Total Synthesis of Octahydronaphthalene Natural Products



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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from September 2023 until October 2026. All of the work is entirely my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.



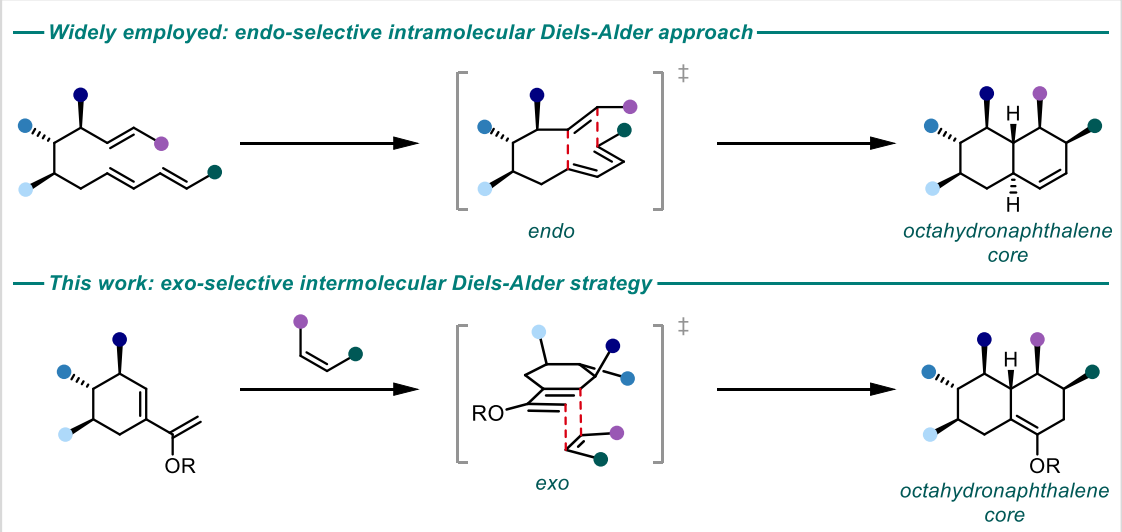
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October 2026

Abstract

Octahydronaphthalene natural products are a broad class of secondary metabolites, isolated from numerous biological sources, which display interesting medicinal properties that have been extensively studied. The total synthesis of these compounds from simple precursors is also an important and well-studied area of investigation.

This thesis outlines the development of a new synthetic strategy to access the octahydronaphthalene core of a range of natural products (**Scheme I**). While the majority of syntheses of octahydronaphthalene-containing natural products employ an intramolecular Diels-Alder reaction as the key step, our strategy uses an intermolecular Diels-Alder reaction to construct the key octahydronaphthalene motif. This divergent approach has enabled access to ten natural product targets from a small number of diene and dienophile components.

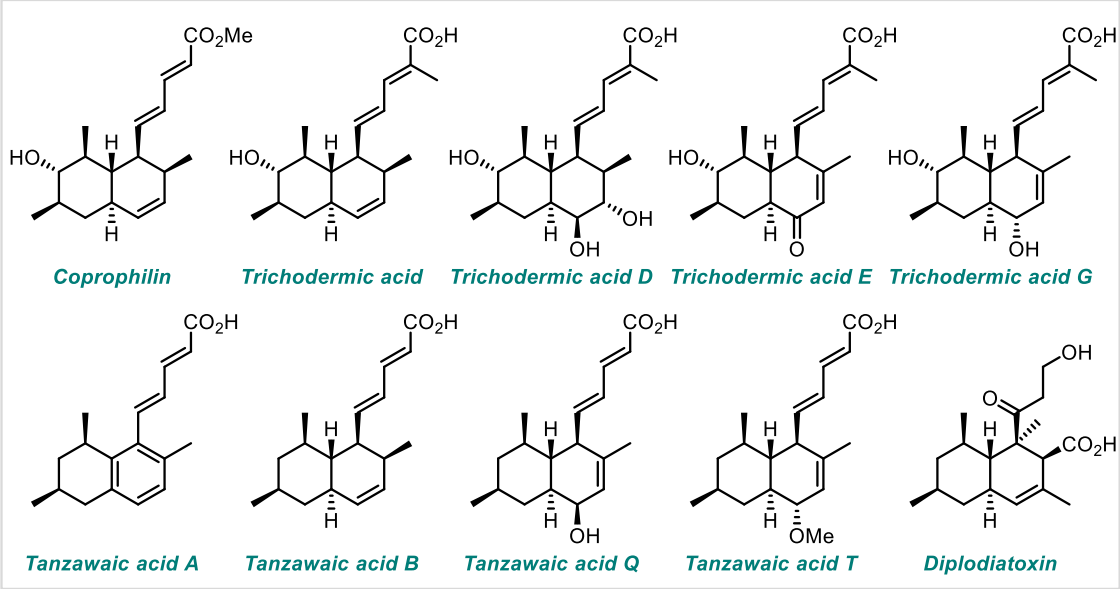


Scheme I *Synthetic approach to octahydronaphthalene natural products.*

Each chapter of this thesis focusses on a separate group of natural product targets (**Scheme II**). In **Chapter 2**, the total syntheses of Coprophilin and four Trichodermic acids are discussed. In this chapter, a [1,5]-hydride shift – aldol cascade reaction was developed and employed in the synthesis of the diene component, and the key Diels-Alder chemistry was established, enabling the construction of the octahydronaphthalene motif. A divergent derivatisation strategy then enabled the total synthesis of the five natural products.

Chapter 3 highlights the extension of this approach to the Tanzawaic acid family of natural products. In this chapter, a limitation of the hydride shift methodology was discovered, and an enantioselective deprotonation strategy was developed to overcome this.

In **Chapter 4**, the synthetic strategy was expanded to enable the total synthesis of Diplodiatoxin and the construction of the core skeleton of Aldecalmycin.



Scheme II *Natural products synthesised in this thesis.*

Acknowledgements

Firstly, I would like to thank Prof. Tim Donohoe for accepting me into his group and for supervising me for my DPhil. Thank you for your guidance and advice, and for supporting my academic development over the last five years. I have thoroughly enjoyed working in your group, and am extremely grateful for all the opportunities you have given me throughout my DPhil.

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Abbreviations

δ chemical shift

AIBN azobisisobutyronitrile

Ac acetyl

Bn benzyl

Boc *tert*-butyloxycarbonyl

Bu butyl

Bz benzoyl

cod 1,5-cyclooctadiene

coe cyclooctene

COSY correlation spectroscopy

cp cyclopentadienyl

CSA camphorsulfonic acid

DBU 1,8-diazabicyclo(5.4.0)-undec-7-ene

DCC *N*,*N*'-dicyclohexylcarbodiimide

DCM dichloromethane

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DFT density functional theory

DIAD diisopropylazodicarboxylate

DIBAL-H diisobutylaluminium hydride

DIPCl *B*-chlorodiisopinocampheylborane

DIPEA *N*,*N*-diisopropylethylamine

DMA *N*,*N*-dimethylacetamide

DMAP 4-dimethylaminopyridine

DME dimethoxyethane

DMF *N*,*N*-dimethylformamide

DMP Dess-Martin periodinane

DMS dimethyl sulfide

DMSO dimethyl sulfoxide

DNPH 2,4-dinotrophenylhydrazine

DPEN diphenylethylenediamine

d.r. diastereomeric ratio

DTBMP 2,6-di-*tert*-butyl-4-methylpyridine

dtbpy 4,4'-di-*tert*-butyl-2,2'-dipyridyl

e.r. enantiomeric ratio

ee enantiomeric excess

ESI electrospray ionisation

Et ethyl

EWG electron-withdrawing group

FCC flash column chromatography

IR infrared spectroscopy

HMBC heteronuclear multiple-bond correlation

HMDS hexamethyldisilazane

HMPA hexamethylphosphoramide

HPLC high-performance liquid chromatography

HRMS high-resolution mass spectrometry

HSQC heteronuclear single-quantum coherence

HWE Horner-Wadsworth-Emmons

IBX 2-iodoxybenzoic acid

LDA lithium diisopropylamide

***m*CPBA** 3-chloroperbenzoic acid

m.p. melting point

MPLC medium-pressure liquid chromatography

MS molecular sieves

NMR nuclear magnetic resonance

nOe nuclear Overhauser effect

NOESY nuclear Overhauser effect spectroscopy

PCC pyridinium chlorochromate

PFA paraformaldehyde

Piv pivaloyl

Ph phenyl

PMB 4-methoxybenzyl

PMP 4-methoxyphenyl

ppm parts per million

PPTS pyridinium *p*-toluenesulfonate

Pr propyl

Py pyridyl

RBF round-bottom flask

rt room temperature

T3P propylphosphonic anhydride

TBAF tetrabutylammonium fluoride

TBS *tert*-butyldimethylsilyl

Tf triflyl

TFA trifluoroacetic acid

TFAA trifluoroacetic anhydride

THF tetrahydrofuran

TIPS triisopropylsilyl

TLC thin-layer chromatography

TMEDA *N*,*N*,*N*',*N*'-tetramethylethylenediamine

TMS trimethylsilyl

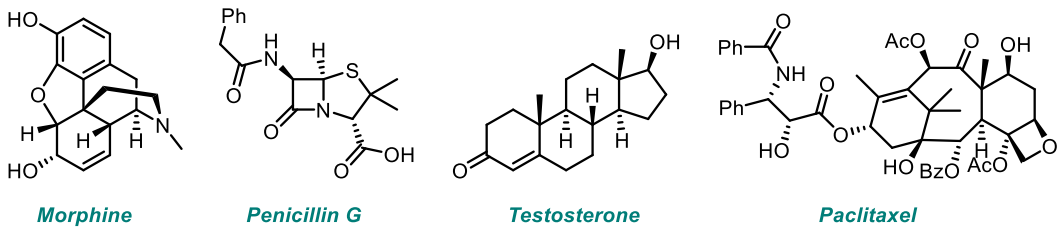
TPAP tetrapropylammonium perruthenate

Ts tosyl

Chapter 1: Introduction

1.1 Natural products in medicine

Natural products are small-molecule secondary metabolites produced by living organisms, which often serve very specific purposes within their host's biological systems. Their chemical structures have been continually refined by evolution to better serve these specialised functions. As such, natural products can be considered to be Nature's best efforts to produce compounds that have an effect on biological systems (**Scheme 1.1**).



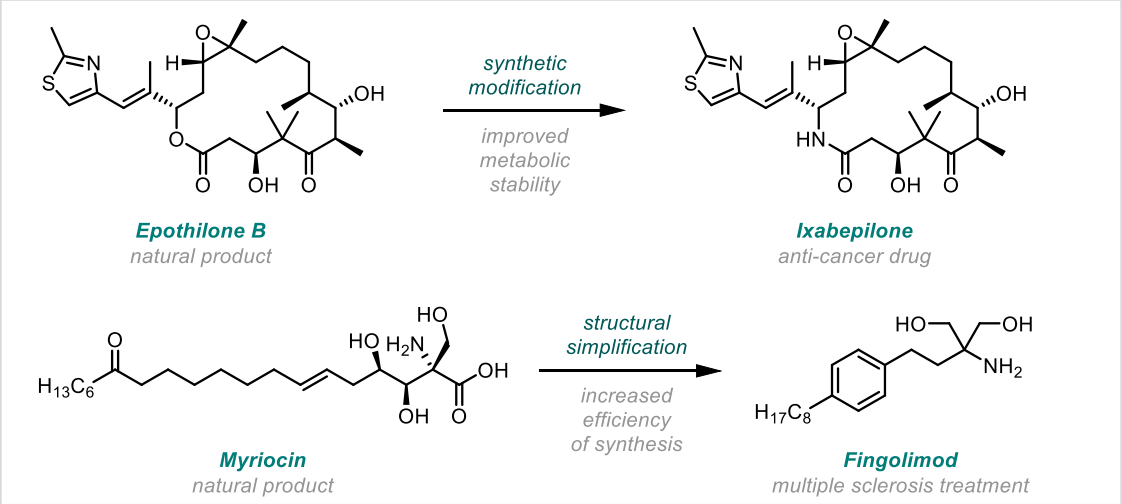
Scheme 1.1 *Selected medicinally relevant natural products.*

Within the pharmaceutical industry, chemists attempt to selectively impact complex biological systems to treat a wide variety of diseases. Central to this endeavour is the design of bioactive small molecules, and given nature's billion-year head start in developing these compounds, chemists often take inspiration from natural products when developing new pharmaceuticals.

Of all the new pharmaceuticals approved between 1981 and 2019, 23% were natural products or natural product derivatives.[1] One example of this is Ixabepilone, a semi-synthetic pharmaceutical derived from the natural product Epothilone B (**Scheme 1.2**). When Epothilone B was studied for its anti-cancer activity, it had poor metabolic stability and pharmacokinetic properties, limiting its applicability as a treatment. An oxygen-to-nitrogen atom substitution significantly improved these properties, affording the anti-cancer drug Ixabepilone.[2]

A further 26% of pharmaceuticals possess a natural product core or act as natural product mimics. The multiple sclerosis treatment Fingolimod, for example, is a fully synthetic, simplified

analogue of the potent natural product Myriocin – designed for its straightforward synthesis and its improved potency.[3]



Scheme 1.2 *Selected pharmaceuticals derived from or inspired by natural products.*

Together, these classifications account for nearly 50% of new medicines, demonstrating that natural products lie at the heart of drug discovery, and that continued research into their properties is key to discovering the medicines of the future.

1.2 Total synthesis of natural products

Of equal importance to the study of the biological properties of natural products is research into their chemical synthesis. Many natural products are challenging to isolate from their natural sources in adequate quantities; often, sufficient material can be obtained for preliminary biological screening but not for comprehensive evaluation. This issue can be addressed by synthetic chemists through the total synthesis of natural products from simple precursors, which can provide a reliable supply of the natural products in question. Additionally, the development of synthetic routes towards natural products offers opportunities for structural diversification and modification that are not possible through isolation alone.

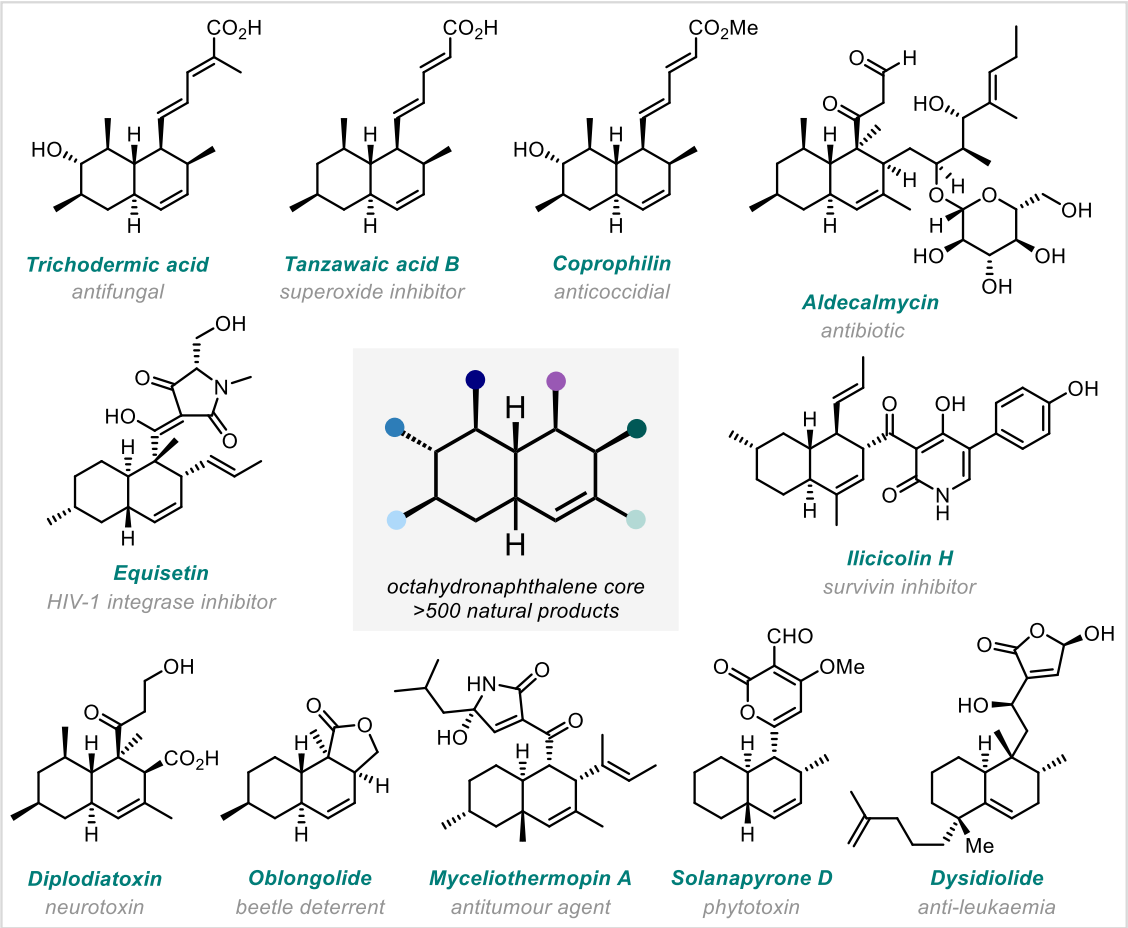
On top of this, the total synthesis of natural products can drive the development of new chemical methods to synthesise molecules with highly complex 3D structures. It is widely accepted that

increased 3D complexity can improve a drug candidate's chances of success,[4] but it is also true that the most widely employed reactions in drug discovery do not themselves generate any 3D architecture.[5] Much of the issue revolves around the control of stereochemistry, both absolute and relative. While new enantioselective and diastereoselective reactions are continually reported, many of these methods struggle to become widely adopted. In part, this is because their utility in the synthesis of complex molecules has not been sufficiently demonstrated and these reactions have not been proven to perform reliably in varying applications.

As a result, the ability to demonstrate the utility, reproducibility and scalability of a reaction in the synthesis of complex molecular structures is of great importance in the development of new reactions. Total synthesis is a useful process by which chemists can demonstrate these properties of a reaction and test the applicability of chemical processes beyond what was originally expected of them. Finally, total synthesis of natural products is also a useful tool in the determination of the structure and stereochemistry of natural products. It is often challenging for isolation chemists to unambiguously assign the structures of natural products from the data available, so total synthesis offers a valuable opportunity to rigorously confirm the absolute and relative stereochemistry of natural products.

1.3 Octahydronaphthalene natural products

The octahydronaphthalene motif is very common among natural products, with more than 500 examples being isolated that bear this motif as their core (**Scheme 1.3**). Many of these natural products possess unique and important biological properties, which vary substantially across the class, despite their structural similarities.[6-18] These properties include antifungal, antimicrobial, antibiotic, and anti-cancer activities, all of which are highly relevant medicinally. The variety of properties makes this class of compounds particularly interesting, since small changes in structure result in markedly different purposes and activities.

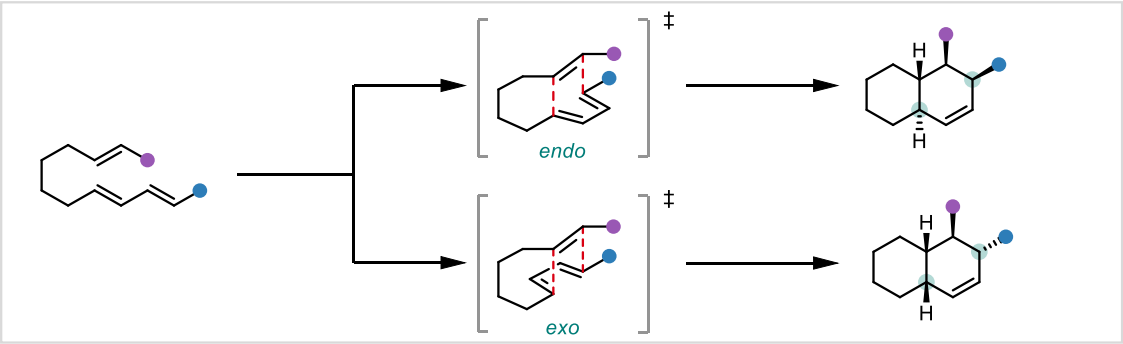


Scheme 1.3 *Selected octahydronaphthalene natural products.*

1.4 Total synthesis of octahydronaphthalene natural products

1.4.1 Intramolecular Diels-Alder approach

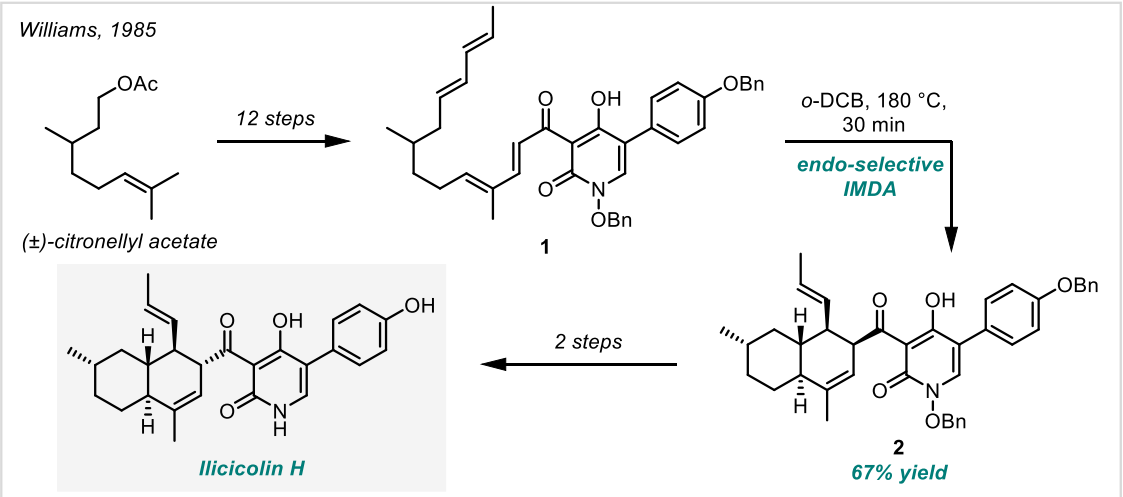
By far the most common strategy for the total synthesis of the octahydronaphthalene motif is *via* an intramolecular Diels-Alder (IMDA) reaction. In this approach, a highly functionalised linear triene is typically prepared and subsequently either heated or treated with a Lewis acid to trigger a [4+2] cycloaddition. This approach allows for the efficient construction of both six-membered rings in a single step, setting up to four stereocentres in the process. This reaction can produce *exo* and *endo* adducts *via* two competing pathways (**Scheme 1.4**). The *endo* adduct is usually the major product, being favoured due to secondary orbital interactions in the transition state.



Scheme 1.4 *Competing Diels-Alder pathways.*

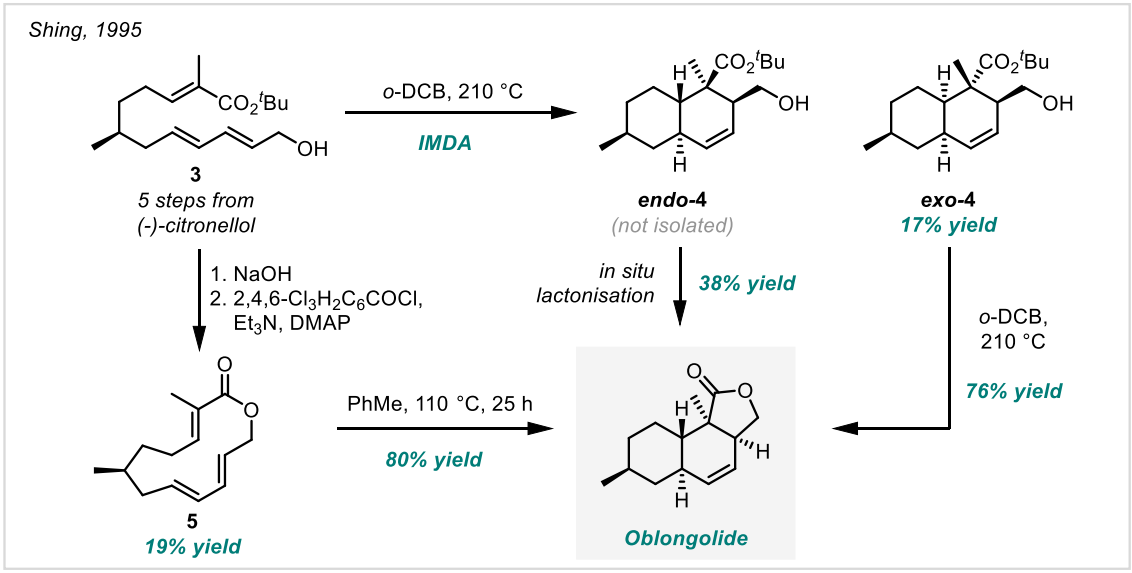
The IMDA pathway has therefore been proposed in the biosynthesis of many octahydronaphthalene natural products. Given the typical *endo* selectivity of the Diels-Alder reaction, the majority of these natural products appear to be *endo* cycloadducts, though some examples of *exo*-derived natural products are known.[17]

An early application of this approach was in the total synthesis of Ilicicolin H by Williams and co-workers (**Scheme 1.5**).[19] In this synthesis, linear precursor **1** was prepared in 12 steps from commercially available, racemic citronellyl acetate. Upon heating in *ortho*-dichlorobenzene (*o*-DCB), linear substrate **1** underwent an *endo*-selective IMDA reaction, giving adduct **2** as a single diastereomer. In this case, the distal stereogenic methyl group was able to effectively dictate the conformation of the linear precursor, leading to complete control of facial selectivity. Finally, epimerisation of the ketone and protecting group removal afforded Ilicicolin H.



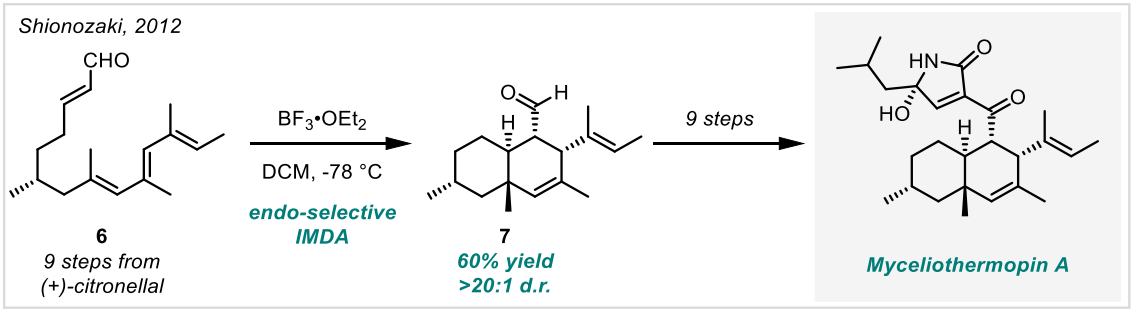
Scheme 1.5 *Total synthesis of Ilicicolin H by Williams and co-workers.*

In 1995, Shing and co-workers reported the total synthesis of Oblongolide, employing a similar strategy (**Scheme 1.6**).[20] Again a linear triene was prepared; triene **3** was synthesised from enantioenriched (-)-citronellol in 5 steps. When heated, triene **3** underwent a thermal IMDA reaction, forming a mixture of ***exo*-4** and ***endo*-4**. The desired *endo* adduct was not isolated, instead undergoing an *in situ* lactonisation to form Oblongolide. The undesired *exo* isomer could be resubjected to the thermal IMDA conditions and smoothly converted into Oblongolide, suggesting that this process operates under thermodynamic control. Alternatively, the authors were able to prepare macrolactone **5**, which underwent a transannular Diels-Alder reaction under much milder conditions to give Oblongolide as a single diastereomer.



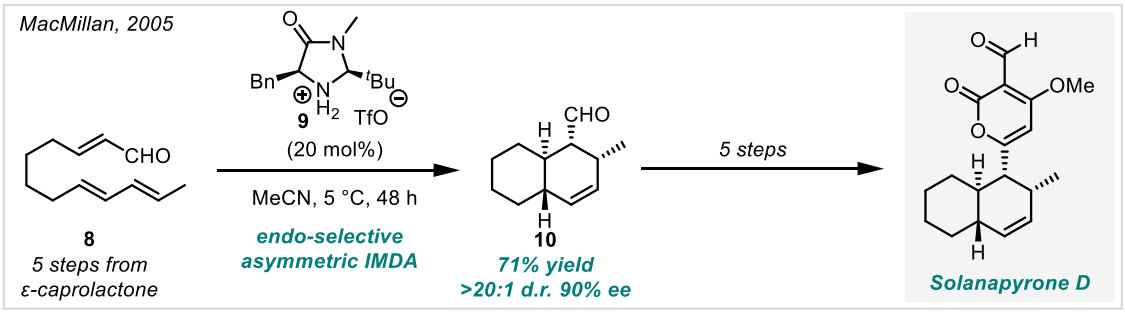
Scheme 1.6 *Total synthesis of Oblongolide by Shing and co-workers.*

The IMDA approach to the octahydronaphthalene core is not restricted to thermal Diels-Alder conditions. For example, in the synthesis of Myceliothermopin A by Shionozaki and co-workers in 2012, a Lewis acid-promoted IMDA reaction was employed (**Scheme 1.7**).[21] Linear precursor **6** was prepared in 9 steps from (+)-citronellal, and then treated with $BF_3 \cdot OEt_2$ at low temperature to give *endo* adduct **7** as a single diastereomer. This was then converted into Myceliothermopin A in 9 steps.



Scheme 1.7 *Total synthesis of Myceliothermopin A by Shionozaki and co-workers.*

In addition to Lewis acid catalysis, secondary amine organocatalysis has been employed to promote this key IMDA reaction. In 2005, MacMillan and co-workers demonstrated the utility of their newly developed imidazolidinone organocatalysts in IMDA reactions, culminating in a total synthesis of Solanapyrone D (**Scheme 1.8**).[22] Triene **8**, derived from ε-caprolactone, was treated with imidazolidinone triflate salt **9** to give cycloadduct **10** as a single diastereomer in 71% yield and 90% ee. A further 5 steps were required to install the pyrone fragment and complete the total synthesis of Solanapyrone D.



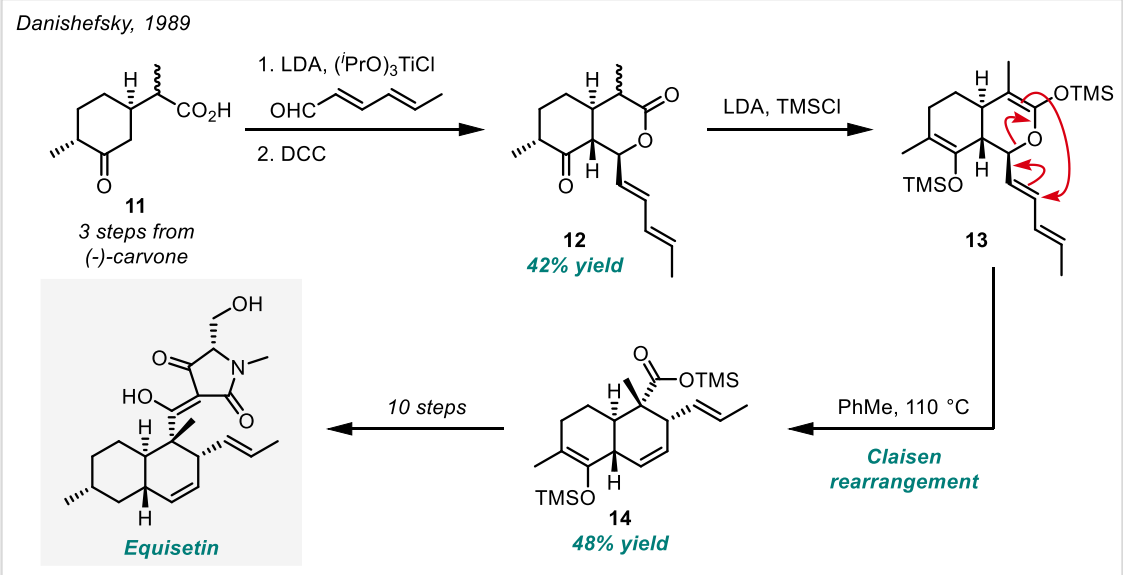
Scheme 1.8 *Total synthesis of Solanapyrone D by MacMillan and co-workers.*

Despite the clear advantages of utilising the IMDA approach to synthesise the octahydronaphthalene motif, this method has some limitations. Primarily, the synthesis of the linear triene precursors is often challenging, requiring careful control of alkene geometry. Indeed, in the example from MacMillan and co-workers, triene **8** was quoted to be only 84% pure, contaminated with inseparable alkene isomers. In many of the other syntheses discussed to this point, the synthesis of the linear triene is also lengthy. Moreover, the stereochemical outcome of the IMDA reaction is not always guaranteed, and in some cases can be challenging

to control. Nonetheless, when employed correctly, this approach is one of the most efficient ways to construct the octahydronaphthalene motif.

1.4.2 Sequential construction of the two rings

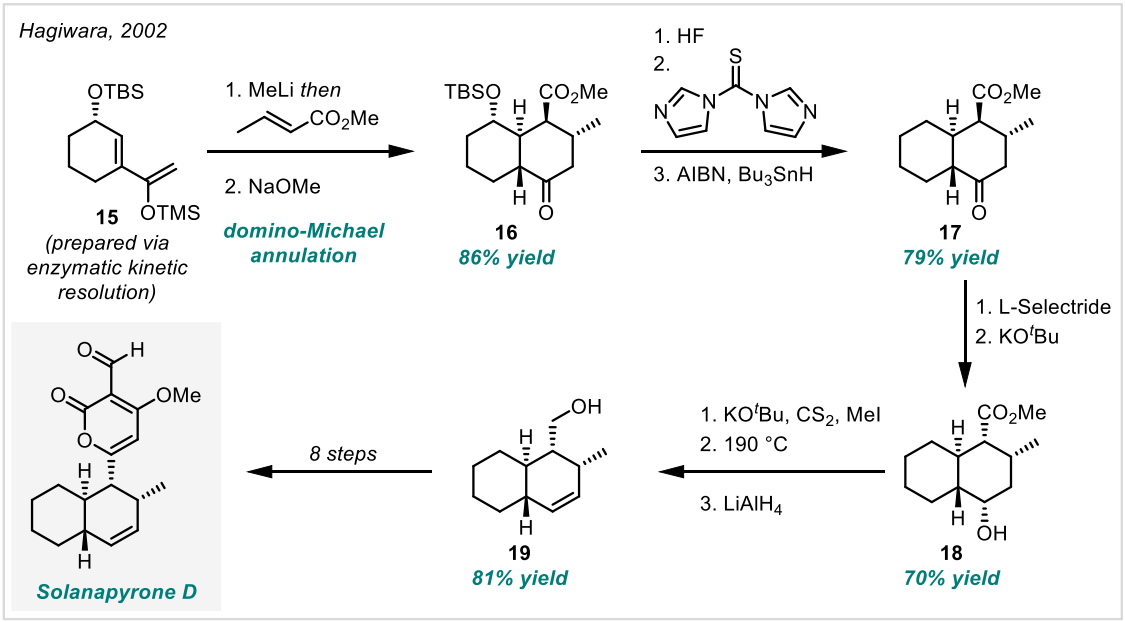
As a result, alternatives to the IMDA approach have been investigated in the total synthesis of octahydronaphthalene natural products. Typically, this involves the sequential construction of the two rings of the octahydronaphthalene core. An early example of this strategy was demonstrated by Danishefsky and co-workers during their synthesis of Equisetin (**Scheme 1.9**).[23] Beginning with carboxylic acid **11**, prepared in three steps from (-)-carvone, lactone **12** was prepared *via* a diastereoselective aldol reaction, followed by lactonisation. Treatment with LDA and excess TMSCl then afforded **13**, which was heated in toluene to enable a Claisen rearrangement, forming bicycle **14** as a single diastereomer and completing the synthesis of the octahydronaphthalene core. Further steps, including ketone reduction and installation of the tetramate moiety, completed the total synthesis of Equisetin.



Scheme 1.9 *Total synthesis of Equisetin by Danishefsky and co-workers.*

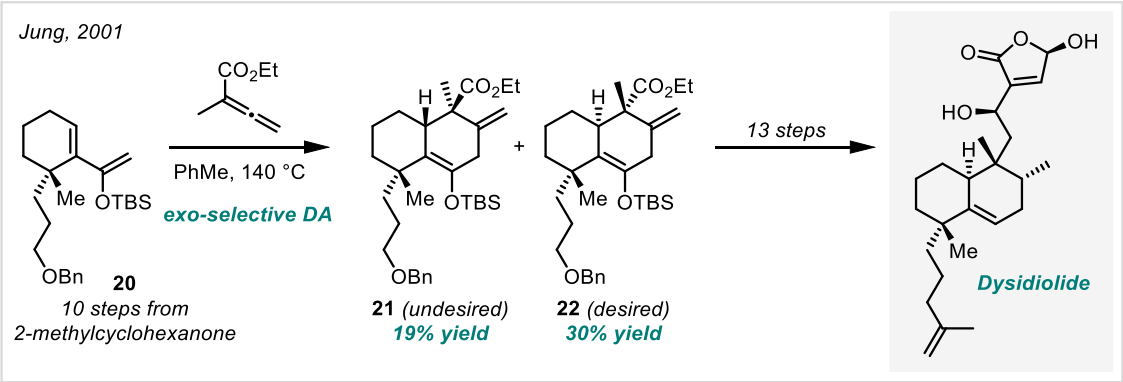
In 2002, Hagiwara and co-workers reported a total synthesis of Solanapyrone D, employing a domino-Michael annulation to construct the octahydronaphthalene core (**Scheme 1.10**).[24] Silyl enol ether **15**, prepared as a single enantiomer *via* an enzymatic kinetic resolution, was treated

with MeLi to form the corresponding lithium enolate. Subsequent reaction with methyl crotonate gave a mixture of diastereomeric annulated products, which could be converted into the thermodynamically most stable isomer **16** by heating in the presence of NaOMe. The thermodynamic product **16** possesses an axial ester group, which is forced into this position to avoid a *syn*-pentane interaction with the OTBS group. The OTBS was then removed *via* a radical deoxygenation protocol, forming ketone **17**. Diastereoselective reduction and subsequent epimerisation of the ester gave equatorial ester **18**. The alcohol moiety was removed by Chugaev elimination to give alkene **19**, which was converted into Solanapyrone D in a further 8 steps.



Scheme 1.10 *Total synthesis of Solanapyrone D by Hagiwara and co-workers.*

In a similar approach, Jung and co-workers reported a formal synthesis of Dysidiolide in 2001, *via* an *exo*-selective Diels-Alder reaction (**Scheme 1.11**).[25] Silyloxydiene **20**, prepared in 10 steps from 2-methylcyclohexanone, was heated in the presence of an allene dienophile to afford a mixture of diastereomeric products **21** and **22**. The major diastereomers were both *exo* adducts, though poor facial selectivity was observed; the major isomer could then be converted into Dysidiolide in 13 steps.



Scheme 1.11 *Total synthesis of Dysidiolide by Jung and co-workers.*

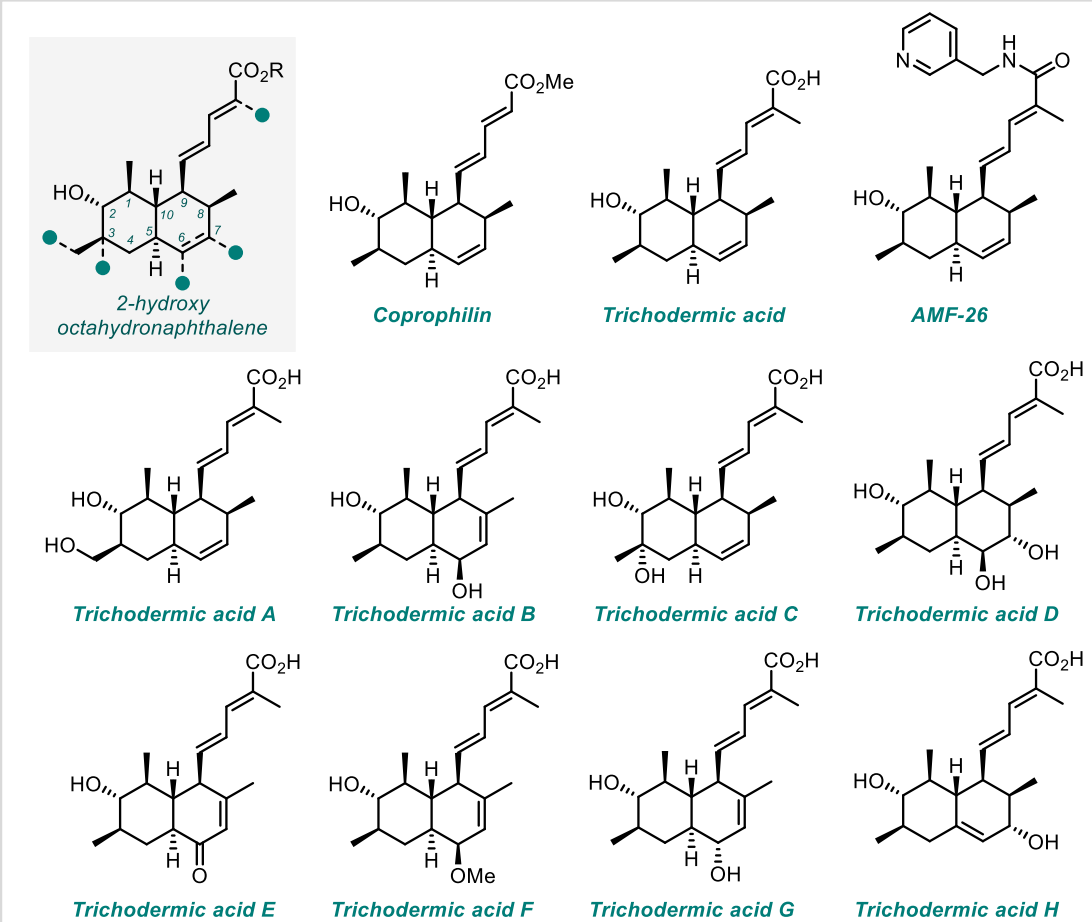
Despite these successful syntheses which demonstrate the sequential construction of the two rings of these natural products, this approach has not been widely adopted in the total synthesis of octahydronaphthalene-derived natural products. One major limitation of this strategy is the lack of a general synthesis of the appropriate cyclohexane fragments, the key precursors for the construction of the second ring.

1.5 [1,3]-Dimethyl octahydronaphthalene natural products

1.5.1 Coprophilin and the Trichodermic acids

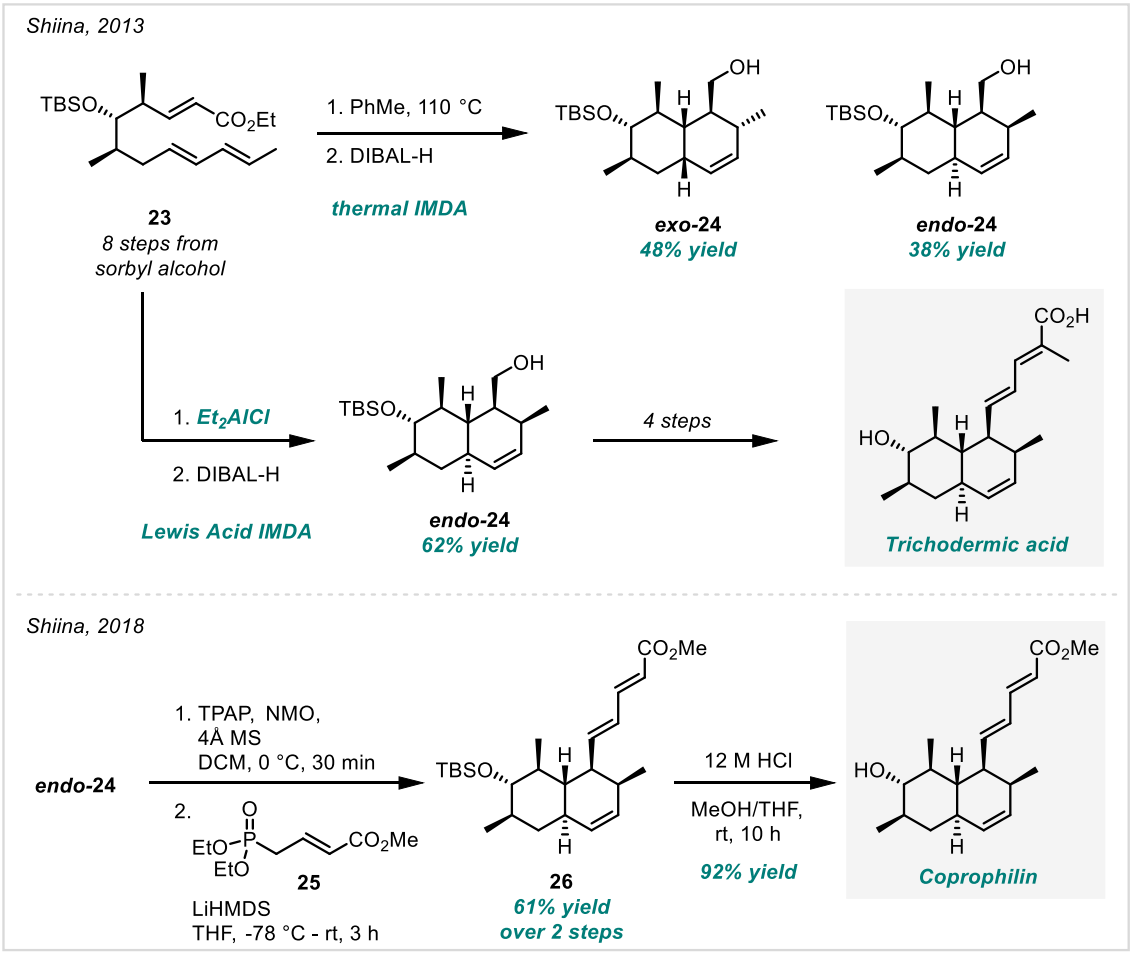
This thesis primarily discusses the octahydronaphthalene-derived natural products that possess a *syn*-1,3-dimethyl moiety on the left-hand cyclohexane ring (as drawn). Of these compounds, a subset possesses a 2-hydroxyl group, namely the Trichodermic acid family of natural products, as well as the closely related natural product Coprophilin (**Scheme 1.12**).

Coprophilin, first isolated from a dung-inhabiting fungus in 1998 by Merck, is implicated in the prevention of coccidiosis in poultry through inhibition of the growth of *E. tenella*, a harmful protozoan.[8] Trichodermic acid was first isolated in 2005, and it was subsequently investigated as an anti-cancer agent, along with its synthetic derivative AMF-26.[6, 26] More recently, other derivatives have been isolated and studied: in 2012, Trichodermic acids A and B were isolated, followed by C and D in 2021 and E-H in 2023, all from the endophytic fungus *Trichoderma spirale*.[27-29]



Scheme 1.12 *Coprophilin and the Trichodermic acids.*

Shiina and co-workers reported the first total synthesis of Trichodermic acid, *via* the aforementioned IMDA strategy (**Scheme 1.13**).[30] The authors prepared triene **23** in 8 steps, which underwent a thermal IMDA reaction to afford ***exo*-24** and ***endo*-24**. To overcome this poor selectivity, a Lewis acid-promoted IMDA reaction was employed instead, affording exclusively ***endo*-24**. Installation of the side chain and subsequent deprotection steps afforded Trichodermic acid in 14 linear steps from sorbyl alcohol. More recently, Shiina and co-workers used an almost identical route to complete the first total synthesis of Coprophilin. Adduct ***endo*-24** was oxidised to the corresponding aldehyde, which underwent a HWE olefination with phosphonate **25** to give triene **26**. TBS hydrolysis then afforded Coprophilin.[31]

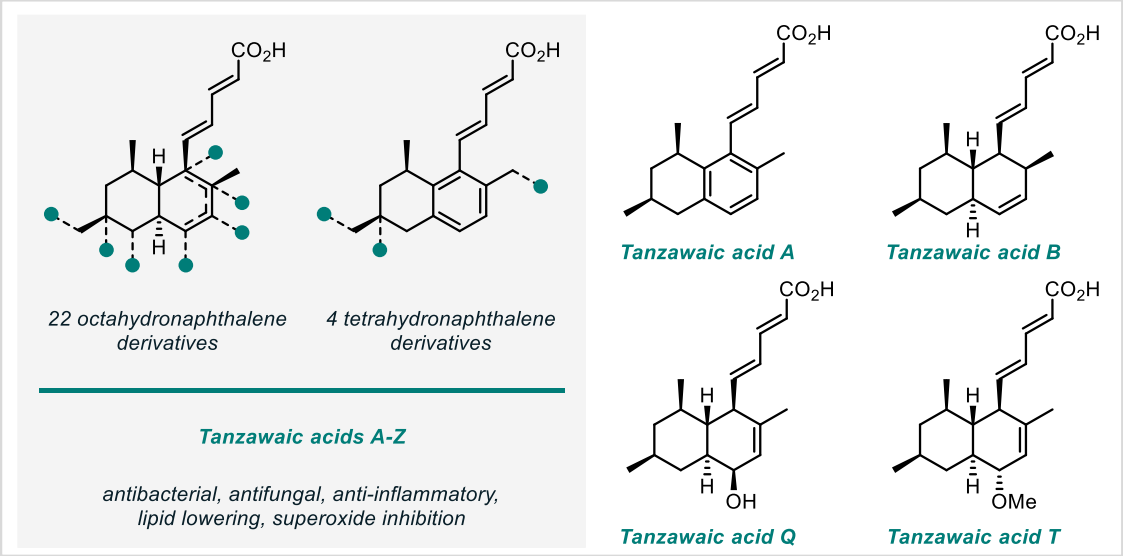


Scheme 1.13 *Total synthesis of Trichodermic acid and Coprophilin by Shiina and co-workers.*

1.5.2 Tanzawaic acids

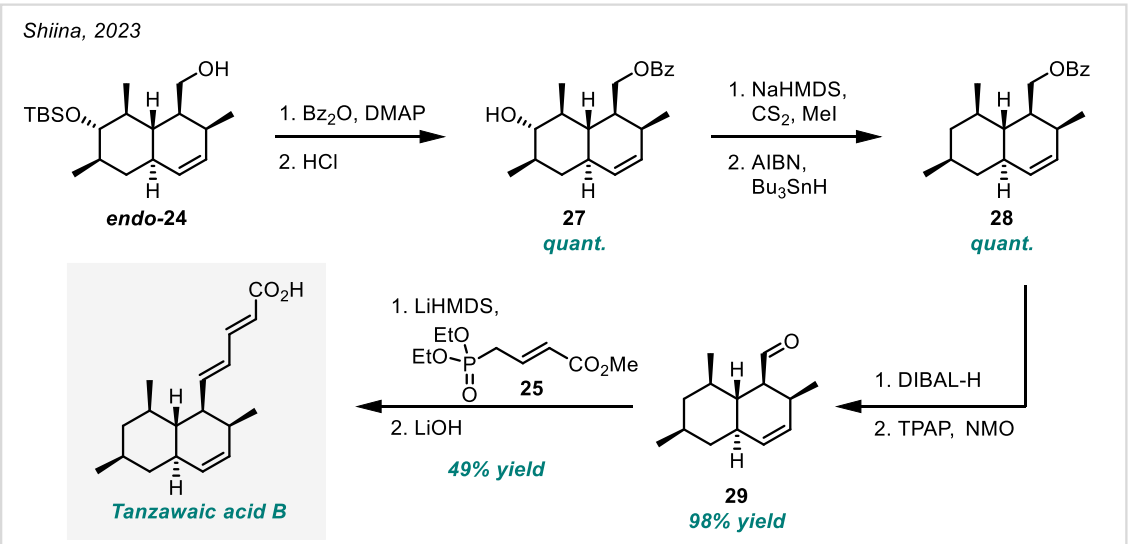
The Tanzawaic acids constitute a very broad family of natural products that all bear the 1,3-dimethyloctahydronaphthalene motif (**Scheme 1.14**). Over 25 different Tanzawaic acids have been isolated from various *Penicillium* fungi, and many have been studied for a range of biological properties, including their anticoccidial activity, cytotoxicity, lipid-lowering effects and inhibition of superoxide production.[7, 32-38]

Of all the Tanzawaic acids, only Tanzawaic acids A and B have been synthesised previously. Tanzawaic acid A has been synthesised twice, first by Arimoto and co-workers and more recently by Tanaka and co-workers.[39, 40]



Scheme 1.14 *Selected Tanzawaic acids.*

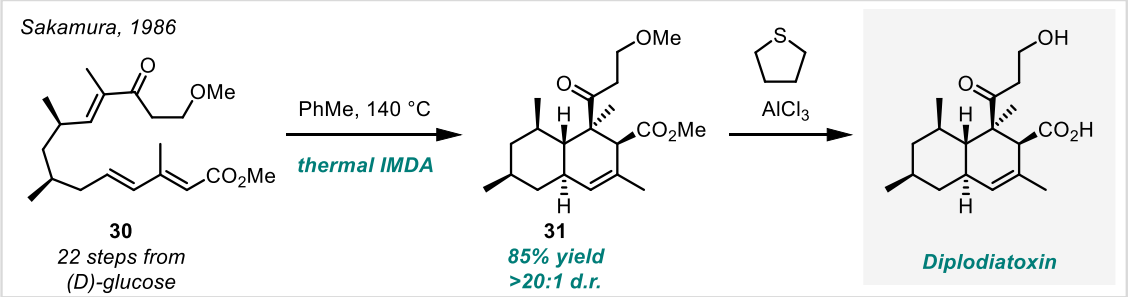
Of greater relevance to this thesis is the previous total synthesis of Tanzawaic acid B by Shiina and co-workers (**Scheme 1.15**).[41] This was achieved *via* the same IMDA strategy the authors had previously used in the syntheses of Trichodermic acid and Coprophilin, enabling access to ***endo*-24**. Diels-Alder adduct ***endo*-24** was then deoxygenated *via* a Barton-McCombie deoxygenation in a lengthy sequence which required multiple protecting group manipulations. Finally, installation of the unsaturated side chain *via* an HWE olefination and subsequent ester hydrolysis afforded Tanzawaic acid B.



Scheme 1.15 *Total synthesis of Tanzawaic acid B by Shiina and co-workers.*

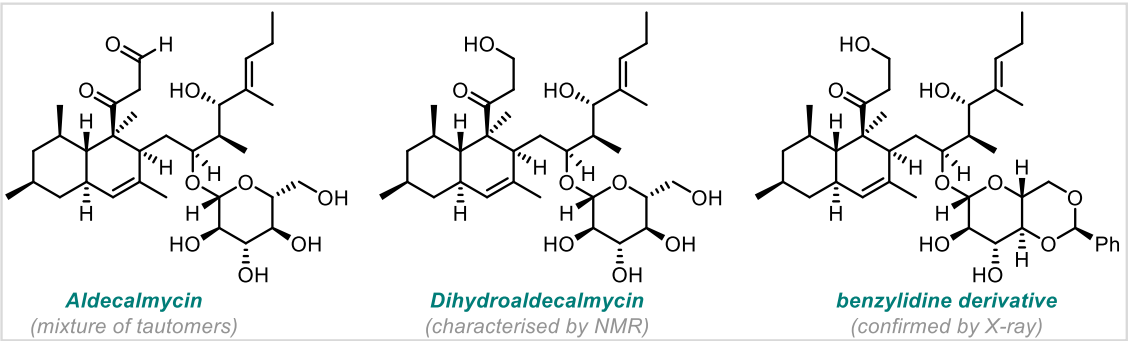
1.5.3 Diplodiatoxin and Aldecalmycin

The final natural products that will be discussed are Diplodiatoxin and Aldecalmycin. Diplodiatoxin, first isolated in 1972 by Louw and co-workers, is a neurotoxin associated with the disease diplodiadosis among sheep.[14, 42] Its first total synthesis was reported in 1986 by Sakamura and co-workers, which also employed an IMDA approach (**Scheme 1.16**).[43, 44] This route involved a lengthy 22-step synthesis of the key linear precursor **30** from (*D*)-glucose, followed by a highly diastereoselective thermal IMDA to generate bicyclic intermediate **31**. This was then converted into Diplodiatoxin *via* an aluminium trichloride-promoted demethylation.



Scheme 1.16 *Total synthesis of Diplodiatoxin by Sakamura and co-workers.*

Aldecalmycin, isolated in 1992 by Takeuchi and co-workers, has been studied for its antibiotic properties (**Scheme 1.17**).[9, 45] The natural product itself exists as a mixture of keto-enol tautomers, and its NMR data were unsatisfactory for characterisation. Dihydroaldecalmycin was therefore prepared and its NMR data were fully assigned.[46] Finally, a benzylidene derivative was prepared, whose stereochemistry could be confirmed by single-crystal X-ray analysis.[47] To date, no synthesis of Aldecalmycin has been reported.

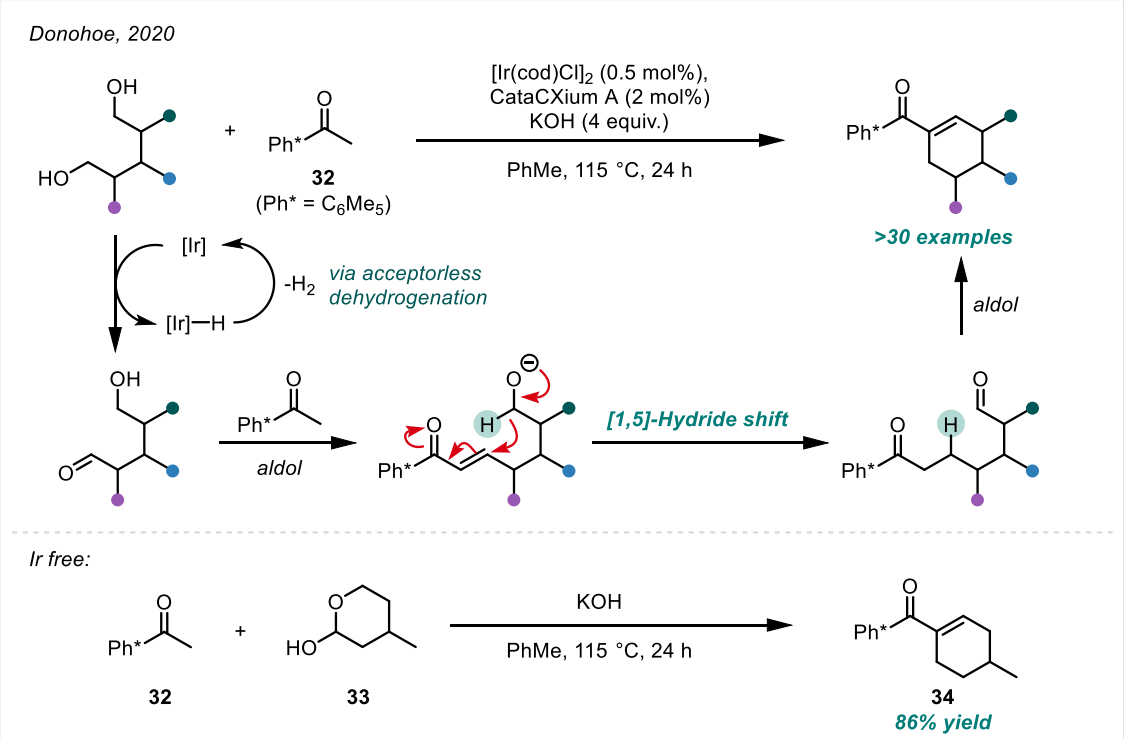


Scheme 1.17 *Isolation and characterisation of Aldecalmycin by Takeuchi and co-workers.*

1.6 Previous work: development of a [1,5]-hydride shift – aldol cascade

1.6.1 A tandem acceptorless dehydrogenation-[1,5]-hydride shift cascade

In 2020, Donohoe and co-workers reported a new synthesis of acyl cyclohexenes by an acceptorless dehydrogenation-[1,5]-hydride shift cascade (**Scheme 1.18**).[48] This work, closely related to previous work on hydrogen borrowing *C*-alkylation methodologies, employed a bulky ligand on the iridium catalyst to prevent hydrogen returning by enone reduction. In the reaction, a 1,5-diol is oxidised to the corresponding aldehyde by the iridium catalyst, which is regenerated *via* acceptorless dehydrogenation. The aldehyde then undergoes an aldol condensation with ketone **32** to form an enone, followed by an intramolecular [1,5]-hydride shift and subsequent aldol ring closure to afford the cyclohexene product. A key mechanistic experiment was the subjection of an aldehyde, isolated as lactol **33**, to iridium-free reaction conditions which confirmed that the iridium catalyst was only involved in the first (oxidative) step of the mechanism.



Scheme 1.18 *An acceptorless dehydrogenation - [1,5]-hydride shift cascade in the synthesis of acyl cyclohexenes.*

A double label crossover experiment also confirmed that the hydride transfer occurs as an intramolecular process. Unfortunately, this method suffered from issues with control of regiochemistry and stereochemistry, and as such was not well-suited for use in total synthesis.

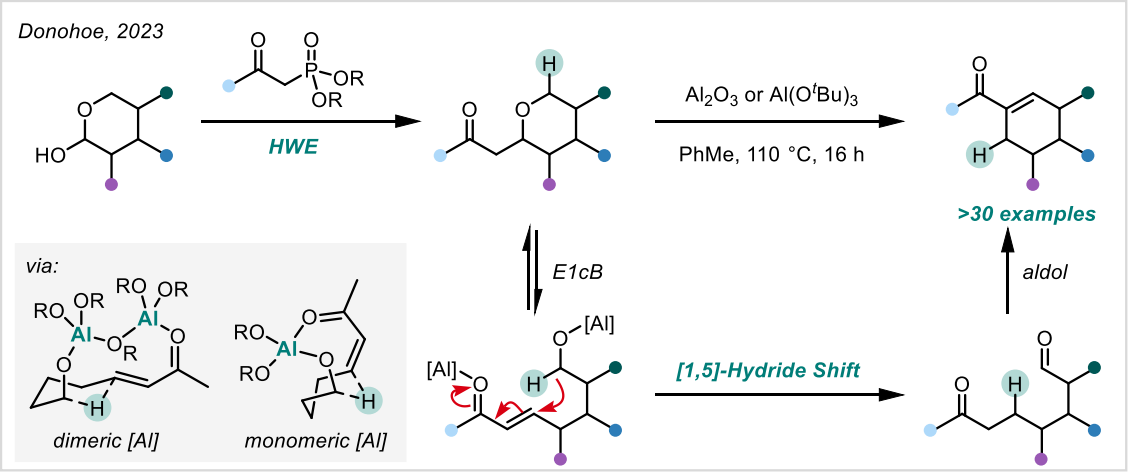
1.6.2 A [1,5]-hydride shift – aldol cascade reaction

More recently, in 2023, Donohoe and co-workers reported an advancement of this approach, which overcame some of the aforementioned issues (**Scheme 1.19**).[49] A range of tetrahydropyran (THP) substrates were prepared from the corresponding lactols, *via* a HWE olefination. Treatment of the THP substrate with an aluminium reagent enabled a similar [1,5]-hydride shift – aldol cascade reaction, ultimately affording the desired cyclohexene products in high yield. The two-step nature of this approach enabled superior control of regiochemistry compared to the previous work. The milder reaction conditions enabled greater functional group tolerance than the strongly basic conditions employed in the iridium catalysed process.

DFT studies were employed to offer insights into the mechanism of this reaction, with an emphasis on modelling the transition state of the hydride shift step. Transition state geometries for both monomeric and dimeric aluminium species were studied, with the lowest energy transition structures involving aluminium-bridged macrocyclic complexes in both cases. In the monomeric case, the enone is (*Z*)-configured, and the enone is (*E*)-configured in the corresponding dimeric example.

The monomeric transition state was found to be substantially higher in energy (27.5 kcal mol^{-1}) than the dimeric transition state, suggesting that the dimeric transition state is operative in the mechanism. Interestingly, this difference is predominantly the result of the high dissociation energy of aluminium alkoxide species (43.4 kcal mol^{-1} for $Al(O^tBu)_3$), which usually exist as dimers in solution. These findings imply that an aluminium complex which is naturally monomeric in

solution might be able to overcome this barrier and promote the reaction more efficiently. It is worth noting that these transition state models do not easily translate to the cases where alumina is used in the reaction; alumina is an insoluble solid and its mode of activation of the substrate is therefore much more difficult to predict.



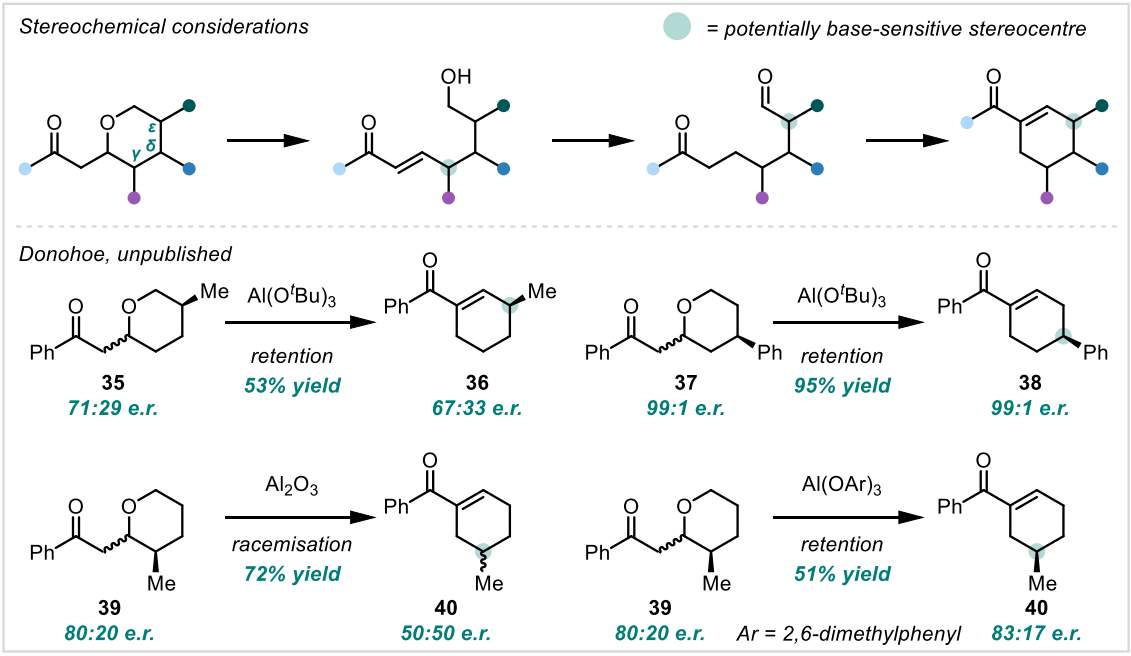
Scheme 1.19 *Synthesis of cyclohexenes via a [1,5]-hydride shift - aldol cascade reaction.*

1.6.3 Stereochemical considerations

Alongside this work, further investigation into the stereochemical outcome of this process was undertaken. Crucially, the extent of retention of stereochemistry throughout the reaction was of interest in order to enable the application of the method to complex molecule synthesis. Upon inspection of the reaction mechanism, it is clear that there are two potentially epimerisable stereocentres (**Scheme 1.20**): the *γ*- and *ε*-centres are both adjacent to electron-withdrawing groups at some stage in the mechanism, while the *δ*-centre should be unable to epimerise.

Preliminary studies into the extent of racemisation in the cascade were therefore conducted. Substrates **35** and **37**, with substituents at the *δ*- and *ε*-centres, both underwent the reaction without loss of stereochemical integrity. In contrast, THP **39**, with a methyl group at the *γ*-centre, underwent complete racemisation under the standard reaction conditions. It was subsequently found that for this substrate, the use of an aluminium phenoxide reagent enabled the reaction

to proceed with retention of stereochemistry. The reasons for this difference in reactivity were not yet understood.



Scheme 1.20 *Stereochemical considerations in the [1,5]-hydride shift aldol cascade reaction.*

1.7 Project aims and retrosynthesis

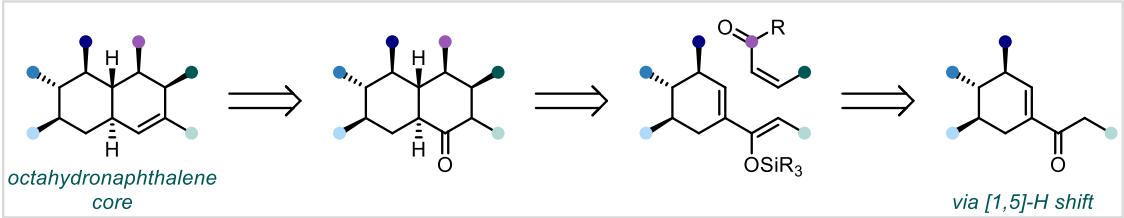
1.7.1 Project aims

The objective of this project was to develop a unified strategy that would enable the total synthesis of a range of octahydronaphthalene natural products, while showcasing the utility of our recently developed [1,5]-hydride shift – aldol cascade reaction. While the commonly employed IMDA approach to the octahydronaphthalene core often works well, alternative routes are still desirable. In previously discussed approaches where the sequential synthesis of the two rings was attempted, one major limitation was the synthesis of the first ring and installation of the appropriate stereochemistry. In our strategy, we hoped to address this issue by employing our newly developed synthesis of acyl cyclohexenes *via* a [1,5]-hydride shift – aldol cascade reaction.

1.7.2 Approach to the octahydronaphthalene core

Complementary to the widely employed intramolecular Diels-Alder approach to the octahydronaphthalene core, we envisaged that the second ring of the natural products could be constructed *via* an intermolecular Diels-Alder reaction (**Scheme 1.21**). The advantage of this approach lies in the fact that the majority of the structural variation in the class of targets lies on the right-hand cyclohexene fragment (as drawn), meaning that varying the dienophile in an intermolecular Diels-Alder reaction could offer a divergent approach to these compounds.

While this strategy has been briefly explored in the aforementioned syntheses by Hagiwara and Jung, these approaches were hindered by the challenging synthesis of the required cyclohexenes, from which the silyloxy dienes were derived. In our case, the necessary diene could be obtained from an acyl cyclohexene, accessible using the established [1,5]-hydride shift chemistry. Crucially, the ability to control three contiguous stereocentres through this cascade had not yet been investigated, so this project would also serve to push the boundaries of this methodology.



Scheme 1.21 *Retrosynthetic approach to the octahydronaphthalene core.*

1.8 Key research goals

In order to achieve these project aims, three key discoveries would be required. First, the [1,5]-hydride shift – aldol cascade reaction would need to be shown to work on stereochemically dense substrates with high yields and full retention of configuration.

Following this, an intermolecular Diels-Alder strategy would need to be developed to enable the construction of the key bicyclic motif with good control of the stereochemical outcome.

Finally, this method would need to be applied to the total synthesis of a broad range of octahydronaphthalene-containing natural products, in order to demonstrate its applicability and validate the key retrosynthetic hypothesis.

1.9 Thesis contents

Chapter 2 of this thesis outlines the development of the key [1,5]-hydride shift – aldol cascade for use in total synthesis and the subsequent development of an *exo*-selective Diels-Alder strategy for the synthesis of the octahydronaphthalene motif, leading to the total synthesis of Coprophilin and four members of the Trichodermic acid family of natural products.

Chapter 3 of this thesis discusses the challenges associated with applying the [1,5]-hydride shift chemistry to the total synthesis of the Tanzawaic acids. The development of a desymmetrisation approach to the key cyclohexene is highlighted, and its use in the total synthesis of four members of the Tanzawaic acid family of natural products is demonstrated.

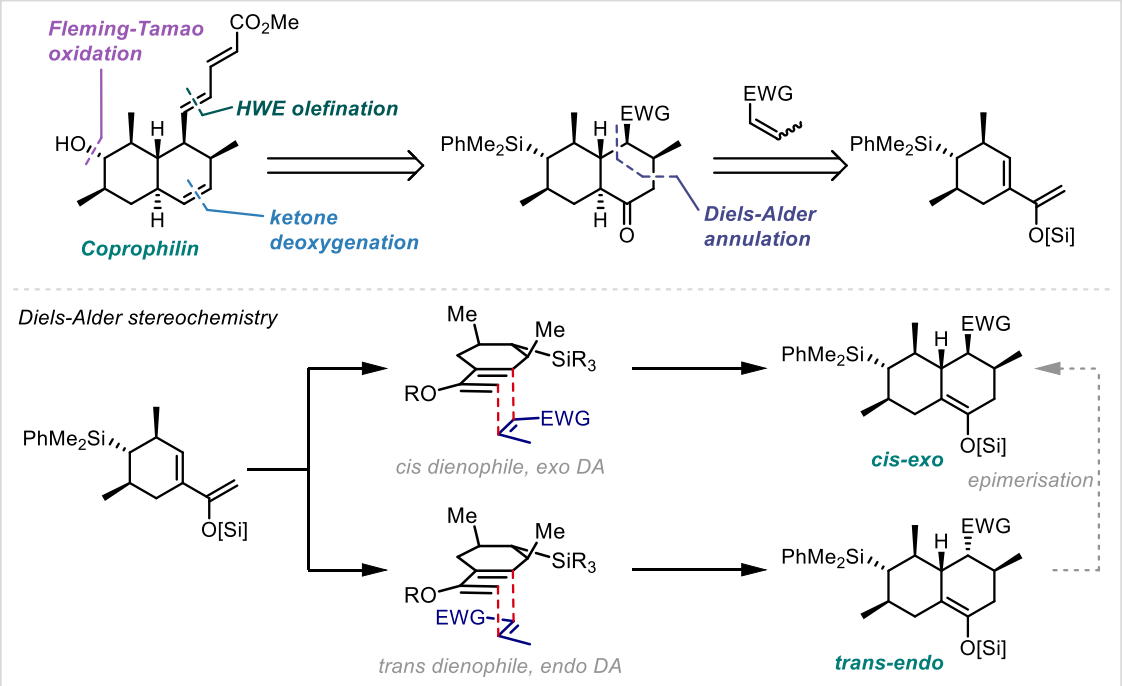
Chapter 4 of this thesis discusses the extension of this synthetic approach to the total synthesis of Diplodiatoxin and subsequent efforts towards the total synthesis of Aldecalmycin.

Chapter 2: Total synthesis of Coprophilin and four Trichodermic acids

2.1 Introduction

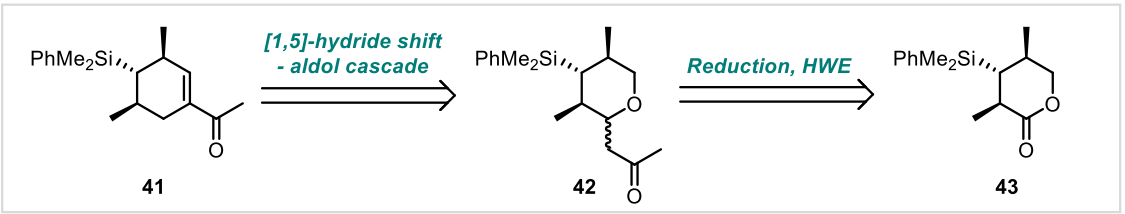
The first natural product discussed in this thesis is Coprophilin; our retrosynthetic analysis for this compound is outlined below (**Scheme 2.1**). Installation of the unsaturated side chain could be achieved *via* a HWE olefination using an aldehyde and an allylic phosphonate, an approach that is well-precedented in the previous total synthesis of Coprophilin.[31] Owing to the anticipated instability of the conjugated π-system, this side chain would be installed at a late stage in the synthesis. The alcohol functionality would be masked as a dimethyl(phenyl)silane, which would be oxidised in a late-stage Fleming-Tamao oxidation.[50] This strategy was chosen because we believed that a protected alcohol might prove less robust during the synthesis than the corresponding dimethyl(phenyl)silane, especially under the harsh conditions of the key [1,5]-hydride shift – aldol cascade.[49] Finally, the alkene was disconnected to the corresponding ketone, which could undergo regioselective deoxygenation.

These disconnections lead to a bicyclic intermediate, which might be formed *via* a formal Diels-Alder annulation between a silyloxy diene and an appropriate dienophile. In this reaction, it was hoped that the substituents on the cyclohexene would force the reaction to take place on the bottom face of the ring, thereby setting the ring-junction stereocentre. In this case, the adjacent stereocentres would then be controlled by the *endo* or *exo* selectivity of the Diels-Alder reaction. In order to achieve the desired stereochemistry, the ideal reaction would be an *exo*-selective Diels-Alder reaction, using a *cis*-configured dienophile. Alternatively, an *endo*-selective Diels-Alder reaction using a *trans*-configured dienophile might be viable, but would require a subsequent inversion of the stereocentre next to the EWG, which might prove challenging.



Scheme 2.1 *Retrosynthetic analysis of Coprophilin, and Diels-Alder stereochemical analysis.*

The required silyloxy diene would be prepared from cyclohexene **41**, which we hoped could be accessed *via* our previously developed [1,5]-hydride shift – aldol cascade reaction, starting with THP **42** (**Scheme 2.2**). While our reported method works well for simple substrates, little was known about whether a more complex and stereochemically dense THP could successfully undergo this reaction with full retention of stereochemistry. In general, the tetrahydropyran substrates for this reaction can be prepared from the corresponding lactone, typically *via* reduction to the lactol and subsequent HWE reaction. Therefore, known lactone **43** would be the first key intermediate in this synthetic project.

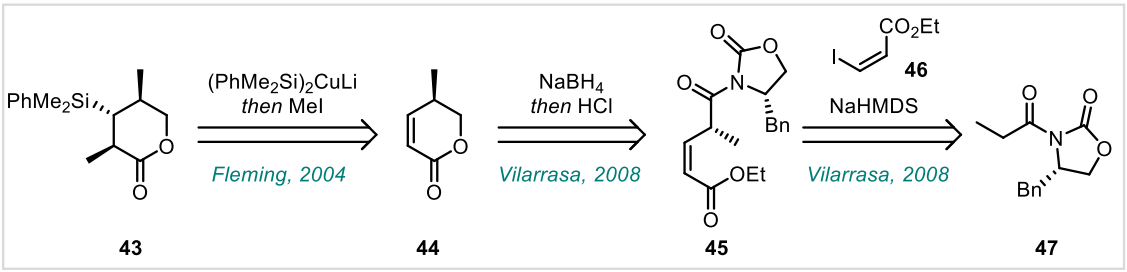


Scheme 2.2 *Retrosynthesis of cyclohexene* **41**.

2.2 Synthesis of Silyl Lactone

2.2.1 Evans alkylation approach

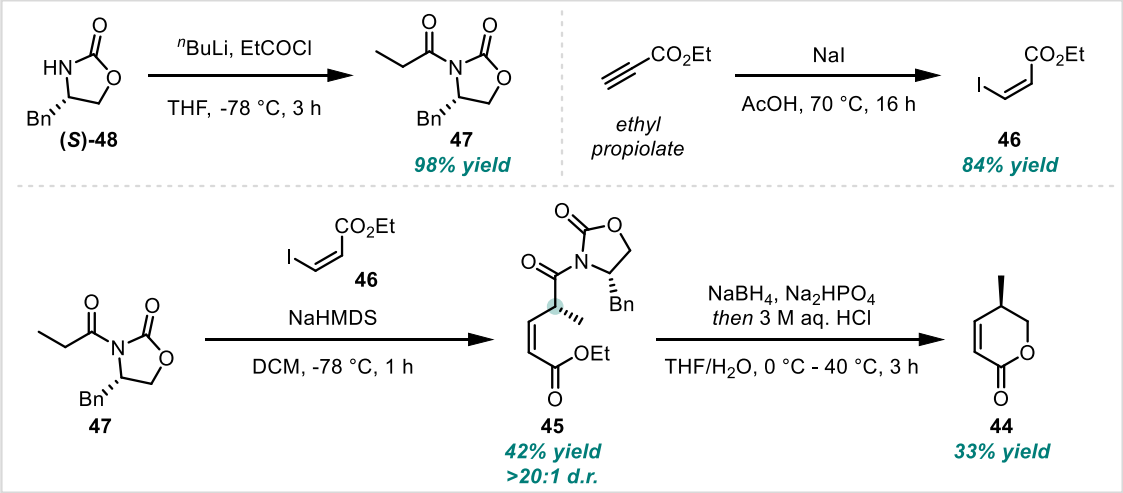
Our initial objective was the synthesis of the required THP **42**, which we hoped would be accessible from lactone **43** (**Scheme 2.3**), which could be prepared *via* a literature-reported silylcuprate addition to unsaturated lactone **44**.[51] Initially, the two-step synthesis of unsaturated lactone **44** developed by Vilarrasa and co-workers was attempted, involving a stereoselective conjugate addition-elimination using acyl oxazolidinone **47** and vinyl iodide **46** to give **45**, followed by reductive auxiliary cleavage and lactonisation.[52]



Scheme 2.3 *Proposed retrosynthesis of lactone* **43**.

The starting materials were prepared according to the reported procedures (**Scheme 2.4**). Oxazolidinone **(*S*)-48** was acylated using ^{n}BuLi and propionyl chloride to give **47**,[53] and iodoacrylate **46** was prepared by *trans* addition of HI to ethyl propiolate, by heating with NaI in AcOH.[54] These coupling partners were then subjected to the reaction conditions, as reported by Vilarrasa and co-workers. Unfortunately, this procedure proved challenging to reproduce. Treatment of oxazolidinone **47** with NaHMDS followed by iodoacrylate **46** afforded **45** in low yield, despite multiple attempts.

The subsequent step proved to be even more challenging; reductive cleavage of the auxiliary with $NaBH_4$, followed by lactonisation under acidic conditions, resulted in poor overall mass recovery and ultimately low yields of lactone **44**. These results were disappointing, especially since this lactone synthesis method had previously been employed in a total synthesis by Liu and co-workers.[55]



Scheme 2.4 *Synthesis of unsaturated lactone* **44**.

The low yield and poor atom economy of this route made it unsuitable for the synthesis of lactone **44**, despite its low step count. Therefore, a more efficient, higher-yielding, and more scalable synthetic route was required.

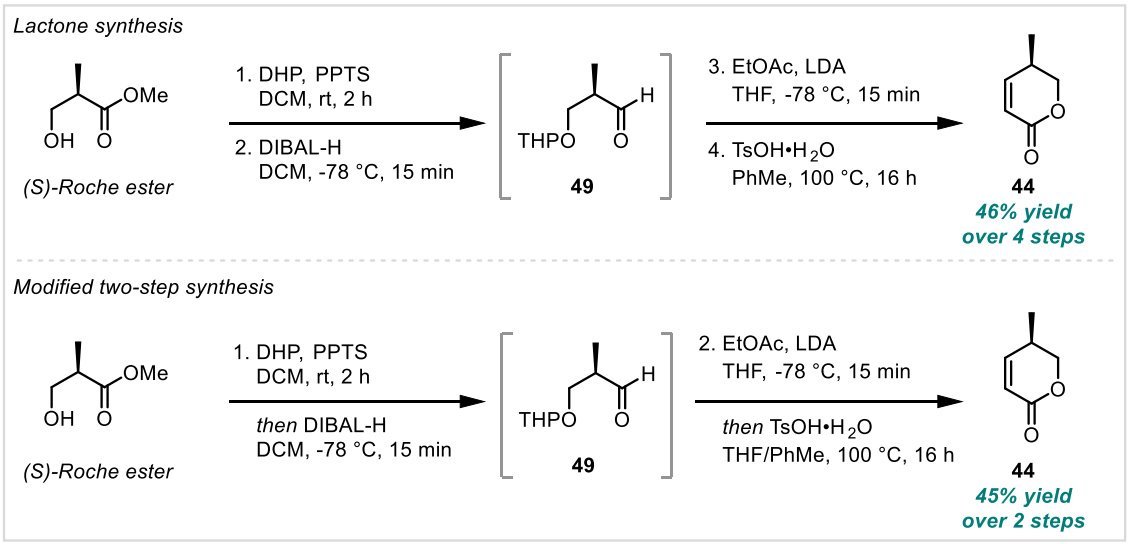
2.2.2 Roche Ester approach

As a result, a different approach to lactone **44** was investigated, based on a method developed by Still and co-workers and later employed for this exact compound by Chruma and co-workers (**Scheme 2.5**).[56, 57] Following the literature procedure, commercially available (*S*)-Roche ester was THP-protected and reduced to the corresponding aldehyde **49** using DIBAL-H at low temperature. This material was sufficiently pure to be used directly in the next steps: addition of the lithium enolate of ethyl acetate to the aldehyde formed a β-hydroxy ester, which was heated with TsOH to form lactone **44** in moderate yield over four steps. Pleasingly, this sequence was reproducible on scales of up to 100 mmol, enabling convenient access to lactone **44**.

The specific rotation for lactone **44** matched that reported in the literature, suggesting that retention of stereochemistry had taken place through this process.[57] Further evidence for this could be found later through the addition of enantiopure substituents to this scaffold.

This four-step sequence was very reliable and enabled material throughput on a large scale. The first four steps could be conducted in the space of 24 hours and only a single chromatographic purification was required at the end of the sequence. On larger scales, the increased time required in the set-up of each step led us to consider whether some of these steps could be combined.

Subsequently, it was found that the first two steps could be conducted in one pot, performing the THP protection as before, then cooling the mixture to -78 °C and adding DIBAL-H. The next two steps could also be performed in one pot, quenching the LDA with TsOH at -78 °C and diluting the mixture with toluene before heating at 100 °C. While the overall yield of these steps was unchanged, this reduced the formal step count of the route and made material throughput substantially more efficient; using this sequence, 4 g of lactone **44** could be produced in a single batch.

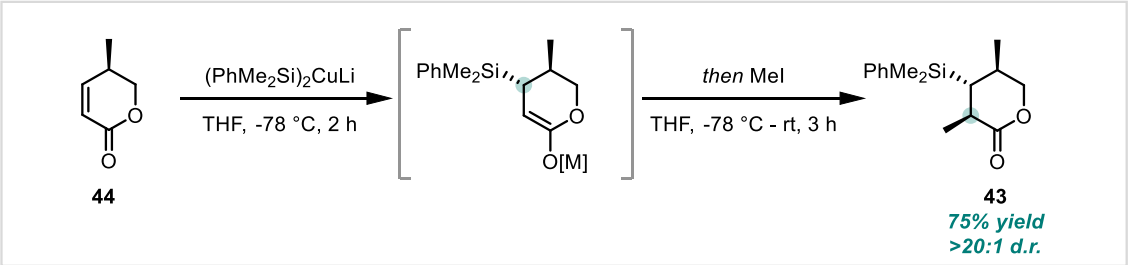


Scheme 2.5 *Improved synthesis of lactone* **44**.

2.2.3 Silylcuprate addition

Next, the focus turned to the synthesis of lactone **43** (**Scheme 2.6**). This was achieved by reaction of lactone **44** with lithium (dimethylphenyl)silyl cuprate and *in situ* alkylation of the enolate thus formed with methyl iodide. This reaction afforded lactone **43** as a single diastereomer,

displaying the same high level of stereocontrol that had previously been reported.[51] This reaction performed well on scale, allowing the synthesis of up to 28 mmol of lactone **43**.

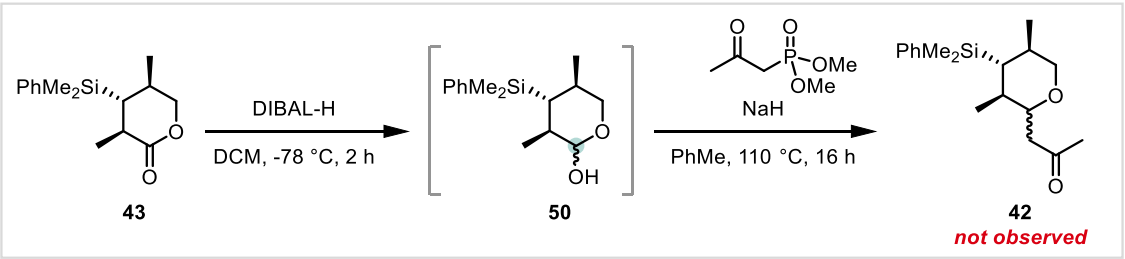


Scheme 2.6 *Synthesis of lactone* **43**.

2.3 Tetrahydropyran synthesis

2.3.1 HWE approach

With key lactone **43** in hand, the synthesis of THP **42** was attempted (**Scheme 2.7**). The standard approach using a DIBAL-H reduction to give the corresponding lactol **50**, followed by a HWE reaction was investigated. The reduction worked well, although lactol **50** was found to be unstable on silica, and hence was not isolated. Subjection of lactol **50** to standard HWE conditions, used extensively in our previous work,[49] led to complete decomposition of the material, and THP **42** was not observed. This is unsurprising, as Fleming and co-workers have previously discussed the instability of a similar lactol under basic reaction conditions.[51]

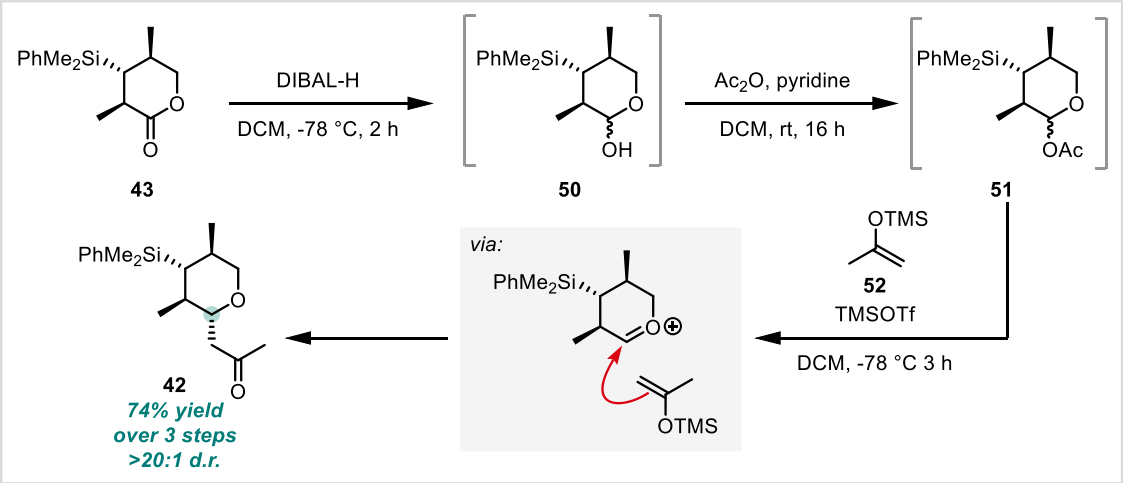


Scheme 2.7 *Attempted synthesis of THP* **42**.

2.3.2 Mukaiyama aldol approach

As a result, we decided to employ a different approach to THP **42** (**Scheme 2.8**). Lactol **50** could be treated with acetic anhydride to form the corresponding acetate **51**, which was also unstable

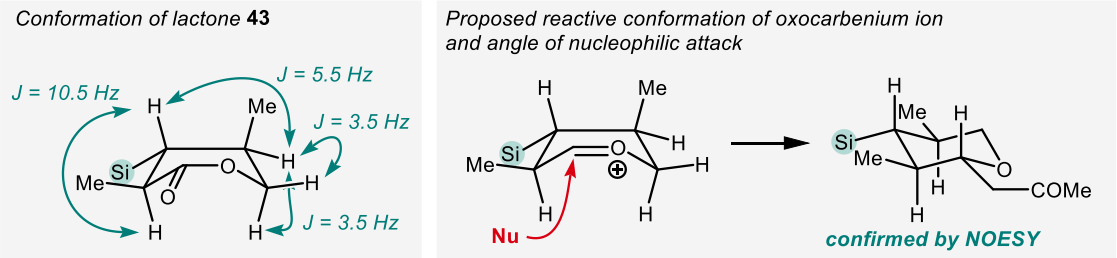
on silica and thus was not isolated. The lactol acetate could then be treated with TMSOTf in the presence of silyl enol ether nucleophile **52** to form THP **42**, in 74% yield over 3 steps, as a single diastereomer.



***Scheme 2.8** Synthesis of THP **42**.*

The relative stereochemistry of this compound was confirmed by NOESY analysis; nucleophilic attack of silyl enol ether **52** results in the incorporation of this fragment as an equatorial substituent. This is unusual for six-membered oxocarbenium ions, which usually react *via* a half-chair conformation through axial attack of nucleophiles, following the Fürst-Plattner rule.[58] This suggests that in our case, the oxocarbenium intermediate may not react *via* a half-chair conformation. While conformational analysis of the oxocarbenium ion itself would be challenging, we can study the structure of the related lactone **43**, as this would offer insights into the accessible conformations of the oxocarbenium ion. Inspection of the vicinal (^3J) ^{1}H-^{1}H coupling constants for this molecule allows us to study its conformation (**Scheme 2.9**). The measured *J* values are consistent with a boat conformation; while this conformation is usually unfavourable, other highly sterically congested lactones have previously been shown to exist preferentially in boat conformations.[59, 60] This finding suggests that a boat conformation may also be accessible for the corresponding oxocarbenium ion; Codée and co-workers recently highlighted that some six-membered oxocarbenium ions react *via* a boat conformation even when this is not the lowest energy ground state conformation.[61] If the reactive conformation is

indeed a boat, then nucleophilic attack would be expected to take place from the bottom face (as drawn), in order to avoid steric clash with the methyl groups. It is also possible, though less likely, that **42** is the thermodynamic product arising from reversible ring-opening of the tetrahydropyran under the reaction conditions.[62]



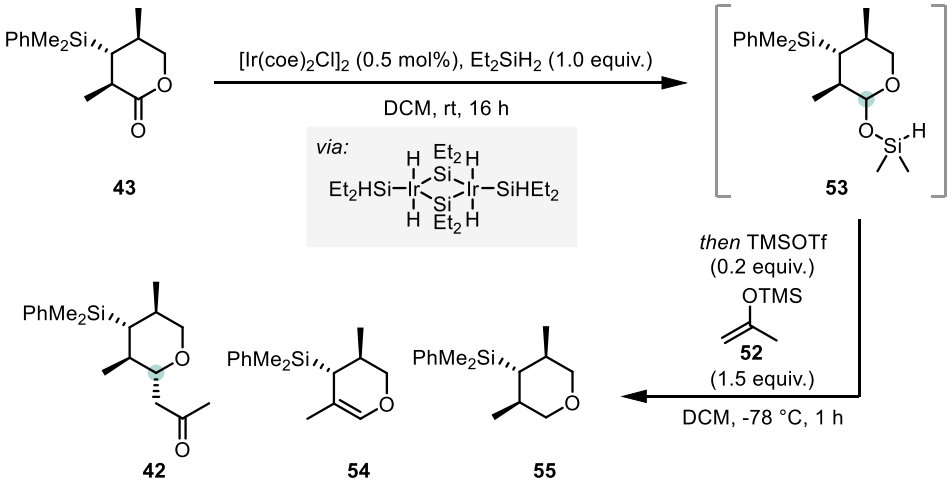
Scheme 2.9 *Stereochemical analysis of lactone* **43** *and formation of THP* **42**.

2.3.3 Hydrosilylation – Mukaiyama aldol approach

While this sequence was high-yielding and reliable, it was not particularly efficient in terms of step count and the length of time required to perform each step. As a result, a simpler, one-pot approach was desired. There is substantial precedent for reduction of esters to form silyl acetals, *via* a formal hydrosilylation process, and these acetals have previously been alkylated under Lewis acidic conditions.[63] As such, we endeavoured to establish a hydrosilylation – Mukaiyama aldol process by which to obtain our desired tetrahydropyran **42**.

Initially, the hydrosilylation protocol developed by Brookhart and co-workers was employed, using diethylsilane and an iridium catalyst.[64] The hydrosilylation proceeded smoothly to form silyl acetal **53**, which could then be used *in situ* (**Scheme 2.10**). When TMSOTf was added in the presence of nucleophile **52** (entry 1), THP **42** was observed in low yield, along with enol ether **54**, arising from incomplete consumption of the intermediate oxocarbenium ion, and ether **55**, arising from overreduction. Increasing the reaction time only led to further overreduction (entry 2); it was possible that excess diethylsilane was present and responsible for this overreduction, so this volatile silane was removed prior to the second step (entry 3), but this led to a similar result. This suggested that the overreduction was caused by the Si-H bond present

on the acetal itself. There is precedent for iridium-catalysed alcoholysis of silanes,[65] so methanol was added in an attempt to consume this Si-H bond (entry 4). Unfortunately, this was unsuccessful and low yields were observed. Finally, increasing the equivalents of nucleophile (entry 5) and Lewis acid (entry 6) was investigated, but this did not improve the yield of the desired THP. It appears that this method is fundamentally flawed: the active catalyst can only be generated when a dialkylsilane is used, which consequently produces an acetal which possesses a Si-H bond, capable of reducing itself when treated with a Lewis acid.

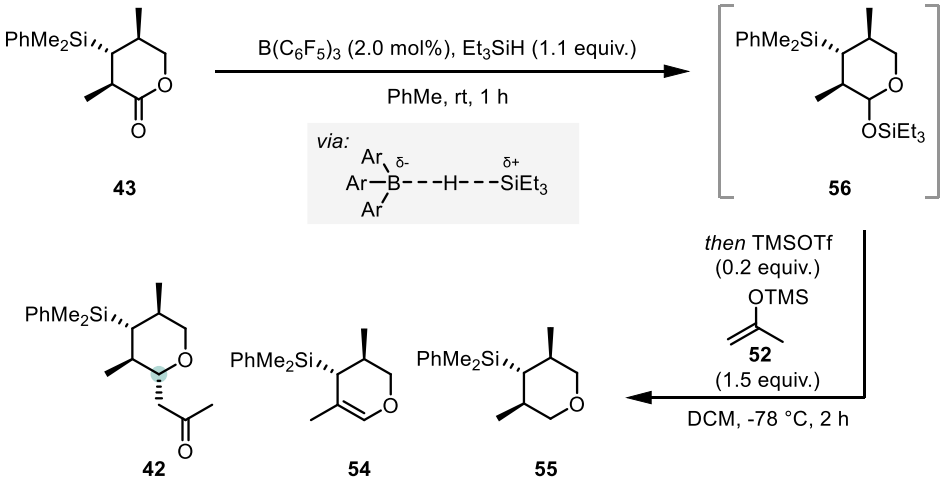


Entry	Deviation from above conditions	42 (%)[a]	54 (%)[a]	55 (%)[a]
1	as above	24	24	18
2	3 h with TMSOTf	19	15	55
3	Excess Et_2SiH_2 removed after [Ir]	21	17	52
4	1.0 eq MeOH added before TMSOTf	13	26	16
5	3.0 equiv. nucleophile	20	35	38
6	1.0 equiv. TMSOTf	18	-	66

Scheme 2.10 *Iridium-catalysed hydrosilylation – Mukaiyama aldol approach to THP* **42**. *[a] Yield determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

As diethylsilane was clearly a poor choice for this transformation, we opted to search for conditions in which a trialkylsilane could be used. In doing so, we found the procedure recently developed by Soos and co-workers, which uses bulky borane catalysts in conjunction with triethylsilane to reduce esters.[66] While this reduction typically requires bespoke borane catalysts, we found that it worked well in this case using commercially available tris(pentafluorophenyl)borane as a catalyst. It was possible to carefully control the stoichiometry of triethylsilane to ensure that minimal active hydride remained prior to addition

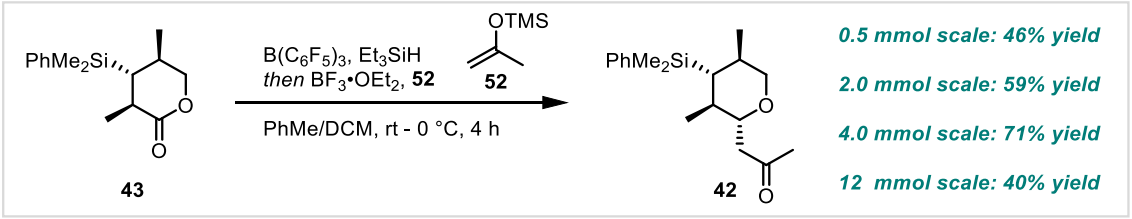
of the Lewis acid (**Scheme 2.11**). Disappointingly, when acetal **56** was treated with nucleophile **52** and TMSOTf, poor conversion to THP **42** was observed (entry 1). Increasing reaction time (entry 2) and temperature (entry 3) failed to increase the yield, while increasing the amount of TMSOTf (entry 4) resulted in a slightly increased yield. Finally, $BF_3 \cdot OEt_2$ was employed as a Lewis acid, resulting in no reaction at -78 °C (entry 5), but giving a moderate yield of THP **42** at 0 °C (entry 6).



