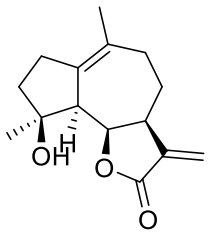
Total Synthesis of Complex Polycyclic Natural Products

Using a Novel Cascade Reaction



Arwa Alqahtani

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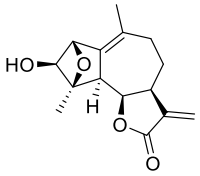
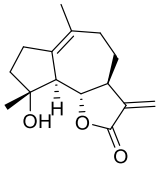
School of Chemistry
College of Science and Engineering
University of Glasgow

Abstract

The guaianolides comprise a large family of natural products, which includes moroccolide A and micheliolide. The guaianolide natural products contain a 5,7,5 fused tricyclic system. Members of the guaianolide family of natural products have been shown to exhibit potent biological activities following their discovery. Extensive studies have been performed to establish the biomolecular mechanisms responsible for the biological activities of these compounds and assess their potential use as prophylactic and therapeutic agents.



moroccolide A



micheliolide

The significant synthetic challenges presented by the guaianolides combined with their biological activities make them interesting targets. There have been numerous syntheses of the structurally related guaianolides family, but to date no total synthesis have been reported for either moroccolide A or micheliolide, due the complexity of their structures, and only a semi-synthesis of micheliolide has been attempted. With this in mind, a synthetic strategy has been developed for formation of the 5,7,5 fused tricyclic core of both natural products by application of a reaction sequence developed previously within the Clark group. This involved several key transformations including a ynenone formation, Brønsted acid mediated cyclisation to form furan followed by [3,3]-sigmatropic Cope rearrangement to construct the tricyclic core of both guaianolides.

This thesis presents a synthetic strategy for guaianolide synthesis and progress toward testing the effectiveness of this synthetic strategy for rapid construction of the tricyclic core structures from simple starting materials. After an appropriate model system had been tested, the methodology was to be applied to the synthesis of the natural products micheliolide and moroccolide A. This will be the first attempted total synthesis toward both morocolide A and micheliolide.

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Acknowledgements

I would like to express my greatest appreciation towards my academic supervisor Professor J. Stephen Clark whose help and encouragement has been incredibly beneficial towards the research within this thesis. The opportunity to work in his group on such an exciting and rewarding project won't be forgotten anytime in the future.

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A particular note of thanks goes to the proof readers of this thesis, Sophie and Dan . I cannot thank you enough for all your help!

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that the substance of this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Arwa Alqahtani

Prof. J. Stephen Clark

Abbreviation

Ac	acetyl
ACDC	asymmetric counteranion-directed catalysis
aq.	aqueous
Ar	aryl
ATR	attenuated total reflectance
BINOL	1,1’-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinone
brsm	based on recovered starting material
Bu	*n*-butyl
Bz	benzoyl
CI	chemical ionisation
CSA	camphorsulfonic acid
decomp.	decomposition
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DOSP	*N*-(*p*-dodecylphenylsulfonyl)prolinato]
dr	diastereomeric ratio
ee	enantiomeric ratio

DVCPR	divinylcyclopropane rearrangement
EE	Ethoxyethyl
ESI	electrospray ionisation
EI	electron-impact ionisation
Et	ethyl
EWG	electron-withdrawing group
FTIR	Fourier transform infrared spectroscopy
GSK	GlaxoSmithKline
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMRS	high-resolutions mass spectrometry
HPLC	high performance liquid chromatography
i	iso
IPr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]
leu	leucine
Me	methyl
MDR	multiple-drug resistant
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
n	normal (e.g. unbranched alkyl chain)
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
p	para
Ph	phenyl
PMB	*p*-methoxybenzyl

PPTS	pyridinium *p*-toluenesulfonate
Pr	*n*-propyl
PTC	phase-transfer catalyst
Pyr	pyridine
R	generalised group
Rf	retention factor in chromatography
rt	room temperature
SES	2-(trimethylsilyl)ethanesulfonyl
SM	starting material
t	*tert*
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
Tc	trichloro
TEBAC	benzyltriethylammonium chloride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THT	tetrahydrothiophene
TIPB	triisopropylbenzene
TLC	thin layer chromatography
TMS	trimethylsilyl
TRIP-H	3,3’-bis(2,4,6-triisopropylphenyl)-1,1’-binaphthyl-2,2’-diyl

	hydrogenphosphate
Ts	tosyl
UV	ultraviolet
ACPs	alkylidene cyclopropanes

1. Introduction

1.1 Guaianolides

The guaianolides are one of the most abundant families of natural products. The biological effects of members of this family include potent antitumor and anti-inflammatory activities, which makes the compounds interesting in the pharmaceutical field.[1] The general structure of the family is based on a 5,7,5-ring system and it can be split into three main subclasses, the most common of which are the guaian-6,12-olides and guaian-8,12-olides.[2] The seco-guaianolides lack the central seven-membered ring and are the least common sub-group within the guaianolide family. The difference between the guaian-6,12-olides and the guaian-8,12-olides is the site of the fused γ-butyrolactone – the guaian-6,12-olides have an angular structure whereas the guaian-8,12-olides are linear guaianolides (Figure 1).

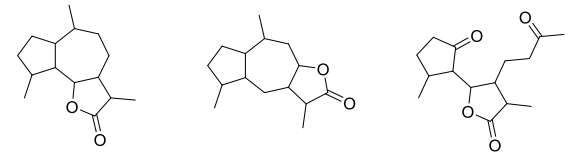


Figure 1

1.2 Biological properties of Guaianolides

The guaianolides have been shown to exhibit potent biological activities since their discovery and some examples are shown in (Figure 2).[3,4,5] The cytotoxic and anti-inflammatory activities of members of this family depend on the α,β-unsaturated carbonyl functionality, which suggests that the cyclopentenone and α-methylene-γ-lactone groups undergo nucleophilic attack by cellular components.[6]

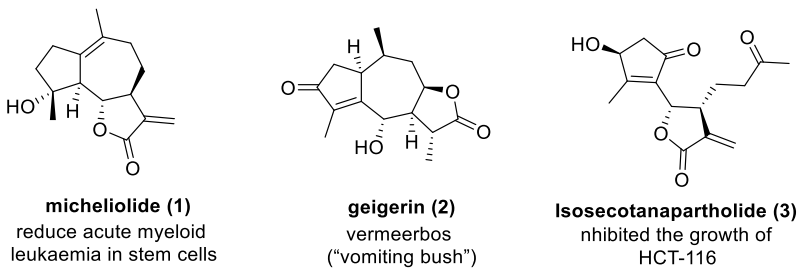


Figure 2

In 2001, Hilmi and co-workers isolated six new cytotoxic guaianolide compounds from the leaves of the *Warionia saharae* plant, found in Morocco and Algeria (Figure 3).[7] Two of the isolated compounds contain 6,7-*trans* fused lactone rings (**4** and **5**) and four of them contain a 6,7-*cis* fused lactone, which is a rare configuration, and features an ether bridge between C-2 and C-4 to give an oxetane (**6**-**9**).

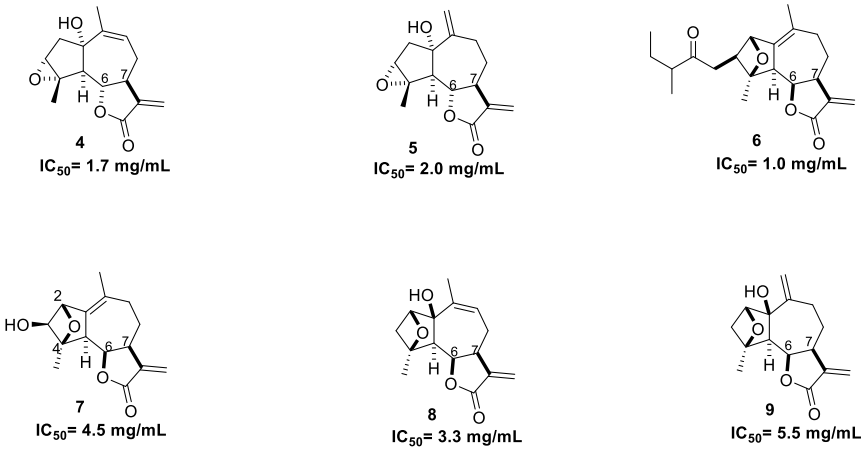


Figure 3

These compounds exhibit significant cytotoxicity against the KB cancer cell line. The compounds also possess other significant biological activities including anti-inflammatory, antimicrobial, antiviral and anti-feedant properties. They are also display cytotoxic activity against various tumour cell lines, have fungicidal activity and show potential allelopathy amongst other bioactivities. Chen and co-workers found that micheliolide (MCL) **1**, can be used to reduce the proportion of acute myeloid leukaemia (AML) stem cells ($CD34^+$ $CD38^-$) in primary AML cells (Figure 4).[3,8] DMAMCL (the dimethylamino Michael adduct of MCL) releases MCL in vivo and in plasma and showed noticeable therapeutic efficacy in non-obese diabetic/severe combined immunodeficiency AML mouse models. These findings indicate that guaianolide sesquiterpene lactones (GSL) function as chemical agents against AML stem cells or progenitor cells and that guaianolide sesquiterpene lactones are potentially highly useful for the exploration of anti-cancer stem cell (CSC) approaches. A potential consequence of this fact is that the polycyclic core could be used as a scaffold for the development of novel drug candidates.

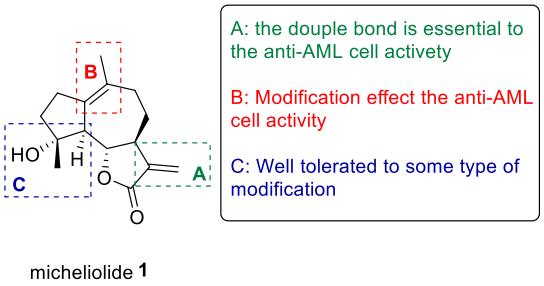


Figure 4

1.3 Synthesis of guaianolide natural products

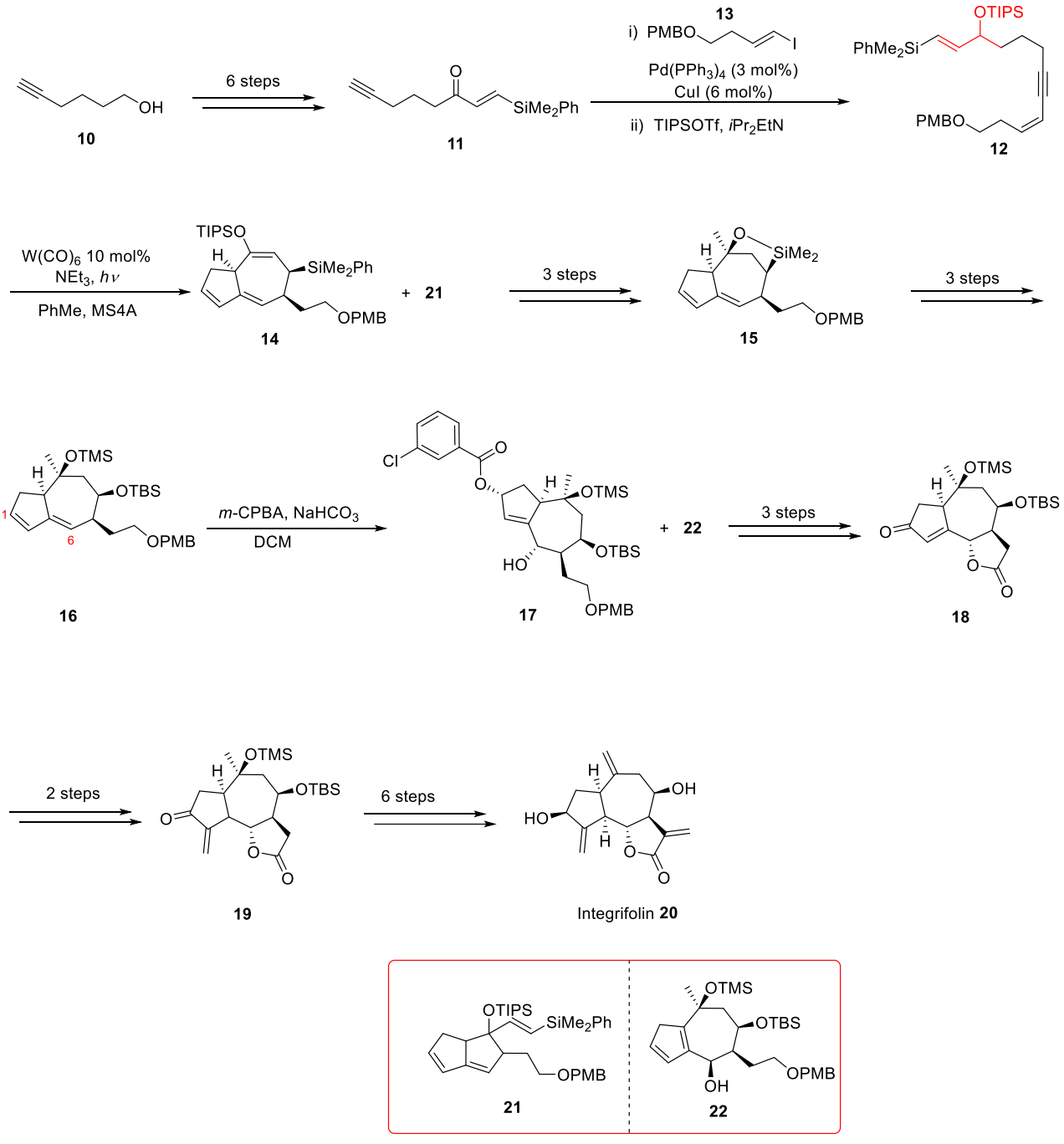
The guaianolides are alluring synthetic targets because of their structural complexity and their biological activities. Semi-synthetic approaches to the synthesis of guaianolides are common because of the complexity of their structures; a good review covering this area was discussed by Macías.[2] Many strategies for the total synthesis of the guaianolides have been explored. The most recent syntheses of guaianolide natural products will be discussed.

1.3.1 Synthesis Using Tungsten-Catalyzed Cyclization Strategy

In 2016, Iwasawa used tungsten-catalyzed cyclization reactions of acyclic trienynes under photoirradiation conditions to give fused bicyclic intermediates.[9] His synthesis started with the preparation of enone **11** in six steps from 5-hexyn-1-ol **10** (Scheme 1). Enyne **12** was synthesised by Sonogashira coupling of **11** with (*E*)-vinyl iodide **13** followed by silyl enol ether formation using triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) to give the trienyne **12** as a single (*Z*)-isomer. Having prepared the main intermediate **12**, Iwasaw was able to apply the tungsten-catalyzed cyclization reaction to construct the bicycle **14**. Treatment of **12** with 10 mol% tungsten hexacarbonyl afforded the product **14** in high yield as a single isomer, with small amounts of by-product **21**, which proved difficult to separate.

Cyclic silyl ether **15** was obtained by hydrolysis of **14** followed by methylation using methyllithium, and addition of 1,2-dimethoxyethane (DME) to the mixture. Protected diol **16** was obtain by Tamao oxidation which removed the silyl group and installed the required hydroxy group, followed by protection of the resulting diol to give **16**. The next key transformation in the synthesis was introduction of the oxygen at C1 and C6 positions. This was achieved by oxidation with *m*-CPBA to give **17** in 52% along with the by-product diene

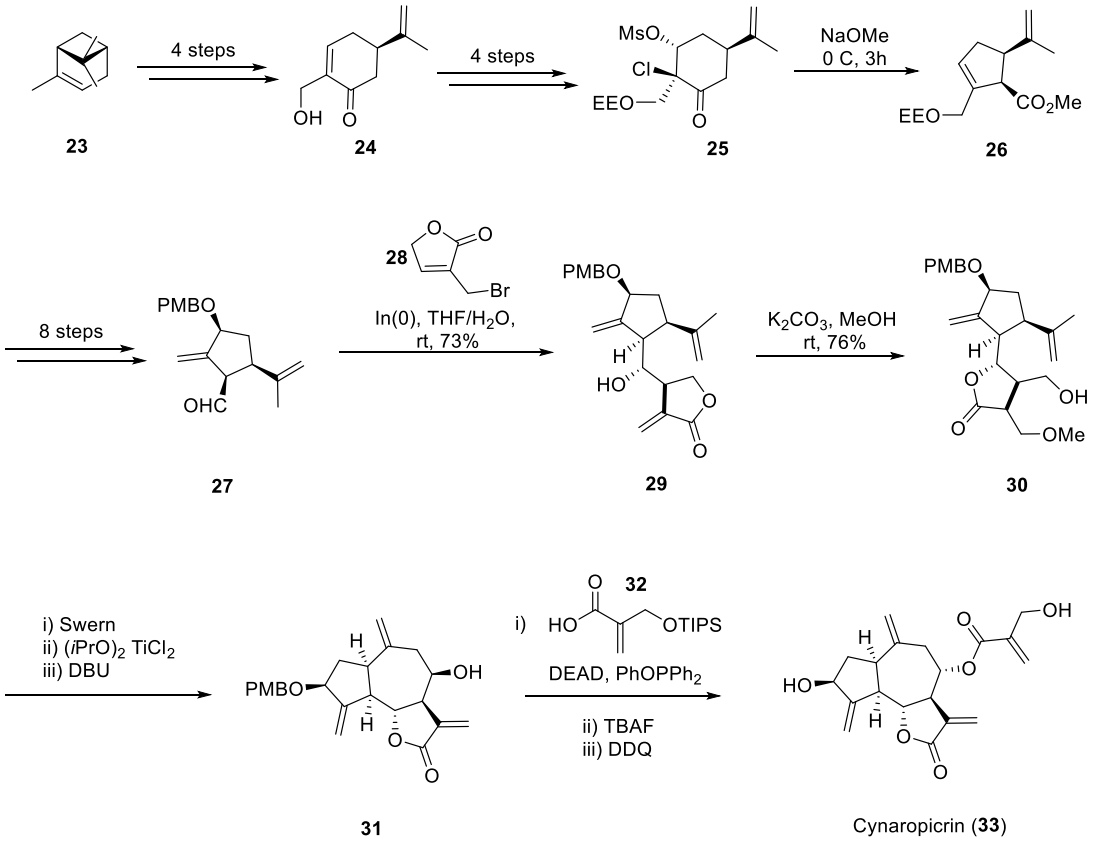
22. Lactone **18** was obtained in three steps from benzoyl ester **17**. The *exo*-methylene group was introduced to tricycle **18** by reaction with Eschenmoser's salt followed by methylation and elimination to give **19**. The natural product integrifolin **20** was synthesised in a further six steps.



Scheme 1

1.3.2 Synthesis Using Tandem Favorskii Rearrangement−Elimination Strategy

Usuki reported the first total synthesis of the natural product cynaropicrin in 2021 by use of a Favorskii rearrangement and a Barbier reaction as the key transformations in their route.[10] The chiral natural product α-pinene (**23**) was converted into alcohol **24** in 4 steps (Scheme 2). Alcohol **24** was transformed into a diol by epoxidation and treatment with LiCl and this compound was then protected to give the chloride **25**, the starting material required for the Favorskii rearrangement reaction. Many conditions for the Favorskii rearrangement reaction were screened; ester **26** was delivered with high stereoselectivity in excellent 96% yield by treatment of **25** with 6 equivalents of NaOMe at 0 °C for 3 hours. Aldehyde **27** was obtained from ester **26** in 8 steps.

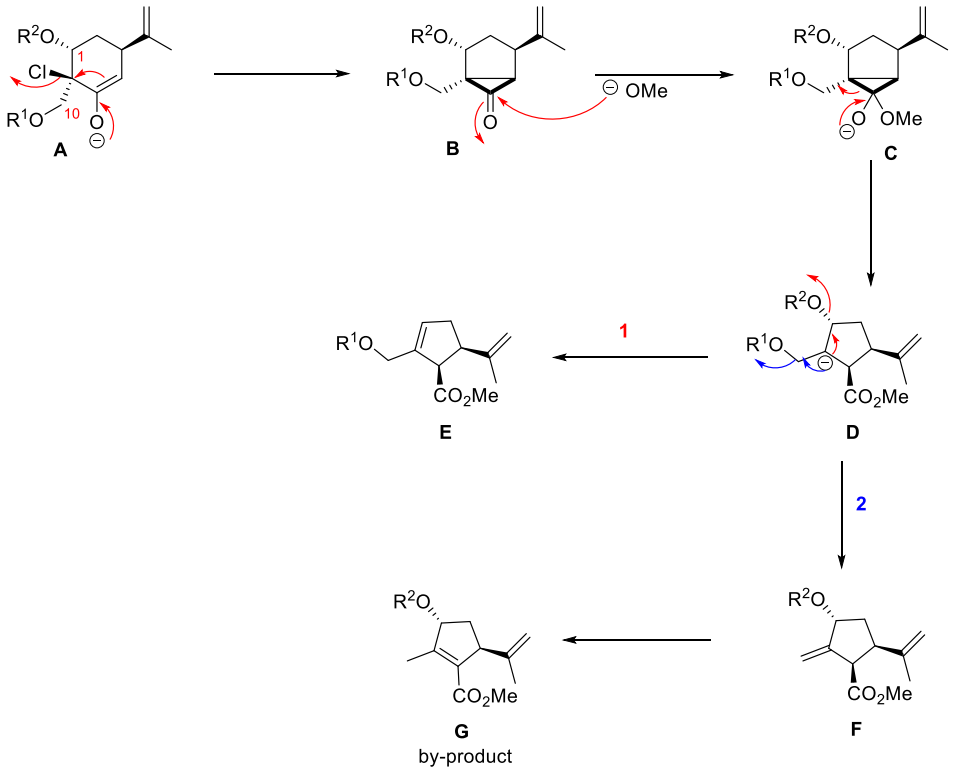


Scheme 2

Aldehyde **27** underwent a Barbier reaction with bromolactone **28**: treatment of the aldehyde with 3 equivalents of In(0) metal and 2.5 equivalents of **28** in THF/H_2O (1:2) for 15 hours produced alcohol **29** in 73% yield and with good diastereoselectivity. Translactonization of **29**

then took place to deliver primary alcohol **30** upon treatment with K_2CO_3 in MeOH. Swern oxidation of alcohol **30** was carried out followed by Lewis acid mediated ene cyclisation and elimination of MeOH to construct the tricycle **31** in three steps from **30**. Carboxylic acid **32** was chosen for a Mitsunobu–Mukaiyama inversion of alcohol **31** using DEAD and ($PhOPPh_2$). Subsequent removal of (TIPS) and PMB protecting groups furnished (+)-cynaropicrin **33**.

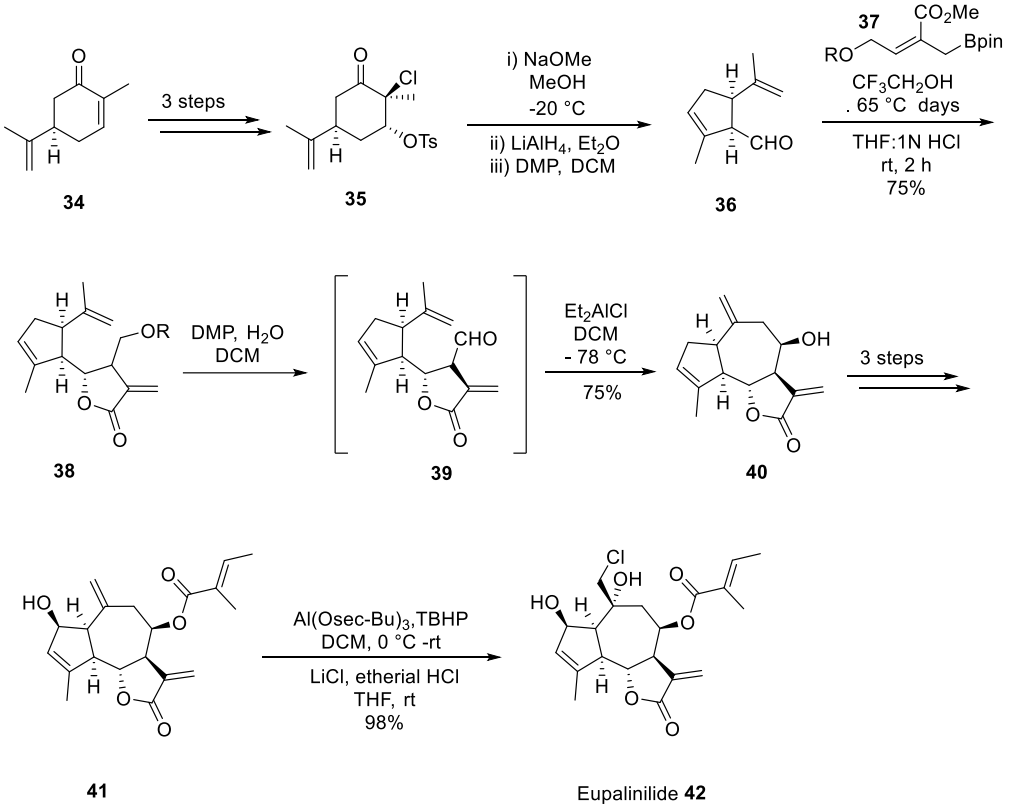
The choice of groups at C1 and C10 in **A** (Scheme 3) was important to avoid epimerization and by-product formation. A Ms group was chosen to activate the secondary alcohol and EE (ethoxyethyl) was chosen to protect the primary alcohol. In the proposed mechanism, elimination of Cl using NaOMe occurs to afford cyclopropenone **B**. The carbonyl group in **B** undergoes nucleophilic addition of OMe to produce **C** followed by ring opening to provide carbanion **D**. Elimination of the activate OR^2 group results in the desired kinetic product **E**. If OR^1 had been a better leaving group than activated OR^2 group this might have resulted in the formation of the by-product G through the intermediate F.



Scheme 3

Maity and Hajra also used the tandem Favorskii rearrangement−elimination reaction as the key transformation in their synthesis of eupalinilde **42**.[11] The *O*-tosylchlorohydrin **35** was obtained

in 3 steps from (*R*)-(−)-carvone **34** (Scheme 4). The chloride **35** then underwent tandem Favorskii rearrangement−elimination upon treatment with NaOMe in methanol at –20 °C. Reduction of the resulting ester and followed re-oxidation afforded aldehyde **36**. Favorskii rearrangement at a low temperature was essential to avoid epimerization and improve the diastereoselectivity. After synthesis of the aldehyde **36** the second key reaction was allylboration/lactonization with *Z*-allylboronate **37**. Aldehyde **36** was found to be prone to isomerization in the presence of both acid and base, and so extensive studies were caried out to find the optimum conditions to achieve this transformation. Reaction of the aldehyde **36** without catalyst in trifluoroethanol (TFE) under 65 °C followed by acidic work-up proved to be the best conditions and delivered lactone **38** in 75% yield with excellent diastereoselectivity.



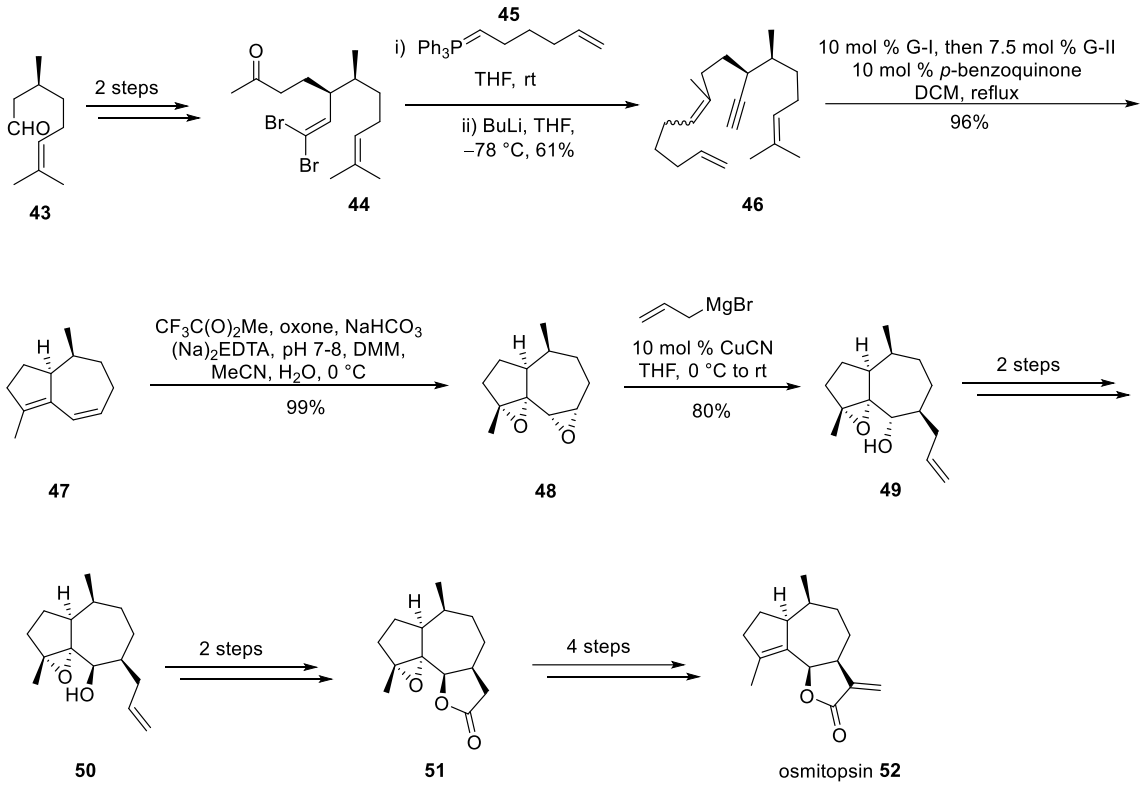
Scheme 4

Tricyclic alcohol **40** was synthesised in two steps from lactone **38** by oxidation of the hydroxyl group using Dess Martin periodinane followed by ene cyclisation in one-pot reaction to give **40** in 75% yield. The alcohol **40** was converted to ester **41** by a three-step procedure that included protection of the hydroxy group, oxidation and reduction. Selective epoxidation of

homoallylic olefin followed by regioselective epoxide ring-opening in the same pot delivered the natural product eupalinilde **42** efficiently in excellent (98%) yield.

1.3.3 Synthesis Using Domino Ene-Yne-Ene Metathesis Strategy

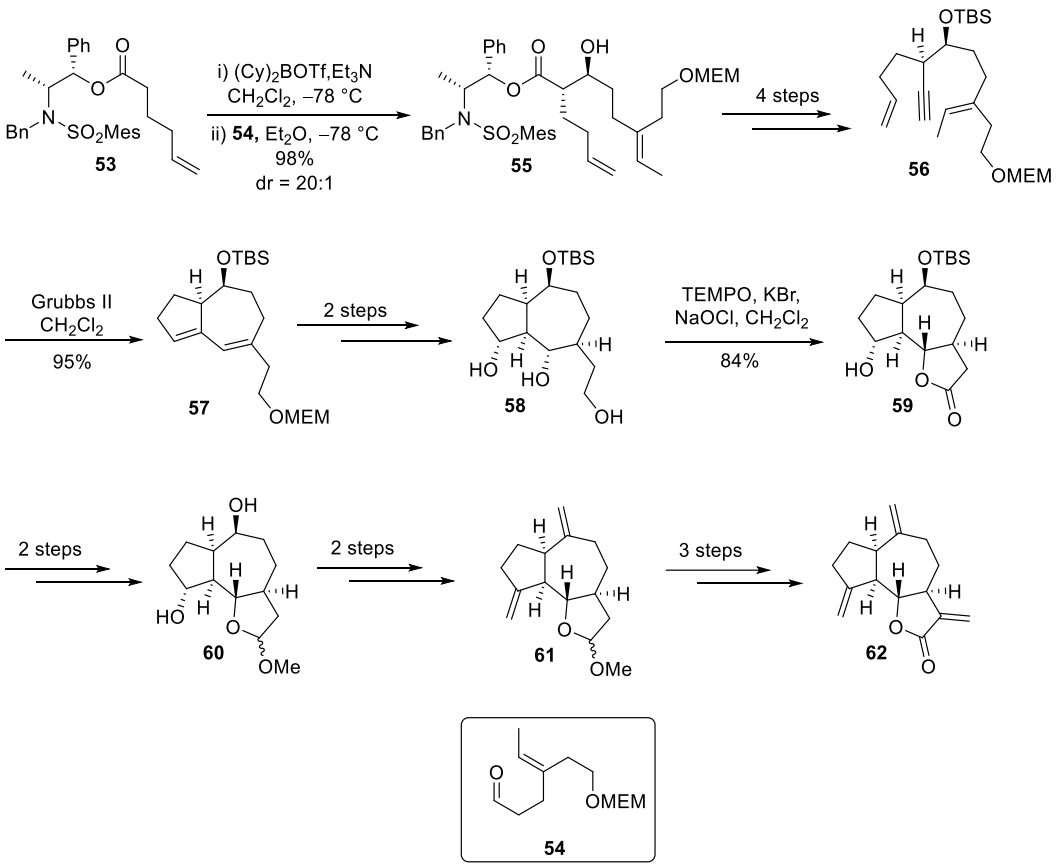
Metz utilised a synthetic strategy for the synthesis of numerous members of the guaianolide family e.g. osmitopsin (**52**).[12] The key reactions included relay metathesis to form the bicyclic ring system and diastereoselective diepoxide opening. The initial steps in the synthesis of osmitopsin involved the conversion of (*S*)-citronellal **43** into ketone **44** in two steps (Scheme 5). This sequence was followed by Wittig reaction with phosphonium ylide **45** and then alkyne **46** was generated by treatment with BuLi in the same pot to give trienyne **46**. The key relay metathesis reaction of the trienyne **46** was performed using Grubbs G-I and then G-II catalyst in the presence of *p*-benzoquinone to provide the corresponding hydroazulene **47** in excellent yield (96%) and good diastereoselectivity.



Scheme 5

The bisepoxidation reaction of **47** was investigated. Under optimum conditions, reaction of the substrate with $CF_3C(O)_2Me$ resulted in formation of the bis-epoxide **48** (structure confirmed by X-ray analysis) in excellent yield. Opening of the epoxide using allylmagnesium bromide and a catalytic amount of CuCN resulted in a highly regio- and diastereoselective reaction to afford diastereoisomer **49**. Oxidation and subsequent reduction with L-Selectride corrected the stereochemistry of alcohol position. Dihydroxylation of the alkene **50** followed by oxidation installed the lactone and gave the late-stage intermediate **51**. The lactone **51** was used to construct the osmitopsin **52** in 4-step sequence that included epoxide deoxygenation and exo methyl group installation.

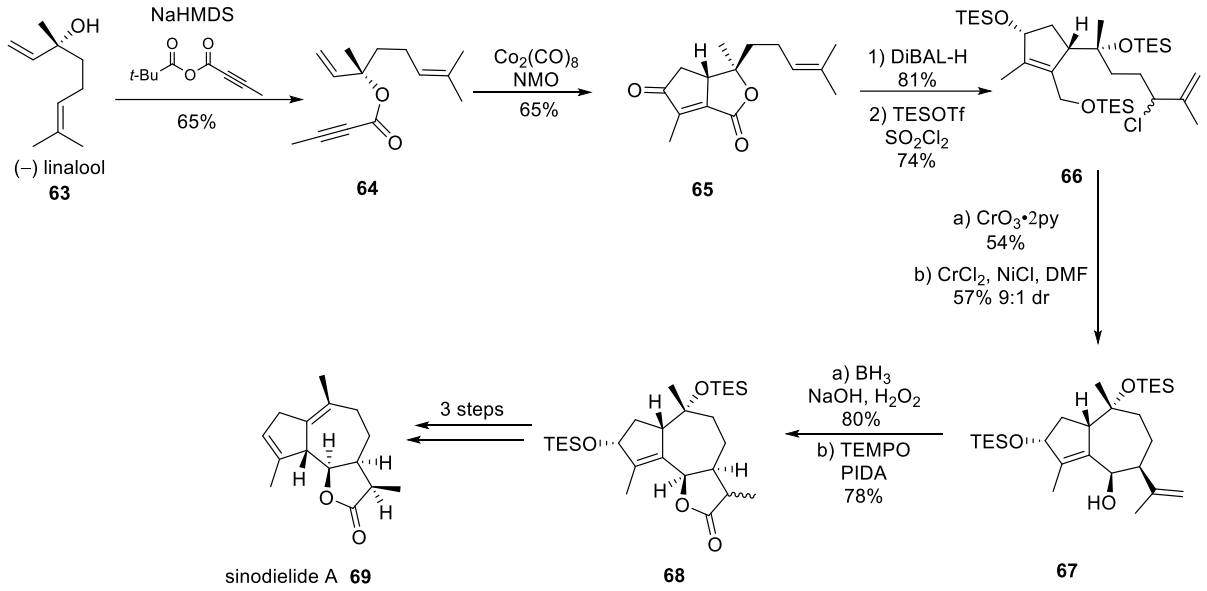
In 2021, Metz and co-workers used domino ene-yne-ene metathesis as the key reaction to construct the hydroazulene core of GSL.[13] Their synthesis started with the known aldehyde **54** and the ester **53**. Reaction of the aldehyde **54** with the boron enolate generated from ester **53** produced aldol product **55 (**Scheme 6). The alcohol **55** was then converted into the alkyne **56**, the precursor required for the domino metathesis reaction. Domino ring-closing metathesis was performed by treatment of the substrate **56** with Grubbs II catalyst and the hydroazulene **57** was obtained in excellent yield. Double hydroboration of diene **57** followed by removal of the MEM protecting group gave the triol **58** in 84% yield over two steps. The triol **58** then underwent oxidative lactonization to form hydroxylactone **59**. Reduction of lactone **59** using DiBAl-H and heating of the lactol in methanol at reflux under acidic conditions delivered the acetal **60**. Oxidation of the diol **60** followed by ketone methylenation furnished diene **61** in good yield. The sesquiterpenoid dehydrocostus lactone (**62**) was obtained in a further three steps in 17% yield.



Scheme 6

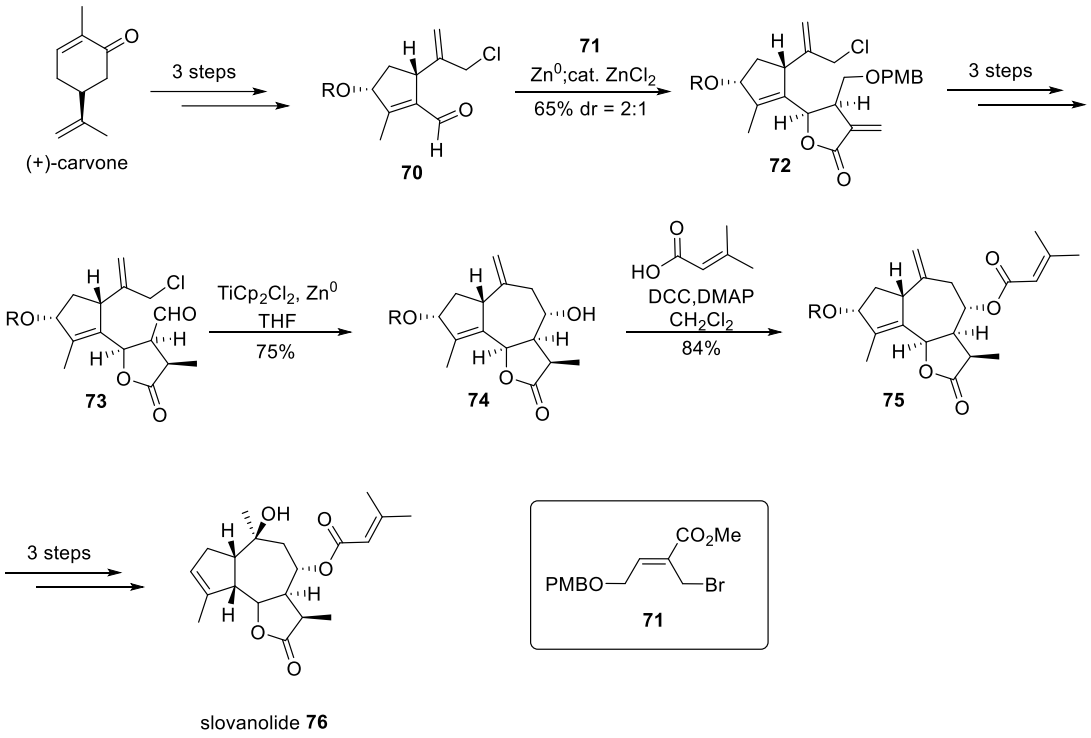
1.3.4 Synthesis Using Allylative Strategy

Maimone and co-workers synthesised sinodielide A (**69**) starting from chiral tertiary alcohol (−)-linalool (**63**) (Scheme 7).[14] The chiral pool starting material was transformed into the ester **64** and an intramolecular Pauson−Khand cyclisation reaction then provided the bicyclic lactone **65**. Reduction of both the ketone and lactone carbonyl groups using DIBAL followed by protection of resulting alcohols and allylic chlorination with sulfuryl chloride furnished the key products **66**. Selective oxidation of the protected primary allylic alcohol afforded the key aldehyde required for the ring-forming reaction. This key intermediate then underwent NHK-type coupling to provide the guaianolide product **67**. The lactone **68** was obtained by a hydroboration-oxidation sequence and this intermediate was then converted into the natural product sinodielide A (**69**) in a further three steps.



Scheme 7

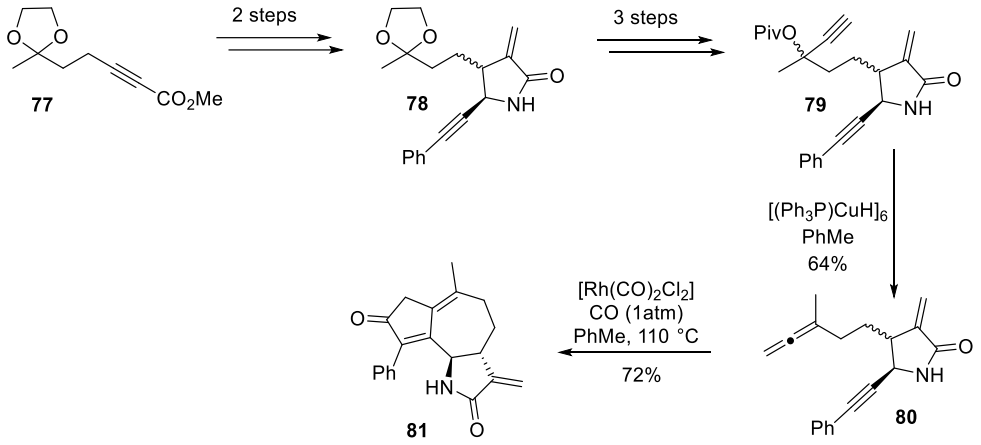
The same group synthesised the natural product slovanolide (**76**).[14] The synthesis commenced with the three-step conversion of carvone into the aldehyde **70** (Scheme 8). Zinc-mediated nucleophilic addition of allylic bromide **71** to the aldehyde **70** produced the lactone **72** with good diastereocontrol and in good yield. $ZnCl_2$ was an essential reagent for cyclization to form lactone **72**. Aldehyde **73** was then obtained by sequential reduction of exocyclic methylene group, removal of the PMB group and oxidation of the alcohol. A reductive, titanocene-mediated allylation reaction ($TiCp_2Cl_2$, Zn^0) of aldehyde **73** was used to generate tricycle **74** as a single isomer. DCC-coupling of the alcohol **74** with senecioic acid gave **75** which was then converted into the natural product slovanolide (**76**) in a further three steps.



Scheme 8

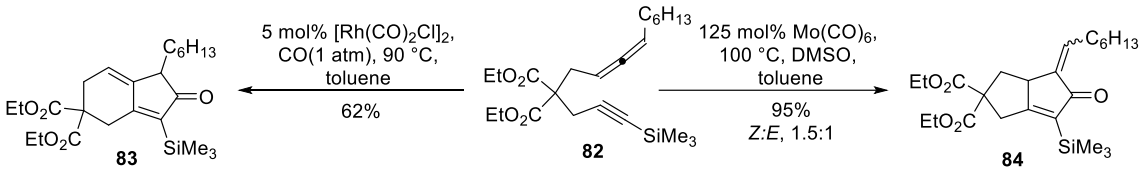
1.3.5 Synthesis Using Allenic Pauson−Khand (APKR) Strategy

In 2020 Brummond and co-workers were able to synthesise the guaianolide analogue **81** starting from the simple ketal **77** (Scheme 9).[15] Their synthesis started with the conversion of alkynoate **77** into the lactam **78** in two steps. Subsequent sequential removal of the ketal-protecting group, alkynylation and conversion of the tertiary hydroxyl group into pivalate ester furnished the propargylic ester **79**. The propargylic pivalate ester **79** was reduced using Stryker's reagent under optimised conditions to afford the key 3,3-disubstituted allene **80** and an allenic Pauson−Khand reaction (APKR) was then performed to produce the desired guaianolide analogue **81** in good yield.



Scheme 9

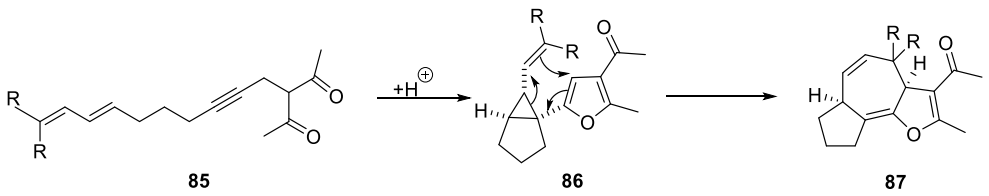
In 2022, Brummond use the same strategy to synthesise more guaianolide analogues to validate the methodology and test their biological activity.[16,17] They found that when rhodium biscarbonyl chloride dimer ($[Rh(CO)_2Cl]_2$) was used as a catalyst to react with diester allene-yne **82**, the rhodium catalyst reacted selectively with the distal π-system to give the fully conjugated dienone **83** (Scheme 10).[18] However, when molybdenum hexacarbonyl complex ($Mo(CO)_6$) was employed as a catalyst, reaction occurred at the proximal π-system of the allene-yne **82** to deliver the bicyclic enone **84**.



Scheme 10

1.3.6 Synthesis Using Cope rearrangement Strategy

Clark and co-workers developed methodology to construct the tricyclic core when making furan **86**. In 2018, they applied a Brønsted acid cascade reaction to the synthesis of functionalised furans bearing a cyclopropane, which were converted into cycloheptafurans thereafter by thermal Cope rearrangement (Scheme 11).[19]



85 86 87

Scheme 11

This methodology allows rapid access to 5,7,5 fused tricyclic systems which constitutes the main core structure found in the guaianolide family of natural products.

2 Aim of the project

2.1 Studies towards the total synthesis of micheliolide and morocolide A

The aim of this work was to carry out the total synthesis of novel antitumor guaianolides micheliolide **1** and morocolide **7** (Figure 5) by applying the strategy previously developed by the Clark group for efficient and rapid construction of the tricyclic core present in guaianolide natural products.[19] The structural features of morocolide **7** and micheliolide **1** make them good targets for synthesis by a strategy that involves the use of the Brønsted acid catalysed synthesis of fused cycloheptadienes previously developed within the Clark group. In order to assess the viability of the proposed synthetic strategy, a simplified version of this reaction was to be tested on model substrates. It was anticipated that once the synthesis of the fused cycloheptadiene core had been optimised on these model substrates, the methodology would be applied to the more complex systems found in the targets of interest.

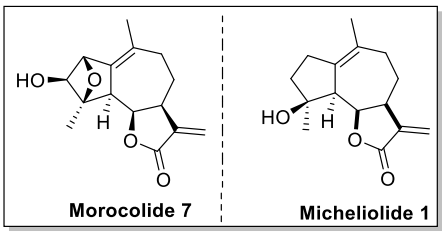
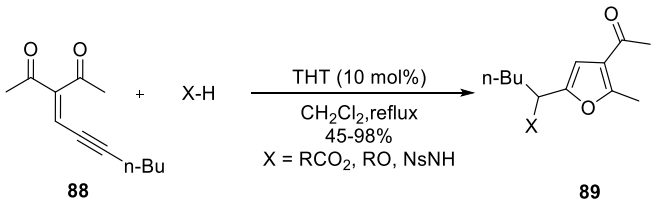


Figure 5

3 Previous Work in the Clark Group

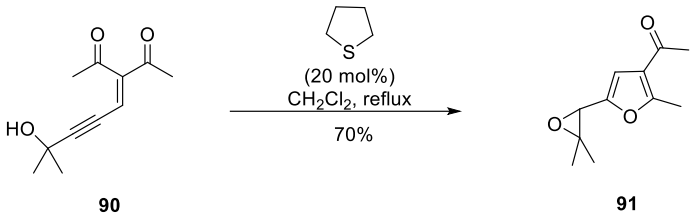
3.1 Organosulfur-catalysed synthesis of furans from ynenones

Clark *et al.* concluded that a cascade reaction of ynenones would occur when using organosulfur catalysis. In 2012, the Clark group published novel methodology for the synthesis of substituted furans in which a sub-stoichiometric amount of a thioether was used as the catalyst.[20] Their approach relied on the reaction of ynenone **88** with tetrahydrothiophene (THT) and an acidic nucleophile to give furan **89** (Scheme 12). The reaction did not proceed in the absence of THT, a finding that demonstrates the important role played by the organocatalyst in converting the ynenone **88** into the substituted furan. They also explored various other organocatalysts in the hope of forming the furan, but only starting materials were recovered in each case.



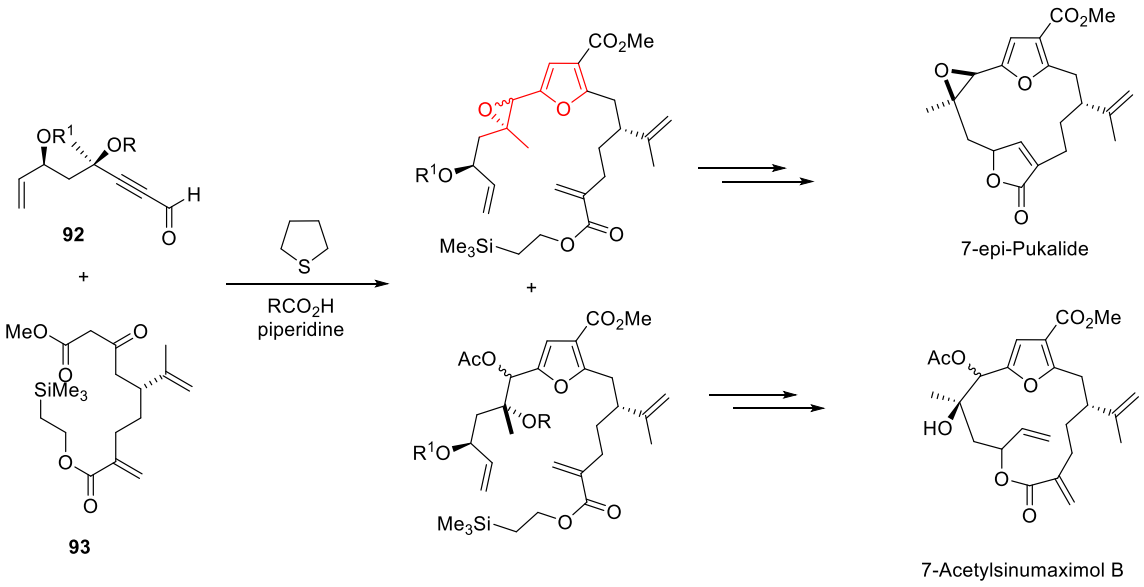
Scheme 12

Reaction conditions were optimised in order to introduce a wide range of nucleophiles. The use of aryl carboxylic acids (electron-rich and electron-poor), as well as alcohols resulted in the formation of trisubstituted furans with excellent yields. However, a low yield was obtained when a bulky alcohol was used. A higher yield was obtained when the fluorinated *tert*-butanol was used as a nucleophile, which illustrated the crucial role of the acid pK_a. Another important finding was that the alcohol or carboxylic acid nucleophile can be replaced with a sulfonamide. It was also found that furan formation could be accomplished using substrates that possess a wide range of alkyne substituents – aryl, alkyl, or trialkylsilyl substituted alkynes were all used successfully. In general, the reaction is robust and the tetrasubstituted carbon close to the nucleophilic attack was unaffected. The reaction was also tested and found to be successful using substrates in which one of the ketone carbonyl groups was replaced with another electron-withdrawing substituent such as an ester, phosphonate, sulfone or nitrile group.



Scheme 13

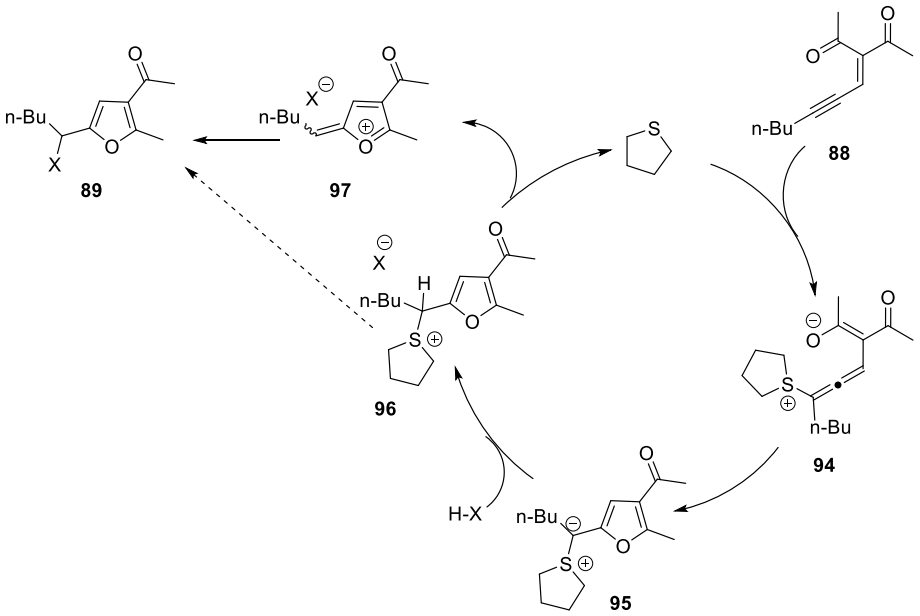
The epoxyfuran **91** was formed in good yield, when electron-deficient enynedione **90** possessing a hydroxyl group was used under these reaction conditions (Scheme 13). The formation of the epoxyfuran **91** under mild conditions is very useful because this structural motif is present in many of the furanocembranes. In 2017, Clark and his group were able to use this methodology to synthesise 7-epi-pukalide and 7-acetylsinumaximol B by one-pot Knoevenagel condensation and cyclisation of aldehyde **92** and β-keto ester **93** (Scheme 14).[21]



Scheme 14

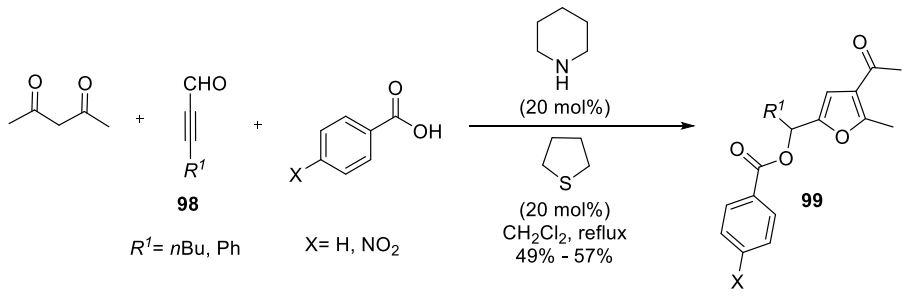
The proposed reaction mechanism proceeds by conjugate addition of the sulfur nucleophile to the alkyne **88** to produce the intermediate dipole **94** (Scheme 15).[19] Subsequent intramolecular cyclisation of the enolate **94** onto the central carbon of the allenyl system to give the intermediate **95**, in which the furan is formed adjacent to a sulfur ylide. In the presence of an appropriate acidic nucleophile, protonation of the ylide **95** results in sulfonium salt **96**. It is thought that the final product is formed via an S_N1 pathway, which would generate the

oxocarbenium ion **97** and return tetrahydrothiophene to the catalytic cycle. The final yield of furan **89** results from attack by the nucleophile on **97**.



Scheme 15

Clark and co-workers postulated that this methodology, which used THT as a catalyst to form furan, would work in a one-pot manner in which the condensation reaction and the furan-formation were combined. This process offers several significant benefits over the stepwise method, such as an improvement in synthetic efficiency and a reduction in chemical waste. The furan **99** was formed from a one-pot reaction of acetylacetone, benzoic acid and aldehyde **98**, with THT and piperidine; the yields ranged from 49% to 57%, which are similar to the combined yields obtained when separate reactions were performed (Scheme 16). The amount of acid used in the reaction was increased from 1.1 to 1.2 equivalents due to the dual role that acid played as both a catalyst and a nucleophile.

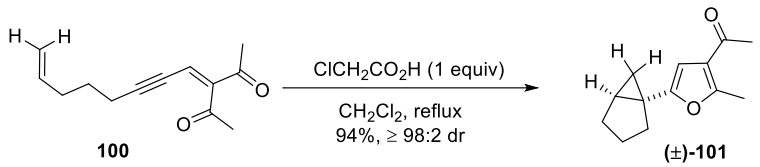


Scheme 16

This novel methodology is an effective method for the synthesis of furans in good yields and under mild conditions. Furthermore, a wide variety of substrates and nucleophiles can be used, which illustrates the potential of this reaction for the synthesis of more complex systems.

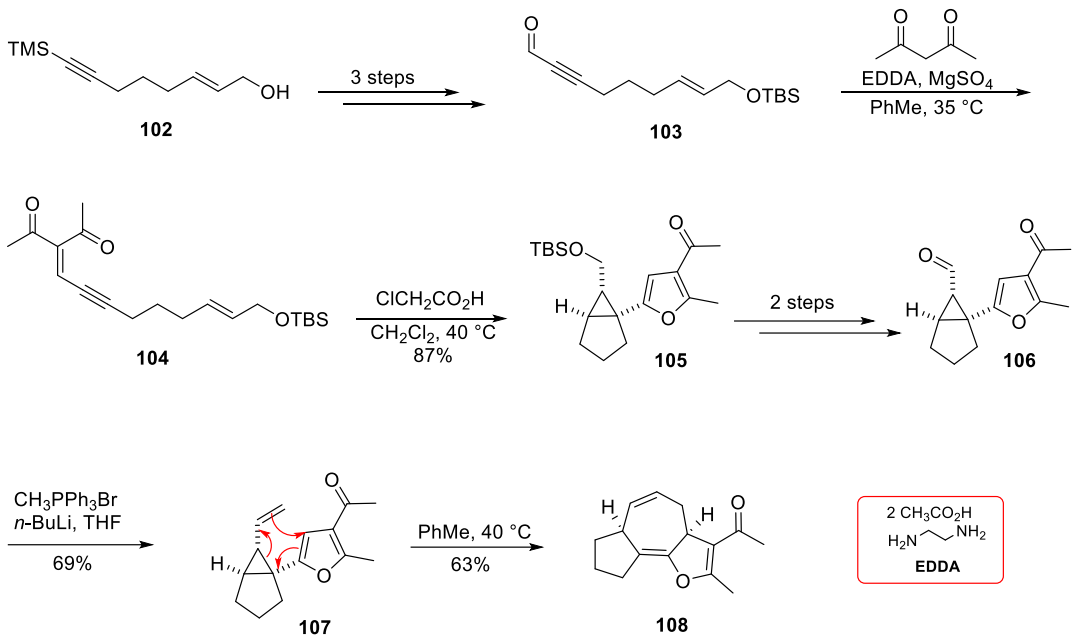
3.2 Brønsted acid promoted cascade to form cyclopropanated furans

Clark *et al.* also developed a furan-forming reaction in which chloroacetic acid was used as a Brønsted acid promoter on a wide variety of ynenones that possessed an unsaturated side chain. For example, subjection of compound **100** to chloroacetic acid formed the trisubstituted furan **101** as a single diastereoisomer. (Scheme 17).[19]



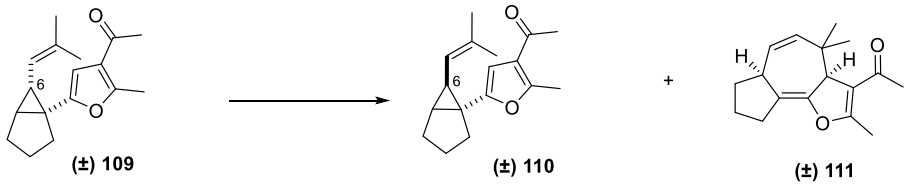
Scheme 17

In 2018, the Clark group applied the Brønsted acid cascade reaction to the synthesis of more functionalised furans bearing a cyclopropane, which were converted into cyclohepta[b]furans thereafter by thermal rearrangement.[19] The synthesis started with alcohol **102** which was converted into the propargylic aldehyde **103** in three steps (Scheme 18). The aldehyde **103** was then subjected to a Knoevenagel condensation reaction to deliver the ynenedione **104**. Application of the Brønsted acid mediated reaction that had been developed for cyclisation of the ynenedione **104** resulted in formation of the furan **105** in good yield. Desilylation of **105** followed by Dess-Martin oxidation of the alcohol produced the aldehyde **106**. The aldehyde **106** was then convert to alkene **107** by Wittig olefination. Reflux of **107** in toluene resulted in thermal Cope rearrangement to give the cyclohepta[b]furan **108** in 36% yield. The Cope rearrangement reaction was optimised and the best conditions involved reduction of the reaction temperature to 40 °C, which resulted in longer times reaction times but improved the yield significantly to 63%.



