Towards the Total Synthesis of Anthracimycin

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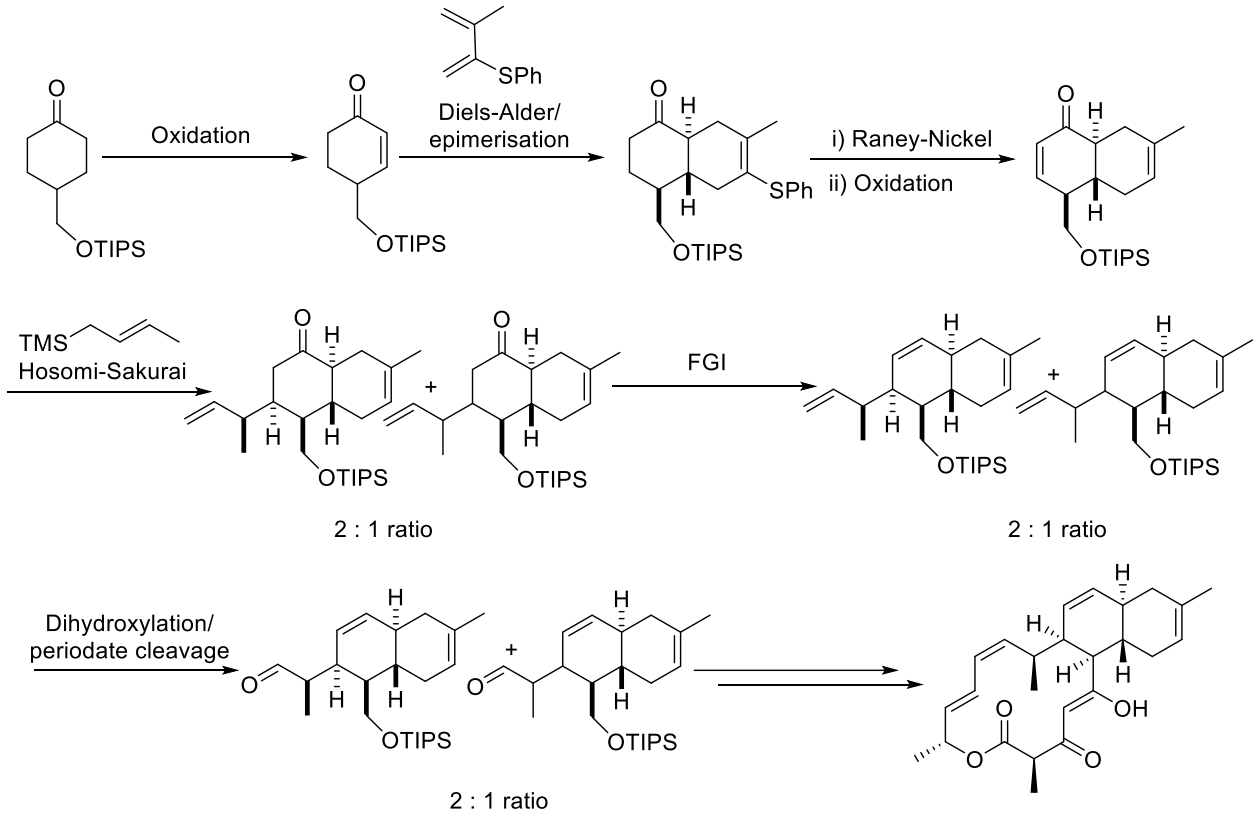
1. Abstract

In 2013 W. Fenical *et al.* reported the isolation of a natural product from a marine microorganism of *streptomyces* species, which possessed significant activity against Gram-positive pathogens *Bacillus anthracis*, methicillin-resistant and vancomycin resistant *Staphylococcus aureus* (MRSA).[15] The compound responsible for the antibiotic activity was found to be the 14-membered macrolide named anthracimycin. The research detailed in this thesis describes the efforts towards the total synthesis of this natural product and specifically the formation of the core of anthracimycin in 12-steps. Direct palladium catalysed oxidation formed the enone used as a dienophile in a stereo- and regio-selective Diels–Alder/epimerisation sequence, which afforded the *trans*-decalin. A facial and stereoselective Hosomi–Sakurai 1,4-addition reaction, followed by a selective borylation/dihydroxylation sequence on the exocyclic alkene, allowed the formation of the core of anthracimycin (**Scheme 1**).



Scheme 1. The formation of the decalin core of anthracimcyin.

2. Contents

3. List of Figures

4. List of Schemes

5. List of Tables

6. Acknowledgements

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The last thanks goes to my housemates Francesco, Mik and Miky of my last year in York. They have been enjoyable friends and true brothers and during the course of the year, we became a family.

7. Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.

8. Introduction

8.1 Natural product synthesis

The role of total synthesis in the development of new natural product based drugs is of particular importance.[1] In many cases new synthetic methodology has been developed to allow the synthesis of natural products. For example, the development of asymmetric alkylation and aldol methodology by Evans, gave access to the complex antibiotic cytovaricin.[2] Hydroboration reactions have been used by Kishi to develop a new methodology to form propionate fragments for the total synthesis of monensin A.[3] Plants and natural substances are used in traditional medicine to treat a wide range of illnesses. The active compounds, isolated from them, find use in conventional medicine such as taxol in the treatment of cancer, acetylsalicyclic acid as an anti-inflammatory drug and pilocarpine in the treatment of chronic and acute gluacoma.[4, 5] Mother Nature produces molecules which play an important role in drug discovery and development processes. These are continuing to expand the chemotherapeutic armory and organic chemists are devising new and ingenious strategies to develop synthesis of these natural products.[4] The pharmaceutical industry seems to have recognised this trend and is shifting away from large libraries of simple compounds towards focused libraries of complex, natural product-like collections.[4]

However, in many cases, supply issues have hindered the development of natural products into drugs. This can be because the source organism is not always known, and when it is known the active compound is often found in only miniscule quantities. The answer to these supply issues would seem to be total chemical synthesis.[6]

It is generally accepted that the synthesis of compounds of any complexity can be achieved, given enough time and resources.[6] However, the vast majority of the reported total synthesis provide only milligram quantities of the target compound.[7] These amounts are insufficient for significant biological studies and therefore have little impact in drug development, especially when the compound can not be simplified without the loss of activity. Fortunately, in the last decades several groups have

successfully addressed this issue with an increased focus on scalability of the total synthesis. They have succeeded in the production of several highly complex natural products in multigram quantities for biological studies.[7]

With the excellent potential of natural products as biologically active molecules, and the increased focus on the scalability of the synthesis, one can only expect the role of total synthesis in chemistry, biology and medicine to increase in the coming years.

8.2 The need for new antibiotics

The Government and the World Health Organisation (WHO) have called for research into new anti-infective drugs, triggered by the rising threat of the methicillin resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* (C. Diff) and *Enterobacteriaceae,* as well as other resistant pathogens. [8] These strongly antibiotic resistant bacteria or "superbugs" are untreatable with current antibiotics and new research in this area is necessary. Over the years, two parallel and different lines of antibiotic discovery and development have been explored: i) the antibacterial activity of natural products (such as cephalosporins, quinolones, macrolides and tetracyclines), and, ii) the antibiotic activity of synthetic aromatic sulfonamides. After "the golden age of antibiotics research" (1940-1960), different generations of the natural antibiotics were developed to overcome bacterial resistance, by modification of their chemical scaffolds (**Figure 1**). [8]

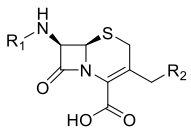
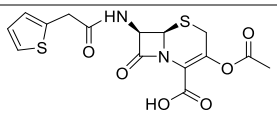
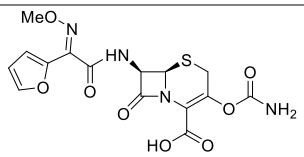
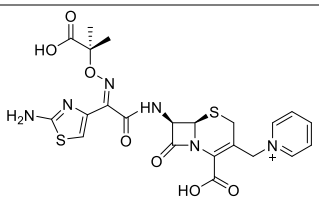
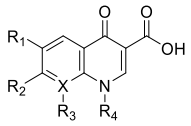
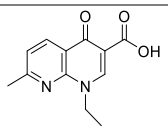
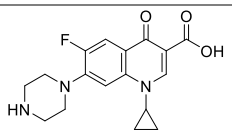
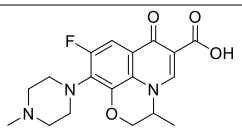
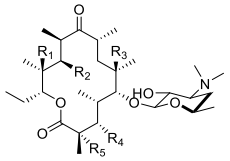
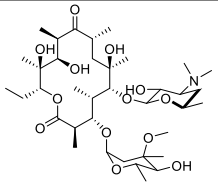
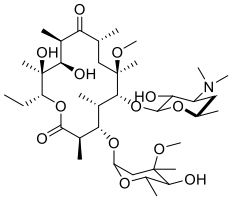
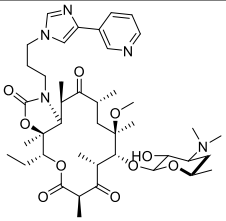
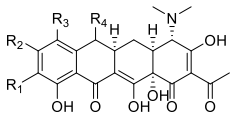
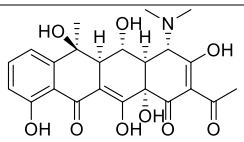
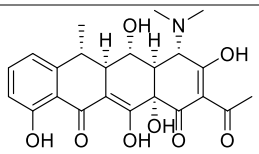
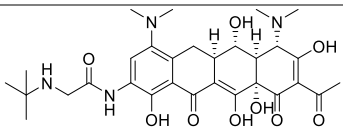
Antibiotic Class	Generation 1	Generation 2	Generation 3
Cephalosporins 			
Quinolones 			
Macrolides 			
Tetracyclines 			

Figure 1. Generations of different antibiotics.[8]

Figure 1 shows the different antibiotic classes, in which the lead structure has been modified to create different generations to overcome bacteria resistance.

The widespread introduction and the inappropriate use of antibiotics in human and veterinary contexts, led to an increase of resistant bacteria and the need of new antibiotic molecules. In 2014, a table to compare the year of antibiotics discovery with the year of resistance observed, was published showing how quick the clinical resistance has been developed by bacteria (**Table 1**).[8]

Antibiotic	Year Discovery	Clinical resistance observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s
Nalidixic acid	1962	1962
Fluoroquinolones	1980s	1980s
Linezolid	1999	1999
Daptomycin	2003	2003
Retapamulin	2007	2007
Fidaxomycin	2011	2011

Table 1. Year of resistence observed.[8]

8.2.1 The mechanism of action of antibiotics

Different classes of antibiotic possess different mechanisms of action against bacteria and five major antibacterial targets/pathways have been studied: β–lactams and the vancomycin type glycopeptides target bacterial peptidoglycan/cell wall biosynthesis (**Figure 2**). Another target of antibiotics is bacterial protein synthesis, with macrolide-based drugs attacking the ribosome. Fluoroquinolones targets DNA replication and transcription to RNA.[9] Two other targets are the folate biosynthetic pathway (sulfamides) [9] and the disruption of bacterial membrane integrity (daptomycin).[9] The resistance against these antibiotics is different for each class: for example, the substitution of the D-Ala-D-Ala sequence in the peptidoglycan wall with a D-Ala-D-lactate unit, represents the *enterococci-type* bacteria resistance against vancomycin. This causes the loss of one H-bond between the antibiotic and the target. Gene mutation in the sequence that encodes for DNA-gyrase enzyme, represents the mechanism of resistance against the fluoroquinolone antibiotics class.[8]

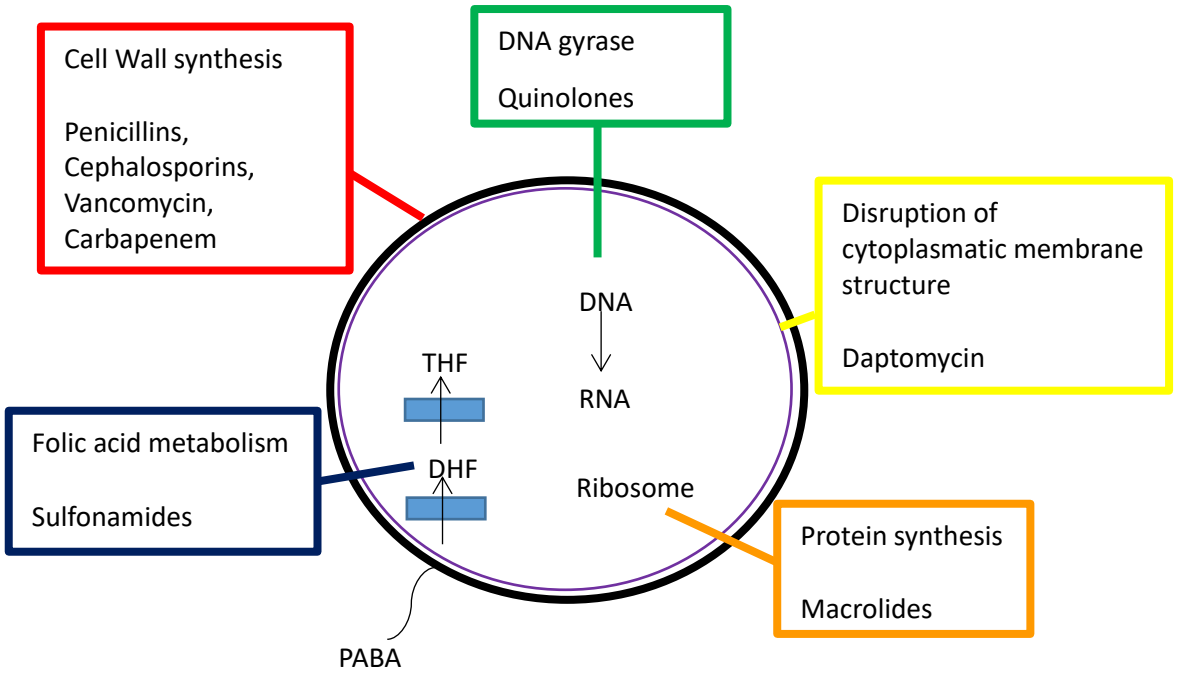


Figure 2. Mode of action of different antiobitoics.[8]

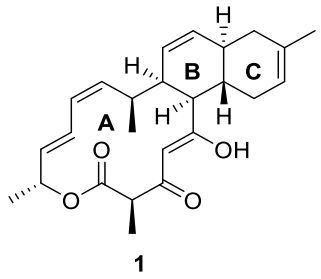
8.3 Anthracimycin: a new molecule active against MRSA bacteria

As mentioned in the previous section, the prevalence of methicillin-resistant *Staphylococcus aureus* infections and the slow development of new antibiotics, represents a major clinical challenge.[10, 11] The availability of novel molecules for treating multi-resistant bacteria, is becoming a problem and new structures are needed.[12] Natural products, such as secondary metabolites isolated from microorganisms, such as fungi and actinomycetes, were found to possess antimicrobial activities and this led to new lead structures for drug discovery.[13] In some of these specific bioactive secondary metabolites such as monacolins, macrolides, pyrrolidine-2-one and 4-hydroxy-2-pyridone alkaloids, a common feature in the chemical structure was found to be a "decalin" motif, substituted with variuos functional groups. This peculiar scaffold could be biosynthesised by two different pathways: the mevalonate pathway for isoprenoids and the acetate pathway for polyketides.[14] In 2013, Fenical and his group reported the isolation of a marine microorganism of *Streptomyces* species from near-shore marine sediments near Santa Barbara, CA.[15] The culture extracts were found to possess significant activity against *Bacillus anthracis*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant of *Staphylococcus aureus*. The fractionations of the extract afforded a compound called anthracimycin **1**, responsible for the antibiotic activity (**Figure 3**).[15] The *Bacillus anthracis* disease is one of the most common infections in farm animals and has also been used as a bioterrorism weapon. In 2001, *Bacillus anthracis* spores were spread by someone sending letters through the US postal system, after the World Trade Center attack.[15]

Anthracimycin was isolated as a white solid with a molecular formula of $C_{25}H_{32}O_4$ and its structure was determined by NMR spectroscopy analysis and X-ray crystallographic data.[15] Upon this analysis, the structure of this natural compound appeared to be a combination of a 14-, 6- and 6-membered rings of polyketide origin. The 14-membered ring is characterised by the presence of a lactone and an enolised β-diketone. The equidistant position of the proton between each oxygen, in the X-ray data, confirmed the keto-enol tautomerisation. Anthracimycin is also characterised by the presence of two double bonds in the 14-membered ring. One in a *Z*-configuration and the other as an *E*-alkene, which

was confirmed by the vicinal coupling constants of 10.5 Hz and 15.2 Hz, respectively. This molecule possesses a *trans*-decalin core scaffold, characterised by the presence of two double bonds. Anthracimycin also features stereogenic centers at C-2, C-6, C-7, C-12, C-15, C-16 and C-21 and a *cis*-orientation of A/B rings, as well as a *trans*-ring junction of B/C rings.

This polyketide belongs to the macrolide antibiotic class but is structurally distinct from the typical members of this group, by the presence of the tricyclic system characterised by a decalin scaffold and the absence of a deoxyhexose motif.[16]



1

Figure 3. The chemical structure of anthracimycin **1**.[15]

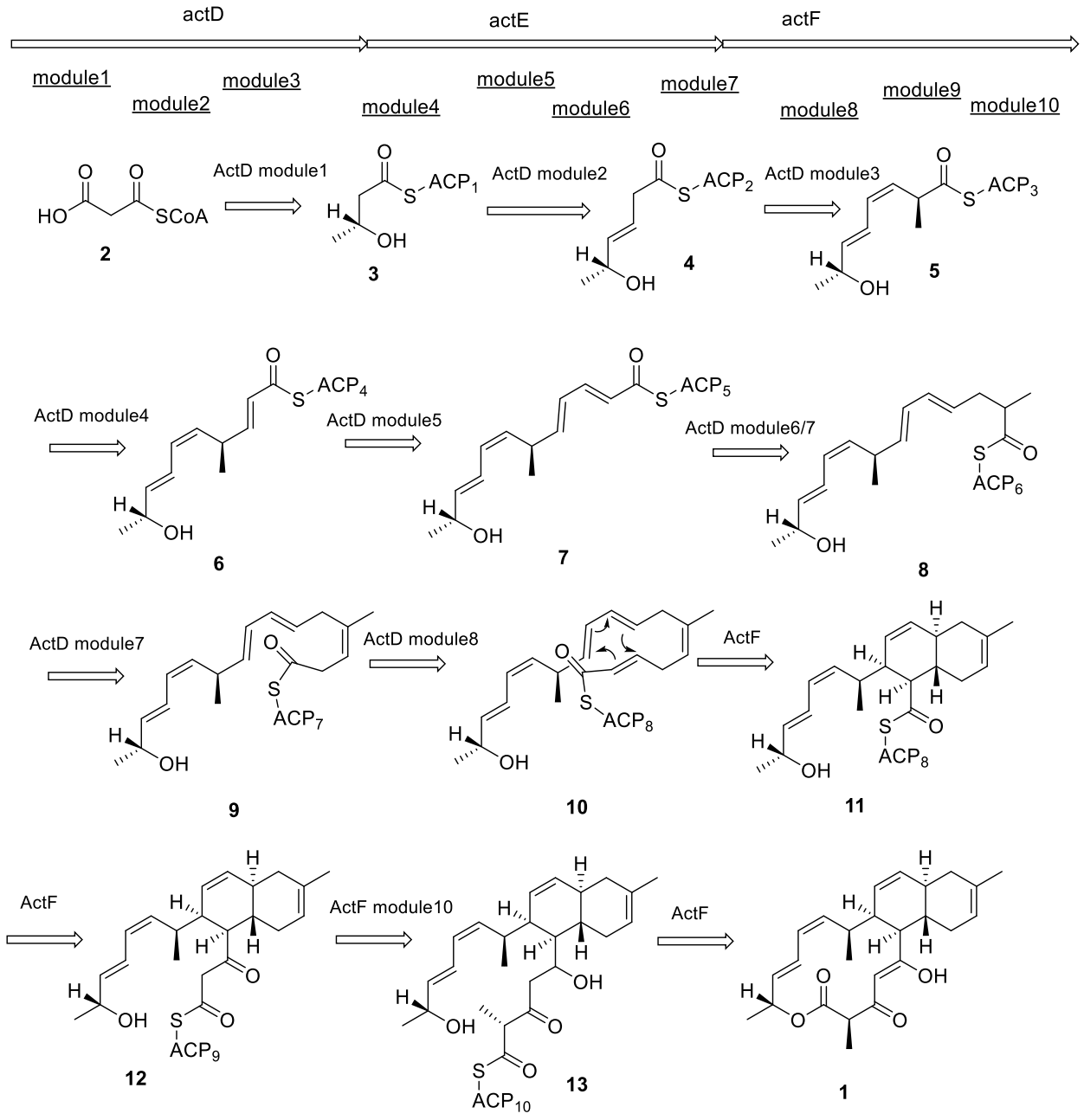
8.3.1 The biosynthesis of anthracimycin

In 2015, the biosynthesis of this polyketide was reported and a type I polyketide synthase (PKS) was found to be the enzyme responsible for chain assembly.[16] Generally, three classes of PKSs have been reported: type I, iterative type II and the acyl-carrier protein type III. Type I PKSs contain a β-ketoacyl-ACP synthase, an acyltransferase and an acyl carrier protein domain, which are responsible for choosing and loading the carboxylic acid units for the successive condensation reactions in the chain assembly.[17] This PKSs catalysed series of Claisen-like condensations, for the formation of metabolite intermediates in the chain elongation process (**Scheme 2**).[17]

The biosynthetic pathway of anthracimycin may be initiated by decarboxylation of the malonyl residue **2**, to form the acylated ACP_1 metabolite intermediate **3**.[18, 19] Chain elongation would proceed to provide ACP_2 **4**, introducing a β,γ-double bond, which would also be introduced in fragment **5** to form a conjugated diene. Module 4 and 5 could be characterised by a chain elongation with the introduction of α,β-double bonds to form fragment **6**.[19] Then, α-methylation and β-keto reduction, followed by the introduction of a β,γ-shifted double bond with *cis*-geometry, would generate intermediate **8**.[20] Further chain elongation would allow the formation of the α,β-unsaturated compound **10**, suitable for [4 + 2] cycloaddition, to generate the *trans*-decalin scaffold of the natural product. An *endo*-transition state of **10** could be envisioned for the formation of this *trans*-decalin core. The last two-step sequence of chain elongation, would be characterised by a TE domain to catalyse macrocyclisation and chain release (**Scheme 2**).[16]

A small number of natural product biosynthetic pathways, are characterised by the presence of an enzyme that is able to catalyse intramolecular [4 + 2] cycloadditions, for the formation of decalin scaffolds.[21-27] Recently, a FAD-dependent enzyme capable of generating a *trans*-decalin motif in the pyrroindomycin biosynthetic pathway has been identified,[28] as well as the LovB PKS enzyme responsible for the [4 + 2] cycloaddition involved in the formation of the fungal metabolite lovastatin.[25, 26, 29] Interestingly, in the case of anthracimycin biosynthesis, it is still unknown if the intramolecular Diels–Alder reaction for the formation of the *trans*-decalin is catalysed by the enzyme

or is spontaneous. In this cycloaddition reaction, fragment **10** is characterised by the presence of a dienophile double bond with *E* geometry and a rigid orientation, due to the presence of the two β,γ-shifted double bonds. This leads to a diminished degree of freedom, aiding intramolecular cycloaddition by steric effects rather than stabilisation by any particular transition state.[16]



Scheme 2. The biosynthesis of anthracimycin **1**.[16]

8.3.2 The biological effect of anthracimycin

In most macrolides, the mode of action is the inhibition of protein biosynthesis by binding the 50 S ribosomial subunit.[8] However, macromolecular synthetic studies, suggested that the anthracimycin mechanism of action could involve inhibition of DNA and RNA synthesis, in the absence of DNA intercalation.[30] These assays were performed by measuring the quantitative incorporation of radiolabelled precursors of DNA and RNA. Disruption effects of DNA and RNA synthesis occurred at the Minimum Inhibitory Concentration (MIC) value on [^{3}H] thymidine and [^{3}H] uridine. It was also observed an additional secondary effect of anthracimycin on protein synthesis, at higher concentration of the MIC value.[31]

These assays also showed potent activity of the natural product against all groups of *Staphilococcus aureus* tested, with a MIC value of < 0.25 mgL^{-1}. Anthracimycin also inhibited vancomycin-resistant *Enterococcus faecalis*, MIC < 0.25 mgL^{-1}, but no relevant Gram-negative activity was found, MIC > 64 mgL^{-1} (**Table 2**).[30]

Strain	MIC (mgL^{-1})
MRSA	
Sanger 252 (USA200)	0.063
TCH1516 (USA300)	0.125
ATCC 33591	0.08
NRS192 (ST1)	0.16
Non-S. aureus	
Enterococcus faecalis	0.25
Enterococcus faecalis isolate	0.125
Bacillus anthracis	0.03
Pseudomonas aeruginosa	> 64
Klebsiella pneumoniae	> 64

Table 2. MIC values against major classes of bacteria.[30]

A rapid bactericidal kinetics were also exhibited by this natural compound, with a > 4-log kill of USA 300 MRSA during a 3 hours period at > 5 x MIC. A minimal post-antibiotic effect, compared with vancomycin, and a minimal toxic effect to eukaryotic cells was also observed, having a half maximal inhibitory concentration (IC_{50}) = 70 mgL^{-1}, against human carcinoma cells (**Figure 4**).[30]

An effect below the MIC value and sensitisation of the host immune system at sub-MIC anthracimycin was also observed.[32] The increased effect of human cathelicidin (antimicrobial peptides found in macrophages and involved in the innate human defense) on MSRA growth, occurred at 1/4 x MIC of anthracimycin. This synergy is without precedent and additional studies will investigate this interaction.[32]

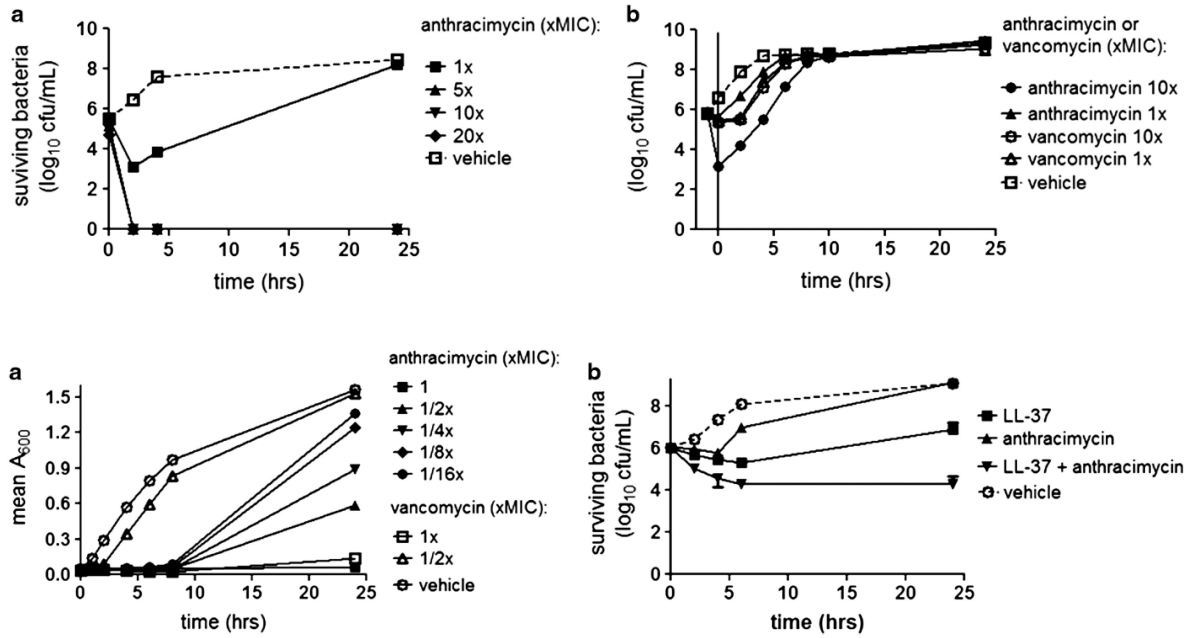
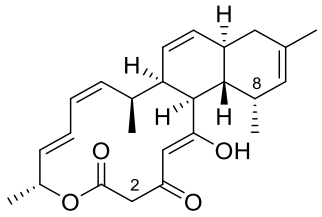


Figure 4. Concentration effect of anthracimycin **1.**[30] *J. Antibiot.* , **2014**

Another biological activity of anthracimycin has recently been discovered. In 2017, suppression of cell proliferation and motility and induction of apoptosis against hepatocellular carcinoma (HCC), was reported.[33] This anticancer property of anthracimycin is associated with the mTOR-signalling activation.[34, 35] The serine/threonine kinase TOR phosphorylates the p70 S6 kinase, which is a protein involved in the regulation of cell growth, cell-cycle progression and metabolism.[36] Playing such a pivotal role in cell metabolism, by activation of protein and lipid synthesis, for example, mTOR-signalling is induced by many types of cancer.[37, 38] The anthracimycin mechanism to deactivate this signalling is still unclear, but many biologists suspect that this natural product could inhibit the phosphorylation pathway of p70 S6 kinase. This anticancer effect has been observed with an IC_{50} value of 2.5 µg/mL in the HCC cell lines.[34]

8.4 Isolation of an anthracimycin analogue **14**

In 2017, anthracimycin BII-2619 **14** was isolated from *Nocardiopsis kunsanensis*, an actinobacterial microorganism (**Figure 5**).[39] This natural product was purified as a white powder and was found to have the same molecular formula of anthracimycin **1**. *Via* NMR spectroscopy analysis, the structure and relative configuration of **14** was assumed to be the same as anthracimycin, except for the presence of the methyl group at C-8 instead of C-2. This analogue of anthracimycin **14** was found to have antimicrobial activity against Gram-positive bacteria, but compared to data for anthracimycin the MIC values were found to be between 50 and 100-fold lower.



14

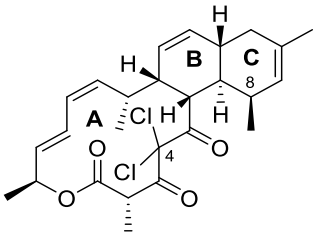
Figure 5. The chemical structure of anthracimycin BII-2619 **14**.[39]

Target Organism or Cell line	Activity (µg/ml) **1**	Activity (µg/ml) **14**
Gram Positive bacteria		
MRSA (ATCC 33591)	0.06	0.125
MSSA (ATCC 25923)	0.06	1
Bacillus subtilis (ATCC 6633)	0.5	64
Enterococcus faecalis	0.125	8
Gram Negative bacteria		
Escherichia Coli	>128	>128
Pseudomonas aureoginosa	>128	>128
Mammalian cells		
Human lung carcinoma cells	~32	35

Table 3. Biological activity of anthracimycin BII-2619 **14** compared to anthracimycin **1**.[39]

8.5 A related polyketide: chlorotonil A **15**

A related tricyclic metabolite with a similar carbon skeleton was found in chlorotonil A **15**, isolated from the myxobacteria *Sorangium cellulosum* (**Figure 6**).[40] The pivotal feature of this polyketide is its pseudo-enantiomerism with anthracimycin **1**. In fact, chlorotonil A **15** exhibits the opposite absolute configuration at C-2, C-6, C-7, C-12, C-25, C-21, C-15 and C-6 when compared to anthracimycin **1**. Additional differences are represented by the presence of the methyl group at C-8 in the C-ring and by the presence of a dichloromethylene group at C-4, in the A-ring.[40] In Nature, other examples of enantiomeric products are reported: a linear precursor geranylgeranyl pyrophosphate is cyclised into monoterpenes (+)-limonene and (-)-limonene; (+) notoamide B and (-)-notomamide B are enantiomers of the same intermediate precursors.[41] In these cases, the enantiomeric products are formed by the cyclisation of achiral precursors, instead, in anthracimycin **1** and chlorotonil A **15**, a pair of enantiomeric precursors generate highly modified related structures.[42] These two secondary metabolites **1** and **15** share a similar carbon framework and this is a rare case, because anthracimycin **1** is produced by actinomycetes, whereas, chlorotonil A **15** is produced by myxobacteria. This is also the first reported example of pseudo-enantiomers polycyclic secondary metabolites derived from a type I PKS.[42]



15

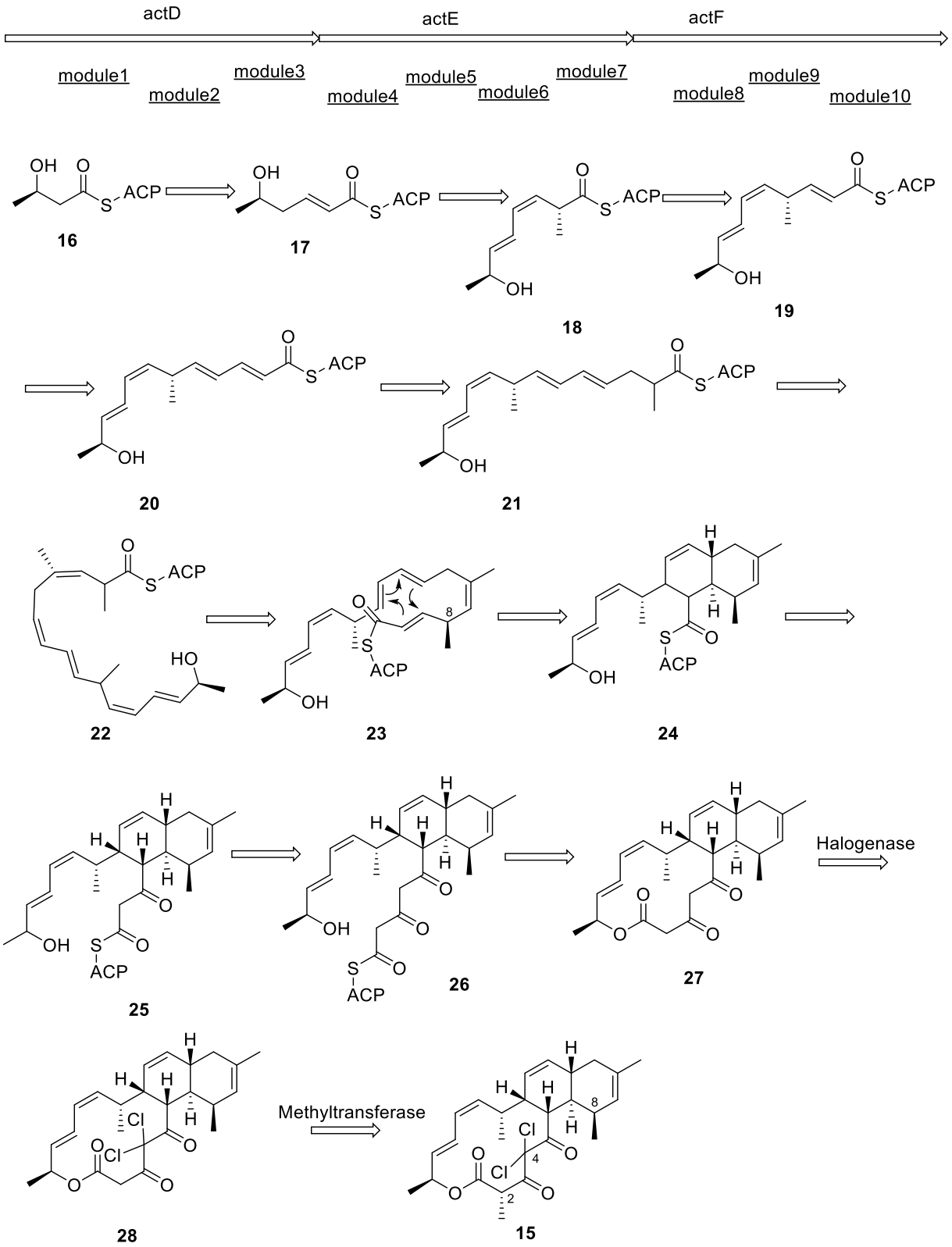
Figure 6. The chemical structure of chlorotonil A **15**.[40]

The molecular formula of chlorotonil A **15** is $C_{26}H_{32}Cl_2O_4$, and this polyketide features an unsaturated *trans*-decalin core scaffold between B/C-rings and an unusual gem-dichloro-1,3-dione functionality in the A-ring. A *cis*-relationship between the A/B rings is also observed, as well as the presence of stereogenic centers at C-2, C-6, C-7, C-12, C-25, C-21, C15, C-6 and C-8.[40]

Compared to anthracimycin **1**, chlorotonil A **15** exhibits potent bioactivity against Gram-negative bacteria, such as *Pseudomonas aeruginosa* and also against the malaria protozoan pathogen *Plasmodium falciparum.*[43] The ability to penetrate external bacteria membranes, relies upon the presence of the gemdichloro-1,3-dione and on the methyl group at C-8, which enhance the lipophilicity of this polyketide.

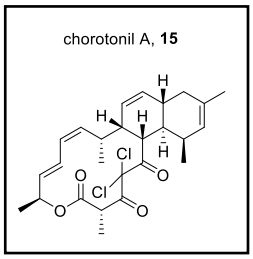
The biosynthesis of chlorotonil A **15** was studied and biological data showed a PKS pathway responsible for the formation of this polyketide in parallel with the biosynthetic route of anthracimycin **1** (**Scheme 3**).[13] This similarity, could explain the several homogeneity features in the structure of these two secondary metabolites.

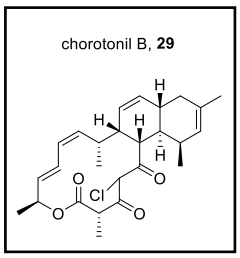
Starting with a malonyl residue-ACP **16**, chain elongation takes place *via* a series of Claisen condensation reactions, as reported in the biosynthesis of anthracimycin. Again, the key step in this pathway is the intramolecular Diels–Alder reaction to form the *trans*-decalin core of the molecule, intermediate **24**. A hypothesis to explain the inversion of the stereocenters in the *trans*-decalin scaffold compared to anthracimycin, relies on the presence of the methyl group at C-8, which could play a role in "pre-organising" the structure of **23**, during cycloaddition. [13] After chain elongation, the advanced intermediate **27** is released by the PKS domain and an unprecedented double chlorination reaction at C-4, between the two carbonyl groups, and a methylation reaction at C-2 take place to form chlorotonil A **15** (**Scheme 3**).[13]

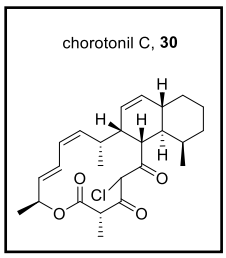


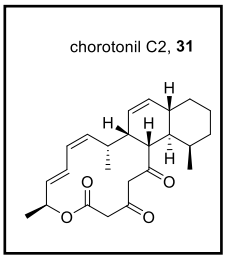
Scheme 3. The biosynthesis of chlorotonil A **15**. [13]

Interestingly, chlorotonil A congeners such as chlorotonil B **29**, chlorotonil C **30** and chlorotonil C2 **31** have also been isolated.[13] Chlorotonil B **29** and chlorotonil C **30** differ from chlorotonil A by the lack of one chlorine atom at C-4, in the A-ring. Chlorotonil B **29** also differs from chlorotonil A by the lack of a double bond and the methyl group in the C-ring. In addition, chlorotonil C2 **31** differs from chlorotonil C **30** by the lack of the methyl group at C-2 and the presence of no chlorine atom. These differences in the structure, made the congeners less potent towards bacteria, as highlighted by the MIC values (**Table 4**). This fact indicates that the presence of two chlorine atoms is pivotal for the biological acitivty. [13]









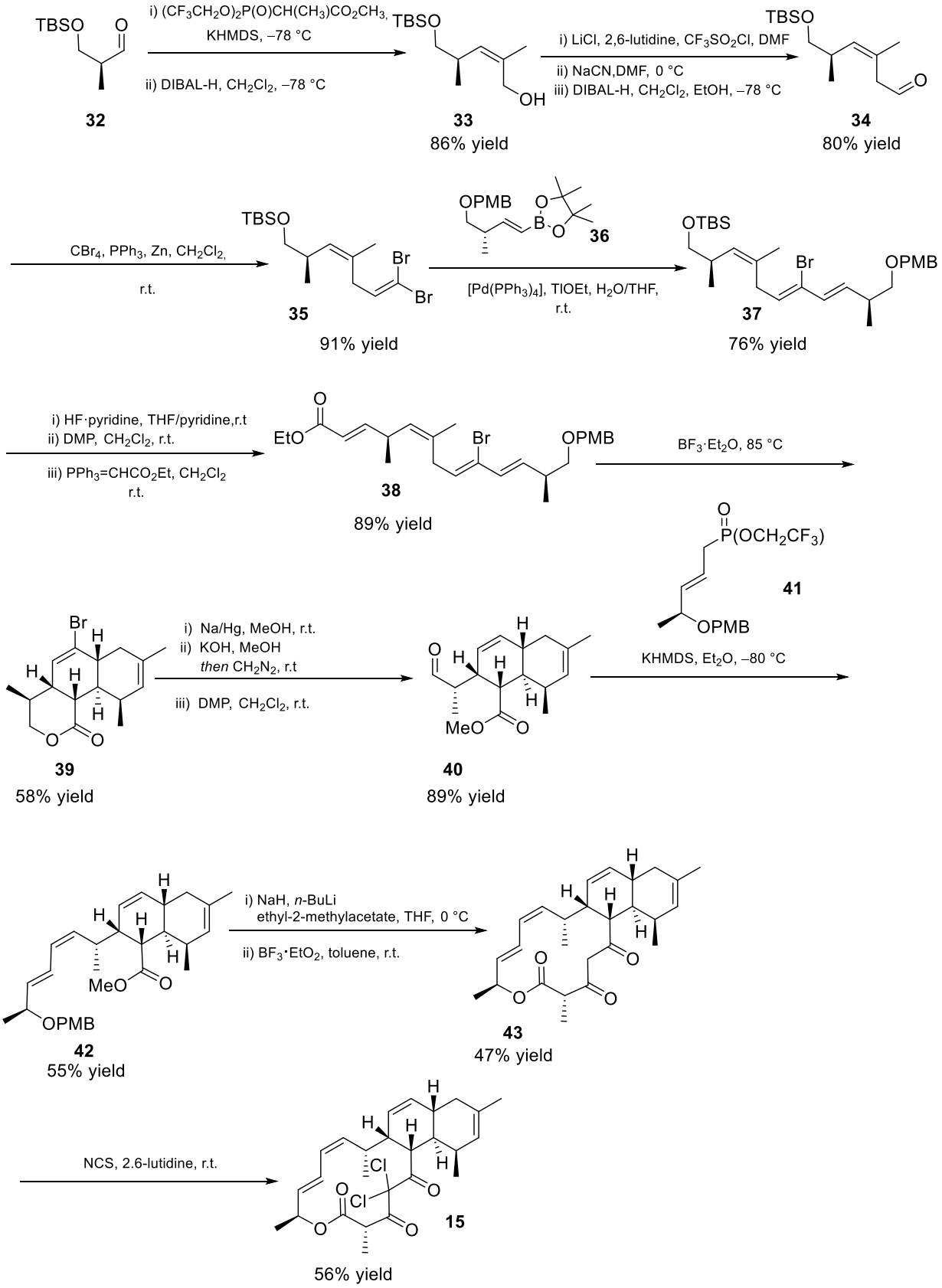
MIC	µg/ml µM	µg/ml µM	µg/ml µM	µg/ml µM	µg/ml µM	µg/ml µM	µg/ml µM	µg/ml µM
M.luteus **DSM-1790**	0.0125	0.025	> 3.2	> 6.4	> 3.2	> 6.4	1.6	3.8
B.subtilis **DSM-10**	≤0.003	≤0.006	> 3.2	> 6.4	> 3.2	> 6.4	1.6	3.8
S.aureus **Newman**	0.006	0.012	> 3.2	> 6.4	> 3.2	> 6.4	1.6	3.8
E.faecalis **ATCC-29212**	> 3.2	> 6.4	> 3.2	> 6.4	> 3.2	> 6.4	> 3.2	> 6.4
S.penumoniae **DSM-20566**	0.0125	0.025	> 3.2	> 6.4	> 3.2	> 6.4	> 3.2	> 6.4
E.Coli	> 3.2	> 6.4	> 3.2	> 6.4	> 3.2	> 6.4	> 3.2	> 6.4

Table 4. The biological activity of chlorotonil A compared with the congeners.[13]

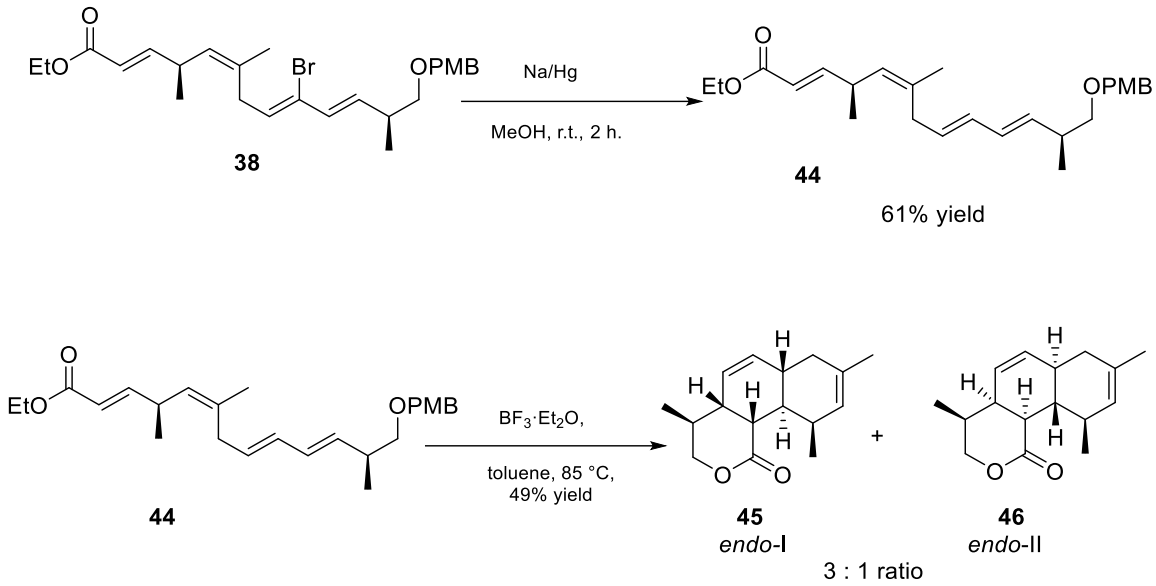
8.5.1 The total synthesis of chlorotonil A **15**

In 2008, Kalesse *et al.* reported the total synthesis of chlorotonil A **15**, using a biomimetic and stereocontrolled strategy (**Scheme 4**).[44] The synthesis started with derivatisation of the Roche ester to give the TBS-protected aldehyde **32**, which was subjected to a Still-Gennari olefination and DIBAL-H reduction to afford allyl alcohol **33**. Homologation and oxidation formed aldehyde **34**, which was subjected to a Corey-Fuchs transformation, to generate the dibromoolefin **35**.[45, 46, 47]

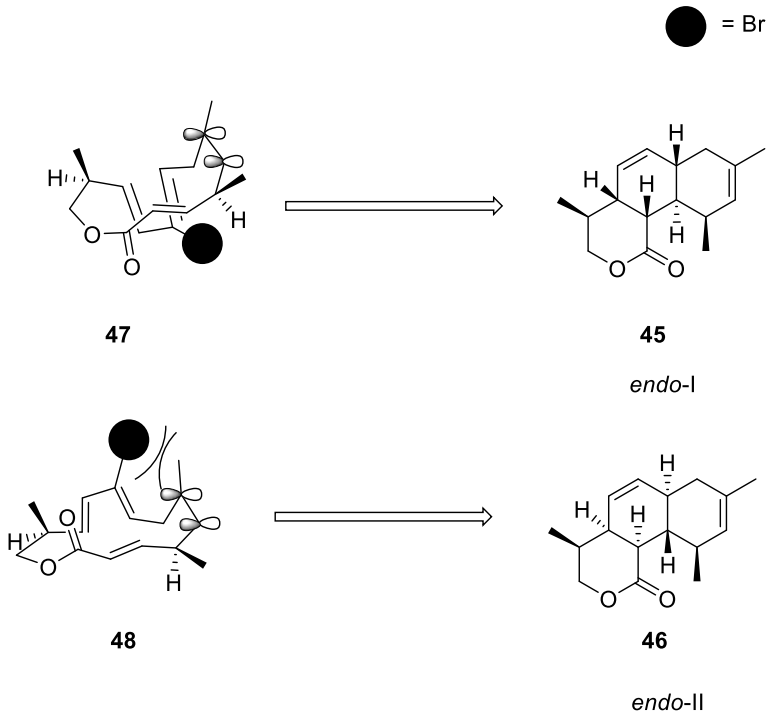
Suzuki coupling between the dibromoolefin **35** and the boronic ester **36** gave intermediate **37**,[48] which after deprotection, oxidation and chain elongation *via* a Wittig reaction, generated the key intermediate **38**. A Lewis acid triggered the formation of the *trans*-decalin **39**, with high diastereoselectivity due to the presence of the bromine atom (d.r. 13 : 1).[49, 50] Lactone opening followed by esterification afforded compound **40**, which was coupled with the novel allyl phosphonate reagent **41**, to form **42** *Z*,*E*/*E*,*E* with a ratio of 3 : 1. Finally, dianion addition of ethyl-2-methylacetoacetate, followed by macrocyclisation in the presence of a Lewis acid, yielded chlorotonil A **15**, as a single isomer. To further explain the high selectivity obtained in the Diels–Alder cycloaddition reaction and the key role played by the bromine substituent, the dehalogenated intermediate **44** was prepared and subjected to the reaction conditions (**Scheme 5**). As a result, a mixture of the *endo*-I and *endo*-II products **45** and **46** were obtained in a 3 : 1 ratio, decreasing the selectivity of this cycloaddition reaction. The explanation of this result relied on the conformation of transition states **47** and **48**, in which the presence of the bromine substituent disfavoured the *endo-II* transition state due to electronic and steric repulsion (**Scheme 6**).



Scheme 4. The total synthesis of chlorotonil A **15** by Kalesse *et al*.[44]



Scheme 5. Diels–Alder reaction without bromine: different ratio of products obtained.[44]



Scheme 6. Transition state of *endo-I* and *endo-II* products.[44]

8.6 Computational investigations into IMDA synthesis of anthracimycin

The initial strategy considered towards the total synthesis of anthracimycin **1** was a biomimetic approach. The published total synthesis by Kalesse of chlorotonil A **15**, utilised a bromine atom to direct the intramolecular Diels–Alder formation of the *trans*-decalin core in a biomimetic route. Computational studies were conducted to decide whether to follow a similar approach or whether a new total synthesis would be more appropriate. As highlighted in the biosynthetic pathway of anthracimycin **1**, whilst the polyketide is still bound to the enzyme, a Diels–Alder reaction forms the *trans*-decalin scaffold.[14] This intramolecular [4 + 2] cycloaddition could generate four possible decalin products, yet only one has been isolated.

Dr. Ian George (postdoctoral researcher in the Clarke group), conducted DFT computational studies to better understand the formation of the molecule *via* a biomimetic synthesis (**Figure 7**). Interestingly, these calculations showed the formation of two compounds **11** and **51** with a considerably lower activation barrier (ΔE) than the others. Compound **11** had a structure of the proposed anthracimycin intermediate and is both the kinetic and thermodynamic product, based on the activation energy value ΔE = 58 $KJmol^{-1}$ and the energy difference ΔH = -259.9 $KJmol^{-1}$ between the energy of the starting material precursor and the product. The *exo*-Diels–Alder product **51**, generated from the diene approaching the opposite face of the dienophile, also appeared to have a low energy barrier (ΔE = 65 $KJmol^{-1}$). The *exo*-Diels–Alder compound **49**, formed when the diene approached the same face of the dienophile, and the *endo*-Diels–Alder compound **50**, instead, each showed a high activation energy value (ΔE = 335.36 $KJmol^{-1}$ and 268.55 $KJmol^{-1}$ respectively). The data suggests it would be unlikely for these two products **49** and **50** to form. However, as the ΔE of **11** and **51** showed similar values, the possibility of forming a mixture of decalin intermediates was potentially very likely and so, the biomimetic approach was not pursued any further.

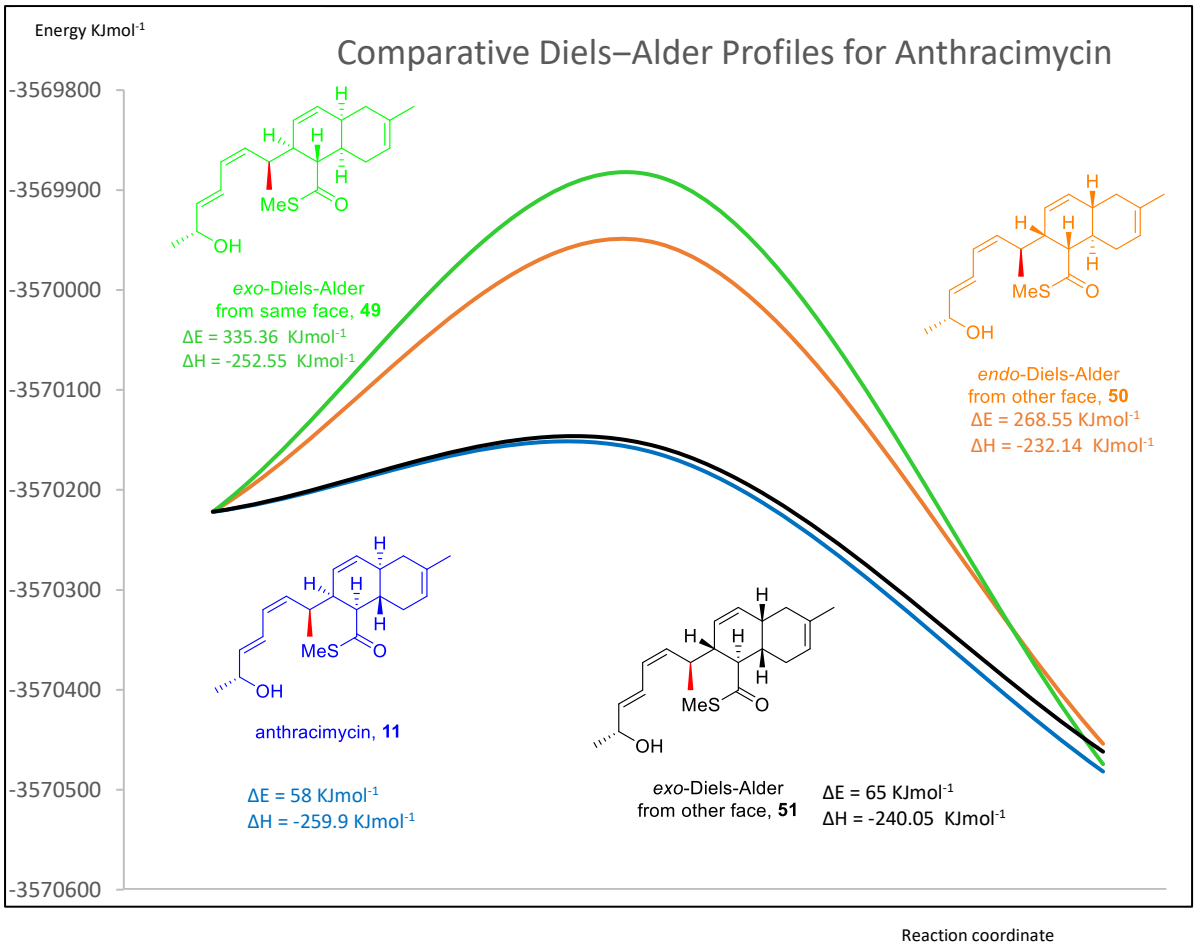


Figure 7. Computational calculation to study the biomimetic cycloaddition to form the decalin scaffold of anthracimycin, by Dr. Ian George.

These studies also showed that the stereochemistry of the Diels–Alder cycloaddition reaction was determined by the methyl group, shown in red, presumably due to the steric clash generated in the transition state giving a higher barrier to the energy of activation for the disfavoured products **49** and **50** (**Figure 8**).

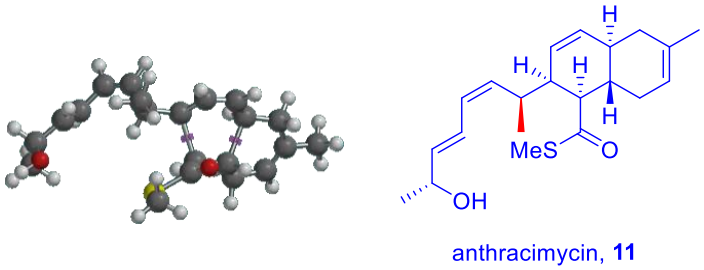
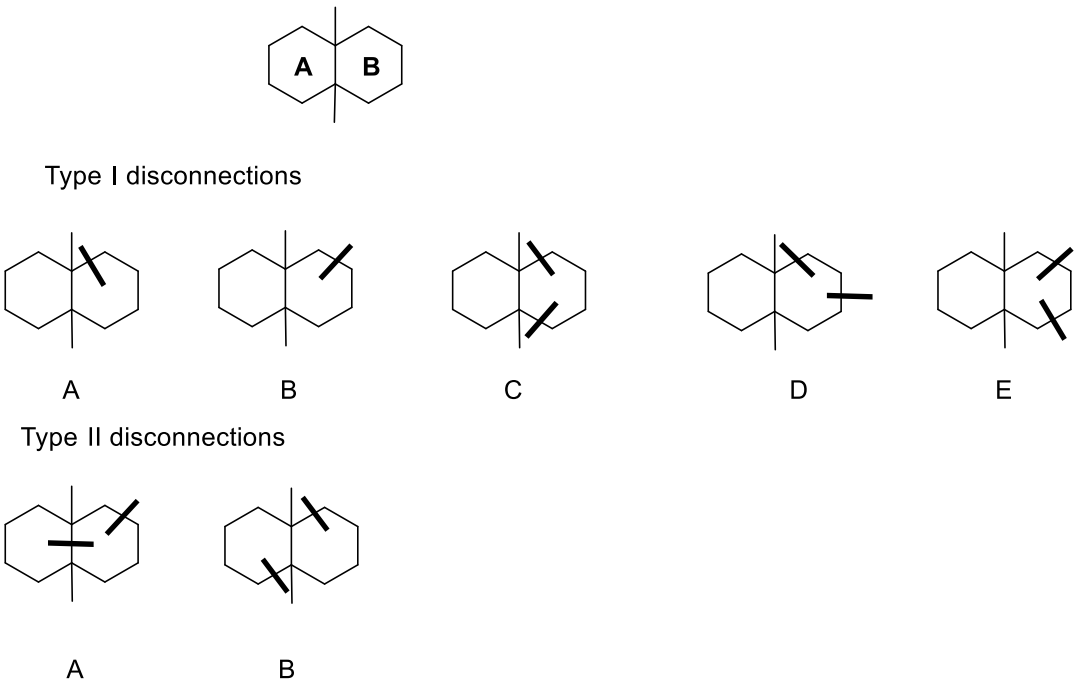


Figure 8. The transition of anthracimycin **11**.

8.7 Synthesis of functionalised decalin scaffold

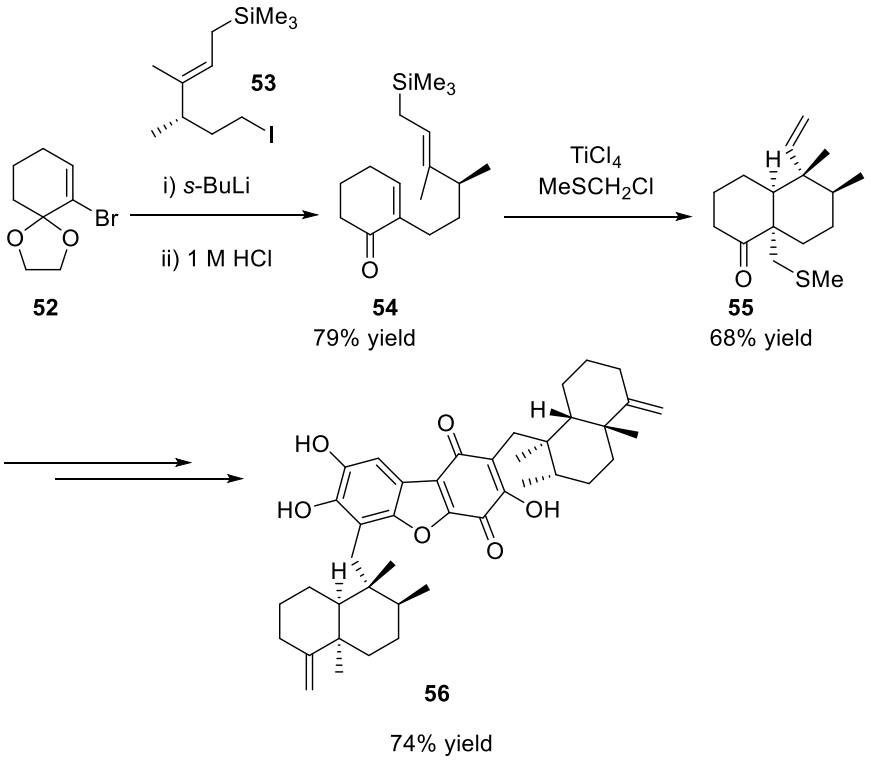
Computational studies showed that formation of a mixture of intramolecular Diels–Alder products was possible, therefore, an alternative strategy was explored for the synthesis of anthracimycin **1**. In Natural product total synthesis, different strategies for the stereoselective formation of functionalised decalins have been reported.[51] In general, there are two types of disconnection for the formation of these bicyclic systems. In the type I disconnection, functionalisation of the cyclohexane ring (cycle A or B) is followed by C-C bond formation, allowing the construction of the AB cycle. In the type II disconnection, a single process is involved in the formation of the AB decalin system (**Scheme 7**).[51]



Scheme 7. The disconnection strategies to form a decalin system.[51]

Type I A disconnection

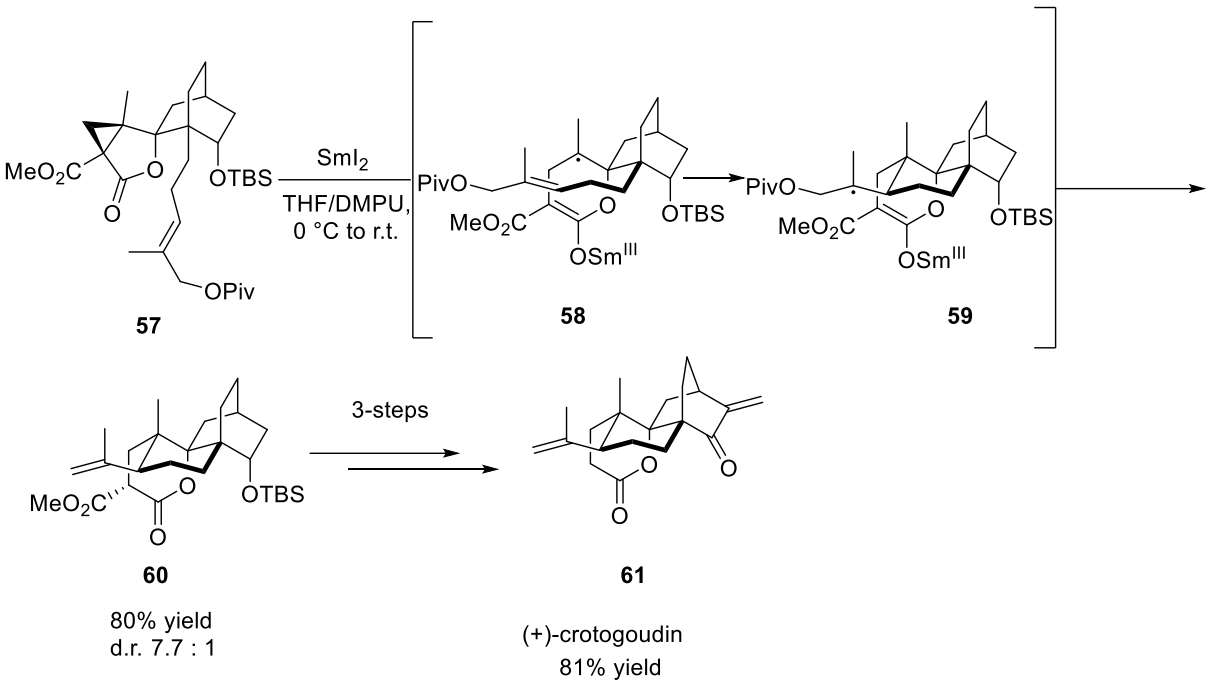
Intramolecular allylation reactions are an example of a type I A disconnection, as reported by Anderson for the construction of the *cis*-decalin **55**, in the total synthesis of popolohuanone E **56** (**Scheme 8**). An intramolecular Hosomi–Sakurai 1,4-addition, in the presence of $TiCl_4$ and allylsilane was used to generate the *cis*-decalin core of this natural product.[52]



Scheme 8. Allylation reaction as a type I A reaction for the formation of *cis*-decalin.[52]

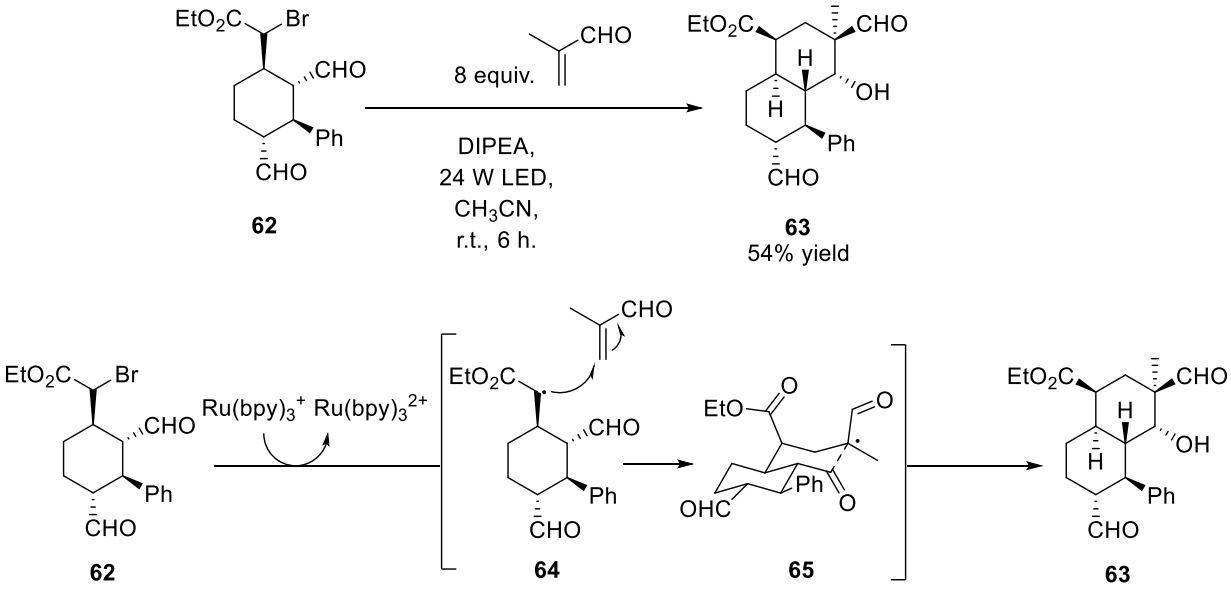
Type I B and I E disconnection

Radical reactions are well established in the construction of decalin systems, as examples of type I B and I E disconnections. In 2013, Carreira *et al.* reported the total synthesis of *ent*-crotogoudin **61**, in which the key step was a radical cyclopropane opening/annulation/elimination reaction promoted by SmI_2 (type I B) (**Scheme 9**).[53]



Scheme 9. Radical cyclopropane opening/annulation/elimination for the formation of decalin **60**.[53]

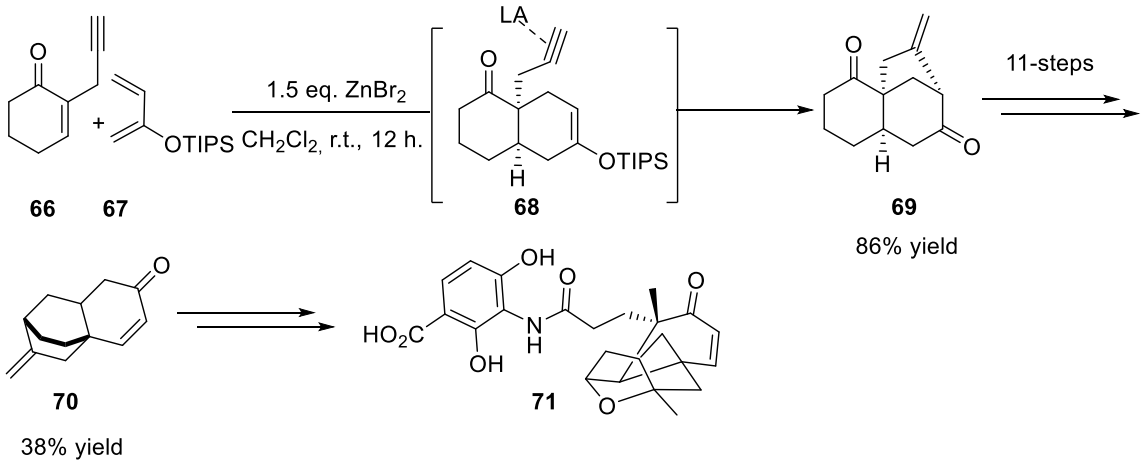
In 2013, Hong reported a one-pot photocatalytic Michael-aldol sequence (type I E) for the enantioselective synthesis of the functionalised decalin system **63** (**Scheme 10**).[54]



Scheme 10. Photocatalytic Michael-aldol sequence for the enantioselective synthesis of decalin **63**.[54]

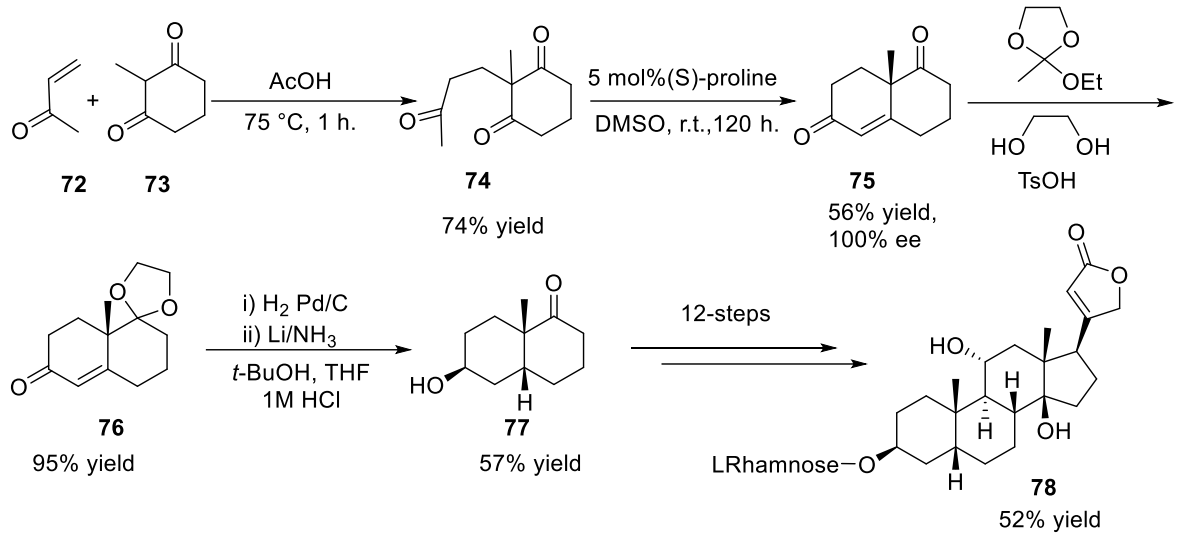
Type I C disconnection

The intermolecular Diels–Alder cycloaddition reaction is an example of a type I C disconnection. In the synthesis of tricyclic *ent*-kaurenoid natural product **71** reported by Zhang, intermolecular Diels–Alder cycloaddition, followed by intramolecular carbocyclisation was developed to form a common building block **70**, for the synthesis of this natural product (**Scheme 11**).[55]



Scheme 11. The Diels–Alder/carbocyclisation sequence reported by Zhang.[55]

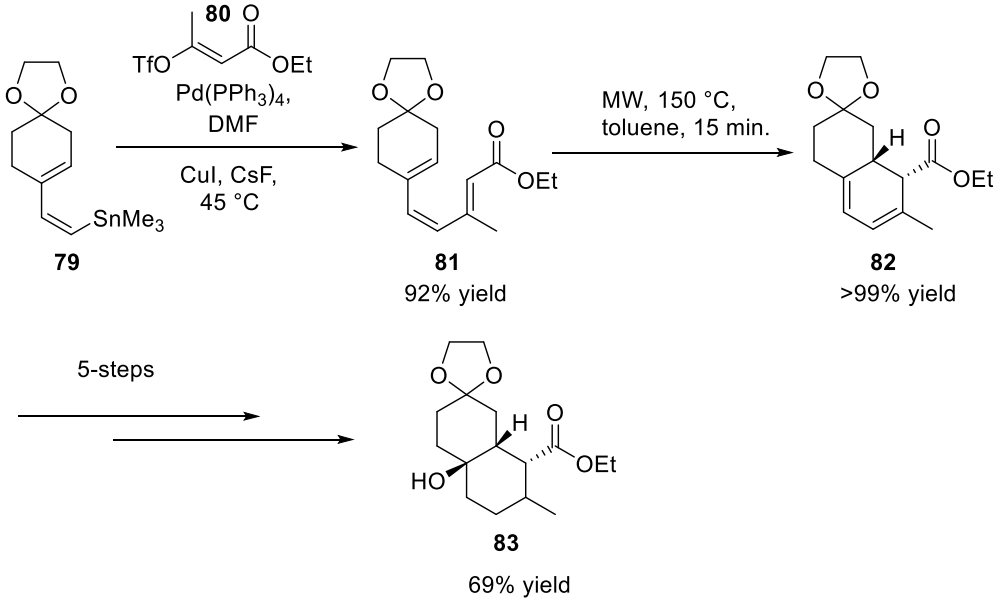
The asymmetric version of the Robinson annulation reaction was reported by Jung in the total synthesis of rhodexin A **78** (**Scheme 12**).[56] In this sequence, acetic acid and (*S*)-proline catalysed a condensation reaction to form compound **75**, which was subsequently transformed into *cis*-decalin **77** using catalytic hydrogenation conditions.