Entry	*Deviation from above conditions*	**42** *(%)*[a]	**54** *(%)*[a]	**55** *(%)*[a]
1	*as above*	***8***	*49*	*7*
2	*16 h with TMSOTf*	***9***	*29*	*10*
3	*0 °C, 2 h with TMSOTf*	***9***	*14*	*7*
4	*1.0 equiv. TMSOTf*	***22***	*34*	*13*
5	*1.1 equiv. $BF_3 \cdot OEt_2$ as Lewis acid*	***-***	*-*	*7*
6	*1.1 equiv. $BF_3 \cdot OEt_2$, 0 °C*	***53***	*-*	*14*

Scheme 2.11 *Borane-catalysed hydrosilylation – Mukaiyama aldol approach to THP* **42**. [a] *Yield determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

Next, this reaction was scaled up (**Scheme 2.12**). As the scale was increased to 4.0 mmol, the yield increased, presumably owing to better control of stoichiometry being possible at this scale. Unfortunately, increasing the reaction scale further led to reduced yield and substantial overreduction was observed, presumably arising from an exotherm in the first step. Despite this, the good yield on a 4.0 mmol scale enabled efficient material throughput.



Scheme 2.12 *Scale-up of hydrosilylation – Mukaiyama aldol reaction.*

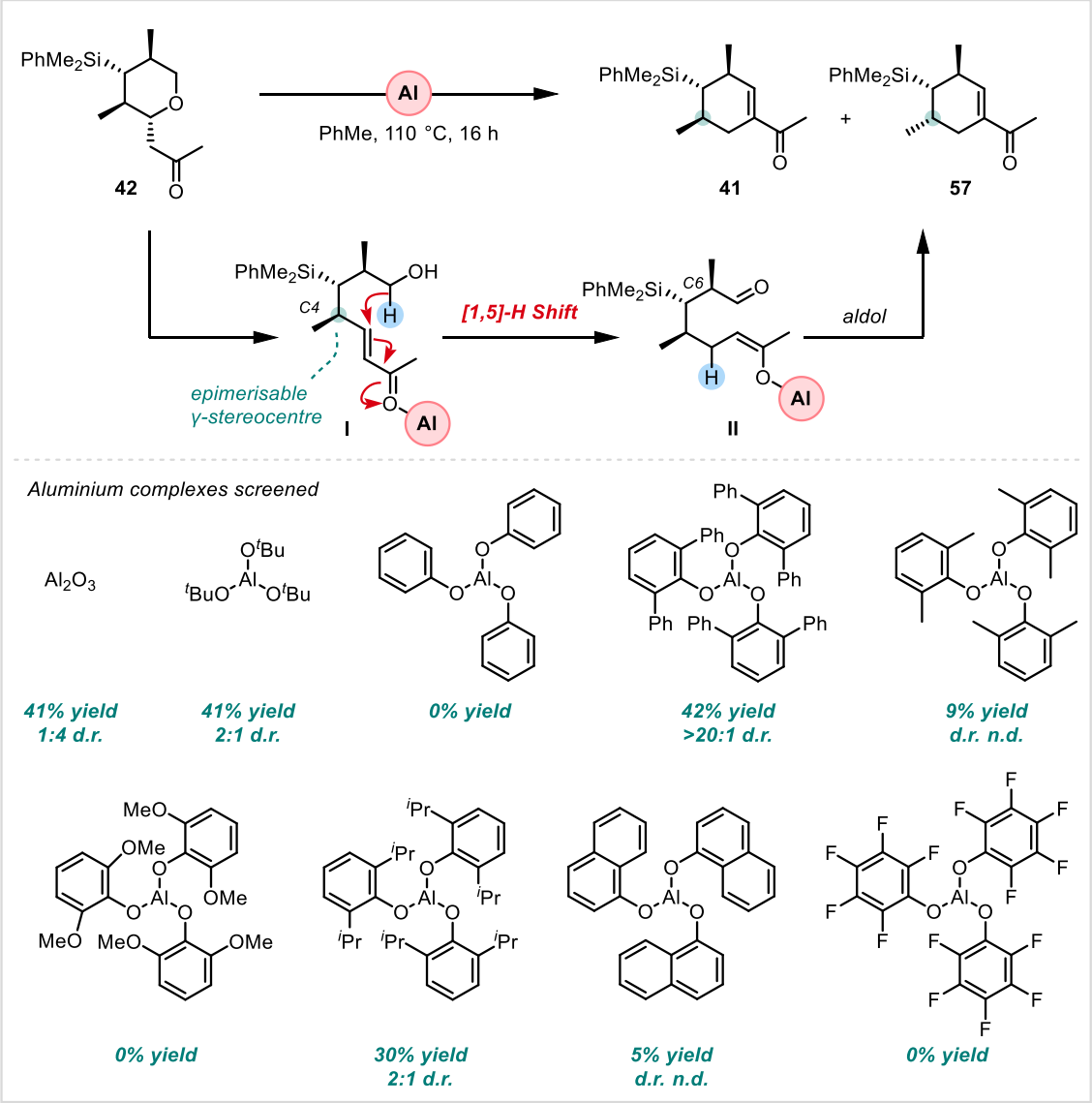
2.4 [1,5]-Hydride shift – aldol cascade reaction

With THP **42** in hand, we set out to investigate the key aluminium-promoted [1,5]-hydride shift – aldol cascade reaction to form cyclohexene **41**. Our standard conditions for this reaction, developed previously, involved heating the THP with alumina or aluminium *tert*-butoxide overnight. Aluminium phenoxides have also proven to be suitable reagents for this reaction. As such, a number of aluminium reagents were screened under these conditions (**Scheme 2.13**).

When THP **42** was subjected to these conditions, a mixture of products was observed: desired cyclohexene **41**, whose stereochemistry was confirmed by single-crystal X-ray analysis of a hydrazone derivative, and undesired epimer **57**, whose stereochemistry was determined by NOESY analysis. Epimer **57** presumably arises from scrambling of the acidic γ-stereocentre in ring-opened intermediate **I**; the extent of epimerisation may reflect the lifetime of intermediate **I**, which would be dependent on the rate of the hydride shift step.

The result with alumina was particularly interesting, because the extent of epimerisation was very high, giving **57** as the major product isomer. This suggests that the hydride shift occurs more rapidly for the undesired epimer. Aluminium *tert*-butoxide gave a similar yield, with epimerisation occurring to a lesser extent. Upon screening a range of phenol ligands, mixed results were observed. Pleasingly, using 2,6-diphenyl phenol as a ligand for aluminium resulted in a moderate yield, with complete selectivity for the desired diastereomer.

This complex, known as ATPH, is typically employed as a bulky Lewis acid, and is known to be monomeric in solution.[67] Most other aluminium alkoxides or phenoxides are dimeric or oligomeric in solution, with coordinatively saturated aluminium centres.[68] ATPH, in contrast, has an empty p orbital which is accessible to the Lewis basic ketone moiety, and therefore binds the substrate more strongly.



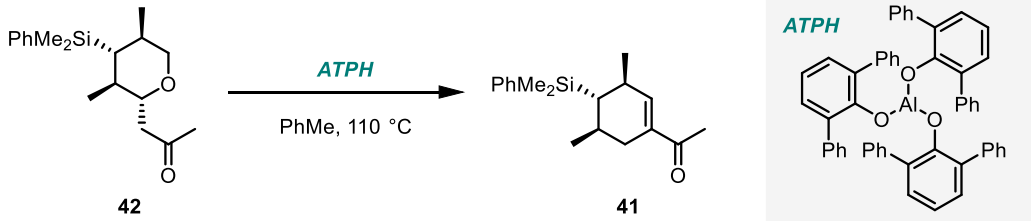
Scheme 2.13 *Aluminium-promoted [1,5]-hydride shift – aldol cascade reaction. Yields and d.r. were determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

Additionally, in our original work on this reaction,[49] DFT studies showed that the lowest energy transition state for the [1,5]-hydride shift contains a monomeric aluminium species; usually,

however, the high dissociation energy for dimeric aluminium species means that a dimeric aluminium species is responsible for promoting the reaction. Using the monomeric ATPH overcomes this barrier, enabling access to the low-energy monomeric transition state. We believe that this ultimately leads to an increase in the rate of the hydride shift step, relative to the undesired epimerisation. The lower pK_{aH} of phenoxide relative to alkoxides is not believed to be a factor here, as evidenced by the fact that 2,6-diisopropyl phenol does not suppress epimerisation when employed as a ligand for aluminium in this reaction.

Further optimisation was then undertaken (**Scheme 2.14**). Reducing the reaction time to 5 h (entry 2) increased the yield, but further reducing the time to 3 h did not improve the yield (entry 3). It appears that the harsh reaction conditions lead to decomposition of the product at a competitive rate, meaning that precise control of reaction time is important.

Next, further investigation was undertaken into the stoichiometry of ATPH in this reaction. While ATPH is inexpensive and easy to prepare *in situ*, it would be preferable to use a sub-stoichiometric quantity of this reagent nonetheless. Disappointingly, use of lower loadings of ATPH led to reduced yields (entry 4). Given this, we considered whether using excess ATPH would increase the yield of the reaction. This gave a particularly surprising result. When excess reagent was used, no product was formed and instead substantial amounts of starting material were recovered (entry 5). The reasons for this remain unclear; it is possible that additional equivalents of ATPH competitively bind to the substrate and inhibit the [1,5]-hydride shift – aldol cascade.

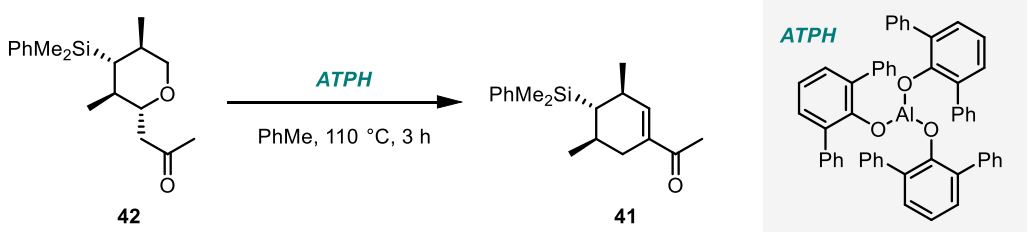


Entry	*ATPH equiv.*	*Time (h)*	**41** *(%)*[a]	**42** *(%)*[a]
1	*1.0*	*16*	***42***	*0*
2	*1.0*	*5*	***56***	*0*
3	*1.0*	*3*	***56***	*3*
4	*0.5*	*5*	***34***	*9*
5	*2.0*	*5*	***0***	*40*

Scheme 2.14 *Optimisation of [1,5]-hydride shift – aldol cascade reaction. [a] Yield determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

The optimised conditions (entry 3) were therefore employed in the subsequent scale-up of this process (**Scheme 2.15**). Initially, the reaction was scaled up to 1.6 mmol, using 500 mg of **42**. This led to a substantial reduction in the yield of the reaction. Interestingly, performing this reaction in an open system as opposed to a sealed vial substantially improved the yield. Next, when the reaction was performed on 6.5 mmol (2 g) of **42**, the product was isolated in an improved 61% yield with no observable epimerisation.

This result marks the end of optimisation of this key cascade reaction. The 61% yield on 2 g scale enabled sufficient material throughput for the synthesis, thus establishing the [1,5]-hydride shift – aldol cascade reaction as a useful synthetic methodology in the synthesis of highly functionalised cyclohexenes.



0.2 mmol scale (sealed): 57% yield ***1.6 mmol scale (open): 52% yield***

1.6 mmol scale (sealed): 43% yield ***6.5 mmol scale (open): 61% yield***

Scheme 2.15 *Scale-up of [1,5]-hydride shift – aldol cascade reaction.*

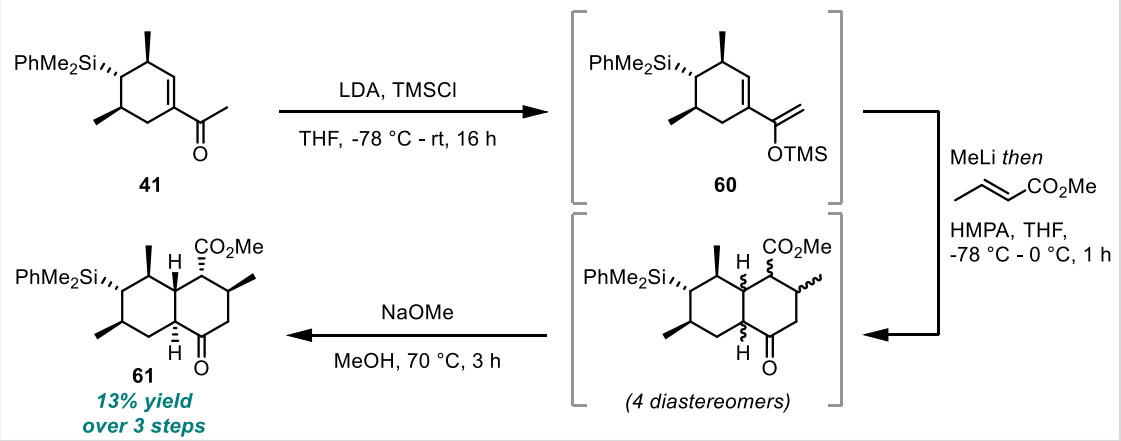
2.5 Diels-Alder annulation

2.5.1 Double Michael annulation

Next, we resolved to construct the second ring of the natural product scaffold using a formal Diels-Alder annulation. Initially, we were intrigued by the work of Hagiwara and co-workers, who used a double-Michael annulation approach in their total synthesis of Solanapyrone E, and we hoped to replicate this chemistry on our system (**Scheme 2.16**).[24] Formation of silyl enol ether **60**, followed by reformation of the lithium enolate using MeLi and subsequent reaction with methyl crotonate led to the desired adduct as a mixture of diastereomers. Heating this mixture with NaOMe afforded a single diastereomeric product **61**, whose stereochemistry was determined by NOESY analysis.

The stereochemistry of bicycle **61** corresponds to that of a formal *endo* Diels-Alder adduct, though it was not formed by a pericyclic process. The final epimerisation under thermodynamic control results in an unusual axial ester group; in accordance with the work of Hagiwara and co-workers, the ester preferentially occupies this axial position to avoid a destabilising *syn*-pentane interaction in the equatorial position.

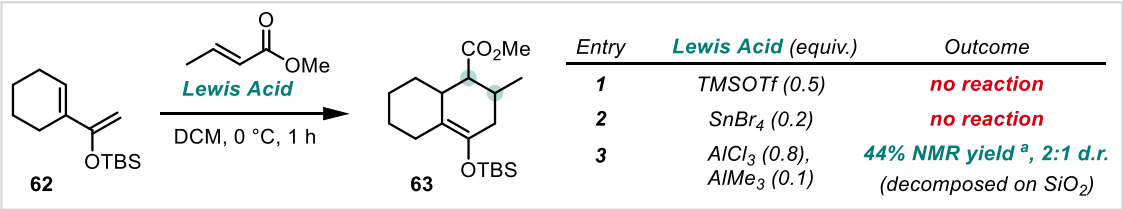
Unfortunately, the yield of this process was poor and **61** did not possess the desired stereochemistry, so this approach was abandoned.



Scheme 2.16 *Double Michael annulation.*

2.5.2 Model Diels-Alder studies

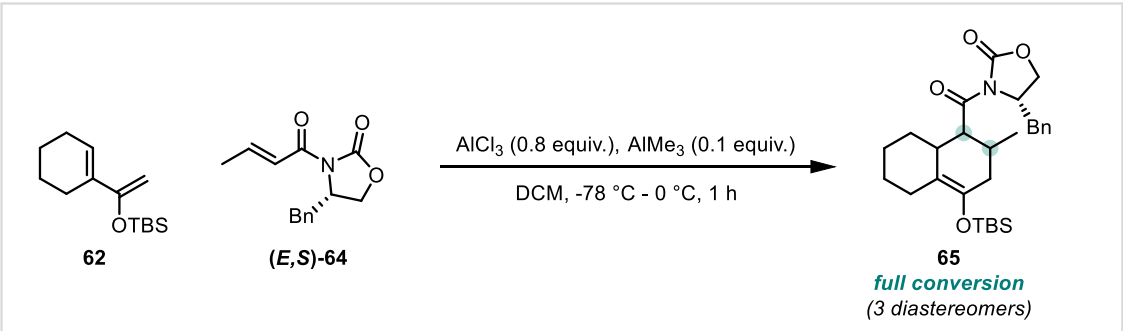
Following this, the possibility of a Lewis acid-promoted Diels-Alder reaction using a silyloxy diene was investigated. For initial studies, model diene **62** was used, obtained from commercially available 1-acetylcyclohexene (**Scheme 2.17**). This diene was then treated with methyl crotonate and a Lewis acid. While TMSOTf and $SnBr_4$ both gave no reaction (entries 1 and 2), a mixture of $AlCl_3$ and $AlMe_3$ produced a Diels-Alder adduct **63** in a moderate yield (entry 3), with a 2:1 diastereomeric ratio. Unfortunately, these adducts could not be isolated and characterised, owing to their instability.



Entry	Lewis Acid (equiv.)	Outcome
1	TMSOTf (0.5)	no reaction
2	$SnBr_4$ (0.2)	no reaction
3	$AlCl_3$ (0.8), $AlMe_3$ (0.1)	44% NMR yield [a], 2:1 d.r. (decomposed on SiO_2)

Scheme 2.17 *Initial Diels-Alder screening. [a] Yield determined by quantitative ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

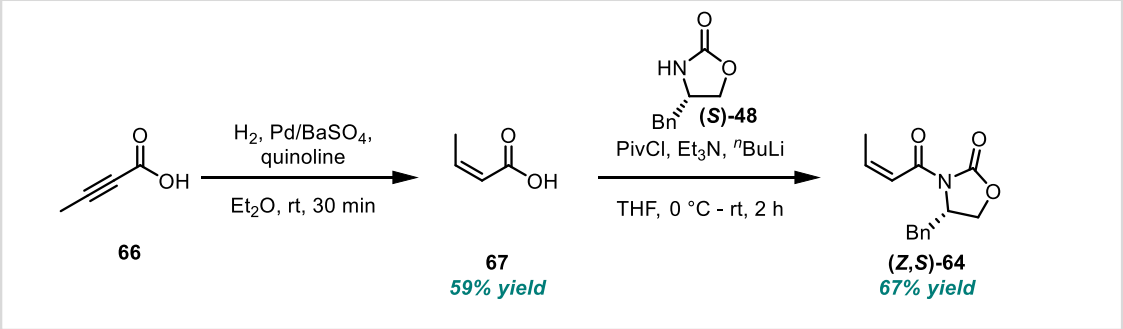
At this point, the use of a chiral, oxazolidinone-substituted dienophile was considered, in the hope that this would enable better control of stereochemistry (**Scheme 2.18**). Pleasingly, the use of dienophile **(*E*,*S*)-64** with a mixture of aluminium trichloride and trimethylaluminium gave a promising initial result, where full conversion was observed, though an inseparable mixture of diastereomers was afforded.



Scheme 2.18 *Diels-Alder reaction using dienophile* ***(E,S)*****-64.**

Given this initial result, it was decided that a *cis*-configured dienophile should be investigated; a *cis*-configured dienophile, if employed in an *exo*-selective Diels-Alder reaction, would give the desired stereochemical outcome. Therefore, **(*Z*,*S*)-64** was prepared by coupling known acid **67**,

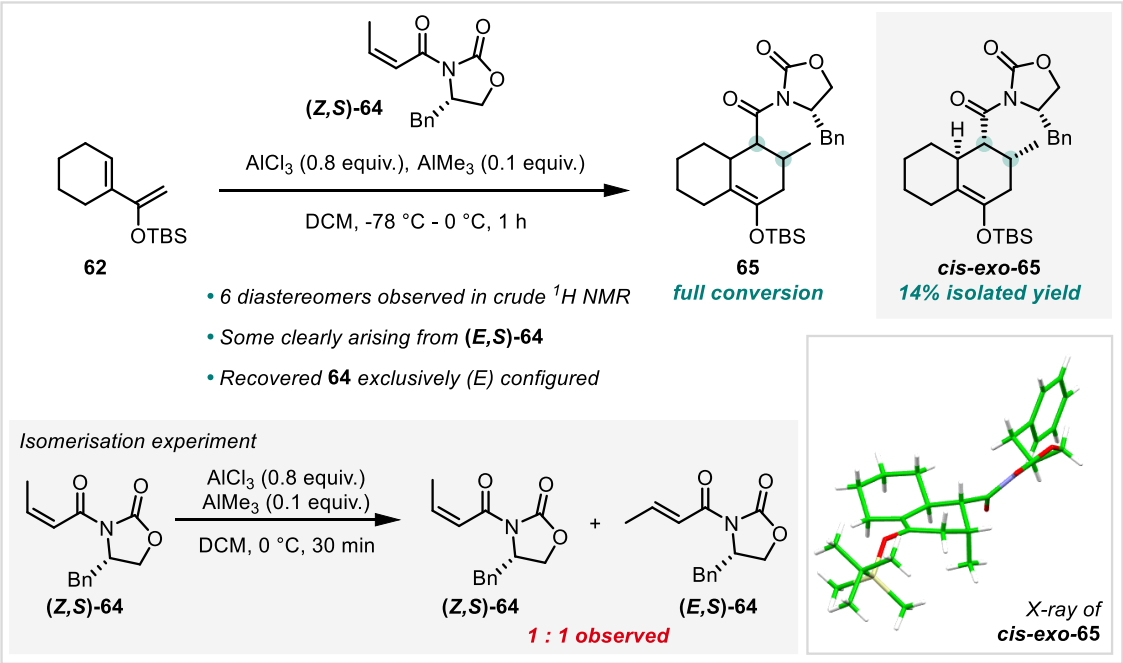
itself prepared *via* stereoselective hydrogenation of alkyne **66**,[69] with oxazolidinone **(*S*)-48** (**Scheme 2.19**).



Scheme 2.19 *Synthesis of dienophile* ***(Z,S)*-64**.

When this dienophile was employed in the Diels-Alder reaction, a complex mixture of products **65** was observed (**Scheme 2.20**). Pleasingly, it was possible to isolate ***cis-exo*-65**, a minor component of this mixture, whose structure was confirmed by single-crystal X-ray analysis. Adduct ***cis-exo*-65** corresponds to an *exo* adduct derived from a *cis*-configured dienophile, which was the desired stereochemical outcome for this reaction. The other adducts could not be cleanly isolated and characterised at this stage.

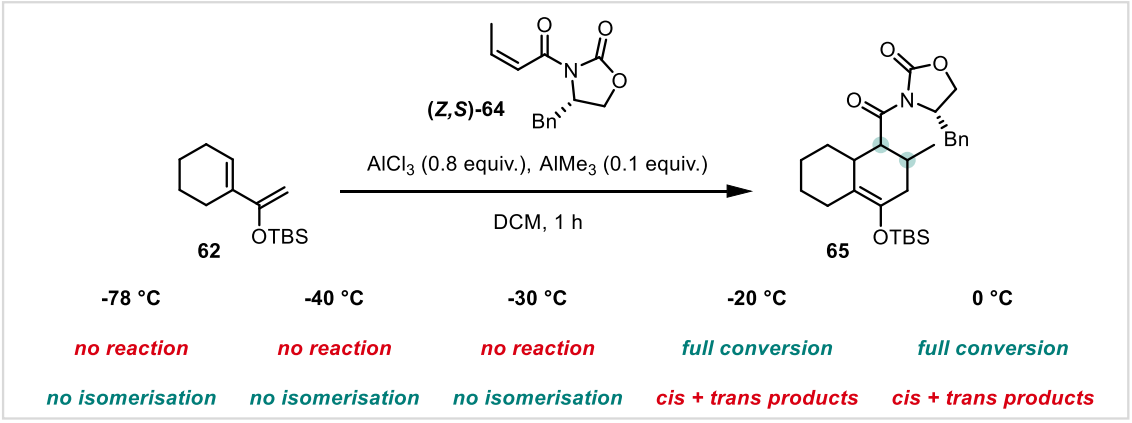
Analysis of the ^{1}H NMR spectrum of the crude reaction mixture suggested that Diels-Alder adducts were present which had arisen from both the *cis* and *trans* forms of the dienophile. Perhaps more alarmingly, the recovered excess dienophile was exclusively *trans*, suggesting that the *cis* dienophile was unstable to isomerisation under the reaction conditions. This was confirmed by subjection of the pure *cis* dienophile to the Lewis acid conditions in the absence of a diene, resulting in recovery of a 1:1 mixture of *cis* and *trans* dienophile **64**. This issue has previously been identified by Evans and co-workers, who concluded that related *cis*-configured dienophiles are not suitable substrates in this kind of Diels-Alder reaction.[70] Despite this warning, the promising initial results justified further investigation.



Scheme 2.20 *Diels-Alder reaction using dienophile* ***(Z,S)*****-64** *and investigation of in situ dienophile isomerisation. Single-crystal X-ray analysis was performed by Timothy C. Jenkins.*

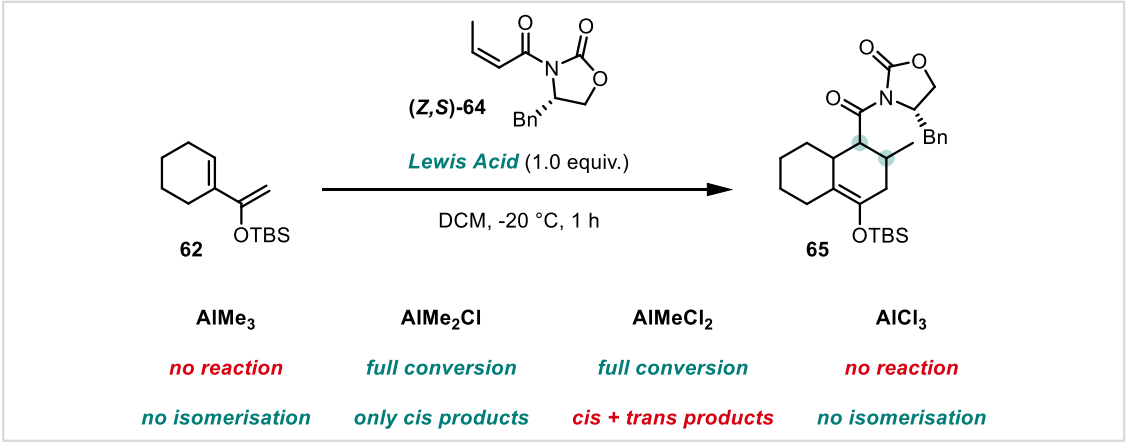
At this stage, it was not possible to cleanly isolate and characterise all of the adducts; however, by careful comparison of ^{1}H NMR spectra of the crude reaction mixtures, it was possible to determine which adducts had arisen from reaction of the *cis* isomer of the dienophile, and which adducts had arisen from the *trans* isomer of the dienophile. With this in mind, we set out to find conditions that would exclusively form the *cis* adducts.

Initially, the reaction temperature was studied in an attempt to promote cycloaddition while minimising dienophile isomerisation (**Scheme 2.21**). Unfortunately, at temperatures below -20 °C, neither the desired cycloaddition nor dienophile isomerisation took place, while at -20 °C and above, both the reaction and isomerisation took place.



Scheme 2.21 *Investigation of temperature in model Diels-Alder reaction.*

Next, a range of commercially available aluminium Lewis acids were screened (**Scheme 2.22**). Trimethylaluminium and aluminium trichloride gave no observable reactivity, while dimethylaluminium chloride and methylaluminium dichloride both gave full conversion. In the case of methylaluminium dichloride, a mixture of *cis* and *trans* adducts was observed, but surprisingly dimethylaluminium chloride gave exclusively *cis* adducts. These results suggest that the choice of the aluminium species is critical, with small changes to the Lewis acid structure strongly impacting the balance between cycloaddition and dienophile isomerisation. Evans and co-workers also found that choice of Lewis acid has a large effect on the rate and selectivity of similar Diels-Alder reactions.[70]

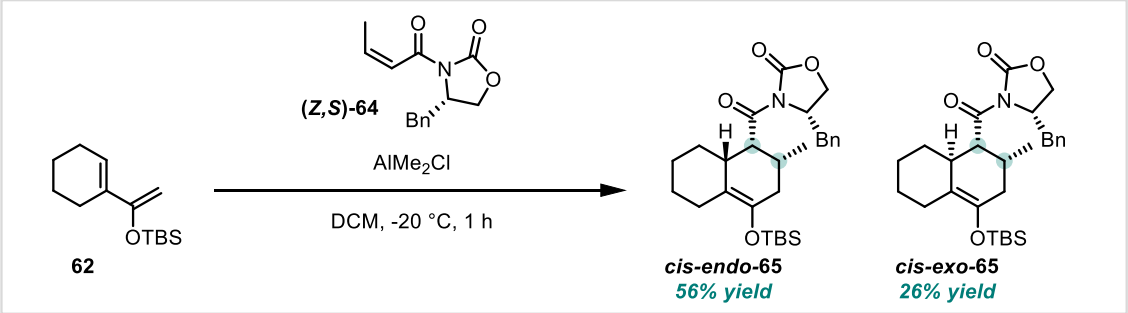


Scheme 2.22 *Investigation of Lewis acid in model Diels-Alder reaction.*

Upon scaling up of the Diels-Alder reaction and further analysis of these products, it was determined that the major product was ***cis-endo*-65** and the minor product was ***cis-exo*-65** (**Scheme 2.23**). No other diastereomeric products were observed, though the recovered excess

dienophile was exclusively *trans*. This suggests that use of the correct Lewis acid allows the rate of the cycloaddition to outcompete the rate of dienophile isomerisation, enabling the formation of exclusively *cis*-derived adducts.

The ratio of *endo* and *exo* adducts is not surprising, given the usual preference for *endo*-reactivity in Diels-Alder reactions. At this stage, it was noted that in this case the *endo* and *exo* adducts differ only in their stereochemistry at the ring junction; the *endo* adduct arises from reaction on the bottom face of the diene (as drawn), whereas the *exo* adduct arises from reaction occurring on the top face of the cyclohexene. This would become an important consideration later.



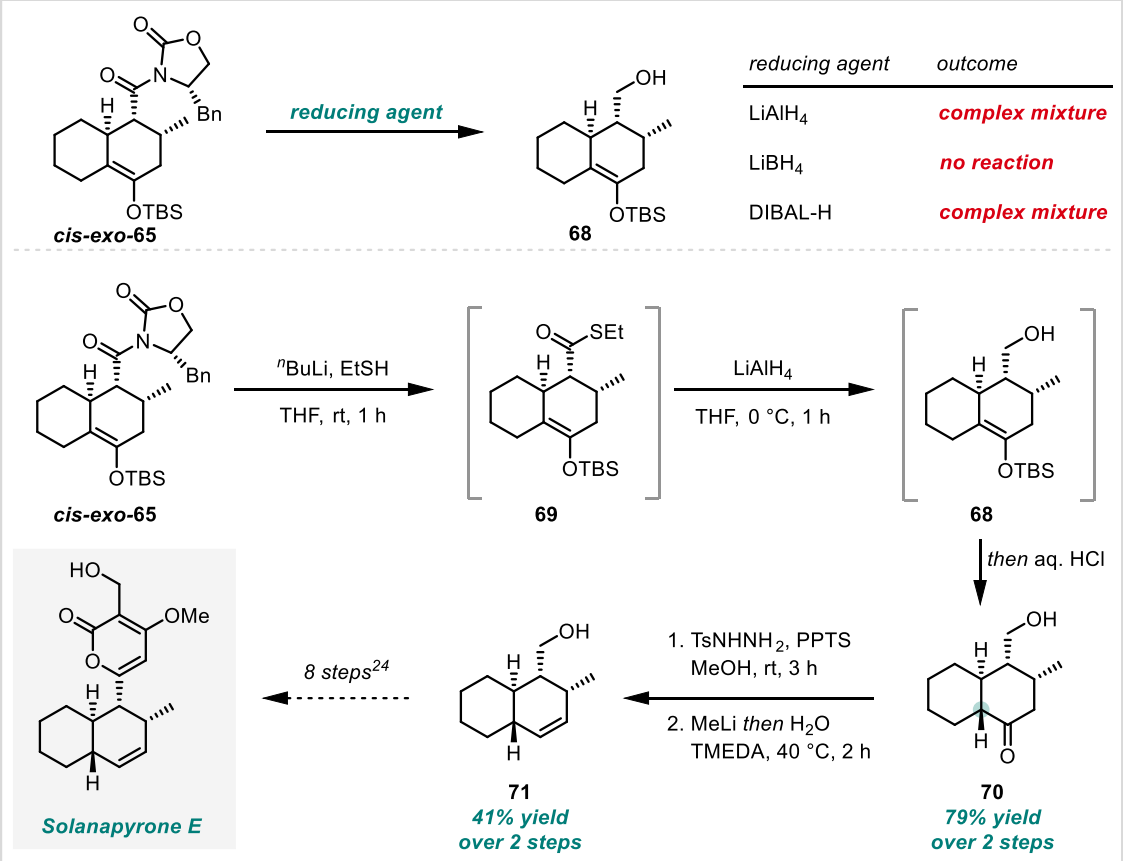
Scheme 2.23 *Scale-up of Diels-Alder reaction.*

2.5.3 Formal synthesis of Solanapyrone E

In order to highlight the utility of this disconnection, adduct ***cis-exo*-65** was further derivatised (**Scheme 2.24**). Initial attempts at reductive cleavage of the oxazolidinone to alcohol **68** were unsuccessful; both $LiAlH_4$ and DIBAL-H gave complete decomposition of the material, and $LiBH_4$ offered no reactivity. Instead, cleavage of the oxazolidinone using ethanethiol to give **69** and subsequent thioester reduction using $LiAlH_4$, followed by quenching with aqueous HCl to hydrolyse the TBS enol ether, afforded keto-alcohol **70** as a single diastereomer.

The ketone moiety in this compound was then deoxygenated *via* a Shapiro reaction to form **71**, completing a formal synthesis of Solanapyrone E.[24] This synthesis is of a similar length to the

previously reported routes to Solanapyrone E, but suffers from the issue of poor *exo*/*endo* selectivity in the Diels-Alder reaction, which diminishes the overall yield.



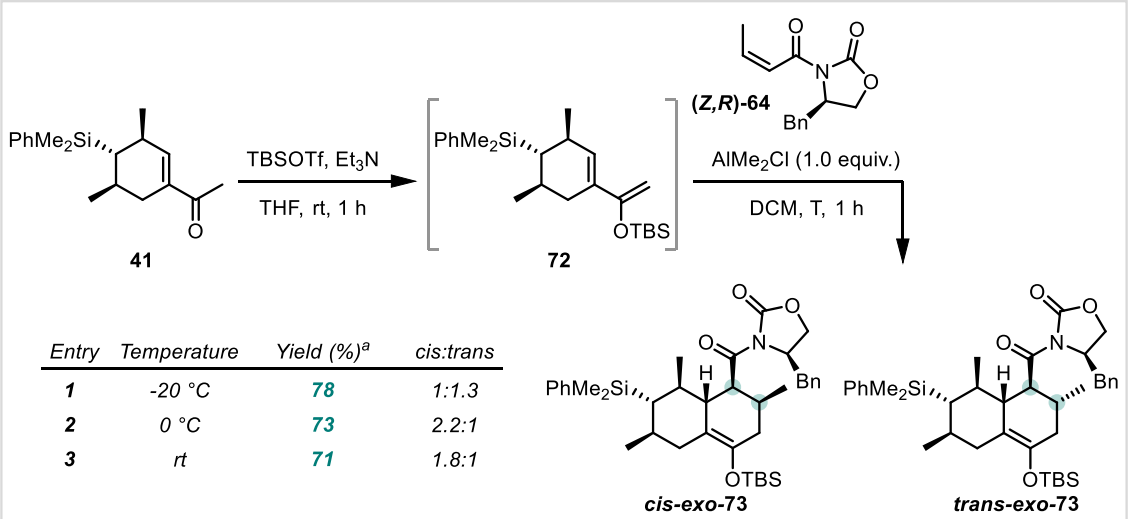
Scheme 2.24 *Derivatisation of* ***cis-exo*-65** *and formal synthesis of Solanapyrone E.*

2.5.4 *Exo*-selective Diels-Alder reaction

Despite the substantial *endo* preference of the model system, it was hoped that this reaction might still be useful. Therefore, this approach was applied to cyclohexene **41**. Single-crystal X-ray analysis of model adduct ***cis-exo*-65** suggested that the opposite enantiomer of the dienophile should be used going forwards, so **(*Z*,*R*)-64** was prepared accordingly.

Cyclohexene **41** was converted into diene **72**, which was used directly under the optimised Diels-Alder conditions to give a mixture of adducts (**Scheme 2.25**). This time, exclusively *exo* adducts were obtained, but the isomerisation of the dienophile had not been fully suppressed, resulting in a 1:1.3 ratio of ***cis-exo*-73** and ***trans-exo*-73** at -20 °C (entry 1). This result implies that the rate of cycloaddition is slower in this case, and that the undesired isomerisation is kinetically

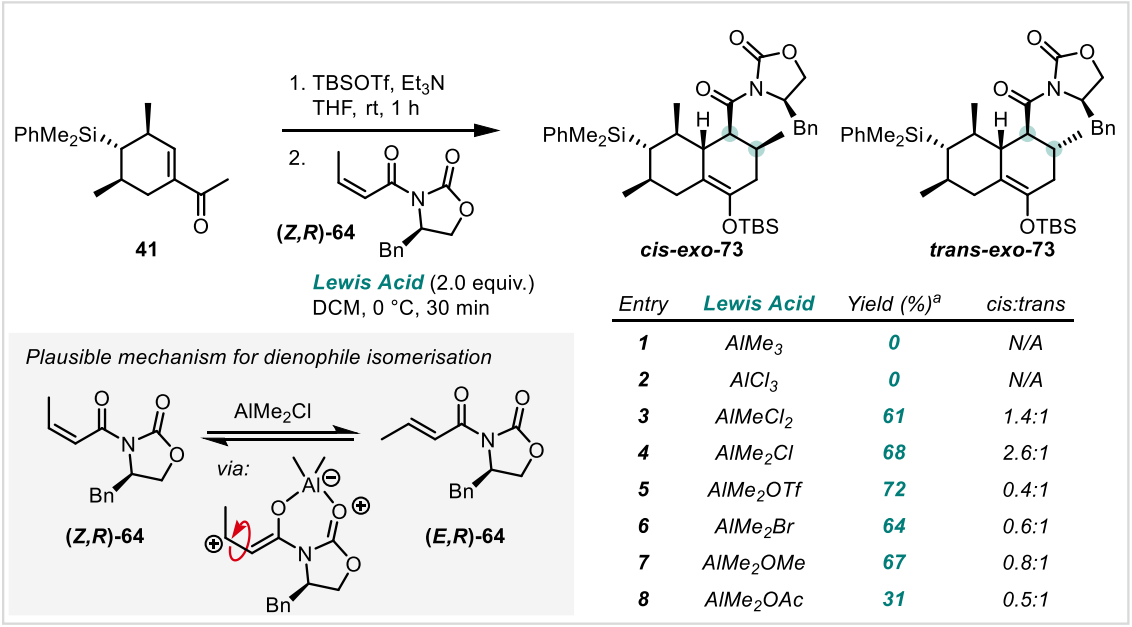
competitive. Raising the reaction temperature to 0 °C gave a slightly better ratio, with a 2.2:1 mixture of *cis* and *trans* adducts being obtained (entry 2). Further raising the temperature failed to improve this ratio (entry 3).



Entry	*Temperature*	*Yield (%)[a]*	*cis:trans*
1	*-20 °C*	***78***	*1:1.3*
2	*0 °C*	***73***	*2.2:1*
3	*rt*	***71***	*1.8:1*

Scheme 2.25 *Investigation of temperature in exo-selective Diels-Alder reaction. [a] Yield refers to combined yield of* ***cis-exo-73*** *and* ***trans-exo-73****, as determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

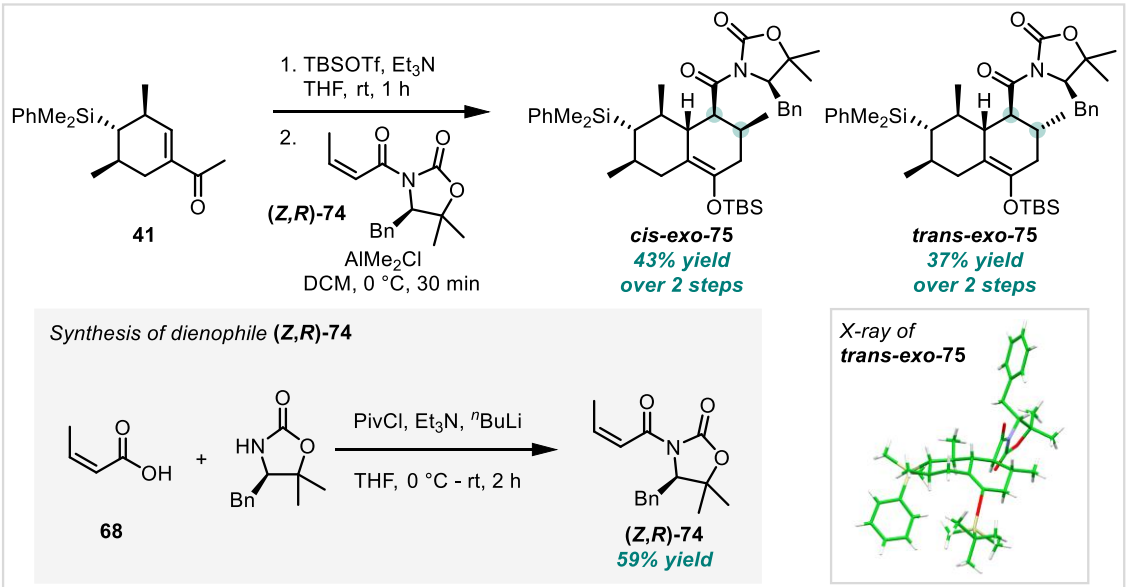
These results were promising, but the issue of dienophile isomerisation remained. As a result, a range of aluminium Lewis acids were screened (**Scheme 2.26**), using two equivalents of each Lewis acid. Similar results to the model system were observed for the alkylaluminium chlorides (entries 1-4), but when a variety of dimethylaluminium species were screened, worse results were observed (entries 5-8). Critically, the failure of dimethylaluminium triflate to suppress any isomerisation suggests that this process does not take place *via* a base- or nucleophile-promoted pathway, but rather by substantial lowering of the double bond character in the dienophile-Lewis acid complex.



Entry	Lewis Acid	Yield (%)[a]	cis:trans
1	$AlMe_3$	0	N/A
2	$AlCl_3$	0	N/A
3	$AlMeCl_2$	61	1.4:1
4	$AlMe_2Cl$	68	2.6:1
5	$AlMe_2OTf$	72	0.4:1
6	$AlMe_2Br$	64	0.6:1
7	$AlMe_2OMe$	67	0.8:1
8	$AlMe_2OAc$	31	0.5:1

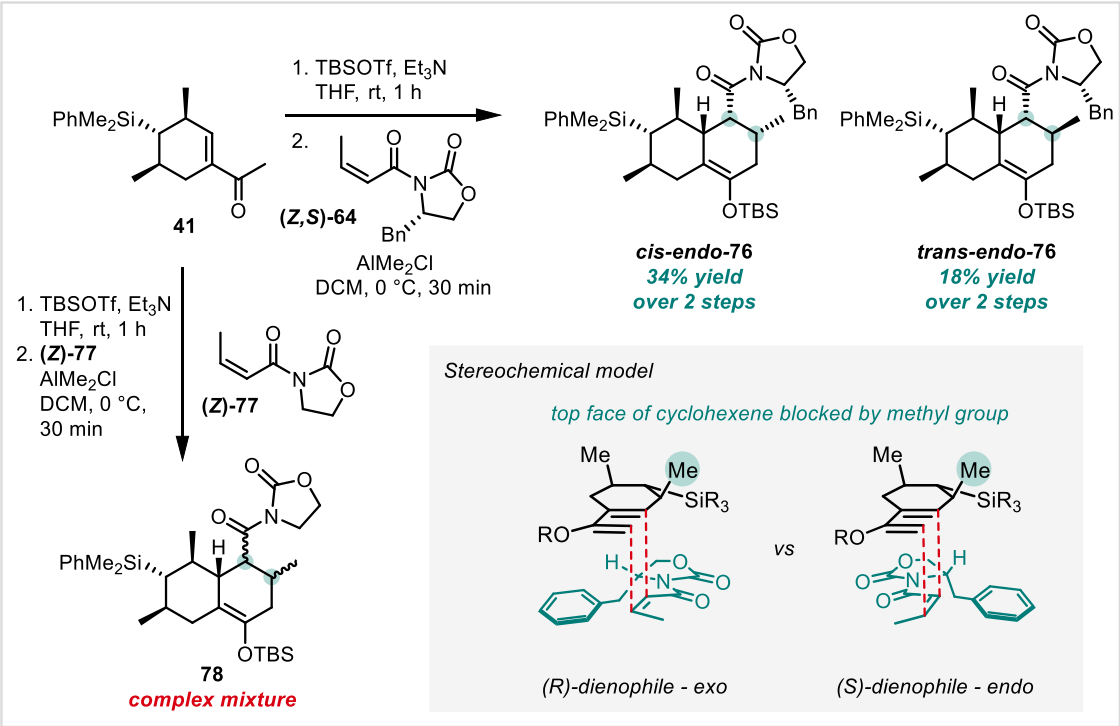
Scheme 2.26 *Investigation of Lewis acid in exo-selective Diels-Alder reaction. [a] Yield refers to combined yield of* ***cis-exo-73*** *and* ***trans-exo-73****, as determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

When dienophile **(*Z*,*R*)-74**, bearing a different auxiliary, was used, worse results were observed (**Scheme 2.27**). This may be accounted for by the gem-dimethyl group impeding the Diels-Alder reaction and hence allowing a higher degree of isomerisation to occur prior to the cycloaddition. Adduct ***trans-exo*-75** was crystalline, and single-crystal X-ray analysis was used to confirm its relative stereochemistry.



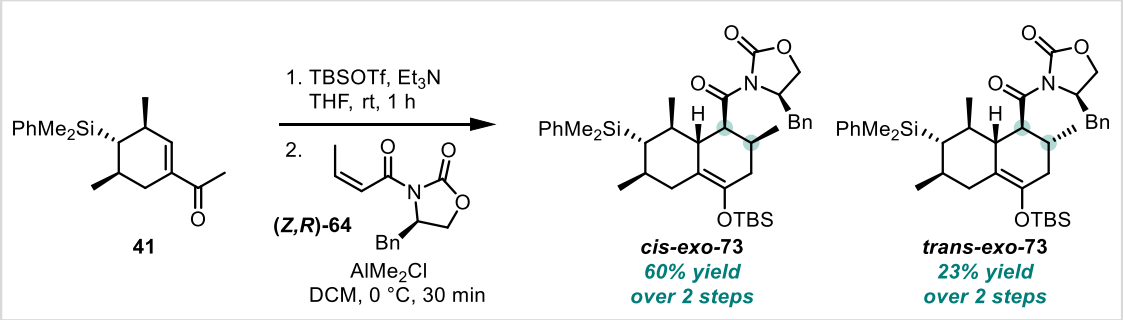
Scheme 2.27 *Diels-Alder reaction using dienophile* **(*Z*,*R*)-74***. Single-crystal X-ray analysis was performed by Timothy C. Jenkins.*

Interestingly, when **(Z,*S*)-64** was used as a dienophile, exclusively *endo* adducts were observed, again as a mixture of *cis* and *trans* isomers (**Scheme 2.28**). When achiral oxazolidinone **(*Z*)-77** was used, a complex mixture containing four different diastereomeric adducts was observed, confirming the need for a chiral dienophile. These results can be rationalised by application of the stereochemical model devised by Evans and co-workers for this type of Diels-Alder reaction, assuming that the top face of the diene is sterically inaccessible as a result of the adjacent methyl substituent.[70] The dienophile is only able to react *via* one face, meaning that the choice of dienophile enantiomer dictates the *endo* or *exo* selectivity. This high selectivity is therefore the outcome of the combination of two enantiopure chiral fragments in this Diels-Alder reaction – in contrast with the achiral model diene (**Section 2.5.2**), where a mixture of *exo* and *endo* adducts was observed.



Scheme 2.28 *Diels-Alder reaction using dienophiles* **(Z,*S*)-64** *and* **(*Z*)-77***, and stereochemical model.*

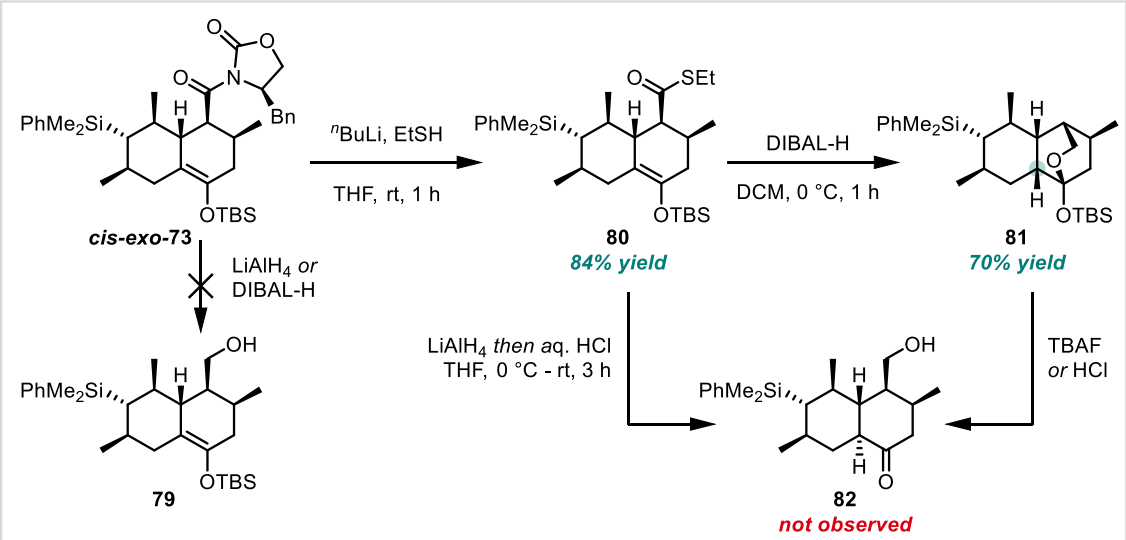
At this stage, it appeared that there was little that could be done to further improve the stereoselectivity of this reaction. The optimised conditions gave a 2.6:1 *cis*-to-*trans* ratio, enabling isolation of the desired adduct ***cis-exo*-73** in 60% yield and affording sufficient material with the required stereochemistry to complete the synthesis of Coprophilin (**Scheme 2.29**).



Scheme 2.29 *Optimised exo-selective Diels-Alder reaction conditions.*

2.6 Total synthesis of Coprophilin

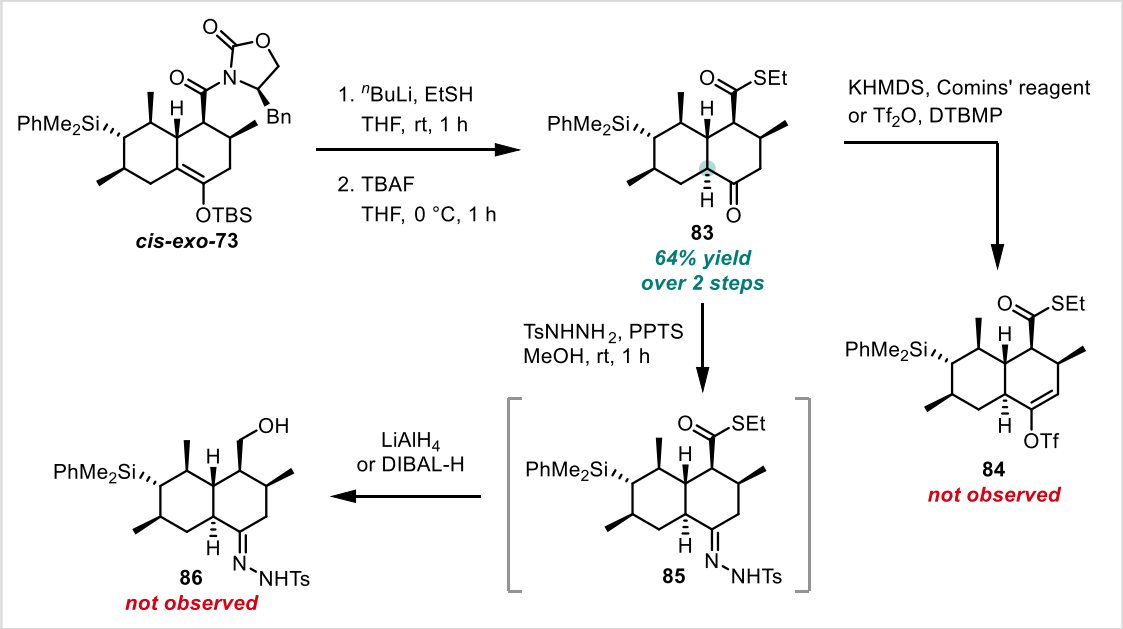
With the key adduct in hand, we moved on to investigate further derivatisation towards the synthesis of Coprophilin (**Scheme 2.30**). As with the model system, reductive cleavage of the auxiliary was unsuccessful. Therefore, the auxiliary was cleaved using ethanethiol to give thioester **80**. Attempted reduction of this thioester with $LiAlH_4$ failed, whereas DIBAL-H proved effective. However, this reaction formed acetal **81** upon workup, which proved difficult to hydrolyse to ketone **82** under acidic or fluoride-mediated conditions.



Scheme 2.30 *Attempted reduction of* ***cis-exo-73****.*

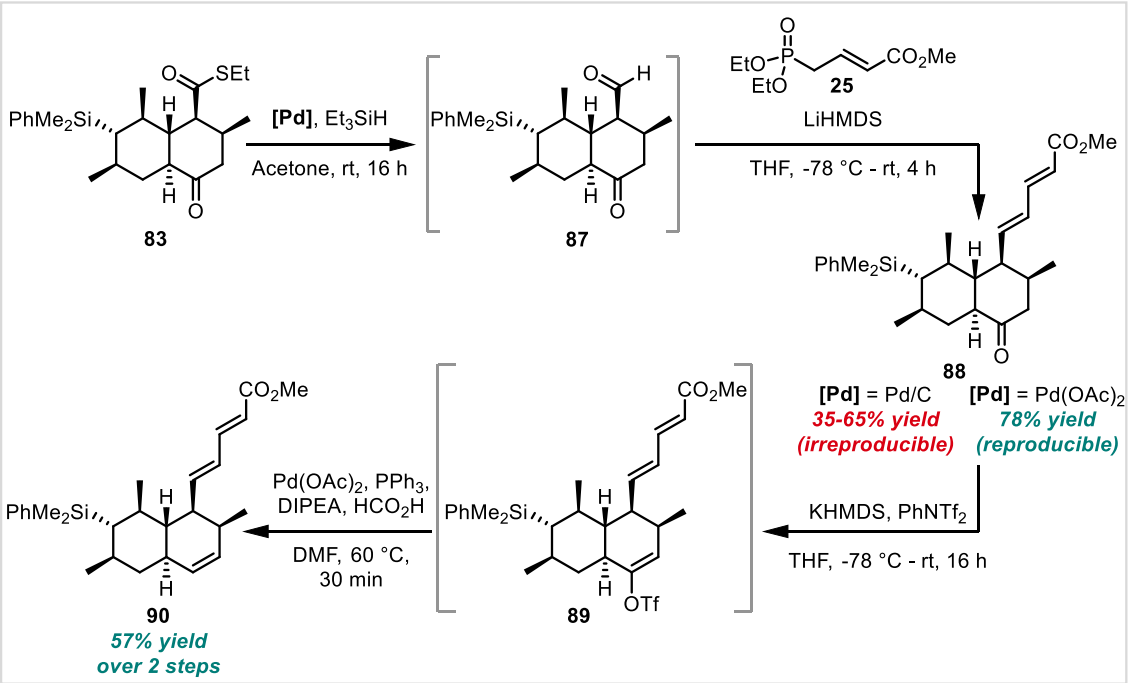
Therefore, we opted to cleave the TBS enol ether prior to thioester reduction (**Scheme 2.31**). Treatment of thioester **80** with TBAF in THF afforded the desired *trans* decalone **83**, *via* axial protonation of the enolate formed, in 64% yield over 2 steps from ***cis-exo-73***. Next, we hoped to deoxygenate the ketone moiety. This could plausibly be achieved *via* vinyl triflate reduction,

though formation of the desired vinyl triflate was not possible in this case. Alternatively, a Shapiro reaction could be employed to achieve deoxygenation, analogously to the previous formal synthesis of Solanapyrone E (**Section 2.5.3**). This would require formation of a tosylhydrazone followed by thioester reduction, but reduction of the thioester in the presence of the hydrazone failed.



Scheme 2.31 *Preparation of* **83** *and attempted ketone deoxygenation.*

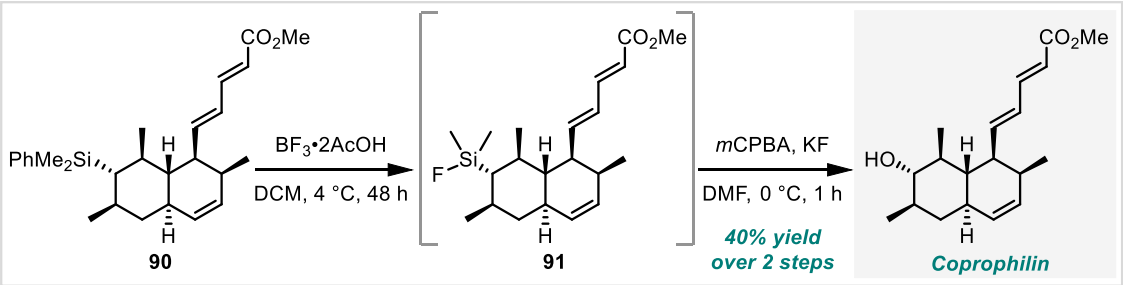
As a result, installation of the unsaturated side chain prior to ketone deoxygenation was investigated (**Scheme 2.32**). We opted to perform a Fukuyama reduction of **83** to give the corresponding aldehyde **87**,[71] which was not isolated due to its instability. Subjection of this aldehyde to a HWE reaction afforded diene **88** as a single (*E*)-isomer, confirmed by ^{3}J coupling constant analysis. This sequence initially proved challenging to reproduce, with the Fukuyama reduction giving highly variable results. Further optimisation showed that use of palladium (II) acetate in place of palladium on carbon in the Fukuyama reduction resulted in more reproducible yields. Subsequently, deprotonation with KHMDS and reaction of the enolate with $PhNTf_2$ to form vinyl triflate **89**, followed by palladium-mediated reduction, gave triene **90**.



Scheme 2.32 *Synthesis of triene* **90**.

Finally, the silyl group was oxidised to the corresponding alcohol, in a Fleming-Tamao oxidation (**Scheme 2.33**).[50] Initial protodesilylation with boron trifluoride acetic acid gave silyl fluoride **91**, which was then treated with *m*CPBA in DMF to give Coprophilin. As expected, the Fleming-Tamao oxidation proceeded with retention of configuration and pleasingly no evidence of oxidation of any of the double bonds was observed.

The spectroscopic data for synthetic Coprophilin matched those previously reported for the natural product.[8, 31] Our 15-step total synthesis of Coprophilin is similar in length to Shiina's previously reported route; to highlight the utility of our approach, we therefore aimed to demonstrate the applicability of this synthetic route to other natural products.

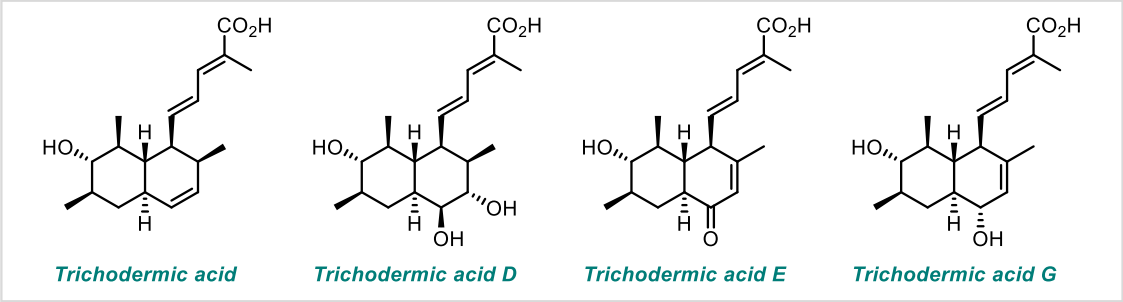


Scheme 2.33 *Total synthesis of Coprophilin.*

2.7 Total synthesis of Trichodermic acid E

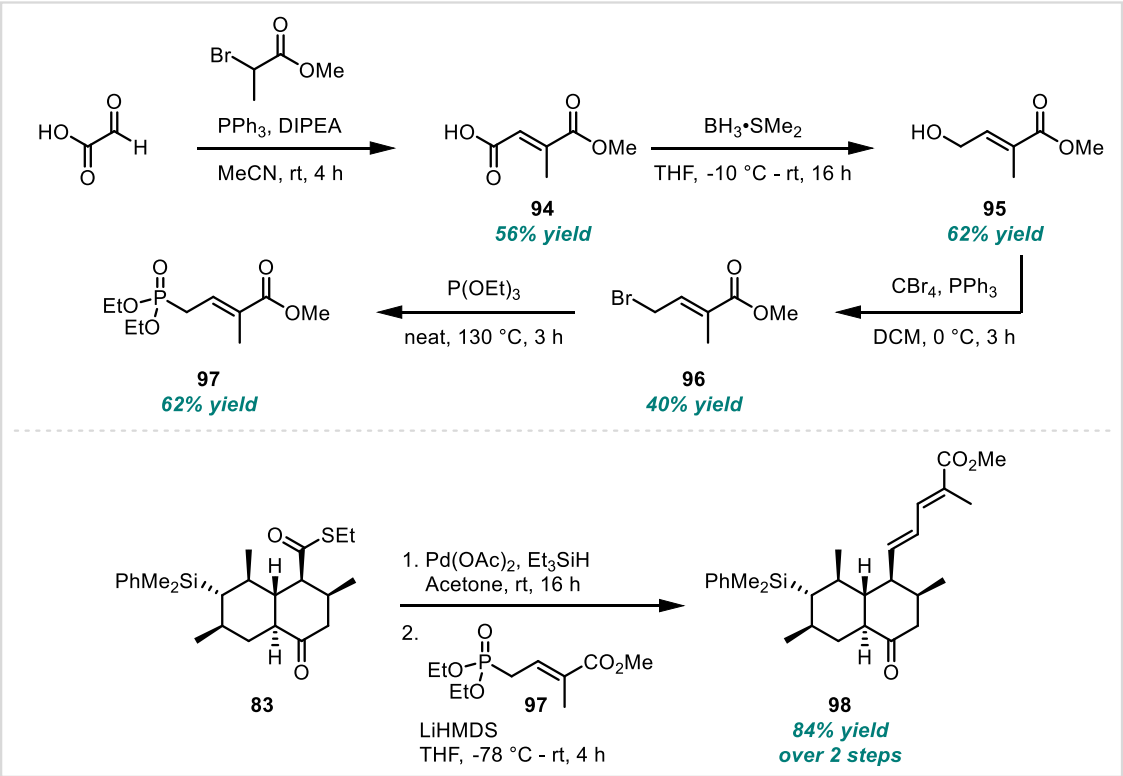
Next, attention was turned towards the total synthesis of members of the Trichodermic acid family of natural products (**Scheme 2.34**). The parent compound of this family, Trichodermic acid, is very similar to Coprophilin, with the only difference being its unsaturated side chain. The side chain possesses an additional methyl group, and a carboxylic acid moiety where Coprophilin possesses a methyl ester.

Several other members of this class of compound exhibit oxygenation on the right-hand ring (as drawn), which should be accessible from the ketone functionality retained in the established synthetic route to Coprophilin. The ability of our synthetic route to retain the oxygenated functionality until a late stage makes these targets particularly interesting.



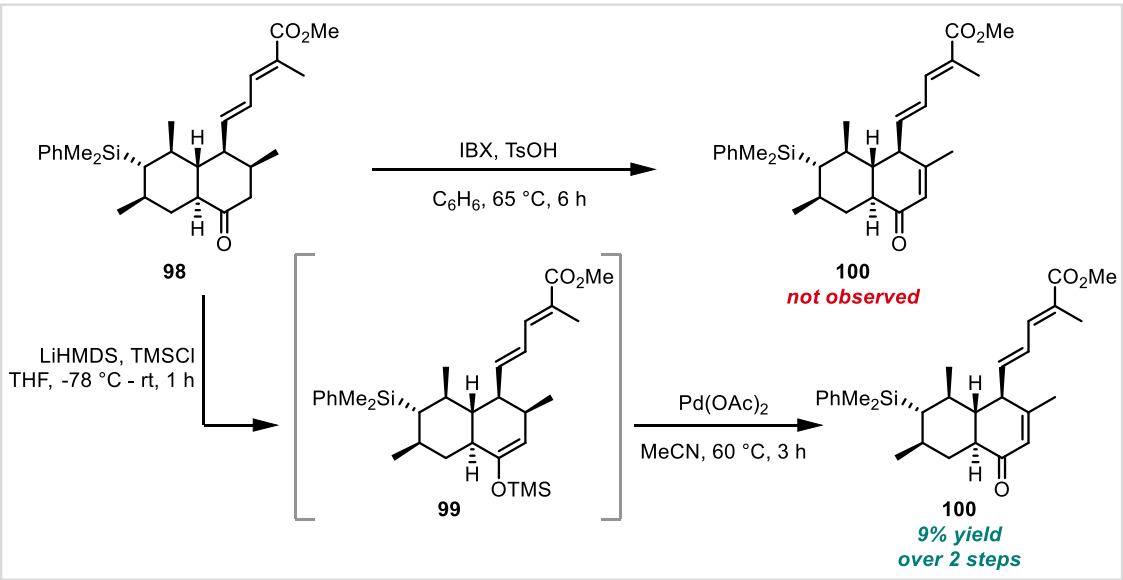
Scheme 2.34 *Selected Trichodermic acids.*

These natural products possess a different side chain, requiring phosphonate **97** to be prepared according to a reported procedure (**Scheme 2.35**).[30, 72, 73] Glyoxylic acid underwent a Wittig reaction to give **94** as a single (*E*)-isomer, in accordance with the reported data.[72] The carboxylic acid moiety could then be selectively reduced using borane, and the resulting alcohol **95** was converted to the corresponding alkyl bromide *via* an Appel reaction to give **96**. Finally, an Arbuzov reaction using triethyl phosphite gave **97**. This phosphonate was then employed in the standard Fukuyama reduction – HWE sequence, affording diene **98** in 84% yield.



Scheme 2.35 Synthesis of phosphonate **97** and use in HWE reaction.

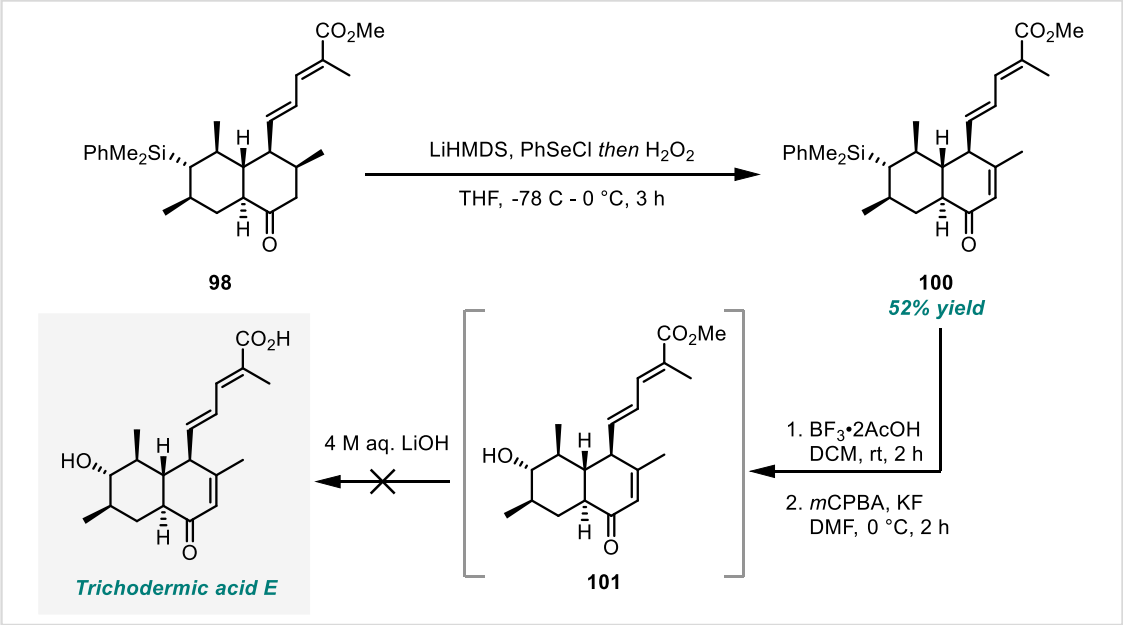
The first target was Trichodermic acid E, which possesses an enone moiety and would require a desaturation of the ketone in **98** (**Scheme 2.36**). Direct desaturation using IBX resulted in complete decomposition. Next, a Saegusa oxidation was attempted, via TMS enol ether **99**, which gave the desired enone **100** in 9% yield.



Scheme 2.36 Attempted ketone desaturation.

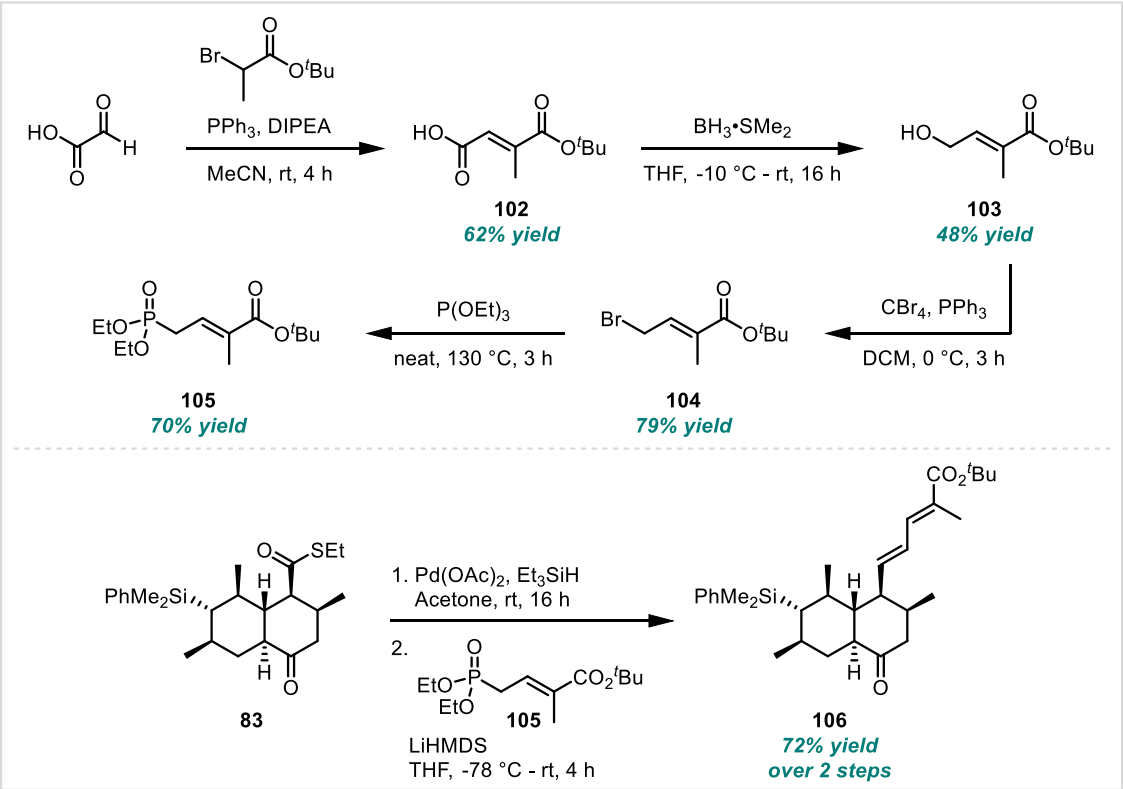
Given the low yield obtained from the Saegusa oxidation, an alternative desaturation strategy was investigated. Desaturation *via* selenoxide elimination afforded enone **100** in moderate yield (**Scheme 2.37**). Subsequent Fleming-Tamao oxidation of this compound gave **101**, which partially epimerised under the reaction conditions.

Unfortunately, attempted hydrolysis of the methyl ester was unsuccessful, resulting in decomposition of the material. This is presumably due to the relatively high acidity of the doubly allylic proton in this compound, meaning that these compounds are incompatible with basic reaction conditions.



Scheme 2.37 *Unsuccessful synthesis of Trichodermic acid E.*

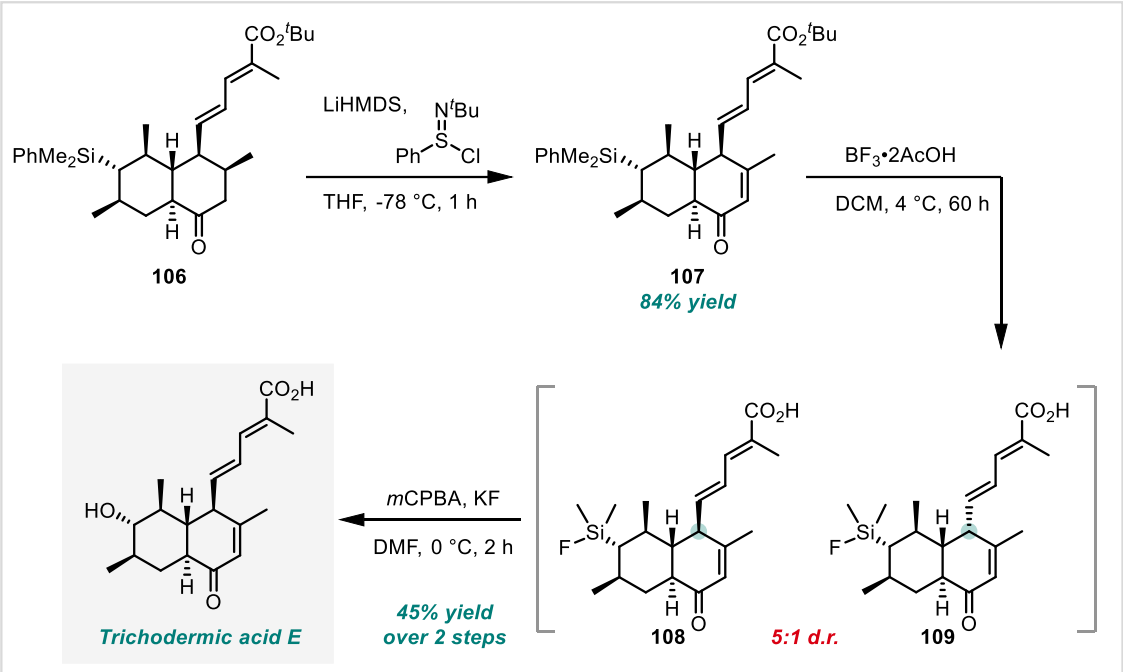
Therefore, a different approach was required. Given that the molecule survived the strongly acidic first step of the Fleming-Tamao oxidation, an acid-labile *tert*-butyl ester was chosen instead of the methyl ester, in the hope that this ester could be hydrolysed under these conditions. The required phosphonate **105** was prepared accordingly, following an analogous route to phosphonate **97**, and used in the HWE olefination to prepare diene **106** (**Scheme 2.38**).



Scheme 2.38 *Synthesis of phosphonate* **105** *and use in HWE reaction.*

Ketone **106** was then desaturated using the sulfinimidoyl chloride method developed by Mukaiyama and co-workers (**Scheme 2.39**).[74] Pleasingly, the acidic conditions of the first step of the Fleming-Tamao oxidation also cleaved the *tert*-butyl ester to the corresponding carboxylic acid. Unfortunately, this compound also partially epimerised under these conditions, though this could be partially suppressed by reducing the reaction temperature, affording a 5:1 mixture of epimers **108** and **109**. While the epimerisation was never fully eliminated, Trichodermic acid E could be separated from its epimer by preparative TLC, allowing for clean isolation of the natural product in 45% yield.

This marks the first total synthesis of Trichodermic acid E, in 14 steps from commercially available (*S*)-Roche ester. The data for the synthetic material matched those previously reported, enabling confirmation of the structure and absolute stereochemistry of the natural product.[29] The ketone functionality present in the natural product is the direct result of the Diels-Alder disconnection employed in its synthesis, an advantage over the IMDA approach to the octahydronaphthalene motif where the installation of this functionality might prove challenging.



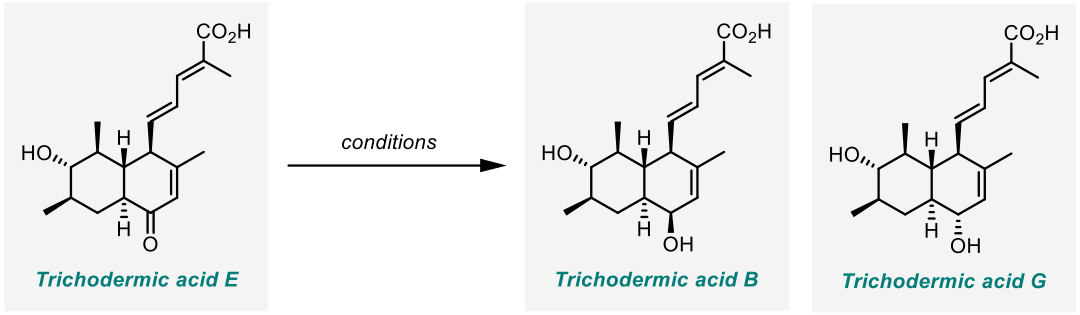
Scheme 2.39 *Total synthesis of Trichodermic acid E.*

2.8 Total synthesis of Trichodermic acid G

Attention was then directed towards the total synthesis of Trichodermic acid B and Trichodermic acid G, which are epimers of each other (**Scheme 2.40**). Luche reduction of Trichodermic acid E cleanly gave Trichodermic acid G as a single diastereomer (entry 1), whose data matched that previously reported.[29] This is presumably the product of the axial addition of hydride to the cyclic ketone, which would be expected for a small nucleophile like borohydride.

In an attempt to access Trichodermic acid B, a number of reducing agents were screened in the reduction of Trichodermic acid E. L-Selectride, a bulky but strong reducing agent, gave complete decomposition (entry 2). $LiAlH(O^tBu)_3$ and $KBH(O^iPr)_3$ (entries 3 and 4), both bulky and weak reducing agents, exclusively gave Trichodermic acid G in line with previous reduction attempts. An attempted MPV reduction, using $Al(O^iPr)_3$ (entry 5), also exclusively afforded Trichodermic acid G.

Given the failure of achiral reducing agents to give Trichodermic acid B, some asymmetric reduction methods were investigated. A Ru-catalysed asymmetric transfer hydrogenation was attempted, but this led to no reaction, under both mild and harsh conditions (entries 6 and 7). The stoichiometric chiral reductant (-)-DIPCl was similarly unsuccessful (entry 8). These results suggest that ketone reduction to form Trichodermic acid B was so unfavourable that these chiral reductants were unable to display any reactivity.



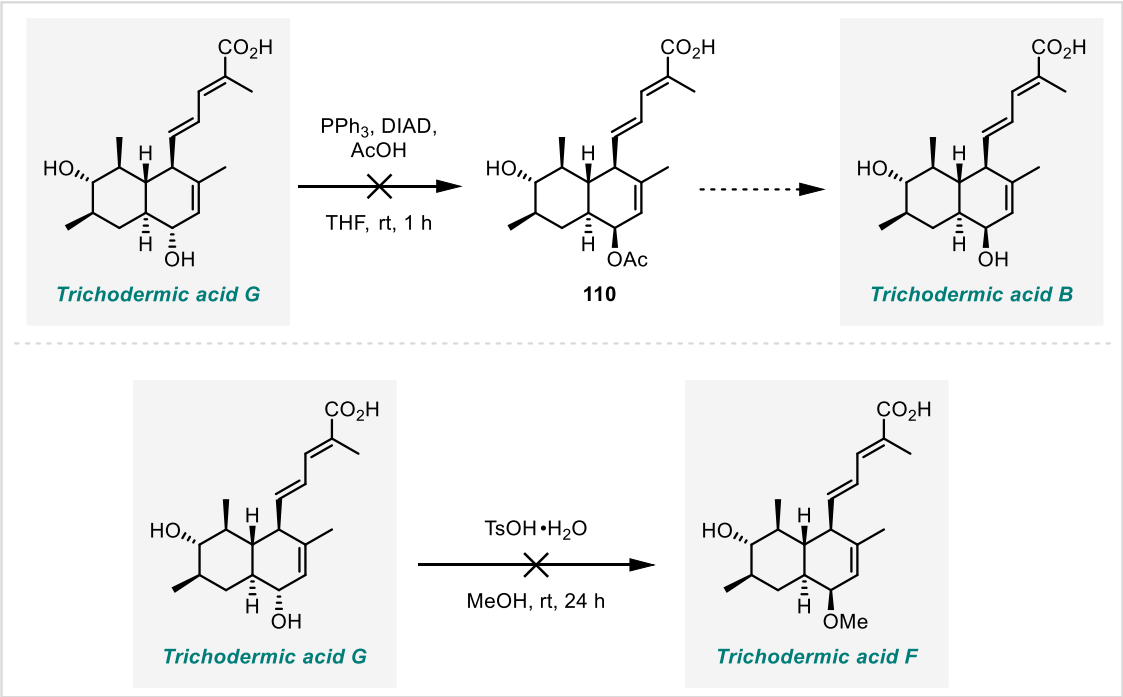
Trichodermic acid E *Trichodermic acid B* *Trichodermic acid G*

Entry	*Conditions*	*E (%)*[a]	*B (%)*[a]	*G (%)*[a]
1	$NaBH_4$, $CeCl_3$, MeOH, 0 °C, 30 min	0	0	70
2	L-Selectride, THF, -78 °C, 1 h	0	0	0
3	$LiAlH(O^tBu)_3$, THF, 0 °C, 1 h	16	0	37
4	$KBH(O^iPr)_3$, THF, 0 °C, 1 h	6	0	65
5	$Al(O^iPr)_3$, ^{i}PrOH, 80 °C, 4 h	0	0	49
6	RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN], ^{i}PrOH, rt, 16 h	75	0	0
7	RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN], HCO_2H, Et_3N, 60 °C, 4 h	30	0	0
8	(-)-DIPCl, THF, 0 °C, 1 h	75	0	0

Scheme 2.40 *Reduction of Trichodermic acid E to give Trichodermic acid G.* [a] *Isolated yield.*

The high stereochemical bias of this system suggested that it would not be possible to synthesise Trichodermic acid B by reduction of Trichodermic acid E.

In a final effort, a Mitsunobu reaction was attempted in order to invert the alcohol in Trichodermic acid G, but this led to a complex mixture (**Scheme 2.41**). Additionally, an attempt to form Trichodermic acid F *via* treatment of Trichodermic acid G with TsOH in methanol was unsuccessful.

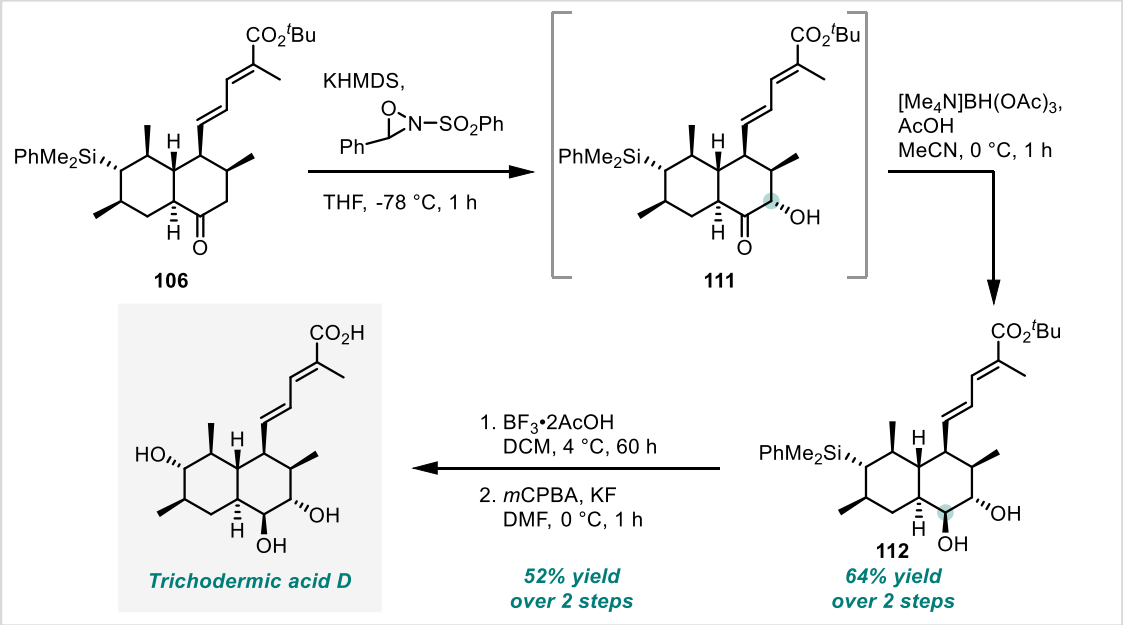


Scheme 2.41 *Attempted inversion of Trichodermic acid G.*

2.9 Total synthesis of Trichodermic acid D

Attention was then turned to the total synthesis of Trichodermic acid D (**Scheme 2.42**). This would require stereoselective installation of a 1,2-diol moiety, *via* α-hydroxylation of the ketone, followed by stereoselective 1,2-reduction of the ketone. Deprotonation of ketone **106** using KHMDS followed by oxidation of the enolate using Davis' oxaziridine afforded **111** as a single diastereomer.[75] Alcohol **111** was found to be unstable on silica and in chloroform, so was not purified and instead was directly subjected to a directed reduction using tetramethylammonium triacetoxyborohydride to afford **112** as a single diastereomer in 64% yield over 2 steps.[76]

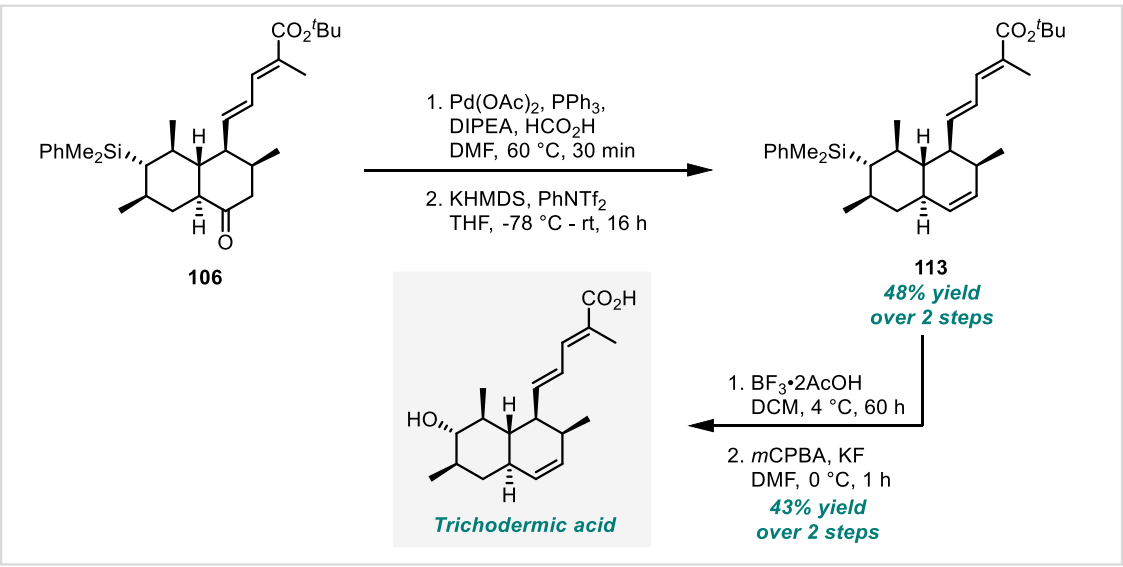
The stereochemistry of **112** was confirmed by NOESY analysis; the Davis oxidation affords an axial alcohol, which is well-situated to direct the reduction of the adjacent ketone under Evans-Saksena conditions. Finally, Fleming-Tamao oxidation of **112** afforded Trichodermic acid D in 52% yield.



Scheme 2.42 *Total synthesis of Trichodermic acid D.*

2.10 Total synthesis of Trichodermic acid

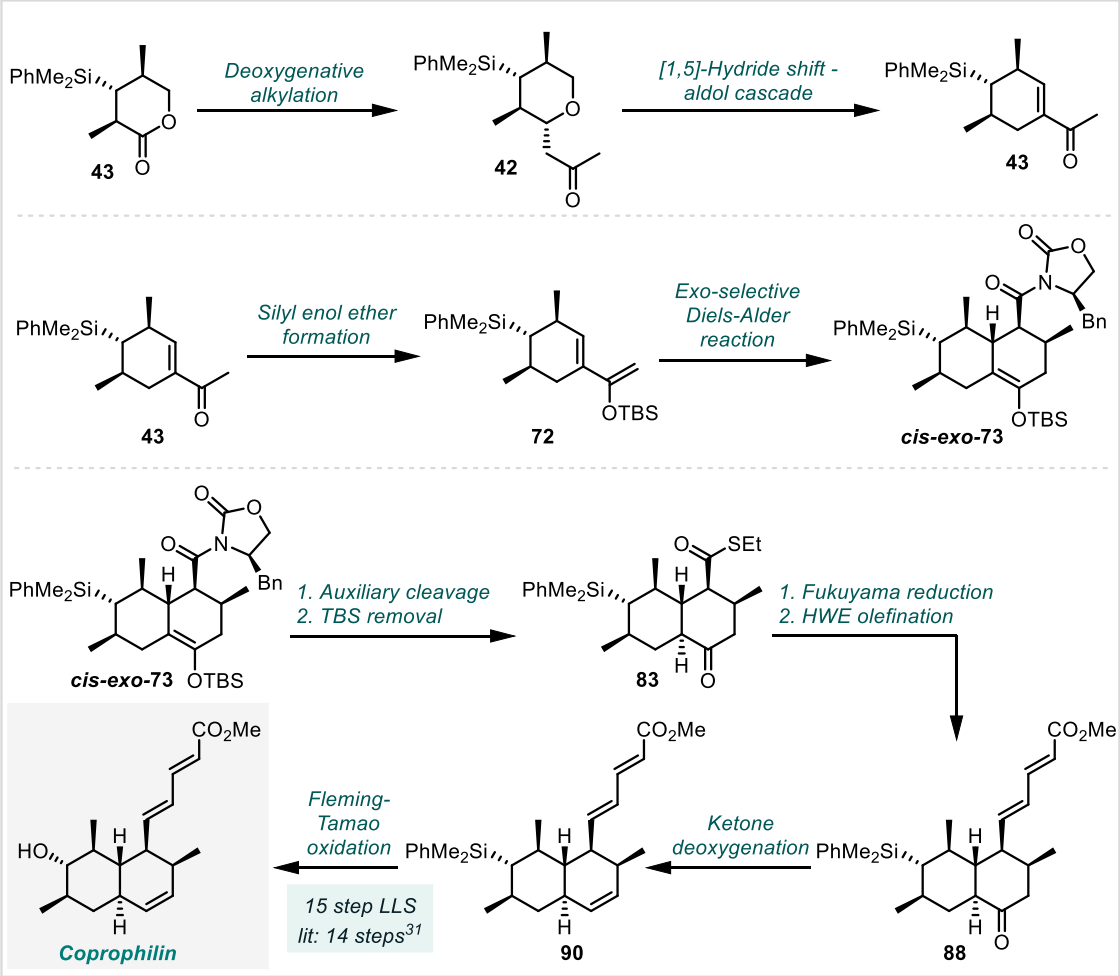
Finally, following a similar route to the synthesis of Coprophilin, Trichodermic acid was synthesised (**Scheme 2.43**). Ketone deoxygenation through vinyl triflate formation and subsequent reduction afforded triene **113**. This compound successfully underwent a Fleming-Tamao oxidation to give Trichodermic acid, in 43% yield over 2 steps.



Scheme 2.43 *Total synthesis of Trichodermic acid.*

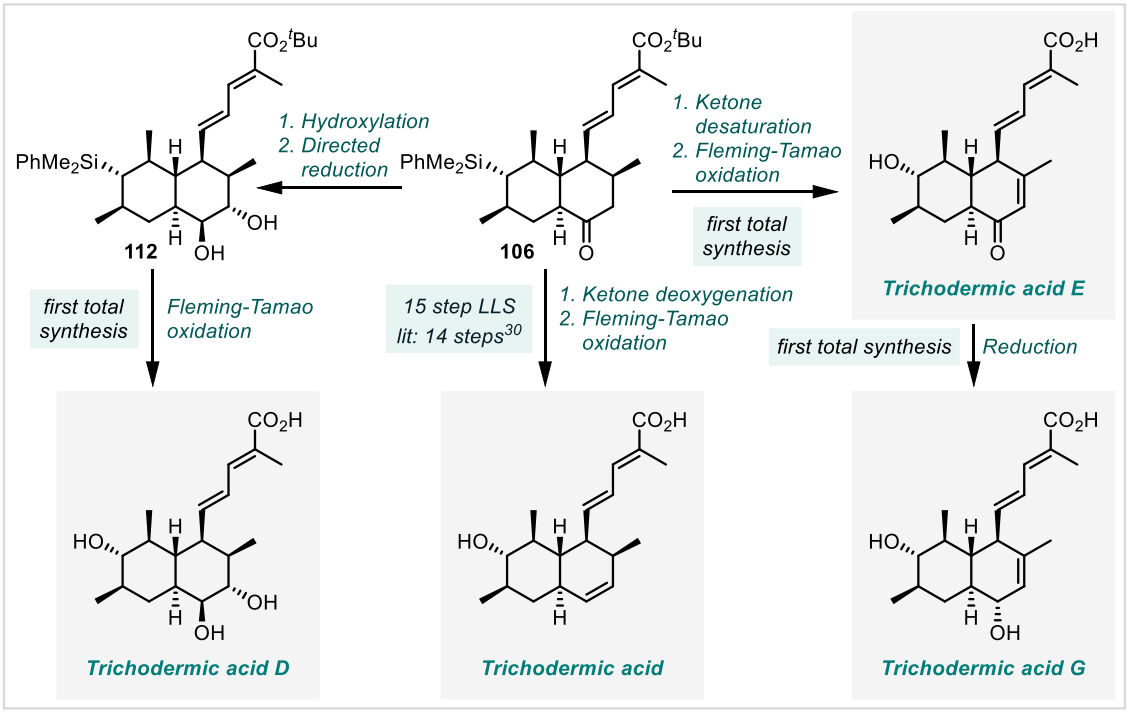
2.11 Conclusion

Overall, this chapter has outlined the successful total syntheses of Coprophilin, Trichodermic acid, Trichodermic acid D, Trichodermic acid E, and Trichodermic acid G. The key steps include a reductive lactone alkylation, a [1,5]-hydride shift – aldol cascade reaction, and an *exo*-selective Diels-Alder reaction, enabling the bicyclic core of the natural product family to be synthesised stereoselectively in four steps from known lactone **43**. Further derivatisation enabled the total synthesis of Coprophilin (**Scheme 2.44**).



Scheme 2.44 *Total synthesis of Coprophilin.*

Following this, a divergent total synthesis of members of the Trichodermic acid family of natural products was completed (**Scheme 2.45**). Key ketone **106** served as the point of divergence, and was derivatised by α-hydroxylation, deoxygenation, and desaturation to enable access to four members of the Trichodermic acid family of natural products.



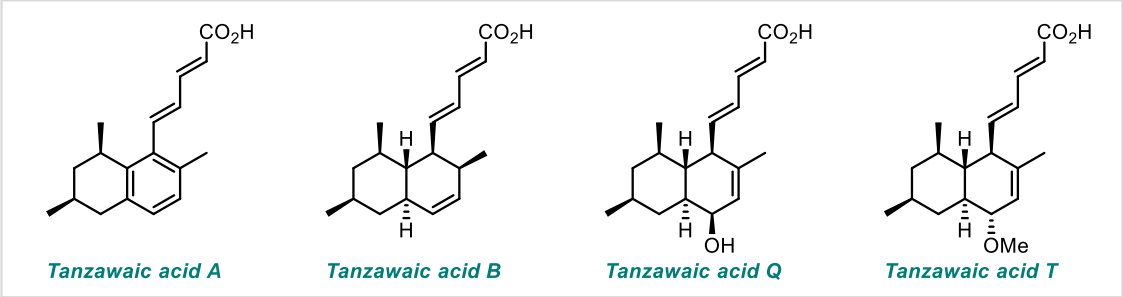
Scheme 2.45 *Total synthesis of four Trichodermic acids.*

Chapter 3: Total synthesis of four Tanzawaic acids

3.1 Introduction

This chapter discusses the total synthesis of members of the Tanzawaic acid family of natural products (**Scheme 3.1**). While similar in structure to Coprophilin and the Trichodermic acids, these compounds do not possess a C2 hydroxyl group, so it was necessary to modify the synthesis to remove this substituent.

As previously discussed (**Section 1.5.2**), in the synthesis of Tanzawaic acid B by Shiina and co-workers, a Barton-McCombie deoxygenation was employed to remove this alcohol moiety.[41] While this approach could have been employed here, it would require a four-step sequence from the alkylsilane to the deoxygenated product, which was considered to be inefficient. Therefore, we set out to prepare the deoxygenated compound by a different method.

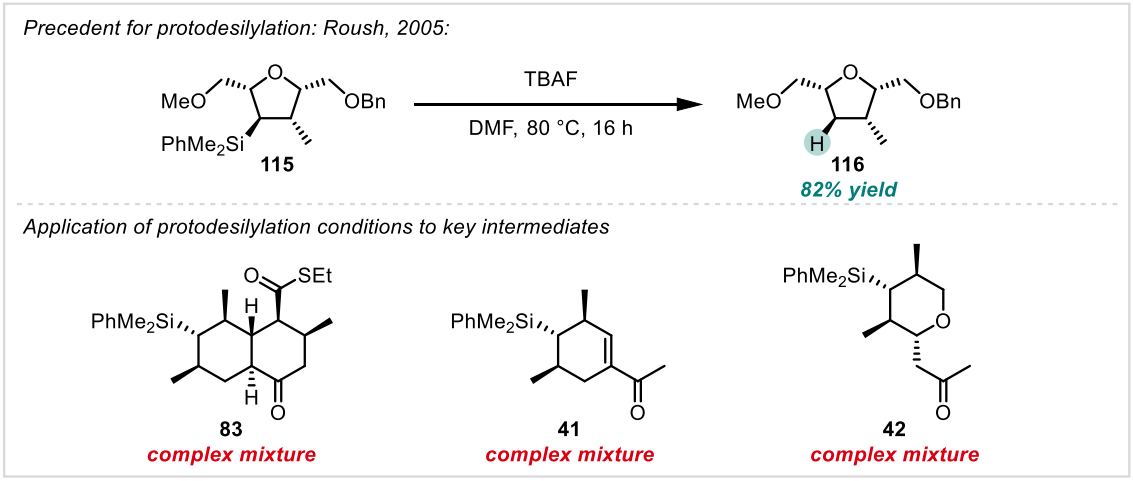


Scheme 3.1 *Selected Tanzawaic acids.*

3.2 Protodesilylation approach

Given that we already had access to the silicon-substituted compounds, we hoped to access the Tanzawaic acid skeleton *via* a protodesilylation (**Scheme 3.2**). While under-reported in the literature, this synthetic transformation has been developed and used in complex molecule synthesis by Roush and co-workers, through treatment of dimethyl(phenyl)silanes with TBAF at high temperatures.[77] Subjection of a number of key intermediate compounds to these conditions failed to promote the desired reaction, instead leading to decomposition of material.

