Studies towards the Synthesis of Hexacyclinic Acid

Michael Mathieson (MChem)

A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

School of Chemistry
College of Science & Engineering
University of Glasgow

November 2014

Contents

Acknowledgements

Firstly I would like to extend my gratitude to my PhD supervisor Dr Joëlle Prunet (The boss, JP) for giving me the opportunity to undertake a PhD in her group. Joëlle has been incredibly supportive and encouraging throughout my time at Glasgow, not to mention her **never-ending** patience.

I would also like to thank my fellow Prunets – Sébastien and Raphaël for all their help at the start of my PhD**,** Toni for enduring me for the last 4 years, Aurelien, Stéphane (The Beast), Alex (Phillibert), Amaia and also all past and present project students, it's been great working with you all.

Thanks to Dr David France for all his advice throughout my time here and to the France group – Jo and Pooja. Big shout out to the France Boyz, Lewis and Craig, for all the great laughs. Thanks to all the other members of the Raphael and Loudon labs for stimulating chemistry and non-chemistry chat.

My gratitude goes to the EPSRC for funding my PhD.

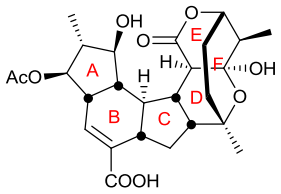
I would also like to show my appreciation to Olga, who has supported and encouraged me for these last few difficult months. I am just annoyed I have met you at the end of my time at Glasgow.

Finally I would like to thank my family, specifically my parents for all their encouragement and support for the last 28 years, not to mention all the financial assistance they have given me.

Author's Declaration

This thesis represents the original work of Michael Mathieson unless otherwise explicitly stated and referenced in the text. The research was carried out at the University of Glasgow in the Loudon and Raphael Laboratories under the supervision of Dr Joëlle Prunet during the period from the 1st of October 2009 to 16th of December 2012.

Abstract



hexacyclinic acid

Hexacyclinic acid is a polyketide isolated from *Streptomyces cellulosae* bacteria in 2001. It possesses a complex and challenging hexacyclic ring system with various oxygen functionalities throughout. Hexacyclinic acid has also demonstrated some cytotoxic activity, making it an attractive target for total synthesis. However to date no full synthesis has been reported.

Previously within the group significant progress had been made towards the synthesis of hexacyclinic acid, with construction of the ABC 5/6/5 tricyclic core being achieved via a diastereoselective Michael addition and Snider radical cyclisation. The synthesis ran into difficulties however when hydrolysis of the ethyl ester could not be accomplished and removal of the superfluous carboxylic acid moiety could not be realised.

The approach within the group for the formation of the ABC tricycle was to continue the current strategy, joining the A and C-rings via the diastereoselective Michael reaction, and the closure of the 6-membered B-ring by Snider radical cyclisation. Progress was made using the *tert*-butyl and 2,2,2-trimethylsilylethyl ester analogues in an attempt to improve diastereoselectivities

Progress was also made on the synthesis of the CDEF tricyclic system, utilising (*R*)-isopropylcyclopentenone as a C-ring model system. The DEF framework was attached to the model by a Michael addition, with further functionalisation setting up the necessary functionalities for cyclisation. Conditions were attempted to effect a challenging aldol condensation to form the 9-membered ring, however all attempts effect this transformation were fruitless.

It was discovered that 2,2,2-trifluoromethylacetophenone can act as a replacement for benzaldehyde in the synthesis of protected *syn*-1,3-diols from homoallylic alcohols, with comparable yields and easier purification.

Finally, an investigation was also made into the use of a bispidine ligand as a replacement for (−)-sparteine in Crimmins asymmetric aldol reactions, with the bispidine shown to give superior yields and diastereoselectivity when compared to TMEDA.

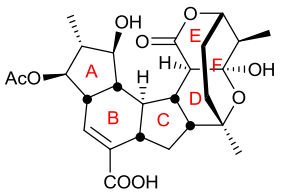
Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
BHT	butylhydroxytoluene
BT	benzothiazole
BRSM	based on recovered starting material
Bu	butyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
Dibal-H	diisobutylaluminum hydride
DIPEA	*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
Dppe	1,2-bis(diphenylphosphino)ethane
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
HMPA	hexamethylphosphoramide
i-Bu	*iso*-butyl
IBX	iodoxybenzoic acid
IMDA	intramolecular Diels-Alder
IMHDA	intramolecular hetero-Diels-Alder
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
*m*CBPA	*meta*-chloroperoxybenzoic acid
Me	methyl
NMO	*N*-methylmorpholine *N*-oxide
MOM	methoxymethyl ether
NMP	*N*-methylpyrrolidone
Nu	nucleophile
PE	petroleum ether (40-60)
Pg	protecting group
PMP	*para*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
RCM	ring-closing metathesis
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl

TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide
TMEDA	tetramethylethylendiamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

1 - Introduction

In 2000, the OSMAC (one strain, many compounds) technique was utilised by Zeeck *et al.* on *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S 1013).[1] By altering certain parameters, production of secondary metabolites can be induced and/or increased. Using this method, a compound was isolated, which after extensive spectroscopic and X-ray studies, was shown to be the polyketide natural product hexacyclinic acid (Fig 1).[2]



1

Fig 1: Structure of hexacyclinic acid **1**

Labelling studies were performed by feeding the growth medium with ^{13}C labelled acetic and propionic acid so as to incorporate these isotopic labels within the structure of **1**. From these experiments, it was hypothesised that **1** is constructed from seven acetic acid and three propionic acid units (Fig 2).

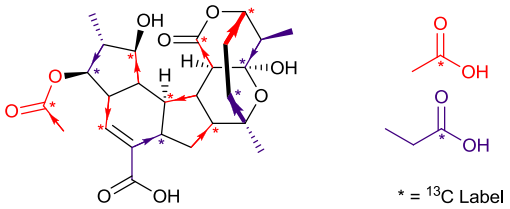
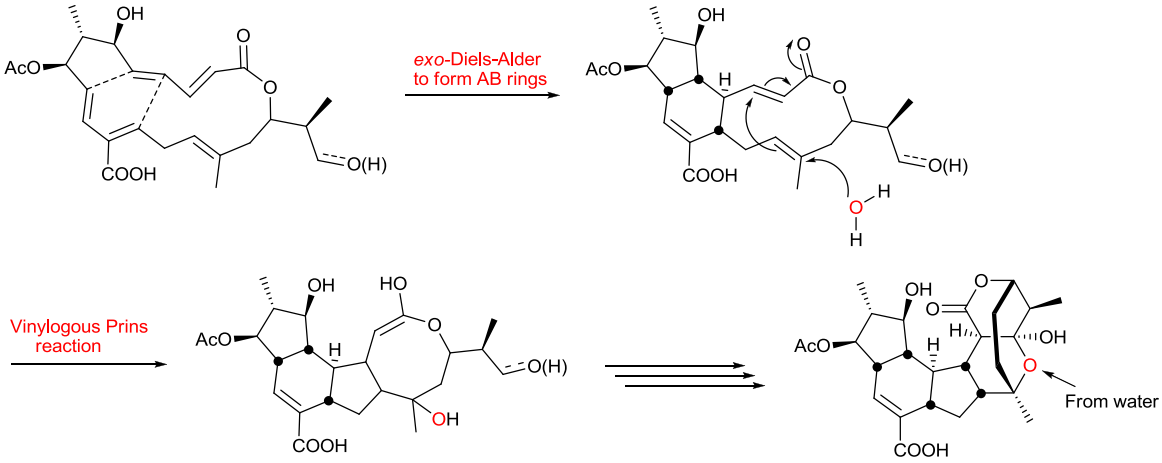


Fig 2: Labelling study performed by Zeeck

The proposed biosynthesis by Zeeck involved an intramolecular Diels-Alder reaction to set up the AB bicyclic ring system, with a vinylogous Prins reaction theorised to form the C ring. As reported by Kalesse *et al.*, it was shown that the hemiketal oxygen was not from any of the acid subunits, but from an external source such as H_2O (Scheme 1).[3]



Scheme 1: Proposed biosynthesis of **1**

Compound **1** was shown to exhibit some cytotoxic activity with an IC_{50} of 14 μmol^{-1} against three cell lines (HM02, HEPG2, MCF7).[2] Moreover **1** possesses a unique hexacyclic carbon skeleton which poses a significant challenge for the modern synthetic organic chemist. To date no complete synthesis of **1** has been published, however the synthesis of **1** is underway in many groups with several partial syntheses published so far.[3-4]

1.1 - Hexacyclinic Acid 1 and (-)-FR182877 2

A related compound to **1**, (−)-FR182877 **2**, was also isolated from *Streptomyces* bacteria by the Fujisawa Chemical company in 1998. Compound **2** possesses a remarkably similar structure to **1**, though there are some key differences; namely the stereochemistry at the ABC ring junctions and the lack of the hemiketal, carboxylic acid and acetate groups (Fig 3). Owing to their structural similarities, it could be assumed that both **1** and **2** could be accessed from a common intermediate. To date, three complete total syntheses of **2** have been reported;[5] this is attributed to its greater cytotoxic activity in comparison to **1**, making it a more attractive target. It has been postulated that the activity of **2** may be due to the presence of the strained alkene, as when the alkene is oxidised by molecular oxygen, a significant drop in activity is observed. This strained olefin was also shown to be an efficient Michael acceptor, reacting with a variety of nucleophiles, such as amines, thiols and even imidazole (Scheme 2). The driving force for this reaction is due to the release of strain with no elimination product ever observed.[5a] Despite this, other differences such as the lack of acetate or carboxylic acid groups cannot be ignored for the effect they might have on the activity of **2**.

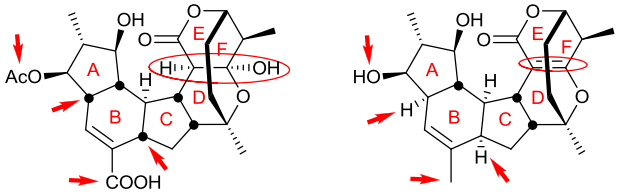
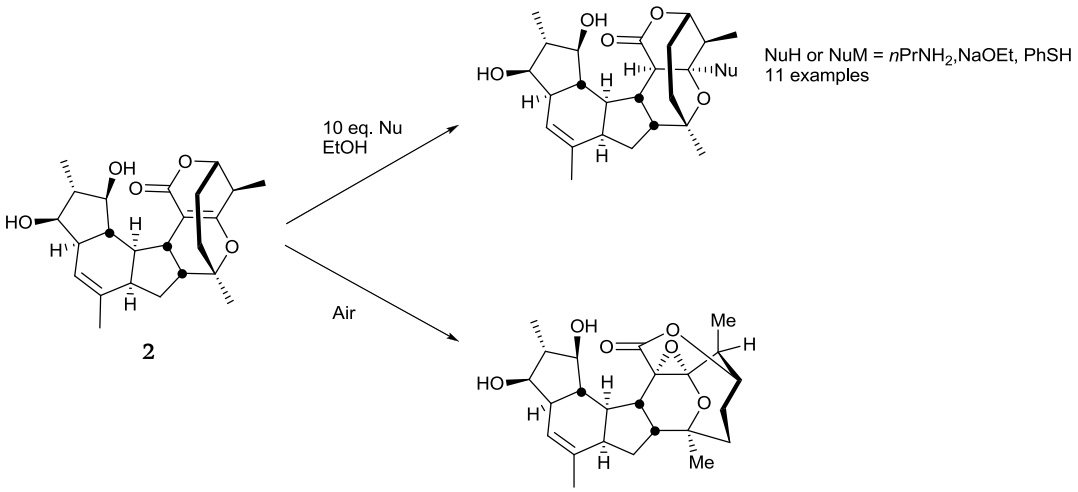
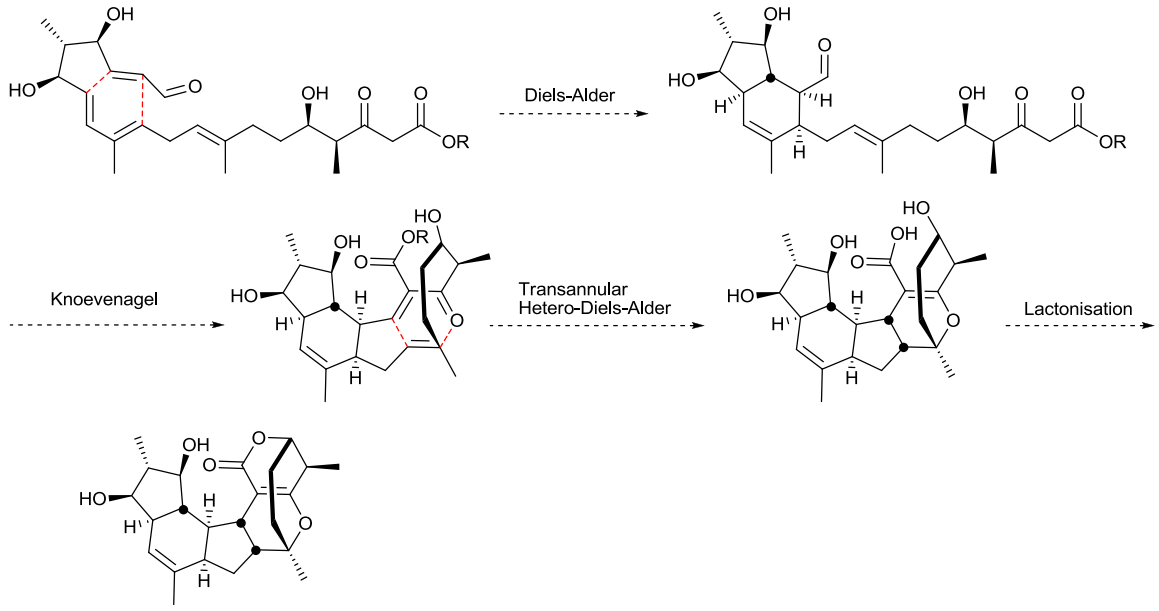


Fig 3: Structural differences between Hexacyclinic Acid **1** and (−)-FR182877 **2**.



Scheme 2: Reactivity of the strained alkene of **2**

Compound **2** has been shown to have similar activity *in vitro* to Taxol for microtubule stabilisation (IC_{50} 21 to 73 $nmolL^{-1}$). A biosynthesis of **2** was postulated by Sorensen,[5a, 6] involving an intramolecular Diels-Alder reaction to form the AB ring system and setting up the 4 new stereocentres at the ring junctions (Scheme 3). This is followed by a Knoevenagel condensation between the β-ketoester functionality and the aldehyde position, and a trans-annular hetero-Diels-Alder setting up the CDF ring system. A final lactonisation closes the E ring and forms **2**.



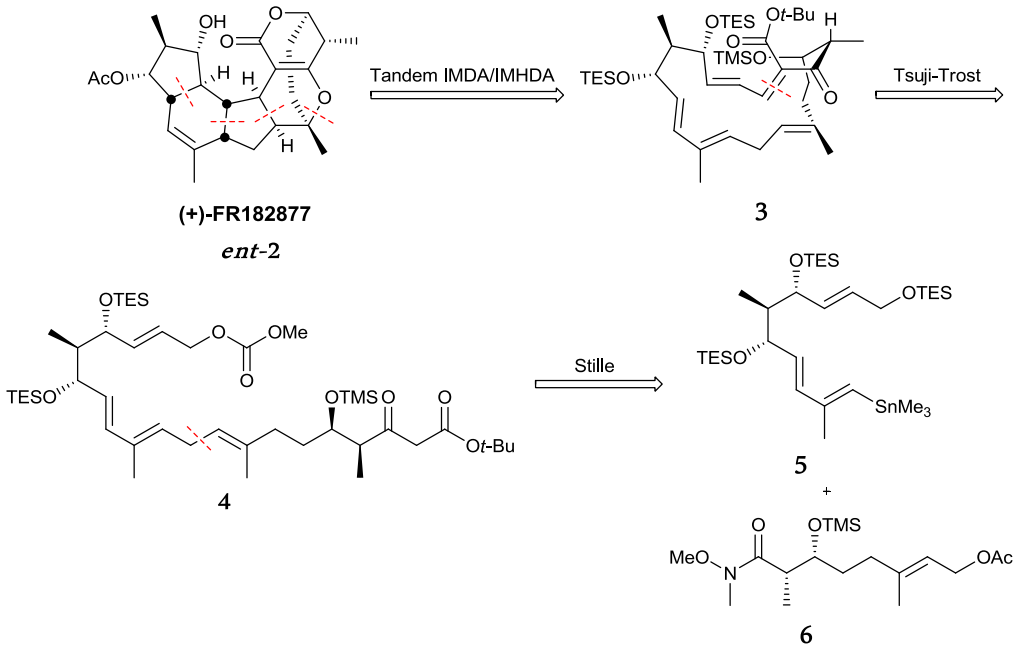
2

Scheme 3: Proposed biosynthesis of **2** by Sorensen

1.2 - Literature syntheses of (−)-FR182877

1.2.1 – Sorensen

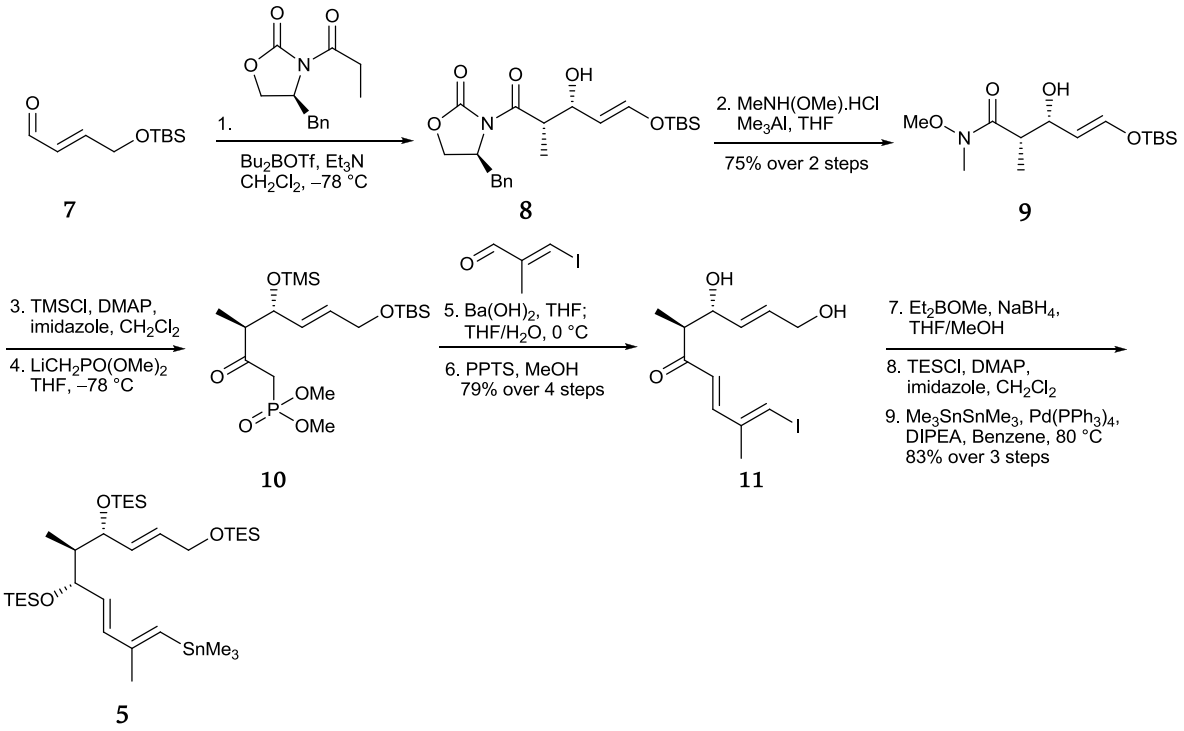
Originally basing their retrosynthesis of ***ent*-2** on their proposed biosynthesis (Scheme 3), Sorensen *et al.* had to make an alteration to their synthetic strategy. Their synthesis was based on the enantiomer ***ent*-2**, and not **2** because only the relative stereochemistry had been determined, and not the absolute stereochemistry. They planned the use of a tandem intramolecular Diels-Alder/Hetero-Diels-Alder to form the ABCDF ring system, with a lactonisation forming the E ring (Scheme 4). In contrast to the condensation reaction used in the biosynthesis, it was proposed to use a Tsuji-Trost alkylation to form the 19-membered macrocycle **3**. β-Ketoester **4** was to be synthesised by a Stille coupling of stannane **5** and allylic acetate **6**.



Scheme 4: Retrosynthesis of ***ent*-2** by Sorensen group

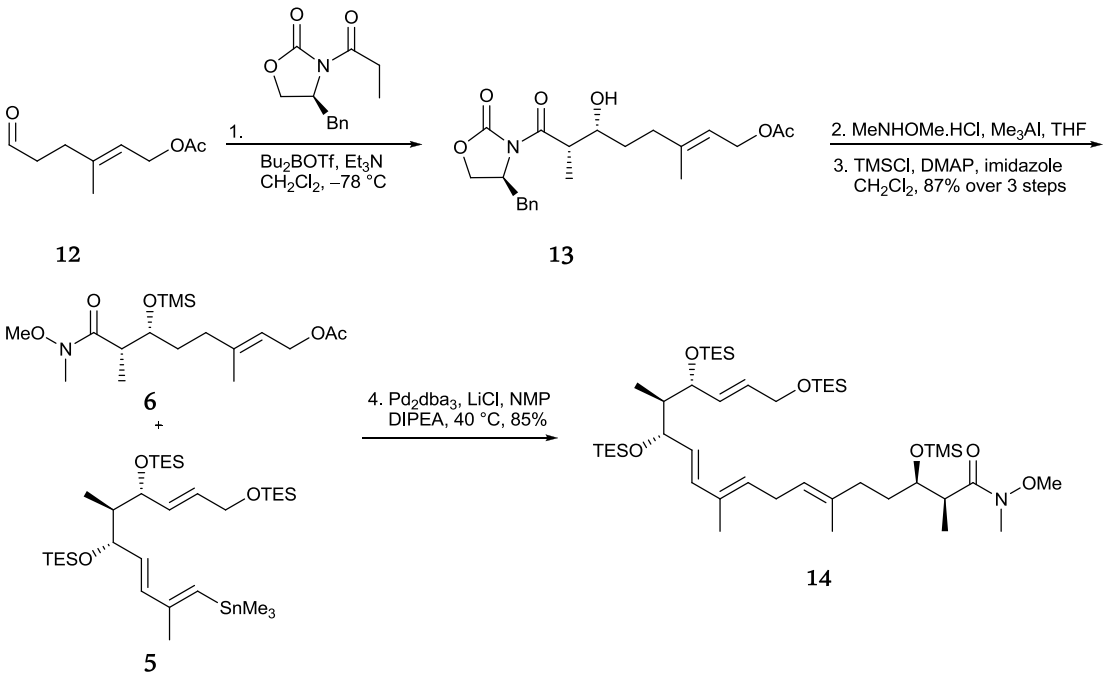
Synthesis of fragment **5** began by an asymmetric aldol reaction of aldehyde **7** (synthesised in two steps from *cis*-2-butene-1,4,-diol)[7] with Evans auxiliary to form adduct **8** (Scheme 5). Transformation to the Weinreb amide **9** proceeded smoothly with a 75% yield over the 2 steps. Protection of the secondary alcohol with TMSCl, followed by reaction with dimethyl lithiomethylphosphonate provided the β-phosphonate **10**. This reacted in a Horner-Wadsworth-Emmons reaction with 3-iodomethacrolein and activated $Ba(OH)_2$,[8] followed by removal of the silyl protecting groups to afford the triene **11** with an exceptional 79% yield over 4 steps. Chelation-controlled reduction of the ketone provided

the *cis*-diol exclusively, which was then protected as the *bis*-TES ether. Finally a palladium-catalysed stannylation with hexadimethyltin completed the synthesis of **5** with an 83% yield over the final 3 steps.



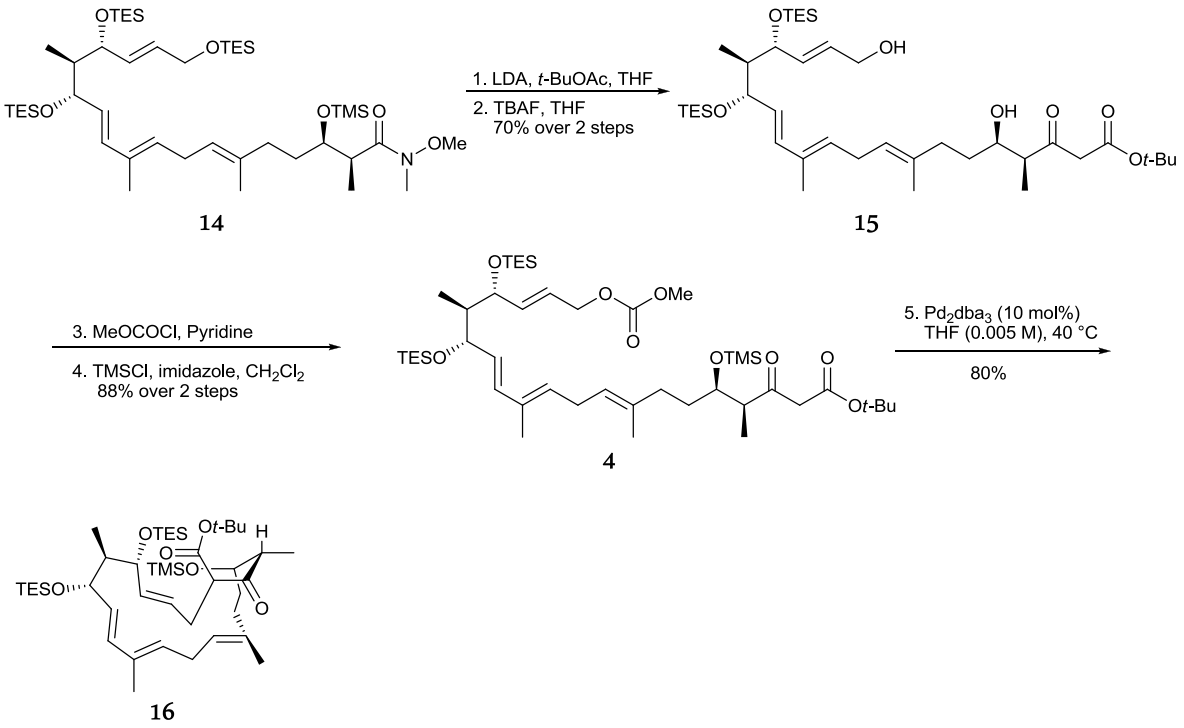
Scheme 5: Synthesis of stannane **5**

As with the other fragment, synthesis of **6** began with an asymmetric aldol with aldehyde **12** (Scheme 6),[9] to form **13**. This adduct was then converted to the Weinreb amide and protected as a trimethylsilyl ether, forming **6** with an 87% yield over 3 steps. Efficient coupling of **5** and **6** was accomplished using a relatively high (10 mol%) catalyst loading of Pd_2dba_3, with the use of DIPEA being vital for obtaining **14** in an 85% yield.



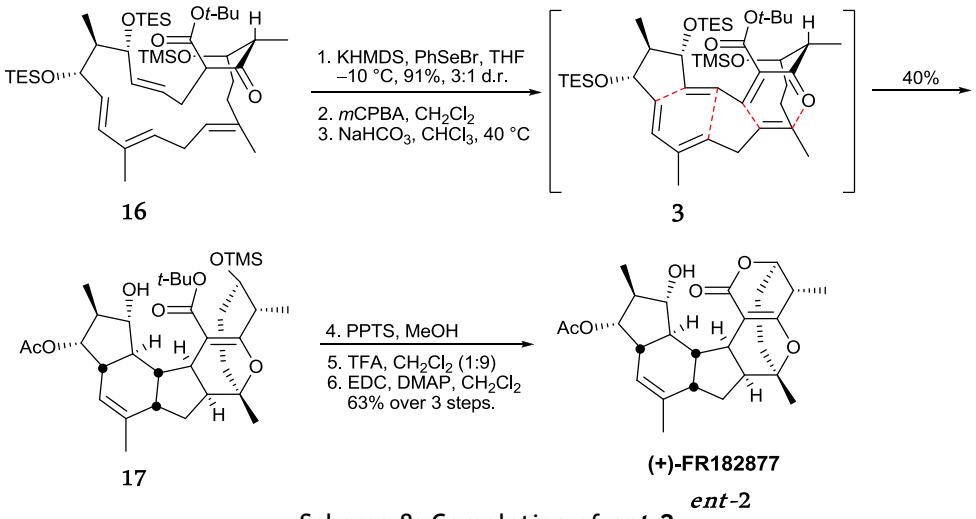
Scheme 6: Synthesis of **6** and Stille coupling

Reaction of Weinreb amide **14** with the lithium enolate of *tert*-butyl acetoacetate accessed the β-ketoester functionality of **15** in one step (Scheme 7).[10] Selective deprotection of the primary TES and secondary TMS silyl groups was achieved with 2 equivalents of TBAF. The primary alcohol then reacted with methyl chloroformate forming the carbonate ester **4**. Reprotection of the secondary hydroxyl using TMSCl proceeded smoothly giving the necessary Tsuji-Trost substrate **4** with 88% yield over the 2 steps. Ring closure of the 19-membered macrocycle was accomplished using catalytic Pd_2dba_3 in a dilute solution of THF to furnish the Tsuji-Trost product **16** in an 80% yield as a single diastereomer.



Scheme 7: Formation of cycloaddition precursor **16** by Tsuji-Trost alkylation

For the desired IMDA/IMHDA to occur it was necessary to introduce the enone double bond. This was achieved by formation of the enolate using KHMDS and addition of PhSeBr to form the α-selenoproduct in excellent yield in a 3:1 mixture of diastereomers (Scheme 8). Efficient oxidation and elimination of the selenoxide was achieved using *m*CPBA in CH_2Cl_2 forming the enone functionality as an equimolar mixture of E/Z isomers. The cycloaddition cascade of **3** was found to be accelerated by warming in chloroform buffered with $NaHCO_3$ to give **17** as the major product formed in a modest 40% yield after 4 hours. Removal of the silyl protecting groups using PPTS, cleavage of the *tert*-butyl ester with TFA and EDC mediated lactonisation furnished ***ent*-2**.

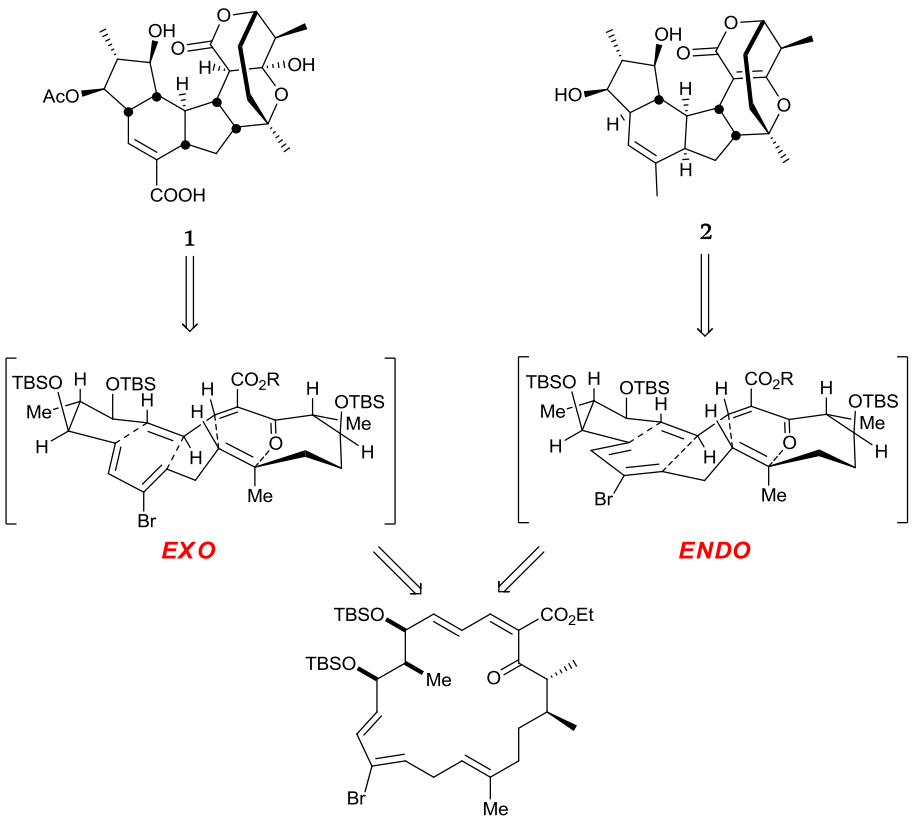


Scheme 8: Completion of ***ent*-2**

The Sorensen synthesis of ***ent*-2** was achieved in 22 steps with a 2% overall yield. Key steps were the Tsuji-Trost alkylation to form the macrocycle and the tandem IMDA/IMHDA reaction to efficiently form the pentacyclic ring system. One limitation of the synthesis is the selenoxide elimination which gives a 1:1 mixture of the *E*-isomer with the undesired *Z*-isomer which does not cyclise. Nonetheless the synthesis was very successful in producing grams of ***ent*-2**.

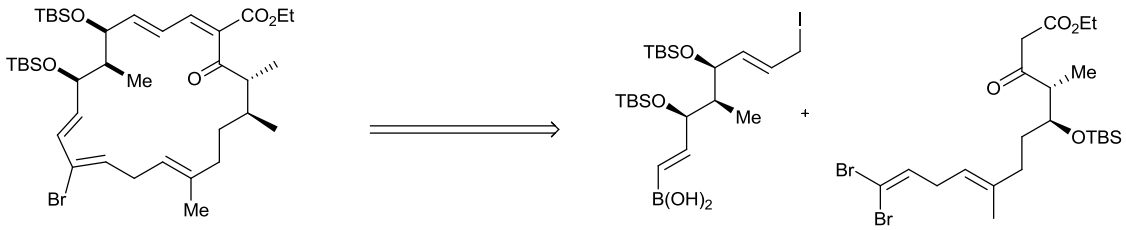
1.2.2 - Evans

Evans *et al.* embarked on a synthesis of **1** and **2**, believing that they both could be accessed *via* the macrolide precursor **18** (Scheme 9).[5d] Evans planned sequential double [4+2] cycloaddition reaction to form the carbocyclic skeleton. The initiating Diels-Alder reaction would form the AB rings, with this step differentiating which product would be formed. The *exo*- transition state of the initial Diels-Alder reaction would form **1,** while the *endo*-variant would give **2,** though it was unknown which would be favoured. An ensuing hetero-Diels-Alder cycloaddition would then construct the CDF rings. As it was unknown which product would be formed, Evans included a bromide functional group allowing for conversion to either product.



Scheme 9: Evans retrosynthesis of **1** and **2** from macrolide **18** and proposed DA transition states

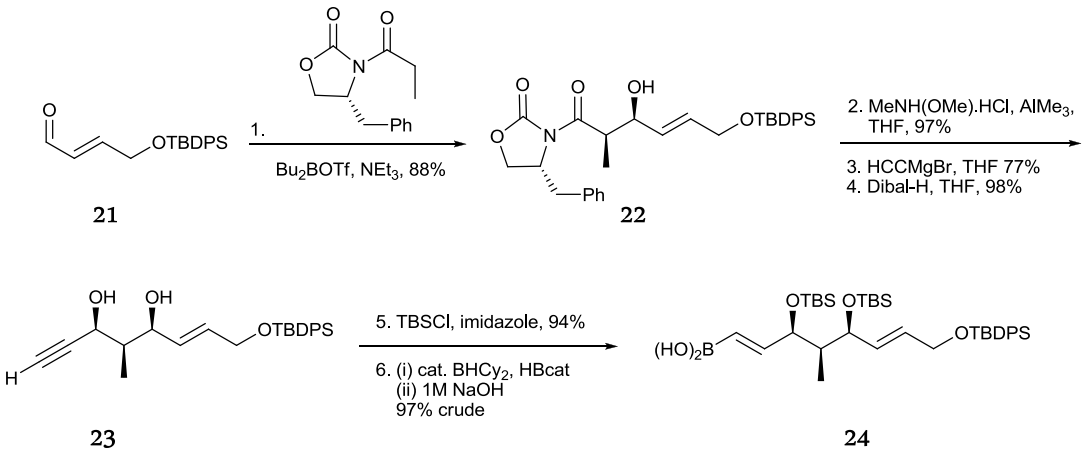
The macrolide **18** could be formed by the coupling of the iodide **19** and the dibromoalkene **20**, making use of a Suzuki coupling and alkylation to join the terminal positions (Scheme 10).



Scheme 10: Retrosynthesis of macrocycle **18**

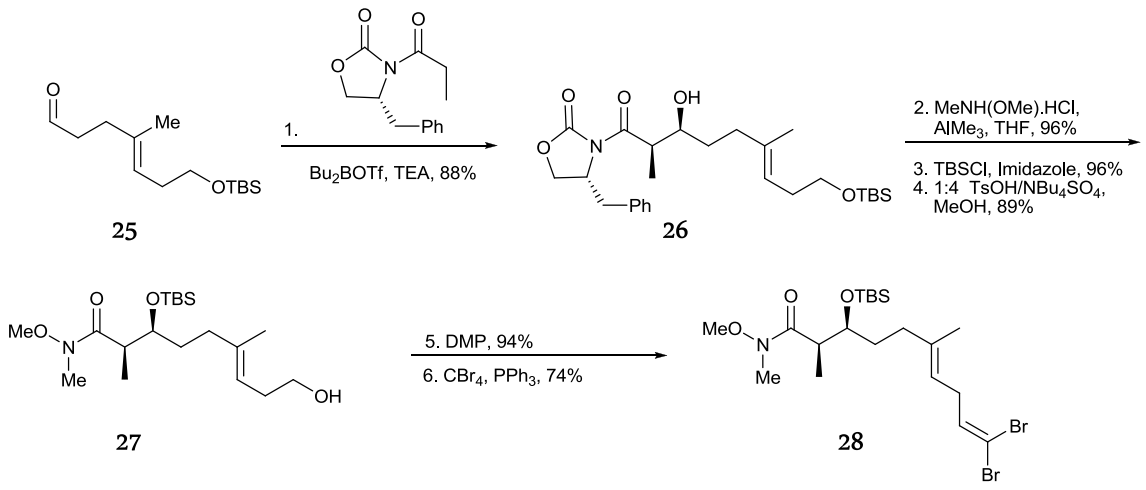
The synthesis of fragment **19** began by an asymmetric aldol reaction of aldehyde **21** (synthesised in two steps from *cis*-2-butene-1,4-diol)[11] with Evans oxazolidinone chiral auxiliary using dibutylboron triflate, forming the *syn* aldol adduct **22** in an excellent 88% yield (Scheme 11). Conversion to the Weinreb amide using standard conditions proceeded in near quantitative yield, and reaction of the amide with ethynylmagnesium bromide furnished the alkynone in good yield. Reduction of the ketone using Dibal-H formed the

1,3-diol **23** in near quantitative yield with the desired diastereomer being formed in 20:1 dr. Double TBS protection of diol **23**, followed by hydroboration with catecholborane (HBcat) and hydrolysis of the resulting boronic ester with 1 M aqueous NaOH solution gave the boronic acid fragment **24** in a 97% crude yield.



