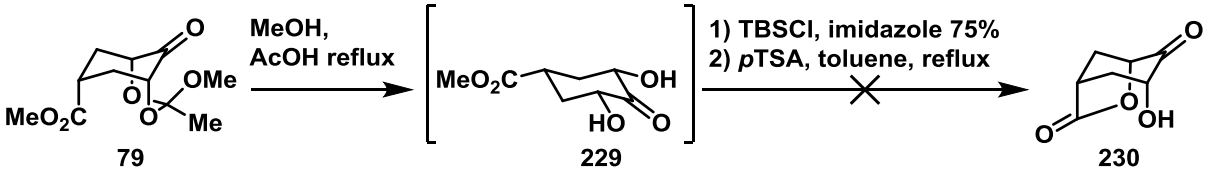
Scheme 70

Monti *et al.*[98] successfully formed a lactone on a system that is structurally similar to **79**. This was achieved via refluxing **227** in toluene in the presence of TsOH. This promoted an intramolecular addition to remove the TBS group and promoted formation of lactone **228** (Scheme 71).



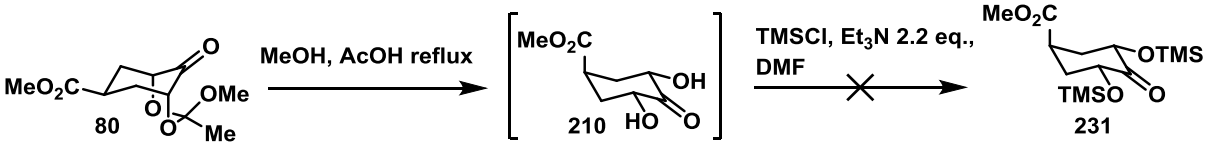
Scheme 71

Previous work in the Grainger group successfully installed TBS groups on **211** and so there was good precedent for lactone formation to give **230** if **229** could be protected with TBS groups. The TBS groups were successfully installed on **229**; however, after their removal, the equatorial ester would not undergo intramolecular cyclisation in the presence of *p*TSA in refluxing toluene. A small amount of starting material was recovered, and the remaining material was assumed to have converted into diol **210** which was lost in subsequent work-up (Scheme 72).



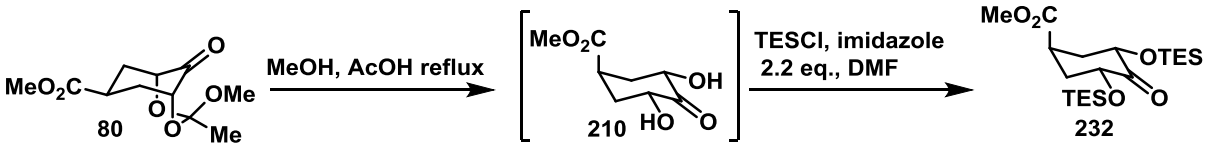
Scheme 72

Finally, the smaller silicon protecting groups TMS and TES were investigated. TMS installation occurred smoothly, but unfortunately this protecting group was found to be highly labile, resulting in **231** reverting back to starting material (Scheme 73).



Scheme 73

TES protection was successfully achieved to afford **232** in an 82% yield, a comparable yield to the already known TBS protection to form **87** (Scheme 74)[91]

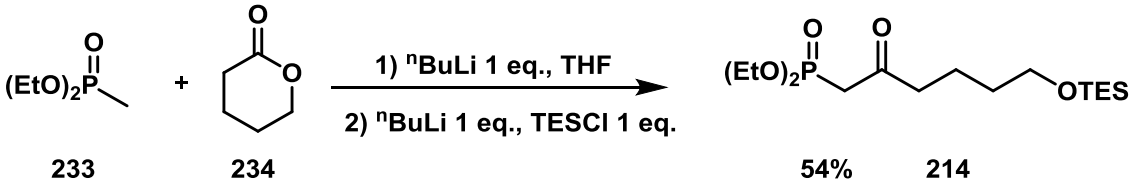


Scheme 74

Reinvestigation of HWE reaction

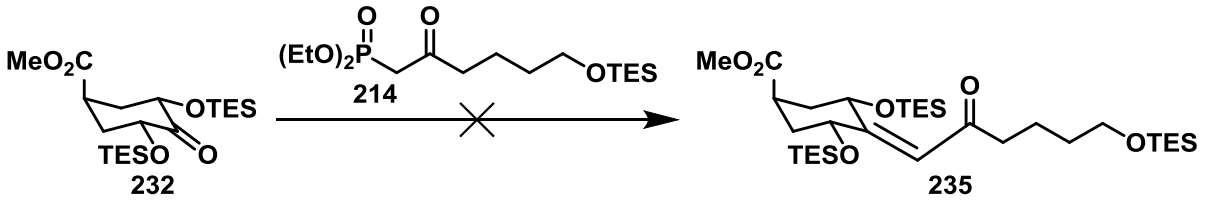
A TES group is similar in size to a TBS group; however, a HWE reaction was still attempted in the hope that an enone could be formed. If this was the case then the previous route shown in Scheme 64 could be reinvestigated with this slightly smaller silicon protecting group.

In order to have a fair comparison to the TBS system, the same ylide **214** was used as in the previous HWE investigations on **211**[91]. The synthesis of **214** was relatively straightforward, using the anion of phosphonate **233** to cleave lactone **234**, and was achieved in a modest 54% yield (Scheme 75).



Scheme 75

Phosphonate **214** was then used to investigate the HWE on **232** (Scheme 76). Two main solvents and bases were used; however, no trace of **235** was isolated in any of the reactions with staring material being recovered (Table 15). This is consistent with the conditions attempted on the TBS protected system by a previous member of the group.[91]



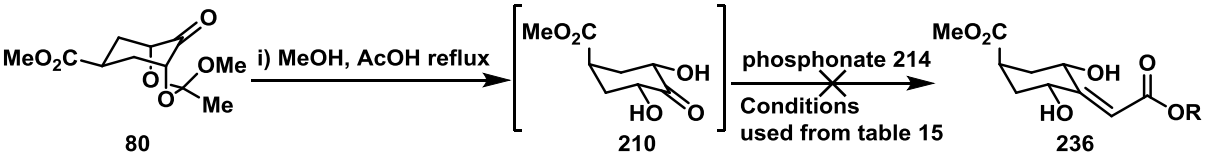
Scheme 76

Entry	Phosphonate eq.	Base	Solvent	Temperature	Yield
1	1.2	NaH 1eq.	DMF	-78°C- reflux	-
2	1.2	NaH 1eq.	THF	-78°C- reflux	-
3	1.2	^{n}BuLi 1eq.	THF	-78°C- reflux	-

Table 15

The least sterically demanding system toward nucleophilic addition would be on the diol **210**. Conveniently, diol **210** has poor solubility in most solvents but good solubility in DMF. This gives rise to the opportunity of performing an *in situ* HWE reaction on the diol to form enone **236** (Scheme 77). This proposed route would open up the possibility of using different protecting groups in the subsequent stages to form the natural product.

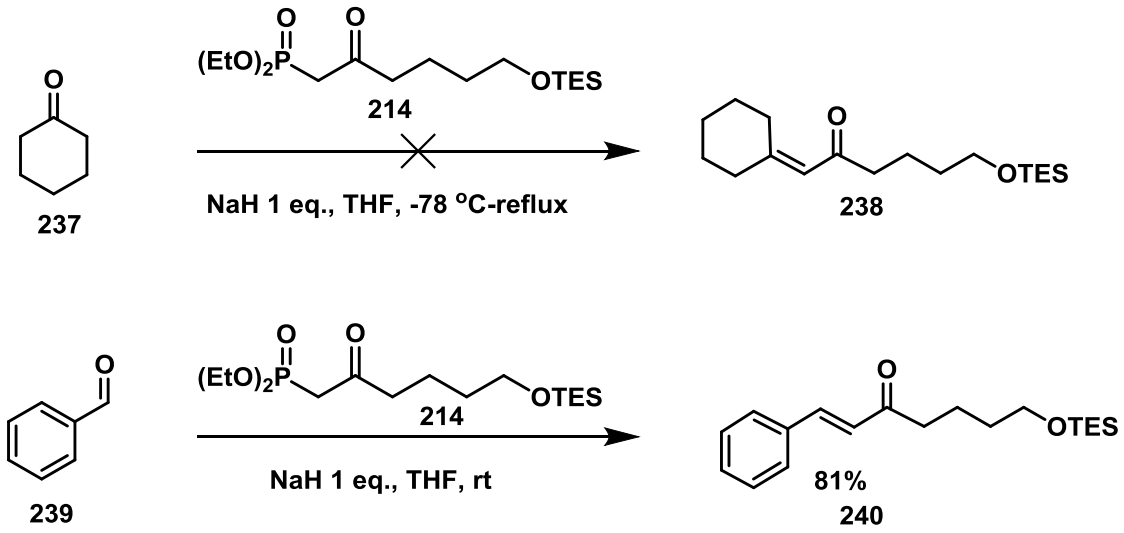
The same conditions were used as described above in Table 15 but, unfortunately, no desired material **236** was isolated (Scheme 77).



Scheme 77

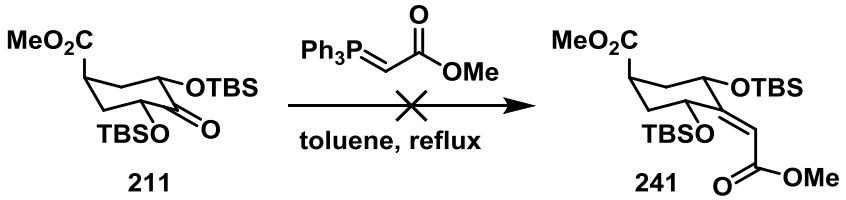
To confirm that the phosphonate **214** is able to undergo a HWE reaction, a test reaction was carried out on cyclohexanone **237**. Surprisingly, again no reaction was observed. Using benzaldehyde **239** as a more reactive electrophile saw conversion to the enone **240** in good yield (Scheme 78). It was concluded that the phosphonate is a poor nucleophile as it would not react with cyclohexanone to form **238**. This shows that **214** is generally not compatible

with secondary/ cyclic ketones, and goes some way to explaining why neither **210** nor **211** were able to react with this substrate. This result led to the conclusion that the direct HWE route is not viable due to the low reactivity of the phosphonate.



Scheme 78

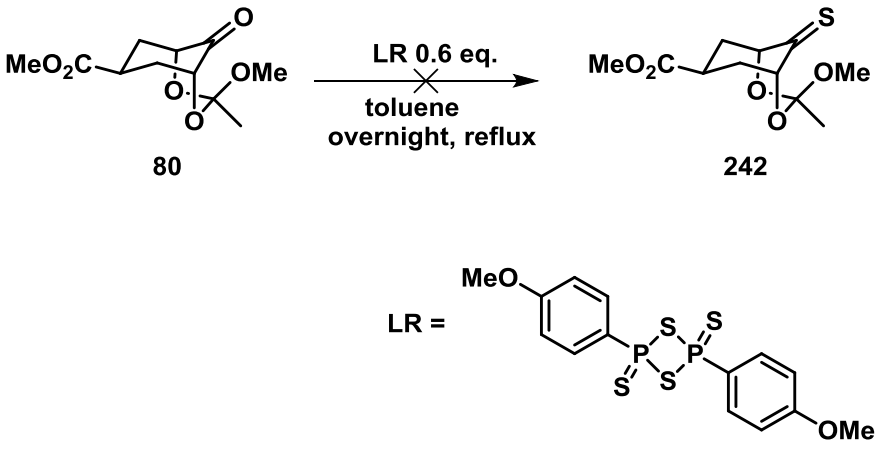
To complete the study, it was envisaged that a stabilised ylide could potentially give us the desired enone functionality and form **241**. Therefore, this reaction was attempted using methyl (triphenyl)phosphoranylidene)acetate. Again, after careful monitoring of the reaction, only starting material was isolated (Scheme 79).



Scheme 79

The Barton-Kellogg[99] reaction between a thiocarbonyl and a diazo compound has been used to prepare sterically hindered alkenes.

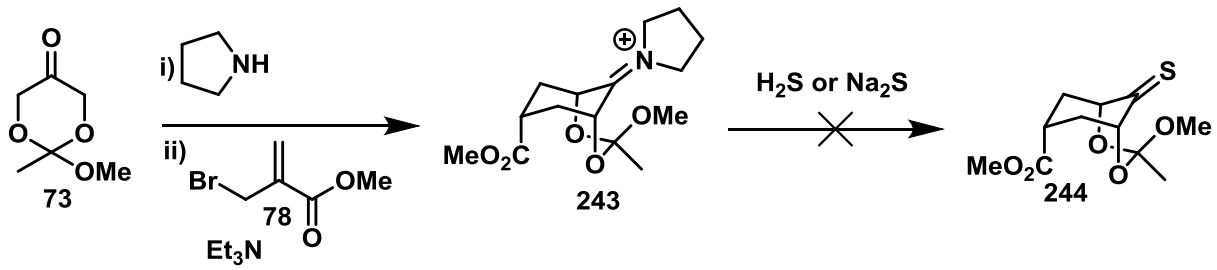
A new approach was therefore envisaged based on first converting ketone **80** to thioketone **242**.[100] The first attempts to convert the ketone in **80** to a thioketone used the classic Lawesson's reagent (Scheme 80).[101]



Scheme 80

The reaction unfortunately yielded none of the thioketone **242**. This may be due to the issues with intermolecular addition to **80** as discussed previously.

However, a more elegant way of preparing the thioketone **244** was postulated based on previous studies (Scheme 13). It was proposed that during the quench at the end of the α,α'-annulation reaction, the iminium ion **243** could be converted to a thioketone in the presence of a sulfur nucleophile. This would then yield the bicyclic thioketone **244** and by-pass the unreactive bicyclic ketone **80** (Scheme 81).



Scheme 81

The first attempts to quench the iminium (Table 16) used a large excess of sodium sulfide in MeOH (entry 1). Na_2S has poor solubility in most organic solvents and only partial solubility in MeOH. The omission of water from the reaction was desired and so MeOH was used as the solvent. This led to complete degradation of the system and nothing was recovered from the reaction. A 1:1 eq. ratio of iminium to Na_2S was used with the Na_2S dissolved in water; this again led to degradation (entry 2). Literature precedent suggested that the use of H_2S in the presence of pyridine would be able to facilitate the transformation.[102] The equipment for the use of H_2S gas was not available therefore commercially available H_2S in a 20% THF solution was used. However, when applied to quench **243**, only degradation occurred (entry 3). It is postulated that the methyl ester may not be compatible with the H_2S, causing degradation to occur.

Entry	dioxanone mmol	Quench reagent	Yield
1	9.2	Na_2S 32.5 mmol in 100 mL of MeOH	degradation
2	3.4	Na_2S 3.4 mmol 5 mL water	degradation
3	10.3	12.8 mmol H_2S 20% THF	degradation

Table 16

Conclusions and summary

This chapter has revisited the HWE approach that was previously investigated by the group. The HWE reaction would be the most direct route towards the desired spiroacetalisation precursor **74**. The route was reinvestigated in detail because **211** would not undergo a HWE transformation but it could form a methylene upon treatment under Wittig reaction conditions. It was concluded that the reason for this was the large TBS groups flanking either side of the ketone; these were large enough to preclude attack by the HWE reagent but not the Wittig reagent. Based on this conclusion small electron withdrawing acyl groups were installed; however, the product quickly re-arranged to form **223** (Scheme 67).

Different protecting groups were studied to try and find a suitable candidate that was compatible with a HWE reaction. Unfortunately, it became apparent that diol **210** has poor solubility and so the number of different protecting groups which could be successfully installed was limited. Further complications included the inability to follow the reaction and the difficulty in isolating the starting material.

The smaller silicon protecting group TES was successfully installed to form **232** which was used in a HWE reaction with the phosphonate **214**. This was the same phosphonate used in the previous investigations on **211** and, unfortunately, gave the same outcome of no reaction.

An *in situ* HWE on diol **210** was attempted to overcome the problems of protecting the diol. Unfortunately, again no reaction was observed.

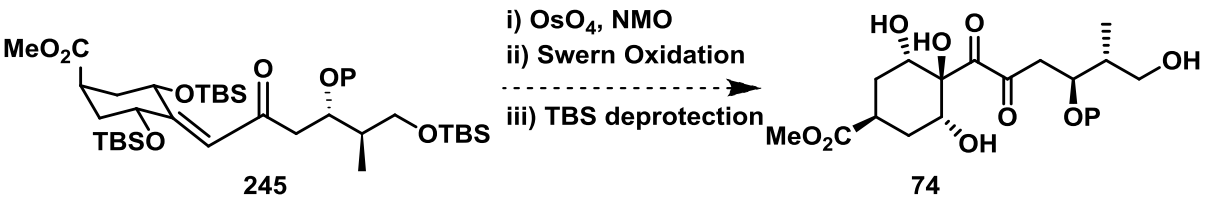
The phosphonate **214** was found to have poor reactivity towards cyclohexanone, indicating that reacting this type of phosphonate with hindered ketones is generally challenging. A stabilised ylide also failed to react with the ketone on **211** and so it was concluded that an enone could not be formed under the conditions investigated.

An alternative approach involved converting the ketone in **80** to a thioketone (Scheme 80). Lawesson's reagent was first investigated, but presumably due to the already documented steric problems again no reaction was observed. A novel idea was postulated, namely attempting to quench the iminium with a nucleophilic sulfur source as work-up of the α,α'-annulation reaction (Scheme 81). This would have led to a system with a thioketone in place of the ketone. Unfortunately, only degradation occurred and this route towards phyllaemblic acid was abandoned.

Chapter 4 The Meyer-Schuster rearrangement and other alkyne-based routes

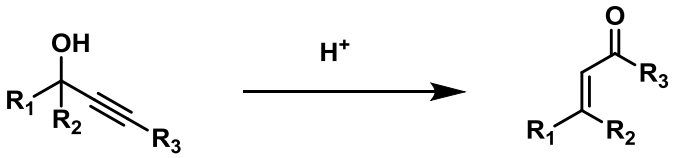
Introduction

Enone functionality, as discussed in chapter three and exhibited in **245**, could provide convenient access to the spiroacetalisation precursor **74** in three steps, ready for subsequent investigation towards phyllaemblic acid (Scheme 82). A HWE approach was unsuccessful (chapter three) so an alternative route based on a Meyer-Schuster rearrangement was envisaged.



Scheme 82

The Meyer-Schuster rearrangement is an acid-catalysed rearrangement of secondary and tertiary propargyl alcohols (Scheme 83). It was developed in 1922 and results in the formation of an enone.[103]



Scheme 83

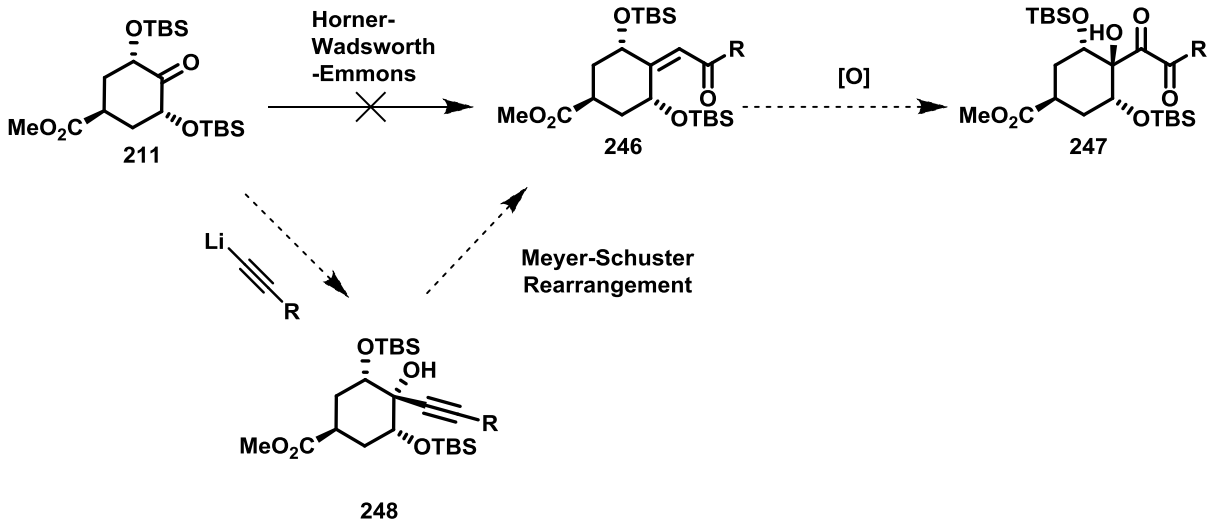
More recently gold and several other metals have been used to promote the Meyer-Schuster rearrangement, which has significantly increased the scope of the reaction. A recent review by Dudley conveniently summarises these approaches.[104]

The problem with this route towards an enone such as **245** is that it still relies on a nucleophilic addition to the ketone in **211**.

Aims and Objectives

Alkynyl anions had yet to be tested as nucleophiles against ketone **211**. Alkynyl anions are small and reactive and addition to **211** would result in the required propargyl alcohol functionality **248**, allowing a potential Meyer-Schuster rearrangement to **246**.[103]

Intermolecular addition of an acetylide would alleviate the problem of the tertiary alcohol residing *cis* to the OTBS groups. A Meyer-Schuster rearrangement, followed by subsequent dihydroxylation, would give the required *trans* geometry (Scheme 84). The same previously discussed methodology in chapter three (Scheme 64) would then apply to form diketone **247**.

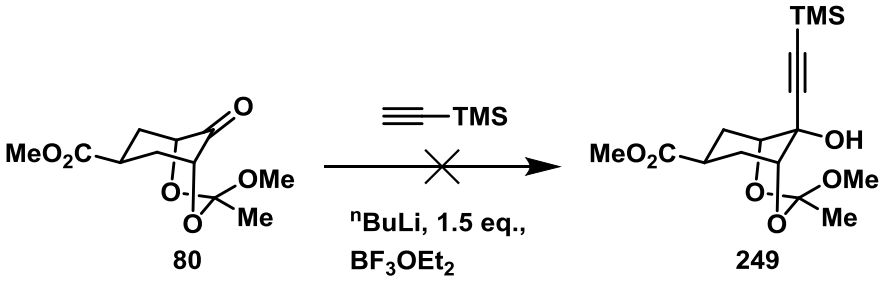


Scheme 84

Results and Discussion

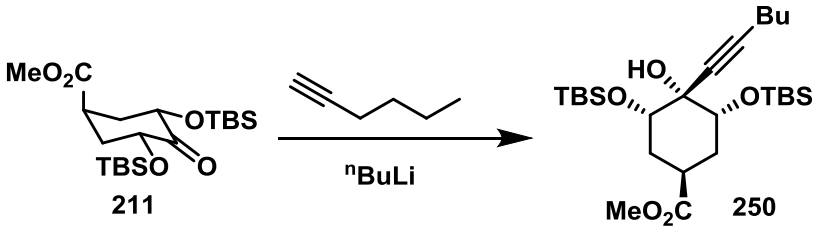
Intermolecular addition of an alkyne

Alkyne addition was first attempted on bicyclic ketone **80**, using TMS-acetylene as a model alkyne to give **249** but as expected, and consistent with previous results, no reaction was observed (Scheme 85).



Scheme 85

Attention therefore turned to reaction of the monocyclic bisTBS ether **211**. Addition of hexyne as a model alkyne containing a carbon chain successfully gave propargyl alcohol **250** (Scheme 86). However, reproducibility was a problem. Various conditions were attempted to find the optimum procedure; however, an average yield of 35-45% was obtained for the formation of the propargyl alcohol (Table 17).



Scheme 86

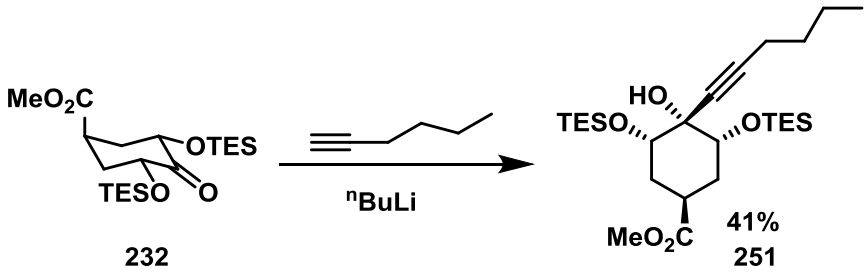
Entry	Alkyne mmol	^{n}BuLi mmol	211 eq.	Solvent	Temp	Time	Additive	Yield
1	hexyne 0.24	0.24	1	THF	-78 ^{o}C- rt[a]	2 hr	-	83%
2	hexyne 0.59	0.59	1	THF	-78 ^{o}C-rt[b]	2 hr	-	69%
3	hexyne 0.24	0.24	1	THF	-78 ^{o}C- rt[a]	2 hr	-	51%
4	hexyne 0.59	0.59	1	THF	rt	2 hr	-	51%
5	hexyne 0.24	0.24	1	THF	-78 ^{o}C-rt[b]	2 hr	-	34%
6	TMS-Acetylene 0.23	0.23	0.8	THF	-78 ^{o}C- rt[a]	2 hr	-	35%
7	hexyne 0.59	0.59	1	toluene	-78 ^{o}C- rt	1.5 hr	-	31%
8	hexyne 0.88	0.88	0.8	toluene	-78 ^{o}C- rt[a]	2 hr	-	46%
9	hexyne 2.39	2.39	0.8	toluene	-78 ^{o}C- rt[a]	2 hr	-	39%
10	hexyne 2.66	2.66	0.8	toluene	-78 ^{o}C- rt[c]	3 hr	$CeCl_3$	32%

Table 17

[a]Anion formation kept at -78 ^{o}C for 1 hr, **211** added, then allowed to warm to rt stirred for 1 hr. [b]Anion formed at -78 ^{o}C for 1 hr warmed to rt then electrophile **211** added, left for 1 hr. [c] Anion formation at -78 ^{o}C for 1 hr, $CeCl_3$ 1.1 eq. then added at -78 ^{o}C and left for 1 hr, then electrophile **211** added and allowed to warm to rt.

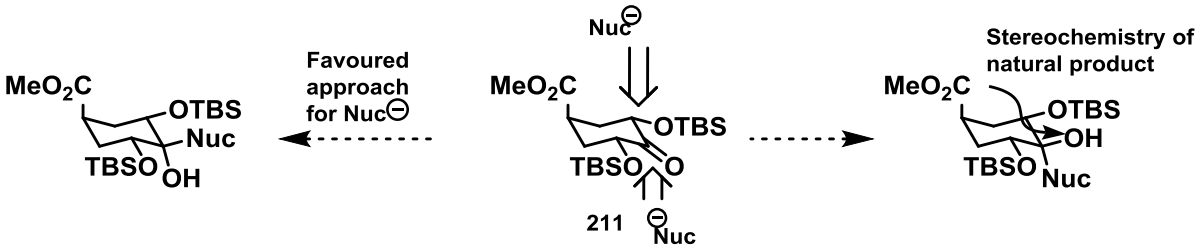
THF gave the best results (Table 17 entries 1-3). Toluene was used as the main solvent in entries 7-10 due to problems with the THF drying equipment. $CeCl_3$ was used in an attempt to improve the yield; however, this had no effect (entry 10). Using TMS-acetylene (entry 6) or modifying the equivalents of reagents (entries 1-10) had little effect on the yield.

The bis-TES ether **232** was also subjected to the same conditions as **211** but again inconsistent and relatively moderate yields were obtained. The best yield obtained for **251** was 41% using 1 eq. of ^{n}BuLi and hexyne with THF as the solvent (Scheme 87).



Scheme 87

Based on previous results from nucleophilic additions on **211**, the expected configuration was for the alcohol to be *cis* to the two TBS groups (Scheme 88). It was also assumed that the ring in **251** had adopted a chair conformation with the ester sitting in an axial position.



Scheme 88

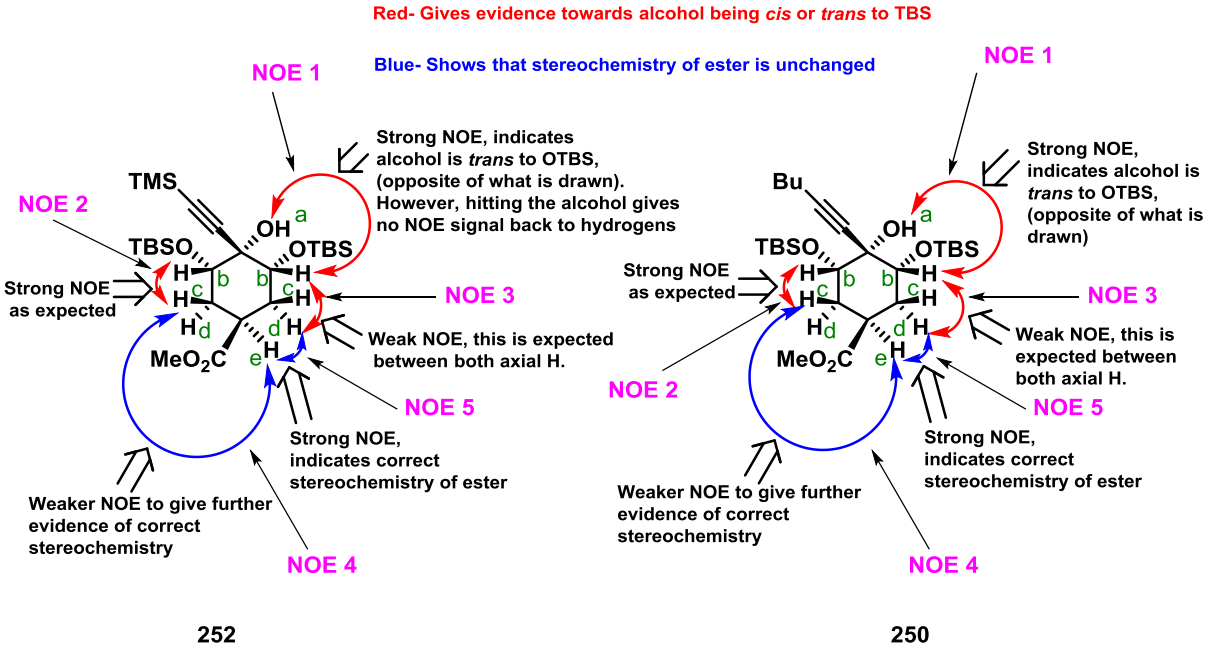
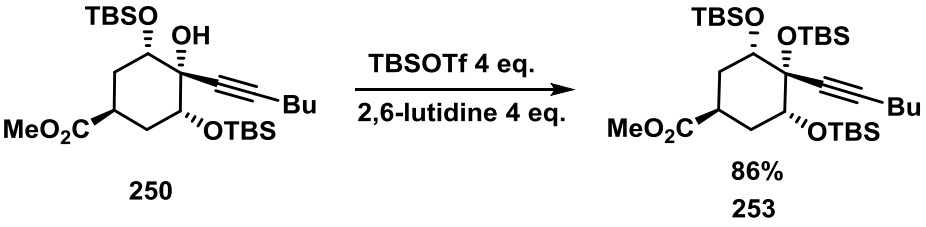


Figure 10

The GHOESY results for **250** and **252** (Figure 10) show a strong NOE signal (NOE 1) on both **250** and **252** from Hb to the alcohol Ha. Hb also have a strong NOE signal (NOE 2) between themselves and Hc on the adjacent CH_2 groups. A weak NOE signal (NOE 3) is observed between Hb and Hd indicating that they are on opposite sides to each other, which is to be expected in the assumed chair conformation. To confirm the rest of the configuration, an NOE was run from the CH attached to the ester, He. This gave a weak NOE signal (NOE 4) to Hc on the CH_2 and a strong NOE signal (NOE 5) to Hd on the same carbon. This also indicates that the ring may be sitting in the conformation shown in (Scheme 88)

From these data, the stereochemistry of the alcohol was assigned as *trans* to the OTBS groups. However, no NOE signal was observed from the alcohol Ha to Hb (NOE 1 in reverse). This contradicted the evidence that a *trans* configuration had been obtained.

Due to the contradictory results from the NOE experiments, a crystal structure of **253** was obtained once the alcohol had been protected with a TBS group (Scheme 89) (Figure 11).



Scheme 89

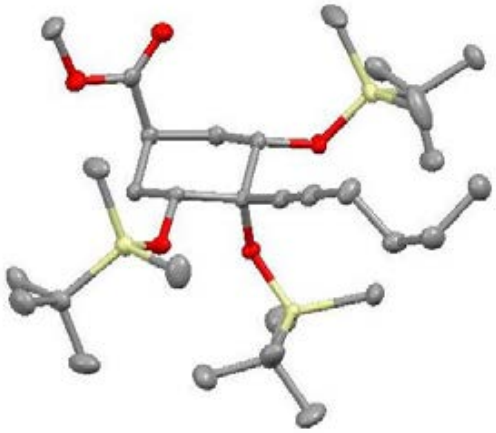
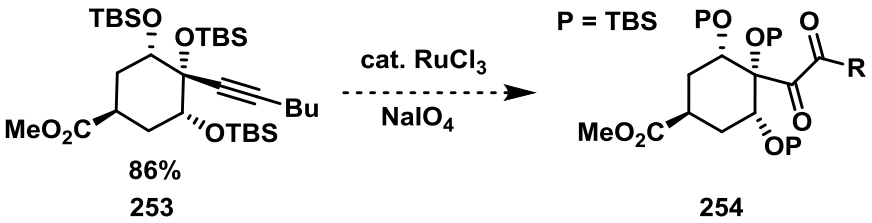


Figure 11 Crystal structure of 253 with ellipsoids drawn at the 50% probability level.

The crystal structure shows that the compound adopts a chair conformation with an axial OTBS group and an equatorial alkyne group. The three silicon-oxygen bonds are all approximately 1.65Å in length which is at the limit of a silicon oxygen bond 1.55-1.65Å with the normal value about 1.59Å.[105] After acetylide addition, the resultant alcohol is *cis* to the OTBS groups and not *trans* as required for phyllaemblic acid. This was disappointing as if the alcohol was *trans* after alkyne addition it would have led to the possibility of oxidation of an alkyne to the desired diketone functionality (Scheme 90). This would have resulted in spiroacetalisation studies which could have led to the natural product.

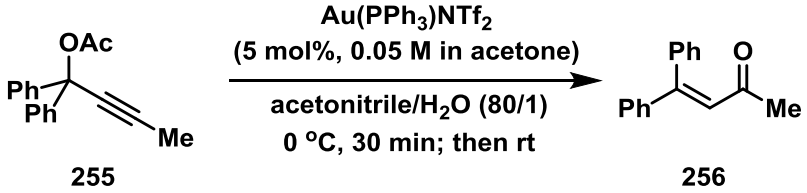


Scheme 90

The successful addition of an alkyne to **211** did allow the potential of a Meyer-Schuster rearrangement to be explored. This would then result in the desired enone functionality (Scheme 84).

Attempted rearrangement and formation of enones

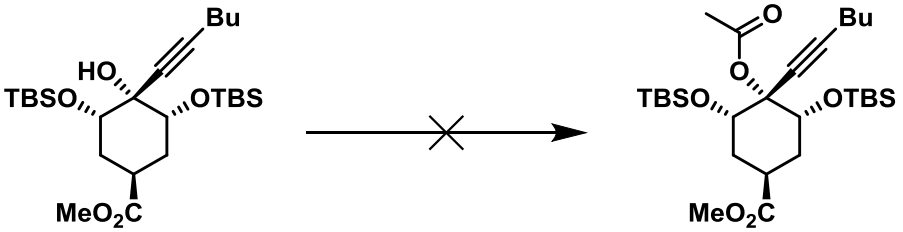
A classic Meyer-Schuster rearrangement involves the use of high temperatures and strong acids; this obviously would not suit the proposed system **250**. However, Zhang *et al.*[106] demonstrated Meyer-Schuster rearrangements can be performed under mild conditions using gold catalysis once the propargyl alcohol has been converted to an acetate (Scheme 91).



255 **256**

Scheme 91

As a TBS group was used to successfully protect the tertiary alcohol in **250**, acylation of the same alcohol was assumed to be relatively straightforward. However, the attempted acetylation of **250** proved to be problematic under a variety of conditions (Table 18). Classic conditions of acetic anhydride, pyridine and DMAP were used[107], along with acetyl chloride and Et_3N.[108] Unfortunately, the tertiary alcohol was unable to be protected as an acyl ester (Scheme 92). A carbon-oxygen bond cf. ~1.43Å[109] is shorter than an oxygen-silicon bond cf. 1.59Å[105]. Therefore, the shorter bond length in the tetrahedral intermediate may be a main factor in not being able to protect the sterically hindered tertiary alcohol to form **257**.



250 **257**

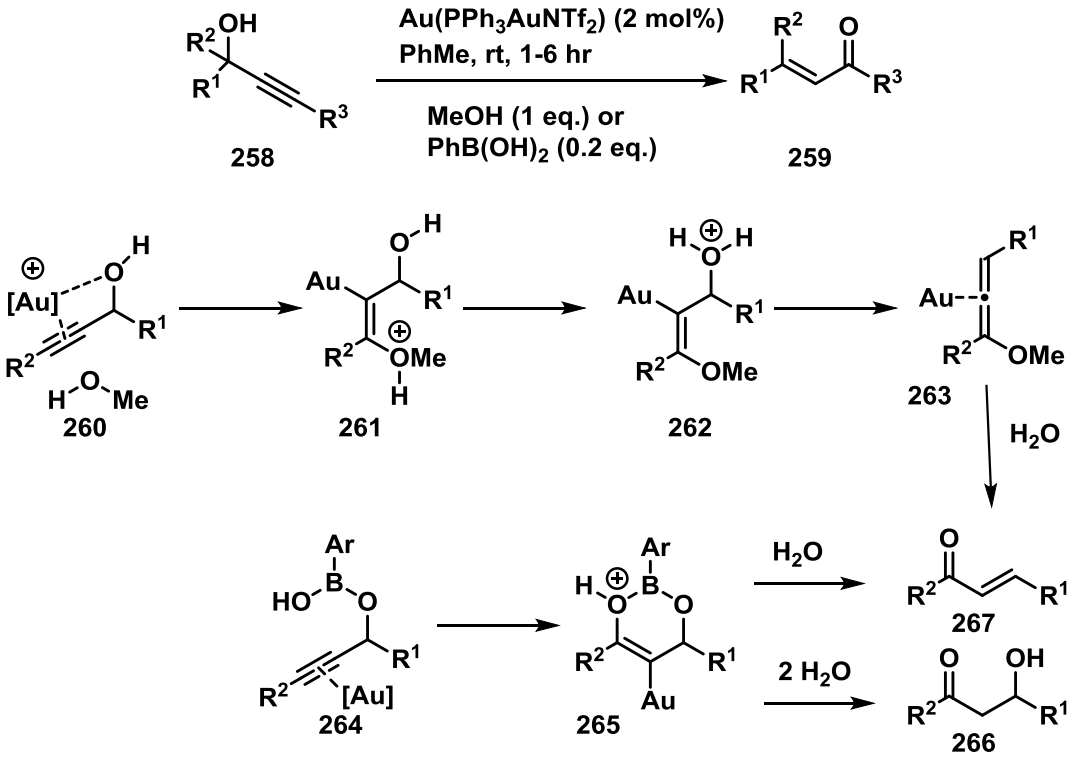
Scheme 92

Entry	Ac_2O	Pyridine	Et_3N	DMAP	Acetyl Chloride	Temp	Solvent	Yield
1	×	×	×	×	1.2 eq.	-70 °C-reflux	THF	sm[a]
2	×	×	1.2 eq.	×	1.2 eq.	rt	THF	degradation
3	2.2 eq.	1 mL	×	10 mol%	×	rt	pyridine	sm/ degradation

Table 18

[a]Propargyl alcohol formed then the crude reaction worked up by adding acetyl chloride and Et_3N.

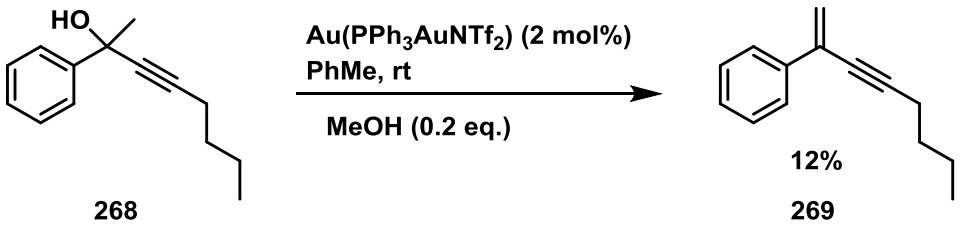
Sheppard *et al.*[110] had taken unprotected tertiary propargyl alcohols and converted them to enones. This was achieved by *in situ* protection of the alcohol using either MeOH or phenylboronic acid in the presence of $AuPh_3NTf_2$ (Scheme 93). The proposed mechanisms for both pathways are similar. Gold activates the alkyne to form **260**. The addition of methanol then gives **261**, followed by proton transfer to give **262**. Subsequent elimination of water forms the allenyl ether **263**. Finally, hydrolysis of **263** which may involve activation by the gold catalyst, gives the enone **267**. The pathway for enone formation from the boronic acid-mediated route can also yield the β-hydroxyketone **266**. It is proposed that **267** and **266** are produced via the cyclic enol boronate **265**. Initial formation of the boronate half ester **264**, with subsequent cyclisation and protodeauration leads to the cyclic enol boronate **265**. The β-hydroxyketone **266** can then form after direct hydrolysis of **265** and **267** can form after a concerted rearrangement.



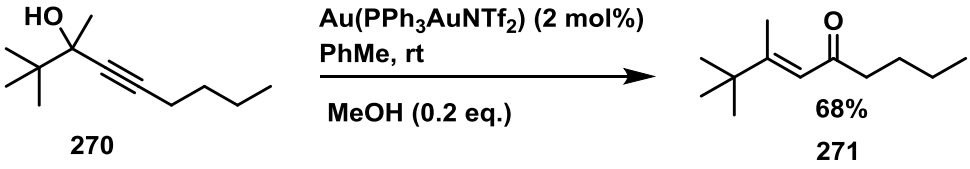
Scheme 93

It was assumed that the TBS protecting groups on **250** were blocking the alcohol from being protected with an acyl group. Using this new method, it was predicted that MeOH would be able to activate the system *in situ* and the rearrangement could take place.

Initial attempts to make the reported literature compounds were problematic, as elimination of the tertiary alcohol was occurring (Scheme 94). It was determined that the concentration of the solution must be 1M in order for the Meyer-Schuster rearrangement to successfully take place (Scheme 95).



Scheme 94



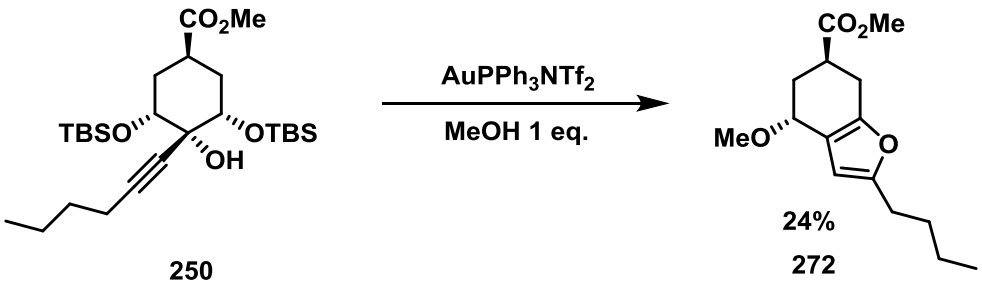
Scheme 95

The methodology was then applied to the propargyl alcohols **250**, **251** and **252** (Table 19).

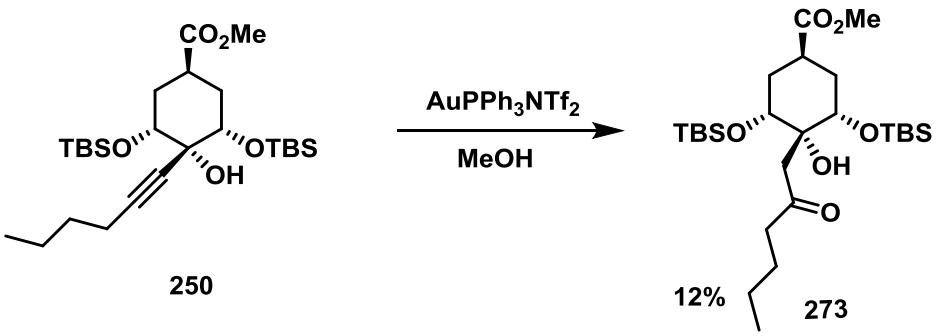
Entry	mmol of propargyl alcohol	Additive mmol	Gold loading	Temp	Time	Yield
1	0.13 of **250**	MeOH 0.13	5%	rt	overnight	12% of **273**
2	0.2 of **250**	MeOH 0.2	5%	rt	overnight	24% of **272**, 5% of **273**
3	0.1 **250**	$PhB(OH)_2$ 0.02	5%	rt	overnight	13% of **274**
4	0.2 **250**	$PhB(OH)_2$ 0.2	5%	rt	overnight	64% of **274**
5	0.4 **250**	$PhB(OH)_2$ 0.4	5%	200 °C	2 hr	40% of **274**
6	0.07 **275**	$PhB(OH)_2$ 0.014	5%	rt	overnight	sm
7	0.13 of **250**	$PhB(OH)_2$ 0.13	-	rt	overnight	sm
8	0.13 of **250**	-	5%	rt	overnight	sm
9	0.07 **251**	$PhB(OH)_2$ 0.07	5%	rt	overnight	degradation
10	0.32 **251**	$PhB(OH)_2$ 0.32	5%	rt	overnight	17% of **278**

Table 19

It was assumed that MeOH would be the best additive to use as this is small, allowing the alcohol to be activated ready for rearrangement. However, when this chemistry was applied in entries 1 and 2, only the beta-hydroxy ketone **273** or the furan **272** were isolated. Large amounts of degradation were also present, making the crude mixture difficult to purify (Scheme 96) (Scheme 97). The reactions were repeated several times, but enone formation was not obtained and the yields of **272** or **273** could not be improved.



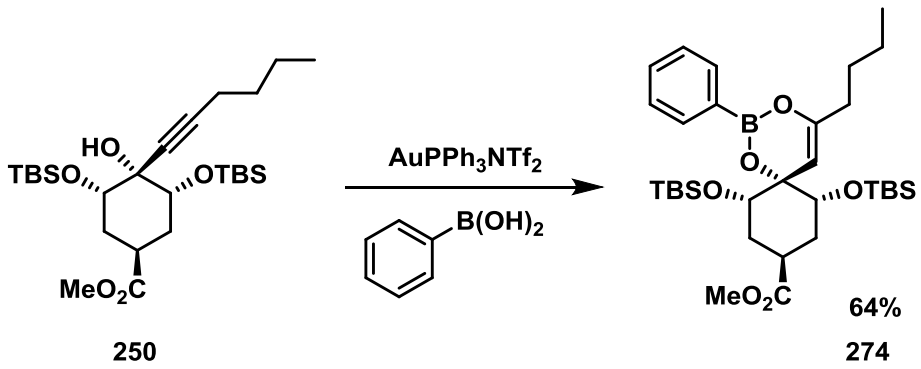
Scheme 96



Scheme 97

The formation of the furan **272** will be discussed later on with a similar compound. The formation of the beta-hydroxy ketone **273** is thought to resemble a classic hydration of an alkyne via mercury catalysis.[111] A recent report by Zhang *et al*. has shown it possible to hydrate alkynes in the presence of gold at room temperature.[112]

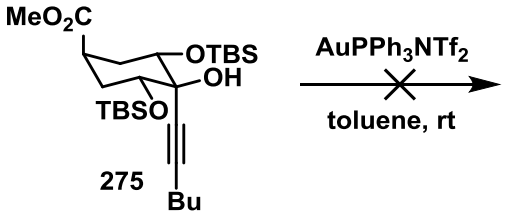
Phenylboronic acid was used as an alternative to MeOH which again resulted in no enone formation; however, the first successful synthesis of a cyclic enol boronate **274** using gold catalysis was achieved (Table 19 entries 3-4 Scheme 98).



Scheme 98

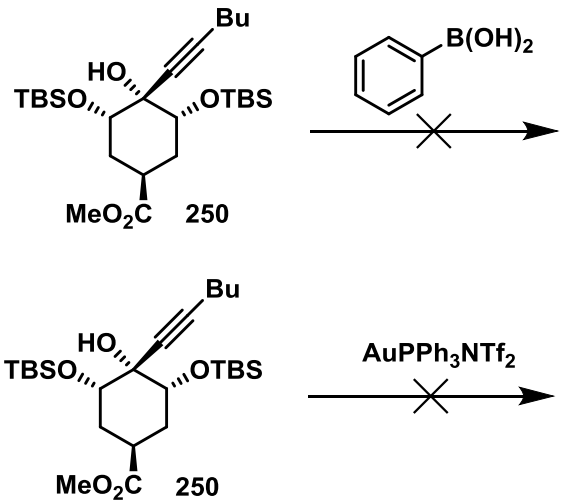
The formation of the cyclic enol boronate **274** was also successfully achieved in a microwave reactor (entry 5). The purpose of this reaction was to see if the enone formation could be achieved at higher temperatures. Surprisingly, **274** proved stable up to 200 ^{o}C for 2 hours although it is noted that the yield of the reaction was reduced.

A very small amount of **275** was isolated as a minor compound in a significantly scaled up formation of **250**. The propargyl alcohol, with the alcohol *trans* to the OTBS, was subjected to the same conditions used to form **274** (entry 6). Interestingly, no reaction was observed (Scheme 99). Again, this gives further evidence that the TBS groups are blocking access to the alkyne, preventing the reaction from starting.



Scheme 99

Two test reactions were carried out with the omission of either boronic acid or the gold catalyst (Scheme 100). Only starting material was isolated in both cases (entries 7 and 8).



Scheme 100

Although the formation of a cyclic enol boronate was frustrating as it was hampering enone synthesis, it was a rather exciting discovery. This was the first time this functionality had been formed using gold catalysis and there are only two references in the literature on cyclic enol boronates.[113, 114]

When analysing the data for **274**, ^{1}H NMR showed the enolic proton is found at approximately 4.5 ppm, the literature shows similar structures with these values have been reported; however the ^{11}B NMR shift of 10.8 ppm for **274** does not match literature data (Figure 12 Table 20)[114].

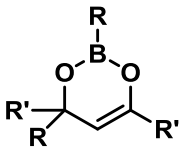


Figure 12

Entry	R	R'	^{1}H NMR shift for alkene	^{11}B NMR
1	Me	Me	4.53 ppm	30.0 ppm
2	^{i}Pr	Me	4.46 ppm	31.0 ppm
3	^{t}Bu	Me	4.61 ppm	32.0 ppm
4	Me	CF_3	5.34 ppm	33.0 ppm

Table 20

Another key feature of this functionality is the alkene IR stretch, 1696 cm^{-1}, comparable to the literature value of 1695 cm^{-1}.[113] A crystal was successfully grown which led to the first crystal structure of a cyclic enol boronate (Figure 13).

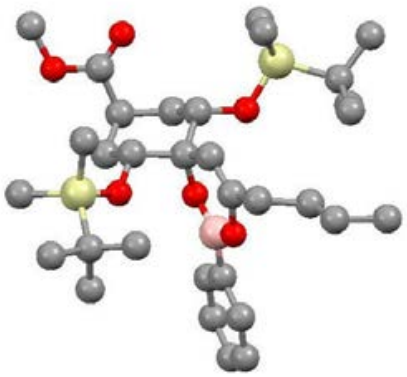
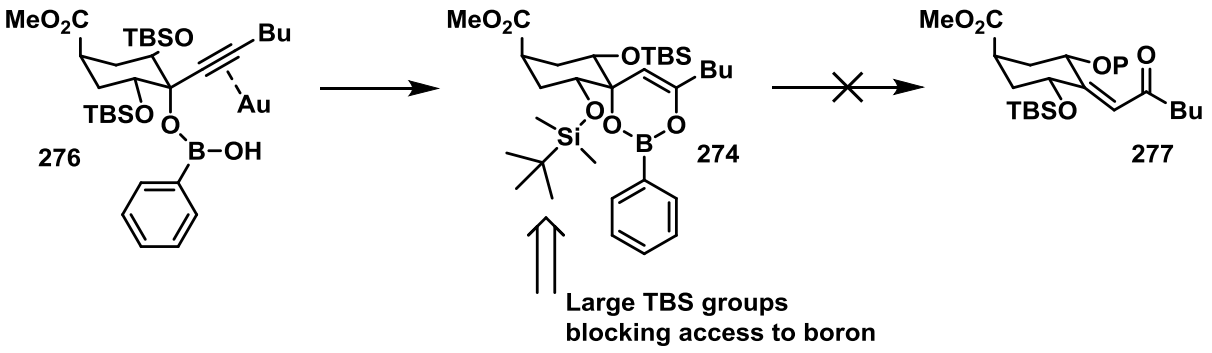


Figure 13 Crystal structure of 274 with ellipsoids drawn at the 50% probability level. The structure contains two crystallographically-independent molecules.

The bond lengths surrounding the cyclic enol boronate are all in the normal ranges for carbon-boron (1.59-1.72 Å)[109] and boron-oxygen (1.28-1.43 Å)[115] bonds. The X-ray depicts that a chair conformation is present for the cyclohexane ring, presumably locked in place by the large TBS groups. The cyclic enol boronate is planar with the boron and its empty p-orbital is orthogonal to the ring.

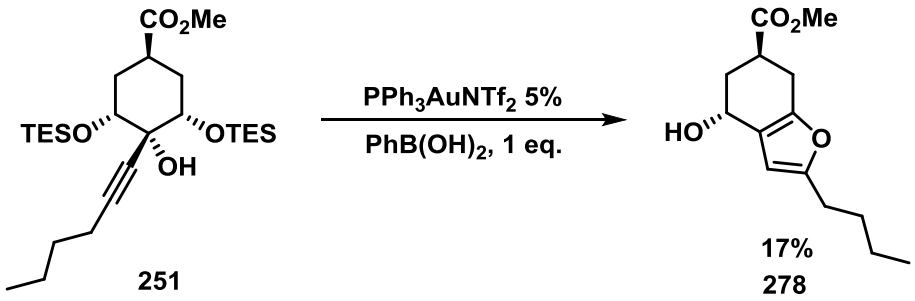
The crystal structure clearly shows the TBS groups are surrounding the cyclic enol boronate. This gave an indication of how this type of product could form from the reaction (Scheme 101).



Scheme 101

Sheppard *et al.* postulated that the gold complex helps to form the cyclic enol boronate *in situ*. Water then approaches to release the boronate and gold, with the system collapsing into enone **267** (Scheme 93). Following gold activation in **276**, cyclisation occurs to give **274**. It is assumed that the TBS groups flanking either side of the boron and alkene are blocking the water from activating the system, preventing the system from collapsing to enone **277**.

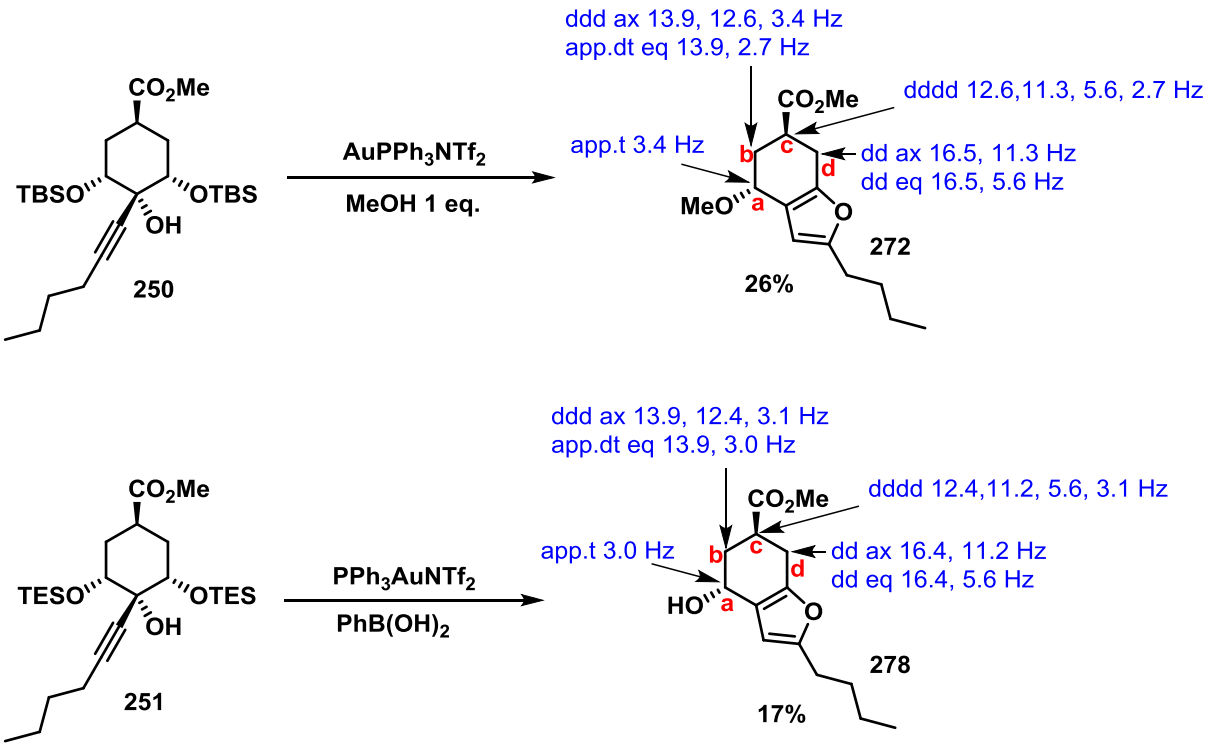
The propargyl alcohol **251** has slightly smaller silicon protecting groups compared to the TBS groups in **250**. It was postulated that with the TES protection in place enough space would be present for the boronate to collapse to the target enone. The system **251** was found to be more reactive than **250**, demonstrated through multiple R_f. products observed upon T.L.C. analysis (Table 19, entries 9 and 10). This further complicated the purification. ^{1}H NMR analysis of the crude reaction mixture suggested that an enone had formed. The conditions were repeated several times but no enone could be isolated. Eventually, a scaled up reaction led to the isolation of furan **278** in a 17% yield (Scheme 102). Unfortunately, this was the only product that could be isolated from the reaction and so it was decided that even if the enone was being formed it was not a viable method.



Scheme 102

The formation of the two furans **272** and **278** has shown two different product outcomes for the resulting alcohol or methyl ether. The first example run with MeOH shows a methyl ether present on the ring in **272**, whereas, an alcohol is present on the ring in **278** when the

reaction was carried out in the presence of $PhB(OH)_2$. The stereochemistry for the methyl ether in **272** or alcohol in **278** was confirmed using coupling constants (Scheme 103). The substituents at position (a) in both compounds were determined to be pseudo-axial; the axial proton at position (b) has two large coupling constants: one for the geminal protons ~13.9 Hz and one for the *trans* di-axial coupling constant, with position (c) ~12.5 Hz. A final coupling of ~3.2 Hz is then obtained which is indicative of the proton at position (a) being pseudo axial.

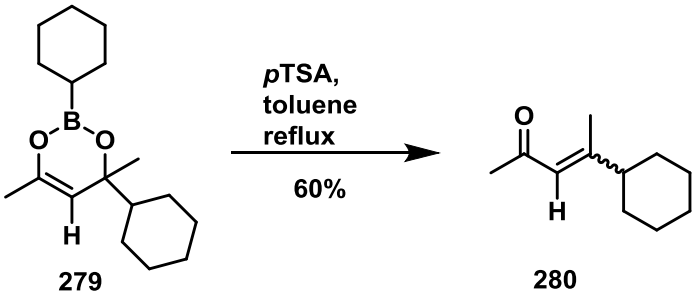


Scheme 103

It is assumed that the formation of **278** is due to the TES group being sufficiently labile in the presence of boronic acid.

The formation of **272** in the presence of MeOH is challenging to explain because of the retention of stereochemistry. A 26% yield of the diastereomer was isolated so it is conceivable that the other diastereomer was being formed but unable to be isolated.

The paper by Okada *et al.*[113] detailed that cyclic enol boronate **279** could be converted to enone **280** by refluxing in toluene and *p*TSA (Scheme 104).



Scheme 104

This led to an investigation of potential transformations to functionalise the cyclic enol boronate **274** (Table 21).

Entry	Mmol of enol boronate	Reactant	Time	Temp	Yield
1	0.14	*p*TSA 0.14	12 hr	reflux	trace amount of **273**
2	0.041	*p*TSA 0.041	12 hr	rt	48% **273**
3	0.38	0.38 boronic acid and 10% gold	12 hr	rt	48% of **274**
4	0.041	TBAF 0.041	2 hr	0 ^{o}C-rt	degradation
5	0.041	-	2 hr	200 ^{o}C	sm
6	0.041	NBS 0.082	3 days	rt	degradation
7	0.041	*m*CPBA 0.08	1 hr	0 ^{o}C-rt	trace amount of **273**
8	0.041	H_2O_2 0.041	15 min	0 ^{o}C	degradation
9	0.041	butyraldehyde	4 hr	rt-100 ^{o}C	trace amount of **273**

Table 21

A trace amount of beta-hydroxy-ketone **273** was observed when **274** was subjected to *p*TSA in toluene at reflux (entry 1). Running the reaction at rt led to a 48% yield of **273** (entry 2) but, unfortunately, no enone was formed. The cyclic enol boronate **274** was formed *in situ*

and worked up with a solution of 1 M HCl (entry 3). It was expected that the acidic work up would convert the cyclic boronate to an enone; however a 48% yield of the enol boronate **274** was recovered.

TBAF was used in an attempt to either cleave the boronate or remove the TBS groups to allow for the rest of the system to collapse to an enone. The reaction started with 1 eq. of TBAF with the intention to add more as the reaction progressed. However, this quickly led to degradation after only 2 hours and 1 eq. of TBAF (entry 4).

It was decided to confirm the stability of the cyclic enol boronate by placing pure **274** in a microwave and taking the system up to 200 ^{o}C. After 2 hours, the reaction gave all of the starting material back (entry 5).

NBS was used to halogenate the alkene (entry 6); this was based on unpublished work from Tom Sheppard. It was proposed that the halo-boron enolate could then be oxidised but unfortunately degradation occurred.

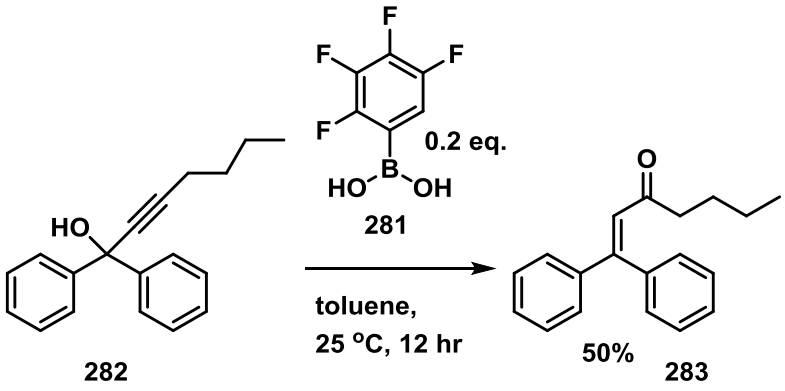
*m*CPBA and H_2O_2/NaOH were both used in an attempt to oxidise the boron, based on literature precedent by Sheppard *et al*.[116] (entries 7-8), but again only degradation occurred.

Enol boronates can be used in aldol reactions.[117] Therefore, it was decided to probe the reactivity of the cyclic boron enolate **274** with butyraldehyde. Although this would not have been a helpful reaction towards the synthesis of the natural product, there was the possibility of developing new novel methodology within the aldol literature using the cyclic enol boronate **274**. When attempting this type of chemistry, no aldol products were

obtained. Degradation mainly occurred; however, trace amounts of the beta-hydroxy ketone were observed (entry 9).

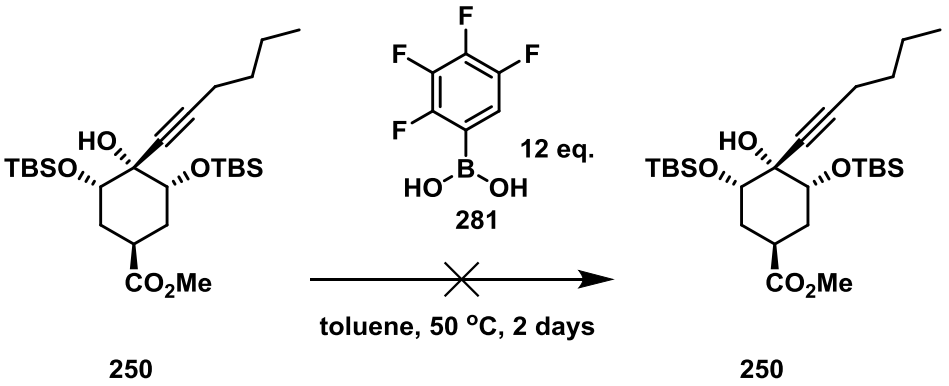
Hall *et al.*[118] reported the use of (2,3,4,5-tetrafluorophenyl)boronic acid **281** as a catalyst for the Meyer-Schuster rearrangement on unprotected tertiary alcohols without the presence of gold. Therefore, it was decided to attempt this chemistry on **250** and **251** due to the problems of protecting the tertiary alcohol.

After the boronic acid **281** was synthesised, the chemistry was successfully tested on a simple test substrate **282** giving **283**, thus confirming the paper's findings (Scheme 105).



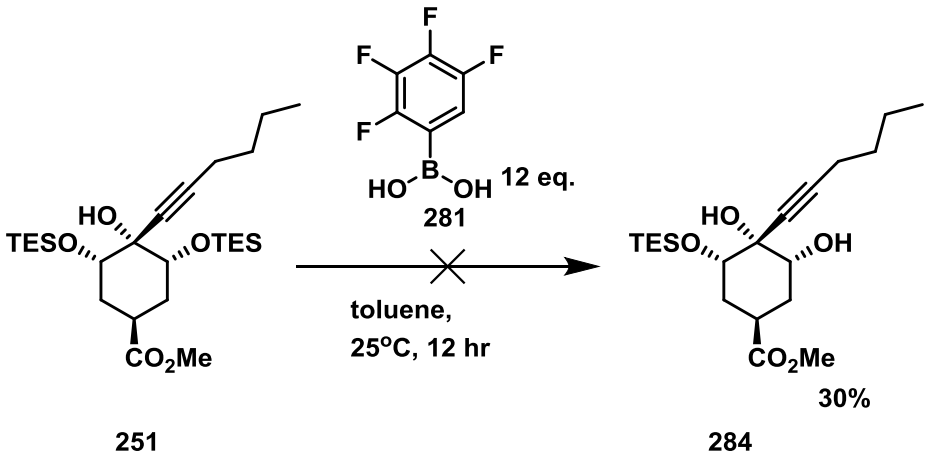
Scheme 105

Application to **250**, however, resulted in no enone formation. The TBS protected system **250** gave only starting material even after increasing the temperature and adding up to twelve equivalents of the catalyst. After two days degradation started to appear in the T.L.C. and so the reaction was worked up and the majority of starting material was isolated (Scheme 106).



Scheme 106

Using TES as an alternative protecting group **251** led to the mono protected version **284** in a 30% yield (Scheme 107). Presumably this was due to how labile TES is compared to TBS in the presence of the boronic acid.



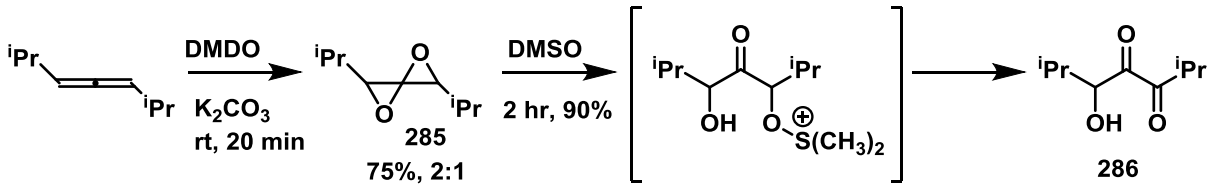
Scheme 107

From the data obtained it was assumed that the silicon protecting groups are once again blocking the approach of the catalyst, therefore stopping the reaction.

Spiro epoxide formation

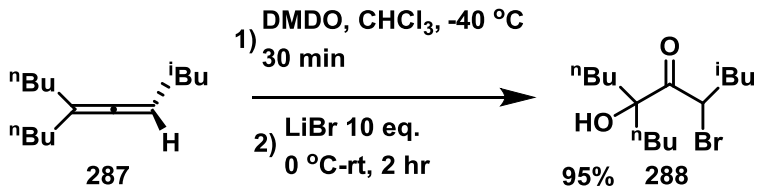
Due to the inability to perform a Meyer-Schuster rearrangement on **250** or **251**, an alternative rearrangement route was investigated. The idea was postulated that the propargylic alcohol on **250** could be converted to form an allene. This in turn could then be transformed to the desired hydroxy-1,2-diketone functionality. This was introduced by

Crandall *et al.*[119], using the Murray methodology[120], allowing them to access various substituted spirodioxides from substituted allenes. One spirodioxide **285** was of particular interest as after addition of DMSO it spontaneously decomposed to form hydroxy-diketone **286** (Scheme 108).



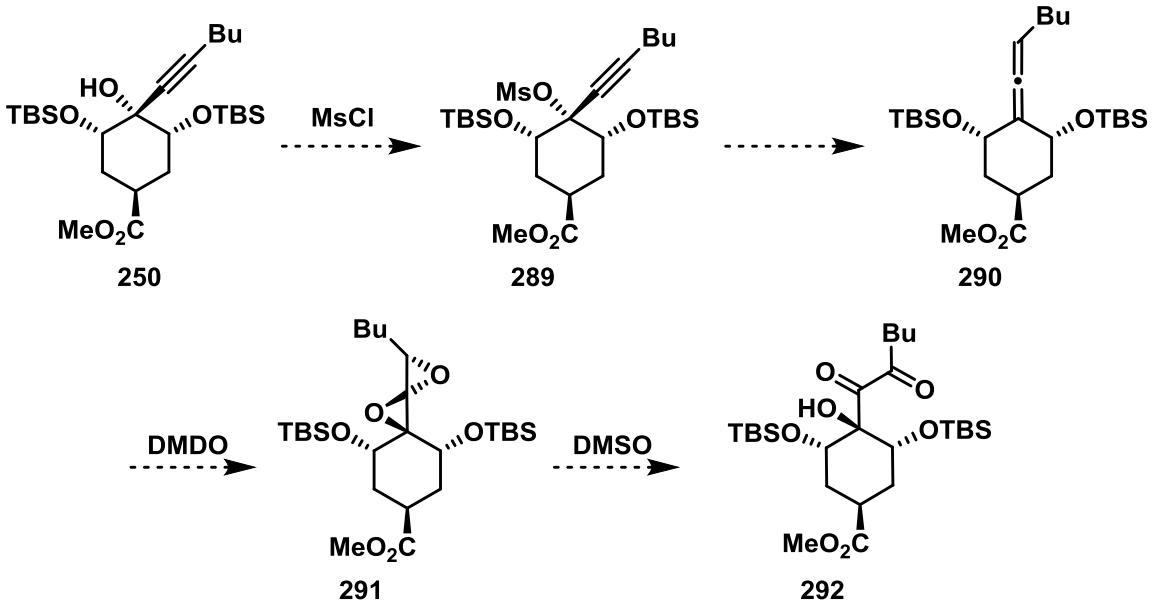
Scheme 108

A similar report by Williams *et al.*[121] converted an allene **287** into an alpha-hydroxy-halo-ketone **288**; one step away from being converted into a hydroxy-diketone.



Scheme 109

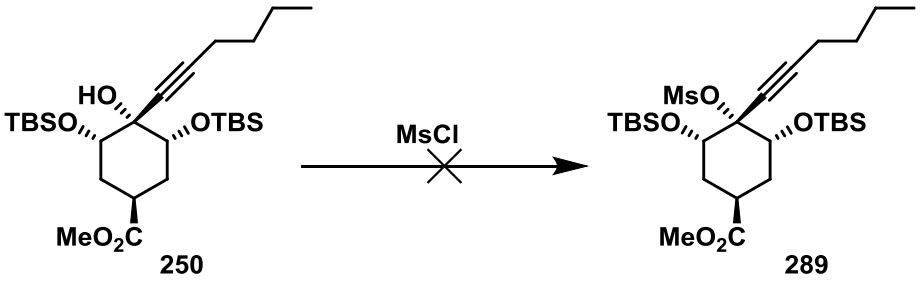
It was proposed that if propargyl alcohol **250** could be converted to the mesylate **289**, reduction could yield allene **290**. Based on the previously proven concept that OsO_4 adds to the top face of the alkene **219** (Chapter 3, Scheme 64), it is assumed that DMDO will form the spirodioxide **291**. Subsequent oxidation will then present the resultant alcohol as *trans* to the OTBS groups in **292** (Scheme 110).



Scheme 110

In order to attempt this kind of chemistry a mesylate must first be formed on propargylic alcohol **250**. Unfortunately, this was very problematic and so the proposed synthesis of **289** could not be carried out (Scheme 111).

The equivalents of MsCl and Et_3N were increased from 1.1 to 12 in order to form **289** but no product was observed (entry 1, Table 22). ^{n}BuLi was used to deprotonate the alcohol, followed by addition of MsCl and Et_3N, but again only starting material was isolated (entry 2). MsCl was added to quench the alkoxide anion of **250** after addition of hexyne to ketone **250** but again no trace of **289** was identified (entry 3).



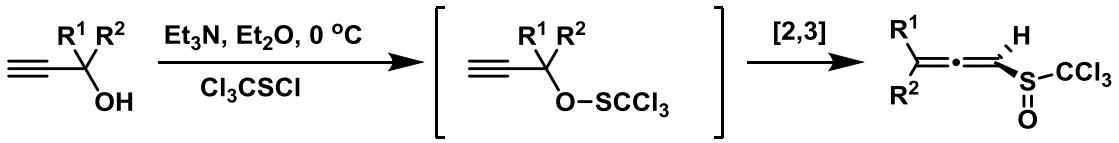
Scheme 111

Entry	Propargyl Alcohol	MsCl	Et_3N	^nBuLi	Solvent	Temperature	Yield
1	0.06 mmol	1.1 eq.	1.1 eq.	×	CH_2Cl_2	0 °C- rt	sm[a]
2	0.06 mmol	2 eq.	2 eq.	1 eq.	THF	-78 °C- rt	sm[b]
3	0.24 mmol	2 eq.	2 eq.	×	THF	-78 °C- rt	30%[c]

Table 22

[a] Equivalents of MsCl and Et_3N increased to 12. [b] -78°C for ^nBuLi addition at -78 °C followed by MsCl and Et_3N. [C] Propargyl alkoxide formed *in situ* followed by MsCl and Et_3N as a quench 30% yield of propargyl alcohol.

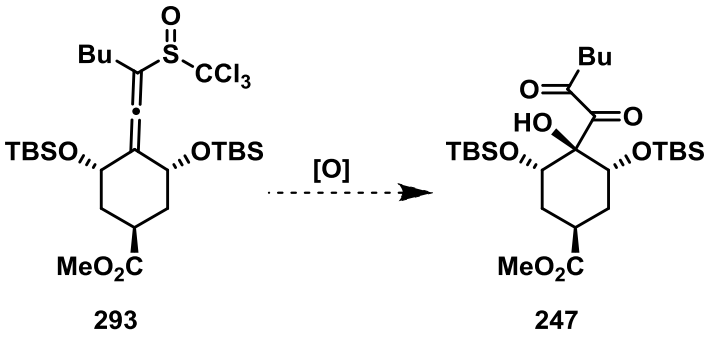
An alternative approach to form an allenic system by a 2,3-sigmatropic rearrangement of a propargyl sulfenate to an allenic sulfoxide was proposed; first introduced by Braverman and Stabinsky *et al.*[122] Their work showed that many different propargyl alcohols could be rearranged via a sulfenate (Scheme 112).



$R^1 = R^2 = H$; $R^1 = H$, $R^2 = Ph$; $R^1 = R^2 = Me$

Scheme 112

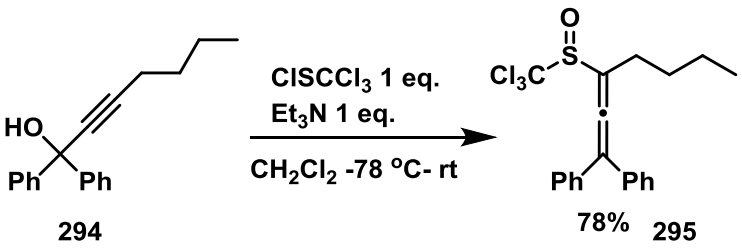
If the rearrangement was carried out on **250** or **251**, then a similar approach to the allenic system above (Scheme 110) could be envisaged to access the diketone functionality (Scheme 113).



293 247

Scheme 113

As previously described, the attachment of a mesylate and an acyl group to the tertiary alcohol in **250** were unsuccessful. The reasons for this are difficult to explain as although there is a lot of steric hindrance around **250**, a TBS group was successfully installed in good yield (Scheme 89). It is assumed that one of the primary reasons a TBS group attaches is due to the Si-O bond being longer than a C-O bond. It was hoped that as a O-S in a mesylate c.f. 1.56 Å[109] is comparable in length to an O-Si 1.59Å bond and conversion to a mesylate would take place.



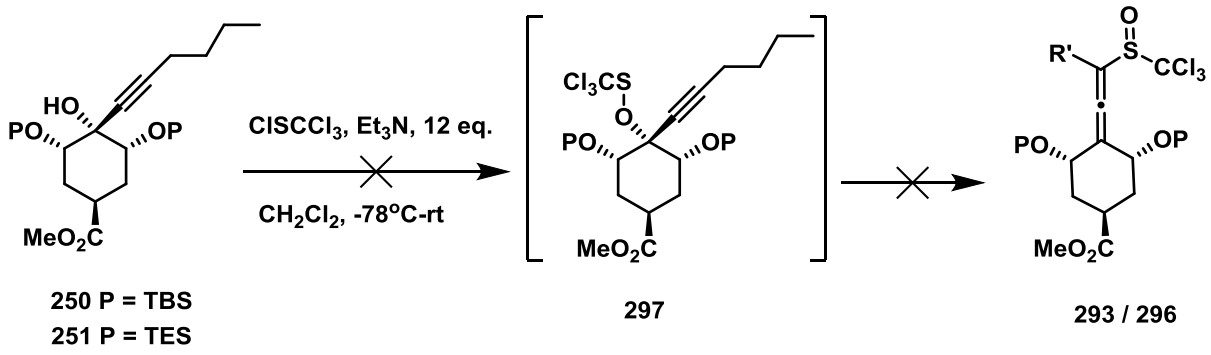
294 78% 295

Scheme 114

A test reaction was first carried out using propargyl alcohol **294** which gave the trichloromethanesulfinyl **295** in good yield. This confirmed that the chemical transformation was able to be carried out, and that the reagent $ClSCCl_3$ was of good quality (Scheme 114).

Attention then turned to the conversion of propargyl alcohol **250**/**251** to the allenic sulfoxide. Both TES and TBS protected diols were subjected to the reaction conditions.

Unfortunately, **250** or **251** could not be converted to either of the substrates **293** or **296** and it is proposed that this is due to the unsuccessful *in situ* formation of sulfenate **297**.

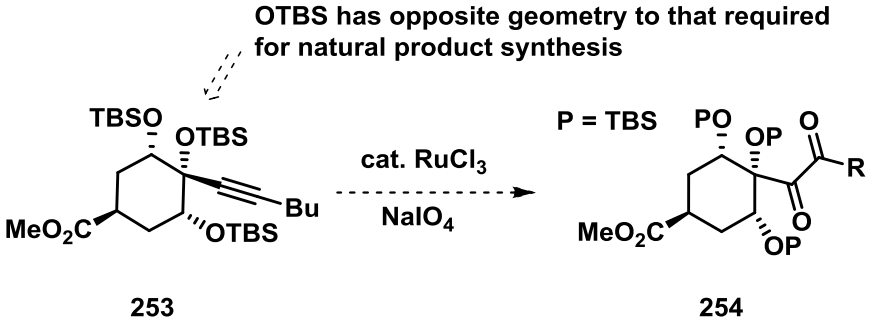


Scheme 115

Alternative disconnection approach

Introduction

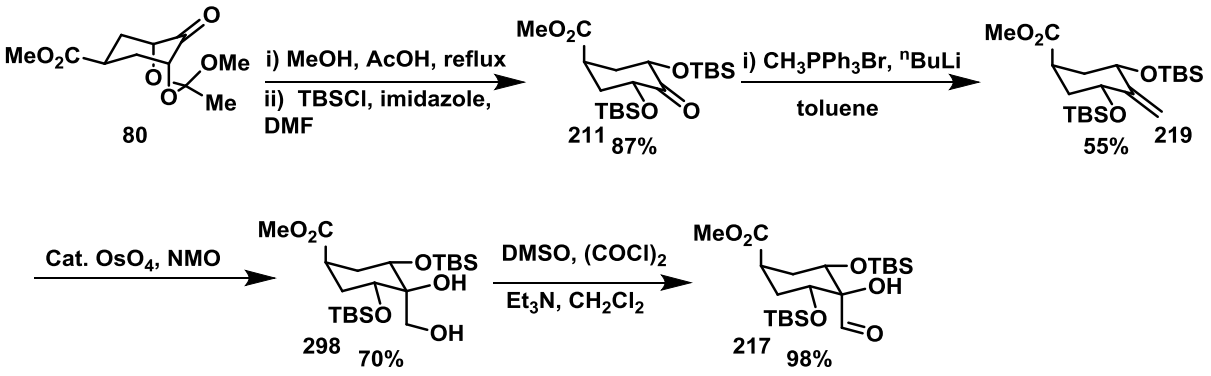
Due to the Meyer-Schuster rearrangement failing to deliver the required enone, along with the failed attempts to make an allene, an alternative strategy was developed. Alkyne addition had been shown to give the incorrect stereochemistry needed for the natural product. However, the alkyne functionality offered convenient access to a diketone via a single step (Scheme 116).



Scheme 116

The most successful route to date towards a synthesis of phyllaemblic acid is via a simple Wittig reaction to install a methylene group to give **219**. This was stereoselectively dihydroxylated to form diol **298**, which positioned the tertiary alcohol *trans* to the two OTBS

groups. The primary alcohol was then oxidised to give the aldehyde **217**. This route gave access to all four stereocentres found on the cyclohexane ring in phyllaemblic acid (Scheme 117).

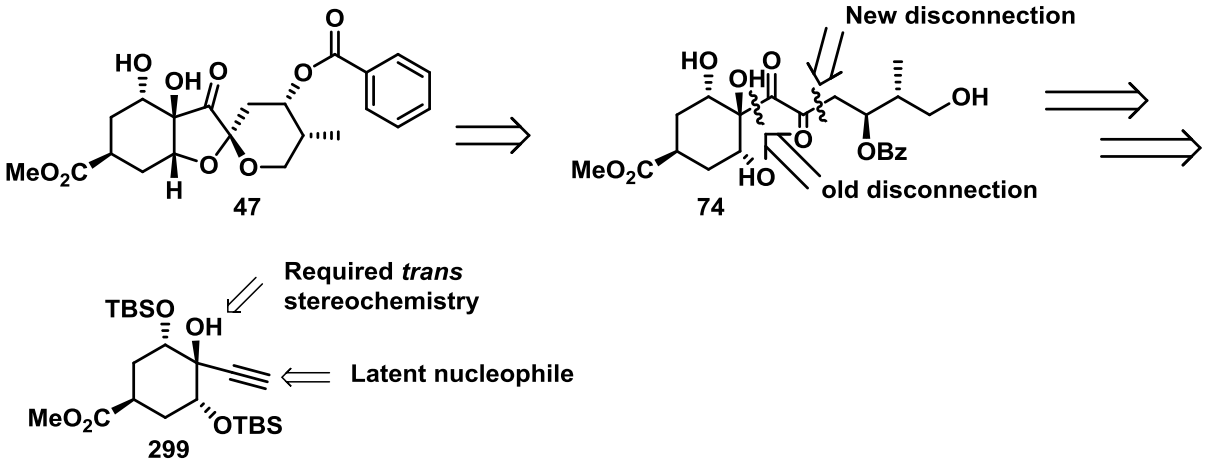


Scheme 117

However, this approach suffered from low reactivity of the resulting aldehyde and the Wittig reaction gave yields of around 50%.

A new disconnection and approach

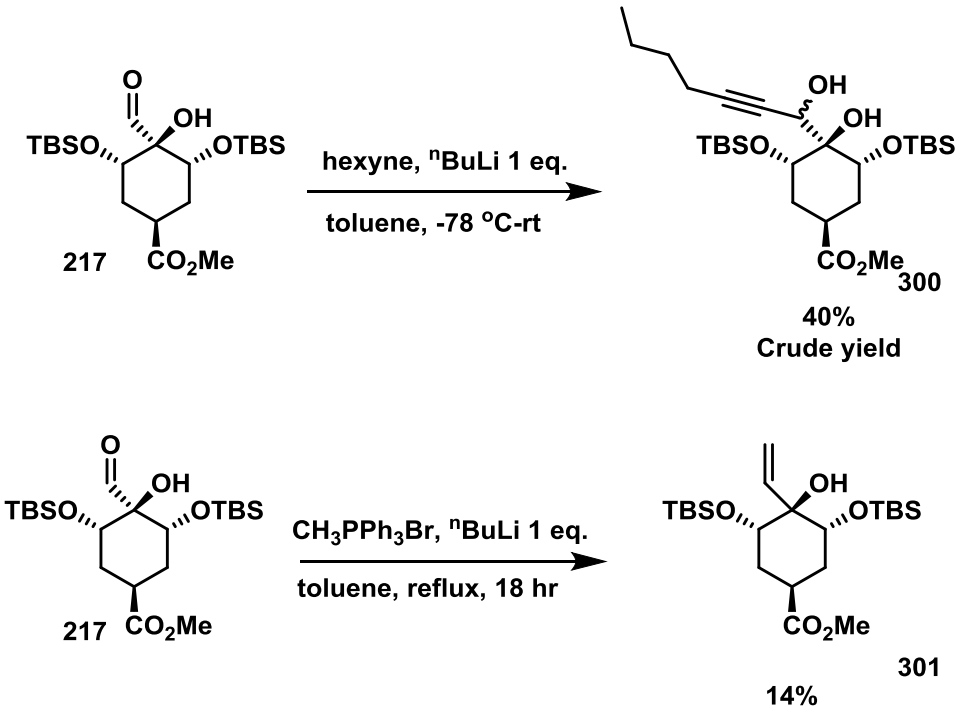
Despite the low reactivity of aldehyde **217**, a new approach was envisaged. If the aldehyde could be transformed into alkyne **299**, this would lead to a new disconnection where all four stereocentres are already in place, as opposed to only three in the previous approach. The problematic electrophile would be replaced with an alkyne that can be deprotonated and used as a nucleophile (Scheme 118).



Scheme 118

Results and Discussion

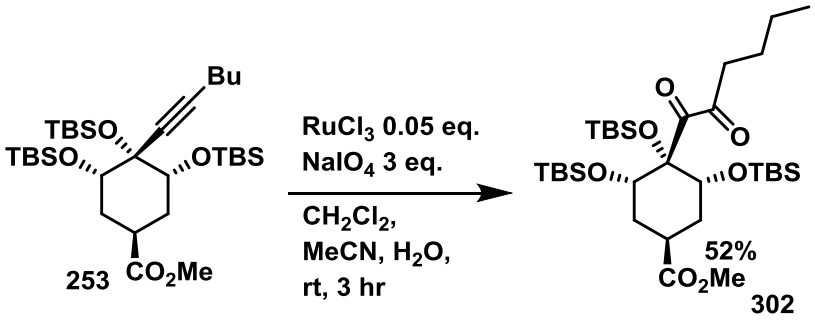
To confirm the low reactivity, an alkyne addition and a simple Wittig reaction were performed on aldehyde **217**. As expected, neither of the reactions worked well. The alkyne addition reaction was only able to be semi-purified to give **300**, and the Wittig reaction gave the alkene **301** in a 14% yield with starting material being recovered (Scheme 119).



Scheme 119

For this synthesis to be successful the yield of **219** must be improved to make the route viable and form **299** (Scheme 117).

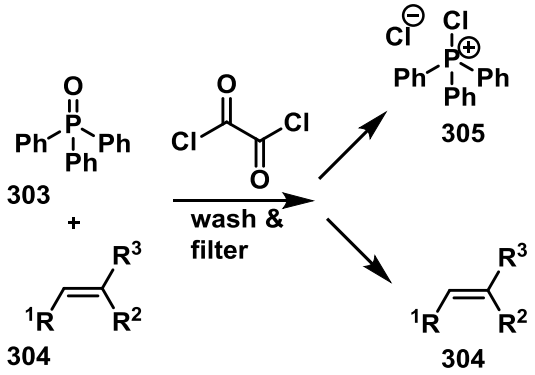
As the epimeric propargyl alcohol **253** had been successfully prepared, it was decided to undertake a model study in order to see if the alkyne could be oxidised to form the diketone **302**[123] (Scheme 120).



Scheme 120

The oxidation proceeded with a modest 52% yield. Encouraged by this, work began to form **299** with the requisite *trans* stereochemistry between the tertiary alcohol and the OTBS groups.

When repeating work to form **219** it was noted that a clean conversion was always obtained by T.L.C. analysis, but the same poor isolated yields of 30-45% were obtained. This can be a common problem for Wittig reactions and is often attributed to the formation of triphenylphosphine oxide, trapping the compound during purification via column. This problem was overcome by using a method published by Gilheany *et al.*[124] The group used oxalyl chloride to make a chromatography-free purification method for a host of reactions that produce triphenylphosphine oxide as a by-product (Scheme 121).

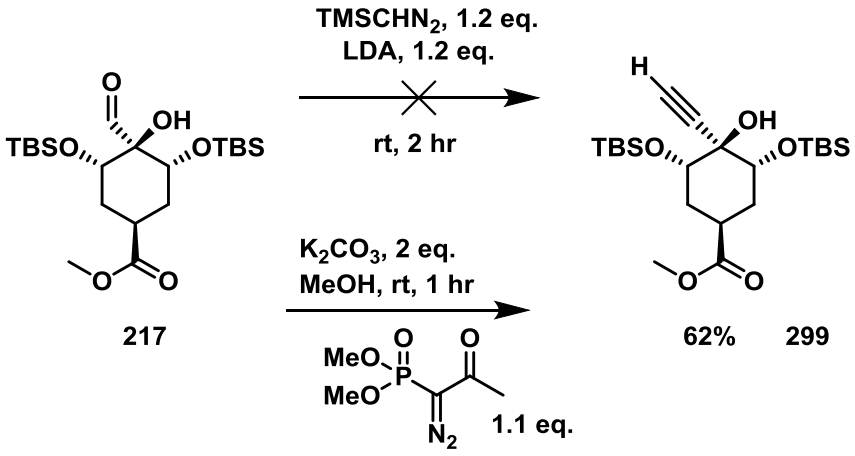


Scheme 121

The method is straightforward; the oxalyl chloride converts triphenylphosphine oxide **303** to a chlorophosphonium salt **305**, which can then be easily removed by filtration and an aqueous wash. When applying this relatively unused method to alkene **219** the yield improved from 52% to 78%.

The rest of the route followed as expected and the aldehyde **217** was obtained in a 98% yield. Investigations now turned to converting the aldehyde **217** into alkyne **299**.[125]

The first method used was the Colvin rearrangement[126] using trimethylsilyldiazomethane in the presence of LDA to convert aldehydes into alkynes. This method unfortunately could not be applied to aldehyde **217** as no reaction took place. Therefore, the Ohira-Bestmann reagent was synthesised and employed to convert aldehyde **217** into alkyne **299** in a 62% yield (Scheme 122).



Scheme 122

A crystal structure of **299** showed that the alcohol is now *trans* to the TBS groups (Figure 14). This has potentially alleviated the problems of nucleophilic addition to ketone **211** as the alkyne **299** can be used as a latent nucleophile with all four of the stereocentres set on the cyclohexane ring. The spacefilling model also gives an indication that the alkyne should be accessible to deprotonation and react with an electrophile.

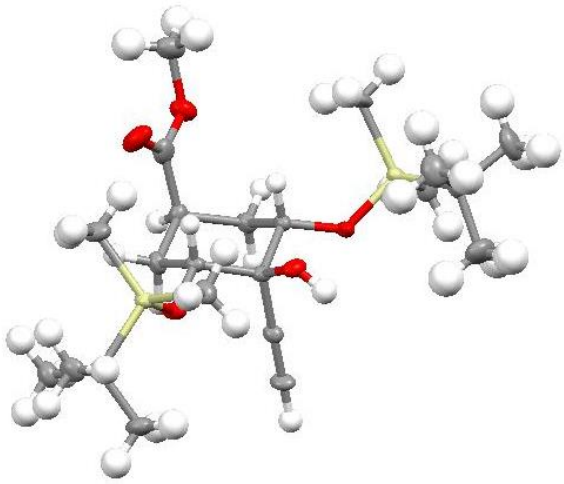


Figure 14 Crystal structure of 299 with ellipsoids drawn at the 50% probability level.

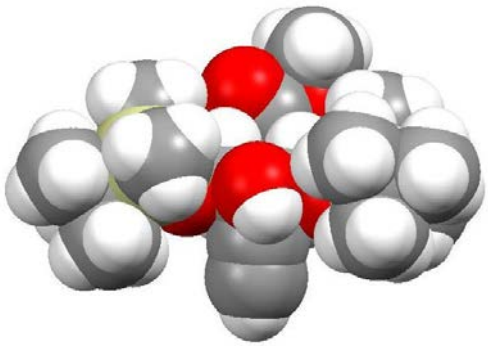
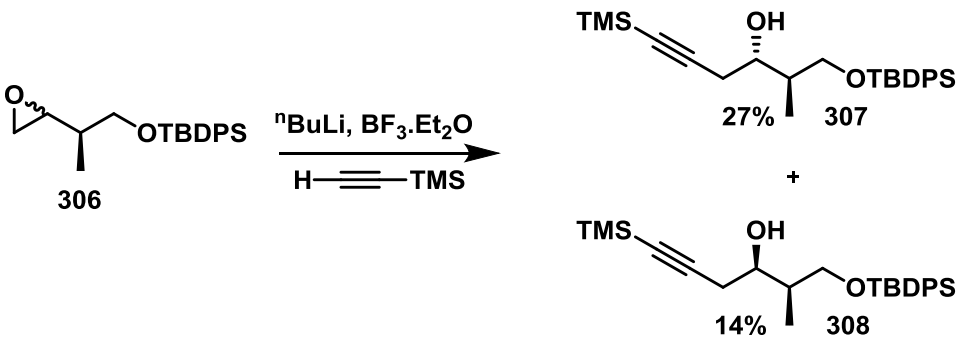


Figure 15

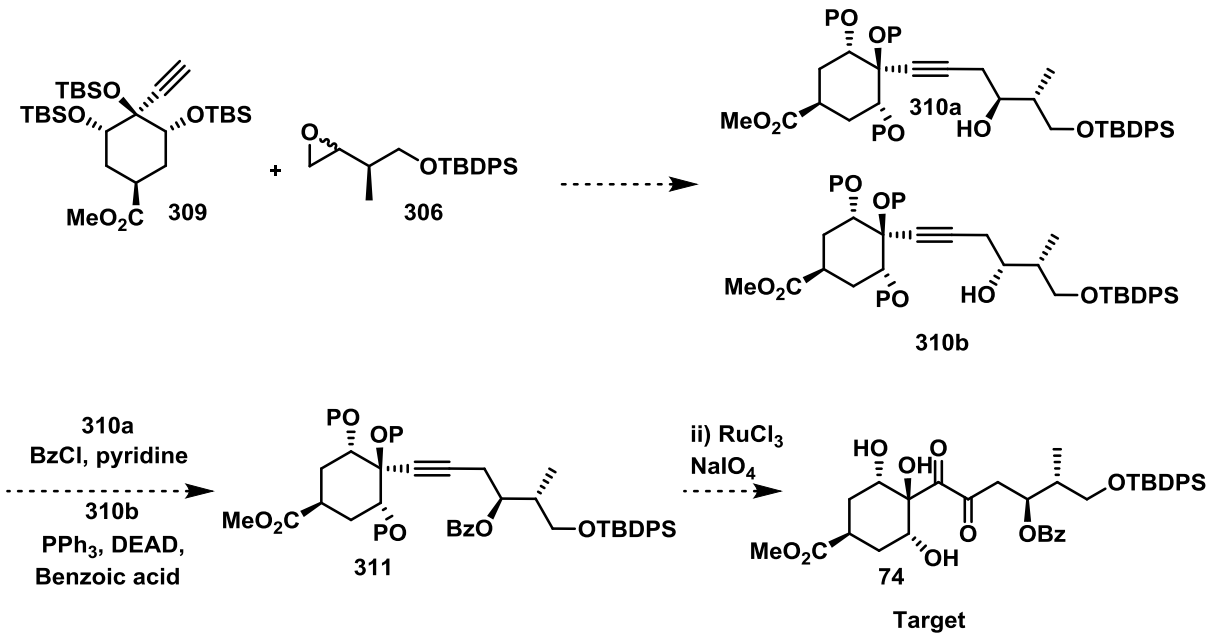
Investigations turned towards synthesising the rest of the carbon linkage in order to perform a convergent synthesis of the desired spiroacetalisation precursor. A paper by Takayama *et al.*[127] gave the synthesis of epoxide **306** as a 1:1 mixture of diastereoisomers. Also reported was the reaction of **306** with TMS acetylene to give the pair of diastereoisomers **307** and **308** that could be separated by column chromatography (Scheme 123).



