Development of a Divergent Synthetic Strategy for the Asbestinins

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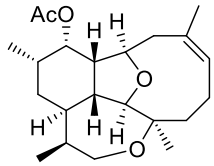
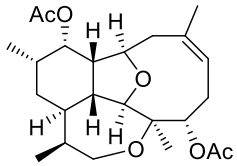
Abstract

Asbestinins are the most complex of the ether bridged 2,11-cyclised cembranoids, isolated from the gorgonian octocoral species *Briareum asbestinum*. They have a complex rigid tetracyclic framework with nine or more contiguous stereocentres and a highly substituted tetrahydrofuran, for example in 11-acetoxy-4-deoxyasbestinin D and asbestinin 12. The asbestinins have been shown to possess significant biological activities including antimicrobial and anticancer properties.



11-acetoxy-4-deoxyasbestinin D



asbestinin 12

The significant synthetic challenge presented by the asbestinins structures combined with their biological activity make them an interesting target for total synthesis. There have been numerous syntheses of the structurally related cladiellin family but only two previous syntheses of the asbestinins which were reported by Crimmins in 2005 and 2008.

Previous work in the Clark group had established methodology for the synthesis of multiple members of the cladiellin family (>10 members synthesised) from a common tricyclic intermediate which could be utilised in the synthesis of the asbestinins. This involved a few key transformations including a tandem oxonium ylide formation, [2,3]-sigmatropic rearrangement to construct the bicyclic core followed by a Stille/Diels–Alder sequence to give a common tricyclic intermediate.

In this thesis, the first total syntheses of five members of the 4-deoxyasbestinin family are reported as well as the second total synthesis of 11-acetoxy-4-deoxyasbestinin D. The syntheses were completed utilising the common tricyclic intermediate previously reported during the synthesis of multiple members of the cladiellin family. The reported total syntheses have allowed for confirmation or re-evaluation of the reported revised structures of members of the asbestinin family.

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Acknowledgements

First, 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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During my time at the University of Glasgow, the technical staff have been of great help and I would like to thank them for that, a special mention must go to Doctor Claire Wilson for her X-ray crystallography work, which has provided invaluable information for the structural elucidation of the absestinins.

I would also like to acknowledge everyone else who I have met during my time at the University of Glasgow who have made the experience more enjoyable than it otherwise would have been.

Lastly, I would like to thank all my family for their support during my PhD and for all the 'free' meals I have gotten during this time.

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.

A portion of the work described herein has been published elsewhere as listed below.

Total Syntheses of 11-Acetoxy-4-deoxyasbestinin D, 4-Deoxyasbestinin C, Asbestinin-10, -20, -21 and -23. Angus Campbell, Ian Mat Som, Claire Wilson and J. Stephen Clark, *Chem. Eur. J.*, accepted for publication 11th November 2019.

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Angus Campbell

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Prof. J. Stephen Clark

Abbreviations

Ac	acetyl
acac	acetylacetonate
BHT	butylated hydroxytoluene, 2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Bu	butyl
Cb	carbamate
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMM	1,2-dimethoxymethane
DMP	Dess–Martin periodinane
dr	diastereoisomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ED_{50}	half maximum effect dose
Epi	epimer
Et	ethyl
hfacac	hexafluoroacetylacetonate
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
hv	irradiation with light
imid.	Imidazole
Ipc	isopinocamphenyl
LDA	lithium diisopropylamide
L-Selectride™	lithium tri-*sec*-butylborohydride
MAD	methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl

Men	mentyl
Ms	mesyl
MS	molecular sieves
MVK	methyl vinyl ketone
NMO	4-methylmorpholine *N*-oxide
p-ABSA	*para*-acetamidobenzenesulfonyl azide
PMB	*para*-methoxybenzyl
Pr	propyl
py.	Pyridine
RCM	ring-closing metathesis
TBAF	tetra-*N*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMCDA	*N*,*N*,*N*′,*N*′ -tetramethyl-1,2-diaminocyclohexane
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TMSOTf	trimethyl trifluoromethane sulfonate
TMP	tetramethylpiperidide
TPA	triphenylacetic acid
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
VAZO 88™	1,1′-azobis(cyclohexanecarbonitrile)

1. Introduction

1.1 2,11-Cyclised Cembranoid Family of Natural Products

Since the initial discovery of eunicellin (**1**) over forty years ago, many members of the ether-bridged 2,11-cyclised cembranoids have been isolated from marine invertebrates of the octocorallia species such as the asbestinins (**2**, Figure 1).[1] They have been shown to possess various biological activities such as cytotoxic, anti-inflammatory and anti-malarial properties.[2] The structural variety of these natural products and the possibility of synthesising members of the family from common late-stage intermediates has led to considerable interest in the area.

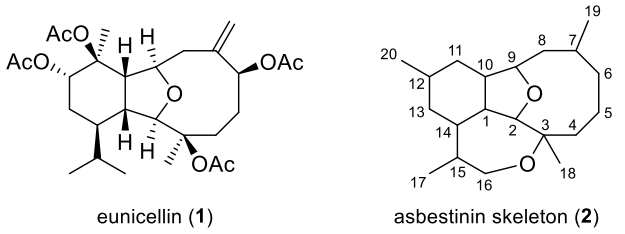
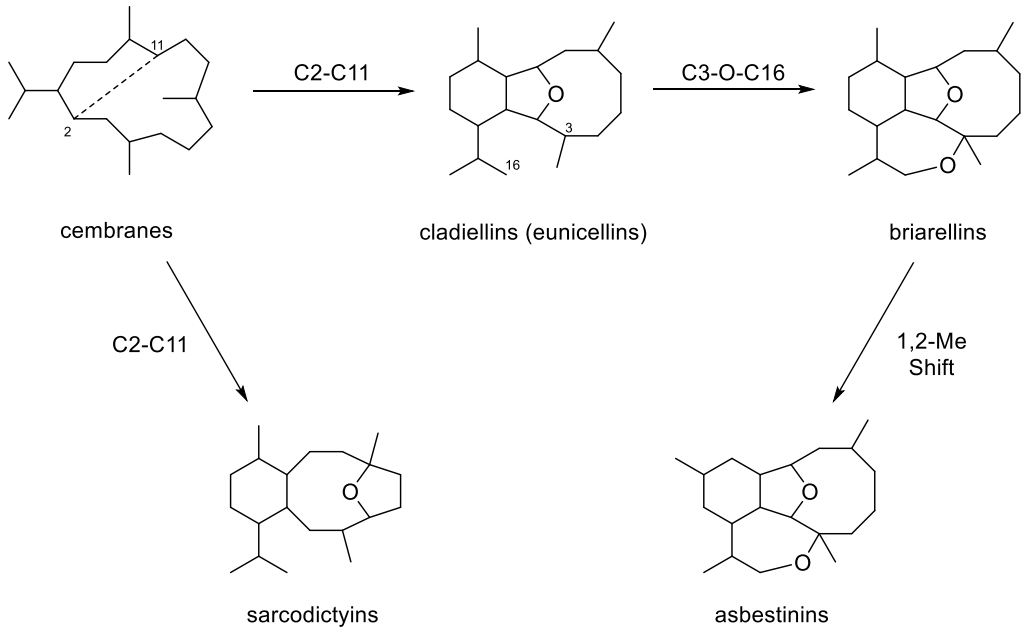


*Figure 1: Structure of Eunicellin (**1**) and Asbestinins Skeleton (**2**)*

The 2,11-cyclised cembranoids can be split into four main subclasses: cladiellins (eunicellins), sarcodictyins, briarellins and asbestinins (Scheme 1).[2]



Scheme 1: Proposed Biosynthesis of the Four Known Families of Oxygenated 2,11-Cyclised Cembranoids

The idea that the four subclasses of 2,11-cyclised cembranoids can be biosynthesised from the same intermediate was first proposed by Faulkner.[3] He proposed that a 2,11-cyclisation (cembrane nomenclature) of the cembrane ring skeleton would result in formation of the cladiellins. The briarellins and asbestinins could then be synthesised by formation of a seven-membered ether ring between C3 and C16 (asbestinin nomenclature). This proposal has yet to be proved, but evidence from isolated metabolites of the three subclasses is consistent with the proposed biosynthetic route.[4]

1.2 Abestinin Family of Natural Products

In recent years, over 30 members of the asbestinin family of natural products have been isolated from the gorgonian octocoral species *Briareum asbestinum*.[5-10] The first members of the family were reported in 1980 by Faulkner, Clardy and co-workers with the isolation and characterisation of asbestinins 1−5 (**3**−**7**, Figure 2).[6]

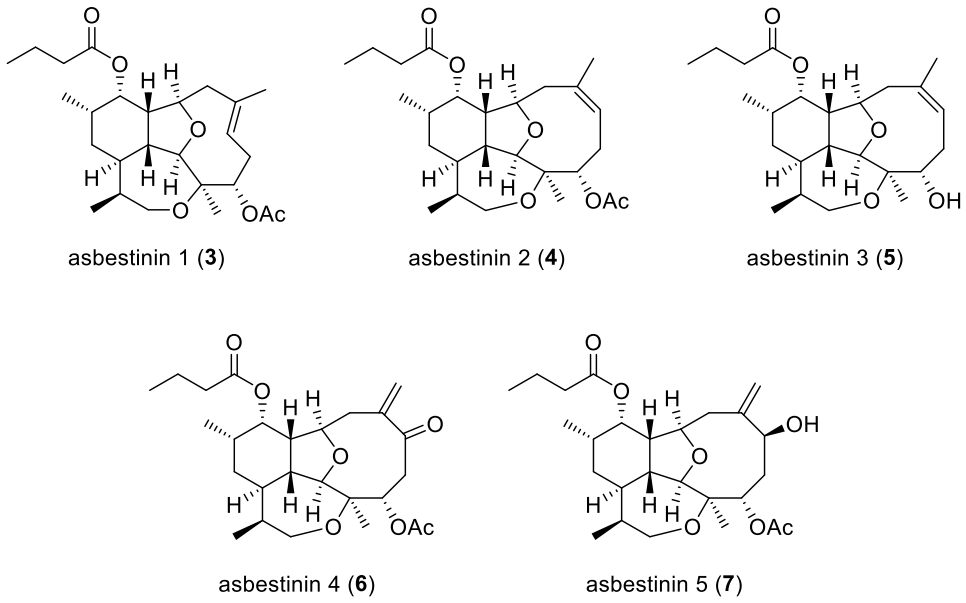
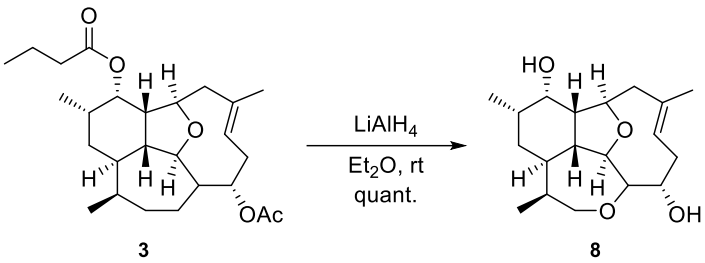


*Figure 2: Proposed Structures of Asbestinins 1−5 (**3**−**7**)*

The structure and relative stereochemistry of each of the isolated asbestinins were determined from deductions based on the reduction of asbestinin 1 (**3**) with lithium aluminium hydride to give corresponding diol **7** which was analysed by single X-ray crystallography (Scheme 2).



*Scheme 2: Reduction of Asbestinin 1 (**3**) with Lithium Aluminium Hydride*

The isolation and characterisation of new asbestinin members stemmed from this initial report with Clardy and co-workers reporting the isolation of two new asbestinin diterpenes in 1981.[7] This was followed by reports of the isolation and characterisation of multiple members of the family by Rodriguez and co-workers in 1991, 1993 and 1994.[8-10]

Difficulties in determining structures and stereochemical assignments of members of the asbestinin family by NMR analysis alone is evident through the isolation publications. For example, Rodriguez and co-workers initially proposed the structure of asbestinin 6 (**9**) in 1993 but following further analysis of their data as well as new data collected from the structurally related natural product asbestinin 11 (**11**), the structure was revised to be **10** in 1994 (Figure 3).[9,10]

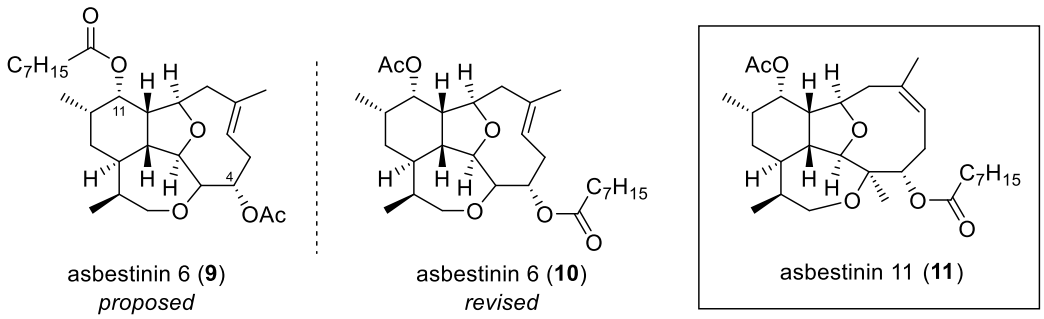


*Figure 3: Revised Structure of Asbestinin 6 (**10**)*

The structural revision of asbestinin 6 (**9**) related to positioning of the caprylic and acetyl functionality at the C-4 and C-11 positions. Several members of the asbestinin family have had their original structures, proposed in the early 1990s, revised as a consequence of the use of new NMR techniques and the acquisition of better-quality NMR data.[10,11]

This can be further seen throughout the 4-deoxyasbestinin series, many members of which were originally assumed to have C-4 oxidation but were later found to have C-6 oxidation instead. An example of this can be seen in the structurally related asbestinins 10 (**12**), 20 (**13**)

and 11-acetoxy-4-deoxyasbestinin F (**14**), which were proposed to have the structures shown in Figure 4.

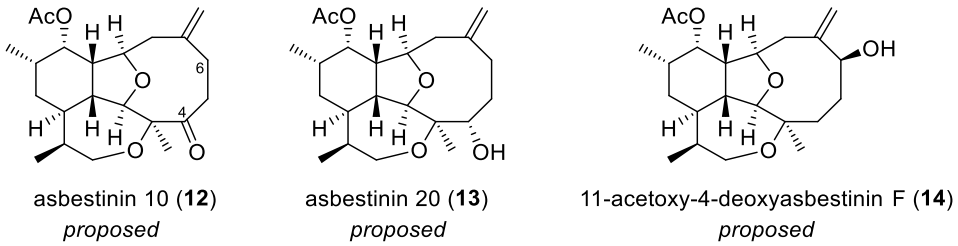
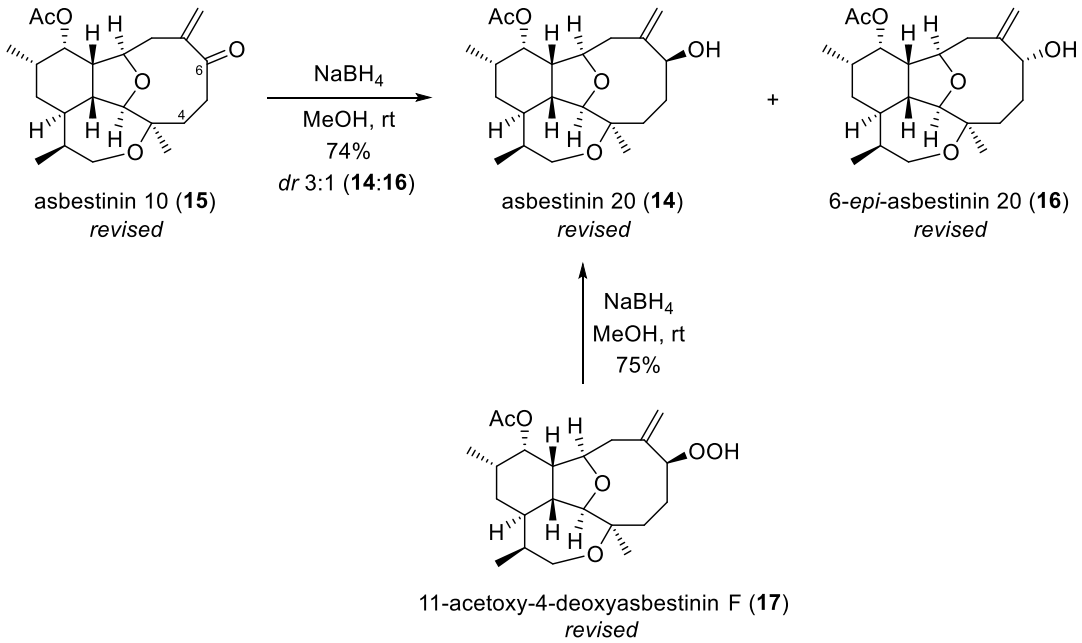


*Figure 4: Proposed Structures of Asbestinin 10 (**12**), 20 (**13**) and 11-Acetoxy-4-deoxyasbestinin F (**14**)*

These compounds were first isolated by Rodriguez and co-workers in 1993 and 1994 but following re-isolation by the same group in 2006, it became evident that the proposed structures were incorrect. Further analysis through chemical interconversions and more in-depth NMR analysis led to their revised structures. The key revision was repositioning of the ketone in asbestinin 10 (**15**), previously located at C-4, to the C-6 position. Reduction of asbestinin 10 (**15**) to give asbestinin 20 (**14**) and 6-*epi*-asbestinin 20 (**16**), allowed the structure of asbestinin 20 (**14**) to be revised as well (Scheme 3).[11]



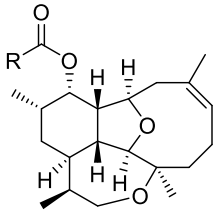
*Scheme 3: Revised Structures of Asbestinin 10 (**15**), 20 (**14**) and 11-Acetoxy-4-deoxyasbestinin F (**17**)*

New mass spectrometry data and reassignment of the structure of asbestinin 20 to that first reported for 11-acetoxy-4-deoxyasbestinin F allowed Rodriguez and co-workers to propose peroxide **17** as the new structure for 11-acetoxy-4-deoxyasbestinin F. To provide additional

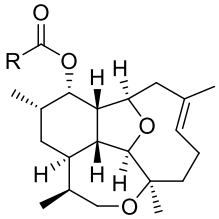
evidence for this, peroxide **17** was treated with sodium borohydride to reduce the peroxide and give asbestinin 20 (**14**).

1.2.1 Biological Activity of the Asbestinins

In 1998, Bernardelli and Paquette described the biological properties of known 2,11-cyclised cembranoids, with many being shown to be biologically active by virtue of their cytotoxic, anti-inflammatory and anti-malarial properties. [2] An example of this can be seen in the 4-deoxyasbestinin series, members which were shown to have possess cytotoxicity against CHO-K1 cells (Table 1).



R = Me 11-acetoxy-4-deoxyasbestinin D (**18**)
R = *n*-Pr 4-deoxyasbestinin C (**19**)



R = Me 11-acetoxy-4-deoxyasbestinin B (**20**)
R = *n*-Pr 4-deoxyasbestinin A (**21**)

Table 1: Cytotoxicity of 4-Deoxyasbestinins Against CHO-K1 Cells

4-Deoxyasbestinin	ED_{50} (µg/mL)
11-Acetoxy-4-deoxyasbestinin D	4.82
4-Deoxyasbestinin C	3.55
11-Acetoxy-4-deoxyasbestinin B	2.50
4-Deoxyasbestinin A	3.55

All four compounds were found to have possess cytotoxicity. The geometry of the double bond did not influence cytotoxic activity as can be seen by comparison of data for 4-deoxyasbestinin A and C. The influence of the ester substituent (acetate or butanoate) is also negligible with minor differences in activity. The biological activities of many of the asbestinins have not been fully determined but it appears that there is a significant difference between the 4-deoxyasbestinins and oxygenated series with the additional oxygenation at the C-4 position seeming to reduce their antimicrobial potency.[2]

1.2.2 Total Synthesis of 11-Acetoxy-4-deoxyasbestinin D (18)

It was not until 2005 that the absolute configuration of the asbestinins were confirmed when Crimmins and Ellis reported the first total synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**). This synthesis was followed by the synthesis of asbestinin 12 (**22**) by the same workers in 2008 (Figure 5). These are the only reported total syntheses for members of the asbestinin family to date.[12,13]

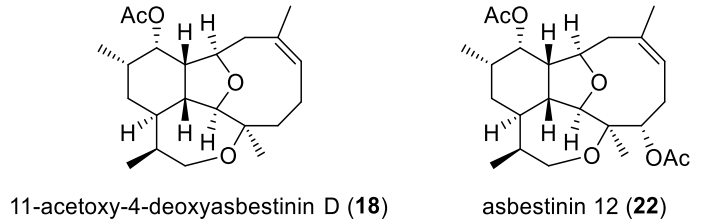


*Figure 5: Structures of 11-Acetoxy-4-deoxyasbestinin D (**18**) and Asbestinin 12 (**22**)*

Crimmins utilised a synthetic strategy for the asbestinins which he had applied to the synthesis of numerous members of the cladiellin family previously, for example in ophirin B (**23**) and astrogorgin (**24**, Figure 6).[14,15]

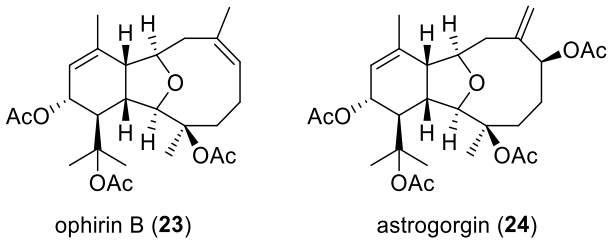


Figure 6: Examples of the Cladiellin Family Synthesised by the Crimmins Group

Key disconnections included glycolate alkylation, ring-closing metathesis (RCM) to form the nine-membered ring, intramolecular Diels–Alder cycloaddition to form the tricyclic ring system and asymmetric hydroboration-etherification to synthesise the tetracyclic core as the forward reactions (Figure 7).[12,13]

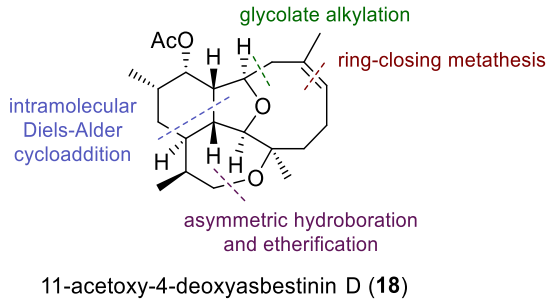
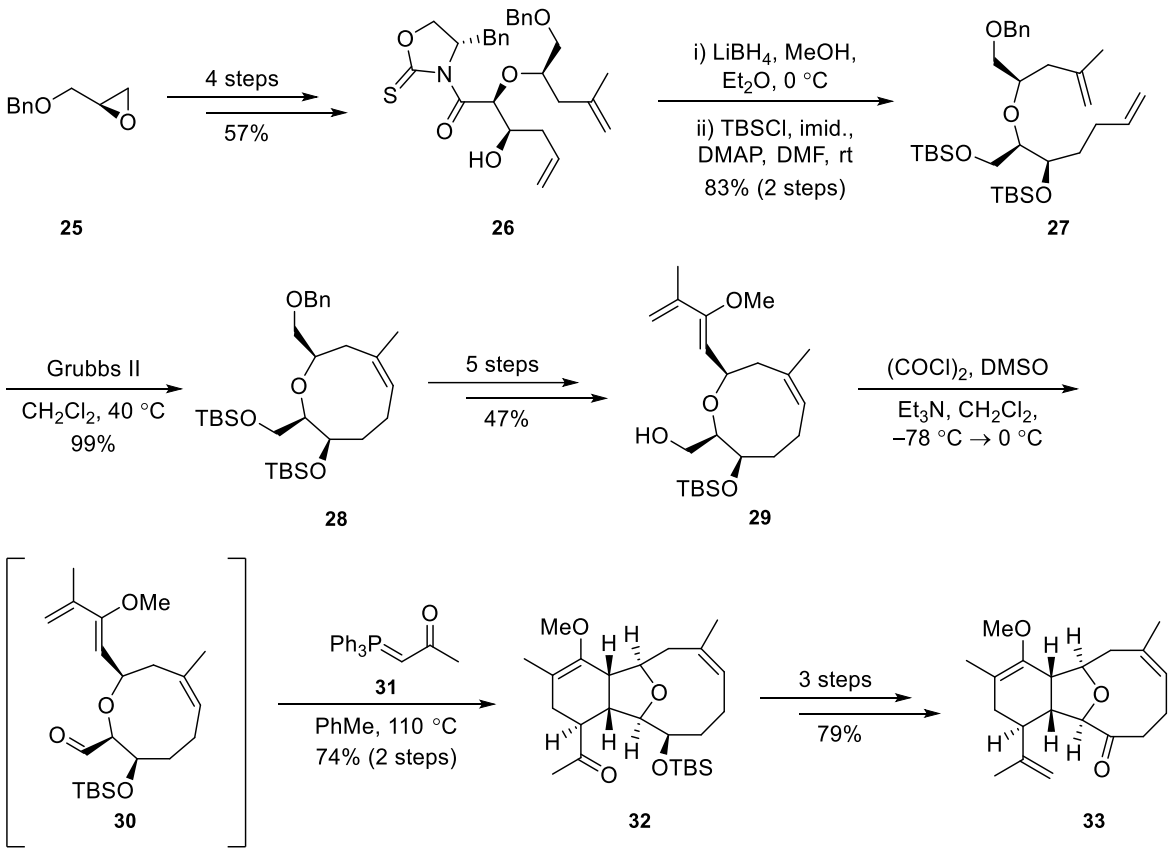


*Figure 7: Key Disconnections in the Synthesis of 11-Acetoxy-4-deoxyasbestinin D (**18**)*

The initial steps in the synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**) and asbestinin 12 (**22**) involved the conversion of *R*-benzyl glycidyl ether **25** into diene **26** (Scheme 4). This sequence was followed by reduction and silyl protection to give diene **27** in order to set up the RCM reaction.

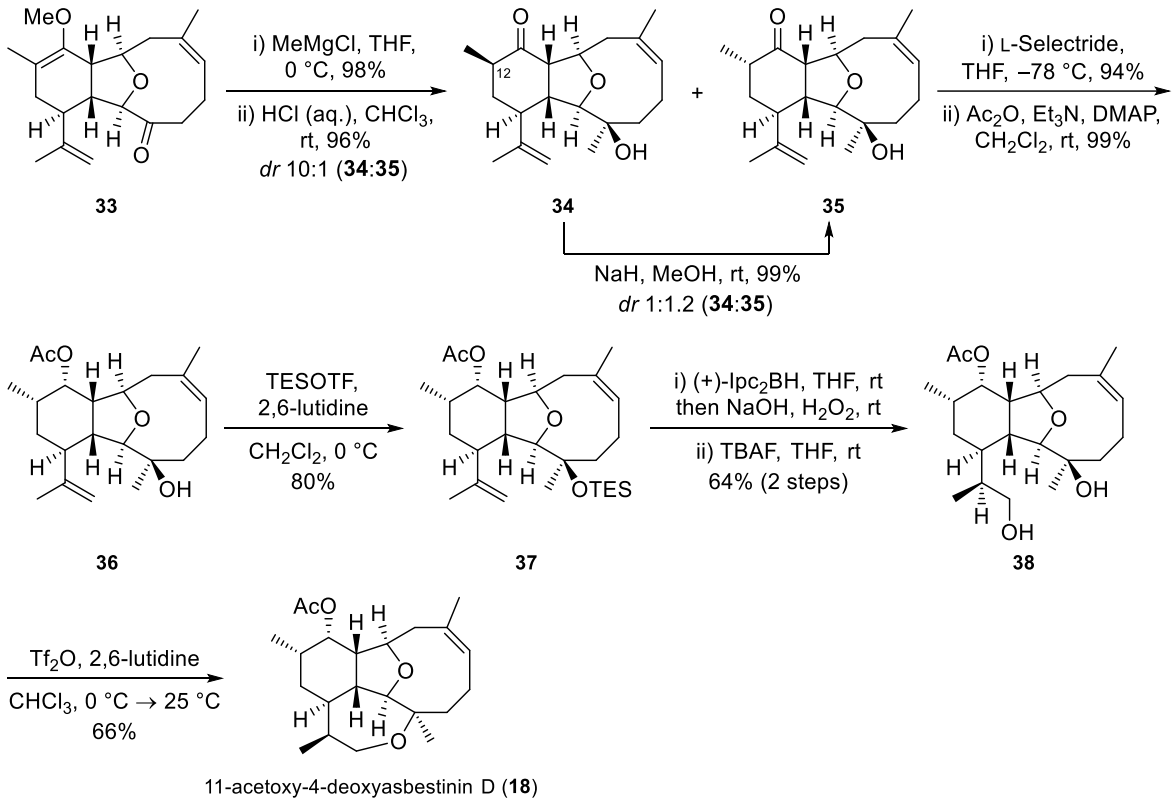


*Scheme 4: Synthesis of Common Tricyclic Intermediate **33***

With diene **27** in hand, RCM was performed using Grubbs II catalyst to provide the corresponding nine-membered cyclic alkene **28** in excellent yield (99%).[16] Cleavage of the benzyl ether followed by oxidation and successive Wittig olefinations to install the desired diene and subsequent cleavage of primary silyl ether gave diene **29** in five steps.[17]

Oxidation of the primary alcohol under Swern conditions gave intermediate aldehyde **30** which was immediately used in a Wittig olefination reaction to give the corresponding enone which underwent immediate intramolecular Diels–Alder cycloaddition to produce tricyclic ketone **32** in excellent yield (74% over two steps).[18,19] The final three steps required to complete the synthesis of common intermediate **33** involved Wittig olefination of the ketone followed by cleavage of the silyl ether and oxidation of the secondary alcohol to give the desired ketone. From here, the syntheses of 11-acetoxy-4-deoxyasbestinin D (**18**) and asbestinin 12 (**22**) diverge.

For 11-acetoxy-4-deoxyasbestinin D (**18**), ketone **33** underwent Grignard addition using methyl magnesium chloride followed by hydrolysis of the enol ether to give corresponding ketones **34** and **35** (*dr* 10:1, **34**:**35**, Scheme 5).

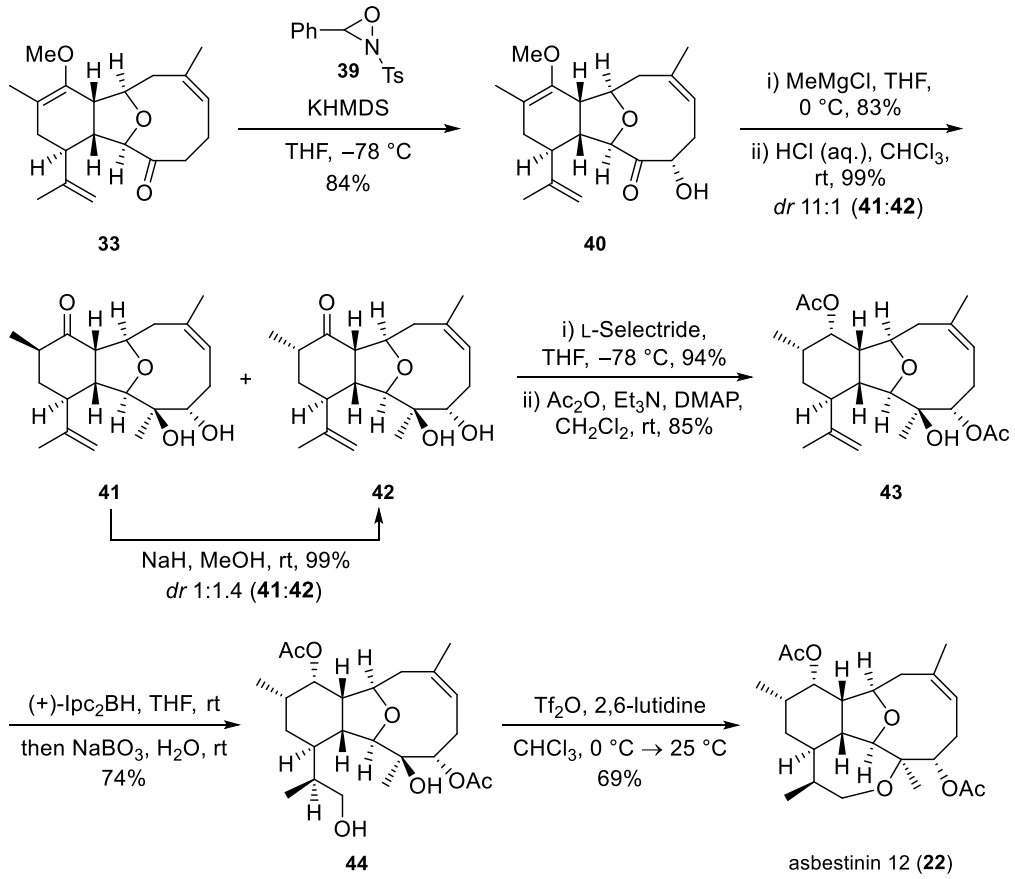


*Scheme 5: Completion of 11-Acetoxy-4-deoxyasbestinin D (**18**)*

Enol ether hydrolysis favoured formation of the diastereoisomer with incorrect configuration at the C-12 position so ketone **34** had to undergo epimerisation with sodium methoxide giving ketones **34** and **35** in a 1:1.2 ratio. This had to be repeated multiple times to produce high quantities of ketone **35**. The ketone **35** produced by epimerisation was reduced with L-Selectride and subsequent acetylation of the secondary alcohol delivered alcohol **36** as a

single diastereoisomer. Silyl protection of the tertiary alcohol gave silyl ether **37**, the precursor to the key asymmetric hydroboration step. Hydroboration of the *exo*-alkene using (+)-diisopinocampheylborane followed by oxidation resulted in highly stereoselective creation of the new stereocentre and the resulting single diastereoisomer was subjected to deprotection to afford the diol **38**.[20,21] The final step in the synthetic route was conversion of the diol **38** into the primary triflate, which then underwent ring closure through nucleophilic displacement by the tertiary alcohol to give 11-acetoxy-4-deoxyasbestinin D (**18**) in 26 steps and an overall yield of 4%.

For asbestinin 12 (**22**), ketone **33** was subjected to the Davis enolate oxidation protocol with with oxaziridine **39** to give α-hydroxyketone **340**. Grignard addition followed by hydrolysis of the enol ether gave ketones **41** and **42** (*dr* 11:1, **41**:**42**, Scheme 6).[22]



*Scheme 6: Completion of Asbestinin 12 (**22**)*

As before, iterative epimerisations of ketone **41** were required in order to obtain sufficient quantities of the intermediate. From this intermediate, the route to asbestinin 12 (**22**) was similar to that for 11-acetoxy-4-deoxyasbestinin D (**18**). Reduction of ketone **42** followed

by treatment with acetic anhydride gave diacetate **43**. This intermediate then underwent asymmetric hydroboration-oxidation to give diol **44**. The diol was treated with triflic anhydride to give the primary triflate, which underwent immediate displacement by the tertiary alcohol to give asbestinin 12 (**22**) in 25 steps and an overall yield of 4%.

1.3 Previous Synthetic Approaches to 2,11-Cyclised Cembranoids

Since the initial isolation of members of the 2,11-cyclised cembranoids, various approaches have been investigated to the form the tricyclic core which is present in the cladiellins, briarellins and asbestinins. Strategies utilised for the synthesis of members of these natural product families will be discussed in the following section.

1.3.1 Overman Group Strategy: Prins-pinacol and Nozaki–Hiyama–Kishi Cyclisation

In 1995, Overman and co-workers published the first total synthesis of a 2,11-cyclised cembranoid: (−)-7-deacetoxyalcyonin acetate (**45**, Figure 8).[23] The synthetic strategy was based on a stereoselective Prins-pinacol condensation-rearrangement reaction as the key transformation to form the bicyclic intermediate.[24,25] The nine-membered ring was later installed by a chromium-mediated Nozaki**–**Hiyama**–**Kishi cyclisation.[26,27] Following this, the Overman group used this key Prins-pinacol rearrangement to synthesise other 2,11-cyclised cembranoids including briarellin E (**46**, Figure 3).[28]

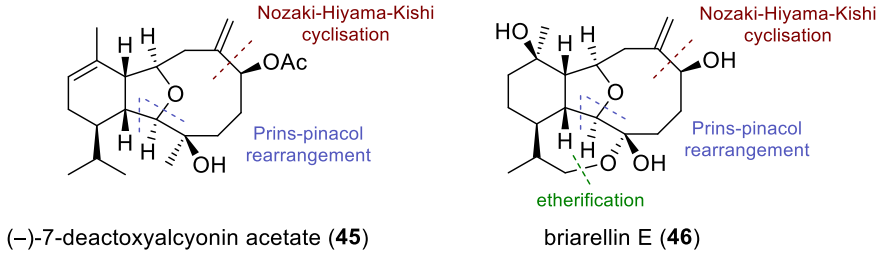
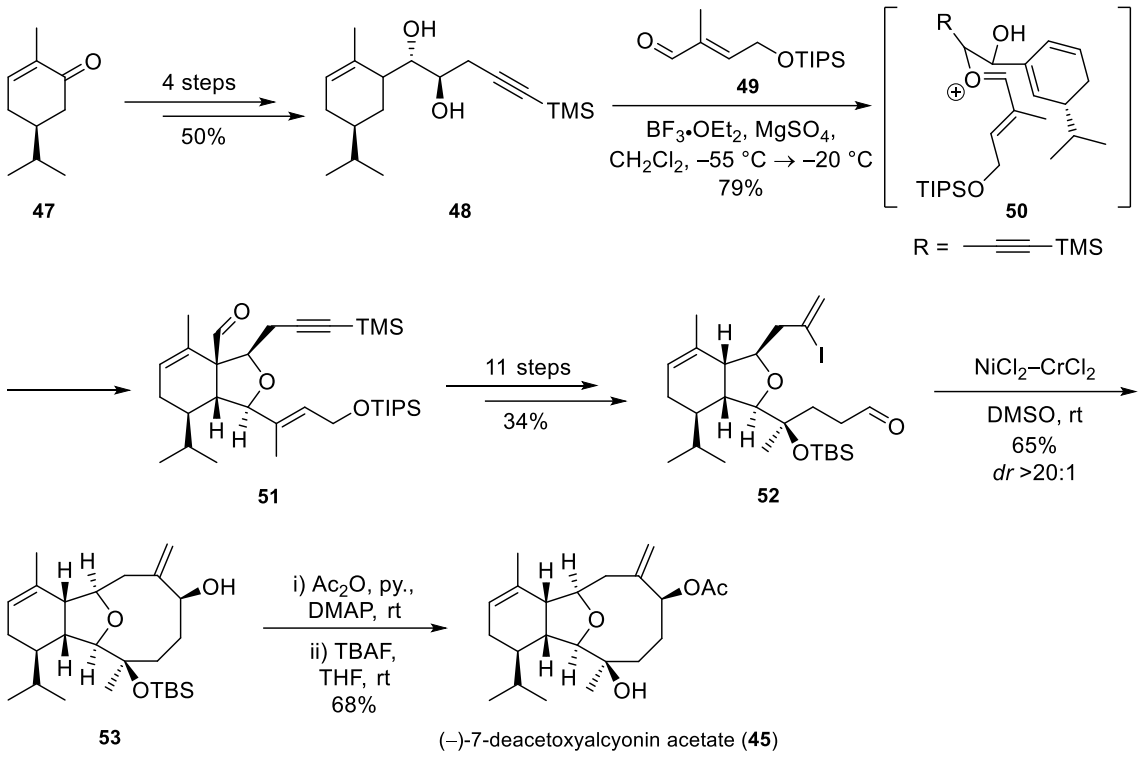


*Figure 8: Key Disconnections Involved in the Synthesis of (−)-7-Deacetoxyalcyonin Acetate (**45**) and Briarellin E (**46**)*

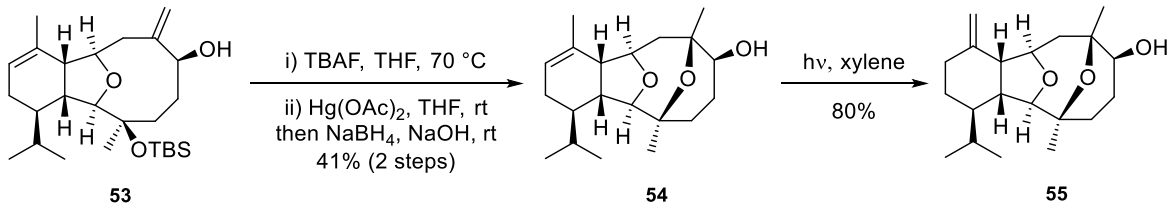
The Overman group chose *S*-hydrocarvone (**47**) as their starting point for the synthesis of (−)-7-deacetoxyalcyonin acetate (**45**) and this compound was transformed into the Prins-pincaol precursor **48** in four steps (Scheme 7).



*Scheme 7: Key Reactions Utilised to Form (−)-7-Deacetoxyalcyonin Acetate (**45**)*

The diol **48** was reacted with enal **49** in the presence of a Lewis acid to form bicyclic oxocarbenium intermediate **50** which underwent rearrangement to give bicyclic ether **51** as a single diastereoisomer in 79% yield. The Nozaki**–**Hiyama**–**Kishi precursor **52** was prepared from bicyclic ether **51** in a further 11 steps. This precursor was then used in the intramolecular coupling reaction to form tricyclic product **53** with high diastereoselectivity (65%, dr >20:1). Finally, acylation followed by cleavage of the silyl ether gave (−)-7-deacetoxyalcyonin acetate (**45**) in 17 linear steps.

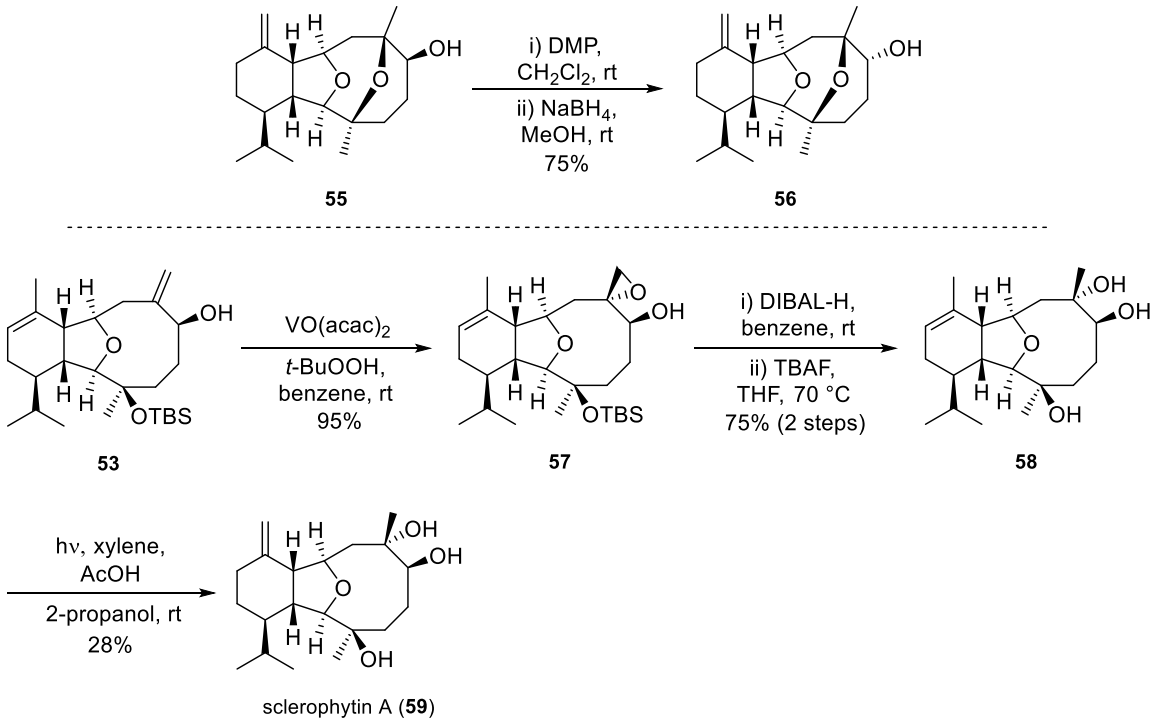
The Overman group used tricyclic alcohol **53** as an advanced intermediate in the synthesis of the proposed structure of sclerophytin A (**55**), a member of the cladiellin family (Scheme 8).[29] From the tricyclic alcohol **53**, cleavage of the silyl ether and subsequent intramolecular oxymercuration using $Hg(OAc)_2$ allowed formation of tetracyclic ether **54**.



*Scheme 8: Synthesis of Proposed Structure of Sclerophytin A (**55**)*

The final step in the synthesis of the proposed structure of sclerophytin A involved photoisomerisation of the endocyclic alkene to produce the *exo*-alkene **55**. The spectroscopic data and optical rotation from the obtained product did not match the data reported for the isolated natural product.

Based on these results, it was proposed that sclerophytin A could be the epimer of alcohol **55** so the stereochemistry at the hydroxyl-bearing stereocentre was inverted through an oxidation-reduction sequence to give alcohol **56** (Scheme 9). The spectroscopic data for the newly-formed compound did not match the data reported for the natural product and so the structure had to be revised. Based from these results and further analysis, it was determined the structure of sclerophytin A should be revised to triol **59**.



*Scheme 9: Synthesis of Sclerophytin A (**59**)*

The revised structure of sclerophytin A (**59**) was synthesised from intermediate **53** by sequential epoxidation of the exocyclic alkene with $VO(acac)_2$ and *tert*-butylhydroperoxide, epoxide opening and deprotection to give triol **58**. The final step was photoisomerisation of the endocyclic alkene as before to produce desired product **59**. The NMR data and optical rotation of the product matched that reported for the isolated natural product, which confirmed the structure of sclerophytin A.

1.3.2 Paquette Group Strategy: Diels–Alder Cycloaddition and Claisen Rearrangement

The Paquette group was also working on the total synthesis of sclerophytin A at the same time as the Overman group. Paquette and co-workers came to the same conclusion as the Overman group that the isolated natural product was not compound **55** (Scheme 8).[30,31]

For their synthetic strategy to prepare the newly proposed structure **59**, Paquette and co-workers identified disconnections that implied Diels–Alder cycloaddition, Claisen rearrangement and conjugate addition reactions as the key transformations in the forward direction (Figure 9).[32,33]

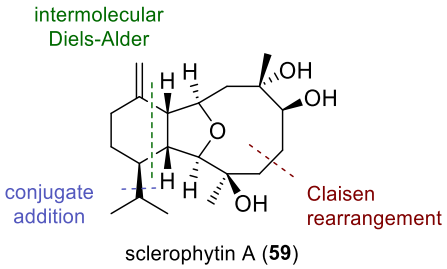
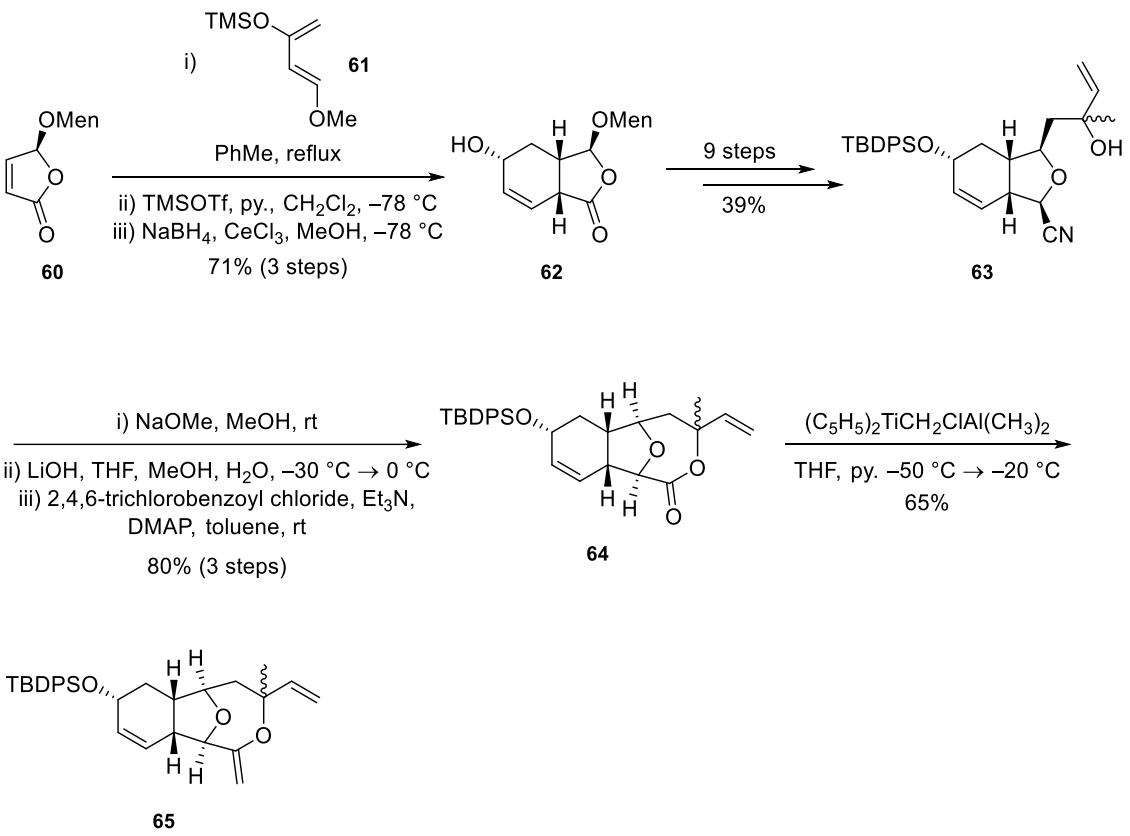


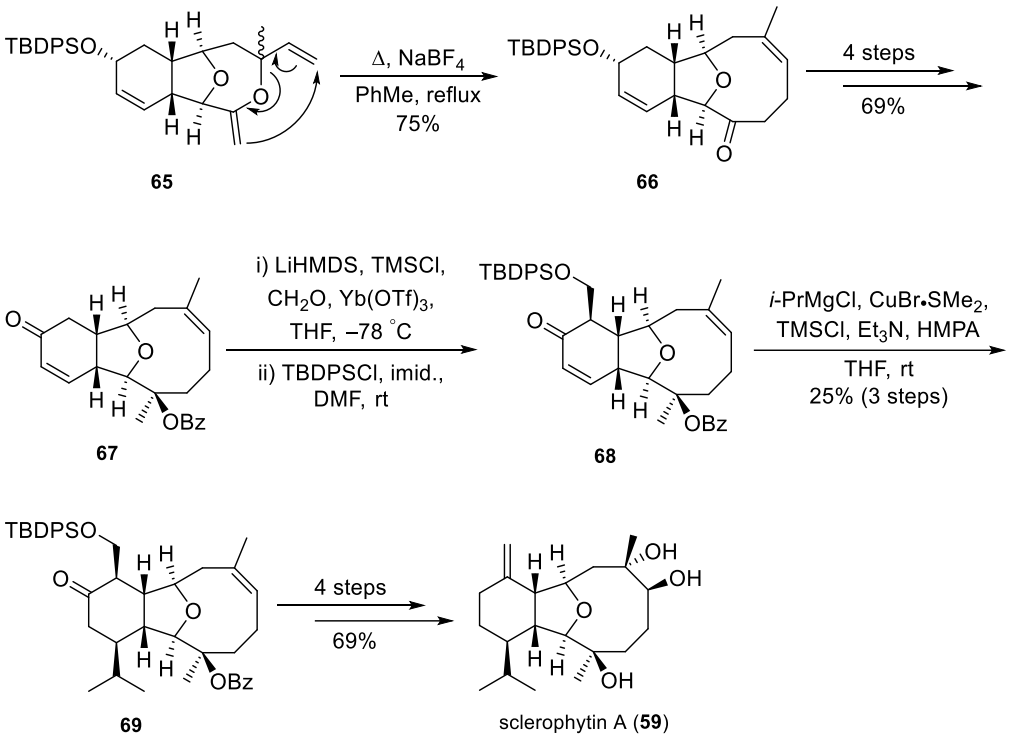
*Figure 9: Key Disconnections for the Synthesis of Sclerophytin A (**59**)*

The initial step in their synthesis was an intermolecular Diels–Alder reaction between diene **61** and dienophile **60** followed by reduction and elimination to form bicyclic lactone **62** (Scheme 10). Bicyclic lactone **62** was converted into nitrile **63** in nine steps and a subsequent three-step procedure gave tricycle **64**. This sequence involved formation of the methyl ester using sodium methoxide, ester hydrolysis with lithium hydroxide to give the acid and lactonisation under Yamaguchi conditions to give tricycle **64** in excellent yield over the three steps. The final step required to produce the Claisen rearrangement precursor was methenylation of the ketone to give triene **65**.



*Scheme 10: Construction of Tricyclic Ketone **65***

The enol ether **65** was heated in toluene at reflux in the presence of sodium tetrafluoroborate to promote Claisen rearrangement to give oxonene **66**. Oxonene **66** was converted into enone **67** over four steps (Scheme 11). From here, enone **67** underwent an aldol condensation reaction with formaldehyde mediated by ytterbium triflate and the resulting alcohol was protected as a silyl ether to give enone **68**.[34]



*Scheme 11: Completion of Sclerophytin A (**59**)*

Conjugate addition to enone **68** gave ketone **69** as the sole diastereoisomer and completed the three-step procedure in a yield of 25%. The synthesis of sclerophytin A (**59**) was completed in a further four steps resulting in a 35-step total synthesis which helped confirm the correct structure of the natural product.

1.3.3 Molander Group Strategy: Formal [4+3]-Annulation and [2+2]-Cycloaddition

Molander and co-workers developed a very efficient formal [4,3]-annulation method to form the tricylic core during their synthesis of (−)-7-deacetoxyalcyonin acetate (**45**).[20] Other key steps included a [2+2]-cycloaddition reaction followed by photochemical rearrangement, a conjugate addition reaction and a Nozaki–Hiyama–Kishi coupling (Figure 10).[35,36]

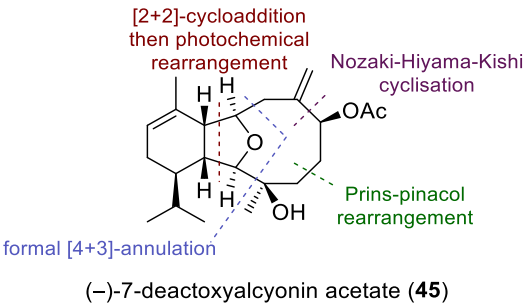
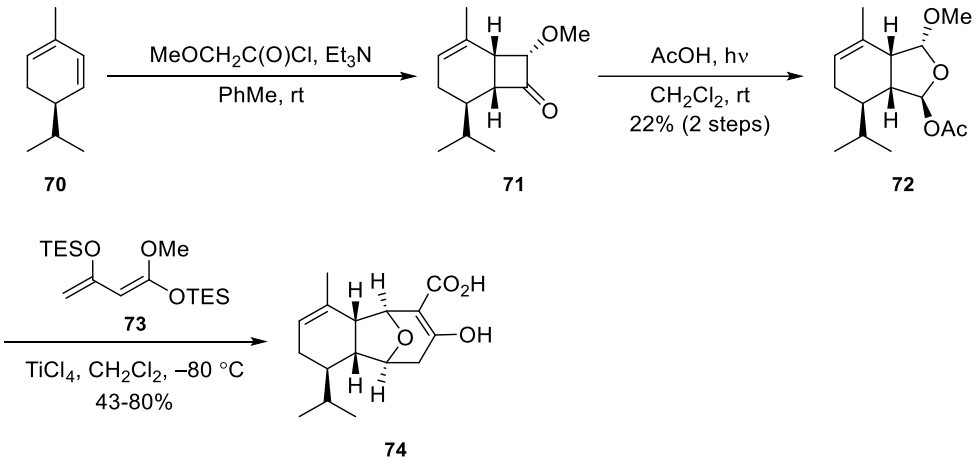


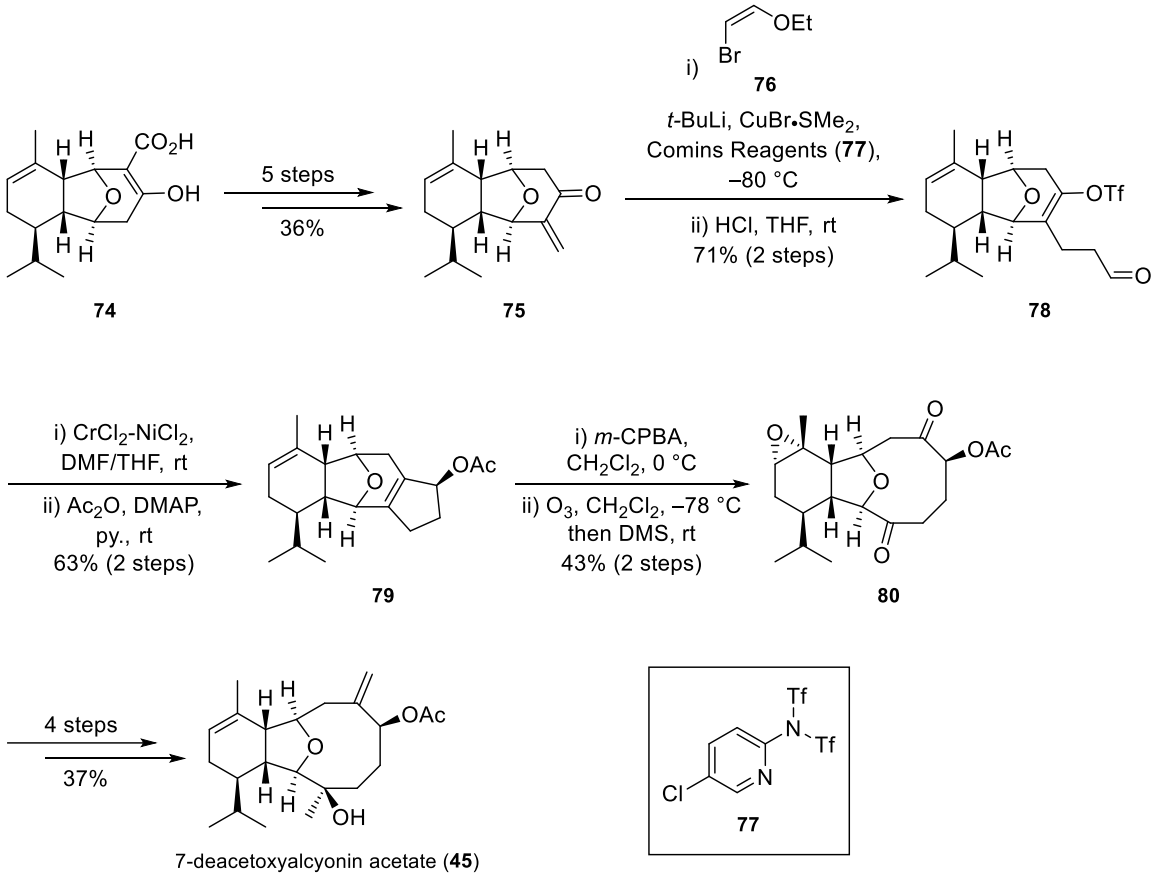
*Figure 10: Molander Group Strategy for Synthesis of (−)-7-Deacetoxyalcyonin Acetate (**45**)*

The synthesis commenced with the [2+2]-cycloaddition reaction of α-phellandrene **70** with methoxyketene to give cyclobutanone **71** which underwent sequential photochemical rearrangement and acetylation to give acetate **72** (Scheme 12). The next step was the formal [4+3]-annulation reaction with diene **73** in the presence of titanium tetrachloride. This afforded tricyclic β-keto acid **74** in a 43-80% yield. The major benefit to this approach was that the majority of the stereocentres in the final compound had been introduced by the third step.



Scheme 12: Tricyclic Formation through Formal [4,3]-Annulation

Next, β-keto acid **74** was converted into the enone **75** in five steps before conjugate addition of an organocopper reagent generated from *Z*-bromo ethyl vinyl ether (**76**, Scheme 13). This reaction was followed by direct formation of an enol triflate using Comins reagent (**77**) and subsequent hydrolysis of the side-chain enol ether to afford corresponding aldehyde **78**.[36]



*Scheme 13: Completion of 7-Deacetoxyalcyonin Acetate (**45**)*

An intramolecular Nozaki–Hiyama–Kishi coupling reaction produced the tetracyclic ring structure and subsequent acetylation gave acetate **79**. The synthesis of (−)-7-deacetoxyalcyonin acetate (**45**) was completed in a further 6 steps that involved epoxidation followed by ozonolysis to give dione **80**. The synthesis was completed in a total of 18 overall steps.

1.3.4 Kim Group Strategy: Intramolecular Amide Enolate Alkylation and Diels–Alder Cycloaddition

In 2006, Kim and co-workers reported the first total synthesis of an *E*-cladiellin – (−)-cladiella-6,11,dien-3-ol (**81**) – as well as four other members of the cladiellin family of natural products.[37] Their strategy involved the use (−)-cladiella-6,11,dien-3-ol as an intermediate to prepare the other members. Key steps in their synthesis involved an intramolecular amide enolate alkylation reaction and an intramolecular Diels–Alder cycloaddition reaction similar to that described by Crimmins and co-workers in their cladiellin synthesis (Figure 11).[12,13]

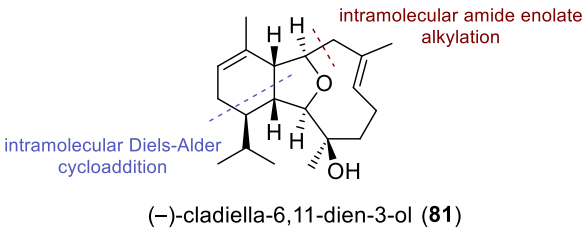
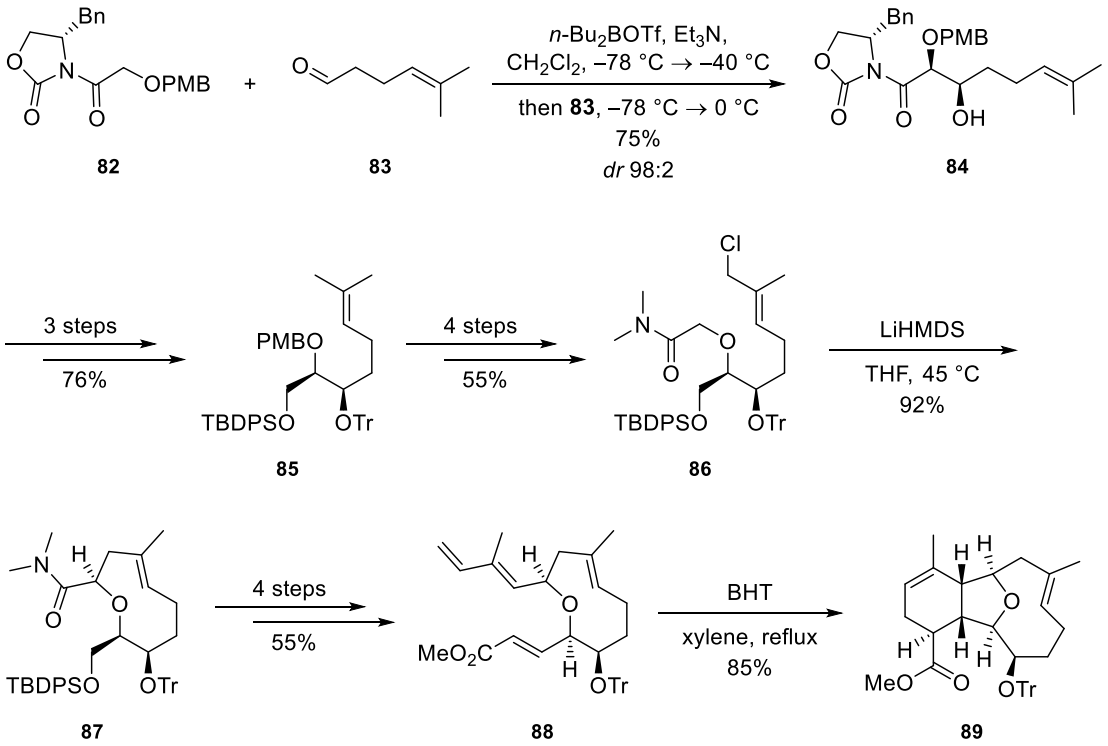


*Figure 11: Key Disconnections in the Synthesis of (−)-Cladiella-6,11,dien-3-ol (**81**)*

The first step in the synthesis was the asymmetric glycolate aldol reaction between oxazolidinone **82** and 5-methylhex-4-enal **83** (Scheme 14).[38,39] This gave the secondary alcohol **84** in 75% yield and with excellent diastereoselectivity (*dr* 98:2).

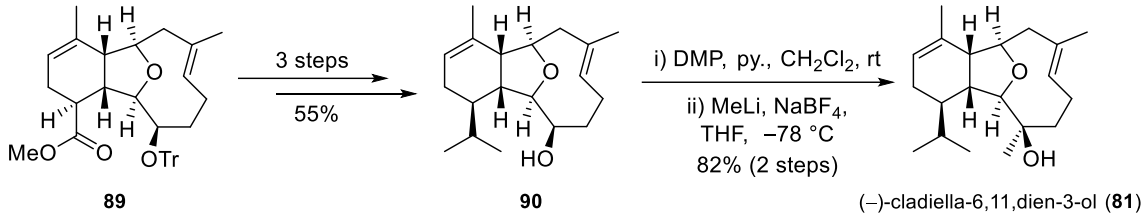


*Scheme 14: Synthesis of Tricyclic Core of (−)-Cladiella-6,11,dien-3-ol (**81**)*

Reduction of the chiral auxiliary followed by protecting group manipulation gave protected triol **85** in three steps. A further four steps were required to convert this intermediate into the cyclisation precursor **86**. The *E*-allylic chloride **86** then underwent the key intramolecular alkylation reaction upon treatment with LiHMDS to give *cis*-*E*-oxonene **87** in excellent yield. *cis*-*E*-Oxonene **87** was obtained as a single diastereoisomer and this amide was converted into the intramolecular Diels**–**Alder cycloaddition precursor **88** in four steps. Triene **88** was treated with butylated hydroxytoluene (BHT) to give the fused tricyclic ester **89** in excellent yield and with high selectivity. BHT was a necessary additive for the

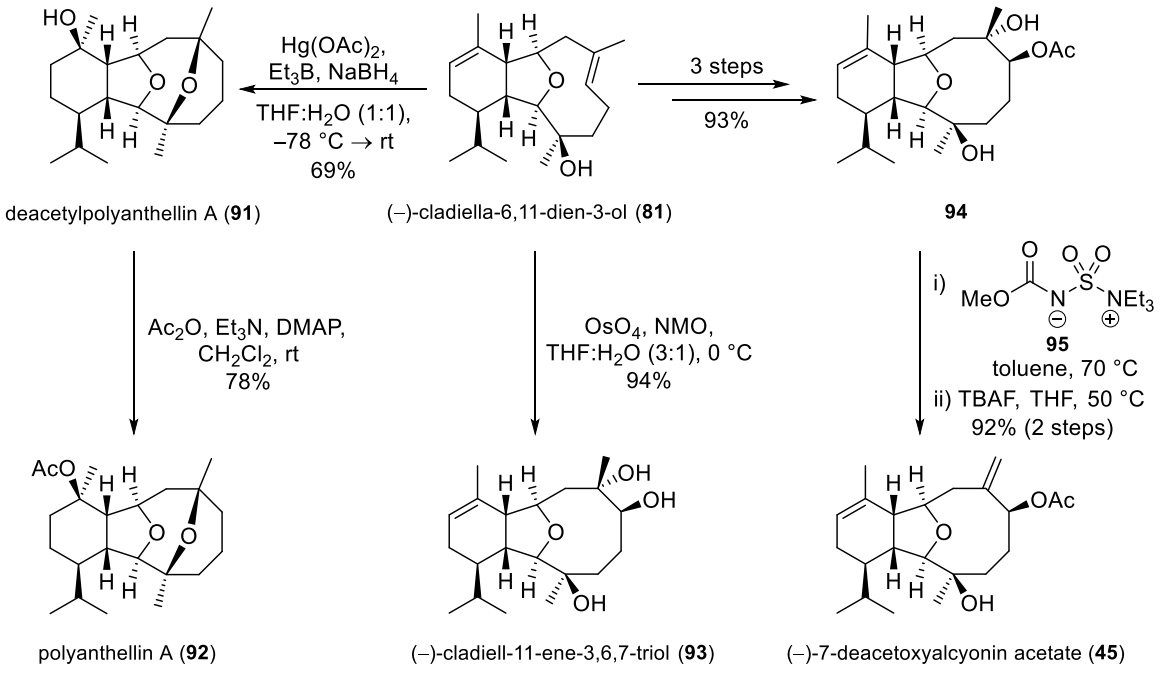
Diels–Alder cycloaddition to proceed as required and complete decomposition of the precursor was observed when the reaction was performed in its absence.

The synthesis of tricycle **89** was followed by double methylation of the *exo*-methyl ester followed by acetylation of tertiary alcohol and chemoselective deoxygenation with concomitant cleavage of trityl ether, which produced alcohol **90** in three steps (Scheme 15).[40] Finally, the synthesis of (−)-cladiella-6,11,dien-3-ol (**81**) was completed through an oxidation-Grignard addition sequence to introduce the methyl group and the last stereocentre. This was accomplished through oxidation of the secondary alcohol with DMP followed by addition of MeLi in the presence of sodium tetrafluoroborate.[41]



*Scheme 15: Completion of (−)-Cladiella-6,11,dien-3-ol (**81**)*

(−)-Cladiella-6,11,dien-3-ol (**81**) was used as a late-stage intermediate for the synthesis of a further four cladiellin natural products (Scheme 16).



*Scheme 16: Synthesis of Four Cladiellin Members from (−)-Cladiella-6,11,dien-3-ol (**81**)*

(−)-Cladiella-6,11,dien-3-ol (**81**) was converted into deactylpolyanthellin A (**91**) through an oxymercuration-demercuration process and acetylation of the tertiary alcohol produced polyanthellin A (**92**) thereafter. Treatment of (−)-cladiella-6,11,dien-3-ol (**81**) under Upjohn dihydroxylation conditions afforded (−)-cladiell-11-ene-3,6,7-triol (**93**) in excellent yield.[42] (−)-Cladiella-6,11,dien-3-ol (**81**) was also converted into diol **94** by use of a three-step route. Exposure of diol **94** to Burgess reagent (**95**) resulted in formation of the exocyclic alkene by regioselective elimination of the tertiary alcohol,[43] and subsequent deprotection gave (−)-7-deacetoxyalcyonin acetate (**45**) in 92% yield over two steps.

1.3.5 Hoppe Group Strategy: Asymmetric Homo-aldol and Ring-closing Metathesis

In 2008, Hoppe and co-workers reported an enantioselective synthesis of (+)-vigulariol (**96**), which was completed in just 10 linear steps (Figure 12).[44] Paquette and co-workers had synthesised (+)-vigulariol in 2001 during their synthesis of sclerophytin A (**59**), but at that time this compound had not been isolated as a natural product and the compound was not fully characterised (Section 1.3.2).[31] The key steps used by Hoppe and co-workers in their synthesis of (+)-vigulariol were an asymmetric homo-aldol reaction, an application of Krämer's THF synthesis to build up the bicycle and a RCM reaction to close the nine-membered ring.[45]

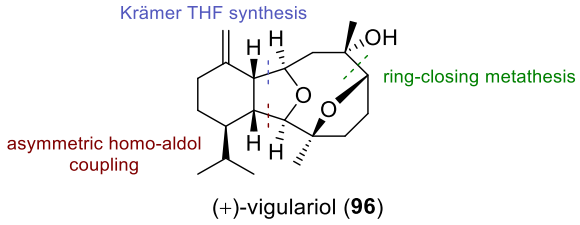
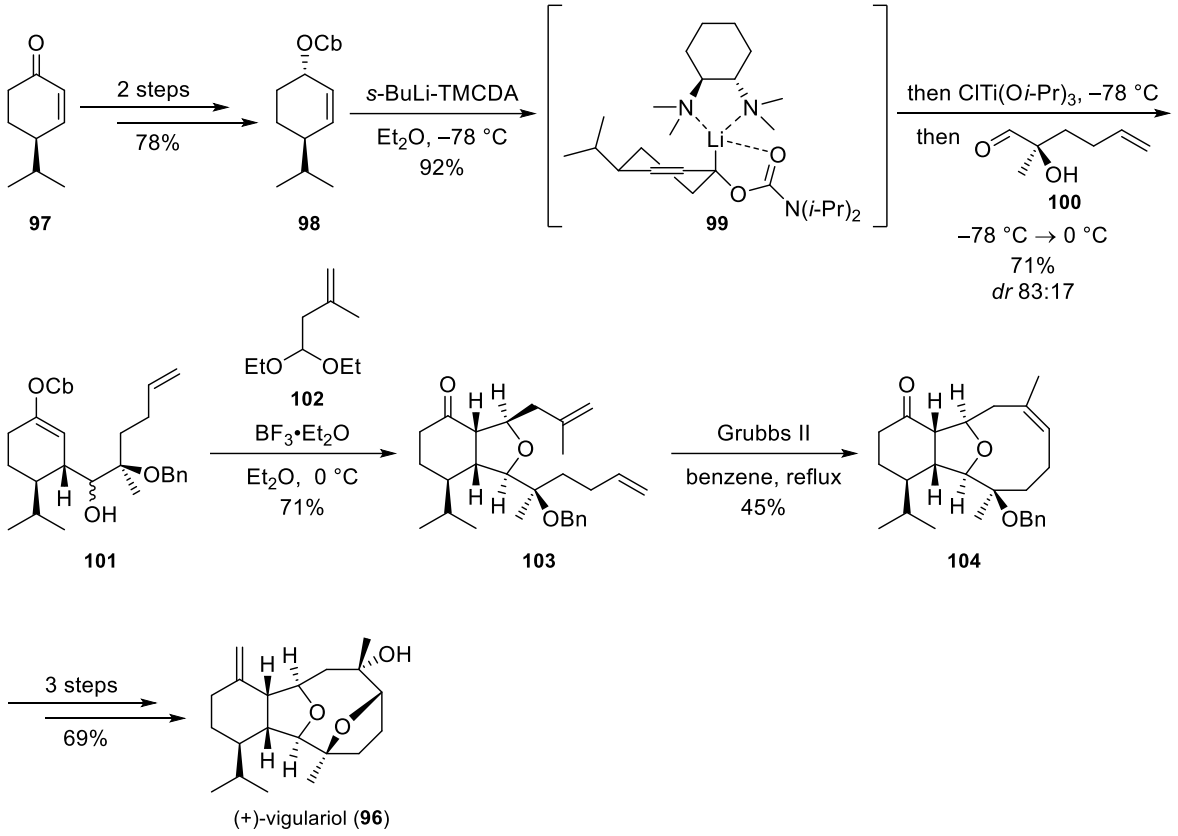


*Figure 12: Key Disconnections in the Synthesis of (+)-Vigulariol (**96**)*

The synthesis started with (−)-cryptone **97**, obtained from commercially available eucalyptus oil through flash column chromatography, which was reduced to give an allylic alcohol that was then converted into the carbamate **98** (Scheme 17).



*Scheme 17: Total Synthesis of (+)-Vigulariol (**96**)*

Stereoselective deprotonation of carbamate **98** with *s*-butyl lithium in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane gave lithiated intermediate **99**. Addition of chlorotriisopropoxytitanium and reaction of the enolate with aldehyde **100** delivered a diastereomeric mixture of alcohols **101** (*dr* 83:13). Lewis acid-promoted condensation of alcohols **101** with acetal **102** gave bicyclic ether **103** in a yield of 71%. Subsequent RCM of diene **103** to close the nine-membered ring gave tricyclic ketone **104** in 45% yield. From ketone **104**, the synthesis of (+)-vigulariol (**96**) was completed in just three further steps.

1.3.6 Johnson Group Strategy: [3+2]-Cycloaddition and Ring-closing Metathesis

In 2009, Johnson and co-workers completed the second asymmetric synthesis of polyanthellin A (**92**) after that of Kim and co-workers in 2006.[46] The key reactions in the strategy employed by Johnson and co-workers included a [3+2]-cycloaddition reaction and RCM (Figure 13).

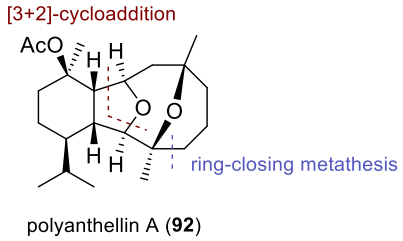
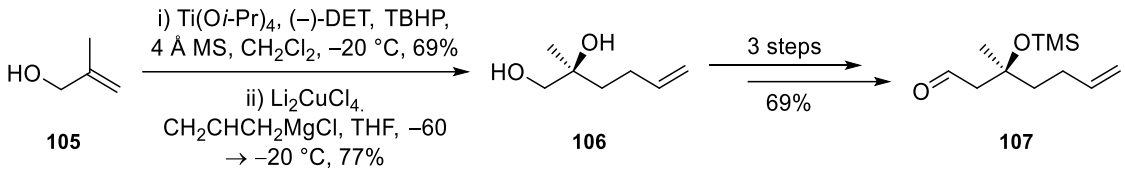


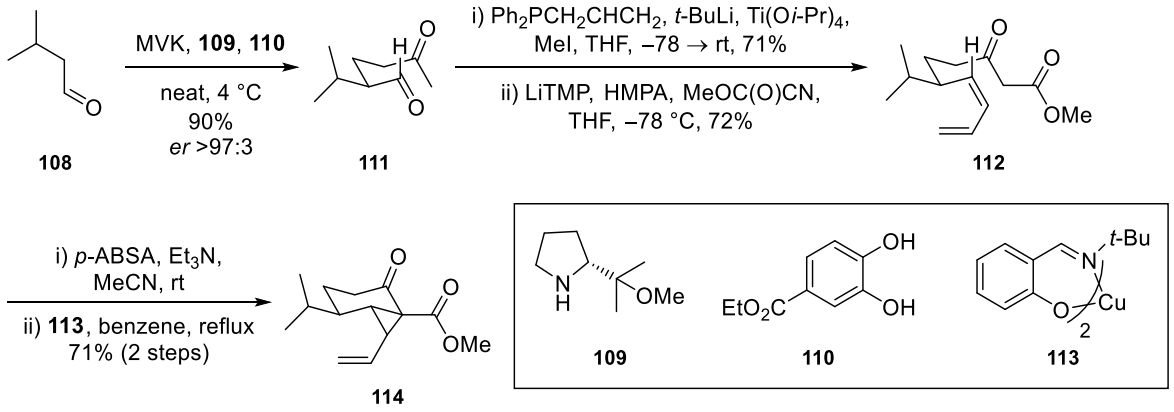
*Figure 13: Key Disconnections in the Synthesis of Polyanthellin A (**92**)*

The Johnson synthesis started with a Sharpless epoxidation of allylic alcohol **105** to create what was to become the C-7 stereocentre with the required configuration followed by cuprate addition to open the epoxide and produce diol **106** (Scheme 18).[47] A further three steps were required to form aldehyde **107**.



*Scheme 18: Synthesis of Enantioenriched Aldehyde **107***

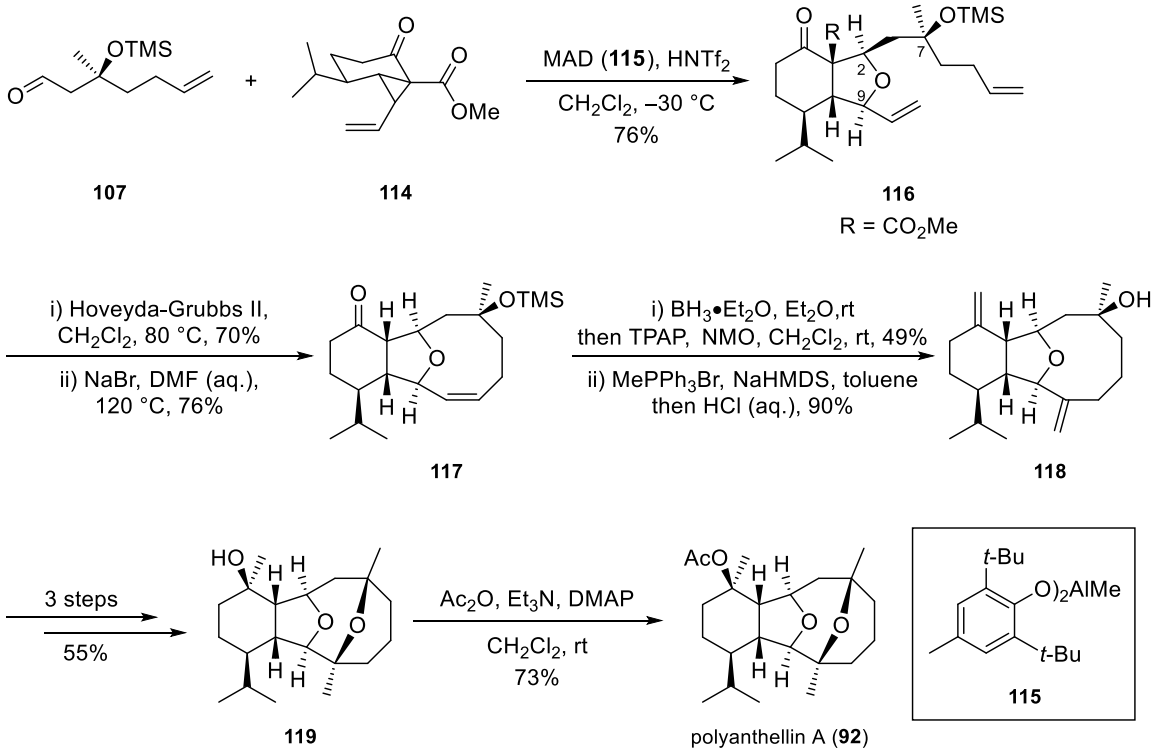
Aldehyde **107** was one component to be used in their [3+2]-cycloaddition reaction. The synthesis of the second component – bicyclo[4.1.0]heptanone **114** – started with an enantioselective organocatalytic conjugate addition reaction of isovaleraldehyde **108** to methyl vinyl ketone to give keto aldehyde **111** (Scheme 19). Johnson and co-workers found the addition of catechol **110** increased both the reaction rate and the yield.



*Scheme 19: Construction of Cyclopropane **114***

From here, keto aldehyde **111** underwent selective Wittig olefination of the aldehyde to give the *Z*-diene and subsequent carboalkoxylation using Mander's reagent giving β-ketoester **112**.[48] Cyclopropanation of dicarbonyl **112** was performed by diazotisation of the β-ketoester followed copper-catalysed intramolecular cyclopropanation using complex **113** to give bicyclo[4.1.0]heptanone **114** in 71% yield over two steps.

The [3+2]-cycloaddition of aldehyde **107** and bicyclo[4.1.0]heptanone **114** was accomplished using the sterically hindered catalyst MADNTf$_2$, which helped drive the formation of bicyclic ether **116** (Scheme 20).



*Scheme 20: Completion of Polyanthellin A (**92**)*

RCM of diene **116** followed by decarboxylation under Krapcho conditions delivered tricyclic ketone **117**.[49] Hydroboration of the tricyclic alkene **117** and TPAP oxidation of the intermediate organoborane led to formation of a diketone which then underwent double Wittig methylenation to produce diene **118**. From here, the synthesis of polyanthellin A (**92**) was completed in a further four steps; the synthesis was accomplished in a total of 15 linear steps.

1.3.7 Morken Group Strategy: Oshima–Utimoto Reaction, Radical Cyclisation and Ring-closing Metathesis

The total synthesis of (−)-sclerophytin A (**59**) has been accomplished several times, but Morken and co-workers reported the shortest total synthesis to date in 2010 (13 steps).[50] The key features of their synthesis were the use of an Oshima–Utimoto reaction to construct the reduced furan, a radical cyclisation reaction to form the hydroisobenzofuran and RCM to close the nine-membered ring forming the oxonene (Figure 14).