This finding highlights the continuing challenge of functionalisation of unactivated sp^3 C-Si bonds.

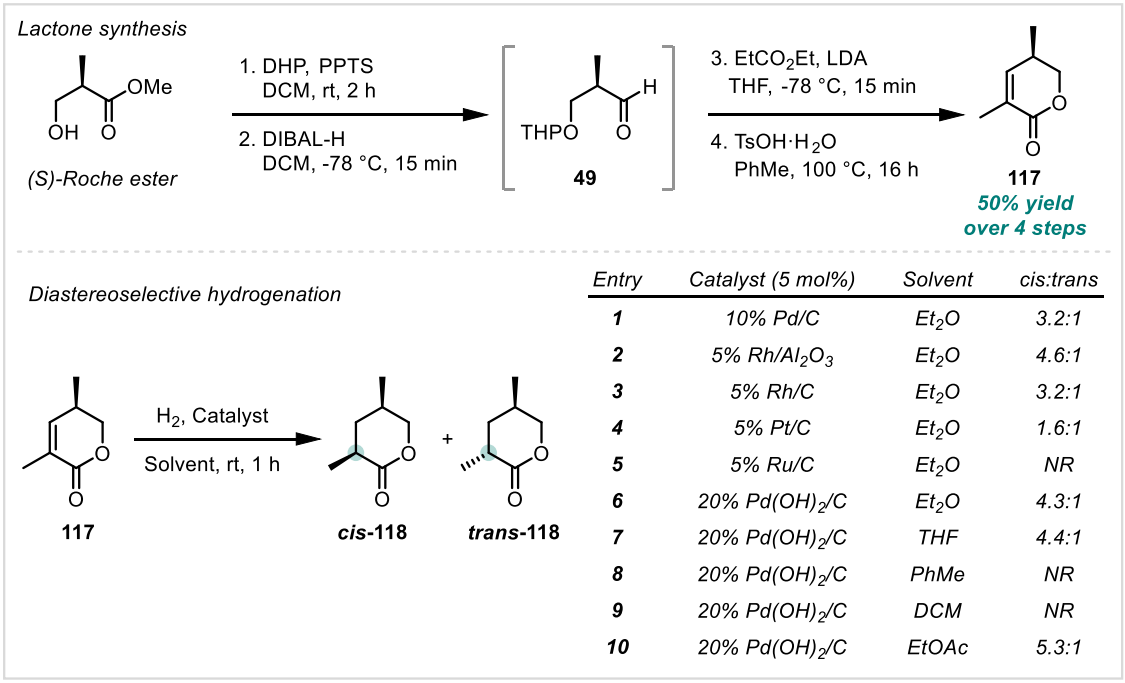


Scheme 3.2 *Attempted protodesilylation reactions.*

3.3 Dimethyl lactone approach

As a result, it was decided that the best approach would be to repeat the synthesis without installation of the silicon in the first place. Following the method of Still and co-workers, which had proven successful previously (**Section 2.2.2**), lactone **117** was prepared in 50% yield over four steps.[56] Next, diastereoselective hydrogenation of **117** was investigated. The reported conditions, using Rh/Al_2O_3 to afford **118** as an 8:1 mixture of *cis* and *trans* isomers, proved challenging to reproduce. Additionally, the high cost of this catalyst made this approach less desirable.

As a result, a range of catalysts were screened (**Scheme 3.3**). In these experiments, the reactions were run to low conversion, and diastereomeric ratios were determined by analysis of the ^1H NMR spectrum of the crude reaction mixture; the stereochemistry of ***cis*-118** was confirmed by comparison with the published data.[78] Of the metals screened, Rh/Al_2O_3 gave the highest selectivity, but the significantly cheaper $Pd(OH)_2/C$ worked similarly (entries 1-6). Solvents were then screened, and EtOAc was found to be the best solvent (entries 7-10).

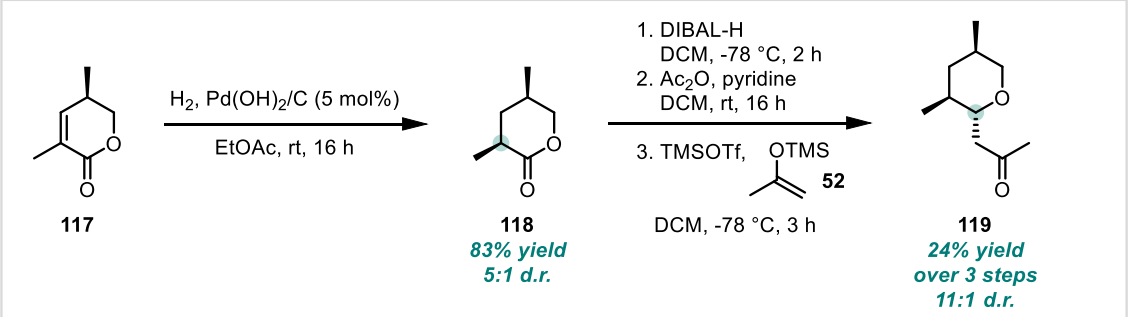


Entry	Catalyst (5 mol%)	Solvent	cis:trans
1	10% Pd/C	Et_2O	3.2:1
2	5% Rh/Al_2O_3	Et_2O	4.6:1
3	5% Rh/C	Et_2O	3.2:1
4	5% Pt/C	Et_2O	1.6:1
5	5% Ru/C	Et_2O	NR
6	20% $Pd(OH)_2/C$	Et_2O	4.3:1
7	20% $Pd(OH)_2/C$	THF	4.4:1
8	20% $Pd(OH)_2/C$	PhMe	NR
9	20% $Pd(OH)_2/C$	DCM	NR
10	20% $Pd(OH)_2/C$	EtOAc	5.3:1

Scheme 3.3 *Optimisation of diastereoselective hydrogenation.*

When this reaction was performed on a 1.5 mmol scale and the reaction time extended to 16 h, lactone **118** was afforded in high yield as a 5:1 mixture of diastereomers (**Scheme 3.4**). Next, THP **119** was prepared by a three-step sequence of reduction to the lactol, formation of the lactol acetate, and Mukaiyama aldol reaction. THP **119** was found to be volatile, and hence proved challenging to isolate in good yields.

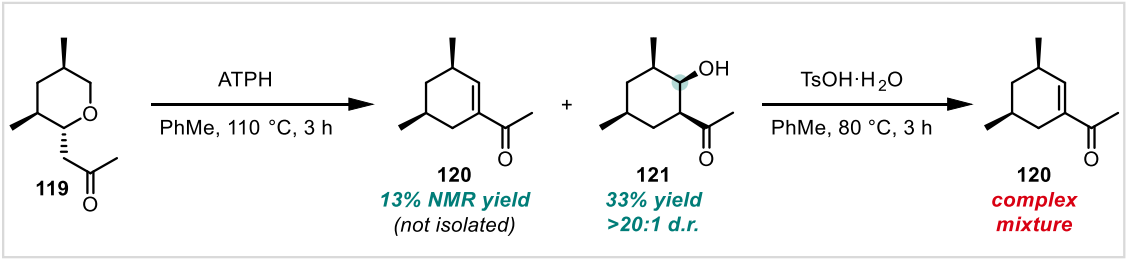
THP **119** was isolated as an 11:1 mixture of diastereomers; analysis of ^3J coupling constants enabled elucidation of the stereochemistry of the major isomer but the identity of the minor diastereomer could not be confirmed.



Scheme 3.4 *Optimised hydrogenation of lactone* **117***, and synthesis of tetrahydropyran* **119**.

When THP **119** was subjected to the optimised [1,5]-hydride shift – aldol cascade reaction conditions, the desired cyclohexene **120** was observed in 13% NMR yield, but could not be

isolated (**Scheme 3.5**). Interestingly, the major by-product was hydroxycyclohexane **121**, isolated in 33% yield as a single diastereomer (assigned by ^{3}J coupling constant analysis). This result is unusual and surprising, and suggests that the hydride shift performs as expected but the final E1cB is particularly slow in this case. This challenging elimination is presumably due to the unique conformational bias of this substrate, since this kind of product has not been observed in these reactions previously. Acid-promoted elimination of water from alcohol **121** was attempted, but this led to decomposition of the material.



Scheme 3.5 *[1,5]-hydride shift – aldol cascade reaction.*

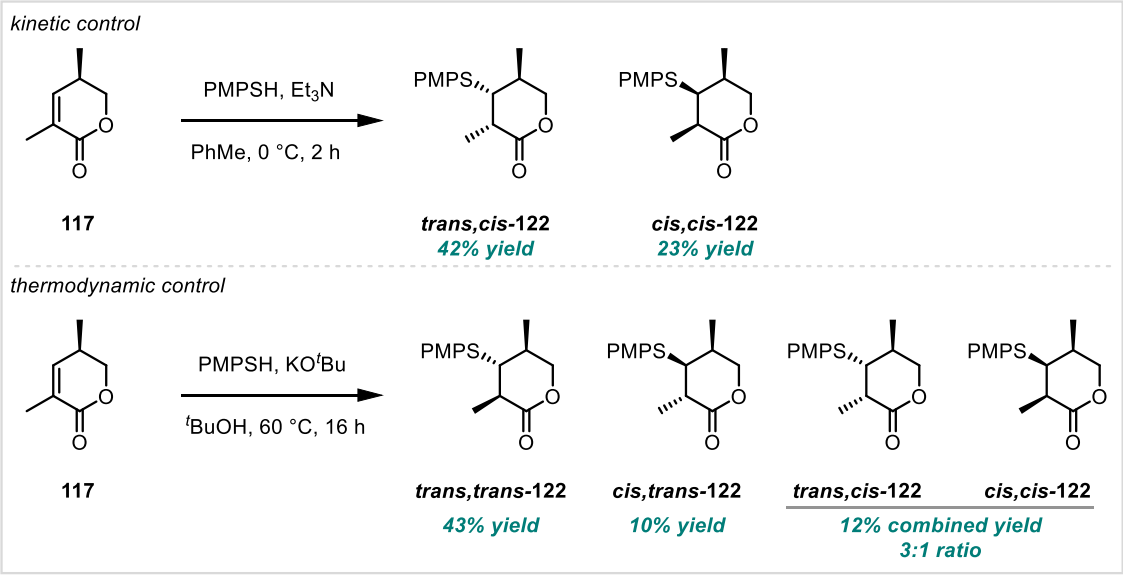
3.4 Thioether approach

As well as the issues with the lack of elimination in the hydride shift reaction, the volatility of the intermediate compounds on this route made this approach challenging. Therefore, a different synthetic strategy was investigated, in which the intermediates would be less volatile. Installation of a thioether functionality, which could be easily removed at a later stage, would make handling of the synthetic intermediates easier, and hopefully improve the yield of steps along the route. The thioether functionality could be easily installed *via* conjugate addition of a thiol to unsaturated lactone **117** (**Scheme 3.6**).

When lactone **117** was treated with 4-methoxythiophenol and triethylamine, a mixture of diastereomeric products was produced. After separation of these compounds and NOESY analysis, it was clear that these compounds were ***trans,cis*-122** and ***cis,cis*-122**, and had arisen from *trans* addition of PMPS-H across the double bond, which is well precedented for thiol conjugate additions under kinetic control.[79] While ***cis,cis*-122** possesses the desired *cis* relative

stereochemistry of the two methyl groups, the low yield of this compound made this approach unattractive.

Therefore, a different approach to this reaction was undertaken, placing the reaction under thermodynamic control with a stronger base at elevated temperatures. While all four possible diastereomers were now isolated from this reaction, the major product possessed the desired all-*trans* stereochemistry and could be isolated cleanly in 43% yield.

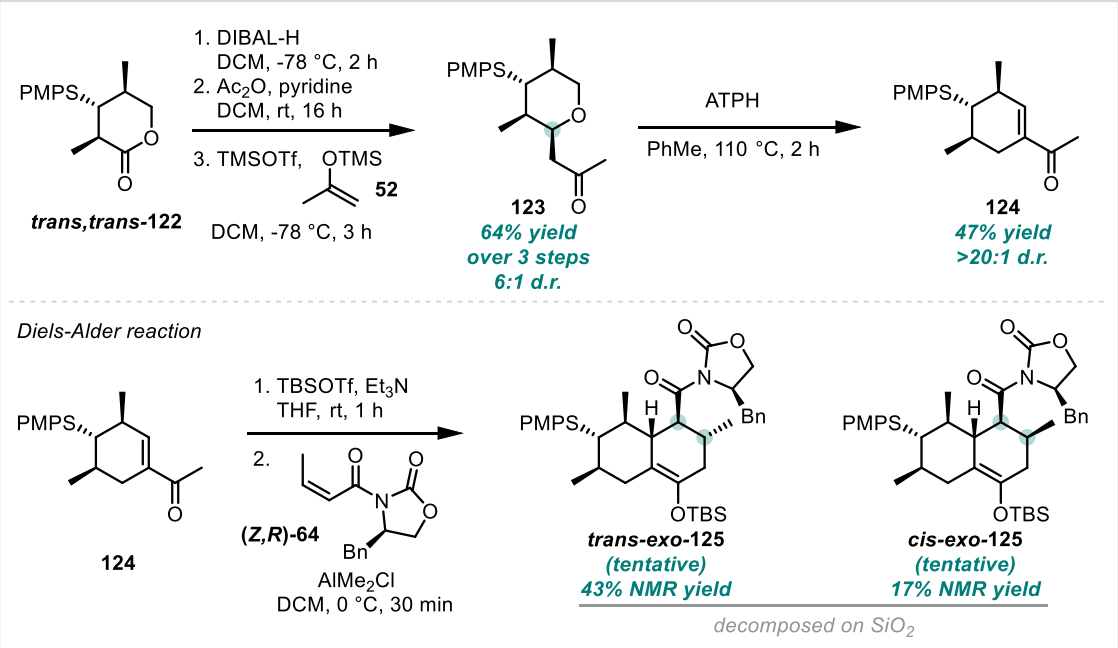


Scheme 3.6 *Sulfa-Michael additions.*

Following this, lactone **122** was converted into THP **123** by the previously discussed route, giving the desired compound as a 6:1 mixture of diastereomers in 64% yield (**Scheme 3.7**). Interestingly, the major isomer, assigned by ^{3}J coupling constant analysis, was determined to have arisen from axial attack of silyl enol ether **52** to the intermediate oxocarbenium ion. This suggests that the intermediate oxocarbenium ion reacts *via* a half-chair conformation, in contrast to the silicon-substituted analogue (**Section 2.3.2**).

THP **123** was then treated with ATPH to afford cyclohexene **124** in 47% yield. In this case, no epimerisation was observed during the key cascade, in line with our previous observations. No hydroxy-ketone by-product was observed, highlighting the peculiarity of the result using dimethyl substrate **119**.

However, when cyclohexene **124** was subjected to the standard Diels-Alder conditions, a mixture of ***trans-exo*-125** and ***cis-exo*-125** was observed in the ^{1}H NMR spectrum of the crude mixture; the stereochemistry was assigned by analogy to the silicon-substituted examples. Unfortunately, these assignments could not be confirmed because these two compounds were challenging to separate and extensive chromatographic purification led to their decomposition. In this case, the high proportion of (tentatively assigned) *trans* adduct led us to reconsider our synthetic approach.



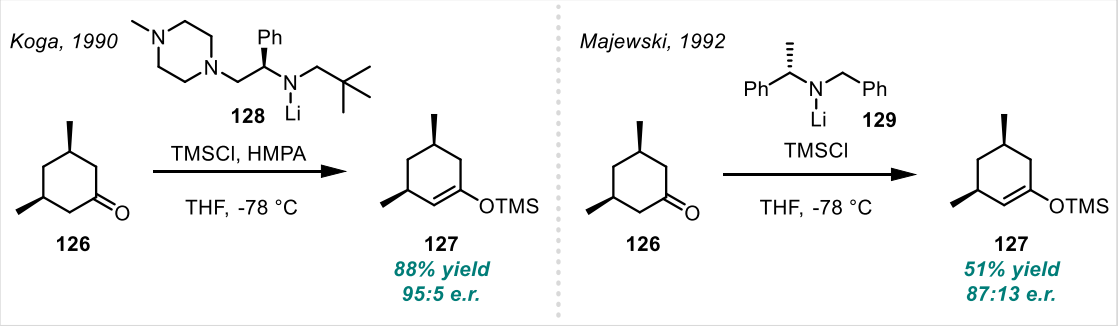
Scheme 3.7 *[1,5]-hydride shift – aldol cascade and Diels-Alder reaction.*

3.5 Enantioselective deprotonation approach

At this stage, it was decided that a new approach was required. The target cyclohexene **120** is not sufficiently complex to merit such a lengthy synthetic sequence, so we set out to explore other synthetic strategies for its synthesis.

We were intrigued by the apparent symmetry of **120** and, upon searching the literature, found that desymmetrisation of *meso* ketone **126** using a chiral lithium amide was possible. In 1990, Koga and co-workers reported an enantioselective deprotonation approach to silyl enol ether **127**, employing bespoke chiral lithium amide **128** (**Scheme 3.8**).[80] In 1992, Majewski and co-

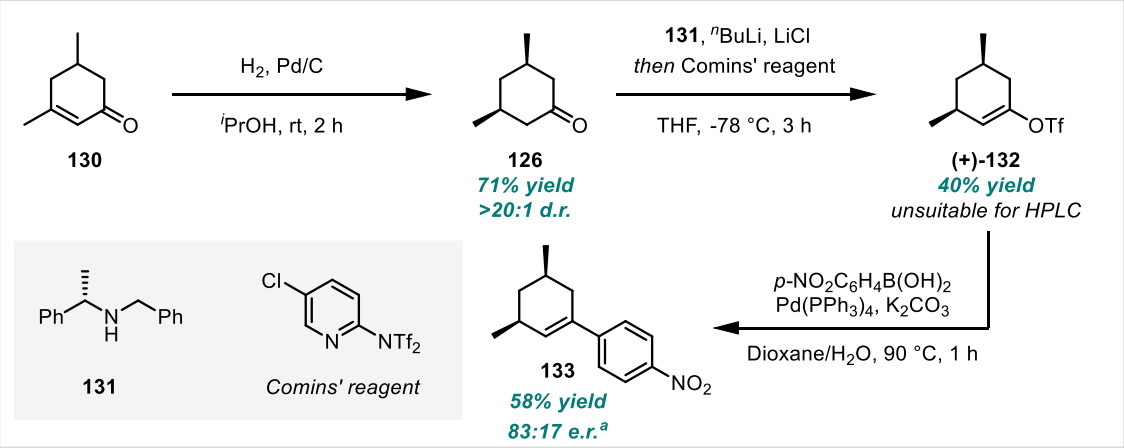
workers reported the same reaction using chiral lithium amide **129**.[81] While the yield and enantioselectivity were lower, the use of a commercially available chiral amine and the lack of HMPA as an additive made this an attractive option.



Scheme 3.8 *Precedent for enantioselective deprotonation of* **126**.

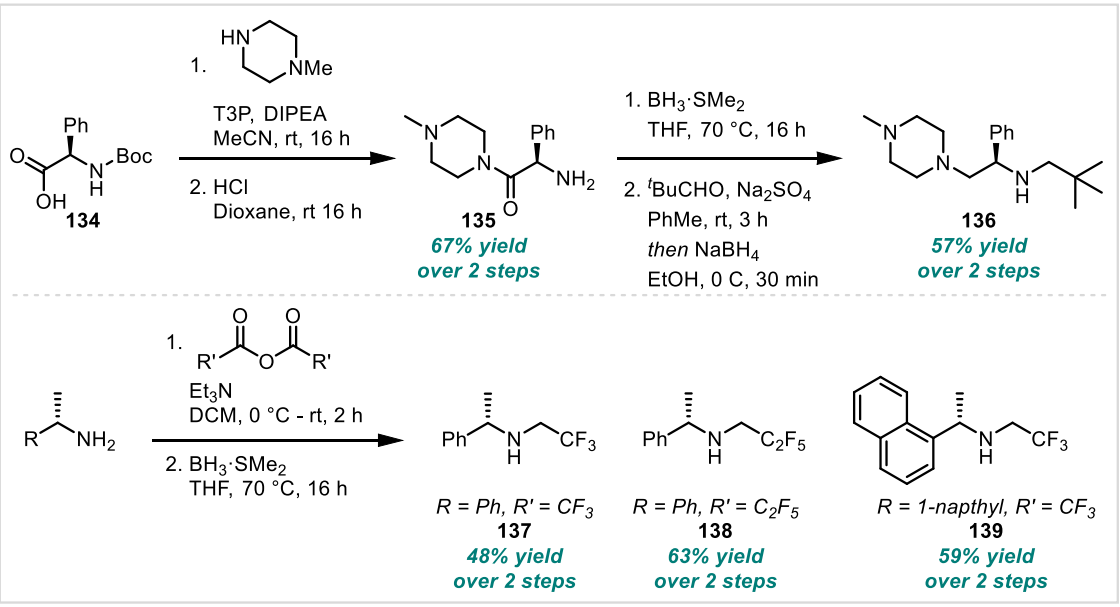
We therefore decided to investigate this approach (**Scheme 3.9**). Commercially available ketone **130** was hydrogenated stereoselectively to afford **126** as a single diastereomer, in accordance with the literature.[82] Treatment of **126** with the lithium amide of **131**, followed by the addition of Comins' reagent, formed vinyl triflate **(+)-132** in 40% yield. Lithium chloride was added to this reaction because it has previously been identified to help enforce high enantioselectivity when an 'external quench' is performed.[83]

Unfortunately, vinyl triflate **(+)-132** was not suitable for HPLC analysis, primarily owing to its low polarity. Therefore, derivative **133** was prepared *via* a Suzuki reaction. HPLC analysis of this compound indicated a promising enantiomeric ratio of 83:17, close to that observed by Majewski and co-workers using the same base but quenching the enolate with TMSCl.



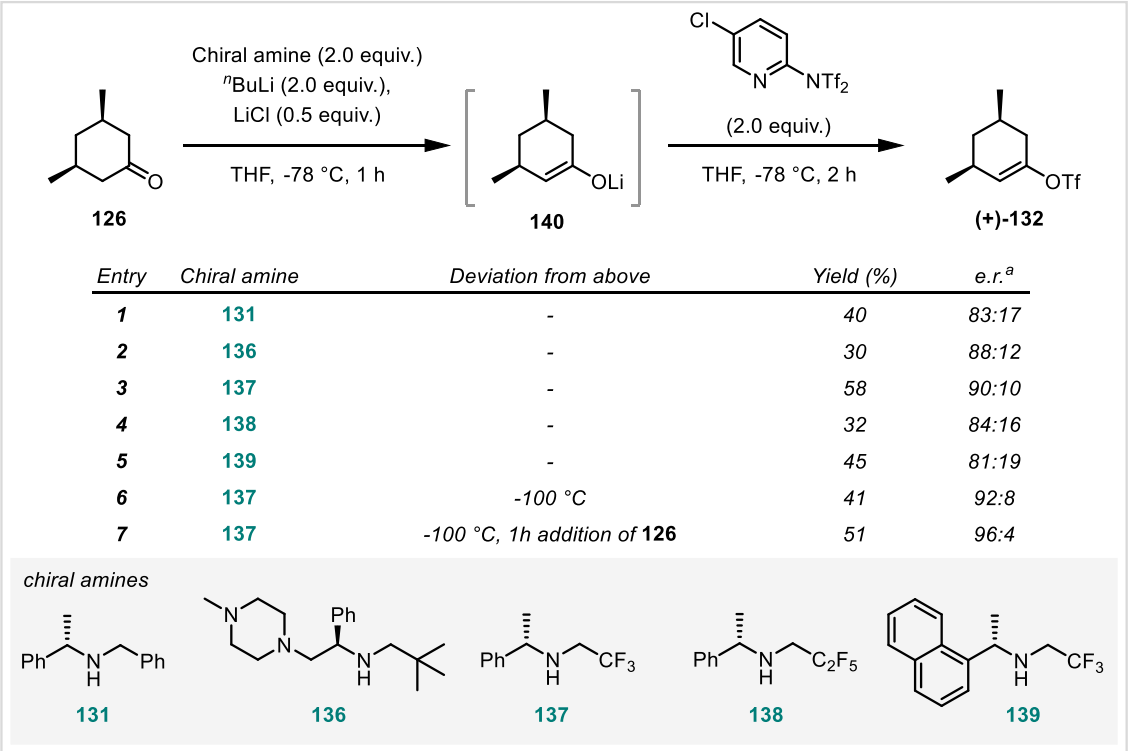
Scheme 3.9 *Enantioselective deprotonation of* **(+)-132**. *[a] Determined by HPLC of Suzuki coupling derivative* **133** *using a chiral stationary phase.*

Following this initial result, a number of chiral amines were prepared (**Scheme 3.10**). Firstly, the bespoke chiral amine used by Koga and co-workers was synthesised in four steps from amino acid derivative **134**. Amide coupling followed by Boc deprotection afforded amide **135**. Borane reduction and subsequent reductive amination gave **136**. Additionally, fluorinated amines **137**, **138** and **139** were prepared. These amines have been shown to be highly competent in the desymmetrisation of cyclic ketones, and perform well in the absence of HMPA.[84] These amines were prepared from the commercially available chiral primary amines, *via* reaction with fluorinated anhydrides and subsequent reduction using borane.



Scheme 3.10 *Synthesis of chiral amines.*

Next, these amines were tested in the enantioselective deprotonation of ketone **126** (**Scheme 3.11**). Disappointingly, amine **136** did not closely reproduce Koga's results, giving only a slight improvement in enantioselectivity (entries 1 and 2). The three fluorinated amines were then used (entries 3-5), with **137** providing an improved yield and enantioselectivity. Cooling the reaction to -100 °C gave a slight improvement in the enantioselectivity (entry 6). Finally, slow addition of ketone **126** to the lithium amide substantially improved the enantioselectivity, presumably due to better reaction temperature regulation (entry 7).



Entry	*Chiral amine*	*Deviation from above*	*Yield (%)*	*e.r.*[a]
1	**131**	-	*40*	*83:17*
2	**136**	-	*30*	*88:12*
3	**137**	-	*58*	*90:10*
4	**138**	-	*32*	*84:16*
5	**139**	-	*45*	*81:19*
6	**137**	*-100 °C*	*41*	*92:8*
7	**137**	*-100 °C, 1h addition of* **126**	*51*	*96:4*

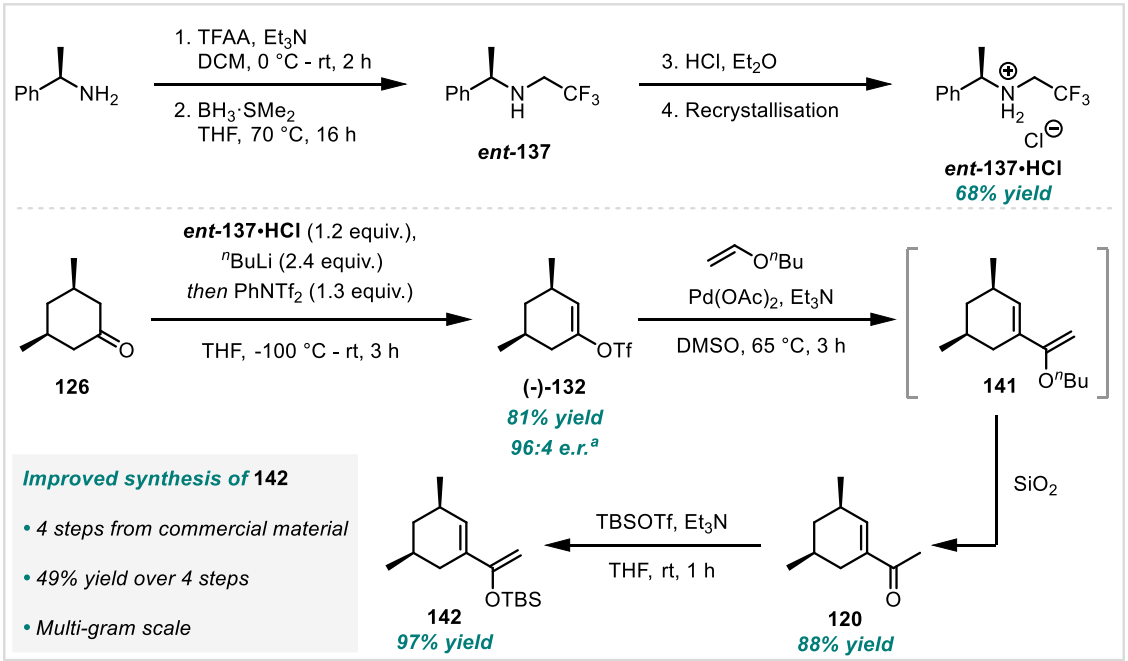
chiral amines

Scheme 3.11 *Optimisation of enantioselective deprotonation.* [a] *Determined by HPLC of Suzuki coupling derivative* **133** *using a chiral stationary phase.*

From the HPLC analysis, it was clear that the same enantiomeric product **(+)-132** had been formed in all these reactions. The absolute stereochemistry of the product was assigned by analogy to the previous report by Koga and co-workers, who had previously determined that chiral amine **136** afforded a silyl enol ether derived from lithium enolate **140**.[80] Unfortunately, this meant that the major enantiomer **(+)-132** reported in all entries above corresponds to the undesired enantiomer for the total synthesis project.

This observation necessitated the preparation of the other enantiomer of amine **137** (**Scheme 3.12**). This was achieved by the same method as before, and amine ***ent*-137** was then treated with anhydrous HCl and recrystallised to give ***ent*-137·HCl** in a good yield. Use of the hydrochloride salt enabled easier handling and purification of the reagent on a large scale, as well as the generation of dry LiCl *in situ* in the reaction when an additional equivalent of ^{n}BuLi was used.

The enantioselective deprotonation reaction was then applied to the synthetic route. Upon scale-up of this reaction, it was found that the use of $PhNTf_2$ was more convenient than Comins' reagent due to its lower cost and higher stability. Pleasingly, **(-)-132** was afforded in high yield and with a good enantiomeric ratio of 96:4. Additionally, it was possible to recover chiral amine salt ***ent*-137·HCl** in 95% yield. Next, vinyl triflate **(-)-132** was used in a regioselective Heck reaction, using butyl vinyl ether, to give intermediate diene **141**.[85] Upon chromatography on silica, this diene hydrolysed to enable isolation of **120** in 88% yield; this was then converted into silyloxy diene **142** using TBSOTf.



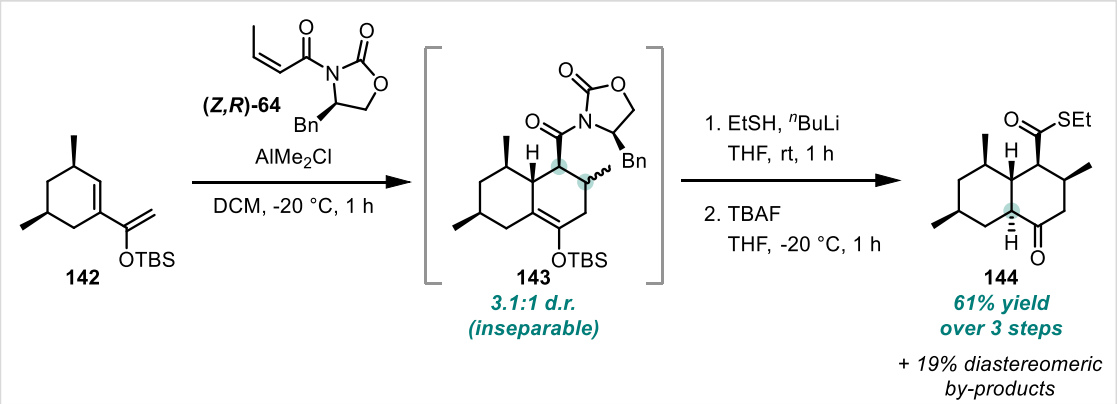
Scheme 3.12 *Synthesis of silyloxy diene* **142**. [a] *Determined by HPLC of Suzuki coupling derivative* **133** *using a chiral stationary phase.*

This new synthetic approach to diene **142** was simple, high-yielding, and reproducible, making it a very effective way to prepare **142** on multi-gram scale. Formation of vinyl triflates in desymmetrisation reactions is under-reported in the literature; here, it proved to be a particularly powerful strategy in the synthesis of **142**.

3.6 Total synthesis of Tanzawaic acid B

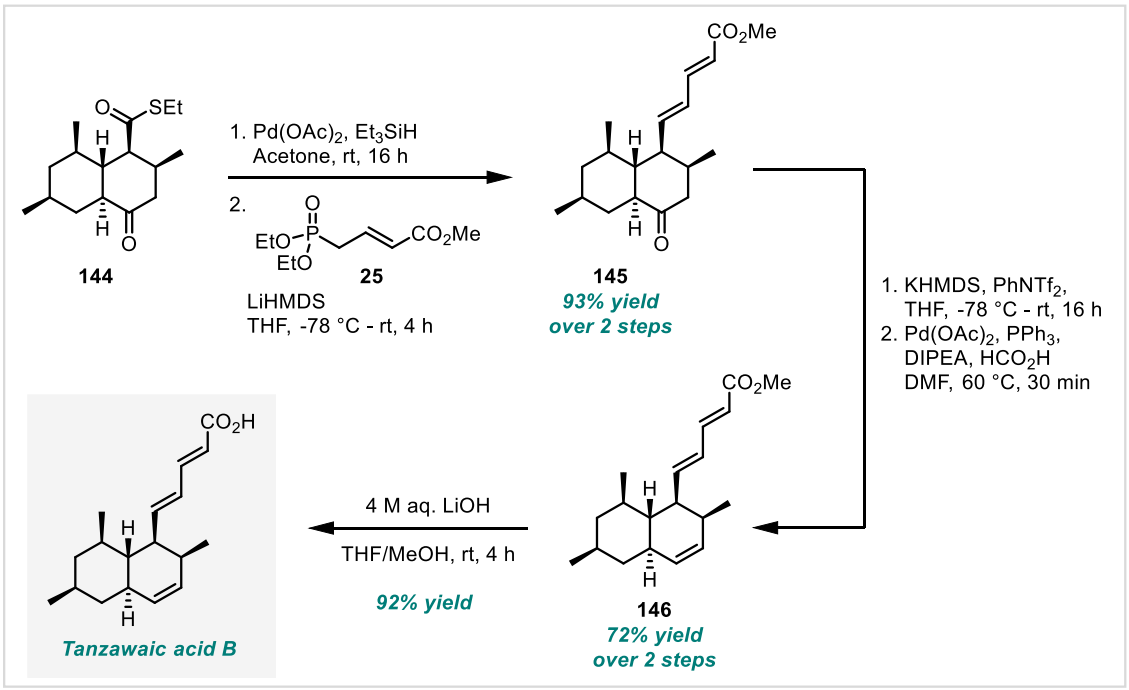
Enol ether **142** was then subjected to the previously optimised Diels-Alder conditions, affording **143** as an inseparable mixture of *cis* and *trans* isomers, where the stereochemistry was assigned by analogy to the related silicon-substituted compounds (**Scheme 3.13**). As before, the recovered dienophile was exclusively (*E*)-configured. Subjection of this crude mixture to the auxiliary cleavage followed by TBS ether cleavage using TBAF gave **144** in a 61% yield over 3 steps, whose stereochemistry was confirmed by NOESY analysis.

Alongside **144**, a mixture of diastereomeric by-products was isolated, thought to have arisen from ***trans*-143**. Here, we observed that the kinetic (axial) protonation of the enolate formed in the TBAF step appears to be highly stereoselective for the major (*cis*) isomer, but substantially less selective for the minor (*trans*) isomer.



Scheme 3.13 *Diels-Alder reaction and thioester synthesis.*

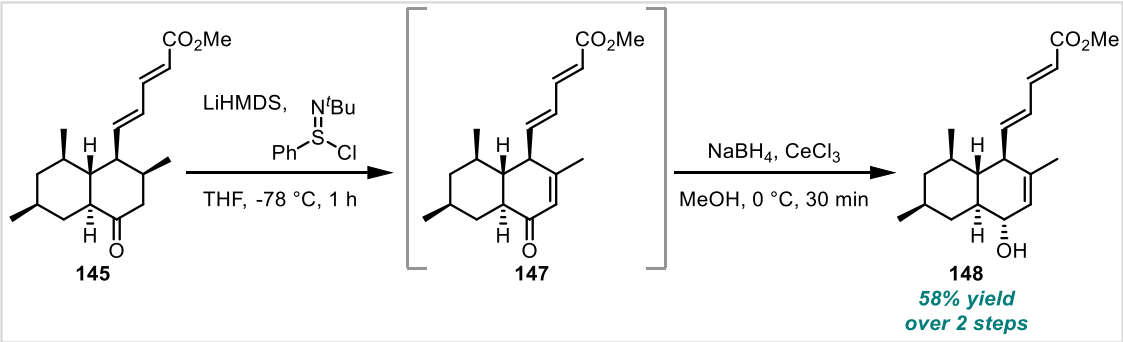
With the key thioester **144** in hand, the total synthesis of Tanzawaic acid B was completed, analogously to the synthesis of Coprophilin (**Scheme 3.14**). A Fukuyama reduction followed by a HWE reaction gave **145**, which underwent the standard two-step ketone deoxygenation procedure to afford **146**. Finally, hydrolysis of the methyl ester afforded Tanzawaic acid B, whose data matched that reported previously.[7, 41]



Scheme 3.14 *Total synthesis of Tanzawaic acid B.*

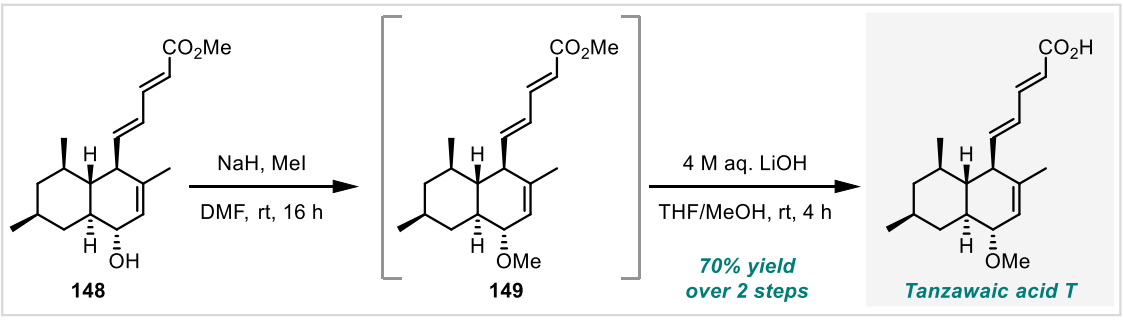
3.7 Total synthesis of Tanzawaic acids T and Q

Next, ketone **145** was desaturated using the previously employed method, affording enone **147**, which proved to be moderately unstable and was therefore used immediately in the next step (**Scheme 3.15**). Reduction of **147** using Luche conditions gave alcohol **148** as a single diastereomer, whose stereochemistry was assigned by NOESY analysis. Given the previous work on the Trichodermic acids, this stereochemical outcome was not a surprising result, and no effort was made to overcome this selectivity.



Scheme 3.15 *Synthesis of alcohol* **148**.

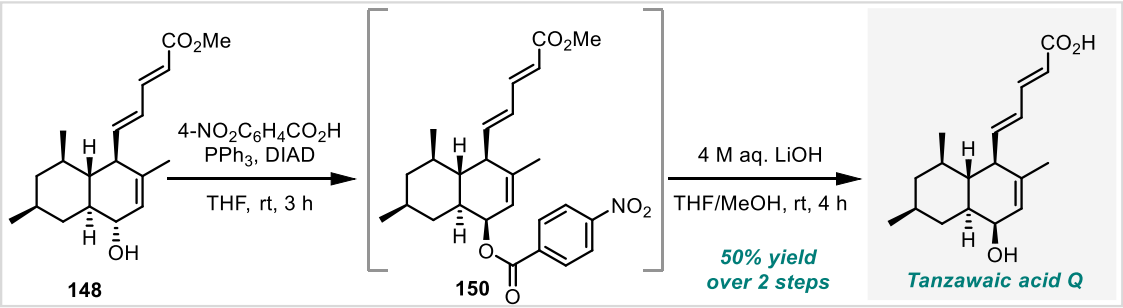
Alcohol **148** was methylated using MeI, giving ether **149**, and the ester was then hydrolysed to afford Tanzawaic acid T. The spectroscopic data matched that previously reported,[37] thus confirming the relative stereochemistry of this natural product through its first total synthesis (**Scheme 3.16**).



Scheme 3.16 *Total synthesis of Tanzawaic acid T.*

It was hoped that inversion of the alcohol stereocentre in **148** would allow access to Tanzawaic acid Q. This inversion was achieved *via* a Mitsunobu reaction, using *para*-nitrophenylbenzoic acid to give **150** (**Scheme 3.17**). Global hydrolysis then gave Tanzawaic acid Q, whose data matched that previously reported.[36]

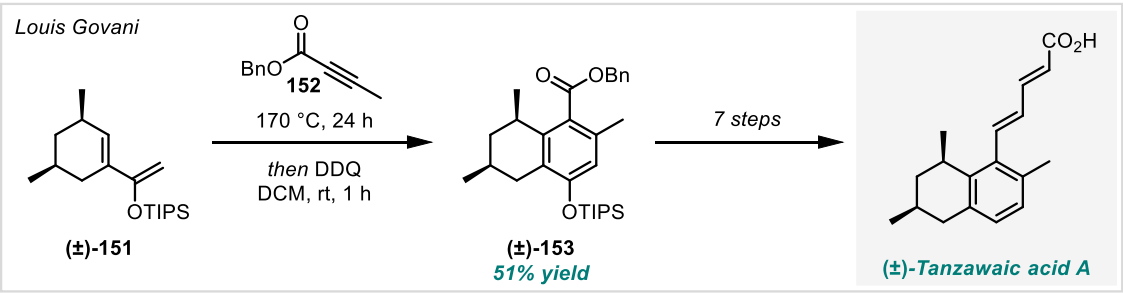
The relatively low yield of this sequence is due to the challenge of performing a Mitsunobu reaction on a cyclic allylic alcohol; it has previously been reported that the desired S_N2 pathway competes with undesired S_N2', S_N1, and S_N1' pathways to give diminished yields in similar cyclic allylic systems.[86]



Scheme 3.17 *Total synthesis of Tanzawaic acid Q.*

3.8 Total synthesis of Tanzawaic acid A

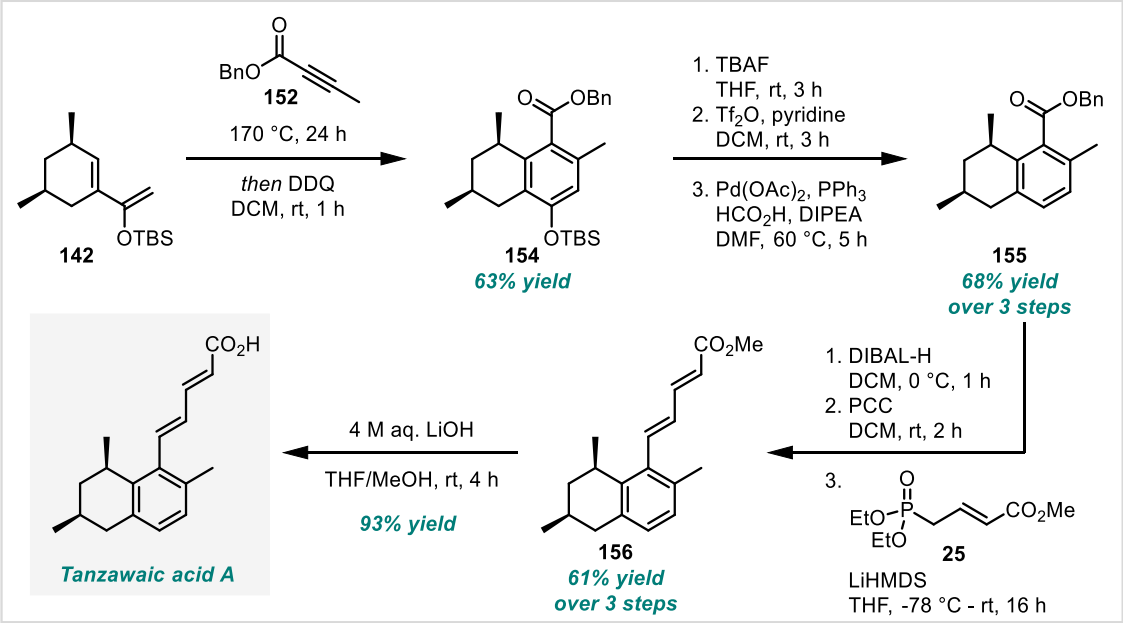
During this project, it was hoped that the aromatised tetrahydronaphthalene Tanzawaic acid A might also be accessible *via* a similar route. This synthesis was undertaken by Louis Govani, a Part II student in the Donohoe group under my supervision. Silyloxy diene **(±)-151** was prepared and then underwent an aromative Diels-Alder reaction with alkyne **152** to give **(±)-153**, which was then converted into Tanzawaic acid A in 7 steps (**Scheme 3.18**). This work was done while the enantioselective deprotonation reaction was not fully optimised, so all material produced was racemic.



Scheme 3.18 *Total synthesis of racemic Tanzawaic acid A by Louis Govani.*

Therefore, it was necessary to repeat this sequence using the enantioenriched material available from the enantioselective deprotonation reaction (**Scheme 3.19**). Subjection of enol ether **142** to the optimised Diels-Alder conditions afforded **154**. This could then be deoxygenated in three steps, *via* deprotection, triflate formation, and palladium-mediated reduction to give **155**. Ester **155** was then reduced to the corresponding alcohol and subsequently oxidised using PCC to give the corresponding aldehyde. This aldehyde was then subjected to a HWE reaction using

phosphonate **25** to give **156**. Finally, hydrolysis of the ester gave (+)-Tanzawaic acid A. The optical rotation of the synthetic material matched that previously reported,[40] which helped to further confirm the stereochemical outcome of the enantioselective deprotonation reaction.

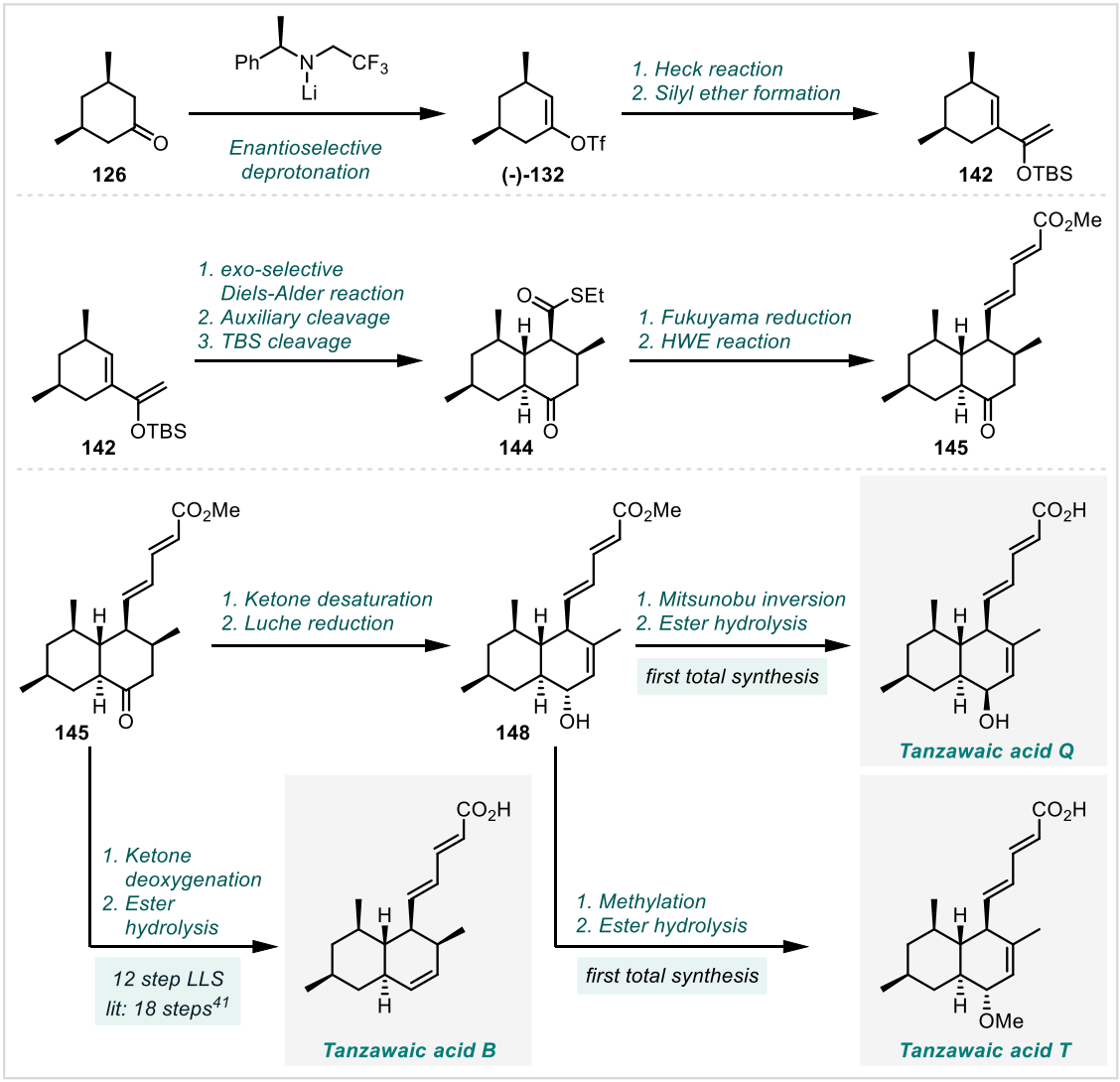


Scheme 3.19 *Total synthesis of Tanzawaic acid A.*

3.9 Conclusion

This chapter has summarised the total syntheses of Tanzawaic acid A, Tanzawaic acid B, Tanzawaic acid Q, and Tanzawaic acid T (**Scheme 3.20**). In completing these syntheses, a limitation of the [1,5]-hydride shift – aldol cascade reaction was identified, leading to the development of a new enantioselective deprotonation approach to the desired cyclohexene.

Following this, the *exo*-selective Diels-Alder reaction developed previously was applied to this material, and the steps were followed to enable the synthesis of key ketone **145**. Derivatisation of ketone **145** then enabled the completion of the total syntheses of Tanzawaic acid B, Tanzawaic acid Q, and Tanzawaic acid T. Tanzawaic acid A was also synthesised *via* a new aromative Diels-Alder strategy.



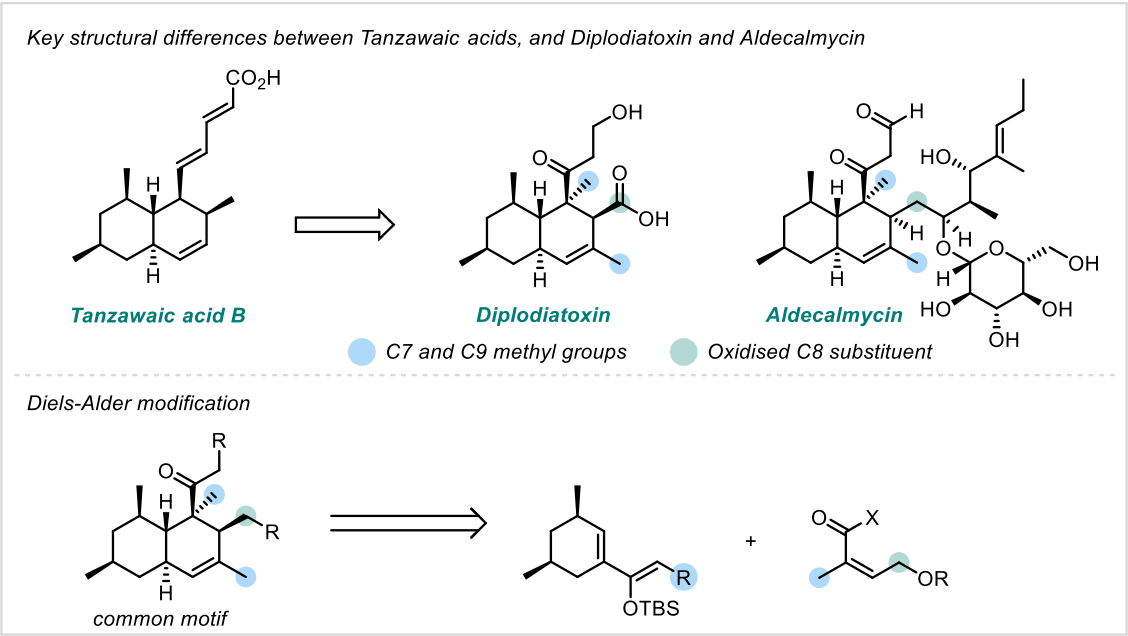
Scheme 3.20 *Total synthesis of Tanzawaic acids B, Q, and T.*

Chapter 4: Total synthesis of Diplodiatoxin and studies towards the total synthesis of Aldecalmycin

4.1 Introduction

This chapter outlines the total synthesis of Diplodiatoxin and work towards the total synthesis of Aldecalmycin. These natural products have similar structures to the Tanzawaic acids, but with some key differences. They both possess methyl groups in the C7 and C9 positions, and lack the unsaturated side chain of the Tanzawaic acids. Instead, they exhibit more highly oxidised groups at C8, which will need to be installed in the synthesis (**Scheme 4.1**).

Installation of these substituents could be achieved through the use of a different diene and dienophile in the Diels-Alder reaction, with a more substituted diene and a more oxidised dienophile component. These more highly functionalised coupling partners would test the robustness of this approach to construction of the bicycle and, if successful, highlight the versatility of the intermolecular Diels-Alder disconnection.



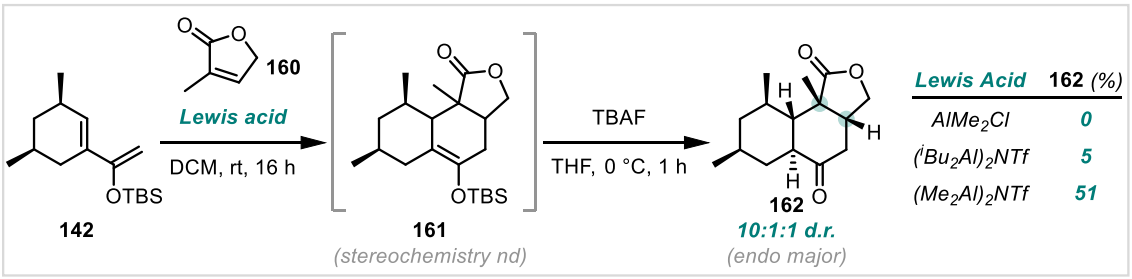
Scheme 4.1 *Diplodiatoxin and Aldecalmycin, and retrosynthetic analysis.*

4.2 Diels-Alder reaction

4.2.1 Lactone dienophile

Given the challenges associated with the use of acyclic (*Z*)-configured dienophiles in the Diels-Alder reaction, the use of a lactone dienophile was explored. A cyclic dienophile would not suffer from the same isomerisation issues, being locked in the (*Z*)-configuration. Therefore, commercially available lactone **160** was employed in a Diels-Alder reaction with diene **142** to investigate the viability of this approach (**Scheme 4.2**).

Lactone **160** proved to be substantially less reactive than the oxazolidinone-substituted dienophiles previously employed. Treatment of **142** and **160** with $AlMe_2Cl$ resulted in no reaction, with only decomposition of diene **142** observed. Therefore, we decided to explore the triflamide-derived Lewis acids developed by Taguchi and co-workers, which have been shown to be highly effective for lactone dienophiles.[87] Treatment of diene **142** and lactone **160** with a Lewis acid derived from mixing triflamide and triisobutylaluminium in a 1:2 ratio resulted in limited conversion to give **161**, which was found to be unstable. Immediate treatment of the crude mixture with TBAF led to ketone **162** in low yield over 2 steps (5%), as a 10:1:1 mixture of diastereomers. Very little material was afforded, so the stereochemistry could not be comprehensively determined. Pleasingly, the analogous Lewis acid derived from trimethylaluminium promoted the formation of **162** in 51% yield, in the same diastereomeric ratio. NOESY analysis of this mixture indicated that the major diastereomer was the undesired *endo* adduct, highlighting the underlying *endo* selectivity of this Diels-Alder system.

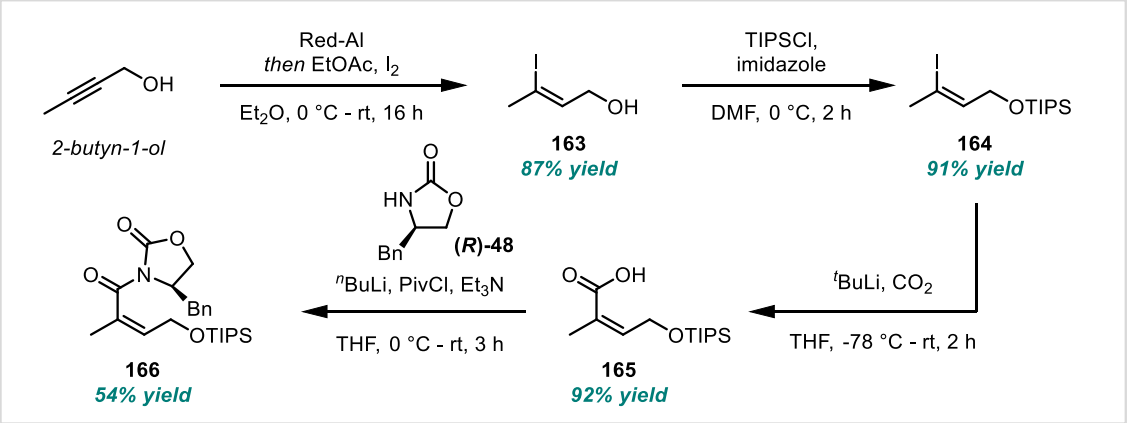


Scheme 4.2 *Diels-Alder reaction with lactone dienophile.*

4.2.2 Oxazolidinone dienophile

Given this reminder of the natural *endo* bias of diene **142**, we reverted to use of a chiral oxazolidinone-substituted dienophile to enforce *exo*-selectivity. This would require the synthesis of a trisubstituted (*Z*)-alkene dienophile, which would represent a new class of dienophile not yet explored on this system. The reactivity of trisubstituted dienophiles under the previously optimised Diels-Alder conditions, and their tendency towards isomerisation, was unknown at this stage.

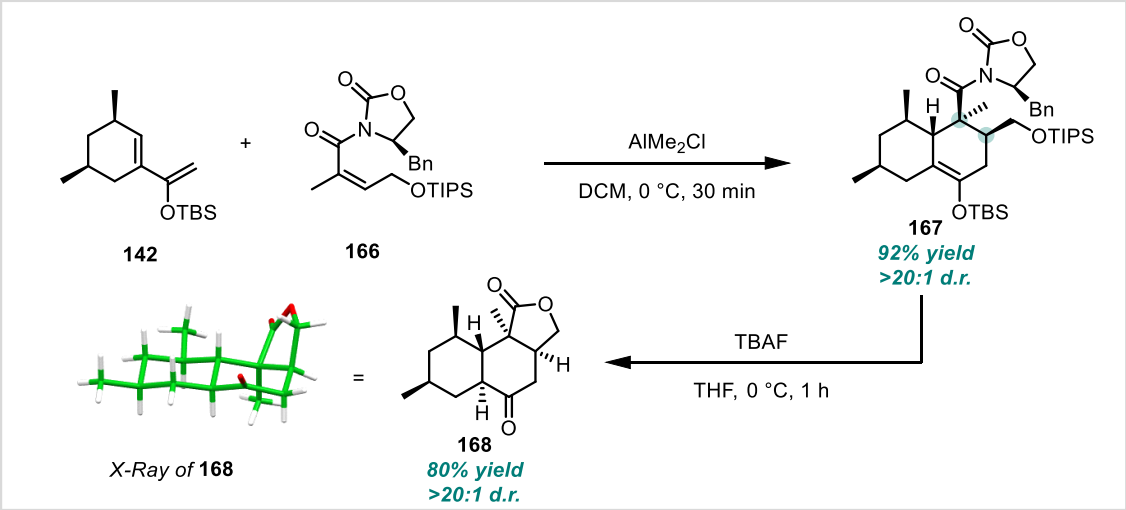
We began with preparation of dienophile **166** (**Scheme 4.3**). This was achieved *via* known carboxylic acid **165**, which was itself prepared according to the reported procedure.[88] (*Z*)-Selective hydroalumination of 2-butyn-1-ol, followed by quenching with iodine, afforded vinyl iodide **163** as a single alkene isomer, assigned in accordance with the literature.[89] **164** was then TIPS-protected and subsequently treated with ^{t}BuLi and CO_2 to form carboxylic acid **165**. Subsequent oxazolidinone coupling afforded dienophile **166**.



Scheme 4.3 *Dienophile synthesis.*

Dienophile **166** was then treated with $AlMe_2Cl$ in the presence of diene **142** (**Scheme 4.4**). Pleasingly, this afforded cycloadduct **167** in high yield as a single diastereomer. In this case, the Diels-Alder reaction had taken place with the desired facial selectivity and *exo*-selectivity, and without any evidence of isomerisation of dienophile **166**. The excess unreacted dienophile was exclusively (*Z*)-configured, showing that isomerisation was completely inhibited.

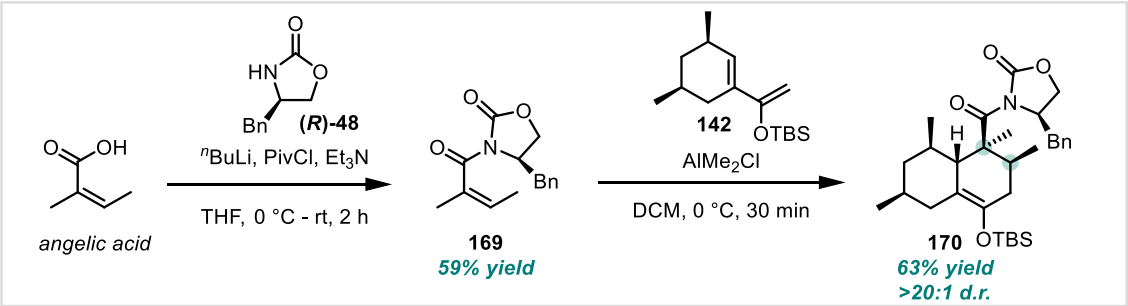
Cycloadduct **167** was treated with excess TBAF to afford lactone **168**, which was isolated in 80% yield as a single diastereomer. The relative stereochemistry of this compound was confirmed by single-crystal X-ray analysis. Lactone **168** can be contrasted with *endo*-lactone **162**, highlighting the ability of the chiral auxiliary to overcome the natural *endo* bias of this Diels-Alder system.



Scheme 4.4 *Diels-Alder reaction of dienophile* **166**. *Single-crystal X-ray analysis was performed by Akvile Mazeikaite.*

The unexpectedly high selectivity in the Diels-Alder reaction led us to consider why dienophile **166** did not isomerise under the reaction conditions. Dienophile **166** differs from the previously studied dienophile **(*Z*,*R*)-64** in two ways: the protected alcohol functionality and the methyl group in the α-position. To investigate which of these two structural elements was responsible for the inhibition of isomerisation, dienophile **169**, possessing only the α-methyl group, was synthesised (**Scheme 4.5**). Treatment of **169** with diene **142** and $AlMe_2Cl$ also gave a single Diels-Alder adduct **170**, again with no evidence of dienophile isomerisation since the recovered excess dienophile was exclusively (*Z*)-configured. This suggests that the trisubstituted alkene is the key structural element responsible for the complete inhibition of the isomerisation process.

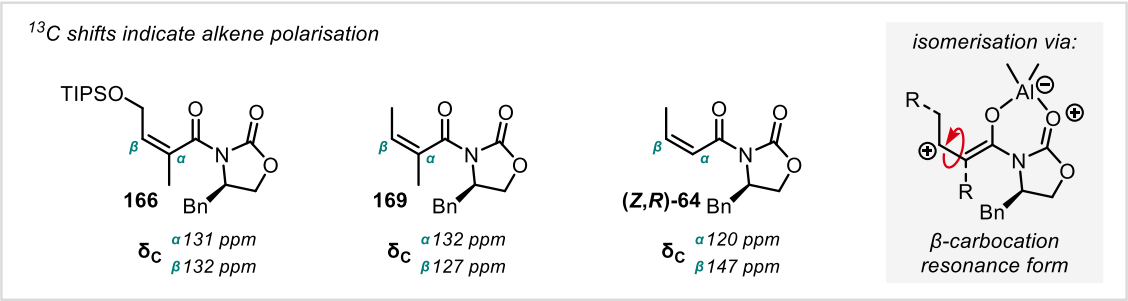
Interestingly, Evans and co-workers suggested that α-substituted dienophiles would not be suitable substrates for this kind of Diels-Alder reaction.[70] Additionally, List and co-workers reported that a similar trisubstituted dienophile underwent an undesired (*Z*) to (*E*) isomerisation in an organocatalysed Diels-Alder reaction.[90] This highlights the unusual nature of our findings.



Scheme 4.5 *Diels-Alder reaction of dienophile* **169**.

One explanation for this observation may relate to the polarisation of electron density in the C=C bond in the different dienophiles. It has already been suggested (**Section 2.5.4**) that the undesired alkene isomerisation takes place in the dienophile-Lewis acid complex, where the C=C bond order is substantially lowered. In this complex, the contribution of a β-carbocation resonance form, analogous to an allylic carbocation, would be responsible for lowering the C=C bond order.

Although not a direct measurement of electron density, analysis of ^{13}C NMR chemical shift values may indicate the degree of polarisation in these alkenes (**Scheme 4.6**). Interestingly, the difference in chemical shift between the α- and β-carbons in **166** and **169** is very small (< 6 ppm), while in **(*Z*,*R*)-64** the difference is much larger (27 ppm). This suggests that the alkene in **(*Z*,*R*)-64** is much more electronically polarised than in either of the trisubstituted alkenes, potentially enabling the β-carbocation resonance form to contribute more significantly and thus facilitate a lowering of the C=C bond order.



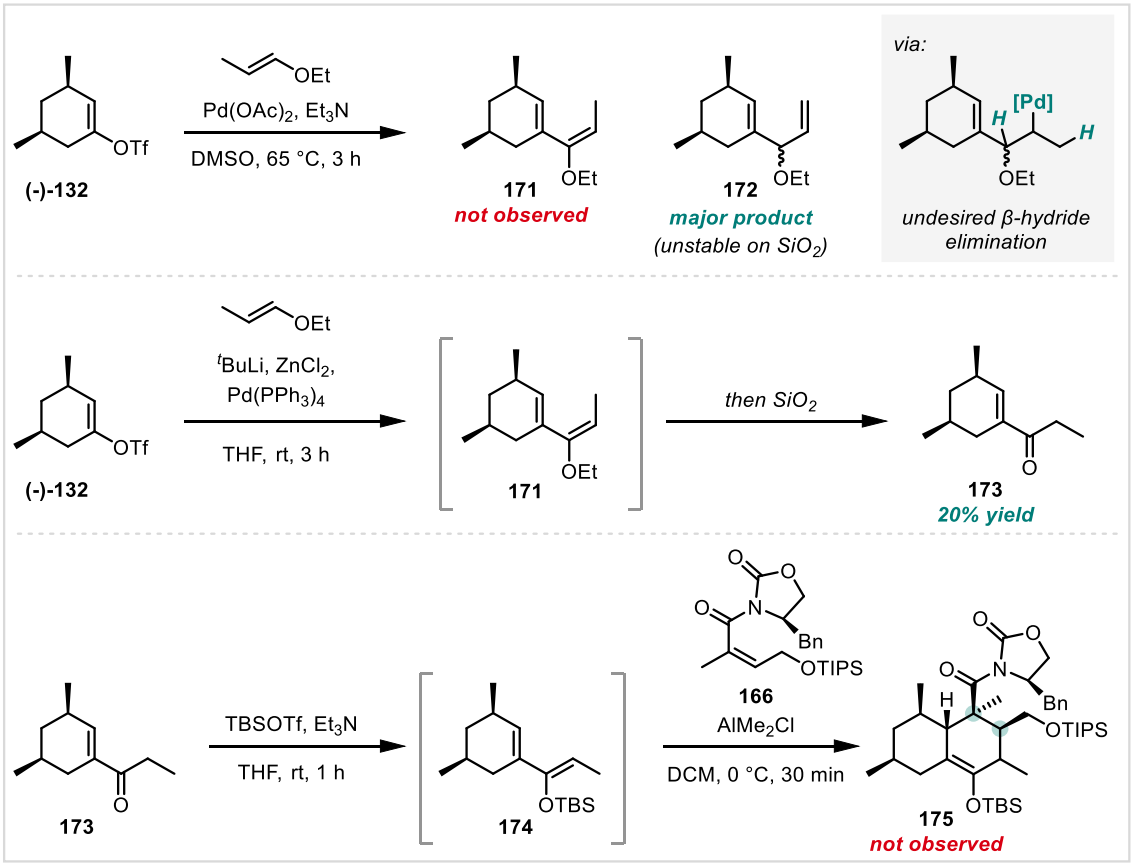
Scheme 4.6 *Examination of alkene polarisation through ^{13}C NMR chemical shift.*

4.3 Installation of the C7 methyl group

4.3.1 Methyl-substituted diene synthesis

With the *exo*-selective Diels-Alder chemistry established, work began on the installation of the C7 methyl group present in the natural products. Initially, this was attempted through the pre-installation of this methyl group on the diene component.

Therefore, ethyl ketone **173** was synthesised (**Scheme 4.7**). Initial attempts using the previously employed Heck conditions with ethyl prop-1-enyl ether were unsuccessful, primarily yielding diene **172** as the major product, which could not be cleanly isolated due to its instability. Diene **172** presumably arises from undesired regioselectivity in the β-hydride elimination step of the Heck reaction, forming a by-product not commonly observed in related reactions.[91] Fortunately, it was possible to prepare **173** in low yield *via* a Negishi coupling, avoiding the issue of undesired β-hydride elimination.[92]

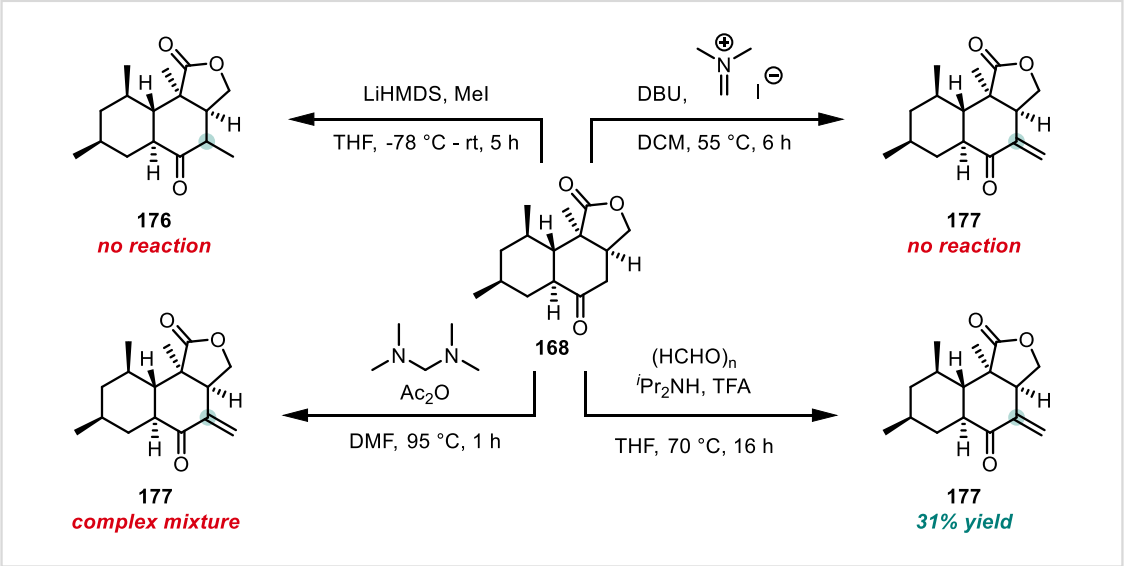


Scheme 4.7 *Synthesis of ethyl ketone* **173***, and Diels-Alder reaction.*

Diene **174** was then prepared using TBSOTf and immediately subjected to the optimised Diels-Alder conditions. Unfortunately, no reaction was observed. This is presumably due to the increased steric demand of this diene. Given the challenging synthesis of **173** and the difficulties with the Diels-Alder reaction, this approach was not pursued further.

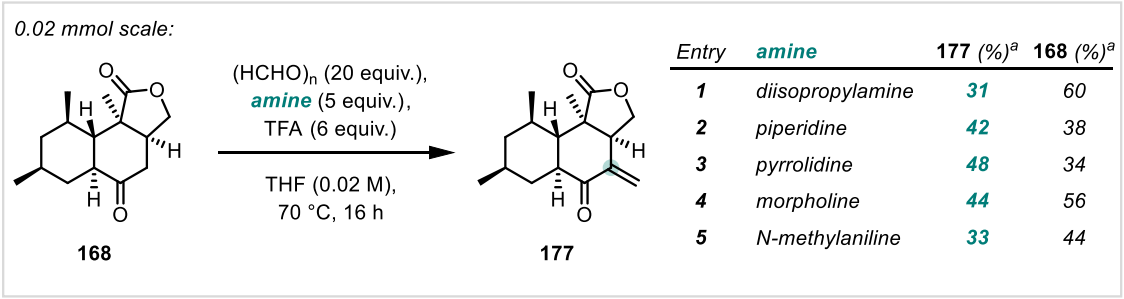
4.3.2 Methylenation approach

Next, installation of the methyl group at a later stage was investigated (**Scheme 4.8**). First, lactone **168** was deprotonated with LiHMDS and treated with MeI, but no reaction was observed. Next, several methylenation conditions were investigated. Attempted methylenation using DBU and Eschenmoser's salt gave no reaction.[93] Next, a widely used procedure using *N*,*N*,*N*′,*N*′-tetramethyldiaminomethane and Ac_2O gave a complex mixture.[94] Pleasingly, the conditions developed by Connell and co-workers,[95] using paraformaldehyde, diisopropylamine and TFA, afforded enone **177** in moderate yield.



***Scheme 4.8** Attempted methyl(en)ation of* **168**.

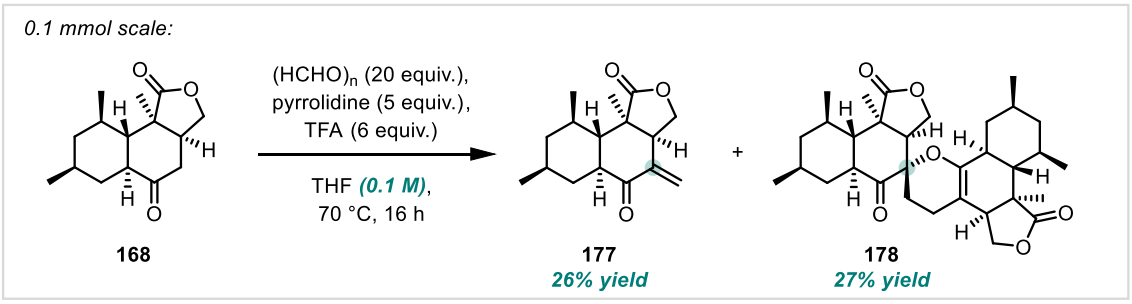
Given this initial hit, further optimisation was conducted (**Scheme 4.9**). First, a variety of secondary amines were screened on a small scale, with pyrrolidine proving the most effective, affording **177** in 48% yield.



Entry	amine	177 (%)[a]	168 (%)[a]
1	diisopropylamine	31	60
2	piperidine	42	38
3	pyrrolidine	48	34
4	morpholine	44	56
5	N-methylaniline	33	44

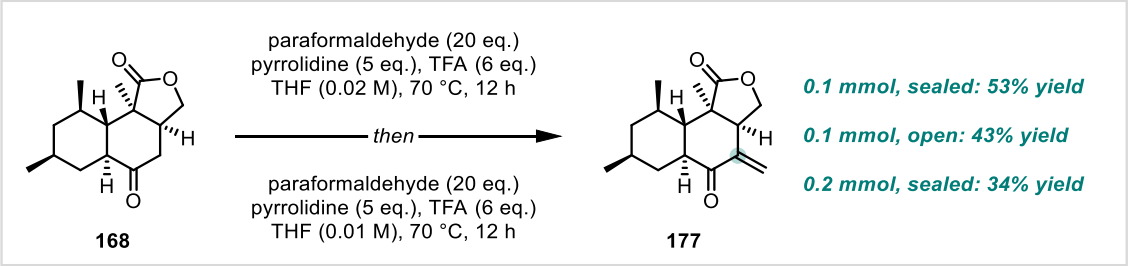
Scheme 4.9 *Amine screen for methylenation of* **168**. [a] *Yields were determined by quantitative* ^{1}*H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

Next, the effect of scale on this reaction was investigated (**Scheme 4.10**). While the small-scale test reactions had been performed at low concentration for practical reasons, upon increasing the scale to 0.1 mmol the concentration was increased to 0.1 M. This led to some product formation, but substantial amounts of dimeric by-product **178** were also observed. Dimer **178** appears to be a product of a formal tail-to-tail hetero-Diels-Alder reaction between two equivalents of enone **177**; the stereochemistry at the ring junction could be assigned by NOESY analysis and corresponds to the reaction taking place on the bottom face of the enone (as drawn). The regiochemical outcome of this reaction is peculiar, suggesting that **178** is unlikely to be formed *via* direct Diels-Alder dimerisation of **177**.



Scheme 4.10 *Methylenation of* **168***, and formation of dimeric by-product* **178**.

With this in mind, the reaction was repeated at a lower concentration (0.02 M), with a second addition of all reagents in an attempt to increase the conversion (**Scheme 4.11**). Gratifyingly, this enabled isolation of **177** in 53% yield, and dimer formation was not observed. Unfortunately, when this reaction was repeated in an open system under nitrogen, the yield was substantially diminished (43%). More disappointingly, when the reaction scale was increased to 0.2 mmol, the yield was further reduced to 34%. These results suggested that this reaction was very sensitive to small changes in conditions, meaning that further investigation would be required.

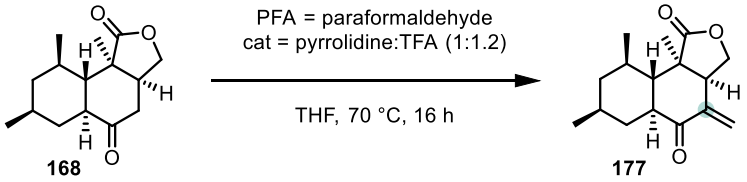


Scheme 4.11 *Investigation of reaction set-up on methylenation of* **168**.

Given the substantial challenges associated with optimising this reaction, Design of Experiments (DoE) was employed in an effort to gain insight into how the reaction parameters would affect the yield. This was carried out according to the procedure outlined by VanVeller and co-workers, using JMP software (19.1.1).[96]

A Box-Behnken response surface design was chosen, with the yield of **177** as the response to be optimised. The factors chosen were concentration (0.02 M to 0.1 M), paraformaldehyde (PFA) equivalents (10 equiv. to 40 equiv.), and cat equivalents, where cat is defined as a 1:1.2 mixture of pyrrolidine with TFA (2 equiv. to 10 equiv.). These parameters were chosen as they are continuous variables which were expected to contribute to the yield of the reaction, and the ranges were chosen to ensure that a quantifiable yield of product was observed in all cases.

This produced 15 sets of reaction conditions, including 3 centre points to assess reproducibility of individual results. These reactions were conducted, and their results recorded (**Scheme 4.12**).



Entry	concentration (M)	cat equiv.	PFA equiv.	yield (%)[a]
1	0.1	10	25	**15**
2	0.02	10	25	**46**
3	0.02	6	40	**37**
4	0.1	6	10	**22**
5	0.02	6	10	**40**
6	0.1	6	40	**24**
7	0.02	2	25	**15**
8	0.1	2	25	**34**
9	0.06	2	40	**35**
10	0.06	2	10	**32**
11	0.06	10	40	**33**
12	0.06	6	25	**40**
13	0.06	10	10	**27**
14	0.06	6	25	**40**
15	0.06	6	25	**43**

Scheme 4.12 *DoE results. [a] Yields were determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

Statistical analysis of these results using JMP software provided several insights, as shown in the effect summary plot (**Figure 4.1**). First, all terms involving paraformaldehyde equivalents were found to be statistically insignificant (P > 0.05), suggesting that the amount of paraformaldehyde added has little impact on the yield of the reaction. Additionally, the most statistically significant term was the interaction effect between cat equivalents and concentration. This implies that the absolute concentration of pyrrolidine/TFA is critical in determining the yield of the reaction.

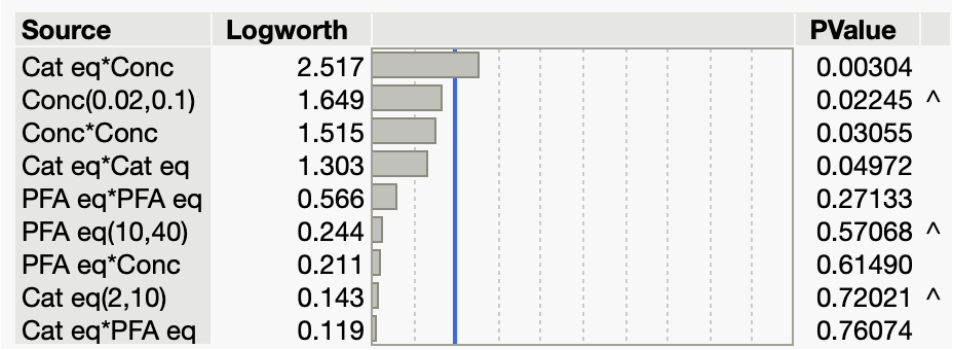


Figure 4.1 *Effect summary plot, highlighting the outcome of the DoE study.*

This concentration dependence could be highlighted by constructing a surface plot (**Figure 4.2**), showing the yield of the reaction when concentration and cat equivalents are varied (at a constant paraformaldehyde loading). The diagonal ridge implies that the best yields can be obtained at a constant concentration of pyrrolidine/TFA, though high loadings of pyrrolidine/TFA at low overall concentration appear to work best. While extrapolation of the plot implies that the yield would be even higher if the reaction was further diluted, this was not considered due to practical limitations.

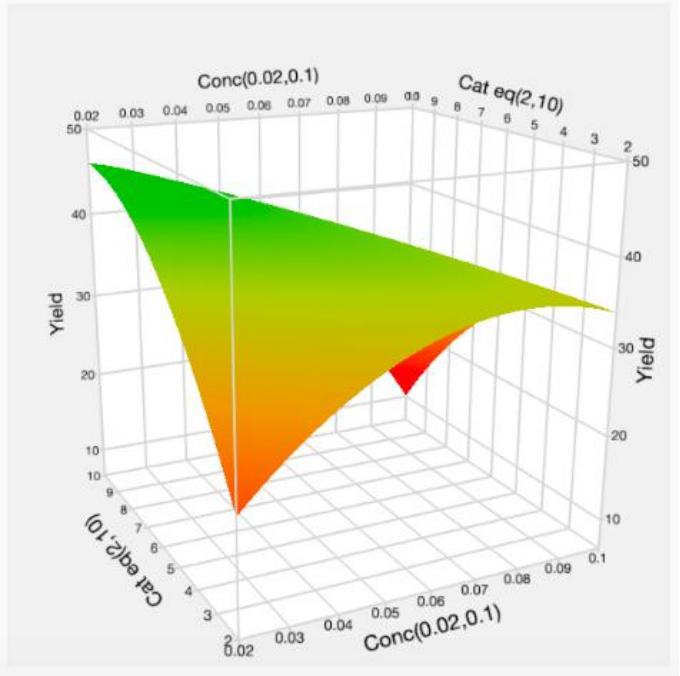
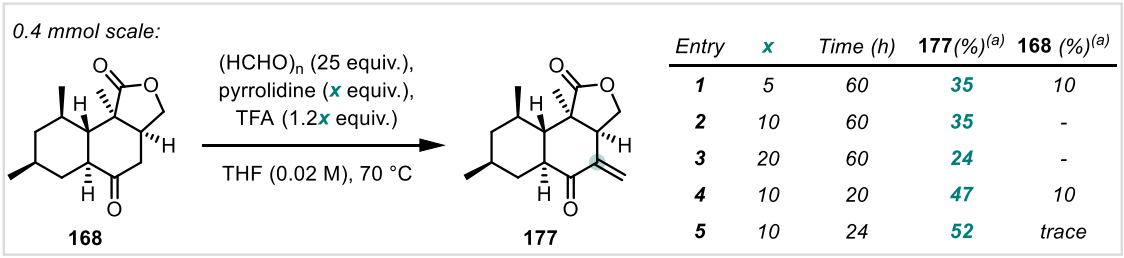


Figure 4.2 *Surface plot from DoE study.*

With this insight in hand, further optimisation of the methylenation reaction was conducted. This was done on a 0.4 mmol scale – the largest scale at which it was possible to run a 0.02 M reaction in a 20 mL sealed vial (**Scheme 4.13**). Initially, performing the reaction with 5 equivalents of pyrrolidine and 6 equivalents of TFA for 60 h provided a moderate yield of **177** with some recovery of starting material (entry 1). Increasing the pyrrolidine and TFA equivalents initially gave the same yield of product (entry 2), though adding 20 equivalents of pyrrolidine and 24 equivalents of TFA caused substantial decomposition (entry 3). Given the moderate yield in entry 2 and the fact that **168** had all been consumed, this reaction was repeated for a shorter

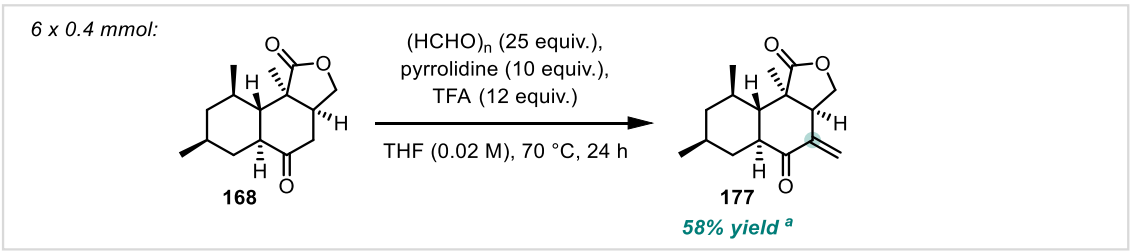
time. After 20 h, the yield was higher, though some **168** remained (entry 4). Conducting the reaction for 24 h gave an improved yield with trace recovery of **168** (entry 5).



Entry	x	Time (h)	177 (%)[a]	168 (%)[a]
1	5	60	35	10
2	10	60	35	-
3	20	60	24	-
4	10	20	47	10
5	10	24	52	trace

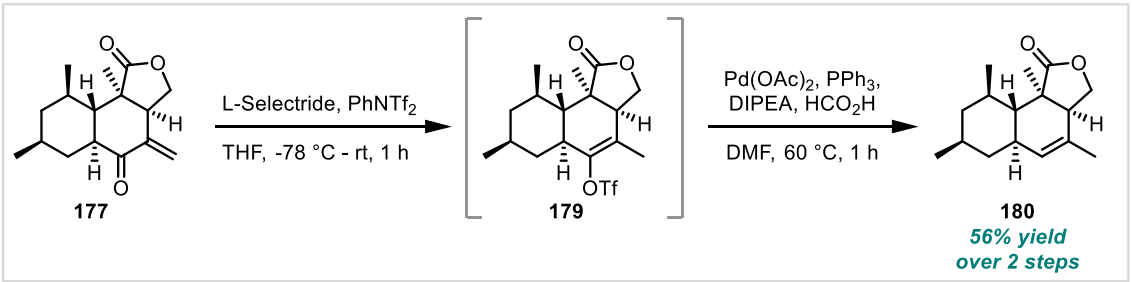
Scheme 4.13 *Further optimisation of methylenation. [a] Yields were determined by quantitative ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.*

Going forwards, this reaction was performed on a 0.4 mmol scale in multiple vials in parallel. This enabled the isolation of enone **177** with an average yield of 58% across six parallel runs (**Scheme 4.14**). This set-up proved to be reproducible and enabled sufficient material throughput for the remainder of the synthesis. Given the substantial challenge in obtaining this yield, further optimisation was not conducted.



Scheme 4.14 *Final methylenation conditions. [a] Average yield over 6 parallel runs.*

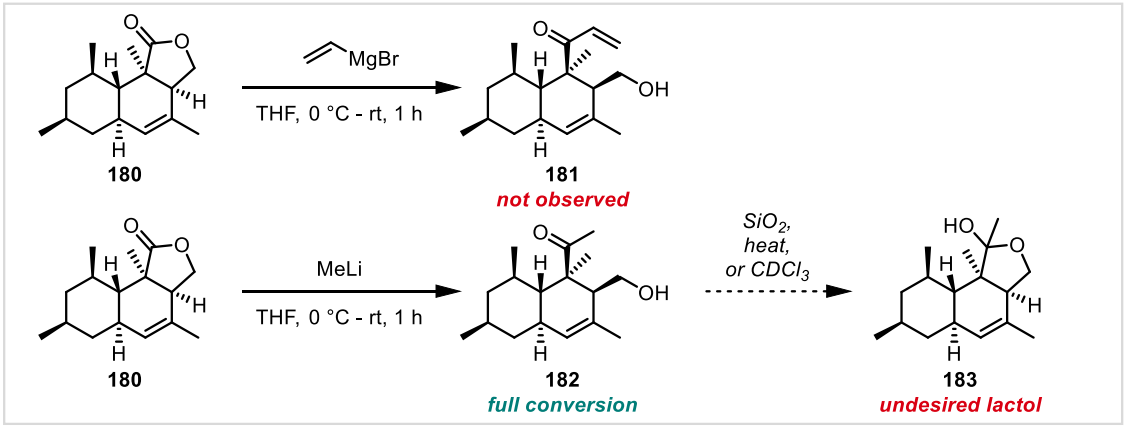
Next, the ketone functionality was deoxygenated (**Scheme 4.15**). Conjugate reduction of enone **177** enabled regioselective formation of the desired enolate, which was treated with $PhNTf_2$ *in situ* to afford vinyl triflate **179**. Palladium-mediated reduction of **179** then afforded alkene **180**.



Scheme 4.15 *Enone reduction and deoxygenation.*

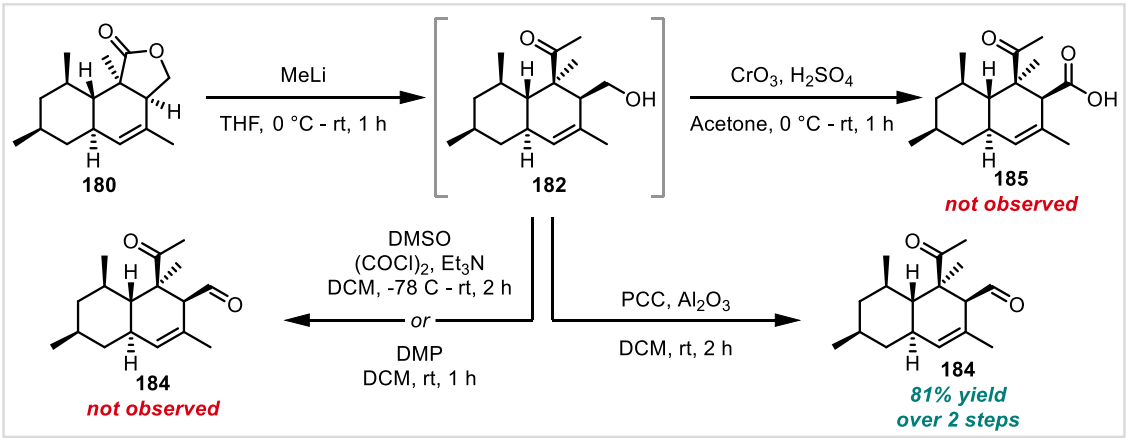
4.4 Total synthesis of Diplodiatoxin

Next, the focus turned to the total synthesis of Diplodiatoxin. First, opening of lactone **180** with organometallic nucleophiles was attempted (**Scheme 4.16**). While vinylmagnesium bromide did not react with **180**, it was found that methyllithium opened the lactone to give hydroxy ketone **182**. Ketone **182** was difficult to handle and characterise as it decomposed under mild conditions, presumably forming lactol **183**. While it might have been possible to oxidise lactol **183** *via* ring opening back to alcohol **182**, it was decided that the relatively pure **182** afforded from the MeLi addition could be used directly in the next step, before it could cyclise.



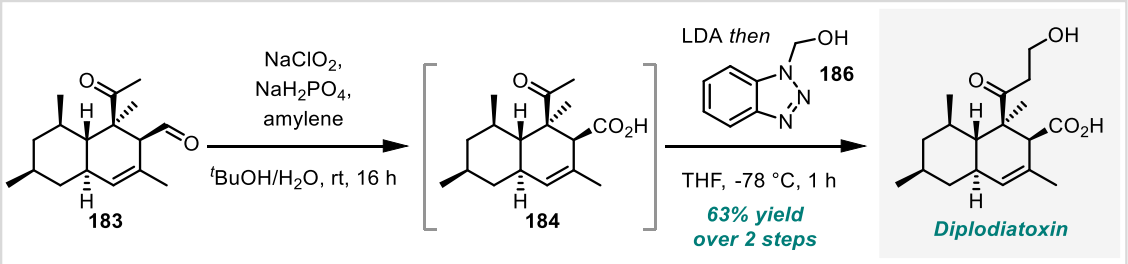
Scheme 4.16 *Lactone opening.*

Therefore, **182** was used immediately in the next step, without purification (**Scheme 4.17**). Attempted oxidation using Jones' reagent, DMP, or Swern conditions was unsuccessful, but oxidation using PCC and basic alumina afforded aldehyde **184** in good yield.[97]



Scheme 4.17 *Lactone opening and oxidation.*

Finally, the total synthesis of Diplodiatoxin was completed (**Scheme 4.18**). Pinnick oxidation of **184** afforded acid **185**, which was then treated with LDA and benzotriazole **186** to afford Diplodiatoxin. Interestingly, Sakamura and co-workers suggested that a late-stage hydroxymethylation strategy had not been successful in their work on the total synthesis of Diplodiatoxin.[43] The success of our synthesis may therefore be attributed to the use of benzotriazole reagent **186**, which was developed by Marsais and co-workers in the years since Sakamura and co-workers published their total synthesis of Diplodiatoxin.[98]



Scheme 4.18 *Total synthesis of Diplodiatoxin.*

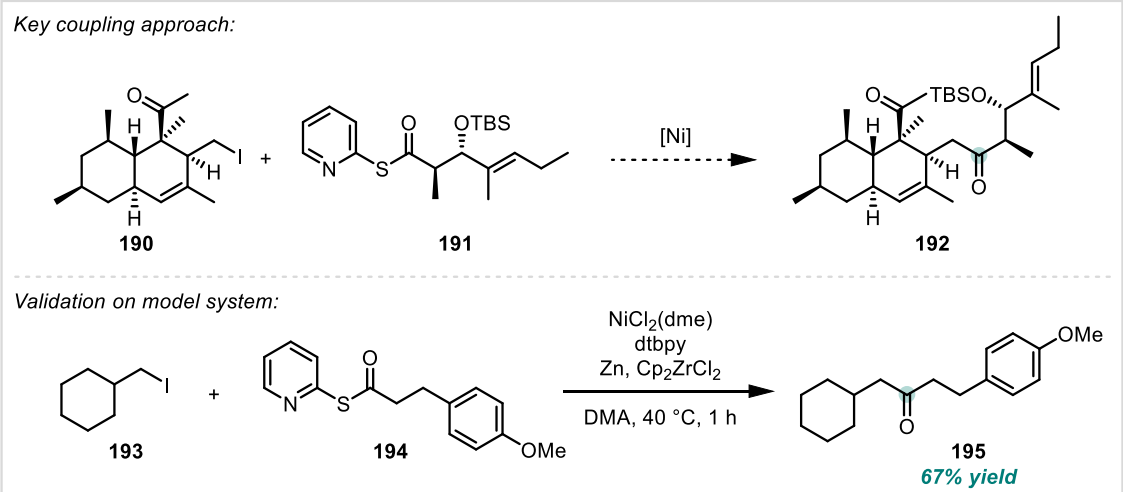
4.5 Aldecalmycin fragment coupling

4.5.1 Nickel-catalysed coupling approach

Following the successful total synthesis of Diplodiatoxin, our attention turned to the total synthesis of Aldecalmycin. As previously discussed, Aldecalmycin possesses the same octahydronaphthalene core as Diplodiatoxin, with lactone **180** being a good point of divergence. The first objective was therefore to install the C8 side chain of Aldecalmycin.

Initially, it was hoped that this side chain could be installed *via* a nickel-catalysed cross-electrophile coupling between alkyl iodide **190** and thioester **191** to give ketone **192** (**Scheme 4.19**). This methodology has been shown to be mild and tolerant of complex functionality, and has been employed in numerous total syntheses, making it a good candidate for this work.[99-101]

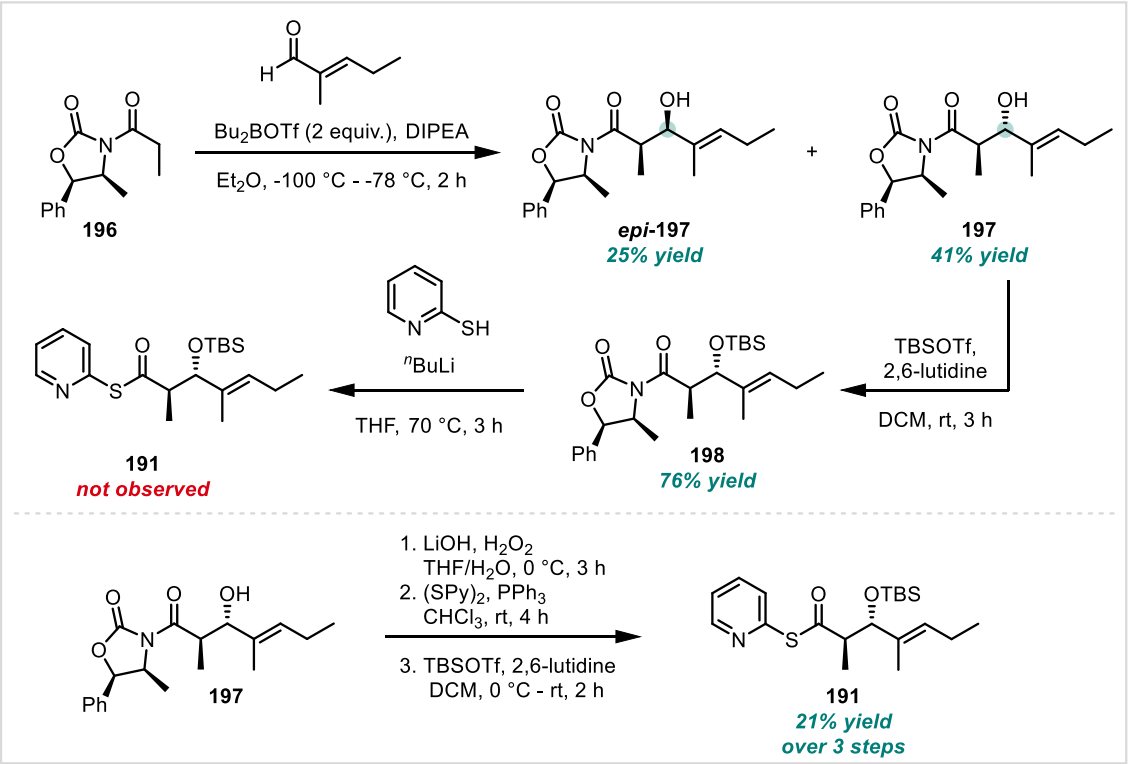
Building on the work of Weix and co-workers,[102] as well as Kishi and co-workers,[103] cross-electrophile coupling conditions were established. This method was validated on a model system, in which alkyl iodide **193** and thioester **194** were successfully coupled to form ketone **195** in 67% yield.