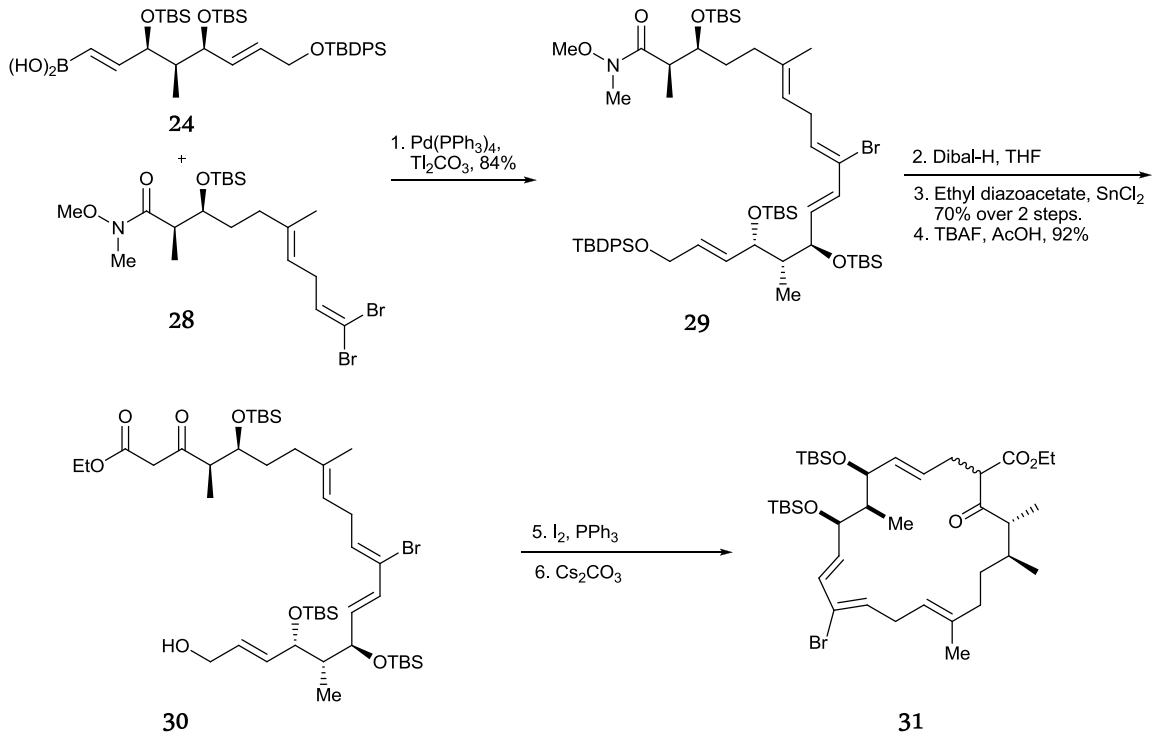
Scheme 11: Synthesis of boronic acid **24**

The synthesis of fragment **28** began as before utilising an aldol reaction of aldehyde **25** (synthesised in 3 steps from 3-buten-1-ol) and Evans auxiliary mediated by dibutylboron triflate giving the Evans-*syn* product **26** (Scheme 12). Conversion to the Weinreb amide, followed by protection of the secondary alcohol as a TBS ether and deprotection of the primary alcohol furnished **27** with excellent yields in 3 steps. Oxidation of **27** with DMP, and Corey-Fuchs olefination of the resulting aldehyde using tetrabromomethane and triphenylphosphine yielded the dibromoalkene **28**.



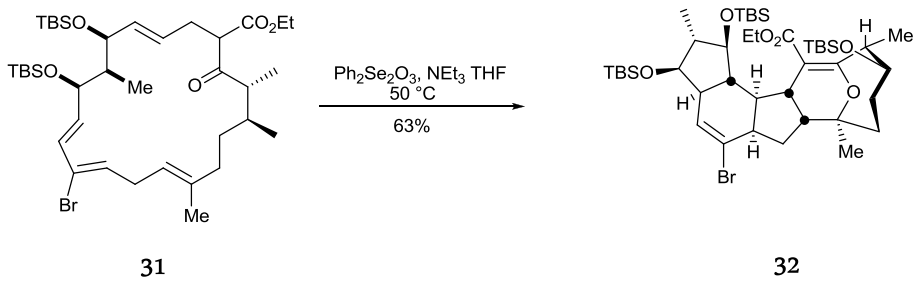
Scheme 12: Synthesis of fragment **28**

Suzuki coupling of **24** and **28** using the unusual Tl_2CO_3 as a base afforded exclusively the diene **29** in an excellent 84% yield (Scheme 13).[12] Thallium bases were found to have a positive effect in Suzuki cross couplings, increasing the reactivity of palladium by generating open coordination sites.[13] Dibal-H reduction of the Weinreb amide formed the corresponding aldehyde, which was followed by a Roskamp homologation to form the 1,3-dicarbonyl moiety. Selective deprotection of the primary alcohol using tetrabutylammonium fluoride yields the cyclisation precursor **30**. Iodination of the allylic alcohol followed by treatment with Cs_2CO_3 induced cyclisation to form the macrolide **31** as a 1:1 mixture of diastereomers.



Scheme 13: Coupling of fragments to form macrolide **31**

Oxidation of **31** with $Ph_2Se_2O_3$ and heating to 50 °C induced the cycloaddition cascade resulting in the formation of the pentacycle of **2** in a single diastereomer in a good yield (Scheme 14). It was shown that the *endo* transition state was preferred with **32** being formed exclusively. It was stated that attempts were being made to manipulate the reaction pathway to access the *exo* product, however it appears that this has been unsuccessful.



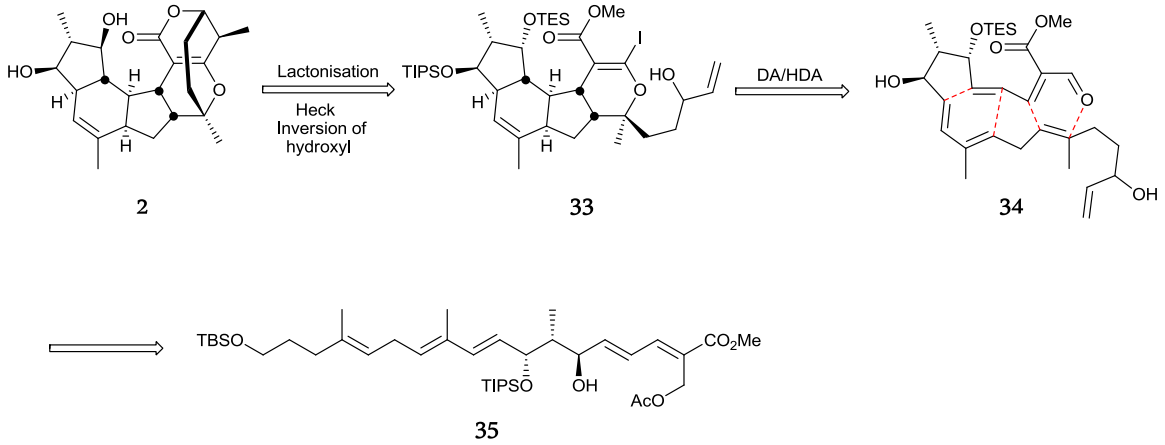
31 32

Scheme 14: Tandem DA/HDA reactions to form **32**

Subsequent steps continue to successfully complete the synthesis of (−)-FR182877 **2** in a total of 17 linear steps with a 6.0% overall yield. Of particular mention in the synthesis was the tandem DA/HDA reaction setting up the ABCDF ring system and 6 stereocentres with an impressive 63% yield. Disappointingly attempts to synthesise **1** by this method were unsuccessful, nonetheless the synthesis of **2** is an impressive total synthesis.

1.2.3 - Nakada

The most recent complete synthesis of **2** was reported by Nakada *et al.* in 2009. Similar to Evans' and Sorensen's syntheses, Nakada also planned a tandem intramolecular Diels-Alder/Hetero Diels-Alder for the construction of the AB and CD ring systems respectively, starting from **35** (Scheme 15). In contrast to the other syntheses however it was planned to close the F ring by an intramolecular Heck reaction.

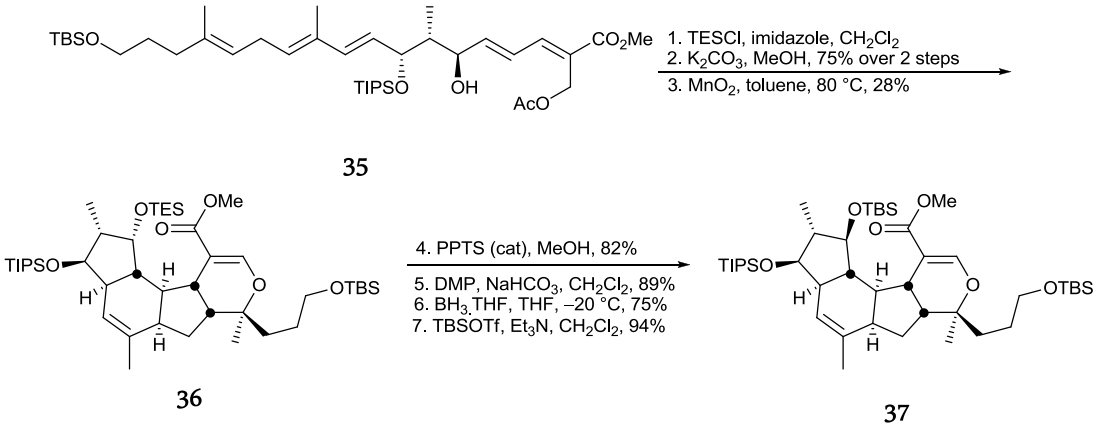


2 33 34 35

Scheme 15: Retrosynthesis of **2** by Nakada group

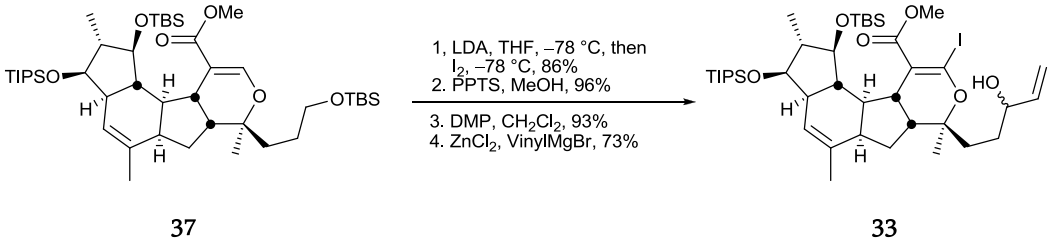
Starting from **35** (synthesised in 9 steps over longest linear sequence),[14] the free hydroxyl group was protected as a TES ether, followed by removal of the acetyl group in a 75% yield over the 2 steps (Scheme 16). Slow oxidation of the resulting primary alcohol by heating MnO_2 in toluene furnished the tetracyclic IMDA/IMHDA product **36** as a single

diastereomer in a modest 28% yield. The low yield was attributed to the successive IMHDA reaction, with previous work showing a 32% yield for a IMHDA reaction in which the substrate incorporates AB bicyclic ring system.[14] It can be seen that the stereochemistry of the OTES group is incorrect; however this *anti*-stereochemistry of the protected diols is necessary to achieving the right stereochemistry at the ring junctions, with *syn*-diols giving rise to poor stereocontrol. This diastereocontrol is attributed allylic 1,3-strain in their transition state models.[15] To achieve the correct stereochemistry, it was necessary to invert the stereogenic centre at the OTES group. This was achieved by cleavage of the TES ether, oxidation of the resultant alcohol using DMP, followed by reduction of the ketone with borane resulting in inversion and giving the correct stereochemistry in a 25:1 dr. The free hydroxyl was then protected as a TBS ether giving **37** with good yields over all steps.



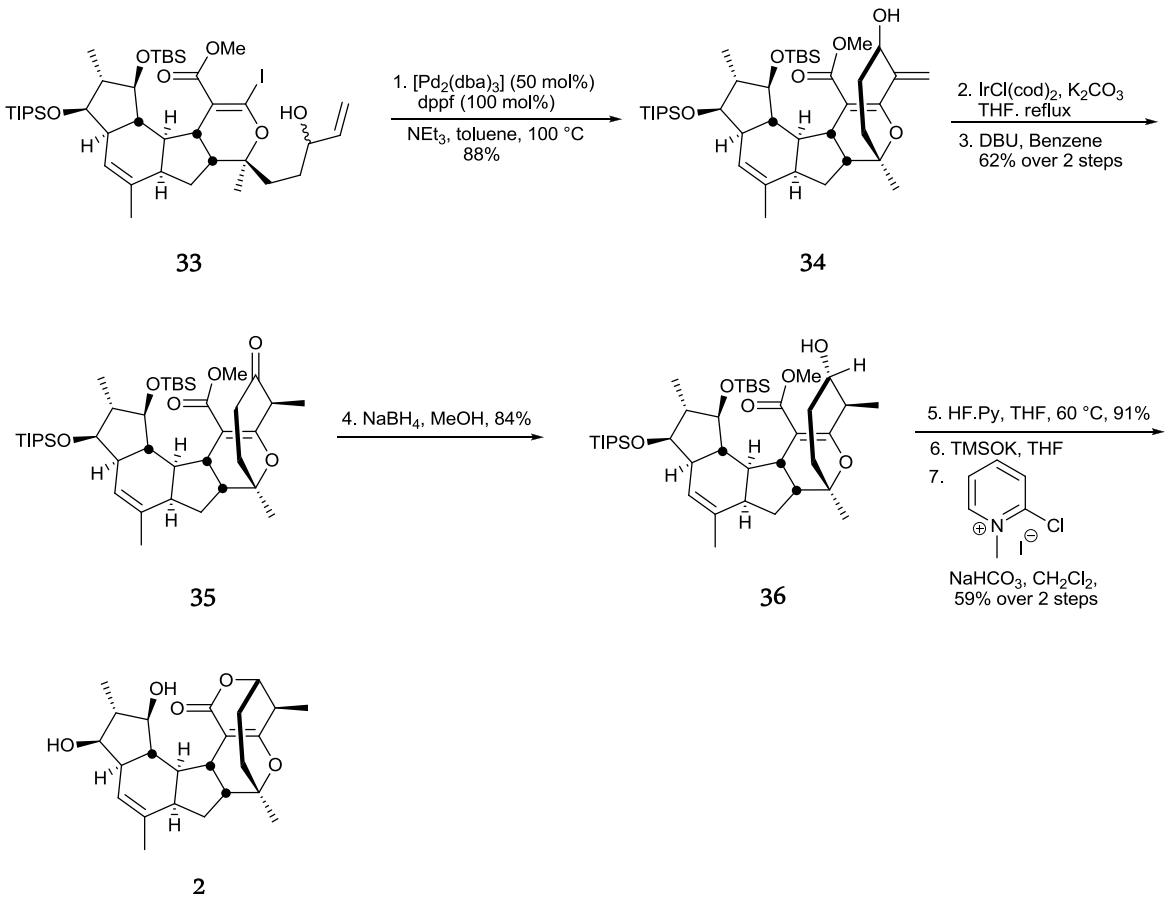
Scheme 16: Synthesis of ABCD-ring system **37**

Treatment of **37** with LDA followed by iodine formed the desired iodoalkene in an excellent yield (Scheme 17). Removal of the primary TBS group and DMP oxidation of the resultant primary alcohol afforded the corresponding aldehyde. This was followed by reaction with vinylzinc bromide to furnish **33** as a 1:1 mixture of diastereomers at the allylic alcohol position.



Scheme 17: Synthesis of Heck precursor **33**

Optimised conditions for the intramolecular Heck reaction required treatment of **33** with $Pd_2(dba)_3$ (using a high catalyst loading of 50 mol%) and dppf in toluene at 100 °C to furnish the 7-*exo-trig* product **34** in an 88% yield (Scheme 18). Isomerisation of the allylic alcohol to the α-methyl ketone **35** was mediated using $IrCl(cod)_2$ affording the product as a mixture of diastereomers. Treatment with 5 equivalents of DBU epimerised this stereogenic centre giving the α-methyl ketone of the necessary stereochemistry. Reduction from the less hindered face using $NaBH_4$ formed **36** as a single diastereomer.



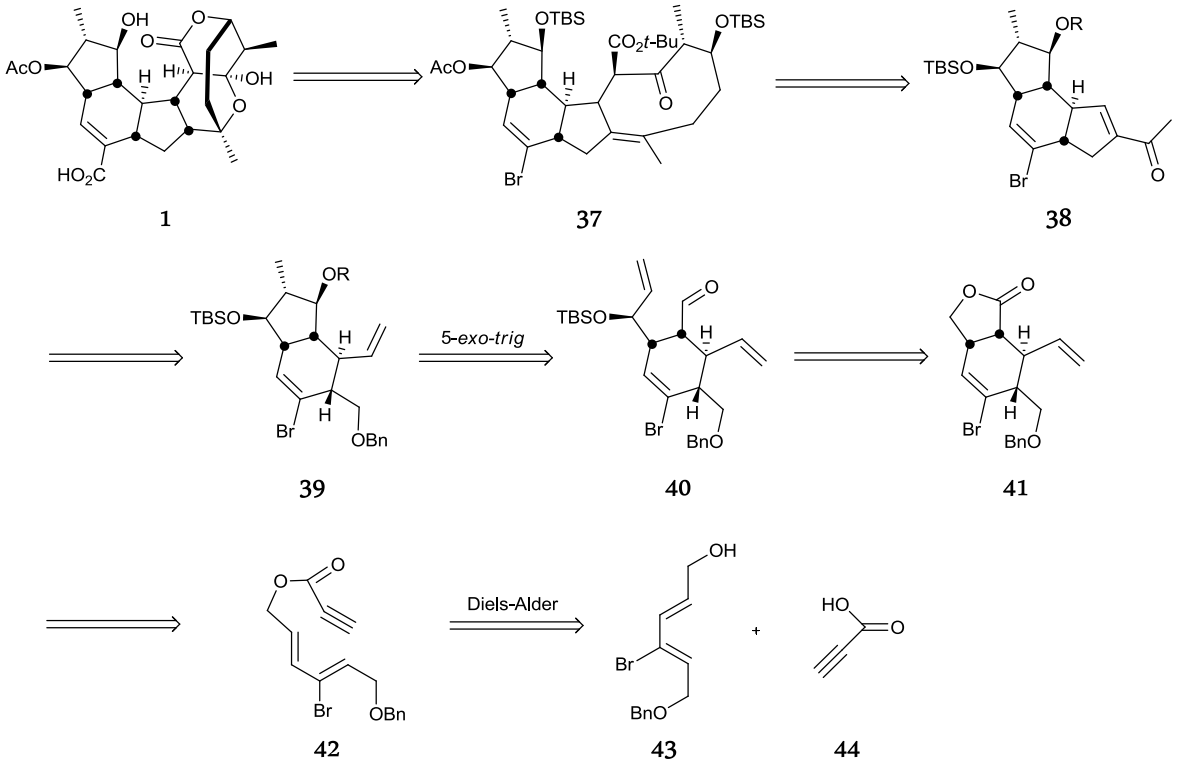
Scheme 18: Completion of **2** by Nakada group

Using the same method as Evans (deprotection of the silyl protecting groups using HF.Py, cleavage of the methyl ester using TMSOK and lactonisation with Mukaiyama's reagent) completed the synthesis of **2**. While a successful synthesis, the Nakada synthesis of **2** lacks novelty, utilising a similar DA/HDA approach as Sorensen and Evans. There are also numerous steps required to correct stereochemistry making for a less graceful synthesis.

1.3 - Literature syntheses of Hexacyclinic acid 1

1.3.1 – Clarke - ABC tricycle

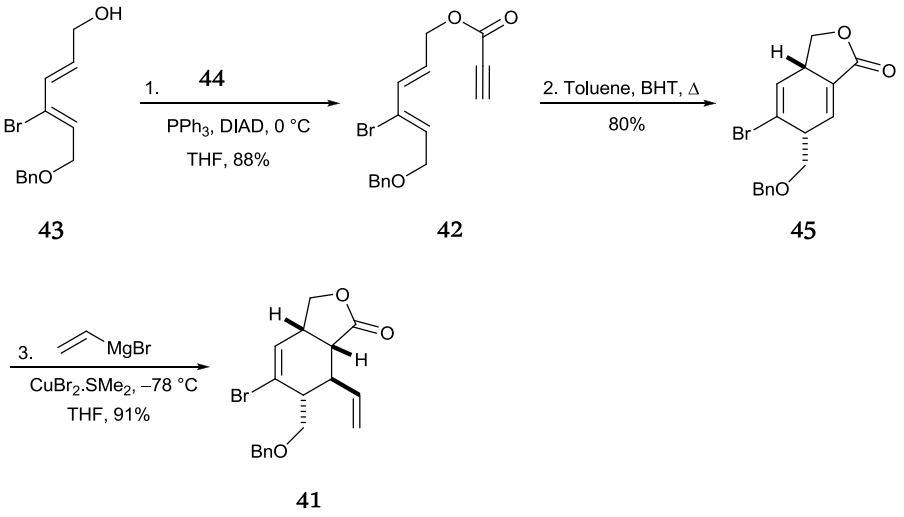
Clarke's retrosynthetic strategy for the formation of hexacyclinic acid **1** is outlined below (Scheme 19). Disconnection of the lactone and the hemiketal gives a highly functionalised 9-membered ring in **37** which could cyclise utilising a novel iodocyclisation through the oxygen of the ketone to form the DEF tricycle in **1**. Further disconnections reveal ABC tricycle **38**. The approach for formation of **38** involved a radical mediated 5-*exo*-*trig* cyclisation to form the A ring, and a key intramolecular ester tethered Diels-Alder reaction of **42** to construct the B-ring skeleton, which, depending on the product formed, could then be used in the synthesis of both **1** and **2**.[4b] The bromine functionality was also included for this reason. The Diels-Alder precursor **42** in turn could be accessed from fragments **43** and **44**.



Scheme 19: Retrosynthesis of 1 by Clarke group

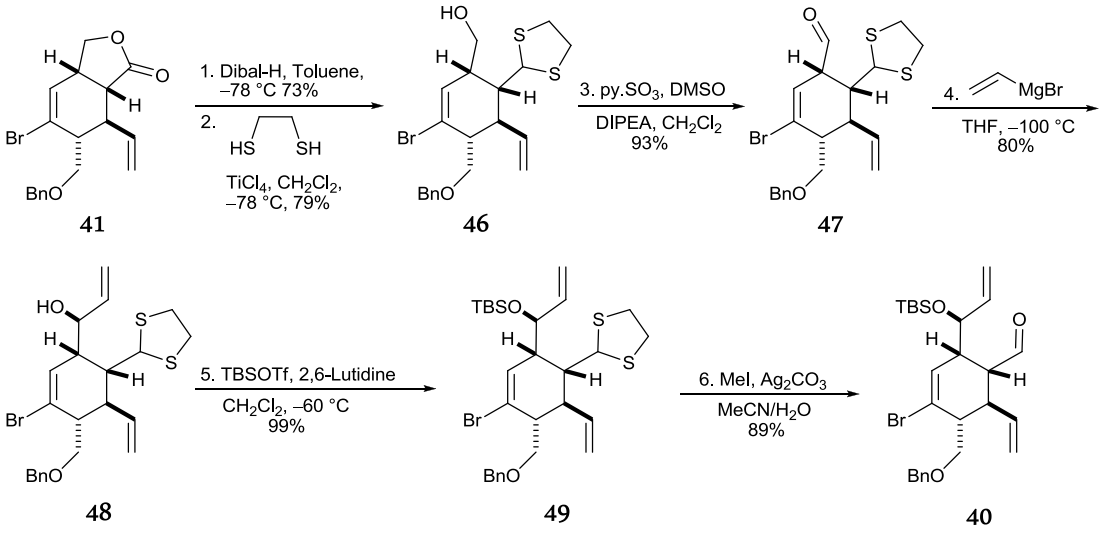
The racemic synthesis of **38** began with the esterification of diene **43** (synthesised in 5 steps from *cis*-butene-1,4-diol)[4d] and propiolic acid **44** under Mitsunobu conditions affording **42** in excellent yield (Scheme 20). This was then cyclised under thermal conditions by refluxing in toluene with catalytic BHT, forming Diels-Alder product **45** in

80% yield. Copper catalysed conjugate addition of vinylmagnesium bromide to the α,β-unsaturated lactone furnished **41** in excellent yield with approach exclusively from the less hindered top face.



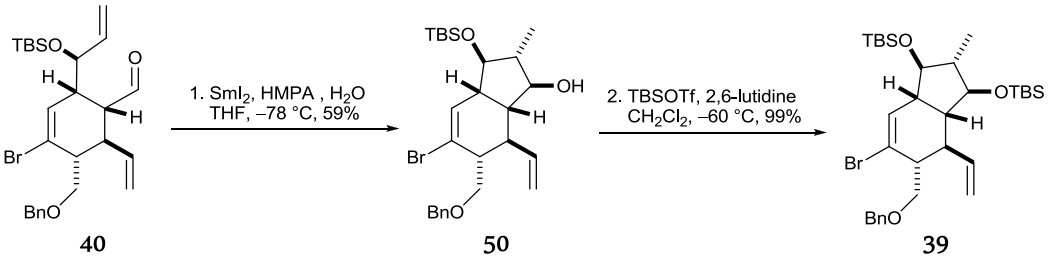
Scheme 20: Synthesis of B-ring system **41**

Reduction of **41** using Dibal-H formed the corresponding lactol, which was followed by formation of the dithiolane **46** using 1,2-ethanedithiol and $TiCl_4$ (Scheme 21). Oxidation of the primary alcohol was accomplished under Parikh-Doering conditions, while use of any other oxidising conditions led to isomerisation of the alkene. Addition of the vinyl group to aldehyde **47** was performed by addition of vinylmagnesium bromide to form allylic alcohol **48** in an 80% yield giving the necessary diastereomer in a 30:1 ratio. Protection of the secondary alcohol as a TBS ether to give **49** proceeded quantitatively, and was followed by removal of the dithiolane group, with the use of methyl iodide and Ag_2CO_3 necessary for efficient removal to furnish the aldehyde **40** in an excellent 89% yield.



Scheme 21: Formation of cyclisation precursor **40**

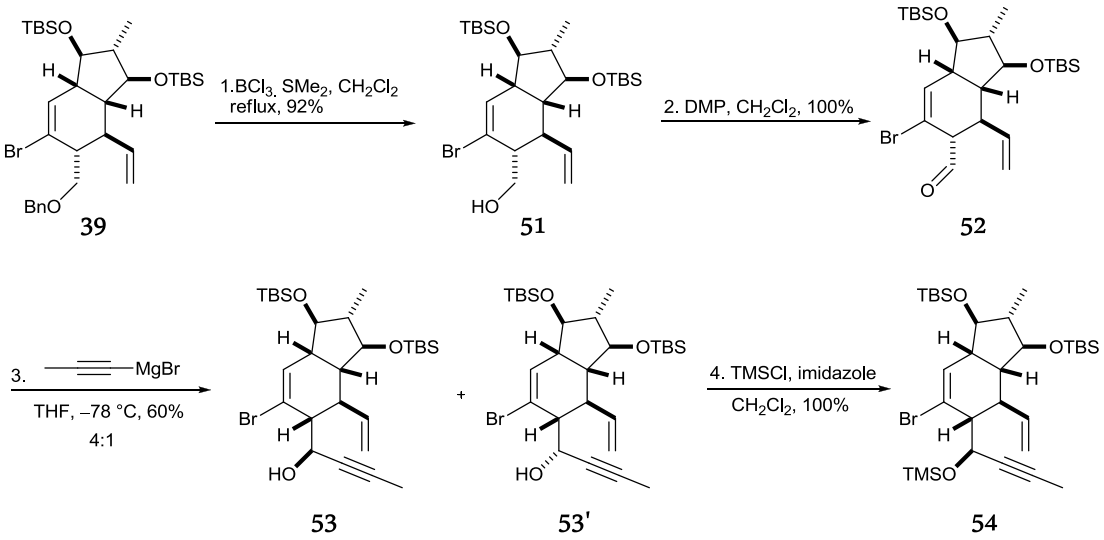
Following synthesis of the aldehyde **40**, the key 5-*exo-trig* reductive cyclisation was achieved by treatment of **40** with SmI_2, using HMPA and H_2O as an additive, to form stereoselectively two new stereocentres and to afford the AB bicyclic system **50** in 59% yield (Scheme 22). A further TBS protection of the resulting hydroxyl group proceeded quantitatively forming **39**.



40 50 39

Scheme 22: SmI_2 radical cyclisation to form A-ring

Removal of the benzyl group was completed using $BCl_3.SMe_2$, and the subsequent alcohol **51** was oxidised using DMP, forming aldehyde **52** (Scheme 23). Addition of propynylmagnesium bromide to the aldehyde forms the propargylic alcohol **53** in a 4:1 mixture with the diastereomer **53'**. Diastereomer **53** was then protected with TMSCl to furnish **54** quantitatively.

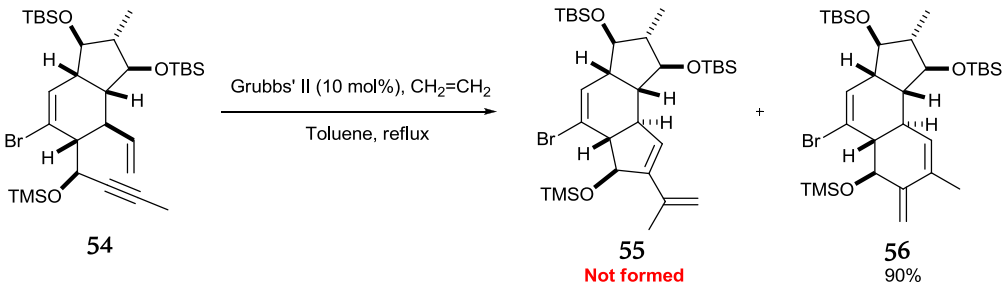


39 51 52

53 53' 54

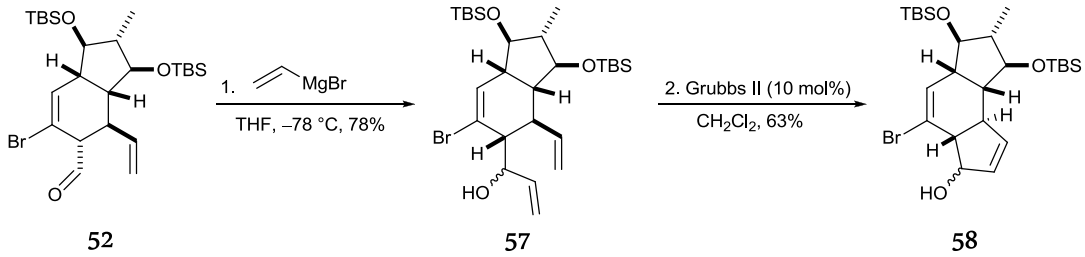
Scheme 23: Further functionalisations to form **54**

An enyne ring-closing metathesis of **54** was attempted, using 10 mol% of Grubbs' 2nd generation catalyst in toluene at reflux, aiming to form the 5-membered C-ring as in **55** (Scheme 24). However it was found that none of the desired product was isolated, with the 6-membered ring being formed preferentially, affording **56** in a 90% yield.



Scheme 24: Attempted enyne metathesis of **54**

With the planned enyne metathesis proving unsuccessful for the formation of the C-ring, it was decided to proceed through more straightforward ring-closing metathesis of a diene. Addition of vinylmagnesium bromide to aldehyde **52** gave the allylic alcohol **57** as a mixture of diastereomers (Scheme 25), which was then subjected to Grubbs' 2nd generation catalyst (10 mol%) generating **58** which contains the desired 5-membered C ring and the ABC ring system of hexacyclinic acid **1**.



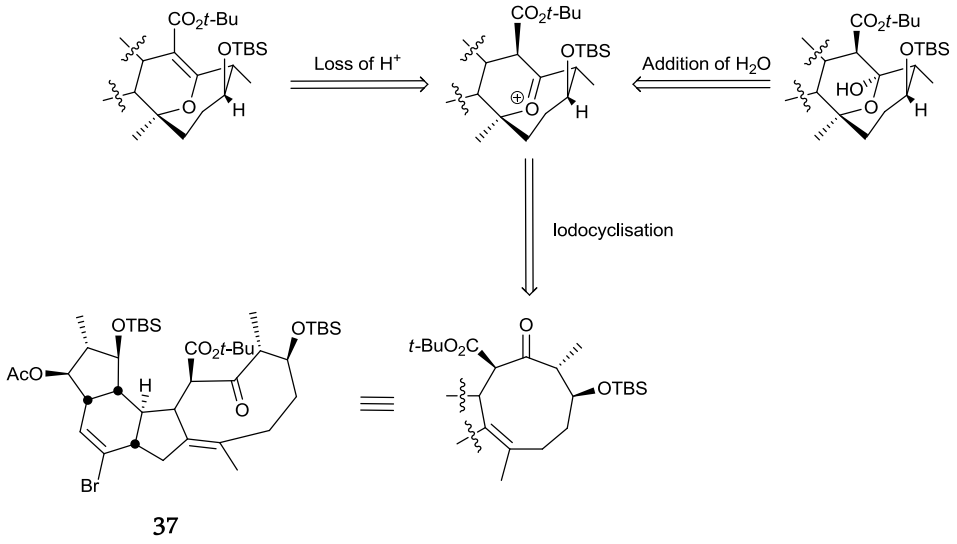
Scheme 25: Completion of ABC model **58** by Clarke group

Clarke's racemic synthesis of the ABC tricycle **58** was achieved in 15 steps with a 6% overall yield. Construction of the B-ring is efficiently achieved by a tethered intramolecular Diels-Alder rection, while the A-ring is completed by a highly stereocontrolled SmI_2 radical reaction. While the desired enyne metathesis was unsuccessful, the C-ring formed has sufficiently functionality to allow further construction on the C-ring.

1.3.2 – Clarke - DEF tricycle

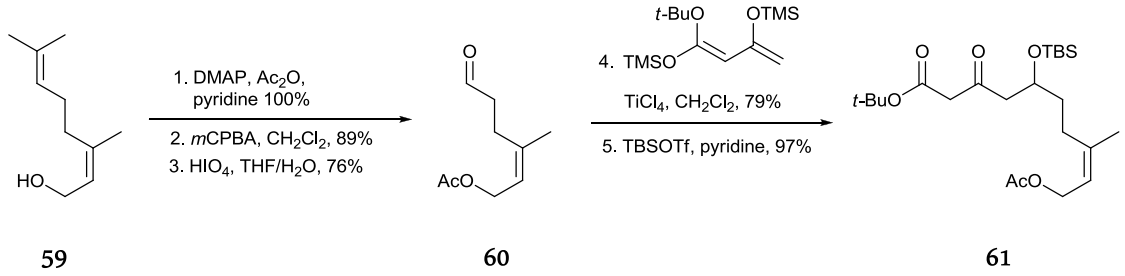
Clarke envisaged that due to the unique hexacyclic structure shared by **1** and **2**, they would share a common biosynthetic route. Furthermore he reasoned that they could be synthesised from the same intermediate as he showed in his model studies of their DEF tricycle – the retrosynthetic route is shown below (Scheme 26).[4a, 4c, 16] It was thought that the DF rings of **1** and **2** could be formed from the oxocarbenium ion by addition of H_2O or

loss of H^+ respectively, followed by deprotection and subsequent lactonisation to form the E-ring. The oxocarbenium ion would be formed by a transannular cationic cyclisation of the carbonyl onto the olefin moiety of the 9-membered precursor.



Scheme 26: Clarke's strategy for formation of the DEF tricycle of **1** and **2**

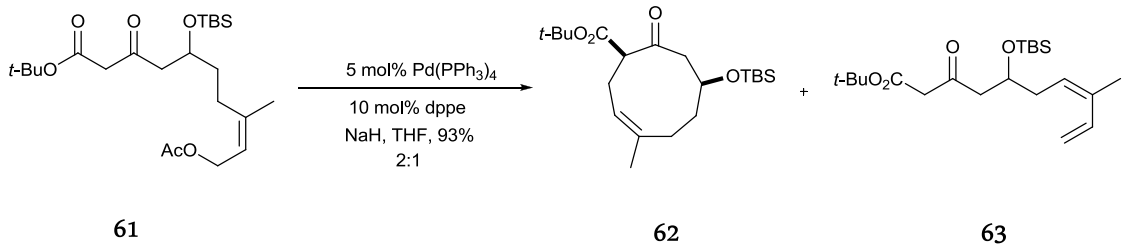
A model 9-membered ring precursor was cleanly accessed over 5 steps using nerol **59** as the starting material (Scheme 27). Acetylation of the primary alcohol, followed by epoxidation of the isoprenyl double bond and subsequent cleavage using periodic acid formed **60** in good yields for all steps. Aldehyde **60** was then used in a Mukaiyama aldol reaction with the *bis*-silyl enol ether of *tert*-butyl acetoacetate, forming the aldol product in 79% yield. The resulting hydroxyl was protected as a TBS ether using TBSOTf to form **61**.