Scheme 12. The total synthesis of rhodexin A **78**, by Jung.[56]

Type I D disconnection

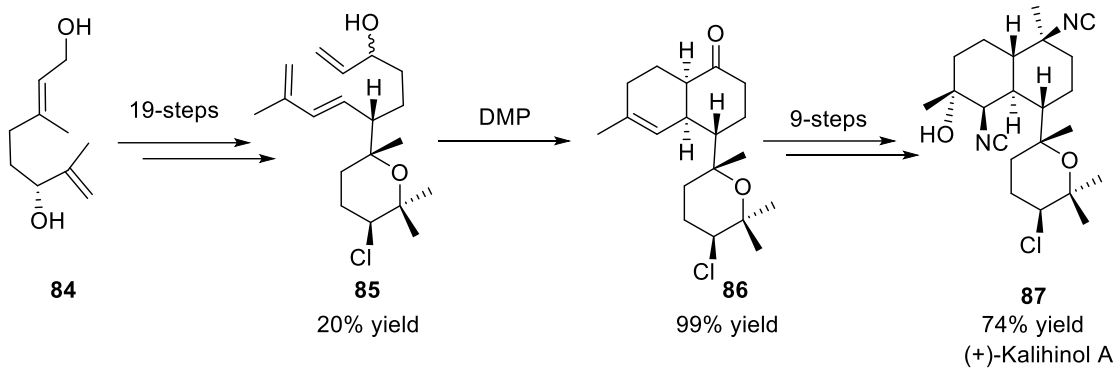
Pericyclic cyclisation reactions, such as 6π-electrocyclisation, were used by Williams for the formation of the *cis*-hydroxydecalin core of crotonins, as an example of a type I D disconnection.[57] A cross-coupling reaction between **79** and **80** afforded the intermediate **81**, which was subjected to a thermal electrocyclisation reaction to form **82** in quantitative yield (**Scheme 13**).



Scheme 13. Pericyclic cyclisations as an example of a type I D disconnection. [57]

Type II A disconnection

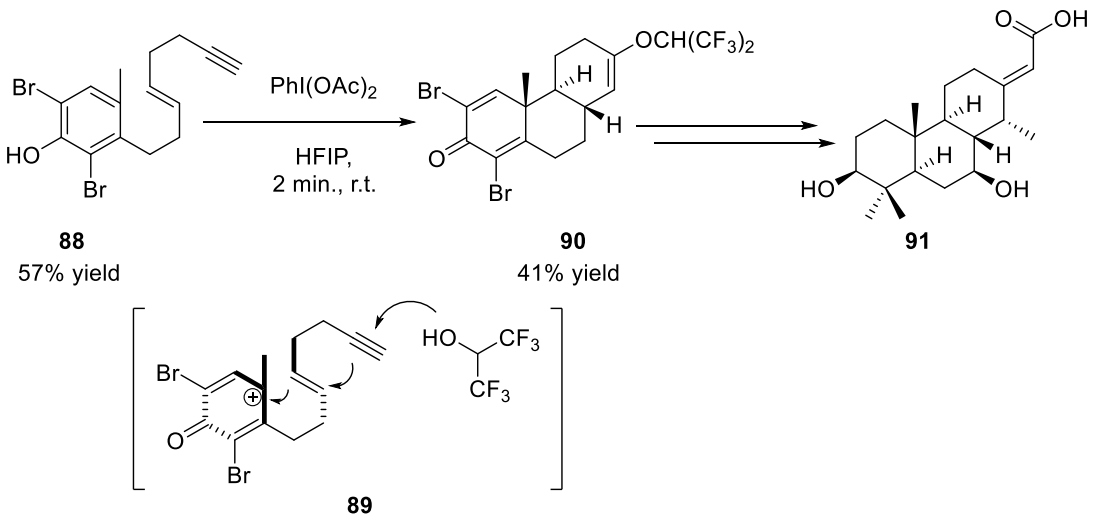
In 2012, Miyaoka reported the synthesis of (+)-kalihinol A **87**, a richly functionalised antimalarial diterpenoid.[58] The synthetic sequence started with the construction of *cis*-decalin **86** in 20 steps using an intramolecular Diels–Alder cycloaddition, as an example of type II A disconnection (**Scheme 14**).



Scheme 14. The intramolecular Diels–Alder (type II A) in the total synthesis of kalihinol A **87**. [58]

Type II B disconnection

An example of a type II B disconnection is represented by cationic cyclisation, which has been used by Canesi *et al.*, to form the *trans*-decalin intermediate **90** during the total synthesis of cassaic acid **91**.[59] In the presence of $PhI(OAc)_2$ and hexafluoroisopropanol, a phenol was transformed into a highly reactive electrophilic species **89** (aromatic ring umpolung). The presence of bromine atoms at the *ortho*-positions, promoted cyclisation at the *para*-position of the molecule to afford **90** in a 41% yield (**Scheme 15**).



Scheme 15. Cationic cyclisation used as an example of type II B disconnection.[59]

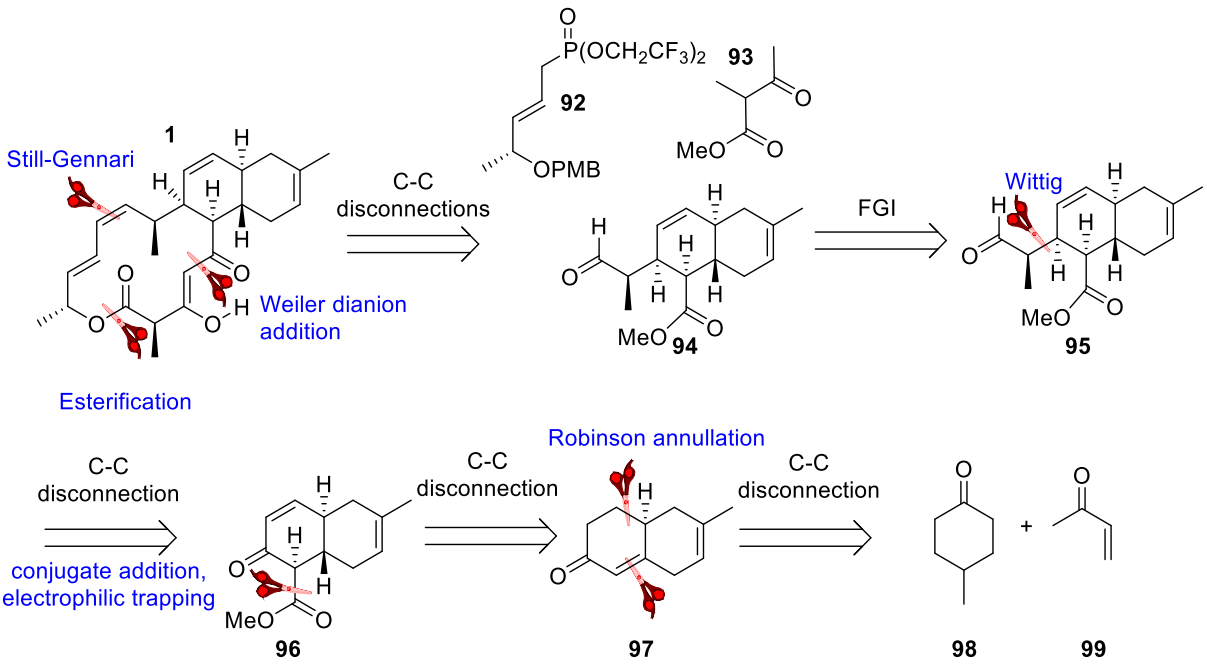
As suggested by the computational studies, the intramolecular Diels–Alder cycloaddition reaction was not a useful strategy to selectively form the *trans*-decalin core of anthracimycin. Consequently, the intermolecular type I disconnections would be explored instead. The intermolecular Diels–Alder cycloaddition and the Robinson annulation (type I C) would be envisioned, as a versatile and common strategy to build bicyclic systems with angular substituents stereoselectively. As the *trans*-decalin core of anthracimycin presents two double bonds in the B and C ring, and two side chains in a *syn*-relationship, key disconnections of these two envisioned strategies will be proposed and discussed in detail in the next chapter.

9. Results and discussion

9.1 The Robinson annulation to form a functionalised *trans*-decalin

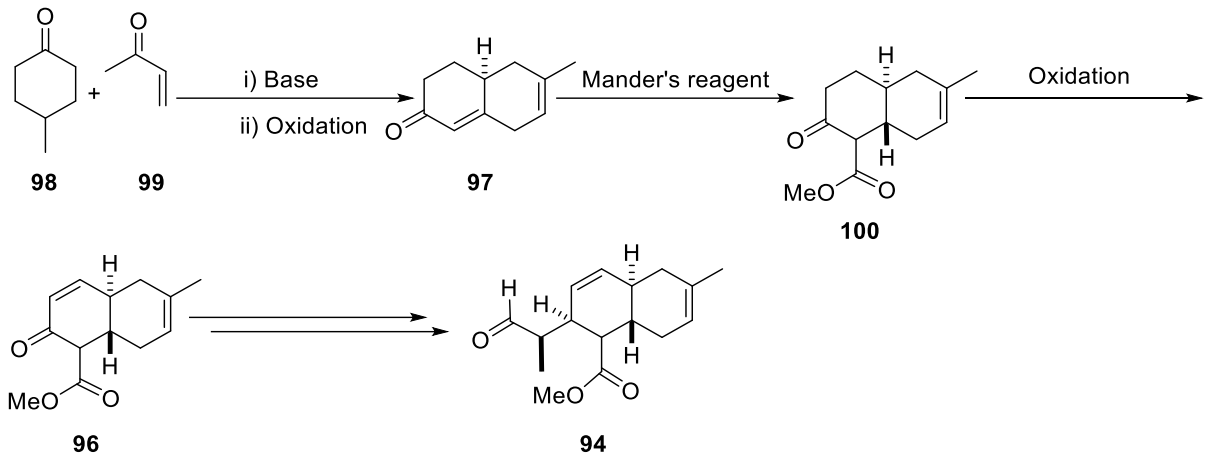
9.1.1 Retrosynthetic analysis

The aim of this project was to complete the total synthesis of anthracimycin **1**. The proposed retrosynthetic strategy (**Scheme 16**) involved dividing the molecule into three major fragments: the Still–Gennari reagent **92**, the β-ketoester **93** and the highly functionalised *trans*-decalin core **94**. The desired *Z*-double bond was envisioned to be formed *via* Still–Gennari olefination, and a Weiler-dianion addition reaction would connect fragment **92** to the *trans*-decalin core **94**. Finally, a macrocyclisation would then generate the 14-membered macrocycle ring and form the desired natural product **1**. Key disconnections for formation of this highly functionalised *trans*-decalin core **94** would involve Wittig olefination and conjugate addition for the installation of the two side chains. A Robinson annulation reaction would be investigated for the synthesis of the decalin system **97**.



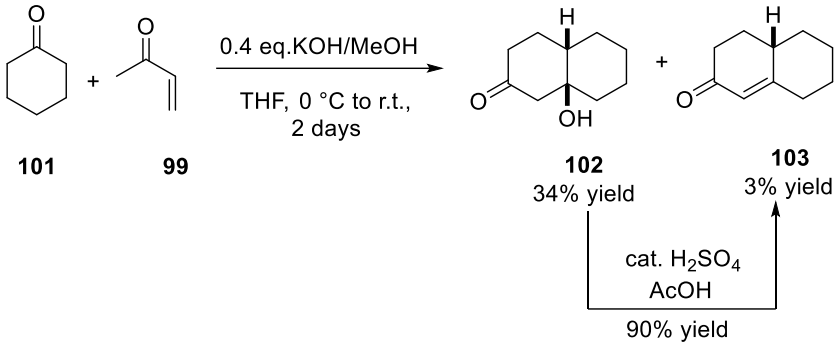
Scheme 16. The retrosynthetic analysis of anthracimycin **1**, using the Robinson annulation strategy.

As illustrated in the type I C disconnection, the Robinson annulation reaction is a three-step sequence, and due to its ability to form fused systems with angular substituents, it is one of the main reactions used for the construction of decalins in natural product synthesis.[60] This reaction would be investigated for the synthesis of the *trans*-decalin **97**. A conjugate addition reaction followed by enolate trapping with Mander's reagent could be employed to install the methyl ester chain yielding **100**. Further transformations of this compound **100**, such as oxidation, Wittig olefination and reduction reactions would be explored to form the core of anthracimycin **94** (**Scheme 17**).



Scheme 17. The Robinson annulation/conjugate addition approach to the synthesis of the decalin core **94**.

The annulation of cyclohexanone **101** in the presence of methylvinylketone **99** and KOH as a base was attempted,[61] and the decalin product **103** was generated in a 3% yield (**Scheme 18**). The isolation of the hydroxyl-decalin intermediate **102** explained the low yield obtained from this cyclisation reaction, as a consequence of the incomplete transformation into the decalin final product **103**. However, the conversion of **102** into the desired decalin **103** was investigated *via* an elimination reaction using a range of acidic and basic conditions. In the presence of strong acid, the desired compound **103** was isolated in high yields (**Table 5**, **entry 1** and **2**). Basic conditions, however, were not as effective for this transformation (**Table 5**, **entry 3** and **4**).[62]

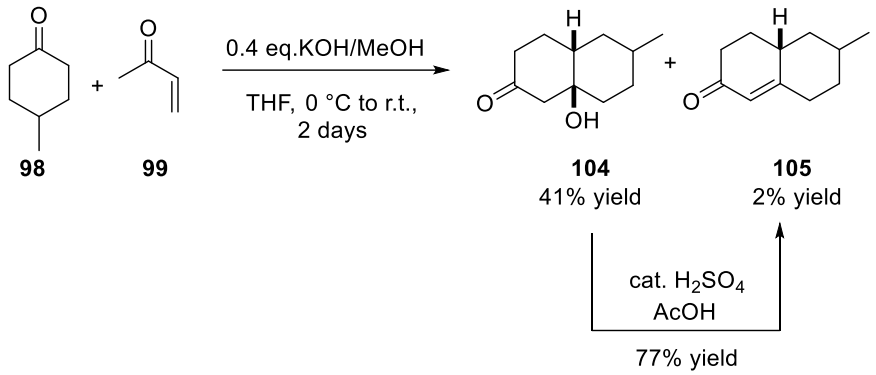


Scheme 18. The Robinson annulation of cyclohexanone **101**.[61]

entry	condition	temperature (°C)	yield (%)
1	glacial AcOH H_2SO_4	r.t.	90
2	HCl 4 M	r.t.	80
3	KOH, ethanol	r.t.	40
4	MsCl, Et_3N, Then DBU CH_2Cl_2	0 °C to r.t.	30

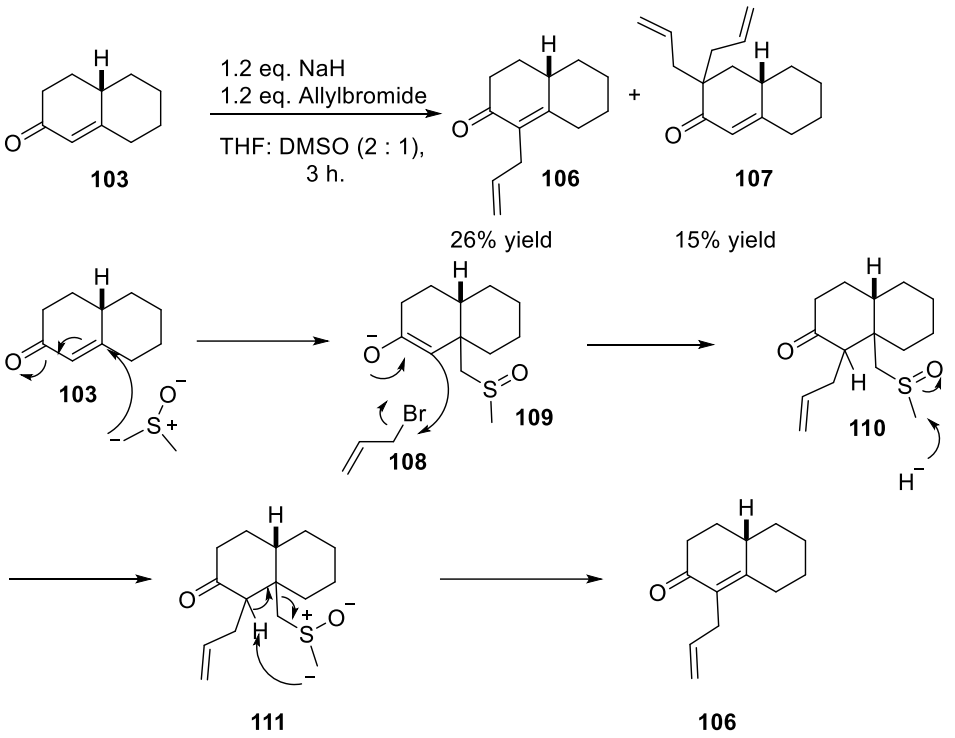
Table 5. The elimination conditions for the conversion of **102** into decalin **103**.[62]

The annulation of 4-methyl cyclohexanone **98** in the presence of methylvinylketone **99** and KOH, generated decalin **105** in a 2% yield and the hydroxyl-decalin **104** in a 41% yield (**Scheme 19**). Acidic conditions-glacial acetic acid and sulfuric acid-were used to complete the conversion of **104** into the desired decalin **105**, which was isolated in a 77% yield.



Scheme 19. The Robinson annulation of 4-methyl cyclohexanone **98**.[61]

Having achieved the formation of decalins **103** and **105** *via* a two-step sequence, the conjugate addition reaction to functionalise these bicyclic compounds was explored. Treatment of **103** in the presence of allyl bromide **108**, DMSO and NaH, formed the desired product **106** in a 26% yield. A doubly alkylated compound **107** was also generated and the decalin starting material **103** was recovered in a 5% yield (**Scheme 20**).[63] A mechanism for this reaction was proposed: (i) the 1,4-addition of the DMSO ylide to the enone decalin **103** generated the enol-decalin **109**, (ii) the alkylation of allyl bromide **108** generated intermediate **110**, which after, (iii) a final elimination of DMSO formed the enone decalin alkylated product **106** (**Scheme 20**).[63]



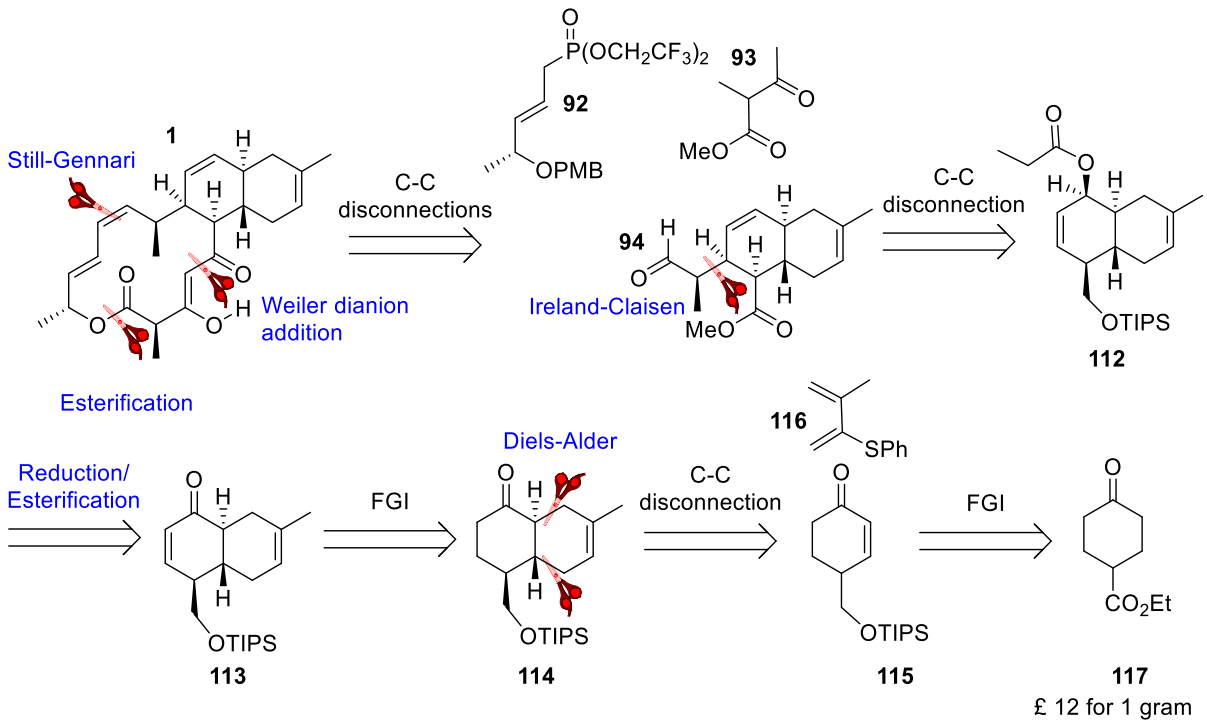
Scheme 20. The conjugate addition of **103** and the proposed mechanism of the reaction.[63]

The conjugated addition of the Mander's reagent instead of allyl bromide, using these conditions was attempted, but formation of the desired product was not observed and the starting material **103** was recovered unreacted. Due to the low yields and the formation of side-products during conjugate addition, this approach towards the synthesis of the highly functionalised *trans*-decalin core **94** was not pursued further.

9.2 Diels–Alder/epimerisation sequence to the *trans*-decalin

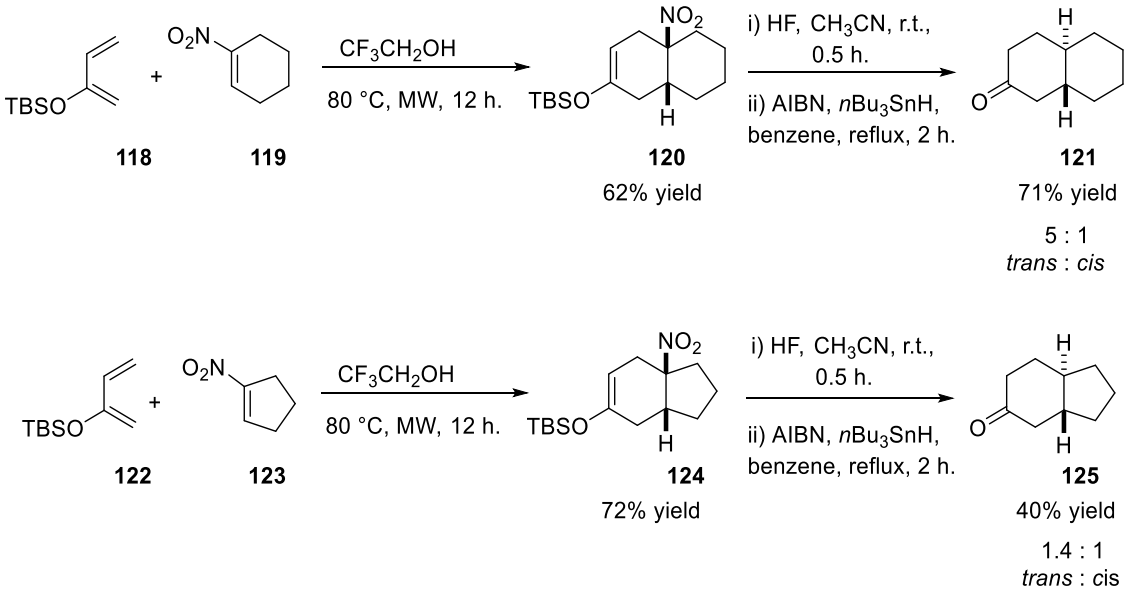
9.2.1 Retrosynthetic analysis

The division of the natural product into three major fragments, the Still–Gennari reagent **92**, the β-ketoester **93** and the highly-functionalised *trans*-decalin core **94**, remained the proposed retrosynthetic strategy (**Scheme 21**). Key reactions to form the highly functionalised *trans*-decalin system **94** would involve a facially selective and diastereoselective Ireland–Claisen rearrangement on the face that presents the triisopropylsilylmethyloxy chain, and a Diels–Alder/epimerisation sequence starting form enone **115** and diene **116**. The conjugated enone **115** would be synthesised *via* an oxidation/reduction sequence of the commercially available keto-ester **117**.



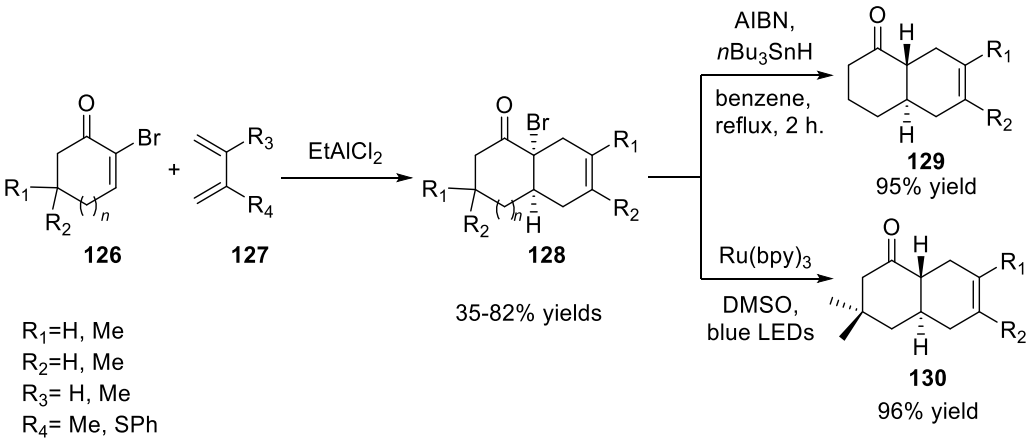
Scheme 21. The retrosynthesis analysis of anthracimycin **1.**

The Diels–Alder cycloaddition reaction has left a special imprint in natural product total synthesis, due to the ability to construct polyfunctional and highly substituted molecules.[64] This approach has been used as a key step in cascade sequences and has enabled synthetic chemists to obtain numerous scaffolds in total synthesis.[65] Pericyclic reactions offer an efficient approach to the synthesis of six-membered rings and bicyclic systems, and have numerous advantages including stereochemical control (always a *cis* addition) and easy predictability of its regiochemistry, with the selectivity of the Diels–Alder cycloaddition rationalised using frontier molecular orbital theory.[65] A classical method to enhance the rate of the reaction is the use of a Lewis acid-mediated Diels–Alder cycloaddition reaction to decrease the energy gap between the LUMO of the dienophile and the HOMO of the diene.[66] As reported in the previous section, a range of natural products containing *cis*- and *trans*-decalins were formed by using this powerful cycloaddition.[67, 68] In 2009, Danishefsky and co-workers reported a two-step "*trans*-Diels–Alder reaction" with the use of nitrocycloalkenes to form bicyclic systems.[69] This pericyclic reaction between diene **118** and dienophile **119** formed the *cis*-fused decalin adduct **120** in a 62% yield. A radical reduction in the presence of AIBN and nBu$_3$SnH, removed the nitro group and triggered the conversion from the *cis*- to the *trans*-fused system **121** in a 71% yield and in a 5 : 1 ratio (**Scheme 22**).[69]



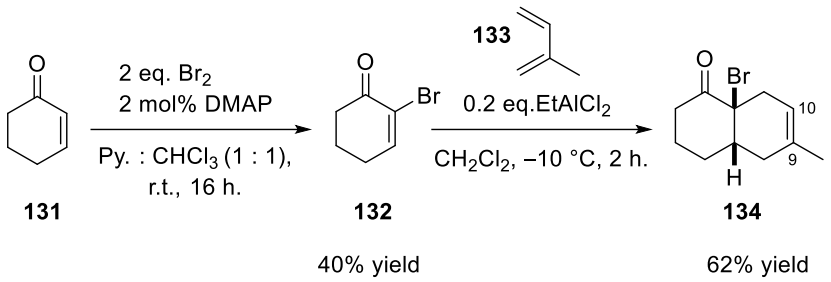
Scheme 22. A two-step "*trans*-Diels–Alder reaction".[69]

In 2010, Danishefsky *et al.* also described a Lewis acid catalysed Diels–Alder reaction between α-bromocyclohexenones **126** and various substituted dienes **127**, to provide *cis*-fused bicyclic systems **128** (**Scheme 23**).[70, 71] Removal of the bromine atom and the consequent epimerisation from *cis*- to *trans*-decalin, was performed by radical reduction using AIBN and nBu$_3$SnH. This conversion from α-halo *cis*-bicyclic systems to *trans*-decalins was also studied by Lee in 2015, who performed a new tin-free photoredox catalysis reaction.[72]



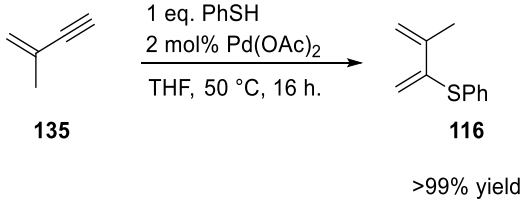
Scheme 23. The epimerisation from *cis*- to *trans*-decalin *via* a radical and a photoredox strategy.[70-72]

With this idea in mind, the Diels–Alder strategy for the formation of the functionalised *trans*-decalin of anthracimycin was explored. The α-bromo-substituted cyclohexenone **132** was prepared from cyclohexanone **131** by treatment with molecular bromine and DMAP, using pyridine and chloroform as solvents.[73, 74] A Lewis acid ($EtAlCl_2$) catalysed the Diels–Alder cycloaddition reaction between **132** and isoprene **133**, afforded the *cis*-decalin **134** in a 62% yield, as a single diastereoisomer (**Scheme 24**).[72]

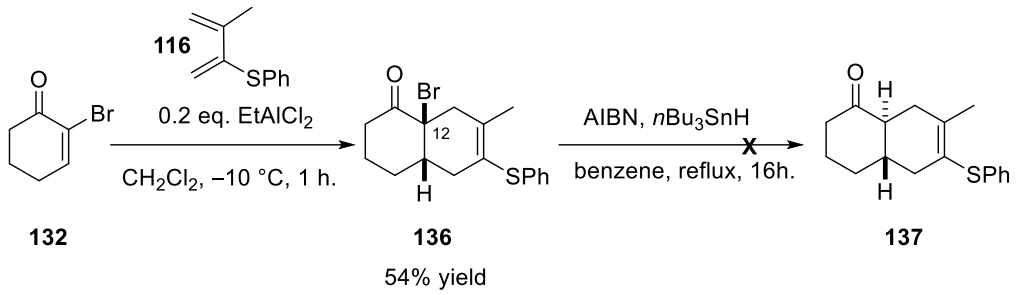


Scheme 24. A Lewis acid-mediated Diels–Alder reaction to form the *cis*-decalin **134**.[70-74]

However, using isoprene **133**, the position of the methyl group at C-9 in the *cis*-decalin **134** was incorrect for the decalin core of anthracimycin **94**. This was not unexpected, due to the largest orbital coefficient of the HOMO of the alkene being next to the methyl group. To influence the regiochemistry of this cycloaddition and install the methyl group at C-10 as required, the sulfur-substituted diene **116** was synthesised, in order to exploit the greater electron-donating effect of the thiophenyl group compared to the methyl substituent. It is noteworthy that this diene **116** was freshly prepared in a quantitative yield before the Diels–Alder (**Scheme 25**).[74] In this case, $EtAlCl_2$ catalysed the cycloaddition between **132** and **116** formed the *cis*-decalin **136** in a 54% yield as a single diastereoisomer (**Scheme 26**). Due to the instability of the α-bromo *cis*-decalin **136** to light and air, the conversion into the corresponding *trans*-diastereoisomer **137** was tested under radical conditions, but just unreacted starting material was recovered. However, the larger orbital coefficient of the HOMO of the alkene next to the thiopenyl group of diene **116**, influenced the regiochemistry of this cycloaddition reaction and installed the methyl group at C-10 as required for anthracimycin **1**.

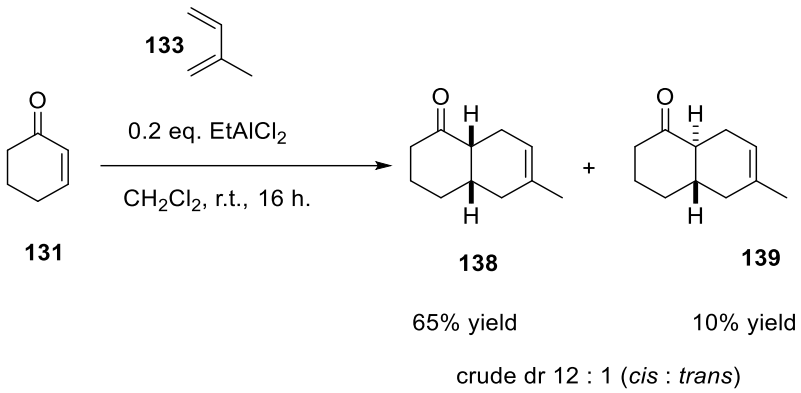


Scheme 25. Palladium catalysed synthesis of the sulfur-substituted diene **116**.[75]

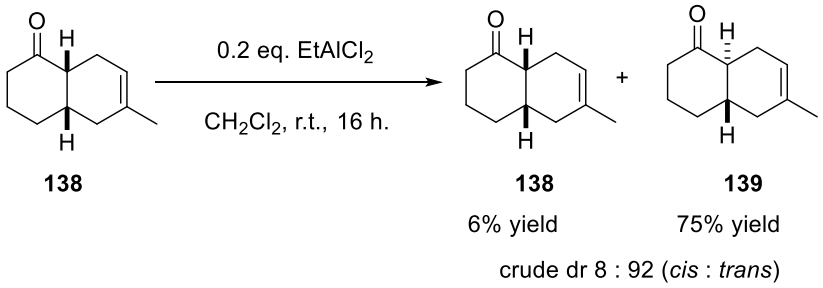


Scheme 26. A regioselective Diels–Alder to form *cis*-decalin **136**.[72]

Due to the instability of the bromine-containing Diels–Alder adducts **134** and **136**, it was decided to investigate the non-halogenated enone **131** as the dienophile in this reaction. The cycloaddition reaction of **131** and **133** was performed and generated two decalin products **138** and **139** in a 12 : 1 crude ratio (*cis* : *trans*) (**Scheme 27**).[76] This result showed evidence of an epimerisation from a *cis*- to a *trans*-decalin under the reaction conditions. Treatment of **138**, with further Lewis acid, generated the *trans*-diastereoisomer **139** in a 8 : 92 ratio (*cis* : *trans*), which confirmed the conversion *via* epimerisation observed during the cycloaddition (**Scheme 28**).

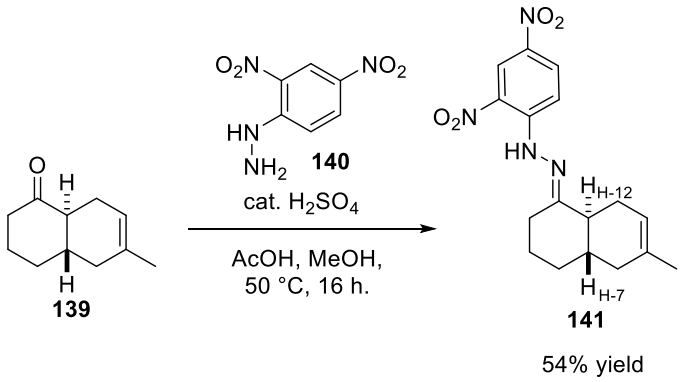


Scheme 27. The Diels–Alder cycloaddition between **131** and **133**.[76]



Scheme 28. The epimerisation from the *cis*- to *trans*-decalin **139**.

In order to confirm the stereochemistry of the *trans*-decalin **139**, the carbonyl was reacted with 2,4-dinitrophenyl hydrazine **140** to form the hydrazone **141** and facilitate the crystallisation of the molecule (**Scheme 29**). The structure of the hydrazone **141**, isolated in a 54% yield, was confirmed unambiguously by single crystal X-ray diffraction (**Figure 9**).



Scheme 29. The derivatisation of the *trans*-decalin **139** into the hydrazone **141**.

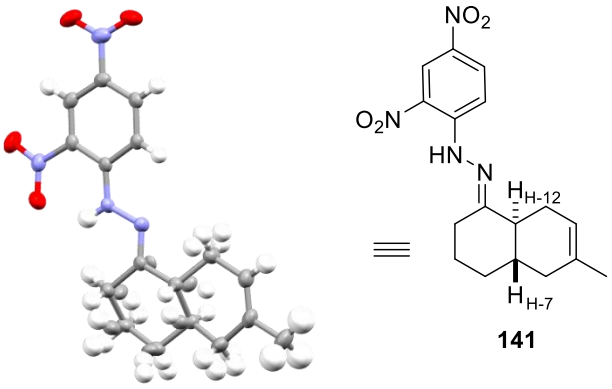


Figure 9. The X-ray diffraction single crystallography of the hydrazone **141** with thermal ellipsoids shown at 50%.

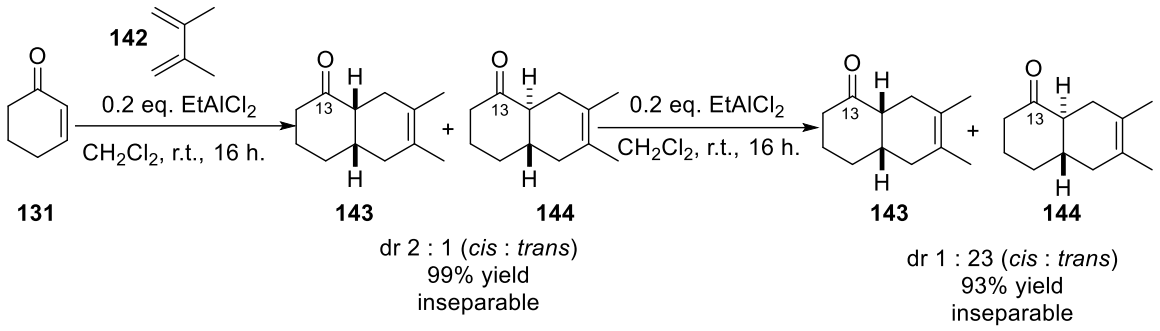
The X-ray crystal structure in **Figure 9** confirmed the *trans*-ring junction between protons H-7 and H-12, which was obtained using a Diels–Alder/epimerisation sequence.

Armed with this knowledge, formation of the *trans*-diastereoisomer **139** in one-pot was attempted during the Diels–Alder cycloaddition reaction. Premixing the catalyst with cyclohexenone (**131**) over a period of 30 minutes, formed the two diastereoisomers **138** and **139** in a 0.85 : 1 ratio (*cis* : *trans*), which were isolated in a 37% and in a 40% yield, respectively. Increasing the amount of catalyst from 0.2 to 1.2 equivalents, did not significantly improve the formation of the *trans*-decalin **139**. A 0.7 : 1 ratio (*cis* : *trans*) was achieved using stoichiometric amount of $EtAlCl_2$, whereas, a 0.6 : 1 ratio (*cis* : *trans*) was obtained by re-addition of the catalyst after the consumption of the cyclohexenone **131**. The epimerisation to the *trans*-decalin **139** was, therefore, not performed in a one-pot reaction and its synthesis was achieved in a Diels–Alder/epimerisation sequence over two-steps. However, to highlight the advantages of this method, different dienophiles and dienes were tested to form *trans*-bicyclic systems. The literature reported an $AlCl_3$-catalysed cycloaddition between different ring size enones in the presence of diverse dienes, to yield bicyclic adducts in various *cis* : *trans* ratio.[77, 78]

The Diels–Alder reaction between cyclohexenone (**131**) and 2,3-dimethyl-1,3-butadiene (**142**) formed *cis*- and *trans*-decalins **143** and **144** in a 2 : 1 ratio as an inseparable mixture of products. After epimerisation, a 1 : 23 ratio (*cis* : *trans*) was observed (**Scheme 30**, **Figure 10**). The cycloaddition of cyclohexenone (**131**) in the presence of *trans*-1,3-pentadiene (**145**), formed the *cis*- and *trans*-decalins **146** and **147** in a 9.8 : 1 ratio (*cis* : *trans*). After epimerisation, the proportion of the *trans*-decalin **147** increased, but the diastereomeric ratio remained in favour of the *cis*-decalin **146**, 1.92 : 1 ratio (*cis* : *trans*) (**Scheme 31**, **Figure 11**). The Diels–Alder reaction between cyclopentenone (**148**) and isoprene (**133**) formed the *cis*- and the *trans*-adducts **149** and **150** in a 1.34 : 1 ratio (*cis* : *trans*), which did not change under the epimerisation conditions (**Scheme 32**, **Figure 12**). In the presence of 2,3-dimethyl-1,3-butadiene **142**, the *cis*- and the *trans*-bicyclic systems **151** and **152** were formed in a 4 : 1 ratio (*cis* : *trans*), which equilibrated to 1.47 : 1 after epimerisation (*cis* : *trans*) (**Scheme 33**, **Figure 13**). The cycloaddition between cycloheptenone (**153**) and isoprene (**133**) generated the *cis*- and *trans*-

diastereoisomers **154** and **155** in a 10 : 1 ratio (*cis* : *trans*), which were isolated in a 52% and 5% yields, respectively (**Scheme 34**, **Figure 14**).[77, 78]

The Diels–Alder/epimerisation between enone **131** and diene **142**, generated *cis*- and *trans*-decalins **143** and **144** in a 1 : 23 ratio (**Scheme 30**). Due to the presence of many overlapping peaks in the ^{1}H NMR spectrum, the diastereomeric ratio of **143** and **144** before and after epimerisation was calculated using quantitative ^{13}C NMR analysis. Using around 100 mg of compound and setting a long relaxation time (10 seconds) during a 16-hour analysis, it was possible to calculate an accurate diastereomeric ratio based on the integration of ketone peaks C-13 of **143** and **144**, at δ 212.5 (*cis*) and at δ 212.4 (*trans*) ppm respectively (**Figure 10**).



Scheme 30. The Diels–Alder/epimerisation reaction between **131** and **133**.

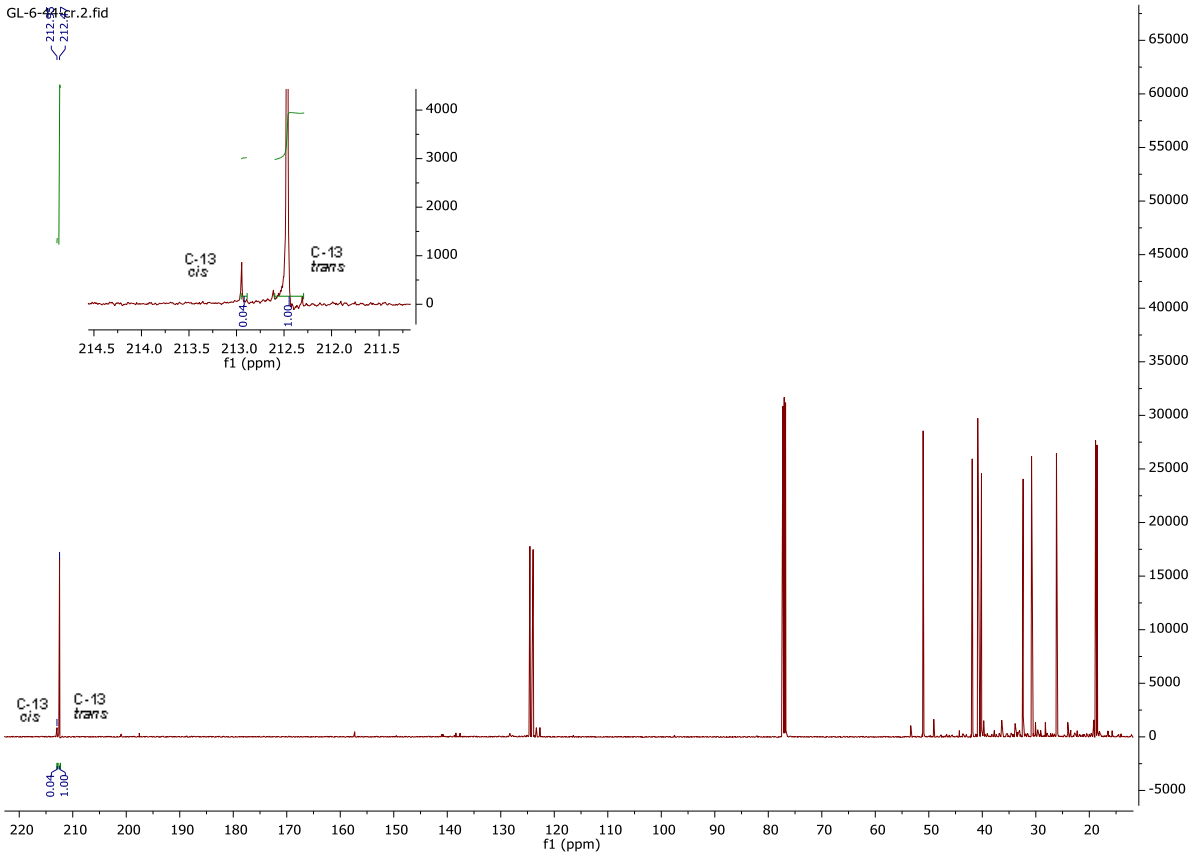
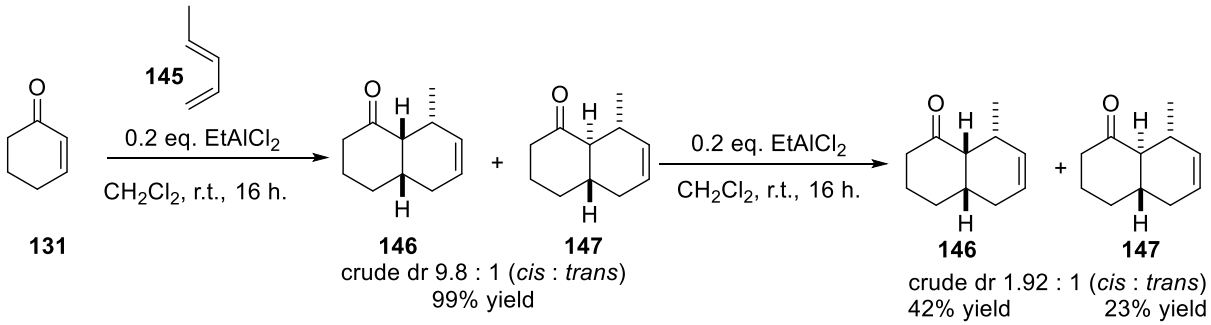


Figure 10. Ratio of *cis*- and *trans*-decalins **143** and **144** calculated on a quantitative ^{13}C NMR spectrum based on ketone C-13 integration.

The Diels–Alder/epimerisation sequence between enone **131** and diene **145** afforded *cis*- and *trans*-decalins **146** and **147** in a 1.92 : 1 ratio (**Scheme 31**). The literature reported a similar ratio (1.8 : 1 *cis* : *trans*) using the same substrates in an $AlCl_3$-catalysed Diels–Alder reaction to form the decalin

products **146** and **147**.[77] As shown in the crude ^{1}H NMR spectrum, the 1.92 : 1 diastereomeric ratio of **146** and **147** after epimerisation was calculated based on integration of methyl groups peaks; a doublet at δ 1.21 ppm (*cis*, **146**) and a doublet at δ 0.94 ppm (*trans*, **147**) (**Figure 11**). These data matched the literature assignments: methyl group of the *cis*-isomer **146** doublet at δ 1.27 ppm, and methyl group of the *trans*-adduct **147** doublet at δ 0.94 ppm.



Scheme 31. The Diels–Alder/epimerisation sequence between **131** and **145**.

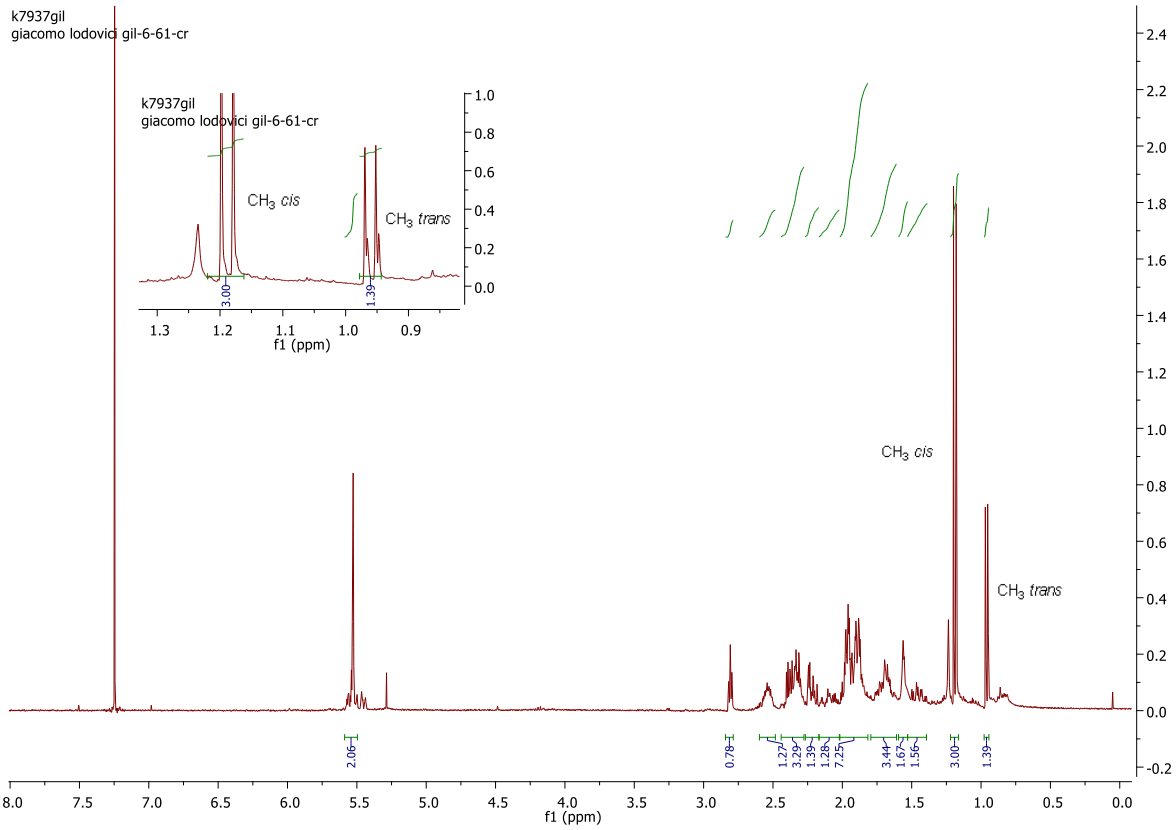
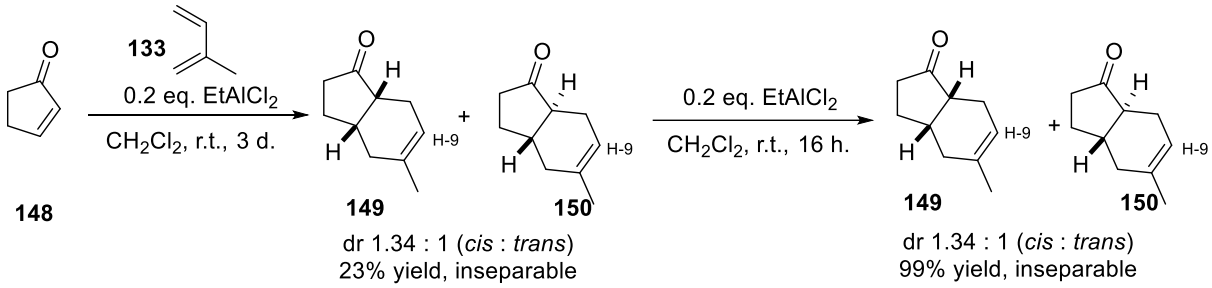


Figure 11. Ratio of *cis*- and *trans*-decalins **146** and **147** calculated on a ^{1}H NMR spectrum based on methyl integration.

The cycloaddition between **148** and **133** was attempted and a 1.34 : 1 ratio *cis* : *trans* was obtained before and after epimerisation and the product was isolated as an inseparable mixture (**Scheme 32**). For these substrates, literature reported a 1.7 : 1 ratio *cis* : *trans*, calculated on integration of proton H-9 at δ 5.39 ppm (*trans*, **150**) and at δ 5.36 ppm (*cis*, **149**).[77] As shown in the crude ^{1}H NMR spectrum, the 1.34 : 1 diastereomeric ratio of **149** and **150** resulting from the Diels–Alder/epimerisation sequence, was calculated based on integration of H-9 protons, multiplets at δ 5.46–5.39 (*trans*, **150**) and at δ 5.36–5.32 ppm (*cis*, **149**) (**Figure 12**).



Scheme 32. The Diels–Alder/epimerisation sequence between **148** and **133**.

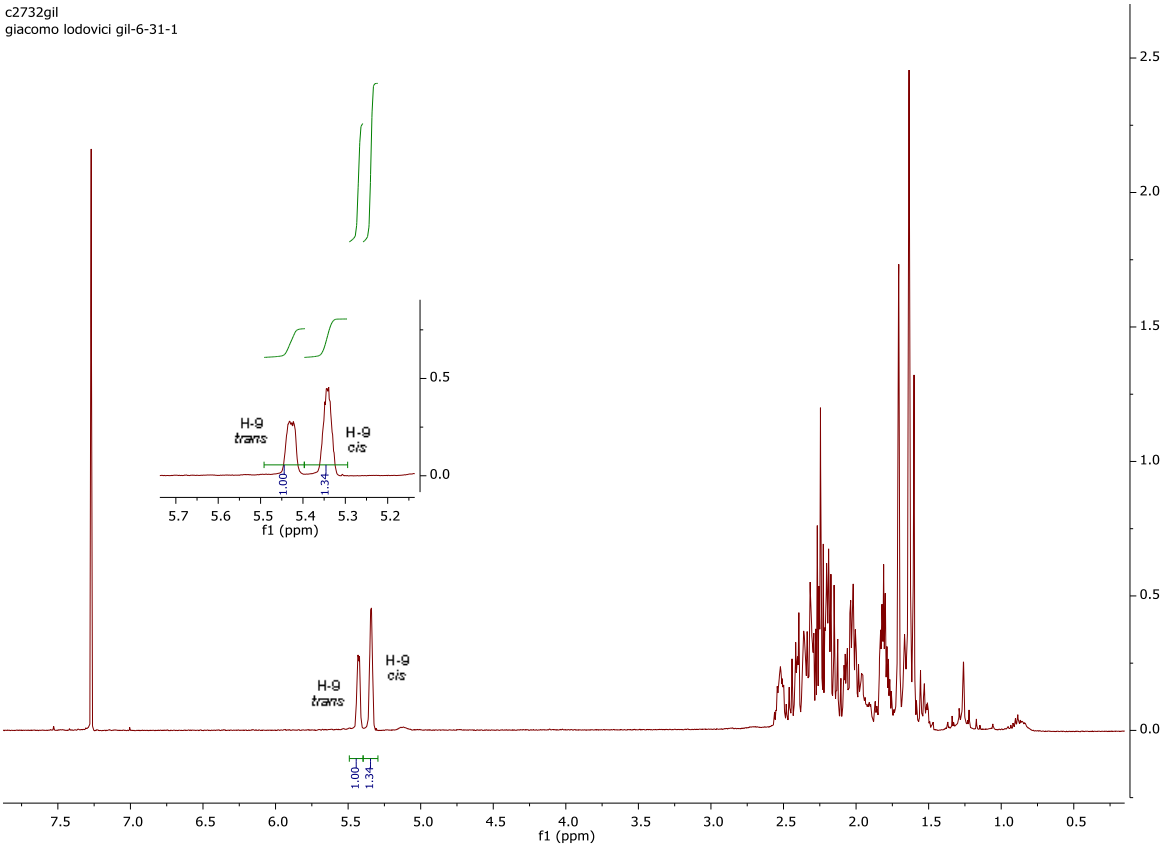
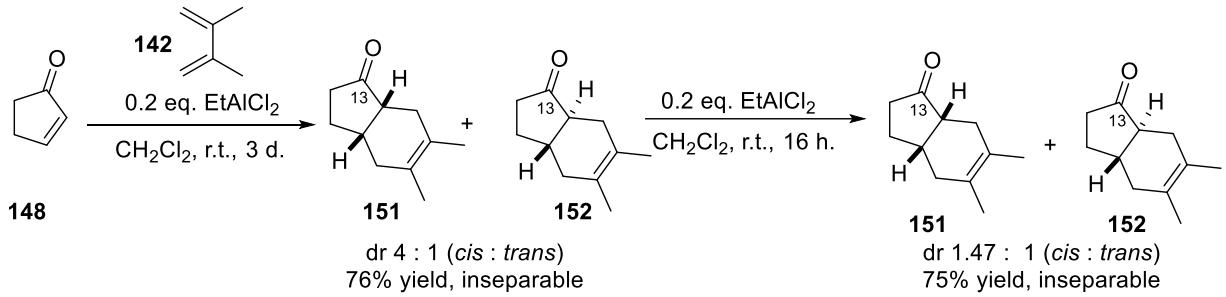


Figure 12. Ratio of *cis*- and *trans*-decalins **149** and **150** calculated on a ^{1}H NMR spectrum based on integration of proton H-9.

The Diels–Alder/epimerisation reaction between enone **148** and diene **142** afforded an inseparable mixture of decalins **151** and **152**, isolated in a 1.47 : 1 ratio *cis* : *trans* (**Scheme 33**). Due to the presence of many overlapping peaks in the ^{1}H NMR spectrum, the 1.47 : 1 diastereomeric ratio of **151** and **152** was calculated using a quantitative ^{13}C NMR analysis. Using around 100 mg of compound and setting a long relaxation time (10 seconds) in a 16-hour experiment, integration of the ketone C-13 peaks of *cis*- and *trans*-decalins **151** and **152** of the crude reaction mixture allowed the determination of the diastereomeric ratio. The carbonyl peaks (C-13) of the *cis*- and *trans*-decalins were found at δ 219.7 (*cis*, **151**) and at δ 218.9 (*trans*, **152**) ppm (**Figure 13**).



Scheme 33. The Diels–Alder/epimerisation sequence between **148** and **142**.

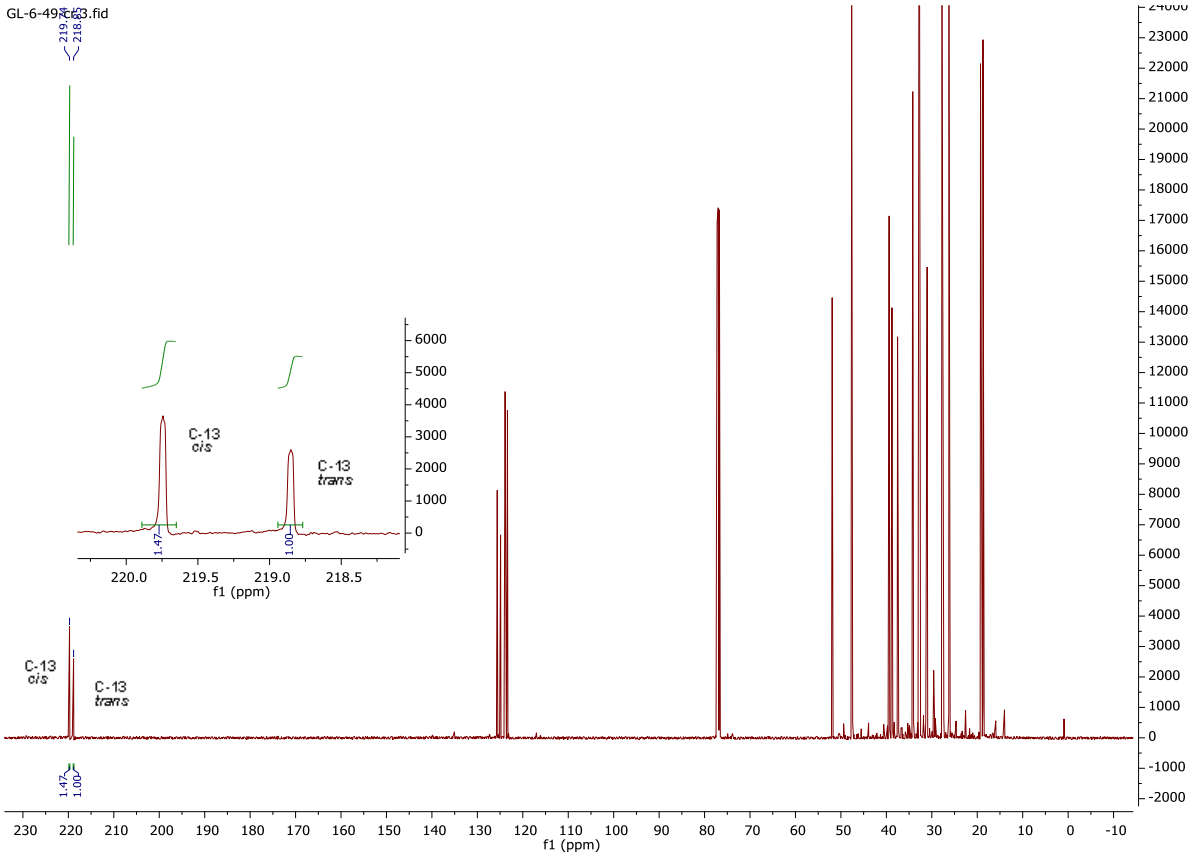
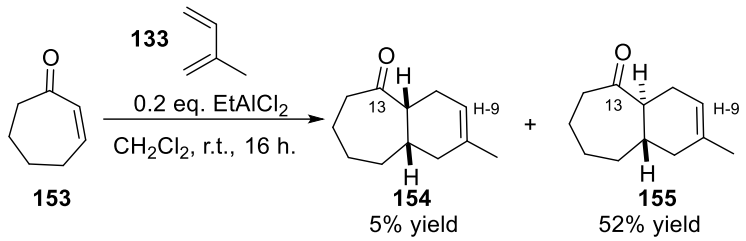


Figure 13. Ratio of *cis*- and *trans*-decalins **151** and **152** calculated on a quantitative ^{13}C NMR spectrum based on ketone carbonyl integration.

The cycloaddition reaction between enone **153** and diene **133** generated decalins **154** and **155** in a 10 : 1 ratio *cis* : *trans*, isolated in a 52% and 5% yields respectively (**Scheme 34**). The diastereomeric ratio of these two products was calculated based on ketone integration C-13 of the crude reaction mixture

using quantitative ^{13}C NMR spectroscopic analysis. The carbonyl peaks (C-13) of the *cis*- and *trans*-decalins were found at δ 215.7 (*cis*, **154**) and at δ 217.1 (*trans*, **155**) ppm (**Figure 14**). The literature reported the formation of *cis*- and *trans*-diastereosiomers **154** and **155** in a 1 : 45 ratio (*cis* : *trans*), reporting carbonyl peaks (C-13) of the *cis*- and *trans*-decalins at δ 214.4 (*cis*, **154**) and at δ 215.9 (*trans*, **155**).[77]



Scheme 34. The Diels–Alder reaction between enone **153** and diene **133**.

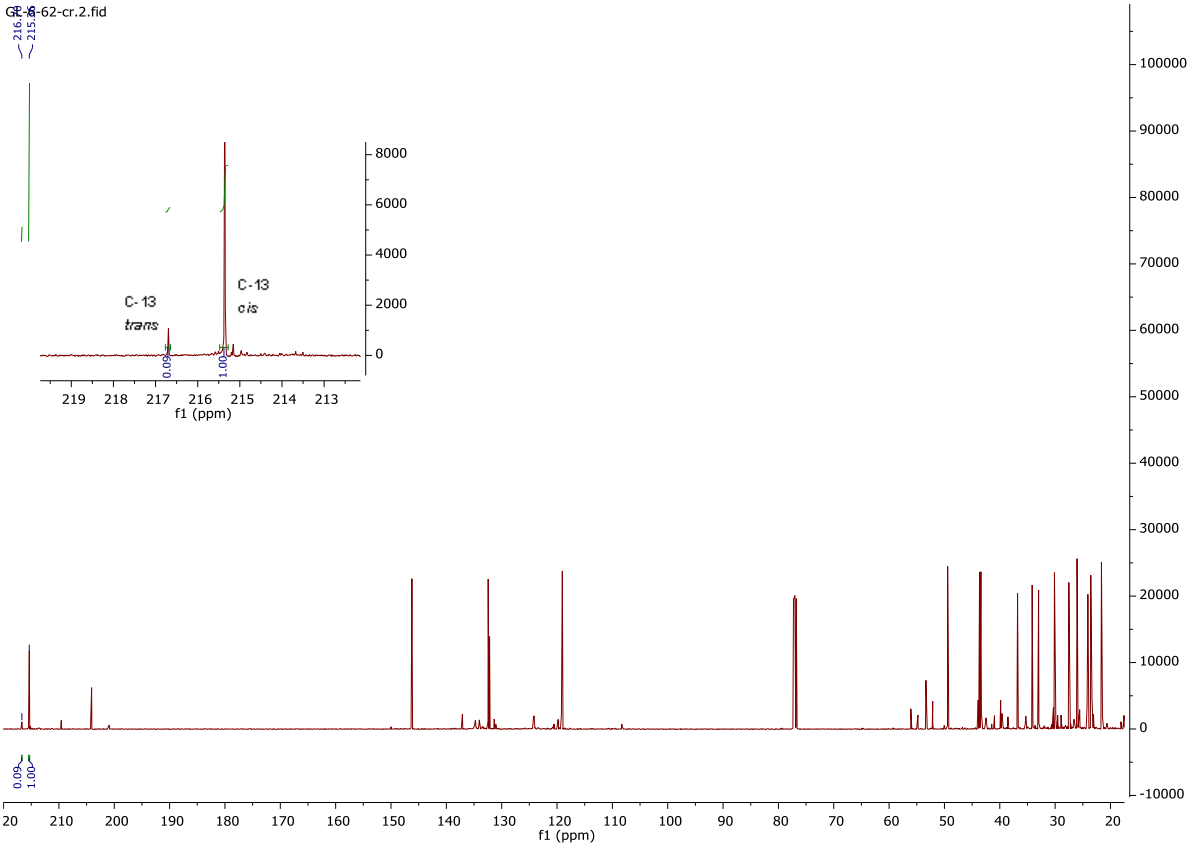
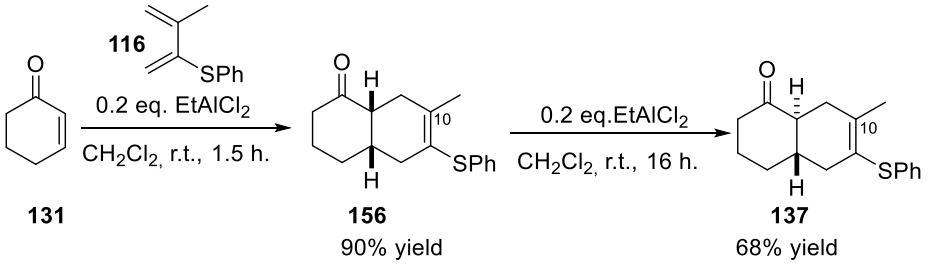


Figure 14. Ratio of *cis*- and *trans*-decalins **154** and **155** calculated on a quantitative ^{13}C NMR spectrum based on ketone C-13 integration.

After this screening, the Diels–Alder between cyclohexeneone (**131**) and the sulfur-substituted diene **116** was attempted, to correct the regioselectivity of the cycloaddition and install the methyl group at C-10. The literature reported an $EtAlCl_2$-catalysed cycloaddition between cyclohexenone **131** and the sulfur substituted diene **116**, to give the *cis*-decalin **156** in a 35% yield.[72] Photoredox conditions then triggered the epimerisation from *cis*- to *trans*-decalin **137**.[72] Repeating the $EtAlCl_2$-catalysed Diels–Alder conditions, the *cis*-decalin **156** was generated as a single diastereoisomer in a 37% yield over a period of 3 hours at –10 °C (**Scheme 35** and **Table 6**, **entry 1**). It was, however, observed that time and temperature had a key role in the formation of impurities, and in the isolation of the desired product **156** in a high yield. A period of 3 hours at room temperature afforded the *cis*-decalin **156** in a 51% yield (**Table 6**, **entry 2**), whereas, a 90% yield of **156** was obtained at room temperature over a period of 1.5 hours (**Table 6**, **entry 3**)**.** Epimerisation, under the same reaction conditions, formed the *trans*-decalin **137** in a 68% yield over a two-step sequence, as observed in the previous studies (**Scheme 35**).