Scheme 123

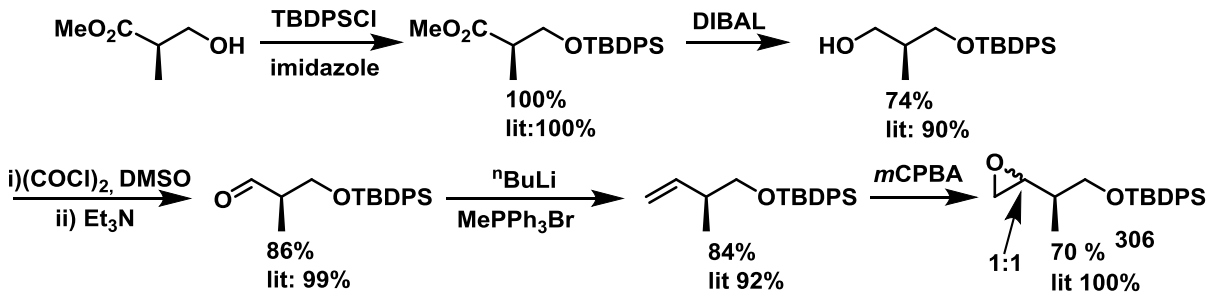
If alkyne **309** reacted with epoxide **306** there is potential to separate the diastereomers **310a**, **310b** by column chromatography. Approximately 50% of the mixture would have the desired stereochemistry for the natural product. Subsequent benzoyl protection of the resultant alcohol and oxidation of alkyne **311** would give the precursor **74** (Scheme 124). Atom efficiency can be achieved by taking the remaining 50% of the unwanted diastereomer

310b through a Mitsunobu inversion[128] which would protect the alcohol as the desired benzoyl group and convert it to the required S configuration **74**.



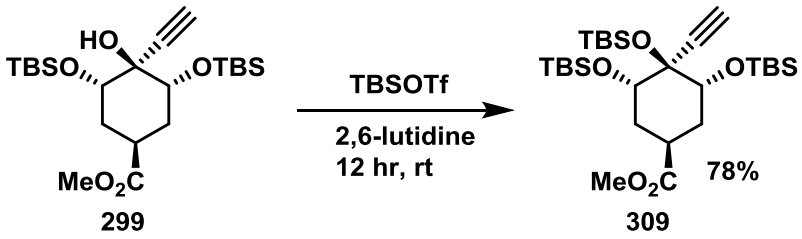
Scheme 124

Repeating the literature was straightforward and the epoxide **306** was obtained as a 1:1 ratio of diastereoisomers (Scheme 125).



Scheme 125

The literature stated that in order to perform the oxidation of propargyl alcohols to diketones, the tertiary alcohol needs to be protected (Scheme 126).



Scheme 126

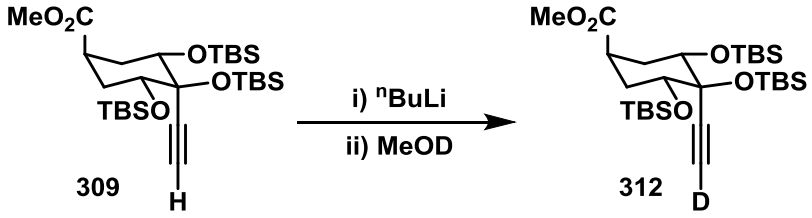
Tertiary alcohol **299** was found to be relatively unreactive when compared to the similar compound **250** and required twelve equivalents of TBSOTf and 2,6-lutidine in order to obtain a 72% yield. Obviously, this is not particularly efficient; however, it is assumed that the equivalents could be drastically reduced when scaling up the reaction, as the concentration of the reaction mixture is assumed to have an effect.

With the stereochemistry confirmed and the tertiary alcohol now protected, attention then turned to the crucial combining of fragments **309** and **306** for a convergent synthesis towards the spiroacetalisation precursor. Unfortunately, the epoxide was unable to be opened with the acetylide of **309**; a variety of different conditions were used (Table 23).

Entry	Alkyne eq.	Epoxide eq.	Base	Lewis acid	Other	Yield
1	1 eq.	1 eq.	LDA 1.1 eq.	$BF_3.Et_2O$	-	sm
2	1 eq.	1 eq.	^nBuLi 1.1 eq.	$BF_3.Et_2O$	-	sm
3	2 eq.	1 eq.	^nBuLi 2 eq.	Et_2AlCl 2 eq.	-	sm
4	1 eq.	1 eq.	^nBuLi 1 eq.	$BF_3.Et_2O$ 2 eq.	Me_3Al 1 eq.	sm
5	tertiary alcohol unprotected	1 eq.	^nBuLi 2 eq.	BF_3Et_2O 2 eq.	-	sm

Table 23

First attempts used LDA and ^{n}BuLi (entries 1 and 2); no epoxide opening was observed, and starting material was recovered. Concerns were raised that no acetylide was forming after deprotonation of the alkyne, so a test reaction was undertaken using MeOD as a quench after addition of ^{n}BuLi (Scheme 127).



Scheme 127

The reaction clearly showed that deprotonation was occurring as the ^{1}H NMR spectrum of the crude reaction mixture showed the disappearance of the signal for the proton on the terminus of the alkyne consistent with formation of **312**. With this information in hand it was obvious that the reactivity of the system needed to be increased in order to open the epoxide with **309**.

Pagenkopf *et al.*[129] showed the differences in reactivity of alanes and aluminates towards the opening of epoxides. Although the report was mainly focused on the regioselectivity of epoxide opening, it was thought that these systems should be more reactive. Unfortunately, neither the alane (entry 3) nor the aluminate (entry 4) gave the increased reactivity needed and alkyne starting material was recovered. The unprotected tertiary alcohol **299** was used with 2 equivalents of base but again only starting material was recovered from the reaction (entry 5). Finally, the epoxide **306** was opened via the known literature reaction using TMS-acetylene, giving **307** and **308** in 75% yield. Therefore, it was concluded that the alkyne on **309** was too hindered to open up the epoxide **306** due to the presence of the large OTBS groups.

Conclusions and summary

This chapter concentrated on the use of the Meyer-Schuster rearrangement in order to obtain the desired enone functionality. First attempts at this reaction involved protecting the tertiary alcohol in **250** as an acetate, ready for subsequent gold-catalysed rearrangement. Unfortunately, the alcohol was unable to be protected as an acetate. It was concluded that the C-O bond formed in an intermediate may be too short for reaction to occur in the sterically hindered environment.

The alkyne of the propargyl alcohol **250** was activated with $Ph_3PAuNTf_2$ in the presence of either MeOH or phenylboronic acid, but this did not lead to the formation of an enone. However, alternative products were isolated: the β-hydroxyketone **273** in 24% yield, the furan **272** in a 12% yield and most interestingly, the cyclic enol boronate **274** in a 63% yield; the first synthesis of this kind of functionality by a gold-catalysed method.

The smaller silicon protecting group TES was used for the propargyl alcohol **251**. This was subjected to the same gold catalysis methods, using phenylboronic acid as an additive. These reactions turned out to be more difficult to purify and although ^{1}H NMR of the crude reaction mixture gave evidence of enone formation, only a 17% yield of furan **278** could be isolated.

The catalyst (2,3,4,5-tetrafluorophenyl)boronic acid was used as an alternative to gold. Again, this route required no protection of the tertiary alcohol. Propargyl alcohols with TBS **250** and TES **251** protection were used but no desired products were obtained. A test reaction carried out on a simple propargyl alcohol gave the expected enone in good yield.

A new approach was postulated based on the elimination of the tertiary alcohol to an allene, with subsequent reactions to yield the desired diketone functionality. This route was quickly abandoned when it became apparent that the formation of a mesylate from the alcohol could not be achieved.

A final attempt at converting the alcohol to a sulfenate, followed by a sigmatropic rearrangement, was also attempted but again the tertiary alcohol proved to be unreactive. A test reaction showed that on a simpler system propargyl alcohol **294** was converted to sulfoxide **295** with good yield.

The TBS groups flanking either side of the tertiary alcohol presented a problem in each of the routes discussed above, preventing reaction due to steric hindrance.

An alternative approach to the spiroacetalisation precursor **74** was envisaged based on a new disconnection (Scheme 118). The route towards the synthesis of aldehyde **217** was improved by increasing the yield of alkene **219** using the method developed by Gilheany *et al.* The Ohira-Bestmann reagent was then used to convert aldehyde **217** into alkyne **299**. This compound now had the required stereochemistry on the cyclohexane ring to be taken forward into a synthesis for the spiroacetalisation precursor. Epoxide **306** was successfully synthesised in good yield which set up a potential convergent synthesis towards the natural product. Unfortunately, the two compounds could not be used in a convergent synthesis. Acetylide formation was confirmed using a deuterium quench and the epoxide was opened with TMS-acetylene using a literature procedure. This confirmed that **309** and **306** were not compatible and, unfortunately, showed that this was not a viable route towards phyllaemblic acid.

Chapter 5 Studies towards the tetrahydrothiophene ring in breynolide

Introduction

Literature review of the synthesis of a tetrahydrothiophene ring

Breynolide **28** is the hydrolysis product of breynin A which was isolated in the 1970s from the Taiwanese woody shrub *Breynia officinalis* (Figure 16).[16] It has potent oral hypocholesterolemic activity.[27]

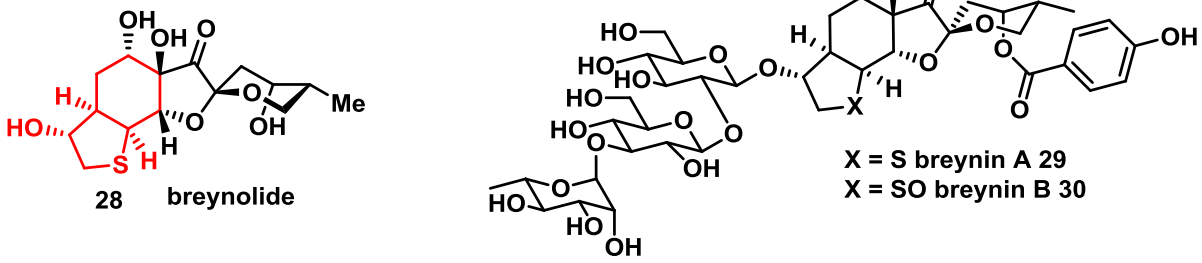
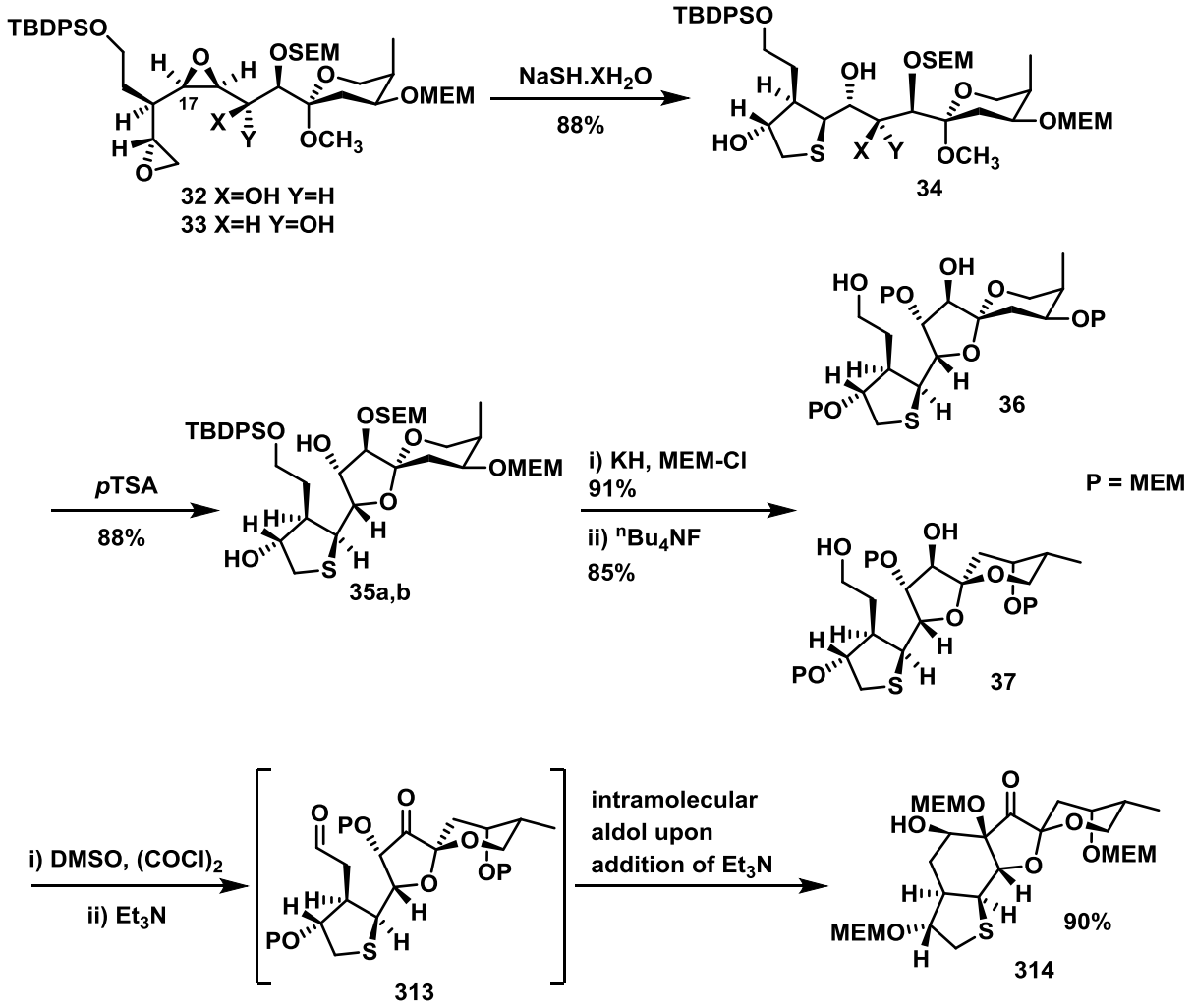


Figure 16

As described in chapter one, there have been three total syntheses of breynolide and one of breynolide sulfone; all of which have employed various approaches at synthesising the perhydrobenzothiophene ring system highlighted in red (Figure 16**)**.

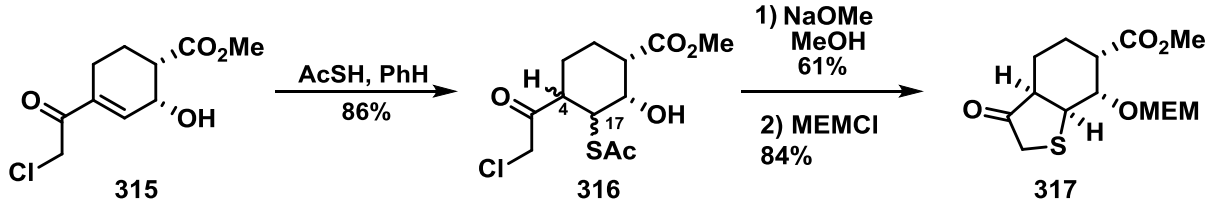
The first total synthesis of breynolide was reported by Williams *et* al.[17] The three heterocyclic rings were formed from the precursors **32** and **33**. Attack by sodium hydrogen sulfide on the terminal epoxide was followed by an intramolecular S_N2 at C_{17} to form the sulfur heterocycle in **34**. Treatment of this compound with *p*-toluenesulfonic acid led to a kinetic acetalisation to give an 88% yield of the diastereoisomers **36** and **37** in a 1:3 ratio. Each of the spiroacetals were then independently taken through a five-step sequence to make breynolide. After protection with MEMCl, a Swern oxidation gave **313.** This was then followed by an intramolecular aldol to form the carbocyclic framework for breynolide. A Mitsunobu inversion to the newly formed secondary alcohol in **314** gave the perhydro

benzothiophene ring system with the correct stereocentres needed for the total synthesis to be completed (Scheme 128).



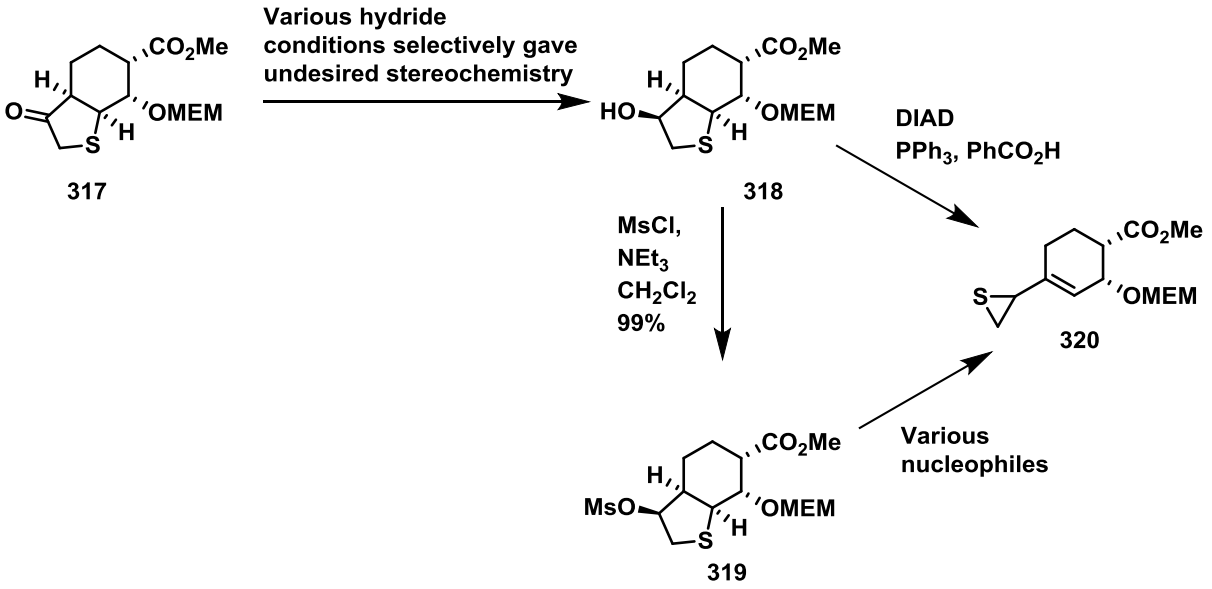
Scheme 128

In the Smith *et al*.[14] synthesis of breynolide, the perhydrobenzothiophene ring formation was initiated by a 1,4-addition of thiolacetic acid to **315** to give **316** in 86% yield as a mixture of epimers at C_4 and C_{17}. Fortunately, the desired product had formed as the major isomer due to attack *anti* to the hydroxyl group. The sulfur heterocycle was then completed after cyclisation induced by NaOMe to give **317** (Scheme 129).



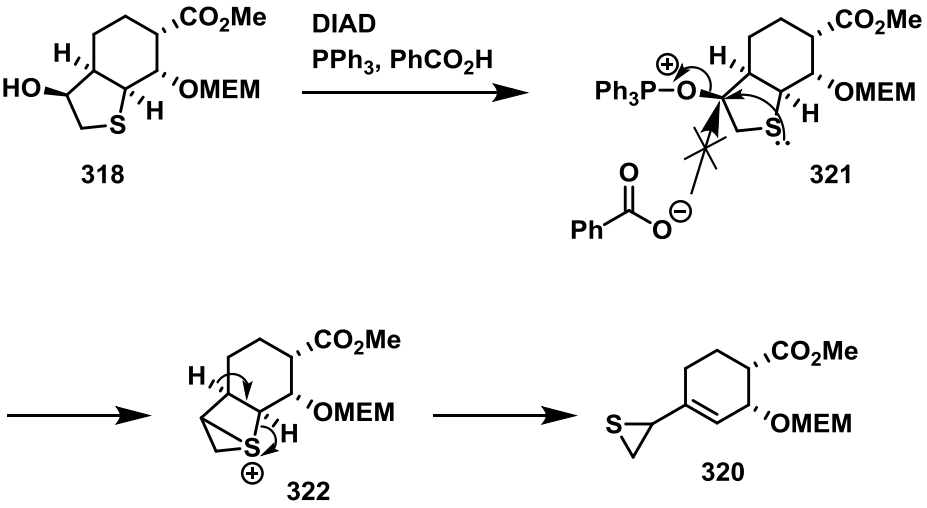
Scheme 129

The main problem with the Smith synthesis arose when attempting to reduce the ketone in **317**. Due to the convex character of **317**, hydride reduction was expected to give the undesired isomer from attack at the more accessible convex face. However, after X-ray analysis of **317**, it was believed that the desired epimer should also be accessible. In total, 14 different hydride sources/conditions were investigated but all gave undesired isomer **318** as the major product. The obvious solution was an inversion; attempts at either Mitsunobu inversion or formation of mesylate **319**, followed by intermolecular addition of various oxygen nucleophiles, resulted in the vinylic episulfide **320** (Scheme 130).



Scheme 130

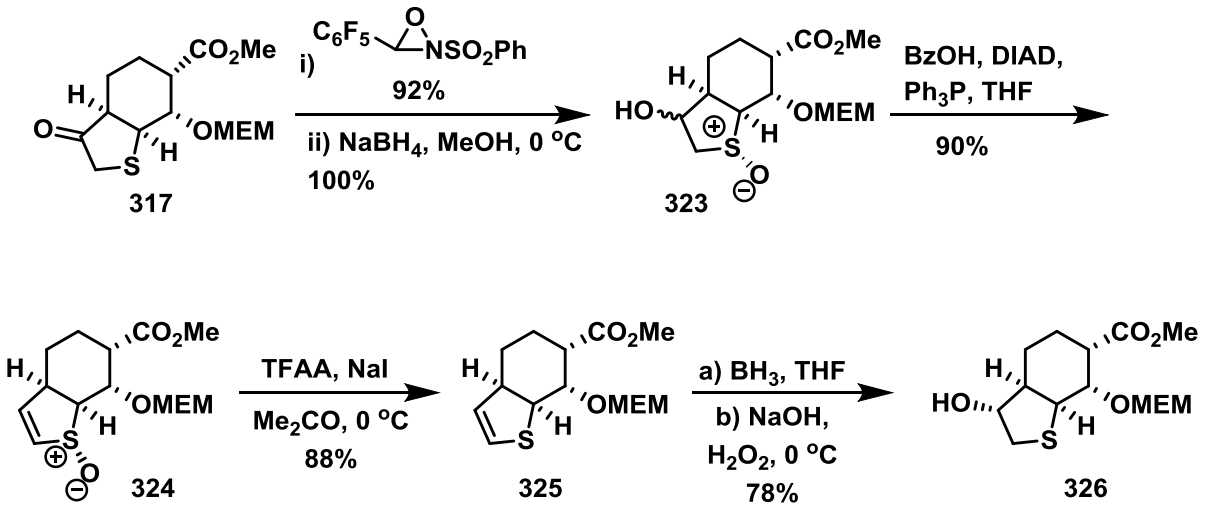
Formation of the episulfide **320** was ascribed to intramolecular alkylation of the sulfur to give **321**, followed by fragmentation of the resultant sulfonium ion **322** (Scheme 131).



Scheme 131

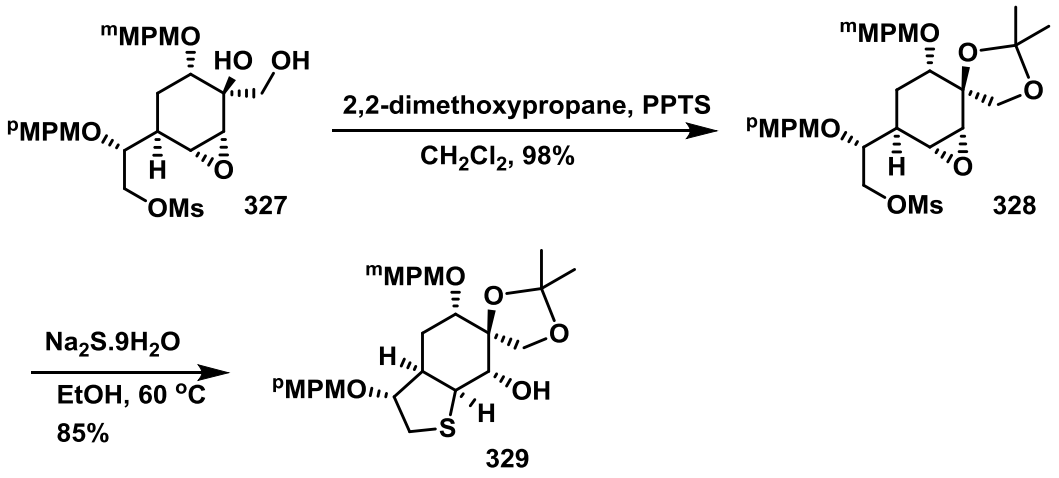
Eventually, this problem was overcome by oxidising the sulfur in **317** to a sulfoxide in order to reduce the nuleophilicity of the sulfur atom. Oxidation to the sulfoxide by the Davis phenyl oxaziridine, followed by reduction with $NaBH_4$ gave **323**, again with the major product being the undesired isomer. Attempted inversion of the alcohol via Mitsunobu

yielded the unexpected but still useful vinyl sulfoxide **324**. Following reduction to yield **325**, the desired alcohol **326** was obtained after hydroboration (Scheme 132).



Scheme 132

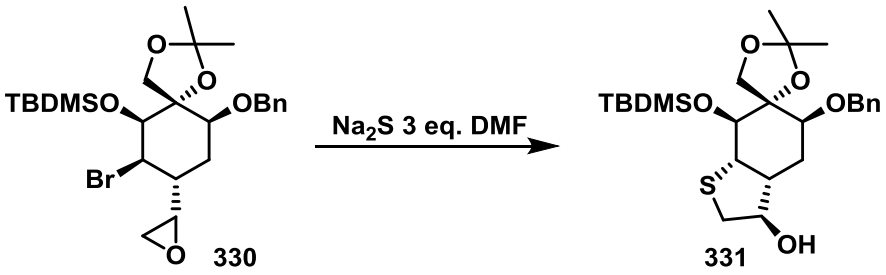
The most recent total synthesis of breynolide was completed by Burke *et al.*[19] in 1999 (Scheme 133). The perhydrobenzothiophene ring formation was based on a related tetrahydrothiophene construction by Whitney *et al.*[130]



Scheme 133

Diol **327** was initially protected as an acetonide, followed by displacement of the primary mesylate **328** with sodium sulfide. This then underwent *in situ* intramolecular attack to open the epoxide, forming the *cis*-fused tetrahydrothiophene ring system in **329**.

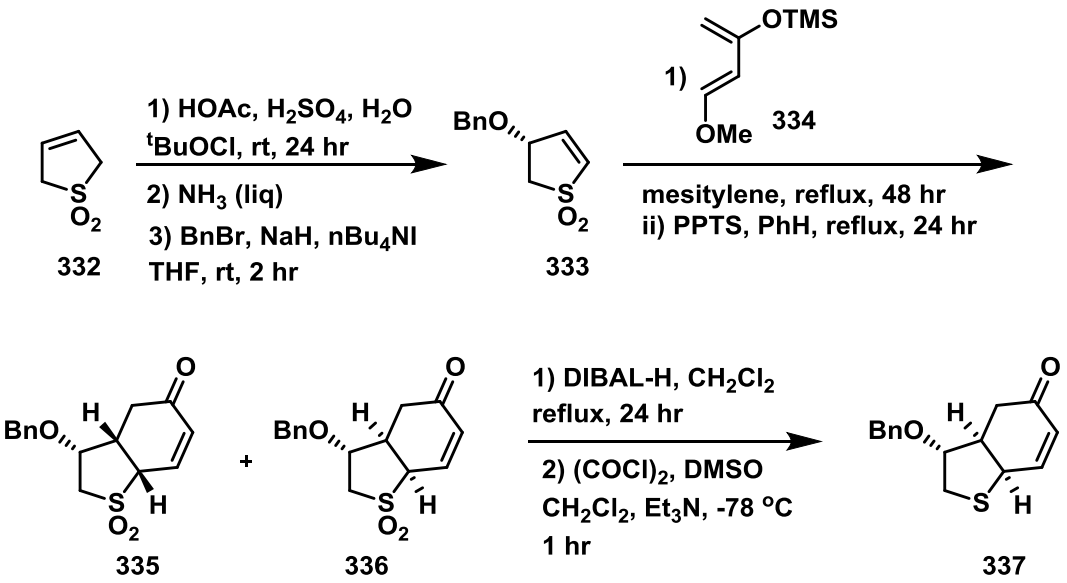
In 1989 Yamamura *et al.*[20] reported the first successful synthesis of breynolide sulfone. The group were attempting the first synthesis of breynolide but ran into problems in the later stages. However, they successfully synthesised the perhydrobenzothiophene ring (Scheme 134).



Scheme 134

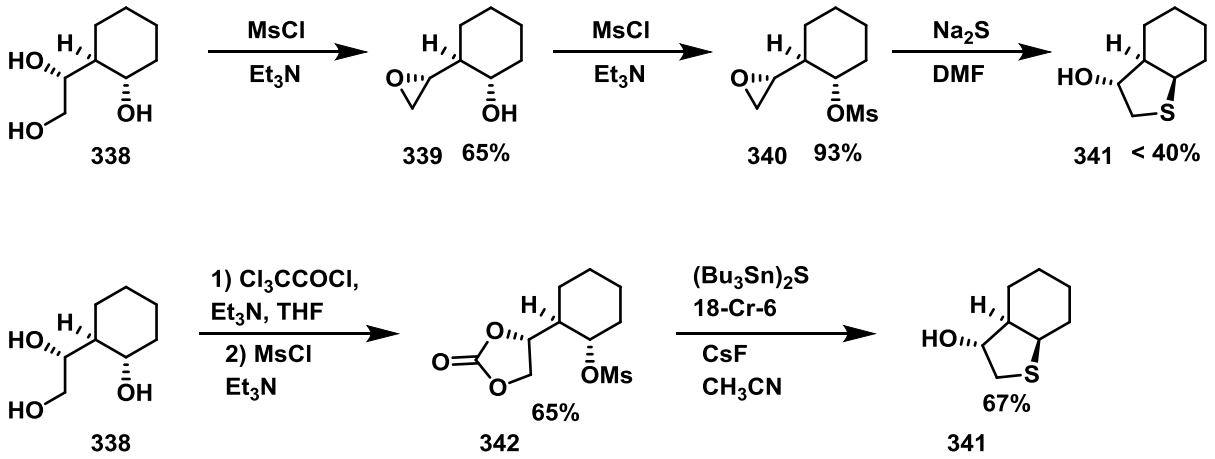
Opening of epoxide **330** with Na_2S, followed by intramolecular displacement of the bromide, formed the heterocyclic ring system **331**.

Martin *et al.*[131] published their novel approach to breynolide in 1993. The group successfully synthesised a perhydrobenzothiophene in six steps starting with the commercially available sulfolene **332**. This was transformed into a chlorohydrin followed by elimination and protection with benzyl bromide to give **333**. The Diels-Alder reaction with Danishefsky's diene[132] **334** was then carried out in a sealed tube with dienophile **333**. The crude material was treated with pyridinium *p*-toluenesulfonate which resulted in the silyl enol ether hydrolysis, with concomitant loss of methanol, affording a mixture of cycloadducts **335** and **336** in a 1:1.2 ratio. Reduction of the sulfone in the desired isomer using DIBAL, followed by subsequent oxidation to give the ketone, yielded the enone **337** ready for further elaboration (Scheme 135).



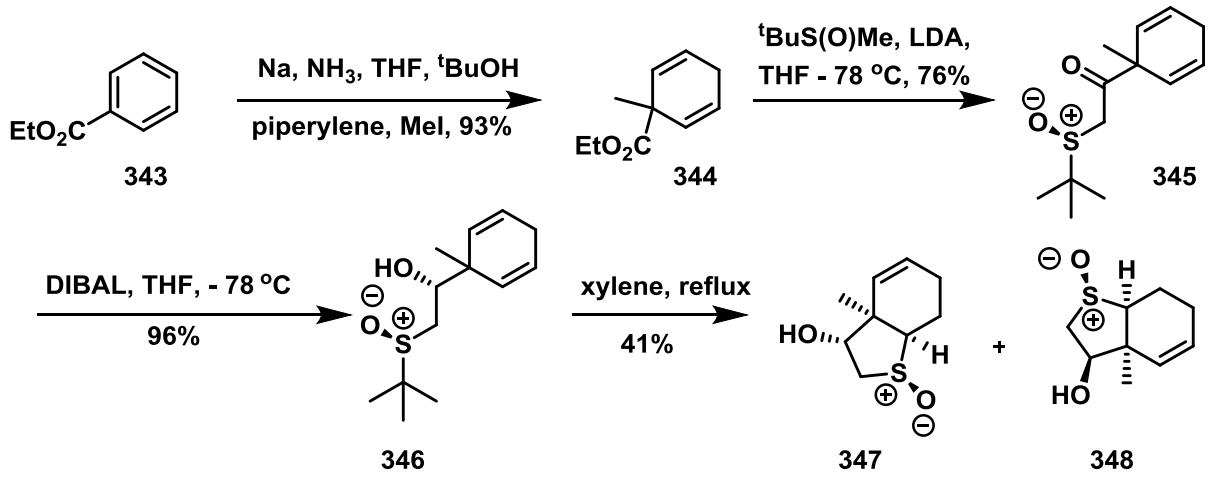
Scheme 135

Linderman *et al.*[133] published a synthesis in 1994 of the perbenzothiophene ring system in their approach towards breynolide. Initial attempts focused on a model study to confirm the validity of the approach. Formation of the epoxide **339**, from commercially available triol **338**, was followed by conversion of the alcohol to the mesylate **340**. Addition of Na_2S resulted in the formation of the tetrahydrothiophene **341** in modest yield. The yield of **341** was improved by formation of a carbonate **342**. This was advantageous as the carbonate could potentially be taken through as a protecting group in a synthesis towards breynolide, whereas the epoxide **340** could not. The carbonate was treated with Na_2S which led to a good yield of a tetrahydrofuran, rather than the tetrahydrothiophene **341**. It was proposed that this is due to the hydroxide present in Na_2S which competes at either the carbonate carbonyl or primary carbon of the cyclic carbonate. This is then followed by intramolecular displacement of the mesylate by the primary alcohol. To overcome this, the group used Harpp's reagent $(Bu_3Sn)_2S$ which gave the tetrahydrothiophene **341** in a reasonable 67% yield (Scheme 136).



Scheme 136

Grainger *et al*[134] successfully synthesised a *cis*-fused perhydrobenzothiophene in five steps starting from ethyl benzoate **343**. Birch reduction, followed by quenching with methyl iodide, gave the 1,4-diene **344** in good yield. The ester was reacted with ^{t}butyl methyl sulfoxide to give the β-keto-sulfoxide **345**. A stereoselective reduction gave the alcohol **346** as a single diastereoisomer. This was then subjected to the thermolysis conditions first proposed by Jones *et al.*[135] to give **347** and **348**. The group found that protecting the alcohol in **346** with different sized groups could affect the product yield and ratio significantly. In essence, the overall process generates a perhydrobenzothiophene with four contiguous stereocentres starting from a simple sulfoxide starting material (Scheme 137).

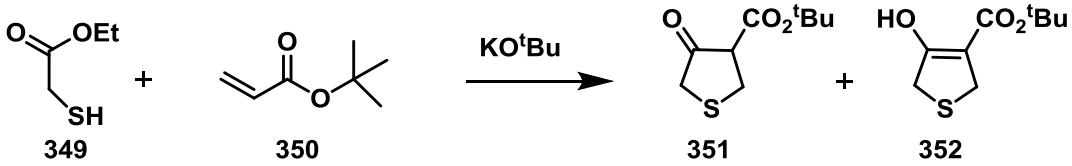


Scheme 137

Synthesis of 5-membered sulfur heterocycles through thiol conjugate addition and subsequent Dieckmann/ intramolecular aldol.

The envisaged approach to the tetrahydrothiophene using the bicyclic ketone **79** will utilise a conjugate addition of a thiolate followed by a subsequent Dieckmann cyclisation/ intramolecular aldol.

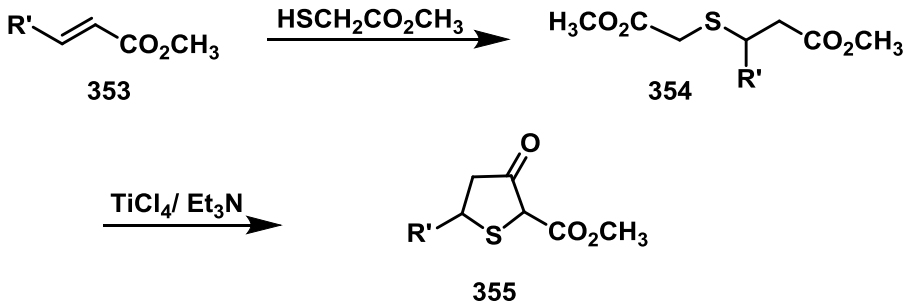
Davies *et al*.[136] used a thiolate to perform a conjugate addition on ^{t}butyl acrylate which then underwent an *in situ* dieckmann cyclisation to form the tautomers **351** and **352** in a 46:54 ratio with an overall yield of 81% (Scheme 138).



349 **350** **351** **352**

Scheme 138

Lin *et al.*[137] performed a conjugate addition on **353** with methyl thioglycolate using catalytic amounts of piperidine to give **354** in almost quantitative yield. Cyclisation was then initiated with $TiCl_4$ and triethylamine in CH_2Cl_2 to obtain the sulfur heterocycle **355** in approximately 60% yield (Scheme 139).

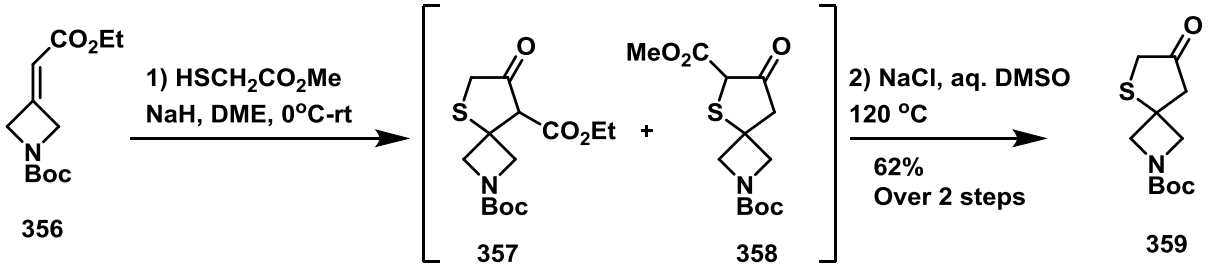


353 **354** **355**

Scheme 139

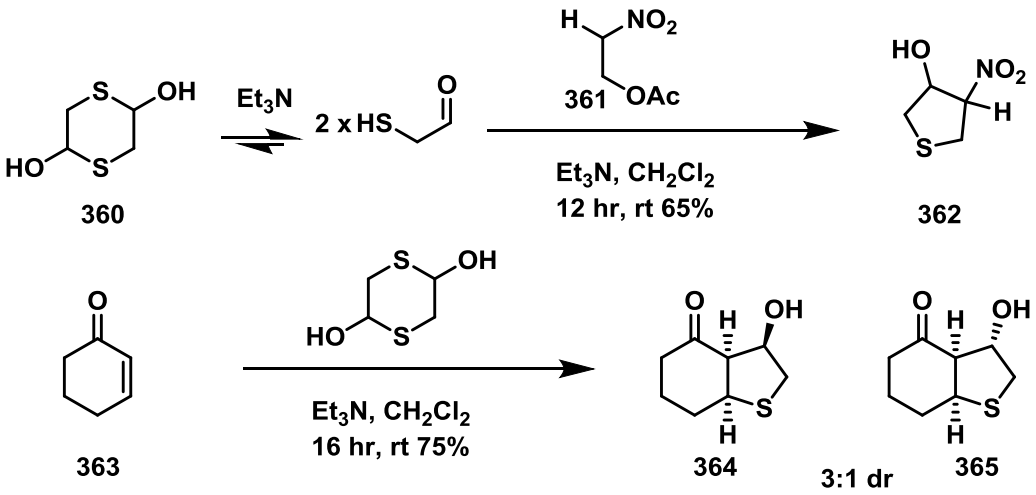
Carreira *et al.*[138] guided by the work from Liu *et al.*[139, 140] and Woodward *et al.*[140] performed a one pot method to form the two ketoesters **357** and **358** after a conjugate addition to **356**. These were then directly subjected to Krapcho decarboxylation to yield the sulfenyl ketone

359 in a 62% yield. This method again utilises a conjugate addition which is followed by an *in situ* Dieckmann cyclisation (Scheme 140).



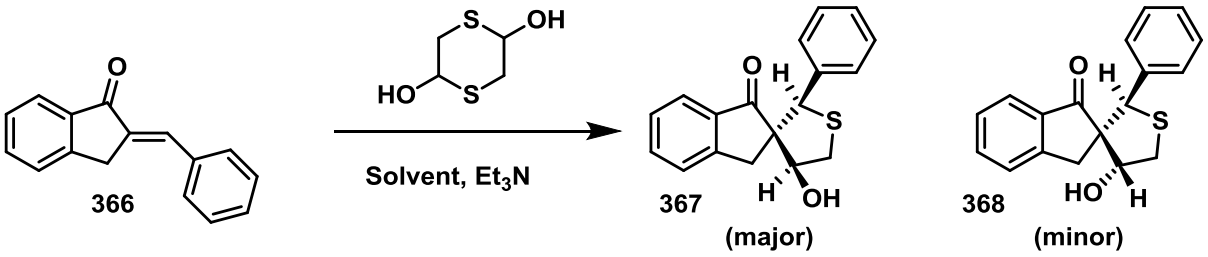
Scheme 140

Risi *et al*.[141] used the commercially available 1,4-dithiane-2,5-diol **360** as the thiolate source in a one-pot tandem reaction to make substituted tetrahydrothiophene derivatives. Based on the work from Southern *et al*.[142] the group first used this dimer with a nitroethylacetate **361** to form the hetrocycle **362** in a 65% yield. Several nitro derivatives were formed this way. The group then used the methodology as a route towards hexahydro-benzothiophene-4-one, which is a scaffold towards several natural products. A suspension of 1,4-dithiane-2,5-diol in CH_2Cl_2 with Et_3N led to the conjugate addition to **363** which then cyclised to form **364** and **365** in a 3:1 ratio (Scheme 141). Tao *et al*.[143] also created the same tandem Michael-intramolecular Henry products seen in the previous paper by using 1,4-dithiane-2,5-diol in the presence of a tertiary amine catalyst.



Scheme 141

Perumal *et al*.[144] recognised the solubility problems of 1,4-dithiane-2,5-diol and so screened a variety of solvents when performing a conjugate addition to an αβ-unsaturated ketone **366** to give the diastereomers **367** and **368**. The group found that water was the optimal solvent, furnishing the product in the highest yield (Scheme 142,Table 24). A related example can be found by Xu *et al*. [145]

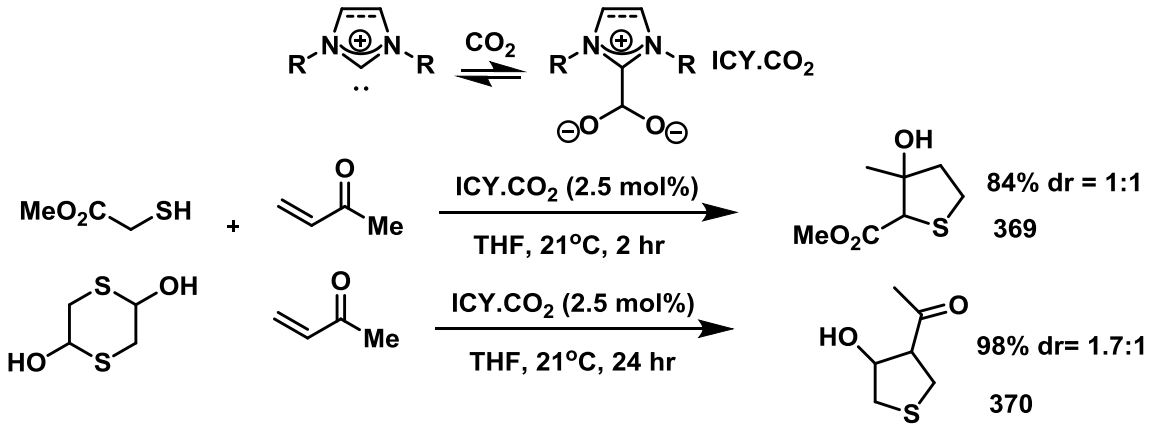


Scheme 142

Entry	Base	Solvent	Time hr	dr	Yield%
1	Et_3N	water	3	84:16	80
2	Et_3N	CH_3CN	3	81:19	63
3	Et_3N	CH_2Cl_2	5	83:17	69
4	Et_3N	MeOH	5	79:21	77
5	Et_3N	EtOH	5	80:20	79
6	Et_3N	DMF	3	78:22	72

Table 24

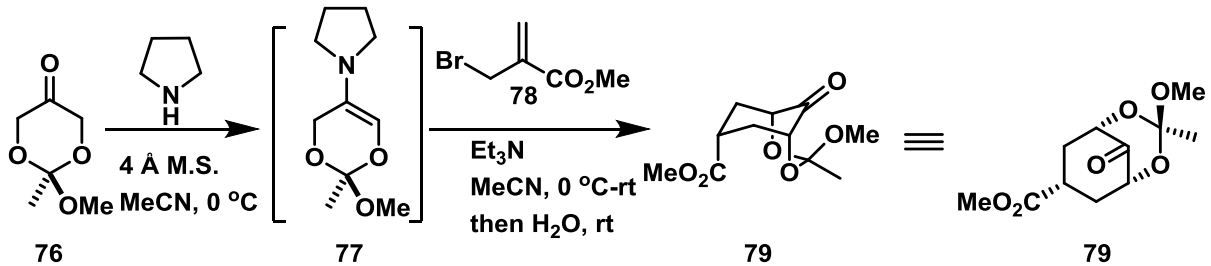
Delaude, Rodriguez and Coquerel *et al*.[146] used a NHC.CO_2 precatalyst in a Michael addition to form tetrahydrothiophenes **369** and **370**. The catalyst was able to be used with both methyl thioglycolate and 1,4-dithiane-2,5-diol. A yield of 98% was reported for the formation of tetrahydrothiophene **370** which is the best reported yield for the conjugate addition and cyclisation using the dimer. It was also noted that no solubility problems were discussed (Scheme 143).



Scheme 143

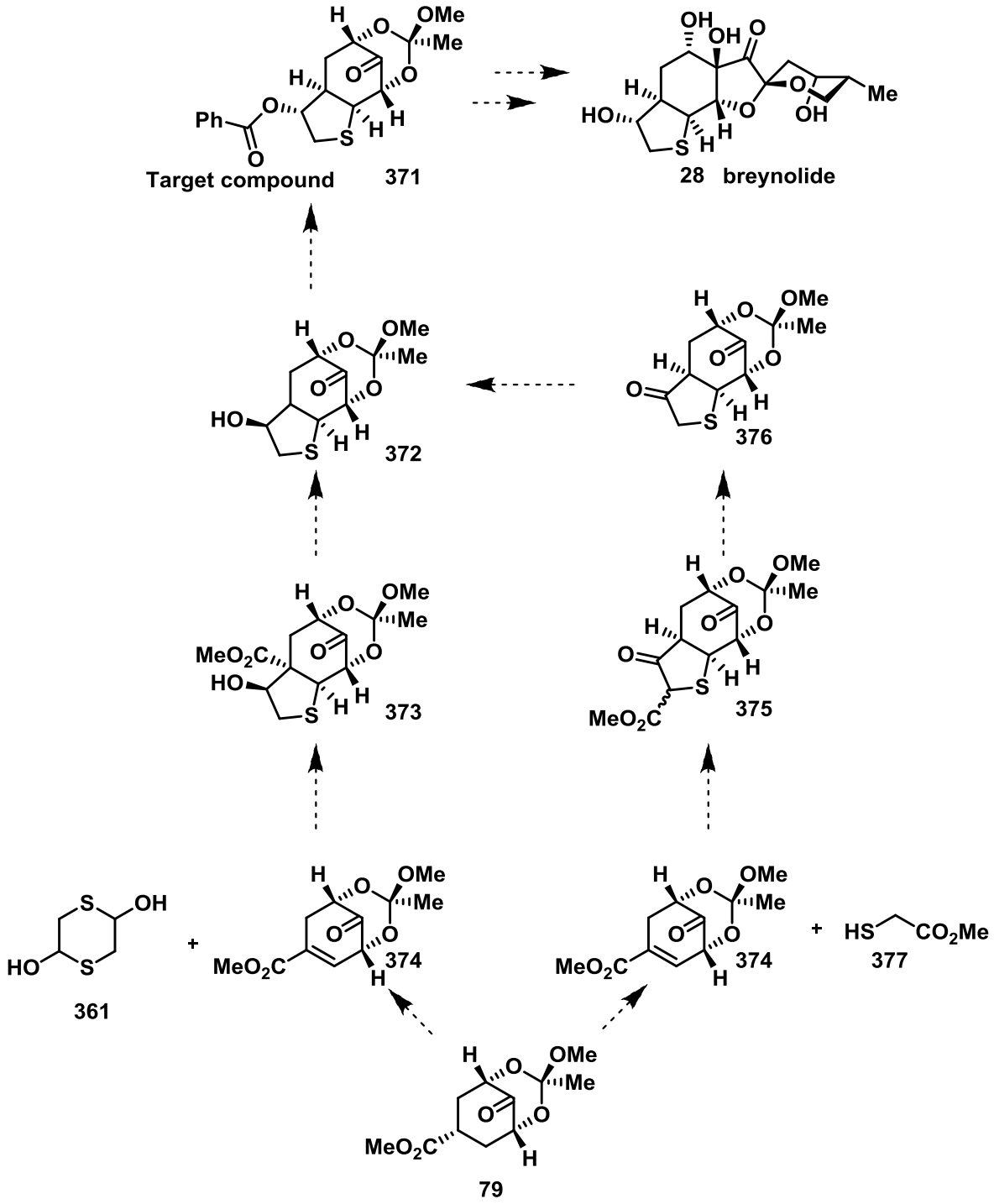
Aims and Objectives

As shown previously in the Grainger group approach to phyllaemblic acid, the bicyclic system **79** can be obtained through α,α'-annulation of 1-3 dioxanones (Scheme 144).[26]



Scheme 144

It was envisaged that the bicyclic system **79** could be used in investigations towards the formation of the perhydrobenzothiophene ring found in breynolide (Scheme 145).



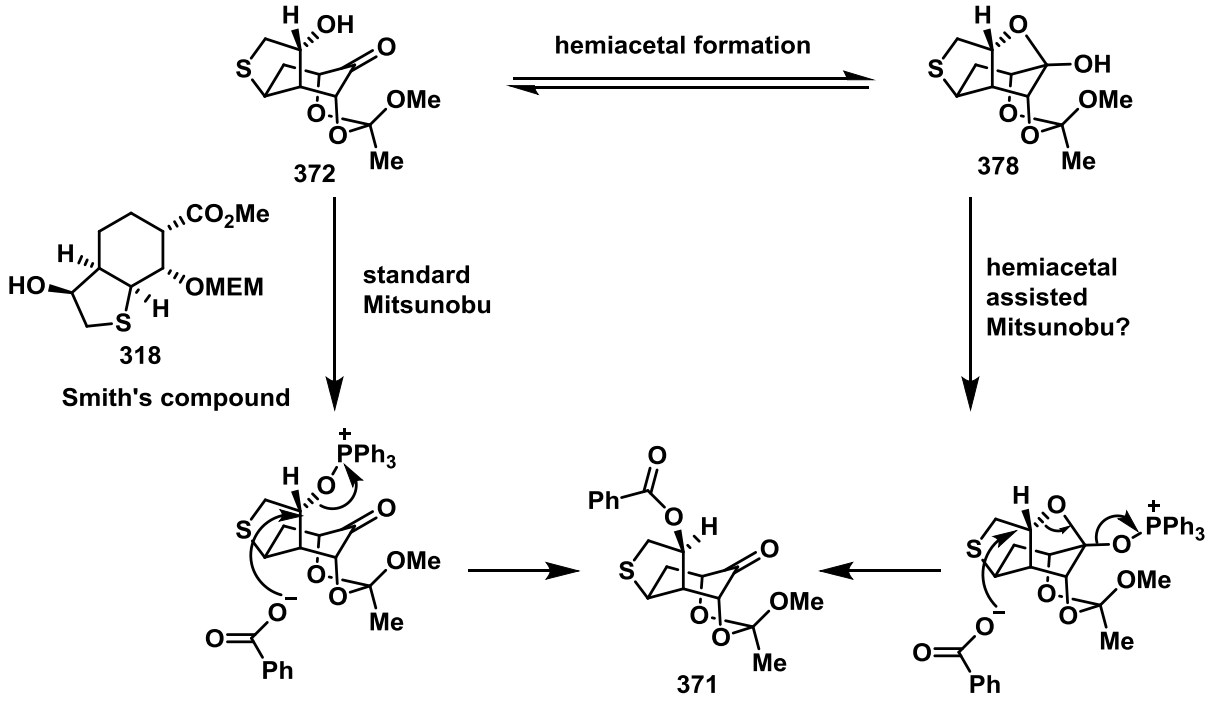
Scheme 145

It was proposed that reacting bicyclic ketone **79** with LDA would form an enolate, which could then be quenched with PhSeBr. Oxidising the selenium would initiate selenoxide elimination and formation of the α,β-unsaturated ester **374**. From this point two approaches are possible. Conjugate addition of methyl thioglycolate **377** would lead to a system that

could undergo a Dieckmann cyclisation **375.** The proposed Dieckmann cyclisation approach should yield only one possible product, based on the rationale that only one pathway yields an acidic proton needed to drive the reaction to completion.

Subsequent Krapcho decarboxylation is required to yield the carbonyl **376**. Reduction would then furnish the alcohol **372** ready for Mitsunobu inversion. An alternative route towards alcohol **372** would require the conjugate addition of 1,4-dithiane-2,5-diol **361** which would lead to an *in situ* intramolecular aldol to yield **373**. Reduction of the ester in **373**, followed by a Barton McCombie decarboxylation, would yield the alcohol **372** that then requires Mitsunobu inversion.

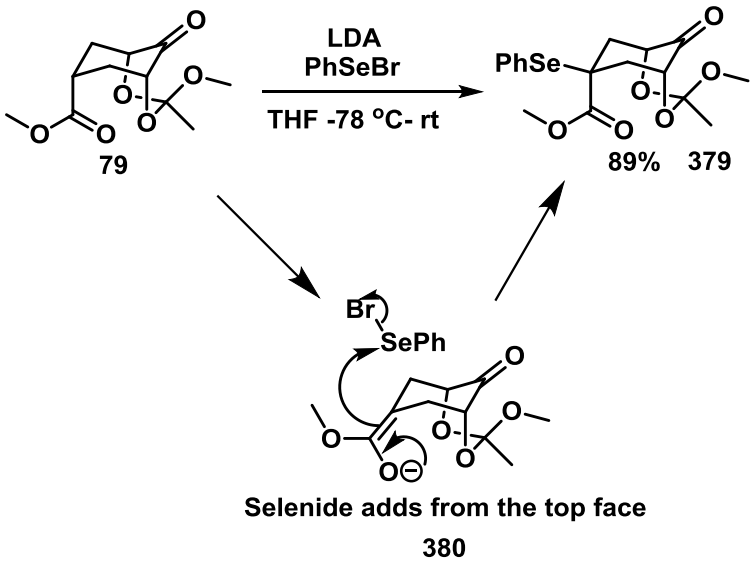
The final proposed step required to invert the stereochemistry of the alcohol **372** to **371** was proven to be problematic in Smith's related system **320 (**Scheme 130). However, the rigidity of the ring in **372** could facilitate the Mitsunobu inversion due to the alcohol residing close to the carbonyl **378** which may allow a different mechanistic pathway (Scheme 146).



Scheme 146

Results and discussion

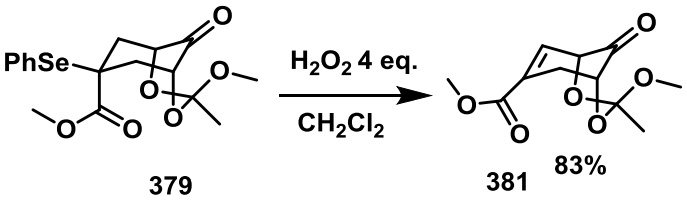
The α,β-unsaturated ester was achieved by first forming the selenide **379** this was able to be synthesised in good yield (Scheme 147).



Scheme 147

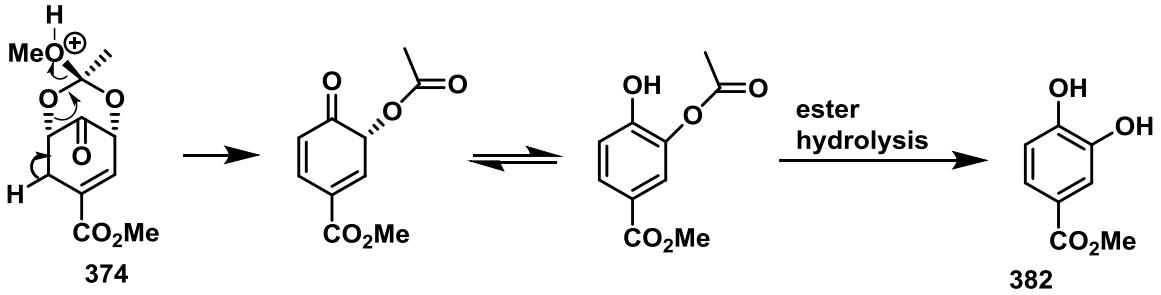
The selenide addition to **79** proceeded with complete stereocontrol through addition to the top face of the enolate **380**. This is expected as the same scenario is seen in the annulation reaction when a kinetic protonation of the enolate forms the bicyclic ketone **79** (Scheme 14).

Problems with the route started to materialise when investigating the oxidation of the selenide to form the α,β-unsaturated ester **381** (Scheme 148).[147]



Scheme 148

Yields were found to be highly variable when undertaking selenoxide elimination. It was found that the α,β-unsaturated ester **374** underwent a fragmentation followed by aromatisation to form the catechol **382** (Scheme 149).

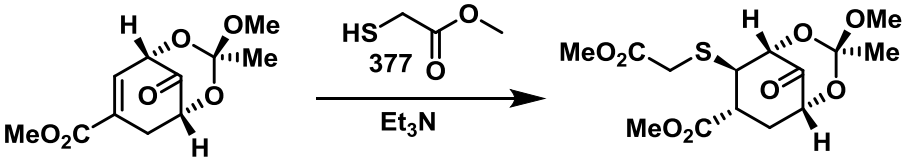


Scheme 149

By-product **382** formed during every oxidation undertaken. It was found that keeping the reaction at 0 ^{o}C and not running the reaction to completion generally suppressed its formation but it could not be completely eradicated. Changing the equivalents of H_2O_2 only slowed formation of the desired product **381**. It was concluded that enoate **381** was a very unstable molecule and decomposed easily. It was also found that during flash chromatography catechol **382** would form on the column; therefore, flash chromatography

had to be completed as quickly as possible. On this basis it is assumed that the formation of **382** is an acid-catalysed process; although, it was later found that the alkene **381** would also decompose to **382** in a variety of different solvents. Formation of the catechol by-product on the column was easily identifiable as it would turn the column orange/brown.[148]

Once a method was established to form **381** the conjugate addition of methyl thioglycolate was investigated (Table 25).



374 **81%** **383**

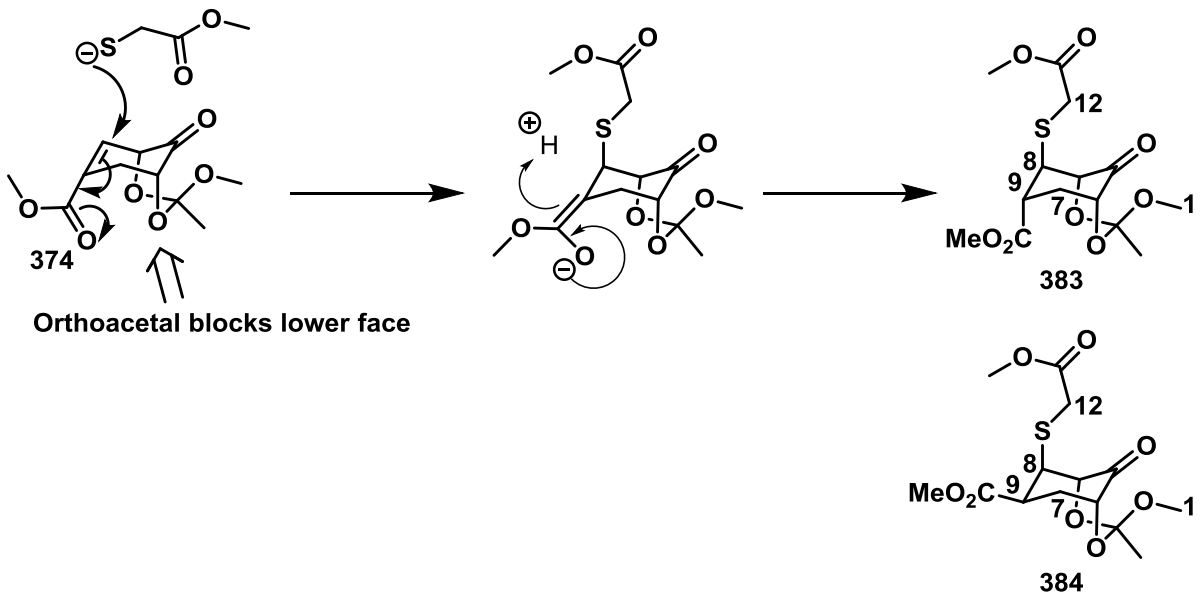
Entry	Alkene eq.	Thioglycolate eq.	Base	Solvent	Yield
1	1	1.2	NaH 1.2	DME	degradation
2	1	1	DBU 2.5	MeCN	9% of catechol **382**
3	1	1	TBAF 10 mol%	THF	degradation
4	1	1	TBAF 10 mol%	CH_2Cl_2	6% catechol **382** 21% **383**
5	1	1	Et_3N 1 eq.	CH_2Cl_2	44% **383**
6	1	5	Et_3N 5 eq.	CH_2Cl_2	81% **383**

Table 25

The first attempt (entry 1) at conjugate addition was followed by an *in situ* Dieckmann cyclisation inspired by Carreira *et al.*[138] Unfortunately, this resulted in complete degradation of starting material. Entries 2-3 also resulted in large amounts of degradation with small amounts of catechol **382** being isolated. It was noted that ^{1}H NMR of the crude reaction mixture often gave multiple resonances in the spectrum; it was suspected that the starting

material was unstable in the solvents used. Using CH_2Cl_2 led to the isolation of **383**, albeit in 21% yield (entry 4).[149] Et_3N was used in conjunction with methyl thioglycolate and gave the product in a 44% yield (entry 5). Using an excess of both reagents led to the successful synthesis of the conjugate addition product **383** in an 81% yield (entry 6).

With the conjugate addition achieved, the stereoselectivity and configuration needed to be assigned before the Dieckmann cyclisation could be undertaken. It was assumed that the methyl thioglycolate **377** would add to the top face of **374** due to approach to the bottom face being blocked by the orthoester (Scheme 150).



Scheme 150

In order to confirm the structure as either **383** or **384** the configuration of the ester needed to be determined. This was difficult to assign as proton 9 overlapped with the protons at position 1 and 12 on the ^1H NMR. The axial and equatorial protons at 7 were also not fully resolved and so it was difficult to unambiguously assign the stereochemistry of the ester at position 9 using coupling constants (Scheme 150). A crystal structure of **383** gave conclusive

evidence that the ester was in an axial position, thiol addition had indeed taken place on the top face of **374** with subsequent protonation also occurring at the top face (Figure 17).

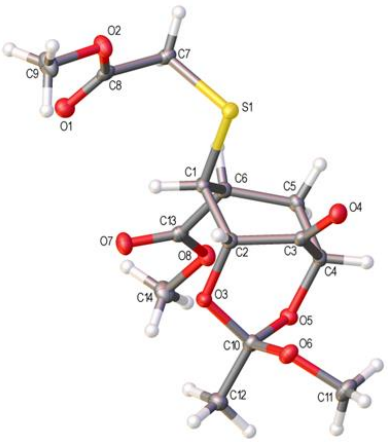
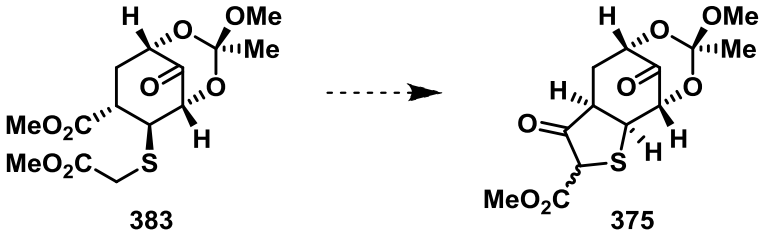


Figure 17 Crystal structure of 383 with ellipsoids drawn at the 50% probability level.

Investigations then proceeded to the Dieckmann cyclisation as although the stereochemistry of the ester was incorrect epimerisation can occur in the presence of a base (Scheme 151) (Table 26).



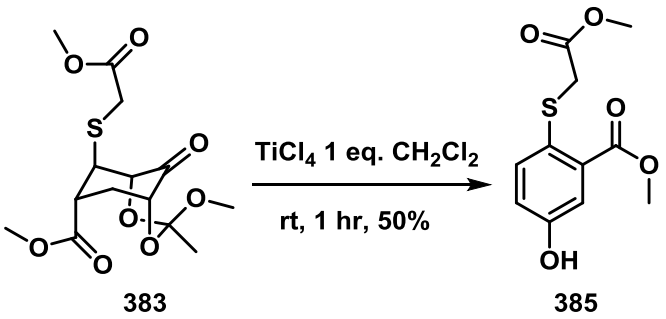
Scheme 151

Entry	Bicyclic ketone 299 mmol	Base/ Lewis acid	Solvent	Time	Temp	Yield
1	0.14	^{t}BuOK 2.2 eq.	toluene	1 hr	rt	trace of alkene **374**
2	0.14	DBU 1 eq.	toluene	1 hr	rt	32% epimerisation **384**
3	0.14	DBU 1 eq.	toluene	3 hr	60 ^{o}C	32% alkene **374** 63% catechol **382**
4	0.14	NaOMe 1 eq.	MeOH	2 hr	rt	trace of alkene **374**
5	0.14	LDA 1.1 eq.	THF	1 hr	rt	trace of alkene **374**
6	0.14	NaH 1 eq.	DME	2 hr	rt	degradation
7	0.14	$TiCl_4$ 1 eq.	DCM	1 hr	rt	50% of **385**

Table 26

Dieckmann cyclisation product **375** could not be isolated after various conditions were attempted. It was assumed that equilibrating conditions would be ideal in order to form the product. The first attempt used ^{t}BuOK; however, only trace amounts of alkene **374** were isolated indicating that the thioglycolate had been eliminated (Entry 1).[150] Entry 2 showed that DBU promoted epimerisation of the ester at rt; however, only a 32% yield of **384** was obtained along with large amounts of degradation.[151] Increasing the temperature to try and initiate a Dieckmann cyclisation only led to elimination and the catechol by-product **382** was again observed (Entry 3).

Stronger bases were used so the protons adjacent to the sulfide would deprotonate and allow a Dieckmann cyclisation to take place (Entries 4 and 5). However, only trace amounts of the alkene **374** were observed with a large amount of degradation.[152] Entry 6 saw the use of Carreira's[138] method, but the use of DME as a solvent resulted in complete degradation; this is likely due to the alkene **374** forming and then degrading. It was thought that a Lewis acid may chelate between the two esters and promote a cyclisation. However, this promoted the removal of the ortho-ester and resulted in another aromatic compound **312** (Scheme 152) (Entry 7).[137]



Scheme 152

As the investigation into the different conditions used for Dieckmann cyclisation was coming to an end, the crystal structure of **383** was obtained. This clearly showed that the sulfide and the ester were not in a configuration suitable for cyclisation to occur. However, the investigation did show that the compound **383** was not compatible with an epimerisation.

Although the position of the ester was still unknown at this point in time, entries 2 and 3 give a clear indication as to what is going on in solution. In the previous investigations of the formation of bicyclic systems **79** and **80**, the hydrogen adjacent to the ester shifts significantly up field after epimerisation (Figure 18). Once the crystal structure of **383** was obtained the ^{1}H NMR was also known. After a new compound was isolated from the DBU

reaction it became apparent that an epimerisation had occurred as the required proton resonances were present along with characteristic proton shift to 3.94 ppm. The J values were again difficult to interpret as the protons at position 7 in **384** were not fully resolved; however the proton at position 9 at 3.94 ppm did give a dt with J = 12.6 and 4.5 with the 12.6 assumed to be a diaxial coupling between 7^{ax} and 9. Based on this precedent it was concluded that an epimerisation had occurred in the presence of DBU to form **384**.

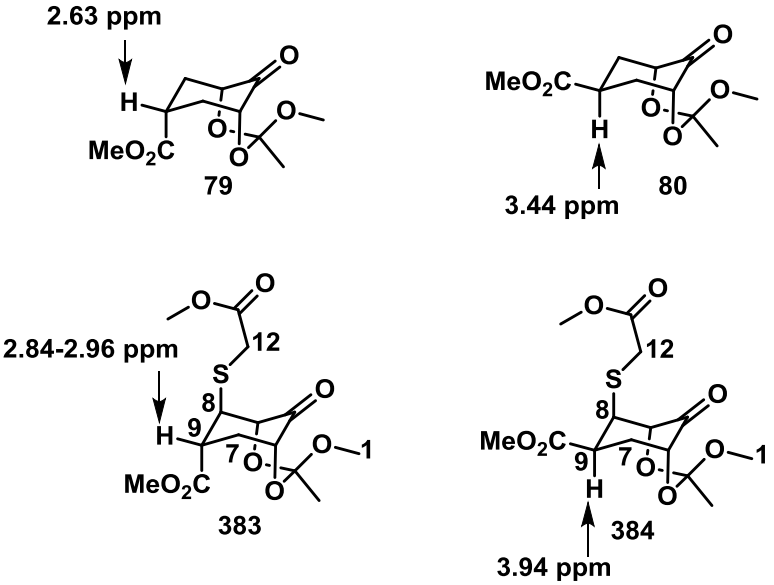
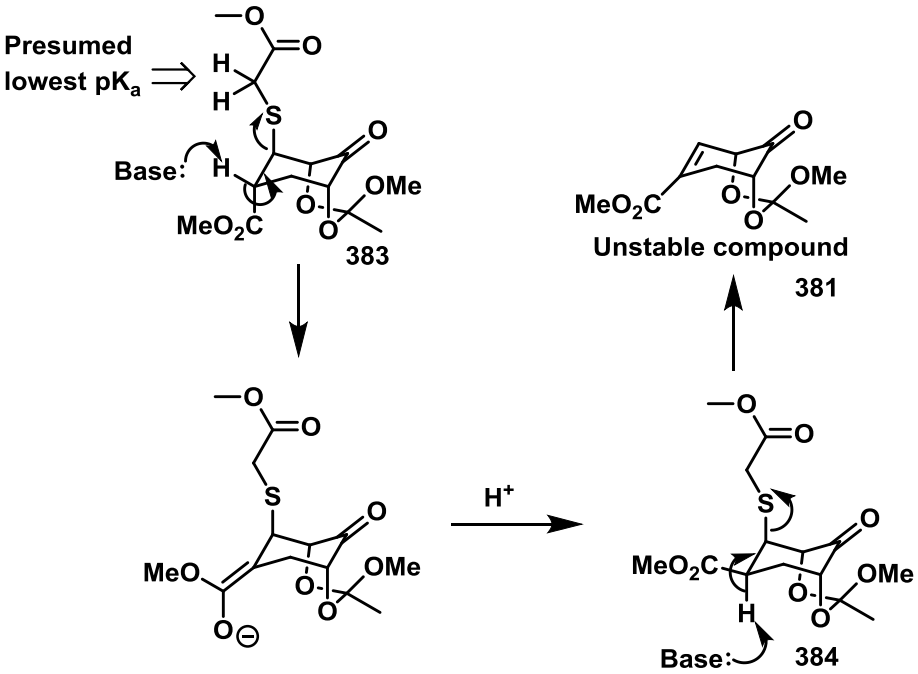


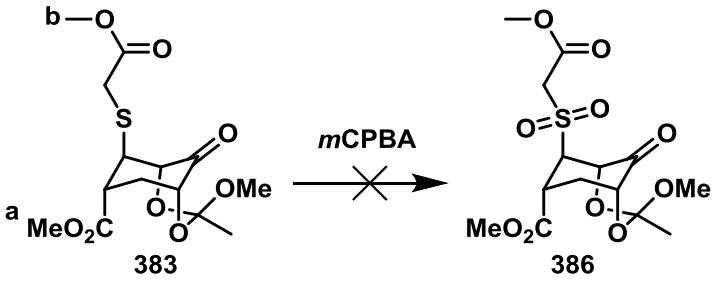
Figure 18

The data obtained suggests that the proton alpha to the ester in **383** is the most accessible. This in turn is then promoting the epimerisation which would be desirable but is then followed by an elimination. As seen in the previous work the α,β-unsaturated ester then degrades readily. The problem of elimination of a thiolate under basic conditions with the presence of a correctly orientated ester ready for Dieckmann cyclisation appears not have been reported before. The nearest example that was found was by Surveit *et al*.[153] although, it should be noted that it was a sulfone that was eliminated and there was no ester present (Scheme 153).



Scheme 153

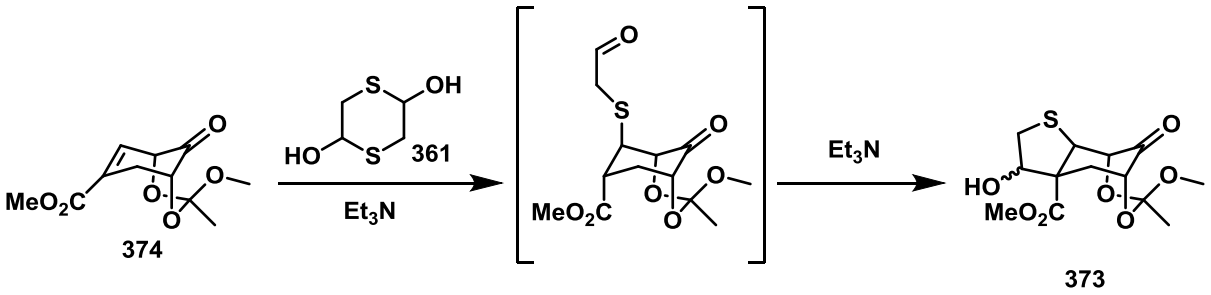
Due to the evidence of deprotonation occurring at the methyl ester[a], it was decided to oxidise the sulfur on ester[b] to increase the acidity of the hydrogens on the CH_2 adjacent to the sulfur. If this was successful then the Dieckmann cyclisation could be re-investigated using the conditions in (Table 26, Scheme 154).



Scheme 154

Unfortunately, the sulfide in **383** could not be oxidised and only degradation occurred. The reasons for this are not immediately clear. The reaction was repeated several times but no material **386** could be isolated.

In order to increase the reactivity of the system to favour cyclisation to give **373**, it was decided to use dithiane **361** in an alternative approach for conjugate addition. This, in turn, would lead to the presence of an aldehyde instead of an ester, which may lead to an *in situ* cyclisation (Scheme 155).



Scheme 155

Entry	Alkene	Dithiane	Et_3N	Temp	Solvent	Yield
1	1 eq.	0.5 eq.	0.2 eq.	rt	CH_2Cl_2	44% of **374**
2	1 eq.	0.5 eq.	0.5 eq.	rt	EtOH	degradation
3	1 eq.	2.5 eq.	10 eq.	reflux	CH_2Cl_2	34% of **374**

Table 27

As alkene **374** was unstable in a variety of different solvents, conjugate addition was, therefore, limited to using CH_2Cl_2.[141] It was found that dithiane **361** had poor solubility in CH_2Cl_2 which led to 44% of alkene being recovered (Entry 1). Entry 2 used EtOH as the solvent to dissolve the dithiane but as expected this resulted in degradation of the alkene. Entry 3 partially solubilised the dithiane and it was postulated that an increase in temperature may give the energy for conjugate addition rather than degradation. Unfortunately, again degradation occurred and 34% of alkene **374** was recovered.

Conclusions and summary

It was hoped that bicyclic ketone **79** would be an excellent building block for the perhydrobenzothiophene ring found in the natural product breynolide. The poor reactivity of the ketone in **79** was now an advantage as the bicyclic ketone was successfully converted to the organoselenide **379** in good yield. After a small investigation the organoselenide was successfully converted into the novel α,β-unsaturated ester **374** ready for conjugate addition. Unfortunately, the alkene **374** was found to be unstable in most solvents which limited the scope of reactions to only using CH_2Cl_2 as a solvent.

After the successful formation of the conjugate addition product **383**, solvent effect issues were again observed when undertaking the Dieckmann cyclisation. This often led to elimination of the thiolate, yielding the problematic alkene **374**, which decomposed to the catechol **382**. A final attempt used *m*CPBA to oxidise the sulfur in **383** in order to try and suppress elimination when undertaking a Dieckmann cyclisation; however, this could not be achieved.

An alternative strategy involved the use of dithiane **361**. A conjugate addition was attempted which would have led to an aldehyde. It was hoped that this aldehyde could have undergone an *in situ* cyclisation. However, the thiolate could not be added to the alkene **374**. It was therefore concluded that **79** was not a suitable building block to form breynolide.

Conclusions and Closing comments

The aim of this thesis was to achieve the first total synthesis of phyllaemblic acid and a new novel route towards the perhydrobenzothiophene ring found in breynolide.

The first chapter of this thesis reviews the key spiroacetalisation step in the natural products phyllanthocin and breynolide. The spiroacetalisation steps used in the previous syntheses of phyllanthocin and breynolide give an invaluable insight into the possible conditions that may be used for similar structural systems such as phyllaemblic acid.

Chapter one concludes by highlighting the current route towards phyllaemblic acid, specifically the key α,α'-annulation reaction which installs three of the four stereocentres found on the cyclohexane ring in the spiroacetalisation precursor (Chapter 1, Scheme 12, Scheme 13.)

The problem with the α,α'-annulation is that the resultant carbonyl in **80** (Chapter 1, Scheme 15) is unreactive to a host of nucleophiles and it was concluded that the spiroacetalisation precursor **74** (Chapter 1, Scheme 12) could not be formed via intermolecular addition to the ketone in **80**.

With this in mind a new intramolecular addition was envisaged (Chapter 2, Scheme 16). A literature review on keto-alkyne cyclisations was completed to review the various ways in which this intramolecular addition could be achieved. However, when formation of the desired keto-alkyne cyclisation precursor **174** was attempted via the α,α'-annulation on dioxanone **158** (Chapter 2, Scheme 44, Scheme 46), tricyclic systems **175** and **177** were isolated. After investigation it was concluded that a proximity effect between the ketone and the alkyne was taking place, resulting in an uncontrollable intramolecular addition.

Future work could investigate replacing the alkyne in **158** with a different functional group. However, this may have an impact on the stereochemical outcome in the α,α'-annulation, as the smaller group prefers to reside in the flagstaff position as described in (Chapter 1, Scheme 14). Ultimately, further chemical manipulation to obtain a useful functional group to reinvestigate intramolecular addition would present a major synthetic challenge.

An intramolecular addition was also attempted using the annulation products **79** and **80**; however, this resulted in the formal loss of CO from the cyclohexane ring. Although the products obtained were interesting (Chapter 2, Scheme 59) the application towards the synthesis of phyllaemblic acid is limited. Labelling studies using ^{18}O would be useful in trying to determine the mechanistic pathway for these products.

Chapter three reinvestigates the HWE reaction. In the previous investigations it was assumed that moving from a bicyclic to a monocyclic system would facilitate nucleophilic attack and increase reactivity (Chapter 3, Scheme 63). Subsequent investigations found that the resulting monocyclic system, protected with TBS groups **211**, was still too sterically crowded to perform a HWE reaction. A variety of different protecting groups were trialled; however, the only alternative protecting group successfully installed was TES. The same HWE conditions previously used were attempted but no reaction was observed. Finally, the phosphonate was shown to be unreactive to a simple model system which gave conclusive evidence that the HWE based approach should be abandoned.

Enone functionality continues to be explored in chapter four and when exhibited in a system such as **245**, the spiroacetalisation precursor **74** could be achieved in just three steps (Chapter 4, Scheme 82). The Meyer-Schuster rearrangement gives the opportunity to install

an enone via a rearrangement of a propargyl alcohol. At this stage an alkynyl anion still remained unused in nucleophilic attack towards the ketone in **211** and so it was proposed that this could be used in a new route towards the formation of phyllaemblic acid (Chapter 4, Scheme 84).

The TBS and TES protected systems **250** and **251** were both subjected to different sets of conditions using $AuPPh_3NTf_2$ and substoichiometric amounts of either MeOH or $PhB(OH)_2$, or the use of (2,3,4,5-tetrafluorophenyl)boronic acid. The most interesting result was obtained using $AuPPh_3NTf_2$ and $PhB(OH)_2$ on **250** which achieved the formation of the novel cyclic enolboronate **274** in good yield (Chapter 4, Scheme 98).

It was concluded that the Meyer-Schuster rearrangement was unable to be utilised in the synthesis of phyllaemblic acid. However, the formation of the cyclic enolboronate is very interesting and there are potential investigations into what chemical transformations can be performed on **274**. Furthermore, it would be interesting to see if additional novel cyclic enolboronates can be formed using these conditions on different systems.

An alternative approach looked at a new disconnection and the use of an alkyne as a latent nucleophile (Chapter 4, Scheme 118). The formation of alkyne **299** was successfully achieved from aldehyde **217**. This route installed all four of the stereocentres on the cyclohexane ring. A convergent synthesis was developed by coupling **309** with epoxide **306**. Various conditions were attempted (Chapter 4, Table 23), but ultimately the two fragments could not be joined together. There is potential for work still to be completed via increasing the reactivity of the epoxide. However, based on the results obtained in chapters three and four it is assumed that the large TBS groups are a main factor in suppressing C-C bond formation at the alkyne,

and as shown in chapter three an alternative protecting group strategy seems to be a significant synthetic challenge.

With regards to a future total synthesis of phyllaemblic acid, if C-C bond formation can be achieved between the disconnection shown in (Chapter 1, Scheme 12) and a correct protecting group strategy can be identified, then the spiroacetalisation precursor could be formed. Once this has been achieved, it is proposed that subsequent spiroacetalisation should be relatively straightforward due to the various conditions previously investigated on the structurally related natural products phyllanthocin and breynolide (Chapter 1).

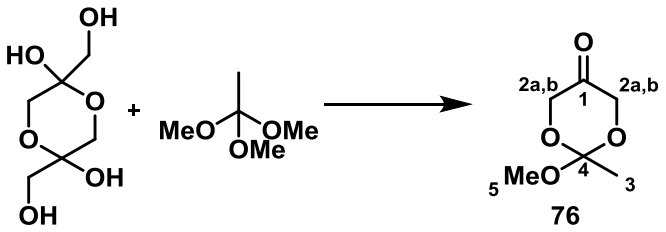
Investigations in Chapter five looked towards using the bicyclic system **79** to form the perhydrobenzothiophene ring found in breynolide. Two separate routes were envisaged, both relying on the successful formation of the α,β-unsaturated ester **374** (Chapter 5, Scheme 145). Conjugate addition to the double bond was successfully achieved; however, the uncontrollable formation of catechol **382** often proceeded due to the instability of **381** and the tendency of elimination reactions occurring in **383** (Chapter 5, Scheme 153). This significantly affected the synthetic application of bicyclic ketone **79** towards the synthesis of the perhydrobenzothiophene ring. The oxidation of the sulfur atom would have potentially alleviated the problems of elimination and allowed a Dieckmann cyclisation to be carried out. However, oxidation of the sulfur with mCPBA was unsuccessful. It would be prudent to investigate the possibility of oxidising the sulfur with a different oxidising agent as only degradation occurred with mCPBA. If the suflur can be successfully oxidised investigations towards the perhydrobenzothiophene ring using the Dieckmann cyclisation could potentially be achieved using the conditions shown in (Table 25).

Experimental Section

General experimental

^{1}H and ^{13}C NMR data were recorded on a Bruker AVIII 300, Bruker AVIII 400 spectrometer. Spectra were recorded in deuterochloroform referenced to residual $CHCl_3$ (^{1}H, 7.26 ppm) or $CDCl_3$ (^{13}C, 77.16 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz. Abbreviations have been used to describe multiplicity. Mass spectra were recorded on Waters (Herts, UK) LCT MicroMass Electrospray Ionisation (ESI) Mass Spectrometer fitted with a time-of –flight (TOF) mass analyser or a Waters Synapt G2-S1 mass spectrometer fitted with an ESI ionisation source and a TOF mass analyser. Compounds were diluted with a 1:1 mixture of water and methanol and are reported as (*m/z* (%)). HRMS were recorded on a LCT spectrometer using lock mass incorporated into the mobile phase. IR spectra were recorded neat on Perkin Elmer 100-series FT-IR spectrometer. Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Analytical T.L.C. was carried out on Merck 60 F245 aluminium backed silica gel plates. Short wave UV radiation (245 nm), $KMnO_4$ and vanillin were used to visualise components. Compounds were purified by flash column chromatography using Merck silica gel 60 (0.040-0.063 nm). THF, toluene, CH_2Cl_2 and CH_3CN were dried by passing through activated alumina columns. Pyridine and triethylamine were distilled from potassium hydroxide. All other reagents and solvents were purchased from Aldrich, Alfa Aesar, Fisher Scientific, Merck or TCI Europe and were used as received. The following cooling baths were used; 0 °C (ice/water) and -78 °C (dry ice/acetone). All reactions in non-aqueous solvents were carried out under argon in oven-dried glassware. Solvents were degassed by bubbling argon through a needle immersed in the solvent for the stated length of time.

Synthesis of 2-Methoxy-2-methyl-1,3-dioxan-5-one 76



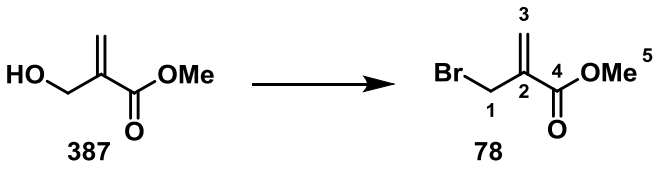
76

Dimeric dihydroxyacetone (4.09 g, 22.7 mmol) and *p*TSA (50 mg, 0.26 mmol) were heated to 60 ^{o}C in dioxane (200 mL). After the dimeric dihydroxyacetone had completely dissolved, trimethyl orthoacetate (60 mL, 454 mmol) was added and the solution stirred overnight at 60 ^{o}C. The reaction was then cooled to rt, concentrated under reduced pressure to roughly a tenth of its original volume and then directly placed onto a silica column for purification (1:1 petroleum ether: diethyl ether) to give title compound **76** as a colourless oil (3.61 g, 54%). R_f 0.54 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.32 (2 H, d, *J* 17.2, H2^a), 4.17 (2 H, d, *J* 17.2, H2^b), 3.37 (3 H, s, H5), 1.57 (3 H, s, H3).
δ_C (101 MHz, Chloroform-*d*)	204.7 (C, C1), 112.5 (C, C4), 67.6 (CH_2, C2), 51.4 (CH_3, C5), 20.6 (CH_3, C3).
ν_{max}	2951, 2840 (CH), 1740 (C=O), 1037 (C-O).

A known compound prepared according to a literature procedure and data agrees with literature values.[154]

Synthesis of Methyl 2-(bromomethyl)acrylate 78

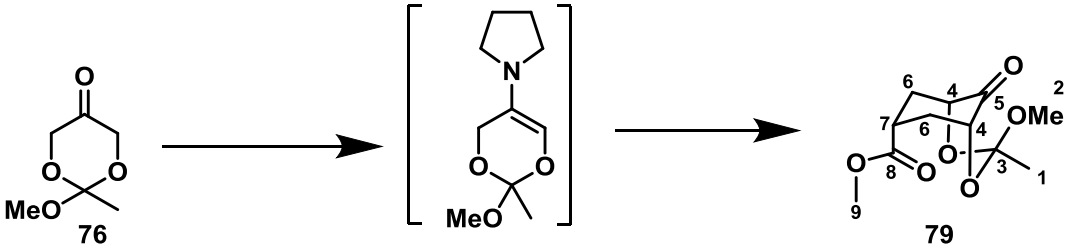


A solution of methyl hydroxymethylacrylate (7.55 g, 65.0 mmol) in diethyl ether (200 mL) was cooled to 0 ^{o}C. PBr_3 (3.08 mL, 32.5 mmol) was added dropwise over 10 minutes and the mixture was allowed to warm to rt. After 4 hr, the solution was quenched with H_2O (50 mL) and extracted with hexane (3 x 30 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield a yellow oil. Purification by column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **78** as a clear oil (9.71 g, 83%). R_f 0.34 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	6.33 (1 H, s, H3), 5.96 (1 H, s, H3), 4.17 (2 H, s, H1), 3.81 (3 H, s H5).
δ_C (101 MHz, Chloroform-*d*)	165.4 (C, C4), 137.4 (C, C2), 129.3 (CH_2, C3), 52.4 (CH_3, C5), 29.4 (CH_2, C1).
MS EI^+	(EI): *m/z*(%) = 99.0- 100% [M - ^{79}Br], 101.1- 40% [M - ^{81}Br], 118.9- 80% [M - $C_2H_3O_2$], 120.9- 78% [M - $C_2H_3O_2$], 149.9- 90% [M - CH_3O], 148.9- 88% [M - CH_3O].

A known compound prepared according to a literature procedure and data agrees with literature values.[26, 155]

Synthesis of Methyl (1*S*,3*S*,7*S*)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate 79

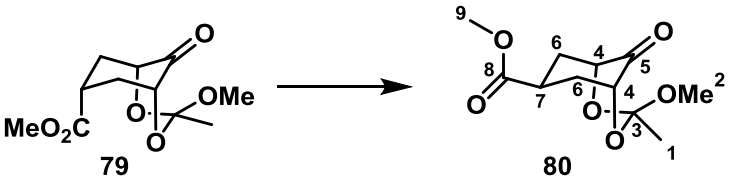


A solution of dioxanone **76** (2.9 g, 19.9 mmol) in CH_3CN (70 mL) was cooled to 0 ^oC. Pyrrolidine (1.4 g, 19.9 mmol) was added and the reaction mixture stirred for 5 hr. Et_3N (2.0 g, 19.9 mmol) was added followed by a solution of α-bromomethylacrylate **78** (3.6 g, 19.9 mmol) in CH_3CN (30 mL). After 16 hr, H_2O (100 mL) was added and the reaction mixture stirred for 3 hr. The reaction mixture was then reduced to half volume under reduced pressure and then extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (1:1 petroleum ether: EtOAc) gave the title compound **79** as a white solid (3 g, 62%). M.p. 65-67 ^oC. R_f 0.24 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.17 (2 H, d, *J* 3.8, H4), 3.77 (3 H, s, H9), 3.27 – 3.18 (5 H, m, H6 eq & H2), 2.63 (1 H, app.t, *J* 7.0, H7), 1.98 (2 H, dd, *J* 14.6, 7.0, H6 ax), 1.43 (3 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	208.0 (C, C5), 173.7 (C, C8), 112.1 (C, C3), 75.2 (CH, C4), 52.1 (CH_3, C9), 51.1 (CH_3, C2), 36.7 (CH_2, C6), 34.0 (CH, C7), 19.9 (CH_3, C1).
ν_{max}	2996, 2950, 2933 (CH), 1744 (CO_2Me), 1725 (C=O).

A known compound prepared according to a literature procedure and data agrees with literature values, except the product obtained was crystalline.[26]

Synthesis of Methyl (1*S*,3*S*,7*R*)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate 80

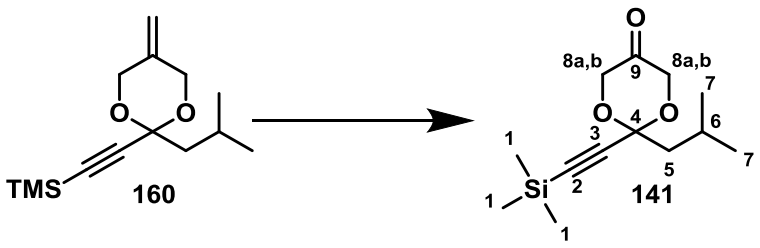


To a solution of methyl-2-methoxy-1,3-dioxane **79** (1 g, 4.09 mmol) in CH_3CN (34 mL) was added DBU (0.62 g, 4.09 mmol). The reaction mixture was heated to 65 ^{o}C and stirred for 24 hr, allowed to cool to rt, concentrated under reduced pressure and directly purified by column chromatography (3:1 petroleum: diethyl ether) to yield the title compound **80** as a white solid (1 g, 100%). R_f 0.45 (4:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.17 (2 H, d, *J* 3.7, (H4), 3.69 (3 H, s, H9) 3.44 (1 H, tt, *J* 12.5, 4.6, H7), 3.25 (3 H, s, H2), 2.60 (2 H, ddd, *J* 14.1, 6.5, 4.6, H6 eq), 1.94 (2 H, app.t, *J* 14.1, H6 ax), 1.57 (3 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	207.0 (C, C5), 174.3 (C, C8), 112.2 (C, C3), 74.7 (CH, C4), 52.2 (CH_3, C2), 51.1 (CH_3, C9), 38.3 (CH_2, C6), 33.4 (CH, C7), 20.2 (CH_3, C1).
ν_{max}	3003, 2965, 2937 (CH), 1753 (CO_2Me), 1730 (C=O).