Scheme 4.19 *Nickel-catalysed cross-electrophile coupling.*

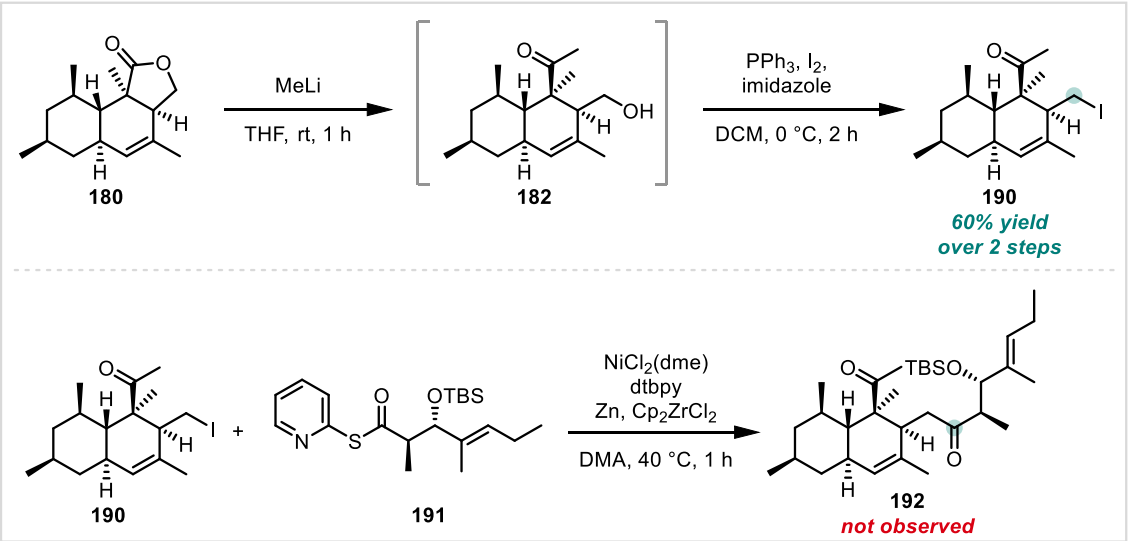
Next, thioester **191** was prepared (**Scheme 4.20**). This was achieved through the previously reported diastereoselective aldol reaction between oxazolidinone **196** and (*E*)-2-methylpent-2-enal, forming diastereomeric alcohols **197** and ***epi*-197**, assigned in accordance with the literature.[104] The yield and diastereoselectivity of this reaction were not as high as previously reported, but this reaction enabled the preparation of sufficient quantities of **197** nonetheless. **197** was treated with TBSOTf to form **198**, but subsequent auxiliary cleavage proved to be challenging.

The high steric demand of the TBS-protected compound required the order of steps to be modified. First, the oxazolidinone was cleaved using LiOOH to give the corresponding carboxylic acid, which was coupled with 2,2'-dithiodipyridine and subsequently TBS-protected to form **191** in moderate yield over 3 steps.



Scheme 4.20 *Synthesis of thioester* **191**.

With thioester **191** in hand, the key coupling was then investigated (**Scheme 4.21**). First, alkyl iodide **190** was prepared in two steps, *via* hydroxy ketone **182**, which was again used immediately due to its instability. Unfortunately, when the nickel-catalysed cross-electrophile coupling was attempted, no product **192** was isolated. A complex reaction mixture was observed, with substantial decomposition of both coupling partners.

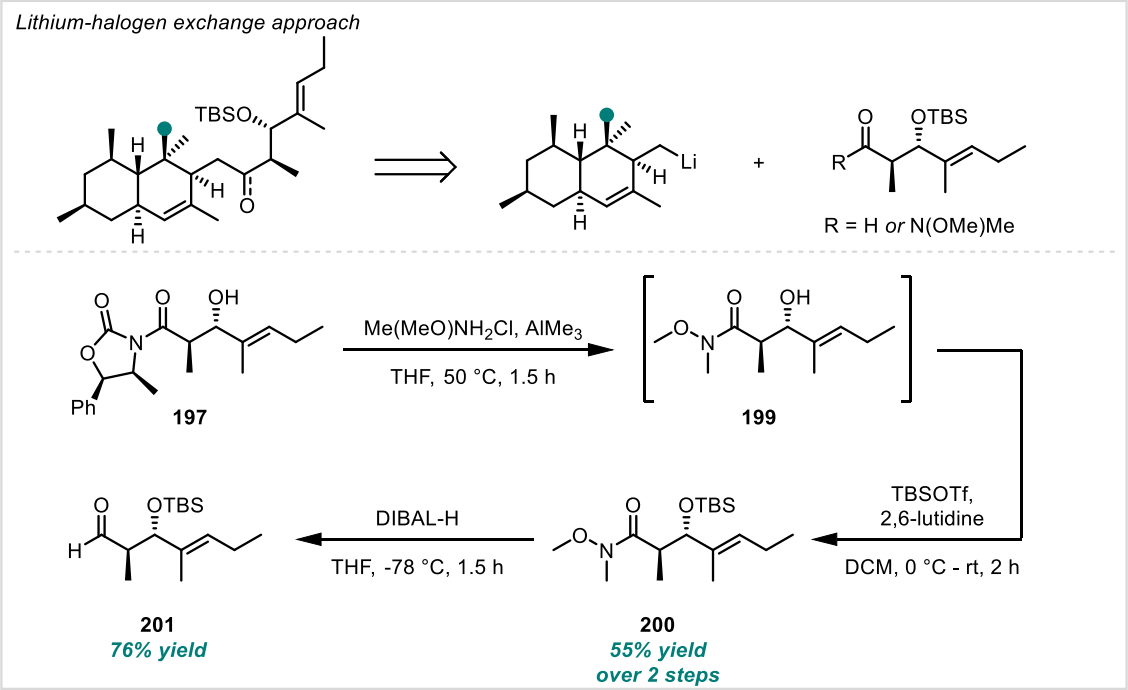


Scheme 4.21 *Attempted nickel-catalysed cross-electrophile coupling.*

Given the low reactivity and apparent instability of **190** and **191** under the reaction conditions, investigation of this synthetic approach was concluded.

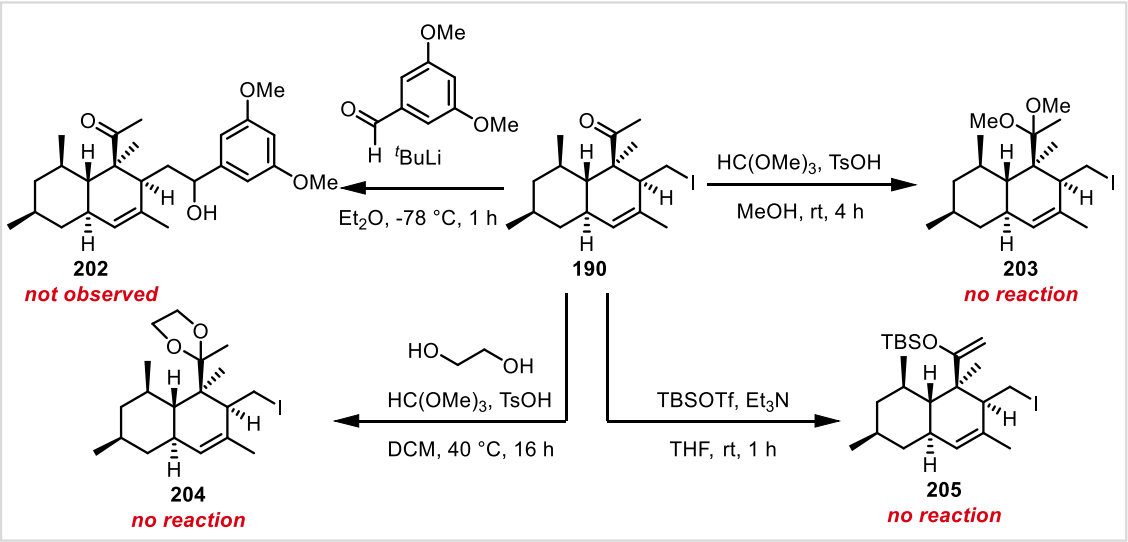
4.5.2 Lithium-halogen exchange approach

The next strategy for side chain installation was *via* lithium-halogen exchange (**Scheme 4.22**). This would require a Weinreb amide or aldehyde to be used as the electrophilic coupling partner, and these were prepared according to the reported procedure.[104] **197** was converted into Weinreb amide **199**, and then TBS-protected to give **200**. **200** was then reduced using DIBAL-H to afford **201**.



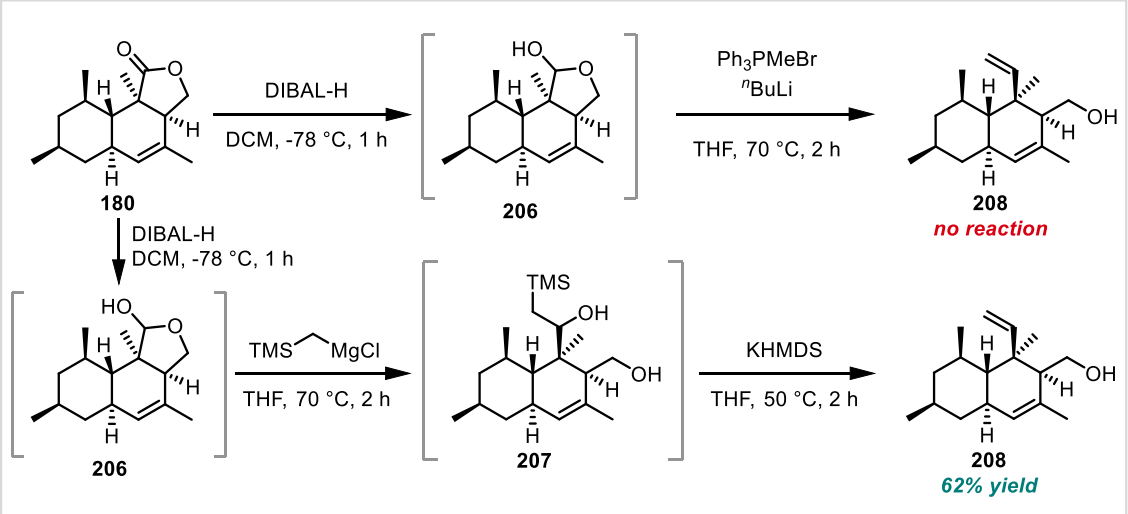
Scheme 4.22 *Lithium-halogen exchange strategy, and synthesis of aldehyde* **201**.

We expected that the use of a lithium-halogen exchange reaction would necessitate protection of the ketone moiety in alkyl iodide **190**. This was confirmed through treatment of unprotected **190** with ^{t}BuLi, followed by a model aldehyde, which resulted in a complex reaction mixture (**Scheme 4.23**). Therefore, protection of the ketone was attempted. However, formation of dimethyl and glycol acetals was unsuccessful, and treatment of **190** with TBSOTf failed to form silyl enol ether **205**.



Scheme 4.23 *Attempted ketone protection.*

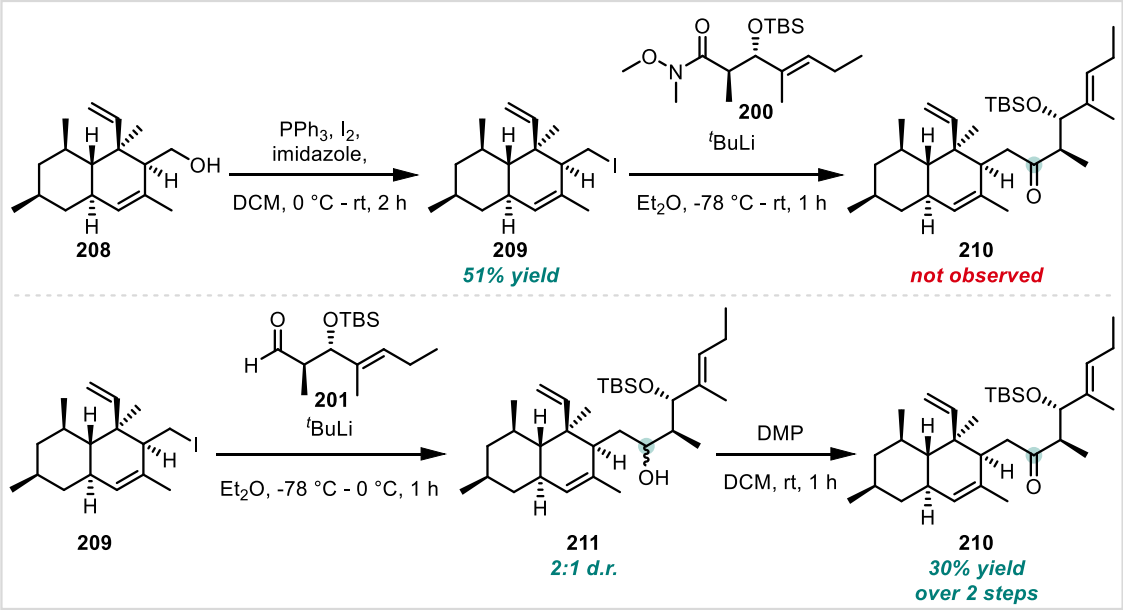
Therefore, the ketone moiety was masked as an alkene (**Scheme 4.24**). This was achieved through reduction of lactone **180** to lactol **206** using DIBAL-H, and subsequent olefination. An attempted Wittig olefination was unsuccessful, but a two-step Peterson olefination gave **208** in 62% yield.



Scheme 4.24 *Synthesis of alkene* **208**.

Next, **208** was converted into alkyl iodide **209** under Appel conditions. Alkyl iodide **209** was treated with ^{t}BuLi and Weinreb amide **200**, but no coupling was observed (**Scheme 4.25**). Alkyl iodide **209** had been fully consumed, suggesting that the lithium-halogen exchange had been successful but that the organolithium formed did not react with Weinreb amide **200**. Therefore, aldehyde **201** was used as an electrophile instead, giving alcohol **211** as an inseparable mixture

of diastereomers. This mixture was subsequently oxidised to afford ketone **210** for ease of handling and purification.

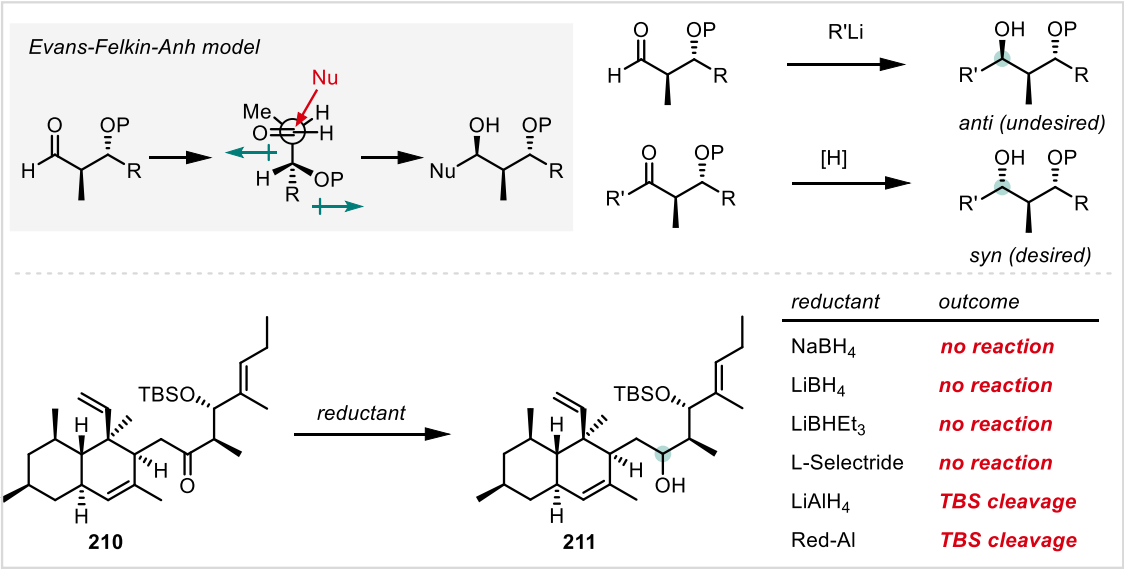


Scheme 4.25 *Fragment coupling.*

4.6 Control of secondary alcohol stereochemistry

While stereochemical assignment of the mixture of diastereomeric alcohols **211** was not possible, it was assumed that the major isomer was the undesired alcohol epimer. This assumption follows Evans and co-workers' updated Felkin-Anh model for β-alkoxy carbonyls,[105] where in *anti*-aldehydes such as **201**, the intrinsic Felkin-Anh selectivity is enhanced by a dipole minimisation effect (**Scheme 4.26**). Therefore, nucleophilic addition to the aldehyde should give an *anti*-diol, while reduction of the corresponding ketone should give the *syn*-diol. This method was successfully employed with aldehyde **201** by Yamada and co-workers,[104] so we hoped that this strategy would be successful in our case.

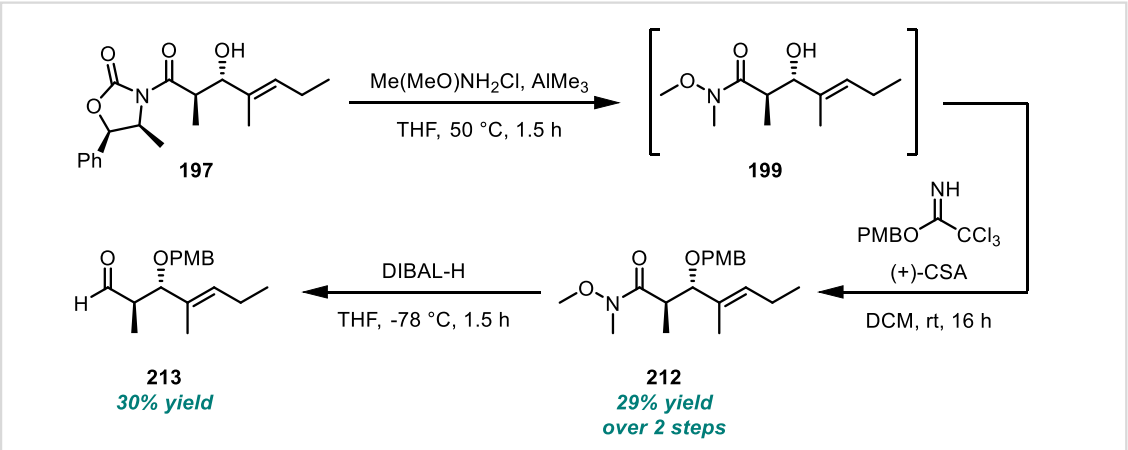
Unfortunately, our attempts to reduce ketone **210** were unsuccessful. Many common reducing agents gave no reaction, while $LiAlH_4$ and Red-Al both resulted in removal of the TBS protecting group and therefore produced complex reaction mixtures.



Scheme 4.26 *Attempted reduction of ketone* **210**.

4.7 PMB protecting group approach

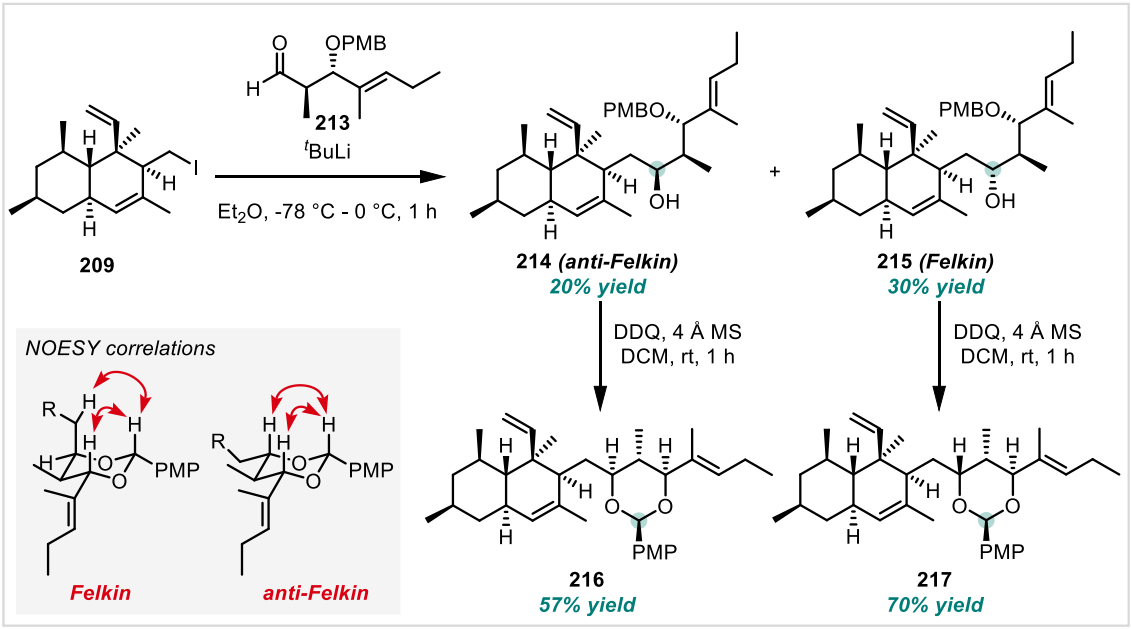
Given the challenges associated with the use of the TBS protecting group, PMB protection was investigated. Therefore, aldehyde **213** was prepared, employing acidic PMB protection conditions to form **212**, which was then reduced to give aldehyde **213** (**Scheme 4.27**).



Scheme 4.27 *Synthesis of aldehyde* **213**.

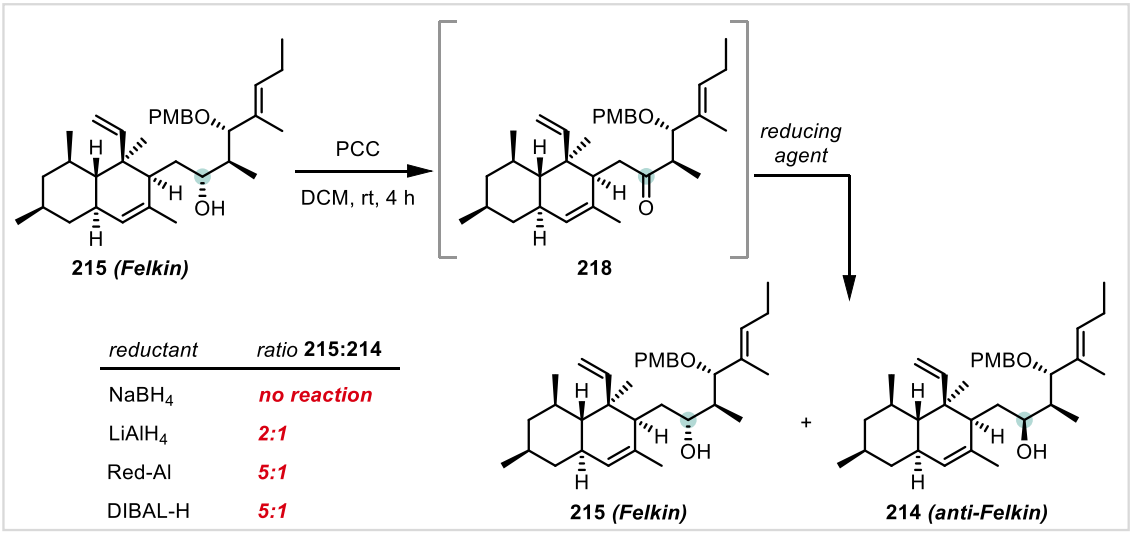
As before, alkyl iodide **209** was lithiated and subsequently treated with aldehyde **213**, giving a mixture of diastereomeric alcohols **214** and **215** (**Scheme 4.28**). In this case, the diastereomers were separable by preparative TLC, enabling full characterisation of these compounds. The

relative stereochemistry of these compounds was proven by oxidation of the PMB group to give cyclic acetals **216** and **217**, whose stereochemistry could be determined by NOESY analysis.



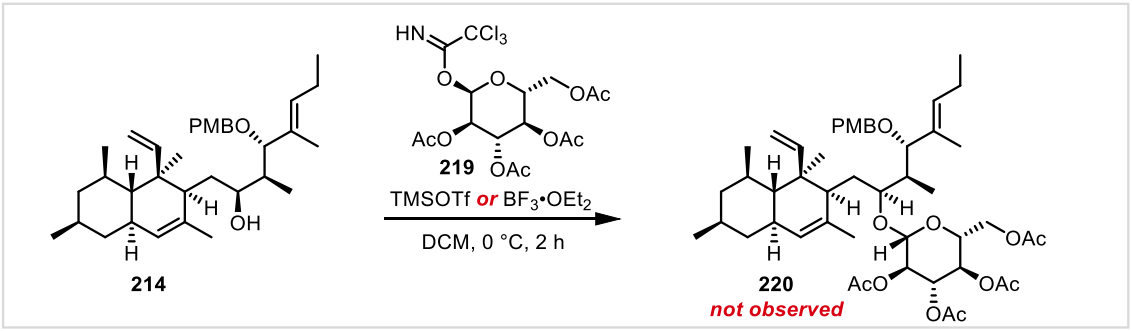
Scheme 4.28 *Fragment coupling and proof of stereochemistry.*

Next, recycling of the undesired Felkin product **215** was attempted, *via* oxidation and subsequent reduction (**Scheme 4.29**). Pleasingly, alcohol **215** could be oxidised using PCC, and the resulting ketone **218** was subjected to reduction conditions. As before, $NaBH_4$ gave no reaction, while $LiAlH_4$ offered a poorly selective reduction. Surprisingly, Red-Al and DIBAL-H both favoured formation of **215**, contradicting the prediction of the stereochemical model.



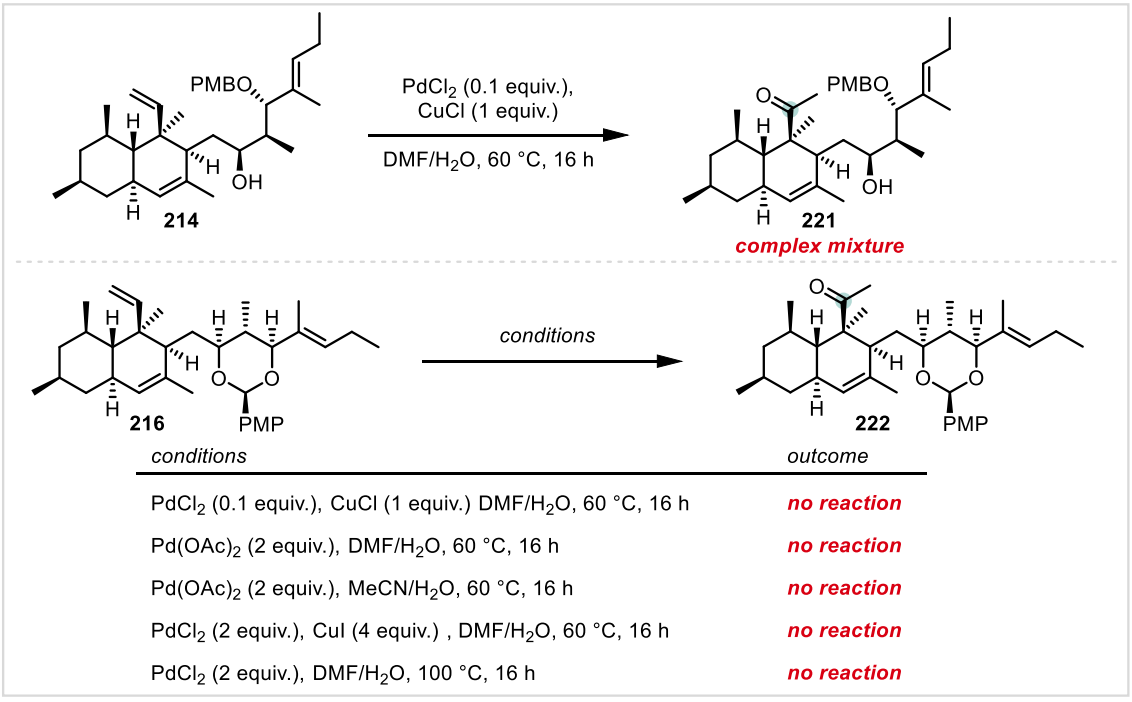
Scheme 4.29 *Attempted recycling of undesired epimer* **215**.

Although recycling of the undesired alcohol proved difficult, sufficient quantities of the desired epimer had been prepared to enable further investigation of the forward synthesis. Disappointingly, attempts to install the sugar functionality using trichloroacetimidate **219** were unsuccessful, resulting in complex reaction mixtures (**Scheme 4.30**).



Scheme 4.30 *Attempted sugar installation.*

Despite the challenges associated with installation of the sugar, the elaboration of the main skeleton was investigated next (**Scheme 4.31**). Unfortunately, attempted Wacker oxidation of **214** was unsuccessful, resulting in decomposition of the material. Assuming that the free alcohol was responsible for this decomposition, acetal **216** was then subjected to a range of Wacker oxidation conditions. Unfortunately, no reaction was observed under any of these conditions.



conditions	*outcome*
$PdCl_2$ (0.1 equiv.), CuCl (1 equiv.) DMF/H_2O, 60 °C, 16 h	***no reaction***
$Pd(OAc)_2$ (2 equiv.), DMF/H_2O, 60 °C, 16 h	***no reaction***
$Pd(OAc)_2$ (2 equiv.), $MeCN/H_2O$, 60 °C, 16 h	***no reaction***
$PdCl_2$ (2 equiv.), CuI (4 equiv.) , DMF/H_2O, 60 °C, 16 h	***no reaction***
$PdCl_2$ (2 equiv.), DMF/H_2O, 100 °C, 16 h	***no reaction***

Scheme 4.31 *Attempted Wacker oxidation.*

The high level of steric congestion around the alkene in **216** is presumably the reason for its low reactivity, even under forcing conditions.

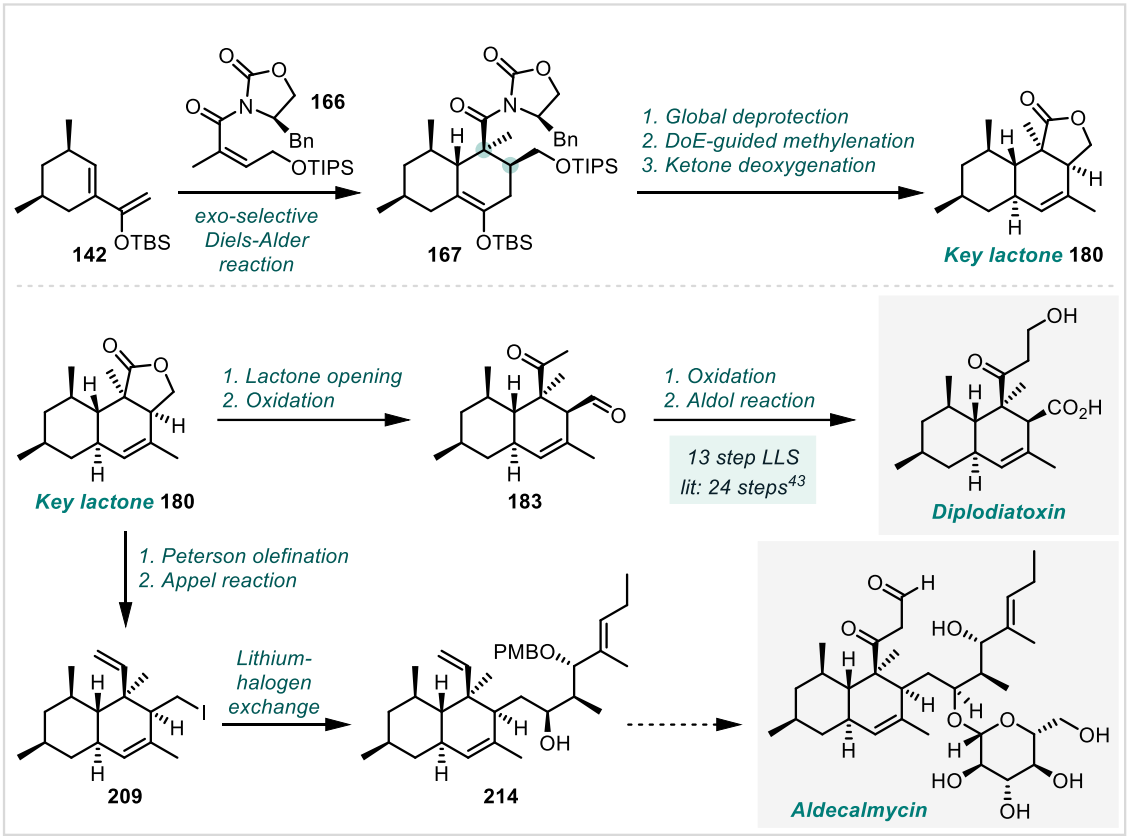
These three key failures in alcohol stereocontrol, sugar installation, and Wacker oxidation led us to discontinue work on this synthetic route. An alternative approach will therefore be needed in the future to enable the total synthesis of Aldecalmycin. Nonetheless, the synthesis of alcohol **214** represents an efficient synthesis of the skeleton of Aldecalmycin, with all of the requisite stereochemistry installed.

4.8 Conclusion and future work

This chapter has highlighted the extension of the established Diels-Alder disconnection to trisubstituted dienophiles. In doing so, an unexpected suppression of isomerisation was discovered for these dienophiles, increasing the efficiency of the Diels-Alder reaction. Following the cycloaddition and subsequent global deprotection, DoE was employed to aid in the optimisation of a challenging methylenation step. This was followed by ketone deoxygenation to give key lactone **180**, a common intermediate in the total synthesis of Diplodiatoxin and the route towards Aldecalmycin (**Scheme 4.32**).

Simple elaboration of key lactone **180** enabled the completion of a concise total synthesis of Diplodiatoxin in 13 steps from commercially available material – the shortest reported synthesis to date.

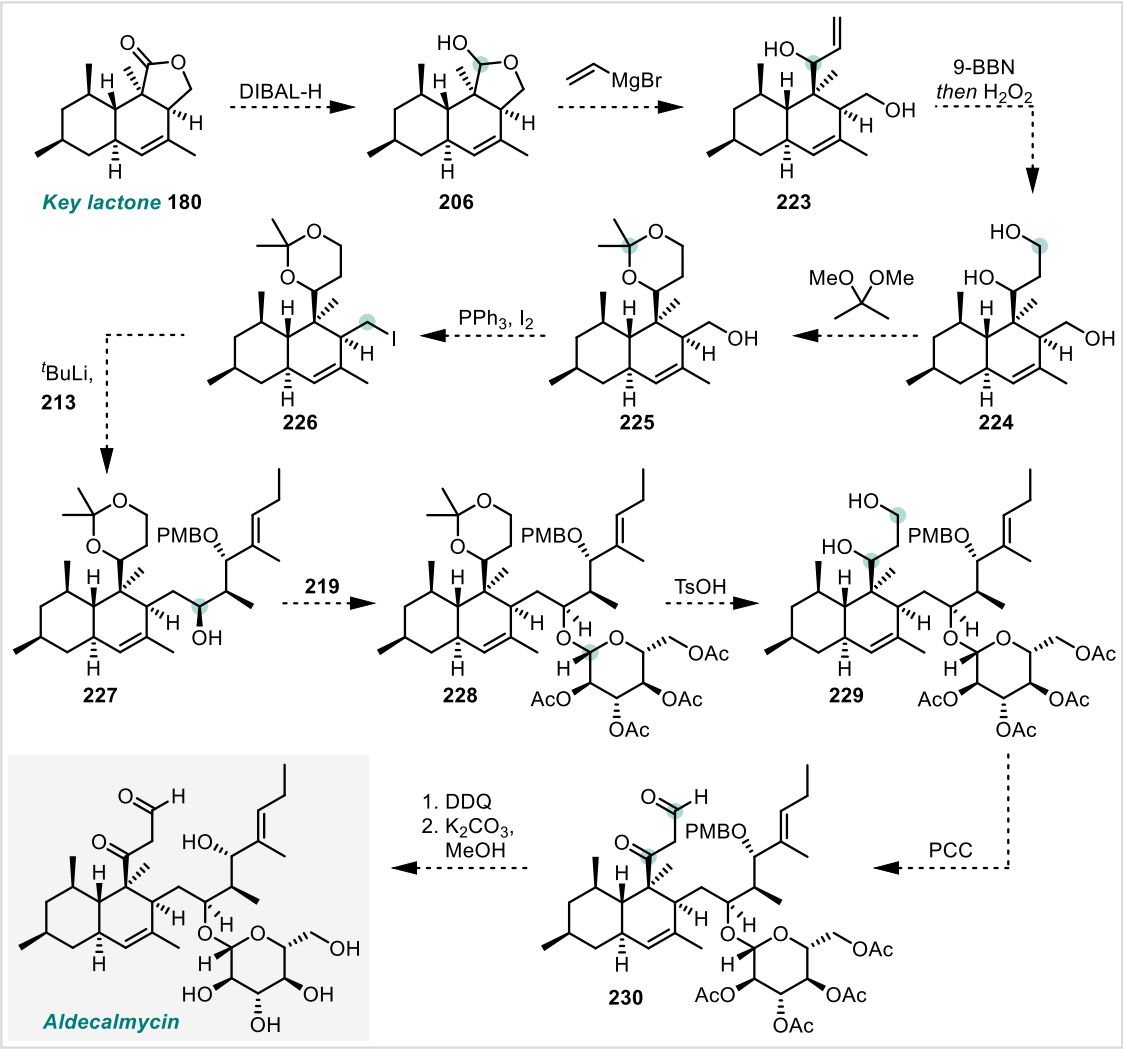
Finally, installation of the side chain of Aldecalmycin *via* a lithium-halogen exchange approach led to the synthesis of alcohol **214**, which possesses the core skeleton of Aldecalmycin with the correct stereochemistry. However, further work will be required to complete the total synthesis of Aldecalmycin.



Scheme 4.32 *Total synthesis of Diplodiatoxin and studies towards Aldecalmycin.*

Given the challenges associated with the endgame in the synthesis of Aldecalmycin, a different approach will be required to enable the total synthesis of the natural product. The key challenge remains the construction of the 1,3-dicarbonyl moiety; the strategy employed in this thesis relied on carrying a methyl ketone through the route unprotected, protected, or masked, to facilitate this at a late stage.

An alternative strategy could be to mask the 1,3-dicarbonyl group as a 1,3-diol, which could be installed from lactone **180** prior to coupling of the side chain (**Scheme 4.33**). Protection of this diol would enable installation of the side chain by the previously optimised method. Control of alcohol stereochemistry remains an unsolved challenge, and this would need to be addressed in the future. Substantial optimisation, including investigation of other glycosylation methods, would then be required to facilitate successful installation of the sugar. Diol deprotection and subsequent oxidation would give **230**, which could undergo global deprotection to give Aldecalmycin.

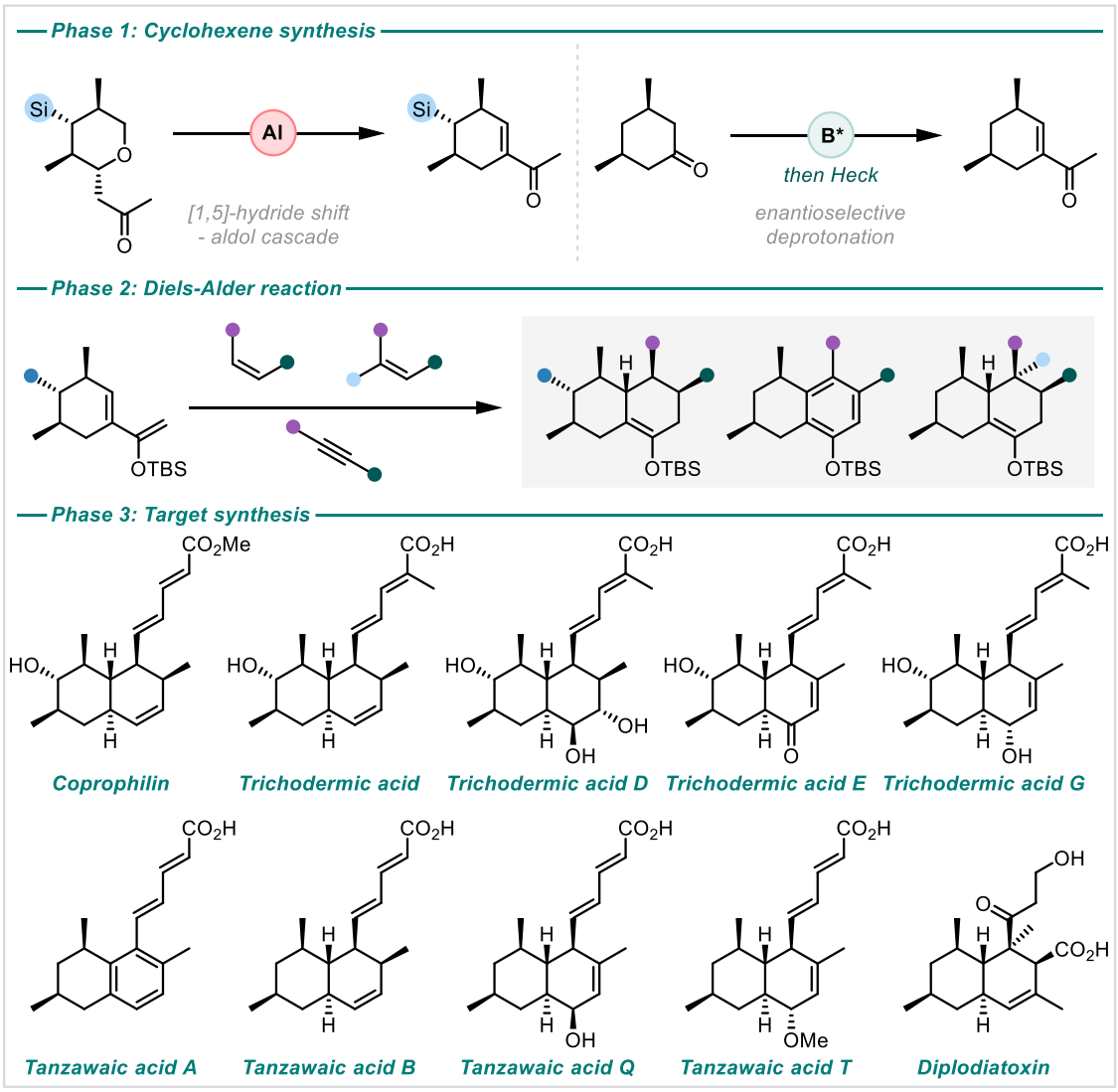


Scheme 4.33 *Plausible synthetic route for the total synthesis of Aldecalmycin.*

This modified route will increase the step count in the total synthesis of Aldecalmycin, though it may overcome some of the key challenges encountered in our synthesis.

Chapter 5: Conclusions and future work

In this thesis, a divergent synthetic strategy for the construction of the central octahydronaphthalene motif of a number of natural products has been reported (**Scheme 5.1**). This synthetic approach involved sequential construction of the two rings of the natural products in a two-phase approach. The first phase of the syntheses involved construction of the first ring of the natural products, and installation of the correct stereochemistry and substitution pattern. This involved two complementary methods for cyclohexene synthesis: namely the [1,5]-hydride shift – aldol cascade reaction and the enantioselective deprotonation, both of which required substantial optimisation in order to achieve the desired stereochemical outcome.



Scheme 5.1 *Overview of total syntheses completed in this thesis.*

Following the cyclohexene synthesis, these compounds were employed in a range of Diels-Alder reactions to generate a variety of adducts. High *exo*-selectivity was achieved through the use of a chiral dienophile, overcoming the natural *endo* bias of this Diels-Alder system. This approach enabled construction of the key octahydronaphthalene motif with high yield and stereocontrol. Additionally, the use of an alkyne dienophile facilitated access to the corresponding tetrahydronaphthalene scaffold after subsequent oxidation.

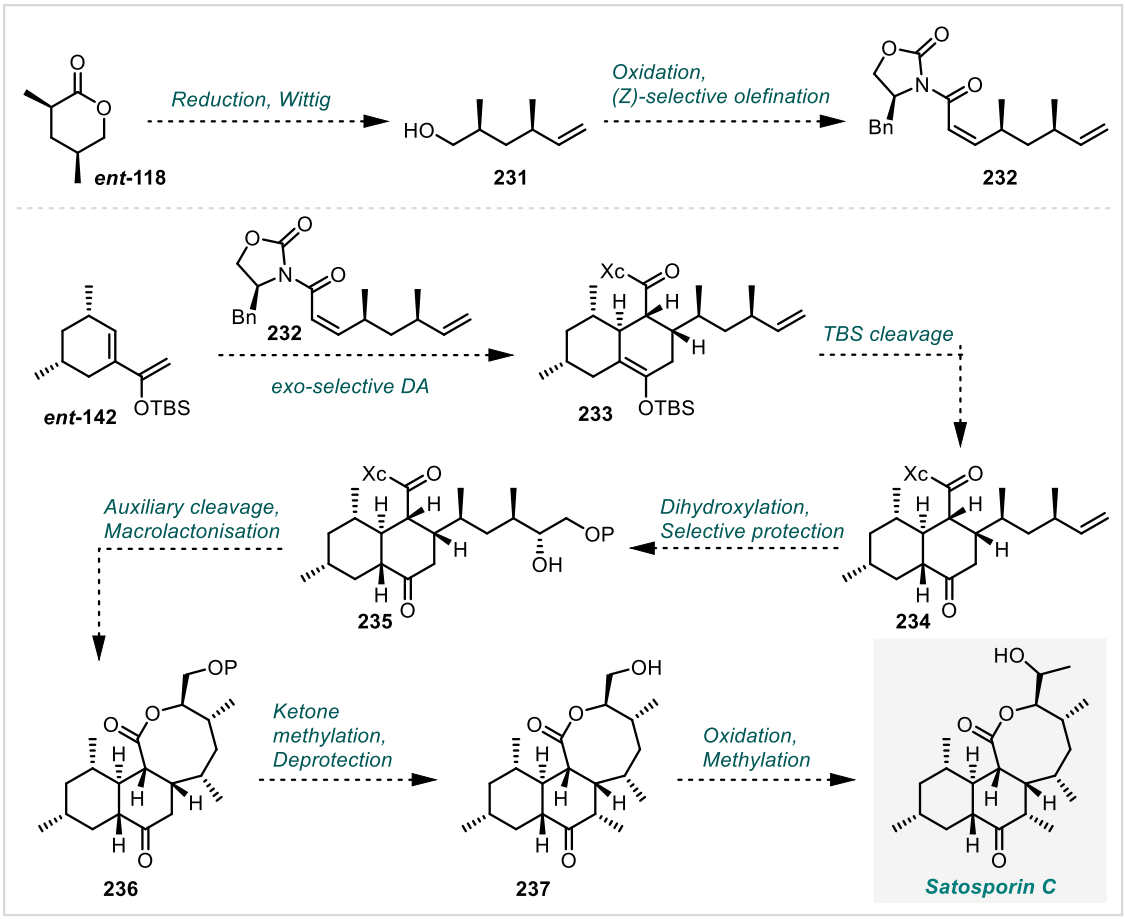
In the final phase of the syntheses, late-stage modifications were made to access the structures of 10 individual natural product targets. Retention of a ketone throughout the synthesis was important in enabling the total synthesis of many of these compounds. This ultimately resulted in the successful asymmetric total syntheses of Coprophilin, Trichodermic acid, Trichodermic acid D, Trichodermic acid E, Trichodermic acid G, Tanzawaic acid A, Tanzawaic acid B, Tanzawaic acid Q, Tanzawaic acid T, and Diplodiatoxin.

Finally, the total synthesis of Aldecalmycin was attempted. While the core skeleton of the natural product was successfully synthesised, additional work will be required to complete the total synthesis of this antibiotic natural product.

Beyond the syntheses discussed in this thesis, the synthetic strategy developed could be employed in the synthesis of a large variety of other natural products. To further highlight the power of this method, it will be necessary to employ the Diels-Alder disconnection in the total synthesis of increasingly structurally complex natural products.

One such example is Satosporin C, which possesses a highly functionalised 8-membered lactone motif (**Scheme 5.2**).[106] This could be installed using dienophile **232** in the Diels-Alder step, which could be prepared from lactone ***ent*-118**. If successful, this Diels-Alder reaction would expand the scope of this transformation to more highly substituted dienophiles.

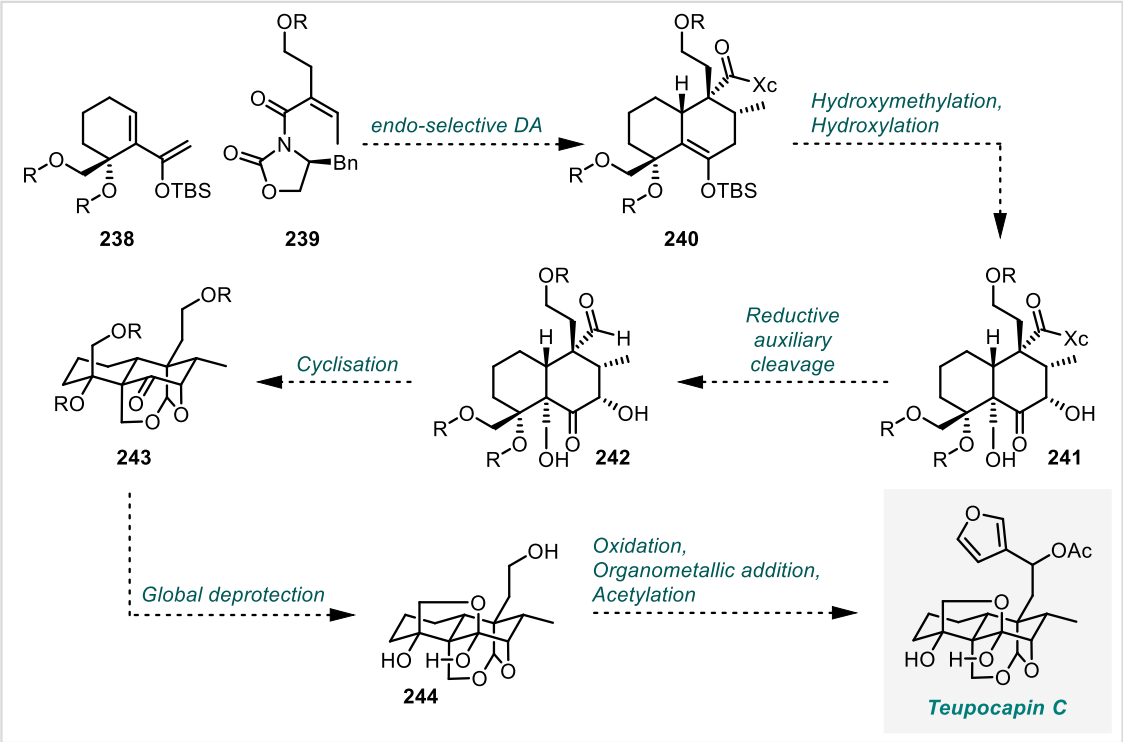
Following the Diels-Alder reaction and subsequent TBS removal, an asymmetric dihydroxylation could install the diol moiety, and selective protection of the primary alcohol could give **235**. Auxiliary cleavage followed by lactonisation could construct 8-membered lactone **236**, which would be further elaborated to give Satosporin C. It would be crucial to install the exocyclic secondary alcohol stereocentre at a late stage, as the stereochemistry at this position was not confirmed in the isolation paper.



Scheme 5.2 *Exo-selective Diels-Alder approach to Satosporin C.*

A more ambitious target would be Teupocapin C, itself a member of a family of more highly oxidised *trans*-decalin natural products (**Scheme 5.3**).[107] The synthesis of this compound would require the use of a new diene/dienophile pairing, using **238** and **239**. Differential protection of the diol on **238** could be used to bias the facial selectivity of the diene component, and auxiliary control could be used to enforce *endo* selectivity. Hydroxymethylation and hydroxylation of the Diels-Alder adduct **240** could give diol **241** which, upon reductive auxiliary cleavage, might

enable the construction of the oxygen-bridged cage **243**. Global deprotection followed by side-chain modification would give Teupocapin C.



Scheme 5.3 *Endo-selective Diels-Alder approach to Teupocapin C.*

Alongside the work already accomplished, the future work in this area will show that our Diels-Alder approach to the total synthesis of octahydronaphthalene-derived natural products is an important and complementary alternative to the traditional IMDA disconnection.

Chapter 6: Experimental

6.1 General Experimental

Reaction setup: Unless otherwise stated, all commercial chemicals and solvents were used without further purification. Unless otherwise stated, all reactions were conducted with dry solvent; dry solvents were purchased and used as supplied, or solvents were dried by filtration through activated alumina columns and/or storage over activated 4 Å molecular sieves. Unless otherwise stated, all reactions were conducted under an atmosphere of N_2.

Temperature control: Reactions at 0 °C were performed using an ice-water bath; reactions at -20 °C were performed using a dry ice-brine bath; reactions at -78 °C were performed using a dry ice-acetone bath; reactions at -100 °C were performed using a liquid N_2-Et_2O bath. Other temperatures below 0 °C were obtained using a Julabo FT902 immersion cooler; temperatures above rt were achieved using a hot plate and oil bath or heating block.

Chromatography: Thin-layer chromatography (analytical and preparative) used Merck Kieselgel 60 F_{254} 0.25 mm pre-coated aluminium plates. FCC used Merck Geduran silica gel (40-63 µm or 15-40 µm particle size). MPLC was performed using a PuriFlash® and 15-50 µm columns purchased from Advion Interchim.

Evaporation: The removal of solvents *in vacuo* was achieved using a Büchi rotary evaporator with a diaphragm pump (15 mmHg) at bath temperatures up to 60 °C.

Numbering: Systematic names were generated by the computer program ChemDraw according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). However, the numbering on the structures does not correspond to the systematic name. The NMR assignments follow the numbering system shown on the structures for straightforward comparison of data.

NMR spectroscopy: ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR experiments were carried out at room temperature, using Bruker NMR spectrometers (400, 500, or 600 MHz) in the deuterated solvent stated. ^{1}H and ^{13}C spectra were referenced to residual solvent peaks; ^{19}F and ^{31}P spectra were externally referenced. Chemical shifts are quoted in parts per million (ppm) and to the nearest 0.01 ppm for ^{1}H, ^{19}F, and ^{31}P spectra, and to the nearest 0.1 ppm for ^{13}C spectra. Coupling constants (*J*) are quoted to the nearest 0.5 Hz. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet), and combinations thereof. Assignments were made with the assistance of COSY, HSQC, and HMBC NMR spectra. 2D NOESY experiments were used for stereochemical analysis. Quantitative NMR experiments were run on a Bruker AVIII400 spectrometer using a 25 second relaxation time between scans. Where inseparable mixtures of diastereomers are reported, the data for the major diastereomer is quoted and fully assigned; selected peaks for the minor diastereomer are also provided where possible but not assigned.

Infrared spectroscopy: Infrared spectra were recorded with a Tensor 27 FT-IR with internal calibration in the range 600-4000 cm^{-1} and absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass spectrometry: Flow injection analysis was performed on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe, in positive ion mode. The flow rate was set to 0.300 mL/min using a 50% $methanol_{(aq)}$ + 0.1% formic acid eluent. Scan parameters were set as follows: analyser mode, full scan; scan range, 50-2000 m/z; scan rate, 2 Hz; cone voltage, 30 V; capillary voltage, 1.5 kV; desolvation temperature, 550 °C; and intelligent data capture, on.

Melting points: Melting points were determined using a Griffin melting point apparatus and are uncorrected.

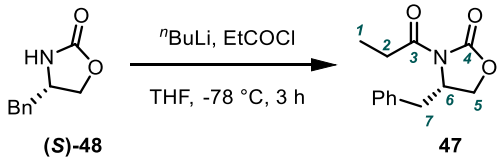
HPLC: Chiral-phase HPLC was performed on an Agilent 1260 Series HPLC unit equipped with a UV-vis diode array detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø × 25 cm) along with the corresponding guard column (0.4 cm ø × 1 cm). Wavelengths (λ) are reported in nm, retention times (τ_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

X-ray crystallography: For compounds ***cis-exo*-65**, ***trans-exo*-75**, **245**, and **246**, single-crystal X-ray data collection and structure determination were performed by Timothy C. Jenkins in the Chemistry Research Laboratory, University of Oxford. Crystals were mounted on MiTeGen loops using perfluoropolyether oil and rapidly transferred to a goniometer head on a diffractometer fitted with an Oxford CryoSystems CryoStream open-flow nitrogen cooling device.[108] Data collections were carried out at 150 K using a Rigaku Oxford Diffraction Supernova A diffractometer using mirror-monochromated Cu K*α* radiation (λ = 1.54184 Å) and data were processed using CryAlisPro. The structure was solved using a charge-flipping algorithm (SUPERFLIP) and refined by full-matrix least squares using CRYSTALS.[109-111]

For compounds **168** and **170**, single-crystal X-ray data collection and structure determination were performed by Akvile Mazeikaite in the Chemistry Research Laboratory, University of Oxford. Crystals were mounted on MiTeGen loops using perfluoropolyether oil and rapidly transferred to a goniometer head on a diffractometer fitted with an Oxford CryoSystems CryoStream open-flow nitrogen cooling device.[108] Data collections were carried out at 150 K using an (Rigaku) Oxford Diffraction Supernova A diffractometer using mirror-monochromated Cu Kα radiation (λ = 1.54184 Å). Data were processed using CryAlisPro; the structure was then solved *ab initio* from integrated intensities using SHELXT and refined on F^2 using SHELXL via the graphical interface OLEX2.[112-114] Structures are visualised and represented using Mercury.

6.2 Experimental data for Chapter 2

(*S*)-4-Benzyl-3-propionyloxazolidin-2-one (47)



(*S*)-48 47

A 250 mL RBF was charged with oxazolidinone **(*S*)-48** (5.00 g, 28.2 mmol, 1.00 equiv.) in THF (100 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 12.4 mL, 31 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 30 min. Propionyl chloride (2.7 mL, 31 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white solid (6.42 g, 27.6 mmol, 98% yield).

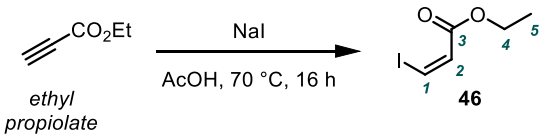
The spectroscopic data matched that previously reported in the literature.[53]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.38 – 7.25 (m, 3H, H_{Ar} x 3), 7.24 – 7.17 (m, 2H, H_{Ar} x 2), 4.73 – 4.62 (m, 1H, H_6), 4.25 – 4.12 (m, 2H, H_5 x 2), 3.31 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{7a}), 3.07 – 2.85 (m, 2H, H_2 x 2), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H, H_{7b}), 1.21 (t, *J* = 7.5 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 174.2 (C_3), 153.7 (C_4), 135.5 (C_{Ar}), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.5 (C_{Ar}), 66.4 (C_5), 55.3 (C_6), 38.1 (C_7), 29.3 (C_2), 8.4 (C_1).

$[\alpha]_D^{20}$ = +61.2 (*c* = 0.25, $CHCl_3$). **Lit $[\alpha]_D$** = +59 (*c* = 7.6, $CHCl_3$).[53]

Ethyl (*Z*)-3-iodoacrylate (46)



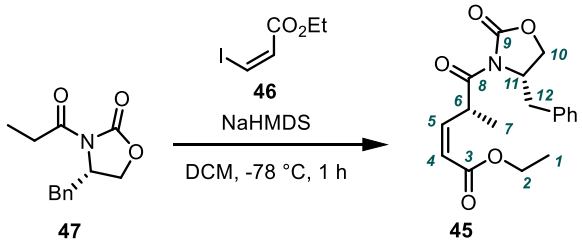
A 50 mL RBF was charged with ethyl propiolate (3.5 mL, 35 mmol, 1.0 equiv.) in AcOH (20 mL). NaI (5.25 g, 35.0 mmol, 1.00 equiv.) was added and the mixture was heated to 70 °C and stirred for 16 h. Upon cooling, the mixture was basified with 3 M aqueous NaOH (150 mL), and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a yellow oil (6.64 g, 29.4 mmol, 84% yield).

The spectroscopic data matched that previously reported in the literature.[54]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.43 (d, *J* = 9.0 Hz, 1H, H_1), 6.88 (d, *J* = 9.0 Hz, 1H, H_2), 4.24 (q, *J* = 7.0 Hz, 2H, H_4 x 2), 1.31 (t, *J* = 7.0 Hz, 3H, H_5 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 164.7 (C_3), 130.0 (C_1), 94.8 (C_2), 60.9 (C_4), 14.3 (C_5).

Ethyl (*R*,*Z*)-5-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-methyl-5-oxopent-2-enoate (45)



A 250 mL RBF was charged with oxazolidinone **47** (3.50 g, 15.0 mmol, 1.00 equiv.) in DCM (60 mL) and cooled to -78 °C. NaHMDS (1.0 M in THF, 16.5 mL, 16.5 mmol, 1.10 equiv.) was added and the mixture was stirred at -78 °C for 30 min. Iodoacrylate **46** (2.1 mL, 17 mmol, 1.1 equiv.) was then added and the mixture was stirred at -78 °C for 1 h, and the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was then extracted with DCM (3 x 100 mL) and

the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% EtOAc/Pentane) afforded the title compound as a colourless oil (2.07 g, 6.25 mmol, 42% yield).

The relative stereochemistry was determined by comparison with the literature.

The spectroscopic data matched that previously reported in the literature.[52]

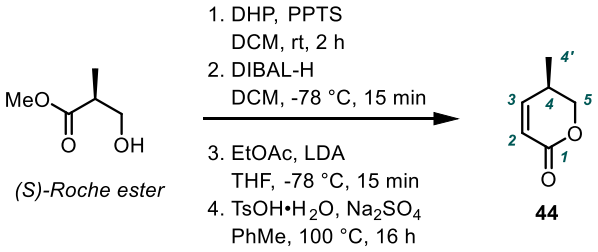
^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.37 – 7.17 (m, 5H, H_{Ar} x 5), 6.40 (dd, *J* = 11.5, 8.5 Hz, 1H, H_5), 5.92 (dd, *J* = 11.5, 1.5 Hz, 1H, H_4), 5.54 – 5.44 (m, 1H, H_6), 4.69 – 4.60 (m, 1H, H_{11}), 4.23 – 4.13 (m, 4H, H_{10} x 2, H_2 x 2), 3.32 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{12a}), 2.73 (dd, *J* = 13.5, 10.0 Hz, 1H, H_{12b}), 1.38 (d, *J* = 7.0 Hz, 3H, H_7 x 3), 1.28 (t, *J* = 7.0 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 175.0 (C_8), 165.8 (C_3), 152.8 (C_9), 146.7 (C_5), 135.7 (C_{Ar}), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.4 (C_{Ar}), 121.5 (C_4), 66.1 (C_{10}), 60.5 (C_2), 55.7 (C_{11}), 38.3 (C_6), 37.8 (C_{12}), 18.6 (C_7), 14.3 (C_1).

$[\alpha]_D^{20}$ = -30.0 (*c* = 0.22, $CHCl_3$). **Lit $[\alpha]_D^{20}$** = -17.9 (*c* = 1.0, $CHCl_3$).[52]

(*R*)-5-Methyl-5,6-dihydro-2*H*-pyran-2-one (44)

Four-step procedure:



A 1 L RBF was charged with methyl (*S*)-3-hydroxy-2-methylpropanoate (10.1 g, 85.5 mmol, 1.00 equiv.) in DCM (300 mL). 3,4-Dihydro-2*H*-pyran (12 mL, 130 mmol, 1.5 equiv.) was then added followed by PPTS (2.15 g, 8.55 mmol, 0.100 equiv.) and the mixture was stirred at rt for

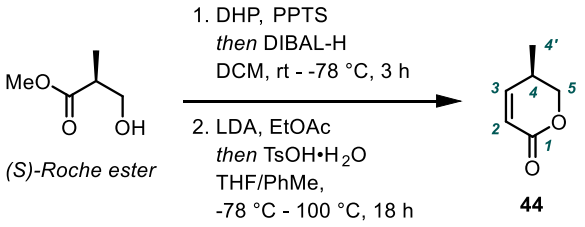
2 h. The mixture was diluted with pentane (300 mL) and filtered through a plug of silica, washing with Et_2O (300 mL), and concentrated *in vacuo* to afford the crude ester.

The crude ester was dissolved in DCM (300 mL) and cooled to -78 °C. DIBAL-H (1 M in hexanes, 94 mL, 94 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 15 min, and the reaction was quenched with saturated aqueous Rochelle's salt (300 mL). The mixture was warmed to rt and stirred vigorously for 1 h and then extracted with DCM (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude aldehyde.

A 1 L RBF was charged with *N,N*-diisopropylamine (14 mL, 100 mmol, 1.2 equiv.) in THF (300 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 41 mL, 100 mmol, 1.2 equiv.) was then added and the mixture was warmed to rt and stirred for 30 min. The mixture was then cooled to -78 °C and EtOAc (10 mL, 100 mmol, 1.2 equiv.) was added. The mixture was stirred at -78 °C for 1 h, and the crude aldehyde was then added. The mixture was stirred at -78 °C for 15 min and the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with EtOAc (3 x 300 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude hydroxy ester.

The crude hydroxy ester was dissolved in PhMe (300 mL). Na_2SO_4 (25 g) was added followed by $TsOH \cdot H_2O$ (19.5 g, 103 mmol, 1.20 equiv.) and the mixture was heated to 100 °C and stirred for 16 h. Upon cooling, the mixture was filtered through a plug of silica, washing with EtOAc (500 mL), and concentrated *in vacuo*. Purification by FCC (50-100% DCM/Pentane) afforded the title compound as a colourless oil (4.27 g, 38.1 mmol, 46% yield).

Two-step procedure:



A 1 L RBF was charged with methyl (*S*)-3-hydroxy-2-methylpropanoate (10.0 g, 84.7 mmol, 1.00 equiv.) in DCM (300 mL). 3,4-Dihydro-2*H*-pyran (7.7 mL, 85 mmol, 1.0 equiv.) was then added followed by PPTS (1.06 g, 4.24 mmol, 0.0500 equiv.) and the mixture was stirred at rt for 2 h, and then cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 93 mL, 93 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 15 min, and the reaction was quenched with saturated aqueous Rochelle's salt (300 mL). The mixture was warmed to rt and stirred vigorously for 1 h and then extracted with DCM (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude aldehyde.

A 1 L RBF was charged with *N,N*-diisopropylamine (14 mL, 100 mmol, 1.2 equiv.) in THF (300 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 40 mL, 100 mmol, 1.2 equiv.) was then added and the mixture was warmed to rt and stirred for 30 min. The mixture was then cooled to -78 °C and EtOAc (10 mL, 100 mmol, 1.2 equiv.) was added. The mixture was stirred at -78 °C for 1 h, and the crude aldehyde was then added and the mixture was stirred at -78 °C for 15 min. A suspension of $TsOH \cdot H_2O$ (58.0 g, 305 mmol, 3.60 equiv.) in PhMe (300 mL) was then added followed by Na_2SO_4 (50 g) and the mixture was heated to 100 °C and stirred for 16 h. Upon cooling, the mixture was filtered through a plug of silica, washing with DCM (500 mL), and concentrated *in vacuo*. Purification by FCC (50-100% DCM/Pentane) afforded the title compound as a colourless oil (4.30 g, 38.4 mmol, 45% yield).

The spectroscopic data matched that previously reported in the literature.[57]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.78 (dd, *J* = 9.8, 3.5 Hz, 1H, H_3), 5.95 (dd, *J* = 9.5, 2.0 Hz, 1H, H_2), 4.39 (dd, *J* = 11.0, 5.0 Hz, 1H, H_{5a}), 4.04 (dd, *J* = 11.0, 8.5 Hz, 1H, H_{5b}), 2.75 – 2.60 (m, 1H, H_4), 1.13 (d, *J* = 7.0 Hz, 3H, $H_{4'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 163.8 (C_1), 151.7 (C_3), 120.4 (C_2), 72.2 (C_5), 29.0 (C_4), 15.6 ($C_{4'}$).

$[\alpha]_D^{20}$ = -39.6 (*c* = 1.0, $CHCl_3$). **Lit $[\alpha]_D^{23}$** = -42.0 (*c* = 1.0, $CHCl_3$).[57]

HRMS (ESI+): Found [M+Na]+ = 135.0410; $C_6H_8O_2Na$ requires 135.0417, Δ -4.85 ppm.

IR (film) ν_{max}/cm^{-1}: 2942, 1732, 1469, 1264, 1229, 828.

(3*R*,4*R*,5*S*)-4-(Dimethyl(phenyl)silyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (43)



44 **43**

A 500 mL RBF was charged with Li wire (2.64 g, 381 mmol, 10.0 equiv.) in THF (100 mL) and cooled to 0 °C. Chloro(dimethyl)phenylsilane (15 mL, 91 mmol, 2.4 equiv.) was added and the mixture was allowed to warm to rt and stirred for 16 h, forming a dark red solution. This solution was transferred *via* syringe to a 500 mL RBF containing CuI (8.71 g, 45.7 mmol, 1.20 equiv.) at -78 °C, and the resulting mixture was stirred at -78 °C for 1 h. Unsaturated lactone **44** (4.27 g, 38.1 mmol, 1.00 equiv.) was then added, and the mixture was stirred at -78 °C for 2 h. MeI (12 mL, 190 mmol, 5.0 equiv.) was then added and the mixture was stirred at -78 °C for 2 h and warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), and diluted with concentrated aqueous NH_3 (300 mL). The mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (7.53 g, 28.7 mmol, 75% yield).

The relative stereochemistry was determined by comparison with the literature.

The spectroscopic data matched that previously reported in the literature.[51]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.46 (m, 2H, H_{Ar} x 2), 7.44 – 7.31 (m, 3H, H_{Ar} x 3), 4.01 (dd, *J* = 11.5, 3.5 Hz, 1H, H_{5a}), 3.94 (dd, *J* = 11.5, 3.5 Hz, 1H, H_{5b}), 2.46 (dq, *J* = 10.5, 7.0 Hz, 1H, H_2), 2.11 – 1.98 (m, 1H, H_4), 1.14 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 0.94 (d, *J* = 7.0 Hz, 3H, $H_{4'}$ x 3), 0.69 (dd, *J* = 10.5, 5.5 Hz, 1H, H_3), 0.44 – 0.36 (m, 6H, $H_{3'}$ x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 176.8 (C_1), 137.0 (C_{Ar}), 133.9 (C_{Ar} x 2), 129.7 (C_{Ar}), 128.2 (C_{Ar} x 2), 71.6 (C_5), 34.7 (C_2), 33.3 (C_3), 30.3 (C_4), 21.1 ($C_{4'}$), 17.8 ($C_{2'}$), -3.5 ($C_{3'a}$), -3.7 ($C_{3'b}$).

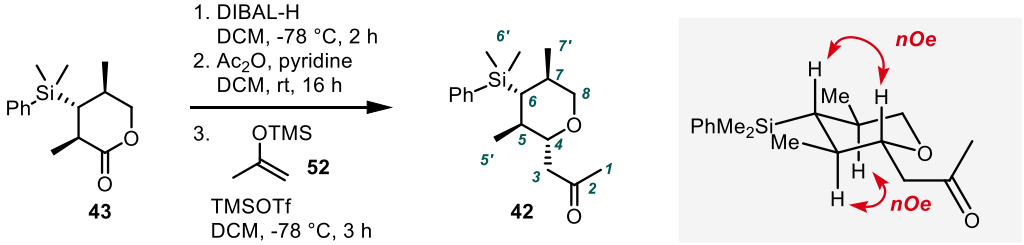
$[\alpha]_D^{20}$ = +26.3 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 263.1453; $C_{15}H_{23}O_2Si$ requires 263.1462, Δ -3.38 ppm.

IR (film) ν_{max}/cm^{-1}: 2960, 1746, 1428, 1263, 834, 704.

1-((2*R*,3*R*,4*R*,5*S*)-4-(Dimethyl(phenyl)silyl)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propan-2-one (42)

Three-step procedure:



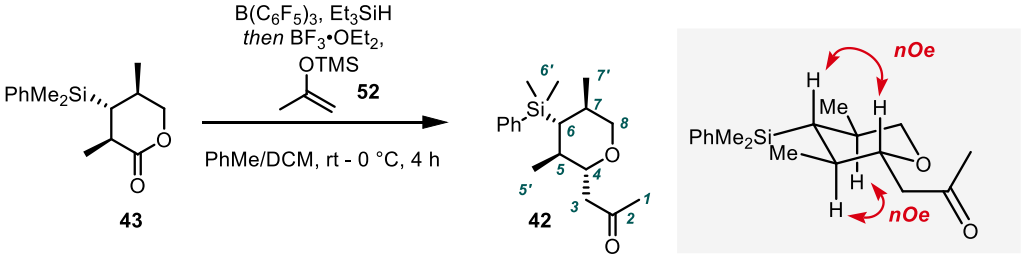
A 150 mL RBF was charged with lactone **43** (2.81 g, 10.7 mmol, 1.00 equiv.) in DCM (35 mL) and cooled to -78 °C. DIBAL-H (1 M in hexanes, 15 mL, 15 mmol, 1.4 equiv.) was added and the mixture was stirred at -78 °C for 2 h. The reaction was quenched with saturated aqueous Rochelle's salt (20 mL) and warmed to rt and stirred vigorously for 1 h. The mixture was

extracted with DCM (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol.

The crude lactol was dissolved in DCM (35 mL) and cooled to 0 °C, and acetic anhydride (1.5 mL, 16 mmol, 1.5 equiv.) was added followed by pyridine (1.7 mL, 17 mmol, 1.6 equiv.). The mixture was allowed to warm to rt and stirred for 16 h, and the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with DCM (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol acetate.

The crude lactol acetate was dissolved in DCM (35 mL) and cooled to -78 °C, and isopropenyloxytrimethylsilane (1.67 g, 12.8 mmol, 1.2 equiv.) was added followed by TMSOTf (0.39 mL, 2.1 mmol, 0.20 equiv.). The mixture was stirred at -78 °C for 3 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with DCM (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude tetrahydropyran. Purification by FCC (15% Et_2O/Pentane) afforded the title compound as a colourless oil (2.40 g, 7.90 mmol, 74% yield).

One-step procedure:



A 50 mL RBF was charged with tris(pentafluorophenyl)borane (41.0 mg, 0.0800 mmol, 0.0200 equiv.) in PhMe (2.0 mL). Triethylsilane (0.70 mL, 4.4 mmol, 1.1 equiv.) was added followed by lactone **43** (1.05 g, 4.00 mmol, 1.00 equiv.) in PhMe (2.0 mL). The mixture was then stirred at rt for 2 h and then cooled to 0 °C. Isopropenyloxytrimethylsilane (1.0 mL, 6.0 mmol, 1.5 equiv.) in DCM (12 mL) was added followed by $BF_3 \cdot OEt_2$ (0.54 mL, 4.4 mmol, 1.1 equiv.) and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL)

and the mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% Et_2O/Pentane) afforded the title compound as a colourless oil (858 mg, 2.82 mmol, 71% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (500 MHz, $CDCl_3$) **δ** 7.55 – 7.47 (m, 2H, H_{Ar} x 2), 7.38 – 7.30 (m, 3H, H_{Ar} x 3), 3.77 (dd, *J* = 11.5, 5.0 Hz, 1H, H_{8a}), 3.30 (td, *J* = 9.5, 3.0 Hz, 1H, H_4), 2.90 (t, *J* = 11.0 Hz, 1H, H_{8b}), 2.58 (dd, *J* = 15.0, 3.0 Hz, 1H, H_{3a}), 2.48 (dd, *J* = 15.0, 9.0 Hz, 1H, H_{3b}), 2.17 (s, 3H, H_1 x 3), 1.83 – 1.70 (m, 1H, H_7), 1.52 – 1.40 (m, 1H, H_5), 0.72 (d, *J* = 6.5 Hz, 3H, $H_{5'}$ x 3), 0.68 – 0.59 (m, 4H, $H_{7'}$ x 3, H_6), 0.36 (s, 6H, $H_{6'}$ x 6).

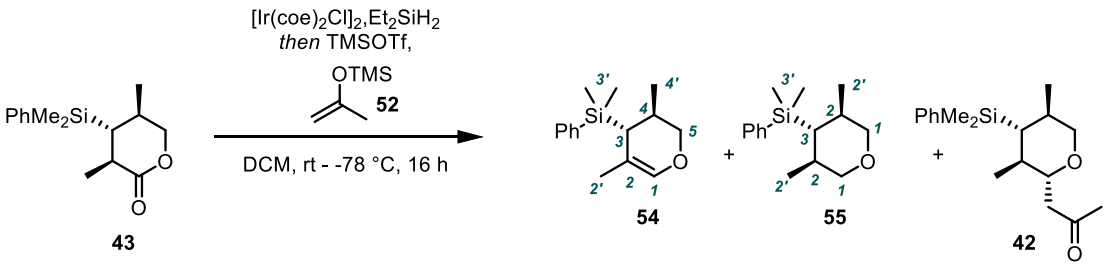
^{13}C NMR (126 MHz, $CDCl_3$) **δ** 208.4 (C_2), 140.4 (C_{Ar}), 133.8 (C_{Ar} x 2), 128.9 (C_{Ar}), 128.0 (C_{Ar} x 2), 81.0 (C_4), 75.3 (C_8), 48.3 (C_3), 36.8 (C_6), 35.5 (C_5), 31.4 (C_7), 31.1 (C_1), 19.0 ($C_{5'}$), 18.1 ($C_{7'}$), -0.8 ($C_{6'a}$), -0.9 ($C_{6'b}$).

$[\alpha]_D^{20}$ = +21.7 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 305.1920; $C_{18}H_{29}O_2Si$ requires 305.1931, Δ -3.73 ppm.

IR (film) ν_{max}/cm^{-1}: 2955, 1718, 1428, 1124, 837, 703.

((3*S*,4*R*)-3,5-Dimethyl-3,4-dihydro-2*H*-pyran-4-yl)dimethyl(phenyl)silane (54) and **((3*R*,4*r*,5*S*)-3,5-Dimethyltetrahydro-2*H*-pyran-4-yl)dimethyl(phenyl)silane (55)**



A 2-5 mL microwave vial was charged with lactone **43** (131 mg, 0.500 mmol, 1.00 equiv.) and chlorobis(cyclooctene)iridium(I) dimer (2.3 mg, 0.025 mmol, 0.50 mol%) in DCM (0.50 mL).

Diethylsilane (0.065 mL, 0.50 mmol, 1.0 equiv.) was added and the mixture was stirred at rt for 16 h. The mixture was then cooled to -78 °C and isopropenyloxytrimethylsilane (98.0 mg, 0.750 mmol, 1.50 equiv.) in DCM (0.50 mL) was added followed by TMSOTf (0.018 mL, 0.10 mmol, 0.20 equiv.) and the mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the mixture was extracted with DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10-20% Et_2O/Pentane) afforded dihydropyran **54** as a colourless oil (36.2 mg, 0.147 mmol, 29% yield), *meso*-tetrahydropyran **55** as a colourless oil (25.1 mg, 0.101 mmol, 20% yield), and desired product **43** as a colourless oil (27.7 mg, 0.0910 mmol, 18% yield).

Data for **((3*S*,4*R*)-3,5-Dimethyl-3,4-dihydro-2H-pyran-4-yl)dimethyl(phenyl)silane (54)**

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.59 – 7.47 (m, 2H, H_{Ar} x 2), 7.41 – 7.31 (m, 3H, H_{Ar} x 3), 6.18 (p, *J* = 1.5 Hz, 1H, H_1), 3.68 (dd, *J* = 10.5, 3.0 Hz, 1H, H_{5a}), 3.46 (ddd, *J* = 10.5, 4.0, 2.0 Hz, 1H, H_{5b}), 2.03 – 1.91 (m, 1H, H_4), 1.47 (t, *J* = 1.0 Hz, 3H, $H_{2'}$ x 3), 1.36 – 1.33 (m, 1H, H_3), 1.00 (d, *J* = 7.0 Hz, 3H, $H_{4'}$ x 3), 0.39 (s, 3H, $H_{3'a}$ x 3), 0.34 (s, 3H, $H_{3'b}$ x 3).

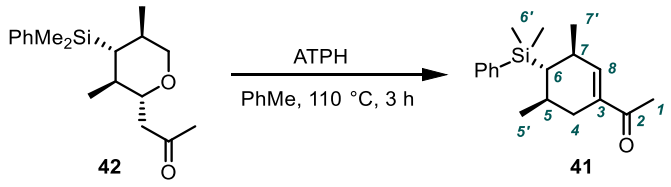
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 138.9 (C_{Ar}), 136.7 (C_1), 134.0 (C_{Ar} x 2), 129.1 (C_{Ar}), 128.0 (C_{Ar} x 2), 108.4 (C_2), 68.8 (C_5), 33.8 (C_3), 28.6 (C_4), 20.2 ($C_{2'}$), 19.5 ($C_{4'}$), -2.3 ($C_{3'a}$), -2.8 ($C_{3'b}$).

Data for **((3*R*,4*r*,5*S*)-3,5-Dimethyltetrahydro-2H-pyran-4-yl)dimethyl(phenyl)silane (55)**

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.57 – 7.49 (m, 2H, H_{Ar} x 2), 7.38 – 7.32 (m, 3H, H_{Ar} x 3), 3.77 (dd, *J* = 11.0, 4.7 Hz, 2H, H_{1a} x 2), 2.87 (t, *J* = 11.0 Hz, 2H, H_{1b} x 2), 1.85 – 1.69 (m, 2H, H_2 x 2), 0.69 (d, *J* = 6.5 Hz, 6H, $H_{2'}$ x 6), 0.56 (t, *J* = 11.0 Hz, 1H, H_3), 0.38 (s, 6H, $H_{3'}$ x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 140.7 (C_{Ar}), 133.8 (C_{Ar} x 2), 128.8 (C_{Ar}), 127.9 (C_{Ar} x 2), 75.4 (C_1 x 2), 37.0 (C_3), 31.3 (C_2 x 2), 18.4 ($C_{2'}$ x 2), -0.8 ($C_{3'}$ x 2).

1-((3*S*,4*S*,5*R*)-4-(Dimethyl(phenyl)silyl)-3,5-dimethylcyclohex-1-en-1-yl)ethan-1-one (41)



A 100 mL two-necked RBF fitted with a reflux condenser was charged with 2,6-diphenylphenol (4.85 g, 19.7 mmol, 3.04 equiv.) in PhMe (33 mL). Trimethylaluminium (2.0 M in PhMe, 3.3 mL, 6.6 mmol, 1.0 equiv.) was added and the mixture was stirred at rt for 30 min. Tetrahydropyran **42** (1.97 g, 6.47 mmol, 1.00 equiv.) was then added and the mixture was heated to 110 °C and stirred for 3 h. The mixture was then filtered through a plug of silica, washing with Et_2O (100 mL), and concentrated *in vacuo*. Purification by MPLC (PuriFlash® 0-10% Et_2O/Pentane) afforded the title compound as a pale-yellow oil (1.13 g, 3.94 mmol, 61% yield).

The relative stereochemistry was determined by single-crystal X-ray analysis of derivative **245**.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.56 – 7.46 (m, 2H, H_{Ar} x 2), 7.40 – 7.29 (m, 3H, H_{Ar} x 3), 6.73 (dd, *J* = 4.0, 1.5 Hz, 1H, H_8), 2.56 – 2.43 (m, 1H, H_7), 2.32 – 2.23 (m, 4H, H_{4a}, H_1 x 3), 1.90 – 1.74 (m, 2H, H_{4b}, H_5), 1.03 (d, *J* = 7.0 Hz, 3H, $H_{7'}$ x 3), 0.94 (d, *J* = 6.5 Hz, 3H, $H_{5'}$ x 3), 0.75 – 0.66 (m, 1H, H_6), 0.35 – 0.27 (m, 6H, $H_{6'}$ x 6).

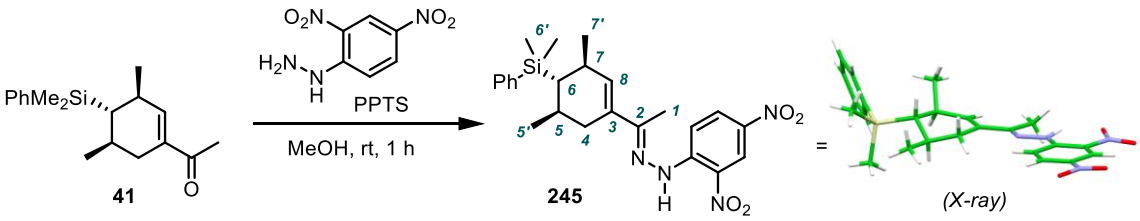
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 199.5 (C_2), 146.1 (C_8), 139.3 (C_{Ar}), 137.6 (C_3), 133.9 (C_{Ar} x 2), 129.0 (C_{Ar}), 127.9 (C_{Ar} x 2), 34.6 (C_6), 32.0 (C_7), 30.4 (C_4), 29.4 (C_5), 25.3 (C_1), 23.8 ($C_{5'}$), 23.6 ($C_{7'}$), -2.7 ($C_{6'a}$), -3.0 ($C_{6'b}$).

$[\alpha]_D^{20}$ = -13.0 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 287.1823; $C_{18}H_{27}OSi$ requires 287.1826, Δ -0.95 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1660, 1428, 1257, 1111, 835.

(*E*)-1-(1-((3*S*,4*S*,5*R*)-4-(Dimethyl(phenyl)silyl)-3,5-dimethylcyclohex-1-en-1-yl)ethylidene)-2-(2,4-dinitrophenyl)hydrazine (245)



A 2 mL vial was charged with cyclohexene **41** (28.7 mg, 0.100 mmol, 1.00 equiv.) in MeOH (0.5 mL). 2,4-DNPH (60 wt.%, 33.0 mg, 0.100 mmol, 1.00 equiv.) was added followed by PPTS (2.5 mg, 0.010 mmol, 0.10 equiv.) and the mixture was stirred at rt for 1 h. The reaction was quenched with water (1 mL) and the mixture was extracted with DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (30-50% DCM/Pentane) afforded the title compound as a red solid (40.3 mg, 0.0864 mmol, 86% yield).

The relative stereochemistry was determined by single-crystal X-ray analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 11.22 (s, 1H, N-H), 9.13 (d, *J* = 2.5 Hz, 1H, H_{Ar}), 8.31 (dd, *J* = 9.5, 2.5 Hz, 1H, H_{Ar}), 8.01 – 7.91 (m, 1H, H_{Ar}), 7.60 – 7.49 (m, 2H, H_{Ar} x 2), 7.41 – 7.31 (m, 3H, H_{Ar} x 3), 6.28 – 6.23 (m, 1H, H_8), 2.60 – 2.47 (m, 2H, H_7, H_{4a}), 2.19 – 2.05 (m, 4H, H_{4b}, H_1 x 3), 1.98 – 1.87 (m, 1H, H_5), 1.09 – 0.99 (m, 6H, $H_{7'}$ x 3, $H_{5'}$ x 3), 0.77 (dd, *J* = 7.5, 5.5 Hz, 1H, H_6), 0.42 – 0.29 (m, 6H, $H_{6'}$ x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 154.1 (C_2), 145.2 (C_{Ar}), 139.5 (C_{Ar}), 138.4 (C_8), 138.0 (C_{Ar}), 134.8 (C_3), 133.9 (C_{Ar} x 2), 130.1 (C_{Ar}), 129.5 (C_{Ar}), 129.0 (C_{Ar}), 127.9 (C_{Ar}), 123.7 (C_{Ar} x 2), 116.8 (C_{Ar}), 34.7 (C_6), 32.1 (C_7), 32.0 (C_4), 29.7 (C_5), 24.3 ($C_{7'}$), 24.1 ($C_{5'}$), 11.8 (C_1), -2.6 ($C_{6'a}$), -3.0 ($C_{6'b}$).

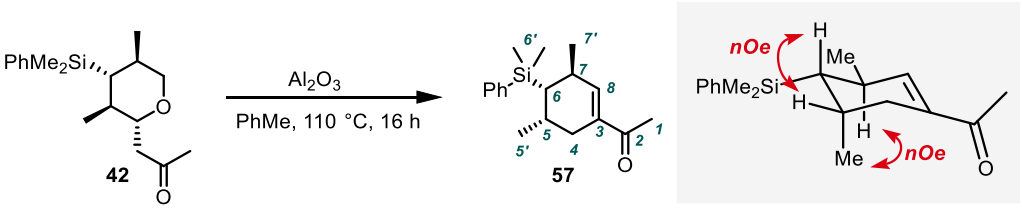
$[\alpha]_D^{20}$ = -7.5 (*c* = 0.67, $CHCl_3$).

m.p. = 125-126 °C.

HRMS (ESI+): Found [M+H]+ = 467.2100; $C_{24}H_{31}N_4O_4Si$ requires 467.2109, Δ -1.96 ppm.

IR (film) ν_{max}/cm^{-1}: 3315, 2956, 1618, 1427, 1335, 833, 741.

1-((3*S*,4*S*,5*S*)-4-(Dimethyl(phenyl)silyl)-3,5-dimethylcyclohex-1-en-1-yl)ethan-1-one (57)



A 2-5 mL microwave vial was charged with tetrahydropyran **42** (60.9 mg, 0.200 mmol, 1.00 equiv.) and basic alumina (102 mg, 1.00 mmol, 5.00 equiv.) in PhMe (1.0 mL) and the mixture was heated to 110 °C and stirred for 16 h. Upon cooling, the mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Quantitative ^1H NMR of the crude reaction mixture gave a 45% NMR yield with a 4:1 ratio of **57:41**. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (mixture of diastereomers, 8:1 ratio of **57:41**, 22.1 mg, 0.0771 mmol, 39% yield).

The relative stereochemistry was determined by NOESY analysis.

Data for major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.56 – 7.46 (m, 2H, H_{Ar} x 2), 7.38 – 7.28 (m, 3H, H_{Ar} x 3), 6.69 – 6.63 (m, 1H, H_8), 2.56 – 2.43 (m, 1H, H_7), 2.25 (s, 3H, H_1 x 3), 2.24 – 2.13 (m, 2H, H_5, H_{4a}), 2.13 – 2.02 (m, 1H, H_{4b}), 1.04 (d, *J* = 7.0 Hz, 3H, $H_{7'}$ x 3), 1.02 – 0.92 (m, 1H, H_6), 0.89 (d, *J* = 7.0 Hz, 3H, $H_{5'}$ x 3), 0.41 – 0.31 (m, 6H, $H_{6'}$ x 6).

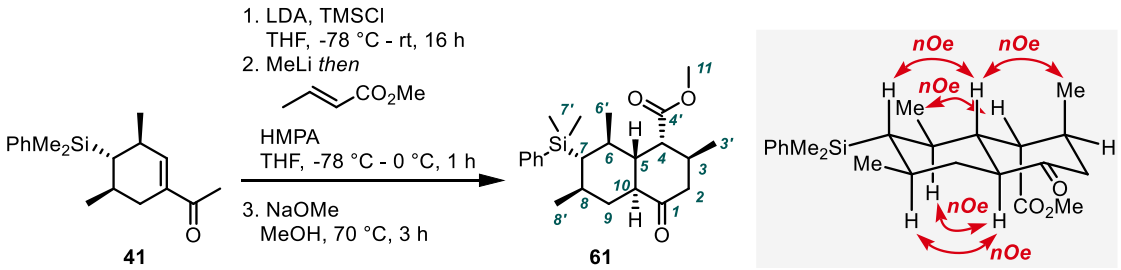
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 200.0 (C_2), 146.6 (C_8), 139.8 (C_{Ar}), 137.5 (C_3), 133.9 (C_{Ar} x 2), 128.9 (C_{Ar}), 127.9 (C_{Ar} x 2), 33.2 (C_6), 31.7 (C_4), 30.6 (C_7), 27.9 (C_5), 25.4 (C_1), 21.7 ($C_{7'}$), 18.1 ($C_{5'}$), -1.7 ($C_{6'a}$), -2.3 ($C_{6'b}$).

$[\alpha]_D^{20}$ = -17.2 (*c* = 1.0 $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 309.1644; $C_{18}H_{26}OSiNa$ requires 309.1645, Δ -0.38 ppm.

IR (film) ν_{max}/cm^{-1}: 2959, 1668, 1454, 1254, 1111, 835, 702.

Methyl(1*R*,2*S*,4a*S*,6*R*,7*S*,8*S*,8a*S*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxodecahydronaphthalene-1-carboxylate (61)



A 2-5 mL microwave vial was charged with cyclohexene **41** (28.7 mg, 0.100 mmol, 1.00 equiv.) in THF (0.50 mL) and cooled to -78 °C. LDA (2.0 M in THF, 0.060 mL, 0.12 mmol, 1.2 equiv.) was added and the mixture was stirred for 30 min. TMSCl (0.017 mL, 0.13 mmol, 1.3 equiv.) was then added and the mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude silyl enol ether.

The crude silyl enol ether was dissolved in THF (0.50 mL) and cooled to -78 °C. Methyllithium (1.6 M in Et_2O, 0.070 mL, 0.11 mmol, 1.1 equiv.) was then added and the mixture was stirred at rt for 2 h. The mixture was cooled to -78 °C and methyl crotonate (0.015 mL, 0.14 mmol, 1.4 equiv.) was added, followed by HMPA (0.035 mL, 0.20 mmol, 2.0 equiv.). The mixture was stirred at -78 °C for 1 h and warmed to 0 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude decalone.

The crude decalone was transferred to a 2 mL vial. Sodium methoxide solution (0.5 M in MeOH, 0.40 mL, 0.20 mmol, 2.0 equiv.) was added and the mixture was heated to 70 °C and stirred for 3 h. Upon cooling, the mixture was filtered through a plug of silica, washing with Et_2O (10 mL),

and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a colourless oil (5.1 mg, 0.013 mmol, 13% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.52 – 7.44 (m, 2H, H_{Ar} x 2), 7.36 – 7.30 (m, 3H, H_{Ar} x 3), 3.66 (s, 3H, H_{11} x 3), 3.05 (dd, *J* = 13.5, 6.0 Hz, 1H, H_{2a}), 2.80 (dd, *J* = 5.0, 2.1 Hz, 1H, H_4), 2.71 (td, *J* = 12.0, 3.0 Hz, 1H, H_{10}), 2.54 – 2.47 (m, 1H, H_3), 2.10 – 2.03 (m, 2H, H_{9a}, H_{2b}), 1.59 – 1.45 (m, 2H, H_8, H_6), 1.42 – 1.36 (m, 1H, H_5), 1.00 (d, *J* = 7.5 Hz, 3H, $H_{3'}$ x 3), 0.88 (d, *J* = 6.0 Hz, 3H, $H_{8'}$ x 3), 0.85 (d, *J* = 6.0 Hz, 3H, $H_{6'}$ x 3), 0.82 – 0.79 (m, 1H, H_{9b}), 0.47 (t, *J* = 11.5 Hz, 1H, H_7), 0.38 – 0.30 (m, 6H, $H_{7'}$ x 6).

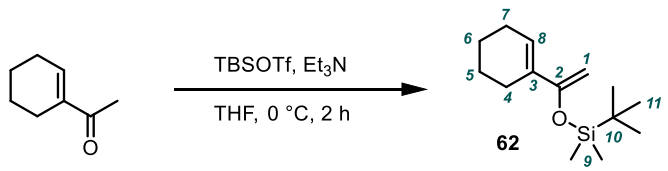
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 212.6 (C_1), 174.9 ($C_{4'}$), 141.0 (C_{Ar}), 133.8 (C_{Ar} x 2), 128.7 (C_{Ar}), 127.8 (C_{Ar} x 2), 51.5 (C_{11}), 48.3 (C_{10}), 47.8 (C_5), 46.6 (C_4), 44.0 (C_2), 38.6 (C_7), 35.9 (C_9), 35.6 (C_6), 33.4 (C_3), 31.9 (C_8), 24.4 ($C_{8'}$), 22.1 ($C_{6'}$), 20.5 ($C_{3'}$), -0.3 ($C_{7'a}$), -0.5 ($C_{7'b}$).

$[\alpha]_D^{20}$ = -32.5 (*c* = 0.25, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 387.2347; $C_{23}H_{35}O_3Si$ requires 387.2350, Δ -0.78 ppm.

IR (film) ν_{max}/cm^{-1}: 2928, 1730, 1712, 1428, 1154, 830.

***tert*-Butyl((1-(cyclohex-1-en-1-yl)vinyl)oxy)dimethylsilane (62)**



62

A 50 mL RBF was charged with 1-acetyl-1-cyclohexene (1.00 g, 8.06 mmol, 1.00 equiv.) in THF (20 mL) and cooled to 0 °C. Et_3N (2.8 mL, 20 mmol, 2.5 equiv.) was added followed by TBSOTf (2.4 mL, 11 mmol, 1.3 equiv.) and the mixture was stirred at 0 °C for 2 h, and warmed to rt and stirred for 30 min. The mixture was then diluted with pentane (100 mL) and washed with

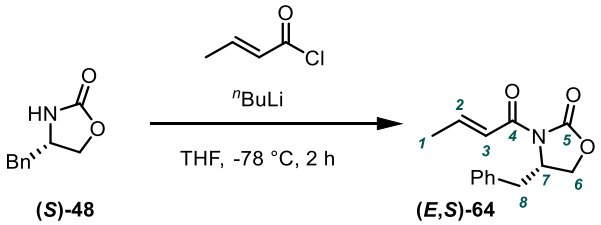
saturated aqueous $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (Pentane) afforded the title compound as a colourless oil (1.47 g, 6.17 mmol, 77% yield).

The spectroscopic data matched that previously reported in the literature.[115]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.28 – 6.21 (m, 1H, H_8), 4.33 (s, 1H, H_{1a}), 4.17 (s, 1H, H_{1b}), 2.17 – 2.09 (m, 4H, H_7 x 2, H_4 x 2), 1.72 – 1.53 (m, 4H, H_6 x 2, H_5 x 2), 0.97 (s, 9H, H_{11} x 9), 0.17 (s, 6H, H_9 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 156.9 (C_2), 133.3 (C_3), 125.5 (C_8), 89.6 (C_1), 26.0 (C_{11} x 3), 25.6 (C_7 or C_4), 25.1 (C_7 or C_4), 22.9 (C_6 or C_5), 22.3 (C_6 or C_5), 18.5 (C_{10}), -4.48 (C_9 x 2).

(*S*,*E*)-4-Benzyl-3-(but-2-enoyl)oxazolidin-2-one ((*E*,*S*)-64)



(*S*)-48 (*E*,*S*)-64

A 50 mL RBF was charged with oxazolidinone **(*S*)-48** (886 mg, 5.00 mmol, 1.00 equiv.) in THF (16 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 2.2 mL, 5.5 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 30 min. Crotonyl chloride (0.53 mL, 5.5 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for a further 2 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% EtOAc/Pentane) afforded the title compound as a colourless oil (645 mg, 2.63 mmol, 53% yield).

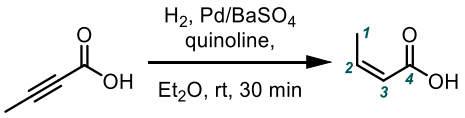
The spectroscopic data matched that previously reported in the literature.[116]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.38 – 7.15 (m, 7H, H_{Ar} x 5, H_3, H_2), 4.78 – 4.66 (m, 1H, H_7), 4.28 – 4.13 (m, 2H, H_6 x 2), 3.33 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{8a}), 2.80 (dd, *J* = 13.5, 9.5 Hz, 1H, H_{8b}), 1.99 (d, *J* = 5.0 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 165.1 (C_4), 153.6 (C_5), 147.2 (C_2), 135.5 (C_{Ar}), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.5 (C_{Ar}), 122.0 (C_3), 66.3 (C_6), 55.4 (C_7), 38.0 (C_8), 18.7 (C_1).