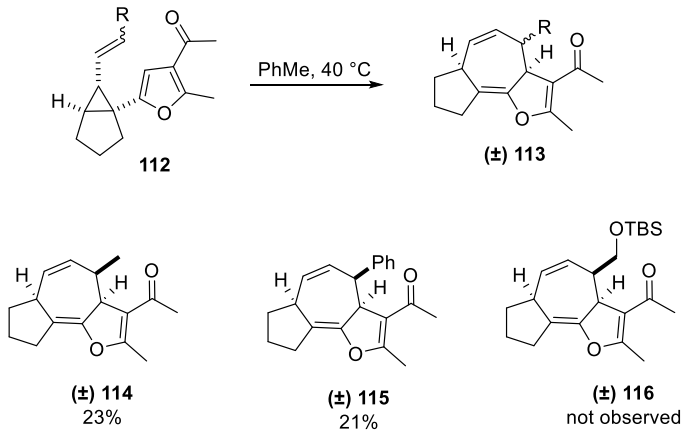
Scheme 18

After the cyclohepta[b]furan **108** had been made, various Wittig reagents were used to produce a variety of alkenyl cyclopropanes as substrates for the Cope rearrangement reaction. Many different alkenes were tested, but when the trisubstituted alkene **109** was used as a substrate for Cope rearrangement reaction under optimised conditions (40 °C) only the starting material was recovered. However, increasing the temperature to 110 °C resulted in the formation of desired products **111**. Results of previous studies performed within the group suggested that at higher temperatures a trace amount of the epimerised cyclopropane **110** at C6 was obtained (Scheme 19).[19] An interesting observation was that the *trans* compound **110** underwent Cope rearrangement at a different rate than **109**.



Scheme 19

Non-terminal alkenes were tested as well and in most cases it was found that the *E* isomer is more reactive than the *Z* isomer (Scheme 20). In the latter case, the rearrangement product was usually obtained in low yield and recovery of the starting material was observed. For trisubstituted alkenes the reaction temperature needed to be increased to 110 °C to achieve any conversion.



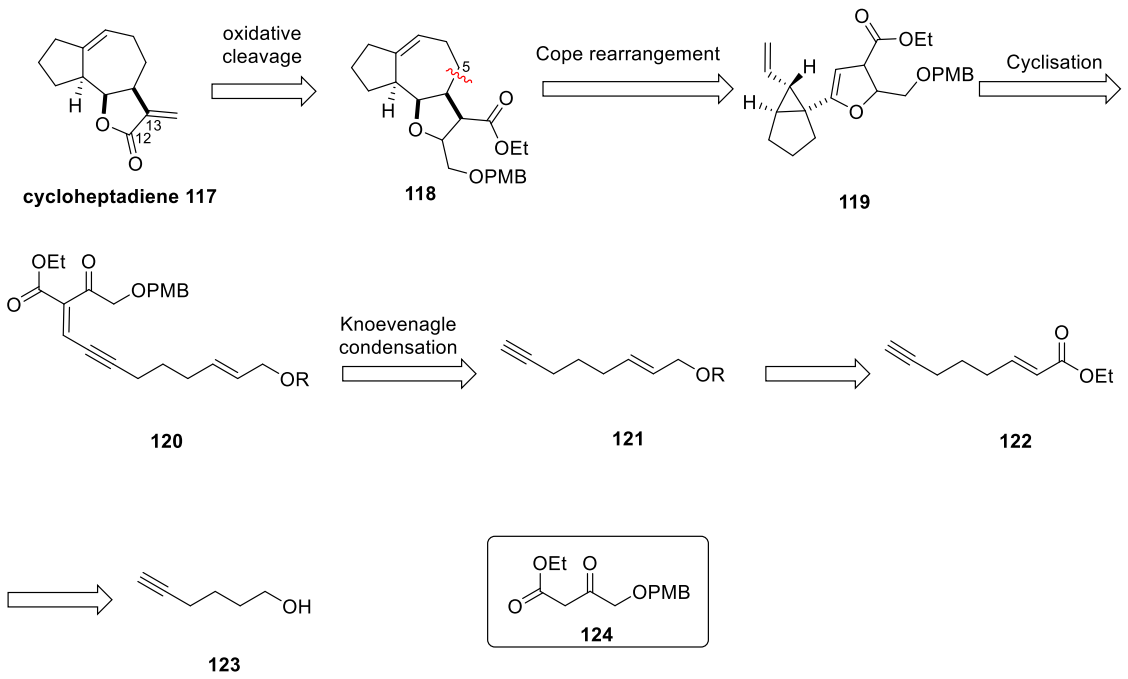
Scheme 20

This methodology allows rapid access to 5,7,5 fused tricyclic systems, which are valuable building blocks and are found in a wide range of natural products. Consequently, it was evident this methodology could be applied to the synthesis of many natural products that have a similar structure core. Inspired by this work, members of the guaianolide family of natural products were chosen as targets amenable to synthesis using this methodology.

4. Results and Discussion

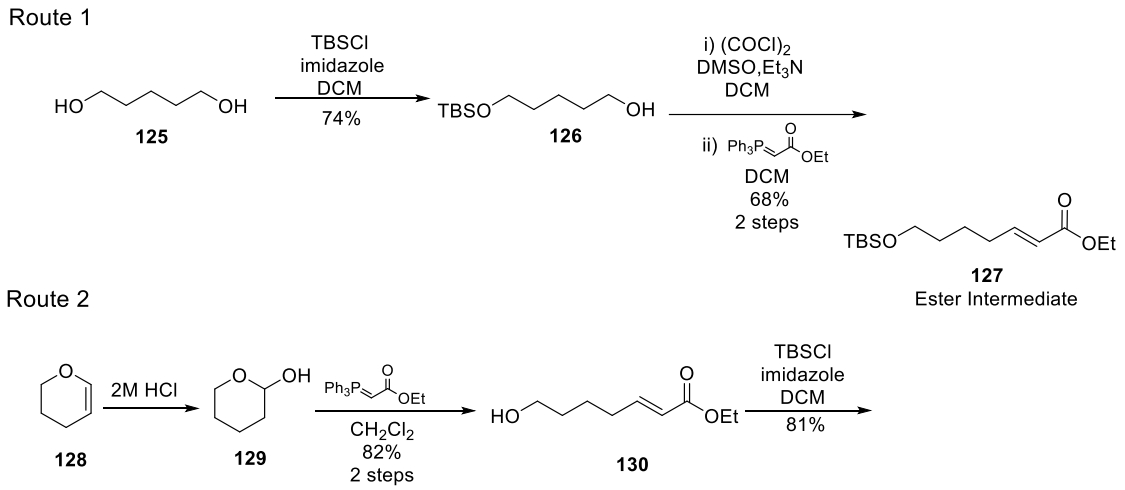
4.1 The First Model System Using The Broønsted Acid Catalyst

Retrosynthetic analysis of the first tricyclic model system **117** relies on several key reactions such as oxidative cleavage, Cope rearrangement, Brønsted acid cyclisation and Knoevenagel condensation. The lactone **117** is expected to be obtained from **118** by reduction of the ester group dehydration to produce the methylene group at C13 (Scheme 21). Deprotection of PMB group followed by oxidative cleavage of resulting alcohol should give the lactone carbonyl group at C12. The cycloheptadiene **118** could be accessed by the Cope rearrangement of the vinyl cyclopropane **119**. Brønsted acid cyclisation of ynenone **120** will furnish the vinyl cyclopropane **119**. Ynenone **120**, the key intermediate, could be synthesised by subjecting the alkyne **121** to a Knoevenagel condensation reaction with the β-keto ester **124.** Reduction of ester **122** followed by protection of resulting alcohol give alkyne **121**. The formation of ester **122** could be done in two steps from the commercially available alcohol **123** by oxidation followed by Wittig reaction.



Scheme 21

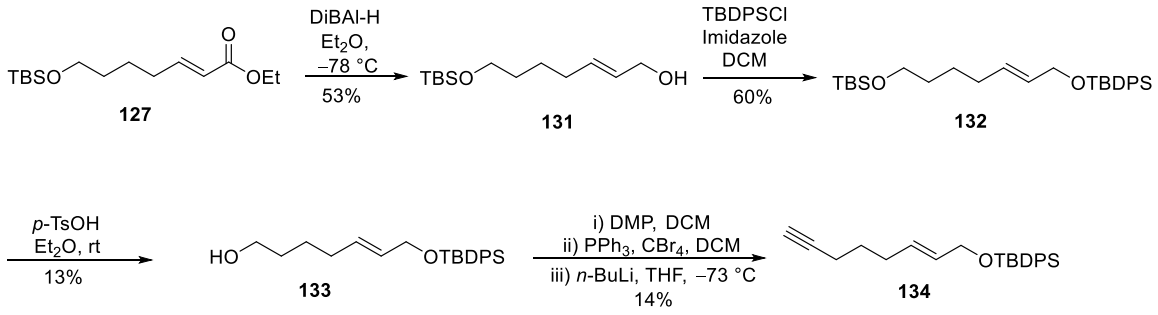
In order to access the ester **127** required for the preparation of the first model system **117** (Scheme 22), two routes were investigated to achieve an efficient synthesis. Route 1 started with mono-protection of diol **125** with TBSCl to afford alcohol **126** (Scheme 22).[23] Alcohol **126** was oxidised using a Swern oxidation reaction to furnish the corresponding aldehyde, which was subjected to a Wittig reaction to obtain the unsaturated ester **127** in 68% yield over two steps (>15:1 (*E*/*Z*) dr by ^{1}H NMR). The second route started with hydrolysis of 2,3-dihydropyran **128** to afford lactol **129** which underwent a Wittig reaction to deliver alcohol **130** in 82% yield over two steps (>10:1 (*E*/*Z*) dr by ^{1}H NMR). Protection of alcohol **130** with TBSCl provided the ester intermediate **127** in 81% yield. Both routes contain 3 steps, but the second route has a better overall yield of 54% compared to the first route which has an overall yield of 47%.



Scheme 22

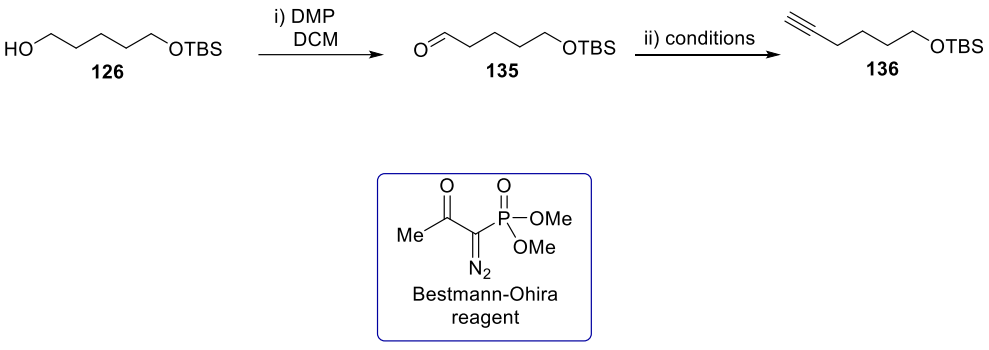
4.1.1 Synthesis of Alkyne Intermediate 134

Following formation of the unsaturated ester **127**, the next steps involved synthesis of the alkyne **134** (Scheme 23). This route started with the reduction of ester **127** using diisobutylaluminium hydride (DiBAl-H) to produce the allylic alcohol **131**,[(23)] which was protected with TBDPSCl to afford alkene **132** in 60% yield. Subsequent cleavage of the TBS ether under acidic conditions delivered the alcohol **133** in modest yield (Scheme 23).



Scheme 23

The alcohol **133** was oxidised to give corresponding aldehyde which was treated under Corey-Fuchs conditions to give alkyne **134**. A low yield of 14% was obtained over the three steps that included oxidation, formation of triphenylphosphine-dibromomethylene ylide, Wittig reaction between the ylide and aldehyde, and elimination to produce the alkyne **134**. The low yield might be due to the harsh conditions used when making the ylide for the Corey-Fuchs reaction. Based on these results, an alternative route was explored in which installation of the alkyne was performed at an earlier stage. The route commenced with oxidation of alcohol **126** to give intermediate aldehyde **135** (Scheme 24). Subsequent installation of the alkyne on this intermediate aldehyde **135** under Corey-Fuchs conditions, in a similar manner as before, resulted in formation of alkyne **136** with a higher yield of 34% (Entry 1, Table 1). However, Seyferth-Gilbert homologation using the Bestmann-Ohira reagent was found to be a better method and resulted in a 72% yield of the alkyne **136** (Entry 2) (Table 1).



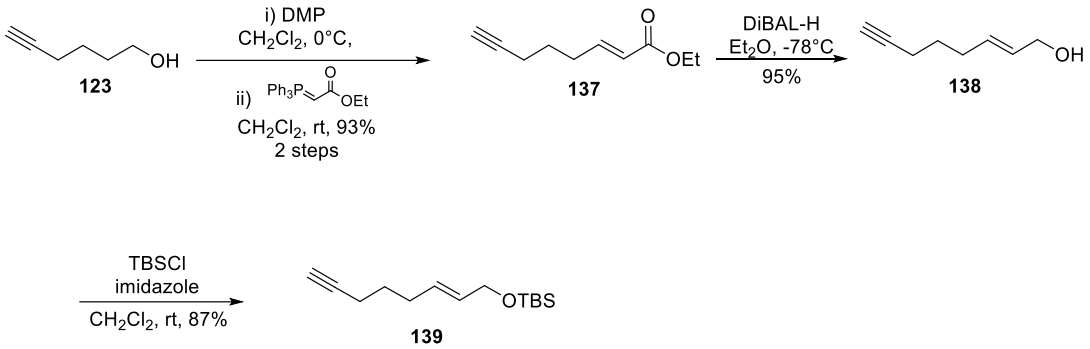
Scheme 24

Table 1

Entry	Conditions	T (ºC)	Time (hour)	Yield (2 steps)
1	*i*) PPh_3, CBr_4, DCM *ii*) *n*-BuLi, THF	-78	4	34%
2	Bestmann-Ohira, K_2CO_3, MeOH	25	16	72%

4.1.2 Alternative Route Towards the Alkyne Intermediate 139

A third route was considered in which the commercially available alkyne **123** was used which had some of the required functional groups. Oxidation of the commercially available hex-5-yn-1-ol **123** to the corresponding aldehyde was achieved using standard Swern conditions and subsequent Wittig olefination produced the corresponding ester **137** with an excellent yield of 93% over two steps (>12:1 (*E*/*Z*) dr by ^{1}H NMR) (Scheme 25).[24]

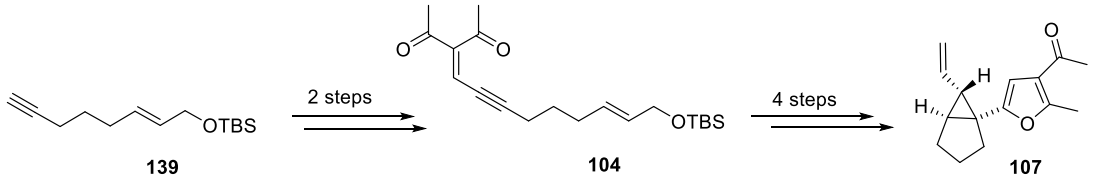


Scheme 25

Reduction of the ester **137** using DIBAl-H produced the alcohol **138** in excellent yield. Alcohol **138** was protected as a TBS ether to furnish intermediate alkyne **139** in 69% yield over four steps.

This intermediate alkyne **139** which was synthesise by Clark group in 2017 using different starting materials as stated in (Chapter 2).[19] After that, the route used by Verena Klaus[(19)] was employed to synthesise **107** to test the viability of the Bronsted acid cyclisation reaction of yenone **140** to produce the furan **107**. The vinyl cyclopropane **107** was produced in 10 steps

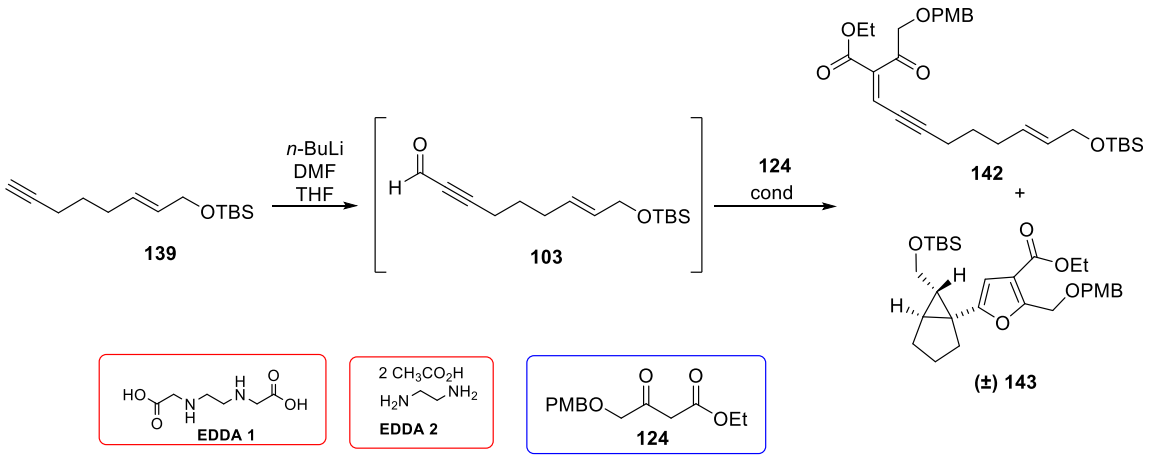
and with 13% overall yield (Scheme 26). More information about each individual step is provided in Chapter 7.



Scheme 26

4.1.3 Knoevenagel Condensation and Cyclisation

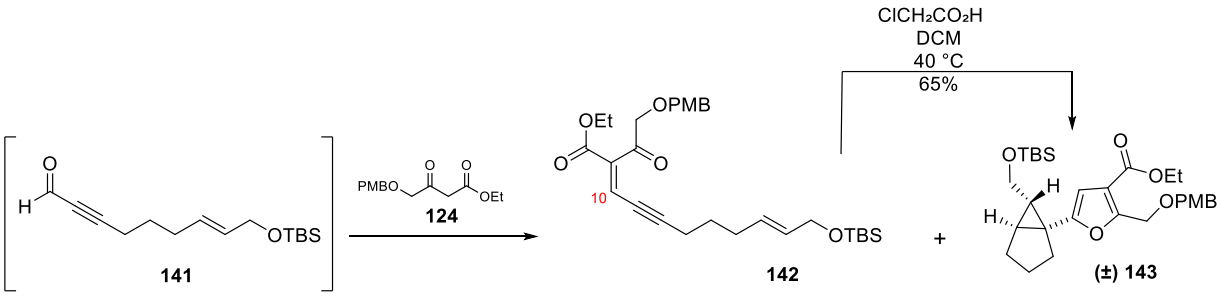
The intermediate alkyne **139** was also used to form the first model system **117**. Conversion of the alkyne **139** into the propargylic aldehyde **103** was accomplished by treating alkyne **139** with *n*-BuLi followed by addition of dimethylformamide (Scheme 27).[19] The resulting aldehyde **103** was taken on to the next step without purification. A Knoevenagel condensation reaction then took place between the aldehyde **103** and the 1,3-dicarbonyl compound **124** which contains an electron-withdrawing group. The reason the 1,3-dicarbonyl compound **124** was used is that it contains both an ester group and a protected primary alcohol that could be modified at a late stage to suit our needs when synthesising the natural products. The Knoevenagel condensation reaction produced a mixture of the ynenone **142** and the furan **143.**



Scheme 27

Optimisation of the Knoevenagel condensation reaction was carried out in order to obtain the best yield. When the reaction was performed with ethylenediamine-*N*,*N*'-diacetic acid (EDDA

1) in toluene at reflux, both the ynenone **142** and the furan **143** were obtained with low yields (Table 2 entry 1). Changing the solvent to dichloromethane and reducing the reaction temperature resulted in a slight improvement of the yield (entry 2). In the absence of solvent, the reaction produced the desired furan in 51% yield (entry 3). However, when EDDA**1** was used, the reaction was incomplete even after prolonged reaction times and starting material was returned. On the other hand, the use of ethylenediamine diacetate (EDDA**2**) solved this issue and full conversion of the starting material to the ynenone **142** and furan **143** was observed (entries 5 and 6). Solvent free conditions proved to be the best for this transformation (entry 7). Although EDDA**2** produced the ynenone **142** in higher yield than the furan **143**, it drove the reaction to completion with good overall yield. It is important to note that both EDDA salts need be completely dry in order to perform this reaction; failure to exclude water results in unidentified products. The contrasting ratios of products obtained from the reactions promoted by EDDA**1** and EDDA**2** might be due to the ability of EDDA**2** to act as base and acid more readily than the conjugated form EDDA**1**, even though they have similar pk_a values of around 6. Ynenone **142** was treated with chloroacetic acid as the Brønsted acid to give the furan **143** in one step and in 65% yield (Scheme 28).[19]



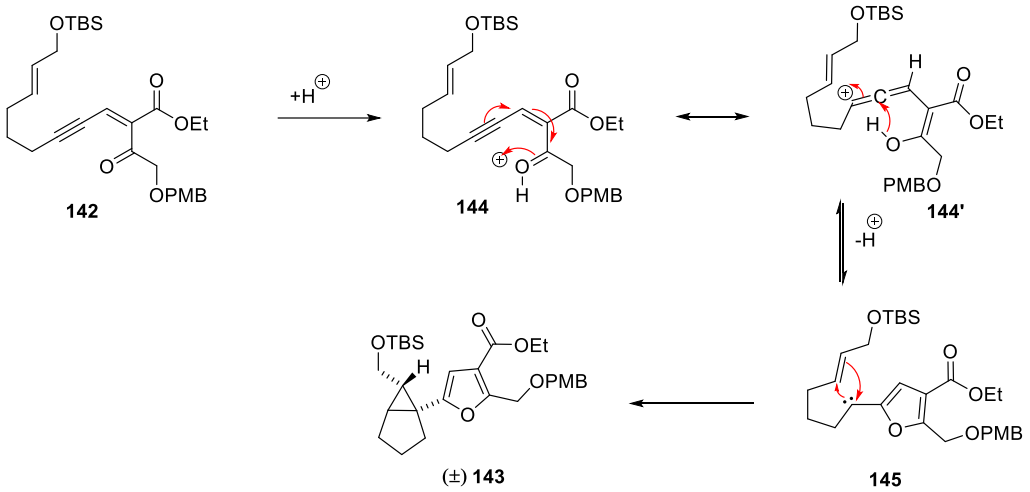
Scheme 28

Table 2:

Entry	Reagent	Solvent	T ˚C	Time	Yield 142	Yield 143
1	EDDA **1=** 0.2 eq $MgSO_4$= 0.2 eq	PhMe	110	1 days	12% brsm	22% brsm
2	EDDA **1=** 0.2 eq $MgSO_4$ = 0.2 eq	DCM	40 ˚C	5 days	18% brsm	26% brsm
3	EDDA **1=** 0.2 eq $MgSO_4$= 0.2 eq	Solvent free	60	4 days	12% brsm	51% brsm
4	EDDA **2=** 0.2 eq $MgSO_4$= 0.2 eq	PhMe	40	2 hours	49%	12%
5	EDDA **2=** 0.2 eq $MgSO_4$= 0.2 eq	DCM	40	2 h	52%	19%
6	EDDA **2=** 0.2 eq $MgSO_4$= 0.2 eq	Solvent free	60	16 hours	63%	16%

The ynenone **142** was formed as a mixture of *E* and *Z* isomers but the ratio was hard to determine precisely due to overlapping signals of the protons of C10 and the PMB protecting group in the ^{1}H NMR. The ratio was estimated from the ^{13}C NMR to be 1:0.60 (*E*/*Z*).

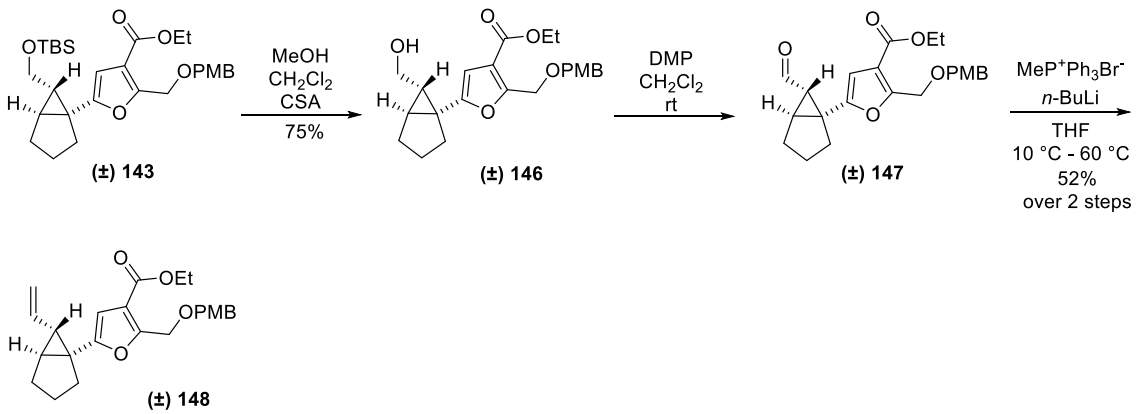
The suggested reaction mechanism for the cyclisation cascade starts with protonation of one of the carbonyl groups in **142** to give **144** (Scheme 29). Internal cyclisation then takes place through the allenyl cation resonance form **144'** of the intermediate **144** due to nucleophilic attack on the central allenic carbon by oxygen of the enol. The final product furan **143** results from the cyclopropanation of the pendant alkene by the resulting carbene **145**.



Scheme 29

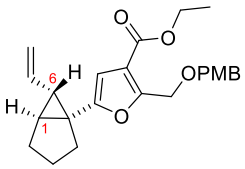
4.1.4 Formation of Vinylcyclopropane of the First Model System

The synthesis of the furans **143** meant that it was now possible to explore construction of fused cycloheptadienes that correspond to the core system of guaianolide. Removal of the TBS group by treatment of **143** with camphorsulfonic acid (CSA) furnished the alcohol **146** in a yield of 75% (Scheme 30).[19] It is worth noting that use of a strong base to remove TBS group results in decomposition, while use of a mild acid such as CSA results in cleavage of the silyl ether in excellent yield. The alcohol was then oxidised using Dess-Martin periodinane to furnish the aldehyde **147**.



Scheme 30

Wittig methylenation of aldehyde **147** was more challenging than expected. The products decomposed when purified using silica gel column chromatography probably due the sensitivity of the products toward acid and so the product was purified using aluminium oxide (activated, basic, Brockmann I). The highest yields of the product **148** from the Wittig reaction were obtained when *n*-BuLi was used as the base, the reaction temperature was lower than −10 °C, and the reaction quenched by the addition of pH 7 buffer.



148

The stereochemistry of Vinylcyclopropane **148** was confirmed by NOESY NMR, C(6)H (located at 2.20–2.14 ppm in the ^{1}H NMR spectrum) did not show a cross-peak with C(1)H (located at 1.84 ppm in the ^{1}H NMR spectrum) in the NOESY spectrum, which shows that the relationship is *trans* (figure 6). This assignment is confirmed by a coupling of J = 3.9 Hz between the protons at C1 and C6, which is typical for adjacent protons with a *trans* relationship on a cyclopropane.

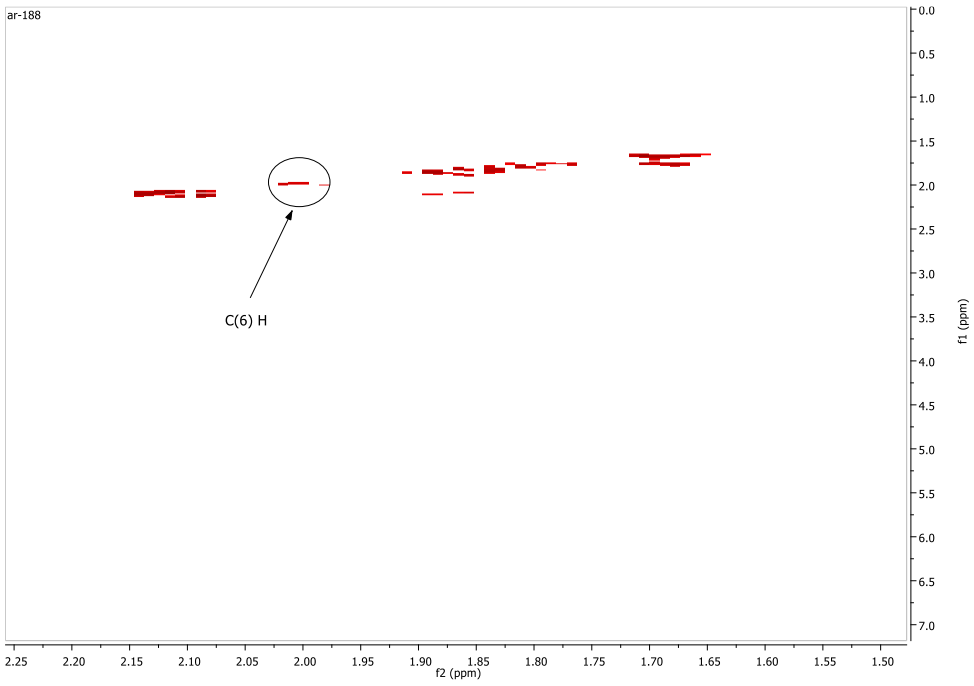


Figure 6

4.2. The Effects of Methyl Group on the Cope Rearrangement Reaction

The target natural products feature a fused 5,7,5 tricyclic system as discussed earlier (Chapter 1), with a methyl group at the C10 position (Figure 7). Therefore, it was necessary to investigate the effect of the presence of a methyl group on the outcome of the Cope rearrangement step, by use of a model system.

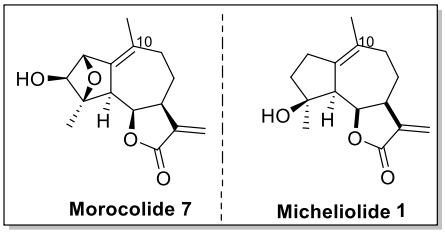
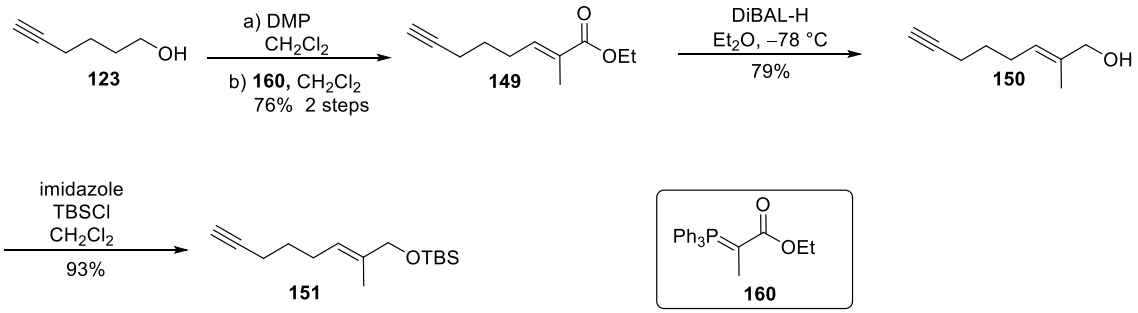


Figure 7

4.2.1 Synthesis of the Second Model System 159

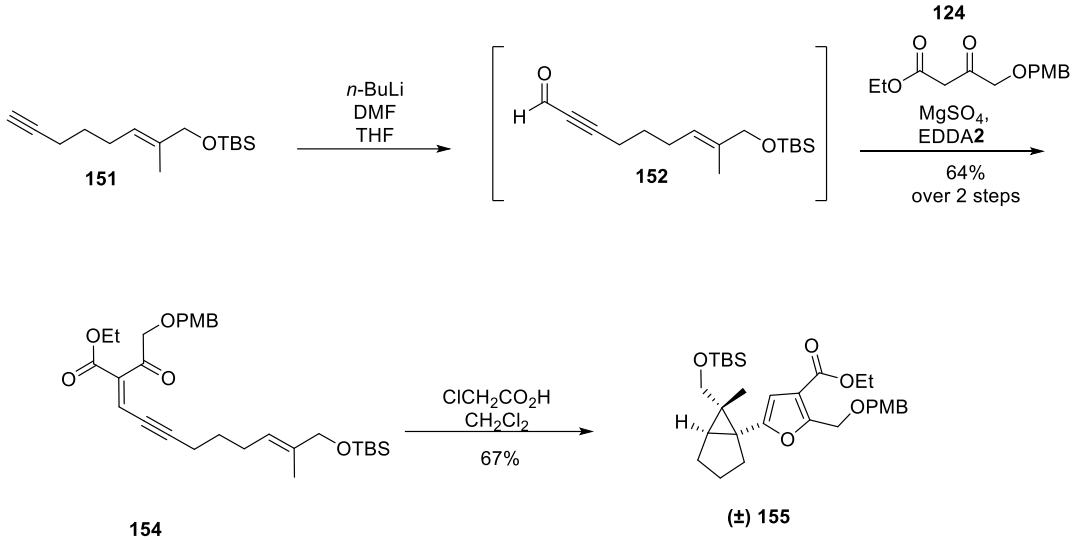
The synthesis of the second model system **159** commenced with oxidation of alcohol **123** to produce intermediate aldehyde, which underwent Wittig olefination with stabilised ylide **160** to form the corresponding α,β-unsaturated ester **149** in excellent yield (76%) over two steps (>45:1 (*E*/*Z*) dr by ^{1}H NMR) and with high selectivity (Scheme 31). The ester **149** was reduced with DiBAl-H to give allylic alcohol **150** in excellent yield [25], which was then protected as TBS ether to furnish intermediate alkyne **151** in 93% yield.



Scheme 31

Knoevenagel condensation was then performed to prepare the cyclisation precursor from the alkyne intermediate **151**. The alkyne **151** was first converted into the propargylic aldehyde **152** by deprotonation with *n*-BuLi followed by addition of the anion to dimethylformamide

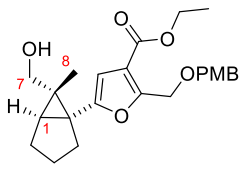
(Scheme 32).[19] Treatment of the aldehyde **152** with **124** under the previously optimised Knoevenagel conditions resulted in formation of the ynenones **154** as 1:0.83 *E*/*Z* dr along with trace amounts of cyclised furans **155**. Cyclisation of ynenone **154** was achieved by treatment with a Brønsted acid which delivered the required furan **155** in very good yield.



Scheme 32

4.2.2 Formation of Fused Cycloheptadiene of the Second Model System

Silyl deprotection of furan **155** gave the primary alcohol **156** in 83% yield (Scheme 33).[19]



156

C(8)H_3 (located at 1.27 ppm in the ^{1}H NMR spectrum) did not show a cross-peak with other protons in the NOESY spectrum which establishes the stereochemistry to be that shown (figure 8).

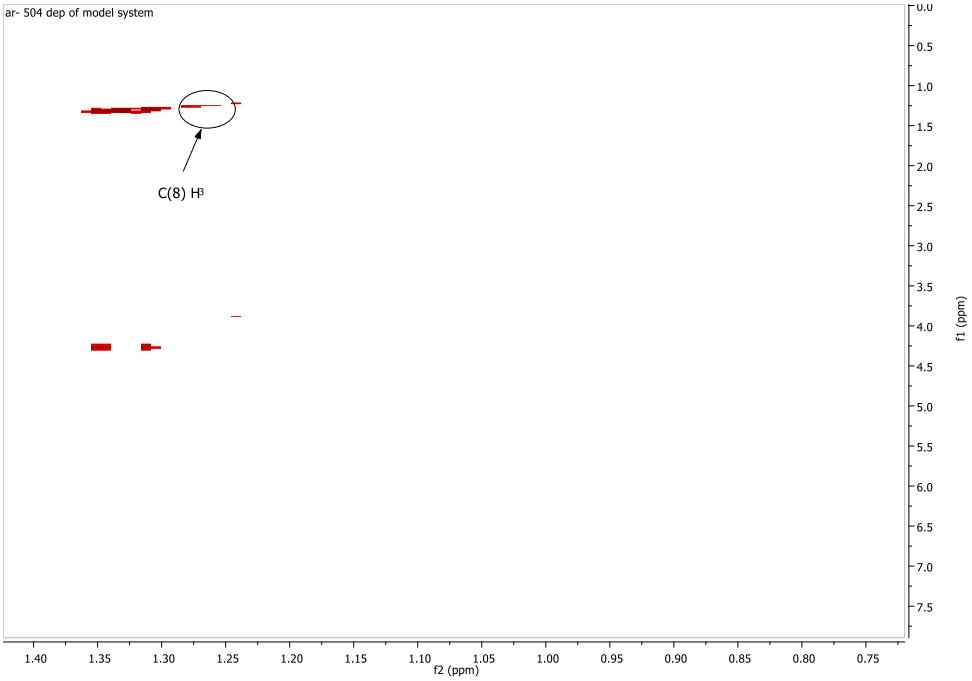
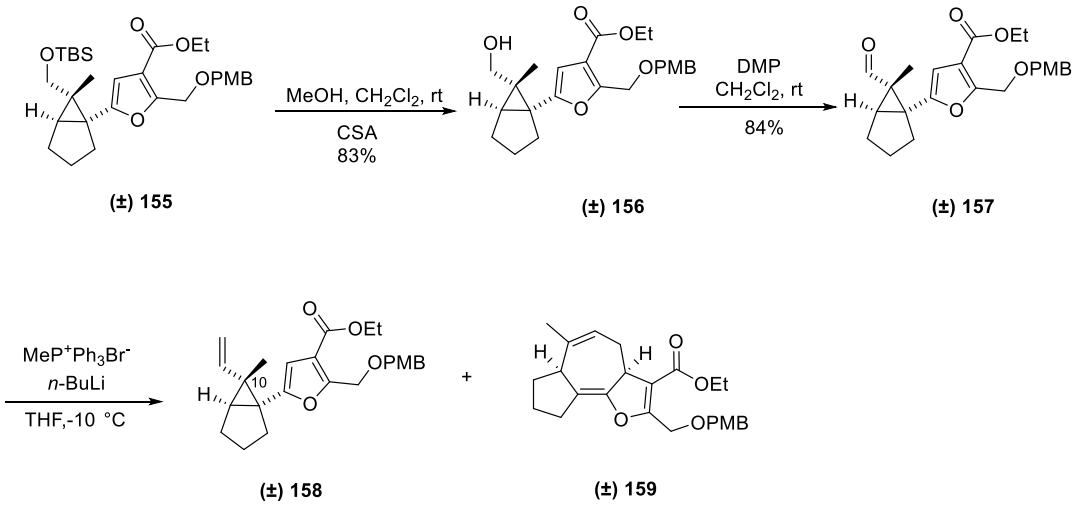


Figure 8

Alcohol **156** was then oxidised using DMP to give the corresponding aldehyde **157**. This aldehyde underwent Wittig olefination to give the vinyl cyclopropane **158**. However, the methylation of aldehyde **157** at low temperature did not deliver only the expected alkene **158** exclusively, instead it delivered an inseparable mixture of the alkene **158** and the tricyclic product **159** with low yield and full conversion. This result was unexpected because the Cope rearrangement typically occurs at elevated reaction temperatures. This result suggests that the methyl group at C10 destabilises the alkene **158** and facilitates immediate rearrangement in the same pot and at a lower temperature (-10 °C) to give the more stable tricyclic products **159**. In an attempt to optimise this reaction, conditions were screened with the aim of improving the product ratio to give more of the of fused tricyclic product.



Scheme 33

4.2.3 Optimisation of the Methylenation and Cope Rearrangement Sequence

Under the optimised Wittig conditions employed for methylenation of the first model system **148** (section 4.1.4) at low temperature, the aldehyde **157** was converted into an inseparable mixture of **158** and **159**. The ratio of **158** to **159** was determined using ^{1}H NMR spectra by integration of the peaks corresponding to alkene peak for C7 at 5.8 ppm in vinylcyclopropane **158** and alkene peak of C9 at 5.48 ppm in tricyclic **159**. When the mixture was stirred for 6 hours and the temperature was maintained at –10 °C, there was full conversion of the starting materials and the compounds **158** and **159** were obtained in 24% yield and a product ratio of 1:1.6 (entry 1) which presented in (Figure 9) with green line. These results suggested that a longer reaction time was needed for the Cope rearrangement reaction to reach completion. The reaction was then stirred overnight starting at –10 °C for 3 hours then the mixture was warmed to RT and stirred for a further 13 hours. Under these conditions there was a further improvement to the yield (30%) and the ratio (1:2.4) (entry 2) (Figure 10). It should be noted that when $CDCl_3$ is used as the NMR solvent it leads to overlapping peaks and the product starts to decompose due to the product being sensitive toward acid. The best NMR solvent to use in this case is C_6D_6 . Raising the temperature after stirring the mixture for 3 hours at –10 °C and then heating the mixture to 60 °C for 18 hours resulted in a further improvement to the yield (41%) and the ratio (1:3.6) (entry 3) which presented in (Figure 9) with red line. Only decomposition products were obtained when the Wittig reaction was performed at –10 °C for 3 hours and the crude product was dissolved in toluene and heated to 110 °C for 18 hours (entry

5). This result suggested that both products are unstable at higher temperatures. The 3,3-sigmatropic rearrangement reaction is a reversible reaction and it is possible that the cycloheptadiene **159** could revert to the cyclopropane **158** which is prone to decomposition at elevated temperatures. The lower yield is attributed to the substrate **158** being thermally unstable and decomposing rather than undergoing the desired rearrangement reaction.

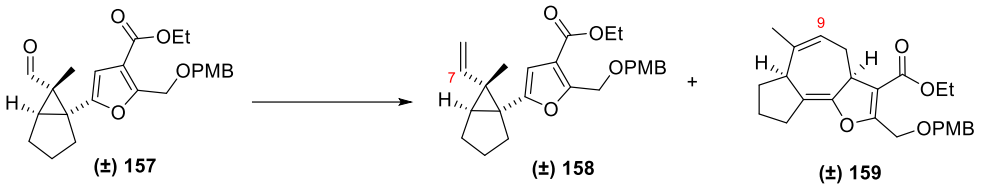


Table 3

Entry	Reagent	Solvent	Temperature	Time	Ratio of 158:159*	Over all yield
1	$MeP^{+}Ph_3Br^{-}$ *n*-BuLi	THF	-10 °C	6 hours	1: 1.6	24%
2	$MeP^{+}Ph_3Br^{-}$ *n*-BuLi	THF	-10 °C - rt	16 hours	1:2.4	30%
3	$MeP^{+}Ph_3Br^{-}$ *n*-BuLi	THF	-10 ˚C - 60 °C	18 hours	1:3.6	47%
4	$MeP^{+}Ph_3Br^{-}$ *n*-BuLi	THF - PhMe	-10 °C - 110 °C	18 hours	_	decomposition

***Ratio was identified using ^{1}H NMR spectra**

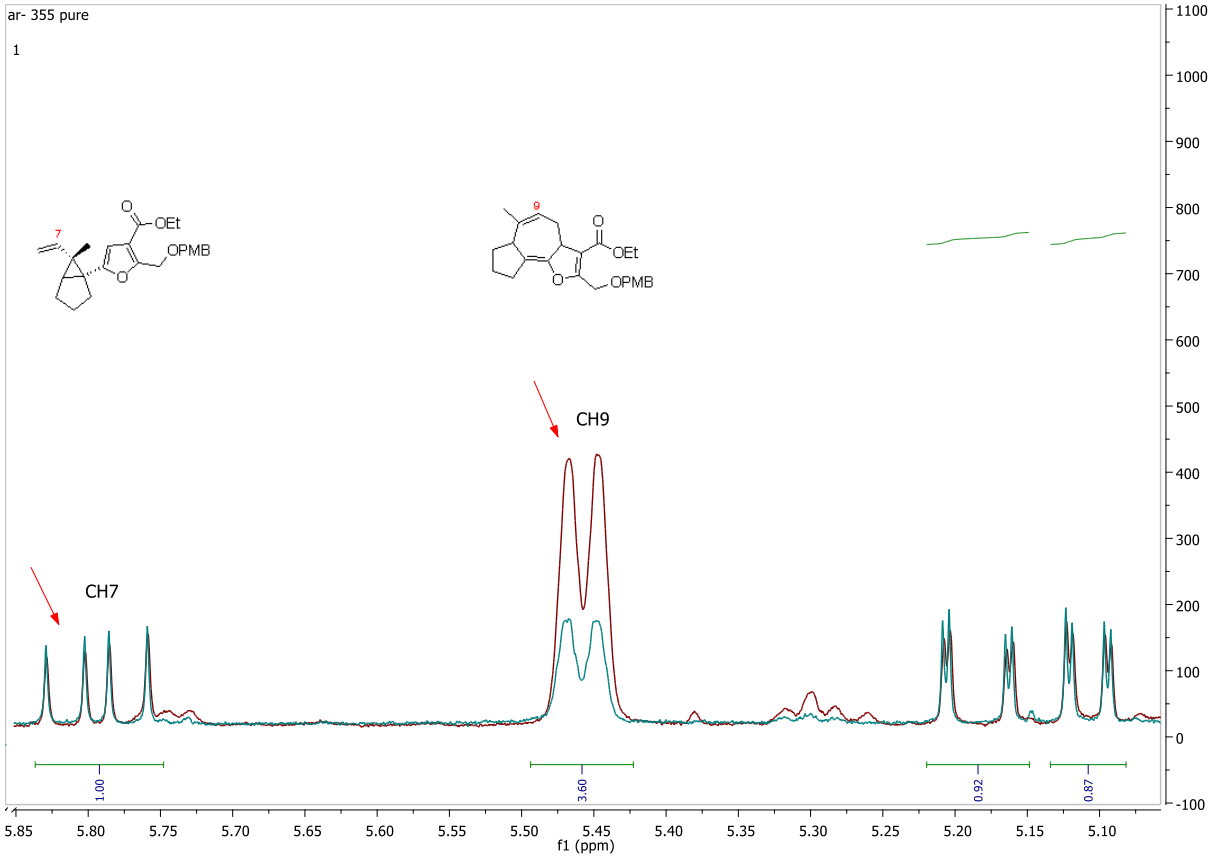


Figure 9

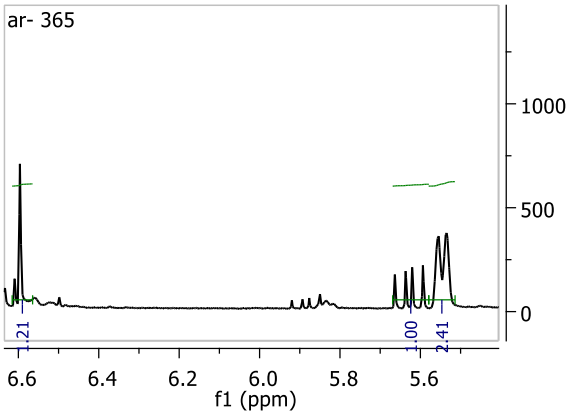
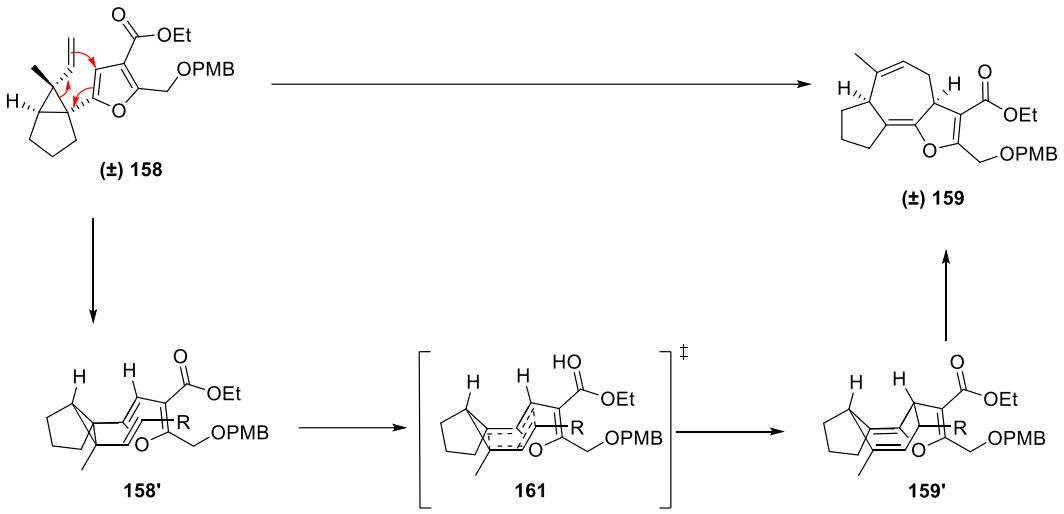


Figure 10

The configuration of the π-systems of the starting material control the stereochemistry of the products of Cope rearrangement reaction. In our case, the alkene **158** undergoes 3,3 sigmatropic rearrangement through the boat-like transition state **161** where both double bonds lie *endo* to each other. This allows Cope rearrangement to take place with excellent stereocontrol to give cycloheptadiene **159** which is more stable than vinylcyclopropane **158** due to the release of strain in the cyclopropane ring (Scheme 34).



Scheme 34

After the synthesis of the model systems, which have similar structures to natural products target by the proposed novel cascade reaction, the reaction sequence was applied to the synthesis of complex natural products that have a similar core system. In this case, the initial natural product targets selected were micheliolide **1** and moroccolide **7** (Figure 11) which have shown activity against KB cancer cells. The reason for choosing them rather than other members of the family is because these compounds could be used as intermediates for the synthesis of many other natural products by functionalisation of the alkene present in the both of them. This would make it possible to synthesise further members of the guaianolide family that are structurally related to micheliolide and morocolide A.

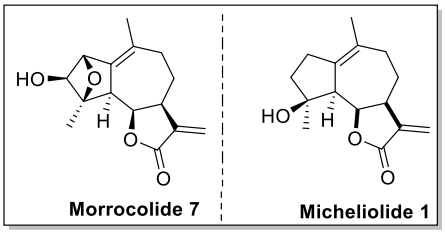
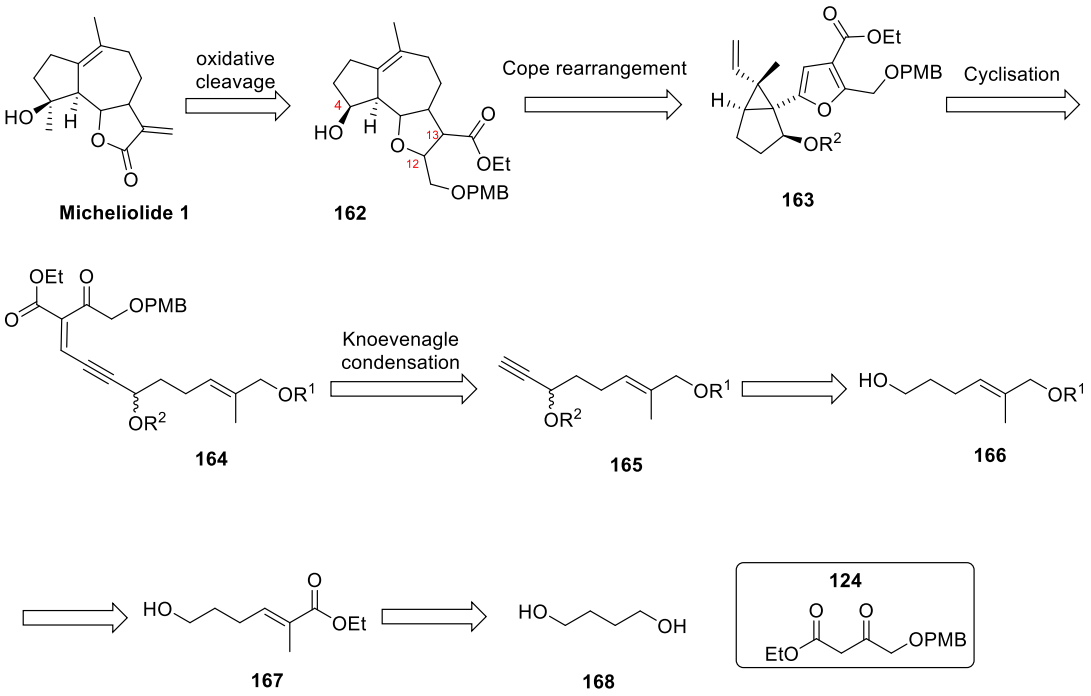


Figure 11

4.3 Micheliolide Synthesis

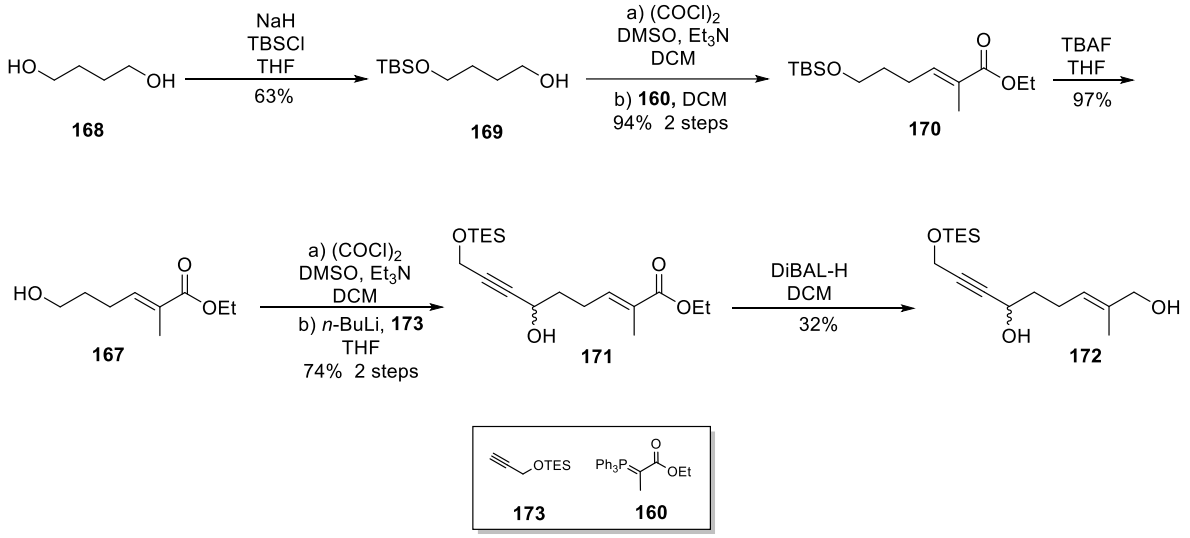
Effort was made to synthesise the core structures of micheliolide and moroccolide A. Retrosynthetic analysis of micheliolide **1** relies on several key reactions which include oxidative cleavage, Cope rearrangement, Brønsted acid cyclisation and Knoevenagel condensation. The retrosynthetic analysis starts with the reduction of ester group of **162** followed by hydration to produce the methylene group at C13. Removal of the PMB group followed by oxidative cleavage of resulting alcohol will produce the lactone carbonyl group at C12. Methylation at C4 of **162** to give tertiary alcohol will furnish the micheliolide **1** (Scheme 35). The cycloheptadiene **162** could be accessed by the Cope rearrangement of the vinyl cyclopropane **163**. Brønsted acid cyclisation of ynenone **164** followed by sequential deprotection, oxidation and methylation will furnish the vinyl cyclopropane **163**. Ynenone **164**, the key acyclic intermediate, could be synthesised by subjecting the aldehyde, prepared from alkyne **165**, to a Knoevenagel condensation reaction with β-keto ester **124**. Alkyne **165** could be obtained by oxidation of alcohol **166** followed by addition of alkyne to resulted aldehyde and protection of the secondary alcohol. Reduction of ester **167** followed by protection of resulting alcohol should give the alcohol **166**. The ester **167** could be accessed in a few steps from the commercially available diol **168**.



Scheme 35

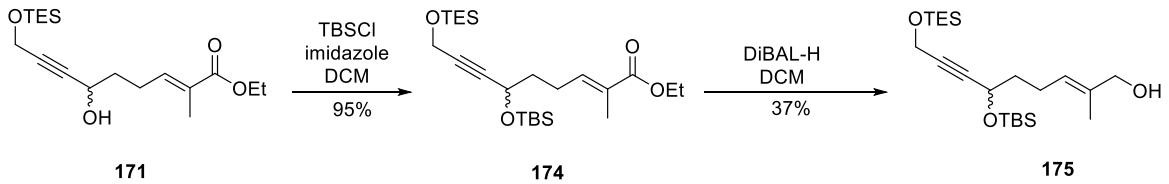
4.3.1 Synthesis of intermediate diol

The initial work toward the synthesis of micheliolide began with mono-protection of butan-1,4-diol (**168**) with TBS to obtain the alcohol **169 (**63%) (Scheme 36).[26] Oxidation of alcohol **169** using standard Swern conditions gave an intermediate aldehyde which underwent Wittig olefination using stabilised Wittig yield **160** to give the α,β-unsaturated ester **170** in excellent yield and with high stereoselectivity (>17:1 (*E*/*Z*) dr by ^{1}H NMR).



Scheme 36

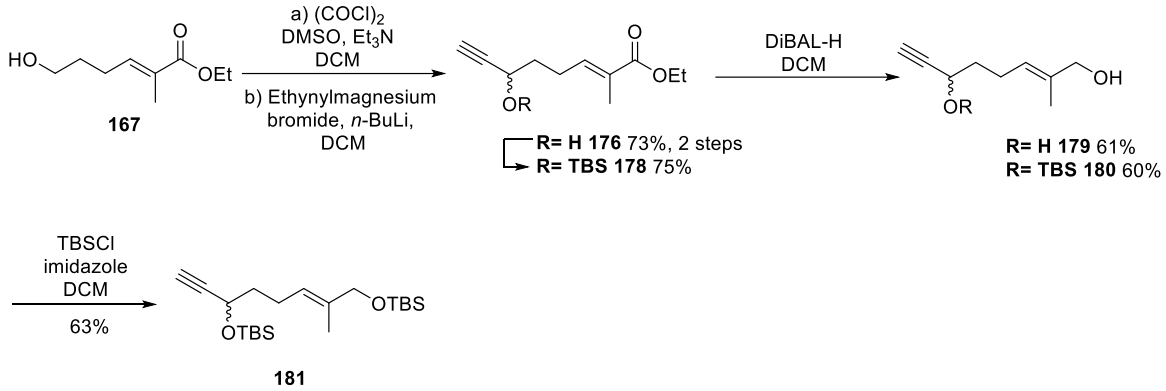
The silyl ether was then cleaved using TBAF to furnish alcohol **167** (97%). Oxidation of alcohol **167** gave the corresponding aldehyde which was subjected directly to nucleophilic addition. Thus, treatment of the alkyne **173** with *n*-BuLi followed by addition of aldehyde produced the secondary alcohol **171** in a yield of 74% over two steps. The ester **171** was reduced with diisobutylaluminium hydride to give diol **172** in low yield, due to loss of the TES group in the presence of the large excess of DiBAL-H that was used to complete the reduction reaction. To improve the yield, the secondary alcohol **171** was first protected with a TBS group to give the ester **174** (Scheme 37). Then ester **174** was reduced to give alcohol **175** and less DiBAl-H was required in the absence of a free hydroxyl group. However, reducing the DiBAL-H equivalents present in the reaction did not result in a dramatic improvement in the yield of **175** because loss of the TES group was still a significant problem under these conditions.



Scheme 37

4.3.2 Alternative alkylation

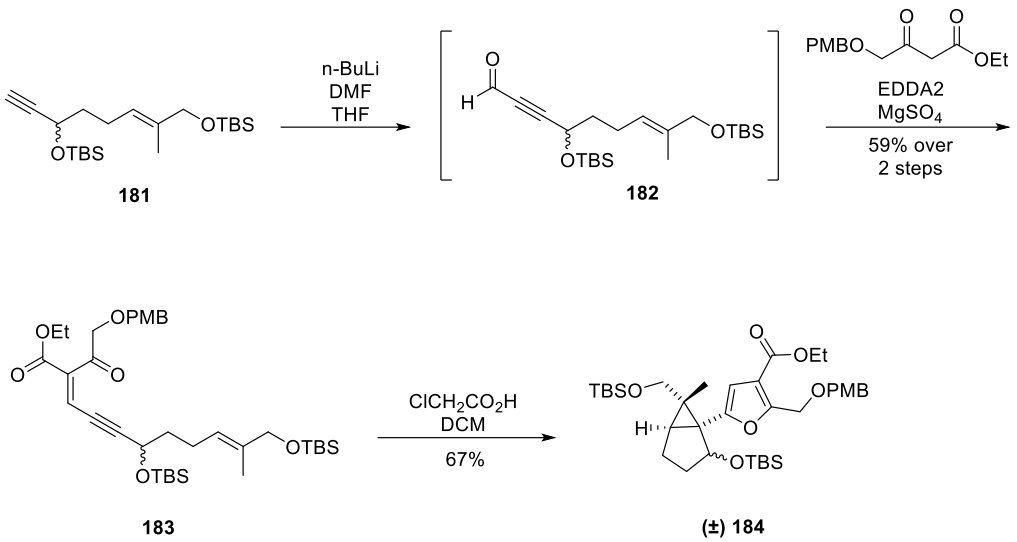
A different alkylation method was investigated in order to improve the yield and reduce the step count. Alcohol **167** was oxidised under Swern oxidation conditions to afford an aldehyde which underwent an alkylation reaction using ethynylmagnesium bromide to give secondary alcohol **176** in 73% over two steps (Scheme 38). The resulting ester **176** was reduced using DiBAl-H to afford the diol **179** in 61% yield and this compound was then reacted with *tert*-butyldimethylsilyl chloride to provide alkyne **181** (63%). The secondary alcohol **176** was protected with a TBS group to reduce the amount of DiBAl-H required and then ester **178** was reduced to give alcohol **180**.