A known compound prepared according to a literature procedure and data agrees with literature values.[26]

Synthesis of 2-Isobutyl-2-((trimethylsilyl)ethynyl)-1,3-dioxan-5-one 141

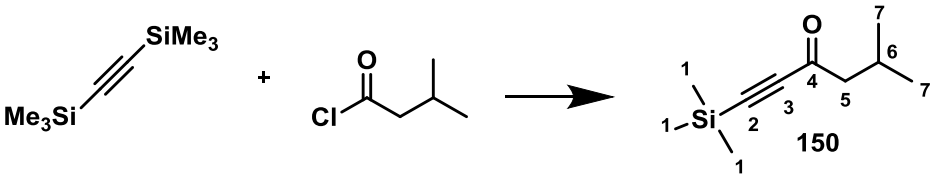


A solution of **160** (1.2 g, 4.75 mmol) in a 3:1 mixture of dioxane: H_2O (24 mL) was treated with OsO_4 (1-2 drops of a 4 wt% aq. solution) and $NaIO_4$ (4.0 g, 19.0 mmol). The mixture was vigorously stirred at 40 ^{o}C for 4 hr then cooled to rt. The mixture was filtered and the filtrate added to saturated solution of sodium bisulfite, followed by a solution of $NaHCO_3$ (25 mL of a 0.1 M aq. solution) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The yellow crude oil was purified by column chromatography (19:1 petroleum ether: diethyl ether) to first recover sm (70 mg), followed by the title compound **141** as a white solid (0.72 g, 63% BRSM). M.p. 41 ^{o}C. R_f 0.63 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.55 (2 H, d, *J* 19.1, H8^{a}), 4.26 (2 H, d, *J* 19.1, CH_2 H8^{b}), 2.03 (1 H, app.Non, *J* 6.5, H6), 1.81 (2 H, d, *J* 6.5, H5), 1.00 (6 H, d, *J* 6.5, H7), 0.19 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	204.3 (C, C9), 99.0 (C, C3), 95.9 (C, C4), 94.5 (C, C2), 70.0 (CH_2, C8), 48.1 (CH_2, C5), 24.4 (CH, C6), 23.9 (CH_3, C7), -0.3 (CH_3, C1).
MS ES^{+}	HRMS (ES): *m/z*(%) = 309.1490 [M + Na + MeOH] (calcd for $C_{14}H_{26}O_4NaSi$: 309.1498), 309.2- 100% [M + Na + MeOH], 265.0- 30%, 165.0- 20%.
ν_{max}	2959, 2873 (CH), 1736 (C=O), C≡C (stretch not visible).

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

Synthesis of 5-Methyl-1-(trimethylsilyl)hex-1-yn-3-one 150



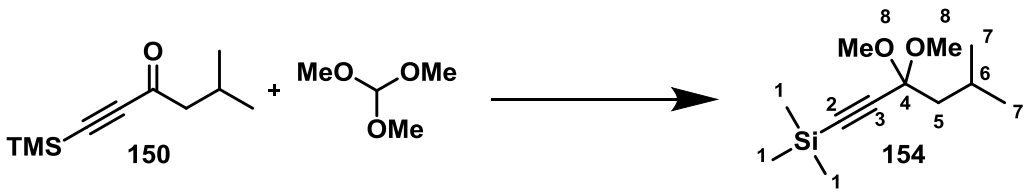
To a solution of BTMSA (9.94 g, 58.3 mmol) and isovaleryl chloride (6.40 g, 53.1 mmol) in CH_2Cl_2 (150 mL) cooled to 0 ^{o}C, was added $AlCl_3$ (8.49 g, 53.1 mmol) in small portions over 30 min. The reaction mixture was allowed to warm to rt over 3 hr then poured onto ice. HCl was added (30 mL of a 1 M aqueous solution) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a black oil which was purified by passing through a plug of silica (19:1 petroleum ether: diethyl ether) to give the title compound **150** as a yellow oil (9.47 g, 98%).

R_f 0.54 (9:1 petroleum ether: ethyl acetate) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	2.36 (2 H, d, *J* 7.0, H5), 2.17 (1 H, app.Non, *J* 7.0, H6), 0.89 (6 H, d, *J* 7.0, H7), 0.17 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	187.4 (C, C4), 102.4 (C, C3), 97.2 (C, C2), 54.2 (CH_2, C5), 25.0 (CH, C6), 22.4 (CH_3, C7), -0.8 (CH_3, C1).
MS TOF EI$^+$	HRMS (EI): *m/z*(%) = 182.1121 [M] (calcd for $C_{10}H_{18}OSi$: 182.1127), 125.0- 100% [M - C_4H_9], 140.1- 40% [M - C_3H_8], 167.1- 30% [M - CH_3].
ν_{max}	2960, 2874 (CH), 2152 (C≡C), 1673 (C=O).

A novel compound prepared according to a modified literature procedure.[68]

Synthesis of (3,3-Dimethoxy-5-methylhex-1-yn-1-yl)trimethylsilane 154

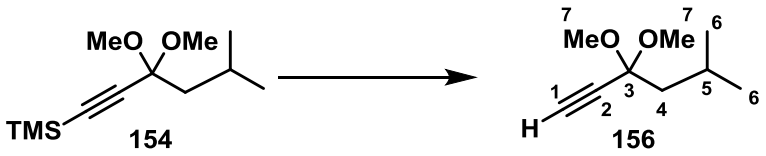


To a solution of *p*TSA (480 mg, 2.52 mmol) in MeOH (19 mL) was added ketone **150** (4.64 g, 25.4 mmol) and trimethylorthoformate (3.23 g, 30.5 mmol). The mixture was stirred for 4 hr at rt. The reaction was quenched with K_2CO_3 (25 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography (99:1 petroleum ether: diethyl ether) to give the title compound **154** as a red/brown oil (3.06 g, 66%). R_f 0.36 (99:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.25 (6 H, s, H8), 1.91 (1 H, app.Non, *J* 6.4, H6), 1.65 (2 H, d, *J* 6.4, H5), 0.95 (6 H, d, *J* 6.4, H7), 0.15 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	102.0 (C, C2), 99.2 (C, C4), 90.7 (C, C3), 49.9 (CH_3, C8), 45.4 (CH_2, C5), 24.6 (CH, C6), 23.8 (CH_3, C7), -0.2 (CH_3, C1).
MS TOF EI^+	HRMS (EI): *m/z*(%) = 251.1446 [M + Na] (calcd for $C_{12}H_{24}O_2NaSi$: 251.1443), 251.1- 70% [M + Na], 197.1- 100% [M - OMe].
ν_{max}	2956, 2872, 2830 (CH), 1070 (OMe), C≡C not observed.

A novel compound prepared according to a modified literature procedure.[156]

Synthesis of 3,3-Dimethoxy-5-methylhex-1-yne 156

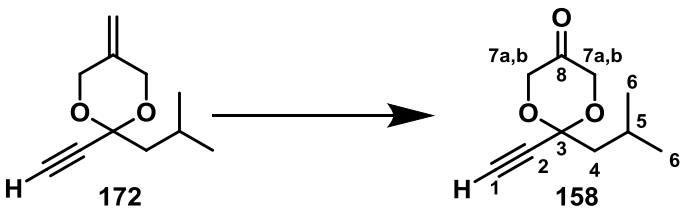


To a stirred solution of **154** (2.69 g, 11.8 mmol) in THF (118 mL), TBAF (11.8 mL of a 1M solution in THF, 11.8 mmol) was added dropwise via syringe over 5 minutes. The mixture was stirred for 24 hr, poured onto K_2CO_3 (50 mL of a saturated aqueous solution), extracted with Et_2O (3 x 20 mL), washed with brine (25 mL), dried over $MgSO_4$, filtered, and then purified by column chromatography (19:1 petroleum ether: diethyl ether) to give the title compound **156** as a colourless oil (0.87 g, 47%). R_f 0.61 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.30 (6 H, s, H7), 2.56 (1 H, s, H1), 1.97 (1 H, app.Non, *J* 6.5, H5), 1.69 (2 H, d, *J* 6.5, H4), 0.98 (6 H, d, *J* 6.5, H6).
δ_C (101 MHz, Chloroform-*d*)	99.3 (C, C3), 80.6 (C, C2), 74.0 (CH, C1), 50.0 (CH_3, C7), 45.2 (CH_2, C4), 24.7 (CH, C5) 23.7 (CH_3, C6).
MS EI^+	HRMS (EI): *m/z*(%) = 156.1153 [M] (calcd for $C_9H_{16}O_2$: 156.1150), 99.0- 100% [M - C_4H_9], 125.1- 90% [M - MeO], 83.0- 70%.
ν_{max}	3308 (C≡C-H), 2956, 2873, 2833 (CH), 2118 (C≡C).

A novel compound.

Synthesis of 2-Ethynyl-2-isobutyl-1,3-dioxan-5-one 158

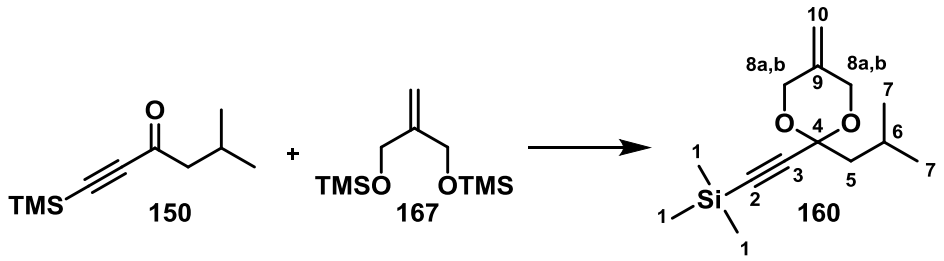


To a solution of cyclic acetal **172** (100 mg, 0.55 mmol) in a 3:1 mixture of dioxane and water (5.5 mL), was added OsO_4 (1-2 drops of a 4 wt% aq. solution) and $NaIO_4$ (471 mg, 2.2 mmol). The reaction was vigorously stirred for 2 hr at 50 ^{o}C. The crude reaction mixture was filtered and added to a saturated aqueous solution of sodium bisulfite. The filtrate was then washed with 0.1 M $NaHCO_3$ (3 x 10 mL), extracted with diethyl ether (3 x 10 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **158** as a colourless oil (84 mg, 84%). R_f 0.32 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	4.55 (2 H, d, *J* 19.1, H7^a), 4.28 (2 H, d, *J* 19.1, H7^b), 2.74 (1 H, s, H1), 2.05 (1 H, app.Non, *J* 6.6, H5), 1.83 (2 H, d, *J* 6.6, H4), 0.99 (6 H, d, *J* 6.6, H6).
δ_C (101 MHz, Chloroform-*d*)	203.9 (C, C8), 95.8 (C, C3), 78.1 (C, C2), 76.8 (CH, C1), 69.9 (CH_2, C7), 48.3 (CH_2, C4), 24.3 (CH, C5), 23.8 (CH_3, C6).
MS EI$^+$	HRMS (EI): *m*/*z*(%) = 182.0941 [M] (calcd for $C_{10}H_{14}O_3$: 182.0943), 125.0-100% [M - C_4H_9], 68.0- 65%.
ν_{max}	3273 (H-C≡C), 2958, 2874 (CH), 2110 (C≡C), 1741 (C=O).

A novel compound.

Synthesis of ((2-Isobutyl-5-methylene-1,3-dioxan-2-yl)ethynyl)trimethylsilane 160

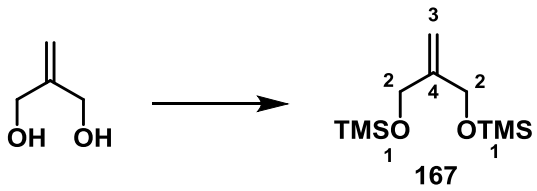


To a solution of TMSOTf (8 µL, 0.04 mmol) in CH_2Cl_2 (0.43 mL) cooled to 0 ^{o}C was added **150** (392 mg, 2.15 mmol) and **167** (1 g, 4.30 mmol) at the same time. The yellow reaction mixture was allowed to warm to rt. After 1 hr the golden brown mixture was added to Na_2CO_3 (15 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 25 mL). This was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (98:2 petroleum ether: diethyl ether) gave the title compound **160** as a colourless oil (0.35 g, 89%). R_f 0.51 (99:1 petroleum ether: diethyl ether) visualised in anisaldehyde.

δ_H (400 MHz, Chloroform-*d*)	4.90 (2 H, s, H10), 4.76 (2 H, d, *J* 13.0, H8^a), 4.14 (2 H, d, *J* 13.0, H8^b), 2.02 (1 H, app.Non, *J* 6.5, H6), 1.73 (2 H, d, *J* 6.5, H5), 0.97 (6 H, d, *J* 6.5, H7), 0.21 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	138.9 (C, C9), 109.9 (CH_2, C10), 100.3 (C, C2), 96.2 (C, C4), 93.3 (C, C3), 66.4 (CH_2, C8), 49.6 (CH_2, C5), 24.3 (CH, C6), 24.0 (CH_3, C7), -0.1 (CH_3, C1).
MS ES$^+$	HRMS (ES): *m/z*(%) = 275.1444 [M + Na] (calcd for $C_{14}H_{24}O_2NaSi$: 275.1443), 275.1- 100% [M + Na], 253.1- 80% [M + H], 197.1- 90%.
ν_{max}	2957, 2850, 2871 (CH), 2163 (C≡C).

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

Synthesis of 2,2,8,8-Tetramethyl-5-methylene-3,7-dioxa-2,8-disilanonane 167

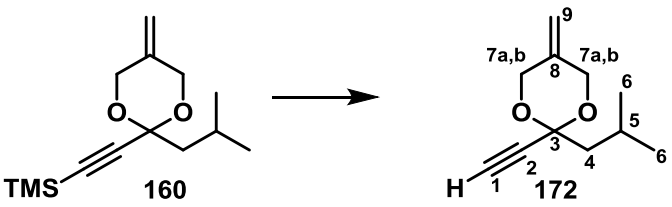


To a solution of 2-methylene-1,3-propane diol **159** (500 mg, 5.65 mmol) and TMSCl (1.29 g, 11.9 mmol) in CH_2Cl_2 (56.5 mL) cooled to 0 ^oC, was added dry Et_3N (1.29 g, 11.9 mmol). The mixture was warmed to rt, and stirred for 24 hr, poured onto H_2O (25 mL) then washed with H_2O (4 x 25 mL) and brine (1 x 25 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound **167** as a clear oil (1.28 g, 97%).

δ_H (400 MHz, Chloroform-*d*)	5.09 (2 H, s, H3), 4.13 (4 H, s, H2), 0.12 (18 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	148.0 (C, C4), 110.5 (CH_2, C3), 63.8 (CH_2, C2), 0.0 (CH_3, C1).
MS EI^+	HRMS (EI): *m/z*(%) = 232.1319 [M] (calcd for $C_{10}H_{24}O_{2S}Si_2$: 232.1315), 129.0- 100% [M - $C_4H_{11}OSi$], 142.0- 70%, 147.0- 60%, 149.0- 55%.
ν_{max}	2958, 2901 (CH), 1660 (C=C).

A novel compound.

Synthesis of 2-Ethynyl-2-isobutyl-5-methylene-1,3-dioxane 172

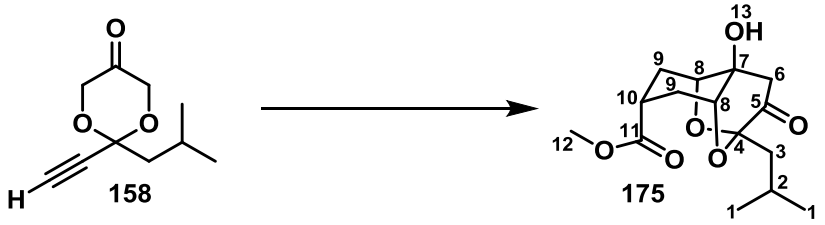


To a solution of cyclic acetal **160** (500mg, 1.98 mmol) in MeOH (30 mL) cooled to 0 ^{o}C, was added a solution of K_2CO_3 (378 mg, 2.73 mmol) in water (8 mL). The reaction was left to stir for 30 minutes then the mixture was separated between $NaHCO_3$ (0.1 M, 10 mL) and Et_2O (10 mL). The aqueous phase was washed with diethyl ether (2 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. Column chromatography (19:1 petroleum ether: diethyl ether) gave the title compound **172** as a colourless oil (288 mg, 80%). R_f 0.64 (19:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.91 (2 H, s, H9), 4.77 (2 H, d, *J* 13.5, H7^{a}), 4.18 (2 H, d, *J* 13.5, H7^{b}), 2.70 (1 H, s, H1), 2.05 (1 H, app.Non, *J* 6.6, H5), 1.76 (2 H, d, *J* 6.6, H4), 0.98 (6 H, d, *J* 6.6, H6).
δ_C (101 MHz, Chloroform-*d*)	138.5 (C, C8), 110.1, (CH_2, C9) 96.2 (C, C2), 79.1 (C, C3), 76.2 (CH, C1), 66.4, (CH_2, C7) 49.6 (CH_2, C4), 24.2 (CH, C5) 24.0 (CH_3, C6).
MS ES^{+}	HRMS (ES): *m*/*z*(%) = 181.1223 [M + H] (calcd for $C_{11}H_{17}O_2$: 181.1229), 213.2- 100% [M + MeOH + H], 181.1- 45% [M + H].
ν_{max}	3302 (C≡C-H), 2957, 2853 (CH), 2107 (C≡C).

A novel compound.

Synthesis of Methyl (4ar,5R,7r,8aS)-4a-hydroxy-2-isobutyl-3-oxooctahydro-2H-2,5-epoxychromene-7-carboxylate 175



To a solution of dioxanone **158** (143 mg, 0.78 mmol) in dry toluene (7.8 mL) with 4 Å MS (2 g) was added pyrrolidine (222 mg, 3.12 mmol). The mixture was stirred overnight at rt, filtered and then quickly washed with brine (3 x 5 mL). The reaction was extracted with diethyl ether (3 x 5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining oil was then placed under vacuum (0.1 mmHg) for approximately 1 hr to give the crude enamine as a crystalline product (161 mg.)

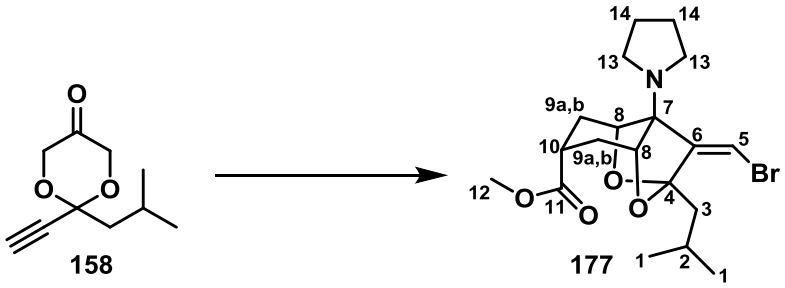
A solution of the crude enamine (161 mg, 0.68 mmol) in MeCN (6.8 mL) was then cooled to 0 ^{o}C and methyl bromomethyl acrylate (122 mg, 0.68 mmol) was added followed by Et_3N (69 mg, 0.68 mmol). The mixture was stirred overnight with gradual warming to rt. Water (5 mL) was then added and the reaction left to stir for 5 hr. The mixture was then extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and then solvents removed under reduced pressure. Column chromatography (1:1 petroleum ether: diethyl ether) gave the title compound **175** as a white solid (44 mg, 20% (over 2 steps)). M.p. 96-98 ^{o}C. R_f 0.15 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.00 (2 H, app.t, *J* 1.8, H8), 3.71 (3 H, s, H12), 2.69 (2 H, dd, *J* 15.1, 1.8, H9 eq), 2.61 (2 H, s, H6), 2.57 (1 H, app.t, *J* 7.3, H10), 2.06 (2 H, dd, *J* 15.1, 7.3, H9 ax), 1.74 (1 H, app.Non, *J* 6.5, H2), 1.49 (2 H, d, *J* 6.5, H3), 0.87 (6 H, d, *J* 6.5, H1). OH not visible by NMR

δ_C (101 MHz, Chloroform-*d*)	197.6 (C, C5), 175.0 (C, C11), 94.7 (C, C4), 74.5 (CH, C8), 63.5 (C, C7), 52.0 (CH_3, C12), 47.7 (CH_2, C6), 39.1 (CH_2, C3), 32.1(CH, C10), 25.8 (CH_2, C9), 24.2 (CH_3, C1), 23.3 (CH, C2).
MS ES^+	HRMS (ES): *m*/*z*(%) = 321.1329 [M + Na] (calcd for $C_{15}H_{22}O_6Na$: 321.1314), 321.1-100% [M+Na].
ν_{max}	3434 (OH), 2952, 2868 (CH), 1742 (CO_2Me), 1715 (C=O).

A novel compound prepared according to a modified literature procedure.[26]

Synthesis of methyl (3ar,4R,6r,7aS,Z)-3-(bromomethylene)-2-isobutyl-3a-(pyrrolidin-1-yl)octahydro-2,4-epoxybenzofuran-6-carboxylate 177



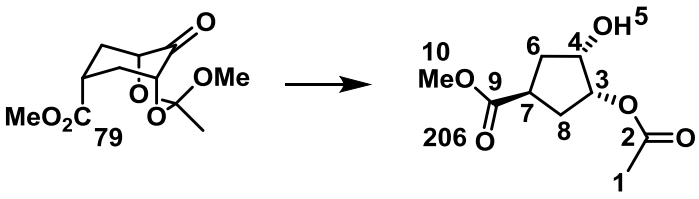
To a solution of **158** (100 mg, 0.55 mmol) in toluene (5.5 mL) with 4 Å MS was added pyrrolidine (156 mg, 2.2 mmol). The mixture was left to stir under an argon atmosphere overnight at rt. The crude reaction mixture was filtered and quickly washed with brine (15 mL). The organic layers were separated, dried with $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude yellow oil was then placed under vacuum (0.1 mmHg) until it crystallised. The crude enamine was then dissolved in MeCN (3.9 mL) followed by the addition of bromomethyl acrylate (70 mg, 0.39 mmol) and NEt_3 (39 mg, 0.39 mmol). The reaction mixture was then heated to 50 ^{o}C and left for 12 hr. The reaction was quenched with H_2O (5 mL) and left to stir for 5 hr, extracted with CH_2Cl_2 (3 x 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure to leave the crude product that was purified by column chromatography, (1:1 petroleum ether: diethyl ether) to give the title compound **177** as a white solid. (90 mg, 39%). M.p. 133-135 ^{o}C. R_f 0.55 (8:2 diethyl ether: petroleum ether) visualised in vanillin.

δ_H (400 MHz, Benzene-d_6) Product degrades in chloroform.	5.56 (1 H, s, H5), 4.03 (2 H, app.t, *J* 1.5, H8), 3.60 (3 H, s, H12), 2.87 – 2.72 (2 H, m, H9^a), 2.41 (1 H, app.Non, *J* 6.4 H2), 2.35 – 2.27 (6 H, m, H13, H14, H3), 2.16 (1 H, tt, *J* 7.1, 1.6, H10), 1.39 (2 H, dd, *J* 14.8, 7.1, H9^b), 1.31 – 1.25 (4 H, m, H14, H13), 1.23 (6 H, d, *J* 6.4, H1).

δ_C (101 MHz, Benzene-d_6)	173.6 (C, C11), 144.6 (C, C6), 105.5 (C, C7), 85.8 (CH, C5), 74.0 (CH, C8), 68.9 (C, C4), 51.4 (CH_3, C12), 46.5 (CH_2, C13), 41.9 (CH_2, C14) 32.2, (CH, C10) 25.3 (CH_2, C3), 25.1 (CH_3, C1), 24.5 (CH_2, C9), 23.6 (CH, C2).
MS TOF ES^+	HRMS (ES): *m*/*z*(%) = 414.1283 [M + H] (calcd for $C_{19}H_{29}NO_4{}^{79}Br$: 414.1280), 414.1- 100% [$M^{79}Br$], 416.1- 90% [$M^{81}Br$].
ν_{max}	2956, 2930, 2912, 2870 (CH), 1722 (CO_2Me), 1205 (C-N), 696 (C-Br).

A novel compound prepared according to a modified literature procedure.[26]

Synthesis of Methyl (1*S*,3*R*,4*S*)-3-acetoxy-4-hydroxycyclopentane-1-carboxylate 206

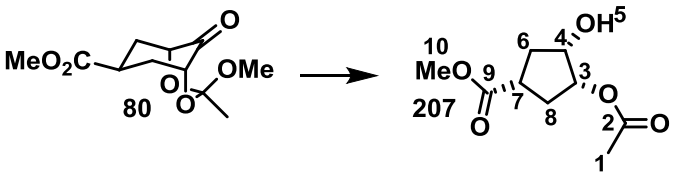


In a Pyrex immersion well reactor a solution of bicyclic ketone **79** (100 mg, 0.4 mmol) in MeCN (57 mL) was degassed using argon for 15 minutes. A medium pressure mercury lamp was then used and the reaction stirred for 4 hr. Solvents were removed under reduced pressure and the crude product purified via column chromatography (1:1 petroleum ether: diethyl ether) to give the title compound **206** as a pale yellow oil (24 mg, 29%). R_f 0.32 (8:2 diethyl ether: petroleum ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	5.07 (1 H, ddd, *J* 7.0, 5.6, 4.0, H3), 4.36 – 4.27 (1 H, m, H4), 3.66 (3 H, s, H10), 3.14 (1 H, tt, *J* 9.8, 6.6, H7), 2.28 – 2.17 (2 H, m, H5, H6/H8), 2.11 – 1.96 (6 H, m, H1, H6/H8).
δ_C (101 MHz, Chloroform-*d*)	176.2 (C, C9), 170.8 (C, C2), 76.3 (CH, C3), 72.6 (CH, C4), 52.1 (CH_3, C10), 38.8 (CH, C7), 34.6 (CH_2, C6/C8), 31.8 (CH_2, C6/C8), 21.1 (CH_3, C1).
MS ES^+	HRMS (ES): *m*/*z*(%) = 225.0733 [M + Na] (calcd for $C_9H_{14}O_5Na$: 225.0739), 225.1- 100% [M + Na].
ν_{max}	3462 (OH), 2954 (CH), 1724 (CO_2Me, C=O).

A novel compound.

Synthesis of Methyl (1*R*,3*R*,4*S*)-3-acetoxy-4-hydroxycyclopentane-1-carboxylate 207

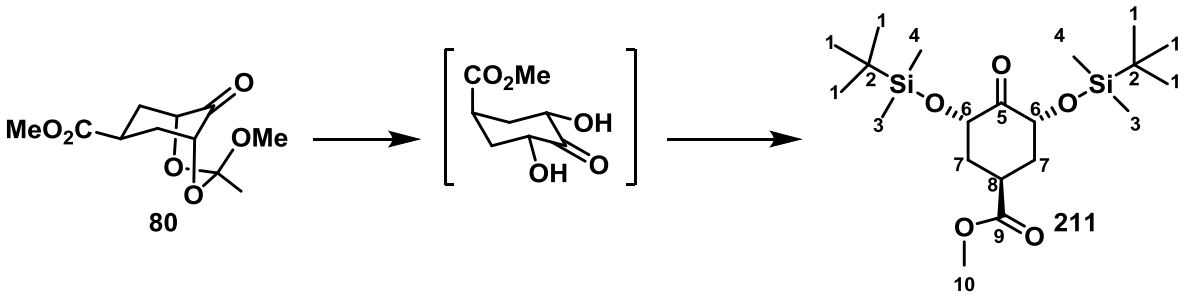


In a Pyrex immersion well reactor a solution of bicyclic ketone **80** (100 mg, 0.4 mmol) in MeCN (57 mL) was degassed using argon for 15 minutes. A medium pressure mercury lamp was then used and the reaction stirred for 4 hr. Solvents were then removed under reduced pressure and the crude product purified via column chromatography (1:1 petroleum ether: diethyl ether) to give the title compound **207** as a colourless oil (14 mg, 17%). R_f 0.35 (8:2 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.94 (1 H, td, *J* 6.8, 4.3, H3), 4.19 (1 H, td, *J* 5.4, 4.3, H4), 3.70 (3 H, s, H10), 3.01 – 2.74 (2 H, m, H5, H7), 2.32 (2 H, ddd, *J* 14.1, 9.5, 6.9, H6, H8), 2.22 – 2.01 (5 H, m, H1, H6, H8).
δ_C (101 MHz, Chloroform-*d*)	176.2 (C, C9), 171.0 (C, C2), 75.9 (CH, C3), 72.4 (CH, C4), 52.4 (CH_3, C10), 38.3 (CH, C7), 34.5 (CH_2, C8), 31.5 (CH_2, C6), 21.2 (CH_3, C1).
MS ES^+	HRMS (ES): *m*/*z*(%) = 225.0743 [M + Na] (calcd for $C_9H_{14}O_5Na$: 225.0739), 225.1- 100% [M + Na].
ν_{max}	3458 (OH), 2955 (CH), 1722 (CO_2Me).

A novel compound.

Synthesis of Methyl (1*S*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexane-1-carboxylate 211

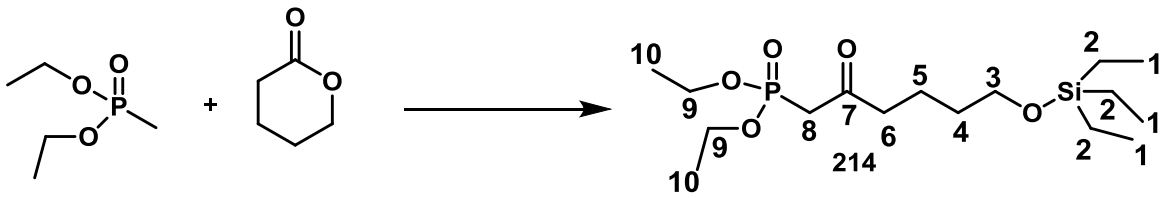


To a solution of **80** (323 mg, 1.32 mmol) in methanol (13.2 mL) was added acetic acid (79 mg, 1.32). The reaction was set to reflux for 2 days. The solution was then allowed to cool to rt and the solvent removed under reduced pressure co-distilled with toluene. The crude white solid was then dissolved in DMF (13 mL). Imidazole (741.3 mg, 3.3 mmol) was added followed by TBSCl (1.60 g, 3.3 mmol). The solution was then allowed to stir at rt for 2 days. The solvent was removed and the remaining slurry washed with brine (3 x 15 mL) and ether (3 x 15 mL). The ether extracts were then dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **211** as a white solid (456 mg, 83%). R_f 0.53 (9:1 Petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.36 (2 H, dd, *J* 12.2, 6.2, H6), 3.77 (3 H, s, H10), 2.94 (1 H, tt, *J* 5.3, 2.4, H8), 2.59 (2 H, ddd, *J* 13.1, 6.2, 2.4, H7 eq), 1.84 (2 H, ddd, *J* 13.1, 12.2, 5.3, H7 ax), 0.90 (18 H, s, H1), 0.13 (6 H, s, H3), 0.02 (6 H, s, H4).
δ_C (101 MHz, Chloroform-*d*)	206.3 (C, C5), 174.6 (C, C9), 73.4 (CH, C6), 52.3 (CH_3, C10), 37.7 (CH_2, C7), 36.6 (CH, C8), 25.9 (CH_3, C1) 18.7 (C, C2), -4.6 (CH_3, C3), -5.4 (CH_3, C4).
ν_{max}	2954, 2927, 2856 (CH), 1728 (C=O).

A known compound prepared according to a PhD thesis procedure and data agrees with publication values.[91]

Synthesis of Diethyl (2-oxo-6-((triethylsilyl)oxy)hexyl)phosphonate 214

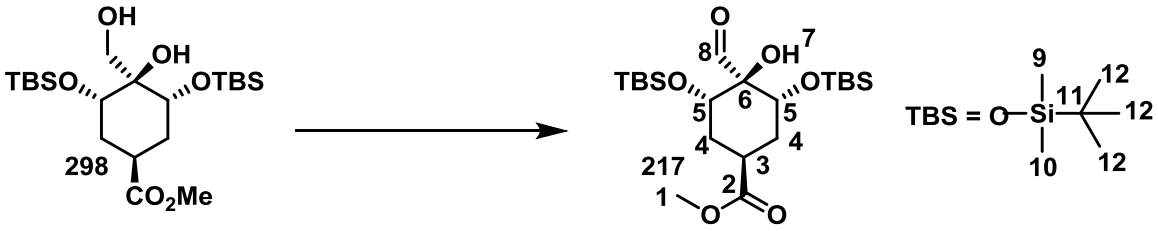


To a solution of diethylmethyl phosphonate (200 mg, 1.3 mmol) in THF (10 mL) at -78 ^{o}C was added ^{n}BuLi (2.1 M solution in ^{n}hexane, 0.62 mL, 1.3 mmol) and the mixture was left to stir for 20 minutes. γ-Valerolactone (130 mg, 1.3 mmol) was added and the mixture stirred for 1 hr with gradual warming to rt. The mixture was then cooled to -78 ^{o}C followed by the addition of ^{n}BuLi (2.1 M solution in ^{n}hexane, 0.62 mL, 1.3 mmol) and stirred for 20 minutes. TESCl (196 mg, 1.3 mmol) was then added and the mixture stirred overnight with gradual warming to rt. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (15 mL) and extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography (ethyl acetate, 100%) gave the title compound **214** as a yellow oil (245 mg, 51%). R_f 0.25 (ethyl acetate 100%) visualised under UV light.

δ_H (400 MHz, Chloroform-*d*)	4.20 – 4.07 (4 H, m, H9), 3.59 (2 H, t, *J* 6.3, H3), 3.06 (2 H, d, *J* 22.7, H8), 2.64 (2 H, t, *J* 6.9, H6), 1.63 (2 H, p, *J* 6.9, H5), 1.57 (2 H, p, *J* 6.9, H4), 1.33 (6 H, t, *J* 7.0, H10), 0.94 (9 H, t, *J* 8.0, H1), 0.58 (6 H, q, *J*, 8.0, H2).
δ_C (101 MHz, Chloroform-*d*)	202.1 (C, C7), 62.6 (CH_2, C9), 62.6 (CH_2, C3), 43.9 (CH_2, C6), 43.1 (CH_2, C8), 41.8 (CH_2, C8), 32.2 (CH_2, C4), 20.0 (CH_2, C5), 16.4 (CH_3, C10), 6.9 (CH_3, C1), 4.5 (CH_2, C2).
MS TOF ES$^+$	HRMS (ES): *m/z*(%) = 389.1893 [M + Na] (calcd for $C_{16}H_{35}O_5NaPSi$: 389.1893), 367.3- 50% [M + H], 389.2- 100% [M + Na].
ν_{max}	2955, 2911, 2877 (CH), 1715 (C=O).

A novel compound prepared according to a PhD thesis procedure, but was not fully characterised.[91]

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-formyl-4-hydroxycyclohexane-1-carboxylate 217

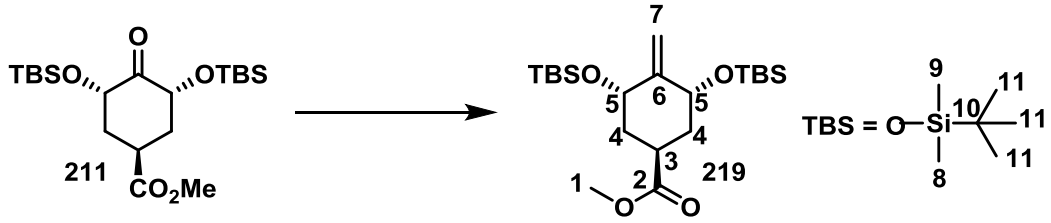


Anhydrous CH_2Cl_2 was cooled to -78°C under an Ar atmosphere. DMSO (48 mg, 0.61 mmol) was added followed by oxalyl chloride (61 mg, 0.48 mmol). The mixture was stirred for 30 minutes maintaining the temperature at -78 °C. Diol **298** (100mg, 0.22 mmol) was dissolved in 1 mL of anhydrous CH_2Cl_2 and added into the mixture. After 1 hr and 20 minutes, triethylamine (111 mg, 1.1 mmol) was added and the reaction stirred for 1 hr whilst being allowed to warm to rt. An aqueous solution of saturated NH_4Cl (5 mL) was added and the reaction extracted with diethyl ether (3 x 15 mL). The organic layers were combined and dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (1:1 petroleum: diethyl ether) gave the title compound **217** as a white solid (96 mg, 98%). R_f 0.54 (8:2 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	9.91 (1 H, s, H8), 3.83 (2 H, dd, *J* 11.5, 5.1, H5), 3.73 (3 H, s, H1), 3.03 – 2.97 (1 H, m, H3), 2.36 (2 H, app.dt, *J* 14.0, 3.6, H4 eq), 2.00 (2 H, ddd, *J* 14.0, 11.5, 5.1, H4 ax), 0.83 (18 H, s, H12), 0.05 (6 H, s, H9), 0.04 (6 H, s, H10).
δ_C (101 MHz, Chloroform-*d*)	202.3 (CH, C8), 174.3 (C, C2), 83.2 (C, C6), 73.3 (CH, C5), 52.1 (CH_3, C1), 36.4 (CH, C3), 33.6 (CH_2, C4), 25.8 (CH_3, C12), 18.1 (C, C11), -4.7 (CH_3, C9), -4.9 (CH_3, C10).
ν_{max}	3522 (OH), 2956, 2929, 2857, 2887 (CH), 1725 (2 x C=O).

A known compound prepared according to a PhD thesis procedure and data agrees with publication values.[91]

Synthesis of Methyl (1*S*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methylenecyclohexane-1-carboxylate 219

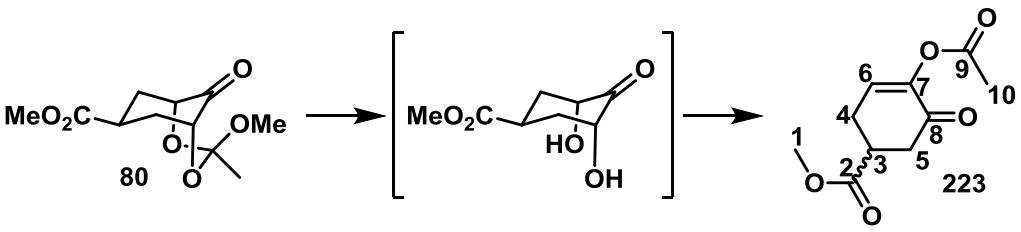


To a suspension of PPh_3CH_3Br (697 mg, 2.0 mmol) in toluene (20 mL) was added ^{n}BuLi (1.9 M solution in ^{n}hexane, 1.02 mL, 1.95 mmol) and stirred for 30 minutes at rt. A solution of **211** (541 mg, 1.30 mmol) in toluene (3 mL) was then added dropwise via syringe over five minutes. The mixture was stirred overnight. The solvent was then removed and the remaining crude solid dissolved in cyclohexane (15 mL). Oxalyl chloride (248 mg, 1.95 mmol) was then added and the mixture agitated until effervescence had ceased. The mixture was then filtered and the filtrate washed with diethyl ether (2 x 15 mL), saturated $NaHCO_3$ (2 x 15 mL) and then saturated NH_4Cl (2 x 15 mL). The remaining organic layers were then dried with magnesium sulfate and the solvent evaporated to yield the title compound **219** as a white solid (421 mg, 78%). R_f 0.41 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	5.08 (2 H, app.t, *J* 1.7, H7), 4.10 (2 H, dd, *J* 11.5, 4.8, H5), 3.72 (3 H, s, H1), 2.83 (1 H, tt, *J* 5.4, 2.6, H3), 2.35 (2 H, ddd, *J* 12.8, 4.8, 2.6, H4 eq), 1.48 (2 H, ddd, *J* 12.8, 11.5, 5.4, H4 ax), 0.92 (18 H, s, H11), 0.08 (6 H, s, H9), 0.07 (6 H, s, H8).
δ_C (101 MHz, Chloroform-*d*)	175.2 (C, C2), 153.2 (C, C6), 103.2 (CH_2, C7), 69.5 (CH, C5), 51.9 (CH_3, C1), 38.0 (CH_2, C4), 37.1 (CH, C3), 26.0 (CH_3, C11), 18.6 (C, C10), -4.9 (CH_3, C9), -5.0 (CH_3, C8).
ν_{max}	2953, 2930, 2857, 2888 (CH), 1728 (C=O Ester).

A known compound prepared according to a PhD thesis procedure and data agrees with publication values.[91]

Synthesis of Methyl 4-acetoxy-5-oxocyclohex-3-ene-1-carboxylate 223

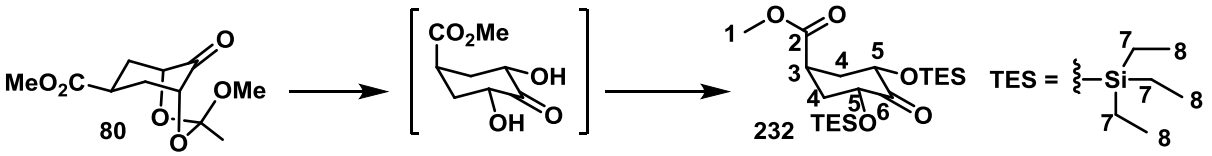


To a solution of ketone **80** (150 mg, 0.61 mmol) in MeOH (6.1 mL) was added acetic acid (37 mg, 0.61 mmol) and the mixture was heated at reflux for 2 days. The reaction was allowed to cool to rt and the solvents removed by co-distillation with toluene. To a solution of the crude solid in pyridine (6.1 mL) was added acetic anhydride (276 mg, 2.7 mmol) and DMAP (61 mg, 10 mol%). The reaction was left to stir at rt for 3 days, poured onto an ice cold solution of saturated $NaHCO_3$ (15 mL) and then extracted with diethyl ether (3 x 15 mL). The solvent was then dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was then purified via column chromatography (1:1 petroleum ether: diethyl ether) to give the title compound **223** as a colourless oil (60 mg, 46%). R_f 0.43 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	6.52 (1 H, t, *J* 4.5, H6), 3.70 (3 H, s, H1), 3.15(1 H, dddd, *J* 12.9, 10.7, 8.0, 4.9, H3), 2.86 – 2.67 (4 H, m, H4, H5), 2.19 (3 H, s, H10).
δ_C (101 MHz, Chloroform-*d*)	189.2 (C, C8), 172.9 (C, C2), 168.7 (C, C9), 145.3 (C, C7), 133.6 (CH, C6), 52.4 (CH_3, C1), 39.7 (CH_2, C4/C5), 39.6 (CH, C3), 27.2 (CH_2, C4/C5), 20.4 (CH_3, C10).
MS ES^+	HRMS (ES): *m/z*(%) = 235.0589 [M + Na] (calcd for $C_{10}H_{12}O_5Na$: 235.0582), 235.1- 100% [M + Na].
ν_{max}	2955 (CH), 1763 (CO_2Me), 1730 (C=O), 1693 (C=O).

A novel compound prepared according to a modified literature procedure.[157]

Synthesis of Methyl (1*S*,3*R*,5*S*)-4-oxo-3,5-bis((triethylsilyl)oxy)cyclohexane-1-carboxylate 232

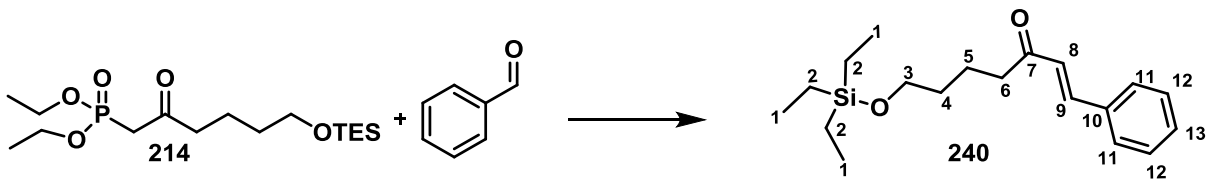


To a solution of bicyclic ketone **80** (500 mg, 2.05 mmol) in MeOH (20.5 mL) was added acetic acid (123 mg, 2.05 mmol) and the mixture set to reflux for 2 days. The reaction was then cooled to rt and the solvents removed under reduced pressure with toluene as an azeotrope. The remaining crude material was then dissolved in DMF (21 mL). TESCl (1.5 mL, 9.0 mmol) and imidazole (614 mg, 9.0 mmol) were added and the reaction left to stir for 2 days at rt. The reaction was then added to brine (30 mL) and extracted with diethyl ether (3 x 25 mL), dried over $MgSO_4$, filtered and solvents removed under reduced pressure. Column chromatography (8:2 petroleum ether: diethyl ether) gave the title compound **232** as a colourless oil (670 mg, 78%). R_f 0.43 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.37 (2 H, dd, *J* 12.1, 6.9, H5), 3.78 (3 H, s, H1), 2.92 (1 H, tt, *J* 5.4, 2.5, H3), 2.57 (2 H, ddd, *J* 13.4, 6.9, 2.5, H4 eq), 1.83 (2 H, ddd, *J* 13.4, 12.1, 5.4, H4 ax), 0.94 (9 H, t, *J* 8.0, H8), 0.60 (6 H, q, *J* 8.0, H7).
δ_C (101 MHz, Chloroform-*d*)	206.2 (C, C6), 174.6 (C, C2), 72.9 (CH, C5), 52.3 (CH_3, C1), 38.0 (CH_2, C4), 36.6 (CH, C3), 6.8 (CH_3, C8), 4.9 (CH_2, C7).
MS ES^+	HRMS (ES): *m*/*z*(%) = 417.2501 [M + H] (calcd for $C_{10}H_{18}OSi$: 417.2493), 417.3 -75% [M + H], 436.3 -80%, 439.3 -100%.
ν_{max}	2954, 2876, 2912 (CH), 1733 (CO_2Me).

A novel compound prepared according to a PhD thesis procedure.[91]

Synthesis of (*E*)-1-Phenyl-7-((triethylsilyl)oxy)hept-1-en-3-one 240

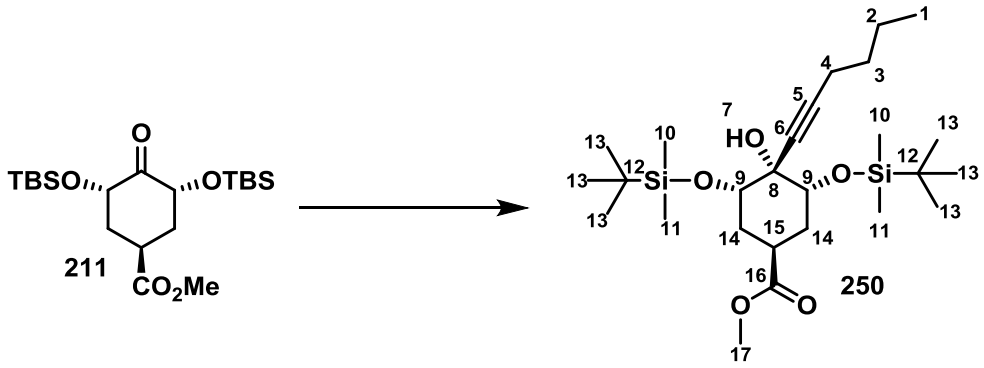


A solution of phosphonate **214** (200 mg, 0.55 mmol) was cooled to 0 ^{o}C under an argon atmosphere. NaH (60% in mineral oil, 22 mg, 0.55 mmol) was added and the reaction stirred for 20 minutes. Benzaldehyde (48 mg, 0.45 mmol) was then added via syringe and the reaction left to stir overnight. The crude mixture was washed with a saturated solution of NH_4Cl (10 mL) and then extracted with diethyl ether (3 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **240** as a colourless oil (166 mg, 81%). R_f 0.34 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	7.60 – 7.51 (3 H, m, H8, 2 x Ar-H), 7.42 – 7.36 (3 H, m, 3 x Ar-H), 6.74 (1 H, d, *J* 16.2, H9), 3.64 (2 H, t, *J* 6.4, H3), 2.70 (2 H, t, *J* 7.2, H6), 1.75 (1 H, p, *J* 7.2, H5/4), 1.59 (1 H, p, *J* 7.2, H5/4), 0.96 (9 H, t, *J* 7.9, H1), 0.60 (6 H, q, *J* 7.9, H2).
δ_C (101 MHz, Chloroform-*d*)	200.5 (C, C7), 142.4 (CH, C8), 134.7 (Ar-C, C10), 130.5 (Ar-C), 129.0 (Ar-C), 128.3 (Ar-C), 126.3 (CH, C9), 62.7 (CH_2, C3), 40.8 (CH_2, C6), 32.5 (CH_2, C5 or 4), 21.0 (CH_2, C5 or 4), 6.9 (CH_3, C1), 4.5 (CH_2, C2).
MS TOF ES$^+$	HRMS (ES): *m*/*z*(%) = 319.2106 [M + H] (calcd for $C_{19}H_{31}O_2Si$: 319.2093), 187.1- 100% [M - $OSi(CH_2CH_3)_3$), 319.2- 50% [M + H].
ν_{max}	2952, 26910, 2875 (CH), 1692, 1662, 1611 (C=O, C=C).

A novel compound prepared according to a PhD thesis procedure.[91]

Synthesis of Methyl (1*S*,3*R*,4*S*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-(hex-1-yn-1-yl)-4-hydroxycyclohexane-1-carboxylate 250



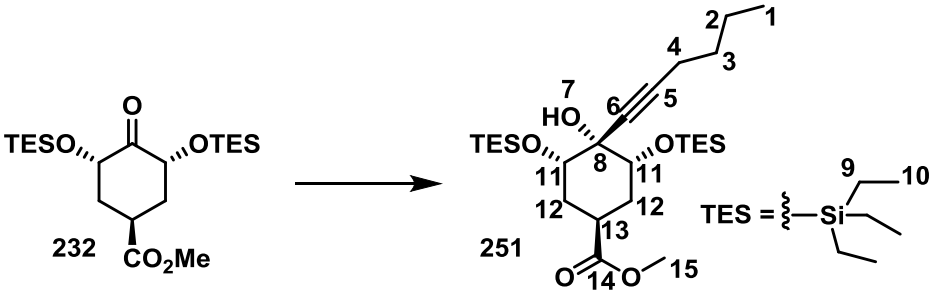
In a flame dried flask a solution of hexyne (19.7 mg, 0.24 mmol) in THF (3.9 mL) was cooled to -78 ^{o}C. ^{n}BuLi (1.67 M solution in ^{n}hexane, 0.14 mL, 0.24 mmol) was added via syringe and the mixture left to stir at -78 ^{o}C for 1 hr. Ketone **211** (100 mg, 0.24 mmol) was dissolved in THF (2 mL) and added dropwise to the reaction over 1 minute. The reaction was allowed to warm to rt and stirred for 1 hr. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (5 mL). The mixture was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **250** as a colourless oil (99 mg, 83%). R_f 0.35 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*) 3.86 (2 H, dd, *J* 6.5, 3.4, H9) 3.68 (3 H, s, H17), 2.95 (1 H, s, H7), 2.90 (1 H, tt, *J* 8.3, 4.2, H15), 2.16 (1 H, t, *J* 7.2, H4), 2.01 (2 H, ddd, *J* 11.8, 8.3, 3.4, H14 ax), 1.91 (2 H, ddd, *J* 11.8, 6.5, 4.2 H14 eq), 1.47 (2 H, p, *J* 7.2, H3), 1.36 (2 H, h, *J* 7.2, H2), 0.93 – 0.85 (21 H, m, H1, H13), 0.10 (6 H, s, H10), 0.09 (6 H, s, H11).

δ_C (101 MHz, Chloroform-*d*)	176.0 (C, C16), 85.9 (C, C5), 81.1 (C, C6), 73.8 (CH, C9) 71.4 (C, C8), 51.7 (CH_3, C17), 33.4 (CH, C15), 32.4 (CH_2, C14), 30.7 (CH_2, C3), 26.0 (CH_3, C13), 22.2 (CH_2, C2), 18.7 (CH_2, C4), 18.3 (C, C12) , 13.7 (CH_3, C1), -4.5 (CH_3, C10), -4.7 (CH_3, C11).
MS ES^+	HRMS (ES): *m*/*z*(%) = 521.3085 [M + Na] (calcd for $C_{26}H_{50}O_5Si_2Na$: 521.3094), 521.3- 100% [M + Na].
ν_{max}	3546 (OH), 2955, 2930, 2857, 2895 (CH), 1735 (CO_2Me).

A novel compound.

Synthesis of Methyl (1*S*,3*R*,4*S*,5*S*)-4-(hex-1-yn-1-yl)-4-hydroxy-3,5-bis((triethylsilyl)oxy)cyclohexane-1-carboxylate 251

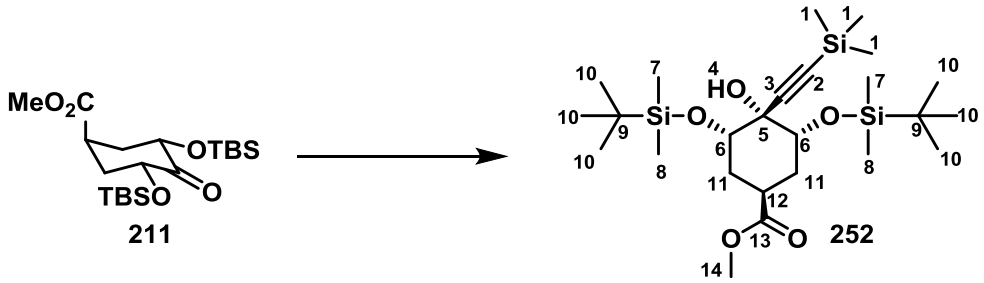


To a solution of hexyne (19 mg, 0.23 mmol) in THF (2.4 mL) cooled to -78 ^{o}C was added ^{n}BuLi (2.3 M solution in ^{n}hexane, 0.1 mL, 0.23 mmol). The mixture was left to stir for 20 minutes then ketone **232** (100 mg, 0.23 mmol) was added and the mixture left to stir for 1 hr with gradual warming to rt. The reaction was quenched with an aqueous saturated solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 x 5 mL) dried over $MgSO_4$, filtered and solvents removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **251** as a colourless oil (47 mg, 41%). R_f 0.33 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.86 (2 H, dd, *J* 7.1, 3.4, H11), 3.69 (3 H, s, H15), 3.04 (1 H, s, H7), 2.91 (1 H, tt, *J* 8.2, 4.3, H13), 2.17 (2 H, t, *J* 7.1, H4), 2.01 (2 H, ddd, *J* 13.6, 8.2, 3.4, H12 eq), 1.90 (2 H, ddd, *J* 13.6, 7.1, 4.3, H12 ax), 1.47 (2 H, p, *J* 7.1, H3), 1.37 (2 H, h, *J* 7.1, H2), 0.97 (9 H, t, *J* 7.9, H10), 0.89 (1 H, t, *J* 7.1, H1), 0.63 (6 H, q, *J* 7.9, H9).
δ_C (101 MHz, Chloroform-*d*)	176.0 (C, C14), 85.7 (C, C6), 81.1 (C, C8), 73.5 (CH, C11), 71.5 (C, C5), 51.9 (CH_3, C15), 33.6 (CH, C13), 32.4 (CH_2, C12), 30.7 (CH_2, C3), 22.2 (CH_2, C2), 18.7 (CH_2, C4), 13.7 (CH_3, C1), 7.0 (CH_3, C10), 5.0 (CH_2, C9).
MS ES$^+$	HRMS (ES): *m/z*(%) = 521.3085 [M + Na] (calcd for $C_{26}H_{50}O_5Si_2Na$: 521.3094), 481.3- 60% [M - OH], 521.3- 100% [M + Na].
ν_{max}	3545 (OH), 2954, 2876, 2912 (CH), 1735 (CO_2Me).

A novel compound.

Synthesis of Methyl (1*S*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-((trimethylsilyl)ethynyl)cyclohexane-1-carboxylate 252

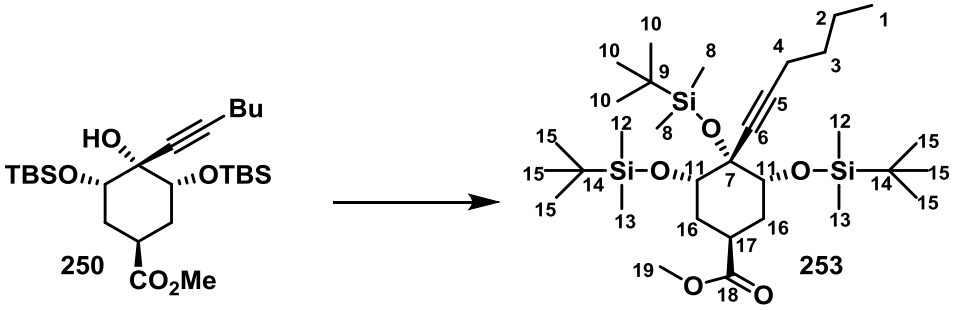


In a flame dried flask a solution of trimethylsilylacetylene (22.6 mg, 0.23 mmol) in THF (1.9 mL) was cooled to -78 °C. ^{n}BuLi (1.73 M solution in ^{n}hexane, 0.13 mL, 0.23 mmol) was added via syringe and the mixture left to stir at -78 °C for 1 hr. Ketone **211** (79 mg, 0.19 mmol) was dissolved in THF (0.5 mL) and added dropwise to the reaction over 1 minute. The reaction was allowed to warm to rt and stirred for 1 hr, before being quenched with a saturated aqueous solution of NH_4Cl (5 mL). The mixture was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried with $MgSO_4$, filtered and solvent removed under reduced pressure. Column chromatography (19:1 petroleum ether: diethyl ether) gave the title compound **252** as a colourless oil (34 mg, 35%). R_f 0.67 (19:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.84 (2 H, dd, *J* 8.6, 3.8, H6), 3.70 (3 H, s, H14), 2.88 (1 H, s, H4), 2.83-2.79 (1 H, m, H12), 2.03 (2 H, ddd, *J* 13.4, 6.1, 3.8, H11 eq), 1.87 (2 H, ddd, *J* 13.4, 8.6, 4.6, H11 ax), 0.91 (18 H, s, H10), 0.15 (9 H, s, H1), 0.13, (6 H, s, H7), 0.11 (6 H, s, H8).
δ_C (101 MHz, Chloroform-*d*)	175.6 (C, C13), 107.4 (C, C3), 88.9 (C, C2), 73.1 (CH, C6), 72.8 (C, C5), 51.9 (CH_3, C14), 34.5 (CH, C12), 31.5 (CH_2, C11), 26.1 (CH_3, C10), 18.3 (C, C9), 0.1 (CH_3, C1), -4.3 (CH_3, C7), -4.6 (CH_3, C8).
MS EI$^+$	HRMS (EI): *m/z*(%) = 537.2878 [M + Na] (calcd for $C_{25}H_{50}O_5Si_3Na$: 537.2864), 537.2- 100% [M + Na].
ν_{max}	3545 (OH), 2954, 2930, 2896 (CH), 1735 (CO_2Me).

A novel compound.

Synthesis of Methyl (1*S*,3*R*,5*S*)-3,4,5-tris((*tert*-butyldimethylsilyl)oxy)-4-(hex-1-yn-1-yl)cyclohexane-1-carboxylate 253

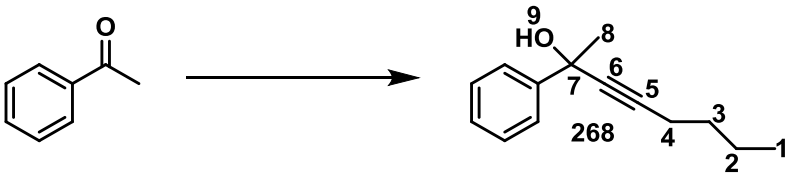


A solution of **250** (40 mg, 0.08 mmol) in CH_2Cl_2 (0.7 mL) was cooled to 0 °C. TBSOTf (85 mg, 0.32 mmol) was added with 2,6-lutidine (34 mg, 0.32 mmol). The reaction was left to stir at rt for 2 hr. The reaction was then poured into an aqueous saturated solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 x 15 mL). The organic extracts were dried with $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (99:1 petroleum ether: diethyl ether) gave the title compound **253** as a white crystalline solid (42 mg, 86%). M.p. 40-42 °C. R_f 0.82 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.69 (3 H, s, H19), 3.54 (2 H, dd, *J* 11.4, 4.3, H11), 2.64 (1 H, tt, *J* 5.5, 2.5, H17), 2.15 (2 H, t, *J* 7.3, H4), 1.92 (2 H, app.dt, *J* 12.9, 2.5, H16 eq), 1.84 (2 H, ddd, *J* 12.9, 11.4, 5.5, H16 ax), 1.48 (2 H, p, *J* 7.3, H3), 1.38 (2 H, h, *J* 7.3, H2), 0.91 (18 H, s, H15), 0.89 (11 H, s, H10 & H1), 0.17 (6 H, s, H8), 0.10 (6 H, s, H12), 0.09 (6 H, s, H13).
δ_C (101 MHz, Chloroform-*d*)	175.5 (C, C18), 84.8 (C, C5), 82.5 (C, C6), 76.4 (C, C7), 74.4 (CH, C11), 51.7 (CH_3,C19), 36.6 (CH, C17), 30.6 (CH_2, C3), 30.1 (CH_2, C16), 26.2 (CH_3, C15), 26.1 (CH_3, C10), 22.5 (CH_2, C2), 19.0 (CH_2, C12), 18.9 (CH_3, C13), 18.4 (CH_2, C4), 13.7 (CH_3, C1), -2.3 (CH_3, C8), -4.0 (C12), -4.8 (C13).
MS EI^+	HRMS (EI): *m/z*(%) = 635.3956 [M + Na] (calcd for $C_{32}H_{64}O_5Si_3Na$: 635.3959), 635.4- 100% [M + Na].
ν_{max}	2954, 2929, 2856, 2891, 2856 (CH), 1736 (C=O). C≡C not seen.

A novel compound.

Synthesis of 2-Phenyloct-3-yn-2-ol 268

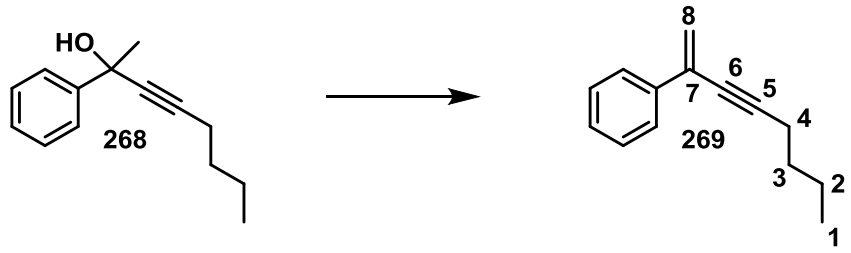


A solution of hexyne (409 mg, 4.99 mmol) in dry THF (49 mL) was cooled to -78 ^{o}C. ^{n}BuLi (2.09 M solution in ^{n}hexane, 2.39 mL, 4.99 mmol) was added dropwise over 5 minutes. The mixture was stirred for 30 minutes then acetophenone (500 mg, 4.16 mmol) was added. The reaction was allowed to warm to rt and stirred for a further 45 minutes. The reaction was then quenched using a saturated solution of NH_4Cl (25 mL), extracted with diethyl ether (3 x 20 mL) dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified via column chromatography (9:1 petroleum ether: diethyl ether) to give the title compound **268** as a colourless oil (603 mg, 72%). R_f 0.27 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	7.70 – 7.62 (2 H, m, Ar-H), 7.41 – 7.24 (3 H, m, Ar-H), 2.40 – 2.32 (1 H, m, H9), 2.29 (2 H, d, *J* 7.3, H4), 1.75 (3 H, s, H8), 1.55 (2 H, p, *J* 7.3, H3), 1.44 (2 H, h, *J* 7.3, H2), 0.94 (3 H, t, *J* 7.3, H1).
δ_C (101 MHz, Chloroform-*d*)	146.4 (Ar-C), 128.3 (Ar-C), 127.6 (Ar-C), 125.1 (Ar-C), 85.8 (C, C5), 83.9 (C, C6), 70.2 (C, C7), 33.7 (CH_3, C8), 30.9 (CH_2, C3), 22.1 (CH_2, C2), 18.6 (CH_2, C4), 13.7 (CH_3, C1).
MS ES$^+$	(ES): *m/z*(%) = 185.1- 50% [M + H - H_2O], 225.1- 100% [M + Na].

A known compound prepared according to a literature procedure and data agrees with literature values.[158]

Synthesis of Oct-1-en-3-yn-2-ylbenzene 269

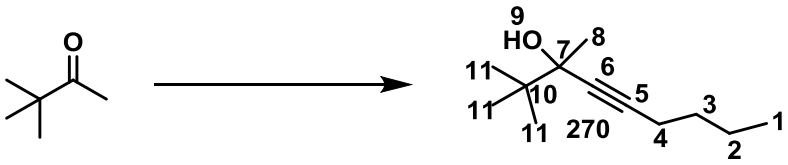


To a solution of propargylic alcohol **268** (100 mg, 0.49 mmol) in toluene (4.9 mL) was added MeOH (15.7 mg, 0.49 mmol) and $AuPPh_3NTf_2$ (3.6 mg, 1 mol%). The reaction was stirred at rt for 3 hr and then the solvent was removed under reduced pressure. The remaining residue was then directly purified via column chromatography (9:1 petroleum ether: diethyl ether) to give the title compound **269** as an oil (11 mg, 12%). R_f 0.74 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	7.70 – 7.62 (2 H, m, Ar-H), 7.40 – 7.27 (3 H, m, Ar-H), 5.84 (1 H, bs, H8), 5.58 (1 H, bs, H8), 2.42 (2 H, t, *J* 7.1, H4), 1.60 (2 H, p, *J* 7.1, H3), 1.49 (2 H, h, *J* 7.1, H2), 0.96 (3 H, t, *J* 7.1, H1).
δ_C (101 MHz, Chloroform-*d*)	138.0 (C, C7), 131.2 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 126.2 (Ar-C), 119.5 (CH_2, C8) 92.2 (C, C6), 79.9 (C, C5), 31.0 (CH_2, C3), 22.2 (CH_2, C2), 19.3 (CH_2, C4), 13.8 (CH_3, C1).
MS ES^+	(ES): *m/z*(%) = 185.1- 100% [M + H].

A known compound prepared according to a modified literature procedure[110] and data agrees with literature values.[159]

Synthesis of 2,2,3-Trimethylnon-4-yn-3-ol 270

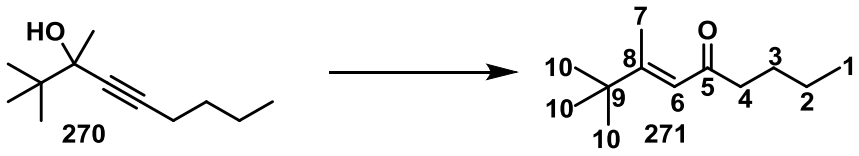


A solution of hexyne (493 mg, 6 mmol) in THF (49 mL) was cooled to -78 ^{o}C. ^{n}BuLi (2.5 M solution in ^{n}hexane, 2.8 mL, 6 mmol) was added dropwise over 5 minutes. The mixture was then left to stir for 20 minutes. 2,2-dimethyl1-3-butanone (500 mg, 6 mmol) was added and the reaction mixture stirred for 2 hr with gradual warming to rt. The reaction was then quenched using a saturated solution of NH_4Cl (25 mL), extracted with diethyl ether (3 x 20 mL) dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography (9:1 petroleum ether: diethyl ether) which gave the title compound **270** as a colourless oil (549 mg, 60%). R_f 0.56 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	2.20 (2 H, t, *J* 6.9, H4), 1.65 (1 H, s, H9), 1.53 – 1.37 (7 H, m, H3, H2, H8), 1.03 (9 H, s, H11), 0.91 (3 H, t, *J* 7.2, H1).
δ_C (101 MHz, Chloroform-*d*)	84.3 (C, C6), 83.9 (C, C5), 74.1 (C, C7), 38.4 (C, C10), 31.0 (CH_2, C3), 25.5 (CH_3, C8), 25.3 (CH_3, C11), 22.1 (CH_2, C2), 18.5 (CH_2, C4), 13.7 (CH_3, C1).
MS ES^+	(ES): *m/z*(%) = 165.2- 100% [M + H - H_2O], 197.2- 70% [M + H - H_2O + MeOH].

A known compound prepared according to a literature procedure and data agrees with literature values.[160]

Synthesis of *(E)*-2,2,3-Trimethylnon-3-en-5-one 271

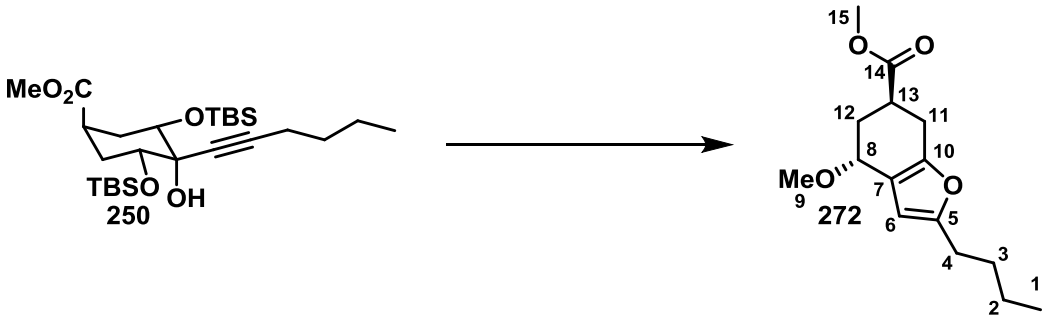


To a solution of propargylic alcohol **270** (100 mg, 0.54 mmol) in toluene (0.54 mL) was added MeOH (17 mg, 0.54 mmol) and $AuPPh_3NTf_2$ (3.9 mg, 1 mol%). The mixture was stirred for 4 hr at rt then purified directly by column chromatography (99:1 petroleum ether: diethyl ether) to give the title compound **271** as a colourless oil (35 mg, 68% BRSM). R_f 0.56 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	6.10 (1 H, d, *J* 1.1, H6), 2.43 (2 H, t, *J* 7.4, H4), 2.10 (3 H, d, *J* 1.1, H7), 1.55 (2 H, p, *J* 7.4, H3), 1.30 (2 H, h, *J* 7.4, H2), 1.09 (9 H, s, H10), 0.89 (3 H, t, *J* 7.4, H1).
δ_C (101 MHz, Chloroform-*d*)	202.6 (C, C5), 165.3 (C, C8), 120.3 (CH, C6), 44.6 (CH_2, C4), 37.9 (C, C9), 28.7 (CH_3, C10), 26.6 (CH_2, C3), 22.6 (CH_2, C2), 15.8 (CH_3, C7), 14.1 (CH_3, C1).
MS ES^+	(ES): *m/z*(%) = 183.1- 100% [M + H], 205.1- 10% [M + Na].

A known compound prepared according to a literature procedure and data agrees with literature values.[110]

Synthesis of Methyl (4*S*,6*R*)-2-butyl-4-methoxy-4,5,6,7-tetrahydrobenzofuran-6-carboxylate 272

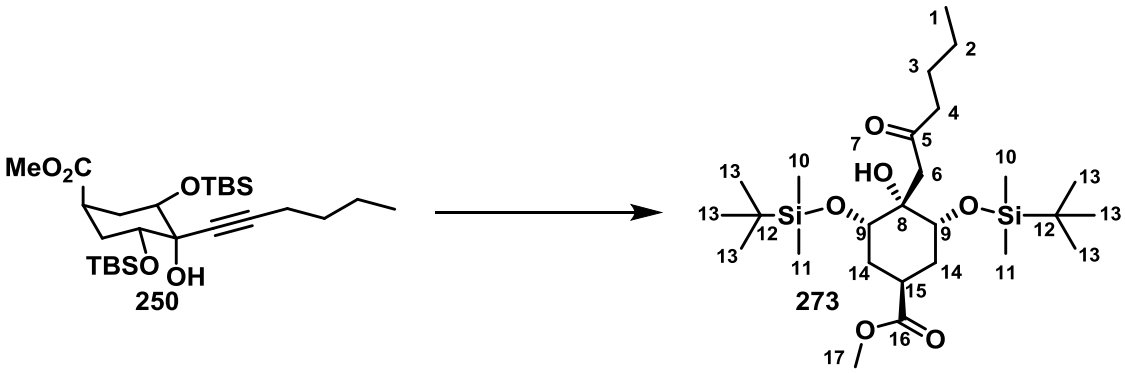


To a solution of propargylic alcohol **250** (100mg, 0.2 mmol) in toluene was added MeOH (6.4 mg, 0.2 mmol) and $AuPPh_3NTf2$ (7.4 mg, 5 mol%). The reaction was stirred overnight, followed by the addition of H_2O (3.6 mg, 0.2 mmol). The mixture was again allowed to stir overnight. The crude reaction mixture was then extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude mixture was purified via column chromatography (1:1 petroleum ether: diethylether) to give the title compound **272** (14 mg, 26%) as a colourless oil. R_f 0.19 (9:1 petroleum ether: diethyl ether).

δ_H (400 MHz, Chloroform-*d*)	5.95 (1 H, s, H6), 4.22 (1 H, app.t, *J* 3.4, H8), 3.73 (3 H, s, H15), 3.40 (3 H, s, H9), 3.10 (1 H, dddd, *J* 12.6, 11.3, 5.6, 2.7, H13), 2.90 (1 H, dd, *J* 16.5, 5.6, H11 eq), 2.72 (1 H, dd, *J* 16.5, 11.3, H11 ax), 2.56 (2 H, t, *J* 7.6, H4), 2.39 (1 H, app.dt, *J* 13.9, 2.7, H12 eq), 1.76 (1 H, ddd, *J* 13.9, 12.6, 3.4, H12 ax), 1.59 (2 H, p, *J* 7.6, H3), 1.36 (2 H, h, *J* 7.6, H2), 0.92 (3 H, t, *J* 7.6, H1).
δ_C (101 MHz, Chloroform-*d*)	175.5 (C, C14), 155.8 (C, C5), 149.4 (C, C10), 117.6 (C, C7), 105.1 (CH, C6), 71.1(CH, C8), 56.6 (CH_3, C9), 52.1 (CH_3, C15), 36.1 (CH, C13), 31.4 (CH_2 C12), 30.3 (CH_2, C3), 27.9 (CH_2, C4), 26.0 (CH_2, C4), 22.4 (CH_2, C2), 14.0 (CH_3, C1).
MS ES^+	HRMS (ES): *m/z*(%) = 235.1342 [M] (calcd for $C_{14}H_{19}O_3$: 235.1334), 235.1- 100% [M - OMe].
ν_{max}	2955, 2929, 2861, 2819 (CH), 1735 (C=O), 1637 (C=C).

A novel compound prepared according to a modified literature procedure.[110]

Synthesis of Methyl (1*S*,3*R*,4*S*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(2-oxohexyl)cyclohexane-1-carboxylate 273

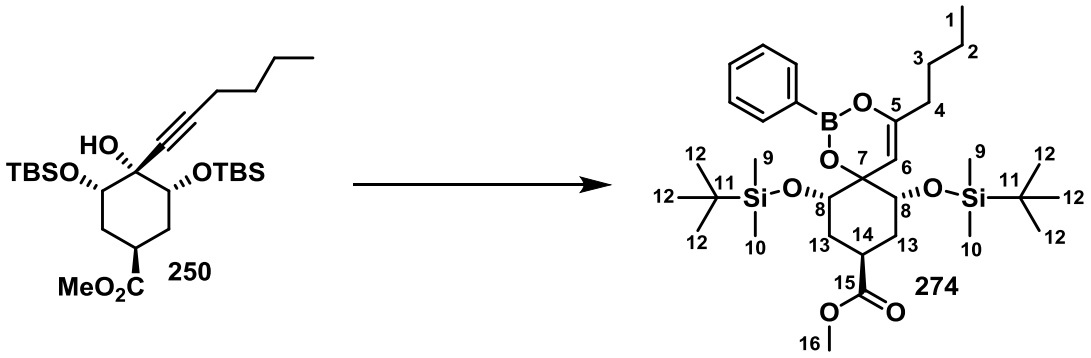


To a solution of propargylic alcohol **250** (67mg, 0.13 mmol) in toluene (0.13 mL) was added $AuPPh_3NTf_2$ (2 mg, 0.23 mmol) and MeOH (4.2 mg, 0.23 mmol). The mixture was stirred overnight at rt. The solvent was evaporated under reduced pressure and the remaining residue purified directly using column chromatography (9:1 petroleum ether: diethyl ether) to give the title compound **273** as a colourless oil (10 mg, 12% BRSM). R_f 0.29 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.98 (2 H, dd, *J* 9.8, 4.7, H9), 3.73 (3 H, s, H17), 2.77 (1 H, tt, *J* 9.8, 4.7, H15), 2.73 (2 H, s, H6), 2.40 (2 H, t, *J* 7.5, H4), 2.00 (2 H, dt, *J* 13.2, 4.7, H14 eq), 1.90 (2 H, ddd, *J* 13.2, 9.8, 4.7, H14 ax), 1.57 (1 H, bs, H7), 1.49 (2 H, p, *J* 7.3, H3), 1.29 (2 H, h, *J* 7.3, H2), 0.93 – 0.85 (21 H, m, H1, H13), 0.08 (6 H, s, H10), 0.01 (6 H, s, H11).
δ_C (101 MHz, Chloroform-*d*)	209.8 (C, C5), 175.2 (C, C16), 75.3 (C, C8) , 70.8 (CH, C9), 52.0 (CH_3, C17), 46.0 (CH_2, C6), 44.0 (CH_2, C4), 35.5 (CH, C15), 30.9 (CH_2, C14), 26.1 (CH_3, C13), 25.7 (CH_2, C3), 22.4 (C, C12), 18.2 (CH_2, C2), 14.0 (CH_3, C1), -4.2 (C10), -4.7 (C11).
MS ES^+	HRMS (ES): *m/z*(%) = 517.3373 [M + H] (calcd for $C_{26}H_{53}O_6Si_2$: 517.3381), 367.2- 100% [M - OH - OTBS - H], 517.3- 80% [M + H].
ν_{max}	3554 (OH), 2954, 2930, 2857, 2895 (CH), 1735 (CO_2Me), 1713 (C=O).

A novel compound prepared according to a modified literature procedure.[110]

Synthesis of Methyl (7R,9s,11S)-4-butyl-7,11-bis((*tert*-butyldimethylsilyl)oxy)-2-phenyl-1,3-dioxa-2-boraspiro[5.5]undec-4-ene-9-carboxylate 274

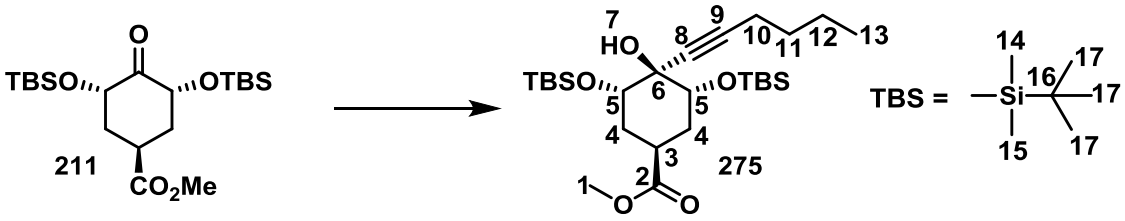


To a solution of **250** (349 mg, 0.7 mmol) in toluene (0.7 mL) was added phenylboronic acid (85 mg, 0.7 mmol) and PPh_3AuNTf_2 (5 mol%). The reaction was left to stir overnight at rt. The crude mixture had the solvent removed under reduced pressure and the remaining residue purified directly by column chromatography (9:1 petroleum ether: diethyl ether) to give the title compound **274** as a white solid (268 mg, 64%). M.p. 33-35 ^{o}C. R_f: 0.69 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Benzene-d_6)	8.32 – 8.24 (2 H, m, Ar-H), 7.41 – 7.33 (3 H, m, Ar-H), 4.44 (1 H, s, H6), 3.77 (2 H, dd, *J* 9.9, 6.1, H8), 3.46 (3 H, s, H16), 2.73 – 2.51 (1 H, m, H14), 2.36 (2 H, t, *J* 7.3, H4), 2.33 – 2.21 (4 H, m, H13 ax & eq), 1.79 (2 H, p, *J* 7.3, H3), 1.49 (2 H, h, *J* 7.3, H2), 1.05 (3 H, t, *J* 7.3, H1), 1.01 (18 H, s, H12), 0.23 (6 H, s, H9), 0.21 (6 H, s, H10).
δ_C (101 MHz, Benzene-d_6)	174.8 (C, C15), 153.1 (C, C5), 134.7 (Ar-C), 131.2 (Ar-C), 128.2 (Ar-C), 127.9 (Ar-C), 103.1 (CH, C6), 80.2 (C, C7), 72.5 (CH, C8), 51.3 (CH_3, C16), 36.9 (CH, C14), 34.4 (CH_2, C4), 30.3 (CH_2, C13), 28.8 (CH_2, C3), 25.9 (CH_3, C12), 23.1 (CH_2, C2), 18.2 (C, C11), 14.2 (CH_3, C1), -4.0 (CH_3, C9) , -4.51 (CH_3, C10).
^{11}B NMR δ (128 MHz, C6D6)	10.8 (B).
MS ES$^+$	HRMS (ES): *m/z*(%) = 603.3713 [M + H] (calcd for $C_{32}H_{56}O_6Si_2{}^{11}B$: 603.3708), 603.4- 100% [M^{11}B + H], 602.4-20% [M^{10}B + H].
ν_{max}	2929, 2954, 2857, 2895 (CH), 1734 (C=O Ester), 1696 (C=C enol boronate stretch).

A novel compound prepared according to a modified literature procedure.[110]

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-(hex-1-yn-1-yl)-4-hydroxycyclohexane-1-carboxylate 275

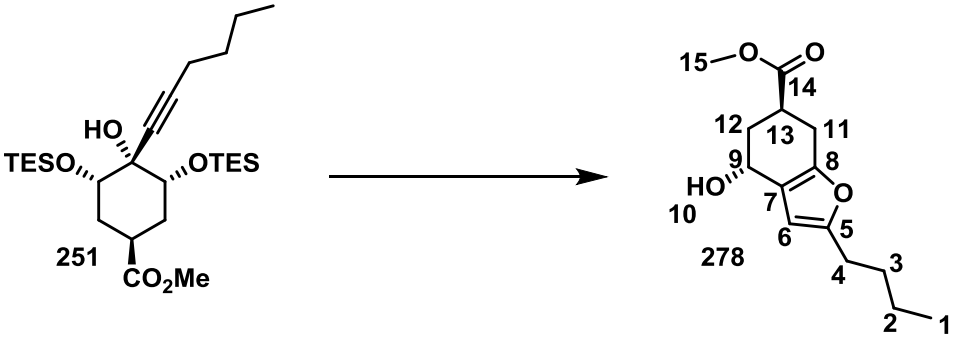


A solution of hexyne (238 mg, 2.9 mmol) was dissolved in dry toluene (24 mL) and cooled to -78 ^{o}C. ^{n}BuLi (2.29 M solution in ^{n}hexane, 1.26 mL, 2.9 mmol) was added dropwise and the reaction left to stir for 20 min. **211** (1 g, 2.39 mmol) was then added and the reaction left to stir for 2 hr with gradual warming to rt. The solution was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with diethyl ether (3 x 15 mL). The organics were separated, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified via column chromatography (9:1 petroleum ether: diethyl ether) to yield the title compound **275** as a colourless oil (54 mg, 5%) and (464 mg, 39% of **256**). R_f 0.56 (19:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.70 (3 H, s, H1), 3.53 (2 H, dd, *J* 11.5, 4.3, H5), 2.69 (1 H, tt, *J* 5.4, 2.5, H3), 2.65 (1 H, s, H7), 2.27 – 2.19 (2 H, m, H10), 2.13 (2 H, ddd, *J* 13.4, 4.3, 2.5, H4 eq), 1.81 (2 H, ddd, *J* 13.4, 11.5, 5.4, H4 ax), 1.51 – 1.41 (4 H, m, H11, H12), 0.90 (21 H, s, H17, H13), 0.09 (6 H, s, H14), 0.09 (6 H, s, H15).
δ_C (101 MHz, Chloroform-*d*)	175.0 (C, C2), 87.2 (C, C8), 78.4 (C, C9), 77.6 (C, C6), 73.4 (CH, C5), 51.9 (CH_3, C1), 36.5 (CH, C3), 33.2 (CH_2, C4), 31.0 (CH_2, C11 or 12), 25.9 (CH_3, C17), 21.9 (CH_2, C11 or 12), 18.6 (CH_2, C10), 18.2 (C, C16), 13.7 (CH_3, C13), -4.4 (CH_3, C14), -4.5 (CH_3, C15).
MS ES$^+$	HRMS (ES): *m/z*(%) = 521.3103 [M + Na] (calcd for $C_{26}H_{50}O_5Si_2Na$: 521.3094), 349.2- 100% [M - OTBS - OH + H], 481.3- 30% [M - OH], 521.3- 20% [M + Na].
ν_{max}	3595 (CH), 2954, 2930, 2856 (CH), 1736 (CO_2Me).

A novel compound.

Synthesis of Methyl (4*R*,6*R*)-2-butyl-4-hydroxy-4,5,6,7-tetrahydrobenzofuran-6-carboxylate 278

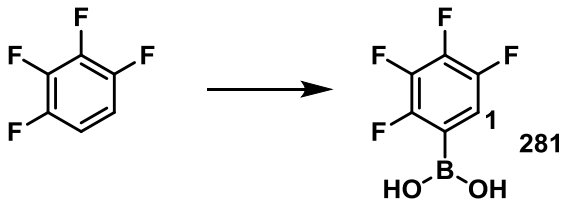


To a solution of propargylic alcohol **251** (160 mg, 0.32 mmol) in toluene (0.3 mL) was added phenyl boronic acid (39 mg, 0.32 mmol) and PPh_3AuNTf_2 (10 mol%). The mixture was left to stir overnight at rt. The solvent was removed under reduced pressure and the remaining residue purified directly by column chromatography (3:7 diethyl ether: petroleum ether) to give the title compound **278** as a colourless oil (14 mg, 17%). R_f 0.63 (3:7 diethyl ether: petroleum ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	5.96 (1 H, s, H6), 4.51 (1 H, app.t, *J* 3.0, H9), 3.13 (1 H, dddd, *J* 12.4, 11.2, 5.6, 3.1, H13), 3.76 (3H, s, H15), 2.88 (1 H, dd, *J* 16.4, 5.6, H11 eq), 2.73 (1 H, dd, *J* 16.4, 11.2, H11 ax), 2.54 (2 H, t, *J* 7.6, H4), 2.40 (1 H, app.dt, *J* 13.9, 3.1, H12 eq), 1.82 (1 H, ddd, *J* 13.9, 12.4, 3.0, H12 ax), 1.63 – 1.52 (3 H, m, H3, H10), 1.36 (2 H, s, *J* 7.4, H2), 0.91 (3 H, t, *J* 7.4, H1).
δ_C (101 MHz, Chloroform-*d*)	175.5 (C, C14), 155.9 (C, C5), 149.4 (C, C8), 118.0 (C, C7), 104.5 (CH, C6), 67.6 (CH, C9), 52.1 (CH_3, C15), 36.0 (CH, C13), 32.4 (CH_2, C12), 30.3 (CH_2, C3), 27.9 (CH_2, C4), 25.8 (CH_2, C11), 22.4 (CH_2, C2), 13.9 (CH_3, C1).
MS TOF ES^+	HRMS (ES): *m*/*z*(%) = 235.1317 [M + OH] (calcd for $C_{14}H_{29}O_3$: 235.1334), 102.1- 100%, 203.0- 70%, 204.0- 80%.
ν_{max}	3454 (OH), 2953, 2928, 2859 (CH), 1728 (C=O).

A novel compound prepared according to a modified literature procedure.[110]

Synthesis of (2,3,4,5-Tetrafluorophenyl)boronic acid 281

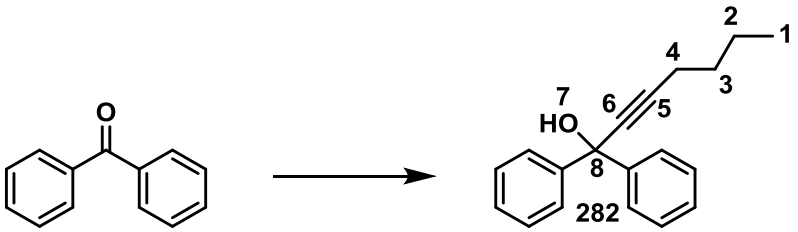


A solution of diisopropylamine (1.2g, 8.3 mmol) in THF (12.5 mL) was cooled to -78 ^{o}C. ^{n}BuLi (2.4 M solution in ^{n}hexane, 3.6 mL, 8.3 mmol) was added and the mixture was stirred for 5 minutes. The resulting solution of LDA was added dropwise over 5 minutes to a solution of tetrafluorobenzene (1g, 6.6 mmol) in THF 37.5 (mL) at -78 ^{o}C, and stirred for 1 hr. Whilst maintaining the mixture at -78 ^{o}C, the solution was then transferred via cannula (cooled to -78 ^{o}C by swabbing the cannula with cotton wool dipped in dry ice and acetone) to a solution of $B(OMe)_3$ (1g, 10 mmol) in THF (12.5 mL) at -78 ^{o}C. The reaction was left to stir overnight with gradual warming to rt. The crude mixture was then added to a saturated aqueous solution of NH_4Cl (30 mL) and the mixture extracted with diethyl ether (3 x 30 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude material was then recrystallised from boiling water and 1 drop of conc. HCl to give the title compound **281** as a white crystalline product (325 mg, 25%).

δ_H (300 MHz, DMSO-d_6 with 1 drop of D_2O)	6.29 (1 H, dddd, *J* 10.4, 8.9, 4.6, 2.7, H1).
δ_F (282 MHz, Methylene Chloride-d_2)	-135.85 – -136.27 (m), -139.22 – -139.80 (m), -151.36 – -151.90 (m), -156.86 – -157.36 (m).
MS ES$^-$	(ES): *m*/*z*(%) = 193.1 -100% [M].

A known compound prepared according to a literature procedure and data agrees with literature values including the inability to obtain a ^{13}C NMR. [118, 161]

Synthesis of 1,1-Diphenylhept-2-yn-1-ol 282

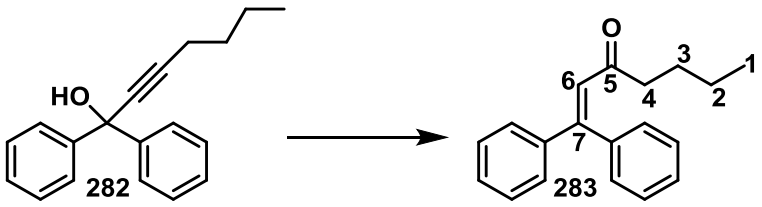


To a solution of hexyne (419 mg, 5.1 mmol) in THF (1.14 mL) at -78 ^{o}C was added ^{n}BuLi (2.29 M solution in ^{n}hexane, 2.2 mL, 5.1 mmol). The mixture was allowed to stir for 20 minutes followed by the addition of benzophenone (250 mg, 1.37 mmol). The reaction was stirred for 3 hr with gradual warming to rt. The mixture was then quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL) extracted with ethyl acetate (3 x 10 mL), dried with $MgSO_4$, filtered and then solvents removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **282** as a colourless oil (246 mg, 67%). R_f 0.37 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (300 MHz, Chloroform-*d*)	7.60 – 7.50 (4 H, m, Ar-H), 7.32 – 7.13 (6 H, m, Ar-H), 2.65 (1 H, s, H7), 2.28 (2 H, t, *J* 7.0, H4), 1.52 (2 H, p, *J* 7.0, H3), 1.39 (2 H, h, *J* 7.0, H2), 0.87 (3H, t *J* 7.0, H1).
δ_C (101 MHz, Chloroform-*d*)	145.6 (C) 128.2 (C) 127.5 (C) 126.0 (C) 88.4 (C) 83.1 (C) 74.6 (C) 30.8 (C) 22.1 (C) 18.6 (C) 13.6 (C).
MS TOF AP$^+$	(AP): *m*/*z*(%) = 264.2- 100% [M], 265.2- 90% [M - H].

A known compound prepared according to a literature procedure and data agrees with literature values.[158]

Synthesis of 1,1-Diphenylhept-1-en-3-one 283



To a solution of propargylic alcohol **282** (50 mg, 0.19 mmol) in toluene (0.5 mL) was added 2,3,4,5-tetrafluorophenylboronic acid (7 mg, 0.038 mmol). The reaction was left overnight at 25 ^{o}C. The solvent was removed by reduced pressure and the residue directly purified by column chromatography (9:1 petroleum ether: diethyl ether) to give the title compound **283** as a colourless oil (25 mg, 50%). R_f 0.49 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (300 MHz, Chloroform-*d*)	7.87 – 7.15 (10 H, m, Ar-H), 6.59 (1 H, s, H6), 2.24 (2 H, t, *J* 7.3, H4), 1.48 (2 H, p, *J* 7.3, H3), 1.19 (2H, h, *J* 7.3, H2), 0.81 (3H, t, *J* 7.3, H1).
δ_C (101 MHz, Chloroform-*d*)	202.7, 153.2, 141.1, 139.2, 132.5, 130.2, 129.4, 128.6, 128.5, 128.4, 126.8, 43.0, 26.6, 22.4, 13.9.
MS AP^+	(AP): *m*/*z*(%) = 265.2- 100% [M + H].
ν_{max}	3058, 2957, 2930, 2872 (CH), 1658 (C=C-C=O).

A known compound prepared according to a modified literature procedure[110] data in agreement with literature values.[116]

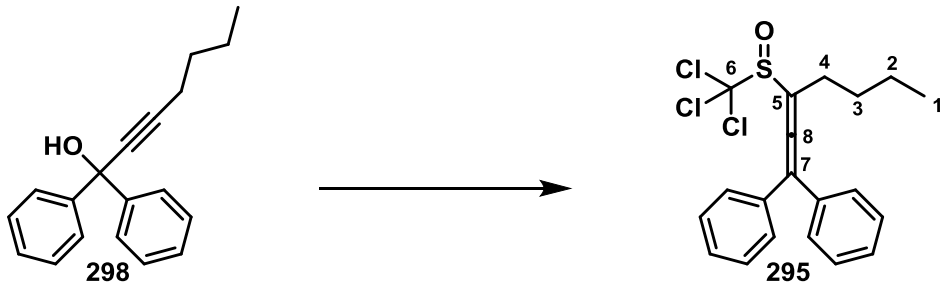
Synthesis of Methyl (1*R*,3*R*,4*R*,5*S*)-4-(hex-1-yn-1-yl)-3,4-dihydroxy-5-((triethylsilyl)oxy)cyclohexane-1-carboxylate 284

To a solution of propargyl alcohol **251** (67 mg, 0.13 mmol) in toluene (0.3 mL) was added 2,3,4,5-tetrafluoroboronic acid (25 mg, 0.13 mmol). The mixture was stirred overnight at 25 ^{o}C. The solvent was then removed under reduced pressure and the residue purified directly by column chromatography (8:2 petroleum ether: diethyl ether) to give the title compound **284** as an oil (15 mg, 30%). R_f 0.56 (8:2 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	4.06 (1 H, dt, *J* 4.1, 1.9, H10), 3.87 (1 H, dt, *J* 8.0, 3.2, H11), 3.70 (3 H, s, H18), 3.46 (1 H, d, *J* 10.4, H7), 3.23 (1 H, s, H9), 2.96 – 2.83 (1 H, m, H16), 2.24 – 2.10 (5 H, m, H4, H14 eq, H15 ax/eq), 1.98 (1 H, dt, *J* 14.4, 4.1, H14 ax), 1.48 (2 H, p, *J* 7.1, H3), 1.38 (2 H, h, *J* 7.1, H2), 0.98 (9 H, t, *J* 7.5, H13), 0.89 (3 H, t, *J* 7.1, H1), 0.66 (6 H, q, *J* 7.5, H12).
δ_C (101 MHz, Chloroform-*d*)	175.7 (C, C17), 88.1 (C, C5) , 79.2 (C, C6), 75.6 (CH, C10), 74.6 (CH, C11), 70.0 (C, C8), 52.0 (CH_3, C18), 33.1 (CH_2, C14), 32.5 (CH_2, C15), 31.9 (CH, C16), 30.6 (CH_2, C3), 22.2 (CH_2, C2), 18.6 (CH_2, C4), 13.7 (CH_3, C1), 6.9 (CH_3, C13), 4.81 (CH_2, C12).
MS TOF ES^+	HRMS (ES): *m/z*(%) = 407.2219 [M + Na] (calcd for $C_{20}H_{36}O_5SiNa$: 407.2230), 407.2- 60% [M + Na], 791.5- 100% [M + M].
ν_{max}	3484 (OH), 2956, 2877 (CH), 1736 (C=O).