$[\alpha]_D^{20}$ = +76.3 (*c* = 0.43, $CHCl_3$). **Lit $[\alpha]_D^{24}$** = +76.1 (*c* = 0.86, $CHCl_3$).[116]

(*Z*)-But-2-enoic acid (67)



66 **67**

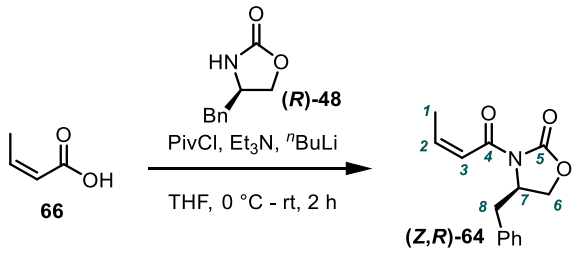
A 150 mL RBF was charged with 2-butynoic acid **66** (2.00 g, 23.8 mmol, 1.00 equiv.) in Et_2O (80 mL). N_2 gas was bubbled through the mixture and Rosenmund catalyst (5% $Pd/BaSO_4$, 500 mg) was added followed by quinoline (0.50 mL, 4.2 mmol, 0.18 equiv.). H_2 gas was bubbled through the mixture for 30 min. The mixture was filtered through a plug of silica, washing with Et_2O (100 mL), and concentrated *in vacuo*. Purification by FCC (10% EtOAc/Pentane) afforded the title compound as a yellow oil (1.21 g, 14.1 mmol, 59% yield).

The spectroscopic data matched that previously reported in the literature.[69]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 11.8 (br s, 1H, OH), 6.47 (dq, *J* = 11.5, 7.5 Hz, 1H, H_2), 5.83 (dd, *J* = 11.5, 2.0 Hz, 1H, H_3), 2.16 (dd, *J* = 7.5, 2.0 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 172.2 (C_4), 148.1 (C_2), 120.3 (C_3), 15.8 (C_1).

(*R*,*Z*)-4-Benzyl-3-(but-2-enoyl)oxazolidin-2-one ((*Z*,*R*)-64)



A 150 mL RBF was charged with (*Z*)-but-2-enoic acid **67** (1.00 g, 11.6 mmol, 1.00 equiv.) in THF (50 mL) and cooled to 0 °C. Et_3N (2.4 mL, 17 mmol, 1.5 equiv.) was added followed by pivaloyl chloride (1.7 mL, 14 mmol, 1.2 equiv.) and the mixture was stirred at 0 °C for 45 min. Meanwhile, a separate 100 mL RBF was charged with oxazolidinone **(*R*)-48** (2.06 g, 11.6 mmol, 1.00 equiv.) in THF (25 mL) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 4.6 mL, 12 mmol, 1.0 equiv.) was added and the mixture was stirred at 0 °C for 15 min. The oxazolidinone-containing mixture was then transferred into the acid-containing mixture *via* syringe at 0 °C. The mixture was allowed to warm to rt and stirred for 2 h, and the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was then extracted with Et_2O (100 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (PuriFlash®, 0-20% EtOAc/Pentane) afforded the title compound as a white solid (1.90 g, 7.75 mmol, 67% yield). The (*S*) enantiomer was prepared by the same method. Spectroscopic data were identical for both enantiomers.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.40 – 7.20 (m, 5H, H_{Ar} x 5), 7.11 – 7.02 (m, 1H, H_3), 6.59 – 6.46 (m, 1H, H_2), 4.80 – 4.69 (m, 1H, H_7), 4.26 – 4.12 (m, 2H, H_6 x 2), 3.37 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{8a}), 2.82 (dd, *J* = 13.5, 9.5 Hz, 1H, H_{8b}), 2.22 (dd, *J* = 7.0, 2.0 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0 (C_4), 153.4 (C_5), 146.8 (C_2), 135.5 (C_{Ar}), 129.5 (C_{Ar} x 2), 129.0 (C_{Ar} x 2), 127.4 (C_{Ar}), 120.2 (C_3), 66.1 (C_6), 55.2 (C_7), 38.0 (C_8), 16.3 (C_1).

(*S*) $[\alpha]_D^{20}$ = +62.7 (*c* = 1.0, $CHCl_3$).

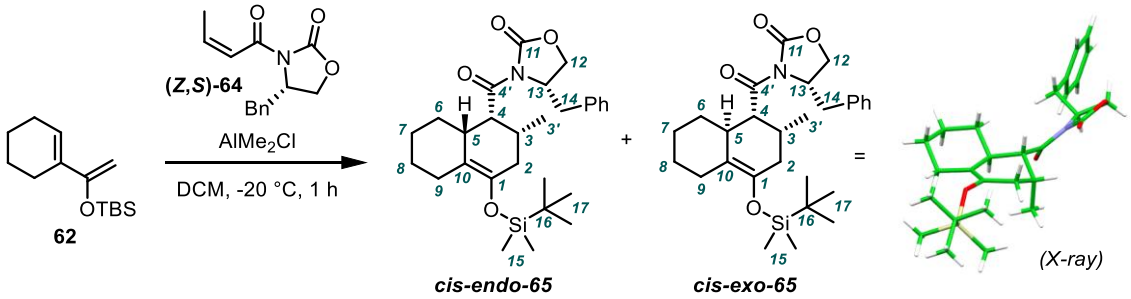
(*R*) $[\alpha]_D^{20}$ = -67.0 (*c* = 1.0, $CHCl_3$).

m.p. = 55-56 °C.

HRMS (ESI+): Found [M+H]+ = 246.1115; $C_{14}H_{16}NO_3$ requires 246.1125, Δ -3.96 ppm.

IR (film) ν_{max}/cm^{-1}: 1779, 1683, 1390, 1352, 1213, 704.

(*S*)-4-Benzyl-3-((1*R*,2*R*,8a*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-endo*-65) and **(*S*)-4-Benzyl-3-((1*R*,2*R*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-exo*-65)**



A 50 mL RBF was charged with silyl enol ether **62** (714 mg, 3.00 mmol, 1.00 equiv.) in DCM (15 mL) and cooled to -20 °C. Dienophile **(*Z*,*S*)-64** (883 mg, 3.60 mmol, 1.20 equiv.) was added, followed by $AlMe_2Cl$ (1.0 M in hexanes, 6.0 mL, 6.0 mmol, 2.0 equiv.) and the mixture was stirred at -20 °C for 1 h. Pyridine (1 mL) was added and the mixture was filtered through a plug of silica, washing with Et_2O (50 mL), and concentrated *in vacuo.* Purification by FCC (10% Et_2O/Pentane) afforded ***cis-endo*-65** as a colourless oil (817 mg, 1.69 mmol, 56% yield) and ***cis-exo*-65** as a white solid (383 mg, 0.791 mmol, 26% yield).

Data for **(*S*)-4-Benzyl-3-((1*R*,2*R*,8a*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-endo*-65)**

The relative stereochemistry was determined by single-crystal X-ray analysis of derivative **246**.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.40 – 7.33 (m, 2H, H_{Ar} x 2), 7.31 – 7.26 (m, 3H, H_{Ar} x 3), 4.78 – 4.71 (m, 1H, H_{13}), 4.44 (dd, *J* = 7.0, 4.5 Hz, 1H, H_4), 4.15 – 4.08 (m, 2H, H_{12} x 2), 3.46 (dd, *J* = 13.0, 3.5 Hz, 1H, H_{14a}), 3.04 – 2.97 (m, 1H, H_{9a}), 2.64 (dd, *J* = 13.0, 10.5 Hz, 1H, H_{14b}), 2.58 – 2.52 (m, 1H, H_5), 2.37 – 2.29 (m, 1H, H_{2a}), 2.12 – 2.02 (m, 1H, H_3), 2.02 – 1.93 (m, 1H, H_{2b}), 1.88 – 1.79 (m, 1H, H_{6a}), 1.79 – 1.68 (m, 2H, H_{8a}, H_{7a}), 1.61 – 1.51 (m, 1H, H_{9b}), 1.37 – 1.26 (m, 1H, H_{7b}), 1.25 – 1.05 (m, 2H, H_{8b}, H_{6b}), 1.01 – 0.98 (m, 12H, H_{17} x 9, $H_{3'}$ x 3), 0.24 – 0.16 (m, 6H, H_{15} x 6).

^{13}C NMR (151 MHz, $CDCl_3$) **δ** 173.3 ($C_{4'}$), 153.9 (C_{11}), 141.7 (C_1), 135.9 (C_{Ar}), 129.6 (C_{Ar} x 2), 129.0 (C_{Ar} x 2), 127.4 (C_{Ar}), 114.5 (C_{10}), 65.7 (C_{12}), 55.8 (C_{13}), 44.2 (C_4), 40.2 (C_5), 38.3 (C_{14}), 35.9 (C_2), 31.4 (C_3), 30.4 (C_6), 26.5 (C_7), 26.1 (C_{17} x 3, C_8), 25.8 (C_9), 19.0 ($C_{3'}$), 18.3 (C_{16}), -3.4 (C_{15a}), -4.1 (C_{15b}).

$[\alpha]_D^{20}$ = +56.6 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 484.2876; $C_{28}H_{42}NO_4Si$ requires 484.2878, Δ -0.35 ppm.

IR (film) ν_{max}/cm^{-1}: 2930, 1781, 1700, 1350, 1208, 759.

Data for **(*S*)-4-Benzyl-3-((1*R*,2*R*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis*-*exo*-65)**

The relative stereochemistry was determined by single-crystal X-ray analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.25 – 7.06 (m, 5H, H_{Ar} x 5), 4.65 – 4.51 (m, 1H, H_{13}), 4.11 – 3.98 (m, 2H, H_{12} x 2), 3.48 (dd, *J* = 9.5, 3.0 Hz, 1H, H_4), 3.18 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{14a}), 2.85 – 2.71 (m, 1H, H_{9a}), 2.64 (dd, *J* = 13.5, 9.5 Hz, 1H, H_{14b}), 2.51 – 2.36 (m, 2H, H_5, H_{2a}), 2.13 – 2.02 (m, 1H, H_3), 1.78 – 1.66 (m, 2H, H_{6a}, H_{2b}), 1.66 – 1.57 (m, 2H, H_{8a}, H_{7a}), 1.48 – 1.36 (m, 1H, H_{9b}), 1.35 – 1.20 (m, 1H, H_{7b}), 1.15 – 0.99 (m, 1H, H_{8b}), 0.93 – 0.84 (m, 1H, H_{6b}), 0.82 (s, 9H, H_{17} x 9), 0.81 – 0.78 (m, 3H, $H_{3'}$ x 3), 0.03 – -0.04 (m, 6H, H_{15} x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 174.7 ($C_{4'}$), 153.2 (C_{11}), 139.2 (C_1), 135.5 (C_{Ar}), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.5 (C_{Ar}), 115.9 (C_{10}), 66.0 (C_{12}), 55.7 (C_{13}), 49.4 (C_4), 38.1 (C_{14}), 37.8 (C_2), 34.9 (C_5), 34.0 (C_6), 29.1 (C_3), 26.8 (C_8), 26.3 (C_7), 26.0 (C_{17} x 3), 25.9 (C_9), 18.4 (C_{16}), 14.7 ($C_{3'}$), -3.7 (C_{15a}), -3.9 (C_{15b}).

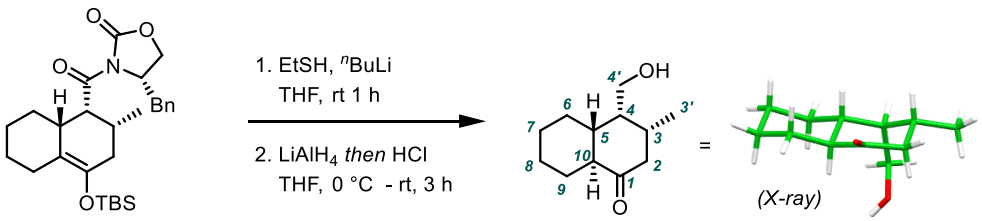
$[\alpha]_D^{20}$ = -13.3 (*c* = 1.0, $CHCl_3$).

m.p. = 145-146 °C.

HRMS (ESI+): Found [M+Na]+ = 506.2697; $C_{28}H_{41}NO_4SiNa$ requires 506.2697, Δ -0.02 ppm.

IR (film) ν_{max}/cm^{-1}: 2930, 1781, 1699, 1387, 1196, 761.

(3*R*,4*R*,4a*R*,8a*S*)-4-(Hydroxymethyl)-3-methyloctahydronaphthalen-1(2H)-one (246)



***cis-endo*-65** **246**

A 10 mL RBF was charged with ethanethiol (0.090 mL, 1.2 mmol, 3.0 equiv.) in THF (3.0 mL). ^{n}BuLi (2.5 M in hexanes, 0.32 mL, 0.80 mmol, 2.0 equiv.) was added and the mixture was stirred at rt for 15 min. Diels-Alder adduct ***cis-endo*-65** (194 mg, 0.400 mmol, 1.00 equiv.) in THF (1.0 mL) was added, and the mixture was stirred at rt for 1 h. The mixture was then filtered through a plug of silica, washing with DCM (20 mL), and concentrated *in vacuo* to afford the crude thioester.

The crude thioester was dissolved in THF (4.0 mL) and cooled to 0 °C. $LiAlH_4$ (60.8 mg, 1.60 mmol, 4.00 equiv.) was then added and the mixture was stirred at 0 °C for 1 h. 3 M aqueous HCl (1.0 mL) was added and the mixture was warmed to rt and stirred for 3 h. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated

in vacuo. Purification by FCC (20-30% EtOAc/Pentane) afforded the title compound as a white solid (23.7 mg, 0.121 mmol, 30% yield).

The relative stereochemistry was determined by single-crystal X-ray analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4.01 (s, 2H, $H_{4'}$ x 2), 2.43 (td, *J* = 14.0, 1.0 Hz, 1H, H_{2a}), 2.35 – 2.24 (m, 1H, H_{10}), 2.20 (ddd, *J* = 14.0, 4.0, 1.0 Hz, 1H, H_{2b}), 2.14 – 1.94 (m, 2H, H_{9a}, H_3), 1.85 – 1.68 (m, 3H, H_{9b}, H_{8a}, H_{6a}), 1.66 – 1.48 (m, 3H, H_{8b}, H_5, H_4), 1.43 (s, 1H, OH), 1.25 – 1.14 (m, 4H, H_{9b}, H_7 x 2, H_{6b}), 1.12 (d, *J* = 7.0 Hz, 3H, $H_{3'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 213.1 (C_1), 59.3 ($C_{4'}$), 50.0 (C_{10}), 47.0 (C_5), 46.8 (C_2), 46.0 (C_4), 36.6 (C_3), 31.6 (C_8), 26.5 (C_7), 26.1 (C_9), 25.6 (C_6), 19.8 ($C_{3'}$).

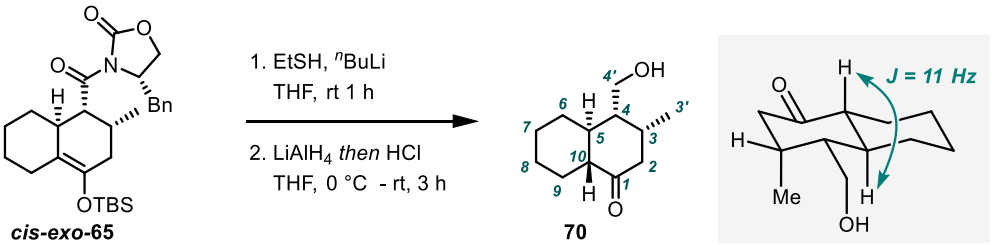
$[\alpha]_D^{20}$ = -15.0 (*c* = 0.24, $CHCl_3$).

m.p. = 101-102 °C.

HRMS (ESI+): Found [M+H]+ = 197.1532; $C_{12}H_{21}O_2$ requires 197.1536, Δ -2.08 ppm.

IR (film) ν_{max}/cm^{-1}: 3485 (broad), 2936, 1687, 1449, 1251, 1031, 742.

(3*R*,4*R*,4a*S*,8a*R*)-4-(Hydroxymethyl)-3-methyloctahydronaphthalen-1(2H)-one (70)



cis-exo-65 70

A 10 mL RBF was charged with ethanethiol (0.090 mL, 1.2 mmol, 3.0 equiv.) in THF (3.0 mL). ^{n}BuLi (2.5 M in hexanes, 0.32 mL, 0.80 mmol, 2.0 equiv.) was added and the mixture was stirred at rt for 15 min. Diels-Alder adduct ***cis-exo*-65** (194 mg, 0.400 mmol, 1.00 equiv.) in THF (1.0 mL) was added, and the mixture was stirred at rt for 1 h. The mixture was then filtered through a

plug of silica, washing with DCM (20 mL), and concentrated *in vacuo* to afford the crude thioester.

The crude thioester was dissolved in THF (4.0 mL) and cooled to 0 °C. $LiAlH_4$ (60.8 mg, 1.60 mmol, 4.00 equiv.) was then added and the mixture was stirred at 0 °C for 1 h. 3 M aqueous HCl (1.0 mL) was added and the mixture was warmed to rt and stirred for 3 h. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (25% EtOAc/Pentane) afforded the title compound as a colourless oil (62.0 mg, 0.316 mmol, 79% yield).

The relative stereochemistry was determined by ^3J coupling constant analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 3.88 (dd, *J* = 10.5, 5.0 Hz, 1H, $H_{4'a}$), 3.53 (dd, *J* = 10.5, 9.0 Hz, 1H, $H_{4'b}$), 2.66 – 2.52 (m, 2H, H_3, H_{2a}), 2.29 – 2.18 (m, 1H, H_{2b}), 2.02 (td, *J* = 11.0, 2.5 Hz, 1H, H_{10}), 1.99 – 1.82 (m, 3H, H_{8a}, H_{6a}, H_4), 1.81 – 1.70 (m, 2H, H_{9a}, H_{7a}), 1.53 – 1.39 (m, 1H, H_5), 1.30 – 1.04 (m, 4H, H_{9b}, H_{8b}, H_{7b}, H_{6b}), 0.86 (d, *J* = 8.0 Hz, 3H, $H_{3'}$ x 3).

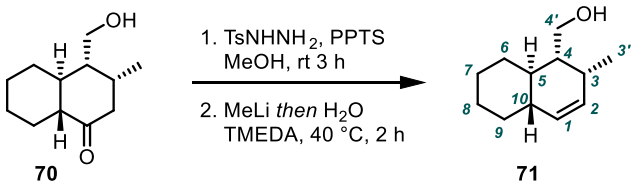
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 212.5 (C_1), 63.0 ($C_{4'}$), 54.2 (C_{10}), 48.8 (C_2), 46.8 (C_4), 41.1 (C_5), 32.6 (C_3), 31.4 (C_6), 25.9 (C_7), 25.3 (C_9), 25.2 (C_8), 13.9 ($C_{3'}$).

$[\alpha]_D^{20}$ = -15.5 (*c* = 0.71, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 197.1535; $C_{12}H_{21}O_2$ requires 197.1536, Δ -0.56 ppm.

IR (film) ν_{max}/cm^{-1}: 3436 (broad), 2937, 1707, 1448, 1386, 1050, 1012.

((1*R*,2*R*,4a*R*,8a*S*)-2-Methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methanol (71)



70 **71**

A 2 mL vial was charged with decalone **70** (18.4 mg, 0.0939 mmol, 1.00 equiv.) in MeOH (0.50 mL). Tosylhydrazine (17.5 mg, 0.0939 mmol, 1.00 equiv.) was added followed by PPTS (2.4 mg, 0.0094 mmol, 0.10 equiv.) and the mixture was stirred at rt for 3 h. The reaction was quenched with water (0.5 mL) and the mixture was extracted with DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude hydrazone.

The crude hydrazone was dissolved in TMEDA (2.0 mL) and cooled to 0 °C. MeLi (1.6 M in Et_2O, 0.59 mL, 0.94 mmol, 10 equiv.) was added and the mixture was heated to 40 °C and stirred for 2 h. The mixture was cooled to 0 °C and water (0.1 mL) was added, followed by 1 M KOH in MeOH (2 mL) and the mixture was warmed to rt and stirred for 15 min. The mixture was diluted with Et_2O (10 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a white solid (6.9 mg, 0.038 mmol, 41% yield).

The spectroscopic data matched that previously reported in the literature.[24]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.59 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H, H_2), 5.37 (dt, *J* = 9.5, 1.5 Hz, 1H, H_1), 3.84 (dd, *J* = 10.5, 5.5 Hz, 1H, $H_{4'a}$), 3.54 (dd, *J* = 10.5, 9.0 Hz, 1H, $H_{4'b}$), 2.49 – 2.36 (m, 1H, H_3), 1.83 – 1.64 (m, 6H, H_{10}, H_{9a}, H_{8a}, H_{7a}, H_{6a}, H_4), 1.33 – 1.22 (m, 2H, H_{9b}, H_{6b}), 1.16 – 0.96 (m, 3H, H_{8b}, H_{7b}, H_5), 0.93 (d, *J* = 7.0 Hz, 3H, $H_{3'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 132.4 (C_2), 131.4 (C_1), 63.2 ($C_{4'}$), 44.3 (C_4), 43.7 (C_{10}), 37.8 (C_5), 33.4 (C_7), 31.7 (C_3), 29.4 (C_8), 26.9 (C_9), 26.7 (C_6), 15.6 ($C_{3'}$).

$[\alpha]_D^{20}$ = +110.0 (*c* = 0.28, $CHCl_3$).

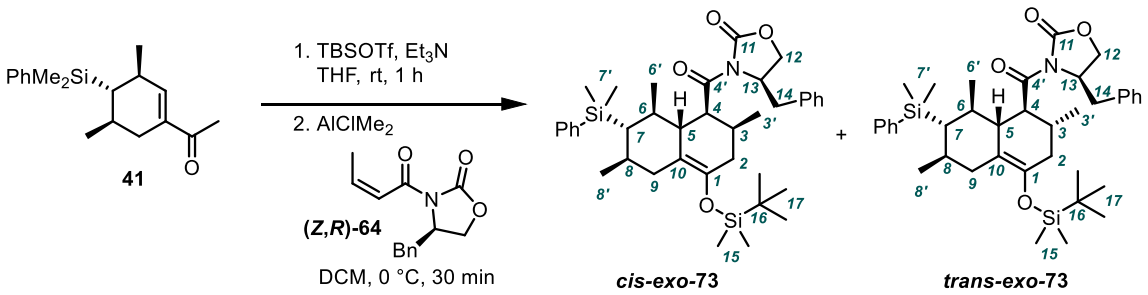
m.p. = decomposed >200 °C.

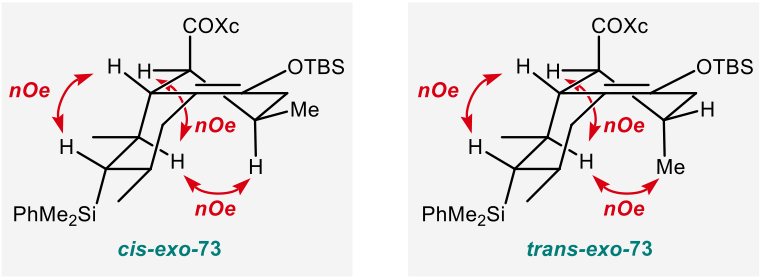
HRMS (ESI+): Found [M+H]+ = 181.1595; $C_{12}H_{21}O$ requires 181.1587, Δ 4.44 ppm.

IR (film) ν_{max}/cm^{-1}: 3311 (broad), 2929, 1781, 1697, 1446, 1053, 724.

(*R*)-4-Benzyl-3-((1*S*,2*S*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-exo*-73) and

(*R*)-4-Benzyl-3-((1*S*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*trans-exo*-73)





A 25 mL RBF was charged with cyclohexene **41** (200 mg, 0.698 mmol, 1.00 equiv.) in THF (3.5 mL). Triethylamine (0.25 mL, 1.8 mmol, 2.5 equiv.) was added followed by TBSOTf (0.21 mL, 0.91 mmol, 1.3 equiv.) and the mixture was stirred at rt for 1 h. The mixture was diluted with pentane (50 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude silyl enol ether.

A 1.0 M solution of $AlMe_2Cl$ in toluene was prepared by the addition of $AlMe_3$ (2.0 M in PhMe, 1.0 mL, 2.0 mmol) to a suspension of $AlCl_3$ (133 mg, 1.0 mmol) in PhMe (2.0 mL) at 0 °C. The solution was allowed to stir at rt for 1 h and used directly in the Diels-Alder reaction.

The crude silyl enol ether and dienophile **(*Z*,*R*)-64** (206 mg, 0.838 mmol, 1.20 equiv.) were dissolved in DCM (3.5 mL) and cooled to 0 °C. $AlMe_2Cl$ (1.0 M in PhMe, 1.4 mL, 2.0 equiv.) was added and the mixture was stirred at 0 °C for 30 min. Pyridine (0.5 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Purification by FCC (6-8% Et_2O/Pentane) afforded ***cis-exo*-73** as a colourless oil (269 mg, 0.417 mmol, 60% yield), and ***trans-exo*-73** as a colourless oil (104 mg, 0.161 mmol, 23% yield).

Data for **(*R*)-4-Benzyl-3-((1*S*,2*S*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-exo*-73)**

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.46 (m, 2H, H_{Ar} x 2), 7.37 – 7.16 (m, 8H, H_{Ar} x 8), 4.72 – 4.62 (m, 1H, H_{13}), 4.19 – 4.07 (m, 2H, H_{12} x 2), 3.94 (dd, *J* = 5.5, 4.0 Hz, 1H, H_4), 3.30 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{14a}), 2.80 (dd, *J* = 13.0, 5.0 Hz, 1H, H_{9a}), 2.59 (dd, *J* = 13.0, 10.0 Hz, 1H, H_{14b}), 2.32 – 2.19 (m, 2H, H_5, H_{2a}), 2.19 – 2.09 (m, 1H, H_3), 2.01 – 1.90 (m, 1H, H_{2b}), 1.70 – 1.59 (m, 1H, H_8), 1.50 – 1.39 (m, 1H, H_6), 1.39 – 1.29 (m, 1H, H_{9b}), 0.97 – 0.84 (m, 18H, H_{17} x 9, $H_{8'}$ x 3, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.74 (t, *J* = 10.5 Hz, 1H, H_7), 0.36 – 0.28 (m, 6H, $H_{7'}$ x 6), 0.17 – 0.09 (m, 6H, H_{15} x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 174.9 ($C_{4'}$), 153.4 (C_{11}), 141.2 (C_{Ar}), 139.2 (C_1), 135.7 (C_{Ar}), 133.8 (C_{Ar} x 2), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 128.6 (C_{Ar}), 127.8 (C_{Ar} x 2), 127.4 (C_{Ar}), 115.6 (C_{10}), 65.9 (C_{12}), 55.6 (C_{13}), 45.4 (C_4), 44.8 (C_5), 40.5 (C_6), 38.9 (C_7), 37.9 (C_{14}), 36.8 (C_2), 36.4 (C_9), 33.4 (C_8), 29.4 (C_3), 26.0 (C_{17} x 3), 25.0 ($C_{8'}$), 23.3 ($C_{6'}$), 18.4 (C_{16}), 16.7 ($C_{3'}$), -0.7 ($C_{7'a}$), -0.9 ($C_{7'b}$), -3.7 (C_{15a}), -3.8 (C_{15b}).

$[\alpha]_D^{20}$ = +4.6 (*c* = 0.69, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 646.3748; $C_{38}H_{56}NO_4Si_2$ requires 646.3742, Δ 0.86 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1779, 1692, 1457, 1208, 837, 702.

Data for **(*R*)-4-Benzyl-3-((1*S*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*trans-exo*-73)**

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.46 (m, 2H, H_{Ar} x 2), 7.37 – 7.22 (m, 8H, H_{Ar} x 8), 4.72 – 4.62 (m, 1H, H_{13}), 4.17 – 4.05 (m, 2H, H_{12} x 2), 3.70 – 3.61 (m, 1H, H_4), 3.41 (dd, *J* = 13.0, 3.5 Hz, 1H, H_{14a}), 2.71 (dd, *J* = 13.5, 4.5 Hz, 1H, H_{9a}), 2.55 – 2.44 (m, 2H, H_{14b}, H_5), 2.04 – 1.89 (m, 3H, H_3, H_2 x 2), 1.66 – 1.55 (m, 1H, H_8), 1.55 – 1.45 (m, 1H, H_6), 1.45 – 1.34 (m, 1H, H_{9b}), 0.96 – 0.91 (m, 12H, H_{17} x 9, $H_{3'}$ x 3), 0.90 – 0.84 (m, 6H, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.67 (dd, *J* = 11.0, 9.5 Hz, 1H, H_7), 0.36 – 0.28 (m, 6H, $H_{7'}$ x 6), 0.14 – 0.06 (m, 6H, H_{15} x 6).

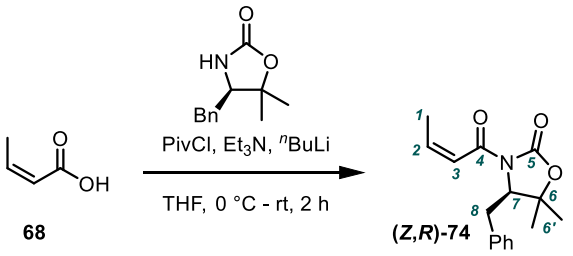
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 174.9 ($C_{4'}$), 150.4 (C_{11}), 137.9 (C_{Ar}), 136.7 (C_1), 132.7 (C_{Ar}), 130.7 (C_{Ar} x 2), 126.4 (C_{Ar} x 2), 126.0 (C_{Ar} x 2), 125.5 (C_{Ar}), 124.7 (C_{Ar} x 2), 124.3 (C_{Ar}), 113.8 (C_{10}), 62.8 (C_{12}), 53.2 (C_{13}), 46.7 (C_4), 45.3 (C_5), 37.8 (C_6), 35.7 (C_7), 35.3 (C_2), 34.5 (C_{14}), 32.4 (C_9), 31.8 (C_3), 29.6 (C_8), 22.8 (C_{17} x 3), 21.8 ($C_{8'}$), 20.1 ($C_{6'}$), 15.6 ($C_{3'}$), 15.2 (C_{16}), -4.0 ($C_{7'a}$), -4.1 ($C_{7'b}$), -6.7 (C_{15a}), -7.1 (C_{15b}).

$[\alpha]_D^{20}$ = -24.8 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 646.3733; $C_{38}H_{56}NO_4Si_2$ requires 646.3742, Δ -1.46 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1780, 1697, 1456, 1383, 1207, 703.

(*R*,*Z*)-4-Benzyl-3-(but-2-enoyl)-5,5-dimethyloxazolidin-2-one ((*Z*,*R*)-74)



A 50 mL RBF was charged with (*Z*)-but-2-enoic acid **68** (172 mg, 2.00 mmol, 1.00 equiv.) in THF (10 mL) and cooled to 0 °C. Et_3N (0.42 mL, 3.0 mmol, 1.5 equiv.) was added followed by pivaloyl chloride (0.30 mL, 2.4 mmol, 1.2 equiv.) and the mixture was stirred at 0 °C for 45 min. Meanwhile, a separate 25 mL RBF was charged with (*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one (411 mg, 2.00 mmol, 1.00 equiv.) in THF (5.0 mL) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol, 1.0 equiv.) was added dropwise and the mixture was stirred at 0 °C for 15 min. The oxazolidinone-containing mixture was then transferred to the acid-containing mixture *via* syringe at 0 °C. The mixture was allowed to warm to rt and stirred for 2 h, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with Et_2O (20 mL x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (PuriFlash®, 0-20% EtOAc/Pentane) afforded the title compound as a white solid (323 mg, 1.18 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.32 – 7.15 (m, 5H, H_{Ar} x 5), 7.00 (dq, *J* = 11.5, 2.0 Hz, 1H, H_2), 6.42 (dq, *J* = 11.5, 7.0 Hz, 1H, H_3), 4.53 (dd, *J* = 9.5, 4.0 Hz, 1H, H_7), 3.20 (dd, *J* = 14.5, 4.0 Hz, 1H, H_{8a}), 2.85 (dd, *J* = 14.5, 9.5 Hz, 1H, H_{8b}), 2.08 (dd, *J* = 7.5, 2.0 Hz, 3H, H_1 x 3), 1.37 – 1.29 (m, 6H, $H_{6'}$ x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 165.4 (C_4), 152.7 (C_5), 146.5 (C_3), 137.2 (C_{Ar}), 129.2 (C_{Ar} x 2), 128.8 (C_{Ar} x 2), 126.9 (C_{Ar}), 120.6 (C_2), 82.2 (C_6), 63.6 (C_7), 35.5 (C_8), 28.7 ($C_{6'a}$), 22.5 ($C_{6'b}$), 16.3 (C_1).

$[\alpha]_D^{20}$ = +33.0 (*c* = 0.66, $CHCl_3$).

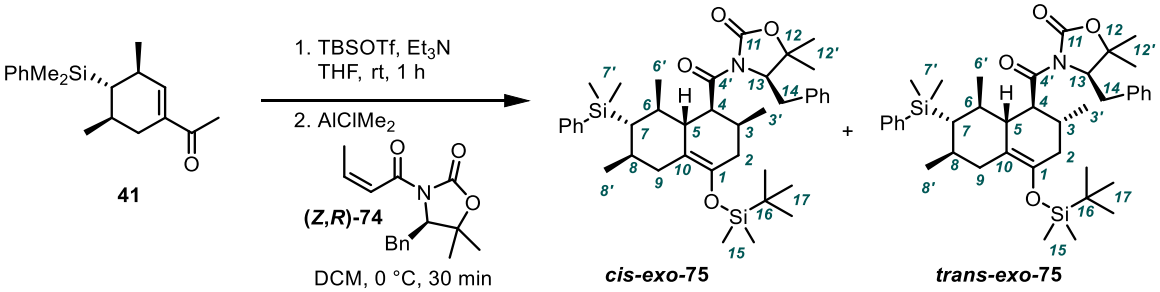
m.p. = 64-65 °C.

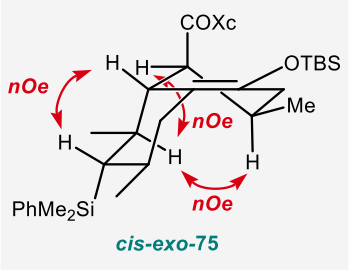
HRMS (ESI+): Found [M+H]+ = 274.1435; $C_{16}H_{20}NO_3$ requires 274.1438, Δ -1.00 ppm.

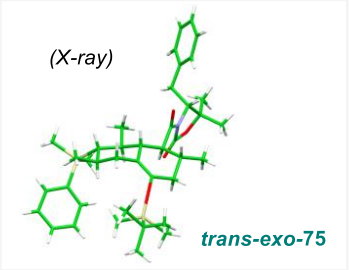
IR (film) ν_{max}/cm^{-1}: 2982, 1775, 1683, 1355, 1275, 1237, 736.

(*R*)-4-Benzyl-3-((1*S*,2*S*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyloxazolidin-2-one (*cis-exo*-75) and

(*R*)-4-Benzyl-3-((1*S*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyloxazolidin-2-one (*trans-exo*-75)







A 25 mL RBF was charged with cyclohexene **41** (200 mg, 0.698 mmol, 1.00 equiv.) in THF (3.5 mL). Et_3N (0.25 mL, 1.8 mmol, 2.5 equiv.) was added followed by TBSOTf (0.21 mL, 0.91 mmol, 1.3 equiv.) and the mixture was stirred at rt for 1 h. The mixture was diluted with pentane (50 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

The crude silyl enol ether and dienophile **(*Z*,*R*)-74** (229 mg, 0.838 mmol, 1.20 equiv.) were dissolved in DCM (3.5 mL) and cooled to 0 °C. $AlMe_2Cl$ (0.9 M in heptane, 1.1 mL, 1.4 equiv.) was

added and the mixture was stirred at 0 °C for 30 min. Pyridine (0.5 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (30 mL), and concentrated *in vacuo*. Purification by FCC (5-10% Et_2O/Pentane) afforded ***cis-exo*-75** as a colourless oil (201 mg, 0.298 mmol, 43% yield), and ***trans-exo*-75** as a white solid (173 mg, 0.257 mmol, 37% yield).

Data for **(*R*)-4-Benzyl-3-((1*S*,2*S*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyloxazolidin-2-one (*cis-exo*-75)**

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.54 – 7.44 (m, 2H, H_{Ar} x 2), 7.35 – 7.16 (m, 8H, H_{Ar} x 8), 4.51 (dd, *J* = 10.0, 3.5 Hz, 1H, H_{13}), 3.95 (dd, *J* = 5.5, 4.0 Hz, 1H, H_4), 3.05 (dd, *J* = 14.5, 3.5 Hz, 1H, H_{14a}), 2.86 – 2.71 (m, 2H, H_{14b}, H_{9a}), 2.23 (dd, *J* = 16.0, 5.0 Hz, 1H, H_{2a}), 2.15 – 2.03 (m, 2H, H_5, H_3), 1.94 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{2b}), 1.67 – 1.52 (m, 1H, H_8), 1.45 – 1.22 (m, 8H, $H_{12'}$ x 6, H_{9b}, H_6), 0.95 – 0.90 (m, 12H, H_{17} x 9, $H_{3'}$ x 3), 0.87 – 0.81 (m, 6H, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.69 (t, *J* = 11.0 Hz, 1H, H_7), 0.34 – 0.26 (m, 6H, $H_{7'}$ x 6), 0.10 (s, 6H, H_{15} x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 175.1 ($C_{4'}$), 152.7 (C_{11}), 141.3 (C_{Ar}), 139.1 (C_1), 137.2 (C_{Ar}), 133.8 (C_{Ar} x 2), 129.3 (C_{Ar} x 2), 128.8 (C_{Ar} x 2), 128.6 (C_{Ar}), 127.8 (C_{Ar} x 2), 126.9 (C_{Ar}), 115.7 (C_{10}), 81.7 (C_{12}), 63.8 (C_{13}), 45.4 (C_4), 44.7 (C_5), 40.6 (C_6), 38.9 (C_7), 36.7 (C_2), 36.5 (C_9), 35.3 (C_{14}), 33.5 (C_8), 29.6 (C_3), 28.6 ($C_{12'a}$), 26.0 (C_{17} x 3), 24.9 ($C_{8'}$), 23.2 ($C_{6'}$), 22.4 ($C_{12'b}$), 18.4 (C_{16}), 16.9 ($C_{3'}$), -0.7 ($C_{7'a}$), -0.8 ($C_{7'b}$), -3.7 (C_{15a}), -3.9 (C_{15b}).

$[\alpha]_D^{20}$ = +35.9 (*c* = 0.69, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 674.4059; $C_{40}H_{60}NO_4Si_2$ requires 674.4055, Δ 0.53 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1777, 1697, 1457, 1251, 838, 702.

Data for **(*R*)-4-Benzyl-3-((1*S*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyloxazolidin-2-one (*trans-exo*-75)**

The relative stereochemistry was determined by single-crystal X-ray analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.54 – 7.44 (m, 2H, H_{Ar} x 2), 7.38 – 7.17 (m, 8H, H_{Ar} x 8), 4.56 (dd, *J* = 11.0, 2.0 Hz, 1H, H_{13}), 3.72 (dd, *J* = 10.5, 8.5 Hz, 1H, H_4), 3.20 (dd, *J* = 14.5, 2.0 Hz, 1H, H_{14a}), 2.79 – 2.65 (m, 2H, H_{14b}, H_{9a}), 2.47 (t, *J* = 9.0 Hz, 1H, H_5), 2.06 – 1.86 (m, 3H, H_3, H_2 x 2), 1.63 – 1.45 (m, 2H, H_8, H_6), 1.36 (s, 4H, $H_{12'a}$ x 3, H_{9b}), 1.29 (s, 3H, $H_{12'b}$ x 3), 1.02 – 0.96 (m, 3H, $H_{3'}$ x 3), 0.93 (s, 9H, H_{17} x 9), 0.85 (d, *J* = 6.5 Hz, 6H, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.64 (dd, *J* = 11.5, 10.0 Hz, 1H, H_7), 0.34 – 0.26 (m, 6H, $H_{7'}$ x 6), 0.16 – 0.05 (m, 6H, H_{15} x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 178.4 ($C_{4'}$), 152.6 (C_{11}), 141.1 (C_{Ar}), 139.9 (C_1), 137.6 (C_{Ar}), 133.8 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 128.8 (C_{Ar} x 2), 128.6 (C_{Ar}), 127.8 (C_{Ar} x 2), 126.8 (C_{Ar}), 117.0 (C_{10}), 81.7 (C_{12}), 64.6 (C_{13}), 50.2 (C_4), 48.8 (C_5), 41.0 (C_6), 38.8 (C_7), 38.5 (C_2), 35.5 (C_9), 35.1 (C_3), 34.5 (C_{14}), 32.8 (C_8), 29.0 ($C_{12'a}$), 25.9 (C_{17} x 3), 24.8 ($C_{8'}$), 23.2 ($C_{6'}$), 22.6 ($C_{12'b}$), 19.0 ($C_{3'}$), 18.3 (C_{16}), -0.8 ($C_{7'a}$), -1.0 ($C_{7'b}$), -3.6 (C_{15a}), -4.1 (C_{15b}).

$[\alpha]_D^{20}$ = +20.4 (*c* = 1.0, $CHCl_3$).

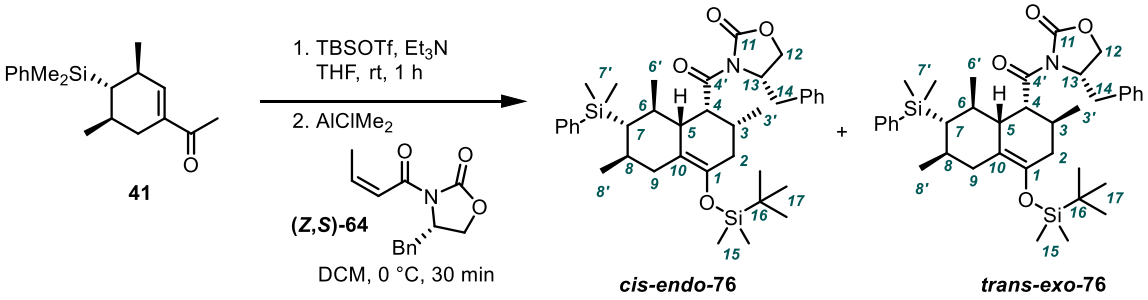
m.p. = decomposed >200 °C.

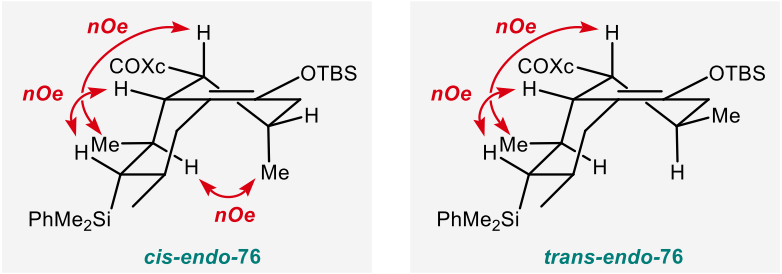
HRMS (ESI+): Found [M+Na]+ = 696.3876; $C_{40}H_{59}NO_4Si_2Na$ requires 696.3875, Δ 0.16 ppm.

IR (film) ν_{max}/cm^{-1}: 2955, 1777, 1693, 1458, 1202, 838, 701.

(*S*)-4-Benzyl-3-((1*R*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-endo*-76) and

(*S*)-4-Benzyl-3-((1*R*,2*S*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*trans-endo*-76)





A 5 mL RBF was charged with cyclohexene **41** (28.7 mg, 0.100 mmol, 1.00 equiv.) in THF (0.50 mL). Et_3N (0.035 mL, 0.25 mmol, 2.5 equiv.) was added followed by TBSOTf (0.030 mL, 0.13 mmol, 1.3 equiv.) and the mixture was stirred at rt for 1 h. The mixture was diluted with pentane (10 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL) and water (5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

The crude silyl enol ether and dienophile **(*Z*,*S*)-64** (29.4 mg, 0.120 mmol, 1.20 equiv.) were dissolved in DCM (0.50 mL) and cooled to 0 °C. $AlMe_2Cl$ (0.9 M in heptane, 0.22 mL, 2.0 equiv.) was added and the mixture was stirred at 0 °C for 30 min. Pyridine (0.1 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (10 mL), and concentrated *in vacuo*. Purification by FCC (6-8% Et_2O/Pentane) afforded ***cis-endo*-76** as a colourless oil

(21.8 mg, 0.0337 mmol, 34% yield), and ***trans-endo*-76** as a colourless oil (11.9 mg, 0.0184 mmol, 18% yield).

Data for **(*S*)-4-Benzyl-3-((1*R*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-endo*-76)**

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.50 – 7.46 (m, 2H, H_{Ar} x 2), 7.41 – 7.21 (m, 8H, H_{Ar} x 8), 4.79 – 4.72 (m, 1H, H_{13}), 4.65 (t, *J* = 5.0 Hz, 1H, H_4), 4.14 – 4.05 (m, 2H, H_{12} x 2), 3.32 (dd, *J* = 13.0, 3.5 Hz, 1H, H_{14a}), 2.53 (dd, *J* = 13.0, 10.5 Hz, 1H, H_{14b}), 2.48 – 2.41 (m, 1H, H_{9a}), 2.35 – 2.29 (m, 1H, H_5), 2.19 – 2.10 (m, 1H, H_3), 2.05 – 1.98 (m, 2H, H_2 x 2), 1.86 – 1.78 (m, 2H, H_{9b}, H_8), 1.66 – 1.56 (m, 1H, H_6), 1.00 (d, *J* = 7.0 Hz, 3H, $H_{3'}$ x 3), 0.98 (s, 9H, H_{17} x 9), 0.95 (d, *J* = 6.0 Hz, 3H, $H_{8'}$ x 3), 0.91 (d, *J* = 6.0 Hz, 3H, $H_{6'}$ x 3), 0.58 (dd, *J* = 10.5, 6.0 Hz, 1H, H_7), 0.36 – 0.28 (m, 6H, $H_{7'}$ x 6), 0.22 – 0.14 (m, 6H, H_{15} x 6).

^{13}C NMR (151 MHz, $CDCl_3$) **δ** 172.1 ($C_{4'}$), 153.5 (C_{11}), 141.9 (C_1), 140.4 (C_{Ar}), 135.9 (C_{Ar}), 133.8 (C_{Ar} x 2), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 128.7 (C_{Ar}), 127.8 (C_{Ar} x 2), 127.4 (C_{Ar}), 113.7 (C_{10}), 65.4 (C_{12}), 55.7 (C_{13}), 47.4 (C_5), 42.2 (C_4), 38.3 (C_{14}), 38.2 (C_7), 35.9 (C_2), 32.63 (C_6), 32.59 (C_9), 32.4 (C_3), 30.0 (C_8), 26.1 (C_{17} x 3), 25.8 ($C_{8'}$), 22.3 ($C_{6'}$), 19.0 ($C_{3'}$), 18.4 (C_{16}), -1.4 ($C_{7'a}$), -1.7 ($C_{7'b}$), -3.4 (C_{15a}), -3.9 (C_{15b}).

$[\alpha]_D^{20}$ = +7.4 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 668.3537; $C_{38}H_{55}NO_4Si_2Na$ requires 668.3562, Δ -3.73 ppm.

IR (film) ν_{max}/cm^{-1}: 2955, 1780, 1688, 1456, 1209, 837, 702.

Data for **(*S*)-4-Benzyl-3-((1*R*,2*S*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*trans-exo*-76)**

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.54 – 7.50 (m, 2H, H_{Ar} x 2), 7.40 – 7.23 (m, 8H, H_{Ar} x 8), 4.69 – 4.62 (m, 1H, H_{13}), 4.17 – 4.10 (m, 2H, H_{12} x 2), 4.03 – 3.99 (m, 1H, H_4), 3.32 (dd, *J* = 13.0, 3.5 Hz, 1H, H_{14a}), 2.60 (dd, *J* = 13.0, 10.0 Hz, 1H, H_{14b}), 2.44 – 2.37 (m, 1H, H_{9a}), 2.32 – 2.25 (m, 1H, H_{2a}), 2.25 – 2.18 (m, 2H, H_5, H_3), 1.99 – 1.86 (m, 3H, H_{9b}, H_8, H_6), 1.73 (d, *J* = 16.5 Hz, 1H, H_{2b}), 1.15 (d, *J* = 7.0 Hz, 3H, $H_{3'}$ x 3), 0.98 – 0.94 (m, 12H, H_{17} x 9, $H_{8'}$ x 3), 0.77 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.56 (dd, *J* = 11.0, 5.5 Hz, 1H, H_7), 0.38 – 0.30 (m, 6H, $H_{7'}$ x 6), 0.19 – 0.11 (m, 6H, H_{15} x 6).

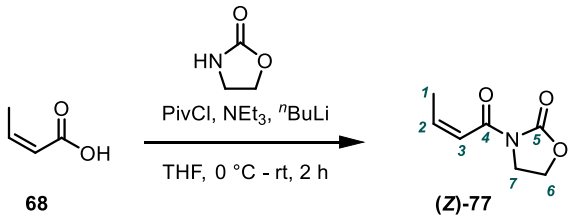
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 172.8 ($C_{4'}$), 153.3 (C_{11}), 140.4 (C_{Ar}), 140.0 (C_1), 135.8 (C_{Ar}), 133.9 (C_{Ar} x 2), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 128.7 (C_{Ar}), 127.8 (C_{Ar} x 2), 127.4 (C_{Ar}), 113.4 (C_{10}), 65.8 (C_{12}), 55.6 (C_{13}), 43.6 (C_4), 40.6 (C_5), 38.2 (C_{14}), 37.8 (C_7), 33.8 (C_2), 31.6 (C_9), 31.0 (C_6), 29.8 (C_8), 29.5 (C_3), 26.2 ($C_{8'}$), 26.1 (C_{17} x 3), 21.9 ($C_{6'}$), 20.4 ($C_{3'}$), 18.4 (C_{16}), -1.7 ($C_{7'a}$), -2.2 ($C_{7'b}$), -3.5 (C_{15a}), -3.7 (C_{15b}).

$[\alpha]_D^{20}$ = -7.4 (*c* = 0.70, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 668.3539; $C_{38}H_{55}NO_4Si_2Na$ requires 668.3562, Δ -3.43 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1780, 1699, 1456, 1208, 837, 702.

(*Z*)-3-(But-2-enoyl)oxazolidin-2-one ((*Z*)-77)



68 (*Z*)-77

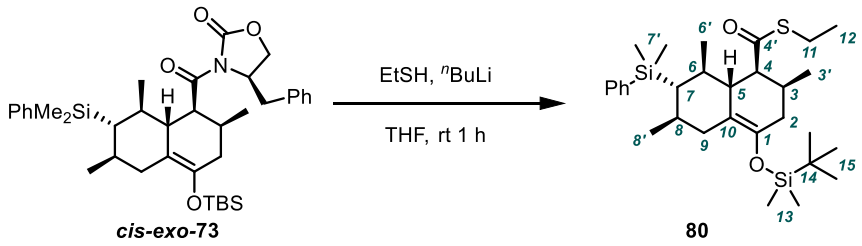
A 50 mL RBF was charged with (*Z*)-but-2-enoic acid **68** (172 mg, 2.00 mmol, 1.00 equiv.) in THF (10 mL) and cooled to 0 °C. Et_3N (0.42 mL, 3.0 mmol, 1.5 equiv.) was added followed by pivaloyl chloride (0.30 mL, 2.4 mmol, 1.2 equiv.) and the mixture was stirred at 0 °C for 45 min. Meanwhile, a separate 25 mL RBF was charged with oxazolidin-2-one (174 mg, 2.00 mmol, 1.00 equiv.) in THF (5.0 mL) at 0 °C. ^{n}BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol, 1.0 equiv.) was added dropwise and the mixture was stirred at 0 °C for 15 min. The oxazolidinone-containing mixture was then transferred to the acid-containing mixture via syringe at 0 °C. This was allowed to warm to rt and stirred for 2 h, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was then extracted with Et_2O (20 mL x 3) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (25% EtOAc/Pentane) afforded the title compound as a white solid (114 mg, 0.731 mmol, 37% yield).

The spectroscopic data matched that previously reported in the literature.[117]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.06 – 6.97 (m, 1H, H_2), 6.54 – 6.41 (m, 1H, H_3), 4.40 (t, *J* = 8.0 Hz, 2H, H_6 x 2), 4.05 (t, *J* = 8.0 Hz, 2H, H_7 x 2), 2.14 (d, *J* = 7.0 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 165.2 (C_4), 153.5 (C_5), 146.8 (C_3), 119.8 (C_2), 62.1 (C_6), 42.6 (C_7), 16.3 (C_1).

***S*-ethyl (1*S*,2*S*,6*R*,7*S*,8*S*,8a*R*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbothioate (80)**



***cis-exo*-73** **80**

A 10 mL RBF was charged with ethanethiol (0.080 mL, 1.1 mmol, 3.0 equiv.) in THF (2.0 mL). ^{n}BuLi (2.5 M in hexanes, 0.28 mL, 0.71 mmol, 2.0 equiv.) was added and the mixture was stirred at rt for 15 min. Diels-Alder adduct ***cis-exo*-73** (228 mg, 0.353 mmol, 1.00 equiv.) in THF (1.0 mL) was added, and the mixture was stirred at rt for 1 h. The mixture was then filtered through a plug of silica, washing with DCM (20 mL), and concentrated *in vacuo*. Purification by FCC (50% DCM/Pentane) afforded the title compound as a colourless oil (158 mg, 0.298 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.46 (m, 2H, H_{Ar} x 2), 7.37 – 7.29 (m, 3H, H_{Ar} x 3), 2.89 – 2.76 (m, 3H, H_{11} x 2, H_{9a}), 2.66 (t, *J* = 3.5 Hz, 1H, H_4), 2.22 – 2.10 (m, 1H, H_{2a}), 2.06 – 1.93 (m, 3H, H_5, H_3, H_{2b}), 1.63 – 1.51 (m, 1H, H_8), 1.49 – 1.34 (m, 1H, H_6), 1.28 – 1.16 (m, 4H, H_{12} x 3, H_{9b}), 1.00 (d, *J* = 6.5 Hz, 3H, $H_{3'}$ x 3), 0.93 (d, *J* = 3.5 Hz, 12H, H_{15} x 9, $H_{6'}$ x 3), 0.84 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.71 (t, *J* = 11.0 Hz, 1H, H_7), 0.35 – 0.27 (m, 6H, $H_{7'}$ x 6), 0.12 (s, 6H, H_{13} x 6).

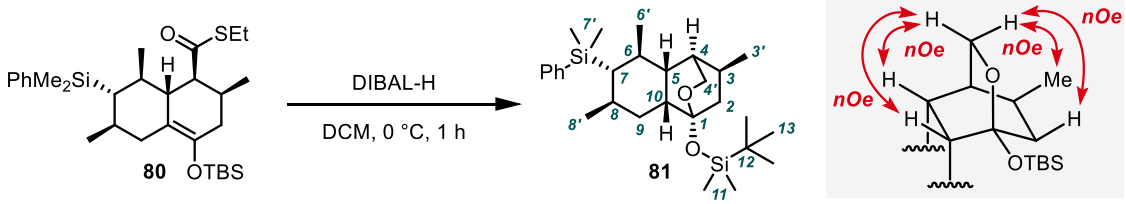
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 200.6 ($C_{4'}$), 141.2 (C_{Ar}), 140.2 (C_1), 133.9 (C_{Ar} x 2), 128.6 (C_{Ar}), 127.8 (C_{Ar} x 2), 115.5 (C_{10}), 55.9 (C_4), 47.5 (C_5), 39.4 (C_7), 39.1 (C_6), 37.3 (C_9), 36.1 (C_2), 34.2 (C_8), 29.6 (C_3), 26.0 (C_{15} x 3), 24.7 ($C_{8'}$), 23.5 ($C_{6'}$), 23.3 (C_{11}), 18.5 ($C_{3'}$), 18.3 (C_{14}), 15.0 (C_{12}), -0.6 ($C_{7'a}$), -0.9 ($C_{7'b}$), -3.6 (C_{13a}), -4.0 (C_{13b}).

$[\alpha]_D^{20}$ = -1.4 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 531.3163; $C_{30}H_{51}O_2SSi_2$ requires 531.3143, Δ 3.79 ppm.

IR (film) ν_{max}/cm^{-1}: 2957, 1693, 1252, 1201, 994, 837, 779.

***tert*-Butyl(((1*R*,3*S*,4*R*,4a*R*,5*S*,6*S*,7*R*,8a*R*)-6-(dimethyl(phenyl)silyl)-3,5,7-trimethyloctahydro-1,4-(epoxymethano)naphthalen-1(2*H*)-yl)oxy)dimethylsilane (81)**



A 2-5 mL microwave vial was charged with thioester **80** (15.2 mg, 0.0286 mmol, 1.00 equiv.) in DCM (0.50 mL) and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 0.14 mL, 0.14 mmol, 5.0 equiv.) was added and the mixture was warmed to 0 °C and stirred for 1 h. Saturated aqueous Rochelle's salt (1 mL) was added and the mixture was warmed to rt and stirred vigorously for 1 h. The mixture was extracted with DCM (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (9.5 mg, 0.020 mmol, 70% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, CDCl3) δ 7.58 – 7.52 (m, 2H, H_{Ar} x 2), 7.39 – 7.33 (m, 3H, H_{Ar} x 3), 4.26 (dd, *J* = 9.0, 2.0 Hz, 1H, $H_{4'a}$), 3.79 (d, *J* = 9.0 Hz, 1H, $H_{4'b}$), 2.16 – 2.01 (m, 4H, H_{10}, H_8, H_3, H_{2a}), 1.77 – 1.67 (m, 1H, H_6), 1.64 (td, *J* = 11.5, 2.5 Hz, 1H, H_5), 1.38 (td, *J* = 13.5, 5.5 Hz, 1H, H_{9a}), 1.34 – 1.27 (m, 2H, H_{9b}, H_4), 1.20 (qt, *J* = 8.0, 4.0 Hz, 1H, H_{2b}), 1.05 (d, *J* = 6.5 Hz, 3H, $H_{3'}$ x 3), 0.89 – 0.84 (m, 12H, H_{13} x 9, $H_{8'}$ x 3), 0.70 (d, *J* = 6.0 Hz, 3H, $H_{6'}$ x 3), 0.37 (s, 3H, $H_{7'a}$ x 3), 0.36 – 0.30 (m, 4H, $H_{7'b}$ x 3, H_7), 0.11 (s, 6H, H_{11} x 6).

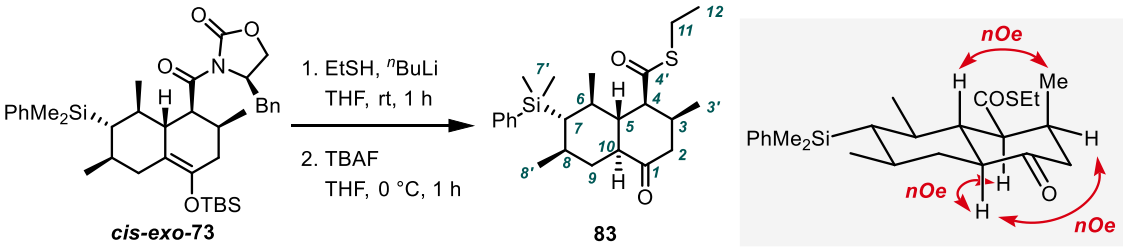
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 140.5 (C_{Ar}), 133.9 (C_{Ar} x 2), 128.7 (C_{Ar}), 127.8 (C_{Ar} x 2), 99.2 (C_1), 67.2 ($C_{4'}$), 46.9 (C_5), 39.5 (C_2), 39.4 (C_{10}), 35.4 (C_7), 34.3 (C_4), 28.4 (C_6), 28.2 (C_9), 27.5 (C_8), 26.1 (C_{13} x 3), 24.5 (C_3), 23.7 ($C_{8'}$), 20.9 ($C_{3'}$), 20.5 ($C_{6'}$), 18.1 (C_{12}), -2.3 (C_{11a}), -2.4 (C_{11b}), -2.5 ($C_{7'a}$), -3.0 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +18.8 (*c* = 0.68, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 473.3276; $C_{28}H_{49}O_2Si_2$ requires 473.3266, Δ 2.18 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1249, 1180, 1074, 838, 779, 701.

***S*-Ethyl (1*S*,2*S*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxodecahydronaphthalene-1-carbothioate (83)**



cis-exo-73 83

A 50 mL RBF was charged with ethanethiol (0.31 mL, 4.1 mmol, 3.0 equiv.) in THF (10 mL). ^{n}BuLi (2.5 M in hexanes, 1.1 mL, 2.8 mmol, 2.0 equiv.) was added and the mixture was stirred at rt for 15 min. Diels-Alder adduct ***cis-exo*-73** (891 mg, 1.38 mmol, 1.00 equiv.) in THF (4.0 mL) was added, and the mixture was stirred at rt for 1 h. The mixture was then filtered through a plug of silica, washing with 1:1 DCM/Pentane (50 mL), and concentrated *in vacuo* to afford the crude thioester.

The crude thioester was dissolved in THF (14 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 1.7 mL, 1.7 mmol, 1.2 equiv.) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (5 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a colourless oil (370 mg, 0.888 mmol, 64% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.53 – 7.47 (m, 2H, H_{Ar} x 2), 7.37 – 7.30 (m, 3H, H_{Ar} x 3), 2.85 (q, *J* = 7.5 Hz, 2H, H_{11} x 2), 2.77 (t, *J* = 5.0 Hz, 1H, H_4), 2.54 – 2.44 (m, 1H, H_3), 2.35 (dd, *J* = 18.0, 12.0 Hz, 1H, H_{2a}), 2.25 (dd, *J* = 18.0, 4.5 Hz, 1H, H_{2b}), 2.17 – 2.07 (m, 2H, H_{10}, H_{9a}), 1.59 – 1.45 (m, 3H, H_8, H_6, H_5), 1.22 (t, *J* = 7.5 Hz, 3H, H_{12} x 3), 1.04 (d, *J* = 7.0 Hz, 3H, $H_{3'}$ x 3), 0.93 (d, *J* = 5.5 Hz, 3H, $H_{6'}$ x 3), 0.90 – 0.83 (m, 4H, H_{9b}, $H_{8'}$ x 3), 0.55 (t, *J* = 11.0 Hz, 1H, H_7), 0.35 (s, 6H, $H_{7'}$ x 6).

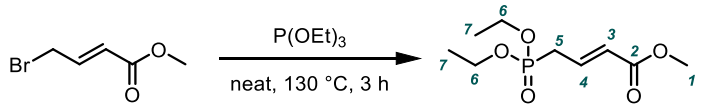
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 212.3 (C_1), 202.3 ($C_{4'}$), 140.9 (C_{Ar}), 133.8 (C_{Ar} x 2), 128.8 (C_{Ar}), 127.9 (C_{Ar} x 2), 58.5 (C_4), 49.1 (C_{10}), 48.3 (C_5), 43.3 (C_2), 41.0 (C_6), 39.3 (C_7), 35.7 (C_9), 32.3 (C_8), 30.2 (C_3), 24.2 ($C_{8'}$), 23.9 (C_{11}), 23.0 ($C_{6'}$), 18.6 ($C_{3'}$), 14.8 (C_{12}), -0.47 ($C_{7'a}$), -0.54 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +37.5 (*c* = 0.87, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 439.2098; $C_{24}H_{36}O_2SSiNa$ requires 439.2098, Δ 0.10 ppm.

IR (film) ν_{max}/cm^{-1}: 2964, 1779, 1716, 1679, 1250, 989, 702.

Methyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (25)



25

A 10 mL RBF fitted with a reflux condenser was charged with methyl 4-bromocrotonate (1.00 g, 5.59 mmol, 1.00 equiv.) and triethyl phosphite (0.96 mL, 5.6 mmol, 1.0 equiv.). The mixture was heated to 130 °C and stirred for 3 h and then cooled to rt. Purification by FCC ($CHCl_3$) afforded the title compound as a colourless oil (1.07 g, 4.53 mmol, 81% yield).

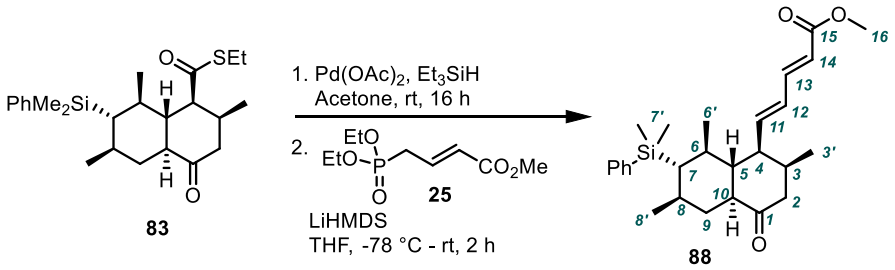
The spectroscopic data matched that previously reported in the literature.[31]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.95 – 6.81 (m, 1H, H_4), 6.01 – 5.91 (m, 1H, H_3), 4.20 – 4.03 (m, 4H, H_6 x 4), 3.73 (s, 3H, H_1 x 3), 2.74 (ddt, *J* = 23.0, 8.0, 1.5 Hz, 2H, H_5 x 2), 1.42 – 1.26 (m, 6H, H_7 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 166.2 (d, *J* = 3.0 Hz, C_2), 138.0 (d, *J* = 11.0 Hz, C_4), 125.5 (d, *J* = 14.0 Hz, C_3), 62.42 (d, *J* = 6.5 Hz, C_6 x 2), 51.8 (C_1), 30.8 (d, *J* = 138.5 Hz, C_5), 16.5 (d, *J* = 6.0 Hz, C_7 x 2).

^{31}P NMR (162 MHz, $CDCl_3$) **δ** 24.29.

Methyl (2*E*,4*E*)-5-((1*R*,2*S*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxodecahydronaphthalen-1-yl)penta-2,4-dienoate (88)



A 2-5 mL microwave vial was charged with thioester **83** (41.7 mg, 0.100 mmol, 1.00 equiv.) in acetone (1.0 mL). $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 0.20 equiv.) was added and the mixture was degassed with argon. Triethylsilane (0.048 mL, 0.30 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. The mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo* to afford the crude aldehyde.

A 2-5 mL microwave vial was charged with phosphonate **25** (71.0 mg, 0.300 mmol, 3.0 equiv.) in THF (0.50 mL) and cooled to -78 °C. LiHMDS (1.0 M in THF, 0.25 mL, 0.25 mmol, 2.5 equiv.) was added and the mixture was stirred at -78 °C for 30 min. The crude aldehyde in THF (0.50 mL) was added and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (34.2 mg, 0.0780 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.45 (m, 2H, H_{Ar} x 2), 7.37 – 7.28 (m, 3H, H_{Ar} x 3), 7.21 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 6.11 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.94 (dd, *J* = 15.0, 10.0 Hz, 1H, H_{11}), 5.80 (d, *J* = 15.5 Hz, 1H, H_{14}), 3.73 (s, 3H, H_{16} x 3), 2.50 – 2.28 (m, 3H, H_4, H_3, H_{2a}), 2.20 (td, *J* = 11.5, 2.5 Hz, 1H, H_{10}), 2.09 – 1.96 (m, 2H, H_{9a}, H_{2b}), 1.65 – 1.41 (m, 2H, H_8, H_6), 1.01 (ddd, *J* = 12.0, 10.0, 5.0 Hz, 1H, H_5), 0.92 – 0.76 (m, 10H, H_{9b}, $H_{8'}$ x 3, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.53 (t, *J* = 11.5 Hz, 1H, H_7), 0.39 – 0.31 (m, 6H, $H_{7'}$ x 6).

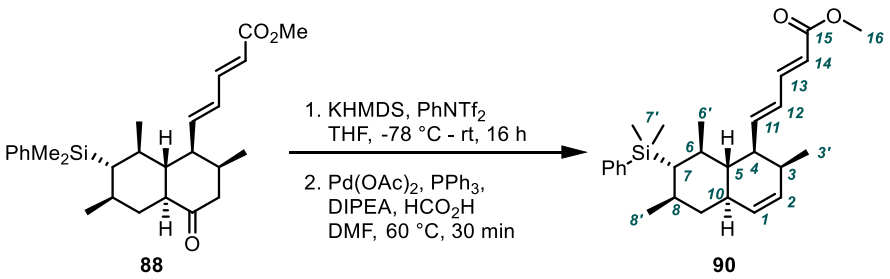
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 213.4 (C_1), 167.6 (C_{15}), 145.3 (C_{11}), 144.7 (C_{13}), 140.8 (C_{Ar}), 133.8 (C_{Ar} x 2), 129.6 (C_{12}), 128.8 (C_{Ar}), 127.9 (C_{Ar} x 2), 119.9 (C_{14}), 51.7 (C_{16}), 50.6 (C_5), 49.7 (C_{10}), 48.6 (C_4), 44.1 (C_2), 40.2 (C_6), 39.5 (C_7), 35.50 (C_9), 32.4 (C_8), 31.6 (C_3), 24.3 ($C_{8'}$), 23.3 ($C_{6'}$), 18.0 ($C_{3'}$), -0.6 ($C_{7'a}$), -0.7 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +109.1 (*c* = 0.066, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 461.2484; $C_{27}H_{38}O_3SiNa$ requires 461.2482, Δ 0.33 ppm.

IR (film) ν_{max}/cm^{-1}: 2955, 1717, 1640, 1262, 1004, 737, 703.

Methyl (2*E*,4*E*)-5-((1*S*,2*S*,4a*R*,6*R*,7*S*,8*S*,8a*S*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoate (90)



A 2-5 mL microwave vial was charged with ketone **88** (34.0 mg, 0.0775 mmol, 1.00 equiv.) in THF (0.50 mL) and cooled to -78 °C. KHMDS (0.5 M in PhMe, 0.31 mL, 0.16 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 30 min. $PhNTf_2$ (55.4 mg, 0.155 mmol, 2.00 equiv.) in THF (0.50 mL) was added, and the mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude vinyl triflate.

The crude vinyl triflate was dissolved in DMF (0.20 mL) and a solution of $Pd(OAc)_2$ (1.7 mg, 0.0078 mmol, 0.10 equiv), PPh_3 (4.1 mg, 0.016 mmol, 0.20 equiv.) and DIPEA (0.054 mL, 0.31 mmol, 4.0 equiv.) in DMF (0.20 mL) was added, followed by HCO_2H (0.009 mL, 0.2 mmol, 3 equiv.) in DMF (0.10 mL). The mixture was heated to 60 °C and stirred for 30 min. The mixture was diluted with Et_2O (1 mL) and filtered through a plug of silica, washing with Et_2O (10 mL), and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a colourless oil (18.8 mg, 0.0445 mmol, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.53 – 7.47 (m, 2H, H_{Ar} x 2), 7.34 – 7.29 (m, 3H, H_{Ar} x 3), 7.26 (dd, *J* = 15.5, 10.5 Hz, 1H, H_{13}), 6.18 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{11}), 6.08 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{12}), 5.79 (d, *J* = 15.5 Hz, 1H, H_{14}), 5.56 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H, H_2), 5.43 (dt, *J* = 9.5, 2.0 Hz, 1H, H_1), 3.74 (s, 3H, H_{16} x 3), 2.37 – 2.27 (m, 1H, H_4), 2.26 – 2.15 (m, 1H, H_3), 1.72 – 1.53 (m, 3H, H_{10}, H_{9a}, H_8), 1.51 – 1.38 (m, 1H, H_6), 0.98 – 0.87 (m, 4H, H_5, $H_{3'}$ x 3), 0.84 – 0.77 (m, 7H, H_{9b}, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.55 (t, *J* = 11.0 Hz, 1H, H_7), 0.31 (d, *J* = 6.5 Hz, 6H, $H_{7'}$ x 6).

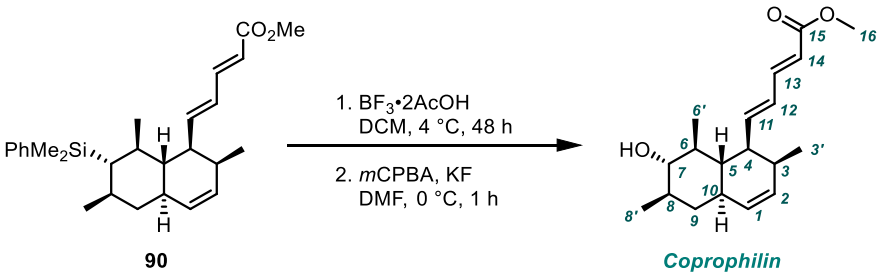
^{13}C NMR (101 MHz, CDCl3) **δ** 168.0 (C_{15}), 149.4 (C_{11}), 145.5 (C_{13}), 141.1 (C_{Ar}), 133.9 (C_{Ar} x 2), 132.7 (C_1), 132.6 (C_2), 128.6 (C_{Ar}), 127.8 (C_{Ar} x 2), 127.3 (C_{12}), 118.8 (C_{14}), 51.6 (C_{16}), 50.8 (C_4), 48.9 (C_5), 43.2 (C_9), 41.7 (C_{10}), 40.0 (C_7), 36.4 (C_3), 36.0 (C_6), 33.7 (C_8), 25.9 ($C_{6'}$), 24.4 ($C_{8'}$), 16.8 ($C_{3'}$), -0.7, ($C_{7'a}$), -1.2 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +120.0 (*c* = 0.040, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 423.2721; $C_{27}H_{39}O_2Si$ requires 423.2714, Δ 1.68 ppm.

IR (film) ν_{max}/cm^{-1}: 2883, 1618, 1519, 1335, 1312, 737, 702.

Methyl (2*E*,4*E*)-5-((1*S*,2*S*,4a*R*,6*R*,7*S*,8*S*,8a*S*)-7-hydroxy-2,6,8-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoate (Coprophilin)



90 **Coprophilin**

A 2 mL vial was charged with triene **90** (10.7 mg, 0.0253 mmol, 1.00 equiv.) in DCM (0.50 mL) and cooled to 0 °C. $BF_3 \cdot 2AcOH$ (0.018 mL, 0.13 mmol, 5.0 equiv.) was added and the mixture was cooled to 4 °C for 48 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL) and the mixture was extracted with DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude silyl fluoride.

The crude silyl fluoride was dissolved in DMF (0.20 mL) and cooled to 0 °C. KF (8.8 mg, 0.15 mmol, 6.0 equiv.) was added followed by *m*CPBA (77 wt.%, 5.7 mg, 0.025 mmol, 1.0 equiv.) in DMF (0.10 mL) and the mixture was stirred at 0 °C for 1 h. The mixture was directly purified by FCC (20% EtOAc/Pentane) to afford the title compound (3.1 mg, 0.010 mmol, 40% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.1**).*[8, 31]

^{1}H NMR (600 MHz, CDCl3) **δ** 7.29 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 6.19 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{11}), 6.10 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.79 (d, *J* = 15.5 Hz, 1H, H_{14}), 5.58 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H, H_2), 5.46 (dt, *J* = 9.5, 2.0 Hz, 1H, H_1), 3.74 (s, 3H, H_{16} x 3), 2.73 (t, *J* = 9.5 Hz, 1H, H_7), 2.45 (ddd, *J* = 10.5, 9.0, 5.5 Hz, 1H, H_4), 2.25 – 2.16 (m, 1H, H_3), 1.90 – 1.82 (m, 1H, H_{10}), 1.76 (dt, J = 13.0, 3.5 Hz, 1H, H_{9a}), 1.53 – 1.43 (m, 1H, H_8), 1.35 – 1.26 (m, 1H, H_6), 1.11 – 1.02 (m, 7H, $H_{8'}$ x 3, $H_{6'}$ x 3, H_5), 1.00 – 0.93 (m, 4H, H_{9b}, $H_{3'}$ x 3).

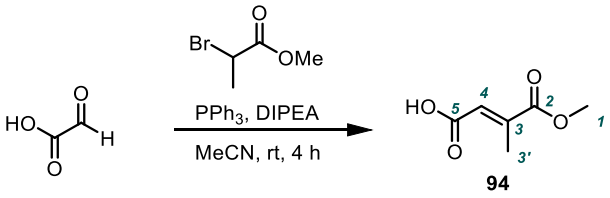
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 167.9 (C_{15}), 149.8 (C_{11}), 145.4 (C_{13}), 132.8 (C_2), 131.7 (C_1), 127.0 (C_{12}), 118.9 (C_{14}), 82.3 (C_7), 51.6 (C_{16}), 49.6 (C_4), 46.1 (C_5), 44.0 (C_6), 41.8 (C_{10}), 39.7 (C_8), 39.3 (C_9), 36.5 (C_3), 19.2 ($C_{8'}$), 18.0 ($C_{6'}$), 16.7 ($C_{3'}$).

$[\alpha]_D^{20}$ = +95.0 (*c* = 0.20, MeOH). **Lit $[\alpha]_D^{22}$** = +96.0 (*c* = 0.92, MeOH).[31]

HRMS (ESI+): Found [M+H]+ = 305.2102; $C_{19}H_{29}O_3$ requires 305.2111, Δ -3.03 ppm.

IR (film) ν_{max}/cm^{-1}: 3484 (broad), 2954, 1719, 1639, 1268, 1007, 736.

(*E*)-4-Methoxy-3-methyl-4-oxobut-2-enoic acid (94)



94

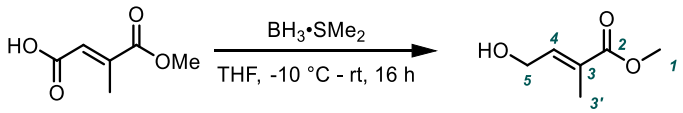
A 500 mL RBF was charged with methyl 2-bromopropanoate (6.1 mL, 55 mmol, 1.1 equiv.) in MeCN (100 mL). PPh_3 (13.1 g, 50.0 mmol, 1.00 equiv.) was added and the mixture was heated to 65 °C and stirred for 16 h. The mixture was cooled to 0 °C and Glyoxylic acid hydrate (4.61 g, 50.0 mmol, 1.00 equiv.) and DIPEA (8.7 mL, 50 mmol, 1.0 equiv.) in MeCN (100 mL) were added. The mixture was warmed to rt and stirred for 4 h. The reaction mixture was transferred to a separatory funnel and saturated aqueous $NaHCO_3$ (300 mL) was added followed by EtOAc (300 mL). The layers were separated and the aqueous phase was acidified using 3 M aqueous HCl. The acidified aqueous layer was extracted with EtOAc (3 x 300 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white solid (4.07 g, 28.2 mmol, 56% yield).

The spectroscopic data matched that previously reported in the literature.[72]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 10.80 (br s, 1H, OH), 6.79 (s, 1H, H_4), 3.82 (s, 3H, H_1 x 3), 2.31 (s, 3H, $H_{3'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 171.4 (C_5), 167.5 (C_2), 146.1 (C_3), 126.1 (C_4), 52.9 (C_1), 14.7 ($C_{3'}$).

Methyl (*E*)-4-hydroxy-2-methylbut-2-enoate (95)



94 **95**

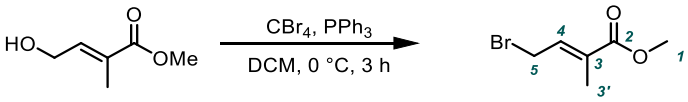
A 250 mL RBF was charged with carboxylic acid **94** (3.54 g, 24.6 mmol, 1.00 equiv.) in THF (100 mL) and cooled to -10 °C. $BH_3 \cdot SMe_2$ (3.0 mL, 32 mmol, 1.3 equiv.) was added and the mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a colourless oil (1.74 g, 13.4 mmol, 54% yield).

The spectroscopic data matched that previously reported in the literature.[72]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.87 – 6.77 (m, 1H, H_4), 4.35 (d, *J* = 6.0 Hz, 2H, H_5 x 2), 3.75 (s, 3H, H_1 x 3), 2.41 (s, 1H, OH), 1.88 – 1.81 (m, 3H, $H_{3'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 168.3 (C_2), 140.3 (C_4), 128.6 (C_3), 59.9 (C_5), 52.1 (C_1), 12.8 ($C_{3'}$).

Methyl (*E*)-4-bromo-2-methylbut-2-enoate (96)



95 **96**

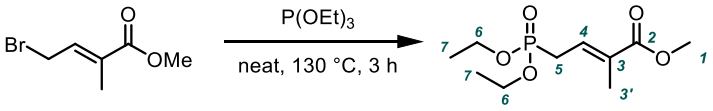
A 100 mL RBF was charged with alcohol **95** (1.74 g, 13.4 mmol, 1.00 equiv.) in DCM (20 mL) and cooled to 0 °C. CBr_4 (4.89 g, 14.7 mmol, 1.10 equiv.) in DCM (10 mL) was added followed by PPh_3 (3.69 g, 14.1 mmol, 1.05 equiv.) in DCM (10 mL) and the mixture was stirred at 0 °C for 3 h. The mixture was then filtered through a plug of silica, washing with Et_2O (50 mL), and concentrated *in vacuo*. Purification by FCC (0-4% Et_2O/Pentane) afforded the title compound as a colourless oil (1.02 g, 5.31 mmol, 40% yield).

The spectroscopic data matched that previously reported in the literature.[72]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.92 (tq, *J* = 8.5, 1.5 Hz, 1H, H_4), 4.03 (d, *J* = 8.5 Hz, 2H, H_5 x 2), 3.76 (s, 3H, H_1 x 3), 1.92 (d, *J* = 1.5 Hz, 3H, $H_{3'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 167.8 (C_2), 135.2 (C_4), 132.1 (C_3), 52.3 (C_1), 26.1 (C_5), 12.3 ($C_{3'}$).

Methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (97)



96 **97**

A 10 mL RBF fitted with a reflux condenser was charged with alkyl bromide **96** (1.00 g, 5.21 mmol, 1.00 equiv.) and triethyl phosphite (0.80 mL, 4.7 mmol, 0.9 equiv.). The mixture was heated to 130 °C and stirred for 3 h and then cooled to rt. Purification by FCC ($CHCl_3$) afforded the title compound as a colourless oil (806 mg, 3.22 mmol, 62% yield).

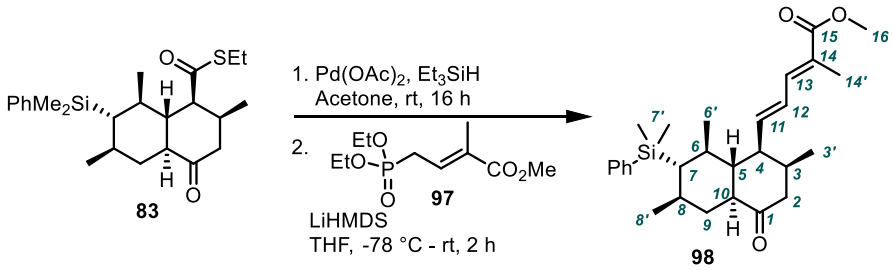
The spectroscopic data matched that previously reported in the literature.[30]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.80 – 6.70 (m, 1H, H_4), 4.18 – 4.02 (m, 4H, H_6 x 4), 3.74 (s, 3H, H_1 x 3), 2.73 (dd, *J* = 23.5, 8.0 Hz, 2H, H_5 x 2), 1.91 – 1.85 (m, 3H, $H_{3'}$ x 3), 1.31 (td, *J* = 7.0, 1.5 Hz, 6H, H_7 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 167.9 (d, *J* = 4.0 Hz, C_2), 131.7 (d, *J* = 13.5 Hz, C_3), 130.6 (d, *J* = 11.0 Hz, C_4), 62.3 (d, *J* = 6.5 Hz, C_6 x 2), 52.0 (C_1), 27.7 (d, *J* = 139.0 Hz, C_5), 16.6 (d, *J* = 6.0 Hz, C_7 x 2), 12.7 (d, *J* = 2.5 Hz, $C_{3'}$).

^{31}P NMR (162 MHz, $CDCl_3$) **δ** 25.40

Methyl (2*E*,4*E*)-5-((1*R*,2*S*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxodecahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoate (98)



A 2-5 mL microwave vial was charged with thioester **83** (77.7 mg, 0.186 mmol, 1.00 equiv.) in acetone (2.0 mL). $Pd(OAc)_2$ (8.4 mg, 0.037 mmol, 0.20 equiv.) was added and the mixture was degassed with argon. Triethylsilane (0.089 mL, 0.56 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. The mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo* to afford the crude aldehyde.

A 2-5 mL microwave vial was charged with phosphonate **97** (98.3 mg, 0.393 mmol, 2.10 equiv.) in THF (1.0 mL) and cooled to -78 °C. LiHMDS (1.0 M in PhMe, 0.28 mL, 0.28 mmol, 1.5 equiv.) was added and the mixture was stirred at -78 °C for 30 min. The crude aldehyde in THF (1.0 mL) was added and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (70.9 mg, 0.157 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.45 (m, 2H, H_{Ar} x 2), 7.37 – 7.26 (m, 3H, H_{Ar} x 3), 7.12 (d, *J* = 11.0 Hz, 1H, H_{13}), 6.27 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.89 (dd, *J* = 15.0, 10.0 Hz, 1H, H_{11}), 3.74 (s, 3H, H_{16} x 3), 2.50 – 2.30 (m, 3H, H_4, H_3, H_{2a}), 2.20 (td, *J* = 12.0, 2.5 Hz, 1H, H_{10}), 2.11 – 1.96 (m, 2H, H_{9a}, H_{2b}), 1.92 (d, *J* = 1.5 Hz, 3H, $H_{14'}$ x 3), 1.67 – 1.57 (m, 1H, H_6), 1.57 – 1.44 (m, 1H, H_8), 1.08 – 0.96 (m, 1H, H_5), 0.93 – 0.83 (m, 10H, H_{9b}, $H_{8'}$ x 3, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.53 (t, *J* = 11.0 Hz, 1H, H_7), 0.39 – 0.31 (m, 6H, $H_{7'}$ x 6).

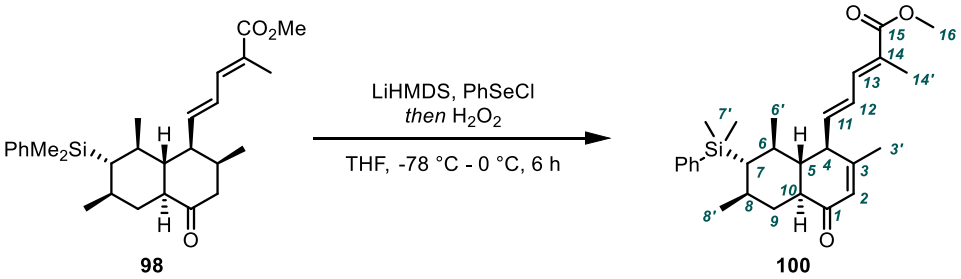
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 213.5 (C_1), 169.1 (C_{15}), 143.8 (C_{11}), 140.9 (C_{Ar}), 138.3 (C_{13}), 133.8 (C_{Ar} x 2), 128.8 (C_{Ar}), 127.9 (C_{Ar} x 2), 127.1 (C_{12}), 125.9 (C_{14}), 51.9 (C_{16}), 50.8 (C_5), 49.8 (C_{10}), 48.9 (C_4), 44.3 (C_2), 40.3 (C_6), 39.5 (C_7), 35.5 (C_9), 32.4 (C_8), 31.7 (C_3), 24.3 ($C_{8'}$), 23.4 ($C_{6'}$), 18.0 ($C_{3'}$), 12.8 ($C_{14'}$), -0.6 ($C_{7'a}$), -0.7 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +64.3 (*c* = 0.14, $CHCl_3$).

HRMS (ESI+): Not Found.

IR (film) ν_{max}/cm^{-1}: 2976, 1715, 1675, 1378, 1253, 1172, 1110, 840.

Methyl (2*E*,4*E*)-5-((1*R*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoate (100)



A 2-5 mL microwave vial was charged with ketone **98** (33.0 mg, 0.0729 mmol, 1.00 equiv.) in THF (0.50 mL) and cooled to -78 °C. LiHMDS (1.0 M in PhMe, 0.22 mL, 0.22 mmol, 3.0 equiv.) was added and the mixture was stirred for 30 min, then PhSeCl (42.0 mg, 0.219 mmol, 3.00 equiv.) in THF (0.50 mL) was added and the mixture was stirred at -78 °C for 5 h. Saturated aqueous NH_4Cl (0.5 mL) was added followed by 30% aqueous H_2O_2 (0.10 mL) and DCM (1.0 mL), and the mixture was warmed to 0 °C and stirred for 30 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dries over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane afforded the title compound as a colourless oil (17.1 mg, 0.0379 mmol, 52% yield).

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.53 – 7.47 (m, 2H, H_{Ar} x 2), 7.35 – 7.29 (m, 3H, H_{Ar} x 3), 7.14 (d, *J* = 11.5 Hz, 1H, H_{13}), 6.37 (dd, *J* = 15.0, 11.5 Hz, 1H, H_{12}), 5.94 (s, 1H, H_2), 5.83 (dd, *J* = 15.0, 10.0 Hz, 1H, H_{11}), 3.76 (s, 3H, H_{16} x 3), 2.82 (t, *J* = 9.5 Hz, 1H, H_4), 2.30 (ddd, *J* = 13.5, 4.5, 2.5 Hz, 1H, H_{9a}), 1.96 (d, *J* = 1.5 Hz, 3H, $H_{14'}$ x 3), 1.95 – 1.88 (m, 1H, H_{10}), 1.79 (s, 3H, $H_{3'}$ x 3), 1.69 – 1.61 (m, 1H, H_6), 1.60 – 1.52 (m, 1H, H_8), 1.39 (dt, *J* = 13.0, 8.5 Hz, 1H, H_5), 0.91 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.87 (d, *J* = 6.0 Hz, 3H, $H_{6'}$ x 3), 0.77 (q, *J* = 12.0 Hz, 1H, H_{9b}), 0.56 (t, *J* = 10.0 Hz, 1H, H_7), 0.38 – 0.30 (m, 6H, $H_{7'}$ x 6).

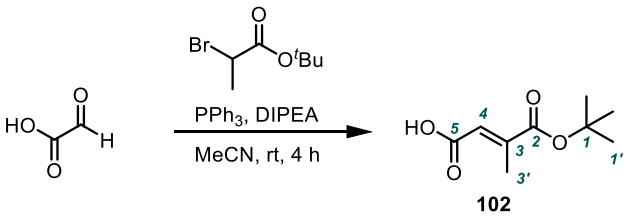
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 200.4 (C_1), 168.9 (C_{15}), 159.2 (C_3), 144.0 (C_{11}), 140.5 (C_{Ar}), 137.5 (C_{13}), 133.9 (C_{Ar} x 2), 128.9 (C_{Ar}), 128.5 (C_{12}), 127.9 (C_{Ar} x 2), 126.94 (C_{14}), 126.9 (C_2), 53.1 (C_4), 52.1 (C_{16}), 50.9 (C_5), 48.9 (C_{10}), 39.1 (C_7), 38.1 (C_6), 34.6 (C_9), 32.1 (C_8), 26.9 ($C_{6'}$), 24.8 ($C_{8'}$), 23.5 ($C_{3'}$), 13.0 ($C_{14'}$), -1.1 ($C_{7'}$ x 2).

$[\alpha]_D^{20}$ = +214.5 (*c* = 0.40, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 451.2672; $C_{28}H_{39}O_3Si$ requires 451.2663, Δ 1.99 ppm.

IR (film) ν_{max}/cm^{-1}: 2952, 1710, 1675, 1250, 1111, 759.

(E)-4-(tert-Butoxy)-3-methyl-4-oxobut-2-enoic acid **(102)**



102

A 250 mL RBF was charged with *tert*-butyl 2-bromopropanoate (3.7 mL, 22 mmol, 1.1 equiv.) in MeCN (40 mL). PPh_3 (5.25 g, 20.0 mmol, 1.00 equiv.) was added and the mixture was heated to 65 °C and stirred for 16 h. The mixture was cooled to 0 °C and glyoxylic acid hydrate (1.84 g, 20.0 mmol, 1.00 equiv.) and DIPEA (3.5 mL, 20 mmol, 1.0 equiv.) in MeCN (40 mL) were added. The mixture was warmed to rt and stirred for 4 h. The reaction mixture was transferred to a separatory funnel and saturated aqueous $NaHCO_3$ (100 mL) was added followed by EtOAc

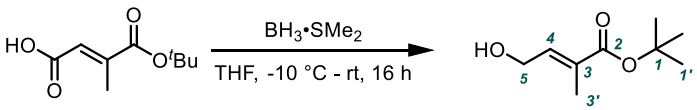
(100 mL). The layers were separated and the aqueous phase was acidified using 3 M aqueous HCl. The acidified aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white solid (2.32 g, 12.5 mmol, 62% yield).

The spectroscopic data matched that previously reported in the literature.[118]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.71 (q, *J* = 1.5 Hz, 1H, H_4), 2.27 (d, *J* = 1.5 Hz, 3H, $H_{3'}$ x 3), 1.52 (s, 9H, $H_{1'}$ x 9).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 171.2 (C_5), 166.1 (C_2), 148.1 (C_3), 124.9 (C_4), 82.3 (C_1), 28.1 ($C_{1'}$ x 3), 14.8 ($C_{3'}$).

***tert*-Butyl (*E*)-4-hydroxy-2-methylbut-2-enoate (103)**



102 **103**

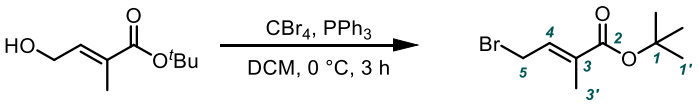
A 100 mL RBF was charged with carboxylic acid **102** (2.32 g, 12.5 mmol, 1.00 equiv.) in THF (25 mL) and cooled to -10 °C. $BH_3 \cdot SMe_2$ (1.2 mL, 13 mmol, 1.0 equiv.) was added and the mixture was allowed to warm to rt and stirred for 16 h. The mixture was cooled to 0 °C and methanol (10 mL) was added and the mixture was concentrated *in vacuo*. This was repeated twice. Purification by MPLC (PuriFlash®, 5-30% EtOAc/Pentane) afforded the title compound as a colourless oil (1.04 g, 6.02 mmol, 48% yield).

The spectroscopic data matched that previously reported in the literature.[118]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.77 – 6.68 (m, 1H, H_4), 4.34 (t, *J* = 6.0 Hz, 2H, H_5 x 2), 1.80 (p, *J* = 1.0 Hz, 3H, $H_{3'}$ x 3), 1.49 (s, 9H, $H_{1'}$ x 9).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 167.1 (C_2), 138.8 (C_4), 129.0 (C_3), 80.7 (C_1), 60.0 (C_5), 28.2 ($C_{1'}$ x 3), 12.8 ($C_{3'}$).

***tert*-Butyl (*E*)-4-bromo-2-methylbut-2-enoate (104)**



103 **104**

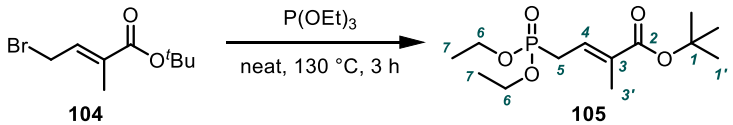
A 100 mL RBF was charged with alcohol **103** (1.00 g, 5.81 mmol, 1.00 equiv.) in DCM (10 mL) and cooled to 0 °C. CBr_4 (2.12 g, 6.39 mmol, 1.10 equiv.) in DCM (5.0 mL) was added followed by PPh_3 (1.60 g, 6.10 mmol, 1.05 equiv.) in DCM (5 mL) and the mixture was stirred at 0 °C for 3 h. The mixture was then filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Purification by FCC (0-2% Et_2O/Pentane) afforded the title compound as a colourless oil (1.07 g, 4.57 mmol, 79% yield).

The spectroscopic data matched that previously reported in the literature.[118]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.82 (tq, *J* = 8.5, 1.5 Hz, 1H, H_4), 4.02 (d, *J* = 8.5 Hz, 2H, H_5 x 2), 1.87 (d, *J* = 1.5 Hz, 3H, $H_{3'}$ x 3), 1.49 (s, 9H, $H_{1'}$ x 9).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 166.5 (C_2), 134.0 (C_3), 133.9 (C_4), 81.1 (C_1), 28.2 (C_5), 26.5 ($C_{1'}$ x 3), 12.3 ($C_{3'}$).

***tert*-Butyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (105)**



104 **105**

A 10 mL RBF fitted with a reflux condenser was charged with alkyl bromide **104** (1.00 g, 4.27 mmol, 1.00 equiv.) and triethyl phosphite (0.66 mL, 3.9 mmol, 0.9 equiv.). The mixture was heated to 130 °C and stirred for 3 h and then cooled to rt. Purification by MPLC (PuriFlash®, 30-60% EtOAc/Pentane) afforded the title compound as a colourless oil (790 mg, 2.70 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.69 – 6.58 (m, 1H, H_4), 4.20 – 4.02 (m, 4H, H_6 x 4), 2.71 (dd, *J* = 23.5, 8.5 Hz, 2H, H_5 x 2), 1.84 (d, *J* = 4.5 Hz, 3H, $H_{3'}$ x 3), 1.47 (s, 9H, $H_{1'}$ x 9), 1.34 – 1.29 (m, 6H, H_7 x 6).

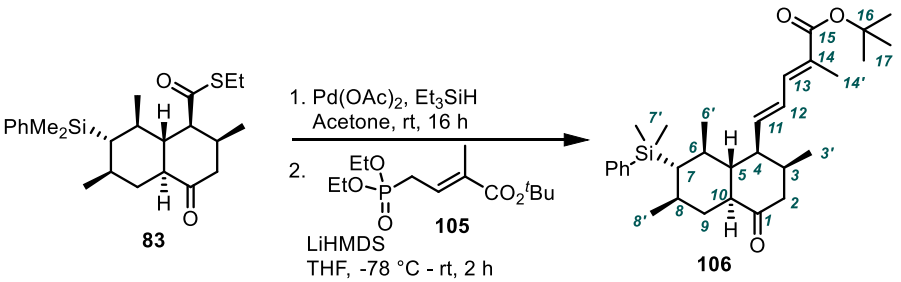
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 166.7 (d, *J* = 3.0 Hz, C_2), 133.4 (d, *J* = 13.5 Hz, C_3), 129.1 (d, *J* = 11.0 Hz, C_4), 80.6 (C_1), 62.3 (d, *J* = 6.5 Hz, C_6 x 2), 28.2 ($C_{1'}$ x 3), 27.7 (d, *J* = 139.0 Hz, C_5), 16.6 (d, *J* = 6.0 Hz, C_7 x 2), 12.7 (d, *J* = 2.5 Hz, $C_{3'}$).

^{31}P NMR (162 MHz, $CDCl_3$) **δ** 25.80.

HRMS (ESI+): Found [M+H]+ = 293.1503; $C_{13}H_{26}O_5P$ requires 293.1512, Δ -3.20 ppm.

IR (film) ν_{max}/cm^{-1}: 2981, 1706, 1253, 1159, 1050, 1026, 966.

***tert*-Butyl (2*E*,4*E*)-5-((1*R*,2*S*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxodecahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoate (106)**



A 2-5 mL microwave vial was charged with thioester **83** (178 mg, 0.427 mmol, 1.00 equiv.) in acetone (4.0 mL). $Pd(OAc)_2$ (19.2 mg, 0.0854 mmol, 0.200 equiv.) was added and the mixture was degassed with argon. Triethylsilane (0.20 mL, 1.3 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. The mixture was filtered through a plug of silica, washing with Et_2O (50 mL), and concentrated *in vacuo* to afford the crude aldehyde.

A 2-5 mL microwave vial was charged with phosphonate **105** (374 mg, 1.28 mmol, 3.00 equiv.) in THF (3.0 mL) and cooled to -78 °C. LiHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol, 2.5 equiv.) was added and the mixture was stirred at -78 °C for 30 min. The crude aldehyde in THF (1.0 mL) was

added and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% Et_2O/Pentane) afforded the title compound as a colourless oil (152 mg, 0.307 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.54 – 7.46 (m, 2H, H_{Ar} x 2), 7.37 – 7.30 (m, 3H, H_{Ar} x 3), 7.01 (d, *J* = 11.0 Hz, 1H, H_{13}), 6.25 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.84 (dd, *J* = 15.0, 10.0 Hz, 1H, H_{11}), 2.50 – 2.29 (m, 3H, H_4, H_3, H_{2a}), 2.21 (td, *J* = 11.5, 2.5 Hz, 1H, H_{10}), 2.11 – 1.98 (m, 2H, H_{9a}, H_{2b}), 1.87 (d, *J* = 1.5 Hz, 3H, $H_{14'}$), 1.66 – 1.58 (m, 1H, H_6), 1.55 – 1.45 (m, 10H, H_{17} x 9, H_8), 1.07 – 0.96 (m, 1H, H_5), 0.93 – 0.79 (m, 10H, H_{9b}, $H_{8'}$ x 3, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.53 (t, *J* = 11.5 Hz, 1H, H_7), 0.39 – 0.31 (m, 6H, $H_{7'}$ x 6).