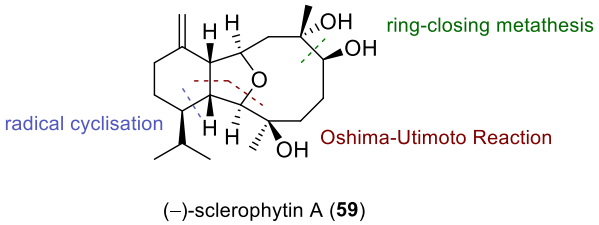
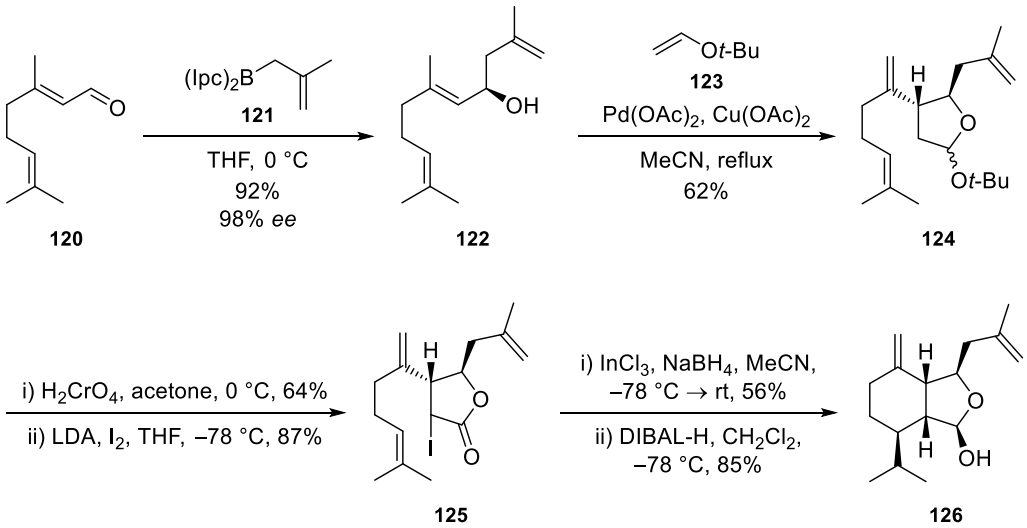


*Figure 14: Key Disconnections in the Synthesis of (−)-Sclerophytin A (**59**)*

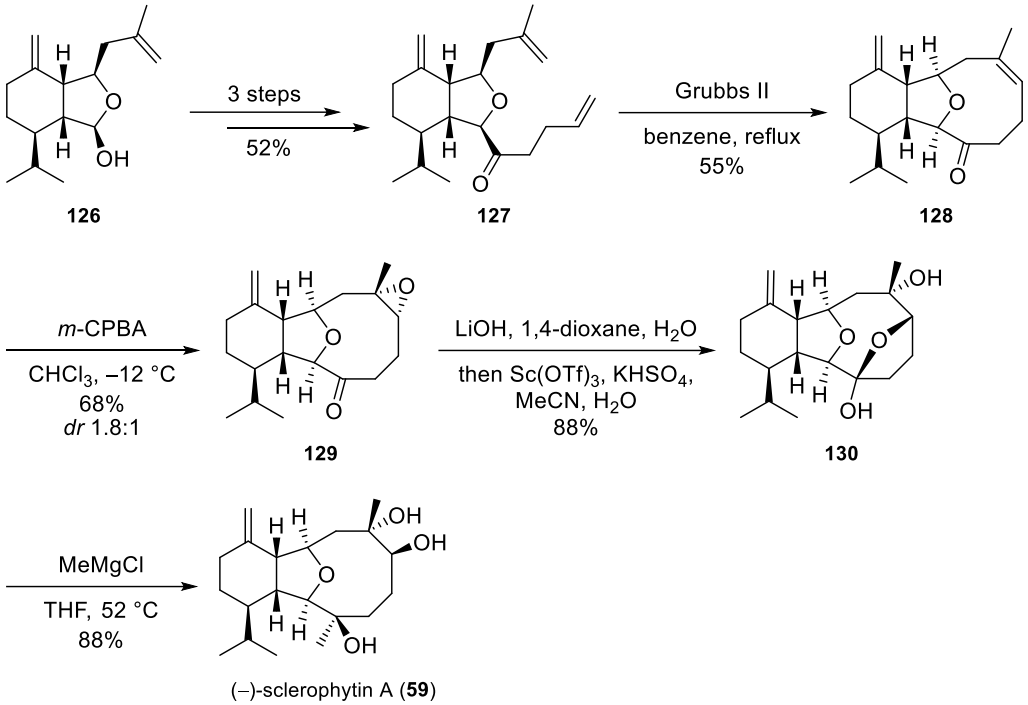
The synthesis started with Brown methallyation of geranial **120** to give allylic alcohol **122** which was subjected to Oshima–Utimoto reaction to deliver THF **124** (Scheme 21).[51,52] This was followed by subsequent Jones oxidation then α-iodination of the lactone to give iodide **125**.



*Scheme 21: Synthesis of Bicycle **126** through Radical Cyclisation*

Radical cyclisation under reductive conditions using indium trichloride and sodium borohydride followed by diisobutylaluminium hydride reduction of lactone delivered lactol **126** with excellent selectivity (>10:1). Lactol **126** was then converted into triene **127** in a

further 3 steps (Scheme 22). Oxonene **128** was synthesised from triene **127** by RCM in a 55% yield.



*Scheme 22: Completion of (−)-Sclerophytin A (**59**)*

Regioselective epoxidation (*dr* 1.8:1) delivered epoxide **129** which then was treated with lithium hydroxide followed by scandium triflate and potassium bisulfate to give the lactol **130**. This reaction occurs through initial hydroxide addition to the ketone followed by attack of the resulting alcohol to spontaneously cyclise, mediated by scandium triflate with potassium bisulfate acting as a mild base which was described by Clark in 2007.[53] Finally, subjection of lactol **130** to a Grignard addition reaction with methyl magnesium chloride gave (−)-sclerophytin A (**59**).

1.3.8 Yang Group Strategy: Gold-catalysed Cascade and Ring-closing Metathesis

In 2014, Yang and co-workers reported the synthesis of nine members of cladiellin family of natural products stemming from a common intermediate.[54] Their strategy relied upon the gold-catalysed tandem reaction of a 1,7-diyne to construct the reduced benzofuran core before RCM to form the oxonene (Figure 15).

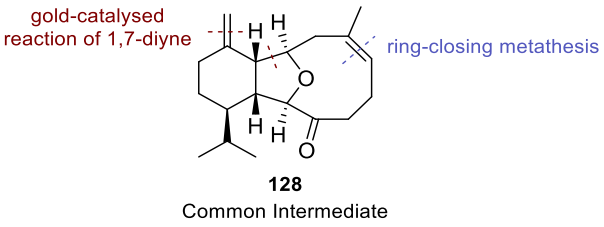
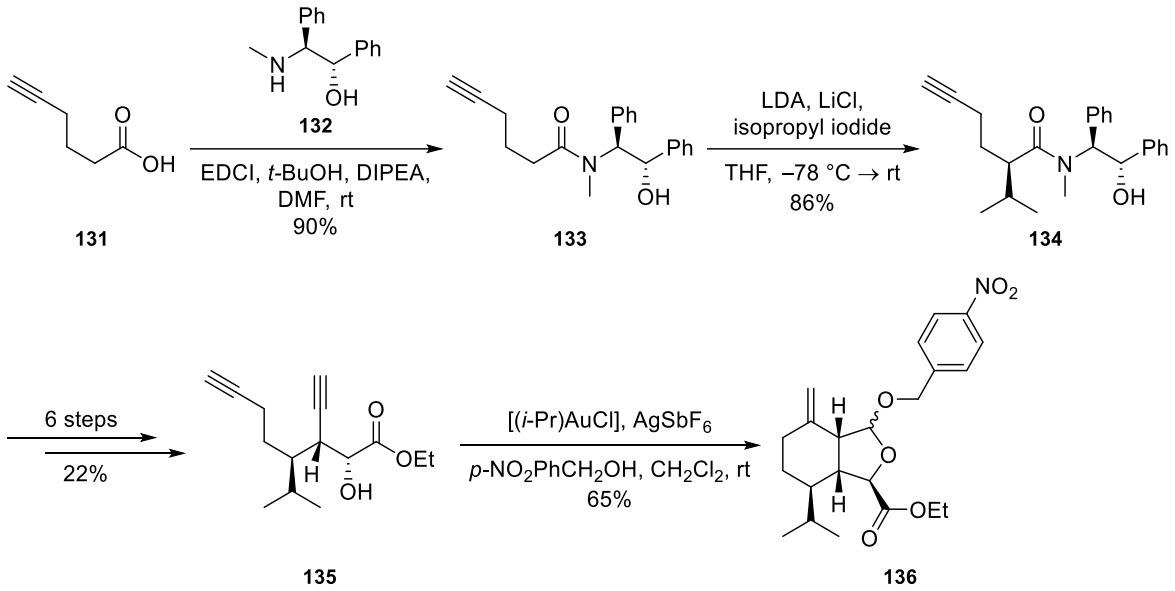


*Figure 15: Key Disconnections in the Synthesis of Common Intermediate **128***

Their synthesis started from commercially available hex-5-ynoic acid **131** which was coupled with amine **132** using EDCI to give amide **133** (Scheme 23). Diastereoselective α-alkylation using lithium diisopropylamine followed by addition of isopropyl iodide gave amide **134**.

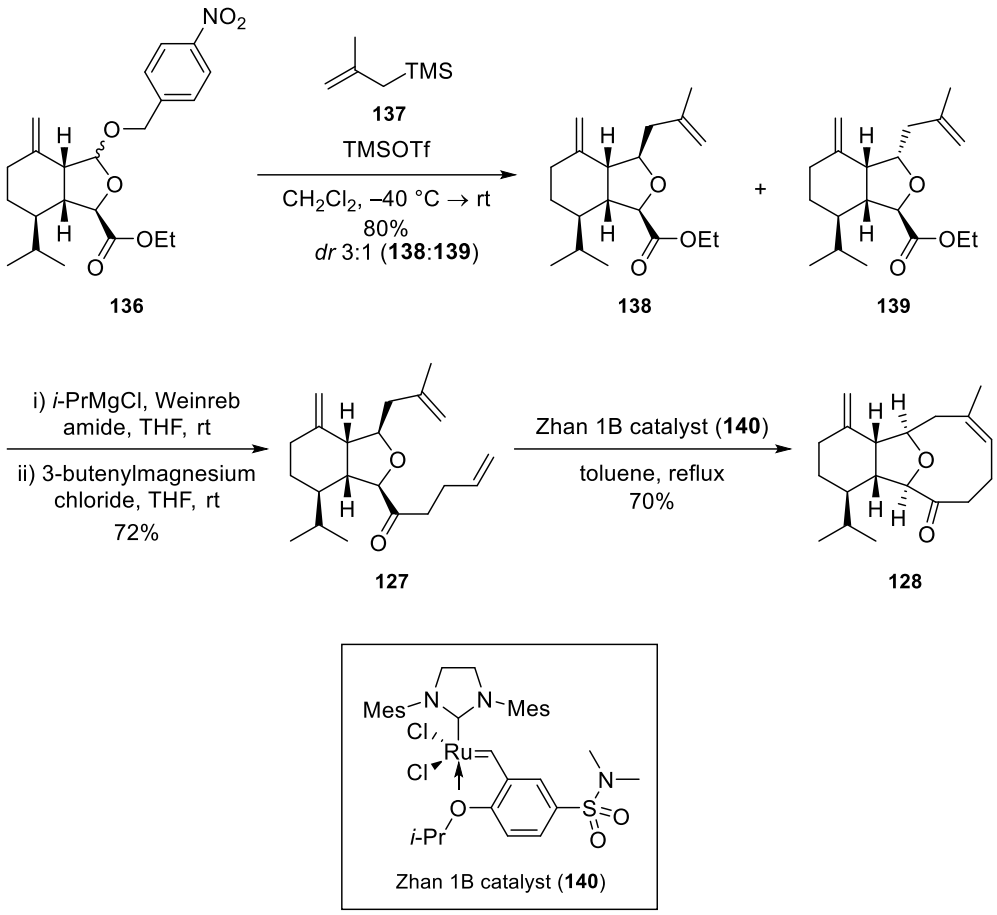


*Scheme 23: Synthesis of Bicyclic Core **136** of the Common Intermediate*

Amide **134** was then converted into 1,7-diyne **135**, the precursor to the key gold-catalysed cascade reaction, in a further six steps. 1,7-Diyne **135** underwent rearrangement in the presence of a gold-catalyst and *p*-nitrobenzyl alcohol to produce the reduced benzofuran **136**. This product was obtained as a mixture of diastereoisomers (*dr* 3:1) and these isomers were used the next reaction before the resulting isomeric compounds were separated.

The bicyclic intermediate **136** was reacted with TMSOTf and excess (methylallyl)trimethylsilane **137** to give diastereoisomeric dienes **138** and **139** (Scheme 24).

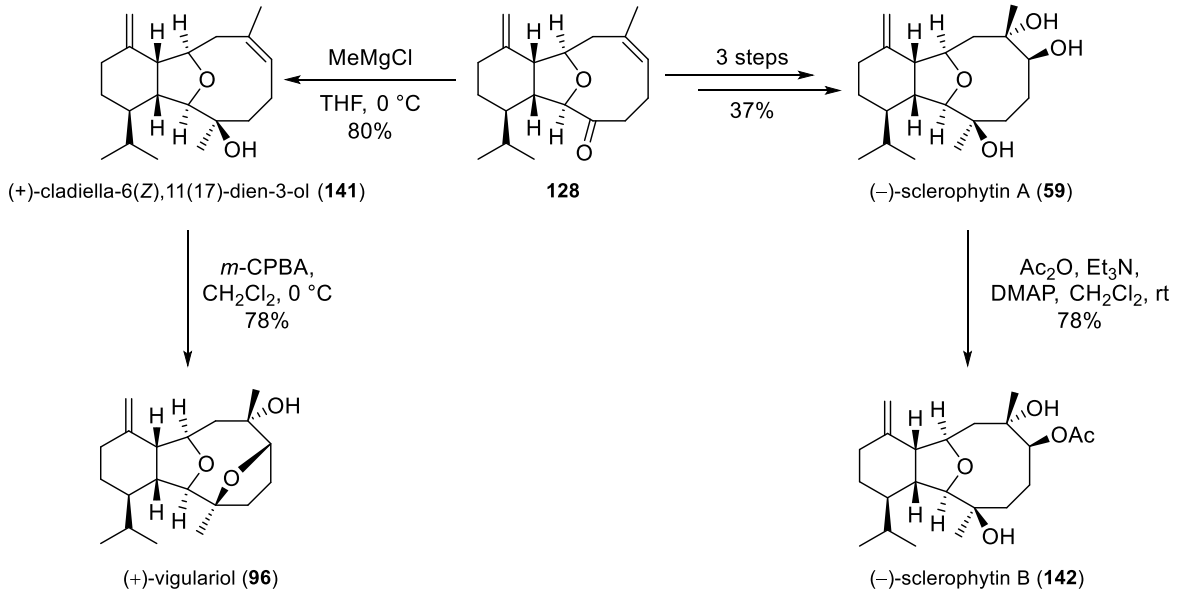
Ester **138** was then converted to the triene **127** by formation of the Weinreb amide followed by the Grignard addition of 3-butenylmagnesium chloride.



*Scheme 24: Synthesis of Common Tricyclic Intermediate **124***

The final step necessary to prepare the advanced tricyclic intermediate **128** was RCM to form the oxonene. Initially, Yang and co-workers utilised the conditions that had been described by Morken and co-workers, but they found use of the Zhan 1B catalyst **140** resulted in a significant increase in the yield of the RCM reaction.[50,55]

Nine members of the cladiellin family were synthesised from the ketone **128** following protocols similar to those previously discussed (Scheme 25). Ketone **128** was converted into (+)-cladiella-6(*Z*)-11(17)-dien-3-ol (**141**) by reaction with methyl magnesium chloride. This alcohol was then oxidised with *m*-CPBA to deliver (+)-vigulariol (**96**).



*Scheme 25: Synthesis of Four Members of the Cladiellin Family from Common Intermediate **128***

The ketone **128** was also converted into (−)-sclerophytin A (**59**) in three steps before acetylation gave (−)-sclerophytin B (**142**). Five further members of the cladiellin family were synthesised from this late-stage intermediate but this work will not be described in detail (Figure 16).

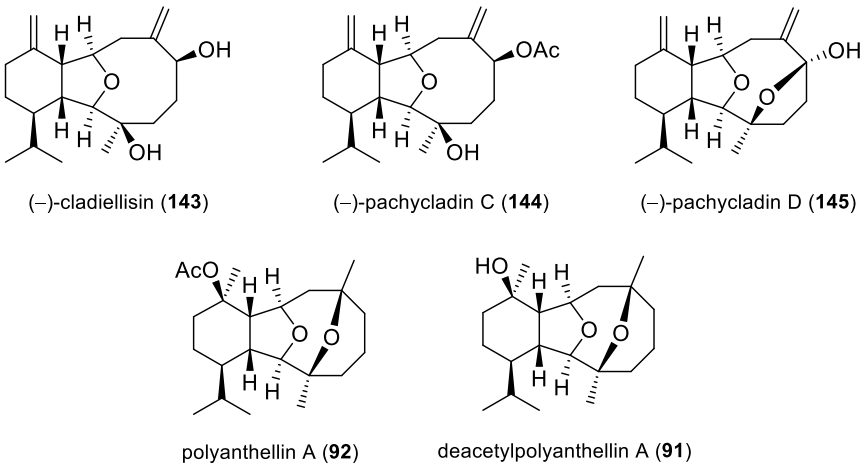
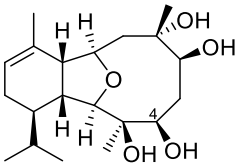


Figure 16: Five Further Members of the Cladiellin Family Synthesised by Yang and Co-workers

1.3.9 Inoue Group Strategy: Radical Polar Crossover Coupling Reaction and Ring-closing Metathesis

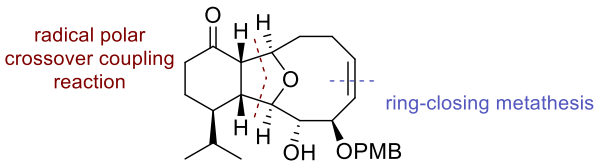
Recently, Inoue and co-workers have published work that is directed towards the synthesis of cladieunicellin D (**146**) in which the tricyclic core is built up in concise fashion (Figure 17).[56] A key difference in this synthesis is the requirement to install the additional hydroxyl group that is present at the C-4 position.



cladieunicellin D (**146**)

*Figure 17: Structure of Cladieunicellin D (**146**)*

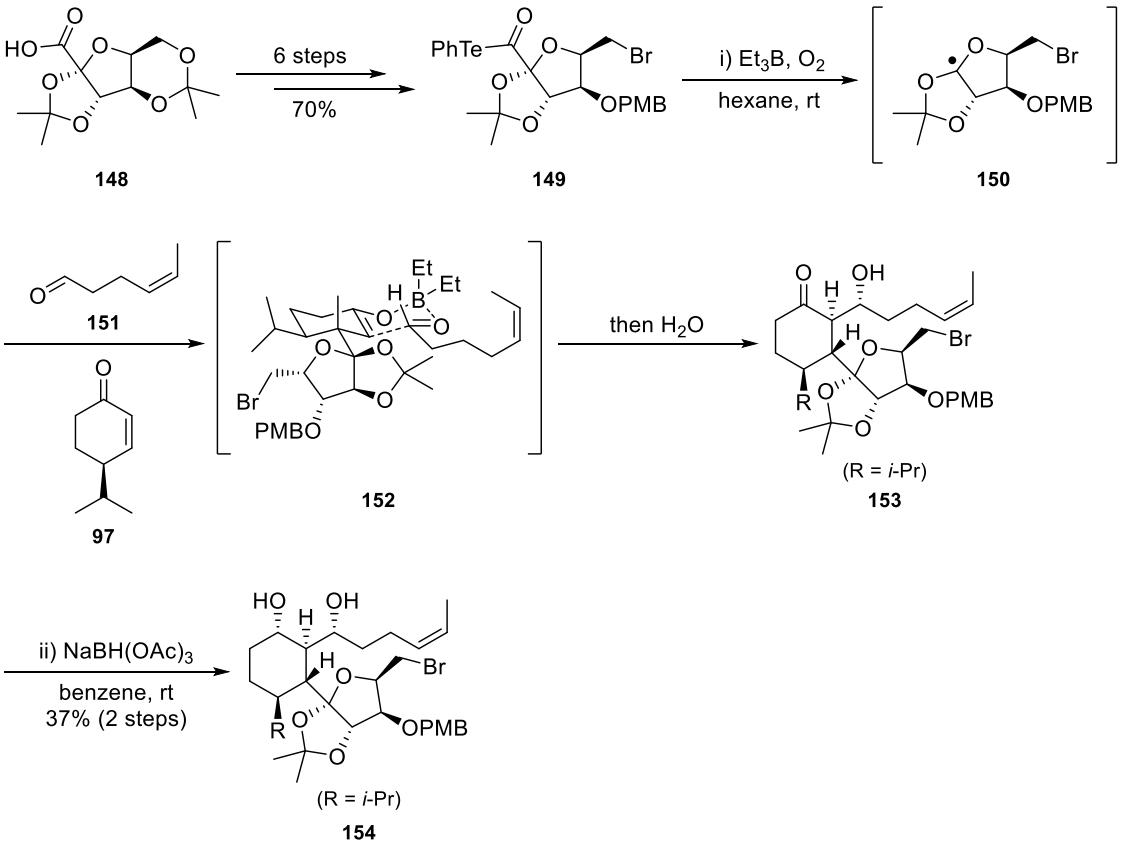
The synthesis of this tricyclic core relied on the use of a three-component radical coupling reaction and a subsequent rearrangement reaction to give the reduced benzofuran core (Figure 18).[57,58] The oxonene could then be completed using RCM.[56]



tricyclic core **147**

*Figure 18: Key Disconnections in Synthesis of Tricyclic Core **147** of Cladieunicellin D (**146**)*

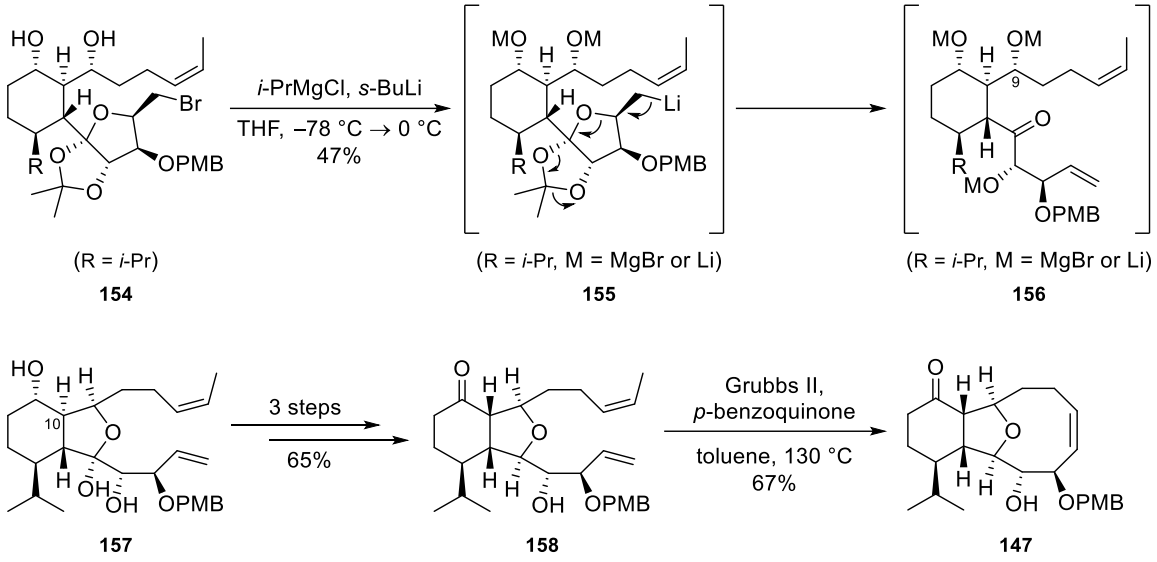
For the three-component radical coupling reaction, α-alkoxyacyl telluride **149** was used as the radical precursor. This intermediate was synthesised in six steps from commercially available diprogulic acid **148** (Scheme 26).



Scheme 26: Radical Polar Crossover Coupling Reaction Sequence

Treatment of α-alkoxyacyl telluride **149** with triethylborane under air produced the radical **150** which then reacted with radical acceptor (−)-cryptone **97** to give a boron enolate. The enolate was trapped by *Z*-4-hexenal **151** in an aldol reaction that proceeded through transition state **152** to give product **153** after aqueous work-up. This β-hydroxyketone was then reacted with sodium triacetoxyborohydride to give diol **154** in a 37% yield over two steps.

From here, the diol **154** was converted into the bicyclic intermediate **157** by sequential addition of isopropyl magnesium chloride and *sec*-butyl lithium which resulted in reductive cleavage of the bromo ether (Scheme 27).



*Scheme 27: Synthesis of Tricyclic Core **147** of Cladieunicellin D (**146**)*

Initially, both hydroxyl groups are deprotonated with isopropyl magnesium chloride then lithium-halogen exchange occurs to give lithiated intermediate **155**. This intermediate then undergoes ring opening with fragmentation to eliminate acetone giving ketone **156** before nucleophilic addition from the C-9 alkoxide to the ketone produces the hemi-acetal **157**. The remaining steps required to form tricyclic core **147** involved reductive etherification to convert hemi-acetal **157** into diene **158** followed by an oxidation and epimerisation sequence to set the stereocentre at C-10. Finally, RCM in the presence of *p*-benzoquinone gave oxonene **147**. This completed the synthesis of the tricyclic core of cladieunicellin D.

2. Clark Group Strategy and Previous Work

The Clark group have been interested in the synthesis of members of the 2,11-cyclised cembranoids for many years, with initial reported studies towards the cladiellins in 2000 and 2006.[59,60] In 2007, Clark and co-workers reported the total synthesis of (±)-vigulariol (**96**) utilising a novel oxonium ylide formation, [2,3]-sigmatropic rearrangement reaction to construct an oxabicyclic intermediate and a subsequent intermolecular Diels–Alder cycloaddition reaction to yield the tricyclic core (Figure 19).[53]

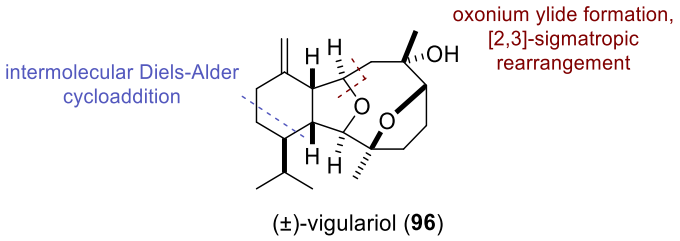
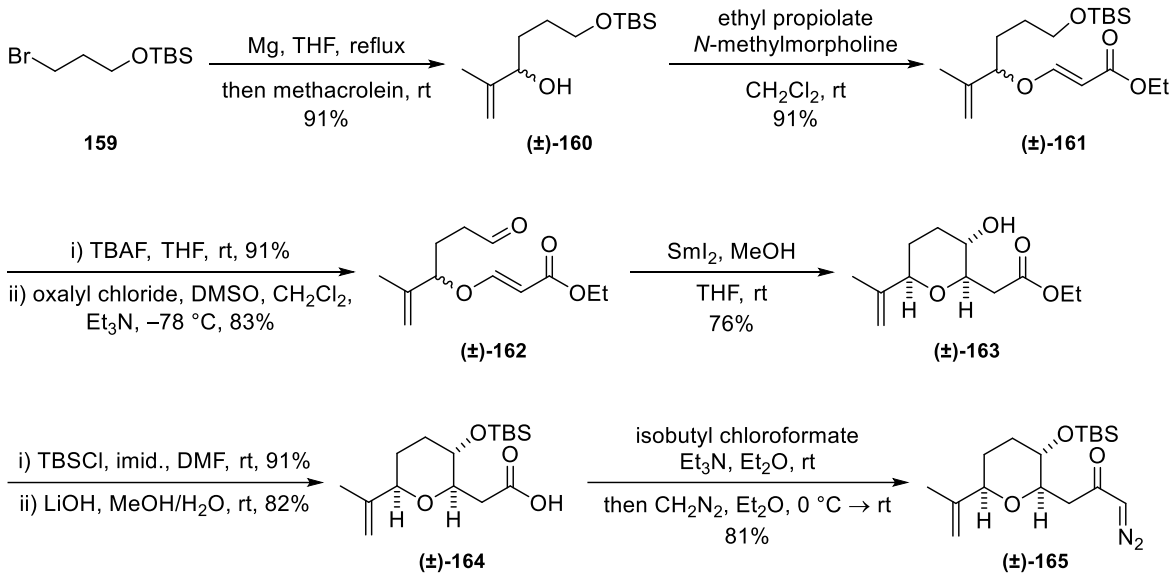


*Figure 19: Clark Group Strategy Towards (±)-Vigulariol (**96**)*

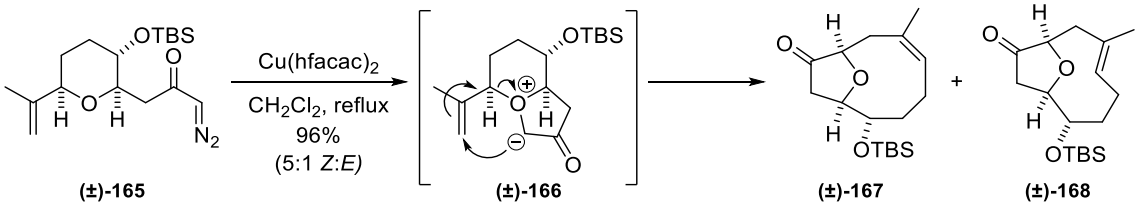
Their synthesis started with addition of the Grignard reagent prepared from bromide **159** to methacrolein to give allylic alcohol **(±)-160** (Scheme 28). Bromide **159** was easily prepared from propan-1,3-diol.[61]



*Scheme 28: Construction of Diazo-ketone **(±)-165***

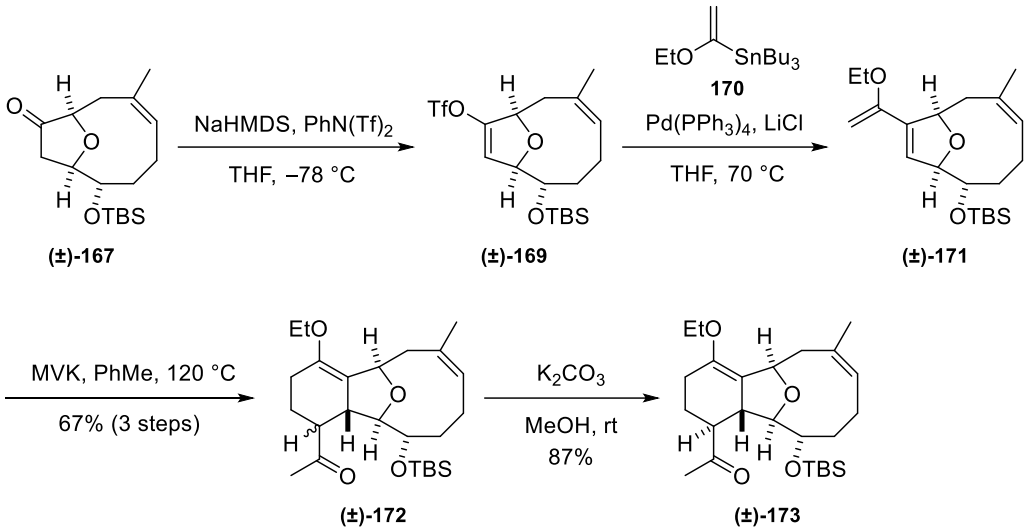
Allylic alcohol **(±)-160** was then converted to α,β-unsaturated ester **(±)-161** through a hetero-Michael addition with ethyl propiolate. Deprotection of the hydroxyl group followed by a Swern oxidation resulted in formation of aldehyde **(±)-162**. Reductive cyclisation mediated by samarium diiodide gave tetrahydropyranol **(±)-163** which was converted to carboxylic acid **(±)-164** through silyl ether formation and saponification of the ester with lithium hydroxide.[62,63] Finally, diazo-ketone **(±)-165** was synthesised by reaction of the carboxylic acid **(±)-164** with isobutyl chloroformate and treatment of the resulting mixed anhydride with diazomethane to produce diazo-ketone **(±)-165**.

Treatment of the diazo-ketone **(±)-165** with copper hexafluoroacetylacetone produced an electrophilic copper carbenoid that underwent tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement through intermediate **(±)-166** to give a mixture of bicyclic ethers **(±)-167** and **(±)-168** (*Z*:*E*, 5:1) which could be separated by column chromatography (Scheme 29).



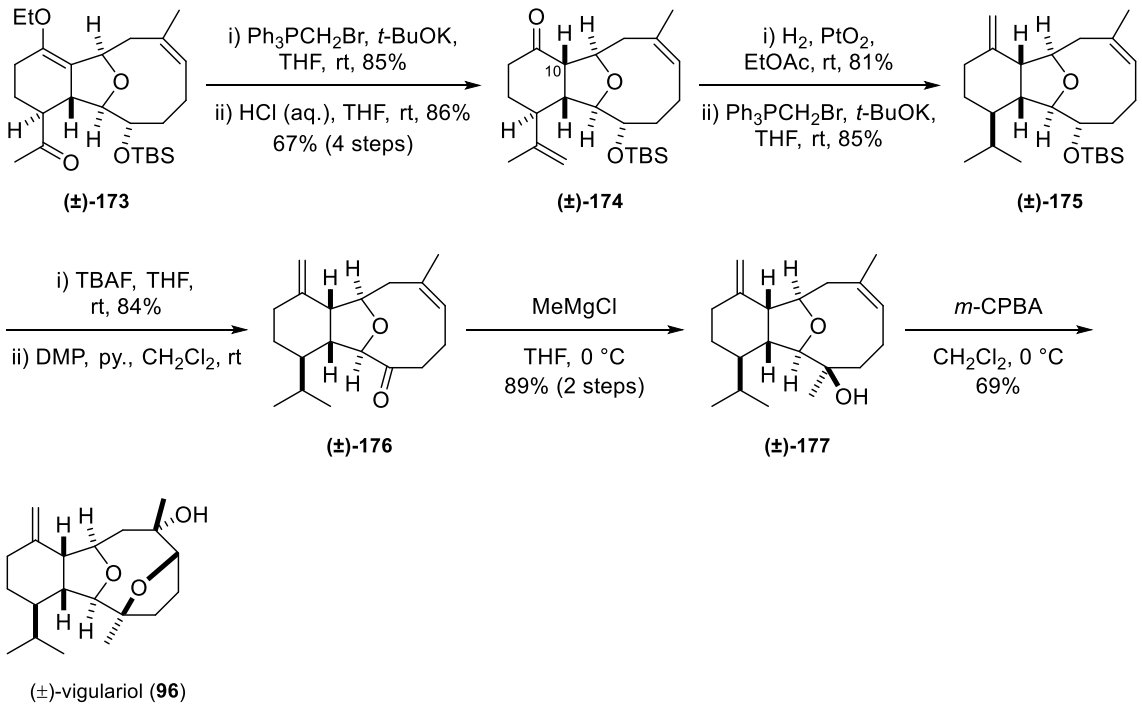
*Scheme 29: Synthesis of Bicycles **(±)-163** and **(±)-164** from Diazo-ketone **(±)-165***

The *Z*-bicyclic ketone **(±)-167** was subjected to the Stille/Diels–Alder cycloaddition sequence to build up the tricyclic core. This started with conversion of *Z*-bicyclic ketone **(±)-167** into the enol triflate **(±)-169** followed by Stille cross-coupling with readily available tributyl(1-ethoxyvinyl)tin **170** to give triene **(±)-171** (Scheme 30).



Scheme 30: Tricyclic Core Formation through Intermolecular Diels–Alder Cycloaddition

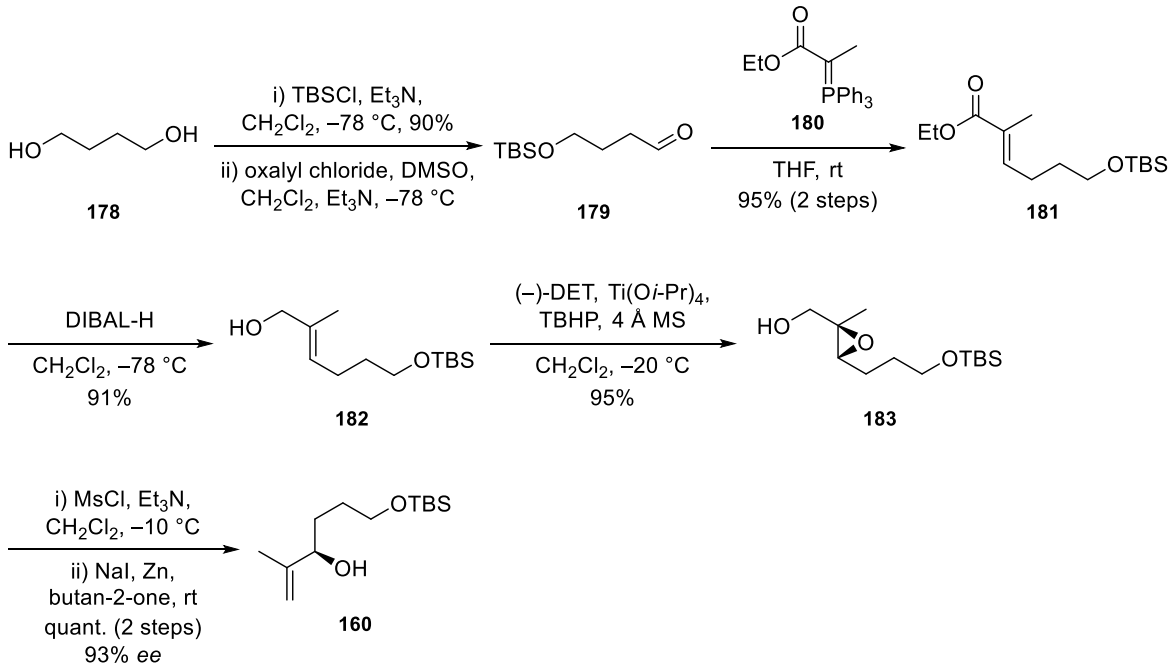
This triene then underwent intermolecular Diels–Alder cycloaddition with methyl vinyl ketone to deliver a 1:1 mixture of *exo*:*endo* adducts **(±)-172** and subsequent epimerisation with potassium carbonate and methanol resulted in formation of the diastereoisomer **(±)-173** exclusively. Wittig methenylation of tricyclic ketone **(±)-173** followed by acid hydrolysis of the enol ether gave ketone **(±)-174** with the required configuration at C-10 (Scheme 31).



*Scheme 31: Completion of (±)-Vigulariol (**96**)*

Hydrogenation of *exo*-alkene and a second Wittig methenylation reaction produced the diene **(±)-175** which was converted to ketone **(±)-176** by deprotection followed by oxidation of the resulting alcohol. The ketone **(±)-176** then underwent Grignard addition with methyl magnesium chloride giving alcohol **(±)-177** setting the stereocentre of the tertiary alcohol with the required configuration. The final step of the synthesis was selective epoxidation of the tri-substituted alkene with concomitant nucleophilic epoxide opening to give (±)-vigulariol (**96**).

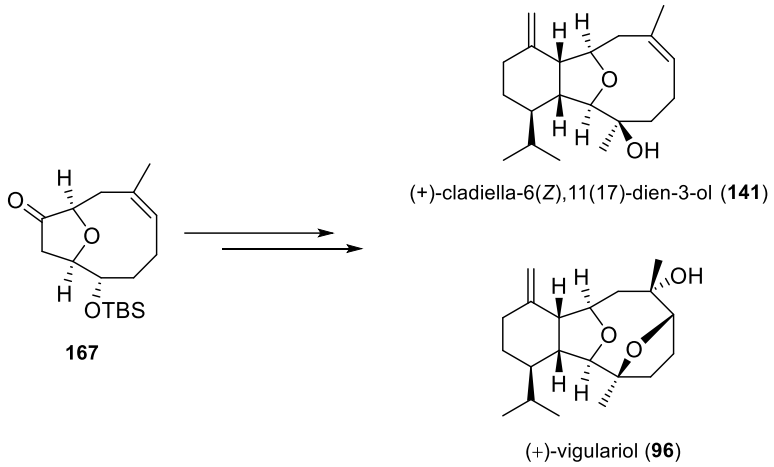
This route to racemic vigulariol was used as a basis for the enantioselective synthesis of multiple members of the cladiellin family.[64,65] In this case, the synthesis commenced with commercially available butan-1,4-diol **178** which was converted to aldehyde **179** by mono-silyl protection and Swern oxidation (Scheme 32).



*Scheme 32: Enantioenriched Synthesis of Allylic Alcohol **160***

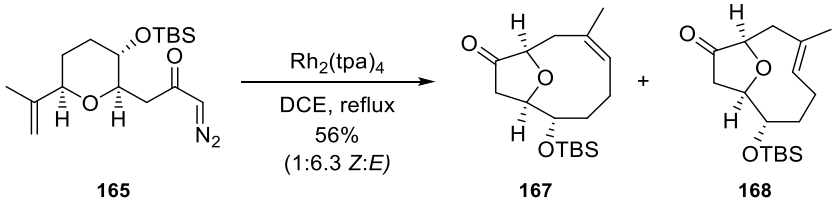
Aldehyde **179** underwent Wittig olefination with stabilised ylide **180** to give α,β-unsaturated ester **181** in excellent yield and with high selectivity. The ester was reduced with diisobutylaluminium hydride to give allylic alcohol **182** before a Sharpless epoxidation reaction gave epoxide **183**. Mesylate formation on the primary alcohol followed by displacement by sodium iodide and zinc-mediated epoxide opening gave enantioenriched allylic alcohol **160** in excellent yield over two steps and with a high enantiomeric excess (93% *ee*).

Enantioenriched allylic alcohol **160** was then into *Z*-bicyclic ketone **167** using the same route previously employed in the synthesis of (±)-vigulariol. From here, the enantioselective syntheses of (+)-cladiella-6(*Z*),11(17)-dien-3-ol (**141**) and (+)-vigulariol (**96**) were completed following a similar route to that previously discussed (Scheme 33).[64]



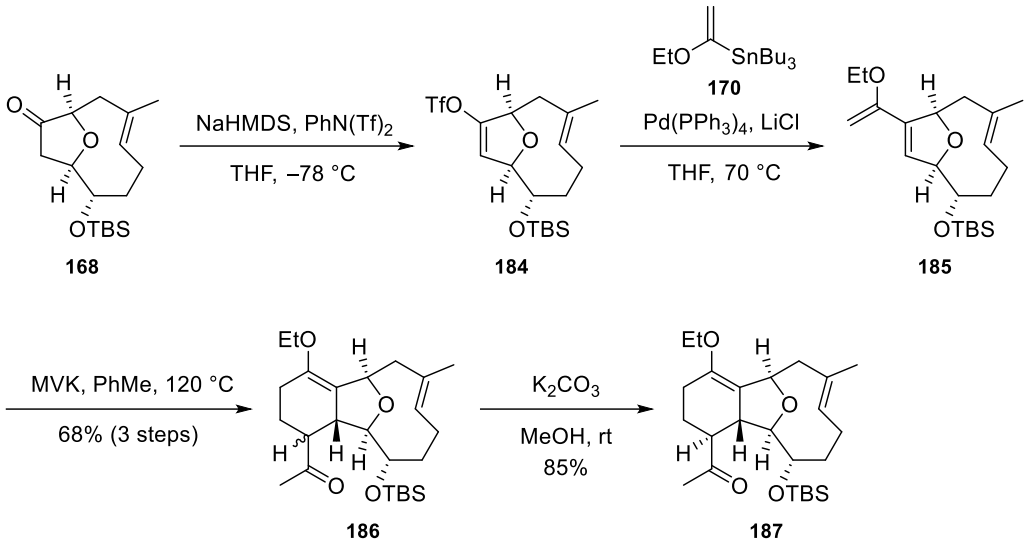
*Scheme 33: Members of Cladiellin Family Synthesised from Z-Bicyclic Ketone **167***

The Clark group then used *E*-bicyclic ketone **168** as a key intermediate for the synthesis of further members of the cladiellin family.[64,66] This approach required conversion of diazo-ketone **165** selectively into *E*-bicyclic ketone **168** instead of the previously favoured *Z*-bicyclic ketone **167** (Scheme 34). This involved switching from a copper catalyst (5:1, *Z*:*E*) to a rhodium catalyst (1:6.3, *Z*:*E*).



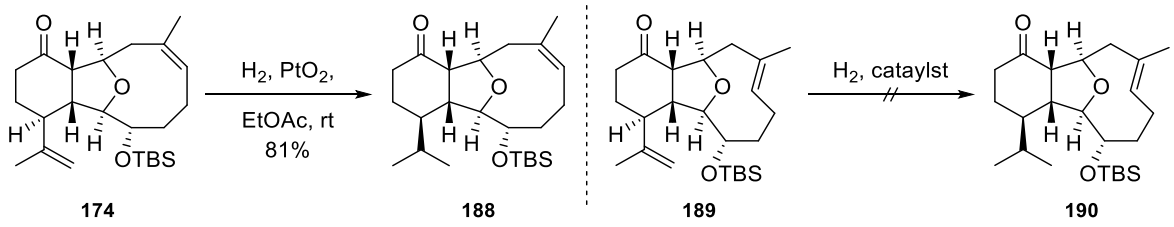
*Scheme 34: Conversion of Diazo-ketone **165** Under Rhodium Catalysis*

The *E*-bicyclic ketone **168** was converted into the tricyclic core of the cladiellins by a the Stille/Diels–Alder cycloaddition sequence that was analogous to the one used before (Scheme 35).



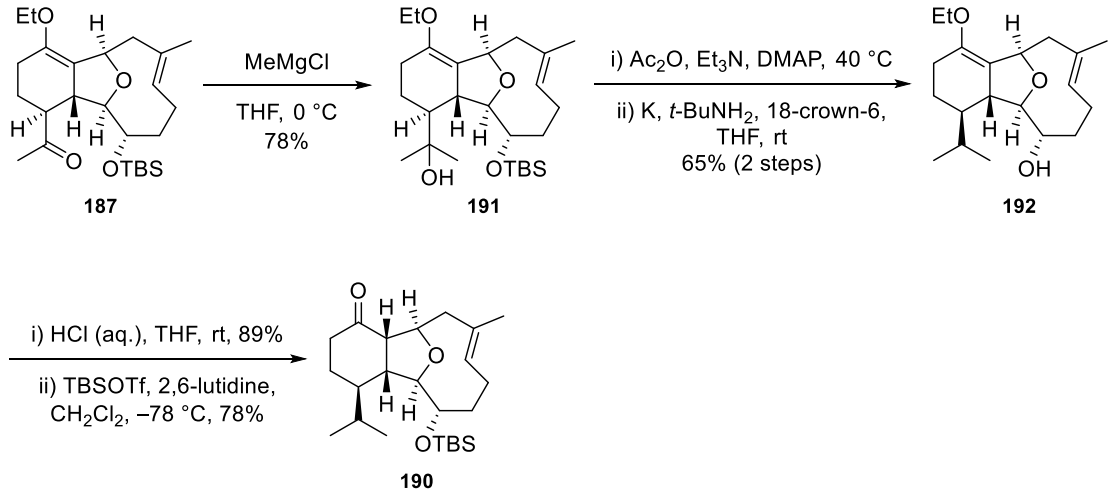
*Scheme 35: Stille/Diels–Alder Cycloaddition Sequence of E-Bicyclic Ketone **168***

An important difference between routes of the *Z*- and *E*-tricyclic cores was the reactivity of the tri-substituted alkene in each case. Previously, selective hydrogenation of an *exo*-alkene was used to install the isopropyl group but this approach was not possible with the *E*-alkene (Scheme 36).[66]



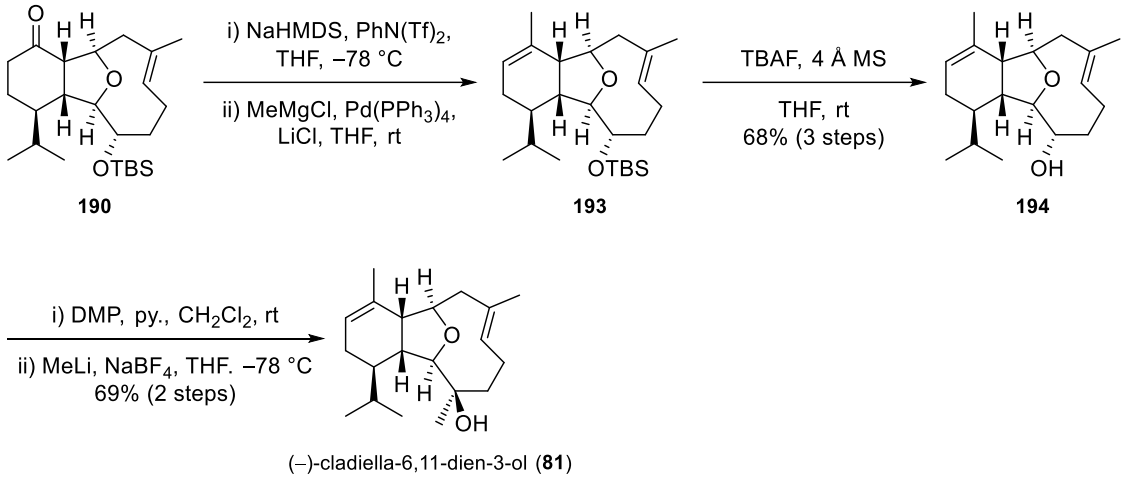
*Scheme 36: Attempted Hydrogenation of E-Tricyclic Ketone **189***

To overcome this problem, the tricyclic ketone **187** was converted into alcohol **191** by a Grignard addition reaction with methyl magnesium chloride (Scheme 37). Acetylation of alcohol **191** followed by reductive removal of the acetate gave tricyclic alcohol **192**. Prevention of silyl deprotection of the secondary alcohol was not possible so reprotection of secondary alcohol using TBSOTf was necessary after hydrolysis of the enol ether.



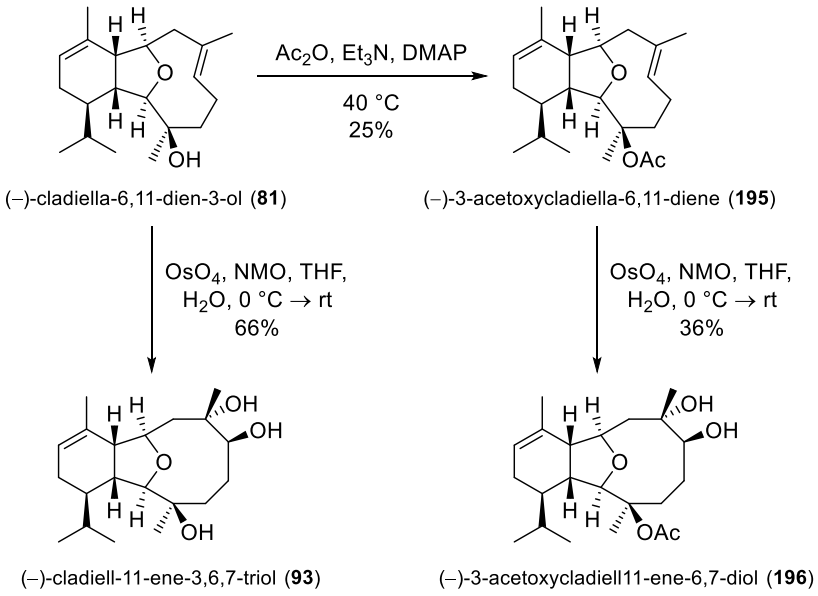
*Scheme 37: Elaboration of Tricyclic Ketone **187** to Overcome Hydrogenation Incompatibility*

The resulting ketone **190** was converted into diene **193** through vinyl triflate formation and a palladium-catalysed Kumada-type coupling with methyl magnesium chloride (Scheme 38).



*Scheme 38: Synthesis of (−)-Cladiella-6,11-dien-3-ol (**81**)*

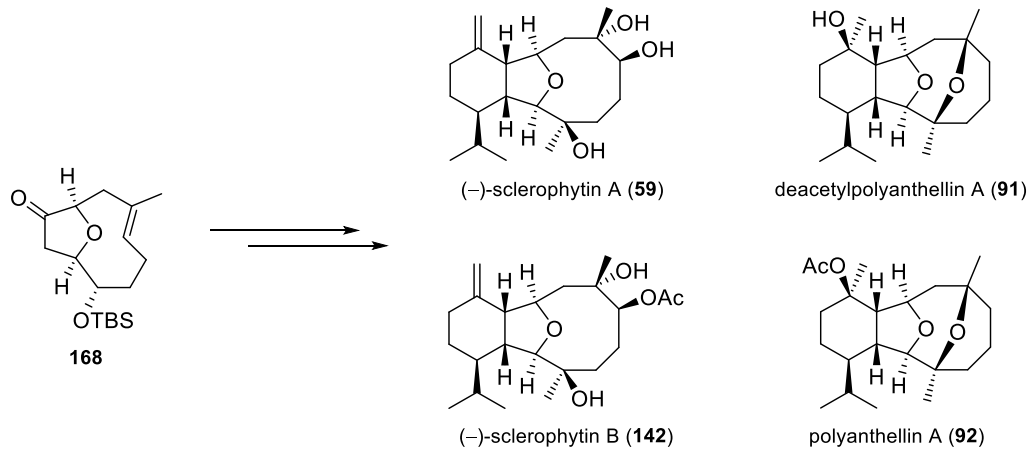
Diene **193** then underwent deprotection followed by oxidation and methyl addition to give (−)-cladiella-6,11-dien-3-ol (**81**).[64,66] This natural product was then used an intermediate to prepare other cladiellins. Kim and co-workers had previously reported that (−)-cladiell-11-ene-3,6,7-triol (**93**) could be obtained by dihydroxylation of (−)-cladiella-6,11-dien-3-ol (**81**, Scheme 39).[37]



*Scheme 39: Synthesis of Multiple Members of the Cladiellin Family from (−)-Cladiella-6,11-dien-3-ol (**81**)*

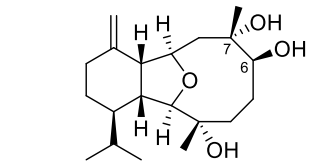
Prior to dihydroxylation, acetylation afforded (−)-3-acetoxycladiella-6,11-diene (**195**) but acetylation proved to be very difficult and a low yield when acetic anhydride was used as the solvent and it was necessary to perform the reaction at 40 °C to observe any conversion. Dihydroxylation of (−)-3-acetoxycladiella-6,11-diene (**195**) resulted in formation of (−)-3-acetoxycladiell-11-ene-6,7-diol (**196**) in modest yield.

The Clark group synthesised four further members of the cladiellin family from *E*-bicyclic ketone **168** (Scheme 40) following similar protocols to those used by Paquette and co-workers and Kim and co-workers as discussed previously.[31,37]



Scheme 40: Four Further Members of the Cladiellin Family Synthesised by the Clark Group

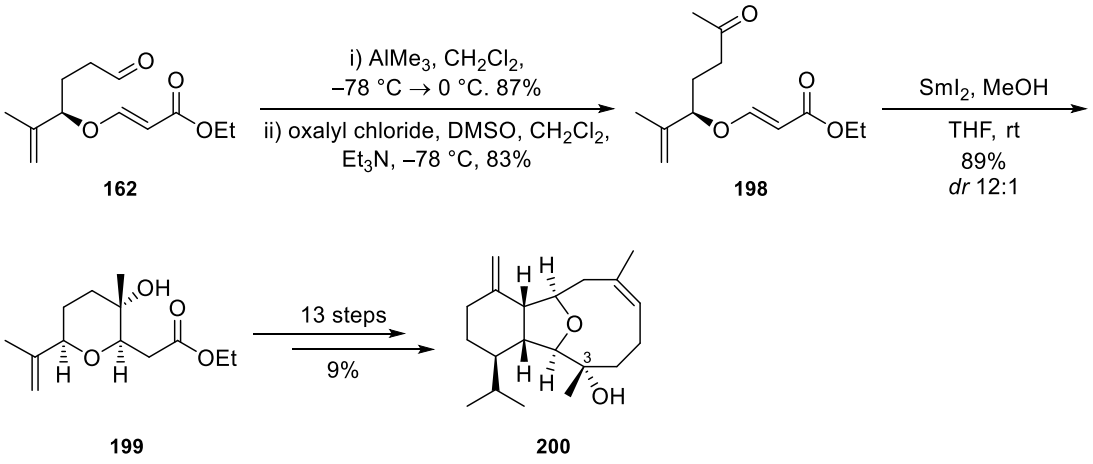
After the completion of the syntheses of these members of the cladiellin family of natural products, attention was turned to the synthesis of the proposed structure of sclerophytin F (**197**, Figure 20).[67-69]



purported structure of sclerophytin F (**197**)

*Figure 20: Purported Structure of Sclerophytin F (**197**)*

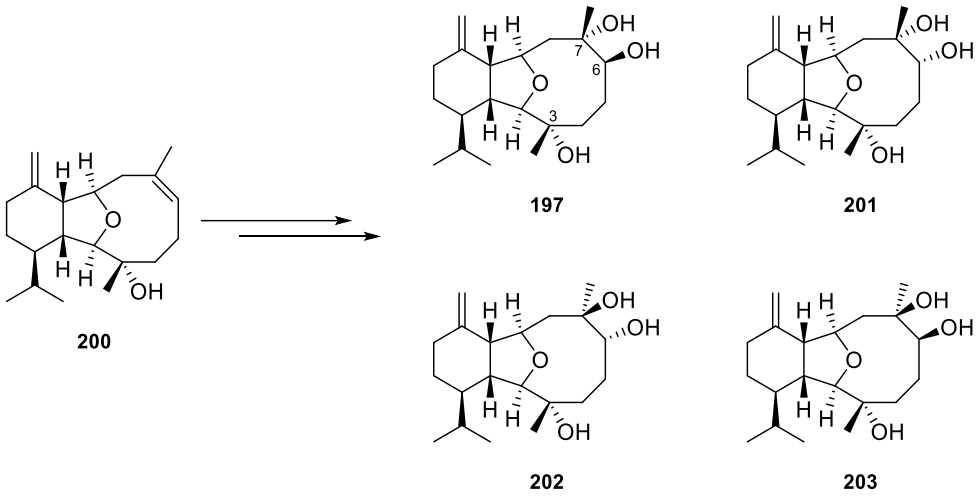
Clark and co-workers reported the synthesis of the purported structure of sclerophytin F (**197**) in 2014 along with three diastereoisomeric (at C-6 and C-7 positions) triols in 2015 which allowed re-evaluation of the structure of the natural product. The synthesis started with methylation of aldehyde **162** (Scheme 41).[67-69]



*Scheme 41: Synthesis of Tricyclic Core of Sclerophytin F (**197**)*

Methylation prior to tricycle formation was necessary because it had been shown previously that Grignard addition to a ketone in the C-3 position late in the synthesis would give the opposite stereochemistry to that required (Section 2, Scheme 31). Following methylation, Swern oxidation gave ketone **198** which underwent reductive cyclisation to give tetrahydropyranol **199** with excellent selectivity (*dr* 12:1). This intermediate was converted into the tricyclic core **200** of sclerophytin F in a further 13 steps using a similar route as before.

The compound corresponding to the purported structure of sclerophytin F (**197**) and its three diastereoisomers at the C-6 and C-7 positions were then synthesised in a further 4-6 steps from tricyclic alcohol **200** (Scheme 42).[68,69]



*Scheme 42: Synthesis of the Purported Structure of Sclerophytin F (**197**) and Three Diastereoisomers*

Comparison of the NMR data for the four diastereoisomers with the data reported for sclerophytin F revealed that the natural product was not any of these four compounds. The structure also did not match any of the structures with an inversion of stereochemistry at the C-3 position. Through extensive analysis of the data described from the original isolation, it was concluded that the structure of sclerophytin F was in fact identical to that reported for sclerophytin E (**204**) and there had been a mistake during characterisation of the compound (Figure 21).

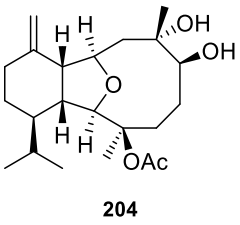
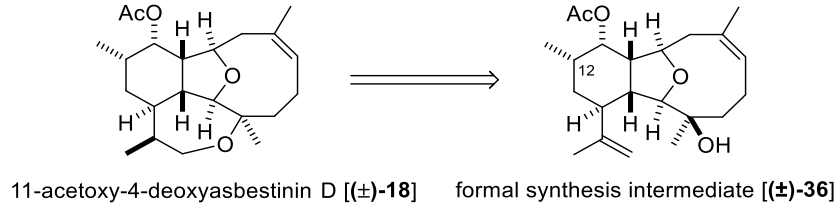


*Figure 21: Structure of Sclerophytins E and F (**204**)*

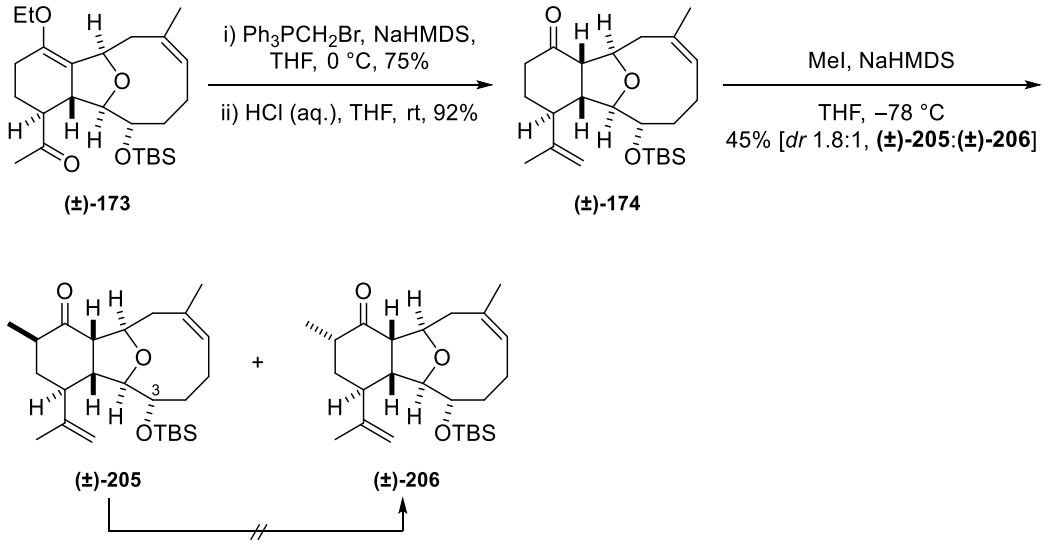
2.1 Previous Work on Asbestinins Within the Clark Group

In unpublished work performed by the Clark group, the formal synthesis of 11-acetoxy-4-deoxyasbestinin D [**(±)-18**] was completed.[70] This was through the synthesis of a tricyclic intermediate **(±)-36** previously prepared by Crimmins and co-workers during their published synthesis (Scheme 43).[12,13]



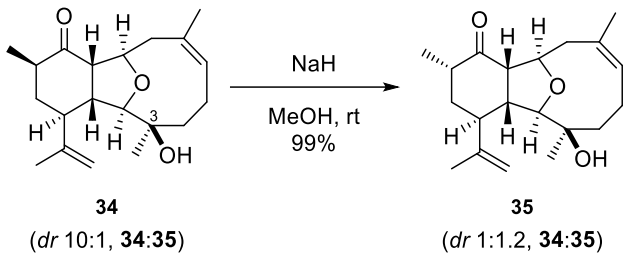
Scheme 43: Formal Synthesis of 11-Acetoxy-4-deoxyasbestinin D [(±)-18]

The synthesis of intermediate **(±)-36** began from tricycle **(±)-173** which underwent Wittig methenylation followed by hydrolysis of the ethyl vinyl ether to give ketone **(±)-174** (Scheme 44).[70] Methylation of ketone **(±)-174** was performed to produce a mixture of the diastereoisomers **(±)-205** and **(±)-206**, favouring diastereoisomer **(±)-205** (*dr* 1.8:1).



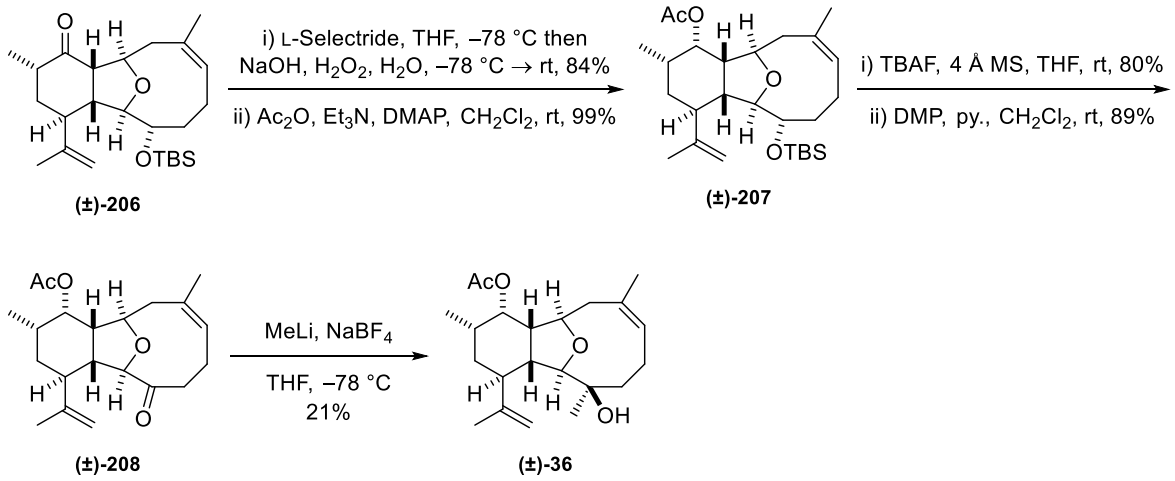
Scheme 44: Methylation of Tricyclic Core (±)-174

When epimerisation of diastereoisomer **(±)-205** was performed under various conditions, only diastereoisomer **(±)-205** was obtained. This result showed the important influence that the C-3 stereocentre has on epimerisation in comparison to a similar transformation performed by Crimmins and Ellis on a substrate that possesses a quaternary centre at the C-3 position (Scheme 45).[12,13]



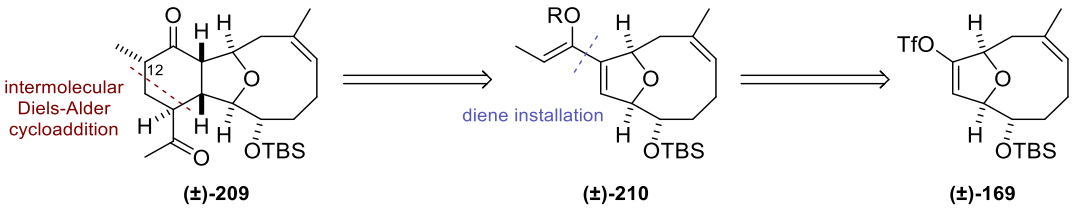
Scheme 45: Epimerisation Performed by Crimmins and Co-workers

The synthesis of ketone **(±)-206** allowed the formal synthesis of 11-acetoxy-4-deoxyasbestinin D [**(±)-18**] to be completed in five steps. The first step involved reduction of the ketone with L-Selectride and this reaction was followed by acetylation to give acetate **(±)-207**. Cleavage of the silyl ether and oxidation of the resulting alcohol afforded the ketone **(±)-208** before nucleophilic addition of methyllithium in the presence of sodium tetrafluoroborate gave formal intermediate **(±)-36**.



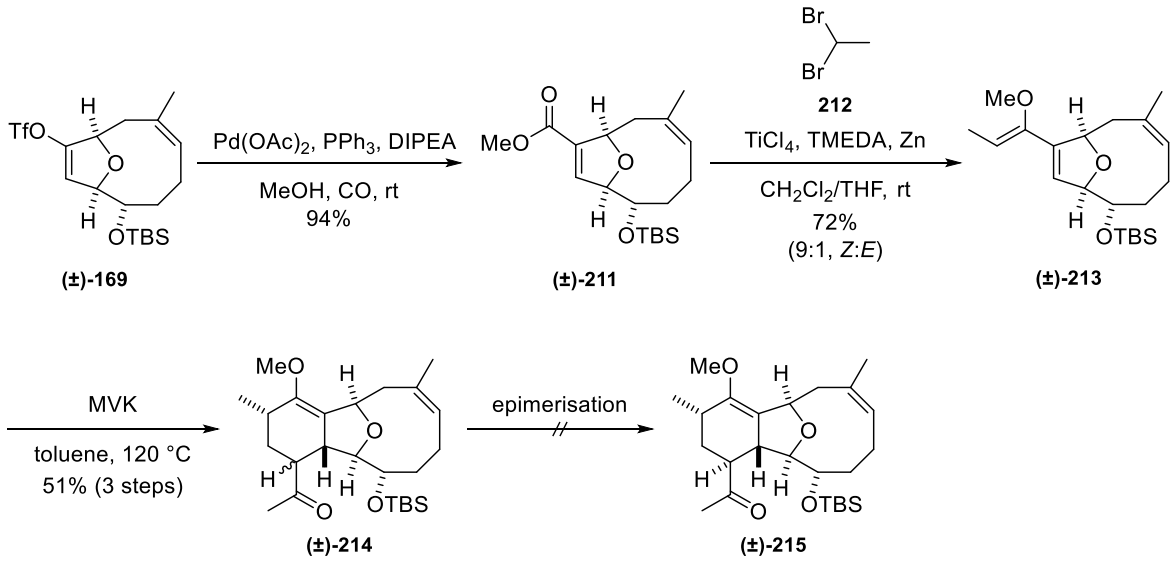
Scheme 46: Completion of Formal Synthesis of 11-Acetoxy-4-deoxyasbestinin D [(±)-18]

The problems concerning the installation of the methyl group selectively at C-12 meant that an alternative approach was investigated to allow completion of the total synthesis of 11-acetoxy-4-deoxyasbestinin D (Scheme 47).[71] It was envisaged that having the methyl substituent installed prior to the Diels–Alder cycloaddition reaction would allow the stereochemistry to be set during this reaction. This approach relied on stereoselective formation of the *Z*-diene **(±)-210** as a substrate for the intermolecular Diels–Alder cycloaddition. In principle, triene **(±)-210** should be readily prepared from previously-prepared triflate **(±)-169**.



Scheme 47: Alternative Approach to Installation of Methyl Substituent

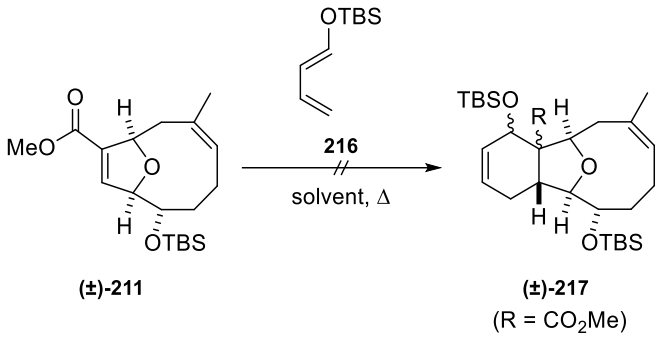
The triflate **(±)-169** was subjected to a palladium-catalysed carbonylation reaction to give α,β-unsaturated ester **(±)-211** and a subsequent Takai olefination reaction with 1,1-dibromoethane **212** gave *Z*-diene **(±)-213** (Scheme 48).[72] This diene then underwent an intermolecular Diels–Alder cycloaddition reaction with methyl vinyl ketone.



Scheme 48: Installation of Methyl Substituent Prior to Diels–Alder Cycloaddition

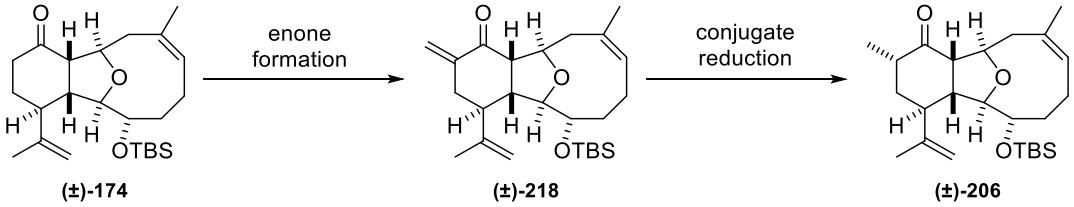
The Diels–Alder cycloaddition was successful and produced a 1:1 mixture of *endo*:*exo* adducts **(±)-214** as before. However, attempts to epimerise this mixture to obtain mainly the required diastereoisomer **(±)-215** were unsuccessful and a mixture of adducts was obtained in each case. Epimerisation was performed under various basic and acidic conditions and changes were made to the enol ether substituent but none of these approaches was successful.[71]

An alternative approach was investigated in which the α,β-unsaturated ester **(±)-211** was reacted with the diene **216** to discover whether the Diels–Alder cycloaddition would proceed, but this approach was unsuccessful (Scheme 49).[71]



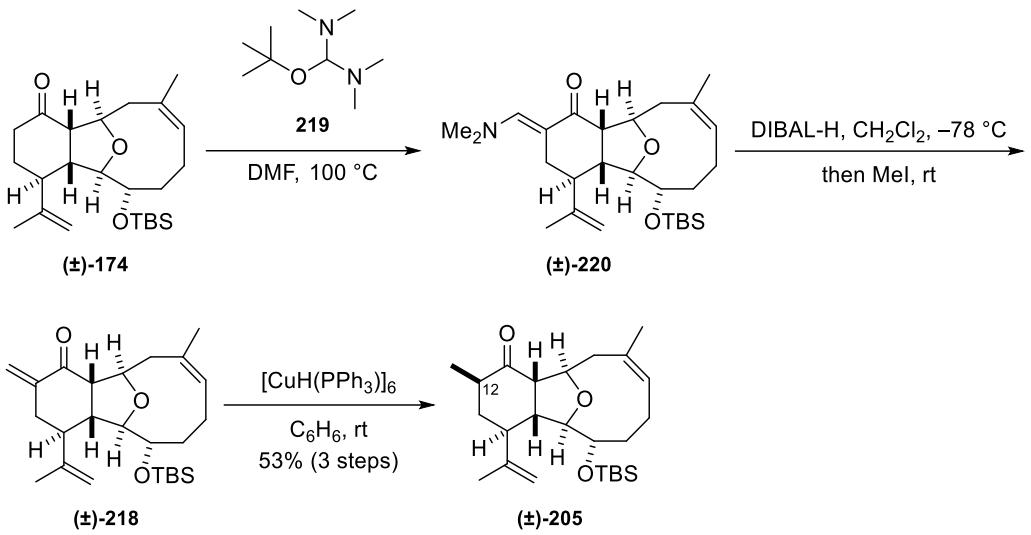
Scheme 49: Alternative Diels–Alder Cycloaddition Approach

Installation of the methyl substituent prior to the Diels–Alder cycloaddition was problematic and so a different approach was investigated. It was proposed that the tricyclic ketone **(±)-206** could be synthesised by conjugate reduction of the enone **(±)-218**, which in turn could be synthesised from the ketone **(±)-174** (Scheme 50).



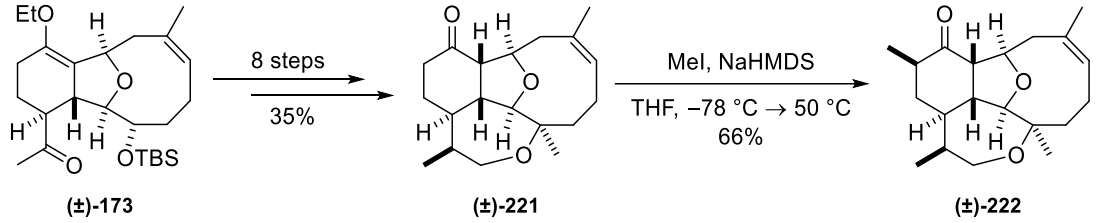
Scheme 50: Third Strategy for Installation of Methyl substituent

The synthesis of enone **(±)-218** started with the reaction of the tricyclic ketone **(±)-174** with Bredereck's reagent **219** to give enaminone **(±)-220** (Scheme 51).[73] Reduction of enaminone **(±)-220** with diisobutylaluminium hydride followed by addition of methyl iodide led to formation of enone **(±)-218**.



Scheme 51: 1,4-Conjugate Reduction of Enone ***(±)-218***

Enone **(±)-218** underwent 1,4-conjugate reduction with Stryker's reagent to give diastereoisomer **(±)-205** as the sole product.[74] The finding that conjugate reduction of the enone led to formation of the epimer at the C-12 position, meant that an alternative route was required. It was proposed that direct methylation of tetracyclic ketone **(±)-221** might lead to an improved ratio of diastereoisomers being formed (previously, a *dr* 1.8:1 had been obtained for a similar tricyclic system, Scheme 52).



Scheme 52: Direct Methylation of Tetracycle ***(±)-221***

Tetracyclic ketone **(±)-221** was synthesised in 8 steps from tricyclic enol ether **(±)-173** before the attempted methylation with methyl iodide and sodium hexamethyldisilazide. When the methylation was performed only diastereoisomer **(±)-222** was obtained.[71]

Even though the routes discussed above were unsuccessful or led to poor diastereoselectively when installing the methyl substituent at the C-12 position, they demonstrated that it was possible to construct the tetracyclic core and that this would serve as an excellent building block for the synthesis of the asbestinins. However, an alternative method to set the methyl stereocentre at the C-12 position late in the synthesis would be required.

3. Results and Discussion

3.1 Synthetic Strategy

Previous work performed by the Clark group had established an efficient and rapid method for construction of the tricyclic core present in both the cladiellins and asbestinins (Figure 22).[59-61,64-71] Further work had been performed to elaborate this tricyclic core to give the tetracyclic structure of the asbestinins in racemic form (Section 2).[70,71] Previous attempts to install the methyl substituent at C-12 had either led to poor diastereoselectivity or formation of the epimer as the major product. Consequently, stereoselective introduction of this methyl group was one of the issues that needed to be addressed.[70,71]

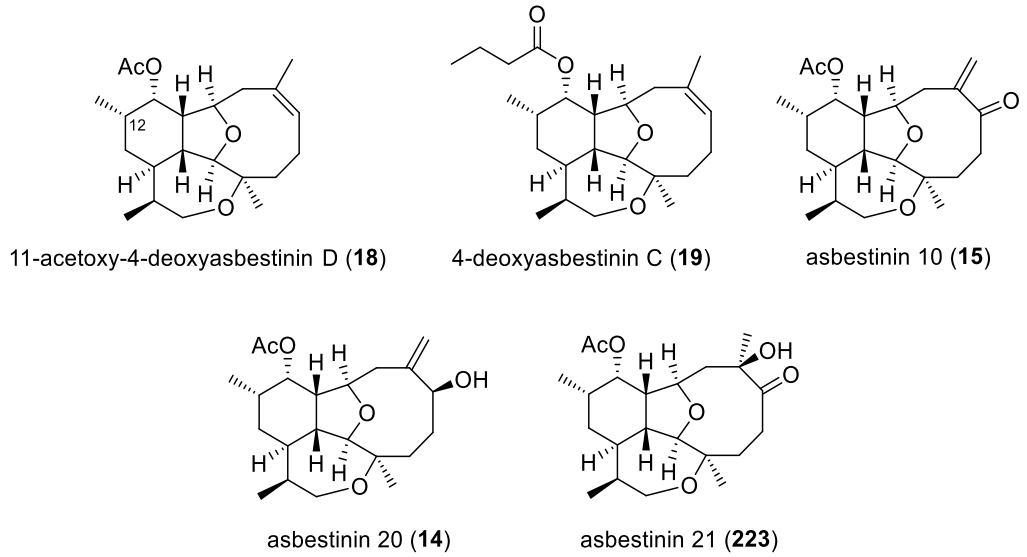
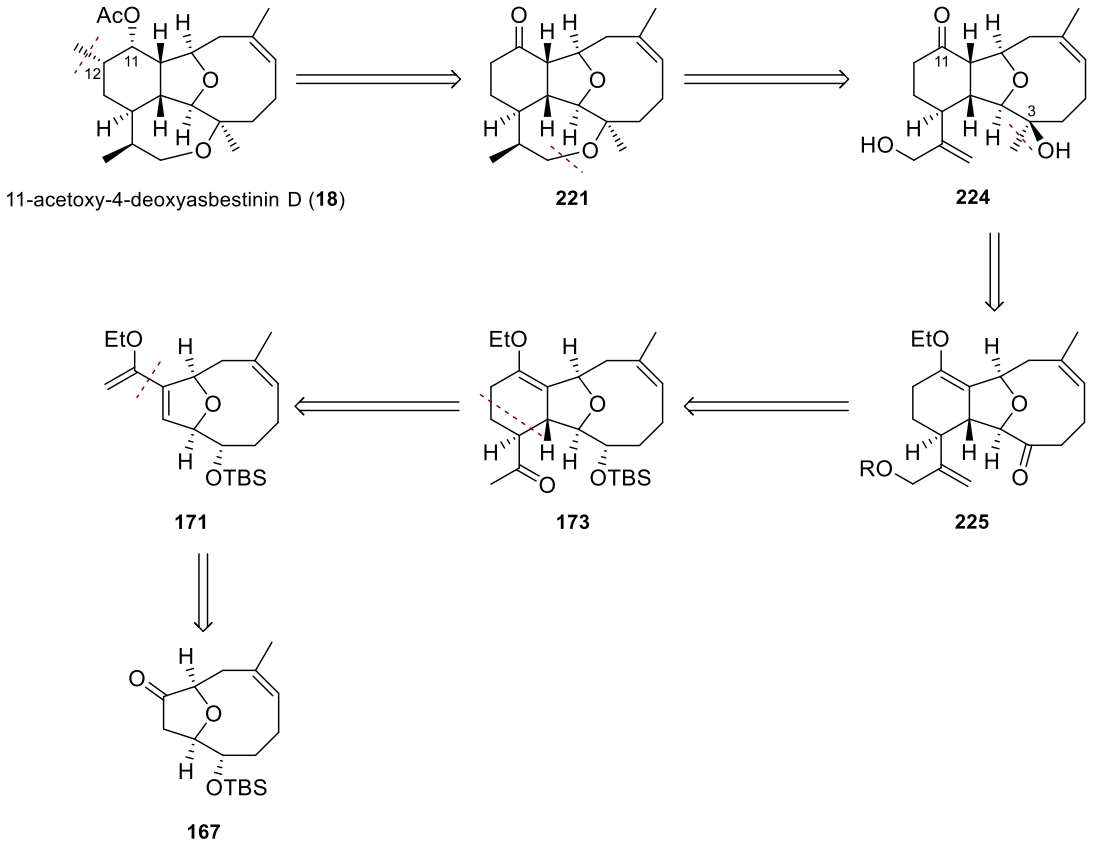


*Figure 22: Structures of 11-Acetoxy-4-deoxyasbestinin D (**18**), 4-Deoxyasbestinin C (**19**) and Asbestinins Derived from 11-Acetoxy-4-deoxyasbestinin D (**18**)*

The initial natural product target selected for synthesis was 11-acetoxy-4-deoxyasbestinin D (**18**) because this compound could be used as an intermediate for the synthesis of many other members of the family such as asbestinin 10 (**15**), asbestinin 20 (**14**) and asbestinin 21 (**2239**) by functionalisation of the trisubstituted alkene present in the oxonene.[9-11] The structurally related butyrate derivative, 4-deoxyasbestinin C (**19**) would also be a feasible target because it could be obtained from the same advanced intermediate used to prepare 11-acetoxy-4-deoxyasbestinin D (**18**). This would make it possible to synthesise further members of the asbestinin family derived from 4-deoxyasbestinin C (**19**).[10]

Retrosynthetic analysis of 11-acetoxy-4-deoxyasbestinin D (**18**) starts with cleavage of the ester at the C-11 position and formation of the ketone (Scheme 53). Subsequent removal of the methyl substituent at the C-12 position gives the tetracyclic core of the asbestinins **221**.



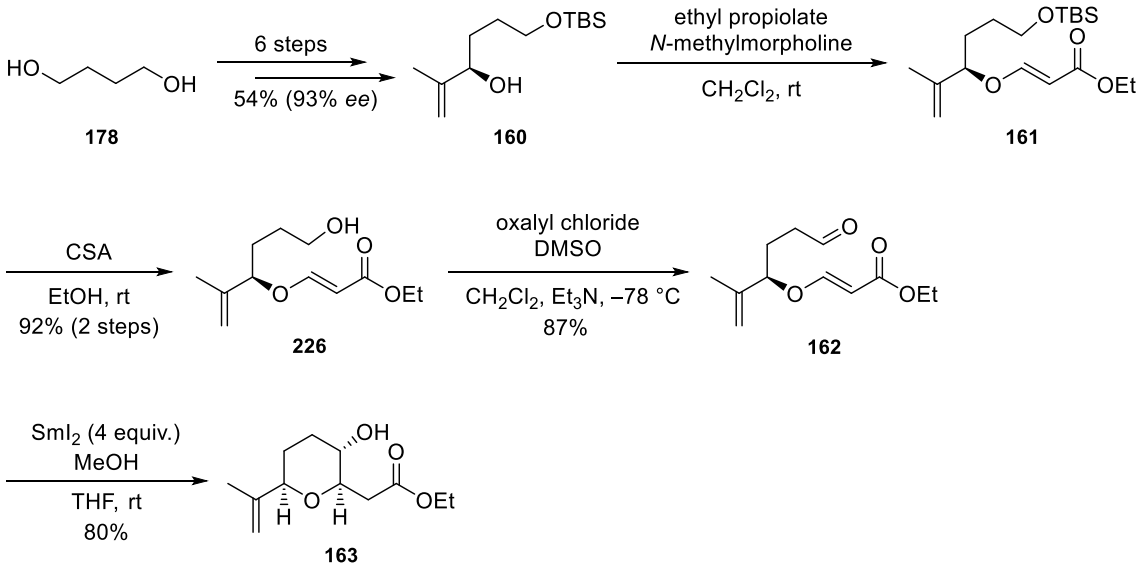
*Scheme 53: Retrosynthetic Analysis of 11-Acetoxy-4-deoxyasbestinin D (**18**)*

Sequential opening of the oxepane affords a tertiary alcohol at the C-3 position and conversion of the methyl substituent into a methylene group leads to the diol **224**. Transformation of the ketone at C-11 into an enol ether followed by removal of the C-3 methyl substituent suggests tricyclic ketone **225** as an intermediate. Subsequent conversion of the allylic ether into a ketone gives tricyclic ketone **173**. This ketone has been shown to be available from bicyclic triene **171** through a Diels–Alder cycloaddition reaction in previous studies. The bicyclic triene **171** is available from bicyclic ketone **167** and an intermediate that had been used in previous total syntheses of the cladiellins family reported by Clark and co-workers.[64,65]

The synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**) commenced with the synthesis of tricyclic ketone **173** on a large scale following the previously developed route (Section 2).