Scheme 27: Formation of **61**

For the formation of the 9-membered ring, Clarke utilised a Pd(0)-catalysed intramolecular π-allyl substitution reaction using $Pd(PPh_3)_4$, wherein the β-ketoester nucleophile attacks the allylic position forming the 9-membered ring (Scheme 28). Initial results were poor, with only trace amounts of **62** being formed, however further optimisation by using 1,2-*bis*(diphenylphosphino)ethane as the ligand resulted in formation of **62** in a 2:1 ratio with

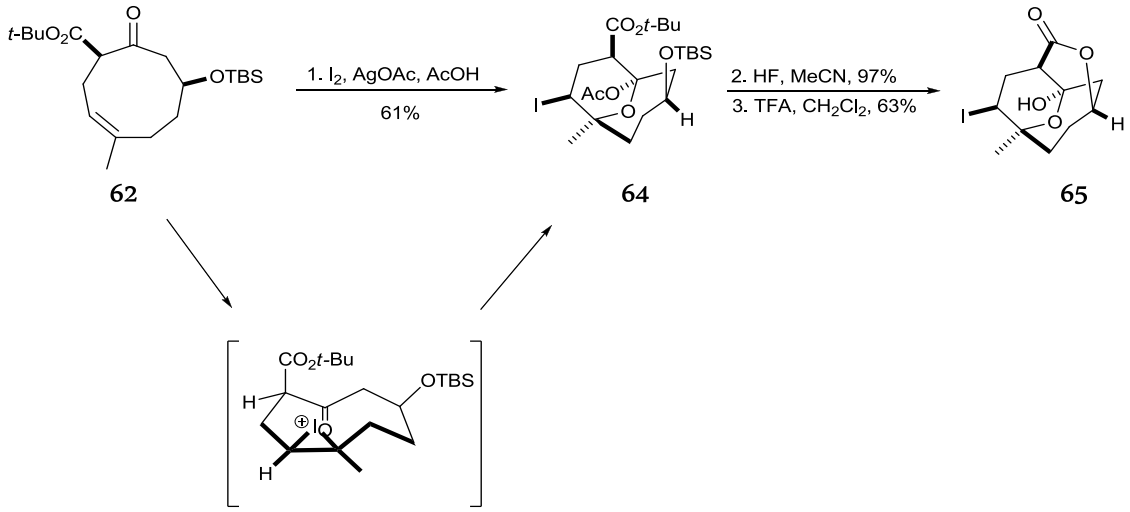
the elimination by-product **63**. While separation of the two products was difficult, it was achieved by using silica gel impregnated with $AgNO_3$.[17]



61 62 63

Scheme 28: Cyclisation to form 9-membered ring **62**

With the synthesis of **62** in hand, attempts were made to induce cyclisation to form the DF model **64** using $Hg(OTf)_2$;[18] however this resulted in a complex mixture of products, with no sign of **64**. Instead focus shifted to the use of iodine reagents, with treatment of **62** with I_2 and silver acetate in acetic acid forming compound **64** in 61% yield (Scheme 29). This compound is analogous to the DF ring system of **1**. This reaction was thought to proceed *via* an iodonium ion formed from the top face leading to the desired product. Treatment of **64** with HF to remove the TBS protecting group, followed by trifluoroacetic acid to induce lactonisation formed the DEF model system **65**.[17]

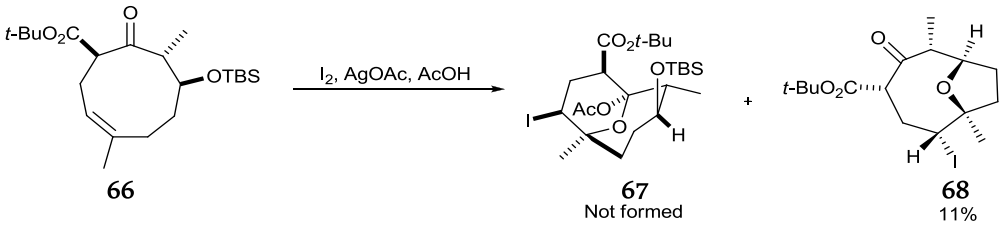


62 64 65

Scheme 29: Cyclisation to give DEF model **65**

Together with their ABC tricycle synthesis, the work published by Clarke *et al.* represents the closest attempt at the synthesis of hexacyclinic acid **1**. Clarke's DEF model synthesis utilised an impressive iodocyclisation, efficiently constructing the DF ring system, however it must be noted that the model system lacks the methyl group necessary in **1** and **2**. It was later reported by Clarke that when the 9-membered **66** was subjected to the

iodocyclisation conditions, the desired product **67** was not formed (Scheme 30). Instead **68** was isolated in an 11% yield, with mostly starting material recovered. This product can be rationalised by deprotection of the TBS ether, with cyclisation occurring through the free hydroxyl as opposed to the desired ketone. Modelling studies of **66** revealed an eclipsing interaction between the methyl and OTBS group which they believe inhibits cyclisation to form **67**. To date no synthesis of the model **67** has been published.

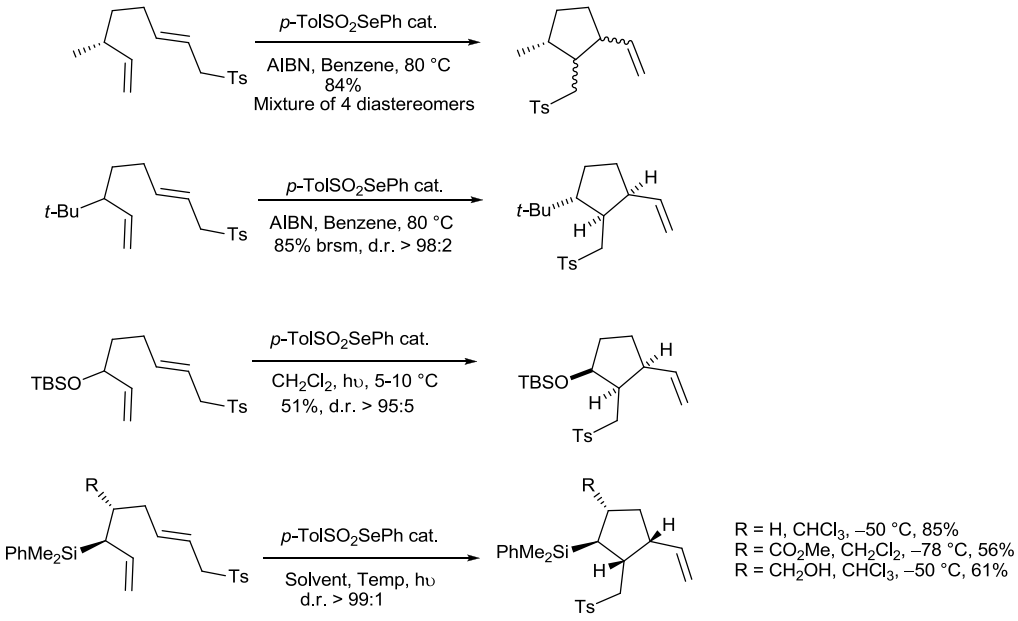


66 67 Not formed 68 11%

Scheme 30: Attempted iodocyclisation of **66**

1.3.3 – Landais – ABC tricycle

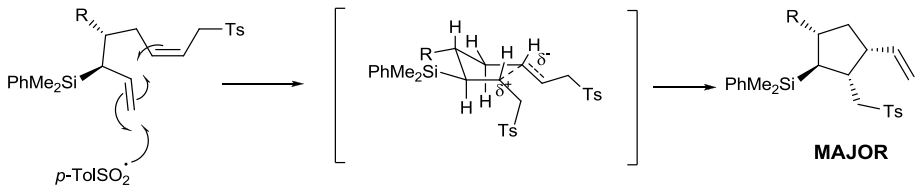
Landais *et al* developed a methodology involving the radical cyclisation of 3-silylhepta-1,6-dienes for the formation of highly substituted cyclopentane rings in a stereocontrolled manner (Scheme 31).[4g] The cyclisation was built on the idea that sterically bulky substituents would limit the number of conformations available in the transition state, affording greater diastereocontrol. This was confirmed experimentally, with the smaller methyl substituent giving a mixture of 4 diastereomers, while the cyclisation with the larger *tert*-butyl group gives a dr of > 98:2. The reaction was also shown to proceed with silyl and protected hydroxyl substituents, where both steric and electronic factors induced excellent control.



Scheme 31: 5-*exo-trig* cyclisations with a variety of substituents

The reaction proceeds by addition of a tosyl radical (generated from *p*-TolSO$_2$SePh) to the terminal alkene. This is followed by the 5-*exo-trig* cyclisation to form the cyclopentane ring and *β*-fragmentation to form the new terminal alkene and regenerate the radical to propagate the reaction.

The stereochemical outcome can be rationalised using the Beckwith-Houk model, with the major product resulting from a chair-like transition state, all the substituents in *pseudo* equatorial positions (Scheme 32). This transition state also allows overlap between the developing partial positive charge and the silicon sp3 orbitals. The silicon contributes to the stereocontrol by the "silicon effect", stabilising the partial positive charge.



Scheme 32: Proposed transition states for radical cyclisation

The β-silicon effect is an observation where β-carbocations are stabilised due to silicon hyperconjugation (Fig 4). Electron donation into the carbocation due to the overlap between the larger silicon sp3 orbital and the empty p-orbital stabilises the positive charge.

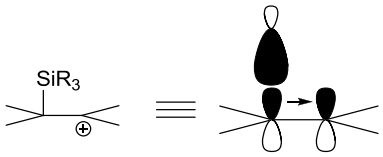
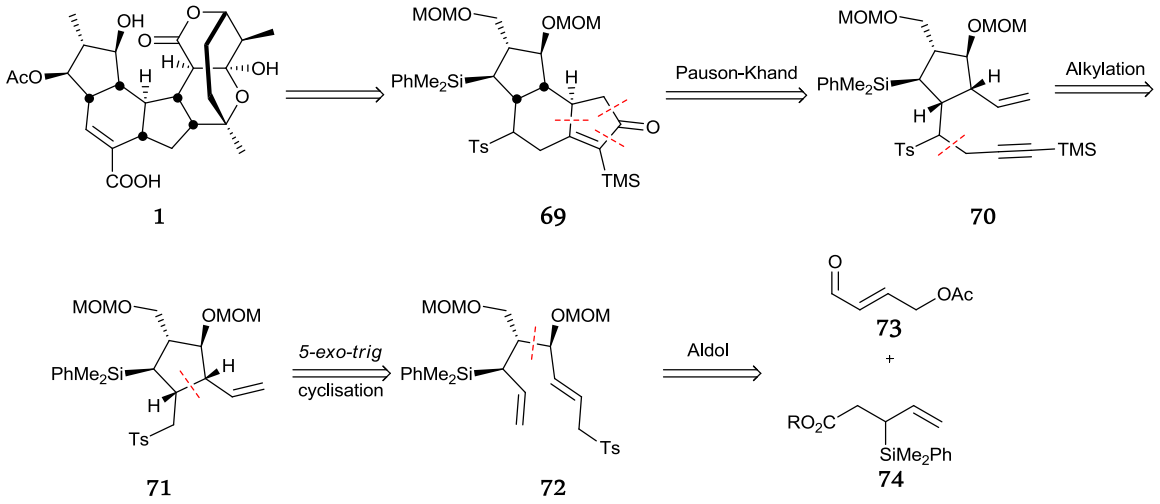


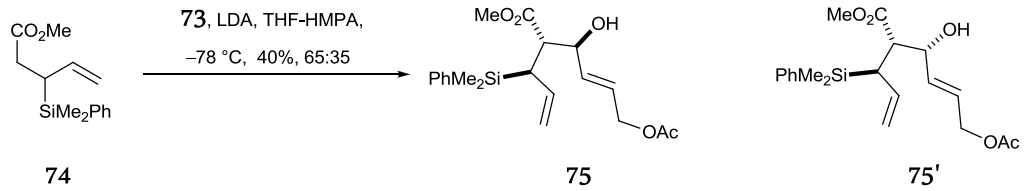
Fig 4: ß-silicon effect

To prove the synthetic worth of their method, they envisaged that it could be used to build the A-ring of **1** and set about the synthesis of the ABC tricycle of **1** (Scheme 33).[19] An intramolecular Pauson-Khand reaction to form the BC-ring system and a 5-*exo*-*trig* radical cyclisation to build the densely functionalised A ring.



Scheme 33: Retrosynthesis of **1** by Landais group

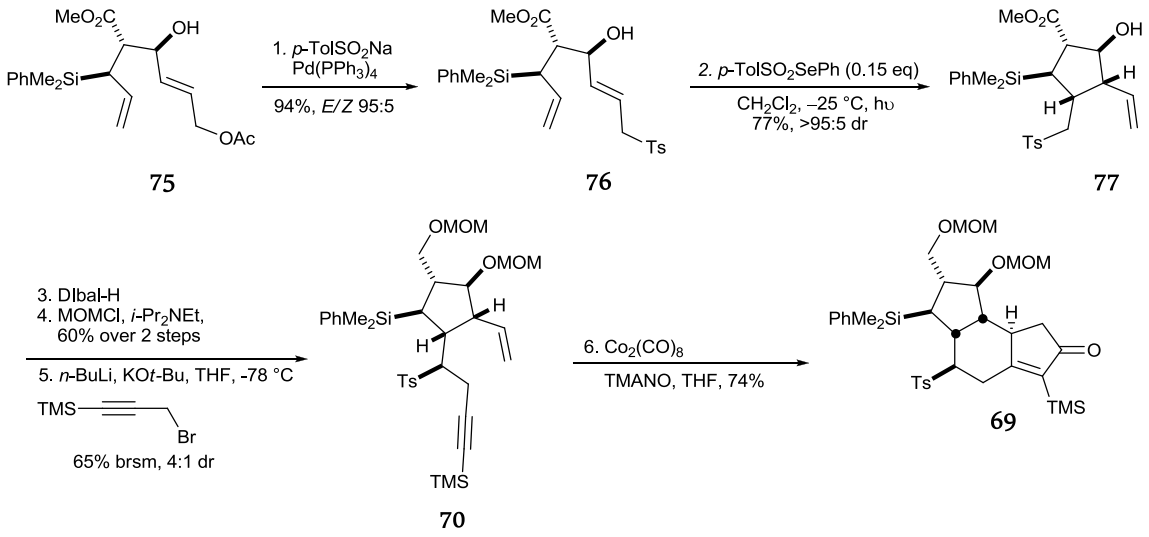
Aldol reaction of the β-silane ester **74** and aldehyde **73** (prepared in 3 steps from butyn-1,4-diol) using LDA required a mixture of THF and HMPA to furnish the aldol adducts **75/75'** in a 65:35 dr and modest yield (Scheme 34).



Scheme 34: Formation of dienes **75/75'**

The allylic acetate **75** underwent a palladium-catalysed substitution reaction with sodium *p*-toluenesulfonate to form sulfone **76** in excellent yield (Scheme 35). Compound **76** was then submitted to the sulfonyl radical cyclisation conditions to furnish the highly substituted cyclopentane **77** in good yield and excellent diastereocontrol. Compound **77** is

then reduced using Dibal-H, and the resulting hydroxyl groups are protected as MOM ethers. Alkylation with 3-trimethylsilylpropargyl bromide, optimised using Schlosser's superbase, furnished enyne **70** in 65% yield (brsm). This was then cyclised in a trimethylamine *N*-oxide (TMANO) promoted Pauson-Khand reaction to give the tricyclic ring system **69** in a 74% yield.

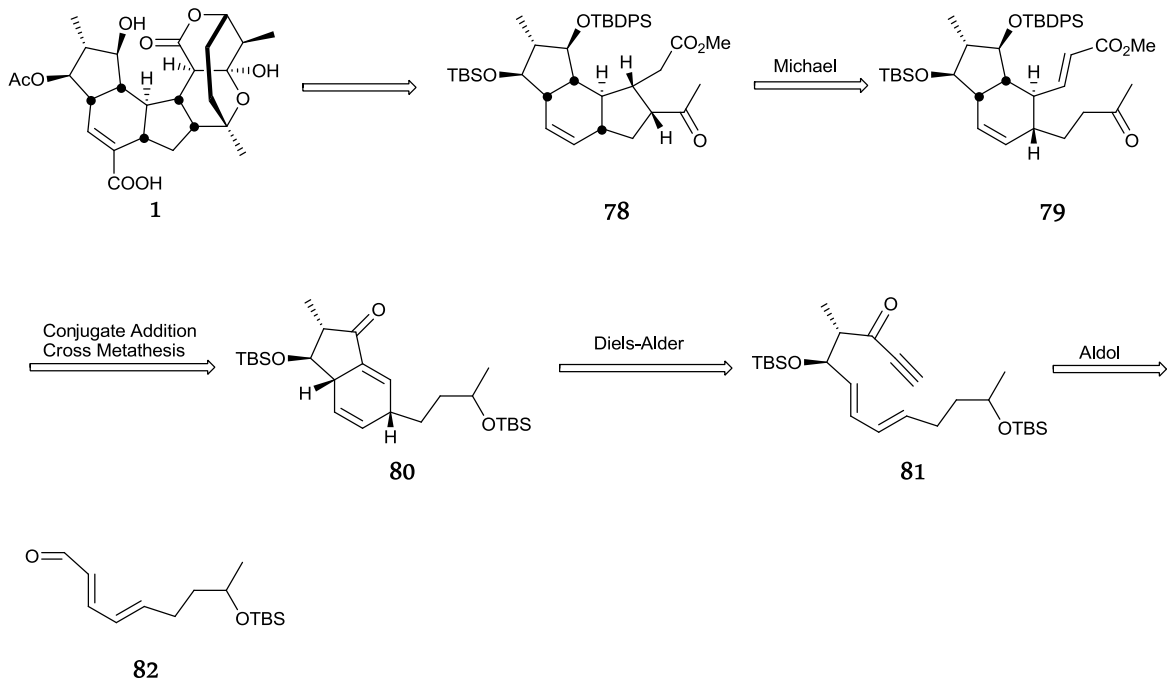


Scheme 35: Formation of ABC tricycle **69**

The synthesis by Landais contains some interesting methods, building up the complex tricyclic skeleton in only 7 steps. Of particular note is the 5-*exo-trig* radical cyclisation, setting up the stereochemistry of the AB ring junctions with excellent control. However his tricycle **69** would require several more steps, such as formation of the double bond in the B ring and installation of the hydroxyl in the A ring, as well as forming an additional stereocentre at the B/C-ring junction, to access a fully functionalised ABC tricycle. While some functionality is included on the C-ring, no mention is made of their strategy for completion of **1**.

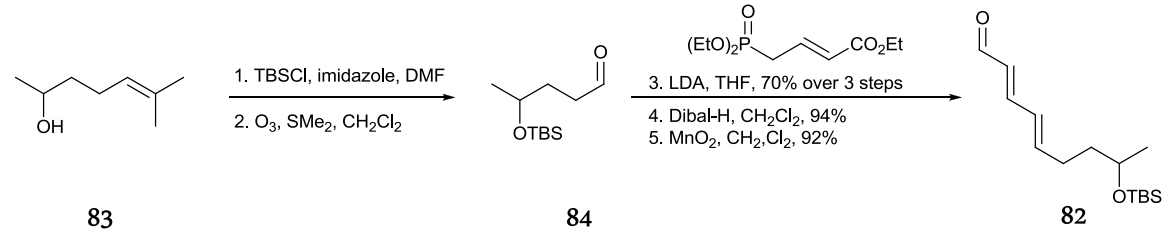
1.3.4 – Kalesse – ABC tricycle

Retrosynthesis of Kalesse's ABC tricycle **78** utilised an intramolecular Michael addition for the formation of the C ring from **79** (Scheme 36).[3] The enone moiety was to be added by conjugate addition and subsequent cross metathesis from diene **80**. In a similar fashion to Clarke's route, the Kalesse group also utilised an intramolecular Diels-Alder reaction for the formation of the B ring, with the Diels-Alder precursor **81** being produced by an aldol reaction with aldehyde **82**.



Scheme 36: Retrosynthesis of ABC tricycle of **1** by Kalesse group

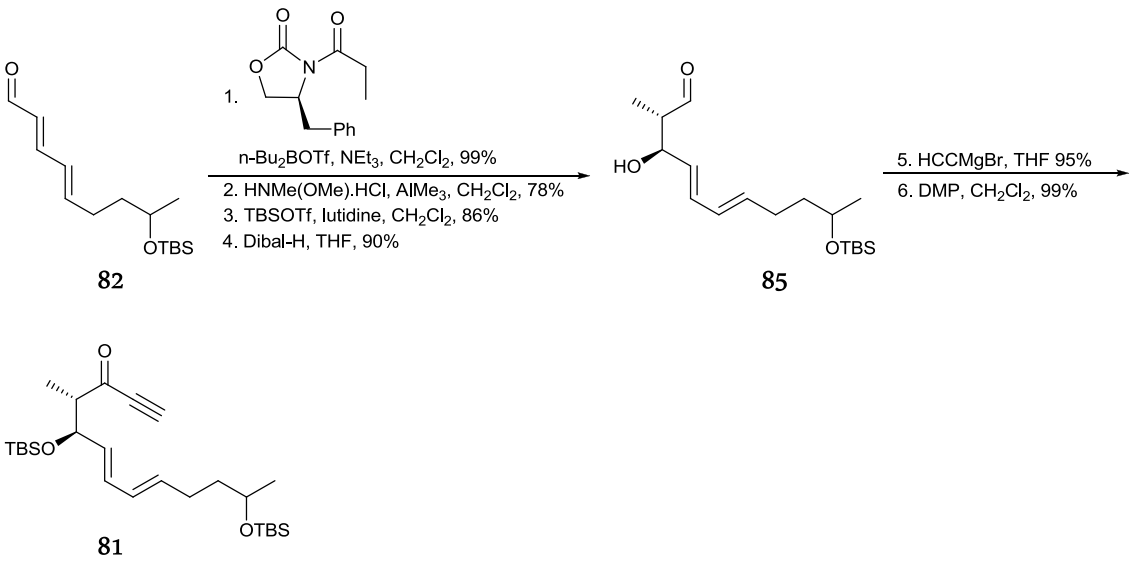
Protection of alcohol **83** with TBSCl, followed by cleavage of the alkene by ozonolysis gave the aldehyde **84**, and a subsequent HWE reaction with the phosphonate ester gave the corresponding enone ester in 70% yield over the 3 steps (Scheme 37). Reduction with Dibal-H followed by oxidation of the resulting alcohol using MnO_2 gave aldehyde **82** in excellent yield for both steps.



83 84 82

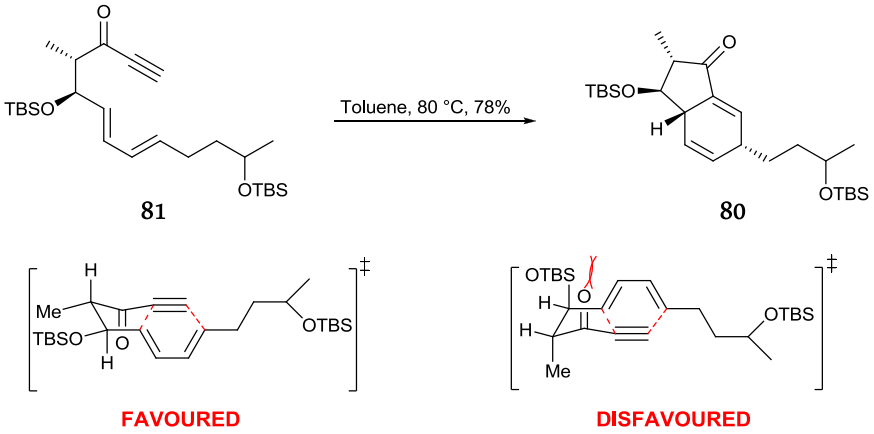
Scheme 37: Synthesis of aldehyde **82**

An Evans aldol reaction of **82** with Evans auxiliary formed the aldol adduct in near quantitative yield, efficiently setting up the 2 new stereogenic centres of the A ring (Scheme 38). Formation of the Weinreb amide, followed by TBS protection of the secondary alcohol and Dibal-H reduction of the Weinreb amide afforded the corresponding aldehyde **85** with good yield over all steps. Addition of ethynylmagnesium bromide and oxidation of the resulting alcohol using DMP formed the Diels-Alder precursor **81**.



Scheme 38: Synthesis of ketone **81**

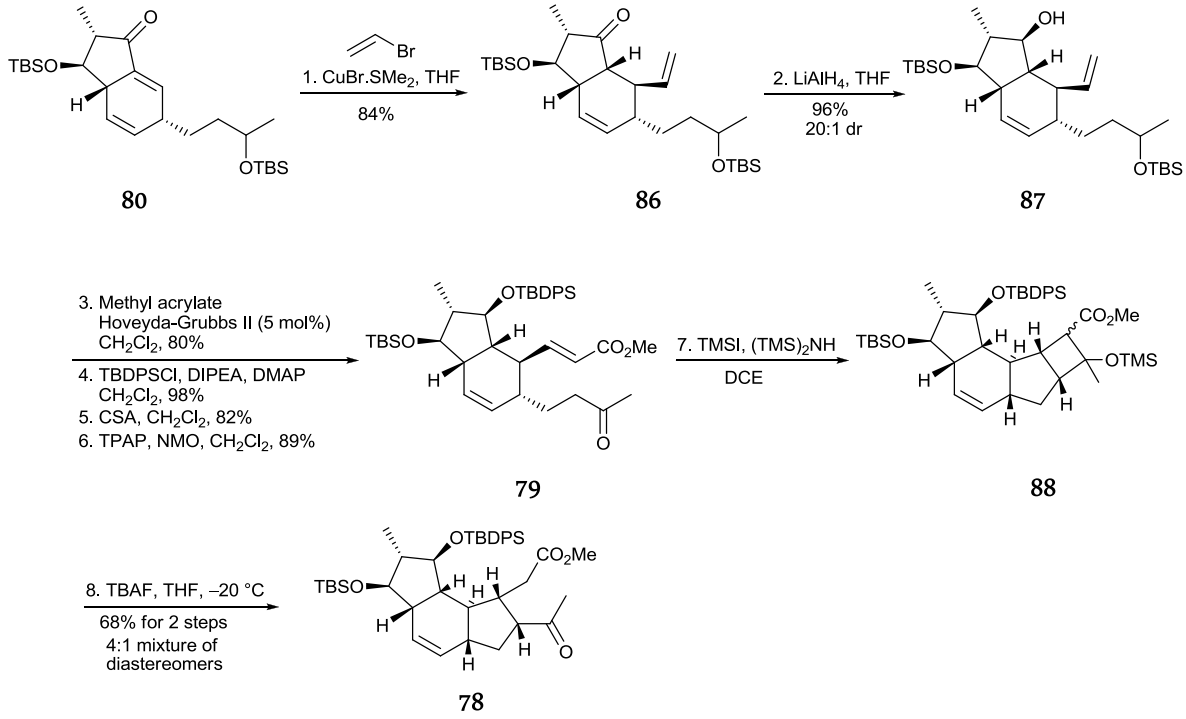
Diels-Alder reaction of **81** proceeded well in toluene at reflux to afford the adduct **80** with the desired diastereomer being formed exclusively (Scheme 39). This is imagined to proceed *via* the favoured transition state shown, with the bulky OTBS group taking a *pseudo* equatorial position. The alternate conformation is disfavoured due to the 1,3-allylic strain between the diene and the OTBS group.



Scheme 39: Diels-Alder reaction to from AB bicycle and proposed Transition state

In another parallel to the Clarke synthesis, Kalesse's group used a copper-catalysed conjugate addition to deliver selectively the vinyl group onto the top face of the B ring, setting up the correct stereochemistry and generating a synthetic handle for use in the C ring synthesis as seen in **86** (Scheme 40). Reduction of the ketone using $LiAlH_4$ resulted in delivery of the hydride from the lower face being favoured, with alcohol **87** being formed in excellent yield. Cross-metathesis reaction of the new exocyclic vinyl group using 4

equivalents of methyl acrylate and Hoveyda-Grubbs' 2nd generation catalyst formed the enone for use as an acceptor in the Michael reaction in very good yield. Protection of the cyclic alcohol, followed by deprotection and oxidation of the acyclic alcohol resulted in formation of **79**. Treatment with TMSI resulted in TMS-enol ether formation, which cyclised and formed the cyclopentane C ring, along with a highly strained cyclobutane ring as seen in **88**. Deprotection of the TMS group opened this 4-membered ring and furnished the ABC tricycle model **78** as an inseparable 4:1 mixture of diastereomers in a 68% yield for the last 2 steps.



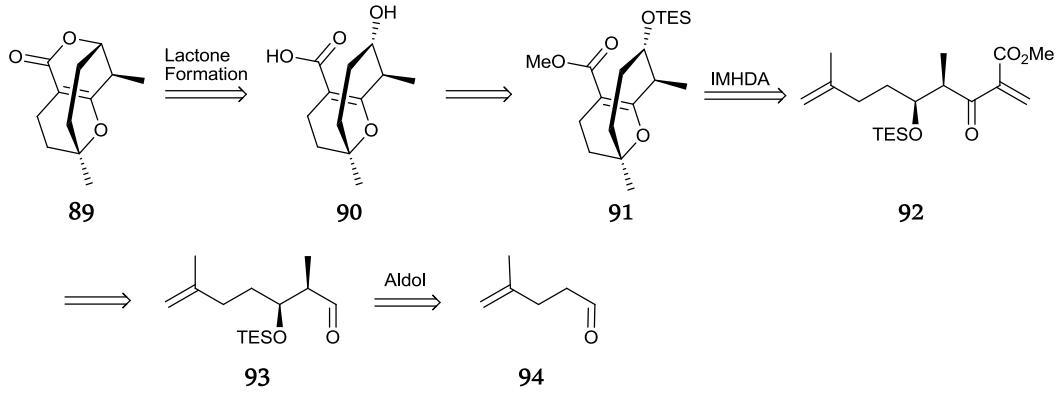
Scheme 40: Completion of ABC model **78**

Kalesse's asymmetric synthesis of the model ABC tricycle **78** showed a high degree of stereocontrol, utilising an Evans aldol reaction and intramolecular Diels-Alder reaction as key stereoselective steps, forming the model system in 20 steps from **83** with 10.7% overall yield. This model is comparable to the ABC tricycle of **1**; however it is missing the carboxylic acid function, with no mention of how it could be installed. However it could be possible to include the methyl group earlier on in the synthesis, with the carboxylic acid being made by an allylic oxidation.

1.3.5 – Nakada - DEF tricycle

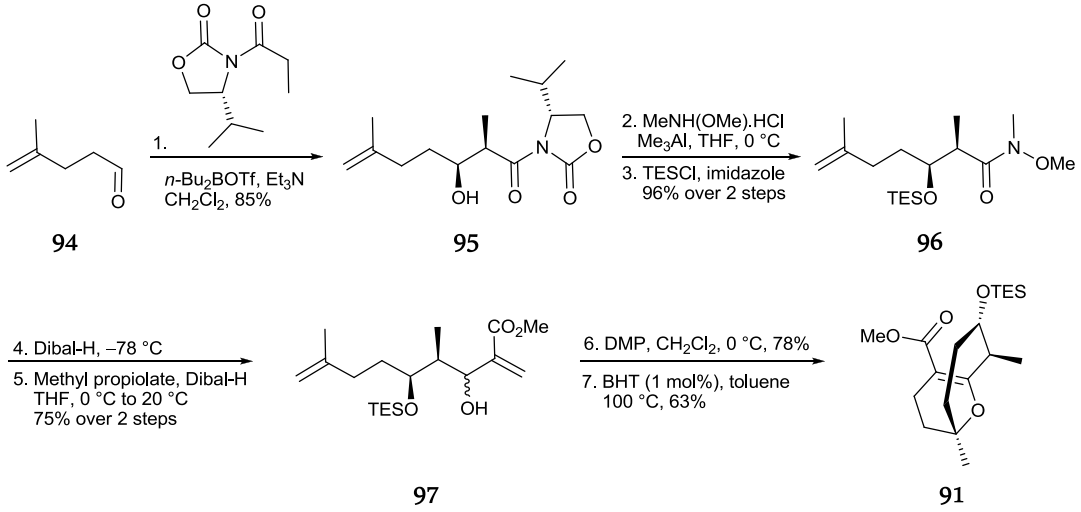
The most recent literature relating to **1** and **2** is the synthesis of the DEF tricycle reported by Nakada *et al*. Interested in the biological activity of this fragment, they set about the

synthesis of the tricycle **89** (Scheme 41).[20] Their retrosynthetic strategy involved a challenging inverse electron demand hetero-Diels Alder (IMHDA) reaction to construct the ring systems, with the final ring being closed by lactonisation. The stereogenic centres would be installed by an asymmetric aldol reaction with aldehyde **94**.



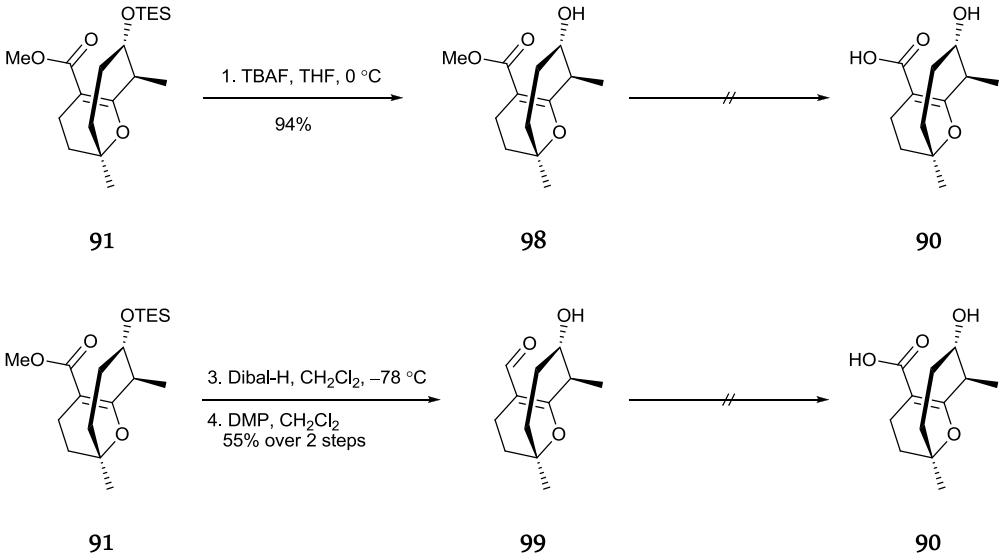
Scheme 41: Retrosynthesis of DEF tricycle of FR182877 by Nakada group

Aldehyde **94** (prepared in 2 steps from ethyl 4-methyl-pent-4-en-1-oate)[21] was reacted with Evans auxiliary using dibutylboron triflate and triethylamine to furnish the aldol adduct **95** in an excellent yield (Scheme 42). Conversation to the Weinreb amide, followed by TES protection of the hydroxyl group formed **96** near quantitatively over the 2 steps. This was followed by Dibal-H reduction of the amide to the corresponding aldehyde **93**. The reaction between ethyl propiolate and Dibal-H generated a reactive vinylaluminium species, which underwent nucleophilic addition to the aldehyde to form the enone **97**.[22] Oxidation of the resultant hydroxyl group using DMP produced the diene necessary for the hetero-Diels-Alder. The inverse electron demand IMHDA reaction was achieved using a catalytic amount of BHT and heating to 100 °C in toluene. This reaction proceeded very slowly, requiring 4 days of heating to complete, however it afforded **91** as a single diastereomer in a good 63% yield.



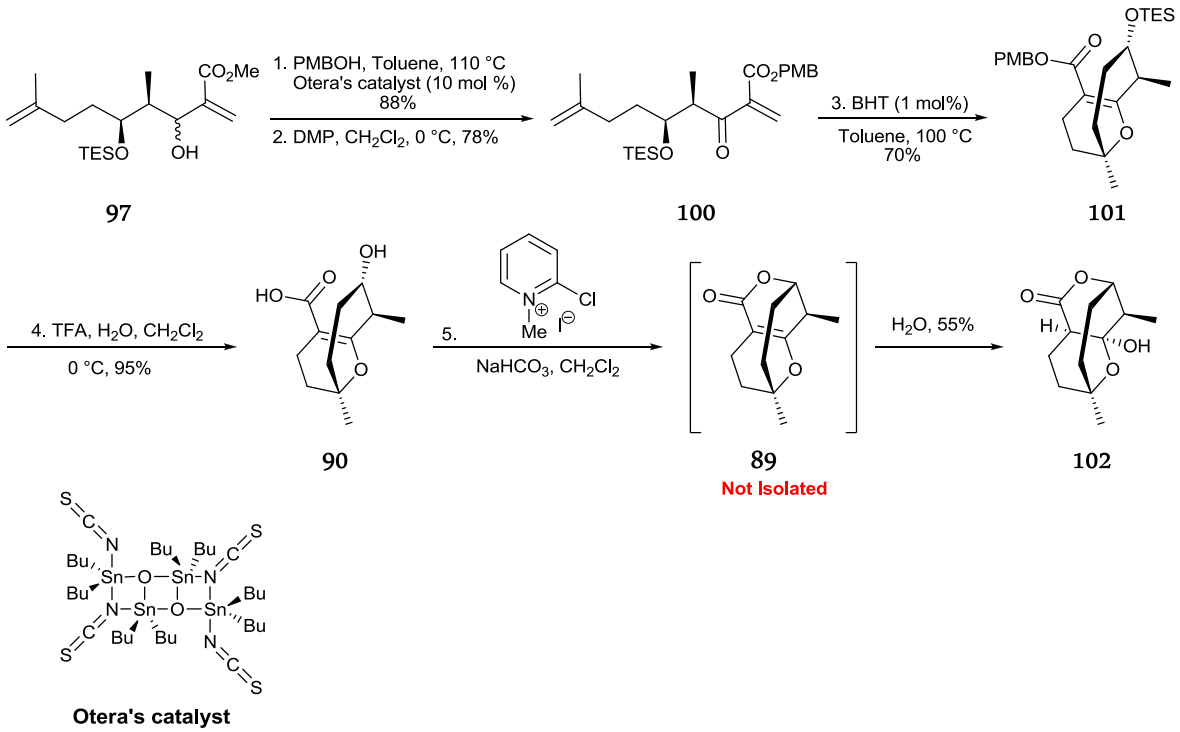
Scheme 42: Synthesis of DF bicycle **91**

Removal of the TES ether of **91** was achieved using TBAF in THF to form the vinylogous carbonate **98** in 94% yield (Scheme 43). Unfortunately all attempts to hydrolyse the ester were unsuccessful, with the presumed stability of the vinylogous carbonate system attributed to its lack of reactivity. Consequently it was attempted to reduce and then oxidise the ester to the corresponding aldehyde **99**, followed by a further oxidation to the acid **90**, however this was also unsuccessful. Subsequently the group decided to change the methyl ester to a PMB ester, which could be removed by DDQ or acid, and bring about the lactonisation.



Scheme 43: Failed attempts to access lactonisation precursor **90**

Conversion of the methyl ester **97** to the PMB ester **100** was achieved by transesterification using PMBOH and Otera's catalyst,[23] followed by oxidation using DMP (Scheme 44). Using the same conditions as before the IMHDA reaction proceeded smoothly giving the product **101** as a single diastereomer with a slightly improved 70% yield. The PMB and TES groups were easily removed using TFA to form the cyclisation precursor **90**.