A novel compound prepared according to a modified literature procedure.[118]

Synthesis of (3-((Trichloromethyl)sulfinyl)hepta-alene-1,1-diyl)dibenzene 295

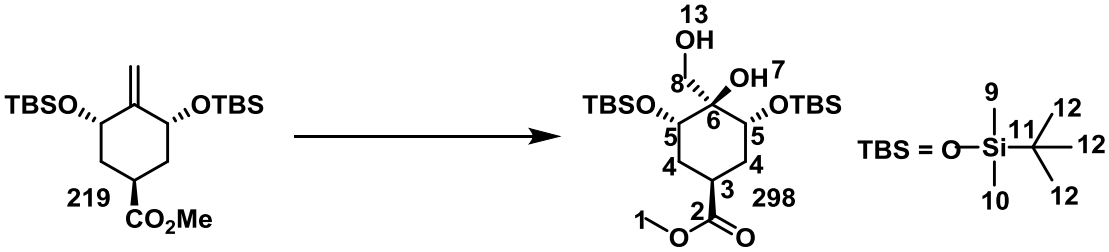


To a solution of propargyl alcohol **283** (100 mg, 0.38 mmol) in CH_2Cl_2 (3.8 mL) cooled to -78 ^oC was added $SClCCl_3$ (41 µL, 0.38 mmol) and Et_3N (52 µL, 0.38 mmol). The mixture was stirred overnight with gradual warming to rt. The mixture was then added to brine (10 mL) and extracted with diethyl ether (3 x 10 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **295** as a yellow oil (122 mg, 78%). R_f 0.36 (9:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	7.43 – 7.32 (10 H, m, Ar-H), 2.68 (1 H, ddd, *J* 15.7, 9.3, 6.4, H4), 2.56 (1 H, ddd, *J* 15.7, 9.2, 5.9, H4), 1.72 – 1.49 (2 H, m, H3), 1.38 (2 H, h, *J* 7.4, H2), 0.87 (3 H, t, *J* 7.4, H1).
δ_C (101 MHz, Chloroform-*d*)	207.1 (C, C6), 134.2 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 119.9 (C, C7), 114.0 (C, C5), 108.8 (C, C8), 30.4 (CH_2, C4), 25.1 (CH_2, C3), 22.3 (CH_2, C2), 13.8 (CH_3, C1).
MS TOF ES^+	HRMS (ES): *m/z*(%) = 247.1489 [M- Cl_3CSO] (calcd for $C_{19}H_{19}$: 247.1487), 247.2- 100% [M - Cl_3CSO].
ν_{max}	3059, 2958, 2930, 2871 (CH).

A novel compound prepared according to a modified literature procedure.[162]

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(hydroxymethyl)cyclohexane-1-carboxylate 298

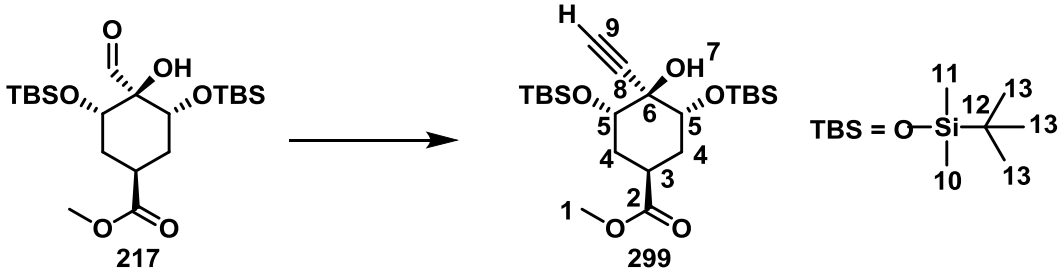


To a solution of alkene **219** (269 mg, 0.65 mmol) in acetone (2.6 mL), water (2.6 mL) and ^{t}butanol (1.3 mL) was added NMO (83 mg, 0.71 mmol) followed by OsO_4 (2 drops of a 4% w/v in water). The mixture was then heated to 45 ^{o}C for 2 hr. The reaction was then quenched with a saturated aqueous sodium bisulfite solution (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined washed with 1 M HCl (10 mL) and brine (10 mL) then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure column chromatography (1:1 petroleum ether: diethyl ether) to afford the title compound **298** as a white solid (163 mg, 56%). R_f 0.43 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.91 (2 H, d, *J* 6.2, H8), 3.72 (2H, dd, *J* 11.7, 4.5, H5), 3.71 (3H, s, H1) 3.16 (1 H, t, *J* 6.2, H13), 3.05 (1 H, s, H7), 2.76 (1 H, tt, *J* 5.4, 3.0, H3), 2.21 (2 H, app.dt, *J* 13.6, 3.0, H4 eq), 1.61 (2 H, ddd, *J* 13.6, 11.7, 5.4, H4 ax), 0.89 (18 H, s, H12), 0.12 (6 H, s, H9), 0.10 (6 H, s, H10).
δ_C (101 MHz, Chloroform-*d*)	174.6 (C, C2), 75.3 (C, C6), 74.3 (CH, C5), 61.6 (CH_2, C8), 52.0 (CH_3, C1), 36.3 (CH, C3), 32.8 (CH_2, C4), 25.9 (CH_3, C12), 18.1 (C, C11), -4.7 (CH_3, C9), -4.8 (CH_3, C10).
ν_{max}	3487 (OH), 2954, 2929, 2857, 2890 (CH), 1723 (C=O Ester).

A known compound prepared according to a PhD thesis procedure and data agrees with publication values.[91]

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-ethynyl-4-hydroxycyclohexane-1-carboxylate 299

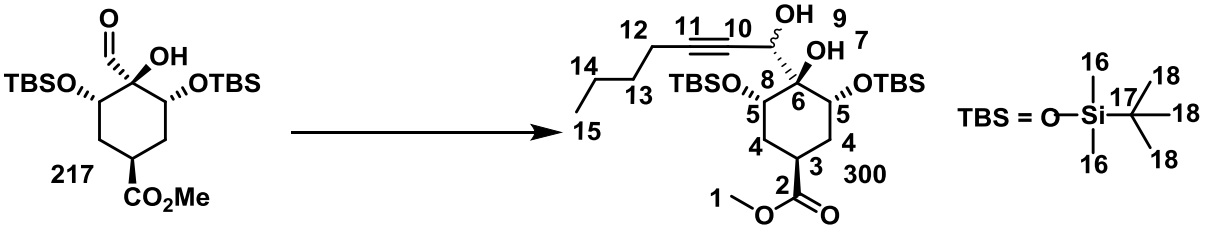


To a solution of Ohira-Bestmann reagent (23 mg, 0.12 mmol) in MeOH (1.1 mL) was added aldehyde **217** (50 mg, 0.11 mmol). K_2CO_3 (30 mg, 0.22 mmol) was then added and the reaction stirred at rt for 1 hr. The reaction was then added to brine (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (9:1 petroleum ether: diethyl ether) to yield the title compound **299** as a white crystalline solid (30mg, 62%). M.p. 63-65 ^{o}C. R_f 0.26 (9:1 petroleum ether: diethyl ether).

δ_H (400 MHz, Chloroform-*d*)	3.71 (3 H, s, H1), 3.58 (2 H, dd, *J* 11.8, 4.4, H5), 2.78 (1 H, s, H7), 2.73 (1 H, tt, *J* 5.5, 2.5, H3), 2.39 (1 H, s, H9), 2.18 (2 H, ddd, *J* 13.5, 4.4, 2.5, H4 eq), 1.85 (2 H, ddd, *J* 13.5, 11.8, 5.5, H4 ax), 0.91 (18 H, s, H13), 0.11 (6 H, s, H11), 0.10 (6 H, s, H10).
δ_C (101 MHz, Chloroform-*d*)	174.9 (C, C2), 81.5 (C, C8), 78.4 (C, C6), 74.8 (CH, C9), 73.1 (CH, C5), 52.0 (CH_3, C1), 36.5 (CH, C3), 33.0 (CH_2, C4), 25.9 (CH_3, C13), 18.3 (C, C12), -4.4 (CH_3, C11), -4.5 (CH_3, C10).
MS ES$^+$	HRMS (ES): *m/z*(%) = 465.2460 [M + Na] (calcd for $C_{22}H_{42}O_5NaSi_2$: 465.2468), 465.2- 100% [M + Na].
ν_{max}	3307 (C≡C-H), 2951, 2929, 2856, 2888 (CH), 1736 (CO_2Me).

A novel compound prepared according to a modified literature procedure.[163]

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(1-hydroxyhept-2-yn-1-yl)cyclohexane-1-carboxylate 300

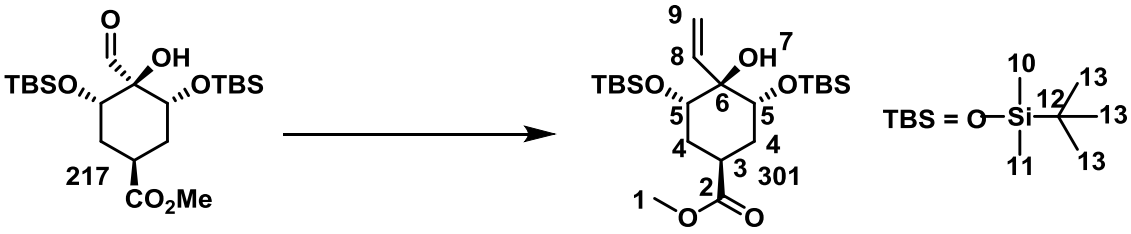


To a solution of hexyne (18 mg, 0.22 mmol) in toluene (11 mL) cooled to –78 ^{O}C, ^{n}BuLi (2.29 M solution in ^{n}hexane, 96 µL, 0.22 mmol) was added and the mixture left to stir for 20 minutes. Aldehyde **217** (50 mg, 0.11 mmol) was added and the mixture stirred for 2 hr with gradual warming to rt. The reaction was then quenched with saturated aqueous NH_4Cl (15 mL) and extracted with diethyl ether (3 x 5 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure to give the title compound **300** as an oil (10 mg, 40%). R_f 0.33 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.85 (1 H, app.t, *J* 2.0, H8), 3.96 (2 H, dt, *J* 12.3, 3.3, H5), 3.68 (3 H, s, H1), 3.04 (1 H, tt, *J* 9.9, 5.5, H3), 2.24 (2 H, td, *J* 7.3, 2.0, H12), 2.03 – 1.91 (4 H, m, H4 ax/eq), 1.51 (2 H, p, *J* 7.3, H13), 1.40 (2 H, h, *J* 7.3, H14), 0.92 (3 H, t, *J* 7.3, H15), 0.91 (18 H, s, H9) 0.89 (18 H, s, H9), 0.10 (3 H, s, H16), 0.09 (3 H, s, H16), 0.08 (3 H, s, H16), 0.08 (3 H, s, H16). H7, H9 not visible. 1:1 mixture of diastereoisomers
δ_C (101 MHz, Chloroform-*d*)	191.7 (C, C2), 88.7 (C), 78.7 (C), 74.8 (C), 69.6 (C5), 64.8 (CH, C8), 51.8 (CH_3, C1), 32.9 (CH_2, C4), 32.1 (CH_2, C13), 30.8 (C, C17), 26.1 (C, C2), 22.2 (CH_2, C12), 18.7 (C), 18.2 (CH_3, C15), 13.7 (C), -4.7 (C), -4.8 (C).
MS ES$^+$	HRMS (ES): *m/z*(%) = 529.3386 [M + H] (calcd for $C_{27}H_{53}O_6Si_2$: 529.3381), 551.3- 100% [M + Na], 511.3- 60% [M + H - H_2O], 529.3- 40% [M + H].

A novel compound.

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-vinylcyclohexane-1-carboxylate 301

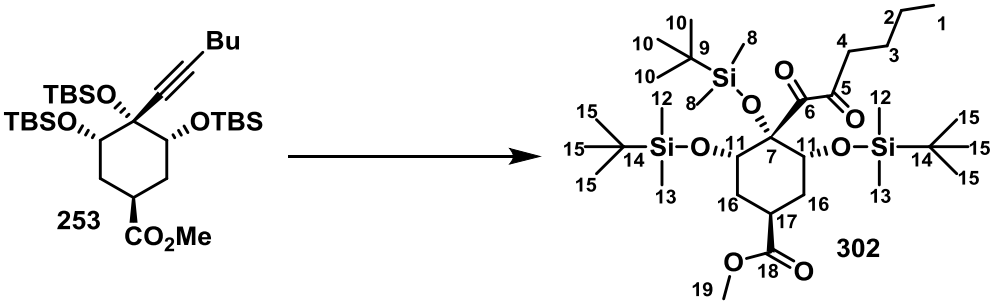


To a suspension of CH_3PPh_3Br (57 mg, 0.17) in toluene (1.1 mL) was added ^{n}BuLi (2.29 M solution in ^{n}hexane, 4 µL, 0.17 mmol). The mixture was then stirred at rt for 20 minutes. Aldehyde **217** (50 mg, 0.11 mmol) was added and the reaction left to stir for 1 hr at rt. The solvents were then removed under reduced pressure and the remaining material re-suspended in cyclohexane (5 mL). Oxalyl chloride (14 µL, 0.17 mmol) was added and the reaction swirled until effervescence had stopped. The mixture was then washed with $NaHCO_2$ (2 x 15 mL) and NH_4Cl (2 x 15 mL), extracted with diethyl ether (3 x 15 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give the title compound **301** as a colourless oil (7 mg, 14%). R_f 0.46 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	6.15 (1 H, dd, *J* 17.4, 11.1, H8), 5.44 (1 H, dd, *J* 17.4, 2.0, H9 *cis*), 5.31 (1 H, dd, *J* 11.1, 2.0, H9 *trans*), 3.71 (3 H, s, H1), 3.63 (2 H, dd, *J* 10.7, 4.2, H5), 2.85 – 2.76 (1 H, m, H3), 2.21 – 2.11 (2 H, m, H4 eq), 1.68 (2 H, ddd, *J* 13.7, 10.7, 5.2, H4 ax), 0.87 (18 H, s, H13), 0.08 (12 H, s, H10/H11).
δ_C (101 MHz, Chloroform-*d*)	175.2 (C), 136.3 (C), 117.3 (C), 73.9 (C), 51.9 (C), 35.9 (C), 32.9 (C), 29.9 (C), 25.9 (C), 18.3 (C), -4.5 (C), -4.6 (C).
MS ES$^+$	HRMS (ES): *m/z*(%) = 467.2629 [M + Na] (calcd for $C_{22}H_{44}O_5NaSi_2$: 467.2625), 467.3- 100% [M + Na].
ν_{max}	3482 (OH), 2955, 2930, 2857 (CH), 1735 (C=O Ester).

A novel compound.

Synthesis of Methyl (1*S*,3*R*,5*S*)-3,4,5-tris((*tert*-butyldimethylsilyl)oxy)-4-(2-oxohexanoyl)cyclohexane-1-carboxylate 302

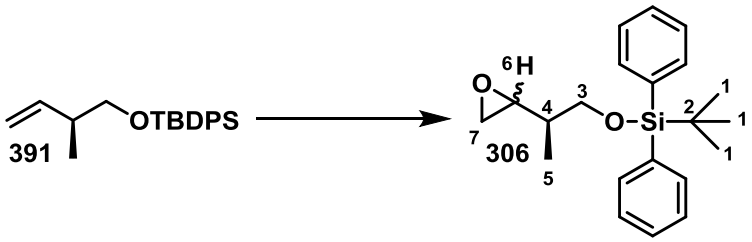


A solution of **253** (40 mg, 0.065 mmol) in CH_2Cl_2 (2 mL) and MeCN (2 mL) was added to a solution of $NaIO_4$ (0.038 mmol, 5.4 mmol) in water (3 mL). The mixture was stirred before the addition of $RuCl_3.xH_2O$ (0.038 mmol, 5.4 mmol) as a solution in water (1 mL). The reaction was stirred for 1.5 hr and filtered through a pad of silica. The filtrate was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **302** as a yellow oil (22 mg, 52%). R_f 0.48 (19:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.51 (2 H, dd, *J* 11.9, 4.4, H11), 3.77 (3 H, s, H19), 2.77 (2 H, t, *J* 7.3, H4), 2.75 – 2.72 (1 H, m, H17), 2.05 (2 H, ddd, *J* 12.7, 4.4, 2.2, H16 eq), 1.96 (2 H, ddd, *J* 12.7, 11.9, 5.5, H16 ax), 1.51 (2 H, p, *J* 7.3, H3), 1.33 (2 H, h, *J* 7.3, H2), 0.93 (9 H, s, H10), 0.90 (3 H, t, *J* 7.3, H1), 0.79 (18 H, s, H15), 0.18 (6 H, s, H12), 0.03 (6 H, s, H13), -0.11 (6 H, s, H8).
δ_C (101 MHz, Chloroform-*d*)	198.8 (C, C5/6), 196.6 (C, C5/6), 175.0 (C, C18), 89.5 (C, C7), 72.2 (CH, C11), 52.1 (CH_3, C19), 38.0 (CH_2, C4), 36.8 (CH, C17), 29.9 (CH_2, C16), 26.9 (CH_3, C10), 26.0 (CH_3, C15), 24.9 (CH_2, C3), 22.3 (CH_2, C2), 20.0 (C, C9), 18.1 (C, C14), 14.0 (CH_3, C1), -1.50 (CH_3, C8), -4.09 (CH_3, C12), -4.54 (CH_3, C13).
MS ES^+	HRMS (ES): *m*/*z*(%) = 667.3862 [M + Na] (calcd for $C_{32}H_{64}O_7NaSi_3$: 667.3858), 513.3- 100 % [M - OTBS], 667.4- 50 % [M + Na].
ν_{max}	2956, 2930, 2857, 2896 (CH), 1736 (C=O), 1715 (CO_2Me).

A novel compound prepared according to a modified literature procedure.[164]

Synthesis of *tert*-Butyl((2*R*)-2-(oxiran-2-yl)propoxy)diphenylsilane 306

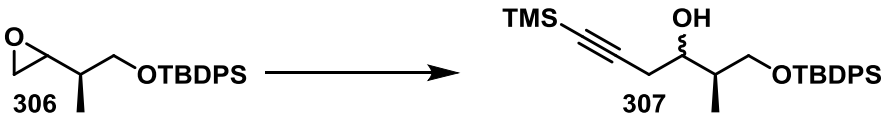


To a solution of alkene **391** (1.26g, 3.88 mmol) in dry CH_2Cl_2 (39 mL) was added *m*CPBA (77% w/w 1.6 g, 9.3 mmol) under argon. The resultant solution was stirred for 15 minutes at 0 ^{o}C then allowed to stir overnight at rt. The mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine (25 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford a white powder which was then purified by column chromatography (19:1 petroleum ether: diethyl ether) to afford the title compound **306** as a colourless oil in quantitative yield. R_f 0.33 (19:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*) (1:1 Mixture of diastereoisomers)	7.73 – 7.63 (4 H, m, Ar-H), 7.49 – 7.34 (6 H, m, Ar-H), 3.75 (1 H, dd, *J* 9.9, 5.3, H3, diast1), 3.70 (1 H, dd, *J* 9.9, 4.8, H3, diast1), 3.68 – 3.59 (2 H, m, H3, diast2), 2.99 (1 H, ddd, *J* 6.9, 4.0, 2.8, H6, diast1), 2.87 (1 H, ddd, *J* 6.8, 4.0, 2.7, H6, diast2), 2.76 (2 H, ddd, *J* 9.3, 5.0, 4.0, H7, diast1), 2.61 (1 H, dd, *J* 5.0, 2.7,H7, diast2), 2.55 (1 H, dd, *J* 5.1, 2.8, H7, diast2), 1.68 – 1.49 (2 H, m, H4), 1.07 (18 H, d, *J* 4.6, H1), 1.01 (6 H, d, *J* 6.8, H5).
δ_C (101 MHz, Chloroform-*d*) (1:1 Mixture of diastereoisomers)	135.7 (Ar-C), 135.6 (Ar-C), 133.8 (Ar-C), 133.8 (Ar-C), 133.7 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 66.5 (C3), 66.2 (C3), 55.2 (C6), 54.1 (C6), 47.0 (C7), 45.8 (C7), 39.2 (C4), 38.6 (C4), 26.9 (C1), 19.4 (C2), 19.3 (C2), 13.4 (C5), 12.7 (C5).
ν_{max}	3071 (CH epoxide), 2930, 2899 (CH).

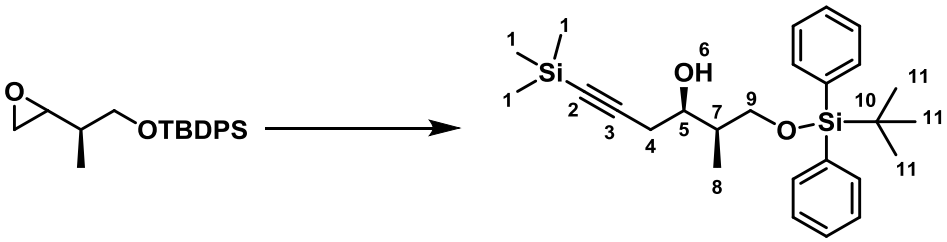
A known compound prepared according to a literature procedure.[127] Data is correct but literature has data missing from ^{1}H NMR. Data agrees with literature values.[165]

Synthesis of (2*R*,3*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol and (2*R*,3*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol 307

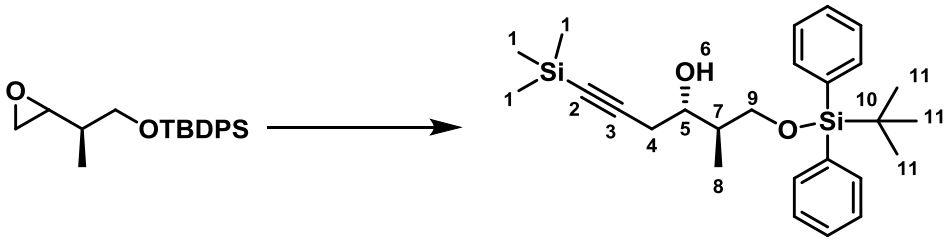


A solution of trimethylsilylacetylene (367 mg, 3.74 mmol) in dry THF (5.3 mL) was cooled to -78 ^{o}C. ^{n}BuLi (1.9 M solution in ^{n}hexane, 1.68 mL, 3.21 mmol) was added and the reaction left to stir for 20 minutes. The reaction was then allowed to warm to 0 ^{o}C followed by the addition of $BF_3.OEt_2$ (0.26 mL, 2.14 mmol) and a solution of epoxide **306** (365 mg, 1.07 mmol) in dry THF (5.3 mL). The reaction was then stirred for 1 hr with gradual warming to rt, before being quenched with a saturated aqueous solution of NH_4Cl (10 mL) and then extracted with diethyl ether (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude oil was then purified by column chromatography (9:1 petroleum ether: diethyl ether) to give firstly (*R*)(*R*) (141 mg, 30%) R_f 0.33 followed by (*R*)(*S*) R_f 0.29 (66 mg, 14%), along with mixed fractions of (263 mg) visualised in vanillin.

(*R*)(*R*)
Diastereomer

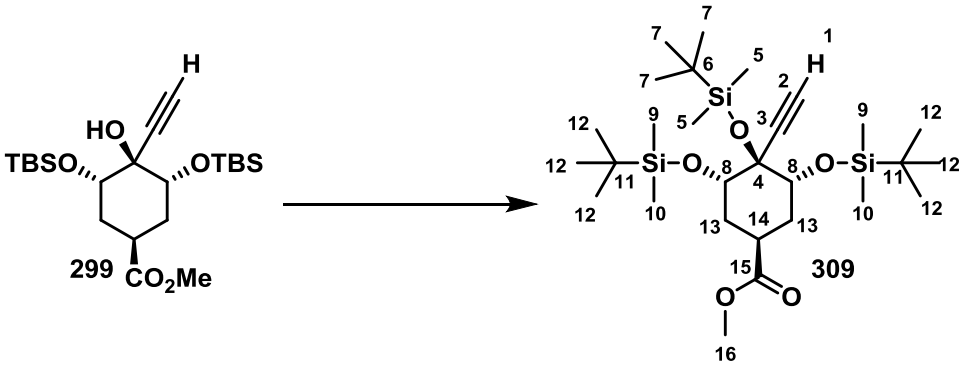


δ_H (400 MHz, Chloroform-*d*) 7.72 – 7.64 (4 H, m, Ar-H), 7.47 – 7.35 (6 H, m, Ar-H), 3.79 (1 H, dd, *J* 10.3, 4.3, H4), 3.79 – 3.70 (1 H, m, H6), 3.67 (1 H, dd, *J* 10.3, 6.5, H4), 3.50 – 3.43 (1 H, m, H6), 2.51 (2 H, dq, *J* 17.0, 4.8, H9), 2.02 – 1.91 (1 H, m, H5), 1.06 (9 H, s, H11), 0.91 (3 H, d, *J* 7.0, H8), 0.16 (9 H, s, H1).

δ_C (101 MHz, Chloroform-*d*)	135.7 (Ar-C), 135.7 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 127.9 (Ar-C), 103.8 (C, C3), 87.1 (C, C2), 73.8 (CH, C5), 67.7 (CH_2, C9), 39.3 (CH, C7), 27.0 (CH_3, C11), 26.8 (CH_2, C4), 19.3 (C, C10), 13.7 (CH_3, C8), 0.3 (CH_3, C1).
MS ES^+	(ES): *m*/*z*(%) = 461.2- 100% [M + Na], 421.2- 80% [M + H - H_2O].
(*S*)(*R*) Diastereomer	
δ_H (400 MHz, Chloroform-*d*)	7.71 – 7.63 (4 H, m, Ar-H), 7.47 – 7.36 (6 H, m, Ar-H), 4.04 (1 H, tt, *J* 6.5, 2.7, H5), 3.76 (1 H, dd, *J* 10.1, 4.1, H9), 3.69 (1 H, dd, *J* 10.1, 5.4, H9), 2.88 (1 H, s, H6), 2.51 (1 H, dd, *J* 16.8, 6.5, H4), 2.42 (1 H, dd, *J* 16.8, 7.1, H4), 1.93 (1 H, dddd, *J* 7.1, 5.4, 4.1, 2.7, H7), 1.07 (9 H, s, H11), 0.97 (3 H, d, *J* 7.1, H8) 0.14 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	135.7 (Ar-C), 133.3 (Ar-C), 133.2 (Ar-C), 123.0 (Ar-C), 127.9 (Ar-C), 103.9 (C, C3), 87.0 (C, C2), 72.4 (CH, C5), 68.3 (CH_2, C9), 38.5 (CH, C7), 27.0 (CH_3, C11), 26.2 (CH_2, C4), 191 (C, C10), 10.3 (CH_3, C8), 0.23 (CH_3, C1).

A known compound prepared according to a literature procedure.[127] Data is correct but literature has data missing from ^{1}H NMR.

Synthesis of Methyl (1*S*,3*R*,4*R*,5*S*)-3,4,5-tris((*tert*-butyldimethylsilyl)oxy)-4-ethynylcyclohexane-1-carboxylate 309

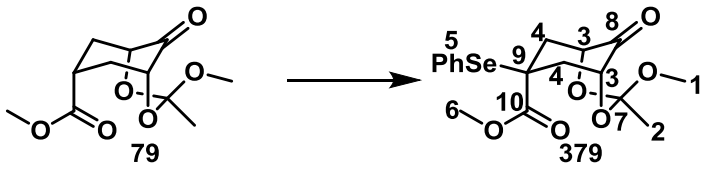


A solution of **299** (68 mg, 0.15 mmol) in dry CH_2Cl_2 (1.5 mL) was cooled to 0 ^{o}C. 2,6-lutidine (192.8 mg, 1.8 mmol) was added dropwise followed by the addition of TBS-OTf (476 mg, 1.8 mmol). The mixture was warmed to rt overnight. The crude mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (99:1 petroleum ether: diethyl ether) gave the title compound **309** as a white crystalline material (60 mg, 72%). M.p. 51-53 ^{o}C. R_f 0.71 (99:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	3.79 (2 H, t, *J* 2.4, H8), 3.67 (3 H, s, H16), 3.08 (1 H, tt, *J* 12.1, 3.3, H14), 2.41 (1 H, s, H1), 2.01 – 1.77 (4 H, m, H13 ax/eq), 0.90 (18 H, s, H12) 0.86 (9 H, s, H7), 0.19 (6H, s, H5), 0.10 (6 H, s, H9), 0.07 (6 H, s, H10).
δ_C (101 MHz, Chloroform-*d*)	177.1 (C, C15), 86.8 (C, C4), 76.1 (CH, C2), 73.9 (CH, C8), 72.4 (C, C3), 51.7 (CH_3, C16), 32.3 (CH_2, C13), 31.0 (CH, C14), 26.2 (CH_3, C12), 26.0 (CH_3, C7), 18.4 (C, C6), 18.3 (C, C11), -2.75, (CH_3, C5), -3.94 (CH_3, C9), -4.88 (CH_3, C10).
MS ES^+	HRMS (ES): *m*/*z*(%) = 579.3328 [M + Na] (calcd for $C_{28}H_{56}O_5NaSi_3$: 579.3333), 579.3- 100% [M + Na].
ν_{max}	3307 (C≡CH), 2951, 2929, 2856, 2889 (CH), 1736 (C=O Ester).

A novel compound.

Synthesis of Methyl (1*S*,3*S*,7*R*)-3-methoxy-3-methyl-9-oxo-7-(phenylselenyl)-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate 379

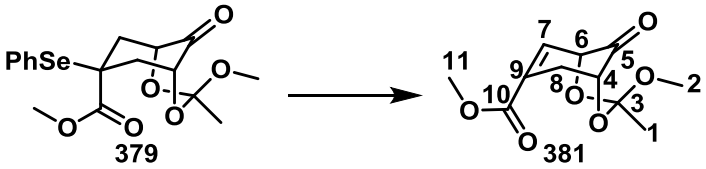


To a solution of DIPA (304 mg, 3 mmol) in THF (10 mL) cooled to -78 °C was added ^{n}BuLi (2M solution in ^{n}hexane, 1.5 mL, 3 mmol). The solution was stirred for 5 minutes then ketone **79** (500 mg, 2 mmol) was added and the mixture stirred for 20 minutes at -78 °C. A solution of PhSeBr (708 mg, 3 mmol) in THF (10 mL) was then added dropwise over 5 minutes whilst maintaining the temperature at -78 °C. The mixture was allowed to warm to rt and then added to brine (25 mL), extracted with diethyl ether (3 x 25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography (1:1 petroleum ether: diethyl ether) gave the title compound **379** as an off-white solid (710 mg, 89%). M.p. 78-80 °C. R_f 0.33 (1:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	7.58 – 7.27 (5 H, m, H5), 4.11 (2 H, m, H3), 3.66 (3 H, s, H6), 3.37 (2 H, m, H4 ax/eq), 3.18 (3 H, s, H1), 2.22 (2 H, dt, *J* 14.8, 2.9, H4 eq/ax), 1.38 (3 H, s, H2).
δ_C (101 MHz, Chloroform-*d*)	206.9 (C, C8), 172.4 (C, C10), 138.1 (C-Ar, C5), 130.0 (C-Ar, C5), 129.1 (C-Ar, C5), 126.3 (C-Ar, C5), 112.1 (C, C7), 75.1 (CH, C3), 52.2 (CH_3, C6), 51.1 (CH_3, C1), 44.0 (CH_2, C4), 19.7 (CH_3, C2). (CH, C9) signal not observed.
MS TOF ES$^+$	HRMS (ES): *m*/*z*(%) = 423.0330 [M + Na] (calcd for $C_{17}H_{20}O_6Na^{80}Se$: 423.0323), 423.0- 100% [M + Na], 421.1- 50% [M ^{78}Se + Na], 419.1- 30% [M^{76}Se + Na].
ν_{max}	3010 (CH), 2945 (CH), 2837 (CH), 1747 (C=O), 1718 (C=O).

A novel compound prepared according to a modified literature procedure.[166]

Synthesis of Methyl (3*S*,5*S*)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]non-6-ene-7-carboxylate 381

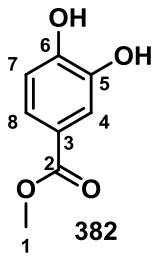


A solution of phenyl selenide **379** (300 mg, 0.75 mmol) in CH_2Cl_2 (7.5 mL) was cooled to 0 ^oC. A solution of H_2O_2 in water (8.8 M, 0.34 mL, 3 mmol) was then added via syringe. The mixture was stirred for 45 minutes and then added to a saturated solution of $Na_2S_2O_3$ (10 mL). The mixture was then extracted with CH_2Cl_2 (3 x 10 mL) dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (7:3 petroleum ether: diethyl ether) gave the title compound **381** as a white solid (151 mg, 83%). M.p. 44-46 ^oC. R_f 0.54 (7:3 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	7.05 (1 H, app.dd, *J* 6.1, 2.7, H7), 4.33 (1 H, app.q, *J* 2.7, H4), 4.21 (1 H, dd, *J* 6.1, 2.7, H6), 3.77 (3 H, s, H11), 3.27 (3 H, s, H2), 3.23 (1 H, dd, *J* 18.3, 2.7, H8), 2.79 (1 H, dt, *J* 18.3, 2.7, H8), 1.52 (3 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	205.3 (C, C5), 166.2 (C, C10), 136.9 (CH, C7), 131.7 (C, C9), 111.2 (C, C3), 73.0 (CH, C4), 68.3 (CH, C6), 52.5 (CH_3, C11), 51.2 (CH_3, C2), 37.7 (CH_2, C8), 20.5 (CH_3, C1).
MS TOF ES^+	HRMS (ES): *m*/*z*(%) = 251.0525 [M + Na - CH_2] (calcd for $C_{10}H_{12}O_6Na$: 251.0532), 251.0- 100% [M + Na - CH_2].
ν_{max}	3009, 2952, 2844 (CH), 1756 (C=O), 1713 (CO_2Me).

A novel compound prepared according to a modified literature procedure.[167]

Synthesis of Methyl 3,4-dihydroxybenzoate 382



382

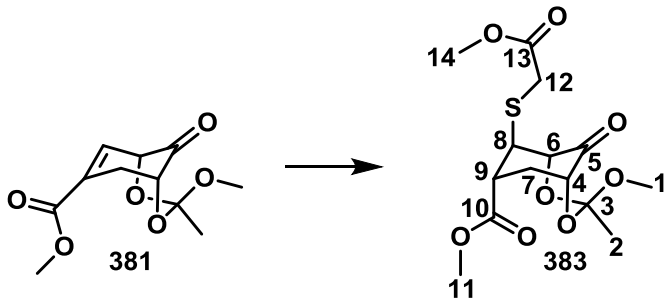
Product isolated from synthesis of methyl (3S,5S)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]non-6-ene-7-carboxylate and methyl (3*S*,5*R*,6*R*,7*R*)-3-methoxy-6-((2-methoxy-2-oxoethyl)thio)-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate.

R_f 0.26 (ethyl acetate) visualised in vanillin.

δ_H (400 MHz, Methanol-d_4)	7.43 – 7.36 (2 H, m, H8/H4), 6.81 – 6.74 (2 H, m, H7), 3.81 (3 H, s, H1), 3.29 (2 H, s, H6/H5).
δ_C (101 MHz, Methanol-d_4)	169.0 (C, C2), 151.8 (Ar-C, C6 or 5), 146.3 (Ar-C, C6 or 5), 123.8 (Ar-C, C8 or 4), 122.7 (Ar-C, C3), 117.6 (Ar-C, C8 or 4), 116.0 (Ar-C, C7), 52.4 (CH_3, C1).
TOF MS ES^+	(ES): *m*/*z*(%) = 169.1- 100% [M + H], 168.1- 100% [M].

A known compound prepared according to a literature procedure and data agrees with literature values.[148]

Synthesis of Methyl (3*S*,5*R*,6*R*,7*S*)-3-methoxy-6-((2-methoxy-2-oxoethyl)thio)-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate 383

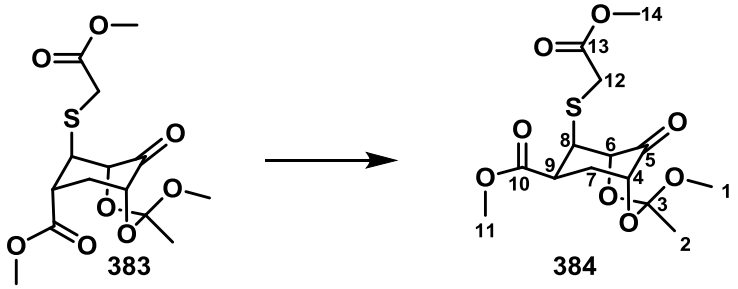


To a solution of alkene **381** (94 mg, 0.39 mmol) in CH_2Cl_2 (3.9 mL) was added methyl thioglycolate (0.17 mL, 1.95 mmol) and Et_3N (0.27 mL, 1.95 mmol). The solution was stirred overnight at rt. The reaction mixture was then reduced to half volume *in vacuo* and purified directly by column chromatography (4:1 diethyl ether: petroleum ether) to give the title compound **383** as an off-white solid (110 mg, 81%). M.p. 63-65 ^{o}C. R_f 0.13 (1:1 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Benzene-d_6)	4.72 (1 H, ddd, *J* 4.0, 2.7, 1.2, H8), 4.39 (1 H, dd, *J* 4.0, 2.7, H6), 4.03 (1 H, app.p, *J* 4.3, 2.4, 1.7, H4), 3.41 (3 H, s, H14), 3.22 (3 H, s, H11), 2.96 – 2.84 (5 H, m, H12, H9, H1) 2.75 (1 H, d, *J* 15.1, H12), 2.56 (1 H, dt, *J* 6.9, 1.7, H7 eq/ax), 1.98 (1 H, ddd, *J* 15.1, 6.9, 1.7, H7 ax/eq), 1.32 (3 H, s, H1).
δ_C (101 MHz, Benzene-d_6)	202.6 (C, C5), 171.5 (C, C10), 169.9 (C, C13), 112.6 (C, C3), 77.0 (CH, C6), 75.0 (CH, C4), 51.9 (CH_3, C14), 51.6 (CH_3, C11), 50.9 (CH_3, C1), 50.6 (CH, C8), 41.4 (CH, C9), 33.4 (CH_2, C12), 33.1 (CH_2, C7), 20.1 (CH_3, C2).
MS TOF ES$^+$	HRMS (ES): *m/z*(%) = 371.0770 [M + Na] (calcd for $C_{14}H_{20}O_8NaS$: 371.0777), 371.2- 100% [M + Na].
ν_{max}	2952, 2841 (CH), 1731 (C=O).

A novel compound prepared according to a modified literature procedure.[168]

Synthesis of Methyl (3*S*,5*R*,6*R*,7*R*)-3-methoxy-6-((2-methoxy-2-oxoethyl)thio)-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate 384

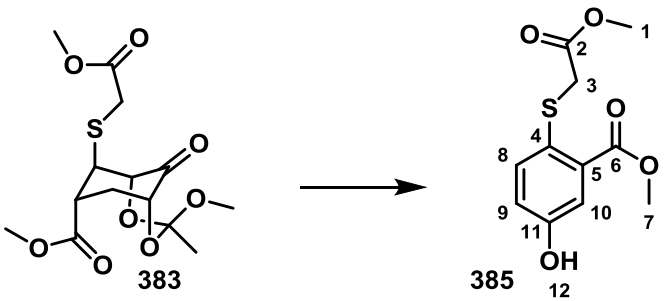


To a solution of **383** (50 mg, 0.14 mmol) in toluene (1.4 mL) was added DBU (21.3 mg, 0.14 mmol) and the mixture stirred for 1 hr at rt. The solvent was removed by reduced pressure and the residue purified by column chromatography (8:2 diethyl ether: petroleum ether) to give the title compound **384** as a colourless oil (16 mg, 32%). R_f 0.53 (8:2 diethyl ether: petroleum ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	4.24 (1 H, dd, *J* 4.4, 2.9, H6), 4.15 (1 H, ddd, *J* 4.4, 2.7, 1.5, H4), 4.02 (1 H, app.ddd, *J* 4.5, 2.9, H8), 3.94 (1 H, dt, *J* 12.6, 4.5, H9), 3.74 (3 H, s, H11), 3.74 (3 H, s, H14), 3.33 (1 H, d, *J* 15.0, H12), 3.26 (3 H, s, H1), 3.22 (1 H, d, *J* 15.0, H12), 2.48 (1 H, app.dtd, *J* 14.6, 4.4, 2.7, H7 eq), 2.06 (1 H, ddd, *J* 14.6, 12.6, 1.5, H7 ax), 1.57 (3 H, s, H2).
δ_C (101 MHz, Chloroform-*d*)	202.5 (C, C5), 172.1 (C, C10), 170.2 (C, C13), 112.7 (C, C3), 76.9 (CH, C6), 74.3 (CH, C4), 52.7 (CH_3, C14), 52.3 (CH_3, C11), 52.1 (CH, C8), 51.2 (CH_3, C1), 38.1 (CH, C9), 34.0 (CH_2, C12), 33.5 (CH_2, C7), 20.2 (CH_3, C2).
MS TOF ES^+	HRMS (ES): *m*/*z*(%) = 371.0776 [M + Na] (calcd for $C_{14}H_{20}O_8NaS$: 371.0777), 371.1- 100% [M + Na].
ν_{max}	2953 (CH), 1734 (C=O).

A novel compound prepared according to a modified literature procedure.[151]

Synthesis of Methyl 5-hydroxy-2-((2-methoxy-2-oxoethyl)thio)benzoate 385

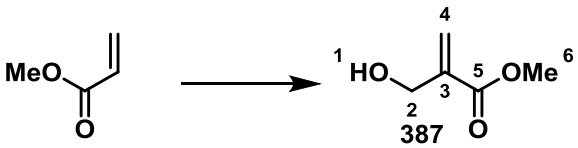


To a solution of **383** (25 mg, 0.07 mmol) in CH_2Cl_2 (0.7 mL) at 0 ^oC was added $TiCl_4$ (13.3 µg, 0.07 mmol). The mixture was stirred for 1 hr at 0 ^oC, then Et_3N (7 mg, 0.07 mmol) was added and the mixture allowed to warm to rt. The mixture was then directly purified by column chromatography (8:2 diethyl ether: petroleum ether) to give the title compound **385** as a yellow oil (9 mg, 50%). R_f 0.44 (8:2 diethyl ether: petroleum ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	8.23 (1 H, d, *J* 2.1, H10), 8.15 (1 H, s, H12 exchanges with D_2O), 7.97 (1 H, dd, *J* 8.6, 2.1, H9), 7.02 (1 H, d, *J* 8.6, H8), 3.88 (3 H, s, H7), 3.73 (3 H, s, H1), 3.53 (2 H, s, H3).
δ_C (101 MHz, Chloroform-*d*)	171.7 (C, C2), 166.2 (C, C6), 162.1 (C, C11), 139.0 (Ar-C, C9), 133.8 (Ar-C, C10), 123.0 (Ar-C, C5), 118.5 (Ar-C, C4), 116.1 (Ar-C, C8), 53.3 (CH_3, C7), 52.1 (CH_3, C1), 39.3 (CH_2, C3).
MS TOF ES^+	HRMS (ES): *m*/*z*(%) = 279.0290 [M + Na] (calcd for $C_{11}H_{12}O_5NaS$: 279.0303), 279.1- 100% [M + Na].
ν_{max}	3261 (OH), 2959, 2912 (CH), 2426 (S-Ar).

A novel compound.

Synthesis of Methyl 2-(hydroxymethyl)acrylate 387

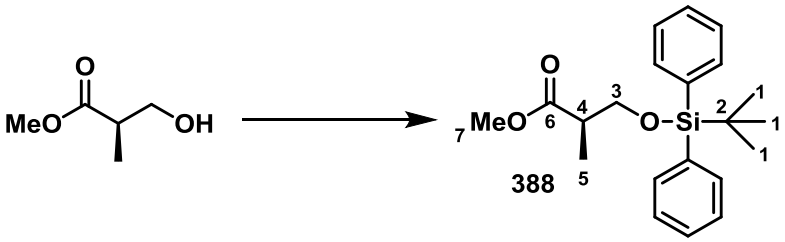


Paraformaldehyde (3.50 g, 117 mmol) was dissolved in a 1:1 mixture of 1,4-dioxane: H_2O (16 mL). The solution was stirred for 45 minutes at rt. Methyl acrylate (21.0 mL, 233 mmol) and DABCO (13.1 g, 117 mmol) were added and the reaction mixture was vigorously stirred for 72 hr. Brine (50 mL) was added and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (1:1 petroleum ether: diethyl ether) to yield the title compound **387** as a colourless oil (7.66 g, 56%). R_f (0.29 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	6.24 (1 H, s, H4), 5.83 (1 H, s, H4), 4.31 (2 H, d, *J* 6.4, H2), 3.77 (3 H, s, H6), 2.57 (1 H, t, *J* 6.4, H1).
δ_C (101 MHz, Chloroform-*d*)	166.8 (C, C5), 139.4 (C, C3), 125.9 (CH_2, C4), 62.5 (CH_2, C2), 52.0 (CH_3, C6).
ν_{max}	3444 (OH), 2955 (CH), 1716 (C=O).

A known compound prepared according to a literature procedure.[169] Data agrees with literature values.[170]

Synthesis of Methyl (*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanoate 388

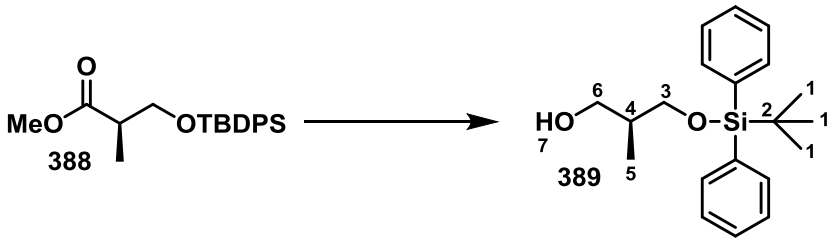


To a stirred solution of methyl (*R*)-3-hydroxy-2-methylpropionate (1 g, 8.46 mmol) and imidazole (1.26 g, 18.61 mmol) in dry CH_2Cl_2 (42 mL) was added TBDPSCl (2.8 g, 10.15 mmol) at 0 ^{o}C. After the ice bath was removed the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was washed with brine (15 mL), dried over magnesium sulfate and filtered. The solvent was then removed under vacuum and the crude product purified by column chromatography (99:1 petroleum: diethyl ether) to yield the title compound **388** as a colourless oil in quantitative yield. R_f 0.55 (8:2 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	7.70 – 7.63 (4 H, m, Ar-H), 7.48 – 7.34 (6 H, m, Ar-H), 3.88 – 3.71 (2 H, m, H3), 3.70 (3 H, s, H7), 2.73 (1 H, app.h, *J* 6.2, H4), 1.17 (3 H, d, *J* 6.2, H5), 1.05 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	175.5 (C, C6), 135.7 (Ar-C), 133.7 (Ar-C), 133.6 (Ar-C), 129.8 (Ar-C), 127.8 (Ar-C), 66.1 (CH_2, C3), 51.7 (CH_3, C7), 42.5 (CH, C4), 26.9 (C, C2), 19.4 (CH_3, C1), 13.6 (CH_3, C5).
ν_{max}	3071, 2932, 2858 (CH), 1738 (CO_2Me), 700 (Si-C).

A known compound prepared according to a literature procedure.[127] Data is correct but literature has data missing from ^{1}H NMR. Data agrees with literature values.[171]

Synthesis of (*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol 389

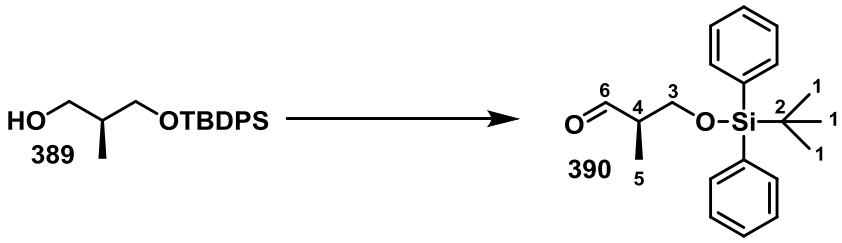


To a solution of ester **388** (100 mg, 0.28 mmol) dissolved in dry toluene (2.8 mL) was added DIBAL (1.0 M in toluene, 0.56 mL, 0.56 mmol) at -78 ^{o}C under argon. Stirring was continued for 1 hr after which Rochelle's salt (2 mL of a saturated solution) was added and the reaction allowed to warm to rt. The mixture was then extracted with ethyl acetate (3 x 5 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (4:1 petroleum ether: diethyl ether) to give the title compound **389** as a colourless oil (68 mg, 74%). R_f 0.12 (8:2 petroleum ether: diethyl ether) visualised in $KMnO_4$.

δ_H (400 MHz, Chloroform-*d*)	7.74 – 7.64 (4 H, m, Ar-H), 7.49 – 7.36 (6 H, m, Ar-H), 3.77 – 3.57 (4 H, m, H3, H6), 2.78 (1 H, bs, H7), 2.01 (1 H, m, H4), 1.08 (9 H, s, H1), 0.84 (3 H, d, *J* 7.0, H5).
δ_C (101 MHz, Chloroform-*d*)	135.7 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 127.9 (Ar-C), 68.8 (CH_2, C3 or 6), 67.7 (CH_2, C3 or 6), 37.5 (CH, C4), 27.0 (CH_3, C1), 19.3 (C, C2), 13.3 (CH_3, C5)
ν_{max}	3360 (OH), 3071, 2958, 2930, 2858 (CH), 699 (Si-Ph).

A known compound prepared according to a literature procedure.[127] Data is correct but literature has data missing from ^{1}H NMR. Data agrees with literature values.[172]

Synthesis of (*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropanal 390

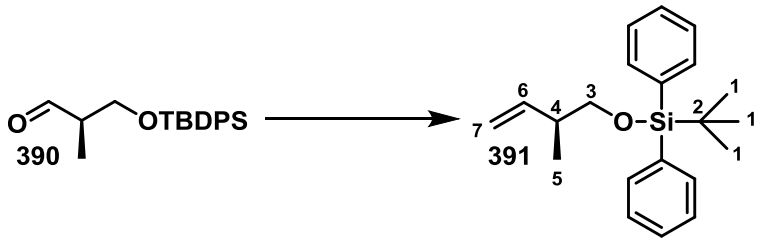


Freshly distilled oxalyl chloride (0.45 mL, 5.28 mmol) in CH_2Cl_2 (52. 8 mL) was cooled to -78 ^{o}C. Freshly distilled DMSO (0.48 mL, 6.72 mmol) in a solution of CH_2Cl_2 (15 mL) was slowly added and the reaction stirred for 5 minutes. A solution of alcohol **389** (800 mg, 2.4 mmol) dissolved in CH_2Cl_2 (15 mL) was added dropwise over 5 minutes and the reaction stirred for 1 hr 20 minutes maintaining the temperature at -78 ^{o}C. Et_3N (1.2 g, 12 mmol) was then added and the reaction allowed to warm to rt. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the mixture extracted with CH_2Cl_2 (3 x 25 mL). The solvent was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a crude product which was purified by column chromatography (9:1 petroleum ether: diethyl ether) to give the title compound **390** as a colourless oil (676 mg, 86%). R_f 0.38 (8:2 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	9.78 (1 H, d, *J* 1.6, H6), 7.69 – 7.62 (4 H, m, Ar-H), 7.49 – 7.38 (6 H, m, Ar-H), 3.96 – 3.81 (2 H, m, H3), 2.62 – 2.53 (1 H, m, H4), 1.11 (3 H, d, *J* 7.0, H5), 1.05 (9 H, s, H1).
δ_C (101 MHz, Chloroform-*d*)	204.5 (C6), 135.7 (Ar-C), 133.3 (Ar-C), 129.9 (Ar-C), 127.9 (Ar-C), 64.3 (C3), 49.0 (C4), 26.9 (C1), 19.4 (C2), 10.5 (C5).
ν_{max}	2931, 2858, 2175 (CH), 1732 (CHO).

A known compound prepared according to a literature procedure.[127] Data is correct but literature has data missing from ^{1}H NMR. Data agrees with literature values.[173]

Synthesis of (*S*)-*tert*-Butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane 391

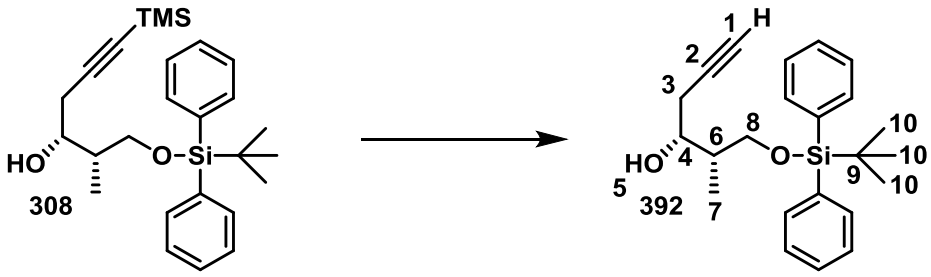


To a stirred suspension of methyltriphenylphosphonium bromide (22.4 mg, 0.62 mmol) in THF (6.2 mL) was added ^{n}BuLi (1.78 M solution in ^{n}hexane, 0.43 mL, 0.78 mmol) under argon at 0 ^{o}C. The resulting mixture was stirred for 20 minutes, followed by the addition of a solution of aldehyde **390** (100 mg, 0.31 mmol) in THF (6.2 mL). The reaction was stirred for 15 minutes at 0 ^{o}C followed by 45 minutes at rt. Saturated aqueous NH_4Cl (15 mL) was added and the mixture extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield a crude product that was purified via column chromatography (9:1 petroleum ether: diethyl ether) to yield the title compound **391** as a colourless oil (85 mg, 84%). R_f 0.36 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	7.73 – 7.61 (4 H, m, Ar-H), 7.50 – 7.30 (6 H, m, Ar-H), 5.81 (1 H, ddd, *J* 17.3, 10.4, 6.9, H6), 5.09 – 4.89 (2 H, m, H7), 3.58 (1H, dd, *J* 9.7, 6.2, H3^{a}), 3.50 (1 H, dd, *J* 9.7, 6.2, H3^{b}), 2.50 – 2.29 (1 H, m, H4), 1.06 (9 H, s, H1), 1.04 (3 H, d, *J* 6.8 H5).
δ_C (101 MHz, Chloroform-*d*)	141.5 (CH, C6) 135.8 (Ar-C), 134.1 (Ar-C), 129.7 (Ar-C), 127.7 (Ar-C), 114.2 (CH_2, C7), 68.7 (CH_2, C3), 40.4 (CH, C4), 27.0 (CH_3, C1), 19.5 (C, C2), 16.3 (CH_3, C5).
ν_{max}	3071, 2959, 2930, 2858, 2896 (CH), 1641 (C=C), 698 (Si-C).

A known compound prepared according to a literature procedure.[127] Data is correct but literature has data missing from ^{1}H NMR. Data agrees with literature values.[174]

Synthesis of (2*S*,3*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhex-5-yn-3-ol 392

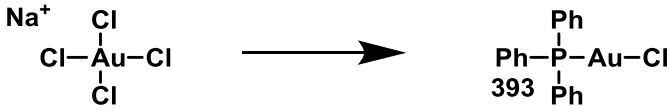


Alkyne **308** (87 mg, 0.2 mmol) was dissolved in MeOH (2 mL), K_2CO_3 (55 mg, 0.4 mmol) was added and the reaction mixture left to stir at rt for 3 hr. The reaction was then added to brine (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic fractions were combined and dried over $MgSO_4$, filtered and solvents removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **392** as a colourless oil (75 mg, 73%). R_f 0.20 (9:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	7.71 – 7.66 (4 H, m, Ar-H), 7.48 – 7.37 (6 H, m, Ar-H), 3.83 – 3.74 (3 H, m, H8, H5, H4), 3.66 (1 H, dd, *J* 10.3, 7.2, H8), 2.53 (1 H, ddd, *J* 16.8, 4.4, 2.7, H3), 2.43 (1 H, ddd, *J* 16.8, 6.1, 2.7, H3), 2.04 (1 H, t, *J* 2.7, H1), 1.99 (1 H, dq, *J* 7.1, 4.2, H6), 1.07 (18 H, s, H10), 0.88 (3 H, d, *J* 7.1, H7).
δ_C (101 MHz, Chloroform-*d*)	135.8 (Ar-C), 133.0 (Ar-C), 130.0 (Ar-C), 127.9 (Ar-C), 81.3 (C, C2), 74.1 (CH, C4), 70.4 (C1), 68.2 (CH_2, C8), 39.1 (CH, C6), 27.0 (CH_3, C10), 25.3 (CH_2, C3), 19.3 (C, C9), 13.6 (CH_3, C7).
MS ES^+	HRMS (ES): *m*/*z*(%) = 389.1906 [M + Na] (calcd for $C_{23}H_{30}O_2NaSi$: 389.1913), 389.2- 100% [M + Na].
ν_{max}	3477 (OH), 3307 (C≡C-H), 2960, 2931, 2858 (CH), 700 (Si-Ph).

A novel compound.

Synthesis of Chloro(triphenylphosphine)gold(I) 393

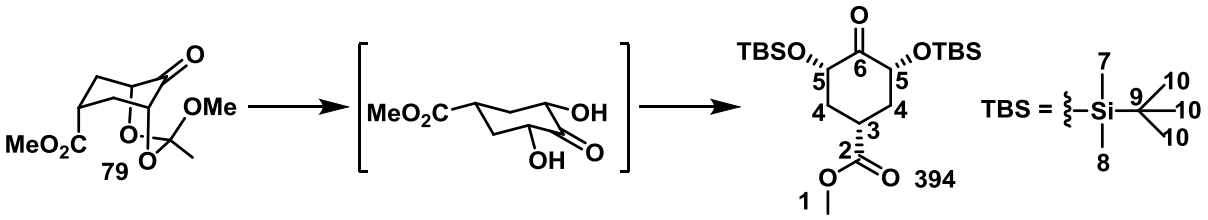


To a solution of $NaAuCl_4$ (250 mg, 0.63 mmol) in water (5 mL) cooled to 0 ^oC was added 2-thio-ethanol (250 mg, 2.0 mmol) over 45 minutes. PPh_3 (132 mg, 0.50 mmol) in ethanol (5 mL) was then added over 1 hr and the reaction left to stir for 15 minutes. The precipitate that formed was then filtered and dried to give the title compound **393** as a white solid (217 mg, 70%).

δ_H (300 MHz, Chloroform-*d*)	7.59 – 7.42 (15 H, m, Ar-H).
δ_P (121 MHz, Chloroform-*d*)	33.2 P.
MS ES^+	(ES): *m/z*(%) = 500.1 [M - Cl + H], 721.2 [M - Cl + PPh_3], 953.0 [M + PPh_3].

A known compound prepared according to a literature procedure and data agrees with literature values.[175]

Synthesis of Methyl (1*R*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexane-1-carboxylate 394

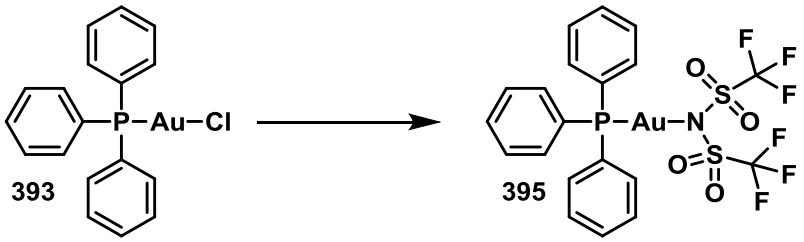


To a solution of ketone **80** (150 mg, 0.61 mmol) in MeOH (6.1 mL) was added acetic acid (35 µL, 0.61 mmol) and the mixture heated to reflux for 2 days. The reaction was then cooled to rt and the solvents removed by co-distillation with toluene. The crude solid was then dissolved in DMF (6.1 mL) to which was added TBSCl (405 mg, 2.7 mmol) and imidazole (183 mg, 2.7 mmol). The reaction was stirred for 2 days at rt. The mixture was then added to brine (25 mL) and extracted with diethyl ether (3 x 25 mL), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography (9:1 petroleum ether: diethyl ether) gave the title compound **394** as a clear oil (190 mg, 75%). R_f 0.48 (1:1 petroleum ether: diethyl ether) visualised in vanillin.

δ_H (400 MHz, Chloroform-*d*)	4.20 (2 H, dd, *J* 11.5, 5.8, H5), 3.71 (3 H, s, H1), 2.82 (1 H, tt, *J* 12.9, 3.0, H3), 2.44 (2 H, ddd, *J* 11.5, 5.8, 3.0, H4 eq), 1.86 (2 H, app.q, *J* 12.9, H4 ax), 0.89 (18 H, s, H10), 0.13 (6 H, s, H7), 0.01 (6 H, s, H8).
δ_C (101 MHz, Chloroform-*d*)	205.7 (C, C6), 173.4 (C, C2), 74.5 (CH, C5), 52.3 (CH_3, C1), 38.9 (CH_2, C4), 37.6 (CH, C3), 25.9 (CH_3, C10), 18.6 (C, C9), -4.4 (CH_3, C7), -5.4 (CH_3, C8).
MS ES^+	HRMS (ES): *m/z*(%) = 417.2501 [M + H] (calcd for $C_{20}H_{41}O_5Si_2$: 417.2493), 269.2- 100% [M - OTBS - O], 285.2- 80% [M - OTBS], 399.3- 90% [M - O], 417.3- 40% [M + H].
ν_{max}	2929 (CH), 2949 (CH), 2856 (CH), 2882 (CH), 1748 (CO_2Me), 1718 (C=O).

A novel compound prepared according to a PhD thesis procedure.[91]

Synthesis of Triphenylphosphinegold triflimidate 395

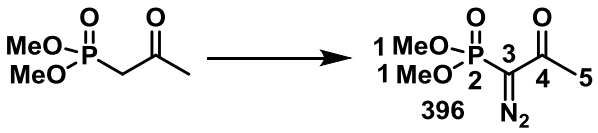


To a solution of Ph_3PAuCl in CH_2Cl_2 (2.5 mL) was added $AgNTf_2$ (25 mg, 0.06 mmol). The reaction was stirred for 15 minutes at rt then filtered through a pad of celite. The solvent was removed under reduced pressure to give the title compound **394** as a white crystalline solid (40 mg, 90%).

δ_H (300 MHz, Chloroform-*d*)	7.63 –7.44 (15 H, m).
δ_F (282 MHz, Chloroform-*d*)	-75.48.
δ_P (121 MHz, Chloroform-*d*)	30.33.
MS ES^+	(ES): *m*/*z*(%) = 721.2- 100% [M - F].

A known compound prepared according to a literature procedure and data agrees with literature values.[176]

Synthesis of Dimethyl (1-diazo-2-oxopropyl)phosphonate 396



Dimethyl 2-oxopropylphosphonate (500 mg, 3.01 mmol) was dissolved in dry THF (8 mL) and cooled to 0 °C. NaH (60% in mineral oil, 144 mg, 3.61 mmol) was added and the reaction mixture left to stir for 1 hr. A solution of 4-acetamidobenzenesulfonyl azide (800 mg, 3.31 mmol) in THF (4 mL) was then added to the crude reaction mixture dropwise over 10 minutes and left to stir for 2 hr with gradual warming to rt. The reaction mixture was then filtered through celite. The solvent was removed under reduced pressure and the crude product purified via column chromatography (ethyl acetate) to give the title compound **396** as a yellow oil (420 mg, 73%). R_f 0.23 (ethyl acetate) visualised under UV light.

δ_H (300 MHz, Chloroform-*d*)	3.83 (6 H, d, J_{Hp} 11.9, H1), 2.25 (3 H, s, H5).
δ_C (101 MHz, Chloroform-*d*)	189.9 (C, C4), 125.6 (C, C3), 53.6 (CH_3, C1), 27.2 (CH_3, C5).
δ_P (122 MHz, Chloroform-*d*)	14.3 (P2).
ν_{max}	2221, 2117 (N=N, C=N), 1654 (C=O).

A known compound prepared according to a literature procedure and data agrees with literature values.[177, 178]

Appendices

Crystallographic data

X-ray for 175

Crystallised from slow evaporation from CH_2Cl_2 and Hexane (1:1)

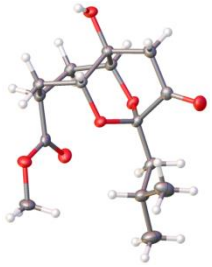


Table 1 Crystal data and structure refinement for 175

Identification code	MPK3-262
Empirical formula	$C_{15}H_{22}O_6$
Formula weight	298.32
Temperature/K	100.15
Crystal system	triclinic
Space group	P-1
a/Å	8.9894(5)
b/Å	13.2792(8)
c/Å	19.0407(13)
α/°	84.876(6)
β/°	87.433(6)
γ/°	79.098(6)
Volume/Å^3	2222.1(2)
Z	6
ρ_{calc}g/cm^3	1.338
μ/mm^{-1}	0.103
F(000)	960.0
Crystal size/mm^3	0.19 × 0.06 × 0.01
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.044 to 54.966
Index ranges	-11 ≤ h ≤ 11, -15 ≤ k ≤ 17, -24 ≤ l ≤ 24
Reflections collected	29761
Independent reflections	10173 [R_{int} = 0.0322, R_{sigma} = 0.0415]
Data/restraints/parameters	10173/0/606
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0477, wR_2 = 0.1263
Final R indexes [all data]	R_1 = 0.0821, wR_2 = 0.1423
Largest diff. peak/hole / e Å^{-3}	0.37/-0.29

X-ray for 177

Crystallised from slow evaporation from CH_2Cl_2 and Hexane (1:1)

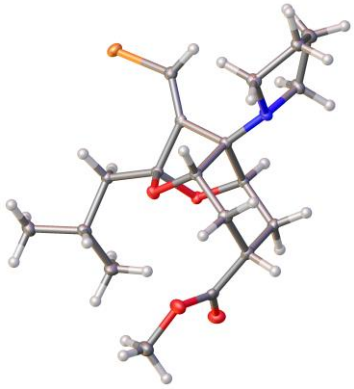


Table 1 Crystal data and structure refinement for 177

Identification code	MPK_288
Empirical formula	$C_{19}H_{28}BrNO_4$
Formula weight	414.33
Temperature/K	100.15
Crystal system	monoclinic
Space group	I2/a
a/Å	17.4828(2)
b/Å	11.60060(11)
c/Å	18.3644(2)
α/°	90
β/°	101.2536(12)
γ/°	90
Volume/Å^3	3652.91(7)
Z	8
ρ_{calc}g/cm^3	1.507
μ/mm^{-1}	3.267
F(000)	1728.0
Crystal size/mm^3	0.18 × 0.177 × 0.125
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	12.716 to 140.122
Index ranges	-19 ≤ h ≤ 21, -13 ≤ k ≤ 14, -21 ≤ l ≤ 22
Reflections collected	6618
Independent reflections	3412 [R_{int} = 0.0132, R_{sigma} = 0.0168]
Data/restraints/parameters	3412/0/229
Goodness-of-fit on F^2	1.076
Final R indexes [I>=2σ (I)]	R_1 = 0.0243, wR_2 = 0.0619
Final R indexes [all data]	R_1 = 0.0254, wR_2 = 0.0626
Largest diff. peak/hole / e Å^{-3}	0.73/-0.36

X-ray for 253

Crystallised from slow evaporation from CH_2Cl_2 and Hexane (1:1)

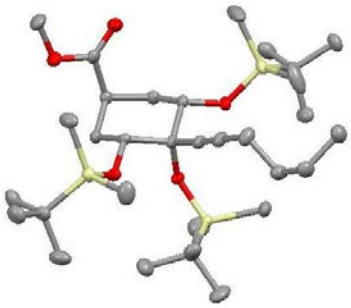


Table 1 Crystal data and structure refinement for 253

Identification code	MPK_366
Empirical formula	$C_{32}H_{64}O_5Si_3$
Formula weight	613.1
Temperature/K	100.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	11.9365(4)
b/Å	12.5296(3)
c/Å	15.1663(5)
α/°	75.771(2)
ß/°	67.468(3)
γ/°	65.100(3)
Volume/Å3	1890.67(11)
Z	2
ρ_{calc}g /cm3	1.077
μ/mm-1	1.412
F(000)	676
Crystal size/mm3	0.2556 × 0.2188 × 0.1667
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.342 to 146.802
Index ranges	-14 ≤ h ≤ 14, -15 ≤ k ≤ 15, -18 ≤ l ≤ 18
Reflections collected	68475
Independent reflections	7529 [R_{int} = 0.0199, R_{sigma} = 0.0092]
Data/restraints/parameters	7529/0/378
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2 σ (I)]	R_1 = 0.0296, wR_2 = 0.0791
Final R indexes [all data]	R_1 = 0.0308, wR_2 = 0.0800
Largest diff. peak/hole / e $Å^{-3}$	0.42/-0.24

X-ray for 274

Crystallised from slow evaporation from CH_2Cl_2 and Hexane (1:1)

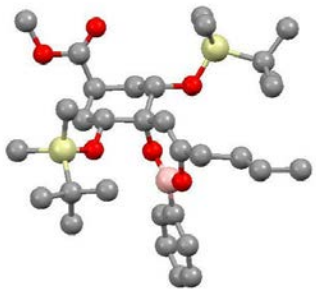


Table 1 Crystal data and structure refinement for 274

Identification code	MPK_7-569
Empirical formula	$C_{32}H_{55}BO_6Si_2$
Formula weight	602.75
Temperature/K	99.97(17)
Crystal system	triclinic
Space group	P-1
a/Å	11.2926(3)
b/Å	17.6773(4)
c/Å	19.8735(5)
α/°	101.118(2)
β/°	98.960(2)
γ/°	107.432(2)
Volume/Å^3	3616.08(17)
Z	4
ρ_{calc}g/cm^3	1.107
μ/mm^{-1}	1.186
F(000)	1312.0
Crystal size/mm^3	0.3037 × 0.1819 × 0.1667
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.418 to 148.978
Index ranges	-10 ≤ h ≤ 14, -22 ≤ k ≤ 20, -24 ≤ l ≤ 24
Reflections collected	51067
Independent reflections	14790 [R_{int} = 0.0329, R_{sigma} = 0.0331]
Data/restraints/parameters	14790/0/763
Goodness-of-fit on F^2	1.018
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.0986
Final R indexes [all data]	R_1 = 0.0521, wR_2 = 0.1068
Largest diff. peak/hole / e Å^{-3}	0.59/-0.47

X-ray for 300

Crystallised from slow evaporation from CH_2Cl_2 and Hexane (1:1)

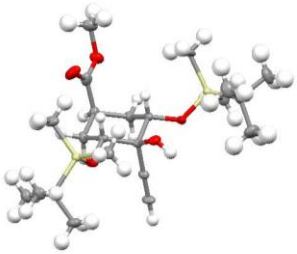


Table 1 Crystal data and structure refinement for 300

Identification code	MPK_443	
Empirical formula	$C_{22}H_{42}O_5Si_2$	
Formula weight	442.73	
Temperature	99.97(11) K	
Wavelength	1.5418 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.4792(3) Å	α= 99.123(3)°.
	b = 12.1150(5) Å	β= 94.664(3)°.
	c = 17.0386(7) Å	γ = 95.240(3)°.
Volume	1308.76(10) $Å^3$	
Z	2	
Density (calculated)	1.123 Mg/m^3	
Absorption coefficient	1.446 mm^{-1}	
F(000)	484	
Crystal size	0.120 x 0.050 x 0.030 mm^3	
Theta range for data collection	6.895 to 66.597°.	
Index ranges	-7 ≤ h ≤ 7, -14 ≤ k ≤ 14, -20 ≤ l ≤ 20	
Reflections collected	18306	
Independent reflections	4613 [R_{int} = 0.0865]	
Completeness to theta = 67.680°	97.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.61694	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4613 / 2 / 276	
Goodness-of-fit on F^2	1.204	
Final R indices [I>2 σ (I)]	R_1 = 0.0916, wR_2 = 0.2175	
R indices (all data)	R_1 = 0.1173, wR_2 = 0.2247	
Largest diff. peak and hole	0.423 and -0.458 $e.Å^{-3}$	

X-ray for 383

Crystallised from slow evaporation from CH_2Cl_2 and Hexane (1:1)

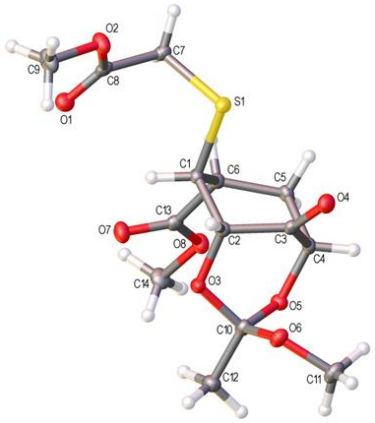
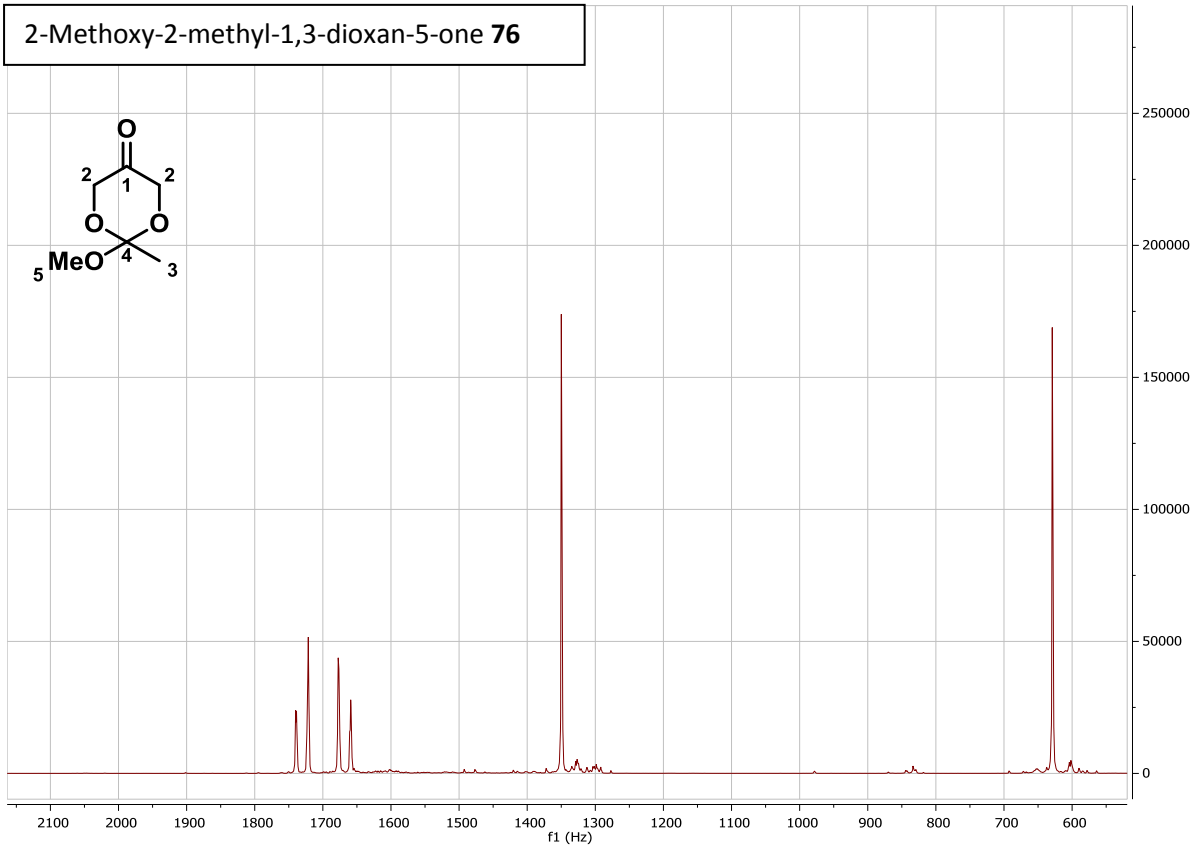


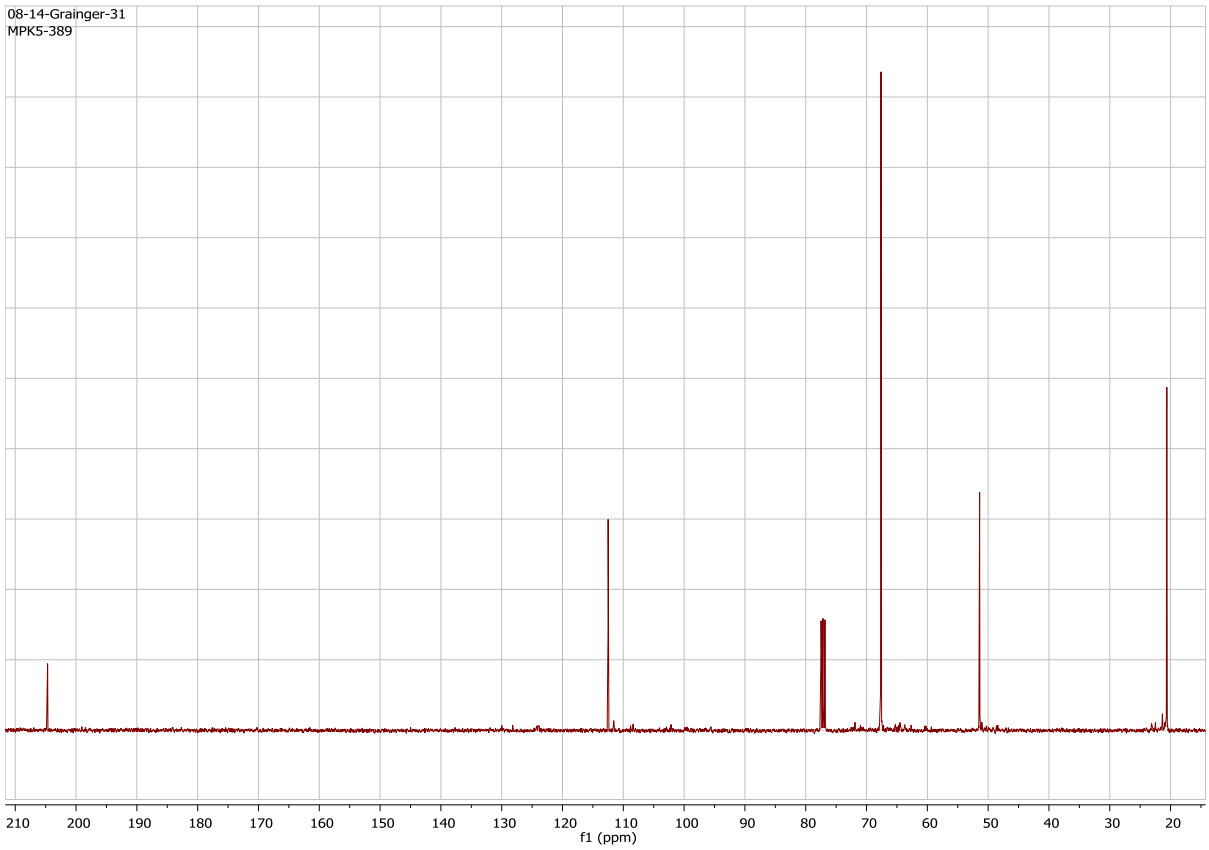
Table 1 Crystal data and structure refinement for 383

Identification code	MPK 737
Empirical formula	$C_{14}H_{20}O_8S$
Formula weight	348.36
Temperature/K	100.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	6.71588(18)
b/Å	8.2594(2)
c/Å	14.7967(4)
α/°	98.207(2)
β/°	92.755(2)
γ/°	99.715(2)
Volume/Å^3	798.52(4)
Z	2
ρ_{calc}g/cm^3	1.449
μ/mm^{-1}	0.242
F(000)	368.0
Crystal size/mm^3	0.2885 × 0.2131 × 0.1936
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.144 to 52.742
Index ranges	-8 ≤ h ≤ 8, -10 ≤ k ≤ 10, -18 ≤ l ≤ 18
Reflections collected	32848
Independent reflections	3279 [R_{int} = 0.0281, R_{sigma} = 0.0139]
Data/restraints/parameters	3279/0/212
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0291, wR_2 = 0.0692
Final R indexes [all data]	R_1 = 0.0333, wR_2 = 0.0721
Largest diff. peak/hole / e Å^{-3}	0.37/-0.26

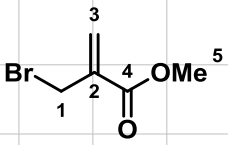
NMR spectra

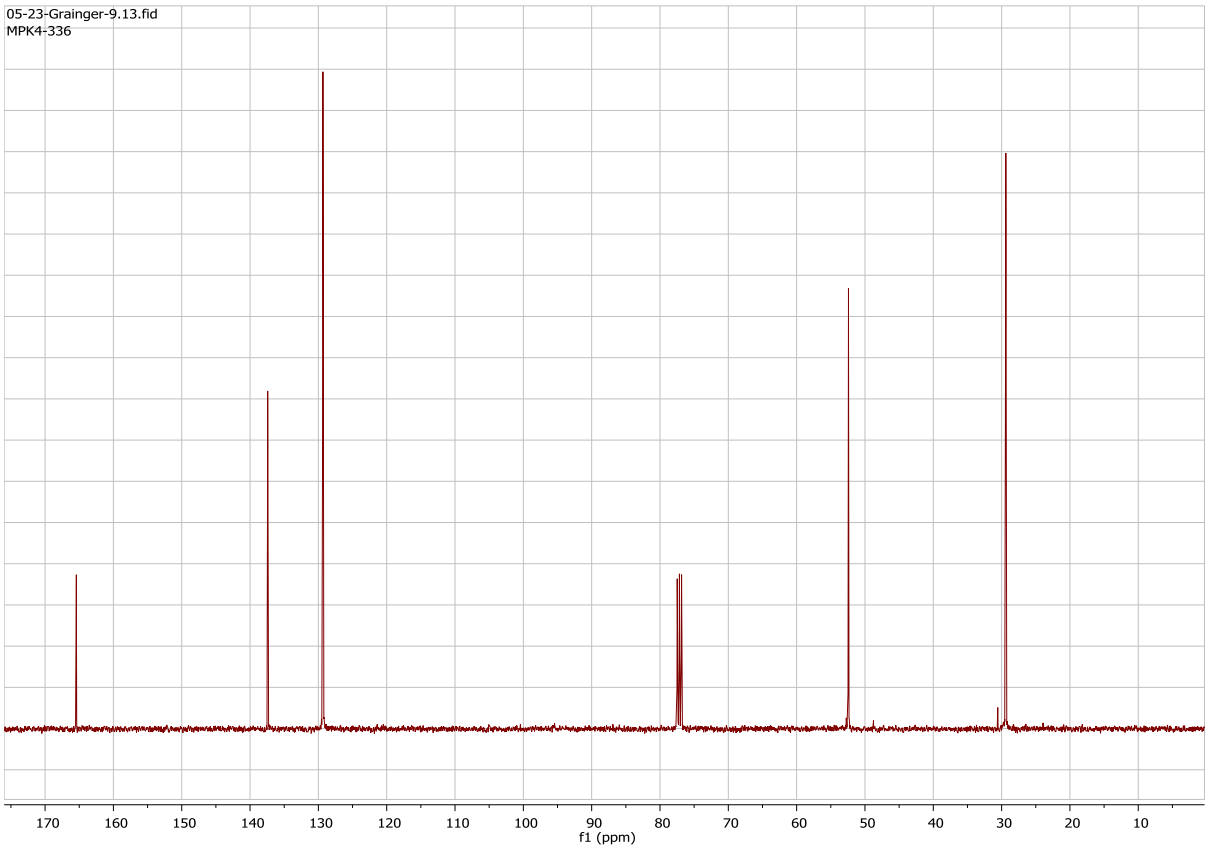
2-Methoxy-2-methyl-1,3-dioxan-5-one **76**



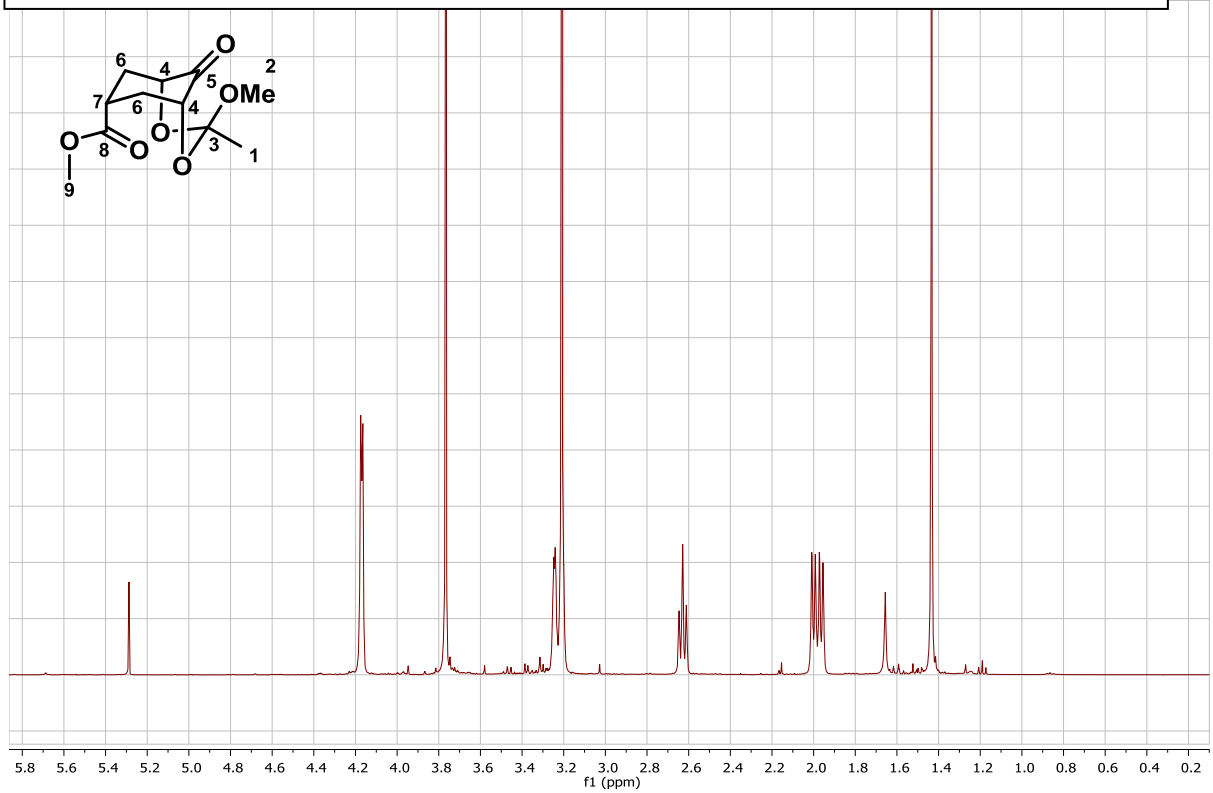


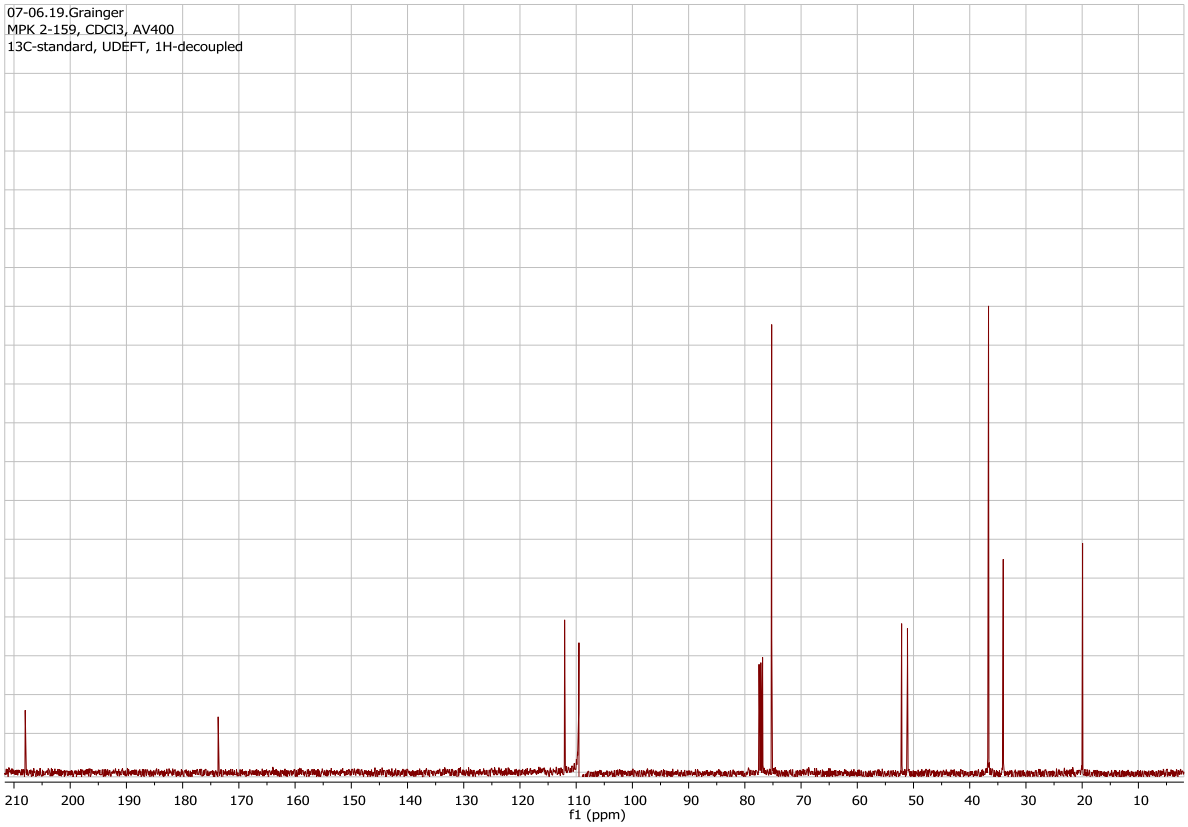
Methyl 2-(bromomethyl)acrylate **78**



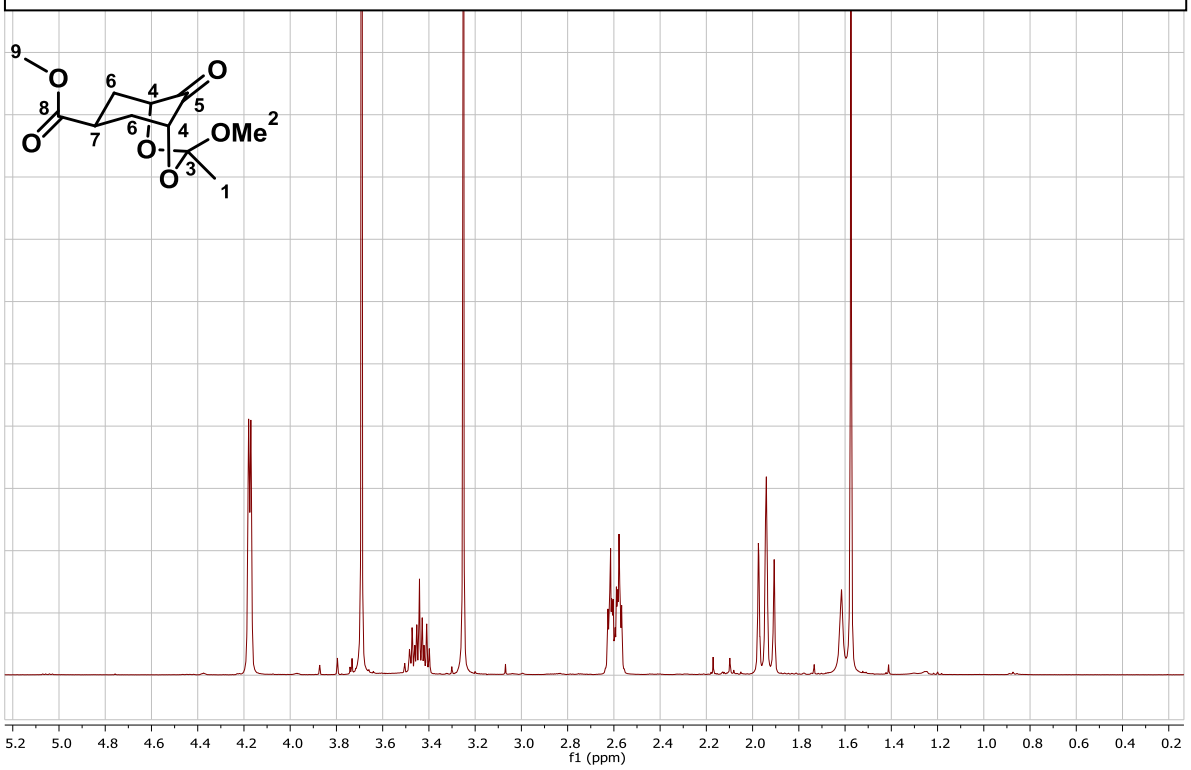


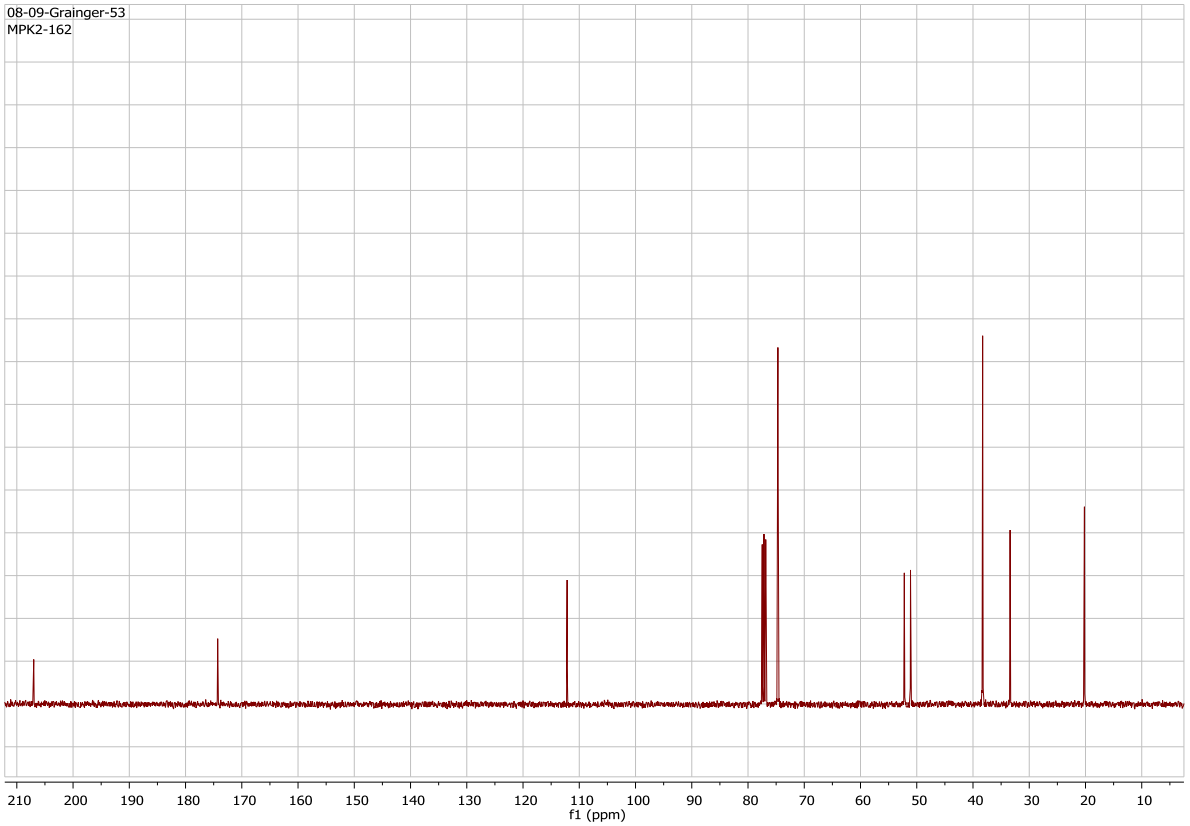
Methyl (1S,3S,7S)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate **79**