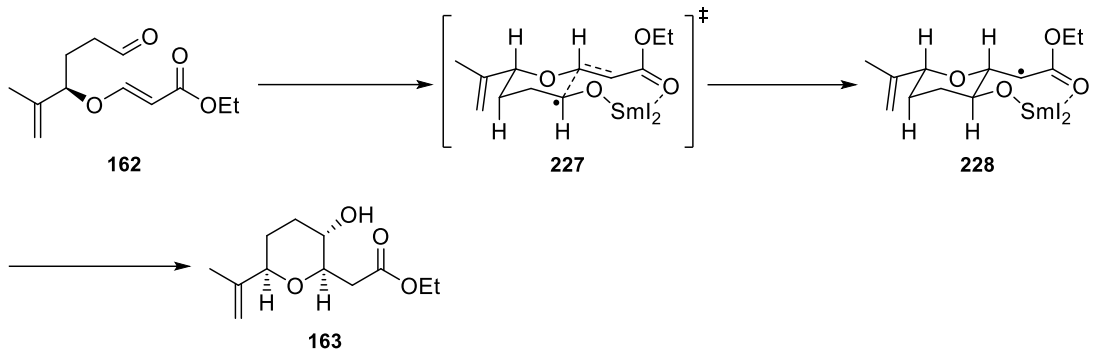
3.2 Synthesis of Tetrahydropyranol 163

The synthesis of tetrahydropyranol **163** began with conversion of butan-1,4-diol **178** to allylic alcohol **160** in 6 steps (54%, 93% *ee*, Scheme 54).[64] The next steps involved the transformation of allylic alcohol **160** into *E*-vinylogous carbonate **226** through hetero-Michael addition with ethyl propiolate and subsequent acid-catalysed cleavage of the *tert*-butyldimethylsilyl group. Purification was performed after silyl deprotection because purification of ester **161** resulted in significant loss of material and the alcohol **226** was obtained in 92% yield.



*Scheme 54: Synthesis of Tetrahydropyranol **163** from Butan-1,4-diol **178***

The primary alcohol **226** then underwent Swern oxidation to give aldehyde **162** in excellent yield (87%) and this compound was then converted into tetrahydropyranol **163** through a samarium-mediated cyclisation reaction.[62,53] This yielded the tetrahydropyranol core in 80% yield and with excellent diastereoselectivity (*dr* >20:1). The formation of tetrahydropyranol **163** proceeds through formation of the radical anion **227** followed by cyclisation onto the α,β-unsaturated ester to give tetrahydropyranol radical **228** (Scheme 55).

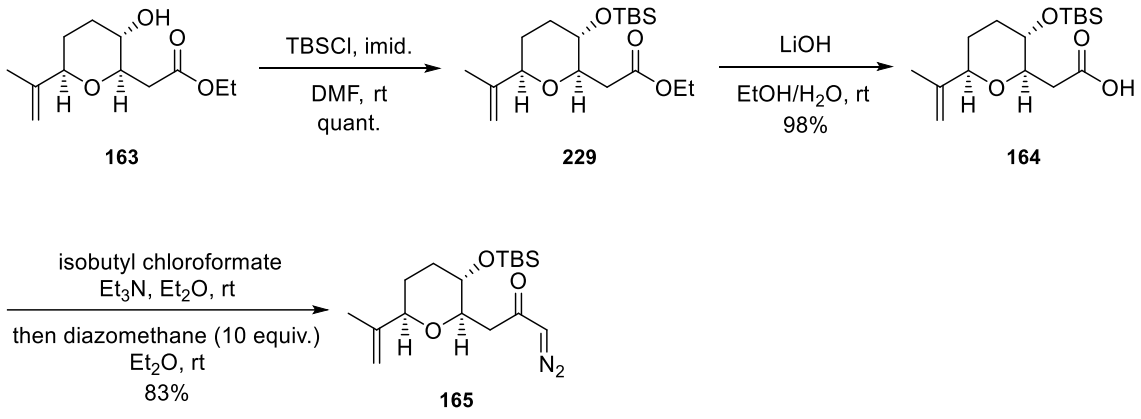


Scheme 55: Rationale for the Stereochemical Outcome of the Samarium-mediated Cyclisation Reaction

Radical **228** undergoes single-electron reduction with a second equivalent of samarium diiodide to give the carbanion which undergoes protonation with methanol to form desired tetrahydropyranol **163**. The stereochemical outcome of the reaction is dictated by chelation of the samarium to the aldehyde and ester functionality in a chair-like structure to form a seven-membered ring. The well-defined transition state for the reaction results in high diastereoselectivity. [62,75]

3.3 Synthesis of Diazo-ketone 165

The next objective was the synthesis of the diazo-ketone **165**, the precursor for the pivotal oxonium ylide formation, [2,3]-sigmatropic rearrangement reaction (Scheme 56). Tetrahydropyranol **163** was initially reacted with *tert*-butyldimethylsilyl chloride to provide silyl ether **229** in quantitative yield.



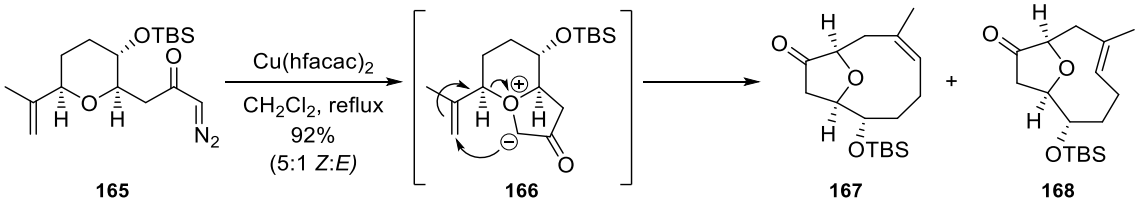
*Scheme 56: Synthesis of Diazo-ketone **165***

The silyl ether **229** then underwent lithium hydroxide-mediated saponification to form the corresponding carboxylic acid **164**. The acid **164** was converted into a mixed anhydride through the reaction with isobutyl chloroformate in the presence of triethylamine and this

intermediate was reacted immediately with a freshly prepared ethereal solution of diazomethane. The formation of diazo ketone **165** required a large excess of diazomethane (10 equiv.) for high yields to be obtained (80%). Diazomethane was prepared and reacted according to a literature procedure.[76,77]

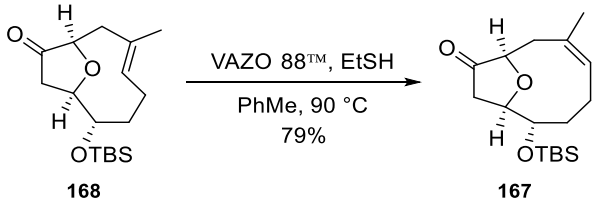
3.4 Synthesis of *Z*-Bicyclic Ketone 167

Diazo ketone **165** was converted into the bicyclic ketones **167** and **168** through treatment with copper hexafluoroacetyacetone.[61,64-66] The catalyst promoted the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement through the presumed intermediate **166** or the metal-bound equivalent of this ylide (Scheme 57).



*Scheme 57: Synthesis of Bicyclic Ketones **167** and **168***

At this stage, the isomeric bicyclic ketones were separated by chromatography using silica gel impregnated with silver nitrate.[78,79] The *E*-bicyclic ketone **168** was isomerised to *Z*-bicyclic ketone **167** through the reaction with 1,1′-azobis(cyclohexanecarbonitrile) (VAZO 88™) and ethanethiol (Scheme 58). In previous studies, it had been noted that direct isomerisation of the mixture of bicyclic ketones had delivered lower yields of *Z*-bicyclic ketone **167** overall.[71]



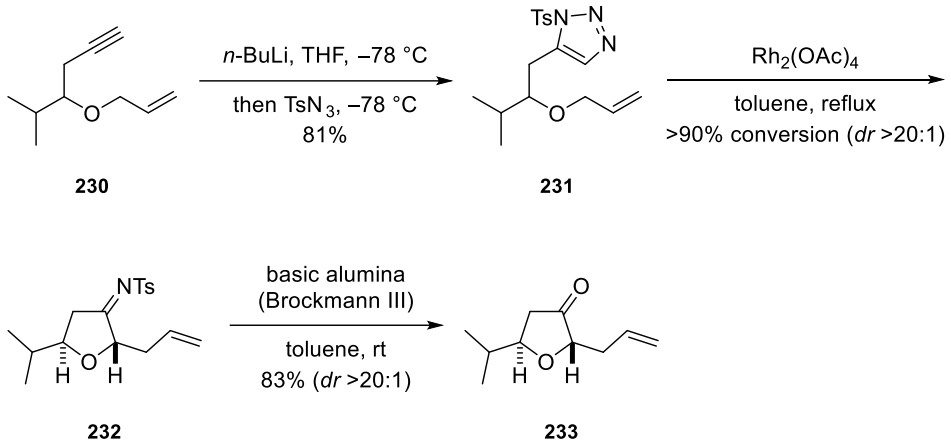
*Scheme 58: Isomerisation of E-Bicyclic Ketone **168** to Z-Bicyclic Ketone **167***

3.5 Alternative Routes to *Z*-Bicyclic Ketone 167

The explosive nature of diazomethane, which can make it problematic to handle on a large scale, coupled with the need for specialised glassware, meant that alternative routes to the *Z*-bicyclic ketone **167** were investigated.

3.5.1 Rearrangement of Triazole 237

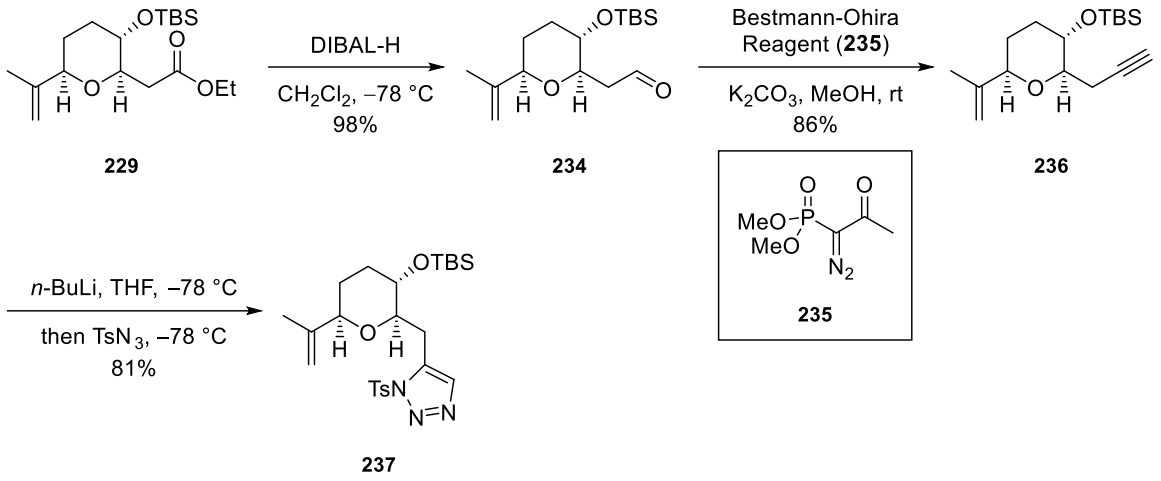
In 2014, Boyer reported the use of 1-sulfonyl-1,2,3-triazoles for the stereoselective synthesis of dihydrofuran-3-imines through rhodium-catalysed denitrogenation followed by [2,3]-sigmatropic rearrangement (Scheme 59).[80]



Scheme 59: Boyer's Synthesis of Dihydrofuran-3-imines from 1-Tosyl-1,2,3-triazoles

The synthesis of dihydrofuran-3-imine **232** started with conversion of alkyne **230** into the 1-tosyl-1,2,3-triazole **231** through deprotonation of the alkyne with *n*-butyl lithium and subsequent addition of tosyl azide. From here, the triazole could be reacted with rhodium acetate to give a reactive carbenoid which undergoes [2,3]-sigmatropic rearrangement to give desired *trans*-dihydrofuran-3-imine **232** in excellent yield and diastereoselectivity.[81] *trans*-Dihydrofuran-3-imine **232** is converted into the ketone **233** by hydrolysis of the imine using basic alumina (Brockmann III).[82] This methodology was applied to the synthesis of *Z*-bicyclic ketone **167**, to provide a scalable alternative route that avoids formation of the diazo ketone **165**.

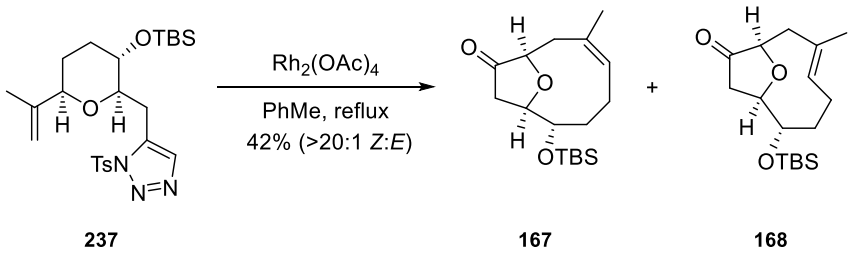
Initial work focussed on the synthesis of triazole **237** from tetrahydropyranol **229** (Scheme 60). Reduction of ester **229** with diisobutylaluminium hydride afforded aldehyde **234** and the alkyne **236** was obtained by treatment of this aldehyde with the Bestmann-Ohira reagent (**235**) under basic conditions.[83,84]



*Scheme 60: Synthesis of Triazole **237** from Tetrahydropyranol **229***

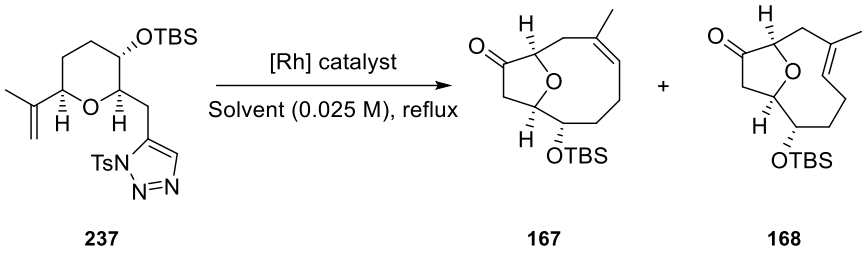
Finally, the triazole was synthesised according to the Boyer protocol: deprotonation of the alkyne **235** with *n*-butyl lithium followed by rapid addition of tosyl azide afforded the triazole **237** in 81% yield.[80] An efficient method for the synthesis of triazole **237** had been established, which meant that reaction of the triazole under rhodium-catalysed conditions could be investigated.[85]

The triazole **237** was converted into the bicyclic system under the standard conditions reported by Boyer for the synthesis dihydrofuran-3-imines (rhodium acetate, toluene, reflux) (Scheme 61).[80] After work-up with basic alumina (Brockmann III), the *Z*-bicyclic ketone **167** was isolated with excellent diastereoselectivity (>20:1, *Z*:*E*).



*Scheme 61: Synthesis of Z-*Bicyclic Ketone **167** from Triazole **237** through Rhodium-catalysis

Although an excellent level of diastereocontrol had been obtained for formation of the *Z*-alkene, the yield was modest. Optimisation experiments were performed to investigate if the yield of the reaction could be improved. Optimisation involved screening the catalyst, reaction solvent and time. The findings of these studies are summarised in Table 2.



237 167 168

*Table 2: Optimisation of the Rhodium-catalysed Formation of Z-Bicyclic Ketone **167***

Entry	[Rh] Catalyst	Solvent	Time (min)	Yield of *Z*-bicyclic ketone 167 (%) [a,b]
1	$Rh_2(OAc)_4$	PhMe	30	42[c]
2	$Rh_2(TPA)_4$	PhMe	30	–
3	$Rh_2(TFA)_4$	PhMe	30	–
4	$Rh_2(Oct)_4$	PhMe	30	39
5	$Rh_2(OAc)_4$	PhMe	120	39
6	$Rh_2(OAc)_4$	DCE	30	11
7	$Rh_2(OAc)_4$	DCE	120	49[d]
8	$Rh_2(OAc)_4$	DCE	240	47
9	$Rh_2(OAc)_4$	DCE	120	44[e]
10	$Rh_2(OAc)_4$	PhMe	90	19 (10% **168**)[f]

[a] Yield determined by ^{1}H NMR analysis of crude material after work-up using 1,3,5-trimethoxybenzene as an internal standard; [b] Diastereocontrol >20:1 *Z*:*E* unless otherwise stated; [c] Longer work-up with basic alumina (Brockmann III), 30 mins → 90 mins had no effect on yield; [d] isolated yield, no starting material recovered; [e] Performed at higher concentration (0.075 M); [f] Performed at 90 °C

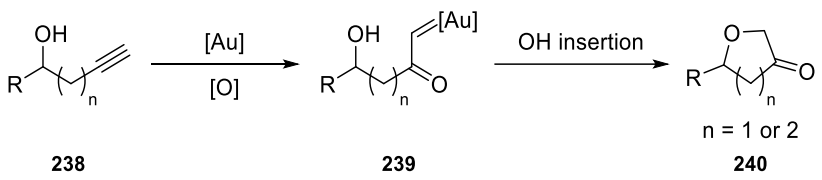
When rhodium(II) acetate was replaced with a rhodium(II) catalyst that possessed bulkier or more electron-withdrawing groups (e.g. triphenyl- and trifluoroacetyl-), the required product was not obtained and starting material isolated (Entries 2 and 3). Switching to a bulkier catalyst in the form of rhodium(II) octanoate had negligible effect on the yield of the reaction (Entry 4). Rhodium(I) and iridium(I) catalysts were also tested, but the required product was not obtained and starting material was recovered.

Rhodium(II) acetate delivered the best results from the catalyst screening and so the reaction time and choice of solvent were investigated. The use of rhodium(II) acetate in toluene and an increased reaction time had no effect on the yield (Entry 5). When dichloroethane was used as the solvent, a longer reaction time was required to yield the best results (Entries 6–8). The reaction time had to be increased from 30 minutes to 120 minutes for the highest yield to be obtained. An increase in concentration of the reaction mixture did not alter the yield of the reaction (Entry 9).

Interestingly, when rhodium(II) acetate was employed as the catalyst in toluene at 90 °C, a much lower yield of the *Z*-bicyclic ketone **167** was obtained (19%) and a higher proportion of the *E*-bicyclic ketone **168** was obtained (10%, approx. 2:1 *Z*:*E* compared to previous >20:1 *Z*:*E*). The highest yield of the *Z*-bicyclic ketone **167** was obtained when the reaction was performed using rhodium(II) acetate as the catalyst in dichloroethane over 120 minutes (Entry 7).

3.5.2 Direct Reaction of Alkyne 236

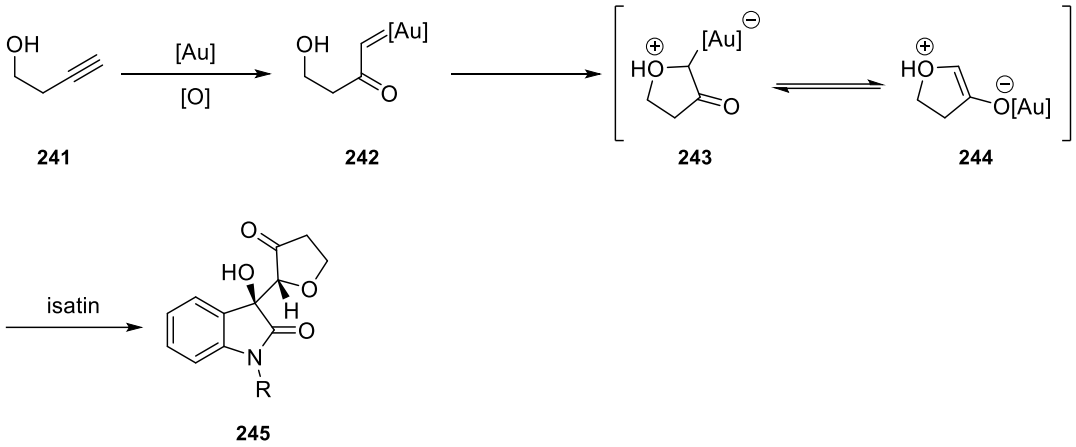
In 2010, Zhang and co-workers reported the first α-oxo gold carbene, which was prepared by intermolecular oxidation of a terminal alkyne followed by OH insertion (Scheme 62).[86] Alkyne **238** was reacted with a gold catalyst in the presence of an oxidant to give α-oxo gold carbene **239** which then underwent OH insertion to yield cyclic product **240**.



Scheme 62: General Procedure by Zhang and Co-workers

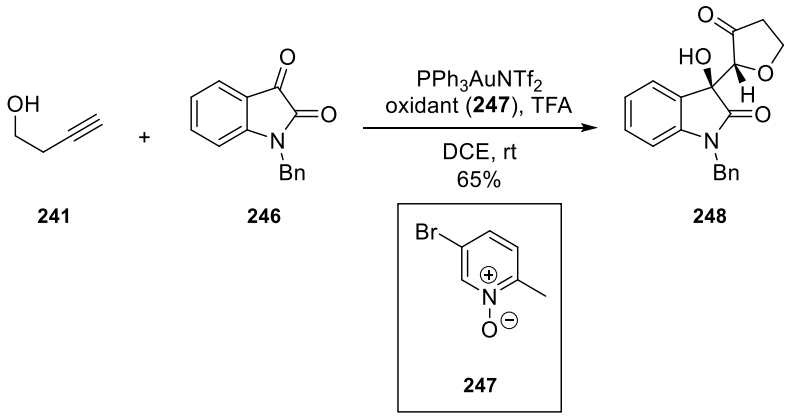
In 2019, Xu and co-workers expanded on this work and reported the gold-catalysed oxidative cyclisation/aldol addition of homopropargyl alcohols with isatins (Scheme 63).[87]

Homopropargylic alcohol **241** can be reacted with a gold catalyst in the presence of an oxidant and an acid to give gold carbene **242**. Subsequent rearrangement is believed produce the metal-bound ylides **243** and **244**. The required product **245** is obtained by addition to isatin in an aldol-type reaction.



Scheme 63: General Approach Employed by Xu and Co-workers

Xu and co-workers demonstrated that 3-hydroxyoxindole **248** could be synthesised using the reaction (Scheme 64).[87] It was noted that only one diastereoisomer was formed and its structure was confirmed by X-ray crystallography.



*Scheme 64: Synthesis of 3-Hydroxyoxindole **248***

The direct oxidative gold-catalysed cyclisation reaction offered an alternative approach to -the synthesis of the *Z*-bicyclic ketone **167** without the need to prepare the diazo-ketone **165** or the triazole **237**. The alkyne **236** was reacted with $SPhosAuNTf_2$ in the presence of oxidant 5-bromo-2-methyl-pyridine-*N*-oxide (**247**) and an acid to promote the formation of *Z*-bicyclic ketone **167**.The findings of this study are summarised in Table 3.

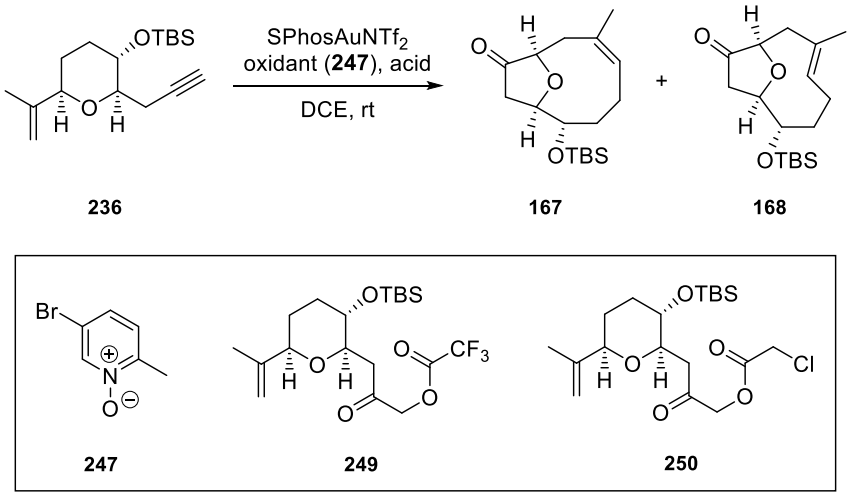


*Table 3: Attempted Direct Gold-catalysed Oxidative Cyclisation of Alkyne **236***

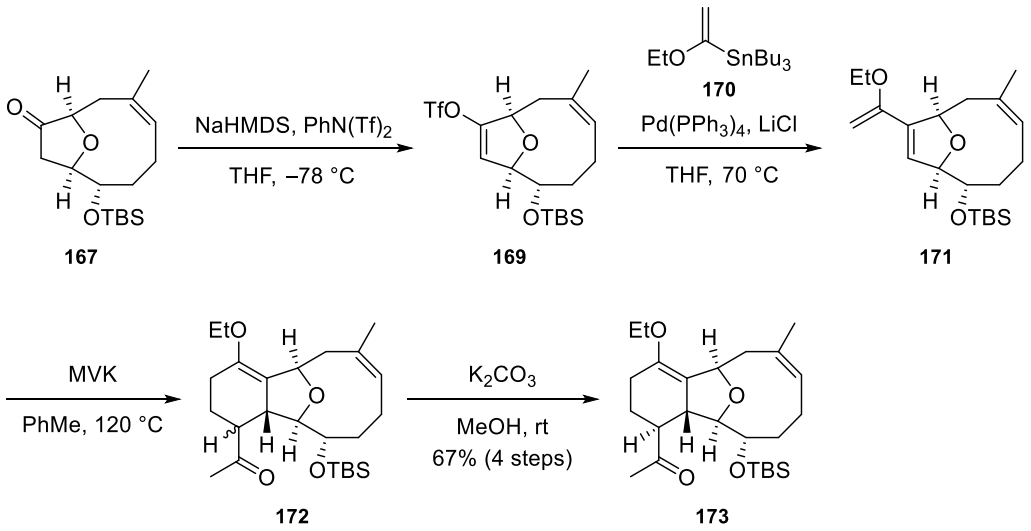
Entry	Acid	Outcome
1	TFA	By-product **249** (47%)
2	MsOH	Decomposition
3	TPA	No reaction
4	Chloroacetic acid	By-product **250** (36%)
5	No acid	No reaction

When the reaction was performed under conditions reported by Xu and co-workers in the presence of trifluoroacetic acid (TFA), the bicyclic ketones **167** and **168** were not produced and the by-product **249** was obtained instead (Entry1). Tetrahydropyranol ester **249** results from addition of TFA to the intermediate α-oxo gold carbene species that is formed. Xu and co-workers reported that methanesulfonic acid could be used as an alternative to TFA but use of these conditions resulted in decomposition of the starting material (Entry 2). It was hypothesised that the use of a weaker and more hindered base such as triphenyl acetic acid (TPA) would prevent formation of the analogous by-product to that observed during the TFA reaction. However, no reaction occurred when TPA was used as an additive and only starting material was isolated (Entry 3). Chloroacetic acid was chosen as an alternative to TFA

because it is less acidic, but in this case the ester **250** was obtained as the by-product (Entry 4). When the reaction was performed in the absence of an acid source, only starting material was recovered and no reaction observed (Entry 5). The results in presented in Entries 1 and 4 appear to show that [2,3]-sigmatropic rearrangement occurs at a much slower rate than the addition of the acid source to the α-oxo gold carbene species under these conditions.

3.6 Synthesis of Tricyclic Ketone 173

Two routes were available to synthesise the bicyclic ketone **167** and so the next objective was to synthesise the tricyclic core present in the asbestinins. This transformation had been optimised by the Clark group during the synthesis of several members of the cladiellin family of natural products and involved a Stille/Diels–Alder cycloaddition sequence.[64,65] The synthesis started with conversion of *Z*-bicyclic ketone **167** into the vinyl triflate **169** followed by Stille cross-coupling with tributyl(1-ethoxyvinyl)tin **170** to give triene **171** (Scheme 65).

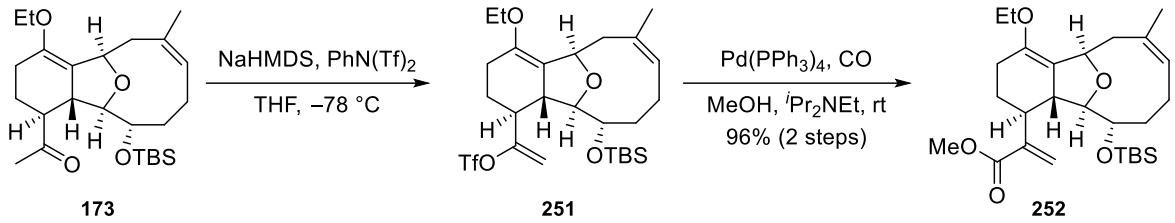


*Scheme 65: Synthesis of Tricyclic Ketone **173** by an Intermolecular Diels–Alder Cycloaddition Reaction*

Triene **171** then underwent intermolecular Diels–Alder cycloaddition with methyl vinyl ketone to give a 1:1 mixture of *exo*:*endo* adducts **172** which upon epimerisation with potassium carbonate in methanol resulted in the isolation of diastereoisomer **173** exclusively.

3.7 Synthesis of Tetracyclic Core 221 of the Asbestinins

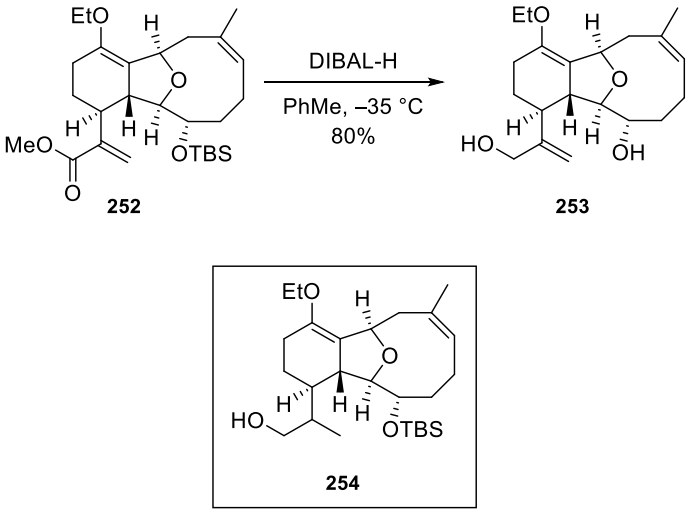
The next objective in the synthesis was conversion of the tricyclic intermediate into the complete tetracyclic core.[71] The next transformation was conversion of the methyl ketone into an α,β-unsaturated ester. Vinyl triflate **251** was obtained from tricyclic ketone **173** by deprotonation with sodium hexamethyldisilazide and treatment of the resulting enolate with *N*-phenyltriflimide (Scheme 66). Vinyl triflate **251** then underwent a palladium-catalysed carbonylation to afford α,β-unsaturated ester **252** in excellent yield over two steps.



173 **251** **252**

*Scheme 66: Synthesis of α,β-Unsaturated Ester **252***

The next step was reduction of α,β-unsaturated ester **252** to deliver the corresponding allylic alcohol (Scheme 67). Selective reduction of the α,β-unsaturated ester **252** was achieved by reaction with diisobutylaluminium hydride. Cleavage of the silyl ether was observed upon aqueous work-up to give diol **253** as the product.



252 **253**

254

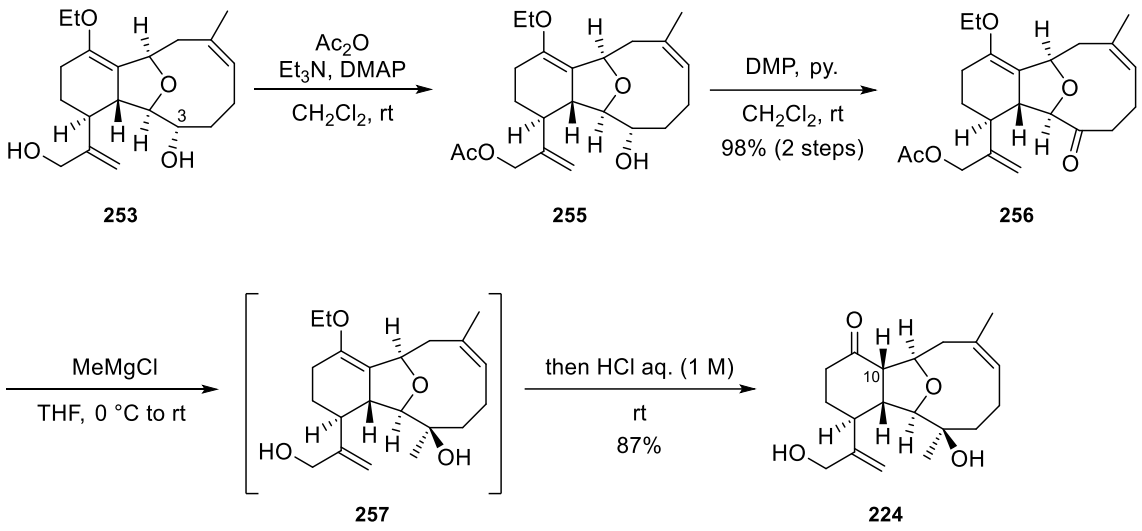
*Scheme 67: Selective Reduction of α,β-Unsaturated Ester **252***

Alcohol **254** was obtained as a by-product from the reduction reaction and was formed as a result of conjugate reduction prior to reduction of the ester carbonyl group. This side reaction could be minimised by lowering the reaction temperature from −20 °C (49% **253**) to −35 °C (84% **253**). If the reaction temperature was lowered further (−40 °C or below), the reaction

proceeded extremely slowly and only trace quantities of the allylic alcohol **253** were obtained after three hours.

As mentioned above, cleavage of the silyl ether was observed upon work-up of the reduction reaction. The likely cause was the close proximity of the secondary silyl ether to the primary hydroxyl group / alkoxide formed by reduction of the α,β-unsaturated ester. This could promote migration of the *tert*-butyldimethylsilyl which would weaken the oxygen-silicon bond allowing the silyl ether to be cleaved upon aqueous work-up. Diol **253** proved to be acid-sensitive; exposure to acidic conditions caused decomposition to occur.

To introduce the methyl substituent regioselectively at C-3 it was necessary to oxidise the C-3 hydroxyl group selectively and so the more reactive allylic alcohol had to be protected first. Selective acetylation of diol **253** using acetic anhydride furnished acetate **255** (Scheme 68).

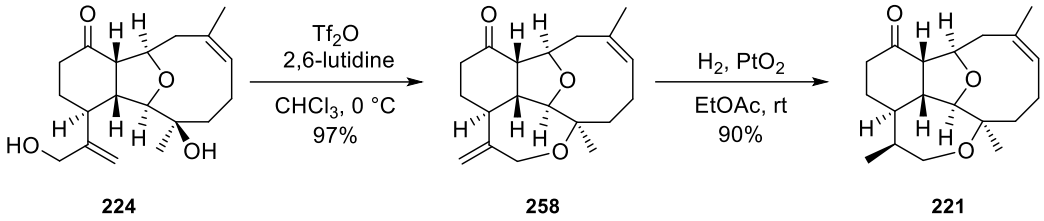


*Scheme 68: Synthesis of Tetracyclic Precursor **224***

Now that the allylic alcohol had been protected, the secondary alcohol was oxidised using Dess–Martin periodinane to afford ketone **256** in excellent yield.[88] It was found that a two-step procedure (acetylation then oxidation) from diol **255** resulted in a higher yield of ketone **256** being obtained (98% over two steps) than if performed stepwise with purification of the intermediate ester which gave yields of 98% and 83% respectively (81% over two steps). Grignard addition of methyl magnesium chloride to ketone **256** resulted in stereoselective formation of the tertiary alcohol and removal of the acetate group to afford allylic alcohol **257**. The resulting product **257** was treated with aqueous hydrochloric acid,

which cleaved the ethoxy enol ether and delivered diol **224**. The C-10 stereocentre was created stereoselectively.[71]

To form the bridging oxepane present in the tetracyclic core, the diol **224** was treated with triflic anhydride to yield the primary triflate which then underwent displacement by the tertiary alcohol to give tetracyclic ketone **258** (Scheme 69).[71,12,13]

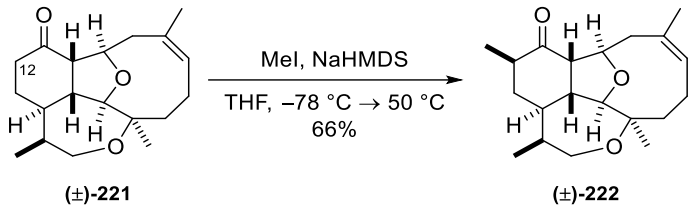


*Scheme 69: Synthesis of Tetracyclic Core **221** of the Asbestinins*

Selective hydrogenation of the 1,1-disubstituted alkene resulted in formation of tetracycle **221** as a single diastereoisomer. It was necessary to avoid over-reduction of the trisubstituted alkene because this led to a difficult separation of the resulting products. The selectivity of the hydrogenation reaction is dictated by the conformation of the tetracycle with only one face of the alkene accessible which results in formation of a single diastereoisomer.

3.8 Installation of Methyl Substituent at the C-12 Position

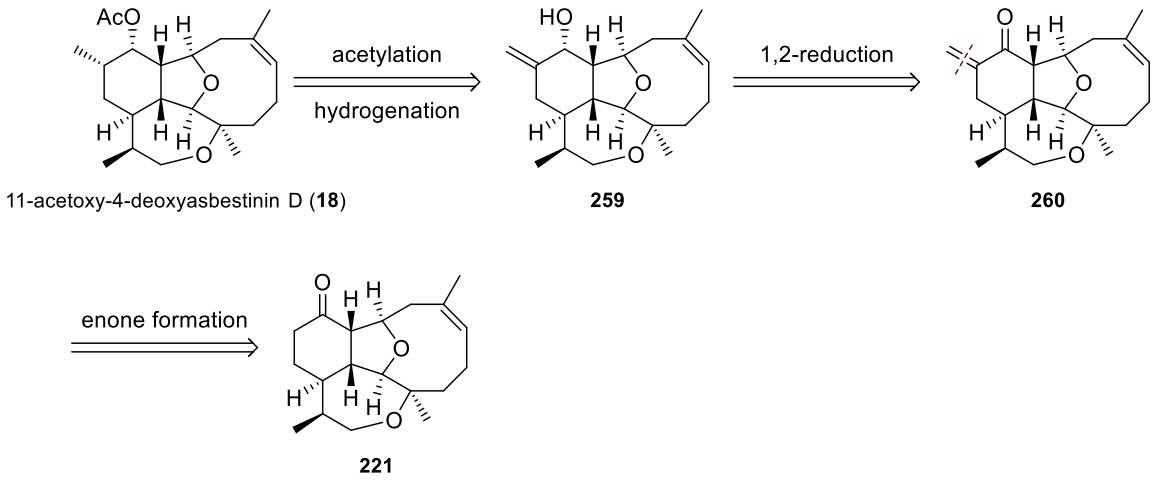
The tetracyclic core of the asbestinins had now been synthesised and so the next objective was stereoselective introduction of the methyl substituent at the C-12. Previous attempts to introduce this substituent to the tricyclic or tetracyclic core of the asbestinins had been unsuccessful or had failed to deliver the required diastereoisomer (Section 2.1).[70,71] For example, it had been shown that direct methylation of the tetracyclic ketone **(±)-221** led solely to formation of the undesired diastereoisomer **(±)-222**(Scheme 70).[71]



*Scheme 70: Direct Methylation of Tetracyclic Ketone **(±)-221***

Since direct methylation was not possible, an alternative approach to complete the synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**) was undertaken. It was envisaged that

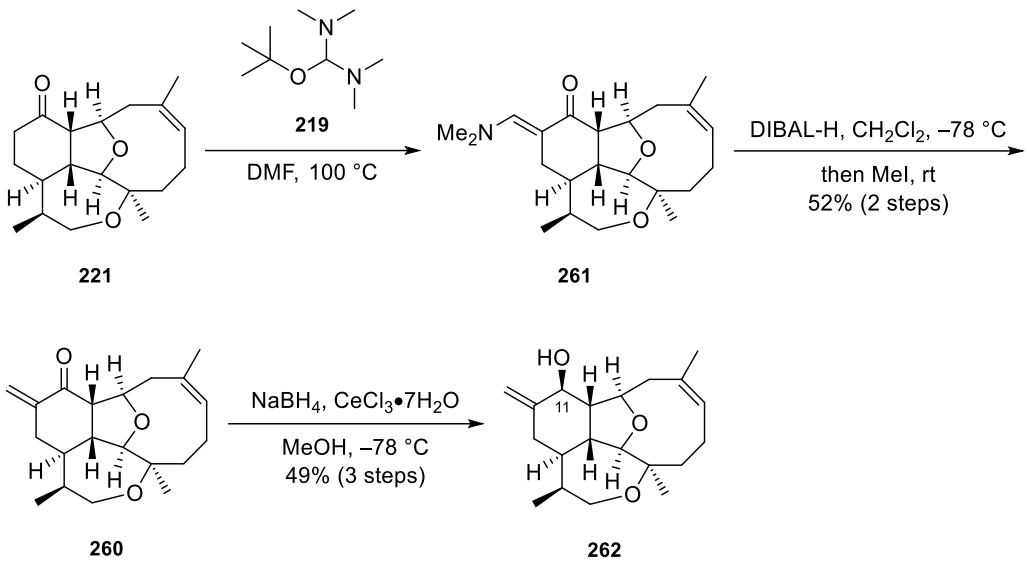
hydrogenation of allylic alcohol **259** followed by acetylation would give 11-acetoxy-4-deoxyasbestinin D (**18**, Scheme 71). This would allow the stereocentre at the C-12 position to be introduced stereoselectively by having the C-11 alcohol stereocentre set previously.



*Scheme 71: Retrosynthetic Analysis of 11-Acetoxy-4deoxyasbestinin D (**18**) from Tetracyclic Ketone **221***

Allylic alcohol **259** could be synthesised from the corresponding enone **260** by 1,2-reduction which could be accessible from the readily prepared tetracyclic ketone **221**. This route was very similar to one used by the Clark group to functionalise the tricyclic core of the asbestinins that had involved 1,4-conjugate reduction of an enone in an attempt to control the configuration of the C-12 stereocentre (Section 2.1, Scheme 51).[71]

The synthesis of enone **260** started by treatment of the tetracyclic ketone **221** with Bredereck's reagent **219** to give enaminone **261** (Scheme 72).[73] Reduction of enaminone **261** with diisobutylaluminium hydride followed by addition of methyl iodide led to formation of enone **260**. Attempts to prepare the enone **260** directly by use of Eschenmoser's salt were unsuccessful and only starting material was recovered from the reaction.[89]



*Scheme 72: Synthesis of Allylic Alcohol **262** through 1,2-Reduction of Enone **260***

At this stage, enone **260** could be isolated and characterised. However, higher yields were obtained when the enone was subjected to immediate 1,2-reduction under Luche conditions.[90] This procedure afforded the allylic alcohol **262** as the sole diastereoisomer in a 49% yield (over three steps). Allylic alcohol **262** had the undesired configuration at the C-11 position and there was no evidence for formation of the other diastereoisomer. The stereochemistry of the C-11 position was confirmed by single crystal X-ray analysis (Figure 23).

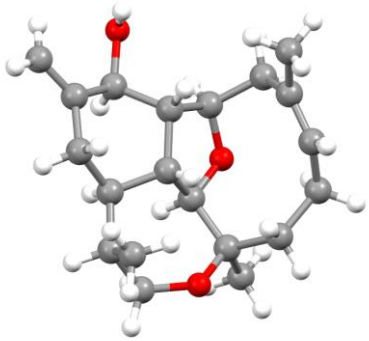
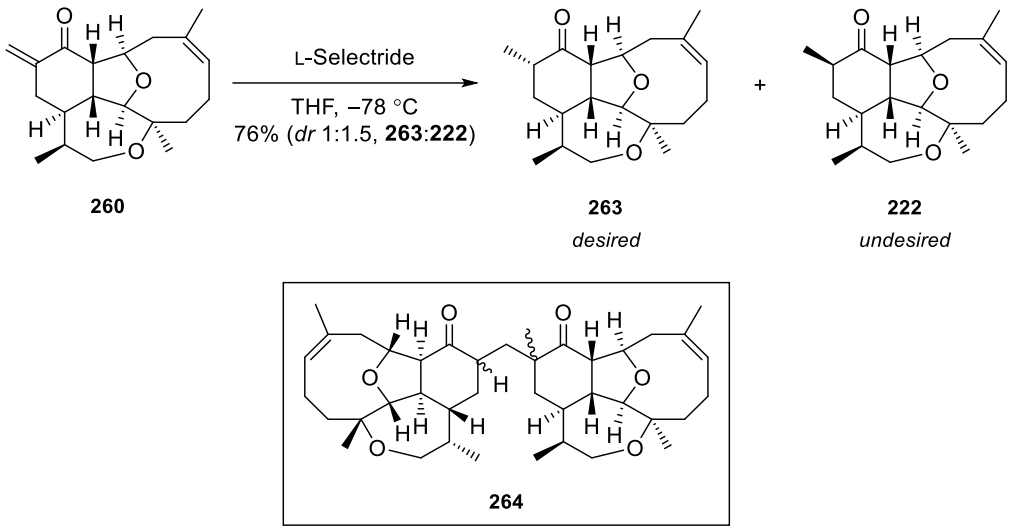


*Figure 23: Crystal Structure of Allylic Alcohol **262***

1,2-Reduction of the enone under Luche conditions produced the C-11 epimer of the required allylic alcohol and so a bulkier reducing agent was explored to discover whether it might be possible to reverse the selectivity observed previously (Scheme 73).[91]



*Scheme 73: 1,4-Conjugate Reduction of Enone **260** using L-Selectride*

Enone **260** was treated with L-Selectride but there was no evidence of the 1,2-reduction products. Instead, enone **260** underwent 1,4-conjugate reduction to produce a separable mixture of diastereomeric ketones **263** and **222** (*dr* 1:1.5, **263**:**222**). The desired diastereoisomer **263** was formed as the minor conjugate reduction product. Reproducibility of the reaction was a major issue because formation of the dimer **264** was difficult to control. Altering reaction conditions (concentration, temperature, reactant equivalents and order of addition) had a negligible effect on preventing formation of this dimer and variable yields were obtained. Both diastereoisomers were fully characterised in order to establish the relative stereochemistry of the newly formed centre. This was accomplished by single crystal X-ray analysis of major diastereoisomer **222** (C-12 epimer, Figure 24).

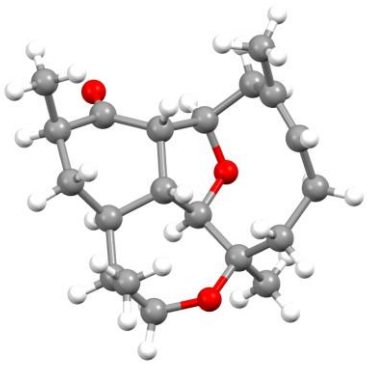
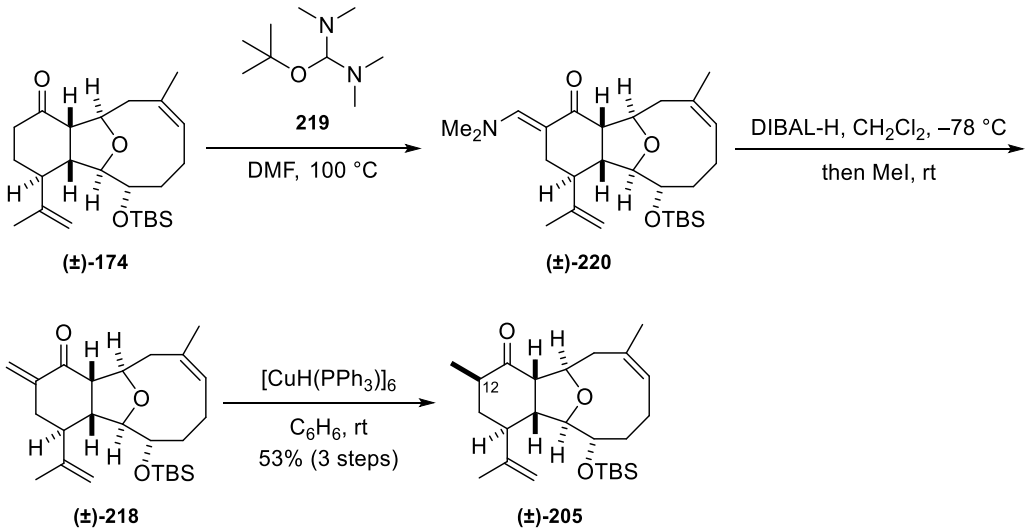


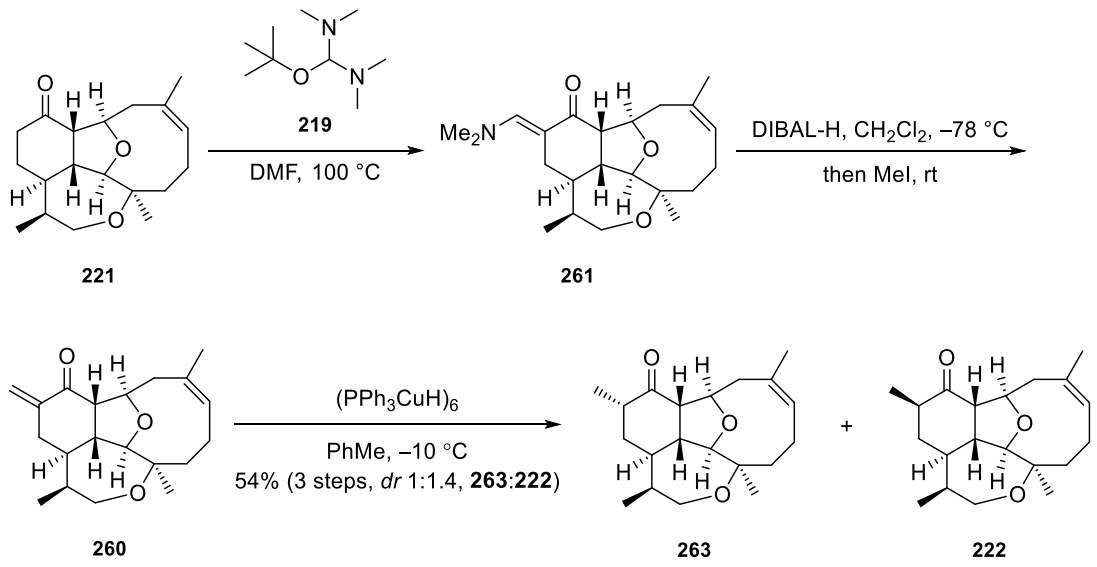
*Figure 24: Crystal Structure of Major Diastereoisomer **222***

Reduction of enone **260** using L-Selectride enabled formation of the desired diastereoisomer **263**. Unfortunately, the diastereoselectivity of the reaction was poor (*dr* 1:1.5, **263**:**222**) and there were issues with reproducibility as a consequence of dimer formation. To address these issues, alternative reducing conditions were explored based on previous work within the Clark group that had shown Stryker's reagent to be a useful alternative for the 1,4-conjugate reduction.[71] This reagent had been used to reduce the tricyclic enone **(±)-218** during initial attempts to install the methyl substituent at the C-12 position (Scheme 74). Even though the product with incorrect configuration at the C-12 stereocentre was produced, the reaction shows that 1,4-conjugate reduction of related systems in possible with Stryker's reagent.



*Scheme 74: Previous Work Concerning 1,4-Conjugate Reduction of Enone **(±)-218** with Stryker's Reagent*

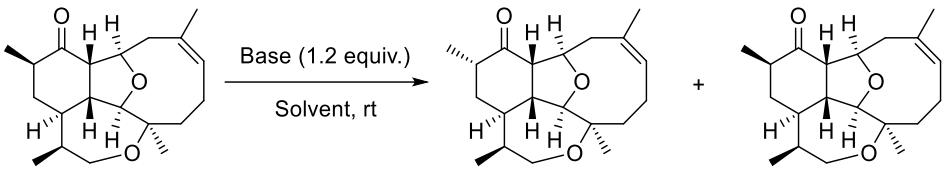
When 1,4-conjugate reduction of tetracyclic enone **260** was performed using Stryker's reagent, it resulted in the formation of diastereomeric ketones **263** and **222** (*dr* 1:1.4, **263**:**222**, Scheme 75).[74] Crucially, even though the ratio of diastereoisomers was nearly identical to that obtained when the reduction reaction was performed with L-Selectride, there was no evidence that dimerisation had occurred. Ketones **263** and **222** were isolated in a 54% yield with no starting material recovered.



*Scheme 75: 1,4-Conjugate Reduction of Enone **260** with Stryker's Reagent*

A possible explanation for the abolition of dimerisation is the strength of the complex formed between copper and enolate generated. Stronger complexation would make the enolate less nucleophilic and thus reduce the rate of competitive Michael addition to unreacted enone.

The diastereoisomers were separable and so epimerisation at C-12 of **222** to give the required ketone **263** was investigated under various conditions (Table 4).



222 **263** **222**

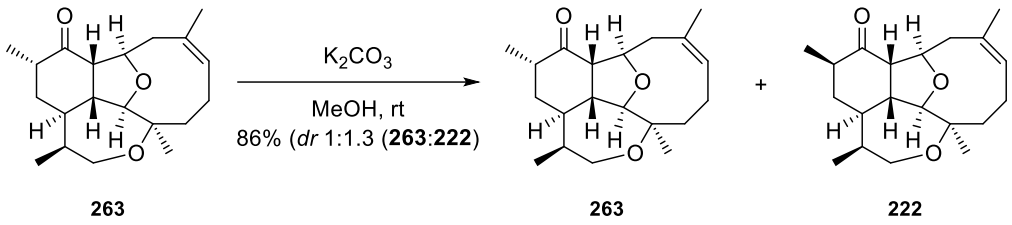
*Table 4: Epimerisation of **222***

Entry	Base	Solvent	Time (h)	Ratio (*dr* 263:222)[a]
1	K_2CO_3	MeOH	16	1:1.3[b]
2	DBU	THF	16	1:4
3	Et_3N	CH_2Cl_2	16	1:9
4	K_2CO_3	MeOH	64	1:1.3

[a] *dr* determined was by ^{1}H NMR analysis of crude material after aqueous work-up; [b] isolated yield of 99%

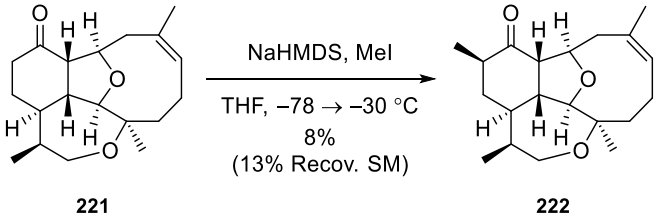
Under conditions previously employed after the Diels–Alder cycloaddition reaction to form the tricyclic core of the asbestinins (potassium carbonate in methanol for 16 hours), a diastereomeric ratio of 1:1.3 (**263**:**222**) was obtained (Entry 1). The ratio of diastereoisomers was not improved when weaker bases such as DBU and triethylamine were employed (Entries 2 and 3). Prolonged reaction times had no effect on the ratio of diastereomeric products when the reaction was performed with potassium carbonate and methanol (Entry 4). The observation that extended reaction times had no effect on the diastereomeric ratio (1:1.3, **263**:**222**) suggested that this the final thermodynamic mixture of products had been obtained.

To confirm the thermodynamic ratio of products, the required diastereoisomer **263** was treated with potassium carbonate and methanol under identical conditions (Scheme 76). The diastereomeric ratio was identical to that obtained from the epimerisation of **222**, which proved that this was the thermodynamic ratio for the diastereomeric ketones.



*Scheme 76: Epimerisation of Desired Diastereoisomer **263***

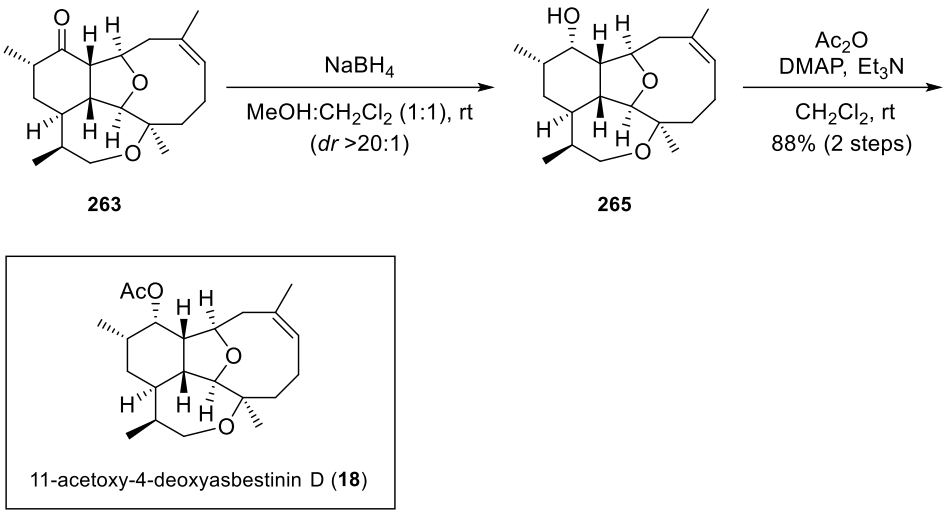
At this stage, direct methylation of tetracyclic ketone **221** was revisited because full characterisation of both diastereoisomers permitted easier analysis of the reaction products. Direct methylation was performed by treating tetracyclic ketone **221** with sodium hexamethyldisilazide followed by addition of methyl iodide (Scheme 77).[71] Even though the yield of the reaction could not be replicated, the stereochemical outcome was identical to that obtained previously and the ketone **222** was obtained without formation of the required diastereoisomer **263**. Direct alkylation of **221** was not explored further because it was clear that the facial selectivity for reaction of the enolate with electrophiles would result in formation of the diastereoisomer with the incorrect configuration at C-12.



*Scheme 77: Direct Methylation of Tetracyclic Ketone **221** with Methyl Iodide*

3.9 Completion of the Total Syntheses of 11-Acetoxy-4-deoxyasbestinin D (18) and 4-Deoxyasbestinin C (19)

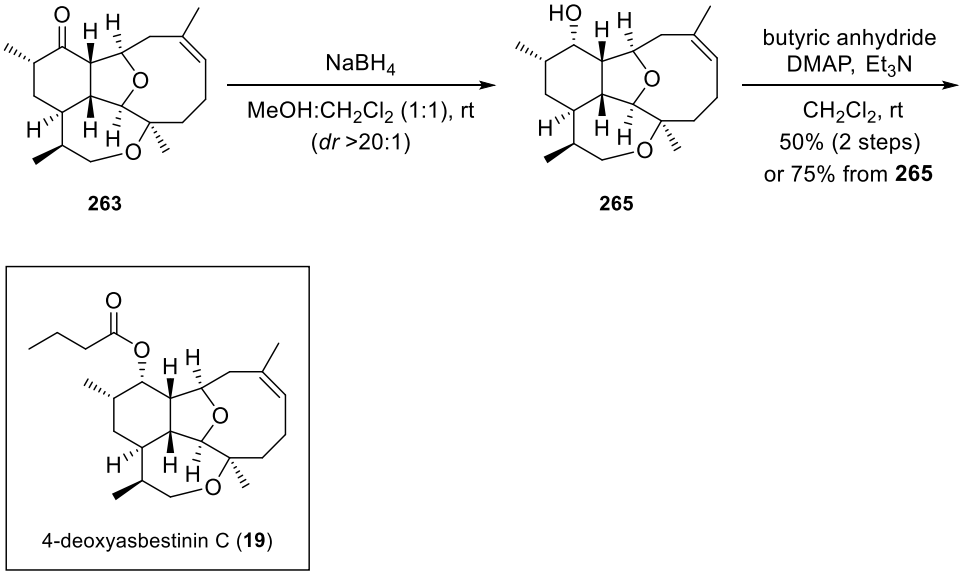
Successful synthesis of the required diastereoisomer **263** meant that the final steps of the synthesis of natural product 11-acetoxy-4-deoxyasbestinin D (**18**) could be explored (Scheme 78). The first step was stereoselective reduction of ketone **263**. Reduction of the ketone with sodium borohydride was highly diastereoselective (*dr* >20:1) and gave the required alcohol **265**, which was of sufficient purity to be used directly in the subsequent reaction. Immediate acetylation of alcohol **265** delivered the natural product 11-acetoxy-4-deoxyasbestinin D (**18**) in excellent yield over two steps (88%).



*Scheme 78: Completion of Total Synthesis of 11-Acetoxy-4-deoxyasbestinin D (**18**)*

This sequence completed the second total synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**). The synthesis had been accomplished in a total of 31 steps and with an overall yield of 2% from butan-1,4-diol **178**. The spectroscopic and other characterisation data (optical rotation, mass spectrometry, IR spectrum) matched those reported for the isolated natural product as well as those reported by Crimmins and co-workers for the synthetic material.[8,12,13]

The next synthetic target was 4-deoxyasbestinin C (**19**) which could be obtained by esterification of the alcohol **265** to form a butanoate instead of an acetate.[8] The natural product was synthesised from ketone **263** in two steps (Scheme 79).



*Scheme 79: Completion of Total Synthesis of 4-Deoxyasbestinin C (**19**)*

As before, reduction of ketone **263** with sodium borohydride gave alcohol **265** with excellent diastereoselectivity. Subsequent esterification with butyric anhydride gave the natural product 4-deoxyasbestinin C (**19**) in 50% yield over two steps. Thus, the first total synthesis of 4-deoxyasbestinin C (**19**) was completed in 31 steps and with an overall yield of 1% from butan-1,4-diol **178**. The spectroscopic and other characterisation data matched those reported for the isolated natural product.[8] 4-Deoxyasbestinin C (**19**) was also synthesised from purified alcohol **265** in 75% yield.

3.10 Synthesis of Further Members of the 4-Deoxyasbestinin Series

Completion of 11-acetoxy-4-deoxyasbestinin D (**18**) and 4-deoxyasbestinin C (**19**) allowed the synthesis of other members of the 4-deoxyasbestinin series to be explored. Several targets (proposed structures) that could be synthesised from 11-acetoxy-4-deoxyasbestinin D (**18**) are shown in Figure 25.[9-11]

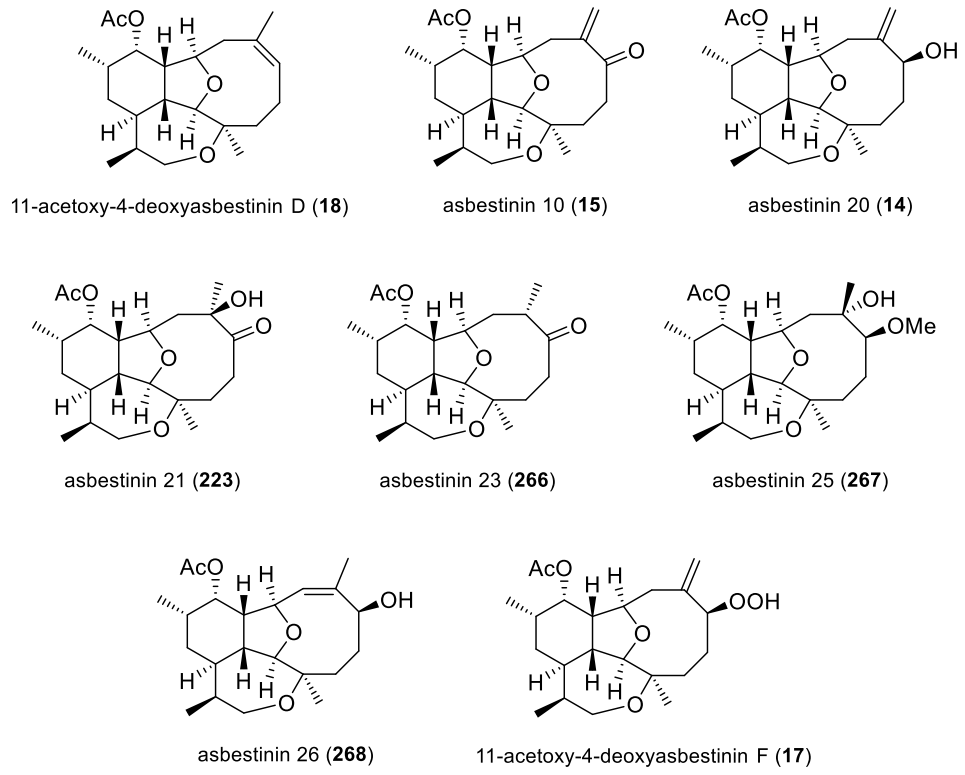


*Figure 25: Members of the Asbestinin Family (Proposed Structures) Accessible from 11-Acetoxy-4-deoxyasbestinin D (**18**)*

3.10.1 Synthesis of Asbestinin 20 (14) and 6-*epi*-Asbestinin 20 (16)

The initial goal was to use 11-acetoxy-4-deoxyasbestinin D (**18**) as a starting point for the synthesis of asbestinin 20 (**14**).[10] Asbestinin 20 (**14**) had originally been identified as the alcohol **13**, but its structure had been revised upon re-isolation of the natural product by Rodriguez and Ospina in 2006 (Figure 26).[11]

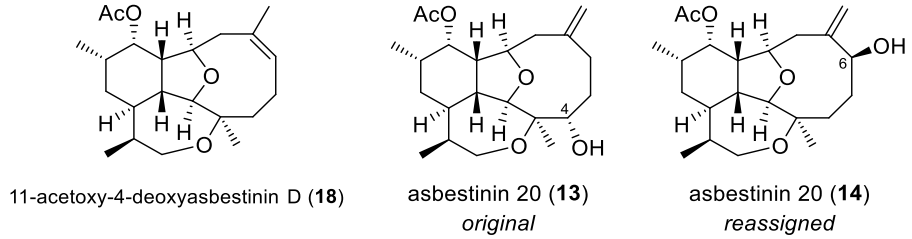
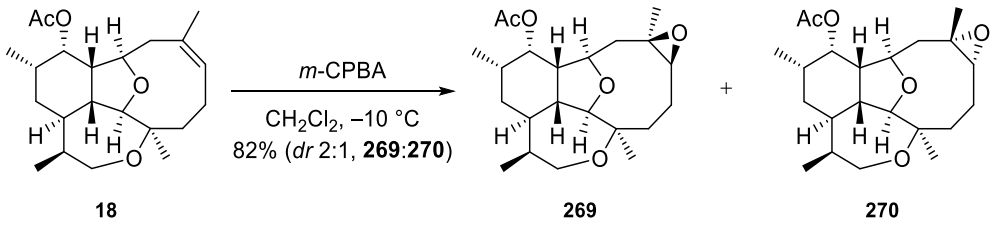


*Figure 26: Original (**13**) and Revised (**14**) Structures of Asbestinin 20*

Structural reassignment related to relocation of the hydroxyl group at the C-4 position in the originally proposed structure **13** to the C-6 position to give **14** as the new structure for asbestinin 20. This reassignment applies to the whole 4-deoxyasbestinin series and completion of the total synthesis of asbestinin 20 (**14**) would either confirm the reassignment or provide evidence that further structural revision was required. The strategy employed to synthesise asbestinin 20 (**14**) was to epoxidise 11-acetoxy-4-deoxyasbestinin D (**18**) and then rearrange the epoxide to give an allylic alcohol.

Initially, epoxidation was performed by treatment of 11-acetoxy-4-deoxyasbestinin D (**18**) with *meta*-chloroperoxybenzoic acid (Scheme 80). This reaction delivered diastereomeric epoxides **269** and **270** in excellent yield with a diastereomeric ratio of 2:1 (**269**:**270**).



*Scheme 80: Epoxidation of 11-Acetoxy-4-deoxyasbestinin D (**18**) with meta-Chloroperoxybenzoic Acid*

The crystalline epoxides **269** and **270** were separable by chromatography and their structures established by single crystal X-ray analysis (Figure 27). Identification of the diastereoisomers meant that studies to enhance or reverse the diastereoselectivity could be undertaken.

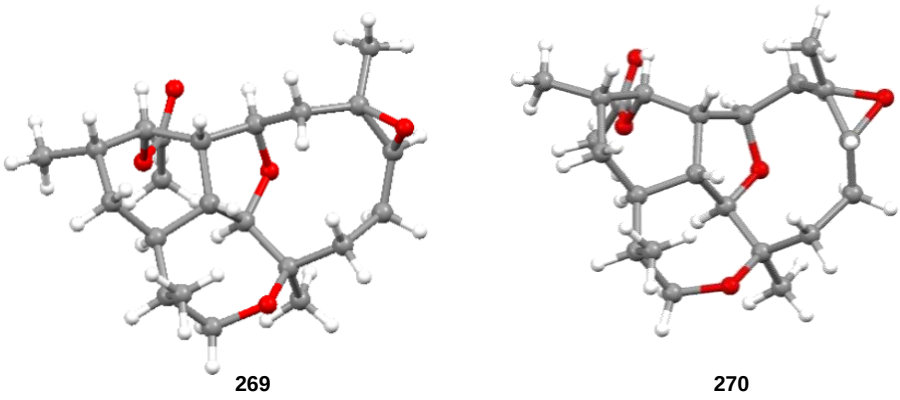
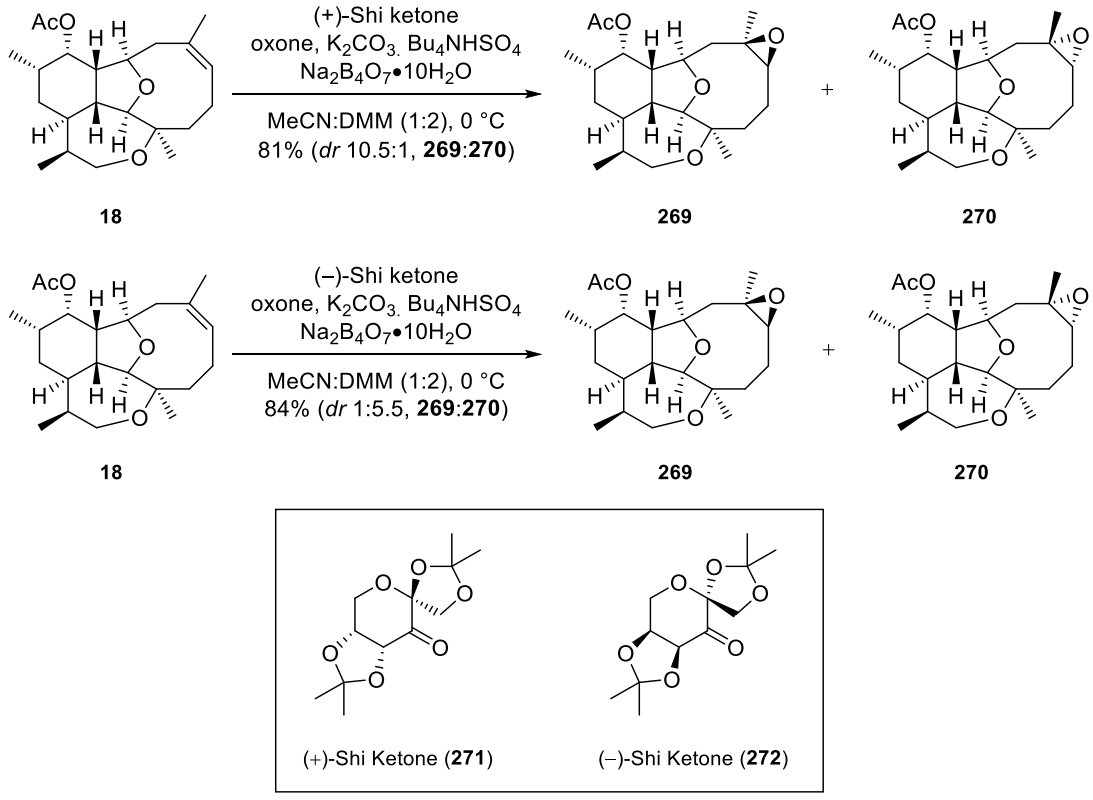


*Figure 27: Crystal Structures of Diastereomeric Epoxides **269** and **270***

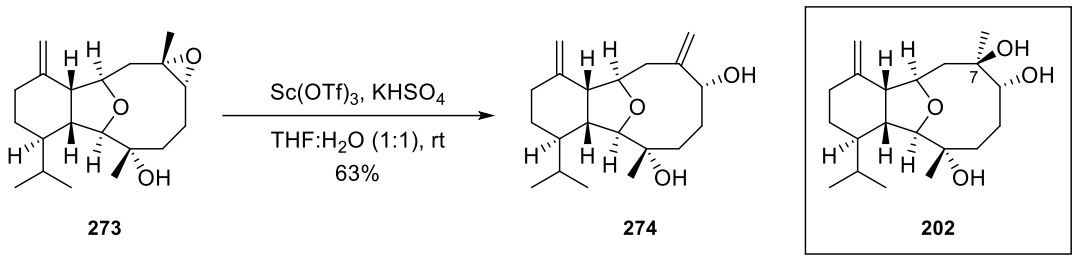
Shi's asymmetric protocol was investigated as a method to amplify or reverse the weak substrate bias of the epoxidation reaction.[93,94] Both enantiomers of Shi's fructose-derived catalyst were prepared and employed in the epoxidation reaction (Scheme 81). For the catalyst derived from unnatural fructose [(+)-Shi ketone (**271**)], the weak substrate bias was reinforced and the ratio of diastereoisomers improved to 10.5:1 (**269**:**270**). In the mismatched case where the catalyst derived from natural fructose [(−)-Shi ketone (**272**)] was used, the substrate bias was overturned and a 1:5.5 mixture of diastereoisomers (**269**:**270**) was obtained.



*Scheme 81: Shi Epoxidation of 11-Acetoxy-4-deoxyasbestinin D (**18**)*

The use of Shi's asymmetric epoxidation protocol allowed both epoxides to be obtained in a highly diastereoselective manner, which would allow the synthesis of asbestinin 20 as well its C-6 diastereoisomer. This would provide conclusive proof of the configuration of the hydroxyl-bearing carbon and also confirm the position of the hydroxyl group on the nine membered ring.

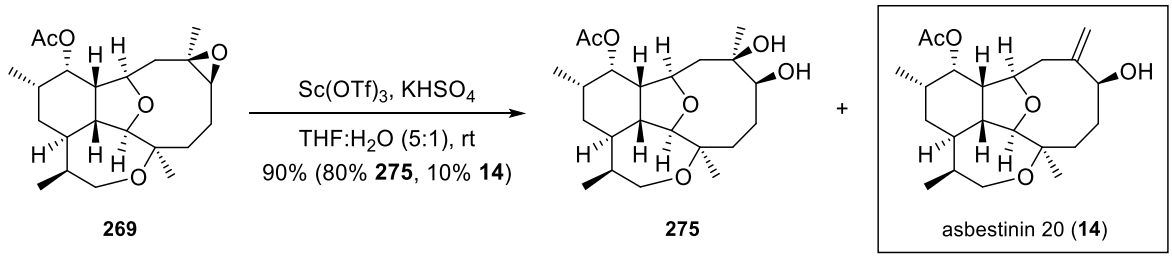
Previous work performed within the Clark group during the total synthesis of members of the cladiellin family of natural products showed that an analogous Lewis acid-mediated epoxide rearrangement reaction was possible (Scheme 82).[69]



*Scheme 82: Rearrangement of Epoxide **273** under Lewis Acid Conditions Used in the Synthesis of Members of the Cladiellin Family*

It had been shown that reaction of epoxide **273** with scandium triflate in the presence of potassium bisulfate afforded the allylic alcohol **274** in reasonable yield. Interestingly, when the reaction was performed under strong Brönsted acid conditions (sulfuric acid in this case) the triol **202** was obtained as a side product. It is likely that the triol was obtained by protonation of the epoxide followed by formation of a stable tertiary carbocation at the C-7 position. Subsequent addition of water present in the reaction mixture, results in formation of the triol **202**.

Based on this precedent, epoxide **269** was treated with scandium triflate in the presence of potassium bisulfate (Scheme 83). Two products were formed from the rearrangement reaction and the major product was diol **275** in contrast to the result obtained for the cladiellin system. The allylic alcohol was asbestinin 20 (**14**), but it was a minor product and was obtained in a yield of 10%.



*Scheme 83: Rearrangement of Epoxide **269** under Lewis Acid Conditions*

The spectroscopic and other characterisation data for allylic alcohol **14** matched those of the isolated natural product reported by Rodriguez and Ospina. The relative structures of the diol **275** and asbestinin 20 (**14**) were established unambiguously by single crystal X-ray analysis (Figure 28). Thus, the first total synthesis of asbestinin 20 had been completed and structural revision proposed by Rodriguez and Ospina had been confirmed.[10,11,95]

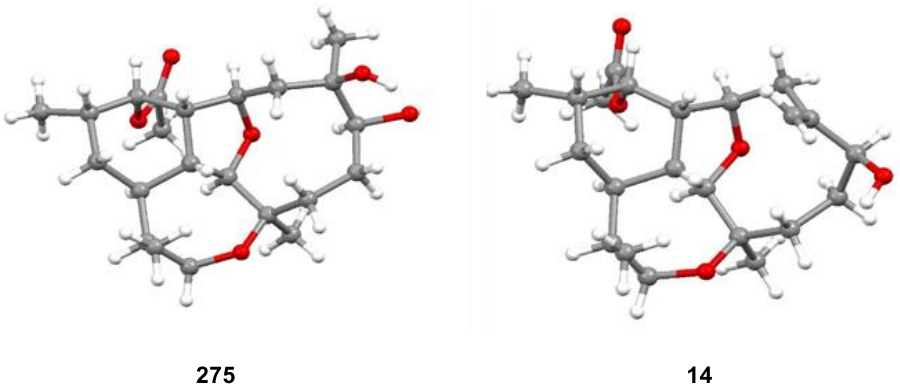
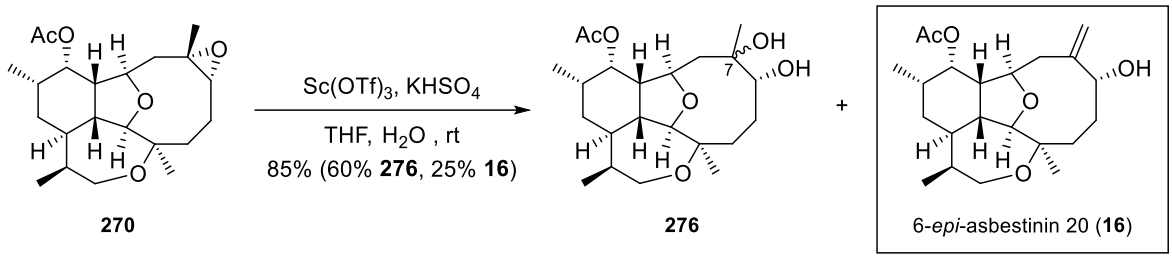


*Figure 28: Crystal Structures of Diol **275** and Asbestinin 20 (**14**)*

When the rearrangement reaction of the epoxide **269** is compared to that for cladiellin **273**, some keys differences are apparent. Firstly, the allylic alcohol **13** was the minor product and the diol **275** was the major product. Secondly, the relative stereochemistry of diol **275** differs from that of diol **274**, which suggests that the oxepane ring influences the reactivity of the epoxide and the conformation of the cationic intermediate.

Following completion of the synthesis of asbestinin 20, rearrangement of epoxide **270** to produce the diastereomeric alcohol was investigated. In the case of epoxide **269**, rearrangement led to the formation of asbestinin 20 (**14**) and diol **275** and so it was expected that rearrangement of epoxide **270** would produce 6-*epi*-asbestinin 20 (**16**) and the corresponding diol.[11] Reaction conditions were altered slightly and the amount of water was decreased in an effort to favour formation the allylic alcohol by making nucleophilic attack less likely. When the reaction was performed under these conditions, the epoxide **270**

underwent rearrangement to give a mixture of diols **276** and 6-*epi*-asbestinin 20 (**16**, Scheme 84).



*Scheme 84: Rearrangement of Epoxide **270** under Lewis Acid Conditions*

Synthetic 6-*epi*-asbestinin 20 (**16**) had spectroscopic and other characterisation data that matched data reported by Rodriguez and Ospina in 2006 for compound obtained by reduction of natural asbestinin 10.[11,95] The relative stereochemistry and structure of 6-*epi*-asbestinin 20 (**16**) was established unambiguously by single crystal X-ray (Figure 29).

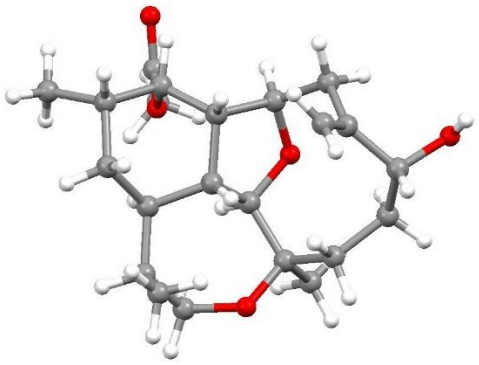
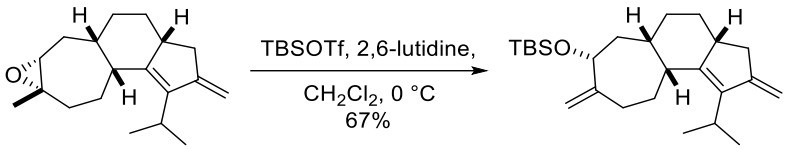


*Figure 29: Crystal Structure of 6-epi-Asbestinin 20 (**16**)*

The diols **276** obtained from the rearrangement reaction were inseparable and it was not possible to obtain a diastereomeric ratio from this mixture of the C-7 diol diastereoisomers due to overlapping peaks in the proton NMR.

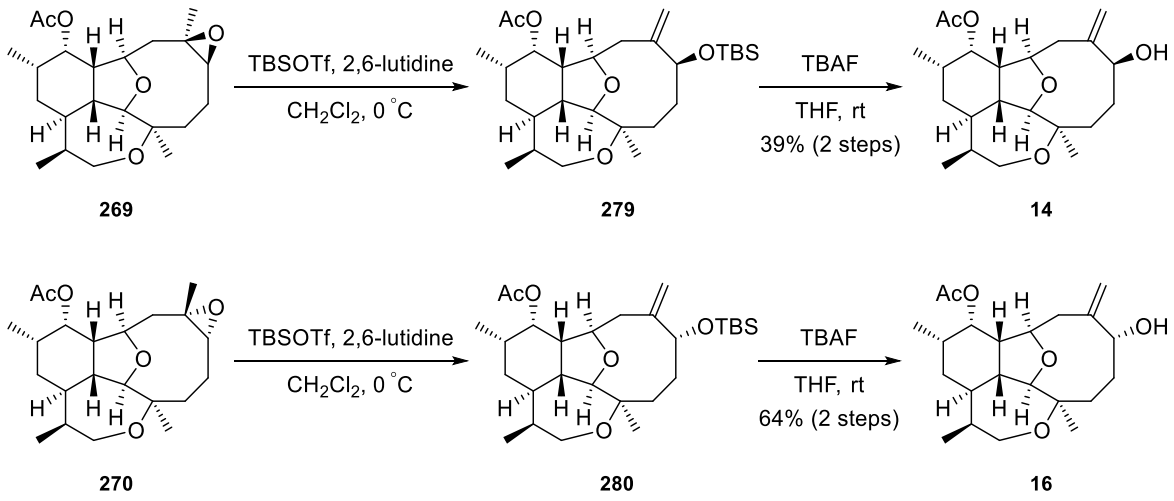
Neither epoxide rearrangement reaction had provided the allylic alcohol as the major product and so alternative routes to accomplish this rearrangement reaction were investigated. Yang and co-workers had reported the use of *tert*-butyldimethylsiyl trifluoromethanesulfonate to rearrange the tricyclic epoxide **277** to give the silyl protected allylic alcohol **278** in reasonable yield (67%) during their stereoselective total synthesis of (±)-5-*epi*-cyanthiwigin I (Scheme 85).[96]



277 278

*Scheme 85: Rearrangement of Epoxide **277** During the Synthesis of (±)-5-*epi*-Cyanthiwigin I*

This procedure was applied to rearrangement of the epoxides **269** and **270** and they were treated with *tert*-butyldimethylsiyl trifluoromethanesulfonate in the presence of 2,6-lutidine (Scheme 86). For epoxide **269**, asbestinin 20 (**14**) was obtained by initial formation of silyl-protected allylic alcohol **279** and then treated with *tetra-N*-butylammonium fluoride. This procedure gave asbestinin 20 (**14**) in moderate yield over two steps (39%). In the case of epoxide **270**, sequential rearrangement followed by silyl deprotection gave 6-*epi*-asbestinin 20 (**16**) in a much higher yield over two steps (64%). The difference in yield for the two reactions is likely to be due to the different conformations adopted by the epoxides, with the conformation of the epoxide **270** allowing easier silylation of the epoxide in this case. This hypothesis is supported by examination of the X-ray crystal structures of the epoxides **269** and **270** (Section 3.10.1): the epoxide oxygen of **269** points to the interior of the ring whereas the epoxide lies outside the medium-sized ring in **270**.



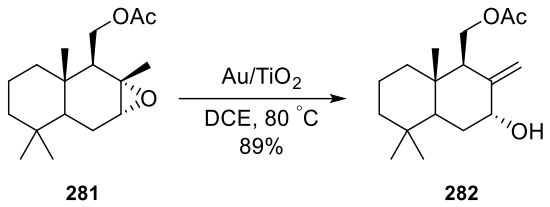
269 279 14

270 280 16

*Scheme 86: Rearrangement of Epoxides **269** and **270** to Give Allylic Alcohols **14** and **16***

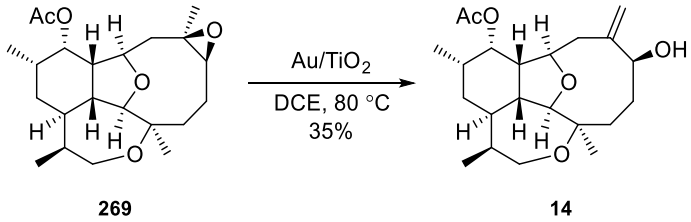
An alternative method for the epoxide rearrangement was investigated in an attempt to improve the yield of the allylic alcohol **14** from the epoxide **269**. The new method was based on work performed by Garcia and Stratakis.[97] These workers had reported the

rearrangement of epoxide **281** to give allylic alcohol **282** by reaction with titania-supported gold nanoparticles (Scheme 87).



*Scheme 87: Rearrangement of Epoxide **281** Reported by Garcia and Stratakis*

It had been shown that the reaction was generally applicable to a variety of different epoxides and exhibits high selectivity for formation of the allylic alcohol over other products and so the procedure was applied to the rearrangement of epoxide **269**.Treatment of epoxide **269** with titania-supported gold nanoparticles afforded asbestinin 20 (**14**) in 35% yield, a yield that was comparable to that obtained from the previous the two-step procedure using *tert*-butyldimethylsilyl trifluoromethanesulfonate (Scheme 88).