Scheme 38

4.3.3 Furan Formation

Preparation of the intermediate alkyne **181** allowed furan formation to be investigated. Alkyne **181** was subjected to deprotonation using *n*-butyl lithium and subsequent addition of DMF afforded the aldehyde **182** (Scheme 39).[19] A Knoevenagel condensation reaction then produced a mixture of the ynenone **183** (dr 1:0.55 (*E*/*Z*)) and furan **184**. Ynenone **183** was converted into the furan **184** using chloroacetic acid in 67% yield.



Scheme 39

Attempts to cleave the TBS group of **184** were unsuccessful, when conditions that had been used for the model system (section 3.2.2) were employed (Entry 1, Table 4). Reaction of **184** with various acids resulted in decomposition or the recovery of the starting material (Entry 2-4).

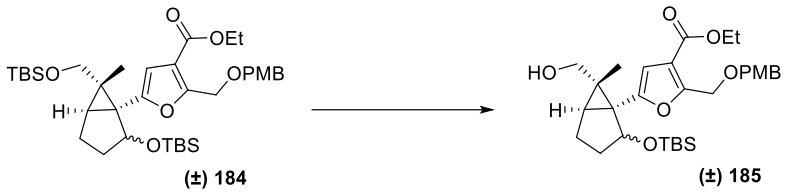
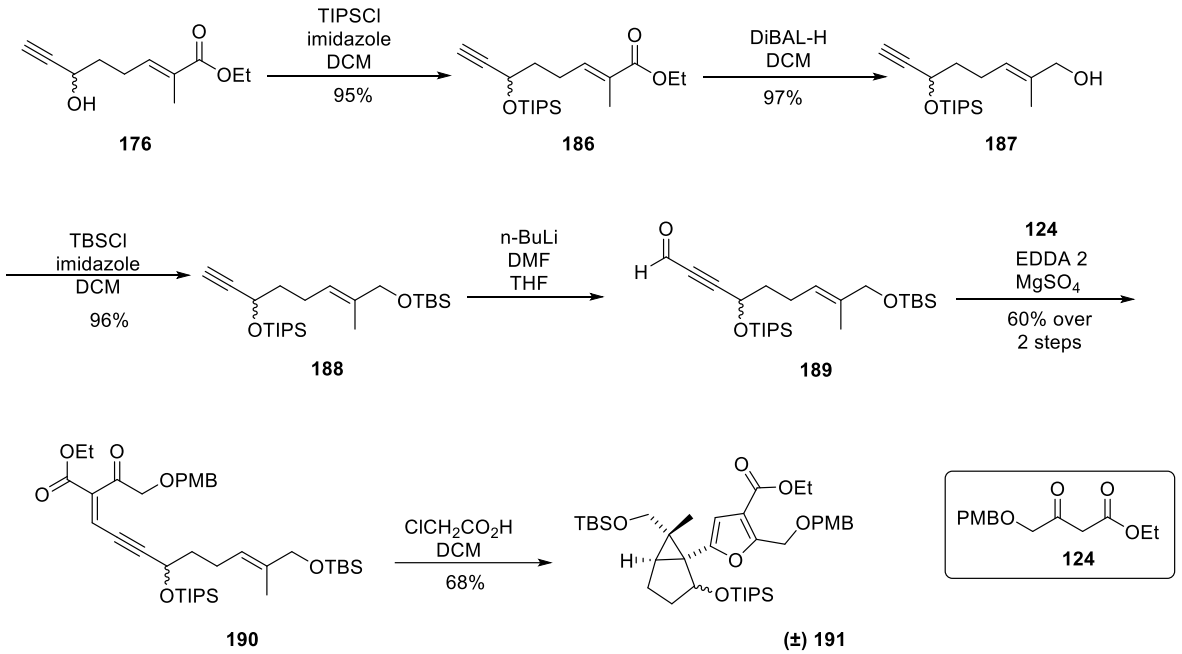


Table 4

Entry	Reagent	Solvent	Temperature	Time	Yield
1	CSA	MeOH:DCM 5:2	rt	3 hours	Decomposition
2	CSA	MeOH:DCM 1:1	-20 ˚C	5 hours	Decomposition
3	PPTS	THF	-10 ˚C - rt	16 hours	SM
4	AcOH	THF:water 1:1	rt	4 hours	SM

4.3.4 Alternative Protecting Groups

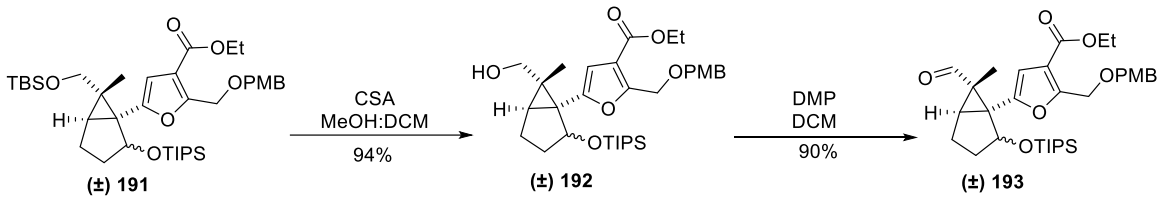
Careful choice of protecting group was necessary to allow for differentiation between the primary alcohol and secondary alcohol when performing deprotection of the primary alcohol later in the synthetic sequence. To overcome this problem the secondary alcohol **176** was protected with a TIPS group to give alkyne **186** in 95% yield (Scheme 40). Alkyne **186** was then subjected to the sequence of reactions used previously. Reduction of ester **186** was achieved in good yield (97%) using DiBAl-H and the resulting alcohol **187** was then protected with TBS group to give **188**. Formylation of alkyne **188** to give the aldehyde **189** was achieved by treatment with *n*-BuLi followed by DMF. Aldehyde **189** was subjected to Knoevenagel condensation to give the ynenone **190** (dr 1:0.49 (*E*/*Z*)) and this compound was treated with acid to induce cyclisation and produce the furan **191** in good yield.



Scheme 40

4.3.5 Cycloheptadiene Formation by Cope Rearrangement

The furan **191** was deprotected to give alcohol **192** in excellent yield 94% (Scheme 41).[19] Oxidation of alcohol **192** using Dess Martin periodinane resulted in formation of aldehyde **193** (91% yield).



Scheme 41

Wittig methylation of the aldehyde **193** gave only tricyclic ester **195** with no evidence of vinyl cyclopropane **194** formation as can be seen in (Figure 12) the disappearance of CH peak corresponding to C7 in **194** which should appear at range of 5.60 ppm to 5.90 ppm in ^{1}H NMR spectra , only the peak at 5.4 ppm corresponding to C9 alkene CH of tricyclic **195** was observed in the ^{1}H NMR spectrum of the product (Figure 11). Prolonging the reaction time at RT resulted in formation of the more stable product **195** in yield 31% (Entry 1, Table 5). Increasing the temperature improved the yield to 47% and only the cycloheptadiene **195** was obtained (Entry 2). Using both a prolonged time and a higher reaction temperature resulted in decomposition. The presence of the substituent at C4 seemed to promote the Cope rearrangement when the outcome of the reaction is compared to the result obtained from the Cope rearrangement of the second model system. The tricyclic triene **195** is very sensitive to air and the absence of an inert atmosphere results in decomposition.

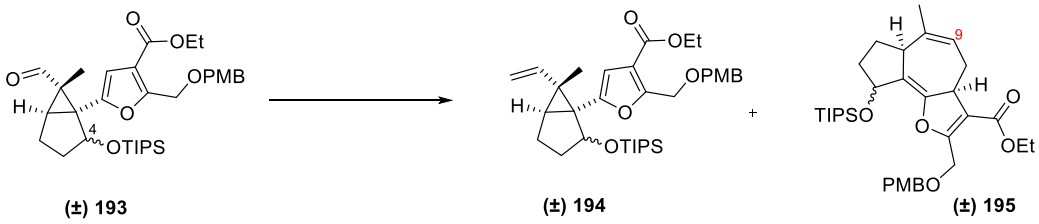


Table 5

Entry	Reagent	Solvent	Temperature	Time	Ratio* 194:195	Yield A
1	$MeP^{+}Ph_3Br^{-}$ *n*-BuLi	THF	-10 ˚C - rt	18 hours	0:1	31%
2	$MeP^{+}Ph_3Br^{-}$ *n*-BuLi	THF	-10 ˚C – 60 ˚C	16 hours	0:1	47%

***Ratio was determined by ^{1}H NMR**

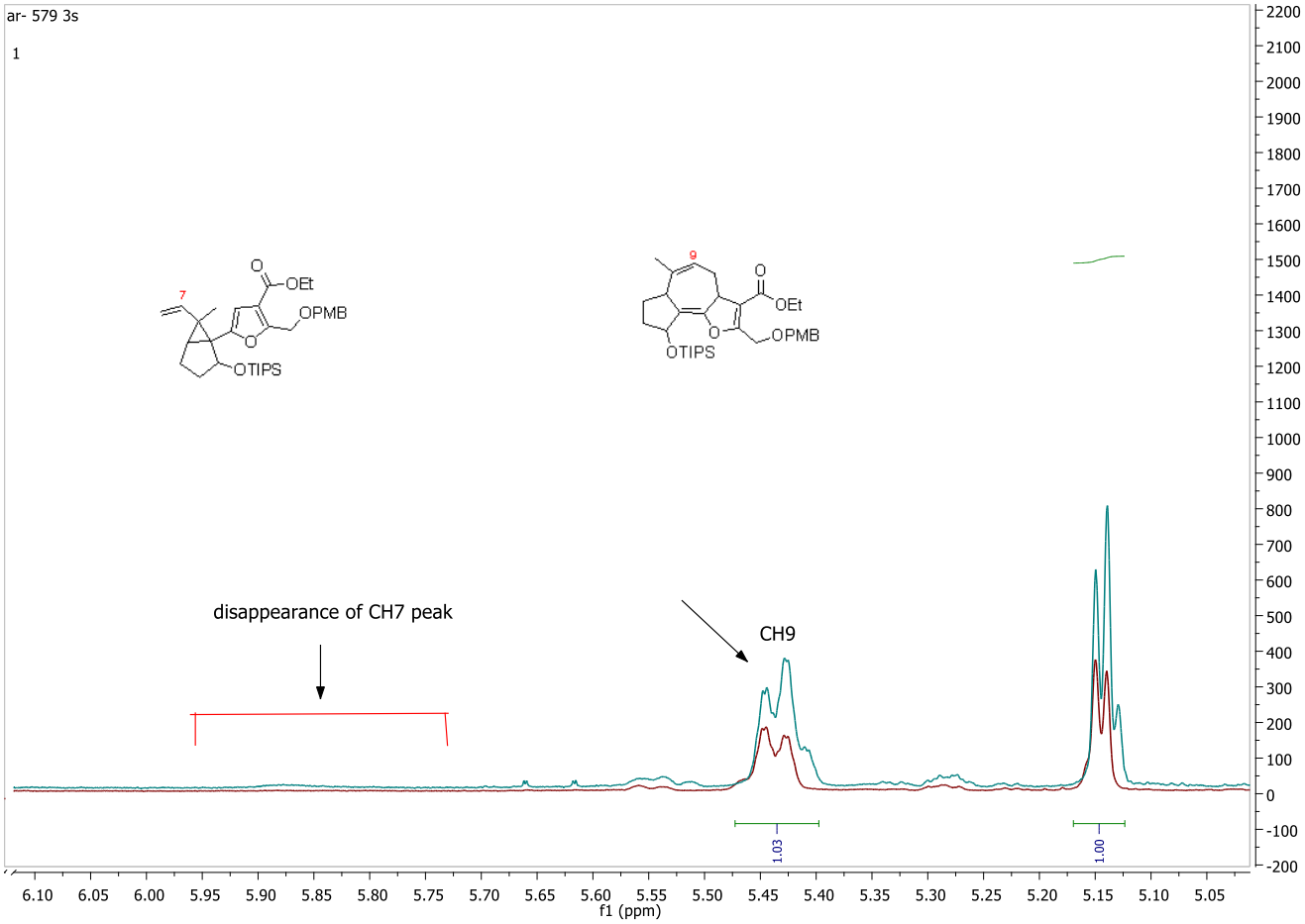

ar- 579 3s
1
7
O
OEt
OPMB
O
OTIPS
9
O
OEt
O
OPMB
OTIPS
disappearance of CH7 peak
CH9
1.03
1.00
6.10 6.05 6.00 5.95 5.90 5.85 5.80 5.75 5.70 5.65 5.60 5.55 5.50 5.45 5.40 5.35 5.30 5.25 5.20 5.15 5.10 5.05
f1 (ppm)
2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200

Figure 12

4.3.6 Reduction of Cycloheptadiene 195

As the micheliolide natural products feature only one alkene inside the tricyclic system (Figure 13), it was essential to be able to reduce the alkenes selectively while retaining the required alkene (C9-C10). Several methods were investigated in an attempt to achieve selective reduction of the highly unsaturated intermediate.

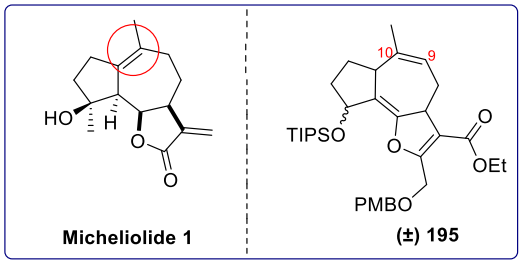
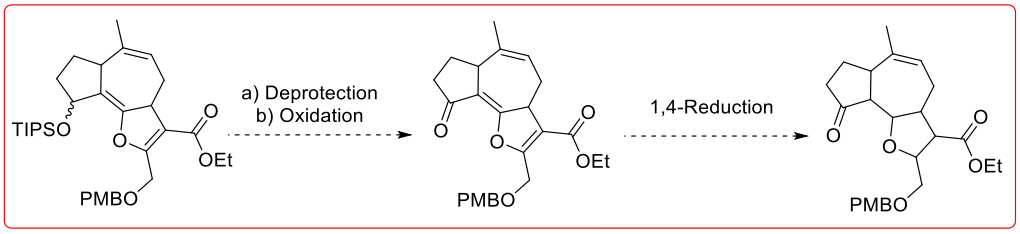


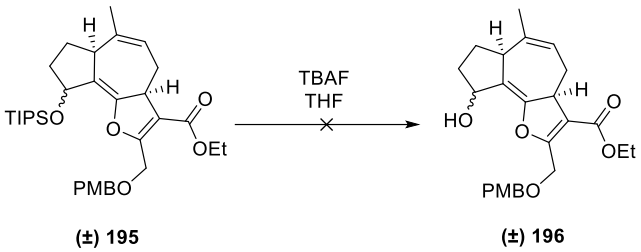
Figure 13

Selective alkene reduction while retaining the desired alkene proved to be very challenging. The first method proposed to achieve this type of reduction was 1,4 reduction because both unwanted alkenes are positioned close to appropriate oxygen functionality. One alkene is conjugated with an ester while the other has an allylic silyl ether that could be converted into a ketone by removal of TIPS group and subsequent oxidation. The resulting enone could then be subjected to 1,4-reduction to deliver the partially saturated product (Scheme 42).



Scheme 42

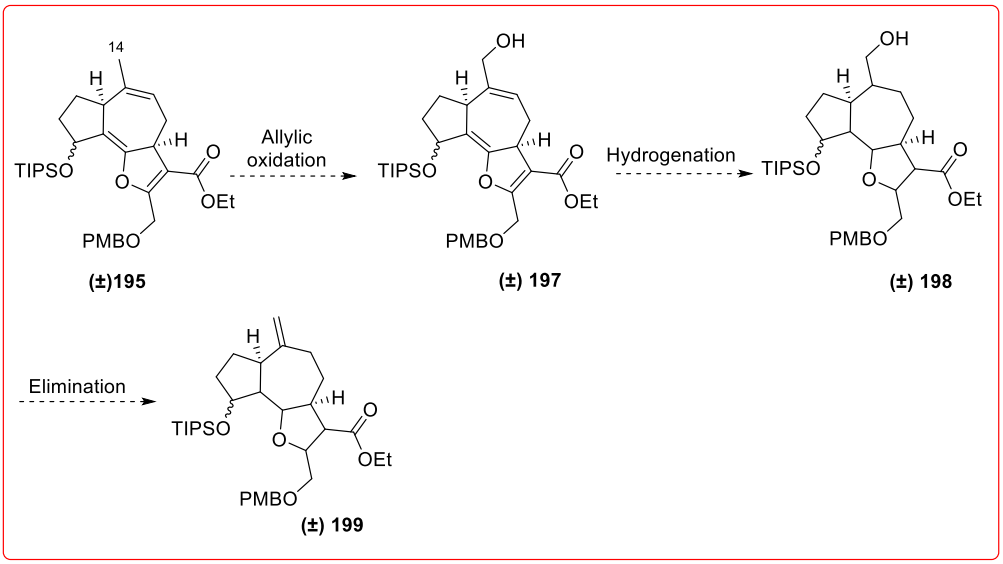
The high reactivity of the system in **195** presented significant challenges. All attempts to remove the TIPS group in **195** failed to deliver the required allylic alcohol and led to decomposition instead (Scheme 43).



Scheme 43

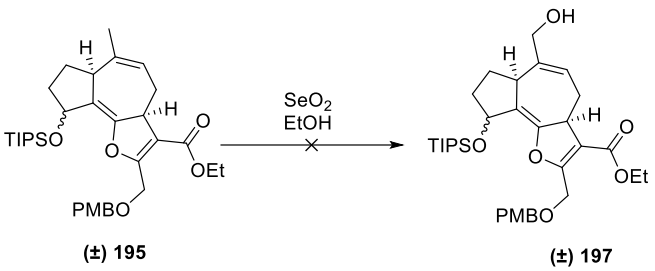
4.3.8 Allylic Oxidation of Tricyclic 195

The second approach to access the desired product involved allylic oxidation of the methyl substituent to install the hydroxyl group at C-14 in **195** to give the alcohol **197** (Scheme 44). Subjection of the tricyclic alcohol **197** to hydrogenation using Pd/H_2 to give the fully saturated alcohol **198** followed by dehydration was expected to give alkene **199**. It should be possible to isomerise this compound and so migrate the olefin at the required position.



Scheme 44

Unfortunately, allylic oxidation of the cycloheptadiene **195** resulted in decomposition because this tricyclic compound is very sensitive to oxidative conditions. In fact, the compound appears to be unstable even to prolonged exposure to air (Scheme 45).



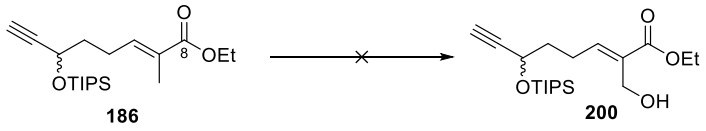
(±) 195 (±) 197

Scheme 45

At this stage the installation of the hydroxyl group at an earlier stage in the route was considered, so as to avoid late-stage decomposition.

4.3.8 Allylic Oxidation of Ester 186 and Alkyne 188

The ester **186** subjected to the allylic oxidation conditions. In this case, the ester group blocks the unwanted oxidation at C-8 (Table 6). Unfortunately, both sets of oxidation conditions failed to deliver the required product **200** and only unreacted starting material was isolated.



186 200

Table 6

Entry	Reagent	Solvent	Temperature	Time	Yield
1	1 eq SeO_2 4 eq t-BuOOH	DCM	RT	19 hours	SM
2	0.8 eq SeO_2	Ethanol	60 ˚C	2 days	SM

The alkyne **188** was also subjected to allylic oxidation conditions (Table 7), but in both cases the aldehyde by-product **202** was obtained instead of the required allylic alcohol **201**.

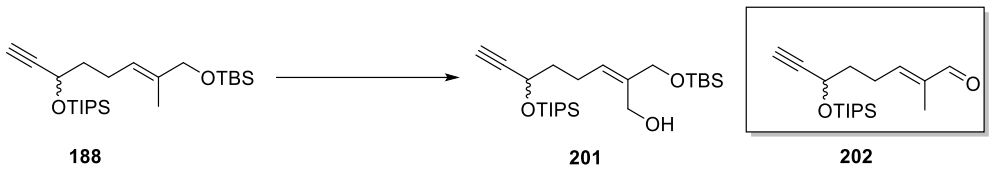
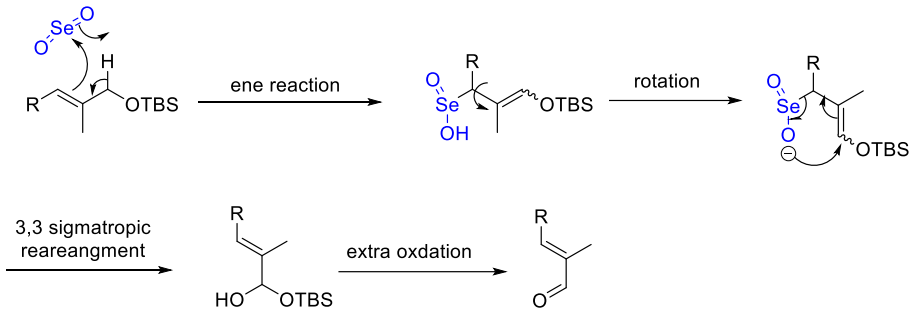


Table 7

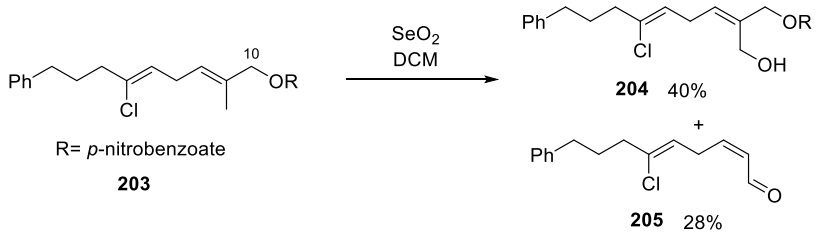
Entry	Reagent	Solvent	Temperature	Time	Yield 304	Yield 305
1	1 eq SeO_2 4 eq t-BuOOH	DCM	RT	2 days	0	60%
2	0.8 eq SeO_2	Ethanol	60 ˚C	16 hours	0	98%

Hideo Kigoshi and co-workers have suggested that in this type of structure the oxygen substituent activates the CH_2 position to oxidation in preference to CH_3 group.[27] The transformation of alkyne **188** to undesired aldehyde **202** could be explained by oxidation at the C-3 oxymethylene group (Scheme 46).



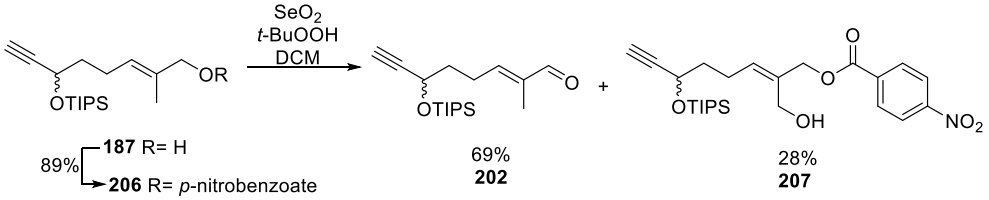
Scheme 46

Considering that the electron density of the allylic position is important for the regioselectivity of this allylic oxidation reaction, a reduction in the electron-density at the C-10 oxymethylene group in **203** could improve the regioselectivity of the reaction. Hideo Kigoshi and co-workers found that the best electron-withdrawing group at C-10 in compound **203** for allylic oxidation was *p*-nitrobenzoate. Although this group gave the best results, they still obtained low yields 40% of the desired products **204** and 28% of the unwanted aldehyde **205** (Scheme 47).[27]



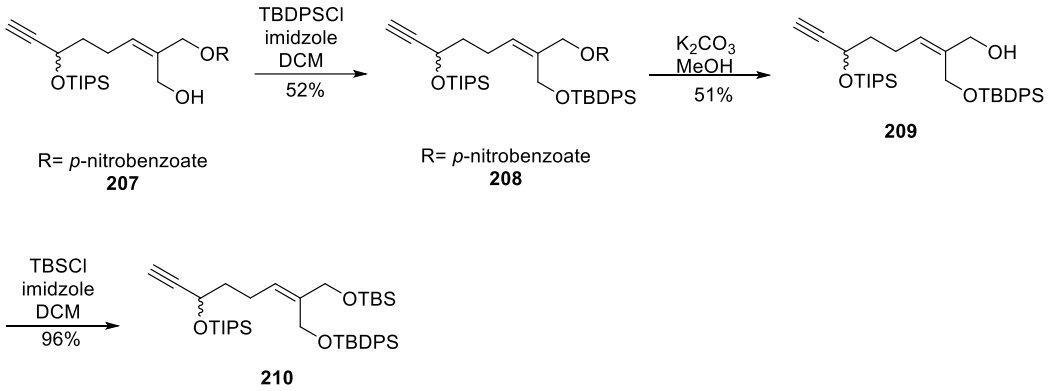
Scheme 47

Inspired by their finding, we applied this approach in our system. Alcohol **187** was first protected as a *p*-nitrobenzoate ester to give **206** in 89% yield (Scheme 48). The alkyne **206** was then treated with selenium dioxide to give alcohol **207** in a low yield of 28% along with the aldehyde **202** (69% yield).



Scheme 48

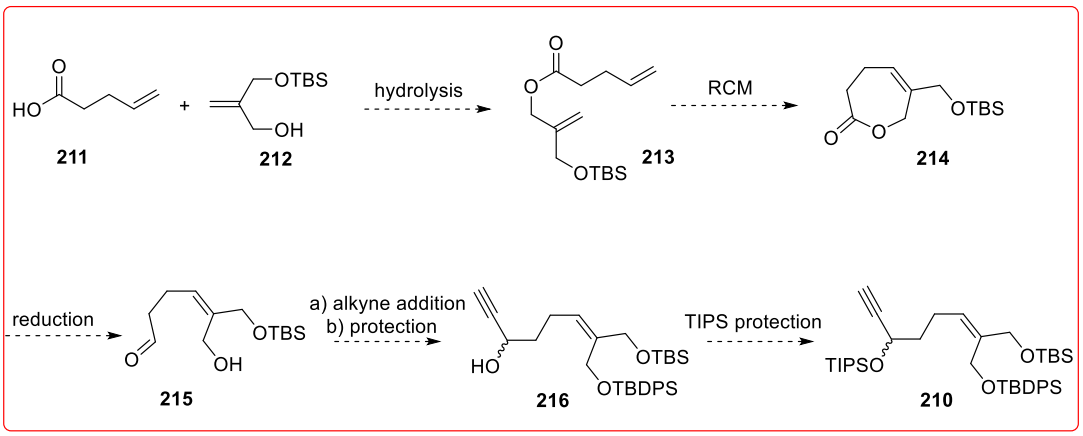
The alcohol **207** was then protected with TBDPS group to yield alkyne **208** and the *p*-nitrobenzoate group was removed by treatment with K_2CO_3 in methanol to afford the alcohol **209** in 53% yield (Scheme 49). Protection of alcohol **209** with a TBS group gave the alkyne **210** in 84% yield. However, the overall yield using allylic oxidation was poor and not convenient because only a small amount of the desired product was obtained and the major product was a by-product. For this reason, a different method to access intermediate alkyne **210** was essential.



Scheme 49

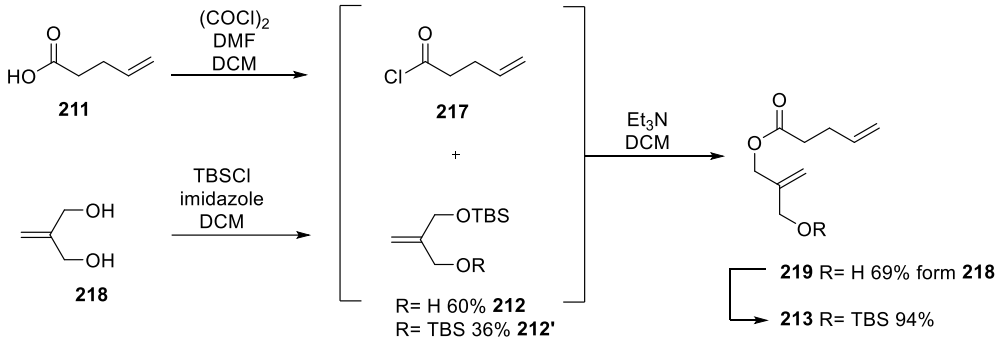
4.3.9 RCM Route to Access the Intermediate Alkyne 210

A completely different route was devised to access the required alkyne **210** (Scheme 50). The proposed route relied on an RCM reaction to form the seven-membered lactone **214** which would secure the stereochemistry of our alkyne intermediate **210**. This lactone **214** could be synthesised by coupling of the acid **211** and allylic alcohol **212** by esterification to give diene **213** (Scheme 50). The diene **213** would then undergo RCM to produce the lactone **214**. The lactone **214** would then be reduced using a suitable reducing agent to give the aldehyde **215**. Addition of alkyne to aldehyde **215** followed by protection of the primary alcohol with a TBDPS group would then yield the alcohol **216**. Protection of the secondary alcohol **216** with a TIPS group would then complete the stereocontrolled synthesis of the alkyne **210**.



Scheme 50

The new route started with the chlorination of acid **211** to give crude acid chloride **217** (Scheme 51). Mono-protection of diol **218** afforded known alcohol **212** in reasonable yield.[28] Coupling of the acyl chloride **217** and the alcohol **212** resulted in formation of the diene **219** in good yield. The TBS was removed due to the acidic environment and it was re-introduced to give **213**.



Scheme 51

The diene **213** was then subjected to RCM using Grubbs second generation catalyst to give the seven-membered lactone **214**. However, it transpired that the reaction was more challenging than expected and even after efforts to optimise it the major product was the dimer **220**.

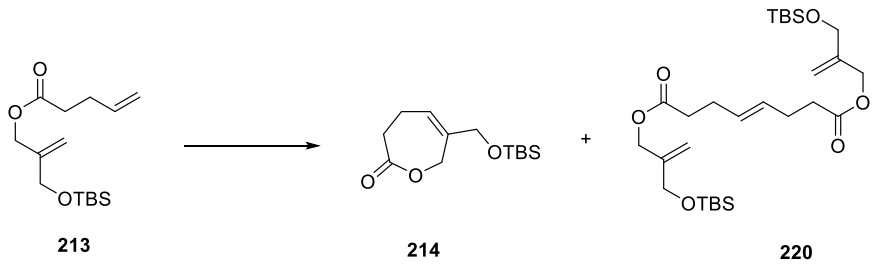


Table 8

Entry	Solvent	Gr^{2end}	Time	T ˚C	Lactone **214**	Dimer **220**
1	DCM 250 ml for 200 mg	8%	18 hours	40 ˚C	20%	53%
2	DCM 350 ml for 200 mg	5%	18 hours	40 ˚C	21%	45%

3	PhMe 200 ml for 200 mg	7%	18 hours	70 ˚C	10%	39%
4	PhMe 200 ml for 100 mg	5%	18 hours	70 ˚C	15%	40%

When DCM was used as a solvent and an 8% catalyst loading was employed, just a 20% yield of the desired ketone **214** and a 53% yield of dimer **220** was obtained (entry 1, Table 8). Reducing the loading of the catalyst to 5% and making the mixture more dilute in DCM resulted in a 45% yield of the dimer and 21% yield of the ketone (entry 2). Switching the solvent to PhMe did not improve either the yield or the product ratio (entries 3 and 4).

The nature of the alkene and the length of the tether that links the reacting alkene is important in RCM reactions. In our system, there is an allylic ester group and coordination of the carbonyl oxygen to the Ru complex could deactivate the catalyst or prevent reaction of the intermediate metal alkylidene with the remaining alkene (Figure 14).[29]

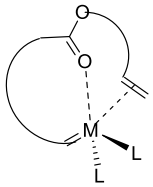
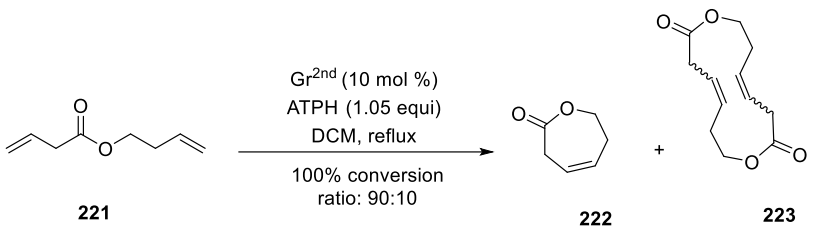


Figure 14

To overcome this type of problem, Nguyen suggested a Lewis acid additive could be used to prevent coordination of the carbonyl oxygen to Ru and improve the outcome of the RCM reaction. Many Lewis acid were used with dialkene **221** (Scheme 52) and the best result was obtained when the aluminium tris(2,6-diphenyl)phenoxide (ATPH) was used. Addition of this Lewis acid resulted a 100% conversion of the starting materials with the formation of the desired product **222** and the dimeric by-product **223** with 90:10 ratio respectively.[30] The bulky Lewis acid aluminium tris(2,6-diphenyl)phenoxide (ATPH) (Figure 15) is thought to create a pocket by coordination to Ru and orientate the two alkenes to favour direct cyclisation rather than dimerisation.[30]



Scheme 52

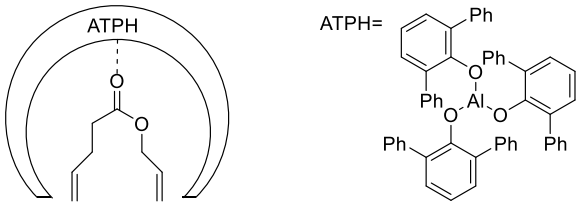
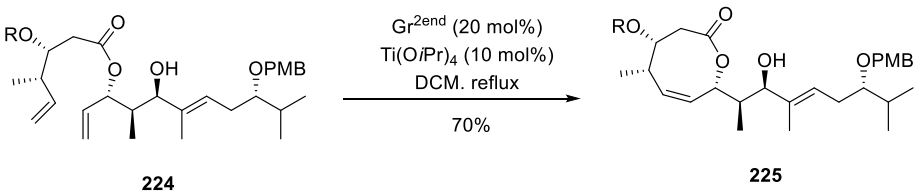


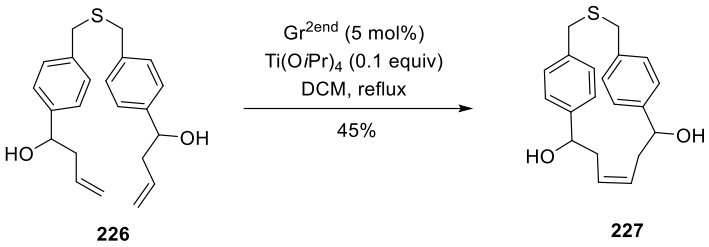
Figure 15

Many Lewis acid can be used to break up internal chelation and the most common and effective procedure involves the use of a catalytic amount of Ti(O*i*Pr)$_4$ as an additive with the second generation Grubbs catalyst. White and his group synthesised the lactone **225** in good yield by direct RCM using Ti(O*i*Pr)$_4$ as an additive (Scheme 53).[31]



Scheme 53

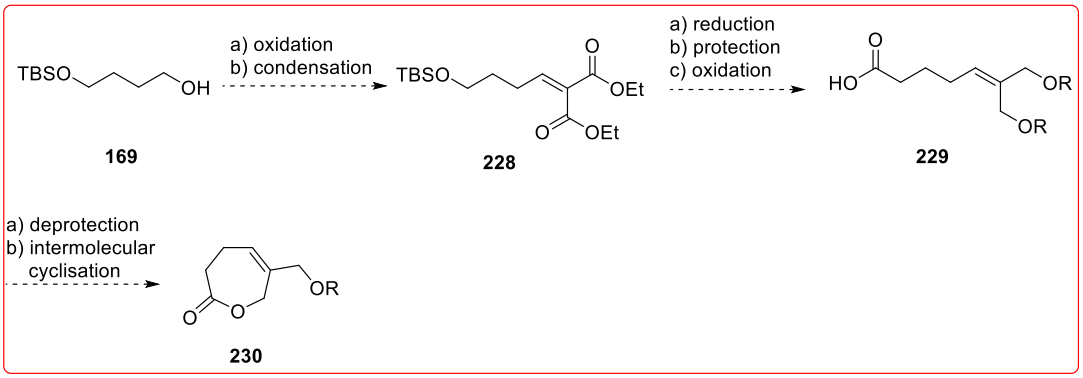
In 2020, Ansari used Ti(O*i*Pr)$_4$ in an RCM reaction to form thiametaparacyclophane **227** from diene **226** (Scheme 54). The RCM reaction did not occur in the absence of Ti(O*i*Pr)$_4$ and this clearly shows the importance of the Lewis acid to induce RCM reaction.[32]



Scheme 54

4.3.10 Intermolecular Base Route to Access Lactone 230

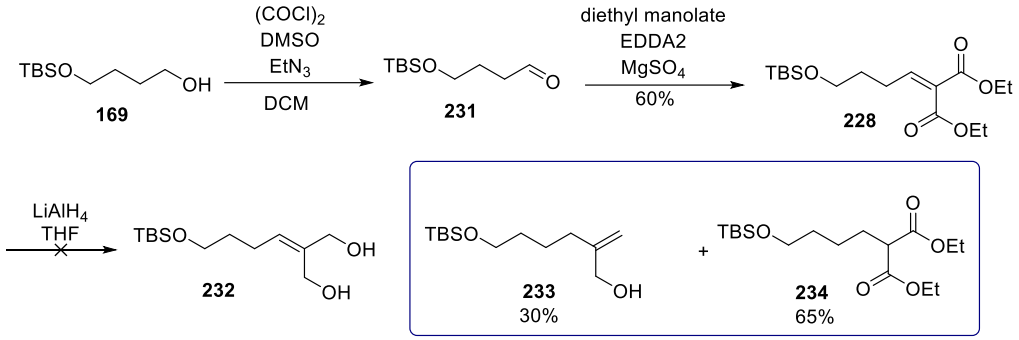
A second route that involved intramolecular cyclisation but avoided the unsuccessful RCM reaction was devised. This route commenced with oxidation of alcohol **169** to give an intermediate aldehyde followed by Knoevenagel condensation to give alkene **228** (Scheme 55). The diester **228** would be reduced to a diol which would be protected with suitable groups. Removal of the silyl group and oxidation of the alcohol would give carboxylic acid **229**. Deprotection of diol **229** would allow the intermolecular cyclisation to take place to give the lactone **230**.



Scheme 55

The new route started with a Swern oxidation of alcohol **169** to give aldehyde **231** (Scheme 56). Reaction of the aldehyde **231** with diethyl malonate under optimised Knoevenagel condensation conditions furnished alkene **228**. Attempted reduction of the diester **228** using $LiAlH_4$ was not successful and the desired diol (**232**) was not obtained. Instead, the by-products

233 (30%) and **234** (65%) were obtained due to the conjugate reduction of the alkene prior to, or instead of, reduction of the ester carbonyl group.



Scheme 56

To avoid these unwanted by-products DiBAl-H, which is a weaker reducing agent than $LiAlH_4$, was used under various reaction with the expectation that conjugate reduction of the alkene would be avoided. When the reduction reaction was performed in DCM at low temperature, the alcohol (**235**) was produced in 21% yield alongside the saturated diester **234** in 61% yield (entry 1, Table 9). Some reports suggest that solvent choice is important when seeking to avoid the conjugate reduction.[33] The solvent was consequently changed to toluene and three different conditions were screened. Reactions at all three temperatures resulted in formation of the alcohol **235** as a major product and the diester **234** as a minor product (entries 2-4, Table 9). It appears that the temperature did not affect the product ratio significantly and it was most efficient to perform the reaction at rt. The choice of solvent did have a profound effect on the by-product ratio (compare entries 1 and 2, Table 9). However, all conditions failed to deliver the required diol **232**.

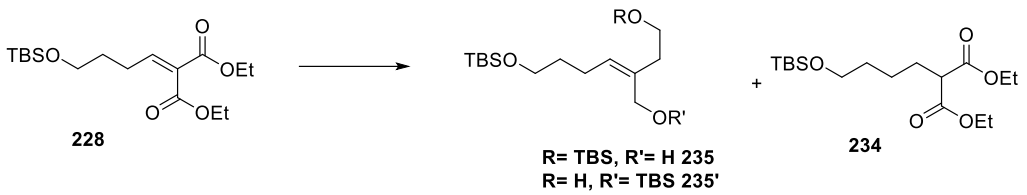
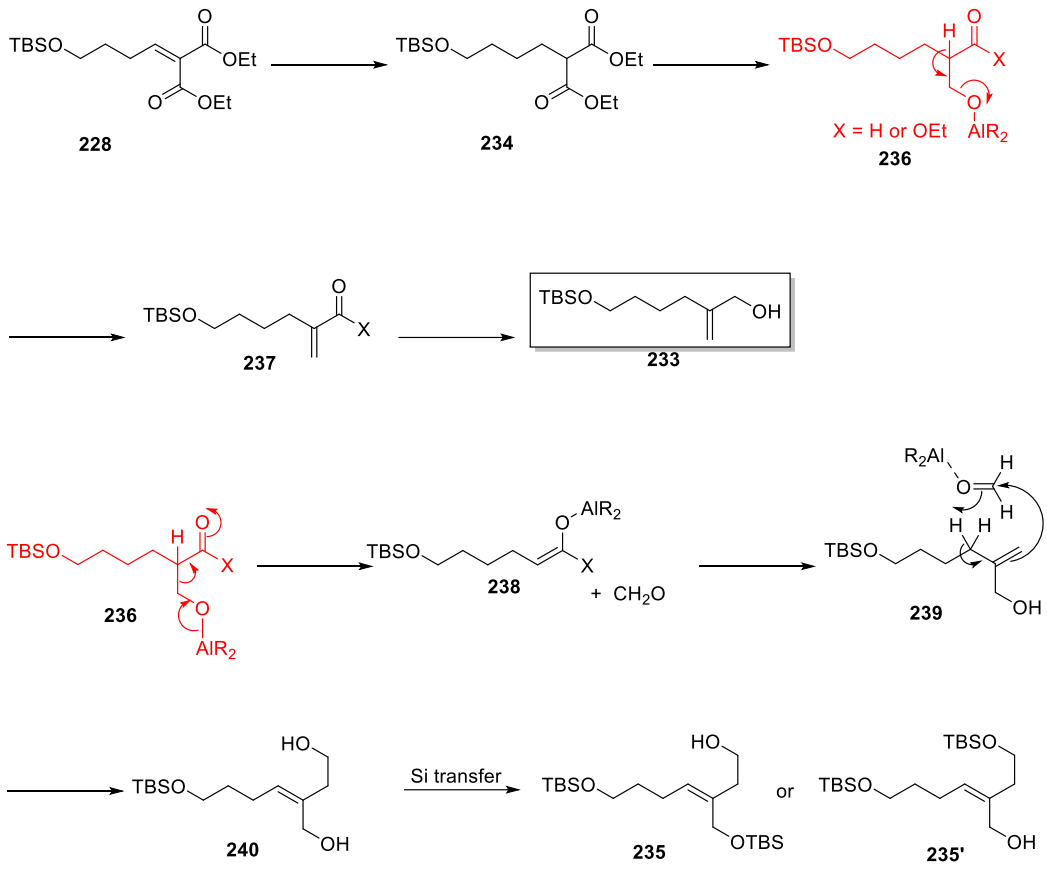


Table 9

Entry	Solvent	Temperature	228 or 228’	227
1	DCM	-78 ˚C	21%	61%
2	PhMe	-78 ˚C	62%	22%
3	PhMe	-30 ˚C	62%	34%
4	PhMe	rt	58%	26%

In order to produce both by-products (**233** and **235**) the proposed mechanism suggests that the by-products come from the same intermediate **236** (Scheme 57). The conjugate reduction occurs first to give diester **234**. This is followed by elimination of the O-AlR_2 group giving the alkene **236**. Ester **236** is further reduced and results in formation of alcohol **233**. The mechanism of formation for by-product **235** involves the intermediate **236**, where AlR_2 attack the O-C bond to result in formation of the enolate **238** and formaldehyde. Elimination of O-AlR_2 followed by an ene reaction between the intermediate **238** and formaldehyde produces the diol **240**. Subsequent silyl group migration delivers the alcohol **235**. It was suggested in 2008 by Nobuyuki Imai that having aromatic ring conjugated to the alkene will prevent conjugate reduction of the alkene, but this functionality is absent in our system.[34]



Scheme 57

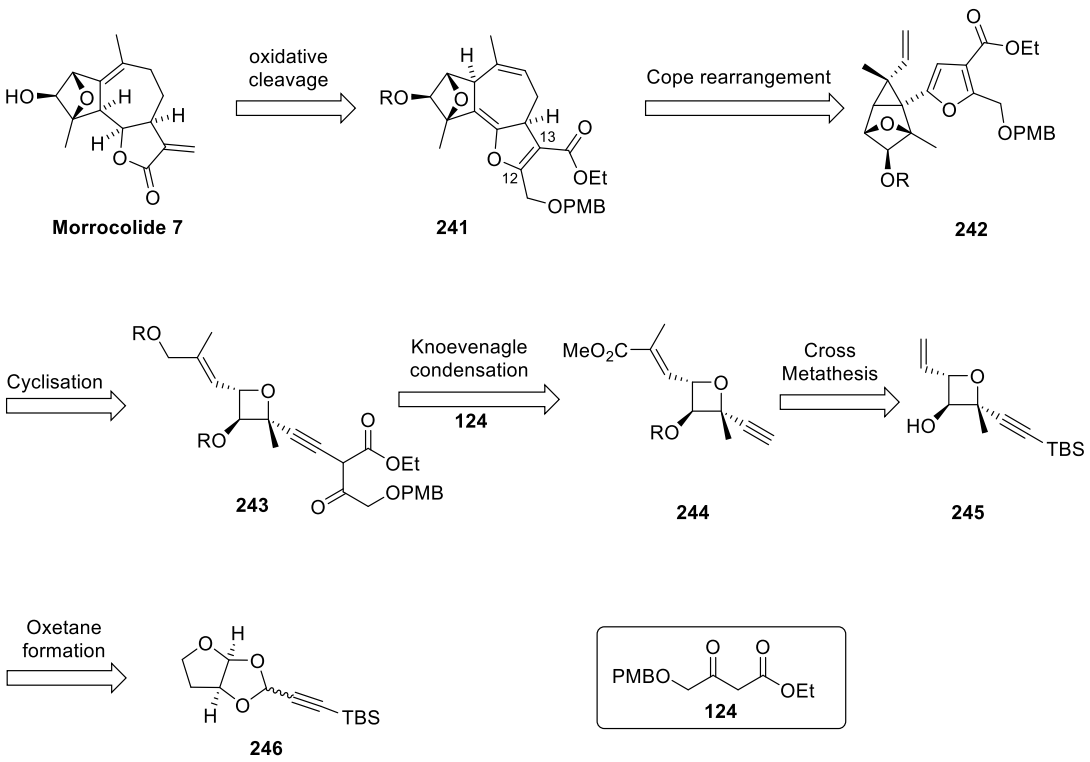
Due to time constraints, the synthesis of micheliolide stopped at this point. However, the synthesis of the alkyne **210** intermediate represents an area for future work.

4.4 Moroccolide 7

Moroccolide 7 possesses an oxetane in its structure core. Oxetane is a heterocyclic organic compound having a four-membered ring with three carbon atoms and one oxygen atom. Oxetanes are useful building blocks and are found as sub-units in many bioactive natural products e.g. Taxol.

4.4.1 Retrosynthetic Analysis of Morocloide 7

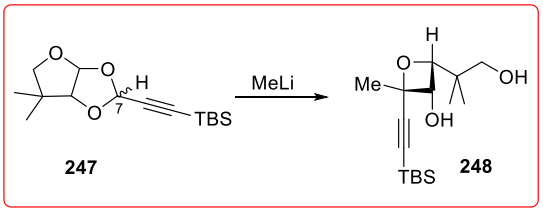
The retrosynthetic analysis of morocolide **7** begins with reduction of ester group of **241** followed by hydration to produce the methylene group at C13 (Scheme 58). Removal of the PMB group followed by oxidative cleavage of resulting alcohol to give ketone at C12 will furnish the morocolide **7**. The cycloheptadiene **241** could be accessed by the Cope rearrangement of the vinyl cyclopropane **242**. Brønsted acid cyclisation of ynenone **243** followed by deprotection of primary alcohol, oxidation and olefination will furnish the vinyl cyclopropane **242**. Ynenone **243**, the key intermediate, could be synthesised by reduction of the ester **244** and protection of resulted alcohol followed by Knoevenagel condensation reaction with β-keto ester **124**. Ester **244** could be obtained by protection of the alcohol **245** and then CM (cross metathesis) with methyl methacrylate. Oxetane **245** would then be obtained from the acetal **246**.



Scheme 58

4.4.2 Synthesis of the Oxetane Unit from Dihydrofuran

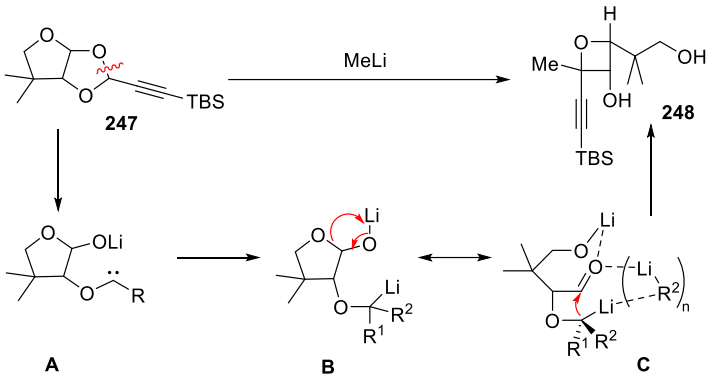
To access the required oxetane intermediate several routes were proposed. The first route involved a stereoselective approach using the Tomooka's method, in which the acetal **247** was treated with MeLi in order to methylate at C-7 (Scheme 59).[35] This methylation reaction resulted in ring opening and rearrangement to form the oxetane **248** in one step.



Scheme 59

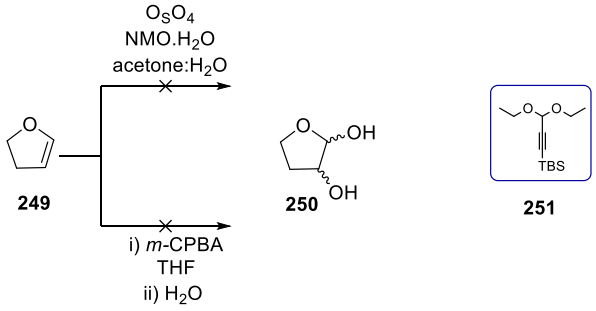
The reaction mechanism most likely involves the carbene intermediate **A** which is formed by the O-C bond cleavage in acetal anion **247** (Scheme 60). The carbene **A** inserts into the alkyl lithium to form a lactol alkoxide **B** that then isomerizes to give the aldehyde **C**. Finally,

aldehyde **C** undergoes intramolecular nucleophilic addition to produce the oxetane **248**. The key to this process is the generation of the lactol alkoxide **B**, which acts as a masked aldehyde and reacts only with an intramolecular nucleophile but does not react with the alkyl lithium reagent.



Scheme 60

The initial work concerning formation of the intermediate oxetane commenced with dihydroxylation of dihydrofuran (**249**) to give the hydroxylactol **250** and trapping with the protected alkyne **251** (Scheme 61). However, the dihydroxylation reaction failed to deliver the desire diol **250**.

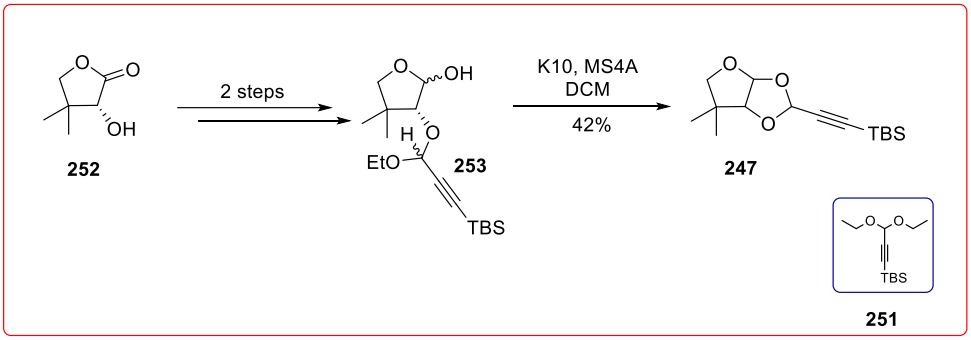


Scheme 61

Dihydrofuran **249** underwent epoxidation using *m*-CPBA followed by opening of the epoxide with water to give diol **250** (Scheme 61). The diol could not be isolated efficiently due to the diol being soluble in very water and consequently being very difficult to extract from the water.

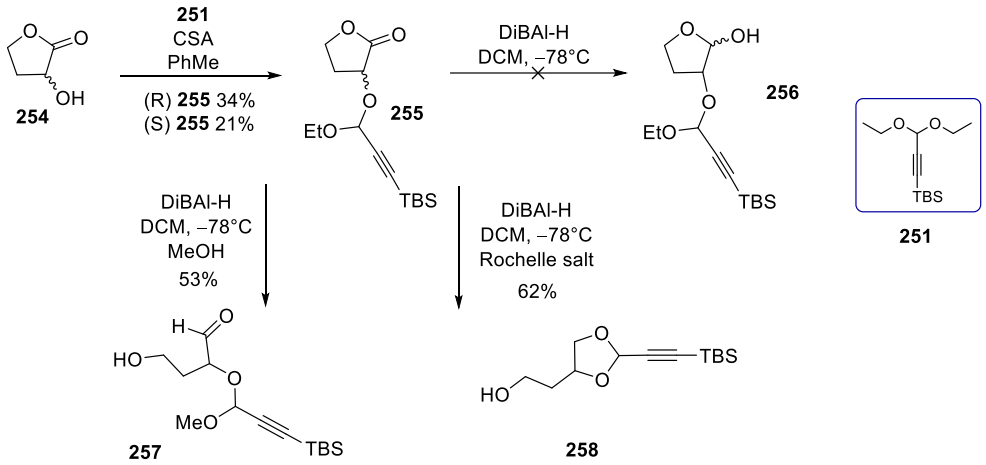
4.4.3 Synthesis of Oxetane from α-Hydroxy-γ-butyrolactone

The second attempt to synthesise the intermediate oxetane used similar starting materials to those employed by Tomooka in 2004.[35] In this case, reaction of (–)-pantolactone **252** with protected alkyne **251**, followed by reduction of the lactone gave lactol **253** (Scheme 62). Then lactol **253** was then cyclised to give the bicyclic acetal **247** in a 42% yield.



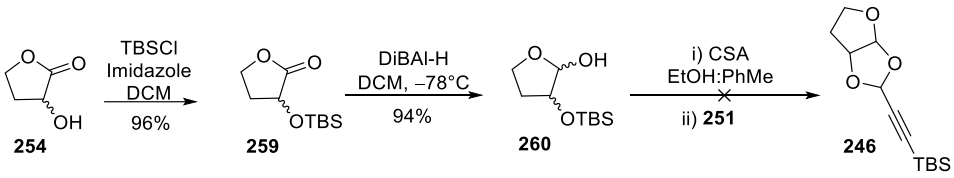
Scheme 62

The initial work toward the synthesis of the required oxetane started with coupling of α-hydroxy-γ-butyrolactone **254** with acetal **251** using CSA in PhMe to give the lactone (*R*)-**255** in 34% yield and (*S*)-**255** in 21% yield (Scheme 63). Lactone **255** was then reduced using DiBAl-H in an attempt to prepare the lactol **256**. However, reduction did not give the required product and afforded the alcohol **258** instead after the reaction was quenched with an aqueous solution of Rochelle's salt. The alcohol **258** was obtained as a result of over-reduction followed by cyclic acetal formation due to the salt being acidic. When MeOH was used to quench the reduction reaction, the aldehyde **257** was isolated instead of the alcohol **256**.



Scheme 63

The hydroxyl group of the lactone **254** was protected with a TBS group to give lactone **259** in 96% yield (Scheme 64). Subsequent partial reduction of the lactone by treatment with DiBAl-H afforded the lactol **260** which was taken to the next step. Deprotection of the hydroxyl group by cleavage of the silyl ether gave an intermediate diol. Attempted transacetalisation with the protected alkyne **251** did not deliver the required cyclic acetal **246**.

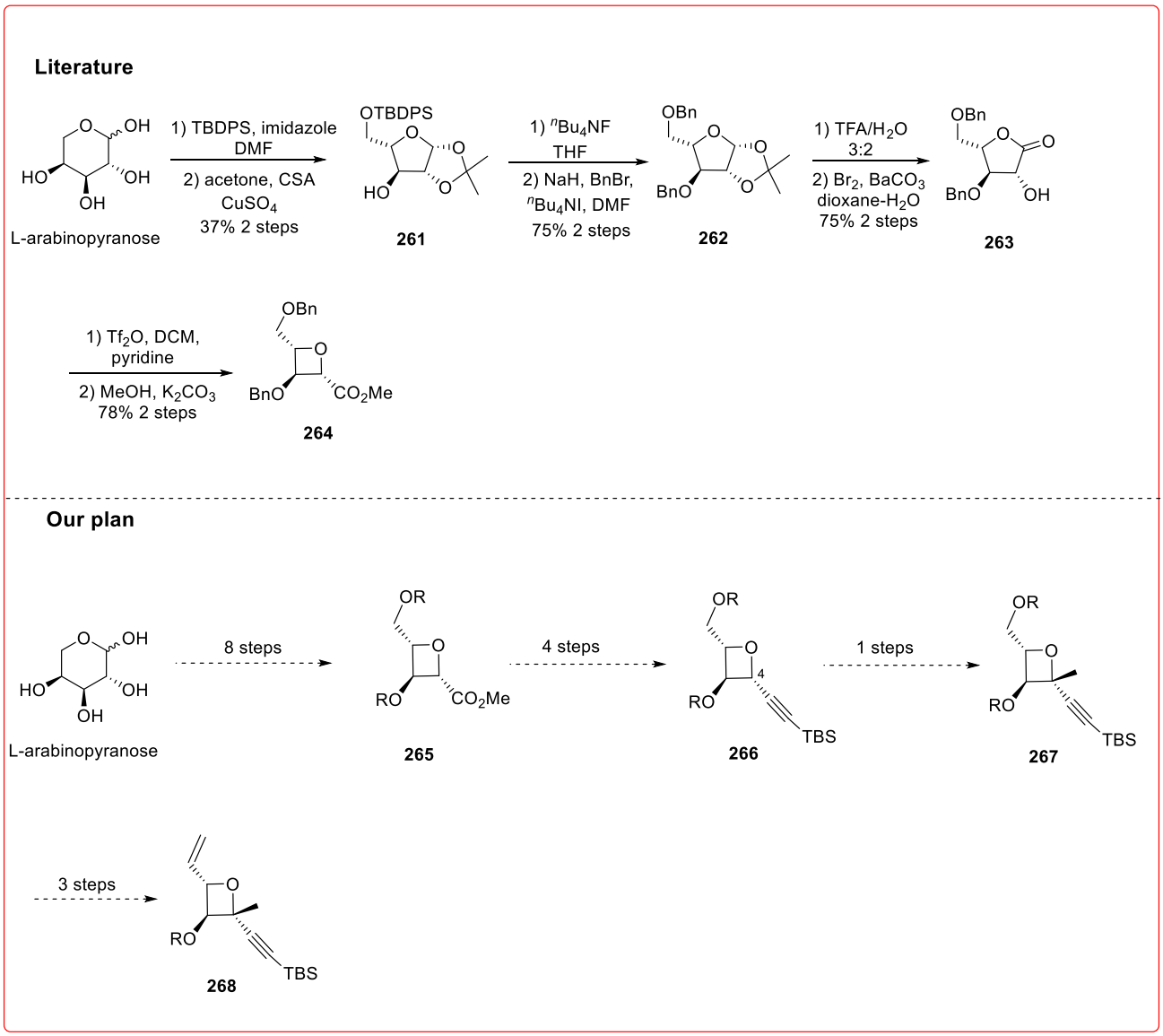


Scheme 64

4.4.4 Synthesis of Oxetane from L-Arabinopyranose

The third attempt to prepare the required oxetane was performed using the chiral pool compound L-arabinopyranose and following the work of Fleet published in 2008.[36] In this case, L-arabinopyranose had been converted into secondary alcohol **261** in 2 steps (Scheme 65). Cleavage of the silyl group followed by protection of both the primary and secondary hydroxyl groups as benzyl ethers furnished **262**. The acetonide protecting group was removed and the resulting diol was selectively oxidised to produce the lactone **263** in 75% yield using $BaCO_3$ and Br_2. The lactone **263** was then converted into the oxetane **264** in two steps. In our work we planned to use the same method and modify the resulting oxetane **264** to suit our

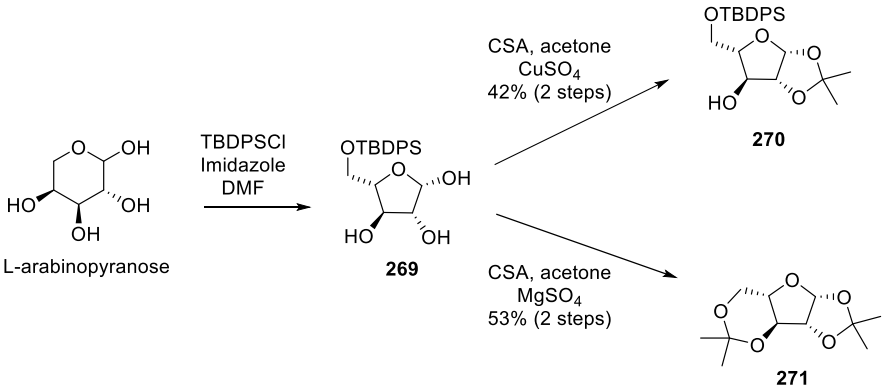
synthesis. Reduction of the ester group of **265** to alcohol followed by oxidation to give aldehyde was to be followed by a Corey-Fuchs reaction to install the protected alkyne **266**. Methylation at C-4 would then be performed to give **267** and the primary alcohol would be deprotected and then oxidised. The resulting aldehyde would be methylenated to give the alkene **268**.