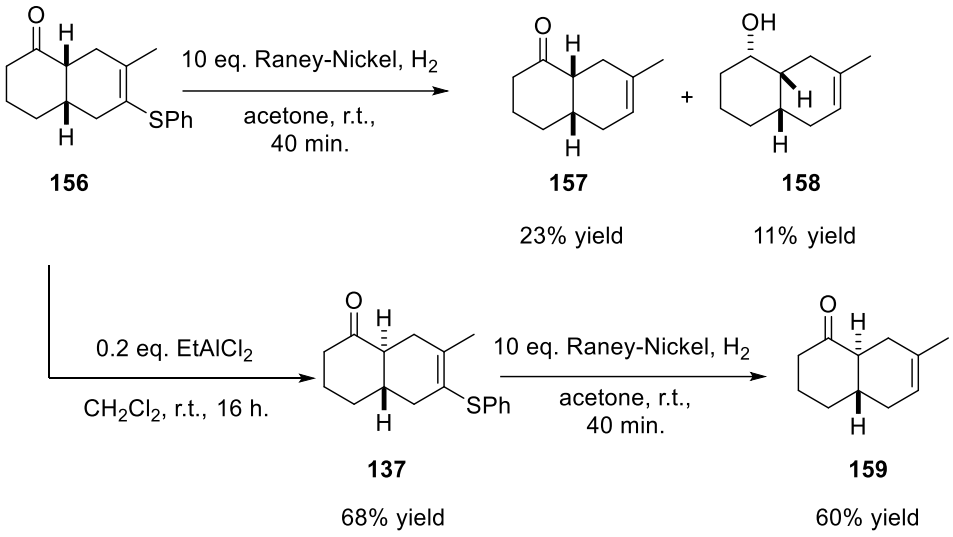


Scheme 35. The Diels–Alder/epimerisation sequence to form the *trans*-decalin **137**.

entry	catalyst	temperature (°C)	time (h.)	yield of 156 (%)
1	0.2 eq. $EtAlCl_2$	–10 °C	3	37
2	0.2 eq. $EtAlCl_2$	r.t.	3	51
3	0.2 eq. $EtAlCl_2$	r.t.	1.5	90

Table 6. The optimization of the Diels–Alder reaction between cyclohexanone **131** and diene **116**.

A selective Raney-Nickel reduction was performed in an attempt to remove the thiophenyl group from compounds **156** and **137**. However, the treatment of the *cis*-diastereoisomer **156** under these conditions generated **157** and **158** in a 23% and 11% yield respectively, where over-reduction to the hydroxyl had occurred. In contrast, Raney-Nickel reduction of the *trans*-diastereoisomer **137** selectively cleaved the thiophenyl bond, forming exclusively the model *trans*-decalin **159** that possesses the stereochemistry and regiochemistry required for the core of anthracimycin **94** (**Scheme 36**).[79]



Scheme 36. The Raney-Nickel reduction of *cis*- and *trans*-decalins **156** and **137**.[79]

To summarise, a Lewis acid catalysed Diels–Alder/epimerisation sequence allowed the formation of a model *trans*-decalin in a good yield and selectivity as required for anthracimycin, without the need for a radical reduction of unstable bromine-containing Diels–Alder adducts. The scope of this cycloaddition was explored using different ring size enones in the presence of diverse dienes, to form *trans*-bicyclic products with a high diastereomeric ratio. The use of the sulfur-substitued diene **116** permitted us to influence the regiochemistry of the Diels–Alder cycloaddition reaction, exploiting the greater electron-donating effect of the thiophenyl group, and the *cis*-decalin **156** was obtained in a 90% yield, optimising the literature reported conditions. Epimerisation to the *trans*-decalin **137** in 68% yield was followed by a selective Raney-Nickel reduction to remove the thiophenyl group, which

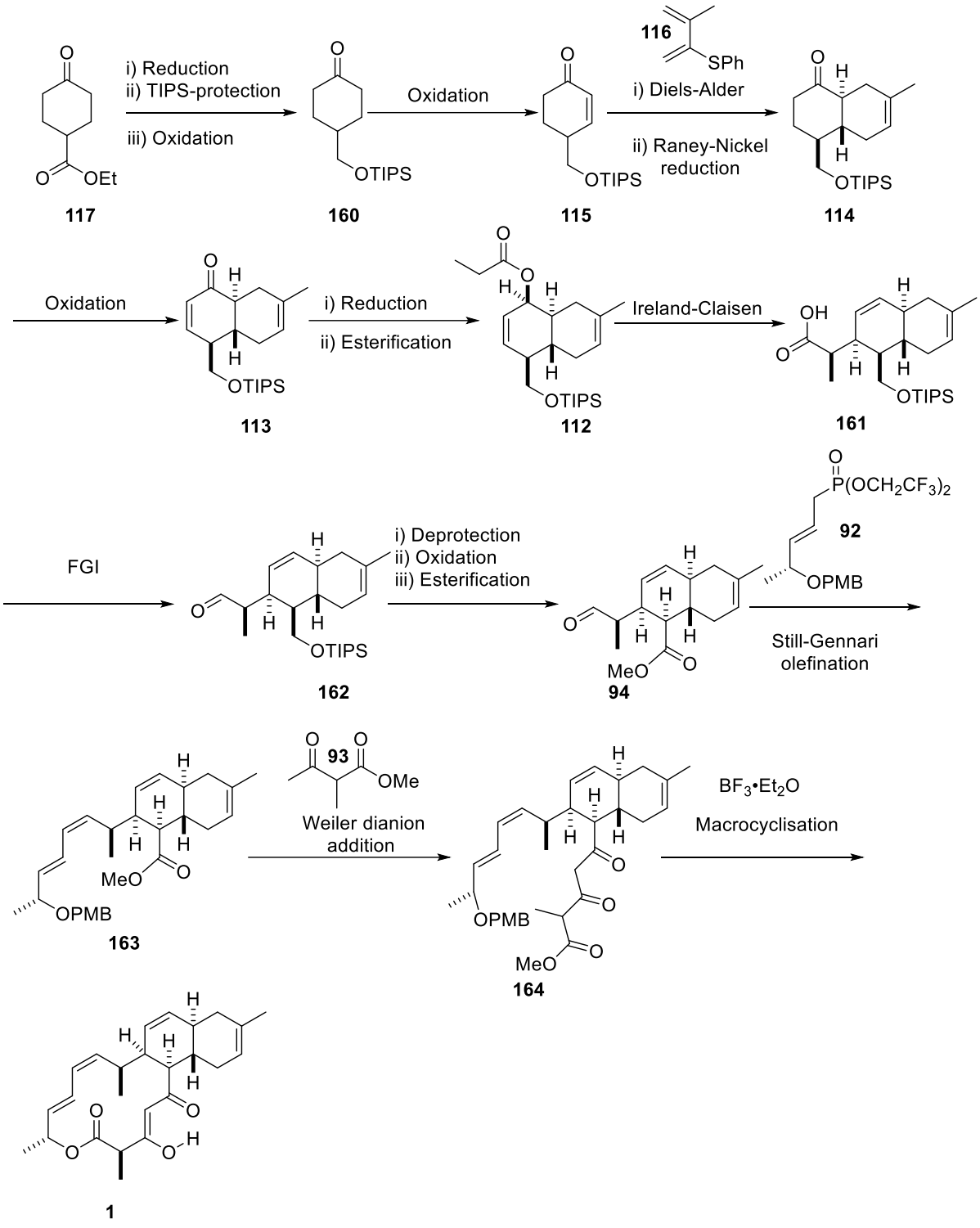
generated **159** as a model *trans*-decalin system for that required for the total synthesis. Application of these conditions to form the *trans*-decalin core of anthracimycin will be discussed in the next section.

9.3 Formation of the *trans*-decalin core of anthracimycin **114**

9.3.1 The synthetic plan

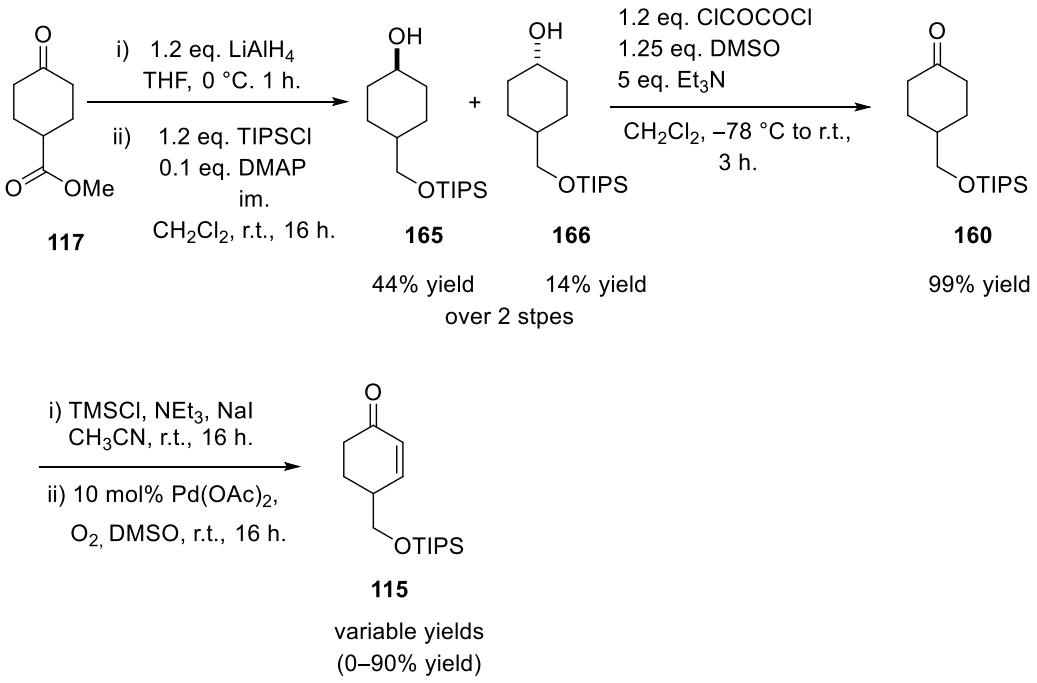
Based on the retrosynthetic plan (**Scheme 21**), the following synthetic route was proposed (**Scheme 37**). Starting with a lithium aluminiun hydride reduction of the cheap and commercially available ethyl 4-oxocyclohexanecarboxylate **117**, TIPS-protection of the primary alcohol and oxidation of the secondary alcohol would generate ketone **160**. Oxidation of **160** to enone **115** would yield the dienophile suitable for the Diels–Alder/epimerisation sequence, optimised in the presence of the sulfur substituted diene **116**. A selective Raney-Nickel reduction to remove the thiophenyl group would afford the required *trans*-decalin **114**. Oxidation of this compound **114** to the enone *trans*-decalin **113**, would yield a key α,β-unsaturated synthetic intermediate. A stereoselective 1,2-reduction of **113** to generate the axial hydroxyl group, followed by treatment with propionyl chloride would form the propionate ester of *trans*-decalin **112**. The axial position of the propionate ester would ensure a facial and diastereoselective Ireland–Claisen rearrangement of **112** occurring from the same face of the triisopropylsilylmethyloxy chain, to afford the core of anthracimycin **162**. Formation of the *E*-enolate of **112** in the presence of LDA should also provide the correct stereochemistry of the methyl group in **162**. Esterification of **161** would be followed by DIBAL-H reduction to form aldehyde **162**, setting the required functional group for a Still-Gennari olefination reaction to install fragment **92**. Protecting group removal (TIPS) from **162**, followed by an oxidation/esterification sequence would afford the highly functionalised *trans*-decalin core **94**. Compound **94** represents the opposite enantiomer of the core of chlorotonil A **40** (except for the absence of the methyl group at C-8), reported by Kalesse.[41] Following the published total synthesis of this chlorinated polyketide **15**,[41]

installation of fragment **92** would be performed by a Still-Gennari olefination reaction with the phosphonate reagent **92** and KHMDS at –78 °C, to generate the advanced intermediate **163**. Subsequent, Weiler dianion addition of the commercially available β-ketoester **93** with the use of LDA, as base would yield compound **164**. Removal of the protecting group (PMB) by treatment with $BF_3{\cdot}Et_2O$ would also trigger the final macrocyclisation reaction, allowing the conclusion of the total synthesis in a total of 19 steps (**Scheme 37**).



Scheme 37. The synthetic plan for anthracimycin **1**.

Dr. Ian George (postdoctoral researcher in the Clarke group) working on a related *trans*-decalin natural product called streptosetin A, had developed a scalable synthesis of enone **115**. Reduction of commercially available compound **117**, followed by TIPS-protection of the primary hydroxyl group, afforded a mixture of alcohols **165** and **166** in a 44% and 14% yield respectively. Swern oxidation, scalable to 10 g, was used to convert **165** and **166** into a single ketone **160** in excellent yield (99%). An Ito–Saegusa oxidation was used to transform **160** to enone **115** (**Scheme 38**). However, the instability of the silyl enol-ether intermediate and its unreliable conversion into **115** and the reaction sensitivity to scale, forced us to find a more predictable and scalable synthesis of this early intermediate **115**.[80]

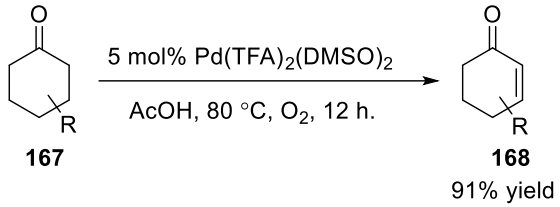


Scheme 38. The formation of the enone **115** developed by Dr. Ian George.

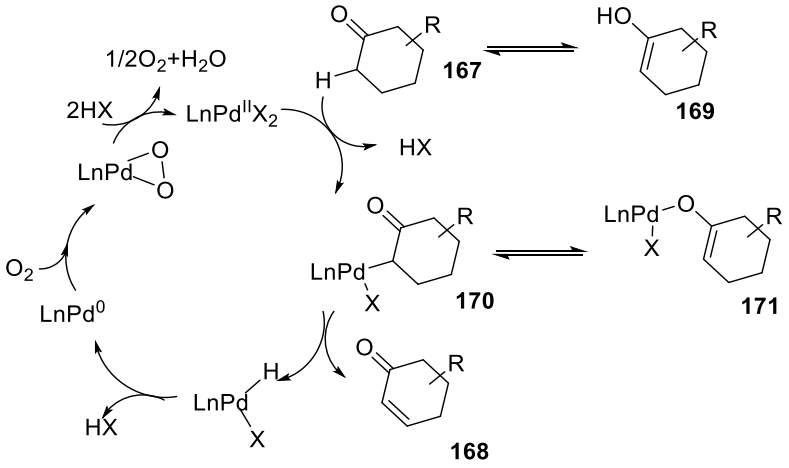
9.4 Direct palladium catalysed oxidation studies

9.4.1 Direct palladium catalysed oxidation studies: Stahl conditions

A new palladium-catalysed direct oxidation of ketone **160** to enone **115**, which obviated the need to go *via* the silyl enol-ether, was developed by Dr. Ian George (postdoctoral researcher in the Clarke group) and myself, in collaboration with the Fairlamb group. Inspired by the work of Stahl (**Scheme 39**),[81] Dr. Ian George investigated conditions to perform the oxidation directly from the starting ketone **160**. In the Stahl proposed oxidation mechanism (**Scheme 40**),[80] the first step would require the formation of the α-Pd^{II}-ketone intermediate **170**, which is in equilibrium with the Pd^{II}-enolate species **171**. The β-hydride elimination would then afford the enone product **168**. Oxidation of the Pd^0 complex in the presence of oxygen, would regenerate the Pd^{II}-catalyst ready for the catalytic cycle.

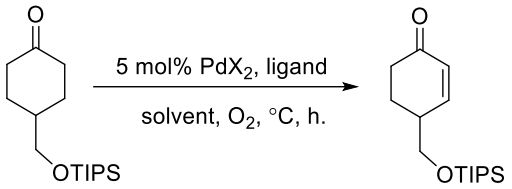


Scheme 39. Stahl reported condition of direct ketone oxidation.[81]



Scheme 40. The proposed mechanism for Pd^{II}-catalysed oxidation of cyclic ketone.[81]

Following Stahl's reported conditions in the presence $Pd(OAc)_2(DMSO)_2$ and $Pd(TFA)_2(DMSO)_2$ as the catalyst, the direct oxidation of ketone **160** to enone **115** was tested. However, after 16 hours at room temperature or at 80 °C in AcOH only traces of the enone **115** were formed (**Table 7**, **entry 2-6**). Using EtOAc, as the solvent, the conversion was not improved (**Table 7**, **entry 7**). A conversion of 5% to the desired product was observed over a period of 96 hours at room temperature in AcOH (**Table 7**, **entry 1**). As this conversion matched the catalyst loading (5 mol% of $Pd(OAc)_2(DMSO)_2$), the catalytic cycle was probably arrested and the addition of additives was tested to overcome this problem.



160 **115**

PdX_2 = $Pd(OAc)_2$, $Pd(OTFA)_2$

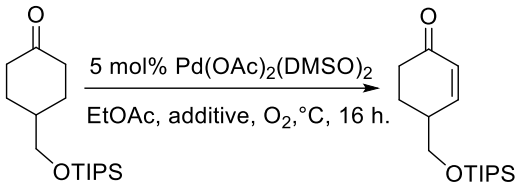
ligand = DMSO

entry	Solvent	Temp (°C)	Time (h.)	Conversion (%)
1	AcOH	rt	96	5
2	AcOH	80	16	trace
3	AcOH	rt	16	trace
4	AcOH	80	16	trace
5	EtOAc	rt	16	trace
6	AcOH	80	16	trace
7	EtOAc	rt	16	trace

Table 7. Stahl's conditions on target ketone **160**.

9.4.2 Direct palladium catalysed oxidation studies: additives effect

The use of additives was explored to improve the conversion. In most cross-coupling reactions, the presence of a base (K_2CO_3, Et_3N, $NaHCO_3$) generally helps the β-hydride elimination and improves the yield.[82] The control experiment in the absence of an additive showed no conversion to the enone **115** as expected (**Table 8**, **entry 1**). The use of 2 equivalents of K_2CO_3 and Et_3N, also showed no improvement in the conversion (**Table 8**, **entry 2-3-4**).

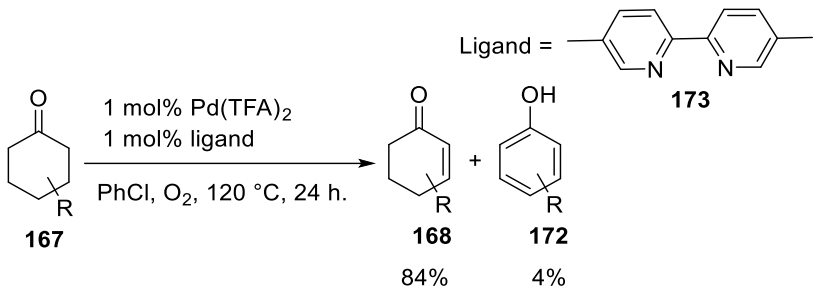


160 **115**

entry	Temp (°C)	Additive (2 eq.)	Conversion (%)
1	60	-	-
2	60	K_2CO_3	-
3	rt	K_2CO_3	-
4	60	NEt_3	-

Table 8. Additive screening to increase the conversion to the desired enone **115**.

In 2007, Tsuji reported the direct palladium-catalysed oxidation of cyclic ketones to conjugated enones, in chlorobenzene at 120 °C with the use of pyridine and bipyridine ligands as more efficient additives for this oxidation (**Scheme 41**).[83] A stabilisation effect of the active palladium species, preventing aggregation and extending the catalyst lifetime, could be the role played by these bipyridine ligands.[82]



Scheme 41. Tsuji optimised conditions for direct ketone oxidation.[83]

Inspired by this work,[83] the addition of pyridine and bipyridine ligands was tested for the oxidation of ketone **160** to the enone **115**, using $Pd(OAc)_2$ and $Pd(OAc)_2(DMSO)_2$ complex as catalysts, in chlorobenzene at 120 °C (**Figure 15**). Little differences were observed in the conversion between the $Pd(OAc)_2$ and the $Pd(OAc)_2(DMSO)_2$ complex, using pyridine **174** as a ligand (**Table 9**, **entry 1** and **5**). The addition of 2,6-lutidine **175** and 1,10-phenathroline **176** did not lead to efficient oxidation by either catalyst complex (**Table 9**, **entry 2-3** and **6-7**). The use of 2,2′-bipyridyl **177** was found to be a highly effective ligand for the $Pd(OAc)_2$ catalyst, increasing the conversion to 58% (**Table 9**, **entry 8**). In contrast, the addition of this ligand to the $Pd(OAc)_2(DMSO)_2$ complex did not improve the level of conversion (**Table 9**, **entry 4**). A conversion of 76% to the desired enone **115** was finally obtained with the use of 4,4′-^{t}Bu-2,2′-dipyridyl ligand **178** with $Pd(OAc)_2$ as the catalyst (**Table 9**, **entry 9**).

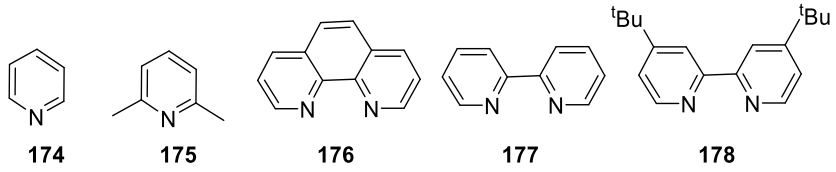
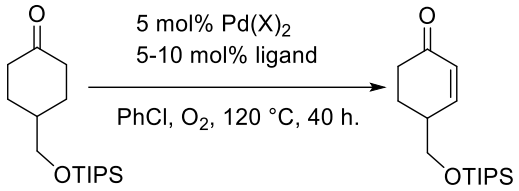


Figure 15. Pyridine and bipyridine ligands used.



160 **115**

$Pd(X)_2$ = $Pd(OAc)_2(DMSO)_2$
$Pd(OAc)_2$

entry	Catalyst	Ligand (mol%)	Conversion (%)
1	$Pd(OAc)_2(DMSO)_2$	**174** (10)	19
2	$Pd(OAc)_2(DMSO)_2$	**175** (10)	-
3	$Pd(OAc)_2(DMSO)_2$	**176** (5)	-
4	$Pd(OAc)_2(DMSO)_2$	**177** (5)	17
5	$Pd(OAc)_2$	**174** (10)	18
6	$Pd(OAc)_2$	**175** (10)	-
7	$Pd(OAc)_2$	**176** (5)	-
8	$Pd(OAc)_2$	**177** (5)	58
9	$Pd(OAc)_2$	**178** (5)	76

Table 9. Pyridyl and bipyridyl ligand screening to improve the conversion of ketone **160** into enone **115**.

Having identified the oxidation conditions, the conversion of ketone **160** into the enone **115** was monitored over time. The rate of this transformation followed an exponential growth, slowing at approximately 35% conversion. To improve conversion, additional catalyst was added which restored the reaction rate. A 92% conversion to the desired enone **115** was achieved after two subsequent additions of catalyst and ligand: 15 mol% $Pd(OAc)_2$ and 15 mol% ligand total (**Figure 16**).

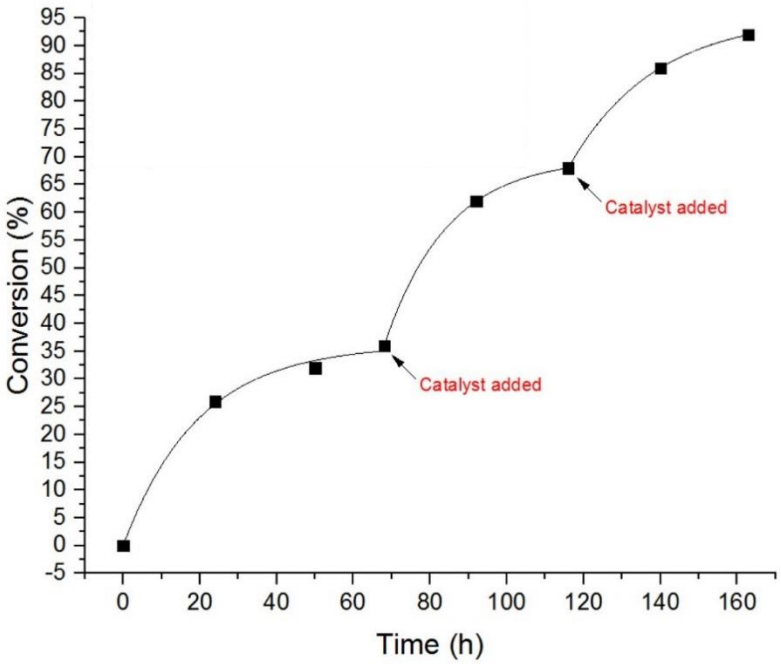


Figure 16. The re-addition of the catalyst restored the conversion rate of the oxidation.

9.4.3 Direct palladium catalysed oxidation studies: the nitrate effect

In the proposed reaction mechanism reported by Stahl (**Scheme 40**), the Pd^0-species was oxidised by oxygen to Pd^{II} to re-start the catalytic cycle. However, during the reoxidation of palladium, aggregation and deactivation of the catalyst could take place arresting the cycle.[82] The need of two subsequent additions of $Pd(OAc)_2$ and ligand to reach a 92% conversion to the enone **115**, suggested that deactivation of the catalyst was occurring during the oxidation reaction. The Fairlamb group have previously reported the nitrate effect in a range of oxidative palladium mediated processes, highlighting the role of the NO_3^- anion as a co-catalyst of the palladium complex.[84, 85] To progress the conversion without the need of subsequent additions of $Pd(OAc)_2$, the role of the nitrate was tested. In the presence of 19 mol% of KNO_3, a rate enhancement was indeed observed: over a period of 80 hours, a 60% conversion was seen (**Figure 17**). A conversion of 80% over the same period was observed with the use of 50 mol% of KNO_3, whereas, in the presence of stoichiometric KNO_3 a slower conversion was detected compared to the 50 mol% KNO_3 experiment. A possible poison effect of stoichiometric quantities of the NO_3^- anion to the $Pd(OAc)_2$ catalyst may explain this result (**Figure 17**).[84, 85]

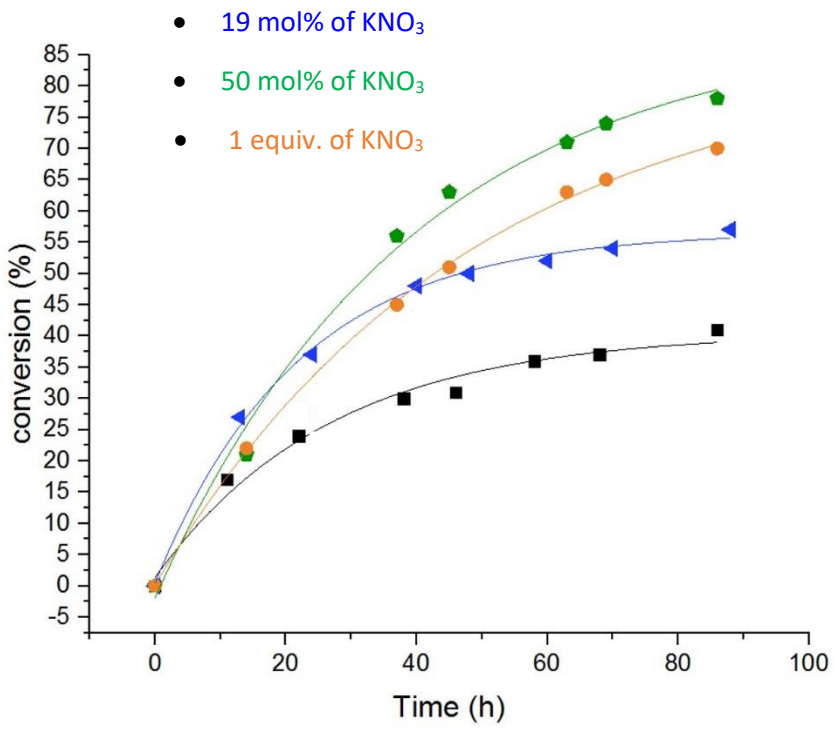


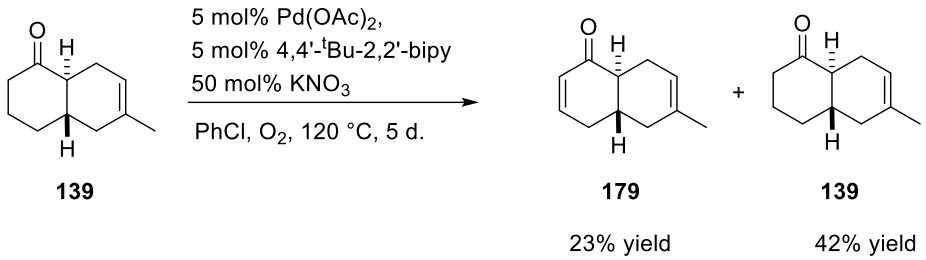
Figure 17. The effect of KNO_3 concentration on the oxidation rate of the formation of the enone **115**.

The optimised reaction conditions, 5 mol% of $Pd(OAc)_2$, 5 mol% of 4,4′-^{t}Bu-2,2′-dipyridyl as a ligand and 50 mol% of KNO_3 as a co-catalyst, were performed on a 10 g scale oxidation of ketone **160** to the enone **115**, which was isolated in an 85% yield (9.0 g).

In conclusion, a scalable and robust synthesis of the enone **115** was performed to afford the dienophile required for the Diels–Alder cycloaddition, for the formation of the *trans*-decalin core of anthracimycin. The reported Stahl and Tsuji direct palladium-catalysed oxidation conditions were tested with no success, and a new catalytic system was developed. The use of the nitrate anion as a co-catalyst was found to be pivotal for the rate of conversion of ketone **160** into the enone **115**. However, more studies need to be performed to investigate the appropriate mechanism of this reaction, which is still unknown, and to obtain the same level of conversion and yield in a shorter period of time.

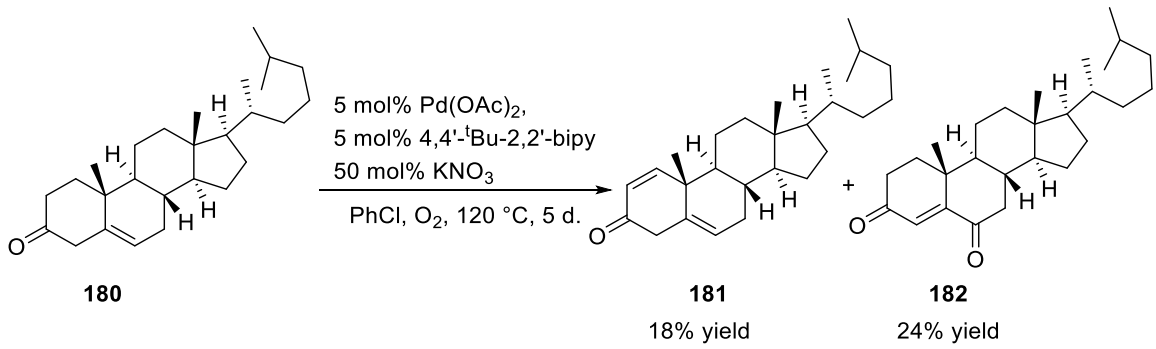
9.4.4 Direct palladium catalysed oxidation studies: substrate scope

To investigate if the optimised oxidation conditions were applicable to the formation of other enone systems, various ketone substrates were tested. A 50% conversion of the model *trans*-decalin **139** into the model enone *trans*-decalin **179**, was achieved after 5 days. However, compound **179** was isolated in a 23% yield and unreacted ketone **139** was recovered in a 42% yield (**Scheme 42**). Purification issues explained the poor yield of **179**, as enone **179** may remain coordinated to the Pd^0 species.



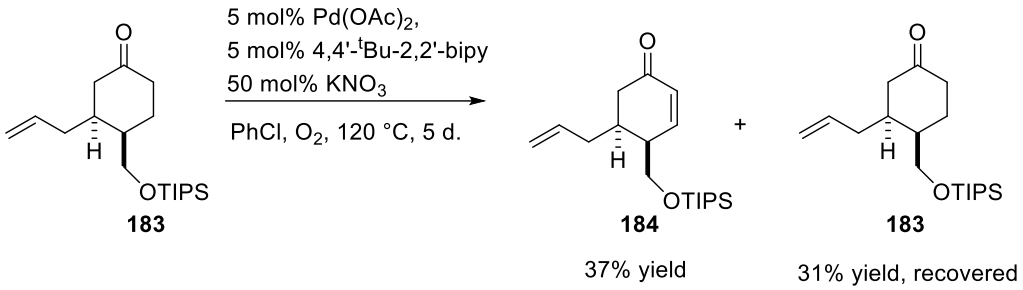
Scheme 42. The optimised oxidation conditions to form the model enone *trans*-decalin **179**.

The oxidation of cholesterone **180** generated enone **181** in 18% yield; compound **182** was also isolated in a 24% yield due to an unexpected addition of nucleophilic oxygen to the γ-alkene, and the consequent α,β migration of the double bond (**Scheme 43**).



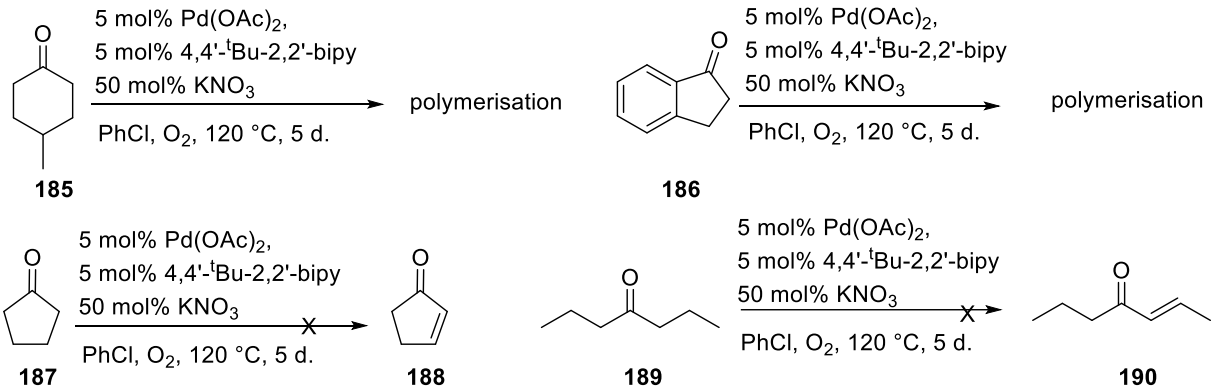
Scheme 43. Palladium catalysed direct oxidation of cholesterone **180**.

The allyl-substituted enone **184** was isolated in a 37% yield as a consequence of the direct oxidation of **183**, occurring exclusively on the less hindered side of the molecule (**Scheme 44**). This selectivity was hypothesised to be due to the steric repulsion between the palladium complex and the allyl substituent, which directed the oxidation to the less hindered position, α to the carbonyl group of **184**. However, the starting material **183** was recovered in a 31% yield.



Scheme 44. Palladium catalysed direct oxidation of allyl-substituted cyclohexanone **183**.

The oxidation of ketones **185**, **186**, **187** and **189** did not yield any enone products. Ketones **185** and **186** exclusively formed polymerised material, whereas, the volatility of cyclopentanone **187** and heptanone **189** was responsible of the failure of these reactions (**Scheme 45**).

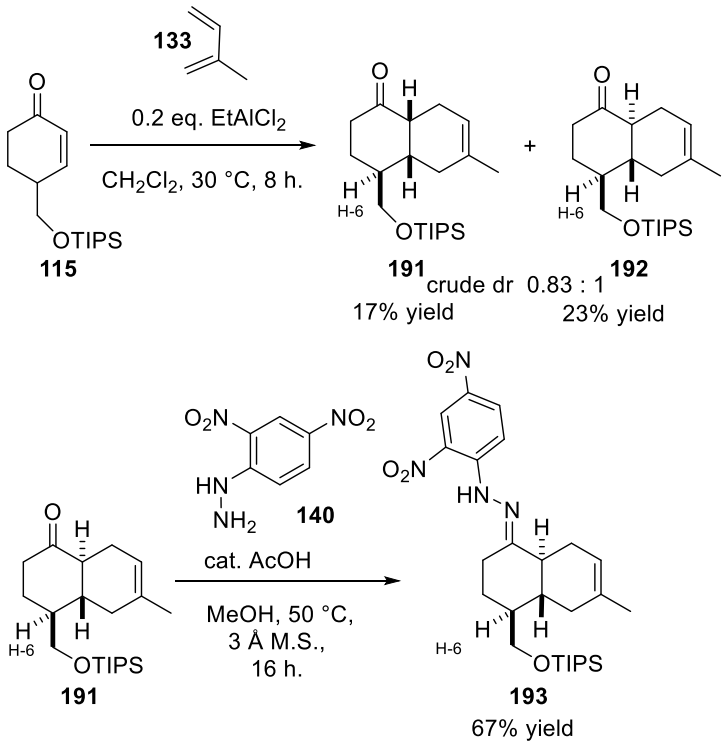


Scheme 45. Substrate scope using the optimised oxidation conditions.

In conclusion, the optimised palladium-catalysed direct oxidation conditions were not always applicable for the dehydrogenation of diverse substrates. Enones **179**, **181** and **184** were formed in poor yields compared to the 85% isolated yield of enone **115**. The reason is still unclear and more work is required to optimise and apply these conditions to the oxidation of various ketone substrates to enones in high yields.

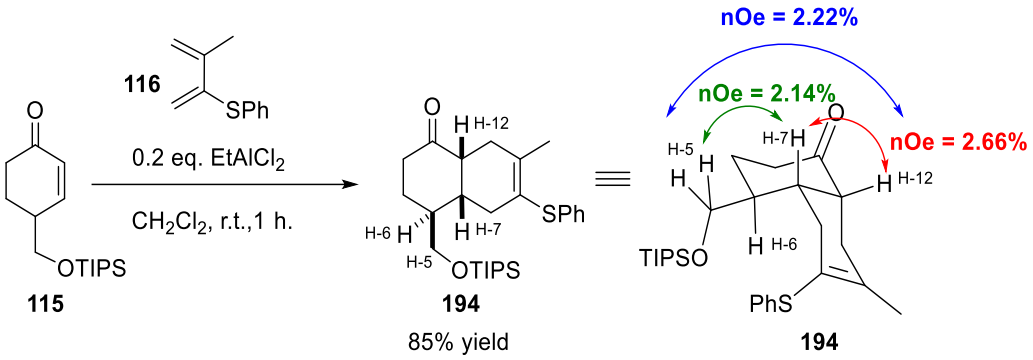
9.5 Enone **115** in the Diels-Alder reaction

The power of this oxidation reaction allowed the synthesis of the enone **115** to be performed on a multi-gram scale and this compound was used as a dienophile in the Diels–Alder/epimerisation sequence. In the presence of isoprene **133** as a diene, *cis*- and *trans*-decalins **191** and **192** were formed in a 0.83 : 1 ratio (*cis* : *trans*) (**Scheme 46**). Determination of the stereochemistry at C-6 was required. To this end, the *trans*-diastereoisomer **191** was converted into the hydrazone **193** by treatment with 2,4-dinitrophenyhydrazine **140**, in dry methanol and catalytic acetic acid. However, good quality single crystal X-ray diffraction could not be obtained.

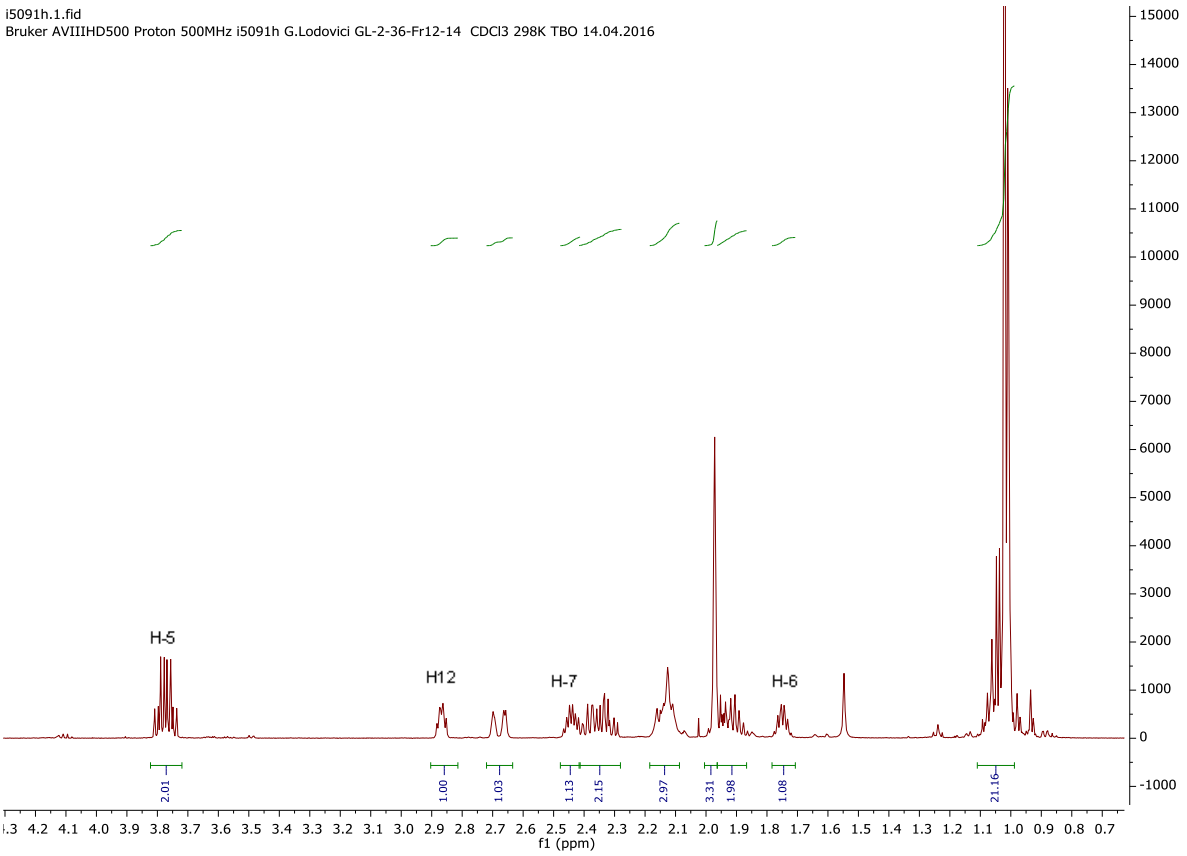


Scheme 46. The Diels–Alder/epimerisation sequence between enone **115** and isoprene **133**.

Following these results, the Diels–Alder cycloaddition between enone **115** and the sulfur-substituted diene **116** was attempted. After 10 minutes, diene **116** was consumed completely and the desired product **194** was isolated in a 10% yield. Under the standard conditions, the rate of decomposition of diene **116** was faster than the rate of product formation and this explained the poor yield. To solve this problem, a large excess of diene **116** (10 equivalents) was used and compound **194** was isolated in an 85% yield, as a single *cis*-diastereoisomer (**Scheme 47**). Determination of the stereochemistry of the ring junction protons C-12 and C-7 and between C-7 and C-6, was the key information needed to progress in the total synthesis (**Figure 18**). The nOe ^{1}H NMR analysis showed a prominent through-space interaction between H-7 and H-12 (nOe = 2.66%), as well as a strong correlation between H-5 and both ring junctions protons (nOe = 2.22% and 2.14%, H-12 and H-7 respectively) (**Figure 18**). No through-space interaction was observed between H-6 and the ring junction proton H-12 (**Figure 19**). According to these nOe data, the structure of **194** was deduced to be a *cis*-decalin with an *anti*-relationship between protons H-6 and H-7. This stereochemical assignment was later confirmed by single crystal X-ray diffraction of derivative **196**.



Scheme 47. The Diels-Alder cycloaddition between enone **115** and the sulfur substituted diene **116**.



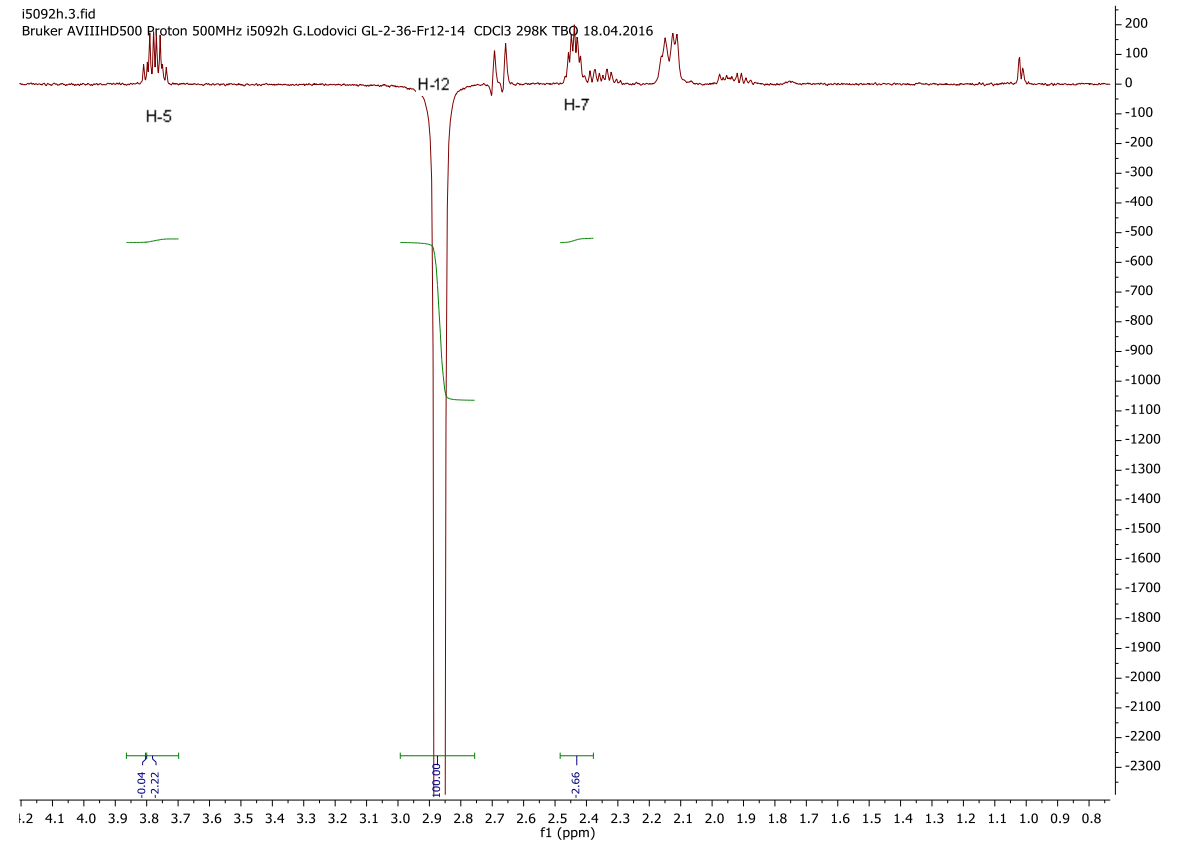


Figure 18. The ^{1}H NMR spectrum of *cis*-decalin **194** and the nOe analysis of H-12.

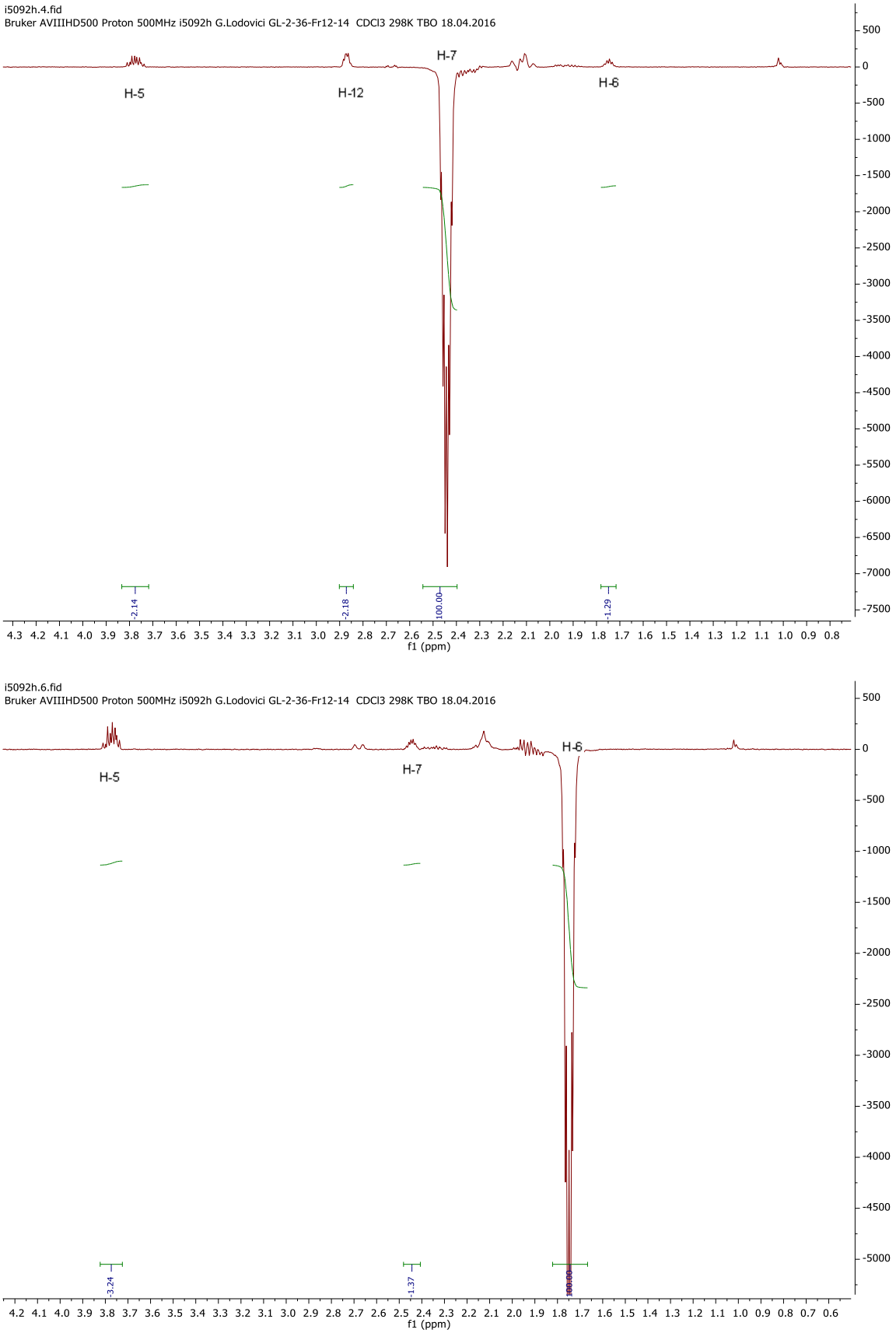
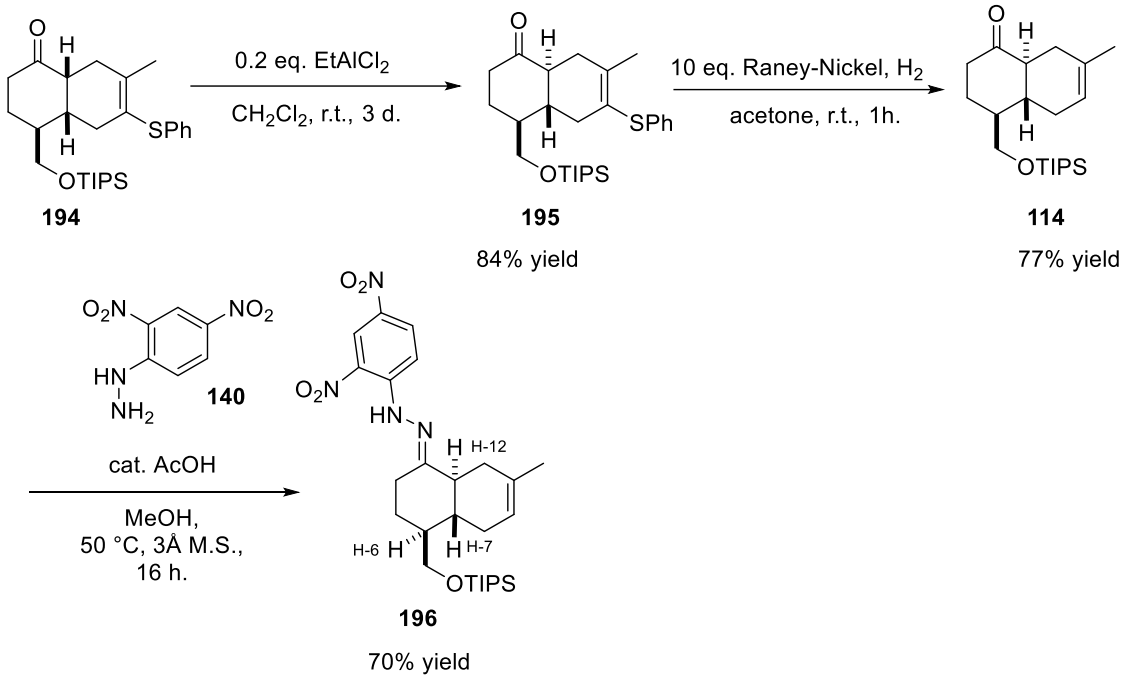


Figure 19. The nOe analysis of H-7 and H-6.

Figure 18 shows the ^{1}H NMR expansion between δ 4.3 and 0.7 ppm to highlight the key protons (H-5, H-12, H-7 and H-6) involved in the determination of the stereochemistry of the *cis*-decalin **194**. The expansion between δ 4.3 and 0.7 ppm of the nOe spectrum of proton H-12 showed the through-space interaction with H-7 (nOe = 2.66%) and H-5 (nOe = 2.22%). **Figure 19** shows the expansion between δ 4.3 and 0.7 ppm of the nOe of H-7, in which a correlation of 2.14% with H-5 and 2.18% with H-12 was observed, whereas, the nOe of H-6 showed no through-space interaction with H-12 (nOe = 0%) and a correlation with H-7 of 1.37%.

Consequently, $EtAlCl_2$-catalysed epimerisation of the *cis*-cycloadduct **194** gave the *trans*-diastereoisomer **195**, after 3 days at room temperature in an 84% yield. The thiophenyl group was removed using selective Raney-Nickel reduction and the desired *trans*-decalin **114** was obtained in 77% yield (**Scheme 48**). To confirm the stereochemistry determined by nOe ^{1}H NMR analysis, *trans*-decalin **114** was converted into the hydrazone **196** using 2,4-dinitrophenylhydrazine **140** in dry methanol and catalytic glacial acetic acid. Compound **196** was isolated in 70% yield as an orange solid and crystallised in a hexane/EtOAc, antisolvent-solvent system. Gratifyingly, single crystal X-ray diffraction confirmed the stereochemistry determined by nOe ^{1}H NMR studies. An *anti*-relationship between the protons H-6 and H-7 and a *trans*-stereochemistry of the ring junction protons, H-12 and H-7, were observed (**Figure 20**). The ^{1}H NMR spectroscopic analysis of the *trans*-decalins **114** and **192** were identical and it was concluded that both compounds had the same *anti*-relationship between protons H-6 and H-7 and a *trans*-stereochemistry of the ring junction protons, H-7 and H-12.



Scheme 48. The formation of the *trans*-decalin core **114**.

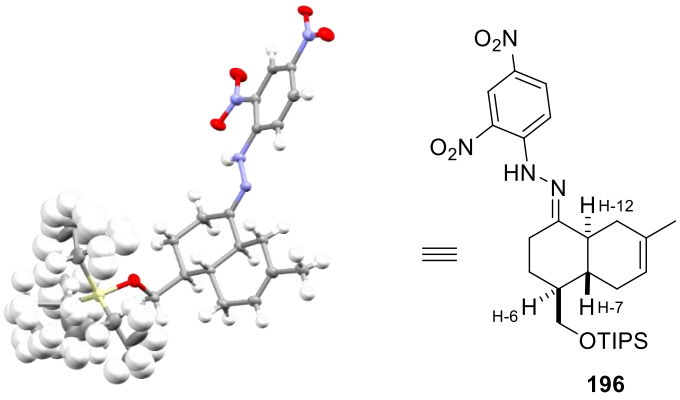


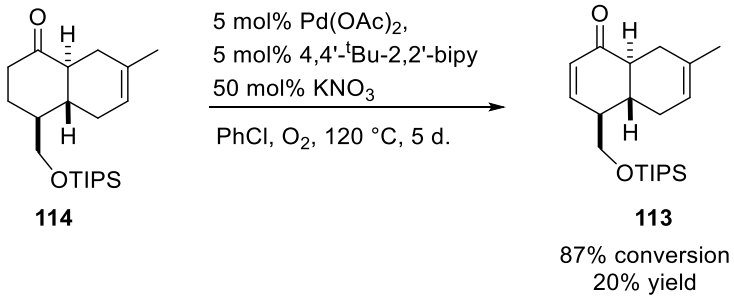
Figure 20. Single crystal X-ray diffraction of hydrazone **196** with thermal ellipsoids shown at 50%.

Figure 20 shows the structure of the hydrazone *trans*-decalin **196**. A *trans*-relationship at the ring junction protons H-7 and H-12 and an *anti*-relationship between protons H-7 and H-6 is evident, as required for the *trans*-decalin core of anthracimycin.

9.6 Oxidation of *trans*-decalin **114** to enone *trans*-decalin **113**

9.6.1 The Ito–Saegusa oxidation

To progress the synthesis, the conversion of the *trans*-decalin **114** into the enone *trans*-decalin **113** was required, but this transformation was very challenging and so various oxidation methods were explored. Firstly, this oxidation was attempted using the optimised conditions of the direct palladium-mediated oxidation. However, this transformation was particularly slow and the catalyst and the ligand had to be re-added every 24 hours. After 5 days, 87% conversion to the desired enone **113** was seen by ^{1}H NMR analysis, but enone **113** was isolated in only 20% yield (**Scheme 49**). Purification issues could explain the poor yield of **113**, becuase the enone *trans*-decalin **113** could have remained coordinated to the Pd^{0} species formed during the reoxidation process of the catalyst. The presence of two double bonds in the product may be responsible for this coordination, because under the same oxidation conditions the model enone *trans*-decalin **179** was also isolated in poor yield (50% conversion, 23% yield).

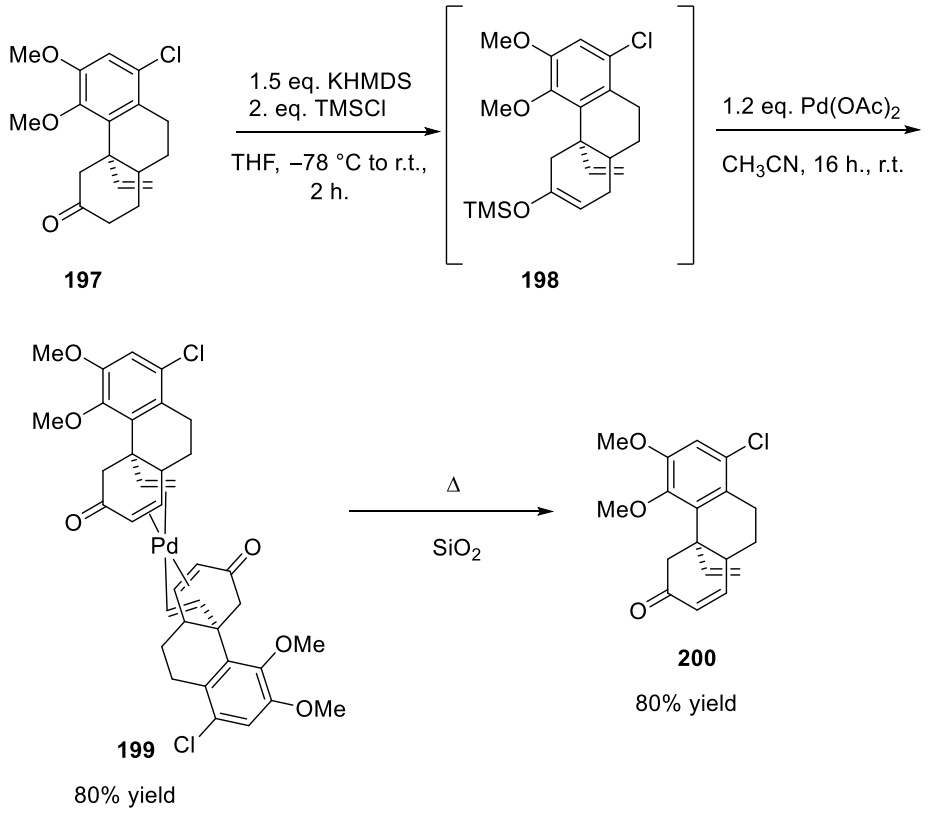


114 **113**

87% conversion
20% yield

Scheme 49. The conversion of the *trans*-decalin **114** to the enone *trans*-decalin **113** applying the optimised palladium oxidation conditions.

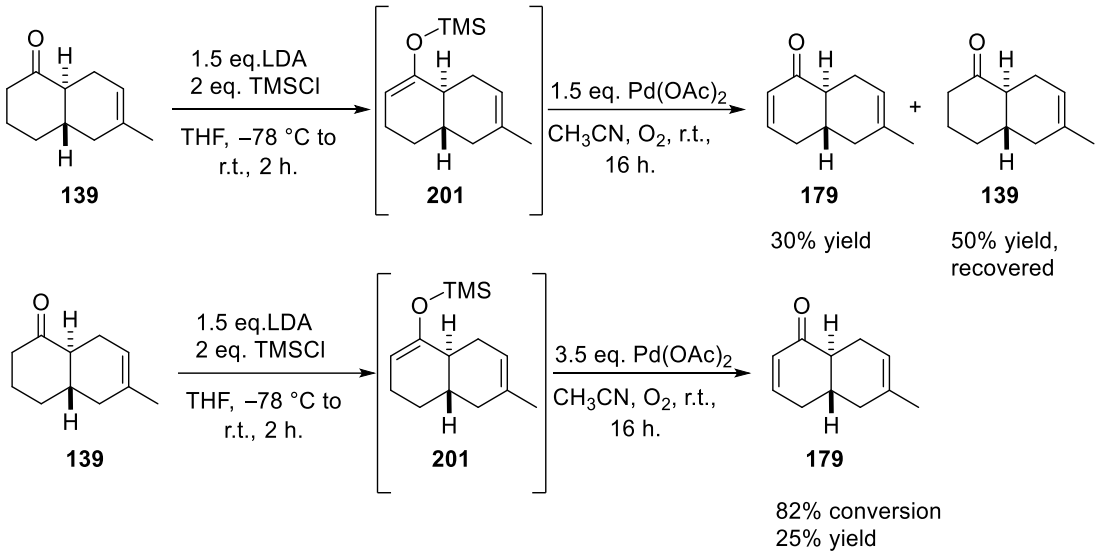
The Ito–Saegusa oxidation reaction was attempted in order to improve the yield of enone **113**. In 1999, Dirk Trauner *et al.* reported the crystallisation and isolation of the Pd^0-tetrolefin complex **199** to highlight the mechanism of this reaction.[86] Ketone **197** was converted into the silyl enol ether **198** using KHMDS and TMSCl, and subsequently oxidised in the presence of stoichiometric $Pd(OAc)_2$ in CH_3CN (**Scheme 50**).



Scheme 50. The Ito–Saegusa oxidation conditions reported by Dirk Trauner.[86]

Inspired by these conditions,[86] the model *trans*-decalin **139** was converted into the TMS-enol ether intermediate **201** in the presence of LDA at –78 °C and TMSCl. Due to the propensity for hydrolysis of **201** to the ketone starting material **139** in water, air and any non-anhydrous solvent suitable for the work-up of the reaction, it was not possible to isolate this compound. However, the formation of this TMS-enol ether was detected by TLC and was subsequently oxidised in the presence of $Pd(OAc)_2$ to

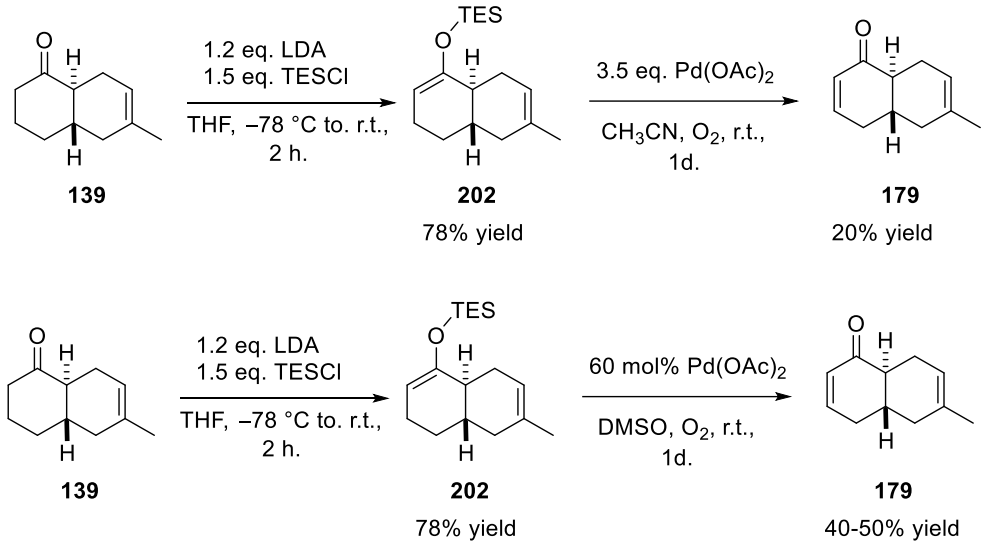
form the model enone *trans*-decalin **179**. Catalytic quantities of $Pd(OAc)_2$ did not produce the desired product, but in the presence of 1.5 equivalents of $Pd(OAc)_2$ the model enone *trans*-decalin **179** was generated in a 30% yield (**Scheme 51**). Hydrolysis of the TMS-enol ether **201** to the ketone starting material **139** occurred over time and this decomposition competed with the formation of the product **179**. To avoid this hydrolysis, the use of a large excess (3.5 equivalents) of $Pd(OAc)_2$ was tested. A conversion of 82% to the model enone *trans*-decalin **179** was seen by ^1H NMR analysis, but the desired product was isolated in just 25% yield (**Scheme 51**). Again, purification issues may explain the poor yield; elevated quantities of the catalyst may lead to high levels of Pd^0 species in the reoxidation process, causing coordination of **179** and reduction of the yield.



Scheme 51. The Ito–Saegusa oxidation to form the enone **179**.

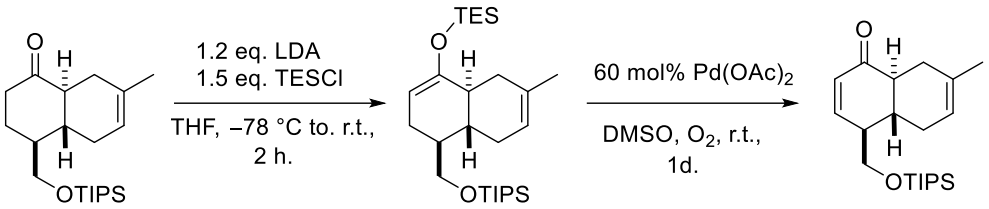
In 2011, Nishida *et al*. reported the Ito–Saegusa oxidation of various TES-enol ether substrates, highlighting the high stability of these silyl enol ethers for this transformation.[87] Inspired by this report, the model TES-enol ether *trans*-decalin **202** was formed and isolated in 78% yield. The ease of isolation was a consequence of the stability of the silyl enol ether in water and on silica chromatography. Treatment of **202** with stoichiometric $Pd(OAc)_2$ in CH_3CN formed the desired product **179**, but only in

20% isolated yield (**Scheme 52**). The low yield was thought to be due to purification issues caused by the presence of the Pd^0 species, and so this transformation was attempted using catalytic $Pd(OAc)_2$ loading. However, the desired product **179** was not obtained after five days, and the starting TES-enol ether **202** was recovered unreacted. The use of DMSO as a solvent resulted in formation and isolation of the desired product **179** in variable yields, of between 40% and 50%, when 60 mol% of $Pd(OAc)_2$ was used (**Scheme 52**).[88]



Scheme 52. The Ito–Saegusa oxidation of the model TES-enol ether *trans*-decalin **202**.[87, 88]

Following these encouraging results, the conversion of the *trans*-decalin **114** to the enone *trans*-decalin **113** was attempted (**Scheme 53**). Formation of the TES-enol ether **203** in a 79% yield, was followed by the Ito–Saegusa oxidation, which had a similar outcome; enone **113** was isolated in variable yields (30%-50%) in the presence of 60 mol% of $Pd(OAc)_2$ in DMSO (**Table 10**, **entry 1**). The use of CH_3CN as solvent did not increase the yield (**Table 10**, **entry 2** and **3**). The use of additives to increase the catalyst efficiency during the reoxidation process of the Pd^0 species was tested. However, the presence of benzoquinone and Oxone® had a negative effect on this transformation; enone **113** was isolated in 20% and 10% yield respectively (**Table 10**, **entry 4** and **5**).[89, 90]



114 **203** **113**

79% yield 30-50% yield

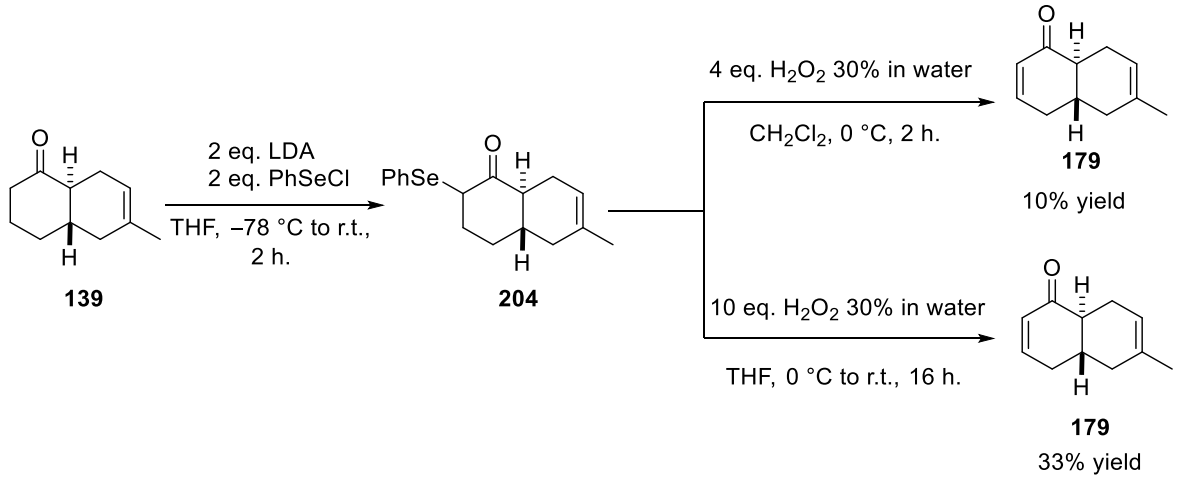
Scheme 53. The Ito–Saegusa oxidation to form enone **113**.[89, 90]

entry	additives	solvent	temperature (°C)	yield (%)
1	-	DMSO	40	30-50
2	-	CH_3CN	23	20
3	-	CH_3CN	40	20
4	benzoquinone	CH_3CN	23	20
5	Oxone®	CH_3CN	23	10

Table 10. The attempted Ito–Saegusa oxidation conditions.[89, 90]

9.6.2 The selenoxide elimination

Low yields had been obtained, and so the model *trans*-decalin **139** was used to scope other oxidation methods suitable for this transformation. Treatment of *trans*-decalin **139** in the presence of LDA at –78 °C and phenylselenium chloride formed the selenide intermediate **204**, which was oxidised with an excess of 30% H_2O_2 in water. The model enone *trans*-decalin **179** was generated in yields of 10% and 33%, using CH_2Cl_2 and THF as solvents respectively (**Scheme 54**).

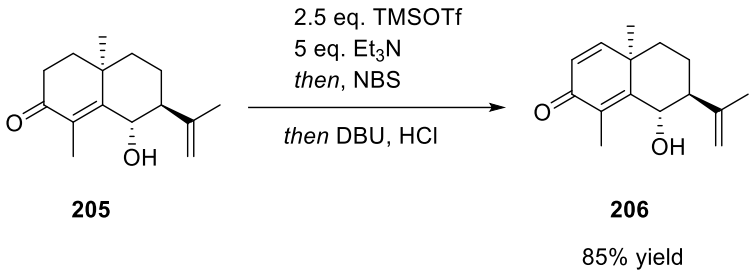


Scheme 54. The selenoxide chemistry used for the oxidation of **139**.

This oxidation method formed the model enone *trans*-decalin **179** in low yields due to the formation of many impurities, (confirmed by ^{1}H NMR analysis), and so the conversion of the *trans*-decalin **114** into the enone *trans*-decalin **113** under these conditions was not attempted.