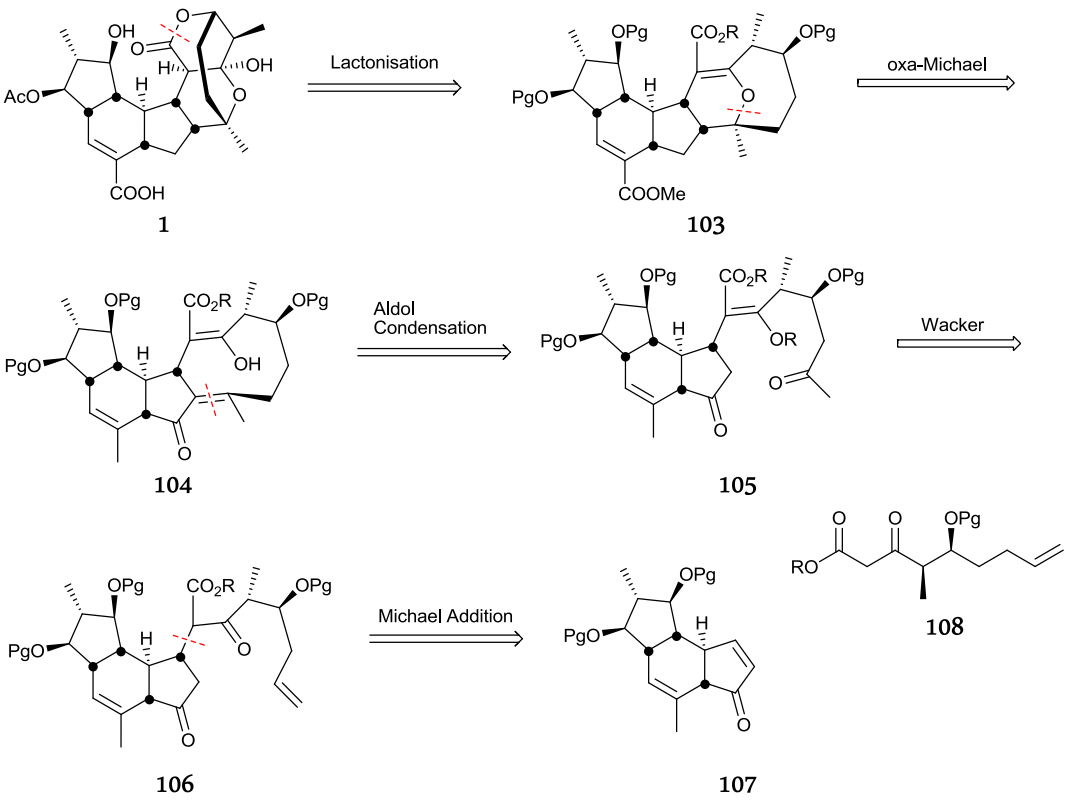


Scheme 44: Transesterification and subsequent lactonisation

Lactonisation was achieved using 2-chloromethylpyridinium iodide (Mukaiyama's reagent), however the isolated product was found not to be **89** but the hemiketal **102**, forming the DEF tricycle of hexacyclinic acid **1** instead. Compound **102** is thought to be formed during the workup, with the addition of H_2O to the distorted alkene in the highly reactive **89**. Nakada's synthesis of the DEF tricycle of **1** is achieved in 8 steps from aldehyde **94**. Of particular mention is the inverse electron demand IMHDA reaction which efficiently constructs the ring system.

2 - Previous work in the Prunet group towards Hexacyclinic acid 1

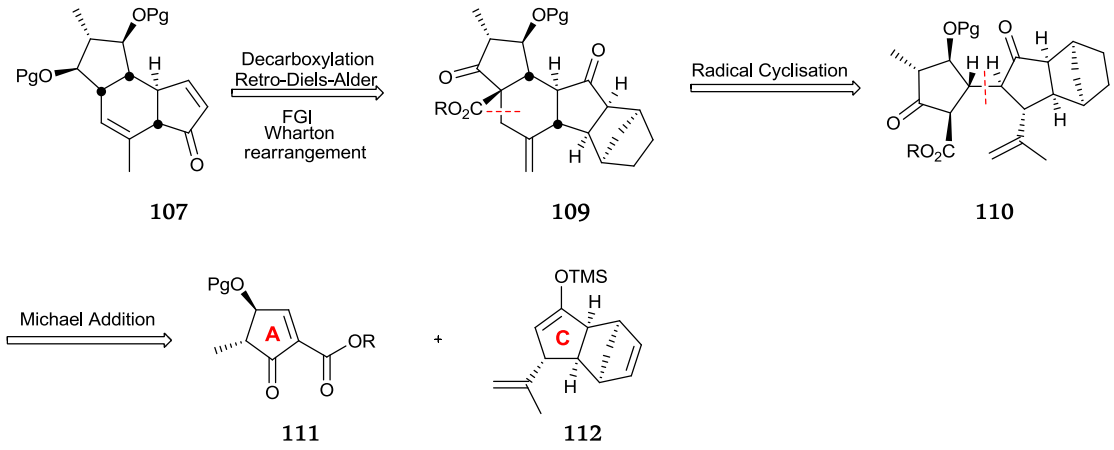
In contrast to strategies by other groups, the approach to **1** within the Prunet group did not utilise a Diels-Alder for the construction of the AB ring system, instead involving a more convergent route (Scheme 45). Opening the lactone to the pentacyclic system **103**, followed by breaking the C-O bond of **103** would give the 9-membered ring in **104**. Formation of the DF ring system in **103** would be accomplished by an intramolecular oxa-Michael addition. The next disconnection would be the enone double bond of **104** to the diketone **105**. It was planned to access the 9-membered ring by a challenging aldol condensation between these two ketones from precursor **105**. Functional group interconversion of the methyl ketone to a terminal alkene reveals **105** could be afforded from **106** by Wacker oxidation. C-C disconnection shows the DEF framework **108** would be grafted onto the C ring of the ABC tricycle **107** by a Michael addition.



Scheme 45: Prunet group retrosynthesis of **1**

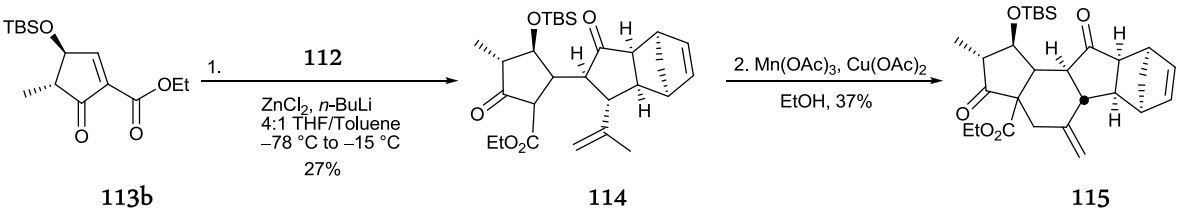
The retrosynthesis of the ABC tricycle **107** involved various functional group interconversion of **107** to **109**. A Wharton rearrangement would flip the position of the C ring oxygen. Decarboxylation, isomerisation of the *exo*-cyclic double bond and a retro-Diels-Alder would furnish **107** (Scheme 46). A C-C disconnection to open the 6-membered B-ring would give **110**. Construction of the B-ring will be achieved by a 6-*endo-trig* Snider radical cyclisation of **110**. A further C-C disconnection between the two rings would give

the 5-membered enone A-ring and enol ether C-ring. Grafting of these two rings would utilise a highly selective diastereoselective Michael reaction for the synthesis of **110**, uniting the A-ring **111** and C-ring **112**. This reaction would be a key step in the synthesis, joining the two fragments and forming 3 new stereocentres, with the addition occurring *anti* to the isopropenyl group on the C-ring.



Scheme 46: Retrosynthesis of ABC tricycle **107**

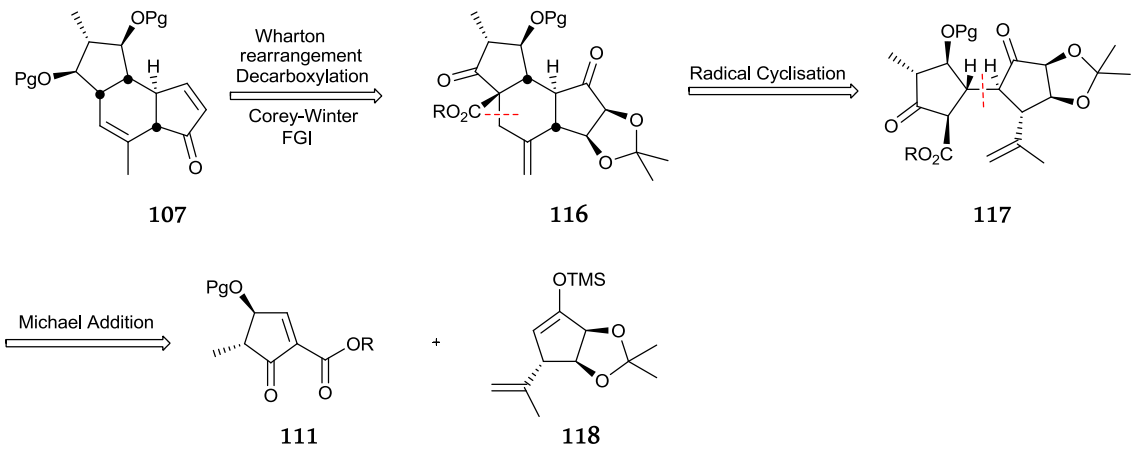
Development of the diastereoselective Michael addition involved screening a wide variety of conditions. Ultimately the optimal Lewis acid was found to be $ZnCl_2$, with the use of *n*-BuLi to generate the lithium enolate from silyl enol ether **112** (Scheme 47). Unfortunately the maximum yield obtained for the formation of adduct **114** was 27%, although the diastereoselectivity was excellent: the product was obtained as a single diastereomer, the stereochemistry of which was unassigned. Attempts to increase the yield by increasing the number of equivalents (up to 5 equiv) of silyl enol ether **112** were unsuccessful. Snider radical cyclisation using $Mn(OAc)_3$ closed the B ring in 37% yield, although the conditions were unoptimised.



Scheme 47: Diastereoselective Michael addition of **112** to **113b**

While the desired product was obtained, the low yield was unacceptable for such a key synthetic step. This modest yield was attributed to the low reactivity of the enolate due to the steric bulk of the bridged cyclic system. It was decided to proceed using a less

sterically encumbered chiral acetonide. The revised retrosynthesis of **107** proceeds as before, although the enone functionality on the C-ring would be introduced from **116** by a Corey-Winter olefination instead of a retro Diels-Alder (Scheme 48). The diastereoselective Michael-type addition would be used to form **117**, from the double acceptor **111** and silyl enol ether **118**, which contains the acetonide moiety.

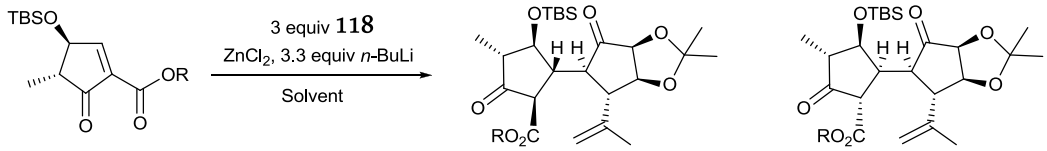


107 **116** **117**

111 **118**

Scheme 48: Revised retrosynthesis of **107**

The Michael addition proceeded using 3 equivalents of acetonide **118**, giving a mixture of diastereomers (Scheme 49). Interestingly it was observed that the nature of the solvent used had a dramatic effect on the diastereoselectivity of the reaction. When diethyl ether was employed as the solvent, the yield was a good 60%, with the diastereoselectivity favouring the undesired diastereomer **119'** in a 7:1 ratio. A THF/toluene mix gave reasonable yields but with low selectivities. Switching to a highly polar 4:1 DMF/THF solvent mixture gave a good yield as well as favouring the desired diastereomer **119** in a 7:1 ratio (Table 1).



113a = Me
b = Et
c = *t*-Bu

119a = Me
b = Et
c = *t*-Bu
Desired

119'a = Me
b = Et
c = *t*-Bu
Undesired

Scheme 49: Diastereoselective Michael-type additions of **118** to **113**

R = Et

Solvent	Yield	119b/119'b
Et_2O	60%	1:7
1:4 THF/Toluene	50%	1:2.5
4:1 THF/Toluene	46%	2.5:1
4:1 DMF/THF	60%	7:1

Table 1: Solvent effect on yields and diastereoselectivities

The reaction is proposed to go through one of two transition states; an open transition state with attack *anti* to the OTBS forming the product **119**, and a cyclic transition state with attack *anti* to the methyl group forming **119'**. When the highly polar DMF is used, it coordinates to the zinc and disrupts the cyclic transition state, instead favouring the open transition state (Fig 5).

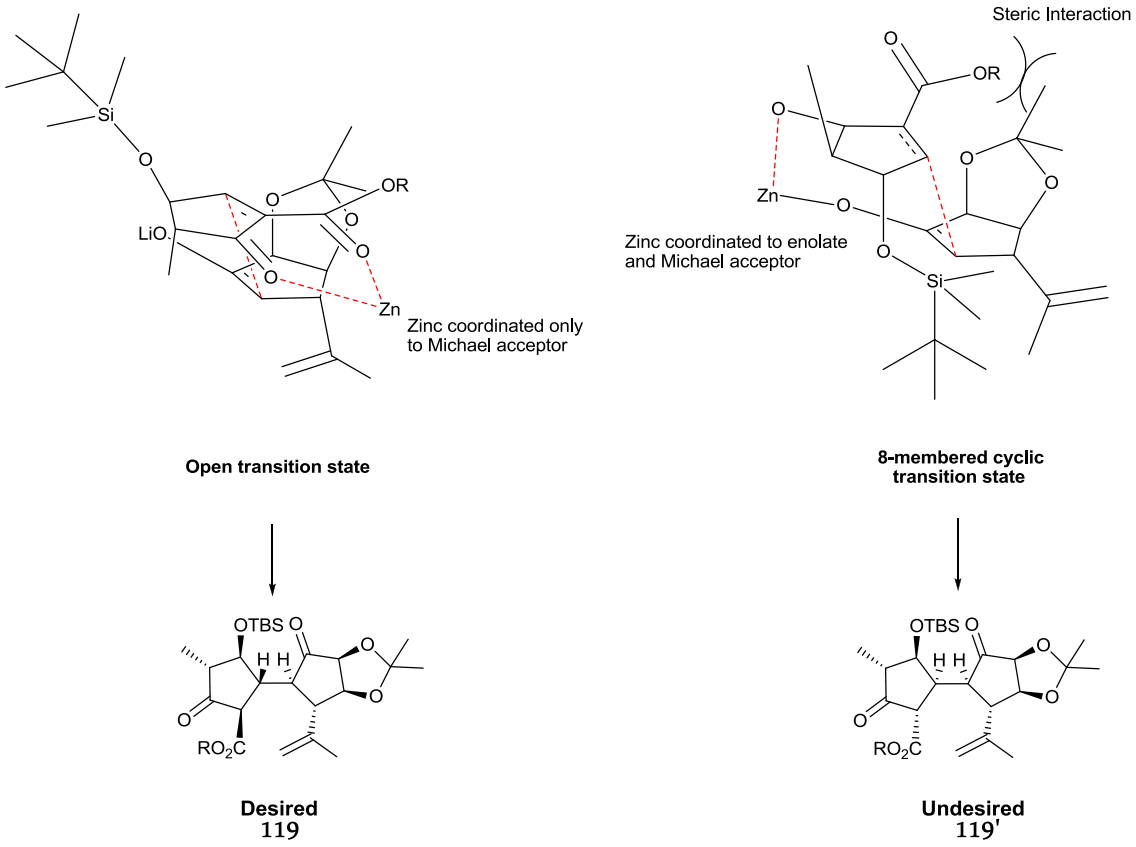


Fig 5: Proposed transition states for Michael-type addition

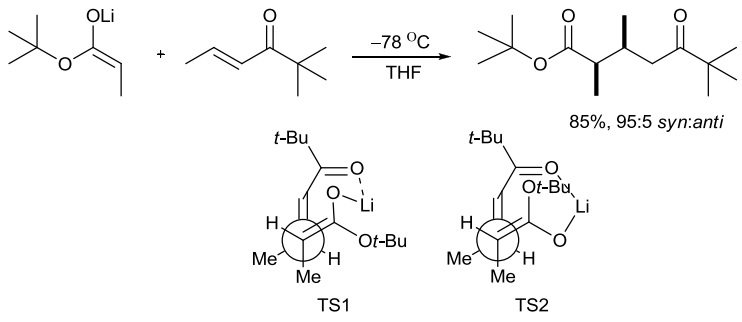
Attempts were made to favour the open transition state by using additives that would increase the solvent complexation of the zinc metal, such as HMPA and TMEDA; however this gave no improvement.

From the proposed transition state, there is also a visible steric effect between the ester and the acetonide in the cyclic transition state. It can be assumed that a larger R group would also disrupt this transition state and favour the desired diastereomer **119**. This effect can be observed when the methyl ester **113a** is used, reducing the dr to 3:1. Conversely the bulky *tert*-butyl ester **113c** gives a single diastereomer **119c** in a 55% yield (Table 2).

R	Yield	119/119'
Me	30-40%	3:1
Et	60%	7:1
t-Bu	55%	1 diastereomer

Table 2: Effects of varying R group of ester

While this postulated transition state goes some way towards explanation of the diastereoselectivity observed in the Michael addition, it has yet to be confirmed, with no further experiments or modelling having been performed in the Prunet group. If the reaction was proceeding through the proposed transition states, use of a highly coordinating additive would be expected to improve diastereoselectivities. However there is precedent for similar transition states, with Heathcock's model for predicting the diastereoselectivity of Michael additions assuming a bridging lithium coordinated by the two oxygen functionalities as in TS1 (Scheme 50).[24] The anti product could be formed via TS2, however this is disfavoured due to the undesirable steric interaction. Recent computational studies by Evans *et al.* validate Heathcock's model,[25] wherein these closed transition states effectively predicted the product of the intermolecular Michael additions.

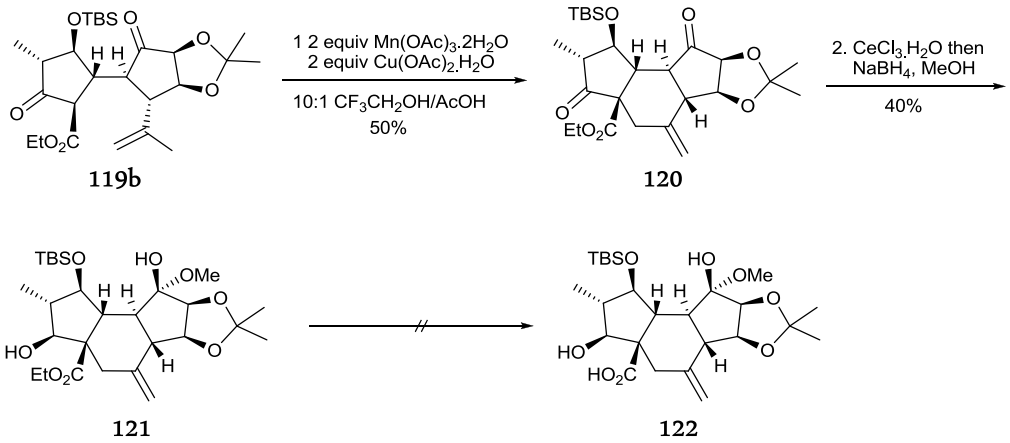


Scheme 50: Heathcock's model for predicting the stereochemistry of Michael additions

In their synthesis of Englerin A,[26] the Chain group utilised a diastereoselective Michael addition proceeding through an 8-membered closed transition state. In their synthesis both the enolate and Michael acceptor are coordinated through their respective oxygens to a

lithium centre. Using the mildly coordinating solvent THF they obtain their desired diastereomer as the major product, in a 2:1 ratio with a number of others. It could be assumed that using a highly coordinating solvent such as DMF, the selectivity would be completely altered.

Using the ethyl ester of the Michael-type adduct **119b**, Snider radical cyclisation was achieved by treatment with manganese(III) acetate, with the optimal solvent found to be a 10:1 mixture of 2,2,2-trifluoroethanol/acetic acid, forming the ABC ring system **120** in 50% yield (Scheme 50). Luche reduction of the ketone of the A-ring proceeded exclusively from the lower face, setting up **121** with the necessary stereochemistry in a 40% yield. This also protects the ketone of the C-ring as a hemiacetal in the same step. Unfortunately at this stage all attempts to form the carboxylic acid **122** from the ethyl ester were unsuccessful; therefore the required decarboxylation could not be achieved.



Scheme 51: Snider radical cyclisation and further transformations

3 - Results and Discussion

3.1 - Project Aim

3.1.1 - Total synthesis of hexacyclinic acid

Despite having its detractors, total synthesis still has an important and necessary role in modern organic chemistry. Total synthesis remains one of the best methods to trial and develop new methodologies – such as Clarke's iodocyclisation in his synthesis of the DEF model or Landais' radical cyclisation of the A-ring. Natural products often pose synthetic challenges which many a chemist seeks to overcome, pushing the boundaries of synthetic organic chemistry.

Another important role of total synthesis is the structural reassignment of misassigned structures and/or stereocentres. With modern analytical techniques constantly improving, it is often possible to completely characterise newly isolated natural product, though often, due to their complexity, this is not always possible and it is here that total synthesis can be of use. One of the most famous and controversial examples of this was in the structural reassignment of hexacyclinol (Fig 6). The originally postulated structure was reported by Gräfe *et al.*,[27] who isolated hexacyclinol as a secondary metabolite from *Panus rudus* fungus. The proposed structure of hexacyclinol contained an unusual strained endoperoxide motif and was assigned by extensive NMR and mass spectroscopy. The total synthesis of this postulated structure was reported by La Clair.[28] However Rychnovsky followed this with a structural reassignment of hexacyclinol, with the endoperoxide absent and the revised structure containing diepoxide moieties. This reassignment was based on computationally calculated ^{13}C NMR.[29] It wasn't until this reassigned structure was synthesised by Porco *et al.* and compared with the sample of natural hexacyclinol that the structure of hexacyclinol could finally be confirmed,[30] with the La Clair paper later being retracted.

As an X-ray structure and Mosher's ester analogue of **1** was obtained, there are no structural ambiguities or misassigned stereocentres to rectify. Nonetheless the total synthesis of **1** is still rightfully viewed as an important task.

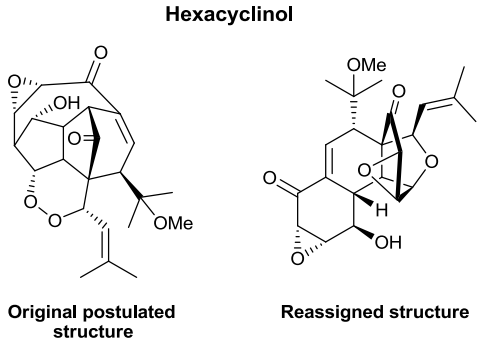


Fig 6: Original postulated structure and reassigned structure of hexacyclinol

Finally, isolated natural products are often viewed as a source of inspiration in the synthesis of novel therapeutic agents. While the structural complexity and low natural abundance of **1** may preclude its use as a therapeutic agent, its synthesis could allow analogues to be made and the active pharmacophore probed, which could potentially aid in the synthesis of a new generation of cytotoxic drugs. Artemisinin is a sesquiterpene natural product isolated from the plant *Artemisia annua,* and is used as a treatment for malaria (Fig 7). The structure contains an unusual peroxide, which is believed to be responsible for its activity. Various semi-synthetic analogues of artemisinin containing this bridging peroxide, such as artesunate, have given rise to a new generation of antimalarials. With the active pharmacophore identified, various entirely synthetic drug candidates containing such a peroxide functional group have been developed, such as arterolane.[31]

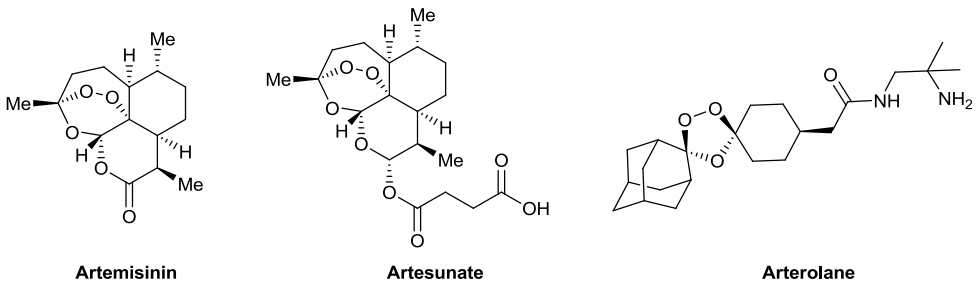
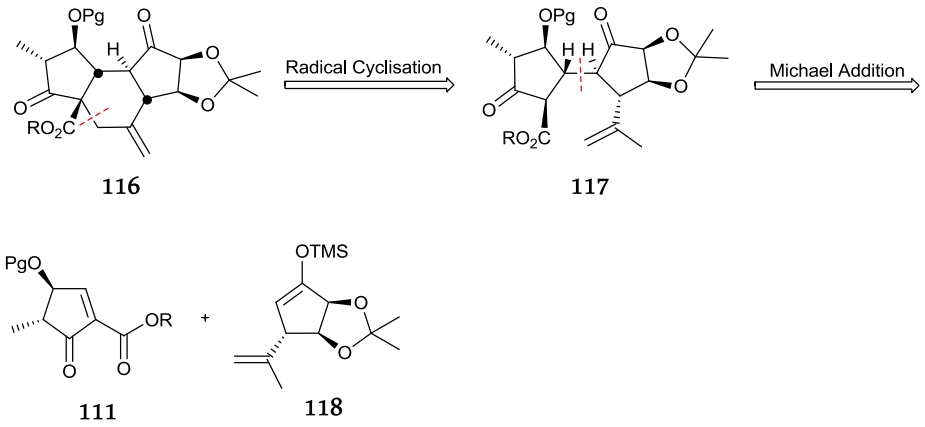


Fig 7: Structures of artemisinin, artersunate and arterolane

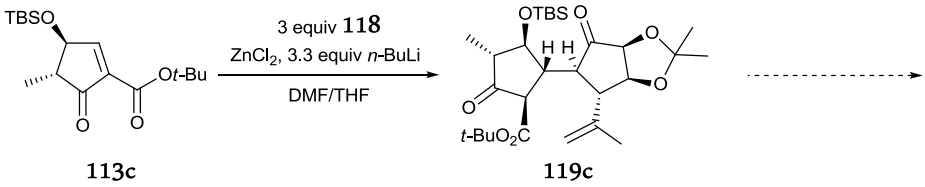
ABC tricycle

Following on from previous work within the Prunet group, the current strategy for the synthesis of the ABC tricycle remains largely unchanged. The route developed within the group, joining the A-ring **111** and the C-ring **118** by a diastereoselective Michael addition and closing the B-ring by a Snider radical cyclisation (Scheme 52). This route is highly convergent, building the chiral A and C-rings before their combination. Another feature of this approach is its novelty, with other groups building the AB or ABC ring systems utilising the Diels-Alder reaction (with the exception of Landais).



Scheme 52: Strategy for synthesis of ABC tricycle within Prunet group

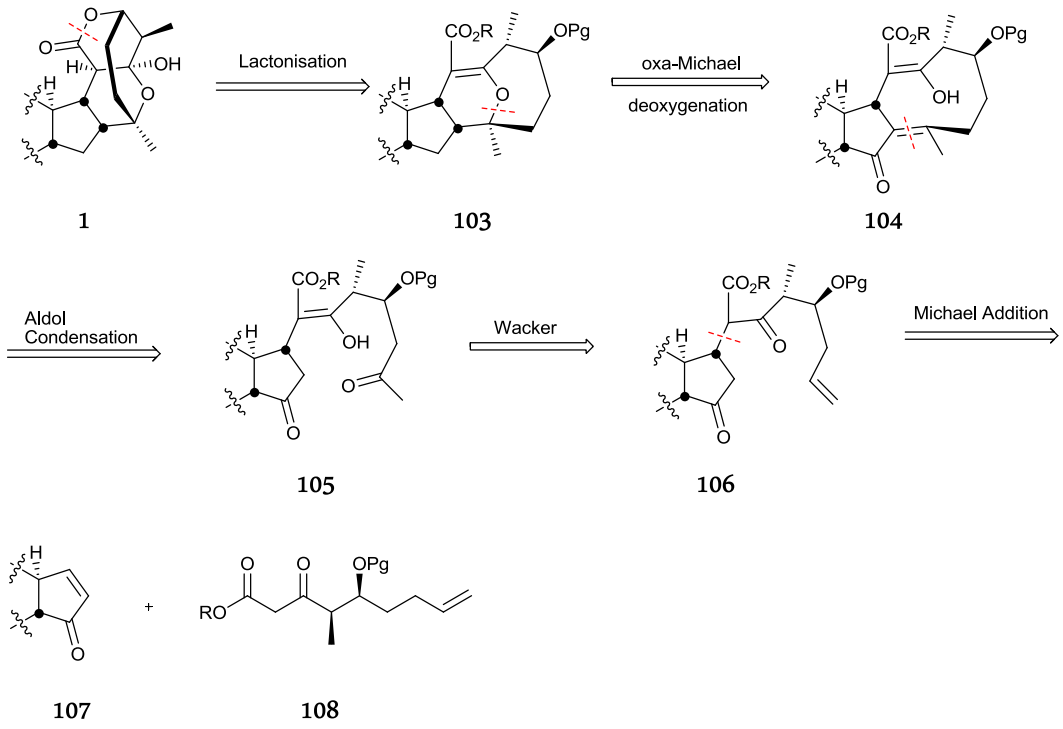
The diastereoselective Michael addition will be performed using the *tert*-butyl ester **113c** as this was previously found to give the best diastereoselectivities and an acceptable yield (Scheme 53). Due to the difficulties previously encountered when trying to hydrolyse the ethyl ether, it is hoped the *tert*-butyl ester will easily removed under acidic conditions. It is also planned to make a 2,2,2-trimethylsilylethanol ester analogue, believing this could be more easily removed using TBAF.



Scheme 53: Strategy for synthesis of ABC tricycle within Prunet group

DEF tricycle

The first work towards the DEF tricycle within the Prunet group will be untaken during this project. Current retrosynthetic strategy in the Prunet group is the same as had been mentioned previously (Scheme 45). The approach for the synthesis of the DEF tricycle is to build the framework **108** utilising the Crimmins aldol reaction to build the stereocentres. Again this highlights the convergent route, building **108** and then grafting it onto the C-ring of the ABC tricycle **107** (Scheme 54). The method features a challenging 9-membered ring **104** (similar to that seen in Clarke's retrosynthesis), with plans to form this ring via an aldol condensation, though due to the inherent difficulties in forming rings of this size, it will be investigated whether this is possible by this method.



Scheme 54: Strategy for synthesis of DEF tricycle within Prunet group

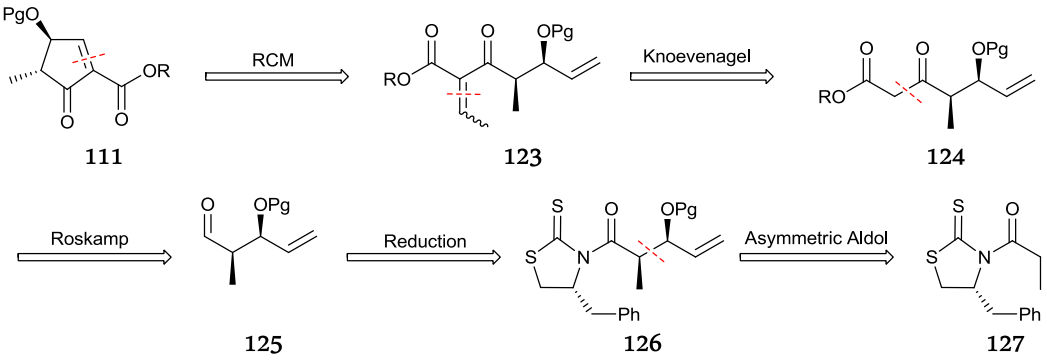
3.2 - Synthesis of ABC system

3.2.1 - Synthesis of A-ring 113c/113d

Retrosynthesis

Disconnecting the C=C enone double bond of **111** affords the dialkene **123**. The electron deficient enone in **111** will be formed by a challenging ring-closing metathesis reaction from enone **123** (Scheme 55). Again disconnecting this C=C enone in **123** gives the β-ketoester **124**. This enone **123** can be accessed by a Knoevenagel condensation from β-

ketoester **124** and acetaldehyde. A C-C disconnection in compound **124**, yields aldehyde **125**. This transformation will achieved by Roskamp homologation with aldehyde **125**. C-C cleavage shows the stereochemistry of the A-ring can be installed by an asymmetric aldol reaction using Crimmins auxiliary **127** and acrolein to form the Evans-type adduct **126**.

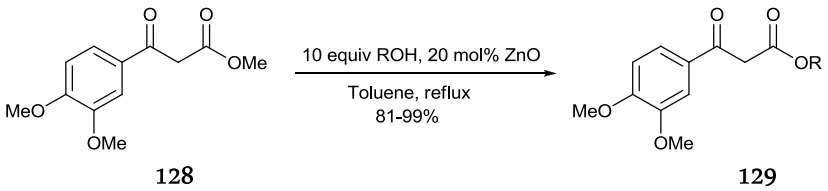


Scheme 55: Retrosynthesis of A-ring **111**

Attempted transesterification of A-ring

Due to the quantities of the methyl ester of the A-ring **113a** available within the group, it was thought that it could participate in a transesterification reaction to the more synthetically useful *tert*-butyl ester **113c** (see Scheme 51).

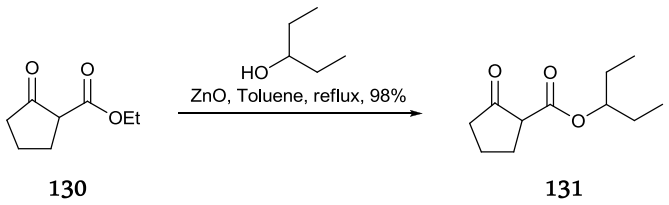
The use of ZnO as an effective catalyst for the transesterification of β-ketoesters was reported by Vallribera *et al*.[32] The transesterification of methyl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate **128** was achieved using 20 mol% of ZnO in toluene under reflux with 10 equivalents of the alcohol (Scheme 56). The reaction was seen to proceed with a primary, secondary and tertiary alcohol furnishing the transesterification product **129** in excellent yields (81—99%) with typical reaction times of 5 hours, though if a volatile alcohol was used, longer reaction times was required for full conversion.



Scheme 56: Transesterifications using ZnO by Vallribera group

While the reaction was optimised with **128**, which contains an aromatic substituent, the reaction scope was extended to aliphatic compounds; ethyl 2-oxocyclopentylcarboxylate

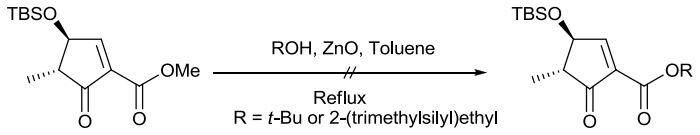
130 undergoes transesterification using 10 equivalents of 3-pentanol, affording product **131** in only 2 hours in 98% yield (Scheme 57).



130 **131**

Scheme 57: Transesterification of aliphatic substrates by Vallribera group

An attempt was made to access the more useful *tert*-butyl **113c** or 2-(trimethylsilyl)ethyl ester **113d** by transesterification of available **113a** using these conditions (Scheme 58); however after several days of reaction time no product was observed with only starting material being recovered. It is likely that the alcohol is attacking the electron deficient alkene, resulting in an oxa-Michael adduct, which could then undergo a reversible Michael reaction. This would account for the lack of desired product.

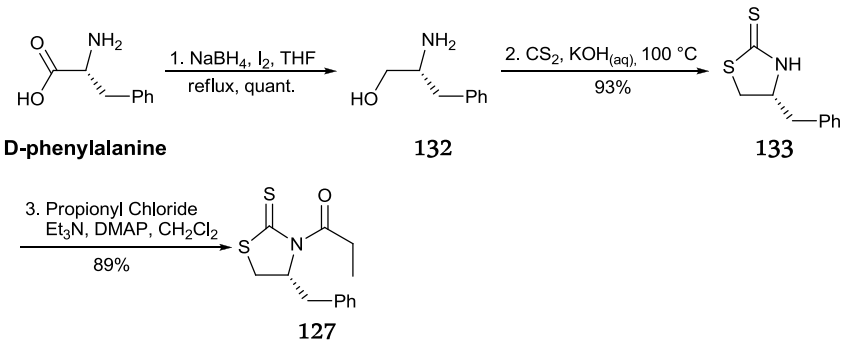


113a **113c/113d**

Scheme 58: Attempted transesterifications of A-ring **113a**

Synthesis of Crimmins chiral auxiliary 127

Synthesis of Crimmins chiral auxiliary **127** utilised D-phenylalanine as the starting material, and started by reducing the carboxylic acid group with BH_3, generated *in situ* with $NaBH_4$ and I_2 (Scheme 59).[33] This formed amino alcohol **132** very efficiently in a quantitative yield. Cyclisation to form the thiazolidinethione **133** was achieved by refluxing CS_2 in a highly basic aqueous KOH solution in an excellent yield.[34] Acylation of the nitrogen of the dithiocarbamate moiety was achieved using propionyl chloride furnishing **127** in good yields over all 3 steps.

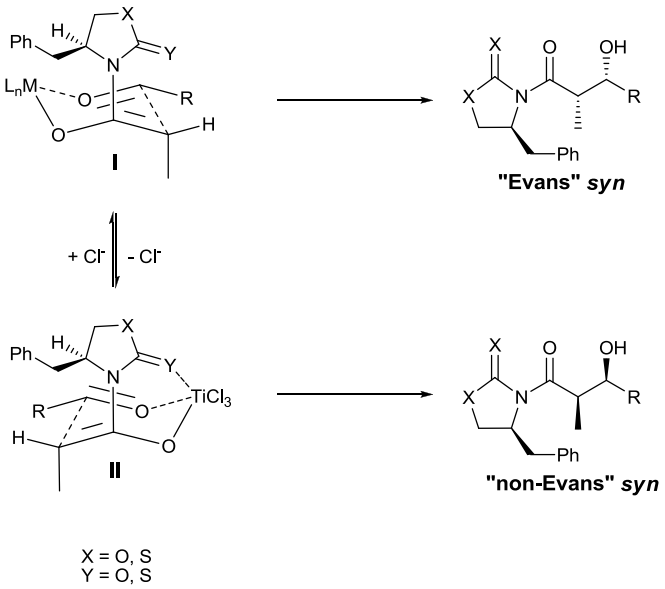


Scheme 59: Synthesis of Crimmins auxiliary **127**

Crimmins asymmetric aldol reaction

Asymmetric aldol reactions are an essential part of the modern synthetic chemists' toolkit, being utilised in a number of syntheses. David A. Evans has been a pioneer in this field, demonstrating the use of dibutylboron enolates of acyl oxazolidinones in asymmetric aldol reactions.[35] This method has been used to prepare a variety of β-hydroxycarbonyl compounds with a high degree of optical purity, often with diastereomeric ratios of >250:1 being achieved. Titanium enolates of oxazolidinones have also been investigated; however these were seen to be less selective than the boron equivalents. Diastereoselectivities were found to be lower (88%–96% de), with a much greater drop observed with α,β-unsaturated aldehydes. In addition, to achieve good reaction rates and conversion, it is necessary to use 2–5 equivalents of aldehyde, which precludes the use of expensive or synthetically complex aldehydes.