Scheme 65

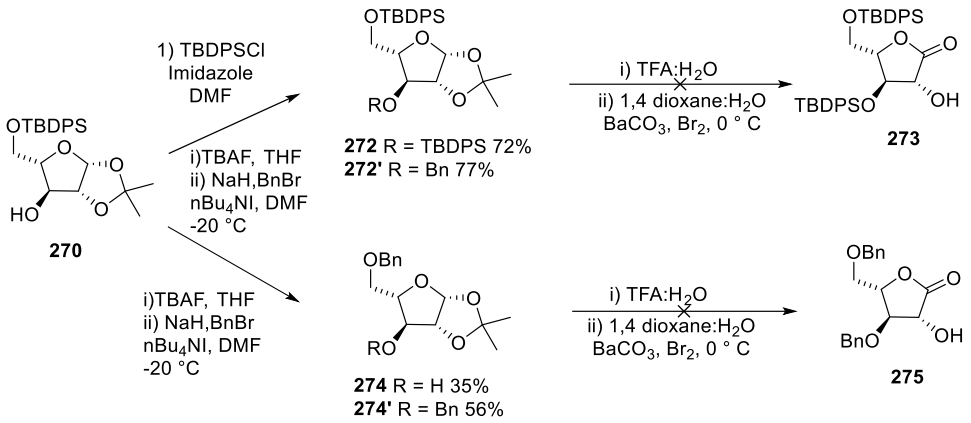
Work commenced with selective protection of the primary hydroxyl group of L-arabinopyranose with a TBDPS group to give the triol **269**, which was taken to next step

without extensive purification (Scheme 66). Protection of the 1,2-*cis* hydroxyl groups with an acetonide group using CSA and $CuSO_4$ in acetone delivered the required secondary alcohol **270** in 42% over two steps. The purpose of $CuSO_4$ in this type of protection reaction is to absorb the resulting water, and so the use of anhydrous $MgSO_4$ as an alternative was explored. However, this resulted in unexpected loss of the silyl group and protection of the resulting 1,3-diol to furnish the bis-acetonide **271** in 53% over two steps.



Scheme 66

Following preparation of the secondary alcohol **270**, the free hydroxyl group was protected as a TBDPS ether to give fully protected compound **272** (Scheme 67). Deprotection of diol using TFA and water followed by selective oxidation of the resulting lactol using $BaCO_3$ and bromine was expected to give the lactone **273**. However, this reaction merely resulted in decomposition of the starting material. In the original paper, the TBDPS in **270** is removed and replaced with a benzyl group prior to deprotection of diol. Consequently, the TBDPS was removed and replaced with a benzyl group to give the monobenzylated product **274** in 35% yield along with the dibenzylated product **274'** in 56% yield. The debenzylated compound **274'** was then subjected to attempted acetal cleavage and selective oxidation, but once again this reaction resulted in decomposition of the starting material.



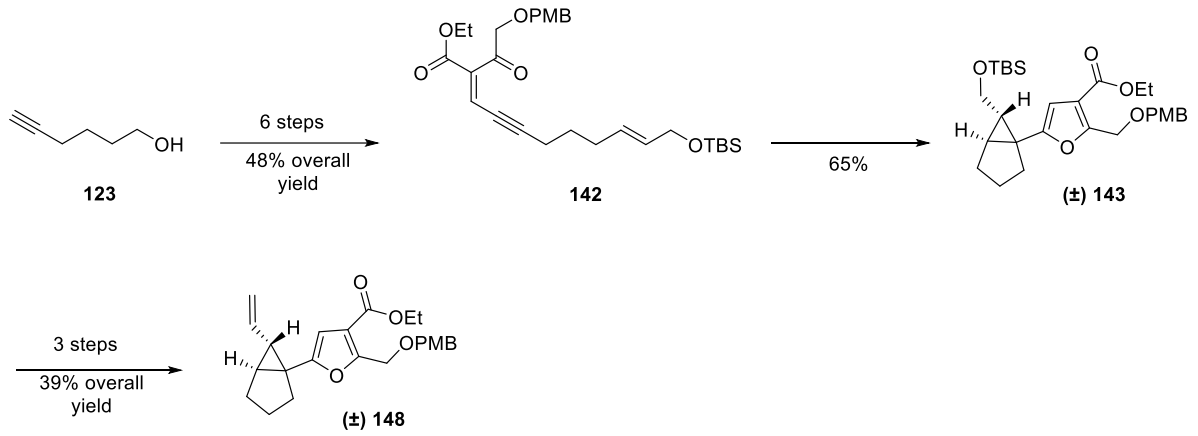
Scheme 67

Due to time constraints this part of the research project was halted at this stage. Future work will be directed to the synthesis of the required functionalised oxetane by completion of this route.

5. Conclusions

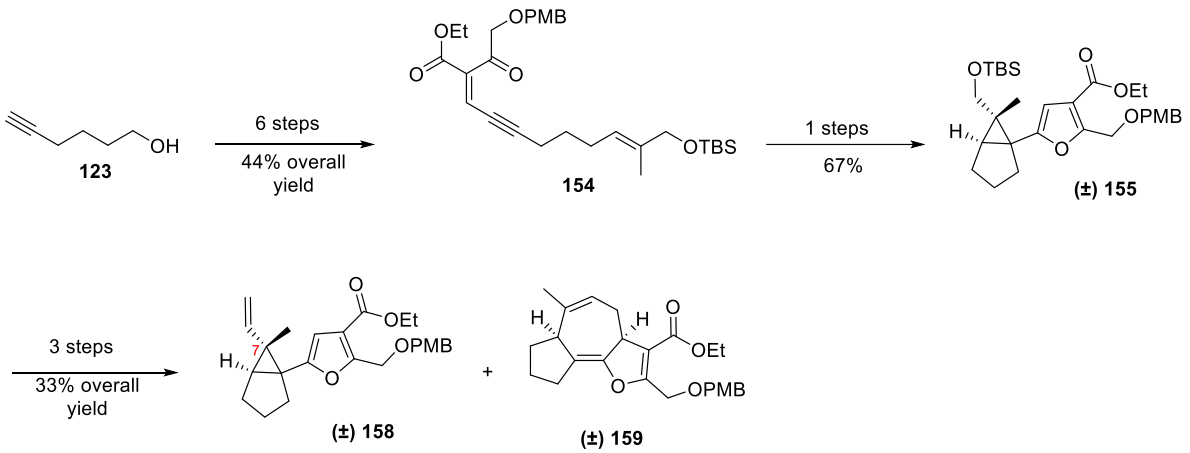
5.1 Summary of Work

A model reaction was used to test the methodology developed by our group in which the vinyl cyclopropane **148** was constructed from intermediate ynenone **142** by treatment with a Brønsted acid. The synthetic route started from hex-5-yn-1-ol **123** which could be transformed into ynenone **142** in 6 steps. From here, ynenone **142** was converted into furan **143** in single step and this intermediate was then converted into the vinyl cyclopropane **148** in 3 steps (Scheme 68). The total synthesis of **148** was achieved from hex-5-yn-1-ol **123** in 10 steps and with an overall yield of 0.12%.



Scheme 68

The total synthesis of a second model system **158**, which differs from the first model system **148** by having extra methyl group at C7, was also accomplished (Scheme 69). Starting from the same starting material, hex-5-yn-1-ol **123**, the ynenone **154** was obtained in 6 steps. Ynenone **154** was treated with chloroacetic acid to effect the cyclisation cyclisation reaction which afforded furan **155**. A mixture of **158** and **159** was obtained from furan **155** in 3 steps and the synthesis was completed in 10 steps and with an overall yield of 0.1% (Scheme 69).

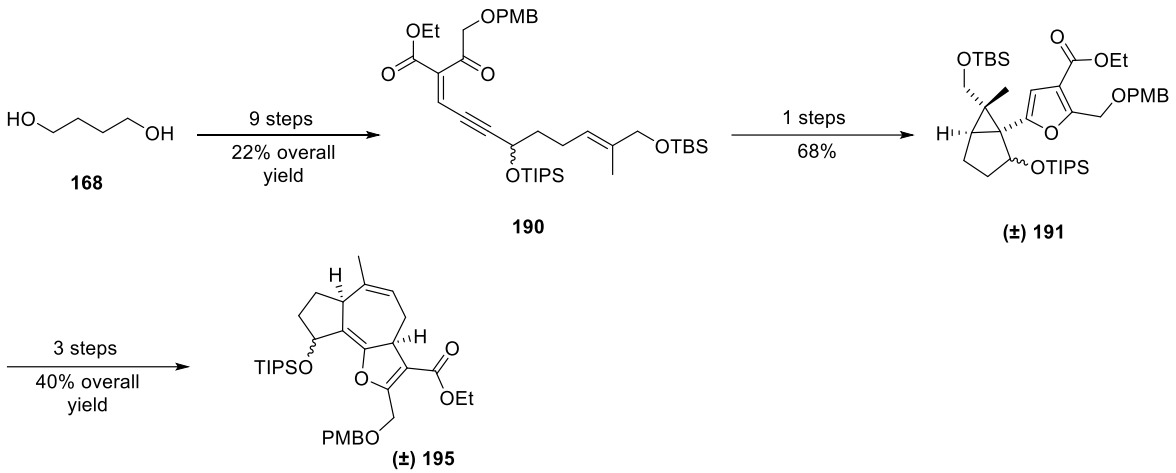


Scheme 69

Key reactions in the synthesis of this cycloheptadiene included formation of the ynenone by Knoevenagel condensation of an intermediate propargylic aldehyde with a β-keto ester, Brønsted acid mediated cyclisation to furnish furan and [3,3]-sigmatropic Cope rearrangement to give the tricyclic core structure.

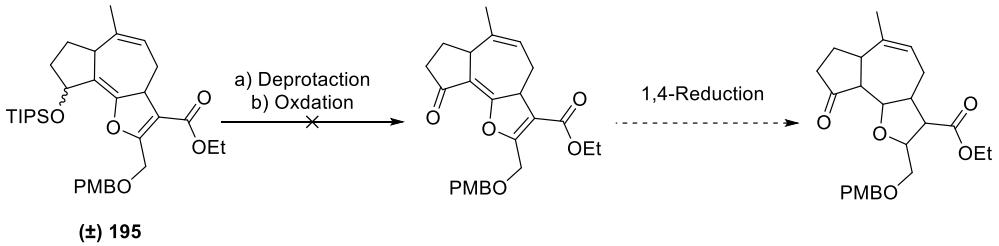
5.2 Micheliolide 1 synthesis

The synthesis of micheliolide **1** started with butan-1,4-diol **168** which was transformed into the ynenone **190** in 9 steps and 67% overall yield (Scheme 70). Ynenone **190** was then converted into the furan **191** in a single step using a Brønsted acid to promote the cyclisation reaction. The tricyclic core **195** of the micheliolide **1** was prepared from the furan **191** in three further steps and in 40% overall yield. The sequence involves a [3,3]-sigmatropic Cope rearrangement reaction to construct the cycloheptadiene **195**.



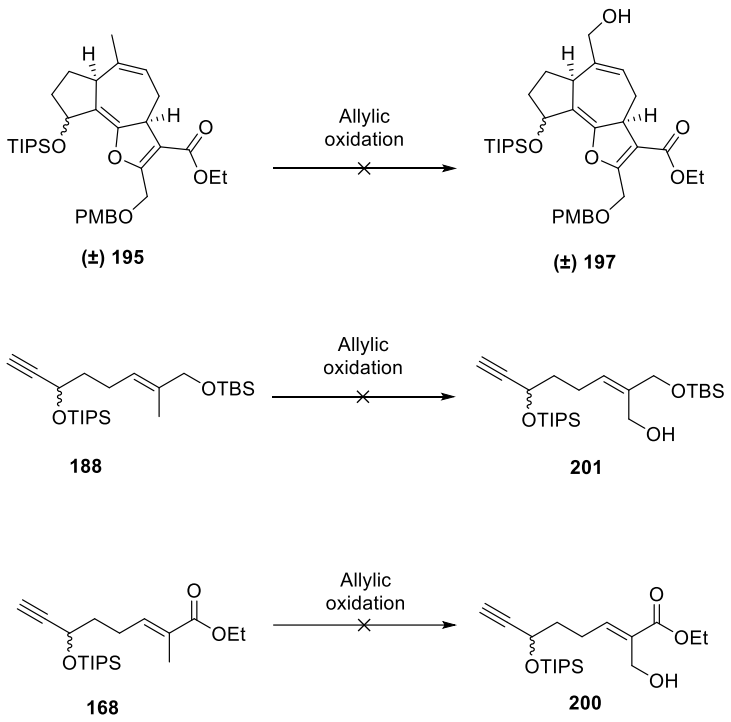
Scheme 70

Attempts were made to functionalise the cycloheptadiene **195.** Subjection of the tricyclic ester **195** to TIPS deprotection to give the free alcohol followed by oxidation to set up a 1,4-reduction reaction was unsuccessful (scheme 71).



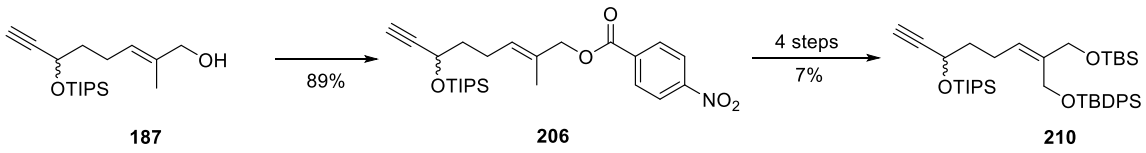
Scheme 71

Attempts to perform exocyclic allylic oxidation of the tricyclic triene **195** also failed. The tricyclic compound was unstable when exposed to air (Scheme 72). Attempted allylic oxidation of both the alkyne **188** intermediate and ester **186** was also unsuccessful.



Scheme 72

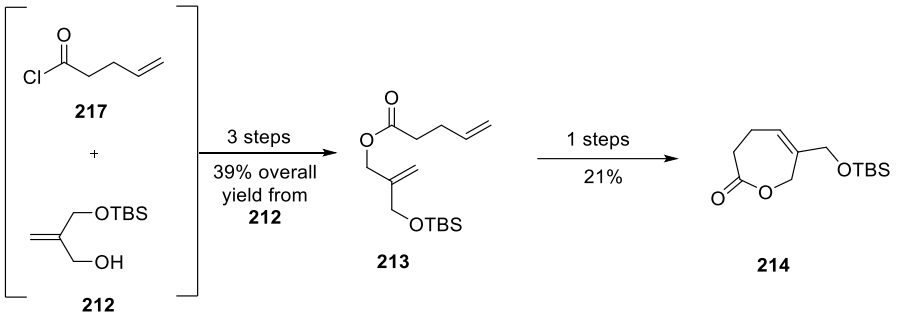
Conversion of the OH group of alkyne **187** into a *p*-nitrobenzoyl ester gave alkyne **206**.Allylic oxidation of this substrate could be performed to give the desired allylic alcohol. Four further steps were required to give the desired intermediate alkyne **210** in 7% overall yield (Scheme 73).



Scheme 73

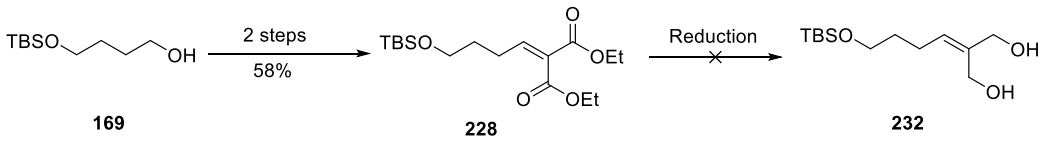
Due to a poor yield obtained from allylic oxidation reaction to give the intermediate alkyne **210**, an alternative route based on RCM was explored. The route commenced with a reaction between the acyl chloride **217** and the allylic alcohol **212** to give diene **213** in three steps and 39% overall yield (Scheme 74). Subjection of the diene **213** to RCM under different conditions

resulted in formation of a dimer as a major product and gave a low yield (21%) of the required lactone **214**.



Scheme 74

Various other methods to construct the lactone **214** by intramolecular cyclisation were considered. An alternative route started with oxidation of alcohol **169** followed by condensation with diethyl malonate to give the diester **228** (Scheme 75). All efforts to reduce the diester **228** directly to the 1,3-diol **232** were unsuccessful and instead conjugated reduction occurred prior reduction of one or both ester groups which resulted in by-product formation.

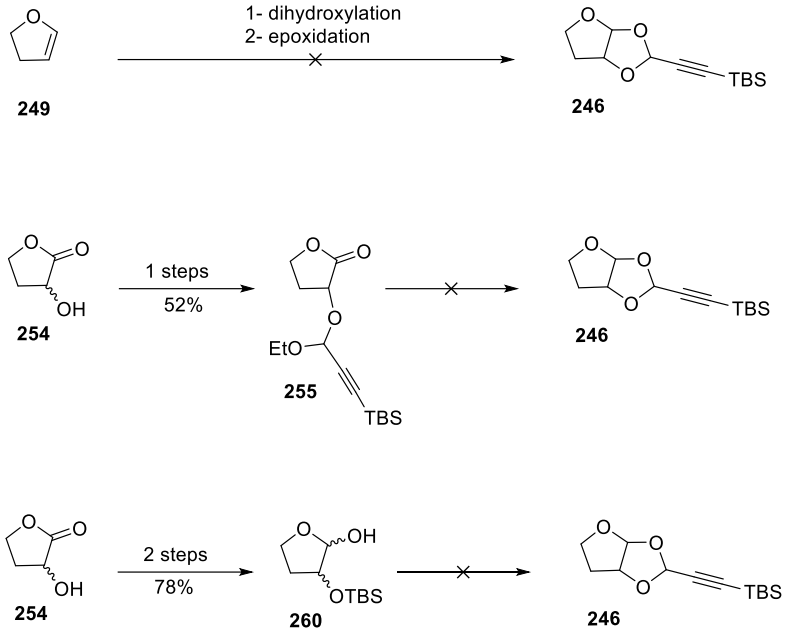


Scheme 75

5.3 Moroccolide (7) synthesis

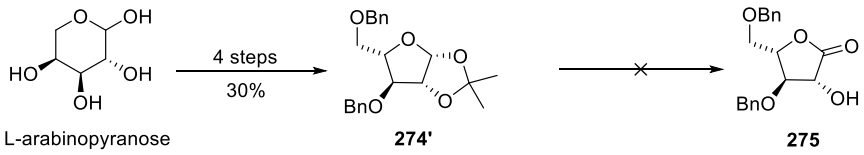
Moroccolide (**7**) has an oxetane embedded in its structure and addressing the synthesis of this ring is the key to any synthesis of the natural product. Many methods were used in an attempt to access the acetal **246** (Scheme 76). The first attempt involved dihydroxylation of the dihydrofuran **249** and reaction of the resulting hydroxy hemiacetal with TBS-protected diethoxypropyne to give **246**. Unfortunately, it was not possible to isolate the intermediate hemiacetal. Subjecting the dihydrofuran **249** to epoxidation followed by the epoxide opening to deliver desired hemiacetal was not successful. The second method started with coupling of α-hydroxy-γ-butyrolactone (**254**) with TBS-protected diethoxypropyne to furnish lactone **255**. Subsequent lactone reduction failed to deliver the acetal **246**. TBS-Protection of α-hydroxy-γ-

butyrolactone (**254**) followed by lactone reduction gave the alcohol **260** in 78% yield over two steps. Deprotection followed by coupling with TBS-protected diethoxypropyne failed to deliver the required compound because it was difficult to extract the intermediate hydroxy lactol from the aqueous phase.



Scheme 76

The third route to the oxetane ring started with TBDPS protection of L-arabinopyranose. The product was converted into the ribose derivative **274'** in three steps (Scheme 77). Attempted removal of the acetonide group of **274'** followed by selective oxidation to deliver the lactone **275** was not successful.

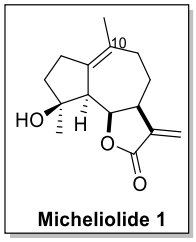


Scheme 77

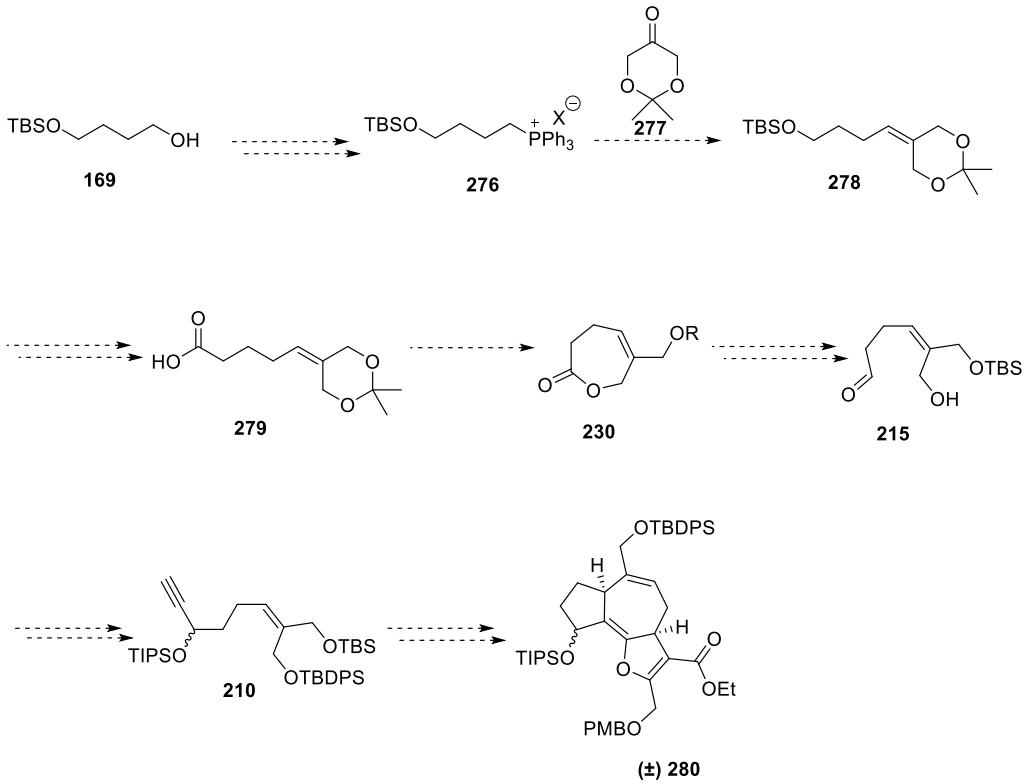
6. Future work

6.1 Micheliolide 1

Future work on micheliolide **1** must first address the failure of the allylic oxidation reaction that is required to functionalise the C-10 methyl group of the tricyclic core.

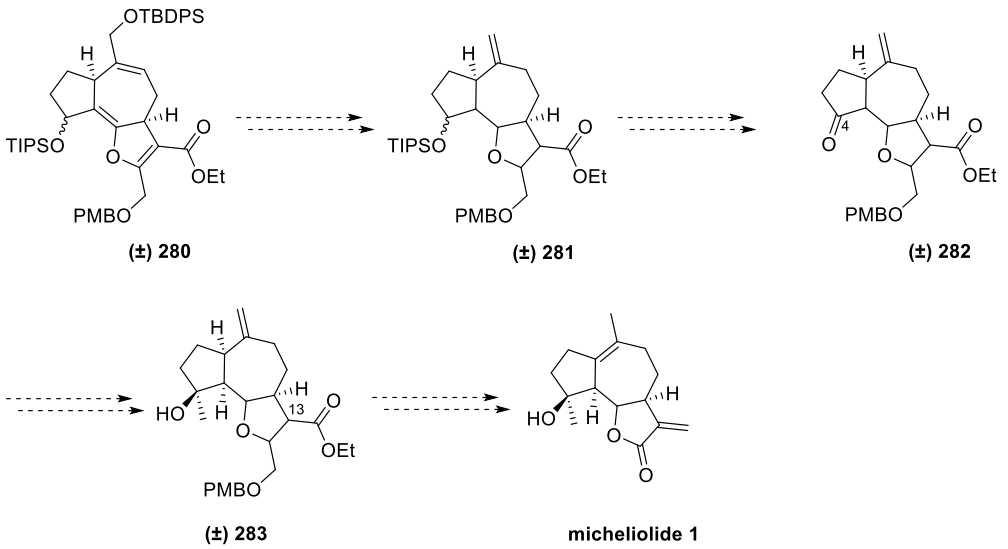


This problem could be avoided by introduction of hydroxyl group at an earlier stage in the synthesis. Conversion of the alcohol **169** into the phosphonium salt **276** followed by Wittig reaction with dimethyl-dioxaneone **277** will give alkene **278** (Scheme 78). Cleavage of silyl group will be followed by oxidation of the alcohol to give the carboxylic acid **279**. Deprotection of **279** to reveal the 1,3-diol will allow intermolecular cyclisation to take place to give lactone **230**. Reduction of lactone **230** will give aldehyde **215** which will then be converted into the alkyne **210** in three steps. Following the same method used for the model system, the alkyne **210** will be converted into the tricyclic core structure **280.**



Scheme 78

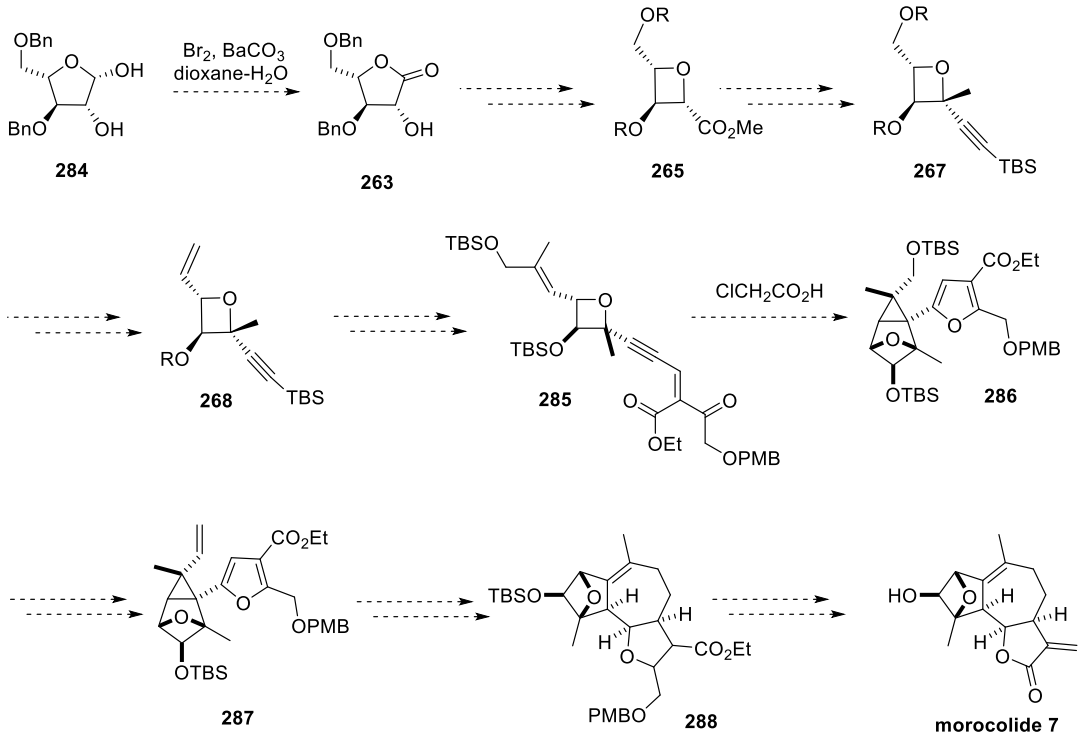
After formation of the desired tricyclic ester **280**, further elaboration of the core will take place. Hydrogenation of **280** followed by deprotection of primary hydroxyl group and elimination of alcohol will give the alkene **281** (Scheme 79). Removal of the TIPS group followed by oxidation will provide the ketone **282**. Methylation at C-4 carbonyl group will result on the formation of secondary alcohol **283**. Ester reduction followed by dehydration to form the methylene group at C-13 position and side chain cleavage to give the lactone will furnish micheliolide **1**.



Scheme 79

6.2 Morocolide (7)

Future work on morocolide (**7**) must address the failure to form the lactone **263** during selective oxidation of the lactol **284** (Scheme 80); the rest of the synthesis could be performed as planned if this problem is solved. Key reactions in the synthesis will include olefination to form **268** from **267**, subjection of the alkene **268** to cross-metathesis and Knoevenagel condensation to give the ynenone **285**, which is the key intermediate. Treatment of the ynenone **285** with a Brønsted acid will produce the furan **286** and this will be converted into the vinyl cyclopropane **287**. The cope rearrangement then will take place to form the tricyclic ester **288.** Further functionalisation of the tricyclic ester **288** will produce the natural product moroccolide (**7**).


OBn
OH
BnO
OH
284
Br2, BaCO3
dioxane-H2O
OBn
O
BnO
OH
263
OR
RO
CO2Me
265
OR
RO
TBS
267
RO
TBS
268
TBSO
TBSO
285
O
OEt
O
OPMB
ClCH2CO2H
OTBS
CO2Et
O
OPMB
OTBS
286
CO2Et
O
OPMB
OTBS
287
TBSO
H
H
H
O
CO2Et
PMBO
288
HO
H
H
H
O
O
morocolide 7

Scheme 80

7 Experimental Section:

7.1 General Information:

All reagents and solvents were obtained from commercial suppliers and were used without further purification, unless otherwise stated.

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame-dried apparatus. THF, toluene, acetonitrile, CH_2Cl_2 and Et_2O were purified using a Pure-SolvTM 500 Solvent Purification System. Flash column chromatography was performed with silica gel (Geduran Si 60 35-70 µm, purchased from Merck) as the solid support. Petroleum ether used for column chromatography was the 40−60 °C fraction.

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plated F254. TLC plates were visualised under UV light and stained using potassium permanganate solution or acidic ethanolic anisaldehyde solution.

IR spectra were recorded as thin films employing a Shimadzu FTIR-8400S spectrometer equipped with Pike Technologies MIRacle ATR accessory; selected frequencies (ν_{max}) are reported. NMR spectra were recorded using dilute solutions in deuterated solvents on a Bruker AvanceIII 400 MHz, or Bruker AvanceIII Ultrashield 500 MHz spectrometer using the deuterated solvent as the internal deuterium lock. ^{1}H chemical shift data are given as units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm, (C_6D_6) = 7.16 ppm and (MeOD)= 3.35, 4.78 ppm. ^{1}H signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), or broad (br) or a combination of these, which refers to the coupling patterns observed. ^{13}C chemical shift data were recorded with broadband proton decoupling and are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.1 ppm, (C_6D_6) = 128.1 ppm and (MeOD) = 49.0. Assignments were determined using 2D NMR spectra (COSY and HSQC). High resolution mass spectrometry (HRMS) were recorded using positive ion impact ionisation (EI+) on a Joel MStation JMS-700 instrument or using positive ion electrospray (ESI+) technique on a Bruker microOTOF-Q instrument by technical staff of the University of Glasgow.

Melting points were recorded using a Barnstead Electrothermal 9100 melting point apparatus. Where no solvent is indicated, the solids obtained from the described procedure were melted

directly without recrystallisation. Optical rotations ($[\alpha]_D$) were determined using a Rudolph Research Analytical Autopol V digital polarimeter.

7.2 Procedures

7.2.1 First model system 148

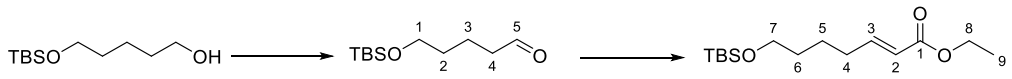
[(*tert*-Butyldimethylsilyl)oxy]pentan-5-ol (162)

To a solution of 1,5-pentanediol **125** (2.00 g, 19.2 mmol) in anhydrous CH_2Cl_2 (60 ml) was added imidazole (1.30 g, 19.1 mmol) and *tert*-butyldimethylsilyl chloride (2.89 g, 19.2 mmol) and stirred at rt for 18 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with H_2O (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduce pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded alcohol **162** (3.10 g, 14.3 mmol, 74% yield) as a colourless oil.

R_f = 0.42 (petroleum ether:ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66–3.57 (4H, m, CH_2-C1, CH_2-C5), 1.63–1.51 (4H, m, CH_2-C2, CH_2-C4), 1.45–1.37 (2H, m, CH_2-C3), 1.31 (1H, t, *J* = 5.3 Hz, OH), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.1 (CH_2-C5), 63.0 (CH_2-C1), 32.5 (CH_2-C4, CH_2-C2), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 22.0 ($CH_2$-C3), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), -5.1 $Si(\underline{C}H_3)_2C(CH_3)_3$; HMRS (ESI) calcd for $C_{11}H_{26}NaO_2Si$ $[M+Na]^+$ 241.1594, found 241.1602.

Analytical data was in full agreement with that previously reported.[23]

(*E*)-ethyl 7-((*tert*-butyldimethylsilyl)oxy)hept-2-enoate (127)



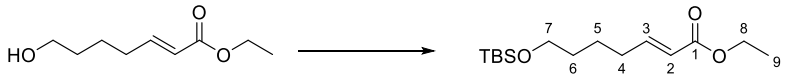
Method A:

To a solution of oxalyl chloride (0.959 mL, 11.2 mmol) in CH_2Cl_2 (90 mL) was added DMSO (1.42 mL, 19.9 mmol) dropwise at – 78 °C. The reaction was stirred for 15 min, and a solution of alcohol **126** (1.74 g, 7.98 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for 30 min at − 78 °C and Et_3N (5.53 mL, 39.9 mmol) was added. The reaction was then allowed to warm to rt. After 3 h, H_2O (60 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with 1M HCl (3 × 30 mL), saturated aq. $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude aldehyde **224** was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, t, *J* = 1.8 Hz, CH-C5), 3.63 (2H, t, *J* = 6.2 Hz, CH_2-C1), 2.36 (2H, td, *J* = 7.3, 1.8 Hz, CH_2-C4), 1.65–1.56 (2H, m, CH_2-C2), 1.49–1.42 (2H, m, CH_2-C3), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$).

To a solution of phosphonium ylide (ethyl(triphenylphosphoraanylidene)acetate) (3.65 g, 10.5 mmol) in CH_2Cl_2 (90 mL) was added the aldehyde (1.74g, 8.05 mmol) at rt and the reaction was stirred for 18 h. The reaction mixture was quenched with H_2O (60 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduce pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) gave ester **127** (1.56 g, 5.47 mmol, 68% over 2 steps) (>15:1 (*E*/*Z*) dr by ^{1}H NMR) as a colourless oil.

Method B:



To a solution of alcohol **130** (7.40 g, 43.0 mmol) in anhydrous CH_2Cl_2 (90 ml) was added imidazole (2.91 g, 43.0 mmol) and *tert*-butyldimethylsilyl chloride (6.48 g, 43.0 mmol) and the mixture was stirred at rt for 18 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with H_2O (3 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) afforded ester **127** (10.0 g, 34.8 mmol, 81%) as a colourless oil.

R_f = 0.55 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, dt, *J* = 15.6, 7.0 Hz, CH-C3), 5.81 (1H, dt, *J* = 15.6, 1.6 Hz, CH-C2), 4.18 (2H, q, *J* = 7.1 Hz, CH_2-C8), 3.61 (2H, t, *J* = 5.7 Hz, CH_2-C7), 2.22 (2H, ddt, *J* = 7.0, 1.6, 3.5 Hz, CH_2-C4), 1.58–1.47 (4H, m, CH_2-C2, CH_2-C5), 1.28 (3H, t, *J* = 7.1 Hz, CH_3-C9), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), −0.05 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C-C1), 149.2 (CH-C3), 121.4 (CH-C2), 62.7 (CH_2-C7), 60.1 (CH_2-C8), 32.2 (CH_2-C6), 32.0 (CH_2-C4), 26.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 24.4 ($CH_2$-C5), 18.4 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 14.3 ($CH_3$-C9), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

Analytical data was in full agreement with that previously reported.[23]

(*E*)-ethyl 7-hydroxyhept-2-enoate (130)

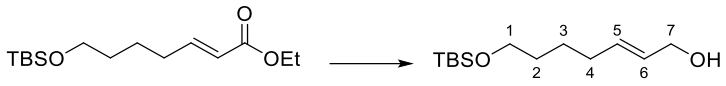
To 2,3-dihydropyran (10.1 mL, 119 mmol), HCl (100 mL, 2M aq) was added at 0 °C and the mixture was stirred for 2 h. The reaction was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude lactol **129** (7.00 g, 68.6 mmol), which was used in the next step without further purification.

To a solution of phosphonium ylide (ethyl(triphenylphosphoraanylidene)acetate) (23.9 g, 68.6 mmol) in CH_2Cl_2 (150 mL) was added lactol **129** (7.00 g, 68.6 mmol) at rt and the reaction was stirred for 18 hours. The reaction was quenched by the addition of H_2O (80 mL) and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided ester **130** (9.66 g, 56.1 mmol, 82% over two steps) (>10:1 (*E*/*Z*) dr by ^{1}H NMR) as a colourless oil.

R_f = 0.25 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, dt, *J* = 15.6, 7.0 Hz, CH-C2), 5.84 (1H, dt, *J* = 15.6, 1.6 Hz, CH-C3), 4.20 (2H, q, *J* = 7.1 Hz, CH_2-C8), 3.67 (2H, t, *J* = 6.1 Hz, CH_2-C7), (2H, dtd, *J* = 7.0, 3.5, 1.6 Hz, CH_2-C4)] 1.66–1.52 (4H, m, CH_2-C6, CH_2-C5), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-C9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C-C1), 148.8 (CH-C2), 121.6 (CH-C3), 62.5 (CH_2-C7), 60.2 (CH_2-C8), 32.1 (CH_2-C6), 31.9 (CH_2-C4), 24.2 (CH_2-C5), 14.3 (CH_3-C9); HMRS (ESI) calcd for $C_9H_{16}NaO_3$ $[M+Na]^+$ 195.0999, found 195.0991.

Analytical data was in full agreement with that previously reported.[37]

(*E*)-1-((*tert*-butyldimethylsilyl)oxy)hept-5-en-7-ol (131)

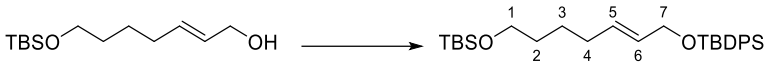


To a solution of ester **127** (8.00 g, 27.8 mmol) in Et_2O (200 mL) was added DiBAl-H (1.0 M in hexanes, 55.7 mL, 55.7 mmol) dropwise at −78 °C and the mixture was allowed to warm to rt and stirred for 6 h. The reaction was quenched by the addition of sat. aq. Rochelle salt (200 mL) and the mixture was stirred for 18 h. The aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 60 mL) and brine (90 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) afforded alcohol **131** (3.75 g, 15.3 mmol, 53%) as a colourless oil.

R_f = 0.33 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75–5.58 (2H, m, CH-C5, CH-C6), 4.09 (2H, t, *J* = 5.4 Hz, CH_2-C7), 3.61 (2H, t, *J* = 6.4 Hz, CH_2-C1), 2.09–2.02 (2H, m, CH_2-C4), 1.57–1.48 (2H, m, CH_2-C2), 1.47–1.36 (2H, m, CH_2-C3), 1.22 (1H, dd, *J* = 7.6, 4.1 Hz, OH), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3 (CH-C5), 129.1 (CH-C6), 63.9 (CH_2-C7), 63.0 (CH_2-C1), 32.3 (CH_2-C2), 32.0 (CH_2-C4), 26.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.4 ($CH_2$-C3), 18.4 ($Si(CH_3)_2C(\underline{C}H_3)_3$), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

Analytical data was in full agreement with that previously reported.[23]

(*E*) -(1-(*tert*-Butyl-dimethyl-silanyloxy) -7-(*tert*-butyl-diphenyl-silyloxy)-hept-5-ene (132)



To a solution of alcohol **131** (2.00 g, 8.16 mmol) in CH_2Cl_2 (90 mL) was added imidazole (0.73 g, 11 mmol) and TBDPSCl (2.55 mL, 9.79 mmol) in CH_2Cl_2 (5 mL) at rt and stirred for 6 h. The reaction was quenched with H_2O (60 mL) and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) yielded alkene **132** (2.36 g, 4.90 mmol, 60%) as a colourless oil.

R_f = 0.07 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.63 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.43–7.33 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$, 5.67–5.48 (2H, m, CH-C6, CH-C5), 4.14 (2H, dd, *J* = 4.9, 1.2 Hz, CH_2-C7), 3.59 (2H, t, *J* = 6.5 Hz, CH_2-C1), 2.02 (2H, td, *J* = 7.4, 1.0 Hz, CH_2-C4), 1.55–1.46 (2H, m, CH_2-C2), 1.44–1.35 (2H, m, CH_2-C3), 1.03 (9H, s,Si(Ph)$_2$C(CH$_3$)$_3$), 0.88 (9H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$), −0.05 (6H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 134.0 (Si(Ph)$_2$C(CH$_3$)$_3$), 131.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 128.9 (CH-C6), 127.6 (CH-C5), 64.7 (CH_2-C1), 63.1 (CH_2-C7), 32.4 (CH_2-C2), 32.0 (CH_2-C4), 26.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 26.0 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 25.5 (CH_2-C3), 19.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 18.4 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), −5.24 (Si(CH$_3$)$_2$C(CH$_3$)$_3$).

Analytical data was in full agreement with that previously reported.[38]

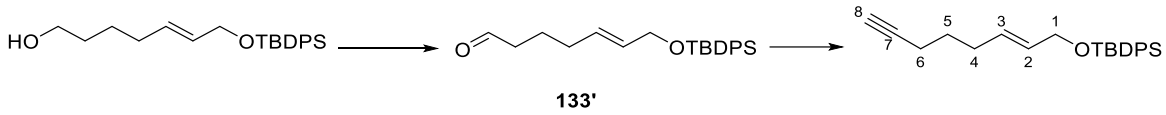
(*E*)-7-(*tert*-Butyl-diphenyl-silanyloxy)-hept-5-en-1-ol (133)

To a solution of alkene **132** (2.36 g, 4.90 mmol) in ethanol (50 mL) was added *p*-toluenesulfonic acid (0.19 g, 0.98 mmol) at rt and the mixture was stirred for 24 h. The reaction mixture was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2) delivered alcohol **133** (0.23 g, 0.64 mmol, 13%) as a colourless oil.

R_f = 0.25 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.60 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.39–7.49 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.63–5.44 (2H, m, CH-C5, CH-C6), 4.09 (2H, dd, *J* = 4.9, 1.2 Hz, CH$_2$-C7), 3.57 (2H, dt, *J* = 11.6, 6.4 Hz, CH$_2$-C1), 2.02–1.95 (2H, m, CH$_2$-C4), 1.55–1.43 (2H, m, CH$_2$-C2), 1.42–1.32 (2H, m, CH$_2$-C3), 0.98 (9H, s, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 133.9 (CH-C5), 130.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.1 (CH$_2$-C6), 127.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 64.6 (CH$_2$-C1), 62.9 (CH$_2$-C7), 32.2 (CH$_2$-C2), 31.9 (CH$_2$-C4), 26.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 25.3 (CH$_2$-C3), 19.2 (Si(Ph)$_2$C(CH$_3$)$_3$).

Analytical data was in full agreement with that previously reported.[38]

***(E)*-1-*tert*-butyl-diphenyl-silyloxy-(oct-2-en-7-yn) (134)**



133'

To a stirred solution of alcohol **133** (0.23 g, 0.63 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DMP (0.40 g, 0.94 mmol) portion wise. The mixture was stirred at rt for 3 h and then the reaction was quenched by sequential addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (10 mL), stirred until two clear layers were obtained and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the aldehyde **133'**, which was used in the next step without further purification.

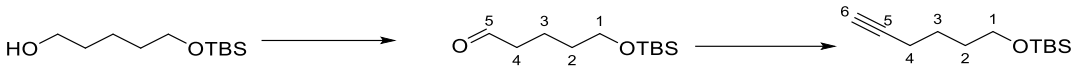
To a solution of carbon tetrabromide (0.42 g, 1.3 mmol) in CH_2Cl_2 (10 mL) was added triphenylphosphine (0.66 g, 2.5 mmol) at 0 °C. After 30 min, a solution of aldehyde **133'** (0.23 g, 0.63 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C and the reaction mixture was allowed to warm to rt. After 1 h, the mixture was filtered through a short plug of silica and the filter cake was washed with a mixture of Et_2O and petroleum ether (1:5, 100 mL). The filtrate was concentrated under reduced pressure to give crude dibromo olefin.

To a solution of the crude dibromo olefin in THF (10 mL) was added *n*-BuLi (2.31 M in hexanes, 0.79 mL, 1.6 mmol) at –78 °C. After 20 min, saturated aq. NH_4Cl solution (10 mL) was added to the reaction mixture and the aqueous phase was extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduce pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) gave the alkyne **134** (33.1 mg, 0.09 mmol, 14%) as a colourless oil.

R_f = 0.05 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.60 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.46–7.38 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.71–5.56 (2H, m, CH-C2, CH-C3), 4.19 (2H, d, *J* = 3.7 Hz, CH$_2$-C1), 2.24–2.12 (4H, m, CH$_2$-C4, CH$_2$-C6), 1.98 (1H, t, *J* = 2.6 Hz, CH-C8), 1.67–1.58 (2H, m, CH$_2$-C5), 1.09 (9H, s, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 133.9 (CH-C3), 129.8 (CH-C2), 129.7 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.6

(Si(Ph)$_2$C(CH$_3$)$_3$), 127.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 84.4 (C-C7), 68.4 (CH-C8), 64.5 (CH_2-C1), 31.1 (CH_2-C4), 26.5 (Si(Ph)$_2$C(CH$_3$)$_3$), 22.2 (CH_2-C5), 19.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 17.8 (CH_2-C6); IR ν_{max} (film) 2858, 1427, 1111, 700 cm^{-1}; HMRS (ESI^+) calcd for $C_{24}H_{30}NaOSi$ $[M+Na]^+$ 385.1958, found 385.1949.

1- *tert*-Butyl-dimethyl-silyloxy-(hex-5-yn) (136)



To a stirred solution of oxalyl chloride (0.60 mL, 6.9 mmol) in CH_2Cl_2 (120 mL) at −78 °C was added DMSO (0.81 mL, 12 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **126** (1.00 g, 4.58 mmol) in CH_2Cl_2 (15 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h. Et_3N (3.22 mL, 22.9 mmol) was added and the mixture was allowed to warm to rt. The reaction was quenched by the addition of water (80 mL). The phases were separated and the organic phase was washed with 1M HCl (50 mL), H_2O (2 × 50 mL) and brine (50 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde **135** as a yellow oil. The aldehyde **135** was used directly in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, t, *J* = 1.8 Hz, CH-C5), 3.63 (2H, t, *J* = 6.2 Hz, CH_2-C1), 2.36 (2H, td, *J* = 7.3, 1.8 Hz, CH_2-C4), 1.65–1.56 (2H, m, CH_2-C2), 1.49–1.42 (2H, m, CH_2-C3), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$).

Method A:

To a solution of carbon tetrabromide (3.04 g, 9.16 mmol) in CH_2Cl_2 (50 mL) was added triphenylphosphine (4.80 g, 18.3 mmol) at 0 °C. After 30 min, a solution of crude aldehyde **135** in CH_2Cl_2 (1 mL) made from (1.00 g, 4.58 mmol) of alcohol **162** was added and the reaction mixture was allowed to warm to rt. After 1 h, the mixture was filtered through a short plug of silica and the filter cake was washed with a mixture of Et_2O and petroleum ether (1:5, 150 mL). The filtrate was concentrated under reduced pressure to give the crude dibromo olefin.

To a solution of the crude dibromo olefin in THF (50 mL) was added *n*-BuLi (2.31 M in hexanes, 5.72 mL, 11.5 mmol) at –78 °C. After 20 min, saturated aq. NH_4Cl solution (30 mL) was added to the reaction mixture, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with saturated aq. NaCl (30 mL) and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated under reduce pressure. Purification of

the residue by column chromatography on silica gel (petroleum ether) delivered the alkyne **136** (0.33 g, 1.55 mmol, 34%) as a colourless oil.

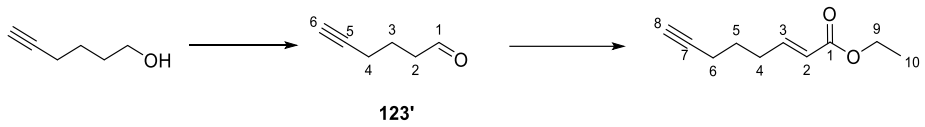
Method B:

To a solution of crude aldehyde **135** that formed from alcohol **126** (0.90 g, 4.12 mmol) in MeOH (50 mL) was added dimethyl(1-diazo-2-oxopropyl)phosphonate (0.87 g, 4.5 mmol) and K_2CO_3 (1.3 g, 9.1 mmol) at rt. The mixture was stirred for 16 h at room temperature and then diluted with Et_2O (50 mL). The mixture was washed with saturated aq. $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) provided the alkyne **136** (0.63 g, 3.00 mmol, 72%) as a pale yellow oil.

R_f = 0.05 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (2H, t, *J* = 6.0 Hz, CH_2-C1), 2.21 (2H, td, *J* = 6.8, 2.7 Hz, CH_2-C4), 1.94 (1H, t, *J* = 2.7 Hz, CH-C6), 1.67 – 1.55 (4H, m, CH_2-C2, CH_2-C3), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$);^{13}C NMR (101 MHz, $CDCl_3$) δ 84.6 (C-C5), 68.3 (CH-C6), 62.6 (CH_2-C1), 31.8 (CH_2-C2), 26.1 (CH_2-C3), 25.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 18.3 ($CH_2$-C4), 18.2 ($Si(CH_3)_2C(\underline{C}H_3)_3$), −5.30 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

Analytical data was in full agreement with that previously reported.[39]

(*E*)-ethyl oct-2-en-7-ynoate (137)



To a stirred solution of hex-5-yn-1-ol **123** (1.50 g, 15.0 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added DMP (9.70 g, 23.0 mmol). The mixture was stirred at rt for 3 h and then the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous $NaHCO_3$ (40 mL). The mixture was diluted with Et_2O (70 mL) and stirred until two clear layers were obtained and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude aldehyde **123'** which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H, CH-C1), 2.59 (td, *J* = 7.0, 1.3 Hz, 2H, CH_2-C2), 2.25 (td, *J* = 7.0, 2.6 Hz, 2H, CH_2-C4), 1.96 (t, *J* = 2.6 Hz, 1H, CH-C6), 1.84 (m, 2H, CH_2-C3).

To a solution of phosphonium ylide (ethyl(triphenylphosphoraanylidene)acetate) (21.3 g, 61.2 mmol) in CH_2Cl_2 (90 mL) was added aldehyde **123'** (1.50 g, 15.0 mmol) at rt and the reaction was stirred for 24 h. The reaction was quenched by the addition of H_2O (90 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 30 mL) and brine (30 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded the ester **137** (2.36 g, 14.2 mmol, 93%) (>12:1 (*E*/*Z*) dr by ^{1}H NMR) over two steps as a colourless oil.

R_f = 0.43 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, dt, *J* = 15.6, 7.1 Hz, CH-C3), 5.88 (1H, dt, *J* = 15.6, 1.6 Hz, CH-C2), 4.21 (2H, q, *J* = 7.1 Hz, CH_2-C9), 2.36 (2H, tdd, *J* = 7.2, 7.1, 1.6 Hz, CH_2-C3), 2.25 (2H, td, *J* = 7.1, 2.6 Hz, CH_2-C6), 1.99 (1H, t, *J* = 2.6 Hz, CH-C8), 1.76 – 1.68 (2H, m, CH_2-C5), 1.31 (3H, t, *J* = 7.1 Hz, CH_3-C10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C-C1), 147.8 (CH-C1), 122.1 (CH-C2), 83.5 (C-C7), 69.0 (CH-C8), 60.2 (CH_2-C9), 30.9 (CH_2-C6), 26.7 (CH_2-C4), 17.9 (CH_2-C5), 14.3 (CH_3-C10); ν_{max} (film) 3028, 2940, 1713, 1651, 1265, 1188, 1150, 1042, 979, 756 cm^{-1}; HMRS (ESI$^+$) calcd for

$C_{10}H_{14}NaO_2$ $[M+Na]^+$ 189.0886, found 189.0879.

(*E*)-oct-2-en-7-yn-1-ol (138)

To a solution of ester **137** (2.36 g, 14.2 mmol) in Et_2O (100 mL) was added DiBAl-H (1.0 M in hexanes, 31.2 mL, 31.2 mmol) dropwise at –78 °C and the mixture was allowed to warm to rt and stirred for 9 hours. The reaction was quenched by the addition of sat, aq Rochelle salt (100 mL) and stirred for 18 h. The aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 40 mL) and brine (40 mL), then dried over $MgSO_4$, filtered and concentrated under reduce pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded alcohol **138** (1.67 g, 13.5 mmol, 95%) as a colourless oil.

R_f = 0.23 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74–5.67 (2H, m, CH-C2, CH-C3), 4.15–4.10 (2H, m, CH_2-C1), 2.26–2.17 (4H, m, CH_2-C4, CH_2-C6), 1.98 (1H, t, *J* = 2.6 Hz, CH-C8), 1.66–1.59 (2H, m, CH_2-C5), 1.29 (1H, t, *J* = 5.8 Hz, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9 (CH-C2), 129.9 (CH-C3), 84.2 (C-C7), 68.5 (CH-C8), 63.7 (CH_2-C1), 31.1 (CH_2-C4), 27. (CH_2-C5), 17.8 (CH_2-C6).

Analytical data was in full agreement with that previously reported.[40]

***(E)* 1-(*tert*-butyl-dimethyl- silyloxy)-(oct-2-en-7-yn) (139)**

To a solution of alcohol **138** (1.67 g, 13.5 mmol) in CH_2Cl_2 (90 mL) was added imidazole (1.00 g, 13.5 mmol) and a solution of TBSCl (2.04 g, 13.5 mmol) in CH_2Cl_2 (5 mL) at rt. The mixture was stirred for 6 h and then the reaction was quenched by the addition of H_2O (60 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 30 mL) and brine (30 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) delivered the alkene **139** (2.80 g, 11.8 mmol, 87%) as a colourless oil.

R_f = 0.04 (petroleum ether);.^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65–5.51 (2H, m, CH-C2, CH-C3), 4.12–4.09 (2H, m, CH_2-C1), 2.21–2.10 (4H, m, CH_2-C4, CH_2-C6), 1.92 (1H, t, *J* = 2.6 Hz, CH-C8), 1.60 (2H, m, CH_2-C5), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.0 (CH-C3), 129.9 (CH-C2), 84.4 (C-C7), 68.4 (CH-C8), 64.0 (CH-C1), 31.1 (CH_2-C4), 28.0 (CH_2-C5), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.6 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 17.9 ($CH_2$-C6), −5.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$); HMRS ($ESI^+$) calcd for $C_{14}H_{26}NaOSi$ $[M+Na]^+$ 261.1645, found 261.1636.

Analytical data was in full agreement with that previously reported.[19]

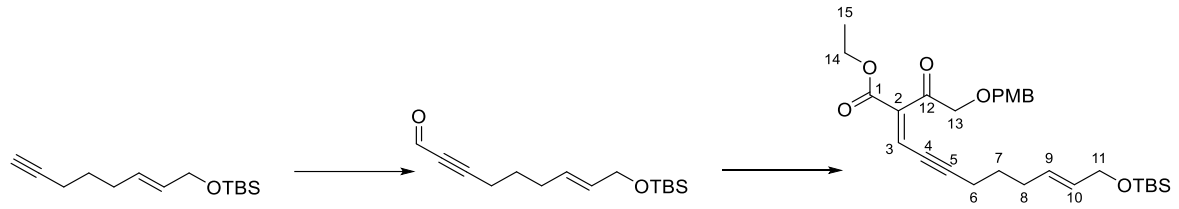
Ethyl 4-[(4-methoxybenzyl)oxy]-3-oxobutanoate 124

To a stirred solution of NaH (60% in mineral oil, 2.67 g, 66.80 mmol) in anhydrous THF (20 mL) at 0 °C was added *p*-methoxybenzyl alcohol (4.4 g, 31.9 mmol) dropwise over 10 min. After hydrogen evolution ceased, the thick slurry was stirred for a further 2 h. Ethyl 4-chloroacetoacetate (5 g, 30 mmol) was then added dropwise and the mixture was stirred for 16 h. The reaction was quenched by careful addition to HCl (5 % aq.; 20 mL) at 5 °C. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 6 mL) and brine (6 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane;EtOAc, 9:1) to give diketone **124** (7.26 g, 93 %) as a pale yellow oil.

R_f = 0.50 (petroleum ether:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.21 (2H, m, $CH_2C_6\underline{H_4}OMe$), 6.93–6.85 (2H, m, $CH_2C_6\underline{H_4}OMe$), 4.52 (2H, s, $C\underline{H_2}C_6H_4OMe$), 4.17 (2H, q, *J* = 7.1 Hz, CH_2-C5), 4.11 (2H, s, CH_2-C4), 3.81 (3H, s, $CH_2C_6H_4O\underline{Me}$), 3.52 (2H, s, CH_2-C2), 1.25 (3H, t, *J* = 7.1 Hz, CH_3-C6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8 (C-C3), 167.1 (C-C1), 159.7 ($CH_2\underline{C_6}H_4OMe$), 129.61 ($CH_2\underline{C_6}H_4OMe$), 128.9 ($CH_2\underline{C_6}H_4OMe$), 114.0 ($CH_2\underline{C_6}H_4OMe$), 74.5 ($CH_2$-C4), 73.2 ($\underline{CH_2}C_6H_4OMe$), 61.4 ($CH_2$-C5), 55.3 ($CH_2C_6H_4\underline{OMe}$), 46.1 ($CH_2$-C2), 14.1 ($CH_3$-C6).

Analytical data was in full agreement with that previously reported.[72]

(*E*)-Ethyl 11-((*tert*-butyl-dimethyl-silyloxy)-2-(2-((4-methoxybenzyl)oxy)acetyl)undeca-2,9-dien-4-ynoate (142)



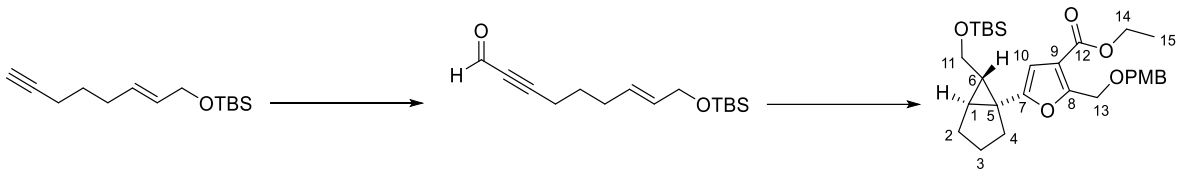
To a stirred solution of alkyne **139** (1.02 g, 4.29 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (2.2 M solution in hexanes, 2.93 mL, 6.44 mmol,) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.65 mL, 8.58 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of a solution of NaH_2PO_4 (2.06 g, 17.2 mmol) in H_2O and Et_2O (16 mL, 1:1). The mixture was stirred for 30 min and then the phases were separated. The organic phase was washed with sat. aq LiCl (14 mL), H_2O (2 × 14 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude propargylic aldehyde **103** as a yellow oil. The aldehyde was used directly in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (1H, t, *J* = 0.8 Hz, CH-C9), 5.56–5.50 (2H, m, CH-C5, CH-C6), 4.08–4.03 (2H, m, CH_2-C7), 2.35 (2H, td, *J* = 7.2, 0.8 Hz, CH_2-C2), 2.16–2.03 (2H, m, CH_2-C4), 1.63 (2H, m, CH_2-C3), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$).