9.6.3 The α-bromination/elimination sequence

An oxidation method to progress in the total synthesis had to be identified and so, model studies were used to test other conditions. In 2002, Baran and his group reported a robust and high yielding method to form dienone **206**, as a key intermediate in their concise synthesis of (–)-thapsigargin.[91] The use of TMSOTf and Et_3N converted ketone **205** into the TMS-enol ether, which was subsequently α-brominated in the presence of NBS. Treatment of this intermediated with DBU formed the desired dienone product **206** in an 85% yield (**Scheme 55**).

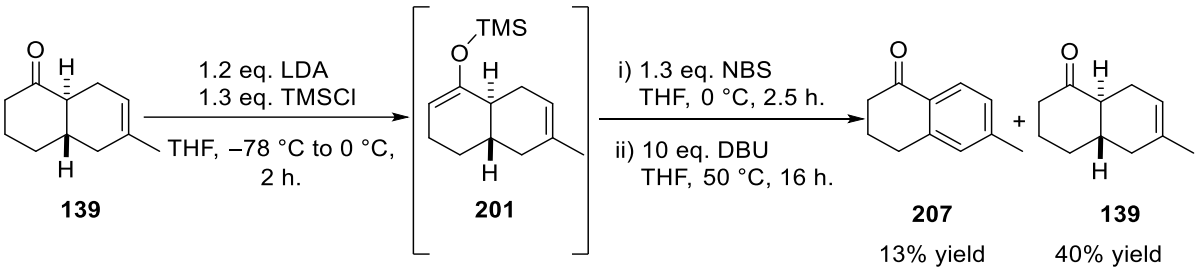


205 **206**

85% yield

Scheme 55. The oxidation conditions reported by Baran and his group.[91]

Following the described method,[91] the model *trans*-decalin **139** was converted to the model TMS-enol ether **201** by treatment with LDA at −78 °C and TMSCl. After formation of TMS-enol ether **201** had been established by TLC analysis, the α-bromination/elimination sequence in the presence of NBS and DBU generated tetralone **207** in a 13% yield (**Scheme 56**). The starting *trans*-decalin **139** was recovered in 40% yield, likely due to the hydrolysis of the TMS-enol ether **201**. A possible explanation for the formation of tetralone **207**, is equilibration of the kinetic to the thermodynamic enol ether, which occurred when the reaction was warmed to 0 °C in the α-bromination step.



139 **201** **207** **139**

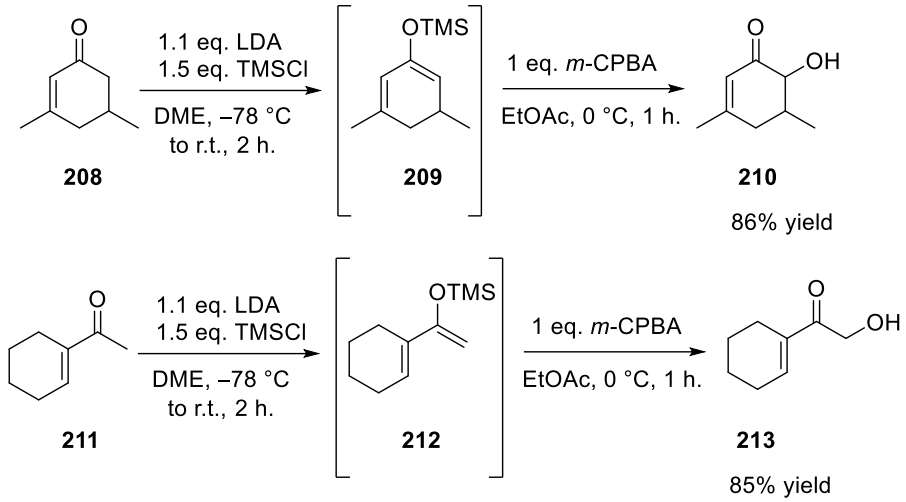
13% yield 40% yield

Scheme 56. Oxidation of ketone **139** in the presence of NBS and DBU, as reported by Baran *et al.*[91]

9.6.4 The Rubottom oxidation

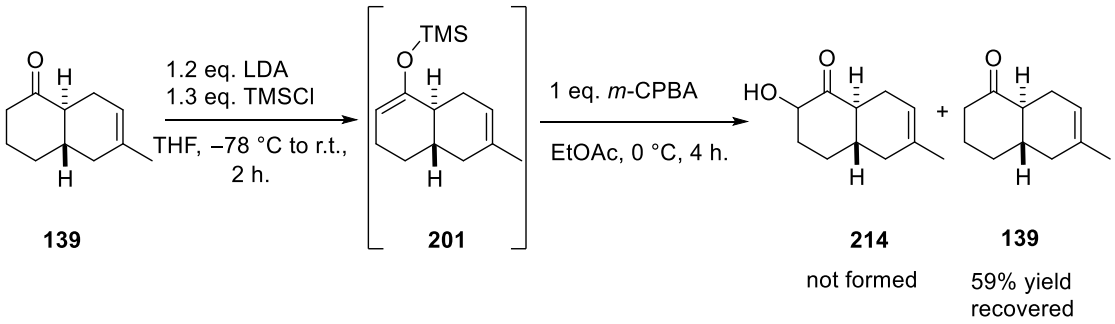
The α-functionalisation of ketone **139** with a leaving group suitable for elimination, and the subsequent formation of the enone **179** was investigated using the Rubottom oxidation reaction.[92] Literature reported this mild method to synthesise α-hydroxy ketones, *via* formation of silyl enol ether

intermediates followed by oxidation in the presence of *m*-CPBA (**Scheme 57**). This approach would allow the formation of the α-hydroxy *trans*-decalin **214**, which could be subjected to a mesylation/elimination sequence to yield the desired model enone **179**.



Scheme 57. Literature examples of Rubottom oxidation.[92]

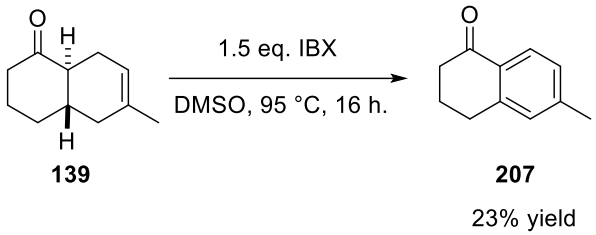
Treatment of the model *trans*-decalin **139** in the presence of LDA at –78 °C and TMSCl generated the TMS-enol ether **201**. However, hydrolysis of the silyl enol ether **201** to the starting ketone *trans*-decalin **139** occurred in the oxidation step (**Scheme 58**). This oxidation method was therefore not pursued further.



Scheme 58. The Rubottom oxidation method to form the model enone *trans*-decalin.[92]

9.6.5 The oxidation in the presence of IBX

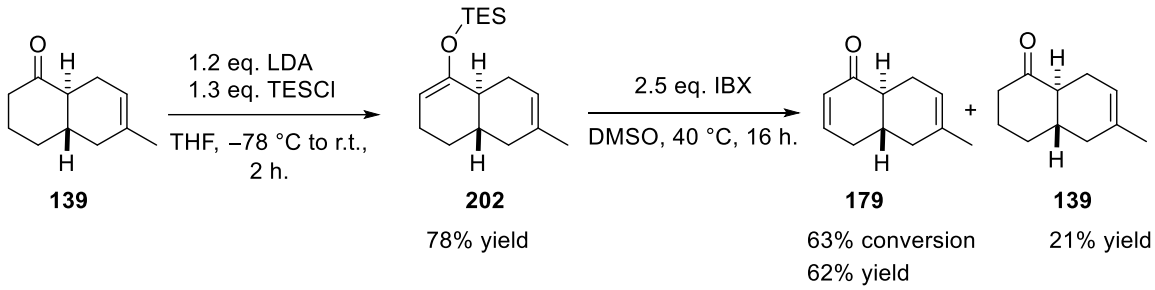
Model studies to discover a robust and reliable oxidation method continued to be explored to progress the total synthesis. In 2002 Nicolaou *et al.*,[93] reported the direct oxidation of various ketone substrates to generate enones by treatment with 2-iodoxy benzoic acid (IBX) at elevated temperatures. Inspired by this work, the model *trans*-decalin **139** was treated with 1.5 equivalents of IBX at 95 °C, but after 16 hours only tetralone **207** was formed in a 23% yield (**Scheme 59**). Presumably, generation of tetralone **207** was a consequence of the thermodynamic enol formation followed by oxidation/aromatisation, occurring at elevated temperature.



Scheme 59. Oxidation of the model *trans*-decalin **139** using the reported literature conditions.[93]

To avoid the formation of the thermodynamic enol, the synthesis of the TES-enol ether *trans*-decalin **202** at a lower temperature was proposed. Treatment of the model *trans*-decalin **139** with LDA and TESCl at −78 °C formed TES-enol ether **202** in a 78% yield, which was then subjected to the IBX oxidation at 40 °C, the minimum temperature needed to dissolve IBX (**Scheme 60**). Interestingly, it was observed that the stoichiometry of IBX played an important role in the formation of the desired product in good yield. The use of 1.5 equivalents of IBX formed the model enone *trans*-decalin **179** and the ketone *trans*-decalin **139** in a 1 : 1 ratio (**Table 11**, **entry 1**). Increasing the stoichiometry of IBX to 2.5 equivalents formed **179** and **139** in a 1 : 0.37 ratio with the isolation of **179** in a 62% yield (**Table 11**, **entry 2**). The use of a large excess of IBX (5 and 10 equivalents) did not improve the

conversion from 63%, as **179** and **139** were isolated in a 1 : 0.46 and 1 : 0.47 ratios respectively (**Table 11**, **entry 3** and **4**).



Scheme 60. The IBX oxidation of the model TES-enol *trans*-decalin **202**.

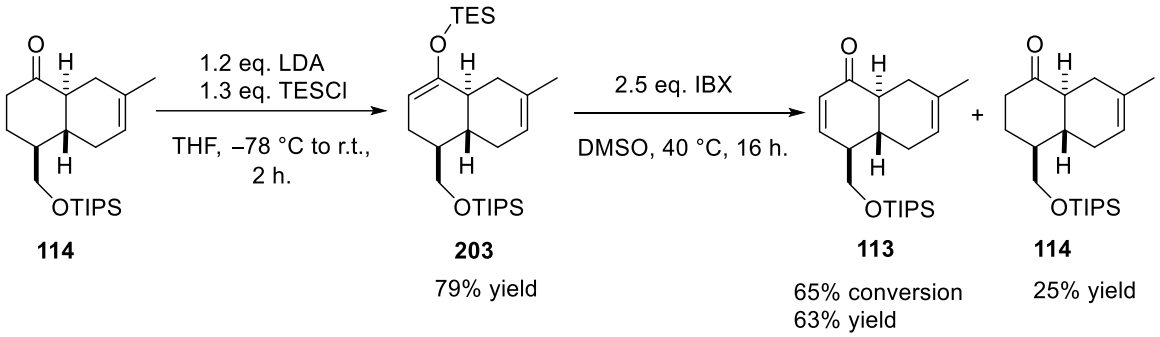
entry	equivalents of IBX	crude ratio 179 : 139	combined yield of 179 and 139 (%)
1	1.5	1 : 1	78 (a)
2	2.5	1 : 0.37	62 (b)
3	5	1 : 0.46	80 (a)
4	10	1 : 0.47	75 (a)

(a) crude yield, (b) isolated yield of enone *trans*-decalin **179**

Table 11. The IBX oxidation of the model TES-enol intermediate **202**.

The formation of the model enone *trans*-decalin **179** in a good yield under IBX oxidation, prompted the application of these conditions to convert the *trans*-decalin **114** to the enone *trans*-decalin **113**. After formation of the TES-enol ether intermediate **203** in a 79% yield, oxidation of TES-enol ether **203** in the presence of 2.5 equivalents of IBX formed the desired enone **113** in a 65% conversion and a 63% yield (**Scheme 61**, **Table 12**, **entry 2**). The amount of IBX played an important role in the formation of enone **113** in a good ratio and yield. The use of 1.5 equivalents of IBX formed **113** and **114** in a 1 : 1

ratio (**Table 12**, **entry 1**), whereas, a large excess of IBX (5 equivalents) did not improve the conversion and yield from 65% and 63% respectively (**Table 12**, **entry 3**).



Scheme 61. The IBX oxidation to form the enone *trans*-decalin **113**.

entry	equivalents of IBX	crude ratio 113 : 114	yield (%)
1	1.5	1 : 1	45
2	2.5	1 : 0.35	63
3	5	1 : 0.42	62

Table 12. The IBX oxidation of the model TES-enol intermediate **203**.

In conclusion, the formation of the enone *trans*-decalin **113** was found to be very challenging and several oxidation methods were studied to afford **113** in a good yield to progress the total synthesis. The model *trans*-decalin **139** was therefore used to scope an appropriate strategy. The direct palladium-oxidation method developed by Dr. Ian George and the Ito–Saegusa reaction, formed the desired enone products in a good conversion. Nevertheless, purification issues explained the low

yields of **113** and **179**. Model studies involving selenoxide chemistry were not successful and afforded the desired product in low yields with many impurities.

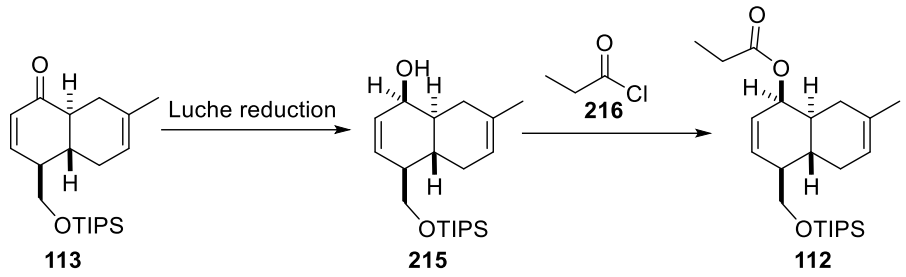
The strategies used by Baran and Rubottom to α-functionalise the model *trans*-decalin **139** with a suitable leaving group prone to elimination were found to be unreliable. The Nicolaou IBX oxidation protocol, generated tetralone **207** due to the formation of the thermodynamic enol followed by an oxidation/aromatisation reaction. In contrast, the formation of the model TES-enol ether intermediate **202** allowed the IBX-mediated formation of the model enone *trans*-decalin **179** to be accomplished in a good yield. The identification of this reliable, consistent and robust oxidation method permitted the isolation of the desired enone *trans*-decalin **113** in a good yield, allowing progression of the total synthesis.

Stereoselective 1,2 reduction of this key intermediate **113** followed by treatment with propionyl chloride to form the propionate ester *trans*-decalin **112**, suitable for the facial and diasteroselective Ireland–Claisen rearrangement will be discussed in the next section.

9.7 Strategies to the core of anthracimycin **162**

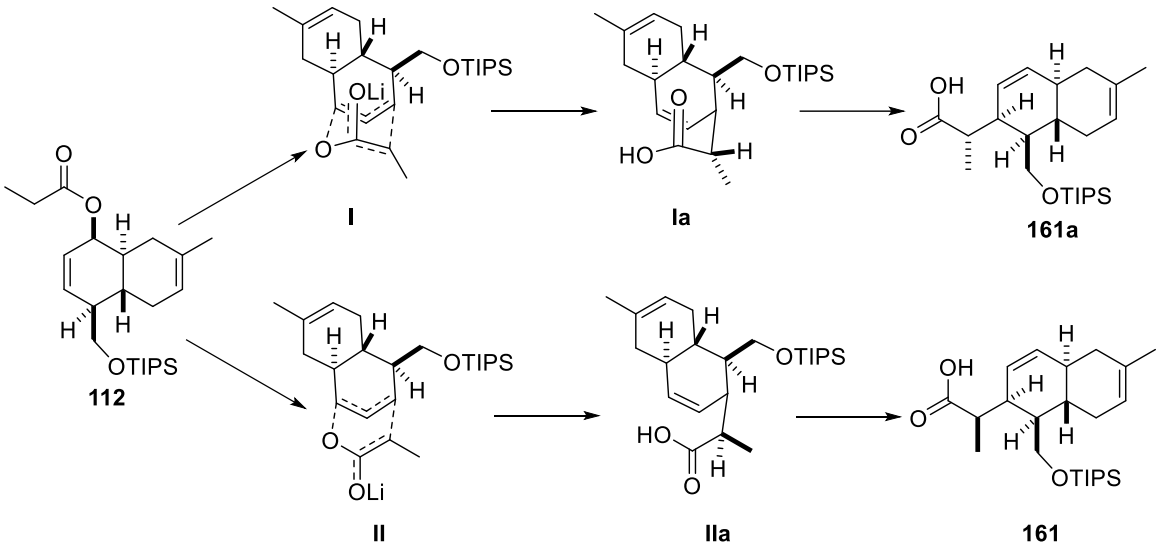
9.7.1 The Ireland–Claisen rearrangement

The use of an Ireland–Claisen rearrangement was the reaction envisioned for functionalisation to give the core of anthracimycin **162**. This approach would start with a stereoselective Luche reduction of **113**,[95] followed by treatment with propionyl chloride to provide **112**, an allylic ester suitable for the rearrangement reaction (**Scheme 62**).

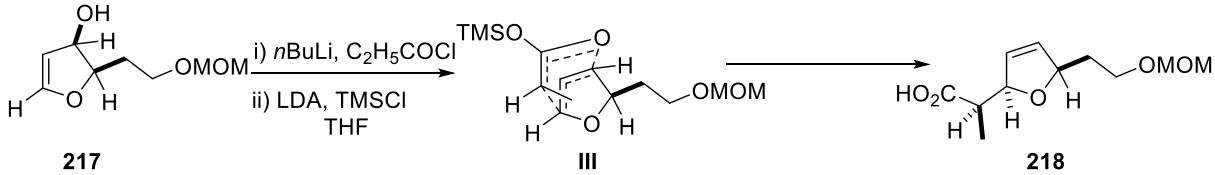


Scheme 62. Formation of the propionate ester *trans*-decalin **112**.

The axial position of the propionate ester would ensure the rearrangement occurring from the same face of the triisopropylsilylmethyloxy side chain, to install the double bond and the side chain in the correct positions. Rearrangement of the *E*-enolate would proceed *via* chair-like or boat-like transition states **I** and **II**. A chair-like transition state **I** would form **161a** with the stereochemistry of the methyl group opposite to anthracimycin, whereas, a boat-like transition state **II** would install the methyl group with the required stereochemistry for the natural product (**Scheme 63**). In his synthesis of Monensin, Ireland amply demonstrated the formation of substituted cyclohexenyl fragments by using the Ireland-Claisen rearrangement, which proceeded *via* a boat-like transition state (**Scheme 64**).[96, 97, 98, 99, 100, 101, 102]

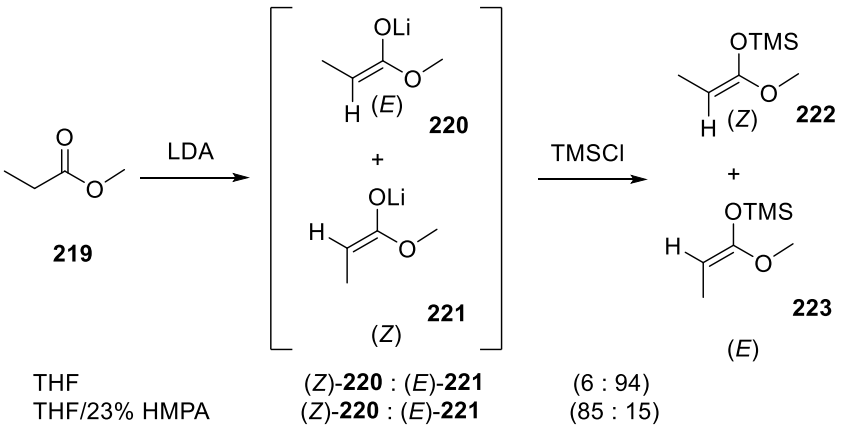


Scheme 63. Proposal for stereocontrol in the Ireland–Claisen rearrangement.



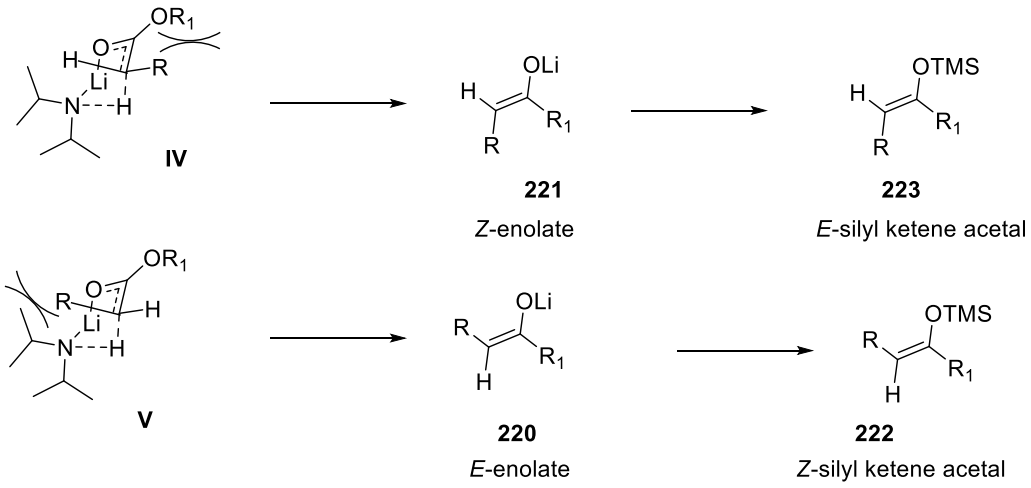
Scheme 64. Boat-like transition state in a Ireland–Claisen rearrangement, applied to the total synthesis of Monensin. [96, 97, 98, 99, 100, 101, 102]

Methods to control the formation of the *E*-enolates were investigated for the synthesis of the core of anthracimycin **162**. In 1991, Ireland and his group reported kinetically controlled enolate formation for the stereoselective formation of both *Z*- and *E*-silyl ketene acetals in THF and THF/dipolar solvent system with the use of LDA.[103] According to their studies, various ratios of *Z*- and *E*-enolates **220** and **221** were formed depending on the solvent effect. A 6 : 94 ratio (*Z*- : *E*-) was produced in THF, whereas in the presence of additives, such as DMPU (30% in THF) and HMPA (23% in THF) ratios of 98 : 2 and a 85 : 15 (*Z*- : *E*-) respectively were observed (**Scheme 65**).



Scheme 65. The *Z*- and *E*-enolate formation.[103]

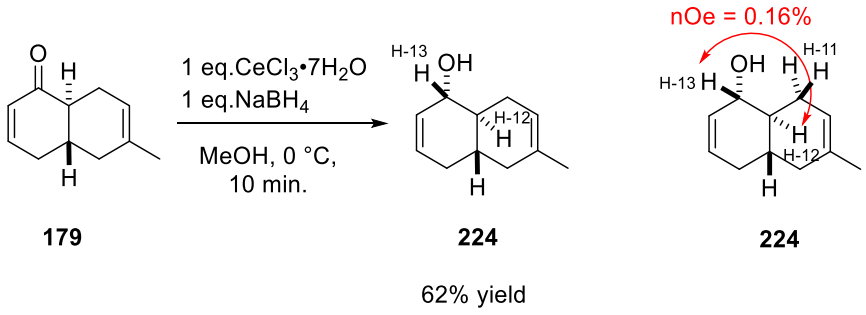
The 6-membered ring transition states **IV** and **V** were rationalised to explain the stereochemical control during enolate formation (**Scheme 66**). The transition state **IV** permitted a close interaction between the lithium cation, carbonyl oxygen and the base; in the presence of HMPA as an additive, transition state **V** was preferred. The transition state **V** is characterised by a 1,3-diaxial interaction between the *N*-isopropyl group and the R enolate group. However, this strain was reduced in the presence of DMPU or HMPA due to the greater degree of solvation of the lithium cation. As a result, in transition state **V** the association between ester and base diminished minimising the 1,3-diaxial interaction, whereas, the transition state **IV** is still destabilised by the 1,3-diaxial strain.[103]



Scheme 66. The two transition states in kinetic enolisation of esters.[103]

Stereoselective 1,2-reduction was investigated with the use of the model enone *trans*-decalin **179** as the substrate. Luche conditions were tested in the presence of equimolar amounts of $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in MeOH, in order to favour 1,2-reduction over possible 1,4-reduction. This reaction produced the allylic alcohol **224** in a 62% yield as a single diastereoisomer (**Scheme 67**).[95]

The nOe ^1H NMR analysis was used to assign the stereochemistry of **224** at H-13. However, the only prominent through-space interaction (nOe = 0.16%) was found between protons H-13 and H-12 and one of the two H-11 (**Scheme 67**, **Figure 21**). Due to this ambiguous nOe result and the absence of other clear evidence, the stereochemistry of **224** was tentatively assigned based on the known mechanism of the sodium borohydride reduction. Wigfield amply demonstrated that hydrides preferentially attack from a pseudo-axial trajectory in unhindered cyclohexanones, to give the hydroxyl group in the equatorial position.[104] As the model enone *trans*-decalin **179** was considered an unhindered cyclohexanone, the hydroxyl was tentatively assigned as having an equatorial positon, as a result of pseudo-axial attack of the hydride on the carbonyl group.



Scheme 67. The Luche reduction of the model enone *trans*-decalin **179**.[95, 104]

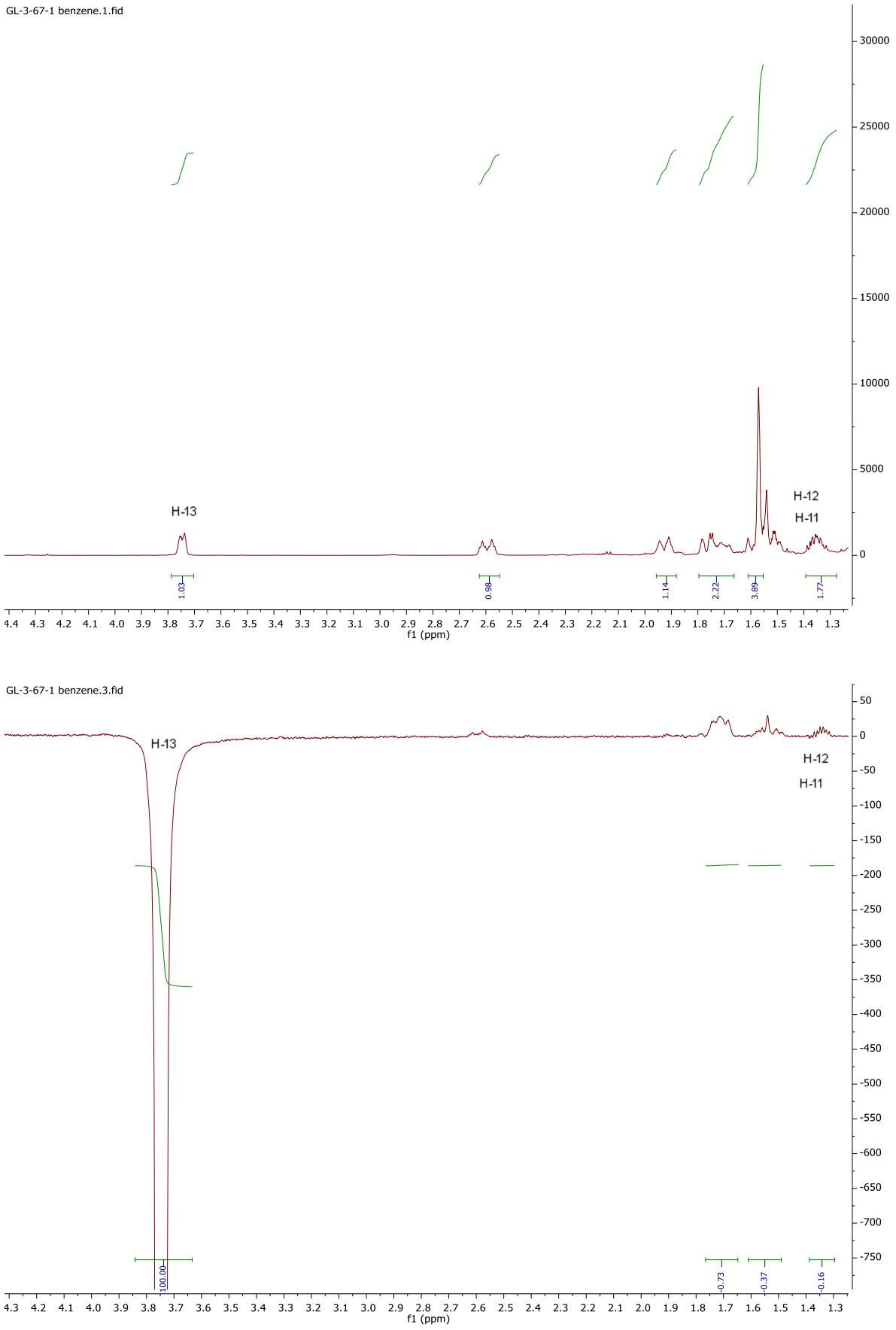
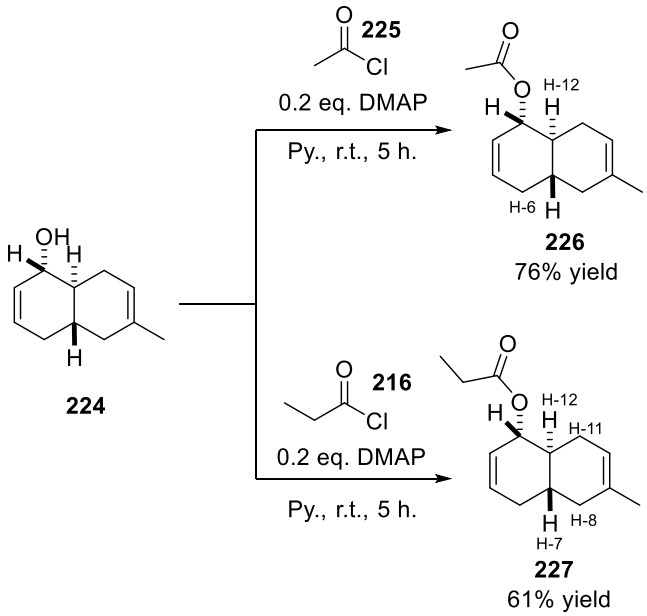


Figure 21. The ^{1}H NMR spectrum of alcohol **224** in d_6 benzene.

The expansion of the ^{1}H NMR spectrum between δ 4.44-1.32 ppm showed the key peaks H-13 and H-12 needed to be irradiated to determine the stereochemistry of **224**. The expansion between δ 4.31-1.32 ppm of the nOe analysis of H-13 showed the through-space interaction with H-12 (nOe = 0.16%), which was in a multiplet with H-11. Due to the overlap of these two protons (H-12 and H-11) it was not possible to determine the stereochemistry of **224** at H-13 unambiguously (**Figure 21**).

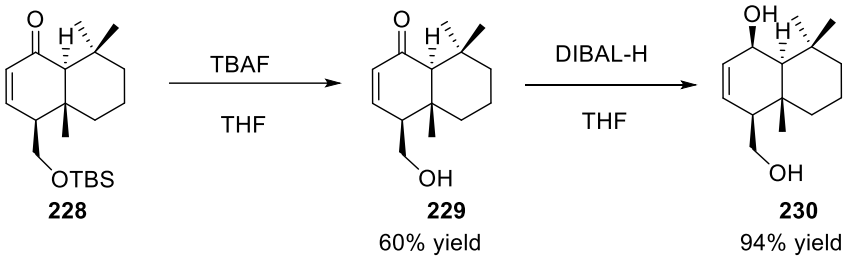
The allylic alcohol **224** was derivatised to produce the propionate and acetate esters **226** and **227**, in order to clarify the stereochemistry of H-13 by nOe ^{1}H NMR analysis (**Scheme 68**). However, the formation of these two esters did not help to establish the configuration of **224**, due to the overlap of key peaks in the ^{1}H NMR spectrum. In the acetate ester **226**, H-12 was overlapping with H-6 between δ 1.80-1.75 ppm, whereas, in the propionate ester **227** H-12 was in a multiplet with H-11, H-7 and H-8 between δ 1.93-1.84 ppm.



Scheme 68. The esterification of **224** to understand the stereochemistry of H-13.

Pseudo axial attack of the hydride onto the model enone *trans*-decalin **179** with consequent formation of the equatorial hydroxyl-substituted *trans*-decalin **224** was expected, so various reducing agents

were tested to explore their influence on the selectivity of this reduction reaction. In 2000, De Groot reported the stereoselective 1,2-reduction of ketone **229** to give alcohol **230** by the use of DIBAL-H.[105] The presence of the methyl group at the ring junction of the *trans*-decalin system **229** ensured the high selectivity of this reduction reaction. In this case, attack of hydride from the equatorial face of the ketone, ensured formation of the axial hydroxyl group in **230** (**Scheme 69**)**.**[105]



228 **229** 60% yield **230** 94% yield

Scheme 69. The stereoselective reduction of ketone **229**.[105]

The use of DIBAL-H as the reducing agent produced the alcohol **224** as the major product, but in the ^{1}H NMR spectrum of **224**, other related decalin peaks were seen (**Figure 22**). A possible explanation for the presence of these peaks was formation of the axial alcohol **231**, because the bulkier reducing agent influenced the selectivity of the 1,2-reduction, directing pseudo-equatorial hydride attack. However, it was not possible to unambiguously determine this because the two possible diastereoisomers, **224** and **231**, were isolated as an inseparable mixture.

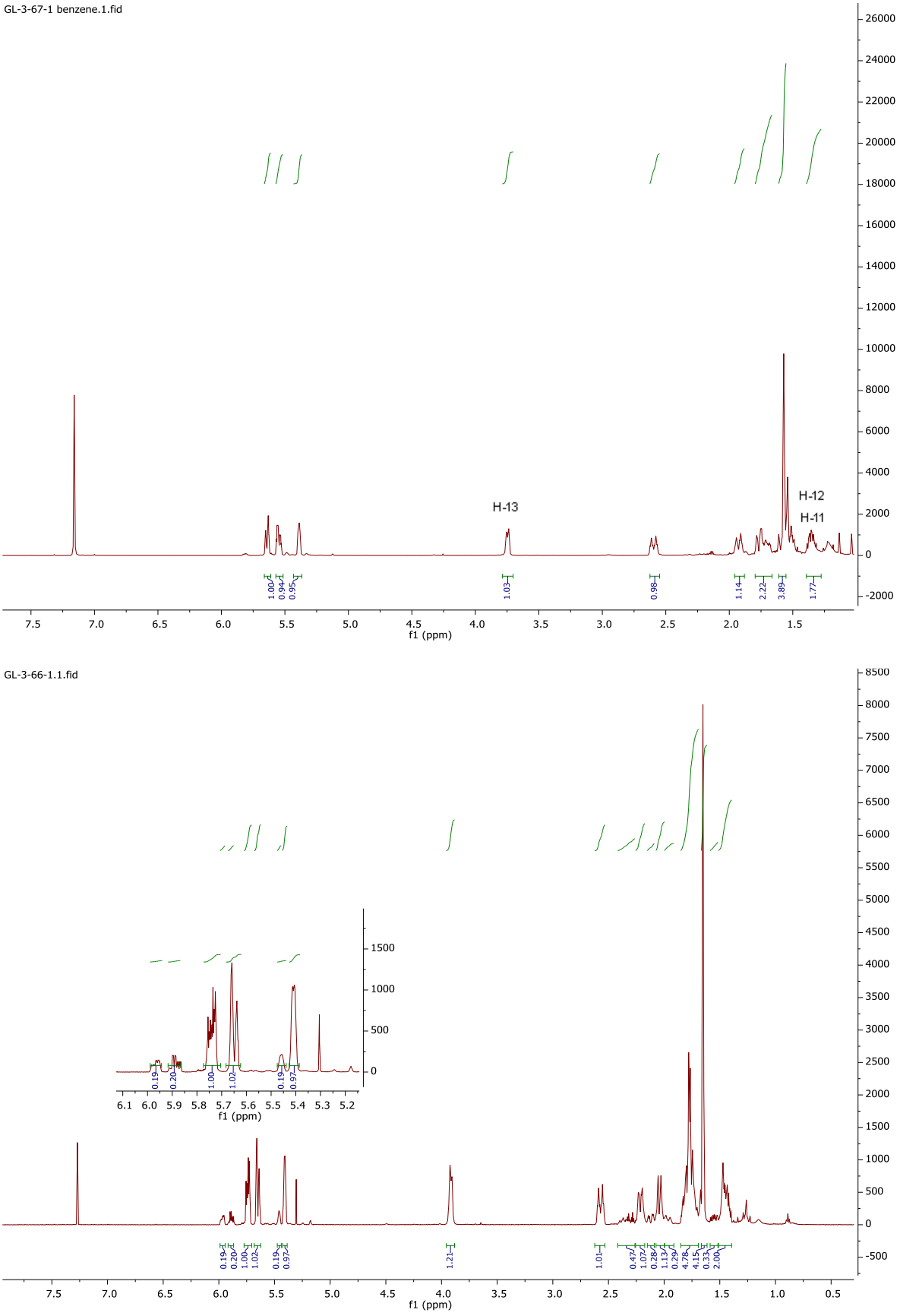
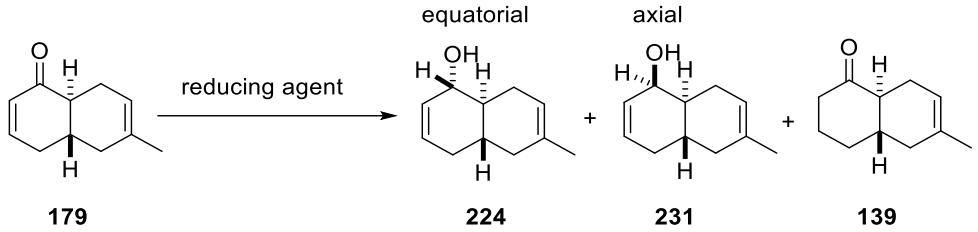


Figure 22. The ^{1}H NMR spectrum of the possible formation of the axial hydroxyl **231**.

Figure 22 shows the ^{1}H NMR spectrum of alcohol **224** formed as a single compound under the Luche conditions, and the ^{1}H NMR spectrum of alcohol **224** under DIBAL-H reduction, in which the presence of extra-olefin peaks between δ 6.00-5.31 ppm suggested formation of the axial alcohol **231** as the minor diastereoisomer.

Nevertheless, DIBAL-H 1,2-reduction of the model enone **179** generated the equatorial and axial alcohols **224** and **231** as an inseparable mixture, in an 8 : 2 ratio in toluene and in a 9 : 1 ratio in THF (**Table 13**, **entry 2** and **3**). The use of a bulkier reducing agent such as Red-Al® also formed the alcohol **224**, as the major diastereoisomer in an 8 : 2 ratio (**Table 13**, **entry 4**). Interestingly, Al(iOPr)$_3$ and IPA formed alcohol **224** exclusively, whereas, with L-selectride only the model ketone **139** was isolated, as a consequence of a 1,4-reduction (**Table 13**, **entry 1** and **5**).[105] These results showed that the substrate controlled 1,2-reduction of **179**, biases hydride to attack from the axial face of **179**.

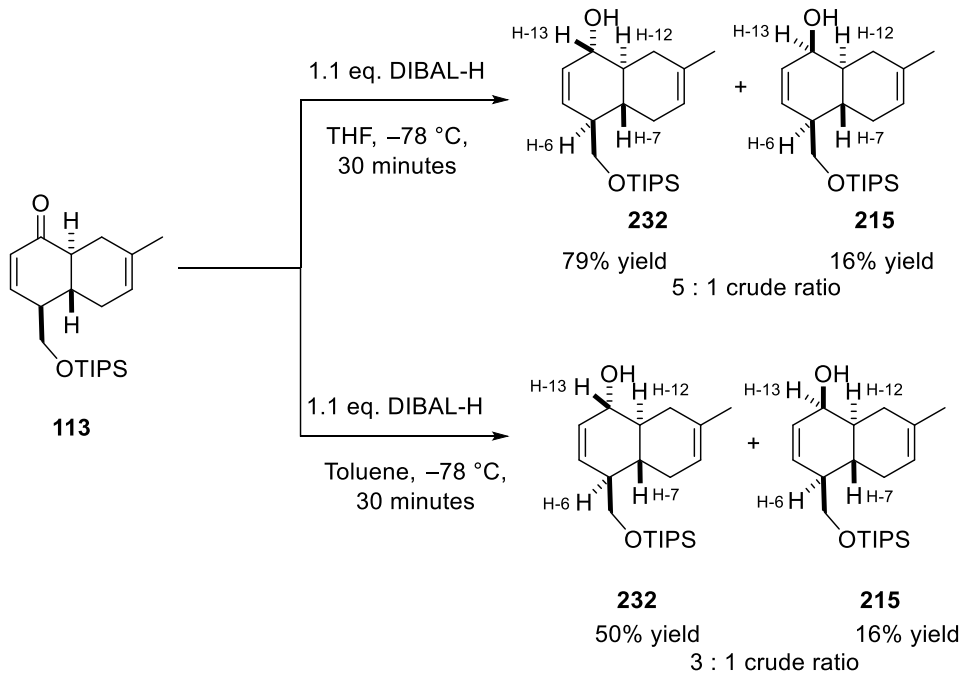


entry	reagent	temperature (°C)	solvent	time (minutes)	selectivity 224 : 231	yield (%)
1	L-selectride	–78	THF	30	**139**	70
2	DIBAL-H	–78	Toluene	30	8 : 2	74
3	DIBAL-H	–78	THF	30	9 : 1	76
4	Red-Al®	–78	THF	30	8 : 2	56
5	Al(iOPr)$_3$	50	IPA/Toluene	5 days	**224**	20

Table 13. The 1,2-reduction of the enone *trans*-decalin **179**.[106]

In conclusion, the Luche reduction of ketone **179** generated the alcohol *trans*-decalin **224** in which the stereochemistry of H-13 was assigned tentatively based on the mechanism of sodium borohydride reduction of unhindered cyclic ketones, and the nOe ^{1}H NMR analysis. Inversion of the selectivity, forcing the hydride attack from the equatorial face of ketone **179**, was attempted with the use of a bulkier reducing agents such as DIBAL-H, Red-Al, L-selectride and $Al(iOPr)_3$ in IPA. Under these conditions, alcohol **224** was formed as the major product and in the ^{1}H NMR spectrum new key olefin decalin peaks were indeed observed, suggesting the possible formation of the axial alcohol **231**. However, it was not possible to prove this outcome unambiguously because alcohols **224** and **231** were isolated as an inseparable mixture of products.

As the literature reported the 1,2-reduction of a related decalin system similar to the enone **228** by the use of DIBAL-H,[105] treatment of this compound under these conditions was attempted with the hope of achieving the correct stereoselectivity. However, the 1,2-reduction of ketone **113** in the presence DIBAL-H generated the diastereoisomeric alcohols **232** and **215** in a 5 : 1 ratio in toluene, and in a 3 : 1 ratio in THF (**Scheme 70**).



Scheme 70. The 1,2-reduction of the enone *trans*-decalin **113.**[105]

The stereochemistry of the alcohols **232** and **215** was determined by nOe ^{1}H NMR analysis. In the major diastereoisomer **232**, a significant through-space interaction (nOe = 0.74%) between H-13 and axial H-7 was detected, whereas, no interaction (nOe = 0%) between protons H-13 and H-6 was observed (**Figure 23**). In the minor diastereoisomer **215** a significant through-space interaction (nOe = 1.03%) between H-13 and H-6 was detected, as well as between protons H-13 and H-12 (nOe = 1.32%). This nOe analysis allowed tentative assignment of the stereochemistry of the major and minor alcohols **232** and **215** (**Figure 23**).

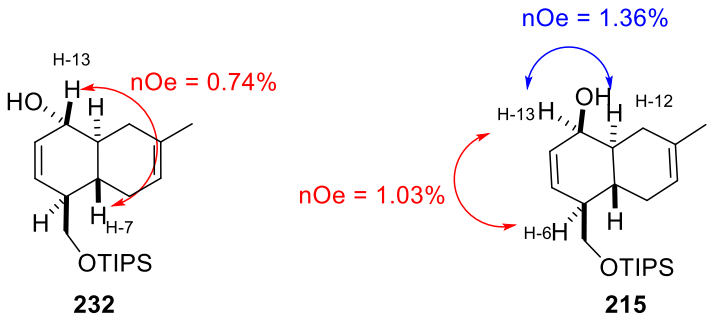
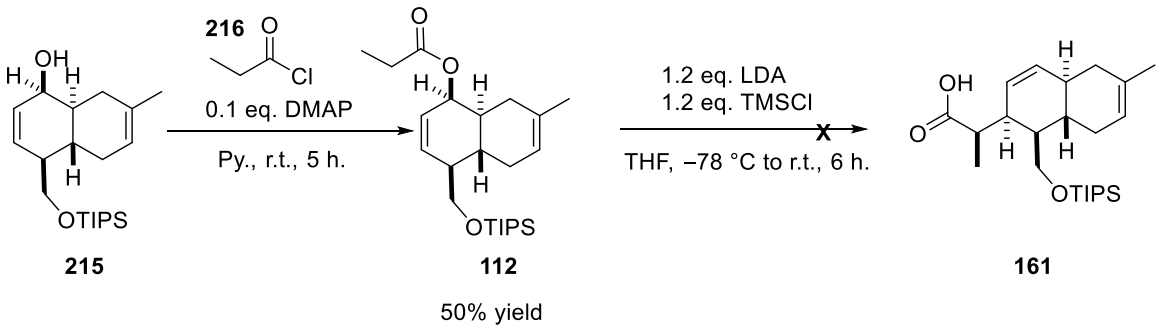


Figure 23. The nOe correlation of compounds **232** and **215**.

These reduction conditions were found to be non-selective for formation of the desired axial alcohol **215**, which was isolated as the minor diastereoisomer. As shown in the model studies, the use of Red-Al, L-selectride and $Al(iOPr)_3$ in IPA did not improve the selectivity, and favoured formation of the equatorial hydroxyl group, and so other conditions were not tested.

After separation and isolation of the alcohols *trans*-decalins **232** and **215**, the minor diastereoisomer **215** was converted into the propionate ester **112** to test the Ireland–Claisen rearrangement reaction (**Scheme 71**). However, in the presence of LDA and TMSCl, compound **112** did not rearrange to form the expected compound **161**.[103]

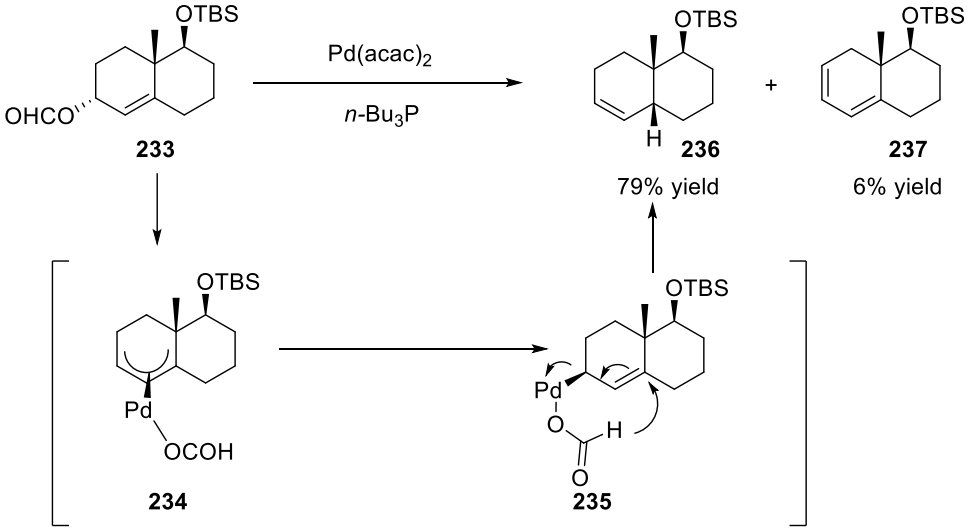


Scheme 71. The attempted Ireland–Claisen rearrangement.[103]

In conclusion, due to the low selectivity of the 1,2-reduction reaction to give the alcohol **215** and the difficulties encountered when attempting to form compound **161** *via* the Ireland–Claisen rearrangement, this approach to the synthesis of the core of anthracimycin was not taken further.

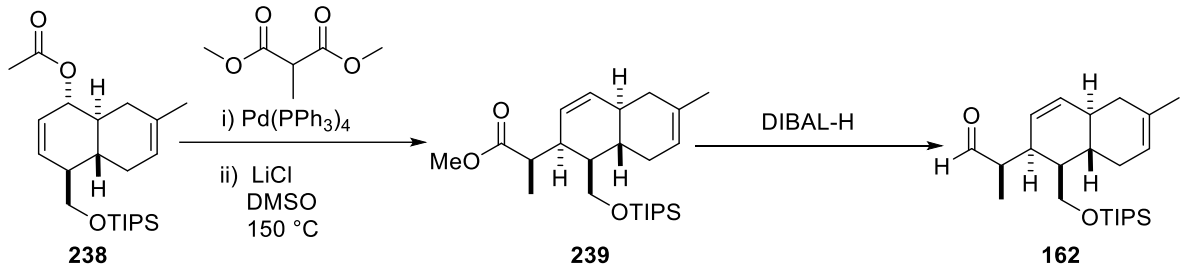
9.7.2 The Tsuji–Trost transformation

In 1993, Tsuji reported a stereocontrolled method to generate *cis*-ring junctions in decalins, in which compound **233** was converted into the *cis*-bicyclic product **236** in a 79% yield by use of a Tsuji–Trost reaction. This approach to the synthesis of the core of the natural product was explored (**Scheme 72**).[107]



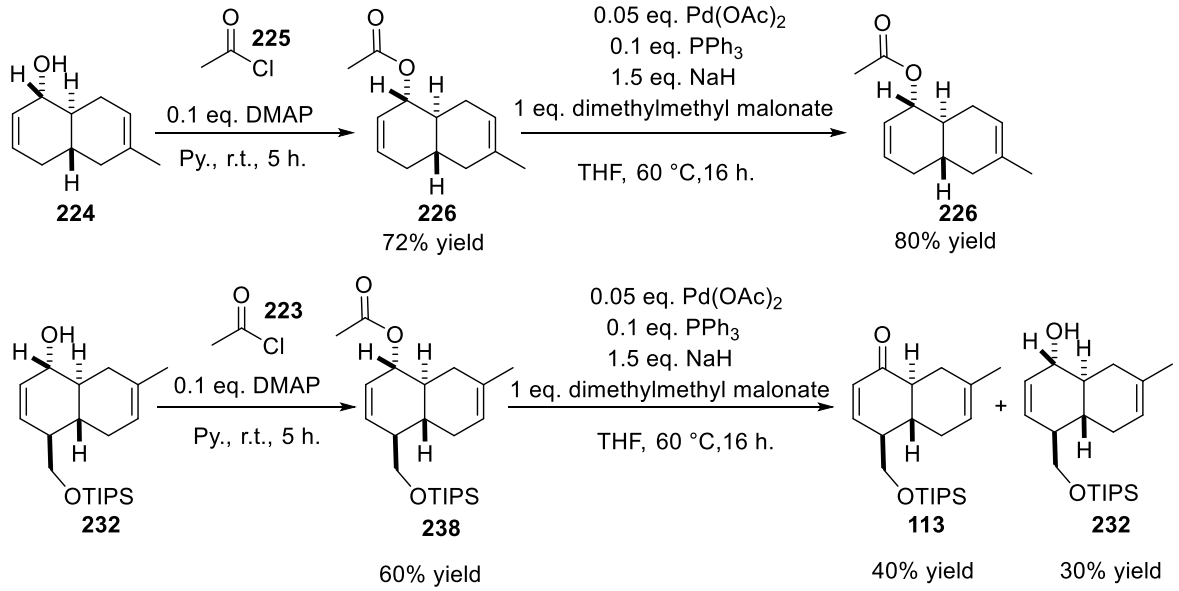
Scheme 72. The stereocontrolled formation of *cis*-ring junction decalin by Tsuji.[107]

A second strategy was therefore envisioned to generate the core of anthracimycin **162**. The major diastereoisomeric alcohol **232** was derivatised to give the acetate **238**, and used as a substrate for the Tsuji–Trost transformation (**Scheme 73**).



Scheme 73. The proposal Tsuji–Trost reaction to the core of anthracimycin **162**.

Following this strategy, the model allylic alcohol **224** was converted into the corresponding acetate **224** in a 72% yield. In the presence of $Pd(OAc)_2$, PPh_3 and dimethylmethylmalonate, as a soft nucleophile, unreacted model acetate **224** was recovered in 80% yield (**Scheme 74**). Acetylation of the allylic alcohol **232** formed the acetate ester **238**, which under the Tsuji–Trost conditions generated the enone **113** and the alcohol **232** in yields of 40% and 30% respectively (**Scheme 74**).[108, 109, 110, 111, 112] The presence of water, in the solvent and/or in the atmosphere of the reaction, may explain the formation of these products. Once the $Pd^{(II)}$ π-decalin system had formed, water could have added as a nucleophile to generate the alcohol *trans*-decalin **232**, which could then oxidised to the enone **113** under the reaction conditions.

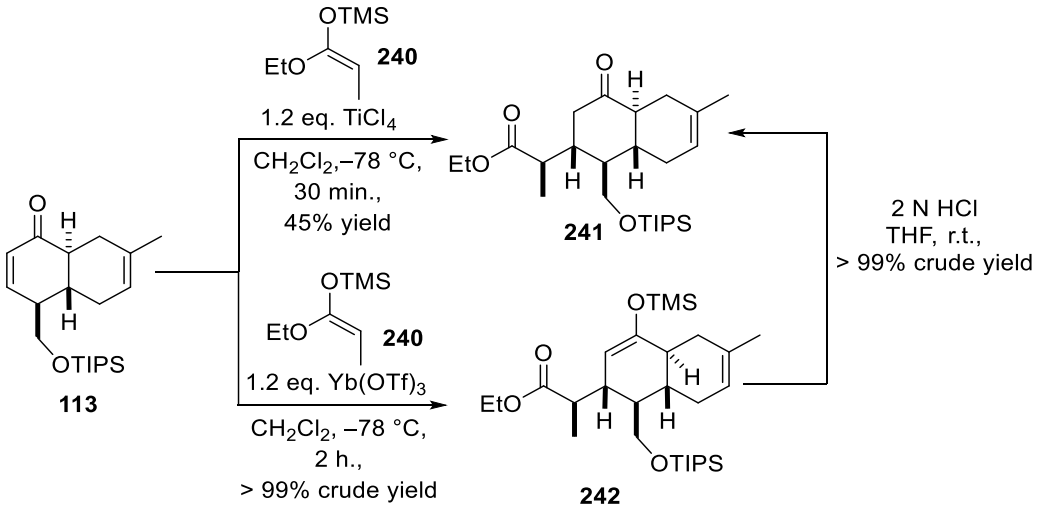


Scheme 74. The Tsuji–Trost transformation of esters **226** and **238**, as substrates.[108, 109, 110, 111, 112]

In conclusion, the 1,2-reduction of the enone **113** afforded the desired alcohol **215** as the minor diastereoisomer. This compound **215** was converted to the ester **112**, which did not rearrange to form the core of anthracimycin **162**, using the Ireland–Claisen transformation. The major alcohol diastereoisomer **232** was converted to the acetate **238** and subjected to the Tsuji–Trost conditions. However, this strategy also failed to deliver the core of anthracimycin **162** and, hence, a new approach to functionalise the enone **113** was required.

9.7.3 The Mukaiyama–Michael strategy

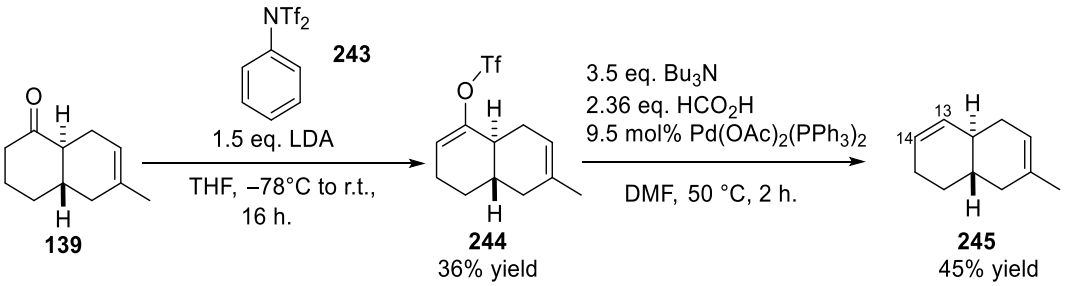
The Mukaiyama–Michael approach to synthesise the core of anthracimycin **162** was next explored. To this end, *E*-ethyl-propanoate silyl ketene acetal **240** was synthesised and used as a nucleophile to accomplish 1,4-addition to the enone **113**.[113] When $TiCl_4$ was employed as a Lewis acid, compound **241** was isolated as a single diastereoisomer in a 45% yield (**Scheme 75**). When $Yb(OTf)_3$ was used to promote the addition reaction, compound **242** was obtained in quantitative crude yield and was converted into **241** under acidic conditions (**Scheme 75**). The instability of **241** on silica explained the poor yield.[114, 115, 116]



Scheme 75. The Mukaiyama–Michael 1,4-addition.[114, 115, 116]

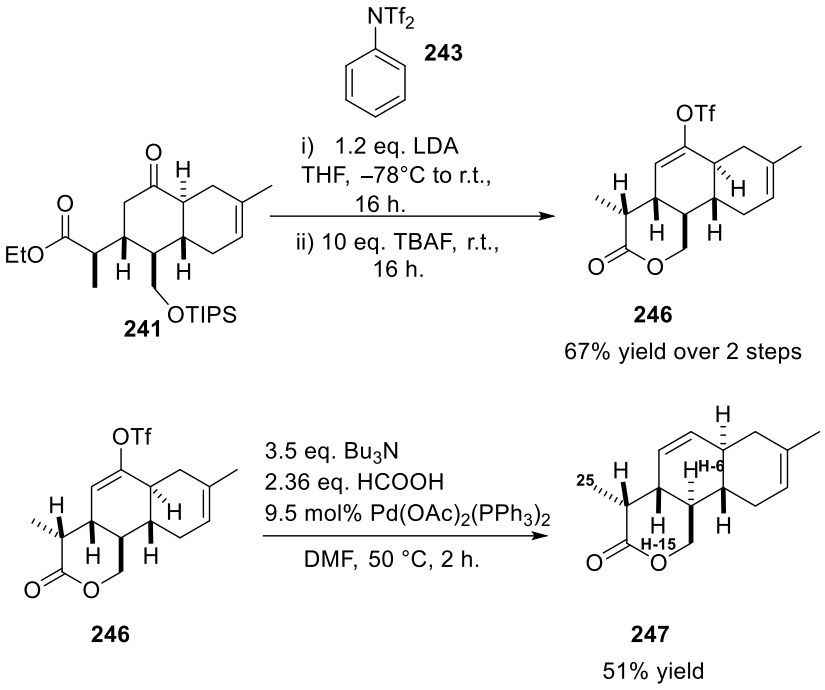
Determination of the stereochemistry of **241** was required and the conversion of this compound into the tricyclic system **247** was proposed (**Scheme 77**), in order to determine its configuration *via* nOe ^1H NMR analysis. To this end, the ketone of Mukaiyama–Michael adduct **241** needed to be converted into an alkene by use a triflation-enol formation/palladium reduction sequence reported by Ishibashi.[116] In the first instance, these conditions were studied using the model *trans*-decalin **139** as the substrate. Treatment of ketone **139** in the presence of LDA and *N*-phenyl-*bis*-trifluoromethanesulfonimide **243** formed the triflate enol *trans*-decalin **244** in a 36% yield.

Palladium-mediated reduction in the presence of $Pd(OAc)_2(PPh_3)_2$, Bu_3N and formic acid completed this transformation to form the alkene between C-13 and C-14, to generate the diene **245** (**Scheme 76**).[117]



Scheme 76. The model studies of the conversion of a ketone into an alkene.[117]

Following these studies, the triflation of the Mukaiyama–Michael adduct **241** in the presence of LDA and *N*-phenyl-*bis*-trifluoromethanesulfonimide **243**, was followed by TIPS-removal using TBAF to generate the tricyclic system **246**, which was isolated in 67% yield over two-steps (**Scheme 77**). Palladium reduction conditions converted enol triflate **246** into alkene **247** in a 51% yield (**Scheme 77**, **Figure 24**). The single crystal X-ray diffraction of the tricyclic lactone **247**, showed that the addition of the *E*-ethyl-propanoate silyl ketene acetal **240** had occurred selectively opposite to the face of the bicyclic system **113** presenting the triisopropylsilylmethyloxy group. The methyl group at C-25 had the required stereochemistry for the core of the natural product (**Figure 24**)



Scheme 77. The transformation of **239** to the tricyclic system **245**.[117]

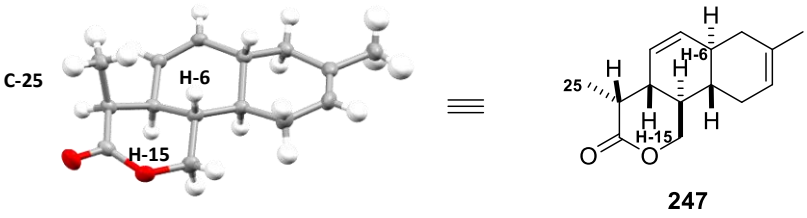


Figure 24. The single crystal X-ray diffraction of **247** with thermal ellipsoids shown at 50%.

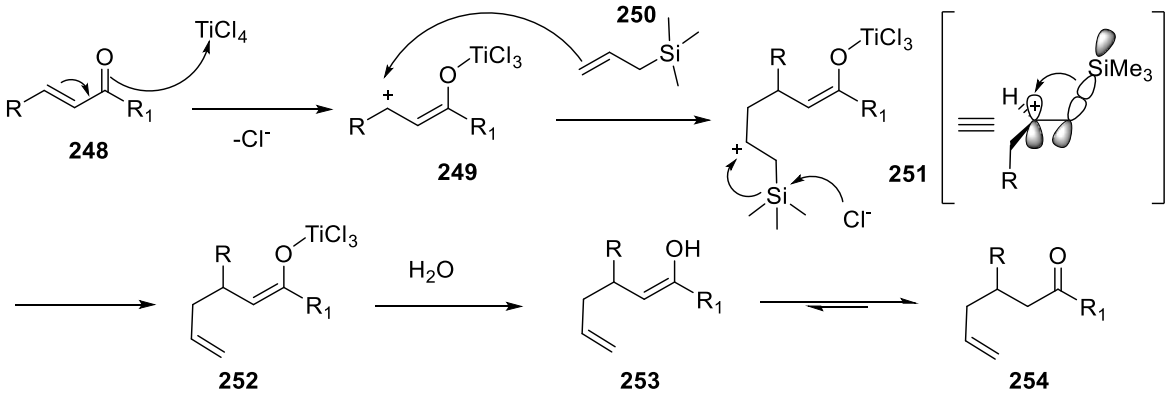
Figure 24 shows the *anti*-relationship between protons H-15 and H-6, and shows that addition of the *E*-ethyl-propanoate silyl ketene acetal **240** occurred from the face opposite to that presenting the triisopropylsilylmethyloxy chain. The stereochemistry of the methyl group at C-25 was instead correct for the core of the natural product.

In conclusion, the Mukaiyama–Michael strategy formed the "*epi*-core of anthracimycin **247**", upon selective 1,4-addition to **113** from the face of the decalin opposite to that presenting the

triisopropylsilylmethyloxy chain. However, contemporaneous studies towards the decalin-core of streptosetin A **260** performed by Dr. Ian George, showed an Hosomi–Sakurai approach might be the answer to the problem of selectivity in this 1,4-addition reaction and might allow continuation of the total synthesis.

9.7.4 The Hosomi–Sakurai strategy

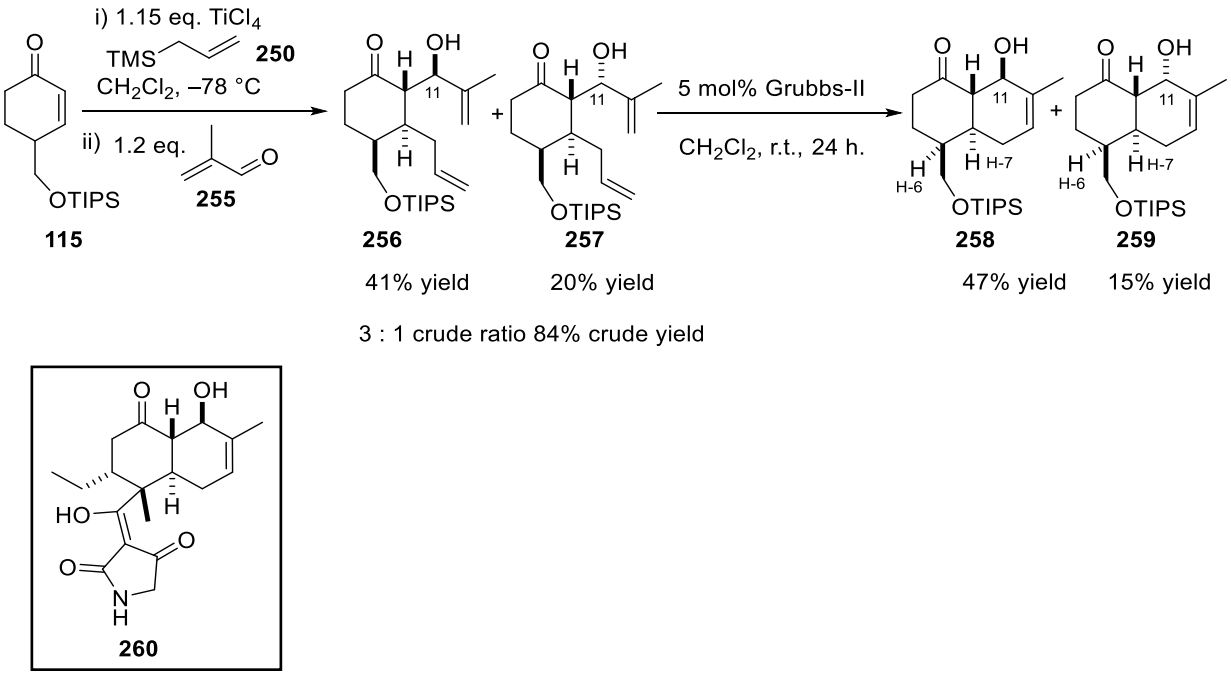
The Hosomi–Sakurai transformation was explored to synthesise the core of anthracimycin **162**. As reported in the literature, this 1,4-addition process involves a Lewis acid-promoted allylation of various electrophiles such as aldehydes, ketones and enones in the presence of allyltrimethylsilane **250**.[118] This strategy is recognised as a mild method for C-C bond formation, and has the possibility to generate new stereogenic centres. Generally, the reaction proceeds by the addition of the alkene of the allyltrimethylsilane **250** to the carbon electrophile **249**, leading to the formation of a carbocation intermediate **251** stabilised by the presence of the β-silicon atom. Stabilisation arises from the orbital overlap between the empty orbital on the carbocation and the co-planar C–Si σ-bond (**Scheme 78**).[119]



Scheme 78. The mechanism of the Hosomi–Sakurai 1,4-addition.[119]

9.7.5 The Hosomi–Sakurai to the core of streptosetin A

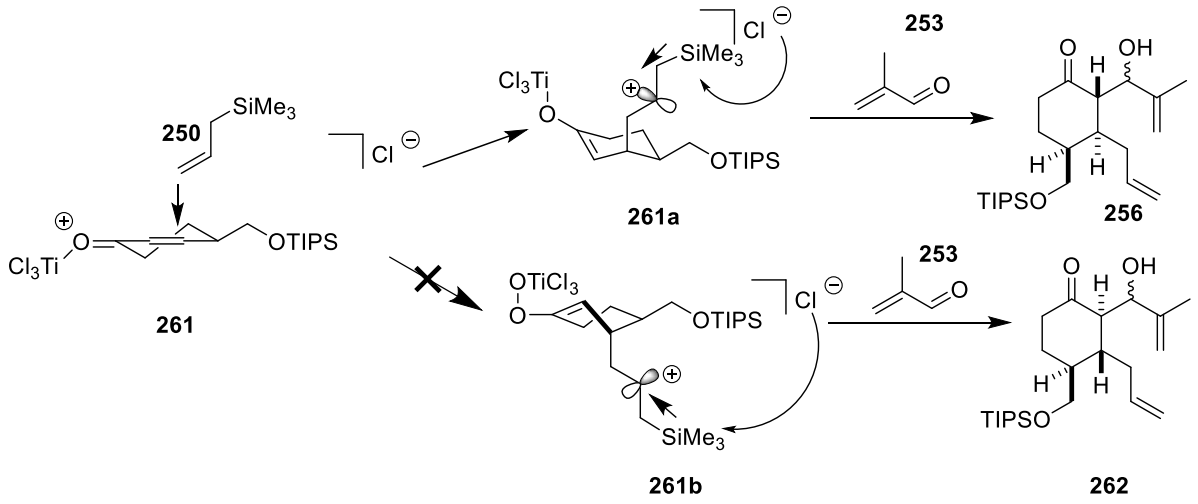
This 1,4-addition reaction was studied by the group, during the synthesis of the core of streptosetin A **260** (Dr. Ian George). The decalin core of this natural product was synthesised using the Hosomi–Sakurai transformation between allyltrimethylsilane **250** and the enone **115**, followed by an aldol addition reaction in the presence of aldehyde **255**. The reaction sequence generated a mixture of **256** and **257** in a 3 : 1 ratio (**Scheme 79**). An alkene metathesis reaction of **255** and **257** formed decalins **258** and **259**, which were crystallised to confirm the stereochemistry of the two diastereoisomers. The single crystal X-ray diffraction of **258** and **259**, showed a *syn*-selective addition of allyltrimethylsilane **250** to enone **115**, as highlighted by the *syn*-relationship of protons H-7 and H-6 in both compounds (**Figure 25**). The aldol addition reaction, instead, generated the two diastereoisomers **256** and **257** at C-11 in a 3 : 1 crude ratio (**Scheme 79**).



Scheme 79. The Hosomi–Sakurai approach to streptosetin A **260**.

In compounds **258** and **259**, a *syn*-relationship of protons H-7 and H-6 was observed, whereas, the diastereoselectivity at C-11, is a consequence of the aldol addition reaction (**Figure 25**).

A possible hypothesis based on the transition state conformation of the titanium-complex **261** was used to rationalise these results. The addition of allyltrimethylsilane **250** from the same face of the triisopropylsilylmethyloxy chain of **261**, led to a favoured "chair" intermediate **261a**, forming the *syn*-adduct. If the addition of **250**, instead, occurred from the opposite face of the triisopropylsilylmethyloxy chain, a disfavoured "twist boat" intermediate **261b** was formed, leading to the *anti*-adduct **262** (**Scheme 80**).

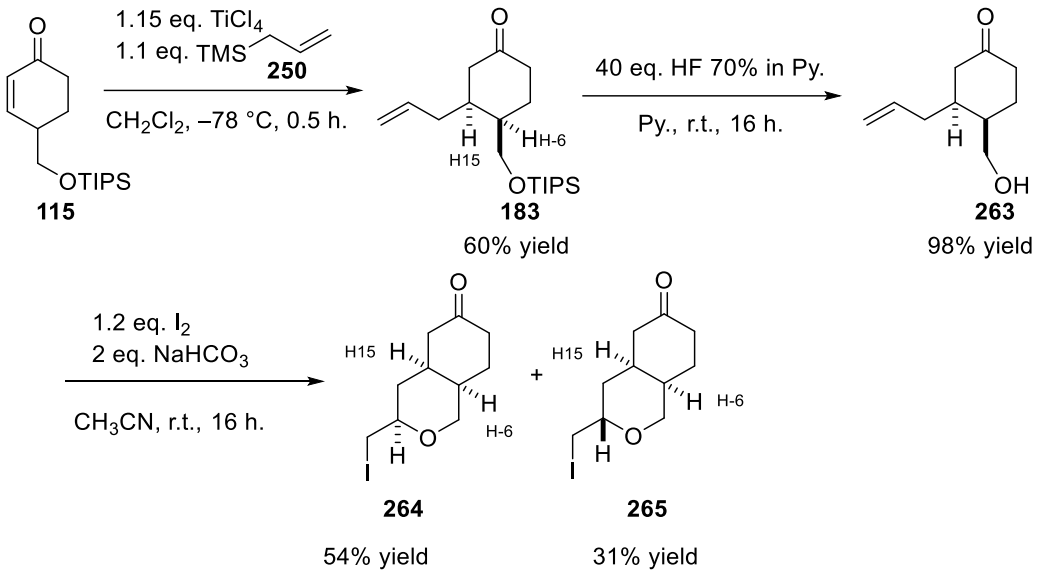


Scheme 80. A possible explanation for the formation of the major *syn*-adduct.