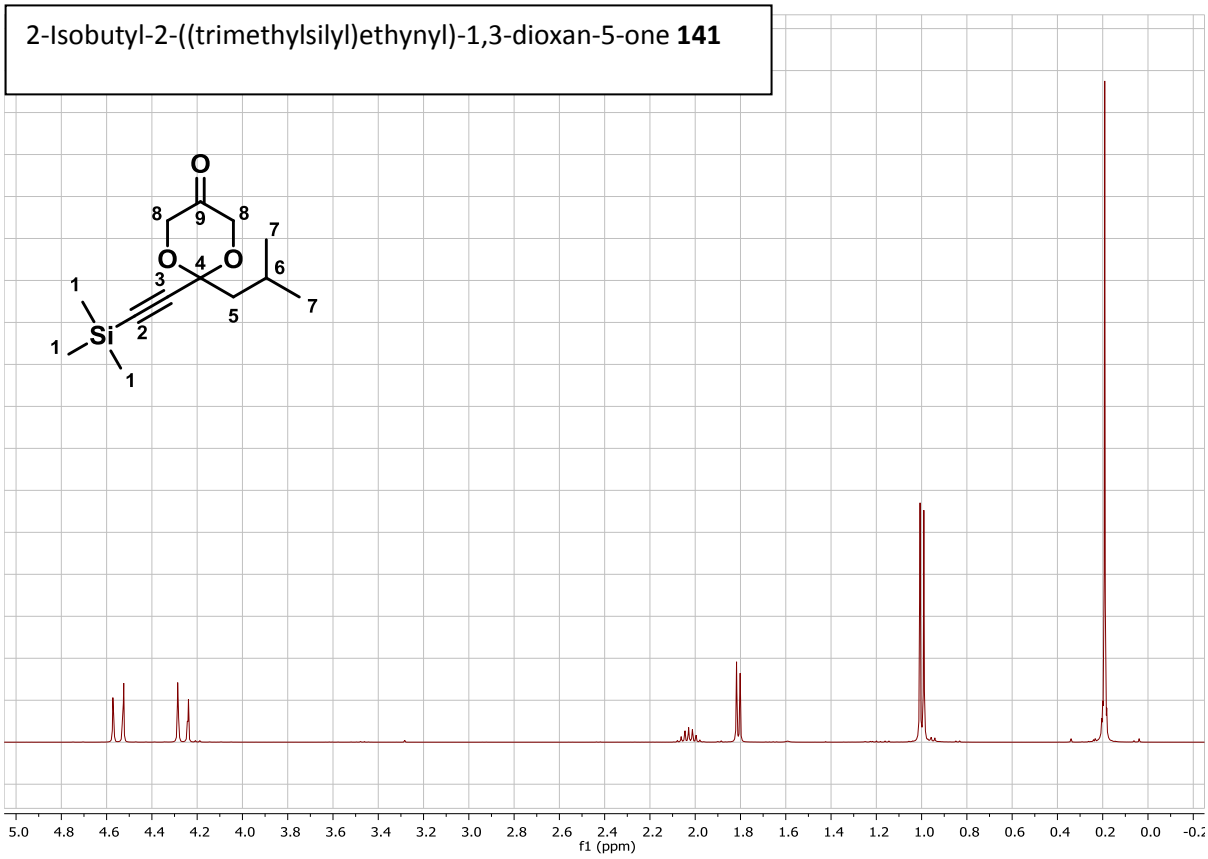


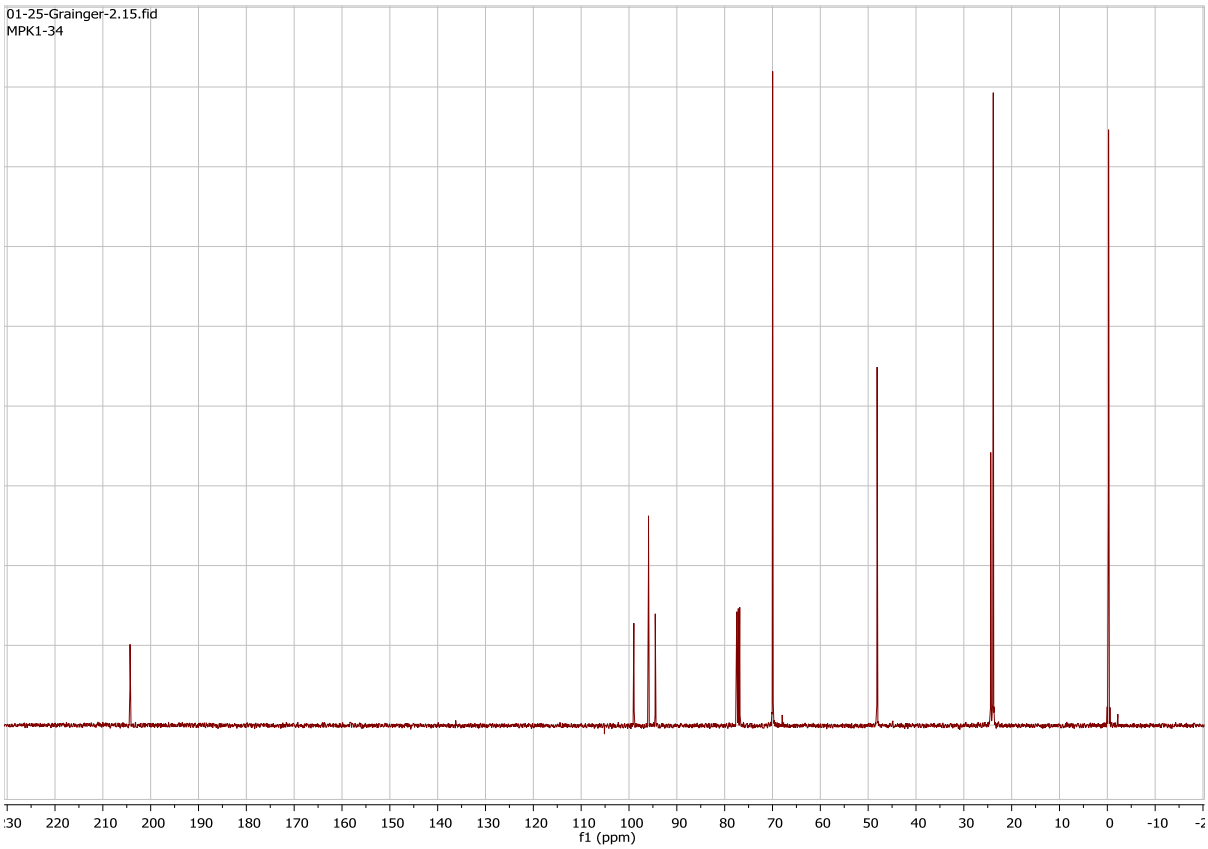
Methyl (1S,3S,7R)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate **80**



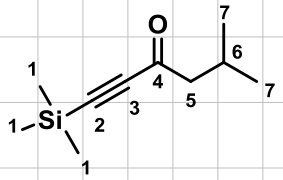


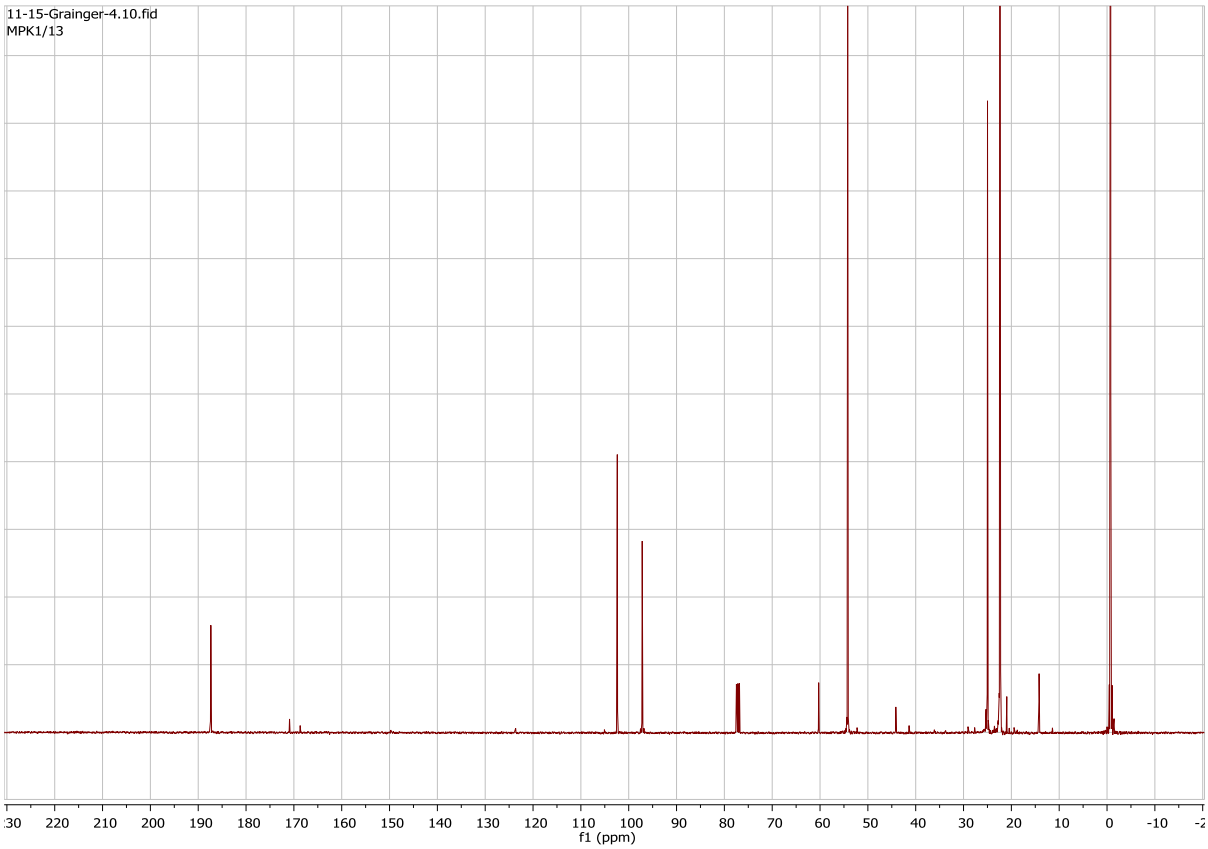
2-Isobutyl-2-((trimethylsilyl)ethynyl)-1,3-dioxan-5-one **141**



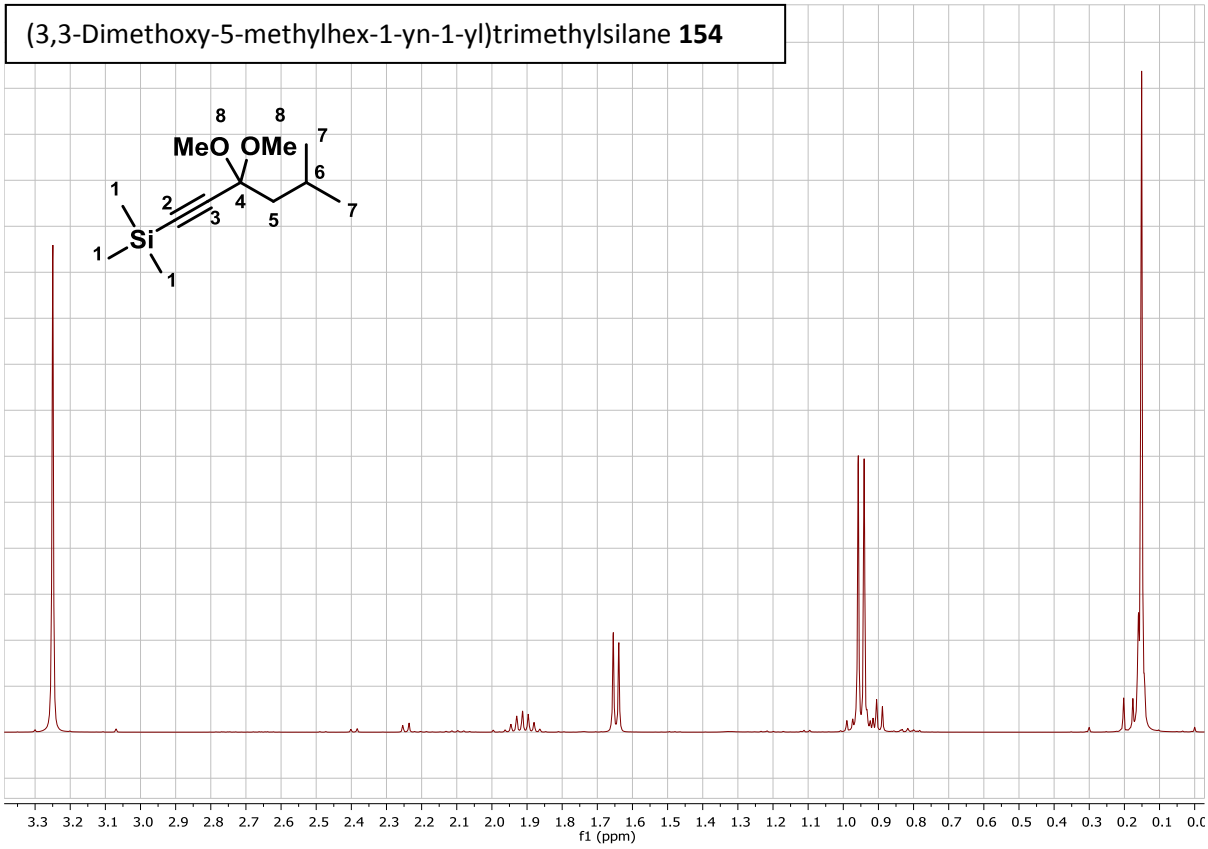


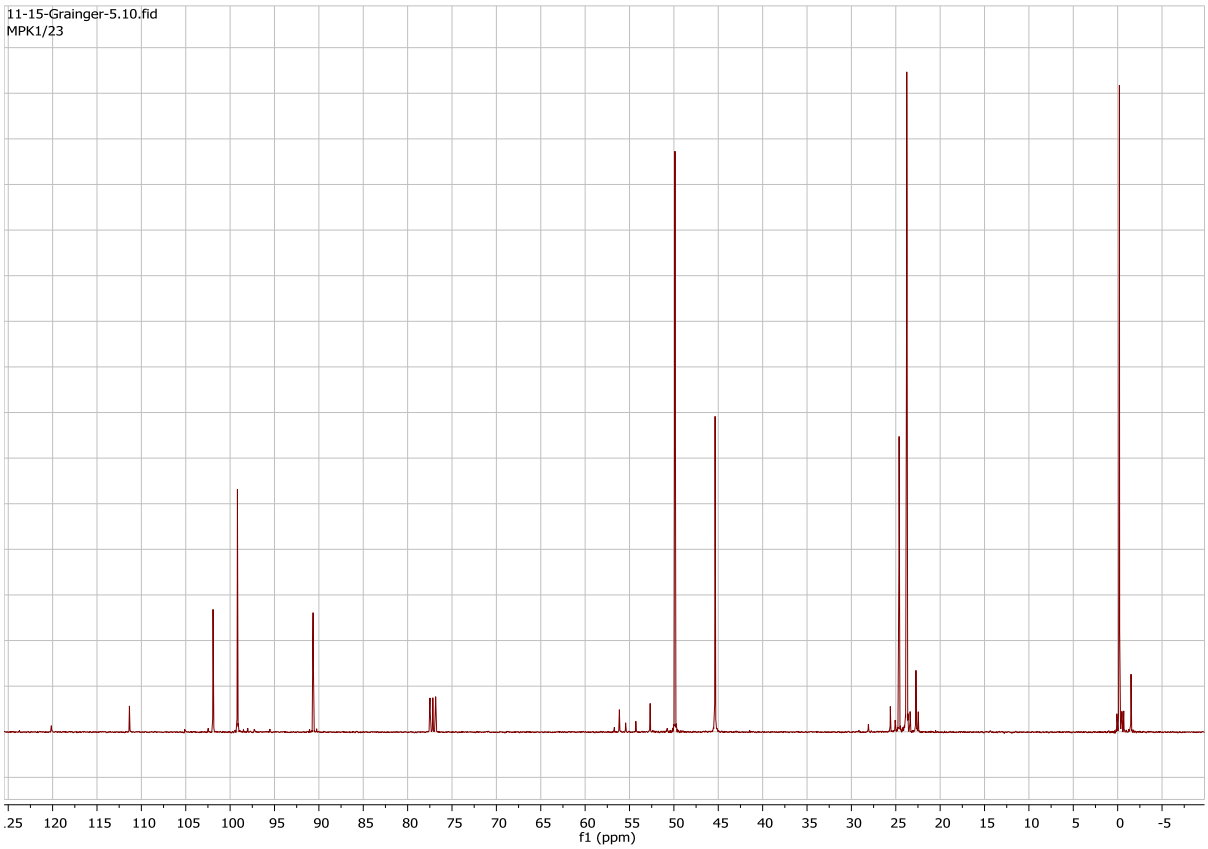
5-Methyl-1-(trimethylsilyl)hex-1-yn-3-one **150**



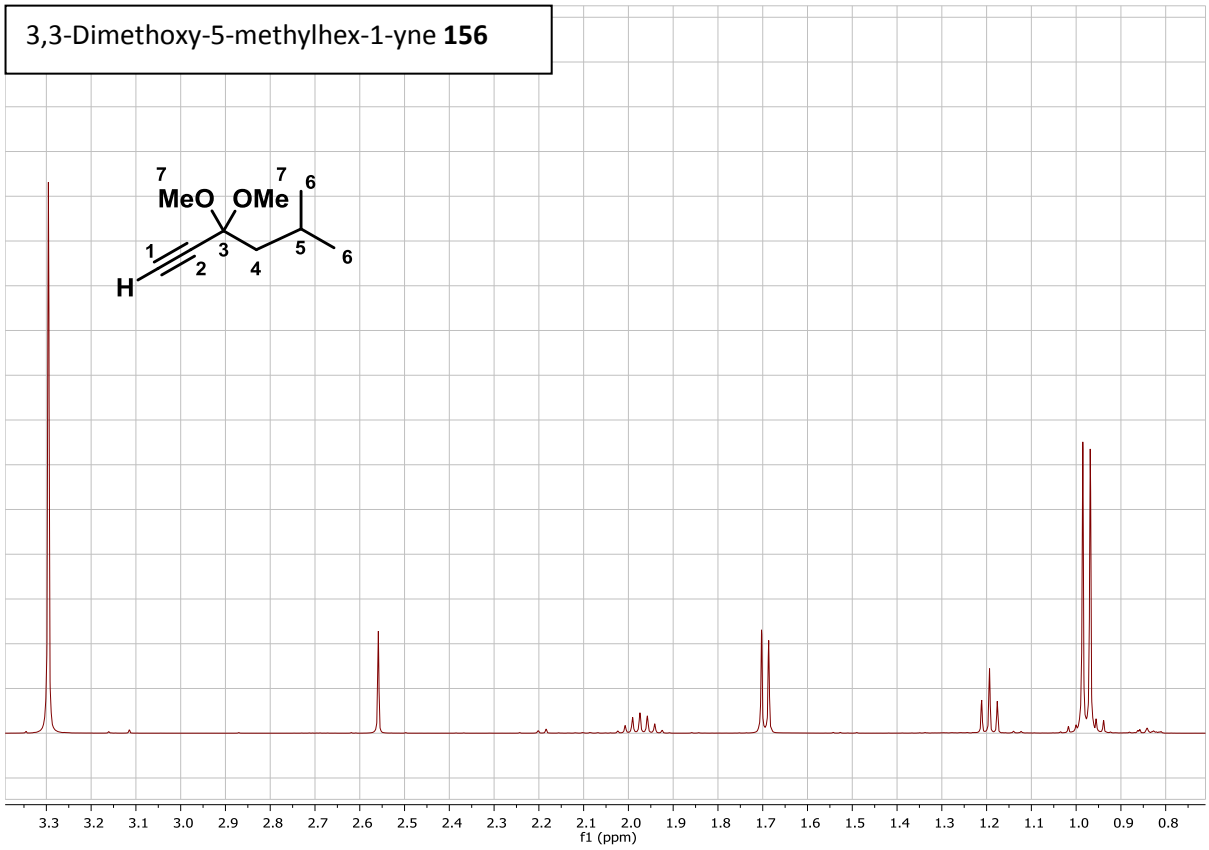


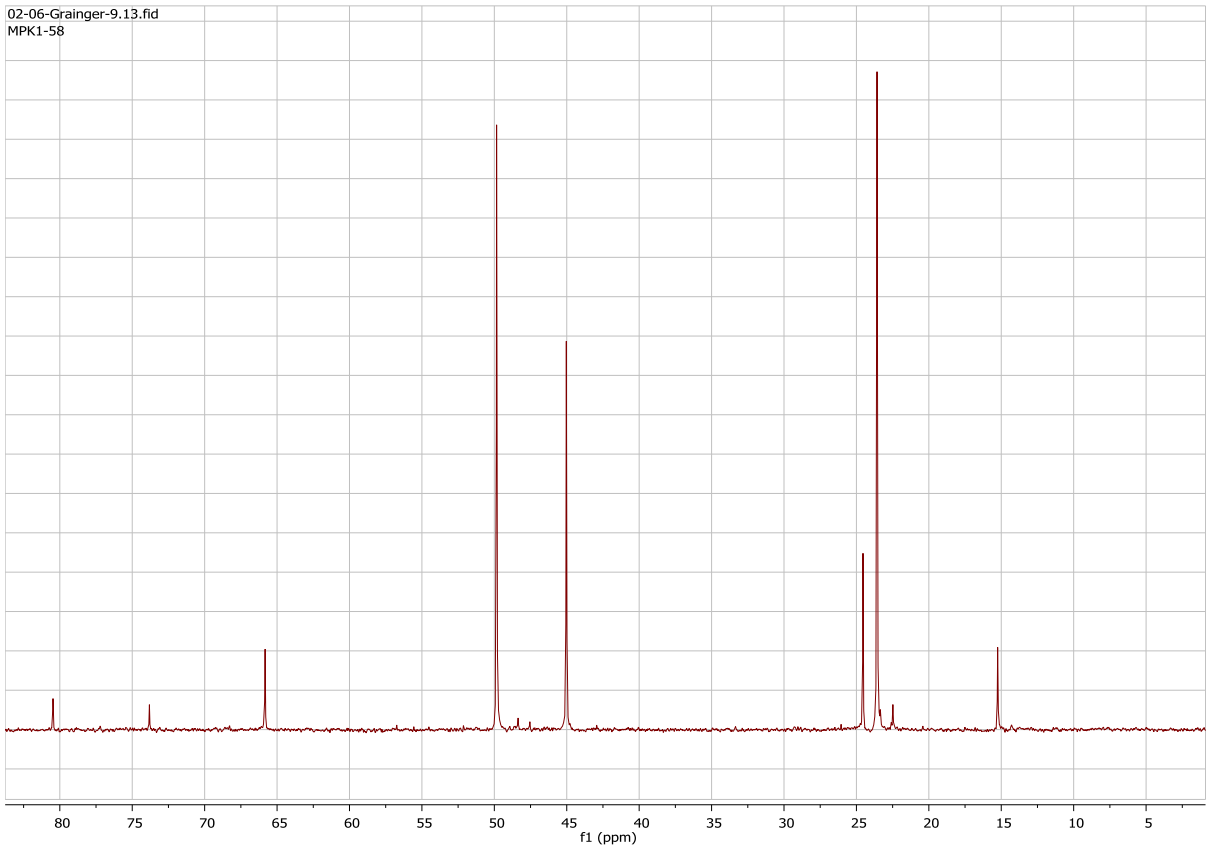
(3,3-Dimethoxy-5-methylhex-1-yn-1-yl)trimethylsilane **154**



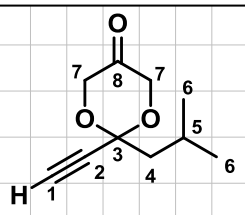


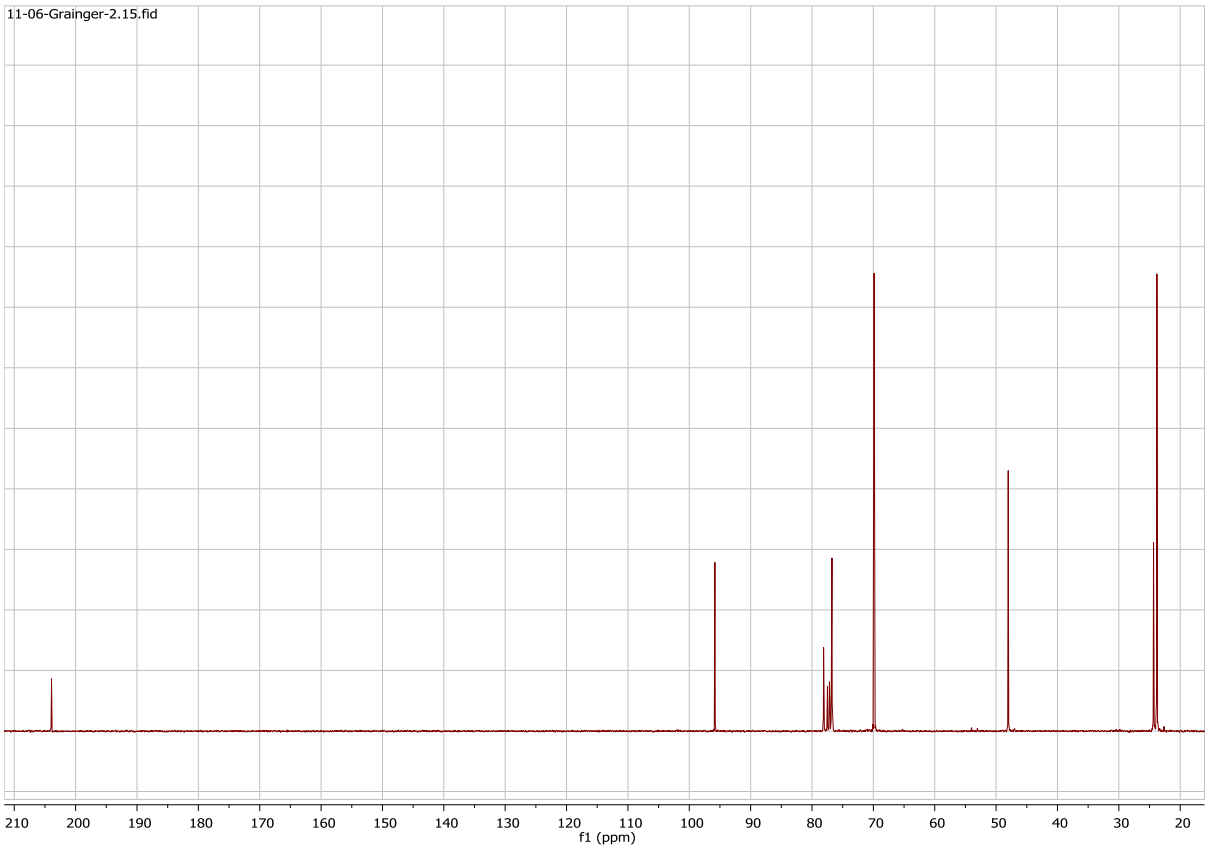
3,3-Dimethoxy-5-methylhex-1-yne **156**



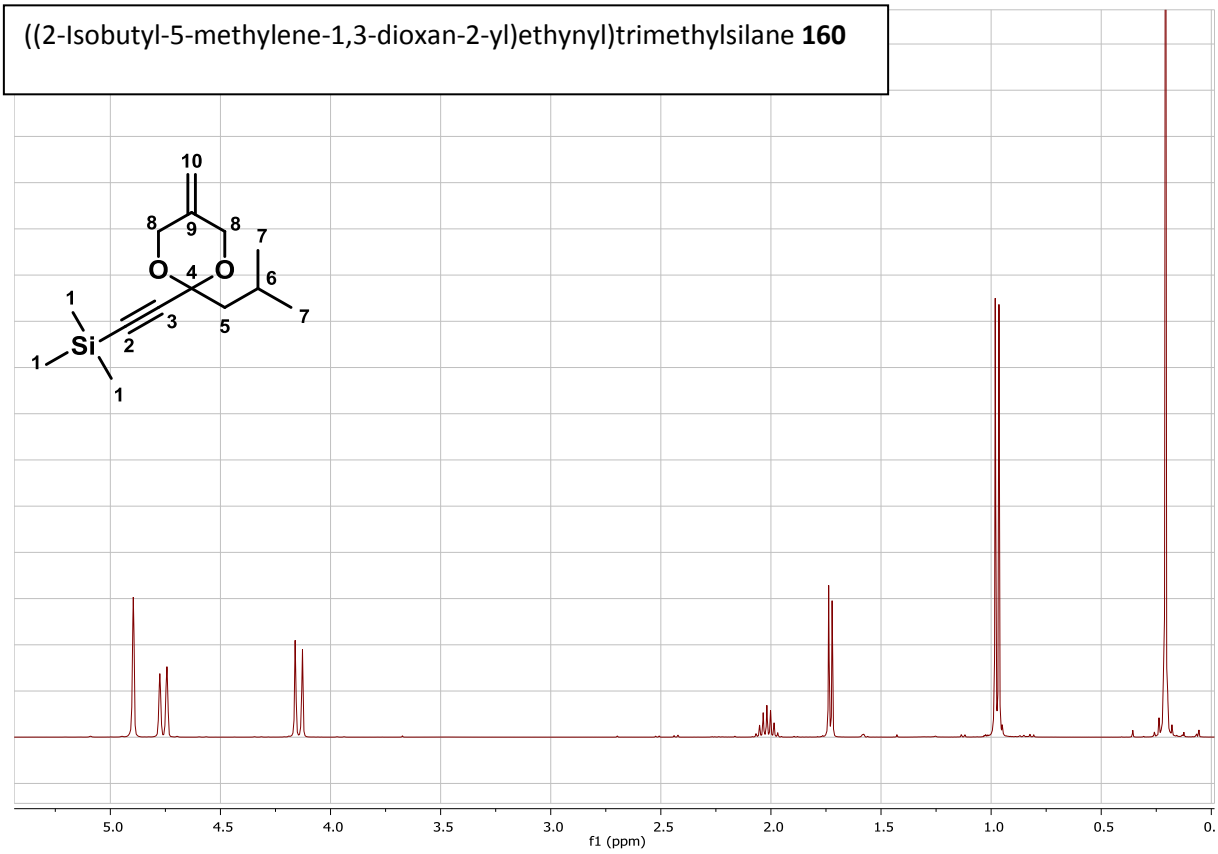


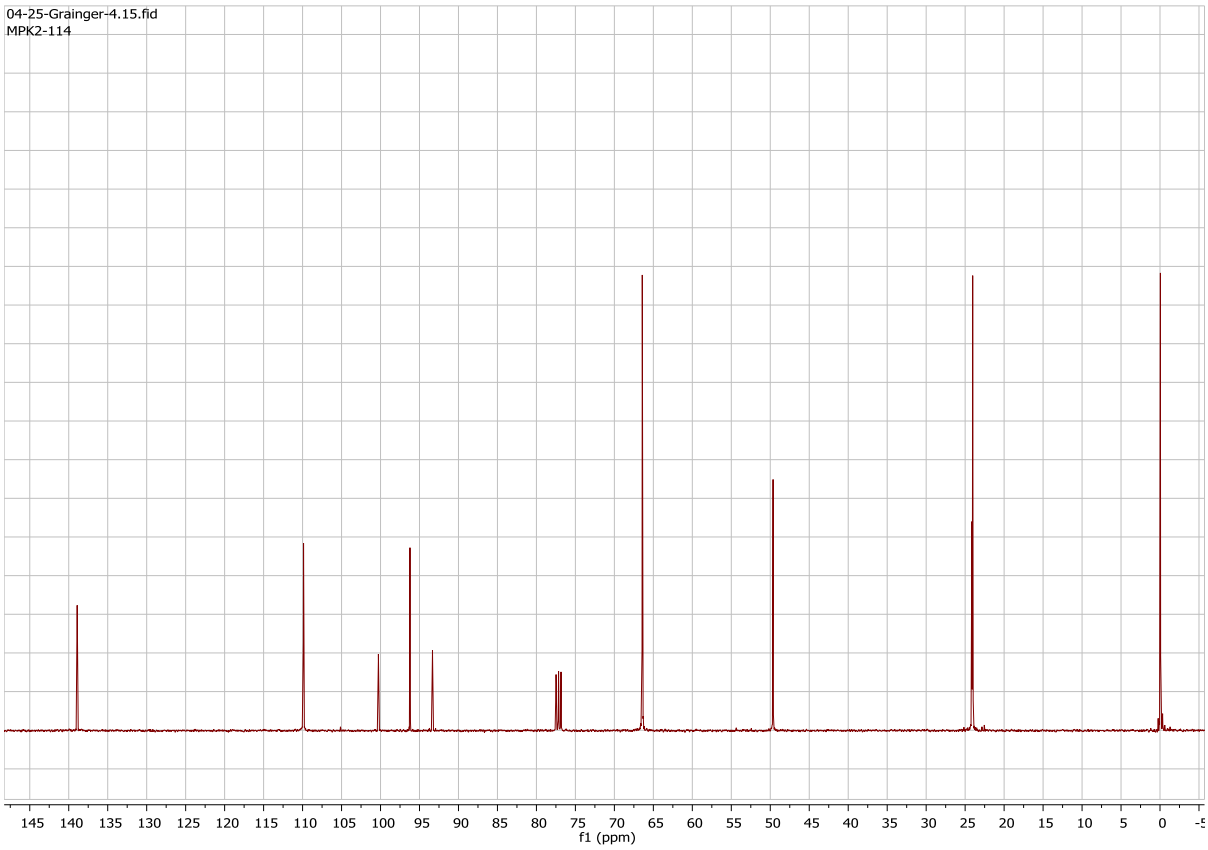
2-Ethynyl-2-isobutyl-1,3-dioxan-5-one **158**



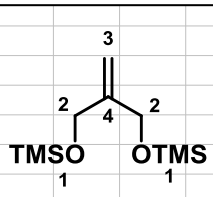


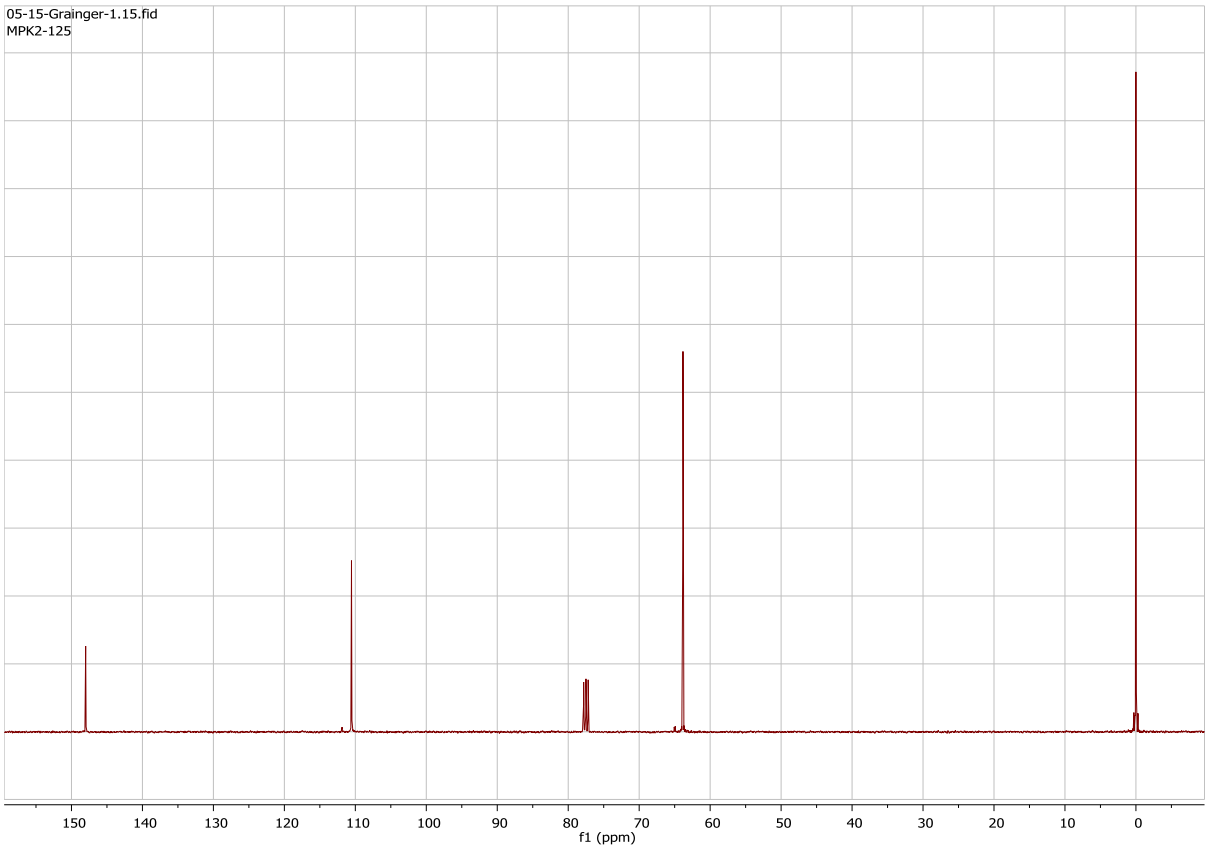
((2-Isobutyl-5-methylene-1,3-dioxan-2-yl)ethynyl)trimethylsilane **160**



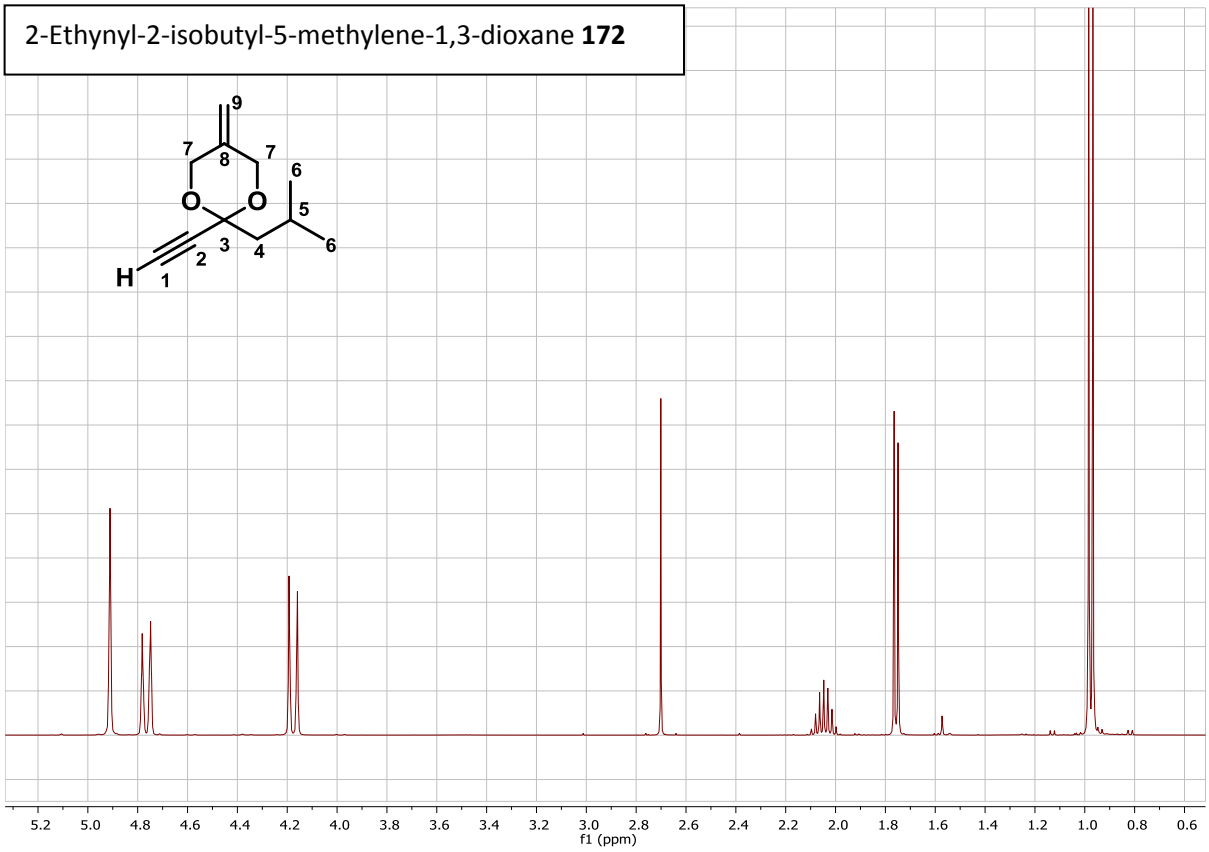


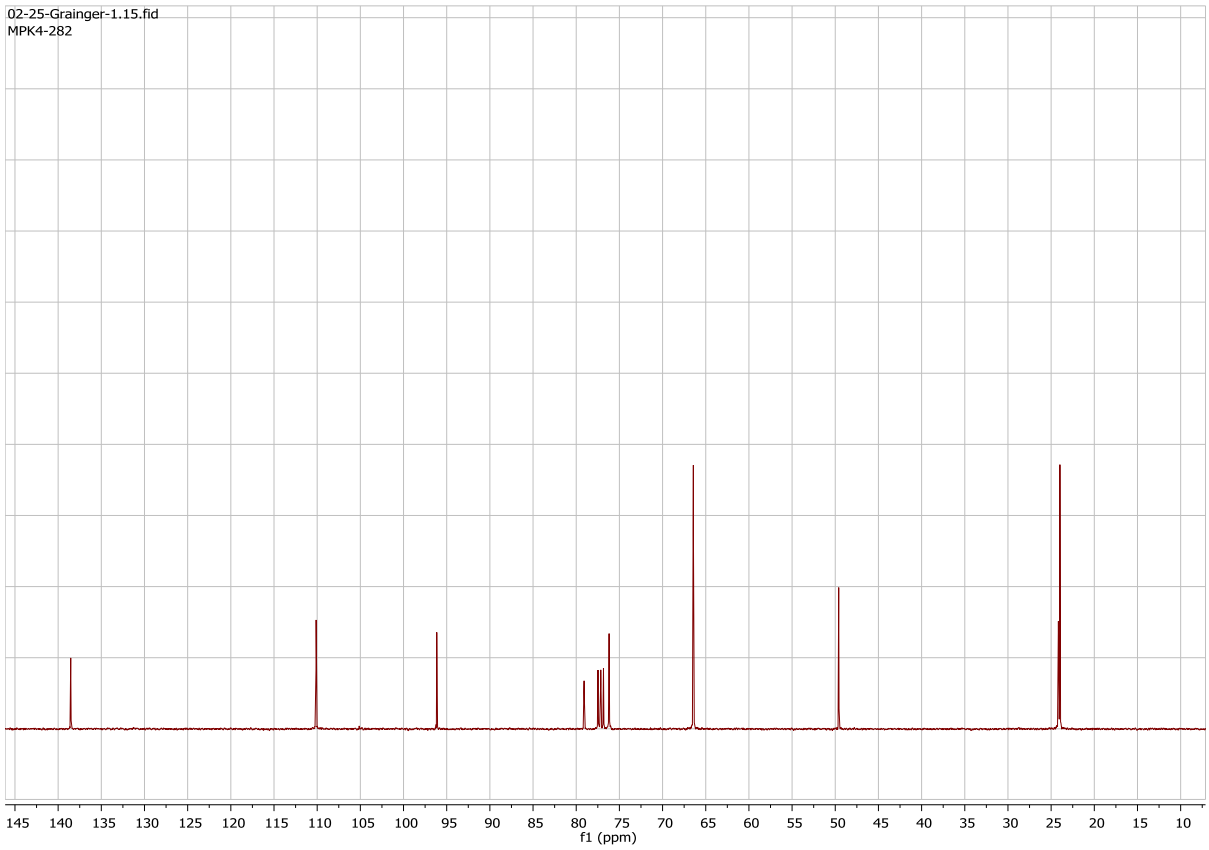
2,2,8,8-Tetramethyl-5-methylene-3,7-dioxa-2,8-disilanonane **167**



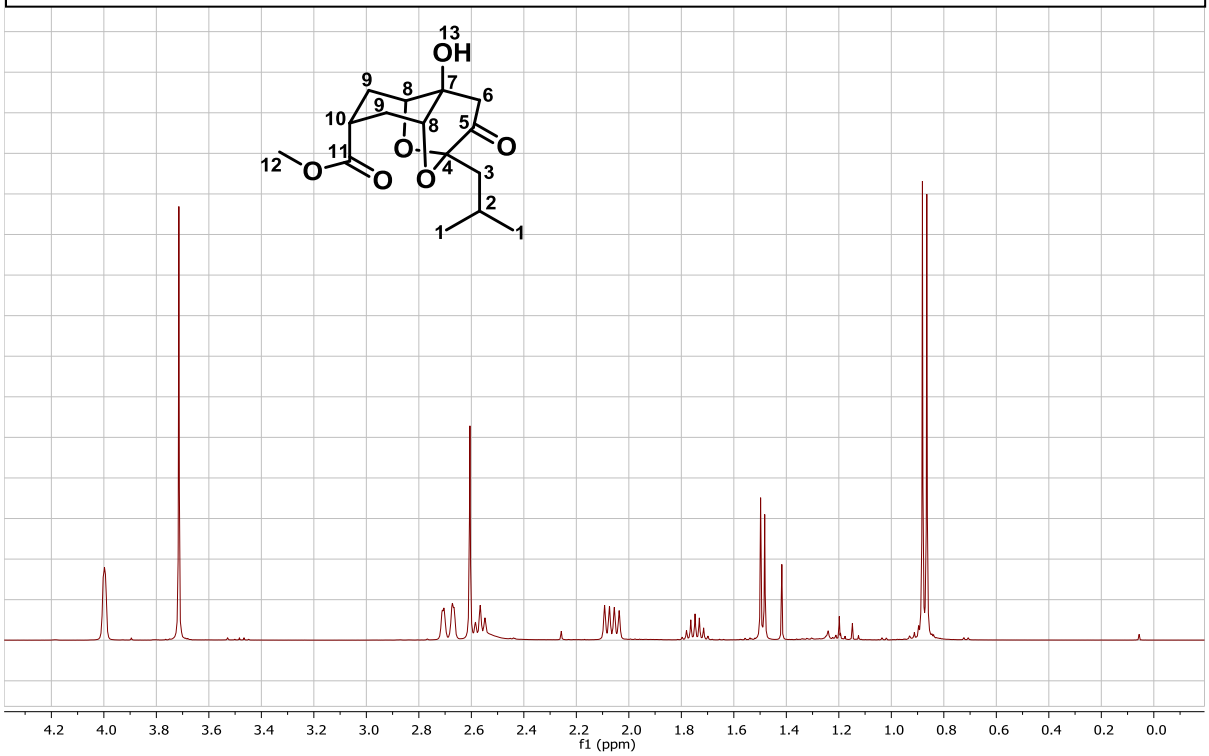


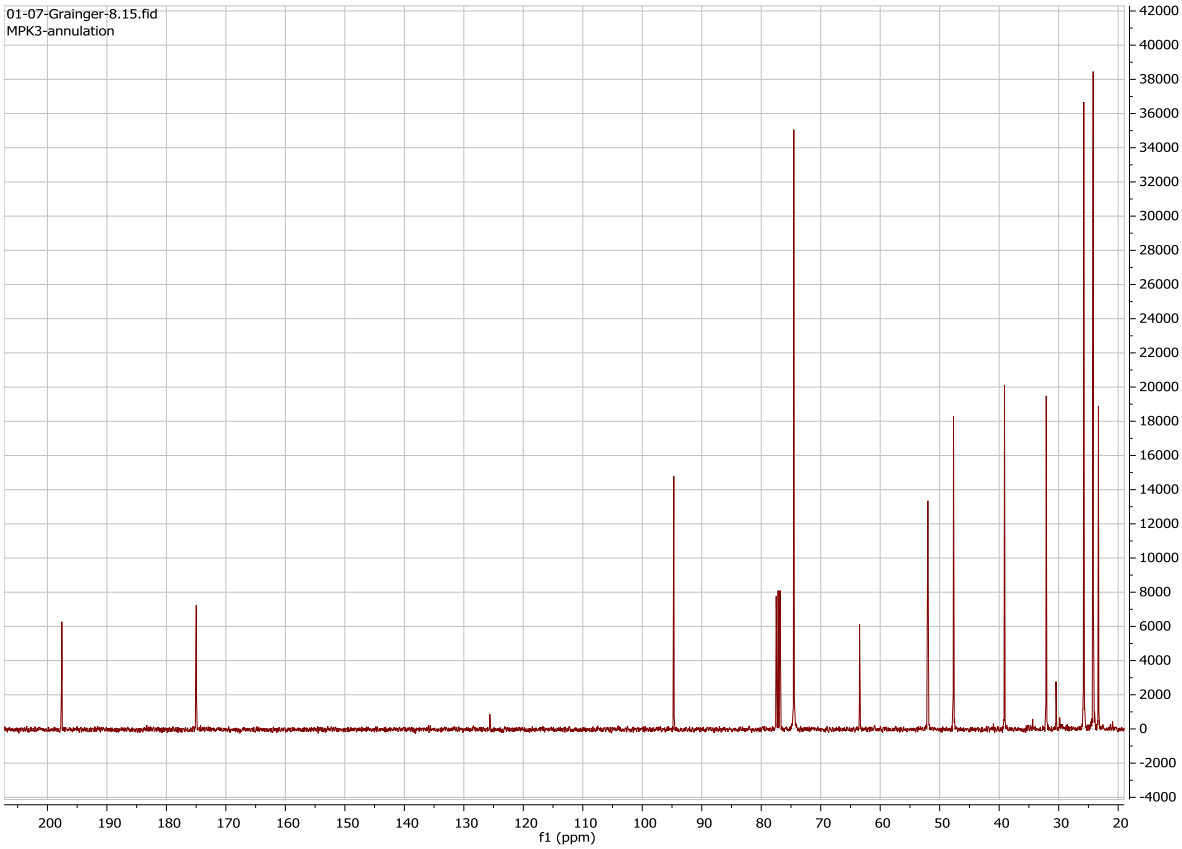
2-Ethynyl-2-isobutyl-5-methylene-1,3-dioxane **172**



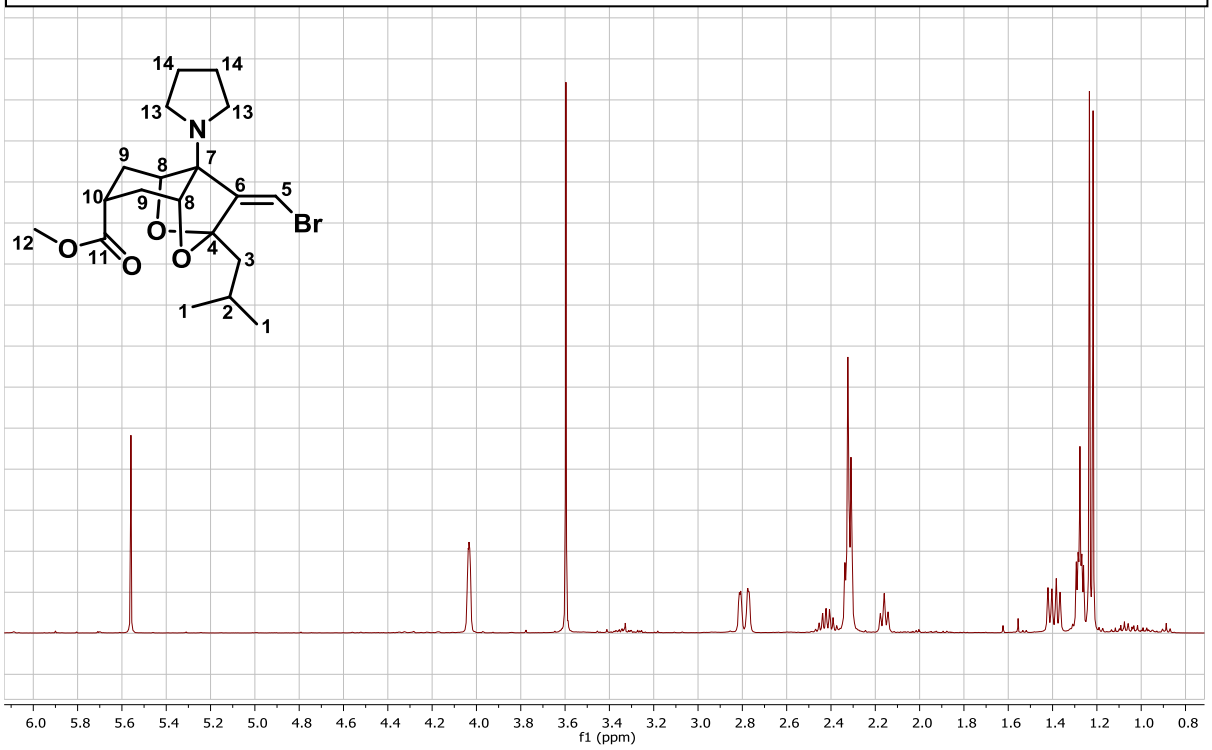


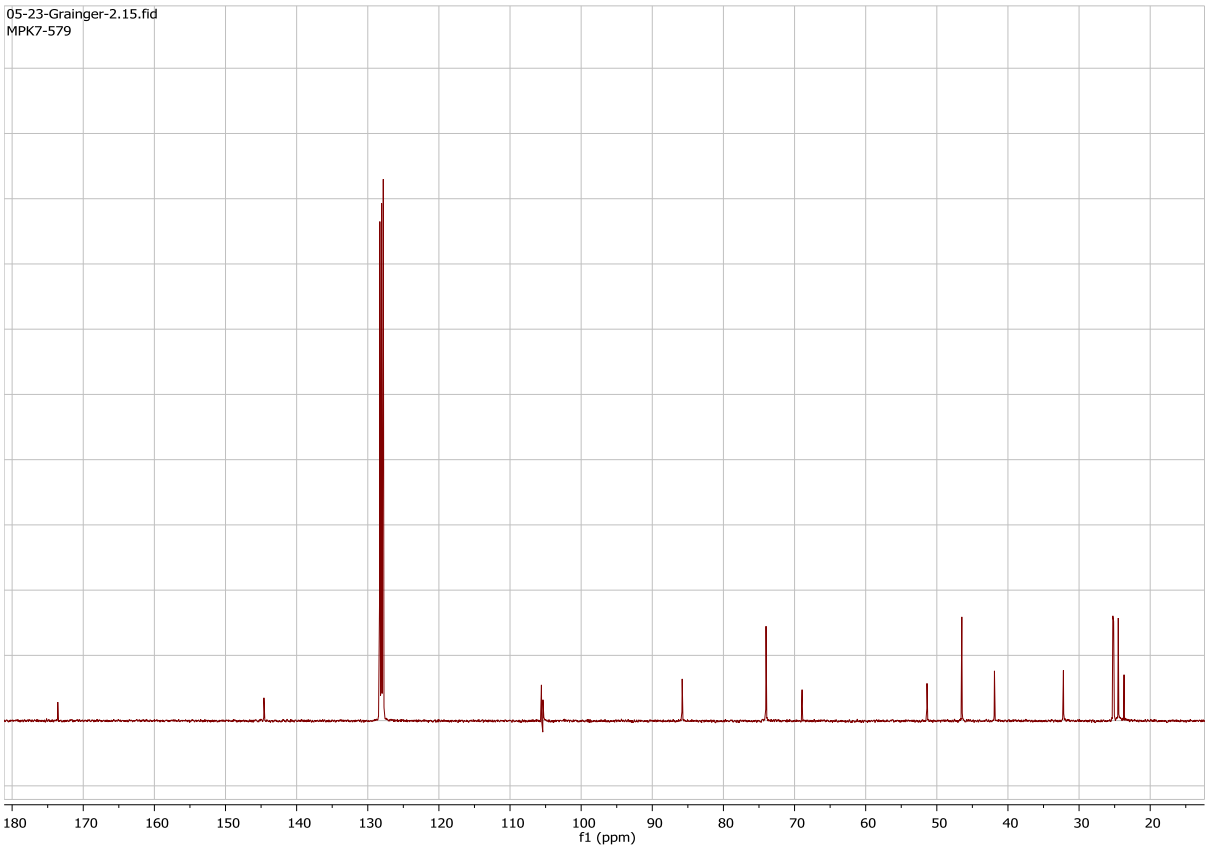
Methyl (4'*R*,5*R*,7*R*,8*S*)-4-hydroxy-2-isobutyl-3-oxooctahydro-2H-2,5-epoxychromene-7-carboxylate **175**



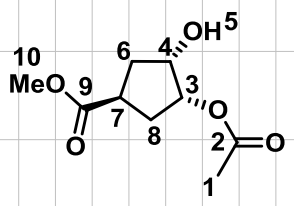


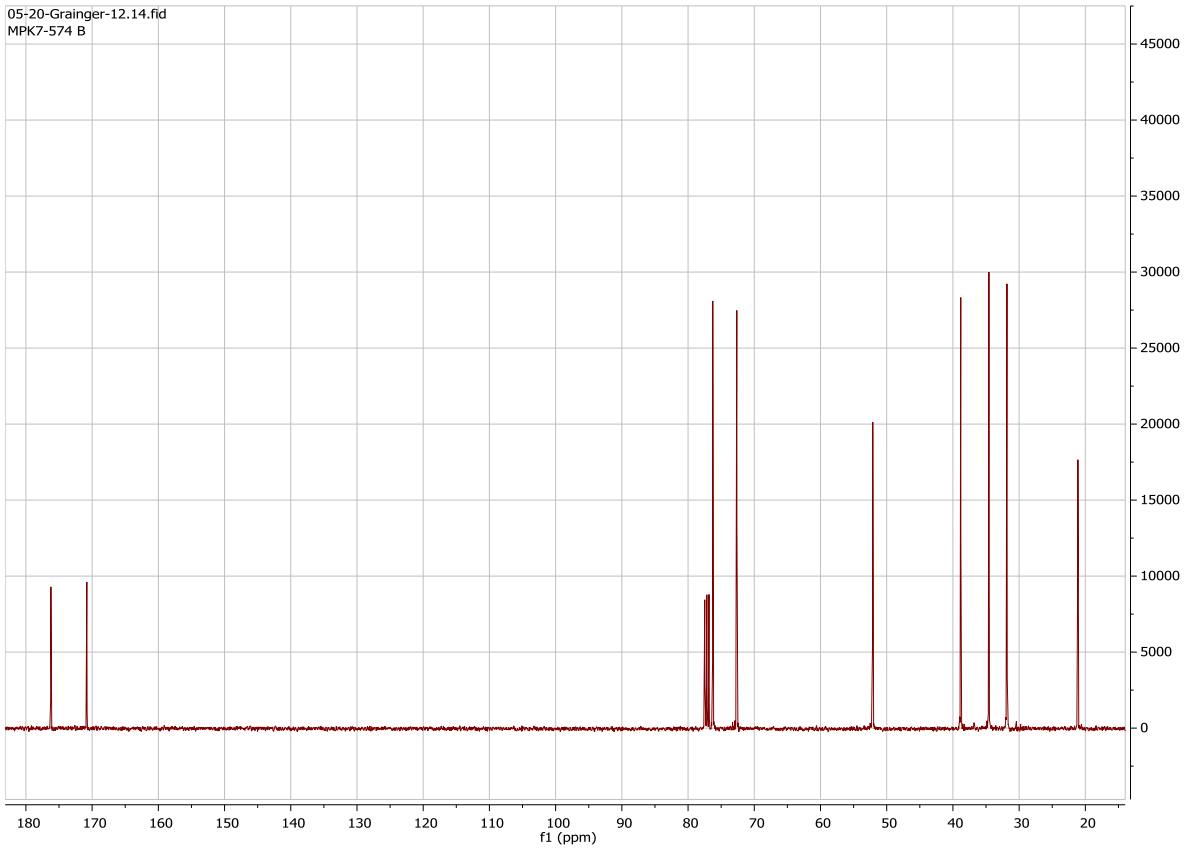
Methyl (3'*R*,4*R*,6*R*,7*S*,Z)-3-(bromomethylene)-2-isobutyl-3-(pyrrolidin-1-yl)octahydro-2,4-epoxybenzofuran-6-carboxylate **177**



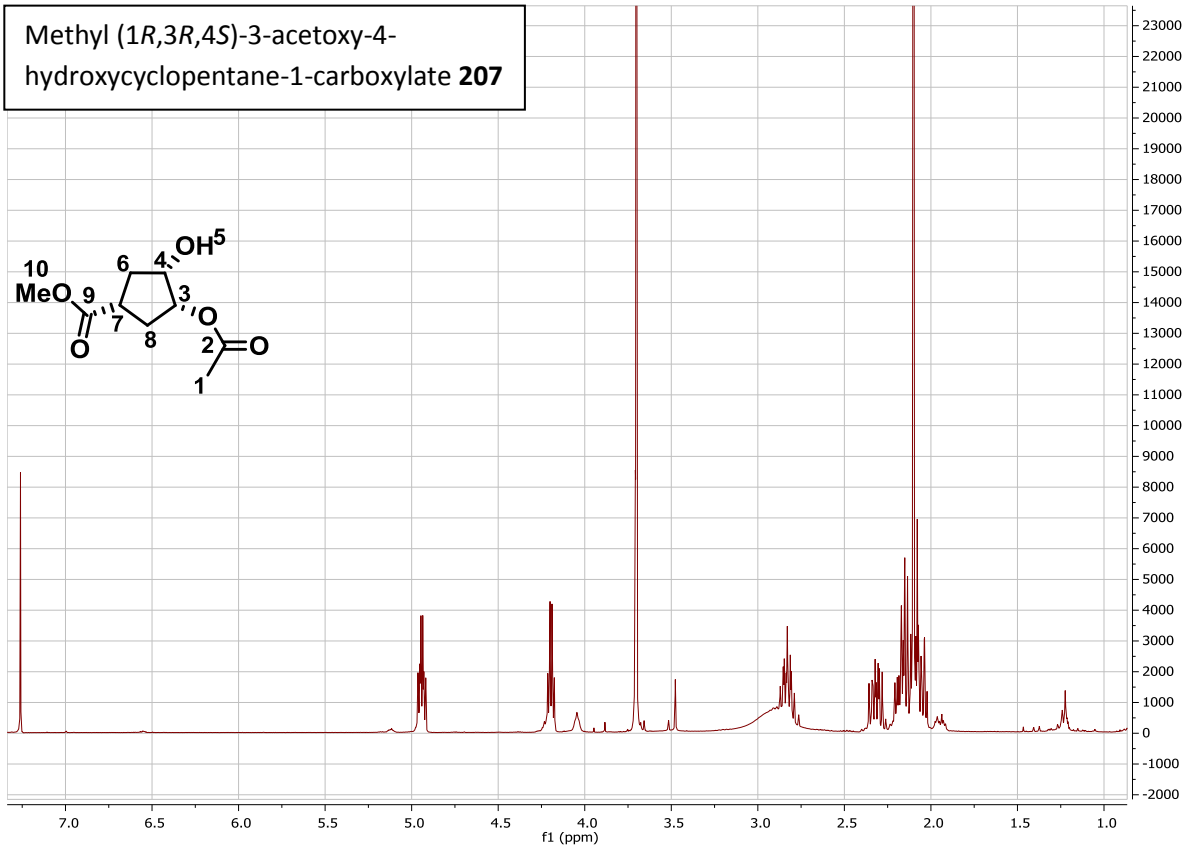


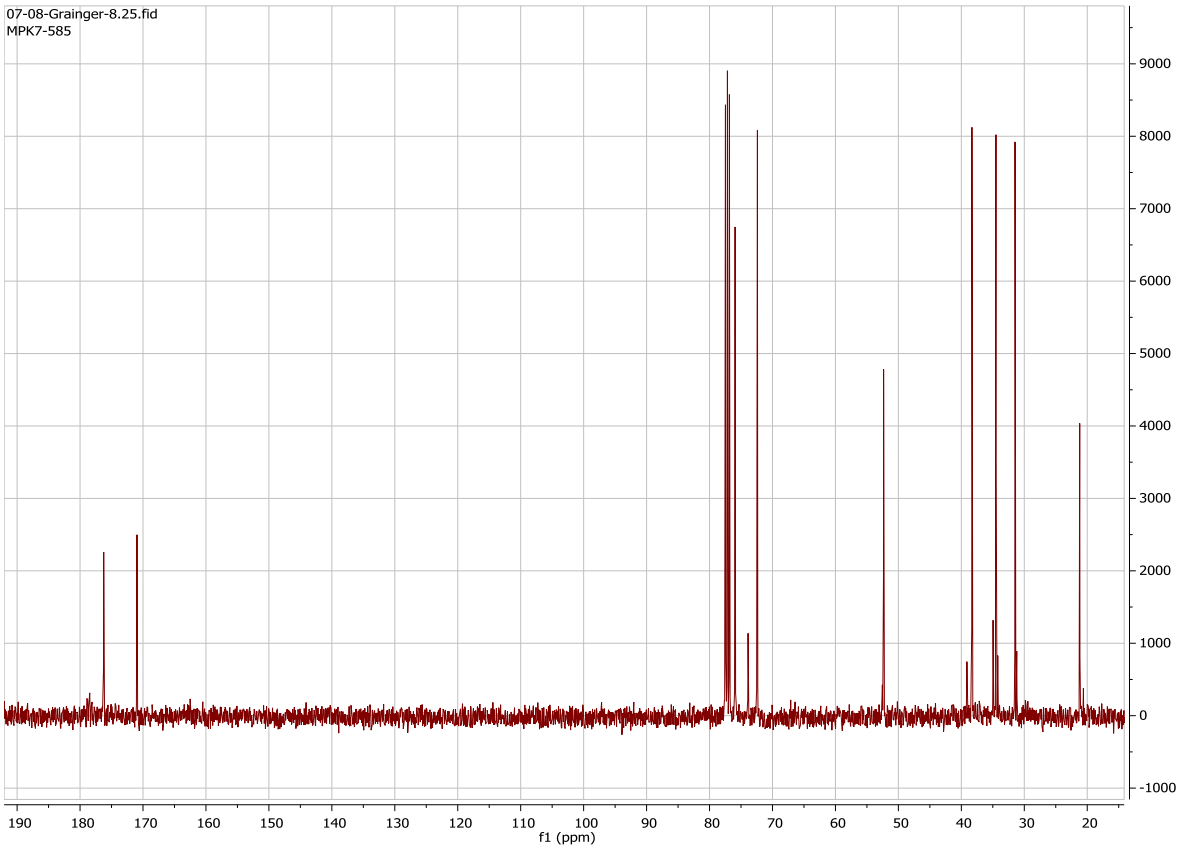
Methyl (1*S*,3*R*,4*S*)-3-acetoxy-4-hydroxycyclopentane-1-carboxylate **206**



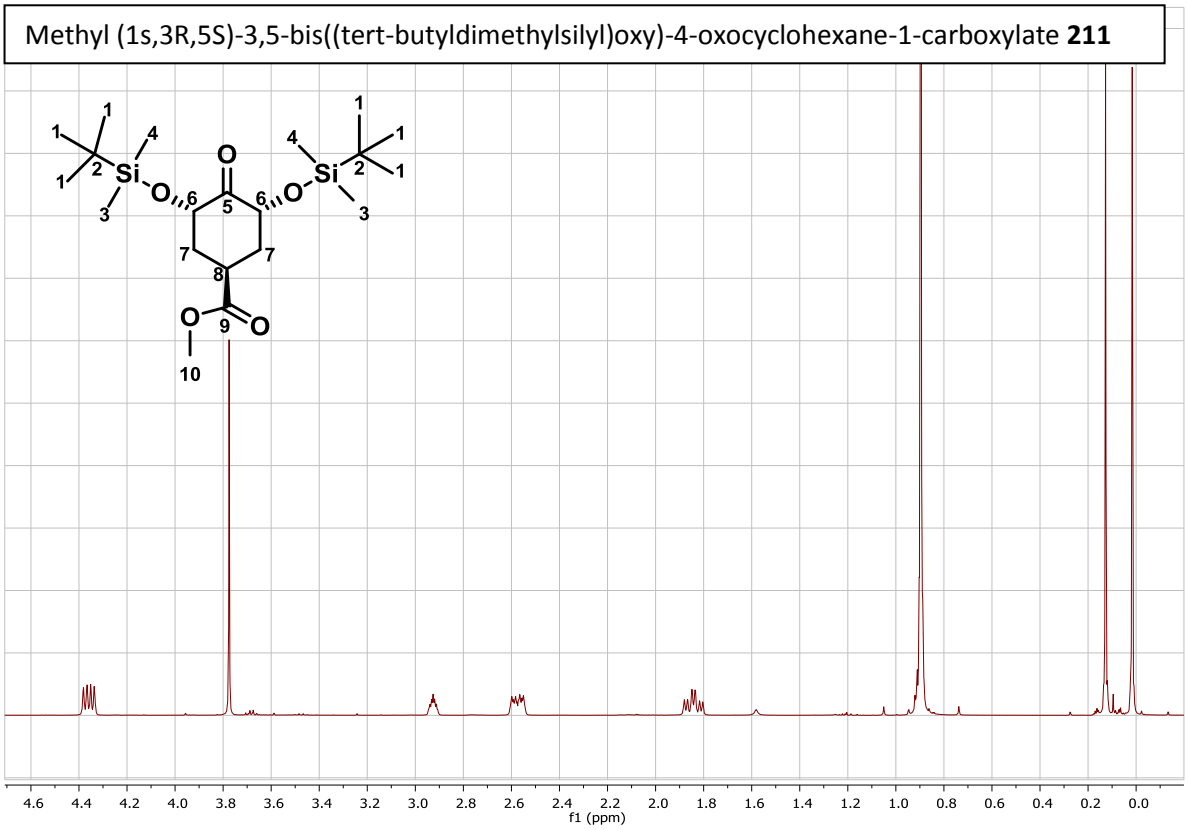


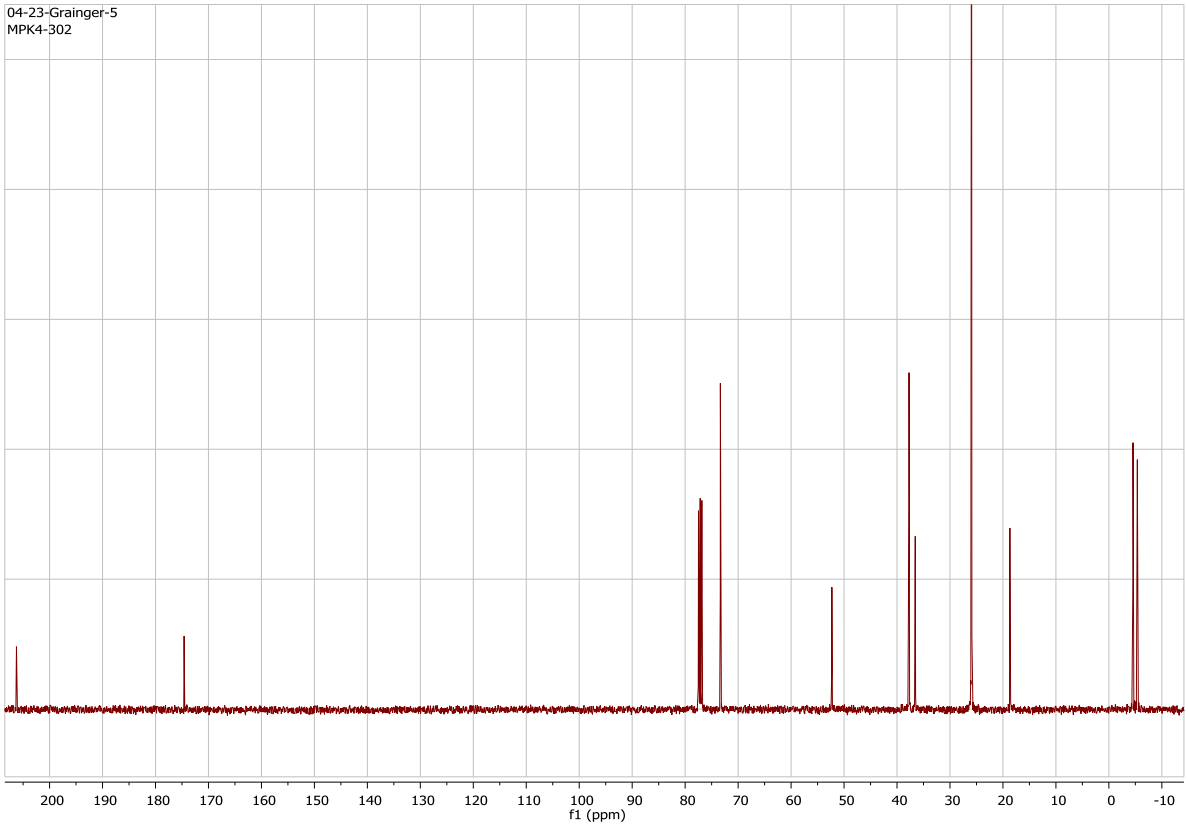
Methyl (1*R*,3*R*,4*S*)-3-acetoxy-4-hydroxycyclopentane-1-carboxylate **207**



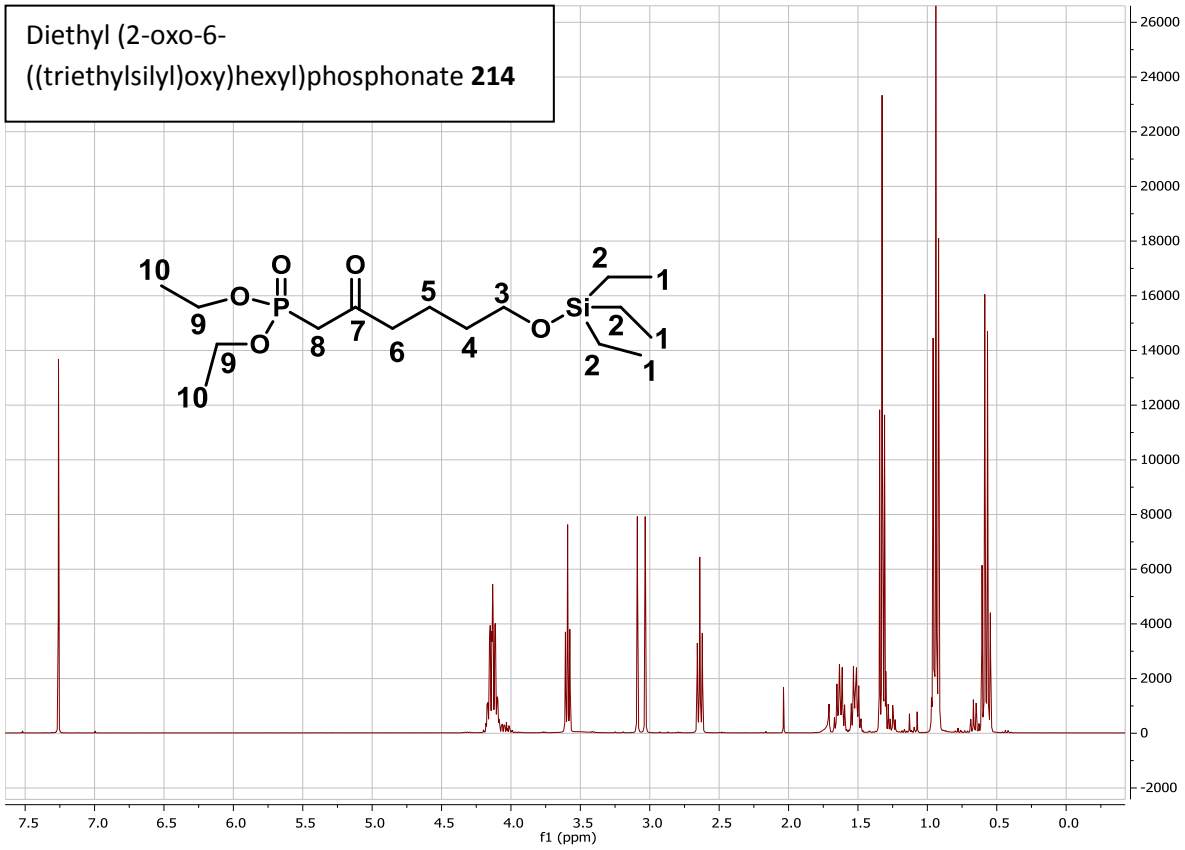


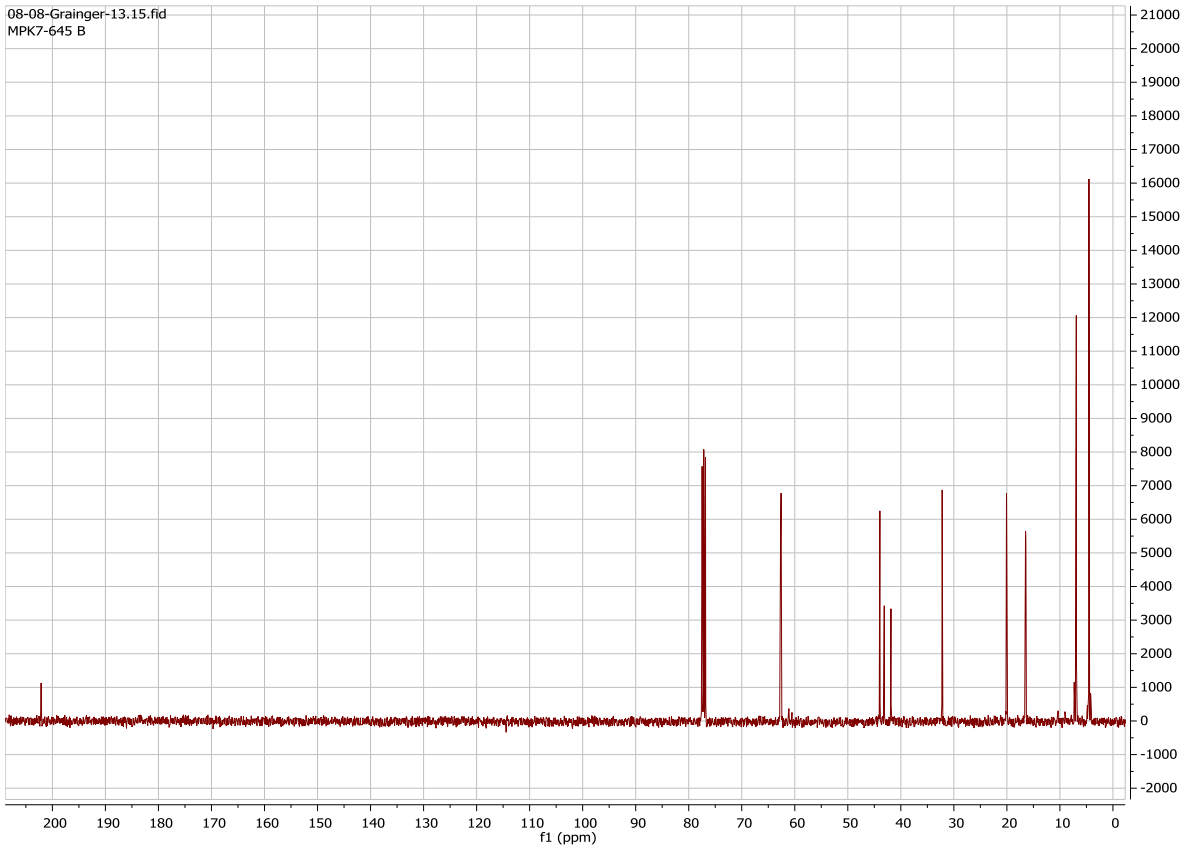
Methyl (1s,3R,5S)-3,5-bis((tert-butyldimethylsilyl)oxy)-4-oxocyclohexane-1-carboxylate **211**



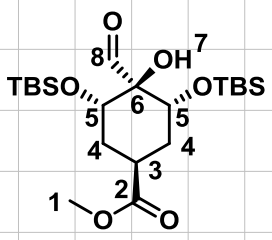


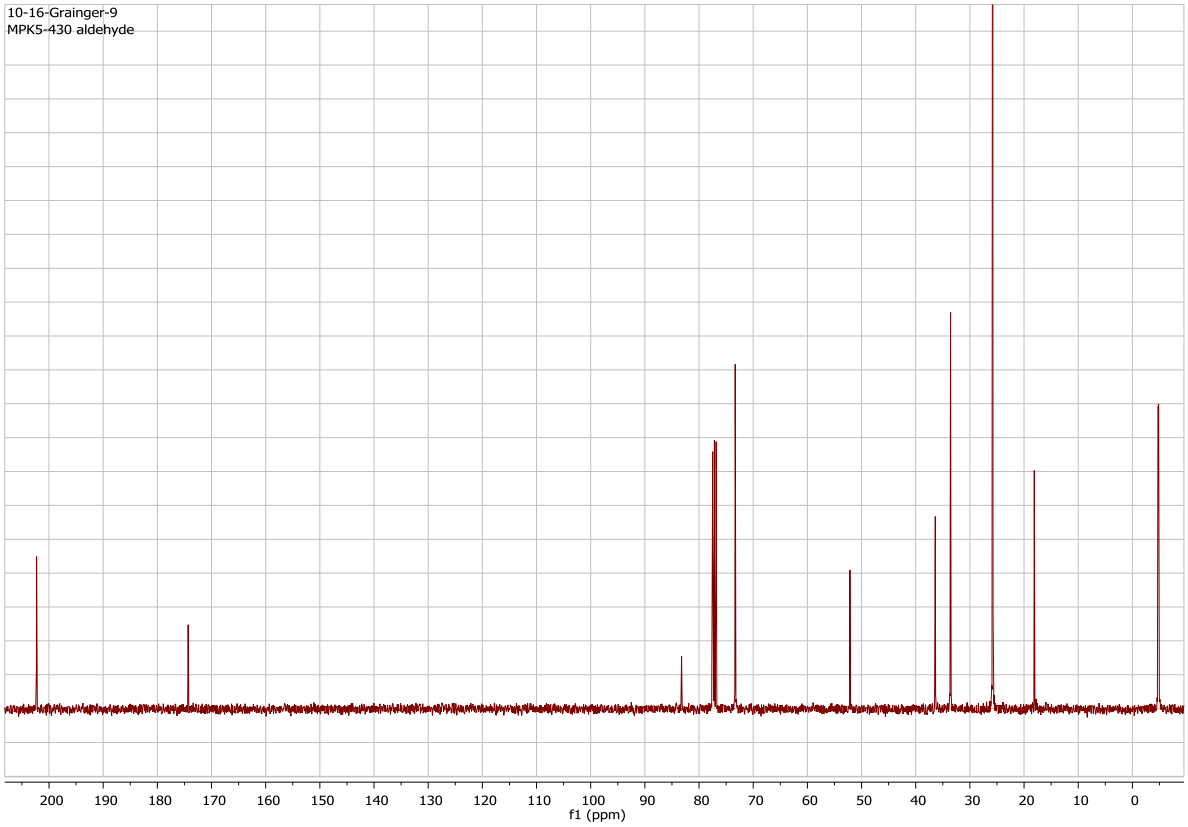
Diethyl (2-oxo-6-((triethylsilyl)oxy)hexyl)phosphonate **214**



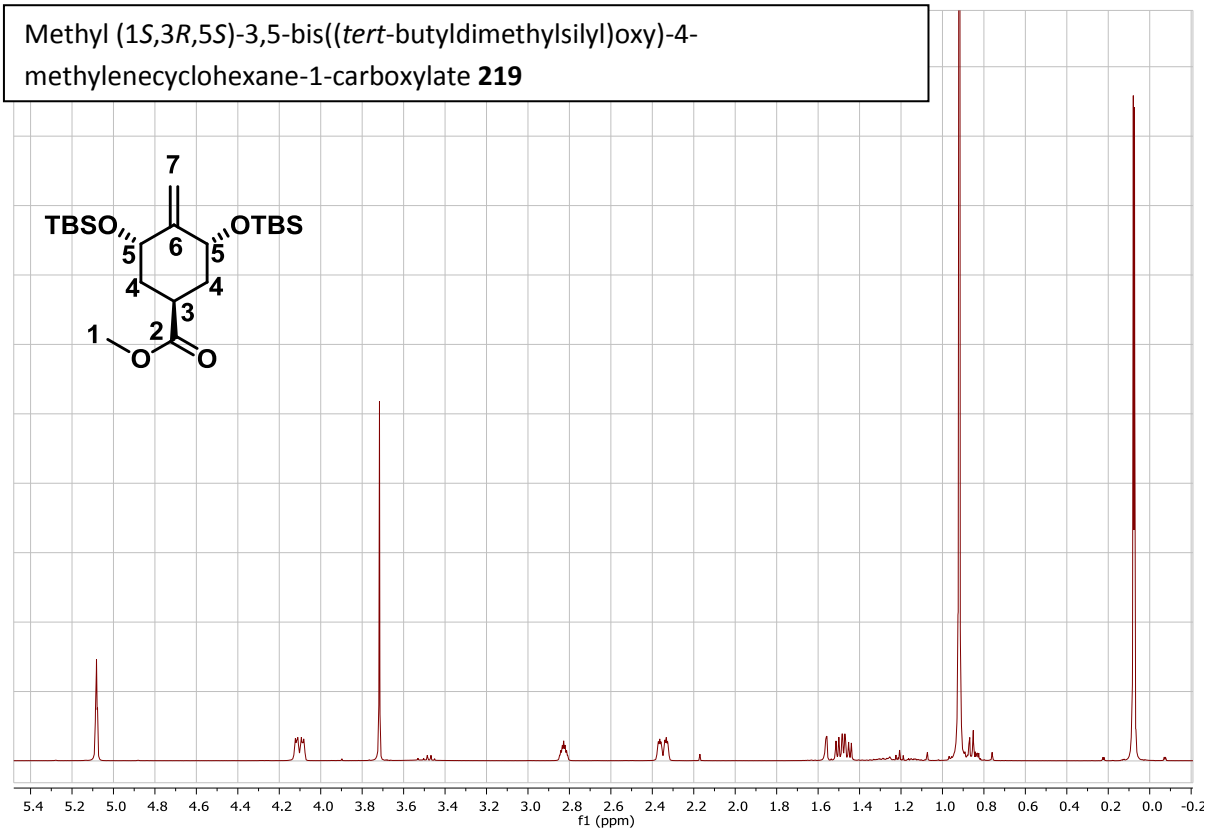


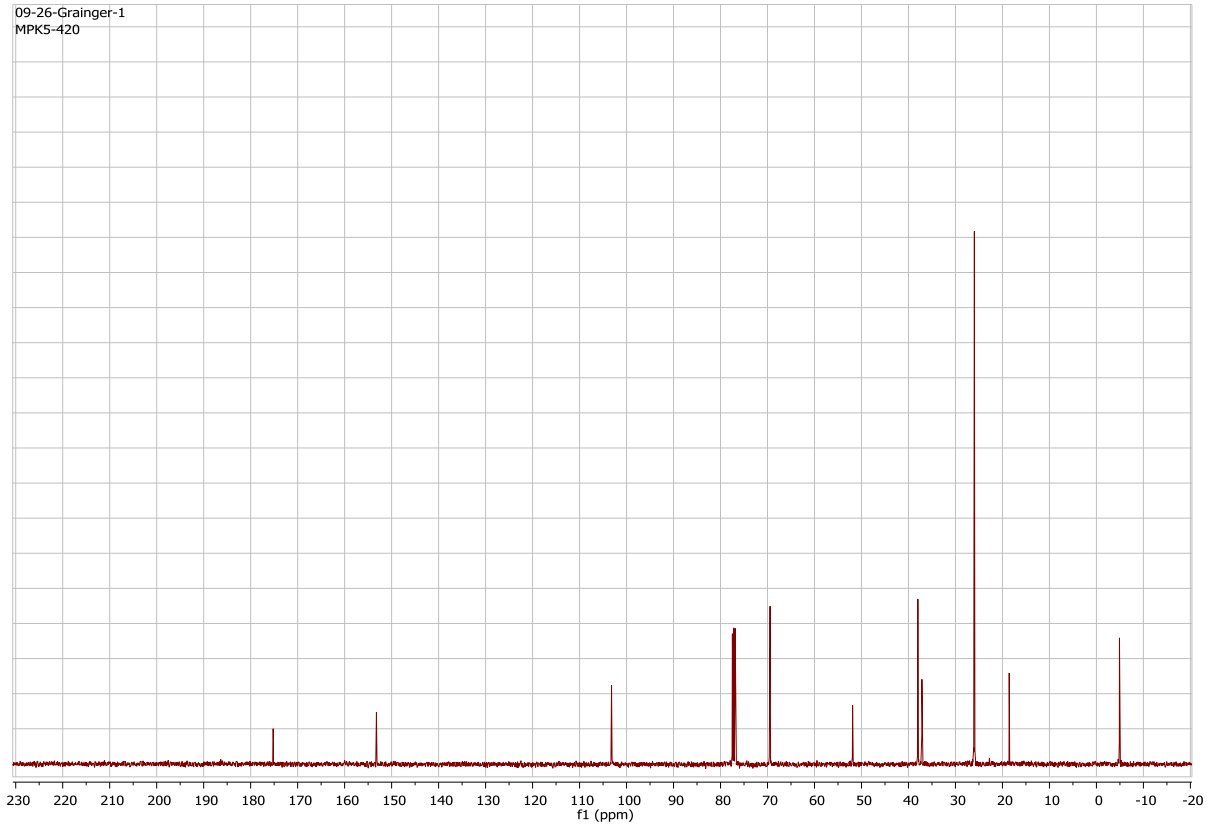
Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-formyl-4-hydroxycyclohexane-1-carboxylate **217**



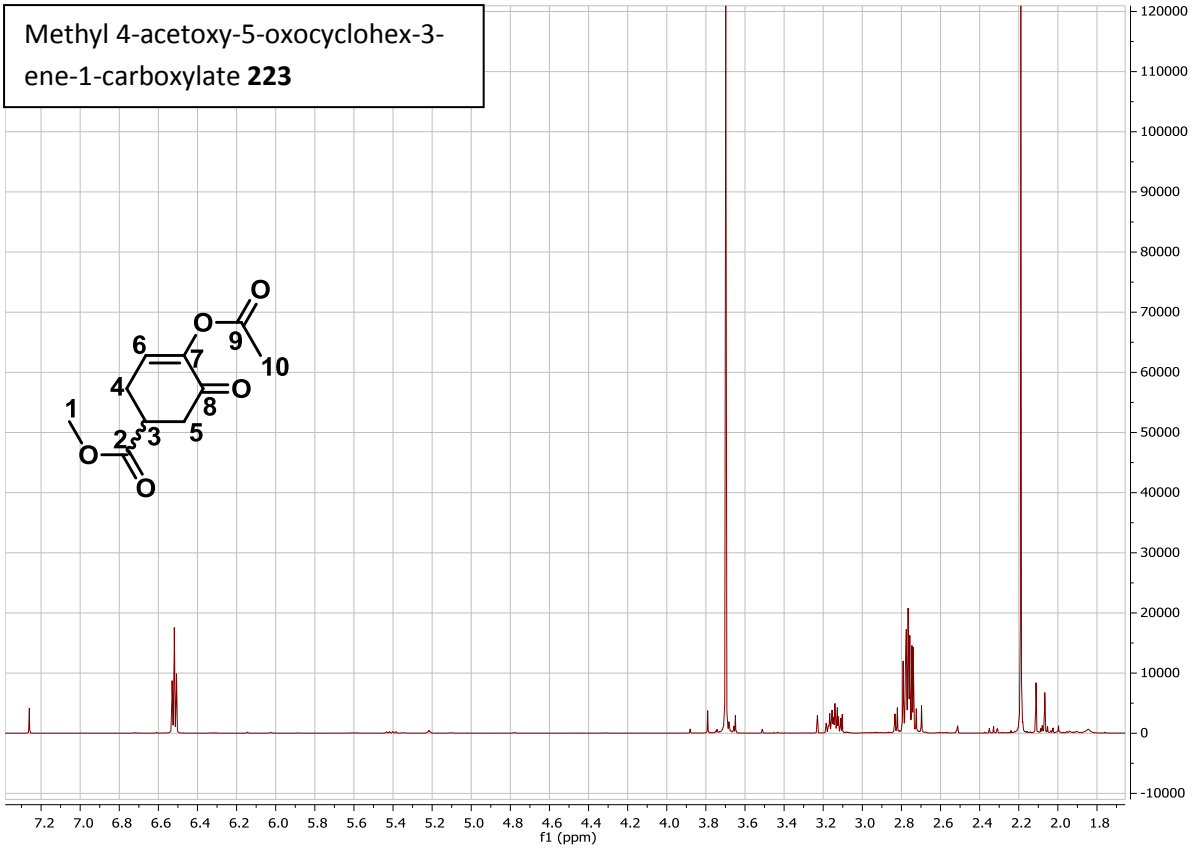


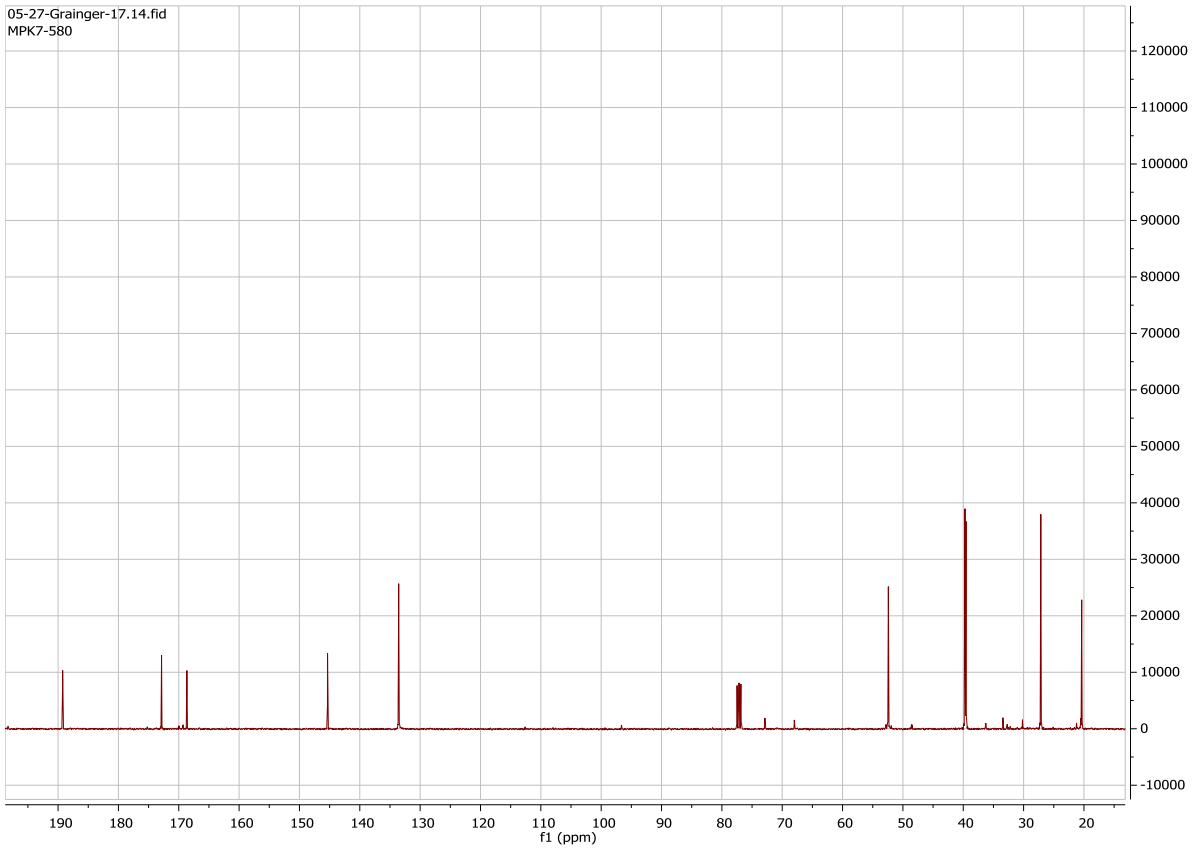
Methyl (1*S*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methylenecyclohexane-1-carboxylate **219**