To a stirred solution of crude acetylenic aldehyde **103** and ethyl 4-[(4-methoxybenzyl)oxy]-3-oxobutanoate (1.12 g, 4.29 mmol) at rt were added $MgSO_4$ (102 mg, 0.86 mmol) and EDDA2 (155 mg, 0.86 mmol). The mixture was stirred at 40 °C for 1 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (5 mL). The mixture was diluted with Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 9:1) to afford ynenone **142** (0.77 g, 1.5 mmol, 63% over two steps) (1:0.60 (*E*/*Z*) dr by ^{13}C NMR) as a pale yellow oil

R_f = 0.21 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (2H, m, $CH_2C_6\underline{H_4}OMe$), 6.90 (1H, t, *J* = 2.4 Hz, CH-C3), 6.86 (2H, m, $CH_2C_6\underline{H_4}OMe$), 5.63–5.52 (2H, m, CH-C9, CH-C10), 4.50 (2H, d, *J* = 19.7 Hz, CH_2-C13), 4.35 (2H, d, *J* = 5.2 Hz, $C\underline{H_2}C_6H_4OMe$), 4.23 (2H, q, *J* = 7.1 Hz, CH_2-C14), 4.11 (2H, dd, *J* = 4.4, 3.7 Hz, CH_2-C11), 3.80 (3H, s, $CH_2C_6H_4O\underline{Me}$), 2.39 (2H, td, *J* = 7.1, 2.4 Hz, CH_2-C6), 2.19–2.07 (2H, m, CH_2-C8), 1.70–1.58 (2H, m, CH_2-C7), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C15), 0.90 (9H, d, *J* = 1.2 Hz, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.06 (6H, d, *J* = 1.6 Hz, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (C=O-C12), 163.8 (C=O-C1), 159.5 ($CH_2\underline{C_6}H_4OMe$), 140.1 (C-C2), 130.5 (CH-C9), 129.7 ($CH_2\underline{C_6}H_4OMe$), 129.6 ($CH_2\underline{C_6}H_4OMe$), 129.4 (CH-C10), 127.2 (CH-C3), 125.7 (C-C5), 113.8 ($CH_2\underline{C_6}H_4OMe$), 108.1 (C-C4), 74.5 ($CH_2$-C13), 73.0 ($\underline{C}H_2C_6H_4OMe$), 63.8 ($CH_2$-C11), 61.6 ($CH_2$-C14), 55.3 ($CH_2C_6H_4O\underline{Me}$), 31.2 ($CH_2$-C7), 27.6 ($CH_2$-C8), 26.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 19.6 ($CH_2$-C6), 18.4 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 14.1 ($CH_3$-C15), -5.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2965, 2865, 2213, 1711, 1610, 1512, 1251 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{29}H_{42}NaO_6Si$ $[M+Na]^+$ 537.2643 found 537.2639.

Ethyl 5-((1R,5S,6S)-6-(((*tert*-butyl-dimethyl-silyloxy)methyl)bicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate (143)



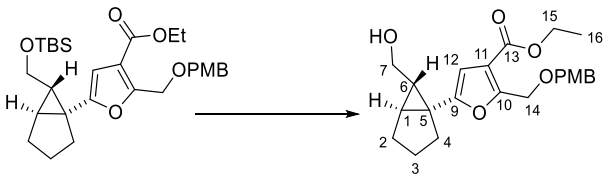
Method A: To a stirred solution of alkyne **139** (0.52 g, 2.20 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (2.2 M solution in hexanes, 1.50 mL, 3.30 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.33 mL, 4.40 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of a solution of NaH_2PO_4 (1.06 g, 8.80 mmol) in H_2O and Et_2O (10 mL, 1:1). The mixture was stirred for 30 min and then the phases were separated. The organic phase was washed with sat. aq LiCl (10 mL), H_2O (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude propargylic aldehyde **103** as a yellow oil. The aldehyde was used directly in the next step without further purification.

To a stirred solution of crude acetylenic aldehyde **103** and ethyl 4-[(4-methoxybenzyl)oxy]-3-oxobutanoate (0.58 g, 2.2 mmol) at rt was added $MgSO_4$ (52 mg, 0.43 mmol) and EDDA2 (77 mg, 0.43 mmol). The mixture was stirred at 40 °C for 18 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (3 mL). The mixture was diluted with Et_2O (3 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford furan **143** (0.58 g, 1.12 mmol, 51% over two steps) as a pale yellow oil.

Method B: To a stirred solution of ynenone **142** (1.20 g, 2.33 mmol) in CH_2Cl_2 (18 mL) at rt was added chloroacetic acid (0.22 g, 2.3 mmol) in one portion. The mixture was stirred at 40 °C for 4 d and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford furan **143** (0.78 g, 1.5 mmol, 65%) as a pale yellow oil.

R_f = 0.35 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (2H, m, Ar-H), 6.86–6.81 (2H, m, Ar-H), 6.37 (1H, s, CH-C10), 4.73 (2H, s, CH_2-C13), 4.48 (2H, s, $C\underline{H_2}C_6H_4OMe$), 4.20 (2H, q, *J* = 7.1 Hz, CH_2-C14), 3.78 (3H, s, O<u>Me</u>), 3.54 (2H, dd, *J* = 11.5, Hz, CH_2-C11a), 3.52 (2H, dd, *J* = 11.5, Hz, CH_2-C11b), 2.11 (1H, dd, *J* = 12.4, 8.0 Hz, CH_2-C4a), 1.93 – 1.79 (3H, m, CH_2-C4b, CH_2-C2), 1.75–1.64 (1H, m, CH_2-C3a), 1.58 (1H, t, *J* = 4.0 Hz, CH-C1), 1.38–1.30 (2H, m, CH-C6, CH_2-C3b), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C15), 0.82 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), −0.05 (6H, d, *J* = 3.0 Hz, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (C-C12), 159.3 (Ar), 156.6 (C-C8), 155.3 (C-C7), 130.2 (Ar), 129.5 (Ar), 117.1 (C-C9), 113.8 (Ar), 106.9 (CH-C10), 72.1 ($\underline{C}H_2C_6H_4OMe$), 62.7 ($CH_2$-C11), 62.5 ($CH_2$-C13), 60.3 ($CH_2$-C14), 55.3 (OMe), 32.7 (CH_2-C4), 30.7 (C-C5), 29.3 (CH_2-C2), 27.9 (CH-C1), 27.4 (CH-C6), 25.9 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 21.9 ($CH_2$-C3), 18.3 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 14.3 ($CH_3$-C15), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.3 ($CH_3$-$(Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2926, 1716, 1512, 1382, 1247, 1080 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{29}H_{42}NaO_6Si$ $[M+Na]^+$ 537.2643, found 537.2643.

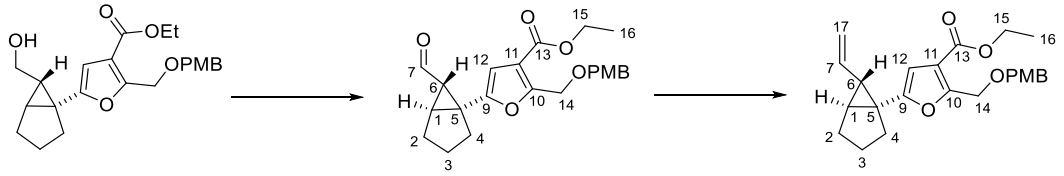
Ethyl 5-((1R,5S,6S)-6-(hydroxymethyl)bicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate (146)



To a stirred solution of protected alcohol **143** (1.30 g, 2.46 mmol) in MeOH/CH_2Cl_2 (3:1, 12 mL) at rt was added camphorsulfonic acid (114 mg, 0.50 mmol) in one portion. The mixture was stirred for 18 h and then the reaction was quenched by the addition of H_2O (12 mL) and saturated aq. $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (18 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 2:1) to afford alcohol **146** (0.77 g, 1.9 mmol, 75%) as a colourless oil.

R_f = 0.07 (petroleum ether:EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (2H, m, Ar-H), 6.88–6.82 (2H, m, Ar-H), 6.38 (1H, s, CH-C12), 4.74 (2H, d, *J* = 4.7 Hz, CH_2-C14), 4.47 (2H, s, $C\underline{H}_2C_6H_4OMe$), 4.25 (2H, q, *J* = 7.1 Hz, CH_2-C15), 3.78 (3H, s, OMe), 3.65 (1H, dt, *J* = 11.0, 5.9 Hz, CH_2-C7a), 3.34 (1H, dt, *J* = 11.0, 5.9 Hz, CH_2-C7b), 2.17 (1H, dd, *J* = 12.4, 7.9 Hz, CH_2-C4a), 1.92–1.81 (3H, m, CH_2-C4b, CH_2-C2), 1.76–1.67 (1H, m, CH_2-C3a), 1.61 (1H, t, *J* = 4.0 Hz, CH-C1), 1.42 (1H, ddd, *J* = 8.7, 7.9, 4.1 Hz, CH_2-C3b), 1.38–1.32 (1H, m, CH-C6), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (C-C13), 159.3 (Ar), 156.5 (C-C10), 155.4 (C-C9), 130.0 (Ar), 129.6 (Ar), 117.3 (C-C11), 113.8 (Ar), 107.3 (CH-C12), 72.2 ($\underline{C}H_2C_6H_4OMe$), 62.6 ($CH_2$-C7), 62.5 ($CH_2$-C14), 60.5 ($CH_2$-C15), 55.3 (OMe), 32.8 (CH_2-C4), 30.6 (CH_2-C5), 29.3 (CH_2-C2), 27.9 (CH-C1), 27.3 (CH-C6), 21.9 (CH_2-C3), 14.3 (CH_3-C16); ν_{max} (film) 3320, 2935, 1712, 1512, 1246, 1064 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{23}H_{28}NaO_6$ $[M+Na]^+$ 423.1778, found 423.1766.

Ethyl 2-(((4-methoxybenzyl)oxy)methyl)-5-((1R,5S,6S)-6-vinylbicyclo[3.1.0]hexan-1-yl)furan-3-carboxylate (148)



To a stirred solution of alcohol **146** (0.17 g, 0.44 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added DMP (0.2 g, 0.74 mmol). The mixture was stirred at rt for 16 h and then the reaction was quenched by sequential addition of saturated aq. $Na_2S_2O_3$ (10 mL) and saturated aq. $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (10 mL), stirred until two clear layers were obtained (ca. 30 min) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The aldehyde **147** was taken to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (1H, d, *J* = 6.5 Hz, CH-C7), 7.27–7.22 (2H, m, $CH_2C_6\underline{H_4}OMe$), 6.88–6.82 (2H, m, $CH_2C_6\underline{H_4}OMe$), 6.38 (1H, s, CH-C12), 4.74 (2H, s, $C\underline{H_2}C_6H_4OMe$), 4.47 (2H, s, CH_2-C14), 4.25 (2H, q, *J* = 7.1 Hz, CH_2-C15), 3.78 (3H, s, $CH_2C_6H_4O\underline{Me}$), 2.18 (1H, t, *J* = 3.9 Hz, CH-C1), 2.17 (1H, dd, *J* = 12.4, 7.9 Hz, CH_2-C4a), 2.08–2.03 (3H, m, CH_2-C4b, CH_2-C2), 1.76 – 1.67 (2H, m, CH_2-C3),1.32–1.30 (1H, m, CH-C6), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-C16).

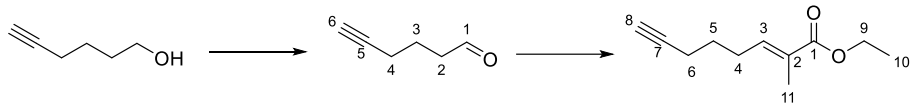
To a stirred solution of methyltriphenylphosphonium bromide (0.30 g, 0.86 mmol) in THF (8 mL) at −10 °C was added *n*-BuLi (2.3 M solution in hexanes, 0.37 mL, 0.86 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **147** (0.17 g, 0.43 mmol) in THF (5 mL) at −10 °C. The mixture was allowed to warm to rt and stirred for 18 h and then the reaction was quenched by pouring the solution into a mixture of pH 7 buffer (50 mL) and Et_2O (20 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I,

petroleum ether:EtOAc, 10:1) to afford the vinylcyclopropane **148** (88 mg, 0.22 mmol, 52% over two steps) as a colourless oil.

R_f = 0.65 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (2H, m, Ar-H), 6.89–6.79 (2H, m, Ar-H), 6.33 (1H, s, CH-C12), 5.46–5.35 (1H, ddd, *J* = 17.1, 10.3, 9.3 Hz, CH-C7), 5.05 (1H, dd, *J* = 17.1, 1.8 Hz, CH_2-C17a), 4.84 (1H, dd, *J* = 10.3, 1.8 Hz, CH_2-C17b), 4.75 (2H, d, *J* = 3.4 Hz, CH_2-C14), 4.46 (2H, s, $C\underline{H_2}C_6H_4OMe$), 4.24 (2H, q, *J* = 7.1 Hz, CH_2-C15), 3.78 (3H, s, OMe), 2.20–2.14 (1H, m, CH-C6), 1.96–1.88 (3H, m, CH_2-C4b, CH_2-C2), 1.84 (1H, t, *J* = 3.9 Hz, CH-C1), 1.78 (1H, d, *J* = 4.1 Hz, CH_2-C3a), 1.75 (1H, d, *J* = 4.1 Hz, CH_2-C3b), 1.36 (1H, m, CH_2-C4a), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (C-C13), 159.3 (Ar), 156.5 (C-C9), 155.4 (C-C10), 136.8 (CH-C7), 130.0 (Ar), 129.6 (Ar), 117.3 (C-C11), 113.9 (CH_2-C17), 113.7 (Ar), 107.3 (CH-C12), 72.2 ($\underline{C}H_2C_6H_4OMe$), 62.5 ($CH_2$-C14), 60.5 ($CH_2$-C15), 55.3 (OMe), 32.8 (CH_2-C4), 30.6 (CH_2-C5), 29.3 (CH_2-C2), 27.9 (CH-C1), 27.3 (CH-C6), 21.9 (CH_2-C3), 14.3 (CH_3-C16); ν_{max} (film) 2900, 1701, 1610, 1246, 1028 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{24}H_{28}NaO_5$ $[M+Na]^+$ 419.1829 found 419.1824.

7.2.2 Second Model System 159

Ethyl (*E*) - 2 - methyloct - 2 - en - 7 - ynoate (149)



To a stirred solution of alcohol **123** (3.50 g, 35.7 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added DMP (12.9 g, 53.5 mmol) in small portions. The mixture was stirred at rt for 3 h and then the reaction was quenched by sequential addition of saturated aq. $Na_2S_2O_3$ (100 mL) and saturated aq. $NaHCO_3$ (100 mL). The mixture was diluted with Et_2O (200 mL) and stirred until two clear layers were obtained (ca. 30 min). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 90 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude aldehyde **123'** was taken to the next step without further purification.

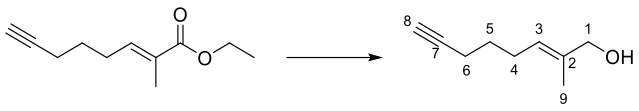
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.3 Hz, CH-C1), 2.59 (2H, tq, *J* = 7.2, 1.3 Hz, CH_2-C2), 2.25 (2H, td, *J* = 6.9, 2.6 Hz, CH_2-C4), 1.96 (1H, t, *J* = 2.6 Hz, CH-C6), 1.84 (2H, m, CH_2-C3).

To a solution of ethyl 2-(triphenylphosphoranylidene)propionate **160** (22.0 g, 60.5 mmol) in CH_2Cl_2 (150 mL) was added crude aldehyde **123'** (3.42 g, 35.6 mmol) at rt and the reaction was stirred for 24 h. The reaction was quenched by the addition of H_2O (100 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 50 mL) and brine (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded the ester **149** (4.90 g, 27.2 mmol, 76% over two steps) (>45:1 (*E*/*Z*) dr by ^{1}H NMR) as a colourless oil.

R_f = 0.42 (petroleum ether:ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, tq, *J* = 7.5, 1.4 Hz, CH-C3), 4.21 (2H, q, *J* = 7.1 Hz, CH_2-C9), 2.24 (2H, q, *J* = 7.5 Hz, CH_2-C4), 2.16 (2H, td, *J* = 7.0, 2.6 Hz, CH_2-C6), 1.90 (1H, t, *J* = 2.6 Hz, CH-C8), 1.84–1.82 (2H, m, CH_2-C5), 1.78 (3H, s, CH_3-C11), 1.31 (3H, t, *J* = 7.1 Hz, CH_3-C10); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 168.1 (C-C1), 140.7 (C-C2), 128.8 (CH-C3), 83.8 (C-C7), 68.8 (CH-C8), 60.5 (CH_2-C9), 27.5 (CH_2-C6), 27.4 (CH_2-C4), 18.0 (CH_2-C5), 14.3 (CH_3-C10), 12.4 (CH_3-C11); ν_{max} (film) 1707, 1651, 1255, 1111 cm^{-1}; HMRS (ESI^+) calcd for $C_{11}H_{16}NaO_2$ $[M+Na]^+$ 203.1043, found 203.1038.

(*E*)-2-Methyloct-2-en-7-yn-1-ol (150)

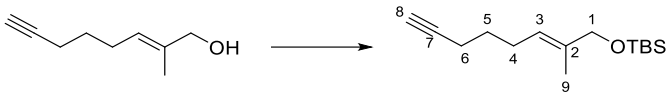


To a solution of ester **149** (4.90 g, 27.2 mmol) in Et_2O (200 mL) was added DiBAl-H (1.0 M in hexanes, 55 mL, 54.4 mmol) dropwise at –78 °C. The mixture was allowed to warm to rt and then stirred for a further 9 hours. The reaction was quenched with a sat. aq solution of Rochelle salt (200 mL) and stirred for 18 hours. The aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 100 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) delivered the alcohol **150** (2.95 g, 21.4 mmol, 79%) as a colourless oil.

R_f = 0.13 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, tq, *J* = 7.3, 1.3 Hz, CH-C3), 3.94 (2H, d, *J* = 3.5 Hz, CH_2-C1), 2.13 (2H, td, *J* = 7.1, 2.6 Hz, CH_2-C6), 2.13–2.06 (2H, m, CH_2-C4), 1.88 (1H, t, *J* = 2.6 Hz, CH-C8), 1.61 (3H, s, CH_3-C9), 1.58–1.49 (2H, m, CH_2-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (C-C2), 124.9 (CH-C3), 84.4 (C-C7), 68.9 (CH-C8), 68.4 (CH_2-C1), 28.3 (CH_2-C4), 26.5 (CH_2-C5), 17.9 (CH_2-C6), 13.7 (CH_3-C9).

Analytical data was in full agreement with that previously reported.[41]

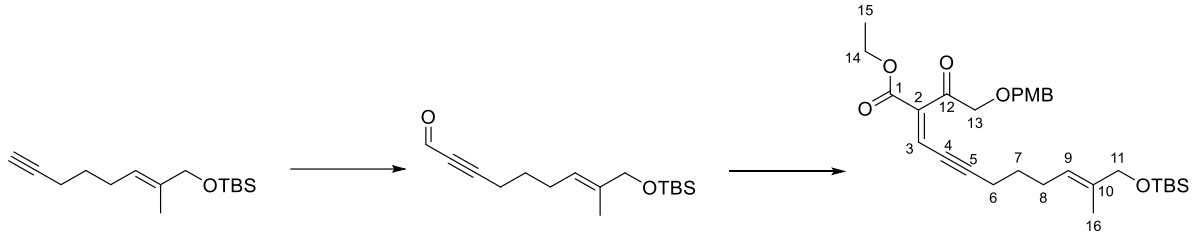
1-(*tert*-Butyl-dimethyl- silyloxy)-((*E*)-2-methyloct-2-en-7-yn) (151)



To a solution of alcohol **150** (2.95 g, 21.4 mmol) in CH_2Cl_2 (100 mL) was added imidazole (1.50 g, 21.4 mmol) and TBSCl (3.30 g, 21.4 mmol) in CH_2Cl_2 (5 mL) at rt and the reaction stirred for 6 h. The reaction was quenched by the addition of H_2O (90 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 60 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) delivered the alkene **151** (4.98 g, 19.7 mmol, 93%) as a colourless oil.

R_f = 0.06 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, tq, *J* = 7.3, 1.2 Hz, CH-C3), 3.99 (2H, s, CH_2-C1), 2.17 (2H, td, *J* = 7.1, 2.6 Hz, CH_2-C6), 2.14–2.09 (2H, m, CH_2-C4), 1.92 (1H, t, *J* = 2.6 Hz, CH-C8), 1.59 (3H, s, CH_3-C9), 1.62–1.53 (2H, m, CH_2-C5), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5 (CH-C3), 123.3 (C-C2), 84.6 (C-C7), 68.5 (CH-C8), 68.2 (CH-C1), 28.4 (CH_2-C4), 26.5 (CH_2-C5), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 18.0 ($CH_2$-C6), 13.5 ($CH_3$,C9), −5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2927, 1251, 1109, 1070, 775 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{15}H_{28}NaOSi$ $[M+Na]^+$ 275.1802, found 275.1800.

(*E*)-Ethyl 11-(*tert*-butyl-dimethyl-silyloxy)-2-{2-[(4-methoxybenzyl)oxy]acetyl}-10-methylundeca-12,13-dien-4-ynoate (154)



To a stirred solution of alkyne **151** (1.00 g, 3.96 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.2 M solution in hexanes, 2.7 mL, 5.95 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.60 mL, 7.9 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of a solution of NaH_2PO_4 (1.90 g, 15.84 mmol) in H_2O/Et_2O (12 ml, 1:2). The mixture was stirred for 30 min and the phases were separated. The organic phase was washed with saturated aq. LiCl (10 mL) and H_2O (2 × 10 mL) then washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **152** as a yellow oil. The crude aldehyde **152** was used directly in the next step without further purification.

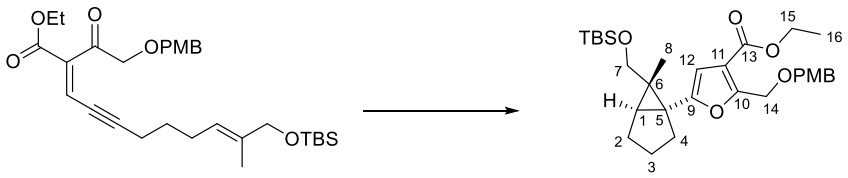
To a stirred solution of crude acetylenic aldehyde **152** and ethyl 4-[(4-methoxybenzyl)oxy]-3-oxobutanoate (1.05 g, 3.96 mmol) at 40 °C was added $MgSO_4$ (95 mg, 0.79 mmol) and EDDA (0.14 g, 0.79 mmol). The mixture was stirred for 1 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (10 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford ynenone **154** (1.33 g, 2.50 mmol, 64%) (1:0.83 (*E*/*Z*) dr by ^{13}C NMR) as a pale yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (2H, m, $CH_2C_6\underline{H_4}OMe$), 6.91 (1H, t, *J* = 2.4 Hz, CH-C3), 6.89–6.85 (2H, m, $CH_2C_6\underline{H_4}OMe$), 5.39–5.31 (1H, m, CH-C9), 4.50 (2H, d, *J* = 4.8 Hz, CH_2-C13), 4.35 (2H, d, *J* = 4.8 Hz, $C\underline{H_2}C_6H_4OMe$), 4.24 (2H, dq, *J* = 14.2, 7.1 Hz, CH_2-C14), 4.00 (2H, s, CH_2-C11), 3.80 (3H, s, $CH_2C_6H_4O\underline{Me}$), 2.45 (1H, td, *J* = 7.1, 2.4 Hz, CH_2-C6a), 2.38 (1H, td, *J* = 7.1, 2.4 Hz, CH_2-C6b), 2.20–2.06 (2H, m, CH_2-C8), 1.64 (2H, dt, *J* = 7.9, 6.0 Hz, CH_2-C7), 1.59 (3H, s, CH_3-C16), 1.26 (3H, t, *J* = 7.1 Hz, CH_2-C15), 0.90 (9H, s,

$Si(CH_3)_2C(C\underline{H_3})_3$), 0.05 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (C-C12), 194.7 (C-C1), 159.5 ($CH_2\underline{C_6}H_4OMe$), 140.0 (C-C2), 135.8 (C-C10), 129.7 ($CH_2\underline{C_6}H_4OMe$), 129.6 ($CH_2\underline{C_6}H_4OMe$), 127.3 (CH-C3), 125.8 (CH-C9), 122.9 (C-C5), 113.9 ($CH_2\underline{C_6}H_4OMe$), 74.5 ($CH_2$-C13), 73.0 ($C\underline{H_2}C_6H_4OMe$), 68.4 ($CH_2$-C11), 61.6 (C-C4), 61.4 (CH_2-C14), 55.3 ($CH_2C_6H_4O\underline{Me}$), 28.0 ($CH_2$-C6), 26.6 ($CH_2$-C8), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 19.7 ($CH_2$-C7), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.0 ($CH_3$-C15), 13.5 ($CH_3$-C16), −5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2930, 2856, 1715, 1611, 1247 cm^{-1}; HMRS (ESI^+) calcd for $C_{30}H_{44}NaO_6Si$ $[M+Na]^+$ 551.2799 found 551.2789.

Ethyl 5-((1R,5S,6S)-6-((*tert*-butyl-dimethyl-silyloxy)methyl)-6-methylbicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate

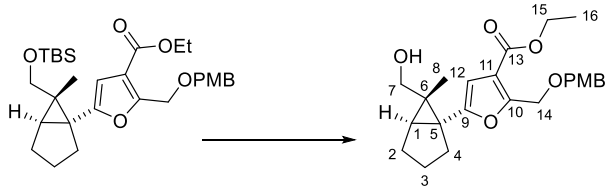
(155)



To a stirred solution of ynenone **154** (1.30 g, 2.46 mmol) in CH_2Cl_2 (15 mL) at rt was added chloroacetic acid (0.23 g, 2.5 mmol) in one portion. The mixture was stirred at 40 °C for 4 d and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford furan **155** (0.87 g, 1.7 mmol, 67%) as a pale yellow oil.

R_f = 0.32 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (2H, m, Ar-H), 6.86–6.81 (2H, m, Ar-H), 6.37 (1H, s, CH-C12), 4.73 (2H, d, *J* = 7.9 Hz, CH_2-C14), 4.48 (2H, s, $C\underline{H}_2C_6H_4OMe$), 4.20 (2H, q, *J* = 7.1 Hz, CH_2-C15), 3.78 (3H, s, $\underline{O}Me$), 3.33 (1H, d, *J* = 10.2 Hz, CH_2-C7a), 3.20 (1H, d, *J* = 10.2 Hz, CH_2-C7b), 2.02 (4H, m, CH_2-C4, CH_2-C2), 1.68 (2H, m, CH_2-C3), 1.58 (1H, t, *J* = 4.0 Hz, CH-C1), 1.28 (3H, t, *J* = 7.1 Hz, CH_3-C16), 1.11 (3H, s, CH_3-C8), 0.81 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), −0.06 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$), −0.10 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (C-C13), 159.3 (Ar), 157.8 (C-C10), 155.0 (C-C9), 130.2 (Ar), 129.6 (Ar), 117.0 (C-C11), 113.8 (Ar), 106.6 (CH-C12), 72.1 ($\underline{C}H_2C_6H_4OMe$), 68.7 ($CH_2$-C7), 62.5 (C H_2-C14), 60.2 (C H_2-C15), 55.3 ($\underline{OMe}$), 36.0 (CH_2-C4), 34.2 (C-C5), 32.8 (C H_2-C2), 31.6 (CH-C1), 27.6 (C-C6), 25.9 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 22.7 ($CH_2$-C3), 18.3 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 14.3 (C H_3-C16), 11.0 (CH_3-C8), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2925, 1717, 1513, 1248, 1090 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{30}H_{44}NaO_6Si$ $[M+Na]^+$ 551.2799, found 551.2791.

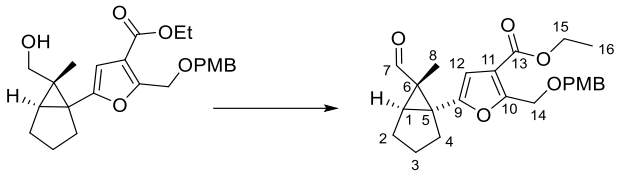
Ethyl 5-((1*R*,5*S*,6*S*)-6-(hydroxymethyl)-6-methylbicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate (156)



To a stirred solution of protected alcohol **155** (1.40 g, 2.65 mmol) in MeOH/CH_2Cl_2 (3:1, 16 mL) at rt was added camphorsulfonic acid (0.12 g, 0.53 mmol) in one portion. The mixture was stirred for 18 h and then the reaction was quenched by addition of H_2O (12 mL) and saturated aq. $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 2:1) to afford the alcohol **156** (0.91 g, 2.2 mmol, 83%) as a pale yellow oil.

R_f = 0.08 (petroleum ether:EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.16 (2H, m, Ar-H), 6.86–6.75 (2H, m, Ar-H), 6.34 (1H, s, CH-C12), 4.74 (2H, d, *J* = 5.5 Hz, CH_2-C14), 4.47 (2H, d, *J* = 1.8 Hz, CH_2C$_6$H$_4$OMe), 4.24 (2H, q, *J* = 7.1 Hz, CH_2-C15), 3.78 (3H, s, OMe), 3.43 (1H, d, *J* = 11.5 Hz, CH_2-C7a), 3.15 (1H, d, *J* = 11.5 Hz, CH_2-C7b), 2.13–1.95 (4H, m, CH_2-C4, CH_2-C2), 1.75–1.61 (3H, m, CH_2-C3, CH-C1), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C16), 1.20 (3H, s, CH_3-C8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (C-C13), 159.3 (Ar), 156.5 (C-C10), 155.4 (C-C9), 130.0 (Ar), 129.6 (Ar), 117.3 (C-C11), 113.8 (Ar), 107.3 (CH-C12), 72.2 (CH_2C$_6$H$_4$OMe), 69.3 (CH_2-C7), 62.5 (CH_2-C14), 60.5 (CH_2-C15), 55.3 (OMe), 32.8 (CH_2-C4), 30.6 (C-C5), 29.3 (CH_2-C2), 27.9 (CH-C1), 27.3 (CH-C6), 21.9 (CH_2-C3), 14.3 (C-C16), 11.0 (CH_3-C8); ν_{max} (film) 3600, 2933, 1714, 1244, 1061 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{24}H_{30}NaO_6$ $[M+Na]^+$ 437.1935, found 437.1926.

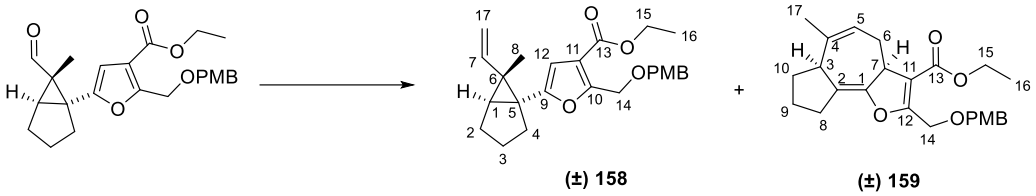
Ethyl 5-((1*R*,5*R*,6*S*)-6-formyl-6-methylbicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate (157)



To a stirred solution of alcohol **156** (0.39 g, 0.94 mmol) in CH_2Cl_2 (9 mL) at 0 °C was added DMP (0.60 g, 1.4 mmol). The mixture was stirred at rt for 16 h and then the reaction was quenched by sequential addition of saturated aq. $Na_2S_2O_3$ (10 mL) and saturated aq. $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (12 mL), stirred until two clear layers were obtained (ca. 30 min) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 9:1) to afford aldehyde **157** (0.33 mg, 0.79 mmol, 84%) as a pale yellow oil.

R_f = 0.20 (petroleum ether:EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, s, CH-C7), 7.30–7.23 (2H, m, Ar-H), 6.91–6.86 (2H, m, Ar-H), 6.42 (1H, s, CH-C12), 4.76 (2H, s, C$\underline{H_2}$C$_6$H$_4$OMe), 4.49 (2H, s, CH$_2$-C14), 4.27 (2H, q, *J* = 7.1 Hz, CH$_2$-C15), 3.81 (3H, s, $\underline{\text{OMe}}$), 2.54 (1H, d, *J* = 5.4 Hz, CH-C1), 2.40–2.29 (1H, m, CH$_2$-C4a), 2.19 (2H, dq, *J* = 11.6, 4.1 Hz, CH$_2$-C4b, CH$_2$-C2a), 2.05–1.95 (1H, m, CH$_2$-C2b), 1.90–1.82 (1H, m, CH$_2$-C3a), 1.63–1.51 (1H, m, CH$_2$-C3b), 1.32 (3H, t, *J* = 7.1 Hz, CH$_3$-C16), 1.28 (3H, s, CH$_3$-C8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (CH-C7), 162.8 (C-C13), 159.0 (Ar), 155.7 (C-C10), 144.4 (C-C9), 130.0 (Ar), 129.4 (Ar), 116.6 (C-C11), 113.8 (Ar), 108.0 (CH-C12), 72.3 (C$\underline{H_2}$C$_6$H$_4$OMe), 62.4 (CH$_2$-C14), 60.5 (CH$_2$-C15), 55.3 ($\underline{\text{OMe}}$), 41.1 (CH$_2$-C4), 39.8 (C-C5), 36.5 (CH$_2$-C2), 32.4 (CH-C1), 25.7 (C-C6), 25.2 (CH$_2$-C3), 14.3 (C-C16), 6.25 (CH$_3$-C8). HMRS (ESI$^+$) calcd for $C_{24}H_{28}NaO_6$ $[M+Na]^+$ 435.1778, found 435.1767.

(3a*S*,7a*S*)-Ethyl 2-(((4-methoxybenzyl)oxy)methyl)-6-methyl-3a,4,6a,7,8,9-hexahydroazuleno[4,5-*b*]furan-3-carboxylate (159)



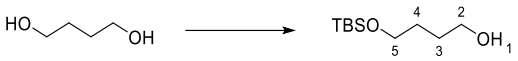
To a stirred solution of methyltriphenylphosphonium bromide (1.00 g, 2.82 mmol) in THF (8 mL) at −10 °C was added *n*-BuLi (2.3 M in hexanes, 0.82 mL, 1.88 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **157** (0.39 g, 0.94 mmol) in THF (5 mL) at −10 °C. The mixture was stirred at the same temperature for 2 h and then the reaction was heated to 60 °C and stirred for 18 h. The reaction was quenched by pouring the solution into a mixture of pH 7 buffer (20 mL) and Et_2O (10 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I, petroleum ether:EtOAc, 10:1) to afford a mixture of the vinylcyclopropane **158** and the cycloheptadiene **159** (0.18 g, 0.44 mmol 47%, ratio of 1:3.6 respectively) as a colourless oil. The ratio was determined by comparison of the ^{1}H NMR signals (C7 in **158** = 5.8 ppm, C9 in **159** = 5.48 ppm).

159: R_f = 0.49 (petroleum ether-EtOAc, 8:1); ^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (2H, d, *J* = 8.6 Hz, Ar-H **159**), 7.24 (2H, d, *J* = 8.6 Hz, Ar-H **158**), 6.78–6.74 (2H, m, Ar-H **159**), 6.78–6.74 (2H, m, Ar-H **158**), 6.53 (1H, s, CH-C12 **158**), 5.79 (1H, dd, *J* = 17.4, 10.7 Hz, CH-C7 **158**). 5.45 (1H, d, *J* = 7.6 Hz, CH-C5 **159**), 5.18 (1H, dd, *J* = 17.4, 1.8 Hz, CHH-C17 **158**), 5.11 (1H, dd, *J* = 10.7, 1.8 Hz, CHH-C17 **158**), 4.89 (2H, s, C<u>H$_2$</u>C$_6$H$_4$OMe **158**), 4.67 (2H, dddd, *J* = 13.0, 0.6 Hz, C<u>H$_2$</u>C$_6$H$_4$OMe **159**). 4.53 (2H, s, CH$_2$-C14 **159**), 4.51 (2H, s, CH$_2$-C14 **158,** 4.19–4.12 (1H, m, CH-C7 **159**), 4.09 (2H, ddd, *J* = 14.2, 7.1, 1.2 Hz, CH$_2$-C15 **158**), 4.04–3.93 (2H, m, CH$_2$-C15 **159**), 3.28 (3H, s, <u>OMe</u> **159**), 3.27 (3H, s, <u>OMe</u> **158**), 3.06 (1H, d, *J* = 11.4 Hz, CH-C3 **159**), 2.85 (1H, dd, *J* = 15.9, 8.4 Hz, CH$_2$-C6a **159**), 2.63 (1H, dd, *J* = 16.7, 6.8 Hz, CH$_2$-C10a **159**), 2.49–2.33 (1H, m, CH$_2$-C10b **159**), 2.49–2.33 (1H, m, CH$_2$-C4a **158**), 2.26–2.14 (1H, m, CH$_2$-C6b **159**), 2.26–2.14 (1H, m, CH$_2$-C4b **158**), 2.08 (2H, ddd, *J* = 14.0, 8.4, 4.0 Hz, CH$_2$-C2 **158**). 1.93 (1H, t, *J* = 5.1 Hz, CH$_2$-C8a **159**), 1.84 – 1.77 (1H, m, CH-C1 **158**),

1.62 (3H, s, CH_3-C17 **159**), 1.57–1.48 (1H, m, CH_2-C9a **159**), 1.25–1.17 (2H, m, CH_2-C9b, CH_2-C8b **159**) 1.26 –1.18 (2H,m, CH_2-C3 **158**), 1.09 (1H, s, 3H, CH_3-C8 **158**), 0.99 (3H, t, *J* = 7.1 Hz, CH_3-C16 **158**), 0.93 (3H, t, *J* = 7.1 Hz, CH_3-C16 **159**); ^{13}C NMR (101 MHz, C_6D_6) δ 164.5 (C-C13 **159**), 164.5 (C-C13 **158**),163.7 (Ar **159**), 163.7 (Ar **158**), 159.5 (C-C12 **159**), 159.5 (C-C10 **158**), 150.8 (C-C1 **159**), 150.8 (C-C9 **158**), 143.0 (C-C7 **158**), 135.6 (C-C4 **159**), 135.6 (C-C17 **158**), 130.4 (Ar **159**), 130.4 (Ar **158**), 129.4 (Ar **159**), 129.4 (Ar **158**), 122.7 (C-C2 **159**), 115.6 (CH-C5 **159**), 115.2 (CH-C12 **158**), 113.7 (Ar **159**), 113.7 (Ar **158**), 110.5 (C-C11 **159**), 110.5 (C-C11 **158**), 72.6 ($\underline{C}H_2C_6H_4OMe$ **159**), 72.6 ($\underline{C}H_2C_6H_4OMe$ **158**), 63.0 (CH_2-C14 **158**), 62.9 (CH_2-C14 **159**), 59.5 (CH_2-C15 **159**), 59.4 (CH_2-C15 **158**), 54.4 (<u>OMe</u> **159**), 54.4 (<u>OMe</u> **158**), 46.3 (CH-C7 **159**), 43.4 (CH-C3 **159**), 36.2 (C-C5 **158**),34.6 (CH_2-C8 **159**), 33.6 (CH_2-C4 **158**), 32.0 (CH_2-C6 **159**), 29.2 (C-C6 **158**), 29.0 (CH_2-C10 **159**), 29.0 (CH_2-C2 **158**), 27.9 (CH-C1, **158**), 25.9 (CH_2-C9 **159**), 23.9 (CH_3-C17 **159**), 23.4 (CH_2-C3 **158**), 14.0 (CH_3-C16 **159**), 13.9 (CH_3-C16 **158**); ν_{max} (film) 2926, 2870, 1716, 1512, 1456, 1247 cm^{-1}; HMRS (ESI^+) calcd for $C_{25}H_{30}NaO_5$ $[M+Na]^+$ 433.1985, found 433.1979.

7.2.3 Micheliolide synthesis

5-[(*tert*-Butyldimethylsilyl)oxy]butan-2-ol (169)

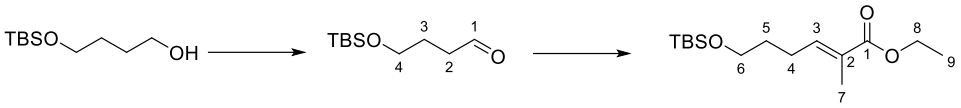


To a stirred solution of butan-1,4-diol **168** (10.0 g, 0.11 mol) in CH_2Cl_2 (150 mL) at rt was added imidazole (7.50 g, 0.11 mol). TBSCl (16.6 g, 111 mmol) was add dropwise over 30 min. The mixture was stirred for 2 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (10 mL). The mixture was diluted with Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 8:2) to afford protected alcohol **169** (14.3 g, 70.1 mmol, 63%) as a colourless oil.

R_f = 0.16 (petroleum ether:EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69–3.61 (4H, m, CH_2-C2, CH_2-C5), 1.69–1.59 (4H, m, CH_2-C4, CH_2-C3), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.06 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.4 (CH_2-C2), 62.8 (CH_2-C5), 30.2 (CH_2-C3), 29.9 (CH_2-C4), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 (($Si(\underline{C}H_3)_2C(CH_3)_3$).

Analytical data was in full agreement with that previously reported.[26]

(*E*)-Ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-methylhex-2-enoate (170)



To a stirred solution of oxalyl chloride (5.73 mL, 67.9 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added DMSO (8.61 mL, 121 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **168** (9.90 g, 48.5 mmol) in CH_2Cl_2 (5 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h and Et_3N (35.0 mL, 243 mmol) was added. The mixture was allowed to warm to rt and then the reaction was quenched by addition of H_2O (150 mL). The phases were separated and the organic phase was washed with 1M HCl (100 mL), H_2O (2 × 100 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde **168'** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.67 (petroleum ether:EtOAc, 9:1);^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 1.4 Hz, CH-C1), 3.64 (2H, t, *J* = 6.0 Hz, CH_2-C4), 2.50 (2H, td, *J* = 6.2, 1.4 Hz, CH_2-C2), 1.89–1.82 (2H, m, CH_2-C3), 0.88 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.03 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6 (CH-C1), 62.1 (CH_2-C4), 40.8 (CH_2-C2), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.5 ($CH_2$-C3), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), -5.4 (($Si(\underline{C}H_3)_2C(CH_3)_3$).

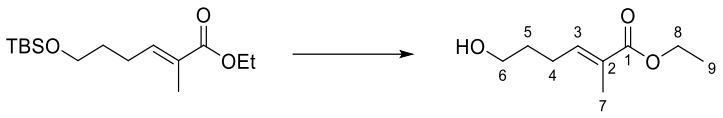
To a solution of ethyl 2-(triphenylphosphoranylidene)propionate **160** (26.3 g, 72.7 mmol) in CH_2Cl_2 (200 mL) was added aldehyde at rt and the reaction was stirred for 24 h. The reaction was quenched by the addition of water H_2O (150 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (2 × 70 mL) and brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) delivered ester **170** (13.0 g, 45.5 mmol, 94% over two steps) (>17:1 (*E*/*Z*) dr by ^{1}H NMR) as a colourless oil.

R_f = 0.42 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (1H, tq, *J* = 7.4, 1.3 Hz, CH-C3), 4.17 (2H, q, *J* = 7.1 Hz, CH_2-C8), 3.62 (2H, t, *J* = 6.2 Hz, CH_2-C6), 2.24 (2H, q, *J* = 7.4 Hz, CH_2-C4), 1.83 (3H, d, *J* = 1.3 Hz, CH_3-C7), 1.69–1.60 (2H, m, CH_2-C5), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C9), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C-C1), 141.8 (C-C2), 128.1 (CH-C3), 62.3 (CH_2-C6),

60.4 (CH_2-C8), 31.7 (CH_2-C4), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.1 ($CH_2$-C5), 18.3 ($(Si(CH_3)_2\underline{C}(CH_3)_3$), 14.3 ($CH_3$-C9), 12.3 ($CH_3$-C7), −5.3 ($(Si(\underline{C}H_3)_2C(CH_3)_3$).

Analytical data was in full agreement with that previously reported.[26]

(*E*)-Ethyl 6-hydroxy-2-methylhex-2-enoate (167)

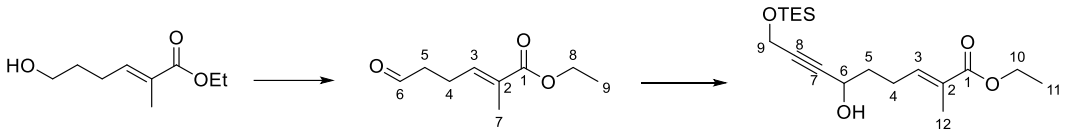


To a stirred solution of ester **170** (10.0 g, 35.0 mmol) in THF (120 mL) was added a solution of TBAF (52.0 mL, 52.4 mmol, 1M in THF). The mixture was stirred at rt for 3 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (120 mL). The mixture was diluted with Et_2O (200 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with H_2O (2 × 50 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded alcohol **167** (5.80 g, 33.7 mmol, 97%) as a colourless oil.

R_f = 0.21 (petroleum ether-EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, tq, *J* = 7.5, 1.3 Hz, CH-C3), 4.16 (2H, q, *J* = 7.1 Hz, CH_2-C8), 3.64 (2H, t, *J* = 6.4 Hz, CH_2-C6), 2.25 (2H, q, *J* = 7.5, 0.6 Hz, CH_2-C4), 1.86 (1H, s, br, OH), 1.82 (3H, d, *J* = 1.3 Hz, CH_3-C7), 1.72–1.65 (2H, m, CH_2-C5), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C-C1), 141.3 (C-C2), 128.3 (CH-C3), 62.1 (CH_2-C6), 60.5 (CH_2-C8), 31.5 (CH_2-C4), 25.0 (CH_2-C5), 14.2 (CH_3-C9), 12.3 (CH_3-C7).

Analytical data was in full agreement with that previously reported.[26]

(*E*)-Ethyl 6-hydroxy-2-methyl-9-((triethylsilyl)oxy)non-2-en-7-ynoate (171)



To a stirred solution of oxalyl chloride (0.89 mL, 11 mmol) in CH_2Cl_2 (130 mL) at −78 °C was added DMSO (1.34 mL, 18.9 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **167** (1.30 g, 7.55 mmol) in CH_2Cl_2 (10 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h and Et_3N (5.45 mL, 37.7 mmol) was added. The mixture was allowed to warm to rt and then the reaction was quenched by addition of H_2O (50 mL). The phases were separated and the organic phase was washed with 1M HCl (1× 30 mL), H_2O (2 × 10 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde as a yellow oil. The aldehyde **167'** was used directly in the next step without further purification.

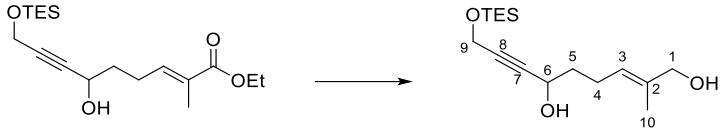
R_f = 0.48 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.1 Hz, CH-C6), 6.66 (1H, tq, *J* = 7.3, 1.4 Hz, CH-C3), 4.16 (2H, q, *J* = 7.1 Hz, CH_2-C8), 2.64–2.59 (2H, m, CH_2-C4), 2.51–2.44 (2H, m, CH_2-C5), 1.84 (3H, d, *J* = 1.4 Hz, CH_3-C7), 1.27 (3H, t, *J* = 7.1 Hz, CH_3-C9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (CH-C6), 167.9 (C-C1), 139.6 (CH-C3), 129.3 (C-C2), 60.6 (CH_2-C8), 42.6 (CH_2-C4), 21.2 (CH_2-C5), 14.3 (CH_3-C9), 12.4 (CH_3-C7).

To a stirred solution of triethyl(prop-2-yn-1-yloxy)silane **173** (2.32 g, 15.1 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.2 M in hexanes, 4.46 mL, 9.81 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of aldehyde **167'** (1.30 g, 7.55 mmol) in THF (5 mL) was added slowly. The mixture was stirred at same temperature for 1 h and then the reaction was quenched by the addition of H_2O (50 mL). The mixture was diluted with Et_2O (20 mL) and the aqueous phase was extracted with Et_2O (3 × 9 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2) yielded alcohol **171** (1.85 g, 5.44 mmol, 72%) over two steps as a colourless oil.

R_f = 0.61 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, tq, *J* = 7.5,

1.4 Hz, CH-C3), 4.41 (1H, td, *J* = 5.9, 4.8 Hz, CH-C6), 4.32 (2H, d, *J* = 1.7 Hz, CH_2-C9), 4.17 (2H, q, *J* = 7.1 Hz, CH_2-C8), 2.34 (2H, q, *J* = 7.5 Hz, CH_2-C4), 2.15 (1H, d, *J* = 4.2 Hz, OH), 1.83 (3H, d, *J* = 1.4 Hz, CH_3-C12), 1.83–1.77 (2H, m, CH_2-C5), 1.30–1.25 (3H, t, *J* = 7.1 Hz, CH_3-C11), 0.98 (9H, t, *J* = 8.2 Hz, $Si(CH_2C\underline{H}_3)_3$, 0.66 (6H, q, *J* = 8.2 Hz, $Si(C\underline{H}_2CH_3)_3$ $(C\underline{H}_2)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C-C1), 140.7 (CH-C3), 128.7 (C-C2), 85.2 (C-C7), 83.8 (C-C8), 61.8 (CH-C6), 60.5 (CH_2-C10), 51.3 (CH_2-C9), 36.2 (CH_2-C5), 24.4 (CH_2-C4), 14.2 (CH_3-C11), 12.3 (CH_3-C12), 6.6 $Si(CH_2\underline{C}H_3)_3$, 4.4 $Si(\underline{C}H_2CH_3)_3$; ν_{max} (film) 3383, 2953, 29873, 1689, 1267, 1139 cm^{-1}; HMRS (ESI^+) calcd for $C_{18}H_{32}NaO_4Si$ $[M+Na]^+$ 363.1962, found 363.1957.

(*E*)-2-methyl-9-((triethylsilyl)oxy)non-2-en-7-yne-1,6-diol (172)

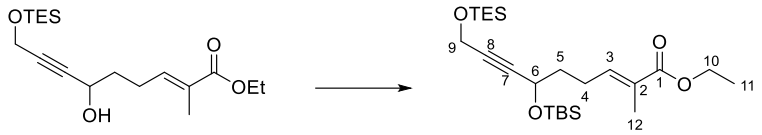


To a solution of ester **171** (1.85 g, 5.44 mmol) in CH_2Cl_2 (90 mL) was added DiBAl-H (1.0 M in hexanes, 16.3 mL, 16.3 mmol) dropwise at –78 °C. The reaction was allowed to warm to rt and stirred for 4 hours. The reaction mixture was quenched by the addition of an aqueous solution of Rochelle salt (50 mL) and stirred for 18 hour. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 7:3) yielded diol **172** (0.52 g, 1.74 mmol, 32%) as a colourless oil.

R_f = 0.35 (petroleum ether:EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (1H, tq, *J* = 7.2, 1.2 Hz, CH-C3), 4.38 (1H, t, *J* = 6.4 Hz, CH-C4), 4.33 (2H, d, *J* = 1.7 Hz, CH_2-C9), 3.98 (2H, s, CH_2-C1), 2.33 – 2.25 (1H, m, OH), 2.24 (2H, q, *J* = 7.5 Hz, CH_2-C4), 1.78 – 1.72 (2H, m, CH_2-C5), 1.66 (3H, s, CH_3-C10), 0.98 (9H, t, *J* = 8.2 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.66 (6H, q, *J* = 8.2 Hz, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8 (CH-C3), 124.7 (C-C2), 85.7 (C-C8), 83.4 (C-C7), 68.7 (CH-C6), 61.9 (CH_2-C1), 51.3 (CH_2-C9), 37.2 (CH_2-C5), 23.4 (CH_2-C4), 13.7 (CH_3-C10), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 4.4 ($Si(\underline{C}H_2CH_3)_3$); ν_{max} (film) 3325, 2953, 29873, 1714, 1674, 1456, 1236, 1064 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{16}H_{30}NaO_3Si$ $[M+Na]^+$ 321.1856, found 321.1850.

(*E*)-ethyl 6-((*tert*-butyldimethylsilyl)oxy)-2-methyl-9-((triethylsilyl)oxy)non-2-en-7-ynoate

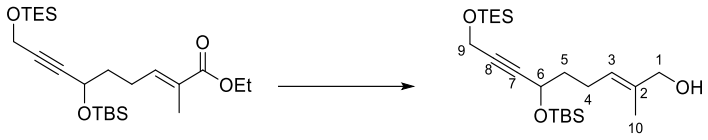
(174)



To a stirred solution of alcohol **171** (6.20 g, 18.2 mmol) in CH_2Cl_2 and DMF (30 mL, 2:1) at rt was added sequentially imidazole (1.86 g, 27.3 mmol) and TBSCl (2.73 g, 18.2 mmol). The mixture was stirred for 2 h and then the reaction was quenched by addition of H_2O (20 mL). The phases were separated and the organic phase was washed with H_2O (3 × 7 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 9:1) to afford protected ester **174** (7.85 g, 17.3 mmol, 95%) as a colourless oil.

R_f = 0.26 (petroleum ether:EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, tq, *J* = 7.4, 1.2 Hz, CH-C3), 4.45 – 4.39 (1H, m, CH-C6), 4.33 (2H, d, *J* = 1.5 Hz, CH_2-C9), 4.18 (2H, dt, *J* = 14.2, 5.3 Hz, CH_2-C10), 2.32 (2H, q, *J* = 7.5 Hz, CH_2-C4), 1.83 (3H, s, CH_3-C12), 1.82 – 1.74 (2H, m, CH_2-C5), 1.28 (3H, dd, *J* = 8.7, 5.5 Hz, CH_3-C11), 1.00 – 0.93 (9H, m, $Si(C\underline{H}_3)_2(CH_2)_3$), 0.90 – 0.87 (9H, m, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.64 (4H, qd, *J* = 7.8, 2.6 Hz, $Si(CH_3)_2(C\underline{H}_2)_3$), 0.14 – 0.08 (6H, m, $Si(CH_3)_2C(C\underline{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C-C1), 141.3 (CH-C3), 128.3 (C-C2), 85.7 (C-C7), 83.0 (C-C8), 62.4 (CH-C6), 60.4 (CH_2-C10), 51.3 (CH_2-C9), 37.3 (CH_2-C5), 25.8 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 24.4 ($CH_2$-C4), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.3 ($CH_3$-C11), 12.3 ($CH_3$-C12), 6.7 ($Si(\underline{C}H_3)_2(CH_2)_3$), 4.5 ($Si(CH_3)_2(\underline{C}H_2)_3$), −4.5 ($Si(CH_3)_2C(\underline{C}H_3)_3$), −5.1 ($Si(\underline{C}H_2CH_3)_3$); ν_{max} (film) 2953, 1710, 1562, 1255, 1082 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{24}H_{46}NaO_4Si_2$ $[M+Na]^+$ 477.2827, found 477.2820.

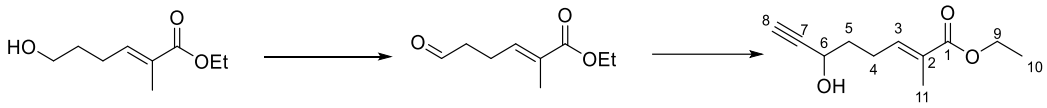
(*E*)-6-((*tert*-butyldimethylsilyl)oxy)-2-methyl-9-((triethylsilyl)oxy)non-2-en-7-yn-1-ol (175)



To a solution of ester **174** (1.00 g, 2.20 mmol) in CH_2Cl_2 (50 mL) was added DiBAl-H (1.0 M in hexanes, 3.30 mL, 3.30 mmol) dropwise at –78 °C. The reaction was allowed to warm to rt and stirred for 4 hours. The reaction mixture was quenched with Rochelle salt (50 mL) and stirred for 18 hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduce pressure. Purification by column chromatography on silica gel (petroleum ether:ethyl acetate, 8:1) yielded alcohol **175** (0.34 g, 0.82 mmol, 37%) as a colourless oil.

R_f = 0.30 (petroleum ether:EtOAc, 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (1H, t, *J* = 7.2 Hz, CH-C3), 4.31–4.23 (1H, m, CH-C6), 4.21 (2H, d, *J* = 1.6 Hz, CH_2-C9), 3.87 (2H, s, CH_2-C1), 2.14–1.97 (2H, m, CH_3-C4), 1.60 (2H, dt, *J* = 11.9, 5.3 Hz, CH_3-C5), 1.55 (3H, s, CH_3-C10), 0.85 (9H, t, *J* = 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.77 (9H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.52 (6H, q, *J* = 8.0 Hz, $Si(C\underline{H}_2CH_3)_3$, 0.02–−0.04 (6H, m, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4 (C-C2), 125.3 (CH-C3), 86.2 (C-C7), 82.6 (C-C8), 68.9 (CH_2-C1), 62.5 (CH-C6), 51.4 (CH_2-C9), 38.3 (CH_2-C5), 25.9 (CH_2-C4), 23.4 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 13.6 ($CH_3$-C6), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 4.5 ($Si(\underline{C}H_2CH_3)_3$), −4.5 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.0 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 3329, 2953, 2856, 1708, 1462, 1251, 1076 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{16}H_{30}NaO_3Si$ $[M+Na]^+$ 435.2829, found 435.2884.

(*E*)-Ethyl 6-hydroxy-2-methyloct-2-en-7-ynoate (176)

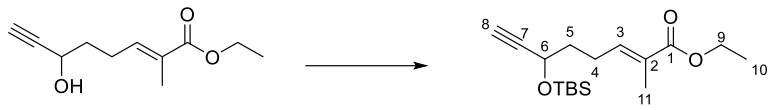


To a stirred solution of oxalyl chloride (2.81 mL, 33.3 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added DMSO (4.22 mL, 59.5 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **167** (4.10 g, 23.8 mmol) in CH_2Cl_2 (30 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h and Et_3N (17.1 mL, 119 mmol) was added. The mixture was allowed to warm to rt and then the reaction was quenched by addition of H_2O (150 mL). The phases were separated and the organic phase was washed with 1M HCl (1× 100 mL), H_2O (2 × 70 mL) and brine (70 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde as a yellow oil. The aldehyde **167'** was used directly in the next step without further purification.

To a stirred solution of aldehyde **167'** in CH_2Cl_2 (100 mL) at 0 °C was added ethynylmagnesium bromide (0.5 M solution in THF, 61.9 mL, 30.9 mmol) in small portions. The mixture was stirred at 0 °C for 16 h and then the reaction was quenched with H_2O (100 mL). The mixture was diluted with Et_2O (120 mL) and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) provided the alcohol **176** (3.40 g, 17.3 mmol, 73%) over two steps as a colourless oil.

R_f = 0.26 (petroleum ether:EtOAc, 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, tq, *J* = 7.5, 1.3 Hz, CH-C3), 4.53 (1H, td, *J* = 5.9, 2.1 Hz, CH-C6), 4.21 (2H, q, *J* = 7.1 Hz, CH_2-C9), 2.41 (1H, d, *J* = 2.1 Hz, CH-C8), 2.45 (2H, q, *J* = 7.5 Hz, CH_2-C4), 2.18 (1H, s, OH), 1.90–1.78 (2H, m, CH_2-C5), 1.85 (3H, d, *J* = 1.3 Hz, CH_3-C11), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-C10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C-C1), 141.3 (CH-C3), 128.4 (C-C2), 85.0 (C-C7), 72.5 (CH-C8), 62.3 (CH-C6), 60.4 (CH_2-C9), 37.4 (CH_2-C5), 24.0 (CH_2-C4), 14.3 (CH_3-C10), 12.2 (CH_3-C11); ν_{max} (film) 3437, 2982, 1693, 1260, 1087 cm^{-1}; HRMS calcd for $C_{11}H_{16}NaO_3$ $[M+Na]^+$ 219.0992, found 219.0993.

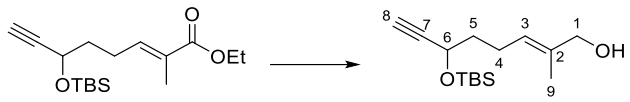
(*E*)-Ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-methyloct-2-en-7-ynoate (176)



To a stirred solution of alcohol **176** (4.20 g, 21.4 mmol) in CH_2Cl_2 (50 mL) at rt was added sequentially imidazole (2.00 g, 27.8 mmol) and TBSCl (4.17 g, 27.8 mmol). The mixture was stirred for 5 hours and then the reaction was quenched by addition of H_2O (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 4:1) to afford the protected alcohol **178** (4.98 g, 16.1 mmol, 75%) as a colourless oil.

R_f = 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (1H, tq, *J* = 7.5, 1.4 Hz, CH-C3), 4.39 (1H, td, *J* = 6.1, 2.1 Hz, CH-C6), 4.19 (2H, q, *J* = 7.1 Hz, CH_2-C9), 2.40 (1H, d, *J* = 2.1 Hz, CH-C8), 2.34 (2H, q, *J* = 7.5 Hz, CH_2-C4), 1.84 (3H, d, *J* = 1.0 Hz, CH_3-C11), 1.80 (2H, td, *J* = 6.1, 1.2 Hz, CH_2-C5), 1.29 (3H, t, *J* = 7.1 Hz, CH_3-C10), 0.90 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.14 (3H, s, $Si(\underline{CH_3})_2C(CH_3)_3$), 0.14 (3H, s, $Si(\underline{CH_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C-C1), 141.0 (CH-C3), 128.4 (C-C2), 85.0 (C-C7), 72.5 (CH-C8), 62.2 (CH-C6), 60.4 (CH_2-C9), 37.2 (CH_2-C5), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 24.3 ($CH_2$-C4), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.3 ($CH_3$-C10), 12.3 ($CH_3$-C11), −5.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

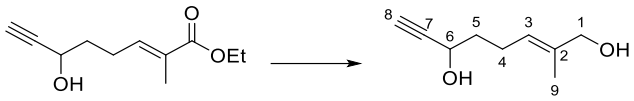
(*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-methyloct-2-en-7-yn-1-ol (180)



To a solution of ester **178** (4.98 g, 16.1 mmol) in THF (50 mL) was added DiBAl-H (1.0 M in hexanes, 32.2 mL, 32.2 mmol) dropwise at –78 °C. The reaction was allowed to warm to rt and stirred for 4 hours. The reaction was quenched by the addition of an aqueous solution of Rochelle salt (50 mL) and stirred for 18 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 7:2) delivered the diol **180** (2.56 g, 9.66 mmol, 60%) as a colourless oil.