9.7.6 The Hosomi–Sakurai approach towards anthracimycin core **162**

Inspired by this work, model studies of the Hosomi–Sakurai 1,4-addition between enone **115** and allyltrimethylsilane **250** were performed, and compound **183** was generated as a single product in a 60% yield. The determination of the stereochemistry of **183** was achieved following a deprotection/iodoetherification sequence.[120] Removal of the TIPS-group of the allyl-substituted cyclohexanone **183** under HF/pyridine conditions generated alcohol **263**, which was subjected to

cyclisation by an iodoetherification reaction upon treatment with I_2 and $NaHCO_3$. This formed two bicyclic products **264** and **265** in a 2.7 : 1 crude ratio (**Scheme 81**). The major diastereoisomer **264** was crystallised and the single crystal X-ray diffraction showed a *syn*-relationship between protons H-6 and H-15, as required for anthracimycin (**Figure 26**).



Scheme 81. Formation of **183** and the use of a deprotection/iodocyclisation sequence to determine its stereochemistry.[120]

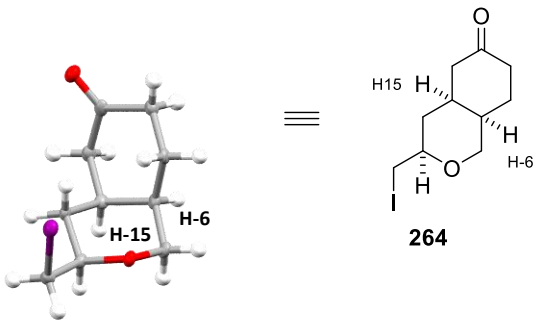
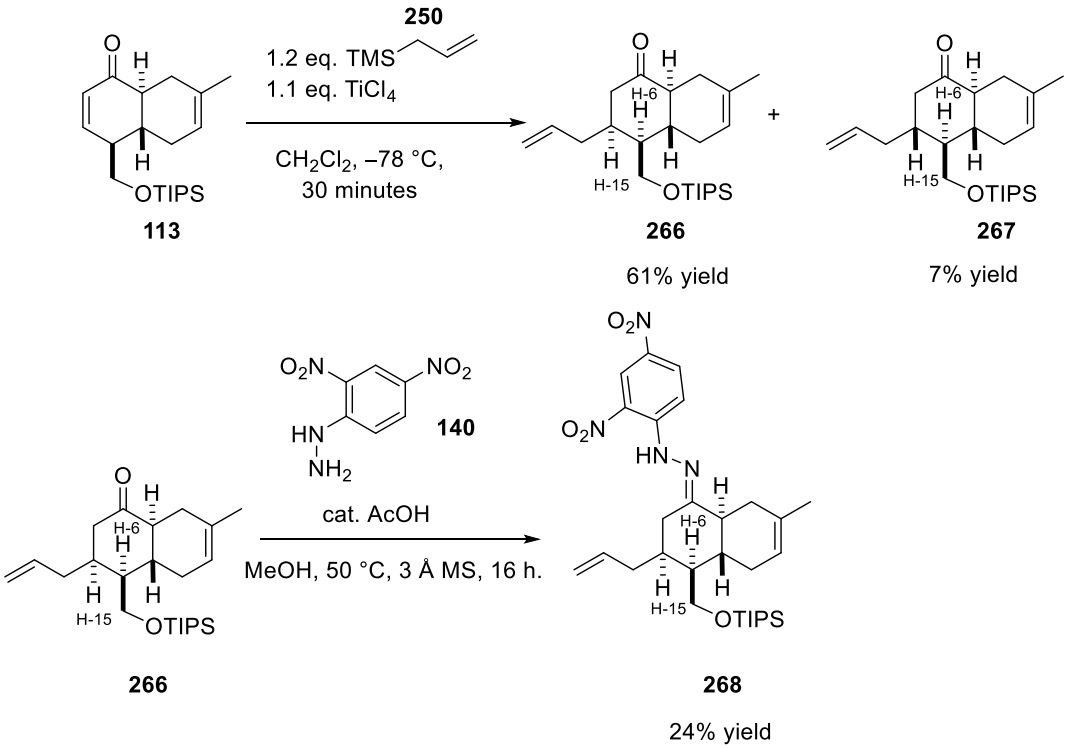


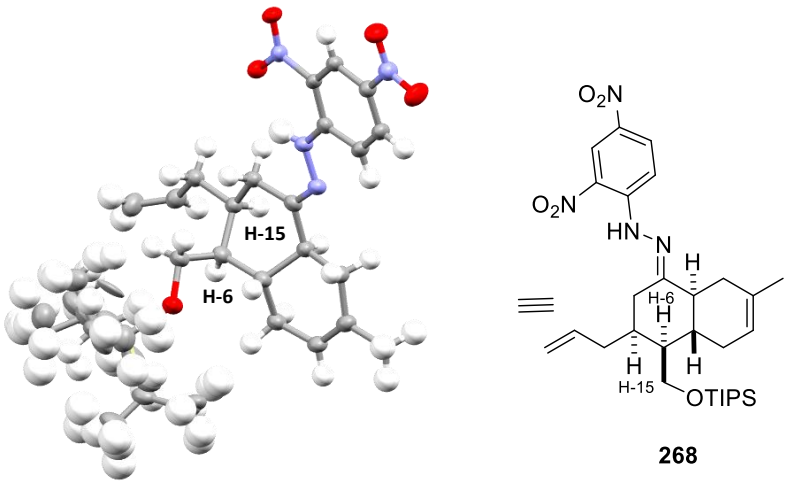
Figure 25. The single crystal X-ray diffraction of **264** with thermal ellipsoids shown at 50%.

Figure 25. Structure of **264** established by single crystal X-ray diffraction showing the *syn*-relationship between protons H-6 and H-15.

Following these studies, the 1,4-addition reaction between allyltrimethylsilane **250** and the enone *trans*-decalin **113** was tested and two diastereoisomeric products **266** and **267** were generated in a 61% and 7% yield, respectively (**Scheme 82**). Derivatisation of the major diastereoisomer **266** to give the hydrazone **268** by treatment with 2,4-dinitrophenylhydrazine **140** and acetic acid, allowed the determination of the stereochemistry of the addition reaction (**Scheme 82**). The single crystal X-ray diffraction of **268** showed a *syn*-relationship between protons H-15 and H-6, which confirmed the outcome of the Hosomi–Sakurai 1,4-addition of allyltrimethylsilane **250** (**Figure 27**).



Scheme 82. The Hosomi–Sakurai addition between **113** and **250**, and formation of hydrazone **268** from the major diastereoisomer **266**.

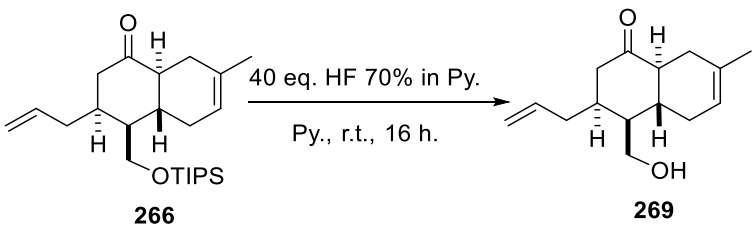


268

Figure 26. The single crystal X-ray diffraction of compound **268** with thermal ellipsoids shown at 50%.

Figure 26. Single crystal X-ray diffraction of hydrazone **268** produced from the product of the Hosomi–Sakurai 1,4 addition reaction.

Following determination of the stereochemistry of the major diastereoisomer **266**, the biological activity of compound **269** was tested by the biologist collaborators in this project: Dr. Gavin Thomas and Dr. Emmanuele Severi. To this end, TIPS-removal of the major diastereoisomer allyl *trans*-decalin **266** was performed under HF/pyridine conditions and compound **269** was isolated in a 98% yield (**Scheme 83**). However, this advanced intermediate in the synthesis of the core of anthracimycin did not possess antimicrobial activity.

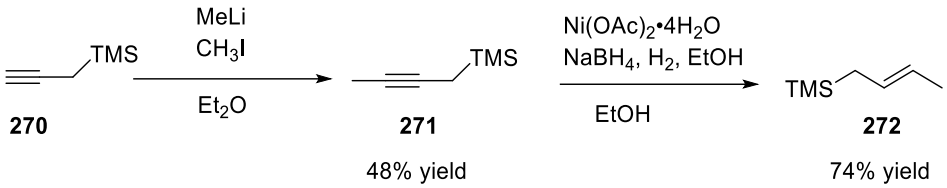


266 269

98% yield

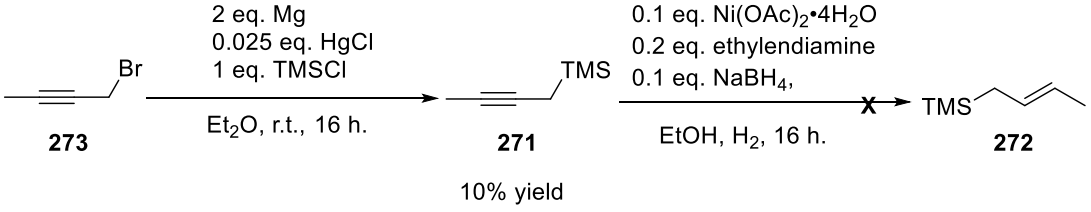
Scheme 83. The TIPS-removal of **266** to test the antimicrobial activity.

To install the methyl group at C-25 *via* this strategy, the use of the *E*-crotyltrimethylsilane **272**, as a nucleophile, was envisioned, but the synthesis of this compound was found to be challenging. The literature reported a number of different approaches to synthesise the *E*-crotyltrimethylsilane **272**: [121, 122] in one of them, the treatment of propargyl trimethylsilane **270** with methyl lithium and iodomethane formed compound **271** in a 48% yield.[121] Conversion of **271** into *E*-crotyltrimethylsilane **272** was achieved by treatment with $Ni(OAc)_2 \cdot 4H_2O$ and $NaBH_4$ under H_2 atmosphere (**Scheme 84**).[121]



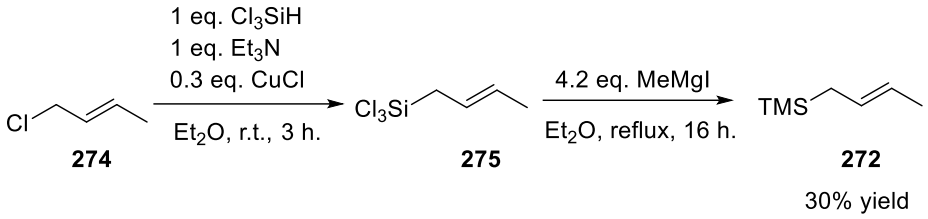
Scheme 84. An approach to the synthesis of *E*-crotyltrimethylsilane **272**.[121]

Inspired by this work, the formation of the *E*-crotyltrimethylsilane **272** was explored. Commercially available methyl propargyl bromide **274** was converted into methyl propargyl trimethylsilane **271**, following the conditions reported by Xiao *et al.* by treatment with stoichiometric quantities of Mg and TMSCl, and a catalytic amount of HgCl.[123] However, **271** was isolated in just 10% yield due to the volatility of this compound (**Scheme 85**). Conversion of **271** into **272** was attempted by treatment with $Ni(OAc)_2 \cdot 4H_2O$ and $NaBH_4$,[121] but crude ^1H NMR analysis, showed that the desired compound **272** was not formed and only polymerisation was detected (**Scheme 85**).



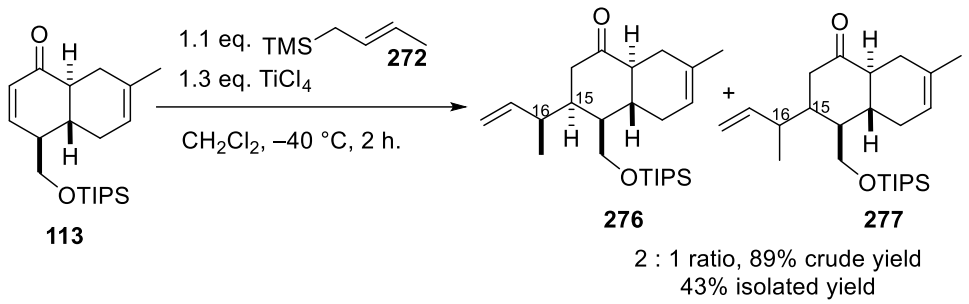
Scheme 85. The attempted synthesis of *E*-crotyltrimethylsilane **272**.[121, 123]

In order to synthesise *E*-crotyltrimethylsilane **272**, another strategy involving a two-step sequence was explored.[122] In the first step, the *trans*-crotylchloride **274** was converted into intermediate **275** by reaction with Et_3N, CuCl and Cl_3SiH. This was followed by the methylation of **275** using MeMgI to form the desired *E*-crotyltrimethylsilane **272** in a 59% yield.[122] Following these conditions, the *E*-crotyltrimethylsilane **272** was isolated in only 30% yield when working on a large scale and under rigorously inert atmospheric conditions (N_2). The low yield was attributed to the instability in air of **276** and the volatility of the desired product **272** (**Scheme 86**).



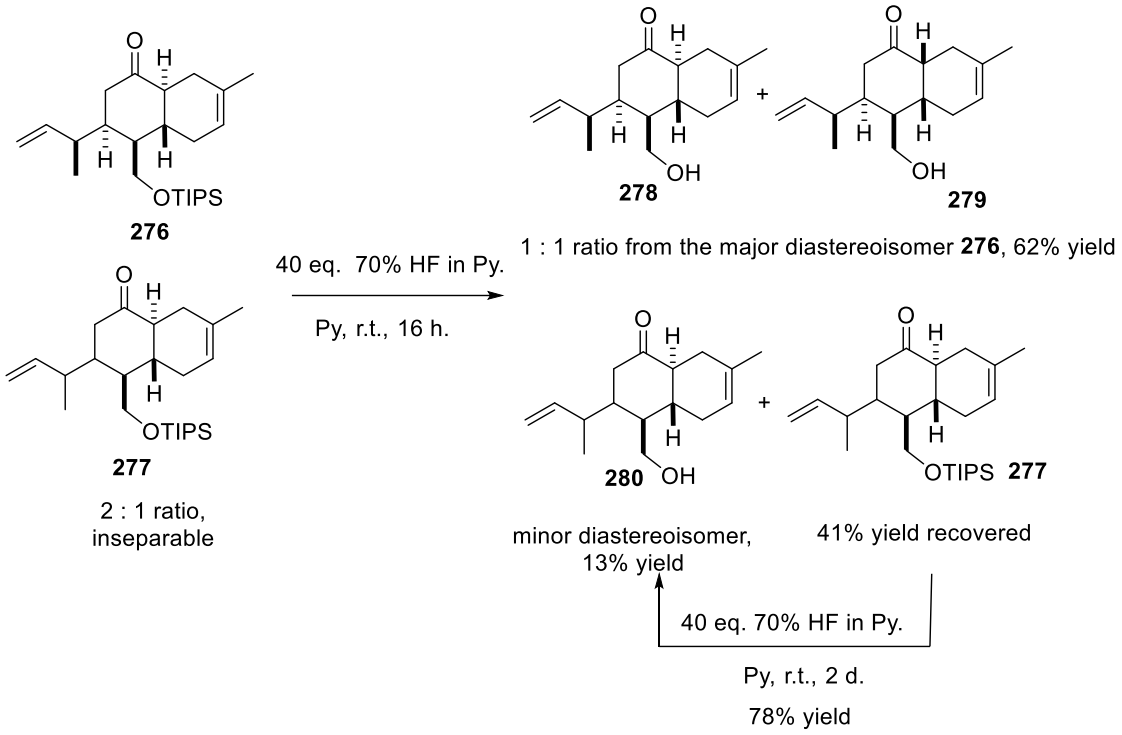
Scheme 86. The synthesis of the *E*-crotyltrimethylsilane **272**.[122]

With compound **272** in hand, the 1,4-addition between the enone *trans*-decalin **113** and the *E*-crotyltrimethylsilane **272** was investigated. When this reaction was performed at –78 °C, the product was not formed and the starting material **113** was recovered unreacted. When the temperature was increased to –40 °C, an inseparable mixture of two diastereoisomers **276** and **277** was generated in a 2 : 1 ratio (43% yield) (**Scheme 87**). The instability of **276** and **277** on silica explained the poor yield, as all of the enone **113** was consumed to form the products.



Scheme 87. The Hosomi–Sakurai addition between the enone *trans*-decalin **113** and *E*-crotyltrimethylsilane **272**.

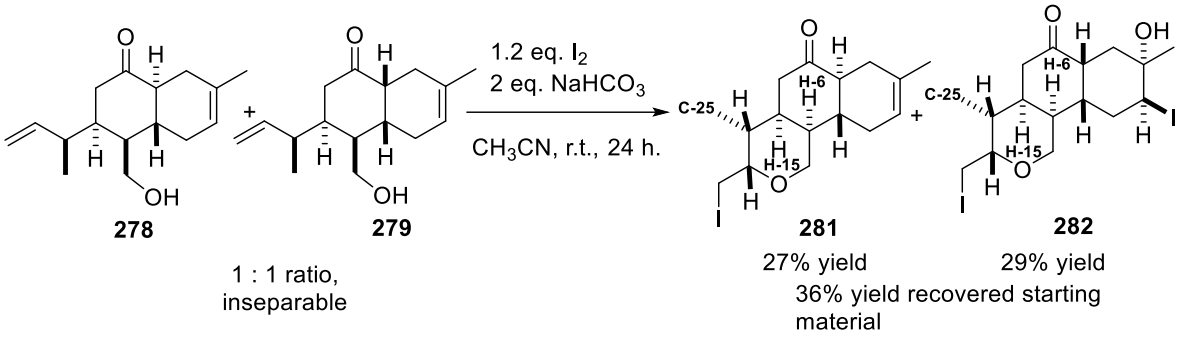
This 1,4-addition reaction generated an inseparable mixture of two diastereoisomeric products, and two new stereogenic centres at C-15 and C-16 were created. Determination of the stereochemistry of the major and the minor diastereoisomers **276** and **277** was needed to progress in the total synthesis. To this end, a deprotection/iodocyclisation sequence was envisioned to separate and derivatise these two diastereoisomers to form two tricyclic systems, facilitating the determination of the stereochemistry by nOe ^{1}H NMR analysis.[120] It was hoped that the TIPS-removal of **276** and **277** would allow the separation of the major and the minor diastereoisomers, and so this inseparable mixture of compounds was treated with HF/pyridine (**Scheme 88**). The reaction, however, produced multiple products. The major diastereoisomer **276** was fully deprotected and generated an inseparable mixture of two diastereoisomer alcohols **278** and **279** in a 1 : 1 ratio, as a consequence of an epimerisation from a *trans*- to a *cis*-decalin (**Scheme 88**). Partial deprotection of the minor diastereoisomer **277** was accomplished, and alcohol **280** was isolated in just 13% yield after a 16-hour reaction (**Scheme 88**). Unreacted minor diastereoisomer **277** was recovered in 41% yield. Treatment of **277** over an extended period of time (2 days) under HF/pyridine conditions, allowed the isolation of alcohol **280** in a 78% yield (**Scheme 88**).



Scheme 88. The TIPS-removal of the inseparable mixture of the major and the minor diastereoisomers **276** and **277**.

After TIPS-removal and the separation of the major and minor diastereoisomers **276** and **277**, an iodoetherification cyclisation reaction was used to derivatise these compounds.[120] Treatment of the inseparable mixture of alcohol products **278** and **279**, isolated from the deprotection of the major diastereoisomer **276**, in the presence of I_2 and $NaCHO_3$, generated two tricyclic systems **281** and **282** in a 27% and 29% yields respectively (**Scheme 89**).[120] Both products **281** and **282** were isolated as solids and the presence of iodine facilitated the crystallisation of these molecules. The X-ray diffraction single crystallography of **281** and **282** allowed the determination of the stereochemistry of the major diastereoisomer **276** (**Scheme 89**, **Figure 28**). As shown in the crystal structures of **281** and **282**, the major diastereoisomer **276** had the required *syn*-relationship between protons H-15 and H-6, as well as the correct stereochemistry at the methyl-bearing stereocentre C-25 needed for anthracimycin. However, in compound **282** a *cis*-decalin ring junction was observed, indicating that epimerisation

from a *trans*- to a *cis*-decalin had occurred during the deprotection of the major diastereoisomer **276** under HF/pyridine conditions.



Scheme 89. The iodocyclisation reaction used to establish the stereochemistry of the major diastereoisomer **276**.[120]

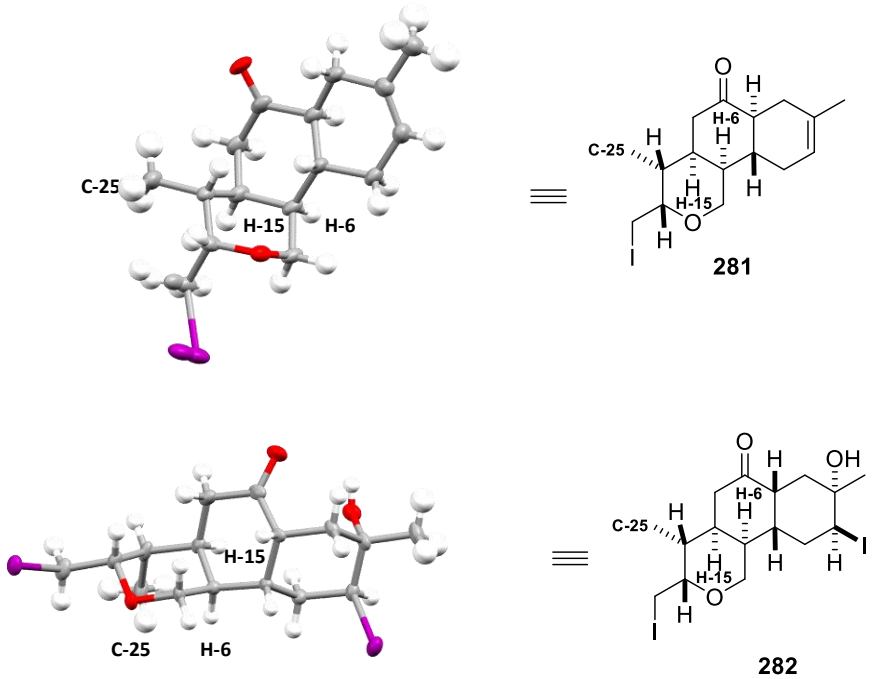
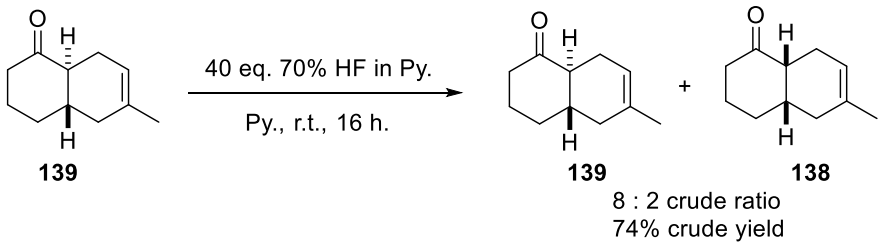


Figure 27. The X-ray diffraction single crystallography of **281** and **282** with thermal ellipsoids shown at 50%.

Figure 27 shows the stereochemistry of the derivatives of the major diastereoisomer **281** and **282** of the Hosomi–Sakurai reaction, which was what was required for the synthesis of anthracimycin. A *syn*-

relationship between protons at H-15 and H-6 was observed, as well as the correct stereochemistry of the methyl group at C-25 required for the core of anthracimycin **162**.

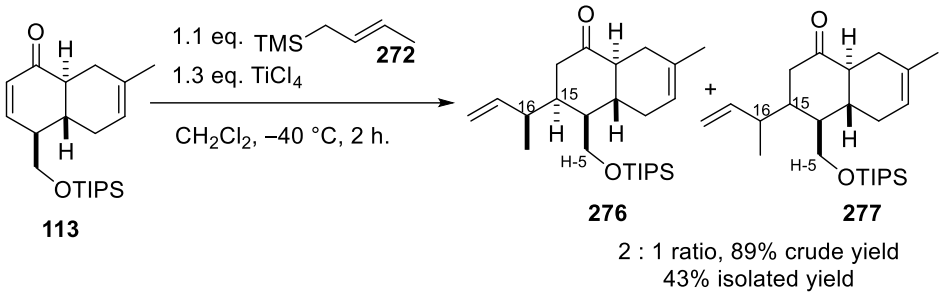
The epimerisation from a *trans*- to a *cis*-decalin was also studied using the model *trans*-decalin **139**, as the substrate. Treatment of *trans*-decalin **139** with 40 equivalents of 70% HF in pyridine, triggered the epimerisation from the *trans*-decalin **139** to the *cis*-cycloadduct **138** in an 8 : 2 ratio, over the same period of time as the deprotection reaction (16-hour) (**Scheme 90**).



Scheme 90. The epimerisation of the model *trans*-decalin **139** to the *cis*-decalin **138**.

Having established the stereochemistry of the major diastereoisomer **276**, the deprotected minor diastereoisomer **280** was treated under the iodoetherification conditions to determine its configuration. However, no iodocyclisation occurred and compound **280** was recovered unreacted, which meant that it was impossible to determine the stereochemistry of the minor diastereoisomer **277** using this approach.

To summarise, the Hosomi–Sakurai 1,4-addition reaction between the enone **113** and the *E*-crotyltrimethylsilane **272** generated an inseparable mixture of products **276** and **277** in a 2 : 1 ratio (**Scheme 88**). A deprotection/iodoetherification sequence allowed the determination of the stereochemistry of the major diastereoisomer **276**, which confirmed that the stereochemistry at both stereogenic centres C-15 and C-25 had been established correctly for the core of anthracimycin.



Scheme 87. The Hosomi–Sakurai addition between the enone *trans*-decalin **113** and *E*-crotyltrimethylsilane **272**.

As highlighted in **Figure 28**, **276** and **277** were isolated as an inseparable mixture of diastereoisomers in a 2 : 1 ratio. Due to the presence of many overlapping peaks in the ^{1}H NMR spectrum, the diastereomeric ratio was calculated based on the integration of resolved resonances for proton H-5. The expansion between δ 4.01 and 3.70 ppm shows a major **276** doublet-doublet at δ 3.77 and a doublet-doublet at δ 3.74 ppm, as well as a minor **277** multiplet at δ 3.95–3.89 ppm. The methyl groups at C-25 were also resolved peaks: a major **276** doublet at δ 0.99 ppm, and a minor **277** doublet at δ 0.94 ppm.

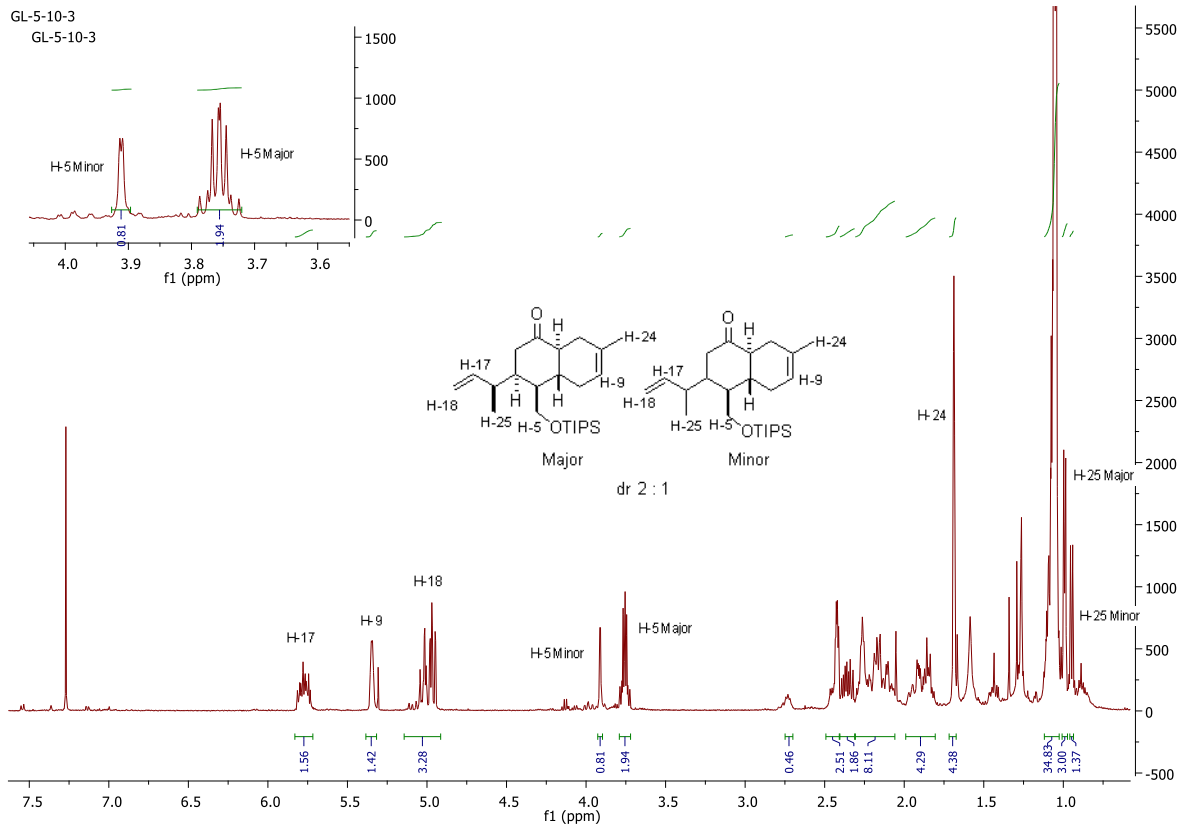


Figure 28. The ^{1}H NMR data of the inseparable mixture of the two diastereoisomers of the Hosomi–Sakurai addition between **276** and **277**.

The ^{1}H NMR spectrum of the inseparable mixture (1 : 1 ratio) of **278** and **279**, generated during the TIPS-removal of the major diastereoisomer **276** under HF/pyridine conditions was obtained (**Figure 29**). Due to the 1 : 1 ratio and the presence of many overlapping peaks in the ^{1}H NMR spectrum, analysis of the ^{1}H-H COSY was too challenging to determine which resolved proton peaks belonged to which isomer.

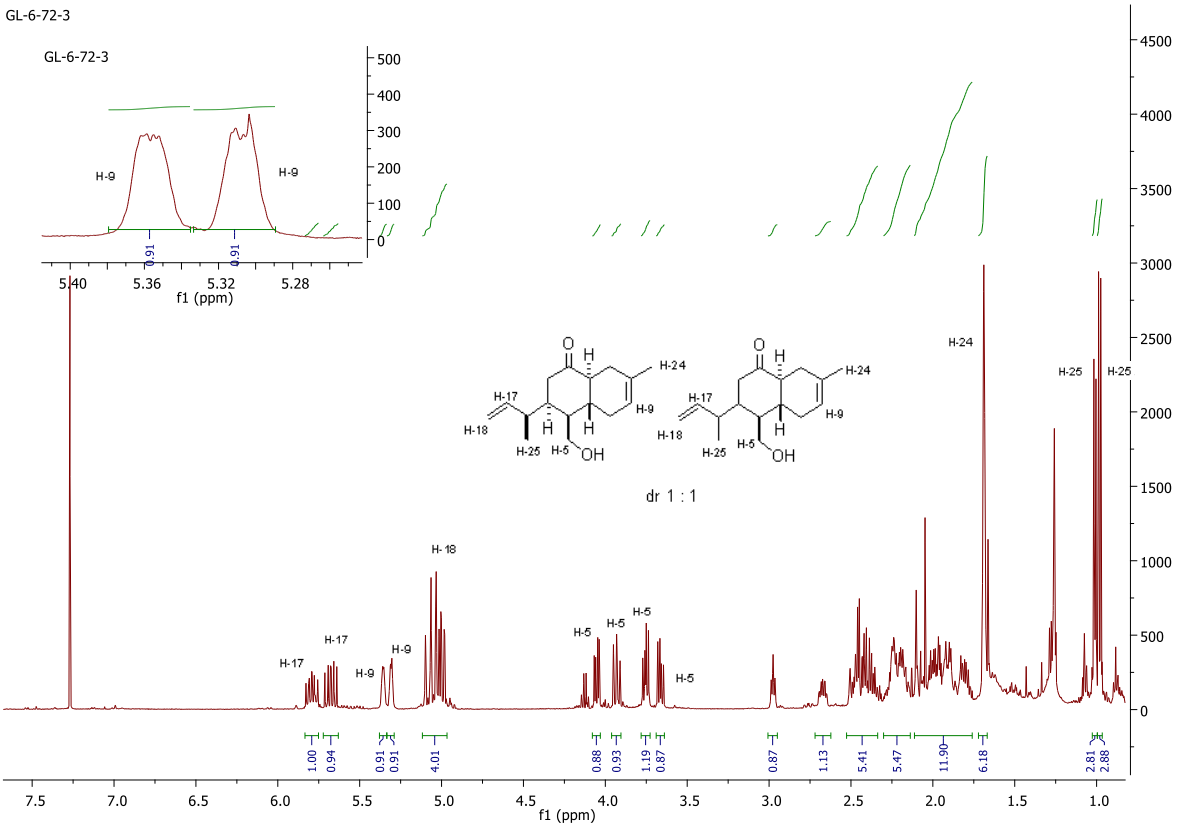
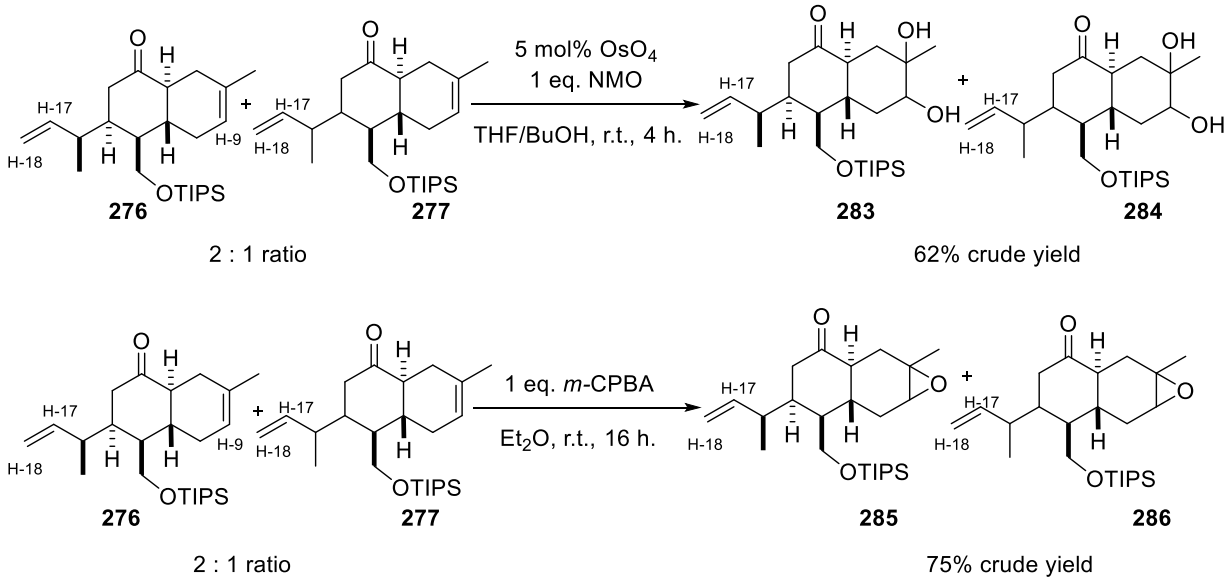


Figure 29. The ^{1}H NMR data of the inseparable mixture of the deprotected *trans*- and *cis*-decalins **278** and **279** (1 : 1 ratio).

Figure 29 shows the ^{1}H NMR spectrum of the *trans*- and *cis*-decalins **278** and **279**, isolated as inseparable mixture of deprotected products. The 1 : 1 ratio of these two diastereoisomers was calculated based on the integration of resolved resonances for proton H-17, doublet-doublet-doublet at δ 5.79 and at δ 5.68 ppm; protons H-9 multiplets at δ 5.38–5.33 and at δ 5.33–5.28 ppm; protons H-5 doublet-doublet at δ 4.05, at δ 3.93, at δ 3.75 and at δ 3.66 ppm; methyl groups of H-25 doublet at δ 1.01 and at δ 0.98 ppm.

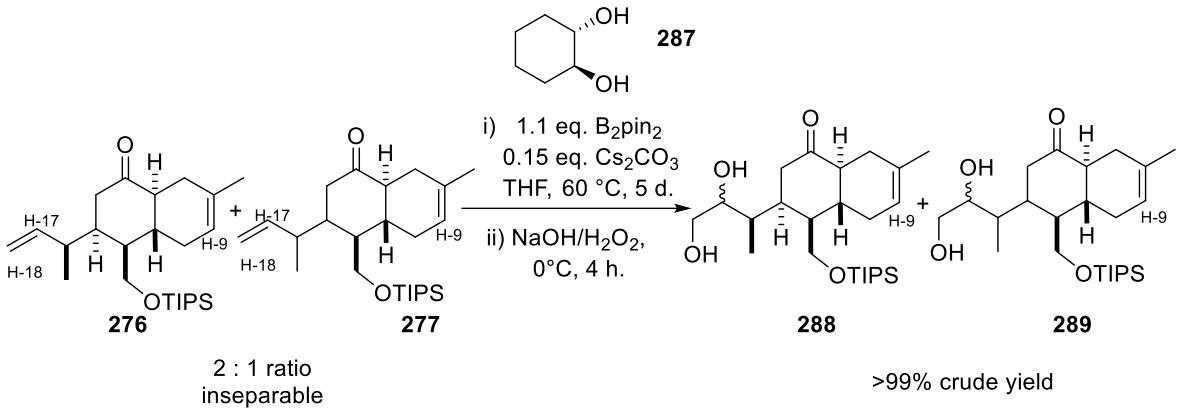
9.7.7 Functionalisation of the exocyclic double bond

Now that the stereochemistry of the major diastereoisomer **276** had been established, selective functionalisation of the exocyclic alkene became the new challenge. Epoxidation and dihydroxylation reactions were attempted, with the hope that the less sterically demanding exocyclic double bond would react preferentially. In the presence of catalytic OsO_4 (5 mol%) and 1 equivalent of NMO, diols **283** and **284** were formed exclusively by reaction of the endocyclic alkene (**Scheme 91**). Determination of the reactivity was established by the ^1H NMR analysis of the crude reaction mixture, in which the absence of the olefin peak of proton H-9 was seen. The exocyclic peaks of H-17 and H-18 remained unchanged. Treatment of the inseparable mixture of diastereoisomers **276** and **277** with *m*-CPBA, also formed epoxide at the endocyclic alkene as a consequence of the higher reactivity of this alkene (**Scheme 91**). Determination of the selectivity of this epoxidation reaction was again established by ^1H NMR analysis of the crude reaction mixture, in which the absence of proton H-9 was seen.



Scheme 91. Epoxidation and dihydroxylation functionalised the endocyclic alkene preferentially.

Under these conditions, electronic effects predominated over steric hindrance and epoxide and diols were formed selectively at the endocyclic double bond, as a consequence of the higher reactivity of this alkene. Other conditions were therefore explored to selectively functionalise the exocyclic double bond. In the last few years, Morken and his group have focused their chemistry research on the enantioselective diborylation and hydroboration of alkenes, forming enantioriched diols.[124, 125, 126] The selective functionalisation of the exocyclic alkene was attempted by use of this borylation/dihydroxylation sequence in the presence of a boronic ester reagent, *trans*-cyclohexanediol and Cs_2CO_3, followed by the addition of 3 M NaOH and 30% H_2O_2 aqueous solutions.[123, 124, 125] Under these conditions, selective functionalisation of the exocyclic alkene was possible and diols **288** and **289** were generated (**Scheme 92**). The formation of these products was determined by ^{1}H NMR analysis of the crude mixture; the NMR spectrum showed an absence of the olefin peaks (protons H-17 and H-18), whereas, the endocyclic alkene (proton H-9) remained unchanged. The use of 1 equivalent of B_2pin_2 and methanol formed diols **288** and **289** in a 56% conversion and in a 40% yield, along with the recovery of the starting material **276** and **277** in a 37% yield (**Table 14**, **entry 1**). In the presence of 1 equivalent of B_2pin_2 and 0.3 equivalents of *trans*-cyclohexanediol **287**, the diols **288** and **289** were instead formed with 53% conversion, whereas, with the use of 1 equivalent of *trans*-cyclohexanediol **287** 90% conversion into the desired products **288** and **289** was achieved (**Table 14**, **entry 2** and **3**). The use of a catalyst such as $Pt_2(dba)_3$ was also tested to increase the level of conversion and the yield. A conversion of 80% was obtained, but diols **288** and **289** were isolated in just 39% yield (**Table 14**, **entry 4**).[124, 125, 126]



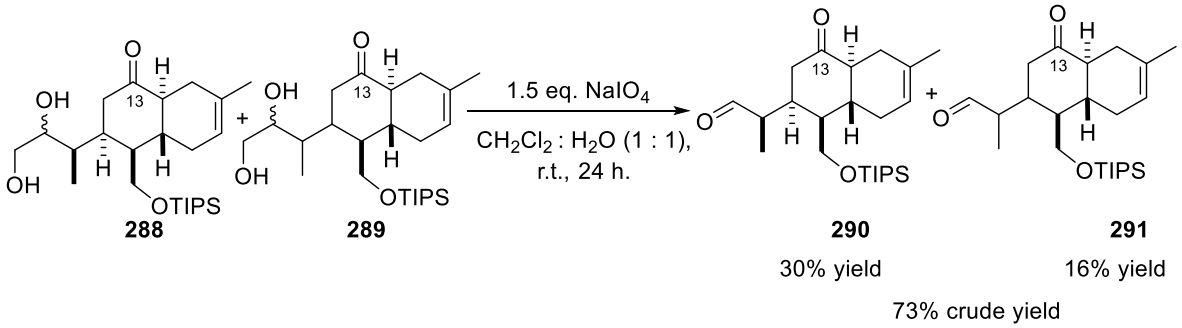
Scheme 92. A selective dihydroxylation reaction of the exocyclic alkene. [124, 125, 126]

entry	conditions	time (d.)	conversion (%)	yield (%)
1	B_2pin_2, 5 eq. MeOH, 0.15 eq. Cs_2CO_3	5	56	40
2	B_2pin_2, 0.3 eq. diol, 0.15 eq. Cs_2CO_3	5	53	40
3	B_2pin_2, 1 eq. diol, 0.15 eq. Cs_2CO_3	5	90	41
4	B_2pin_2, 2.5 mol.% $Pt_2(dba)_3$, 0.15 eq. Cs_2CO_3	2	80	39

Table 14. The reaction conditions tested for the borylation of **276** and **277**. [124, 125, 126]

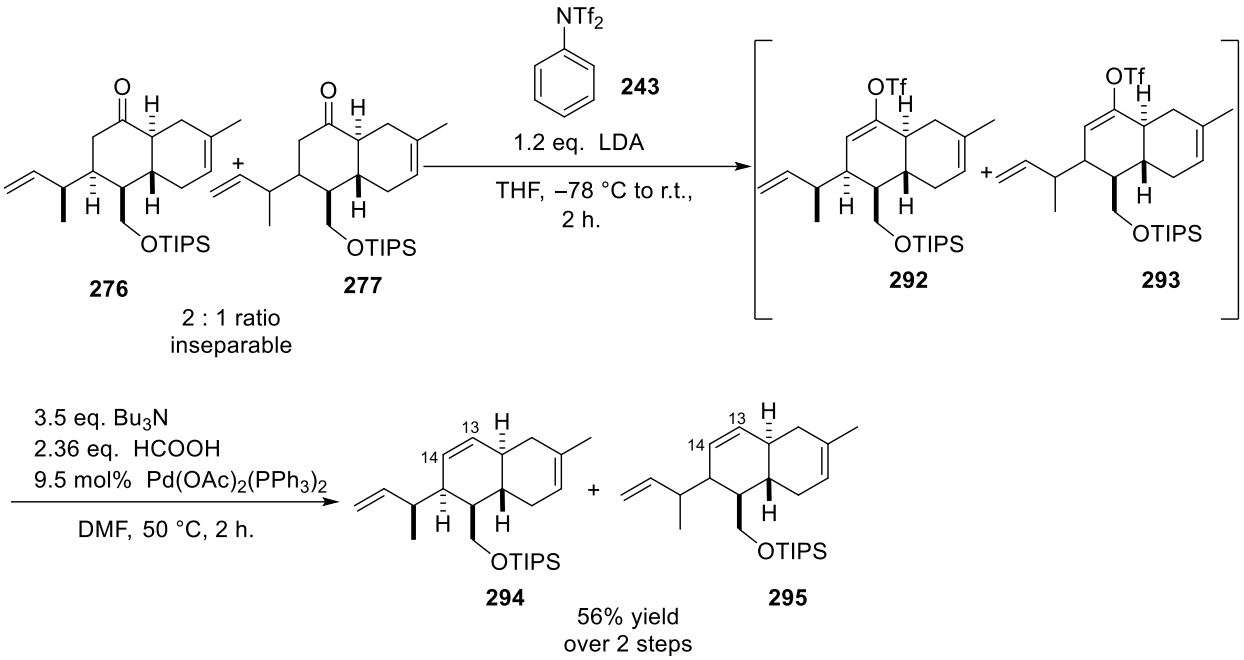
Morken's conditions allowed the selective functionalisation of the less sterically demanding and less electronically reactive exocyclic alkene of the molecule. The use of 1 equivalent of B_2pin_2 and *trans*-cyclohexanediol **287** allowed the formation of diols **288** and **289** with 90% conversion, but a 41% yield was obtained upon isolation of the products (**Table 14**, **entry 3**). The instability on silica of **288** and **289**, was responsible for the low yield and these dihydroxylated intermediates were carried into the next step without silica chromatography purification. A periodate cleavage reaction was used to

convert the diol into an aldehyde, the functionality required for the subsequent Still–Gennari olefination. Treatment of the crude reaction mixture of diols **288** and **289** with $NaIO_4$ in CH_2Cl_2 : H_2O (1 : 1), delivered the aldehydes **290** and **291** in 30% and 16% yield respectively (**Scheme 93**). Instability on silica chromatography again explained the low yields.



Scheme 93. The periodate cleavage to the advanced precursor **290** and **291.**

The presence of the ketone at C-13 made **290** and **291** unstable to silica chromatography and could give rise to selectivity issues in the Still–Gennari olefination with the phosphonate reagent **92**, competing with the aldehyde functionality. To this end, the previously studied conditions that had been used to convert the carbonyl group into an alkene, were used to avoid these problems. The inseparable mixture of diastereoisomers **276** and **277** produced by the Hosomi–Sakurai 1,4-addition reaction was treated with LDA and *N*-phenyl-*bis*-trifluoromethanesulfonimide **243**. This reaction yielded the enol triflates **292** and **293** with quantitative conversion, as evident by ^{13}C NMR analysis of the crude reaction mixture.[116] Palladium-mediated reduction of the enol triflates with $Pd(OAc)_2(PPh_3)_2$, Bu_3N and formic acid completed the transformation to form the alkene, between C-13 and C-14, and generated the *trans*-decalins **294** and **295** in a 56% yield as an inseparable mixture of isomers in a 2 : 1 ratio (**Scheme 94**, **Figure 30**).[117]



Scheme 94. Conversion of the carbonyl functionality into an alkene to form **294** and **295**.[117]

The 56% yield of **294** and **295** was the highest yield obtained in the enol triflate formation/palladium reduction sequence. As the second step always gave full conversion into the desired products **294** and **295**, the triflation of **276** and **277** was identified as the problematic-step. The purity of the *N*-phenyl-*bis*-trifluoromethanesulfonimide (**243**), a small scale reaction in which it was difficult to prevent moisture and water destroying freshly prepared LDA solution, and the purity of **276** and **277** isolated as a crude mixture due to the instability on silica, are factors that could have led to decrease in the yield. To solve these problems, Comin's reagent was used instead of *N*-phenyl-*bis*-trifluoromethanesulfonimide (**243**), and the crude mixture of **276** and **277** was concentrated *in vacuo* with benzene to azeotrope any residual water. However, the yield could not be increased from 56%.

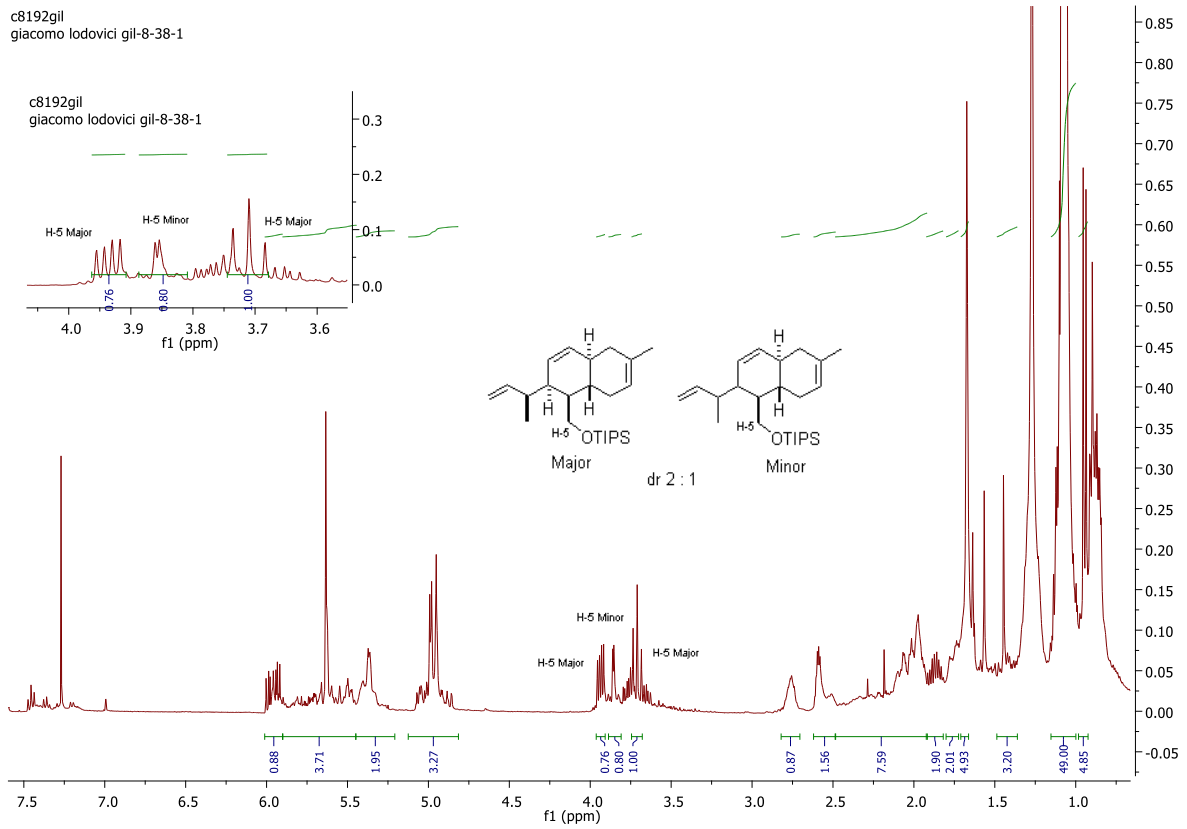
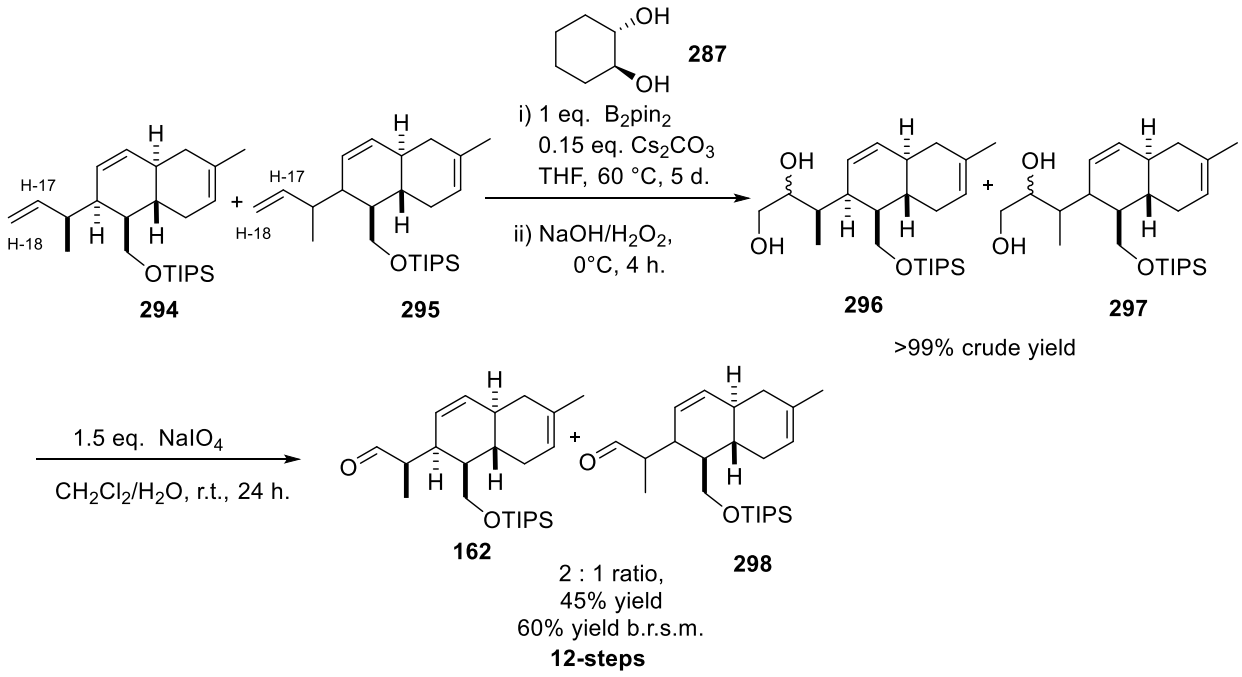


Figure 30. The ^{1}H NMR spectrum of **294** and **295** after the triflation/palladium reduction sequence.

Figure 30 shows the ^{1}H NMR spectrum of **294** and **295** after the triflation/palladium reduction sequence. The region between δ 4.00 and 3.59 ppm contained the only resolved resonances for proton H-5 of the major and the minor diastereoisomers **294** and **295**. Based on the integration of these peaks it was possible to measure an unchanged 2 : 1 ratio of **294** and **295** after the two-step sequence.

Following conversion of the carbonyl functionality into an alkene, as the B-ring of anthracimycin required, selective functionalisation of the exocyclic double bond was performed using the borylation/dihydroxylation sequence. Reaction of trienes **294** and **295** with 1 equivalent of B_2pin_2 and *trans*-cyclohexanediol **287** and 0.15 equivalents of Cs_2CO_3 as a base, followed by the addition of aqueous solutions of NaOH and H_2O_2, resulted in selective dihydroxylation of the exocyclic alkene. [124, 125, 126] These conditions allowed the selective functionalisation of the less reactive double bond based

on steric hindrance. The formation of diols **296** and **297** at the exocyclic alkene was confirmed by ^{1}H NMR analysis, which showed the absence of the olefin peak of protons H-17 and H-18. Cleavage of diols **296** and **297** to afford the aldehyde functionality was attempted by reaction with $NaIO_4$. These conditions formed the aldehyde **162** corresponding to the core of anthracimycin **162**, which was isolated as an inseparable mixture with **298** (2 : 1 ratio) in a 60% isolated yield b.r.s.m. (**Scheme 95**).

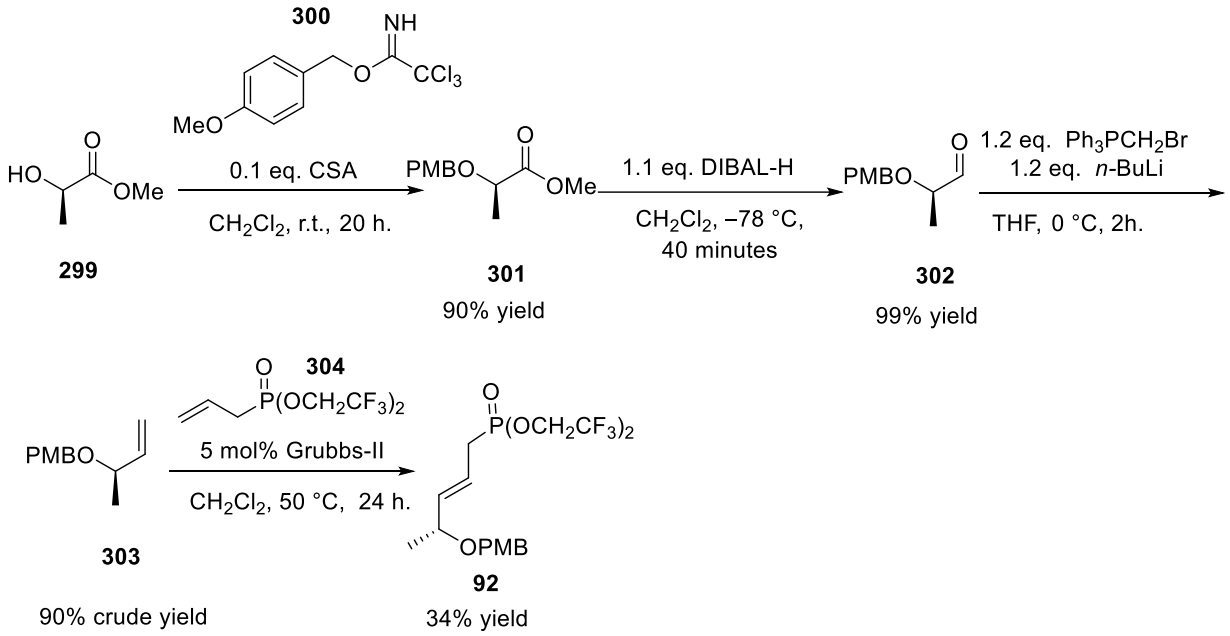


Scheme 95. The formation of the core of anthracimycin **162**.

In conclusion, the Hosomi–Sakurai 1,4-addition reaction between the *E*-crotyltrimethylsilane **272** and the enone **113**, allowed the formation of all the C-C bonds with the required stereochemistry for the core of anthracimycin **162**. Subsequent selective borylation/dihydroxylation of the exocyclic alkene and periodate cleavage of diols **296** and **297** delivered the desired core of the molecule. The aldehyde **162** was isolated as an inseparable mixture with **298** in a 2 : 1 ratio in a 45% yield (60% yield b.r.s.m.). Overall, the aldehyde **162** was obtained in 12-steps.

9.7.8 The synthesis of the Still–Gennari reagent **92**

To progress the total synthesis, the formation of the side chain **92** was prepared following Kalesse's procedure.[44] To this end, PMB protection of the enantiopure D-(+)-lactate methyl ester (**299**) afforded the ester **301**, which was converted into the aldehyde **302** by DIBAL-H reduction. This was followed by Wittig methylenation and an alkene metathesis reaction between **303** and **304** using Grubbs-II catalyst, which generated side chain **92** in a 34% yield (**Scheme 96**).[44]



Scheme 96. The synthesis of the Still–Gennari reagent **92**.[44]

To summarise, different strategies were explored for the synthesis of the core of anthracimycin **162**. The 1,2-reduction of key intermediate **113** was found to be non-selective and two diastereoisomeric alcohols **232** and **215** were isolated and used to scope the Ireland–Claisen rearrangement reaction and the Tsuji–Trost reaction. However, these two approaches did not yield the core of anthracimycin **162**.

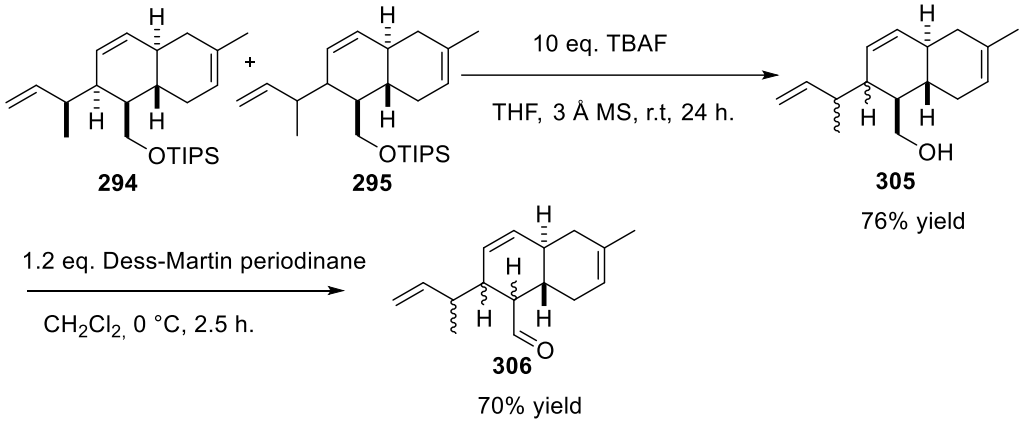
The Mukaiyama–Michael addition afforded the lactone **247** corresponding to the C-15 epimer of the core of the natural product, suitable for the synthesis of analogues.

Inspired by previous work in the group towards the synthesis of the core of streptosetin A, the Hosomi–Sakurai 1,4-addition reaction was explored to yield the desired core of anthracimycin **162**. This approach introduced the allyl side chain with a high *syn*-selectivity forming compound **266**, but the synthesis of the *E*-crotyltrimethylsilane **272** was needed. In the presence of this nucleophile, the Hosomi–Sakurai 1,4-addition reaction gave products **276** and **277** as an inseparable mixture in a 2 : 1 ratio, with the major diastereoisomer **276** having the stereochemistry necessary for the core of anthracimycin. Selective functionalisation of the exocyclic alkene was performed using Morken's diborylation/hydroxylation conditions, which allowed the selective functionalisation of the exocyclic double bond. This strategy permitted the formation of the core of anthracimycin **162**, which was isolated with **298**, as an inseparable mixture of products in a 2 : 1 ratio.

Having achieved the synthesis of **162**, the phosphonate reagent **92** was formed following the synthetic route reported by Kalesse. However, the Still–Gennari olefination could not be explored due to the difficulty in the separation of **162** and **298**.

The core of anthracimycin was formed as an inseparable mixture of diastereoisomers, which hindered the progression of the total synthesis.

Removal of the TIPS-group of compounds **294** and **295** was performed in order to convert the major diastereoisomer **294** into the core of anthracimycin **162** and test the Still–Gennari olefination reaction. However, deprotection followed by Dess-Martin oxidation yielded a mixture of products, which was impossible to interpret by ^{1}H NMR and ^{13}C NMR analysis or to separate by silica chromatography (**Scheme 97**, **Figure 31**). Identification of the major diastereoisomer was not possible. The ^{1}H NMR and ^{13}C NMR analysis of the products obtained from the Dess-Martin oxidation reaction showed the presence of multiple unexpected aldehyde peaks, in the region between δ 10.0 and 9.48 ppm in the ^{1}H NMR spectrum, as well as in the region between δ 207.5 and 203.5 ppm in the ^{13}C NMR spectrum (**Figure 32**).



Scheme 97. The attempted isolation of the major diastereoisomer **294**.

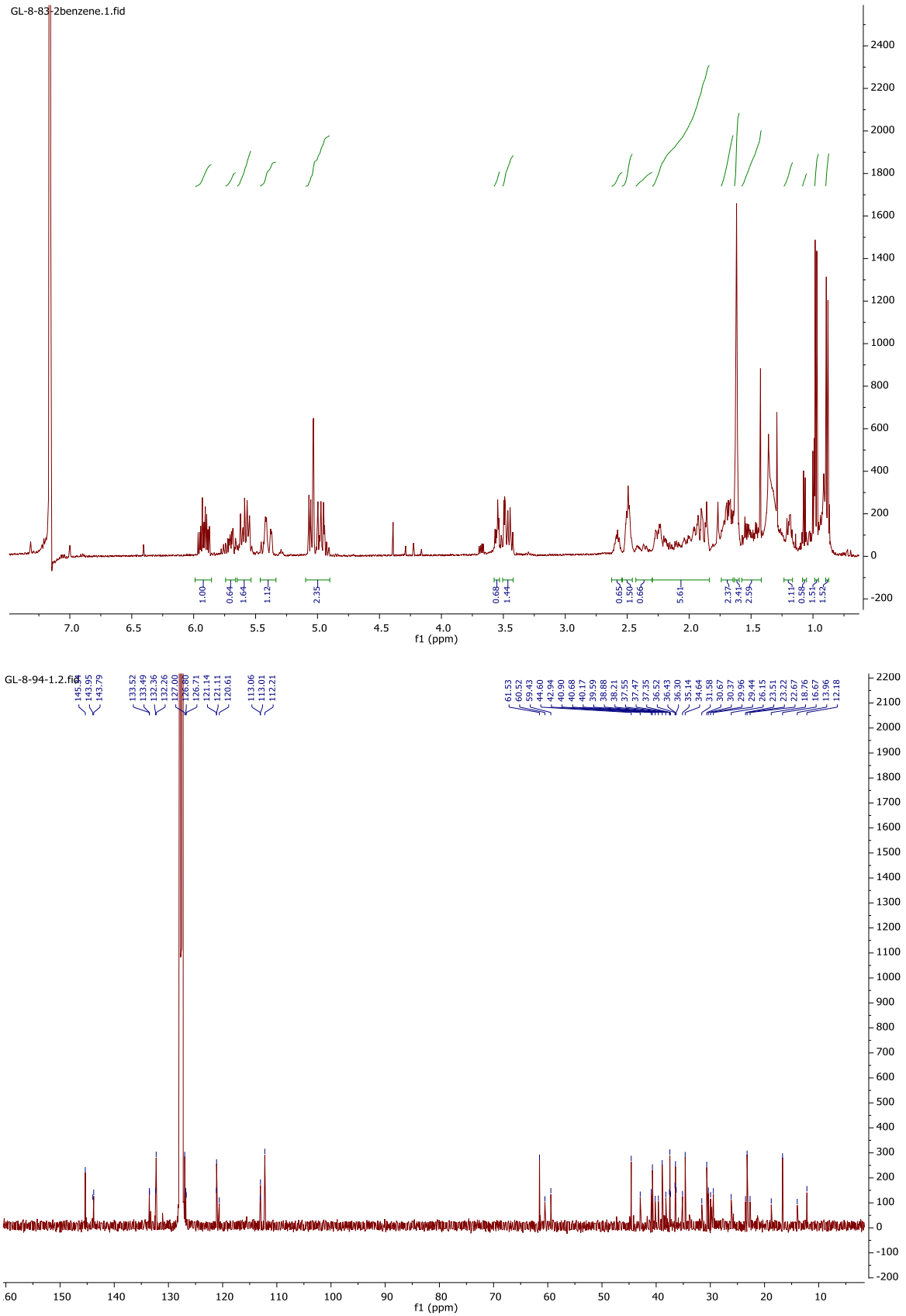


Figure 31. The ^{1}H NMR and ^{13}C NMR spectrum of the deprotection reaction.

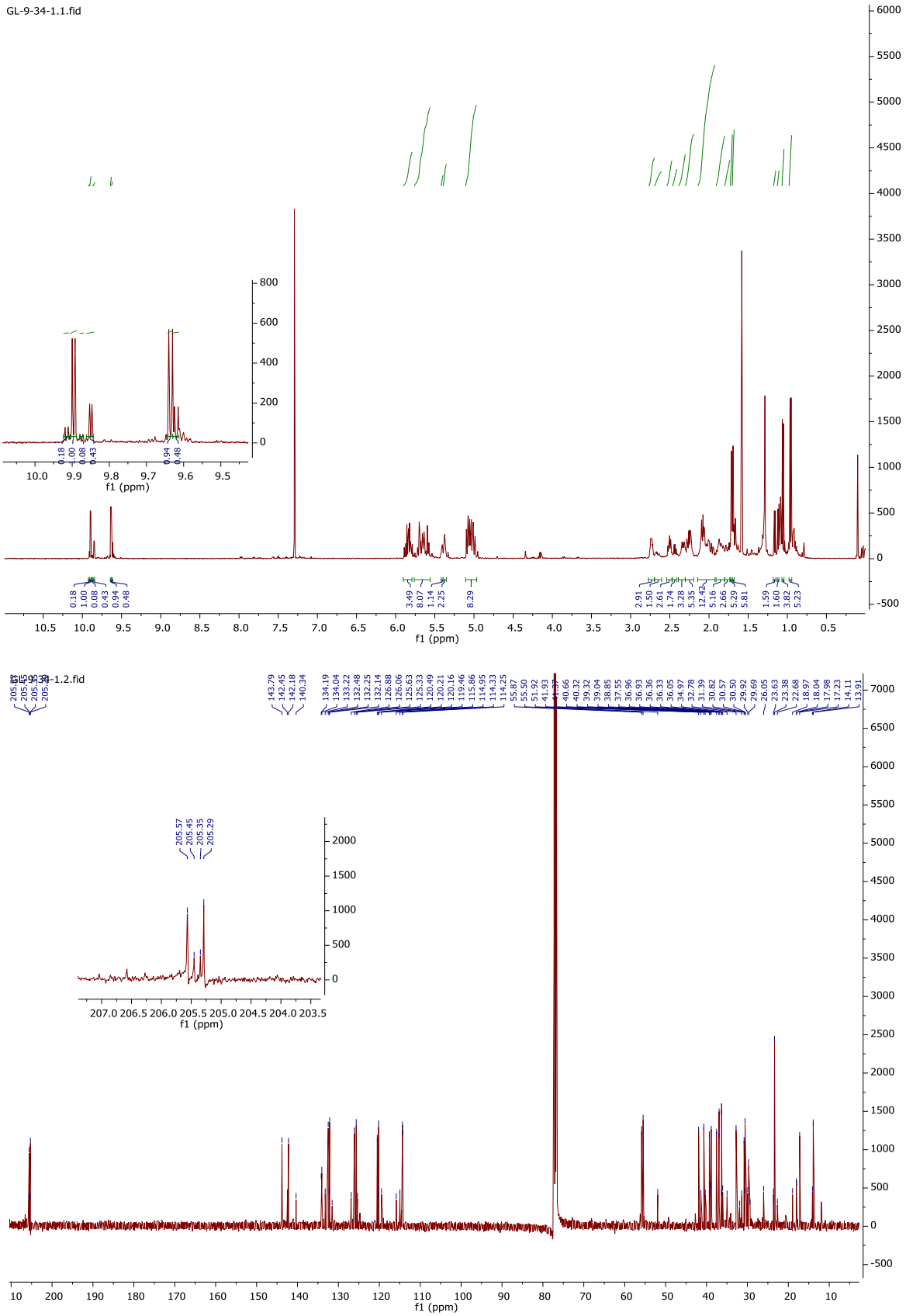
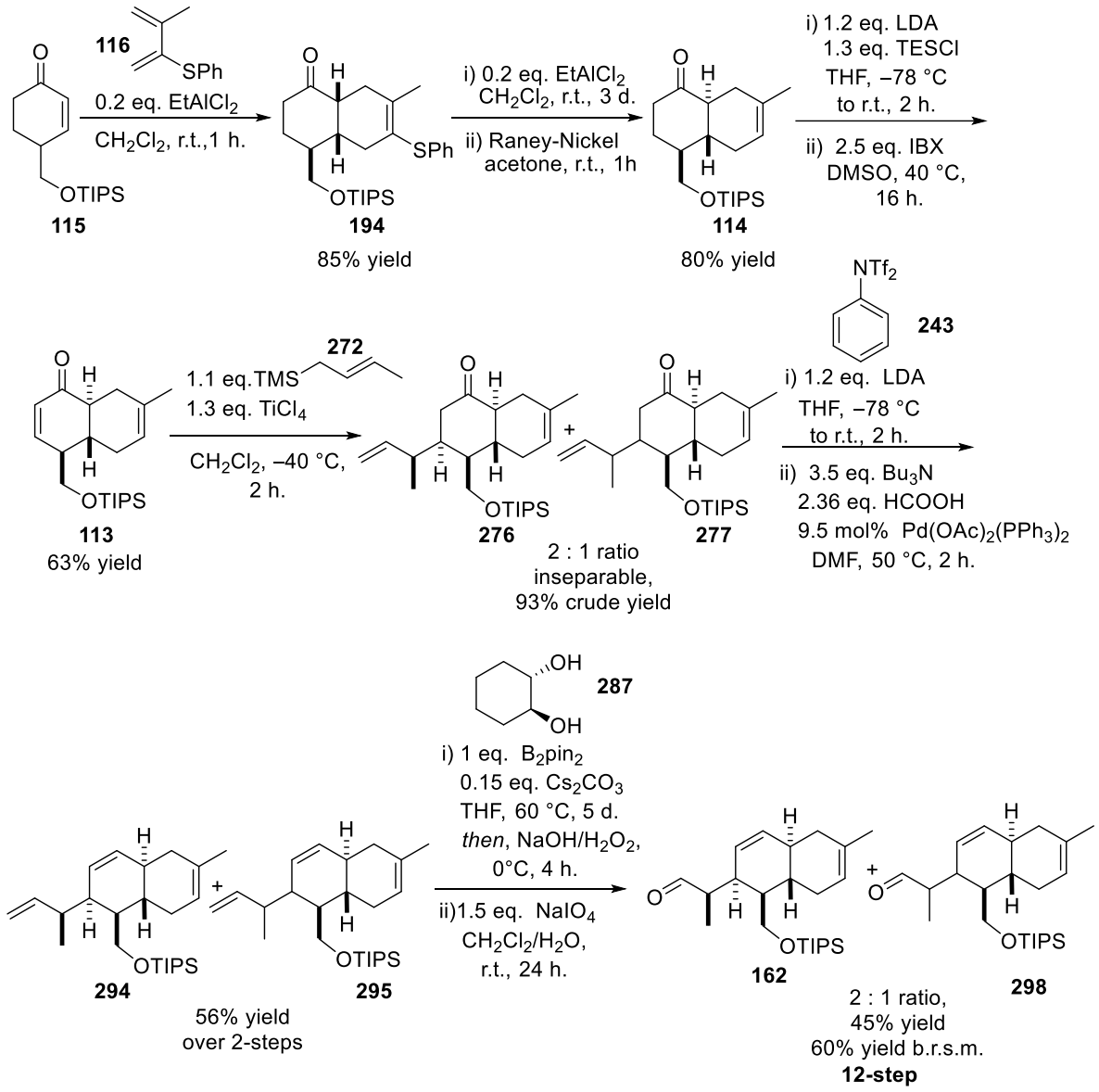


Figure 32. The ^{1}H NMR and ^{13}C NMR spectrum of the Dess-Martin oxidation.