The proposed transition state **I** for the formation of the Evans *syn* product is shown in Scheme 60. Following formation of the *Z*-enolate, the molecule reacts via a 6-membered chair transition state to form the Evans *syn* product. If the titanium loses a chloride ion, the reaction could proceed through transition state **II**, with the titanium coordinated to both the aldehyde and the auxiliary. The molecule takes either of these two conformations in order to minimise the dipole interaction. This pathway provides the non-Evans *syn* product, due to the change in π-facial selectivity – reducing the overall diastereoselectivity.



Scheme 60: Transition states of the Evans and Crimmins aldol reactions

Crimmins set about to induce a more highly ordered transition state and greatly increase the diastereoselectivity, investigating the use of an acyl thiazolidinethione or oxazolidinethione auxiliary.[36] Due to the greater affinity of sulfur for titanium (compared to oxygen),[37] it was theorised that the reactions would proceed exclusively through the more rigid transition state **II** (Scheme 60)**.**

The titanium enolates of *N*-acyloxazolinethiones and *N*-acylthiazolinethiones were tested under a variety of different conditions with a diverse range of aldehydes (Scheme 61). It was observed that the yields, conversions and diastereoselectivities were highly dependent on the nature and number of equivalents of the base, as well as the amount of $TiCl_4$ used to generate the titanium enolate. However, it was observed that the best yields and selectivities were obtained using 2.5 equivalents of (−)-sparteine (Fig 8), with the reaction often being complete in 30 seconds to 1 minute. Diastereoselectivities were shown to be exceptional (>98:2 Evans/non-Evans and >99:1 *syn*/*anti*). The reason for this is unclear, though the improved kinetics is possibly due to some effect of the bidentate coordination of (−)-sparteine on the titanium metal (Table 3).

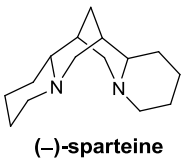
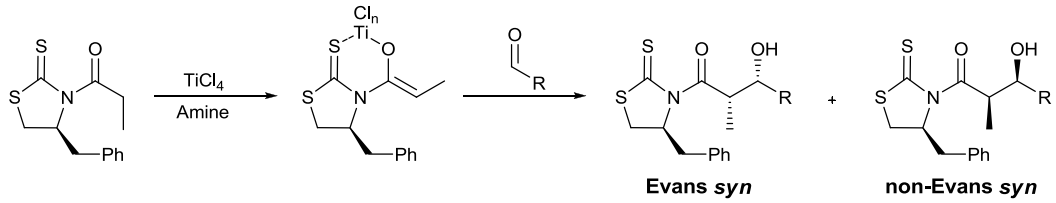


Fig 8: Structure of (−)-sparteine

Because of the high cost of (−)-sparteine, the required 2.5 equivalents posed a problem for Crimmins, particularly if the reaction is to be performed on a large scale. However, the use of 1.0 equivalent of *N*-methylpyrrolidone as an additive allows the number of equivalents of (−)-sparteine to be lowered to 1.0, greatly reducing the cost of the reaction (Table 3). The more Lewis basic amide functionality is able to occupy the coordination sphere of the titanium, while maintaining excellent yields and diastereoselectivities. *N*-Acylthiazolidinethiones were shown to be superior to *N*-acyloxazolidinethiones, in terms of yields and selectivities, and also were more easily cleaved.

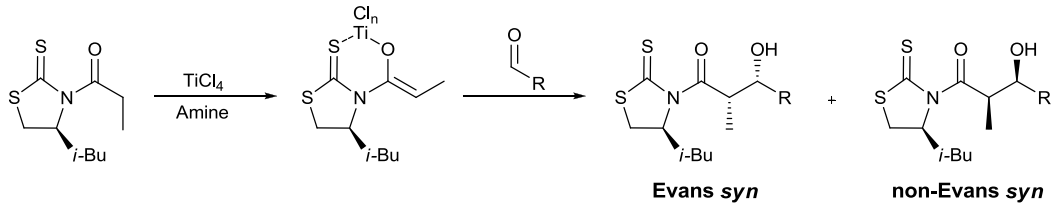


Scheme 61: Generation of titanium enolate and subsequent aldol reaction

Conditions	R	Yield	Evans/non-Evans
1 equiv $TiCl_4$ 2.5 equiv (−)-sparteine	PhCH=CH	66%	99:1
	MeCH=CH	64%	>99:1
	CH_2=CH	77%	>99:1
	Me_2CH	75%	97:3
	Me_2CHCH_2	71%	98:2
1.05 equiv $TiCl_4$ 1 equiv (−)-sparteine 1 equiv NMP	PhCH=CH	77%	99:1
	MeCH=CH	84%	98:2
	CH_2=CH	84%	94:6
	Me_2CH	79%	98:2
	Me_2CHCH_2	74%	96:4

Table 3: Yields and selectivities for Crimmins aldol reactions using (−)-sparteine

It is also possible to use TMEDA as the diamine, mimicking the bidentate effect of (−)-sparteine. While the diastereoselectivities remain excellent, the yields and reaction rate are observed to decrease. However due to the cost and diminishing availability of (−)-sparteine, the use of TMEDA remains a viable reagent for asymmetric aldol reactions (Table 4).

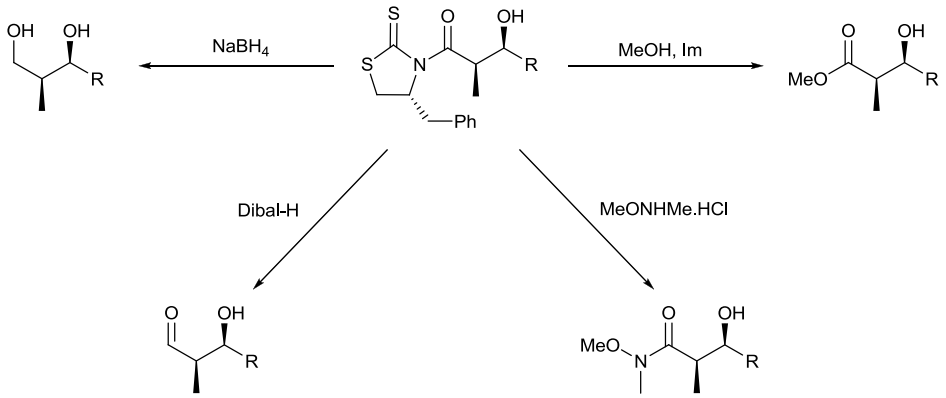


Scheme 62: Generation of titanium enolate and subsequent aldol reaction

Conditions	R	Yield	Evans/non-Evans
1.0 equiv $TiCl_4$ 2.5 equiv (−)-sparteine	PhCH=CH	80%	96:4
	MeCH=CH	66%	>99:1
	CH_2=CH	72%	>99:1
	Me_2CH	84%	95:5
	Me_2CHCH_2	81%	97:3
1.0 equiv $TiCl_4$ 2.5 equiv TMEDA	PhCH=CH	75%	98:2
	MeCH=CH	53%	>99:1
	CH_2=CH	42%	>99:1
	Me_2CH	57%	96:4
	Me_2CHCH_2	60%	96:4

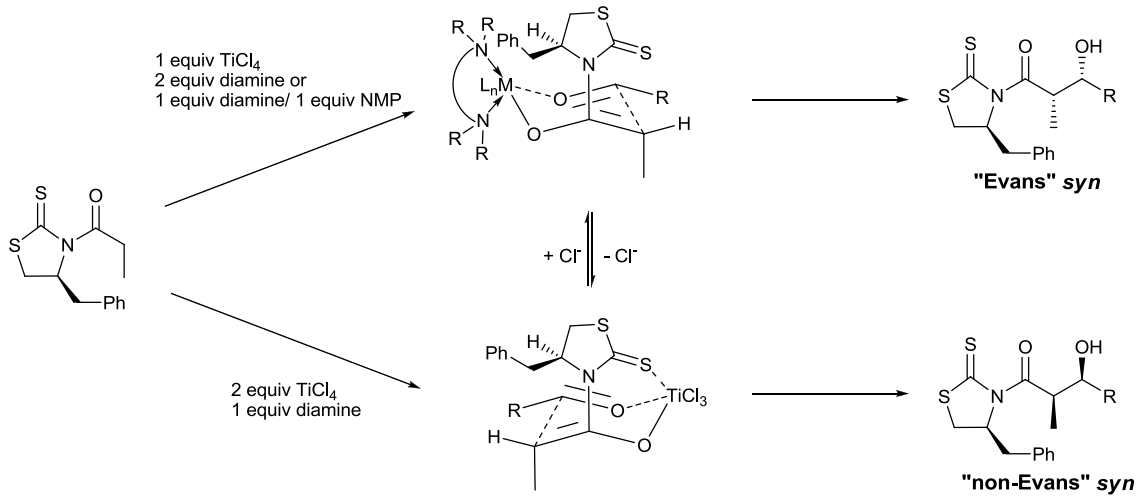
Table 4: Comparison of TMEDA to (−)-sparteine in Crimmins aldol reactions

As with the equivalent oxazolidinone aldol adduct, a variety of methods can be used for the cleavage of the thiazolidinethione auxiliary. Of particular mention however is the direct transformation to the aldehyde by treatment with Dibal-H; with the equivalent oxazolidinone it is necessary to convert the group to a Weinreb amide before reduction with Dibal-H (Scheme 63).



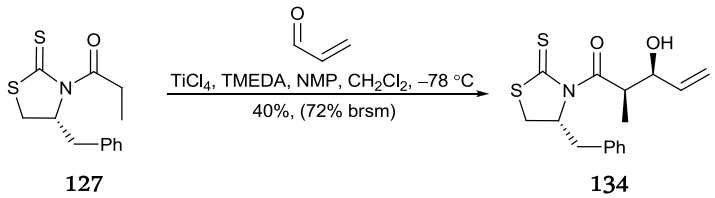
Scheme 63: Methods for cleavage of Crimmins auxiliary

It is interesting to note that excellent yields and diastereoselectivities were also observed for the *syn* non-Evans product by altering the reagent quantities, with the use of 2.0 equivalents of $TiCl_4$ and 1 equivalent of (−)-sparteine favouring the non-Evans aldol adduct. Based on the proposed transition states for the asymmetric aldol reactions, an excess of $TiCl_4$ in relation to the diamine forms the non-Evans product, proceeding through the more rigid transition state where the titanium is coordinated to the sulfur of the auxiliary. With an excess of diamine the titanium is chelated, favouring the 'open' transition state and the Evans type product (Scheme 64).



Scheme 64: Effect of number of equivalents of base on diastereocontrol

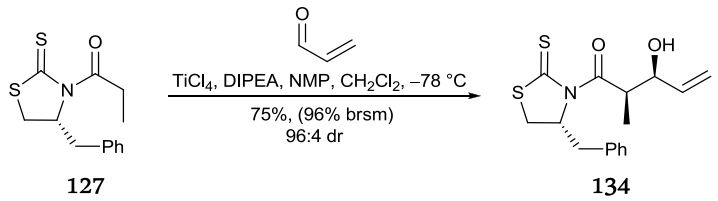
As was done previously within the group, synthesis of the A-ring began with an asymmetric aldol reaction of auxiliary **127** with acrolein (Scheme 65). However, utilising the conditions that had been used previously, with 1 equivalent of TMEDA and NMP, the reaction was sluggish, with yields of around 40% for the formation of **134**.



Scheme 65: Crimmins aldol of **127** and acrolein

Due to the modest yields using TMEDA, and the cost/unavailability of (−)-sparteine, it was necessary to find an improved procedure for asymmetric aldol reactions. Fortunately substituting TMEDA for DIPEA, and using a slight excess (1.1 equivalents) of acrolein,

the reaction proceeded smoothly in CH_2Cl_2 at −78 °C, giving the desired adduct **134** in a 78% yield with a 96:4 ratio of the Evans/non-Evans product (Scheme 66).[38]



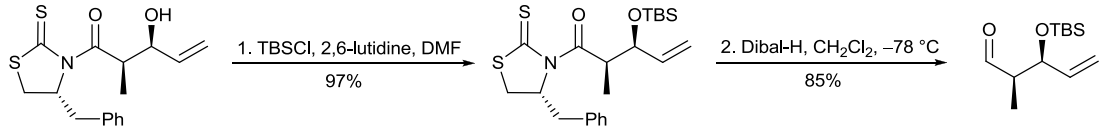
127 134

Scheme 66: Crimmins aldol **127** and acrolein using DIPEA

It should be noted that chiral auxiliary **127** is synthesised from D-phenylalanine, which is the more expensive enantiomer. When the aldol reaction was performed using an auxiliary prepared from the natural enantiomer (L-phenylalanine), 2 equivalents of $TiCl_4$ and 1 equivalent of TMEDA very poor yields of product were obtained. However, these reactions were performed towards the beginning of the project, and repeating the reaction using DIPEA as a base should allow the aldol reaction to be done in a more cost effect manner.

Protection and Cleavage of auxiliary

Protection of the aldol adduct **134** as a TBS ether with TBSCl forming **135** proceeded near quantitatively (Scheme 67), followed by Dibal-H cleavage of the auxiliary to furnish aldehyde **136** in 85% yield, along with the recovered auxiliary **133** (85%).

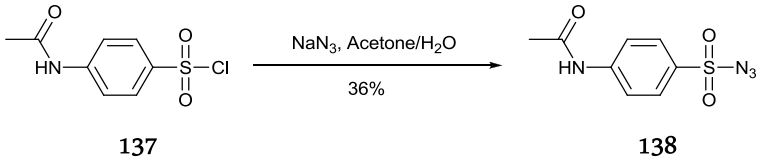


134 135 136

Scheme 67: TBS protection and Dibal-H reduction to form aldehyde **136**

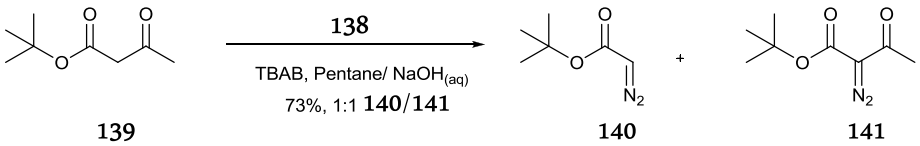
Roskamp Homologation and Knoevenagel reactions

For the formation of the alkyl diazoacetate reagents required for the Roskamp homologation, it was necessary to synthesise *N*-acetylsulfanilyl azide **138** as the diazo transfer reagent (Scheme 68). This was achieved by reaction of *N*-acetylsulfanilyl chloride **137** with NaN_3 in acetone, with addition of water precipitating **138** in a 36% yield.[39]



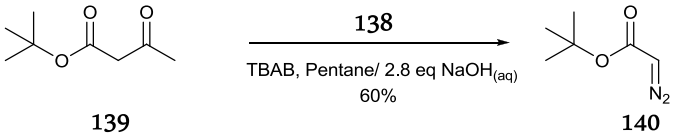
Scheme 68: Synthesis of *N*-sulfanilylazide **138**

Using previous conditions for the synthesis of diazoacetates, treatment of *tert*-butyl acetoacetate **139** with *N*-acetylsulfanilyl azide in pentane/H_2O with 1.8 equivalents of NaOH and a substoichiometric amount of TBAB as a phase transfer catalyst gave the desired diazoacetate **140** along with the byproduct **141** (Scheme 69) in a 1:1 ratio.



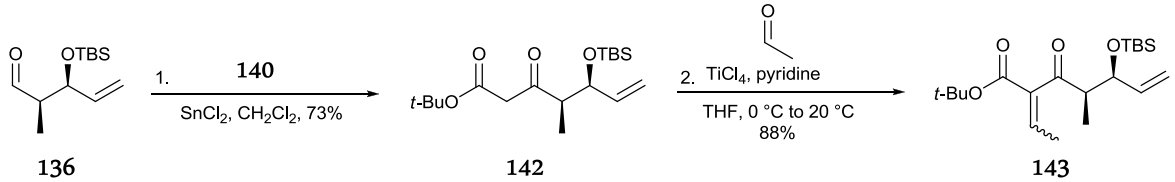
Scheme 69: Attempted formation of diazoacetate **140**

However a simple alteration of the procedure, increasing the number of equivalents of NaOH to 2.8, gave only one product, the desired diazoacetate **140** in a 60% yield (Scheme 70).[40]



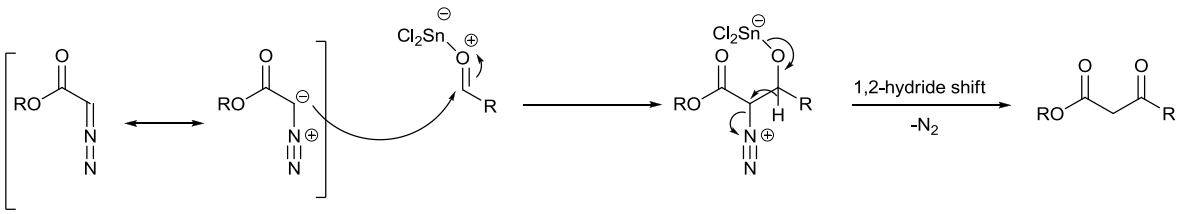
Scheme 70: Improved formation of diazoacetate **140**

Roskamp homologation of aldehyde **136** was accomplished using 2 equivalents of *tert*-butyl diazoacetate **140** with 0.5 equivalents of $SnCl_2$ in dichloromethane, affording β-ketoester **142** in 73% yield (Scheme 71). Further functionalisation to the cyclisation precursor was achieved by a Knoevenagel condensation; formation of the titanium enolate using $TiCl_4$, which then condensed with acetaldehyde, led to the α,β-unsaturated moiety in **143** as an inseparable 1.5:1 mixture of geometric isomers in an excellent 88% yield.



Scheme 71: Formation of cyclisation precursor **143**

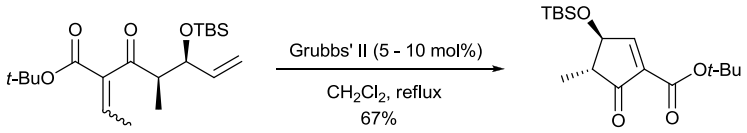
The mechanism for the Roskamp homologation begins with coordination of the aldehyde to the Lewis acidic $SnCl_2$, which enhances the electrophilicity of this substrate (Scheme 72). It is then attacked from the α-position of the alkyl diazoacetate. Removal of $SnCl_2$ to reform the ketone results in a 1,2-hydride shift, eliminating a molecule of N_2 to form the desired β-ketoester product.



Scheme 72: Mechanism of Roskamp homologation

Ring-closing metathesis to form 113c

Ring-closing metathesis of **143** using Grubbs' 2nd generation catalyst in dichloromethane at reflux afforded the A-ring **113c** in 67% yield (Scheme 73). This reaction was observed to be slower using the *tert*-butyl ester compared to the methyl or ethyl analogues, requiring two days for complete conversion. It is thought that the methyl group of the trisubstituted alkene leads to a more electron rich alkene for the ring closing metathesis. However due to the high amount of Grubbs catalyst required - 5 mol%, although up to 10 mol% of catalyst may be required - the hindered alkene may be hampering the reaction.



143 113c

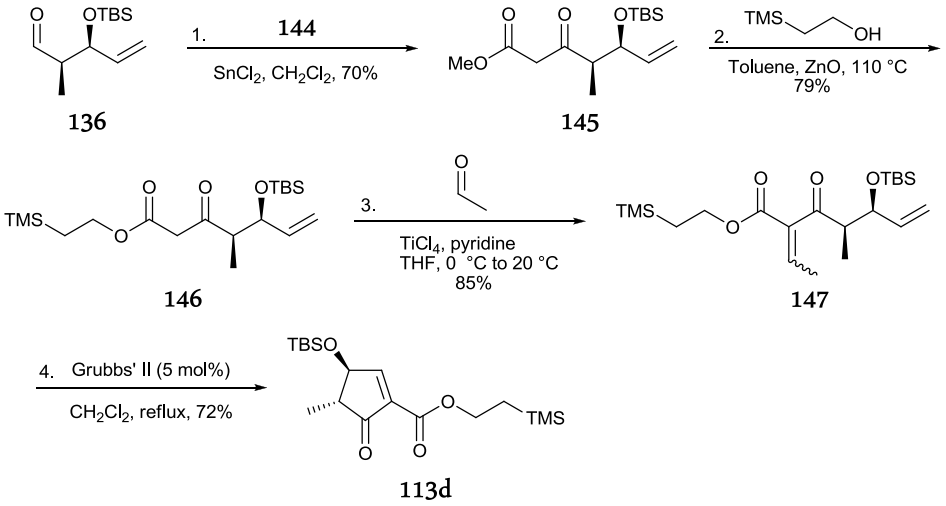
Scheme 73: Ring-closing metathesis of **143** forming A-ring **113c**

Structural assignment of **113c** was relatively straightforward, with the characteristic doublet at 7.67 ppm of the electron deficient alkene indicating cyclisation has occurred. (Appendix – page 163).

Synthesis of 2-(trimethylsilyl)ethyl A-ring 113d

Due to the failed transesterifications using the A-ring **113a**, it was decided to introduce the 2-(trimethylsilyl)ethyl ester at an earlier stage. Roskamp homologation of aldehyde **136** with methyl diazoacetate **144** gave the methyl β-ketoester **145** in a 70% yield (Scheme 74).

Treatment of **145** with 10 equivalents of 2-(trimethylsilyl)ethanol and 20 mol% of ZnO in toluene at 110 °C for 12 hours successfully formed the transesterification product **146** in 79% yield. As before, Knoevenagel condensation and ring-closing metathesis from **147** formed the 2-(trimethylsilyl)ethyl A-ring **113d** in good yields for both steps.

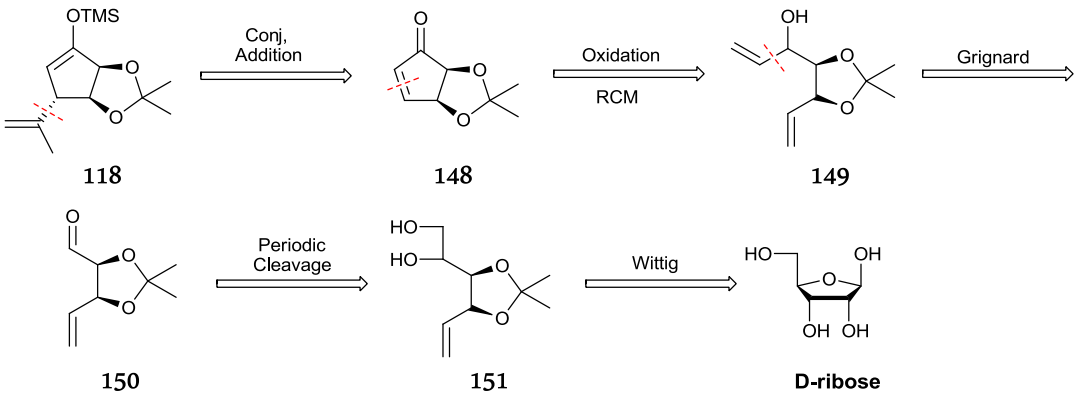


Scheme 74: Synthesis of 2-(trimethylsilyl)ethyl ester **113d**

3.2.2 - Synthesis of C-ring 12

Retrosynthesis

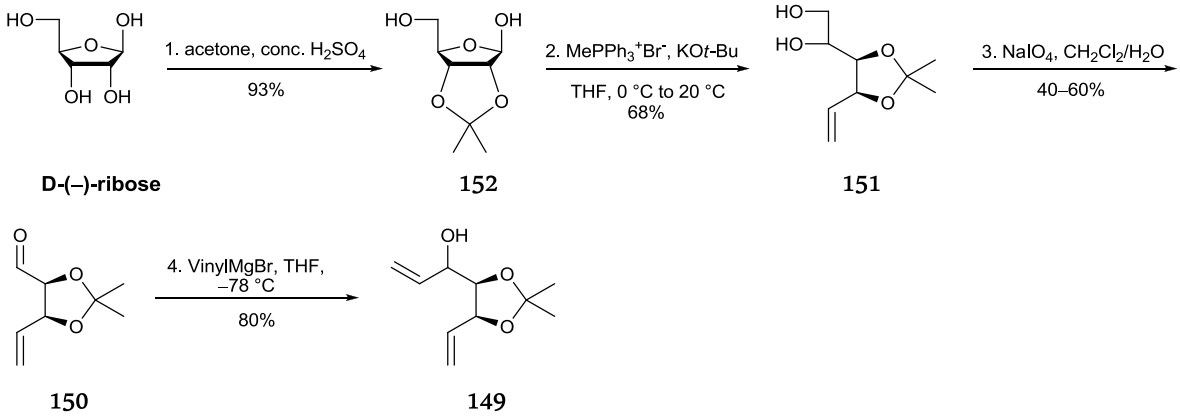
Functional group interconversion of the silyl enol ether, followed by C-C cleavage shows that the silyl enol ether **118** will be formed by a conjugate addition of isopropenylmagnesium bromide to chiral cyclopentenone **148**, trapping the enolate with TMSCl (Scheme 75). Synthesis of **148** follows reported literature procedures, using a chiral pool synthesis from D-(−)-ribose.[41]



Scheme 75: Retrosynthesis of silyl enol ether **118**

Synthesis of diene 149

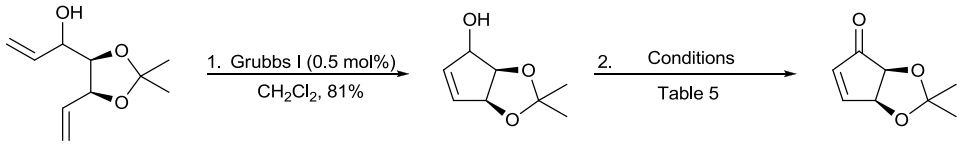
Protection of D-(−)-ribose using acetone and catalytic H_2SO_4 provided the acetonide **152**, which was used in the next step without further purification (Scheme 76).[42] Wittig reaction of the aldose form of **152** using methyltriphenylphosphonium bromide and KO-*t*Bu afforded the diol **151** in 68% yield. Cleavage of the vicinal diol using sodium periodate in a CH_2Cl_2/H_2O solvent mixture formed the corresponding aldehyde **150**, although the yield was not reproducible varying between 40% and 60%. This was attributed to volatility and instability of the aldehyde; because of this the aldehyde was used straight away in the next step, and reacted with vinylmagnesium bromide to form allylic alcohol **149** as an inseparable 2:3 mixture of diastereomers.[41a, 42]



Scheme 76: Synthesis of diene **149** from D-(−)-ribose

Ring-closing metathesis and oxidation

Formation of the C-ring was accomplished by ring-closing metathesis of **149**, with a very low catalyst loading of 0.5 mol% of Grubbs' 1st generation catalyst, effecting closure of the cyclopentenone ring in 4 hours (Scheme 77).[43] The crude allylic alcohol **153** was carried over to the next step without purification. Oxidation of **153** using MnO_2, as reported in the literature, was unsuccessful leading only to product degradation. Swern oxidation gave the desired product in a 93% yield;[44] however when the reaction scale was increased, the yield was not reproducible, dropping to 47%. It was reported by Finney *et al.*, that IBX oxidations could be performed in common organic solvents, taking advantage of the partial solubility of IBX at higher temperatures.[45] The IBX residue could then just be filtered off, simplifying the product purification. Ultimately oxidation using IBX was found to be the best solution, forming the desired enone **148** in a scalable 90% yield (Table 5).



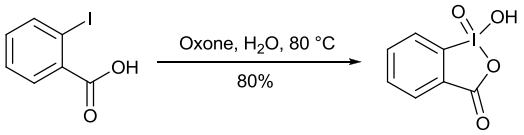
149 153 148

Scheme 77: RCM and oxidation to form **148**

Conditions	Yield
10 equiv MnO_2, CH_2Cl_2	Decomposition
5 equiv MnO_2 (activated), CH_2Cl_2	Decomposition
2.5 equiv DMSO, 1.4 equiv oxalyl chloride, 5 equiv NEt_3, CH_2Cl_2, −78 °C	93%
2.5 equiv DMSO, 1.4 equiv oxalyl chloride, 5 equiv NEt_3, CH_2Cl_2, −78 °C*	47% + unidentified side product
3 eq. IBX, EtOAc	90%

Table 5: Oxidation conditions - * on large scale (>10 g)

An improved synthesis of IBX was reported from 2-iodobenzoic acid **154** using Oxone® as the oxidant (Scheme 78). This proceeds well under fairly mild conditions, without the need for $KBrO_3$ and a highly acidic environment. The IBX **155** formed is also of a higher purity with less shock sensitive impurities.[46]

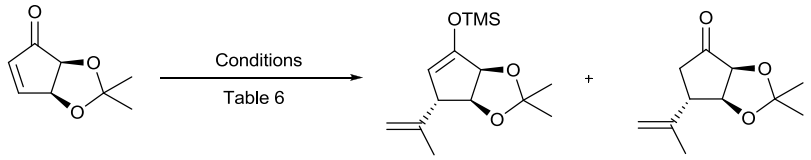


154 155

Scheme 78: Synthesis of IBX **155**

Conjugate addition

Introduction of the isopropenyl group in **118** by *in situ* generation of the lithium isopropenyl reagent using 2-bromopropene and *tert*-BuLi,[47] and using CuI as the copper source, resulted in very poor yields. Using commercially available isopropenylmagnesium bromide gave improved yields, with $CuBr.SMe_2$ found to be the optimal copper source. The best yield was obtained using HMPA as an additive; however, due to its high toxicity, TMEDA was used instead for larger scale reactions (Table 6). To isolate the highly labile silyl enol ether **118**, it was necessary to use oven-dried silica gel (dried in the oven for 3 days at 120 °C) for column chromatography, with humid silica leading to rapid hydrolysis of the silyl group.



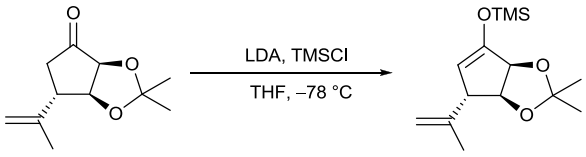
148 118 118'

Scheme 79: Conjugate addition of isopropenyl group to **148**

Conditions	Yield –118/118’
2 equiv 2-bromopropane, 4 equiv *t*-BuLi, 1 equiv CuI, Et_2O, −78 °C	-
1.4 equiv isopropenylmagnesium bromide, 0.1 equiv CuBr.SMe_2, 2.8 equiv HMPA, 3 equiv TMSCl, THF , −78 °C	41%/60%
1.4 equiv isopropenylmagnesium bromide, 0.1 equiv CuBr.SMe_2, 2.8 equiv TMEDA, 3 equiv TMSCl, THF , −78 °C	34%/59%

Table 6: Conditions for conjugate addition to **148**

Transformation of **118’** to **118** was easily achieved by treatment with LDA, trapping the resulting enolate with TMSCl (Scheme 80). When the reaction was repeated using LiHMDS instead of LDA, only trace amounts of the desired product were isolated.



118' 118

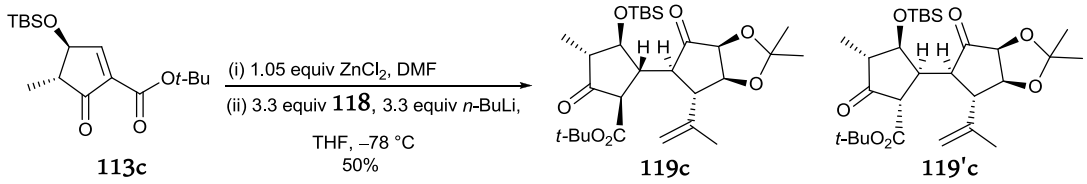
Scheme 80: Conversion of **118’** to **118** using LDA

3.2.3 - Diastereoselective Michael addition

With both optically pure partners in hand, attempts could be made for the diastereoselective conjugate addition of **118** to **113c** (Scheme 81). As has previously been mentioned, a highly polar 4:1 DMF/THF solvent mixture favours formation of the desired diastereomer, with the use of THF necessary for the formation of the lithium enolate of **118** and to ensure the solution is liquid at −78 °C. Using the ethyl ester, satisfactory yields and diastereoselectivities were obtained, however hydrolysis of the ethyl ester could not be achieved. The methyl ester was too reactive and gave poor yields and selectivities, however, the *tert*-butyl ester forms only a single diastereomer, which could then potentially be cleaved under acidic conditions. The 2-(trimethylsilyl)ethyl ester was expected to give

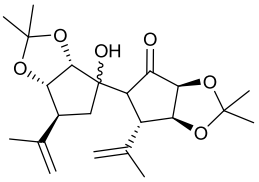
results similar to the ethyl ester; however removal of the ester can be achieved by treatment with TBAF.

Using the *tert*-butyl ester **113c**, attempts were made utilising the conditions previously optimised in the group. Using 1.05 equivalents of $ZnCl_2$ as the Lewis acid and slowly adding 3.3 equivalents of the lithium enolate of donor **118**, poor yields of less than 20% of the Michael product were obtained. In addition, the major product of the reaction was found to be **156**, a dimer of the C-ring (Fig 9). These low yields and formation of the dimer **156** were attributed to traces of water in the reaction, quenching the enolate of **118** prematurely. A dramatic improvement in yield was obtained by changing the order of addition of the reagents, switching to the slow addition of the A-ring **113c** DMF solution to the solution containing the lithium enolate. The best results were obtained by slowly increasing the temperature from −78 °C to −10 °C over 4 hours, with the reaction seen to begin around −40 °C, giving the adduct **119c** in 50% yield. However, contrary to work previously performed in the group, the product was isolated as a 3:1 mixture **119c** to the undesired diastereomer **119'c** (Scheme 81).



113c 119c 119'c

Scheme 81: Diastereoselective Michael addition of **113c**

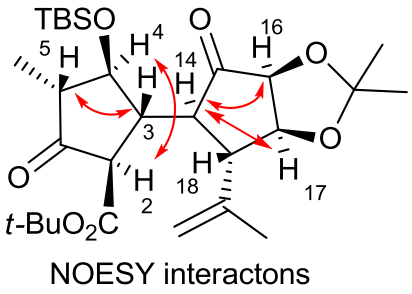


156

Fig 9: C-ring dimer **156**

The ^{1}H NMR spectra indicated the product formed contained two alkenic protons, with COSY data showing these signals coupling exclusively to each other – consistent with the terminal alkene in the product (Appendix, page 165). The product was seen to contain two *tert*-butyl groups as would be expected. All three methyl groups are seen indicating coupling of the A and C-rings. Disappearance of the electron deficient A-ring alkene and formation of a new ddd signal corresponding to the C^3 C-H confirms Michael addition of the two rings. NOESY spectra confirms the desired product as the major diastereomer. On

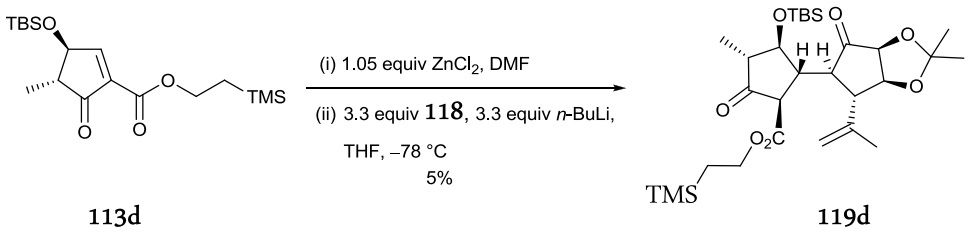
the A-ring the *syn* relationship between the H^2/H^4 and the H^3/H^5 hydrogens can be seen. Similarly this *syn* relationship is seen on the C-ring the $H^{14}/H^{16}/H^{17}$ hydrogens.



NOESY interactons

Fig 10: NOESY interactions of **119c**

Diastereoselective reaction of the 2-(trimethylsilyl)ethyl ester **113d** using the original conditions gave only impure trace amounts of the desired Michael product **119d** (Scheme 82), with the major product being the dimer **156**. However this reaction was performed early on in the project before the *tert*-butyl analogue **119c** had been accessed. Using the altered conditions (addition of the Michael acceptor to the enolate solution) it should be possible to afford **119d** in a practical yield.



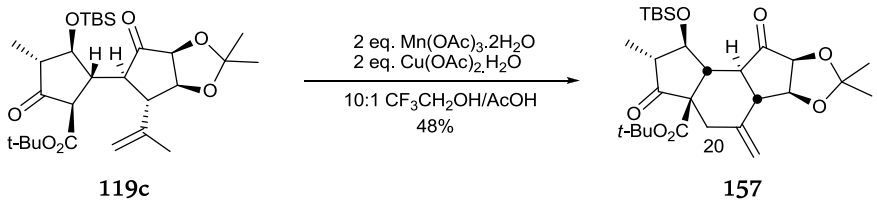
113d **119d**

Scheme 82: Diastereoselective Michael-type addition of ester **113d**

3.2.4 - Formation of the B ring – 6-*endo-trig* radical cyclisation

Closure of the B-ring will be achieved as before by a Snider radical cyclisation from **119c**, which is accessed from the Michael-type addition as a mixture of diastereomers. It had been shown previously in the group that the solvent used had a large effect on the yield of the reaction, with the more acidic solvent such as acetic acid giving improved yields.[48] However, due to the presence of the acid sensitive acetonide, these yields were not reproducible. After further experimentation, the optimal solvent was found to be 2,2,2-trifluoroethanol using acetic acid as a co-solvent in a 10:1 mixture, which was necessary to give full dissolution of the copper. Snider radical cyclisation was achieved by dissolving **119c** in a 10:1 solvent mixture of 2,2,2-trifluoroethanol/acetic acid and 2 equivalents each

of $Mn(OAc)_3.3H_2O$ and $Cu(OAc)_2.H_2O$ (Scheme 83). The reaction was seen to be complete after 2 hours and ABC tricyclic system **157** was isolated in 48% yield.