R_f = 0.19 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, tq, *J* = 7.2, 1.2 Hz, CH-C3), 4.30 (1H, td, *J* = 6.3, 2.1 Hz, CH-C6), 3.94 (2H, s, CH_2-C1), 2.33 (1H, d, *J* = 2.1 Hz, CH-C8), 2.13 (2H, q, *J* = 7.5 Hz, CH_2-C4), 1.67 (2H, dd, *J* = 14.6, 7.1 Hz, CH_2-C5), 1.62 (3H, s, CH_3-C9), 0.85 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.06 (6H, d, *J* = 11.1 Hz, $Si(C\underline{H}_3)_2C(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5 (C-C2), 125.1 (CH-C3), 85.4 (C-C7), 72.2 (CH-C8), 68.9 (CH-C6), 62.3 (CH_2-C1), 38.3 (CH_2-C5), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.3 ($CH_2$-C4), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 13.6 ($CH_3$-C9), −4.5 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

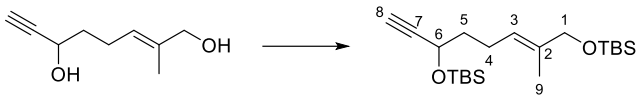
(*E*)-2-Methyloct-2-en-7-yne-1,6-diol (179)



To a solution of ester **176** (2.00 g, 10.2 mmol) in CH_2Cl_2 (50 mL) was added DiBAl-H (1.0 M in hexanes, 20.4 mL, 20.4 mmol) dropwise at –78 °C. The reaction was allowed to warm to rt and stirred for 4 hours. The reaction was quenched by the addition of an aqueous solution of Rochelle salt (50 mL) and stirred for 18 hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 7:2) yielded diol **179** (0.96 g, 6.22 mmol, 61%) as a colourless oil.

R_f = 0.19 (petroleum ether:EtOAc, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, tq, *J* = 7.3, 1.4 Hz, CH-C3), 4.37 (1H, td, *J* = 7.3, 2.1 Hz, CH-C6), 4.00 (2H, s, CH_2-C1), 2.48 (1H, d, *J* = 2.1 Hz, CH-C8), 2.27–2.19 (2H, m, CH_2-C4), 1.83–1.77 (2H, m, CH_2-C5), 1.68 (3H, s, CH_3-C9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (C-C1), 124.6 (CH-C3), 84.8 (C-C7), 73.1 (CH-C8), 68.7 (CH_2-C1), 61.8 (CH-C6), 37.2 (CH_2-C5), 23.2 (CH_2-C4), 13.7 (CH_3-C9); ν_{max} (film) 3282, 2864, 1452, 1064 cm^{-1}; HMRS (ESI$^+$) calcd for $C_9H_{14}NaO_2$ $[M+Na]^+$ 177.0886, found 177.0887.

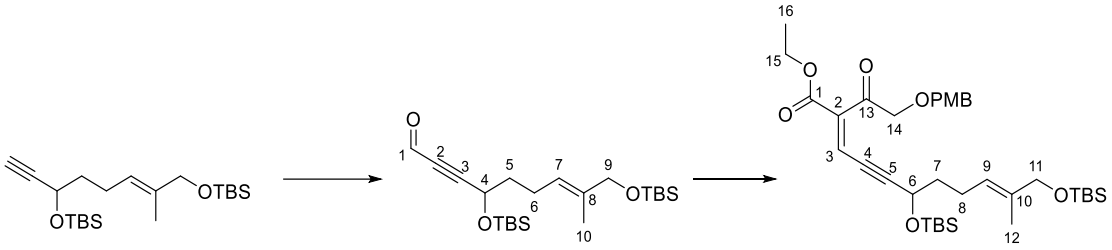
(*E*)-2-Methyloct-2-en-7-yne-1,6-(*tert*-Butyldimethylsilyl) (181)



To a solution of diol **179** (1.77 g, 11.5 mmol) in CH_2Cl_2 (100 mL) was added imidazole (1.56 g, 23.0 mmol) and TBSCl (3.45 g, 23.0 mmol) in CH_2Cl_2 (10 mL) at rt and the reaction stirred for 6 h. The reaction was quenched by the addition of water H_2O (90 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with H_2O (2 × 20 mL) and brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) yielded alkyne **181** (2.77 g, 7.25 mmol, 63%) as a colourless oil.

R_f = 0.20 (petroleum ether:EtOAc, 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, tq, *J* = 7.2, 1.3 Hz, CH-C3), 4.35 (1H, td, *J* = 6.4, 2.1 Hz, CH-C6), 4.00 (2H, s, CH_2-C1), 2.38 (1H, d, *J* = 2.1 Hz, CH-C8), 2.25–2.10 (2H, m, CH_2-C4), 1.78–1.68 (2H, m, CH_2-C5), 1.61 (3H, s, CH_3-C9), 0.91 (18H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.14 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.11 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.06 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (C-C2), 123.3 (CH-C3), 85.5 (C-C7), 72.1 (CH-C8), 68.5 (CH_2-C1), 62.3 (CH-C6), 38.4 (CH_2-C5), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.2 ($CH_2$-C4), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 13.4 ($CH_3$-C9), −4.5 ($Si(CH_3)_2C(\underline{C}H_3)_3$), −5.1 ($Si(CH_3)_2C(\underline{C}H_3)_3$); ν_{max} (film) 2954, 2856, 1251, 586 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{21}H_{42}NaO_2Si_2$ $[M+Na]^+$ 405.2616, found 405.2617.

(2*E*,9*E*)-Ethyl 6,11-bis((*tert*-butyldimethylsilyl)oxy)-2-(2-((4-methoxybenzyl)oxy)acetyl)-10-methylundeca-2,9-dien-4-ynoate (183)



To a stirred solution of alkyne **181** (1.50 g, 3.92 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.14 mL, 4.71 mmol, 2.2 M in hexanes) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.64 mL, 7.84 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of NaH_2PO_4 (1.88 g, 15.7 mmol) in H_2O/Et_2O (30 ml, 1:1). The mixture was stirred for 30 min and then the phases were separated. The combined organic extracts were washed with saturated aq. LiCl (15 mL), H_2O (2 x 10 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **182** as a yellow oil. The aldehyde was used directly in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, s, CH-C1), 5.36 (1H, td, *J* = 7.3, 1.2 Hz, CH-C7), 4.53 (1H, t, *J* = 6.4 Hz, CH-C4), 4.00 (2H, s, CH_2-C9), 2.26–2.17 (2H, m, CH_2-C6), 1.87–1.70 (2H, m, CH_2-C5), 1.60 (3H, s, 3H, CH_3-C10), 0.91 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.15 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.12 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$, 0.06 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6 (CH-C1), 135.8 (C-C8), 122.5 (CH-C7), 97.8 (C-C2), 83.7 (C-C3), 68.4 (CH_2-C9), 62.3 (CH-C4), 37.6 (CH_2-C5), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.0 ($CH_2$-C6), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 13.5 ($CH_3$-C10), −4.6 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

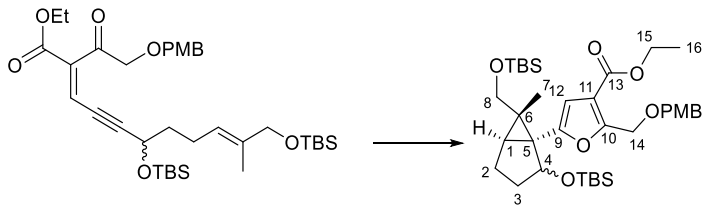
To a stirred solution of crude acetylenic aldehyde **182** (3.92 mmol) and ethyl 4-[(4-methoxybenzyl)oxy]-3-oxobutanoate (1.04 g, 3.92 mmol) at rt was added $MgSO_4$ (94.0 mg, 0.78 mmol) and EDDA1 (0.14 g, 0.78 mmol). The mixture was stirred for 3 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (8 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash

column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford ynenone **183** (1.52 g, 2.31 mmol, 59%) (1:0.55 (*E*/*Z*) dr by ^{13}C NMR) as a pale yellow oil.

R_f = 0.20 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (2H, m, Ar-H), 6.93–6.84 (3H, m, CH-C3, Ar-H), 5.37 (1H, ddd, *J* = 8.6, 7.1, 3.5 Hz, CH-C9), 4.53 (1H, dd, *J* = 7.1, 5.4 Hz, CH-C6), 4.50 (2H, d, *J* = 12.4 Hz, CH_2-C14), 4.34 (2H, d, *J* = 8.2 Hz, $C\underline{H_2}C_6H_4OMe$), 4.29–4.18 (2H, m, CH_2-C15), 3.99 (2H, s, *J* = 6.2 Hz, CH_2-C11), 3.80 (3H, s, OMe), 2.23–2.09 (2H, m, CH_2-C8), 1.80–1.69 (2H, m, CH_2-C7), 1.59 (3H, s, CH_3-C12), 1.13 (3H, t, *J* = 7.1 Hz, CH_2-C16), 0.90 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.12–0.08 (6H, m, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.01 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.01 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9 (C-C13), 163.6 (C-C1), 159.4 (Ar), 140.9 (C-C2), 135.5 (C-C10), 132.0 (C-C5), 129.6 (Ar), 125.8 (Ar), 124.4 (CH-C9), 123.0 (CH-C3), 113.9 (Ar), 74.5 (CH_2-C14), 73.7 ($C\underline{H_2}C_6H_4OMe$), 68.4 ($CH_2$-C11), 63.0 (CH-C6), 61.5 (CH_2-C15), 55.3 (OMe), 33.8 (CH_2-C7), 28.4 (CH_2-C8), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 17.5 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 17.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.6 ($CH_3$-C12), 13.5 ($CH_3$-C16), −4.5 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2927, 1716, 1361, 1249, 1093 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{36}H_{58}NaO_7Si_2$ $[M+Na]^+$ 681.3613, found 681.3583.

Ethyl 5-((1*R*,5*S*,6*S*)-4,6-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-methylbicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate

(184)



To a stirred solution of ynenone **183** (1.50 g, 2.28 mmol) in CH_2Cl_2 (25 mL) at rt was added chloroacetic acid (0.53 g, 2.3 mmol) in one portion. The mixture was stirred at 40 °C for 4 d and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford furan **184** (1.00 g, 1.52 mmol, 67%) as a pale yellow oil.

R_f = 0.46 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (2H, m, Ar-H), 6.89–6.84 (2H, m, Ar-H), 6.56 (1H, s, CH-C12), 4.76 (2H, d, *J* = 1.8 Hz, CH_2-C14), 4.76–4.68 (1H, m, CH-C4), 4.49 (2H, s, $C\underline{H_2}C_6H_4OMe$), 4.29–4.22 (2H, m, CH_2-C15), 3.80 (3H, s, OMe), 3.27 (1H, d, *J* = 10.1 Hz, CH_2-C8a), 3.15 (1H, d, *J* = 10.1 Hz, CH_2-C8b), 2.23–2.06 (2H, m, CH_2-C3a, CH_2-C2a), 1.91–1.82 (1H, m, CH-C1), 1.63–1.53 (1H, m, CH_2-C3b), 1.50 (1H, d, *J* = 5.5 Hz, CH_2-C2b), 1.42 (3H, s, CH_3-C7), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-C16), 0.86 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.85 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), −0.04 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), −0.09 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), −0.12 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), −0.13 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (C-C13), 159.2 (Ar), 156.3 (C-C10), 155.0 (C-C9), 130.3 (Ar), 129.5 (CAr), 117.3 (CH-C12), 113.7 (Ar), 108.5 (C-C11), 80.3 (CH-C4), 72.0 ($\underline{C}H_2C_6H_4OMe$), 69.4 ($CH_2$-C14), 62.5 ($CH_2$-C8), 60.2 ($CH_2$-C15), 55.3 ($\underline{OMe}$), 39.9 (C-C5), 35.3 (CH-C1), 32.8 (C-C6), 31.9 (CH_2-C3), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.6 ($CH_2$-C2), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 17.8 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.3 ($CH_3$-C16), 12.6 ($CH_3$-C10), −4.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), −5.2 ($Si(CH_3)_2C(\underline{C}H_3)_3$), −5.5 ($Si(CH_3)_2C(\underline{C}H_3)_3$); ν_{max} (film) 2927, 1716, 1361, 1249, 1093 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{36}H_{58}NaO_7Si_2$ $[M+Na]^+$ 681.3613, found 681.3583.

(*E*)-Ethyl 2-methyl-6-[(triisopropylsilyl)oxy]oct-2-en-7-ynoate (186)

To a stirred solution of alcohol **176** (1.30 g, 6.62 mmol) in CH_2Cl_2 (50 mL) at rt was added imidazole (1.12 g, 16.6 mmol) and TIPSCl (1.42 mL, 6.62 mmol). The mixture was stirred for 4 h and then the reaction was quenched by addition of H_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford protected alcohol **186** (2.21 g, 6.28 mmol, 95%) as a colourless oil.

R_f = 0.69 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.74 (1H, tq, *J* = 7.3, 1.2 Hz, CH-C3), 4.53 (1H, td, *J* = 5.9, 2.1 Hz, CH-C6), 4.18 (2H, q, *J* = 7.1 Hz, CH_2-C9), 2.41 (1H, d, *J* = 2.1 Hz, CH-C8), 2.45 – 2.35 (2H, m, CH_2-C4), 1.90–1.78 (2H, m, CH_2-C5), 1.85 (3H, d, *J* = 1.2 Hz, CH_3-C11), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-C10), 1.10–1.06 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C-C1), 141.3 (CH-C3), 128.4 (C-C2), 85.0 (C-C7), 72.5 (CH-C8), 62.3 (CH_2-C9), 60.4 (CH-C6), 37.4 (CH_2-C5), 24.0 (CH_2-C4), 18.0 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 14.3 (CH_3-C10), 12.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), 12.2 (CH_3-C11); ν_{max} (film) 2943, 2866, 1705, 1463, 1265,1086 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{20}H_{36}NaO_3Si$ $[M+Na]^+$ 375.2326, found 375.2326.

(*E*)-2-Methyl-6-{[tris(propan-2-yl)silyl]oxy}oct-2-en-7-yn-1-ol (187)

To a solution of ester **186** (2.21 g, 6.28 mmol) in CH_2Cl_2 (150 mL) was added DiBAl-H (1.0 M in hexanes, 12.6 mL, 12.6 mmol) dropwise at –78 °C and the mixture was allowed to warm to rt and stirred for 5 hours. The reaction was quenched by the addition of sat. aq Rochelle salt (100 mL) and the mixture was stirred for 18 hours. The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded alcohol **187** (1.90 g, 6.13 mmol, 97%) as a colourless oil.

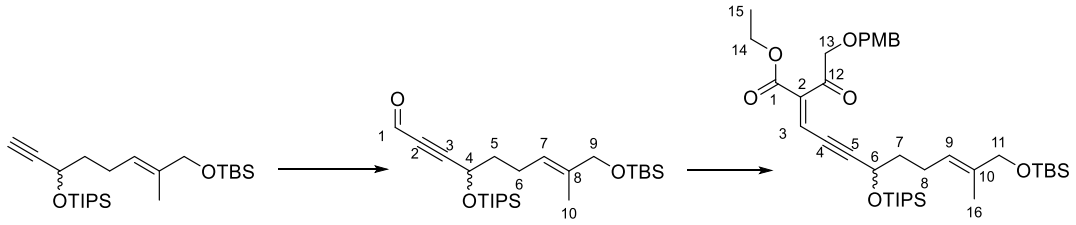
R_f = 0.69 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (1H, td, *J* = 7.5, 1.3 Hz, CH-C3), 4.50 (1H, td, *J* = 6.1, 2.1 Hz, CH-C6), 4.00 (2H, s, CH_2-C1), 2.40 (1H, d, *J* = 2.1 Hz, CH-C8), 2.24 (2H, q, *J* = 7.5 Hz, CH_2-C4), 1.82–1.72 (2H, m, CH_2-C5), 1.68 (3H, s, CH_3-C9), 1.29 (1H, s, OH), 1.14–1.03 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5 (CH-C3), 125.3 (C-C2), 85.4 (C-C7), 72.3 (CH-C8), 67.0 (CH_2-C1), 62.5 (CH-C6), 38.5 (CH_2-C5), 23.0 (CH_2-C4), 18.4 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 13.6 (CH_3-C9), 12.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$); ν_{max} (film) 3200, 2943, 1708, 1262, 1093 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{18}H_{34}NaO_2$ Si $[M+Na]^+$ 333.2220, found 333.2219.

(*E*)-2-Methyloct-2-en-7-yne-1-(*tert*-Butyl-dimethyl-silyloxy)- 6-[tris(propan-2-yl)silyl] (188)

To a solution of alcohol **187** (1.80 g, 5.80 mmol) in CH_2Cl_2 (80 mL) was added imidazole (0.39 g, 5.8 mmol) and TBSCl (0.87 g, 5.8 mmol) in CH_2Cl_2 (1 mL) at rt and stirred for 4 h. The reaction mixture was quenched with H_2O (50 mL) and the aqueous phase was extracted with Et_2O (3 × 6 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) delivered the alkyne **188** (2.37 g, 7.25 mmol, 96%) as a colourless oil.

R_f = 0.61 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, t, *J* = 7.3 Hz, CH-C3), 4.48 (1H, td, *J* = 6.2, 1.8 Hz, CH-C6), 4.00 (2H, s, CH_2-C1), 2.39 (1H, d, *J* = 1.8 Hz, CH-C8), 2.23 (2H, q, *J* = 7.3 Hz, CH_2-C4), 1.81–1.71 (2H, m, CH_2-C5), 1.61 (3H, s, CH_3-C9), 1.16–1.03 (21H, m, Si((C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 0.91 (9H, s, Si(CH$_3$)$_2$C(C<u>H</u>$_3$)$_3$), 0.06 (6H, s, Si(C<u>H</u>$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (CH-C3), 123.5 (C-C2), 85.5 (C-C7), 72.2 (CH-C8), 68.6 (CH-C6), 62.7 (CH_2-C1), 38.6 (CH_2-C5), 26.0 (Si(CH$_3$)$_2$C(<u>C</u>H$_3$)$_3$), 23.0 (CH_2-C4), 18.4 (Si(CH$_3$)$_2$<u>C</u>(CH$_3$)$_3$), 18.0 (Si(CH-<u>C</u>H$_6$)$_3$), 13.4 (CH_3-C9), 12.3 (Si(<u>C</u>HCH$_6$)$_3$), −5.3 (Si(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$); ν_{max} (film) 2945, 2360, 1251, 1105 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{24}H_{48}NaO_2Si_2$ [M+Na]$^+$ 447.3082, found 447.3082.

(2*E*,9*E*)-Ethyl 11-((*tert*-butyldimethylsilyl)oxy)-2-(2-((4-methoxybenzyl)oxy)acetyl)-10-methyl-6-((triisopropylsilyl)oxy)undeca-2,9-dien-4-ynoate (190)



To a stirred solution of alkyne **188** (1.00 g, 2.36 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (2.2 M in hexanes, 1.61 mL, 3.54 mmol) over a period of 10 min. The mixture was stirred at −78 °C for 15 min and then anhydrous DMF (0.36 mL, 4.7 mmol) was added. The mixture was stirred at −78 °C for a further 30 min and then the reaction was quenched by addition of 10% aqueous KH_2PO_4 (60 mL). The mixture was diluted with Et_2O (50 mL), stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude acetylenic aldehyde **189** as a yellow oil. The aldehyde was used directly in the next step without further purification.

R_f = 0.89 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, s, CH-C1), 5.39 (1H, td, *J* = 7.3, 1.3 Hz, CH-C7), 4.67 (1H, t, *J* = 6.2 Hz, CH-C6), 4.00 (2H, s, CH_2-C9), 2.23 (2H, q, *J* = 7.3 Hz, CH_2-C6), 1.83 (2H, ddd, *J* = 15.0, 6.2, 2.6 Hz, CH_2-C5), 1.61 (3H, s, CH_3-C10), 1.13–1.04 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$, 0.91 (9H, s, Si(CH$_3$)$_2$C(C<u>H</u>$_3$)$_3$), 0.06 (6H, s, Si(C<u>H</u>$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4 (s, CH-C1), 135.8 (C-C8), 122.6 (CH-C7), 98.0 (C-C2), 83.9 (C-C3), 68.3 (CH_2-C9), 62.6 (CH-C4), 37.8 (CH_2-C5), 25.9 (Si(CH$_3$)$_2$C(<u>C</u>H$_3$)$_3$), 22.9 (CH_2-C6), 18.1 (Si(CH$_3$)$_2$<u>C</u>(CH$_3$)$_3$), 18.0 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 13.4 (CH_3-C10), 12.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$), –5.3 (Si(<u>C</u>H$_3$)$_2$C(CH$_3$)$_3$).

To a stirred solution of crude acetylenic aldehyde **189** and ethyl 4-[(4-methoxybenzyl)oxy]-3-oxobutanoate **124** (0.63 mL, 2.4 mmol) at rt was added $MgSO_4$ (57 mg, 0.47 mmol) and EDDA2 (85 mg, 0.47 mmol). The mixture was stirred at 40 °C for 1 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (10 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered

and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford ynenone **190** (0.99 g, 1.41 mmol, 60% over two steps) (1:0.49 (*E*/*Z*) dr by ^{13}C NMR) as a pale yellow oil.

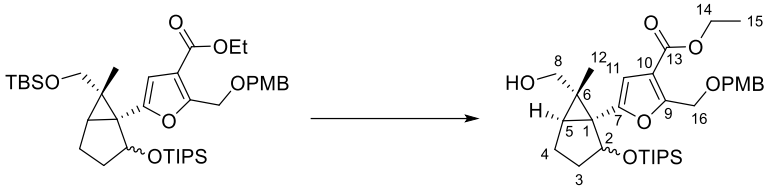
R_f = 0.27 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (2H, m, Ar-H), 6.93 (1H, d, *J* = 2.0 Hz, CH-C3), 6.89–6.84 (2H, m, Ar-H), 5.38 (1H, ddd, *J* = 12.6, 7.1, 1.3 Hz, CH-C9), 4.65 (1H, td, *J* = 6.2, 1.8 Hz, CH-C6), 4.49 (2H, d, *J* = 9.7 Hz, CH_2-C13), 4.35 (2H, d, *J* = 9.7 Hz, $C\underline{H_2}C_6H_4OMe$), 4.24 (2H, q, *J* = 7.1 Hz, CH_2-C14), 3.99 (2H, s, CH_2-C11), 3.80 (3H, s, O<u>Me</u>), 2.29–2.13 (2H, m, CH_2-C8), 1.87–1.69 (2H, m, CH_2-C7), 1.60 (3H, s, CH_3-C16), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C15), 1.12–1.02 (21H, m, $Si(C\underline{H}(C\underline{H_3})_2)_3$), 0.90 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.06 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.05 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6 (C-C12), 163.7 (C-C1), 159.2 (Ar), 156.0 (Ar), 155.2 (C-C3), 130.3 (C-C10), 129.4 (CH-C9), 117.2 (Ar), 113.8 (Ar), 109.0 (C-C4), 80.8 (C-C5), 71.9 ($\underline{C}H_2C_6H_4OMe$), 69.5 ($CH_2$-C11), 68.4 (CH-C6), 62.4 (CH_2-C13), 60.1 (CH_2-C14), 55.3 (OMe), 35.7 (CH_2-C7), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.6 ($CH_2$-C8), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 18.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.3 ($CH_3$-C15), 12.7 ($CH_3$-C16), 12.2 ($Si(\underline{C}H\text{-}(CH_3)_2)_3$), −5.6 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2934, 2879, 2360, 1714, 1603,1462, 1250, 1093 cm^{-1}; HMRS (ESI^+) calcd for $C_{39}H_{64}NaO_7Si_2$ $[M+Na]^+$ 723.4083 found 723.4065.

Ethyl 5-{(1*R,5*S**,6*S**)-(6-{[(*tert*-butyldimethylsilyl)oxy]methyl}-6-methyl-2-{[tris(propan-2-yl)silyl]-oxy}bicyclo[3.1.0]hexan-1-yl)-2-{[(4-methoxyphenyl) methoxy]methyl}furan-3-carboxylate (191)**

To a stirred solution of ynenone **190** (0.99 g, 1.4 mmol) in CH_2Cl_2 (15 mL) at rt was added chloroacetic acid (0.13 g, 1.4 mmol) in one portion. The mixture was stirred at 40 °C for 4 d and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford furan **191** (0.95 g, 1.4 mmol, 68%) as a pale yellow oil.

R_f = 0.59 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.4 Hz, Ar-H), 6.91–6.87 (2H, m, Ar-H), 6.66 (1H, s, CH-C11), 4.94 (1H, dd, *J* = 9.1, 7.0 Hz, CH-C4), 4.79 (2H, s, CH_2-C16), 4.51 (2H, d, *J* = 2.5 Hz,C$\underline{H}_2C_6H_4$OMe), 4.25 (2H, q, *J* = 7.1 Hz, CH_2-C14), 3.82 (3H, s, OMe), 3.37 (1H, d, *J* = 10.2 Hz, CH_2-C8a), 3.16 (1H, d, *J* = 10.2 Hz, CH_2-C8b), 2.31–2.20 (1H, m, CH_2-C3a), 2.15 (1H, m, CH_2-C4a), 1.89 (1H, m, CH_2-C4b), 1.67–1.57 (1H, m, CH_2-C3b), 1.48 (3H, s, CH_3-C12), 1.44 (1H, d, *J* = 5.6 Hz, CH-C5), 1.32 (3H t, *J* = 7.1 Hz, CH_3-C15), 0.99–0.95 (21H, m, Si(C$\underline{H}$(C$\underline{H_3}$)$_2$)$_3$), 0.90 (9H, s, Si(CH$_3$)$_2$C(C$\underline{H_3}$)$_3$), −0.02 (3H, s, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$), −0.05 (3H, s, Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (C-C13), 159.2 (Ar), 156.0 (C-C9), 155.2 (C-C7), 130.3 (Ar), 129.5 (Ar), 117.2 (C-C10), 113.7 (Ar), 109.0 (CH-C11), 80.8 (CH-C2), 72.0 (CH_2-C16), 69.5 (CH_2-C8), 62.5 (C$\underline{H}_2C_6H_4$OMe), 60.1 (CH_2-C14), 55.3 (OMe), 40.3 (C-C1), 35.7 (CH_2-C3), 32.8 (CH-C5), 31.7 (C-C6), 25.9 (Si(CH$_3$)$_2$C(C$\underline{H_3}$)$_3$), 23.6 (CH_2-C4), 18.2 (Si(CH$_3$)$_2$C$\underline{(CH_3)_3}$), 18.0 (Si(CH(C$\underline{H_3}$)$_2$)$_3$), 14.3 (CH_3-C15), 12.7 (CH_3-C12), 12.3 (Si(C$\underline{H}$(CH$_3$)$_2$)$_3$), −5.5 (Si(C$\underline{H_3}$)$_2$C(CH$_3$)$_3$); ν_{max} (film) 2928, 2863,1727, 1247, 1070 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{39}H_{64}NaO_7Si_2$ [M+Na]$^+$ 723.4083, found 723.4069.

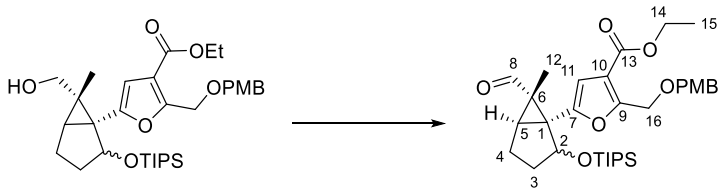
Ethyl 5-{(1*R,5*S**,6*S**) [6-(hydroxymethyl)-6-methyl-2-{[tris(propan-2-yl)silyl]oxy}bicyclo[3.1.0]hexan-1-yl]-2-{[(4-methoxyphenyl)methoxy]methyl}furan-3-carboxylate (192)**



To a stirred solution of protected alcohol **191** (1.28 g, 1.83 mmol) in MeOH/CH_2Cl_2 (5:2, 14 mL) at rt was added camphorsulfonic acid (85 mg, 0.37 mmol) in one portion. The mixture was stirred for 1 h and then the reaction was quenched by addition of H_2O (5 mL) and saturated aq. $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 7:1) to afford alcohol **192** (1.00 g, 1.71 mmol, 94%) as a colourless oil.

R_f = 0.21 (petroleum ether:EtOAc, 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 6.5 Hz, Ar-H), 6.82 (2H, d, *J* = 8.4 Hz, Ar-H), 6.43 (1H, s, CH-C11), 4.81 (1H, dd, *J* = 9.1, 7.0 Hz, CH-C4), 4.79 (1H, d, *J* = 12.7 Hz, CH_2-C16a), 4.58 (1H, d, *J* = 12.7 Hz, CH_2-C16b), 4.43 (2H, d, *J* = 5.3 Hz, C$\underline{H_2}$C$_6$H$_4$OMe), 4.21–4.19 (2H, m, CH_2-C14), 3.75 (3H, s, OMe), 3.33 (1H, dd, *J* = 11.5, 5.1 Hz, CH_2-C8a), 2.97 (1H, d, *J* = 11.5 Hz, CH_2-C8b), 2.28–2.20 (1H, m, CH_2-C3a), 2.14–2.03 (1H, m, CH_2-C4a), 1.89–1.79 (1H, m, CH_2-C4b), 1.65–1.55 (2H, m, CH_2-C3b, CH-C5), 1.50 (3H, s, CH_3-C12), 1.49 (1H, d, *J* = 5.7 Hz, OH), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C15), 0.92 (21H, s, Si(C$\underline{H}$(C$\underline{H_3}$)$_2$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (C-C13), 159.3 (Ar), 157.1 (C-C9), 155.3 (C-C7), 130.0 (Ar), 129.5 (Ar), 117.2 (C-C10), 113.8 (Ar), 108.4 (CH-C11), 81.7 (CH-C2), 72.2 (CH_2-C16), 70.3 (CH_2-C8), 62.4 ($\underline{C}H_2C_6H_4OMe$), 60.4 ($CH_2$-C14), 55.3 (OMe), 39.8 (C-C1), 35.8 (CH_2-C3), 33.5 (CH-C5), 32.2 (C-C6), 23.3 (CH_2-C4), 18.0 (Si(CH(C$\underline{H_3}$)$_2$)$_3$), 14.3 (CH_3-C15), 12.5 (CH_3-C12), 12.2 (Si(C$\underline{H}$(CH$_3$)$_2$)$_3$); ν_{max} (film) 2940, 1714, 1244, 1066 cm^{-1}. HMRS (ESI$^+$) calcd for $C_{33}H_{50}NaO_7Si$ [M+Na]$^+$ 609.3218, found 609.3199.

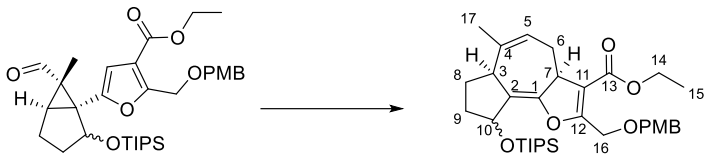
Ethyl 5-((1*R*,5*R*,6*S*)-6-formyl-6-methyl-2-((triisopropylsilyl)oxy)bicyclo[3.1.0]hexan-1-yl)-2-(((4-methoxybenzyl)oxy)methyl)furan-3-carboxylate (193).



To a stirred solution of alcohol **192** (0.93 g, 1.6 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DMP (1.01 g, 2.38 mmol) in small portions. The mixture was stirred at rt for 16 h and then the reaction was quenched by sequential addition of saturated aq. $Na_2S_2O_3$ (5 mL) and saturated aq. $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (15 mL), stirred until two clear layers were obtained (ca. 30 min) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:3) to afford aldehyde **193** (0.84 g, 1.44 mmol, 90 %) as a pale yellow oil.

R_f = 0.36 (petroleum ether:EtOAc, 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, s, CH-C8), 7.30–7.21 (2H, m, Ar-H), 6.90–6.82 (2H, m, Ar-H), 6.45 (1H, s, CH-C11), 4.96 (1H, dd, *J* = 9.0, 7.4 Hz, CH-C2), 4.74 (2H, d, *J* = 9.2 Hz, C CH_2-C16), 4.47 (2H, s, C$\underline{H_2}C_6H_4OMe$), 4.30–4.20 (2H, m, CH_2-C14), 3.80 (3H, s, OMe), 2.41–2.20 (3H, m, CH_2-C3a, CH_2-C4), 2.02–1.93 (1H, m, CH_2-C3b), 1.59 (3H, s, CH_3-C12), 1.63–1.52 (1H, m, CH-C5), 1.32 (3H, t, *J* = 7.1 Hz, CH_3-C15), 1.01–0.81 (21H, m, Si(C$\underline{H}$($C\underline{H_3}$)$_2$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (CH-C8), 163.1 (C-C13), 159.2 (Ar), 156.1 (C-C9), 153.2 (C-C7), 130.0 (Ar), 129.5 (Ar), 117.3 (C-C10), 113.7 (Ar), 110.2 (CH-C11), 81.6 (CH-C2), 72.2 (CH_2-C16), 62.3 ($\underline{C}H_2C_6H_4OMe$), 60.5 ($CH_2$-C14), 55.3 (OMe), 42.6 (C-C6), 40.0 (C-C1), 34.7 (CH_2-C3), 34.1 (CH-C5), 23.1 (CH_2-C4), 17.9 (Si(CH($\underline{C}H_3$)$_2$)$_3$), 14.3 (CH_3-C15), 12.1 (Si($\underline{C}$H(CH_3)$_2$)$_3$), 7.5 (CH_3-C12); HMRS (ESI^+) calcd for $C_{33}H_{48}NaO_7Si$ $[M+Na]^+$ 607.3062, found 607.3061.

Ethyl (3a*S,7a*S**)- 1-(((1-methoxybenzyl)oxy)methyl)-4-methyl-10-((triisopropylsilyl)oxy)-3a, 4,6, 7, 8, 9a, -hexahydroazuleno[4,5-b]furan-3-carboxylate (195)**

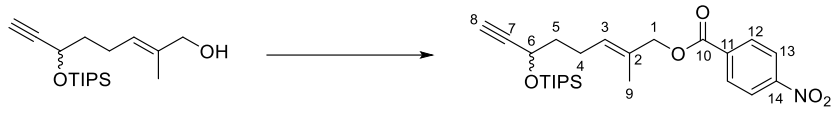


To a stirred solution of methyltriphenylphosphonium bromide (1.80 g, 5.04 mmol) in THF (15 mL) at −10 °C was added *n*-BuLi (2.3 M in hexanes, 1.25 mL, 2.88 mmol). The mixture was stirred at −10 °C for 1 h and then added to a stirred solution of aldehyde **193** (0.84 g, 1.4 mmol) in THF (2 mL) at −10 °C. The mixture was stirred at rt for 2 h and then the mixture was heated to 60 °C and stirrer 16 h. The reaction was quenched by pouring the solution into a mixture of pH 7 buffer (15 mL) and Et_2O (10 mL). The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 7 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide (activated, basic, Brockmann I, petroleum ether:EtOAc, 10:1) to afford cycloheptadiene **195** (0.40 g, 0.67 mmol 47%) as a colourless oil.

R_f = 0.56 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, C_6D_6) δ 7.19–7.13 (2H, m, Ar-H), 6.72–6.67 (2H, m, Ar-H), 5.23 (1H, d, *J* = 6.4 Hz, CH-C5), 4.94 (1H, d, *J* = 4.0 Hz, CH_2-C16a), 4.75–4.71 (1H, m, CH_2-C16b), 4.47–4.42 (1H, m, C$\underline{H_2}$C$_6$H$_4$OMe), 4.41 (1H, s, C$\underline{H_2}$C$_6$H$_4$OMe), 4.04–3.98 (1H, m, CH-C10), 3.94–3.83 (2H, m, CH_2-14), 3.18 (3H, s, OMe), 3.03–2.93 (1H, m, CH-C7), 2.71–2.61 (1H, m, CH-C3), 2.20–2.09 (1H, m, CH_2-C6a), 1.89 (1H, ddd, *J* = 11.9, 9.1, 3.3 Hz, CH_2-C6b), 1.73 (2H, dd, *J* = 12.0, 6.1 Hz, CH_2-C9a), 1.67 (2H, dd, *J* = 12.0, 6.1 Hz, CH_2-C8a) 1.53 (3H, s, *J* = 1.0 Hz, CH_3-C17), 1.38–1.22 (2H, m, *J* = 9.7, 5.0, 2.5 Hz, CH_2-C9b, CH_2-C8b), 1.18–1.04 (21H, m, Si(C$\underline{H}$(C$\underline{H_3}$)$_2$)$_3$), 0.83 (3H, t, *J* = 7.1 Hz, CH_3-C15); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1 (C-C13), 163.6 (C-C12), 159.6 (Ar), 153.9 (C-C1), 135.5 (C-C4), 130.3 (Ar), 129.4 (Ar), 122.0 (CH-C5), 119.5 (C-C2), 113.8 (Ar), 111.1 (C-C11), 72.8 (CH-C10), 71.8 (C$\underline{H_2}$C$_6$H$_4$OMe), 62.9 (CH_2-C16), 59.7 (CH_2-C14), 54.5 (OMe), 44.2 (CH-C3), 43.8 (CH_2-C9), 40.9 (CH-C7), 35.6 (CH_2-C6), 25.2 (CH_3-C17), 18.3 (Si(CH(C$\underline{H_3}$)$_2$)$_3$), 14.0 (CH_2-C8), 12.7 (Si(C$\underline{H}$(CH$_3$)$_2$)$_3$), 12.4 (CH_3-C15); ν_{max} (film) 2928,

2279, 1722, 1455, 1097 cm^{-1}; HMRS (ESI^+) calcd for $C_{34}H_{50}NaO_6Si$ $[M+Na]^+$ 605.3269, found 605.3257.

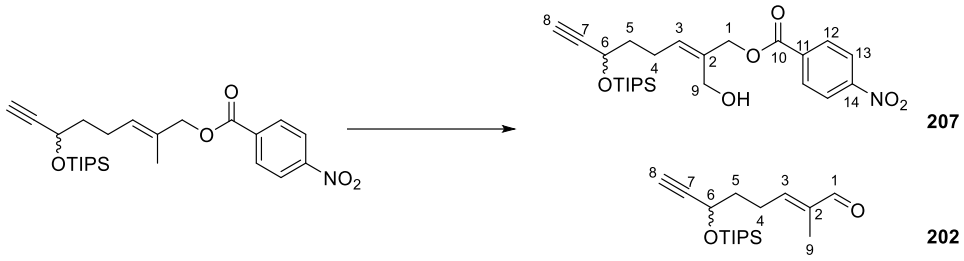
(*E*)-2-Methyl-6-((triisopropylsilyl)oxy)oct-2-en-7-yn-1-yl 1-nitrobenzoate (206)



To a solution of alcohol **187** (1.00 g, 3.22 mmol) in THF (80 mL) was added Et_3N (1.86 mL, 12.9 mmol) and *p*-nitrobenzyl chloride (2.40 g, 12.9 mmol) in THF (3 mL) at 55 °C and stirred for 16 h. The reaction mixture was quenched with H_2O (50 mL) and diluted with Et_2O (20 ml). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 10 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduce pressure. Purification by column chromatography on silica gel (petroleum ether:EtOAc, 10:1) yielded alkyne **206** (1.32 g, 2.87 mmol, 89%) as a colourless oil.

R_f = 0.56 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31–8.27 (2H, m, CH-C12), 8.24–8.19 (2H, m, CH-C13), 5.64–5.58 (1H, m, CH-C3), 4.76 (2H, s, CH_2-C1), 4.51 (1H, td, *J* = 6.1, 2.1 Hz, CH-C6), 2.41 (1H, d, *J* = 2.1 Hz, CH-C8), 2.30 (2H, q, *J* = 7.6 Hz, CH_2-C4), 1.87–1.77 (2H, m, CH_2-C5), 1.77 (3H, s, CH_3-C9), 1.19–1.03 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5 (C-C10), 150.6 (C-C14), 135.8 (C-C2), 130.7 (CH-C12), 130.2 (CH-C3), 129.8 (C-C11), 123.5 (CH-C13), 85.3 (C-C7), 72.4 (CH-C8), 71.6 (CH-C6), 62.4 (CH_2-C1), 38.2 (CH_2-C5), 23.2 (CH_2-C4), 18.0 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 14.1 (C-C9), 12.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$); ν_{max} (film) 2954, 2930, 1731, 1462, 1252, 1096 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{25}H_{37}NNaO_5Si$ $[M+Na]^+$ 482.2333, found 482.2333.

(*E*)-2-(Hydroxymethyl)-6-((triisopropylsilyl)oxy)oct-2-en-7-yn-1-yl 4-nitrobenzoate (207)

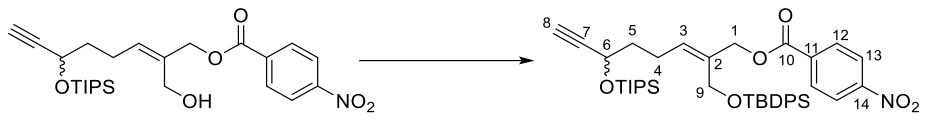


To a solution of alkyne **206** (1.20 g, 2.79 mmol) in CH_2Cl_2 (20 mL) was added SeO_2 (0.62 g, 5.6 mmol) and *t*-BOOH (1.10 mL, 11.2 mmol, 70% in H_2O) at rt and stirred for 16 h. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (8 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduce pressure. The resulting residue was dissolve in MeOH (10 mL) and then cooled to 0 °C. $NaBH_4$ (53 mg, 1.4 mmol) was the added portion-wise and the reaction stirred at 0 °C for 2 h. The reaction mixture was quenched with saturated aq. NH_4Cl (7 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 9 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:EtOAc, 8:3) affforded alcohol **207** (0.37 g, 0.78 mmol, 28%) as a pale yellow oil and aldehyde **202** (0.59 g, 1.91 mmol, 69%) as a pale yellow oil.

207: R_f = 0.20 (petroleum ether:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31–8.26 (2H, m, CH-C12), 8.22–8.18 (2H, m, CH-C13), 5.85 (1H, t, *J* = 7.6 Hz, CH-C3), 5.02 (2H, s, CH_2-C9), 4.53 (1H, td, *J* = 6.3, 2.1 Hz, CH-C6), 4.20 (2H, s, CH_2-C1), 2.44 (2H, q, *J* = 7.7 Hz, CH_2-C4), 2.40 (1H, d, *J* = 2.1 Hz, CH-C8), 1.89–1.73 (2H, m, CH_2-C5), 1.10–1.02 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C-C10), 150.6 (C-C14), 135.5 (C-C2), 133.7 (CH-C3), 133.7 (C-C11), 130.8 (CH-C12), 123.6 (CH-C13), 85.0 (C-C7), 72.7 (CH-C8), 65.8 (CH_2-C1), 62.3 (CH-C6), 61.4 (CH_2-C9), 38.3 (CH_2-C5), 23.2 (CH_2-C4), 18.0 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 12.2 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$); ν_{max} (film) 3308, 2928, 2864, 2360, 1727, 1530, 1463, 1272, 1102 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{25}H_{37}NNaO_6Si$ [M+Na]$^+$ 498.2282, found 498.2287.

202: R_f = 0.89 (petroleum ether:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, s, CH-C1), 6.54 (1H, td, *J* = 7.4, 1.3 Hz, CH-C3), 4.58 (1H, td, *J* = 5.6, 2.1 Hz, CH-C6), 2.59 (2H, q *J* = 7.9 Hz, CH_2-C4), 2.43 (1H, d, *J* = 2.1 Hz, CH-C8), 1.97–1.83 (2H, m, CH_2-C5), 1.77 (3H, d, *J* = 0.7 Hz, CH_3-C9), 1.07 (21H, dd, *J* = 12.6, 6.3 Hz, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2 (CH-C1), 153.9 (C-C2), 139.7 (CH-C3), 84.7 (C-C7), 72.9 (CH-C8), 62.2 (CH-C6), 37.1 (CH_2-C5), 25.7 (CH_2-C4), 24.4 (CH_3-C9), 18.0 (Si(CH(<u>C</u>H$_3$)$_2$)$_3$), 12.3 (Si(<u>C</u>H(CH$_3$)$_2$)$_3$); ν_{max} (film) 2941, 2863, 1717, 1513, 1463, 1381, 1242, 1031 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{18}H_{32}NaO_2Si$ $[M+Na]^+$ 331.2064, found 331.2065.

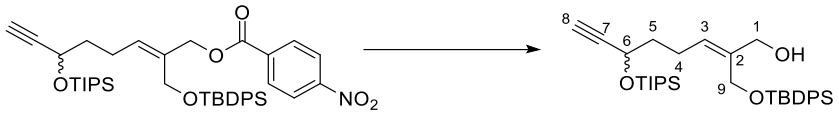
(*E*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-6-[(triisopropylsilyl)oxy]oct-2-en-7-yn-1-yl 1-nitrobenzoate (208)



To a solution of alcohol **207** (0.30 g, 0.63 mmol) in CH_2Cl_2 (12 mL) was added imidazole (4.00 mg, 0.63 mmol) and TBDPSCl (0.17 mL, 0.63 mmol) in CH_2Cl_2 (1 mL) at rt. The mixture was stirred for 4 h and then the reaction was quenched by the addition of H_2O (10 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) provided the alkyne **208** (0.23 g, 0.32 mmol, 52%) as a colourless oil.

R_f = 0.56 (petroleum ether:EtOAc, 9:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.12 (2H, m, CH-C12), 8.00–7.96 (2H, m, CH-C13), 7.69–7.57 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.37–7.25 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.74 (1H, t, *J* = 7.6 Hz, CH-C3), 4.88 (2H, s, CH_2-C1), 4.44 (1H, td, *J* = 6.1, 2.0 Hz, CH-C6), 4.18 (2H, s, CH_2-C9), 2.33 (2H, q, *J* = 7.8 Hz, CH_2-C4), 2.31 (1H, d, *J* = 2.0 Hz, CH-C8), 1.76–1.68 (2H, m, CH_2-C5), 1.10–1.02 (21H, m, Si(CH(CH$_3$)$_2$)$_3$); 0.99 (9H, s, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C-C10), 150.9 (C-C14), 135.2 (C-C11), 134.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 134.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 133.4 (C-C2), 130.7 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.7 (CH-C12), 129.5 (Si(Ph)$_2$C(CH$_3$)$_3$), 127.6 (CH-C13), 123.4 (CH-C3), 85.1 (C-C7), 72.7 (CH-C8), 66.0 (CH_2-C1), 62.3 (CH_2-C9), 61.2 (CH-C6), 32.0 (CH_2-C5), 26.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 23.8 (CH_2-C4), 19.0 (Si(Ph)$_2$C(CH$_3$)$_3$), 17.5 (Si(CH(CH$_3$)$_2$)$_3$), 12.2 (Si(CH(CH$_3$)$_2$)$_3$).

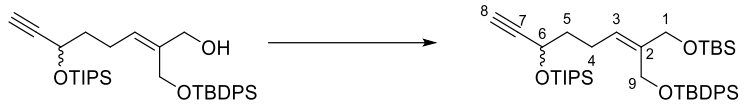
(*E*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-6-((triisopropylsilyl)oxy)oct-2-en-7-yn-1-ol (209)



To a stirred solution of protected alcohol **208** (200 mg, 0.28 mmol) in MeOH/H_2O (6:2, 8 mL) at rt was added K_2CO_3 (85 mg, 0.61 mmol) in one portion. The mixture was stirred for 2 h and then the solvent was removed under reduced pressure. The mixture was diluted with Et_2O (10 mL) and washed with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 3 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 9:2) to afford alcohol **209** (100 mg, 0.18 mmol, 51%) as a colourless oil.

R_f = 0.32 (petroleum ether:EtOAc, 9:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.69 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.44–7.36 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.46 (1H, t, *J* = 7.6 Hz, CH-C3), 4.50 (1H, td, *J* = 6.1, 2.1 Hz, CH-C6), 4.29 (2H, d, *J* = 3.0 Hz, CH_2-C1), 4.26 (2H, s, CH_2-C9), 2.42 (1H, d, *J* = 2.1 Hz, CH-C8), 2.22 (2H, q, *J* = 7.8 Hz, CH_2-C4), 2.16 (1H, s, br, OH), 1.86–1.67 (2H, m, CH_2-C5), 1.07 (30H, m, Si(CH(CH$_3$)$_2$)$_3$, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (C-C2), 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 134.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 133.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.7 (Si(Ph)$_2$C(CH$_3$)$_3$), 127.8 (CH-C3), 85.2 (C-C7), 72.6 (CH-C8), 68.5 (CH-C6), 62.4 (CH_2-C9), 59.8 (CH_2-C1), 38.5 (CH_2-C5), 26.9 (CH_2-C4), 22.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 19.0 (Si(Ph)$_2$C(CH$_3$)$_3$), 18.0 (Si(CH(CH$_3$)$_2$)$_3$), 12.3 (Si(CH(CH$_3$)$_2$)$_3$); ν_{max} (film) 3364, 2930, 2857, 1716, 1472, 1111 cm^{-1}. HMRS (ESI$^+$) calcd for $C_{34}H_{52}NaO_3Si_2$ [M+Na]$^+$ 587.3455, found 587.3326.

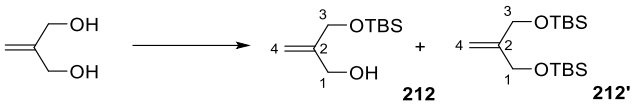
(*E*)- 2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-6-((triisopropylsilyl)oxy)oct-2-en-7-yn (210)



To a solution of alcohol **209** (50.0 mg, 0.08 mmol) in CH_2Cl_2 (10 mL) was added imidazole (6.00 mg, 0.08 mmol) and TBSCl (12.0 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) at rt and the mixture was stirred for 4 h. The reaction was quenched by the addition of H_2O (3 mL). The aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with H_2O (2 × 3 mL) and brine (8 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether) yielded alkyne **210** (52 mg, 0.08 mmol, 96%) as a colourless oil.

R_f = 0.88 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.42–7.34 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.56 (1H, t, *J* = 7.5 Hz, CH-C3), 4.51 (1H, td, *J* = 6.2, 2.1 Hz, CH-C6), 4.24 (2H, d, *J* = 5.4 Hz, CH_2-C9), 4.23 (2H, s, CH_2-C1), 2.41 (1H, d, *J* = 2.1 Hz, CH-C8), 2.34–2.23 (2H, m, CH_2-C4), 1.81–1.72 (2H, m, CH_2-C5), 1.13–1.05 (30H, m, Si(CH(CH$_3$)$_2$)$_3$, Si(Ph)$_2$C(CH$_3$)$_3$), 0.84 (9H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$), 0.02 (6H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0 (C-C2), 134.5 (Si(Ph)$_2$C(CH$_3$)$_3$), 132.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 128.5 (Si(Ph)$_2$C(CH$_3$)$_3$), 126.5 (Si(Ph)$_2$C(CH$_3$)$_3$), 124.3 (CH-C3), 84.4 (C-C7), 71.3 (CH-C8), 64.4 (CH-C6), 61.4 (CH_2-C9), 57.7 (CH_2-C1), 37.8 (CH_2-C5), 25.8 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 24.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 21.8 (CH_2-C4), 18.3 (Si(CH$_3$)$_2$C(CH$_3$)$_3$), 17.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 17.0 (Si(CH(CH$_3$)$_2$)$_3$), 11.2 (Si(CH(CH$_3$)$_2$)$_3$), −6.4 (Si(CH$_3$)$_2$C(CH$_3$)$_3$); ν_{max} (film) 2930, 2857, 1472, 1255,1104 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{40}H_{66}NaO_3Si_3$ [M+Na]$^+$ 701.4320, found 701.4090.

2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}prop-2-en-1-ol (212)



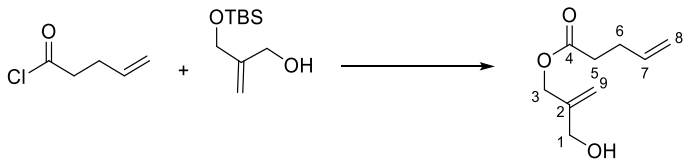
To a solution of diol **218** (5.00 g, 56.7 mmol) in CH_2Cl_2 (150 mL) was added imidazole (9.60 g, 142 mmol) and TBSCl (6.79 g, 45.3 mmol) in CH_2Cl_2 (10 mL) at rt and stirred for 4 h. The reaction was quenched by the addition of H_2O (80 mL) and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 30 mL) and brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 10:1) yielded alcohol **212** (6.87 g, 34.0 mmol, 60%) as a colourless oil and alkene **212'** (6.45 g, 20.4 mmol, 36%) as a colourless oil.

212: R_f = 0.43 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11–5.05 (2H, m, CH_2-C4), 4.23 (2H, s, CH_2-C3), 4.16 (2H, s, CH_2-C1), 2.14 (1H, s, br, OH), 0.90 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.08 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (C-C2), 111.0 (CH_2-C4), 65.1 (CH_2-C1), 64.6 (CH_2-C3), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

Analytical data was in full agreement with that previously reported.[28]

212': R_f = 0.89 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09–5.06 (2H, m, CH_2-C4), 4.16 (4H, t, J = 1.2 Hz, CH_2-C1, CH_2-C3), 0.91 (18H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.07 (12H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (C-C2), 109.0 (CH_2-C4), 63.9 (CH_2-C1, CH_2-C3), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$) ; ν_{max} (film) 2954, 2856, 1471, 1252,1077 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{16}H_{36}NaO_2Si_2$ $[M+Na]^+$ 339.2146, found 339.2146.

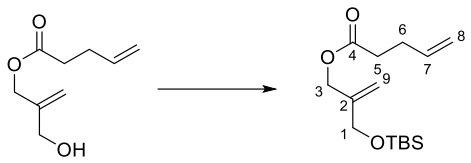
2-(Hydroxymethyl)allyl pent-4-enoate (219)



To a solution of alcohol **212** (5.00 g, 24.7 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (3.58 mL, 24.7 mmol) and the mixture was stirred for 10 min. Acyl chloride **217** (2.42 g, 20.5 mmol) in CH_2Cl_2 (5 mL) was added at rt and the mixture stirred for 5 h. The reaction was quenched by the addition of H_2O (80 mL) and the aqueous phase was extracted with EtOAc (3 × 7 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 10:1) afforded the diene **219** (4.84 g, 17.0 mmol, 69%) as a colourless oil.

R_f = 0.38 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, ddt, *J* = 16.3, 10.2, 6.2 Hz, CH-C7), 5.22 (1H, s, CH_2-C9a), 5.15 (1H, s, CH_2-C9b), 5.04 (1H, dd, *J* = 16.3, 1.4 Hz , CH_2-C8a), 4.99 (1H, dd, *J* = 10.2, 1.4 Hz, CH_2-C8b), 4.63 (2H, s, CH_2-C3), 4.12 (2H, s, CH_2-C1), 2.47–2.41 (2H, m, CH_2-C6), 2.40–2.33 (2H, m, CH_2-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C-C4), 143.4 (C-C2), 136.5 (CH-C7), 115.7 (CH_2-C8), 114.2 (CH_2-C9), 64.7 (CH_2-C3), 63.6 (CH_2-C1), 33.5 (CH_2-C5), 28.8 (CH_2-C6); ν_{max} (film) 3357, 2924, 1732, 1256, 1161 cm^{-1}; HMRS (ESI$^+$) calcd for $C_9H_{14}NaO_3$ $[M+Na]^+$ 193.0835, found 193.0838.

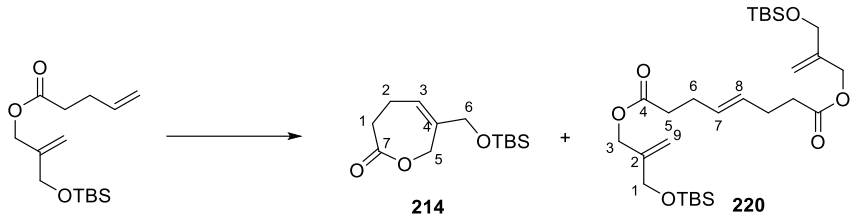
2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}allyl pent-4-enoate (213)



To a solution of alcohol **219** (4.84 g, 17.0 mmol) in CH_2Cl_2 (50 mL) was added imidazole (1.73 g, 25.5 mmol) and TBSCl (2.55 g, 17.0 mmol) in CH_2Cl_2 (3 mL) at rt and the mixture was stirred for 4 h. The reaction was quenched by the addition of H_2O (20 mL) and the aqueous phase was extracted with Et_2O (3 × 6 mL). The combined organic extracts were washed with H_2O (2 × 7 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 10:1) yielded protected alcohol **213** (4.59 g, 16.2 mmol, 94%) as a colourless oil

R_f = 0.68 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 16.3, 10.3, 6.2 Hz, CH-C7), 5.17–5.15 (1H m, CH_2-C9a), 5.06 (1H d, *J* = 1.3 Hz, CH_2-C9b), 4.99 (1H dd, *J* = 16.3, 1.4 Hz, CH_2-C8a), 4.94 (1H, dd, *J* = 10.3, 1.4 Hz, CH_2-C8b), 4.53 (2H, s, CH_2-C3), 4.09 (2H, s, CH_2-C1), 2.41–2.27 (4H, m, CH_2-C5, CH_2-C6), 0.84 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C-C4), 143.3 (C-C2), 136.6 (CH-C7), 115.5 (CH_2-C9), 112.9 (CH_2-C8), 64.6 (CH_2-C3), 63.8 (CH_2-C1), 33.5 (CH_2-C4), 28.8 (CH_2-C6), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2885, 1739, 1472, 1254, 1113 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{15}H_{28}NaO_3Si$ $[M+Na]^+$ 307.1700, found 307.1700.

6-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3,4-dihydrooxepin-2(7*H*)-one (214)

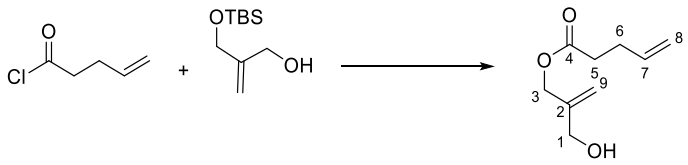


To a solution of dialkene **213** (0.50 g, 1.8 mmol) in CH_2Cl_2 (350 mL) was added Grubbs II catalyst (75 mg, 0.09 mmol) and the reaction was stirred under reflux for 19 hours. The mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded lactone **214** (94.0 mg, 0.36 mmol, 21%) as a pale yellow oil and dimer **220** (0.20 g, 0.37 mmol, 45%) as a pale yellow oil.

214: R_f = 0.29 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.73 (1H, m, CH-C3), 4.90–4.83 (1H, m, CH_2-C5a), 4.67 (1H, s, CH_2-C5b), 4.17–4.14 (1H, m, CH_2-C6a), 4.17–4.14 (1H, d, *J* = 1.5 Hz, CH_2-C6b), 3.12–3.07 (1H, m, CH_2-C1a), 2.93–2.87 (1H, m, CH_2-C1b), 2.51 (1H, dtd, *J* = 9.9, 3.9, 2.0 Hz, CH_2-C2a), 1.57–1.46 (1H, m, CH_2-C2b), 0.90 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.07 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.06 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (C-C7), 133.3 (C-C4), 125.9 (CH-C3), 66.5 (CH_2-C6), 65.5 (CH_2-C5), 31.1 (CH_2-C1), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 24.6 ($CH_2$-C2), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2856, 1739, 1463, 1213 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{13}H_{24}NaO_3Si$ $[M+Na]^+$ 279.1387, found 279.1390.

220: R_f = 0.72 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.58 (1H, m, CH-C8), 5.49–5.46 (1H, m, CH-C7), 5.23 (2H, d, *J* = 1.0 Hz, CH_2-C9a), 5.12 (2H, d, *J* = 1.0 Hz, CH_2-C9b), 4.59 (4H, d, *J* = 2.3 Hz, CH_2-C3), 4.16 (4H, s, CH_2-C1), 2.43–2.30 (8H, m, CH_2-C5, CH_2-C6), 0.91 (18H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.07 (12H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C-C4), 143.3 (C-C2), 129.5 (C-C7, C-C8), 112.9 (CH_2-C9), 64.5 (CH_2-C3), 63.8 (CH_2-C1), 34.1 (CH_2-C5), 27.8 (CH_2-C6), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2953, 2855, 1738,1251, 1083 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{28}H_{52}NaO_6Si_2$ $[M+Na]^+$ 563.3190, found 563.3195.

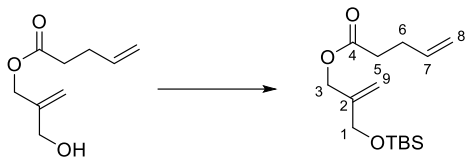
2-(Hydroxymethyl)allyl pent-4-enoate (219)



To a solution of alcohol **212** (5.00 g, 24.7 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (3.58 mL, 24.7 mmol) and the mixture was stirred for 10 min. Acyl chloride **217** (2.42 g, 20.5 mmol) in CH_2Cl_2 (5 mL) was added at rt and the mixture stirred for 5 h. The reaction was quenched by the addition of H_2O (80 mL) and the aqueous phase was extracted with EtOAc (3 × 7 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 10:1) afforded the diene **219** (4.84 g, 17.0 mmol, 69%) as a colourless oil.