10. Conclusions

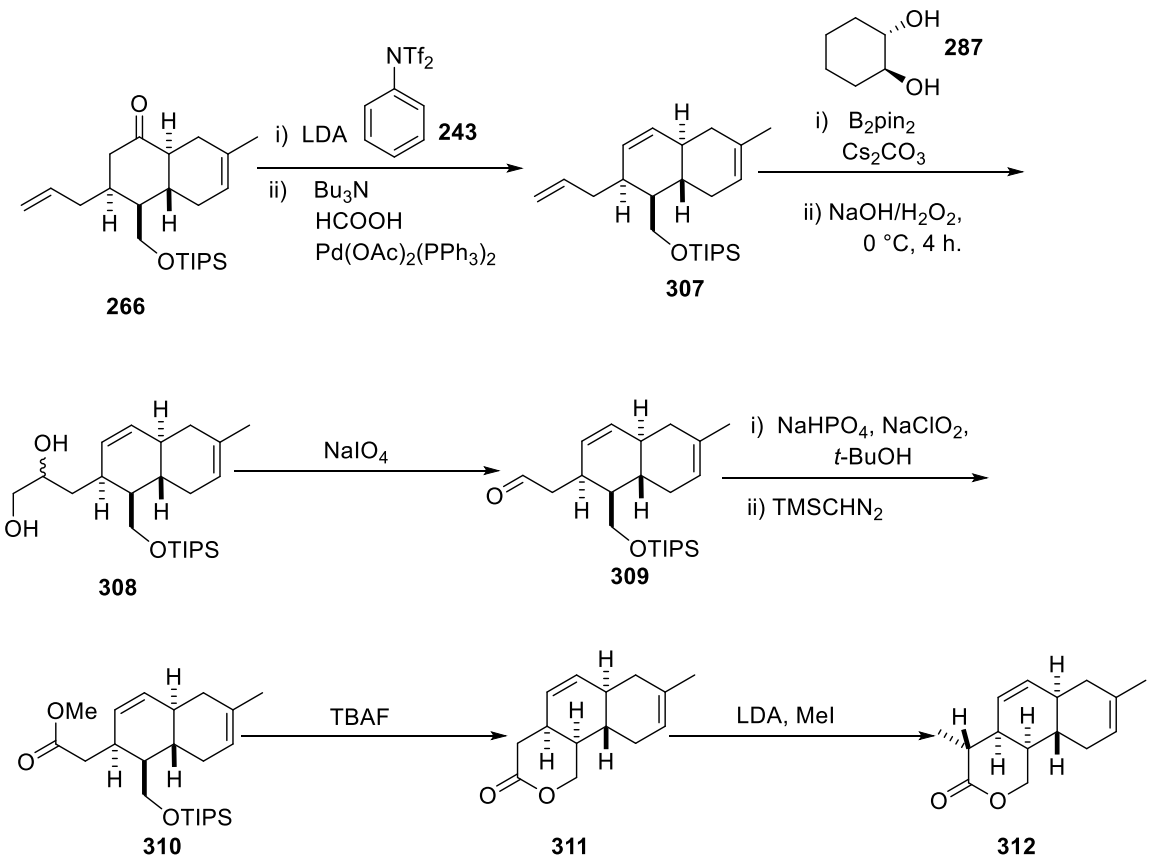
The formation of the core of anthracimycin **162** was achieved in a 12-step sequence. The development of the direct palladium oxidation conditions in the presence of $Pd(OAc)_2$, 4,4′-^{t}Bu-2,2′-dipyridyl and KNO_3, allowed the formation of enone **115**, suitable for the Diels–Alder cycloaddition to generate the *cis*-decalin **194** in an 85% yield. This was followed by epimerisation and Raney-Nickel reduction to afford the *trans*-decalin **114**, which was oxidised to **113** in the presence of IBX. The planned Luche reduction/ Ireland–Claisen rearrangement sequence failed to deliver the core of the natural product. However, the Hosomi–Sakurai 1,4-addition between the enone **113** and the *E*-crotyltrimethylsilane **272**, allowed the installation of the crotyl chain and delivered **276** and **277** as an inseparable mixture of diastereoisomers in a 2 : 1 ratio. The major diastereoisomer **276** had the stereochemistry required for the core of anthracimycin, which was determined by a deprotection/iodoetherification sequence. Conversion of the ketone carbonyl group of **276** and **277** into an alkene was performed *via* a triflation/palladium reduction sequence, which afforded **294** and **295** in a 56% yield. Morken's conditions allowed the selective dihydroxylation of the exocyclic double bond in the presence of two potentially reactive endocyclic alkenes, using B_2pin_2, *trans*-cyclohexanediol and Cs_2CO_3. This was followed by diol cleavage with the use of $NaIO_4$, which formed the core of anthracimycin **162** in an inseparable mixture with **298** in a 2 : 1 ratio in a 45% yield (60% yield b.r.s.m.). (**Scheme 98**).



Scheme 98. The formation of the core of anthracimycin **162**.

11. Future work

The inability to separate the major and the minor diastereoisomers **294** and **295** and the difficulties in interpretation of the NMR spectrum of the deprotection and Dess-Martin oxidation products **305** and **306**, represented a real challenge of this strategy. This has forced the redesign of the Hosomi–Sakurai 1,4-addition approach to give the core of the natural product as a single compound. The new route will involve a Hosomi–Sakurai reaction between allyltrimethylsilane **250** and the enone **113**, to generate compound **266** as the major diastereoisomer. This compound could be derivatised to give the core of the natural product, by converting the carbonyl group into an alkene **307**, *via* enol-triflation formation and palladium reduction. Selective dihydroxylation of the exocyclic alkene followed by periodate cleavage could form aldehyde **309**, which would then be converted into the methyl ester **310**. Removal of the TIPS-group, would yield the tricyclic system **311**. Installation of the methyl group as required for the core of the natural product, could be achieved with the use of LDA and methyl iodide (**Scheme 99**). The concave shape of the A/B-ring, as a *cis*-decalin, should ensure installation of the methyl group with the required stereochemistry, forming the core of anthracimycin as a single diastereoisomer **312**.



Scheme 99. The new strategy envisioned for the core of anthracimycin **162**.

Compound **312** would then be used to complete the synthesis. Subsequent functionalisation would involve DIBAL-H reduction, Still–Gennari olefination and a Weiler dianion addition reaction after oxidation of the hydroxyl methylene to an ester. Macrocyclisation would then allow the completion of anthracimycin **1**.

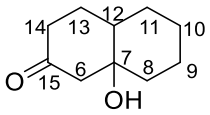
12. Experimental

12.1 General experimental

Melting points were determined using a Stuart SMP3 apparatus. Optical rotations were carried out using a JASCO-DIP370 polarimeter and $[\alpha]_D$ values are given in 10^{-1}deg.cm^2.g^{-1}. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECX-400, a Jeol ECS-400, Bruker DRX 500 at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: $CDCl_3$ 7.27 ppm, C_6D_6 7.16 ppm for ^{1}H NMR; $CDCl_3$ 77.0 ppm, central line of triplet, C_6D_6 128.4 ppm, central line of triplet for ^{13}C NMR.^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI), electron ionization (EI) and atmospheric pressure chemical ionization (APCI) techniques. All the Mass-spectra data were in a 5 ppm error. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich. Hexane, CH_2Cl_2, toluene, THF and Et_2O were all purified using Innovative Technology Solvent Purification System; diisopropylamine was distilled from calcium hydride. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules. Compounds numbers are reported in relation to anthracimycin numbers.[15]

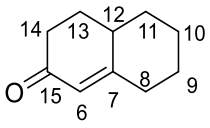
12.2 Methods and Characterisation of Compounds

7-Hydroxyoctahydronaphthalen-15(1H)-one, **102**



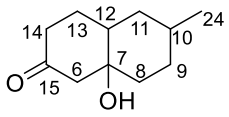
To a solution of cyclohexanone **101** (5.28 mL, 50.9 mmol) in dry THF (63.3 mL) at 0 °C, a solution of KOH/MeOH (0.74 M, 7.79 mmol, 1.04 mL) and a solution of methylvinyl ketone **99** (2.07 mL, 25.5 mmol) in dry THF (63.3 mL) were added slowly over 30 minutes. The reaction was stirred at room temperature for 2 days. After this time, the solvent was removed *in vacuo* and the residue was dissolved with EtOAc (60 mL) and the organic phase was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was triturated with hexane (30 mL), filtered and the desired product **102** was isolated, without further purification, as a white solid (1.41 g, 34% yield).[61] **Melting point** = 142–144 °C. **Rf** = 0.11 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 3353 (C-OH), 2952, 2854, 1706 (C=O), 1451, 1346, 1296, 958, 656 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47–2.27 (4H, m), 1.89–1.62 (5H, m), 1.53–1.47 (4H, m), 1.39–1.24 (2H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 210.6 (C=O), 73.9 (C-OH), 55.3 (CH_2), 42.6 (CH), 41.4 (CH_2), 39.6 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 25.7 (CH_2), 20.8 (CH_2) ppm. **MS** (ESI): m/z 191 ($M+Na^+$); HRMS: found: ($M+Na^+$) 191.1042. $C_{10}H_{16}NaO_2$ requires ($M+Na^+$) 191.1043.

13,12,11,10,9,8-Hexahydronaphthalen-15(3H)-one, **103**[61]



To a solution of hydroxyl decalin **102** (720 mg, 4.23 mmol) in glacial acetic acid (11.5 mL), was added H_2SO_4 98% solution in water (1.0 mL) and the reaction was stirred at 50 °C for 30 minutes. After this time, the reaction was quenched with cold water (10 mL) and saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The desired product **103** was obtained without further purification as an orange oil (570 mg, 90% yield).[62] **Rf** = 0.23 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2926, 2855, 1667 (C=O), 1205, 858 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82 (1H, s), 2.48–2.40 (1H, m), 2.40–2.36 (1H, m), 2.35–2.25 (2H, m), 2.25–2.15 (1H, m), 2.09 (1H, dddd, *J* = 13.3, 4.9, 4.9, 4.9 Hz), 2.00–1.79 (3H, m), 1.63 (1H, dddd, *J* = 13.3, 13.3, 9.0, 4.9 Hz), 1.55–1.33 (2H, m), 1.28–1.4 (1H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 200.1 (C=O), 167.4 (C=C), 124.3 (CH), 37.6 (CH), 36.6 (CH_2), 35.4 (CH_2), 34.4 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 25.5 (CH_2) ppm. **MS** (ESI): m/z 173 ($M+Na^+$); HRMS: found: ($M+Na^+$) 173.0937. $C_{10}H_{14}NaO$ requires ($M+Na^+$) 173.0937. m/z 151 ($M+H^+$); HRMS: found: ($M+H^+$) 151.1113. $C_{10}H_{15}O$ requires ($M+H^+$) 151.1117. Characterisation of this compound matched the compound reported in the literature.[61]

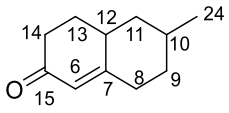
7-Hydroxy-10-methyloctahydronaphthalen-15(1H)-one, **104**



To a solution of 4-methyl-cyclohexanone **98** (5.40 mL, 44.6 mmol) in dry THF (65.5 mL) at 0 °C, a solution of KOH/MeOH (0.74 M, 8.22 mmol, 1.20 mL) and a solution of methylvinyl ketone **99** (1.86 mL, 22.4 mmol) in dry THF (65.5 mL) were added slowly over 30 minutes. The reaction was stirred at

room temperature for 2 days. After this time, the solvent was removed *in vacuo* and the residue was dissolved with EtOAc (60 mL) and the organic phase was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was triturated with hexane (30 mL), filtered and the desired product **104** was isolated, without further purification, as a white solid (1.67 g, 41% yield).[61] **Melting point** = 137–139 °C. **Rf** = 0.11 (EtOAc : hexane 10% : 90 %). **IR** (ATR): ν_{max} 3358 (C-OH), 2925, 2856, 1709 (C=O), 1458, 1402, 1268, 1252, 960, 640 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.49–2.28 (3H, m), 2.13–2.08 (1H, m), 1.96–1.56 (4H, m), 1.55–1.53 (5H, m), 1.48–1.40 (1H, m), 1.30 (3H, d, *J* = 7.8 Hz) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 210.8 (C=O), 74.1 (C-OH), 55.3 (CH_2), 41.5 (CH_2), 36.5 (CH), 33.9 (CH_2), 33.2 (CH_2), 28.6 (CH_2), 26.8 (CH), 25.8 (CH_2), 17.5 (CH_3) ppm. **MS** (ESI): m/z 205 ($M+Na^+$); HRMS: found: ($M+Na^+$) 205.1201. $C_{11}H_{18}NaO_2$ requires ($M+Na^+$) 205.1199.

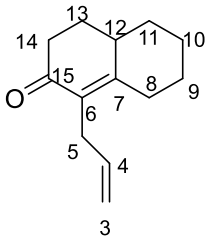
10-Methyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)one, **105**



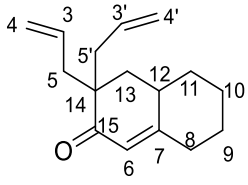
To a solution of hydroxyl decalin **104** (100 mg, 0.560 mmol) in glacial acetic acid (1.50 mL), was added H_2SO_4 98% solution in water (0.50 mL). The reaction was stirred at 50 °C for 30 minutes. After this time, the reaction was quenched with cold water (10 mL) and saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The desired product **105** was obtained without further purification as an orange oil (71.0 mg, 77% yield).[62] **Rf** = 0.21 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2922, 2856, 1664 (C=O), 1503, 1455, 1329, 1256, 1243, 894, 848 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.83 (1H, s), 2.49–2.40 (2H, m), 2.40–2.25 (3H, m), 2.09 (1H, ddd, *J* = 13.3, 9.6, 5.0 Hz), 1.95–1.82 (2H, m), 1.73–1.56 (3H, m), 1.17–1.03 (1H, m), 0.95 (3H, d, *J* = 6.4 Hz) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 200.2 (C=O), 166.9 (C=C), 124.3 (CH), 42.8 (CH_2), 37.5 (CH), 36.7 (CH_2), 35.3 (CH_2), 35.0 (CH_2), 31.9 (CH), 29.2 (CH_2), 21.9 (CH_3) ppm. **MS** (ESI): m/z 187 ($M+Na^+$);

HRMS: found: ($M+Na^+$) 187.1095. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. m/z 165 ($M+H^+$); HRMS: found: ($M+H^+$) 165.1268. $C_{11}H_{17}O$ requires ($M+H^+$) 165.1274.

6-Allyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **106**



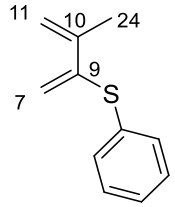
14-Diallyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **107**



Anhydrous DMSO (1.50 mL) was added to a NaH (60% dispersion in mineral oil, 28.0 mg, 0.72 mmol) and the mixture was stirred at 50 °C for 1 hour. After this time, it was cooled to room temperature and dry THF (1.50 mL) was added and then the reaction was cooled to 0 °C. A solution of decalin **103** (100 mg, 0.610 mmol) in dry THF (1.50 mL) was added dropwise (5 minutes) and stirred at 0 °C for 2 hours. Allyl bromide (0.060 mL, 0.72 mmol) was added and the reaction was warmed to room temperature and stirred for 16 hours. The reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **106** as a pale yellow oil (30.0 mg, 26% yield) and **107** as a pale yellow oil (20.0 mg, 15% yield).[63] 6-Allyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **106**; **Rf** = 0.62 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2925, 2855, 1667 (C=O), 1450, 1363, 1194, 910 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85–5.70 (1H, m), 4.96–4.89 (2H, m), 3.13–3.06 (1H, m), 2.88–2.77 (1H, m), 2.52–2.39 (2H, m), 2.37–2.27 (2H, m), 2.07 (1H,

dddd, *J* = 13.7, 5.4, 5.4, 5.4 Hz), 2.01–1.77 (3H, m), 1.70–1.54 (2H, m), 1.49 (1H, dddd, *J* = 13.7, 13.7, 3.2, 3.2 Hz), 1.42–1.20 (2H, m) ppm.**^{13}C NMR** (400 MHz, $CDCl_3$): δ 198.8 (C=O), 161.6 (C=C), 136.3 (CH), 130.5 (C=C), 114.4 (CH_2), 38.9 (CH), 36.4 (CH_2), 35.0 (CH_2), 31.4 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 26.9 (CH_2), 25.5 (CH_2) ppm. **MS** (ESI): m/z 213 ($M+Na^+$); HRMS: found: ($M+Na^+$) 213.1249. $C_{13}H_{18}NaO$ requires ($M+Na^+$) 213.1250. m/z 191 ($M+H^+$); HRMS: found: ($M+H^+$) 191.1421. $C_{13}H_{19}O$ requires ($M+H^+$) 191.1430. 14-Diallyl-13,12,11,10,9,8-hexahydronaphthalen-15(3H)-one, **107**; **Rf** = 0.57 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 2857, 1705 (C=O), 1443, 1325, 1212, 1169, 994, 911 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.71–5.54 (2H, m), 5.06–4.99 (4H, m), 4.97 (1H, s), 2.60 (1H, dddd, *J* = 14.5, 7.2, 1.3, 1.3 Hz), 2.48 (1H, dddd, *J* = 13.5, 6.9, 1.4, 1.4 Hz), 2.44–2.39 (2H, m), 2.39–2.27 (1H, m), 2.23 (1H, dddd, *J* = 13.5, 7.6, 1.4, 1.4 Hz), 2.12–2.06 (2H, m), 1.94–1.83 (2H, m), 1.77–1.66 (1H, m), 1.54–1.40 (2H, m), 1.36–1.24 (2H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 213.8 (C=O), 139.5 (C=C), 135.1 (CH), 133.5 (CH), 123.7 (CH), 117.9 (CH_2), 117.1 (CH_2), 58.0 (C-C), 44.5 (CH_2), 39.5 (CH_2), 39.2 (CH), 34.8 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 25.6 (CH_2), 21.1 (CH_2) ppm. **MS** (ESI): m/z 253 ($M+Na^+$); HRMS: found: ($M+Na^+$) 253.1559. $C_{16}H_{22}NaO$ requires ($M+Na^+$) 253.1563.

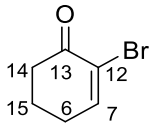
(10-Methylbuta-11,7-dien-9-yl)(phenyl)sulfane, **116**[75]



In a pressure vessel were placed $Pd(OAC)_2$ (134 mg, 0.600 mmol), dry THF (15.2 mL), 2-methyl-1-buten-3-yne **135** (2.88 mL, 30.2 mmol) and thiophenol (3.10 mL, 30.2 mmol) were added. The reaction was stirred at 60 °C for 16 hours. After this period, the mixture was filtrated through celite with EtOAc (50 mL) and the solvent was concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield **116** as a pale yellow liquid (5.32 g, quantitative yield).[75] **Rf** = 0.66 (100% hexane). **IR** (ATR): ν_{max} 2978, 2952, 1617, 1574, 1478, 1458, 1440, 1375, 1119,

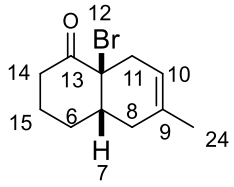
1025 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34–7.16 (5H, m, Ar-H), 5.55 (1H, s, H-11), 5.51 (1H, s, H-11), 5.22 (1H, d, *J* = 1.4 Hz, H-7), 5.05 (1H, d, *J* = 1.4 Hz, H-7), 1.96 (3H, s, H-24) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 143.8 (C-9), 140.4 (C-10), 134.4 (Ar), 130.9 (Ar-H), 128.7 (Ar-H), 126.7 (Ar-H), 117.1 (C-11), 116.4 (C-7), 20.9 (C-24) ppm. **MS** (APCI): m/z 177 ($M+H^+$); HRMS: found: ($M+H^+$) 177.0736. $C_{11}H_{13}S$ requires ($M+H^+$) 177.0732. Characterisation of this compound matched the compound reported in the literature.[75]

12-Bromocyclohex-13-enone, **132**[74]



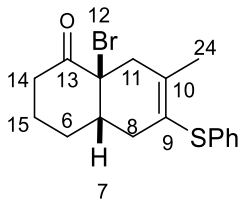
To a solution of cyclohexenone **131** (0.500 mL, 5.21 mmol) in pyridine : $CHCl_3$ (1 : 1, 4.0 mL) at 0 °C, were added DMAP (127 mg, 1.04 mmol) and a solution of bromine (0.500 mL, 10.4 mmol) in pyridine : $CHCl_3$ (1 : 1, 4.0 mL) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was diluted with EtOAc (100 mL), washed with aqueous solution of 2 M HCl (20 mL), water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **132** as a white solid (360 mg, 40% yield).[74] **Melting point** = 75–76 °C. **Rf** = 0.24 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2942, 2872, 1678 (C=O), 1461, 1424, 1315, 1124, 971, 813 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (1H, dd, *J* = 4.6, 4.6 Hz, H-7), 2.65 (2H, ddd, *J* = 6.4, 3.2, 3.2 Hz, H-14), 2.45–2.43 (2H, m, H-6), 2.14 (2H, ddd, *J* = 6.4, 6.4, 4.6 Hz, H-15) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 191.3 (C-13), 151.1 (C-7), 123.9 (C-12), 38.3 (C-14), 28.4 (C-15), 22.7 (C-6) ppm. **MS** (ESI): m/z 196 ($M+Na^+$), 198 ($M+Na^+$); HRMS: found: ($M+Na^+$) 196.9568. $C_6H_7{}^{79}BrNaO$ requires ($M+Na^+$) 196.9572. Characterisation of this compound matched the compound reported in the literature[74]

(12*S**, 7*S**)-12-Bromo-9-methyl-15,6,7,6,11,12-hexahydronaphthalen-13(2H)-one, **134**[70]



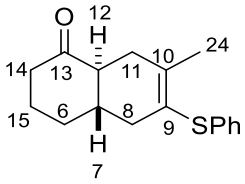
To a solution of 2-bromocyclohexenone **132** (173 mg, 1.00 mmol) in dry CH_2Cl_2 (5.0 mL) at –10 °C, were sequentially added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and isoprene **133** (1.00 mL, 10.0 mmol) and the reaction was stirred at –10 °C for 2 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the mixture was stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **134** as pale yellow oil (150 mg, 62% yield).[70] **Rf** = 0.44 (EtOAc : hexane 5% : 95%). **IR** (ATR): ν_{max} 2912, 1714 (C=O), 1447, 1424, 1310, 1168, 1071, 783 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.28–5.23 (1H, m, H-10), 3.20 (1H, ddd, *J* = 15.1, 10.5, 7.3 Hz, H-14), 3.18–3.10 (1H, m, H-11), 2.71–2.58 (2H, m, H-14 + H-7), 2.45–2.34 (2H, m, H-15 + H-11), 2.15 (1H, dd, *J* = 17.4, 6.9 Hz, H-8), 2.08–1.58 (4H, m, H-8 + H-15 + H-6), 1.63 (3H, s, H-24) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 204.0 (C-13), 131.7 (C-9), 118.2 (C-10), 70.6 (C-12), 43.5 (C-7), 36.3 (C-14), 36.3 (C-11), 33.0 (C-8), 26.7 (C-15), 23.0 (C-24), 22.5 (C-6) ppm. **MS** (ESI): m/z 265 ($M+Na^+$), 267 ($M+Na^+$); HRMS: found: ($M+Na^+$) 265.0197. $C_{11}H_{15}{}^{79}BrNaO$ requires ($M+Na^+$) 265.0198. Characterisation of this compound matched the compound reported in the literature.[70]

(12*S**, 8*S**)-12-Bromo-10-methyl-9-(phenylthio)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **136**[72]



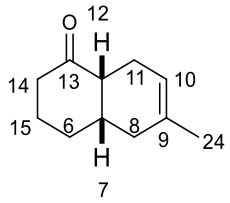
To a solution of 2-bromocyclohexenone **132** (36.0 mg, 0.210 mmol) in dry CH_2Cl_2 (0.50 mL) at –10 °C, was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.04 mL, 0.04 mmol) and stirred for 10 minutes. A solution of sulfur substituted diene **116** (150 mg, 0.850 mmol) in dry CH_2Cl_2 (0.55 mL) was then added and the reaction was stirred at –10 °C for 2 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 5% EtOAc in hexanes) to yield **136** as a pale yellow oil (40.0 mg, 54% yield).[72] **Rf** = 0.56 (EtOAc : hexane 5% : 95%). **IR** (ATR): ν_{max} 2931, 1716 (C=O), 1477, 15852, 1477, 1233, 1024, 741, 760 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22–7.13 (2H, m, Ar-H), 7.09–7.00 (3H, m, Ar-H), 3.24 (1H, d, *J* = 17.9 Hz, H-11), 3.16 (1H, ddd, *J* = 15.1, 9.2, 9.2 Hz, H-14), 2.74 (1H, d, *J* = 17.9, Hz, H-11), 2.64–2.57 (1H, m, H-7), 2.37–2.23 (3H, m, H-14 + H-15 + H-6), 2.22–2.11 (1H, m, H-6), 1.90 (3H, s, H-24), 1.81–1.75 (2H, m, H-8), 1.53–1.45 (1H, m, H-15) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 203.7 (C-13), 139.5 (C-9), 135.8 (Ar), 129.0 (Ar-H), 128.0 (Ar-H), 125.6 (Ar-H), 120.7 (C-10), 68.8 (C-12), 44.5 (C-7), 43.0 (C-11), 36.0 (C-14), 34.1 (C-6), 26.1 (C-15), 22.2 (C-8), 20.9 (C-24) ppm. **MS** (ESI): m/z 373 ($M+Na^+$), 375 ($M+Na^+$); HRMS: found: ($M+Na^+$) 373.0229. $C_{17}H_{19}{}^{79}BrNaOS$ requires ($M+Na^+$) 373.0232. Characterisation of this compound matched the compound reported in the literature.[72]

(12*S**, 7*S**)-10-Methyl-9-(phenylthio)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **137**[72]

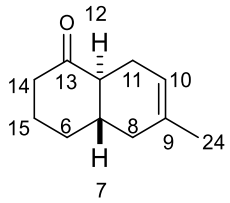


To a solution of thiophenyl *cis*-declalin **156** (100 mg, 0.370 mmol) in dry CH_2Cl_2 (2.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.07 mL, 0.07 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The reunited organic layers were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **137** as a white solid (68.0 mg, 68% yield). **Melting point** = 76–79 °C. **Rf** = 0.45 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 1709 (C=O), 1581, 1476, 1438, 1370, 1085, 740, 691 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29–7.25 (2H, m, Ar-H), 7.21–7.13 (3H, m, Ar-H), 2.52–2.39 (1H, m, H-11), 2.42 (1H, dddd, *J* = 13.8, 4.4, 2.5, 1.9 Hz, H-14), 2.41–2.29 (4H, m, H-14 + H-12 + H-8 + H-11), 2.21–2.13 (1H, m, H-8), 2.11–2.05 (1H, m, H-15), 2.01 (3H, s, H-24), 1.83 (1H, dddd, *J* = 13.3, 6.6, 3.4, 1.6 Hz, H-6), 1.78–1.72 (1H, m, H-7), 1.68–1.59 (1H, m, H-15), 1.42 (1H, dddd, *J* = 13.3, 13.3, 11.7, 3.7 Hz, H-6) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 211.3 (C-13), 140.5 (C-9), 136.0 (Ar), 128.7 (Ar-H), 127.9 (Ar-H), 125.2 (Ar-H), 121.2 (C-10), 50.7 (C-12), 42.1 (C-14), 41.9 (C-7), 39.9 (C-8), 32.3 (C-6), 32.1 (C-11), 26.3 (C-15), 21.8 (C-24) ppm. **MS** (ESI): m/z 295 ($M+Na^+$); HRMS: found: ($M+Na^+$) 295.1119. $C_{17}H_{20}NaOS$ requires ($M+Na^+$) 295.1127. Characterisation of this compound matched the compound reported in the literature[72]

(12*R**, 7*S**)-9-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **138**[76]



(12*S**, 7*S**)-9-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **139**[70]



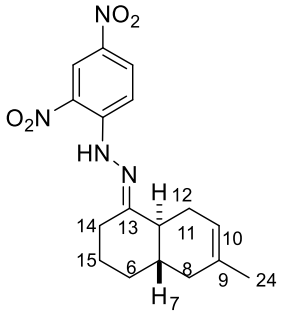
To a solution of cyclohexeneone **131** (0.50 mL, 5.0 mmol) in dry CH_2Cl_2 (25.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (1.0 mL, 1.0 mmol) and stirred at room temperature for 30 minutes. Isoprene **133** (5.0 mL, 50 mmol) was then added, and the reaction was stirred at 30 °C for 8 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **138** as a pale yellow oil (305 mg, 37% yield) and **139** as a pale yellow oil (371 mg, 40% yield). (12*R**, 7*S**)-9-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **138**; **Rf** = 0.42 (EtOAc : hexane 5% : 95%). **IR** (ATR): ν_{max} 2922, 2866, 1708 (C=O), 1444, 1377, 1310, 1234, 1179, 919, 889 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.31–5.27 (1H, m, H-10), 2.63 (1H, ddd, *J* = 10.9, 4.5, 2.0 Hz, H-12), 2.47–2.45 (1H, m, H-11), 2.43–2.31 (2H, m, H-14 + H-7), 2.24 (1H, dddd, *J* = 15.1, 9.2, 5.7, 1.3 Hz, H-14), 2.02–1.90 (2H, m, H-8 + H-11), 1.89–1.66 (4H, m, H-8 + H-6 + H-15), 1.74–1.67 (1H, m, H-6), 1.59 (3H, s, H-24) ppm.**^{13}C NMR** (500 MHz, $CDCl_3$): δ 213.1 (C-13), 131.9 (C-9), 118.2 (C-10), 48.0 (C-12), 40.0 (C-14), 36.3 (C-7), 32.2 (C-15), 28.5 (C-6), 24.2 (C-8), 24.1 (C-11), 23.8 (C-24) ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1090. $C_{11}H_{16}NaO$

requires ($M+Na^+$) 187.1093. m/z 165 ($M+H^+$); HRMS: found: ($M+H^+$) 165.1273. $C_{11}H_{17}O$ requires ($M+H^+$) 165.1274. Characterisation of this *cis*-decalin **138** matched the compound reported in the literature[76] (12*S**, 7*S**)-9-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **139**; **Rf** = 0.48 (EtOAc : hexane 5% : 95%). **IR** (ATR): ν_{max} 2921, 1705 (C=O), 1439, 1378, 1340, 1310, 1149, 1060, 824 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.39–5.34 (1H, m, H-10), 2.04 (1H, dddd, *J* = 13.7, 4.5, 2.8, 1.7 Hz, H-14), 2.34 (1H, dddd, *J* = 13.7, 13.7, 5.7, 0.7 Hz, H-14), 2.40–2.11 (3H, m, H-12 + H-11), 2.10–2.01 (2H, m, H-8 + H-15), 1.93–1.84 (2H, m, H-8 + H-6), 1.76–1.66 (2H, m, H-7 + H-15), 1.64 (3H, s, H-24), 1.45 (1H, dddd, *J* = 13.2, 13.2, 11.7, 3.4 Hz, H-6) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.1 (C-13), 132.1 (C-9), 118.7 (C-10), 50.0 (C-12), 41.8 (C-14), 40.2 (C-7), 38.1 (C-8), 32.4 (C-6), 25.9 (C-15), 24.4 (C-11), 22.9 (C-24) ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1091. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. m/z 165 ($M+H^+$); HRMS: found: ($M+H^+$) 165.1221. $C_{11}H_{17}O$ requires ($M+H^+$) 165.1274. Characterisation of this *trans*-decalin **139** matched the compound reported in the literature[70]

Epimerisation Method

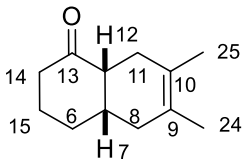
To a solution of *cis*-decalin **138** (326 mg, 1.99 mmol), in dry CH_2Cl_2 (10.0 mL), was added a 1.0 M solution of $EtAlCl_2$in hexane (0.40 mL, 0.40 mmol) and stirred for 16 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the reaction was stirred vigorously for 1 hour. The mixture was diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **139** as a pale yellow oil (245 mg, 75% yield).

13-(2,4-Dinitrophenyl)-14-((12*S**, 7*S**)-9-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-ylidene)hydrazine, **141**

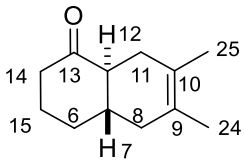


To a solution of *trans*-decalin **139** (40.0 mg, 0.270 mmol) in methanol (1.0 mL), were added 2,4-dinitrophenyl hydrazine **140** (120 mg, 0.540 mmol), glacial acetic acid (0.50 mL) and H_2SO_4 98% solution in water (0.10 mL). The reaction was stirred at 50 °C for 2 hours and after this period the reaction was cooled to room temperature and then quenched with cold water (10 mL) and saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **141** as an orange solid (50.0 mg, 54% yield). Crystallized using solvent/antisolvent system: EtOAc/hexane. **Melting point** = 192–194 °C. **Rf** = 0.55 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 3328, 2927, 1615 (C=N), 1587, 1514, 1500, 1264, 1296, 741 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.29 (1H, s, NH), 9.14 (1H, d, *J* = 2.5 Hz, Ar-H), 8.31 (1H, dd, *J* = 9.6, 2.5 Hz, Ar-H), 7.98 (1H, d, *J* = 9.6 Hz, Ar-H), 5.51–5.47 (1H, m, H-10), 2.95–2.92 (1H, m, H-14), 2.41–2.32 (2H, m, H-11), 2.19 (1H, ddd, *J* = 11.4, 7.8, 6.5 Hz, H-12), 2.14–2.04 (3H, m, H-14 + H-8 + H-15), 1.95–1.91 (1H, m, H-6), 1.92–1.84 (1H, m, H-8), 1.69 (3H, s, H-24), 1.64–1.60 (1H, m, H-7), 1.55–1.51 (1H, m, H-15), 1.33 (1H, dddd, *J* = 13.1, 13.1, 11.2, 3.1 Hz, H-6) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 162.1 (C=N), 145.7 (C-9), 137.5 (Ar), 132.5 (Ar), 128.9 (Ar-H), 128.4 (Ar), 123.7 (Ar-H), 120.2 (C-10), 116.5 (Ar-H), 44.9 (C-12), 40.1 (C-7), 38.6 (C-8), 33.0 (C-6), 27.5 (C-14), 26.8 (C-11), 25.3 (C-15), 23.4 (C-24) ppm. **MS** (ESI): m/z 367 ($M+Na^+$); HRMS: found: ($M+Na^+$) 367.1375. $C_{17}H_{20}N_4NaO_4$ requires ($M+Na^+$) 367.1377.

(12*R**, 7*S**)-9,10-Dimethyl,15,6,7,8,11,12-hexahydronaphthalen-13-(2H)-one, **143**[77]



(12*S**, 7*S**)-9,10-Dimethyl,15,6,7,8,11,12-hexahydronaphthalen-13-(2H)-one, **144**[77]



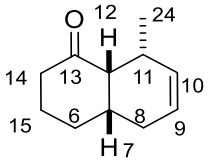
To a solution of cyclohexanone **131** (0.10 mL, 1.0 mmol) in dry CH_2Cl_2 (5.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. 2,3-Dimethyl-1,3-butadiene **142** (1.20 mL, 10.0 mmol) was added and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the mixture was stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **143** and **144** in a 2 : 1 ratio as pale yellow oil (178 mg, 99% yield).

Epimerisation

To a solution of the inseparable mixture of *cis*-decalin **143** and *trans*-decalin **144** 2: 1 ratio (178 mg, 1.00 mmol) in dry CH_2Cl_2 (5.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and

concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield **144** as a pale yellow oil in a 23 : 1 ratio (166 mg, 93% yield). Data reported for the *trans*-diasteroisomer **144** only, after epimerization. **Rf** = 0.52 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2911, 1708 (C=O), 1445, 1380, 1237, 1180, 1131, 515 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.40 (1H, dddd, *J* = 13.7, 4.3, 2.6, 1.6 Hz, H-14), 2.33 (1H, dddd, *J* = 13.7, 13.7, 5.6, 0.9 Hz, H-14), 2.21–2.13 (2H, m, H-11 + H-12), 2.10–1.98 (3H, m, H-15 + H-7), 1.97–1.86 (2H, m, H-11 + H-6), 1.72–1.63 (2H, m, H-8), 1.61 (3H, s, H-24), 1.57 (3H, s, H-25), 1.41 (1H, dddd, *J* = 13.0, 13.0, 11.9, 3.7 Hz, H-6) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.5 (C-13), 124.5 (C-9), 123.9 (C-10), 51.0 (C-12), 41.8 (C-14), 40.9 (C-7), 40.2 (C-8), 32.3 (C-6), 30.7 (C-11), 26.1 (C-15), 18.8 (C-24), 18.6 (C-25) ppm. **MS** (ESI): m/z 179 ($M+H^+$); HRMS: found: ($M+H^+$) 179.1441. $C_{12}H_{19}O$ requires ($M+H^+$) 179.1430.

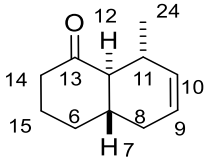
(12*S**, 7*S**)-10-Methyl,15,6,7,8,11,12-hexahydronaphthalen-13-(2H)-one, **146**[77]



To a solution of cyclohexanone **131** (0.10 mL, 1.0 mmol) in dry CH_2Cl_2 (5.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. *trans*-1,3-Pentadiene **145** (1.00 mL, 10.0 mmol) was added and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield **146** as a pale yellow oil (164 mg, 99% yield). **Rf** = 0.54 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2899, 1710 (C=O), 1444, 1367, 1212, 1139, 1063, 803 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.57–5.53 (2H, m, H-10 + H-9), 2.83 (1H, dd, *J* = 4.6, 4.6 Hz, H-12), 2.60–2.52 (1H, m, H-7), 2.44–2.31 (2H, m, H-14 + H-

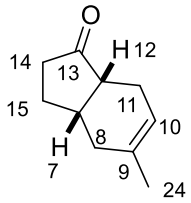
11), 2.29–2.21 (1H, m, H-14), 2.05–1.88 (5H, m, H-15 + H-6 + H-8), 1.76–1.68 (1H, m, H-8), 1.21 (3H, d, *J* = 7.3 Hz, H-24) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 211.3 (C-13), 131.2 (C-10), 123.8 (C-9), 53.8 (C-12), 43.3 (C-14), 39.6 (C-7), 32.7 (C-11), 30.0 (C-15), 26.2 (C-8), 24.9 (C-6), 17.9 (C-24) ppm. **MS** (APCI): m/z 165 ($M+H^+$); HRMS: found: ($M+H^+$) 165.1277. $C_{11}H_{17}O$ requires ($M+H^+$) 165.1274. Characterisation of this compound matched the compound reported in the literature.[77]

(12*R**, 7*S**)-10-Methyl,15,6,7,8,11,12-hexahydronaphthalen-13-(2H)-one, **147**[77]

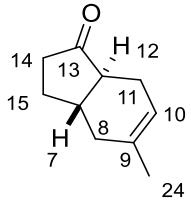


To a solution of *cis*-decalin **146** (164 mg, 1.00 mmol) in dry CH_2Cl_2 (5.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The reunited organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **147** as a pale yellow oil (38.0 mg, 23% yield). **Rf** = 0.56 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2924, 2870, 1707 (C=O), 1447, 1363, 1278, 1109, 895 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.57 (1H, dddd, *J* = 10.0, 5.0, 2.7, 2.3 Hz, H-9), 5.55–5.45 (1H, m, H-10), 2.59 (1H, dqdd, *J* = 9.1, 6.9, 4.5, 2.7 Hz, H-11), 2.44–2.37 (2H, m, H-14), 2.20–2.06 (2H, m, H-8 + H-6), 2.00–1.85 (3H, m, H-12 + H-15 + H-8), 1.80–1.63 (2H, m, H-15 + H-7), 1.47 (1H, dddd, *J* = 13.0, 13.0, 11.9, 3.7 Hz, H-6), 0.98 (3H, d, *J* = 6.9 Hz, H-24) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.2 (C-13), 133.0 (C-10), 123.5 (C-9), 58.2 (C-12), 43.0 (C-14), 41.0 (C-7), 33.1 (C-6), 33.0 (C-8), 29.1 (C-11), 27.2 (C-15), 21.1 (C-24) ppm. **MS** (APCI): m/z 165 ($M+H^+$); HRMS: found: ($M+H^+$) 165.1278. $C_{11}H_{17}O$ requires ($M+H^+$) 165.1274. Characterisation of this compound matched the compound reported in the literature.[77]

(12*R**, 7*S**)-9-Methyl-14-15-7,8,11,12-hexahydro-inden-13-one, **149**[77]



(12*S**, 7*S**)-9-Methyl-14-15-7,8,11,12-hexahydro-inden-13-one, **150**[77]



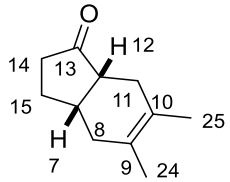
To a solution of cyclopenteone **148** (0.10 mL, 1.2 mmol) in dry CH_2Cl_2 (6.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.24 mL, 0.24 mmol) and stirred at room temperature for 30 minutes. Isoprene **133** (1.20 mL, 12.0 mmol) was added and the reaction was stirred at room temperature for 3 days. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **149** and **150** in a 1.34 : 1 ratio as a pale yellow oil (41.0 mg, 23% yield). **Rf** = 0.51 (EtOAc : hexane 10% : 90%). On a mixture **IR** (ATR): ν_{max} 2923, 1738 (C=O), 1438, 1377, 1172, 1125, 886, 783 cm^{-1}. Integration of the ^1H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.46–5.39 (1H, m, **150**), 5.36–5.32 (1H, m, **149**), 2.57–2.48 (1H, m, **149**), 2.47–2.39 (1H, m, **149**), 2.38–2.29 (3H, m, 2H x **149** + 1H x **150**), 2.28–2.23 (3H, m, 1H x **149** + 2H x **150**), 2.23–2.12 (4H, m, 1H x **149** + 3H x **150**), 2.11–1.93 (5H, m, 3H x **149** + 2H x **150**), 1.85–1.76 (3H, m, 1H x **149** + 2H x **150**), 1.71 (3H, s, **150**), 1.63 (3H, s, **149**) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 219.8 (C=O), 218.5 (C=O), 134.3 (C=C), 132.3 (C=C), 120.3 (CH), 118.7 (CH), 51.2 (CH_2), 46.6 (CH), 39.4 (CH), 37.7 (CH), 37.3 (CH_2), 34.2 (CH_2), 32.8 (CH), 30.8 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 24.8 (CH_2), 23.9 (CH_3),

23.6 (CH_3), 21.7 (CH_2) ppm. On a mixture **MS** (ESI): m/z 173 ($M+Na^+$); HRMS: found: ($M+Na^+$) 173.0938. $C_{10}H_{14}NaO$ requires ($M+Na^+$) 173.0937. Characterisation of this compound matched the compound reported in the literature[77]

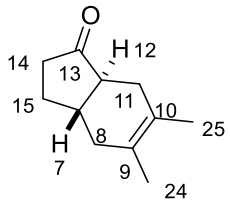
Epimerisation

To a solution of the inseparable mixture of *cis*-decalin **149** and *trans*-decalin **150** 1.34 : 1 (41.0 mg, 0.270 mmol) in dry CH_2Cl_2 (2.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.05 mL, 0.05 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (10 mL) was added and the mixture stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **149** and **150** in an unchanged 1.34 : 1 ratio as a pale yellow oil (39.0 mg, 99% yield).

(12*R**, 7*S**)-9,10-Dimethyl,14,15,7,8,11,12-hexahydro-1H-inden-13-one, **151**



(12*S**, 7*S**)-9,10-Dimethyl,14,15,7,8,11,12-hexahydro-1H-inden-13-one, **152**



To a solution of cyclopenteone **148** (0.10 mL, 1.2 mmol) in dry CH_2Cl_2 (6.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.24 mL, 0.24 mmol) and the reaction was stirred at room temperature for 30 minutes. 2,3-Dimethyl-1,3-butadiene **142** (1.40 mL, 12.0 mmol) was added and the reaction was

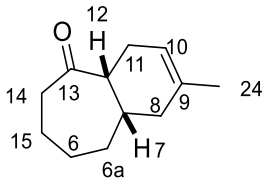
stirred at room temperature for 3 days. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and the mixture was stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **151** and **152** in a 4 : 1 ratio as a pale yellow oil (149 mg, 76% yield).

Epimerisation

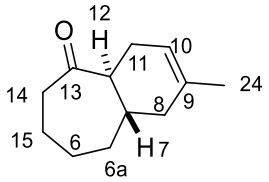
To a solution of the inseparable mixture of *cis*-decalin **151** and *trans*-decalin **152** 4 : 1 (149 mg, 0.910 mmol) in dry CH_2Cl_2 (4.50 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.18 mL, 0.18 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (10 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield as an inseparable mixture **151** and **152** in a 1.47 : 1 ratio as a pale yellow oil (113 mg, 75% yield). **Rf** = 0.54 (EtOAc : hexane 10% : 90%). On a mixture **IR** (ATR): ν_{max} 2914, 2831, 1737 (C=O), 1439, 1380, 1274, 1128, 1020 cm^{-1}. Integration of the ^1H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.49–2.41 (1H, m), 2.41–2.34 (1H, m), 2.33–2.24 (2H, m), 2.23–2.11 (6H, m), 2.10–1.88 (6H, m), 1.84–1.64 (4H, m), 1.62 (6H, s), 1.59 (3H, s), 1.56 (3H, s) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 219.7 (C=O, **151**), 218.9 (C=O, **152**), 125.6 (C=C, **152**), 124.9 (C=C, **152**), 123.9 (C=C, **151**), 123.4 (C=C, **151**), 51.9 (CH, **152**), 47.6 (CH, **151**), 39.4 (CH, **152**), 38.8 (CH_2, **152**), 37.5 (CH_2, **152**), 34.2 (CH_2, **151**), 32.8 (CH, **151**), 32.7 (CH_2, **151**), 31.0 (CH_2, **152**), 27.8 (CH_2, **151**), 27.7 (CH_2, **152**), 26.4 (CH_2, **151**), 19.3 (CH_3, **151**), 19.2 (CH_3, **152**), 19.1 (CH_3, **152**), 18.7 (CH_3, **151**) ppm. On a mixture **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1099. $C_{11}H_{16}NaO$

requires (M+Na$^+$) 187.1093. m/z 165 (M+H$^+$); HRMS: found: (M+H$^+$) 165.1276. $C_{11}H_{17}O$ requires (M+H$^+$) 165.1274.

(12*R**, 7*S**)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, **154**[77]



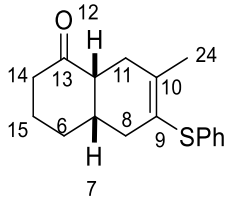
(12*S**, 7*S**)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, **155**[77]



To a solution of cycloheptenone **153** (0.10 mL, 1.0 mmol) in dry CH_2Cl_2 (5.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. Isoprene **133** (1.00 mL, 10.0 mmol) was added and the reaction was stirred at room temperature for 24 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 1 hour. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (10 : 1 *cis* : *trans*) was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **154** as a pale yellow oil (92.0 mg, 52% yield) and **155** as a pale yellow oil (8.0 mg, 5% yield). (12*R**, 7*S**)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, **154**; **Rf** = 0.48 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2920, 2854, 1693 (C=O), 1436, 1377, 1145, 942 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.39–5.34 (1H, m, H-10), 2.71–2.60 (2H, m, H-12 + H-14) 2.50–2.40 (1H, m, H-14), 2.32–2.23 (3H, m, H-15 + H-6 + H-7), 2.17–2.06 (1H, m, H-8), 1.97–1.86 (4H, m, H-8 + H-6a + H-11), 1.67-1.59 (6, m, H-24 + H-6 + H-6a + H-15) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 215.7 (C-13), 132.3

(C-9), 119.1 (C-10), 49.5 (C-12), 43.8 (C-14), 36.9 (C-8), 34.2 (C-7), 33.1 (C-11), 27.6 (C-6), 26.1 (C-15), 24.2 (C-6a), 23.7 (C-24) ppm. **MS** (ESI): m/z 201 ($M+Na^+$); HRMS: found: ($M+Na^+$) 201.1254. $C_{12}H_{18}NaO$ requires ($M+Na^+$) 201.1250. m/z 179 ($M+H^+$); HRMS: found: ($M+H^+$) 179.1435. $C_{12}H_{19}O$ requires ($M+H^+$) 179.1430. (12*S**, 7*S**)-10-Methyl-11,12,15,6,6a,7-hexahydro-1H-benzo[15]annulen-13(6H)-one, **155**; **Rf** = 0.51 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2920, 1698 (C=O), 1444, 1340, 1150, 521 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.39–5.34 (1H, m), 2.72–2.61 (2H, m), 2.51–2.40 (1H, m), 2.39–2.34 (1H, m), 2.29–2.17 (2H, m), 2.12–2.04 (3H, m), 2.02–1.87 (5H, m), 1.66 (3H, s) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 217.1 (C=O), 134.2 (C=C), 119.3 (CH), 54.9 (CH), 41.1 (CH_2), 38.6 (CH_2), 36.9 (CH), 35.4 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 23.2 (CH_3) ppm. **MS** (ESI): m/z 201 ($M+Na^+$); HRMS: found: ($M+Na^+$) 201.1253. $C_{12}H_{18}NaO$ requires ($M+Na^+$) 201.1250. m/z 179 ($M+H^+$); HRMS: found: ($M+H^+$) 179.1431. $C_{12}H_{19}O$ requires ($M+H^+$) 179.1430. Characterisation of this compound matched the compound reported in the literature.[77]

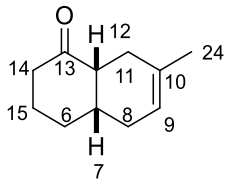
(12*R**, 7*S**)-10-Methyl-9-(phenylthio)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **156**[72]



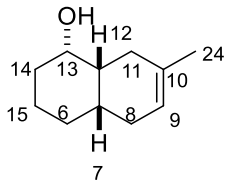
To a solution of cyclohexenone **131** (0.10 mL, 1.0 mmol) in dry CH_2Cl_2 (2.5 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol). After 15 minutes, a soluton of sulfur substituted diene **116** (704 mg, 4.00 mmol) in dry CH_2Cl_2 (2.5 mL) was added and the reaction was stirred at room temperature for 1.5 hours. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **156** as a

pale yellow solid (242 mg, 90% yield).[72] **Melting point** = 95–97 °C. **Rf** = 0.43 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2922, 1698 (C=O), 1580, 1475, 1370, 1306, 1138, 1023, 737 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.25–7.21 (3H, m, Ar-H), 7.14–7.07 (2H, m, Ar-H), 2.81–2.76 (1H, m, H-12), 2.70 (1H, dd, *J* = 18.7, 2.3 Hz, H-11), 2.48–2.43 (1H, m, H-7), 2.39 (1H, dddd, *J* = 9.9, 9.9, 5.1, 1.5 Hz, H-14), 2.33–2.25 (1H, m, H-14), 2.19–2.12 (1H, m, H-11), 2.10–2.07 (2H, m, H-8), 1.97 (3H, s, H-24), 1.95–1.80 (3H, m, H-15 + H-6), 1.73–1.65 (1H, m, H-6) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 211.9 (C-13), 139.9 (C-9), 136.6 (Ar), 128.9 (Ar-H), 127.7 (Ar-H), 125.3 (Ar-H), 120.8 (C-10), 48.6 (C-12), 40.4 (C-14), 37.4 (C-7), 33.6 (C-8), 31.3 (C-11), 28.4 (C-6), 23.9 (C-15), 21.4 (C-24) ppm. **MS** (ESI): m/z 295 ($M+Na^+$); HRMS: found: ($M+Na^+$) 295.1119. $C_{17}H_{20}NaOS$ requires ($M+Na^+$) 295.1127. m/z 273 ($M+H^+$); HRMS: found: ($M+H^+$) 273.1310. $C_{17}H_{21}OS$ requires ($M+H^+$) 273.1308. Characterisation of this compound matched the compound reported in the literature.[72]

(12*R**, 7*S**)-10-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **157**[72]



(12*R**, 7*S**)-10-Methyl-13,14,15,6,7,8,11,12-octahydronaphthalen-13-ol, **158**

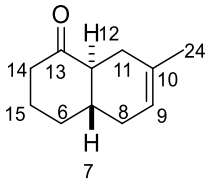


To a solution of thiophenyl *cis*-declalin **156** (75.0 mg, 0.280 mmol) in acetone (30.0 mL), was added an excess of unwashed Raney Nickel (0.240 mg, 2.80 mmol) and the reaction was stirred at room temperature for 45 minutes under H_2 atm. After this time, the reaction was filtered through a pad of celite with CH_2Cl_2 (50 mL) and the filtrate was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in

hexanes) to yield **157** as a pale yellow oil (10.0 mg, 23% yield) and **158** as a white solid (5.0 mg, 11% yield).[72] (12*R**, 7*S**)-10-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **157**; **Rf** = 0.48 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2911, 1709 (C=O), 1444, 1375, 1225, 1135, 1024, 597, 497 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.35–5.31 (1H, m, H-9), 2.74–2.68 (1H, m, H-12), 2.39 (1H, dddd, *J* = 14.2, 5.8, 5.8, 0.9 Hz, H-14), 2.36–2.23 (3H, m, H-11 + H-7 + H-14), 2.07–1.84 (5H, m, H-11 + H-6 + H-15), 1.81–1.68 (2H, m, H-8), 1.69 (3H, s, H-24) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.9 (C-13), 131.4 (C-10), 119.1 (C-9), 48.9 (C-12), 40.0 (C-14), 35.7 (C-7), 28.6 (C-11), 28.5 (C-8), 27.6 (C-15), 24.3 (C-6), 23.5 (C-24) ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1093. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. m/z 165 ($M+H^+$); HRMS: found: ($M+H^+$) 165.1257. $C_{11}H_{17}O$ requires ($M+H^+$) 165.1274. Characterisation of this compound matched the compound reported in the literature.[72]

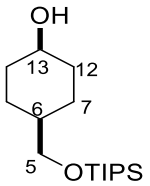
(12*R**, 7*S**)-10-Methyl-13,14,15,6,7,8,11,12-octahydronaphthalen-13-ol, **158**; **Melting point** = 74–77 °C. **Rf** = 0.22 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 3338 (C-OH), 2923, 2855, 1377, 1447, 1088, 1034, 571 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.37–5.31 (1H, m), 3.82 (1H, ddd, *J* = 10.9, 4.6, 4.6 Hz), 2.31–2.20 (1H, m), 2.01–1.90 (2H, m), 1.89–1.73 (2H, m), 1.67 (3H, s), 1.64–1.48 (1H, m), 1.47–1.40 (2H, m), 1.39–1.23 (4H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 131.3 (C=C), 119.3 (CH), 73.3 (CH), 38.7 (CH), 33.2 (CH_2), 31.5 (CH), 30.3 (CH_2), 29.1 (CH_2), 26.1 (CH_2), 23.7 (CH_2), 20.3 (CH_3) ppm. **MS** (ESI): m/z 189 ($M+Na^+$); HRMS: found: ($M+Na^+$) 189.1251. $C_{11}H_{18}NaO$ requires ($M+Na^+$) 189.1250.

(12*S**, 7*S**)-10-Methyl-15,6,7,8,11,12-hexahydronaphthalen13(2H) one, **159**[72]

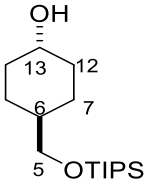


To a solution of thiophenyl *trans*-declalin **137** (171 mg; 0.630 mmol) in acetone (66.0 mL), was added an excess of unwashed Raney Nickel (540 mg, 6.30 mmol) and the reaction was stirred at room temperature for 45 minutes under H_2 atm. After this time, the reaction was filtered through a pad of celite with CH_2Cl_2 (50 mL) and the filtrate was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **159** as a white solid (61.0 mg, 60% yield).[72] **Melting point** = 49–51 °C. **Rf** = 0.51 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2902, 2844, 2828, 1701 (C=O), 1428, 1374, 1236, 1182, 845 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.36–5.29 (1H, m, H-9), 2.47–2.41 (1H, dddd, *J* = 13.5, 4.6, 2.6, 1.8 Hz, H-14), 2.36 (1H, dddd, *J* = 13.5, 13.5, 5.0, 0.9 Hz, H-14), 2.28–2.13 (3H, m, H-12 + H-8), 2.12–2.02 (2H, m, H-6 + H-11), 1.96–1.85 (2H, m, H-15), 1.76–1.69 (1H, m, H-7), 1.68 (3H, s, H-24), 1.65–1.56 (1H, m, H-11), 1.44 (1H, dddd, *J* = 13.5, 13.5, 11.4, 3.5 Hz, H-6) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.5 (C-13), 133.1 (C-9), 119.3 (C-10), 50.7 (C-12), 42.0 (C-14), 40.4 (C-7), 33.7 (C-8), 32.2 (C-6), 29.2 (C-11), 26.1 (C-15), 23.5 (C-24) ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1084. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. Characterisation of this compound matched the compound reported in the literature.[72]

(13*S**, 6*S**)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, **165**



(13*R**, 6*S**)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, **166**

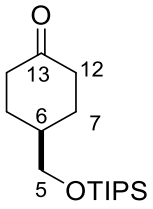


To a suspension of lithium aluminium hydride (2.07 g, 54.4 mmol) in dry THF (200 mL) at 0 ˚C, ethyl-4-oxocyclohexane carboxylate **117** (10.0 mL, 54.6 mmol) was added dropwise (10 minutes). The reaction was stirred for 45 minutes and then quenched with water (2.10 mL), followed by 15% sodium hydroxide aqueous solution (2.10 mL), and then more water (4.20 mL) and stirred for a further 30 minutes. $MgSO_4$ was added and filtered through celite, which was washed with copious amounts of Et_2O and concentrated *in vacuo* to give the title compound as a white sticky residue which was used directly in the next reaction without further purification.

To a solution of the title compound (8.23 g, 63.2 mmol) in dry CH_2Cl_2 (250 mL), were added imidazole (6.46 g, 94.8 mmol), DMAP (772 mg, 6.30 mmol) and triisopropylsilyl chloride (15.0 mL, 70.1 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, an aqueous solution of 2 M HCl (100 mL) was added and the organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give a mixture of diastereoisomers as a colourless oil. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **165** as a pale yellow oil (8.01 g, 44%) and **166** as a colourless oil (2.50 g, 14%). (13*S**, 6*S**)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, **165**; **Rf** = 0.28 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max}

3350 (C-OH), 2924, 2890, 1463, 1254, 881, 679 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.56 (1H, dddd, *J* = 10.5, 10.5, 4.1, 4.1 Hz, H-13), 3.52–3.49 (2H, m, H-5), 2.04–1.96 (2H, m, H-12), 1.88–1.79 (3H, m, H-12 + H-7), 1.52–1.40 (1H, m, H-6), 1.33–1.19 (3H, m, H-7), 1.15–0.96 (21H, m, $OSiCH(CH_3)_2$) ppm.**^{13}C NMR** (400 MHz, $CDCl_3$): δ 67.9 (C-13), 67.1 (C-5), 39.4 (C-6), 32.0 (C-12), 23.4 (C-7), 18.0 ($OSiCH(\underline{C}H_3)_2$), 12.0 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 309 ($M+Na^+$); HRMS: Found ($M+Na^+$) 309.2216. $C_{16}H_{34}NaO_2Si$ requires ($M+Na^+$) 309.2220. m/z 287 ($M+H^+$); Found ($M+H^+$), 287.2392. $C_{16}H_{35}O_2Si$ requires ($M+H^+$) 287.2401. (13*R**, 6*S**)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanol, **166**; **Rf** = 0.26 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 3261 (C-OH), 2924, 2890, 2864, 1463, 1383, 1254, 1111, 1064, 881, 679 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.03–3.97 (1H, m, H-13), 3.56–3.53 (2H, m, H-5), 1.77–1.68 (2H, m, H-12 + H-7), 1.61–1.50 (5H, m, H-12 + H-7 + H-6), 1.46–1.32 (2H, m, H-12 + H-7), 1.13–1.00 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 68.0 (C-13), 67.1 (C-5), 39.4 (C-6), 32.2 (C-12), 23.4 (C-7), 18.0 ($OSiCH(\underline{C}H_3)_2$), 12.0 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 309 ($M+Na^+$); HRMS: Found ($M+Na^+$), 309.2216. $C_{16}H_{34}NaO_2Si$ requires ($M+Na^+$) 309.2220. m/z 287 ($M+H^+$); Found ($M+H^+$), 287.2392. $C_{16}H_{35}O_2Si$ requires ($M+H^+$) 287.2401.

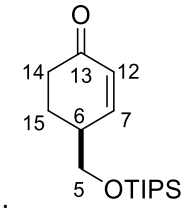
(6*S**)-6-(((Triisopropylsilyl)oxy)methyl)cyclohexanone, **160**



Dimethyl sulfoxide (3.30 mL, 46.9 mmol) was added slowly to a stirred solution of oxalyl chloride (3.81 mL, 45.0 mmol) in dry CH_2Cl_2 (360 mL) at –78 ˚C and stirred for 1 hour. A solution of cyclohexanols **165** and **166** (10.7 g, 37.5 mmol) in dry CH_2Cl_2 (40.0 mL) was added slowly and the reaction stirred at –78 ˚C for 1 hour. After this time, Et_3N (26.0 mL, 188 mmol) was added and the mixture was warmed to room temperature and after a further 2.5 hours, water (20 mL) was added, followed by aqueous solution of 2 M HCl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the

combined organic layers were washed with aqueous solution of 2 M HCl (50 mL) and brine (20 mL), dried with Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **160** as a pale yellow oil (10.6 g, 98% yield). **Rf** = 0.39 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2942, 2865, 1716 (C=O), 1463, 1120, 1103, 881, 680, 658 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.66–3.64 (2H, m, H-5), 2.42 (2H, dddd, *J* = 14.8, 4.7, 3.3, 1.8 Hz, H-12), 2.35 (2H, ddd, *J* = 14.8, 12.9, 6.1 Hz, H-12), 2.11 (2H, dddd, *J* = 13.2, 6.2, 6.1, 3.3 Hz, H-7), 1.95 (1H, dddddd, *J* = 12.9, 12.9, 6.2, 6.2, 3.3, 3.3 Hz, H-6), 1.47 (2H, dddd, *J* = 13.2, 12.9, 12.9, 4.7 Hz, H-7), 1.15–1.03 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.4 (C-13), 67.3 (C-5), 40.6 (C-12), 39.0 (C-6), 29.2 (C-7), 18.0 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 307 ($M+Na^+$); HRMS: Found ($M+Na^+$), 307.2070. $C_{16}H_{32}NaO_2Si$ requires ($M+Na^+$) 307.2064. m/z 285 ($M+H^+$); Found ($M+H^+$), 285.2249. $C_{16}H_{33}O_2Si$ requires ($M+H^+$) 285.2244.

(6*S**)-6-(((Triisopropylsilyl)oxy)methyl)cyclohex-13-enone, **115**



Example procedure for re-addition experiment

To a solution of cyclohexanone **160** (1.67 g, 5.88 mmol) in chlorobenzene (60.0 mL) were added $Pd(OAc)_2$ (66.0 mg, 0.290 mmol) and 4,4′-^{t}Bu-2,2′-dipyridyl (79.0 mg, 0.290 mmol) and the reaction was stirred at 120 ˚C in an aluminium drysyn® under a O_2 balloon. After 72 hours, additional $Pd(OAc)_2$ (66.0 mg, 0.290 mmol) and 4,4′-di-tert-butyl-2,2′-dipyridyl (79.0 mg, 0.290 mmol) were added and the O_2 balloon refreshed. After a further 44 hours, additional $Pd(OAc)_2$ (66.0 mg, 0.290 mmol) and 4,4′-di-tert-butyl-2,2′-dipyridyl (79.0 mg, 0.290 mmol) were added and the O_2 balloon refreshed. The reaction was stirred for a further 45 hours, then concentrated *in vacuo* to give a brown oil (2.50 g). The crude

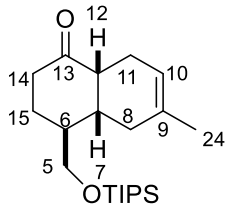
product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) and by kugelrohr disitillation to yield **115** as a pale yellow oil (1.17 g, 70% yield).

Example reaction for nitrate experiment

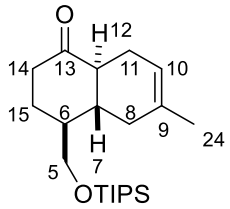
To a solution of cyclohexanone **160** (10.6 g, 37.5 mmol) in chlorobenzene (375 mL), were added $Pd(OAc)_2$ (420 mg, 1.88 mmol), 4,4'-^{t}Bu-2,2'-dipyridyl (510 mg, 1.88 mmol) and KNO_3 (1.90 g, 18.8 mmol) and the reaction was stirred at 120 ˚C in an aluminium drysyn® under a balloon of O_2. After 48 hours, additional $Pd(OAc)_2$ (420 mg, 1.88 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (510 mg, 1.88 mmol) were added and the O_2 balloon refreshed. The O_2 balloon was refreshed every 24 hours and after a further 5 days, the reaction was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) and by kugelrohr disitillation to yield **115** as a pale yellow oil (9.0 g, 85% yield, 92% conversion).

B.P. 147 ˚C @ 0.6 mbar; **Rf** = 0.38 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2942, 2891, 2865, 1682 (C=O), 1462, 1389, 1110, 881, 783, 681 cm^{-1}.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.00 (1H, ddd, *J* = 10.2, 2.7, 1.4 Hz, H-7), 6.05 (1H, dd, *J* = 10.2, 2.5 Hz, H-12), 3.76 (1H, dd, *J* = 9.6, 6.4 Hz, H-5), 3.68 (1H, dd, *J* = 9.6, 6.9 Hz, H-5), 2.63 (1H, dddddd, *J* = 9.6, 6.9, 6.4, 4.6, 2.7, 2.5 Hz, H-6), 2.54 (1H, ddd, *J* = 16.5, 4.6, 4.6 Hz, H-14), 2.39 (1H, ddd, *J* = 16.5, 12.8, 5.0 Hz, H-14), 2.10 (1H, ddddd, *J* = 13.3, 5.0, 4.6, 4.6, 1.4 Hz, H-15), 1.79 (1H, dddd, *J* = 13.3, 12.8, 9.6, 4.6 Hz, H-15), 1.15–1.00 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 199.9 (C-13), 152.1 (C-7), 129.8 (C-12), 65.8 (C-5), 29.4 (C-14), 36.7 (C-6), 25.4 (C-15), 17.9 ($OSiCH(\underline{C}H_3)_2$), 11.8 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 305 ($M+Na^+$); HRMS: Found ($M+Na^+$), 305.1899 $C_{16}H_{30}NaO_2Si$ requires ($M+Na^+$) 305.1907. m/z 283 ($M+H^+$); Found ($M+H^+$), 283.2083. $C_{16}H_{31}O_2Si$ requires ($M+H^+$) 283.2088.