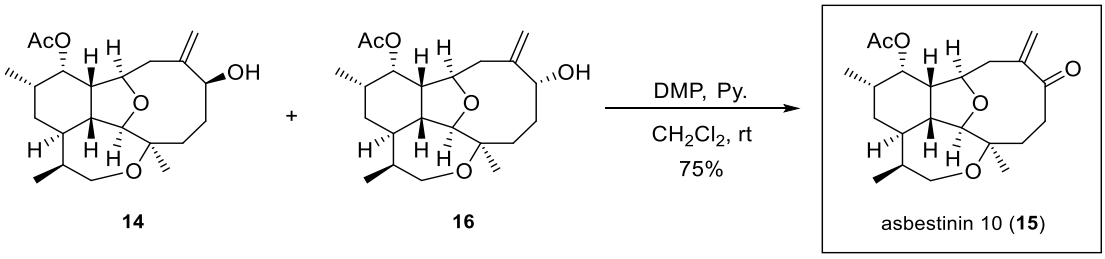


*Scheme 88: Rearrangement of Epoxide **269** using Titania-supported Gold Nanoparticles*

The reaction progressed slowly and it was necessary to heat the reaction mixture for an extended period (two days compared to 30 minutes reported by Garcia and Stratakis in their general procedure).[97] The reaction of epoxide **269** in the presence of the titania-supported gold nanoparticles not only gave allylic alcohol **14** but also led to formation of decomposition products. The only characterisable product isolated from the reaction was asbestinin 20 (**14**) and starting material was not recovered.

3.10.2 Synthesis and Reduction of Asbestinin 10 (15)

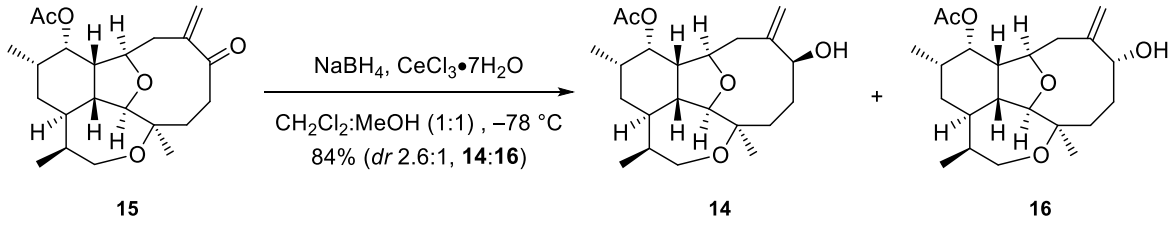
Following the successful total synthesis of asbestinin 20 (**14**) and the synthesis of 6-*epi*-asbestinin 20 (**16**), the next objective was the synthesis of asbestinin 10 (**15**, Scheme 89).[9] This goal was achieved by oxidation of a mixture of the allylic alcohols (1:2, **14**:**16**) with Dess–Martin periodinane to give asbestinin 10 (**15**).



*Scheme 89: Completion of the Total Synthesis of Asbestinin 10 (**15**)*

This oxidation reaction completed the first total synthesis of asbestinin 10 (**15**) and this natural product had been obtained from 11-acetoxy-4-deoxyasbestinin D (**18**) in three steps. The spectroscopic and other characterisation data for compound **15** matched those reported for isolated of asbestinin 10 (**15**) by Rodriguez and Ospina and confirmed their structural reassignment.[9,95]

In 2006, Rodriguez and Ospina reported that reduction of asbestinin 10 (**15**) with sodium borohydride produced asbestinin 20 (**14**) and 6-*epi*-asbestinin 20 (**16**) in a 3:1 ratio (**14**:**16**).[11] A similar reduction of asbestinin 10 (**15**) was performed under Luche conditions to limit competitive conjugate reduction (Scheme 90).



*Scheme 90: Reduction of Asbestinin 10 (**15**) under Luche Conditions*

The 1,2-reduction afforded the allylic alcohols in a 2.6:1 ratio (**14**:**16**) which was consistent with the product ratio reported by Rodriguez and Ospina. Completion of the synthesis of asbestinin 10 (**15**) meant that attention could be focussed on the synthesis of the butanoate derivative asbestinin 9 (**283**).

3.10.3 Towards the Synthesis of Asbestinin 9 (283)

Asbestinin 9 (**283**) is structurally related to asbestinin 10 and the only difference in their structures is the presence of a butanoate group instead of an acetate group at C-11 (Figure 30).[9] It was expected that asbestinin 9 (**283**) could be synthesised from

4-deoxyasbestinin C (**19**) following the previously described route for the synthesis of asbestinin 10 (**14**).

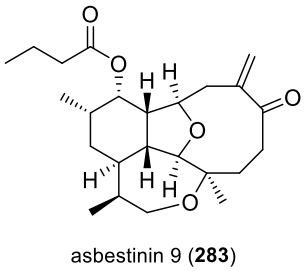
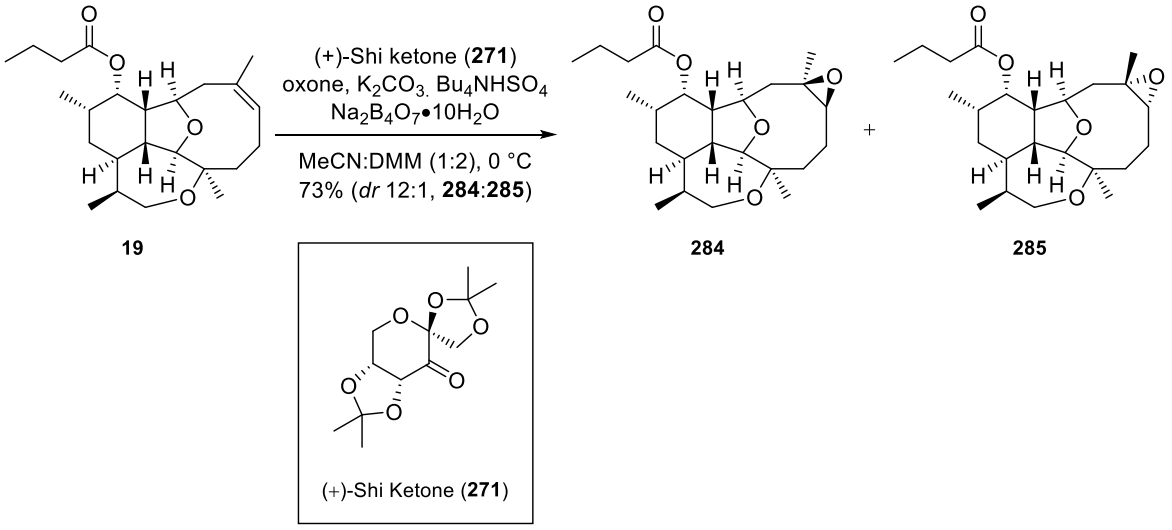


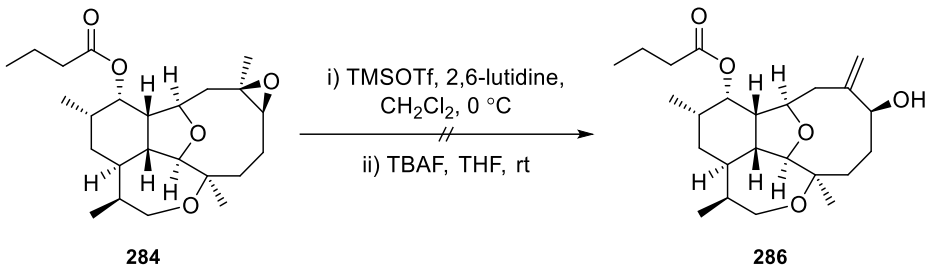
*Figure 30: Structure of Asbestinin 9 (**283**)*

The synthesis of asbestinin 9 (**283**) commenced with epoxidation of 4-deoxyasbestinin C (**19**) using Shi's asymmetric protocol and employing the (+)-Shi ketone (**271**) as the catalyst (Scheme 91).[93] This reaction afforded the required epoxide **284** with extremely high diastereoselectivity (*dr* 12:1, **284**:**285**).



*Scheme 91: Synthesis of Epoxide **284** from 4-Deoxyasbestinin C (**19**)*

The rearrangement of the newly formed epoxide **284** was attempted (Scheme 92). It was expected that switching from the use of *tert*-butyldimethylsilyl trifluoromethanesulfonate to trimethylsilyl trifluoromethanesulfonate would allow silyl deprotection to been accomplished during work-up and the allylic alcohol would be obtained directly from the rearrangement reaction. Epoxide **284** was treated with trimethylsiyl trifluoromethanesulfonate in the presence of 2,6-lutidine but only decomposition was observed.



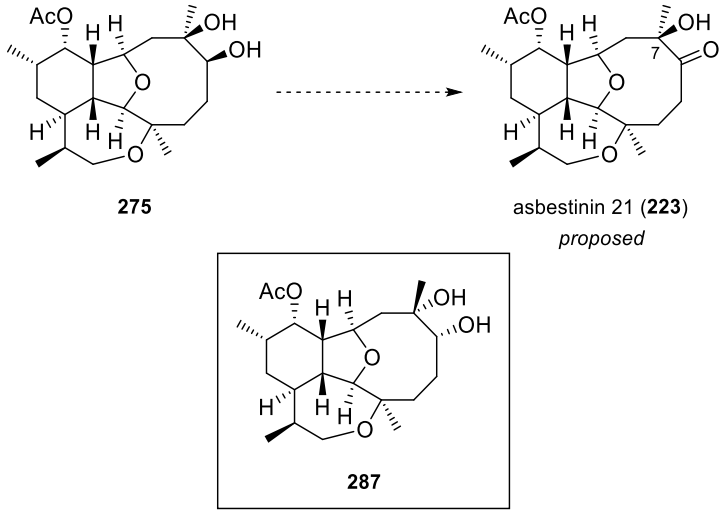
284 **286**

*Scheme 92: Attempted Rearrangement of Epoxide **284***

This unfortunate result combined with a lack of material meant that the synthesis of asbestinin 9 (**283**) was not completed. Instead, work focussed on the synthesis of other members of the asbestinin family that could be prepared from 11-acetoxy-4-deoxyasbestinin D (**18**).

3.10.4 Synthesis of Asbestinin 21 (288) by Dihydroxylation of 11-Acetoxy-4-deoxyasbestinin D (18)

The diol **275** had been obtained during the synthesis of asbestinin 20 (**14**) and it was envisaged that this diol could be used for the synthesis of the proposed structure of asbestinin 21 (**223**) by simple oxidation of the secondary hydroxyl group (Scheme 93).[10,11]



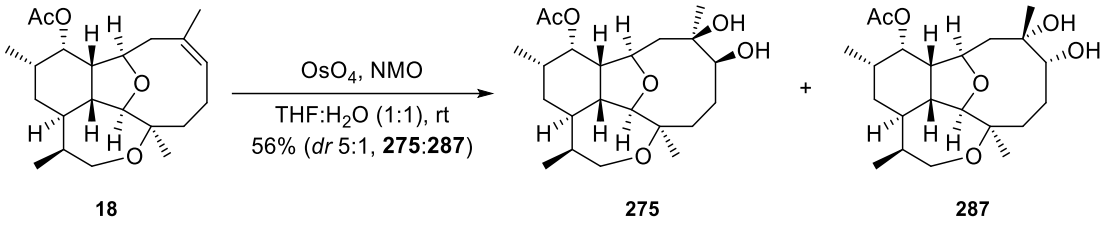
275 asbestinin 21 (**223**) *proposed*

287

*Scheme 93: Proposed Route for the Synthesis of Asbestinin 21 (**223**)*

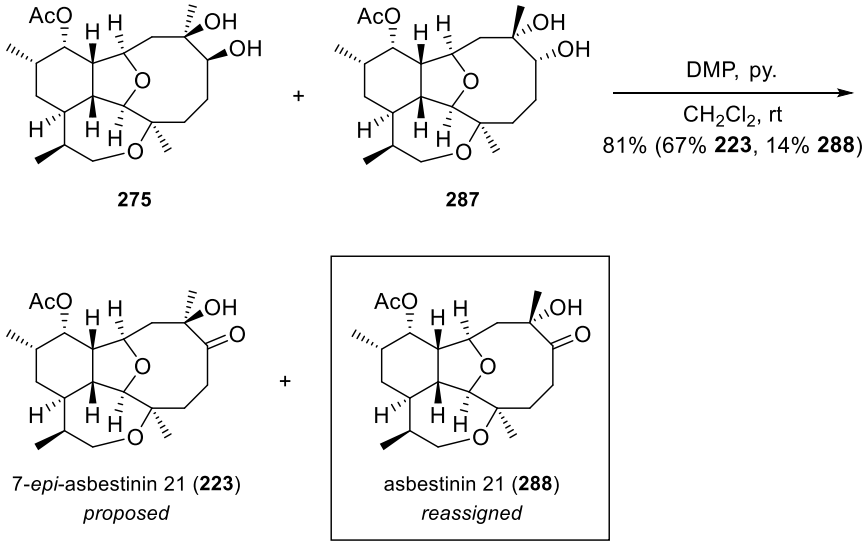
The goal was to synthesise asbestinin 21 (**223**) and its C-7 epimer which would be available from diol **287**. Since it was not possible to obtain diol **287** by use of the previously described routes, the dihydroxylation reaction of 11-acetoxy-4-deoxyasbestinin D (**18**) was investigated. Treatment of 11-acetoxy-4-deoxyasbestinin D (**18**) with osmium tetroxide

under Upjohn conditions provided a diastereomeric mixture of *syn*-diols **275** and **287** (*dr* 5:1, **275**:**287**) in moderate yield (Scheme 94).[98]



*Scheme 94: Dihydroxylation of 11-Acetoxy-4-deoxyasbestinin D (**18**) under Upjohn Conditions*

The diols were difficult to separate but they were later found to be separable by chromatography using a mixture of dichloromethane and methanol. At this stage, the 5:1 mixture of diols was oxidised directly with Dess–Martin periodinane to deliver a mixture of asbestinin 21 (**288**) and 7-*epi*-asbestinin 21 (**223**, Scheme 95).

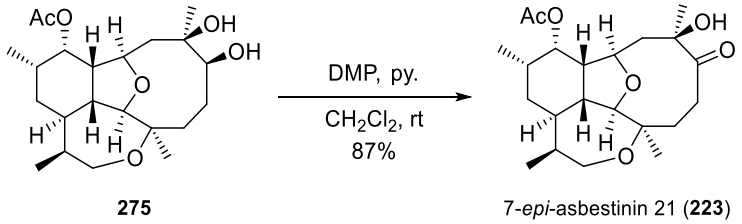


*Scheme 95: Oxidation of Diols **275** and **287** to Afford Asbestinin 21 (**288**) and 7-epi-*Asbestinin 21 (**223**)

The α-hydroxy ketones were separable by chromatography and permitted full characterisation of both asbestinin 21 (**288**) and 7-*epi*-asbestinin 21 (**223**) to be accomplished. Comparison of the proton and carbon NMR data of the α-hydroxy ketones **288** and **223** with the data reported for asbestinin 21 isolated from natural sources revealed that the natural product had been mis-assigned by Rodriguez and Ospina when they performed their structural revision (Appendix 7.1).[10,11,95] The proposed structure of asbestinin 21 in fact corresponded to the C-7 epimer **223** and the natural product was

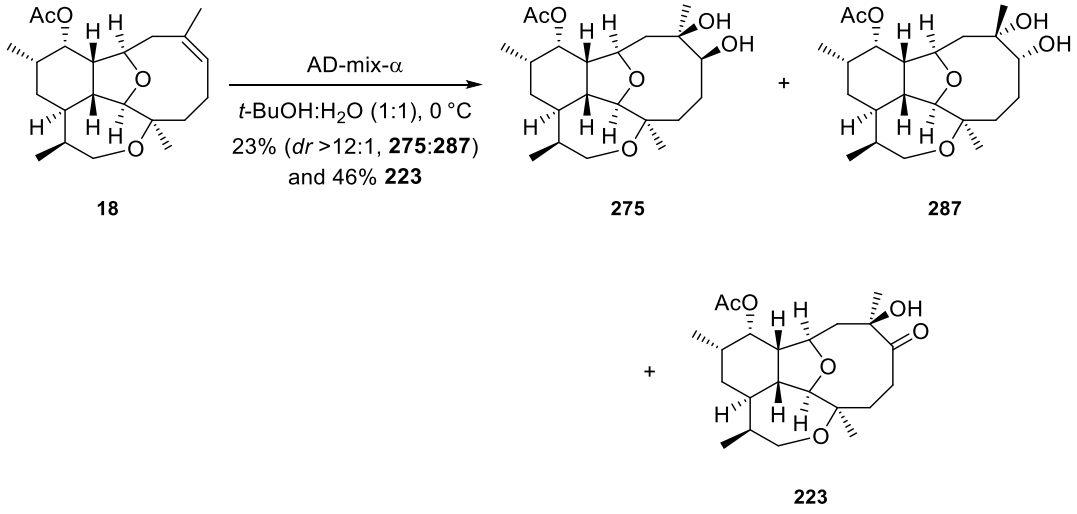
compound **288**. The other characterisation data for α-hydroxy ketone **288** matched those reported for the isolated asbestinin 21 (**288**).[10]

7-*epi*-Asbestinin 21 (**223**) was also synthesised directly in 87% yield by oxidation of the diol **275** with Dess–Martin periodinane (Scheme 96).



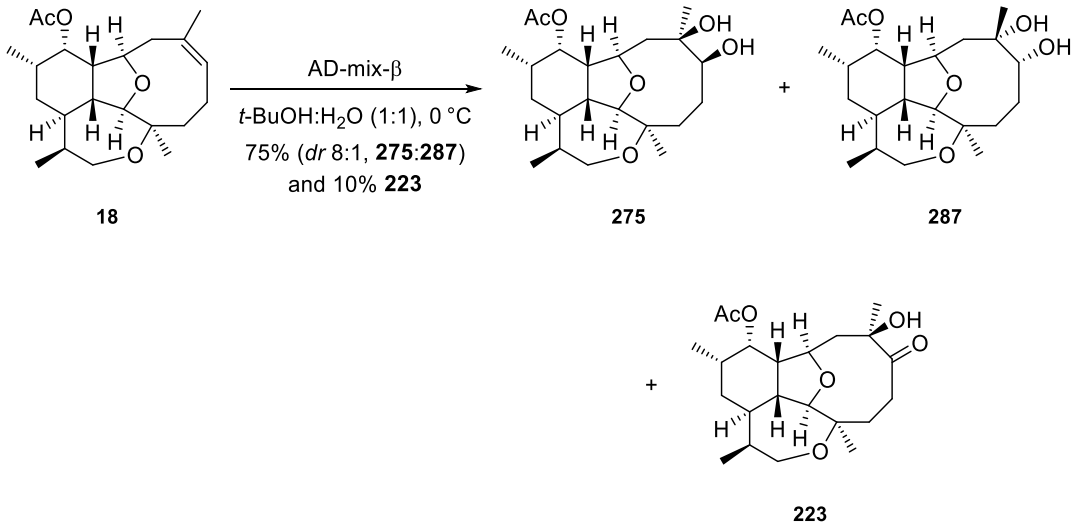
*Scheme 96: Oxidation of Diol **275** to give 7-epi-Asbestinin 21 (**223**)*

After completion of the total synthesis of asbestinin 21 (**288**) and its C-7 epimer **223**, attempts were made to reverse the selectivity of the dihydroxylation reaction of 11-acetoxy-4-deoxyasbestinin D (**18**). The dihydroxylation of **18** was performed according to the Sharpless asymmetric protocol with the expectation that there would be a matched-mismatched relationship between the catalyst and substrate (Scheme 97).[99] Use of AD-mix-α to perform the dihydroxylation reaction resulted in enhanced selectivity for the diol **275** (5:1, **275**:**287** → >12:1, **275**:**287**) but the diols were isolated in only 23% yield. The major product was the α-hydroxy ketone **223** (7-*epi*-asbestinin 21), which is produced by over oxidation of the diol during the reaction.



*Scheme 97: Dihydroxylation of 11-Acetoxy-4-deoxyasbestinin D (**18**) Using AD-mix-α*

In what was expected to be the mis-matched case, the use of AD-mix-β resulted in a higher level of diastereocontrol than had been obtained from the reactions performed under standard Upjohn conditions (5:1, **275**:**287** → 8:1, **275**:**287**, Scheme 98). The cause of this unexpected increase in diastereocontrol is likely to have resulted from the larger steric bulk of the chiral osmium complex and so the reaction proceeds under substrate control instead of reagent control.



*Scheme 98: Dihydroxylation of 11-Acetoxy-4-deoxyasbestinin D (**18**) Using AD-mix-β*

The diols **275** and **287** were obtained in a combined yield of 75% and 7-*epi*-asbestinin 21 (**223**) was also obtained in 10% yield. The lower yield of the α-hydroxy ketone than in the previous reaction can be attributed to a shorter reaction time and the lower catalyst loading. The use of Sharpless asymmetric dihydroxylation protocol allowed for enhanced diastereocontrol for the synthesis of diol **275** but it could not overcome the substrate bias.

3.10.5 Synthesis of Asbestinin 23 (266) and 7-*epi*-Asbestinin 23 (289)

Following the completed synthesis of asbestinin 21 (**288**), the synthesis of asbestinin 23 (**266**) and its C-7 epimer (**289**) was investigated (Figure 31).[10,11] The intention was to perform hydroboration-oxidation of 11-acetoxy-4-deoxyasbestinin D (**18**) and then oxidise the resulting alcohols.

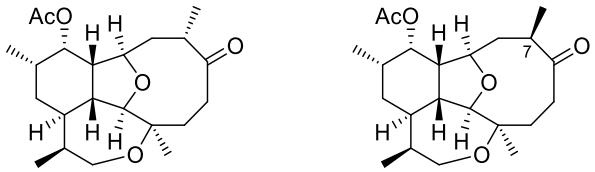
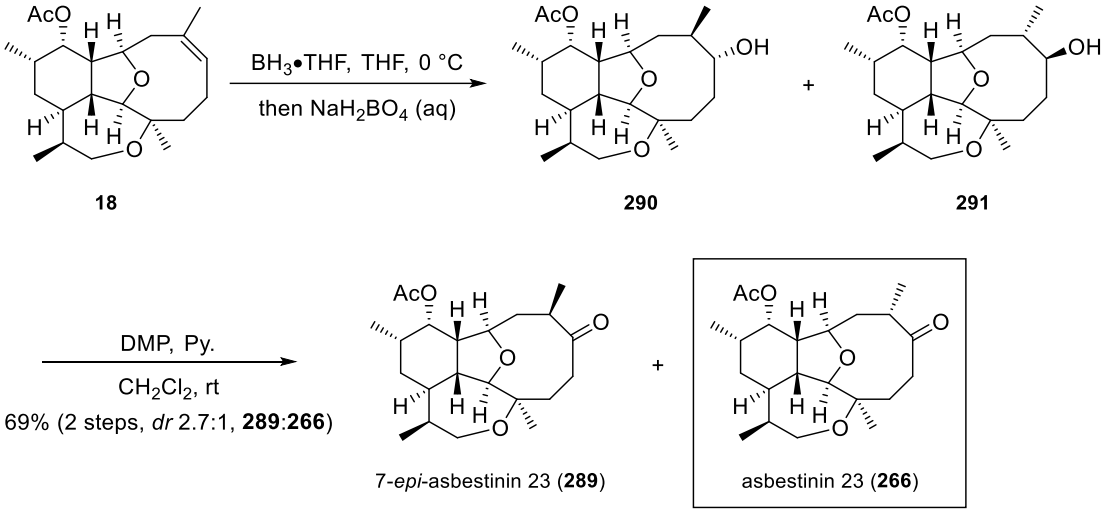


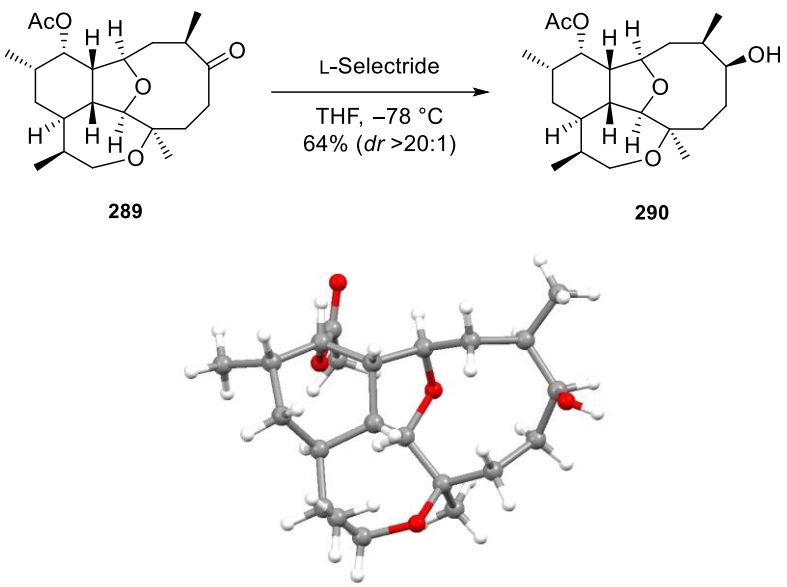
*Figure 31: Structures of Asbestinin 23 (**266**) and 7-epi-Asbestinin 23 (**289**)*

The synthesis of asbestinin 23 (**266**) and 7-*epi*-asbestinin 23 (**289**) started with hydroboration of 11-acetoxy-4-deoxyasbestinin D (**18**) with borane-THF complex and by oxidative work-up using sodium perborate (Scheme 99). This reaction delivered an inseparable mixture of alcohols **290** and **291**.



*Scheme 99: Hydroboration-Oxidation of 11-Acetoxy-4-deoxyasbestinin D (**18**)*

Immediate oxidation of the diastereomeric mixture of alcohols **290** and **291** with Dess–Martin periodinane afforded a separable mixture of 7-*epi*-asbestinin 23 (**289**) and asbestinin 23 (**266**) in a 69% yield over two steps (*dr* 2.7:1, **289**:**266**). The spectroscopic data for the major ketone **289** obtained from the two-step sequence did not match that of the natural product asbestinin 23 and it was identified to be the C-7 epimer. The stereochemistry of the proposed C-7 epimer was determined by the reduction of 7-*epi*-asbestinin 23 (**289**) with L-Selectride to give a pure sample of the crystalline alcohol **290** (Scheme 100). Alcohol **290** was obtained with an excellent diastereomeric ratio (*dr* >20:1) and the its structure was established conclusively by single crystal X-ray analysis.



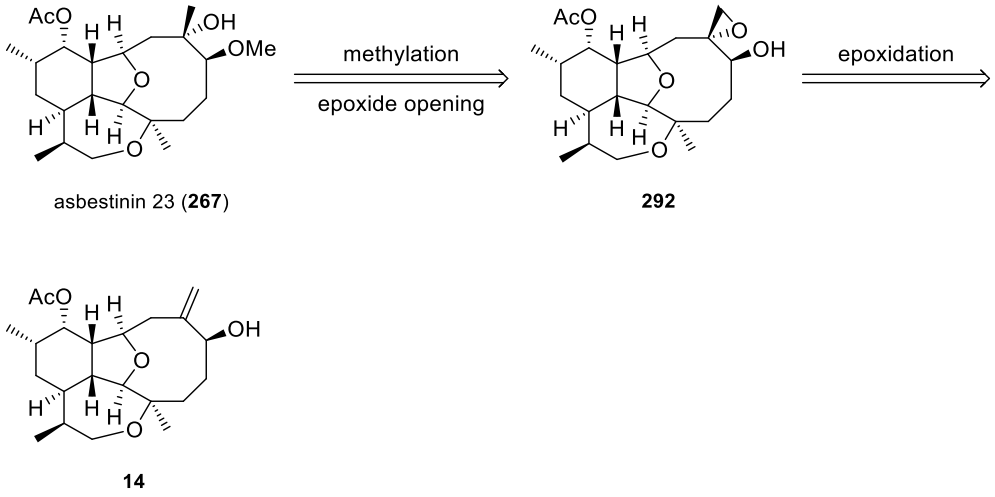
289 **290**

*Scheme 100: Synthesis of Alcohol **290** by Reduction of 7-*epi*-Asbestinin 23 (**289**)*

Unambiguous assignment of the structure of alcohol **290** enabled the configuration of the methyl-bearing carbon in both asbestinin 23 (**266**) and 7-*epi*-asbestinin 23 (**289**) to be confirmed as well. The spectroscopic and other characterisation data obtained for the ketone **266** matched those of asbestinin 23 reported for by Rodriguez and Ospina.[10,11,95] The total synthesis of asbestinin 23 (**266**) was completed in two steps from 11-acetoxy-deoxyasbestinin D (**18**) with the structure and relative configuration of the stereocentres in 7-*epi*-asbestinin 23 (**289**) being established by X-ray analysis and so confirmed the structure of asbestinin 23 (**266**) with certainty.

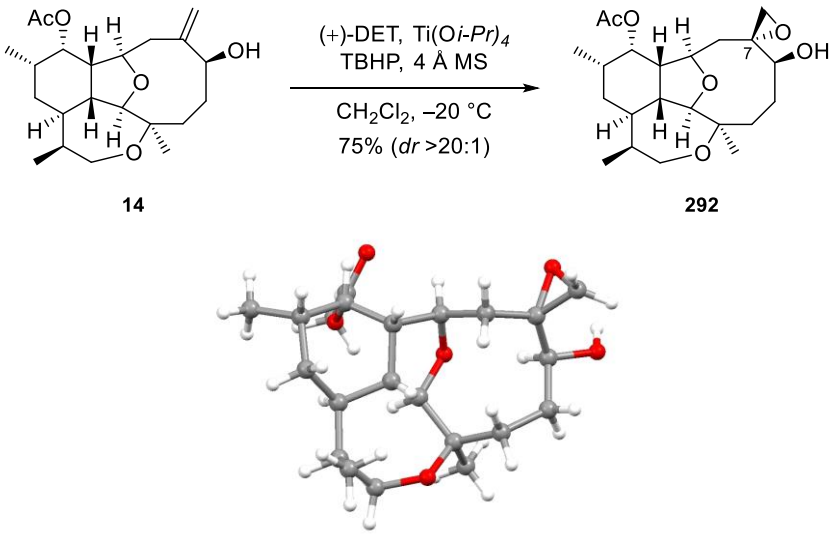
3.10.6 Towards the Synthesis of Asbestinin 25 (267)

The final member of the 4-deoxyasbestinin series that was selected for synthesis was asbestinin 25 (**267**).[11] Asbestinin 25 (**267**) was to be synthesised from epoxide **292** by epoxide opening and methylation of the secondary hydroxyl group of the resulting diol (Scheme 101). Epoxide **292** would be available from the previously synthesised asbestinin 20 (**14**).



*Scheme 101: Synthesis of Asbestinin 25 (**267**) from Asbestinin 20 (**14**)*

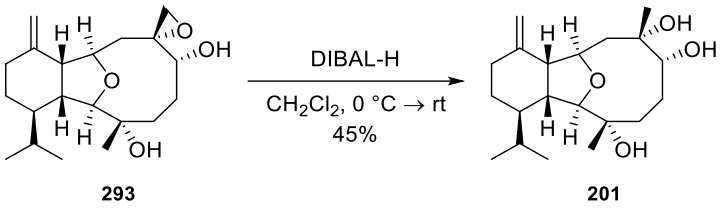
The synthesis of asbestinin 25 (**267**) started with epoxidation of asbestinin 20 (**14**) using the Sharpless asymmetric protocol.[47] This reaction produced the epoxide **292** in a yield of 75% and with excellent stereoselectivity (*dr* >20:1, Scheme 102). The epoxide **292** was a crystalline solid and so the structure of the epoxide was established unambiguously by single crystal X-ray analysis.



*Scheme 102: Epoxidation of Asbestinin 20 (**14**)*

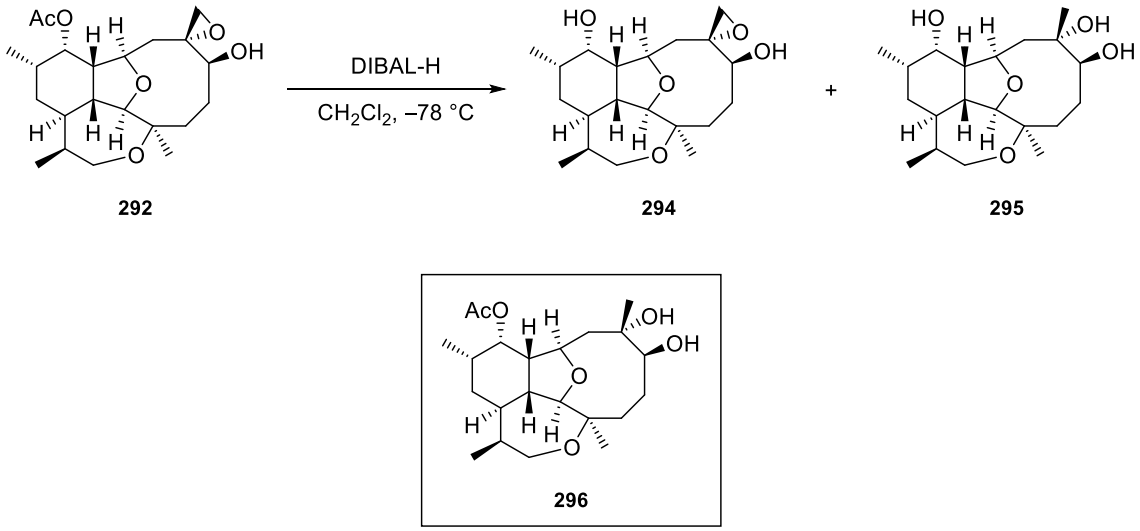
In previous work performed in the Clark group, diisobutylaluminium hydride had been used for regioselective epoxide opening of an analogous epoxide during the synthesis of the compound proposed to be sclerophytin F (Scheme 103).[67-69] A complicating issue was potential reduction of the labile acetate group by diisobutylaluminium hydride.

Consequently, the reaction was performed at a low temperature (−78 °C) and monitored carefully in an attempt to avoid this problem.



*Scheme 103: Regioselectively Opening of Epoxide **293** Using Diisobutylaluminium Hydride*

Attempted reductive epoxide opening with diisobutylaluminium hydride delivered a complex mixture of products (Scheme 104). Due to the scale of the reaction, products could not be characterised fully but mass spectrometry data and NMR data of related compounds aided the elucidation of possible products. The masses for diol **294** and triol **295** were obtained and this suggests that these products were formed. There was evidence of unreacted starting material by crude NMR analysis and by mass spectrometry. Diol **294** is likely formed by reductive cleavage of the ester and triol **295** would result from epoxide opening and ester cleavage.



*Scheme 104: Attempted Opening of Epoxide **292***

Further work towards the synthesis of asbestinin 25 (**267**) was not undertaken due to the lack of material and a focus on the synthesis of the C-4 hydroxylated asbestinins.

3.11 α-Hydroxylation of Tricyclic Ketone 256

The total synthesis of several members of the asbestinin family from the 4-deoxyasbestinin series encouraged a broadening of the scope of the project to include the C-4 hydroxylated asbestinins such as asbestinin 11 (**297**) and asbestinin 12 (**22**, Figure 32).[10] The strategy was to adapt the now established synthetic route to the 4-deoxyasbestinins and perform α-hydroxylation on a tricyclic intermediate prior to construction of the oxepane.

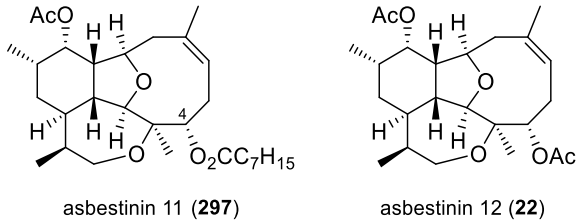
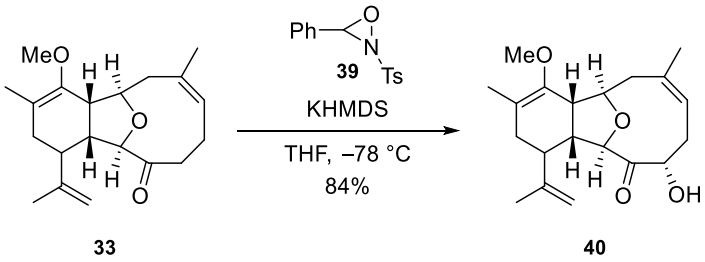


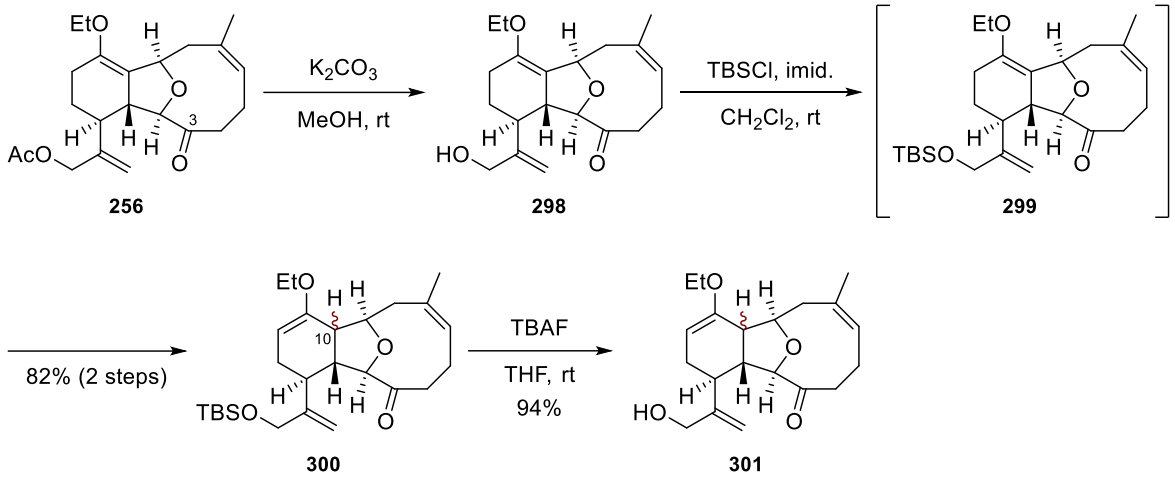
*Figure 32: Structures of Asbestinin 11 (**297**) and Asbestinin 12 (**22**)*

Crimmins and Ellis had reported that it is possible to perform α-hydroxylation of an enolate generated from the tricyclic ketone **33**, using Davis oxaziridine **39**, to give the α-hydroxy ketone **40** as the sole product, during their total synthesis of asbestinin 12 (**22**, Scheme 105).[13] This precedent showed that highly diastereoselective α-hydroxylation on the tricyclic core of the asbestinins should be possible.



*Scheme 105: α-Hydroxylation of Tricyclic Ketone **33** Performed by Crimmins and Ellis*

The synthesis started from tricyclic ketone **256** which had been used as an intermediate in our synthesis of members of the 4-deoxyasbestinin series (Scheme 106). The presence of an acetate group was problematic because it was likely to undergo competitive deprotonation when the substrate was treated with base and might also undergo transesterification with the enolate formed at the C-3 position. Consequently, it was necessary to remove the acetate group and this was achieved by treatment of **256** with potassium carbonate in methanol to give alcohol **298**.

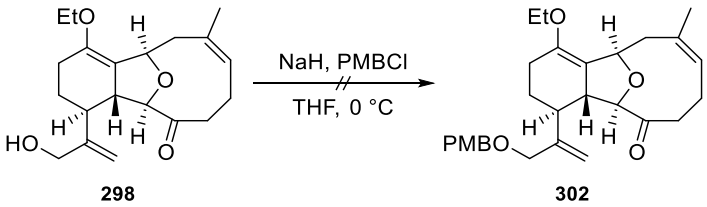


*Scheme 106: Attempted Synthesis of Tricyclic Ketone **299***

Following removal of the acetate group, silyl protection of the allylic alcohol was performed with initial formation of tricyclic ketone **299**. However, tricyclic ketone **299** underwent unexpected isomerisation at room temperature to produce the tricyclic ketone **300** as the sole product after 2-3 hours.[100] The isomerisation of tricyclic ketone **299** generated the stereocentre at the C-10 position (*dr* >20:1). It is possible that isomerisation of the alkene occurs after silylation due to the increased steric bulk of the silyl protecting group which results in a significant conformational change in the 6,5,9-tricyclic system.

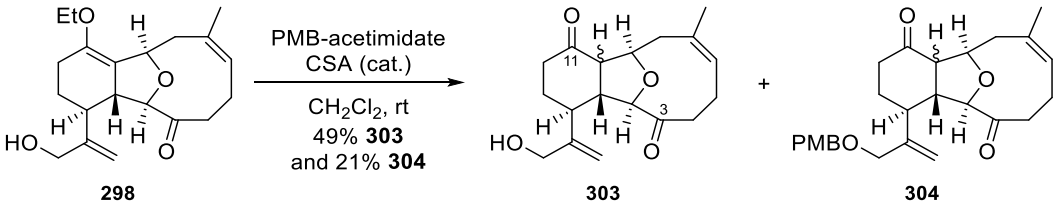
To determine the configuration of the newly created stereocentre at the C-10 position, selective ^{1}H NMR NOE spectroscopy was performed but the results were inconclusive and so the relative stereochemistry could not be determined. In an attempt to solve this problem, the tricyclic ketone **300** was treated with *tetra*-*N*-butylammonium fluoride to give alcohol **301**. However, NMR analyse was again inconclusive.

The silyl protecting group seemed to have resulted in this unexpected issue and so the *para*-methoxybenzyl protecting group was investigated as a potential alternative. Allylic alcohol **298** was deprotonated with sodium hydride and *para*-methoxybenzyl chloride was added, but this reaction was unsuccessful and starting material was recovered (Scheme 107).



*Scheme 107: Attempted PMB Protection of Allylic Alcohol **298***

Alternative conditions for introduction of the *para*-methoxybenzyl protection were investigated.[101] This involved the use of *para*-methoxybenzyl acetimidate and sub-stoichiometric quantities of camphorsulfonic acid; the quantity of the acid was minimised because of the acid-sensitive nature of the enol ether. When these conditions were employed, the required tricyclic ketone **302** was not formed and starting material was not recovered. Instead, the enol ether underwent hydrolysis to give diketone **303** along with *para*-methoxybenzyl protected diketone **304** (Scheme 108).



298 **303** **304**

*Scheme 108: Attempted Protection of Allylic Alcohol **298** with* para-*Methoxybenzyl Acetimidate*

The diketones **303** and **304** were isolated as single diastereoisomers but the relative stereochemistry of the newly formed centre at the C-10 position was not determined because neither of the compounds **303** and **304** were further functionalised. This was because any attempt to α-hydroxylate the ketone at the C-3 position in either compound was likely to result in hydroxylation of the ketone at C-11 as well.

3.12 Biological Testing of Asbestinin Natural Products and Related Intermediates

Completion of the synthesis of several members of the 4-deoxyasbestinin series of natural products along with their various diastereoisomers meant that the anti-cancer activities of these compounds could be tested (Figure 33).[2,5] Structurally-related late-stage intermediates generated after the synthesis of 11-acetoxy-deoxyasbestinin D (**18**) were also tested.

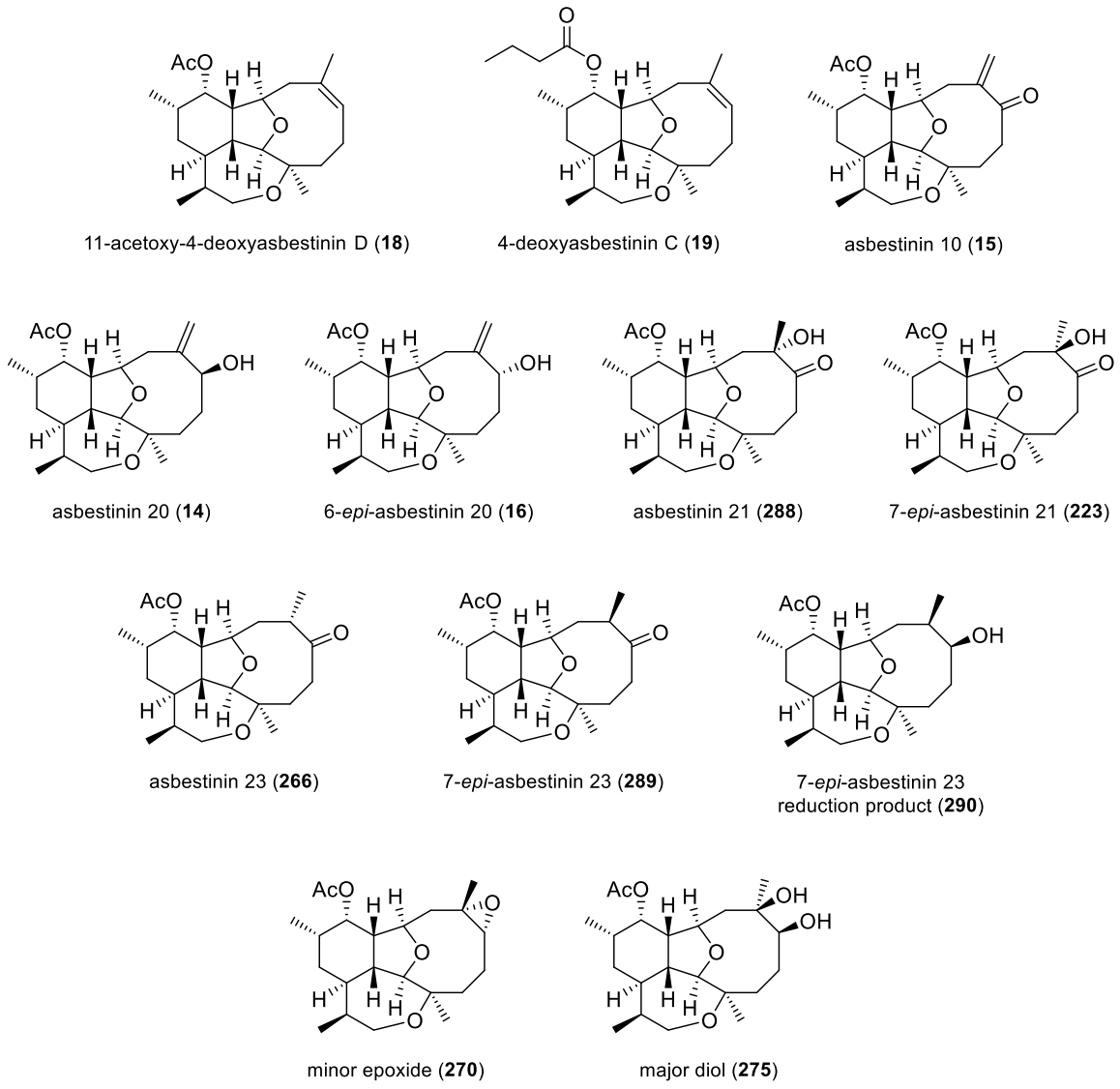


Figure 33: Asbestinin Natural Products and Related Compounds Tested

The compounds were tested against two different cancer cell lines, breast cancer cell line MCF7 and brain cancer cell line U87MG, in viability assay studies.[102,103] Preliminary results from testing by Dr. S. Sharp from the Institute of Cancer Research, London showed that none of the compounds tested had detectable activity at concentrations of up to 10 µM for either cell line (Figure 34).[104] When the assays were repeated at higher concentration (up to 100 µM), no activity was detected either.

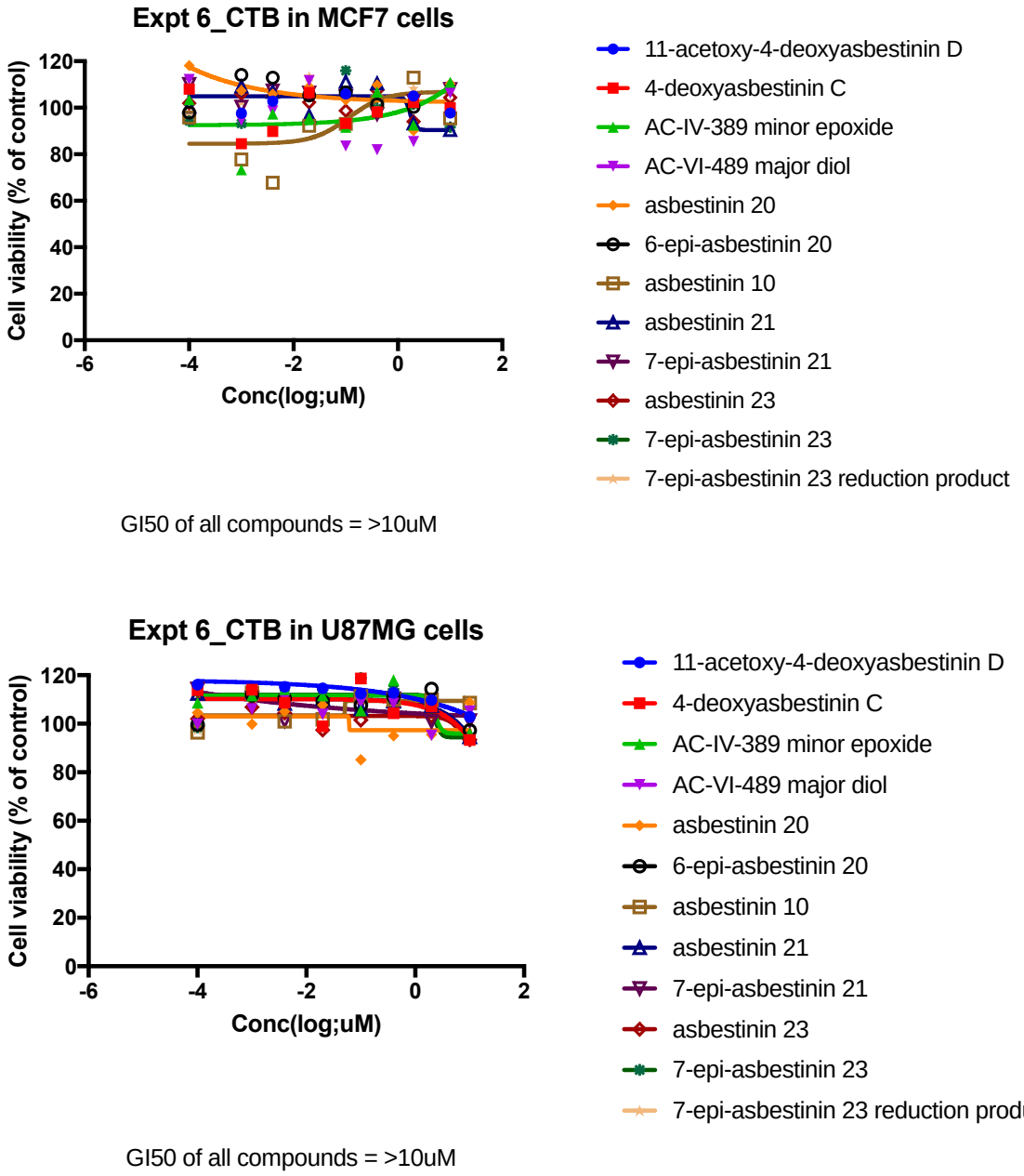


Figure 34: Viability Assay Results for Tested Asbestinin Compounds

The results obtained from these preliminary studies raises doubts about anti-cancer activities of members of the asbestinin family that have been reported in the past.[2,5] Further biological testing is required before any conclusions can be drawn regarding the activities of these asbestinins members and the validity of previously published activities.

4. Conclusions

4.1 Summary of Work

The second enantioselective total synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**) was achieved from butan-1,4-diol **178** in 31 steps and an overall yield of 2% (Figure 35). The first enantioselective total syntheses of five further members of the 4-deoxyasbestinin series of natural products were also accomplished: 4-deoxyasbestinin C (**19**), asbestinin 10 (**15**), asbestinin 20 (**14**), asbestinin 21 (**288**) and asbestinin 23 (**266**). Syntheses of the natural product epimers, 6-*epi*-asbestinin 20 (**16**), 7-*epi*-asbestinin 21 (**223**) and 7-*epi*-asbestinin 23 (**289**) were also completed.

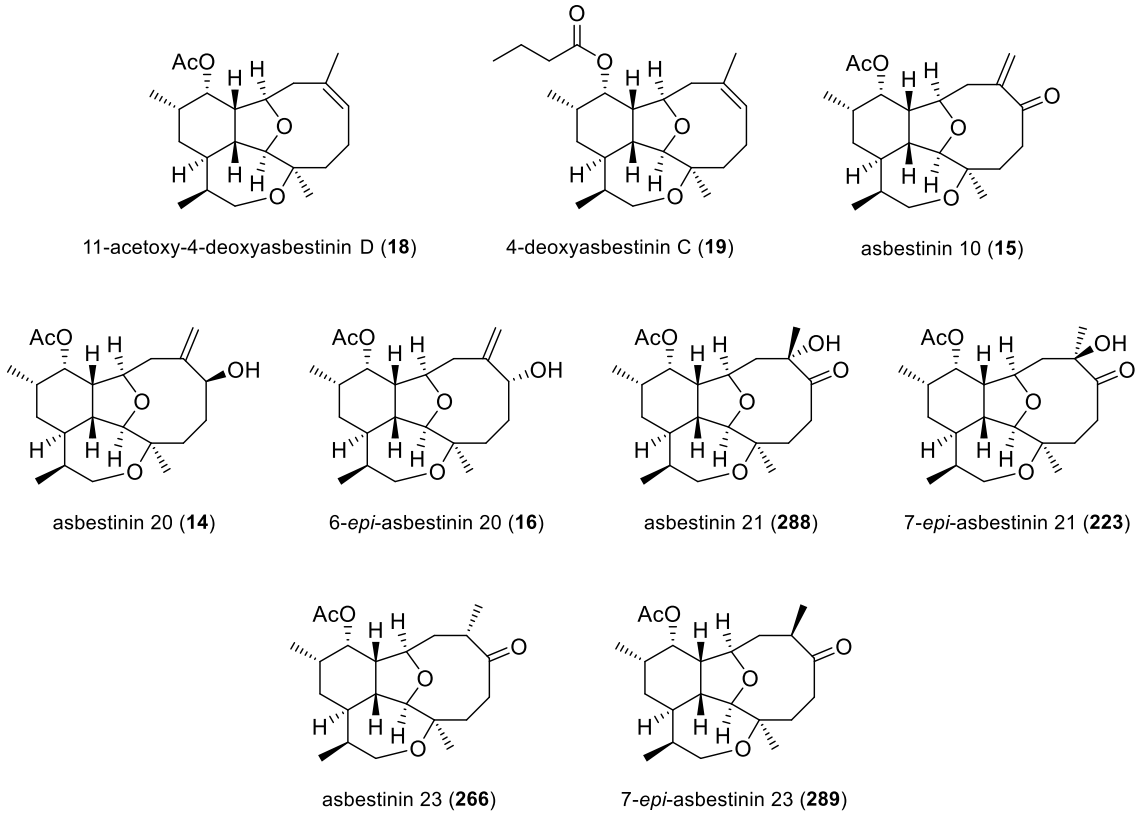
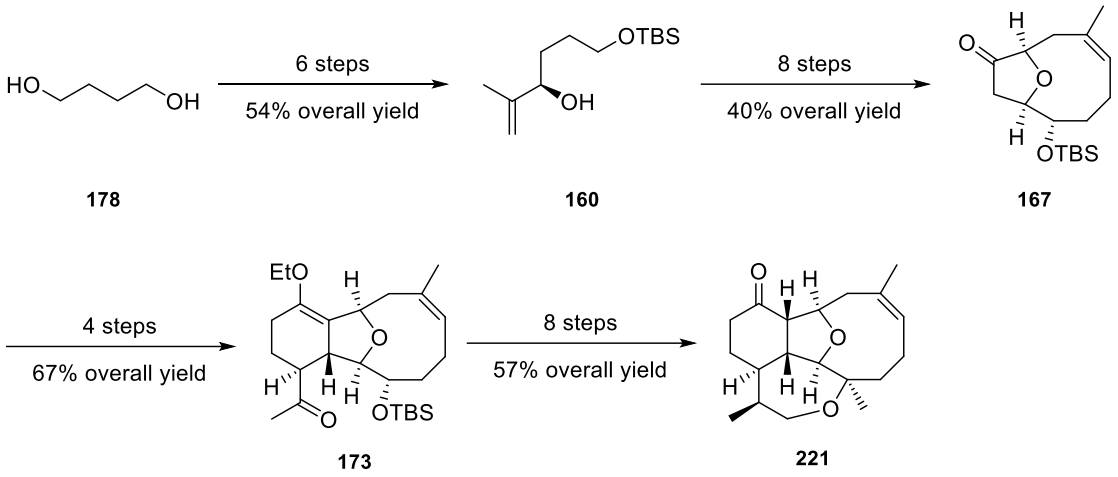


Figure 35: Structures of Members of the Asbestinin Family Synthesised

The completed total syntheses of asbestinin 10 (**15**), asbestinin 20 (**14**) and asbestinin 23 (**266**) confirmed the structural reassignment of these natural products by Rodriguez and Ospina.[11] In the case of asbestinin 21 (**288**), completion of the total synthesis resulted in its structural reassignment because the structure (**223**) that had been assigned to it previously was in fact an epimer of the natural product.

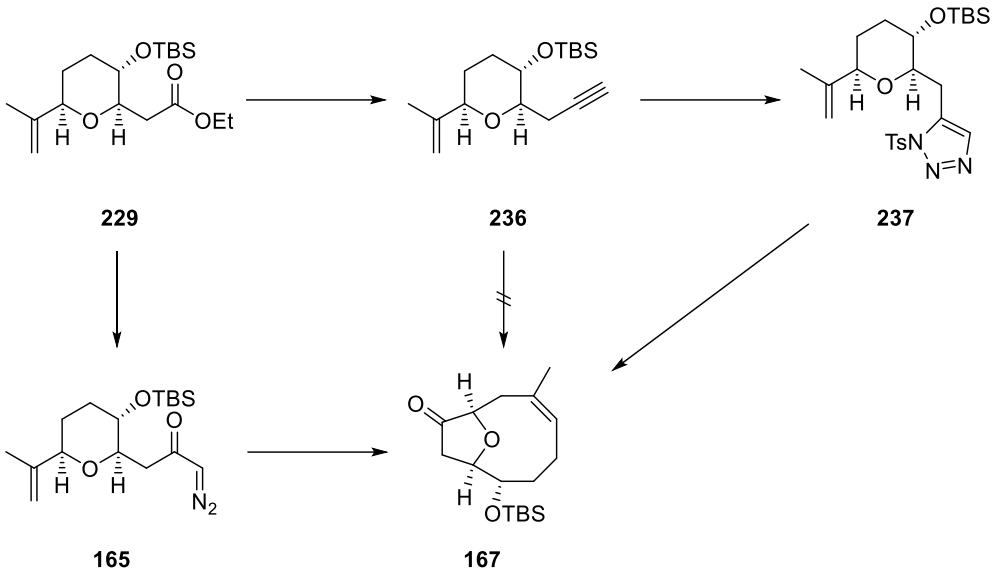
The synthetic route towards the asbestinins started from butan-1,4-diol **178** which could be transformed into allylic alcohol **160** in 6 steps. From here, allylic alcohol **160** was converted into ketone **167** in eight steps to give the bicyclic core of the asbestinins (Scheme 109). Key reactions in the synthesis of this bicyclic core included a samarium-mediated reductive cyclisation to from a tetrahydropyranol and subsequent tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement to give the core structure.



*Scheme 109: General Synthetic Route for the Synthesis of Tetracyclic Ketone **221***

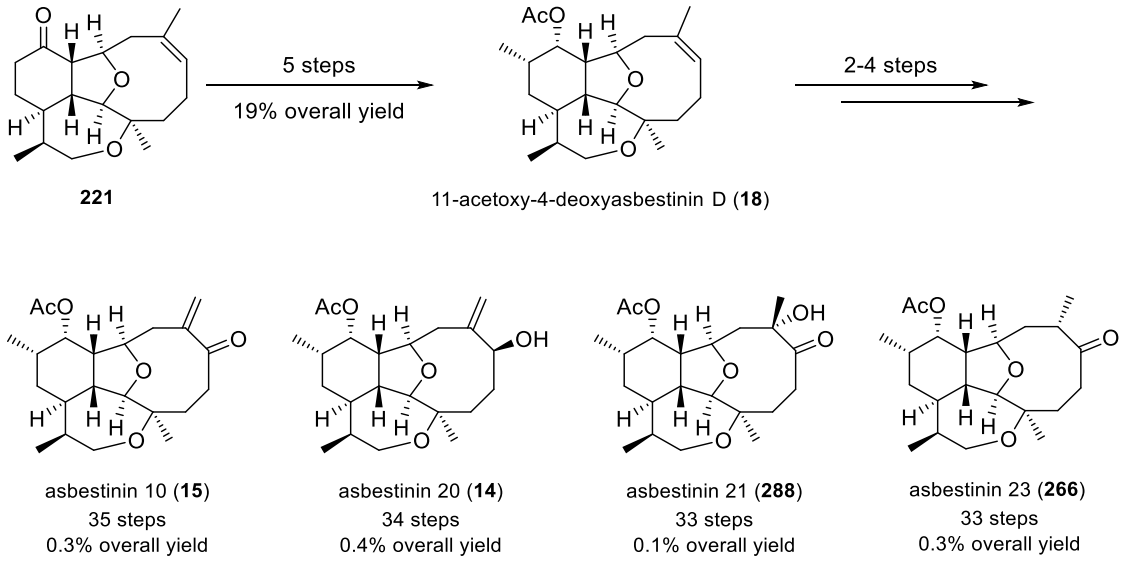
The tricyclic core of the asbestinins was prepared from the bicyclic ketone **167** in four further steps. The sequence involves a Stille/Diels–Alder cycloaddition sequence to construct the cyclohexyl ring. The tricyclic ketone **173** was then converted into the tetracyclic core of the asbestinins in eight steps. Key reactions in the synthesis of the tetracyclic core included triflation followed by palladium-mediated carbonylation, to insert an additional one-carbon unit, and triflate displacement to form the oxepane.

Diazomethane is required to synthesise the diazoketone **165** which is then converted to bicyclic ketone **167** by tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement (Scheme 110). Diazomethane can be difficult to handle on large scale because of its explosive nature and the limitations of the specialised glassware required to generate it. For this reason, alternative routes to prepare the bicyclic ketone **167** were investigated. It was demonstrated that a rhodium-mediated reaction of the triazole **237** could be used to synthesise the bicyclic ketone **167** with high selectivity. Subjection of the alkyne **236** to sequential gold-catalysed α-oxo gold carbene formation and oxonium ylide generation followed by [2,3]-sigmatropic rearrangement was unsuccessful.



*Scheme 110: Routes to the Bicyclic Ketone **167***

Tetracyclic ketone **221** was converted into 11-acetoxy-4-deoxyasbestinin D (**18**) in five steps (Scheme 111). 4-Deoxyasbestinin C (**19**) was also synthesised from the tetracyclic ketone **221** in five steps. Four further members of the 4-deoxyasbestinin group of natural products were synthesised from 11-acetoxy-4-deoxyasbestinin D (**18**), in 2-4 steps.



*Scheme 111: Summary of Synthetic Routes to 11-Acetoxy-4-deoxyasbestinin D (**18**) and Related Natural Products*

4.1.1 Comparison of Strategies Employed in the Synthesis of 11-Acetoxy-4-deoxyasbestinin D (18)

A direct comparison of total step count shows that Crimmins and Ellis completed the synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**) in 26 steps starting from commercially available *R*-benzyl glycidyl ether **26** (Section 1.2.2). The expensive nature of *R*-benzyl glycidyl ether **26** would result in an increased step count when synthesised from cheaper starting materials. In comparison, starting from butan-1,4-diol **178**, the synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**) was completed in 31 steps using a readily abundant starting material. Comparable overall yields of 4% and 2% respectively were achieved.

Crimmins and Ellis utilised a RCM approach for the synthesis of the nine-membered oxonene followed by intramolecular Diels–Alder cycloaddition to form the 6,5,9-tricyclic ring system. This differs from the strategy detailed in Section 3 which involved a samarium-mediated cyclisation to form a tetrahydropyranol which then underwent tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement to give the 9,5-bicyclic ring system. From here, a Stille/intermolecular Diels–Alder cycloaddition sequence built up the 6,5,9-tricyclic core.

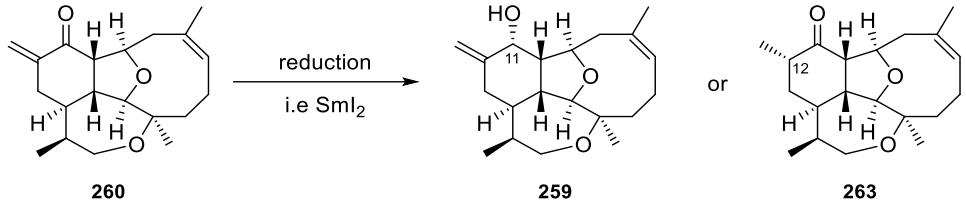
A key difference in synthetic strategy related to construction of the final seven-membered ring. Crimmins and Ellis had to perform an asymmetric hydroboration-etherification procedure using a chiral borane reagent to install the desired stereochemistry at the C-15 position and the required alcohol for etherification. Subsequent silyl deprotection followed by triflate formation and displacement gave the desired tetracycle and completed their synthesis of 11-acetoxy-4-deoxyasbestinin D (**18**). In comparison, the C-15 stereocentre was installed stereoselectively using substrate control through initial formation of the tetracyclic system by etherification followed by hydrogenation of the *exo*-alkene.

The C-12 methyl stereocentre proved difficult in both syntheses with the need for epimerisation of the C-12 epimer being performed in the synthetic routes. Crimmins and Ellis formed the C-12 stereocentre on the tricyclic system through hydrolysis of an enol ether while reduction of a tetracyclic enone was the method chosen in the work detailed in this thesis.

4.2 Future Work

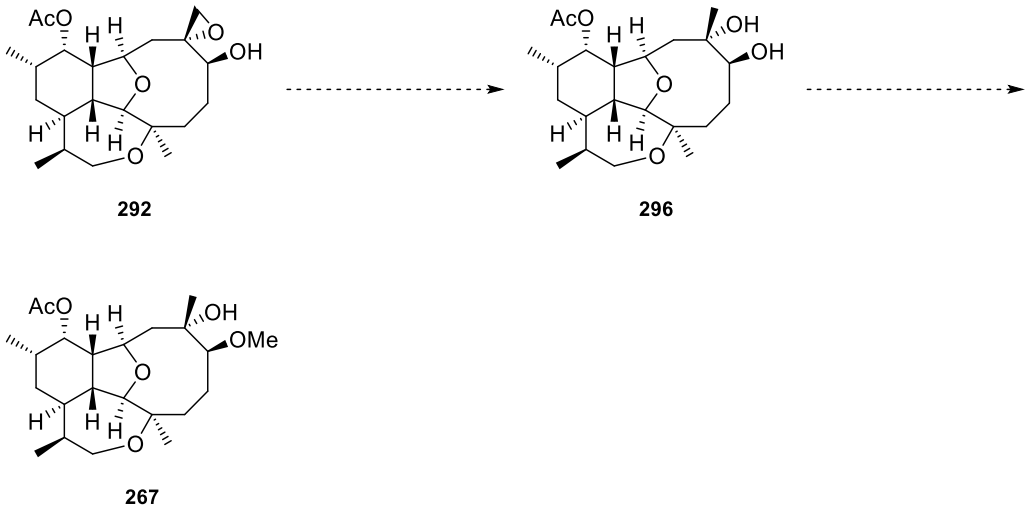
Future work on the asbestinins should focus on three main areas: improving the diastereoselectivity during introduction of the methyl substituent at the C-12 position on the tetracyclic core, completion of further members of the 4-deoxyasbestinin series and α-hydroxylation of the tricyclic ketone so that members of the 4-hydroxylated asbestinin series can be synthesised.

Introduction of the methyl substituent at the C-12 position could be achieved diastereoselectively by screening various reducing reagents such as samarium diiodide which has been shown to reduce enones (Scheme 112).[105-109]



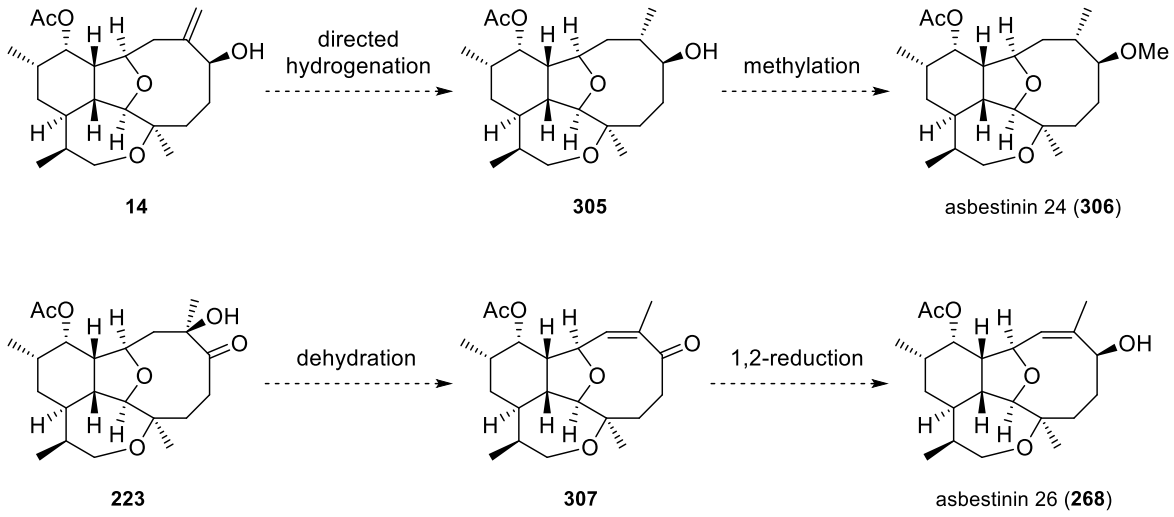
*Scheme 112: Reduction of Tetracyclic Enone **260***

To address the failure to open the epoxide **292** to give diol **296**, further work should focus on the discovery of alternative conditions to facilitate ring-opening while leaving the acetate group intact (Scheme 113). This would then allow the completion of the proposed structure of asbestinin 25 (**267**) after methylation of the secondary alcohol. As an alternative, the acetate should be replaced by a temporary protecting group.



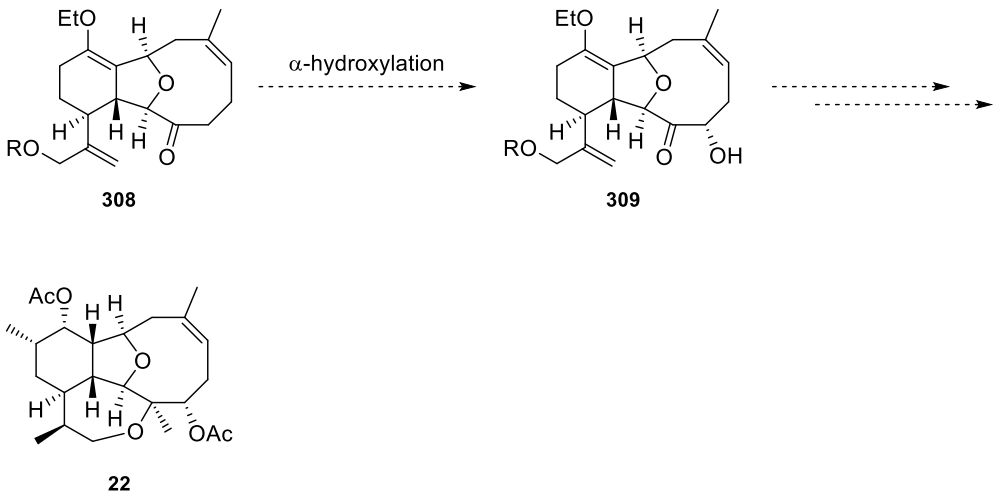
*Scheme 113: Strategy for the Synthesis of Asbestinin 25 (**267**)*

Other members of the 4-deoxyasbestinin series that could be synthesised are asbestinin 24 (**306**) and asbestinin 26 (**268**, Scheme 114).[11] Asbestinin 24 (**306**) could be synthesised from asbestinin 20 (**14**) by directed hydrogenation followed by methylation of the hydroxyl group. For asbestinin 26 (**268**), dehydration of 7-*epi*-asbestinin 21 (**223**) might produce enone **307** which could then undergo 1,2-reduction to give asbestinin 26 (**268**).



*Scheme 114: Proposed Synthetic Routes for Asbestinins 24 (**306**) and 26 (**268**)*

Finally, the α-hydroxylation of tricyclic ketone **308** would be investigated further and an appropriate hydroxyl protecting group would be used so that α-hydroxylation using Davis oxaziridine could be explored (Scheme 115).[22] This would allow the completion of members of the 4-hydroxylated series of asbestinins such as asbestinin 12 (**22**).[10]



*Scheme 115: Synthetic Route to Asbestinin 12 (**22**)*

5. Experimental

5.1 General Experimental

Reagents and solvents were purchased 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, dichloromethane and diethyl ether were purified using a Pure-SolvTM 500 Solvent Purification System. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plates F254. TLC plates were visualised under UV light and stained using potassium permanganate solution or acidic ethanolic anisaldehyde solution. Flash column chromatography was performed with silica gel (Geduran Si 60 35-70 µm, purchased from Merck and SilicaGel 60A 40-63 µm, purchased from Fluorochem) as the solid support. Petroleum ether used for column chromatography was the 40–60 °C fraction.

IR spectra were recorded as thin films employing a Shimadzu FTIR-8400S spectrometer equipped with a Pike Technologies MIRacle ATR accessory; selected frequencies (ν_{max}) are reported. NMR spectra were recorded using dilute solutions in deuterated chloroform or benzene 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 in units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm and δ (C_6D_6) = 7.16 ppm. ^{1}H signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), broad (br), apparent (app) or a combination of these. ^{13}C chemical shift data were recorded with broadband proton decoupling and are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.16 ppm and δ (C_6D_6) = 128.1 ppm. Assignments were determined using 2D NMR spectra (COSY, HSQC and HMBC). High resolution mass spectra (HRMS) were recorded using positive chemical ionisation (CI+) and ion impact (EI+) on a Joel MStation JMS-700 instrument or using positive ion electrospray (ESI+) technique on a Bruker micrOTOF-Q instrument by technical staff at 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 IV or V digital polarimeter. Elemental analyses were performed using an Exeter Analytical Elemental Analyser EA 440. X-ray crystallography was performed at the University of Glasgow by Dr. Claire Wilson.

5.1.1 Nomenclature

The carbon numbering drawn on the molecule corresponds to the conventional asbestinin numbering used for NMR signal assignment (Figure 36).[2] IUPAC numbering was used for the molecular names.

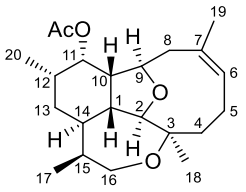
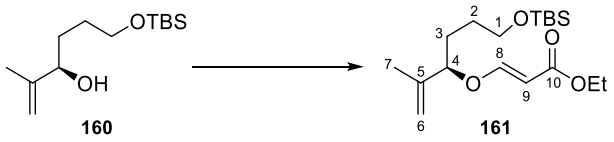


Figure 36: Carbon Numbering in the Asbestinins Skeleton

5.2 Experimental Procedures

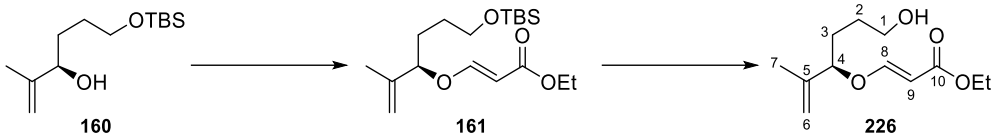
Ethyl (2*E*)-3-{[(3*R*)-6-[(*tert*-butyldimethylsilyl)oxy]-2-methylhex-1-en-3-yl]oxy}prop-2-enoate (161)[64]



To a stirred solution of allylic alcohol **160** (1.0 g, 4.1 mmol) in anhydrous dichloromethane (10 mL) was added ethyl propiolate (0.83 mL, 8.2 mmol) and *N*-methylmorpholine (0.90 mL, 8.2 mmol) at room temperature. The resulting solution was left to stir for 16 hours before being concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 15:1) to afford ester **161** (0.51 g, 36%) as a colourless oil.

R_f = 0.68 (petroleum ether-ethyl acetate, 5:1); ν_{max} 2955, 2930, 2858, 1711, 1642, 1472, 1254, 833, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 12.4 Hz, CH-C8), 5.21 (1H, d, *J* = 12.4 Hz, CH-C9), 4.94 (1H, s, CH_2-C6a), 4.92 (1H, s, CH_2-C6b), 4.22 (1H, dd, *J* = 7.6, 5.2 Hz, CH-C4), 4.11 (2H, app qd, *J* = 7.2, 1.6 Hz, CH_2-OEt), 3.62−3.53 (2H, m, CH_2-C1), 1.78−1.65 (2H, m, CH_2-C2), 1.62 (3H, s, CH_3-C7), 1.58−1.41 (2H, m, CH_2-C3), 1.22 (3H, app t, *J* = 7.2 Hz, CH_3-OEt), 0.84 (9H, s, CH_3-*t*Bu OTBS), 0.00 (6H, s, 2 × CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C-C10), 161.6 (CH-C8), 142.9 (C-C5), 114.8 (CH_2-C6), 98.0 (CH-C9), 86.7 (CH-C4), 62.7 (CH_2-C1), 59.8 (CH_2-OEt), 29.6 (CH_2-C2), 28.6 (CH_2-C3), 26.1 (CH_3-*t*Bu OTBS), 18.5 (C-*t*Bu OTBS), 17.0 (CH_3-C7), 14.5 (CH_3-OEt), −5.2 (2 × CH_3-OTBS); $[\alpha]_D^{23}$ −11.2 (*c* = 0.505, $CHCl_3$) {Lit.[64] $[\alpha]_D^{18}$ −7.94 (*c* = 1.41, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{18}H_{34}O_4SiNa$ 365.2106, found 365.2119, Δ 3.5 ppm.

Ethyl (2*E*)-3-{[(3*R*)-6-hydroxy-2-methylhex-1-en-3-yl]oxy}prop-2-enoate (226)[64]

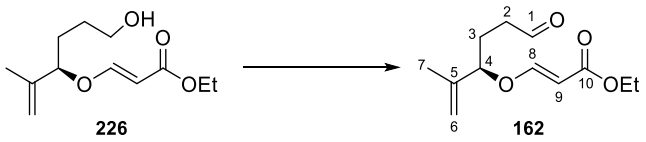


To a stirred solution of allylic alcohol **160** (20.0 g, 82.0 mmol) in anhydrous dichloromethane (200 mL) was added ethyl propiolate (16.3 mL, 164 mmol) and *N*-methylmorpholine (18.0 mL, 164 mmol) at room temperature. The resulting solution was left to stir for 16 hours before being concentrated under reduced pressure. The crude mixture was passed through a small column of silica (petroleum ether-ethyl acetate, 4:1) to remove any polar impurities giving vinylogous carbonate **161**, which was used in the next without further purification.

To a stirred solution of vinylogous carbonate **161** in ethanol (660 mL) was added camphorsulfonic acid (3.80 g, 16.4 mmol) in one portion. The resulting solution was stirred for 16 hours before the reaction was quenched by the addition of sodium bicarbonate (1.38 g, 16.4 mmol). The remaining solids were removed by filtration before the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 5:1 → 1:1) to afford alcohol **226** (15.6 g, 83%) as a yellow oil.

R_f = 0.30 (petroleum ether-ethyl acetate, 2:1); ν_{max} 3439, 2949, 1705, 1638, 1620, 1447, 1228, 959, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 12.4 Hz, CH-C8), 5.28 (1H, d, *J* = 12.4 Hz, CH-C9), 5.01 (1H, s, CH_2-C6a), 4.99 (1H, s, CH_2-C6b), 4.30 (1H, dd, *J* = 7.6, 5.2 Hz, CH-C4), 4.14 (2H, app qd, *J* = 7.2, 1.5 Hz, CH_2-OEt), 3.71−3.67 (2H, m, CH_2-C1), 1.89−1.73 (2H, m, CH_2-C2), 1.70 (3H, s, CH_3-C7), 1.67−1.55 (2H, m, CH_2-C3), 1.51 (1H, br s, OH), 1.28 (3H, app t, *J* = 7.2 Hz, CH_3-OEt); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C-C10), 161.3 (CH-C8), 142.7 (C-C5), 114.7 (CH_2-C6), 98.1 (CH-C9), 86.4 (CH-C4), 62.4 (CH_2-C1), 59.7 (CH_2-OEt), 29.5 (CH_2-C3), 28.5 (CH_2-C2), 17.0 (CH_3-C7), 14.5 (CH_3-OEt); $[\alpha]_D^{23}$ −10.8 (*c* = 0.495, $CHCl_3$) {Lit.[64] $[\alpha]_D^{24}$ −8.30 (*c* = 1.01, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{12}H_{20}O_4Na$ 251.1245, found 251.1254, Δ 3.5 ppm.

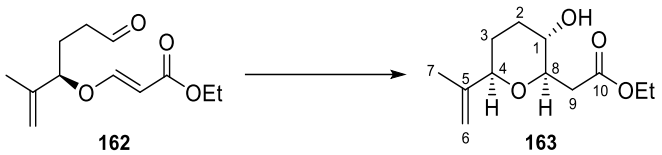
Ethyl (2*E*)-3-{[(3*R*)-2-methyl-6-oxohex-1-en-3-yl]oxy}prop-2-enoate (162)[64]



To a stirred solution of oxalyl chloride (6.86 mL, 81.1 mmol) in anhydrous dichloromethane (75 mL) at −78 °C was added a solution of anhydrous DMSO (5.76 mL, 81.1 mmol) in anhydrous dichloromethane (75 mL) dropwise by cannula. The resulting solution was stirred for 30 minutes before a solution of alcohol **226** (15.3 g, 67.0 mmol) in anhydrous dichloromethane (80 mL) was added dropwise by cannula. The reaction mixture was left to stir for 3 hours and to this was added triethylamine (37.6 mL, 268 mmol) and warmed to room temperature over 1 hour. The reaction mixture was diluted with dichloromethane (100 mL) and water (150 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 → 5:1) to afford aldehyde **162** (13.2 g, 87%) as a colourless oil.

R_f = 0.45 (petroleum ether-ethyl acetate, 5:1); ν_{max} 2980, 2729, 1705, 1640, 1622, 1447, 1283, 955, 912, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.2 Hz, CH-C1), 7.45 (1H, d, *J* = 12.4 Hz, CH-C8), 5.27 (1H, d, *J* = 12.4 Hz, CH-C9), 5.03 (1H, s, CH_2-C6a), 4.99 (1H, s, CH_2-C6b), 4.31 (1H, dd, *J* = 7.6, 5.2 Hz, CH-C4), 4.17 (2H, app qd, *J* = 7.2, 1.5 Hz, CH_2-OEt), 2.58−2.54 (2H, m, CH_2-C2), 2.12−1.94 (2H, m, CH_2-C3), 1.70 (3H, s, CH_3-C7), 1.27 (3H, app t, *J* = 7.2 Hz, CH_3-OEt); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (CH-C1), 167.8 (C-C10), 160.9 (CH-C8), 142.1 (C-C5), 115.0 (CH_2-C6), 98.5 (CH-C9), 85.0 (CH-C4), 59.8 (CH_2-OEt), 39.6 (CH_2-C2), 25.6 (CH_2-C3), 17.0 (CH_3-C7), 14.4 (CH_3-OEt); $[\alpha]_D^{23}$ −18.0 (*c* = 0.500, $CHCl_3$) {Lit.[64] $[\alpha]_D^{23}$ −1.90 (*c* = 1.00, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{12}H_{18}O_4Na$ 249.1098, found 249.1097, Δ 0.3 ppm.

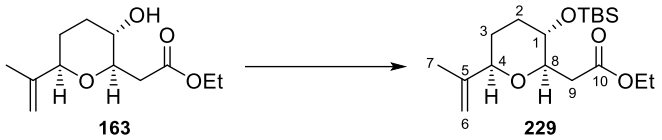
Ethyl 2-[(2*R*,3*S*,6*R*)-3-hydroxy-6-(prop-1-en-2-yl)oxan-2-yl] acetate (163)[64]



To a stirred solution of aldehyde **162** (4.00 g, 19.7 mmol) and anhydrous methanol (2.90 mL, 70.7 mmol) in anhydrous THF (170 mL) at room temperature was added a freshly prepared solution of samarium diiodide (0.2 M in THF) until the solution remained dark blue in colour (approx. 4 equiv.). The resulting solution was stirred for 30 minutes before the reaction was quenched with saturated aqueous solution of sodium thiosulfate (240 mL) and diluted with ethyl acetate (90 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 6:1 → 2:1) to afford tetrahydropyranol **163** (3.22 g, 79%) as a colourless oil.

R_f = 0.45 (petroleum ether-ethyl acetate, 2:1); ν_{max} 3451, 2942, 1736, 1721, 1651, 1439, 1258, 990, 901 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (1H, s, CH_2-C6a), 4.82 (1H, s, CH_2-C6b), 4.17 (2H, q, *J* = 7.2 Hz, CH_2-OEt), 3.76 (1H, d, *J* = 9.6 Hz, CH-C4), 3.65−3.60 (1H, ddd, *J* = 9.2, 6.8, 4.8 Hz, CH-C8), 3.44−3.37 (1H, m, CH-C1), 2.84 (1H, dd, *J* = 15.2, 4.8 Hz, CH_2-C9a), 2.59 (1H, dd, *J* = 15.2, 6.8 Hz, CH_2-C9b), 2.20−2.15 (2H, m, CH_2-C2a, HO-C1), 1.88−1.83 (1H, m, CH_2-C3a), 1.73 (3H, s, CH_3-C7), 1.57−1.52 (2H, m, CH_2-C2b, CH_2-C3b), 1.28 (3H, t, *J* = 7.2 Hz, CH_3-OEt); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C-C10), 145.0 (C-C5), 110.5 (CH_2-C6), 80.1 (CH-C4), 78.9 (CH-C8), 70.4 (CH-C1), 60.6 (CH_2-OEt), 38.8 (CH_2-C9), 33.1 (CH_2-C2), 29.7 (CH_2-C3), 19.1 (CH_3-C7), 14.2 (CH_3-OEt); $[\alpha]_D^{23}$ +34.6 (*c* = 0.500, $CHCl_3$) {Lit.[64] $[\alpha]_D^{25}$ +42.6 (*c* = 1.02, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{12}H_{20}O_4Na$ 251.1254, found 251.1254, Δ 0.2 ppm.