R_f = 0.38 ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, ddt, *J* = 16.3, 10.2, 6.2 Hz, CH-C7), 5.22 (1H, s, CH_2-C9a), 5.15 (1H, s, CH_2-C9b), 5.04 (1H, dd, *J* = 16.3, 1.4 Hz , CH_2-C8a), 4.99 (1H, dd, *J* = 10.2, 1.4 Hz, CH_2-C8b), 4.63 (2H, s, CH_2-C3), 4.12 (2H, s, CH_2-C1), 2.47–2.41 (2H, m, CH_2-C6), 2.40–2.33 (2H, m, CH_2-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C-C4), 143.4 (C-C2), 136.5 (CH-C7), 115.7 (CH_2-C8), 114.2 (CH_2-C9), 64.7 (CH_2-C3), 63.6 (CH_2-C1), 33.5 (CH_2-C5), 28.8 (CH_2-C6); ν_{max} (film) 3357, 2924, 1732, 1256, 1161 cm^{-1}; HMRS (ESI$^+$) calcd for $C_9H_{14}NaO_3$ $[M+Na]^+$ 193.0835, found 193.0838.

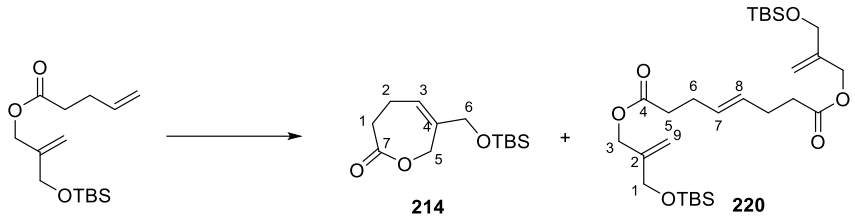
2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}allyl pent-4-enoate (213)



To a solution of alcohol **219** (4.84 g, 17.0 mmol) in CH_2Cl_2 (50 mL) was added imidazole (1.73 g, 25.5 mmol) and TBSCl (2.55 g, 17.0 mmol) in CH_2Cl_2 (3 mL) at rt and the mixture was stirred for 4 h. The reaction was quenched by the addition of H_2O (20 mL) and the aqueous phase was extracted with Et_2O (3 × 6 mL). The combined organic extracts were washed with H_2O (2 × 7 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 10:1) yielded protected alcohol **213** (4.59 g, 16.2 mmol, 94%) as a colourless oil

R_f = 0.68 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 16.3, 10.3, 6.2 Hz, CH-C7), 5.17–5.15 (1H m, CH_2-C9a), 5.06 (1H d, *J* = 1.3 Hz, CH_2-C9b), 4.99 (1H dd, *J* = 16.3, 1.4 Hz, CH_2-C8a), 4.94 (1H, dd, *J* = 10.3, 1.4 Hz, CH_2-C8b), 4.53 (2H, s, CH_2-C3), 4.09 (2H, s, CH_2-C1), 2.41–2.27 (4H, m, CH_2-C5, CH_2-C6), 0.84 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C-C4), 143.3 (C-C2), 136.6 (CH-C7), 115.5 (CH_2-C9), 112.9 (CH_2-C8), 64.6 (CH_2-C3), 63.8 (CH_2-C1), 33.5 (CH_2-C4), 28.8 (CH_2-C6), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2885, 1739, 1472, 1254, 1113 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{15}H_{28}NaO_3Si$ $[M+Na]^+$ 307.1700, found 307.1700.

6-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3,4-dihydrooxepin-2(7*H*)-one (214)

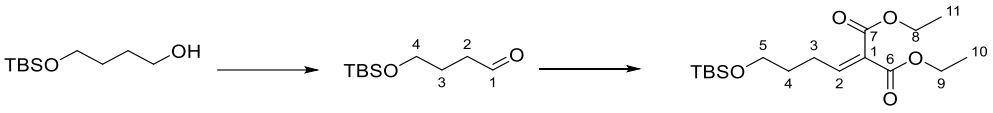


To a solution of dialkene **213** (0.50 g, 1.8 mmol) in CH_2Cl_2 (350 mL) was added Grubbs II catalyst (75 mg, 0.09 mmol) and the reaction was stirred under reflux for 19 hours. The mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded lactone **214** (94.0 mg, 0.36 mmol, 21%) as a pale yellow oil and dimer **220** (0.20 g, 0.37 mmol, 45%) as a pale yellow oil.

214: R_f = 0.29 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.73 (1H, m, CH-C3), 4.90–4.83 (1H, m, CH_2-C5a), 4.67 (1H, s, CH_2-C5b), 4.17–4.14 (1H, m, CH_2-C6a), 4.17–4.14 (1H, d, *J* = 1.5 Hz, CH_2-C6b), 3.12–3.07 (1H, m, CH_2-C1a), 2.93–2.87 (1H, m, CH_2-C1b), 2.51 (1H, dtd, *J* = 9.9, 3.9, 2.0 Hz, CH_2-C2a), 1.57–1.46 (1H, m, CH_2-C2b), 0.90 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.07 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.06 (3H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (C-C7), 133.3 (C-C4), 125.9 (CH-C3), 66.5 (CH_2-C6), 65.5 (CH_2-C5), 31.1 (CH_2-C1), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 24.6 ($CH_2$-C2), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2856, 1739, 1463, 1213 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{13}H_{24}NaO_3Si$ $[M+Na]^+$ 279.1387, found 279.1390.

220: R_f = 0.72 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.58 (1H, m, CH-C8), 5.49–5.46 (1H, m, CH-C7), 5.23 (2H, d, *J* = 1.0 Hz, CH_2-C9a), 5.12 (2H, d, *J* = 1.0 Hz, CH_2-C9b), 4.59 (4H, d, *J* = 2.3 Hz, CH_2-C3), 4.16 (4H, s, CH_2-C1), 2.43–2.30 (8H, m, CH_2-C5, CH_2-C6), 0.91 (18H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.07 (12H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C-C4), 143.3 (C-C2), 129.5 (C-C7, C-C8), 112.9 (CH_2-C9), 64.5 (CH_2-C3), 63.8 (CH_2-C1), 34.1 (CH_2-C5), 27.8 (CH_2-C6), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2953, 2855, 1738,1251, 1083 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{28}H_{52}NaO_6Si_2$ $[M+Na]^+$ 563.3190, found 563.3195.

Diethyl 1-{5-[(*tert*-butyldimethylsilyl)oxy]butylidene}malonate (228)



To a stirred solution of oxalyl chloride (0.67 mL, 7.4 mmol) in CH_2Cl_2 (120 mL) at −78 °C was added DMSO (0.69 mL, 9.8 mmol) dropwise. The mixture was stirred at −78 °C for 15 min and then a solution of alcohol **169** (1.00 g, 4.90 mmol) in CH_2Cl_2 (5 mL) was added slowly. The mixture was stirred at −78 °C for a further 1 h and then Et_3N (3.53 mL, 24.5mmol) was added. The mixture was allowed to reach rt and then the reaction was quenched by addition of H_2O (80 mL). The phases were separated and the organic phase was washed with 1M HCl (1× 50 mL), H_2O (2× 50 mL) and brine (50 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde **231** as a yellow oil. The aldehyde was used directly in the next step without further purification.

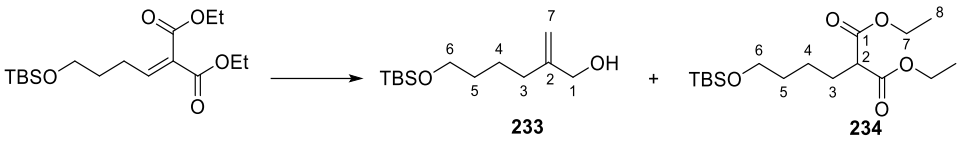
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.7 Hz, CH-C1), 3.65 (2H, t, *J* = 6.0 Hz, CH_2-C4), 2.50 (2H, td, *J* = 7.1, 1.7 Hz, CH_2-C2), 1.90– 1.81 (2H, m, CH_2-C4), 0.88 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (C-C1), 62.1 (C-C4), 40.8 (C-C3), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.5 (C-C2), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$).

To a stirred solution of crude acetylenic aldehyde **231** and diethyl malonate (1.30 g, 4.90 mmol) at rt were added $MgSO_4$ (0.12 mg, 0.98 mmol) and EDDA2 (0.18 g, 0.98 mmol). The mixture was stirred at 40 °C for 1 h and then the reaction was quenched by addition of saturated aq. NH_4Cl (9 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 10:1) to afford the diester **228** (1.01 g, 2.94 mmol, 60%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, t, *J* = 7.8 Hz, CH-C2), 4.29 (2H, q, *J* = 7.1 Hz, CH_2-C8), 4.23 (2H, q, *J* = 7.1 Hz, CH_2-C9), 3.63 (2H, t, *J* = 6.1 Hz, CH_2-C5), 2.37 (2H, td, *J* = 13.5, 7.8 Hz, CH_2-C3), 1.69 (2H, tt, *J* = 13.5, 6.1 Hz, CH_2-C4), 1.32 (3H, t, *J* = 7.1 Hz, CH_3-C11),

1.28 (3H, t, *J* = 7.1 Hz, CH_3-C10), 0.88 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (C-C7), 164.0 (C-C6), 149.2 (CH-C2), 128.7 (C-C1), 62.3 (CH_2-C5), 61.2 (CH_2-C8), 61.2 (CH_2-C9), 40.8 (CH_2-C4), 31.5 (CH_2-C3), 26.6 (CH_3-C10), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.1 ($CH_3$-C11), −5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 29529, 2856, 1725, 1472, 1255, 1096 cm^{-1}; HMRS (ESI^+) calcd for $C_{17}H_{32}NaO_5Si$ $[M+Na]^+$ 367.1911, found 367.1912.

6-((*tert*-butyldimethylsilyl)oxy)-2-methylenehexan-1-ol (233)



To a solution of $LiAlH_4$ (1.14 g, 30.2 mmol) in Et_2O (100 mL) was added ester **228** (2.6 g, 7.6 mmol) in Et_2O (8 mL) dropwise at 0 °C and the reaction was stirred for 2 hours. The reaction was quenched by the careful addition of H_2O (30 mL) and 20% NaOH (30 mL) and the resulting mixture was stirred for 10 min. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded the alcohol **233** (0.55 g, 2.27 mmol, 30%) as a pale yellow oil and the diester **234** (1.70 g, 4.91 mmol, 65%) as a pale yellow oil.

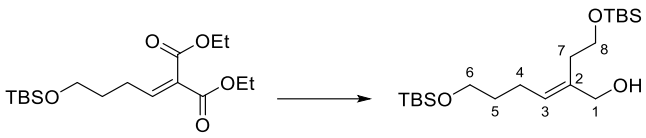
233: R_f = 0.31 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (1H, s, CH_2-C7a), 4.88 (1H, d, *J* = 1.2 Hz, CH_2-C7b), 4.08 (2H, d, *J* = 5.5 Hz, CH_2-C1), 3.62 (2H, t, *J* = 6.0 Hz, CH_2-C6), 2.08 (2H, t, *J* = 6.8 Hz, CH_2-C3), 1.57–1.49 (4H, m, CH_2-C4, CH_2-C5), 1.36 (1H, t, *J* = 5.1 Hz, OH), 0.89 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (C-C2), 109.3 (CH_2-C7), 65.9 (CH_2-C1), 63.0 (CH_2-C6), 32.7 (CH_2-C3), 32.5 (CH_2-C4), 26.0 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 24.0 ($CH_2$-C5), 18.4 (TBS), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 3336, 2929, 1724, 1651, 1471, 1254, 1100 cm^{-1}; HMRS (ESI^+) calcd for $C_{13}H_{28}NaO_2Si_1$ $[M+Na]^+$ 267.1756, found 267.1736.

Analytical data was in full agreement with that previously reported.[78]

234: R_f = 0.52 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (4H, q, *J* = 7.1 Hz, CH_2-C7, CH_2-C7'), 3.59 (2H, t, *J* = 6.3 Hz, CH_2-C6), 3.31 (1H, t, *J* = 7.6 Hz, CH-C2), 1.93–1.88 (2H, m, CH_2-C3), 1.55–1.46 (2H m, CH_2-C5), 1.34 (2H, tt, *J* = 11.8, 5.6 Hz, CH_2-C4), 1.23 (6H, t, *J* = 7.1 Hz, CH_3-C8, CH_3-C8'), 0.85 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5 (C-C1), 62.8 (CH_2-C6), 61.2 (CH_2-

C7, CH_2-C7'), 52.1 (CH-C2), 32.4 (CH_2-C5), 28.6 (CH_2-C3), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 23.8 ($CH_2$-C4), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.1 ($CH_3$-C8, CH_3-C8'), −5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2930, 1731, 1462, 1252, 1096 cm^{-1}; HMRS (ESI^+) calcd for $C_{17}H_{34}NaO_5Si$ $[M+Na]^+$ 369.2068, found 369.2068.

(*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}hex-1-en-1-ol (235)

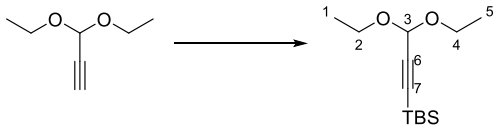


To a solution of ester **228** (1.00 g, 2.90 mmol) in toluene (100 mL) was added DiBAl-H (1.0 M in hexanes, 10.2 mL, 10.7 mmol) dropwise at –78 °C and the reaction stirred for 5 hours. The reaction was quenched with an aqueous solution of Rochelle salt (100 mL), and the mixture was stirred for 12 hours. The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (90 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) produced the alcohol **235** (0.70 g, 1.80 mmol, 62%) as a pale yellow oil and the previously described diester **234** (0.34 g, 0.99 mmol, 34%) as a pale yellow oil.

R_f = 0.60 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, t, *J* = 7.3 Hz, CH-C3), 3.98 (2H, d, *J* = 5.4 Hz, CH_2-C1), 3.69 (2H, t, *J* = 6.0 Hz, CH_2-C8), 3.60 (2H, t, *J* = 6.3 Hz, CH_2-C6), 3.11 (1H, t, *J* = 5.4 Hz, OH), 2.37 (2H, t, *J* = 6.0 Hz, CH_2-C7), 2.08 (2H, q, *J* = 7.2 Hz, CH_2-C4), 1.61–1.52 (2H, m, CH_2-C5), 0.89 (9H, s, $Si(CH_3)_2C(\underline{C}H_3)_3$), 0.88 (9H, s, $Si(CH_3)_2C(\underline{C}H_3)_3$), 0.07 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.03 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1 (C-C2), 129.1 (CH-C3), 68.5 (CH_2-C1), 62.9 (CH_2-C8), 62.5 (CH_2-C6), 32.7 (CH_2-C4), 32.3 (CH_2-C7), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 24.1 ($CH_2$-C5), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$), −5.5 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 2954, 2930, 1731, 1462, 1252, 1096 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{20}H_{44}NaO_3Si_2$ $[M+Na]^+$ 411.2721, found 411.2721

7.2.4 Morocolide 7

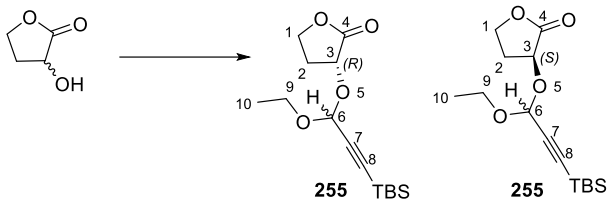
tert-Butyl(3,3-diethoxyprop-6-yn-6-yl)dimethylsilane (251)



To a solution of 3,3-diethoxyprop-1-yne (2.00 g, 15.6 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.2 M in hexanes, 9.22 mL, 20.3 mmol) over a period of 10 min and the mixture was stirred for 1h. TBSCl (3.04 g, 20.3 mmol) in THF (2 mL) at −78 °C was added and the reaction mixture was stirred for 1 h. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched by the addition of H_2O (20 mL). The aqueous phase was extracted with Et_2O (3 × 6 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether) yielded protected alkyne **251** (3.70 g, 15.3 mmol, 98%) as a colourless oil.

R_f = 0.78 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (1H, s, CH-C3), 3.75 (2H, dq, *J* = 14.3, 7.2 Hz, CH_2-C4), 3.64–3.53 (2H, dq , *J* = 14.3, 7.2 Hz, CH_2-C2), 1.23 (6H, t, *J* = 7.2 Hz, CH_3-C1, CH_3-C5), 0.94 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.12 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 100.9 (CH-C3), 91.3 (C-C6), 88.6 (C-C7), 60.9 (CH_2-C4, CH_2-C2), 26.1 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 16.5 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 15.1 ($CH_3$-C1, CH_3-C5), −4.6 ($Si(\underline{C}H_3)_2C(CH_3)_3$); HMRS ($ESI^+$) calcd for $C_{13}H_{26}NaO_2$ Si $[M+Na]^+$ 265.1594, found 265.1589.

3-{[3-(*tert*-Butyldimethylsilyl)-1-ethoxyprop-2-yn-1-yl]oxy}dihydrofuran-2(3*H*)-one (255)



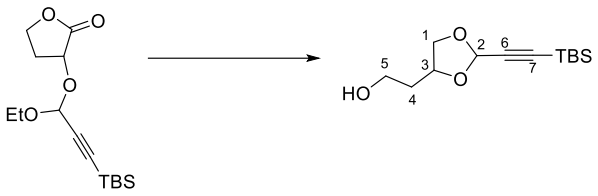
To a solution of alcohol **254** (1.00 g, 9.80 mmol) in toluene (50 mL) was added camphorsulfonic acid (0.23 g, 0.98 mmol) and *tert*-butyl(3,3-diethoxyprop-1-yn-1-yl)dimethylsilane (2.37 g, 9.80 mmol) in toluene (1 mL) at rt. The reaction mixture was refluxed for 18 h. The reaction was quenched by the addition of saturated aq. $NaHCO_3$(30 mL). The aqueous phase was extracted with Et_2O (3 × 6 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded the distereomeric alkynes **(*R*) 255** (0.99 g, 3.3 mmol, 34%) and **(*S*) 255'** (0.61 g, 2.1 mmol, 21%) as colourless oils.

(*R*) 255; R_f = 0.52 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, s, CH-C6), 4.79 (1H, dd, *J* = 10.6, 3.4 Hz, CH-C3), 4.32 (1H, dd, *J* = 11.5, 3.0 Hz, CH_2-C1a), 4.25 (2H, q, *J* = 7.1 Hz, CH_2-C9), 3.92 (1H, ddd, *J* = 11.5, 4.7, 2.9 Hz, CH_2-C1b), 2.05–1.88 (2H, m, CH_2-C2), 1.31 (3H, t, *J* = 7.1 Hz, CH_3-C10), 0.96 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.15 (6H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C-C4), 98.4 (C-C7), 92.2 (C-C8), 88.3 (CH-C6), 69.5 (CH-C3), 61.5 (CH_2-C1), 61.0 (CH_2-C9), 28.3 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 26.1 ($CH_2$-C2), 16.5 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.2 ($CH_3$-C10), −4.8 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 3462, 2262, 1612, 1132. 999 cm^{-1}; HMRS (ESI^+) calcd for $C_{15}H_{26}NaO_4Si$ $[M+Na]^+$ 321.1493, found 321.1487.

(*S*) 255'; R_f = 0.49 (petroleum ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (1H, s, CH-C6), 4.31 (1H, dd, *J* = 11.9, 2.6 Hz, CH-C3), 4.28–4.22 (3H, m, CH_2-C1a, CH_2-C9), 3.84 (1H, ddd, *J* = 12.0, 9.3, 2.6 Hz, CH_2-C1b), 2.15– .03 (1H, m, CH_2-C2a), 1.79 (1H, ddd, *J* = 12.0, 4.1, 2.6 Hz, CH_2-C2b), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-C10), 0.94 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$),

0.13 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 (C-C4), 99.3 (C-C7), 91.4 (CH-C6), 89.5 (C-C8), 75.4 (CH-C3), 66.7 (CH_2-C1), 61.5 (CH_2-C9), 27.8 (CH_2-C2), 26.1 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 16.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 14.1 ($CH_3$-C10), −4.9 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 3130, 2276, 1755, 1548, 1462, 1130 cm^{-1}; HMRS (ESI^+) calcd for $C_{15}H_{26}NaO_4Si$ $[M+Na]^+$ 321.1493, found 321.1489.

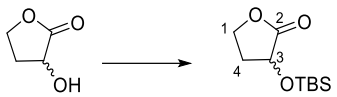
2-{2-[(*tert*-Butyldimethylsilyl)ethynyl]-1,3-dioxolan-4-yl}ethanol (258)



To a solution of the lactone **255** (0.19 g, 0.64 mmol) in THF (20 mL) was added DiBAl-H (1.0 M in hexanes, 0.70 mL, 0.70 mmol) dropwise at –78 °C and the reaction was stirred for 1 h. The reaction mixture was quenched by the addition of an aqueous solution of Rochelle salt (20 mL) and the mixture was diluted with Et_2O (10 mL) and stirred for 5 hours. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 8:2) yielded alcohol **258** (0.10 g, 0.40 mmol, 62%) as a colour less oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, s, CH-C3), 4.35– .26 (2H, m, CH_2-C1), 3.90 (1H, ddd, *J* = 11.4, 5.2, 1.2 Hz, CH-C3), 3.70–3.53 (2H, m, CH_2-C5), 1.88 (2H, td, *J* = 12.8, 6.5 Hz, CH_2-C4), 1.43–1.40 (1H, m, OH), 0.97 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.15 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 99.3 (C-C2), 91.5 (C-C6), 88.2 (C-C7), 70.9 (CH-C3), 65.6 (CH_2-C5), 60.4 (CH_2-C1), 26.9 (CH_2-C4), 26.1 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 16.5 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −4.8 ($Si(\underline{C}H_3)_2C(CH_3)_3$); ν_{max} (film) 3500, 2953, 1714, 1248, 1001, 779 cm^{-1};HMRS (ESI^+) calcd for $C_{13}H_{24}NaO_3Si$ [M+Na]+ 279.137, found 279.1379.

3-[(*tert*-Butyldimethylsilyl)oxy]dihydrofuran-2(3*H*)-one (259)

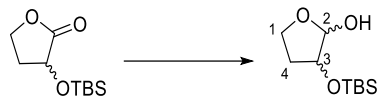


To a solution of alcohol **255** (500 mg, 4.90 mmol) in CH_2Cl_2 (8 mL) was added imidazole (0.33 g, 4.9 mmol) and TBSCl (0.74 g, 4.9 mmol) in CH_2Cl_2 (1 mL) at rt and stirred for 4 h. The reaction mixture was quenched with H_2O (5 mL) and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with H_2O (2 × 3 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether) yielded lactone **259** (1.01 g, 4.67 mmol, 96%) as a colourless oil.

R_f = 0.87 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30–4.20 (2H, m, CH_2-C1), 4.05 (1H, td, *J* = 9.1, 6.3 Hz, CH-C3), 2.31 (1H, dddd, *J* = 12.7, 7.1, 6.3, 3.3 Hz, CH_2-C4a), 2.08 (1H, dddd, *J* = 12.7, 9.1, 8.4, 8.4 Hz, CH_2-C4b), 0.97 (9H, s, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.05 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.04 (3H, s, $Si(C\underline{H_3})_2C(CH_3)_3$); ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (C-C2), 68.2 (CH_2-C1), 64.8 (CH-C3), 32.4 (CH_2-C4), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$); HMRS ($ESI^+$) calcd for $C_{10}H_{20}NaO_3Si$ $[M+Na]^+$ 239.1074, found 239.1072.

Analytical data was in full agreement with that previously reported.[42]

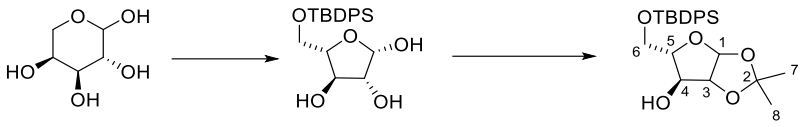
3-[(*tert*-Butyldimethylsilyl)oxy]tetrahydrofuran-2-ol (260)



To a solution of ketone **259** (200 mg, 0.93 mmol) in CH_2Cl_2 (10 mL) was added DiBAl-H (1.0 M in hexanes, 1.39 mL, 1.39 mmol) dropwise at –78 °C. The mixture was allowed to warm to rt and stirred for 3 hours and then the reaction was quenched by the addition of an aqueous solution of Rochelle salt (10 mL) and stirred for 18 h. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded alcohol **260** (19.0 mg, 0.87 mmol, 94%) as a colourless oil.

R_f = 0.49 (petroleum ether:EtOAc, 9:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, dd, *J* = 8.6, 4.0 Hz, CH-C2), 4.27–4.22 (1H, m, CH-C3), 4.11–4.05 (1H, m, CH_2-C1a), 3.81 (1H, td, *J* = 8.1, 3.9 Hz, CH_2-C1b), 2.32 (1H, d, *J* = 2.3 Hz,OH), 2.13–2.03 (1H, m, CH_2-C4a), 1.86 (1H, dtd, *J* = 10.3, 7.0, 3.9 Hz, CH_2-C4b), 0.92 (9H, s, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.13 (6H, s, $Si(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 97.3 (CH-C2), 72.2 (CH-C3), 64.8 (CH_2-C1), 33.8 (CH_2-C4), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 18.1 ($Si(CH_3)_2\underline{C}(CH_3)_3$), −4.9 ($Si(\underline{C}H_3)_2C(CH_3)_3$); HMRS ($ESI^+$) calcd for $C_{10}H_{22}NaO_3Si$ $[M+Na]^+$ 241.1230, found 241.1225.

(4*S*,5*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-4-ol (270)



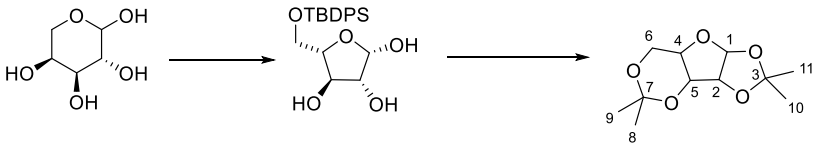
To a solution of L-arabinose (5.00 g, 33.3 mmol) in DMF (20 mL) was added imidazole (4.53 g, 66.7 mmol) and TBDPSCl (8.47 g, 33.3 mmol) in DMF (2 mL) at 60 °C and the mixture was stirred for 4 h. The reaction was quenched by the addition of 1M HCl (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were washed with H_2O (10 mL) and saturated aq. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude triol **269** was taken forward to the next step without purification.

To a solution of the crude triol **269** in acetone (50 mL) was added camphorsulfonic acid (1.55 g, 6.66 mmol) and $CuSO_4$ (12g, 75.2 mmol). The mixture was stirred at rt for 16 h and then the reaction was quenched carefully with saturated aq. $NaCO_3$ (10 mL). The mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was dissolve in CH_2Cl_2 (10 ml) and washed with H_2O (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 3:2) yielded alcohol **270** (5.98 g, 14.0 mmol, 42% over two steps) as a colourless oil.

R_f = 0.46 (petroleum ether:EtOAc, 9:1); $[\alpha]_D$ = –5.2 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (4H, dd, *J* = 7.8, 1.5 Hz, Si(Ph)$_2$C(CH$_3$)$_3$), 7.48–7.33 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.88 (1H, d, *J* = 4.0 Hz, CH-C1), 4.54 (1H, d, *J* = 4.0 Hz, CH-C3), 4.43 (1H, t, *J* = 3.0 Hz, CH-C4), 4.09–4.03 (1H, m, CH-C5), 3.84 (1H, d, *J* = 3.3 Hz, CH$_2$-C6a), 3.82 (1H, d, *J* = 1.8 Hz, CH$_2$-C6b), 2.02 (1H, d, *J* = 4.2 Hz, OH), 1.33 (3H, s, CH$_3$-C7), 1.29 (3H, s, CH$_3$-C8), 1.07 (9H, s, *J* = 2.7 Hz, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 133.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 127.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 112.6 (C-C2), 105.6 (CH-C1), 87.5 (CH-C3), 87.1 (CH-C5), 76.4 (CH-C4), 63.7 (CH$_2$-C6), 26.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 26.8 (CH$_3$-C6) 26.1 (CH$_3$-C8), 19.2 (Si(Ph)$_2$C(CH$_3$)$_3$); HMRS (ESI$^+$) calcd for $C_{24}H_{32}NaO_5Si$ $[M+Na]^+$ 451.1911, found 451.1898.

Analytical data was in full agreement with that previously reported.[43]

3,3,7,7-tetramethyltetrahydro-3aH-[1,3]dioxolo[4',5':4,5]furo[3,2-d][1,3]dioxine (271)



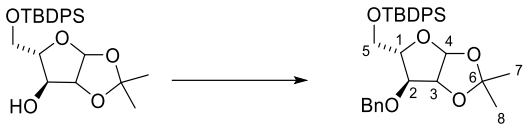
To a solution of L-arabinose (2.00 g, 13.3 mmol) in DMF (10 mL) was added imidazole (1.81 g, 26.6 mmol) and TBDPSCl (3.66 g, 13.3 mmol) in DMF (1 mL) at 60 °C and stirred for 4 h. The reaction was quenched by the addition of 1M HCl (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with H_2O (5 mL) and saturated aq. $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude triol **269** was taken forward to the next step without purification.

To a solution of the crude triol **269** in acetone (25 mL) was added camphorsulfonic acid (0.62 g, 2.66 mmol) and $MgSO_4$ (6g, 50.0 mmol). The reaction mixture was stirred at rt for 16 h. The reaction was quenched by the careful addition of saturated aq. $NaCO_3$ (10 mL) and the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was dissolve in CH_2Cl_2 (10 ml). The solution was washed with H_2O (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 3:2) yielded **271** (1.62 g, 7.05 mmol, 53% over two steps) as a colourless oil.

R_f = 0.52 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, d, *J* = 4.8 Hz, CH-C1), 4.56 (1H, d, *J* = 7.9 Hz, CH-C2), 4.32–4.28 (1H, m, CH-C4), 4.22 (1H, d, *J* = 7.9 Hz, CH-C5), 3.83 (1H, d, *J* = 12.9 Hz, CH_2-C6a), 3.66 (1H, d, *J* = 12.9 Hz, CH_2-C6b), 1.53 (3H, s, CH_3-C10), 1.48 (3H, s, CH_3-C11), 1.35 (3H, s, CH_3-C8), 1.33 (3H, s, CH_3-C9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 108.9 (C-C7), 108.4 (C-C3), 95.9 (CH-C1), 70.8 (CH-C2), 70.6 (CH-C5), 69.9 (CH-C4), 60.2 (CH_2-C6), 26.1 (CH_3-C8), 26.0 (CH_3-C9), 25.0 (CH_3-C10), 24.3 (CH_3-C11).

Analytical data was in full agreement with that previously reported.[44]

{[(1*S*,2*S*)-2-(Benzyloxy)-6,6-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy]-(*tert*-butyl)diphenylsilyloxy (272')

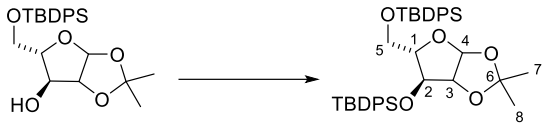


To a solution of NaH (0.42 g, 18 mmol) in DMF (20 mL) at –20 ° C was added the alcohol **270** (4.00 g, 11.7 mmol) in DMF (2 mL) dropwise. The rmixture was allowed to warm to rt over 30 min and then cooled to –20 °C before the addition of *n*-Bu_4NI (0.43g, 1.17 mmol) and BnBr (1.86 mL,15.2 mmol). The mixture was allowed to warm to rt and stirred for 16 h and then the reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL). The aqueous phase was extracted with EtAOc (3 × 6 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 4:1) yielded **272'** (4.67 g, 9.02 mmol, 77%) as a colourless oil.

R_f = 0.46 (petroleum ether:EtOAc, 10:1); $[\alpha]_D$ = –5.2 (*c* = 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.45–7.36 (11H, m, Si(Ph)$_2$C(CH$_3$)$_3$, CH$_2$-C$_6$H$_5$), 5.91 (1H, d, *J* = 4.1 Hz, CH-C4), 4.69 (1H, d, *J* = 4.1 Hz, CH-C3), 4.64 (2H, d, *J* = 1.7 Hz, CH$_2$-C$_6$H$_5$), 4.26–4.23 (2H, m, CH-C1,CH,C2), 3.85–3.80 (2H, m, CH$_2$-C5), 1.37 (3H, s, CH$_3$-C7), 1.32 (3H, s, CH$_3$-C8), 1.07 (9H, s, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (CH$_2$-C$_6$H$_5$), 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 134.8 (CH$_2$-C$_6$H$_5$), 133.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 128.5 (CH$_2$-C$_6$H$_5$), 127.9 (CH$_2$-C$_6$H$_5$), 127.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 112.5 (C-C6), 105.8 (CH-C4), 85.2 (CH-C3), 85.2 (CH-C1), 82.9 (CH-C2), 71.7 (CH$_2$-C$_6$H$_5$), 63.5 (CH$_2$-C5), 27.0 (CH-C7), 26.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 26.2 (CH-C8) 19.2 (Si(Ph)$_2$C(CH$_3$)$_3$); ν_{max} (film) 3439, 2929, 1427, 1112 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{31}H_{38}NaO_5Si$ [M+Na]$^+$ 541.2381, found 541.2370.

Analytical data was in full agreement with that previously reported.[43]

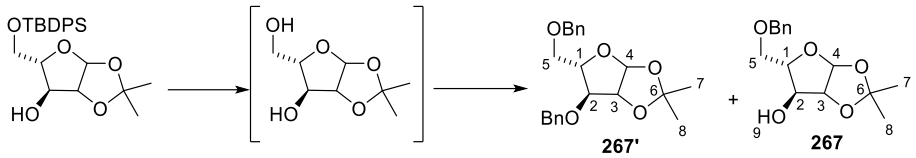
1-*tert*-Butyl-diphenyl-silyloxy-{[(1*S*,2*S*)-2-(*tert*-butyl-diphenyl-silyloxy)-6,6-dimethyltetrahydrofuro[2,3-d][1,3]-dioxol-5-yl]methoxy} (272)



To a solution of alcohol **270** (1.50 g, 3.50 mmol) in CH_2Cl_2 (80 mL) was added imidazole (0.36 g, 5.3 mmol) and TBDPSCl (0.92 mL, 3.5 mmol) in CH_2Cl_2 (1mL) at 40 °C and stirred for 16 h. The reaction mixture was quenched with 1M HCl (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were washed with H_2O (10 mL) and saturated aq. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (petroleum ether:ethyl acetate, 9:1) yielded fully protected carbohydrate **272** (1.64 g, 2.52 mmol, 72% over two steps) as a colourless oil.

R_f = 0.62 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.70 – 7.65 (4H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.57 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 7.33 (6H, m, Si(Ph)$_2$C(CH$_3$)$_3$), 5.94 (1H, d, *J* = 3.7 Hz, CH-C4), 4.47 (1H, s, CH-C2), 4.44 (1H, d, *J* = 3.5 Hz, CH-C3), 4.32 (1H, t, *J* = 6.8 Hz, CH-C1), 3.61 (2H, dt, *J* = 18.2, 10.2 Hz, CH_2-C5), 1.17 (6H, s, CH_3-C7, CH_3-C8), 1.10 (18H, d, *J* = 4.1 Hz, Si(Ph)$_2$C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 135.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 134.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 129.7 (Si(Ph)$_2$C(CH$_3$)$_3$), 127.7 (Si(Ph)$_2$C(CH$_3$)$_3$), 127.6 (Si(Ph)$_2$C(CH$_3$)$_3$), 112.0 (C-C6), 105.9 (CH-C4), 89.1 (CH-C3), 86.7 (CH-C1), 65.9 (CH-C2), 63.9 (CH_2-C5), 26.9 (Si(Ph)$_2$C(CH$_3$)$_3$), 26.8 (Si(Ph)$_2$C(CH$_3$)$_3$), 26.6 (CH_3-C7, CH_3-C8), 19.2 (Si(Ph)$_2$C(CH$_3$)$_3$), 19.1 (Si(Ph)$_2$C(CH$_3$)$_3$); ν_{max} (film) 2927, 1427, 1112 cm^{-1}; HMRS (ESI$^+$) calcd for $C_{40}H_{50}NaO_5Si_2$ [M+Na]$^+$ 689.3089, found 689.3084.

(1*S*,2*S*)-2-(Benzyloxy)-5-[(benzyloxy)methyl]-6,6-dimethyltetrahydrofuro[2,3-d][1,3]-dioxole (267')



To a solution of alcohol **270** (6.00 g, 14.0 mmol) in THF (250 mL) at 0 °C was added TBAF (1.0 M in hexanes, 28.0 mL, 28.0 mmol). The reaction mixture was allowed to warm to rt and stirred for 5 h. The reaction was quenched by the addition of saturated aq. NH_4Cl (20 mL) and the phases were separated. The aqueous phase was extracted with EtAOc (3 × 5 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude diol was taken to next step without further purification.

To a solution of NaH (1.00 g, 42.0 mmol) in DMF (25 mL) at –20 °C was added crude diol in DMF (2 mL) dropwise. The reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was cooled to –20 °C and *n*-Bu_4NI (1.19 g 3.22 mmol) and BnBr (4.44 mL, 36.4 mmol) were added. The mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched by the addition of saturated aq. NH_4Cl (15 mL) and the aqueous phase was extracted with EtOAc (3 × 8 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether:ethyl acetate, 4:1) yielded bis benzyl ether **274'** (2.80 g, 7.57 mmol, 56%) as a colourless oil and alcohol **274** (1.33 g, 4.75 mmol, 35%) as a colourless oil .

267': R_f = 0.65 (petroleum ether:EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (10H, m, CH_2-$C_6\underline{H_5}$), 5.91 (1H, d, *J* = 4.1 Hz, CH-C4), 4.65 (1H, d, *J* = 4.1 Hz, CH-C3), 4.61–4.55 (4H, m, $C\underline{H_2}$-C_6H_5), 4.28 (1H, td, *J* = 6.0, 2.9 Hz, CH-C1), 4.04 (1H, d, *J* = 2.9 Hz, CH-C2), 3.65 (2H, t, *J* = 6.0 Hz, CH_2-C5), 1.45 (3H, s, CH_3-C7), 1.33 (3H, s, CH_3-C8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 (CH_2-$\underline{C_6H_5}$), 137.4 (CH_2-$\underline{C_6H_5}$), 134.8 (CH_2-$\underline{C_6H_5}$), 128.4 (CH_2-$\underline{C_6H_5}$), 127.8 (CH_2-$\underline{C_6H_5}$), 112.7 (C-C6), 105.7 (CH-C4), 85.2 (CH-C2), 83.6 (CH-C3), 83.1 (CH-C1), 73.4 ($\underline{C}H_2$-C_6H_5), 71.7 ($\underline{C}H_2$-C_6H_5), 70.1 (CH_2-C5), 27.1 (CH_3-C7), 26.3 (CH_3-C8); ν_{max} (film)

3439, 2933, 1722, 1660, 1375, 1211, 1070 cm^{-1}; HMRS (ESI^+) calcd for $C_{22}H_{26}NaO_5$ $[M+Na]^+$ 393.1672, found 393.1658.

Analytical data was in full agreement with that previously reported.[43]

267: R_f = 0.39 (petroleum ether:EtOAc, 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (5H, m, CH_2-C_6H_5), 5.91 (1H, d, *J* = 4.1 Hz, CH-C4), 4.71–4.66 (2H, m, CH_2-C_6H_5), 4.63 (1H, d, d, *J* = 15.4 Hz, CH-C2), 4.20 (1H, td, *J* = 5.4, 3.4 Hz, CH-C1), 3.97 (1H, dd, *J* = 3.4, 0.8 Hz, CH-C2), 3.73 (2H, d, *J* = 5.4 Hz, CH_2-C5), 1.53 (3H, s, CH_3-C7), 1.34 (3H, s, CH_3-C8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2 (CH_2-C_6H_5), 128.6 (CH_2-C_6H_5), 128.0 (CH_2-C_6H_5), 127.8 (CH_2-C_6H_5), 112.9 (C-C6), 105.6 (CH-C4), 85.6 (CH-C3), 85.3 (CH-C2), 82.8 (CH-C1), 71.9 (CH_2-C_6H_5), 62.7 (CH_2-C5), 27.1 (CH_3-C7), 26.3 (CH_3-C8); ν_{max} (film) 3394, 2935, 1653, 1373, 1211, 1070 cm^{-1}; HMRS (ESI^+) calcd for $C_{15}H_{20}NaO_5$ $[M+Na]^+$ 303.1203, found 303.1201.

8. References

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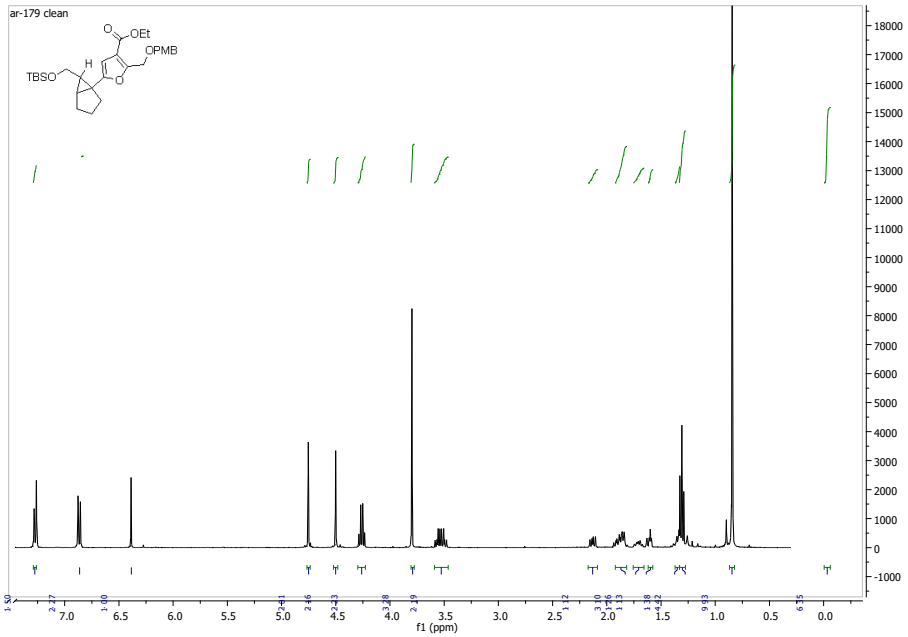
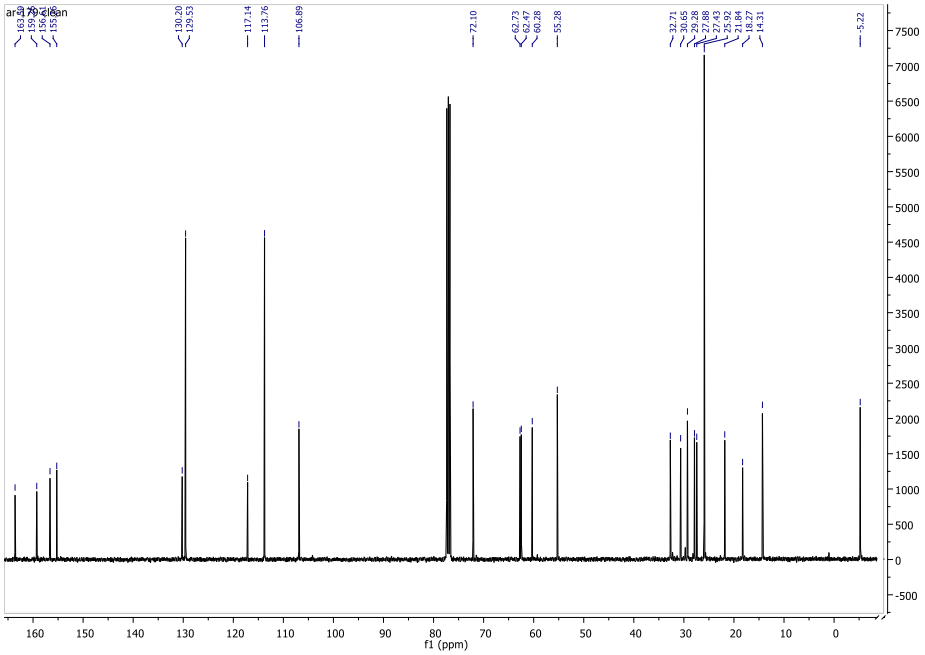
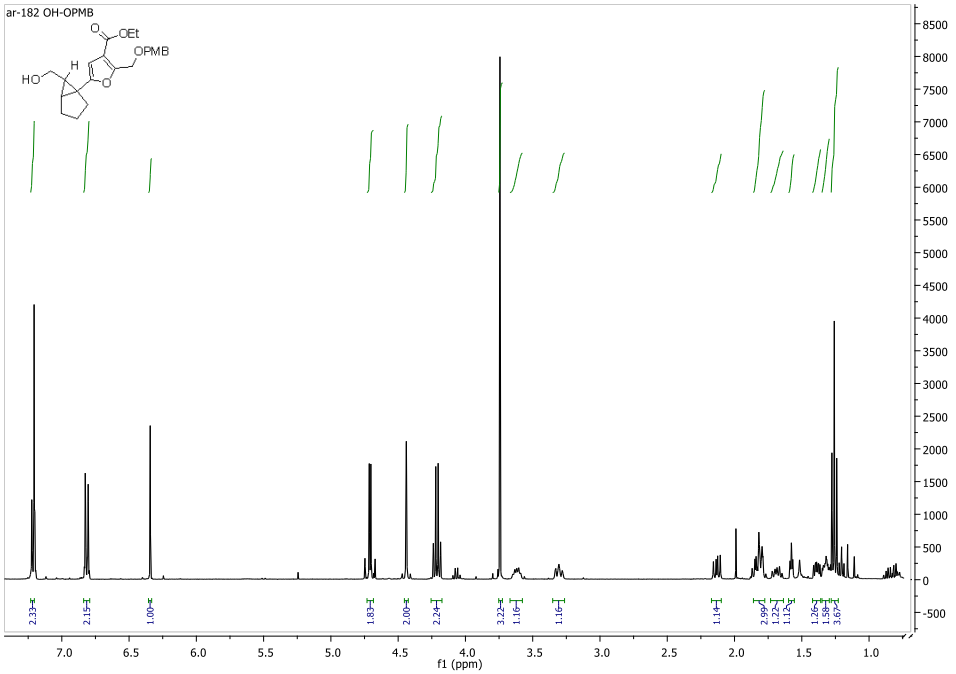
9 Appendix

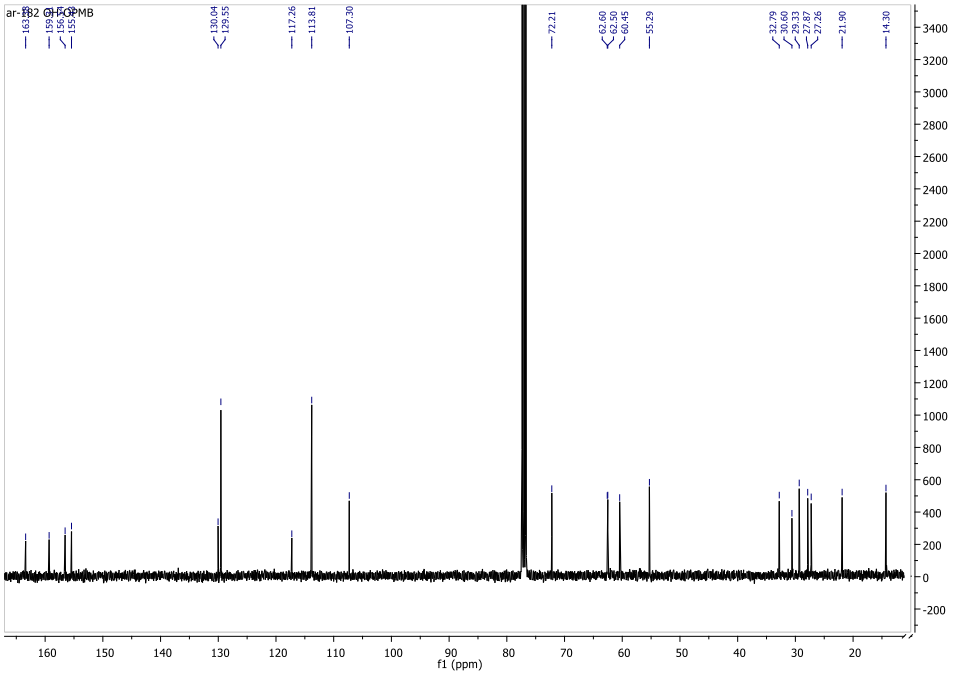
^{1}H and ^{13}C NMR Spectra of Compound **143**



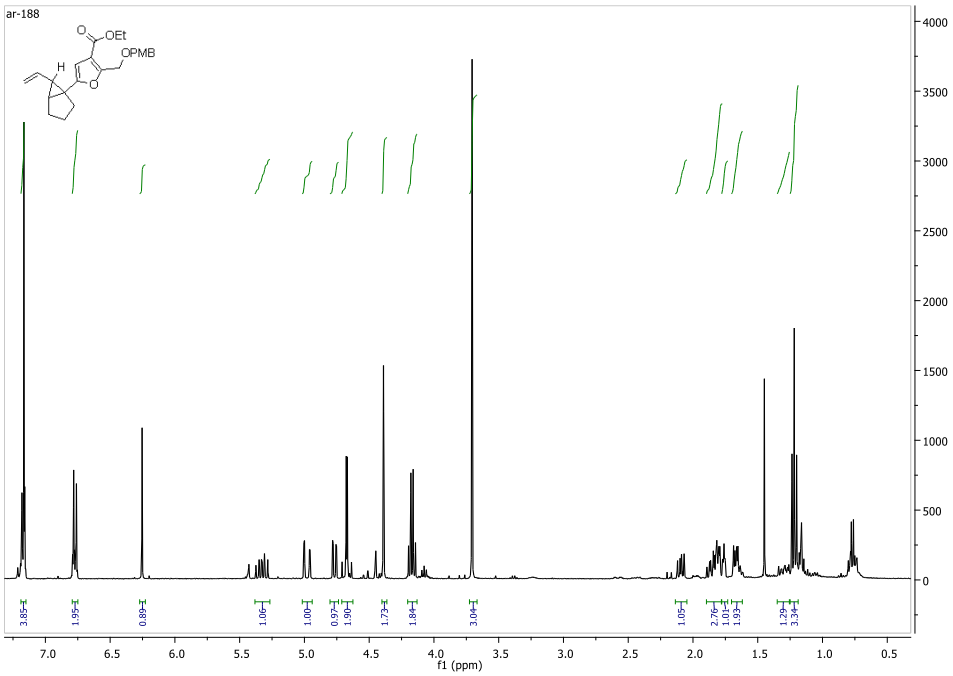


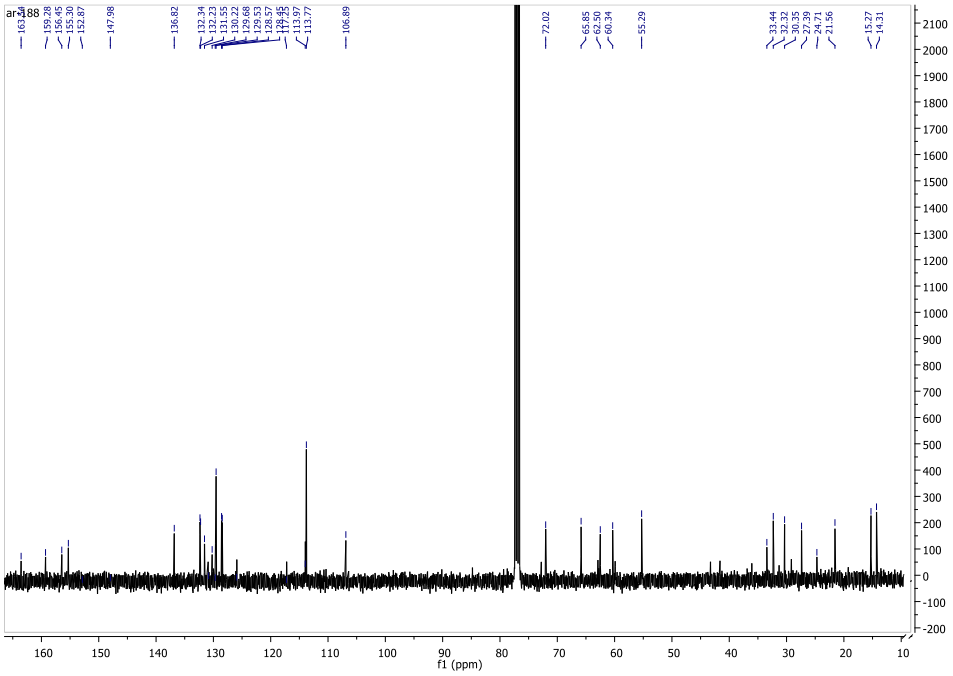
^{1}H and ^{13}C NMR Spectra of Compound **146**



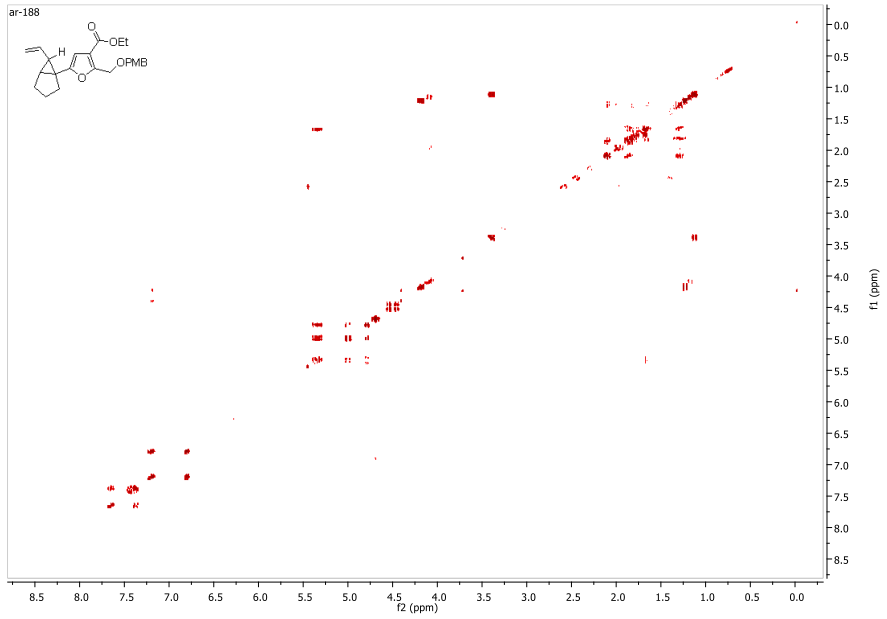


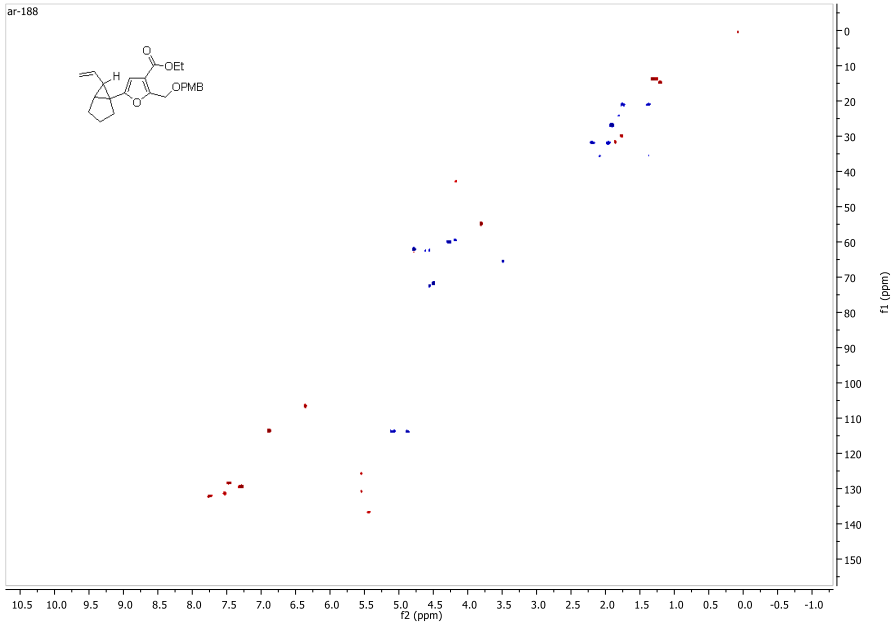
^{1}H and ^{13}C NMR Spectra of Compound **148**



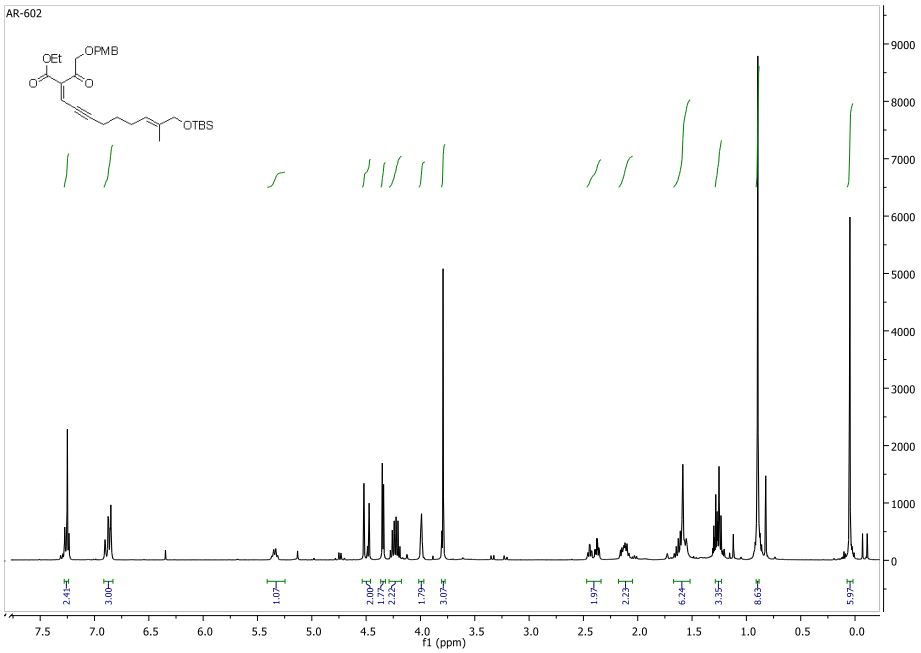


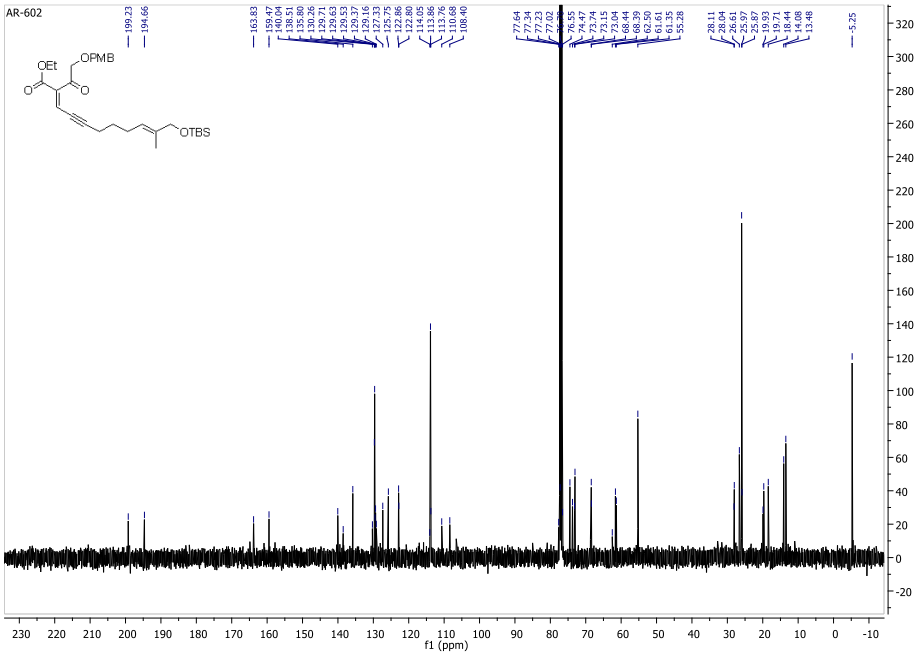
NOESY and **COSY** Spectra of Compound **148**