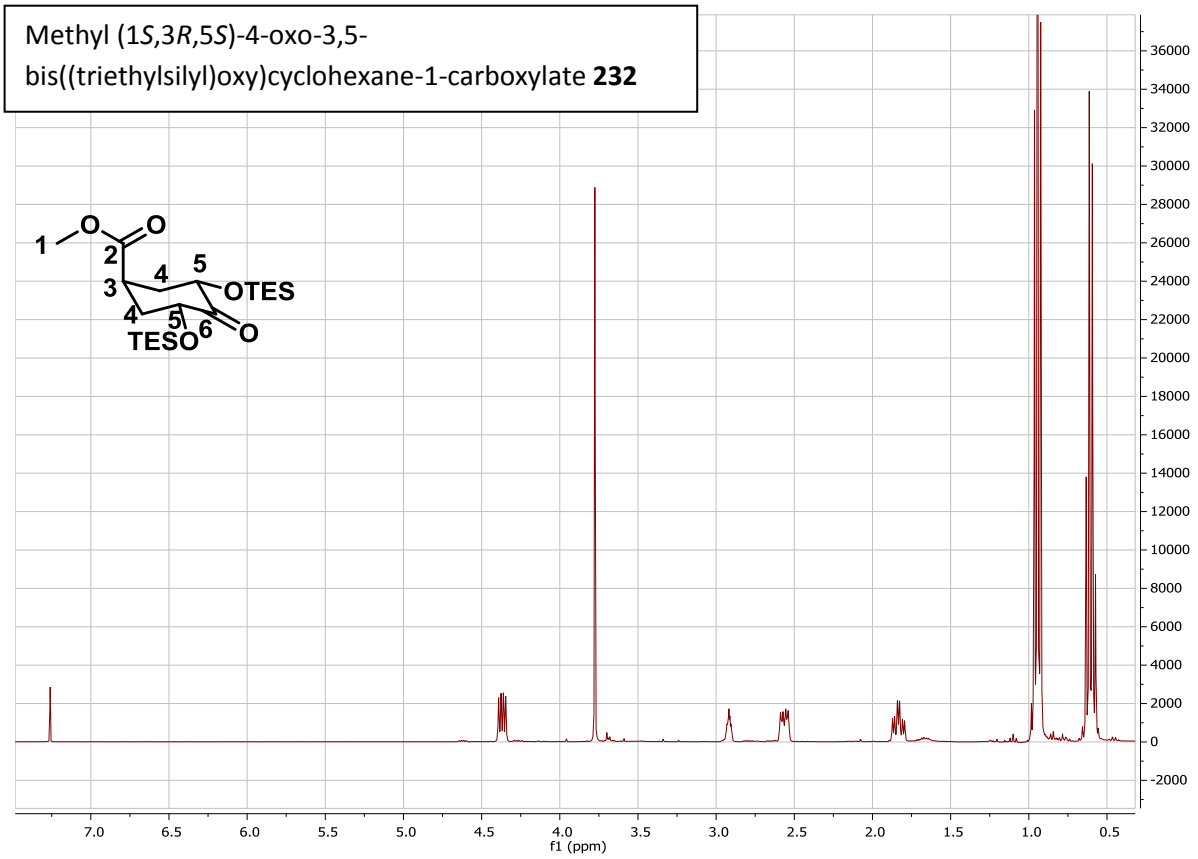


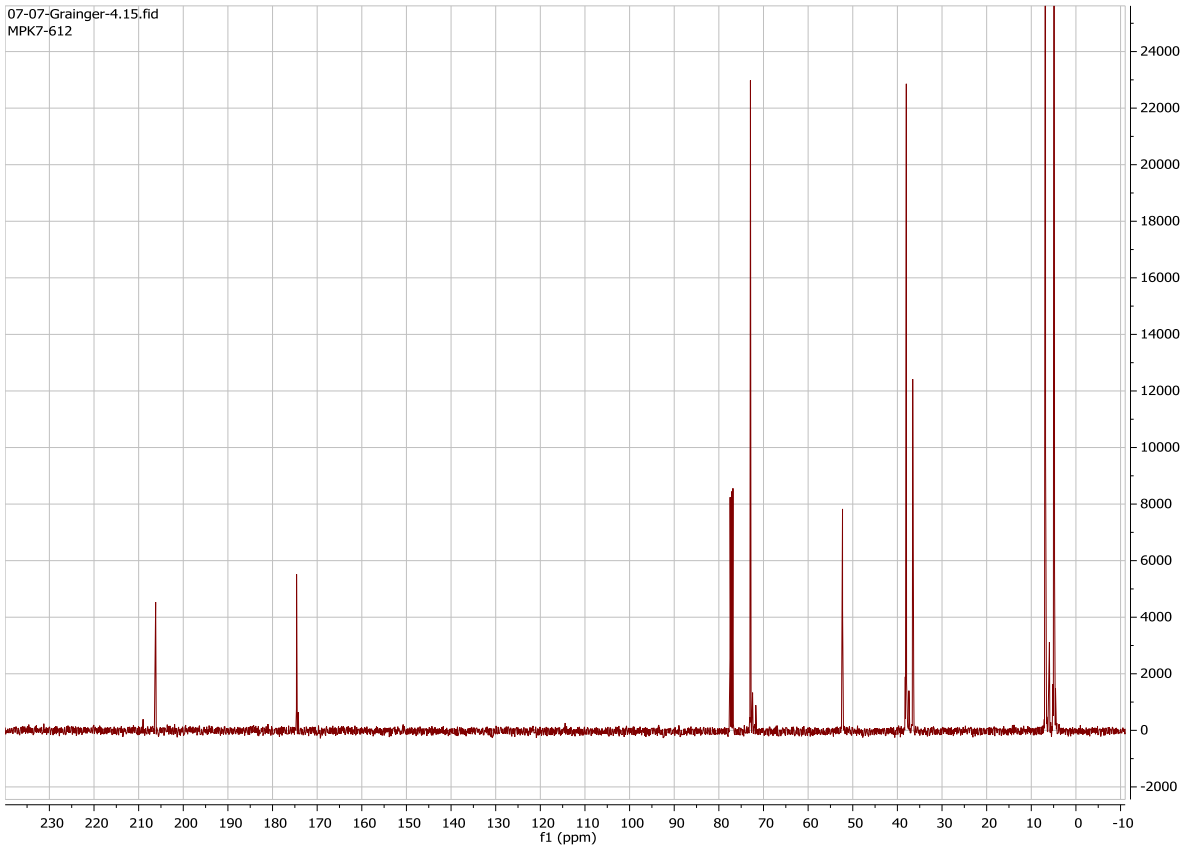
Methyl 4-acetoxy-5-oxocyclohex-3-ene-1-carboxylate **223**



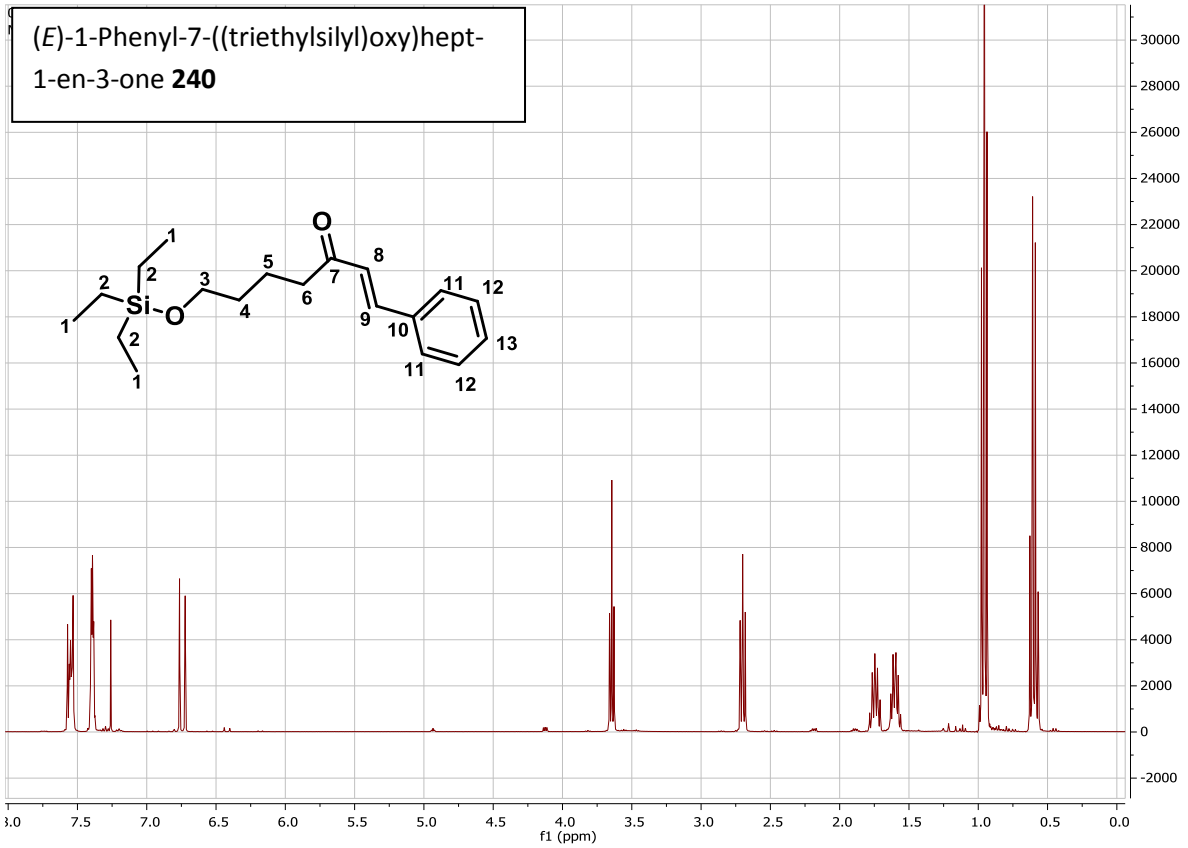


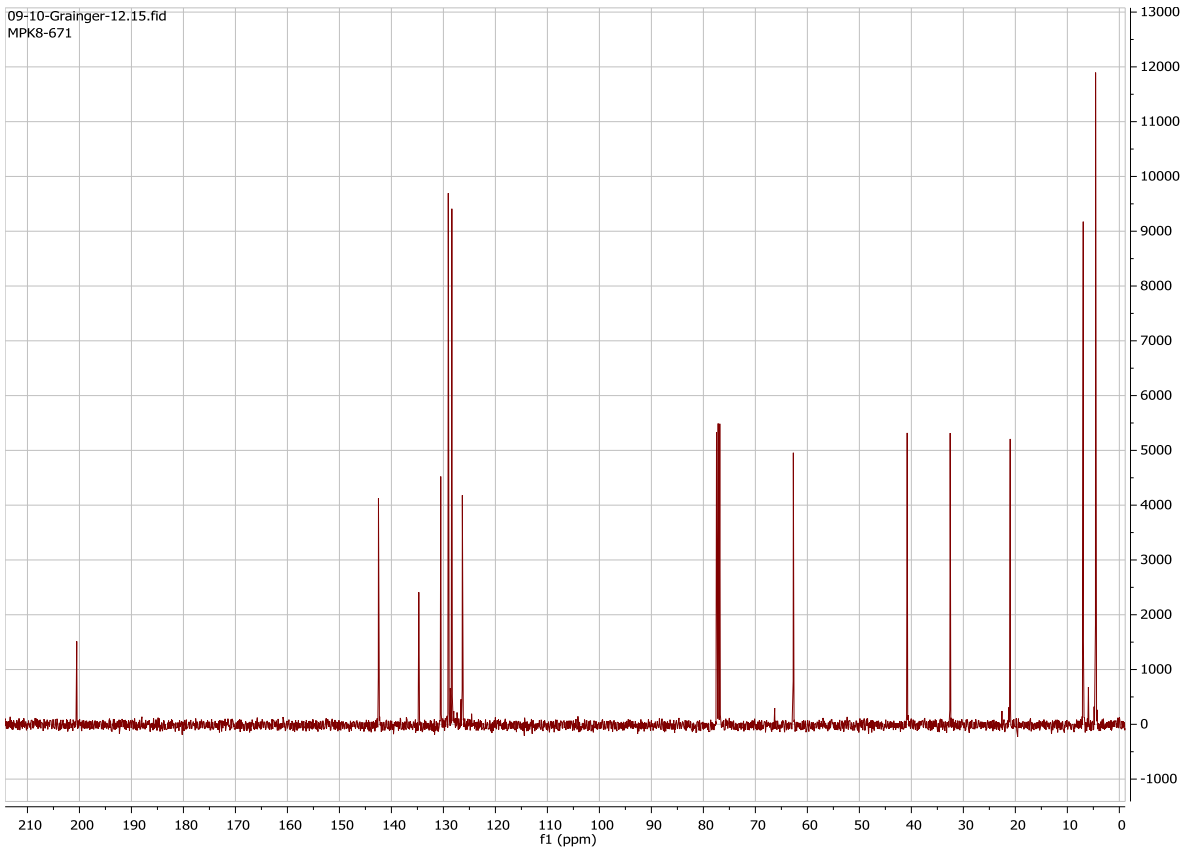
Methyl (1*S*,3*R*,5*S*)-4-oxo-3,5-bis((triethylsilyl)oxy)cyclohexane-1-carboxylate **232**



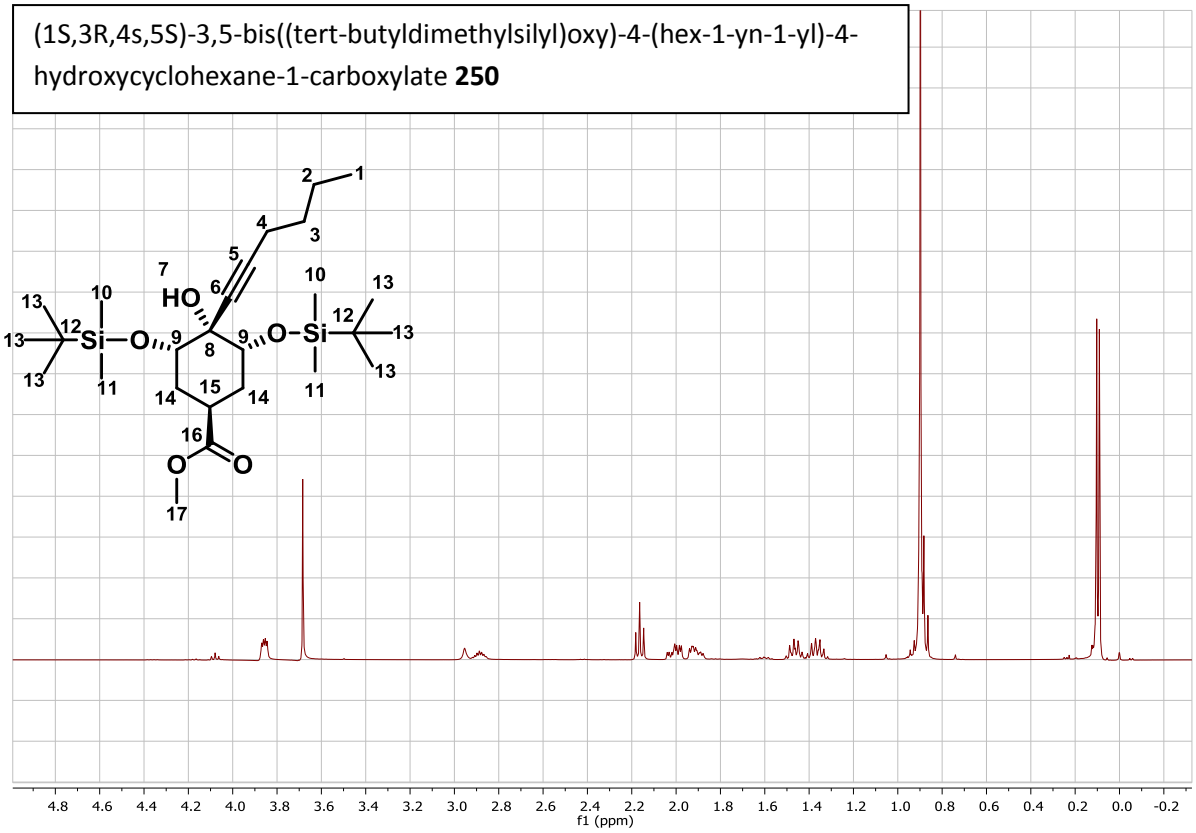


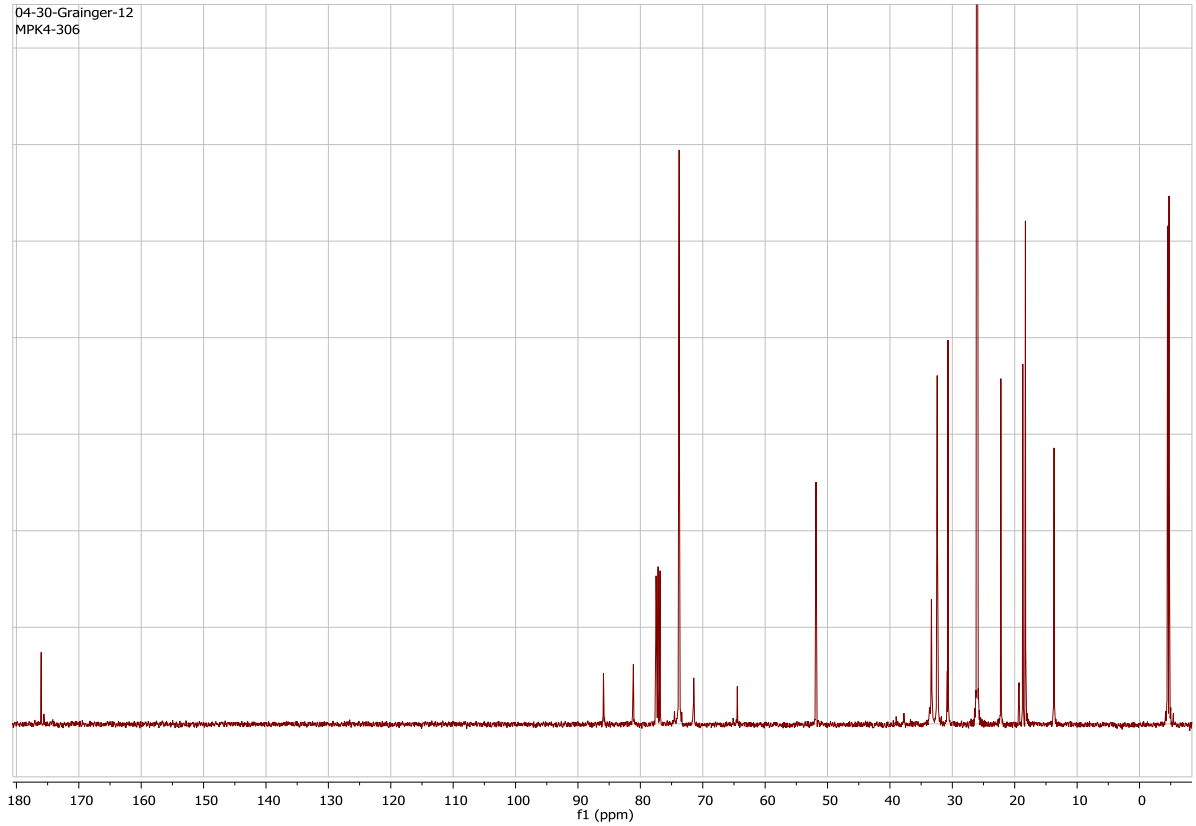
(*E*)-1-Phenyl-7-((triethylsilyl)oxy)hept-1-en-3-one **240**



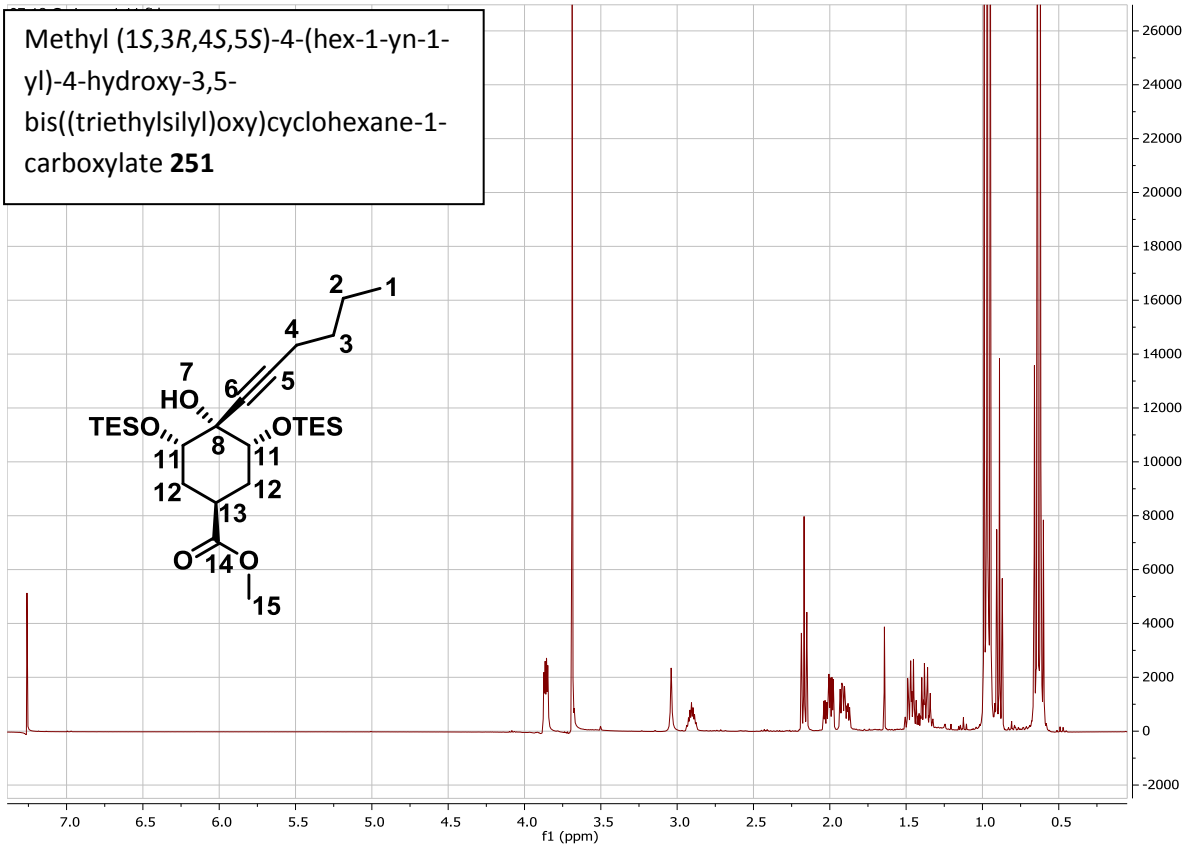


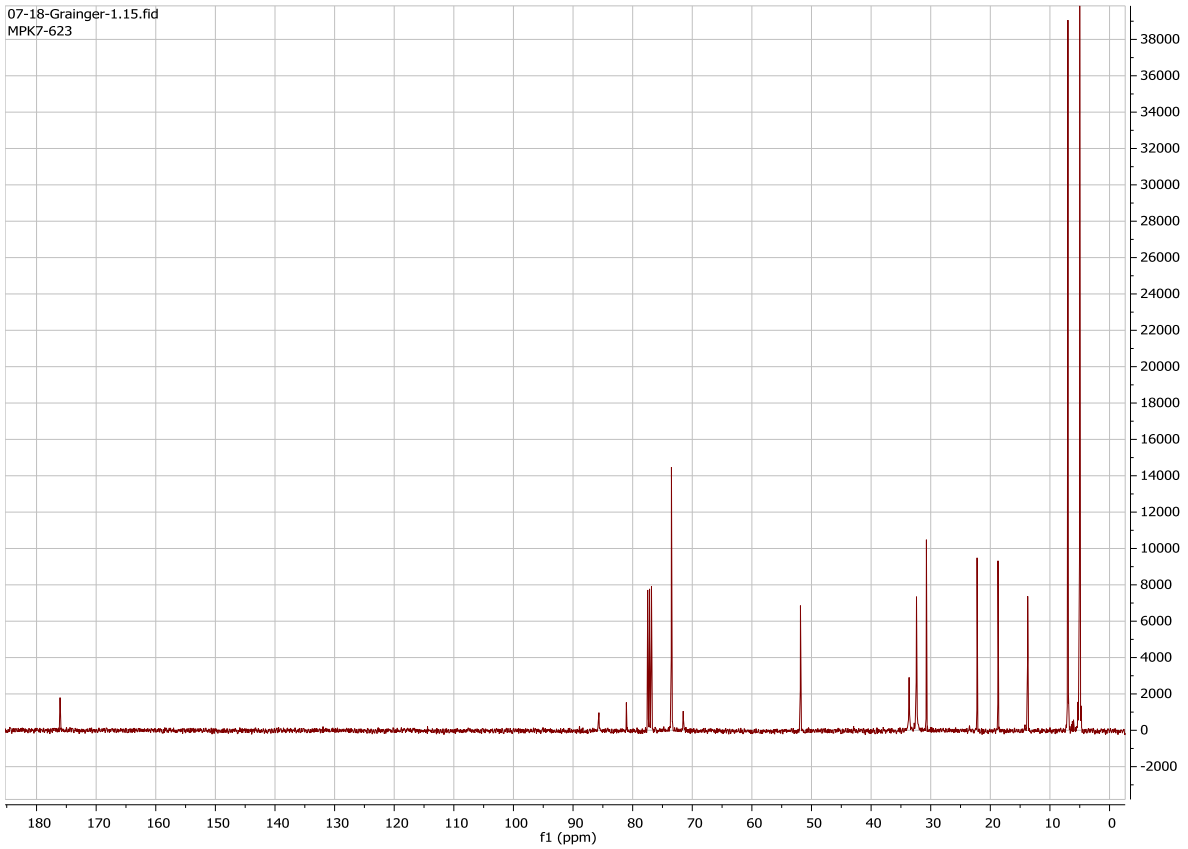
(1S,3R,4s,5S)-3,5-bis((tert-butyldimethylsilyl)oxy)-4-(hex-1-yn-1-yl)-4-hydroxycyclohexane-1-carboxylate **250**



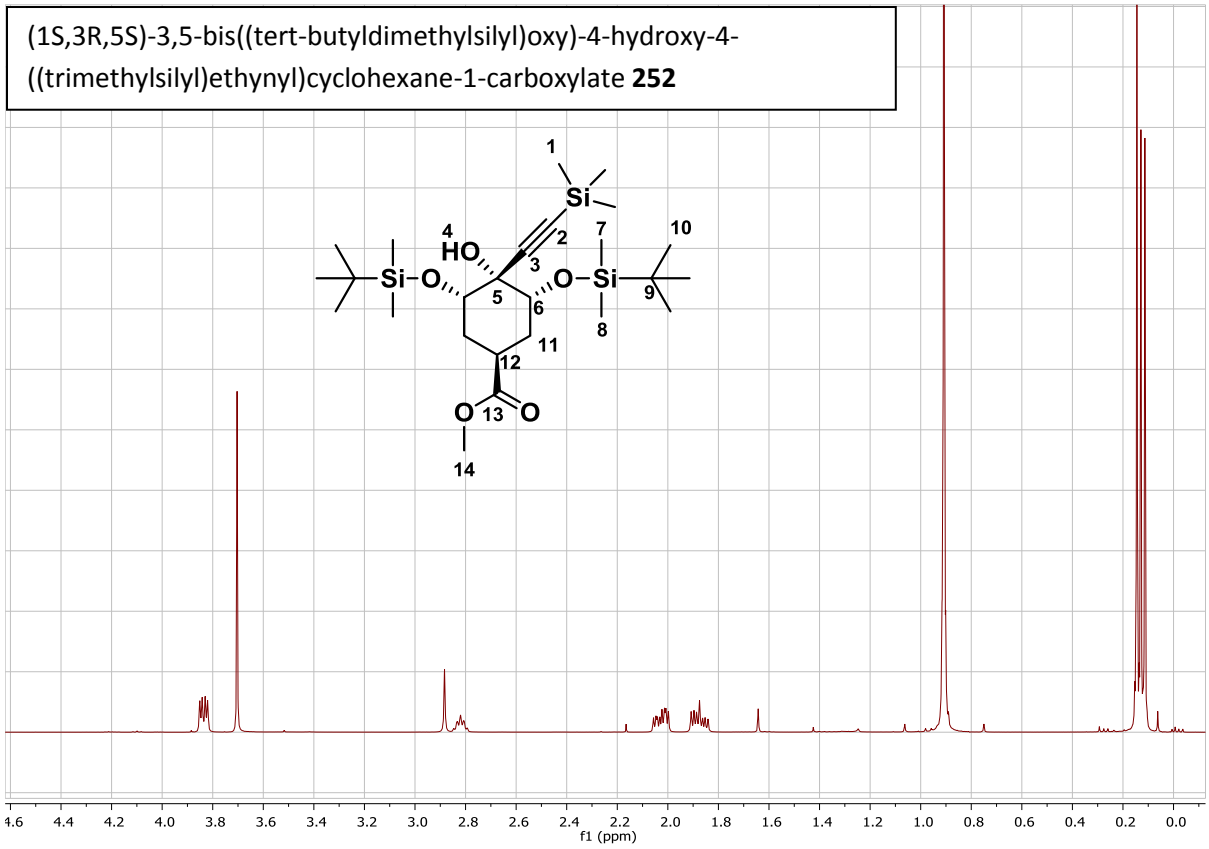


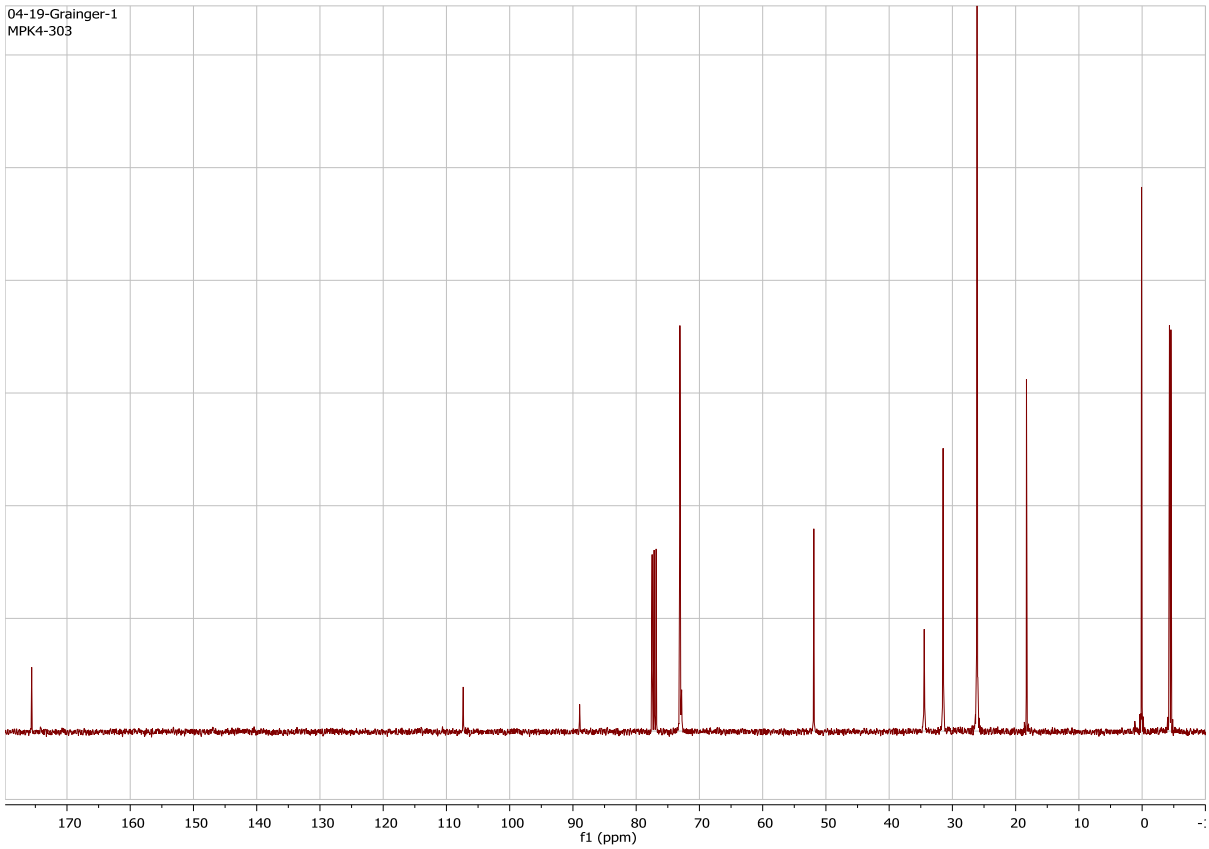
Methyl (1*S*,3*R*,4*S*,5*S*)-4-(hex-1-yn-1-yl)-4-hydroxy-3,5-bis((triethylsilyl)oxy)cyclohexane-1-carboxylate **251**



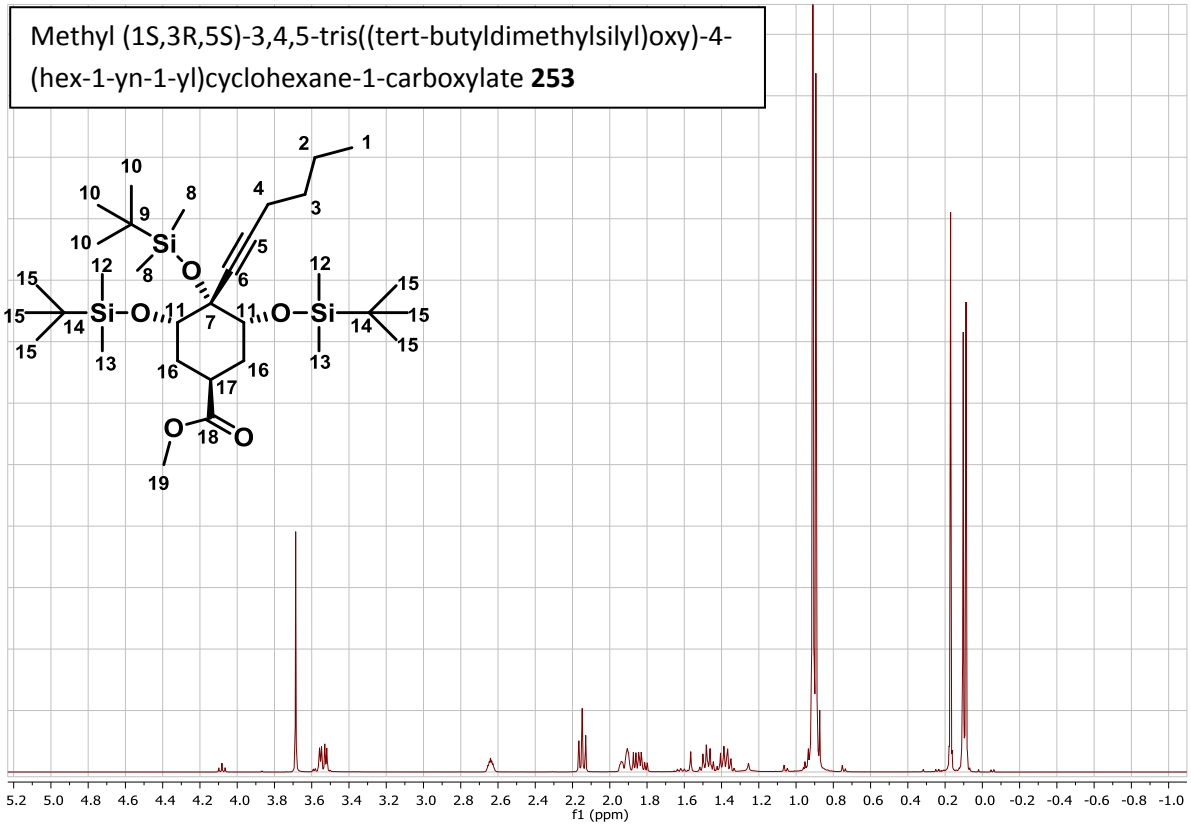


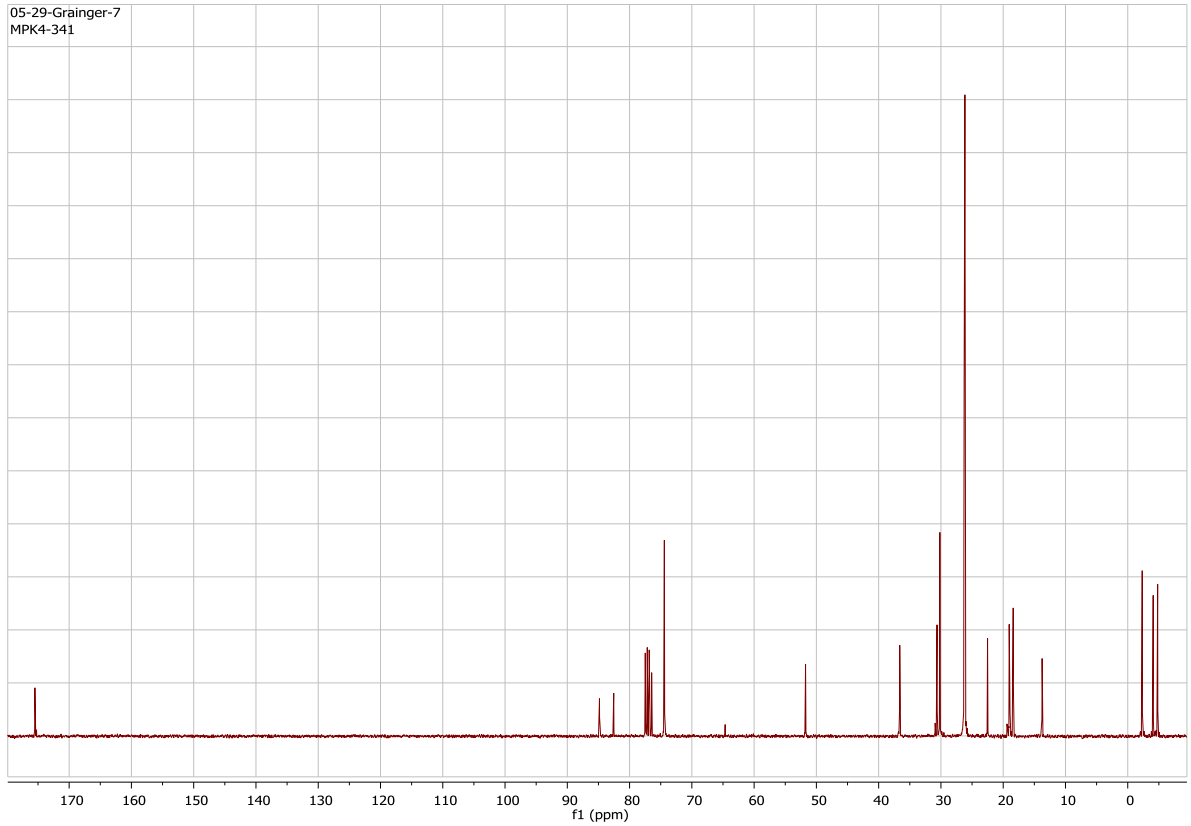
(1S,3R,5S)-3,5-bis((tert-butyldimethylsilyl)oxy)-4-hydroxy-4-((trimethylsilyl)ethynyl)cyclohexane-1-carboxylate **252**



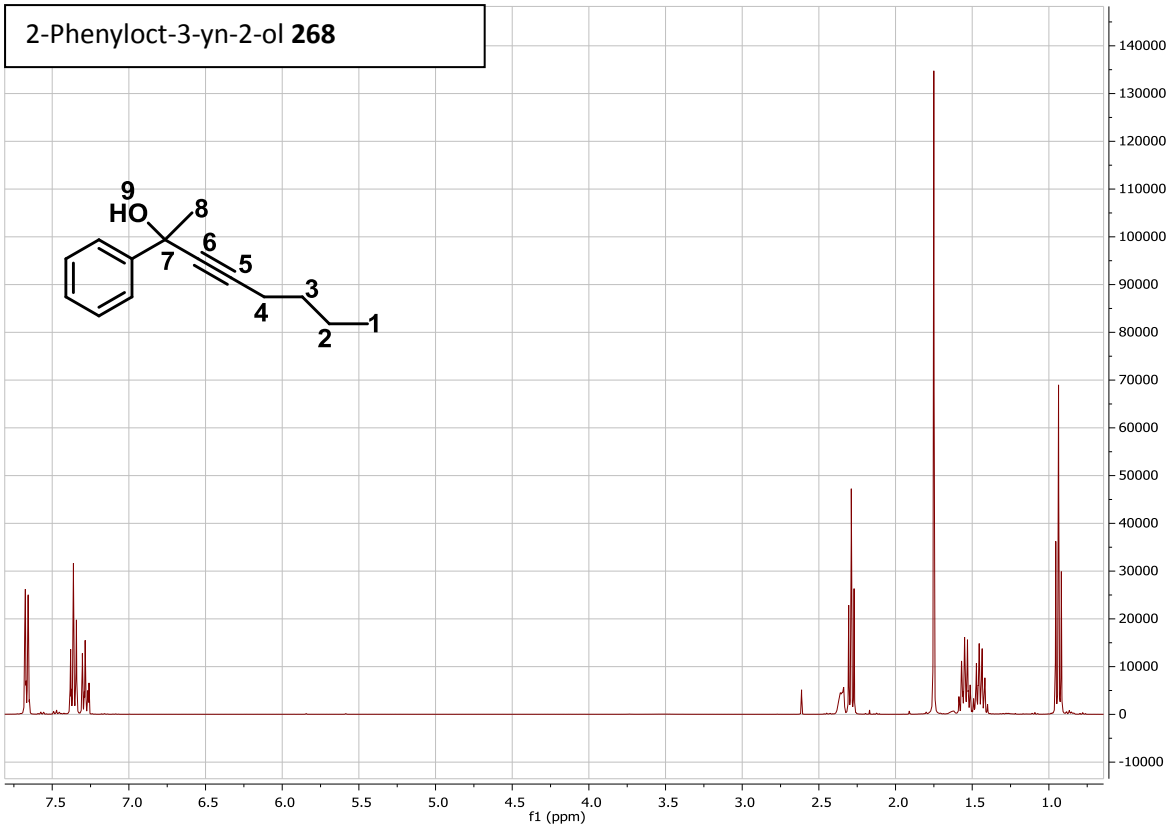


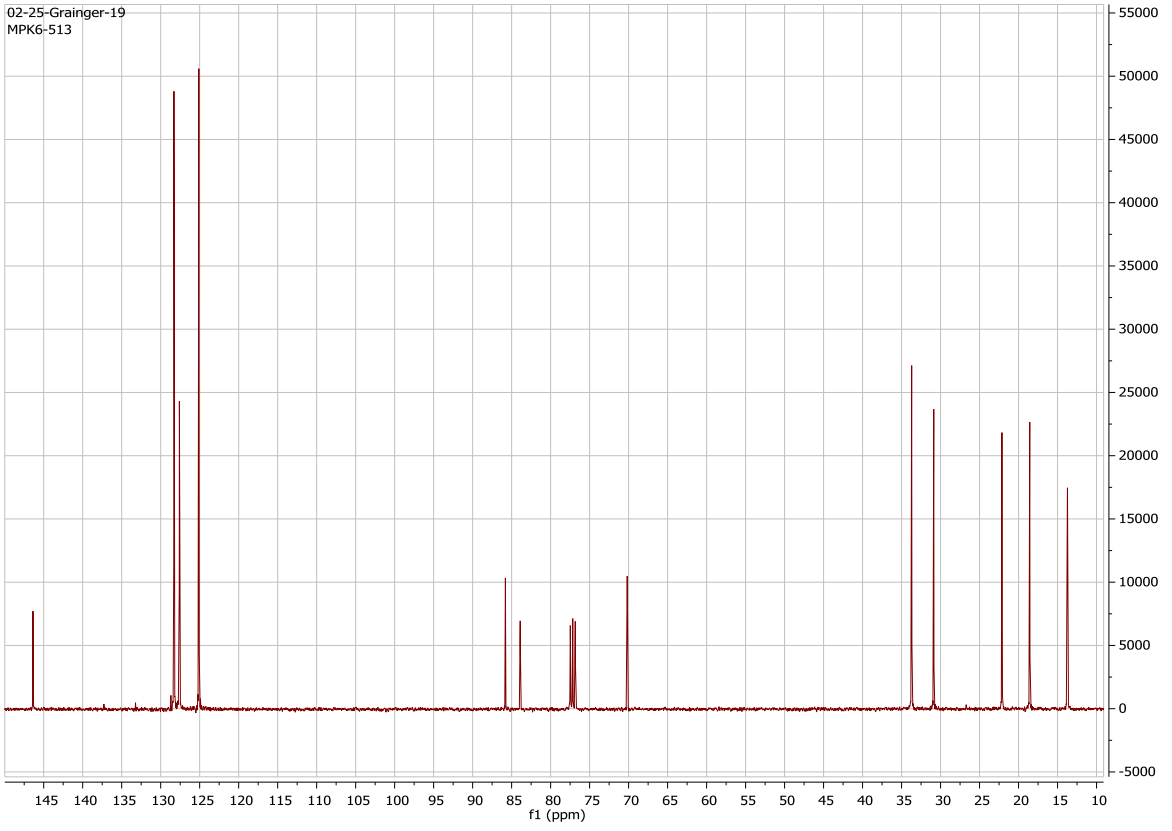
Methyl (1S,3R,5S)-3,4,5-tris((tert-butyldimethylsilyl)oxy)-4-(hex-1-yn-1-yl)cyclohexane-1-carboxylate **253**



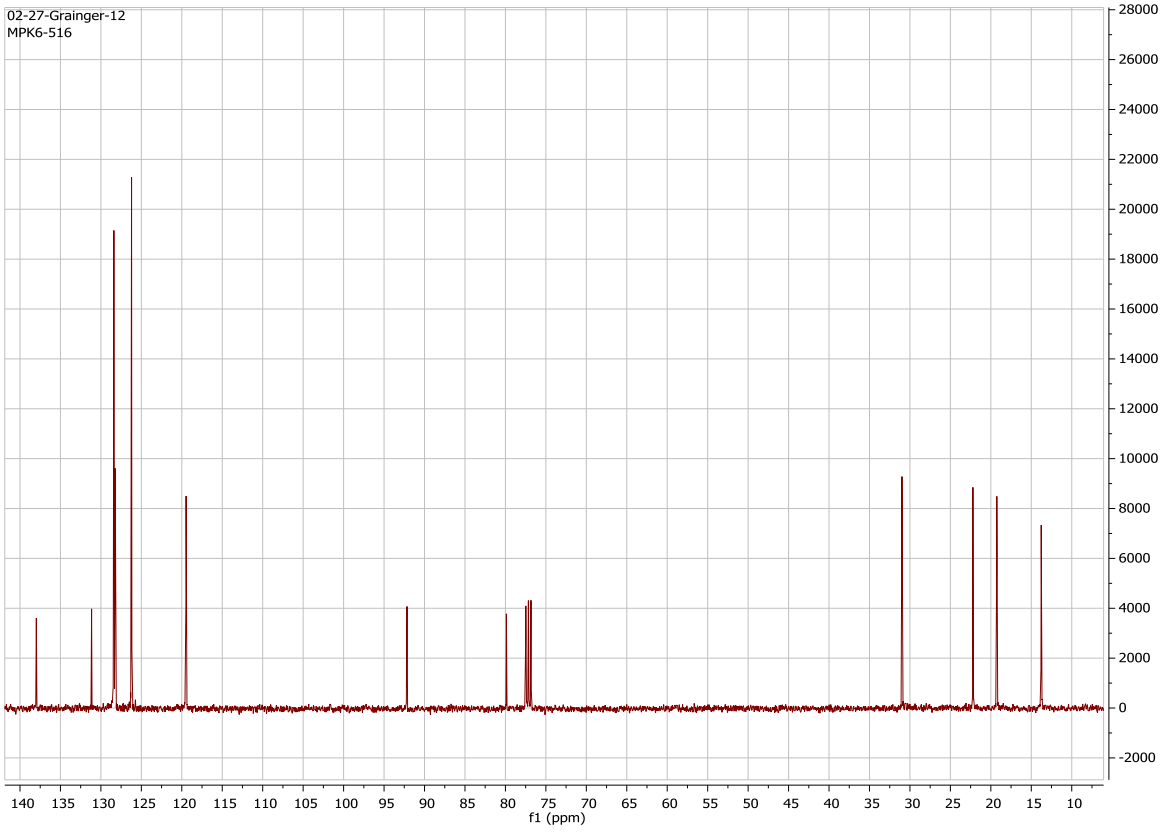


2-Phenyloct-3-yn-2-ol **268**

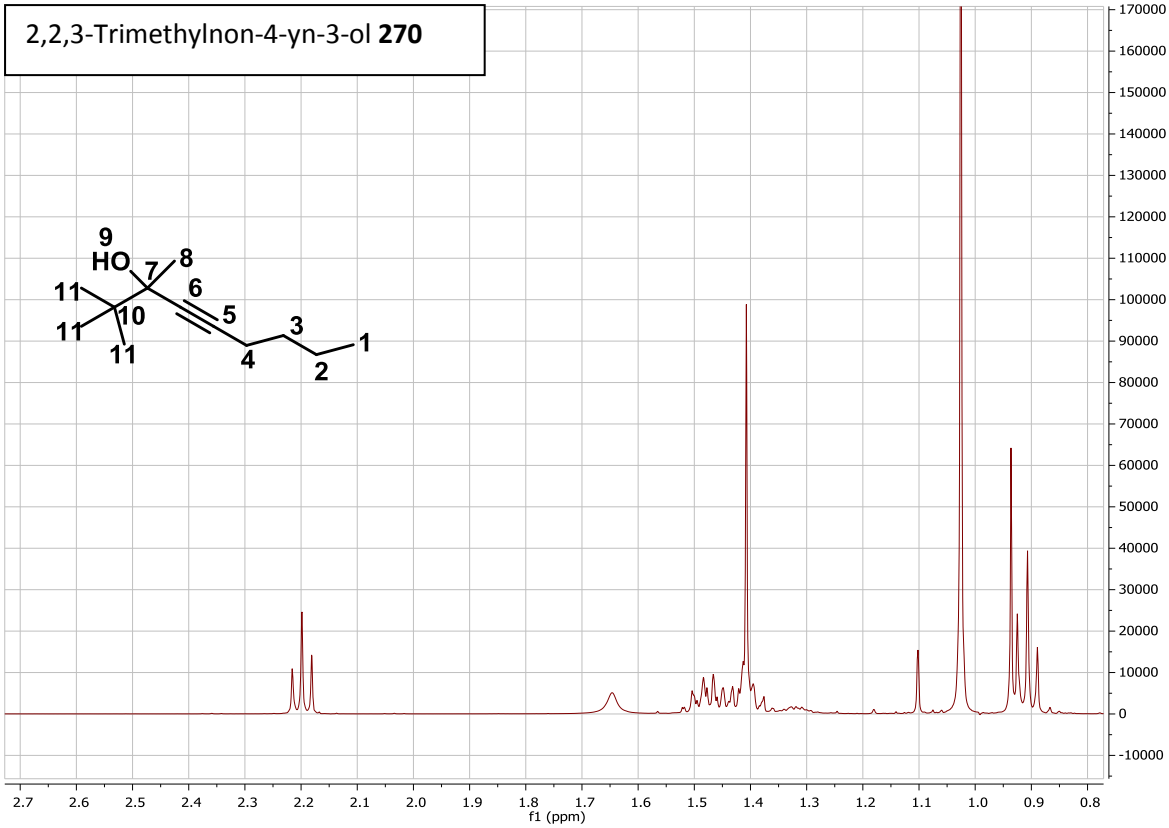


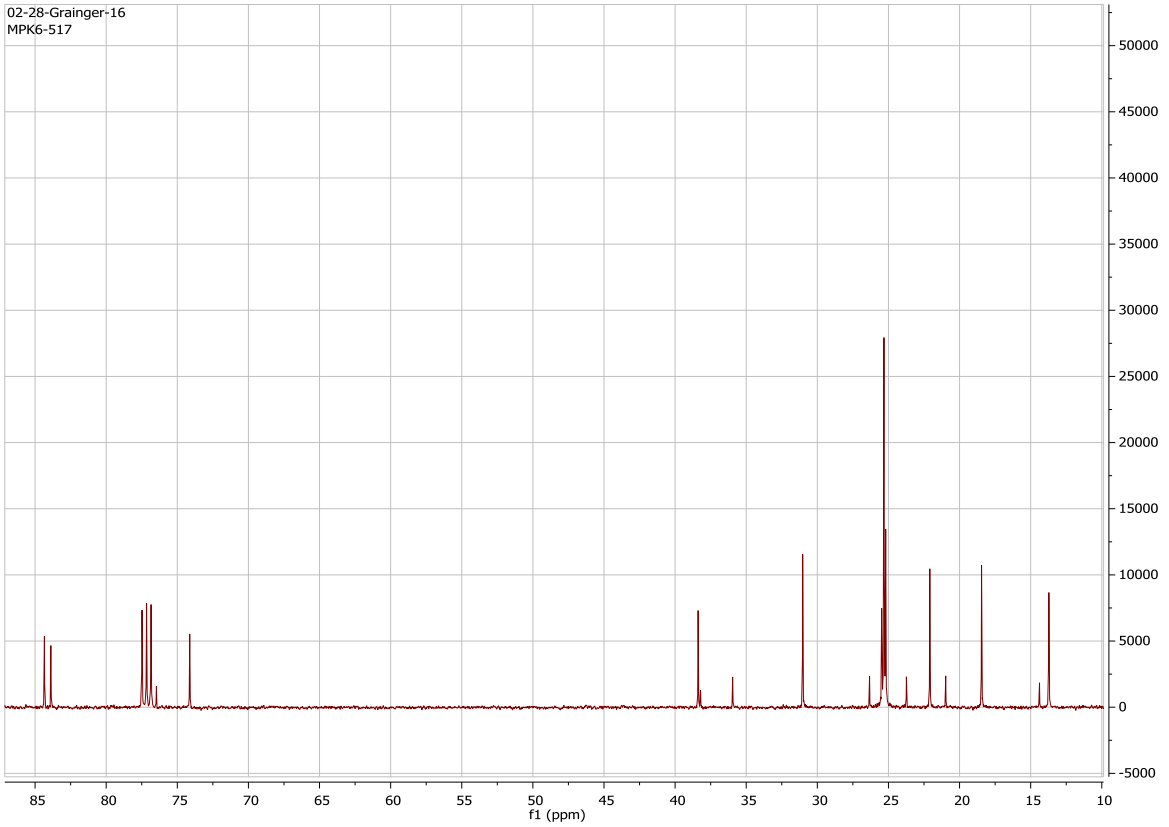


Oct-1-en-3-yn-2-ylbenzene **269**

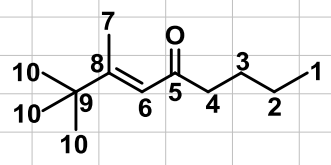


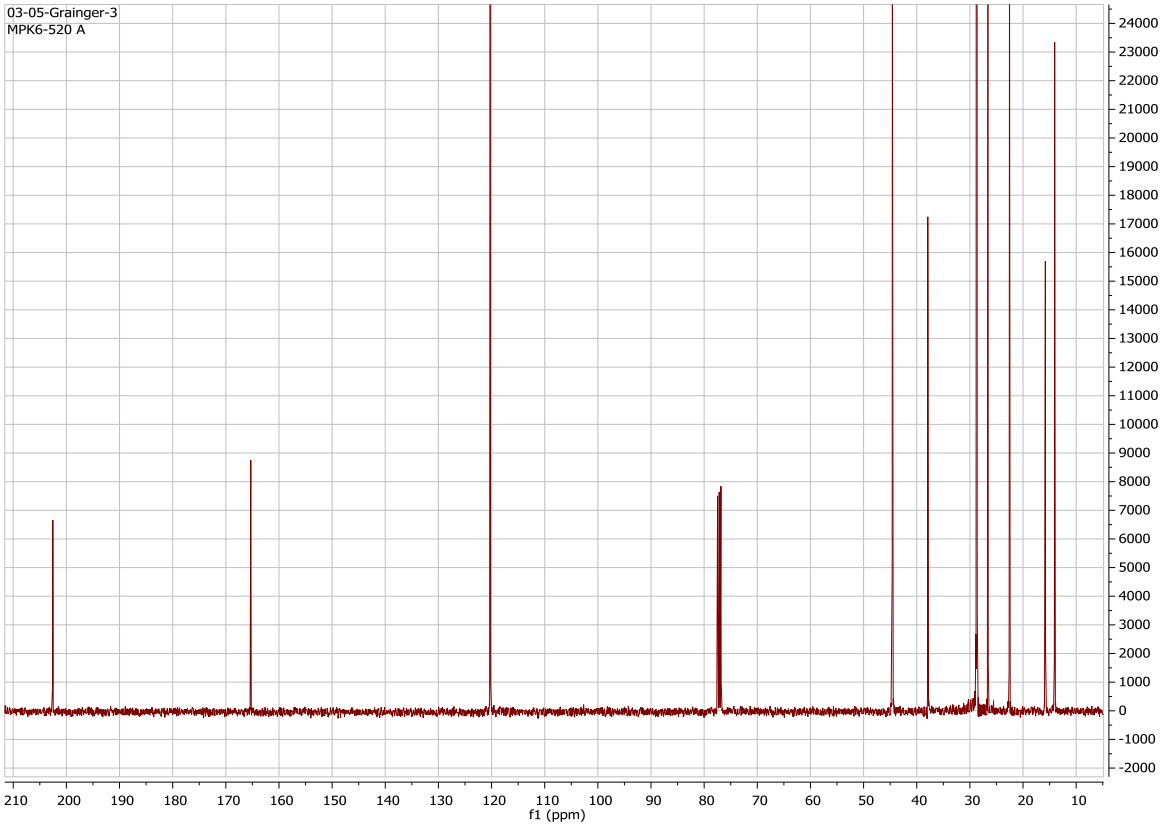
2,2,3-Trimethylnon-4-yn-3-ol **270**



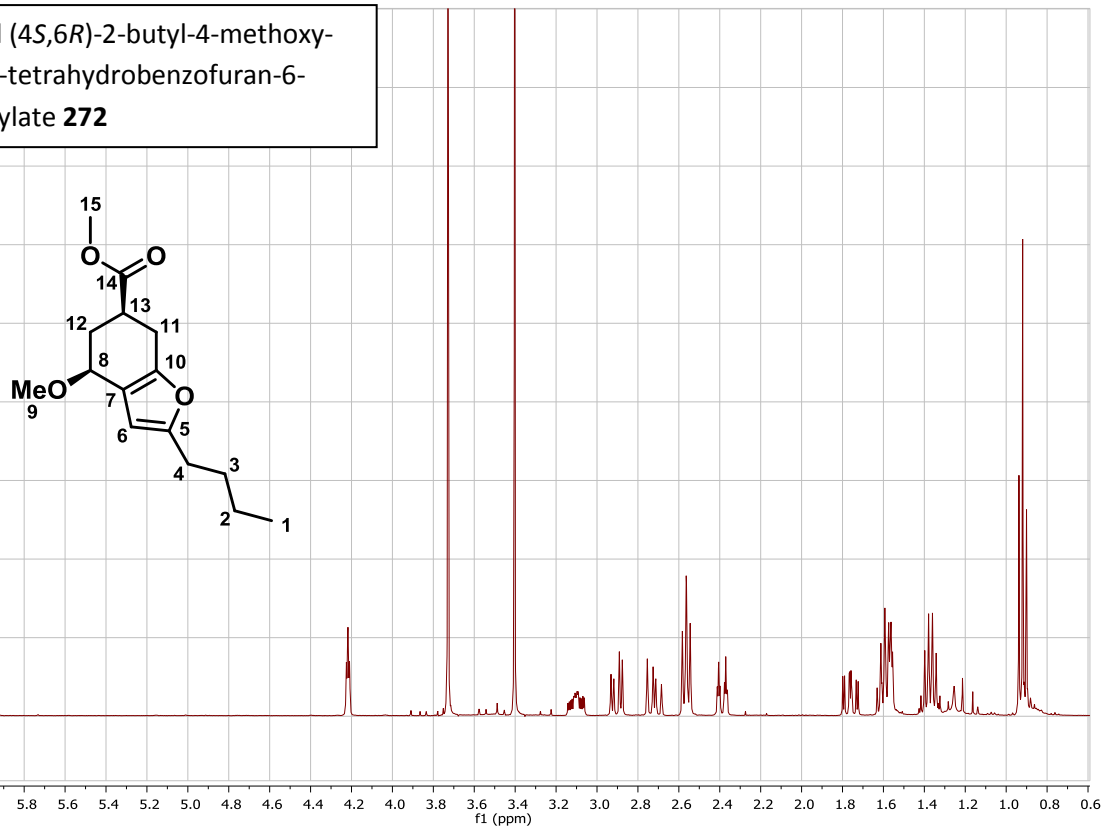


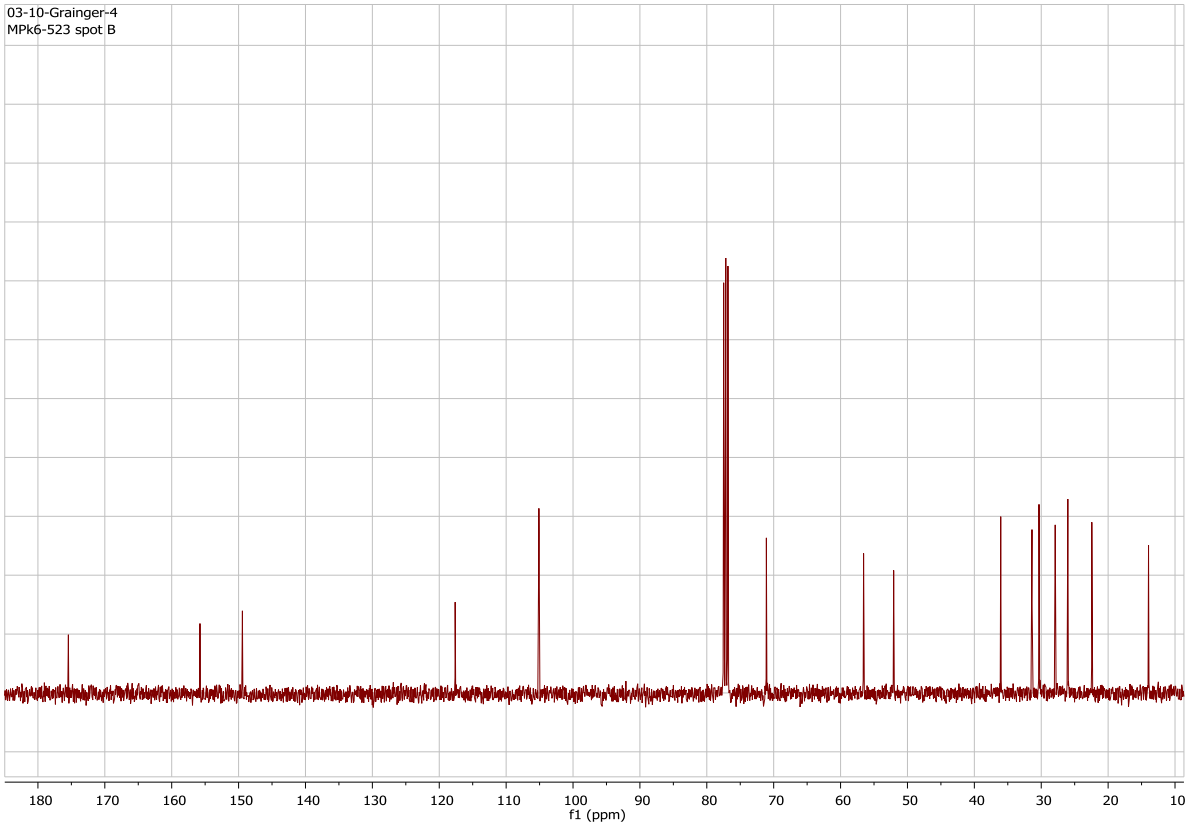
(*Z*)-2,2,3-Trimethylnon-3-en-5-one **271**



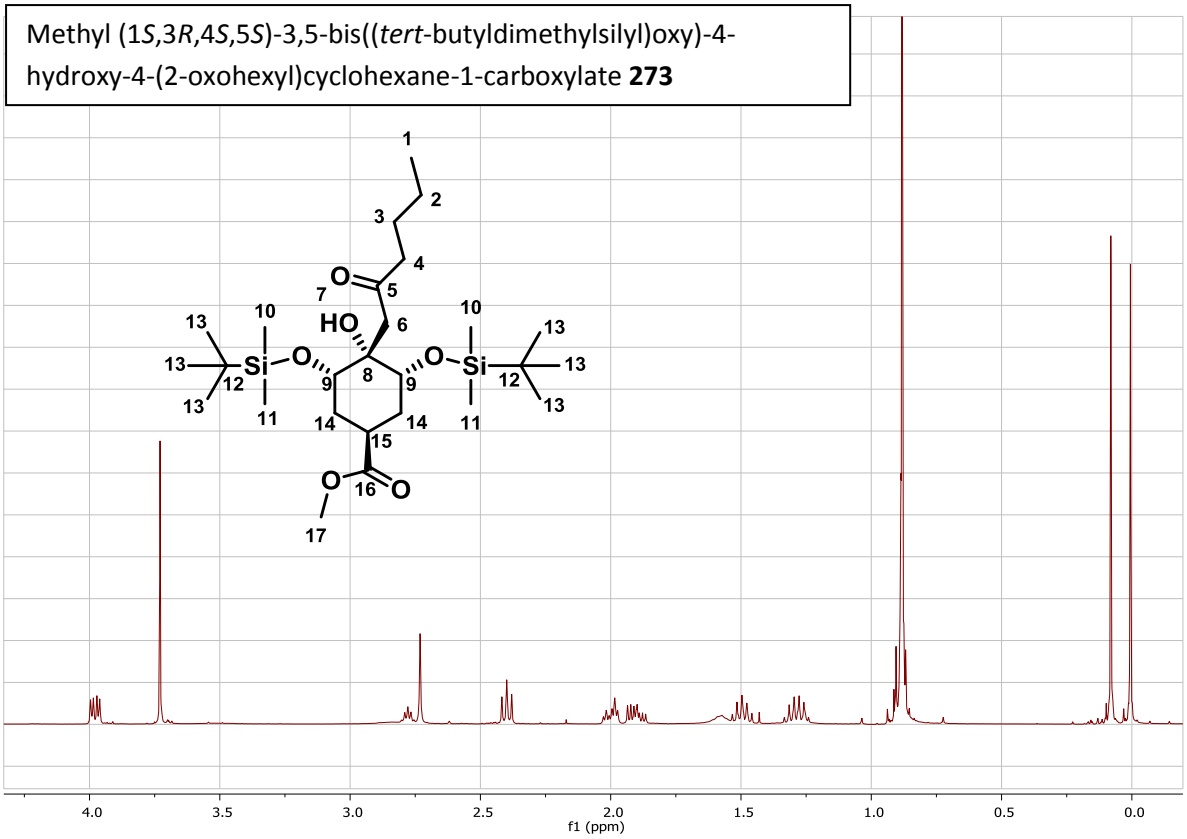


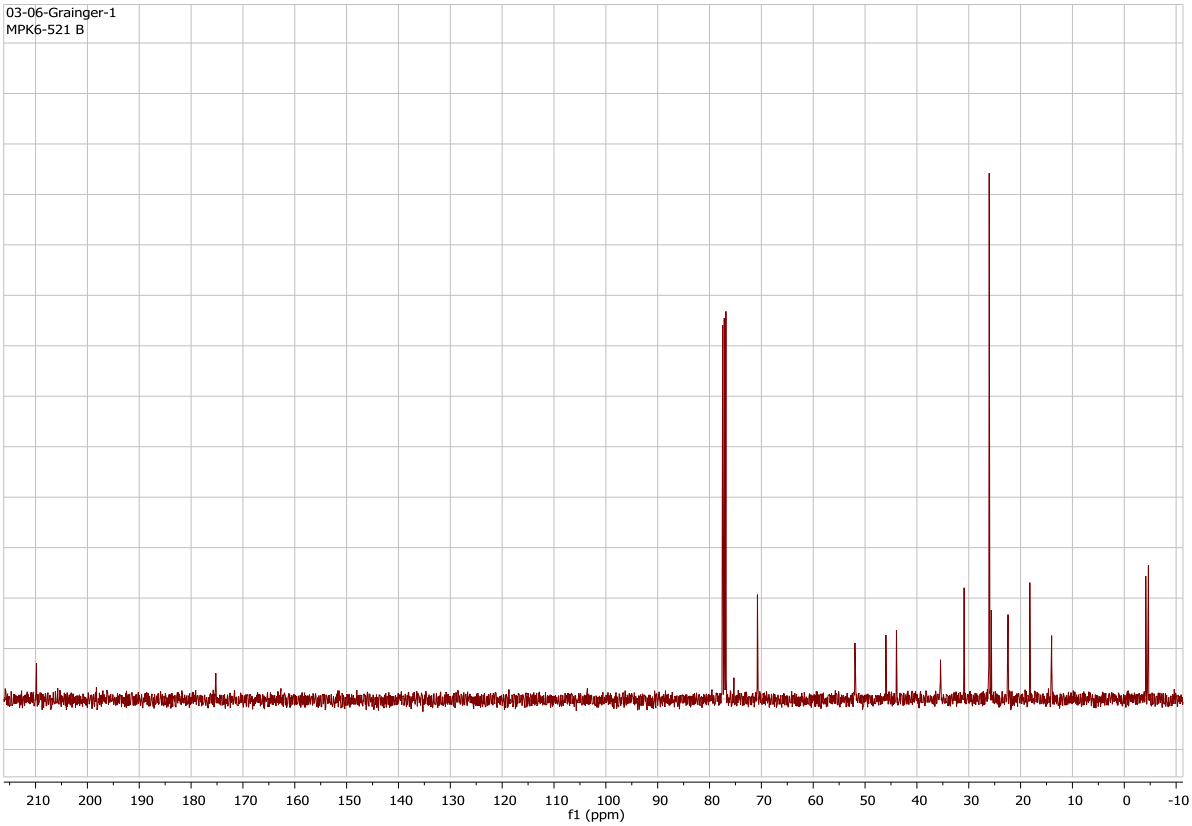
Methyl (4*S*,6*R*)-2-butyl-4-methoxy-4,5,6,7-tetrahydrobenzofuran-6-carboxylate **272**



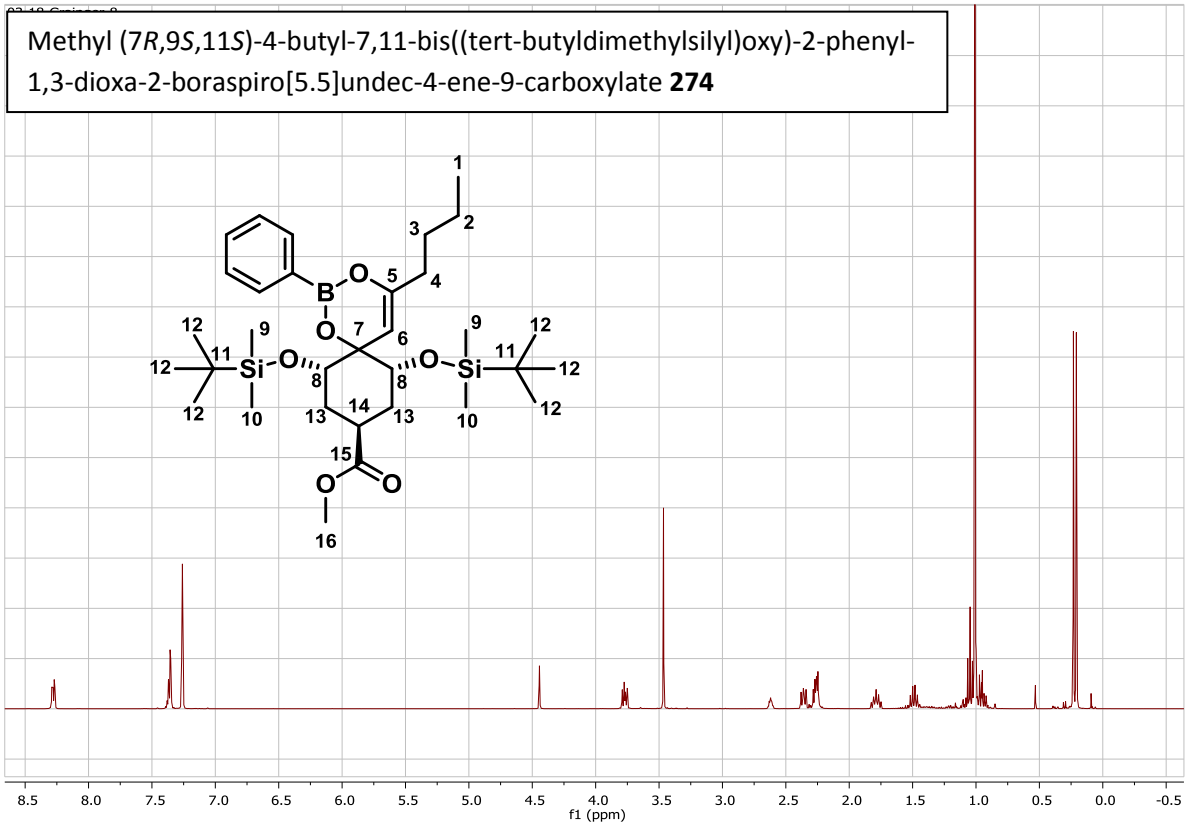


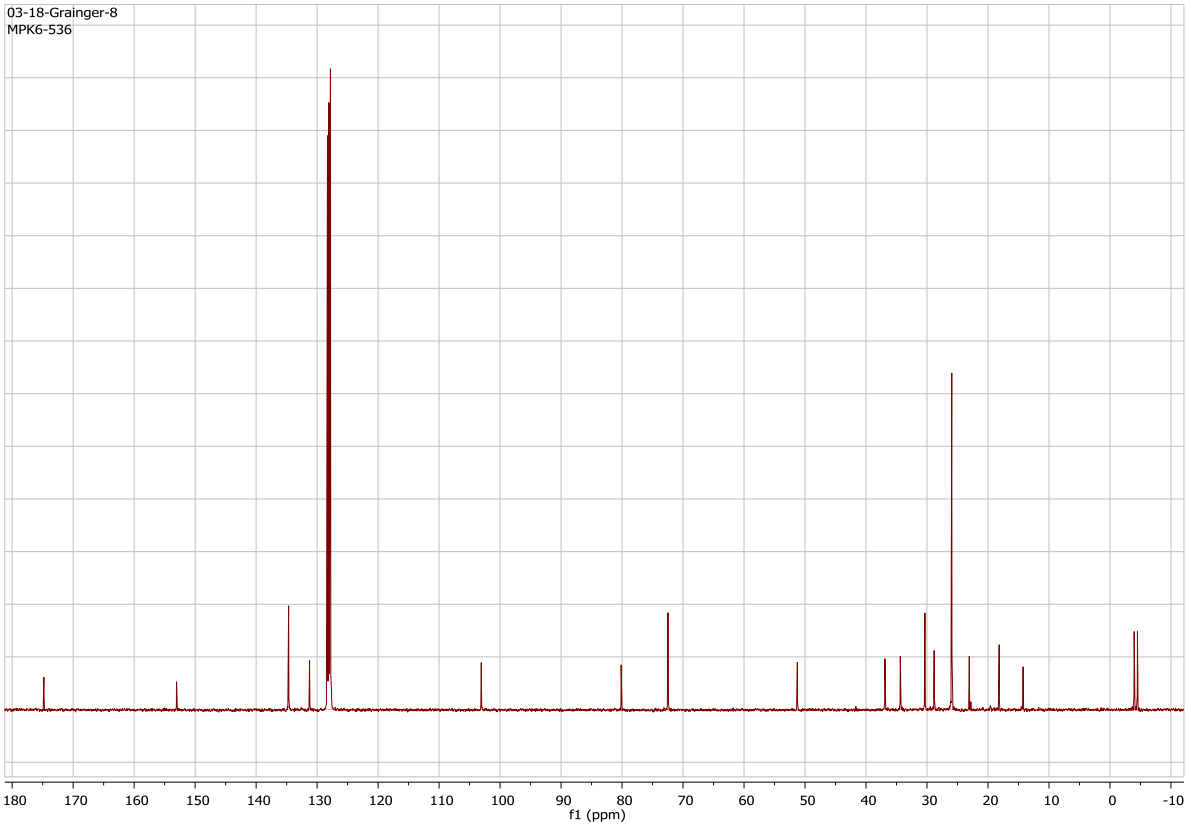
Methyl (1*S*,3*R*,4*S*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(2-oxohexyl)cyclohexane-1-carboxylate **273**



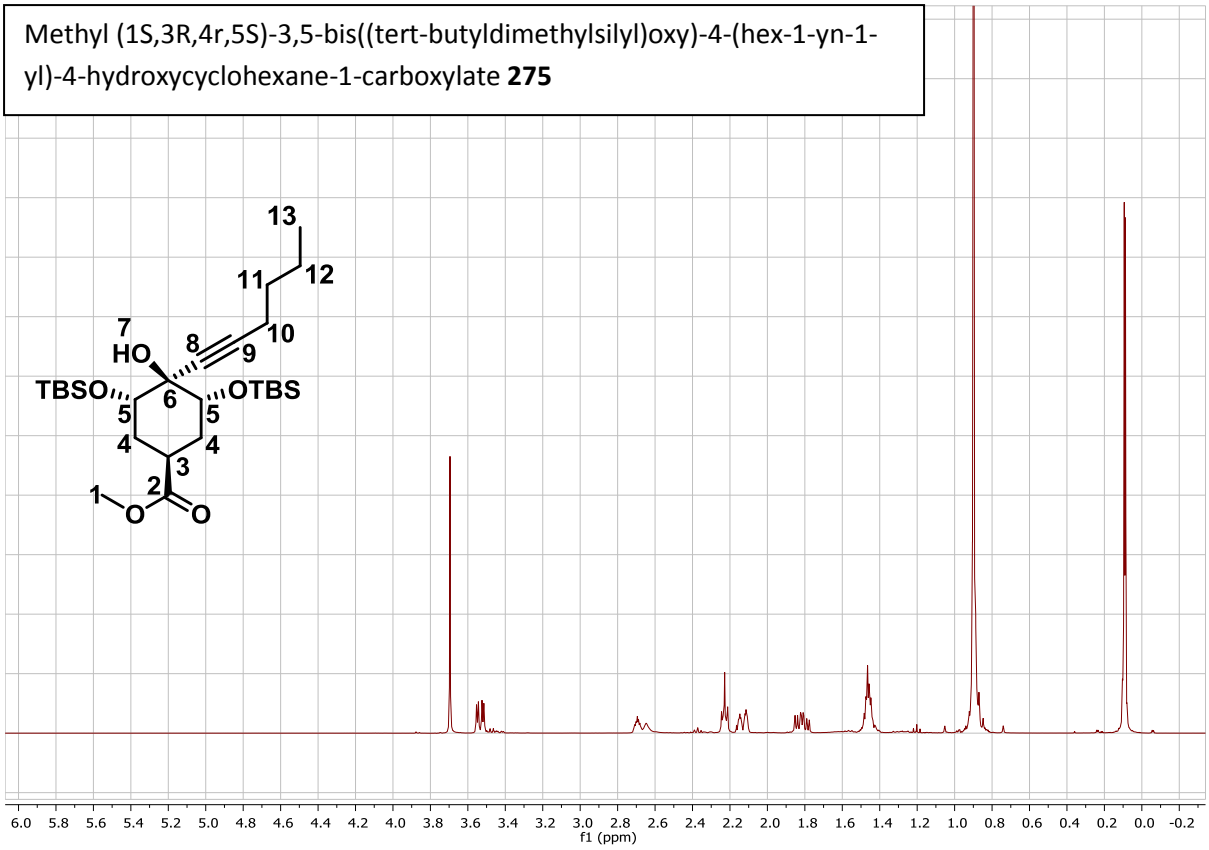


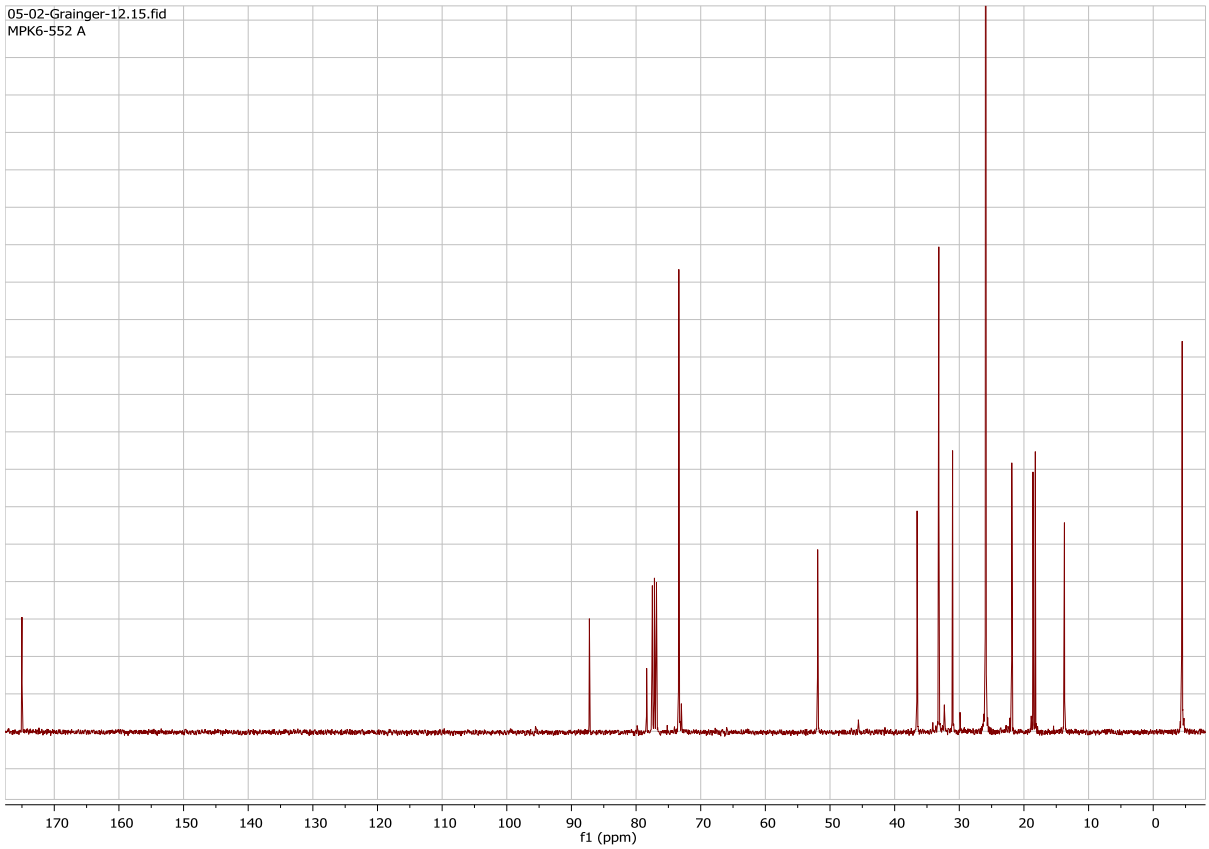
Methyl (7*R*,9*S*,11*S*)-4-butyl-7,11-bis((tert-butyldimethylsilyl)oxy)-2-phenyl-1,3-dioxa-2-boraspiro[5.5]undec-4-ene-9-carboxylate **274**



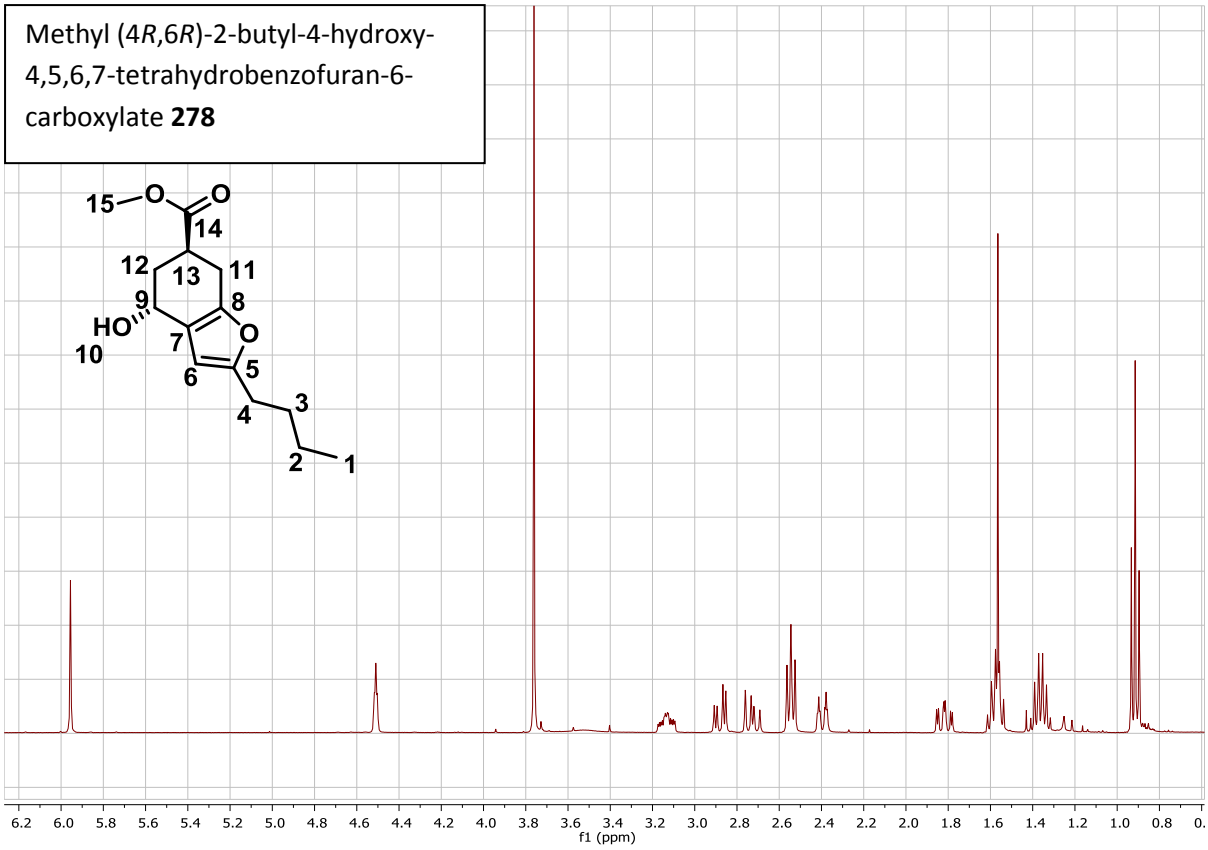


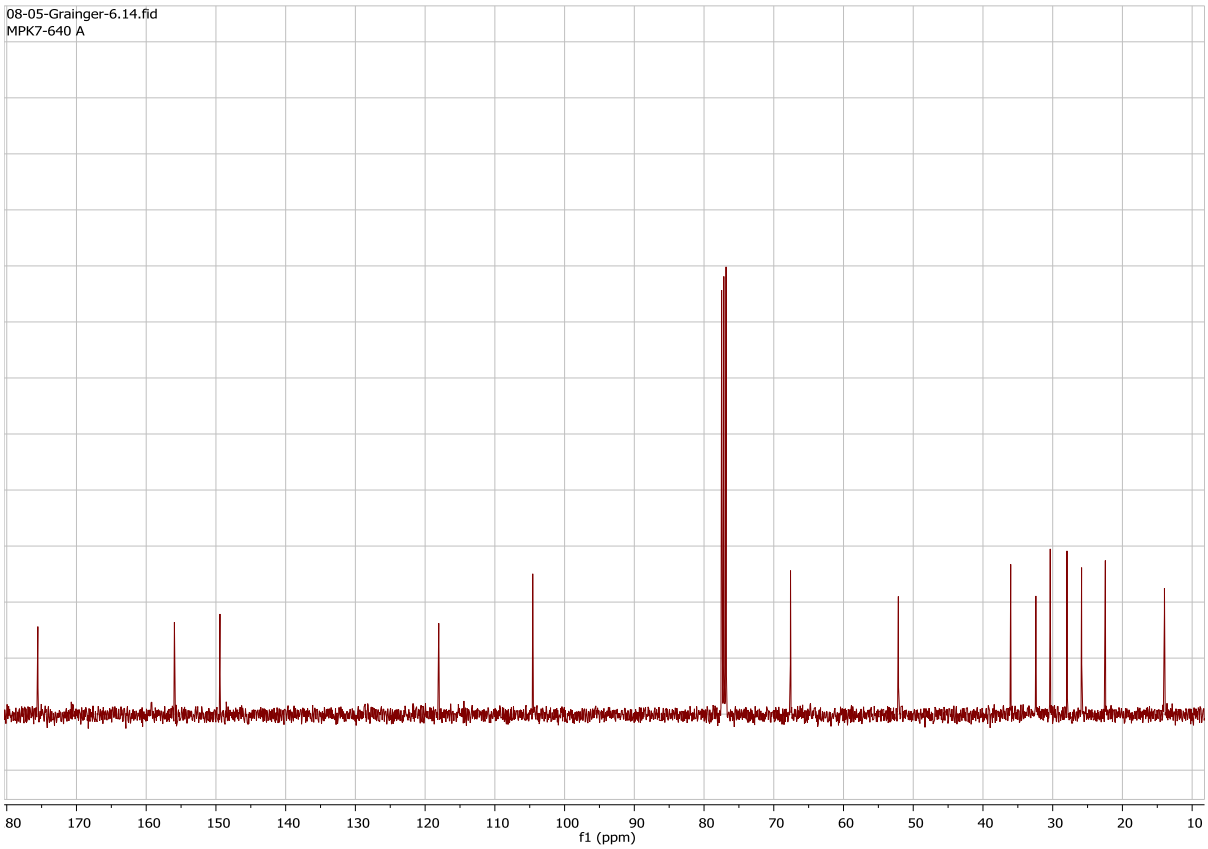
Methyl (1S,3R,4r,5S)-3,5-bis((tert-butyldimethylsilyl)oxy)-4-(hex-1-yn-1-yl)-4-hydroxycyclohexane-1-carboxylate **275**



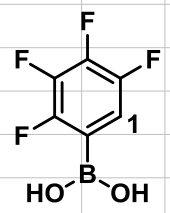


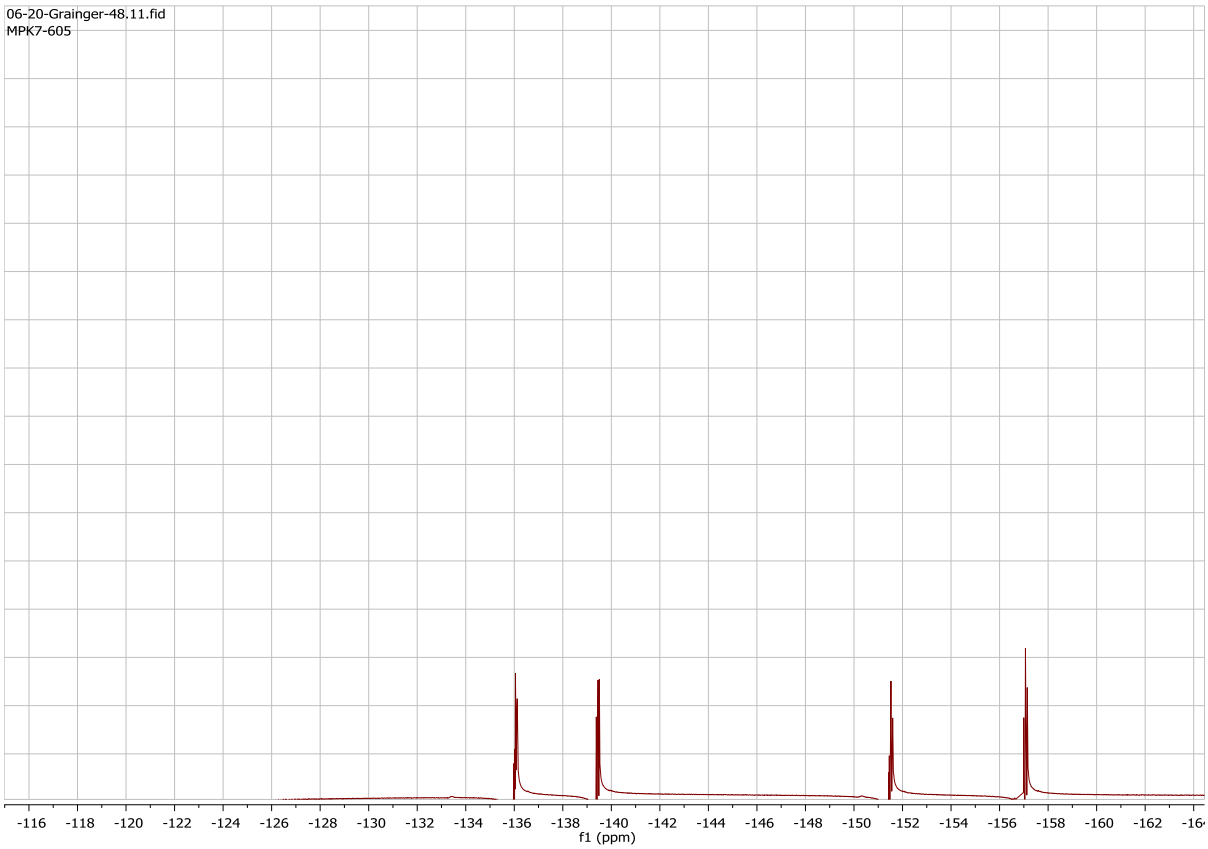
Methyl (4*R*,6*R*)-2-butyl-4-hydroxy-4,5,6,7-tetrahydrobenzofuran-6-carboxylate **278**