(12*R**, 7*R**, 6*S**)-9-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **191**



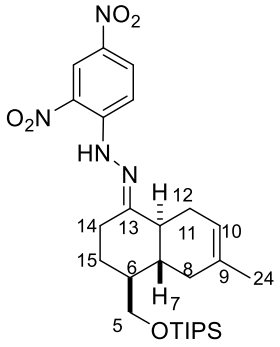
(12*S**, 7*R**, 6*S**)-9-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **192**



To solution of enone **115** (282 mg, 1.00 mmol) in dry CH_2Cl_2 (5.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.20 mL, 0.20 mmol) and the reaction was stirred at room temperature for 30 minutes. After this time, isoprene **133** (1.00 mL, 10.0 mmol) was added and the reaction was stirred at 30°C for a further 8 hours. Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **191** as a pale yellow oil (61.0 mg, 17% yield) and **192** as a pale yellow oil (80.0 mg, 23% yield). (12*R**, 7*R**, 6*S**)-9-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one **191**; **Rf** = 0.34 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2866, 1707 (C=O), 1110, 905, 729, 646, 597 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.38–5.35 (1H, m, H-10), 3.88 (1H, dd, *J* = 9.3, 5.3 Hz, H-5), 3.84 (1H, dd, *J* = 9.3, 3.2 Hz, H-5), 2.77–2.68 (1H, m, H-12), 2.52–2.44 (1H, m, H-11), 2.42–2.32 (3H, m, H-14 + H-6), 2.01–1.81 (5H, m, H-8 + H-11 + H-7 + H-15), 1.76–1.65 (1H, m, H-15), 1.63 (3H, s, H-24), 1.15–1.11 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 213.5 (C-13), 132.0 (C-9), 118.7 (C-10), 65.5 (C-5), 45.2 (C-12), 42.6 (C-7), 39.0 (C-14), 37.4 (C-6), 36.5 (C-8), 33.1 (C-11), 25.9 (C-15), 23.7 (C-24), 18.0

(OSiCH(CH_3)$_2$), 11.9 (OSiCH(CH_3)$_2$) ppm. **MS** (ESI): m/z 373 (M+Na$^+$); HRMS: found: (M+Na$^+$) 373.2540. $C_{21}H_{38}NaO_2Si$ requires (M+Na$^+$) 373.2533. m/z 351 (M+H$^+$); HRMS: found: (M+H$^+$) 351.2725. $C_{21}H_{39}O_2Si$ requires (M+H$^+$) 351.2714. (12*S**, 7*R**, 6*S**)-9-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one **192**; **Rf** = 0.38 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2924, 2865, 1714 (C=O), 1462, 1118, 881, 794, 682 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.41–5.36 (1H, m, H-10), 3.82 (1H, dd, *J* = 9.7, 2.3 Hz, H-5), 3.66 (1H, dd, *J* = 9.7, 5.1 Hz, H-5), 2.48–2.36 (2H, m, H-14), 2.22–2.11 (5H, m, H-12 + H-11 + H-15 + H-8), 1.91–1.82 (1H, m, H-11), 1.71–1.64 (3H, m, H-6 + H-7 + H-15), 1.63 (3H, s, H-24), 1.15–1.11 (21H, m, OSiCH(CH_3)$_2$) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.5 (C-13), 132.2 (C-9), 119.9 (C-10), 64.7 (C-5), 48.9 (C-12), 45.2 (C-6), 41.3 (C-14), 40.8 (C-7), 36.4 (C-11), 29.9 (C-8), 25.1 (C-15), 23.5 (C-24), 18.1 (OSiCH(CH_3)$_2$), 12.1 (OSiCH(CH_3)$_2$) ppm. **MS** (ESI): m/z 373 (M+Na$^+$); HRMS: found: (M+Na$^+$) 373.2542. $C_{21}H_{38}NaO_2Si$ requires (M+Na$^+$) 373.2533.

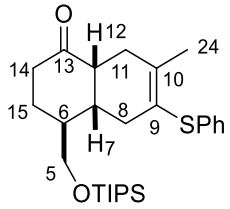
15,6,7,8,11,12-hexahydronaphthalen-13(2H)-ylidene)hydrazine, **193**



To a solution of *trans*-decalin **192** (15 mg, 0.040 mmol) in dry methanol (2.0 mL) and 3Å molecular sieves, were added 2,4-dinitrophenylhydrazine **140** (15 mg, 0.080 mmol) and glacial acetic acid (0.25 mL). The reaction was stirred at 50 °C for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (5 mL) and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL) dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 20% EtOAc in hexane) to yield **193** as an orange solid (14 mg, 67% yield). Crystalizaion method attempted: slow evaporation of solvent from a solution of **193** in a

minimum amount of $CHCl_3$ and solvent/antisolvent system such as EtOAc/hexane and CH_2Cl_2/hexane. **Melting point** = 140–142 °C. **Rf** = 0.61 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 3323, 2940, 2864, 1616 (C=N), 1518, 1461, 1116, 871 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.28 (1H, s, N-H), 9.14 (1H, d, *J* = 2.3 Hz, Ar-H), 8.31 (1H, dd, *J* = 9.6, 2.3 Hz, Ar-H), 7.98 (1H, d, *J* = 9.6 Hz, Ar-H), 5.52–5.48 (1H, m, H-10), 3.84 (1H, dd, *J* = 9.6, 3.4 Hz, H-5), 3.66 (1H, dd, *J* = 9.6, 5.0 Hz, H-5), 2.98 (1H, ddd, *J* = 14.7, 3.7, 3.7 Hz, H-14), 2.48–2.32 (2H, m, H-11), 2.31–2.19 (3H, m, H-12 + H-8 + H-14), 2.18–2.08 (2H, m, H-15), 1.94–1.82 (1H, m, H-8), 1.70 (3H, s, H-24), 1.65–1.49 (2H, m, H-6 + H-7), 1.15–0.99 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 161.9 (C=N), 145.6 (C-9), 137.5 (Ar), 132.1 (Ar), 129.9 (Ar), 128.9 (Ar-H), 123.6 (Ar-H), 120.0 (C-10), 116.4 (Ar-H), 64.6 (C-5), 45.2 (C-6), 43.6 (C-12), 40.3 (C-7), 36.4 (C-8), 28.5 (C-15), 26.9 (C-11), 26.5 (C-14), 23.4 (C-24), 18.0 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 529 ($M\text{-}H^+$); HRMS: found: ($M\text{-}H^+$) 529.2863. $C_{27}H_{41}N_4O_5Si$ requires ($M\text{-}H^+$) 529.2852.

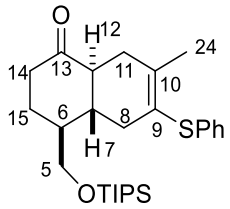
(12*R**, 7*R**, 6*S**)-10-Methyl-9-(phenylthio)-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **194**



To a solution of enone **115** (854 mg, 3.02 mmol) in dry CH_2Cl_2 (7.5 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.60 mL, 0.60 mmol). After 10 minutes, a solution of sulfur substituted diene **116** (5.30 g, 30.2 mmol) in dry CH_2Cl_2 (7.5 mL) was added and the reaction was stirred at room temperature for 1 hour. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified

by silica gel flash column chromatography (2% to 5% EtOAc in hexane) to yield **194** as a yellow oil (1.18 g, 85% yield). **Rf** = 0.48 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2925, 2864, 1703 (C=O), 1582, 1476, 1104, 1068, 882, 739 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26–7.22 (2H, m, Ar-H), 7.17–7.10 (3H, m, Ar-H), 3.82 (1H, dd, *J* = 9.9, 5.9 Hz, H-5), 3.78 (1H, dd, *J* = 9.9, 6.1 Hz, H-5), 2.90 (1H, ddd, *J* = 6.1, 5.8, 3.2 Hz, H-12), 2.71 (1H, dd, *J* = 17.2, 3.2 Hz, H-11), 2.47 (1H, dddd, *J* = 9.5, 9.5, 6.1, 4.9 Hz, H-7), 2.40–2.30 (2H, m, H-14), 2.21–2.12 (3H, m, H-8 + H-11), 2.00 (3H, s, H-24), 1.98–1.87 (2H, m, H-15), 1.78–1.72 (1H, m, H-6), 1.11–0.98 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.4 (C-13), 140.1 (C-9), 136.4 (Ar), 128.9 (Ar-H), 127.9 (Ar-H), 125.3 (Ar-H), 121.1 (C-10), 65.1 (C-5), 45.4 (C-12), 38.9 (C-6), 37.4 (C-7), 37.4 (C-14), 35.0 (C-8), 31.2 (C-11), 25.4 (C-15), 21.3 (C-24), 18.0 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 481 ($M+Na^+$); HRMS: found: ($M+Na^+$) 481.2552. $C_{27}H_{42}NaO_2SSi$ requires ($M+Na^+$) 481.2567. m/z 459 ($M+H^+$); HRMS: found: ($M+H^+$) 459.2750. $C_{27}H_{43}O_2SSi$ requires ($M+H^+$) 459.2748.

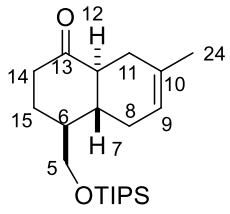
(12*S**, 7*R**, 6*S**)-10-Methyl-9-(phenylthio)-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12 hexahydronaphthalen-13(2H)-one, **195**



To a solution of thiophenyl *cis*-decalin **194** (542 mg, 1.18 mmol) in dry CH_2Cl_2 (6.0 mL), was added a 1.0 M solution of $EtAlCl_2$ in hexane (0.30 mL, 0.30 mmol) and the reaction was stirred at room temperature for 3 days. After this time, Rochelle's salt 10% aqueous solution (20 mL) was added and stirred vigorously for 16 hours. The mixture was then diluted with water (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **195** as an

orange oil (459 mg, 84% yield). **Rf** = 0.48 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2865, 1712 (C=O), 1476, 1119, 882, 739, 689 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27–7.21 (2H, m, Ar-H) 7.20–7.11 (3H, m, Ar-H), 3.65 (1H, dd, *J* = 10.1, 3.2 Hz, H-5), 3.61 (1H, dd, *J* = 10.1, 5.0 Hz, H-5), 2.57–2.42 (4H, m, H-14 + H-8 + H-11), 2.41–2.23 (2H, m, H-12 + H-11), 2.19–2.08 (2H, m, H-15 + H-8), 2.00 (3H, s, H-24), 1.87–1.70 (2H, m, H-15 + H-7), 1.70–1.60 (1H, m, H-6), 1.01–0.89 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 211.6 (C-13), 140.5 (C-9), 136.0 (Ar), 128.9 (Ar-H), 128.1 (Ar-H), 125.5 (Ar-H), 121.5 (C-10), 64.1 (C-5), 48.9 (C-12), 44.6 (C-6), 41.5 (C-7), 41.1 (C-14), 37.9 (C-8), 32.3 (C-11), 29.8 (C-15), 21.5 (C-24), 17.9 ($OSiCH(\underline{C}H_3)_2$), 11.8 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 481 ($M+Na^+$); HRMS: found: ($M+Na^+$) 481.2572. $C_{27}H_{42}NaO_2SSi$ requires ($M+Na^+$) 481.2567. m/z 459 ($M+H^+$); HRMS: found: ($M+H^+$) 459.2753. $C_{27}H_{43}O_2SSi$ requires ($M+H^+$) 459.2748.

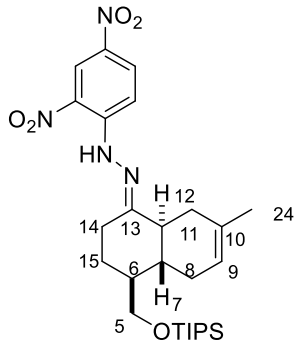
(12*S**, 7*R**, 6*S**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **114**



To a solution of sulfur *trans*-decalin **195** (401 mg, 0.880 mmol) in acetone (88.0 mL), was added an excess of unwashed Raney Nickel (0.754 mg, 8.80 mmol) and the reaction was stirred at room temperature for 40 minutes under H_2 atm. After this time, the reaction was filtered through celite with CH_2Cl_2 (50 mL) and the filtrate was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (1% to 2% EtOAc in hexane) to yield **114** as a white solid (238 mg, 77% yield). **Melting point** = 51–53 °C. **Rf** = 0.58 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2924, 2865, 1713 (C=O), 1462, 1118, 882, 682 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.37–5.26 (1H, m, H-9), 3.83 (1H, dd, *J* = 9.9, 2.5 Hz, H-5), 3.65 (1H, dd, *J* = 9.9, 5.5 Hz, H-5), 2.47–2.45 (2H, m, H-14), 2.38–2.14 (5H, m, H-12 + H-11 + H-15 + H-7 + H-8), 2.08–2.04 (1H, m, H-11),

1.94–1.83 (1H, m, H-8), 1.68 (3H, s, H-24), 1.66–1.59 (1H, m, H-6 + H-15), 1.10–1.02 (21H, m, OSiCH(CH_3)$_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.5 (C-13), 132.9 (C-10), 119.0 (C-9), 64.6 (C-5), 49.3 (C-12), 45.0 (C-6), 41.2 (C-14), 40.1 (C-7), 31.6 (C-8), 29.9 (C-11), 29.5 (C-15), 23.4 (C-24), 18.0 (OSiCH($\underline{C}H_3$)$_2$), 11.9 (OSi$\underline{C}$H(CH_3)$_2$) ppm. **MS** (ESI): m/z 373 ($M+Na^+$); HRMS: found: ($M+Na^+$) 373.2527. $C_{21}H_{38}NaO_2Si$ requires ($M+Na^+$) 373.2533.

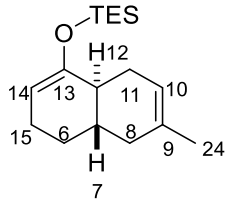
13-(2,4-Dinitrophenyl)-14-((12*S**, 7*R**, 6*S**)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-ylidene)hydrazine, **196**



To a solution of *trans*-decalin **114** (25 mg, 0.070 mmol) in dry methanol (4.0 mL) and 3Å molecular sieves, were added 2,4-dinitrophenylhydrazine **140** (28 mg, 0.14 mmol) and glacial acetic acid (0.50 mL). The reaction was stirred at 50 °C for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (5 mL) and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL) dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 20% EtOAc in hexane) to yield **196** as an orange solid (26 mg, 70% yield). Crystalizaion method: slow evaporation of solvent from a solution of **196** in a minimum amount of $CHCl_3$. **Melting point** = 71–73 °C. **Rf** = 0.61 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 3006, 2942, 2864, 1617 (C=N), 1518, 1422, 1333, 1119, 1092 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.29 (1H, s, N-H), 9.15 (1H, d, *J* = 2.8 Hz, Ar-H), 8.34 (1H, dd, *J* = 9.6, 2.8 Hz, Ar-H), 8.00 (1H, d, *J* = 9.6 Hz, Ar-H), 5.41–5.37 (1H, m, H-9), 3.83 (1H, dd, *J* = 10.1, 2.8 Hz, H-5), 3.64 (1H, dd, *J* = 10.1, 5.5 Hz, H-5), 3.01 (1H, ddd, *J* = 14.2, 3.2, 3.2 Hz, H-14), 2.45–2.30 (4H, m, H-12 + H-11 + H-8), 2.29–2.20 (1H, m, H-14), 2.18–

2.03 (1H, m, H-15), 1.94–1.82 (1H, m, H-8), 1.78 (3H, s, H-24), 1.57–1.49 (3H, m, H-6 + H-7 + H-15), 1.09–1.02 (21H, m, OSiCH(CH_3)$_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 162.1 (C=N), 145.6 (C-10), 137.5 (Ar), 132.9 (Ar), 130.0 (Ar), 128.9 (Ar-H), 123.4 (Ar-H), 119.2 (C-9), 116.4 (Ar-H), 64.6 (C-5), 45.2 (C-6), 44.0 (C-12), 39.8 (C-7), 31.7 (C-8), 31.5 (C-11), 28.6 (C-15), 26.5 (C-14), 23.7 (C-24), 18.0 (OSiCH($\underline{C}H_3$)$_2$), 11.9 (OSi$\underline{C}$H(CH_3)$_2$) ppm. **MS** (ESI): m/z 529 (M-H$^+$); HRMS: found: (M-H$^+$) 529.2847. $C_{27}H_{41}N_4O_5Si$ requires (M-H$^+$) 529.2852.

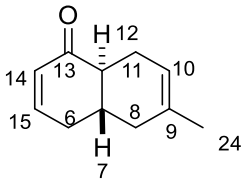
Triethyl-(((8*S**, 7*S**)-9-methyl,15,6,7,8,11,12-hexahydronaphthalen-13-yl)oxy)silane, **202**



To a solution of freshly distilled diisopropylamine (0.12 mL, 0.83 mmol) in dry THF (0.80 mL) at −78 °C, was added *n*-BuLi (0.390 mL, 2.11 M) and the solution was stirred at −78 °C for 30 minutes. A solution of the model *trans*-decalin **139** (106 mg, 0.640 mmol) in dry THF (2.41 mL) was added to the LDA solution and stirred at −78 °C for 1 hour. After this time, freshly distilled TESCl (0.15 mL, 0.89 mmol) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to warm to room temperature for 30 minutes. The reaction was then quenched with water (2 mL), extracted with Et_2O (20 mL) and the organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield **202** as a pale yellow oil (138 mg, 78% yield). **Rf** = 0.88 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2954, 2875, 1412, 1243, 1196 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.45–5.41 (1H, m, H-10), 4.81–4.78 (1H, m, H-14), 2.38 (1H, ddd, *J* = 17.4, 4.7, 4.7 Hz, H-11), 2.17–1.89 (5H, m, H-12 + H-6 + H-15 + H-7), 1.85–1.73 (3H, m, H-11 + H-8), 1.68 (3H, s, H-24), 0.68 (9H, t, *J* = 8.1 Hz, OSiCH$_2\underline{C}H_3$), 0.52 (6H, q, *J* = 8.1 Hz, OSi$\underline{C}$H$_2$CH$_3$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 152.6 (C-13), 133.9 (C-9), 121.3 (C-10), 102.9 (C-14), 41.2 (C-12), 38.1 (C-8), 37.5 (C-7), 29.3 (C-11), 29.2 (C-6), 23.7 (C-15), 23.2 (C-24), 6.4 (OSiCH$_2\underline{C}H_3$), 4.4

(OSi<u>C</u>H_2CH_3) ppm. **MS** (ESI): m/z 279 ($M+H^+$); HRMS: found: ($M+H^+$) 279.2141. $C_{17}H_{31}OSi$ requires ($M+H^+$) 279.2139.

(12*S**, 7*S**)-9-Methyl-7,8,11,12-tetrahydronaphthalen-13(4H)-one, **179**



Ito-Saegusa conditions

To a solution of TES-enol *trans*-decalin **202** (781 mg, 2.81 mmol) in dry DMSO (14.0 mL), was added $Pd(OAc)_2$ (378 mg, 1.69 mmol) and the reaction was stirred at room temperature for 1 day under an O_2 atm. After this time, the reaction was diluted with water (10 mL) and extracted with hexane (4 × 50 mL). The reunited organic layers were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexane) to yield **179** as an orange oil (234 mg, 52% yield).

IBX conditions

To a solution of TES-enol *trans*-decalin **202** (122 mg, 0.440 mmol) in dry DMSO (7.0 mL), was added IBX (616 mg, 2.20 mmol) and the reaction was stirred at 40 °C for 16 hours. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with hexane (4 × 10 mL). The reunited organic layers were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexane) to yield **179** as an orange oil (88.0 mg, 62% yield).

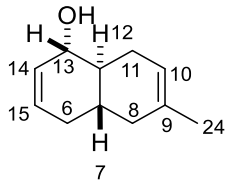
Direct palladium oxidation conditions

To a solution of *trans*-decalin **139** (100 mg, 0.610 mmol) in dry chlorobenzene (6.0 mL), were added $Pd(OAc)_2$ (7.0 mg, 3.0 µmol), 4,4'-^{t}Bu-2,2'-dipyridyl (8.0 mg, 3.0 µmol) and KNO_3 (31 mg, 0.030 mmol)

and the reaction was stirred at 120 °C for 7 days under an O_2 atm. After this time, the solvent was removed *in vacuo* and the crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexane) to yield **179** as an orange oil (23.0 mg, 23% yield).

Rf = 0.39 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 1668 (C=O), 1549, 1434, 1386, 1291, 1115, 772 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (1H, ddd, *J* = 10.1, 6.2, 1.6 Hz, H-15), 6.05 (1H, dd, *J* = 10.1, 3.2 Hz, H-14), 5.49–5.38 (1H, m, H-10), 2.56–2.45 (2H, m, H-6 + H-11), 2.27–1.91 (6H, m, H-11 + H-12 + H-8 + H-7 + H-6), 1.67 (3H, s, H-24) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 201.2 (C-13), 148.8 (C-15), 132.0 (C-9), 129.8 (C-14), 120.1 (C-10), 46.3 (C-12), 37.4 (C-8), 35.6 (C-7), 33.0 (C-6), 25.3 (C-11), 23.2 (C-24) ppm. **MS** (ESI): m/z 185 ($M+Na^+$); HRMS: found: ($M+Na^+$) 185.0930. $C_{11}H_{14}NaO$ requires ($M+Na^+$) 185.0937. m/z 163 ($M+H^+$); HRMS: found: ($M+H^+$) 163.1120. $C_{11}H_{15}O$ requires ($M+H^+$) 163.1117.

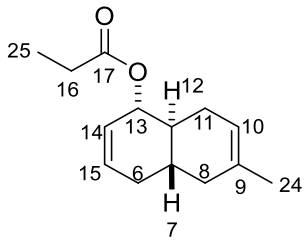
(13*S**, 12*S**, 7*S**)-9-Methyl-13,6,7,8,11,12-hexahydronaphthalen-13-ol, **224**



To a solution of enone *trans*-decalin **179** (47.0 mg, 0.290 mmol) in dry MeOH (3.0 mL) at 0 °C, was added $CeCl_3 \cdot 7H_2O$ (108 mg, 0.290 mmol) and stirred for 10 minutes. Solid $NaBH_4$ (11.0 mg, 0.290 mmol) was added and the mixture was stirred for further 10 minutes. After this time, the reaction was quenched with saturated aqueous solution of NH_4Cl (7 mL) at 0 °C and allowed to warm to room temperature for 40 minutes at which time the mixture was diluted further with water (5 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield **224** as a white solid (30.0 mg, 62% yield). **Melting point** = 73–75°C. **Rf** = 0.35 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3348 (C-OH), 2922, 1435, 1178, 1089, 1026, 959, 772 cm^{-1}. **^{1}H NMR** (400 MHz, C_6D_6): δ 5.65 (1H, ddd, *J* = 10.1, 3.3,

1.5 Hz, H-14), 5.55 (1H, dddd, *J* = 10.1, 4.8, 2.0, 2.0 Hz, H-15), 5.41–5.37 (1H, m, H-10), 3.77–3.71 (1H, m, H-13), 2.64–2.55 (1H, m, H-11), 1.97–1.89 (1H, m, H-7), 1.81–1.66 (2H, m, H-8), 1.57 (3H, s, H-24), 1.52–1.48 (2H, m, H-6), 1.39–1.31 (2H, m, H-12 + H-11) ppm. **^{13}C NMR** (400 MHz, C_6D_6): δ 132.9 (C-9), 132.5 (C-14), 127.7 (C-15), 121.2 (C-10), 74.7 (C-13), 42.8 (C-12), 38.3 (C-8), 33.4 (C-6), 33.2 (C-7), 31.4 (C-11), 24.2 (C-24) ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1095. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093.

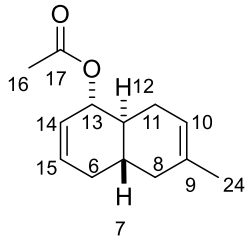
(13*S**, 12*S**, 7*S**)-9-Methyl-13,6,7,8,11,12-hexahydronaphthalen-13-yl propionate, **227**



To a solution of hydroxyl *trans*-decalin **224** (24.0 mg, 0.150 mmol) in pyridine (1.50 mL), were added DMAP (4.0 mg, 0.030 mmol) and propionyl chloride **216** (0.13 mL, 1.5 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the reaction was diluted with EtOAc (10 mL) and the pyridine was removed by washing with saturated aqueous solution of Cu_2SO_4 (3 × 10 mL). The organic layer was washed with water (4 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield **227** as a pale yellow oil (20.0 mg, 61% yield). **Rf** = 0.82 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2913, 2849, 1735 (C=O), 1179, 597 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82 (1H, dddd, *J* = 10.1, 5.0, 2.0, 2.0 Hz, H-14), 5.56 (1H, dddd, *J* = 10.1, 3.2, 1.5, 1.5 Hz, H-15), 5.42–5.32 (1H, m, H-10), 5.21–5.16 (1H, m, H-13), 2.36 (2H, q, *J* = 7.4 Hz, H-16), 2.31–2.20 (2H, m, H-6), 2.09–2.05 (1H, m, H-11), 1.93–1.84 (5H, m, H-11 + H-7 + H-8 + H-12), 1.65 (3H, s, H-24), 1.16 (3H, t, *J* = 7.4 Hz, H-25) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 174.6 (C-17), 132.7 (C-9), 129.4 (C-15), 126.8 (C-14), 119.6 (C-10), 76.1 (C-13), 34.1 (C-12), 30.1 (C-11), 29.5 (C-6), 29.4 (C-7), 27.9 (C-8), 23.4 (C-16), 22.7 (C-25),

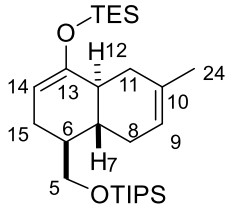
9.3 (C-24) ppm. **MS** (ESI): m/z 243 ($M+Na^+$); HRMS: found: ($M+Na^+$) 243.1365. $C_{14}H_{20}NaO_2$ requires ($M+Na^+$) 243.1356.

(13*S**, 12*S**, 7*S**)-9-Methyl-13,6,7,8,11,12-hexahydronaphthalen-13-yl acetate, **226**



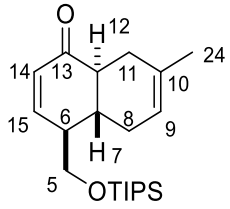
To a solution of hydroxyl *trans*-decalin **224** (17.0 mg, 0.110 mmol) in pyridine (1.0 mL), were added DMAP (3.0 mg, 0.020 mmol) and acetyl chloride **225** (0.10 mL, 1.0 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the reaction was diluted with EtOAc (10 mL) and the pyridine was removed by washing with saturated aqueous solution of Cu_2SO_4 (3 × 10 mL). The organic layer was washed with water (4 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield **226** as a pale yellow oil (17.0 mg, 76% yield). **Rf** = 0.80 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2962, 2907, 2830, 1731 (C=O), 1435, 1370, 1235, 1020 cm^{-1}. **^{1}H NMR** (400 MHz, C_6D_6): δ 5.73 (1H, dddd, *J* = 10.1, 3.5, 2.0, 1.3 Hz, H-14), 5.59 (1H, dddd, *J* = 10.1, 5.0, 2.0, 2.0 Hz, H-15), 5.39–5.33 (1H, m, H-13), 5.32–5.29 (1H, m, H-10), 2.40–2.33 (1H, m, H-11), 1.87 (1H, ddddd, *J* = 17.6, 5.0, 5.0, 1.7, 1.7 Hz, H-7), 1.80–1.75 (2H, m, H-12 + H-6), 1.77 (3H, s, H-16), 1.73–1.67 (2H, m, H-11 + H-8), 1.53 (3H, s, H-24), 1.51–1.41 (2H, m, H-8 + H-6) ppm. **^{13}C NMR** (400 MHz, C_6D_6): δ 170.3 (C-17), 132.4 (C-9), 129.2 (C-15), 127.5 (C-14), 120.0 (C-10), 76.3 (C-13), 38.8 (C-12), 37.4 (C-8), 32.9 (C-6), 32.5 (C-7), 30.5 (C-11), 23.4 (C-24), 20.8 (C-16) ppm. **MS** (ESI): m/z 229 ($M+Na^+$); HRMS: found: ($M+Na^+$) 229.1204. $C_{13}H_{18}NaO_2$ requires ($M+Na^+$) 229.1199.

Triethyl(((12*S**,7*R**, 6*S**)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13-yl)oxy)silane, **203**



To a solution of freshly distilled diisopropylamine (0.200 mL, 1.42 mmol) in dry THF (1.42 mL) at −78 °C, was added *n*-BuLi (0.72 mL, 1.97 M) and the solution was stirred at −78 °C for 30 minutes. A solution of *trans*-decalin **114** (414 mg, 1.18 mmol) in dry THF (4.48 mL) was added and the mixture was stirred at −78 °C for 1 hour. After this time, distilled TESCl (0.260 mL, 1.53 mmoL) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to warm to room temperature for 30 minutes. The reaction was then quenched with water (2 mL) and extracted with of Et_2O (20 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield **203** as a colourless oil (401 mg, 79% yield). **Rf** = 0.91 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2957, 1462, 1378, 1199, 1092, 904, 649 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.41–5.33 (1H, m, H-9), 4.84 (1H, ddd, *J* = 5.6, 1.6, 1.6 Hz, H-14), 3.77 (1H, dd, *J* = 9.6, 3.4 Hz, H-5), 3.59 (1H, dd, *J* = 9.6, 6.1 Hz, H-5), 2.31–2.27 (1H, m, H-11), 2.24–1.97 (4H, m, H-8 + H-15 + H-12), 1.80–1.71 (2H, m, H-15 + H-11), 1.68 (3H, s, H-24), 1.53–1.40 (2H, m, H-7 + H-6), 1.11–1.03 (21H, m, $OSiCH(CH_3)_2$), 0.99 (9H, t, *J* = 8.1 Hz, $OSiCH_2\underline{C}H_3$), 0.69 (6H, q, *J* = 8.1 Hz, $OSi\underline{C}H_2CH_3$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 151.9 (C-13), 134.1 (C-10), 120.3 (C-9), 102.2 (C-14), 65.1 (C-5), 41.4 (C-12), 41.1 (C-6), 38.2 (C-7), 34.1 (C-11), 30.2 (C-8), 27.7 (C-15), 23.7 (C-24), 18.1 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$), 6.8 ($OSiCH_2\underline{C}H_3$), 5.1 ($OSi\underline{C}H_2CH_3$) ppm. **MS** (ESI): m/z 487 ($M+Na^+$); HRMS: found: ($M+Na^+$) 487.3375. $C_{27}H_{52}NaO_2Si_2$ requires ($M+Na^+$) 487.3398. m/z 465 ($M+H^+$); HRMS: found: ($M+H^+$) 465.3579. $C_{27}H_{53}O_2Si_2$ requires ($M+H^+$) 465.3578.

(12*S**, 7*R**, 6*S**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-7,8,11,12-tetrahydronaphthalen-13(4H)-one, **113**



Ito-Saegusa oxidation

To a solution of TES-enol *trans*-decalin **203** (234 mg, 0.500 mmol) in dry DMSO (2.5 mL), was added $Pd(OAc)_2$ (67 mg, 0.30 mmol) and the reaction was stirred at room temperature for 2 days under O_2 atm. After this time, the reaction was diluted with water (10 mL) and extracted with MTBE (3 × 30 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexane) to yield **113** as a yellow solid (82.0 mg, 47% yield).

Direct oxidation

To a solution of *trans*-decalin **114** (100 mg, 0.290 mmol) in dry chlorobenzene (3.0 mL), were added $Pd(OAc)_2$ (3 mg, 0.02 mmol), 4,4′-^{t}Bu-2,2′-dipyridyl (4 mg, 0.02 mmol) and KNO_3 (12 mg, 0.15 mmol) and the reaction was stirred at 120 °C for 7 days under O_2 atm. After this time, the solvent was removed *in vacuo* and the crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexane) to yield **113** as a yellow solid (20 mg, 20% yield).

IBX oxidation

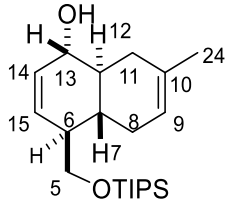
To a solution of TES-enol *trans*-decalin **203** (401 mg, 0.860 mmol) in dry DMSO (7.2 mL), was added IBX (605 mg, 2.16 mmol) and the reaction was stirred at 40 °C for 2 days. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with MTBE (5 × 30 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexane) to yield **113** as a yellow solid (188 mg, 63% yield). **Melting point** = 48–50 °C. **Rf** = 0.56 (EtOAc : hexane 10% : 90%). **IR**

(ATR): ν_{max} 2942, 2891, 2865, 1671 (C=O), 1462, 1112, 1068, 731 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.09 (1H, dd, *J* = 10.2, 1.8 Hz, H-15), 6.09 (1H, dd, *J* = 10.2, 2.8 Hz, H-14), 5.37–5.34 (1H, m, H-9), 3.98 (1H, dd, *J* = 9.8, 4.1 Hz, H-5), 3.66 (1H, dd, *J* = 9.8, 7.1 Hz, H-5), 2.47–2.30 (4H, m, H-11 + H-6 + H-12), 2.09–1.84 (3H, m, H-7 + H-8), 1.71 (3H, s, H-24), 1.13–1.01 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 201.2 (C-13), 152.1 (C-15), 133.2 (C-10), 129.1 (C-14), 118.7 (C-9), 63.7 (C-5), 45.9 (C-12), 45.8 (C-6), 36.1 (C-7), 31.0 (C-8), 30.1 (C-11), 23.4 (C-24), 17.9 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) pm. **MS** (ESI): m/z 371 ($M+Na^+$); HRMS: found: ($M+Na^+$) 371.2356. $C_{21}H_{36}NaO_2Si$ requires ($M+Na^+$) 371.2377. m/z 349 ($M+H^+$); HRMS: found: ($M+H^+$) 349.2538. $C_{21}H_{37}O_2Si$ requires ($M+H^+$) 349.2557.

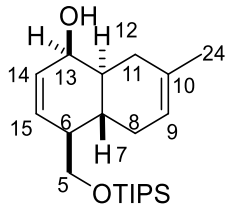
Tsuji Trost conditions

To a solution of $Pd(OAc)_2$ (1.0 mg, 2.0 µmol) and PPh_3 (1.0 mg, 3.0 µmol) in dry THF (0.20 mL), was added a solution of acetate *trans*-decalin **236** (11 mg, 0.030 mmol) in dry THF (0.20 mL) and the reaction was stirred at room temperature for 10 minutes. After this time, a pre-cooled solution at 0 °C of dimethylmalonate (4 µL, 0.04 mmoL) and NaH (60% dispersion in mineral oil, 6.0 mg, 0.10 mmoL) in dry THF (0.20 mL) was added and the reaction was stirred at 60 °C for 16 hours. The reaction was cooled to room temperature and diluted with Et_2O (10 mL), washed with water (2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 20% EtOAc in hexanes) to yield **113** as a yellow solid (4.0 mg, 38% yield) and **232** as a pale yellow oil (3.0 mg, 29% yield).

(13*S**, 12*S**, 7*R**, 6*S**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-ol, **232**



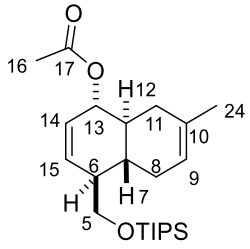
(13*R**, 12*S**, 6*S**, 7*R**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-ol, **215**



To a solution of enone *trans*-decalin **113** (30 mg, 0.090 mmol) in dry THF (0.90 mL) at −78 °C, was added a 1.0 M solution of Dibal-H in toluene (0.09 mL, 0.09 mmol) and the reaction was stirred at −78 °C for 30 minutes. After this time, the reaction was quenched with acetone (1.20 mL) at −78 °C, warmed to room temperature and then Rochelle's salt 10% aqueous solution (10 mL) was added and stirred for 16 hours. The mixture was diluted with water (5 mL), extracted with EtOAc (4 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexane) to yield **232** as a pale yellow oil (25.0 mg, 79% yield) and **215** as a pale yellow oil (5.0 mg, 16% yield). (13*S**, 12*S**, 7*R**, 6*S**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-ol, **232**; **Rf** = 0.41 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3318 (C-OH), 2941, 2863, 1462, 1390, 1114, 1091, 881 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84 (1H, ddd, *J* = 10.1, 2.3, 2.3 Hz, H-14), 5.72 (1H, ddd, *J* = 10.1, 2.3, 2.3 Hz, H-15), 5.39–5.34 (1H, m, H-9), 3.91–3.87 (1H, m, H-13), 3.81 (1H, dd, *J* = 9.6, 4.1 Hz, H-5), 3.51 (1H, dd, *J* = 9.6, 7.3 Hz, H-5), 2.45 (1H, dd, *J* = 15.1, 5.5 Hz, H-11), 2.40–2.31 (1H, m, H-8), 2.08–1.99 (1H, m, H-6), 1.86–1.75 (2H, m, H-11 + H-8), 1.68 (3H, s, H-24), 1.52–1.45 (1H, m, H-12), 1.43–1.37 (1H, m, H-7), 1.14–0.99 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 132.7 (C-10), 130.8 (C-14), 130.6 (C-15), 119.8 (C-9), 73.9 (C-13),

65.6 (C-5), 45.9 (C-6), 42.3 (C-12), 34.9 (C-11), 33.3 (C-7), 31.3 (C-8), 23.4 (C-24), 18.0 (OSiCH($\underline{C}H_3)_2$), 11.9 (OSi$\underline{C}$H$(CH_3)_2$) ppm. **MS** (ESI): m/z 373 ($M+Na^+$); HRMS: found: ($M+Na^+$) 373.2517. $C_{21}H_{38}NaO_2Si$ requires ($M+Na^+$) 373.2533. m/z 351 ($M+H^+$); HRMS: found: ($M+H^+$) 351.2677. $C_{21}H_{39}O_2Si$ requires ($M+H^+$) 351.2714. (13*R**, 12*S**, 6*S**, 7*R**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-ol, **215**; **Rf** = 0.38 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3386 (C-OH), 2922, 2864, 1462, 1379, 1093, 1013, 930 cm^{-1}. **^{1}H NMR** (500 MHz, C_6D_6): δ 6.04 (1H, ddd, *J* = 9.7, 5.6, 2.4 Hz, H-14), 5.94 (1H, dd, *J* = 9.7, 2.4 Hz, H-15), 5.43–5.37 (1H, m, H-9), 3.78–3.72 (1H, m, H-13), 3.68 (1H, dd, *J* = 9.4, 3.9 Hz, H-5), 3.49 (1H, dd, *J* = 9.4, 6.7 Hz, H-5), 2.62–2.53 (1H, m, H-11), 2.41–2.32 (1H, m, H-8), 1.89–1.82 (1H, m, H-6), 1.72–1.69 (3H, m, H-11 + H-7 + H-8), 1.68 (3H, s, H-24), 1.62–1.58 (1H, m, H-12), 1.12–1.02 (21H, m, OSiCH$(CH_3)_2$) ppm. **^{13}C NMR** (500 MHz, C_6D_6): δ 133.8 (C-10), 132.9 (C-14), 130.1 (C-15), 119.3 (C-9), 65.8 (C-13), 64.9 (C-5), 46.9 (C-6), 38.9 (C-12), 32.4 (C-8), 32.1 (C-11), 28.6 (C-7), 23.8 (C-24), 18.2 (OSiCH($\underline{C}H_3)_2$), 12.3 (OSi$\underline{C}$H$(CH_3)_2$) ppm. **MS** (ESI): m/z 373 ($M+Na^+$); HRMS: (ESI): m/z ($M+Na^+$) 373.2518, $C_{21}H_{38}NaO_2Si$ requires ($M+Na^+$) 373.2533.

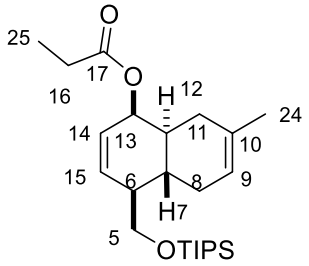
(13*S**, 12*S**, 7*R**, 6*S**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-yl acetate, **238**



To a solution of hydroxyl *trans*-decalin **232** (25 mg, 0.080 mmol) in pyridine (1.0 mL), were added DMAP (2 mg, 0.01 mmol) and acetyl chloride **225** (0.050 mL, 0.80 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous solution of Cu_2SO_4 (3 × 10 mL), water (2 × 10 mL) and brine (2 × 10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield **238** as a pale yellow oil (18.0 mg,

58% yield). **Rf** = 0.83 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2942, 2922, 2865, 1728 (C=O), 1462, 1368, 1238, 732 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.91 (1H, ddd, *J* = 10.1, 2.3, 2.3 Hz, H-14), 5.62 (1H, ddd, *J* = 10.1, 2.3, 2.3 Hz, H-15), 5.43–5.37 (1H, m, H-9), 5.19–5.11 (1H, m, H-13), 3.81 (1H, dd, *J* = 9.6, 4.6 Hz, H-5), 3.52 (1H, dd, *J* = 9.6, 7.3 Hz, H-5), 2.39 (1H, ddd, *J* = 16.9, 6.0, 6.0 Hz, H-8), 2.20–2.13 (1H, m, H-11), 2.11 (3H, s, H-16), 2.05 (1H, ddddd, *J* = 9.6, 7.3, 4.6, 2.3, 2.3 Hz, H-6), 1.80–1.78 (3H, m, H-11 + H-8 + H-12), 1.65 (3H, s, H-24), 1.55 (1H, dddd, *J* = 12.4, 9.6, 9.6, 6.0 Hz, H-7), 1.13–0.99 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 171.2 (C-17), 132.4 (C-10), 132.2 (C-14), 126.6 (C-15), 119.3 (C-9), 76.1 (C-13), 65.5 (C-5), 45.7 (C-6), 38.6 (C-12), 34.6 (C-11), 33.3 (C-7), 31.2 (C-8), 23.3 (C-24), 21.3 (C-16), 18.0 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 415 ($M+Na^+$); HRMS: found: ($M+Na^+$) 415.2642. $C_{23}H_{40}NaO_3Si$ requires ($M+Na^+$) 415.2639. m/z 393 ($M+H^+$); HRMS: found: ($M+H^+$) 393.2884. $C_{23}H_{41}O_3Si$ requires ($M+H^+$) 393.2819.

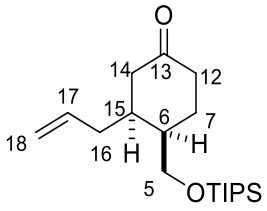
(13*R**, 12*S**, 7*R**, 6*S**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-13,6,7,8,11,12-hexahydronaphthalen-13-yl propionate, **112**



To a solution of hydroxyl *trans*-decalin **215** (8.0 mg, 0.023 mmol) in pyridine (1.0 mL), were added DMAP (1.0 mg, 0.050 mmol) and propionyl chloride **216** (0.05 mL, 0.23 mmol) and the reaction was stirred at room temperature for 5 hours. After this time, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous solution of Cu_2SO_4 (3 × 10 mL), water (2 × 10 mL) and brine (2 × 10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield **112** as a pale yellow oil (5.0 mg, 62% yield). **Rf** = 0.83 (EtOAc : hexane 10 % : 90%). **IR** (ATR): ν_{max} 2941, 2865, 1724 (C=O), 1462, 1189, 1066, 907, 731 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.08 (1H, dd, *J* = 10.1, 2.4 Hz, H-14), 5.95 (1H,

ddd, *J* = 10.1, 5.0, 2.4 Hz, H-15), 5.39–5.33 (1H, m, H-9), 5.17–5.13 (1H, m, H-13), 3.85 (1H, dd, *J* = 9.5, 4.4 Hz, H-5), 3.58 (1H, dd, *J* = 9.5, 7.4 Hz, H-5), 2.46–2.39 (1H, m, H-8), 2.31 (2H, q, *J* = 7.6 Hz, H-16), 1.99–1.97 (2H, m, H-8 + H-11), 1.83–1.80 (3H, m, H-11 + H-12 + H-6), 1.79–1.70 (1H, m, H-7), 1.67 (3H, s, H-24), 1.14 (3H, t, *J* = 7.6 Hz, H-25), 1.08–1.05 (21H, m, OSiCH(CH_3)$_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 174.3 (C-17), 135.3 (C-10), 132.9 (C-14), 124.5 (C-15), 119.3 (C-9), 67.9 (C-13), 65.5 (C-5), 46.8 (C-6), 36.7 (C-12), 31.9 (C-8), 31.3 (C-11), 29.0 (C-7), 27.8 (C-16), 23.5 (C-24), 18.0 (OSiCH($\underline{C}H_3$)$_2$), 11.9 (OSi$\underline{C}$H(CH_3)$_2$), 9.2 (C-25) ppm. **MS** (ESI): m/z 429 ($M+Na^+$); HRMS: found: ($M+Na^+$) 429.2788. $C_{24}H_{42}NaO_3Si$ requires ($M+Na^+$) 429.2795.

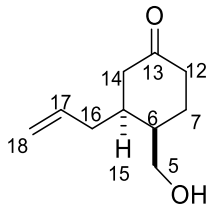
(15*S**, 6*R**)-15-Allyl-6-(((triisopropylsilyl)oxy)methyl)cyclohexanone, **183**



To a solution of enone **115** (50 mg, 0.18 mmol) in dry CH_2Cl_2 (1.8 mL) at –78 °C, was added $TiCl_4$ (0.030 mL, 0.25 mmol) and the orange solution was stirred for 5 minutes. Allyltrimethylsilane **250** (0.030 mL, 0.24 mmol) was added and the reaction was stirred at –78 °C for a further 30 minutes. After this time, saturated aqueous solution of $NaHCO_3$ (8 mL) was added at –78 °C and then allowed to warm to room temperature for 30 minutes. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **183** as a pale yellow oil (34.0 mg, 59% yield). **Rf** = 0.52 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2941, 2864, 1714 (C=O), 1462, 1382, 1246, 1109, 1066 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.72 (1H, dddd, *J* = 16.5, 10.6, 8.2, 5.5 Hz, H-17), 5.08–5.05 (1H, m, H-18), 5.04–5.01 (1H, m,H-18), 3.86–3.74 (2H, m, H-5), 2.48–2.39 (2H, m, H-14), 2.37–2.30 (3H, m, H-12 + H-7), 2.19–2.16 (2H, m, H-6 + H-16), 1.88–1.78 (3H, m, H-16 + H-

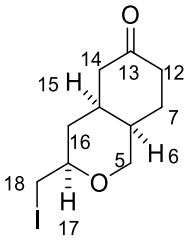
15 + H-7), 1.09–1.03 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.2 (C-13), 136.2 (C-17), 116.9 (C-18), 63.3 (C-5), 44.7 (C-14), 40.6 (C-6), 39.6 (C-12), 37.9 (C-15), 33.6 (C-16), 25.4 (C-7), 18.0 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 347 ($M+Na^+$); HRMS: found: ($M+Na^+$) 347.2380. $C_{19}H_{36}NaO_2Si$ requires ($M+Na^+$) 347.2377. m/z 325 ($M+H^+$); HRMS: found: ($M+H^+$) 325.2560. $C_{19}H_{37}O_2Si$ requires ($M+H^+$) 325.2557.

(15*S**, 6*R**)-15-Allyl-6-hydroxymethyl-cyclohexanone, **263**

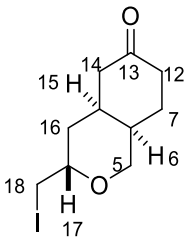


In a plastic vial, to a solution of allyl-cyclohexanone **183** (30 mg, 0.090 mmol) in dry pyridine (0.90 mL), was added hydrogen fluoride 70% in pyridine (0.070 mL, 3.6 mmol) and the reaction was stirred at room temperature for 24 hours. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with 2 M HCl (2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (20% to 50% EtOAc in hexanes) to yield **263** as a pale yellow oil (13.0 mg, 98% yield). **Rf** = 0.25 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3405 (C-OH), 2923, 1702 (C=O), 1035, 913, 597 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.73 (1H, dddd, *J* = 16.5, 10.6, 8.2, 5.5 Hz, H-17), 5.11–5.06 (1H, m, H-18), 5.06–5.02 (1H, m, H-18), 3.76 (1H, dd, *J* = 10.6, 6.9 Hz, H-5), 3.71 (1H, dd, *J* = 10.6, 7.1 Hz, H-5), 2.47–2.35 (3H, m, H-14 + H-12), 2.34–2.23 (2H, m, H-12 + H-15), 2.23–2.13 (2H, m, H-16 + H-6), 1.94–1.78 (3H, m, H-7 + H-16) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 211.9 (C-13), 136.2 (C-17), 117.3 (C-18), 62.9 (C-5), 44.9 (C-14), 40.6 (C-6), 39.6 (C-12), 30.1 (C-15), 33.8 (C-16), 25.4 (C-7) ppm. **MS** (APCI): m/z 169 ($M+H^+$); HRMS: found: ($M+H^+$) 169.1226. $C_{10}H_{17}O_2$ requires ($M+H^+$) 169.1223.

(17*R**, 15*S**,6*R**)-15-Iodomethyl-octahydro-isochromen-13-one, **264**



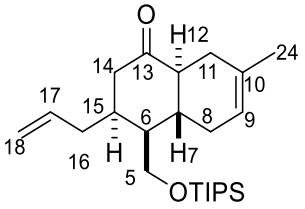
(17*S**, 15*S**,6*R**)-15-Iodomethyl-octahydro-isochromen-13-one, **265**



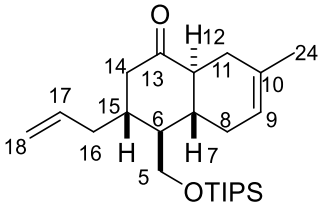
To a solution of allyl-hydroxyl-cyclohexanone **263** (13 mg, 0.090 mmol) in dry CH_3CN (0.90 mL) at 0 °C, were added iodine (28 mg, 0.11 mmol) and solid $NaHCO_3$ (15 mg, 0.18 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of Na_2SO_3 (2 mL) and extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with 2 M HCl (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (20% to 40% EtOAc in hexanes) to yield **264** as a white solid (14.0 mg, 54% yield) and **265** as a pale yellow oil (8.0 mg, 31% yield).[120] (17*R**, 15*S**,6*R**)-15-Iodomethyl-octahydro-isochromen-13-one, **264**; Crystallized using a solvent/antisolvent system: EtOAc/hexane. **Rf** = 0.44 (EtOAc : hexane 20% : 80%). **Melting point** = 57–59 °C. **IR** (ATR): ν_{max} 2925, 2853, 1709 (C=O), 1463, 1376, 1108, 1095, 904 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.92 (1H, dd, *J* = 11.4, 0.6 Hz, H-5), 3.72 (1H, dd, *J* = 11.4, 2.6 Hz, H-5), 3.30 (1H, dddd, *J* = 11.2, 6.3, 4.4, 2.1 Hz, H-17), 3.22 (1H, dd, *J* = 10.6, 4.4 Hz, H-18), 3.17 (1H, dd, *J* = 10.6, 6.3 Hz, H-18), 2.66 (1H, dd, *J* = 14.3, 6.3 Hz, H-14), 2.46–2.38 (3H, m, H-16 + H-12), 2.35–2.21 (3H, m, H-16 + H-15 + H-7), 2.18 (1H, ddd, *J* = 14.3, 1.6, 1.6 Hz, H-14), 2.03–1.96 (2H, m, H-6 + H-7) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 210.7 (C-13), 76.9 (C-17), 71.6 (C-5), 46.6 (C-14), 40.5 (C-12), 36.4 (C-6), 34.5 (C-15), 32.8 (C-

16), 25.1 (C-7), 9.1 (C-18) ppm. **MS** (APCI): m/z 295 ($M+H^+$); HRMS: found: ($M+H^+$) 295.0188. $C_{10}H_{16}IO_2$ requires ($M+H^+$) 295.0189. (17*S**, 15*S**,6*R**)-15-Iodomethyl-octahydro-isochromen-13-one, **265**; **Rf** = 0.41 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 2922, 2852, 1711 (C=O), 1459, 1081 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.06 (1H, dd, *J* = 11.6, 3.7 Hz, H-5), 3.75 (1H, dd, *J* = 11.6, 4.7 Hz, H-5), 3.65–2.59 (1H, m, H-17), 3.25–3.19 (2H, m, H-18), 2.52–2.37 (5H, m, H-14 + H-6 + H-12), 2.29–2.25 (3H, m, H-16 + H-15), 1.94–1.88 (2H, m, H-7) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 209.6 (C-13), 76.1 (C-17), 66.3 (C-5), 48.6 (C-14), 42.3 (C-6), 40.8 (C-12), 38.6 (C-15), 31.9 (C-16), 26.5 (C-7), 8.9 (C-18) ppm. **MS** (APCI): m/z 295 ($M+H^+$); HRMS: found: ($M+H^+$) 295.0186. $C_{10}H_{16}IO_2$ requires ($M+H^+$) 295.0189.

(15*S**, 12*S**, 7*R**, 6*S**)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **266**



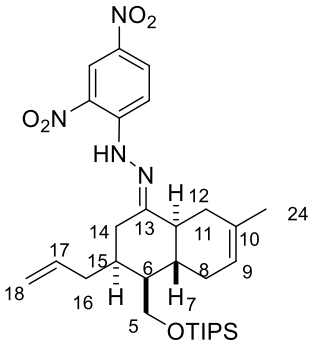
(15*R**, 12*S**, 7*R**, 6*S**)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **267**



To a solution of enone *trans*-decalin **113** (40 mg, 0.12 mmol) in dry CH_2Cl_2 (1.2 mL) at –78 °C, was added $TiCl_4$ (0.020 mL, 0.14 mmol). After 5 minutes allyltrimethylsilane **250** (0.020 mL, 0.13 mmol) was also added and the reaction was stirred at –78 °C for 30 minutes. After this time, saturated aqueous solution of $NaHCO_3$ (4.5 mL) was added at –78 °C, stirred for 45 minutes and then allowed to warm to room temperature for 30 minutes. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was

purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **266** as a pale yellow oil (25.0 mg, 61% yield) and **267** as a pale yellow oil (3.0 mg, 7% yield). (15*S**, 12*S**, 7*R**, 6*S**)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **266**; **Rf** = 0.52 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2921, 2864, 1710 (C=O), 1462, 1331, 1118, 1097, 881 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.72 (1H, dddd, *J* = 16.5, 10.6, 8.2, 5.5 Hz, H-17), 5.14–5.12 (1H, m, H-9), 5.07–5.01 (2H, m, H-18), 3.76 (1H, dd, *J* = 9.9, 1.4 Hz, H-5), 3.62 (1H, dd, *J* = 9.9, 9.9 Hz, H-5), 2.60–2.51 (2H, m, H-15 + H-14), 2.45–2.40 (1H, m, H-14), 2.32–2.23 (2H, m, H-12 + H-16), 2.18–2.12 (2H, m, H-8 + H-11), 2.10–1.99 (2H, m, H-6 + H-11), 1.94–1.84 (1H, m, H-8), 1.68 (3H, s, H-24), 1.65–1.56 (2H, m, H-16 + H-7), 1.10–1.02 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.2 (C-13), 136.5 (C-17), 133.2 (C-10), 119.1 (C-9), 116.9 (C-18), 62.6 (C-5), 49.7 (C-12), 47.3 (C-6), 44.7 (C-14), 36.9 (C-15), 36.8 (C-7), 31.8 (C-16), 31.9 (C-8), 29.4 (C-11), 23.4 (C-24), 18.1 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 413 ($M+Na^+$); HRMS: found: ($M+Na^+$) 413.2830. $C_{24}H_{42}NaO_2Si$ requires ($M+Na^+$) 413.2846. m/z 391 ($M+H^+$); HRMS: found: ($M+H^+$) 391.3033. $C_{24}H_{43}O_2Si$ requires ($M+H^+$) 391.3027. (15*R**, 12*S**, 7*R**, 6*S**)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **267**; **Rf** = 0.54 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 2865, 1712 (C=O), 1462, 1247, 1097, 873, 685 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.77 (1H, dddd, *J* = 16.5, 10.6, 8.2, 5.5 Hz, H-17), 5.34–5.32 (1H, m, H-9), 4.99–4.97 (2H, m, H-18), 3.85 (1H, dd, *J* = 9.2, 4.9 Hz, H-5), 3.60 (1H, dd, *J* = 9.2, 9.2 Hz, H-5), 2.65–2.60 (1H, m, H-15), 2.53 (1H, dd, *J* = 13.2, 3.2 Hz, H-14), 2.45 (1H, dd, *J* = 13.2, 5.8 Hz, H-14), 2.28–2.15 (3H, m, H-16 + H-12 + H-8), 2.12–2.05 (2H, m, H-11), 1.93–1.81 (1H, m, H-6), 1.86–1.80 (1H, m, H-8), 1.75–1.70 (1H, m, H-16), 1.68 (3H, s, H-24), 1.66–1.58 (1H, m, H-7), 1.10–1.05 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.2 (C-13), 137.0 (C-17), 133.2 (C-10), 119.3 (C-9), 116.1 (C-18), 62.6 (C-5), 49.7 (C-12), 48.1 (C-6), 45.1 (C-14), 39.8 (C-16), 37.2 (C-7), 34.2 (C-15), 33.7 (C-8), 32.1 (C-11), 29.7 (C-24), 18.1 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 413 ($M+Na^+$); HRMS: found: ($M+Na^+$) 413.2842. $C_{24}H_{42}NaO_2Si$ requires ($M+Na^+$) 413.2846.

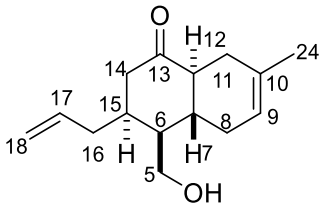
13-((15*S**, 12*S**, 7*S**, 6*S**)-15-Allyl-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-ylidene)-14-(2,4-dinitrophenyl)hydrazine, **268**



To a solution of allyl-*trans*-decalin **266** (10 mg, 0.030 mmol) in dry MeOH (1.0 mL) and 3Å molecular sieves, were added 2,4-dinitrophenyl hydrazine **140** (12 mg, 0.060 mmol) and glacial acetic (0.50 mL) and the reaction was stirred at 50 °C with for 16 hours. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **268** as an orange solid (4.0 mg, 24% yield). Crystallization method: slow evaporation of CH_2Cl_2 from a solution of **268** in CH_2Cl_2. **Melting point** = 135–137 °C. **Rf** = 0.58 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 1617 (C=N), 1334, 1099 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.23 (1H, s, N-H), 9.15 (1H, d, *J* = 2.6 Hz, Ar-H), 8.33 (1H, d, *J* = 9.6, 2.6 Hz, Ar-H), 8.00 (1H, d, *J* = 9.6 Hz, Ar-H), 5.82–5.72 (1H, m, H-17), 5.41–5.38 (1H, m , H-9), 5.07–4.87 (2H, m, H-18), 3.91 (1H, dd, *J* = 9.7, 5.5 Hz, H-5), 3.61 (1H, dd, *J* = 9.7, 9.7 Hz, H-5), 3.01 (1H, dd, *J* = 14.8, 3.8 Hz, H-14), 2.61–2.52 (1H, m, H-15), 2.46–2.41 (1H, m, H-12), 2.39–2.33 (3H, m, H-16 + H-14 + H-11), 2.27–2.26 (2H, m, H-8), 1.91–1.88 (2H, m, H-6 + H-11), 1.77 (3H, s, H-24), 1.71–1.58 (2H, m, H-16 + H-7), 1.13–1.02 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 160.9 (C=N), 145.4 (Ar), 137.5 (C-17), 137.3 (C-10), 133.3 (Ar), 129.9 (Ar), 128.8 (Ar-H), 123.7 (C-9), 119.2 (Ar-H), 117.3 (Ar-H), 116.3 (C-18), 62.7 (C-5), 47.5 (C-6), 44.2 (C-12), 37.1 (C-8), 35.9 (C-15), 32.2 (C-7), 31.6 (C-16),

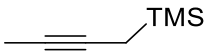
30.7 (C-11), 29.7(C-14), 23.6 (C-24), 18.1 (OSiCH($\underline{C}H_3)_2$), 11.9 (OSi$\underline{C}$H$(CH_3)_2$) ppm. **MS** (ESI): m/z 569 (M-H^+); HRMS: found: (M-H^+) 569.3209. $C_{30}H_{45}N_4O_5Si$ requires (M-H^+) 569.3165.

(15*S**, 12*S**, 7*R**, 6*S**)-15-Allyl-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **269**



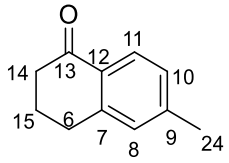
In a plastic vial, to a solution of allyl-*trans*-decalin **266** (20 mg, 0.050 mmol) in pyridine (1.0 mL), was added hydrogen fluoride 70% in pyridine (0.200 mL, 1.47 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 2 M HCl (20 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 40% EtOAc in hexanes) to yield **269** as a pale yellow oil (10.0 mg, 85% yield). **Rf** = 0.28 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3417 (C-OH), 2919, 2852, 1704 (C=O), 1436, 1376, 1027, 911 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.80–5.71 (1H, m, H-17), 5.36–5.31 (1H, m, H-9), 5.10–5.01 (2H, m, H-18), 3.90 (1H, dd, *J* = 10.8, 4.9 Hz, H-5), 3.65 (1H, dd, *J* = 10.8, 9.2 Hz, H-5), 2.56 (1H, dd, *J* = 12.8, 2.7 Hz, H-14), 2.53–2.43 (3H, m, H-15 + H-14 + H-16), 2.39–2.13 (5H, m, H-12 + H-6 + H-8 + H-11 + H-16), 2.12–2.04 (2H, m, H-7 + H-11), 2.00–1.87 (1H, m, H-8), 1.71–1.65 (3H, s, H-24) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 211.7 (C-13), 136.4 (C-17), 133.2 (C-10), 119.1 (C-9), 117.2 (C-18), 62.3 (C-5), 49.8 (C-12), 47.1 (C-6), 45.0 (C-14), 37.1 (C-15), 37.1 (C-7), 31.8 (C-11), 29.7 (C-16), 29.4 (C-8), 23.4 (C-24) ppm. **MS** (ESI): m/z 257 (M+Na^+); HRMS: found: (M+Na^+) 257.1503. $C_{15}H_{22}NaO_2$ requires (M+Na^+) 257.1512. m/z 235 (M+H^+); HRMS: found: (M+H^+) 235.1672. $C_{15}H_{23}O_2$ requires (M+H^+) 235.1693.

But-2-yn-1-yltrimethylsilane, **271**[123]



To a suspension of magnesium (290 mg, 11.9 mmol) in dry Et_2O (2.71 mL), was added mercurydichloride (40 mg, 0.15 mmol) and stirred for 30 minutes. The grey mixture was cooled to 0 °C and a solution of 1-bromo-2-butyne **273** (0.50 mL, 5.9 mmol) in dry Et_2O (5.50 mL) was added over 10 minutes. The resulting mixture was stirred at room temperature for 30 minutes and then re-cooled to 0 °C before the addition of TMSCl (0.75 mL, 5.9 mmol). The resulting reaction was stirred vigorously at room temperature for 16 hours. The reaction was then filtrated through celite with Et_2O (10 mL) and the filtrate was distilled at atmospheric pressure (80–90 °C) to yield the desired compound **271** as a colourless liquid (50.0 mg, 6% yield). [123] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.78 (3H, t, *J* = 2.8 Hz), 1.40 (2H, q, *J* = 2.8 Hz), 0.08 (9H, s, $Si(CH_3)_3$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 76.7 (CH), 74.1 (CH), 7.2 (CH_3), 3.9 (CH_2), 1.8 ($Si(CH_3)_3$) ppm. This compound was characterized only by ^{1}H NMR due to its volatilty and instability, and the data matched the literature.[123]

9-methyl-15,6-dihydronaphthalen-13(2H)-one, **207**[94]



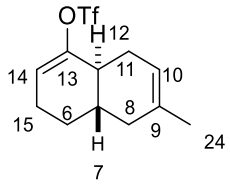
To a solution of freshly distilled diisopropylamine (0.150 mL, 1.09 mmol) in dry THF (1.09 mL) at –78 °C, was added *n*-BuLi (0.510 mL, 2.15 M) and the resulting solution was stirred at –78 °C for 30 minutes. At this time, a solution of model *trans*-decalin **139** (89 mg, 0.54 mmol) in dry THF (1.61 mL) was introduced and the resulting solution was stirred for 1 hour at –78 °C. Freshly distilled TMSCl (0.210 mL, 1.62 mmol) was added and the reaction was stirred at –78 °C for a further 30 minutes and then allowed to warm to room temperature for 1 hour. The reaction was cooled to 0 °C and NBS (recriystallised, 125 mg, 0.710 mmol) was added as a solid, and the resulting reaction was stirred at 0

°C for 3 hours. The reaction was allowed to warm to room temperature and DBU (0.81 mL, 5.40 mmol) was added and the reaction was stirred at 50 °C for 16 hours. A solution of 2 M HCl (10 mL) was added and stirred for 2 hours and then the mixture was washed with saturated aqueous solution of $NaHCO_3$ (3 × 10 mL) and brine (20 mL) dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% to 10% EtOAc in hexanes) to yield **207** as a pale yellow oil (11.0 mg, 14% yield).[91]

IBX oxidations

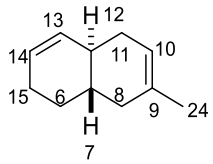
To a solution of IBX (207 mg, 0.740 mmol) in dry DMSO (2.0 mL) at 40 °C, was added a solution of model *trans*-decalin **139** (61 mg, 0.37 mmol) in dry DMSO (0.47 mL) and the reaction was stirred at 95 °C for 16 hours. After this time, the reaction was cooled to room temperature and quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with MTBE (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **207** as a pale yellow oil (12.0 mg, 20% yield).[93] **Rf** = 0.38 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 2854, 1680 (C=O), 1435, 1347, 1284, 1184, 817 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 (1H, d, *J* = 8.0 Hz, Ar-H), 7.12 (1H, d, *J* = 8.0 Hz, Ar-H), 7.07 (1H, s, Ar-H), 2.93 (2H, t, *J* = 6.2 Hz, H-14), 2.64 (2H, t, *J* = 6.4 Hz, H-6), 2.40 (3H, s, H-24), 2.19–2.08 (2H, m, H-15) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 198.2 (C-13), 144.6 (Ar), 144.2 (Ar), 130.3 (Ar), 129.2 (Ar-H), 127.6 (Ar-H), 127.3 (Ar-H), 39.1 (C-14), 29.7 (C-6), 23.3 (C-15), 21.7 (C-24) ppm. **MS** (ESI): m/z 161 ($M+H^+$); HRMS: found: ($M+H^+$) 161.0968. $C_{11}H_{13}O$ requires ($M+H^+$) 161.0961. Characterisation of this compound matched the compound reported in the literature.[94]

(12*S**, 7*S**)-9-Methyl-15,6,7,8,11,12-hexahydronaphthalen-13-yl trifluoromethanesulfonate, **244**



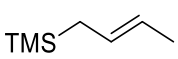
To a solution of freshly distilled diisopropylamine (0.13 mL, 0.92 mmol) in dry THF (0.92 mL) at –78 °C, was added *n*-BuLi (0.390 mL, 2.38 M) and the solution was stirred at –78 °C for 30 minutes. A solution of *trans*-decalin **139** (100 mg, 0.610 mmol) in dry THF (1.33 mL) was added and stirred for a further 1 hour at –78 °C. After this time, a solution of *N*-phenylbistrifluoromethanesulfonimide **243** (327 mg, 0.920 mmol) in dry THF (1.33 mL) was added at –78 °C and the reaction was allowed to warm to room temperature for 2 hours. After this time, the reaction was quenched with water (5 mL) and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **244** as a pale yellow oil (66.0 mg, 36% yield). **Rf** = 0.75 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2918, 1414, 1247, 1203, 1141, 1033, 877 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.80–5.70 (1H, m, H-14), 5.46–5.38 (1H, m, H-10), 2.40–2.29 (2H, m, H-12 + H-11), 2.27–2.22 (2H, m, H-15), 2.01 (1H, dd, *J* = 15.1, 5.0 Hz, H-8), 1.95–1.80 (3H, m, H-7 + H-6 + H-11), 1.80–1.72 (1H, m, H-8), 1.70 (3H, s, H-24), 1.46–1.24 (1H, m, H-6) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 151.8 (C-13), 134.1 (C-9), 119.7 (C-10), 118.4 (C-14), 39.7 (C-12), 37.7 (C-7), 37.2 (C-8), 28.3 (C-11), 27.8 (C-6), 23.8 (C-15), 23.3 (C-24) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.5, -73.9, -75.8 ppm. **MS** (APCI): m/z 297 ($M+H^+$); HRMS: found: ($M+H^+$) 297.0755. $C_{12}H_{16}F_3O_3S$ requires ($M+H^+$) 297.0767.

(12*S**, 7*S**)-9-Methyl-13,14,7,8,11,12-hexahydronaphthalene, **245**



To a solution of triflate-enol *trans*-decalin **244** (66 mg, 0.20 mmol) in dry DMF (12.5 mL), were added Bu_3N (0.17 mL, 0.70 mmol), bis(acetato)bis(triphenylphosphine)palladium (II) (14 mg, 0.020 mmol) and formic acid (0.020 mL, 0.47 mmol) and the reaction was heated at 50 °C for 3 hours. After this time, the reaction was cooled to room temperature and Et_2O (10 mL) was added and it was filtrated through a celite pad. The filtrate was washed with water (5 × 20 mL), brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **245** as a pale yellow oil (13.0 mg, 45% yield). **Rf** = 0.89 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2911, 2852, 1449, 1376, 1047, 915, 873, 800, 735 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.69–5.64 (1H, m, H-14), 5.55–5.49 (1H, m, H-13), 5.42–5.38 (1H, m, H-10), 2.14–2.04 (3H, m, H-12 + H-11), 1.97–1.86 (2H, m, H-8), 1.82–1.70 (3H, m, H-15 + H-7), 1.67 (3H, s, H-24), 1.50–1.36 (2H, m, H-6) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 134.4 (C-10), 131.3 (C-13), 126.6 (C-14), 121.1 (C-9), 38.0 (C-8), 37.5 (C-12), 36.5 (C-7), 32.5 (C-15), 29.3 (C-6), 25.7 (C-11), 23.6 (C-24) ppm. **MS** (EI): m/z 148 ($M+H^+$); HRMS: found: ($M+H^+$) 148.1256. $C_{11}H_{16}$ requires ($M+H^+$) 148.1252.

(*E*)-But-2-en-1-yltrimethylsilane, **272**[122]

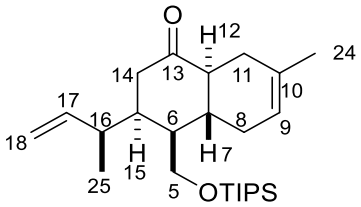


To a suspension of CuCl (980 mg, 10.0 mmol) and Et_3N (4.60 mL, 33.0 mmol) in dry Et_2O (7.0 mL) at 0 °C, a solution of *trans*-crotyl chloride **274** (3.0 mL, 33.0 mmol) and Cl_3SiH (3.30 mL, 33.0 mmol) in dry Et_2O (3.0 mL) was transferred over 10 minutes. The reaction was stirred at room temperature for 3

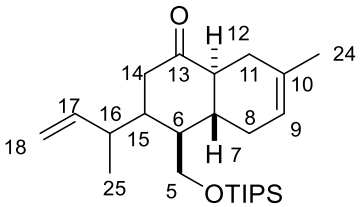
hours and was then diluted with Et_2O (50 mL) and filtered under nitrogen. The resulting ethereal solution was transferred into a solution of MeMgI (63.5 mL, 140 mmoL) in dry Et_2O (60 mL) at 0 °C, and the reaction was stirred at 50 °C for 16 hours. After this time, the reaction was cooled to 0 °C and quenched with a pre-cooled saturated aqueous solution of NH_4Cl (30 mL) and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and the ether was evaporated at 45 °C and the orange liquid was distilled at ambient pressure (112–115 °C) to yield **272** as a colourless liquid (1.44 g, 34% yield).[122] **IR** (ATR): ν_{max} 2953, 2891, 1452, 1398, 1244, 1038, 962, 834 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.44–5.34 (1H, m), 5.31–5.21 (1H, m), 1.65 (3H, dtd, *J* = 7.0, 1.3, 1.2 Hz), 1.39 (2H, dqd, *J* = 7.8, 1.3, 1.0 Hz), 0.04 (9H, s, $Si(CH_3)_3$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 127.0 (CH), 123.1 (CH), 22.6 (CH_2), 18.0 (CH_3), 2.0 ($Si(CH_3)_3$) ppm. **MS** (EI): m/z 128 ($M+H^+$); HRMS: found: ($M+H^+$) 128.1024. $C_7H_{16}Si$ requires ($M+H^+$) 128.1021.