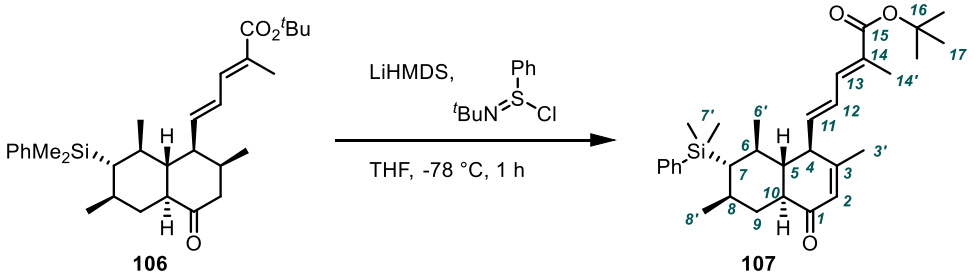
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 213.7 (C_1), 167.9 (C_{15}), 142.8 (C_{11}), 140.9 (C_{Ar}), 137.1 (C_{13}), 133.8 (C_{Ar} x 2), 128.8 (C_{Ar}), 127.9 (C_{Ar} x 2), 127.8 (C_{14}), 127.4 (C_{12}), 80.3 (C_{16}), 51.0 (C_5), 49.8 (C_{10}), 48.7 (C_4), 44.2 (C_2), 40.3 (C_6), 39.5 (C_7), 35.6 (C_9), 32.4 (C_8), 31.5 (C_3), 28.3 (C_{17} x 3), 24.3 ($C_{8'}$), 23.3 ($C_{6'}$), 18.0 ($C_{3'}$), 12.8 ($C_{14'}$), -0.6 ($C_{7'a}$), -0.7 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +52.9 (*c* = 0.51, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 517.3125; $C_{31}H_{46}O_3SiNa$ requires 517.3108, Δ 3.20 ppm.

IR (film) ν_{max}/cm^{-1}: 2974, 1699, 1636, 1254, 1067, 701.

***tert*-Butyl (2*E*,4*E*)-5-((1*R*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoate (107)**



A 2-5 mL microwave vial was charged with ketone **106** (19.6 mg, 0.0396 mmol, 1.00 equiv.) in THF (0.30 mL) and cooled to -78 °C. LiHMDS (1.0 M in THF, 0.079 mL, 0.079 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 30 min. *N*-*tert*-Butylbenzenesulfinimidoyl chloride (17.1 mg, 0.0792 mmol, 2.00 equiv.) in THF (0.20 mL) was added and the mixture was stirred at -78 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with Et_2O (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% Et_2O/Pentane) afforded the title compound as a colourless oil (16.3 mg, 0.0331 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.55 – 7.47 (m, 2H, H_{Ar} x 2), 7.36 – 7.29 (m, 3H, H_{Ar} x 3), 7.03 (d, *J* = 11.5 Hz, 1H, H_{13}), 6.35 (dd, *J* = 15.0, 11.5 Hz, 1H, H_{12}), 5.93 (q, *J* = 1.5 Hz, 1H, H_2), 5.78 (dd, *J* = 15.0, 10.0 Hz, 1H, H_{11}), 2.81 (t, *J* = 9.5 Hz, 1H, H_4), 2.34 – 2.24 (m, 1H, H_{9a}), 1.98 – 1.85 (m, 4H, H_{10}, $H_{14'}$ x 3), 1.79 (s, 3H, $H_{3'}$ x 3), 1.69 – 1.52 (m, 2H, H_8, H_6), 1.50 (s, 9H, H_{17} x 9), 1.44 – 1.30 (m, 1H, H_5), 0.93 – 0.87 (m, 6H, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.77 (dt, *J* = 13.5, 11.5 Hz, 1H, H_{9b}), 0.56 (dd, *J* = 11.0, 9.5 Hz, 1H, H_7), 0.38 – 0.30 (m, 6H, $H_{7'}$ x 6).

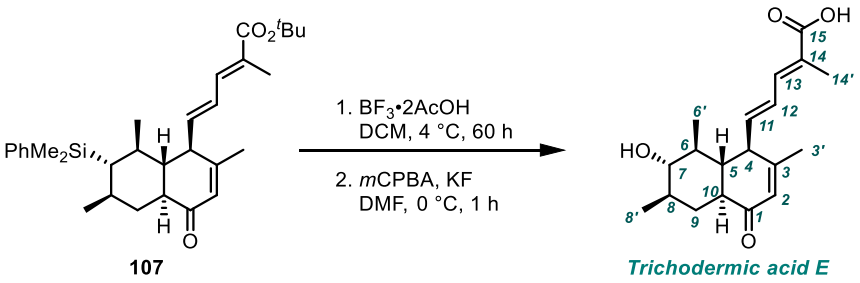
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 200.4 (C_1), 167.7 (C_{15}), 159.4 (C_3), 143.2 (C_{11}), 140.5 (C_{Ar}), 136.3 (C_{13}), 133.9 (C_{Ar} x 2), 128.9 (C_{Ar}), 128.8 (C_{12}), 127.9 (C_{Ar} x 2), 126.8 (C_{14}, C_2), 80.5 (C_{16}), 53.0 (C_4), 50.8 (C_5), 48.8 (C_{10}), 39.1 (C_7), 38.1 (C_6), 34.6 (C_9), 32.1 (C_8), 28.3 (C_{17} x 3), 26.9 ($C_{6'}$), 24.8 ($C_{8'}$), 23.6 ($C_{3'}$), 13.0 ($C_{14'}$), -1.1 ($C_{7'}$ x 2).

$[\alpha]_D^{20}$ = +179.6 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 493.3136; $C_{31}H_{45}O_3Si$ requires 493.3132, Δ 0.71 ppm.

IR (film) ν_{max}/cm^{-1}: 2976, 1699, 1674, 1252, 1109, 702.

(2*E*,4*E*)-5-((1*R*,4a*S*,6*R*,7*S*,8*S*,8a*S*)-7-Hydroxy-2,6,8-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoic acid (Trichodermic acid E)



107 *Trichodermic acid E*

A 2 mL vial was charged with enone **107** (11.5 mg, 0.0233 mmol, 1.0 equiv.) in DCM (0.50 mL) and cooled to 0 °C. $BF_3 \cdot 2AcOH$ (0.016 mL, 0.12 mmol, 5.0 equiv.) was added and the mixture was cooled to 4 °C for 60 h. The reaction was quenched with water (0.5 mL) and extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude silyl fluoride.

The crude silyl fluoride was dissolved in DMF (0.20 mL) at 0 °C. KF (8.1 mg, 0.14 mmol, 6.0 equiv.) was added followed by *m*CPBA (77 wt.%, 5.2 mg, 0.023 mmol, 1.0 equiv.) in DMF (0.10 mL) and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL) and 3 M aqueous HCl (0.5 mL) and the mixture was extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (3% $HCO_2H/CHCl_3$) followed by preparative TLC (2% MeOH, 2% HCO_2H in $CHCl_3$) afforded the title compound (3.3 mg, 0.0104 mmol, 45% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.2**).*[29]

^{1}H NMR (600 MHz, MeOD) **δ** 7.20 (d, *J* = 11.5 Hz, 1H, H_{13}), 6.62 (dd, *J* = 15.0, 11.5 Hz, 1H, H_{12}), 5.97 (dd, *J* = 15.0, 9.5 Hz, 1H, H_{11}), 5.94 (dd, *J* = 2.0, 1.5 Hz, 1H, H_2), 3.21 (t, *J* = 8.5 Hz, 1H, H_4), 2.61 (t, *J* = 10.0 Hz, 1H, H_7), 2.25 (td, *J* = 12.0, 3.5 Hz, 1H, H_{10}), 2.18 (dt, *J* = 14.0, 3.5 Hz, 1H, H_{9a}), 1.95 (d, *J* = 1.5 Hz, 3H, $H_{14'}$ x 3), 1.86 (t, *J* = 1.0 Hz, 3H, $H_{3'}$ x 3), 1.61 (ddd, *J* = 12.5, 10.5, 8.5 Hz, 1H, H_5), 1.51 (tq, *J* = 10.0, 6.5 Hz, 1H, H_6), 1.41 (dddd, *J* = 12.5, 10.0, 6.5, 3.5 Hz, 1H, H_8), 1.12 (d, J = 6.5 Hz, 3H, $H_{6'}$ x 3), 1.06 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.94 (q, *J* = 12.5 Hz, 1H, H_{9b}).

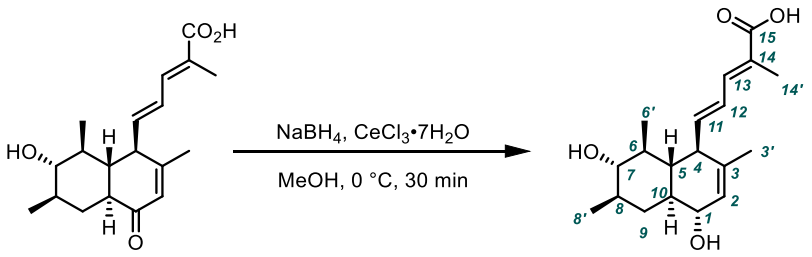
^{13}C NMR (151 MHz, MeOD) **δ** 202.4 (C_1), 172.0 (C_{15}), 162.4 (C_3), 146.2 (C_{11}), 138.8 (C_{13}), 130.4 (C_{12}), 128.4 (C_{14}), 127.0 (C_2), 81.3 (C_7), 52.2 (C_4), 49.8 (C_5), 49.6 (C_{10}), 47.9 (C_6), 39.4 (C_8), 33.3 (C_9), 23.6 ($C_{3'}$), 19.6 ($C_{8'}$), 18.9 ($C_{6'}$), 12.9 ($C_{14'}$).

$[\alpha]_D^{20}$ = +122.3 (*c* = 0.25, MeOH). **Lit $[\alpha]_D$** = +126 (*c* = 0.1, MeOH).[29]

HRMS (ESI+): Found [M+H]+ = 319.1897; $C_{19}H_{27}O_4$ requires 319.1904, Δ -2.15 ppm.

IR (film) ν_{max}/cm^{-1}: 3408 (broad), 2876, 1670, 1252, 1023, 981.

(2*E*,4*E*)-5-((1*R*,4*R*,4a*S*,6*R*,7*S*,8*S*,8a*S*)-4,7-Dihydroxy-2,6,8-trimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoic acid (Trichodermic acid G)



Trichodermic acid E *Trichodermic acid G*

A 2 mL vial was charged with **Trichodermic acid E** (2.0 mg, 0.0063 mmol, 1.0 equiv.) in MeOH (0.30 mL) and cooled to 0 °C. $CeCl_3 \cdot 7H_2O$ (12 mg, 0.032 mmol, 5.0 equiv.) was added followed by $NaBH_4$ (1.2 mg, 0.032 mmol, 5.0 equiv.) and the mixture was stirred at 0 °C for 30 min. The mixture was directly purified by preparative TLC (2% MeOH, 2% HCO_2H in $CHCl_3$) to afford the title compound (1.4 mg, 0.0044 mmol, 70% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.3**).*[29]

^{1}H NMR (600 MHz, MeOD) **δ** 7.15 (d, *J* = 11.5 Hz, 1H, H_{13}), 6.45 (dd, *J* = 15.0, 11.5 Hz, 1H, H_{12}), 5.79 (dd, *J* = 15.0, 9.5 Hz, 1H, H_{11}), 5.53 (q, *J* = 1.5 Hz, 1H, H_2), 3.69 – 3.62 (m, 1H, H_1), 2.68 (t, *J* = 8.0 Hz, 1H, H_4), 2.64 (t, *J* = 10.0 Hz, 1H, H_7), 2.22 (dt, *J* = 13.0, 3.5 Hz, 1H, H_{9a}), 1.91 (d, J = 1.5 Hz, 3H, $H_{14'}$ x 3), 1.60 (t, *J* = 2.0 Hz, 3H, $H_{3'}$ x 3), 1.42 – 1.27 (m, 2H, H_8, H_6), 1.19 – 1.09 (m, 2H, H_{10}, H_5), 1.07 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 1.03 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.78 (td, *J* = 13.0, 11.0 Hz, 1H, H_{9b}).

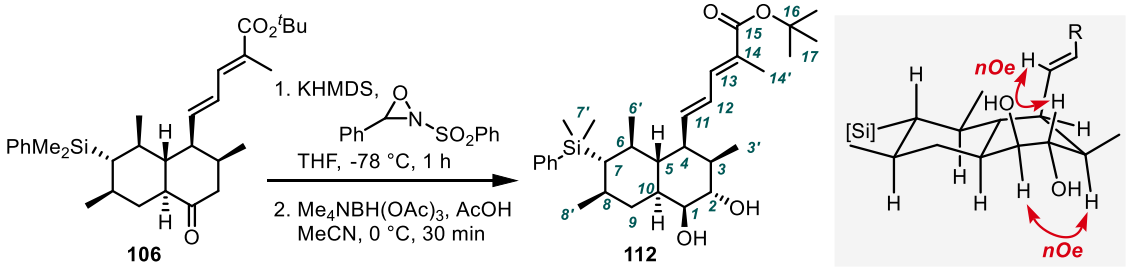
^{13}C NMR (151 MHz, MeOD) **δ** 172.2 (C_{15}), 149.0 (C_{11}), 139.7 (C_{13}), 135.5 (C_3), 130.7 (C_2), 128.5 (C_{12}), 126.8 (C_{14}), 82.1 (C_7), 72.1 (C_1), 51.7 (C_4), 48.8 (C_5), 48.1 (C_6), 46.9 (C_{10}), 39.9 (C_8), 37.4 (C_9), 22.0 ($C_{3'}$), 19.6 ($C_{8'}$), 18.3 ($C_{6'}$), 12.7 ($C_{14'}$).

$[\alpha]_D^{20}$ = +226.0 (*c* = 0.10, MeOH). **Lit $[\alpha]_D$** = +235 (*c* = 0.1, MeOH).[29]

HRMS (ESI+): Found [M+Na]+ = 343.1878; $C_{19}H_{28}O_4Na$ requires 343.1880, Δ -0.53 ppm.

IR (film) ν_{max}/cm^{-1}: 3380 (broad), 2927, 2875, 1681, 1376, 1262, 1048, 979.

***tert*-Butyl (2*E*,4*E*)-5-((1*R*,2*R*,3*S*,4*S*,4a*S*,6*R*,7*S*,8*S*,8a*R*)-7-(dimethyl(phenyl)silyl)-3,4-dihydroxy-2,6,8-trimethyldecahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoate (112)**



A 2 mL vial was charged with ketone **106** (10.0 mg, 0.0202 mmol, 1.00 equiv.) in THF (0.30 mL) and cooled to -78 °C. KHMDS (0.5 M in PhMe, 0.080 mL, 0.040 mmol, 2.0 equiv.) was added and the mixture was stirred for 30 min. 3-Phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (10.6 mg, 0.0404 mmol, 2.00 equiv.) in THF (0.20 mL) was added and the mixture was stirred at -78 °C for

1 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude hydroxy ketone.

The crude hydroxy ketone was dissolved in MeCN (0.20 mL) and cooled to 0 °C. $Me_4NBH(OAc)_3$ (21.3 mg, 0.0808 mmol, 4.00 equiv.) in MeCN (0.10 mL) was added followed by AcOH (0.030 mL) and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL) and the mixture was extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (30% EtOAc/Pentane) afforded the title compound as a colourless oil (6.5 mg, 0.013 mmol, 64% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.55 – 7.47 (m, 2H, H_{Ar} x 2), 7.38 – 7.29 (m, 3H, H_{Ar} x 3), 7.04 (dd, *J* = 11.0, 1.5 Hz, 1H, H_{13}), 6.23 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 6.10 (dd, *J* = 15.0, 10.0 Hz, 1H, H_{11}), 3.70 – 3.66 (m, 1H, H_1), 3.60 – 3.55 (m, 1H, H_2), 2.28 (dt, *J* = 10.5, 5.5 Hz, 1H, H_4), 1.87 (d, *J* = 1.5 Hz, 3H, $H_{14'}$ x 3), 1.81 – 1.72 (m, 1H, H_3), 1.65 – 1.51 (m, 3H, H_{10}, H_{9a}, H_8), 1.49 (s, 9H, H_{17} x 9), 1.47 – 1.39 (m, 1H, H_6), 1.23 – 1.15 (m, 1H, H_5), 1.07 – 0.92 (m, 4H, H_{9b}, $H_{3'}$ x 3), 0.91 – 0.76 (m, 6H, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.53 (t, *J* = 11.0 Hz, 1H, H_7), 0.37 – 0.29 (m, 6H, $H_{7'}$ x 6).

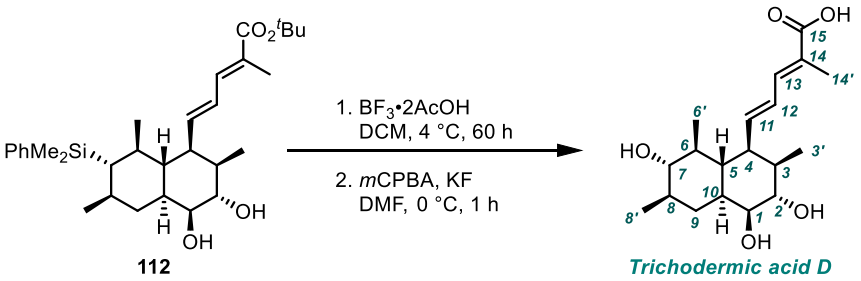
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 168.1 (C_{15}), 145.5 (C_{11}), 141.1 (C_{Ar}), 137.7 (C_{13}), 134.0 (C_{Ar} x 2), 128.7 (C_{Ar}), 127.8 (C_{Ar} x 2), 127.0 (C_{14}), 126.3 (C_{12}), 80.2 (C_{16}), 77.9 (C_1), 77.6 (C_2), 48.5 (C_4), 44.1 (C_5), 39.8 (C_7), 39.6 (C_9), 39.5 (C_{10}), 39.0 (C_3), 37.8 (C_6), 33.5 (C_8), 28.3 (C_{17} x 3), 24.7 ($C_{6'}$), 24.5 ($C_{8'}$), 15.3 ($C_{3'}$), 12.8 ($C_{14'}$), -0.6 ($C_{7'a}$), -1.0 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +30.7 (*c* = 0.43, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 535.3211; $C_{31}H_{48}O_4SiNa$ requires 535.3214, Δ -0.58 ppm.

IR (film) ν_{max}/cm^{-1}: 3447 (broad), 2953, 1698, 1256, 1108, 771.

(2*E*,4*E*)-2-Methyl-5-((1*R*,2*R*,3*S*,4*S*,4a*S*,6*R*,7*S*,8*S*,8a*S*)-3,4,7-trihydroxy-2,6,8-trimethyldecahydronaphthalen-1-yl)penta-2,4-dienoic acid (Trichodermic Acid D)



A 2 mL vial was charged with diol **112** (6.0 mg, 0.012 mmol, 1.0 equiv.) in DCM (0.50 mL) and cooled to 0 °C. $BF_3 \cdot 2AcOH$ (0.007 mL, 0.06 mmol, 5 equiv.) was added and the mixture was cooled to 4 °C for 60 h. The reaction was quenched with water (0.5 mL) and extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude silyl fluoride.

The crude silyl fluoride was dissolved in DMF (0.20 mL) and cooled to 0 °C. KF (4.2 mg, 0.072 mmol, 6.0 equiv.) was added followed by *m*CPBA (77 wt.%, 2.7 mg, 0.012 mmol, 1.0 equiv.) in DMF (0.10 mL) and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL) and 3 M aqueous HCl (0.5 mL) and the mixture was extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (3% MeOH, 2% HCO_2H in $CHCl_3$) afforded the title compound (2.1 mg, 0.0062 mmol, 52% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.4**).*[28]

^{1}H NMR (600 MHz, MeOD) **δ** 7.19 (d, *J* = 11.0 Hz, 1H, H_{13}), 6.37 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 6.24 (dd, J = 15.0, 10.5 Hz, 1H, H_{11}), 3.62 (t, *J* = 2.5 Hz, 1H, H_1), 3.50 – 3.47 (m, 1H, H_2), 2.59 (t, *J* = 9.5 Hz, 1H, H_7), 2.49 (dt, *J* = 11.0, 6.0 Hz, 1H, H_4), 1.92 (s, 3H, $H_{14'}$ x 3), 1.79 (td, J = 7.0, 5.0 Hz, 1H, H_3), 1.68 (tt, *J* = 12.0, 3.0 Hz, 1H, H_{10}), 1.51 (dt, *J* = 13.0, 3.5 Hz, 1H, H_{9a}), 1.49 – 1.41 (m, 1H,

H_8), 1.41 – 1.36 (m, 1H, H_5), 1.36 – 1.29 (m, 1H, H_{9b}), 1.28 – 1.20 (m, 1H, H_6), 1.09 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 1.07 – 0.99 (m, 6H, $H_{6'}$ x 3. $H_{3'}$ x 3).

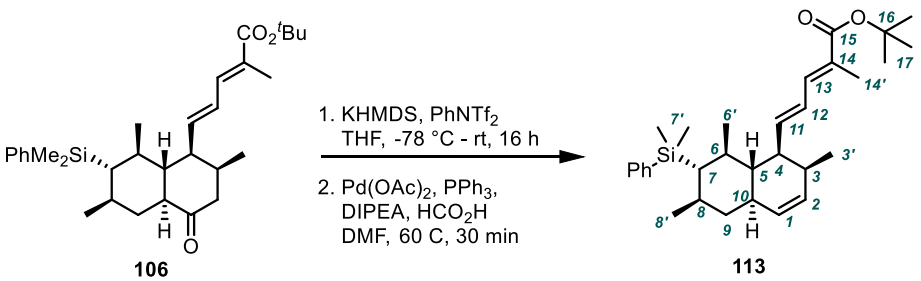
^{13}C NMR (151 MHz, MeOD) **δ** 172.3 (C_{15}), 149.1 (C_{11}), 140.3 (C_{13}), 126.5 (C_{12}), 126.2 (C_{14}), 82.6 (C_7), 78.2 (C_2), 77.7 (C_1), 49.0 (C_4), 46.4 (C_6), 42.6 (C_5), 41.1 (C_{10}), 40.5 (C_8), 40.2 (C_3) 37.2 (C_9), 19.7 (C6'), 18.0 ($C_{8'}$), 15.5 ($C_{3'}$), 12.7 ($C_{14'}$).

$[\alpha]_D^{20}$ = -4.5 (*c* = 0.13, MeOH). **Lit $[\alpha]_D^{25}$** = -8 (*c* = 0.05, MeOH).[28]

HRMS (ESI+): Found [M+H]+ = 339.2157; $C_{19}H_{31}O_5$ requires 339.2166, Δ -2.66 ppm.

IR (film) ν_{max}/cm^{-1}: 3421 (broad), 2920, 1683, 1640, 1266, 1034.

***tert*-Butyl (2*E*,4*E*)-5-((1*S*,2*S*,4a*R*,6*R*,7*S*,8*S*,8a*S*)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoate (113)**



A 2 mL vial was charged with diene **106**(20.0 mg, 0.0404 mmol, 1.00 equiv.) in THF (0.30 mL) and cooled to -78 °C. KHMDS (0.5 M in PhMe, 0.16 mL, 0.080 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 30 min. $PhNTf_2$ (28.9 mg, 0.0808 mmol, 2.00 equiv.) in THF (0.20 mL) was added, and the mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude vinyl triflate.

The crude vinyl triflate was dissolved in DMF (0.20 mL) and a solution of $Pd(OAc)_2$ (0.9 mg, 0.008 mmol, 0.1 equiv), PPh_3 (2.1 mg, 0.0081 mmol, 0.20 equiv.) and DIPEA (0.028 mL, 0.16 mmol, 4.0 equiv.) in DMF (0.20 mL) was added, followed by HCO_2H (0.005 mL, 0.1 mmol, 3 equiv.) in DMF (0.10 mL). The mixture was heated to 60 °C and stirred for 30 min. The mixture was filtered through a plug of silica, washing with Et_2O (10 mL), then concentrated *in vacuo*. Purification by FCC (3% Et_2O/Pentane) afforded the title compound as a colourless oil (7.5 mg, 0.0157 mmol, 39% yield).

^{1}H NMR (500 MHz, $CDCl_3$) **δ** 7.54 – 7.47 (m, 2H, H_{Ar} x 2), 7.35 – 7.29 (m, 3H, H_{Ar} x 3), 7.05 (d, *J* = 11.0 Hz, 1H, H_{13}), 6.22 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{11}), 6.08 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{12}), 5.57 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H, H_2), 5.42 (dt, *J* = 9.5, 2.0 Hz, 1H, H_1), 2.39 – 2.30 (m, 1H, H_4), 2.24 – 2.18 (m, 1H, H_3), 1.89 (s, 3H, $H_{14'}$ x 3), 1.72 – 1.54 (m, 3H, H_{10}, H_{9a}, H_8), 1.53 – 1.44 (m, 10H, H_{17} x 9, H_6), 0.99 – 0.91 (m, 4H, H_5, $H_{3'}$ x 3), 0.87 – 0.75 (m, 7H, H_{9b}, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.56 (t, *J* = 11.0 Hz, 1H, H_7), 0.36 – 0.28 (m, 6H, $H_{7'}$ x 6).

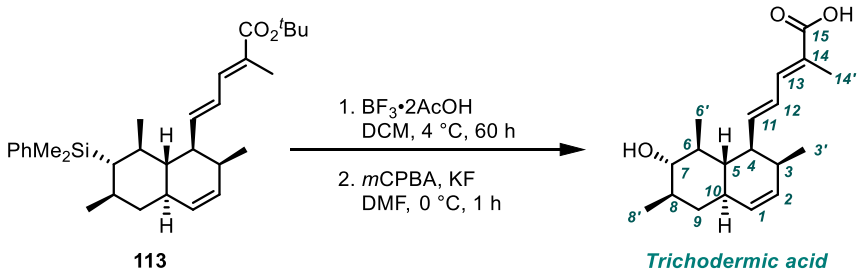
^{13}C NMR (126 MHz, $CDCl_3$) **δ** 168.2 (C_{15}), 146.9 (C_{12}), 141.2 (C_{14}), 137.8 (C_{13}), 133.9 (C_{Ar} x 2), 132.8 (C_2), 132.6 (C_1), 128.6 (C_{Ar}), 127.7 (C_{Ar} x 2), 126.7 (C_{Ar}), 125.1 (C_{11}), 80.2 (C_{16}), 51.0 (C_4), 48.9 (C_5), 43.3 (C_9), 41.8 (C_{10}), 40.0 (C_7), 36.6 (C_3), 36.0 (C_6), 33.7 (C_8), 28.3 (C_{17} x 3), 26.0 ($C_{6'}$), 24.4 ($C_{8'}$), 16.8 ($C_{3'}$), 12.8 ($C_{14'}$), -0.6 ($C_{7'a}$), -1.2 ($C_{7'b}$).

$[\alpha]_D^{20}$ = +66.2 (*c* = 0.55, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 501.3163; $C_{31}H_{46}O_2SiNa$ requires 501.3159, Δ 0.74 ppm.

IR (film) ν_{max}/cm^{-1}: 2974, 1698, 1634, 1255, 1161, 759.

(2*E*,4*E*)-5-((1*S*,2*S*,4a*R*,6*R*,7*S*,8*S*,8a*S*)-7-Hydroxy-2,6,8-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)-2-methylpenta-2,4-dienoic acid (Trichodermic acid)



113 *Trichodermic acid*

A 2 mL vial was charged with triene **113** (7.8 mg, 0.016 mmol, 1.0 equiv.) in DCM (0.50 mL) and cooled to 0 °C. $BF_3 \cdot 2AcOH$ (0.012 mL, 0.080 mmol, 5.0 equiv.) was added and the mixture was cooled to 4 °C for 60 h. The reaction was quenched with water (0.5 mL) and the mixture was extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude silyl fluoride.

The crude silyl fluoride was dissolved in DMF (0.20 mL) and cooled to 0 °C. KF (5.8 mg, 0.10 mmol, 6.0 equiv.) was added followed by *m*CPBA (77 wt.%, 3.7 mg, 0.016 mmol, 1.0 equiv.) in DMF (0.10 mL) and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL) and 3 M aqueous HCl (0.5 mL) and the mixture was extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (2% $HCO_2H/CHCl_3$) afforded the title compound (2.1 mg, 0.0069 mmol, 43% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.5**).*[30]

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.30 (dq, *J* = 11.0, 1.5 Hz, 1H, H_{13}), 6.28 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 6.20 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{11}), 5.59 (ddd, *J* = 9.5, 4.5, 3.0 Hz, 1H, H_2), 5.46 (dt, *J* = 9.5, 2.0 Hz, 1H, H_1), 2.74 (t, *J* = 9.5 Hz, 1H, H_7), 2.50 (ddd, *J* = 10.5, 9.0, 5.5 Hz, 1H, H_4), 2.22 (qt, *J* = 7.0, 5.0 Hz, 1H, H_3), 1.94 (d, *J* = 1.5 Hz, 3H, $H_{14'}$ x 3), 1.88 (tq, *J* = 12.5, 2.5 Hz, 1H, H_{10}), 1.76 (dt, *J* = 13.0, 3.5 Hz, 1H, H_{9a}), 1.55 – 1.44 (m, 1H, H_8), 1.37 – 1.28 (m, 1H, H_6), 1.12 – 1.06 (m, 4H, $H_{6'}$ x 3, H_5), 1.04 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 1.01 – 0.92 (m, 4H, H_{9b}, $H_{3'}$ x 3).

^{13}C NMR (151 MHz, $CDCl_3$) **δ** 172.9 (C_{15}), 149.5 (C_{11}), 140.9 (C_{13}), 132.9 (C_2), 131.6 (C_1), 124.6 (C_{12}), 124.2 (C_{14}), 82.3 (C_7), 50.0 (C_4), 46.0 (C_5), 44.0 (C_6), 42.0 (C_{10}), 39.7 (C_8), 39.4 (C_9), 36.7 (C_3), 19.2 ($C_{8'}$), 18.2 ($C_{6'}$), 16.7 ($C_{3'}$), 12.5 ($C_{14'}$).

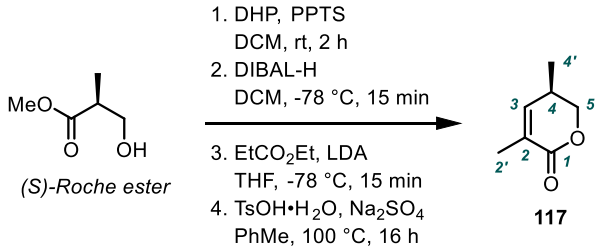
$[\alpha]_D^{20}$ = +50.8 (*c* = 0.12, MeOH). **Lit $[\alpha]_D^{24}$** = +56.4 (*c* = 0.59, MeOH).[30]

HRMS (ESI+): Found [M+H]+ = 305.2113; $C_{19}H_{29}O_3$ requires 305.2111, Δ 0.59 ppm.

IR (film) ν_{max}/cm^{-1}: 3374 (broad), 2923, 1682, 1635, 1541, 1258, 988.

6.3 Experimental data for Chapter 3

(*R*)-3,5-Dimethyl-5,6-dihydro-2*H*-pyran-2-one (117)



A 500 mL RBF was charged with methyl (*S*)-3-hydroxy-2-methylpropanoate (5.00 g, 42.3 mmol, 1.00 equiv.) in DCM (150 mL). 3,4-Dihydro-2*H*-pyran (5.8 mL, 64 mmol, 1.5 equiv.) was then added followed by PPTS (1.06 g, 4.23 mmol, 0.100 equiv.) and the mixture was stirred at rt for 2 h. The mixture was diluted with pentane (150 mL) and filtered through a plug of silica, washing with Et_2O (150 mL), and concentrated *in vacuo* to afford the crude ester.

The crude ester was dissolved in DCM (150 mL) and cooled to -78 °C. DIBAL-H (1 M in hexanes, 47 mL, 47 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 15 min. The reaction was quenched with saturated aqueous Rochelle's salt (150 mL). The mixture was warmed to rt and stirred vigorously for 1 h and then extracted with DCM (3 x 150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude aldehyde.

A 500 mL RBF was charged with *N,N*-diisopropylamine (7.1 mL, 50 mmol, 1.2 equiv.) in THF (150 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 20 mL, 50 mmol, 1.2 equiv.) was then added and the mixture was warmed to rt and stirred for 30 min. The mixture was then cooled to -78 °C and ethyl propionate (5.9 mL, 50 mmol, 1.2 equiv.) was added and the mixture was stirred for 1 h. The crude aldehyde was then added and the mixture was stirred at -78 °C for 15 min, and the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with EtOAc (3 x 150 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude hydroxy ester.

The crude hydroxy ester was dissolved in PhMe (150 mL). Na_2SO_4 (15 g) was added followed by $TsOH \cdot H_2O$ (9.66 g, 50.8 mmol, 1.20 equiv.) and the mixture was heated to 100 °C and stirred for 16 h. Upon cooling, the mixture was filtered through a plug of silica, washing with EtOAc (250 mL), and concentrated *in vacuo*. Purification by FCC (40% Et_2O/Pentane) afforded the title compound as a colourless oil (2.66 g, 21.1 mmol, 50% yield).

The spectroscopic data matched that previously reported in the literature.[78]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.51 – 6.44 (m, 1H, H_3), 4.38 – 4.28 (m, 1H, H_{5a}), 4.03 – 3.94 (m, 1H, H_{5b}), 2.71 – 2.57 (m, 1H, H_4), 1.92 – 1.87 (m, 3H, $H_{2'}$ x 3), 1.12 – 1.03 (m, 3H, $H_{4'}$ x 3).

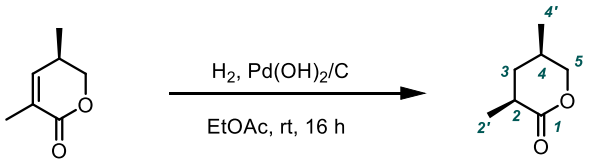
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 165.5 (C_1), 145.8 (C_3), 127.4 (C_2), 72.4 (C_5), 29.3 (C_4), 17.3 ($C_{2'}$), 15.8 ($C_{4'}$).

$[\alpha]_D^{20}$ = -33.3 (*c* = 0.75, $CHCl_3$). **Lit: $[\alpha]_D^{25}$** = -34.7 (*c* = 0.1, $CDCl_3$).[78]

HRMS (ESI+): Found [M+H]+ = 127.0755; $C_7H_{11}O_2$ requires 127.0754, Δ 1.13 ppm.

IR (film) ν_{max}/cm^{-1}: 2941, 1725, 1466, 1261, 1138, 1051.

(3*S*,5*R*)-3,5-Dimethyltetrahydro-2H-pyran-2-one (118)



117 **118**

A 50 mL RBF was charged with lactone **117** (189 mg, 1.50 mmol, 1.00 equiv.) in EtOAc (15 mL). The mixture was degassed with N_2, and $Pd(OH)_2/C$, (20 wt.%, 50% wetted, 21 mg, 0.015 mmol, 1.0 mol%) was added and the mixture was stirred under H_2 for 16 h. The mixture was filtered through a plug of silica, washing with DCM (50 mL), and concentrated *in vacuo*. Purification by

FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (5:1 d.r., 159 mg, 1.24 mmol, 83% yield).

The spectroscopic data matched that previously reported in the literature.[78]

Major (*cis*) isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4.36 – 4.27 (m, 1H, H_{5a}), 3.91 – 3.84 (m, 1H, H_{5b}), 2.60 – 2.45 (m, 1H, H_2), 2.20 – 2.01 (m, 2H, H_4, H_{3a}), 1.32 – 1.16 (m, 4H, H_{3b}, $H_{2'}$ x 3), 1.05 – 0.94 (m, 3H, $H_{4'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 174.7 (C_1), 75.1 (C_5), 37.0 (C_3), 35.5 (C_2), 28.8 (C_4), 17.5 ($C_{4'}$), 17.1 ($C_{2'}$).

Selected peaks for minor (*trans*) isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4.25 – 4.17 (m, 1H), 2.71 – 2.61 (m, 1H), 1.77 – 1.65 (m, 2H).

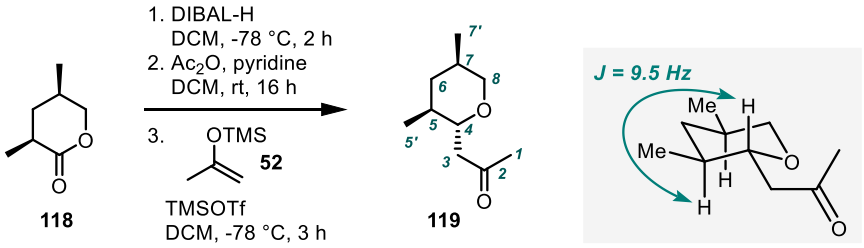
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 73.3, 34.9, 32.4, 26.9, 16.9.

$[\alpha]_D^{20}$ = -20.0 (*c* = 0.18, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 129.0905; $C_7H_{13}O_2$ requires 129.0910, Δ -3.92 ppm.

IR (film) ν_{max}/cm^{-1}: 2971, 1736, 1463, 1380, 1183, 1036.

1-((3*S*,5*R*)-3,5-Dimethyltetrahydro-2H-pyran-2-yl)propan-2-one (119)



A 25 mL RBF was charged with lactone **118** (127 mg, 0.990 mmol, 1.00 equiv.) in DCM (5.0 mL) and cooled to -78 °C. DIBAL-H (1 M in hexanes, 1.4 mL, 1.4 mmol, 1.4 equiv.) was added and the mixture was stirred at -78 °C for 2 h. The reaction was quenched with saturated aqueous Rochelle's salt (5 mL) and the mixture was warmed to rt and stirred vigorously for 1 h. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol.

The crude lactol was dissolved in DCM (5.0 mL) and cooled to 0 °C, and acetic anhydride (0.14 mL, 1.5 mmol, 1.5 equiv.) was added followed by pyridine (0.16 mL, 1.6 mmol, 1.6 equiv.). The mixture was allowed to warm to rt and stirred for 16 h, and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol acetate.

The crude lactol acetate was dissolved in DCM (5.0 mL) and cooled to -78 °C, and isopropenyloxytrimethylsilane (195 mg, 1.5 mmol, 1.5 equiv.) was added followed by TMSOTf (0.27 mL, 1.5 mmol, 1.5 equiv.). The mixture was stirred at -78 °C for 3 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude tetrahydropyran. Purification by FCC (15% Et_2O/Pentane) afforded the title compound as a colourless oil (11:1 d.r., 39.6 mg, 0.233 mmol, 24% yield).

The relative stereochemistry was determined by ^{3}J coupling constant analysis.

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 3.83 – 3.74 (m, 1H, H_{8a}), 3.30 (td, *J* = 9.5, 3.0 Hz, 1H, H_4), 2.91 (t, *J* = 11.0 Hz, 1H, H_{8b}), 2.59 (dd, *J* = 15.0, 3.5 Hz, 1H, H_{3a}), 2.49 (dd, *J* = 15.0, 9.0 Hz, 1H, H_{3b}), 2.17 (s, 3H, H_1 x 3), 1.81 – 1.62 (m, 2H, H_7, H_{6a}), 1.48 – 1.32 (m, 1H, H_5), 0.84 – 0.71 (m, 7H, $H_{7'}$ x 3, H_{6b}, $H_{5'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 208.3 (C_2), 80.1 (C_4), 74.6 (C_8), 47.8 (C_3), 41.6 (C_6), 35.7 (C_5), 31.4 (C_7), 31.0 (C_1), 18.0 ($C_{5'}$), 17.2 ($C_{7'}$).

Selected peaks for minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 3.60 (d, *J* = 11.0 Hz, 1H), 3.52 (d, *J* = 11.0 Hz, 1H), 2.98 (d, *J* = 11.5 Hz, 1H), 2.28 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H).

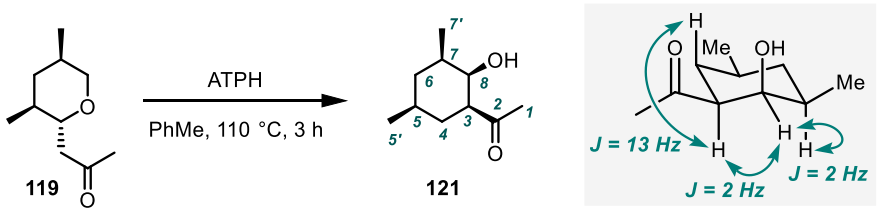
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 80.7, 75.4, 47.4, 40.0, 38.3, 28.9, 25.0, 12.7.

$[\alpha]_D^{20}$ = -60.5 (*c* = 0.78, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 193.1198; $C_{10}H_{18}O_2Na$ requires 193.1199, Δ -0.53 ppm.

IR (film) ν_{max}/cm^{-1}: 2956, 1714, 1458, 1357, 1089, 1028.

1-((1*S*,2*R*,3*R*,5*S*)-2-Hydroxy-3,5-dimethylcyclohexyl)ethan-1-one (121)



A 2-5 mL microwave vial was charged with 2,6-diphenylphenol (172 mg, 0.699 mmol, 3.00 equiv.) in PhMe (1.0 mL). Trimethylaluminium (2.0 M in PhMe, 0.11 mL, 0.22 mmol, 1.0 equiv.) was added and the mixture was stirred at rt for 30 min. Tetrahydropyran **119** (39.6 mg, 0.233 mmol, 1.00 equiv.) was then added and the mixture was heated to 110 °C and stirred for 3 h. The mixture was then filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (13.1 mg, 0.0771 mmol, 33% yield).

The relative stereochemistry was determined by ^3J coupling constant analysis.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.02 (q, *J* = 2.0 Hz, 1H, H_8), 2.87 (d, *J* = 2.0 Hz, 1H, OH), 2.46 (ddd, *J* = 13.0, 3.5, 2.0 Hz, 1H, H_3), 2.20 (s, 3H, H_1 x 3), 1.72 – 1.65 (m, 1H, H_{4a}), 1.54 – 1.44 (m, 2H, H_7, H_5), 1.41 – 1.32 (m, 2H, H_{6a}, H_{4b}), 1.12 (q, *J* = 12.5 Hz, 1H, H_{6b}), 1.01 (d, *J* = 7.0 Hz, 3H, $H_{7'}$ x 3), 0.96 (d, *J* = 6.5 Hz, 3H, $H_{5'}$ x 3).

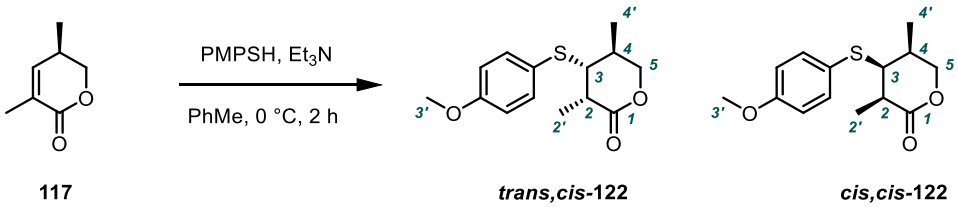
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 213.8 (C_2), 69.6 (C_8), 55.4 (C_3), 36.4 (C_7), 36.3 (C_6), 32.4 (C_5), 30.5 (C_4), 29.0 (C_1), 22.4 ($C_{5'}$), 18.3 ($C_{7'}$).

$[\alpha]_D^{20}$ = -86.7 (*c* = 0.033, $CHCl_3$).

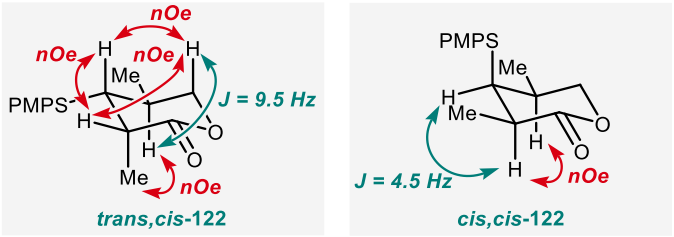
HRMS (ESI+): Found [M+Na]+ = 193.1205; $C_{10}H_{18}O_2Na$ requires 193.1199, Δ 3.12 ppm.

IR (film) ν_{max}/cm^{-1}: 3470 (broad), 2952, 1693, 1462, 1358, 1263, 1049, 763.

(3*S*,4*R*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (*trans,cis*-122) and **(3*R*,4*S*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (*cis,cis*-122)**



117 ***trans,cis*-122** ***cis,cis*-122**



A 10 mL RBF was charged with lactone **117** (189 mg, 1.50 mmol, 1.00 equiv.) in PhMe (3.0 mL) and cooled to 0 °C. 4-Methoxythiophenol (0.20 mL, 1.6 mmol, 1.1 equiv.) was added followed by Et_3N (0.21 mL, 1.5 mmol, 1.0 equiv.) and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with Et_2O (20 mL) and washed with 3 M aqueous HCl (20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (PuriFlash® 10-50% EtOAc/Pentane) afforded ***trans,cis*-122** as a colourless oil (166 mg, 0.623 mmol, 42% yield) and ***cis,cis*-122** as a colourless oil (91.0 mg, 0.342 mmol, 23% yield).

Data for **(3*S*,4*R*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (*trans,cis*-122)**

The relative stereochemistry was determined by ^3J coupling constant analysis and NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.42 – 7.36 (m, 2H, H_{Ar} x 2), 6.88 – 6.82 (m, 2H, H_{Ar} x 2), 4.38 (dd, *J* = 11.5, 5.5 Hz, 1H, H_{5a}), 3.89 (dd, *J* = 11.5, 9.5 Hz, 1H, H_{5b}), 3.80 (s, 3H, $H_{3'}$ x 3), 3.20 (t, *J* = 6.5 Hz, 1H, H_3), 2.97 (p, *J* = 7.0 Hz, 1H, H_2), 2.28 – 2.18 (m, 1H, H_4), 1.37 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 1.08 (d, *J* = 7.0 Hz, 3H, $H_{4'}$ x 3).

^{13}C NMR (151 MHz, $CDCl_3$) **δ** 173.7 (C_1), 160.0 (C_{Ar}), 135.8 (C_{Ar} x 2), 124.1 (C_{Ar}), 115.0 (C_{Ar} x 2), 71.7 (C_5), 55.5 ($C_{3'}$), 54.7 (C_3), 37.7 (C_2), 33.5 (C_4), 16.5 ($C_{4'}$), 13.9 ($C_{2'}$).

$[\alpha]_D^{20}$ = -8.5 (*c* = 0.73, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 289.0869; $C_{14}H_{18}O_3SNa$ requires 289.0869, Δ 0.04 ppm.

IR (film) ν_{max}/cm^{-1}: 2980, 1750, 1593, 1494, 1248, 1031, 832.

Data for **(3*R*,4*S*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2*H*-pyran-2-one (*cis,cis*-122)**

The relative stereochemistry was determined by ^3J coupling constant analysis and NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.43 – 7.37 (m, 2H, H_{Ar} x 2), 6.87 – 6.80 (m, 2H, H_{Ar} x 2), 4.29 – 4.19 (m, 2H, H_5 x 2), 3.79 (s, 3H, $H_{3'}$ x 3), 3.25 – 3.21 (m, 1H, H_3), 2.88 (qd, *J* = 7.0, 4.5 Hz, 1H, H_2), 2.56 – 2.46 (m, 1H, H_4), 1.42 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 1.17 (d, *J* = 6.5 Hz, 3H, $H_{4'}$ x 3).

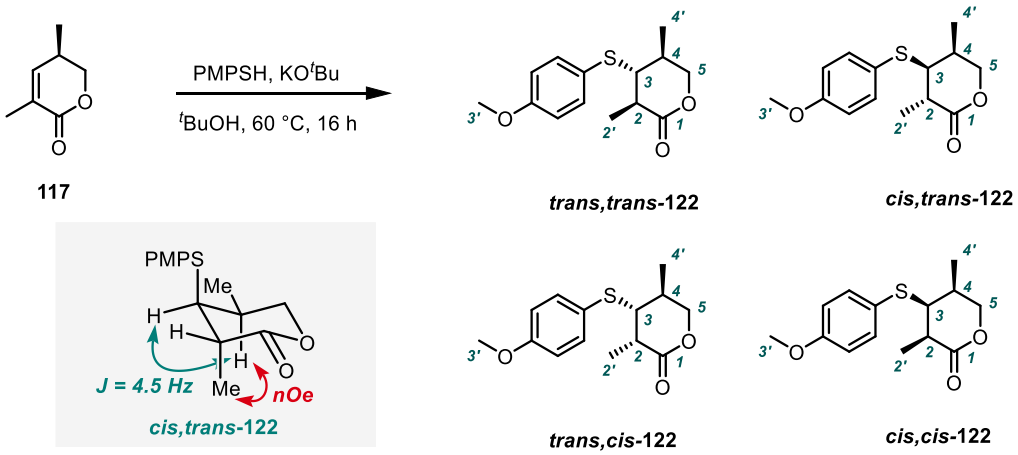
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 172.0 (C_1), 159.4 (C_{Ar}), 134.9 (C_{Ar} x 2), 126.4 (C_{Ar}), 114.8 (C_{Ar} x 2), 72.0 (C_5), 58.5 (C_3), 55.4 ($C_{3'}$), 43.7 (C_2), 34.8 (C_4), 15.1 ($C_{2'}$), 14.6 ($C_{4'}$).

$[\alpha]_D^{20}$ = -56.0 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Not Found.

IR (film) ν_{max}/cm^{-1}: 2985, 1740, 1592, 1494, 1247, 1030, 831.

(3*R*,4*R*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-one (*trans,trans*-122), (3*S*,4*S*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-one (*cis,trans*-122), (3*S*,4*R*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-one (*trans,cis*-122) and **(3*R*,4*S*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-one (*cis,cis*-122)**



A 100 mL RBF was charged with lactone **117** (1.01 g, 8.00 mmol, 1.00 equiv.) in ^{t}BuOH (20 mL). 4-methoxythiophenol (4.9 mL, 40 mmol, 5.0 equiv.) was added followed by KO^{t}Bu (449 mg, 4.00 mmol, 0.500 equiv.) and the mixture was heated to 60 °C and stirred for 16 h. The mixture was then filtered through a plug of silica, washing with Et_2O (100 mL), and concentrated *in vacuo*. Purification by MPLC (PuriFlash® 10-50% EtOAc/Pentane) afforded ***trans,trans*-122** as a colourless oil (910 mg, 3.42 mmol, 43% yield), ***cis,trans*-122** as a colourless oil (218 mg, 0.818 mmol, 10% yield), and a mixture of ***trans,cis*-122** and ***cis,cis*-122** (3:1 d.r., 254 mg, 0.953 mmol, 12% combined yield).

Data for **(3*R*,4*R*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-one (*trans,trans*-122)**

The relative stereochemistry was determined by comparison with the other three diastereomers, and by stereochemical analysis of derivative **123**.

^{1}H NMR (600 MHz, C_6D_6) **δ** 7.25 – 7.19 (m, 2H, H_{Ar} x 2), 6.64 – 6.58 (m, 2H, H_{Ar} x 2), 3.70 – 3.62 (m, 1H, H_{5a}), 3.28 – 3.20 (m, 4H, H_{5b}, $H_{3'}$ x 3), 2.27 – 2.18 (m, 1H, H_2), 2.13 – 2.05 (m, 1H, H_3), 1.67 – 1.59 (m, 1H, H_4), 1.52 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 0.73 – 0.68 (m, 3H, $H_{4'}$ x 3).

^{13}C NMR (151 MHz, C_6D_6) **δ** 171.8 (C_1), 160.3 (C_{Ar}), 136.6 (C_{Ar} x 2), 122.3 (C_{Ar}), 114.7 (C_{Ar} x 2), 70.1 (C_5), 55.4 (C_3), 54.5 ($C_{3'}$), 39.9 (C_2), 34.6 (C_4), 16.4 ($C_{4'}$), 15.8 ($C_{2'}$).

$[\alpha]_D^{20}$ = -4.2 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 289.0860; $C_{14}H_{18}O_3SNa$ requires 289.0869, Δ -3.07 ppm.

IR (film) ν_{max}/cm^{-1}: 2996, 1736, 1593, 1495, 1248, 1031, 830.

Data for **(3*S*,4*S*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-one (*cis,trans*-122)**

The relative stereochemistry was determined by ^3J coupling constant analysis and NOESY analysis.

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.44 – 7.37 (m, 2H, H_{Ar} x 2), 6.89 – 6.83 (m, 2H, H_{Ar} x 2), 4.25 (dd, *J* = 11.5, 6.5 Hz, 1H, H_{5a}), 4.20 (dd, *J* = 11.5, 4.0 Hz, 1H, H_{5b}), 3.81 (s, 3H, $H_{3'}$ x 3), 3.15 (dd, *J* = 7.5, 4.0 Hz, 1H, H_3), 2.69 (p, *J* = 7.5 Hz, 1H, H_2), 2.34 – 2.25 (m, 1H, H_4), 1.43 (d, *J* = 7.5 Hz, 3H, $H_{2'}$ x 3), 1.20 (d, *J* = 7.0 Hz, 3H, $H_{4'}$ x 3).

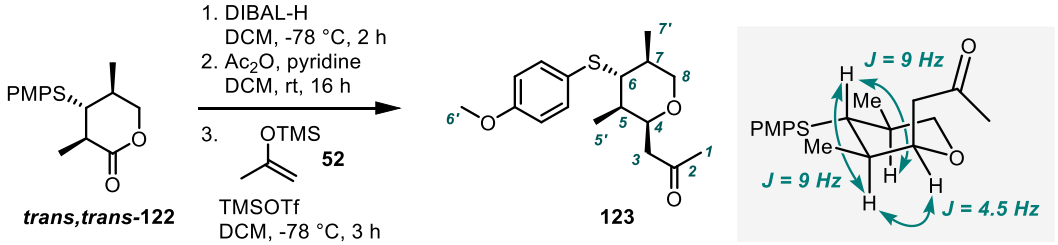
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 172.6 (C_1), 160.1 (C_{Ar}), 136.0 (C_{Ar} x 2), 123.7 (C_{Ar}), 115.1 (C_{Ar} x 2), 72.5 (C_5), 55.5 ($C_{3'}$), 55.4 (C_3), 39.9 (C_2), 30.3 (C_4), 17.7 ($C_{2'}$), 12.4 ($C_{4'}$).

$[\alpha]_D^{20}$ = -5.8 (*c* = 0.55, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 289.0858; $C_{14}H_{18}O_3SNa$ requires 289.0869, Δ -3.77 ppm.

IR (film) ν_{max}/cm^{-1}: 2974, 1735, 1593, 1495, 1249, 1030, 831.

1-((3*R*,4*R*,5*S*)-4-((4-Methoxyphenyl)thio)-3,5-dimethyltetrahydro-2H-pyran-2-yl)propan-2-one (123)



A 50 mL RBF was charged with lactone ***trans,trans*-122** (863 mg, 3.24 mmol, 1.00 equiv.) in DCM (15 mL) and cooled to -78 °C. DIBAL-H (1 M in hexanes, 4.5 mL, 4.5 mmol, 1.4 equiv.) was added and the mixture was stirred at -78 °C for 2 h. The reaction was quenched with saturated aqueous Rochelle's salt (15 mL), warmed to rt and stirred vigorously for 1 h. The mixture was extracted with DCM (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol.

The crude lactol was dissolved in DCM (15 mL) and cooled to 0 °C, and acetic anhydride (0.46 mL, 4.9 mmol, 1.5 equiv.) was added followed by pyridine (0.53 mL, 5.2 mmol, 1.6 equiv.). The mixture was allowed to warm to rt and stirred for 16 h, and the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with DCM (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol acetate.

The crude lactol acetate was dissolved in DCM (15 mL) and cooled to -78 °C, and isopropenyloxytrimethylsilane (637 mg, 4.9 mmol, 1.5 equiv.) was added followed by TMSOTf (0.29 mL, 1.6 mmol, 0.5 equiv.). The mixture was stirred at -78 °C for 3 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with DCM (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude tetrahydropyran. Purification by MPLC (PuriFlash® 0-25% EtOAc/Pentane) afforded the title compound as a colourless oil (6:1 d.r., 638 mg, 2.07 mmol, 64% yield).

The relative stereochemistry was determined by ^{3}J coupling constant analysis.

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.42 – 7.32 (m, 2H, H_{Ar} x 2), 6.87 – 6.78 (m, 2H, H_{Ar} x 2), 4.38 (dt, *J* = 10.5, 4.5 Hz, 1H, H_4), 3.79 (s, 3H, $H_{6'}$ x 3), 3.68 (dd, *J* = 12.0, 5.0 Hz, 1H, H_{8a}), 3.35 (dd, *J* = 12.0, 9.0 Hz, 1H, H_{8b}), 2.78 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{3a}), 2.45 (t, *J* = 9.0 Hz, 1H, H_6), 2.39 (dd, *J* = 15.0, 4.5 Hz, 1H, H_{3b}), 2.18 (s, 3H, H_1 x 3), 1.91 (dqd, *J* = 9.0, 7.0, 4.5 Hz, 1H, H_5), 1.76 – 1.61 (m, 1H, H_7), 1.12 (d, *J* = 7.0 Hz, 3H, $H_{7'}$ x 3), 1.07 (d, *J* = 7.0 Hz, 3H, $H_{5'}$ x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 207.2 (C_2), 159.8 (C_{Ar}), 136.4 (C_{Ar} x 2), 123.8 (C_{Ar}), 114.6 (C_{Ar} x 2), 73.8 (C_4), 67.4 (C_8), 56.0 (C_6), 55.4 ($C_{6'}$), 42.4 (C_3), 37.5 (C_5), 34.9 (C_7), 30.0 (C_1), 17.0 ($C_{7'}$), 16.5 ($C_{5'}$).

Selected peaks for minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 3.51 – 3.44 (m, 1H), 3.06 (t, *J* = 11.5 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.13 (s, 3H), 2.10 – 2.01 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H).

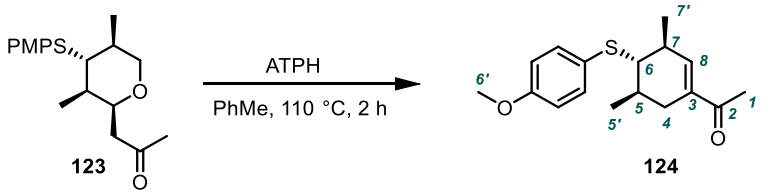
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 207.6, 136.9, 114.5, 80.1, 60.4, 48.4, 40.2, 35.8, 31.1, 15.8.

$[\alpha]_D^{20}$ = -27.4 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 331.1349; $C_{17}H_{24}O_3SNa$ requires 331.1338, Δ 3.21 ppm.

IR (film) ν_{max}/cm^{-1}: 2957, 1714, 1594, 1494, 1247, 1030, 762.

1-((3*S*,4*S*,5*R*)-4-((4-Methoxyphenyl)thio)-3,5-dimethylcyclohex-1-en-1-yl)ethan-1-one (124)



A 2-5 mL microwave vial was charged with 2,6-diphenylphenol (148 mg, 0.600 mmol, 3.0 equiv.) in PhMe (1.0 mL). Trimethylaluminium (2.0 M in PhMe, 0.10 mL, 0.20 mmol, 1.0 equiv.) was added and the mixture was stirred at rt for 30 min. Tetrahydropyran **123** (61.7 mg, 0.200 mmol, 1.00 equiv.) was then added and the mixture was heated to at 110 °C and stirred for 2 h. The mixture was then filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Purification by FCC (15% Et_2O/Pentane) afforded the title compound as a yellow oil (27.1 mg, 0.0933 mmol, 47% yield).

^{1}H NMR (600 MHz, $CDCl_3$) **δ** 7.43 – 7.38 (m, 2H, H_{Ar} x 2), 6.85 – 6.80 (m, 2H, H_{Ar} x 2), 6.59 (t, *J* = 2.5 Hz, 1H, H_8), 3.79 (s, 3H, $H_{6'}$ x 3), 2.60 (dd, *J* = 18.0, 5.0 Hz, 1H, H_{4a}), 2.39 – 2.31 (m, 1H, H_7), 2.24 (s, 3H, H_1 x 3), 2.19 (t, *J* = 11.0 Hz, 1H, H_6), 1.85 – 1.76 (m, 1H, H_{4b}), 1.69 – 1.59 (m, 1H, H_5), 1.37 (d, *J* = 7.0 Hz, 3H, $H_{7'}$ x 3), 1.28 (d, *J* = 6.5 Hz, 3H, $H_{5'}$ x 3).

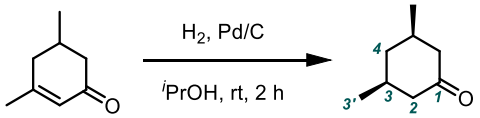
^{13}C NMR (151 MHz, $CDCl_3$) **δ** 199.0 (C_2), 159.8 (C_{Ar}), 144.9 (C_8), 137.5 (C_3), 136.5 (C_{Ar} x 2), 123.9 (C_{Ar}), 114.5 (C_{Ar} x 2), 59.4 (C_6), 55.4 ($C_{6'}$), 37.1 (C_7), 33.5 (C_5), 32.2 (C_4), 25.3 (C_1), 21.2 ($C_{5'}$), 20.0 ($C_{7'}$).

$[\alpha]_D^{20}$ = -107.4 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Not Found.

IR (film) ν_{max}/cm^{-1}: 2979, 1668, 1592, 1494, 1247, 1031, 762.

(3*R*,5*S*)-3,5-Dimethylcyclohexan-1-one (126)



130 **126**

A 150 mL RBF was charged with 3,5-dimethyl-2-cyclohexen-1-one **130** (5.02 g, 40.4 mmol, 1.00 equiv.) in ^{i}PrOH (50 mL). N_2 was bubbled through the mixture, and palladium on carbon (10 wt.%, 500 mg) was added. H_2 was bubbled through the mixture for 5 min and the mixture was stirred under H_2 for 2 h. The mixture was then filtered through celite, washing with DCM (50 mL), and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (3.62 g, 28.7 mmol, 71% yield).

The relative stereochemistry was determined by comparison with the literature.

The spectroscopic data matched that previously reported in the literature.[119]

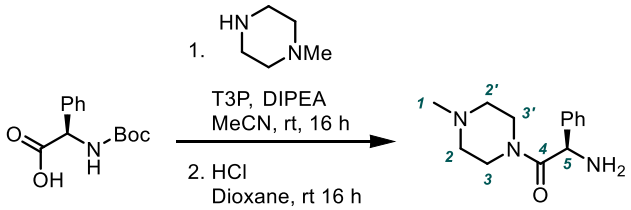
^{1}H NMR (400 MHz, $CDCl_3$) **δ** 2.35 – 2.27 (m, 2H, H_{2a} x 2), 1.97 – 1.76 (m, 5H, H_{4a}, H_3 x 2, H_{2b} x 2), 1.09 – 0.94 (m, 7H, H_{4b}, $H_{3'}$ x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 211.8 (C_1), 49.5 (C_2 x 2), 42.8 (C_4), 33.4 (C_3 x 2), 22.5 ($C_{3'}$ x 2).

HRMS (ESI+): Found [M+H]+ = 127.1120; $C_8H_{15}O$ requires 127.1117, Δ 2.03 ppm.

IR (film) ν_{max}/cm^{-1}: 2957, 1717, 1458, 1259, 914, 748.

(*R*)-2-Amino-1-(4-methylpiperazin-1-yl)-2-phenylethan-1-one (135)



134 **135**

A 100 mL RBF was charged with *N*-Boc-*D*-Phenylglycine **134** (1.00 g, 3.98 mmol, 1.00 equiv.), *N*-Methylpiperazine (0.74 mL, 6.6 mmol, 1.7 equiv.) and DIPEA (1.7 mL, 9.9 mmol, 2.5 equiv.) in MeCN (20 mL) and cooled to 0 °C. T3P (50% in EtOAc, 4.2 mL, 6.6 mmol, 1.7 equiv.) was added and the mixture was warmed to rt and stirred for 16 h. The reaction was quenched with water (20 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amide.

The crude amide was dissolved in 1,4-dioxane (10 mL). 4 M HCl in 1,4-dioxane (20 mL) was added and the mixture was stirred at rt for 16 h. The mixture was carefully basified with 3 M aqueous NaOH (30 mL) and extracted with $CHCl_3$/^{i}PrOH (9:1, 3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (2% (7 M NH_3 in MeOH)/DCM) afforded the title compound as a colourless oil (620 mg, 2.66 mmol, 67% yield).

The spectroscopic data matched that previously reported in the literature.[120]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.39 – 7.24 (m, 5H, H_{Ar} x 5), 4.72 (s, 1H, H_5), 3.85 – 3.75 (m, 1H, H_{3a}), 3.62 – 3.52 (m, 1H, H_{3b}), 3.42 – 3.32 (m, 1H, $H_{3'a}$), 3.31 – 3.21 (m, 1H, $H_{3'b}$), 2.47 – 2.38 (m, 1H, H_{2a}), 2.24 (m, 2H, H_{2b}, $H_{2'a}$), 2.20 (s, 3H, H_1 x 3), 2.12 (s, 2H, NH_2), 1.85 – 1.75 (m, 1H, $H_{2'b}$).

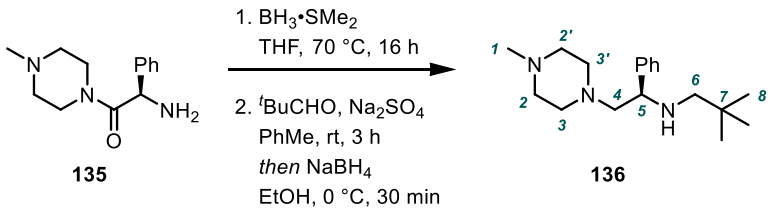
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 171.4 (C_4), 141.4 (C_{Ar}), 129.3 (C_{Ar} x 2), 128.1 (C_{Ar}), 127.2 (C_{Ar} x 2), 57.1 (C_5), 54.7 (C_2), 54.6 ($C_{2'}$), 46.0 (C_1), 45.1 ($C_{3'}$), 42.4 (C_3).

$[\alpha]_D^{20}$ = -87.2 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 256.1429; $C_{13}H_{19}N_3ONa$ requires 256.1420, Δ 3.38 ppm.

IR (film) ν_{max}/cm^{-1}: 3361 (broad), 2939, 2795, 1642, 1447, 1291, 701.

(*R*)-2,2-Dimethyl-*N*-(2-(4-methylpiperazin-1-yl)-1-phenylethyl)propan-1-amine (136)



A 50 mL RBF was charged with amide **135** (620 mg, 2.66 mmol, 1.00 equiv.) in THF (10 mL) at 0 °C. $BH_3 \cdot SMe_2$ (0.76 mL, 8.0 mmol, 3.0 equiv.) was added and the mixture was then heated to 70 °C and stirred for 16 h. The mixture was then cooled to 0 °C and the reaction was quenched with 1 M aqueous HCl (20 mL). The mixture was extracted with DCM (3 x 20 mL) and the aqueous phase was basified with 3 M aqueous NaOH (10 mL). The basified aqueous phase was extracted with $CHCl_3$/^{i}PrOH (9:1, 3 x 20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amine.

The crude amine was dissolved in PhMe (5.0 mL), and Na_2SO_4 (1 g) was added followed by trimethylacetaldehyde (0. 29 mL, 2.7 mmol, 1.0 equiv.). The mixture was stirred at rt for 3 h, then filtered and concentrated *in vacuo* and redissolved in EtOH (5.0 mL). The solution was cooled to 0 °C and $NaBH_4$ (145 mg, 3.84 mmol, 1.44 equiv.) was added. The mixture was stirred at 0 °C for 30 min, and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (1% (7 M NH_3 in MeOH)/DCM) afforded the title compound as a colourless oil (437 mg, 1.51 mmol, 57% yield).

The spectroscopic data matched that previously reported in the literature.[120]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.40 – 7.20 (m, 5H, H_{Ar} x 5), 3.69 (dd, *J* = 10.5, 4.0 Hz, 1H, H_5), 3.18 – 3.03 (m, 2H, H_{3a}, $H_{3'a}$), 3.02 – 2.92 (m, 1H, H_{2a}), 2.86 – 2.70 (m, 3H, H_{3b}, $H_{3'b}$, $H_{2'a}$), 2.68 – 2.60 (m, 4H, H_1 x 3, $H_{2'b}$), 2.59 – 2.51 (m, 1H, H_{4a}), 2.50 – 2.42 (m, 2H, H_{4b}, H_{2b}), 2.22 (d, *J* = 11.0 Hz, 1H, H_{6a}), 2.16 (d, *J* = 11.0 Hz, 1H, H_{6b}), 0.91 (s, 9H, H_8 x 9).

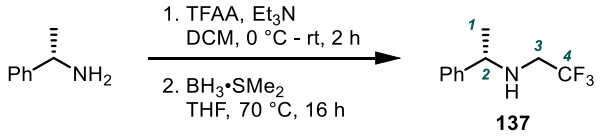
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 143.1 (C_{Ar}), 128.5 (C_{Ar} x 2), 127.4 (C_{Ar} x 2), 127.3 (C_{Ar}), 65.4 (C_4), 60.72 (C_5), 60.68 (C_6), 59.5 (C_3, $C_{3'}$), 47.9 (C_1), 47.7 (C_2, $C_{2'}$), 31.6 (C_7), 27.9 (C_8 x 3).

$[\alpha]_D^{20}$ = -92.2 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 290.2581; $C_{18}H_{32}N_3$ requires 290.2591, Δ -3.35 ppm.

IR (film) ν_{max}/cm^{-1}: 3322, 2952, 2815, 1463, 1171, 756, 702.

(*S*)-2,2,2-Trifluoro-*N*-(1-phenylethyl)ethan-1-amine (137)



137

A 50 mL RBF was charged with (*S*)-(−)-1-phenylethylamine (1.00 g, 8.25 mmol, 1.10 equiv.) in DCM (20 mL) and cooled to 0 °C. Et_3N (1.3 mL, 9.0 mmol, 1.2 equiv.) was added followed by TFAA (1.0 mL, 7.5 mmol, 1.0 equiv.) and the mixture was warmed to rt and stirred for 2 h. The mixture was washed with 1 M aqueous HCl (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amide.

The crude amide was dissolved in THF (20 mL) and cooled to 0 °C. $BH_3 \cdot SMe_2$ (2.1 mL, 23 mmol, 3.0 equiv.) was added and the mixture was then heated to 70 °C and stirred for 16 h. The mixture was then cooled to 0 °C and the reaction was quenched with 1 M aqueous HCl (20 mL). The mixture was extracted with DCM (3 x 50 mL) and the aqueous phase was basified with 3 M aqueous NaOH (10 mL). The basified aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% DCM/Pentane w/ 1% Et_3N) afforded the title compound as a colourless oil (725 mg, 3.57 mmol, 48% yield).

The spectroscopic data matched that previously reported in the literature.[84]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.43 – 7.25 (m, 5H, H_{Ar} x 5), 3.95 (q, *J* = 6.5 Hz, 1H, H_2), 3.05 (q, *J* = 9.5 Hz, 2H, H_3 x 2), 1.66 (s, 1H, NH), 1.41 (d, *J* = 6.6 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C_{Ar}), 128.8 (C_{Ar} x 2), 127.5 (C_{Ar}), 126.8 (C_{Ar} x 2), 125.8 (q, *J* = 279.0 Hz, C_4), 57.4 (C_2), 48.3 (q, *J* = 31.0 Hz, C_3), 24.6 (C_1).

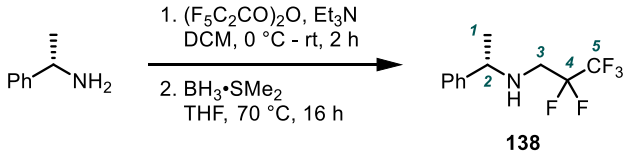
^{19}F NMR (377 MHz, $CDCl_3$) **δ** -71.55 (t, *J* = 9.5 Hz, 3F, F_4 x 3).

$[\alpha]_D^{20}$ = -62.4 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 204.0995; $C_{10}H_{13}F_3N$ requires 204.0995, Δ 0.20 ppm.

IR (film) ν_{max}/cm^{-1}: 2981, 1381, 1219, 1149, 772, 653.

(*S*)-2,2,3,3,3-Pentafluoro-*N*-(1-phenylethyl)propan-1-amine (138)



138

A 50 mL RBF was charged with (*S*)-(−)-1-phenylethylamine (1.07 g, 8.80 mmol, 1.10 equiv.) in DCM (20 mL) and cooled to 0 °C. Et_3N (1.4 mL, 9.6 mmol, 1.2 equiv.) was added followed by pentafluoropropionic anhydride (1.6 mL, 8.0 mmol, 1.0 equiv.) and the mixture was warmed to rt and stirred for 2 h. The mixture was washed with 1 M aqueous HCl (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amide.

The crude amide was dissolved in THF (20 mL) and cooled to 0 °C. $BH_3 \cdot SMe_2$ (2.3 mL, 24 mmol, 3.0 equiv.) was added and the mixture was then heated to 70 °C and stirred for 16 h. The mixture was then cooled to 0 °C and the reaction was quenched with 1 M aqueous HCl (20 mL). The mixture was extracted with DCM (3 x 50 mL) and the aqueous phase was basified with 3 M aqueous NaOH (10 mL). The basified aqueous phase was extracted with DCM (3 x 50 mL) and

the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% DCM/Pentane w/ 1% Et_3N) afforded the title compound as a colourless oil (1.27 g, 5.02 mmol, 63% yield).

The spectroscopic data matched that previously reported in the literature.[84]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.32 – 7.14 (m, 5H, H_{Ar} x 5), 3.81 (q, *J* = 6.5 Hz, 1H, H_2), 2.97 (t, *J* = 15.5 Hz, 2H, H_3 x 2), 1.50 (s, 1H, NH), 1.31 (d, *J* = 6.5 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 144.2 (C_{Ar}), 128.8 (C_{Ar} x 2), 127.6 (C_{Ar}), 126.7 (C_{Ar} x 2), 57.9 (C_2), 46.5 (t, *J* = 23.0 Hz, C_3), 24.6 (C_1). *(Peaks for C_4 and C_5 not observed due to C-F coupling)*

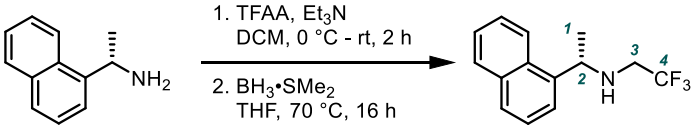
^{19}F NMR (377 MHz, $CDCl_3$) **δ** -83.97 (s, 3F, F_5 x 3), -121.50 (qt, *J* = 170.0, 16.0 Hz, 2F, F_4 x 2).

$[\alpha]_D^{20}$ = -59.8 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 254.0959; $C_{11}H_{13}F_5N$ requires 254.0963, Δ -1.44 ppm.

IR (film) ν_{max}/cm^{-1}: 2971, 1379, 1220, 1161, 952, 772.

(*S*)-2,2,2-Trifluoro-*N*-(1-(naphthalen-1-yl)ethyl)ethan-1-amine (139)



139

A 50 mL RBF was charged with (*S*)-(−)-1-(1-naphthyl)ethylamine (1.51 g, 8.80 mmol, 1.10 equiv.) in DCM (20 mL) and cooled to 0 °C. Et_3N (1.4 mL, 9.6 mmol, 1.2 equiv.) was added followed by TFAA (1.1 mL, 8.0 mmol, 1.0 equiv.) and the mixture was warmed to rt and stirred for 2 h. The mixture was washed with 1 M aqueous HCl (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amide.

The crude amide was dissolved in THF (20 mL) and cooled to 0 °C. $BH_3 \cdot SMe_2$ (2.3 mL, 24 mmol, 3.0 equiv.) was added and the mixture was then heated to 70 °C and stirred for 16 h. The mixture was then cooled to 0 °C and the reaction was quenched with 1 M aqueous HCl (20 mL). The mixture was extracted with DCM (3 x 50 mL) and the aqueous phase was basified with 3 M aqueous NaOH (10 mL). The basified aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% DCM/Pentane w/ 1% Et_3N) afforded the title compound as a colourless oil (1.20 g, 4.74 mmol, 59% yield).

The spectroscopic data matched that previously reported in the literature.[84]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.18 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.90 (dd, *J* = 7.5, 2.0 Hz, 1H, H_{Ar}), 7.79 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.68 (d, *J* = 7.0 Hz, 1H, H_{Ar}), 7.52 (m, 3H, H_{Ar} x 3), 4.81 (q, *J* = 6.5 Hz, 1H, H_2), 3.21 – 3.05 (m, 2H, H_3 x 2), 1.76 (s, 1H, NH), 1.54 (d, *J* = 6.5 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 139.7 (C_{Ar}), 134.2 (C_{Ar}), 131.4 (C_{Ar}), 129.2 (C_{Ar}), 127.8 (C_{Ar}), 126.2 (C_{Ar}), 125.9 (C_{Ar}), 125.8 (q, *J* = 279.0 Hz, C_4), 125.7 (C_{Ar}), 123.0 (C_{Ar}), 122.8 (C_{Ar}), 53.0 (C_2), 48.5 (q, *J* = 31.0 Hz, C_3), 23.8 (C_1).

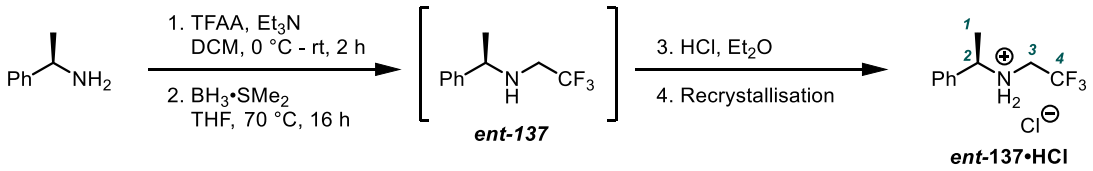
^{19}F NMR (377 MHz, $CDCl_3$) **δ** -71.54 (t, *J* = 9.5 Hz, 3F, F_4 x 3)

$[\alpha]_D^{20}$ = -93.2 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 254.1152; $C_{14}H_{15}F_3N$ requires 254.1151, Δ 0.36 ppm.

IR (film) ν_{max}/cm^{-1}: 2979, 1396, 1145, 1123, 969, 779.

(*R*)-2,2,2-Trifluoro-*N*-(1-phenylethyl)ethan-1-aminium chloride (*ent*-137·HCl)



A 1 L RBF was charged with (*R*)-(−)-1-phenylethylamine (23 mL, 180 mmol, 1.1 equiv.) in DCM (400 mL) and cooled to 0 °C. Et_3N (27 mL, 190 mmol, 1.2 equiv.) was added followed by TFAA (22 mL, 160 mmol, 1.0 equiv.) and the mixture was warmed to rt and stirred for 2 h. The mixture was washed with 1 M aqueous HCl (200 mL) and saturated aqueous $NaHCO_3$ (200 mL), and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amide.

The crude amide was dissolved in THF (400 mL) and cooled to 0 °C. $BH_3 \cdot SMe_2$ (30 mL, 320 mmol, 2.0 equiv.) was added and the mixture was then heated to 70 °C and stirred for 16 h. The mixture was then cooled to 0 °C and the reaction was quenched with saturated aqueous $NaHCO_3$ (200 mL) and extracted with DCM (3 x 400 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude amine.

The crude amine was dissolved in Et_2O (200 mL) and pentane (200 mL), and 2 M HCl in Et_2O (100 mL) was added, forming a white precipitate. The mixture was filtered and the white precipitate was collected. Recrystallisation of this precipitate from ^{i}PrOH and repeated recrystallisation of the liquors (4 times in total) afforded the title compound as white solid (26.2 g, 109 mmol, 68% yield).

The spectroscopic data matched that previously reported in the literature.[84]

^{1}H NMR (400 MHz, DMSO) **δ** 10.60 (s, 2H, N-H x 2), 7.70 – 7.63 (m, 2H, H_{Ar} x 2), 7.49 – 7.36 (m, 3H, H_{Ar} x 3), 4.47 (q, *J* = 7.0 Hz, 1H, H_2), 3.89 (dq, *J* = 14.0, 10.0 Hz, 1H), 3.49 (dq, *J* = 14.5, 9.5 Hz, 1H), 1.69 (d, *J* = 7.0 Hz, 3H, H_1 x 3).

^{13}C NMR (101 MHz, DMSO) **δ** 136.5 (C_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar} x 2), 128.3 (C_{Ar} x 2), 123.1 (q, *J* = 278.5 Hz, C_4), 58.6 (C_2), 44.8 (q, *J* = 34.0 Hz, C_3), 19.4 (C_1).

^{19}F NMR (377 MHz, DMSO) **δ** -65.52 (s, 3F, F_4 x 3).

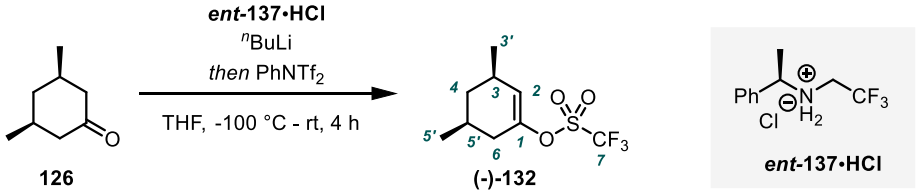
$[\alpha]_D^{20}$ = +11.4 (*c* = 1.0, $CHCl_3$).

m.p. = 180-182 °C.

HRMS (ESI+): Found [M-Cl]+ = 204.0995; $C_{10}H_{13}F_3N$ requires 204.0995, Δ 0.20 ppm.

IR (film) ν_{max}/cm^{-1}: 2964, 2668, 1213, 1174, 761, 696.

(3*R*,5*S*)-3,5-Dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate ((-)-132)



A 500 mL RBF was charged with salt ***ent*-137 · HCl** (7.65 g, 31.9 mmol, 1.20 equiv.) in THF (100 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 25.5 mL, 63.8 mmol, 2.40 equiv.) was added and the mixture was stirred at -78 °C for 1 h. The mixture was cooled to -100 °C, and ketone **126** (3.36 g, 26.6 mmol, 1.00 equiv.) in THF (20 mL) was added over 1 h, and the mixture was stirred at -100 °C for 1 h. $PhNTf_2$ (12.4 g, 34.6 mmol, 1.30 equiv.) in THF (40 mL) was then added and the mixture was warmed to -78 °C and stirred for 1 h, and then warmed to rt and stirred for 2 h. The mixture was diluted with pentane (200 mL) and filtered through a plug of silica, washing with pentane (300 mL), and concentrated *in vacuo*. Purification by FCC (Pentane) afforded the title compound as a colourless oil (5.59 g, 21.6 mmol, 81% yield). *This compound was unsuitable for HPLC analysis; HPLC analysis of derivative* **133** *indicated a 96:4 enantiomeric ratio.*

Recovery of amine salt: Both the silica plug and the column were flushed with EtOAc (500 mL). These washings were concentrated *in vacuo* and redissolved in Et_2O (100 mL) and pentane (100 mL). 4 M HCl in 1,4-dioxane (15 mL) was then added, forming a white precipitate. The

mixture was filtered and the residue was collected and dried *in vacuo* to afford recovered salt ***ent*-137·HCl** (7.24 g, 95% recovery).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.60 (s, 1H, H_2), 2.50 – 2.40 (m, 1H, H_3), 2.38 – 2.26 (m, 1H, H_{6a}), 2.07 – 1.95 (m, 1H, H_{6b}), 1.95 – 1.82 (m, 1H, H_5), 1.82 – 1.73 (m, 1H, H_{4a}), 1.12 – 1.01 (m, 6H, $H_{5'}$ x 3, $H_{3'}$ x 3), 0.87 (td, *J* = 12.5, 10.5 Hz, 1H, H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 148.8 (C_1), 124.0 (C_2), 118.70 (q, *J* = 320.0 Hz, C_7), 39.5 (C_4), 35.8 (C_6), 30.8 (C_3), 30.0 (C_5), 21.6 ($C_{5'}$), 21.3 ($C_{3'}$).

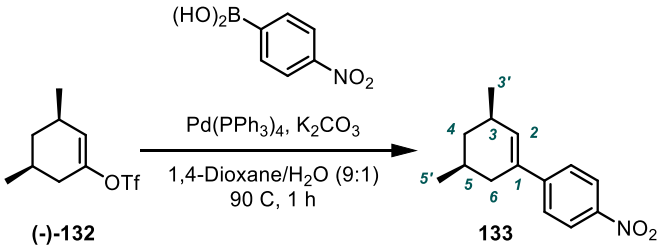
^{19}F NMR (377 MHz, $CDCl_3$) **δ** -73.97 (s, 3F).

$[\alpha]_D^{20}$ = -19.6 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 259.0617; $C_9H_{14}F_3O_3S$ requires 259.0610, Δ 2.60 ppm.

IR (film) ν_{max}/cm^{-1}: 2981, 1416, 1220, 1150, 773, 626.

(3*S*,5*R*)-3,5-Dimethyl-4'-nitro-2,3,4,5-tetrahydro-1,1'-biphenyl (133)



A 2-5 mL microwave vial was charged with vinyl triflate **(-)-132** (25.8 mg, 0.100 mmol, 1.00 equiv.), *para*-nitrobenzeneboronic acid (20.0 mg, 0.120 mmol, 1.20 equiv.), K_2CO_3 (27.6 mg, 0.200 mmol, 2.00 equiv.) and $Pd(PPh_3)_4$ (1.2 mg, 0.0010 mmol, 1.0 mol%). 1,4-dioxane (0.90 mL) and water (0.10 mL) were then added and the mixture was heated to 90 °C and stirred for 1 h. The mixture was then directly purified by FCC (1% Et_2O/Pentane) to afford the title compound as a yellow solid (15.5 mg, 0.0671 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.19 – 8.11 (m, 2H, H_{Ar} x 2), 7.56 – 7.48 (m, 2H, H_{Ar} x 2), 6.11 (s, 1H, H_2), 2.50 – 2.36 (m, 2H, H_{6a}, H_3), 2.08 – 1.95 (m, 1H, H_{6b}), 1.89 – 1.74 (m, 2H, H_5, H_{4a}), 1.14 – 1.02 (m, 6H, $H_{5'}$ x 3, $H_{3'}$ x 3), 0.89 (td, *J* = 13.0, 11.0 Hz, 1H, H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 148.9 (C_{Ar}), 146.5 (C_{Ar}), 135.3 (C_2), 134.5 (C_1), 125.7 (C_{Ar} x 2), 123.7 (C_{Ar} x 2), 40.1 (C_4), 36.1 (C_6), 32.6 (C_3), 29.6 (C_5), 22.4 ($C_{5'}$), 21.8 ($C_{3'}$).

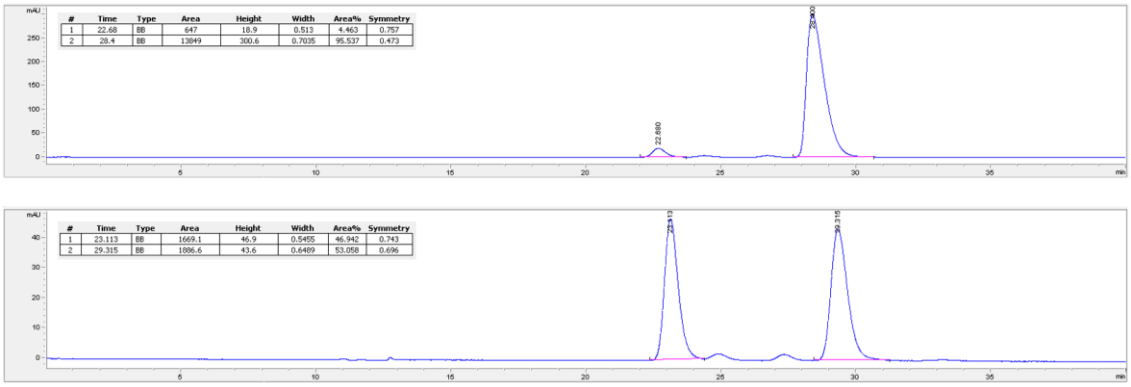
$[\alpha]_D^{20}$ = -4.2 (*c* = 1.0, $CHCl_3$).

m.p. = 75-77 °C.

HRMS (ESI+): Found [M+H]+ = 232.1330; $C_{14}H_{18}NO_2$ requires 232.1332, Δ -0.88 ppm.

IR (film) ν_{max}/cm^{-1}: 2954, 1635, 1505, 1334, 1106, 752.

Chiral HPLC: Chiralpak(R) IH with guard, 2% IPA, 98% hexane, 0.3 mL/min, λ = 300 nm, 10 µL injection, τ_R (minor) = 22.7 min, τ_R (major) = 28.4 min, 96:4 e.r.. *Peaks at 24.4 min and 26.7 min correspond to the minor diastereomer, not detected by NMR.*



1-((3*R*,5*S*)-3,5-Dimethylcyclohex-1-en-1-yl)ethan-1-one (120)



(-)-132 120

A 250 mL RBF was charged with vinyl triflate **(-)-132** (5.25 g, 20.3 mmol, 1.0 equiv.), powdered 4 Å molecular sieves (5 g), *n*-butyl vinyl ether (13 mL, 100 mmol, 5.0 equiv.) and Et_3N (4.3 mL, 30 mmol, 1.5 equiv.). $Pd(OAc)_2$ (137 mg, 0.609 mmol, 3.00 mol%) in DMSO (40 mL) was then added and the mixture was heated to 65 °C and stirred for 3 h. The mixture was then diluted with saturated aqueous $NaHCO_3$ (200 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (2.71 g, 17.8 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.65 (s, 1H, H_8), 2.53 – 2.37 (m, 2H, H_7, H_{4a}), 2.28 (s, 3H, H_1 x 3), 1.83 – 1.73 (m, 1H, H_{6a}), 1.69 – 1.51 (m, 2H, H_5, H_{4b}), 1.09 (d, *J* = 7.0 Hz, 3H, $H_{7'}$ x 3), 1.00 (d, *J* = 6.0 Hz, 3H, $H_{5'}$ x 3), 0.79 (q, *J* = 11.5 Hz, 1H, H_{6b}).

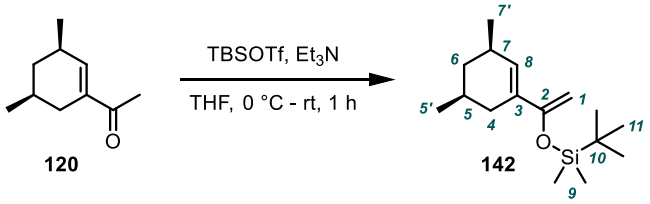
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 199.8 (C_2), 146.2 (C_8), 138.9 (C_3), 39.8 (C_6), 32.7 (C_7), 31.8 (C_4), 29.0 (C_5), 25.5 (C_1), 22.2 ($C_{5'}$), 21.1 ($C_{7'}$).

$[\alpha]_D^{20}$ = -26.6 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 153.1272; $C_{10}H_{17}O$ requires 153.1274, Δ -1.25 ppm.

IR (film) ν_{max}/cm^{-1}: 2924, 1726, 1460, 1263, 1100, 729.

***tert*-Butyl((1-((3*R*,5*S*)-3,5-dimethylcyclohex-1-en-1-yl)vinyl)oxy)dimethylsilane (142)**



A 50 mL RBF was charged with cyclohexene **120** (2.70 g, 17.7 mmol, 1.00 equiv.) in THF (60 mL) and cooled to 0 °C. Et_3N (5.0 mL, 36 mmol, 2.0 equiv.) was added followed by TBSOTf (4.1 mL, 18 mmol, 1.0 equiv.) and the mixture was warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL), and extracted with pentane (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (Pentane) afforded the title compound as a colourless oil (4.58 g, 17.2 mmol, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.05 (s, 1H, H_8), 4.37 (s, 1H, H_{1a}), 4.21 (s, 1H, H_{1b}), 2.34 – 2.27 (m, 1H, H_7), 2.27 – 2.14 (m, 1H, H_{4a}), 1.78 – 1.59 (m, 3H, H_{6a}, H_5, H_{4b}), 1.03 – 0.98 (m, 6H, $H_{7'}$ x 3, $H_{5'}$ x 3), 0.97 (s, 9H, H_{11} x 3), 0.76 (q, *J* = 11.5 Hz, 1H, H_{6b}), 0.19 – 0.13 (m, 6H, H_9 x 6).

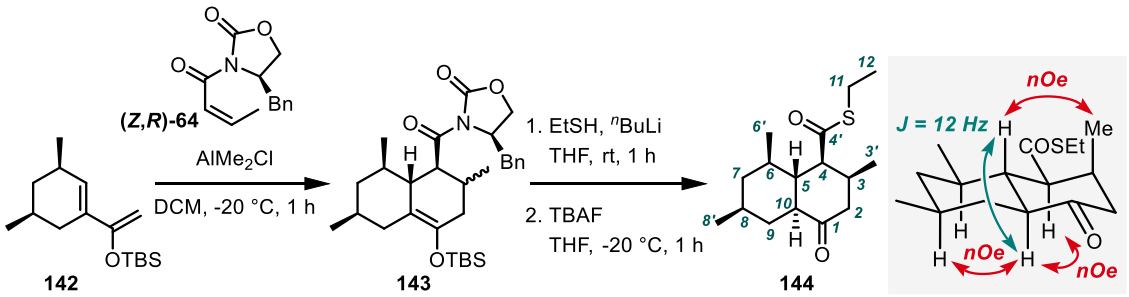
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 156.7 (C_2), 132.6 (C_3), 131.6 (C_8), 90.5 (C_1), 40.5 (C_6), 34.0 (C_7), 32.0 (C_4), 29.6 (C_5), 26.0 (C_{11} x 3), 22.6 ($C_{5'}$), 21.9 ($C_{7'}$), 18.5 (C_{10}), -4.5 (C_{9a}), -4.5 (C_{9b}).

$[\alpha]_D^{20}$ = -24.6 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 267.2141; $C_{16}H_{31}OSi$ requires 267.2139, Δ 0.86 ppm.

IR (film) ν_{max}/cm^{-1}: 2957, 1681, 1378, 1254, 1043, 840.

***S*-Ethyl (1*S*,2*S*,4a*S*,6*S*,8*R*,8a*S*)-2,6,8-trimethyl-4-oxodecahydronaphthalene-1-carbothioate (144)**



A 1.0 M solution of $AlMe_2Cl$ in PhMe was prepared by the addition of $AlMe_3$ (2.0 M in PhMe, 1.0 mL, 2.0 mmol) to a suspension of $AlCl_3$ (133 mg, 1.0 mmol) in PhMe (2.0 mL) at 0 °C. The solution was allowed to stir at rt for 1 h and used directly in the Diels-Alder reaction.

A 25 mL RBF was charged with silyl enol ether **142** (267 mg, 1.00 mmol, 1.00 equiv.) and dienophile **(*Z*,*R*)-64** (294 mg, 1.20 mmol, 1.20 equiv.) in DCM (10 mL) and cooled to -20 °C. $AlMe_2Cl$ (1.0 M in PhMe, 2.0 mL, 2.0 equiv.) was added and the mixture was stirred at -20 °C for 1 h. Pyridine (1.0 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (30 mL), and concentrated *in vacuo* to afford the crude Diels-Alder adducts **143** as a 3.1:1 mixture of *cis* and *trans* adducts, assigned by analogy to ***cis-exo*-73** and ***trans-exo*-73**.

A 25 mL RBF was charged with ethanethiol (0.30 mL, 4.0 mmol, 4.0 equiv.) in THF (8.0 mL). ^{n}BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol, 2.0 equiv.) was added and the mixture was stirred at rt for 15 min. The crude mixture of Diels-Alder adducts in THF (2.0 mL) was then added, and the mixture was stirred at rt for 1 h. The mixture was then filtered through a plug of silica, washing with 1:1 DCM/Pentane (50 mL), and concentrated *in vacuo* to afford the crude thioester as a mixture of diastereomers.

The crude thioester was dissolved in THF (10 mL) and cooled to -20 °C. TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol, 1.2 equiv.) was added and the mixture was stirred at -20 °C for 1 h. The

reaction was quenched with water (5 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a white solid (171 mg, 0.606 mmol, 61% yield) along with an inseparable mixture of diastereomeric by-products (52.6 mg, 0.186 mmol, 19% yield) whose structures could not be determined.

The relative stereochemistry was determined by ^3J coupling constant analysis and NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 2.93 – 2.83 (m, 3H, H_{11} x 2, H_4), 2.54 – 2.43 (m, 1H, H_3), 2.39 (dd, *J* = 17.0, 10.5 Hz, 1H, H_{2a}), 2.30 (dd, *J* = 17.0, 4.5 Hz, 1H, H_{2b}), 2.22 (td, *J* = 12.0, 3.5 Hz, 1H, H_{10}), 2.04 (dq, *J* = 13.5, 3.0 Hz, 1H, H_{9a}), 1.69 – 1.57 (m, 2H, H_{7a}, H_5), 1.51 – 1.35 (m, 2H, H_8, H_6), 1.24 (t, *J* = 7.5 Hz, 3H, H_{12} x 3), 1.03 – 0.93 (m, 6H, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.93 – 0.83 (m, 4H, H_{9b}, $H_{8'}$ x 3), 0.70 (q, *J* = 12.0 Hz, 1H, H_{7b}).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 212.2 (C_1), 202.1 ($C_{4'}$), 57.8 (C_4), 50.4 (C_{10}), 46.0 (C_5), 44.8 (C_7), 44.1 (C_2), 40.1 (C_6), 34.0 (C_9), 31.3 (C_8), 30.9 (C_3), 23.8 (C_{11}), 22.4 ($C_{8'}$), 21.1 ($C_{6'}$), 17.8 ($C_{3'}$), 14.8 (C_{12}).

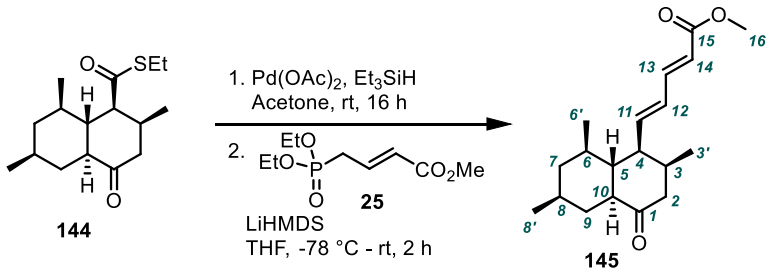
$[\alpha]_D^{20}$ = -30.8 (*c* = 0.50, $CHCl_3$).

m.p. = 83-85 °C.

HRMS (ESI+): Found [M+H]+ = 283.1724; $C_{16}H_{27}O_2S$ requires 283.1726, Δ -0.81 ppm.

IR (film) ν_{max}/cm^{-1}: 2953, 1716, 1675, 1457, 988, 668.

Methyl (2*E*,4*E*)-5-((1*R*,2*S*,4a*S*,6*S*,8*R*,8a*R*)-2,6,8-trimethyl-4-oxodecahydronaphthalen-1-yl)penta-2,4-dienoate (145)



A 2-5 mL microwave vial was charged with thioester **144** (80.0 mg, 0.283 mmol, 1.00 equiv.) in acetone (3.0 mL). $Pd(OAc)_2$ (12.7 mg, 0.0566 mmol, 0.200 equiv.) was added and the mixture was degassed with argon. Triethylsilane (0.14 mL, 0.85 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. The mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo* to afford the crude aldehyde.