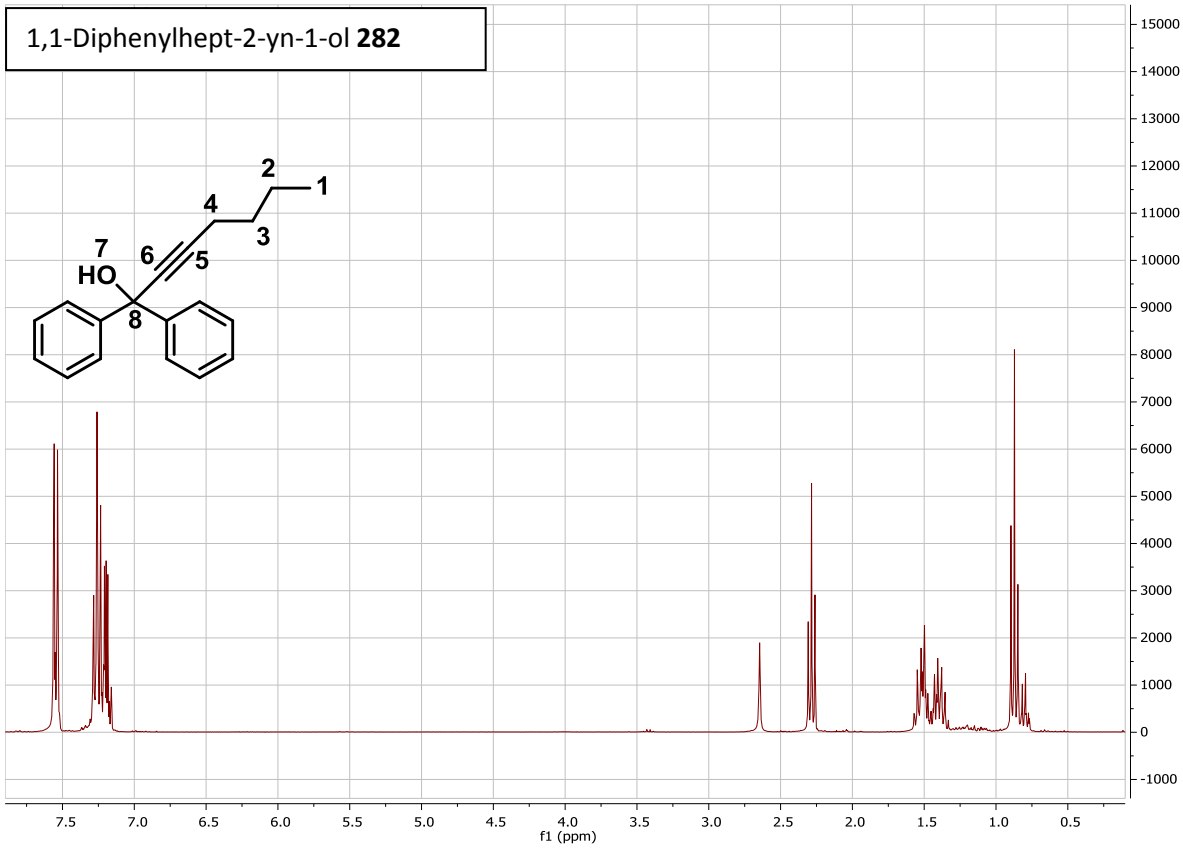


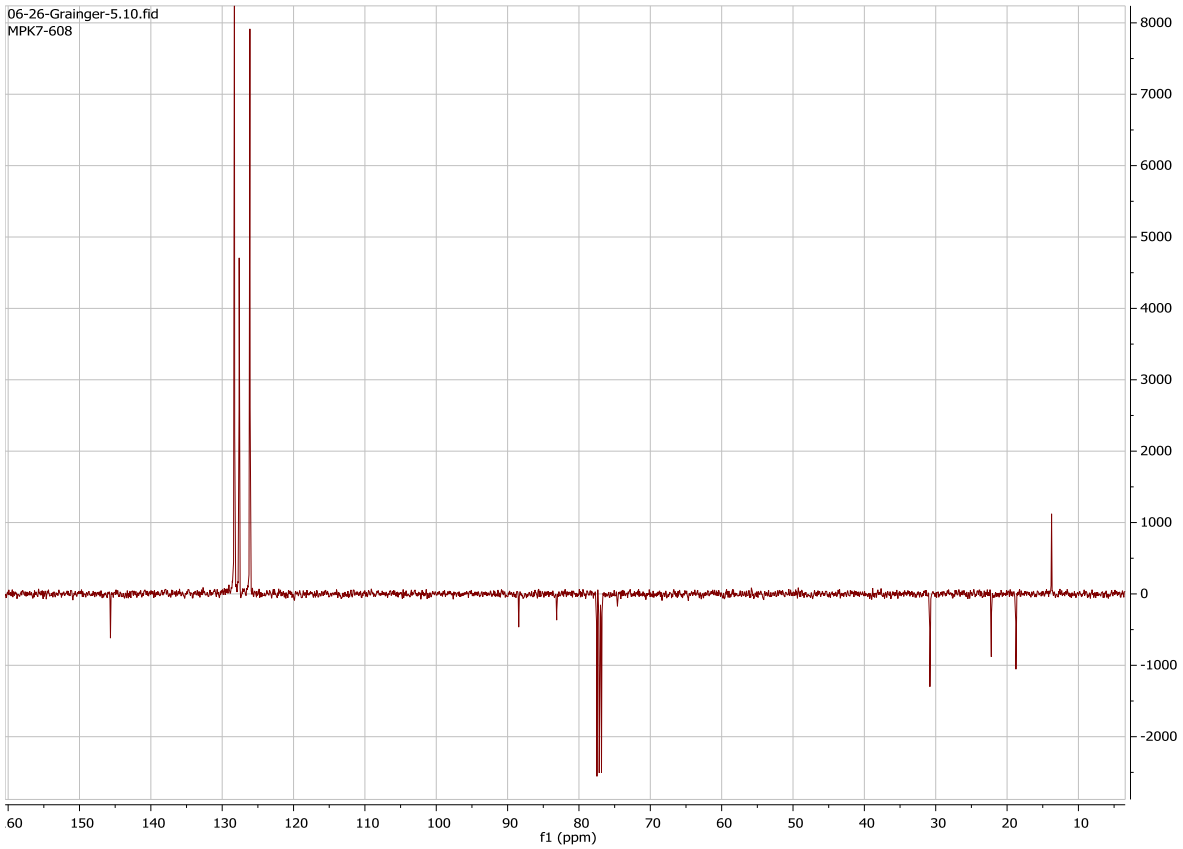
(2,3,4,5-Tetrafluorophenyl)boronic acid **281**



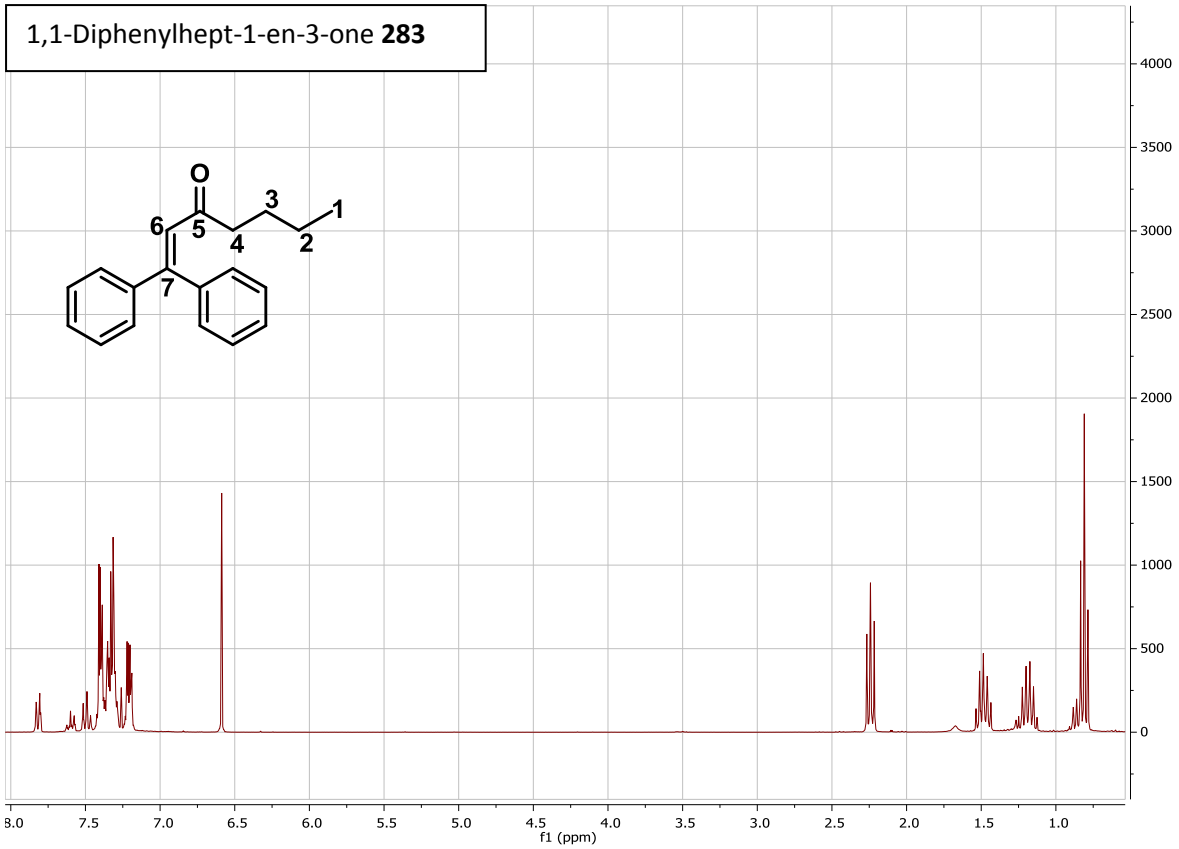


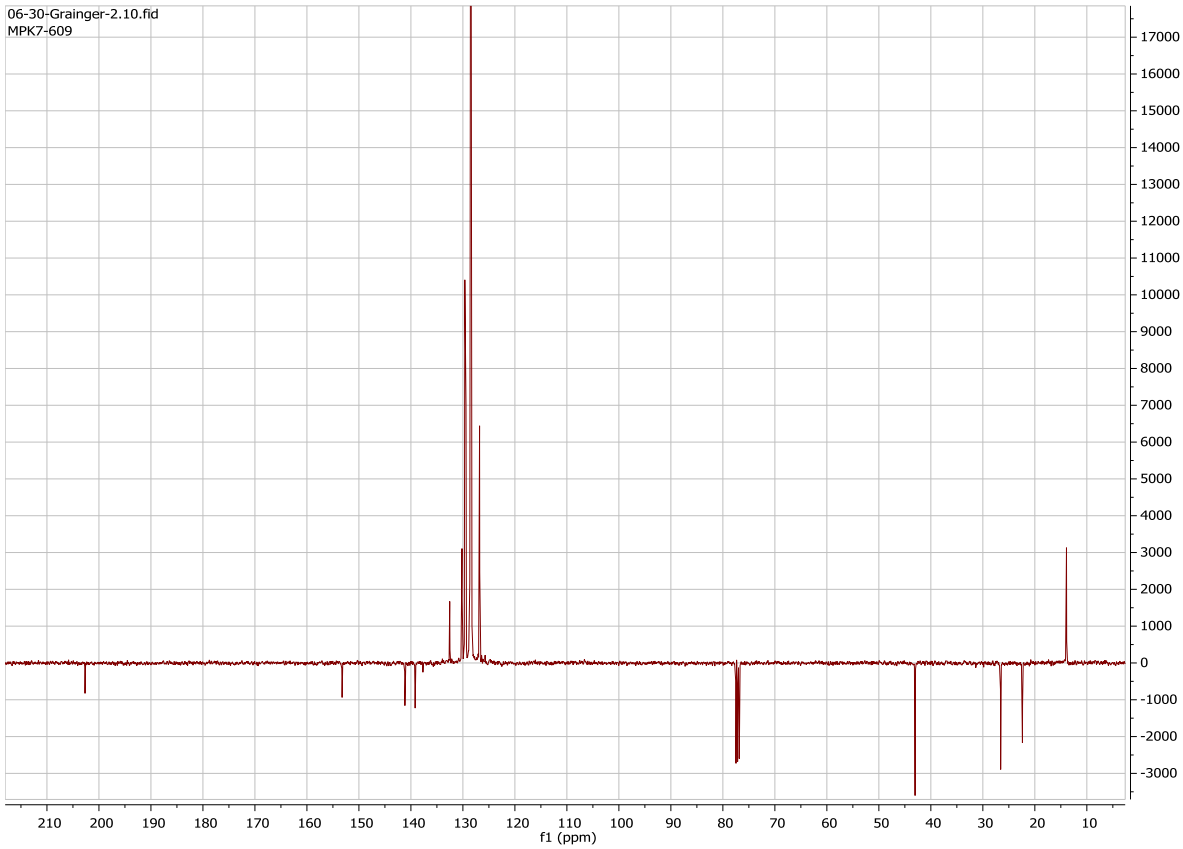
1,1-Diphenylhept-2-yn-1-ol **282**



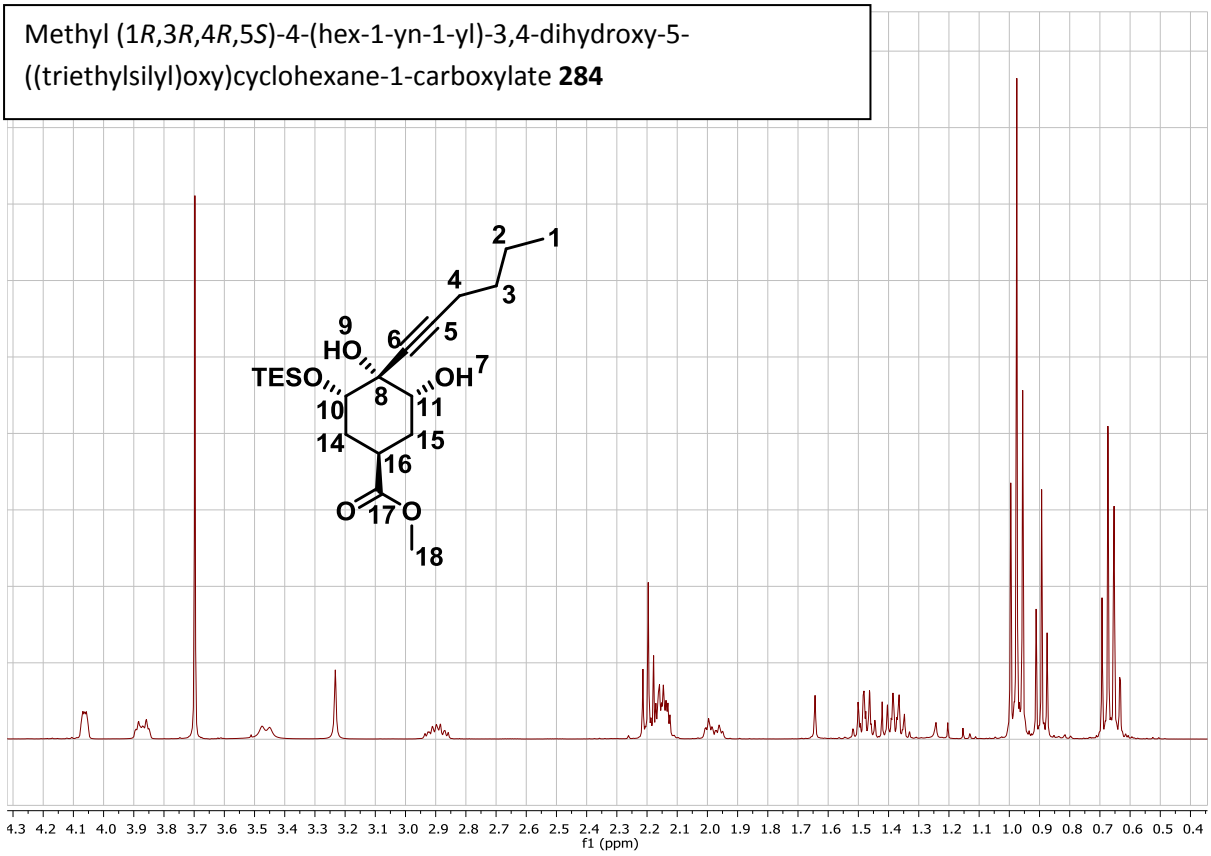


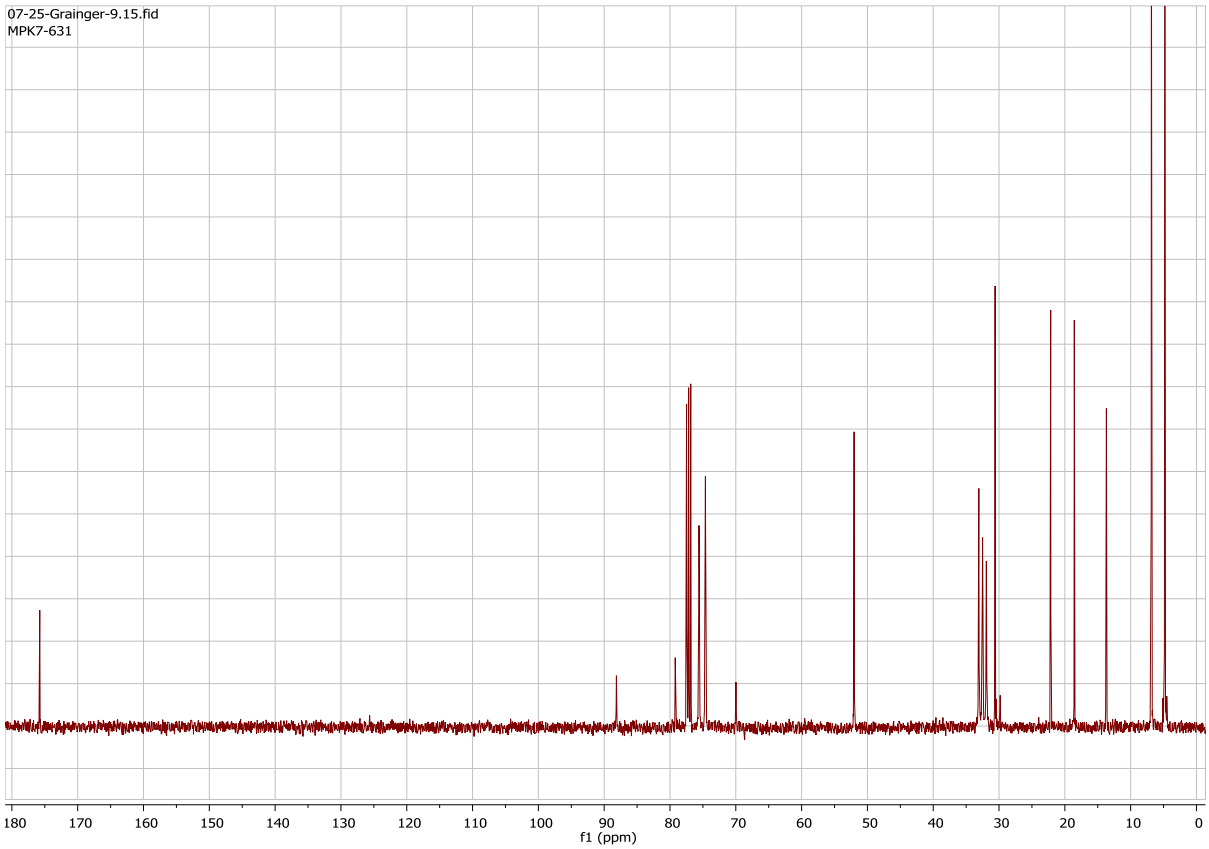
1,1-Diphenylhept-1-en-3-one **283**



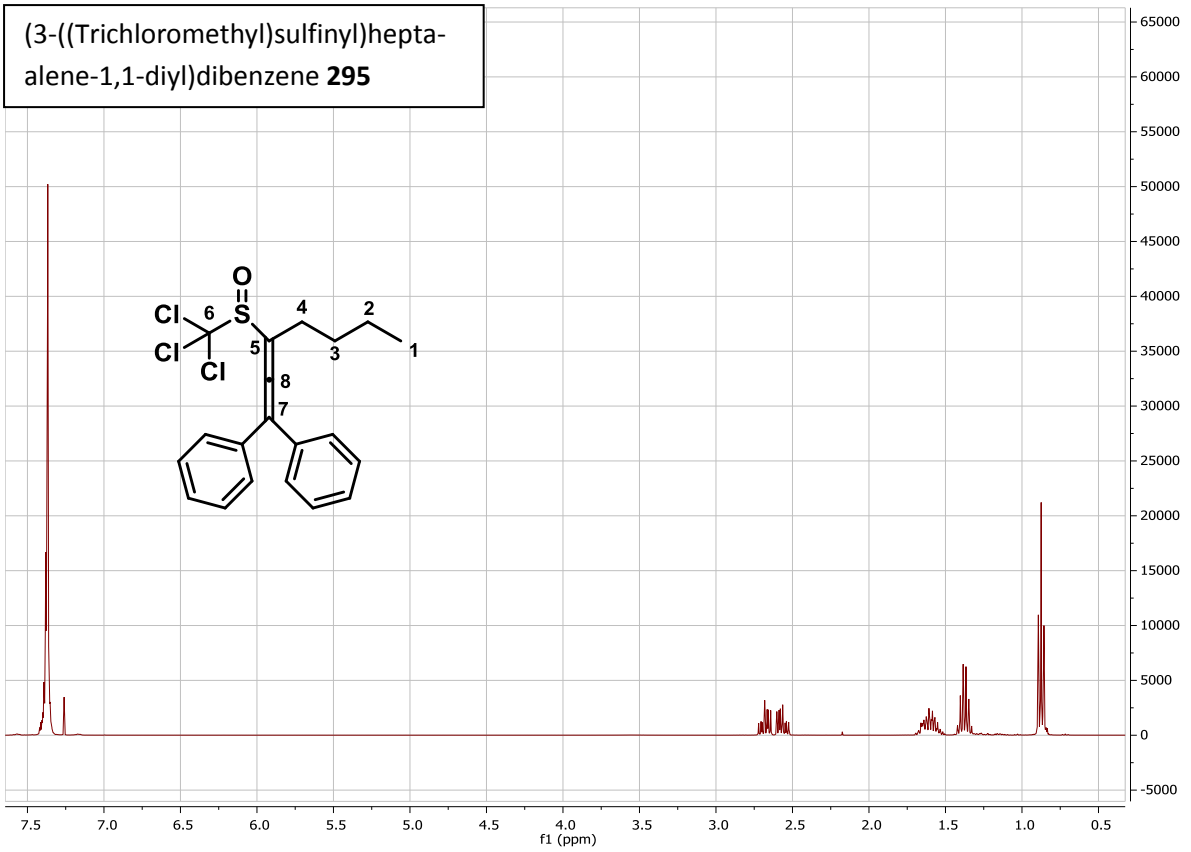


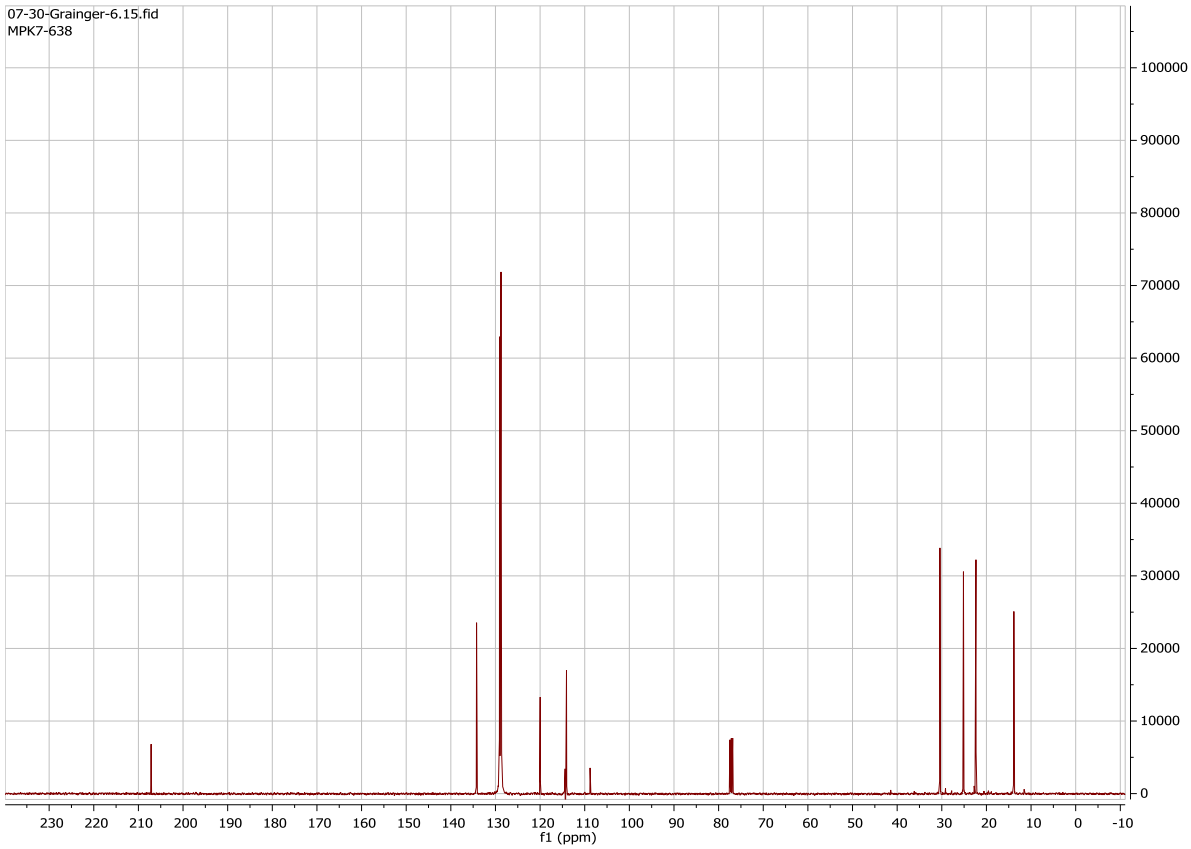
Methyl (1*R*,3*R*,4*R*,5*S*)-4-(hex-1-yn-1-yl)-3,4-dihydroxy-5-((triethylsilyl)oxy)cyclohexane-1-carboxylate **284**



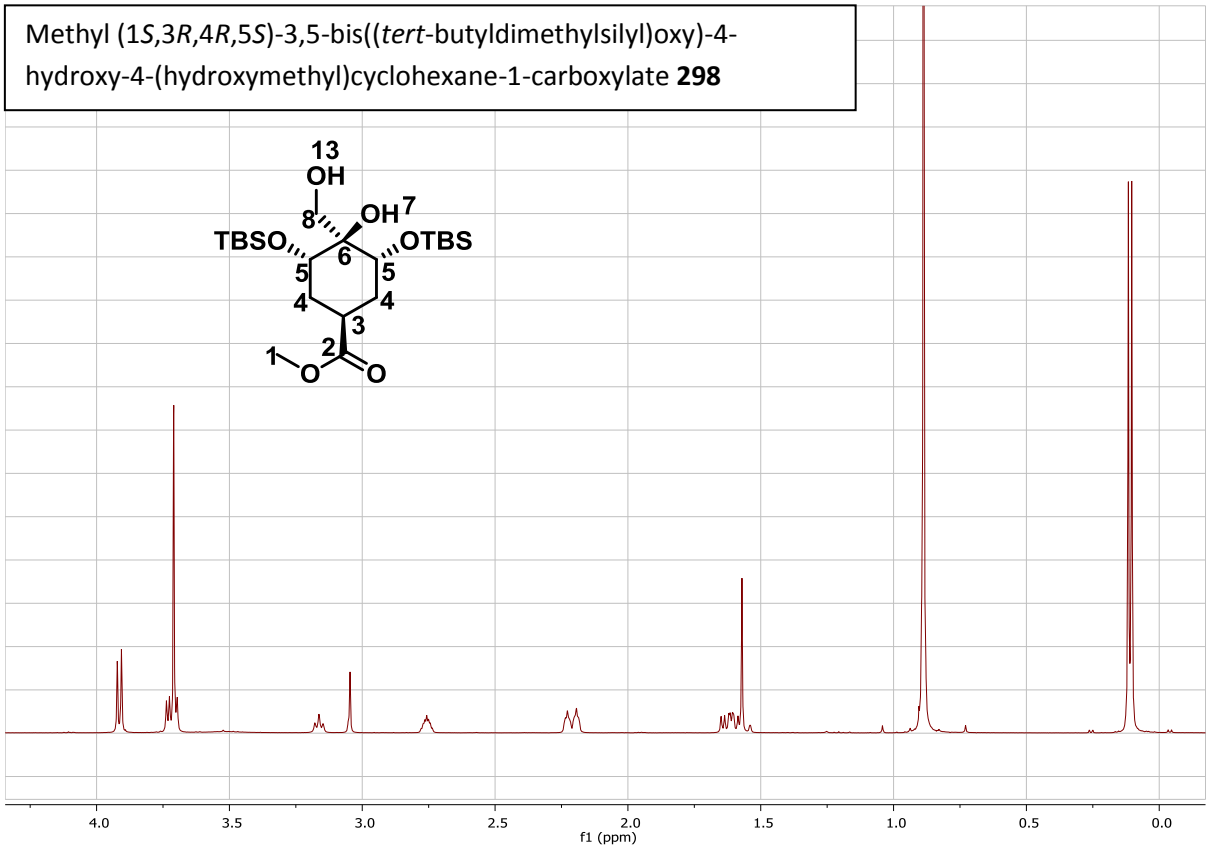


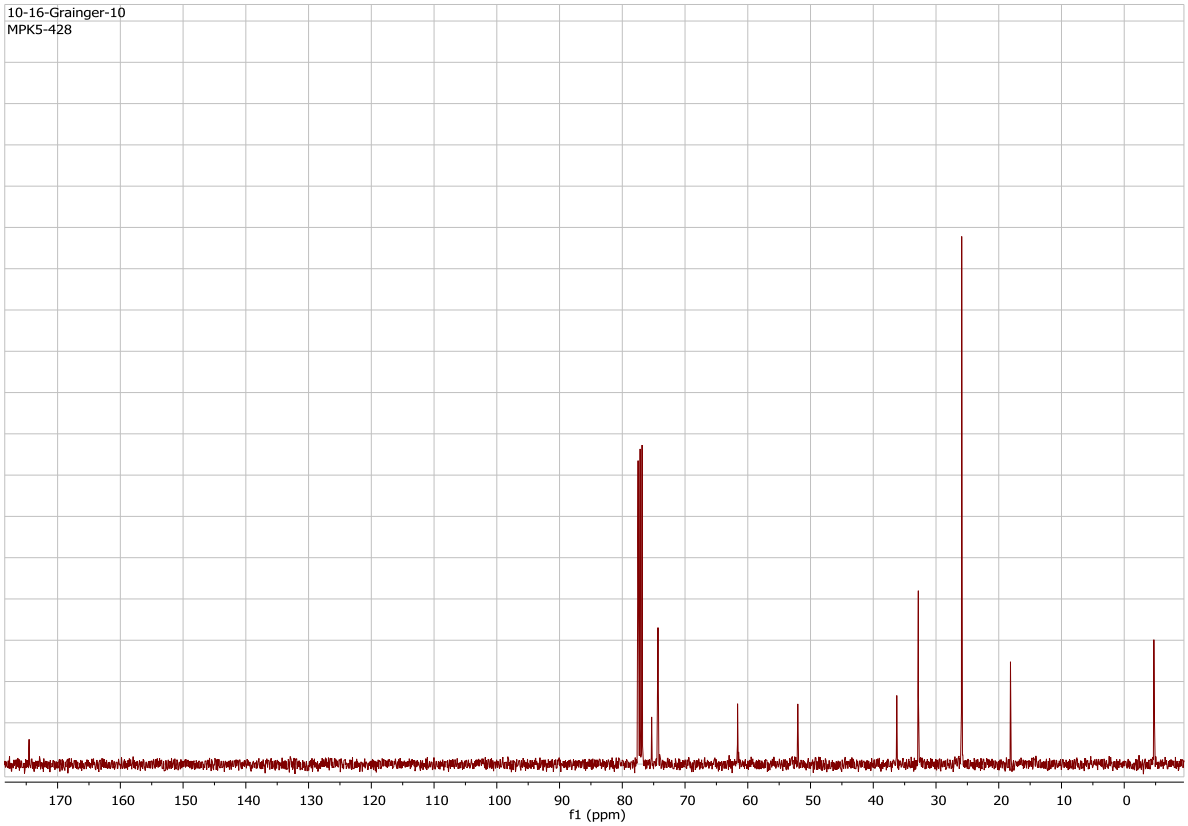
(3-((Trichloromethyl)sulfinyl)hepta-alene-1,1-diyl)dibenzene **295**



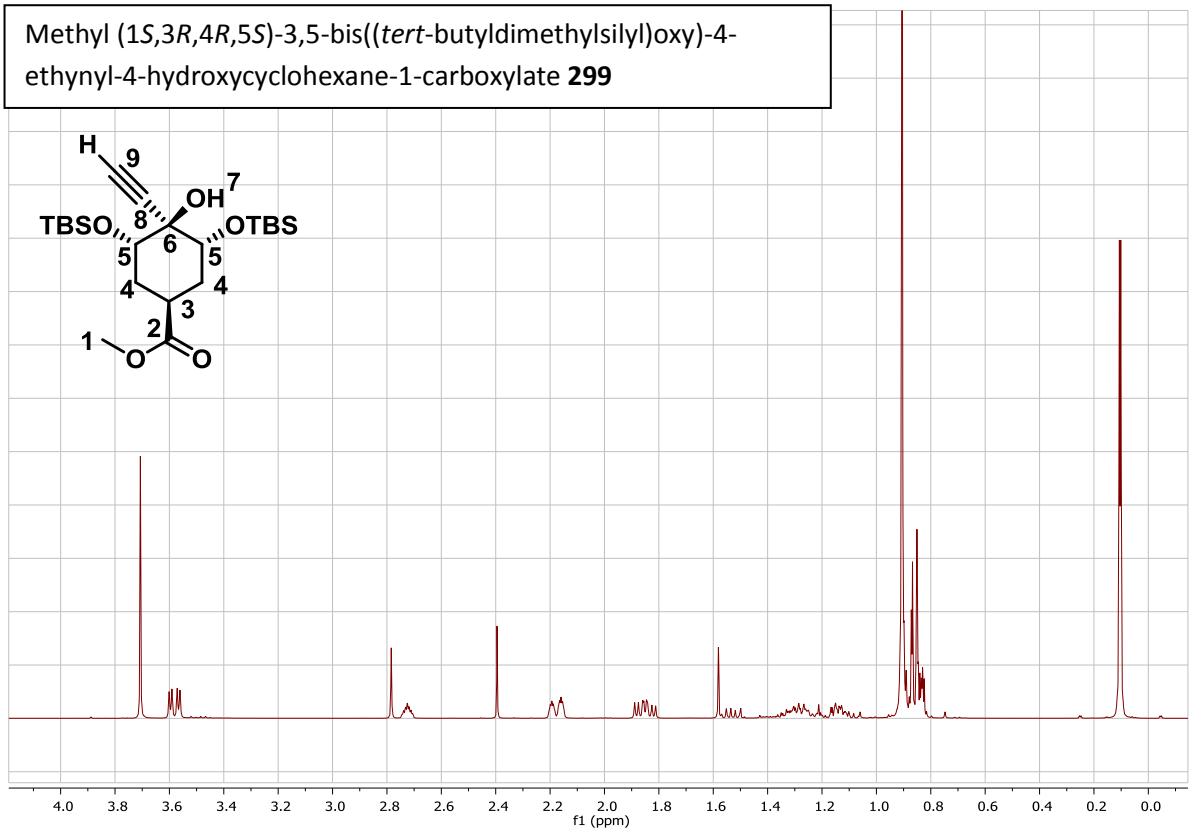


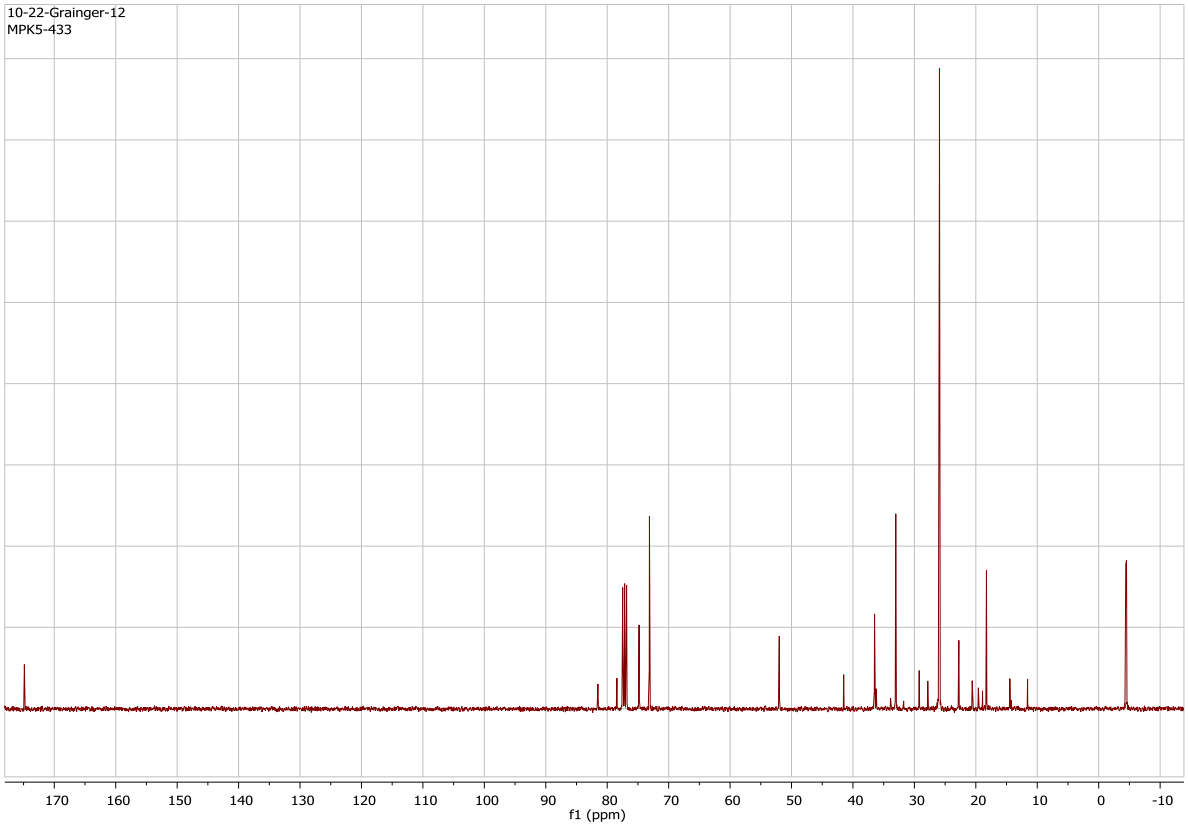
Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(hydroxymethyl)cyclohexane-1-carboxylate **298**



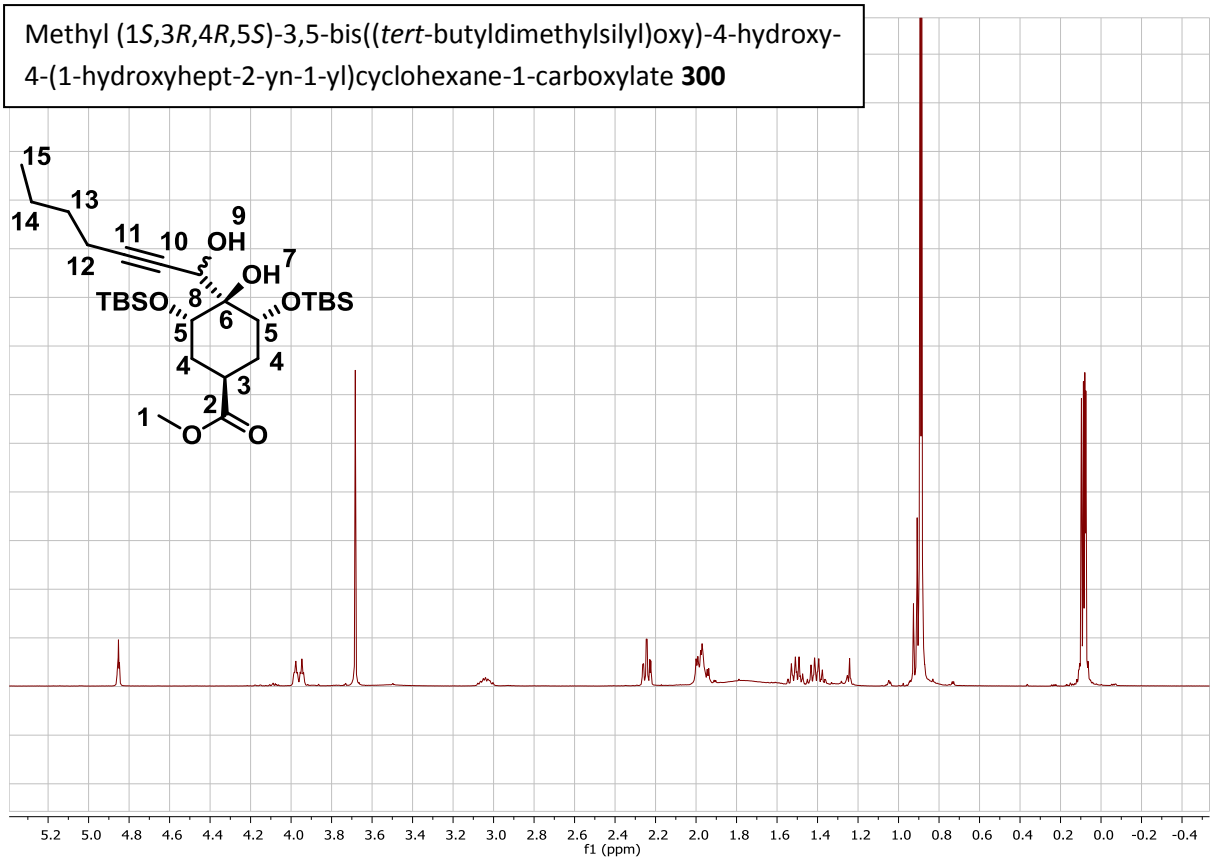


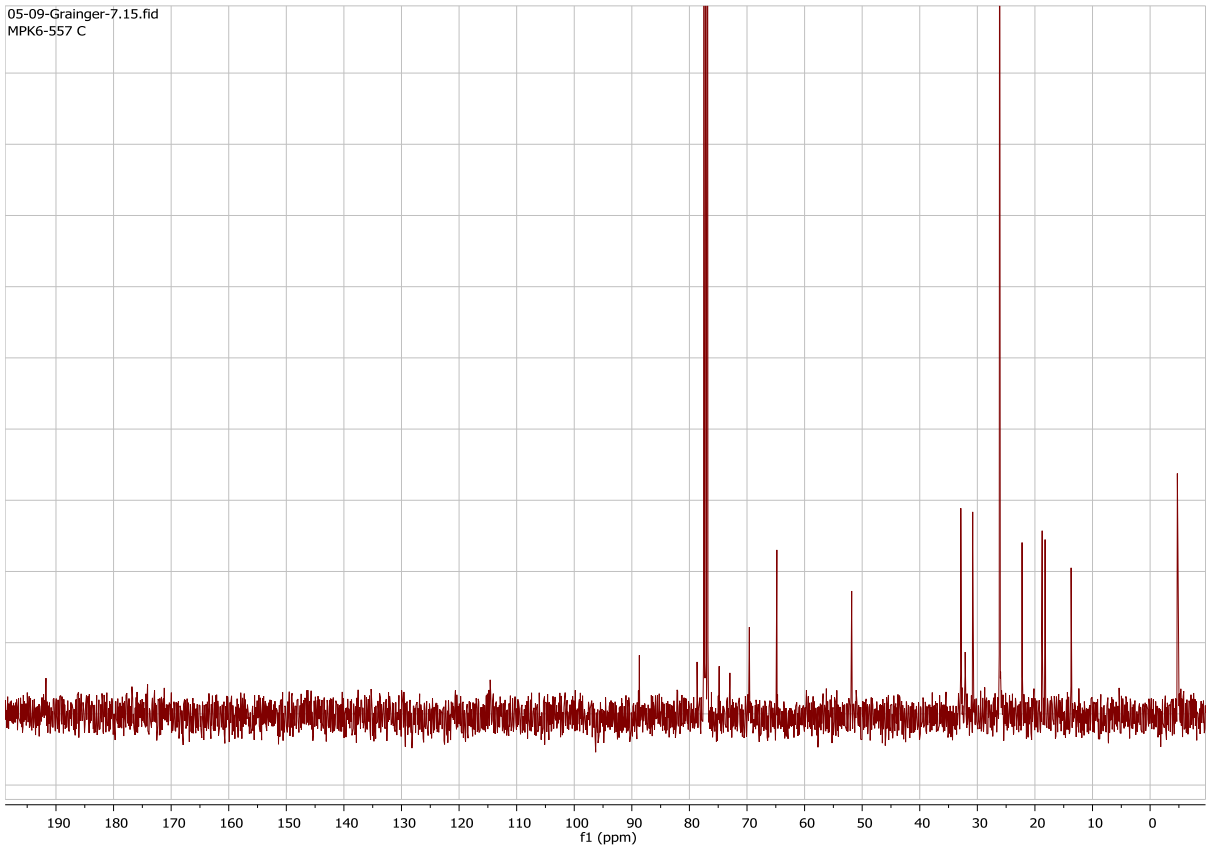
Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-ethynyl-4-hydroxycyclohexane-1-carboxylate **299**



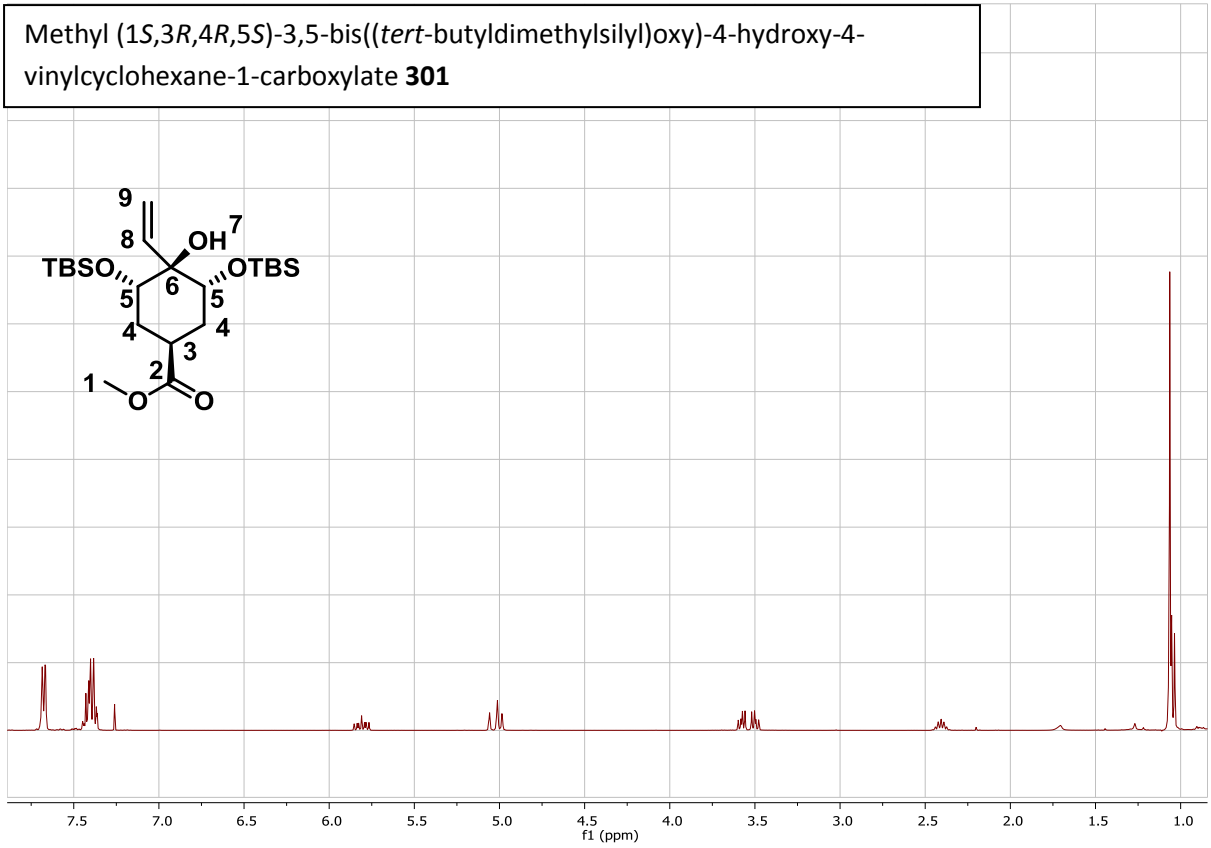


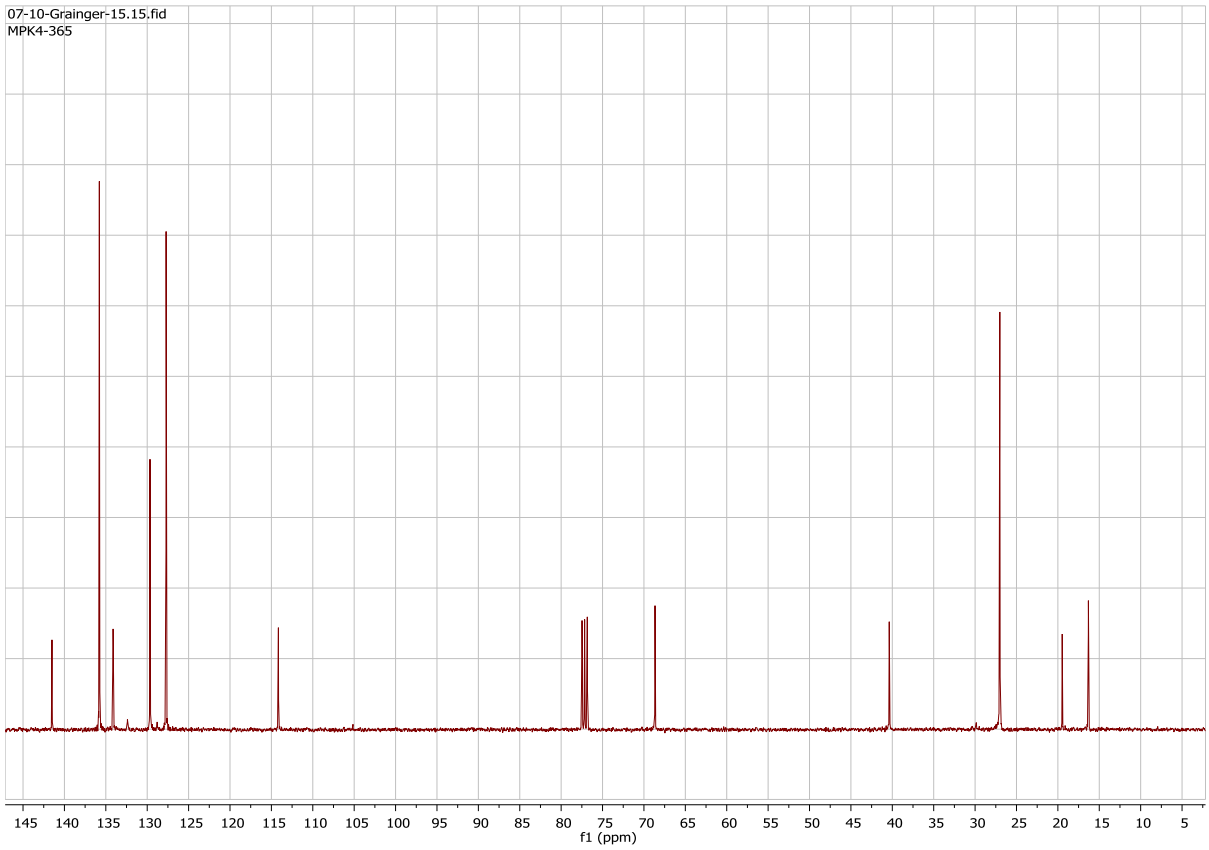
Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(1-hydroxyhept-2-yn-1-yl)cyclohexane-1-carboxylate **300**



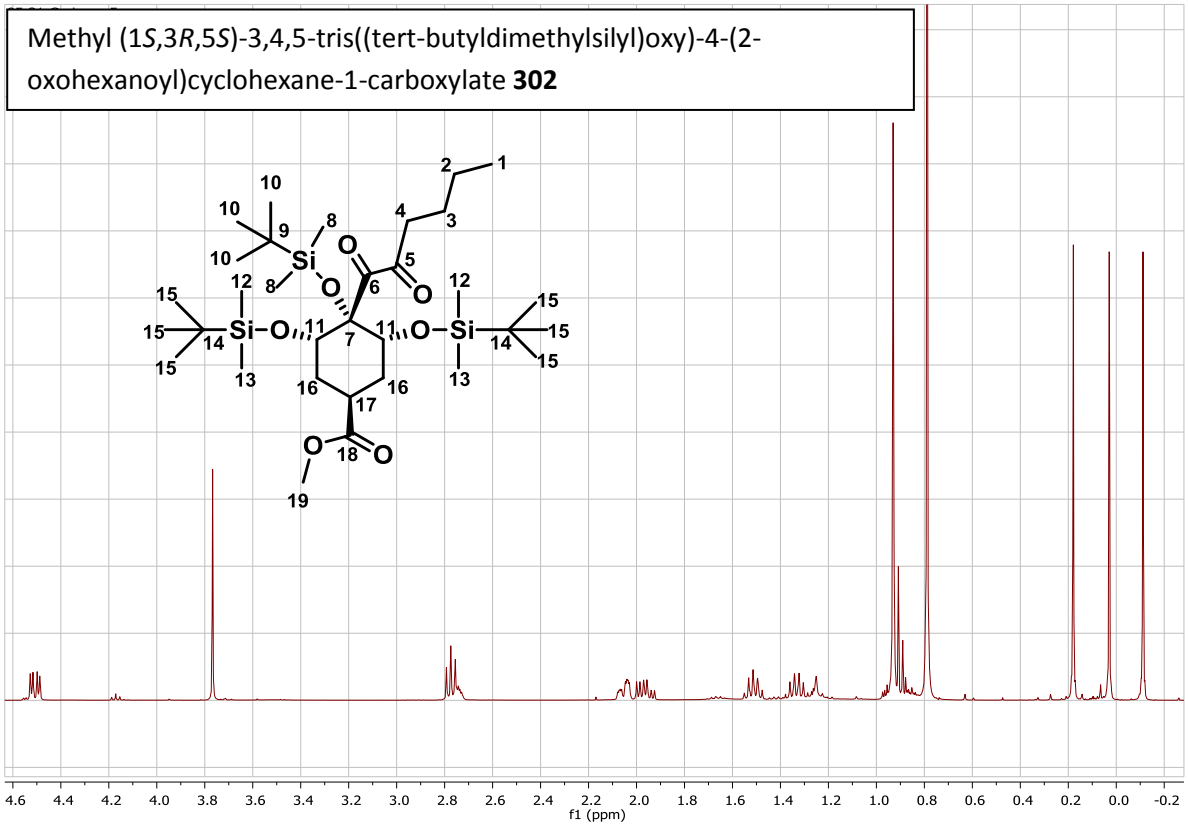


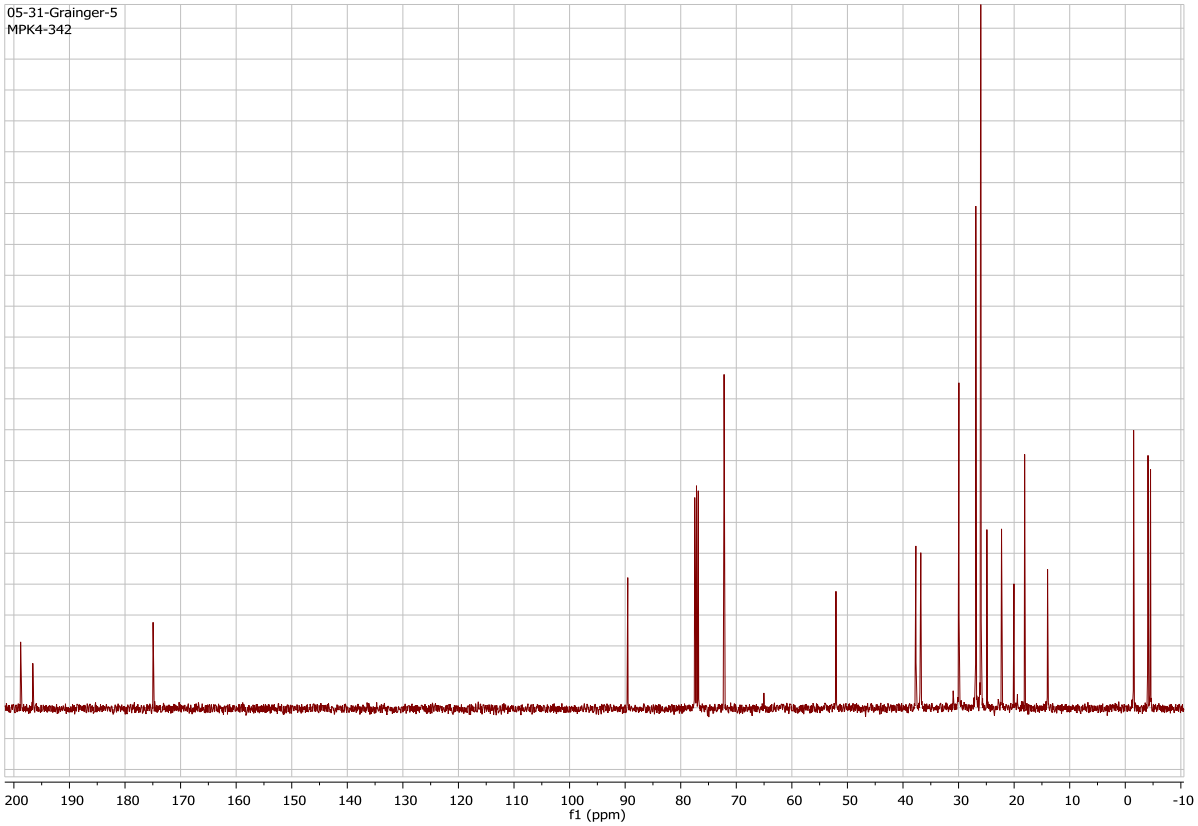
Methyl (1*S*,3*R*,4*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-vinylcyclohexane-1-carboxylate **301**



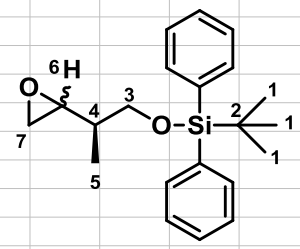


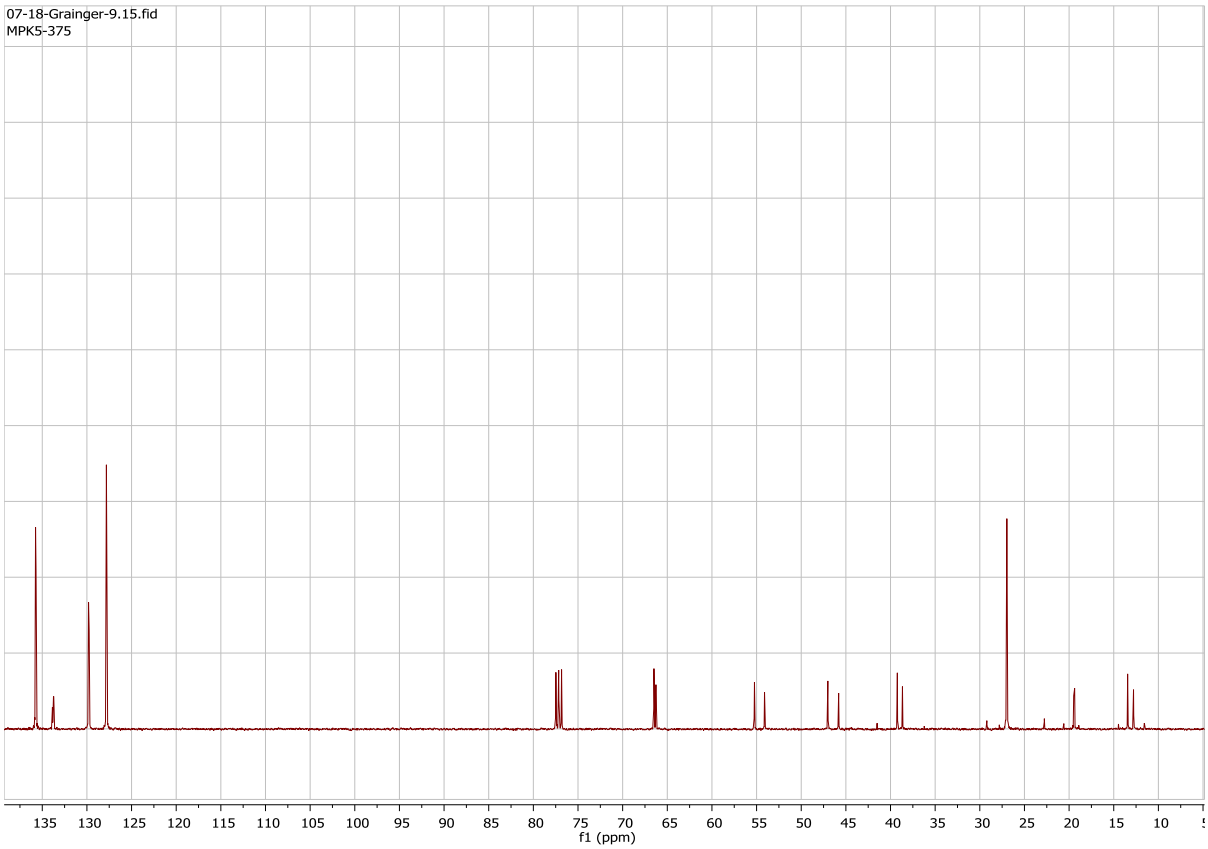
Methyl (1*S*,3*R*,5*S*)-3,4,5-tris((tert-butyldimethylsilyl)oxy)-4-(2-oxohexanoyl)cyclohexane-1-carboxylate **302**



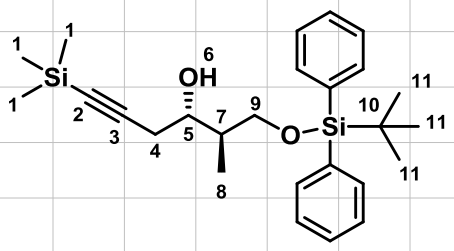


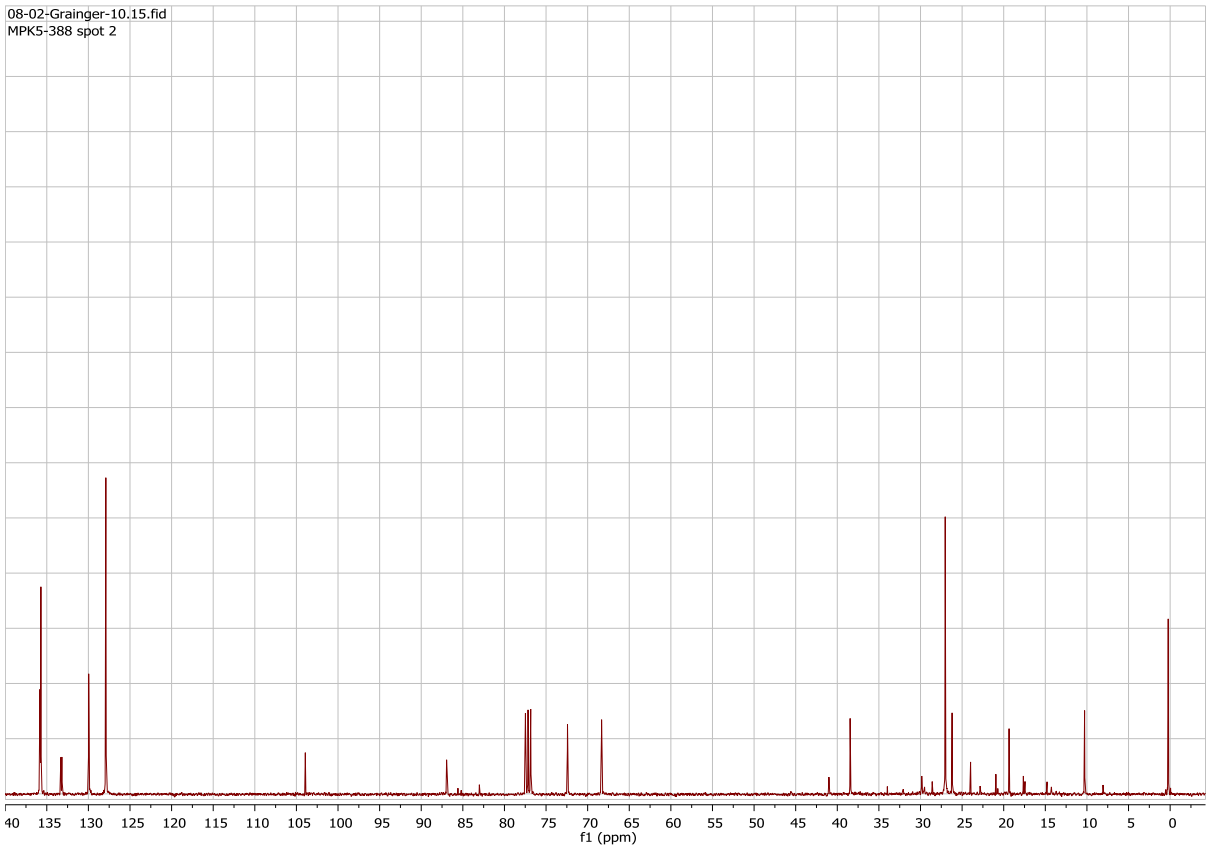
tert-Butyl((2*R*)-2-(oxiran-2-yl)propoxy)diphenylsilane **306**



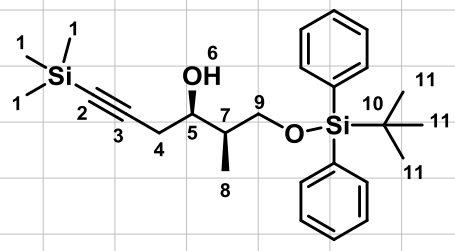


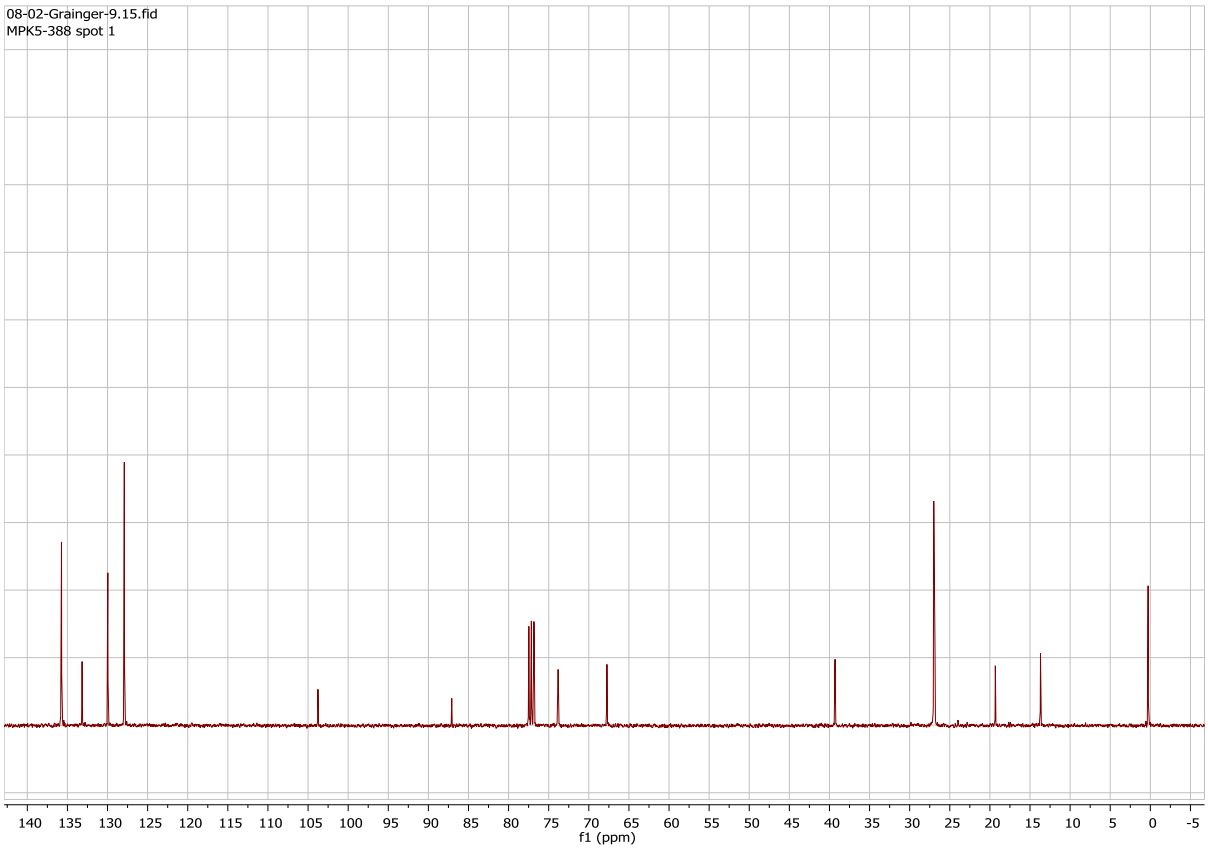
(2*R*,3*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol **307**



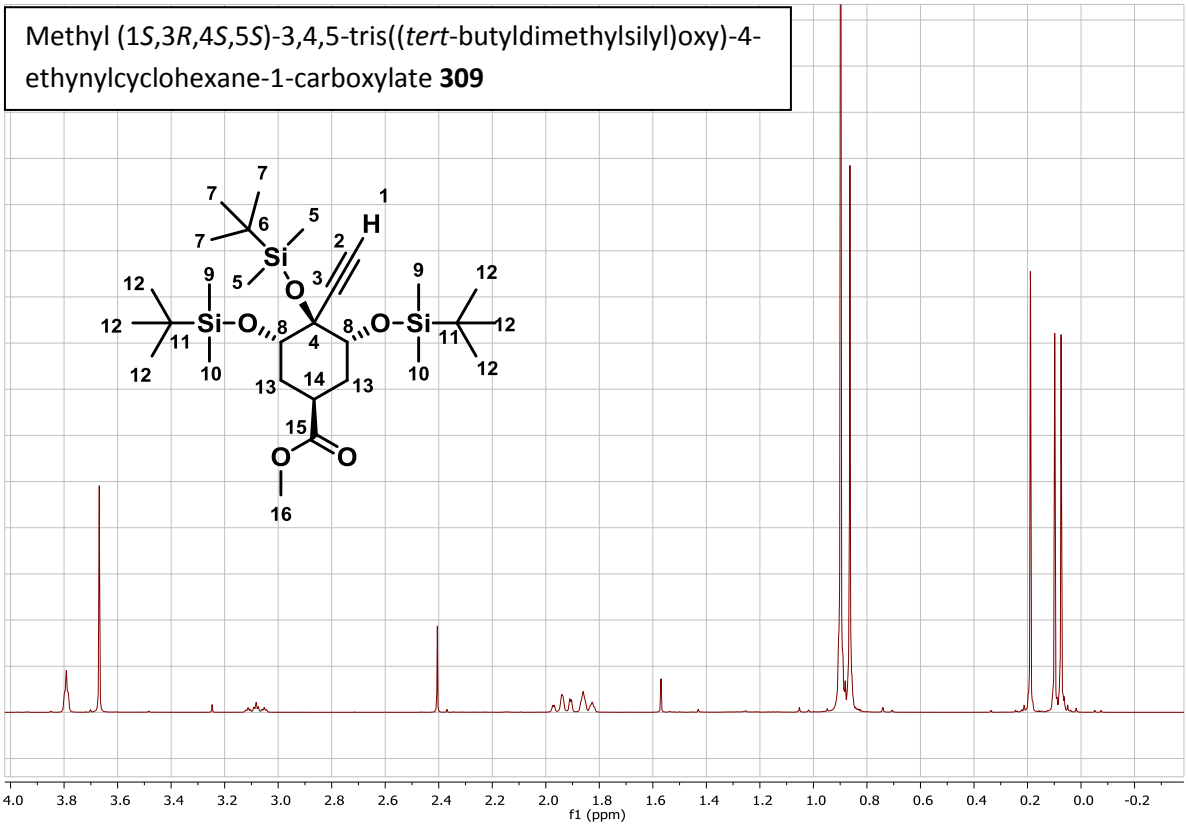


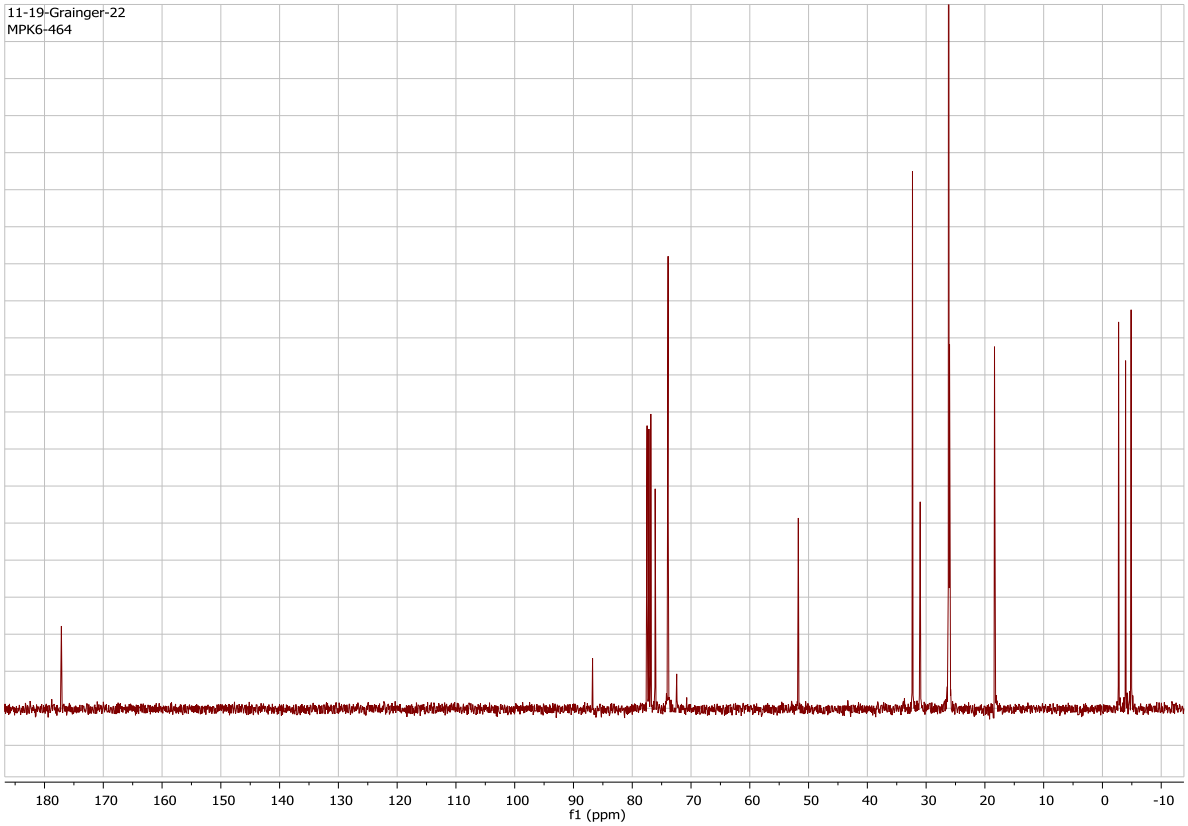
(2*R*,3*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol **308**



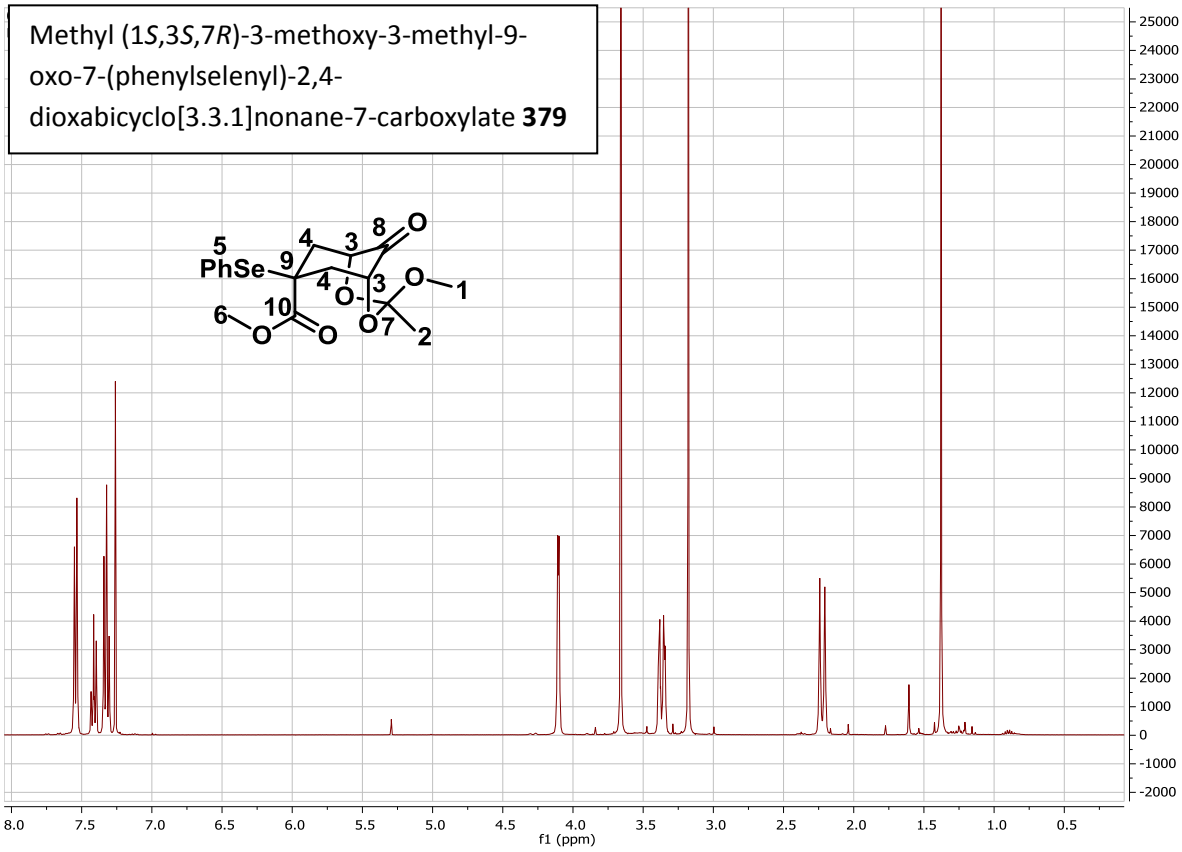


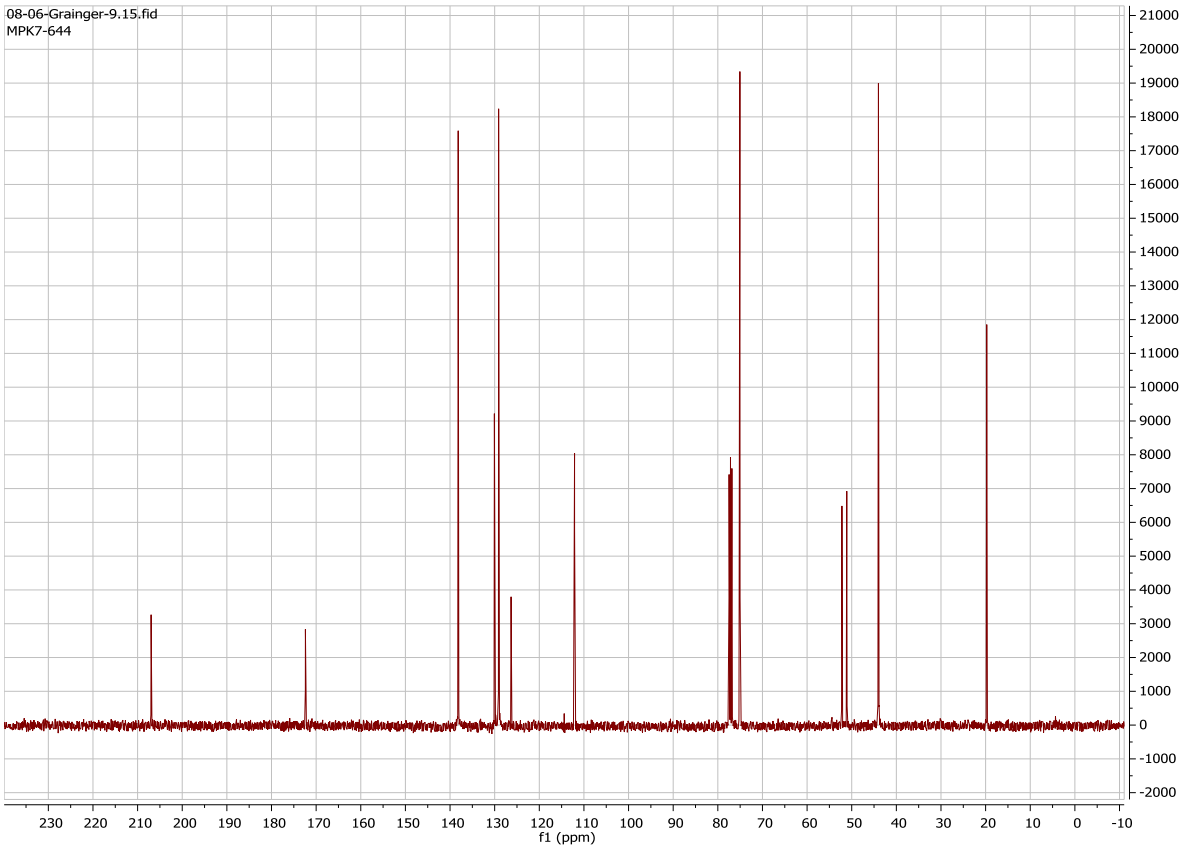
Methyl (1*S*,3*R*,4*S*,5*S*)-3,4,5-tris((*tert*-butyldimethylsilyl)oxy)-4-ethynylcyclohexane-1-carboxylate **309**



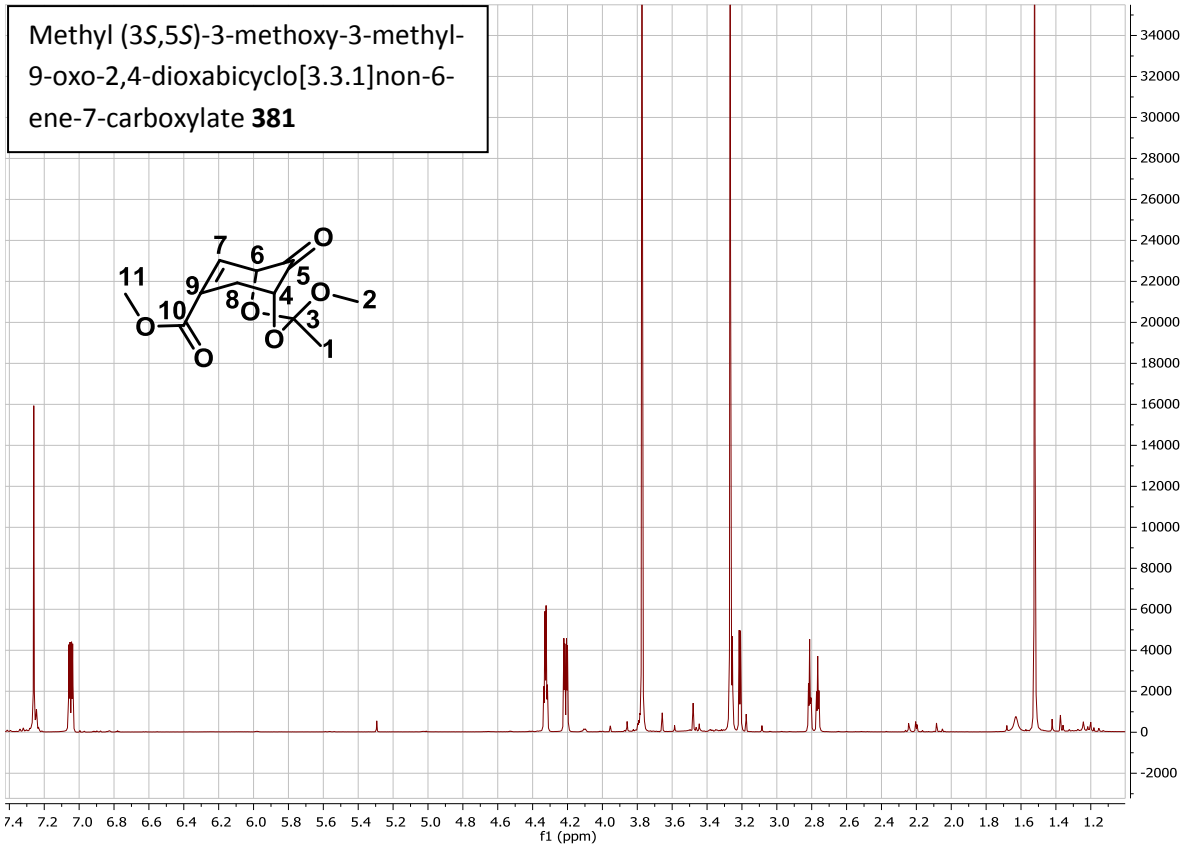


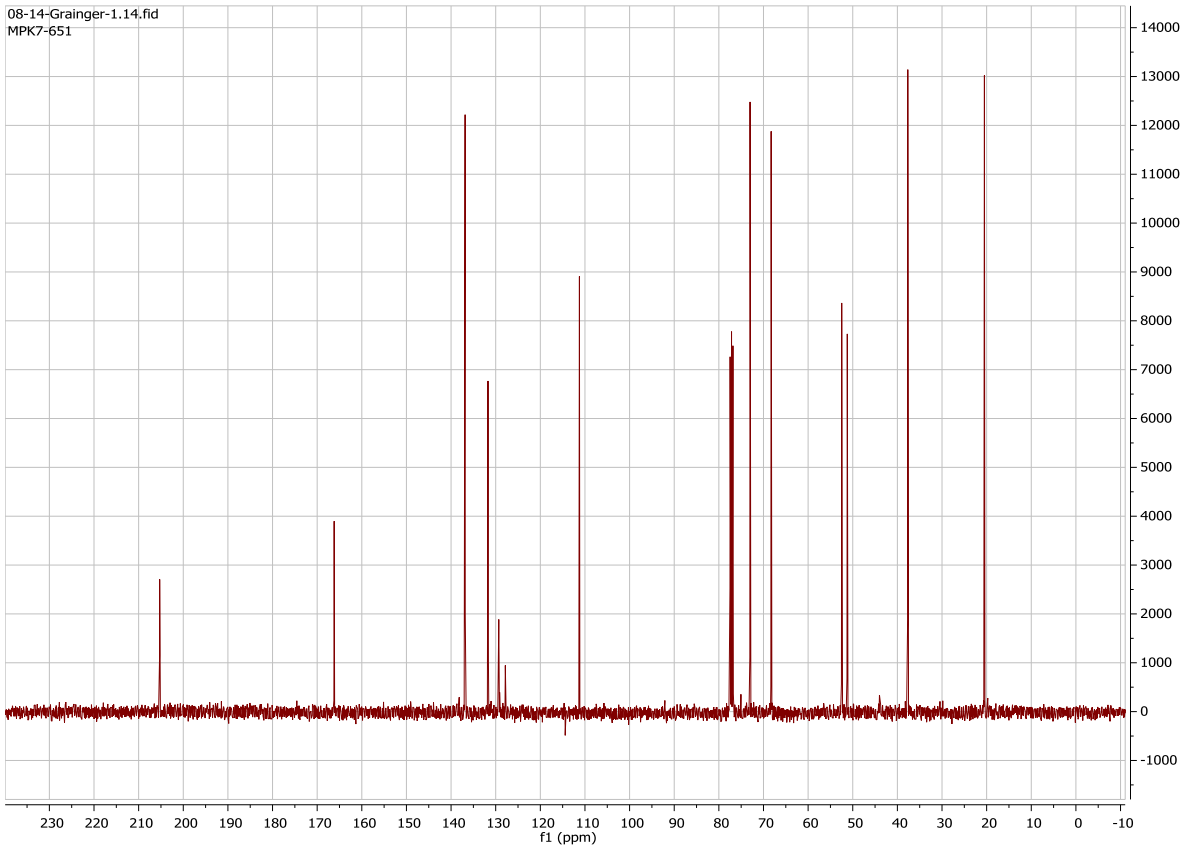
Methyl (1*S*,3*S*,7*R*)-3-methoxy-3-methyl-9-oxo-7-(phenylselenyl)-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate **379**



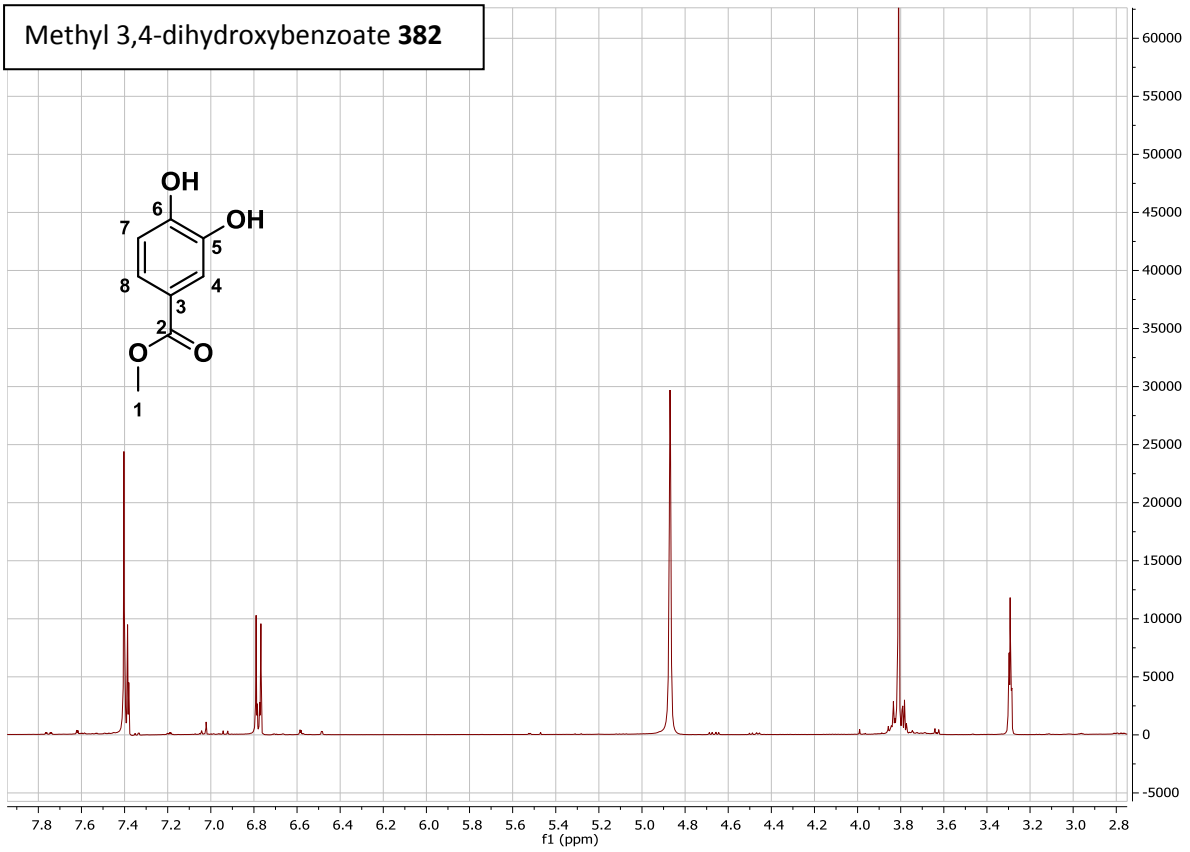


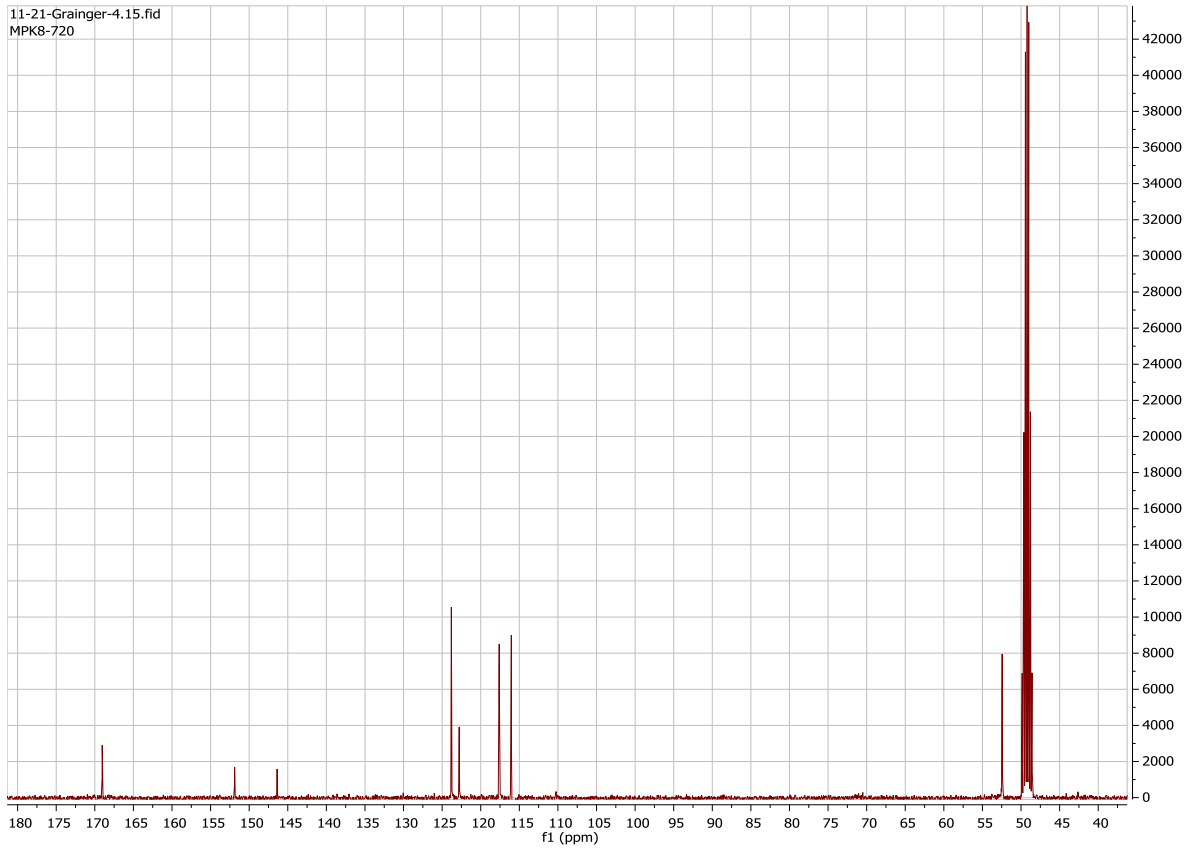
Methyl (3*S*,5*S*)-3-methoxy-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]non-6-ene-7-carboxylate **381**