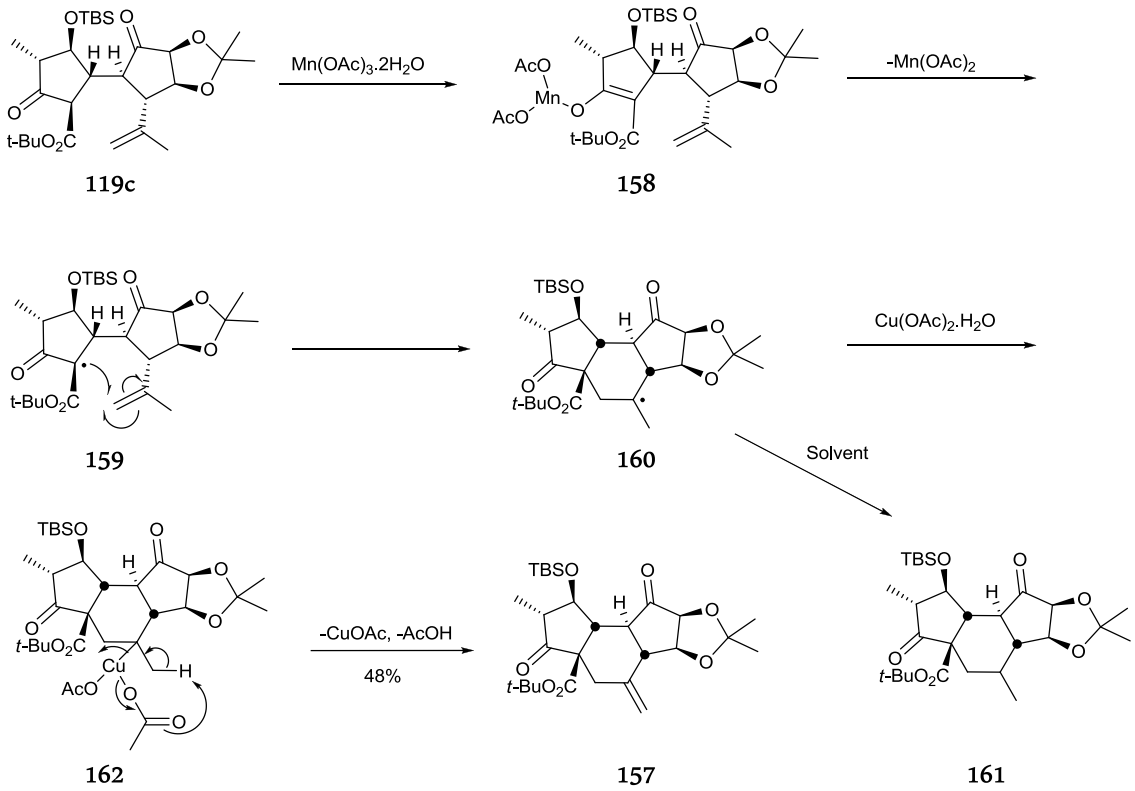
119c **157**

Scheme 83: Snider radical cyclisation of **119c**

Although the cyclisation has been achieved, purification of the product proved to be exceedingly difficult, with a large number of impurities that could not be removed (Appendix, page 168), making assignment of peaks complicated. A new signal was also observed at 2.90 ppm, with a large germinal coupling (J = 14.8 Hz) corresponding to the H^{20} position of the 6-membered B-ring. Disappearance of the H^2 doublet was also observed, indicating cyclisation occurring from this position. Following tentative assignment of signals, the structure was supported by mass spectrometry showing the desired mass.

Mechanism

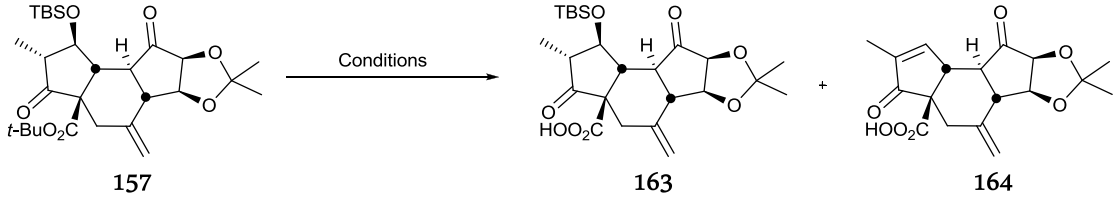
Snider *et al*, reported the radical cyclisation of β-ketoesters onto olefins; the mechanism takes place as follows (Scheme 84). Using $Mn(OAc)_3.2H_2O$ as a source of manganese(III), this generates the manganese enolate **158**, with an elimination of manganese(II) forming the α-radical species **159**. This radical then reacts in a 6-*endo-trig* fashion to form the 6-membered B-ring, forming the tertiary radical **160**. According to Baldwin's rules, a 5-*exo-trig* cyclisation is also possible, however this is disfavoured due to the highly strained system that would be formed. Without $Cu(OAc)_2.H_2O$, oxidation of the primary radical species is slow, with the saturated product **161** being formed instead by proton abstraction from the solvent. However, when the copper is present in the reaction, the tertiary radical is trapped forming the copper(III) intermediate **162**. Elimination of Cu(OAc) and AcOH generates the exocyclic double bond, forming **157** in 48% yield.[49]



Scheme 84: Mechanism of Snider radical cyclisation

3.2.5 – Attempted removal of *tert*-butyl ester

As use of the ethyl ester led to difficulties, with all attempts to hydrolyse it unsuccessful, it was believed that the *tert*-butyl ester could be easily removed under acidic conditions. Attempts to remove the ester group using TMSOTf were unsuccessful, leading to product degradation (Scheme 85). Using a 2:1 mixture of trifluoroacetic acid and CH_2Cl_2 at 0 °C, a new product was seen by TLC. As this was more polar than the startng material **157** it was hoped to be the carboxylic acid **163**. Unfortunately the new product turned out to be the elimination product **164** isolated, with the doublet at 7.10 ppm indicating elimination had occurred, with formation of the electon deficient alkene. Dilution of the TFA had no effect on the yield (Table 7). Although the removal of the *tert*-butyl ester was unsuccessful, the reaction was trialled on a very small scale (~10 mg), and the conditions used were by no means exaustive. The use of triethylsilane to trap the formed carbocation is the reaction mix might also lead to improved yields. However it must be considered that the ester is too hindered to be removed.[50]



157 163 164

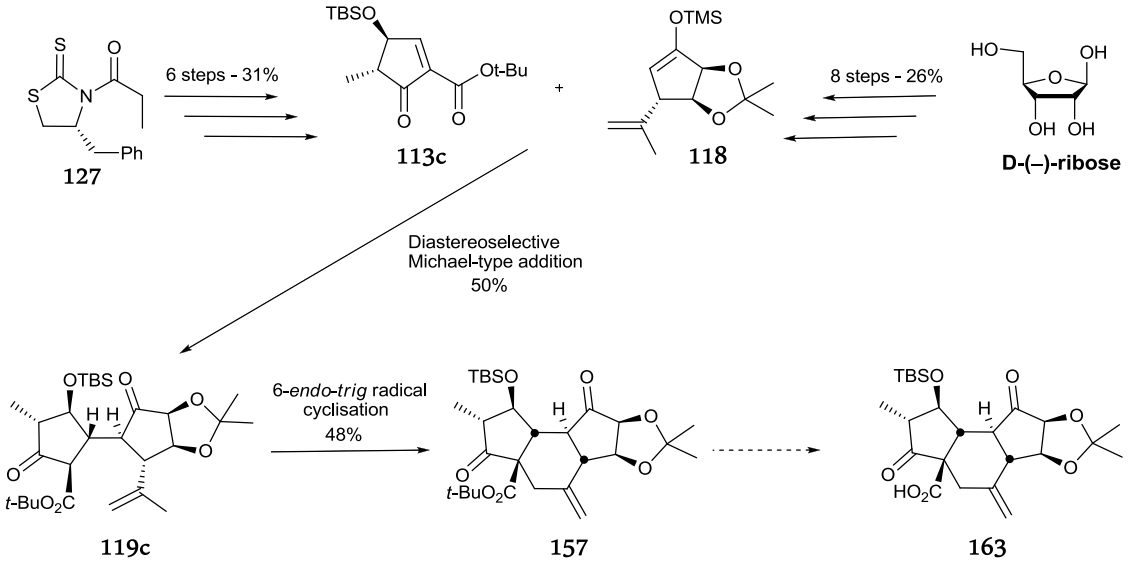
Scheme 85: Removal of *t*-butyl ester from **157**

Conditions	163/164
1.5 equiv TMSOTf, 3 equiv NEt_3, CH_2Cl_2, −78°C	Degradation
2:1 CH_2Cl_2/TFA, 0 °C	0%/7%
10:1 CH_2Cl_2/TFA, 0 °C	0%/5%

Table 7: Attempted removal of *t*ert-butyl ester

3.2.6 – Conclusions and Future Work

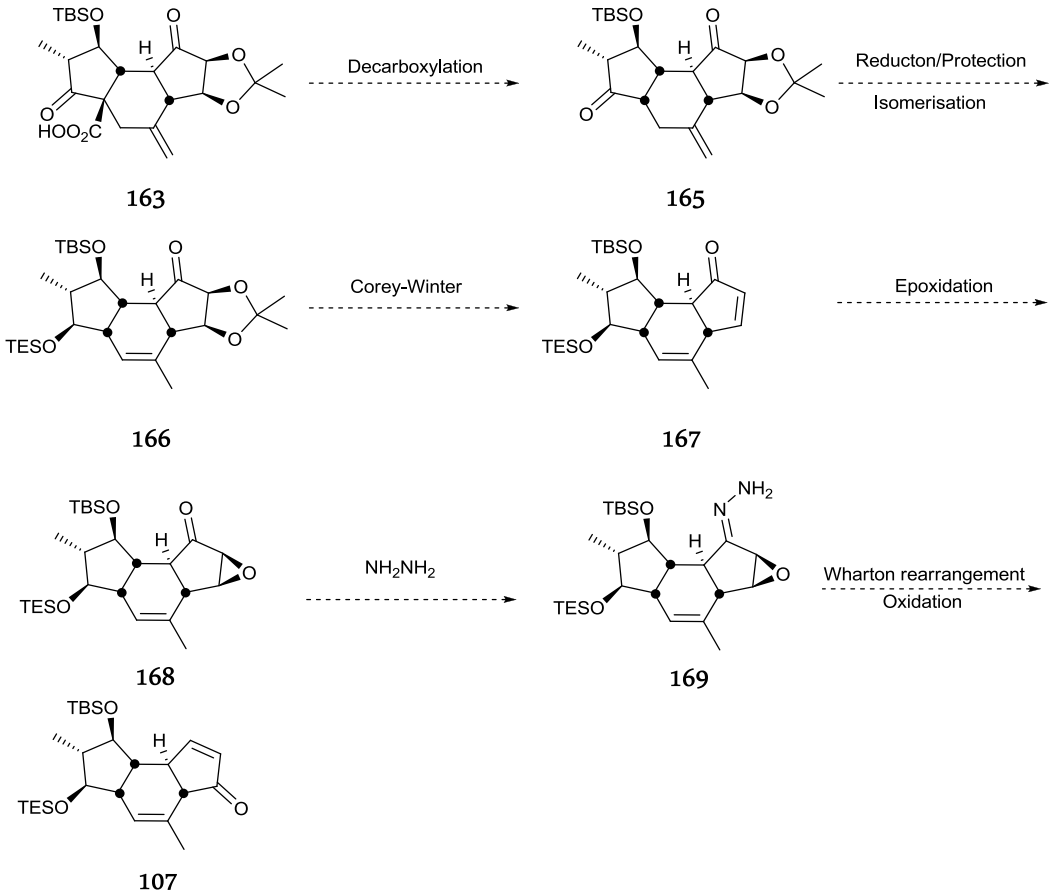
Enantiopure synthesis of *tert*-butyl double Michael acceptor **113c** from Crimmins auxiliary **127** has been achieved in 7 steps in a 30% overall yield (Scheme 86). Of particular mention is the improvement of the Crimmins aldol reaction by substituting TMEDA for DIPEA, giving greater and reproducible yields. Silyl enol ether **118** has been prepared from D-(−)-ribose in 8 steps in 26% overall yield. While this procedure is scalable, it would be ideal if the number of steps could be reduced, however for the moment it remains the best method. The key diastereoselective Michael-type addition of **118** and **113c** to form adduct **119c** has been achieved in a 50% yield, though modifications of the procedure were required to access the product in a reasonable yield. Snider radical cyclisation afforded the ABC tricyclic ring system **157** in a 48% yield, although running this reaction on a larger scale could give an improvement in the yield and possibly make purification easier. Removal of the *tert*-butyl ester has been trialled on very small scale, giving the elimination product **164** with OTBS elimination; however the reaction still needs to be optimised. If the removal of the *tert*-butyl ester is unsuccessful, the reaction should be repeated with the 2,2,2-(trimethylsilyl)ethyl ester analogue, which could hopefully be removed using TBAF or another fluorinating agent. However this may also remove the TBS group.



Scheme 86: Summary of work towards ABC tricycle

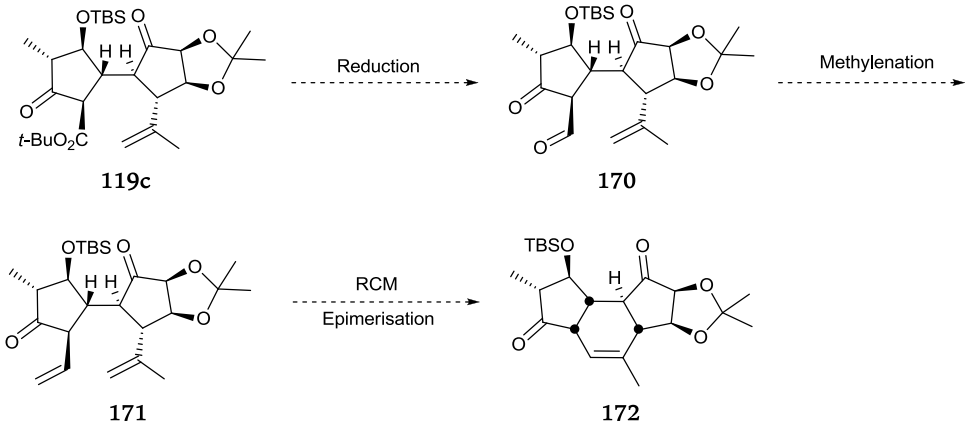
While some progress has been made towards completion of the ABC tricycle utilising the *tert*-butyl analogue, the synthesis has reached a similar point previously reached within the group, with many steps remaining to complete the ABC tricycle. Closure of the B-ring has been achieved as before, although the yield remains moderate. Attempts to remove the superfluous *tert*-butyl ester were unsuccessful.

Following removal of ester moiety, the next step would be the decarboxylation to form **165** (Scheme 87). While many conditions exist to effect this, we would first investigate a Barton decarboxylation.[51] Reduction of the ketone should proceed stereoselectively from the lower face, followed by protection of the resulting alcohol a silyl ether. It is necessary to isomerise the exocyclic alkene, with the use of $RhCl_3$ showing potential for forming the endocyclic alkene **166**.[48] Deprotection of the acetonide would give the corresponding diol, which would undergo a Corey-Winter olefination to form the enone **167**. An epoxidation to **168**, followed by reaction with hydrazine to form hydrazone **169** would allow a Wharton rearrangement to occur, with an oxidation furnishing the enone functionality to form **107**,[52] giving the correct substrate for grafting of the DEF framework onto the C-ring.



Scheme 87: Future work for completion of **ABC tricycle 107**

Alternatively, transformation of the ester moiety of **119c** to an aldehyde as in **170** (Scheme 88), followed by methylenation (Wittig or Tebbe) would set up the diene **171**. Closure of the B-ring by ring-closing metathesis would offer a more atom economical method, without the need for the decarboxylation and circumventing the low yielding Snider cyclisation; however it would be necessary to epimerise the α-vinyl group to give the necessary 1,4-*cis* relationship as seen in **171**. The carboxylic acid of hexacyclinic acid **1** will be introduced at a later stage by an allylic oxidation using SeO_2.

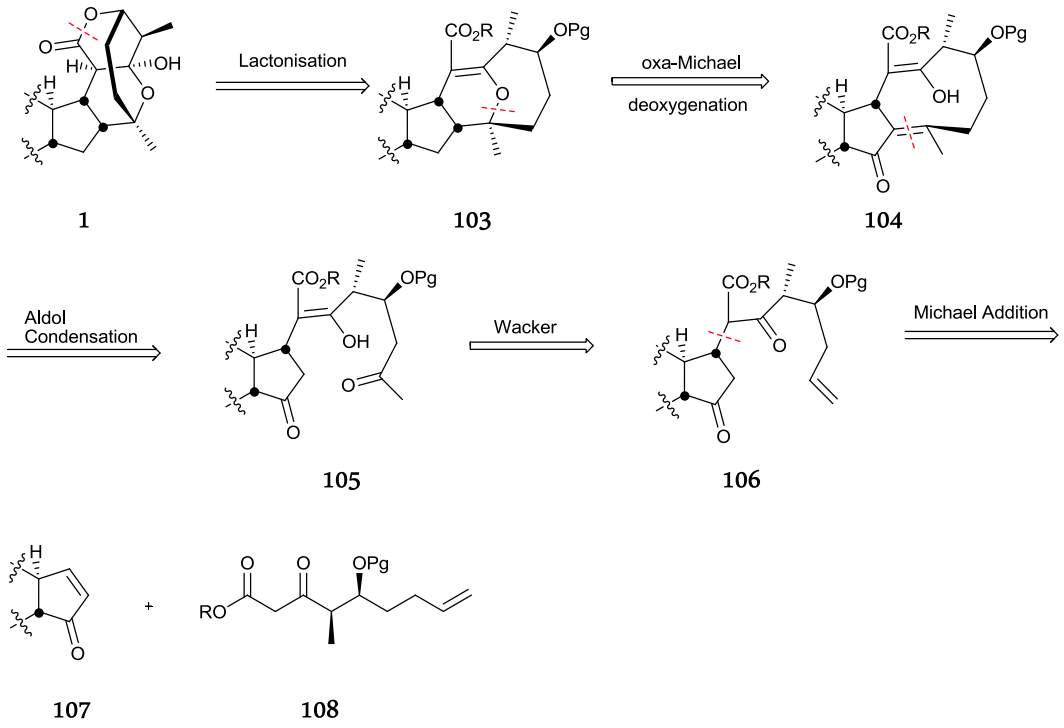


Scheme 88: Alternate closure of B-ring by RCM

3.3 - Current work towards DEF tricycle

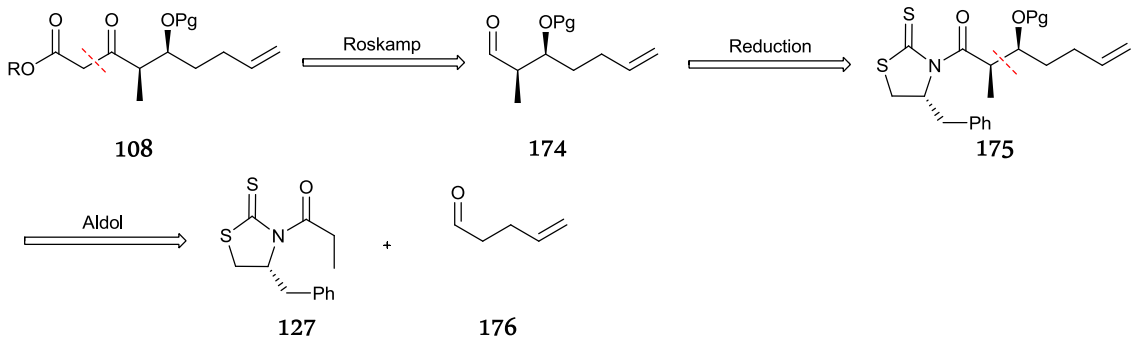
Retrosynthesis

As previously discussed, the synthesis of the DEF tricycle will be among the final steps for the synthesis of **1.** The β-ketoester **108** contains the necessary stereocentres and functionality required and will be attached to the tricycle **107** by a Michael addition.



Scheme 89: Retrosynthesis of DEF tricycle – ABC tricycle omitted

For the synthesis of **108**, the β-ketoester functionality will be installed by a Roskamp homologation from aldehyde **174**. C-C cleavage of **175** to auxiliary **127** and aldehyde **176** shows that the stereogenic centres will be installed by an asymmetric aldol reaction of **127** with **176** to form the aldol adduct **175**.

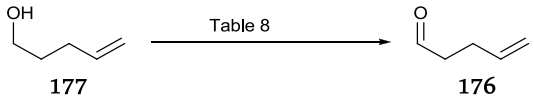


Scheme 90: Retrosynthesis of ß-ketoester **108**

3.3.1 – Synthesis of ß-ketoester

Synthesis of 4-pentenal 176

Oxidation of 4-penten-1-ol **177** under Swern conditions was found to be difficult, due to the volatility of 4-pentenal **176**, with only trace amounts of product being isolated (Scheme 91). Oxidation with IBX in either EtOAc or DCE was completed in 3 hours, however removal of the solvent *in vacuo* also removed the product. Using 3 equivalents of IBX in CH_2Cl_2 required up to 3 days reaction time but led to aldehyde 1**74** in a 45% yield in CH_2Cl_2 (Table 8).



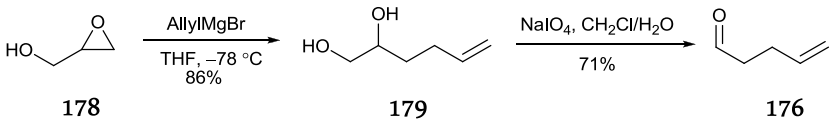
177 **176**

Scheme 91: Oxidation of **177**

Conditions	Yield
Oxalyl chloride, NEt_3, DMSO, CH_2Cl_2, −78 °C	-
1.5 equiv IBX, EtOAc, 80 °C	~5%
1.5 equiv IBX, DCE, 80 °C	~5%
3 equiv IBX, CH_2Cl_2, 40 °C	~45%

Table 8: Conditions for oxidation of **177**

An alternative synthesis of **176** employs glycidol **178** as the starting material (Scheme 87). The epoxide ring is opened by addition of allylmagnesium bromide forming diol **179** in good yield. Cleavage of the diol using sodium periodate furnishes **176** of sufficient purity for the Crimmins aldol reaction.[53]



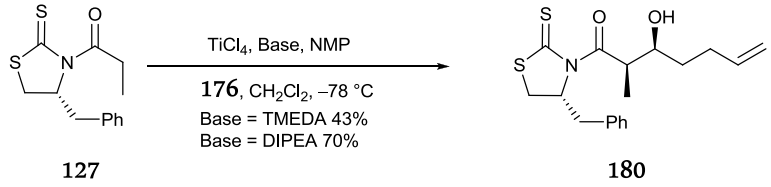
178 **179** **176**

Scheme 92: 2-step synthesis of **176**

Crimmins aldol reaction of 127 with 176

Using the conditions previously utilised within the group for the synthesis of the A-ring (1.0 equivalent each of $TiCl_4$, TMEDA and NMP with 1.1 equivalent of aldehyde in

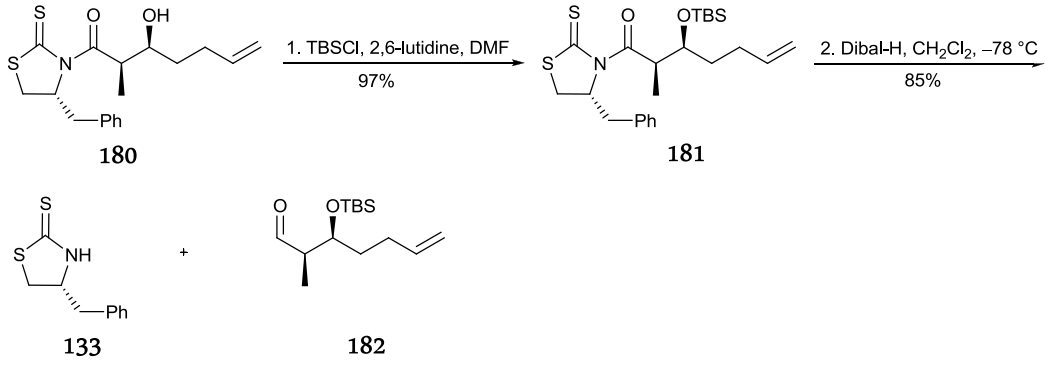
CH_2Cl_2 at −78 °C), the aldol adduct **180** was obtained in a modest 43 % yield with a 97:3 dr (Scheme 93). Using DIPEA as the base gives an improved yield of 70% (96% brsm).



Scheme 93: Crimmins aldol reaction of **127** and **176**

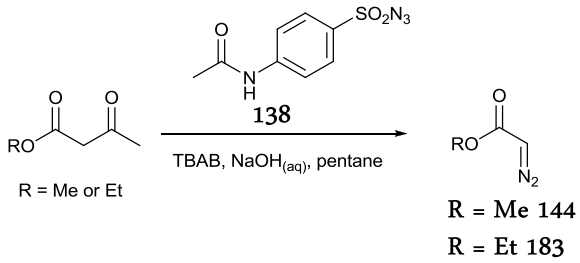
Completion of ß-ketoester

Protection of the aldol adduct **180** as a TBS ether required 3 equivalents of TBSCl to achieve good conversion, however a near quantitative yield of **181** was obtained (Scheme 94). Reduction of **181** was performed using 2 equivalents of Dibal-H in CH_2Cl_2 at −78 °C, effecting efficient cleavage of the auxiliary in only 5 minutes, furnishing aldehyde **182** in an 85% yield. Recovered auxiliary **133** (85%) can then be recycled and used in further aldol reactions.



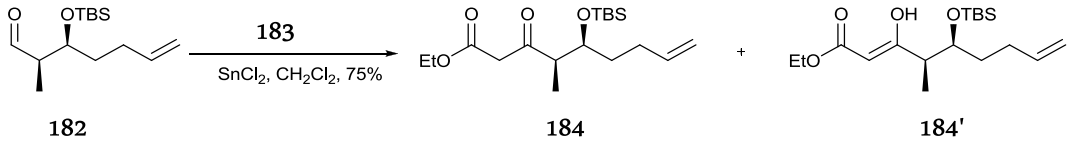
Scheme 94: TBS protection of **180** and subsequent cleavage of the auxiliary

Treatment of methyl or ethyl acetoacetate with **138** in 3 M aqueous NaOH solution and pentane, using TBAB, yielded methyl **144** or ethyl **183** diazoacetate (Scheme 95). Due to its volatility methyl diazoacetate **144** could not be accessed neat, and was instead used as a solution in ether.



Scheme 95: Synthesis of alkyl diazoacetates

Due to the relative ease of isolation of ethyl diazoacetate compared to the methyl analogue, it was decided to proceed using the ethyl β-ketoester. Roskamp homologation of aldehyde **182** with **183** proceeded smoothly with $SnCl_2$ in CH_2Cl_2,[54] furnishing the desired β-ketoester **184** as an inseperable 3:1 mixture with the corresponding enol forms **184'**.

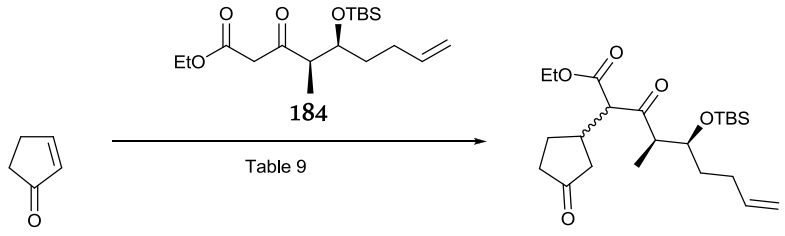


182 184 184'

Scheme 96: Roskamp homologation of **182**

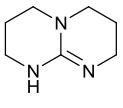
3.3.2 – Michael addition of 184 to cyclopentenone 185

Optimisation of the Michael addition of **184** onto the C-ring was performed using cyclopentenone **185** as a model system – though it gave the product as a mixture of 4 diastereomers (Scheme 97). Using traditional Michael addition conditions with the use of NaOEt in ethanol gave the desired adduct **186** in a modest 40% yield (Table 9). Increasing the number of equivalents of donor **184** or base gave no improvement of the yield, though the low yield may be due to the quality of the base, with greater yields possibly being obtained by using freshly prepared base. It was shown by Tan *et al*., that TBD (Fig. 11) could act as an effective catalyst for Michael additions,[55] but when these conditions were used, no real improvement in the yield was observed. However, by increasing the number of equivalents of **184**, a good 72% yield was obtained, though due to the impracticalities of using 4.0 equivalents of **184** another method was required. Greater improvements were seen by using K_2CO_3 in ethanol, generating the ethoxide base *in situ*. This method allows for a decreased number of equivalents of **184** and affording the Michael adduct **186** in 91% yield.



185 186

Scheme 97: Michael addition of **184** to **185**



TBD

Fig 11: Structure of TBD

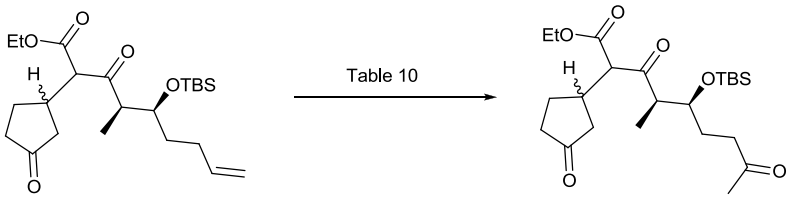
Conditions	Yield
2.0 equiv **184**, 0.2 equiv NaOEt, EtOH	40%
2.0 equiv **184**, 0.5 equiv NaOEt, EtOH	38%
3.0 equiv **184**, 0.5 equiv NaOEt, EtOH	40%
1.5 equiv **184**, 0.2. equiv TBD, Toluene	40%
3.0 equiv **184**, 0.2. equiv TBD, Toluene	41%
4.0 equiv **184**, 0.2. equiv TBD, Toluene	72%
2.0 equiv **184**, 1 equiv HMPA, 3Å MS, CH_2Cl_2	-
2.0 equiv **184**, 0.2 equiv K_2CO_3, EtOH	68%
2.0 equiv **184**, 0.4 equiv K_2CO_3, EtOH	73%
1.5 equiv. **184**, 0.2 equiv K_2CO_3, EtOH	88%
1.5 equiv **184**, 0.4 equiv K_2CO_3, EtOH	91%

Table 9: Conditions for Michael addition of **184** to **185**

The Michael adduct **186** was obtained as an inseparable mixture of 4 diastereomers making characterisation exceedingly difficult with the ^{1}H NMR showing a series of overlapping multiplets, however the correct mass was seen by mass spectrometry. Nonetheless the structure remains unverified.

3.3.3 – Further functionalisation of 186

Wacker oxidation of the terminal olefin of **186** to **187** was easily achieved using the standard Wacker conditions (Scheme 98). Oxidation using stoichiometric $PdCl_2$ in a 4:1 mixture of DMF and water gave the product in a good 62% yield. Attempts to use catalytic amounts of palladium (0.2 equivalents), with 1.2 equivalents of $CuCl_2$ under an oxygen atmosphere initially gave a decreased yield (58%). However increasing the catalyst loading to 0.4 equivalents of catalyst was found to increase the yield, with a more dilute (0.05 M) solution giving the best yield of the tetracarbonyl compound **187** (Table 10). As with the Michael adduct, the Wacker product **187** was isolated as a mixture of inseparable diastereomers, with full assignment in the ^{1}H NMR not possible, however the disappearance of the alkene signals and new singlet at 1.98 ppm corresponding to the methyl group of the newly formed ketone indicate the oxidation is occurring. The desired product mass is also seen by mass spectrometry.



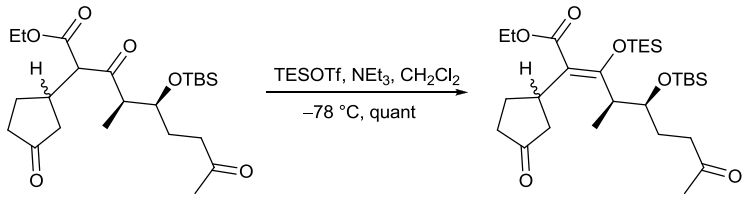
186 187

Scheme 98: Wacker oxidation of **186**

Conditions	Yield
1.05 equiv $PdCl_2$, 4:1 DMF/H_2O	62%
0.2 equiv $PdCl_2$, 1.2 equiv $CuCl_2$, 4:1 DMF/H_2O, O_2	58%
0.4 equiv $PdCl_2$, 1.2 equiv $CuCl_2$, 4:1 DMF/H_2O (0.1 M), O_2	65%
0.4 equiv $PdCl_2$, 1.2 equiv $CuCl_2$, 4:1 DMF/H_2O (0.05 M), O_2	72%

Table 10: Conditions for Wacker oxidation of **186**

Protection of the β-keto functionality in **187** as a silyl enol ether using TESOTf in CH_2Cl_2 at −78 °C gave the product **188** in a quantitative yield; the geometry of the double bond was not determined (Scheme 99).



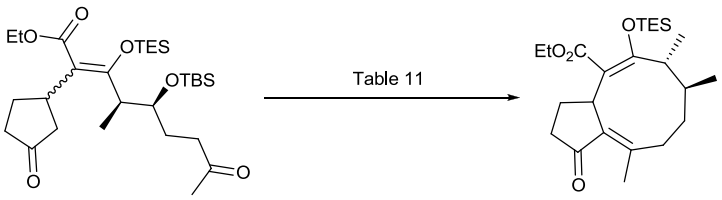
187 188

Scheme 99: TES protection of ß-ketoester **187**

3.3.4 – Aldol condensation attempts

With the silyl enol ether **188** prepared, attempts were made to form the 9-membered ring product **189** by aldol condensation (Scheme 100). First attempts were made using KO*t*-Bu in toluene with slight heating, however only starting material was recovered. Increasing the equivalents of base and concentration of the solution had no effect.[56] Using 5 equivalents of DBU in a dilute solution of **188** in CH_2Cl_2 gave no reaction, with only starting material recovered. An increase in the number of equivalents of DBU and the temperature gave the same result.[57] Treatment with NaOEt in ethanol gave no result either; only starting material was recovered, however the use of freshly prepared reagent might give a better result. The use of a 4:1:1 THF/EtOH/10% aqueous NaOH showed some promise on very small scale,[58] with TLC evidence for the formation of a new product. However when appreciable

quantities of this product were obtained, it was found to be the tricarbonyl **187** (Fig 12), formed by a retro-Michael reaction (Table 11).

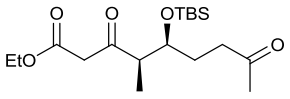


188 **189**

Scheme 100: Aldol condensation of **188**

Conditions	Yield
1.2 equiv KO*t*-Bu, toluene, 0.05 M ,0 °C to 50 °C	Recovered SM
5 equiv KO*t*-Bu, toluene, 0.1 M , 0 °C to 50 °C	Recovered SM
5 equiv DBU, CH_2Cl_2, 0.05 M, 20 °C	Recovered SM
15 equiv DBU, CH_2Cl_2, 0.05 M, 40 °C	Recovered SM
1.5 equiv NaOEt, EtOH, 0.01 M, 0 °C to 50 °C	Recovered SM
4:1:1 THF/EtOH/10% aqueous NaOH, 0.01 M, 20 °C	54% **190**

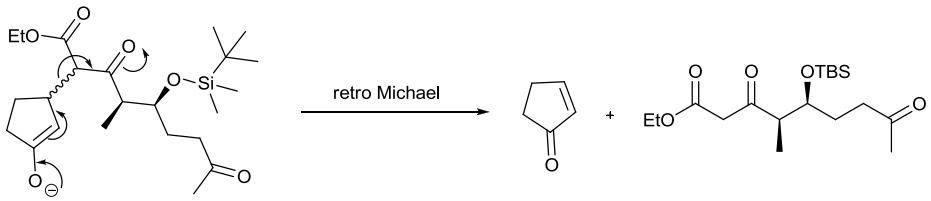
Table 11: Conditions for aldol condensation of **188**



190

Fig 12: Structure of retro-Michael product **190**

The likely mechanism for the retro-Michael is shown below (Scheme 101). Under these conditions the labile TES enol ether is cleaved. The desired enolate is then formed, however compound **187** fragments by a retro-Michael reaction to **185** and compound **190**. The use of a less labile protecting group for the enol ether could potentially allow the cyclisation instead.

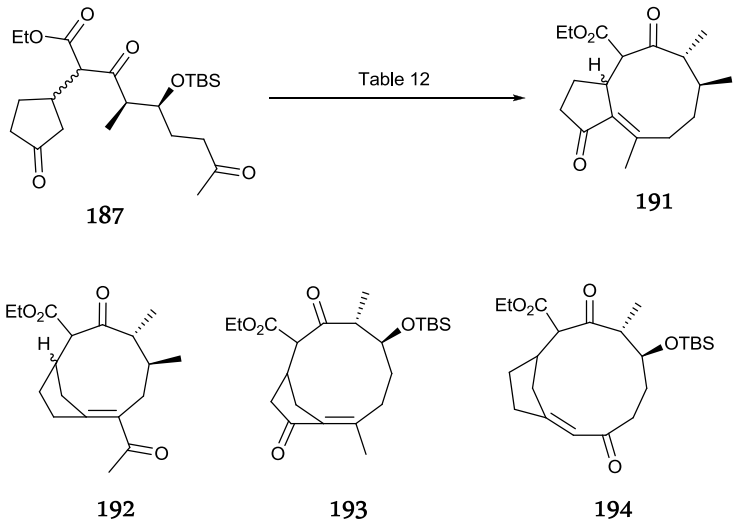


187-enolate **185** **190**

Scheme 101: Mechanism for retro Michael of **187**

It was also attempted to effect the aldol cyclisation using the unprotected product **187**, however as well as 9-membered product **191**, there is also potential for formation of the

other medium sized ring products **192-194** (Scheme 102). There is also a risk of epimerising the α-methyl group. As was expected both conditions attempted for the cyclisation of **187** were unsuccessful, just giving rise to product degradation (Table 12).