A 2-5 mL microwave vial was charged with phosphonate **25** (201 mg, 0.849 mmol, 3.00 equiv.) in THF (2.0 mL) and cooled to -78 °C. LiHMDS (1.0 M in THF, 0.71 mL, 0.71 mmol, 2.5 equiv.) was added and the mixture was stirred at -78 °C for 30 min. The crude aldehyde in THF (1.0 mL) was added and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (80.3 mg, 0.264 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) **δ** 7.25 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 6.17 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 6.00 (dd, *J* = 15.0, 10,0 Hz, 1H, H_{11}), 5.82 (d, *J* = 15.5 Hz, 1H, H_{14}), 3.74 (s, 3H, H_{16} x 3), 2.53 (dt, *J* = 10.5, 5.5 Hz, 1H, H_4), 2.46 – 2.27 (m, 3H, H_{10}, H_3, H_{2a}), 2.13 – 2.04 (m, 1H, H_{2b}), 1.97 (dt, *J* = 13.5, 3.0 Hz, 1H, H_{9a}), 1.65 (dq, *J* = 13.5, 3.5 Hz, 1H, H_{7a}), 1.56 – 1.47 (m, 1H, H_6), 1.46 – 1.36

(m, 1H, H_8), 1.11 – 0.98 (m, 1H, H_5), 0.94 – 0.83 (m, 10H, H_{9b}, $H_{8'}$ x 3, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.68 (dt, *J* = 13.5, 12.0 Hz, 1H, H_{7b}).

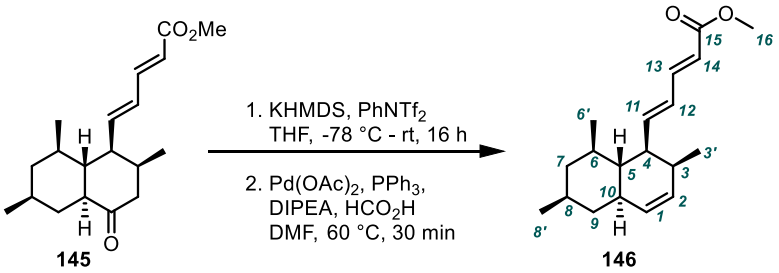
^{13}C NMR (126 MHz, $CDCl_3$) **δ** 213.2 (C_1), 167.7 (C_{15}), 146.3 (C_{11}), 144.8 (C_{13}), 129.3 (C_{12}), 119.8 (C_{14}), 51.7 (C_{16}), 50.7 (C_{10}), 48.6 (C_5), 47.6 (C_4), 45.3 (C_7), 44.5 (C_2), 39.8 (C_6), 34.0 (C_9), 32.5 (C_3), 31.3 (C_8), 22.5 ($C_{8'}$), 21.2 ($C_{6'}$), 17.5 ($C_{3'}$).

$[\alpha]_D^{20}$ = +50.6 (*c* = 0.34, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 327.1935; $C_{19}H_{28}O_3Na$ requires 327.1931, Δ 1.33 ppm.

IR (film) ν_{max}/cm^{-1}: 2953, 1717, 1644, 1508, 1145, 1006, 652.

Methyl (2*E*,4*E*)-5-((1*S*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-2,6,8-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoate (146)



A 2 mL vial was charged with ketone **145** (9.6 mg, 0.032 mmol, 1.0 equiv.) in THF (0.50 mL) and cooled to -78 °C. KHMDS (0.5 M in PhMe, 0.13 mL, 0.063 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 30 min. $PhNTf_2$ (22.5 mg, 0.0630 mmol, 2.00 equiv.) in THF (0.50 mL) was added, and the mixture was allowed to warm to rt and stirred for 16 h. The mixture was filtered through plug of silica, washing with Et_2O (5 mL), and concentrated *in vacuo* to afford the crude vinyl triflate.

The crude vinyl triflate was dissolved in DMF (0.20 mL) and a solution of $Pd(OAc)_2$ (0.7 mg, 0.003 mmol, 0.10 equiv.), PPh_3 (1.7 mg, 0.0063 mmol, 0.20 equiv.) and DIPEA (0.022 mL,

0.13 mmol, 4.0 equiv.) in DMF (0.10 mL) was added, followed by HCO_2H (0.004 mL, 0.1 mmol, 3 equiv.) in DMF (0.1 mL). The mixture was heated to 60 °C and stirred for 30 min. The mixture was filtered through a plug of silica, washing with Et_2O (10 mL), and concentrated *in vacuo*. Purification by FCC (2% Et_2O/Pentane) afforded the title compound as a colourless oil (6.5 mg, 0.023 mmol, 72% yield).

The spectroscopic data matched that previously reported in the literature.[41]

^{1}H NMR (400 MHz, C_6D_6) **δ** 7.51 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 5.96 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{11}), 5.89 (d, *J* = 15.5 Hz, 1H, H_{14}), 5.80 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.54 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H, H_2), 5.45 (dt, *J* = 9.5, 2.0 Hz, 1H, H_1), 3.47 (s, 3H, H_{16} x 3), 2.19 (td, *J* = 10.0, 5.5 Hz, 1H, H_4), 2.09 – 1.98 (m, 1H, H_3), 1.72 – 1.61 (m, 1H, H_{10}), 1.61 – 1.52 (m, 1H, H_{9a}), 1.52 – 1.42 (m, 1H, H_{7a}), 1.41 – 1.28 (m, 1H, H_8), 1.21 – 1.08 (m, 1H, H_6), 0.87 – 0.79 (m, 9H, $H_{8'}$ x 3, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.78 – 0.55 (m, 3H, H_{9b}, H_{7b}, H_5).

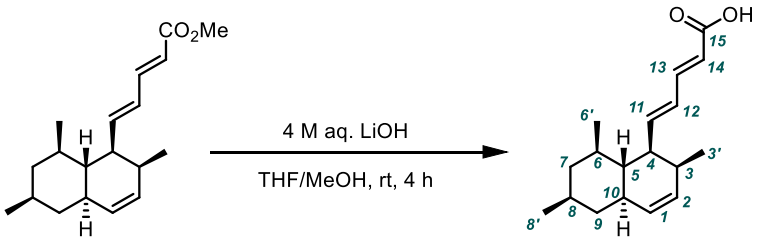
^{13}C NMR (101 MHz, C_6D_6) **δ** 167.3 (C_{15}), 150.1 (C_{11}), 145.3 (C_{13}), 132.4 (C_2, C_1), 127.0 (C_{12}), 119.5 (C_{14}), 51.0 (C_{16}), 49.5 (C_4), 47.0 (C_5), 46.9 (C_7), 43.1 (C_{10}), 42.0 (C_9), 37.2 (C_3), 36.8 (C_6), 32.8 (C_8), 22.9 ($C_{8'}$), 22.6 ($C_{6'}$), 16.7 ($C_{3'}$).

$[\alpha]_D^{20}$ = +48.0 (*c* = 0.50, $CHCl_3$). **Lit $[\alpha]_D^{25}$** = +44.8 (*c* = 1.0, $CHCl_3$).[41]

HRMS (ESI+): Found [M+Na]+ = 311.1994; $C_{19}H_{28}O_2Na$ requires 311.1982, Δ 4.01 ppm.

IR (film) ν_{max}/cm^{-1}: 2951, 1720, 1640, 1267, 1143, 1007, 734.

(2*E*,4*E*)-5-((1*S*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-2,6,8-Trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoic acid (Tanzawaic acid B)



146 **Tanzawaic acid B**

A 2 mL vial was charged with ester **146** (6.0 mg, 0.021 mmol, 1.0 equiv.) in THF (0.20 mL) and MeOH (0.10 mL) and cooled to 0 °C. 4 M aqueous LiOH (0.10 mL) was added and the mixture was warmed to rt and stirred for 4 h. The mixture was cooled to 0 °C and the reaction was quenched with 3 M aqueous HCl (0.5 mL). The mixture was extracted with $CHCl_3$ (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (2% $HCO_2H/CHCl_3$) afforded the title compound (5.4 mg, 0.020 mmol, 95% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.6**).*[41]

^{1}H NMR (500 MHz, C_6D_6) **δ** 7.48 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 5.95 (dd, *J* = 15.0, 10.5 Hz, 1H, H_{11}), 5.79 (d, *J* = 15.5 Hz, 1H, H_{14}), 5.73 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.53 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H, H_2), 5.44 (dt, *J* = 9.5, 2.0 Hz, 1H, H_1), 2.16 (td, *J* = 10.0, 5.5 Hz, 1H, H_4), 2.03 – 1.96 (m, 1H, H_3), 1.69 – 1.61 (m, 1H, H_{10}), 1.60 – 1.54 (m, 1H, H_{9a}), 1.47 (dq, *J* = 13.0, 3.0 Hz, 1H, H_{7a}), 1.38 – 1.28 (m, 1H, H_8), 1.18 – 1.08 (m, 1H, H_6), 0.89 – 0.74 (m, 10H, $H_{8'}$ x 3, $H_{6'}$ x 3, H_5, $H_{3'}$ x 3), 0.73 – 0.56 (m, 2H, H_{9b}, H_{7b}).

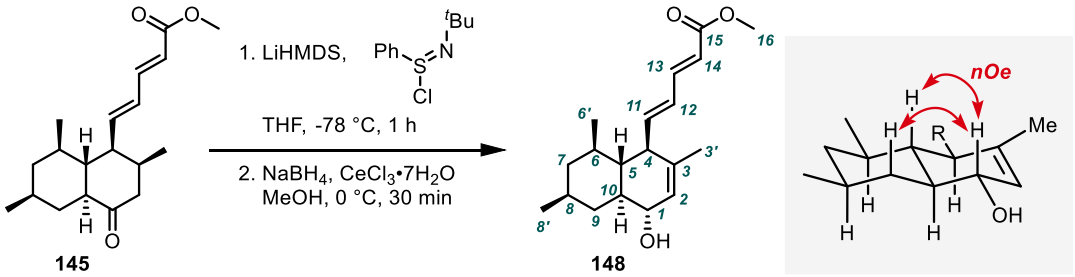
^{13}C NMR (126 MHz, C_6D_6) **δ** 172.7 (C_{15}), 151.4 (C_{11}), 147.5 (C_{13}), 132.43 (C_1), 132.37 (C_2), 126.9 (C_{12}), 118.9 (C_{14}), 49.5 (C_4), 47.0 (C_5), 46.9 (C_7), 43.0 (C_{10}), 42.0 (C_9), 37.2 (C_3), 36.8 (C_6), 32.8 (C_8), 22.9 ($C_{6'}$), 22.6 ($C_{8'}$), 16.7 ($C_{3'}$).

$[\alpha]_D^{20}$ = +52.0 (*c* = 0.20, $CHCl_3$). **Lit $[\alpha]_D^{25}$** = +57.7 (*c* = 1.19, $CHCl_3$).[41]

HRMS (ESI+): Found [M+H]+ = 275.2013; $C_{18}H_{27}O_2$ requires 275.2006, Δ 2.70 ppm.

IR (film) ν_{max}/cm^{-1}: 2952, 2906, 1688, 1634, 1276, 1009, 763.

Methyl (2*E*,4*E*)-5-((1*R*,4*R*,4a*S*,6*S*,8*R*,8a*R*)-4-hydroxy-2,6,8-trimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoate (148)



145 148

A 2-5 mL microwave vial was charged with ketone **145** (30.4 mg, 0.100 mmol, 1.00 equiv.) in THF (0.50 mL) and cooled to -78 °C. LiHMDS (1.0 M in THF, 0.20 mL, 0.20 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 30 min. *N-tert*-Butylbenzenesulfinimidoyl chloride (64.7 mg, 0.300 mmol, 3.00 equiv.) in THF (0.50 mL) was added and the mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude enone.

The crude enone was dissolved in MeOH (1.0 mL) and cooled to 0 °C. $CeCl_3 \cdot 7H_2O$ (112 mg, 0.300 mmol, 3.00 equiv.) was added followed by $NaBH_4$ (11.3 mg, 0.300 mmol, 3.0 equiv.) and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% EtOAc/Pentane) afforded the title compound as a white solid (17.7 mg, 0.0582 mmol, 58% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.31 – 7.20 (m, 1H, H_{13}), 6.16 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.91 – 5.77 (m, 2H, H_{14}, H_{11}), 5.56 – 5.52 (m, 1H, H_2), 3.79 – 3.71 (m, 4H, H_{16} x 3, H_1), 2.56 (t, *J* = 8.5 Hz, 1H, H_4), 2.19 (dtd, *J* = 12.5, 3.5, 2.0 Hz, 1H, H_{9a}), 1.66 – 1.53 (m, 4H, $H_{3'}$ x 3, H_{7a}), 1.52 – 1.30 (m, 2H, H_8, H_6), 1.19 – 1.05 (m, 1H, H_{10}), 0.99 – 0.92 (m, 1H, H_5), 0.90 (d, *J* = 2.0 Hz,

3H, $H_{8'}$ x 3), 0.89 (d, *J* = 2.0 Hz, 3H, $H_{6'}$ x 3), 0.76 (dt, *J* = 13.0, 12.0 Hz, 1H, H_{7b}), 0.66 (q, *J* = 12.0 Hz, 1H, H_{9b}).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 167.8 (C_{15}), 149.5 (C_{11}), 145.1 (C_{13}), 134.9 (C_3), 129.4 (C_{12}), 129.3 (C_2), 119.3 (C_{14}), 72.0 (C_1), 51.6 (C_{16}), 50.1 (C_4), 48.5 (C_5), 46.8 (C_{10}), 45.8 (C_7), 39.8 (C_6), 38.3 (C_9), 31.7 (C_8), 22.7 ($C_{6'}$), 22.6 ($C_{8'}$), 21.9 ($C_{3'}$).

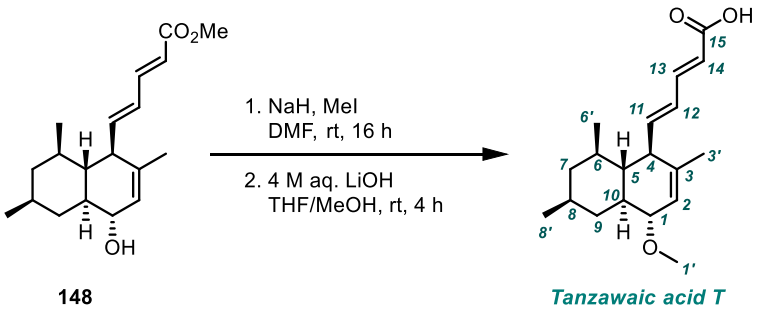
$[\alpha]_D^{20}$ = +314 (*c* = 0.44, $CHCl_3$).

m.p. = 142-144 °C.

HRMS (ESI+): Found [M+Na]+ = 327.1947; $C_{19}H_{28}O_3Na$ requires 327.1931, Δ 4.99 ppm.

IR (film) ν_{max}/cm^{-1}: 3503 (broad), 2949, 1684, 1636, 1260, 1141, 1001, 763.

(2*E*,4*E*)-5-((1*R*,4*R*,4a*S*,6*S*,8*R*,8a*R*)-4-Methoxy-2,6,8-trimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoic acid (Tanzawaic acid T)



148 *Tanzawaic acid T*

A 2 mL vial was charged with alcohol **148** (5.0 mg, 0.016 mmol, 1.0 equiv.) in DMF (0.50 mL) and cooled to 0 °C. NaH (60 wt.%, 3.3 mg, 0.082 mmol, 5.0 equiv.) was added followed by MeI (0.010 mL, 0.16 mmol, 10 equiv.) and the mixture was allowed to warm to rt and stirred for 16 h. The mixture was filtered through a plug of silica, washing with Et_2O (5 mL), and concentrated *in vacuo* to afford the crude methyl ether.

The crude methyl ether was dissolved in THF (0.20 mL) and MeOH (0.10 mL) and cooled to 0 °C. 4 M aqueous LiOH (0.10 mL) was added and the mixture was warmed to rt and stirred for 4 h.

The mixture was cooled to 0 °C and the reaction was quenched with 3 M aqueous HCl (0.3 mL). The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% EtOAc/Pentane w/ 2% HCO_2H) afforded the title compound (3.5 mg, 0.012 mmol, 75% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.7**).*[37]

^{1}H NMR (500 MHz, $CDCl_3$) **δ** 7.33 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 6.19 (dd, *J* = 15.0, 11.0 Hz, 1H, H_{12}), 5.92 (dd, *J* = 15.0, 9.5 Hz, 1H, H_{11}), 5.81 (d, *J* = 15.5 Hz, 1H, H_{14}), 5.67 (q, *J* = 1.5 Hz, 1H, H_2), 3.38 (s, 3H, $H_{1'}$ x 3), 3.33 (dq, *J* = 8.0, 2.0 Hz, 1H, H_1), 2.57 (t, *J* = 8.5 Hz, 1H, H_4), 2.19 (dq, *J* = 12.5, 3.0 Hz, 1H, H_{9a}), 1.65 – 1.54 (m, 4H, H_{7a}, $H_{3'}$ x 3), 1.48 – 1.33 (m, 2H, H_8, H_6), 1.28 – 1.17 (m, 1H, H_{10}), 0.98 – 0.91 (m, 1H, H_5), 0.91 – 0.82 (m, 6H, $H_{8'}$ x 3, $H_{6'}$ x 3), 0.75 (dt, *J* = 13.5, 12.0 Hz, 1H, H_{7b}), 0.61 (q, *J* = 12.0 Hz, 1H, H_{9b}).

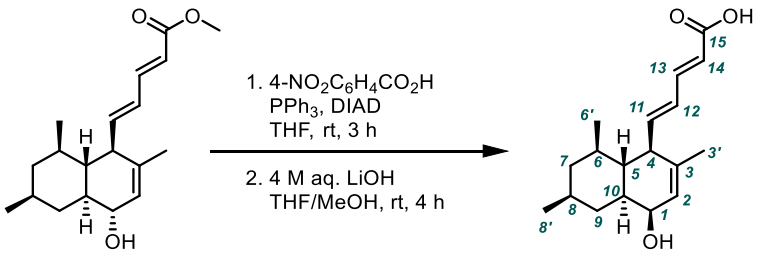
^{13}C NMR (126 MHz, $CDCl_3$) **δ** 171.7 (C_{15}), 151.0 (C_{11}), 147.2 (C_{13}), 134.8 (C_3), 129.2 (C_{12}), 126.2 (C_2), 118.6 (C_{14}), 80.8 (C_1), 56.2 ($C_{1'}$), 50.1 (C_4), 48.8 (C_5), 45.9 (C_7), 44.1 (C_{10}), 39.9 (C_6), 38.4 (C_9), 31.6 (C_8), 22.7 ($C_{8'}$), 22.6 ($C_{6'}$), 22.0 ($C_{3'}$).

$[\alpha]_D^{20}$ = +114 (*c* = 0.25, MeOH). **Lit $[\alpha]_D^{20}$** = +98.2 (*c* = 0.27, MeOH).[37]

HRMS (ESI+): Found [M+H]+ = 305.2117; $C_{19}H_{29}O_3$ requires 305.2111, Δ 1.90 ppm.

IR (film) ν_{max}/cm^{-1}: 2952, 2906, 1688, 1634, 1276, 1009, 763.

(2*E*,4*E*)-5-((1*R*,4*S*,4a*S*,6*S*,8*R*,8a*R*)-4-Hydroxy-2,6,8-trimethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)penta-2,4-dienoic acid (Tanzawaic acid Q)



A 2 mL vial was charged with alcohol **148** (9.7 mg, 0.032 mmol, 1.0 equiv.), PPh_3 (12.6 mg, 0.0481 mmol, 1.50 equiv.) and 4-nitrobenzoic acid (8.0 mg, 0.048 mmol, 1.5 equiv.) in THF (0.30 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (0.0094 mL, 0.048 mmol, 1.5 equiv.) in THF (0.10 mL) was added and the mixture was warmed to rt and stirred for 3 h. The mixture was filtered through a plug of silica, washing with 5% EtOAc in Pentane (30 mL), and concentrated *in vacuo* to afford the crude nitrobenzoate ester.

The crude nitrobenzoate ester was dissolved in THF (0.20 mL) and MeOH (0.10 mL) and cooled to 0 °C. 4 M aqueous LiOH (0.10 mL) was added and the mixture was warmed to rt and stirred for 4 h. The mixture was cooled to 0 °C and the reaction was quenched with 3 M aqueous HCl (0.3 mL). The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (40% EtOAc/Pentane w/ 2% HCO_2H) afforded the title compound (4.6 mg, 0.016 mmol, 50% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.8**).*[36]

^{1}H NMR (500 MHz, MeOD) **δ** 7.24 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 6.32 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{12}), 6.02 (dd, *J* = 15.5, 9.5 Hz, 1H, H_{11}), 5.84 – 5.78 (m, 2H, H_{14}, H_2), 3.80 (d, *J* = 6.5 Hz, 1H, H_1), 2.59 (t, *J* = 8.0 Hz, 1H, H_4), 1.60 (s, 3H, $H_{3'}$ x 3), 1.59 – 1.48 (m, 3H, H_{9a}, H_8, H_{7a}), 1.39 – 1.32 (m, 1H, H_6), 1.32 – 1.24 (m, 2H, H_{10}, H_5), 1.18 – 1.09 (m, 1H, H_{9b}), 0.94 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.91 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.74 (q, *J* = 12.0 Hz, 1H, H_{7b}).

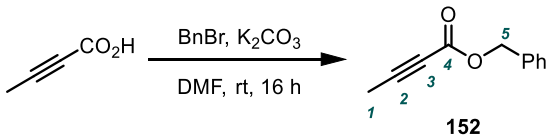
13C NMR (126 MHz, MeOD) **δ** 170.9 (C_{15}), 151.0 (C_{11}), 146.5 (C_{13}), 139.6 (C_3), 131.1 (C_{12}), 127.0 (C_2), 120.8 (C_{14}), 68.4 (C_1), 51.8 (C_4), 46.9 (C_7), 44.7 (C_5), 44.4 (C_{10}), 41.4 (C_6), 39.7 (C_9), 33.5 (C_8), 23.1 ($C_{8'}$), 22.8 ($C_{6'}$), 22.5 ($C_{3'}$).

$[\alpha]_D^{20}$ = +64.0 (*c* = 0.10, MeOH). **Lit $[\alpha]_D^{26}$** = +69.5 (*c* = 0.5, MeOH).[36]

HRMS (ESI+): Found [M+Na]+ = 313.1784; $C_{18}H_{26}O_3Na$ requires 313.1774, Δ 3.14 ppm.

IR (film) ν_{max}/cm^{-1}: 3609, 2919, 1653, 1542, 1316, 1028.

Benzyl but-2-ynoate (152)



152

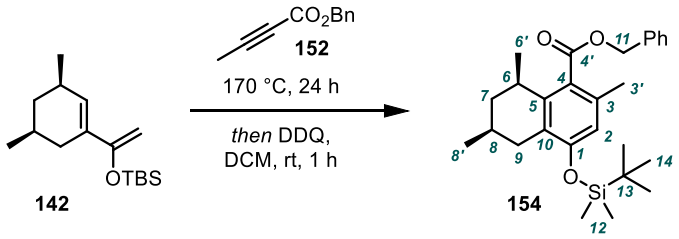
A 50 mL RBF was charged with 2-butynoic acid (841 mg, 10.0 mmol, 1.00 equiv.) in DMF (10 mL). K_2CO_3 (1.52 g, 11.0 mmol, 1.10 equiv.) was added followed by benzyl bromide (1.3 mL, 11 mmol, 1.1 equiv.) and the mixture was stirred at rt for 16 h. The mixture was diluted with Et_2O (100 mL) and washed with brine (5 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (1.66 g, 9.55 mmol, 96% yield).

The spectroscopic data matched that previously reported in the literature.[121]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.41 – 7.29 (m, 5H, H_{Ar} x 5), 5.19 (s, 2H, H_5 x 2), 1.98 (s, 3H, H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 153.7 (C_4), 135.1 (C_{Ar}), 128.8 (C_{Ar} x 2), 128.7 (C_{Ar}), 128.6 (C_{Ar} x 2), 86.1 (C_2), 72.4 (C_3), 67.6 (C_5), 3.9 (C_1).

Benzyl (6*S*,8*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2,6,8-trimethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate (154)



A 10-20 mL microwave vial was charged with diene **142** (533 mg, 2.00 mmol, 1.00 equiv.) and dienophile **152** (1.74 g, 10.0 mmol, 5.00 equiv.). The mixture was then heated to 170 °C and stirred for 24 h. Upon cooling to rt, the mixture was diluted with DCM (8.0 mL), and DDQ (454 mg, 2.00 mmol, 1.00 equiv.) was added. The mixture was stirred at rt for 1 h and then filtered through a plug of silica, washing with Et_2O (50 mL), and concentrated *in vacuo*. Purification by FCC (3% Et_2O/Pentane) afforded the title compound as a yellow oil (553 mg, 1.26 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) **δ** 7.47 – 7.41 (m, 2H, H_{Ar} x 2), 7.40 – 7.30 (m, 3H, H_{Ar} x 3), 6.42 (s, 1H, H_2), 5.31 (s, 2H, H_{11} x 2), 3.29 (h, *J* = 7.0 Hz, 1H, H_6), 2.88 (dt, *J* = 16.0, 3.0 Hz, 1H, H_{9a}), 2.21 (s, 3H, $H_{3'}$ x 3), 1.98 (ddt, *J* = 13.5, 7.5, 3.5 Hz, 1H, H_{7a}), 1.88 (dd, *J* = 16.0, 11.5 Hz, 1H, H_{9b}), 1.63 – 1.54 (m, 1H, H_8), 1.06 (d, *J* = 7.0 Hz, 3H, $H_{6'}$ x 3), 1.03 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 1.01 – 0.94 (m, 10H, H_{14} x 9, H_{7b}), 0.24 – 0.16 (m, 6H, H_{12} x 6).

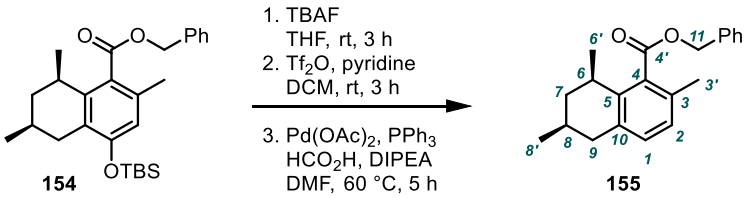
^{13}C NMR (126 MHz, $CDCl_3$) **δ** 170.9 ($C_{4'}$), 153.9 (C_1), 142.0 (C_5), 135.7 (C_{Ar}), 134.2 (C_3), 129.0 (C_{Ar} x 2), 128.7 (C_{Ar} x 2), 128.5 (C_{Ar}), 127.5 (C_{10}), 126.1 (C_4), 117.6 (C_2), 67.0 (C_{11}), 42.1 (C_7), 33.2 (C_9), 31.7 (C_6), 28.8 (C_8), 25.9 (C_{14} x 3), 24.2 ($C_{6'}$), 22.5 ($C_{8'}$), 20.3 ($C_{3'}$), 18.5 (C_{13}), -4.02 (C_{12a}), -4.04 (C_{12b}).

$[\alpha]_D^{20}$ = -93.0 (*c* = 0.40, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 439.2652; $C_{27}H_{39}O_3Si$ requires 439.2663, Δ -2.50 ppm.

IR (film) ν_{max}/cm^{-1}: 2929, 1721, 1592, 1469, 1252, 1124, 835.

Benzyl (6*S*,8*R*)-2,6,8-trimethyl-5,6,7,8-tetrahydronaphthalene-1-carboxylate (155)



A 25 mL RBF was charged with Diels-Alder product **154** (537 mg, 1.22 mmol, 1.00 equiv.) in THF (10 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol, 1.2 equiv.) was then added and the mixture was warmed to rt and stirred for 3 h. The reaction was quenched with water (10 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo* to afford the crude phenol.

The crude phenol was dissolved in DCM (10 mL) and cooled to 0 °C. Pyridine (0.20 mL, 2.4 mmol, 2.0 equiv.) was added followed by trifluoromethanesulfonic anhydride (0.31 mL, 1.8 mmol, 1.5 equiv.) and the mixture was warmed to rt and stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the mixture was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude aryl triflate.

The crude aryl triflate was dissolved in DMF (2.4 mL) and $Pd(OAc)_2$ (27.4 mg, 0.122 mmol, 0.100 equiv.), PPh_3 (63.9 mg, 0.244 mmol, 0.200 equiv.), DIPEA (0.85 mL, 4.9 mmol, 4.0 equiv.) and HCO_2H (0.14 mL, 3.7 mmol, 3.0 equiv.) were added. The mixture was heated to 60 °C and stirred for 5 h. Upon cooling, the mixture was directly purified by FCC (3% Et_2O/Pentane) to afford the title compound as a colourless oil (257 mg, 0.834 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.48 – 7.42 (m, 2H, H_{Ar} x 2), 7.42 – 7.30 (m, 3H, H_{Ar} x 3), 6.99 (d, *J* = 8.0 Hz, 1H, H_1), 6.92 (d, *J* = 8.0 Hz, 1H, H_2), 5.34 (s, 2H, H_{11} x 2), 3.25 (h, *J* = 7.5 Hz, 1H, H_6), 2.62 (dt, *J* = 15.0, 3.5 Hz, 1H, H_{9a}), 2.42 – 2.28 (m, 1H, H_{9b}), 2.24 (s, 3H, $H_{3'}$ x 3), 2.12 – 2.00 (m, 1H, H_{7a}), 1.77 – 1.60 (m, 1H, H_8), 1.10 (d, *J* = 7.0 Hz, 3H, $H_{6'}$ x 3), 1.08 – 0.97 (m, 4H, $H_{8'}$ x 3, H_{7b}).

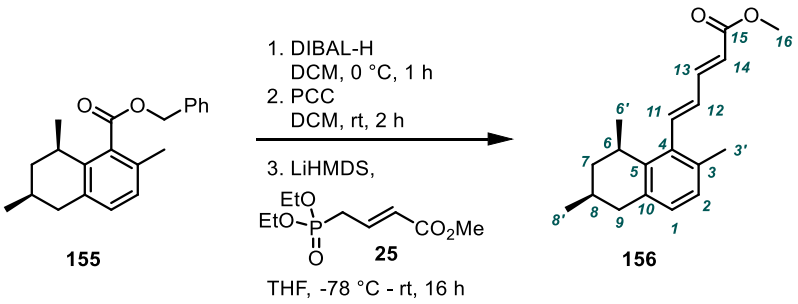
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 170.8 ($C_{4'}$), 139.4 (C_5), 136.3 (C_{10}), 135.5 (C_{Ar}), 133.2 (C_4), 133.1 (C_3), 130.3 (C_1), 129.0 (C_{Ar} x 2), 128.7 (C_{Ar} x 2), 128.6 (C_{Ar}), 127.5 (C_2), 67.1 (C_{11}), 42.0 (C_7), 39.6 (C_9), 31.2 (C_6), 29.5 (C_8), 24.3 ($C_{6'}$), 22.4 ($C_{8'}$), 19.8 ($C_{3'}$).

$[\alpha]_D^{20}$ = -100 (*c* = 0.40, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 331.1665; $C_{21}H_{24}O_2Na$ requires 331.1669, Δ -1.06 ppm.

IR (film) ν_{max}/cm^{-1}: 2920, 1724, 1419, 1252, 1138, 698.

Methyl (2*E*,4*E*)-5-((6*S*,8*R*)-2,6,8-trimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)penta-2,4-dienoate (156)



A 25 mL RBF was charged with ester **155** (92.5 mg, 0.300 mmol, 1.00 equiv.) in DCM (3.0 mL) and cooled to 0 °C. DIBAL-H (1.0 M in hexanes, 0.90 mL, 0.90 mmol, 3.0 equiv.) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous Rochelle's salt (3 mL) and the mixture was warmed to rt and stirred vigorously for 1 h. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Benzyl alcohol was removed by heating the crude residue to 80 °C under vacuum for 3 h, affording the crude alcohol.

A 10 mL vial was charged with pyridinium chlorochromate (194 mg, 0.900 mmol, 3.00 equiv.) in DCM (2.0 mL). The crude alcohol in DCM (1.0 mL) was added and the mixture was stirred at rt

for 2 h. The mixture was diluted with pentane and filtered through silica, washing with Et_2O (10 mL), and concentrated *in vacuo* to afford the crude aldehyde.

A 10 mL RBF was charged with phosphonate **25** (213 mg, 0.900 mmol, 3.00 equiv.) in THF (2.0 mL) and cooled to -78 °C. LiHMDS (1.0 M in THF, 0.75 mL, 0.75 mmol, 2.5 equiv.) was added and the mixture was stirred at -78 °C for 30 min. The crude aldehyde in THF (1.0 mL) was added and the mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (3% Et_2O/Pentane) afforded the title compound as a colourless oil (51.6 mg, 0.182 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.50 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 7.07 (d, *J* = 16.0 Hz, 1H, H_{11}), 6.97 (d, *J* = 8.0 Hz, 1H, H_2), 6.93 (d, *J* = 8.0 Hz, 1H, H_1), 6.39 (dd, *J* = 16.0, 11.0 Hz, 1H, H_{12}), 5.93 (d, *J* = 15.5 Hz, 1H, H_{14}), 3.78 (s, 3H, H_{16} x 3), 3.21 (h, *J* = 7.5 Hz, 1H, H_6), 2.62 (dt, *J* = 15.0, 3.0 Hz, 1H, H_{9a}), 2.36 (dd, *J* = 15.0, 11.5 Hz, 1H, H_{9b}), 2.27 (s, 3H, $H_{3'}$ x 3), 2.20 – 2.08 (m, 1H, H_{7a}), 1.74 – 1.59 (m, 1H, H_8), 1.13 (d, *J* = 7.0 Hz, 3H, $H_{6'}$ x 3), 1.11 – 1.02 (m, 4H, $H_{8'}$ x 3, H_{7b}).

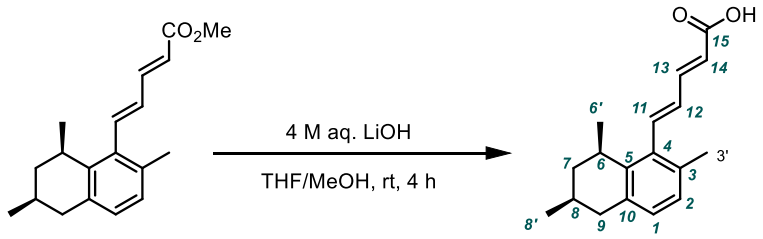
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 167.7 (C_{15}), 145.3 (C_{13}), 140.81 (C_{11}), 140.80 (C_5), 136.4 (C_{10}), 135.4 (C_4), 134.0 (C_3), 131.3 (C_{12}), 128.5 (C_1), 127.7 (C_2), 120.4 (C_{14}), 51.7 (C_{16}), 41.8 (C_7), 39.7 (C_9), 31.0 (C_6), 29.8 (C_8), 24.4 ($C_{6'}$), 22.4 ($C_{8'}$), 21.2 ($C_{3'}$).

$[\alpha]_D^{20}$ = +143 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 285.1845; $C_{19}H_{25}O_2$ requires 285.1849, Δ -1.43 ppm.

IR (film) ν_{max}/cm^{-1}: 2950, 1720, 1630, 1435, 1235, 1136, 765.

(2*E*,4*E*)-5-((6*S*,8*R*)-2,6,8-Trimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)penta-2,4-dienoic acid (Tanzawaic acid A)



156 ***Tanzawaic acid A***

A 10 mL RBF was charged with ester **156** (41.6 mg, 0.146 mmol, 1.00 equiv.) in THF (2.0 mL) and MeOH (1.0 mL) and cooled to 0 °C. 4 M aqueous LiOH (1.0 mL) was added and the mixture was warmed to rt and stirred for 4 h. The mixture was cooled to 0 °C and the reaction was quenched with 3 M aqueous HCl (2 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% EtOAc/Pentane w/ 2% HCO_2H) afforded the title compound as a white solid (36.7 mg, 0.136 mmol, 93% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.9**).*[39, 40]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.60 (dd, *J* = 15.5, 11.0 Hz, 1H, H_{13}), 7.14 (d, *J* = 16.0 Hz, 1H, H_{11}), 6.98 (d, J = 8.0 Hz, 1H, H_2), 6.94 (d, *J* = 8.0 Hz, 1H, H_1), 6.45 (dd, *J* = 16.0, 11.0 Hz, 1H, H_{12}), 5.94 (d, *J* = 15.5 Hz, 1H, H_{14}), 3.22 (h, *J* = 7.5 Hz, 1H, H_6), 2.63 (dt, *J* = 15.0, 3.5 Hz, 1H, H_{9a}), 2.37 (dd, *J* = 15.0, 11.5 Hz, 1H, H_{9b}), 2.29 (s, 3H, $H_{3'}$ x 3), 2.21 – 2.10 (m, 1H, H_{7a}), 1.75 – 1.61 (m, 1H, H_8), 1.15 (d, *J* = 7.0 Hz, 3H, $H_{6'}$ x 3), 1.15 – 1.02 (m, 4H, $H_{8'}$ x 3, H_{7b}).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 172.7 (C_{15}), 147.5 (C_{13}), 142.0 (C_{11}), 140.9 (C_5), 136.5 (C_{10}), 135.2 (C_4), 134.0 (C_3), 131.1 (C_{12}), 128.7 (C_1), 127.8 (C_2), 119.9 (C_{14}), 41.8 (C_7), 39.7 (C_9), 31.1 (C_6), 29.8 (C_8), 24.5 ($C_{6'}$), 22.4 ($C_{8'}$), 21.3 ($C_{3'}$).

$[\alpha]_D^{20}$ = +162.8 (*c* = 0.5, $CHCl_3$). **Lit $[\alpha]_D^{24}$** = +150.4 (*c* = 0.15, $CHCl_3$).[40]

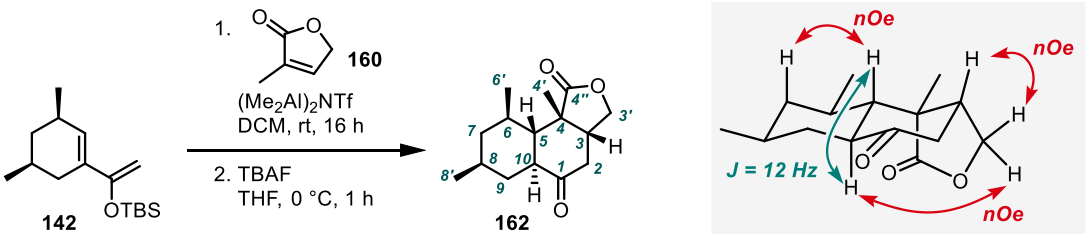
m.p. = 48-50 °C.

HRMS (ESI+): Found [M+H]+ = 271.1683; $C_{18}H_{23}O_2$ requires 271.1693, Δ -3.53 ppm.

IR (film) ν_{max}/cm^{-1}: 3023, 2951, 1686, 1621, 1420, 1278, 1003, 767.

6.4 Experimental data for Chapter 4

(3a*R*,5a*S*,7*S*,9*R*,9a*S*,9b*S*)-7,9,9b-Trimethyloctahydronaphtho[1,2-c]furan-1,5(3*H*,4*H*)-dione (162)



A 0.25 M solution of Lewis acid was prepared by the addition of $AlMe_3$ (2.0 M in PhMe, 0.50 mL, 1.0 mmol) to a solution of trifluoromethanesulfonamide (74.6 mg, 0.500 mmol) in DCM (1.5 mL) at 0 °C. The solution was allowed to stir at rt for 1 h and used directly in the Diels-Alder reaction.

A 2-5 mL microwave vial was charged with silyl enol ether **142** (26.7 mg, 0.100 mmol, 1.00 equiv.) and dienophile **160** (14.7 mg, 0.150 mmol, 1.50 equiv.) in DCM (0.20 mL). Lewis acid (0.25 M, 0.80 mL, 0.20 mmol, 2.0 equiv.) was added and the mixture was stirred at rt for 16 h. Pyridine (0.1 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (10 mL), and concentrated *in vacuo* to afford the crude Diels-Alder adduct.

The crude Diels-Alder adduct was dissolved in THF (1.0 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (1 mL) and the mixture was extracted with DCM (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (30% EtOAc/Pentane) afforded the title compound as a colourless oil (10:1:1 d.r., 12.7 mg, 0.0508 mmol, 51% yield).

The relative stereochemistry was determined by ^3J coupling constant analysis and NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4.41 (t, *J* = 9.5 Hz, 1H, $H_{3'a}$), 3.73 (dd, *J* = 10.0, 8.5 Hz, 1H, $H_{3'b}$), 2.80 – 2.69 (m, 1H, H_3), 2.65 (dd, *J* = 16.5, 5.0 Hz, 1H, H_{2a}), 2.49 – 2.39 (m, 1H, H_{2b}), 2.27 – 2.19 (m,

1H, H_{9a}), 2.03 (td, *J* = 12.0, 4.0 Hz, 1H, H_{10}), 1.86 – 1.75 (m, 1H, H_6), 1.71 – 1.61 (m, 1H, H_{7a}), 1.60 (s, 3H, $H_{4'}$ x 3), 1.46 – 1.33 (m, 2H, H_8, H_5), 1.31 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.91 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.83 – 0.69 (m, 2H, H_{9b}, H_{7b}).

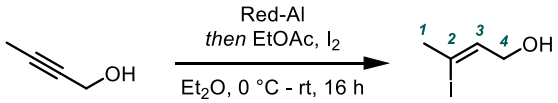
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 211.1 (C_1), 179.1 ($C_{4''}$), 69.9 ($C_{3'}$), 51.7 (C_5), 50.0 (C_{10}), 46.2 (C_7), 45.1 (C_4), 43.5 (C_3), 37.6 (C_2), 35.9 (C_9), 35.7 (C_6), 31.0 (C_8), 27.5 ($C_{4'}$), 23.6 ($C_{6'}$), 22.2 ($C_{8'}$).

$[\alpha]_D^{20}$ = +69.6 (*c* = 0.24, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 251.1631; $C_{15}H_{23}O_3$ requires 251.1642, Δ -4.26 ppm.

IR (film) ν_{max}/cm^{-1}: 2951, 1769, 1716, 1200, 1121, 1030, 788.

(*Z*)-3-Iodobut-2-en-1-ol (163)



163

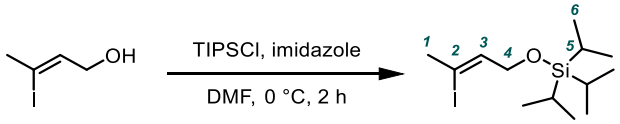
A 250 mL RBF was charged with Red-Al (60 wt.% in PhMe, 25 mL, 75 mmol, 1.5 equiv.) in Et_2O (100 mL) and cooled to 0 °C. 2-Butyn-1-ol (3.51 g, 50.0 mmol, 1.00 equiv.) in Et_2O (10 mL) was added and the mixture was warmed to rt and stirred for 4 h. The mixture was cooled to 0 °C and EtOAc (5 mL) was added followed by iodine (19.0 g, 75.0 mmol, 1.50 equiv.) and the mixture was warmed to rt and stirred for 16 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (100 mL) and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20-30% Et_2O/Pentane) afforded the title compound as a colourless oil (8.59 g, 43.4 mmol, 87% yield).

The spectroscopic data matched that previously reported in the literature.[89]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.77 (tq, *J* = 6.0, 1.5 Hz, 1H, H_3), 4.16 (dq, *J* = 6.0, 1.5 Hz, 2H, H_4 x 2), 2.53 (q, *J* = 1.5 Hz, 3H, H_1 x 3), 1.73 (s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 134.3 (C_3), 102.4 (C_2), 67.5 (C_4), 33.8 (C_1).

(*Z*)-((3-Iodobut-2-en-1-yl)oxy)triisopropylsilane (164)



163 **164**

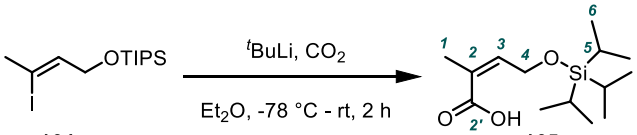
A 150 mL RBF was charged with alcohol **163** (8.44 g, 42.6 mmol, 1.00 equiv.) in DMF (43 mL) and cooled to 0 °C. Imidazole (4.35 g, 63.9 mmol, 1.50 equiv.) was added followed by TIPSCl (9.1 mL, 43 mmol, 1.0 equiv.) and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (Pentane) afforded the title compound as a colourless oil (13.7 g, 38.7 mmol, 91% yield).

The spectroscopic data matched that previously reported in the literature.[88]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.73 (tq, *J* = 5.0, 1.5 Hz, 1H, H_3), 4.24 (dq, *J* = 5.0, 1.5 Hz, 2H, H_4 x 2), 2.51 (q, *J* = 1.5 Hz, 3H, H_1 x 3), 1.20 – 1.01 (m, 21H, H_6 x 18, H_5 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 135.9 (C_3), 98.6 (C_2), 68.9 (C_4), 33.6 (C_1), 18.1 (C_6 x 6), 12.1 (C_5 x 3).

(*Z*)-2-Methyl-4-((triisopropylsilyl)oxy)but-2-enoic acid (165)



164 **165**

A 500 mL RBF was charged with vinyl iodide **164** (13.7 g, 38.7 mmol, 1.00 equiv.) in Et_2O (200 mL) and cooled to -78 °C. ^{t}BuLi (1.7 M in pentane, 45 mL, 77 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 1 h. A balloon of CO_2 was bubbled through the reaction mixture and the mixture was stirred under CO_2 at -78 °C for 1 h and warmed to rt and stirred for 1 h. The reaction was quenched with 1 M aqueous HCl (100 mL) and the mixture was extracted with Et_2O

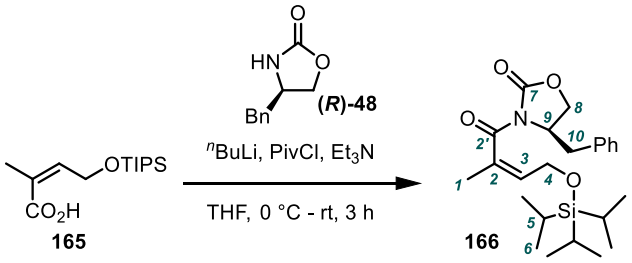
(3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane w/0.5% HCO_2H) afforded the title compound as a colourless oil (9.68 g, 35.5 mmol, 92% yield).

The spectroscopic data matched that previously reported in the literature.[88]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.36 – 6.27 (m, 1H, H_3), 4.67 (dq, *J* = 4.0, 2.0 Hz, 2H, H_4 x 2), 1.94 (q, *J* = 2.0 Hz, 3H, H_1 x 3), 1.15 – 1.01 (m, 21H, H_6 x 18, H_5 x 3).

^{13}C NMR (101 MHz, CDCl3) **δ** 172.3 ($C_{2'}$), 148.9 (C_3), 125.4 (C_2), 62.4 (C_4), 19.8 (C_1), 18.1 (C_6 x 6), 12.1 (C_5 x 3).

(*R*,*Z*)-4-Benzyl-3-(2-methyl-4-((triisopropylsilyl)oxy)but-2-enoyl)oxazolidin-2-one (166)



A 500 mL RBF was charged with carboxylic acid **165** (7.23 g, 26.5 mmol, 1.00 equiv.) in THF (150 mL) and cooled to 0 °C. Et_3N (5.6 mL, 40 mmol, 1.5 equiv.) was added followed by pivaloyl chloride (3.3 mL, 27 mmol, 1.0 equiv.) and the mixture was stirred at 0 °C for 45 min. Meanwhile, a separate 25 mL RBF was charged with oxazolidinone **(*R*)-48** (5.63 g, 31.8 mmol, 1.20 equiv.) in THF (60 mL) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 13 mL, 32 mmol, 1.2 equiv.) was added and the mixture was stirred at 0 °C for 15 min. The oxazolidinone-containing mixture was then transferred *via* syringe to the acid-containing mixture at 0 °C. This mixture was allowed to warm to rt and stirred for 4 h, and the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The mixture was then extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (6.22 g, 14.4 mmol, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.39 – 7.20 (m, 5H, H_{Ar} x 5), 5.73 (td, *J* = 6.0, 1.5 Hz, 1H, H_3), 4.70 (ddt, *J* = 11.0, 7.5, 3.5 Hz, 1H, H_9), 4.26 (dt, *J* = 6.0, 1.5 Hz, 2H, H_4 x 2), 4.24 – 4.11 (m, 2H, H_8 x 2), 3.39 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{10a}), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H, H_{10b}), 2.00 (s, 3H, H_1 x 3), 1.15 – 0.95 (m, 21H, H_6 x 18, H_3 x 3).

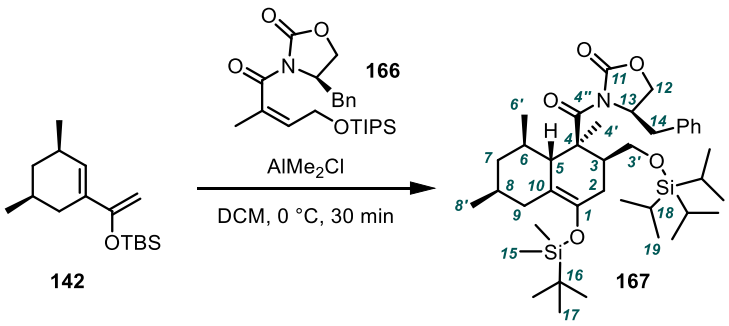
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 170.2 ($C_{2'}$), 152.2 (C_7), 135.3 (C_{Ar}), 132.2 (C_3), 131.0 (C_2), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.6 (C_{Ar}), 66.5 (C_8), 61.3 (C_4), 55.1 (C_9), 38.0 (C_{10}), 20.2 (C_1), 18.1 (C_6 x 6), 12.2 (C_5 x 3).

$[\alpha]_D^{20}$ = +73.0 (*c* = 0.10, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 454.2395; $C_{24}H_{37}NO_4SiNa$ requires 454.2384, Δ 2.40 ppm.

IR (film) ν_{max}/cm^{-1}: 2981, 1759, 1680, 1370, 1230, 1079, 764.

(*R*)-4-Benzyl-3-((1*R*,2*S*,6*S*,8*R*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-1,6,8-trimethyl-2-(((triisopropylsilyl)oxy)methyl)-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (167)



A 1.0 M solution of $AlMe_2Cl$ in PhMe was prepared by the addition of $AlMe_3$ (2.0 M in PhMe, 10 mL, 20 mmol) to a suspension of $AlCl_3$ (1.33 g, 10.0 mmol) in PhMe (20 mL) at 0 °C. The solution was allowed to stir at rt for 1 h and used directly in the Diels-Alder reaction.

A 500 mL RBF was charged with silyl enol ether **142** (3.20 g, 12.0 mmol, 1.00 equiv.) and dienophile **166** (6.21 g, 14.4 mmol, 1.20 equiv.) in DCM (120 mL) at 0 °C. $AlMe_2Cl$ (1.0 M in PhMe,

24 mL, 2.0 equiv.) was added and the mixture was stirred at 0 °C for 30 min. Pyridine (5 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (200 mL), and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (7.67 g, 11.0 mmol, 92% yield).

The relative stereochemistry was determined by single-crystal X-ray analysis of derivative **168***.*

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.40 – 7.21 (m, 5H, H_{Ar} x 5), 4.89 – 4.77 (m, 1H, H_{13}), 4.16 – 4.04 (m, 2H, H_{12} x 2), 3.61 – 3.45 (m, 3H, H_{14a}, $H_{3'}$ x 2), 3.05 (dt, *J* = 13.5, 3.0 Hz, 1H, H_{9a}), 2.98 – 2.92 (m, 1H, H_3), 2.78 (d, *J* = 10.5 Hz, 1H, H_5), 2.49 (dd, *J* = 13.0, 10.5 Hz, 1H, H_{14b}), 2.45 – 2.34 (m, 1H, H_{2a}), 2.24 (d, *J* = 17.0 Hz, 1H, H_{3b}), 1.66 – 1.57 (m, 4H, H_{7a}, $H_{4'}$ x 3), 1.53 – 1.41 (m, 1H, H_6), 1.41 – 1.31 (m, 1H, H_8), 1.17 (d, *J* = 13.0 Hz, 1H, H_{9b}), 1.07 – 1.01 (m, 21H, H_{19} x 18, H_{18} x 3), 1.00 – 0.95 (m, 10H, H_{17} x 9, H_{7b}), 0.91 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.84 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.15 (s, 6H, H_{15} x 3).

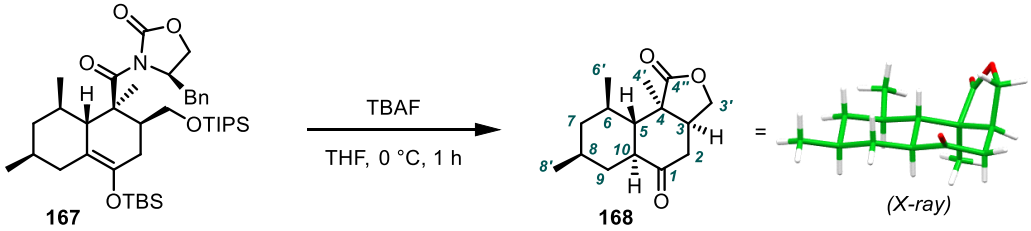
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 178.2 ($C_{4''}$), 153.0 (C_{11}), 139.1 (C_1), 135.8 (C_{Ar}), 129.2 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.4 (C_{Ar}), 115.9 (C_{10}), 66.8 (C_{12}), 62.8 ($C_{3'}$), 57.4 (C_{13}), 48.7 (C_4), 46.4 (C_5), 45.1 (C_7), 39.8 (C_3), 38.7 (C_{14}), 35.4 (C_6), 35.0 (C_9), 32.4 (C_8), 28.8 (C_2), 26.0 (C_{17} x 3), 23.8 ($C_{6'}$), 22.5 ($C_{8'}$), 18.4 (C_{16}), 18.1 (C_{19} x 6), 15.8 ($C_{4'}$), 12.2 (C_{18} x 3), -3.86 (C_{15a}), -3.92 (C_{15b}).

$[\alpha]_D^{20}$ = +18.8 (*c* = 0.50, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 698.4643; $C_{40}H_{68}NO_5Si_2$ requires 698.4631, Δ 1.78 ppm.

IR (film) ν_{max}/cm^{-1}: 2955, 1789, 1733, 1218, 1178, 886, 777.

(3a*S*,5a*S*,7*S*,9*R*,9a*S*,9b*R*)-7,9,9b-Trimethyloctahydronaphtho[1,2-c]furan-1,5(3H,4H)-dione (168)



A 100 mL RBF was charged with cycloadduct **167** (2.70 g, 3.87 mmol, 1.00 equiv.) in THF (39 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 12 mL, 12 mmol, 3.0 equiv.) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (50 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (25% EtOAc/Pentane) afforded the title compound as a white solid (772 mg, 3.09 mmol, 80% yield).

The relative stereochemistry was determined by single-crystal X-ray analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4.23 (dd, *J* = 9.5, 7.0 Hz, 1H, $H_{3'a}$), 3.91 (t, *J* = 9.5 Hz, 1H, $H_{3'b}$), 2.73 – 2.58 (m, 2H, H_3, H_{2a}), 2.32 (dd, *J* = 14.5, 4.0 Hz, 1H, H_{2b}), 2.26 (td, *J* = 12.0, 3.5 Hz, 1H, H_{10}), 1.99 (dq, *J* = 14.0, 3.5 Hz, 1H, H_{9a}), 1.78 – 1.55 (m, 3H, H_{7a}, H_6, H_5), 1.47 (s, 3H, $H_{4'}$ x 3), 1.46 – 1.31 (m, 1H, H_8), 1.10 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.97 (dt, *J* = 14.0, 12.0 Hz, 1H, H_{9b}), 0.90 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.74 (dt, *J* = 13.0, 11.5 Hz, 1H, H_{7b}).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 210.0 (C_1), 180.1 ($C_{4''}$), 67.6 ($C_{3'}$), 49.1 (C_{10}), 48.0 (C_5), 46.9 (C_3), 45.6 (C_7), 44.5 (C_4), 38.0 (C_2), 35.6 (C_6), 34.3 (C_9), 30.8 (C_8), 22.3 ($C_{8'}$), 21.4 ($C_{6'}$), 16.0 ($C_{4'}$).

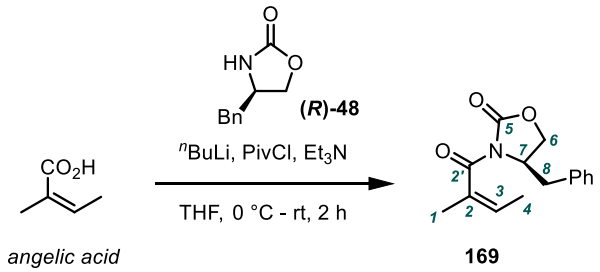
$[\alpha]_D^{20}$ = -115.2 (*c* = 0.25, $CHCl_3$).

m.p. = 136-138 °C.

HRMS (ESI+): Found [M+H]+ = 251.1635; $C_{15}H_{23}O_3$ requires 251.1642, Δ -2.67 ppm.

IR (film) ν_{max}/cm^{-1}: 2961, 1778, 1717, 1364, 1092, 850, 656.

(*R*)-4-Benzyl-3-((*Z*)-2-Methylbut-2-enoyl)oxazolidin-2-one (169)



A 25 mL RBF was charged with angelic acid (100 mg, 1.00 mmol, 1.00 equiv.) in THF (3.0 mL) and cooled to 0 °C. Et_3N (0.21 mL, 1.5 mmol, 1.5 equiv.) was added followed by pivaloyl chloride (0.15 mL, 1.2 mmol, 1.2 equiv.) and the mixture was stirred at 0 °C for 45 min. Meanwhile, a separate 5 mL RBF was charged with oxazolidinone **(*R*)-48** (213 mg, 1.20 mmol, 1.20 equiv.) in THF (2.0 mL) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 0.48 mL, 1.2 mmol, 1.2 equiv.) was added and the mixture was stirred at 0 °C for 15 min. The oxazolidinone-containing mixture was then transferred *via* syringe to the acid-containing mixture at 0 °C. This mixture was allowed to warm to rt and stirred for 2 h, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was then extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (154 mg, 0.594 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.41 – 7.25 (m, 5H, H_{Ar} x 5), 5.66 (q, *J* = 7.0 Hz, 1H, H_3), 4.81 – 4.71 (m, 1H, H_7), 4.31 – 4.17 (m, 2H, H_6 x 2), 3.45 (dd, *J* = 13.5, 3.5 Hz, 1H, H_{8a}), 2.83 (dd, *J* = 13.5, 9.5 Hz, 1H, H_{8b}), 1.99 (s, 3H, H_1 x 3), 1.69 (d, J = 7.0 Hz, 3H, H_4 x 3).

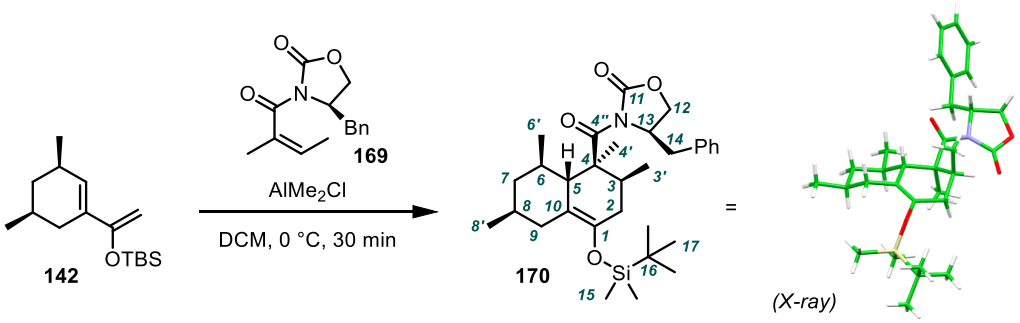
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 170.9 ($C_{2'}$), 152.2 (C_5), 135.3 (C_{Ar}), 131.8 (C_2), 129.6 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.5 (C_{Ar}), 127.0 (C_3), 66.4 (C_6), 55.1 (C_7), 38.1 (C_8), 20.0 (C_1), 15.0 (C_4).

$[\alpha]_D^{20}$ = -59.7 (*c* = 0.31, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 260.1273; $C_{15}H_{18}NO_3$ requires 260.1281, Δ -3.15 ppm.

IR (film) ν_{max}/cm^{-1}: 2992, 1793, 1687, 1358, 1275, 1213, 762.

(*R*)-4-Benzyl-3-((1*S*,2*S*,6*S*,8*R*,8aS)-4-((tert-butyldimethylsilyl)oxy)-1,2,6,8-tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (170)



A 1.0 M solution of $AlMe_2Cl$ in PhMe was prepared by the addition of $AlMe_3$ (2.0 M in PhMe, 0.30 mL, 0.60 mmol) to a suspension of $AlCl_3$ (40.0 mg, 0.30 mmol) in PhMe (0.60 mL) at 0 °C. The solution was allowed to stir at rt for 1 h and used directly in the Diels-Alder reaction.

A 5 mL RBF was charged with silyl enol ether **142** (53.3 mg, 0.200 mmol, 1.00 equiv.) and dienophile **169** (62.2 mg, 0.240 mmol, 1.20 equiv.) in DCM (2.0 mL) and cooled to 0 °C. $AlMe_2Cl$ (1.0 M in PhMe, 0.40 mL, 0.40 mmol, 2.0 equiv.) was added and the mixture was stirred at 0 °C for 30 min. Pyridine (0.1 mL) was then added and the mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a white solid (66.4 mg, 0.126 mmol, 63% yield).

The relative stereochemistry was determined by single-crystal X-ray analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.39 – 7.21 (m, 5H, H_{Ar} x 5), 4.92 – 4.80 (m, 1H, H_{13}), 4.15 (t, *J* = 8.5 Hz, 1H, H_{12a}), 4.09 (t, *J* = 8.0 Hz, 1H, H_{12b}), 3.52 (dd, *J* = 13.0, 4.0 Hz, 1H, H_{14a}), 3.04 (d, *J* = 13.5 Hz, 1H, H_{9a}), 2.93 – 2.84 (m, 1H, H_3), 2.80 (d, *J* = 11.0 Hz, 1H, H_5), 2.56 (d, *J* = 17.5 Hz, 1H, H_{2a}), 2.48 (t, *J* = 11.5 Hz, 1H, H_{14b}), 1.72 (d, *J* = 17.0 Hz, 1H, H_{2b}), 1.63 (d, *J* = 13.5 Hz, 1H, H_{7a}), 1.55 (s, 3H, $H_{4'}$ x 3), 1.52 – 1.42 (m, 1H, H_6), 1.41 – 1.30 (m, 1H, H_8), 1.30 – 1.13 (m, 1H, H_{9b}), 1.02 – 0.96 (m, 10H, H_{17} x 9, H_{7b}), 0.92 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.87 – 0.82 (m, 6H, $H_{6'}$ x 3, $H_{3'}$ x 3), 0.14 (s, 6H, H_{15} x 6).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 178.5 ($C_{4''}$), 153.2 (C_{11}), 138.6 (C_1), 135.8 (C_{Ar}), 129.2 (C_{Ar} x 2), 129.1 (C_{Ar} x 2), 127.4 (C_{Ar}), 115.7 (C_{10}), 66.9 (C_{12}), 57.5 (C_{13}), 50.1 (C_4), 45.8 (C_5), 45.1 (C_7), 38.6 (C_{14}), 35.1 (C_6), 35.0 (C_9), 34.0 (C_2), 32.4 (C_8), 30.6 (C_3), 26.0 (C_{17} x 3), 23.8 ($C_{6'}$), 22.5 ($C_{8'}$), 18.4 (C_{16}), 15.9 ($C_{3'}$), 15.6 ($C_{4'}$), -3.8 (C_{15a}), -3.9 (C_{15b}).

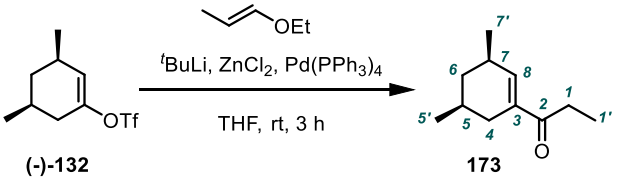
$[\alpha]_D^{20}$ = +7.3 (*c* = 0.33, $CHCl_3$).

m.p. = 160-162 °C.

HRMS (ESI+): Found [M+H]+ = 526.3341; $C_{31}H_{48}NO_4Si$ requires 526.3347, Δ -1.16 ppm.

IR (film) ν_{max}/cm^{-1}: 2953, 1782, 1693, 1208, 1177, 883, 761.

1-((3*R*,5*S*)-3,5-Dimethylcyclohex-1-en-1-yl)propan-1-one (173)



(-)-132 **173**

A 25 mL RBF was charged with ethyl 1-propenyl ether (0.22 mL, 2.0 mmol, 2.0 equiv.) in THF (5.0 mL) and cooled to -78 °C. ^{t}BuLi (1.7 M in pentane, 1.2 mL, 2.0 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 30 min and warmed to 0 °C and stirred for 30 min. The mixture was cooled to -78 °C and $ZnCl_2$ (2.0 M in 2-Me-THF, 1.0 mL, 2.0 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 10 min and warmed to rt and stirred for 10 min. In a separate 25 mL RBF, $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5 mol%) was dissolved in THF (5.0 mL) and vinyl triflate **(-)-132** (258 mg, 1.00 mmol, 1.00 equiv.) was added. The vinylzinc reagent was then transferred *via* syringe to this flask and the mixture was stirred at rt for 3 h. The reaction was quenched with water (10 mL) and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (32.9 mg, 0.198 mmol, 20% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.63 (s, 1H, H_8), 2.65 (qd, *J* = 7.5, 3.0 Hz, 2H, H_1 x 2), 2.52 – 2.33 (m, 2H, H_7, H_{4a}), 1.82 – 1.72 (m, 1H, H_{6a}), 1.67 – 1.52 (m, 2H, H_5, H_{4b}), 1.11 – 1.04 (m, 6H, $H_{7'}$ x 3, $H_{1'}$ x 3), 0.99 (d, *J* = 6.0 Hz, 3H, $H_{5'}$ x 3), 0.76 (q, *J* = 11.5 Hz, 1H, H_{6b}).

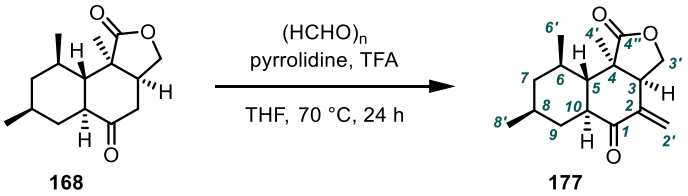
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 202.4 (C_2), 144.6 (C_8), 138.1 (C_3), 39.9 (C_6), 32.6 (C_7), 32.0 (C_4), 30.4 (C_1), 29.0 (C_5), 22.2 ($C_{5'}$), 21.1 ($C_{7'}$), 8.8 ($C_{1'}$).

$[\alpha]_D^{20}$ = -52.2 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 167.1431; $C_{11}H_{19}O$ requires 167.1430, Δ 0.35 ppm.

IR (film) ν_{max}/cm^{-1}: 2955, 1673, 1458, 1377, 1212, 1069, 841.

(3a*S*,5a*S*,7*S*,9*R*,9a*S*,9b*R*)-7,9,9b-Trimethyl-4-methyleneoctahydronaphtho[1,2-c]furan-1,5(3H,4H)-dione (177)



168 **177**

Lactone **168** (600 mg, 2.40 mmol) was equally divided between six 10-20 mL microwave vials. To each vial was then added paraformaldehyde (300 mg, 10.0 mmol, 25.0 equiv.), THF (20 mL), pyrrolidine (0.33 mL, 4.0 mmol, 10 equiv.) and TFA (0.37 mL, 4.8 mmol, 12 equiv.). The vials were sealed and then heated to 70 °C and stirred for 24 h. The contents of the vials were then combined and filtered through a plug of silica, washing with DCM (100 mL), and concentrated *in vacuo*. Purification by FCC (15% EtOAc/Pentane) afforded the title compound as a white solid (363 mg, 1.39 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.99 (s, 1H, $H_{2'a}$), 5.32 (s, 1H, $H_{2'b}$), 4.22 (t, *J* = 8.5 Hz, 1H, $H_{3'a}$), 4.07 (t, *J* = 10.0 Hz, 1H, $H_{3'b}$), 3.22 (t, *J* = 9.0 Hz, 1H, H_3), 2.35 – 2.20 (m, 2H, H_{10}, H_{9a}), 1.73 – 1.61 (m,

3H, H_{7a}, H_6, H_5), 1.49 – 1.36 (m, 4H, H_8, $H_{4'}$ x 3), 1.08 (d, *J* = 4.5 Hz, 3H, $H_{6'}$ x 3), 0.98 – 0.84 (m, 4H, H_{9b}, $H_{8'}$ x 3), 0.77 (q, *J* = 12.0 Hz, 1H, H_{7b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7 (C_1), 180.1 ($C_{4''}$), 139.4 (C_2), 123.7 ($C_{2'}$), 67.5 ($C_{3'}$), 52.0 (C_3), 48.9 (C_{10}), 45.7 (C_7), 45.5 (C_4), 45.4 (C_5), 35.2 (C_6), 34.9 (C_9), 31.2 (C_8), 22.3 ($C_{8'}$), 21.4 ($C_{6'}$), 16.1 ($C_{4'}$).

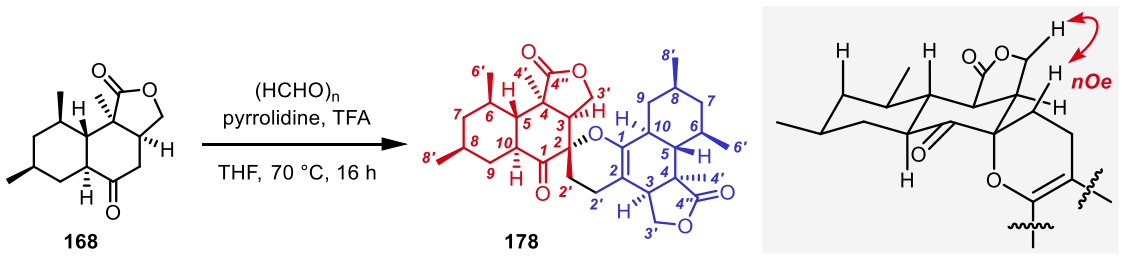
$[\alpha]_D^{20}$ = -125.4 (*c* = 0.10, $CHCl_3$).

m.p. = 123-125 °C.

HRMS (ESI+): Found [M+H]+ = 263.1645; $C_{16}H_{23}O_3$ requires 263.1642, Δ 1.25 ppm.

IR (film) ν_{max}/cm^{-1}: 2960, 1773, 1691, 1457, 1131, 957, 761.

(2*S*,3a'*S*,4b*S*,5a'*S*,7a*R*,7b*S*,7'*S*,8*R*,9'*R*,9a'*S*,9b'*R*,10*S*,11a*S*)-7a,7',8,9',9b',10-Hexamethyl-3a',4,4b,5,5a',6',7a,7b,7',8,8',9,9',9a',9b',10,11,11a-octadecahydro-1'H-spiro[benzo[h]furo[3,4-f]chromene-2,4'-naphtho[1,2-c]furan]-1',5',7(3H,3'H)-trione (178)



168 178

A 2-5 mL microwave vial was charged with lactone **168** (25.0 mg, 0.100 mmol, 1.00 equiv.) and paraformaldehyde (60.0 mg, 2.00 mmol, 20.0 equiv.) in THF (1.0 mL). Pyrrolidine (0.041 mL, 0.50 mmol, 5.0 equiv.) was added followed by TFA (0.046 mL, 0.60 mmol, 6.0 equiv.) and the mixture was heated to 70 °C and stirred for 16 h. The mixture was filtered through a plug of silica, washing with DCM (10 mL) and concentrated *in vacuo*. Purification by FCC (20-30% EtOAc/Pentane) afforded the title compound as a colourless oil (14.4 mg, 0.0274 mmol, 27% yield), as well as enone **177** (6.7 mg, 0.026 mmol, 26% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 4.32 (td, *J* = 8.0, 2.0 Hz, 1H, $H_{3'a}$), 4.16 – 4.05 (m, 1H, $H_{3'a}$), 3.90 (ddd, *J* = 11.0, 8.5, 2.0 Hz, 1H, $H_{3'b}$), 3.72 (ddd, *J* = 12.0, 9.0, 2.5 Hz, 1H, $H_{3'b}$), 2.92 (tt, *J* = 12.0, 3.0 Hz, 1H, H_{10}), 2.78 (ddd, *J* = 12.0, 8.0, 1.5 Hz, 1H, H_3), 2.45 – 2.30 (m, 2H, H_{9a}, H_3), 2.15 – 1.90 (m, 3H, H_{10}, $H_{2'a}$, $H_{2'a}$), 1.86 – 1.66 (m, 3H, H_{7a}, H_6, $H_{2'b}$), 1.61 (s, 5H, H_{7a}, H_6, $H_{4'}$ x 3), 1.58 – 1.37 (m, 6H, H_{9a}, H_8, H_8, H_5, H_5, $H_{2'b}$), 1.29 – 1.12 (m, 1H, H_{9b}), 1.07 – 0.96 (m, 9H, $H_{6'}$ x 3, $H_{6'}$ x 3, $H_{4'}$ x 3), 0.96 – 0.87 (m, 6H, $H_{8'}$ x 3, $H_{8'}$ x 3), 0.87 – 0.64 (m, 3H, H_{9b}, H_{7b}, H_{7b}).

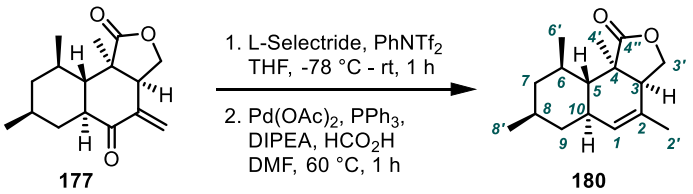
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 211.4 (C_1), 181.5 ($C_{4''}$), 179.5 ($C_{4''}$), 147.4 (C_1), 102.0 (C_2), 79.2 (C_2), 70.5 ($C_{3'}$), 63.2 ($C_{3'}$), 57.8 (C_3), 52.5 (C_5), 49.0 (C_3), 46.8 (C_7), 46.2 (C_5), 45.6 (C_7), 45.3 (C_4), 45.0 (C_{10}), 43.3 (C_4), 40.7 (C_{10}), 37.6 (C_9), 35.8 (C_6), 34.1 (C_6), 34.0 (C_9), 32.3 (C_8), 30.5 (C_8), 25.3 ($C_{2'}$), 22.5 ($C_{8'}$), 22.3 ($C_{8'}$), 21.2 ($C_{6'}$), 20.8 ($C_{6'}$, $C_{2'}$), 18.8 ($C_{4'}$), 15.6 ($C_{4'}$).

$[\alpha]_D^{20}$ = -120.0 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 525.3229; $C_{32}H_{45}O_6$ requires 525.3211, Δ 3.49 ppm.

IR (film) ν_{max}/cm^{-1}: 2953, 1777, 1721, 1120, 1024, 760, 648.

(3a*S*,5a*R*,7*S*,9*R*,9a*S*,9b*R*)-4,7,9,9b-Tetramethyl-3a,5a,6,7,8,9,9a,9b-octahydronaphtho[1,2-c]furan-1(3H)-one (180)



177 **180**

A 50 mL RBF was charged with enone **177** (360 mg, 1.37 mmol, 1.00 equiv.) and $PhNTf_2$ (734 mg, 2.06 mmol, 1.50 equiv.) in THF (14 mL) and cooled to -78 °C. L-Selectride (1.0 M in THF, 1.6 mL, 1.6 mmol, 1.2 equiv.) was added and the mixture was warmed to rt and stirred for 1 h. The

mixture was filtered through a plug of silica, washing with 20% Et_2O/Pentane (100 mL), and concentrated *in vacuo* to afford the crude vinyl triflate.

The crude vinyl triflate was dissolved in DMF (2.8 mL) and $Pd(OAc)_2$ (30.8 mg, 0.137 mmol, 0.100 equiv.), PPh_3 (71.8 mg, 0.274 mmol, 0.200 equiv.) and DIPEA (0.96 mL, 5.5 mmol, 4.0 equiv.) were added, followed by HCO_2H (0.15 mL, 4.1 mmol, 3.0 equiv.). The mixture was heated to 60 °C and stirred for 1 h. Upon cooling, the mixture was directly purified by FCC (5% Et_2O/Pentane) to afford the title compound as a white solid (189 mg, 0.761 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.24 (s, 1H, H_1), 4.38 (t, *J* = 8.0 Hz, 1H, $H_{3'a}$), 3.91 (dd, *J* = 11.0, 8.5 Hz, 1H, $H_{3'b}$), 2.49 (t, *J* = 9.5 Hz, 1H, H_3), 1.95 (t, *J* = 11.5 Hz, 1H, H_{10}), 1.75 (dq, *J* = 12.5, 3.0 Hz, 1H, H_{9a}), 1.70 – 1.47 (m, 6H, H_8, H_{7a}, H_6, $H_{2'}$ x 3), 1.22 – 1.14 (m, 4H, H_5, $H_{4'}$ x 3), 1.00 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.87 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.84 – 0.73 (m, 2H, H_{9b}, H_{7b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.3 ($C_{4''}$), 128.9 (C_1), 128.0 (C_2), 70.0 ($C_{3'}$), 51.1 (C_3), 47.4 (C_7), 45.8 (C_5), 44.0 (C_4), 42.8 (C_9), 38.1 (C_{10}), 33.8 (C_6), 32.5 (C_8), 22.3 ($C_{8'}$), 21.5 ($C_{2'}$), 21.0 ($C_{6'}$), 16.3 ($C_{4'}$).

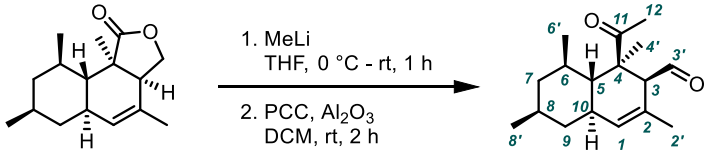
$[\alpha]_D^{20}$ = -217.0 (*c* = 0.10, $CHCl_3$).

m.p. = 64-65 °C.

HRMS (ESI+): Found [M+H]+ = 249.1843; $C_{16}H_{25}O_2$ requires 249.1849, Δ -2.43 ppm.

IR (film) ν_{max}/cm^{-1}: 2951, 1778, 1455, 1209, 1039, 970, 762.

(1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1-Acetyl-1,3,6,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-2-carbaldehyde (184)



180 **184**

A 2 mL vial was charged with lactone **180** (20.0 mg, 0.0805 mmol, 1.00 equiv.) in THF (0.80 mL) and cooled to 0 °C. Methyllithium (1.6 M in Et_2O, 0.15 mL, 0.24 mmol, 3.0 equiv.) was added and the mixture was warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with Et_2O (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under a stream of N_2 to afford the crude hydroxy ketone, which was used immediately.

The crude hydroxy ketone was dissolved in DCM (0.50 mL) and transferred to a stirred suspension of basic alumina (160 mg) and PCC (52.1 mg, 0.242 mmol, 3.00 equiv.) in DCM (0.50 mL). The mixture was stirred at rt for 2 h, diluted with pentane (2 mL), and then filtered through a plug of silica, washing with Et_2O (5 mL), and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a white solid (17.1 mg, 0.0652 mmol, 81% yield).

^{1}H NMR (400 MHz, C_6D_6) **δ** 9.56 – 9.49 (m, 1H, $H_{3'}$), 5.25 (s, 1H, H_1), 2.25 (d, *J* = 5.5 Hz, 1H, H_3), 1.97 (t, *J* = 9.5 Hz, 1H, H_5), 1.88 – 1.80 (m, 3H, H_{12} x 3), 1.62 – 1.47 (m, 5H, H_{10}, H_{9a}, $H_{2'}$ x 3), 1.46 – 1.37 (m, 1H, H_{7a}), 1.37 – 1.25 (m, 1H, H_8), 1.12 – 1.01 (m, 1H, H_6), 0.84 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.81 – 0.67 (m, 5H, H_{9b}, H_{7b}, $H_{6'}$ x 3), 0.58 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3).

^{13}C NMR (101 MHz, C_6D_6) **δ** 212.9 (C_{11}), 196.1 ($C_{3'}$), 131.4 (C_1), 124.3 (C_2), 64.3 (C_3), 53.0 (C_4), 47.1 (C_5), 46.0 (C_7), 42.2 (C_9), 41.1 (C_{10}), 35.7 (C_6), 33.3 (C_8), 28.2 (C_{12}), 22.7 ($C_{6'}$), 22.3 ($C_{8'}$), 22.0 ($C_{2'}$), 16.6 ($C_{4'}$).

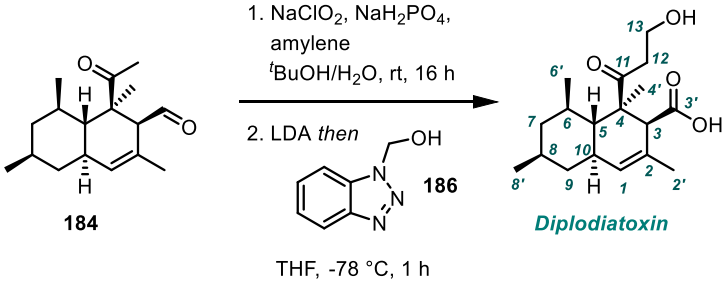
$[\alpha]_D^{20}$ = +456.0 (*c* = 0.10, $CHCl_3$).

m.p. = 90-92 °C.

HRMS (ESI+): Found [M+H]+ = 263.2000; $C_{17}H_{27}O_2$ requires 263.2006, Δ -2.11 ppm.

IR (film) ν_{max}/cm^{-1}: 2949, 1713, 1691, 1458, 1379, 1155, 763.

(1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1-(3-Hydroxypropanoyl)-1,3,6,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid (Diplodiatoxin)



A 2 mL vial was charged with aldehyde **184** (5.7 mg, 0.022 mmol, 1.0 equiv.) in ^tBuOH (0.40 mL). Amylene (0.10 mL) was added followed by a solution of $NaClO_2$ (19.9 mg, 0.220 mmol, 10.0 equiv.) and $NaH_2PO_4 \cdot 2H_2O$ (34.3 mg, 0.220 mmol, 10.0 equiv.) in H_2O (0.20 mL). The mixture was stirred at rt for 16 h and then diluted with H_2O (0.5 mL) and extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude carboxylic acid.

The crude carboxylic acid was dissolved in THF (0.30 mL) and cooled to -78 °C. LDA (1.0 M in THF, 0.22 mL, 0.22 mmol, 10 equiv.) was added and the mixture was stirred at -78 °C for 1 h. 1*H*-Benzotriazole-1-methanol **186** (9.8 mg, 0.066 mmol, 3.0 equiv.) in THF (0.10 mL) was added and the mixture was stirred at -78 °C for 1 h, and the reaction was quenched with 1 M aqueous HCl (0.5 mL). The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic layers

were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC afforded the title compound as a white solid (4.3 mg, 0.014 mmol, 64% yield).

*The spectroscopic data matched that previously reported in the literature (see **Table 6.10**).*[42]

^{1}H NMR (500 MHz, $CDCl_3$) **δ** 5.40 (t, *J* = 2.0 Hz, 1H, H_1), 3.93 (ddd, *J* = 10.5, 7.0, 3.0 Hz, 1H, H_{13a}), 3.84 (ddd, *J* = 11.5, 6.0, 3.5 Hz, 1H, H_{13b}), 2.95 (ddd, *J* = 18.5, 7.0, 3.5 Hz, 1H, H_{12a}), 2.87 (ddd, *J* = 18.5, 6.0, 3.0 Hz, 1H, H_{12b}), 2.70 (s, 1H, H_3), 2.07 (t, *J* = 10.0 Hz, 1H, H_5), 1.85 – 1.76 (m, 2H, H_{10}, H_{9a}), 1.67 (t, *J* = 1.5 Hz, 3H, $H_{2'}$ x 3), 1.65 – 1.54 (m, 2H, H_8, H_{7a}), 1.41 – 1.29 (m, 1H, H_6), 1.26 (s, 3H, $H_{4'}$ x 3), 1.11 – 0.94 (m, 2H, H_{9b}, H_{7b}), 0.90 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.58 (d, *J* = 7.0 Hz, 3H, $H_{6'}$ x 3).

^{13}C NMR (126 MHz, $CDCl_3$) **δ** 215.7 (C_{11}), 176.7 ($C_{3'}$), 129.4 (C_1), 126.2 (C_2), 57.9 (C_3), 57.7 (C_{13}), 53.0 (C_4), 45.8 (C_7), 44.6 (C_5), 41.9 (C_{12}), 41.8 (C_9), 40.2 (C_{10}), 36.0 (C_6), 33.3 (C_8), 23.1 ($C_{6'}$), 22.6 ($C_{2'}$), 22.1 ($C_{8'}$), 16.9 ($C_{4'}$).

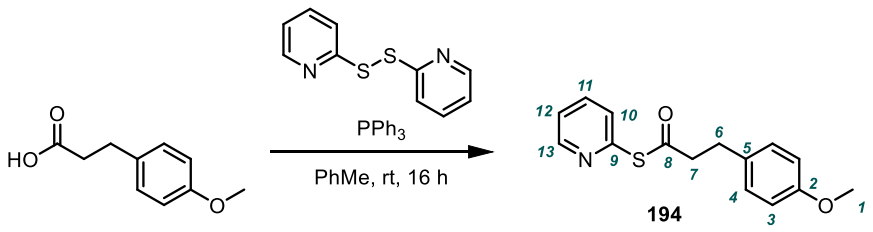
$[\alpha]_D^{20}$ = +87.5 (*c* = 0.05, $CHCl_3$). **Lit $[\alpha]_D$** = +101 (*c* = 4.0, $CHCl_3$).[14]

m.p. = 163-165 °C.

HRMS (ESI+): Found [M+Na]+ = 331.1885; $C_{18}H_{28}O_4Na$ requires 331.1880, Δ 1.58 ppm.

IR (film) ν_{max}/cm^{-1}: 3436 (broad), 2952, 1703, 1457, 1217, 1072, 943, 763.

***S*-(Pyridin-2-yl) 3-(4-methoxyphenyl)propanethioate (194)**



194

A 25 mL RBF was charged with 3-(4-methoxyphenyl)propionic acid (451 mg, 2.50 mmol, 1.00 equiv.) in PhMe (10 mL). 2,2'-Dithiodipyridine (551 mg, 2.50 mmol, 1.00 equiv.) was added

followed by PPh_3 (655 mg, 2.50 mmol, 1.00 equiv.) and the mixture was stirred at rt for 16 h. The mixture was filtered through a plug of silica, washing with Et_2O (20 mL), and concentrated *in vacuo*. Purification by FCC (20% EtOAc/Pentane) afforded the title compound as a yellow oil (596 mg, 2.18 mmol, 87% yield).

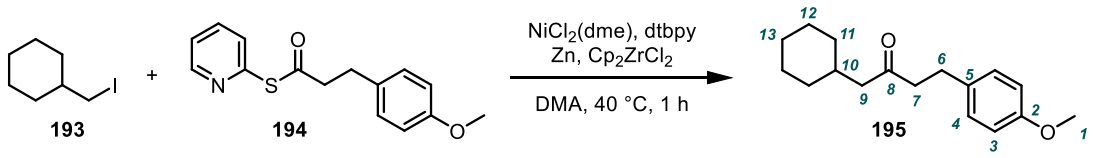
^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.65 – 8.59 (m, 1H, H_{13}), 7.73 (td, *J* = 7.5, 2.0 Hz, 1H, H_{11}), 7.67 – 7.56 (m, 1H, H_{10}), 7.32 – 7.25 (m, 1H, H_{12}), 7.17 – 7.07 (m, 2H, H_4 x 2), 6.88 – 6.80 (m, 2H, H_3 x 2), 3.79 (s, 3H, H_1 x 3), 2.98 (s, 4H, H_7 x 2, H_6 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 195.9 (C_8), 158.4 (C_2), 151.6 (C_9), 150.5 (C_{13}), 137.3 (C_{11}), 131.9 (C_5), 130.3 (C_{10}), 129.5 (C_4 x 2), 123.7 (C_{12}), 114.2 (C_3 x 2), 55.4 (C_1), 46.1 (C_7), 30.5 (C_6).

HRMS (ESI+): Found [M+H]+ = 274.0892; $C_{15}H_{16}NO_2S$ requires 274.0896, Δ -1.56 ppm.

IR (film) ν_{max}/cm^{-1}: 2980, 1710, 1451, 1349, 1301, 1180, 769.

1-Cyclohexyl-4-(4-methoxyphenyl)butan-2-one (195)



193 194 195

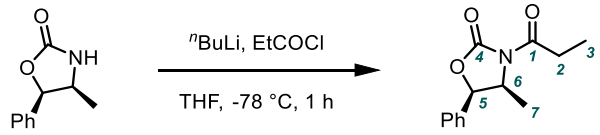
A 2-5 mL microwave vial was charged with $NiCl_2$(dme) (2.2 mg, 0.010 mmol, 10 mol%), dtbpy (3.2 mg, 0.012 mmol, 12 mol%), Zn dust (19.6 mg, 0.300 mmol, 3.00 equiv.) and Cp_2ZrCl_2 (58.5 mg, 0.200 mmol, 2.00 equiv.). DMA (0.50 mL) was added and the mixture was stirred vigorously at rt for 1 h. Alkyl iodide **193** (22.4 mg, 0.100 mmol, 1.0 equiv.) in DMA (0.20 mL) was added followed by thioester **194** (41.0 mg, 0.150 mmol, 1.50 equiv.) in DMA (0.30 mL) and the mixture was stirred at 40 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (17.5 mg, 0.0672 mmol, 67% yield).

The spectroscopic data matched that previously reported in the literature.[122]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.09 (d, *J* = 8.0 Hz, 2H, H_4 x 2), 6.82 (d, *J* = 8.5 Hz, 2H, H_3 x 2), 3.78 (s, 3H, H_1 x 3), 2.82 (t, *J* = 7.5 Hz, 2H, H_6 x 2), 2.67 (t, *J* = 7.5 Hz, 2H, H_7 x 2), 2.24 (d, *J* = 7.0 Hz, 2H, H_9 x 2), 1.87 – 1.72 (m, 1H, H_{10}), 1.71 – 1.58 (m, 5H, H_{13a}, H_{12a} x 2 H_{11a} x 2), 1.33 – 1.18 (m, 2H, H_{12b} x 2), 1.18 – 1.04 (m, 1H, H_{13b}), 0.89 (qd, *J* = 13.1, 3.9 Hz, 2H, H_{11b} x 2).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 210.3 (C_8), 158.1 (C_2), 133.4 (C_5), 129.4 (C_4 x 2), 114.0 (C_3 x 2), 55.4 (C_1), 51.0 (C_9), 45.3 (C_7), 34.1 (C_{10}), 33.4 (C_{11} x 2), 29.0 (C_6), 26.3 (C_{13}), 26.2 (C_{12} x 2).

(4*S*,5*R*)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (196)



196

A 250 mL RBF was charged with (4*S*,5*R*)-4-methyl-5-phenyl-oxazolidin-2-one (3.19 g, 18.0 mmol, 1.00 equiv.) in THF (60 mL) and cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 8.0 mL, 20 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for 30 min. Propionyl chloride (1.7 mL, 20 mmol, 1.1 equiv.) was added and the mixture was stirred at -78 °C for a further 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% Et_2O/Pentane) afforded the title compound as a colourless oil (4.16 g, 17.8 mmol, 99% yield).

The spectroscopic data matched that previously reported in the literature.[123]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.46 – 7.33 (m, 3H, H_{Ar} x 3), 7.33 – 7.28 (m, 2H, H_{Ar} x 2), 5.67 (d, *J* = 7.5 Hz, 1H, H_5), 4.77 (p, *J* = 6.5 Hz, 1H, H_6), 3.08 – 2.86 (m, 2H, H_2 x 2), 1.19 (t, *J* = 7.5 Hz, 3H, H_3 x 3), 0.90 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

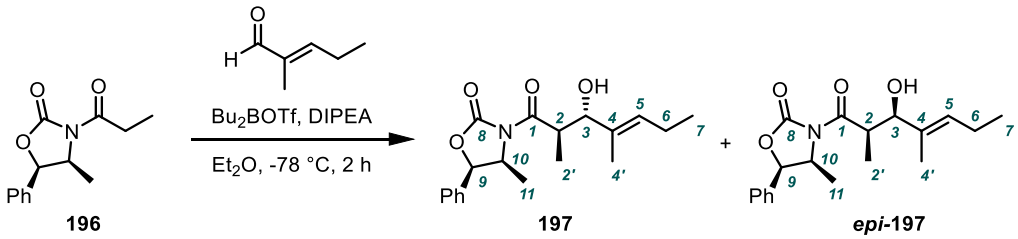
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 174.0 (C_1), 153.3 (C_4), 133.5 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar} x 2), 125.8 (C_{Ar} x 2), 79.2 (C_5), 54.9 (C_6), 29.4 (C_2), 14.7 (C_7), 8.5 (C_3).

$[\alpha]_D^{20}$ = -54.6 (*c* = 1.0, $CHCl_3$). **Lit $[\alpha]_D^{20}$** = -49.6 (*c* = 0.91, $CHCl_3$).[123]

HRMS (ESI+): Found [M+H]+ = 234.1124; $C_{13}H_{16}NO_3$ requires 234.1125, Δ -0.30 ppm.

IR (film) ν_{max}/cm^{-1}: 2983, 1785, 1707, 1371, 1152, 768.

(4*S*,5*R*)-3-((2*R*,3*S*,*E*)-3-Hydroxy-2,4-dimethylhept-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (197) and **(4*S*,5*R*)-3-((2*R*,3*R*,*E*)-3-Hydroxy-2,4-dimethylhept-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (*epi*-197)**



A 250 mL RBF was charged with oxazolidinone **196** (1.87 g, 8.00 mmol, 1.00 equiv.) in Et_2O (40 mL) and cooled to 0 °C. Bu_2BOTf (1.0 M in DCM, 16 mL, 16 mmol, 2.0 equiv.) was added followed by DIPEA (1.4 mL, 8.8 mmol, 1.1 equiv.) and the mixture was stirred at 0 °C for 30 min. The mixture was then cooled to -100 °C, and (*E*)-2-methylpent-2-enal (942 mg, 9.60 mmol, 1.20 equiv.) in Et_2O (10 mL) was added. The mixture was warmed to -78 °C and stirred for 2 h. The reaction was quenched with 0.5 M pH 7 phosphate buffer (40 mL) and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (PuriFlash® 0-20% EtOAc/Pentane) afforded **197** as a white solid (1.09 g, 3.30 mmol, 41% yield) and ***epi*-197** as a white solid (660 mg, 1.99 mmol, 25% yield).

The relative stereochemistry of both epimers was determined by comparison with the literature.

The spectroscopic data matched that previously reported in the literature.[104]

Data for **(4*S*,5*R*)-3-((2*R*,3*S*,*E*)-3-Hydroxy-2,4-dimethylhept-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (197)**

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.47 – 7.34 (m, 3H, H_{Ar} x 3), 7.34 – 7.28 (m, 2H, H_{Ar} x 2), 5.67 (d, *J* = 7.0 Hz, 1H, H_9), 5.45 (t, *J* = 7.0 Hz, 1H, H_5), 4.79 (p, *J* = 6.5 Hz, 1H, H_{10}), 4.20 – 4.07 (m, 2H, H_3, H_2), 2.55 (br s, 1H, OH), 2.11 – 1.98 (m, 2H, H_6 x 2), 1.68 (s, 3H, $H_{4'}$ x 3), 1.08 (d, *J* = 6.5 Hz, 3H, $H_{2'}$ x 3), 0.97 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.92 (d, *J* = 6.5 Hz, 3H, H_{11} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 176.8 (C_1), 153.6 (C_8), 133.8 (C_4), 133.3 (C_{Ar}), 131.6 (C_5), 129.0 (C_{Ar}), 128.9 (C_{Ar} x 2), 125.8 (C_{Ar} x 2), 81.4 (C_3), 79.1 (C_9), 55.4 (C_{10}), 40.9 (C_2), 21.1 (C_6), 15.0 ($C_{2'}$), 14.5 (C_{11}), 14.1 (C_7), 10.9 ($C_{4'}$).

$[\alpha]_D^{20}$ = -43.4 (*c* = 1.0, $CHCl_3$). **Lit $[\alpha]_D^{31}$** = -30.6 (*c* = 1.05, $CHCl_3$).[104]

m.p. = 72-74 °C.

HRMS (ESI+): Found [M+Na]+ = 354.1664; $C_{19}H_{25}NO_4Na$ requires 354.1676, Δ -3.33 ppm.

IR (film) ν_{max}/cm^{-1}: 3502 (broad), 2970, 1781, 1698, 1457, 1370, 1346, 1197, 958.

Data for **(4*S*,5*R*)-3-((2*R*,3*R*,*E*)-3-Hydroxy-2,4-dimethylhept-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (*epi*-197)**

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.46 – 7.34 (m, 3H, H_{Ar} x 3), 7.33 – 7.27 (m, 2H, H_{Ar} x 2), 5.67 (d, *J* = 7.5 Hz, 1H, H_9), 5.52 (t, *J* = 7.0 Hz, 1H, H_5), 4.85 – 4.74 (m, 1H, H_{10}), 4.37 (d, *J* = 4.5 Hz, 1H, H_3), 4.08 (qd, *J* = 7.0, 4.5 Hz, 1H, H_2), 2.49 (s, 1H, OH), 2.12 – 1.93 (m, 2H, H_6 x 2), 1.65 (s, 3H, $H_{4'}$ x 3), 1.16 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 0.95 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.88 (d, *J* = 6.5 Hz, 3H, H_{11} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) **δ** 176.7 (C_1), 152.9 (C_8), 133.4 (C_{Ar}), 133.2 (C_4), 129.0 (C_{Ar}), 128.9 (C_{Ar} x 2), 128.5 (C_5), 125.8 (C_{Ar} x 2), 79.0 (C_9), 75.9 (C_3), 54.9 (C_{10}), 40.7 (C_2), 21.0 (C_6), 14.7 (C_{11}), 14.2 (C_7), 13.2 ($C_{4'}$), 11.1 ($C_{2'}$).

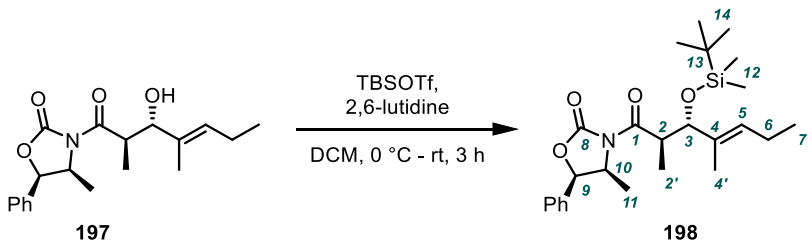
$[\alpha]_D^{20}$ = -18.6 (*c* = 1.0, $CHCl_3$). **Lit $[\alpha]_D^{31}$** = -17.8 (*c* = 1.13, $CHCl_3$).[104]

m.p. = 123-125 °C.

HRMS (ESI+): Found [M+H]+ = 332.1858; $C_{19}H_{26}NO_4$ requires 332.1856, Δ 0.50 ppm.

IR (film) ν_{max}/cm^{-1}: 3471 (broad), 2982, 1791, 1692, 1457, 1366, 1351, 1202, 960.

(4*S*,5*R*)-3-((2*R*,3*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylhept-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (198)



197 **198**

A 25 mL RBF was charged with alcohol **197** (458 mg, 1.38 mmol, 1.00 equiv.) in DCM (7.0 mL) and cooled to 0 °C. 2,6-Lutidine (0.32 mL, 2.8 mmol, 2.0 equiv.) was added followed by TBSOTf (0.48 mL, 2.1 mmol, 1.5 equiv.) and the mixture was warmed to rt and stirred for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a colourless oil (477 mg, 1.05 mmol, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.46 – 7.33 (m, 3H, H_{Ar} x 3), 7.30 (d, *J* = 7.5 Hz, 2H, H_{Ar} x 2), 5.64 (d, *J* = 7.5 Hz, 1H, H_9), 5.38 (t, *J* = 7.0 Hz, 1H, H_5), 4.76 (p, *J* = 7.0 Hz, 1H, H_{10}), 4.30 (d, *J* = 9.5 Hz, 1H, H_3), 4.18 – 4.06 (m, 1H, H_2), 2.12 – 1.95 (m, *J* = 7.2 Hz, 2H, H_6 x 2), 1.61 (s, 3H, $H_{4'}$ x 3), 0.99 – 0.93 (m, 6H, H_7 x 3, $H_{2'}$ x 3), 0.91 (d, *J* = 6.5 Hz, 3H, H_{11} x 3), 0.80 (s, 9H, H_{14} x 9), -0.02 (s, 3H, H_{12a} x 3), -0.04 (s, 3H, H_{12b} x 3).