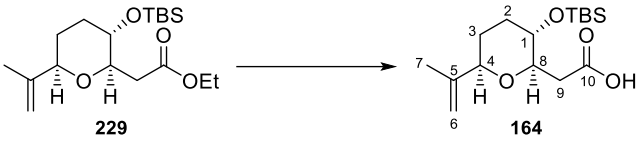
Ethyl 2-[(2*R*,3*S*,6*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-6-(prop-1-en-2-yl)oxan-2-yl] acetate (229)[64]



To a stirred solution of alcohol **163** (6.31 g, 27.6 mmol) and imidazole (3.76 g, 55.3 mmol) in anhydrous DMF (60 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (7.50 g, 49.8 mmol) portionwise over 5 minutes. The resulting solution was stirred for 16 hours before the reaction was quenched by the addition of water (400 mL) and diluted with diethyl ether (200 mL). The aqueous phase was separated and the organic phase washed with water (5 × 150 mL). The aqueous portions were combined and extracted with diethyl ether (250 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 40:1 → 20:1) to afford silyl ether **229** (9.46 g, quant.) as a colourless oil.

R_f = 0.72 (petroleum ether-ethyl acetate, 5:1); ν_{max} 2930, 2857, 1740, 1653, 1464, 1251, 899, 835, 775, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, s, CH_2-C6a), 4.76 (1H, s, CH_2-C6b), 4.08 (2H, q, *J* = 7.2 Hz, CH_2-OEt), 3.67 (1H, d, *J* = 10.0 Hz, CH-C4), 3.58 (1H, ddd, *J* = 9.2, 9.2, 3.2 Hz, CH-C8), 3.34−3.28 (1H, m, CH-C1), 2.74 (1H, dd, *J* = 14.8, 3.2 Hz, CH_2-C9a), 2.31 (1H, dd, *J* = 14.8, 9.2 Hz, CH_2-C9b), 1.99−1.95 (1H, m, CH_2-C2a), 1.76−1.72 (1H, m, CH_2-C3a), 1.64 (3H, s, CH_3-C7), 1.51−1.41 (2H, m, CH_2-C2b, CH_2-C3b), 1.18 (3H, t, *J* = 7.2 Hz, CH_3-OEt), 0.81 (9H, s, CH_3-*t*Bu OTBS), 0.00 (3H, s, CH_3-OTBS), −0.01 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (C-C10), 145.1 (C-C5), 110.2 (CH_2-C6), 79.9 (CH-C4), 79.5 (CH-C8), 70.8 (CH-C1), 60.3 (CH_2-OEt), 38.3 (CH_2-C9), 33.4 (CH_2-C2), 29.6 (CH_2-C3), 25.8 (CH_3-*t*Bu), 19.2 (CH_3-C7), 17.9 (C-*t*Bu), 14.3 (CH_3-OEt), −4.0 (CH_3-Si), −4.8 (CH_3-Si); $[\alpha]_D^{23}$ +70.2 (*c* = 0.505, $CHCl_3$) {Lit.[64] $[\alpha]_D^{24}$ +59.0 (*c* = 1.03, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{18}H_{34}O_4SiNa$ 365.2108, found 365.2119, Δ 3.0 ppm.

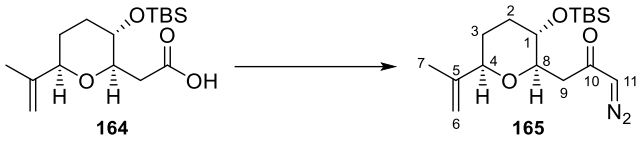
2-[(2*R*,3*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(prop-1-en-2-yl)oxan-2-yl] acetic acid (164)[64]



To a stirred solution of ester **229** (9.40 g, 27.5 mmol) in ethanol (135 mL) and water (45 mL) was added lithium hydroxide (2.63 g, 110 mmol) portionwise over 5 minutes at room temperature. The reaction mixture was stirred for 16 hours before being acidified to pH 2-3 with aqueous HCl (1 M). The reaction mixture was diluted with ethyl acetate (250 mL) and water (150 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 40:1 → 2:1) to afford carboxylic acid **164** (7.39 g, 86%) as a colourless oil.

R_f = 0.28 (petroleum ether-ethyl acetate, 5:1); ν_{max} 2930, 2859, 1713, 1653, 1437, 1252, 899, 835, 775, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (1H, s, CH_2-C6a), 4.75 (1H, s, CH_2-C6b), 3.73 (1H, d, *J* = 10.0 Hz, CH-C4), 3.56 (1H, ddd, *J* = 8.8, 8.8, 3.2 Hz, CH-C8), 3.33−3.27 (1H, m, CH-C1), 2.80 (1H, dd, *J* = 15.6, 3.2 Hz, CH_2-C9a), 2.39 (1H, dd, *J* = 15.6, 8.8 Hz, CH_2-C9b), 2.00−1.96 (1H, m, CH_2-C2a), 1.77−1.71 (1H, m, CH_2-C3a), 1.65 (3H, s, CH_3-C7), 1.51−1.45 (2H, m, CH_2-C2b, CH_2-C3b), 0.81 (9H, s, CH_3-*t*Bu OTBS), 0.00 (6H, s, 2 × CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (C-C10), 144.6 (C-C5), 110.9 (CH_2-C6), 80.5 (CH-C4), 78.9 (CH-C8), 70.6 (CH-C1), 37.7 (CH_2-C9), 33.2 (CH_2-C2), 29.5 (CH_2-C3), 25.7 (CH_3-*t*Bu OTBS), 19.0 (CH_3-C7), 17.9 (C-*t*Bu OTBS), −4.0 (CH_3-OTBS), −4.8 (CH_3-OTBS); $[\alpha]_D^{22}$ +68.0 (*c* = 0.500, $CHCl_3$) {Lit.[64] $[\alpha]_D^{25}$ +67.5 (*c* = 1.00, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{16}H_{30}O_4SiNa$ 337.1800, found 337.1806, Δ 1.8 ppm.

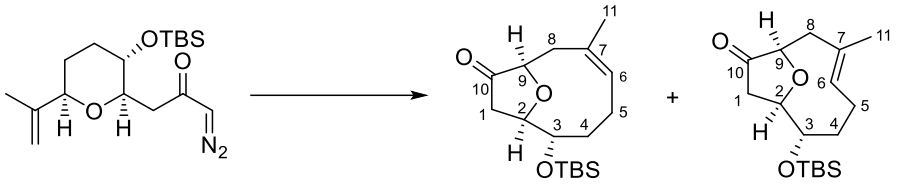
1-[(2*R*,3*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(prop-1-en-2-yl)oxan-2-yl]-3-diazopropan-2-one (165)[64]



To a stirred solution of carboxylic acid **164** (3.00 g, 9.54 mmol) and triethylamine (1.86 mL, 13.4 mmol) in anhydrous diethyl ether (100 mL) was added isobutyl chloroformate (1.61 mL, 12.4 mmol) dropwise over 5 minutes and the resulting solution left to stir for 2.5 hours. The solution was filtered under suction and the residue left behind washed with diethyl ether (10 mL) then immediately added to a freshly prepared ethereal solution of diazomethane (approx. 95 mmol). The resulting solution was left to stir for 3 days before the reaction was quenched by the addition of glacial acetic acid (12.0 mL, 210 mmol) and poured into a saturated aqueous solution of sodium bicarbonate (300 mL) with vigorous stirring and left for 15 minutes. The aqueous phase was separated and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 → 10:1) to afford diazo-ketone **165** (2.69 g, 83%) as a yellow oil.

R_f = 0.46 (petroleum ether-ethyl acetate, 5:1); ν_{max} 3092, 2930, 2857, 2101, 1641,1252, 897, 835, 775, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, br s, CH-C11), 4.86 (1H, s, CH_2-C6a), 4.74 (1H, s, CH_2-C6b), 3.66 (1H, br d, *J* = 10.0 Hz, CH-C4), 3.52 (1H, ddd, *J* = 9.2, 9.2, 2.4 Hz, CH-C8), 3.27 (1H, ddd, *J* = 9.2, 4.8, 4.8 Hz, CH-C1), 2.71 (1H, dd, *J* = 14.4, 2.4 Hz, CH_2-C9a), 2.37−2.31 (1H, m, CH_2-C9b), 2.00−1.95 (1H, m, CH_2-C2a), 1.76−1.72 (1H, m, CH_2-C3a), 1.65 (3H, s, CH_3-C7), 1.53−1.37 (2H, m, CH_2-C2b, CH_2-C3b), 0.81 (9H, s, CH_3-*t*Bu OTBS), 0.00 (6H, s, 2 × CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6 (C-C10), 145.2 (C-C5), 110.3 (CH_2-C6), 80.1 (CH-C4), 79.8 (CH-C8), 70.7 (CH-C1), 55.2 (CH-C11), 44.0 (CH_2-C9), 33.4 (CH_2-C2), 29.7 (CH_2-C3), 25.8 (CH_3-*t*Bu OTBS), 19.2 (CH_3-C7), 17.9 (C-*t*Bu OTBS), −4.0 (CH_3-OTBS), −4.7 (CH_3-OTBS); $[\alpha]_D^{22}$ +88.8 (*c* = 0.500, $CHCl_3$) {Lit.[64] $[\alpha]_D^{23}$ +95.7 (*c* = 1.01, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{17}H_{30}N_2O_3SiNa$ 361.1921, found 361.1918, Δ 1.0 ppm.

(1*R*,2*S*,5*Z*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (167)[64] and (1*R*,2*S*,5*E*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (168)[64]



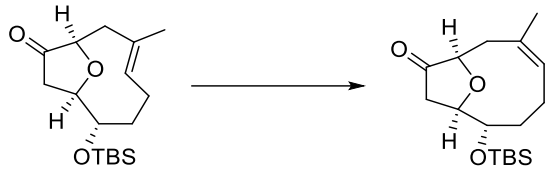
165 167 168

To a stirred solution of Cu(hfacac)$_2$ (263 mg, 0.551 mmol) in anhydrous dichloromethane (130 mL) at reflux was added a solution of diazo-ketone **165** (3.73 g, 11.0 mmol) in anhydrous dichloromethane (570 mL) dropwise over 1 hour while maintaining reflux. The resulting solution was left to stir for 30 minutes before being cooled to room temperature. The volatiles were removed under reduced pressure before rapid flash column chromatography on deactivated alumina (Brockmann III, petroleum ether-ethyl acetate, 15:1) allowed removal of the catalyst. The residue was purified by flash column chromatography on silver nitrate (10% w/w) impregnated silica gel (petroleum ether-ethyl acetate, gradient elution from 40:1 → 10:1) to afford *Z*-alkene **167** (2.53 g, 74%) and *E*-alkene **168** (0.55 g, 16%) as colourless solids.

167: R_f = 0.60 (petroleum ether-ethyl acetate, 5:1); m.p. 87−89 °C; ν_{max} 2928, 2857, 1753, 1470, 1260, 947, 833, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, dd, *J* = 11.6, 5.6 Hz, CH-C6), 4.19 (1H, dd, *J* = 4.4, 4.4 Hz, CH-C9), 4.12 (1H, dd, *J* = 8.4, 8.4 Hz, CH-C2), 3.37 (1H, ddd, *J* = 11.2, 8.4, 2.8 Hz, CH-C3), 2.76−2.64 (3H, m, CH_2-C1a, CH_2-C5a, CH_2-C8a), 2.25 (1H, d, *J* = 17.6 Hz, CH_2-C1b), 2.17 (1H, dd, *J* = 14.8, 4.4 Hz, CH_2-C8b), 1.96−1.89 (1H, m, CH_2-C5b), 1.86−1.78 (1H, m, CH_2-C4a), 1.70 (3H, s, CH_3-C11), 1.64−1.55 (1H, m, CH_2-C4b), 0.81 (9H, s, CH_3-*t*Bu OTBS), 0.00 (3H, s, CH_3-OTBS), −0.04 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8 (C-C10), 132.4 (C-C7), 127.5 (CH-C6), 80.3 (CH-C2), 78.8 (CH-C9), 75.3 (CH-C3), 42.3 (CH_2-C1), 33.3 (CH_2-C8), 33.1 (CH_2-C4), 26.7 (CH_3-C11), 25.8 (CH_2-C5, CH_3-*t*Bu OTBS), 17.9 (C-*t*Bu OTBS), −3.9 (CH_3-OTBS), −4.5 (CH_3-OTBS); $[\alpha]_D^{22}$ +11.2 (c = 0.505, $CHCl_3$) {Lit.[64] $[\alpha]_D^{28}$ +31.8 (c = 1.03, $CHCl_3$); HRMS (CI+, isobutane) $[M+H]^+$ calcd. for $C_{17}H_{31}O_3Si$ 311.2042, found 311.2042, Δ 0.0 ppm.

168: R_f = 0.60 (petroleum ether-ethyl acetate, 5:1); m.p. 57−59 °C ;ν_{max} 2930, 2859, 1755, 1462, 1258, 910, 835, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, dd, *J* = 12.0, 4.2 Hz, CH-C6), 4.16−4.11 (2H, m, CH-C2, CH-C9), 3.02 (1H, dd, *J* = 9.2, 8.0 Hz, CH-C3), 2.77 (1H, ddd, *J* = 17.6, 9.2, 1.2 Hz, CH_2-C1a), 2.56−2.48 (2H, m, CH_2-C8), 2.27 (1H, d, *J* = 17.6 Hz, CH_2-C1b), 2.24−2.12 (2H, m, CH_2-C5), 1.96 (1H, dddd, *J* = 14.0, 11.6, 7.6, 3.6 Hz, CH_2-C4a), 1.70 (1H, ddd, *J* = 14.0, 3.6, 3.6 Hz, CH_2-C4b), 1.55 (3H, s, CH_3-C11), 0.86 (9H, s, CH_3-*t*Bu OTBS), 0.08 (3H, s, CH_3-OTBS), 0.03 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.2 (C-C10), 133.2 (C-C7), 124.7 (CH-C6), 80.8 (CH-C2), 78.3 (CH-C9), 76.5 (CH-C3), 41.9 (CH_2-C1), 40.3 (CH_2-C8), 35.7 (CH_2-C4), 26.9 (CH_2-C5), 25.7 (CH_3-*t*Bu OTBS), 18.8 (CH_3-C11), 17.8 (C-*t*Bu OTBS), −3.9 (CH_3-OTBS), −4.9 (CH_3-OTBS); $[\alpha]_D^{22}$ −3.0 (c = 0.50, $CHCl_3$) {Lit.[64] $[\alpha]_D^{28}$ −38.7 (c = 0.99, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{17}H_{30}O_3SiNa$ 333.1846, found 333.1856, Δ 3.1 ppm.

(1*R*,2*S*,5*Z*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (167)

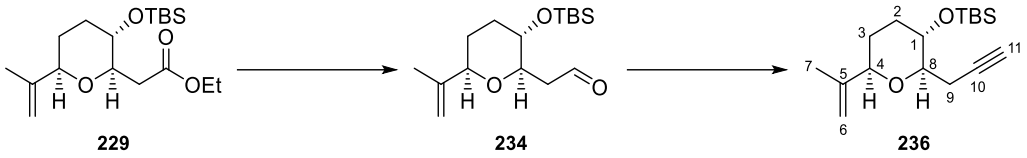


168 **167**

To a stirred solution of *E*-alkene **168** (1.50 g, 4.83 mmol) and ethanethiol (3.50 mL, 48.3 mmol), in anhydrous PhMe (100 mL) was added Vazo™ 88 (0.24 g, 1.0 mmol) in one portion and the resulting solution was heated to 90 °C for 3 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 50:1 → 25:1) to afford *Z*-alkene **167** (1.18 g, 79%) as a colourless solid.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **167** previously (see p. 110).

tert-Butyldimethyl{[(2*R*,3*S*,6*R*)-6-(prop-1-en-2-yl)-2-(prop-2-yn-1-yl)oxan-3-yl]oxy}silane (236)



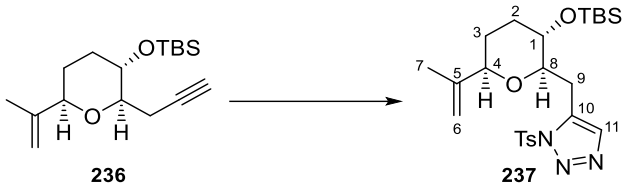
To a stirred solution of ester **229** (1.75 g, 5.11 mmol) in anhydrous dichloromethane (100 mL) at −78 °C was added DIBAL-H (5.50 mL of a 1.0 M solution in dichloromethane, 5.50 mmol) dropwise over 5 minutes. The resulting solution was left to stir for 1 hour before the reaction was quenched by the addition of water (15 mL) and warmed to 0 °C for 15 minutes. A saturated aqueous solution of potassium sodium tartrate (30 mL) was added and the resulting solution stirred vigorously for 1 hour at room temperature (two clear phases were obtained). The aqueous phase was separated and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude aldehyde **234**, which was used in the next step without further purification.

To a stirred solution of aldehyde **234** and potassium carbonate (1.41 g, 10.2 mmol) in anhydrous methanol (100 mL) at room temperature was added Bestmann-Ohira reagent (1.30 mL, 8.66 mmol) dropwise over 5 minutes. The resulting solution was stirred for 16 hours before the reaction was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (40 mL) and diluted with water (80 mL) and ethyl acetate (200 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 100:1) to afford alkyne **236** (1.29 g, 86%) as a colourless oil.

R_f = 0.83 (petroleum ether-ethyl acetate, 20:1); ν_{max} 3314, 2949, 2930, 2885, 2857, 2122, 1653, 1472, 1252, 885, 835, 775, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.00 (1H, br s, CH_2-C6a), 4.82 (1H, s, CH_2-C6b), 3.75 (1H, br d, *J* = 8.9 Hz, CH-C4), 3.54−3.46 (1H, m, CH-C1), 3.27 (1H, ddd, *J* = 8.9, 6.0, 3.4 Hz, CH-C8), 2.63 (1H, ddd, *J* = 16.9, 3.4, 2.8 Hz, CH_2-C9a), 2.47 (1H, ddd, *J* = 16.9, 6.0, 2.7 Hz, CH_2-C9b), 2.09−1.98 (1H, m, CH_2-C2a), 1.95 (1H, dd, *J* = 2.8, 2.7 Hz, CH-C11), 1.82−1.76 (1H, m, CH_2-C3a), 1.75 (3H, s, CH_3-C7), 1.56−1.49 (2H, m, CH_2-C2b, CH_2-C3b), 0.89 (9H, s, CH_3-*t*Bu OTBS), 0.10 (3H, s,

CH_3-OTBS), 0.08 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (C-C5), 110.7 (CH_2-C6), 81.6 (C-C10), 80.4 (CH-C4), 80.2 (CH-C8), 69.8 (CH-C11), 69.4 (CH-C1), 33.4 (CH_2-C2), 29.9 (CH_2-C3), 25.9 (CH_3-*t*Bu OTBS), 22.4 (CH_2-C9), 19.1 (CH_3-C7), 18.1 (C-*t*Bu OTBS), −3.9 (CH_3-OTBS), −4.6 (CH_3-OTBS); $[\alpha]_D^{23}$ +45.5 (*c* = 0.390, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{17}H_{30}O_2SiNa$ 317.1898, found 317.1907, Δ 3.0 ppm. Anal. calcd for $C_{17}H_{30}O_2Si$: C, 69.33%; H, 10.27%. Found: C, 68.93%, H, 10.46%.

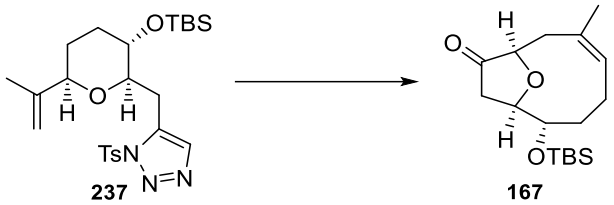
5-{[(2*R*,3*S*,6*R*)-3-[(tert-Butyldimethylsilyl)oxy]-6-(prop-1-en-2-yl)oxan-2-yl]methyl}-1-[(4-methylphenyl)sulfonyl]-1*H*-1,2,3-triazole (237)



To a stirred solution of alkyne **236** (0.22 g, 0.75 mmol) in anhydrous THF (3.8 mL) at −78 °C was added *n*-butyl lithium (0.36 mL of a 2.5 M solution in dichloromethane, 0.90 mmol) dropwise over 5 minutes. The reaction mixture was left to stir for 40 minutes before addition of tosyl azide (0.12 mL, 0.78 mmol) in one portion. The reaction mixture was left to stir for 1 hour before the reaction was quenched by the addition of saturated aqueous solution of ammonium chloride (3 mL), diluted with ethyl acetate (5 mL) and warmed to room temperature. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 → 10:1) to afford triazole **237** (0.32 g, 87%) as a colourless oil.

R_f = 0.46 (petroleum ether-ethyl acetate, 9:1); ν_{max} 2949, 2928, 2857, 1653, 1595, 1545, 1472, 893, 835, 775, 667, 583, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.93 (2H, m, 2 × CH-Ar Ts), 7.55 (1H, s, CH-C11), 7.37−7.31 (2H, m, 2 × CH-Ar Ts), 4.89 (1H, br s, CH_2-C6a), 4.78 (1H, s, CH_2-C6b), 3.71−3.65 (2H, m, CH-C4, CH_2-C9a), 3.47−3.38 (2H, m, CH-C1, CH-C8), 2.94−2.86 (1H, m, CH_2-C9b), 2.44 (3H, s, CH_3-Ts), 2.14−2.07 (1H, m, CH_2-C2a), 1.86−1.80 (1H, m, CH_2-C3a), 1.67 (3H, s, CH_3-C7), 1.60−1.52 (2H, m, CH_2-C2b, CH_2-C3b), 0.94 (9H, s, CH_3-*t*Bu OTBS), 0.15 (3H, s, CH_3-OTBS), 0.12 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (C-Ar Ts), 144.8 (C-C5), 137.8 (C-Ar Ts), 134.3 (C-C10), 134.0 (CH-C11), 130.4 (2 × CH-Ar Ts), 128.7 (2 × CH-Ar Ts), 110.9 (CH_2-C6), 80.5 (CH-C4), 80.4 (CH-C8), 71.2 (CH-C1), 33.6 (CH_2-C2), 29.7 (CH_2-C3), 27.4 (CH_2-C9), 26.0 (CH_3-*t*Bu OTBS), 21.9 (CH_3-Ts), 19.4 (CH_3-C7), 18.1 (C-*t*Bu OTBS), −3.9 (CH_3-OTBS), −4.5 (CH_3-OTBS); $[\alpha]_D^{20}$ −16.6 (c = 0.375, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{24}H_{37}N_3O_4SSiNa$ 514.2166, found 514.2155, Δ 2.1 ppm.

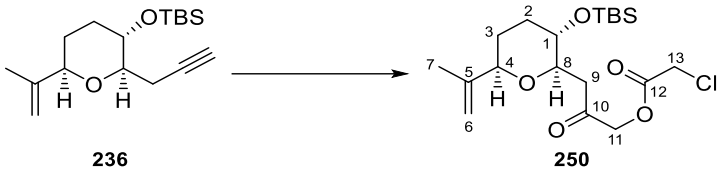
(1*R*,2*S*,5*Z*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (167)



To a solution of triazole **237** (18 mg, 37 μmol) in anhydrous DCE (1.4 mL) was added $Rh(OAc)_4$ (1.6 mg, 3.6 μmol) in one portion. The resulting solution was stirred at reflux in a sealed tube for 2 hours. The reaction mixture was cooled down to room temperature and basic alumina (Brockmann III, 0.37 g) was added in one portion and left to stir for 30 minutes. The resulting mixture was filtered through celite and filter cake washed with DCM (5 mL) before the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 50:1 → 25:1) to afford *Z*-alkene **167** (5.5 mg, 49%) as a colourless solid.

The NMR (^1H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **167** previously (see p. 110).

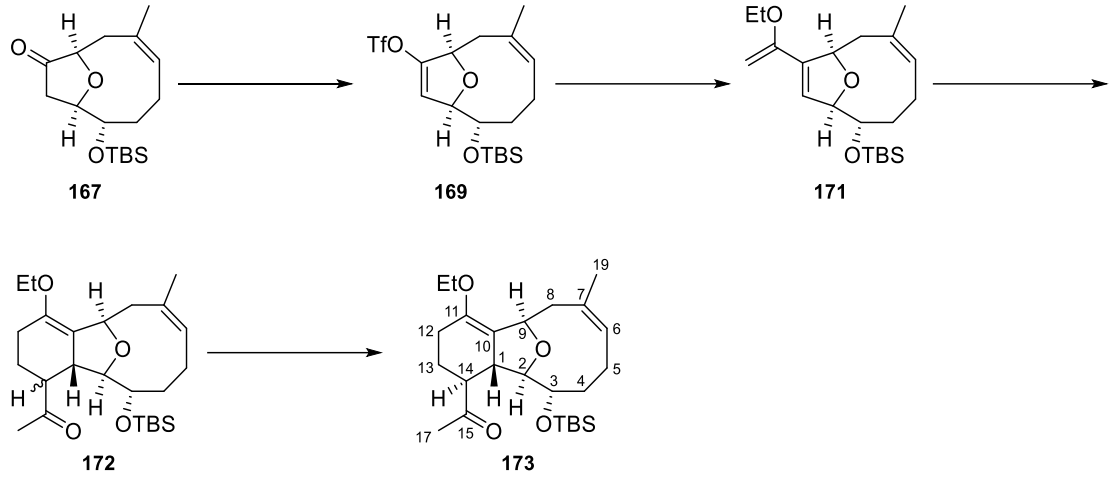
3-[(2*R*,3*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(prop-1-en-2-yl)oxan-2-yl]-2-oxopropyl 2-chloroacetate (250)



To a solution of alkyne **236** (0.50 g, 1.7 mmol) in anhydrous DCE (1.7 mL) was added SPhosAuNTf$_2$ (7.5 mg, 8.5 µmol), chloroacetic acid (32 mg, 0.34 mmol) and 5-bromo-2-methylpyridine-*N*-oxide (38 mg, 0.20 mmol) in one portion. The resulting solution was stirred at room temperature in a sealed vial for 16 hours before being concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 40:1 → 20:1) to afford ester **250** (25 mg, 36%) as a colourless solid.

R_f = 0.45 (petroleum ether-ethyl acetate, 5:1); ν_{max} 2953, 2930, 2857, 1761, 1742, 1655, 1472, 1254, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (1H, dd, *J* = 7.5, 5.6 Hz, CH-C4), 4.99 (1H, br s, CH_2-C6a), 4.96−4.93 (1H, m, CH_2-C6b), 4.21 (1H, ddd, *J* = 8.9, 6.5, 3.3 Hz, CH-C8), 4.05 (2H, s, CH_2-C13), 4.03 (1H, d, *J* = 17.0 Hz, CH_2-C11a), 3.94 (1H, ddd, *J* = 6.5, 5.2, 3.3 Hz, CH-C1), 3.85 (1H, d, *J* = 17.0 Hz, CH_2-C11b), 2.58 (1H, ddd, *J* = 18.0, 8.9, 1.1 Hz, CH_2-C9a), 2.35 (1H, dd, *J* = 18.0, 6.5 Hz, CH_2-C9b), 1.89−1.80 (1H, m, CH_2-C3a), 1.73 (3H, s, CH_3-C17), 1.73−1.65 (1H, m, CH_2-C3b), 1.51−1.35 (2H, m, CH_2-C2), 0.87 (9H, s, CH_3-*t*Bu OTBS), 0.08 (3H, s, CH_3-OTBS), 0.05 (3H, s, CH_3-OTBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9 (C-C10), 166.7 (C-C12), 141.9 (C-C5), 114.1 (CH_2-C6), 80.9 (CH-C8), 79.2 (CH-C4), 72.8 (CH-C1), 71.4 (CH_2-C11), 41.1 (CH_2-C13), 37.3 (CH_2-C9), 30.0 (CH_2-C2), 28.2 (CH_2-C3), 26.0 (CH_3-*t*Bu OTBS), 18.3 (C-*t*Bu OTBS), 18.1 (CH_3-C7), −4.2 (CH_3-OTBS), −4.4 (CH_3-OTBS); $[\alpha]_D^{23}$ +86.4 (c = 0.500, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{19}H_{33}O_5SiClNa$ 427.1678, found 417.1672, Δ 1.3 ppm.

1-[(1*R*,2*R*,3*S*,8*R*,10*Z*,14*S*)-14-[(*tert*-Butyldimethylsilyl)oxy]-6-ethoxy-10-methyltricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]ethan-1-one (173)[64]



To a stirred solution of ketone **167** (501 mg, 1.61 mmol) and *N*-phenyltriflimide (1.15 g, 4.00 mmol) in anhydrous THF (35 mL) at −78 °C was added NaHMDS (4.0 mL of a 1.0 M solution in THF, 4.0 mmol) dropwise over 10 minutes. The resulting solution was stirred for 2.5 hours before the reaction was quenched by the addition of water (15 mL) and diluted with diethyl ether (30 mL) before being allowed to warm to room temperature. The aqueous phase was separated and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude enol triflate **169**, which was used in the next step without further purification.

To a stirred solution of enol triflate **169** and tributyl(1-ethoxyvinyl)stannane (1.62 mL, 4.80 mmol) in anhydrous THF (30 mL) was added lithium chloride (243 mg, 5.73 mmol) and palladium tetrakis(triphenylphosphine) (277 mg, 0.240 mmol) in one portion. The resulting solution was heated at reflux for 16 hours. The reaction mixture was cooled down to room temperature and diluted with ethyl acetate (30 mL), water (20 mL) and brine (20 mL). The organic phase was separated and washed with 5% aqueous solution of ammonium hydroxide (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 15:1 with 1% triethylamine) to afford diene **171** as a colourless oil.

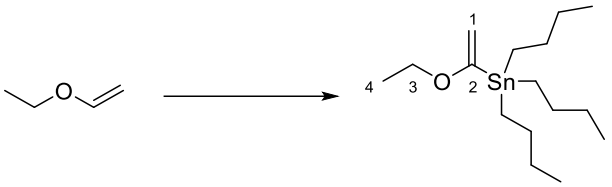
To a solution of diene **171** in anhydrous toluene (50 mL) was added distilled methyl vinyl ketone (1.58 mL, 16.0 mmol) and the resulting solution was heated to 120 °C in a sealed

tube for 16 hours. The volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 15:1) to afford a 1:1 mixture of *endo*:*exo* Diels–Alder cycloadducts **172** as a colourless oil.

To a stirred solution of Diels–Alder cycloadducts **172** in anhydrous methanol (15 mL) was added potassium carbonate (265 mg, 1.92 mmol) and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was diluted with saturated aqueous solution of ammonium chloride (15 mL) and ethyl acetate (30 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford ketone **173** (471 mg, 67%) as a colourless oil.

R_f = 0.47 (petroleum ether-ethyl acetate, 4:1); ν_{max} 2952, 2928, 2858, 1708, 1463, 1251, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (1H, dd, *J* = 11.5, 5.5 Hz, CH-C6), 4.86 (1H, ddd, *J* = 4.0, 2.7, 2.7 Hz, CH-C9), 3.79 (2H, q, *J* = 7.0 Hz, CH_2-OEt), 3.71 (1H, dd, *J* = 9.2, 2.7 Hz, CH-C2), 3.60−3.57 (1H, m, CH-C3), 3.15−3.07 (1H, m, CH_2-C5a), 2.96−2.89 (1H, m, CH-C1), 2.84 (1H, br d, *J* = 14.0 Hz, CH_2-C8a), 2.35−2.22 (3H, m, CH_2-C12, CH-C14), 2.15 (3H, s, CH_3-C17), 2.03 (1H, dddd, *J* = 9.1, 7.4, 4.5, 2.5 Hz, CH_2-C13a), 1.93 (1H, dd, *J* = 14.0, 4.0 Hz, CH_2-C8b), 1.89−1.73 (3H, m, CH_2-C4, CH_2-C5b), 1.67 (3H, s, CH_3-C19), 1.65−1.55 (1H, m, CH_2-C13b), 1.24 (3H, t, *J* = 7.0 Hz, CH_3-OEt), 0.88 (9H, s, CH_3-*t*Bu OTBS), 0.04 (3H, s, CH_3-OTBS), 0.03 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3 (C-C15), 143.8 (C-C11), 130.6 (C-C7), 130.2 (CH-C6), 119.3 (C-C10), 88.2 (CH-C2), 75.2 (CH-C9), 72.0 (CH-C3), 63.2 (CH_2-OEt), 52.4 (CH-C14), 43.6 (CH-C1), 37.5 (CH_2-C8), 33.0 (CH_2-C4), 29.8 (CH_3-C17), 28.4 (CH_3-C19), 27.2 (CH_2-C13), 26.3 (CH_3-*t*Bu OTBS), 24.6 (CH_2-C12), 22.1 (CH_2-C5), 18.7 (C-*t*Bu OTBS), 15.9 (CH_3-OEt), −4.3 (CH_3-OTBS), −4.4 (CH_3-OTBS); $[\alpha]_D^{21}$ +109 (*c* = 1.02, $CHCl_3$) {Lit.[64] $[\alpha]_D^{24}$ +143 (*c* = 0.99, $CHCl_3$)}; HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{25}H_{42}O_4SiNa$ 457.2745, found 457.2730, Δ 3.2 ppm.

2-(Ethoxy)-2-(tributylstannyl)ethene (170)



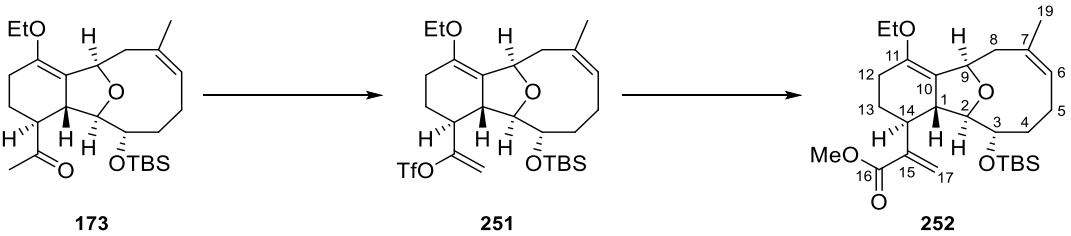
310 **170**

To a stirred solution of distilled ethyl vinyl ether **310** (3.50 mL, 36.4 mmol) in anhydrous THF (25 mL) at −78 °C was added *tert*-butyl lithium (15.0 mL of a 1.7 M solution in pentane, 25.5 mmol) dropwise over 10 minutes. The resulting solution was stirred for 1.5 hours and then allowed to warm to 0 °C over 50 minutes. The reaction mixture was stirred for a further 30 minutes before being cooled down to −78 °C. Tributyltin chloride (4.50 mL, 16.4 mmol) was added dropwise over 10 minutes and the resulting solution was stirred for 20 minutes. The reaction mixture was warmed to room temperature before the reaction was quenched by the addition of water (15 mL) and diluted with diethyl ether (30 mL). The organic phase was separated and washed with water (3 × 15 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by vacuum distillation (b.p. 175−180 °C at 5 mbar) to afford stannane **170** (4.15 g, 70%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (1H, d, *J* = 1.6 Hz, CH_2-C1a), 4.06 (1H, d, *J* = 1.6 Hz, CH_2-C1b), 3.72 (2H, q, *J* = 7.0 Hz, CH_2-C3), 1.59−1.51 (6H, m, CH_2-*n*Bu), 1.34 (6H, app dq, *J* = 14.4, 7.3 Hz, CH_2-*n*Bu), 1.28 (3H, t, *J* = 7.0 Hz, CH_3-C4), 0.99−0.94 (6H, m, CH_2-*n*Bu), 0.91 (9H, t, *J* = 7.3 Hz, CH_3-*n*Bu).

The ^{1}H NMR data was consistent with those reported for compound **170** previously.[70]

Methyl 2-[(1*R*,2*S*,3*S*,8*R*,10*Z*,14*S*)-14-[(*tert*-butyldimethylsilyl)oxy]-6-ethoxy-10-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]prop-2-enoate (252)



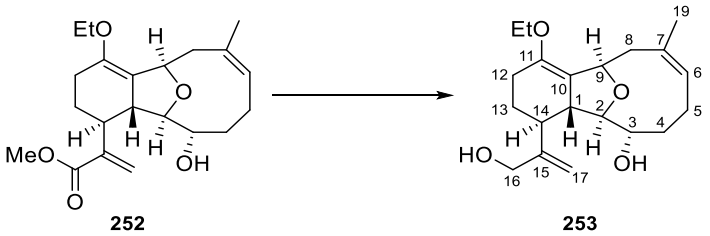
To a stirred solution of ketone **173** (600 mg, 1.38 mmol) and *N*-phenyltriflimide (1.23 g, 3.44 mmol) in anhydrous THF (28 mL) at −78 °C was added NaHMDS (1.4 mL of a 2.0 M solution in THF, 2.8 mmol) dropwise over 10 minutes. The resulting solution was stirred for 2.5 hours before the reaction was quenched by the addition of water (15 mL) and diluted with diethyl ether (20 mL) before being allowed to warm to room temperature. The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude enol triflate **251**, which was used in the next step without further purification.

To a stirred solution of enol triflate **251**, *N*,*N*-diisopropylethylamine (0.96 mL, 5.5 mmol) in anhydrous methanol (69 mL) was added palladium tetrakis(triphenylphosphine) (159 mg, 0.138 mmol) and sparged with CO for 15 minutes. The resulting solution was stirred under an atmosphere of carbon monoxide at room temperature for 16 hours. The reaction was quenched by sparging the reaction mixture with argon for 30 minutes and the reaction mixture concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-diethyl ether, 20:1) to afford ester **252** (633 mg, 96%) as a colourless oil.

R_f = 0.80 (petroleum ether-ethyl acetate, 3:1); ν_{max} 2955, 2930, 2895, 2857, 1721, 941, 833, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (1H, d, *J* = 1.2 Hz, CH_2-C17a), 5.56 (1H, d, *J* = 1.2 Hz, CH_2-C17b), 5.29 (1H, dd, *J* = 11.2, 5.5 Hz, CH-C6), 4.89−4.85 (1H, m, CH-C9), 3.79 (1H, qd, *J* = 7.0, 1.9 Hz, CH_2-OEt), 3.79 (1H, qd, *J* = 7.0, 1.9 Hz, CH_2-OEt), 3.76−3.71 (1H, m, CH-C2), 3.75 (3H, s, CH_3-OMe), 3.58 (1H, ddd, *J* = 3.6, 2.8, 2.8 Hz, CH-C3), 3.14 (1H, app td, *J* = 11.9, 8.9 Hz, CH_2-C5a), 2.86−2.75 (2H, m, CH-C1, CH_2-C8a), 2.35−2.27 (1H, m, CH-C14), 2.27−2.21 (2H, m, CH_2-C12), 1.94 (1H, dd, *J* = 14.0, 4.0 Hz, CH_2-C8b), 1.90−1.72 (4H, m, CH_2-C4a, CH_2-C5b, CH_2-C13), 1.69 (3H, s, CH_3-C19), 1.52 (1H, ddd,

J = 14.3, 8.9, 3.6 Hz, CH_2-C4b), 1.23 (3H, dd, *J* = 7.0, 7.0 Hz, CH_3-OEt), 0.86 (9H, s, CH_3-*t*Bu OTBS), 0.01 (3H, s, CH_3-OTBS), −0.01 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C-C16), 144.3 (C-C15), 143.6 (C-C11), 131.1 (C-C7), 129.8 (CH-C6), 125.5 (CH_2-C17), 120.1 (CH-C10), 88.0 (CH-C2), 75.4 (CH-C9), 72.0 (CH-C3), 63.0 (CH_2-OEt), 52.0 (CH_3-OMe), 46.5 (CH-C1), 42.1 (CH-C14), 37.6 (CH_2-C8), 33.1 (CH_2-C4), 30.9 (CH_2-C13), 28.5 (CH_3-C19), 26.3 (CH_3-*t*Bu OTBS), 25.1 (CH_2-C12), 22.0 (CH_2-C5), 18.6 (C-*t*Bu OTBS), 15.9 (CH_3-OEt), −4.4 (CH_3-OTBS), −4.5 (CH_3-OTBS); $[\alpha]_D^{24}$ +142 (*c* = 0.353, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{27}H_{44}O_5SiNa$ 499.2850, found 499.2832, Δ 3.6 ppm. Anal. calcd for $C_{27}H_{44}O_5Si$: C, 68.03%; H, 9.30%. Found: C, 68.27%, H, 9.30%.

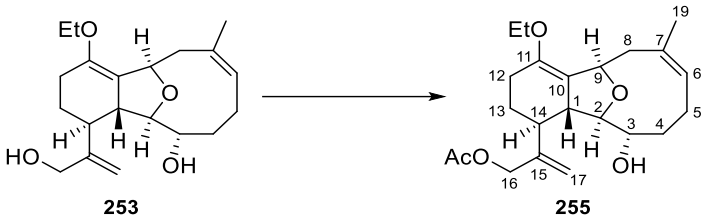
(1*R*,6*S*,7*R*,8*R*,9*S*,12*Z*)-3-Ethoxy-6-(3-hydroxyprop-1-en-2-yl)-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-2,12-dien-9-ol (253)



To a stirred solution of ester **252** (250 mg, 0.524 mmol) in anhydrous dichloromethane (8.6 mL) at −30 °C was added DIBAL-H (1.6 mL of a 1.0 M solution in dichloromethane, 1.6 mmol) dropwise over 15 minutes. The resulting solution was stirred for 1.5 hours before the reaction was quenched by the addition of water (2 mL) and warmed to 0 °C for 15 minutes. A saturated aqueous solution of potassium sodium tartrate (10 mL) was added and the resulting solution stirred vigorously for 1 hour at room temperature (two clear phases were obtained). The aqueous phase was separated and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 2:1 → 1:2) to afford diol **253** (140 mg, 80%) as a colourless solid.

R_f = 0.21 (petroleum ether-ethyl acetate, 1:2); m.p. 108−110 °C; ν_{max} 3366, 2965, 2922, 2857, 1713, 1643, 991, 895, 731 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 5.39 (1H, dd, *J* = 11.2, 5.7 Hz, CH-C6), 5.13−5.08 (1H, m, CH-C9), 5.02 (1H, d, *J* = 1.1 Hz, CH_2-C17a), 4.77 (1H, d, *J* = 1.1 Hz, CH_2-C17b), 3.99 (1H, dd, *J* = 9.0, 3.2 Hz, CH-C2), 3.86−3.71 (3H, m, CH-C3, CH_2-16), 3.45 (1H, dq, *J* = 9.5, 7.0 Hz, CH_2-OEt), 3.40 (1H, dq, *J* = 9.5, 7.0 Hz, CH_2-OEt), 3.07−2.88 (2H, m, CH_2-C5a, HO-C16), 2.87 (1H, br d, *J* = 13.8 Hz, CH_2-C8a), 2.77−2.68 (1H, m, CH-C1), 2.19−2.08 (1H, m, CH_2-C4a), 2.11 (1H, dd, *J* = 13.8, 4.0 Hz, CH_2-C8b), 1.92−1.81 (3H, m, CH_2-C5b, CH_2-C12), 1.80 (3H, s, CH_3-C19), 1.73−1.55 (3H, m, CH_2-C4b, CH_2-C13a, CH-C14), 1.50−1.30 (2H, m, HO-C3, CH_2-C13b), 1.02 (3H, dd, *J* = 7.0, 7.0 Hz, CH_3-OEt); ^{13}C NMR (101 MHz, C_6D_6) δ 152.0 (C-C15), 144.7 (C-C11), 131.5 (C-C7), 129.6 (CH-C6), 120.0 (C-C10), 109.6 (CH_2-C17), 87.9 (CH-C2), 75.6 (CH-C9), 72.2 (CH-C3), 65.0 (CH_2-C16), 62.5 (CH_2-OEt), 47.3 (CH-C1), 43.1 (CH-C14), 37.9 (CH_2-C8), 33.0 (CH_2-C4), 30.8 (CH_2-C13), 28.4 (CH_3-C19), 25.0 (CH_2-C12), 22.4 (CH_2-C5), 15.8 (CH_3-OEt); $[\alpha]_D^{23}$ +150 (*c* = 1.40, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{20}H_{30}O_4Na$ 357.2036, found 357.2031, Δ 1.4 ppm.

2-[(1*R*,2*S*,3*S*,8*R*,10*Z*,14*S*)-6-Ethoxy-14-hydroxy-10-methyl-15-oxatricyclo[6.6.1.0^{2,7}] pentadeca-6,10-dien-3-yl]prop-2-en-1-yl acetate (255)

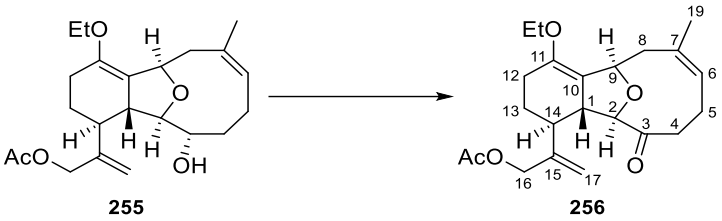


To a stirred solution of diol **253** (250 mg, 0.747 mmol), DMAP (91 mg, 0.74 mmol) and distilled triethylamine (0.21 mL, 1.5 mmol) in anhydrous dichloromethane (30 mL) at 0 °C was added distilled acetic anhydride (4.0 mL of a 0.2 M solution in dichloromethane, 0.80 mmol). The resulting solution was warmed to room temperature and allowed to stir for 45 minutes before being cooled to 0 °C. The reaction was quenched by the addition of saturated aqueous solution of ammonium chloride (20 mL) and diluted with diethyl ether (60 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford acetate **255** (274 mg, 98%) as a colourless oil.

R_f = 0.62 (petroleum ether-ethyl acetate, 1:2); ν_{max} 3439, 2974, 2928, 2882, 2857, 1742, 1709, 1670, 955, 907, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (1H, dd, *J* = 11.2, 5.8 Hz, CH-C6), 5.08 (1H, d, *J* = 1.3 Hz, CH_2-C17a), 4.98 (1H, d, *J* = 1.3 Hz, CH_2-C17b), 4.87−4.83 (1H, m, CH-C9), 4.48 (2H, br s, CH_2-C16), 3.84−3.77 (1H, m, CH-C2), 3.80 (1H, qd, *J* = 7.0, 0.7 Hz, CH_2-OEt), 3.80 (1H, qd, *J* = 7.0, 0.7 Hz, CH_2-OEt), 3.69−3.64 (1H, m, CH-C3), 2.86−2.77 (1H, m, CH_2-C5a), 2.75 (1H, br d, *J* = 14.0, CH_2-C8a), 2.72−2.64 (2H, m, CH-C1, HO-C3), 2.35−2.15 (2H, m, CH_2-C12), 2.10 (3H, s, CH_3-OAc), 2.03−1.95 (1H, m, CH_2-C4a), 1.97 (1H, dd, *J* = 14.0, 4.0 Hz, CH_2-C8b), 1.94−1.86 (1H, m, CH_2-C13a), 1.86−1.74 (2H, m, CH_2-C5b, CH-C14), 1.69 (3H, s, CH_3-C19), 1.67−1.55 (2H, m, CH_2-C4b, CH_2-C13b), 1.24 (3H, dd, *J* = 7.0, 7.0 Hz, CH_3-OEt); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C-OAc), 146.1 (C-C15), 144.8 (C-C11), 131.6 (C-C7), 129.2 (CH-C6), 119.5 (C-C10), 113.4 (CH_2-C17), 87.4 (CH-C2), 75.3 (CH-C9), 71.5 (CH-C3), 65.8 (CH_2-C16), 62.9 (CH_2-OEt), 46.2 (CH-C1), 43.8 (CH-C14), 37.5 (CH_2-C8), 32.4 (CH_2-C4), 30.2 (CH_2-C13), 28.3 (CH_3-C19), 25.0 (CH_2-C12), 21.6 (CH_2-C5), 21.1 (CH_3-OAc), 15.9 (CH_3-OEt);

$[\alpha]_D^{23}$ +142 (c = 1.21, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{22}H_{32}O_5Na$ 399.2142, found 399.2130, Δ 2.9 ppm.

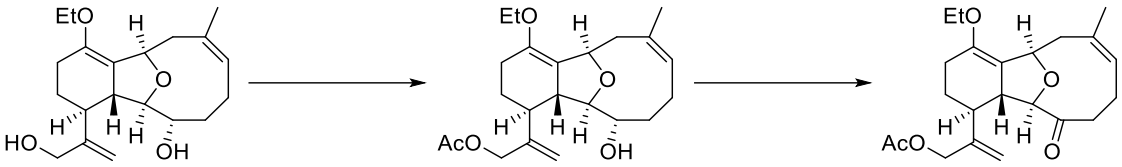
2-[(1*R*,2*S*,3*S*,8*R*,10*Z*)-6-Ethoxy-10-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]prop-2-en-1-yl acetate (256)



To a stirred solution of acetate **255** (270 mg, 0.717 mmol) in anhydrous dichloromethane (11 mL) at room temperature was added pyridine (0.23 mL, 2.9 mmol) and Dess–Martin periodinane (551 mg, 1.30 mmol). The resulting solution was stirred for 2 hours then diluted with diethyl ether (30 mL). The reaction was quenched by the addition of saturated aqueous solution of sodium thiosulfate (10 mL) and left for 5 minutes before the addition of saturated aqueous solution of sodium bicarbonate (5 mL). The resulting solution was stirred vigorously for 30 minutes. The aqueous phase was separated and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 4:1) to afford ketone **256** (223 mg, 83%) as a colourless oil.

R_f = 0.77 (petroleum ether-ethyl acetate, 1:1); ν_{max} 2974, 2930, 2868, 1742, 1705, 1647, 901, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, br s, CH-C6), 5.10 (1H, br s, CH-C9), 5.06 (1H, d, *J* = 1.4 Hz, CH_2-C17a), 5.00 (1H, d, *J* = 1.4 Hz, CH_2-C17b), 4.70 (1H, d, *J* = 14.0 Hz, CH_2-C16a), 4.66 (1H, d, *J* = 14.0 Hz, CH_2-C16b), 3.97 (1H, d, *J* = 6.0 Hz, CH-C2), 3.83 (2H, q, *J* = 7.0 Hz, CH_2-OEt), 2.98 (1H, ddd, *J* = 13.0, 6.0, 3.9 Hz, CH_2-C4a), 2.81 (1H, br s, CH-C1), 2.44−2.31 (2H, m, CH_2-C4b, CH_2-C12a), 2.28−2.16 (1H, m, CH_2-C12b), 2.10 (3H, s, CH_3-OAc), 2.09−1.89 (5H, m, CH_2-C5a, CH_2-C8, CH_2-C13a, CH-C14), 1.74 (3H, s, CH_3-C19), 1.79−1.66 (2H, m, CH_2-C5b, CH_2-C13b), 1.24 (3H, t, *J* = 7.0 Hz, CH_3-OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (C-OAc), 146.0 (C-C15), 145.0 (C-C11), 134.8 (C-C7), 127.1 (CH-C6), 119.5 (C-C10), 113.4 (CH_2-C17), 88.7 (CH-C2), 80.3 (CH-C9), 64.9 (CH_2-C16), 63.3 (CH_2-OEt), 46.7 (CH-C14), 41.5 (CH_2-C4), 37.1 (CH_2-C8), 29.3 (CH_2-C13), 29.3 (CH_3-C19), 24.9 (CH_2-C12), 24.1 (CH_2-C5), 21.2 (CH_3-OAc), 15.7 (CH_3-OEt). Peaks for C-C3 and CH-C1 were not observed; $[\alpha]_D^{31}$ +108 (*c* = 0.980, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{22}H_{30}O_5Na$ 397.1985, found 397.1979, Δ 1.7 ppm. Anal. calcd for $C_{22}H_{30}O_5$: C, 70.56%; H, 8.08%. Found: C, 70.25%, H, 7.89%.

2-[(1*R*,2*S*,3*S*,8*R*,10*Z*)-6-Ethoxy-10-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]prop-2-en-1-yl acetate (256)

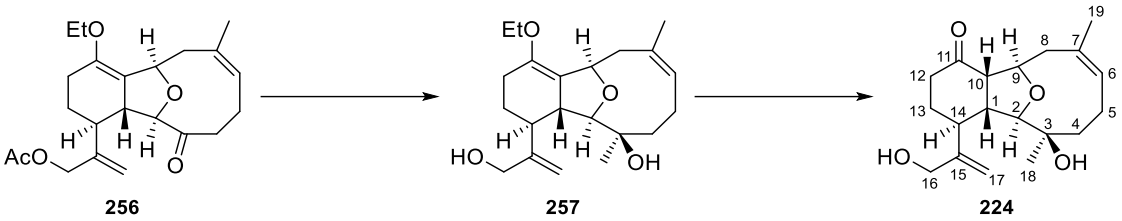


To a stirred solution of diol **253** (820 mg, 2.45 mmol), DMAP (299 mg, 2.45 mmol) and distilled triethylamine (0.68 mL, 4.9 mmol) in anhydrous dichloromethane (98 mL) at 0 °C was added distilled acetic anhydride (13.5 mL of a 0.2 M solution in dichloromethane, 2.70 mmol). The resulting solution was warmed to room temperature and allowed to stir for 45 minutes before being cooled to 0 °C. The reaction was quenched by the addition of saturated aqueous solution of ammonium chloride (75 mL) and diluted with diethyl ether (200 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude acetate **255**, which was used in the next step without further purification.

To a stirred solution of acetate **255** in anhydrous dichloromethane (38 mL) at room temperature was added pyridine (0.79 mL, 9.8 mmol) and Dess–Martin periodinane (1.87 g, 4.41 mmol) in one portion. The resulting solution was stirred for 2 hours then diluted with diethyl ether (80 mL). The reaction was quenched by the addition of saturated aqueous solution of sodium thiosulfate (40 mL) and left for 5 minutes before the addition of saturated aqueous solution of sodium bicarbonate (10 mL). The resulting solution was stirred vigorously for 30 minutes. The aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 4:1) to afford ketone **256** (905 mg, 98%) as a colourless oil.

The NMR (^1H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **256** previously (see p. 126).

(1*R*,2*R*,6*S*,7*S*,8*R*,9*R*,12*Z*)-9-Hydroxy-6-(3-hydroxyprop-1-en-2-yl)-9,13-dimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one (224)

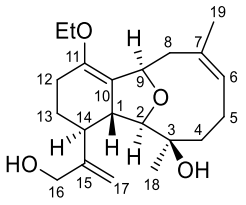


To a stirred solution of MeMgCl (4.60 mL of a 3.0 M solution in THF, 13.8 mmol) in anhydrous THF (32 mL) at 0 °C was added a solution of ketone **256** (520 mg, 1.39 mmol) in anhydrous THF (64 mL) dropwise over 5 minutes. The resulting solution was stirred for 30 minutes before being allowed to warm to room temperature for 1.5 hours. The reaction was quenched by slow transfer of the reaction mixture into a round bottom flask containing an aqueous solution of 1 M HCl (60 mL) over 30 minutes at room temperature. The resulting solution was stirred for 2 hours before being diluted by the addition of saturated aqueous solution of ammonium chloride (60 mL), water (60 mL) and ethyl acetate (120 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 1:2 → 1:5) to afford diol **224** (388 mg, 87%) as a colourless solid.

R_f = 0.22 (petroleum ether-ethyl acetate, 1:2); m.p. 118−120 °C; ν_{max} 3410, 2963, 2926, 2853, 1703, 1530, 977, 899, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, dd, *J* = 11.3, 5.9 Hz, CH-C6), 5.25 (1H, d, *J* = 0.8 Hz, CH_2-C17a), 5.06 (1H, d, *J* = 0.8 Hz, CH_2-C17b), 4.41 (ddd, *J* = 8.9, 3.2, 3.2 Hz, CH-C9), 4.16 (1H, d, *J* = 0.8 Hz, CH_2-C16a), 4.14 (1H, d, *J* = 0.8 Hz, CH_2-C16b), 3.86 (1H, d, *J* = 1.3 Hz, CH-C2), 3.06−2.85 (5H, m, CH-C1, CH_2-C5a, CH_2-C8a, CH-C10, HO-C16), 2.49−2.43 (2H, m, CH_2-C12), 2.38 (1H, ddd, *J* = 11.7, 11.7, 3.0 Hz, CH-C14), 2.09−1.94 (3H, m, CH_2-C5b, CH_2-C8b, CH_2-C13a), 1.91 (3H, s, CH_3-C19), 1.87−1.72 (3H, m, HO-C3, CH_2-C4a, CH_2-C13b), 1.70 (1H, ddd, *J* = 14.6, 10.7, 6.0 Hz, CH_2-C4b), 1.00 (3H, s, CH_3-C18); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0 (C-C11), 150.7 (C-C15), 135.9 (C-C7), 128.8 (CH-C6), 112.2 (CH_2-C17), 91.5 (CH-C2), 79.6 (CH-C9), 74.9 (C-C3), 65.3 (CH_2-C16), 54.0 (CH-C10), 48.7 (CH-C1), 41.2 (CH-C14), 38.8 (CH_2-C12), 38.6 (CH_2-C4), 35.6 (CH_2-C8), 31.1 (CH_2-C13), 28.9 (CH_3-C18), 28.5

(CH_3-C19), 26.6 (CH_2-C5); $[\alpha]_D^{24}$ +29.3 (*c* = 0.420, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{19}H_{28}O_4Na$ 343.1880, found 343.1870, Δ 2.7 ppm.

(1*R*,6*S*,7*R*,8*R*,9*R*,12*Z*)-3-Ethoxy-6-(3-hydroxyprop-1-en-2-yl)-9,13-dimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-2,12-dien-9-ol (257)



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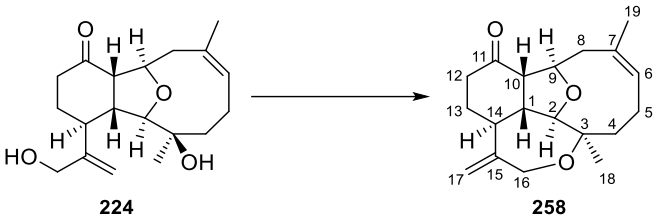
R_f = 0.53 (petroleum ether-ethyl acetate, 1:2); ν_{max} 3381, 2969, 2924, 2857, 1711, 1645, 1443, 910, 897 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, dd, *J* = 11.2, 5.4 Hz, CH-C6), 5.17 (1H, br s, CH_2-C17a), 4.94 (1H, br s, CH_2-C17b), 4.87 (1H, ddd, *J* = 4.0, 1.8, 1.8 Hz, CH-C9), 4.07 (1H, d, *J* = 13.4 Hz, CH_2-C16a), 4.02 (1H, d, *J* = 13.4 Hz, CH_2-C16b), 3.86–3.74 (2H, m, CH_2-OEt), 3.50 (1H, br d, *J* = 8.6 Hz, CH-C2), 2.99 (1H, br s, HO-C16), 2.91 (1H, m, CH-C1), 2.67 (1H, br d, *J* = 14.0 Hz, CH_2-C8a), 2.60 (1H, ddd, *J* = 12.5, 11.2, 8.5 Hz, CH_2-C5a), 2.26-2.21 (2H, m, CH_2-C12), 1.99–1.79 (5H, m, CH_2-C4a, CH_2-C5b, CH_2-C13a, CH-C14, HO-C3), 1.96 (1H, dd, *J* = 14.0, 4.0 Hz, CH_2-C8b) 1.75–1.70 (1H, m, CH_2-C13b), 1.69 (3H, s, CH_3-C19), 1.47 (1H, dd, *J* = 13.5, 8.5 Hz, CH_2-C4b), 1.37 (3H, s, CH_3-C18), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-OEt); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0 (C-C15), 145.0 (C-C11), 132.1 (C-C7), 128.7 (CH-C6), 120.1 (C-C10), 111.2 (CH_2-C17), 91.3 (CH-C2), 77.1 (CH-C9), 73.8 (C-C3), 66.1 (CH_2-C16), 62.8 (CH_2-OEt), 47.0 (CH-C1), 42.6 (CH-C14), 39.7 (CH_2-C4), 37.3 (CH_2-C8), 31.6 (CH_2-C12), 28.3 (CH_3-C19), 27.9 (CH_3-C18), 24.9 (CH_2-C13), 23.2 (CH_2-C5), 15.8 (CH_3-OEt); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{21}H_{32}O_4Na$ 371.2193, found 371.2175, Δ 4.8 ppm.

(1*R*,2*R*,3*S*,7*S*,11*R*,14*Z*,17*R*)-11,15-Dimethyl-8-methylidene-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (258)



To a stirred solution of diol **224** (645 mg, 2.01 mmol) in anhydrous chloroform (101 mL) at 0 °C was added 2,6-lutidine (1.20 mL, 10.4 mmol) followed by trifluoromethanesulfonic anhydride (16.1 mL of a 0.5 M solution in dichloromethane, 8.05 mmol) dropwise over 5 minutes. The resulting solution was stirred for 1 hour before the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (60 mL) and diluted with ethyl acetate (150 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with an aqueous solution of 1 M HCl (2 × 50 mL), brine (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford tetracycle **258** (591 mg, 97%) as a colourless solid.

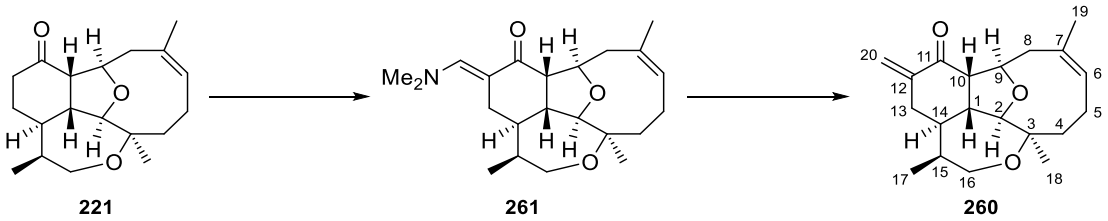
R_f = 0.47 (petroleum ether-ethyl acetate, 4:1); m.p. 137−140 °C; ν_{max} 2980, 2963, 2936, 2917, 2869, 2850, 1708, 1639, 895, 730 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 5.39 (1H, dd, *J* = 10.5, 6.8 Hz, CH-C6), 5.26 (1H, ddd, *J* = 4.3, 2.9, 2.9 Hz, CH-C9), 4.77 (1H, br s, CH_2-C17a), 4.56 (1H, br s, CH_2-C17b), 4.05 (1H, d, *J* = 14.2 Hz, CH_2-C16a), 3.86 (1H, d, *J* = 14.2 Hz, CH_2-C16b), 3.62 (1H, d, *J* = 9.3 Hz, CH-C2), 2.86−2.75 (1H, m, CH_2-C5a), 2.66−2.61 (1H, m, CH_2-C8a), 2.64 (1H, ddd, *J* = 12.0, 11.0, 9.3 Hz, CH-C1), 2.44 (1H, dd, *J* = 12.0, 2.9 Hz, CH-C10), 2.02−1.97 (2H, m, CH_2-C12), 1.88 (1H, dd, *J* = 14.2, 8.7 Hz, CH_2-C4a), 1.86−1.80 (1H, m, CH_2-C5b), 1.74 (1H, dd, *J* = 14.2, 10.7 Hz, CH_2-C4b), 1.64 (1H, dd, *J* = 14.5, 4.3 Hz, CH_2-C8b), 1.57 (3H, s, CH_3-C19), 1.54−1.47 (1H, m, CH_2-C13a), 1.45 (3H, d, *J* = 0.7 Hz, CH_3-C18), 1.44−1.39 (1H, m, CH-C14), 1.37−1.26 (1H, m, CH_2-C13b); ^{13}C NMR (101 MHz, C_6D_6) δ 208.4 (C-C11), 149.9 (C-C15), 131.8 (CH-C6), 129.2 (C-C7), 110.7 (CH_2-C17), 92.4 (CH-C2), 76.9 (C-C3), 76.6 (CH-C9), 67.4 (CH_2-C16), 53.0 (CH-C10), 47.8 (CH-C1), 43.3 (CH-C14), 38.5 (CH_2-C12), 37.2 (CH_2-C8), 36.6 (CH_2-C4), 29.3 (CH_3-C19), 27.2 (CH_3-C18), 25.5 (CH_2-C13), 23.4 (CH_2-C5); $[\alpha]_D^{23}$ −26.6 (*c* = 0.630, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{19}H_{26}O_3Na$ 325.1774, found 325.1768, Δ 1.9 ppm.

(1*R*,2*R*,3*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-8,11,15-Trimethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}] octadec-14-en-4-one (221)

To a stirred solution of tetracycle **258** (590 mg, 1.95 mmol) in ethyl acetate (49 mL) was added PtO_2 (44 mg, 0.19 mmol) and the resulting suspension stirred under an atmosphere of hydrogen for 1.5 hours. The suspension was filtered over celite, washed with ethyl acetate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford ketone **221** (536 mg, 90%) as a colourless solid.

R_f = 0.41 (petroleum ether-ethyl acetate, 3:1); m.p. 113−115 °C; ν_{max} 2961, 2924, 2874, 1713, 851, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56−5.49 (1H, m, CH-C6), 4.94 (1H, ddd, *J* = 4.4, 3.0, 3.0 Hz, CH-C9), 3.80 (1H, dd, *J* = 13.4, 0.6 Hz, CH_2-C16a), 3.76 (1H, d, *J* = 9.0 Hz, CH-C2), 3.46 (1H, dd, *J* = 13.4, 3.3 Hz, CH_2-C16b), 2.85 (1H, ddd, *J* = 11.6, 11.6, 9.0 Hz, CH-C1), 2.69–2.56 (3H, m, CH_2-C5a, CH_2-C8a, CH-C10), 2.50 (1H, dd, *J* = 18.6, 6.9 Hz, CH_2-C12a), 2.31 (1H, ddd, *J* = 18.6, 11.1, 7.9 Hz, CH_2-C12b), 1.95–1.78 (4H, m, CH_2-C4a, CH_2-C5b, CH_2-C8b, CH_2-C13a), 1.76 (3H, s, CH_3-C19), 1.76–1.66 (3H, m, CH_2-C4b, CH_2-13b, CH-C15), 1.37–1.24 (1H, m, CH-C14), 1.33 (3H, s, CH_3-C18), 1.02 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3 (C-C11), 131.7 (CH-C6), 128.9 (C-C7), 90.8 (CH-C2), 77.1 (C-C3), 76.3 (CH-C9), 67.2 (CH_2-C16), 53.2 (CH-C10), 44.5 (CH-C14), 43.8 (CH-C1), 39.4 (CH_2-C4), 39.3 (CH_2-C12), 37.3 (CH-C15), 37.0 (CH_2-C8), 29.4 (CH_3-C19), 26.3 (CH_2-C13), 26.3 (CH_3-C18), 23.2 (CH_2-C5), 11.3 (CH_3-C17); $[\alpha]_D^{23}$ −49.7 (*c* = 0.320, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{19}H_{28}O_3Na$ 327.1931, found 327.1921, Δ 2.9 ppm.

(1*R*,2*R*,3*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-8,11,15-Trimethyl-5-methylidene-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (260)



221 **261** **260**

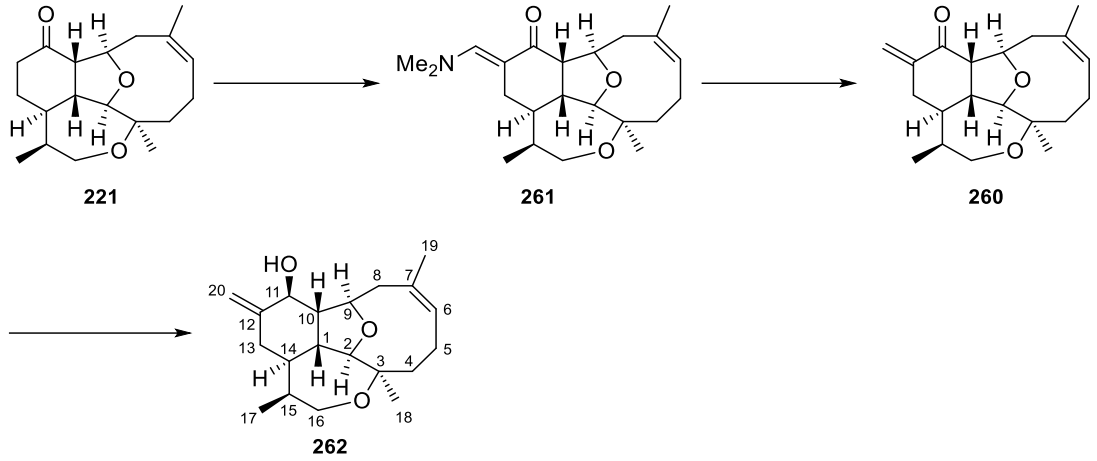
To a solution of ketone **221** (64 mg, 0.20 mmol) in anhydrous DMF (2.1 mL) was added *tert*-butoxy bis(dimethylamino)methane (0.14 mL, 0.68 mmol) in one portion. The resulting solution was stirred at 100 °C in a sealed tube for 2 hours. The reaction mixture was cooled down to room temperature and diluted with ethyl acetate (15 mL) and water (5 mL). The organic phase was separated and washed with water (3 × 5 mL), 10 mol% aqueous solution of lithium chloride (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 2:1 → 1:5) to afford enaminone **261** as a pale yellow solid, which was used in the next step without further purification.

To a stirred solution of enaminone **261** in anhydrous dichloromethane (2.6 mL) at −78 °C was added DIBAL-H (0.30 mL of a 1.0 M solution in dichloromethane, 0.30 mmol) dropwise and stirred for 20 minutes. The resulting solution was warmed to room temperature and allowed to stir for a further 1 hour. A solution of iodomethane (0.13 mL, 2.1 mmol) in anhydrous dichloromethane (4.2 mL) was added and the resulting solution stirred for 1 hour. The reaction mixture was cooled to 0 °C before a saturated aqueous solution of potassium sodium tartrate (8 mL) and diethyl ether (10 mL) was added. The resulting solution was warmed to room temperature and stirred vigorously for 1 hour (two clear phases were obtained). The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford enone **260** (34.5 mg, 52%) as a colourless solid.

R_f = 0.60 (petroleum ether-ethyl acetate, 3:1); m.p. 118−120 °C; ν_{max} 2963, 2924, 2874, 2851, 1699, 1624, 939, 923, 850, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (1H, dd, *J* = 1.1, 1.1 Hz, CH_2-C20a), 5.57−5.50 (1H, m, CH-C6), 5.23 (1H, br s, CH_2-C20b), 5.01−4.96 (1H, m, CH-C9), 3.81 (1H, br d, *J* = 9.0 Hz, CH-C2), 3.81 (1H, dd, *J* = 13.4, 1.5 Hz,

CH_2-C16a), 3.46 (1H, dd, *J* = 13.4, 3.2 Hz, CH_2-C16b), 2.84 (1H, ddd, *J* = 11.9, 11.5, 9.0 Hz, CH-C1), 2.75−2.52 (4H, m, CH_2-C5a, CH_2-C8a, CH-C10, CH_2-C13a), 2.40 (1H, dd, *J* = 14.9, 2.2 Hz, CH_2-C13b), 1.91−1.76 (3H, m, CH_2-C4a, CH_2-C5b, CH-C15), 1.91 (1H, dd, *J* = 14.6, 4.4 Hz, CH_2-C8b), 1.75 (3H, s, CH_3-C19), 1.73−1.65 (1H, m, CH_2-C4b), 1.52 (1H, dddd, *J* = 13.5, 11.5, 4.7, 2.2 Hz, CH-C14), 1.34 (3H, s, CH_3-C18), 1.04 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (C-C11), 143.9 (C-C12), 131.8 (CH-C6), 129.0 (C-C7), 120.8 (CH_2-C20), 91.1 (CH-C2), 78.4 (CH-C9), 76.2 (C-C3), 67.1 (CH_2-C16), 52.4 (CH-C10), 43.7 (CH-C14), 43.3 (CH-C1), 39.4 (CH_2-C4), 37.2 (CH_2-C8), 37.0 (CH-C15), 34.8 (CH_2-C13), 29.6 (CH_3-C19), 26.0 (CH_3-C18), 23.2 (CH_2-C5), 11.3 (CH_3-C17); $[\alpha]_D^{25}$ +1.99 (*c* = 0.795, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{20}H_{28}O_3Na$ 339.1931, found 339.1931, Δ 0.0 ppm.

(1*R*,2*R*,3*R*,4*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-8,11,15-Trimethyl-5-methylidene-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-ol (262)



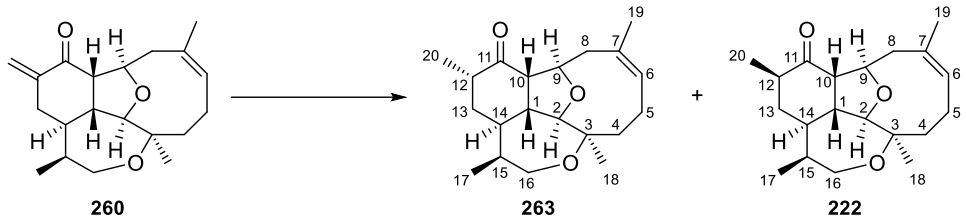
To a solution of ketone **221** (12.3 mg, 40.0 μmol) in anhydrous DMF (0.4 mL) was added *tert*-butoxy bis(dimethylamino)methane (27 μL, 0.13 mmol) in one portion. The resulting solution was stirred at 100 °C in a sealed tube for 2 hours. The reaction mixture was cooled down to room temperature and diluted with ethyl acetate (5 mL) and water (2 mL). The organic phase was separated and washed with water (3 × 2 mL), 10 mol% aqueous solution of lithium chloride (3 mL), brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 2:1 → 1:2) to afford enaminone **261** as a pale yellow solid, which was used in the next step without further purification.

To a stirred solution of enaminone **261** in anhydrous dichloromethane (0.5 mL) at −78 °C was added DIBAL-H (0.05 mL of a 1.0 M solution in dichloromethane, 0.05 mmol) dropwise and stirred for 20 minutes. The resulting solution was warmed to room temperature and allowed to stir for a further 1 hour. A solution of iodomethane (30 μL, 0.48 mmol) in anhydrous dichloromethane (2.4 mL) was added and the resulting solution stirred for 1 hour. The reaction mixture was cooled to 0 °C before a saturated aqueous solution of potassium sodium tartrate (2 mL) and diethyl ether (3 mL) was added. The resulting solution was warmed to room temperature and stirred vigorously for 1 hour (two clear phases were obtained). The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude enone **260**, which was used in the next step without further purification.

To a stirred solution of enone **260** in methanol (0.8 mL) at room temperature was added cerium (III) chloride heptahydrate (30 mg, 81 μmol). The resulting mixture was stirred for 15 minutes before being cooled down to −78 °C. To this sodium borohydride (3 mg, 0.08 mmol) was added in one portion and the resulting solution was stirred for 2.5 hours. The reaction mixture was warmed to room temperature and allowed to stir for a further 1.5 hours. The reaction was quenched by the addition of a 50% aqueous solution of ammonium chloride (1 mL) and diluted with ethyl acetate (3 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 → 4:1) to afford allylic alcohol **262** (6.3 mg, 49%) as a colourless solid.

R_f = 0.43 (petroleum ether-ethyl acetate, 2:1); m.p. 134−136 °C; ν_{max} 3402, 2961, 2928, 2878, 2857, 1647, 905, 899, 729 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$) δ 5.53−5.46 (1H, dd, *J* = 10.2, 6.6 Hz, CH-C6), 5.19 (1H, d, *J* = 2.1 Hz, CH_2-C20a), 4.98 (1H, d, *J* = 2.1 Hz, CH_2-C20b), 4.52 (1H, ddd, *J* = 5.0, 2.8, 2.5 Hz, CH-C9), 4.34−4.24 (1H, m, CH-C11), 3.96 (1H, d, *J* = 8.9 Hz, CH-C2), 3.82 (1H, d, *J* = 13.2 Hz, CH_2-C16a), 3.46 (1H, dd, *J* = 13.2, 3.2 Hz, CH_2-C16b), 2.67–2.57 (2H, m, CH_2-C5a, CH_2-C8a), 2.50 (1H, ddd, *J* = 10.8, 8.9, 8.9 Hz, CH-C1), 2.38–2.31 (2H, m, CH_2-C13), 1.94 (1H, dd, *J* = 14.4, 5.0 Hz, CH_2-C8b), 1.91–1.79 (3H, m, CH_2-C4a, CH_2-C5b, CH-C10), 1.78 (3H, s, CH_3-C19), 1.76–1.61 (3H, m, CH_2-C4b, CH-C14, CH-C15), 1.56 (1H, br s, HO-C11), 1.37 (3H, s, CH_3-C18), 0.94 (3H, d, *J* = 7.0 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C-C12), 131.0 (CH-C6), 129.2 (C-C7), 107.9 (CH_2-C20), 91.4 (CH-C2), 82.9 (CH-C9), 76.2 (C-C3), 71.1 (CH-C11), 67.4 (CH_2-C16), 48.6 (CH-C10), 42.0 (CH-C1), 39.5 (CH-C14), 39.0 (CH_2-C4), 38.1 (CH_2-C8), 36.6 (CH-C15), 34.1 (CH_2-C13), 29.3 (CH_3-C19), 26.0 (CH_3-C18), 23.1 (CH_2-C5), 10.8 (CH_3-C17); $[\alpha]_D^{26}$ +59.5 (*c* = 0.305, $CHCl_3$); HRMS (EI+) $[M]^+$ calcd. for $C_{20}H_{30}O_3$ 318.2195, found 318.2208, Δ 4.1 ppm.

(1*R*,2*R*,3*S*,5*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (263) and (1*R*,2*R*,3*S*,5*R*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (222)

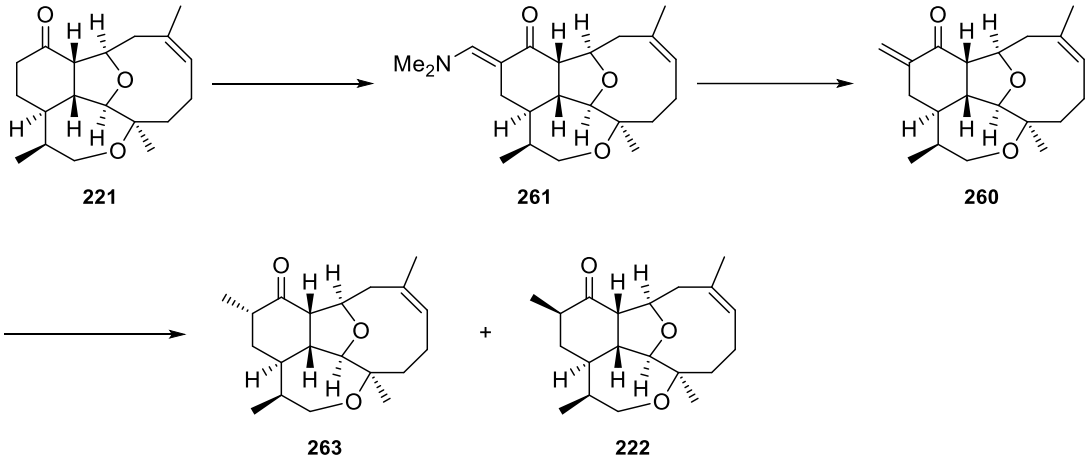


To a stirred solution of enone **260** (12 mg, 38 μmol) in anhydrous THF (0.8 mL) at −78 °C was added L-Selectride (57 μL of a 1.0 M solution in THF, 57 μmol) dropwise. The resulting solution was stirred for 1 hour before being warmed to 0 °C for 30 minutes. The reaction was quenched by the addition of water (0.5 mL) and warmed to room temperature before being diluted with ethyl acetate (2 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 1 mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford diastereoisomeric ketones **263** (3.6 mg, 30%) and **222** (5.5 mg, 46%) as colourless solids.

263: R_f = 0.63 (petroleum ether-ethyl acetate, 4:1); m.p. 109−111 °C; ν_{max} 2963, 2924, 2874, 1713, 922, 856, 806, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55−5.48 (1H, m, CH-C6), 4.98 (1H, ddd, *J* = 4.4, 2.9, 2.9 Hz, CH-C9), 3.79 (1H, d, *J* = 13.3 Hz, CH_2-C16a), 3.71 (1H, d, *J* = 9.1 Hz, CH-C2), 3.44 (1H, dd, *J* = 13.3, 3.3 Hz, CH_2-C16b), 2.87 (1H, ddd, *J* = 11.7, 9.2, 9.1 Hz, CH-C1), 2.70 (1H, dd, *J* = 11.7, 2.9 Hz, CH-C10), 2.69–2.56 (2H, m, CH_2-C5a, CH_2-C8a), 2.50 (1H, dq, *J* = 8.4, 7.1 Hz, CH-C12), 2.26 (1H, ddd, *J* = 13.3, 13.2, 8.4 Hz, CH_2-C13a), 1.92–1.78 (3H, m, CH_2-C4a, CH_2-C5b, CH_2-C8b), 1.77 (3H, s, CH_3-C19), 1.76–1.64 (2H, m, CH_2-C4b, CH-C15), 1.40 (1H, dd, *J* = 13.3, 1.9 Hz, CH_2-C13b), 1.33 (3H, s, CH_3-C18), 1.29–1.19 (1H, m, CH-C14), 1.12 (3H, d, *J* = 7.1 Hz, CH_3-C20), 1.00 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.2 (C-C11), 131.6 (CH-C6), 128.9 (C-C7), 90.3 (CH-C2), 76.6 (CH-C9), 76.2 (C-C3), 67.2 (CH_2-C16), 52.9 (CH-C10), 45.7 (CH-C1), 41.6 (CH-C14), 41.4 (CH-C12), 39.5 (CH_2-C4), 37.4 (CH-C15), 37.0 (CH_2-C8), 35.2 (CH_2-C13), 29.4 (CH_3-C19), 26.3 (CH_3-C18), 23.2 (CH_2-C5), 16.0 (CH_3-C20), 11.3 (CH_3-C17); $[\alpha]_D^{24}$ −12.1 (*c* = 0.162, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{20}H_{30}O_3Na$ 341.2087, found 341.2078, Δ 2.8 ppm.

222: R_f = 0.51 (petroleum ether-ethyl acetate, 4:1); m.p. 139−141 °C; ν_{max} 2963, 2928, 2874, 1709, 914, 845, 806, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56−5.49 (1H, m, CH-C6), 4.92 (1H, ddd, *J* = 4.6, 3.0, 3.0 Hz, CH-C9), 3.78 (1H, dd, *J* = 13.3, 1.2 Hz, CH_2-C16a), 3.74 (1H, br d, *J* = 9.1 Hz, CH-C2), 3.45 (1H, dd, *J* = 13.3, 3.3 Hz, CH_2-C16b), 2.85 (1H, ddd, *J* = 12.2, 11.0, 9.1 Hz, CH-C1), 2.70 (1H, dd, *J* = 12.2, 3.0 Hz, CH-C10), 2.67−2.56 (2H, m, CH_2-C5a, CH_2-C8a), 2.35 (1H, dqd, *J* = 10.8, 7.3, 7.2 Hz, CH-C12), 1.89 (1H, dd, *J* = 14.6, 4.7 Hz, CH_2-C8b), 1.89−1.76 (3H, m, CH_2-C4a, CH_2-C5b, CH_2-C13a), 1.76 (3H, s, CH_3-C19), 1.74−1.67 (2H, m, CH_2-C4b, CH-C15), 1.54 (1H, ddd, *J* = 12.8, 12.8, 10.8 Hz, CH_2-C13b), 1.38−1.29 (1H, m, CH-C14), 1.33 (3H, s, CH_3-C18), 1.16 (3H, d, *J* = 7.3 Hz, CH_3-C20), 1.02 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9 (C-C11), 131.6 (CH-C6), 128.9 (C-C7), 90.8 (CH-C2), 77.0 (CH-C9), 76.4 (C-C3), 67.3 (CH_2-C16), 50.6 (CH-C10), 45.2 (CH-C12), 44.3 (CH-C1), 44.0 (CH-C14), 39.4 (CH_2-C4), 37.2 (CH-C15), 37.0 (CH_2-C8), 35.4 (CH_2-C13), 29.3 (CH_3-C19), 26.2 (CH_3-C18), 23.2 (CH_2-C5), 18.8 (CH_3-C20), 11.3 (CH_3-C17); $[\alpha]_D^{24}$ −61.1 (*c* = 0.195, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{20}H_{30}O_3Na$ 341.2087, found 341.2078, Δ 2.8 ppm.

(1*R*,2*R*,3*S*,5*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (263) and (1*R*,2*R*,3*S*,5*R*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (222)



To a solution of ketone **221** (56.5 mg, 0.186 mmol) in anhydrous DMF (1.9 mL) was added *tert*-butoxy bis(dimethylamino)methane (0.12 mL, 0.58 mmol) in one portion. The resulting solution was stirred at 100 °C in a sealed tube for 2 hours. The reaction mixture was cooled down to room temperature and diluted with ethyl acetate (12 mL) and water (5 mL). The organic phase was separated and washed with water (3 × 3 mL), 10 mol% aqueous solution of lithium chloride (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 1:1 → 1:5) to afford enaminone **261** as a pale yellow solid, which was used in the next step without further purification.

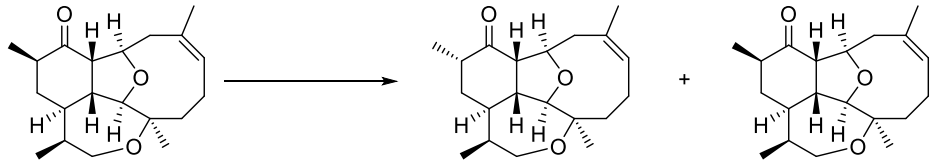
To a stirred solution of enaminone **261** in anhydrous dichloromethane (2.3 mL) at −78 °C was added DIBAL-H (0.22 mL of a 1.0 M solution in dichloromethane, 0.22 mmol) dropwise and stirred for 20 minutes. The resulting solution was warmed to room temperature and allowed to stir for a further 1 hour. A solution of iodomethane (0.12 mL, 1.9 mmol) in anhydrous dichloromethane (3.5 mL) was added and the resulting solution stirred for 1 hour. The reaction mixture was cooled to 0 °C before a saturated aqueous solution of potassium sodium tartrate (5 mL) and diethyl ether (5 mL) was added. The resulting solution was warmed to room temperature and stirred vigorously for 1 hour (two clear phases were obtained). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and

concentrated under reduced pressure to give crude enone **260**, which was used in the next step without further purification.