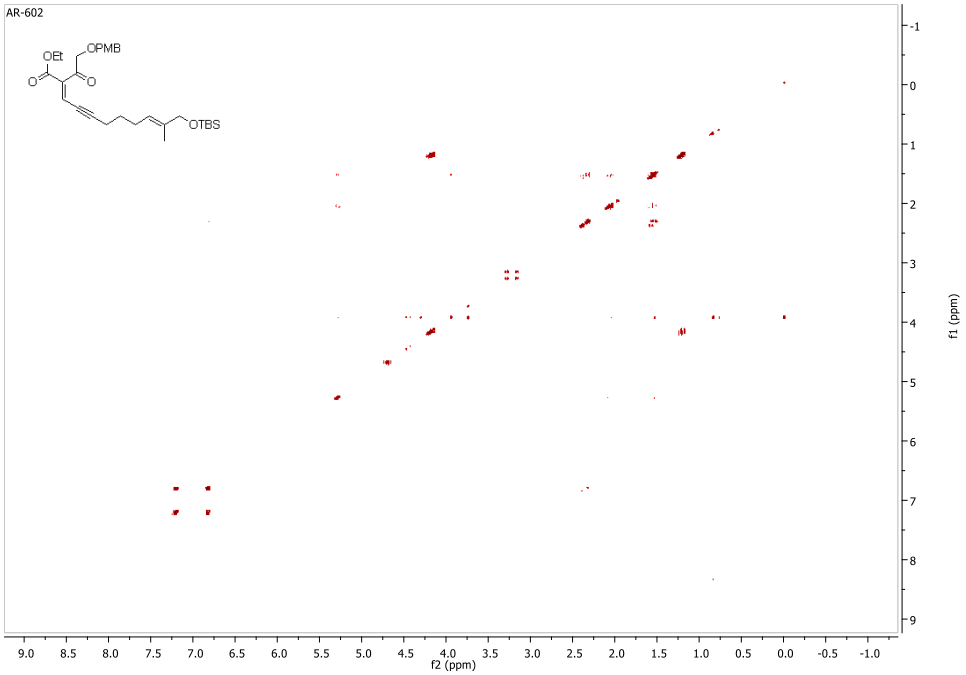


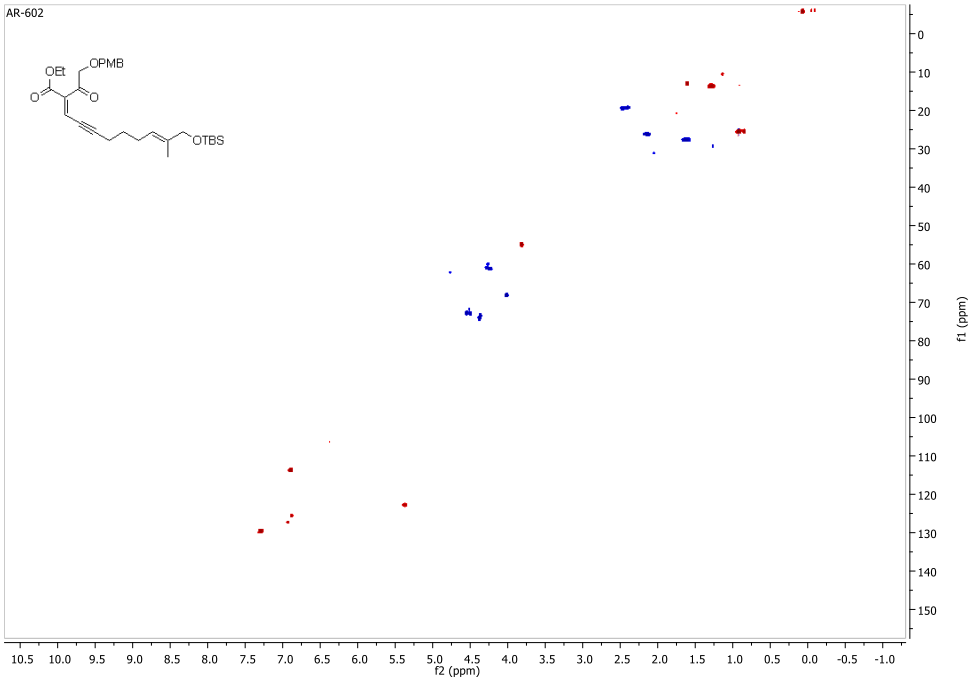
^{1}H and ^{13}C NMR Spectra of Compound **154**



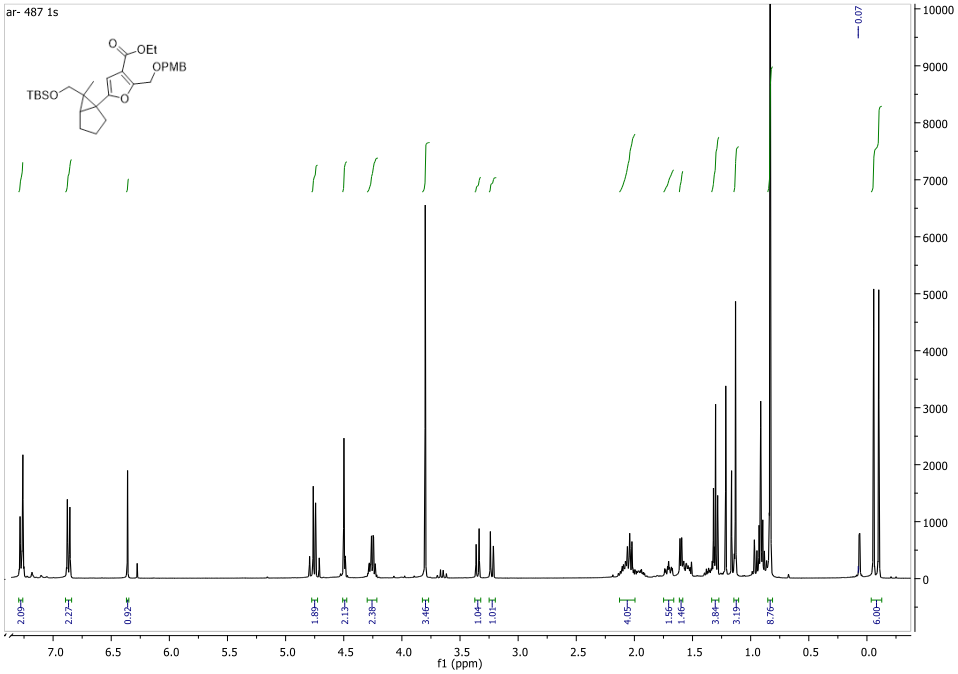


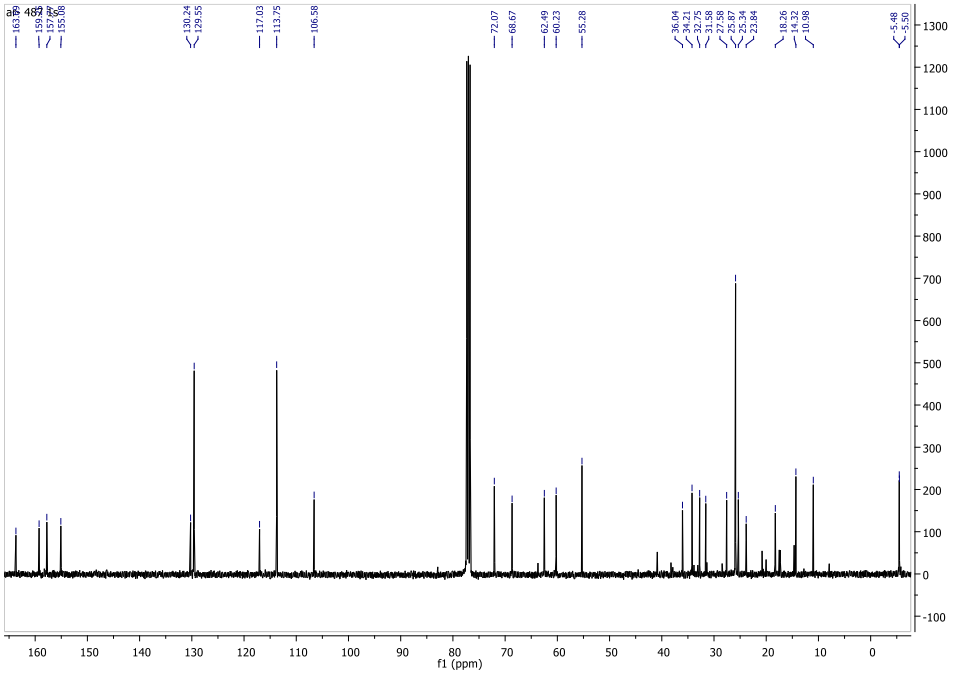
NOESY and COSY Spectra of Compound **154**



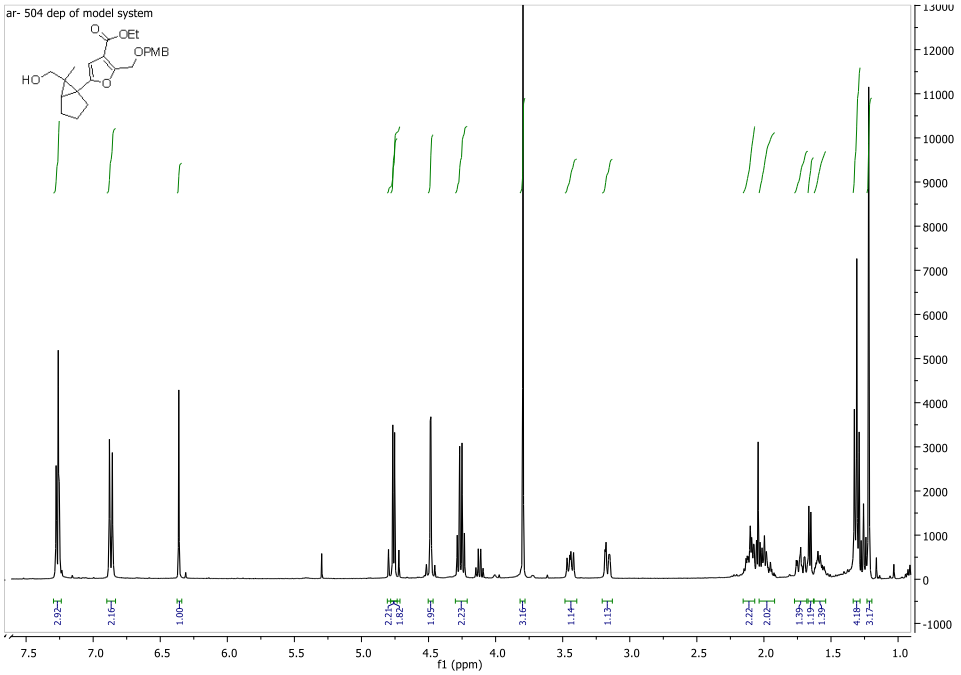


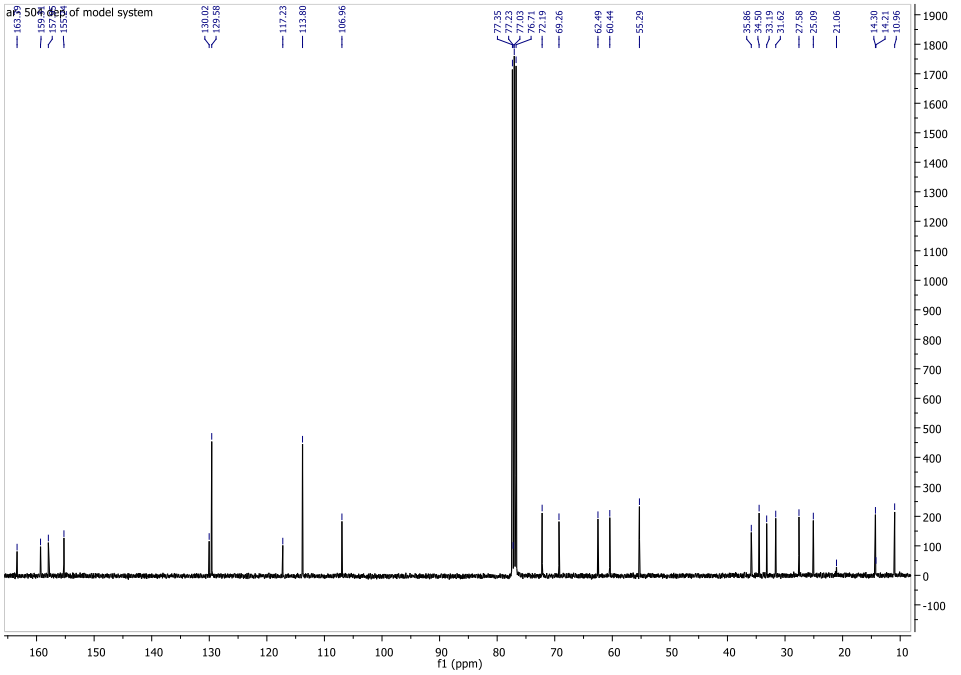
and ^{13}C NMR Spectra of Compound **155**



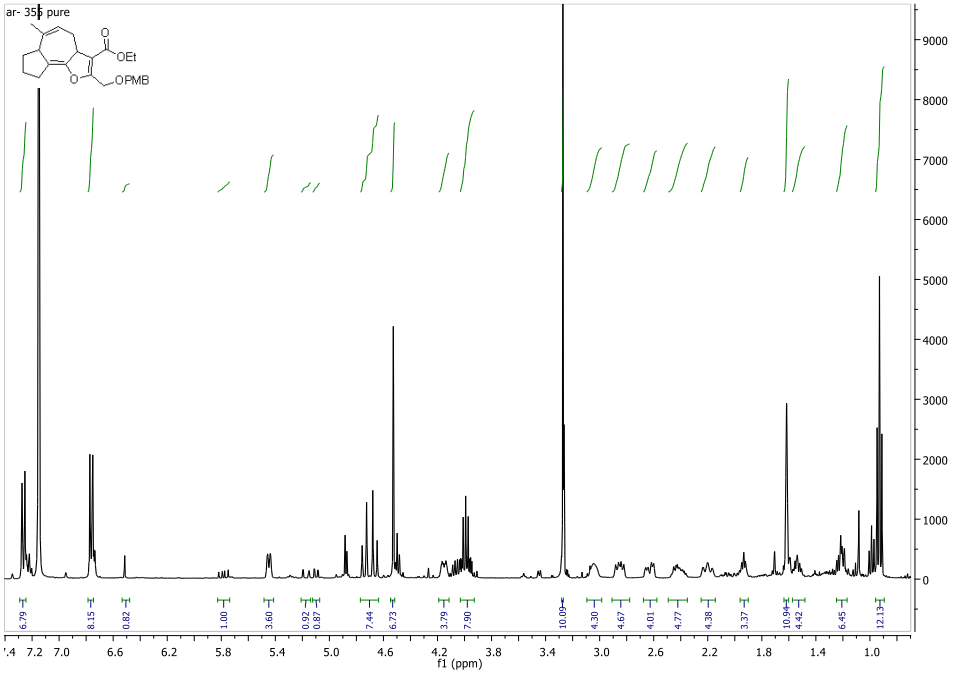


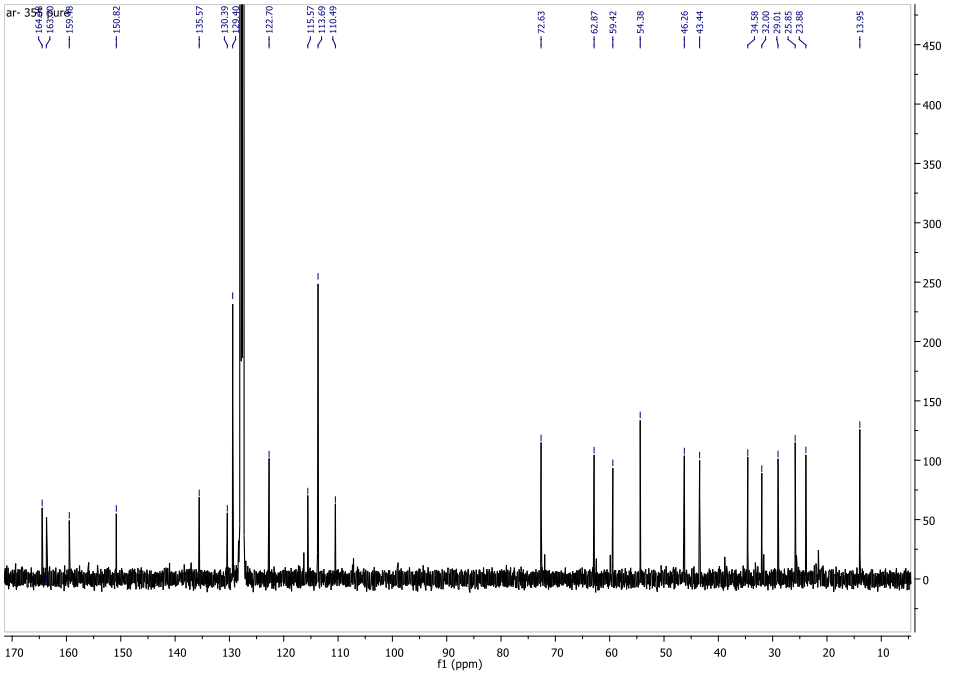
^{1}H and ^{13}C NMR Spectra of Compound **156**



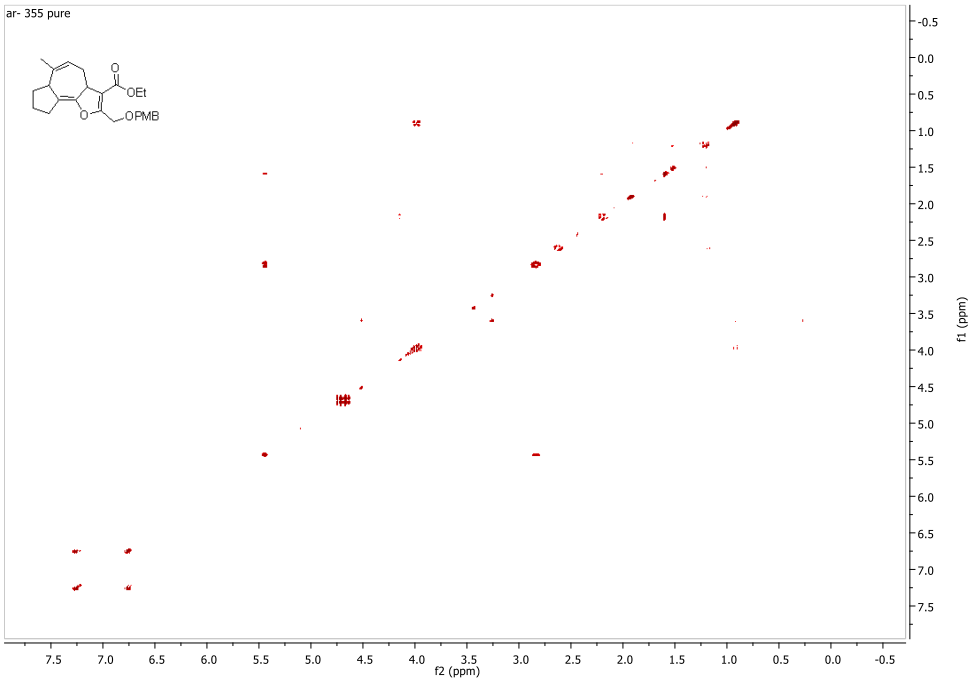


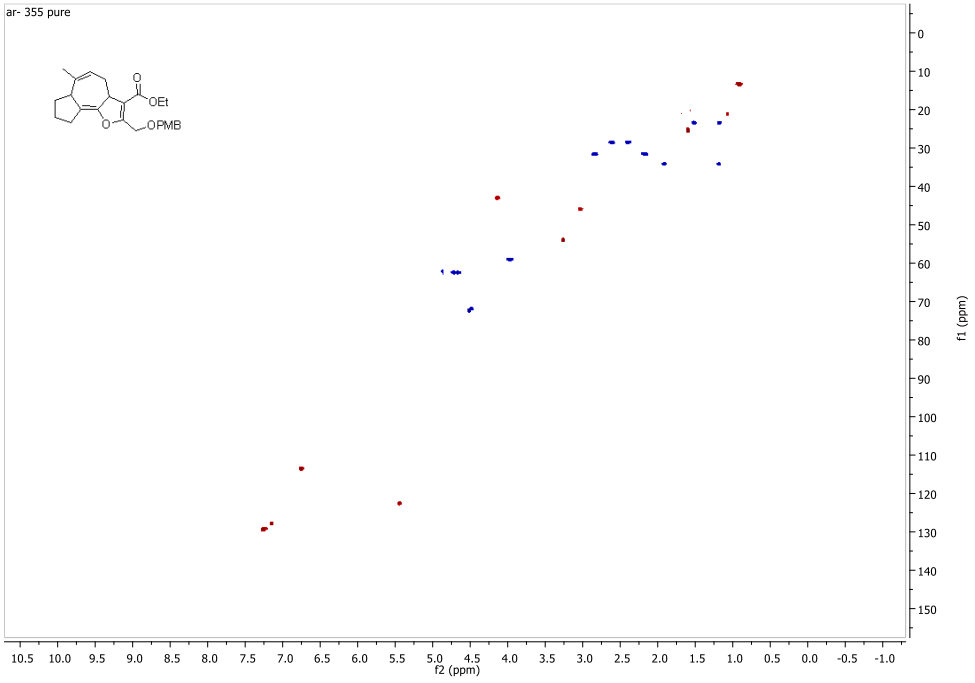
^{1}H and ^{13}C NMR Spectra of Compound **159**



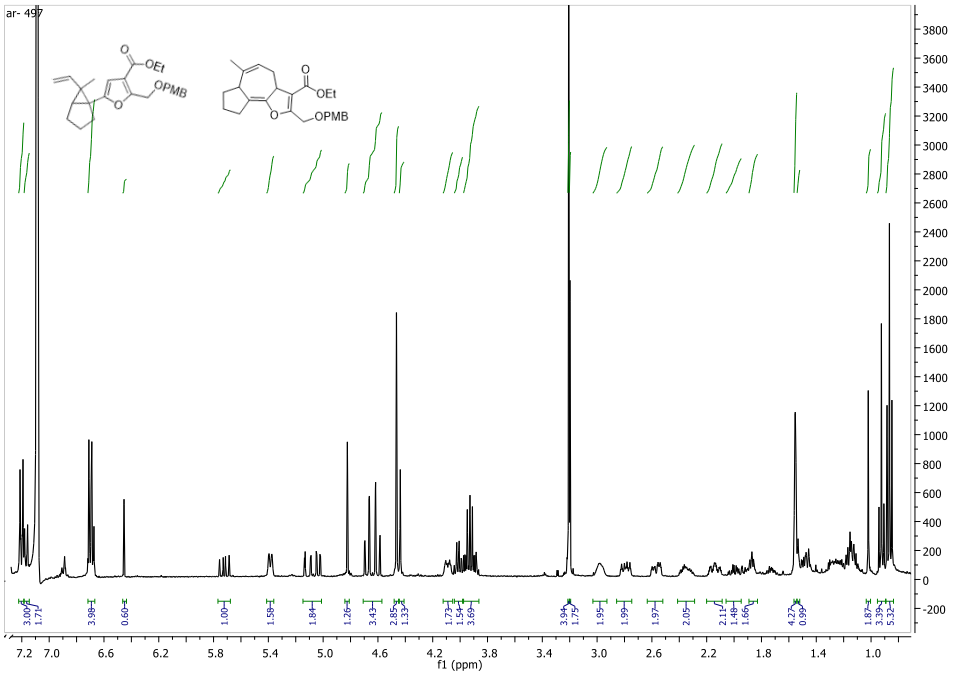


NOESY and COSY Spectra of Compound **159**

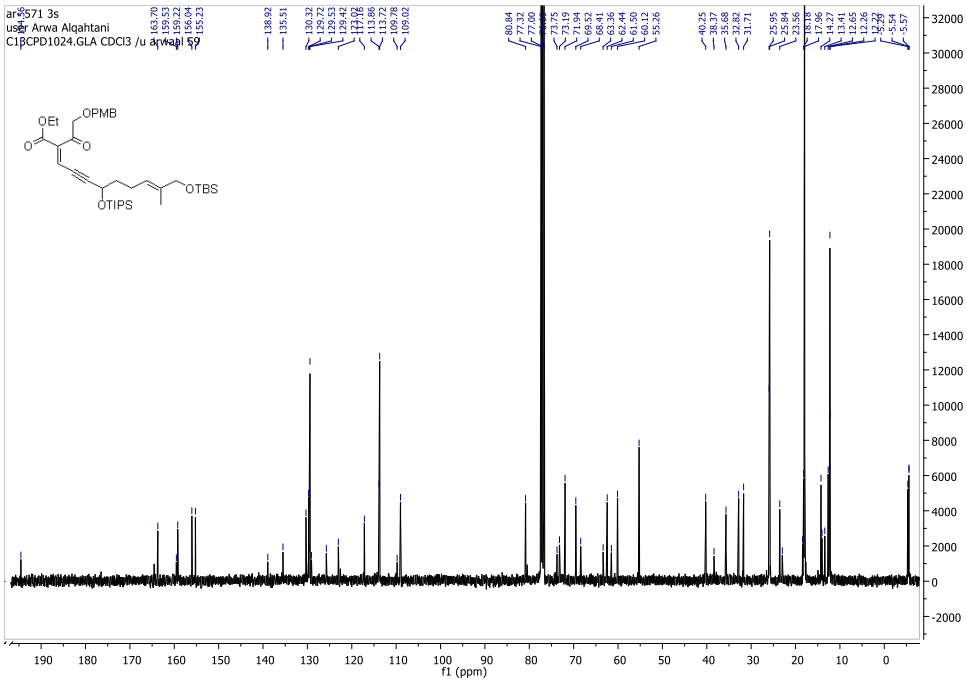


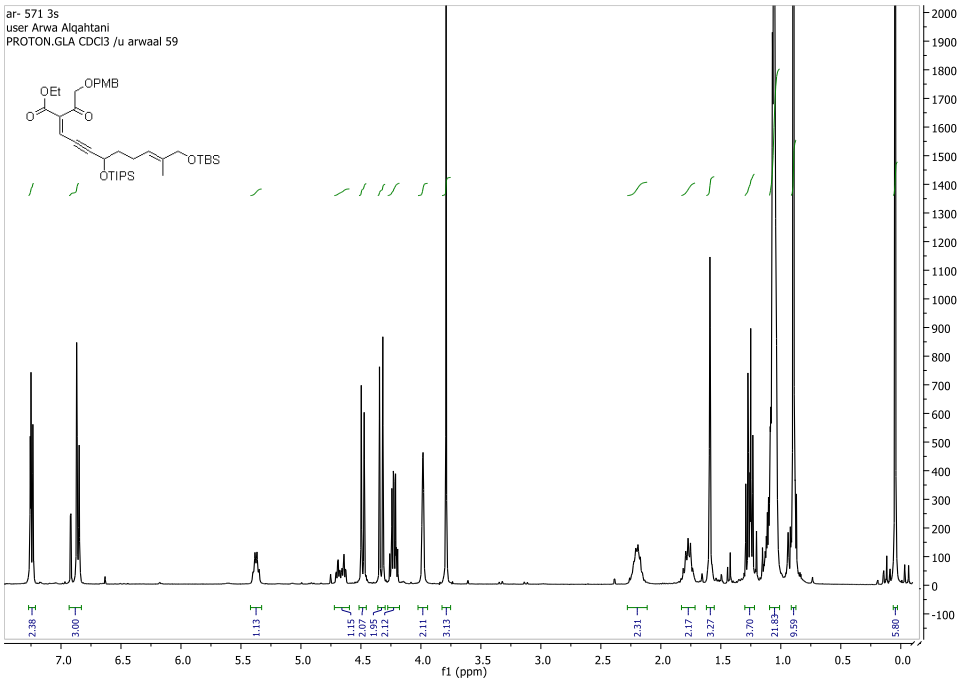


^{1}H and ^{13}C NMR Spectra of Compound **158 + 159**

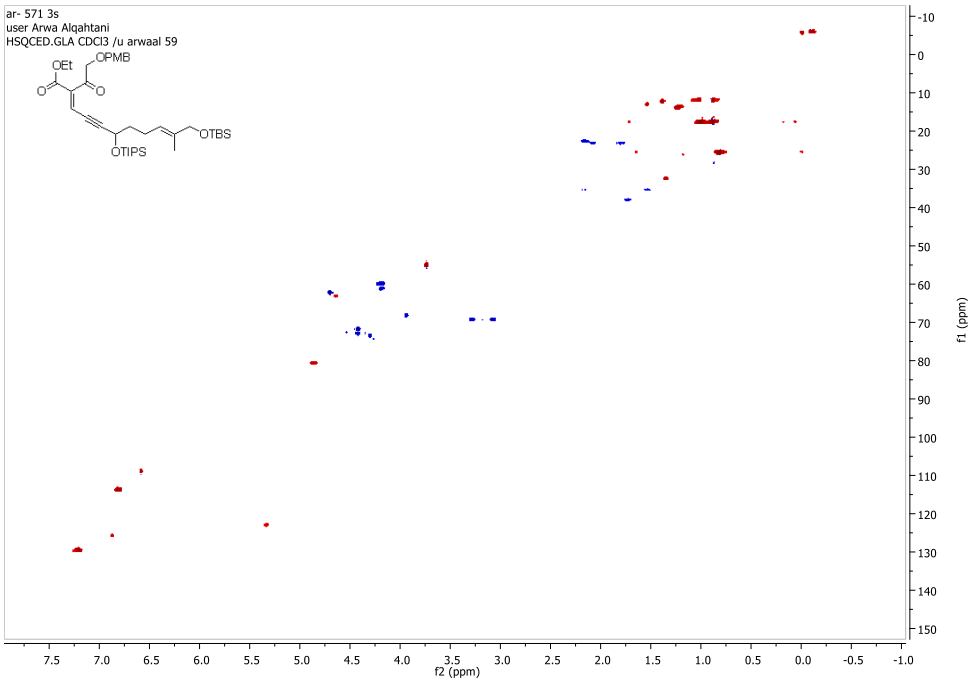


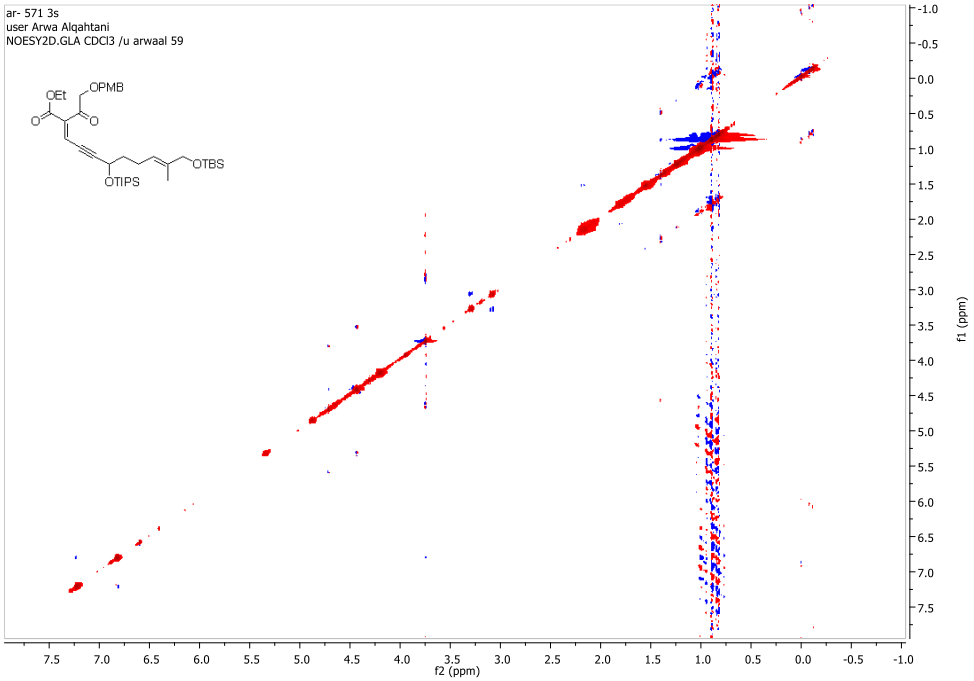
^{1}H and ^{13}C NMR Spectra of Compound **190**



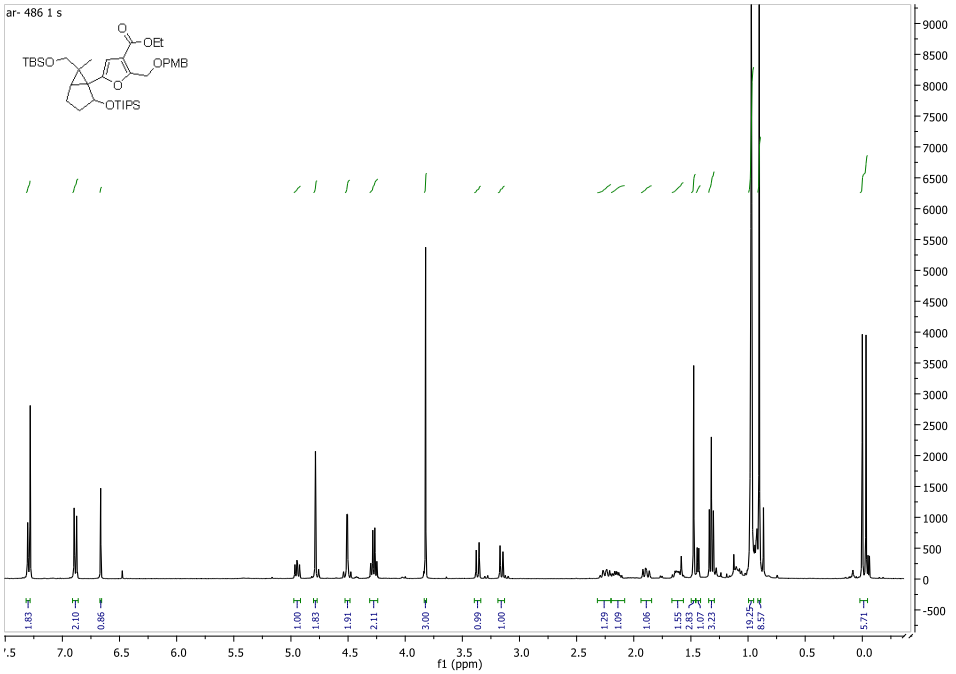


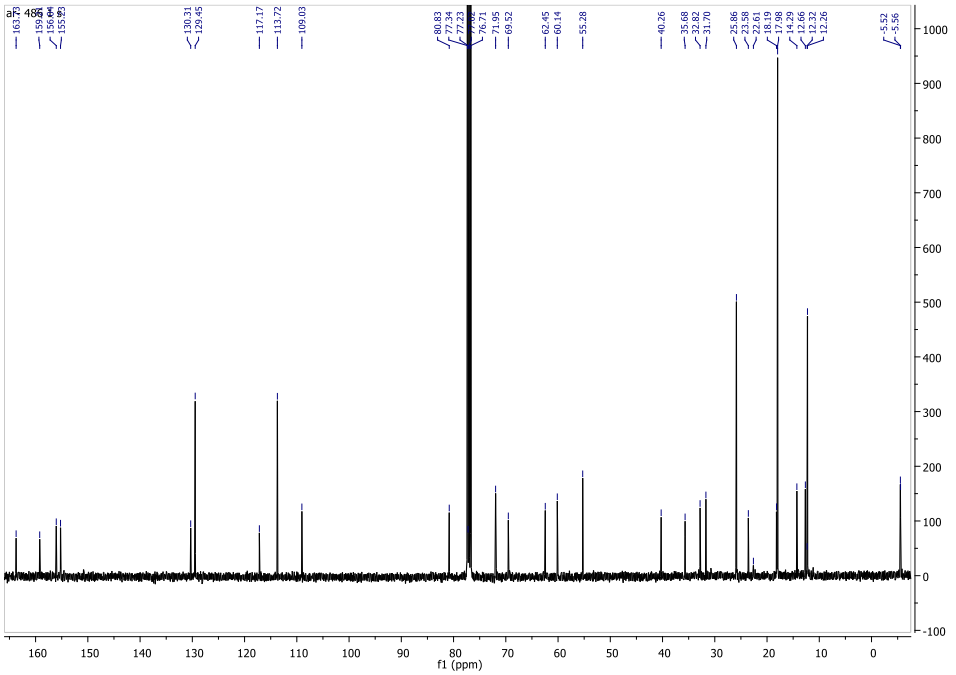
NOESY and COSY Spectra of Compound **190**



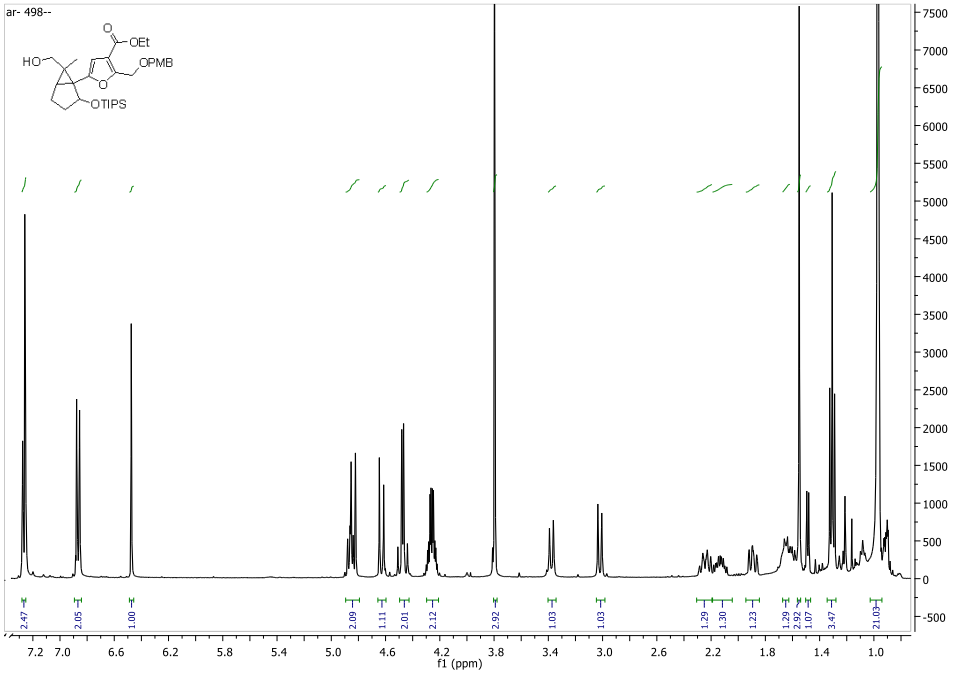


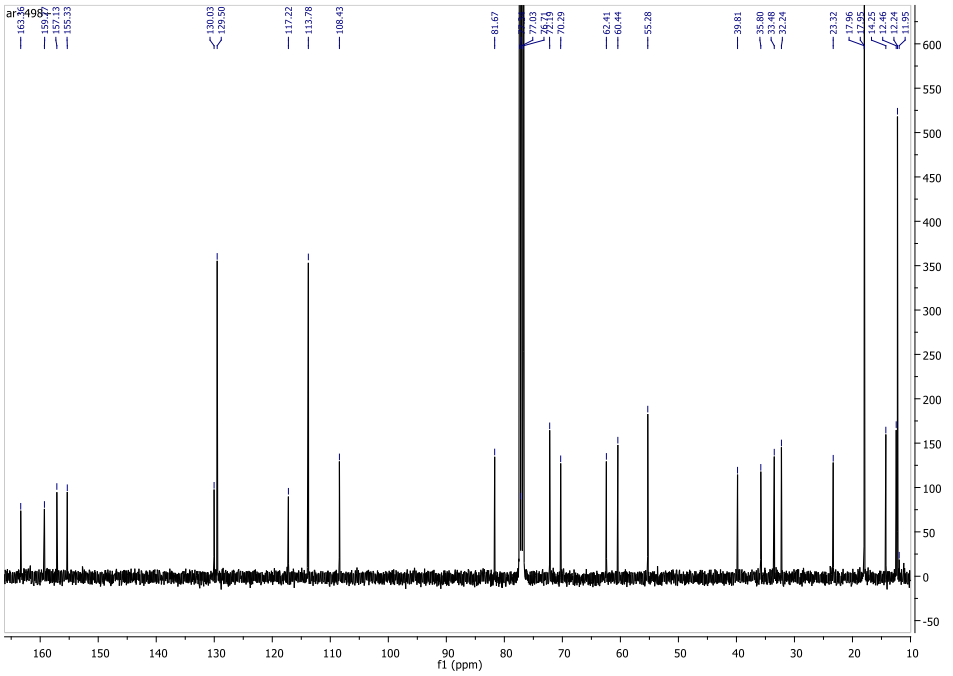
^{1}H and ^{13}C NMR Spectra of Compound **191**



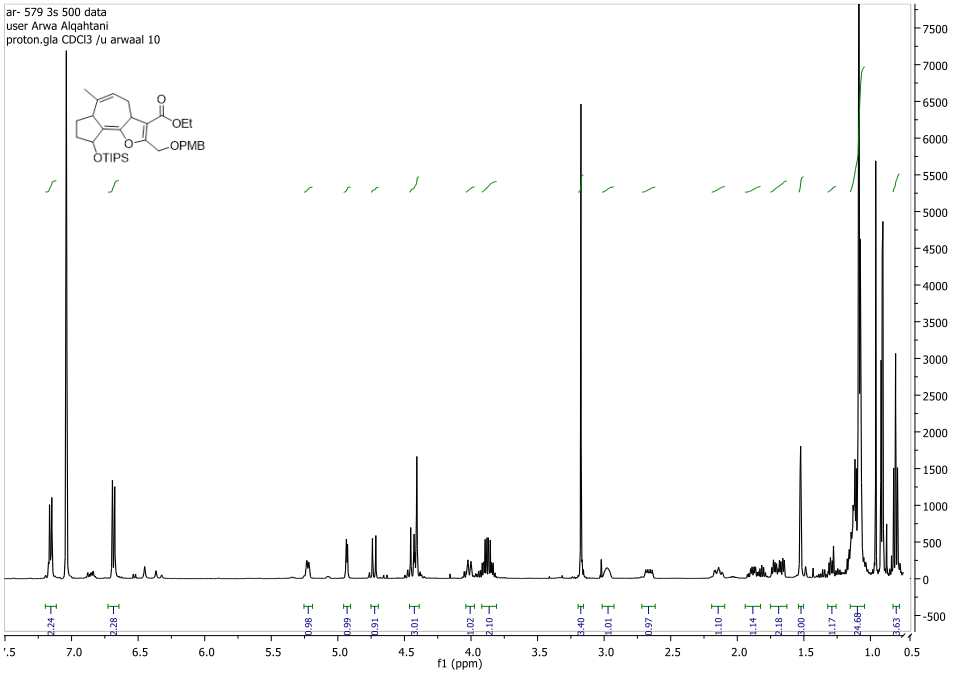


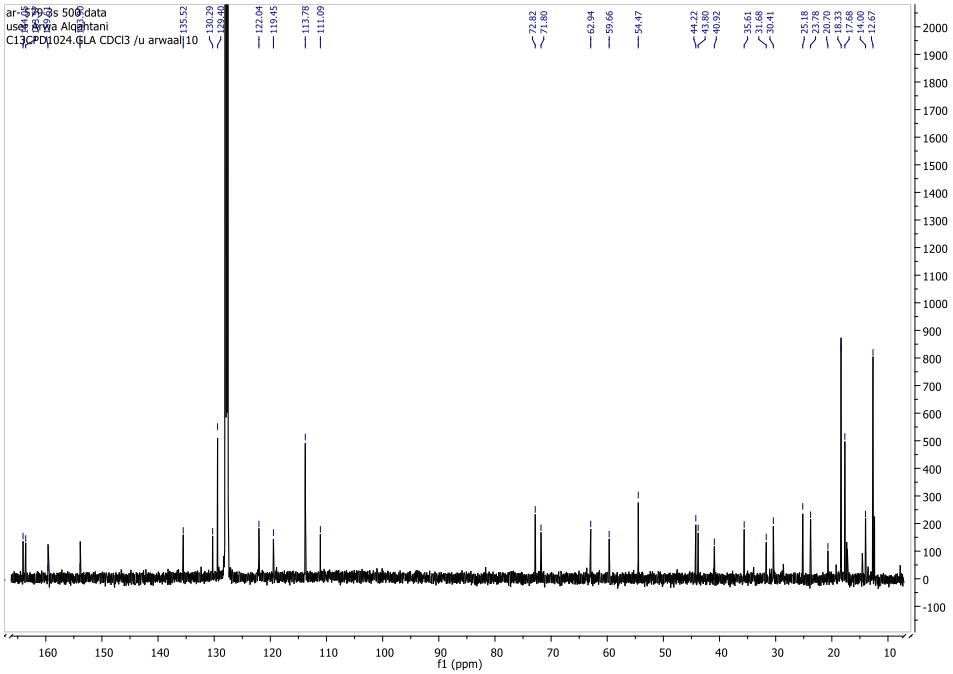
^{1}H and ^{13}C NMR Spectra of Compound **192**



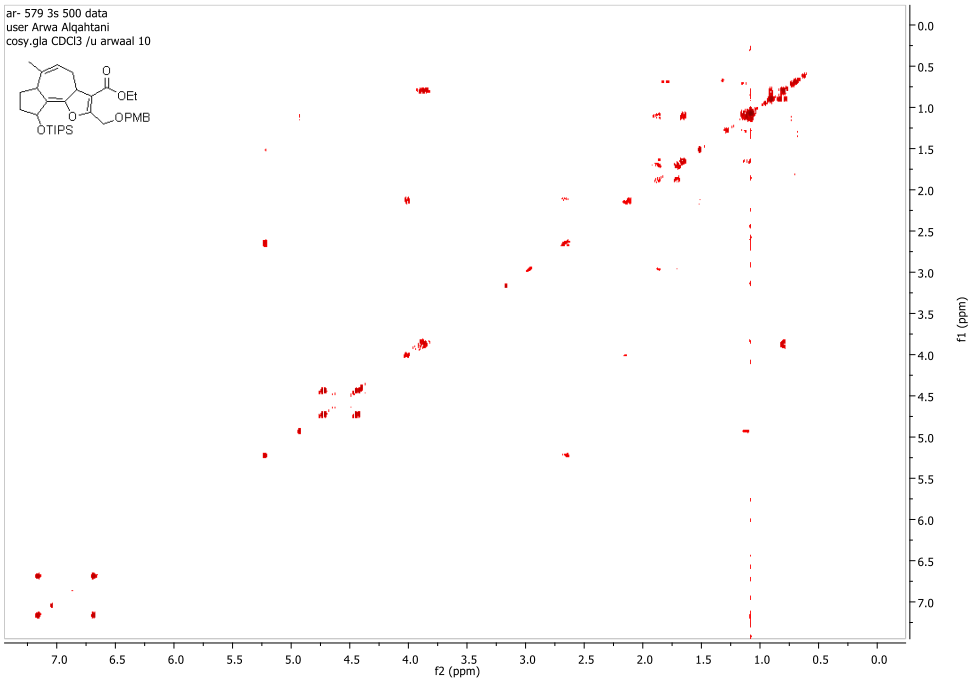


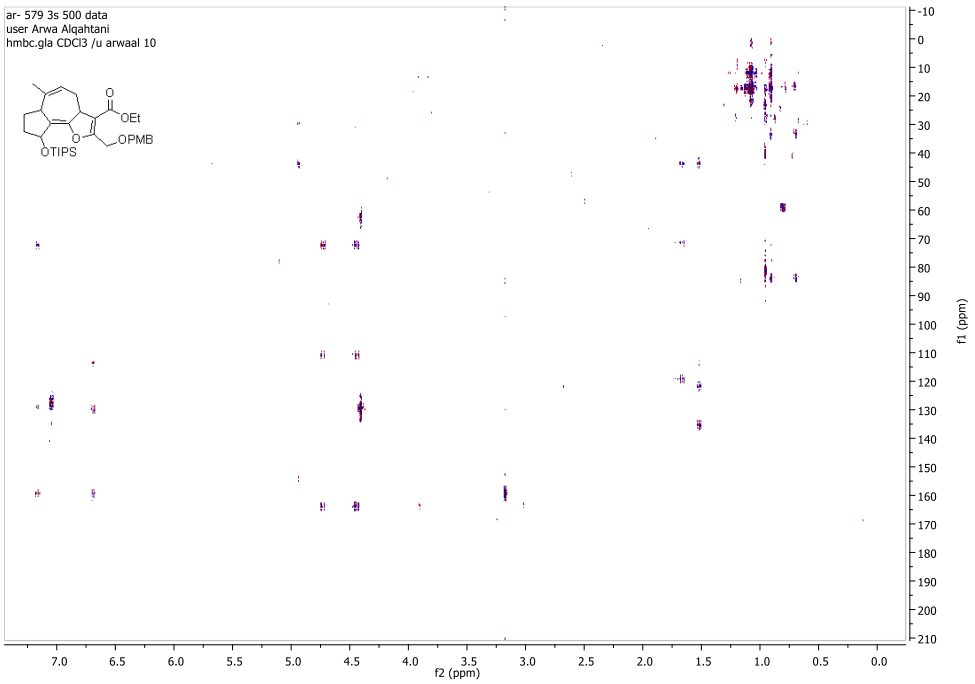
^{1}H and ^{13}C NMR Spectra of Compound **195**



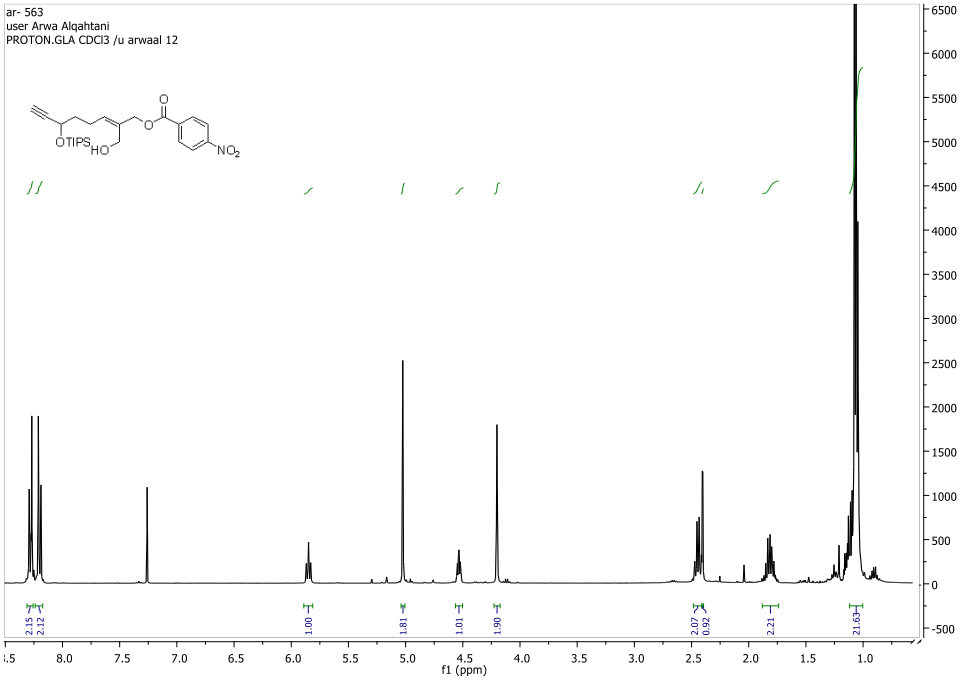


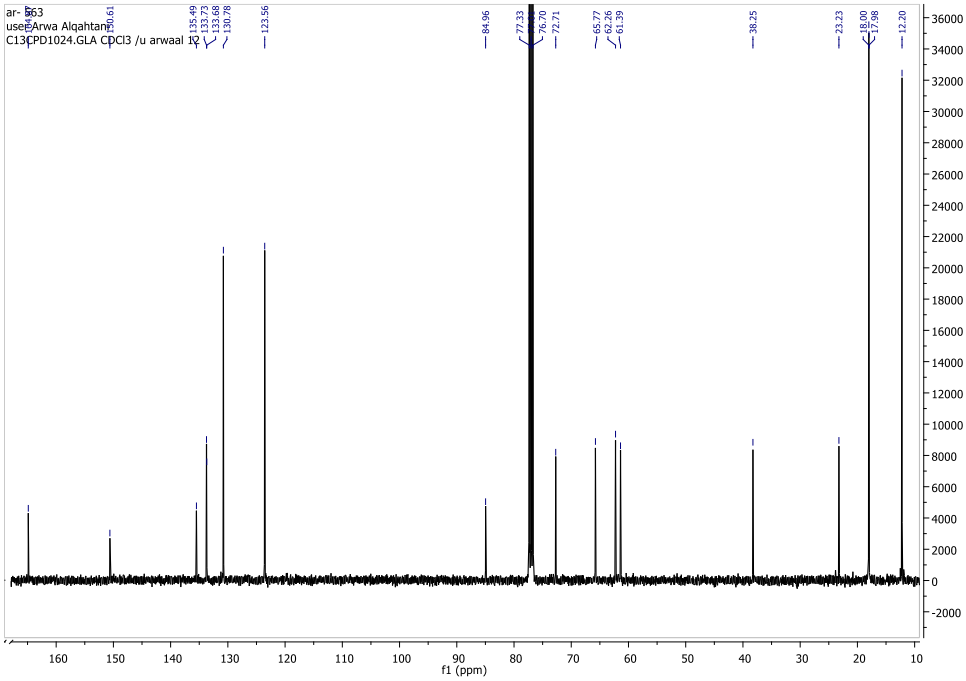
NOESY and COSY Spectra of Compound **195**



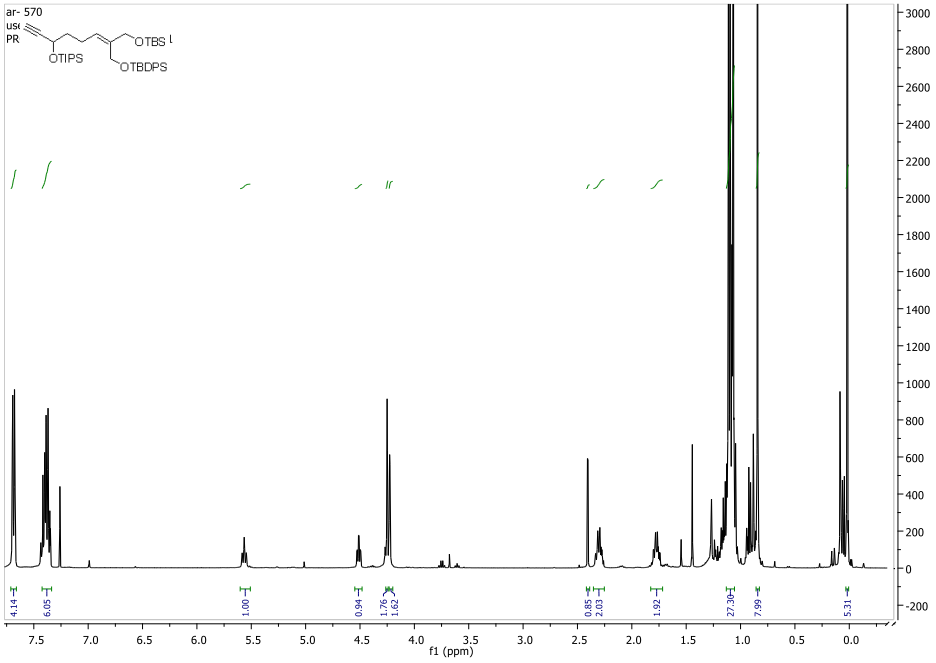


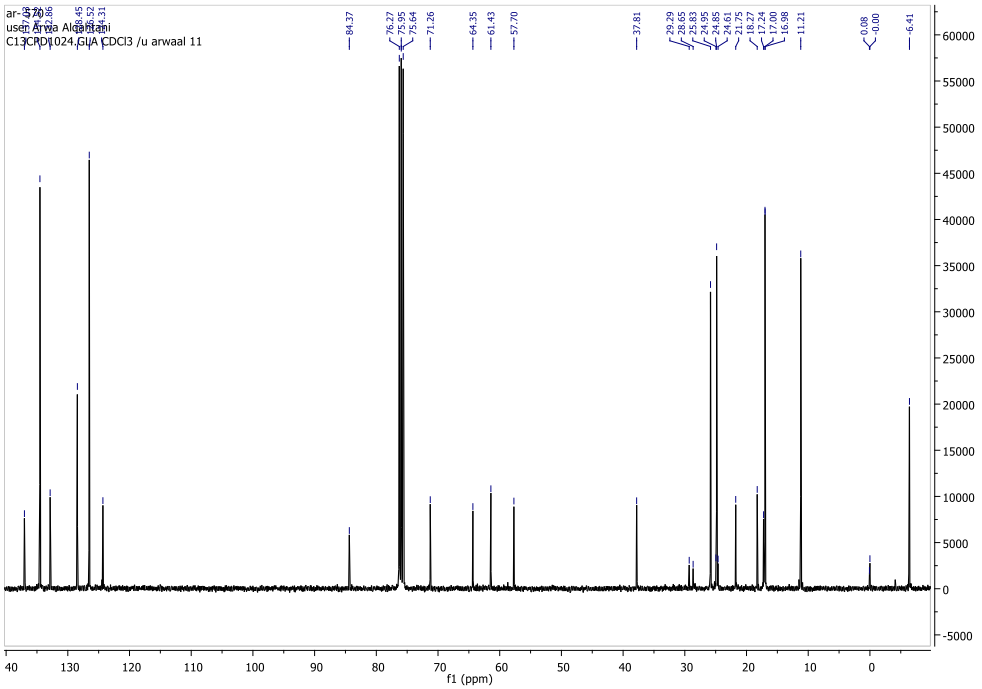
^{1}H and ^{13}C NMR Spectra of Compound **207**



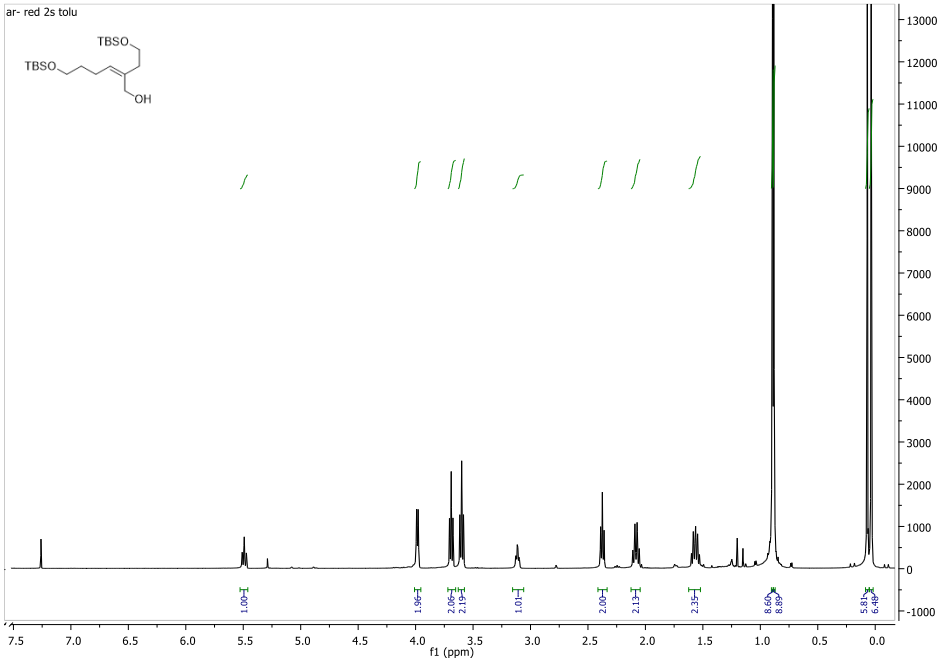


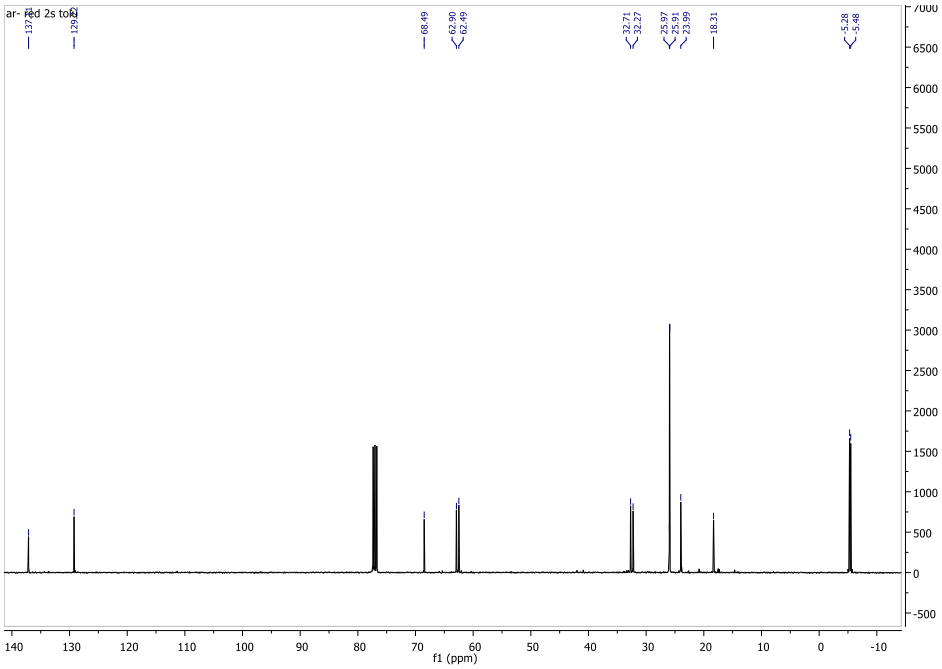
^{1}H and ^{13}C NMR Spectra of Compound **210**





^{1}H and ^{13}C NMR Spectra of Compound **235**





Data Management and Sharing Plan

Data Management:

This project involves collecting data of both novel and previously synthesised compounds. With collected data consisting of experimental techniques and characterisation of the compounds. The experimental procedures will be written up following the RSC style in a word document with the associated NMR, IR, HRMS, $[\propto]D$,and elemental analysis.

Data Storage :

NMR data is stored on chemistry servers, as well as on hard drives alongside having physical copies.IR data is stored on hard drives alongside physical copies. HRMS data is stored as physical copies of the printouts supplied by the in-house service. Elemental analysis is recorded on the submission sheet after being completed by the in-house service.$[\propto]D$values are recorded in the lab book alongside the experimental for the relevant compound, with a further physical copy in a separate folder.

Data Sharing :

Data is shared between student and supervisor, until publication were data will be made available in open-access manuscripts in chemistry journals