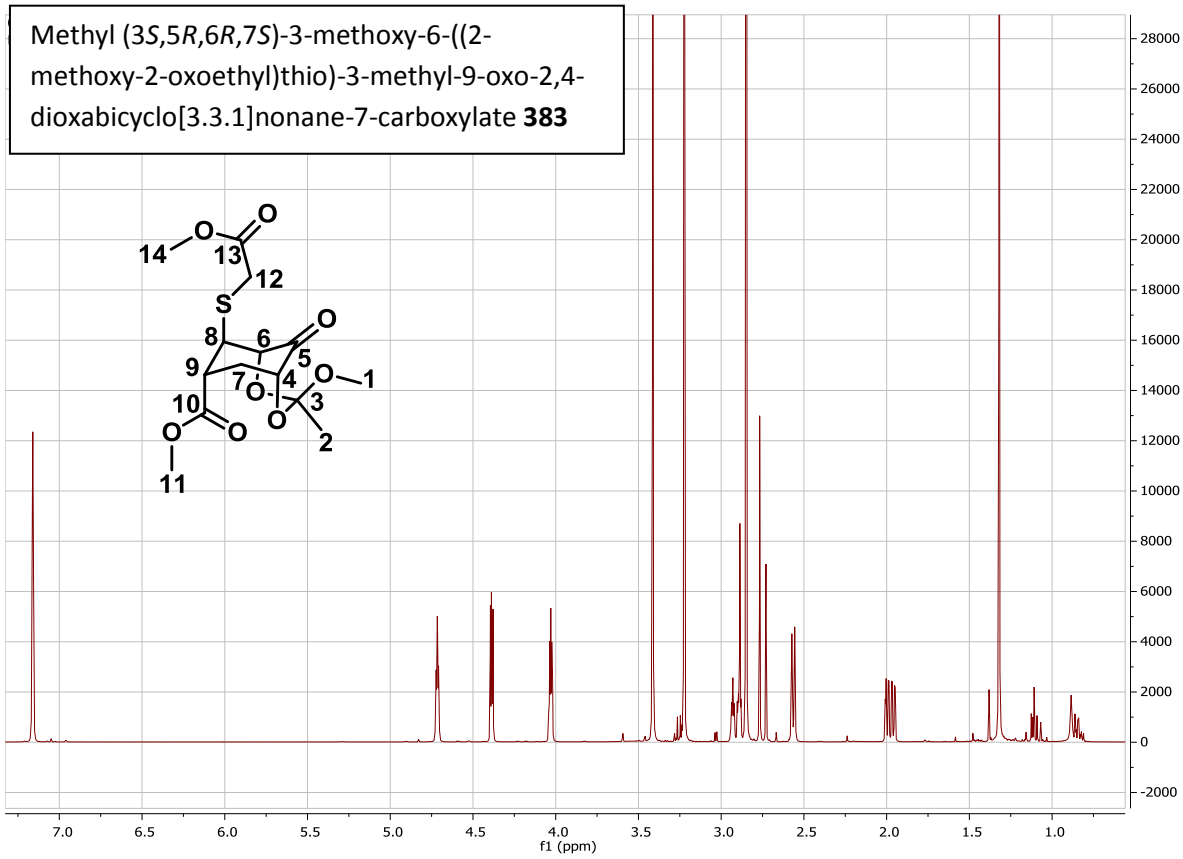


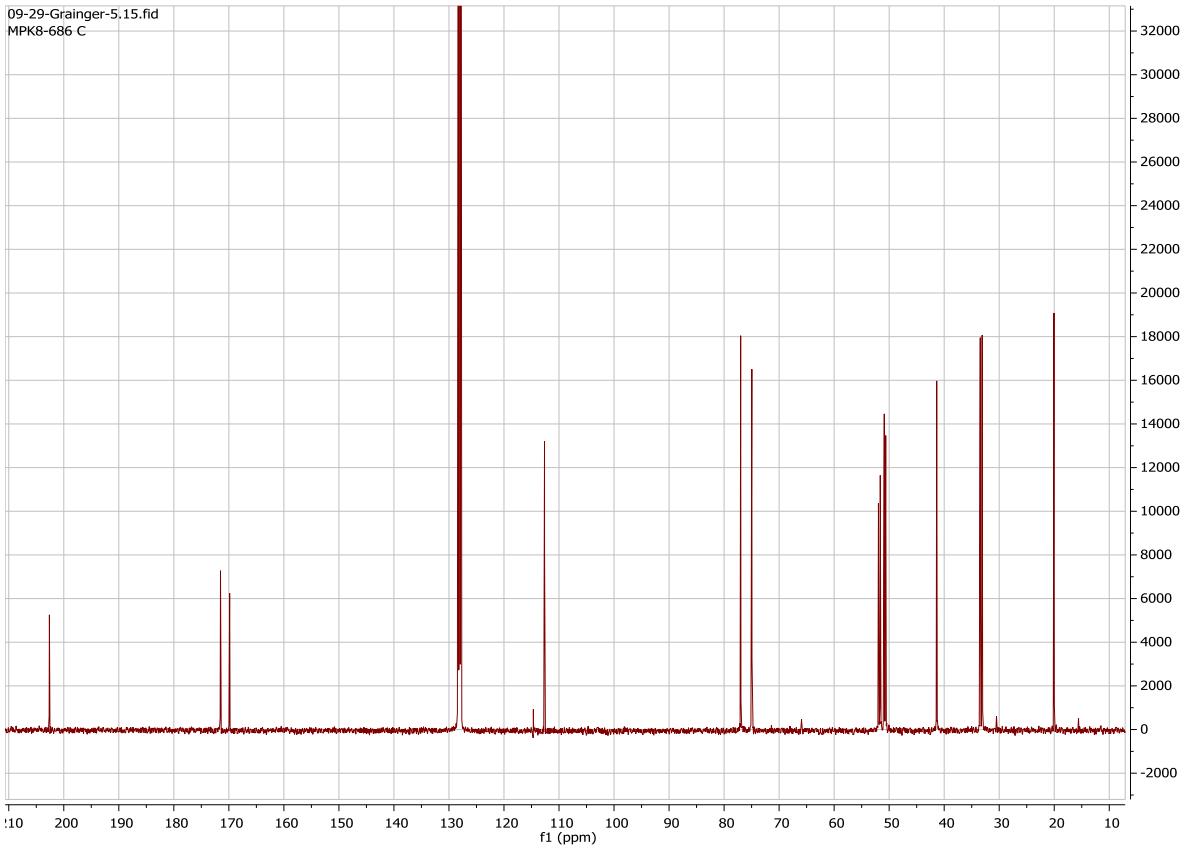
Methyl 3,4-dihydroxybenzoate **382**



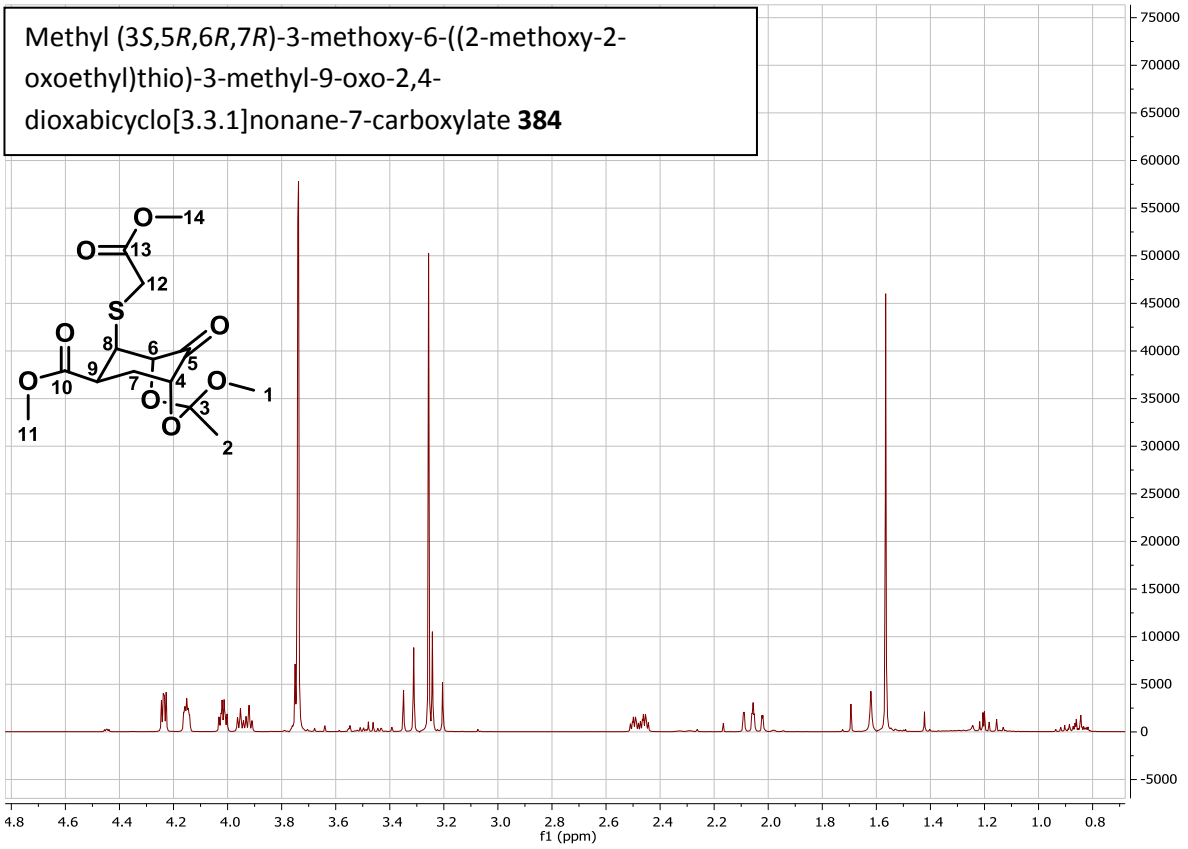


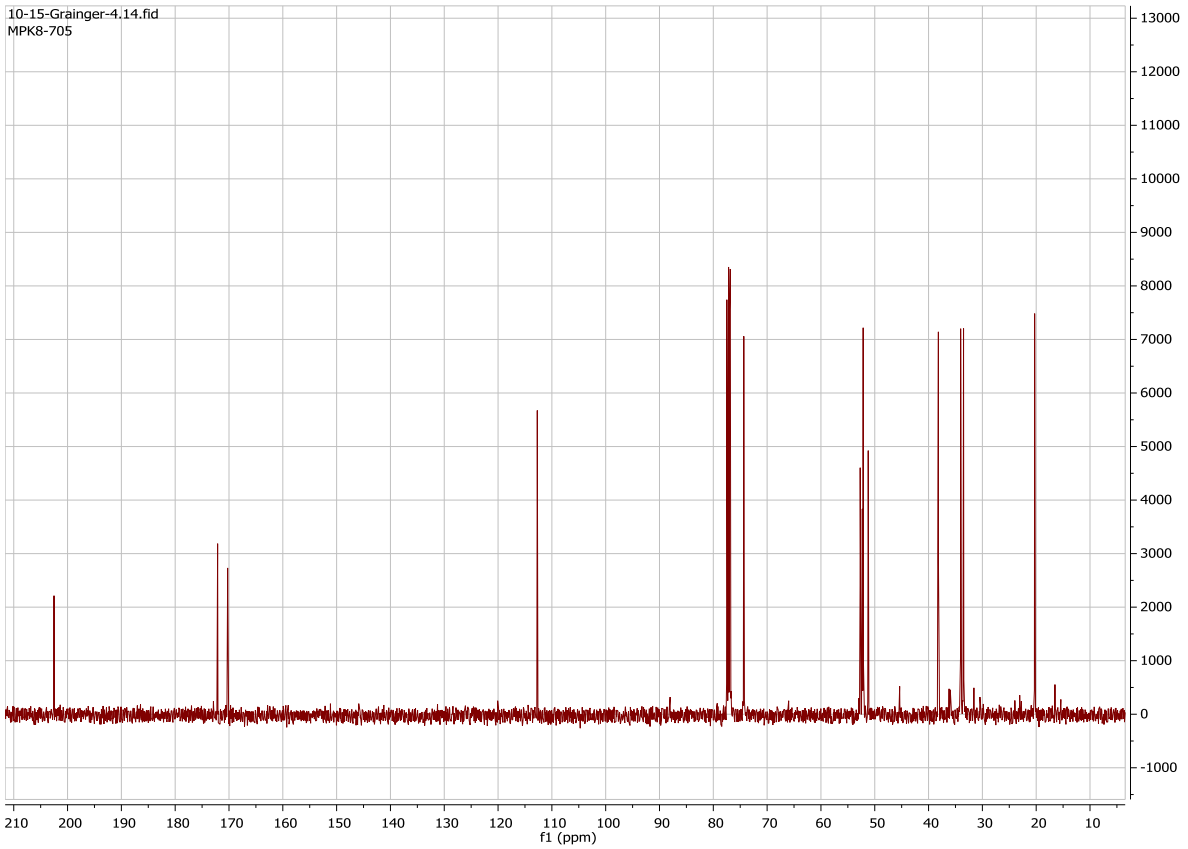
Methyl (3*S*,5*R*,6*R*,7*S*)-3-methoxy-6-((2-methoxy-2-oxoethyl)thio)-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate **383**



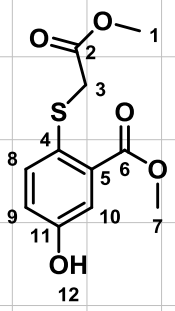


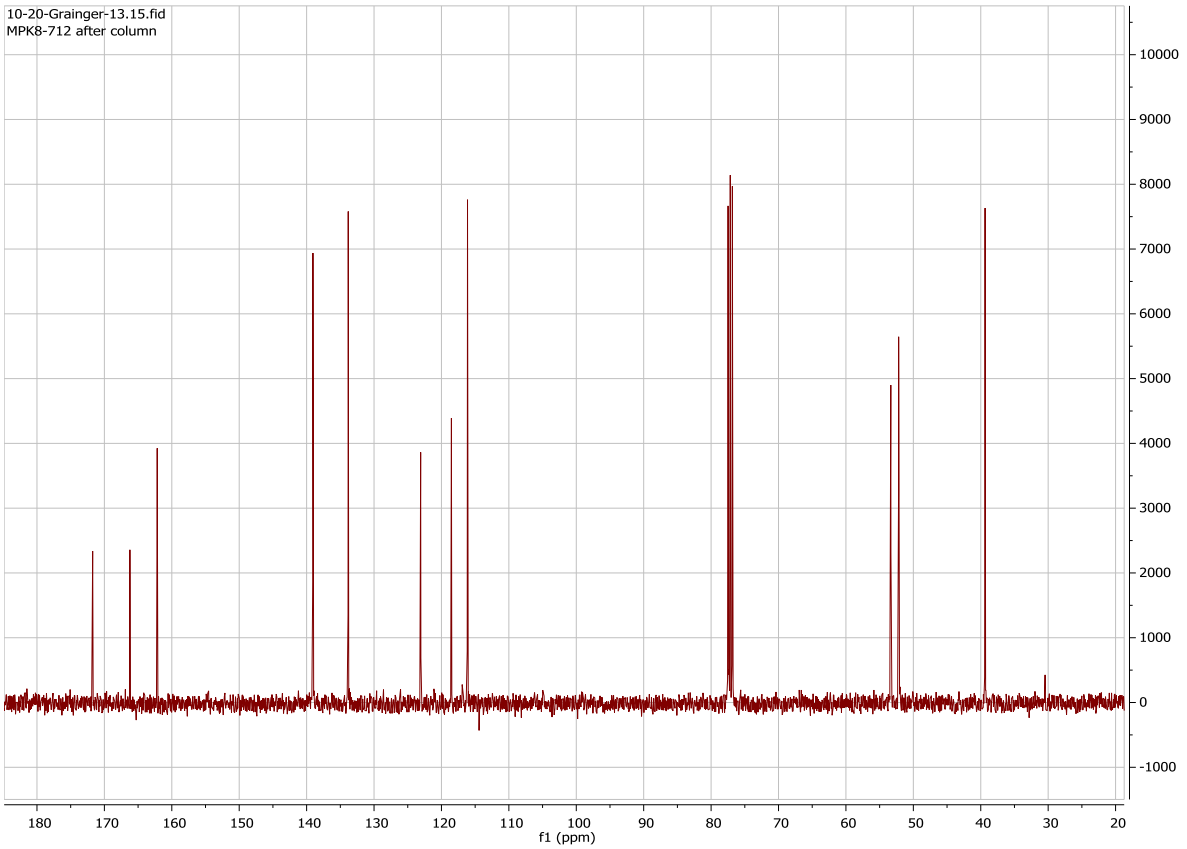
Methyl (3*S*,5*R*,6*R*,7*R*)-3-methoxy-6-((2-methoxy-2-oxoethyl)thio)-3-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7-carboxylate **384**



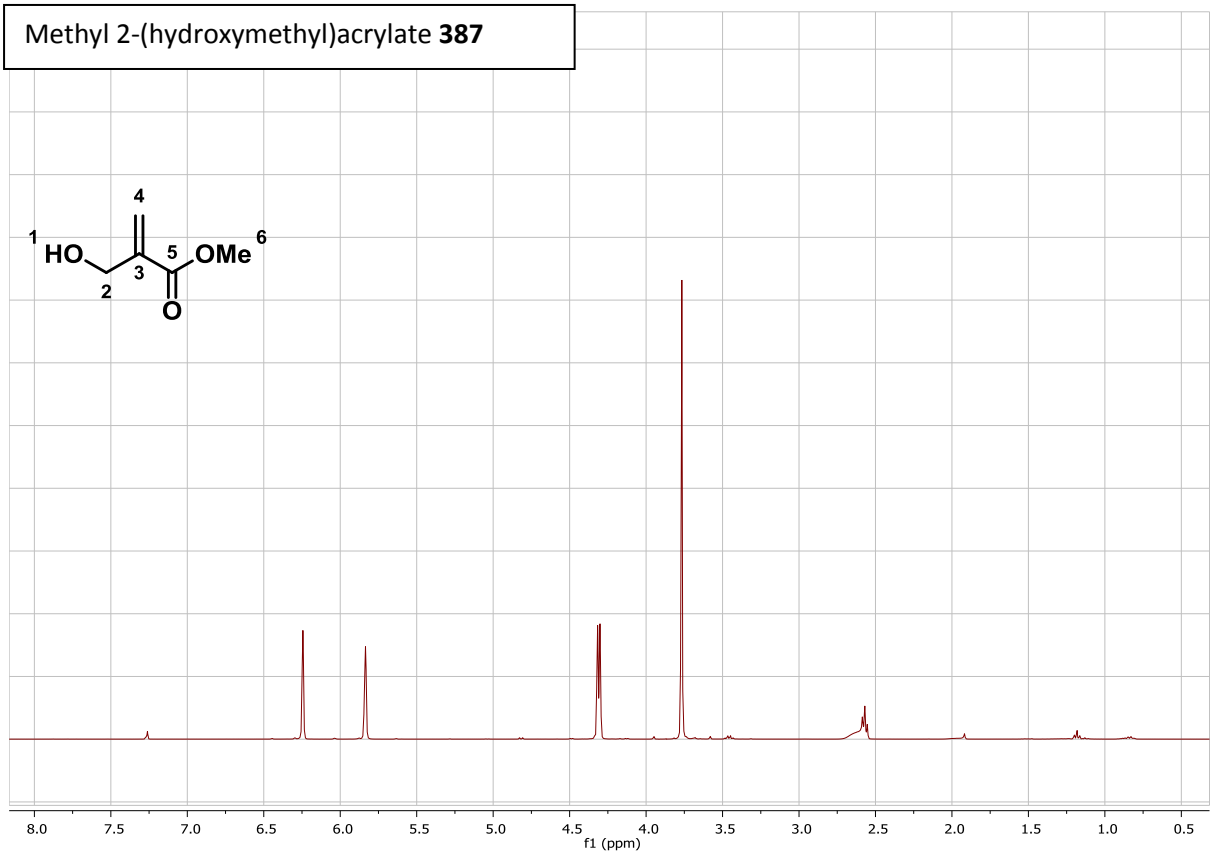


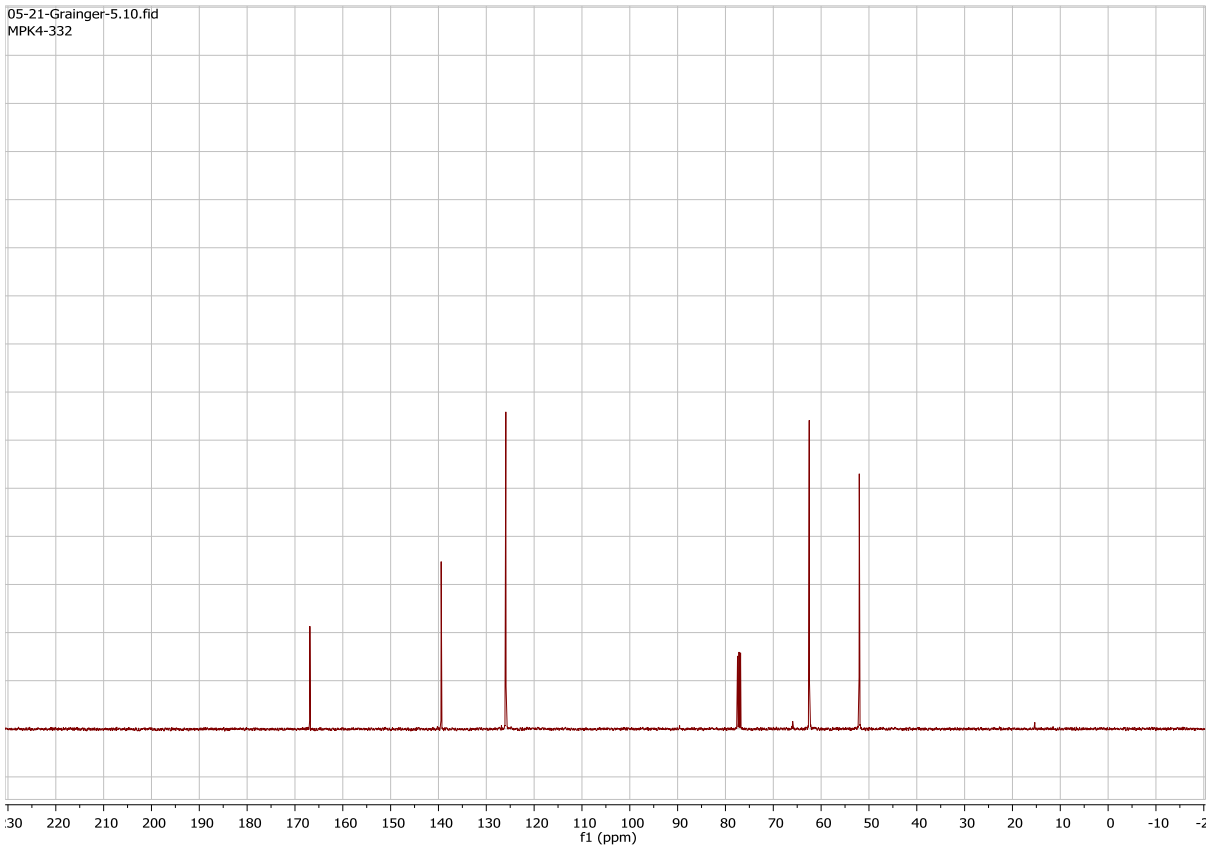
Methyl 5-hydroxy-2-((2-methoxy-2-oxoethyl)thio)benzoate **385**



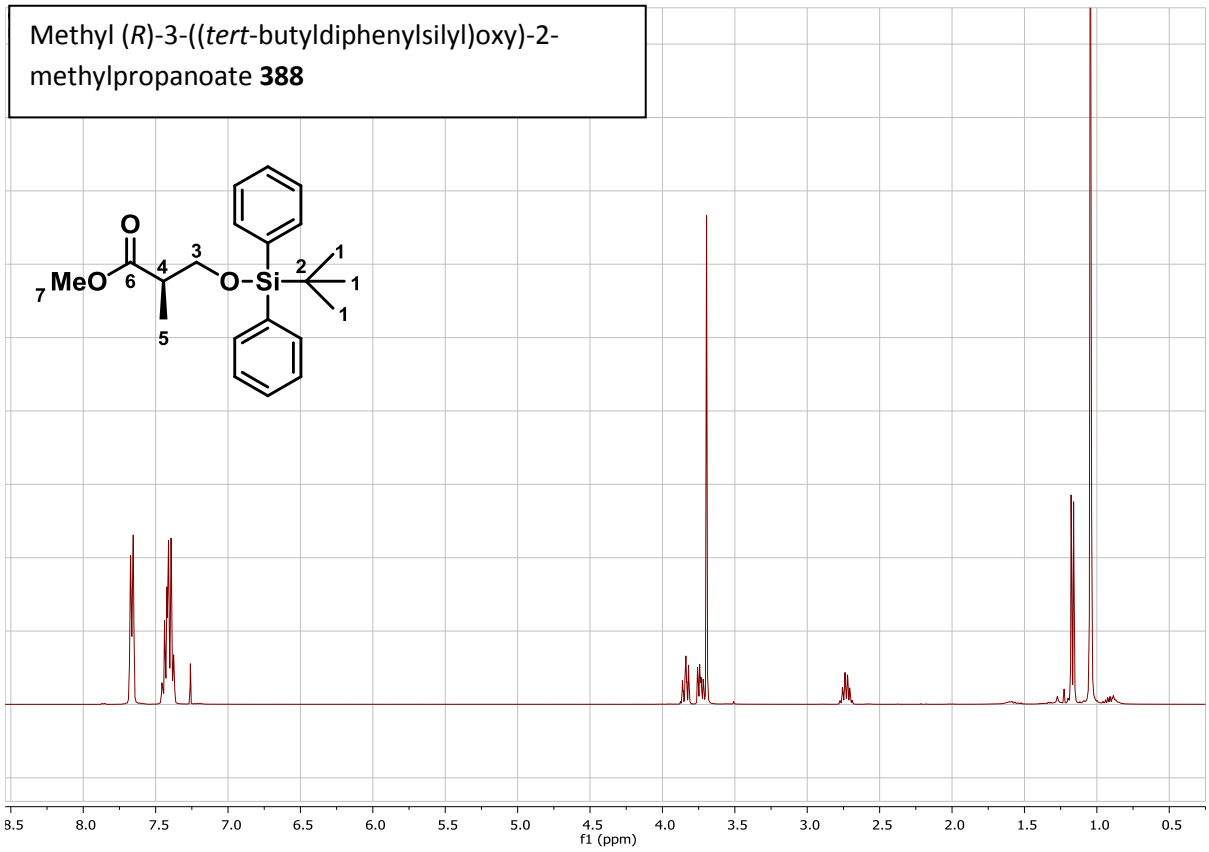


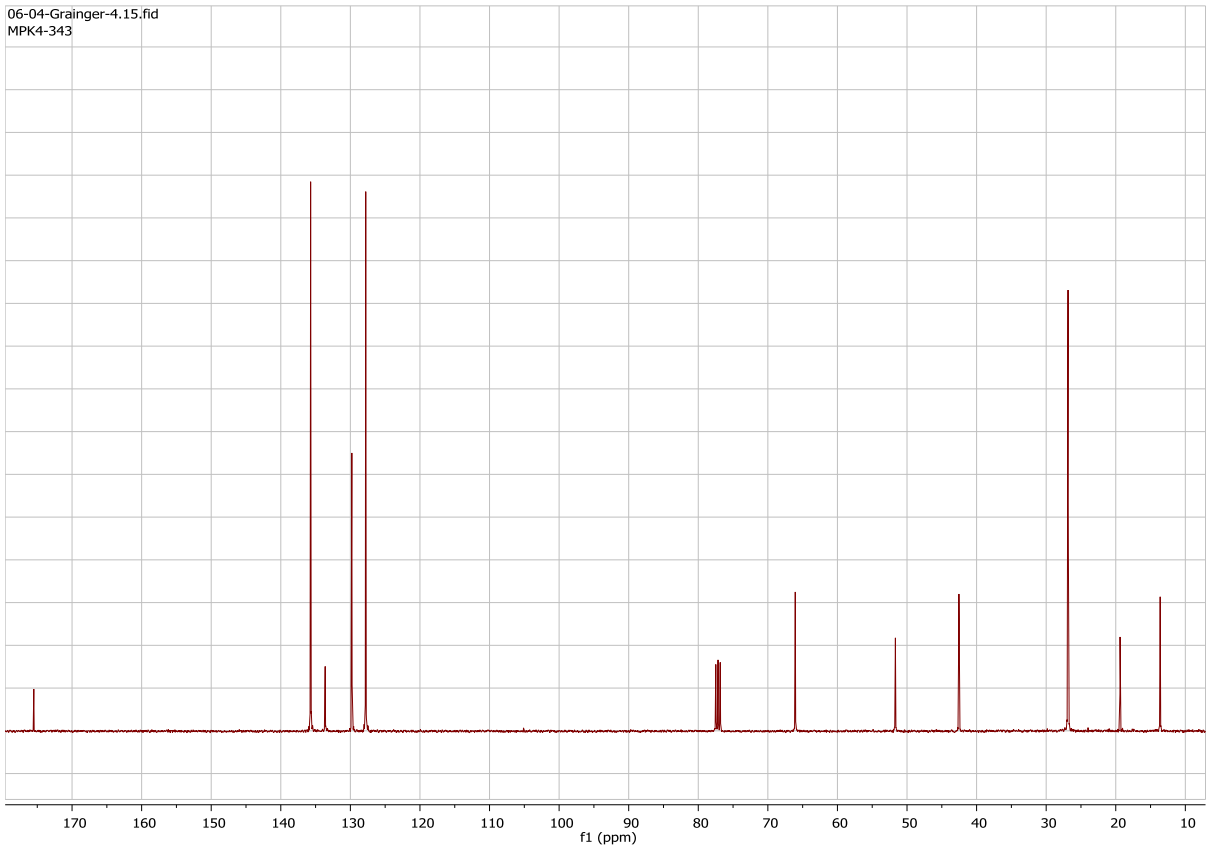
Methyl 2-(hydroxymethyl)acrylate **387**



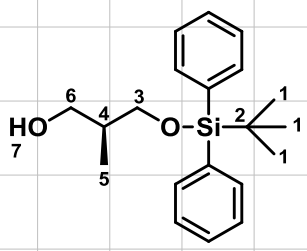


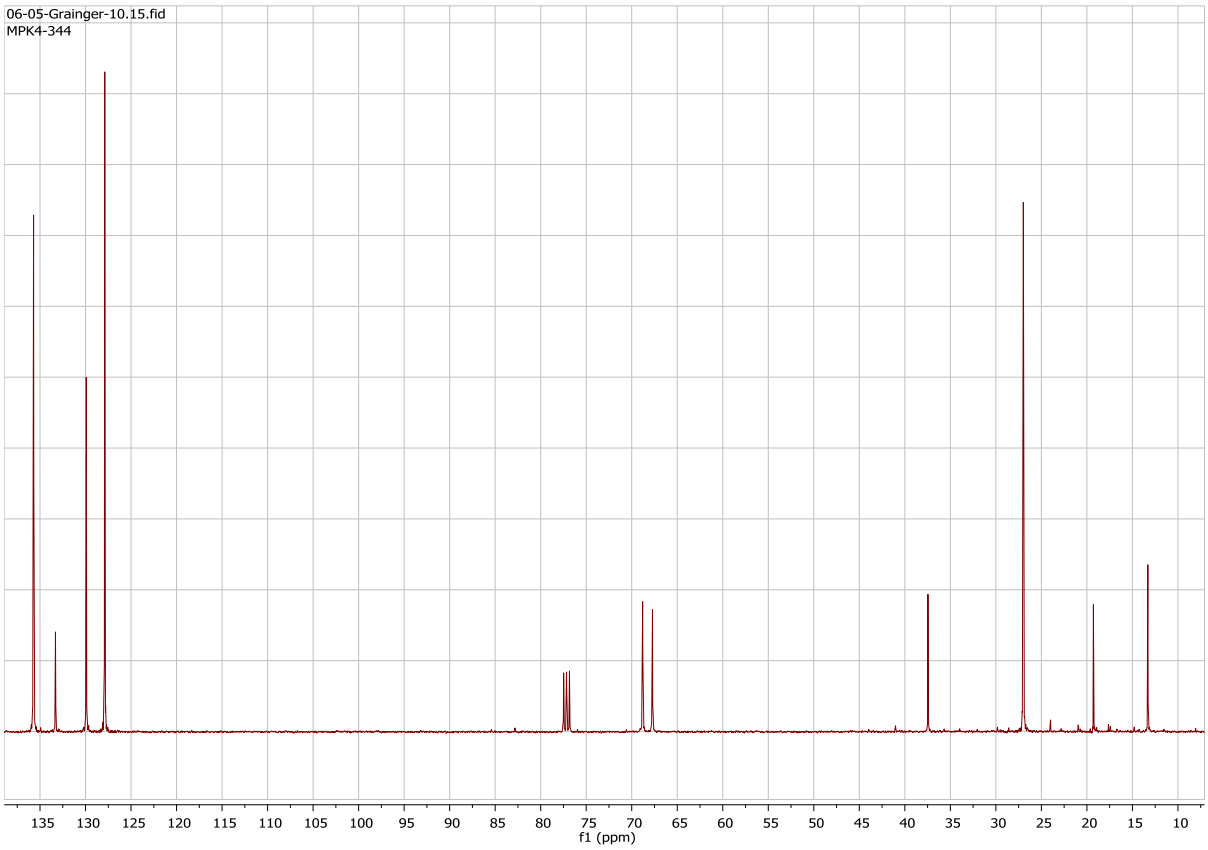
Methyl (*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanoate **388**



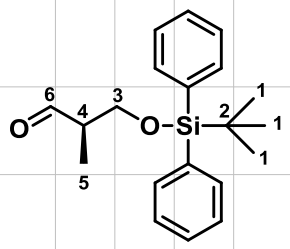


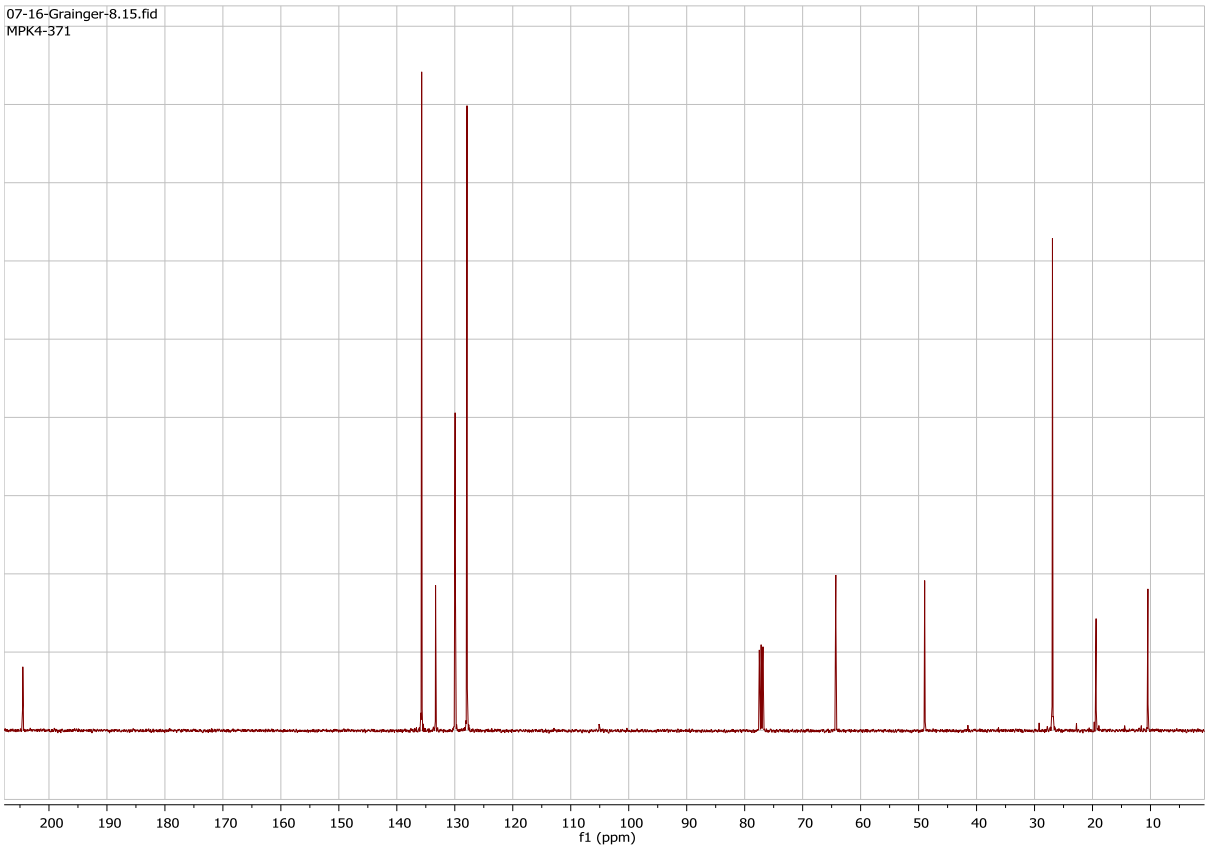
(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol **389**



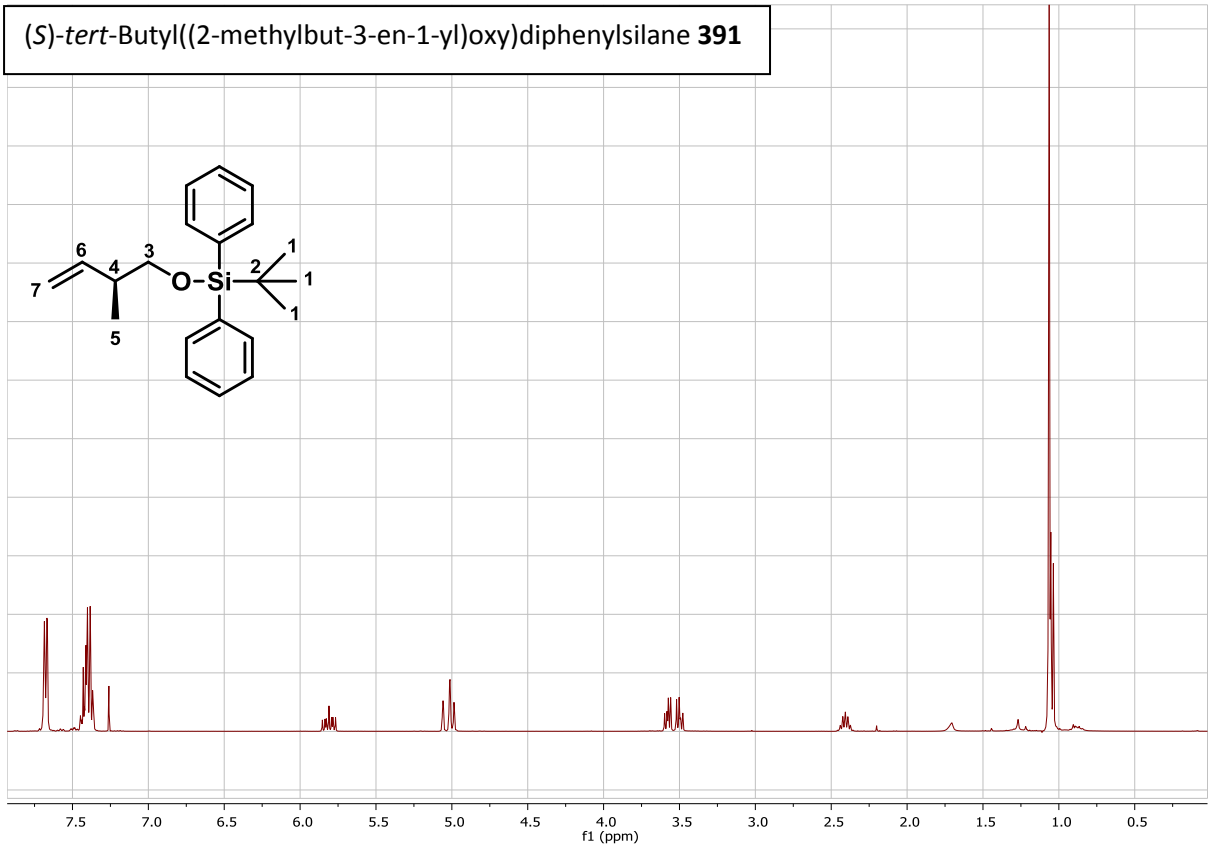


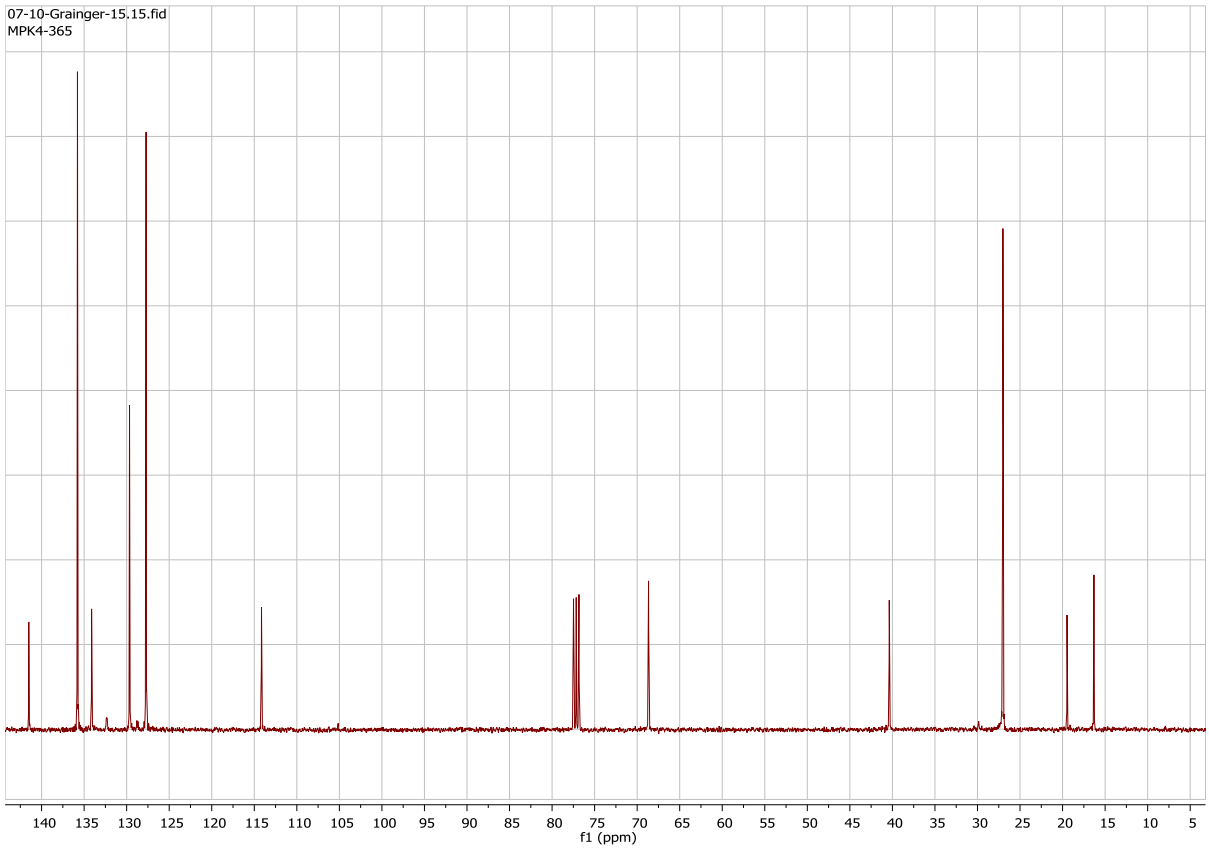
(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropanal **390**



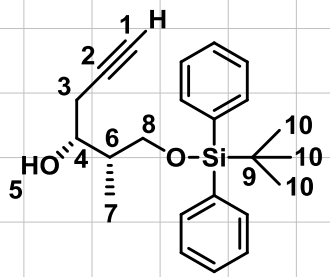


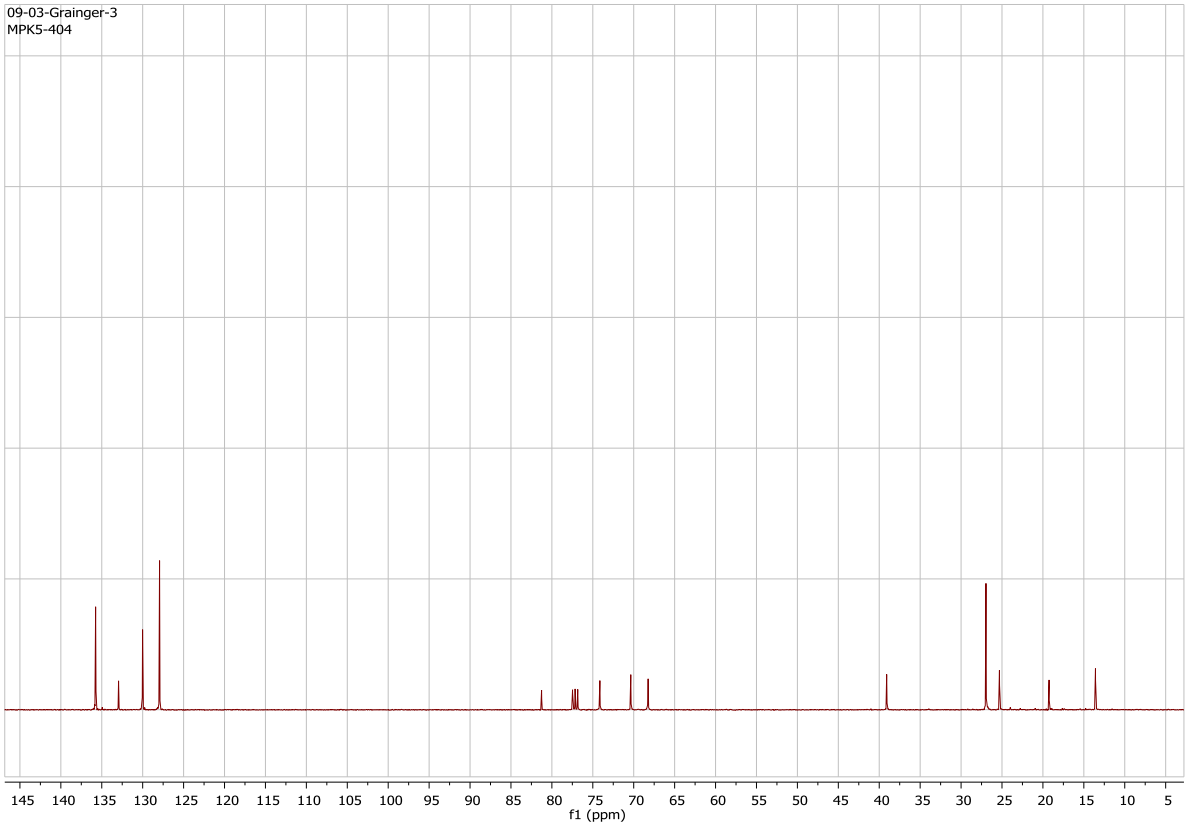
(*S*)-*tert*-Butyl((2-methylbut-3-en-1-yl)oxy)diphenylsilane **391**



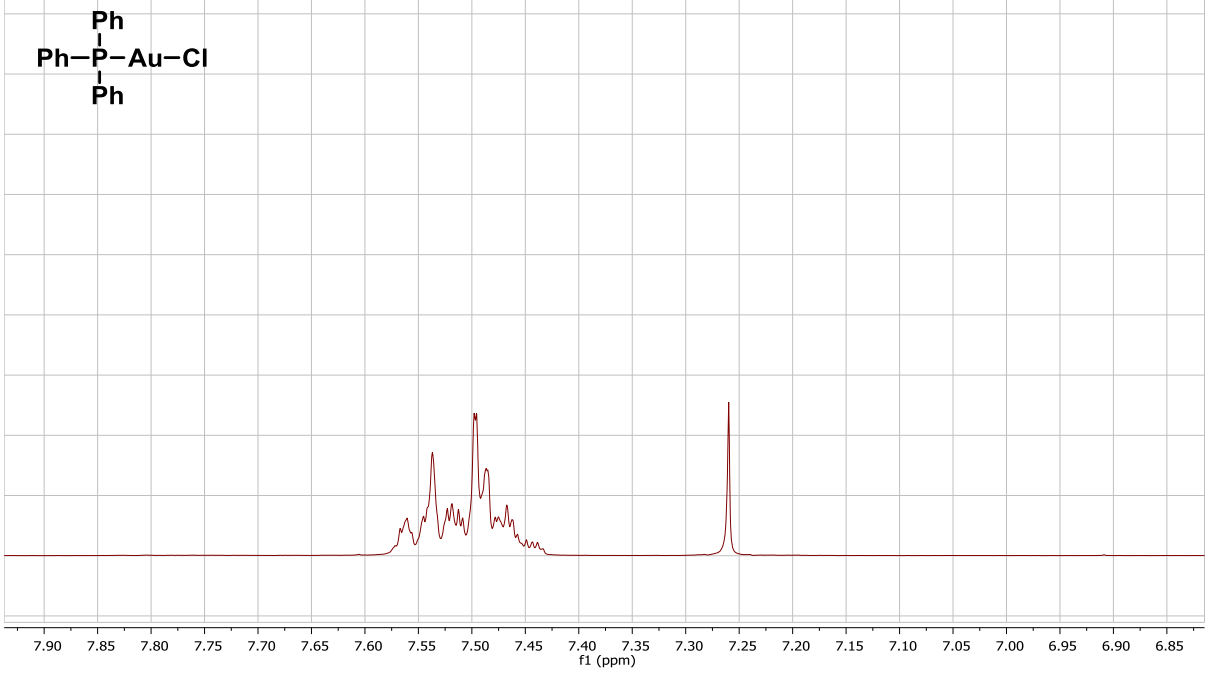


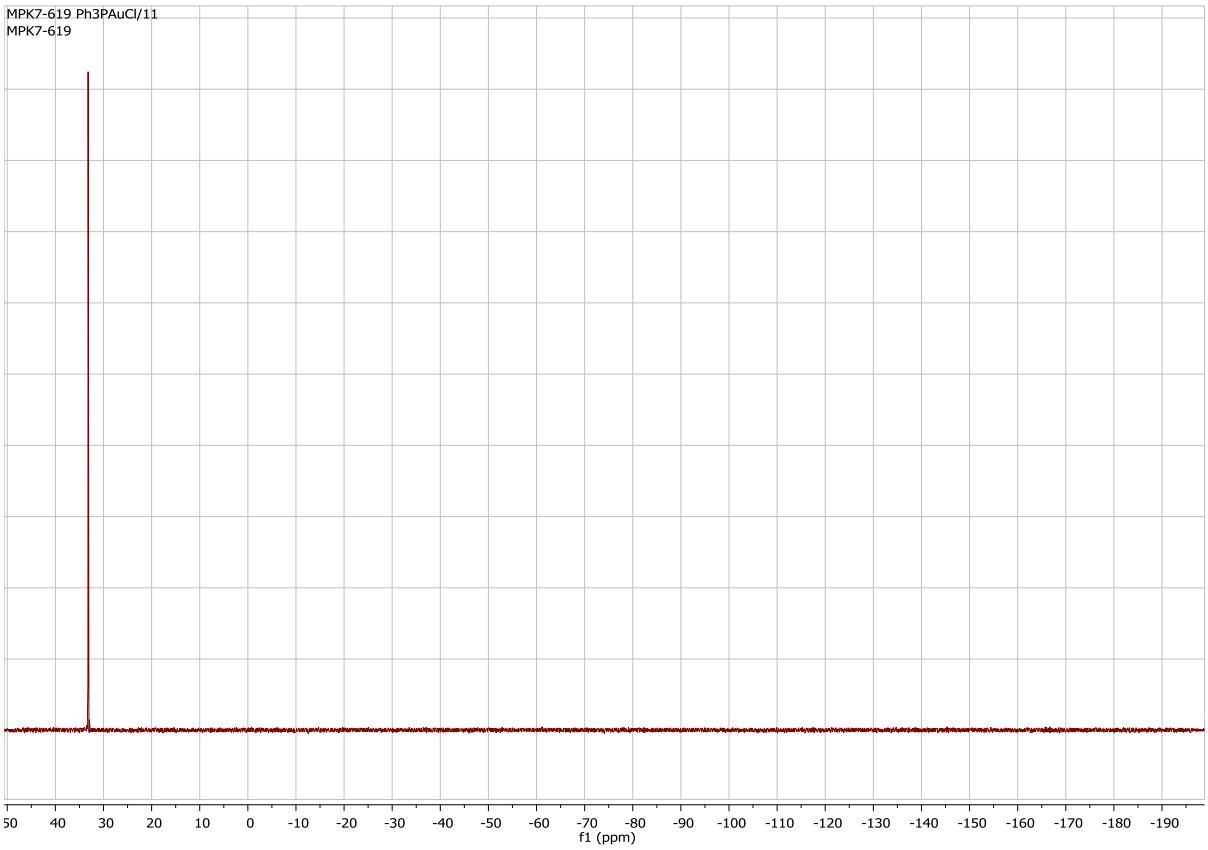
(2*S*,3*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhex-5-yn-3-ol **392**



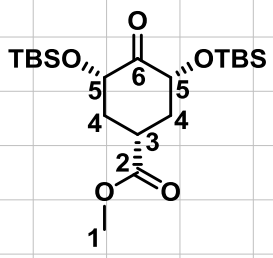


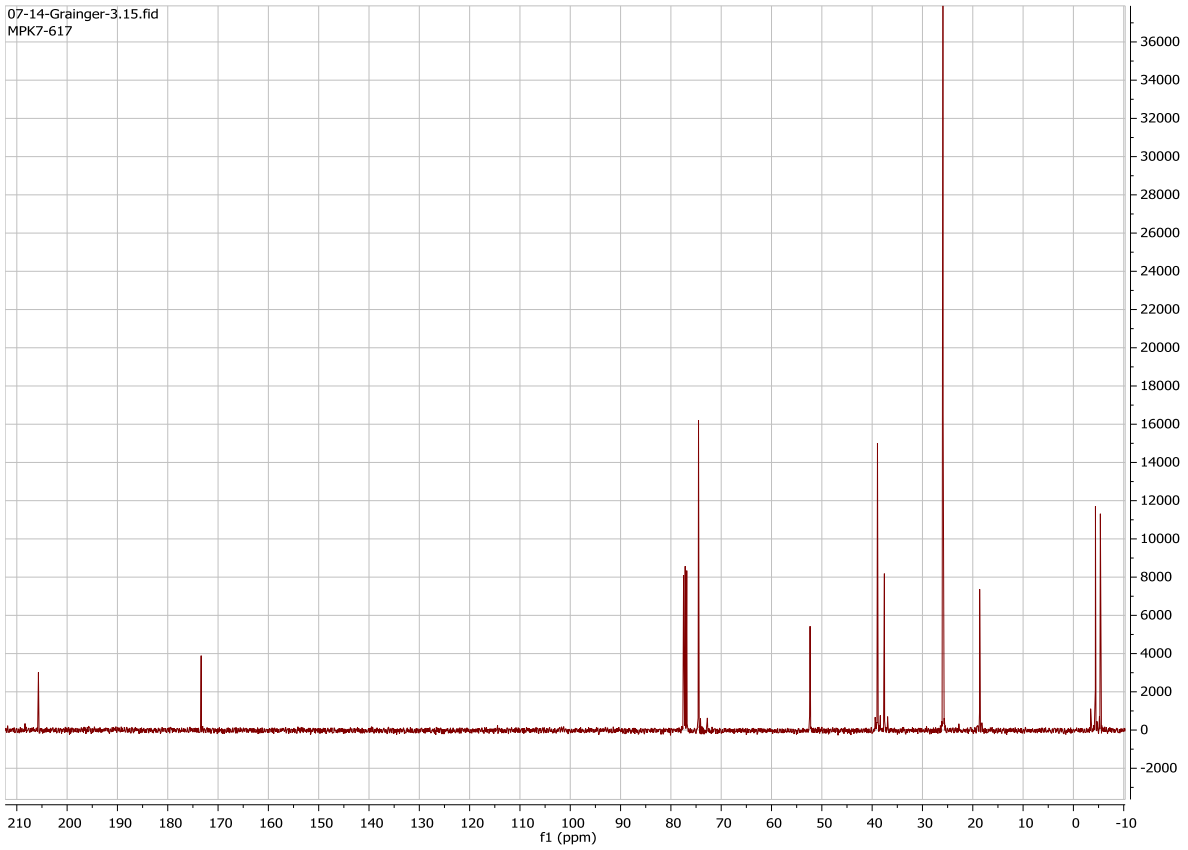
Chloro(triphenylphosphine)gold(I) **393**



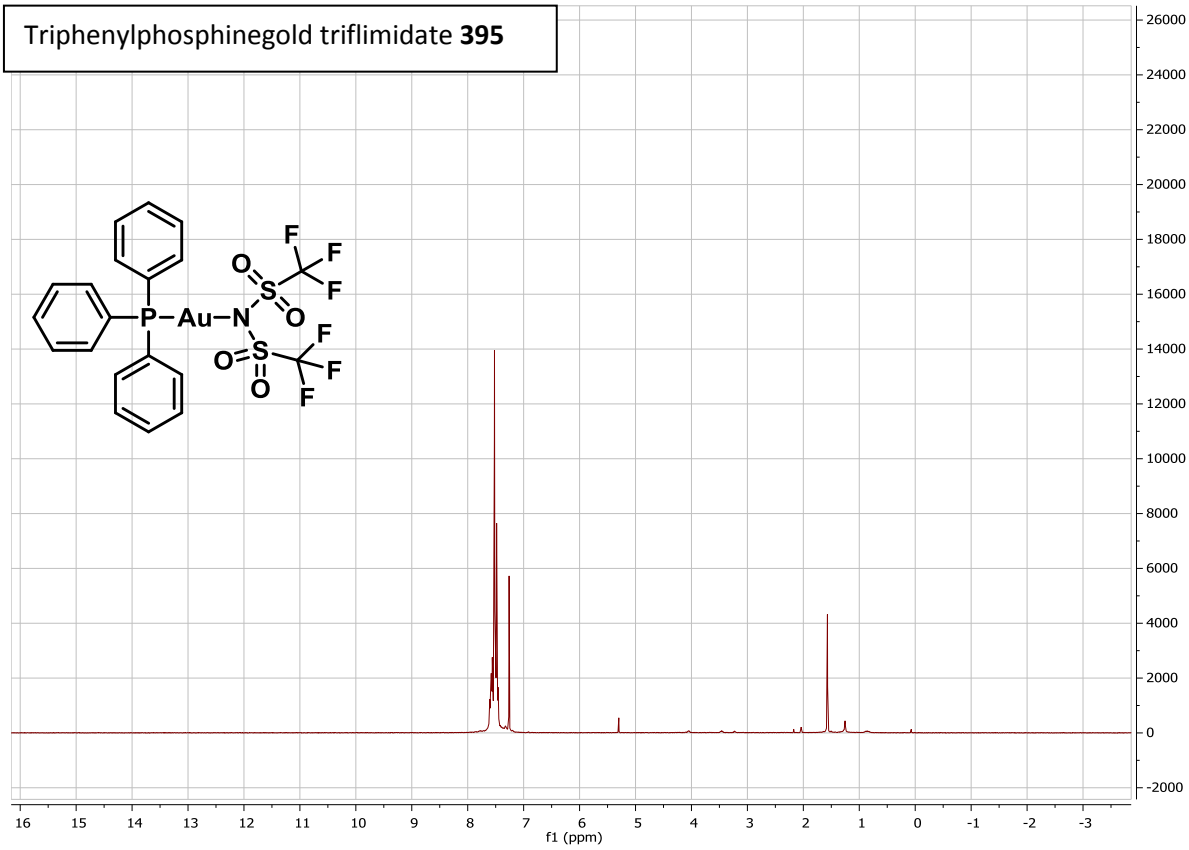


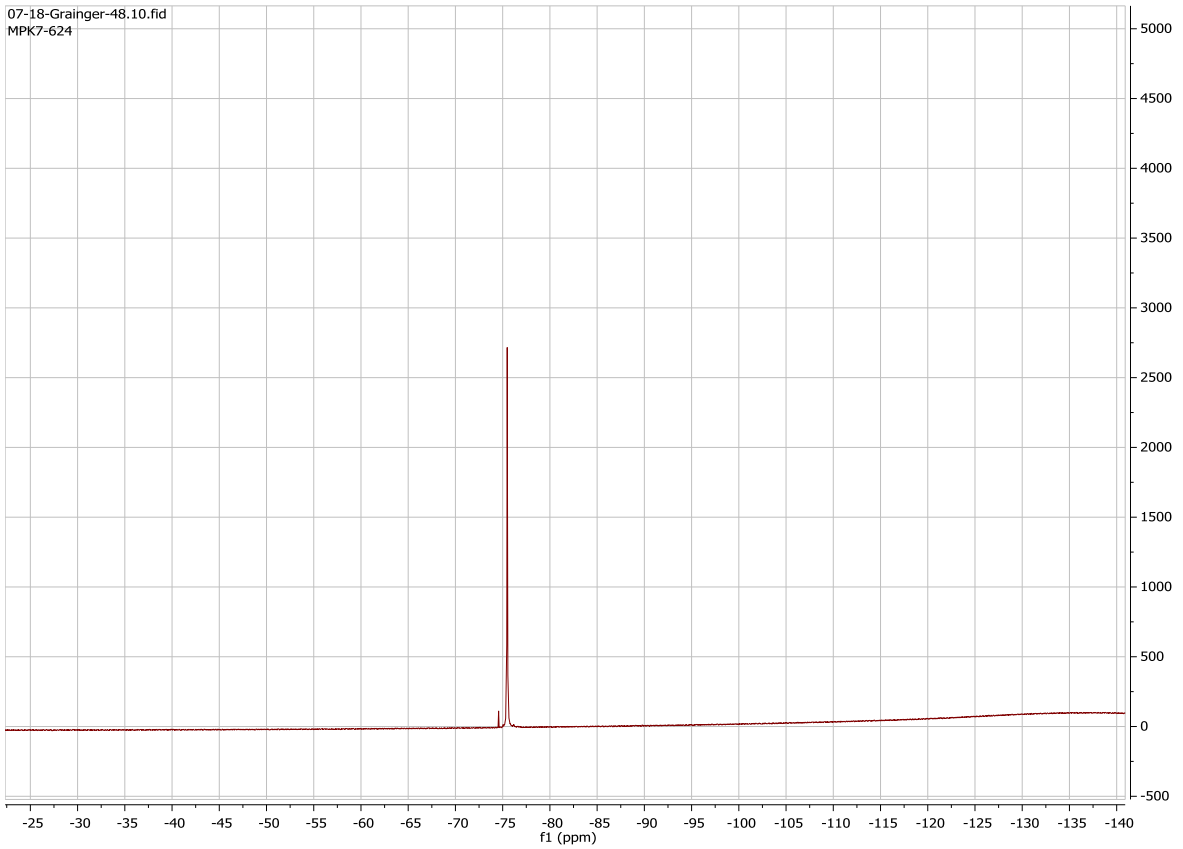
Methyl (1*R*,3*R*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexane-1-carboxylate **394**



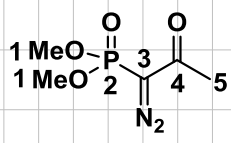


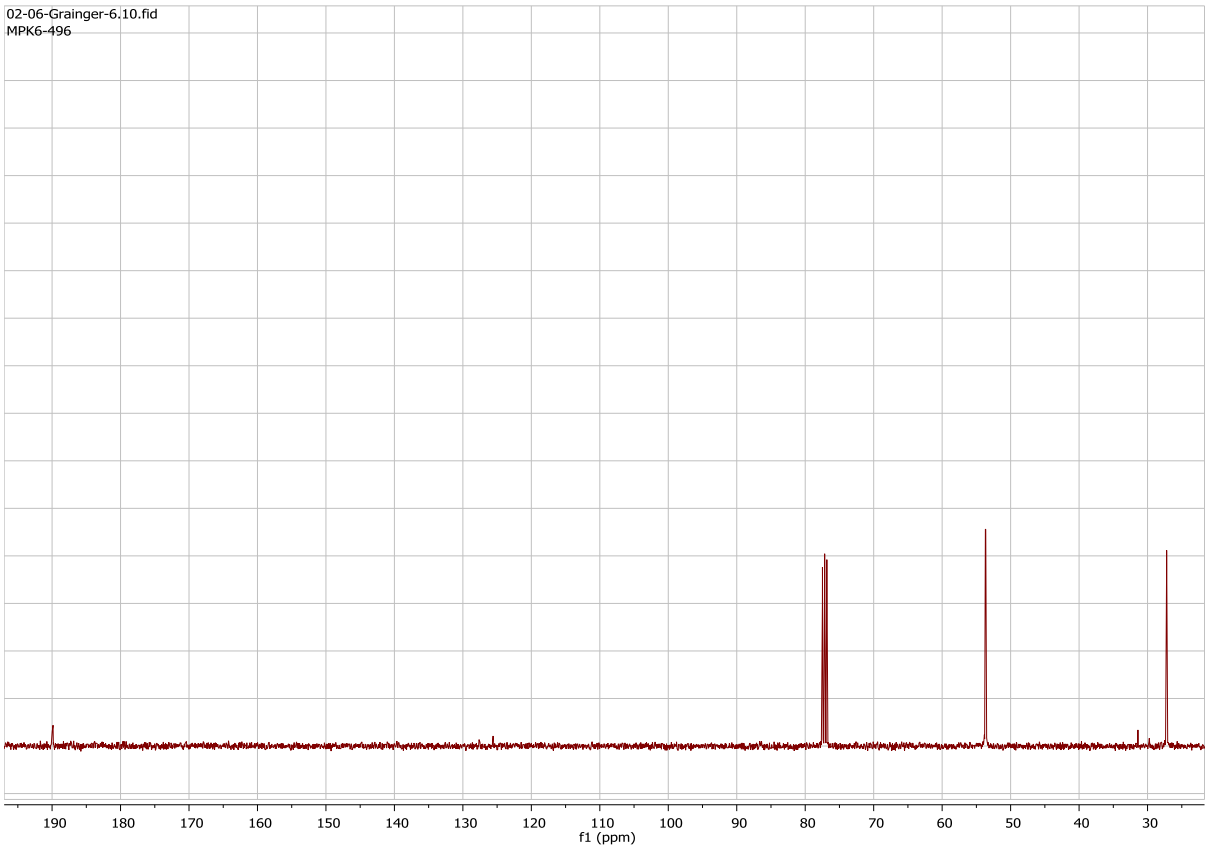
Triphenylphosphinegold triflimidate **395**

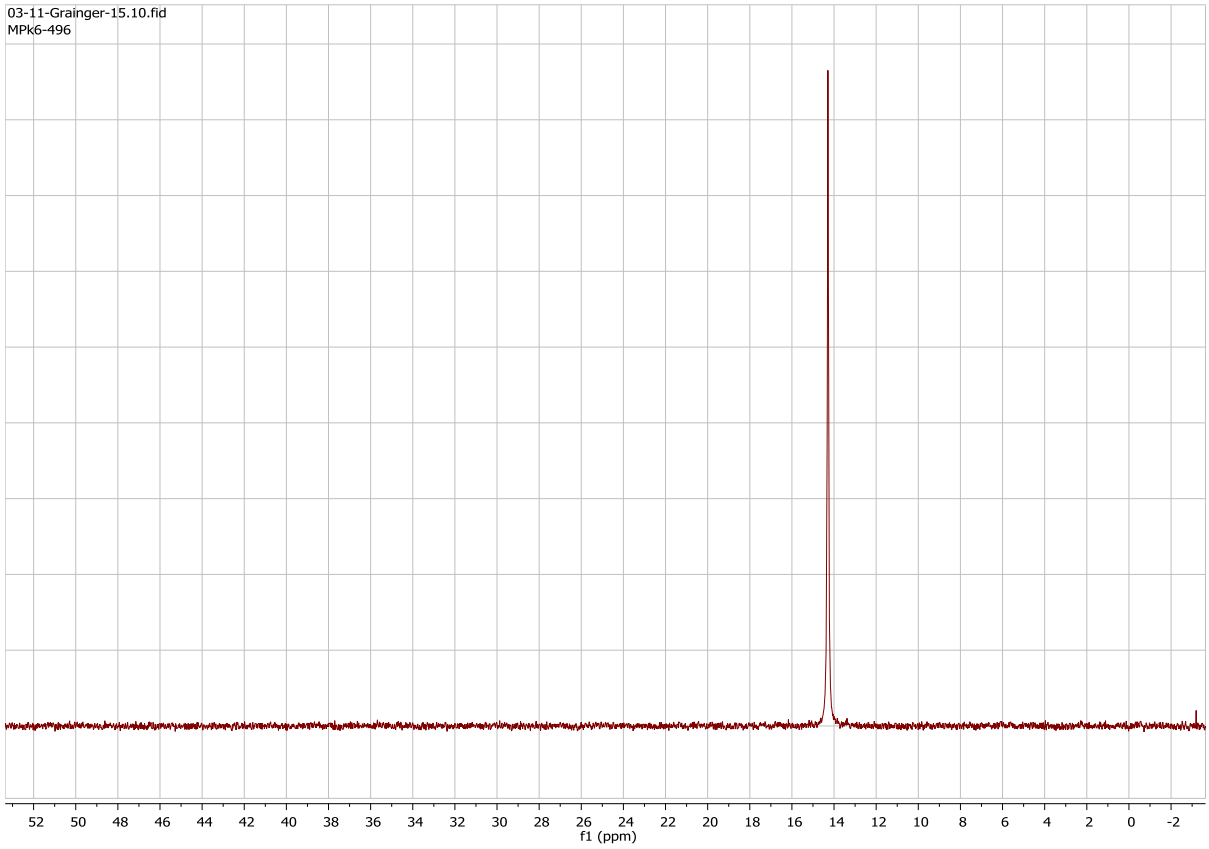




Dimethyl (1-diazo-2-oxopropyl)phosphonate **396**






03-11-Grainger-15.10.fid
MPk6-496
52 50 48 46 44 42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12 10 8 6 4 2 0 -2
f1 (ppm)

References

1. P. M. Pihko, T. K. Rissa and J. E. Aho, *Chem. Rev.*, 2005, **105**, 4406-4440.
2. M. A. Brimble and C. J. Bryant, *Chem. Commun.*, 2006, **43**, 4506-4508.
3. S. Takahashi, A. Toyoda, Y. Sekiyama, H. Takagi, T. Nogawa, M. Uramoto, R. Suzuki, H. Koshino, T. Kumano, S. Panthee, T. Dairi, J. Ishikawa, H. Ikeda, Y. Sakaki and H. Osada, *Nat. Chem. Biol.*, 2011, **7**, 461-468.
4. T. Shimizu, J. Kusaka, H. Ishiyama and T. Nakata, *Tetrahedron Lett.*, 2003, **44**, 4965-4968.
5. B. G. Davis and A. J. Fairbanks, *Carbohydrate Chemistry*, Oxford University Press, Oxford, 2002.
6. S. M. Kupchan, E. J. La Voie, A. R. Branfman, B. Y. Fei, W. M. Bright and R. F. Bryan, *J. Am. Chem. Soc.*, 1977, **99**, 3199-3201.
7. P. R. McGuirk and D. B. Collum, *J. Am. Chem. Soc.*, 1982, **104**, 4496-4497.
8. B.-W. A. Yeung, J. L. M. Contelles and B. Fraser-Reid, *Chem. Commun.*, 1989, 1160-1162.
9. D. R. Williams and S. Y. Sit, *J. Am. Chem. Soc.*, 1984, **106**, 2949-2954.
10. S. F. Martin, J. A. Colapret, M. S. Dappen, B. Dupre and C. J. Murphy, *J. Org. Chem.*, 1989, **54**, 2209-2216.
11. S. D. Burke, J. E. Cobb and K. Takeuchi, *J. Org. Chem.*, 1990, **55**, 2138-2151.
12. B. M. Trost and E. D. Edstrom, *Angew. Chem. Int. Ed.*, 1990, **29**, 520-522.
13. B. M. Trost and Y. Kondo, *Tetrahedron Lett.*, 1991, **32**, 1613-1616.
14. A. B. Smith, M. Fukui, H. A. Vaccaro and J. R. Empfield, *J. Am. Chem. Soc.*, 1991, **113**, 2071-2092.
15. M. A. Ciufolini, S. Zhu and M. V. Deaton, *J. Org. Chem.*, 1997, **62**, 7806-7811.
16. K. Sasaki and Y. Hirata, *Tetrahedron Lett.*, 1973, **14**, 2439-2442.
17. D. R. Williams, P. A. Jass, H. L. A. Tse and R. D. Gaston, *J. Am. Chem. Soc.*, 1990, **112**, 4552-4554.

18. A. B. Smith, J. R. Empfield, R. A. Rivero, H. A. Vaccaro, J. J. W. Duan and M. M. Sulikowski, *J. Am. Chem. Soc.*, 1992, **114**, 9419-9434.

19. S. D. Burke, J. J. Letourneau and M. A. Matulenko, *Tetrahedron Lett.*, 1999, **40**, 9-12.

20. S. Nishiyama, Y. Ikeda, S.-i. Yoshida and S. Yamamura, *Tetrahedron Lett.*, 1989, **30**, 105-108.

21. W. Yi-Fei, Z. Ying-Jun, K. Kitazato, L. Qing, Y. Chong-Ren, J. Jin-Hua, Z. Li-Yun, Z. Yan, W. Qing-Duan, L. Yi-Cheng, Q. Chui-Wen, R. Zhe, W. Xiao-Yan and W. Ya-Feng, *Antiviral Res.*, 2009, **84**, 150-158.

22. Y.-J. Zhang, C.-R. Yang, Y.-F. Wang, M.-Y. Zhang, R.-J. Chen, Y.-F. Wang and Q. Liu, *J. Nat. Prod.*, 2009, **72**, 969-972.

23. I. Kouno, C.-R. Yang, Y. Iwamoto, T. Tanaka and Y. J. Zhang, *J. Nat. Prod.*, 2000, **63**, 1507-1510.

24. I. Kouno, C.-R. Yang, Y. Iwamoto, T. Tanaka and Y.-J. Zhang, *Tetrahedron Lett.*, 2000, **41**, 1781-1784.

25. J.-J. Lv, S. Yu, Y.-F. Wang, D. Wang, H.-T. Zhu, R.-R. Cheng, C.-R. Yang, M. Xu and Y.-J. Zhang, *J. Org. Chem.*, 2014, **79**, 5432-5447.

26. T. C. Casey, J. Carlisle, P. Tisselli, L. Male, N. Spencer and R. S. Grainger, *J. Org. Chem.*, 2010, **75**, 7461-7464.

27. A. B. Smith and J. R. Empfield, *Chem. Pharm. Bull. (Tokyo)*, 1999, **47**, 1671-1678.

28. M. Malacria, L. Fensterbank, P. Devin and M. Chareyron, *Synlett*, 2000, 83-85.

29. A. Nishida, H. Takahashi, H. Takeda, N. Takada and O. Yonemitsu, *J. Am. Chem. Soc.*, 1990, **112**, 902-904.

30. J. T. Njardarson, I. M. McDonald, D. A. Spiegel, M. Inoue and J. L. Wood, *Org. Lett.*, 2001, **3**, 2435-2438.

31. H.-Y. Lee and B. G. Kim, *Org. Lett.*, 2000, **2**, 1951-1953.

32. J. Ardisson, J. P. Férézou, M. Julia and A. Pancrazi, *Tetrahedron Lett.*, 1987, **28**, 2001-2003.

33. G. Stork, S. Malhotra, H. Thompson and M. Uchibayashi, *J. Am. Chem. Soc.*, 1965, **87**, 1148-1149.

34. G. Pattenden and S. J. Teague, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1077-1083.

35. S. K. Pradhan, S. R. Kadam, J. N. Kolhe, T. V. Radhakrishnan, S. V. Sohani and V. B. Thaker, *J. Org. Chem.*, 1981, **46**, 2622-2633.

36. N. M. Teerhuis, I. A. M. Huisman and M. B. Groen, *Tetrahedron Lett.*, 2001, **42**, 2869-2871.

37. M. E. Jung and G. L. Hatfield, *Tetrahedron Lett.*, 1983, **24**, 3175-3178.

38. G. A. Molander and C. Kenny, *J. Am. Chem. Soc.*, 1989, **111**, 8236-8246.

39. G. A. Molander and C. R. Harris, *J. Am. Chem. Soc.*, 1996, **118**, 4059-4071.

40. C. S. Sang, H. Jin-Taik, K. Han-Young and H. C. Moon, *Tetrahedron Lett.*, 1990, **31**, 4765-4768.

41. J. E. Baldwin, S. C. MacKenzie Turner and M. G. Moloney, *Tetrahedron*, 1994, **50**, 9425-9438.

42. G. A. Molander and C. R. Harris, *J. Org. Chem.*, 1997, **62**, 2944-2956.

43. D. Belotti, J. Cossy, J. P. Pete and C. Portella, *J. Org. Chem.*, 1986, **51**, 4196-4200.

44. J. Cossy, D. Belotti and J. P. Pete, *Tetrahedron Lett.*, 1987, **28**, 4547-4550.

45. J. Cossy, D. Belotti and J. P. Pete, *Tetrahedron*, 1990, **46**, 1859-1870.

46. J. Cossy, A. Madaci and J.-P. Pete, *Tetrahedron Lett.*, 1994, **35**, 1541-1544.

47. E. Hasegawa, S. Takizawa, T. Seida, A. Yamaguchi, N. Yamaguchi, N. Chiba, T. Takahashi, H. Ikeda and K. Akiyama, *Tetrahedron*, 2006, **62**, 6581-6588.

48. T. Shono, I. Nishiguchi and H. Omizu, *Chem. Lett.*, 1976, 1233-1236.

49. E. Kariv-Miller and T. J. Mahachi, *J. Org. Chem.*, 1986, **51**, 1041-1045.

50. E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821-2824.

51. S. Jammi, J. Maury, J.-S. Suppo, M. P. Bertrand and L. Feray, *J. Org. Chem.*, 2013, **78**, 12566-12576.

52. N. Saito, Y. Sugimura and Y. Sato, *Org. Lett.*, 2010, **12**, 3494-3497.

53. J. E. Swartz, T. J. Mahachi and E. Kariv-Miller, *J. Am. Chem. Soc.*, 1988, **110**, 3622-3628.

54. K. Takai, S. Sakamoto, T. Isshiki and T. Kokumai, *Tetrahedron*, 2006, **62**, 7534-7539.

55. H. Tsukamoto, T. Ueno and Y. Kondo, *J. Am. Chem. Soc.*, 2006, **128**, 1406-1407.

56. K. Shen, X. Han and X. Lu, *Org. Lett.*, 2013, **15**, 1732-1735.

57. Jang, *Bull. Korean Chem. Soc.*, 2010, **31**, 2085.

58. R. Tanaka, K. Noguchi and K. Tanaka, *J. Am. Chem. Soc.*, 2010, **132**, 1238-1239.

59. J. U. Rhee and M. J. Krische, *J. Am. Chem. Soc.*, 2006, **128**, 10674-10675.

60. N. Morlender-Vais, N. Solodovnikova and I. Marek, *Chem. Commun.*, 2000, 1849-1850.

61. W. E. Crowe and M. J. Rachita, *J. Am. Chem. Soc.*, 1995, **117**, 6787-6788.

62. J. Muñoz-Bascón, C. Hernández-Cervantes, N. M. Padial, M. Álvarez-Corral, A. Rosales, I. Rodríguez-García and J. E. Oltra, *Chem. Eur. J.*, 2014, 801-810.

63. C. Schafer, M. Miesch and L. Miesch, *Org. Biomol. Chem.*, 2012, **10**, 3253-3257.

64. C. F. Heinrich, M. Miesch and L. Miesch, *Org. Biomol. Chem.*, 2015, **13**, 2153-2156.

65. X.-Q. Tang and J. Montgomery, *J. Am. Chem. Soc.*, 2000, **122**, 6950-6954.

66. G. M. Mahandru, G. Liu and J. Montgomery, *J. Am. Chem. Soc.*, 2004, **126**, 3698-3699.

67. M. Lozanov and J. Montgomery, *Tetrahedron Lett.*, 2001, **42**, 3259-3261.

68. C. Heiss and R. S. Phillips, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2821-2825.

69. D. C. Forbes, D. G. Doina and M. P. Doyle, *Synthesis*, 1998, 879-882.

70. G. Grue-Soerensen, I. M. Nielsen and C. K. Nielsen, *J. Med. Chem.*, 1988, **31**, 1174-1178.

71. L. Provencher, H. Wynn, J. B. Jones and A. R. Krawczyk, *Tetrahedron: Asymmetry*, 1993, **4**, 2025-2040.

72. J. A. Marshall and T. M. Warne, *J. Org. Chem.*, 1971, **36**, 178-183.

73. T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357-1358.

74. A. Jégou, C. Pacheco and A. Veyrières, *Tetrahedron*, 1998, **54**, 14779-14790.

75. R. Pappo, J. D. S. Allen, R. U. Lemieux and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478-479.

76. W. Yu, Y. Mei, Y. Kang, Z. Hua and Z. Jin, *Org. Lett.*, 2004, **6**, 3217-3219.

77. V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, **17**, 1973-1976.

78. C. Francavilla, W. Chen and F. R. Kinder, *Org. Lett.*, 2003, **5**, 1233-1236.

79. K. C. Nicolaou, V. A. Adsool and C. R. H. Hale, *Org. Lett.*, 2010, **12**, 1552-1555.

80. G. Cruciani and P. Margaretha, *J. Fluorine Chem.*, 1987, **37**, 95-101.

81. C. H. B. R. G. W. Norrish, *Nature*, 1934, **138**, 1016.

82. V. A. Ignatenko and G. P. Tochtrop, *J. Org. Chem.*, 2013, **78**, 3821-3831.

83. K. Iida, M. Saito and M. Yoshioka, *J. Org. Chem.*, 2000, **65**, 4909-4912.

84. B. Makino, M. Kawai, K. Kito, H. Yamamura and Y. Butsugan, *Tetrahedron*, 1995, **51**, 12529-12538.

85. P. J. Wagner, M. A. Meador and B. S. Park, *J. Am. Chem. Soc.*, 1990, **112**, 5199-5211.

86. T. Sugimura and L. A. Paquette, *J. Am. Chem. Soc.*, 1987, **109**, 3017-3024.

87. P. De Mayo and R. Suau, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2559-2561.

88. P. De Mayo and R. Suau, *J. Am. Chem. Soc.*, 1974, **96**, 6807-6809.

89. S. W. Benson and G. B. Kistiakowsky, *J. Am. Chem. Soc.*, 1942, **64**, 80-86.

90. F. E. Blacet and A. Miller, *J. Am. Chem. Soc.*, 1957, **79**, 4327-4329.

91. T. C. Casey, PhD, University of Birmingham, 2012.

92. M. U. Roslund, O. Aitio, J. Wärnå, H. Maaheimo, D. Y. Murzin and R. Leino, *J. Am. Chem. Soc.*, 2008, **130**, 8769-8772.

93. L. Brecker, M. Mahut, A. Schwarz and B. Nidetzky, *Magn. Reson. Chem.*, 2009, **47**, 328-332.

94. E. A. Pritchina, N. P. Gritsan, G. T. Burdzinski and M. S. Platz, *J. Phys. Chem. A*, 2007, **111**, 10483-10489.

95. D. K. Barma, A. Bandyopadhyay, J. H. Capdevila and J. R. Falck, *Org. Lett.*, 2003, **5**, 4755-4757.

96. V. Saikam, R. Raghupathy, M. Yadav, V. Gannedi, P. P. Singh, N. A. Qazi, S. D. Sawant and R. A. Vishwakarma, *Tetrahedron Lett.*, 2011, **52**, 4277-4279.

97. P. Andersch and M. P. Schneider, *Tetrahedron: Asymmetry*, 1996, **7**, 349-352.

98. J.-M. Galano, G. Audran and H. Monti, *Tetrahedron*, 2000, **56**, 7477-7481.

99. D. H. R. Barton and B. J. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1970, 1225-1226.

100. P. Metzner, in *Organosulfur Chemistry I*, ed. P. B. Page, Springer Berlin Heidelberg, 1999, vol. 204, ch. 2, pp. 127-181.

101. B. S. Pedersen, S. Scheibye, N. H. Nilsson and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, **87**, 223-228.

102. T. Kurz, M. Khankischpur and K. Widyan, *Tetrahedron Lett.*, 2006, **47**, 4241-4243.

103. K. H. Meyer and K. Schuster, *Chem. Ber.*, 1922, **55**, 819-823.

104. D. A. Engel and G. B. Dudley, *Org. Biomol. Chem.*, 2009, **7**, 4149-4158.

105. W. Baur, *Acta Crystallogr. Sect. B*, 1977, **33**, 2615-2619.

106. M. Yu, G. Li, S. Wang and L. Zhang, *Adv. Synth. Catal.*, 2007, **349**, 871-875.

107. B. Yu, X.-J. Shi, J.-l. Ren, X.-N. Sun, P.-P. Qi, Y. Fang, X.-W. Ye, M.-M. Wang, J.-W. Wang, E. Zhang, D.-Q. Yu and H.-M. Liu, *Eur. J. Med. Chem.*, 2013, **66**, 171-179.

108. C. Yang, Y. Shao, X. Zhi, Q. Huan, X. Yu, X. Yao and H. Xu, *Biorg. Med. Chem. Lett.*, 2013, **23**, 4806-4812.

109. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1-S19.

110. M. N. Pennell, M. G. Unthank, P. Turner and T. D. Sheppard, *J. Org. Chem.*, 2011, **76**, 1479-1482.

111. M. Kutscheroff, *Chem. Ber.*, 1881, **14**, 1540-1542.

112. Y. Xu, X. Hu, J. Shao, G. Yang, Y. Wu and Z. Zhang, *Green Chem.*, 2015, **17**, 532-537.

113. K. Okada, Y. Hosoda and M. Oda, *J. Am. Chem. Soc.*, 1986, **108**, 321-322.

114. P. Paetzold, S. Neyses and L. Géret, *Z. Anorg. Allg. Chem.*, 1995, **621**, 732-736.

115. C. A. Coulson and T. W. Dingle, *Acta Crystallogr. Sect. B*, 1968, **24**, 153-155.

116. C. Körner, P. Starkov and T. D. Sheppard, *J. Am. Chem. Soc.*, 2010, **132**, 5968-5969.

117. D. A. Evans, J. V. Nelson, E. Vogel and T. R. Taber, *J. Am. Chem. Soc.*, 1981, **103**, 3099-3111.

118. H. Zheng, M. Lejkowski and D. G. Hall, *Chem. Sci.*, 2011, **2**, 1305-1310.

119. J. K. Crandall, D. J. Batal, D. P. Sebesta and F. Lin, *J. Org. Chem.*, 1991, **56**, 1153-1166.

120. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847-2853.

121. R. Sharma, M. Manpadi, Y. Zhang, H. Kim, N. G. Ahkmedov and L. J. Williams, *Org. Lett.*, 2011, **13**, 3352-3355.

122. S. Braverman and Y. Duar, *J. Am. Chem. Soc.*, 1983, **105**, 1061-1063.

123. S. Kamijo, T. Hoshikawa and M. Inoue, *Tetrahedron Lett.*, 2010, **51**, 872-874.

124. P. A. Byrne, K. V. Rajendran, J. Muldoon and D. G. Gilheany, *Org. Biomol. Chem.*, 2012, **10**, 3531-3537.

125. D. Habrant, V. Rauhala and A. M. P. Koskinen, *Chem. Soc. Rev.*, 2010, **39**, 2007-2017.

126. E. W. Colvin and B. J. Hamill, *Chem. Commun.*, 1973, 151-152.

127. K. Konno, T. Fujishima, S. Maki, Z. Liu, D. Miura, M. Chokki, S. Ishizuka, K. Yamaguchi, Y. Kan, M. Kurihara, N. Miyata, C. Smith, H. F. DeLuca and H. Takayama, *J. Med. Chem.*, 2000, **43**, 4247-4265.

128. O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2380-2382.

129. H. Zhao, D. W. Engers, C. L. Morales and B. L. Pagenkopf, *Tetrahedron*, 2007, **63**, 8774-8780.

130. R. A. Whitney, *Can. J. Chem.*, 1983, **61**, 1158-1160.

131. S. F. Martin, B. G. Anderson, D. Daniel and A. Gaucher, *Tetrahedron*, 1997, **53**, 8997-9006.

132. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807-7808.

133. R. J. Linderman, N. S. Cutshall and B. T. Becicka, *Tetrahedron Lett.*, 1994, **35**, 6639-6642.

134. R. S. Grainger, P. Tisselli and J. W. Steed, *Org. Biomol. Chem.*, 2004, **2**, 151-153.

135. D. N. Jones, D. R. Hill, D. A. Lewton and C. Sheppard, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1574-1587.

136. M. E. Bunnage, S. G. Davies, P. M. Roberts, A. D. Smith and J. M. Withey, *Org. Biomol. Chem.*, 2004, **2**, 2763-2776.

137. Z. Li, G. D. Francisco, W. Hu, P. Labthavikul, P. J. Petersen, A. Severin, G. Singh, Y. Yang, B. A. Rasmussen, Y.-I. Lin, J. S. Skotnicki and T. S. Mansour, *Biorg. Med. Chem. Lett.*, 2003, **13**, 2591-2594.

138. D. B. Li, M. Rogers-Evans and E. M. Carreira, *Org. Lett.*, 2013, **15**, 4766-4769.

139. H.-J. Liu and T. K. Ngooi, *Can. J. Chem.*, 1982, **60**, 437-439.

140. R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, 1946, **68**, 2229-2235.

141. N. Baricordi, S. Benetti, V. Bertolasi, C. De Risi, G. P. Pollini, F. Zamberlan and V. Zanirato, *Tetrahedron*, 2012, **68**, 208-213.

142. C. J. O' Connor, M. D. Roydhouse, A. M. Przybył, M. D. Wall and J. M. Southern, *J. Org. Chem.*, 2010, **75**, 2534-2538.

143. C. Xu, J. Du, L. Ma, G. Li, M. Tao and W. Zhang, *Tetrahedron*, 2013, **69**, 4749-4757.

144. S. Vivek Kumar, P. Prasanna and S. Perumal, *Tetrahedron Lett.*, 2013, **54**, 6651-6655.

145. J.-B. Ling, Y. Su, H.-L. Zhu, G.-Y. Wang and P.-F. Xu, *Org. Lett.*, 2012, **14**, 1090-1093.

146. M. Hans, L. Delaude, J. Rodriguez and Y. Coquerel, *J. Org. Chem.*, 2014, **79**, 2758-2764.

147. K. Paulvannan, R. Hale, R. Mesis and T. Chen, *Tetrahedron Lett.*, 2002, **43**, 203-207.

148. Z. M. Fresco, I. Suez, S. A. Backer and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2004, **126**, 8374-8375.

149. H. O. Hankovszky, K. Hideg and G. Jerkovich, *Synthesis*, 1989, 526-529.

150. M. Capuzzi, D. Perdicchia and K. A. Jørgensen, *Chem. Eur. J.*, 2008, 128-135.

151. F. K. Hansen, M. Khankischpur, I. Tolaymat, R. Mesaros, G. Dannhardt and D. Geffken, *Biorg. Med. Chem. Lett.*, 2012, **22**, 5031-5034.

152. F. Duus, *Tetrahedron*, 1981, **37**, 2633-2640.

153. J.-P. Surivet and J.-M. Vatèle, *Tetrahedron*, 1999, **55**, 13011-13028.

154. S. N. Müller, R. Batra, M. Senn, B. Giese, M. Kisel and O. Shadyro, *J. Am. Chem. Soc.*, 1997, **119**, 2795-2803.

155. S. Brass, N.-S. Chan, C. Gerlach, T. Luksch, J. Böttcher and W. E. Diederich, *J. Organomet. Chem.*, 2006, **691**, 5406-5422.

156. P. D. Thornton, T. S. Cameron and D. J. Burnell, *Org. Biomol. Chem.*, 2011, **9**, 3447-3456.

157. T. Pospieszny, H. Koenig and B. Brycki, *Tetrahedron Lett.*, 2013, **54**, 4700-4704.

158. H. Zhang, H. Tanimoto, T. Morimoto, Y. Nishiyama and K. Kakiuchi, *Org. Lett.*, 2013, **15**, 5222-5225.

159. M. Rubina, M. Conley and V. Gevorgyan, *J. Am. Chem. Soc.*, 2006, **128**, 5818-5827.

160. S. Ma, B. Wu, X. Jiang and S. Zhao, *J. Org. Chem.*, 2005, **70**, 2568-2575.

161. S. P. Lewis, J. Chai, S. Collins, T. J. J. Sciarone, L. D. Henderson, C. Fan, M. Parvez and W. E. Piers, *Organometallics*, 2009, **28**, 249-263.

162. S. Braverman and M. Cherkinsky, *[2,3]Sigmatropic Rearrangements of Propargylic and Allenic Systems* Springer-Verlag Berlin Heidelberg, Online, 2006.

163. S. Müller, B. Liepold, G. J. Roth and H. J. Bestmann, *Synlett*, 1996, **1996**, 521-522.

164. C. Mukai, H. Yamashita, M. Sassa and M. Hanaoka, *Tetrahedron*, 2002, **58**, 2755-2762.

165. S. Khumsubdee, H. Zhou and K. Burgess, *J. Org. Chem.*, 2013, **78**, 11948-11955.

166. M. Amat, F. Arioli, M. Pérez, E. Molins and J. Bosch, *Org. Lett.*, 2013, **15**, 2470-2473.

167. O. Z. Pereira and T. H. Chan, *J. Org. Chem.*, 1994, **59**, 6710-6716.

168. A. F. Moretto, S. J. Kirincich, W. X. Xu, M. J. Smith, Z. K. Wan, D. P. Wilson, B. C. Follows, E. Binnun, D. Joseph-McCarthy, K. Foreman, D. V. Erbe, Y. L. Zhang, S. K. Tam, S. Y. Tam and J. Lee, *Biorg. Med. Chem.*, 2006, **14**, 2162-2177.

169. J. Liu and J. K. De Brabander, *J. Am. Chem. Soc.*, 2009, **131**, 12562-12563.

170. W. J. Vloon, J. C. van den Bos, G.-J. Koomen and U. K. Pandit, *Tetrahedron*, 1992, **48**, 8317-8328.

171. Q. Li, S. Mao, Y. Cui and Y. Jia, *J. Org. Chem.*, 2012, **77**, 4111-4116.

172. R. Bhuniya and S. Nanda, *Tetrahedron*, 2013, **69**, 1153-1165.

173. G. Sourkouni-Argirusi and A. Kirschning, *Org. Lett.*, 2000, **2**, 3781-3784.

174. H. Lebel and V. Paquet, *J. Am. Chem. Soc.*, 2004, **126**, 320-328.

175. S. S. Zalesskiy, A. E. Sedykh, A. S. Kashin and V. P. Ananikov, *J. Am. Chem. Soc.*, 2013, **135**, 3550-3559.

176. T. Iwai, H. Okochi, H. Ito and M. Sawamura, *Angew. Chem. Int. Ed.*, 2013, **52**, 4239-4242.

177. P. Gallant, L. D'Haenens and M. Vandewalle, *Synth. Commun.*, 1984, **14**, 155-161.

178. J. Pietruszka and A. Witt, *Synthesis*, 2006, 4266-4268.