To a stirred solution of (triphenylphosphine)copper hydride hexamer (0.47 mL of a 0.2 M solution in benzene, 0.094 mmol) in anhydrous and de-gassed toluene (3.3 mL) at −10 °C was added a solution of enone **260** in anhydrous and de-gassed toluene (6 mL) dropwise over 10 minutes. The resulting solution was stirred for 1 hour before being quenched by the addition of water (5 mL). The mixture was room temperature before being diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford diastereoisomeric ketones **263** (15 mg, 25%) and **222** (22 mg, 37%) as colourless solids.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compounds **263** and **222** previously (see p. 137).

(1*R*,2*R*,3*S*,5*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (263) and (1*R*,2*R*,3*S*,5*R*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (222)

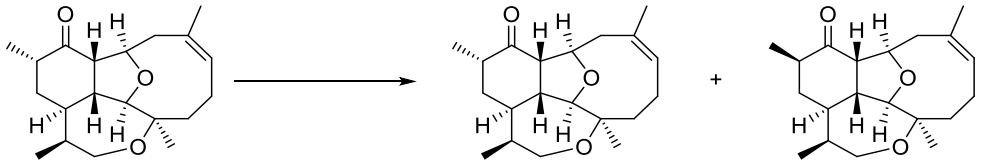


222 263 222

To a stirred solution of ketone **222** (39 mg, 0.12 mmol) in anhydrous methanol (2.5 mL) at room temperature was added potassium carbonate (20 mg, 0.15 mmol) and the resulting solution was stirred for 16 hours. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (5 mL) and ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford diastereoisomeric ketones **263** (15.9 mg, 41%) and **222** (23 mg, 59%) as colourless solids.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compounds **263** and **222** previously (see p. 137).

(1*R*,2*R*,3*S*,5*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (263) and (1*R*,2*R*,3*S*,5*R*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (222)

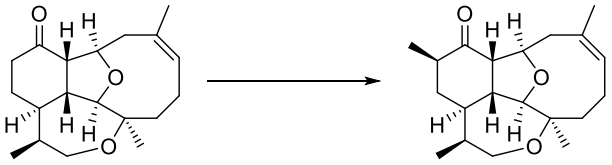


263 263 222

To a stirred solution of ketone **263** (12.6 mg, 39.6 μmol) in anhydrous methanol (0.8 mL) was added potassium carbonate (6.6 mg, 48 μmol) and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (3 mL) and ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford diastereoisomeric ketones **263** (4.5 mg, 36%) and **222** (6.2 mg, 49%) as colourless solids.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compounds **263** and **222** previously (see p. 137).

(1*R*,2*R*,3*S*,5*R*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-one (222)

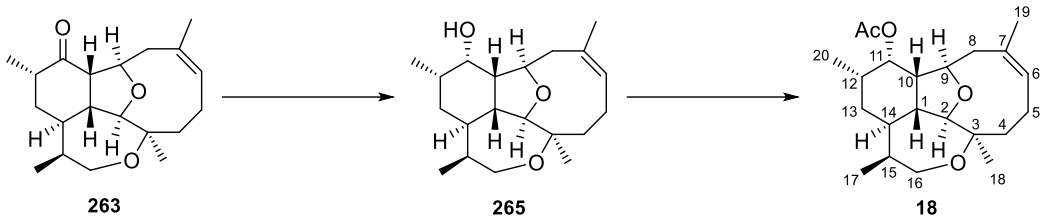


221 **222**

To a stirred solution of ketone **221** (18.6 mg, 61.1 μmol) in anhydrous THF (1.2 mL) at −78 °C was added NaHMDS (0.12 mL of a 1.0 M solution in THF, 0.12 mmol) dropwise over 10 minutes. The resulting solution was stirred for 15 minutes before being warmed to –30 °C for 50 minutes. The reaction mixture afterwards was cooled down to −78 °C before a solution of methyl iodide (0.62 mL of a 0.5 M solution in THF, 0.31 mmol) was added dropwise over 5 minutes. The resulting solution was stirred for 1 hour before being warmed to −30 °C for 30 minutes. The reaction was quenched by the addition of water (2 mL) and diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to afford ketone **222** (1.5 mg, 8%) as a colourless solid.

The NMR (^1H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **222** previously (see p. 137).

11-Acetoxy-4-deoxyasbestinin D (18)[8]



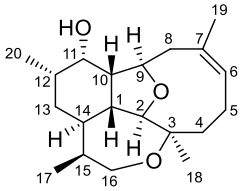
To a stirred solution of ketone **263** (23 mg, 72 μmol) in a mixture of methanol and dichloromethane (1:1, 1.4 mL) at 0 °C was added sodium borohydride (4.9 mg, 0.13 mmol) in one portion and the resulting solution was stirred for 1 hour. The reaction mixture was warmed to room temperature and allowed to stir for a further 30 minutes. The reaction was quenched by the addition of a water (3 mL) before being diluted with ethyl acetate (3 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude alcohol **265**, which was used in the next step without further purification.

To a stirred solution of alcohol **265**, DMAP (8.8 mg, 72 μmol) and distilled triethylamine (20 μL, 0.14 mmol) in anhydrous dichloromethane (1.4 mL) at 0 °C was added distilled acetic anhydride (0.65 mL of a 0.2 M solution in dichloromethane, 0.13 mmol). The resulting solution was warmed to room temperature and stirred for 16 hours. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (3 mL) and diluted with diethyl ether (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, 10:1) to afford 11-acetoxy-4-deoxyasbestinin D (**18**) (23.8 mg, 88%) as a colourless oil.

R_f = 0.67 (petroleum ether-ethyl acetate, 4:1); ν_{max} 2963, 2924, 2878, 1736, 910, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48 (1H, dddd, *J* = 9.8, 6.4, 1.4, 1.4 Hz, CH-C6), 5.31 (1H, dd, *J* = 5.2, 2.8 Hz, CH-C11), 4.10 (1H, ddd, *J* = 5.4, 2.8, 2.8 Hz, CH-C9), 3.88 (1H, dd, *J* = 8.8 Hz, CH-C2), 3.86 (1H, dd, *J* = 13.2, 1.2 Hz, CH_2-C16a), 3.48 (1H, dd, *J* = 13.2, 3.3 Hz, CH_2-C16b), 2.61−2.52 (1H, m, CH_2-C5a), 2.50 (1H, dd, *J* = 14.4, 2.8 Hz, CH_2-C8a), 2.34 (1H, ddd, *J* = 10.8, 10.8, 8.8 Hz, CH-C1), 2.10 (3H, s, CH_3-OAc), 2.08−1.83 (5H, m, CH_2-C5b, CH_2-C8b, CH-C10, CH-C12, CH-C14), 1.77−1.73 (2H, m, CH_2-C4), 1.75 (3H, s,

CH_3-C19), 1.66−1.56 (1H, m, CH-C15), 1.53 (1H, ddd, *J* = 13.5, 13.5, 9.7 Hz, CH_2-C13a), 1.35 (3H, s, CH_3-C18), 1.01 (1H, ddd, *J* = 13.5, 3.2, 1.5 Hz, CH_2-C13b), 0.93 (3H, d, *J* = 7.2 Hz, CH_3-C20), 0.92 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C-OAc), 131.0 (CH-C6), 128.9 (C-C7), 92.4 (CH-C2), 81.2 (CH-C9), 76.6 (C-C3), 73.7 (CH-C11), 68.1 (CH_2-C16), 46.0 (CH-C10), 40.7 (CH-C1), 38.7 (CH_2-C4), 38.2 (CH-C14), 37.7 (CH_2-C8), 37.5 (CH-C15), 31.7 (CH_2-C13), 31.6 (CH-C12), 29.1 (CH_3-C19), 26.2 (CH_3-C18), 23.6 (CH_2-C5), 21.5 (CH_3-OAc), 18.1 (CH_3-C20), 11.1 (CH_3-C17); $[\alpha]_D^{26}$ −13.5 (*c* = 0.445, $CHCl_3$) {Lit.[8] $[\alpha]_D^{29}$ −2.29 (*c* = 1.31, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_4Na$ 385.2349, found 385.2341, Δ 2.2 ppm.

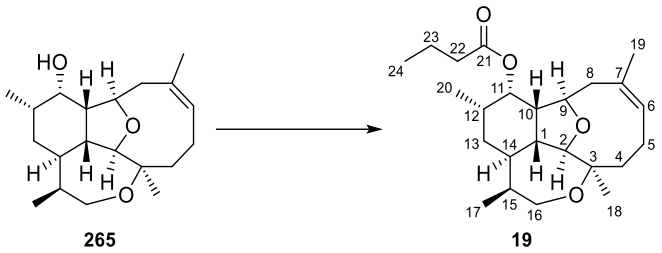
(1*R*,2*R*,3*R*,4*S*,5*S*,7*R*,8*S*,11*R*,14*Z*,17*R*)-5,8,11,15-Tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadec-14-en-4-ol (265)



261

R_f = 0.41 (petroleum ether-ethyl acetate, 2:1); m.p. 126−128 °C; ν_{max} 3292, 2920, 2890, 1721, 986, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, dddd, *J* = 9.9, 6.2, 1.5, 1.5 Hz, CH-C6), 4.42 (1H, ddd, *J* = 5.0, 2.8, 2.8 Hz, CH-C9), 3.94 (1H, br d, *J* = 8.9 Hz, CH-C2), 3.86 (1H, br d, *J* = 13.2 Hz, CH_2-C16a), 3.86−3.82 (1H, m, CH-C11), 3.45 (1H, dd, *J* = 13.2, 3.3 Hz, CH_2-C16b), 2.69−2.57 (2H, m, CH_2-C5a, CH_2-C8a), 2.28 (1H, ddd, *J* = 10.9, 10.7, 8.9 Hz, CH-C1), 2.07 (1H, dddd, *J* = 13.6, 10.9, 4.4, 3.5 Hz, CH-C14), 1.97 (1H, dd, *J* = 14.4, 5.0 Hz, CH_2-C8b), 1.92−1.79 (2H, m, CH_2-C5b, CH-C12), 1.89 (1H, ddd, *J* = 10.7, 2.8, 2.4 Hz, CH-C10), 1.78−1.72 (2H, m, CH_2-C4), 1.77 (3H, s, CH_3-C19), 1.64 (1H, br d, *J* = 3.0 Hz, HO-C11), 1.60−1.54 (1H, m, CH-C15), 1.52 (1H, ddd, *J* = 13.6, 13.5, 10.0 Hz, CH_2-C13a), 1.35 (3H, s, CH_3-C18), 1.08 (3H, d, *J* = 7.3 Hz, CH_3-C20), 1.01 (1H, ddd, *J* = 13.5, 3.5, 1.8 Hz, CH_2-C13b), 0.90 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.0 (CH-C6), 128.9 (C-C7), 92.7 (CH-C2), 81.9 (CH-C9), 76.4 (C-C3), 72.7 (CH-C11), 68.1 (CH_2-C16), 47.2 (CH-C10), 40.7 (CH-C1), 38.8 (CH_2-C4), 37.9 (CH-C14), 37.8 (CH_2-C8), 37.7 (CH-C15), 32.3 (CH-C12), 31.8 (CH_2-C13), 29.3 (CH_3-C19), 26.1 (CH_3-C18), 23.6 (CH_2-C5), 18.5 (CH_3-C20), 11.0 (CH_3-C17); $[\alpha]_D^{17}$ +6.7 (*c* = 0.86, $CHCl_3$); HRMS (EI+) $[M]^+$ calcd. for $C_{20}H_{32}O_3Na$ 343.2244, found 343.2249, Δ 1.6 ppm.

4-Deoxyasbestinin C (19)[8]

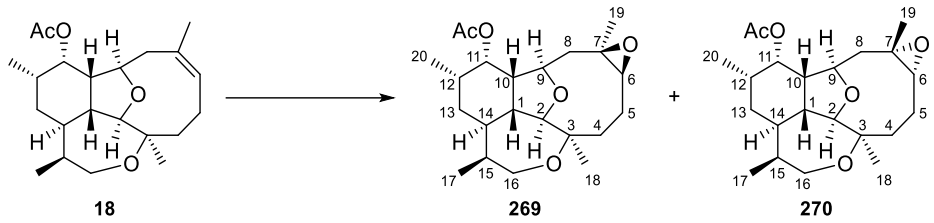


To a stirred solution of alcohol **265** (18 mg, 56 µmol), DMAP (8.2 mg, 67 µmol) and distilled *N*,*N*-diisopropylethylamine (0.23 mL, 0.13 mmol) in anhydrous dichloromethane (1.2 mL) at 0 °C was added butyric anhydride (0.34 mL of a 0.5 M solution in dichloromethane, 0.17 mmol). The resulting solution was warmed to room temperature and stirred for 16 hours. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL) and diluted with diethyl ether (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, 10:1) to afford 4-deoxyasbestinin C (**19**) (16.5 mg, 75%) as a colourless oil.

R_f = 0.81 (petroleum ether-ethyl acetate, 3:1); ν_{max} 2963, 2932, 2874, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ5.51−5.44 (1H, m, CH-C6), 5.33 (1H, dd, *J* = 5.1, 2.8 Hz, CH-C11), 4.08 (1H, ddd, *J* = 5.0, 2.8, 2.8 Hz, CH-C9), 3.88 (1H, d, *J* = 8.9 Hz, CH-C2), 3.86 (1H, d, *J* = 13.3 Hz, CH_2-C16a), 3.48 (1H, dd, *J* = 13.3, 3.3 Hz, CH_2-C16b), 2.63−2.50 (2H, m, CH_2-C5a, CH_2-C8a), 2.41–2.26 (3H, m, CH-C1, CH_2-C22), 2.10–2.01 (1H, m, CH-C12), 1.98 (1H, ddd, *J* = 10.7, 2.8, 2.8 Hz, CH-C10), 1.95 (1H, dd, *J* = 14.5, 5.0 Hz, CH_2-C8b), 1.93−1.84 (2H, m, CH_2-C5b, CH-C14), 1.77–1.48 (5H, m, CH_2-C4, CH-C15, CH_2-C23), 1.76 (3H, s, CH_3-C19), 1.52 (1H, ddd, *J* = 13.5, 13.5, 9.7 Hz, CH_2-C13a), 1.35 (3H, s, CH_3-C18), 1.01 (1H, ddd, *J* = 13.5, 3.2, 1.5 Hz, CH_2-C13b), 0.98 (3H, t, *J* = 7.4 Hz, CH_3-C24), 0.92 (3H, d, *J* = 7.3 Hz, CH_3-C20), 0.92 (3H, d, *J* = 7.0 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.0 (C-C21), 131.1 (CH-C6), 128.9 (C-C7), 92.3 (CH-C2), 81.3 (CH-C9), 76.5 (C-C3), 73.4 (CH-C11), 68.1 (CH_2-C16), 45.9 (CH-C10), 40.8 (CH-C1), 38.9 (CH_2-C4), 38.3 (CH-C14), 37.6 (CH_2-C8), 37.6 (CH-C15), 36.9 (CH_2-C22), 31.8 (CH_2-C13), 31.6 (CH-C12), 29.2 (CH_3-C19), 26.3 (CH_3-C18), 23.4 (CH_2-C5), 18.7 (CH_2-C23), 18.2 (CH_3-C20), 13.9 (CH_3-C24), 11.1 (CH_3-C17); $[\alpha]_D^{20}$ 16.8 (*c* = 0.375,

$CHCl_3$) {Lit.[8] $[\alpha]_D^{29}$ −1.2 (c = 0.84, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{24}H_{38}O_4Na$ 413.2662, found 413.2646, Δ 3.8 ppm.

(1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*S*,16*R*,18*R*)-5,8,11,16-Tetramethyl-10,15,19-trioxapentacyclo[9.8.0.0^{2,7}.0^{3,18}.0^{14,16}]nonadecan-4-yl acetate (269) and (1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*R*,16*S*,18*R*)-5,8,11,16-Tetramethyl-10,15,19-trioxapentacyclo[9.8.0.0^{2,7}.0^{3,18}.0^{14,16}]nonadecan-4-yl acetate (270)



*Epoxidation of 11-Acetoxy-4-deoxyasbestinin D (**18**) with m-CPBA*

To a stirred solution of 11-acetoxy-4-deoxyasbestinin D (**18**) (22 mg, 61 µmol) in anhydrous dichloromethane (1.2 mL) at 0 °C was added *m*-CPBA (0.24 mL of a 0.5 M solution in dichloromethane, 0.12 mmol). The resulting solution was stirred for 2.5 hours. The reaction was quenched by the addition of a saturated aqueous solution of sodium thiosulfate (3 mL) before being warmed to room temperature and diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 → 1:1) to afford diastereoisomeric epoxides **269** (13.6 mg, 59%) and **270** (5.3 mg, 23%) as colourless solids.

*Epoxidation of 11-Acetoxy-4-deoxyasbestinin D (**18**) using Shi's Asymmetric Protocol (Unnatural Enatiomer)*

To a stirred solution of 11-acetoxy-4-deoxyasbestinin D (**18**) (16 mg, 44 µmol), unnatural Shi ketone (3.8 mg, 15 µmol) in a mixture of acetonitrile and dimethoxyethane (1:2, 0.9 mL) was added buffer (0.48 mL of a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), 0.024 mmol) followed by tetrabutylammonium hydrogen sulfate (5.0 µL of a 0.4 M solution in water, 2.0 µmol). The resulting solution was cooled to 0 °C before Oxone™ (1.4 mL of a 0.07 M solution in 4×10^{-4} M aqueous Na_2(EDTA), 0.098 mmol) and potassium carbonate (0.70 mL of a 0.4 M solution in water, 0.28 mmol) were added simultaneously. The reaction mixture was stirred for 1 hour before being diluted with water (5 mL) and ethyl acetate (10 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$)

and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 10:1 → 2:1) to afford diastereoisomeric epoxides **269** (12.5 mg, 75%) and **270** (1.0 mg, 6%) as colourless solids.

*Epoxidation of 11-Acetoxy-4-deoxyasbestinin D (**18**) using Shi's Asymmetric Protocol (Natural Enatiomer)*

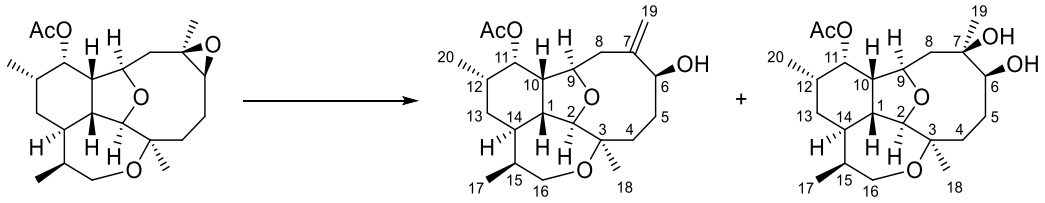
To a stirred solution of 11-acetoxy-4-deoxyasbestinin D (**18**) (27.5 mg, 75.9 μmol), natural Shi ketone (5.9 mg, 0.023 mmol) in a mixture of acetonitrile and dimethoxyethane (1:2, 1.2 mL) was added buffer (1.2 mL of a 0.05 M solution of $Na_2B_4O_7•10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), 0.060 mmol) followed by tetrabutylammonium hydrogen sulfate (7.5 μL of a 0.4 M solution in water, 3.0 μmol). The resulting solution was cooled to 0 °C before Oxone™ (1.9 mL of a 0.4 M solution in 4×10^{-4} M aqueous Na_2(EDTA), 0.76 mmol) and potassium carbonate (1.1 mL of a 0.4 M solution in water, 0.44 mmol) were added simultaneously. The reaction mixture was stirred for 1 hour before being diluted with water (5 mL) and ethyl acetate (10 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 10:1 → 2:1) to afford diastereoisomeric epoxides **269** (3.6 mg, 13%) and **270** (20.4 mg, 71%) as colourless solids.

269: R_f = 0.10 (petroleum ether-ethyl acetate, 2:1); m.p. 156−158 °C; ν_{max} 2959, 2928, 2878, 1736, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, dd, *J* = 6.3, 1.8 Hz, CH-C11), 4.26 (1H, dd, *J* = 11.7, 4.8 Hz, CH-C9), 3.88 (1H, d, *J* = 10.1 Hz, CH-C2), 3.83 (1H, d, *J* = 13.1 Hz, CH_2-C16a), 3.60 (1H, dd, *J* = 13.1, 2.2 Hz, CH_2-C16b), 2.80 (1H, ddd, *J* = 10.1, 9.6, 9.4 Hz, CH-C1), 2.74 (1H, dd, *J* = 9.6, 3.1 Hz, CH-C6), 2.20−2.11 (1H, m, CH-C12), 2.08 (3H, s, CH_3-OAc), 2.03−1.96 (1H, m, CH_2-C5a), 2.02 (1H, dd, *J* = 13.6, 4.8 Hz, CH_2-C8a), 1.91−1.74 (3H, m, CH_2-C4a, CH-C10, CH-C14), 1.71−1.48 (5H, m, CH_2-C4b, CH_2-C5b, CH_2-C8b, CH_2-C13a, CH-C15), 1.34 (3H, s, CH_3-C18), 1.34 (3H, s, CH_3-C19), 1.05 (1H, dd, *J* = 13.5, 2.2 Hz, CH_2-C13b), 0.98 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.92 (3H, d, *J* = 7.2 Hz, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C-OAc), 94.4 (CH-C2), 79.3 (C-C3), 78.5 (CH-C9), 72.8 (CH-C11), 70.3 (CH_2-C16), 66.4 (CH-C6), 59.5 (C-C7), 50.0 (CH-C10), 43.4 (CH_2-C8), 39.6 (CH-C1), 37.6 (CH-C14), 36.4 (CH-C15), 34.3 (CH_2-C4), 32.0 (CH_2-C13), 31.3 (CH-C12), 27.8 (CH_3-C18 or CH_3-C19), 22.5 (CH_3-C18 or CH_3-C19),

21.8 (CH_2-C5), 21.5 (CH_3-OAc), 16.7 (CH_3-C20), 11.2 (CH_3-C17); $[\alpha]_D^{19}$ −37.7 (*c* = 0.247, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_5Na$ 401.2298, found 401.2304, Δ 1.4 ppm.

270: R_f = 0.18 (petroleum ether-ethyl acetate, 2:1); m.p. 167−169 °C ;ν_{max} 2963, 2928, 2874, 1736, 991, 930, 872, 733, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, dd, *J* = 5.1, 3.2 Hz, CH-C11), 4.06 (1H, ddd, *J* = 3.2, 3.2, 3.2 Hz, CH-C9), 3.88 (1H, br d, *J* = 8.8 Hz, CH-C2), 3.85 (1H, br d, *J* = 13.2 Hz, CH_2-C16a), 3.50 (1H, dd, *J* = 13.2, 3.5 Hz, CH_2-C16b), 2.70 (1H, dd, *J* = 10.9, 3.8 Hz, CH-C6), 2.37 (1H, ddd, *J* = 10.8, 3.2, 3.2 Hz, CH-C10), 2.31 (1H, ddd, *J* = 10.8, 10.8, 8.8 Hz, CH-C1), 2.12 (3H, s, CH_3-OAc), 2.07−1.83 (7H, m, CH_2-C4a, CH_2-C5, CH_2-C8, CH-C12, CH-C14), 1.72−1.61 (2H, m, CH_2-C4b, CH-C15), 1.55 (1H, ddd, *J* = 13.5, 13.5, 9.7 Hz, CH_2-C13a), 1.43 (3H, s, CH_3-C19), 1.35 (3H, s, CH_3-C18), 1.07 (1H, ddd, *J* = 13.5, 3.2, 1.6 Hz, CH_2-C13b), 0.95 (3H, d, *J* = 7.6 Hz, CH_3-C20), 0.93 (3H, d, *J* = 7.4 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C-OAc), 92.1 (CH-C2), 80.7 (CH-C9), 76.0 (C-C3), 73.7 (CH-C11), 67.8 (CH_2-C16), 67.0 (CH-C6), 59.2 (C-C7), 44.6 (CH-C10), 40.8 (CH_2-C8), 39.9 (CH-C1), 38.1 (CH-C14), 37.5 (CH-C15), 33.7 (CH_2-C4), 31.8 (CH_2-C13), 31.6 (CH-C12), 28.7 (CH_3-C19), 25.5 (CH_3-C18), 23.9 (CH_2-C5), 21.4 (CH_3-OAc), 18.2 (CH_3-C20), 11.0 (CH_3-C17); $[\alpha]_D^{17}$ +6.74 (*c* = 0.860, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_5Na$ 401.2298, found 401.2286, Δ 3.1 ppm.

Asbestinin 20 (14)[10] and (1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*S*,15*R*,17*R*)-14,15-Dihydroxy-5,8,11,15-tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan-4-yl acetate (275)



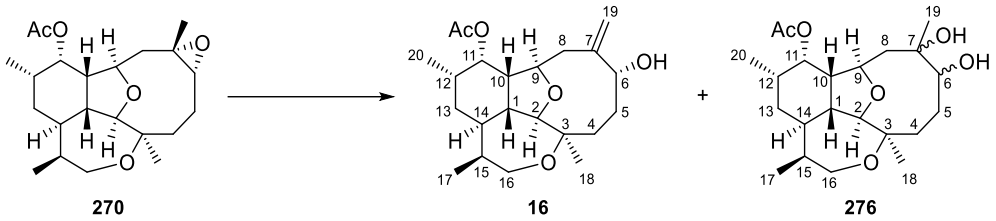
269 **14** **275**

To a stirred solution of epoxide **269** (20 mg, 53 µmol) in a mixture of THF and water (1:1, 1.1 mL) at room temperature was added potassium bisulfate (289 mg, 2.12 mmol) followed by scandium triflate (54 mg, 0.11 mmol). The resulting solution was stirred for 2 hours before being quenched by the addition of saturated aqueous solution of sodium carbonate (3 mL) and diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 5:1 → 1:5) to afford asbestinin 20 (**14**) (2 mg, 10%) and *syn*-diol **275** (16 mg, 80%) as colourless solids.

14: R_f = 0.40 (petroleum ether-ethyl acetate, 1:2); m.p. 185−187 °C; ν_{max} 3433, 2959, 2924, 2874, 1736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37−5.33 (1H, m, CH_2-C19a), 5.36 (1H, dd, *J* = 5.3, 2.2 Hz, CH-C11), 5.05 (1H, br s, CH_2-C19b), 4.27 (1H, br s, CH-C6), 4.17 (1H, ddd, *J* = 4.5, 4.5, 1.8 Hz, CH-C9), 3.85 (1H, d, *J* = 8.7 Hz, CH-C2), 3.76 (1H, d, *J* = 13.0 Hz, CH_2-C16a), 3.45 (1H, dd, *J* = 13.0, 2.9 Hz, CH_2-C16b), 2.51−2.42 (1H, m, CH-C1), 2.32−2.16 (4H, m, CH_2-C5, CH_2-C8a, CH-C10), 2.16−2.07 (1H, m, CH-C12), 2.09 (3H, s, CH_3-OAc), 1.91−1.78 (3H, m, CH_2-C4a, CH_2-C8b, CH-C14), 1.61−1.55 (1H, m, CH-C15), 1.50 (1H, ddd, *J* = 13.5, 13.5, 9.4 Hz, CH_2-C13a), 1.48 (1H, d, *J* = 3.1 Hz, HO-C6), 1.40−1.30 (1H, m, CH_2-C4b), 1.30 (3H, s, CH_3-C18), 1.02 (1H, dd, *J* = 13.5, 2.4 Hz, CH_2-C13b), 0.93 (3H, d, *J* = 7.2 Hz, CH_3-C20), 0.90 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C-OAc), 148.5 (C-C7), 115.0 (CH_2-C19), 94.3 (CH-C2), 83.1 (CH-C9), 76.8 (C-C3), 76.2 (CH-C6), 74.0 (CH-C11), 67.7 (CH_2-C16), 46.3 (CH-C10), 39.3 (CH_2-C8), 39.0 (CH-C1), 38.2 (CH-C14), 36.9 (CH-C15), 31.7 (CH_2-C13), 31.5 (CH-C12), 29.2 (CH_2-C4), 27.4 (CH_2-C5), 23.6 (CH_3-C18), 21.5 (CH_3-OAc), 17.7 (CH_3-C20), 11.1 (CH_3-C17); $[\alpha]_D^{16}$ −14.4 (*c* = 0.250, $CHCl_3$) {Lit.[10] $[\alpha]_D^{25}$ −16.7 (*c* = 5.20, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_5Na$ 401.2298, found 401.2283, Δ 3.8 ppm.

275: R_f = 0.13 (petroleum ether-ethyl acetate, 1:2); m.p. 209−211 °C; ν_{max} 3431, 2963, 2922, 2876, 1734, 991, 974, 930, 918, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.39 (1H, dd, *J* = 5.7, 2.0 Hz, CH-C11), 4.22 (1H, dd, *J* = 12.4, 3.9 Hz, CH-C9), 3.83−3.77 (2H, m, CH-C2, CH_2-C16a), 3.47 (1H, dd, *J* = 13.1, 2.7 Hz, CH_2-C16b), 2.56 (1H, ddd, *J* = 9.4, 9.4, 9.4 Hz, CH-C1), 2.22−1.99 (4H, m, CH_2-C4a, CH-C6, CH_2-C8a, CH-C12), 2.08 (3H, s, CH_3-OAc), 1.96−1.74 (5H, m, CH_2-C4b, CH_2-C5, CH-C10, CH-C14), 1.65−1.57 (1H, m, HO-C7, CH-C15), 1.52−1.43 (2H, m, CH_2-C8b, CH_2-C13a), 1.37 (1H, br s, HO-C6), 1.30 (3H, s, CH_3-C18), 1.30 (3H, s, CH_3-C19), 1.03 (1H, dd, *J* = 13.4, 2.7 Hz, CH_2-C13b), 0.92 (3H, d, *J* = 7.2 Hz, CH_3-C17), 0.92 (3H, d, *J* = 7.2 Hz, CH_3-C20); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C-OAc), 93.4 (CH-C2), 79.3 (CH-C9), 77.5 (C-C3), 75.5 (C-C7), 73.5 (CH-C11), 68.0 (CH_2-C16), 48.5 (CH-C10), 38.3(CH-C14), 37.6 (CH-C1), 37.6 (CH-C15), 31.5 (CH-C12), 31.4 (CH_2-C13), 22.4 (CH_3-C18), 21.6 (CH_3-OAc), 17.4 (CH_3-C20), 11.1 (CH_3-C17). Peaks for CH_2-C4, CH_2-C5, CH-C6, CH_2-C8 and CH_3-C19 were not observed; $[\alpha]_D^{20}$ −8.89 (*c* = 0.450, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{36}O_6Na$ 419.2404, found 419.2387, Δ 4.0 ppm.

6-*epi*-Asbestinin 20 (16)[11] and Diols (276)

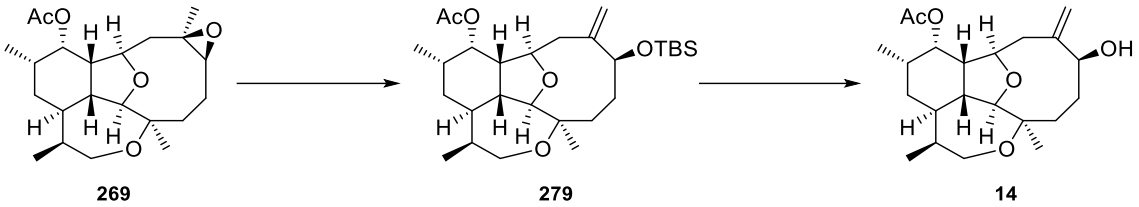


To a stirred solution of epoxide **270** (13 mg, 0.034 mmol) in THF (0.65 mL) and water (30 μL) at room temperature was added potassium bisulfate (185 mg, 1.36 mmol) followed by scandium triflate (33 mg, 0.068 mmol). The resulting solution was stirred for 1.5 hours before being quenched by the addition of saturated aqueous solution of sodium carbonate (0.5 mL) and diluted with ethyl acetate (3 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:1 → 1:3) to afford 6-*epi*-asbestinin 20 (**16**) (3.2 mg, 25%) as a colourless solid and a diastereomeric mixture (ratio and relative stereochemistry not determined) of diols **276** (7.8 mg, 60%) as a colourless oil.

16: R_f = 0.21 (petroleum ether-ethyl acetate, 1:2); m.p. 212−214 °C; ν_{max} 3429, 2957, 2926, 2876, 1736, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, dd, *J* = 5.4, 2.5 Hz, CH-C11), 5.22 (1H, br s, CH_2-C19a), 5.08 (1H, br s, CH_2-C19b), 4.14 (1H, ddd, *J* = 4.7, 2.5, 2.5 Hz, CH-C9), 4.03 (1H, dd, *J* = 11.7, 4.0 Hz, CH-C6), 3.85 (1H, d, *J* = 8.5 Hz, CH-C2), 3.76 (1H, d, *J* = 13.0 Hz, CH_2-C16a), 3.42 (1H, dd, *J* = 13.0, 3.2 Hz, CH_2-C16b), 2.74 (1H, dd, *J* = 14.0, 4.7 Hz, CH_2-C8a), 2.30 (1H, ddd, *J* = 10.5, 10.5, 8.5 Hz, CH-C1), 2.19 (1H, ddd, *J* = 10.5, 2.5, 2.5 Hz, CH-C10), 2.13−2.02 (2H, m, CH_2-C5a, CH-C12), 2.11 (3H, s, CH_3-OAc), 1.97 (1H, dd, *J* = 14.0, 2.5 Hz, CH_2-C8b), 1.87 (1H, dddd, *J* = 13.5, 10.5, 4.5, 3.1 Hz, CH-C14), 1.76−1.65 (1H, m, CH_2-C5b), 1.63−1.35 (5H, m, CH_2-C4, HO-C6, CH_2-C13a, CH-C15), 1.32 (3H, s, CH_3-C18), 1.01 (1H, dd, *J* = 13.5, 3.1 Hz, CH_2-C13b), 0.93 (3H, d, *J* = 7.2 Hz, CH_3-C20), 0.86 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (C-OAc), 147.6 (C-C7), 119.6 (CH_2-C19), 93.9 (CH-C2), 82.0 (CH-C9), 79.1 (CH-C6), 76.0 (C-C3), 74.0 (CH-C11), 67.4 (CH_2-C16), 45.8 (CH-C10), 39.1 (CH-C1), 37.9 (CH-C14), 36.8 (CH-C15), 35.4 (CH_2-C8), 31.6 (CH_2-C4), 31.6 (CH_2-C13), 31.4 (CH-C12), 27.8 (CH_2-C5), 23.5 (CH_3-C18), 21.3 (CH_3-OAc), 17.7 (CH_3-C20), 10.9 (CH_3-C17);

$[\alpha]_D^{20}$ −51.2 (*c* = 0.285, $CHCl_3$) {Lit.[11] $[\alpha]_D^{20}$ −30 (*c* = 0.50, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_5Na$ 401.2298, found 401.2284, Δ 3.6 ppm.

Asbestinin 20 (14)

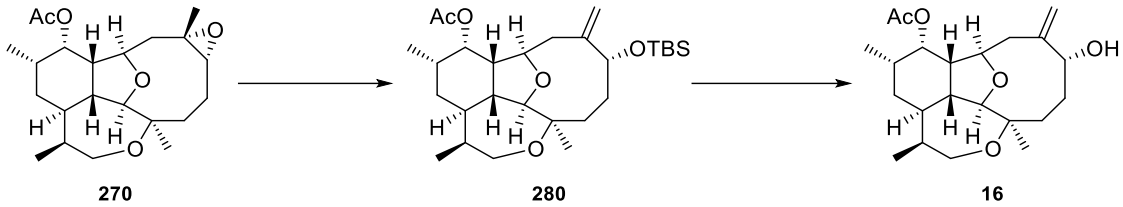


To a stirred solution of epoxide **269** (18 mg, 48 μmol) in anhydrous dichloromethane (1.0 mL) at 0 °C was added 2,6-lutidine (28 μl, 0.24 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.16 mL of a 0.5 M solution in THF, 80 μmol). The reaction mixture was stirred for 3 hours before the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (3 mL) and diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude TBS-protected allylic alcohol **279**, which was used in the next step without further purification.

To a stirred solution of TBS-protected allylic alcohol **279** in THF (1.0 mL) at room temperature was added *tetra*-*N*-butylammonium fluoride (0.19 mL of a 1.0 M solution in THF, 0.19 mmol) in one portion. The reaction mixture was left to stir for 16 hours before being diluted with diethyl ether (5 mL) and water (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane-ethyl acetate, gradient elution from 2:1 → 1:1) to afford asbestinin 20 (**14**) (7.0 mg, 39%) as a colourless solid.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **14** previously (see p. 152).

6-*epi*-Asbestinin 20 (16)



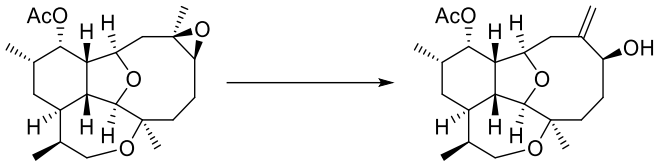
270 **280** **16**

To a stirred solution of epoxide **270** (20 mg, 53 μmol) in anhydrous dichloromethane (1.1 mL) at 0 °C was added 2,6-lutidine (30 μl, 0.27 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.16 mL of a 0.5 M solution in THF, 80 μmol). The reaction mixture was stirred for 3 hours before the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (3 mL) and diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude TBS-protected allylic alcohol **280**, which was used in the next step without further purification.

To a stirred solution of TBS-protected allylic alcohol **280** in THF (1.1 mL) at room temperature was added *tetra-N*-butylammonium fluoride (0.2 mL of a 1.0 M solution in THF, 0.2 mmol) in one portion. The reaction mixture was left to stir for 16 hours before being diluted with diethyl ether (5 mL) and water (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:1 → 1:2) to afford 6-*epi*-asbestinin 20 (**16**) (12.8 mg, 64%) as a colourless solid.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **16** previously (see p. 154).

Asbestinin 20 (14)

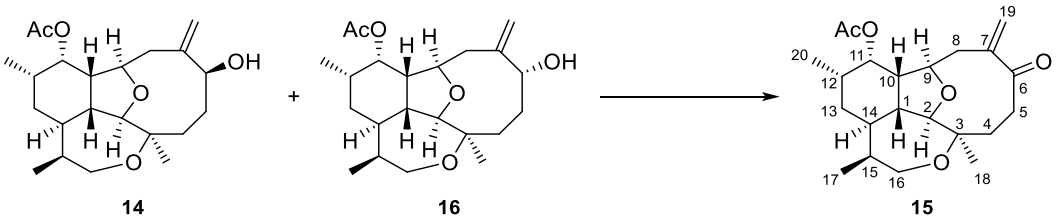


269 **14**

To a solution of epoxide **269** (8.6 mg, 23 µmol) in anhydrous dichloroethane (0.9 mL) was added Au/TiO_2 (2.3 mg) in one portion. The resulting suspension was stirred at 80 °C in a sealed vial for 2 days. The reaction mixture was cooled down to room temperature and diluted with dichloromethane (3 mL) and filtered through a pad of celite, washed with dichloromethane (3 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:1 → 1:3) to afford asbestinin 20 (**14**) (3.0 mg, 35%) as a colourless solid.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **14** previously (see p. 152).

Asbestinin 10 (15)[9]

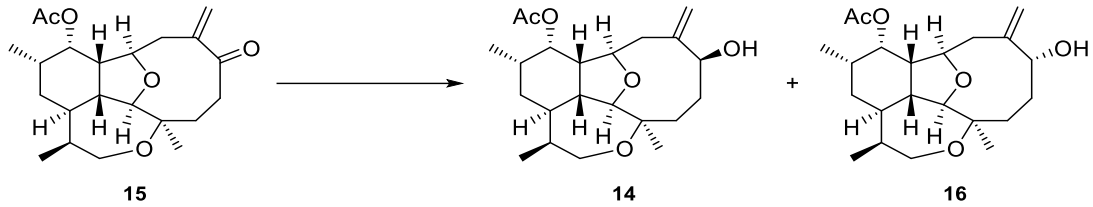


To a stirred solution of allylic alcohols **14** and **16** (1:2 mixture, 16 mg, 42 μmol) in anhydrous dichloromethane (1.0 mL) at room temperature was added anhydrous pyridine (14 μL, 0.17 mmol) followed by Dess–Martin periodinane (32 mg, 75 μmol) in one portion. The reaction mixture was stirred for 2 hours before being diluted with ethyl acetate (5 mL). The reaction was quenched by the addition of saturated aqueous solution of sodium thiosulfate (3 mL) and left for 5 minutes before the addition of saturated aqueous solution of sodium bicarbonate (1 mL). The resulting solution was stirred vigorously for 30 minutes. The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-diethyl ether, 10:1) to afford asbestinin 10 (**15**) (12 mg, 75%) as a colourless oil.

R_f = 0.23 (petroleum ether-ethyl acetate, 2:1); ν_{max} 2961, 2928, 2874, 1736, 1686, 1458, 1371, 1300, 1234, 1107, 1074, 1013, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.28–5.26 (1H, m, CH_2-C19a), 5.26 (1H, dd, *J* = 5.0, 2.8 Hz, CH-C11), 5.18 (1H, br s, CH_2-C19b), 4.04 (1H, dd, *J* = 6.7, 4.1 Hz, CH-C9), 3.77 (1H, d, *J* = 9.4 Hz, CH-C2), 3.75 (1H, d, *J* = 13.0 Hz, CH_2-C16a), 3.49 (1H, dd, *J* = 13.0, 3.0 Hz, CH_2-C16b), 3.36 (1H, ddd, *J* = 13.2, 6.8, 1.5 Hz, CH_2-C8a), 2.81 (1H, ddd, *J* = 15.5, 8.01, 2.1 Hz, CH_2-C5a), 2.49 (1H, ddd, *J* = 15.5, 12.5, 2.0 Hz, CH_2-C5b), 2.41 (1H, ddd, *J* = 11.2, 10.8, 9.4 Hz, CH-C1), 2.30 (1H, ddd, *J* = 14.9, 12.5, 2.1 Hz, CH_2-C4a), 2.15 (1H, br d, *J* = 13.2 Hz, CH_2-C8b), 2.10–1.98 (2H, m, CH-C10, CH-C12), 2.09 (3H, s, CH_3-OAc), 1.89 (1H, dddd, *J* = 14.0, 10.8, 4.0, 3.6 Hz, CH-C14), 1.67 (1H, ddd, *J* = 14.9, 8.1, 2.0 Hz, CH_2-C4b), 1.63–1.51 (2H, m, CH_2-C13a, CH-C15), 1.28 (3H, s, CH_3-C18), 1.05 (1H, ddd, *J* = 13.6, 3.6, 1.9 Hz, CH_2-C13b), 0.94 (3H, d, *J* = 7.2 Hz, CH_3-C20), 0.93 (3H, d, *J* = 7.1 Hz, CH_3-C17); ^1H NMR (400 MHz, C_6D_6) δ 5.23 (1H, dd, *J* = 5.0, 2.9 Hz, CH-C11), 4.79 (1H, br s, CH_2-C19a), 4.77 (1H, br s, CH_2-C19b), 4.07 (1H, dd, *J* = 6.7, 4.0 Hz, CH-C9), 3.77 (1H, d, *J* = 9.4 Hz, CH-C2), 3.49−3.42 (2H, m, CH_2-C8a, CH_2-C16a), 3.33 (1H, dd, *J* = 13.0, 3.0 Hz, CH_2-C16b), 2.63−2.48 (2H, m, CH_2-C5), 2.39–2.24 (2H, m, CH-C1, CH_2-C4a), 1.82–1.71 (4H, m,

CH_2_C4b, CH_2-C8b, CH-C10, CH-C14), 1.70 (3H, s, CH_3-OAc), 1.66–1.57 (1H, m, CH-C12), 1.29–1.18 (2H, m, CH_2-C13a, CH-C15), 1.28 (3H, s, CH_3-C18), 0.88 (3H, d, *J* = 7.1 Hz, CH_3-C20), 0.88 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.75 (1H, ddd, *J* = 13.5, 3.7, 2.0 Hz, CH_2-C13b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (C-C6), 171.1 (C-OAc), 146.7 (C-C7), 114.1 (CH_2-C19), 93.3 (CH-C2), 80.0 (CH-C9), 73.1 (CH-C11), 68.2 (CH_2-C16), 48.0 (CH-C10), 41.6 (CH_2-C8), 40.2 (CH-C1), 37.6 (CH_2-C5), 37.4 (CH-C14), 36.7 (CH-C15), 35.9 (CH_2-C4), 31.7 (CH_2-C13), 31.2 (CH-C12), 24.1 (CH_3-C18), 21.2 (CH_3-OAc), 18.1 (CH_3-C20), 11.0 (CH_3-C17), Peak for at C-C3 was not observed; ^{13}C NMR (101 MHz, C_6D_6) δ 203.0 (C-C6), 169.1 (C-OAc), 146.8 (C-C7), 111.6 (CH_2-C19), 92.5 (CH-C2), 79.2 (CH-C9), 76.4 (C-C3), 71.8 (CH-C11), 66.7 (CH_2-C16), 47.1 (CH-C10), 40.6 (CH_2-C8), 39.1 (CH-C1), 36.7 (CH_2-C5), 36.6 (CH-C14), 36.0 (CH-C15), 35.1 (CH_2-C4), 30.7 (CH_2-C13), 30.3 (CH-C12), 23.0 (CH_3-C18), 19.4 (CH_3-OAc), 17.1 (CH_3-C20), 10.1 (CH_3-C17); $[\alpha]_D^{23}$ −78 (*c* = 0.13, $CHCl_3$) {Lit.[9] $[\alpha]_D^{25}$ −81.5 (*c* = 0.760, $CHCl_3$); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{22}H_{32}O_5Na$ 399.2142, found 399.2131, Δ 2.8 ppm.

Asbestinin 20 (14) and 6-*epi*-Asbestinin 20 (16)

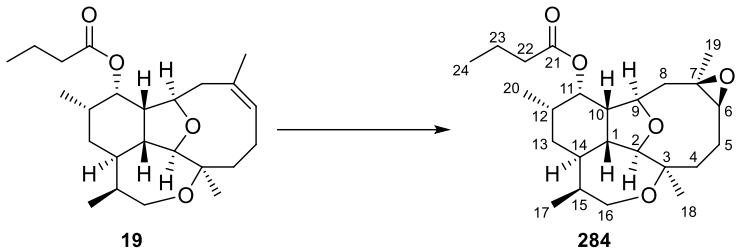


15 **14** **16**

To a stirred solution of enone **15** (10 mg, 27 µmol) in a mixture of methanol and dichloromethane (1:1, 0.6 mL) at room temperature was added cerium (III) chloride heptahydrate (20 mg, 53 µmol). The reaction mixture was stirred for 15 minutes before being cooled down to −78 °C. To this, sodium borohydride (2.0 mg, 53 µmol) was added in one portion and the resulting solution was stirred for 2 hours. The reaction mixture was warmed to room temperature and allowed to stir for a further 20 minutes. The reaction was quenched by the addition of a 50% aqueous solution of ammonium chloride (2 mL) and diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-diethyl ether, gradient elution from 1:2 → 1:5) to afford asbestinin 20 (**14**) (6.4 mg, 64%) and 6-*epi*-asbestinin 20 (**16**) (2.0 mg, 20%) as colourless solids.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compounds **14** and **16** previously (see p. 152 and 154).

(1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*S*,16*R*,18*R*)-5,8,11,16-Tetramethyl-10,15,19-trioxapentacyclo[9.8.0.0^{2,7}.0^{3,18}.0^{14,16}]nonadecan-4-yl butanoate (284)



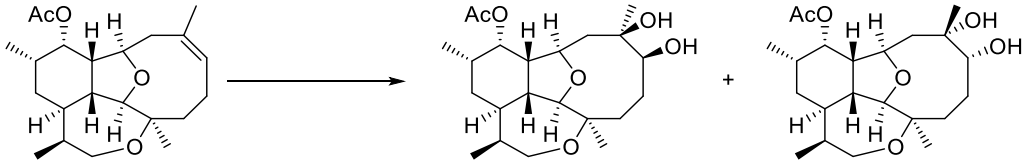
19 284

To a stirred solution of 4-deoxyasbestinin C (**19**) (20 mg, 51 μmol), unnatural Shi ketone (4.0 mg, 15 μmol) in a mixture of acetonitrile and dimethoxyethane (1:2, 1.2 mL) was added buffer (0.52 mL of a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), 26 μmol) followed by tetrabutylammonium hydrogen sulfate (5.0 μL of a 0.4 M solution in water, 2.0 μmol). The resulting solution was cooled to 0 °C before Oxone™ (1.3 mL of a 0.4 M solution in 4×10^{-4} M aqueous Na_2(EDTA), 0.52 mmol) and potassium carbonate (0.75 mL of a 0.4 M solution in water, 0.30 mmol) were added simultaneously. The reaction mixture was stirred for 1 hour before being diluted with water (5 mL) and ethyl acetate (10 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 10:1 → 2:1) to afford epoxide **284** (15.2 mg, 73%) as a colourless solid.

R_f = 0.38 (petroleum ether-ethyl acetate, 2:1); m.p. 123−125 °C; ν_{max} 2961, 2924, 2878, 1732, 839, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (1H, dd, *J* = 6.3, 1.9 Hz, CH-C11), 4.24 (1H,br dd, *J* = 11.7, 5.2 Hz, CH-C9), 3.89 (1H, d, *J* = 10.1 Hz, CH-C2), 3.83 (1H, dd, *J* = 13.2, 1.3 Hz, CH_2-C16a), 3.60 (1H, dd, *J* = 13.2, 2.2 Hz, CH_2-C16b), 2.81–2.71 (2H, m, CH-C1, CH-C6), 2.31 (2H, t, *J* = 7.5 Hz, CH_2-C22), 2.21–2.12 (1H, m, CH-C12), 2.03 (1H, dd, *J* = 13.8, 5.2 Hz, CH_2-C8a), 2.03–1.96 (1H, m, CH_2-C5a), 1.89–1.76 (2H, m, CH_2-C4a, CH-C10, CH-C14), 1.73–1.63 (3H, m, CH_2-C5b, CH_2-C23), 1.61–1.47 (4H, m, CH_2-C4b, CH_2-C8b, CH_2-C13a, CH-C15), 1.33 (3H, s, CH_3-C18), 1.33 (3H, s, CH_3-C19), 1.04 (1H, dd, *J* = 13.4, 2.8 Hz, CH_2-C13b), 0.98 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.97 (3H, t, *J* = 7.4 Hz, CH_3-C24), 0.91 (3H, d, *J* = 7.3 Hz, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C-C21), 94.2 (CH-C2), 78.4 (CH-C9), 79.3 (C-C3), 72.5 (CH-C11), 70.3 (CH_2-C16), 66.4 (CH-C6), 59.5 (C-C7), 50.0 (CH-C10), 43.4 (CH_2-C8), 39.6 (CH-C1), 37.7 (CH-C14), 36.9 (CH_2-C22), 36.4 (CH-C15), 34.5 (CH_2-C4), 32.1 (CH_2-C13), 31.4 (CH-C12), 27.8

(CH_3-C19), 22.5 (CH_3-C18), 21.8 (CH_2-C5), 18.6 (CH_2-C23), 17.0 (CH_3-C20), 13.9 (CH_3-C24), 11.3 (CH_3-C17); $[\alpha]_D^{15}$ –21.1 (*c* = 0.845, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{24}H_{38}O_5Na$ 426.2604, found 429.2611, Δ 1.9 ppm.

(1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*S*,15*R*,17*R*)-14,15-Dihydroxy-5,8,11,15-tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan-4-yl acetate (275) and (1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*R*,15*S*,17*R*)-14,15-Dihydroxy-5,8,11,15-tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan-4-yl acetate (287)

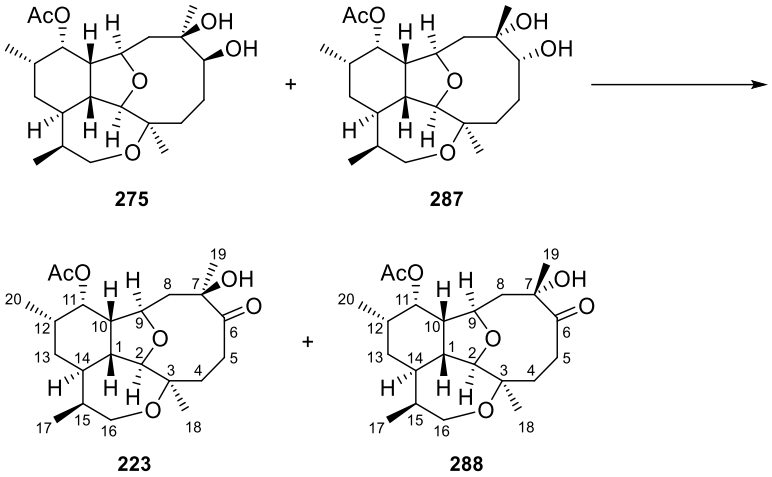


18 275 287

To a stirred of 11-acetoxy-4-deoxyasbestinin D (**18**) (16.6 mg, 45.8 μmol) in a mixture of THF and water (1:1, 1.2 mL) at 0 °C was added *N*-methylmorpholine oxide (54 mg, 0.46 mmol) followed by osmium tetroxide (15 μL of a 4% wt solution in water, 2.4 μmol). The reaction mixture was left to stir for 1.5 hours before the reaction was quenched by the addition of a saturated aqueous solution of sodium thiosulfate (2 mL). The resulting suspension was vigorously stirred for 1 hour before being diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (4 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:2 → 1:5) to afford diols **275** and **287** (5.7:1, 10.2 mg, 56%) as a colourless solid.[1]

[1] Diols were later found to be separable by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from 19:1 → 5.1)

7-*epi*-Asbestinin 21 (223) and Asbestinin 21 (288)[10]



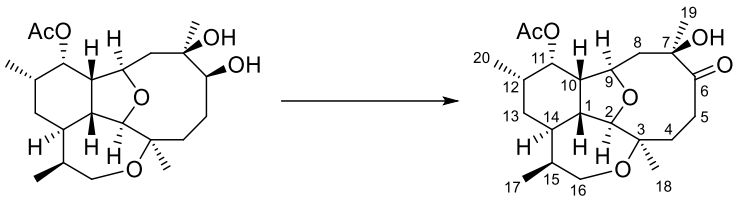
To a stirred solution of diols **275** and **287** (10.2 mg, 25.7 μmol) in anhydrous dichloromethane (1.0 mL) at room temperature was added pyridine (80 μL, 0.10 mmol) and Dess–Martin periodinane (20 mg, 47 μmol). The resulting solution was stirred for 2 hours then diluted with diethyl ether (3 mL). The reaction was quenched by the addition of saturated aqueous solution of sodium thiosulfate (2 mL) and left for 5 minutes before the addition of saturated aqueous solution of sodium bicarbonate (0.5 mL). The resulting solution was stirred vigorously for 30 minutes. The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:1 → 1:3) to afford 7-*epi*-asbestinin 21 (**223**) (6.8 mg, 67%) as a colourless oil and asbestinin 21 (**288**) (1.4 mg, 14%) as a colourless solid.

223: R_f = 0.49 (petroleum ether-ethyl acetate, 1:3); ν_{max} 3451, 2963, 2932, 2876, 1736, 1690, 997, 963, 918, 873, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, dd, *J* = 5.1, 2.6 Hz, CH-C11), 3.92 (1H, ddd, *J* = 6.1, 4.1, 1.8 Hz, CH-C9), 3.78 (1H, br d, *J* = 13.1 Hz, CH_2-C16a), 3.77 (1H, d, *J* = 9.7 Hz, CH-C2), 3.55 (1H, dd, *J* = 13.1, 2.8 Hz, CH_2-C16b), 3.32−3.21 (1H, m, CH_2-C5a), 2.83 (1H, ddd, *J* = 10.4, 9.7, 9.5 Hz, CH-C1), 2.52–2.46 (1H, m, CH-C10), 2.46 (1H, dd, *J* = 14.5, 6.1 Hz, CH_2-C8a), 2.41−2.30 (1H, m, CH_2-C4a), 2.12−1.98 (2H, m, CH_2-C5b, CH-C12), 2.07 (3H, s, CH_3-OAc), 1.93–1.79 (4H, m, CH_2-C4b, HO-C7, CH_2-C8b, CH-C14), 1.63–1.51 (2H, m, CH_2-C13a, CH-C15), 1.38 (3H, s, CH_3-C19), 1.32 (3H, s, CH_3-C18), 1.03 (1H, dd, *J* = 13.5, 2.0 Hz, CH_2-C13b), 0.99 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.92 (3H, d, *J* = 7.2 Hz, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.2 (C-C6), 171.4 (C-OAc), 93.7 (CH-C2), 79.8 (C-C7), 78.9 (CH-C9), 76.7 (C-C3),

73.8 (CH-C11), 69.1 (CH_2-C16), 47.1 (CH-C10), 47.0 (CH_2-C8), 40.1 (CH-C1), 37.5 (CH-C14), 37.1 (CH_2-C4), 37.0 (CH-C15), 32.8 (CH_2-C5), 32.1 (CH_2-C13), 31.3 (CH-C12), 28.4 (CH_3-C19), 25.7 (CH_3-C18), 21.4 (CH_3-OAc), 18.0 (CH_3-C20), 11.2 (CH_3-C17); $[\alpha]_D^{20}$ −25.6 (*c* = 0.245, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_6Na$ 417.2248, found 417.2235, Δ 3.1 ppm.

288: R_f = 0.44 (petroleum ether-ethyl acetate, 1:2); ν_{max} 3439, 2964, 2926, 1736, 1686, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.34 (1H, dd, *J* = 5.6, 2.3 Hz, CH-C11), 4.39 (1H, s, HO-C7), 4.28 (1H, dd, *J* = 11.5, 3.4 Hz, CH-C9), 3.82 (1H, d, *J* = 8.8 Hz, CH-C2), 3.78 (1H, br d, *J* = 13.0 Hz, CH_2-C16a), 3.49 (1H, dd, *J* = 13.0, 2.8 Hz, CH_2-C16b), 2.75 (1H, ddd, *J* = 14.6, 14.6, 3.9 Hz, CH_2-C5a), 2.67−2.61 (1H, m, CH_2-C5b), 2.57 (1H, ddd, *J* = 10.0, 10.0, 8.8 Hz, CH-C1), 2.30 (1H, ddd, *J* = 14.6, 14.6, 3.4 Hz, CH_2-C4a), 2.26−2.18 (1H, m, CH_2-C8a), 2.12–2.03 (2H, m, CH_2-C8b, CH-C12), 2.05 (3H, s, CH_3-OAc), 1.93–1.85 (2H, m, CH-C10, CH-C14), 1.64–1.45 (3H, m, CH_2-C4b, CH_2-C13a, CH-C15), 1.33 (3H, s, CH_3-C18), 1.30 (3H, s, CH_3-C19), 1.04 (1H, dd, *J* = 13.6, 2.6 Hz, CH_2-C13b), 0.94 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.90 (3H, d, *J* = 7.3 Hz, CH_3-C20); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9 (C-C6), 171.0 (C-OAc), 93.7 (CH-C2), 78.4 (CH-C9), 77.2 (C-C3), 76.4 (C-C7), 72.9 (CH-C11), 68.3 (CH_2-C16), 49.4 (CH_2-C8), 47.7 (CH-C10), 38.1 (CH-C1), 38.1 (CH-C14), 36.5 (CH-C15), 36.2 (CH_2-C5), 34.1 (CH_2-C4), 31.6 (CH_2-C13), 31.6 (CH-C12), 27.8 (CH_3-C19), 22.6 (CH_3-C18), 21.6 (CH_3-OAc), 17.4 (CH_3-C20), 11.1 (CH_3-C17); $[\alpha]_D^{21}$ −7.2 (*c* = 0.10, $CHCl_3$) {Lit.[10] $[\alpha]_D^{24}$ −27.1 (*c* = 1.80, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_6Na$ 417.2248, found 417.2233, Δ 3.5 ppm.

7-*epi*-Asbestinin 21 (223)

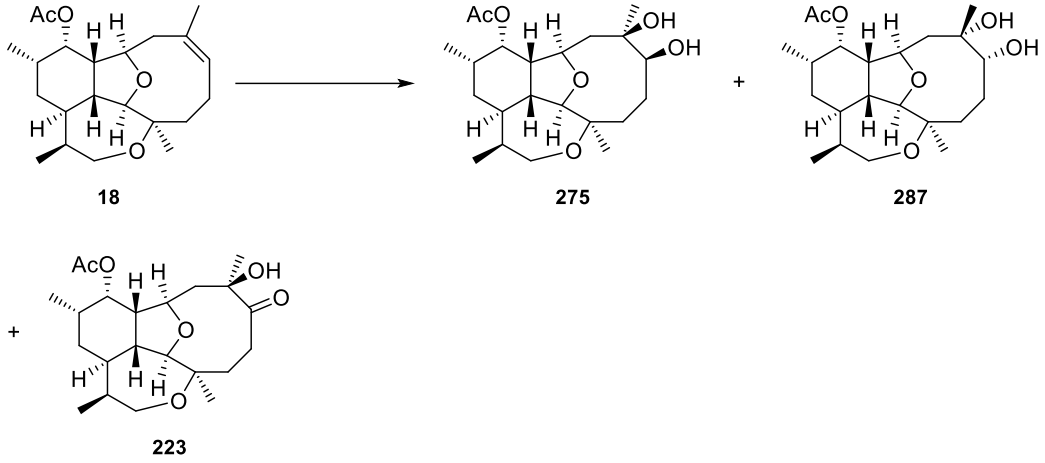


275 **223**

To a stirred solution of diol **275** (10.5 mg, 26.4 μmol) in anhydrous dichloromethane (0.5 mL) at room temperature was added pyridine (8.4 μL, 0.10 mmol) and Dess–Martin periodinane (20 mg, 48 μmol). The resulting solution was stirred for 2 hours then diluted with diethyl ether (5 mL). The reaction was quenched by the addition of saturated aqueous solution of sodium thiosulfate (2 mL) and left for 5 minutes before the addition of saturated aqueous solution of sodium bicarbonate (0.5 mL). The resulting solution was stirred vigorously for 30 minutes. The aqueous phase was separated and extracted with diethyl ether (3 × 1 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, 1:2) to afford 7-*epi*-asbestinin 21 (**223**) (9.1 mg, 87%) as a colourless oil.

The NMR (^1H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compound **223** previously (see p. 165).

(1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*S*,15*R*,17*R*)-14,15-Dihydroxy-5,8,11,15-tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan-4-yl acetate (275), (1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*R*,15*S*,17*R*)-14,15-Dihydroxy-5,8,11,15-tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan-4-yl acetate (287) and 7-*epi*-Asbestinin 21 (223)



*Dihydroxylation of 11-Acetoxy-4-deoxyasbestinin D (**18**) with the Osmium Complex of (DHQ)$_2$PHAL (AD-mix-α)*

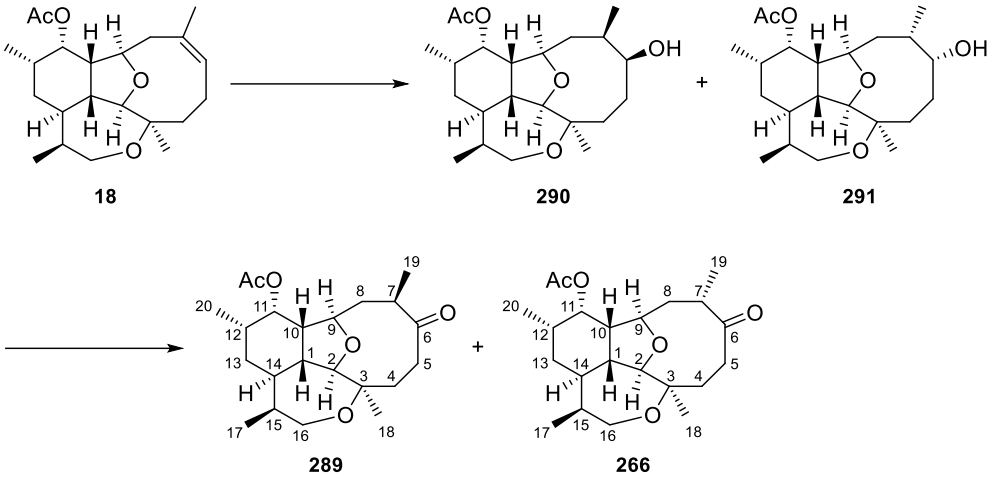
To a stirred solution of (DHQ)$_2$PHAL (9.1 mg, 12 µmol), potassium osmate (2.9 mg, 7.9 µmol), potassium ferricyanate (642 mg, 1.95 mmol) and potassium carbonate (270 mg, 1.95 mmol) in a mixture of *t*-BuOH and water (1:1, 0.8 mL) at 0 °C was added 11-acetoxy-4-deoxyasbestinin D (**18**) (18 mg, 50 µmol) in *t*-BuOH (0.3 mL) in one portion. The reaction mixture was warmed to room temperature over 2 hours before being left to stir for 16 hours. The reaction was quenched by the addition of saturated aqueous solution of sodium metabisulfite (3 mL) and left for 30 minutes before being diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:2 → 1:5) to afford a diastereoisomeric mixture of diols **275** and **287** (>12:1, 4.6 mg, 23%) as a colourless solid and 7-*epi*-asbestinin 21 (**223**) (9.1 mg, 46%) as a colourless oil.

*Dihydroxylation of 11-Acetoxy-4-deoxyasbestinin D (**18**) with the Osmium Complex of (DHQD)$_2$PHAL (AD-mix-β)*

To a stirred solution of (DHQD)$_2$PHAL (23 mg, 30 μmol), potassium osmate (7.4 mg, 20 μmol), potassium ferricyanate (1.64 g, 4.98 mmol) and potassium carbonate (690 mg, 4.99 mmol) in a mixture of *t*-BuOH and water (1:1, 1.1 mL) at 0 °C was added 11-acetoxy-4-deoxyasbestinin D (**18**) (18 mg, 50 μmol) in *t*-BuOH (0.3 mL) in one portion. The reaction mixture was warmed to room temperature over 2 hours before being left to stir for 16 hours. The reaction was quenched by the addition of saturated aqueous solution of sodium metabisulfite (3 mL) and left for 30 minutes before being diluted with ethyl acetate (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 1:2 → 1:5) to afford a diastereoisomeric mixture of diols **275** and **287** (8.0:1, 14.7 mg, 75%) as a colourless solid and 7-*epi*-asbestinin 21 (**223**) (1.9 mg, 10%) as a colourless oil.

The NMR (^{1}H and ^{13}C), IR and mass spectrometry data were consistent with those reported for compounds **275** and **223** previously (see p. 152 and 165).

Asbestinin 23 (266)[10] and 7-*epi*-Asbestinin 23 (289)



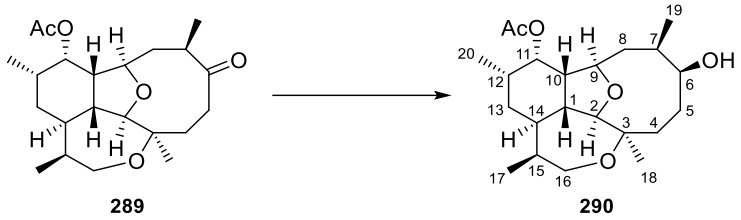
To a stirred solution of 11-acetoxy-4-deoxyasbestinin D (**18**) (26 mg, 72 µmol) in anhydrous THF (1.4 mL) at 0 °C was added BH_3•THF (0.2 mL of a 1.0 M solution in THF, 0.2 mmol). The resulting solution was stirred for 2.5 hours before the reaction was quenched by the addition of a water (2 mL) and sodium perborate tetrahydrate (84 mg, 0.55 mmol). The reaction mixture was warmed to room temperature and left to stir for 16 hours before being diluted with diethyl ether (5 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude alcohols **290** and **291**, which was used in the next step without further purification.

To a stirred solution of alcohols **290** and **291** in anhydrous dichloromethane (1.4 mL) at room temperature was added pyridine (0.30 mL, 0.36 mmol) and Dess–Martin periodinane (73 mg, 0.17 mmol) in one portion. The resulting solution was stirred for 2 hours before being diluted with diethyl ether (5 mL). The reaction was quenched by the addition of saturated aqueous solution of sodium thiosulfate (2 mL) and left for 5 minutes before the addition of saturated aqueous solution of sodium bicarbonate (0.5 mL). The resulting solution was stirred vigorously for 30 minutes. The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 10:1 → 2:1) to afford 7-*epi*-asbestinin 23 (**289**) (13.4 mg, 49%) and asbestinin 23 (**266**) (5.3 mg, 20%) as colourless oils.

289: R_f = 0.44 (petroleum ether-ethyl acetate, 1:1); ν_{max} 2961, 2932, 2872, 1734, 1694, 993, 951, 936, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, dd, *J* = 5.0, 2.7 Hz, CH-C11), 3.98 (1H, ddd, *J* = 6.5, 6.5, 3.3 Hz, CH-C9), 3.77 (1H, br d, *J* = 13.2 Hz, CH_2-C16a), 3.74 (1H, d, *J* = 9.4 Hz, CH-C2), 3.49 (1H, dd, *J* = 13.2, 3.0 Hz, CH_2-C16b), 2.87–2.76 (1H, m, CH-C7), 2.57–2.44 (2H, m, CH_2-C8), 2.42 (1H, ddd, *J* = 10.6, 10.4, 9.4 Hz, CH-C1), 2.26 (1H, ddd, *J* = 14.8, 10.7, 4.1 Hz, CH_2-C4a), 2.07 (3H, s, CH_3-OAc), 2.06–1.92 (4H, m, CH_2-C5, CH-C10, CH-C12), 1.85 (1H, dddd, *J* = 13.7, 10.8, 4.1, 3.7 Hz, CH-C14), 1.73 (1H, ddd, *J* = 14.8, 7.3, 3.6 Hz, CH_2-C4b), 1.65–1.58 (1H, m, CH-C15), 1.51 (1H, ddd, *J* = 13.7, 13.4, 9.7 Hz, CH_2-C13a), 1.33 (3H, s, CH_3-C18), 1.06 (3H, d, *J* = 6.9 Hz, CH_3-C19), 1.01 (1H, ddd, *J* = 13.4, 3.7, 1.8 Hz, CH_2-C13b), 0.95 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.90 (3H, d, *J* = 7.2 Hz, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 (C-C6), 171.2 (C-OAc), 92.9 (CH-C2), 79.3 (CH-C9), 73.1 (CH-C11), 68.0 (CH_2-C16), 49.9 (CH-C10), 44.3 (CH-C7), 42.8 (CH_2-C5), 38.8 (CH_2-C8), 38.3 (CH-C1), 37.9 (CH-C14), 36.7 (CH-C15), 34.6 (CH_2-C4), 31.3 (CH_2-C13), 31.2 (CH-C12), 24.1 (CH_3-C18), 21.3 (CH_3-OAc), 18.0 (CH_3-C19), 17.9 (CH_3-C20), 11.0 (CH_3-C17). Peak for C-C3 was obscured by solvent (~77.0 ppm); $[\alpha]_D^{20}$ −23.6 (*c* = 0.250, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_5Na$ 401.2284, found 401.2298, Δ 3.6 ppm.

266: R_f = 0.39 (petroleum ether-ethyl acetate, 1:1); ν_{max} 2959, 2928, 2872, 1736, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25 (1H, dd, *J* = 5.0, 2.8 Hz, CH-C11), 3.94−3.90 (1H, m, CH-C9), 3.80 (1H, d, *J* = 9.5 Hz, CH-C2), 3.78 (1H, br d, *J* = 13.0 Hz, CH_2-C16a), 3.53 (1H, dd, *J* = 13.0, 2.9 Hz, CH_2-C16b), 2.78 (1H, dqd, *J* = 13.4, 6.7, 1.9 Hz, CH-C7), 2.61−2.53 (2H, m, CH-C1, CH_2-C5a), 2.48 (1H, ddd, *J* = 13.4, 12.4, 6.0 Hz, CH_2-C8a), 2.40−2.32 (1H, m, CH_2-C5b), 2.29−2.22 (1H, m, CH_2-C4a), 2.08 (3H, s, CH_3-OAc), 2.07−2.01 (2H, m, CH-C10, CH-C12), 1.96−1.87 (1H, m, CH-C14), 1.73 (1H, dd, *J* = 14.7, 8.0 Hz, CH_2-C4b), 1.65−1.55 (3H, m, CH_2-C8b, CH_2-C13a, CH-C15), 1.30 (3H, s, CH_3-C18), 1.07 (1H, ddd, *J* = 13.6, 3.5, 1.7 Hz, CH_2-C13b), 1.02 (3H, d, *J* = 6.7 Hz, CH_3-C19), 0.98 (3H, d, *J* = 7.1 Hz, CH_3-C17), 0.94 (3H, d, *J* = 7.2 Hz, CH_3-C20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C-OAc), 93.5 (CH-C2), 79.8 (CH-C9), 77.1 (C-C3), 73.3 (CH-C11), 68.5 (CH_2-C16), 48.5 (CH-C10), 43.1 (CH_2-C8), 40.9 (CH-C1), 39.5 (CH_2-C5), 37.6 (CH-C7), 37.4 (CH-C14), 36.9 (CH-C15), 35.6 (CH_2-C4), 32.0 (CH_2-C13), 31.3 (CH-C12), 24.5 (CH_3-C18), 21.4 (CH_3-OAc), 18.2 (CH_3-C20), 17.7 (CH_3-C19), 11.2 (CH_3-C17). Peak for C-C6 was not observed; $[\alpha]_D^{20}$ −38.3 (*c* = 0.235, $CHCl_3$) {Lit.[10] $[\alpha]_D^{24}$ −22.0 (*c* = 2.30, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_5Na$ 401.2298, found 401.2298, Δ 2.7 ppm.

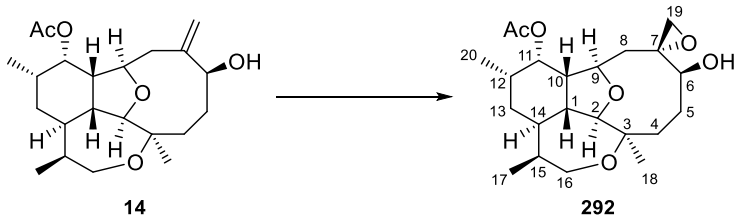
(1*R*,2*R*,3*S*,4*S*,5*S*,7*R*,8*S*,11*R*,14*S*,15*R*,17*R*)-14-Hydroxy-5,8,11,15-tetramethyl-10,18-dioxatetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan-4-yl acetate (290)



To a stirred solution of 7-*epi*-asbestinin 23 (**289**) (12.3 mg, 32.5 μmol) in anhydrous THF (0.6 mL) at −78 °C was added L-selectride (0.04 mL of a 1.0 M solution in THF, 0.04 mmol) dropwise and the resulting solution was stirred for 1 hour. The reaction was quenched by the addition of a water (2 mL) and warmed to room temperature before being diluted with ethyl acetate (3 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 2:1 → 1:2) to afford alcohol **290** (7.9 mg, 64%) as a colourless solid.

R_f = 0.29 (petroleum ether-ethyl acetate, 1:1); m.p. 206−208 °C; ν_{max} 3451, 2963, 2874, 1736, 1462, 1371, 1236, 1109, 1074, 1016, 974, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (1H, dd, *J* = 5.7, 1.6 Hz, CH-C11), 4.09 (1H, app dd, *J* = 12.1, 3.7 Hz, CH-C9), 3.85 (1H, d, *J* = 8.5 Hz, CH-C2), 3.82−3.74 (2H, m, CH-C6, CH_2-C16a), 3.48 (1H, dd, *J* = 12.9, 2.3 Hz, CH_2-C16b), 2.59 (1H, ddd, *J* = 9.9, 9.9, 8.5 Hz, CH-C1), 2.15−1.98 (4H, m, CH_2-C4a, CH_2-C5a, CH_2-C8a, CH-C12), 2.09 (3H, s, CH_3-OAc), 1.93−1.85 (1H, m, CH-C14), 1.84−1.79 (1H, m, CH_2-C4b), 1.77 (1H, dd, *J* = 9.4, 1.6 Hz, CH-C10), 1.72−1.65 (1H, m, CH-C7), 1.64−1.57 (1H, m, CH-C15), 1.48 (1H, ddd, *J* = 13.5, 13.5, 9.2 Hz, CH_2-C13a), 1.33 (3H, s, CH_3-C18), 1.27−1.16 (1H, m, CH_2-C5b), 1.05−0.98 (5H, m, CH_2-C8b, CH_2-C13b, CH_3-C19), 0.93 (3H, d, *J* = 7.2 Hz, CH_3-C17), 0.92 (3H, d, *J* = 7.2 Hz, CH_3-C20); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (C-OAc), 94.9 (CH-C2), 82.1 (CH-C9), 77.8 (C-C3), 73.9 (CH-C6), 73.6 (CH-C11), 68.1 (CH_2-C16), 48.3 (CH-C10), 38.4 (CH-C14), 37.9 (CH-C1), 37.5 (CH_2-C8), 37.3 (CH-C7), 36.5 (CH-C15), 31.6 (CH_2-C13), 31.5 (CH-C12), 29.9 (CH_2-C4), 28.2 (CH_2-C5), 22.9 (CH_3-C19), 22.7 (CH_3-C18), 21.6 (CH_3-OAc), 17.2 (CH_3-C20), 11.1 (CH_3-C17); $[\alpha]_D^{23}$ +12.4 (c = 0.210, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{36}O_5Na$ 403.2455, found 403.2446, Δ 2.1 ppm.

(1′*R*,2*R*,2′*R*,3′*S*,4′*S*,5′*S*,7′*R*,8′*S*,11′*R*,14′*S*,17′*R*)-14′-Hydroxy-5′,8′,11′-trimethyl-10′,18′-dioxaspiro[oxirane-2,15′-tetracyclo[9.7.0.0^{2,7}.0^{3,17}]octadecan]-4′-yl acetate (292)

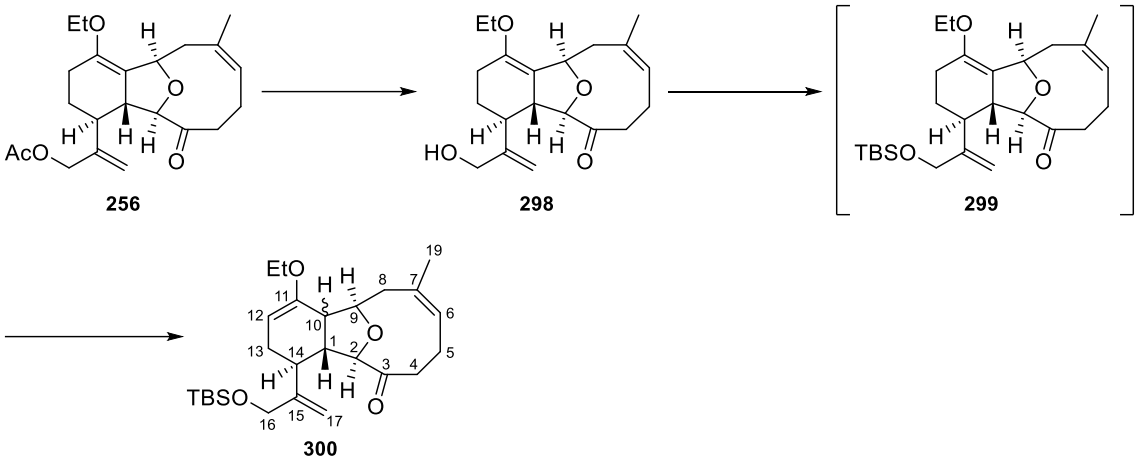


To a suspension of 4 Å powdered molecular sieves (5 mg) in anhydrous CH_2Cl_2 (0.2 mL) at −15 °C were added distilled titanium tetraisopropoxide (10 μL of a 0.11 M solution in CH_2Cl_2, 1.1 μmol), distilled (+)-diethyl tartrate (10 μL of a 0.16 M solution in CH_2Cl_2, 1.6 μmol) and *tert*-butylhydroperoxide (0.10 mL of a 0.42 M solution in CH_2Cl_2, 42 μmol) in one portion. The resulting suspension was stirred for 1 hour before a solution of asbestinin 20 (**14**) (8.0 mg, 21 μmol) in anhydrous CH_2Cl_2 (0.2 mL) was added dropwise over 15 minutes and left to stir for 2 hours. The reaction was quenched by the addition of 50% aqueous solution of $NaHCO_3$ (0.5 mL) before the reaction mixture was warmed to room temperature and diluted with diethyl ether (5 mL) and water (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-diethyl ether, gradient elution from 1:2 → 1:5) to afford epoxide **292** (6.2 mg, 75%) as a colourless solid.

R_f = 0.17 (petroleum ether-ethyl acetate, 1:2); m.p. 228−230 °C; ν_{max} 3452, 2961, 2930, 2874, 1736, 916, 729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (1H, dd, *J* = 5.7, 2.2 Hz), 4.31−4.26 (1H, m), 3.89 (1H, d, *J* = CH-C2), 3.80 (1H, d, *J* = 13.0 Hz), 3.49 (1H, dd, *J* = 13.0 Hz), 2.63 (1H, d, *J* = 5.0 Hz), 2.59−2.50 (1H, m), 2.23−2.06 (3H, m), 2.09 (3H, s), 1.97−1.87 (4H, m), 1.80−1.71 (2H, m), 1.66−1.59 (1H, m), 1.53−1.42 (2H, m), 1.35 (3H, s), 1.05 (1H, dd, *J* = 13.4, 2.6 Hz), 0.94 (3H, d, *J* = 7.1 Hz), 0.92 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 94.1, 79.5, 73.3, 68.0, 48.0, 38.3, 38.3, 36.6, 31.6, 31.5, 27.6, 22.9, 21.5, 17.4, 11.1;[2] $[\alpha]_D^{21}$ −38.6 (c = 0.110, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{22}H_{34}O_6Na$ 417.2238, found 417.2248, Δ 2.1 ppm.

[2] Full assignment of compound **292** was not possible; this is likely caused by conformational change in oxonene ring broadening the peaks. Structure of compound **292** was confirmed by single crystal X-ray analysis.

(1*R*,6*S*,7*R*,8*R*,12*Z*)-6-{3-[(tert-Butyldimethylsilyl)oxy]prop-1-en-2-yl}-3-ethoxy-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-3,12-dien-9-one (300)



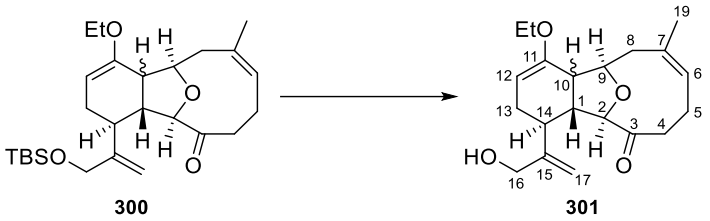
To a stirred solution of ketone **256** (676 mg, 1.80 mmol) in anhydrous methanol (36 mL) at room temperature was added potassium carbonate (302 mg, 2.18 mmol) in one portion. The resulting solution was stirred for 1.5 hours before the reaction was quenched by the addition of saturated aqueous solution of ammonium chloride (20 mL) and diluted with ethyl acetate (30 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give crude alcohol **298**, which was used in the next step without further purification.

To a stirred solution of alcohol **298** in anhydrous dichloromethane (36 mL) at room temperature was added imidazole (248 mg, 3.64 mmol) and *tert*-butyldimethylsilyl chloride (494 mg, 3.28 mmol) in one portion. The resulting solution was stirred for 2 hours before the reaction was quenched by the addition of water (20 mL) and diluted with diethyl ether (50 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 30:1 → 15:1) to afford ketone **299** which underwent isomerisation to give ketone **300** (663 mg, 82%) as a colourless oil.

R_f = 0.83 (petroleum ether-ethyl acetate, 9:1); ν_{max} 2951, 2928, 2857, 1705, 1668, 906, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, dd, *J* = 11.4, 5.7 Hz, CH-C6), 5.15 (1H, d, *J* = 1.6 Hz, CH_2-C17a), 4.94 (1H, d, *J* = 1.6 Hz, CH_2-C17b), 4.58 (1H, br d, *J* = 5.6 Hz,

CH-C12), 4.32–4.27 (1H, m, CH-C9), 4.12 (1H, br s, CH-C2), 4.09 (2H, br s, CH_2-C16), 3.72–3.59 (2H, m, CH_2-OEt), 3.28 (1H, dddd, *J* = 12.2, 12.2, 12.2, 6.2 Hz, CH_2-C5a), 2.97 (1H, app dd, *J* = 11.9, 7.1 Hz, CH-C1), 2.88 (1H, br d, *J* = 14.4 Hz, CH_2-C8a), 2.81 (1H, ddd, *J* = 12.7, 6.1, 2.7 Hz, CH_2-C4a), 2.45–2.35 (2H, m, CH_2-C4b, CH-C10), 2.26–2.01 (5H, m, CH_2-C5b, CH_2-C8b, CH_2-C13, CH-C14), 1.78 (3H, s, CH_3-C19), 1.25 (3H, t, *J* = 7.0 Hz, CH_3-OEt), 0.90 (9H, s, CH_3-^{t}Bu OTBS), 0.05 (3H, s, CH_3-OTBS), 0.04 (3H, s, CH_3-OTBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.7 (C-C3), 154.3 (C-C11 or C-C15), 150.4 (C-C11 or C-C15), 134.9 (C-C7), 126.8 (CH-C6), 110.1 (CH_2-C17), 92.8 (CH-C12), 88.8 (CH-C2), 86.4 (CH-C9), 64.9 (CH_2-C16), 62.1 (CH_2-OEt), 43.3 (CH-C1), 42.6 (CH_2-C4), 41.9 (CH-C10), 38.3 (CH-C14), 36.6 (CH_2-C8), 30.6 (CH_2-C13), 27.1 (CH_3-C19), 26.5 (CH_2-C5), 26.1 (CH_3-^{t}Bu OTBS), 18.6 (C-^{t}Bu OTBS), 14.7 (CH_3-OEt), –5.3 (CH_3-OTBS), –5.3 (CH_3-OTBS); $[\alpha]_D^{19}$ +12.3 (c = 1.08, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{26}H_{42}O_4SiNa$ 469.2745, found 469.2736, Δ 1.8 ppm.