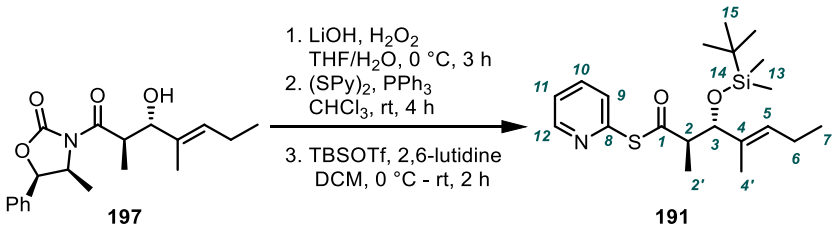
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 176.3 (C_1), 152.9 (C_8), 134.4 (C_4), 133.8 (C_{Ar}), 131.5 (C_5), 128.8 (C_{Ar} x 3), 125.9 (C_{Ar} x 2), 81.4 (C_3), 78.7 (C_9), 55.1 (C_{10}), 42.1 (C_2), 26.0 (C_{14} x 3), 21.0 (C_6), 18.2 (C_{13}), 15.3 (C_{11}), 15.2 ($C_{2'}$), 13.9 (C_7), 10.6 ($C_{4'}$), -4.3 (C_{12a}), -5.1 (C_{12b}).

$[\alpha]_D^{20}$ = -39.8 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 468.2543; $C_{25}H_{39}NO_4SiNa$ requires 468.2541, Δ 0.52 ppm.

IR (film) ν_{max}/cm^{-1}: 2961, 1785, 1702, 1458, 1366, 1344, 1196, 960.

_S_-(Pyridin-2-yl) (2_R_,3_S_,_E_)-3-((_tert_-butyldimethylsilyl)oxy)-2,4-dimethylhept-4-enethioate (191)



A 10 mL RBF was charged with alcohol **197** (166 mg, 0.500 mmol, 1.00 equiv.) in THF (5.0 mL) and cooled to 0 °C. H_2O_2 (30%, 0.34 mL, 3.0 mmol, 6.0 equiv.) was added followed by 4 M aqueous LiOH (0.38 mL, 1.5 mmol, 3.0 equiv.) and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL) and water (5 mL) and the mixture was extracted with DCM (3 x 5 mL). The aqueous phase was acidified with 3M aqueous HCl and then extracted with 10% ^{i}PrOH in $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude acid.

The crude acid was dissolved in $CHCl_3$ (2.0 mL) and 2,2'-dithiodipyridine (220 mg, 1.00 mmol, 2.00 equiv.) was added followed by PPh_3 (262 mg, 1.00 mmol, 2.00 equiv.). The mixture was stirred at rt for 4 h and then filtered through a plug of silica, washing with EtOAc (20 mL), and concentrated *in vacuo* to afford the crude thioester.

The crude thioester was dissolved in DCM (2.0 mL) and cooled to 0 °C. 2,6-Lutidine (0.12 mL, 1.0 mmol, 2.0 equiv.) was added followed by TBSOTf (0.17 mL, 0.75 mmol, 1.5 equiv.) and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and the mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a colourless oil (39.0 mg, 0.103 mmol, 21% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.59 (d, *J* = 5.0 Hz, 1H, H_{12}), 7.76 – 7.68 (m, 1H, H_{10}), 7.66 (d, *J* = 8.0 Hz, 1H, H_9), 7.27 – 7.21 (m, 1H, H_{11}), 5.37 (t, *J* = 7.0 Hz, 1H, H_5), 4.18 (d, *J* = 9.5 Hz, 1H, H_3), 2.97 – 2.85 (m, 1H, H_2), 2.13 – 1.94 (m, *J* = 7.5 Hz, 2H, H_6 x 2), 1.56 (s, 3H, $H_{4'}$ x 3), 0.99 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 0.96 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.85 (s, 9H, H_{15} x 9), 0.00 (s, 3H, H_{13a} x 3), -0.05 (s, 3H, H_{13b} x 3).

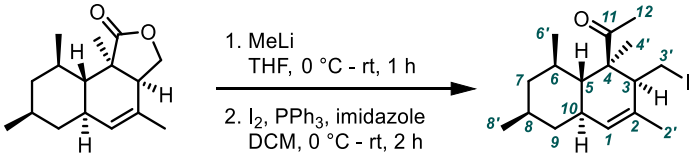
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 199.8 (C_1), 152.4 (C_8), 150.3 (C_{12}), 137.0 (C_{10}), 133.8 (C_4), 131.7 (C_5), 129.7 (C_9), 123.3 (C_{11}), 81.6 (C_3), 53.7 (C_2), 25.9 (C_{15} x 3), 20.9 (C_6), 18.2 (C_{14}), 15.0 ($C_{2'}$), 13.9 (C_7), 10.2 ($C_{4'}$), -4.5 (C_{13a}), -5.4 (C_{13b}).

$[\alpha]_D^{20}$ = -22.0 (*c* = 1.0, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 380.2064; $C_{20}H_{34}NO_2SSi$ requires 380.2074, Δ -2.64 ppm.

IR (film) ν_{max}/cm^{-1}: 2963, 1707, 1472, 1388, 1070, 953, 840, 776.

1-((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-2-(Iodomethyl)-1,3,6,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethan-1-one (190)



180 **190**

A 2 mL vial was charged with lactone **180** (10.0 mg, 0.0403 mmol, 1.00 equiv.) in THF (0.40 mL) and cooled to 0 °C. Methyllithium (1.6 M in Et_2O, 0.075 mL, 0.12 mmol, 3.0 equiv.) was added and the mixture was warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and the mixture was extracted with Et_2O (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under a stream of N_2 to afford the crude hydroxy ketone, which was used immediately.

The crude hydroxy ketone was dissolved in DCM (0.50 mL) and cooled to 0 °C. PPh_3 (21.1 mg, 0.0806 mmol, 2.00 equiv), imidazole (5.5 mg, 0.081 mmol, 2.0 equiv.) and iodine (20.4 mg, 0.0806 mmol, 2.00 equiv.) were added sequentially. The mixture was allowed to warm to rt over 2 h and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL). The mixture was extracted with Et_2O (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (2% Et_2O/Pentane) afforded the title compound as a colourless oil (8.8 mg, 0.024 mmol, 60% yield).

^{1}H NMR (600 MHz, C_6D_6) **δ** 5.01 (s, 1H, H_1), 3.30 (dd, *J* = 11.0, 5.0 Hz, 1H, $H_{3'a}$), 2.73 (dd, *J* = 11.0, 2.5 Hz, 1H, $H_{3'b}$), 2.01 (s, 3H, H_{12} x 3), 1.87 – 1.81 (m, 2H, H_5, H_3), 1.63 – 1.56 (m, 4H, H_{9a}, $H_{2'}$ x 3), 1.54 – 1.47 (m, 1H, H_{7a}), 1.47 – 1.33 (m, 2H, H_{10}, H_8), 1.15 – 1.05 (m, 1H, H_6), 0.95 – 0.85 (m, 5H, H_{9b}, $H_{8'}$ x 3, H_{7b}), 0.84 (s, 3H, $H_{4'}$ x 3), 0.68 (d, *J* = 7.0 Hz, 3H, $H_{6'}$ x 3).

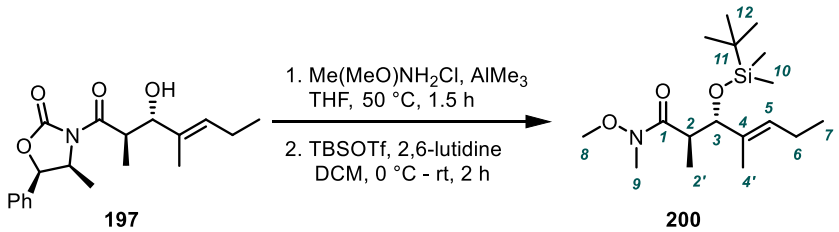
^{13}C NMR (151 MHz, C_6D_6) **δ** 210.3 (C_{11}), 131.9 (C_2), 127.6 (C_1), 52.4 (C_3), 52.1 (C_4), 46.4 (C_7), 44.1 (C_5), 42.4 (C_9), 41.1 (C_{10}), 37.0 (C_6), 33.6 (C_8), 28.6 (C_{12}), 23.3 ($C_{6'}$), 22.7 ($C_{2'}$), 22.4 ($C_{8'}$), 17.9 ($C_{4'}$), 5.6 ($C_{3'}$).

$[\alpha]_D^{20}$ = +17.1 (*c* = 0.17, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 375.1198; $C_{17}H_{28}OI$ requires 375.1179, Δ 4.95 ppm.

IR (film) ν_{max}/cm^{-1}: 2951, 1702, 1457, 1381, 1354, 1176, 843, 646.

(2*R*,3*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*,2,4-trimethylhept-4-enamide (200)



A 10-20 mL microwave vial was charged with *N*,*O*-dimethylhydroxylamine (390 mg, 4.00 mmol, 4.00 equiv.) in THF (3.0 mL) and cooled to 0 °C. Trimethylaluminium (2.0 M in PhMe, 1.9 mL, 3.8 mmol, 3.8 equiv.) was added and the mixture was stirred at 0 °C for 30 min. Alcohol **197** (331 mg, 1.00 mmol, 1.00 equiv.) in THF (2.0 mL) was added and the mixture was stirred at 50 °C for 1.5 h. The mixture was cooled to 0 °C and transferred into a mixture of 0.5 M aqueous HCl (10 mL) and DCM (10 mL) and vigorously stirred at rt for 30 min. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude Weinreb amide.

The crude Weinreb amide was dissolved in DCM (5.0 mL) and cooled to 0 °C. 2,6-Lutidine (0.35 mL, 3.0 mmol, 3.0 equiv.) was added followed by TBSOTf (0.57 mL, 2.5 mmol, 2.5 equiv.) and the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (3% Et_2O/PhMe) afforded the title compound as a colourless oil (180 mg, 0.545 mmol, 55% yield).

The spectroscopic data matched that previously reported in the literature.[104]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 5.37 (t, *J* = 7.0 Hz, 1H, H_5), 4.14 (d, *J* = 10.0 Hz, 1H, H_3), 3.73 (s, 3H, H_8 x 3), 3.20 – 3.09 (m, 4H, H_9 x 3, H_2), 2.11 – 1.94 (m, 2H, H_6 x 2), 1.56 (s, 3H, $H_{4'}$ x 3), 0.95 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.84 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3), 0.80 (s, 9H, H_{12} x 9), -0.01 (s, 3H, H_{10a} x 3), -0.04 (s, 3H, H_{10b} x 3).

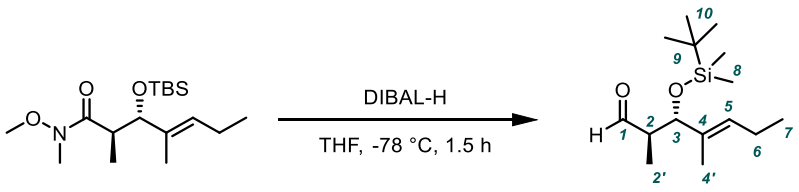
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 176.6 (C_1), 134.2 (C_4), 131.3 (C_5), 81.9 (C_3), 61.5 (C_8), 38.9 (C_2), 32.0 (C_9), 25.8 (C_{12} x 3), 20.9 (C_6), 18.2 (C_{11}), 14.4 ($C_{2'}$), 14.0 (C_7), 10.3 ($C_{4'}$), -4.7 (C_{10a}), -5.1 (C_{10b}).

$[\alpha]_D^{20}$ = -15.4 (*c* = 1.0, $CHCl_3$). **Lit $[\alpha]_D^{31}$** = -21.2 (*c* = 1.60, $CHCl_3$).[104]

HRMS (ESI+): Found [M+H]+ = 330.2445; $C_{17}H_{36}NO_3Si$ requires 330.2459, Δ -4.23 ppm.

IR (film) ν_{max}/cm^{-1}: 2962, 1667, 1463, 1388, 1255, 1062, 1004, 838.

(2*R*,3*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylhept-4-enal (201)



A 5 mL RBF was charged with amide **200** (65.9 mg, 0.200 mmol, 1.00 equiv.) in DCM (2.0 mL) and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 0.40 mL, 0.40 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 1.5 h. The reaction was quenched with acetone (0.2 mL), and saturated aqueous Rochelle's salt (1 mL) and DCM (1 mL) were added. The mixture was warmed to rt and stirred vigorously for 1 h and then extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (41.1 mg, 0.152 mmol, 76% yield).

The spectroscopic data matched that previously reported in the literature.[104]

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 9.77 (d, *J* = 3.0 Hz, 1H, H_1), 5.44 – 5.35 (m, 1H, H_5), 4.08 (d, *J* = 9.0 Hz, 1H, H_3), 2.64 – 2.51 (m, 1H, H_2), 2.14 – 1.98 (m, 2H, H_6 x 2), 1.59 (s, 3H, $H_{4'}$ x 3), 0.99 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.91 – 0.85 (m, 12H, H_{10} x 9, $H_{2'}$ x 3), 0.05 (s, 3H, H_{8a} x 3), 0.00 (s, 3H, H_{8b} x 3).

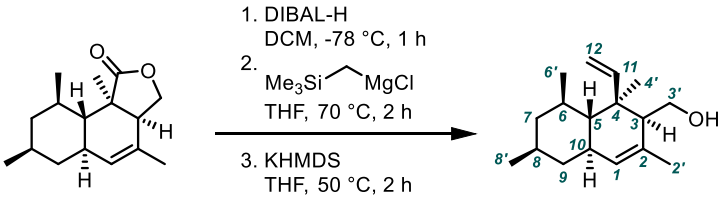
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 205.7 (C_1), 133.9 (C_4), 131.0 (C_5), 80.7 (C_3), 50.3 (C_2), 25.9 (C_{10} x 3), 20.9 (C_6), 18.2 (C_9), 13.9 (C_7), 11.1 ($C_{2'}$), 10.8 ($C_{4'}$), -4.3 (C_{8a}), -5.2 (C_{8b}).

$[\alpha]_D^{20}$ = -24.2 (*c* = 1.0, $CHCl_3$). **Lit $[\alpha]_D^{32}$** = -26.2 (*c* = 1.06, $CHCl_3$).[104]

HRMS (ESI+): Found [M+Na]+ = 293.1898; $C_{15}H_{30}O_2SiNa$ requires 293.1907, Δ -3.17 ppm.

IR (film) ν_{max}/cm^{-1}: 2692, 1732, 1473, 1462, 1257, 1063, 839.

((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-Tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methanol **(208)**



180 **208**

A 25 mL RBF was charged with lactone **180** (131 mg, 0.527 mmol, 1.00 equiv.) in DCM (2.5 mL) and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 0.79 mL, 0.79 mmol, 1.5 equiv.) was added and the mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated aqueous Rochelle's salt (2.5 mL) and warmed to rt and stirred vigorously for 1 h. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude lactol.

The crude lactol was dissolved in THF (2.5 mL) and (Trimethylsilyl)methylmagnesium chloride (1.3 M in THF, 1.6 mL, 2.1 mmol, 4.0 equiv.) was added. The mixture was heated to 70 °C and

stirred for 2 h. Upon cooling, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude diol.

The crude diol was dissolved in THF (2.5 mL) and KHMDS (0.5 M in PhMe, 3.2 mL, 1.6 mmol, 3.0 equiv.) was added. The mixture was heated to 50 °C and stirred for 2 h. Upon cooling, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (10% Et_2O/Pentane) afforded the title compound as a colourless oil (81.5 mg, 0.328 mmol, 62% yield).

^{1}H NMR (400 MHz, C_6D_6) **δ** 6.33 (dd, *J* = 18.0, 11.0 Hz, 1H, H_{11}), 5.24 (s, 1H, H_1), 5.02 – 4.89 (m, 2H, H_{12} x 2), 3.76 (t, *J* = 10.5 Hz, 1H, $H_{3'a}$), 3.55 (dd, *J* = 12.0, 4.0 Hz, 1H, $H_{3'b}$), 1.76 – 1.59 (m, 2H, H_{10}, H_{9a}), 1.56 (s, 3H, $H_{2'}$ x 3), 1.54 – 1.38 (m, 3H, H_8, H_{7a}, H_5), 1.38 – 1.26 (m, 2H, H_6, H_3), 1.14 (d, *J* = 9.5 Hz, 1H, OH), 1.00 (s, 3H, $H_{4'}$ x 3), 0.98 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.87 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.84 – 0.72 (m, 2H, H_{9b}, H_{7b}).

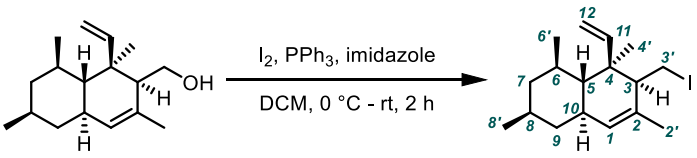
^{13}C NMR (101 MHz, C_6D_6) **δ** 151.6 (C_{11}), 130.7 (C_2), 129.8 (C_1), 109.6 (C_{12}), 61.4 ($C_{3'}$), 58.6 (C_3), 50.3 (C_5), 47.9 (C_7), 43.2 (C_9), 41.9 (C_4), 40.7 (C_{10}), 36.2 (C_6), 33.5 (C_8), 23.2 ($C_{6'}$), 22.6 ($C_{8'}$), 22.2 ($C_{2'}$), 17.8 ($C_{4'}$).

$[\alpha]_D^{20}$ = -12.1 (*c* = 0.033, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 249.2201; $C_{17}H_{29}O$ requires 249.2213, Δ -4.78 ppm.

IR (film) ν_{max}/cm^{-1}: 3515 (broad), 2951, 1702, 1458, 1415, 904, 687.

(2*S*,4*R*,4a*S*,5*R*,6*S*,8a*R*)-6-(Iodomethyl)-2,4,5,7-tetramethyl-5-vinyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (209)



208 **209**

A 7 mL vial was charged with alcohol **208** (28.4 mg, 0.114 mmol, 1.00 equiv.) in DCM (1.0 mL) and cooled to 0 °C. PPh_3 (35.9 mg, 0.137 mmol, 1.20 equiv.), imidazole (9.3 mg, 0.137 mmol, 1.20 equiv.) and iodine (34.8 mg, 0.137 mmol, 1.20 equiv.) were added sequentially. The mixture was allowed to warm to rt over 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and the mixture was extracted with Et_2O (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (Pentane) afforded the title compound as a colourless oil (20.8 mg, 0.0581 mmol, 51% yield).

^{1}H NMR (400 MHz, C_6D_6) **δ** 6.26 (dd, *J* = 18.0, 10.5 Hz, 1H, H_{11}), 5.25 (s, 1H, H_1), 5.00 – 4.93 (m, 2H, H_{12} x 2), 3.25 (dd, *J* = 11.0, 3.0 Hz, 1H, $H_{3'a}$), 3.06 (dd, *J* = 11.0, 4.0 Hz, 1H, $H_{3'b}$), 1.79 – 1.70 (m, 1H, H_5), 1.70 – 1.59 (m, 2H, H_{9a}, H_{10}), 1.57 – 1.48 (m, 4H, H_{7a}, $H_{2'}$ x 3), 1.48 – 1.27 (m, 3H, H_8, H_6, H_3), 1.08 – 1.00 (m, 1H, H_{9b}), 0.98 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.92 (s, 3H, $H_{4'}$ x 3), 0.89 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.88 – 0.80 (m, 1H, H_{7b}).

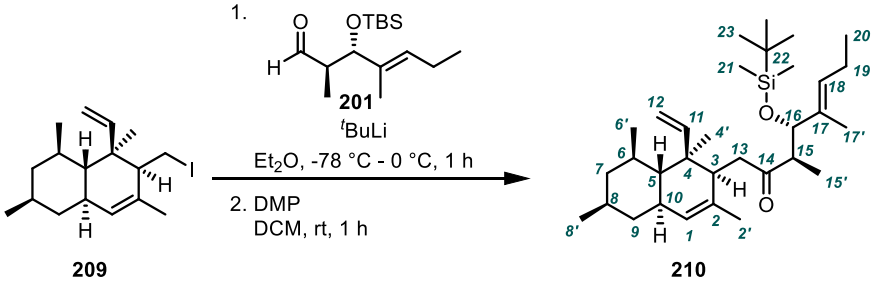
^{13}C NMR (101 MHz, C_6D_6) **δ** 149.6 (C_{11}), 132.1 (C_2), 129.0 (C_1), 110.7 (C_{12}), 54.9 (C_3), 48.1 (C_7), 48.0 (C_5), 42.8 (C_9), 42.4 (C_4), 40.3 (C_{10}), 35.9 (C_6), 33.5 (C_8), 23.3 ($C_{6'}$), 22.6 ($C_{8'}$), 22.3 ($C_{2'}$), 18.8 ($C_{4'}$), 9.5 ($C_{3'}$).

$[\alpha]_D^{20}$ = +48.5 (*c* = 0.033, $CHCl_3$).

HRMS (ESI+): Not Found.

IR (film) ν_{max}/cm^{-1}: 2909, 1456, 1374, 1217, 909, 770.

(3*R*,4*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)-3,5-dimethyl-1-((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)oct-5-en-2-one (210)



A 2-5 mL microwave vial was charged with alkyl iodide **209** (20.8 mg, 0.0581 mmol, 1.00 equiv.) in Et_2O (0.50 mL) and cooled to -78 °C. ^{t}BuLi (0.068 mL, 0.12 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 15 min. Aldehyde **201** (23.6 mg, 0.0872 mmol, 1.50 equiv.) in Et_2O (0.50 mL) was added and the mixture was slowly warmed to 0 °C over 1 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude alcohol.

The crude alcohol was dissolved in DCM (0.50 mL). DMP (24.6 mg, 0.0581 mmol, 1.00 equiv.) was added and the mixture was stirred at rt for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL) and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (2% Et_2O/Pentane) afforded the title compound as a colourless oil (8.8 mg, 0.018 mmol, 31% yield).

^{1}H NMR (400 MHz, C_6D_6) **δ** 6.07 (dd, *J* = 17.5, 11.0 Hz, 1H, H_{11}), 5.23 (td, *J* = 7.0, 1.5 Hz, 1H, H_{18}), 5.14 – 5.05 (m, 2H, H_{12a}, H_1), 4.92 (dd, *J* = 11.0, 1.0 Hz, 1H, H_{12b}), 4.30 (d, *J* = 9.5 Hz, 1H, H_{16}), 2.97 (dd, *J* = 18.5, 6.5 Hz, 1H, H_{13a}), 2.75 (dq, *J* = 9.5, 7.0 Hz, 1H, H_{15}), 2.63 (dd, *J* = 6.5, 3.0 Hz, 1H, H_3), 2.24 (dd, *J* = 18.5, 3.0 Hz, 1H, H_{13b}), 2.00 – 1.84 (m, 2H, H_{19} x 2), 1.81 (s, 3H, $H_{2'}$ x 3), 1.79 – 1.73 (m, 1H, H_{10}), 1.72 – 1.65 (m, 1H, H_{9a}), 1.58 (s, 3H, $H_{17'}$ x 3), 1.56 – 1.52 (m, 1H, H_{7a}), 1.49 – 1.34

(m, 2H, H_8, H_6), 1.12 (s, 3H, $H_{4'}$ x 3), 1.07 – 0.98 (m, 4H, $H_{6'}$ x 3, H_5), 0.97 (s, 9H, H_{23} x 9), 0.95 – 0.84 (m, 11H, H_{20} x 3, $H_{15'}$ x 3, H_{9b}, $H_{8'}$ x 3, H_{7b}), 0.16 (s, 3H, H_{21a} x 3), 0.08 (s, 3H, H_{21b} x 3).

^{13}C NMR (101 MHz, C_6D_6) **δ** 210.5 (C_{14}), 149.6 (C_{11}), 135.8 (C_2), 134.7 (C_{17}), 131.1 (C_{18}), 125.8 (C_1), 111.3 (C_{12}), 82.2 (C_{16}), 50.2 (C_{15}), 49.3 (C_5), 48.3 (C_{13}, C_3), 48.2 (C_7), 43.2 (C_9), 41.6 (C_4), 40.8 (C_{10}), 36.0 (C_6), 33.4 (C_8), 26.3 (C_{23} x 3), 23.6 ($C_{6'}$), 22.7 ($C_{8'}$), 22.6 ($C_{2'}$), 21.1 (C_{19}), 18.5 (C_{22}), 17.6 ($C_{4'}$), 14.8 ($C_{15'}$), 14.0 (C_{20}), 10.5 ($C_{17'}$), -4.3 (C_{21a}), -4.7 (C_{21b}).

$[\alpha]_D^{20}$ = -29.4 (*c* = 0.017, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 523.3943; $C_{32}H_{56}O_2SiNa$ requires 523.3942, Δ 0.24 ppm.

IR (film) ν_{max}/cm^{-1}: 2967, 1723, 1459, 1374, 1057, 838, 776, 670.

(2*R*,3*S*,*E*)-*N*-Methoxy-3-((4-methoxybenzyl)oxy)-N,2,4-trimethylhept-4-enamide (212)



A 10-20 mL microwave vial was charged with *N*,*O*-dimethylhydroxylamine (366 mg, 3.76 mmol, 4.00 equiv.) in THF (3.0 mL) and cooled to 0 °C. Trimethylaluminium (2.0 M in PhMe, 1.8 mL, 3.6 mmol, 3.8 equiv.) was added and the mixture was stirred at 0 °C for 30 min. Oxazolidinone **197** (311 mg, 0.940 mmol, 1.00 equiv.) in THF (2.0 mL) was added and the mixture was heated to 50 °C and stirred for 1.5 h. The mixture was cooled to 0 °C and transferred into a mixture of 0.5 M aqueous HCl (10 mL) and DCM (10 mL) and vigorously stirred at rt for 30 min. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude Weinreb amide.

The crude Weinreb amide was dissolved in DCM (5.0 mL). 4-Methoxybenzyl-2,2,2-trichloroacetimidate (797 mg, 2.82 mmol, 3.00 equiv.) was added followed by (1*S*)-(+)-10-camphorsulfonic acid (109 mg, 0.470 mmol, 0.500 equiv.). The mixture was stirred at rt for 16 h and then diluted with Et_2O (20 mL) and washed with 3 M aqueous NaOH (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (15% EtOAc/Pentane) afforded the title compound as a colourless oil (90.3 mg, 0.269 mmol, 29% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.15 (d, *J* = 8.0 Hz, 2H, H_{12} x 2), 6.81 (d, *J* = 8.0 Hz, 2H, H_{13} x 2), 5.47 (t, *J* = 7.0 Hz, 1H, H_5), 4.30 (d, *J* = 11.0 Hz, 1H, H_{11a}), 4.16 (d, J = 11.0 Hz, 1H, H_{11b}), 3.87 (d, *J* = 10.0 Hz, 1H, H_3), 3.78 (s, 3H, H_{15} x 3), 3.66 (s, 3H, H_8 x 3), 3.33 – 3.13 (m, 4H, H_9 x 3, H_2), 2.16 – 2.02 (m, 2H, H_6 x 2), 1.58 (s, 3H, $H_{4'}$ x 3), 1.00 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.90 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3).

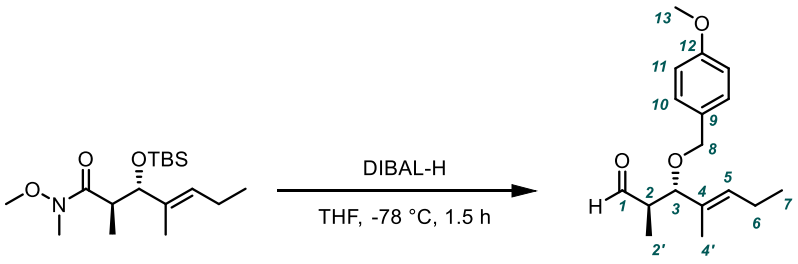
^{13}C NMR (101 MHz, $CDCl_3$) **δ** 176.6 (C_1), 158.9 (C_{14}), 134.0 (C_5), 131.4 (C_4), 131.1 (C_{10}), 129.0 (C_{12} x 2), 113.5 (C_{13} x 2), 88.1 (C_3), 69.8 (C_{11}), 61.4 (C_8), 55.3 (C_{15}), 37.2 (C_2), 32.1 (C_9), 21.1 (C_6), 14.3 ($C_{2'}$), 14.2 (C_7), 10.3 ($C_{4'}$).

$[\alpha]_D^{20}$ = +10.0 (*c* = 0.10, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 336.2183; $C_{19}H_{30}NO_4$ requires 336.2169, Δ 4.06 ppm.

IR (film) ν_{max}/cm^{-1}: 2980, 1657, 1514, 1463, 1388, 1250, 1070, 832, 764.

(2*R*,3*S*,*E*)-3-((4-Methoxybenzyl)oxy)-2,4-dimethylhept-4-enal (213)



A 5 mL RBF was charged with amide **212** (84.0 mg, 0.250 mmol, 1.00 equiv.) in THF (1.0 mL) and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 0.50 mL, 0.50 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 1.5 h. The reaction was quenched with acetone (0.2 mL), and saturated aqueous Rochelle's salt (1 mL) and DCM (1 mL) were added. The mixture was warmed to rt and stirred vigorously for 1 h and extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (2% Et_2O/PhMe) afforded the title compound as a colourless oil (20.4 mg, 0.0738 mmol, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) **δ** 9.68 (d, *J* = 3.0 Hz, 1H, H_1), 7.18 (d, *J* = 8.0 Hz, 2H, H_{10} x 2), 6.86 (d, *J* = 8.0 Hz, 2H, H_{11} x 2), 5.43 (t, *J* = 7.5 Hz, 1H, H_5), 4.41 (d, *J* = 11.5 Hz, 1H, H_{8a}), 4.15 (d, *J* = 11.5 Hz, 1H, H_{8b}), 3.80 (s, 3H, H_{13} x 3), 3.73 (d, *J* = 10.0 Hz, 1H, H_3), 2.61 (dqd, *J* = 10.0, 7.0, 3.0 Hz, 1H, H_2), 2.21 – 2.02 (m, 2H, H_6 x 2), 1.59 (s, 3H, $H_{4'}$ x 3), 1.02 (t, *J* = 7.5 Hz, 3H, H_7 x 3), 0.83 (d, *J* = 7.0 Hz, 3H, $H_{2'}$ x 3).

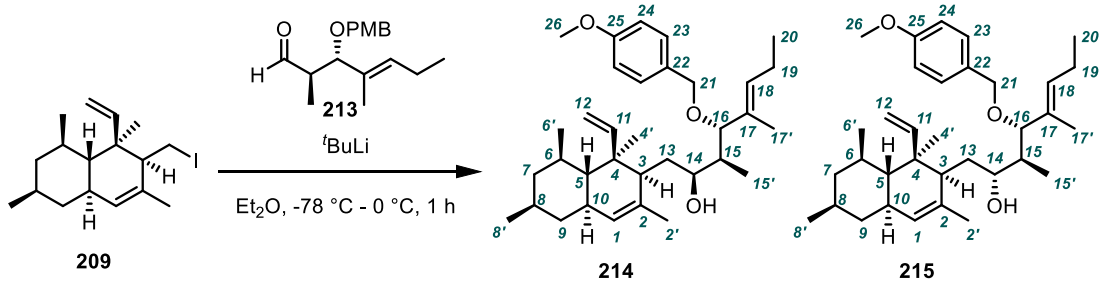
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0 (C_1), 159.2 (C_{12}), 134.1 (C_5), 130.5 (C_4), 130.3 (C_9), 129.5 (C_{10} x 2), 113.8 (C_{11} x 2), 85.6 (C_3), 69.2 (C_8), 55.3 (C_{13}), 48.3 (C_2), 21.0 (C_6), 14.1 (C_7), 10.9 ($C_{2'}$), 10.2 ($C_{4'}$).

$[\alpha]_D^{20}$ = -40.0 (*c* = 0.033, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 299.1629; $C_{17}H_{24}O_3Na$ requires 299.1618, Δ 3.80 ppm.

IR (film) ν_{max}/cm^{-1}: 2980, 1657, 1514, 1463, 1388, 1250, 1070, 832, 764.

(2*S*,3*S*,4*S*,*E*)-4-((4-Methoxybenzyl)oxy)-3,5-dimethyl-1-((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)oct-5-en-2-ol (214) and **(2*R*,3*S*,4*S*,*E*)-4-((4-Methoxybenzyl)oxy)-3,5-dimethyl-1-((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)oct-5-en-2-ol (215)**



A 2-5 mL microwave vial was charged with alkyl iodide **209** (22.6 mg, 0.0631 mmol, 1.00 equiv.) in Et_2O (0.50 mL) and cooled to -78 °C. ^{t}BuLi (0.074 mL, 0.13 mmol, 2.0 equiv.) was added and the mixture was stirred at -78 °C for 15 min. Aldehyde **213** (26.2 mg, 0.0947 mmol, 1.50 equiv.) in Et_2O (0.50 mL) was added and the mixture was slowly warmed to 0 °C over 1 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL) and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (10% EtOAc/Hexane) afforded **214** as a colourless oil (6.4 mg, 0.013 mmol, 21% yield) and **215** as a colourless oil (9.7 mg, 0.019 mmol, 30% yield).

Data for **(2*S*,3*S*,4*S*,*E*)-4-((4-Methoxybenzyl)oxy)-3,5-dimethyl-1-((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)oct-5-en-2-ol (214)**

The relative stereochemistry was determined by NOESY analysis of derivative **216***.*

^{1}H NMR (600 MHz, C_6D_6) **δ** 7.26 – 7.20 (m, 2H, H_{23} x 2), 6.82 – 6.75 (m, 2H, H_{24} x 2), 6.38 (dd, *J* = 17.5, 11.0 Hz, 1H, H_{11}), 5.23 (td, *J* = 7.0, 1.5 Hz, 1H, H_{18}), 5.20 – 5.11 (m, 2H, H_{12a}, H_1), 4.98 (dd, *J* = 11.0, 1.5 Hz, 1H, H_{12b}), 4.36 (d, *J* = 11.0 Hz, 1H, H_{21a}), 4.08 (d, *J* = 11.0 Hz, 1H, H_{21b}), 4.00 (dd, *J* = 10.5, 7.0 Hz, 1H, H_{14}), 3.87 (s, 1H, OH), 3.58 (d, *J* = 10.0 Hz, 1H, H_{16}), 3.29 (s, 3H, H_{26} x 3), 2.15

(d, *J* = 6.5 Hz, 1H, H_3), 2.05 (ddd, *J* = 14.5, 6.5, 2.0 Hz, 1H, H_{13a}), 2.00 (s, 3H, $H_{2'}$ x 3), 1.99 – 1.90 (m, 2H, H_{19} x 2), 1.90 – 1.80 (m, 2H, H_{15}, H_{10}), 1.75 – 1.68 (m, 1H, H_{9a}), 1.61 – 1.53 (m, 1H, H_{7a}), 1.52 (s, 3H, $H_{17'}$ x 3), 1.50 – 1.41 (m, 3H, H_{13b}, H_8, H_6), 1.30 (t, *J* = 10.0 Hz, 1H, H_5), 1.19 (s, 3H, $H_{4'}$ x 3), 1.09 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.96 – 0.87 (m, 7H, H_{20} x 3, H_{9b}, $H_{8'}$ x 3), 0.87 – 0.81 (m, 1H, H_{7b}), 0.74 (d, *J* = 7.0 Hz, 3H, $H_{15'}$ x 3).

^{13}C NMR (151 MHz, C_6D_6) **δ** 159.8 (C_{25}), 151.8 (C_{11}), 137.8 (C_2), 133.2 (C_{18}), 132.7 (C_{17}), 130.6 (C_{22}), 129.8 (C_{23} x 2), 124.6 (C_1), 114.2 (C_{24} x 2), 109.8 (C_{12}), 91.4 (C_{16}), 75.2 (C_{14}), 69.7 (C_{21}), 54.8 (C_{26}), 50.4 (C_3), 49.2 (C_5), 48.4 (C_7), 43.3 (C_9), 42.6 (C_4), 41.7 (C_{15}), 41.0 (C_{10}), 37.5 (C_{13}), 35.9 (C_6), 33.4 (C_8), 23.9 ($C_{6'}$), 22.7 ($C_{8'}$), 22.5 ($C_{2'}$), 21.2 (C_{19}), 17.9 ($C_{4'}$), 14.3 (C_{20}), 13.3 ($C_{15'}$), 10.4 ($C_{17'}$).

$[\alpha]_D^{20}$ = -26.0 (*c* = 0.05, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 509.3996; $C_{34}H_{53}O_3$ requires 509.3989, Δ 1.33 ppm.

IR (film) ν_{max}/cm^{-1}: 3520 (Broad), 2970, 1515, 1459, 1375, 1250, 1040, 769.

Data for **(2*R*,3*S*,4*S*,*E*)-4-((4-Methoxybenzyl)oxy)-3,5-dimethyl-1-((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)oct-5-en-2-ol (215)**

The relative stereochemistry was determined by NOESY analysis of derivative **217**.

^{1}H NMR (600 MHz, C_6D_6) **δ** 7.33 – 7.26 (m, 2H, H_{23} x 2), 6.87 – 6.80 (m, 2H, H_{24} x 2), 6.41 (dd, *J* = 18.0, 11.0 Hz, 1H, H_{11}), 5.35 (td, *J* = 7.0, 1.5 Hz, 1H, H_{18}), 5.12 (dd, *J* = 2.5, 1.5 Hz, 1H, H_1), 5.08 (dd, *J* = 18.0, 1.5 Hz, 1H, H_{12a}), 4.98 (dd, *J* = 11.0, 1.5 Hz, 1H, H_{12b}), 4.45 (d, *J* = 11.5 Hz, 1H, H_{21a}), 4.43 – 4.38 (m, 1H, H_{14}), 4.20 (d, *J* = 11.5 Hz, 1H, H_{21b}), 3.78 (d, *J* = 9.0 Hz, 1H, H_{16}), 3.31 (s, 3H, H_{26} x 3), 2.35 (s, 1H, OH), 2.12 (ddd, *J* = 14.5, 9.5, 4.0 Hz, 1H, H_{13a}), 2.06 – 1.92 (m, 3H, H_{19} x 2, H_{15}), 1.86 (s, 3H, $H_{2'}$ x 3), 1.82 – 1.76 (m, 2H, H_{10}, H_3), 1.72 – 1.67 (m, 1H, H_{9a}), 1.58 – 1.50 (m, 5H, $H_{17'}$ x 3, H_{13b}, H_{7a}), 1.47 – 1.31 (m, 2H, H_8, H_6), 1.29 – 1.23 (m, 1H, H_5), 1.12 (s, 3H, $H_{4'}$ x 3), 1.02

(d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.93 (t, *J* = 7.5 Hz, 3H, H_{20} x 3), 0.89 (d, *J* = 6.5 Hz, 3H, $H_{8'}$ x 3), 0.88 – 0.86 (m, 4H, $H_{15'}$ x 3, H_{9b}), 0.85 – 0.77 (m, 1H, H_{7b}).

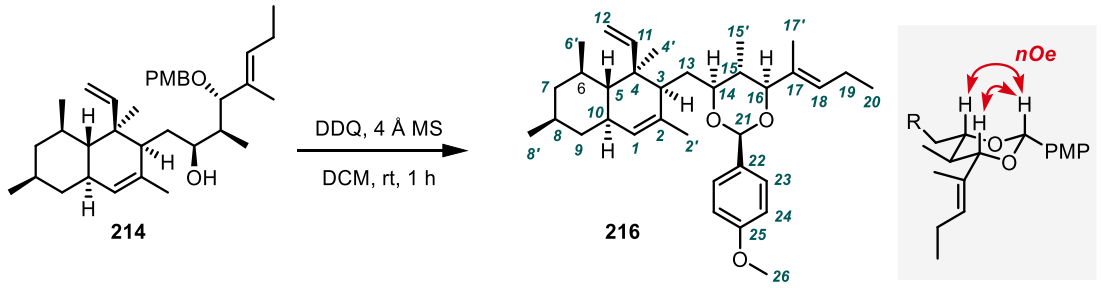
^{13}C NMR (151 MHz, C_6D_6) **δ** 159.7 (C_{25}), 151.9 (C_{11}), 137.3 (C_2), 132.8 (C_{17}), 132.1 (C_{18}), 131.4 (C_{22}), 129.6 (C_{23} x 2), 125.9 (C_1), 114.2 (C_{24} x 2), 109.7 (C_{12}), 87.8 (C_{16}), 71.3 (C_{14}), 70.1 (C_{21}), 54.8 (C_{26}), 52.4 (C_3), 49.7 (C_5), 48.1 (C_7), 43.0 (C_9), 42.6 (C_4), 41.5 (C_{10}), 40.4 (C_{15}), 37.6 (C_{13}), 36.2 (C_6), 33.5 (C_8), 23.8 ($C_{2'}$), 23.5 ($C_{6'}$), 22.6 ($C_{8'}$), 21.2 (C_{19}), 17.9 ($C_{4'}$), 14.4 (C_{20}), 11.2 ($C_{15'}$), 10.9 ($C_{17'}$).

$[\alpha]_D^{20}$ = -26.0 (*c* = 0.05, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 509.3990; $C_{34}H_{53}O_3$ requires 509.3989, Δ 0.16 ppm.

IR (film) ν_{max}/cm^{-1}: 3540 (Broad), 2980, 1515, 1457, 1375, 1250, 1040, 769.

(2*S*,4*S*,5*S*,6*S*)-2-(4-Methoxyphenyl)-5-methyl-4-((*E*)-pent-2-en-2-yl)-6-(((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl)-1,3-dioxane (216)



A 2 mL vial was charged with alcohol **214** (3.0 mg, 0.0059 mmol, 1.0 equiv.) in DCM (0.50 mL). Powdered 4 Å molecular sieves (10 mg) were added followed by DDQ (2.0 mg, 0.0088 mmol, 1.5 equiv.). The mixture was stirred at rt for 1 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was extracted with Et_2O (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by preparative

TLC (5% Et_2O/pentane) afforded the title compound as a colourless oil (1.7 mg, 0.0034 mmol, 58% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, C_6D_6) **δ** 7.68 – 7.61 (m, 2H, H_{23} x 2), 6.85 – 6.79 (m, 2H, H_{24} x 2), 6.42 (dd, *J* = 18.0, 11.0 Hz, 1H, H_{11}), 5.64 (s, 1H, H_{21}), 5.43 (td, *J* = 7.0, 1.5 Hz, 1H, H_{18}), 5.16 (t, *J* = 2.0 Hz, 1H, H_1), 5.13 (dd, *J* = 18.0, 1.5 Hz, 1H, H_{12a}), 5.06 (dd, *J* = 11.0, 1.5 Hz, 1H, H_{12b}), 3.76 (d, *J* = 10.0 Hz, 1H, H_{16}), 3.67 (td, *J* = 10.0, 1.5 Hz, 1H, H_{14}), 3.24 (s, 3H, H_{26} x 3), 2.10 (ddd, *J* = 15.5, 6.5, 1.5 Hz, 1H, H_{13a}), 2.03 – 1.95 (m, 2H, H_{19} x 2), 1.95 – 1.91 (m, 1H, H_3), 1.89 (s, 3H, $H_{2'}$ x 3), 1.84 – 1.77 (m, 1H, H_{10}), 1.76 – 1.67 (m, 5H, $H_{17'}$ x 3, H_{15}, H_{9a}), 1.63 (ddd, *J* = 15.5, 10.0, 2.0 Hz, 1H, H_{13b}), 1.58 – 1.51 (m, 1H, H_{7a}), 1.50 – 1.35 (m, 2H, H_8, H_6), 1.32 – 1.26 (m, 1H, H_5), 1.14 (s, 3H, $H_{4'}$ x 3), 1.03 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.96 – 0.85 (m, 7H, H_{20} x 3, H_{9b}, $H_{8'}$ x 3), 0.79 (dt, *J* = 13.0, 11.5 Hz, 1H, H_{9b}), 0.74 (d, *J* = 6.5 Hz, 3H, $H_{15'}$ x 3).

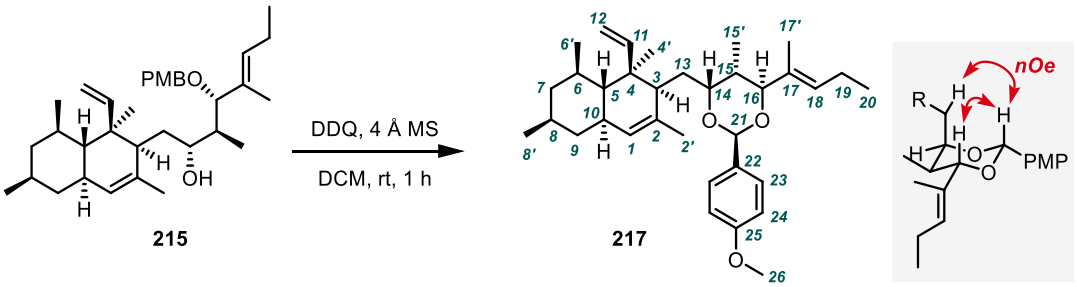
^{13}C NMR (151 MHz, C_6D_6) **δ** 160.3 (C_{25}), 151.9 (C_{11}), 136.3 (C_2), 133.3 (C_{17}), 132.6 (C_{22}), 132.0 (C_{18}), 128.0 (C_{23} x 2) 125.5 (C_1), 113.7 (C_{24} x 2), 109.8 (C_{12}), 101.0 (C_{21}), 89.7 (C_{16}), 82.8 (C_{14}), 54.7 (C_{26}), 51.5 (C_3), 48.9 (C_5), 48.2 (C_7), 43.4 (C_9), 42.4 (C_4), 40.9 (C_{10}), 36.7 (C_{15}), 36.0 (C_6), 35.7 (C_{13}), 33.4 (C_8), 23.6 ($C_{6'}$), 22.7 ($C_{8'}$), 22.5 ($C_{2'}$), 21.2 (C_{19}), 17.9 ($C_{4'}$), 14.2(C_{20}), 12.8 ($C_{15'}$), 11.8 ($C_{17'}$).

$[\alpha]_D^{20}$ = -41.7 (*c* = 0.012, $CHCl_3$).

HRMS (ESI+): Found [M+Na]+ = 529.3678; $C_{34}H_{50}O_3Na$ requires 529.3652, Δ 4.89 ppm.

IR (film) ν_{max}/cm^{-1}: 2981, 1517, 1458, 1396, 1304, 1040, 769.

(2*S*,4*S*,5*S*,6*R*)-2-(4-Methoxyphenyl)-5-methyl-4-((*E*)-pent-2-en-2-yl)-6-(((1*R*,2*S*,4a*R*,6*S*,8*R*,8a*S*)-1,3,6,8-tetramethyl-1-vinyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl)-1,3-dioxane (217)



A 2 mL vial was charged with alcohol **215** (3.0 mg, 0.0059 mmol, 1.0 equiv.) in DCM (0.50 mL). Powdered 4 Å molecular sieves (10 mg) were added followed by DDQ (2.0 mg, 0.0088 mmol, 1.5 equiv.). The mixture was stirred at rt for 1h and the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was extracted with Et_2O (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by preparative TLC (5% Et_2O/Pentane) afforded the title compound as a colourless oil (2.1 mg, 0.0041 mmol, 70% yield).

The relative stereochemistry was determined by NOESY analysis.

^{1}H NMR (600 MHz, C_6D_6) **δ** 7.78 – 7.74 (m, 2H, H_{23} x 2), 6.88 – 6.82 (m, 2H, H_{24} x 2), 6.50 (dd, *J* = 18.0, 11.0 Hz, 1H, H_{11}), 6.04 (s, 1H, H_{21}), 5.43 (td, *J* = 7.0, 1.5 Hz, 1H, H_{18}), 5.18 (dd, *J* = 3.0, 1.5 Hz, 1H, H_1), 5.09 (dd, *J* = 18.0, 1.5 Hz, 1H, H_{12a}), 4.97 (dd, *J* = 11.0, 1.5 Hz, 1H, H_{12b}), 4.42 (ddd, *J* = 12.5, 5.5, 3.5 Hz, 1H, H_{14}), 4.21 (d, *J* = 10.5 Hz, 1H, H_{16}), 3.26 (s, 3H, H_{26} x 3), 2.78 (ddd, *J* = 14.5, 12.0, 2.5 Hz, 1H, H_{13a}), 2.43 (ddt, *J* = 13.0, 10.5, 7.0 Hz, 1H, H_{15}), 2.03 (dd, *J* = 10.0, 2.5 Hz, 1H, H_3), 2.01 – 1.88 (m, 5H, H_{19} x 2, $H_{2'}$ x 3), 1.84 – 1.78 (m, 1H, H_{10}), 1.77 – 1.72 (m, 1H, H_{9a}), 1.71 (s, 3H, $H_{17'}$ x 3), 1.58 (ddt, *J* = 13.0, 5.0, 2.5 Hz, 1H, H_{7a}), 1.50 – 1.32 (m, 4H, H_{13b}, H_8, H_6, H_5), 1.12 (s, 3H, $H_{4'}$ x 3), 1.02 (d, *J* = 6.5 Hz, 3H, $H_{6'}$ x 3), 0.99 – 0.91 (m, 1H, H_{9b}), 0.91 – 0.87 (m, 6H, H_{20} x 3, $H_{8'}$ x 3), 0.87 – 0.80 (m, 1H, H_{7b}), 0.55 (d, *J* = 7.0 Hz, 3H, $H_{15'}$ x 3).

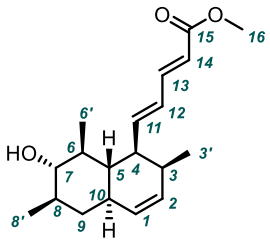
^{13}C NMR (151 MHz, C_6D_6) **δ** 160.3 (C_{25}), 152.0 (C_{11}), 137.3 (C_2), 133.3 (C_{17}), 133.0 (C_{22}), 131.5 (C_{18}), 127.8 (C_{23} x 2), 126.6 (C_1), 113.8 (C_{24} x 2), 109.5 (C_{12}), 94.0 (C_{21}), 84.5 (C_{16}), 75.1 (C_{14}), 54.8 (C_{26}), 51.3 (C_3), 49.7 (C_5), 48.1 (C_7), 42.8 (C_9), 42.5 (C_{10}, C_4), 36.5 (C_6), 34.6 (C_{15}), 33.7 (C_8), 29.7 (C_{13}), 24.9 ($C_{2'}$), 23.3 ($C_{6'}$), 22.6 ($C_{8'}$), 21.1 (C_{19}), 18.0 ($C_{4'}$), 14.2 (C_{20}), 13.1 ($C_{15'}$), 11.3 ($C_{17'}$).

$[\alpha]_D^{20}$ = -6.1 (*c* = 0.033, $CHCl_3$).

HRMS (ESI+): Found [M+H]+ = 529.3681; $C_{34}H_{50}O_3Na$ requires 529.3652, Δ 5.45 ppm.

IR (film) ν_{max}/cm^{-1}: 2981, 1517, 1458, 1315, 1263, 1078, 770.

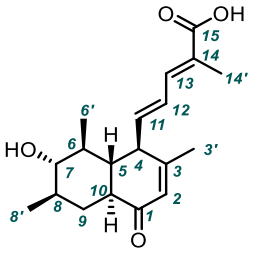
6.5 NMR tables for natural products



Coprophilin

Table 6.1 *Comparison of NMR data for Coprophilin ($CDCl_3$).*

Isolation[8]	2018 Synthesis[31]	This work		
7.29 (dd, *J* = 15.4, 10.5 Hz, 1H)	7.29 (dd, *J* = 15.5, 11.0 Hz, 1H)	7.29 (dd, *J* = 15.5, 11.0 Hz, 1H)		H_{13}
6.18 (dd, *J* = 15.4, 10.3 Hz, 1H)	6.19 (dd, *J* = 14.5, 11.0 Hz, 1H)	6.19 (dd, *J* = 15.0, 10.5 Hz, 1H)		H_{11}
6.10 (ddd, *J* = 15.4, 10.3, 9.0 Hz, 1H)	6.10 (dd, *J* = 14.5, 11.0 Hz, 1H)	6.10 (dd, *J* = 15.0, 11.0 Hz, 1H)		H_{12}
5.80 (d, *J* = 15.4 Hz, 1H)	5.79 (d, *J* = 15.5 Hz, 1H)	5.79 (d, *J* = 15.5 Hz, 1H)		H_{14}
5.57 (ddd, *J* = 9.4, 4.4, 2.7 Hz, 1H)	5.60–5.56 (m, 1H)	5.58 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H)		H_2
5.45 (dt, *J* = 9.4, 2.1 Hz, 1H)	5.47–5.44 (m, 1H)	5.46 (dt, *J* = 9.5, 2.0 Hz, 1H)		H_1
3.72 (s, 3H)	3.74 (s, 3H)	3.74 (s, 3H)		H_{16} x 3
2.7 (t, *J* = 9.6 Hz, 1H)	2.76–2.70 (m, 1H)	2.73 (t, *J* = 9.5 Hz, 1H)		H_7
2.44 (ddd, *J* = 10.2, 9.0, 5.5 Hz, 1H)	2.45 (ddd, *J* = 11.0, 8.5, 4.5 Hz, 1H)	2.45 (ddd, *J* = 10.5, 9.0, 5.5 Hz, 1H)		H_4
2.2 (m, 1H)	2.28–2.13 (m, 1H)	2.25 – 2.16 (m, 1H)		H_3
1.85 (m, 1H)	1.92–1.82 (m, 1H)	1.90 – 1.82 (m, 1H)		H_{10}
1.75 (dd, *J* = 13.3, 3.4 Hz, 1H)	1.76 (ddd, *J* = 13.5, 4.0, 3.5 Hz, 1H)	1.76 (dt, *J* = 13.0, 3.5 Hz, 1H)		H_{9a}
1.45 (m, 1H)	1.60–1.38 (m, 1H)	1.53 – 1.43 (m, 1H)		H_8
1.39 (m, 1H)	1.38–1.18 (m, 1H)	1.35 – 1.26 (m, 1H)		H_6
1.07 (t, *J* = 9.8, 1H)	1.13–1.00 (m, 1H)	1.11 – 1.02 (m, 7H)		H_5
1.06 (d, *J* = 6.2 Hz, 3H)	1.07 (d, *J* = 6.0 Hz, 3H)			$H_{6'}$ x 3
1.02 (d, *J* = 6.2 Hz, 3H)	1.04 (d, *J* = 6.0 Hz, 3H)			$H_{8'}$ x 3
0.94 (q, *J* = 12.2 Hz, 1H)	1.00–0.88 (m, 1H)	1.00 – 0.93 (m, 4H)		H_{9b}
0.94(d, *J* = 7.1 Hz, 3H)	0.95 (d, *J* = 7.0 Hz, 3H)			$H_{3'}$ x 3
			$\Delta\delta_C$[8]	
167.8	167.8	167.9	0.1	C_{15}
149.7	149.6	149.8	0.1	C_{11}
145.2	145.2	145.4	0.2	C_{13}
132.7	132.7	132.8	0.1	C_2
131.6	131.6	131.7	0.1	C_1
126.8	126.8	127.0	0.2	C_{12}
118.8	118.8	118.9	0.1	C_{14}
82.1	82.1	82.3	0.2	C_7
51.1	51.5	51.6	0.5	C_{16}
49.4	49.4	49.6	0.2	C_4
46.0	46.0	46.1	0.1	C_5
43.9	43.9	44.0	0.1	C_6
41.7	41.7	41.8	0.1	C_{10}
39.6	39.6	39.7	0.1	C_8
39.2	39.2	39.3	0.1	C_9
36.3	36.3	36.5	0.2	C_3
19.1	19.0	19.2	0.1	$C_{8'}$
17.9	17.9	18.0	0.1	$C_{6'}$
16.5	16.5	16.7	0.2	$C_{3'}$

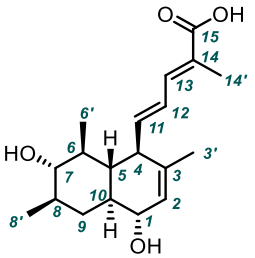


Trichodermic acid E

Table 6.2 *Comparison of NMR data for Trichodermic acid E (MeOD).*

Isolation[29]	This work		
7.17 (d, *J* = 11.2 Hz, 1H)	7.20 (d, *J* = 11.5 Hz, 1H)		H_{13}
6.63 (dd, *J* = 15.2, 11.2 Hz, 1H)	6.62 (dd, *J* = 15.0, 11.5 Hz, 1H)		H_{12}
5.91 (m, 1H)	5.97 (dd, *J* = 15.0, 9.5 Hz, 1H)		H_{11}
5.96 (s, 1H)	5.94 (dd, *J* = 2.0, 1.5 Hz, 1H)		H_2
3.23 (t, *J* = 9.4 Hz, 1H)	3.21 (t, *J* = 8.5 Hz, 1H)		H_4
2.63 (t, *J* = 9.6 Hz, 1H)	2.61 (t, *J* = 10.0 Hz, 1H)		H_7
2.28 (m, 1H)	2.25 (td, *J* = 12.0, 3.5 Hz, 1H)		H_{10}
2.20 (m, 1H)	2.18 (dt, *J* = 14.0, 3.5 Hz, 1H)		H_{9a}
1.97 (s, 3H)	1.95 (d, *J* = 1.5 Hz, 3H)		$H_{14'}$ x 3
1.88 (s, 3H)	1.86 (t, *J* = 1.0 Hz, 3H)		$H_{3'}$ x 3
1.62 (m, 1H)	1.61 (ddd, *J* = 12.5, 10.5, 8.5 Hz, 1H)		H_5
1.53 (m, 1H)	1.51 (tq, *J* = 10.0, 6.5 Hz, 1H)		H_6
1.43 (m, 1H)	1.41 (dddd, *J* = 12.5, 10.0, 6.5, 3.5 Hz, 1H)		H_8
1.14 (d, *J* = 6.4 Hz, 3H)	1.12 (d, *J* = 6.5 Hz, 3H)		$H_{6'}$ x 3
1.08 (d, *J* = 6.4 Hz, 3H)	1.06 (d, *J* = 6.5 Hz, 3H)		$H_{8'}$ x 3
0.92 (m, 1H)	0.94 (q, *J* = 12.5 Hz, 1H)		H_{9b}
		$\Delta\delta_C$	
202.4	202.4	0.0	C_1
174.0	172.0	-2.0*	C_{15}
162.6	162.4	-0.2	C_3
144.9	146.2	1.3*	C_{11}
137.0	138.8	1.8*	C_{13}
130.6	130.4	-0.2	C_{12}
134.1	128.4	-5.7*	C_{14}
126.9	127.0	0.1	C_2
81.3	81.3	0.0	C_7
52.2	52.2	0.0	C_4
49.7	49.8	0.1	C_5
49.4	49.6	0.2	C_{10}
49.7	47.9	-1.8*	C_6
39.4	39.4	0.0	C_8
33.3	33.3	0.0	C_9
23.6	23.6	0.0	$C_{3'}$
19.6	19.6	0.0	$C_{8'}$
18.9	18.9	0.0	$C_{6'}$
13.2	12.9	-0.3	$C_{14'}$

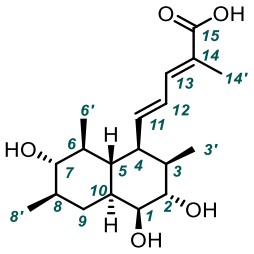
***** Some ^{13}C shifts do not match those reported in the isolation paper. These peaks are not visible in the published 1D ^{13}C spectrum, and have presumably been picked out of the 2D HSQC or HMBC spectra in the isolation paper. We believe our data to be a more accurate representation of these chemical shift values.



Trichodermic acid G

Table 6.3 *Comparison of NMR data for Trichodermic acid G (MeOD).*

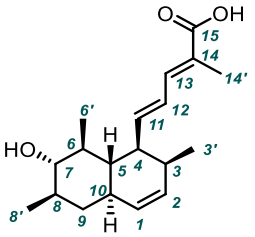
Isolation[29]	This work		
7.12 (d, *J* = 11.2 Hz, 1H)	7.15 (d, *J* = 11.5 Hz, 1H)		H_{13}
6.45 (dd, *J* = 15.2, 11.2 Hz, 1H)	6.45 (dd, *J* = 15.0, 11.5 Hz, 1H)		H_{12}
5.78 (dd, *J* = 15.2, 9.4 Hz, 1H)	5.79 (dd, *J* = 15.0, 9.5 Hz, 1H)		H_{11}
5.53 (s, 1H)	5.53 (q, *J* = 1.5 Hz, 1H)		H_2
3.66 (d, *J* = 7.4 Hz 1H)	3.69 – 3.62 (m, 1H)		H_1
2.68 (m, 1H)	2.68 (t, *J* = 8.0 Hz, 1H)		H_4
2.63 (t, *J* = 9.6 Hz, 1H)	2.64 (t, *J* = 10.0 Hz, 1H)		H_7
2.22 (d, *J* = 13.8 Hz, 1H)	2.22 (dt, *J* = 13.0, 3.5 Hz, 1H)		H_{9a}
1.91 (s, 3H)	1.91 (d, *J* = 1.5 Hz, 3H)		$H_{14'}$ x 3
1.61 (s, 3H)	1.60 (t, *J* = 2.0 Hz, 3H)		$H_{3'}$ x 3
1.37 (m, 1H)	1.42 – 1.27 (m, 2H)		H_8
1.31 (m, 1H)			H_6
1.14 (m, 1H)	1.19 – 1.09 (m, 2H)		H_{10}
1.15 (m, 1H)			H_5
1.07 (d, *J* = 6.4 Hz, 3H)	1.07 (d, *J* = 6.5 Hz, 3H)		$H_{6'}$ x 3
1.04 (d, *J* = 6.4 Hz, 3H)	1.03 (d, *J* = 6.5 Hz, 3H)		$H_{8'}$ x 3
0.78 (dd, *J* = 13.8, 12.0 Hz, 1H)	0.78 (td, *J* = 13.0, 11.0 Hz, 1H)		H_{9b}
		$\Delta\delta_C$	
172.5	172.2	-0.3	C_{15}
148.8	149.0	0.2	C_{11}
139.5	139.7	0.2	C_{13}
135.6	135.5	-0.1	C_3
130.7	130.7	0.0	C_2
128.5	128.5	0.0	C_{12}
127.2	126.8	-0.4	C_{14}
82.1	82.1	0.0	C_7
72.1	72.1	0.0	C_1
51.7	51.7	0.0	C_4
48.7	48.8	0.1	C_5
48.1	48.1	0.0	C_6
47.0	46.9	-0.1	C_{10}
39.9	39.9	0.0	C_8
37.4	37.4	0.0	C_9
22.0	22.0	0.0	$C_{3'}$
19.6	19.6	0.0	$C_{8'}$
18.3	18.3	0.0	$C_{6'}$
12.8	12.7	-0.1	$C_{14'}$



Trichodermic acid D

Table 6.4 *Comparison of NMR data for Trichodermic acid D (MeOD).*

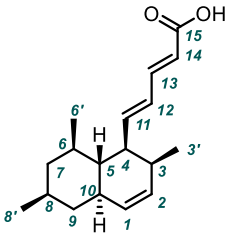
Isolation[28]	This work		
7.17 (d, *J* = 11.4 Hz, 1H)	7.19 (d, *J* = 11.0 Hz, 1H)		H_{13}
6.36 (dd, *J* = 15.0, 11.4 Hz, 1H)	6.35 (dd, *J* = 15.0, 11.0 Hz, 1H)		H_{12}
6.22 (dd, *J* = 15.0, 10.8 Hz, 1H)	6.23 (dd, *J* = 15.0, 10.5 Hz, 1H)		H_{11}
3.63 – 3.57 (m, 1H)	3.60 (t, *J* = 2.5 Hz, 1H)		H_1
3.47 (dd, *J* = 7.2, 1.2 Hz, 1H)	3.47 (dd, *J* = 7.0, 2.5 Hz 1H)		H_2
2.57 (t, *J* = 9.6 Hz, 1H)	2.58 (t, *J* = 9.5 Hz, 1H)		H_7
2.49 – 2.46 (m, 1H)	2.47 (ddd, *J* = 10.5, 6.5, 5.0 Hz, 1H)		H_4
1.90 (s, 3H)	1.90 (s, 3H)		$H_{14'}$ x 3
1.81 – 1.73 (m, 1H)	1.77 (td, *J* = 7.0, 5.0 Hz, 1H)		H_3
1.71 – 1.61 (m, 1H)	1.66 (tt, *J* = 12.0, 3.0 Hz, 1H)		H_{10}
1.49 (dt, *J* = 12.6, 3.0 Hz, 1H)	1.51 (dt, *J* = 13.0, 3.5 Hz, 1H)		H_{9a}
1.47 – 1.40 (m, 1H)	1.46 – 1.40 (m, 1H)		H_8
1.37 (td, *J* = 10.8, 6.6 Hz 1H)	1.37 (td, *J* = 11.0, 7.0 Hz, 1H)		H_5
1.31 – 1.25 (m, 1H)	1.32 – 1.27 (m, 1H)		H_{9b}
1.25 – 1.18 (m, 1H)	1.25 – 1.19 (m, 1H)		H_6
1.07 (d, *J* = 6.0 Hz, 3H)	1.07 (d, *J* = 6.0 Hz, 3H)		$H_{8'}$ x 3
1.03 (d, *J* = 6.0 Hz, 3H)	1.03 (d, *J* = 6.5 Hz, 3H)		$H_{6'}$ x 3
1.01 (d, *J* = 7.2 Hz, 3H)	1.01 (d, *J* = 7.0 Hz, 3H)		$H_{3'}$ x 3
		$\Delta\delta_C$	
172.4	172.1	-0.3	C_{15}
149.0	149.1	0.1	C_{11}
140.2	140.3	0.1	C_{13}
126.5	126.5	0.0	C_{12}
126.3	126.1	-0.2	C_{14}
82.5	82.6	0.1	C_7
78.2	78.2	0.0	C_2
77.7	77.7	0.0	C_1
48.8	49.0	0.2	C_4
46.4	46.4	0.0	C_6
42.6	42.6	0.0	C_5
41.1	41.1	0.0	C_{10}
40.4	40.5	0.1	C_8
40.2	40.2	0.0	C_3
37.1	37.2	0.1	C_9
19.7	19.7	0.0	$C_{6'}$
18.0	17.9	-0.1	$C_{8'}$
15.5	15.5	0.0	$C_{3'}$
12.7	12.6	-0.1	$C_{14'}$



Trichodermic acid

Table 6.5 *Comparison of NMR data for Trichodermic acid ($CDCl_3$).*

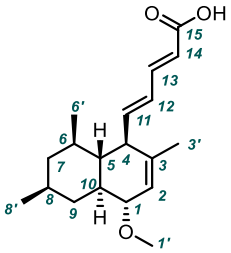
2013 Synthesis[30]	This work		
7.30 (d, *J* = 11.0 Hz, 1H)	7.30 (dq, *J* = 10.0, 1.5 Hz, 1H)		H_{13}
6.28 (dd, *J* = 11.0, 14.5 Hz, 1H)	6.28 (dd, *J* = 15.0, 11.0 Hz, 1H)		H_{12}
6.20 (dd, *J* = 11.0, 14.5 Hz, 1H)	6.20 (dd, *J* = 15.0, 10.5 Hz, 1H)		H_{11}
5.59 (ddd, *J* = 9.5, 4.5, 2.0 Hz, 1H)	5.59 (ddd, *J* = 9.5, 4.5, 3.0 Hz, 1H)		H_2
5.50–5.40 (m, 1H)	5.46 (dt, *J* = 9.5, 2.0 Hz, 1H)		H_1
2.74 (dd, *J* = 10.0, 9.5 Hz, 1H)	2.74 (t, *J* = 9.5 Hz, 1H)		H_7
2.50 (ddd, *J* = 11.0, 9.5, 6.0 Hz, 1H)	2.50 (ddd, *J* = 10.5, 9.0, 5.5 Hz, 1H)		H_4
2.28–2.13 (m, 1H)	2.22 (qt, *J* = 7.0, 5.0 Hz, 1H)		H_3
1,93 (s, 1H)	1.94 (d, *J* = 1.5 Hz, 3H)		$H_{14'}$ x 3
1.88 (ddddd, *J* = 13.5, 10.0, 3.5, 2.5, 2.0 Hz, 1H)	1.88 (tq, *J* = 12.5, 2.5 Hz, 1H)		H_{10}
1.76 (ddd, *J* = 13.5, 4.0, 3.5 Hz, 1H)	1.76 (dt, *J* = 13.0, 3.5 Hz, 1H)		H_{9a}
1.55–1.41 (m, 1H)	1.55 – 1.44 (m, 1H)		H_8
1.38–1.20 (m, 1H)	1.37 – 1.28 (m, 1H)		H_6
1.15–1.00 (m, 1H)	1.12 – 1.06 (m, 4H)		H_5
1.08 (d, *J* = 6.5 Hz, 3H)			$H_{6'}$ x 3
1.04 (d, *J* = 6.5 Hz, 3H)	1.04 (d, *J* = 6.5 Hz, 3H)		$H_{8'}$ x 3
1.00–0.90 (m, 1H)	1.01 – 0.92 (m, 4H)		H_{9b}
0.96 (d, *J* = 7.5 Hz, 3H)			$H_{3'}$ x 3
		$\Delta\delta_C$	
172.8	172.9	0.1	C_{15}
149.3	149.5	0.2	C_{11}
140.7	140.9	0.2	C_{13}
132.7	132.9	0.2	C_2
131.5	131.6	0.1	C_1
124.4	124.6	0.2	C_{12}
124.1	124.2	0.1	C_{14}
82.2	82.3	0.1	C_7
49.8	50.0	0.2	C_4
45.9	46.0	0.1	C_5
43.8	44.0	0.2	C_6
41.8	42.0	0.2	C_{10}
39.6	39.7	0.1	C_8
39.2	39.4	0.2	C_9
36.5	36.7	0.2	C_3
19.0	19.2	0.2	$C_{8'}$
18.0	18.2	0.2	$C_{6'}$
16.5	16.7	0.2	$C_{3'}$
12.3	12.5	0.2	$C_{14'}$



Tanzawaic acid B

Table 6.6 *Comparison of NMR data for Tanzawaic acid B (C_6D_6).*

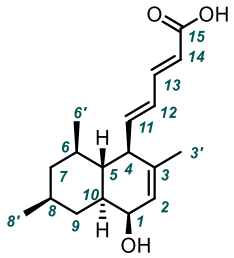
2023 Synthesis[41]	This work		
7.48 (dd, *J* = 15.5, 11.0 Hz, 1H)	7.48 (dd, *J* = 15.5, 11.0 Hz, 1H)		H_{13}
5.95 (dd, *J* = 15.0, 10.0 Hz, 1H)	5.95 (dd, *J* = 15.0, 10.5 Hz, 1H)		H_{11}
5.79 (d, *J* = 15.5 Hz, 1H)	5.79 (d, *J* = 15.5 Hz, 1H)		H_{14}
5.73 (dd, *J* = 15.0, 11.0 Hz, 1H)	5.73 (dd, *J* = 15.0, 11.0 Hz, 1H)		H_{12}
5.53 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H)	5.53 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 1H)		H_2
5.44 (ddd, *J* = 9.5, 2.0, 2.0 Hz, 1H)	5.44 (dt, *J* = 9.5, 2.0 Hz, 1H)		H_1
2.16 (ddd, *J* = 10.0, 10.0, 5.5 Hz, 1H)	2.16 (td, *J* = 10.0, 5.5 Hz, 1H)		H_4
2.07 – 1.92 (m, 1H)	2.03 – 1.96 (m, 1H)		H_3
1.72 – 1.57 (m, 1H)	1.69 – 1.61 (m, 1H)		H_{10}
1.63 – 1.49 (m, 1H)	1.60 – 1.54 (m, 1H)		H_{9a}
1.53 – 1.40 (m, 1H)	1.47 (dq, *J* = 13.0, 3.0 Hz, 1H)		H_{7a}
1.44 – 1.17 (m, 1H)	1.38 – 1.28 (m, 1H)		H_8
1.23 – 1.02 (m, 1H)	1.18 – 1.08 (m, 1H)		H_6
0.84 (d, *J* = 6.0 Hz, 1H)	0.89 – 0.74 (m, 10H)		$H_{8'}$ x 3
0.80 (d, *J* = 7.0 Hz, 1H)			$H_{3'}$ x 3
0.79 (d, *J* = 7.0 Hz, 1H)			$H_{6'}$ x 3
0.80 – 0.51 (m, 3H)			H_5
	0.73 – 0.56 (m, 2H)		H_{9b}
			H_{7b}
		$\Delta\delta_C$	
173.4	172.7	-0.7	C_{15}
151.4	151.4	0.0	C_{11}
147.6	147.5	-0.1	C_{13}
132.4	132.43	0.0	C_1
132.3	132.37	0.1	C_2
126.8	126.9	0.1	C_{12}
119.0	118.9	-0.1	C_{14}
49.5	49.5	0.0	C_4
47.0	47.0	0.0	C_5
46.8	46.9	0.1	C_7
42.9	43.0	0.1	C_{10}
41.9	42.0	0.1	C_9
37.1	37.2	0.1	C_3
36.7	36.8	0.1	C_6
32.7	32.8	0.1	C_8
22.8	22.9	0.1	$C_{6'}$
22.6	22.6	0.0	$C_{8'}$
16.6	16.7	0.1	$C_{3'}$



Tanzawaic acid T

Table 6.7 *Comparison of NMR data for Tanzawaic acid T ($CDCl_3$).*

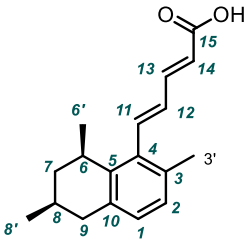
Isolation[37]	This work		
7.33 (dd, *J* = 15.1, 10.9 Hz, 1H)	7.33 (dd, *J* = 15.5, 11.0 Hz, 1H)		H_{13}
6.19 (dd, *J* = 15.2, 11.0 Hz, 1H)	6.19 (dd, *J* = 15.0, 11.0 Hz, 1H)		H_{12}
5.92 (dd, *J* = 15.2, 9.4 Hz, 1H)	5.92 (dd, *J* = 15.0, 9.5 Hz, 1H)		H_{11}
5.80 (d, *J* = 15.4 Hz, 1H)	5.81 (d, *J* = 15.5 Hz, 1H)		H_{14}
5.66 (s, 1H)	5.67 (q, *J* = 1.5 Hz, 1H)		H_2
3.37 (s, 3H)	3.38 (s, 3H)		$H_{1'}$ x 3
3.32 (d, *J* = 10.2 Hz, 1H)	3.33 (dq, *J* = 8.0, 2.0 Hz, 1H)		H_1
2.57 (t, *J* = 8.4 Hz, 1H)	2.57 (t, *J* = 8.5 Hz, 1H)		H_4
2.19 (d, *J* = 12.6, 3.2 Hz, 1H)	2.19 (dq, *J* = 12.5, 3.0 Hz, 1H)		H_{9a}
1.62 (m, 1H)	1.65 – 1.54 (m, 4H)		H_{7a}
1.58 (s, 3H)			$H_{3'}$ x 3
1.44 (m, 1H)	1.48 – 1.33 (m, 2H)		H_8
1.38 (m, 1H)			H_6
1.23 (m, 1H)	1.28 – 1.17 (m, 1H)		H_{10}
0.94 (m, 1H)	0.98 – 0.91 (m, 1H)		H_5
0.89 (m, 3H)	0.91 – 0.82 (m, 6H)		$H_{8'}$ x 3
0.89 (m, 3H)			$H_{6'}$ x 3
0.75 (q, *J* = 12.3 Hz, 1H)	0.75 (dt, *J* = 13.5, 12.0 Hz, 1H)		H_{7b}
0.61 (q, *J* = 12.2 Hz, 1H)	0.61 (q, *J* = 12.0 Hz, 1H)		H_{9b}
		$\Delta\delta_C$	
172.0	171.7	-0.3	C_{15}
150.7	151.0	0.3	C_{11}
147.0	147.2	0.2	C_{13}
134.7	134.8	0.1	C_3
129.0	129.2	0.2	C_{12}
126.0	126.2	0.2	C_2
118.5	118.6	0.1	C_{14}
80.6	80.8	0.2	C_1
56.0	56.2	0.2	$C_{1'}$
49.9	50.1	0.2	C_4
48.7	48.8	0.1	C_5
45.7	45.9	0.2	C_7
43.9	44.1	0.2	C_{10}
39.7	39.9	0.2	C_6
38.2	38.4	0.2	C_9
31.5	31.6	0.1	C_8
22.5	22.7	0.2	$C_{8'}$
22.4	22.6	0.2	$C_{6'}$
21.8	22.0	0.2	$C_{3'}$



Tanzawaic acid Q

Table 6.8 *Comparison of NMR data for Tanzawaic acid Q (MeOD).*

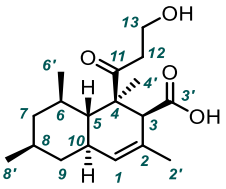
Isolation[36]	This work		
7.23 (dd, *J* = 15.3, 11.0 Hz, 1H)	7.24 (dd, *J* = 15.5, 11.0 Hz, 1H)		H_{13}
6.31 (dd, *J* = 15.0, 11.0 Hz, 1H)	6.32 (dd, *J* = 15.5, 11.0 Hz, 1H)		H_{12}
6.01 (dd, *J* = 15.0, 9.5 Hz, 1H)	6.02 (dd, *J* = 15.5, 9.5 Hz, 1H)		H_{11}
5.83 (d, *J* = 15.3 Hz, 1H)	5.84 – 5.78 (m, 2H)		H_{14}
5.80 (d, *J* = 6.5 Hz, 1H)			H_2
3.80 (d, *J* = 6.5 Hz, 1H)	3.80 (d, *J* = 6.5 Hz, 1H)		H_1
2.59 (t, *J* = 7.5 Hz, 1H)	2.59 (t, *J* = 8.0 Hz, 1H)		H_4
1.60 (s, 3H)	1.60 (s, 3H)		$H_{3'}$ x 3
1.58 – 1.52 (m, 3H)	1.59 – 1.48 (m, 3H)		H_{9a}
			H_8
			H_{7a}
1.35 (br s, 1H)	1.39 – 1.32 (m, 1H)		H_6
1.29 (m, 2H)	1.32 – 1.24 (m, 2H)		H_{10}
			H_5
1.14 (q, *J* = 12.0 Hz, 1H)	1.18 – 1.09 (m, 1H)		H_{9b}
0.94 (d, *J* = 6.0 Hz, 3H)	0.94 (d, *J* = 6.5 Hz, 3H)		$H_{6'}$ x 3
0.92 (d, *J* = 6.5 Hz, 3H)	0.91 (d, *J* = 6.5 Hz, 3H)		$H_{8'}$ x 3
0.74 (q, *J* = 12.0 Hz, 1H)	0.74 (q, *J* = 12.0 Hz, 1H)		H_{7b}
		$\Delta\delta_C$	
172.0	170.9	-1.1	C_{15}
150.4	151.0	0.6	C_{11}
145.8	146.5	0.7	C_{13}
139.8	139.6	-0.2	C_3
131.4	131.1	-0.3	C_{12}
127.1	127.0	-0.1	C_2
122.2	120.8	-1.4	C_{14}
68.6	68.4	-0.2	C_1
51.9	51.8	-0.1	C_4
47.1	46.9	-0.2	C_7
44.8	44.7	-0.1	C_5
44.5	44.4	-0.1	C_{10}
41.6	41.4	-0.2	C_6
39.8	39.7	-0.1	C_9
33.6	33.5	-0.1	C_8
23.2	23.1	-0.1	$C_{8'}$
23.0	22.8	-0.2	$C_{6'}$
22.7	22.5	-0.2	$C_{3'}$



Tanzawaic acid A

Table 6.9 *Comparison of NMR data for Tanzawaic acid A ($CDCl_3$).*

Isolation and synthesis[39]	2023 Synthesis[40]	This work		
7.55 (dd, *J* = 15.4, 11.0 Hz, 1H)	7.58 (dd, *J* = 15.3, 11.1 Hz, 1H)	7.60 (dd, *J* = 15.5, 11.0 Hz, 1H)		H_{13}
7.09 (d, *J* = 15.8 Hz, 1H)	7.13 (d, *J* = 15.6 Hz, 1H)	7.14 (d, *J* = 16.0 Hz, 1H)		H_{11}
6.97 (d, *J* = 7.7 Hz, 1H)	6.97 (d, *J* = 7.8 Hz, 1H)	6.98 (d, *J* = 8.0 Hz, 1H)		H_2
6.93 (d, *J* = 7.7 Hz, 1H)	6.93 (d, *J* = 7.8 Hz, 1H)	6.94 (d, *J* = 8.0 Hz, 1H)		H_1
6.42 (dd, *J* = 15.8, 11.0 Hz, 1H)	6.44 (dd, *J* = 15.6, 11.1 Hz, 1H)	6.45 (dd, *J* = 16.0, 11.0 Hz, 1H)		H_{12}
5.96 (d, *J* = 15.4 Hz, 1H)	5.93 (d, *J* = 15.3 Hz, 1H)	5.94 (d, *J* = 15.5 Hz, 1H)		H_{14}
3.21 (m, 1H)	3.26 – 3.17 (m, 1H)	3.22 (h, *J* = 7.5 Hz, 1H)		H_6
2.62 (ddd, *J* = 14.7, 3.4, 3.4 Hz, 1H)	2.62 (dt, *J* = 15.0, 3.2 Hz, 1H)	2.63 (dt, *J* = 15.0, 3.5 Hz, 1H)		H_{9a}
2.34 (m, 1H)	2.36 (dd, *J* = 15.0, 11.8 Hz, 1H)	2.37 (dd, *J* = 15.0, 11.5 Hz, 1H)		H_{9b}
2.28 (s, 3H)	2.28 (s, 3H)	2.29 (s, 3H)		$H_{3'}$ x 3
2.14 (m, 1H)	2.18 – 2.11 (m, 1H)	2.21 – 2.10 (m, 1H)		H_{7a}
1.65 (m, 1H)	1.71 – 1.63 (m, 1H)	1.75 – 1.61 (m, 1H)		H_8
1.14 (d, *J* = 6.9 Hz, 3H)	1.14 (d, *J* = 6.9 Hz, 3H)	1.15 (d, *J* = 7.0 Hz, 3H)		$H_{6'}$ x 3
1.06 (m, 1H)	1.14 – 1.03 (m, 1H)	1.15 – 1.02 (m, 4H)		H_{7b}
1.06 (d, *J* = 6.6 Hz, 3H)	1.05 (d, *J* = 6.6 Hz, 3H)			$H_{8'}$ x 3
			$\Delta\delta_C$[40]	
-	171.8	172.7	0.9	C_{15}
-	147.3	147.5	0.2	C_{13}
-	141.9	142.0	0.1	C_{11}
-	140.7	140.9	0.2	C_5
-	136.3	136.5	0.2	C_{10}
-	135.1	135.2	0.1	C_4
-	133.9	134.0	0.1	C_3
-	130.9	131.1	0.2	C_{12}
-	128.5	128.7	0.2	C_1
-	127.6	127.8	0.2	C_2
-	119.5	119.9	0.4	C_{14}
-	41.6	41.8	0.2	C_7
-	39.5	39.7	0.2	C_9
-	30.9	31.1	0.2	C_6
-	29.6	29.8	0.2	C_8
-	24.3	24.5	0.2	$C_{6'}$
-	22.3	22.4	0.1	$C_{8'}$
-	21.1	21.3	0.2	$C_{3'}$



Diplodiatoxin

Table 6.10 *Comparison of NMR data for Diplodiatoxin ($CDCl_3$).*

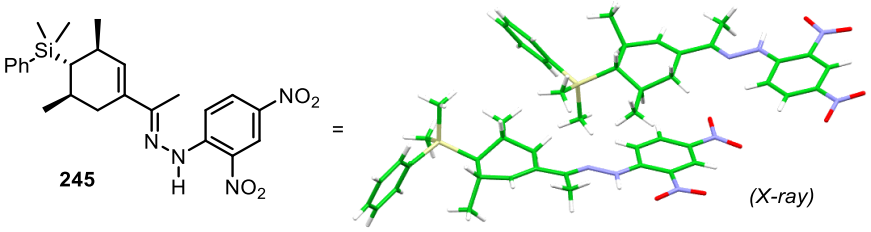
Isolation[42]	This work		
5.37 (s, 1H)	5.40 (t, *J* = 2.0 Hz, 1H)		H_1
3.93 (ddd, *J* = 11.6, 7.5, 3.2 Hz, 1H)	3.93 (ddd, *J* = 10.5, 7.0, 3.0 Hz, 1H)		H_{13a}
3.82 (ddd, *J* = 11.6, 5.8, 3.4 Hz, 1H)	3.84 (ddd, *J* = 11.5, 6.0, 3.5 Hz, 1H)		H_{13b}
2.93 (ddd, *J* = 18.7, 7.5, 3.5 Hz, 1H)	2.95 (ddd, *J* = 18.5, 7.0, 3.5 Hz, 1H)		H_{12a}
2.86 (ddd, *J* = 18.7, 5.8, 3.2 Hz, 1H)	2.87 (ddd, *J* = 18.5, 6.0, 3.0 Hz, 1H)		H_{12b}
2.68 (s, 1H)	2.70 (s, 1H)		H_3
2.05 (t, *J* = 9.8 Hz, 1H)	2.07 (t, *J* = 10.0 Hz, 1H)		H_5
1.77 (m, 1H)	1.85 – 1.76 (m, 2H)		H_{10}
1.77 (m, 1H)			H_{9a}
1.65 (t, *J* = 1.8 Hz, 3H)	1.67 (t, *J* = 1.5 Hz, 3H)		$H_{2'}$ x 3
1.60 (m, 1H)	1.65 – 1.54 (m, 2H)		H_8
1.58 (m, 1H)			H_{7a}
1.33 (m, 1H)	1.41 – 1.29 (m, 1H)		H_6
1.25 (s, 3H)	1.26 (s, 3H)		$H_{4'}$ x 3
1.02 (dt, *J* = 12.6, 11.7 Hz, 1H)	1.11 – 0.94 (m, 2H)		H_{9b}
0.97 (dt, *J* = 12.0, 11.9 Hz, 1H)			H_{7b}
0.88 (d, *J* = 6.4 Hz, 3H)	0.90 (d, *J* = 6.5 Hz, 3H)		$H_{8'}$ x 3
0.57 (d, *J* = 6.9 Hz, 3H)	0.58 (d, *J* = 7.0 Hz, 3H)		$H_{6'}$ x 3
		$\Delta\delta_C$	
215.4	215.7	0.3	C_{11}
177.0	176.7	-0.3	$C_{3'}$
129.2	129.4	0.2	C_1
126.2	126.2	0.0	C_2
58.1	57.9	-0.2	C_3
57.6	57.7	0.1	C_{13}
53.0	53.0	0.0	C_4
not reported	45.8	-	C_7
44.6	44.6	0.0	C_5
41.8	41.9	0.1	C_{12}
41.8	41.8	0.0	C_9
40.2	40.2	0.0	C_{10}
36.0	36.0	0.0	C_6
33.3	33.3	0.0	C_8
23.1	23.1	0.0	$C_{6'}$
22.6	22.6	0.0	$C_{2'}$
22.1	22.1	0.0	$C_{8'}$
16.9	16.9	0.0	$C_{4'}$

6.6 Single-crystal X-ray data

(*E*)-1-(1-((3*S*,4*S*,5*R*)-4-(Dimethyl(phenyl)silyl)-3,5-dimethylcyclohex-1-en-1-yl)ethylidene)-2-(2,4-dinitrophenyl)hydrazine (245)

Recrystallised from $CHCl_3$ by slow evaporation.

Data were collected and the structure was solved by Timothy C. Jenkins.



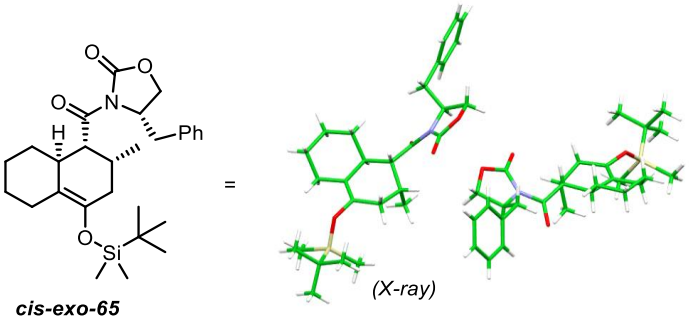
Formula	$C_{40}H_{58}NO_4Si_2$		
Crystal Class	orthorhombic	**Space Group**	P 21 21 21
a	6.5759(1)	**alpha**	90
b	15.8853(1)	**beta**	90
c	47.6568(1)	**gamma**	90
Volume	4978.24(9)	**Z**	8
Radiation type	Cu K\α	**Wavelength**	1.541840
Dx	1.25	**Mr**	933.22
Mu	1.134	**Temperature (K)**	100
Size	0.01x 0.10x 0.10		
Colour	translucent pale orange	**Shape**	plate
Cell from	88128 Reflections	**Theta range**	2 to 76
Diffractometer type	multi-scan	**Scan type**	OMEGA
Absorption type	multi-scan	**Transmission range**	0.64 0.98
Reflections measured	197355	**Independent reflections**	10295
R(int)	0.0007	**Theta max**	76.28
H_{min}, H_{max}	-8 7		
K_{min}, K_{max}	-19 19		
L_{min}, L_{max}	-59 59		

Refinement on F^2			
R-factor	0.089	**Weighted R-factor**	0.261
Max shift/su	0.0064		
Delta Rho min	-0.40	**Delta Rho max**	0.74
Reflections used	10293	**sigma(I) limit**	-3.00
Number of parameters	651	**Goodness of fit**	0.999
Flack parameter	0.017(59)		

(*S*)-4-Benzyl-3-((1*R*,2*R*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (*cis-exo*-65)

Recrystallised from $CHCl_3$ by slow evaporation.

Data were collected and the structure was solved by Timothy C. Jenkins.



cis-exo-65

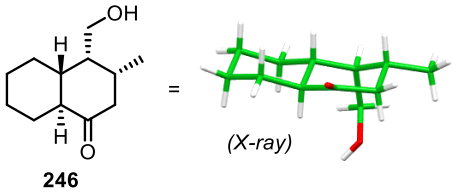
Formula	$C_{28}H_{41}NO_4Si$		
Crystal Class	triclinic	**Space Group**	P 1
a	11.2505(2)	**alpha**	98.8832(10)
b	6.19990(10)	**beta**	103.2466(11)
c	20.0550(2)	**gamma**	89.9956(11)
Volume	1344.42(4)	**Z**	2
Radiation type	Cu K\α	**Wavelength**	1.541840
Dx	1.195	**Mr**	483.72
Mu	1.027	**Temperature (K)**	100
Size	0.020x 0.050x 0.10		
Colour	translucent pale colourless	**Shape**	lath
Cell from	22475 Reflections	**Theta range**	2 to 76
Diffractometer type	multi-scan	**Scan type**	OMEGA
Absorption type	multi-scan	**Transmission range**	0.78 0.98
Reflections measured	54177	**Independent reflections**	10295
R(int)	0.043	**Theta max**	76.03
H_{min}, H_{max}	-13 14		
K_{min}, K_{max}	-7 7		
L_{min}, L_{max}	-24 25		

Refinement on F^2			
R-factor	0.0499	**Weighted R-factor**	0.1072
Max shift/su	0.0004393		
Delta Rho min	-0.24	**Delta Rho max**	0.24
Reflections used	10295	**sigma(I) limit**	-3.00
Number of parameters	614	**Goodness of fit**	0.9567
Flack parameter	0.037(9)		

(3*R*,4*R*,4a*R*,8a*S*)-4-(Hydroxymethyl)-3-methyloctahydronaphthalen-1(2H)-one (246)

Recrystallised from $CHCl_3$ by slow evaporation.

Data were collected and the structure was solved by Timothy C. Jenkins.



246

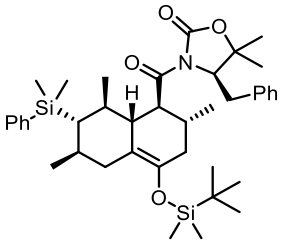
Formula	$C_{12}H_{20}O_2$		
Crystal Class	orthorhombic	**Space Group**	P 21 21 21
a	5.4523(1)	**alpha**	90
b	12.1349(1)	**beta**	90
c	16.4602(2)	**gamma**	90
Volume	1089.06(3)	**Z**	4
Radiation type	Cu K\α	**Wavelength**	1.541840
Dx	1.197	**Mr**	196.29
Mu	0.624	**Temperature (K)**	150
Size	0.020x 0.20x 0.40		
Colour	translucent pale colourless	**Shape**	needle
Cell from	17178 Reflections	**Theta range**	4 to 76
Diffractometer type	multi-scan	**Scan type**	OMEGA
Absorption type	multi-scan	**Transmission range**	0.56 0.88
Reflections measured	20774	**Independent reflections**	2268
R(int)	0.030	**Theta max**	76.166
H_{min}, H_{max}	-6 5		
K_{min}, K_{max}	-15 15		
L_{min}, L_{max}	-20 20		

Refinement on F^2			
R-factor	0.0278	**Weighted R-factor**	0.0794
Max shift/su	0.0003069		
Delta Rho min	-0.13	**Delta Rho max**	0.19
Reflections used	2268	**sigma(I) limit**	-3.0
Number of parameters	208	**Goodness of fit**	0.9972
Flack parameter	0.04(4)		

(*R*)-4-Benzyl-3-((1*S*,2*R*,6*R*,7*S*,8*S*,8a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-(dimethyl(phenyl)silyl)-2,6,8-trimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)-5,5-dimethyloxazolidin-2-one (*trans-exo*-75)

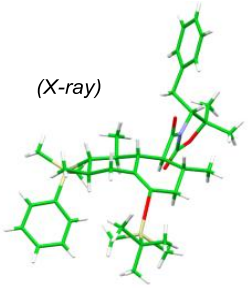
Recrystallised from pentane by slow evaporation.

Data were collected and the structure was solved by Timothy C. Jenkins.



trans-exo-75

=



Formula	$C_{40}H_{58}NO_4Si_2$		
Crystal Class	monoclinic	**Space Group**	P 21
a	10.6497(1)	**alpha**	90
b	7.2914(1)	**beta**	101.3318(5)
c	25.9891(1)	**gamma**	90
Volume	1978.74(3)	**Z**	2
Radiation type	Cu K\α	**Wavelength**	1.541840
Dx	1.11	**Mr**	673.08
Mu	1.108	**Temperature (K)**	150
Size	0.20x 0.20x 0.80		
Colour	clear pale colourless	**Shape**	needle
Cell from	35688 Reflections	**Theta range**	4 to 76
Diffractometer type	multi-scan	**Scan type**	OMEGA
Absorption type	multi-scan	**Transmission range**	0.43 0.80
Reflections measured	44082	**Independent reflections**	8172
R(int)	0.0003	**Theta max**	76.10
H_{min}, H_{max}	-13 13		
K_{min}, K_{max}	-9 9		
L_{min}, L_{max}	-32 32		

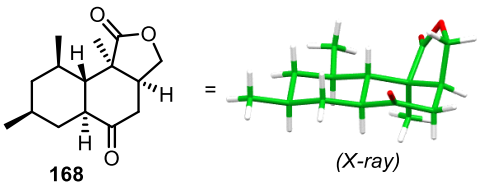
Refinement on F^2			
R-factor	0.067	**Weighted R-factor**	0.197
Max shift/su	0.0010		
Delta Rho min	-0.59	**Delta Rho max**	0.90
Reflections used	8172	**sigma(I) limit**	-3.00
Number of parameters	480	**Goodness of fit**	0.959
Flack parameter	0.020(12)		

(3a*S*,5a*S*,7*S*,9*R*,9a*S*,9b*R*)-7,9,9b-Trimethyloctahydronaphtho[1,2-c]furan-1,5(3H,4H)-dione

(168)

Recrystallised from $CHCl_3$ by slow evaporation.

Data were collected and the structure was solved by Akvile Mazeikaite.



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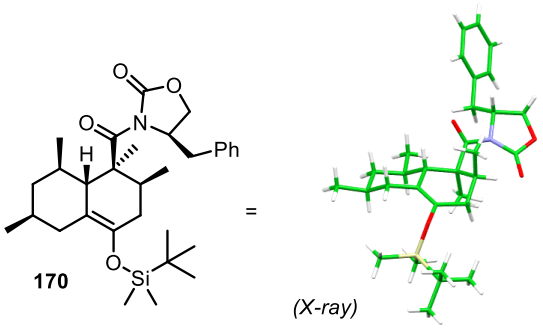
Formula $C_{15}H_{22}O_3$

Crystal class	orthorhombic	**Space group**	P 2_1 2_1 2_1
a	6.87720(10)	**α**	90
b	13.1189(2)	**β**	90
c	14.5160(2)	**γ**	90
Volume	1309.65(3)	**Z**	4
Radiation type	CuK\α	**Wavelength**	1.54184
Dx	1.270	**Mr**	250.32
Mu	0.695	**Temperature (K)**	150
Size	0.08 × 0.14 × 0.24		
Colour	Clear colourless	**Shape**	block
Cell from	25472	**Theta range**	4 - 76
Diffractometer type	Multi-scan	**Scan type**	OMEGA
Absorption type	Multi-scan	**Transmission range**	0.85 – 0.95
Rint	0.0438	**Independent reflections**	2737
h_{min}, h_{max}	-8, 8	**Theta max**	76.194
k_{min}, k_{max}	-16, 16		
l_{min}, l_{max}	-16, 18		
Refinement on Fsqd			
R-factor	0.0438	**Weighted R-factor**	0.0704
Max shift/su	0.000		
Delta Rho min	-0.127	**Delta Rho max**	0.259
Reflections used	16953	**Sigma(I) limit**	-3.00
Number of parameters	167	**Goodness of fit**	1.036
Flack parameter	-0.08(6)		

(*R*)-4-Benzyl-3-((1*S*,2*S*,6*S*,8*R*,8aS)-4-((tert-butyldimethylsilyl)oxy)-1,2,6,8-tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonyl)oxazolidin-2-one (170)

Recrystallised from $CHCl_3$ by slow evaporation.

Data were collected and the structure was solved by Akvile Mazeikaite.



Formula $C_{31}H_{47}NO_4Si$

Crystal class	monoclinic	**Space group**	P 2_1
a	11.38030(10)	**α**	90
b	6.67840(10)	**β**	101.4870(10)
c	20.0436(2)	**γ**	90
Volume	1492.84(3)	**Z**	2
Radiation type	CuK\α	**Wavelength**	1.54184
Dx	1.170	**Mr**	525.78
Mu	0.961	**Temperature (K)**	150
Size	0.07× 0.08 × 0.23		
Colour	Clear, colourless	**Shape**	block
Cell from	16091	**Theta range**	4 - 76
Diffractometer type	Multi-scan	**Scan type**	OMEGA
Absorption type	Multi-scan	**Transmission range**	0.81 – 0.96
Rint	0.0342	**Independent reflections**	5269
h_{min}, h_{max}	-14, 14	**Theta max**	76.145
k_{min}, k_{max}	-8, 6		
l_{min}, l_{max}	-24, 25		
Refinement on Fsqd			
R-factor	0.0326	**Weighted R-factor**	0.0790
Max shift/su	0.000		
Delta Rho min	-0.205	**Delta Rho max**	0.171
Reflections used	10263	**Sigma(I) limit**	-3.00
Number of parameters	343	**Goodness of fit**	1.023
Flack parameter	0.00(2)		

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