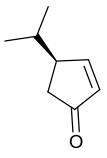
Scheme 102: Attempted aldol condensation of **187**

Conditions	Yield
KO*t*-Bu, *t*-BuOH, 0.01 M, 20 °C	Degradation
4:1:1 THF/EtOH/10% aqueous NaOH, 0.01 M, 20 °C	Degradation

Table 12: Conditions for aldol condensation of **187**

3.3.5 – Synthesis of chiral model C-ring

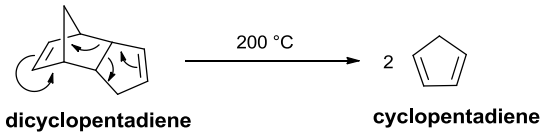
While cyclopenten-2-one **185** serves as an effective C-ring model for the Michael addition, the formation of 4 inseparable diastereomers makes further steps more difficult to analyse. Therefore it was necessary to prepare a model with a chiral substituent that would influence the facial selectivity of the Michael addition, so at most only 2 diastereomers would be formed. It was decided to synthesise (*R)*-isopropylcyclopentenone **195** (Fig 13),[59] with the bulky isopropyl group forcing the β-ketoester **184** to attack exclusively from the bottom face.



195

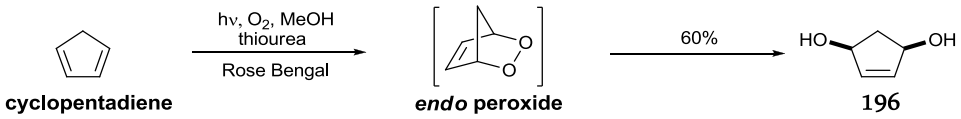
Fig 13: (*R)*-isopropylcyclopentenone **195**

Heating of dicyclopentadiene to 200 °C initiates a retro Diels-Alder reaction, cracking the dicyclopentadiene skeleton into 2 equivalents of cyclopentadiene, which can then be isolated by distillation (Scheme 103). Left at room temperature it will slowly dimerise so it was used immediately in the next step.



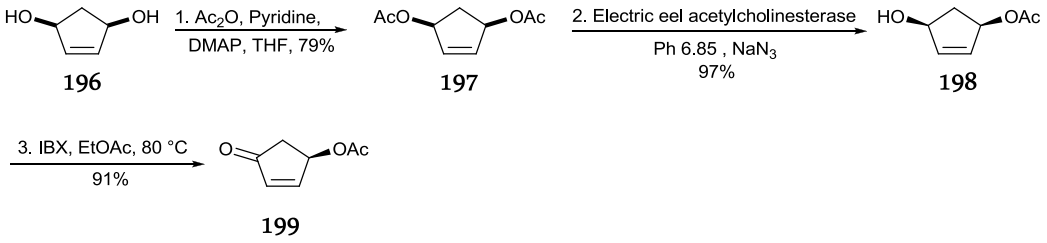
Scheme 103: RetroDiels-Alder of dicyclopentadiene

Cyclopentadiene participates in a [4+2]-cycloaddition with singlet oxygen, which is generated by UV irradiation whilst bubbling oxygen throughout a solution of methanol, with Rose Bengal being used as a sensitiser (Scheme 104). This forms the endoperoxide, which is reduced *in situ* by thiourea to afford the *cis*-diol **196** in 60% yield.



Scheme 104: UV [4+2] cycloaddition using oxygen

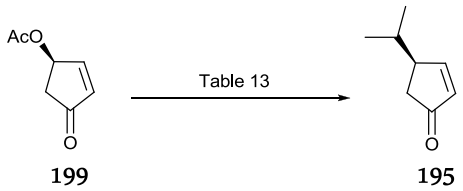
Diacetylation of the diol **196** was effected by acetic anhydride, pyridine and catalytic DMAP in THF, furnishing the diacetate **197** in 79% yield (Scheme 105). Enzymatic desymmetrisation of **94** was achieved using electric eel acetylcholineesterase in a sodium phosphate buffer solution, furnishing allylic alcohol **198** in excellent yield (97%). Oxidation of the alcohol with IBX in ethyl acetate formed the enone **199** in high yield.



Scheme 105: Enzymatic desymmetrisation and synthesis of allylic acetate **199**

For the completion of the model C-ring **195**, it was necessary to deliver an isopropyl group *anti* to the acetate group (Scheme 106). Conjugate addition of isopropylmagnesium bromide, with CuBr.SMe_2 and HMPA, using TMSCl as a Lewis acid and attempting to trap the adduct as a silyl enol ether gave no product, with only starting material being

recovered. In the end a modification of the original conditions, substituting TMSCl with the stronger Lewis acid $BF_3.OEt_2$, allowed access to the adduct, though at least 3 equivalents were required for complete conversion. Treatment with dilute acetic acid was enough to bring about elimination of the acetate functionality and form the enone **92** in 72% yield (Table 13).



199 195

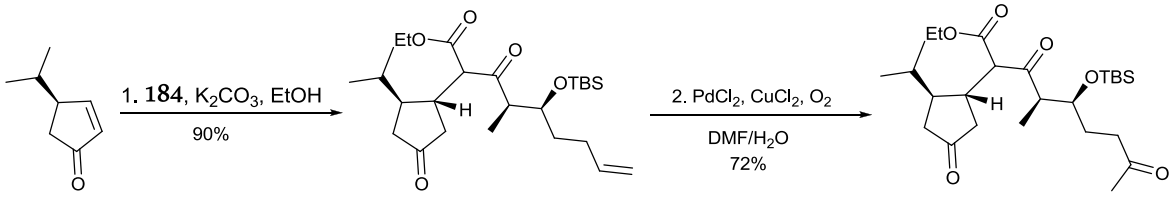
Scheme 106: Conjugate addition to form **195**

Conditions	Yield
1.4 equiv. isopropylmagnesium bromide, 0.1 equiv $CuBr.SMe_2$, 3 equiv TMSCl, THF , −78 °C	-
3.0 equiv isopropylmagnesium bromide, 1 equiv CuI, Et_2O, THF −78 °C	-
1.4 equiv isopropylmagnesium bromide, 0.1 equiv $CuBr.SMe_2$, 2.8 equiv HMPA, 0.5 equiv $BF_3.OEt_2$, THF , −78 °C then $AcOH/CH_2Cl_2$	11%
1.4 equiv isopropylmagnesium bromide, 0.1 equiv $CuBr.SMe_2$, 2.8 equiv HMPA, 1.5 equiv $BF_3.OEt_2$, THF , −78 °C then $AcOH/CH_2Cl_2$	19%
1.4 equiv isopropylmagnesium bromide, 0.1 equiv $CuBr.SMe_2$, 2.8 equiv HMPA, 3 equiv $BF_3.OEt_2$, THF , −78 °C then $AcOH/CH_2Cl_2$	72%
1.4 equiv isopropylmagnesium bromide, 0.1 equiv $CuBr.SMe_2$, 2.8 equiv TMEDA, 3 equiv $BF_3.OEt_2$, THF , −78 °C then $AcOH/CH_2Cl_2$	59%

Table 13: Conditions for conjugate addition to form **195**

3.3.6 – Model CDEF model synthesis

Michael addition of β-ketoester **184** to chiral model **195** using the optimised conditions of 0.4 equivalents of K_2CO_3 in ethanol affords the Michael adduct **200** in an excellent 90% yield (Scheme 107). Attack of **184** comes exclusively from the bottom face with **200** being formed as a 2.5:1 ratio of an inseparable mixture of diastereomers. Wacker oxidation of the terminal olefin proceeds smoothly as before to furnish the methyl ketone **201** in 72% yield.

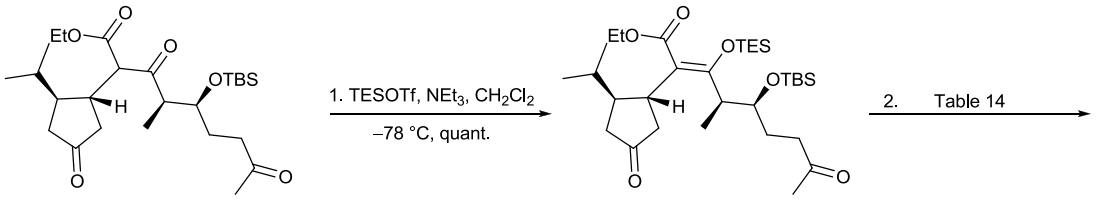


195 200 201

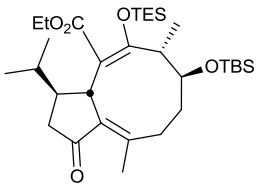
Scheme 107: Michael addition of **184** to **195** and subsequent Wacker oxidation

With only 2 diastereomers being formed, spectroscopic assignment of the 1H NMR spectra of **200** is much more straightforward, however, due to there still being the corresponding enol forms available, the spectra are still very cluttered (Appendix – page 170). As expected, three methyl groups are present, along with an ethyl ester and TBS group. The characteristic ddt of the terminal alkene is also seen at 5.57 ppm. Indicative of the Michael addition occurring is the doublet at 4.09 ppm corresponding to the double α-protons at the H^2 position. A COSY interaction can be seen between this peak and a dddd, corresponding to the H^{13} position. Confirmation of the Wacker oxidation can be seen by the disappearance of the alkene protons and formation of the methyl ketone at 2.15 ppm (Appendix – page 173).

Using a similar protocol as before, compound **201** was protected as a TES silyl enol ether using TESOTf to form **202** quantitatively (Scheme 108). The aldol condensation of **202** was investigated to see if the presence of the bulky isopropyl group had any effect. Using KO*t*-Bu or NaOEt gave no reaction with only starting material recovered. Using the 4:1:1 THF/EtOH/10% NaOH solution conditions the same result was observed, with the retro Michael reaction occurring to furnish the tricarbonyl compound **190** (Table 14).



201 **202**



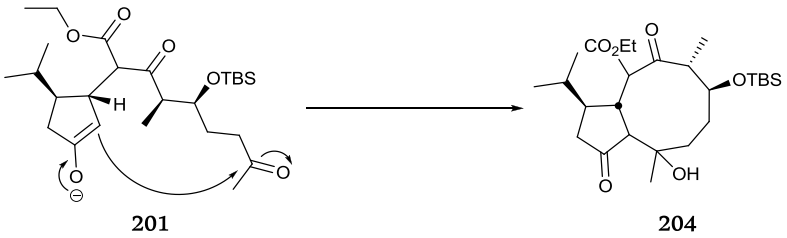
203

Scheme 108: Protection of **201** and attempted formation of **203**

Conditions	Yield
5 equiv KO*t*-Bu, *t*-BuOH, 0.01 M , 0 °C to 50 °C	Recovered SM
3.0 equiv NaOEt, EtOH, 0.01 M, 0 °C to 50 °C	Recovered SM
4:1:1 THF/EtOH/10% NaOH, 0.01 M, 20 °C	50% **190**

Table 14: Conditions for aldol condensation of **202**

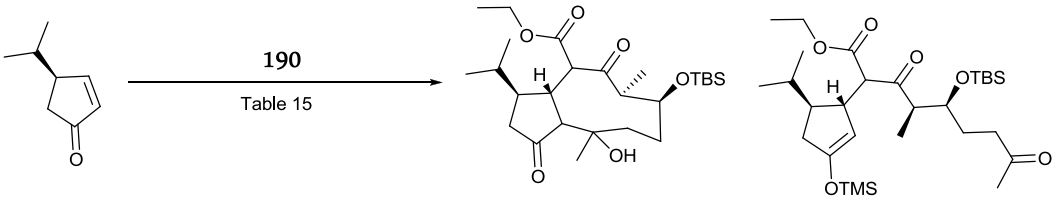
Attempts were made to effect the aldol reaction in a more controlled manner, believing selective formation of the desired enolate of **201**, would lead to formation of the aldol product **204** (Scheme 109). If the enolate could be trapped as a silyl enol ether, a Mukaiyama aldol reaction could potentially occur. While there is little precedent for Muikaiyama aldol reactions onto ketones to form medium sized rings, it was decided to attempt this approach as a means to utilise remaining material.



201 204

Scheme 109: Addition of desired enolate to methyl ketone

An excess of β-ketoester **190** was added to **195** using the optimised Michael conditions with an excess of base (Scheme 110), with the hope that the formed enolate would then react with the methyl ketone and furnish **204**. However, while complete conversion was achieved, no product was isolated. Other attempts to trap the enolate as a TMS silyl enol ether **205** were unsuccessful, with only starting material being recovered (Table 15).



195 204 205

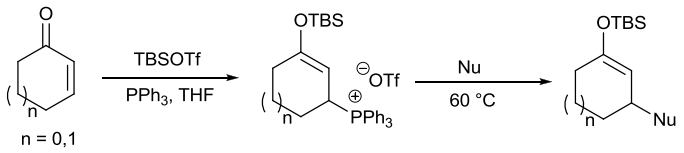
Scheme 110: Michael addition of **190** to **195**

Conditions	Yield
1.5 equiv **190**, 1.5 equiv K_2CO_3, EtOH	-
1.5 equiv **190**, 1.5 equiv NaOEt, 3 equiv TMSCl, THF	No reaction
1.5 equiv **190**, 1.5 equiv KO*t*-Bu, 3 equiv TMSCl, THF	No reaction

Table 15: Conditions for Michael addition of **190** with **195**

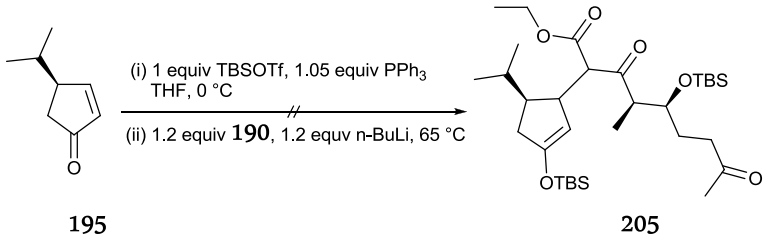
A protocol has been reported for the nucleophilic substitution of 3-*tert*-butyldimethylsilyloxyalk-2-enylphosphonium salts to form OTBS enol ethers,[60] with addition of triphenylphosphine to an enone, trapping the intermediate enol as a TBS enol ether (Scheme 111). Addition of a nucleophile to leads to displacement of the

triphenylphosphine moiety. A variety of nucleophiles were demonstrated, including lithium enolates of β-ketoesters.



Scheme 111: Nucleophilic displacement of triphenylphosphine

It was hoped that these conditions could be used so synthesise **102**, with addition of the DEF framework and trapping the desired enolate as a silyl enol ether all achieved in one step. Addition of PPh_3 and TBSOTf to **195**, followed by the lithium enolate of **184**, gave no product (Scheme 112); however the reaction was only attempted once. It is possible the bulky isopropyl group makes addition of the triphenylphosphine difficult.

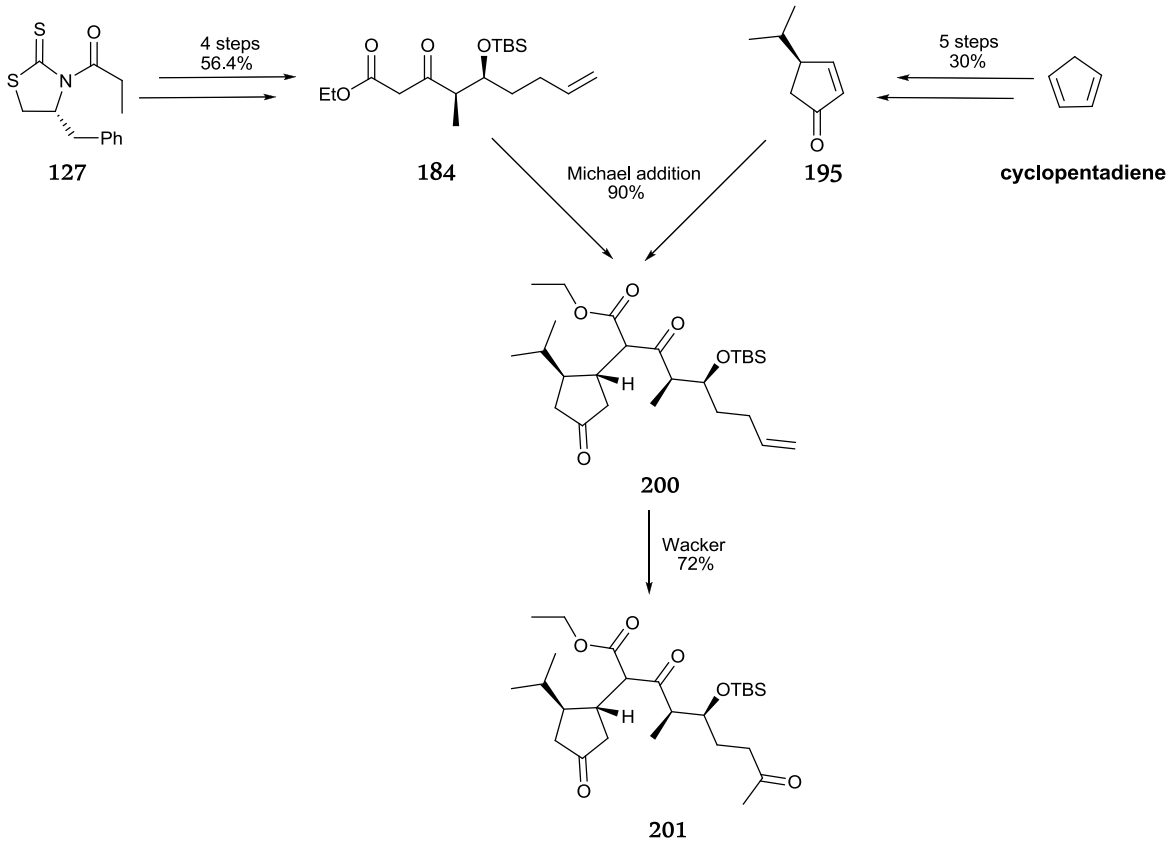


195 205

Scheme 112: Attempted synthesis of TBS enol ether **205**

3.3.7 – Conclusions and Future work

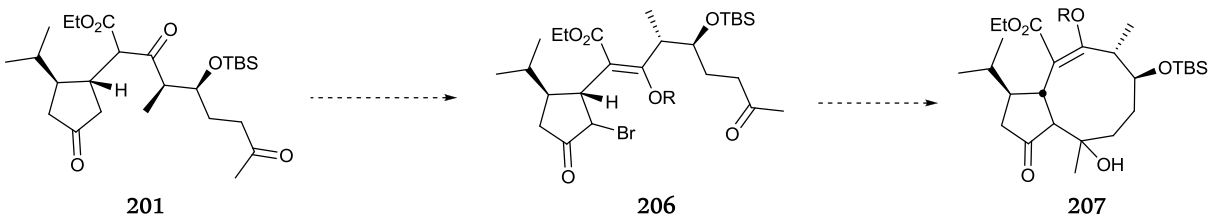
Enantiopure synthesis of β-ketoester **184** was achieved in 4 steps from chiral auxiliary **127**, with the stereogenic centres being installed by an asymmetric aldol reaction and forming the β-ketoester functionality by a Roskamp homologation. Synthesis of the C-ring model **195** from cyclopentadiene is achieved over 5 steps in a 30% overall yield. The key step in the synthesis of **195** is the introduction of chirality by enzymatic desymmetrisation using electric eel acetylcholineesterase. Michael addition of **184** to **195** has been been optimised, accessing the Michael adduct **200** in 91% yield. Functionalisation of the alkene by Wacker oxidation affords **201** in a 72% yield (Scheme 113). While the attempts made to close the 9-membered ring have been unsuccessful so far, further work is in progress to achieve this in the Prunet group.



Scheme 113: Summary of work on DEF tricycle

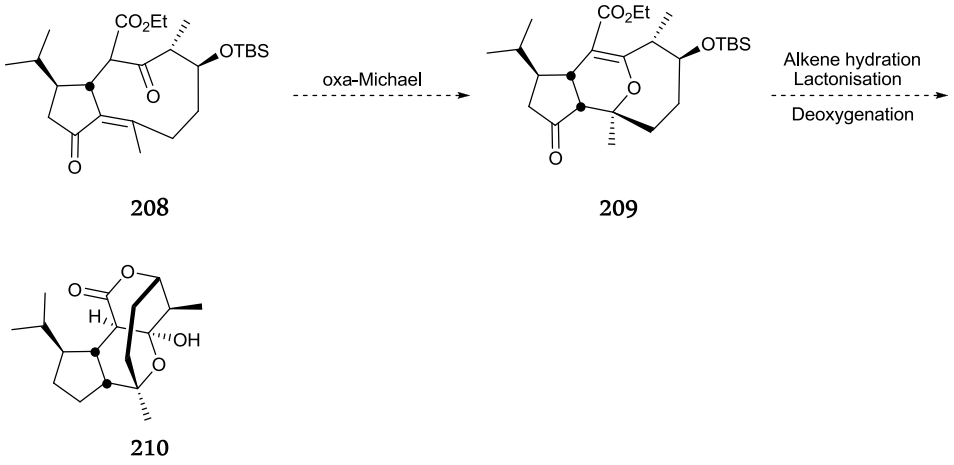
This work represents the first work within the Prunet group on the DEF tricycle of **1**, and while formation of the stereogenic centres and grafting the DEF framework to the C-ring model was optimised, the key cyclisation was unfotunately not realised. While there remain other options to try, the cyclisation has proven extremely difficult, it is possible the route may need redesigned.

Immediate future work will be focussed on the formation of the 9-membered ring **208** (Scheme 114). With the formation of the 9-membered ring proving extremely difficult to cyclise by an aldol condensation it is necessary to explore other approaches to the cyclisation. Bromination of **201** followed by formation of a protected enol ether would give **206**, this could potentially ease the cyclisation, with a Reformatsky reaction to form the 9-membered ring as in **207**. It was also shown by Clarke that an increased number of sp^2 centres limits the destabilising transannular interactions and eases cyclisation – increasing the number of sp^2 centres in the chain might allow the cyclisation to occur.[61]



Scheme 114: Potential Reformatsky reaction to close 9-membered ring

Once **208** has been accessed, the CDF-ring system **209** can be closed by an oxa-Michael addition of the enolate onto the enone acceptor. Following this, hydration of the alkene, lactonisation and deoxygenation of the ketone group will afford the CDEF model **210**. It is hoped that hydration of the double bond will occur spontaneously by addition of water to the strained alkene.[20]

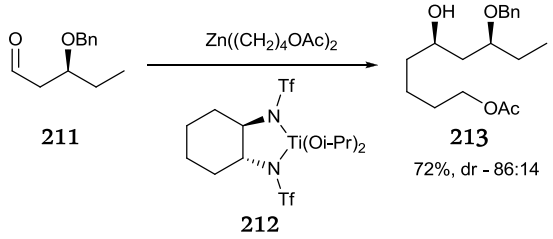


Scheme 115: Future work for synthesis of CDEF model **210**

4 - Diastereoselective synthesis of *syn*-1,3-diols by intramolecular conjugate addition.

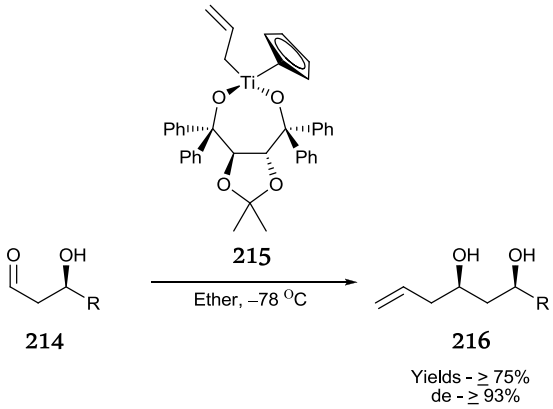
4.1 - Introduction

The *syn*-1,3-diol moiety is a common structural feature in a large number of natural products, therefore synthetic methods for their construction are ubiquitous in modern synthetic chemistry. One of the most common methods is the formation of C-C bonds, such as in a alkylation/allylation reactions and diastereoselective aldol reactions. Knochel *et al.* reported the alkyation of the benzyl protected β-hydroxyaldehyde **211** using a chiral titanium catalyst **212** and alkyl zinc reagents (Scheme 116).[62] This formed the monoprotected *syn*-1,3-diol **213** in a good yield, however the diastereoselectivity was only moderate with a ratio of 86:14 *syn*/*anti*. This method also requires the *in-situ* generation of the catalyst.



Scheme 116: Conjugate addition using benzaldehyde

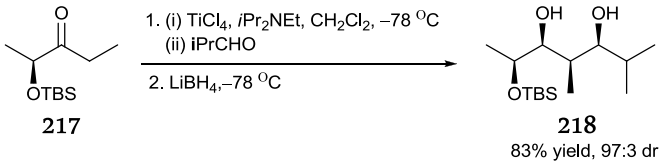
Cossy *et al.* reported the allylation of β-hydroxyaldehydes **214** using stoichiometric amounts of the chiral cyclopentadienyldialkoxyallyl titanium complex **215** in ether at −78 °C (Scheme 117).[63] The reaction was found to proceed well, with good yield and excellent diastereoselectivities for all reported substrates. However, one drawback of this method is that the titanium complex **215** used is not commercially available and must be prepared.



Scheme 117: Conjugate addition using benzaldehyde

Diastereoselective aldol reactions are also a useful tool to access *syn*-1,3-diols. The titanium mediated aldol reaction of chiral α-*tert*-butyldimethylsilyloxyketone **217**,

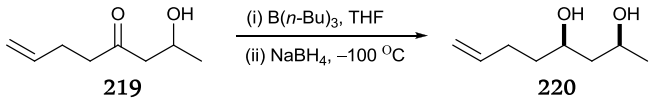
followed immediately by stereoselective reduction using $LiBH_4$ to give the diol **218** has been reported.[64] This represents a powerful method, creating up to three new stereocentres over 2 steps. This method also precludes the use of expensive chiral reagents, relying on substrate and not reagent stereocontrol.



217 **218**
83% yield, 97:3 dr

Scheme 118: Diastereoselective aldol reaction and reduction

Another commonly used method is by stereoselective reduction of β-hydroxycarbonyl compounds. Narasaka and Pai describe the chelation controlled reduction of **219** by addition of tributyl boron, followed by hydride delivery using $NaBH_4$ (Scheme 119).[65] This afforded the *syn* diol **220** in an excellent yield with good stereocontrol. However this method can often give rise to undesired side products.[66] Due to the large amount of literature related to the synthesis of *syn*-1,3-diols the methods described are by no means exhaustive.

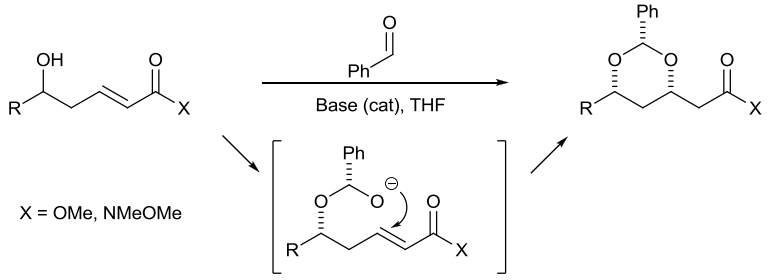


219 **220**
93% yield
dr – 94:6 *syn*/*anti*

.

Scheme 119: Conjugate addition using benzaldehyde

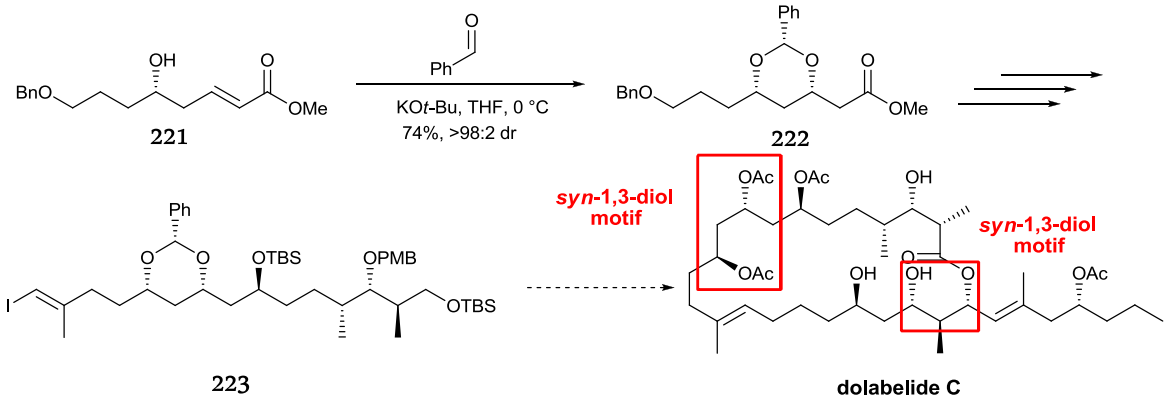
A method for the synthesis of *syn*-1,3-diols was reported by David Evans and Joëlle Prunet using the conjugate addition of a hemiacetal alkoxide, generated by addition of a homoallylic alcohol to benzaldehyde, onto a Michael acceptor such as α,β-unsaturated esters or Weinreb amides (Scheme 120).[67]



Scheme 120: Conjugate addition using benzaldehyde

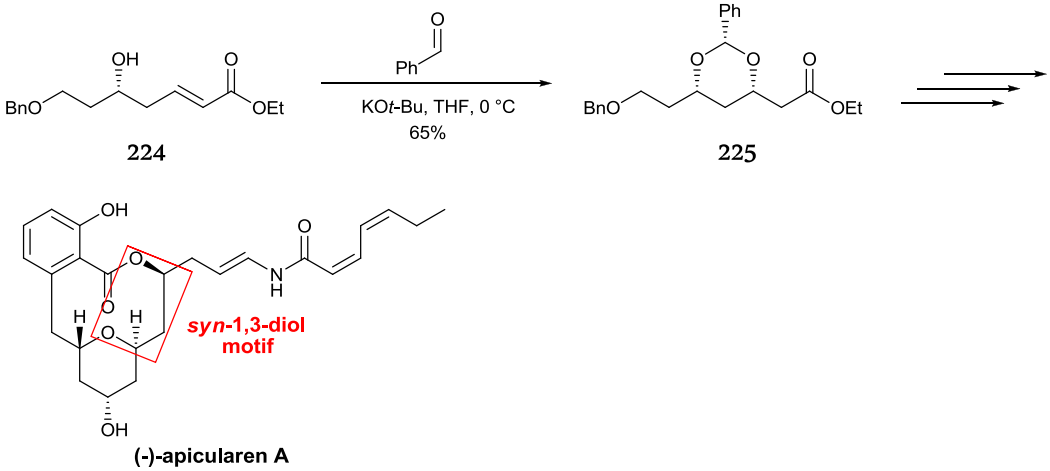
The reaction was shown to work well with a variety of substrates under fairly mild conditions, proceeding in good yields and diastereoselectivity for the *syn* protected diol (typically >95:5). This reaction also precluded the use of expensive and non commercially available catalysts, instead relying on substrate stereocontrol. Because of this, the reaction has been applied to a variety of total synthesis targets.

Within the Prunet group, the reaction has been used in the synthesis of the C1-C15 fragment of dolabelide C (Scheme 121). Treatment of the homoallylic alcohol **221** with benzaldehyde and KO*t*-Bu in THF formed the benzylidene acetal **222** in 74% yield with a dr greater than 98:2. Further steps go on to afford the C1-C15 fragment **223**.[68]



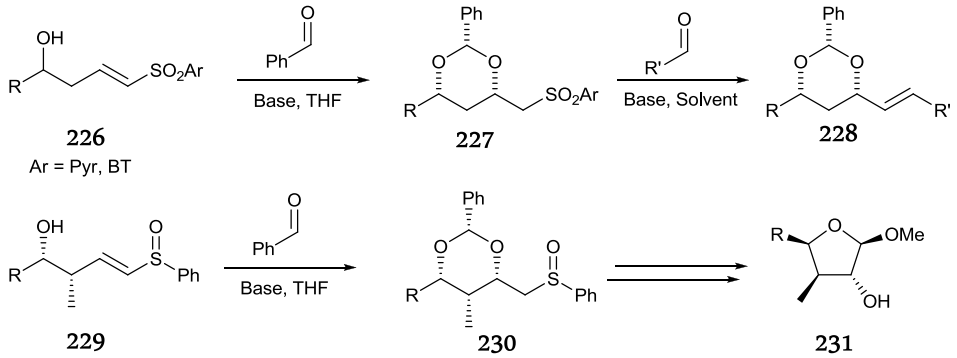
Scheme 121: Synthesis of **223** in Prunet group

Uenishi *et al.*, used a similar protocol in their synthesis of (−)-apicularen A, with the conjugate addition of benzaldehyde to **224** giving the acetal **225** in a 65% yield; however no dr was reported (Scheme 122). They continued with the synthesis to furnish (−)-apicularen A.[69]



Scheme 122: Use of oxa-Michael addition in synthesis of (−)-apicularen A

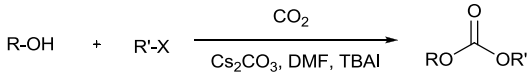
The scope of the reaction has been extended to other Michael acceptors such as heteroaromatic vinylic sulfones **226** and sulfoxides **229** with good yields and selectivity for the *syn* protected diol (Scheme 123). Protected diol products bearing a heteroaromatic sulfone **227** could then be used in modified Julia reactions favouring formation of the *E*-alkenes **228**. The protected sulfoxides **230** have been shown to give rise to 3-deoxyribose analogues **231**.



Scheme 123: Conjugate addition using sulfones and sulfoxides

While the conjugate addition reaction with benzaldehyde works well, the reaction is not without its disadvantages. The benzaldehyde must be purified by distillation prior to use; it is also necessary to do three successive additions, with the excess benzaldehyde making purification more difficult. Moreover, no reaction occurs when the electron-withdrawing group possesses an α-substituent, which limits its application.

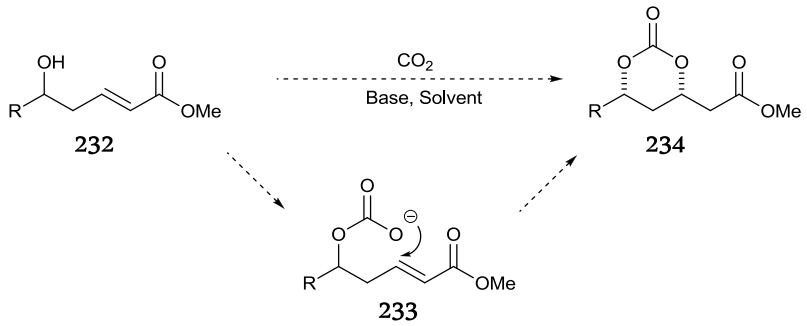
It has been shown by Jung *et al* that carbon dioxide can be used for the formation of asymmetric carbonate esters (Scheme 124).[70] Deprotonation of the free hydroxyl forms the alkoxide anion, which attacks the carbon of CO_2. The resulting carbonate anion can then participate in an S_N2 reaction with an alkyl halide forming the carbonate ester product. The scope of this reaction has been shown to be limited to primary halides, although there are a few examples with secondary halides.



Scheme 124: Use of CO_2 in synthesis of carbonate esters

It was investigated whether carbon dioxide could be used as a reagent in the formation of protected *syn*-1,3-diols **234**, proceeding by nucleophilic addition of **232** to carbon dioxide, with the alkoxide anion then adding to the Michael acceptor in **233** (Scheme 125). The use

of carbon dioxide would make the reaction more atom economical and minimise any difficulties with purification.

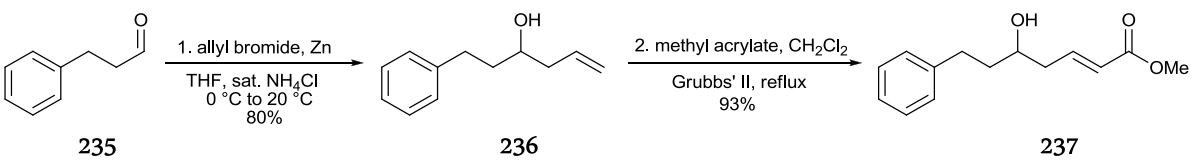


Scheme 125: Proposed synthesis of carbonates using CO_2

4.2 - Results and Discussion

Synthesis of substrate

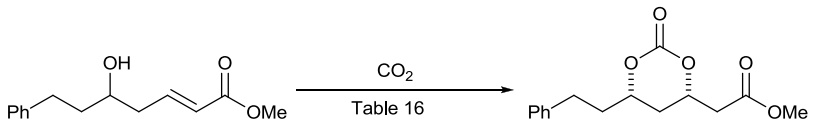
Formation of the substrate began with a Barbier reaction of allyl bromide and hydrocinnamaldehyde **235** mediated by zinc metal.[71] In contrast to other organometallic addition reactions, such as the Grignard reaction, the reaction does not require anhydrous conditions and is performed in a mixture of THF and saturated aqeuous NH_4Cl, furnishing homoallylic alcohol **236** in an 80% yield. While this reaction is analogous to the Grignard reaction, the mechanism is still not understood, possibly proceeding by a radical process.[72] Cross metathesis of **236** with an excess of methyl acrylate using Grubbs' 2nd generation catalyst in dichloromethane under reflux afforded the α,β-unsaturated ester **237** in 93% yield exclusively as the *E*-isomer (Scheme 126). While cross-metathesis reactions are a powerful synthetic tool, they can often give rise to a mixture of products. Grubbs developed a system to determine the favoured product based upon the type of olefins used. According to this model, the homoallylic alcohol **236** is a type I olefin which will rapidly dimerise; however these dimers are very reactive and will participate in further metathesis reactions. Methyl acrylate is a type II olefin which does not dimerise but will react with **236** and its dimer. Using an excess of methyl acrylate drives the reaction to completion.[73]



Scheme 126: Synthesis of substrate **237**

Conjugate addition reactions with CO_2

Using the same conditions reported for the synthesis of carbonate esters, dry CO_2 was bubbled through a solution containing the substrate, 3 equivalents of Cs_2CO_3 and 1 equivalent of TBAI as a phase transfer catalyst. Unfortunately this gave no reaction, with only starting material being recovered. Increasing the temperature or removal of TBAI gave the same result. Using a stronger base such as KO*t*-Bu or NaH in THF had no effect either, however increasing the number of equivalents of base did form a small amount of the alcohol elimination product (Table 16).