Characterisation of this compound matched the compound reported in the literature[122]

(15*R**, 12*S**, 7*R**, 6*S**)-15-((*R**)-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **276**



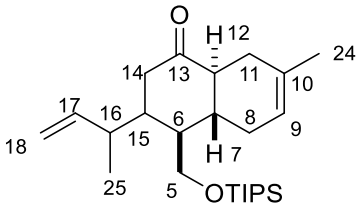
(12*S**, 7*R**, 6*S**)-15-(-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **277**



To a solution of enone *trans*-decalin **113** (100 mg, 0.290 mmol) in dry CH_2Cl_2 (2.90 mL) at –40 °C, was added $TiCl_4$ (0.040 mL, 0.37 mmol). After 5 minutes, *E*-crotyltrimethylsilane **272** (0.060 mL, 0.13 mmol)

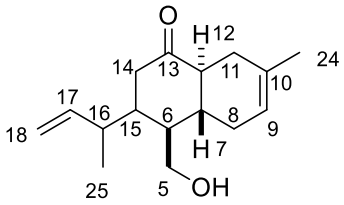
was added and the reaction was stirred at –40 °C for 1.5 hours. After this time, saturated aqueous solution of $NaHCO_3$ (4.5 mL) was added at –40 °C, stirred for 45 minutes and then allowed to warm to room temperature and stirred for an additional 30 minutes. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **276** and **277** as an inseparable mixture in a 2 : 1 ratio as a pale yellow oil (50.0 mg, 43% yield). **Rf** = 0.58 (EtOAc : hexane 10% : 90%). On a mixture **IR** (ATR): ν_{max} 2922, 2865, 1711 (C=O), 1461, 1379, 1247, 1067, 911 cm^{-1}. Integration of the ^1H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82–5.72 (2H, m, **276** + **277**), 5.37–5.31 (2H, m, **276** + **277**), 5.06–4.92 (4H, m, **276** + **277**), 3.95–3.89 (2H, m, **277**), 3.77 (1H, dd, *J* = 9.8, 6.1 Hz, **276**), 3.74 (1H, dd, *J* = 9.8, 4.9 Hz, **276**), 2.77–2.70 (1H, m, **276**), 2.49–2.40 (3H, m, **276** + **277**), 2.39–2.32 (2H, m, **276** + **277**), 2.30–2.04 (11H, m, **276** + **277**), 1.99–1.80 (5H, m, **276** + **277**), 1.69 (6H, **276** + **277**), 1.10–1.03 (42H, m, $OSiCH(CH_3)_2$, **276** + **277**), 0.99 (3H, d, *J* = 6.3 Hz, **276**), 0.94 (3H, d, *J* = 6.9 Hz, **277**) ppm. Major (15*R**, 12*S**, 7*R**, 6*S**)-15-((*R**)-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **276**; **^{13}C NMR** (400 MHz, $CDCl_3$): δ 213.5 (C=O), 143.8 (CH), 133.4 (C=C), 120.0 (CH), 113.5 (CH_2), 65.9 (CH_2), 48.5 (CH), 45.5 (CH), 42.6 (CH_2), 40.1 (CH), 38.7 (CH), 38.5 (CH), 37.2 (CH_2), 33.9 (CH_2), 23.4 (CH_3), 19.4 (CH_3), 18.1 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$); Minor (12*S**, 7*R**, 6*S**)-15-(-But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12- hexahydronaphthalen-13(2H)-one, **277**; **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.9 (C=O), 142.7 (CH), 132.9 (C=C), 119.2(CH), 113.8 (CH_2), 59.3 (CH_2), 49.6 (CH), 46.4 (CH), 41.7 (CH), 40.5 (CH_2), 38.5 (CH), 35.9 (CH), 32.0 (CH_2), 31.9 (CH_2), 23.4 (CH_3), 18.1 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$), 11.0 ($CH_3$) ppm. On a mixture **MS** (ESI): m/z 427 ($M+Na^+$); HRMS: found: ($M+Na^+$) 427.3012. $C_{25}H_{44}NaO_2Si$ requires ($M+Na^+$) 427.3003.

(12*S**,7*R**, 6*S**)-15-(But-17-en-16-yl)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **277**



Exclusively the minor diasteroisomer **277** was recovered unreacted in the deprotection reaction using HF 70% in pyridine and was characterized as single a compound. Pale yellow oil (15.0 mg, 41% yield). **Rf** = 0.58 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 1713 (C=O), 1507, 1102 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82–5.72 (1H, m), 5.37–5.31 (1H, m), 5.06–4.92 (2H, m), 3.95–3.89 (2H, m), 2.77–2.70 (1H, m), 2.49–2.40 (1H, m), 2.39–2.32 (1H, m), 2.30–2.04 (6H, m), 1.99–1.80 (2H, m), 1.69 (3H, s), 1.10–1.03 (21H, m, $OSiCH(CH_3)_2$), 0.94 (3H, d, *J* = 6.9 Hz, CH_3) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 212.9 (C=O), 142.7 (CH), 132.9 (C=C), 119.2(CH), 113.8 (CH_2), 59.3 (CH_2), 49.6 (CH), 46.4 (CH), 41.7 (CH), 40.5 (CH_2), 38.5 (CH), 35.9 (CH), 32.0 (CH_2), 31.9 (CH_2), 23.4 (CH_3), 18.1 ($OSiCH(\underline{C}H_3)_2$), 11.9 ($OSi\underline{C}H(CH_3)_2$), 11.0 ($CH_3$) ppm. **MS** (ESI): m/z 427 ($M+Na^+$); HRMS: found: ($M+Na^+$) 427.3007. $C_{25}H_{44}NaO_2Si$ requires ($M+Na^+$) 427.3003.

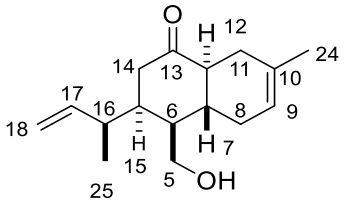
(12*S**, 7*R**, 6*S**)-3-(But-17-en-16-yl)-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **280**



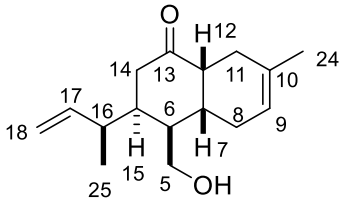
In a plastic vessel, to a solution of minor crotyl-*trans*-decalin **277** (15 mg, 0.040 mmol) in pyridine (0.10 mL), was added hydrogen fluoride 70% in pyridine (0.030 mL, 1.6 mmol) and the reaction was stirred at room temperature for 2 days. After this time, the reaction was quenched with saturated aqueous

solution of $NaHCO_3$ (5 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solution of 2 M HCl (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (20% to 30% EtOAc in hexanes) to yield **280** as a pale yellow oil (7.0 mg, 78% yield). **Rf** = 0.35 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3402 (C-OH), 2915, 1704 (C=O), 911 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.80 (1H, ddd, *J* = 17.5, 10.6, 5.6 Hz, H-17), 5.37–5.35 (1H, m, H-9), 5.06 (1H, ddd, *J* = 10.6, 1.5, 1.5 Hz, H-18), 5.02 (1H, ddd, *J* = 17.5, 1.5, 1.5 Hz, H-18), 3.99–3.86 (2H, m, H-5), 2.72–2.66 (1H, m, H-16), 2.51–2.42 (1H, m, H-11), 2.37 (1H, dd, *J* = 12.9, 3.4 Hz, H-14), 2.32–2.24 (1H, m, H-12), 2.23–2.15 (2H, m, H-8), 2.14–2.06 (2H, m, H-14 + H-15), 1.93–1.85 (1H, m, H-11), 1.82 (1H, dddd, *J* = 12.1, 12.1, 10.5, 4.1 Hz, H-7), 1.69 (3H, s, H-24), 1.50 (1H, dddd, *J* = 10.5, 10.5, 2.3, 2.3 Hz, H-6), 0.94 (3H, d, *J* = 5.9 Hz, H-25) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 212.2 (C-13), 142.4 (C-17), 133.1 (C-10), 119.1 (C-9), 114.1 (C-18), 58.7 (C-5), 49.6 (C-12), 45.8 (C-6), 41.6 (C-16), 40.8 (C-14), 38.4 (C-7), 36.3 (C-15), 31.8 (C-8), 30.0 (C-11), 23.3 (C-24), 11.3 (C-25) ppm. **MS** (ESI): m/z 271 ($M+Na^+$); HRMS: found: ($M+Na^+$) 271.1678. $C_{16}H_{24}NaO_2$ requires ($M+Na^+$) 271.1669.

(15*R**, 12*S**, 7*R**, 6*S**)-15-((*R**)-But-17-en-16-yl)-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **278**



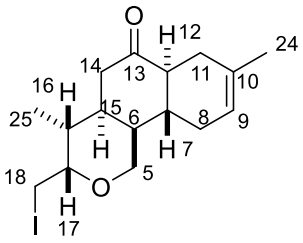
(15*R**, 12*R**, 7*R**, 6*S**)-15-((*R**)-But-17-en-16-yl)-6-(hydroxymethyl)-10-methyl-15,6,7,8,11,12-hexahydronaphthalen-13(2H)-one, **279**



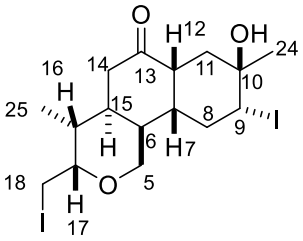
In a plastic vessel, to a solution of a 2 : 1 inseparable mixture of crotyl-*trans*-decalin **276** and **277** (52 mg, 0.13 mmol) in pyridine (0.31 mL), was added hydrogen fluoride 70% in pyridine (0.10 mL, 5.2 mmol) and the reaction was stirred at room temperature for 16 hours. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solution of 2 M HCl (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (20% to 30% EtOAc in hexanes) to yield **278** and **279** as an inseparable mixture in a 1 : 1 ratio as a pale yellow oil (13.0 mg, 62% yield). Due to the 1 : 1 ratio and the presence of many overlapping peaks in the ^{1}H NMR, it was impossible to determine which resolved proton peaks belonged to the *trans*-isomer and which was instead generated from the *cis*-compound. **Rf** = 0.32 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 3417 (C-OH), 2910, 1703 (C=O), 1436, 1376, 1039, 912, 786 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.79 (1H, ddd, *J* = 17.5, 10.2, 9.0 Hz), 5.68 (1H, ddd, *J* = 17.5, 10.2, 9.0 Hz), 5.38–5.33 (1H, m), 5.33–5.28 (1H, m), 5.11–4.98 (4H, m), 4.05 (1H, dd, *J*=10.7, 4.4 Hz), 3.93 (1H, dd, *J* = 10.7, 9.5 Hz), 3.75 (1H, dd, *J* = 10.7, 6.7 Hz),

3.66 (1H, dd, *J* = 10.7, 6.5 Hz), 2.98 (1H, dd, *J* = 5.8, 5.8 Hz), 2.67 (1H, dddd, *J* = 11.6, 5.6, 5.6, 2.0 Hz), 2.52–2.33 (5H, m), 2.30–2.14 (5H, m), 2.11–1.75 (10H, m), 1.69 (6H, s), 1.01 (3H, d, *J* = 6.4 Hz), 0.98 (3H, d, *J* = 6.4 Hz) ppm.**^{13}C NMR** (500 MHz, $CDCl_3$): δ 213.1 (C=O), 211.2 (C=O), 149.9 (CH), 142.7 (CH), 133.5 (C=C), 132.0 (C=C), 119.9 (CH), 118.9 (CH), 114.3 (CH_2), 113.9 (CH_2), 62.5 (CH_2), 59.9 (CH_2), 48.8 (CH), 45.6 (CH), 43.7 (CH), 43.1 (CH_2), 42.4 (CH_2), 42.1 (CH), 41.7 (CH), 40.7 (CH), 40.7 (CH), 38.7 (CH), 37.7 (CH), 35.7 (CH), 33.6 (CH_2), 29.9 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 23.4 (CH_3), 23.4 (CH_3), 19.6 (CH_3), 19.6 (CH_3) ppm. **MS** (ESI): m/z 271 ($M+Na^+$); HRMS: found: ($M+Na^+$) 271.1671. $C_{16}H_{24}NaO_2$ requires ($M+Na^+$) 271.1669. m/z 249 ($M+H^+$); HRMS: found: ($M+H^+$) 249.1851. $C_{16}H_{25}O_2$ requires ($M+H^+$) 249.1849.

(17*S**, 16*R**, 15*R**, 12*S**, 7*R**, 6*S**)-17-(Iodomethyl)-16,10-dimethyl-17,16,15,14,12,11,8,7-octahydro-1H-benzo[h]isochromen-13(6H)-one, **281**



(17*S**,1 6*R**, 15*R**, 12*R**, 10*R**, 9*R**, 7*R**, 6*S**)-10-Hydroxy-9-iodo-17-(iodomethyl)-4,10-dimethyldecahydro-1H-benzo[h]isochromen-13(6H)-one, **282**



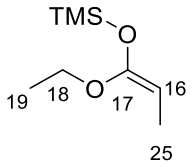
To a solution of crotyl-hydroxyl-*trans*-decalin **278** and **279** (12 mg, 0.060 mmol) in dry CH_3CN (0.60 ml) at 0 °C, were added iodine (15 mg, 0.060 mmol) and solid $NaHCO_3$ (8.0 mg, 0.12 mmol) and the reaction was allowed to stir at room temperature for 24 hours. After this time, the reaction was quenched with saturated aqueous solution of Na_2SO_3 (1 mL) and the aqueous phase was extracted

with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous solution 2 M HCl (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield **281** as a white solid (6.0 mg, 27% yield) and **282** as a white solid (9.0 mg, 29% yield).

(17*S**, 16*R**, 15*R**, 12*S**, 7*R**, 6*S**)-17-(Iodomethyl)-16,10-dimethyl-17,16,15,14,12,11,8,7-octahydro-1H-benzo[h]isochromen-13(6H)-one, **281**; Crystallization method solvent/antisolvent system: EtAOc/hexane. **Melting point** = 110–113 °C. **Rf** = 0.65 (EtOAc : hexane 30% : 70%). **IR** (ATR): ν_{max} 2923, 2854, 1706 (C=O), 1465, 1357, 1161, 817 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.38–5.35 (1H, m, H-9), 3.85 (1H, ddd, *J* = 10.7, 4.5, 4.5 Hz, H-17), 3.76–3.66 (2H, m, H-5), 3.46 (1H, dd, *J* = 10.7, 10.7 Hz, H-18), 3.23 (1H, dd, *J* = 10.7, 4.5 Hz, H-18), 2.58 (1H, dd, *J* = 14.6, 7.7 Hz, H-14), 2.48 (1H, dd, *J* = 14.6, 4.9 Hz, H-14), 2.37–2.35 (2H, m, H-12 + H-8), 2.28–2.22 (1H, m, H-15), 2.19–2.13 (1H, m, H-11), 2.11–2.04 (1H, m, H-8), 1.97–1.86 (3H, m, H-16 + H-11 + H-7), 1.86–1.82 (1H, m, H-6), 1.68 (3H, s, H-24), 0.96 (3H, d, *J* = 7.1 Hz, H-25) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 211.7 (C-13), 133.1 (C-10), 119.3 (C-9), 76.9 (C-17), 62.8 (C-5), 48.2 (C-12), 42.2 (C-14), 39.5 (C-6), 38.1 (C-15), 35.1 (C-7), 33.4 (C-16), 32.9 (C-11), 29.6 (C-8), 23.3 (C-24), 14.2 (C-25), 3.7 (C-18) ppm. **MS** (ESI): m/z 397 ($M+Na^+$); HRMS: found: ($M+Na^+$) 397.0633. $C_{16}H_{23}INaO_2$ requires ($M+Na^+$) 397.0635. (17*S**,1 6*R**, 15*R**, 12*R**, 10*R**, 9*R**, 7*R**, 6*S**)-10-Hydroxy-9-iodo-17-(iodomethyl)-4,10-dimethyldecahydro-1H-benzo[h]isochromen-13(6H)-one, **282**; Crystallization method solvent/antisolvent system: EtAOc/hexane. **Melting point** = 104–107 °C. **Rf** = 0.62 (EtOAc : hexane 30% : 70%). **IR** (ATR): ν_{max} 3417 (C-OH), 2922, 2852, 1659 (C=O), 1430, 1374, 1141, 1081, 597 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.40 (1H, dd, *J* = 5.5, 2.6 Hz, H-9), 3.96–3.91 (2H, m, H-5), 3.88 (1H, ddd, *J* = 7.8, 6.8, 2.3 Hz, H-17), 3.23 (1H, dd, *J* = 10.0, 7.8 Hz, H-18), 3.05 (1H, dd, *J* = 10.0, 6.8 Hz, H-18), 2.90 (1H, dd, *J* = 13.2, 13.2 Hz, H-14), 2.73–2.71 (1H, m, H-12), 2.62–2.58 (1H, m, H-7), 2.37–2.25 (3H, m, H-14 + H-8 + H-15), 2.14–2.02 (3H, m, H-11 + H-6), 1.97–1.92 (1H, m, H-8), 1.76 (1H, dqd, *J* = 13.7, 7.6, 2.3 Hz, H-16), 1.69 (3H, s, H-24), 1.02 (3H, d, *J* = 7.6 Hz, H-25) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 216.4 (C-13), 81.8 (C-10), 75.3 (C-17), 67.7 (C-5), 46.0 (C-12), 42.0 (C-14), 41.7 (C-9), 41.6 (C-15), 37.2 (C-7), 35.8 (C-16), 35.2 (C-11), 34.4 (C-

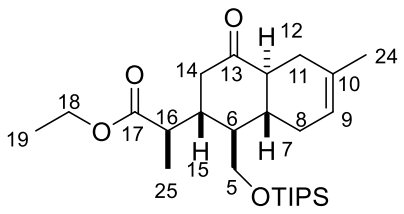
6), 31.2 (C-8), 22.7 (C-24), 12.6 (C-25), 5.5 (C-18) ppm. **MS** (ESI): m/z 540 ($M+Na^+$); HRMS: found: ($M+Na^+$) 540.9707. $C_{16}H_{24}I_2NaO_3$ requires ($M+Na^+$) 540.9707.

(*E)*-((1-Ethoxyprop-1-en-1-yl)oxy)trimethylsilane, **240**[113]



To a solution of freshly distilled diisopropylamine (1.47 mL, 10.4 mmol) in dry THF (10.4 mL) at –78 °C, was added *n*-BuLi (4.42 mL, 2.36 M) and the solution was stirred at –78 °C for 30 minutes. A solution of ethyl-propionate (1.0 mL, 8.7 mmol) in dry THF (11.3 mL) was added to the LDA solution and stirred for 1 hour at –78 °C. After this time, freshly distilled TMSCl (1.32 mL, 10.4 mmol) was added and the reaction was stirred at –78 °C for a further 30 minutes and then allowed to stir at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was dissolved with pentane (10 mL) and filtered through a sinter funnel and the pentane was concentrated *in vacuo*. The crude was purified by kugelrohr distillation pressure 0.2 mmbar at room temperature to yield **240** as a colourless liquid (767 mg, 51% yield).[113] **^{1}H NMR** (400 MHz, C_6D_6): δ 3.90 (1H, q, *J* = 6.5 Hz, CH), 3.79 (2H, q, *J* = 7.0 Hz), 1.74 (3H, d, *J* = 6.5 Hz), 1.10 (1H, t, *J* = 7.0 Hz), 0.17–0.13 (9H, m, $OSi(CH_3)_3$). This compound was characterized only by ^{1}H NMR due to its volatilty and instability and the data matched the literature.[113]

(*R**)-Ethyl-15-((15*R**, 12*S**, 7*R**, 6*R**)-10-methyl-13-oxo-6-(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphthalen-15-yl)propanoate, **241**



Method A

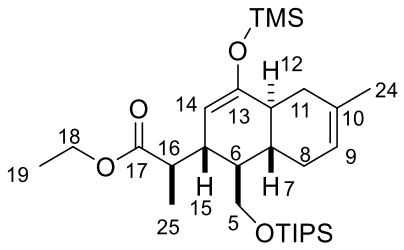
To a solution of enone *trans*-decalin **113** (25 mg, 0.072 mmol) in dry CH_2Cl_2 (0.72 mL) at –78 °C was added $TiCl_4$ (0.010 mL, 0.10 mmol). After 5 minutes, TMS-silyl keten acetal **240** (0.020 mL, 0.14 mmol) was added and the reaction was stirred at –78 °C for 30 minutes. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (1.5 mL) at –78 °C, stirred for 45 minutes and then warmed to room temperature for a further 30 minutes. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **241** as a pale yellow oil (15.0 mg, 48% yield).

Method B

A solution of TMS-enol *trans*-decalin **242** (20 mg, 0.048 mmol) in THF (0.48 mL) and aqueous solution of 2 M HCl (0.48 mL) was stirred at room temperature for 30 minutes. After this time, the reaction was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product **241** was used in the next step without further purification as a pale yellow oil (18.0 mg, 99% crude yield). **Rf** = 0.45 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2924, 2865, 1725 (C=O ester), 1713 (C=O ketone), 1462, 1380, 1146, 881 cm^{-1}. **^{1}H NMR** (500 MHz, C_6D_6): δ 5.36–5.31 (1H, m, H-9), 4.15 (1H, dd, *J* = 10.8, 2.5 Hz, H-5), 3.98–3.87 (2H, m, H-18), 3.85 (1H, dd, *J* = 10.8, 2.1 Hz, H-5), 3.07 (1H, qd, *J* = 7.4, 3.7 Hz, H-16), 2.77 (1H, dd, *J* = 13.5, 3.9 Hz, H-14), 2.54 (1H, dd, *J* = 13.5, 13.5 Hz, H-14), 2.46–2.34 (2H, m, H-8 + H-11),

2.21–2.09 (2H, m, H-15 + H-11), 1.96–1.82 (2H, m, H-12 + H-7), 1.71–1.63 (1H, m, H-8), 1.61–1.58 (1H, m, H-6), 1.57 (3H, s, H-24), 1.08 (3H, d, *J* = 7.4 Hz, H-25), 1.04–0.99 (21H, m, OSiCH(CH_3)$_2$), 0.93 (3H, t, *J* = 7.2 Hz, H-19) ppm. **^{13}C NMR** (500 MHz, C_6D_6): δ 208.7 (C-13), 173.6 (C-17), 133.0 (C-10), 118.9 (C-9), 59.6 (C-18), 59.4 (C-5), 49.2 (C-12), 47.2 (C-6), 41.8 (C-15), 41.1 (C-14), 39.2 (C-16), 38.3 (C-7), 31.9 (C-8), 30.2 (C-11), 23.1 (C-24), 17.8 (OSiCH($\underline{C}H_3$)$_2$), 15.3 (C-25), 13.9 (C-19), 11.9 (OSi$\underline{C}$H(CH_3)$_2$) ppm. **MS** (ESI): m/z 473 ($M+Na^+$); HRMS: found: ($M+Na^+$) 473.3070. $C_{26}H_{46}NaO_4Si$ requires ($M+Na^+$) 473.3058. m/z 451 ($M+H^+$); HRMS: found: ($M+H^+$) 451.3250. $C_{26}H_{47}O_4Si$ requires ($M+H^+$) 451.3238.

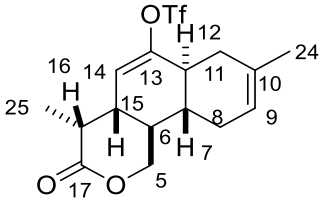
(*R**)-Ethyl-15-((15*S**, 12*S**, 7*R** 6*R**)-10-methyl-6-(((triisopropylsilyl)oxy)methyl)-13-((trimethylsilyl)oxy)-6,15,12,11,8,7-hexahydronaphthalen-15-yl)propanoate, **242**



To a solution of enone *trans*-decalin **113** (25 mg, 0.072 mmol) in dry CH_2Cl_2 (0.72 mL) at –78 °C, was added Yb(OTf)$_3$ (56 mg, 0.072 mmol). After 5 minutes, TMS-silyl keten acetal **240** (0.020 mL, 0.14 mmol) was added and the reaction was stirred at –78 °C for 2 hours. After this time, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (1.5 mL) at –78 °C, stirred for 45 minutes and then the mixture was warmed to room temperature and stirred for an additional 30 minutes. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product **242** was used in the next step without further purification as a pale yellow oil (36.0 mg, 99% crude yield). **Rf** = 0.58 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2866, 1725 (C=O ester), 1462, 1379, 1264, 1191, 876, 704 cm^{-1}. **^{1}H NMR** (500 MHz, C_6D_6): δ 5.41–5.36 (1H, m, H-9), 4.86 (1H, dd, *J* = 2.7, 2.7 Hz, H-14), 4.16–4.00 (2H, m, H-18), 3.97 (1H, dd, *J* = 10.5, 2.3 Hz,

H-5), 3.87 (1H, dd, *J* = 10.5, 2.8 Hz, H-5), 2.87 (1H, qd, *J* = 6.9, 5.6 Hz, H-16), 2.49 (1H, ddd, *J* = 10.6, 5.6, 2.7 Hz, H-15), 2.38–2.29 (1H, m, H-11), 2.27–2.17 (1H, m, H-8), 2.09–1.94 (1H, m, H-12), 1.78–1.71 (3H, m, H-8 + H-11 + H-7), 1.69 (3H, s, H-24), 1.52 (1H, dddd, *J* = 10.6, 10.6, 2.8, 2.3 Hz, H-6), 1.21 (3H, t, *J* = 7.3 Hz, H-19), 1.19 (3H, d, *J* = 6.9 Hz, H-25), 1.10–1.03 (21H, m, $OSiCH(CH_3)_2$), 0.20 (9H, s, $OSi(CH_3)_3$) ppm. **^{13}C NMR** (500 MHz, C_6D_6): δ 174.7 (C-17), 152.9 (C-13), 133.7 (C-10), 120.4 (C-9), 102.7 (C-14), 60.0 (C-18), 59.9 (C-5), 43.5 (C-6), 40.7 (C-12), 40.0 (C-16), 39.9 (C-15), 36.6 (C-7), 33.9 (C-8), 30.6 (C-11), 23.6 (C-24), 18.1 ($OSiCH(\underline{C}H_3)_2$), 15.7 (C-25), 14.4 (C-19), 12.0 ($OSi\underline{C}H(CH_3)_2$), 0.17 ($OSi(CH_3)_3$) ppm. **MS** (ESI): m/z 545 ($M+Na^+$); HRMS: found: ($M+Na^+$) 545.3476. $C_{29}H_{54}NaO_4Si_2$ requires ($M+Na^+$) 545.3453.

(16*R**, 15*S**, 12*S**, 7*R**, 6*R**)-16,10-Dimethyl-17-oxo-17,16,15,12,11,8,7,6-octahydro-1H-benzo[h]isochromen-13-yl trifluoromethanesulfonate, **246**

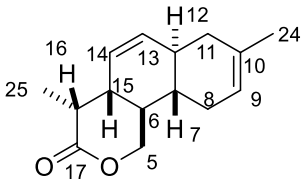


To a solution of freshly distilled diisopropylamine (0.020 mL, 0.12 mmol) in dry THF (0.12 mL) at −78 °C, was added *n*-BuLi (0.0510 mL, 2.36 M) and the solution was stirred at −78 °C for 30 minutes. A solution of ethylester-*trans*-decalin **241** (47 mg, 0.10 mmol) in dry THF (0.4 mL) was added and stirred at −78 °C for 1 hour. After this time, *N*-phenyl-*bis*-(trifluoromethanesulfonimide) **243** (43 mg, 0.12 mmol) in dry THF (1 mL) was added and the reaction was stirred at −78 °C for a further 30 minutes and then allowed to warm to room temperature for 1 hour. The reaction was then quenched with water (2 mL) and extracted with Et_2O (20 mL) and the organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (48 mg, 83% crude yield) was carried into the next step without further purification.

To a solution of this crude (40 mg, 0.071 mmol) in dry THF (0.71 mL), was added a 1.0 M solution of TBAF in THF (0.20 mL, 0.70 mmol) and the reaction was stirred at room temperature for 16 hours.

After this time, the reaction was diluted with EtOAc (10 mL), and washed with water (2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield **246** as a pale yellow oil (14.0 mg, 54% yield). **Rf** = 0.25 (EtOAc : hexane 30% : 70%). **IR** (ATR): ν_{max} 2919, 1735 (C=O), 1416, 1209, 1141, 1057, 825, 624 cm^{-1}. **^{1}H NMR** (500 MHz, C_6D_6): δ 5.07–5.02 (1H, m, H-9), 4.92–4.89 (1H, m, H-14), 3.73 (1H, dd, *J* = 10.7, 5.0 Hz, H-5), 3.15 (1H, dd, *J* = 11.8, 10.7 Hz, H-5), 2.31 (1H, qd, *J* = 7.5, 5.5 Hz, H-16), 2.12–2.04 (3H, m, H-12 + H-7 + H-11), 1.71–1.65 (1H, m, H-15), 1.61–1.49 (3H, m, H-8 + H-11), 1.43 (3H, s, H-24), 1.15–1.05 (1H, m, H-6), 0.94 (3H, d, *J* = 7.5 Hz, H-25) ppm. **^{13}C NMR** (500 MHz, C_6D_6): δ 171.4 (C-17), 151.6 (C-13), 132.7 (C-10), 120.0 (C-9), 118.4 (C-14), 71.5 (C-5), 39.6 (C-12), 38.6 (C-7), 38.5 (C-15), 38.1 (C-16), 32.7 (C-11), 32.5 (C-6), 28.3 (C-8), 23.4 (C-24), 13.8 (C-25) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -73.9 ppm. **MS** (APCI): m/z 381 ($M+H^+$); HRMS: found: ($M+H^+$) 381.0968. $C_{16}H_{20}F_3O_5S$ requires ($M+H^+$) 381.0978.

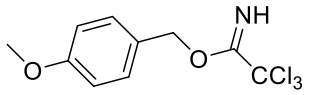
(16*R**, 15*R**, 12*R**, 7*S**, 6*R**)-16,10-Dimethyl-16,15,12,11,8,7-hexahydro-1H-benzo[h]isochromen-17(6H)-one, **247**



To a solution of triflate enol -*trans*-decalin **246** (14 mg, 0.040 mmol) in dry DMF (2.50 mL), were added Bu_3N (0.030 mL, 0.14 mmol), bis(acetate)bis(triphenylphosphine)palladium (II) (3.0 mg, 3.8 µmol) and formic acid (3.39 µL, 0.090 mmol) and the reaction was heated at 50 °C for 3 hours. After this time, the reaction was cooled to room temperature and diluted with Et_2O (10 mL), washed with water (5 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% EtOAc in hexanes) to yield **247** as a pale yellow solid (5.0 mg, 51% yield). **Melting point** = 89–91 °C. **Rf** = 0.31 (EtOAc : hexane 10% : 90%). **IR**

(ATR): ν_{max} 2923, 1736 (C=O), 1459, 1217, 1057, 790, 597 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.69 (1H, ddd, *J* = 9.9, 2.2, 2.2 Hz, H-13), 5.41 (1H, ddd, *J* = 9.9, 2.2, 2.2 Hz, H-14), 5.39–5.36 (1H, m, H-9), 4.50 (1H, dd, *J* = 10.9, 5.0 Hz, H-5), 4.01 (1H, dd, *J* = 11.8, 10.9 Hz, H-5), 2.86 (1H, qd, *J* = 7.5, 5.6 Hz, H-16), 2.64–2.58 (1H, m, H-15), 2.21–2.12 (1H, m, H-12), 2.09–2.00 (2H, m, H-8 + H-11), 1.95–1.74 (3H, m, H-6 + H-8 + H-11), 1.68 (3H, s, H-24), 1.40–1.32 (1H, m, H-7), 1.20 (3H, d, *J* = 7.5 Hz, H-25) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 174.4 (C-17), 134.4 (C-10), 133.2 (C-13), 125.6 (C-9), 119.9 (C-14), 73.4 (C-5), 39.6 (C-15), 38.7 (C-16), 37.6 (C-12), 37.6 (C-7), 36.7 (C-11), 33.7 (C-6), 29.2 (C-8), 23.4 (C-24), 13.6 (C-25) ppm. **MS** (APCI): m/z 233 ($M+H^+$); HRMS: found: ($M+H^+$) 233.1531. $C_{15}H_{21}O_2$ requires ($M+H^+$) 233.1536.

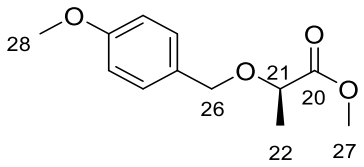
p-methoxybenzyl 2,2,2-trichloroacetimidate, **300**[127]



To a solution of *p*-methoxybenzylalcohol (3.30 g, 12.0 mmol) in dry Et_2O (9 mL) at room temperature, was added NaH (60% dispersion in mineral oil, 241 mg, 6.06 mmol) and the mixture was stirred at room temperature for 30 minutes. After this time, the mixture was cooled to 0 °C and Trichloroacetonitrile (2.40 mL, 12.02 mmol) was added, and the reaction was stirred for 2 hours at room temperature. The reaction was then quenched with saturated solution of $NaHCO_3$ (10 mL) and extracted with Et_2O (4 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product **300** was used into the next step without further purification as a pale yellow oil (3.39 g, >99% crude yield).[127] **IR** (ATR): ν_{max} 2955, 2836, 1661, 1612, 1514, 1175, 1033, 819 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.37 (1H, br. s.), 7.38 (2H, d, J = 8.70 Hz), 6.92 (2H, d, J = 8.70 Hz), 5.28 (2H, s), 3.82 (3H, s) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 162.8 (C), 159.8 (C), 129.8 (CH), 114.0 (CH), 70.8 (CH_2), 55.47 (CH_3) ppm. **MS** (ESI): m/z 303 ($M+Na^+$), m/z 305 ($M+Na^+$); HRMS: found:

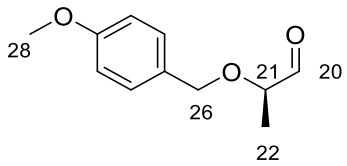
(M+Na$^+$) 303.9652 $C_{10}H_{10}{}^{35}Cl_3NNaO_2$ requires (M+Na$^+$) 303.9669. Characterisation of this compound matched the compound reported in the literature[127]

(*R**)-Methyl-21-((methoxybenzyl)oxy)propanoate, **301**



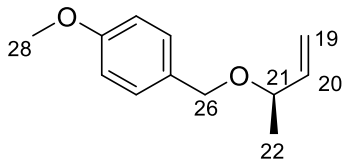
To a solution of (+)-methyl-D-lactate **299** (1.15 mL, 12.0 mmol) in dry CH_2Cl_2 (60.0 mL), were added 4-methoxybenzyl-2,2,2-trichloroacetimidate **300** (6.76 g, 12.0 mmol) in dry CH_2Cl_2 (60.0 mL) followed by CSA (279 mg, 1.20 mmol). The reaction was stirred at room temperature for 24 hours. After this time, the reaction was diluted with CH_2Cl_2 (50 mL) and quenched with saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 20% EtOAc in hexanes) to yield **301** as a pale yellow oil (2.45 g, 91% yield). $[\alpha]^{20}{}_D$ +76.45 (c 0.50, $CHCl_3$). **Rf** = 0.25 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 2952, 1747 (C=O), 1586, 1444, 1205, 1174, 755 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.7 Hz, Ar-H), 6.89 (2H, d, *J* = 8.7 Hz, Ar-H), 4.62 (1H, d, *J* = 11.5 Hz, H-26), 4.40 (1H, d, *J* = 11.5 Hz, H-26), 4.06 (1H, q, *J* = 6.8 Hz, H-21), 3.81 (3H, s, H-28), 3.76 (3H, s, H-27), 1.43 (3H, d, *J* = 6.8 Hz, H-22) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 173.9 (C-20), 159.5 (Ar), 129.8 (Ar-H), 129.7 (Ar), 113.9 (Ar-H), 73.7 (C-21), 71.8 (C-26), 55.4 (C-28), 52.1 (C-27), 18.9 (C-22) ppm. **MS** (ESI): m/z 247 (M+Na$^+$); HRMS: found: (M+Na$^+$) 247.0944. $C_{12}H_{16}NaO_4$ requires (M+Na$^+$) 247.0941.

(*R**)-Methyl 21-((methoxybenzyl)oxy)propanal, **302**[44]



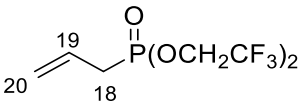
To a solution of PMB-ester **301** (270 mg, 1.20 mmol) in dry CH_2Cl_2 (12.0 mL) at –78 °C, was added a 1.0 M solution of Dibal-H in toluene (1.20 mL, 1.20 mmol) and the reaction was stirred at –78 °C for 1 hour. After this time, the reaction was quenched with dry acetone (1.2 mL) at –78 °C and allowed to warm to room temperature and then Rochelle's salt 10% aqueous solution (20 mL) was added and stirred for 16 hours. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 20% EtOAc in hexanes) to yield **302** as a pale yellow oil (232 mg, 99% yield). $[\alpha]^{20}_D$ +39.89 (c 0.50, $CHCl_3$); **Rf** = 0.25 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 2951, 1730 (C=O), 1612, 1513, 1450, 1371, 1175, 821 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.64 (1H, d, *J* = 1.9 Hz, H-20), 7.30 (2H, d, *J* = 8.7 Hz, Ar-H), 6.89 (2H, d, *J* = 8.7 Hz, Ar-H), 4.58 (1H, d, *J* = 11.5 Hz, H-26), 4.55 (1H, d, *J* = 11.5 Hz, H-26), 3.88 (1H, qd, *J* = 6.9, 1.9 Hz, H-21), 3.82 (3H, s, H-28), 1.32 (3H, d, *J* = 6.9 Hz, H-22) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 203.6 (C-20), 159.6 (Ar), 129.7 (Ar-H), 129.4 (Ar), 114.0 (Ar-H), 79.1 (C-21), 71.7 (C-26), 55.3 (C-28), 15.3 (C-22) ppm. **MS** (ESI): m/z 217 ($M+Na^+$); HRMS: found: ($M+Na^+$) 217.0840. $C_{11}H_{14}NaO_3$ requires ($M+Na^+$) 217.0835. Characterisation of this compound matched the compound reported in the literature[44]

(*R**)-19-((But-20-en-21-yloxy)methyl)-methoxybenzene, **303**[44]



To a suspension of methylphenylphosphonium bromide (405 mg, 1.13 mmol) in dry THF (4.0 mL) at 0 °C, was added *n*-BuLi (0.50 mL, 2.25 M) and the yellow solution was stirred for 1 hour. A solution of PMB-aldehyde **302** (182 mg, 0.930 mmol) in dry THF (2.0 mL) was added and the reaction was stirred at 0 °C for 2 hours. After this time, the reaction was filtered through a pad of silica with MTBE (10 mL) and the solvent was evaporated under nitrogen flow. The crude product **303** was used in the next reaction without further purification as a pale yellow oil (178 mg, >99% crude yield). $[\alpha]^{20}_{D}$ +1.21 (c 0.50, $CHCl_3$); **Rf** = 0.62 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2923, 2853, 1588, 1611, 1462, 1246, 1071, 997 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28 (2H, d, *J* = 8.5 Hz, Ar-H), 6.88 (2H, d, *J* = 8.5 Hz, Ar-H), 5.80 (1H, ddd, *J* = 17.3, 10.2, 7.4 Hz, H-20), 5.21 (1H, ddd, *J* = 17.3, 1.5, 1.5 Hz, H-19), 5.18 (1H, ddd, *J* = 10.2, 1.5, 1.5 Hz, H-19), 4.51 (1H, d, *J* = 11.5 Hz, H-26), 4.33 (1H, d, *J* = 11.5 Hz, H-26), 3.93–3.89 (1H, m, H-21), 3.81 (3H, s, H-28), 1.28 (3H, d, *J* = 6.4 Hz, H-22) ppm. **^{13}C NMR** (500 MHz, $CDCl_3$): δ 159.1 (Ar), 140.9 (C-20), 130.9 (Ar), 129.3 (Ar-H), 115.9 (C-19), 113.8 (Ar-H), 75.7 (C-21), 69.6 (C-26), 55.3 (C-28), 21.4 (C-22) ppm. **MS** (ESI): m/z 215 ($M+Na^+$); HRMS: found: ($M+Na^+$) 215.1045. $C_{12}H_{16}NaO_2$ requires ($M+Na^+$) 215.1043. Characterisation of this compound matched the compound reported in the literature.[44]

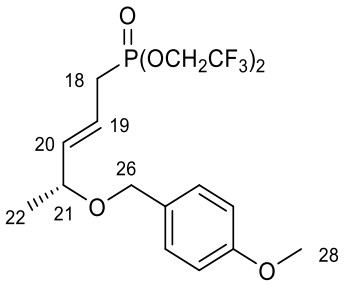
Allyl phosphonate, **304**[44]



A mixture of TBAI (81 mg, 0.22 mmol), tris(2,2,2 trifluoroethyl)phosphite (0.810 mL, 3.62 mmol) and allylbromide (0.50 mL, 5.96 mmol) was stirred in a microwave at 180 °C for 3 hours. After this time,

the crude product was purified by silica gel flash column chromatography (10% to 30% EtOAc in hexanes) to yield **304** as a pale yellow oil (620 mg, 60% yield). **Rf**=0.25 (EtOAc : hexane 30% : 70%). **IR** (ATR): ν_{max} 2659, 1506, 1439, 1210, 1126, 1094, 1004, 943 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85–5.69 (1H, m), 5.41–5.27 (2H, m), 4.47–4.30 (4H, m), 2.80 (2H, dd, *J* = 22.9) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 124.8 (d, *J* = 11.9 Hz), 122.5 (qd, *J* = 277.6, 7.3 Hz), 122.1 (d, *J* = 15.1 Hz), 62.3 (qd, *J* = 37.8, 5.8 Hz), 31.9 (d, *J* = 141.1 Hz) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -75.3 (t, *J* = 7.9 Hz), -75.2 (t, *J* = 7.9 Hz), -75.1 (t, *J* = 7.9 Hz) ppm. **MS** (ESI): m/z 309 ($M+Na^+$); HRMS: found: ($M+Na^+$) 309.0084. $C_7H_9F_6NaO_3P$ requires ($M+Na^+$) 309.0086. Characterisation of this compound matched the compound reported in the literature.[44]

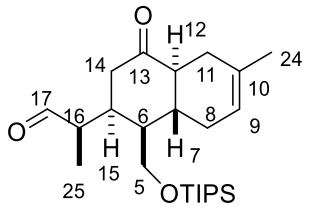
(*R**, *E*)-Bis(2,2,2,-trifluoroethyl)-(((21methoxybenzyl)oxy)pent-19en-18-yl)phosphonate, **92**[44]



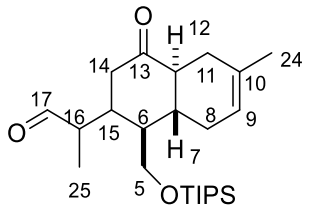
To a solution of PMB-alkene **303** (30.7 mg, 0.160 mmol) and allyl phosphonate **304** (45.8 mg, 0.160 mmol) in dry CH_2Cl_2 (2.5 mL), was added Grubbs II generation catalyst (7.0 mg, 8.0 μmol) and the reaction was stirred under reflux for 36 hours. After this time, the solvent was concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10% to 40% EtOAc in hexanes) to yield **92** as a brown oil (17.0 mg, 34% yield). $[\alpha]^{20}_{D}$ +19.32 (c 0.50, $CHCl_3$). **Rf** = 0.32 (EtOAc : hexane 30% : 70%). **IR** (ATR): ν_{max} 2928, 1613, 1586, 1513, 1296, 1249, 1102 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, *J* = 8.9 Hz), 6.88 (2H, d, *J* = 8.9 Hz), 5.76–5.66 (1H, m), 5.64 (1H, m), 4.48 (1H, d, *J* = 11.5 Hz), 4.45–4.34 (4H, m), 4.31 (1H, d, *J* = 11.5 Hz), 3.97–3.89 (1H, m), 3.81 (3H, s), 2.83 (2H, dd, *J* = 22.0, 7.3 Hz), 1.26 (3H, d, *J* = 6.6 Hz) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 159.1 (C=C), 139.7 (d, *J* = 15.0

Hz, CH), 130.5 (C=C), 129.2 (CH), 121.2 (qd, *J* = 27.7, 6.9 Hz), 118.2 (d, *J* = 12.5 Hz, CH), 113.8 (CH), 74.5 (d, *J* = 2.3 Hz, CH), 69.4 (CH_2), 62.2 (qdd, *J* = 37.9, 6.2, 4.2 Hz, CH_2), 55.2 (CH), 29.6 (d, *J* = 141.1 Hz, CH_2), 21.2 (d, *J* = 3.1 Hz, CH_2) ppm. **^{9}F NMR** (376 MHz, $CDCl_3$): δ -75.3 (q, *J* = 7.8 Hz) ppm. **MS** (ESI): m/z 473 ($M+Na^+$); HRMS: found: ($M+Na^+$) 473.0924. $C_{17}H_{21}F_6NaO_5P$ requires ($M+Na^+$) 473.0923. Characterisation of this compound matched the compound reported in the literature.[44]

*R**-15-((15*S**, 12*S**, 7*R**, 6*S**)-10-Methyl-13-oxo-6(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphtalen-15yl)propanal, **290**



15-((12*S**, 7*R**, 6*S**)-10-Methyl-13-oxo-6(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphtalen-15yl)propanal, **291**

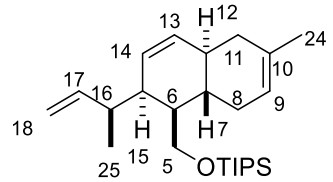


To a solution of crotyl-substituted *trans*-decalins **276** and **277** (227 mg, 0.560 mmol) in dry THF (0.56 mL), were added B_2pin_2 (156 mg, 0.620 mmol), *trans*-cyclohexanediol **287** (64.9 mg, 0.560 mmol) and Cs_2CO_3 (26.9 mg, 0.080 mmol). The reaction was stirred at 60 °C for 5 days and then cooled to 0 °C and an aqueous solution of 3 M NaOH (2.20 mL) was added, followed by addition of an 30% aqueous solution of H_2O_2 (1.10 mL) and the resultant mixture was stirred for 4 hours. Saturated aqueous solution of Na_2SO_3 (4.40 mL) was then added and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product mixture of diols **288** and **289** was directly used in the next step without further purification.

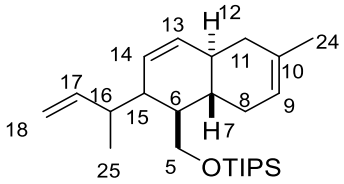
To a solution of the mixture of diol intermediates **288** and **289** (53 mg, 0.12 mmol) in CH_2Cl_2 : H_2O (1 : 1, 1.20 mL) at 0 °C, was added $NaIO_4$ (25.7 mg, 0.120 mmol) and the reaction was allowed to stir at room temperature for 24 hours. After this time, the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% EtOAc in hexanes) to yield **290** as a pale yellow oil (14.0 mg, 30% yield) and **291** as a pale yellow oil (8.0 mg, 16% yield). *R**-15-((15*S**, 12*S**, 7*R**, 6*S**)-10-Methyl-13-oxo-6(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphtalen-15yl)propanal, **290**; **Rf** = 0.38 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 2922, 2864, 1714 (C=O, aldehyde + ketone), 1461, 1379, 1094, 1066, 917 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.62 (1H, d, *J* = 2.7 Hz, H-17), 5.33–5.29 (1H, m, H-9), 4.07 (1H, dd, *J* = 10.4, 5.4 Hz, H-5), 4.00 (1H, dd, *J* = 10.4, 6.5 Hz, H-5), 3.05–3.01 (1H, m, H-15), 2.64 (1H, dqd, *J* = 8.3, 5.2, 2.7 Hz, H-16), 2.61–2.56 (1H, m, H-12), 2.55–2.50 (1H, m, H-7), 2.49–2.43 (2H, m, H-11), 2.39 (1H, dd, *J* = 14.3, 4.6 Hz, H-14), 2.35–2.25 (1H, m, H-14), 1.95–1.83 (3H, m H-8 + H-6), 1.70 (3H, s, H-24), 1.11 (3H, d, *J* = 5.2 Hz, H-25), 1.08–1.02 (21H, m, $OSiCH(CH_3)_2$) ppm . **^{13}C NMR** (500 MHz, $CDCl_3$): δ 210.3 (C-17), 203.3 (C-13), 132.0 (C-10), 118.9 (C-9), 63.2 (C-5), 48.2 (C-16), 44.7 (C-15), 41.6 (C-6), 41.5 (C-14), 38.0 (C-12), 37.5 (C-7), 27.9 (C-11), 27.7 (C-8), 23.4 (C-24), 18.1 ($OSiCH(\underline{C}H_3)_2$), 12.6 (C-25), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 429 ($M+Na^+$); HRMS: found: ($M+Na^+$) 429.2811. $C_{24}H_{42}NaO_3Si$ requires ($M+Na^+$) 429.2795. m/z 407 ($M+H^+$); HRMS: found: ($M+H^+$) 407.2979. $C_{24}H_{43}O_3Si$ requires ($M+H^+$) 407.2976. 15-((12*S**, 7*R**, 6*S**)-10-Methyl-13-oxo-6(((triisopropylsilyl)oxy)methyl)-6,15,14,13,12,11,8,7-octahydronaphtalen-15yl)propanal, **291**; **Rf** = 0.41 (EtOAc : hexane 20% : 80%). **IR** (ATR): ν_{max} 2864, 1714 (C=O, aldehyde + ketone), 1462, 1094, 788, 680 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.57 (1H, d, *J* = 2.9 Hz, H-17), 5.35–5.29 (1H, m, H-9), 3.88 (1H, dd, *J* = 10.7, 5.1 Hz, H-5), 3.58 (1H, dd, *J* = 10.7, 9.4 Hz, H-5), 3.00–2.94 (1H, m, H-15), 2.57–2.52 (1H, m, H-16), 2.51–2.44 (2H, m, H-14), 2.32 (1H, ddd, *J* = 11.8, 7.9, 7.5 Hz, H-12), 2.20–2.14 (1H, m, H-8), 2.14–2.10 (2H, m, H-11), 2.10–2.03 (1H, m, H-6), 1.94–1.86 (1H, m, H-8), 1.76 (1H, dddd, *J* = 12.1, 11.8, 10.3, 3.9, H-7), 1.68 (3H, s, H-24), 1.09 (3H, d, *J* = 5.3 Hz, H-25), 1.09–1.02 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 211.9 (C-17), 204.3 (C-

13), 133.3 (C-10), 119.1 (C-9), 62.4 (C-5), 49.1 (C-12), 46.5 (C-16), 45.9 (C-6), 42.7 (C-14), 37.1 (C-7), 35.5 (C-15), 32.5 (C-8), 29.6 (C-11), 23.4 (C-24), 18.0 (OSiCH($\underline{C}H_3)_2$), 12.6 (C-25), 11.9 (OSi$\underline{C}$H$(CH_3)_2$) ppm. **MS** (ESI): m/z 429 ($M+Na^+$); HRMS: found: 429.2805 ($M+Na^+$). $C_{24}H_{42}NaO_3Si$ requires ($M+Na^+$) 429.2795.

(((15*R**, 12*R**, 7*S**, 6*R**)-15-((*S**)But-14-en-15yl)-10-methyl,-6,15,12,11,8,7-hexahydronaphthalen-6-yl)methoxy)triisoprpylsilane, **294**



(((12*R**, 7*S**, 6*R**)-15-(But-14-en-15yl)-10-methyl,-6,15,12,11,8,7-hexahydronaphthalen-6-yl)methoxy)triisoprpylsilane, **295**

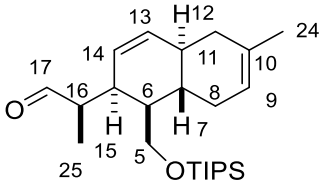


To a solution of freshly distilled diisopropylamine (0.10 mL, 0.65 mmol) in dry THF (0.65 mL) at –78 °C, was added *n*-BuLi (0.31 mL, 2.15 M) and the solution was stirred at –78 °C for 30 minutes. A solution of *trans*-decalin **276** and **277** (220 mg, 0.54 mmol) in dry THF (1 mL) was added and stirred for 1 hour. After this time, *N*-phenyl-*bis*-(trifluoromethanesulfonimide) **243** (232 mg, 0.650 mmol) in dry THF (1 mL) was added and the reaction was stirred at –78 °C for a further 30 minutes and then allowed to warm to room temperature for 1 houd. The reaction was then quenched with water (2 mL) and extracted with Et_2O (20 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (401 mg, 79% yield) was carried out into the next step, without further purification.

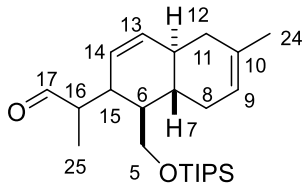
To a solution of model enol triflate *trans*-decalin **292** and **293** (286 mg, 0.530 mmol) in dry DMF (33.1 mL), were added Bu_3N (0.440 mL, 1.86 mmol), bis(acetato)bis(triphenylphosphine)palladium (II) (38

mg, 0.050 mmol) and formic acid (0.050 mL, 1.86 mmol) and the reaction was heated at 50 °C for 2 hours. After this time, the reaction was cooled to room temperature and MTBE (10 mL) was added and washed with water (5 × 20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% to 5% EtOAc in hexanes) to yield **294** and **295** as an inseparable mixture in a 2 : 1 ratio as a pale yellow oil (115 mg, 56% yield over 3 steps). **Rf** = 0.95 (EtOAc : hexane 10% : 90%). On a mixture **IR** (ATR): ν_{max} 2923, 2865, 1461, 1097, 907, 881, 791, 680 cm^{-1}. Integration of the ^1H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks.**^{1}H NMR** (400 MHz, $CDCl_3$) Major **294** + Minor **295**: δ 6.01–5.90 (1H, m, **294**), 5.85–5.44 (5H, m, **294** + **295**), 5.43–5.29 (2H, m, **295**), 5.02–4.94 (4H, m, **294** + **295**), 3.94 (1H, dd, *J* = 10.1, 4.6 Hz, **294**), 3.87–3.82 (2H, m, **295**), 3.72 (1H, dd, *J* = 10.1, 10.1 Hz, **294**), 2.79–2.72 (1H, m, **294**), 2.64–2.56 (2H, m, **294** + **295**), 2.13–1.93 (8H, m, **294** + **295**), 1.92–1.82 (2H, m, **294** + **295**), 1.79–1.73 (2H, m, **294** + **295**), 1.67 (6H, s, **294** + **295**), 1.53–1.35 (3H, m, **294** + **295**), 1.13–1.01 (42H, $OSiCH(CH_3)_2$), 0.95 (6H, d, *J* = 6.9 Hz, **294** + **295**) ppm. (((15*R**, 12*R**, 7*S**, 6*R**)-15-((*S**)But-14-en-15yl)-10-methyl,-6,15,12,11,8,7-hexahydronaphthalen-6-yl)methoxy)triisoprpylsilane, **294**; **^{13}C NMR** (400 MHz, $CDCl_3$): δ 145.3 (CH), 134.2 (C=C), 132.3 (CH), 126.9 (CH), 120.7 (CH), 112.0 (CH_2), 62.6 (CH_2), 45.0 (CH), 40.1 (CH), 38.7 (CH), 35.6 (CH), 34.6 (CH), 31.9 (CH_2), 30.8 (CH_2), 23.4 (CH_3), 18.1 ($OSiCH(\underline{C}H_3)_2$), 16.2 ($CH_3$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. (((12*R**, 7*S**, 6*R**)-15-(But-14-en-15yl)-10-methyl,-6,15,12,11,8,7-hexahydronaphthalen-6-yl)methoxy)triisoprpylsilane, **295**; **^{13}C NMR** (400 MHz, $CDCl_3$): δ 143.9 (CH), 133.8 (C=C), 131.0 (CH), 128.7 (CH), 120.9 (CH), 112.0 (CH_2), 60.4 (CH_2), 45.2 (CH), 43.4 (CH), 41.3 (CH), 38.9 (CH), 37.9 (CH), 31.6 (CH_2), 29.4 (CH_2), 23.5 (CH_3), 18.1 ($OSiCH(\underline{C}H_3)_2$), 14.1 ($CH_3$), 12.0 ($OSi\underline{C}H(CH_3)_2$) ppm. On a mixture **MS** (APCI): m/z 389 ($M+H^+$); HRMS: found: ($M+H^+$) 389.3228. $C_{25}H_{45}OSi$ requires ($M+H^+$) 389.3234.

*R**-15-((15*S**, 12*R**, 7*S**, 6*R**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-6,15,12,11,8,7-hexahydronaphthalen-15-yl)propanal, **162**



15-((12*R**, 7*S**, 6*R**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-6,15,12,11,8,7-hexahydronaphthalen-15-yl)propanal, **298**

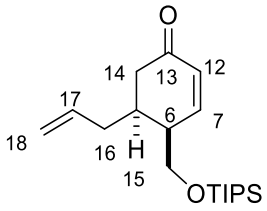


To a solution of crotyl-substituted *trans*-decalin **294** and **295** (115 mg, 0.280 mmol) in dry THF (0.31 mL), were added B_2pin_2 (76 mg, 0.31 mmol), *trans*-cyclohexanediol **287** (35 mg, 0.31 mmol) and Cs_2CO_3 (17 mg, 0.040 mmol). The reaction was stirred at 60 °C for 5 days and then cooled to 0 °C and an aqueous solution of 3 M NaOH (1.20 mL) was added, followed by addition of an 30% aqueous solution of H_2O_2 (0.60 mL) and the resultant mixture was stirred for 4 hours. Saturated aqueous solution of Na_2SO_3 (2.40 mL) was added and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product mixture of diols **296** and **297** was directly used in the next step without further purification.

To a solution of the mixture of diol intermediates **296** and **297** (162 mg, 0.280 mmol) in CH_2Cl_2 : H_2O (1 : 1, 3.0 mL) at 0 °C, was added $NaIO_4$ (128 mg, 0.560 mmol) and the reaction was allowed to stir at room temperature for 24 hours. After this time, the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% EtOAc in hexanes) to yield **162** and **298** as an inseparable mixture in a 2 : 1 ratio as a pale yellow oil (49.0 mg, 60% yield b.r.s.m.). **Rf** = 0.57 (EtOAc : hexane 10% : 90%). On a mixture **IR** (ATR): ν_{max} 2924,

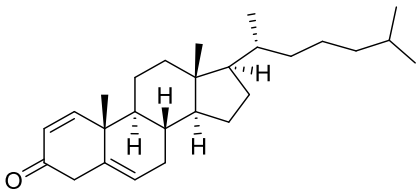
2865, 1725 (C=O), 1462, 1096, 882, 796 cm^{-1}. Integration of the ^{1}H NMR are reported as a 1 : 1 mixture due to the presence of overlapping peaks. **^{1}H NMR** (500 MHz, $CDCl_3$) Major **162** + Minor **298**: δ 9.76 (1H, d, *J* = 5.8 Hz, **298**), 9.70 (1H, d, *J* = 0.9 Hz, **162**), 5.68 (1H, ddd, *J* = 10.4, 1.2, 1.2 Hz, **162**), 5.60 (1H, ddd, *J* = 10.2, 1.2, 1.2 Hz, **298**), 5.43–5.40 (1H, m, **298**), 5.39–5.34 (2H, m, **162**), 5.16 (1H, ddd, *J* = 10.2, 2.3, 2.3 Hz, **298**), 3.97 (1H, dd, *J* = 10.5, 4.8 Hz, **162**), 3.87–3.81 (2H, m, **298**), 3.60 (1H, dd, *J* = 10.5, 10.5 Hz, **298**), 3.21–3.18 (2H, m, **162** + **298**), 2.85–2.76 (3H, m, **162** + **298**), 2.37–2.27 (3H, m, **162** + **298**), 2.09–1.95 (7H, m, **162** + **298**), 1.79–1.70 (3H, m, **162** + **298**), 1.67 (6H, s, **162** + **298**), 1.14-1.00 (42H, $OSiCH(CH_3)_2$, **162** + **298**), 0.98–0.96 (6H, d, *J* = 6.7 Hz, **162** + **298**) ppm. *R**-15-((15*S**, 12*R**, 7*S**, 6*R**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-6,15,12,11,8,7-hexahydronaphthalen-15-yl)propanal, **162**; **^{13}C NMR** (500 MHz, $CDCl_3$): δ 205.5 (C=O), 134.3 (C=C), 133.5 (CH), 125.8 (CH), 120.5 (CH), 62.4 (CH_2), 46.2 (CH), 44.1 (CH), 38.4 (CH), 37.2 (CH_2), 34.5 (CH), 34.5 (CH_2), 30.4 (CH), 23.4 (CH_3), 18.1($OSiCH(\underline{C}H_3)_2$), 14.1 ($CH_3$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm; 15-((12*R**, 7*S**, 6*R**)-10-Methyl-6-(((triisopropylsilyl)oxy)methyl)-6,15,12,11,8,7-hexahydronaphthalen-15-yl)propanal, **298**; **^{13}C NMR** (500 MHz, $CDCl_3$): δ 205.3 (C=O), 133.7 (C=C), 133.6 (CH), 125.9 (CH), 120.8 (CH), 60.9 (CH_2), 47.6 (CH), 42.9 (CH), 37.4 (CH_2), 37.2 (CH), 36.4 (CH), 36.3 (CH_2), 30.3 (CH), 23.4 (CH_3), 18.1($OSiCH(\underline{C}H_3)_2$), 14.2 ($CH_3$), 11.9 ($OSi\underline{C}H(CH_3)_2$) ppm. On a mixture **MS** (ESI): m/z 413 ($M+Na^+$); HRMS: found: ($M+Na^+$) 413.2829. $C_{24}H_{42}NaO_2Si$ requires ($M+Na^+$) 413.2846. m/z 391 ($M+H^+$); HRMS: found: ($M+H^+$) 391.3020. $C_{24}H_{43}O_2Si$ requires ($M+H^+$) 391.3027.

(15*S**, 6*S**)-15-Allyl-6-(((triisopropylsilyl)oxymethyl)cyclohex-13-enone, **184**

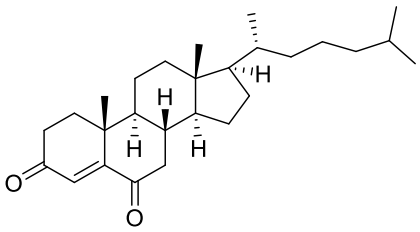


In a microwave tube, to a solution of allyl-cyclohexanone **183** (75.7 mg, 0.230 mmol) in chlorobenzene (2.3 mL), were added $Pd(OAc)_2$ (2.25 mg, 0.010 mmol), 4-4'ditertbutyl-2-2'bypiridyl (2.68 mg, 0.010 mmol) and KNO_3 (12.1 mg, 0.121 mmol). The reaction was stirred at 120 °C for 5 days under O_2 atm. After this time, the reaction was cooled to room temperature and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **184** as a pale yellow oil (23.0 mg, 31% yield, starting material recovered 28.0 mg, 37% yield, 68% yield b.r.s.m.). **Rf** = 0.48 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2941, 2865, 1680 (C=O), 1462, 1382, 1247, 1067, 995 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.95 (1H, dd, *J* = 10.5, 4.6 Hz, H-7), 6.10 (1H, dd, *J* = 10.5, 1.8 Hz, H-12), 5.75 (1H, dddd, *J* = 15.6, 12.5, 7.3, 5.5 Hz, H-17), 5.10–5.03 (2H, m, H-18), 3.94 (1H, dd, *J* = 9.8, 6.4 Hz, H-5), 3.87 (1H, dd, *J* = 9.8, 5.5 Hz, H-5), 2.71–2.65 (1H, m, H-15), 2.58 (1H, dd, *J* = 17.4, 11.3 Hz, H-14), 2.39 (1H, dd, *J* = 17.4, 4.1 Hz, H-14), 2.36–2.32 (1H, m, H-6), 2.26 (1H, ddddd, *J* = 13.7, 6.4, 5.5, 1.4, 1.4 Hz, H-16), 2.10 (1H, ddddd, *J* = 13.7, 7.3, 7.3, 0.9, 0.9 Hz, H-16), 1.14–1.04 (21H, m, $OSiCH(CH_3)_2$) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 199.9 (C-13), 151.4 (C-7), 135.9 (C-17), 130.2 (C-12), 117.1 (C-18), 62.5 (C-5), 41.5 (C-6), 41.4 (C-14), 35.9 (C-15), 35.3 (C-16), 18.0 ($OSiCH(\underline{C}H_3)_2$), 11.8 ($OSi\underline{C}H(CH_3)_2$) ppm. **MS** (ESI): m/z 345 ($M+Na^+$); HRMS: found: ($M+Na^+$) 345.2224. $C_{19}H_{34}NaO_2Si$ requires ($M+Na^+$) 345.2220. m/z 323 ($M+H^+$); HRMS: found: ($M+H^+$) 323.2402. $C_{19}H_{35}O_2Si$ requires ($M+H^+$) 323.2401.

(*S*, *S*, *R*, *R*, *S*, *R*)-Dimethyl-((*R*)-methylheptan-yl)dodecahydrocyclopenta[a]phenanthren-one, **181**



(*S*, *S*, *R*, *R*, *S*, *R*)-Dimethyl-((*R*)-methylheptan-yl)-decahydro-cyclopenta[a]phenanthrene-dione, **182**



In a microwave tube, to a solution of cholesterone **180** (115 mg, 0.300 mmol) in chlorobenzene (3.0 mL), were added $Pd(OAc)_2$ (4.49 mg, 0.020 mmol), 4-4'ditertbutyl-2-2'bypiridyl (5.37 mg, 0.020 mmol) and KNO_3 (15.2 mg, 0.150 mmol). The reaction was stirred at 120 °C for 3 days under O_2 atm. After this time, the reaction was cooled to room temperature and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel flash column chromatography (3% to 10% EtOAc in hexanes) to yield **181** as a pale yellow oil (21.0 mg, 18% yield) and **182** as a pale yellow solid (28.0 mg, 24% yield). (*S*, *S*, *R*, *R*, *S*, *R*)-Dimethyl-((*R*)-methylheptan-yl)dodecahydrocyclopenta[a]phenanthren-one, **181**; $[\alpha]^{20}_D$ -19.2 (c 1.00, $CHCl_3$). **Rf** = 0.31 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2944, 2866, 1663 (C=O), 1585, 1465, 1417, 1325, 967, 924 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.18–6.06 (2H, m), 5.69–5.65 (1H, m, CH), 2.71–2.52 (1H, m), 2.49–2.39 (1H, m), 2.23–2.15 (1H, m), 2.07 (1H, ddd, *J* = 12.5, 2.9, 2.9 Hz), 2.00 (1H, ddd, *J* = 13.2, 5.4, 2.1 Hz), 1.96–1.85 (2H, m), 1.84–1.76 (1H, m), 1.71 (1H, ddd, *J* = 13.7, 13.7, 5.0 Hz), 1.58–1.47 (3H, m), 1.46–1.29 (5H, m), 1.28–1.13 (7H, m), 1.11 (3H, s), 0.92 (3H, d, *J* = 6.4 Hz), 0.88 (3H, d, *J* = 1.8 Hz), 0.86 (3H, d, *J* = 1.8 Hz), 0.76 (3H, s) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 199.8 (C=O), 164.2 (C-C), 141.7 (CH), 127.7 (CH), 123.4 (CH), 56.0 (CH), 53.4 (CH), 50.6 (CH), 43.4 (C-C), 39.5 (CH_2), 39.4 (CH_2), 37.7 (CH), 36.1 (C-C), 36.0 (CH_2), 35.8 (CH), 33.9 (CH_2), 33.8 (CH_2), 28.1 (CH_2), 27.9 (CH), 23.8 (CH_2), 23.7(CH_2), 22.8 (CH_3), 22.5 (CH_3) , 20.6 (CH_2), 18.6 (CH_3), 16.3 (CH_3), 11.9 (CH_3)

ppm. **MS** (ESI): m/z 405 ($M+Na^+$); HRMS: found: ($M+Na^+$) 405.3111. $C_{27}H_{42}NaO$ requires ($M+Na^+$) 405.3128. m/z 383 ($M+H^+$); HRMS: found: ($M+H^+$) 383.3302. $C_{27}H_{43}O$ requires ($M+H^+$) 383.3308. (*S*, *S*, *R*, *R*, *S*, *R*)-Dimethyl-((*R*)-methylheptan-yl)-decahydro-cyclopenta[a]phenanthrene-dione, **182**; $[\alpha]^{20}_D$ -13.9 (c 1.00, $CHCl_3$). **Melting point** = 81–83 °C. **Rf** = 0.28 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2946, 2867, 1683 (C=O), 1465, 1415, 1381, 1327, 1219, 1082, 915 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.16 (1H, s), 2.68 (1H, dd, *J* = 15.8, 3.9 Hz), 2.61–2.41 (2H, m), 2.18–2.06 (2H, m), 2.05–2.02 (1H, m), 1.95–1.82 (4H, m), 1.68–1.58 (2H, m), 1.57–1.44 (3H, m), 1.41–1.19 (6H, m), 1.16 (3H, s), 1.13–1.08 (5H, m), 0.92 (3H, d, *J*=6.4 Hz), 0.87 (3H, d, *J*=1.5 Hz), 0.85 (3H, d, *J* = 1.5 Hz), 0.72 (3H, s) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 202.4 9 (C=O), 199.5 (C=O), 161.1 (C-C), 125.4 (CH), 56.5 (CH), 55.9 (CH), 50.9 (CH), 46.8 (CH_2), 42.5 (C-C), 39.8 (C-C), 39.4 (CH_2), 39.1 (CH_2), 36.0 (CH_2), 35.6 (CH), 35.5 (CH_2), 34.1 (CH), 33.9 (CH_2), 27.6 (CH + CH_2), 23.9 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.8 (CH_2) , 18.6 (CH_3), 17.5 (CH_3), 11.8 (CH_3) ppm. **MS** (ESI): m/z 421 ($M+Na^+$); HRMS: found: ($M+Na^+$) 421.3080. $C_{27}H_{42}NaO_2$ requires ($M+Na^+$) 421.3077.

13. Abbreviations

Å	Ångstrom
ACP	acyl carrier protein
AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
Br_2	bromine
$BF_3{\cdot}Et_2O$	borane trifluoride-diethyl etherate
brsm	based on recovered starting material
n-BuLi	butyl lithium
s-BuLi	*sec*-butyl lithium
t-BuOH	*tert*-butanol
CA	california
CBr_4	carbon tetrabromide
C-C	carbon-carbon
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
CH_3CN	acetonitrile
CH_2N_2	diazomethane
ClPh	chlorobenzene
CSA	camphorsulfonic acid
d	day
D-Ala	D-alanine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethysulfoxide

DNA	deoxyribonucleic acid
dr	diastereomeric ratio
ESI	electrospray ionisation
EI	electron ionisation
Et_2O	diethyl ether
EtOAc	ethylacetate
EtOH	ethanol
Et_3N	triethylamine
FAD	flavin adenine dinucleotide
FGI	functional group interconversion
g	gram
h	hour
H_2	hydrogen
HCC	hepatocellular carcinoma
HCl	hydrochloric acid
HG II	hoveyda-Grubbs 2nd generation catalyst
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HF	hydrogen fluoride
H_2O_2	hydrogen peroxide
Hg	mercury
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
I_2	iodine
IBX	2-iodoxy benzoic acid
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide
KNO_3	potassium nitrate
KOH	potassium hydroxide
kJ	kilojoule

LDA	lithium diisopropylamide
LED	light emitting diodie
Li	lithium
$LiAlH_4$	lithiumaluminium hydride
LiCl	lithium chloride
LovBPKS	lovastatin B polyketide synthase
LUMO	lowest unoccupied molecular orbital
M	molar
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeLi	methylithium
MeMgI	methylmagnesium
MeOH	methanol
MIC	minimum inhibitory concentration
Min.	minutes
Ms	mesyl (methanesulfonyl)
MsCl	mesylchloride
mg	milligram
MHz	megahertz
MRSA	methicillin resistant bacteria
MS	mass spectrometry
M.S.	molecular sieves
MW	microwaves
*m*TOR	mammalian target of rapamycin
$NaHCO_3$	sodium bicarbonate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear overhauser effect
O_2	oxygen
$Pd(OAc)_2$	palladium acetate
Pd/C	palladium on carbon

$Pd(PPh_3)_4$	palladium tetrakis(triphenylphosphine)
Ph	phenyl
$PhI(OAc)_2$	diacetoxyiodo benzene
PhSH	thiophenyl
PKS	polyketide synthase
PPh_3	triphenylphosphine
PMB	*p*-methoxybenzyl
Py	pyridine
RNA	ribonucleic acid
rt	room temperature
SmI_2	samarium diodide
SiO_2	silica
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TS	transition state
v	vibration frequency (cm^{-1})

14. References

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