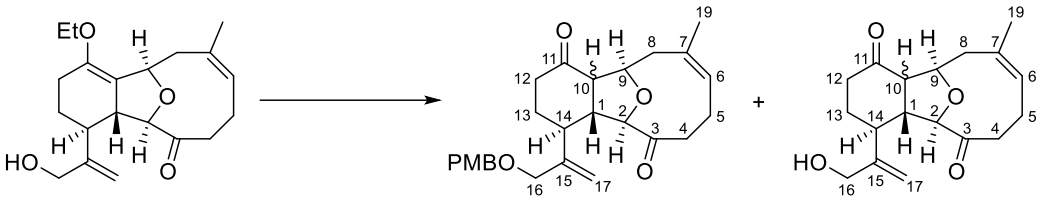
(1*R*,6*S*,7*R*,8*R*,12*Z*)-3-Ethoxy-6-(3-hydroxyprop-1-en-2-yl)-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-3,12-dien-9-one (301)



To a stirred solution of ketone **300** (20.0 mg, 0.381 mmol) in anhydrous THF (0.5 mL) at room temperature was added *tetra-N*-butylammonium fluoride (0.18 ml of a 1.0 M solution in THF, 0.18 mmol) in one portion. The resulting solution was stirred for 1 hour before the reaction mixture was diluted with water (3 mL) and diethyl ether (5 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, gradient elution from 2:1 → 1:1) to afford alcohol **301** (14 mg, 94%) as a colourless oil.

R_f = 0.54 (petroleum ether-ethyl acetate, 1:1); ν_{max} 3464, 2974, 2918, 2886, 1701, 1670, 907, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, dd, *J* = 11.4, 5.7 Hz, CH-C6), 5.15 (1H, d, *J* = 1.2 Hz, CH_2-C17a), 5.01 (1H, br s, CH_2-C17b), 4.60 (1H, dd, *J* = 5.7, 1.8 Hz, CH-C12), 4.32 (1H, ddd, *J* = 8.5, 4.1, 2.8 Hz, CH-C9), 4.15 (1H, br s, CH-C2), 4.11 (2H, br s, CH_2-C16), 3.73–3.60 (2H, m, CH_2-OEt), 3.35−3.25 (1H, m, CH_2-C5a), 2.98 (1H, app dd, *J* = 12.0, 7.1 Hz, CH-C1), 2.90 (1H, br d, *J* = 14.5 Hz, CH_2-C8a), 2.82 (1H, ddd, *J* = 12.9, 6.2, 2.7 Hz, CH_2-C4a), 2.47–2.37 (2H, m, CH_2-C4b, CH-C10), 2.28–2.19 (2H, m, CH_2-C13a, CH-C14), 2.13–2.02 (2H, m, CH_2-C5b, CH_2-C13b), 2.05 (1H, dd, *J* = 14.5, 4.1 Hz, CH_2-C8b), 1.79 (3H, s, CH_3-C19), 1.59 (1H, br s, HO-C16), 1.25 (3H, t, *J* = 7.0 Hz, CH_3-OEt); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.2 (C-C3), 154.2 (C-C11 or C-C15), 150.8 (C-C11 or C-C15), 134.9 (C-C7), 126.8 (CH-C6), 111.9 (CH_2-C17), 92.6 (CH-C12), 88.8 (CH-C2), 86.4 (CH-C9), 64.7 (CH_2-C16), 62.2 (CH_2-OEt), 43.4 (CH-C1), 42.7 (CH_2-C4), 41.8 (CH-C10), 38.8 (CH-C14), 36.5 (CH_2-C8), 30.3 (CH_2-C13), 27.2 (CH_3-C19), 26.4 (CH_2-C5), 14.7 (CH_3-OEt); $[\alpha]_D^{20}$ –15.0 (c = 0.420, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{20}H_{28}O_4Na$ 355.1867, found 355.1880, Δ 3.5 ppm.

(1*R*,6*S*,7*R*,8*R*,12*Z*)-6-{3-[(4-Methoxyphenyl)methoxy]prop-1-en-2-yl}-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-ene-3,9-dione (303) and (1*R*,6*S*,7*R*,8*R*,12*Z*)-6-(3-Hydroxyprop-1-en-2-yl)-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-ene-3,9-dione (304)



To a stirred solution of alcohol **298** (21 mg, 63 μmol) in anhydrous dichloromethane (1.3 mL) at room temperature was added 4-methoxybenzyl-2,2,2-trichloroacetimidate (18 μL, 88 μmol) and CSA (1.4 mg, 6.0 μmol) in one portion. The reaction mixture was left to stir for 16 hours before the reaction was quenched by the addition of saturated aqueous solution of ammonium chloride (3 mL) and diluted with diethyl ether (5 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 15:1 → 2:1) to afford diones **303** (13 mg, 49%) as a colourless wax and **304** (4 mg, 21%) as a colourless solid.

303: R_f = 0.44 (petroleum ether-ethyl acetate, 2:1); ν_{max} 3373, 3321, 3242, 3184, 2955, 2924, 2855, 1694, 1612, 1512, 831, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (2H, m, 2 × CH-Ar PMB), 6.91–6.86 (2H, m, 2 × CH-Ar PMB), 5.53 (1H, dd, *J* = 11.3, 5.8 Hz, CH-C6), 5.20 (1H, d, *J* = 1.1 Hz, CH_2-C17a), 5.09 (1H, br s, CH_2-C17b), 4.52 (1H, ddd, *J* = 8.7, 4.7, 2.8 Hz, CH-C9), 4.46 (1H, d, *J* = 11.5 Hz, CH_2-PMBa), 4.41 (1H, d, *J* = 11.5 Hz, CH_2-PMBb), 4.18 (1H, br s, CH-C2), 4.00 (1H, d, *J* = 12.6 Hz, CH_2-C16a), 3.92 (1H, d, *J* = 12.6 Hz, CH_2-C16b), 3.81 (3H, s, CH_3-OMe PMB), 3.18–3.04 (1H, m, CH_2-C5a), 2.86–2.78 (1H, m, CH_2-C8a), 2.81 (1H, ddd, *J* = 12.6, 5.7, 3.3 Hz, CH_2-C4a), 2.64 (1H, dd, *J* = 8.5, 7.5 Hz, CH-C10), 2.46–2.34 (4H, m, CH_2-C4b, CH_2-C12, CH-C14), 2.14–2.03 (2H, m, CH_2-C5b, CH_2-C13a), 1.88–1.81 (1H, m, CH_2-C8b), 1.83 (3H, s, CH_3-C19), 1.82–1.70 (1H, m, CH_2-C13b); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0 (C-C3), 209.5 (C-C11), 159.4 (C-Ar PMB), 147.0 (C-C15), 134.1 (C-C7), 130.3 (C-Ar PMB), 129.5 (2 × CH-Ar PMB), 127.4 (CH-C6), 114.4 (CH_2-C17), 114.0 (2 × CH-Ar PMB), 89.4 (CH-C2), 82.3 (CH-C9), 72.2 (CH_2-PMB), 71.8 (CH_2-C16), 55.4 (CH_3-OMe PMB), 52.6 (CH-C10), 46.4 (CH-C1),

42.3 (CH_2-C4), 40.5 (CH-C14), 38.8 (CH_2-C12), 35.5 (CH_2-C8), 30.5 (CH_2-C13), 27.1 (CH_3-C19), 26.4 (CH_2-C5); $[\alpha]_D^{19}$ +1.6 (c = 0.25, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{26}H_{32}O_5Na$ 447.2133, found 447.2142, Δ 2.1 ppm.

304: R_f = 0.23 (petroleum ether-ethyl acetate, 1:1); m.p. 90–92 °C; ν_{max} 3321, 2922, 2868, 1699, 1643, 908, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (1H, dd, *J* = 11.2, 5.8 Hz, CH-C6), 5.20 (1H, d, *J* = 0.9 Hz, CH_2-C17a), 5.06 (1H, br s, CH_2-C17b), 4.56 (1H, ddd, *J* = 8.0, 4.9, 2.8 Hz, CH-C9), 4.20–4.12 (3H, m, CH-C2, CH_2-C16), 3.31 (1H, dd, *J* = 12.0, 7.6 Hz, CH-C1), 3.16 (1H, m, CH_2-C5a), 2.85–2.78 (1H, m, CH_2-C8a), 2.83 (1H, ddd, *J* = 12.6, 5.5, 3.6 Hz, CH_2-C4a), 2.66 (1H, dd, *J* = 7.9, 7.9 Hz, CH-C10), 2.49–2.44 (2H, m, CH_2-C12), 2.43–2.34 (2H, m, CH_2-C4b, CH-C14), 2.13–2.04 (2H, m, CH_2-C5b, CH_2-C13a), 1.86 (1H, dd, *J* = 14.8, 4.9 Hz, CH_2-C8b), 1.85–1.80 (1H, m, CH_2-C13b), 1.83 (3H, s, CH_3-C19), 1.70 (1H, br s, HO-C16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.6 (C-C3), 209.2 (C-C11), 149.6 (C-C15), 134.1 (C-C7), 127.4 (CH-C6), 113.0 (CH_2-C17), 89.4 (CH-C2), 82.1 (CH-C9), 64.7 (CH_2-C16), 52.7 (CH-C10), 46.5 (CH-C1), 42.3 (CH_2-C4), 41.1 (CH-C14), 38.7 (CH_2-C12), 35.5 (CH_2-C8), 30.3 (CH_2-C13), 27.0 (CH_3-C19), 26.2 (CH_2-C5); $[\alpha]_D^{20}$ –32.3 (c = 0.420, $CHCl_3$); HRMS (ESI+) $[M]^+$ calcd. for $C_{18}H_{24}O_4Na$ 327.1560, found 327.1567, Δ 2.1 ppm

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7. Appendix

Appendix 1: Comparison of ^{13}C NMR Data for Isolated and Synthetic Asbestinin 21 (**288**) and Synthetic 7-*epi*-Asbestinin 21 (**223**)

Appendix 2: ^{1}H and ^{13}C NMR Spectra of Compound **258**

Appendix 3: ^{1}H and ^{13}C NMR Spectra of Compound **221**

Appendix 4: ^{1}H and ^{13}C NMR Spectra of Compound **260**

Appendix 5: ^{1}H and ^{13}C NMR Spectra of Compound **262**

Appendix 6: ^{1}H and ^{13}C NMR Spectra of Compound **263**

Appendix 7: ^{1}H and ^{13}C NMR Spectra of Compound **222**

Appendix 8: ^{1}H and ^{13}C NMR Spectra of Compound **265**

Appendix 9: ^{1}H and ^{13}C NMR Spectra of 11-Acetoxy-4-Deoxyasbestinin D (**18**)

Appendix 10: ^{1}H and ^{13}C NMR Spectra of 4-Deoxyasbestinin C (**19**)

Appendix 11: ^{1}H and ^{13}C NMR Spectra of Compound **269**

Appendix 12: ^{1}H and ^{13}C NMR Spectra of Compound **270**

Appendix 13: ^{1}H, ^{13}C, HSQC and HMBC NMR Spectra of Compound **275**

Appendix 14: ^{1}H, ^{13}C and HMBC NMR Spectra of Asbestinin 20 (**14**)

Appendix 15: ^{1}H and ^{13}C NMR Spectra of 6-*epi*-Asbestinin 20 (**16**)

Appendix 16: ^{1}H and ^{13}C NMR Spectra of Asbestinin 10 (**15**) ($CDCl_3$)

Appendix 17: ^{1}H and ^{13}C NMR Spectra of Asbestinin 10 (**15**) (C_6D_6)

Appendix 18: ^{1}H and ^{13}C NMR Spectra of Compound **284**

Appendix 19: ^{1}H, ^{13}C, HSQC and HMBC NMR Spectra of Asbestinin 21 (**288**)

Appendix 20: ^{1}H and ^{13}C NMR Spectra of 7-*epi*-Asbestinin 21 (**223**)

Appendix 21: ^{1}H, ^{13}C and HMBC NMR Spectra of Asbestinin 23 (**266**)

Appendix 22: ^{1}H and ^{13}C NMR Spectra of 7-*epi*-Asbestinin 23 (**289**)

Appendix 23: ^{1}H and ^{13}C NMR Spectra of Compound **290**

Appendix 24: ^{1}H and ^{13}C NMR Spectra of Compound **292**

Appendix 25: X-ray Crystallography Data of Compound **262**

Appendix 26: X-ray Crystallography Data of Compound **222**

Appendix 27: X-ray Crystallography Data of Compound **269**

Appendix 28: X-ray Crystallography Data of Compound **270**

Appendix 29: X-ray Crystallography Data of Compound **14**

Appendix 30: X-ray Crystallography Data of Compound **275**

Appendix 31: X-ray Crystallography Data of Compound **16**

Appendix 32: X-ray Crystallography Data of Compound **290**

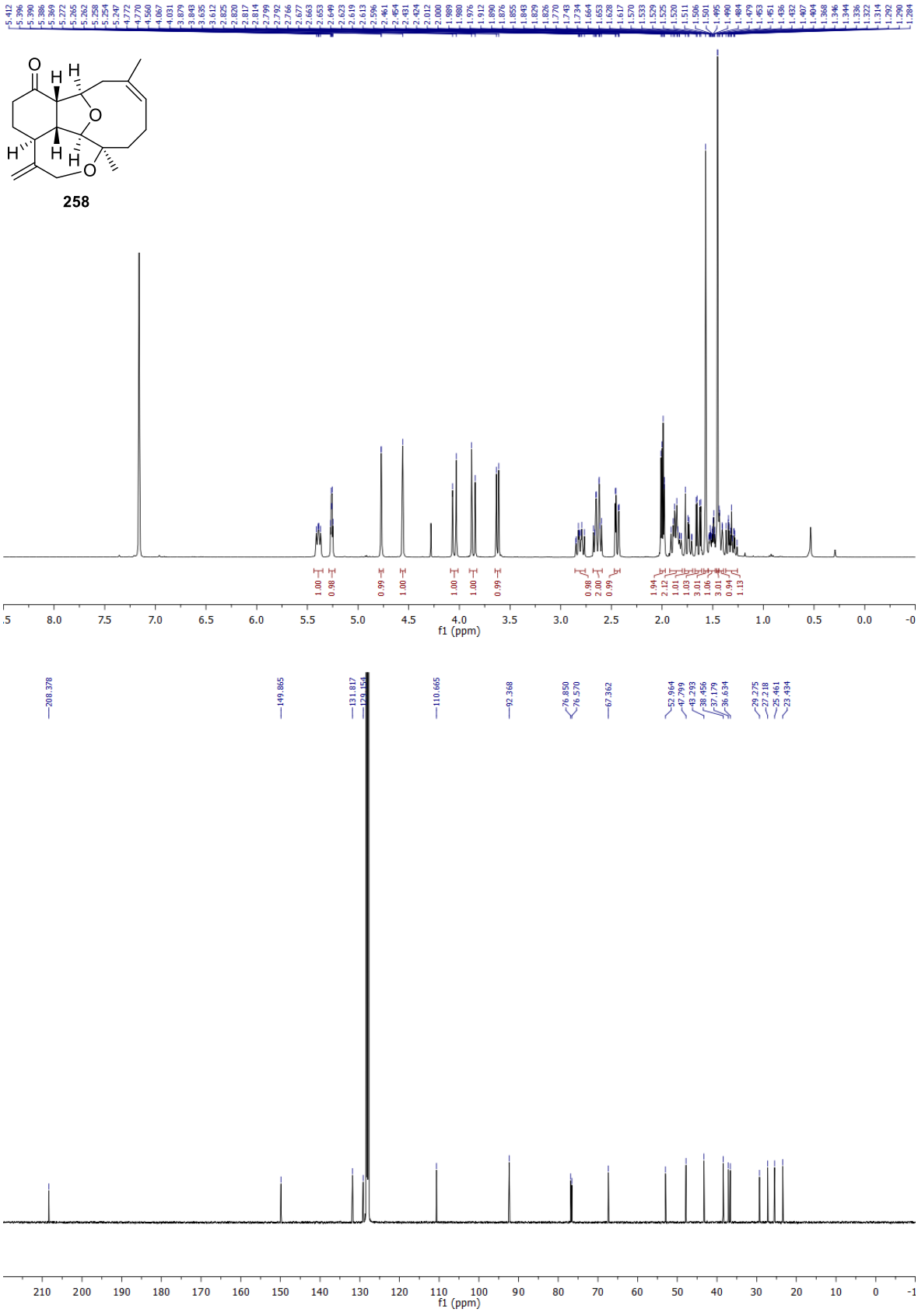
Appendix 33: X-ray Crystallography Data of Compound **292**

Appendix 1: Comparison of ^{13}C NMR Data for Isolated and Synthetic Asbestinin 21 (**288**) and Synthetic 7-*epi*-Asbestinin 21 (**223**)[3]

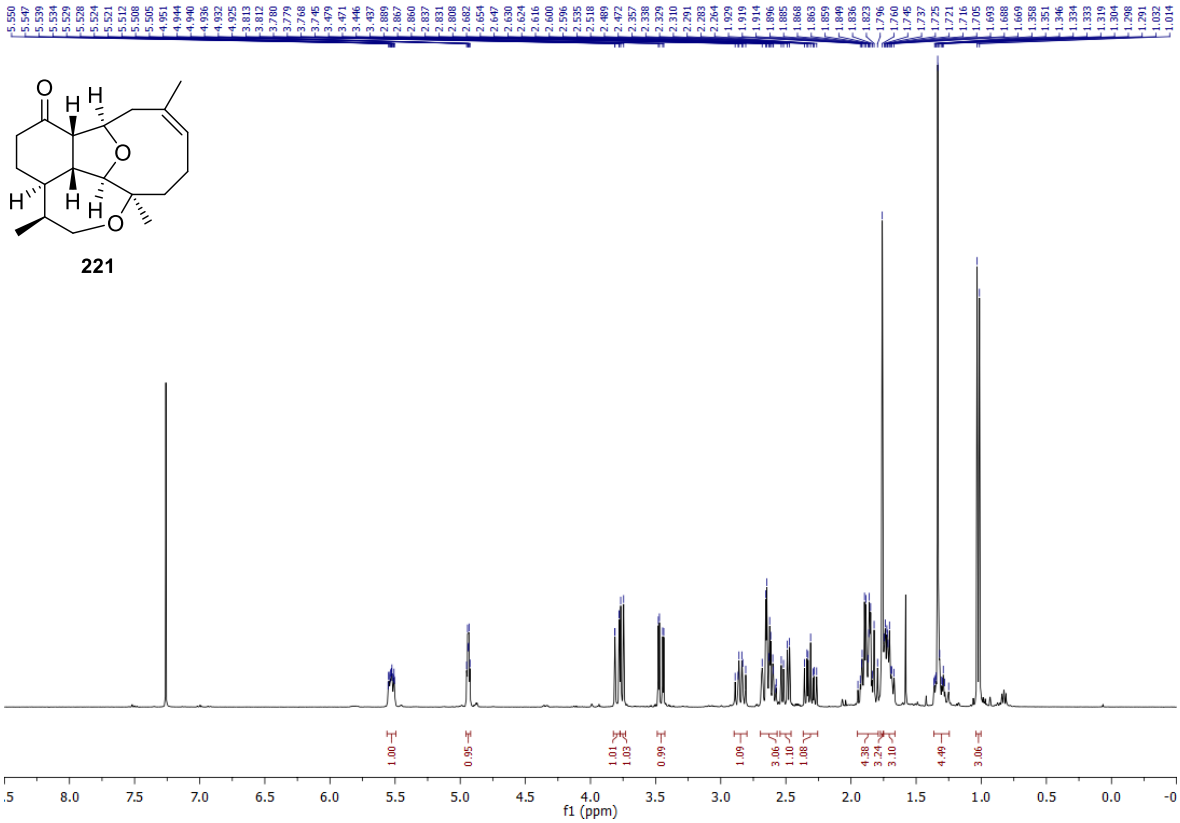
Carbon	Asbestinin 21 (*isolated*)[10]	Asbestinin 21 (synthetic)	7-*epi*-Asbestinin 21
1	38.0	37.9	40.0
2	93.6	93.5	93.6
3	77.2	77.0	76.6
4	34.0	33.9	36.9
5	36.2	36.1	32.7
6	210.8	210.6	214.1
7	76.3	76.2	79.6
8	49.3	49.2	46.9
9	78.2	78.2	78.8
10	47.7	47.5	46.9
11	72.8	72.7	73.6
12	31.5	31.4	31.2
13	31.5	31.4	32.0
14	38.0	37.9	37.3
15	36.5	36.4	36.9
16	68.2	68.1	68.9
17	10.9	10.9	11.0
18	22.5	22.5	25.5
19	27.7	27.7	28.2
20	17.3	17.2	17.8
21	170.8	170.9	171.2
22	21.3	21.4	21.2

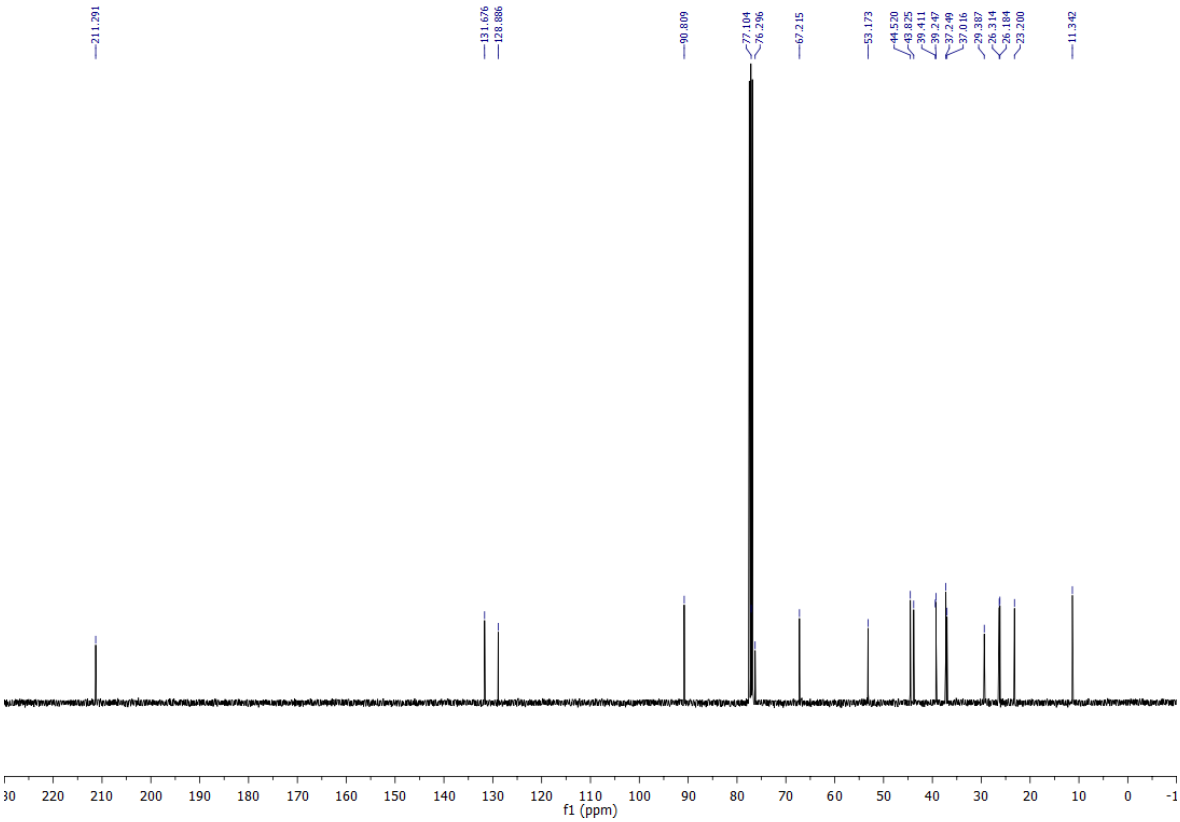
[3] Chemical shifts in ppm relative to $CDCl_3$ (77.0) on the δ scale

Appendix 2: ^{1}H and ^{13}C NMR Spectra of Compound **258**

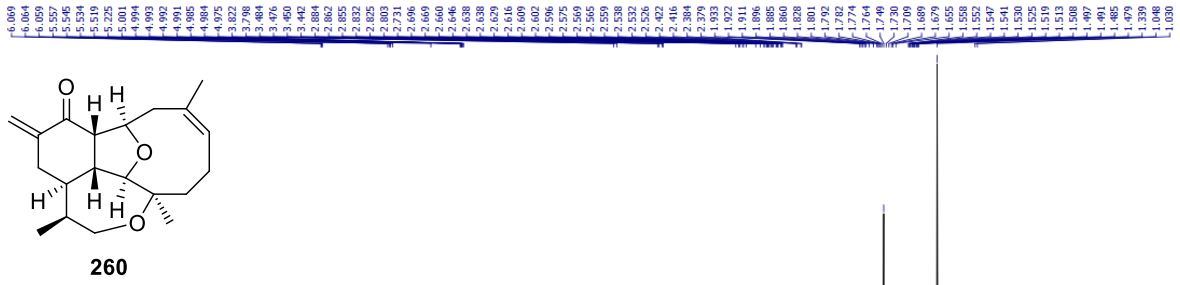


Appendix 3: ^{1}H and ^{13}C NMR Spectra of Compound **221**

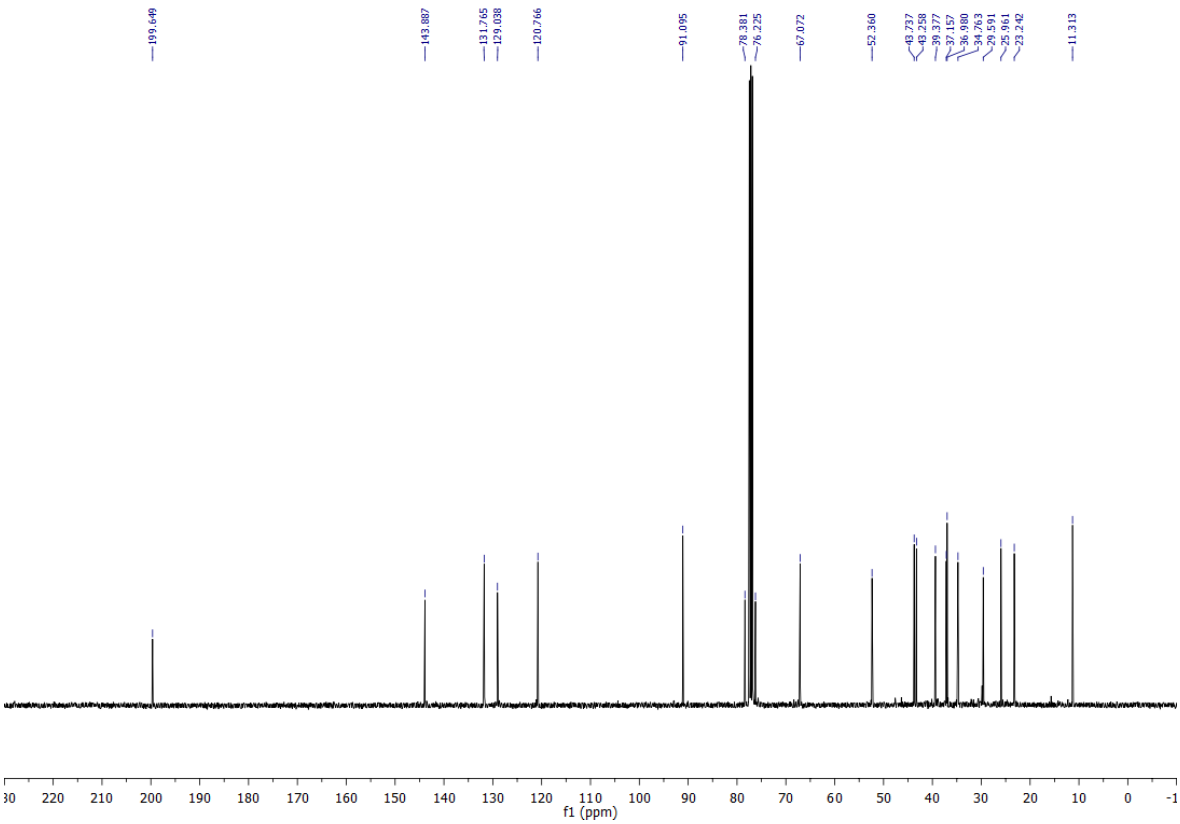




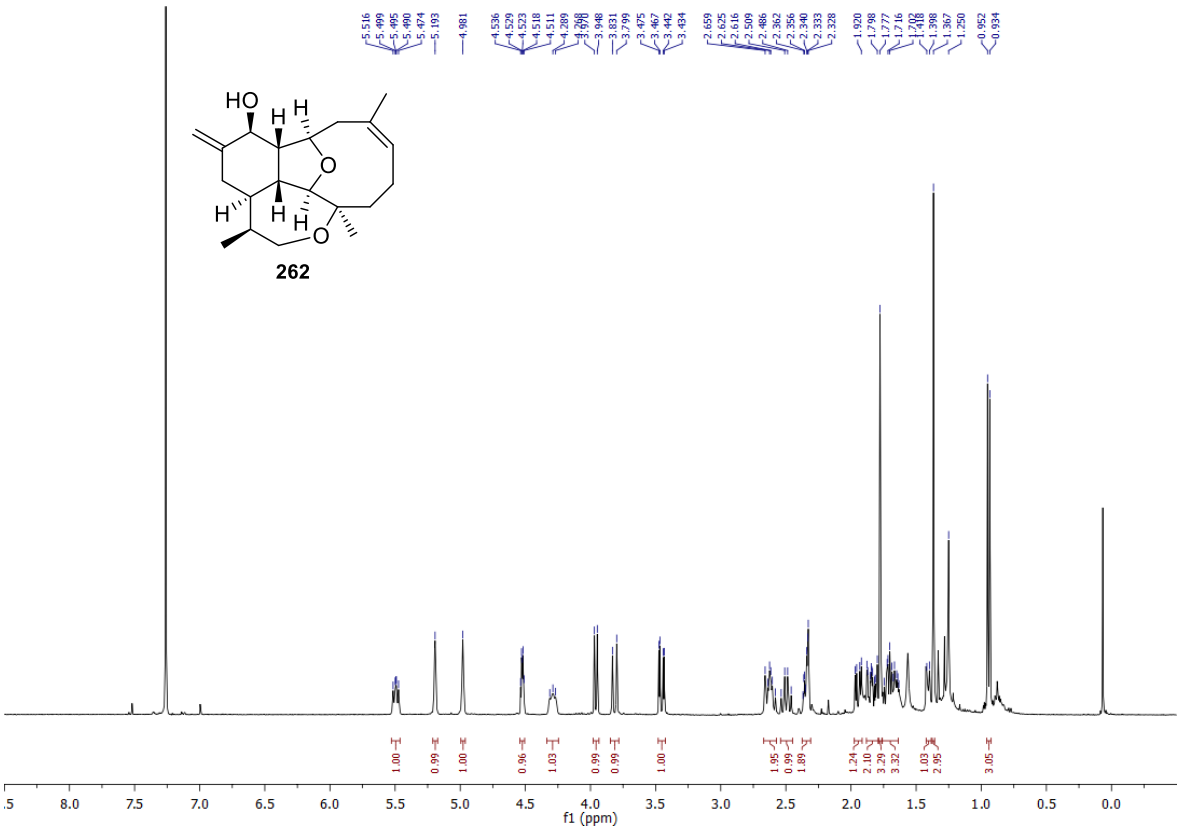
Appendix 4: ^{1}H and ^{13}C NMR Spectra of Compound **260**

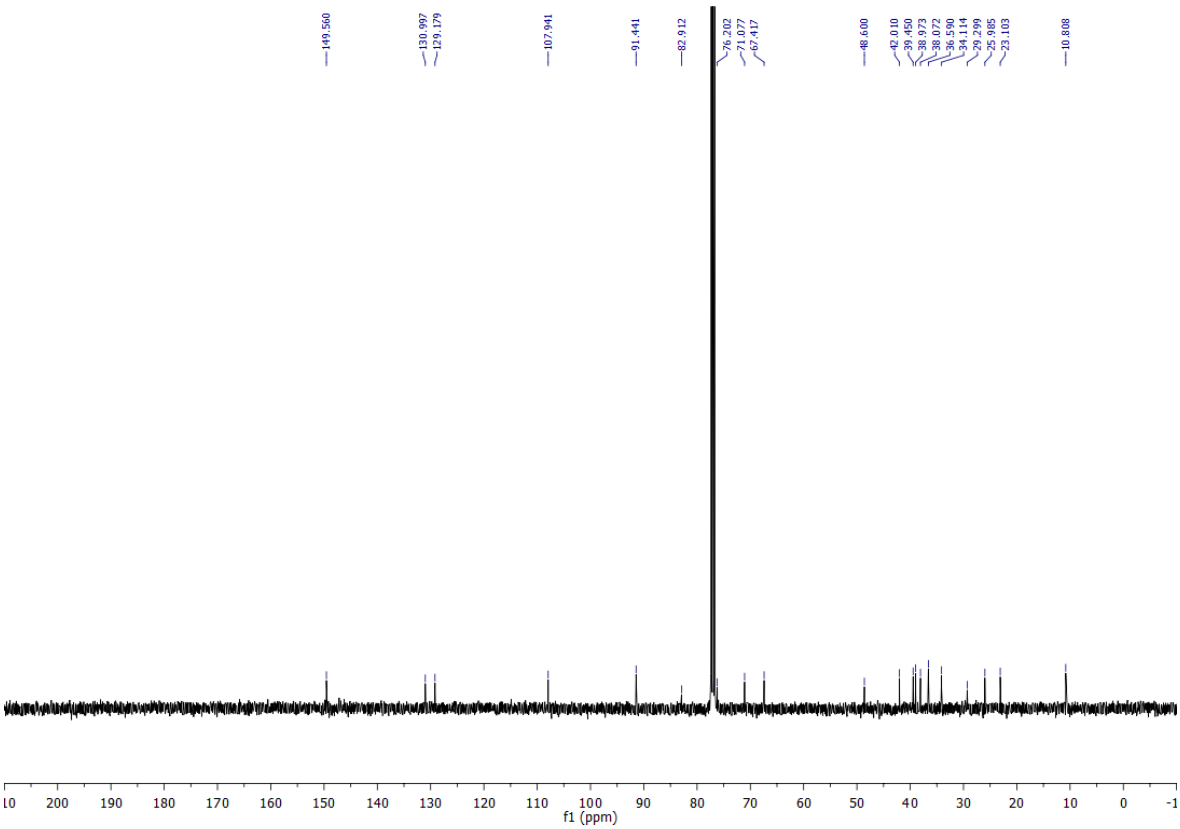


260

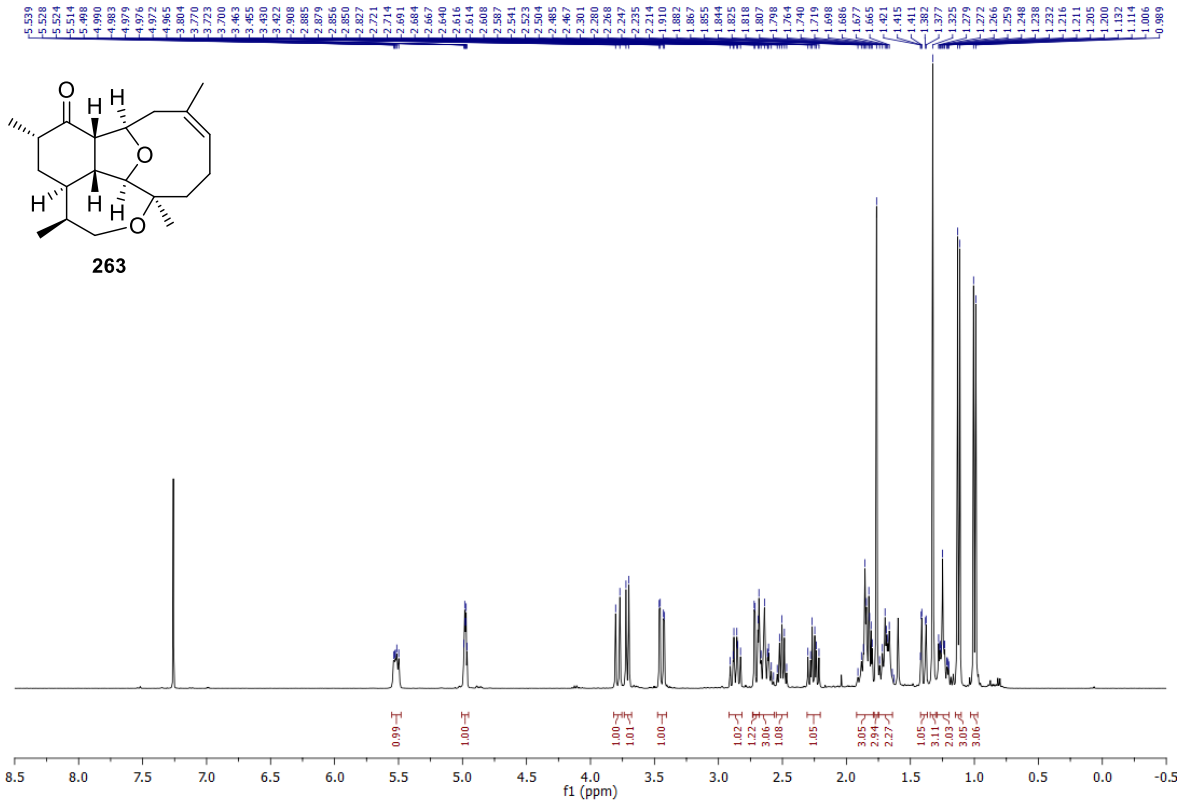


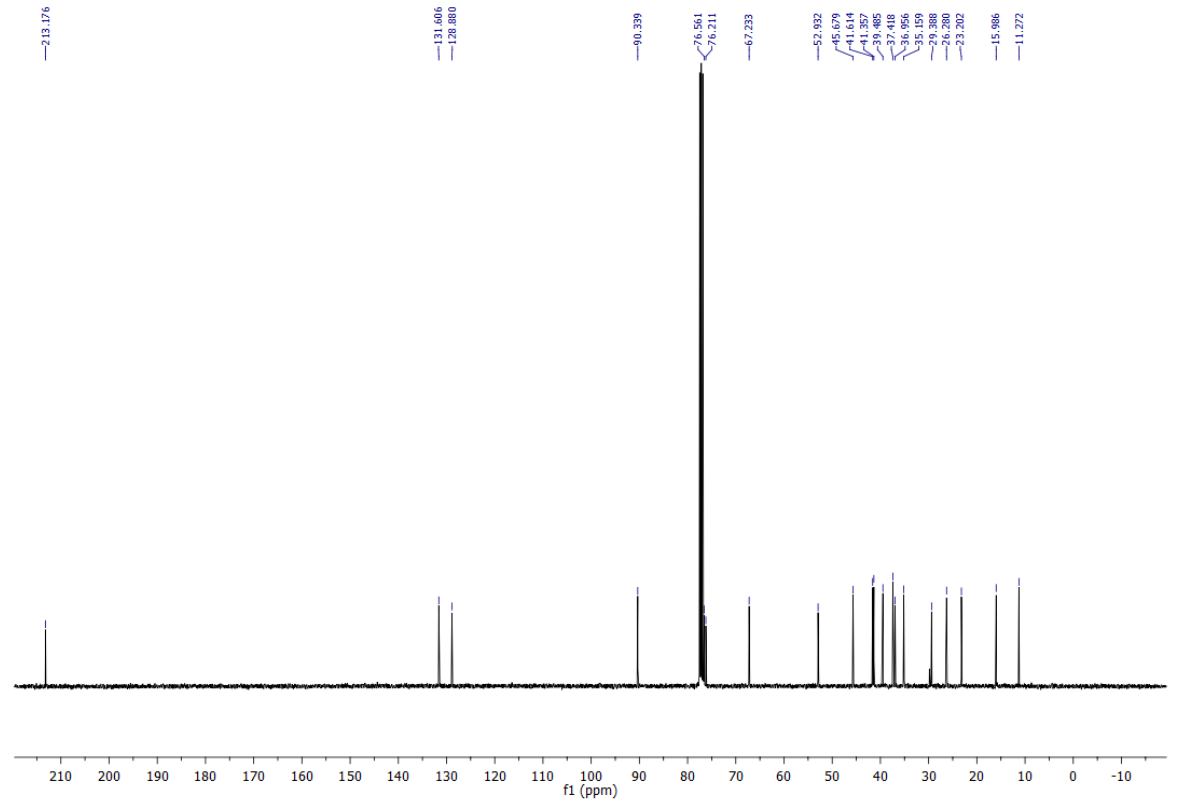
Appendix 5: ^{1}H and ^{13}C NMR Spectra of Compound **262**



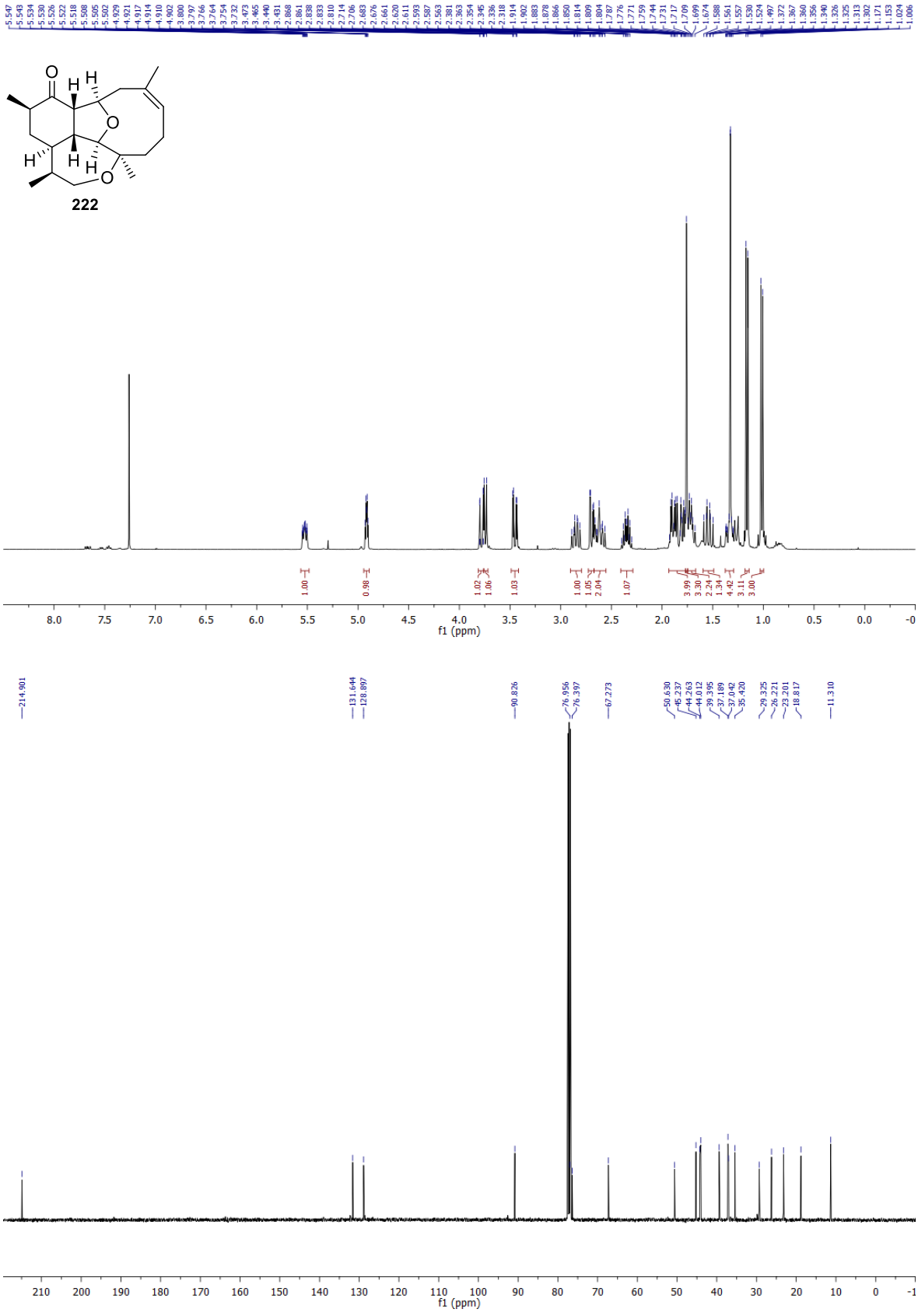


Appendix 6: ^{1}H and ^{13}C NMR Spectra of Compound **263**

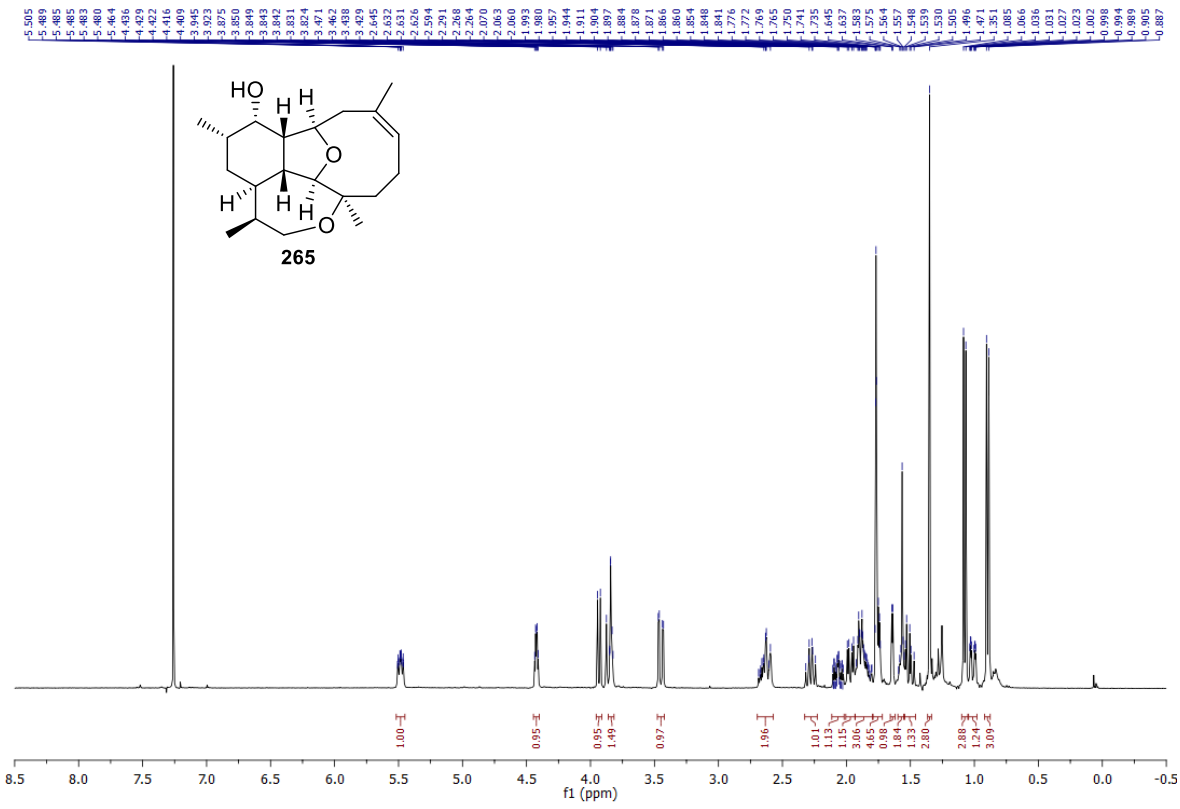


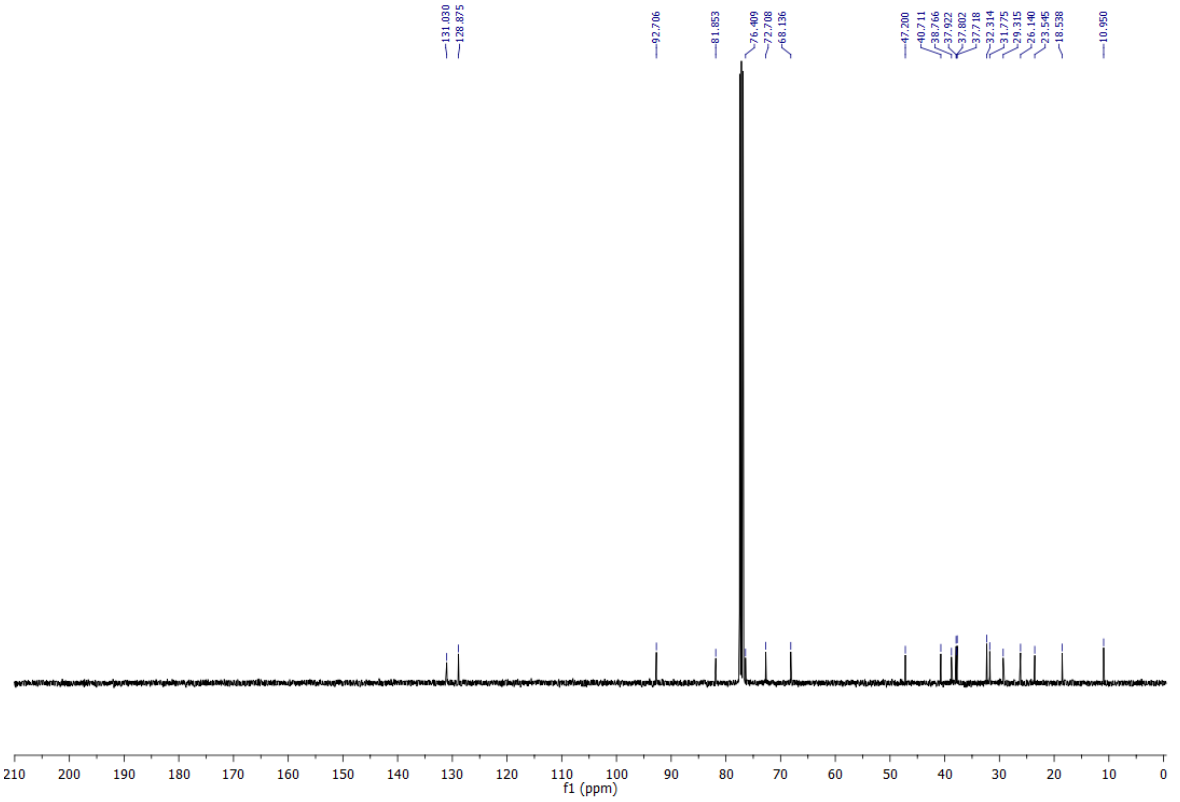


Appendix 7: ^{1}H and ^{13}C NMR Spectra of Compound **222**

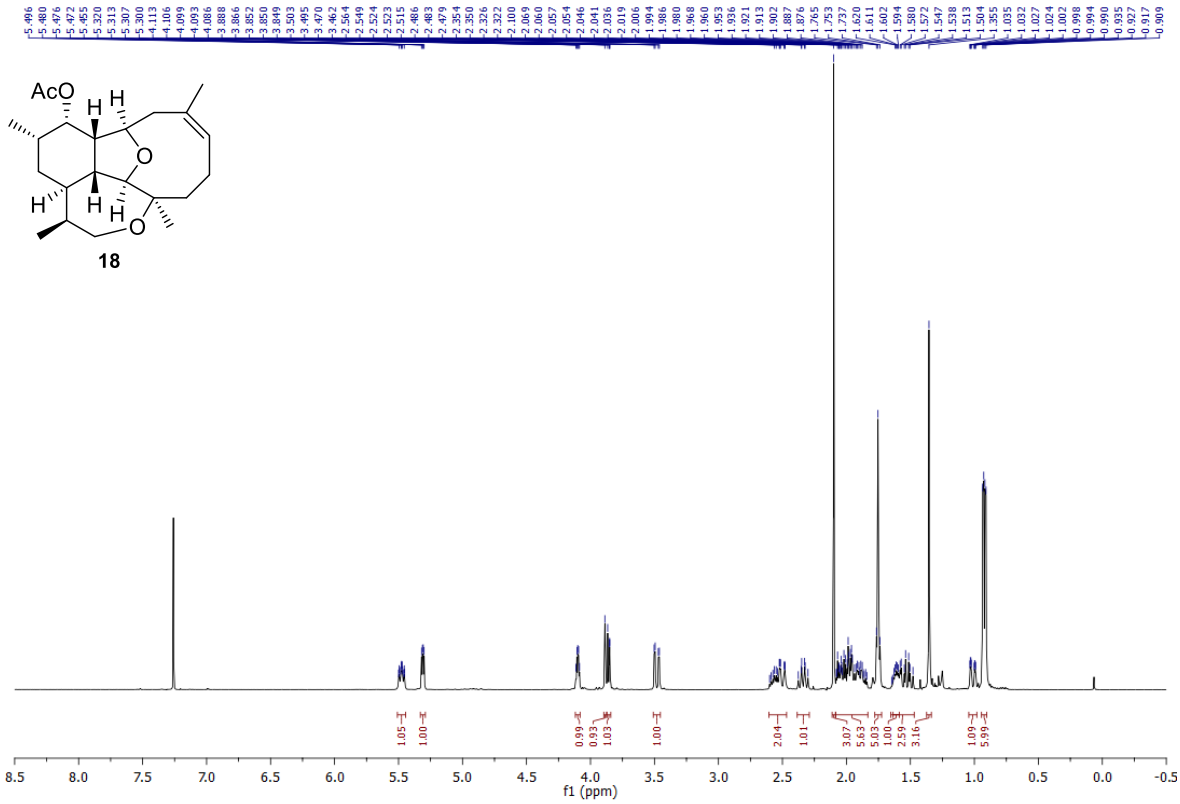


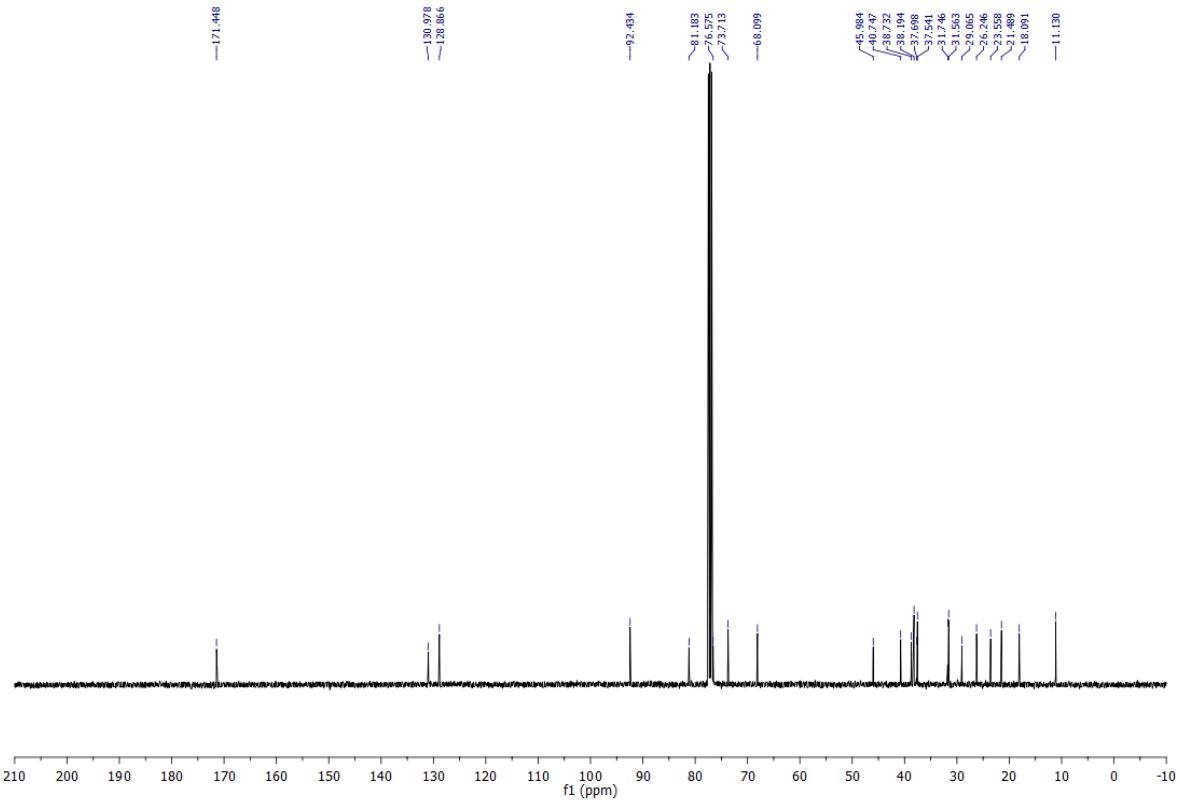
Appendix 8: ^{1}H and ^{13}C NMR Spectra of Compound **265**



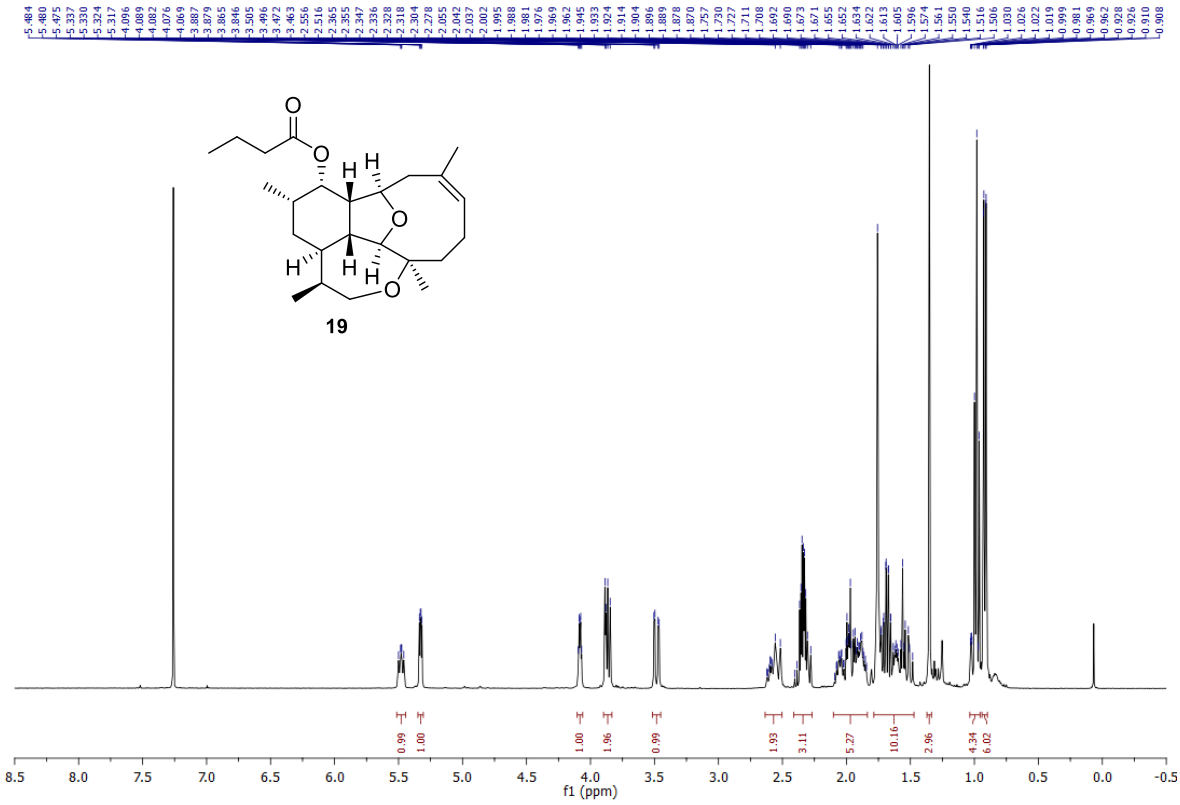


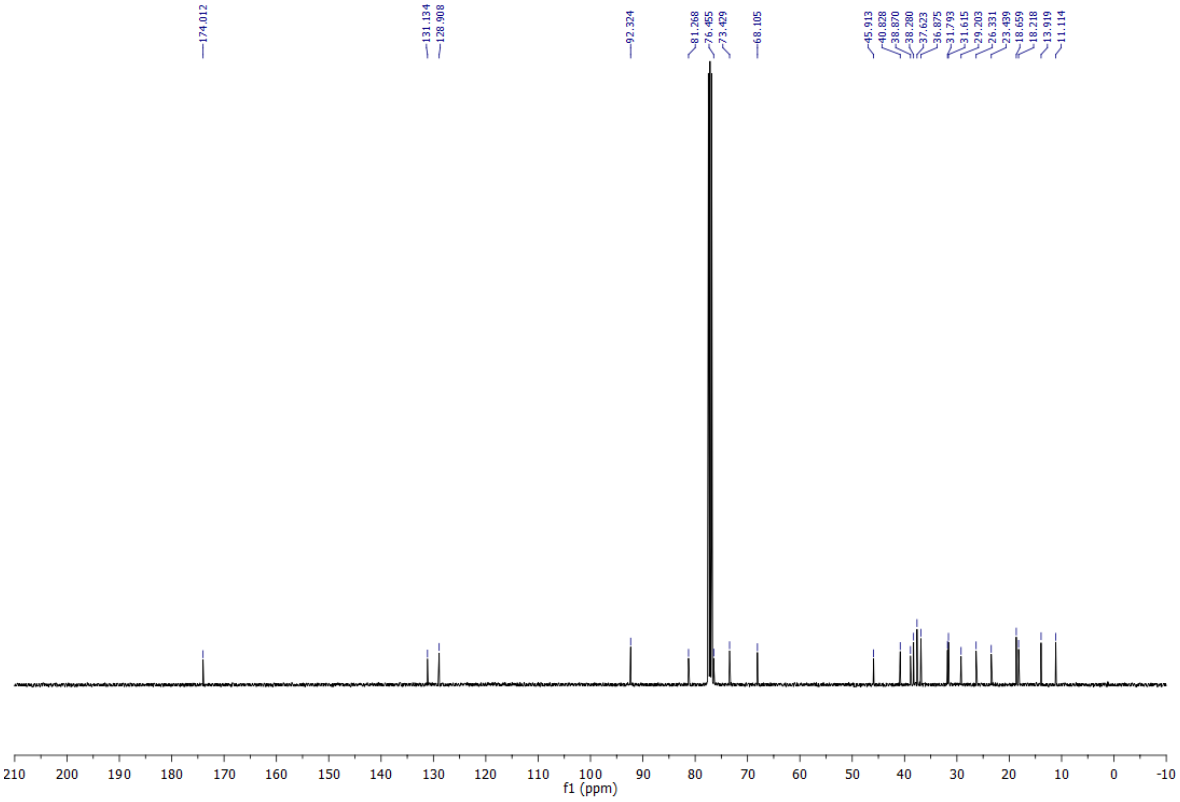
Appendix 9: ^{1}H and ^{13}C NMR Spectra of 11-Acetoxy-4-deoxyasbestinin D (**18**)



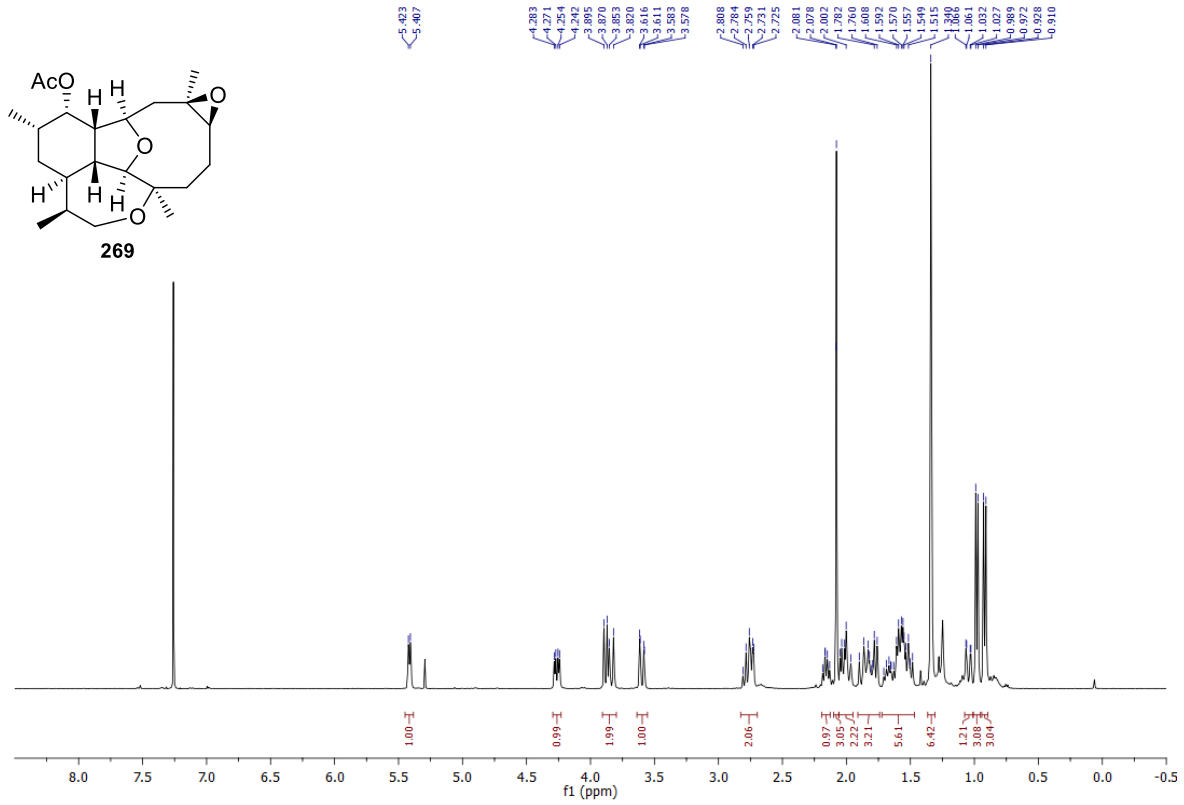


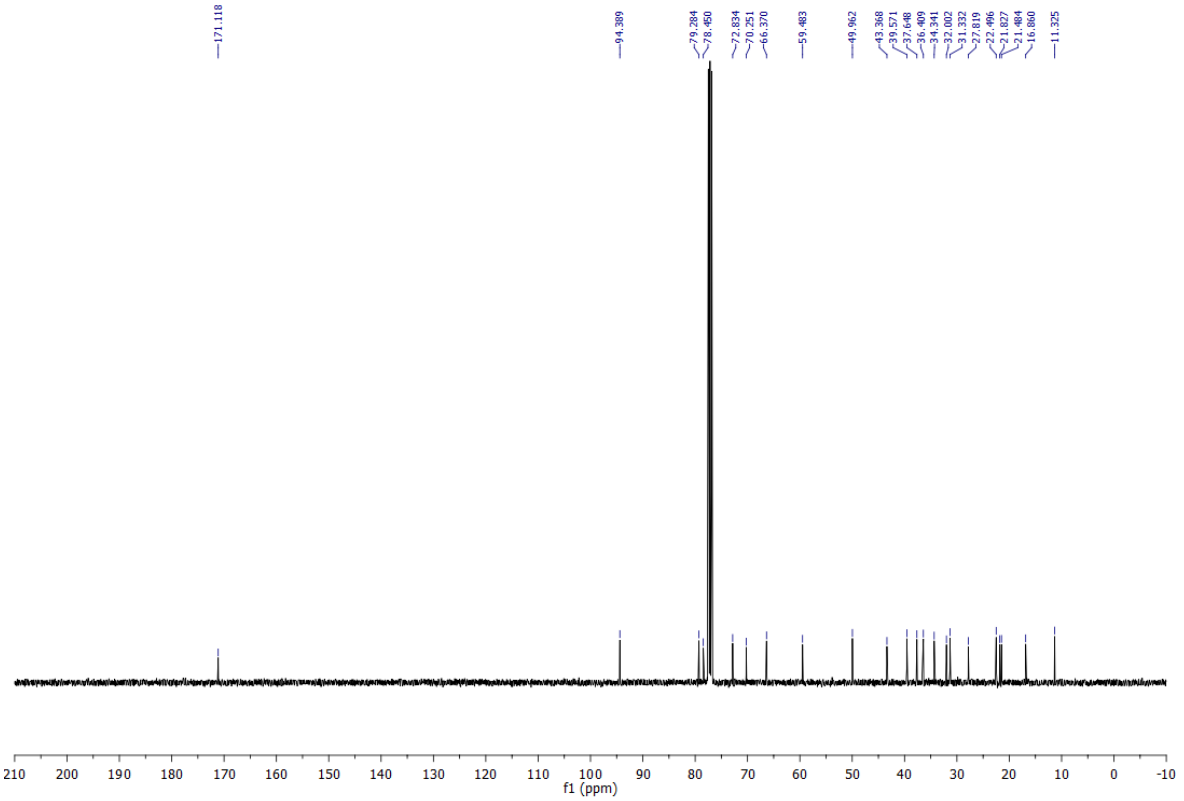
Appendix 10: ^{1}H and ^{13}C NMR Spectra of 4-Deoxyasbestinin C (**19**)



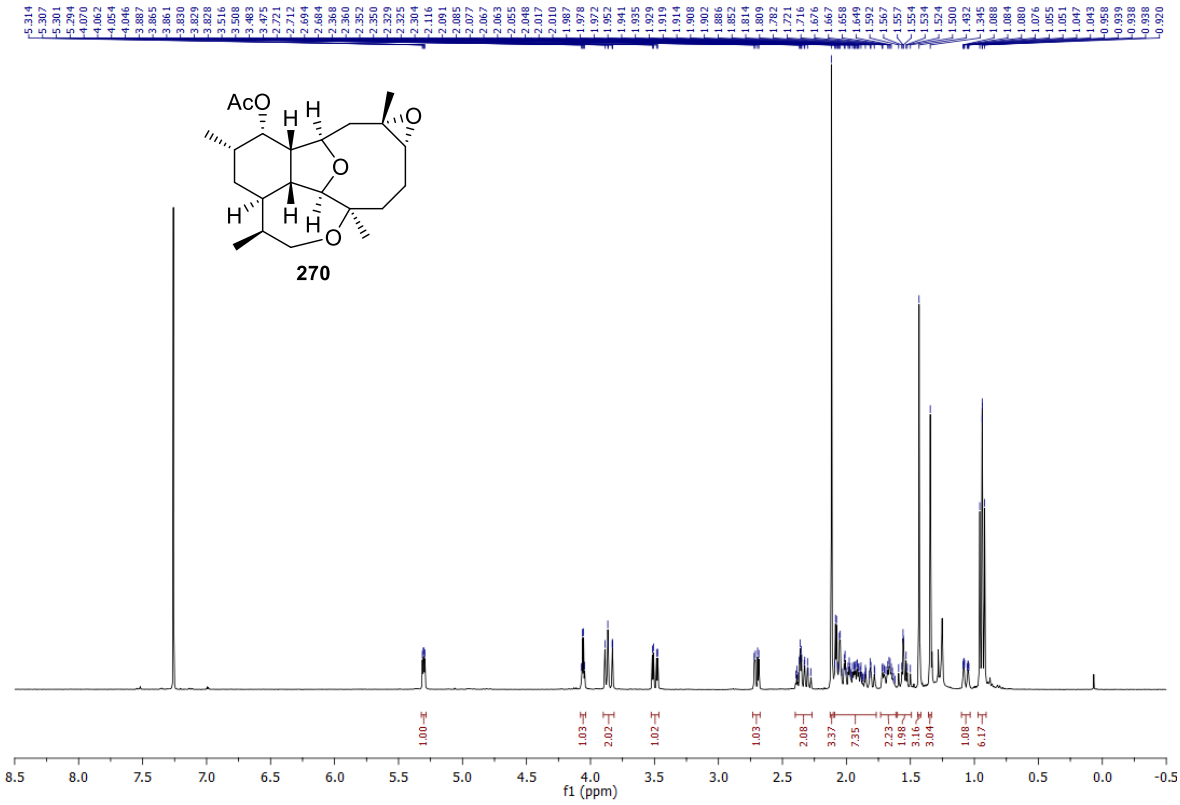


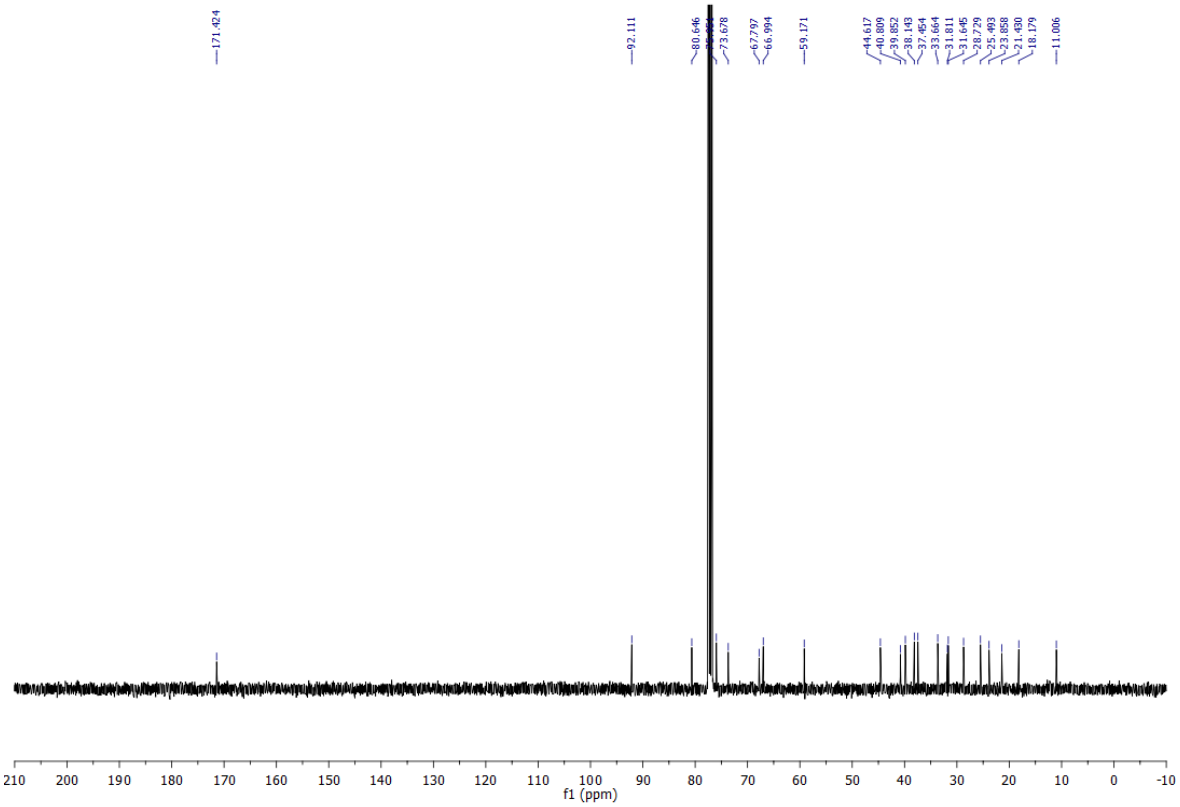
Appendix 11: ^{1}H and ^{13}C NMR Spectra of Compound **269**



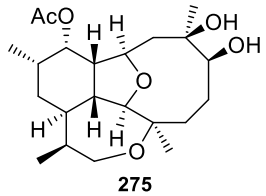


Appendix 12: ^{1}H and ^{13}C NMR Spectra of Compound **270**

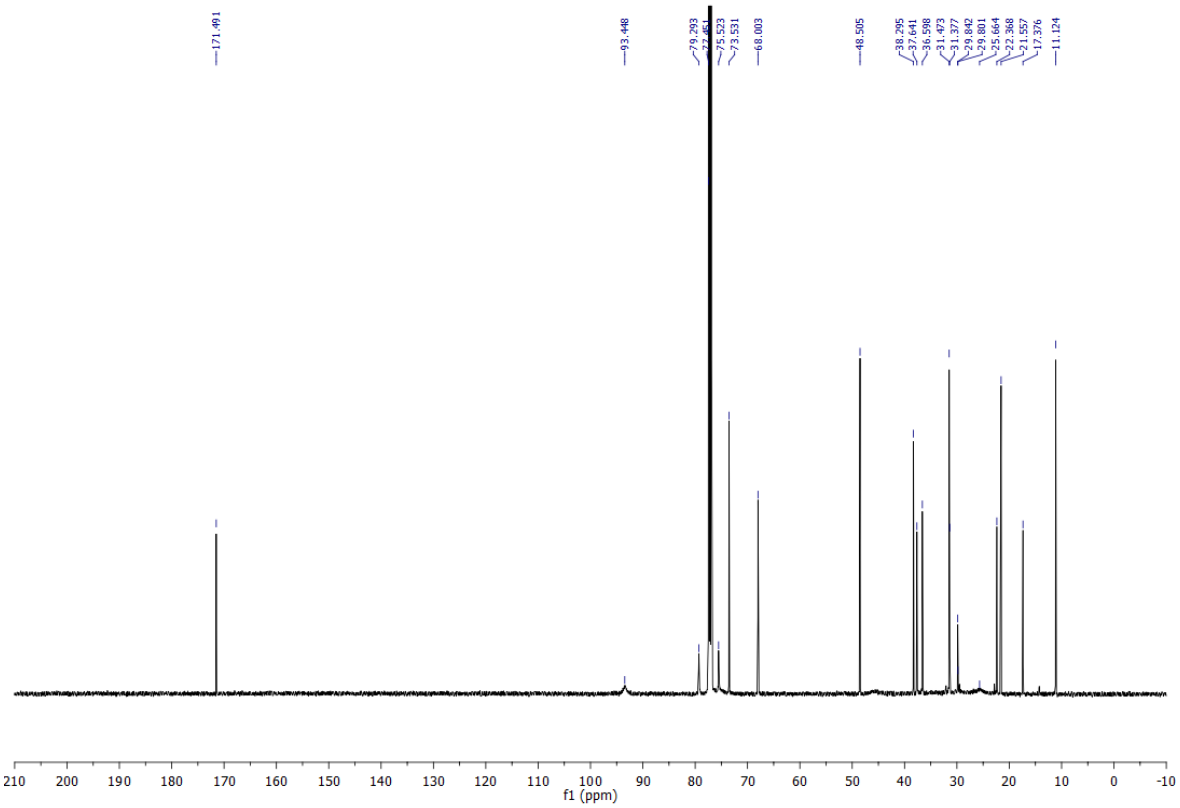


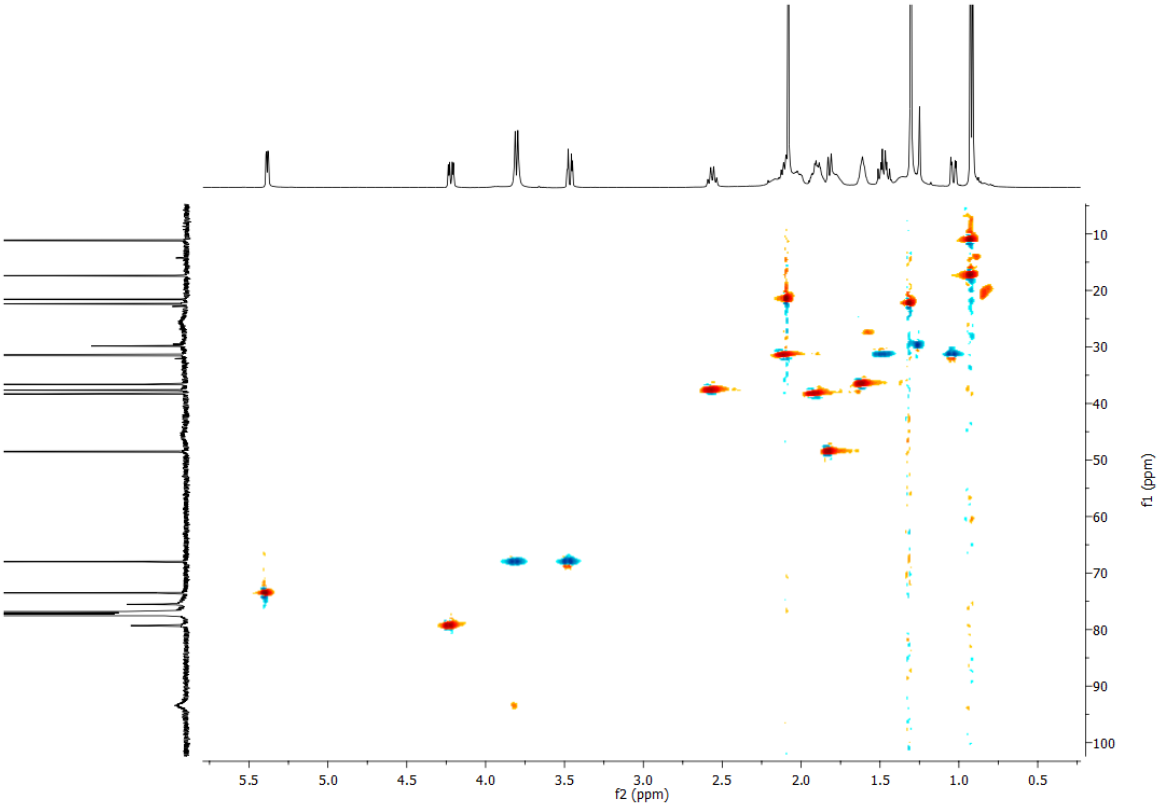


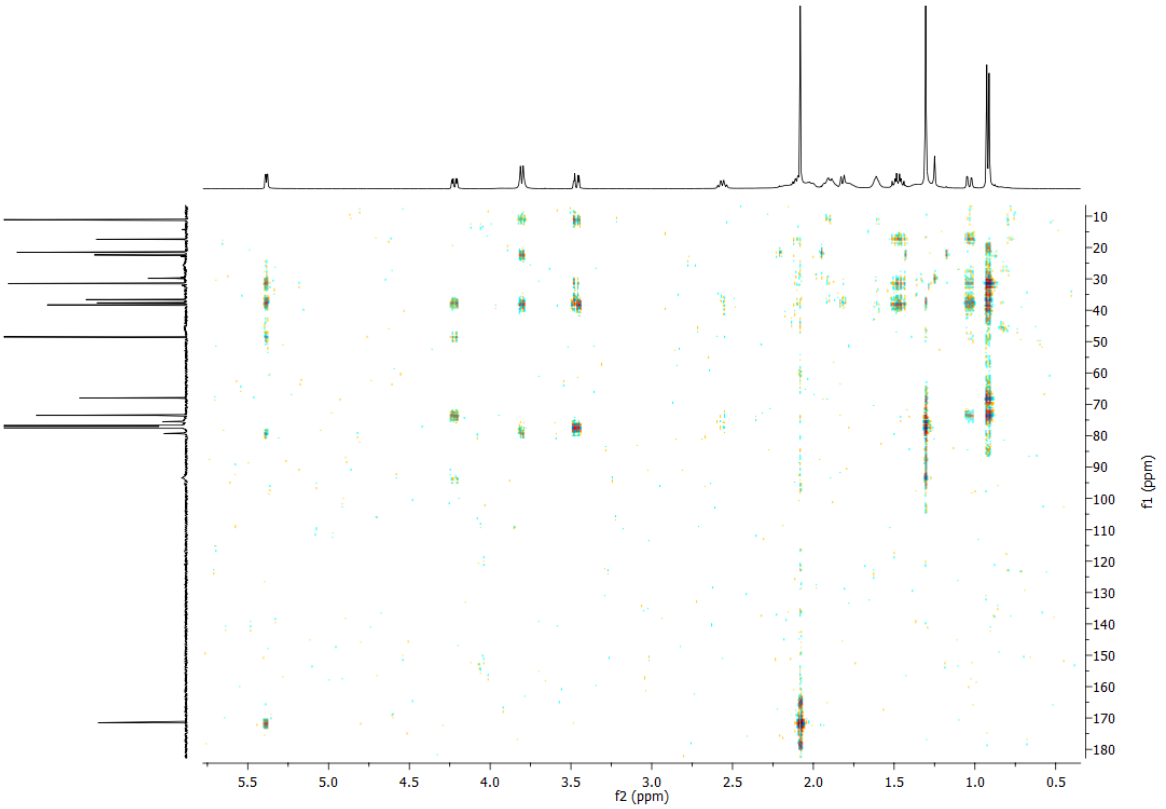
Appendix 13: ^{1}H,^{13}C, HSQC and HMBC NMR Spectra of Compound **275**



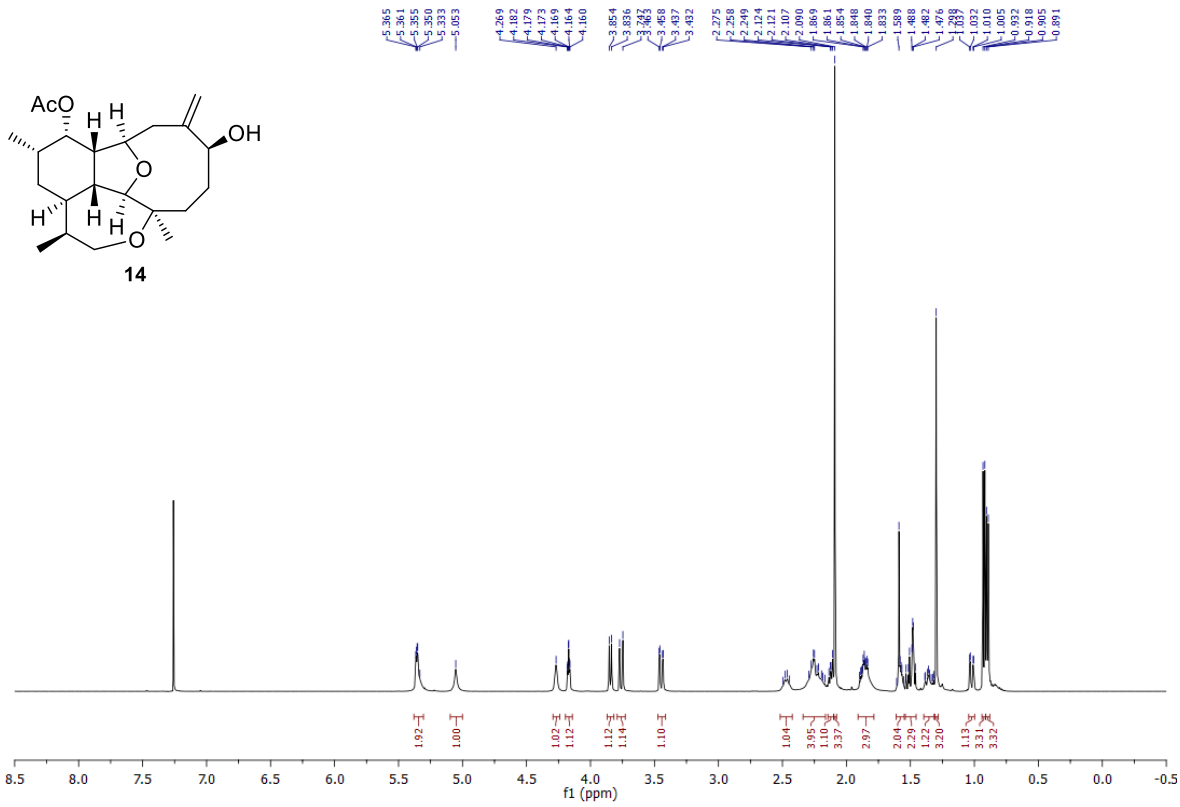
275

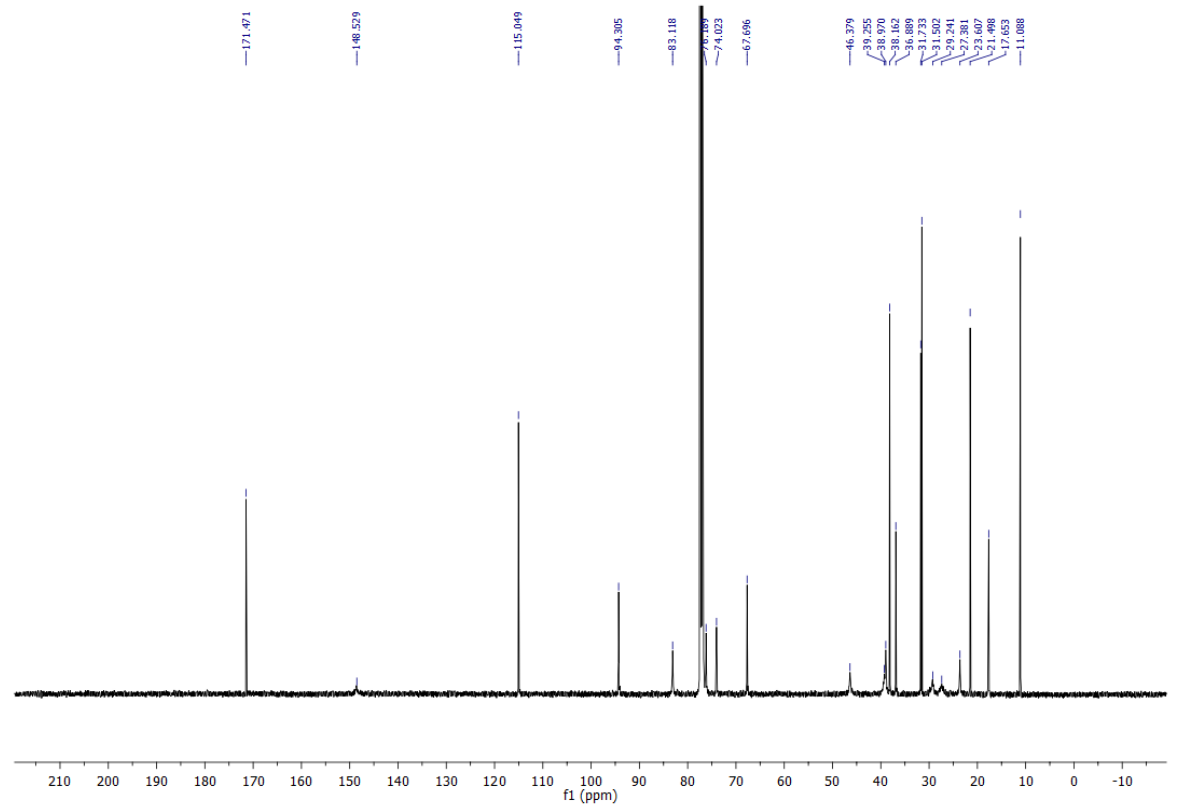


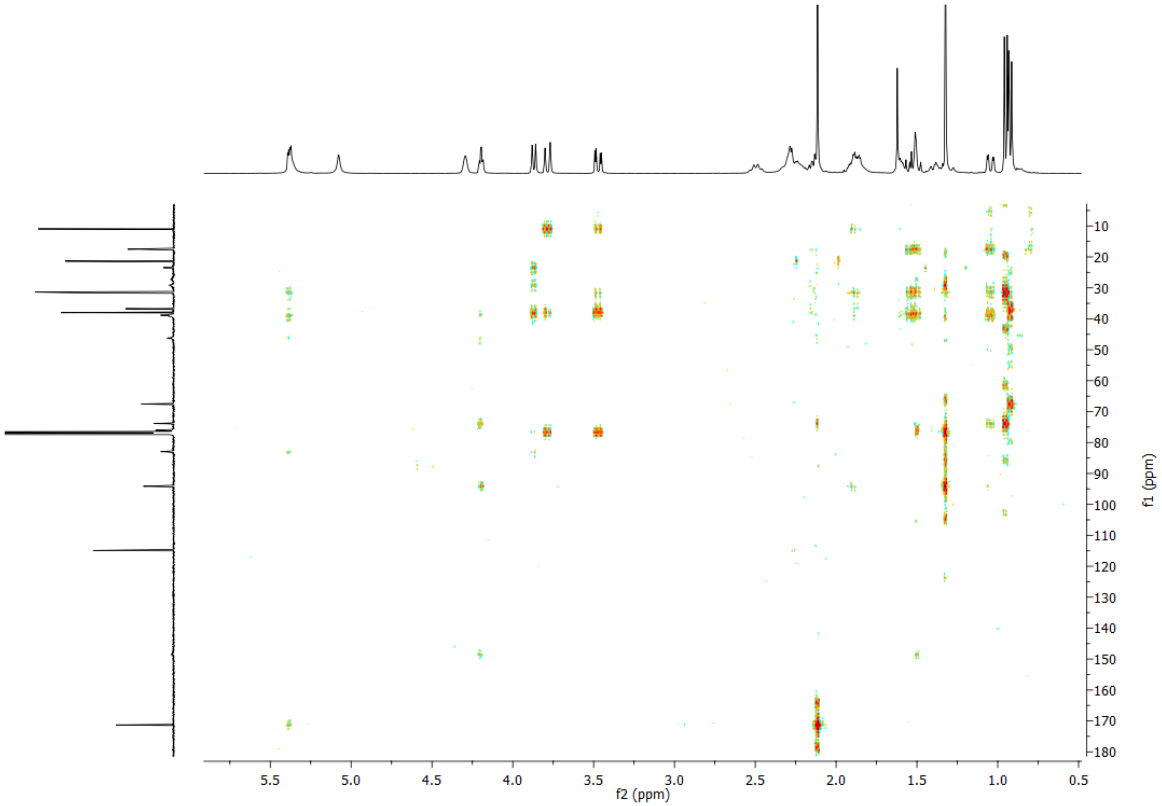

f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)

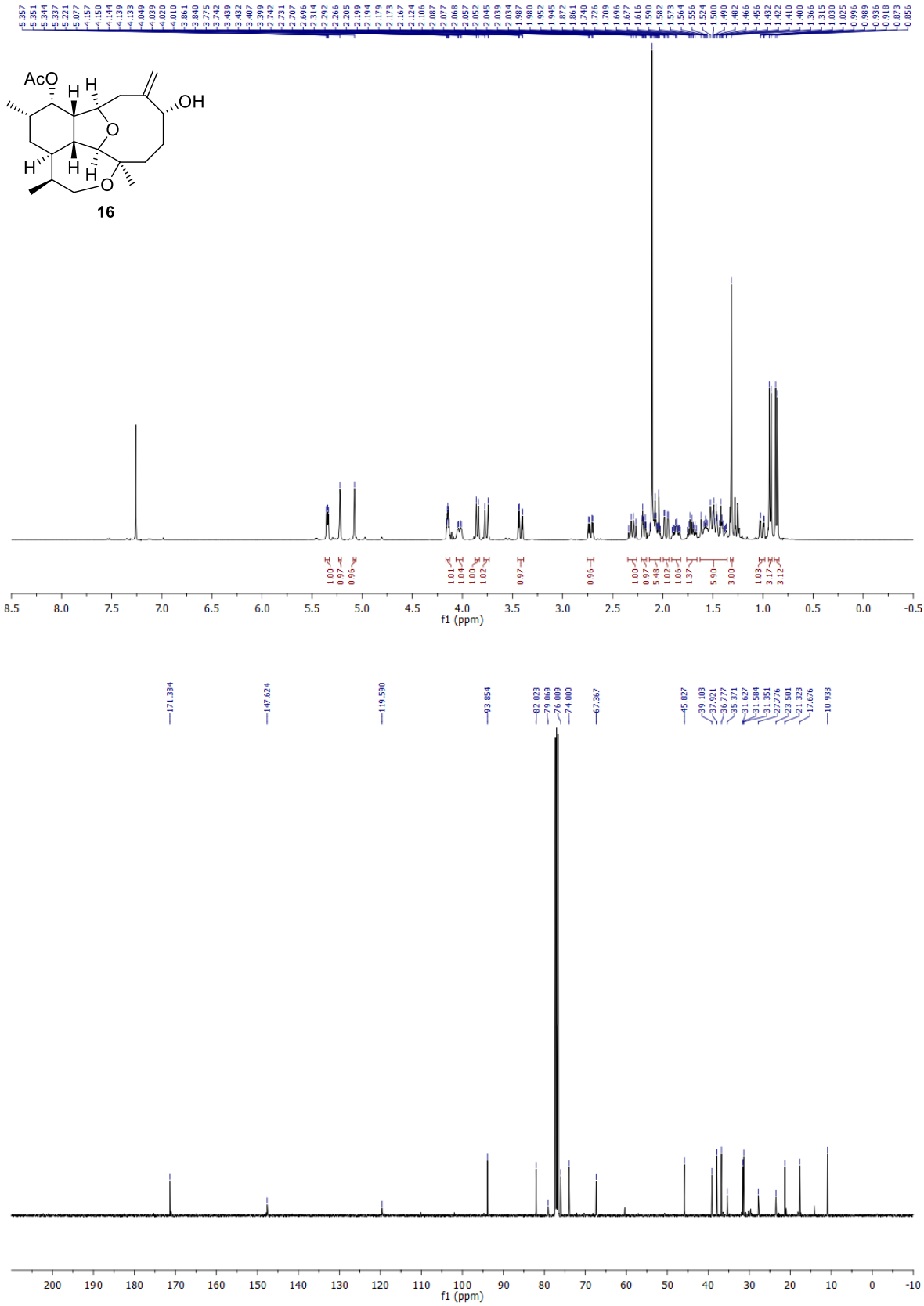
Appendix 14: ^{1}H,^{13}C and HMBC NMR Spectra of Asbestinin 20 (**14**)



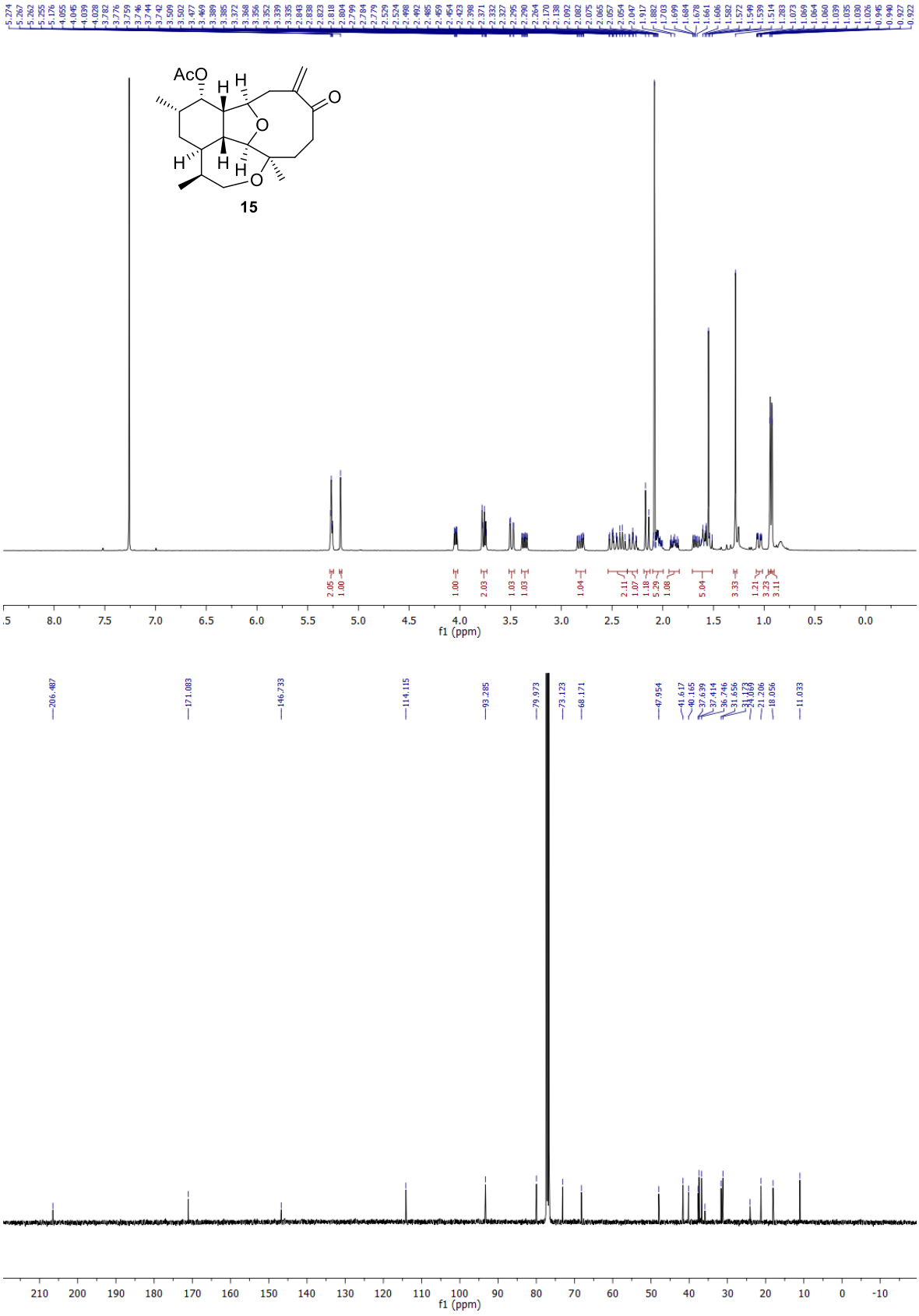



10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

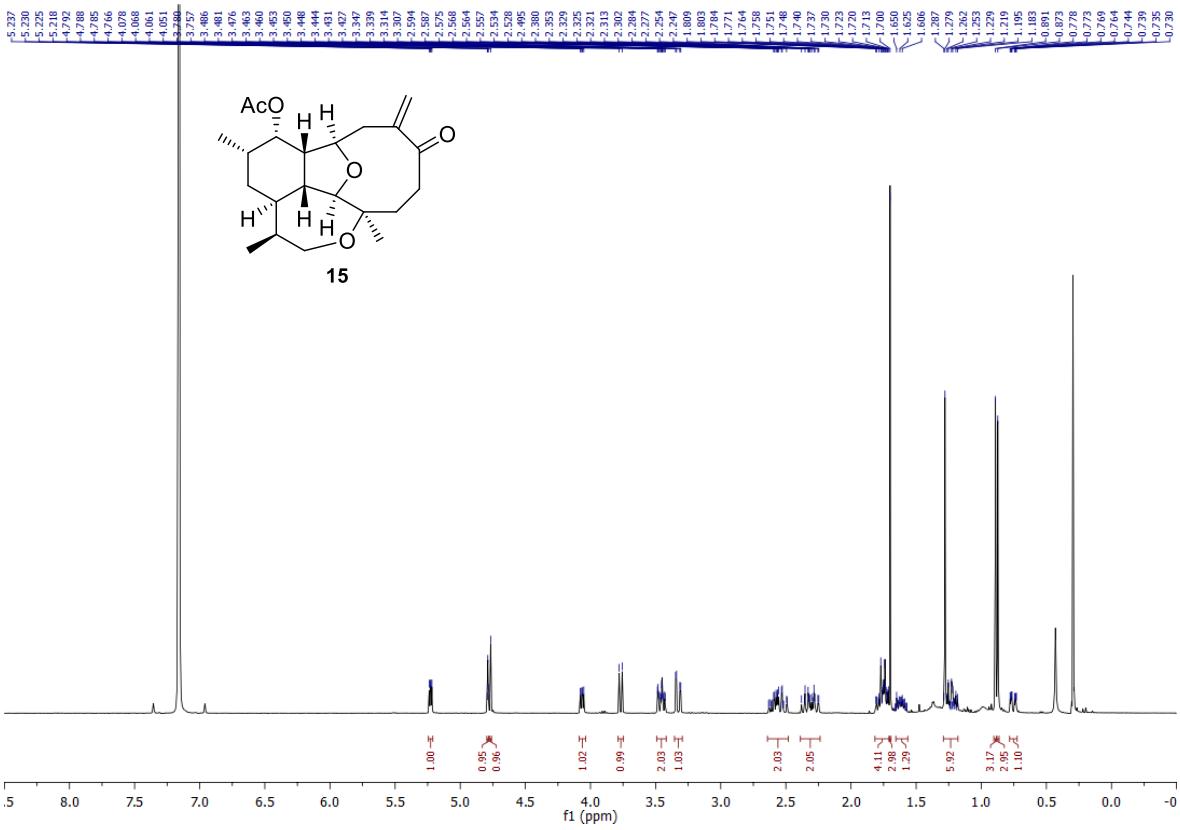
Appendix 15: ^{1}H and ^{13}C NMR Spectra of 6-*epi*-Asbestinin 20 (**16**)

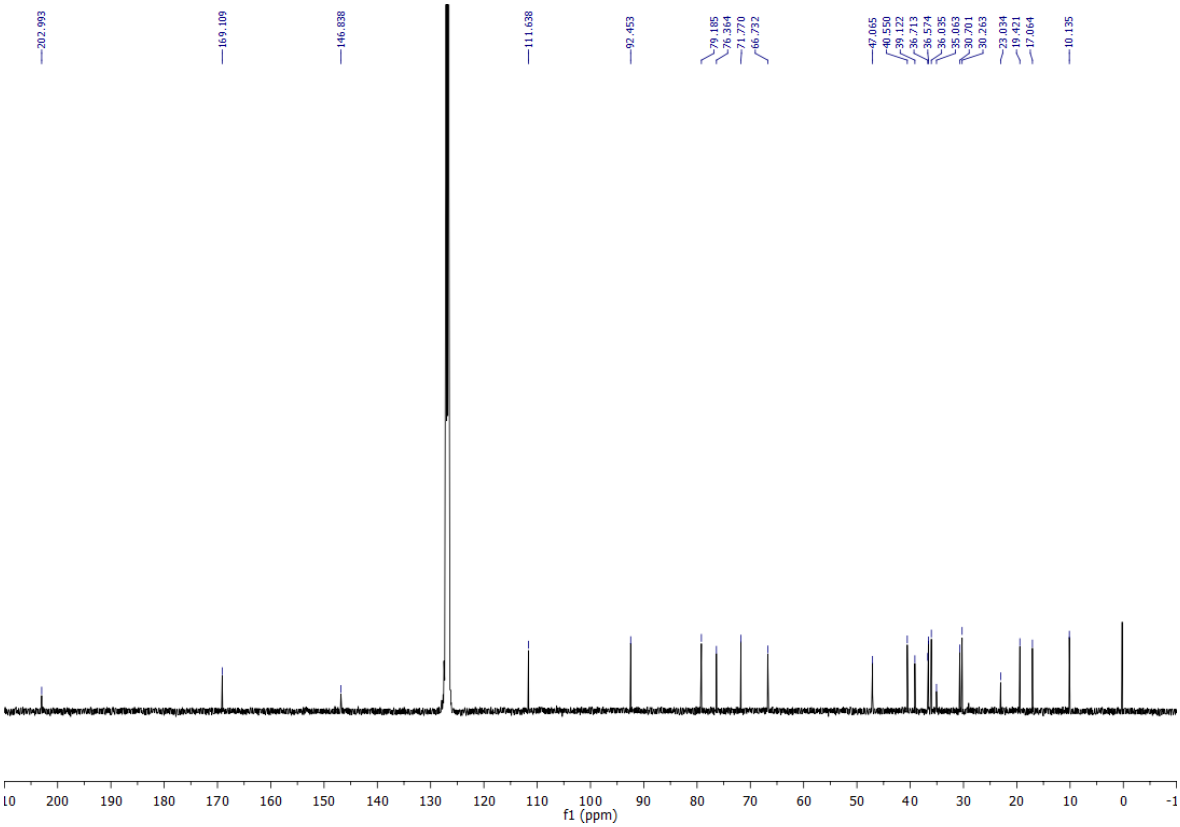


Appendix 16: ^{1}H and ^{13}C NMR Spectra of Asbestinin 10 (**15**) ($CDCl_3$)

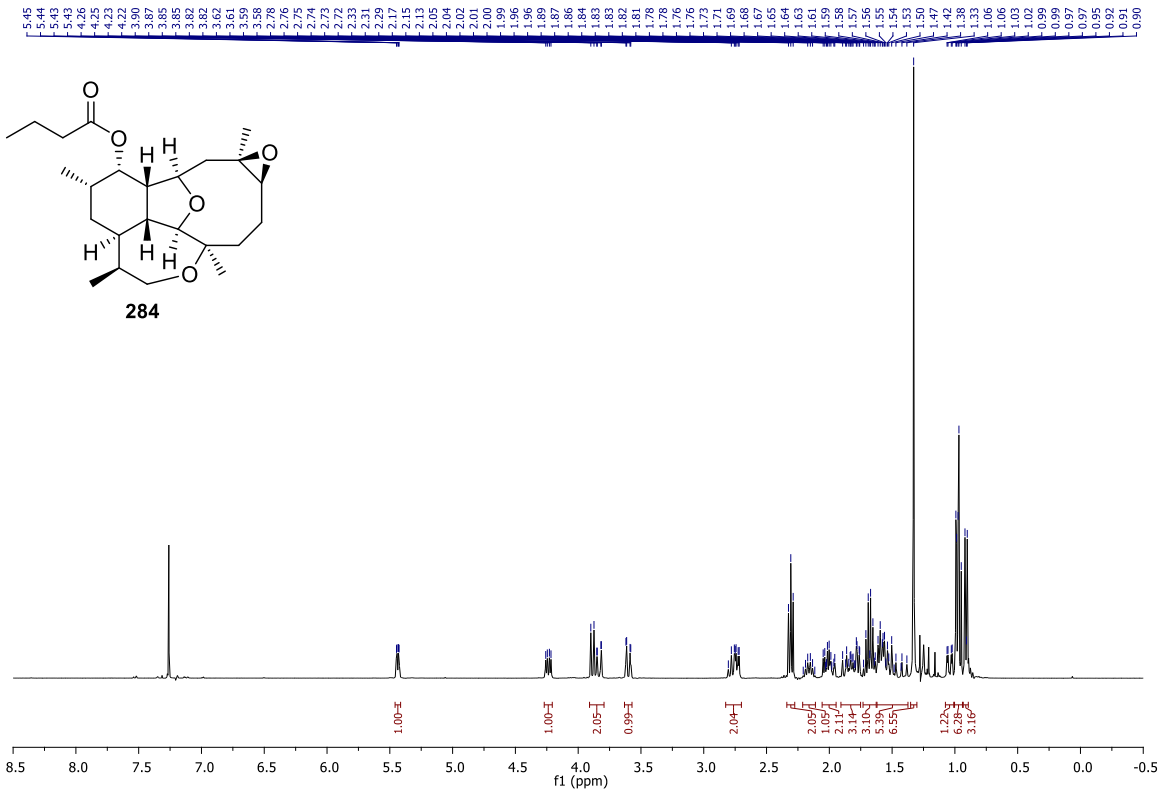


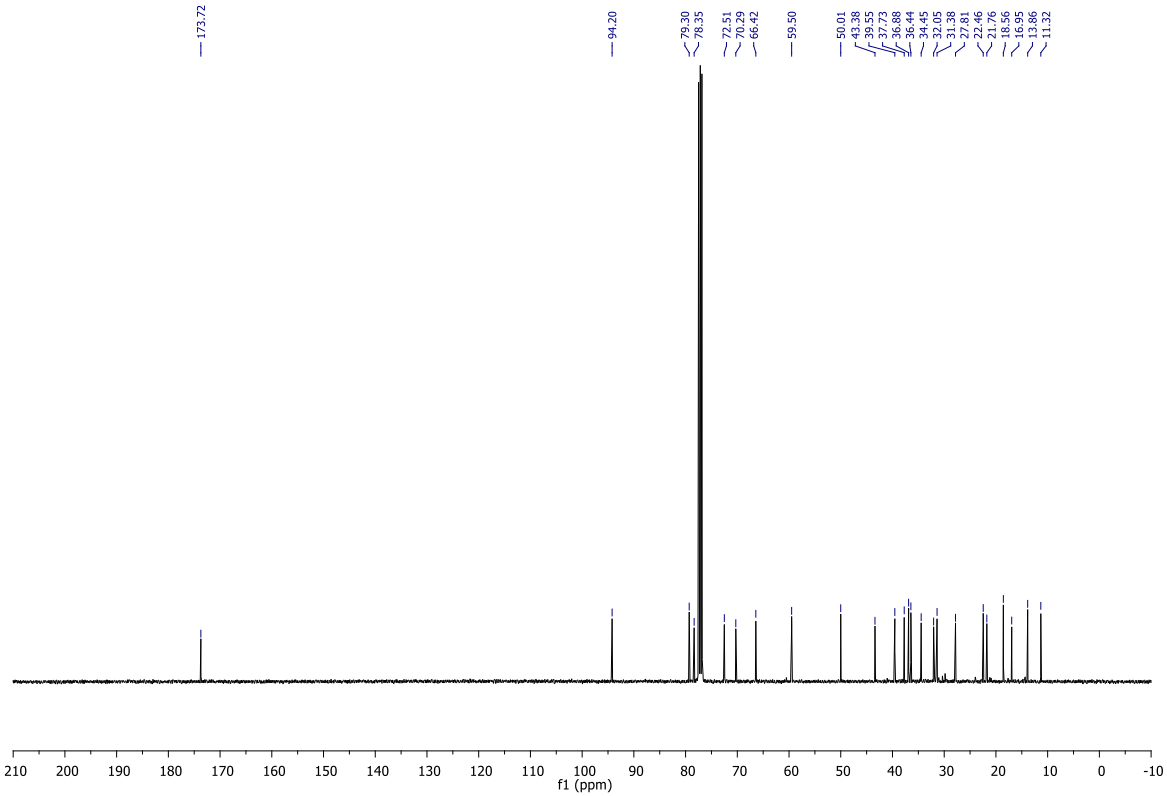
Appendix 17: ^{1}H and ^{13}C NMR Spectra of Asbestinin 10 (**15**) (C_6D_6)



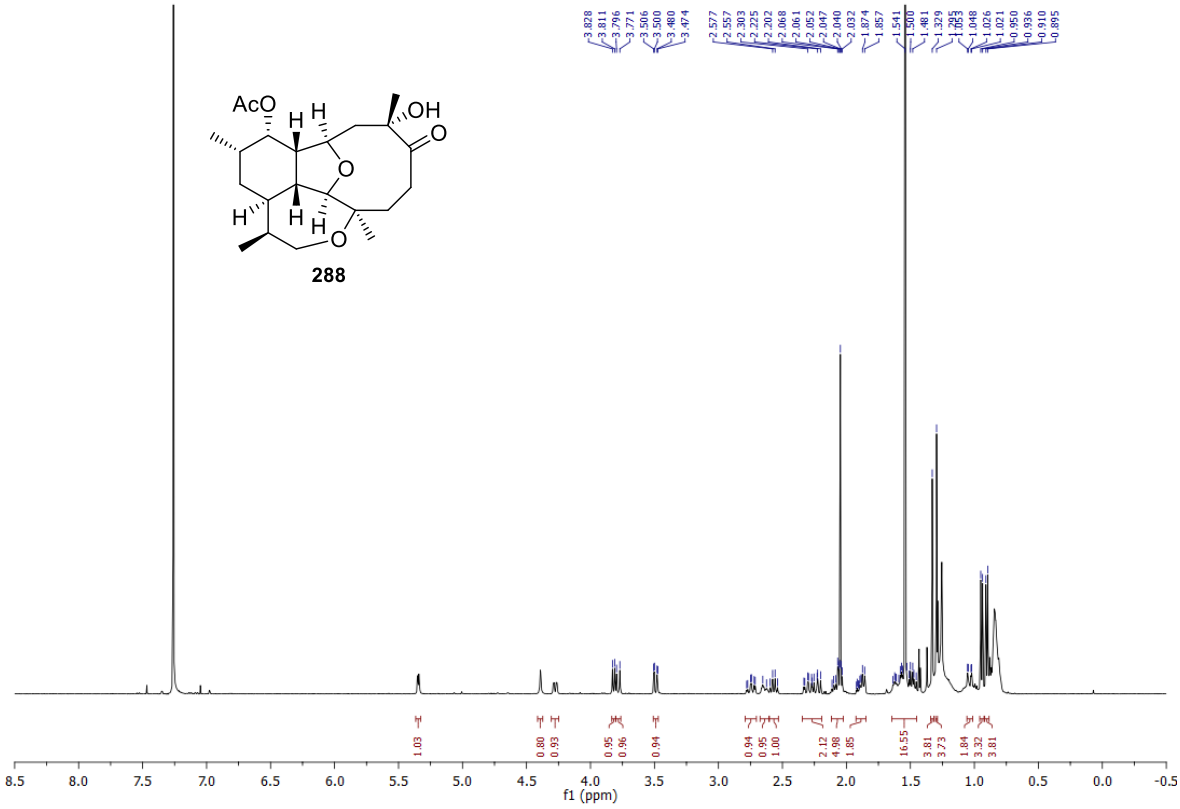


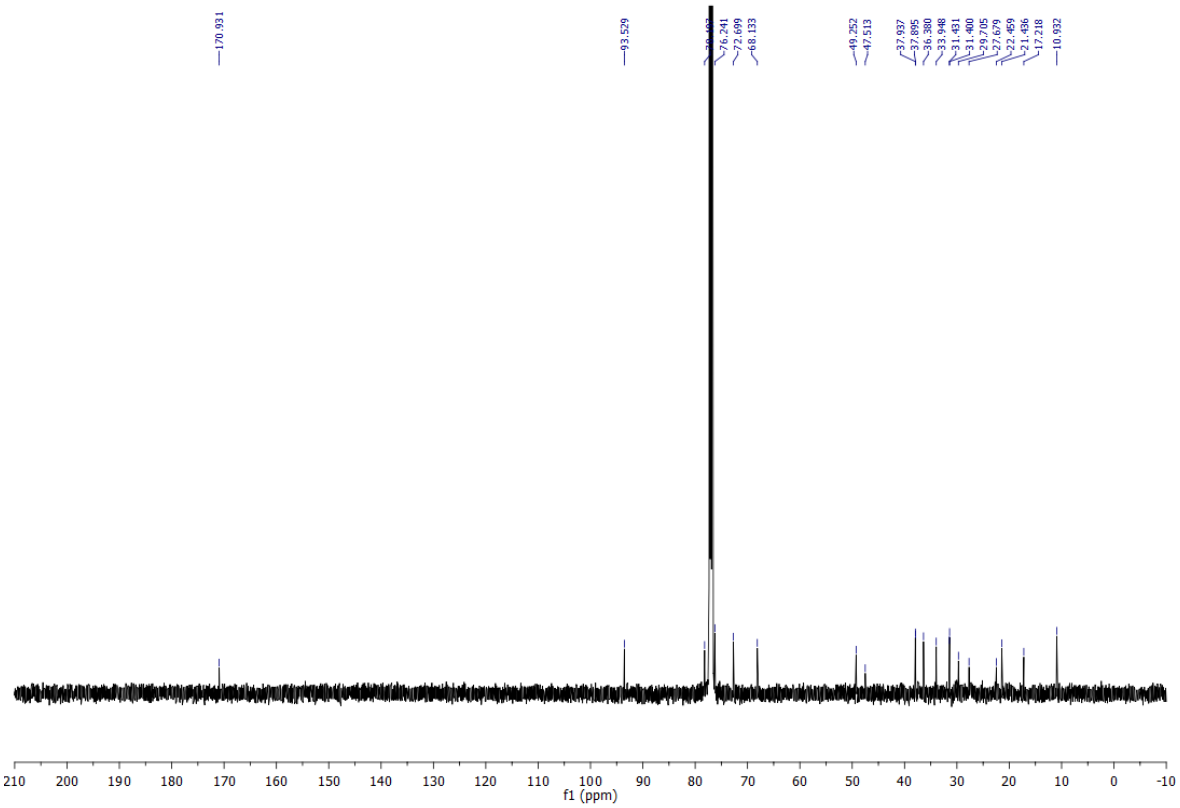
Appendix 18: ^{1}H and ^{13}C NMR Spectra of Compound **284**

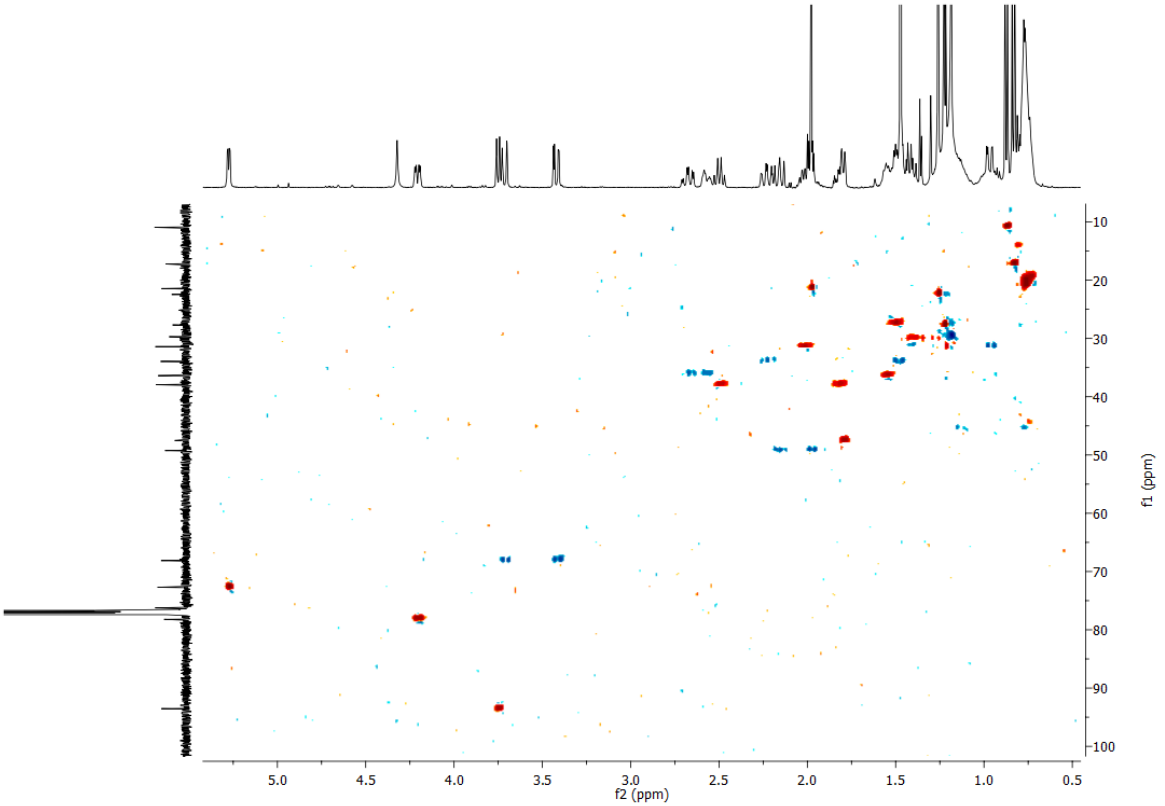


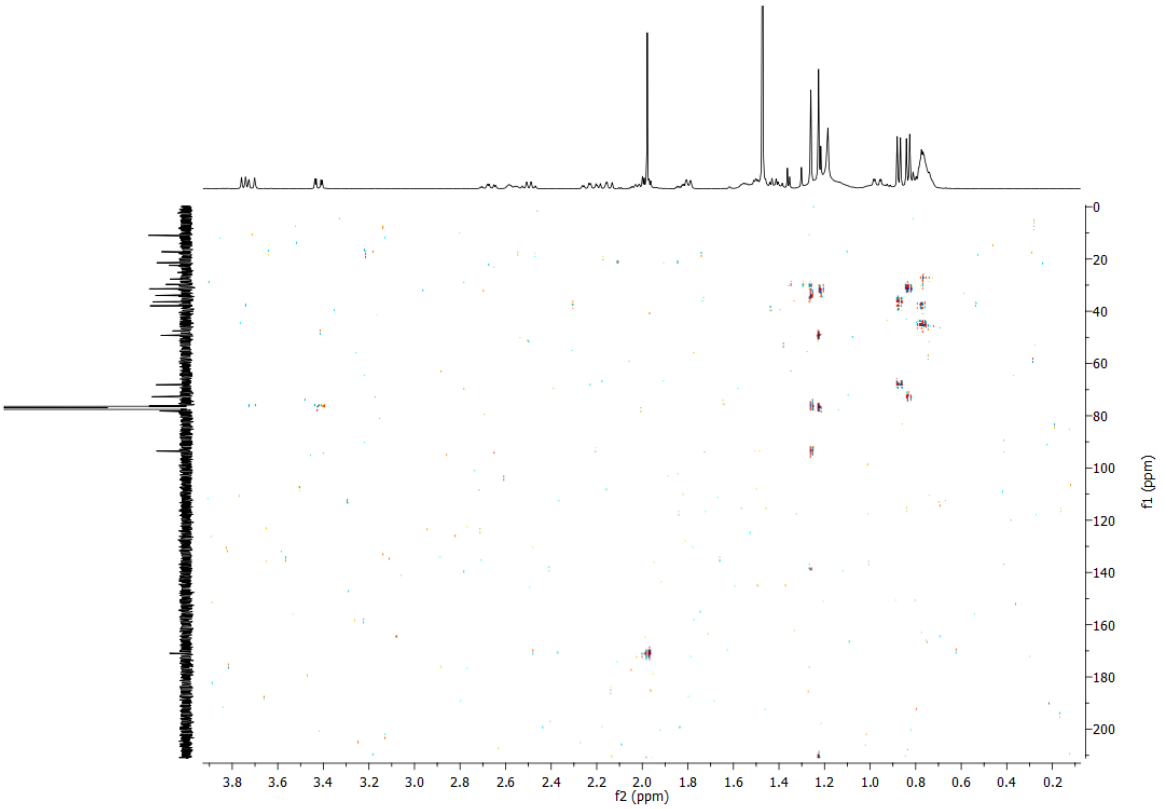


Appendix 19: ^{1}H, ^{13}C, HSQC and HMBC NMR Spectra of Asbestinin 21 (**288**)

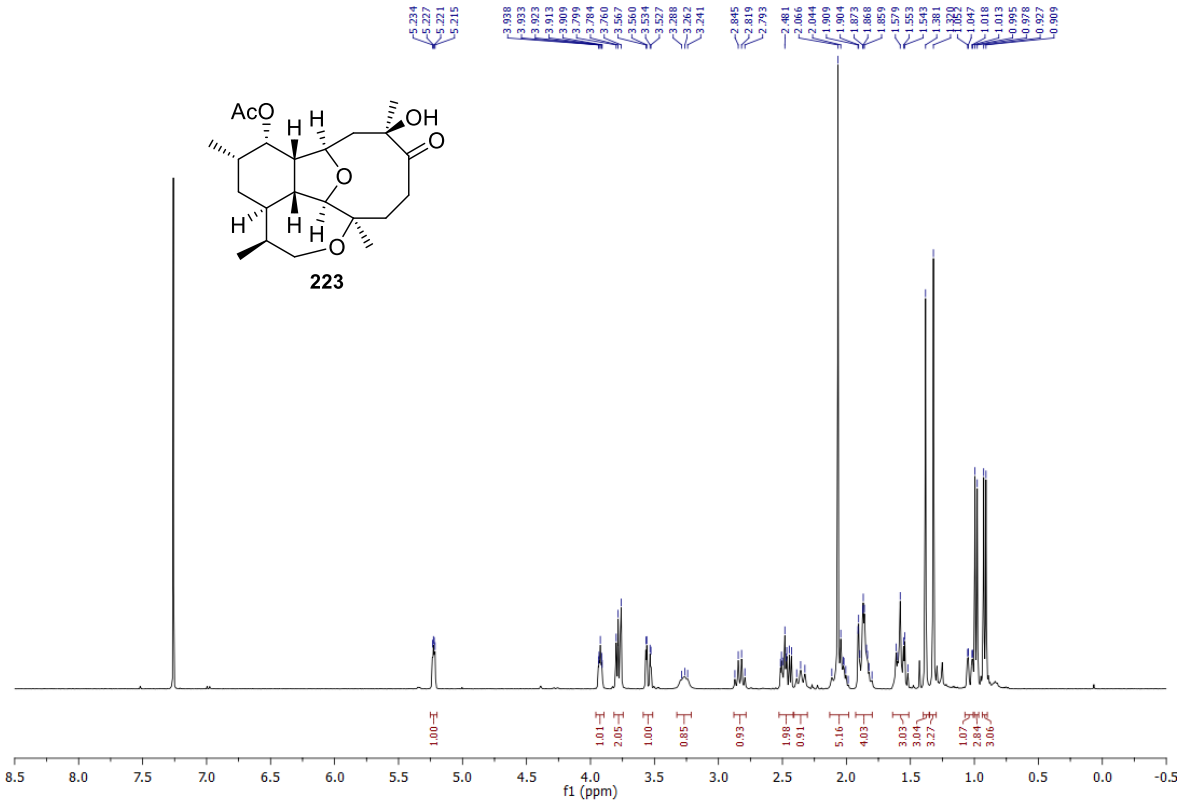


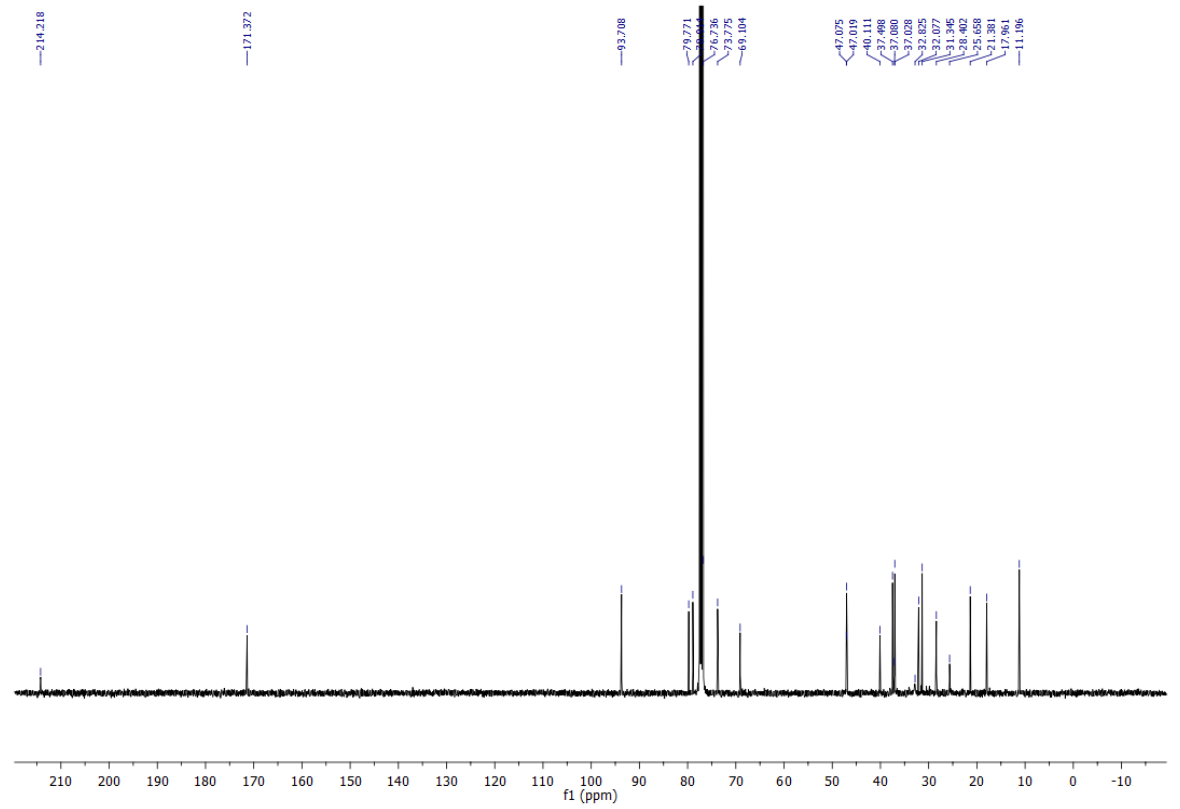



f2 (ppm)
f1 (ppm)

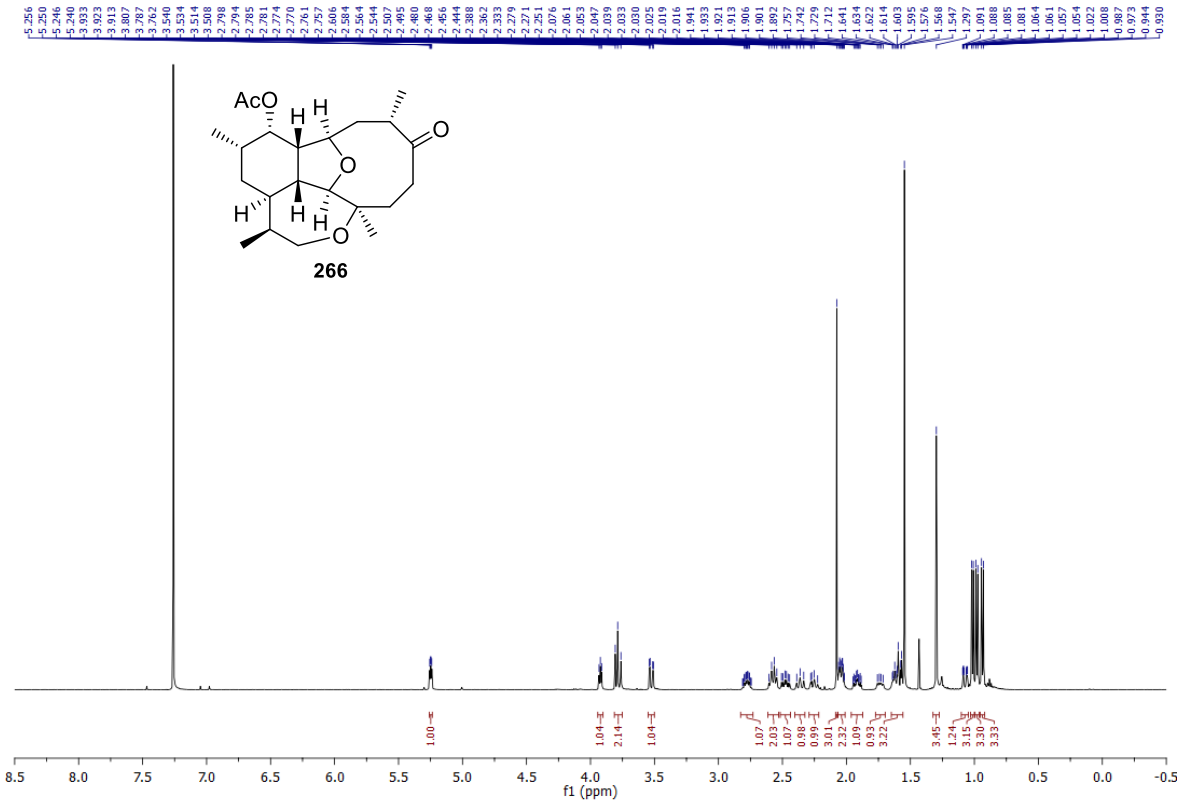

f2 (ppm)
f1 (ppm)

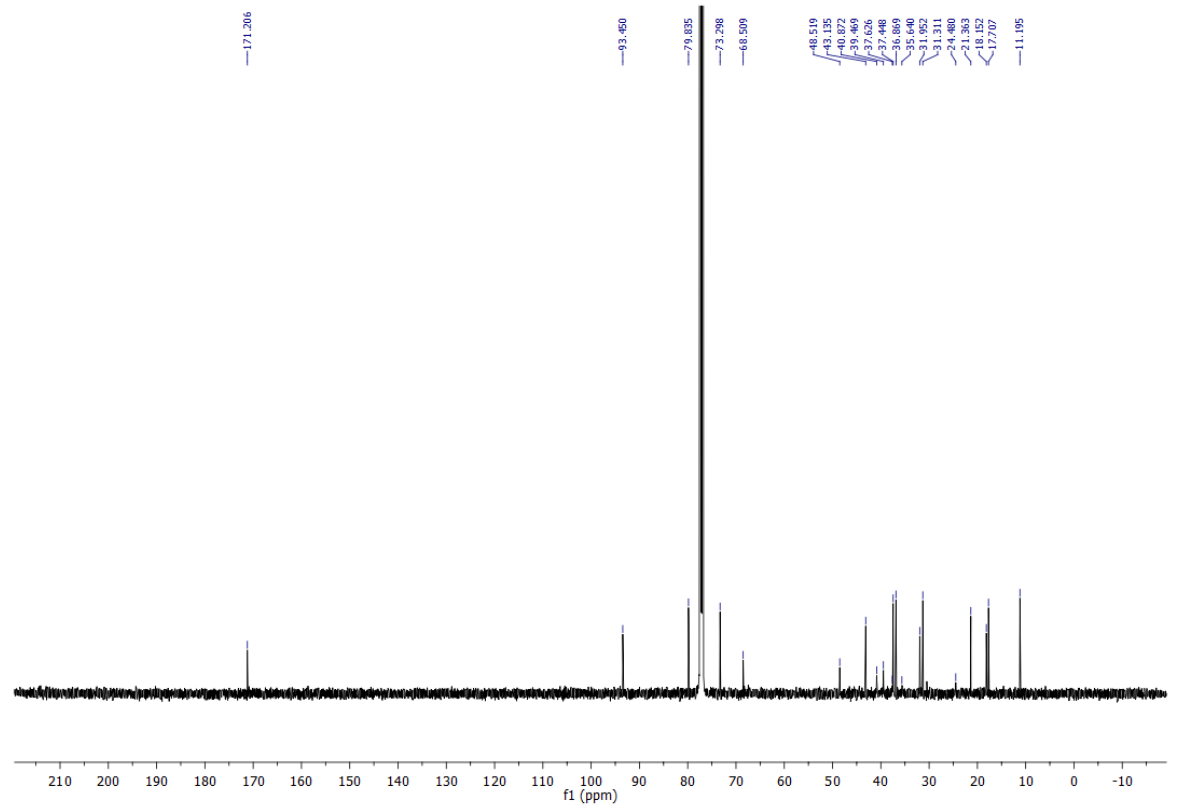
Appendix 20: ^{1}H and ^{13}C NMR Spectra of 7-*epi*-Asbestinin 21 (**223**)

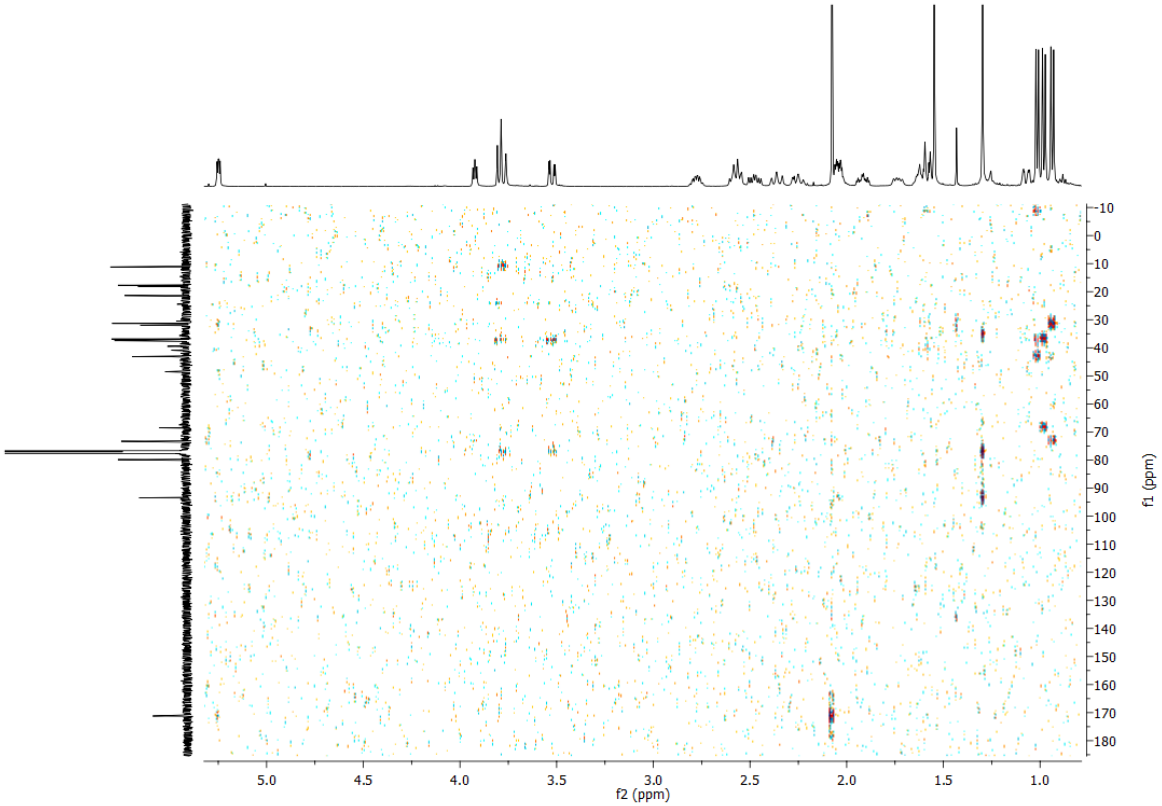




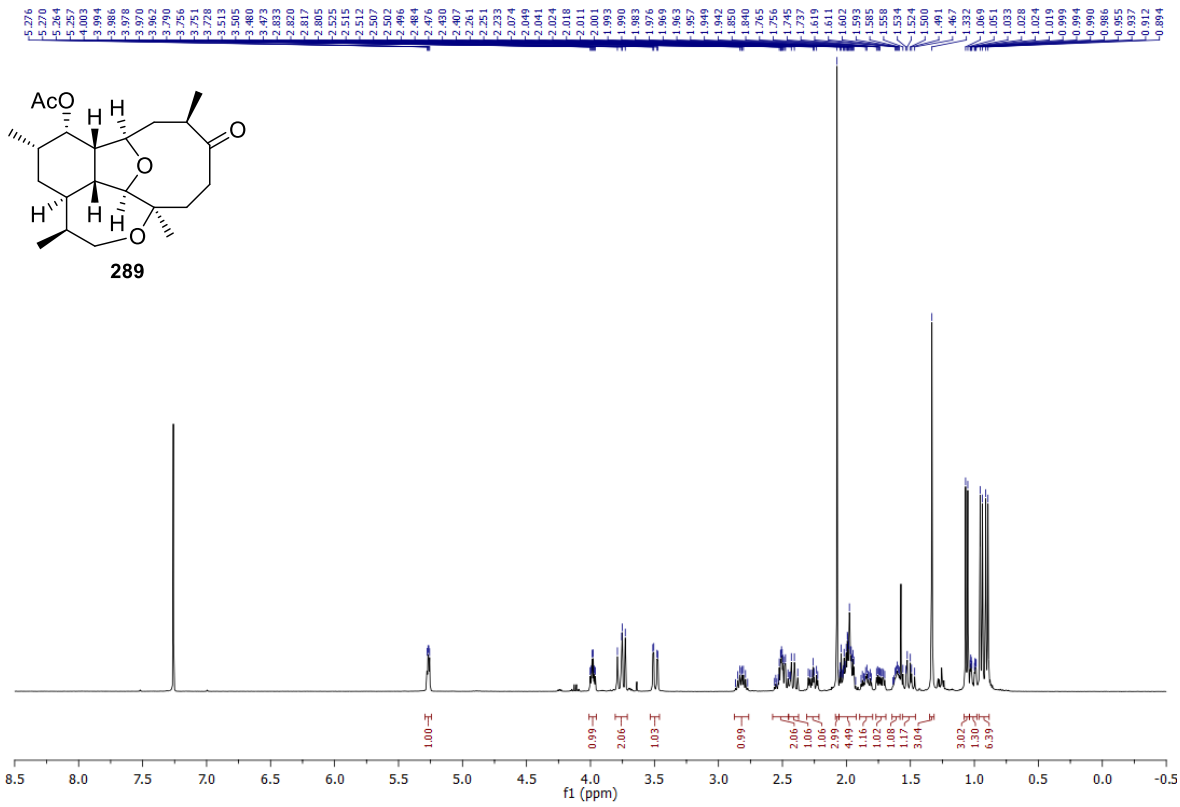
Appendix 21: ^{1}H, ^{13}C and HMBC NMR Spectra of Asbestinin 23 (**266**)

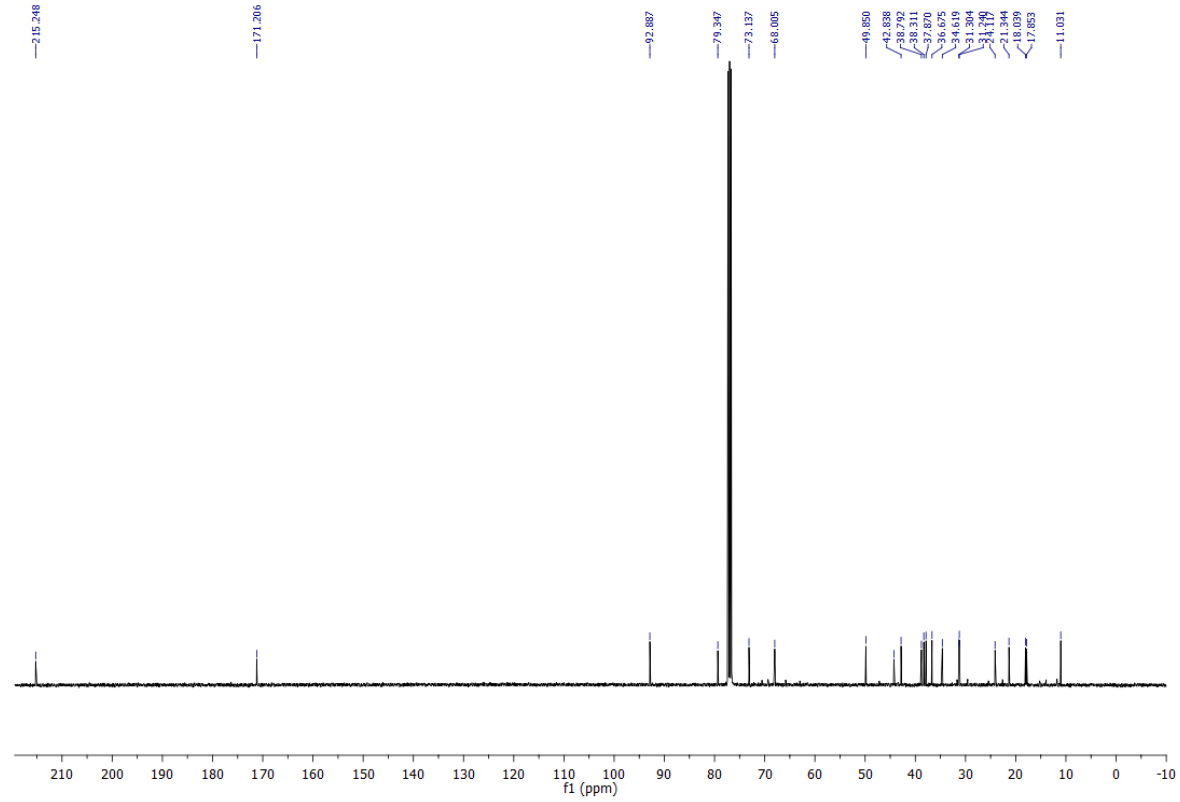




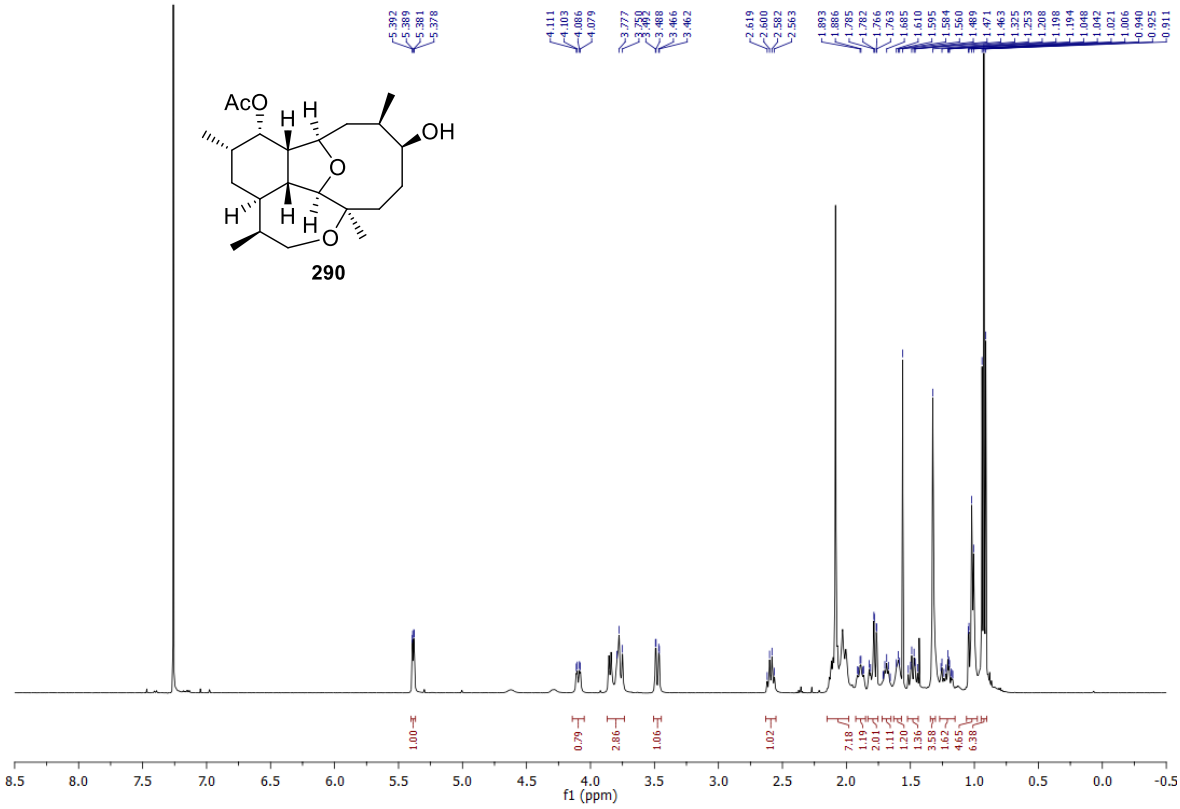

-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

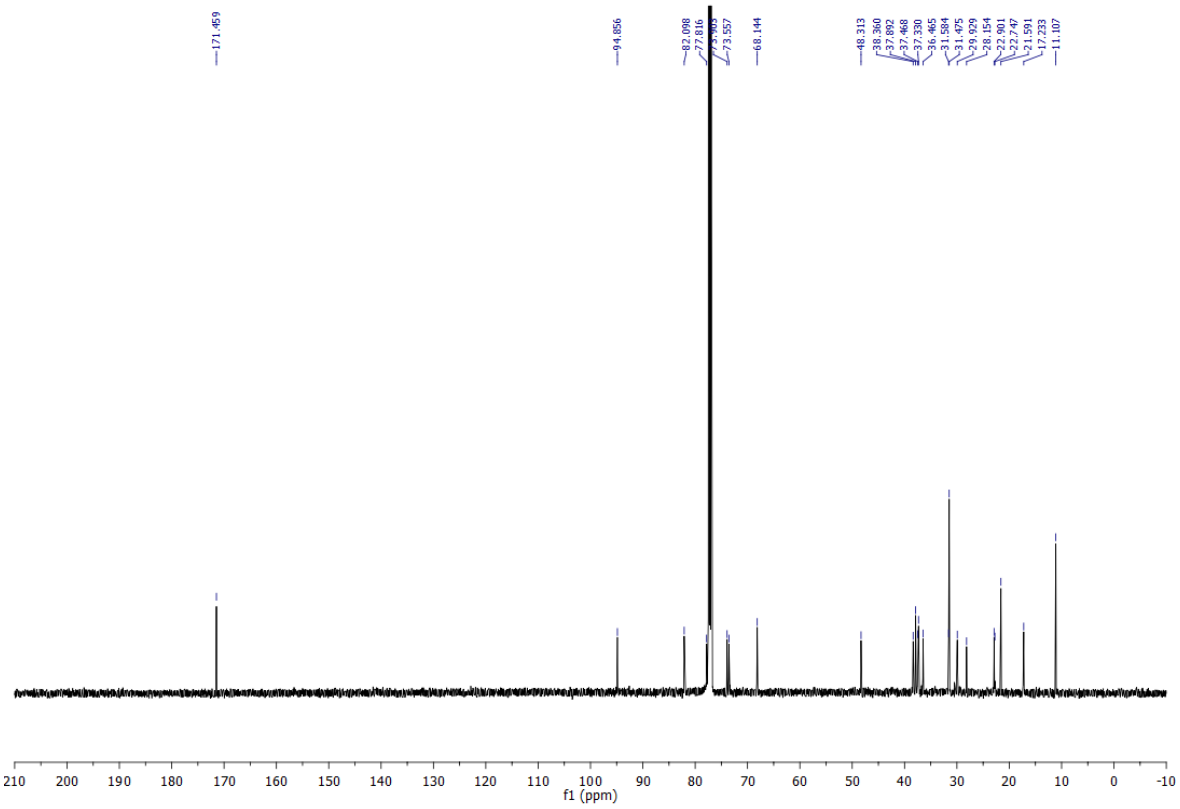
Appendix 22: ^{1}H and ^{13}C NMR Spectra of 7-*epi*-Asbestinin 23 (**289**)



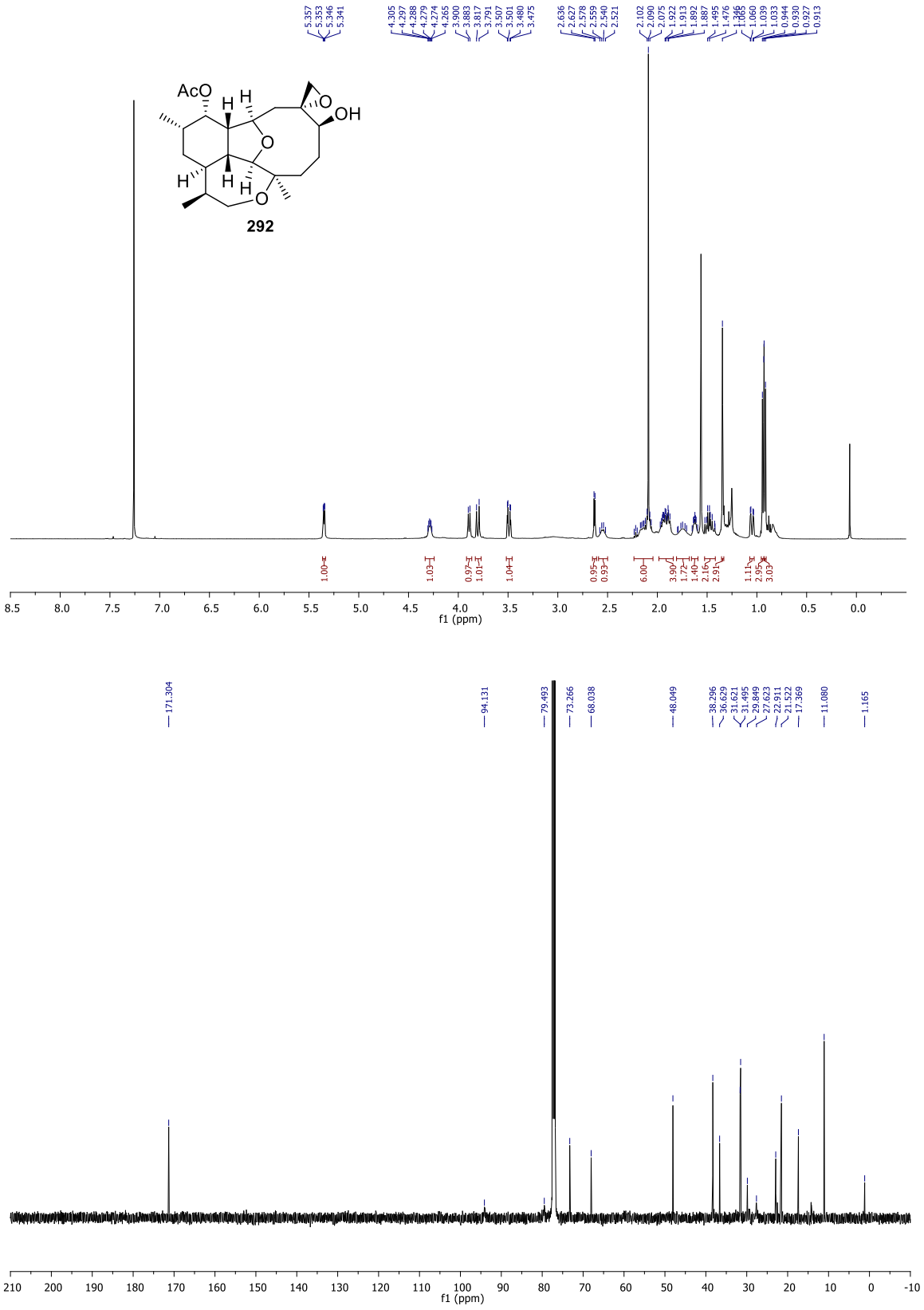


Appendix 23: ^{1}H and ^{13}C NMR Spectra of Compound **290**

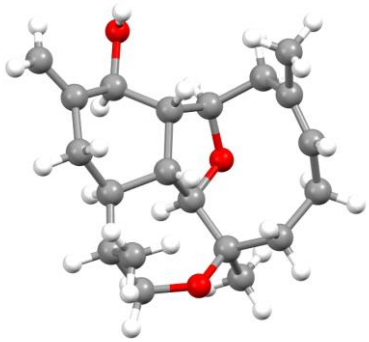




Appendix 24: ^{1}H and ^{13}C NMR Spectra of Compound **292**

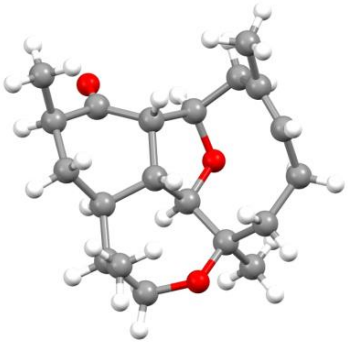


Appendix 25: X-ray Crystallography Data of Compound **262**



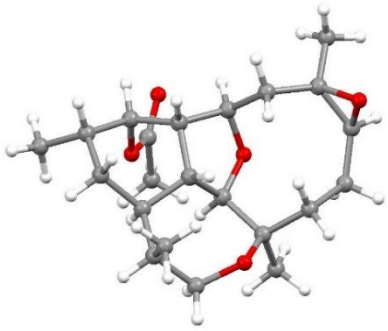
Empirical Formula	$C_{20}H_{30}O_3$	
Formula Weight	318.44	
Temperature	100 K	
Crystal System	Monoclinic	
Space Group	C2	
Unit Cell Dimensions	a = 36.3802(11) Å	α = 90 °
	b = 9.4047(3) Å	β = 123.178(1) °
	c = 24.8585(7) Å	γ = 90 °
Volume	711.6(4) $Å^3$	
Z	16	
Density	1.188 Mg m^{-3}	
Radiation Type	Cu *K*α, λ = 1.54178 Å	
Absorption Coefficient	0.61 mm^{-1}	
F(000)	2784	
Crystal Size	0.27 × 0.24 × 0.11 mm	
Theta range for Data Collection	2.5−74.4 °	
Index Ranges	$-45 \leq h \leq 37$; $-11 \leq k \leq 11$; $-28 \leq l \leq 31$	
Number of Reflections Collected	30711	
Number of Independent Reflections	13848	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.754 and 0.638	
Goodness-of-fit on F^2	1.06	
Final R Indexes [I>=2σ (1)]	R_1 = 0.043	
	wR_2 = 0.113	
Largest Diff. Peak/hole	0.36 and −0.19 e $Å^{-3}$	

Appendix 26: X-ray Crystallography Data of Compound **222**



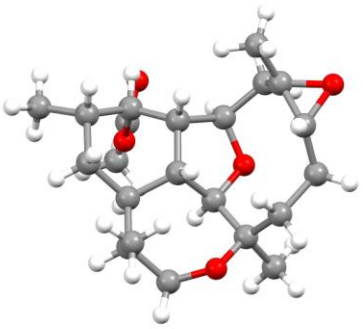
Empirical Formula	$C_{20}H_{30}O_3$	
Formula Weight	318.44	
Temperature	150 K	
Crystal System	Triclinic	
Space Group	*P*1	
Unit Cell Dimensions	a = 6.6385(6) Å	α = 117.319(3) º
	b = 8.6617(7) Å	β = 93.106(4) º
	c = 9.0518(7) Å	γ = 108.575(4) º
Volume	425.75(6) $Å^3$	
Z	1	
Density	1.242 Mg m^{-3}	
Radiation Type	Cu *K*α, λ = 1.54178 Å	
Absorption Coefficient	0.64 mm^{-1}	
F(000)	174	
Crystal Size	0.35 × 0.2 × 0.16 mm	
Theta range for Data Collection	5.7−68.1 º	
Index Ranges	$-7 \leq h \leq 6$; $-10 \leq k \leq 10$; $-10 \leq l \leq 10$	
Number of Reflections Collected	8144	
Number of Independent Reflections	2672	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.753 and 0.545	
Goodness-of-fit on F^2	1.03	
Final R Indexes [I>=2σ (1)]	R_1 = 0.037	
	wR_2 = 0.095	
Largest Diff. Peak/hole	0.21 and −0.19 e $Å^{-3}$	

Appendix 27: X-ray Crystallography Data of Compound **269**



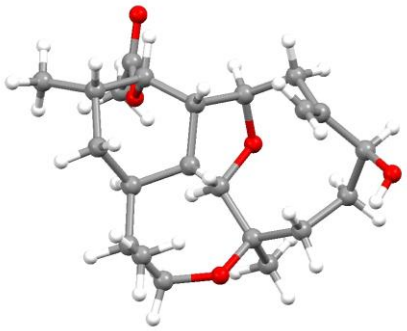
Empirical Formula	$C_{22}H_{34}O_5$	
Formula Weight	378.49	
Temperature	150 K	
Crystal System	Monoclinic	
Space Group	*P*2	
Unit Cell Dimensions	a = 9.6204(7) Å	α = 90 °
	b = 10.7595(7) Å	β = 102.681(2) °
	c = 10.2026(7) Å	γ = 90 °
Volume	1030.32(12) $Å^3$	
Z	2	
Density	1.220 Mg m^{-3}	
Radiation Type	Mo *K*α, λ = 0.71073 Å	
Absorption Coefficient	0.09 mm^{-1}	
F(000)	412	
Crystal Size	0.34 × 0.17 × 0.13 mm	
Theta range for Data Collection	2.9−28.3 °	
Index Ranges	$-12 \leq h \leq 12$; $-14 \leq k \leq 14$; $-13 \leq l \leq 11$	
Number of Reflections Collected	9383	
Number of Independent Reflections	4898	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.746 and 0.652	
Goodness-of-fit on F^2	1.04	
Final R Indexes [I>=2σ (1)]	R_1 = 0.046	
	wR_2 = 0.123	
Largest Diff. Peak/hole	0.34 and −0.18 e $Å^{-3}$	

Appendix 28: X-ray Crystallography Data of Compound **270**



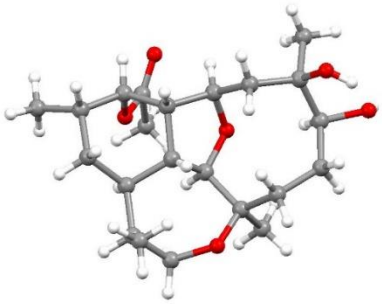
Empirical Formula	$C_{22}H_{34}O_5$	
Formula Weight	378.49	
Temperature	150 K	
Crystal System	Orthorhombic	
Space Group	$P2_12_12_1$	
Unit Cell Dimensions	a = 10.5369(5) Å	α = 90 °
	b = 11.2074(5) Å	β = 90 °
	c = 69.861(3) Å	γ = 90 °
Volume	8249.9(7) $Å^3$	
Z	16	
Density	1.219 Mg m^{-3}	
Radiation Type	Cu *K*α, λ = 1.54178 Å	
Absorption Coefficient	0.68 mm^{-1}	
F(000)	3296	
Crystal Size	0.37 × 0.16 × 0.04 mm	
Theta range for Data Collection	2.5−68.2 °	
Index Ranges	$-12 \leq h \leq 12$; $-13 \leq k \leq 11$; $-84 \leq l \leq 83$	
Number of Reflections Collected	48330	
Number of Independent Reflections	15077	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.753 and 0.634	
Goodness-of-fit on F^2	1.02	
Final R Indexes [I>=2σ (1)]	R_1 = 0.036	
	wR_2 = 0.093	
Largest Diff. Peak/hole	0.16 and −0.20 e $Å^{-3}$	

Appendix 29: X-ray Crystallography Data of Compound **14**



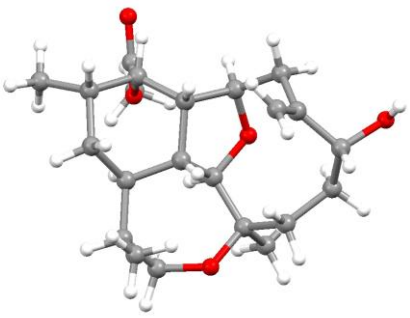
Empirical Formula	$C_{22}H_{34}O_5$	
Formula Weight	378.49	
Temperature	150 K	
Crystal System	Orthorhombic	
Space Group	$P2_12_12_1$	
Unit Cell Dimensions	a = 10.7567(5) Å	α = 90 °
	b = 10.9673(5) Å	β = 90 °
	c = 34.4321(17) Å	γ = 90 °
Volume	4062.0(3) $Å^3$	
Z	8	
Density	1.238 Mg m^{-3}	
Radiation Type	Mo *K*α, λ = 0.71073 Å	
Absorption Coefficient	0.09 mm^{-1}	
F(000)	1648	
Crystal Size	0.22 × 0.15 × 0.09 mm	
Theta range for Data Collection	2.4−26.2 °	
Index Ranges	$-13 \leq h \leq 12$; $-13 \leq k \leq 13$; $-41 \leq l \leq 43$	
Number of Reflections Collected	23463	
Number of Independent Reflections	8267	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.745 and 0.646	
Goodness-of-fit on F^2	1.05	
Final R Indexes [I>=2σ (1)]	R_1 = 0.040	
	wR_2 = 0.086	
Largest Diff. Peak/hole	0.23 and −0.16 e $Å^{-3}$	

Appendix 30: X-ray Crystallography Data of Compound **275**



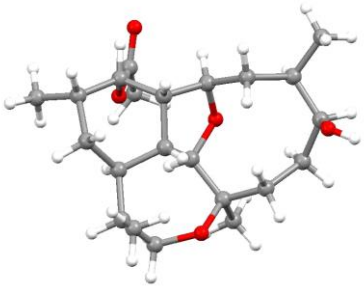
Empirical Formula	$C_{22}H_{36}O_6$	
Formula Weight	396.51	
Temperature	295 K	
Crystal System	Tetragonal	
Space Group	$P4_32_12$	
Unit Cell Dimensions	a = 10.9573(8) Å	α = 90 °
	c = 36.631(3) Å	γ = 90 °
Volume	4398.0(7) $Å^3$	
Z	8	
Density	1.198 Mg m^{-3}	
Radiation Type	Cu *K*α, λ = 1.54178 Å	
Absorption Coefficient	0.70 mm^{-1}	
F(000)	1728	
Crystal Size	0.36 × 0.24 × 0.08 mm	
Theta range for Data Collection	3.6−78.5 °	
Index Ranges	$-13 \leq h \leq 13$; $-12 \leq k \leq 13$; $-46 \leq l \leq 44$	
Number of Reflections Collected	38626	
Number of Independent Reflections	4675	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.754 and 0.589	
Goodness-of-fit on F^2	1.05	
Final R Indexes [I>=2σ (1)]	R_1 = 0.045	
	wR_2 = 0.132	
Largest Diff. Peak/hole	0.24 and −0.19 e $Å^{-3}$	

Appendix 31: X-ray Crystallography Data of Compound **16**



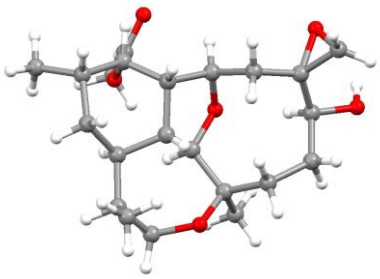
Empirical Formula	$C_{22}H_{34}O_5$	
Formula Weight	378.49	
Temperature	150 K	
Crystal System	Orthorhombic	
Space Group	$P2_12_12_1$	
Unit Cell Dimensions	a = 10.0317(6) Å	α = 90 °
	b = 11.2228(6) Å	α = 90 °
	c = 18.7242(10) Å	γ = 90 °
Volume	2108.0(2) $Å^3$	
Z	4	
Density	1.193 Mg m^{-3}	
Radiation Type	Mo *K*α, λ = 0.71073 Å	
Absorption Coefficient	0.08 mm^{-1}	
F(000)	824	
Crystal Size	0.40 × 0.28 × 0.15 mm	
Theta range for Data Collection	2.3−28.3 °	
Index Ranges	$-13 \leq h \leq 13; -10 \leq k \leq 14; -24 \leq l \leq 24$	
Number of Reflections Collected	14198	
Number of Independent Reflections	5181	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.746 and 0.635	
Goodness-of-fit on F^2	1.05	
Final R Indexes [I>=2σ (1)]	R_1 = 0.039	
	wR_2 = 0.105	
Largest Diff. Peak/hole	0.27 and −0.21 e $Å^{-3}$	

Appendix 32: X-ray Crystallography Data of Compound **290**



Empirical Formula	$C_{22}H_{36}O_5$	
Formula Weight	380.51	
Temperature	150 K	
Crystal System	Orthorhombic	
Space Group	$P2_12_12_1$	
Unit Cell Dimensions	a = 11.5008(7) Å	α = 90 °
	b = 12.9803(11) Å	α = 90 °
	c = 14.0765(10) Å	γ = 90 °
Volume	2101.4(3) $Å^3$	
Z	4	
Density	1.203 Mg m^{-3}	
Radiation Type	Mo *K*α, λ = 0.71073 Å	
Absorption Coefficient	0.08 mm^{-1}	
F(000)	832	
Crystal Size	0.33 × 0.13 × 0.06 mm	
Theta range for Data Collection	2.3−28.2 °	
Index Ranges	$-15 \leq h \leq 13$; $-12 \leq k \leq 17$; $-18 \leq l \leq 18$	
Number of Reflections Collected	15988	
Number of Independent Reflections	5198	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.746 and 0.650	
Goodness-of-fit on F^2	1.02	
Final R Indexes [I>=2σ (1)]	R_1 = 0.048	
	wR_2 = 0.118	
Largest Diff. Peak/hole	0.27 and −0.25 e $Å^{-3}$	

Appendix 33: X-ray Crystallography Data of Compound **292**



Empirical Formula	$C_{22}H_{34}O_6$	
Formula Weight	394.49	
Temperature	150 K	
Crystal System	Orthorhombic	
Space Group	$P2_12_12_1$	
Unit Cell Dimensions	a = 9.7898(5) Å	α = 90 °
	b = 11.4929(5) Å	α = 90 °
	c = 18.8684(13) Å	γ = 90 °
Volume	2122.9(2) $Å^3$	
Z	4	
Density	1.234 Mg m^{-3}	
Radiation Type	Mo *K*α, λ = 0.71073 Å	
Absorption Coefficient	0.09 mm^{-1}	
F(000)	856	
Crystal Size	0.18 × 0.16 × 0.07 mm	
Theta range for Data Collection	2.3−25.7 °	
Index Ranges	$-11 \leq h \leq 11$; $-13 \leq k \leq 13$; $-23 \leq l \leq 12$	
Number of Reflections Collected	8967	
Number of Independent Reflections	3866	
Absorption Correction Type	Multi-scan SADABS2016/2	
Max. and Min. Transmission	0.745 and 0.633	
Goodness-of-fit on F^2	1.04	
Final R Indexes [I>=2σ (1)]	R_1 = 0.040	
	wR_2 = 0.089	
Largest Diff. Peak/hole	0.20 and −0.17 e $Å^{-3}$	