237 238

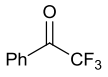
Scheme 127: Attempted synthesis of substrate **238**

Conditions	Yield
3 equiv Cs_2CO_3, 1 equiv TBAI, DMF, 20 °C	Recovered SM
3 equiv Cs_2CO_3, DMF, 20 °C	Recovered SM
3 equiv Cs_2CO_3, 1 equiv TBAI, DMF, 50 °C	Recovered SM
3 equiv Cs_2CO_3, 1 equiv TBAI, DMF, 80 °C	Recovered SM
0.2 equiv KO-*t*Bu, THF, 20 °C	Recovered SM
0.2 equiv KO-*t*Bu, THF, 50 °C	Recovered SM
1 equiv KO-*t*Bu, THF, 20 °C	Recovered SM + Elimination byproduct
3 equiv KO-*t*Bu, THF, 20 °C	Recovered SM + Elimination byproduct
1 equiv NaH, THF, 20 °C	Recovered SM

Table 16: Conditions for conjugate addition using CO_2

Conjugate addition reactions with 2,2,2-trifluoroacetophenone 239

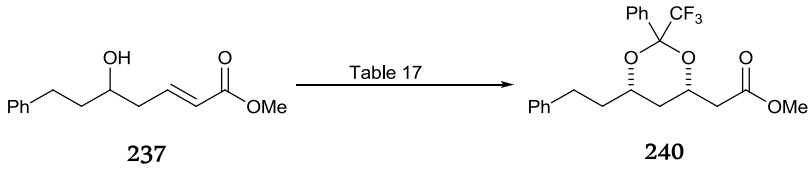
While conjugate additions using CO_2 were unsuccessful, an interesting result was obtained by substituting benzaldehyde for 2,2,2-trifluoroacetophenone **239** (Fig 14), which is similar in reactivity to benzaldehyde. The presence of the strongly electron withdrawing trifluoromethyl group makes **239** more reactive than benzaldehyde.



239

Fig 14: Structure of 2,2,2-trifluoroacetophenone **239**

With 0.2 equivalents of KO*t*-Bu and 1.1 equivalents of **239** in THF at 20 °C, after 12 hours of reaction time, the conversion was found to be 69%, with the protected acetal **240** being isolated in 59% yield (Scheme 128). A slight increase in the equivalents of base and **239** gave an increase in conversion and yield. However when 0.4 equivalents of KO*t*-Bu and 3 equivalents of **239** were used, full conversion was achieved within 5 hours, furnishing the product **240** in an excellent 85% yield (Table 17).



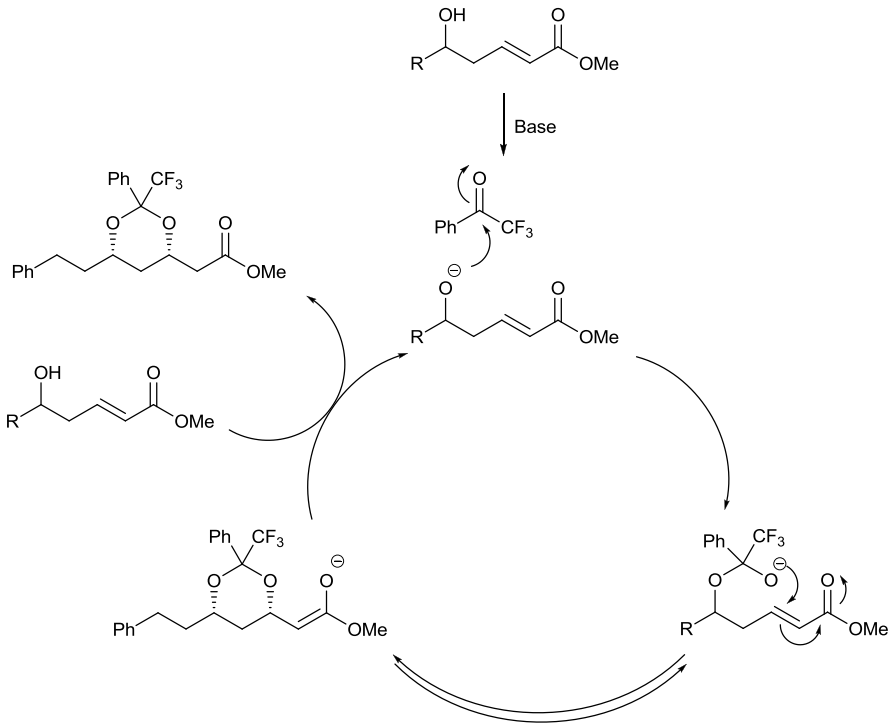
237 **240**

Scheme 128: Synthesis of substrate **240**

Conditions	Conversion/Yield
0.2 equiv KO*t*-Bu, 1.1 equiv **239**, THF, 20 °C	69%/59%
0.4 equiv KO*t*-Bu, 1.1 equiv **239**, THF, 20 °C	70%/60%
0.4 equiv KO*t*-Bu, 1.5 equiv **239**, THF, 20 °C	85%/71%
0.4 equiv KO*t*-Bu, 3.0 equiv **239**, THF, 20 °C	100%/85%

Table 17: Conditions for conjugate addition using **240**

The proposed mechanism for the reaction is based upon the reaction using benzaldehyde. The first step is deprotonation of the hydroxyl, with the resulting alkoxide attacking the ketone functionality forming the hemiacetal alkoxide. This then attacks the Michael acceptor to form the enolate; this step is reversible. This enolate is then basic enough to deprotonate the starting alcohol, allowing the use of substoichiometric quantities of base and completing the reaction cycle (Scheme 129).



Scheme 129: Mechanism of conjugate addition using 2,2,2-trifluoroacetophenone

4.3 - Conclusions and future work

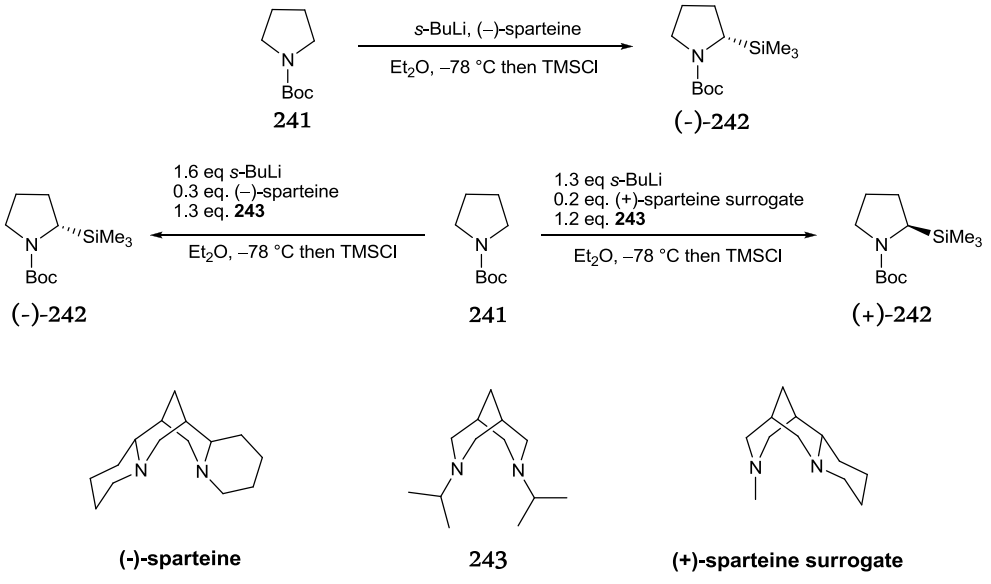
Unfortunately it was found that carbon dioxide was not reactive in the conjugate addition reactions to form the protected carbonate ester, though the reaction conditions were by no means exhausted, there is potential for the reaction using a different set of conditions. However it is possible that the alkoxide formed is not nucleophilic enough to attack the enone. Conversely the use of 2,2,2-trifluoroacetophenone **239** was found to be an excellent replacement for benzaldehyde, giving excellent yields of the *syn* protected diol. This method is more advantageous when compared to using benzaldehyde, as no distillation or multiple additions of **239** are required. The product is also more easily purified as **239** can be removed by rotary evaporation. Future work will be concentrated on optimisation and expansion of the reaction scope, and also on the removal of the acetal masking group.

5 - Investigation of a different base for Crimmins Aldol

5.1 - Introduction

Chiral diamines have been used extensively both as bases in asymmetric synthesis and as chiral ligands in asymmetric catalysis. For these reactions (−)-sparteine is one of the most highly investigated diamines, having been utilised in the asymmetric synthesis of a variety of compounds such as alcohols, amines and phosphines.[74] As had been mentioned previously (−)-sparteine is also the ligand of choice for asymmetric Crimmins aldol reactions.[36] However due to the dramatically rising cost and dwindling supply of (−)-sparteine (1 g for £241.25 from TCI, the only supplier which stocks (−)-sparteine), the most commonly used replacement is TMEDA, although Crimmins' aldol reactions using TMEDA tend to suffer with respect to reaction rates, yields and diastereoselectivities. Prior to the discovery of the use of DIPEA, experiments were performed to find an effective replacement for (−)-sparteine in the Crimmins aldol reactions.

O'Brien *et al.* has demonstrated the use of *s*-BuLi and substoichiometric quantities of (−)-sparteine in the asymmetric deprotonation and trimethylsilylation of *N*-Boc-pyrrolidine (Scheme 130).[74a, 75] Using the sterically hindered *s*-BuLi/(−)-sparteine system, it was believed that the lithiation of **241** would be fairly slow, allowing for ligand exchange with the achiral diamine **243**, freeing (−)-sparteine and recycling the chiral diamine. As would be expected, inversion of the selectivity was also possible by using the equivalent (+)-sparteine surrogate.[76]



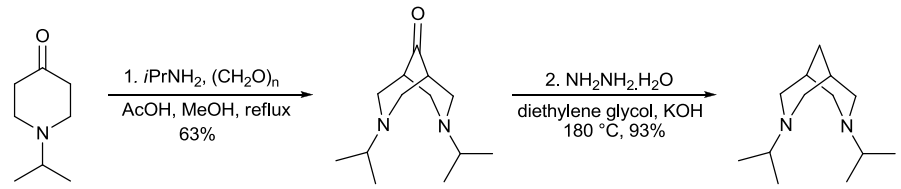
Scheme 130: Use of **243** in asymmetric silylation reactions

Following discussion with Prof. Peter O'Brien, it was decided to synthesise bispidine **243** and investigate its efficacy as a base in Crimmins' aldol reactions. As the stereocontrol of the Crimmins aldol reaction is independent of base used, and the structural similarities of bispidine **243** to (−)-sparteine, it was believed that it would give rise to comparable yields and diastereoselectivities.

5.2 - Results and Discussion

Bispidine Synthesis

Starting from *N*-isopropyl-4-piperidinone **244**, construction of the bicyclic skeleton is achieved by a double Mannich reaction using isopropylamine and paraformaldehyde, heated under reflux in methanol for 24 hours to furnish the diamine **245** (Scheme 131). Removal of the carbonyl group is achieved efficiently using the Huang-Minlon modification of the Wolff-Kishner reaction,[77] allowing a one-pot reduction and forming bispidine **243** in excellent yields over 2 steps.

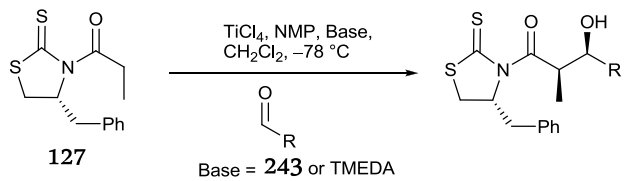


244 245 243

Scheme 131: Synthesis of bispidine **243**

Aldol reactions using bispidine 243

Using the previously optimised conditions for the Crimmins aldol reaction, 1 equivalent each of $TiCl_4$, base and NMP and 1.1 equivalent of the aldehyde in CH_2Cl_2 at −78 °C, the efficacy of the bispidine **243** in the asymmetric aldol reaction was investigated, comparing with TMEDA (Scheme 132). In most of the substrates trialled, the use of bispidine **243** gave rise to improved reaction rates and yields and excellent selectivity for the Evans-type product. The exception is when acetaldehyde is used, with the poor yield most likely caused by the volatility of the aldehyde (Table 18).



127

Scheme 132: Crimmins aldol reactions using bispidine **243**

R	Base	Yield	Evans/non-Evans
$PhCH_2CH_2$-	TMEDA	59%	97:3
	243	72%	98:2
CH_2=CH-	TMEDA	40%	96:4
	243	76%	>99:1
CH_3-	TMEDA	22%	97:3
	243	23%	97:3
$(CH_3)_2CH$-	TMEDA	40%	97:3
	243	56%	>99:1
CH_2=$CHCH_2CH_2$	TMEDA	42%	96:4
	243	79%	>99:1

Table 18: Comparison of **243** and TMEDA in Crimmins aldol reactions

5.3 - Conclusion

Bispidine **243** was found to be an effective replacement for (−)-sparteine in the Crimmins aldol reaction offering better yields and selectivities compared to TMEDA. Compared to commercially available DIPEA, the yields are similar, but **243** gives superior diastereoselectivity. With only 2 synthetic steps **243** can be made cheaply on a large scale, and remains an option in aldol reactions where selectivity is important. However it must be said that DIPEA is commercially available and a much more practical base for the Crimmins aldol reaction.

6 – Experimental

^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrospin spectrometer . Chemical shifts are reported in parts per million (ppm) referenced to chloroform (7.26 ppm). NMR signals are described as follows: δ, chemical shift; multiplicity – recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), septet (sept), multiplet (m) or broad (br) or a combination of these; coupling constants (*J* in Hertz, Hz), integration and assignment.

^{13}C NMR spectra were recorded on the same instruments at 100.6 MHz. The chemical shifts are reported in ppm, reported from the central peak of deuterochloroform (77.16 ppm). Assignments were obtained using DEPT and when necessary HSQC and COSY.

Infra-red spectra (IR) were recorded using a Golden Gate® attachment that allowed the IR of a compound to be detected directing without sample preparation.

Mass spectra (MS) were obtained using a JEOL JMS-700 spectrometer. Ionisation was obtained either by electron impact (EI), chemical ionisation (CI), fast atom bombardment (FAB) or electrospray ionisation (ESI). Mass spectrum data are reported as *m/z.*

Melting points (mp) were recorded using an Electrothermal IA 9100 apparatus.

Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an AA series automatic polarimeter.

Flash chromatography was performed using silica gel (Fluorchem, LC60A, 35-70 micron) as solid support and Fisher HPLC solvents as eluent.

Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 covered alumina plates F254. TLC plates were developed under UV-light and/or with $KMnO_4$, anisaldehyde or ceric ammonium molybdate solutions followed by heating with a heat gun if required.

- $KMnO_4$ solution was prepared by dissolving K_2CO_3 (40 g) and $KMnO_4$ (6 g) in water (600 mL), followed by addition of 10 % $NaOH_{(aq)}$ (5 mL).

- Anisaldehyde solution was prepared by slow addition of conc. H_2SO_4 into ethanol (1 L) at 0 °C, followed by acetic acid (15 mL) and anisaldehyde (20 mL). The solution was stored below 0 °C.

- Ceric ammonium molybdate solution was prepared by dissolving ammonium pentamolybdate (20 g) and cerium sulfate (0.8 g) in 400 mL of dilute H_2SO_4 (1:9 with water v/v).

Purification of solvent and reagents

- Diethyl ether (Et_2O), tetrahydrofuran (THF), and dichloromethane was obtained from a PureSolv 500 MD solvent purification system.

- Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were dried by stirring over Na_2SO_4 overnight, and then distilled under vacuum, discarding the first third.

- Amines (triethylamine, diisopropylamine, 2,6-lutidine, diisopropylethylamine, isopropylamine, TMEDA) and bispidine **243** were distilled over calcium hydride.

- Titanium tetrachloride ($TiCl_4$) was distilled and stored in a Schlenk flask.

- *N*-Methylpyrrolidone (NMP) was dried under vacuum using toluene to form an azeotrope with water.

- HMPA and TMSCl were distilled over calcium hydride.

- $CuBr.SMe_2$ was purified by dissolving in dimethyl sulfide and triturating with pentane.

All other reagents were used as supplied by chemical companies (Acros, Alfa Aesar, Aldrich etc.).

General Procedure

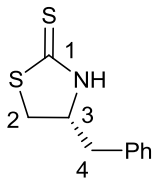
All air and/or water sensitive reactions were carried out in oven dried glassware (oven set at 140 °C) under an argon atmosphere, using dry solvent and standard syringe-cannula/septa techniques.

Yields refer to chromatographically and spectroscopically homogenous materials, unless otherwise stated.

Titration of organometallic bases followed this general procedure – To a solution of (−)-menthol (100 mg, 0.64 mmol) and a catalytic amount of phenanthroline in THF or Et_2O (25 mL) at −78 °C was added by syringe the solution to be titrated. The addition was stopped when the colourless solution turned dark purple which persisted for longer than 5 minutes.

(*R*)-4-Benzylthiazolidine-2-thione (133).[34]

$C_{10}H_{11}NS_2$
Mol. Wt. = 209.34g



In a 3-necked flask, sodium borohydride (5.67 g, 150 mmol, 2.44 equiv) was dissolved in THF (150 mL). (*R*)-Phenylalanine (10.16 g, 61.50 mmol) was added in one portion, and the flask was flushed with argon and then cooled to 0 °C. A solution of I_2 (15.67 g, 61.50 mmol, 1.00 equiv) in THF (50 mL) was added dropwise by syringe over 30 min. After the addition was complete the flask was heated under reflux and left overnight. The flask was then allowed to cool and methanol was cautiously added until the mixture became clear. The solvent was then removed under vacuum yielding a white paste, which was then dissolved in 20% KOH solution. This was left to stir at 20 °C for 3 h, and then the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic extract was dried over Na_2SO_4 and concentrated *in vacuo* giving (*R*)-phenylalaninol **132** as a white solid which was used in the next step without purification.

Crude (*R*)-phenylalaninol **132** was dissolved in 1 M KOH solution (220 mL) and left to stir for 10 min. Carbon disulfide (17.5 g, 230 mmol, 5.00 equiv) was then added dropwise, and the mixture heated under reflux overnight. The flask was cooled to 20 °C and the reaction mixture was extracted with CH_2Cl_2 (3 × 150 mL), then the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then recrystallised from acetonitrile yielding **133** as an off-white solid (12.0 g, 93%).

R_f 0.25 (6:4 PE/EtOAc)

mp - 84–87 °C, lit 79 °C

$[\alpha]_D^{25}$ +136 (*c* 1.0, $CHCl_3$), lit. +117 (*c* 1.45, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.22 (m, 5H, H^{Ar}), 7.11 (brs, 1H, NH), 4.50 (quin, *J* = 7.4 Hz, 1H, H^3), 3.67 (dd, *J* = 11.1, 7.4 Hz, 1H, H^2), 3.38 (dd, *J* = 11.1, 7.4 Hz, 1H, H^2), 3.04 (m, 2H, H^4).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.8 (C^1), 135.9 (C^{Ar}), 129.3 (C^{Ar}), 129.1 (C^{Ar}), 127.6 (C^{Ar}), 65.1 (C^3), 40.2 (C^2 or C^4), 38.4 (C^2 or C^4).

MS (EI) *m/z* 209.06 (M^+)

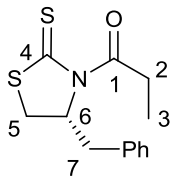
HRMS (EI) for $C_{10}H_{11}NS_2$: 209.0333, found: 209.0336.

In agreement with literature data.[78]

(*R*)-4-Benzyl-3-propionylthiazolidine-2-thione (127).[79]

$C_{13}H_{15}NOS_2$

Mol. Wt = 265.35g



(*R*)-4-Benzylthiazolidine-2-thione **133** (3.78 g, 18.1 mmol) was dissolved in CH_2Cl_2 (50 mL), followed by addition of propionyl chloride (2.51 g, 27.2 mmol, 1.50 equivalents) and freshly distilled triethylamine (4.5 mL, 33 mmol, 1.8 equiv). The reaction was left to stir at 20 °C overnight, after which the mixture was diluted with CH_2Cl_2 and water. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by recrystallisation from acetonitrile to furnish **127** as a bright yellow solid (4.27 g, 89%).

R_f 0.23 (9:1 PE/EtOAc)

mp - 93–95 °C, lit. 105 °C.

$[\alpha]_D^{20}$ −123 (*c* 1.1, $CHCl_3$), lit. −114 (*c* 1.64, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.26 (m, 5H, H^{Ar}), 5.47–5.37 (m, 1H, H^6), 3.53–3.38 (m, 3H, H^2/H^5), 3.27–3.04 (m, 2H, H^5/H^7), 2.91 (d, *J* = 11.6 Hz, 1H, H^7), 1.22 (t, *J* = 7.3 Hz, 3H, H^3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2 (C^4), 175.0 (C^1), 136.6 (C^{Ar}), 129.5 (C^{Ar}), 129.0 (C^{Ar}), 127.3(C^{Ar}), 68.7 (C^6), 36.8 (C^2), 32.4 (C^5 or C^7), 31.9 (C^5 or C^7), 8.9 (C^3).

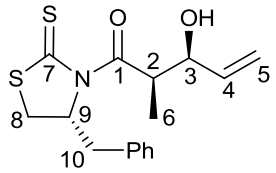
MS (EI) *m/z* 265 (M^+)

HRMS (EI) calculated for $C_{13}H_{15}NOS_2$: 265.0595, found: 265.0594.

In agreement with literature data.[78]

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methyl-pent-4-en-1-one (134).[4f]

$C_{16}H_{19}NO_2S_2$
Mol Wt = 321.46 g



To a solution of **127** (7.60 g, 29 mmol) in CH_2Cl_2 (150 mL) at −10 °C was added dropwise $TiCl_4$ (3.3 mL, 30 mmol, 1.1 equivalents). This was left to stir for 15 min followed by addition of freshly distilled *N*-diisopropylethylamine (5.0 mL, 29 mmol, 1.0 equiv). After stirring for 1 h, the flask was cooled to −78 °C and NMP (2.8 mL, 29 mmol, 1.0 equiv) was added dropwise and left to stir for a further 1 h. Acrolein (2.1 mL, 32 mmol, 1.1 equiv) was introduced by syringe and the mixture left at −78 °C for 1 h, followed by gradual warming to 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (150 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification by flash chromatography (8:2 PE/EtOAc) afforded product **134** as a yellow oil (6.99 g, 75%).

R_f 0.25 (8:2 PE/EtOAc).

$[\alpha]_D^{20}$ −166 (*c* 1.00, $CHCl_3$), lit. −152 (*c* 1.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.29 (m, 5H, H^{Ar}), 5.84 (ddd, *J* = 17.2, 10.4, 5.5 Hz, 1H, H^4), 5.23 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H, H^5), 5.23–5.15 (m, 1H, H^9), 5.10 (ddd, *J* = 10.4, 1.5, 1.5 Hz, 1H, H^5), 4.48 (qd, *J* = 6.8, 4.5 Hz, 1H, H^2), 4.36 (ddd, *J* = 5.5, 4.5, 1.5 Hz, 1H, H^3), 3.29 (dd, *J* = 11.3, 7.1 Hz, 1H, H^{10}), 3.15 (dd, *J* = 13.1, 3.8 Hz, 1H, H^8), 2.95 (dd, *J* = 13.1, 10.6 Hz, 1H, H^8), 2.80 (d, *J* = 11.3 Hz, 1H, H^{10}), 1.16 (d, *J* = 6.8 Hz, 3H, H^6).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6 (C^7), 178.3 (C^1), 137.2 (C^4), 136.4 (C^{Ar}), 129.5 (C^{Ar}), 129.0 (C^{Ar}), 127.3 (C^{Ar}), 116.8 (C^5), 77.0 (C^3), 68.9 (C^9), 43.3 (C^2), 37.9 (C^8), 29.7 (C^{10}), 10.6 (C^6).

IR 2957 (CH), 1695 (C=O), 1604 (C=C), 1494, 1448, 1427, 1345, 1285, 1255, 1193, 1165, 1140, 1038 cm^{-1}.

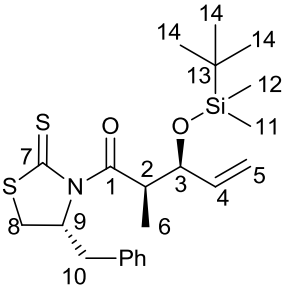
MS (EI) *m/z* 321 (M^+).

HRMS (EI) calculated for $C_{16}H_{19}NOS_2$: 321.0857, found: 321.0860.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-*(tert*-Butyldimethylsilyloxy)-2-methyl-pent-4-en-1-one (135).

$C_{22}H_{33}NS_2SiO_2$

Mol Wt = 435.72 g



A solution of **134** (4.00 g, 11.5 mmol) and TBSCl (6.93 g, 46.0 mmol, 4.0 equiv) in anhydrous DMF (40 mL) was cooled to 0 °C and 2,6-lutidine (6.16 g, 57.5 mmol, 5.0 equiv) was added dropwise. The mixture was left to stir at 20 °C for 3 days and was quenched by addition of ice water. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts washed with saturated aqueous $CuSO_4$ solution (2 × 15 mL). The organic extracts were then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (97:3 PE/EtOAc) furnishing **135** as a bright yellow oil (4.86 g, 97%).

R_f 0.3 (97:3 PE/EtOAc)

$[\alpha]_D^{25}$ −180 (*c* 1.0, $CHCl_3$), lit. −173 (*c* 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.31 (m, 5H, H^{Ar}), 5.85 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H, H^4), 5.16 (ddd, *J* = 17.2, 1.6, 1.2 Hz, 1H, H^5), 5.15–5.09 (m, 2H, H^5/H^9), 4.58 (quin, *J* = 6.6 Hz, 1H, H^2), 4.31 (ddt, *J* = 6.8, 6.6, 1.2, 1H, H^3), 3.33–3.25 (m, 2H, H^8/H^{10}), 3.10 (dd, *J* = 13.4, 10.9 Hz, 1H, H^{10}), 2.87 (d, *J* = 11.4 Hz, 1H, H^8), 1.22 (d, *J* = 6.6 Hz, 3H, H^6), 0.87 (s, 9H, H^{14}), 0.02 (s, 3H, H^{11}) 0.00 (s, 3H, H^{12}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2 (C^7), 176.3 (C^1), 139.2 (C^4), 136.7 (C^{Ar}), 129.5 (C^{Ar}), 128.9 (C^{Ar}), 127.2 (C^{Ar}), 115.7 (C^5), 76.4 (C^3), 69.5 (C^9), 45.9 (C^2), 36.5 (C^{10}), 32.3 (C^8), 25.8 (C^{14}), 18.1 (C^{13}), 11.6 (C^6), −4.3 (C^{11}), −5.0 (C^{12}).

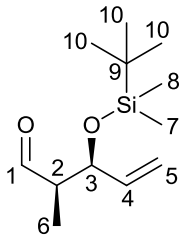
IR 2957(CH), 2858, 1699 (C=O), 1459, 1345, 1287, 1265, 1254, 1192, 1140 (C-O), 1084, 1030 cm^{-1}.

MS (FAB) *m/z* 435 (M^+)

HRMS (FAB) calculated for $C_{22}H_{33}NS_2SiO_2$**:** 435.1722, found**:** 435.1730.

(2*R*,3*S*)-3-*(tert*-Butyldimethylsilyloxy)-2-methyl-4-pentenal (136).

$C_{12}H_{24}SiO_2$
Mol Wt = 228.40 g



A solution of **135** (4.70 g, 10.8 mmol) in CH_2Cl_2 (110 mL) was cooled to −78 °C and a 1M solution of DIBAL-H in hexanes (21.6 mL, 21.6 mmol, 2.0 equiv) was added dropwise. The mixture was left to stir until the bright yellow colour disappeared, then the reaction was quenched with EtOAc. The mixture was then diluted with 10% aqueous Rochelle's salt solution and stirred for 1 h until the organic phase went clear. The mixture was then extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (98:2 PE/EtOAc) switching up to (8:2 PE/EtOAc) to collect **133** (1.92 g, 85%) and **136** as a colourless oil (2.42 g, 85%).

R_f 0.4 (98:2 PE/EtOAc)

$[\alpha]_D^{25}$ −87 (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (d, *J* = 1.3 Hz, 1H, H^1), 5.86 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, H^4), 5.29 (ddd, *J* = 17.2, 1.6, 1.3 Hz, 1H, H^5), 5.20 (ddd, *J* = 10.4, 1.6, 1.3 Hz, 1H, H^5), 4.71 (ddt, *J* = 6.0, 4.3, 1.3 Hz, 1H, H^3), 2.50 (qdd, *J* = 7.0, 4.3, 1.3 Hz, 1H, H^2), 1.07 (d, *J* = 7.0 Hz, 3H, H^6), 0.88 (s, 9H, H^{10}), 0.05 (s, 3H, H^7), 0.03 (s, 3H, H^8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.8 (C^1), 138.4 (C^4), 116.1 (C^5), 76.7 (C^3), 52.7 (C^2), 25.9 (C^9), 18.3 (C^{10}), 8.5 (C^6), −4.1 (C^7), −4.9 (C^8).

IR 2932 (CH), 1728 (C=O), 1255, 1151 (C-O), 1084, 1002 cm^{-1}.

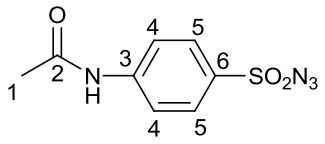
MS (FAB) *m/z* 228 (M+)

HRMS (FAB) calculated for $C_{12}H_{24}SiO_2$: 228.1546, found: 228.1551.

***N*-Acetylsulfaninyl azide (138).**[39]

$C_8H_8N_4O_3S$

Mol. Wt. = 240.24 g



In HPLC grade acetone (150 mL) was dissolved *N*-acetylsulfaninyl chloride **137** (20.3 g, 87.0 mmol) and left to stir for 5 min. A solution of sodium azide (6.77 g, 104 mmol, 1.2 equiv) in H_2O (50 mL) was added slowly over 10 min and the reaction mixture was left to stir overnight. The solution was then split into 3 portions and each one diluted with H_2O (160 mL) and left to stir for 1 h. The precipitate formed was isolated by filtration and recrystallisation from toluene afforded the product **138** as a fluffy white solid (8.70 g, 36%).

mp - 102–103 °C, lit. 106-108 °C[80]

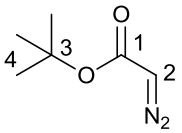
^{1}H NMR ($CDCl_3$, 400MHz) δ 7.93 (d, *J* = 8.1 Hz, 2H, H^4), 7.79 (d, *J* = 8.1 Hz, 2H, H^5), 7.45 (br s, 1H, NH), 2.27 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 (C^2), 144.1 (C^6), 132.8 (C^4), 127.8 (C^4), 119.0 (C^5), 25.0 (C^1).

In agreement with literature data.

***tert*-Butyl diazoacetate (140).**[40]

$C_6H_{10}N_2O_2$
Mol Wt = 142.16 g



tert-Butyl acetoacetate (5.20 g, 37.5 mmol), *N*-acetylsulfaninyl azide **138** (9.61 g, 40.1 mmol, 1.07 equivalents) and NBu_4Br (4.74 g, 15.0 mmol, 0.4 equivalents) were dissolved in pentane (380 mL) and left to stir at 20 °C for 3 min. A 3M aqueous NaOH solution (70 mL, 2.8 equiv) was added slowly over 10 min and the mixture left to stir for 1 h. Once the reaction was complete the mixture was diluted with H_2O (100 mL) and Et_2O (100 mL). The organic phase was isolated and aqueous layer extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **140** as a bright yellow oil (3.20 g, 60%).

R_f 0.45 (8:2 PE:EtOAc)

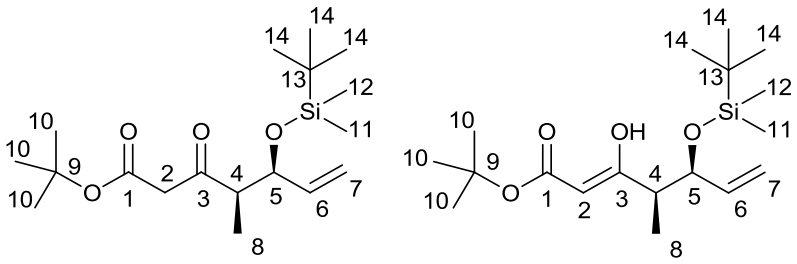
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.62 (br s, 1H, H^2), 3.76 (s, 9H, H^4).

In agreement with literature data.

***tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-oxohept-6-enoate (142).**

$C_{18}H_{34}SiO_4$

Mol Wt = 342.54 g



3.5 : 1

To a solution of $SnCl_2$ (0.88 g, 4.6 mmol, 0.5 equiv) in CH_2Cl_2 (28 mL) was added *tert*-butyl diazoacetate **140** (2.64 g, 18.6 mmol, 2.0 equiv) and **136** (2.12 g, 9.28 mmol) in CH_2Cl_2 (10 mL). The mixture was left to stir at 20 °C for 3 h, filtered and the solvent reduced *in vacuo*. The product was then purified by flash chromatography (95:5 PE/EtOAc) to give product **142** as a pale yellow oil, as inseparable mixture in a 3.5:1 ratio with the enol form **142'** (2.32 g, 73%).

R_f 0.25 (95:5 PE/EtOAc).

$[\alpha]_D^{20}$ −67 (*c* 1.00, $CHCl_3$).

β-ketoester form

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (ddd, *J* = 17.2, 10.4, 6.1 Hz, 1H, H^6), 5.18 (ddd, *J* = 17.2, 1.3, 0.8 Hz, 1H, H^7), 5.11 (ddd, *J* = 10.4, 1.3, 0.8 Hz, 1H, H^7), 4.26 (ddt, *J* = 6.1, 5.5, 1.3 Hz, 1H, H^5), 3.51 (d, *J* = 15.6 Hz, 1H, H^2), 3.41 (d, *J* = 15.6 Hz, 1H, H^2), 2.87 (qd, *J* = 7.0, 5.5 Hz, 1H, H^4), 1.48 (s, 9H, H^{10}), 1.09 (d, *J* = 7.0 Hz, 3H, H^8), 0.90 (s, 9H, H^{14}), 0.07 (s, 3H, H^{12}), 0.03 (s, 3H, H^{12}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.8 (C^3), 178.3 (C^1), 139.3 (C^6), 114.9 (C^7), 82.0 (C^9), 77.3 (C^5), 53.3 (C^2), 49.6 (C^4), 28.2 (C^{10}), 24.7 (C^{14}), 18.1 (C^{13}), 12.5 (C^8), −4.0 (C^{11}), −4.3 (C^{12}).

IR 2932 (CH), 1728 (C=O), 1680 (C=O), 1255, 1151 (C-O), 1084, 1002 cm^{-1}.

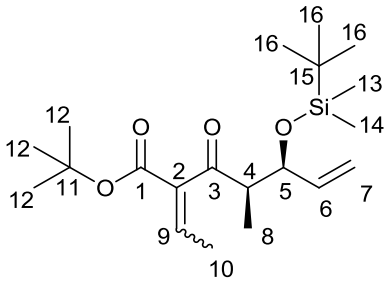
MS (CI) *m/z* 343 (MH^+)

HRMS (CI) calculated for $C_{18}H_{35}SiO_4$: 343.5554, found: 343.5555.

***tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-2-ethylidene-4-methyl-3-oxohept-6-enoate (143).**

$C_{20}H_{36}SiO_4$

Mol Wt = 368.58 g



To a stirred solution of $TiCl_4$ (4.6 mL, 42 mmol, 1.8 equiv) in THF (85 mL) at 0 °C was successfully added freshly distilled acetaldehyde (5.8 mL, 104 mmol, 4.5 equiv), a solution of **142** (7.90 g, 23.1 mmol) in THF (35 mL), and pyridine (6.5 mL, 81 mmol, 3.5 equiv). The reaction was allowed to warm to 20 °C and stirred for 3 h. The mixture was then quenched by a slow addition of water and extracted with Et_2O (3 × 100 mL). The organic extracts were then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was then purified by column chromatography (95:5 PE/EtOAc) to furnish the product **143** as a colourless oil (7.49 g, 88%). Isolated as an inseperable mixture of *E*/Z diastereomers.

R_f 0.3 (95:5 PE/EtOAc).

$[\alpha]_D^{20}$ −44 (*c* 1.00, $CHCl_3$).

Diastereomer A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (q, *J* = 7.3 Hz, H^9), 5.82 (ddd, *J* = 17.1, 10.4, 6.8 Hz 1H, H^6), 5.18 (ddd, *J* = 17.1, 1.5, 1.3 Hz, 1H, H^7), 5.13–5.06 (m, 1H, H^7), 4.32–4.25 (m, 1H, H^5), 3.13 (dq, *J* = 7.1, 6.9 Hz, 1H, H^4), 1.96 (d, *J* = 7.3 Hz, 3H, H^{10}), 1.51 (s, 9H, H^{12}). 1.16 (d, *J* = 7.1 Hz, 3H, H^{10}), 0.90 (s, 9H, H^{16}), 0.08 (s, 3H, H^{13}), 0.04 (s, 3H, H^{14}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4 (C^3), 164.1 (C^1), 144.3 (C^9), 138.8 (C^6), 138.1 (C^2), 115.7 (C^7), 81.7 (C^{11}), 75.5 (C^5), 52.1 (C^4), 28.0 (C^{12}), 25.2 (C^{16}), 18.2 (C^{15}), 15.6 (C^{10}), 12.9 (C^8), −4.3 (C^{13}), −4.9 (C^{14}).

Diastereomer B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79 (q, *J* = 7.3 Hz, 1H, H^9), 5.75 (ddd, *J* = 17.1, 10.4, 6.8 Hz 1H, H^6), 5.17 (ddd, *J* = 17.1, 1.5, 1.3 Hz, 1H, H^7), 5.13–5.06 (m, 1H, H^7), 4.35–4.24

(m, 1H, H^5), 3.13 (dq, *J* = 6.9, 6.9 Hz, 1H, H^4), 1.85 (d, *J* = 7.3 Hz, 3H, H^8), 1.55 (s, 9H, H^{12}). 1.15 (d, *J* = 7.2 Hz, 3H, H^{10}), 0.90 (s, 9H, H^{16}), 0.05 (s, 3H, H^{13}), 0.02 (s, 3H, H^{14}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.1 (C^3), 165.8 (C^1), 142.0 (C^9), 139.4 (C^2), 139.0 (C^6), 115.0 (C^7), 82.1 (C^{11}), 75.2 (C^5), 48.8 (C^4), 27.9 (C^{12}), 25.8 (C^{16}), 18.0 (C^{15}), 15.3 (C^{10}), 13.4 (C^8), −4.2 (C^{13}), −4.9 (C^{14}).

IR 2955 (CH), 2930, 2858, 1722 (C=O), 1697 (C=O), 1643 (C=C), 1462, 1392, 1367, 1249, 1151 (C-O), 1070, 1026, 1005 cm^{-1}.

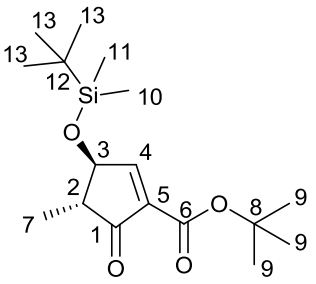
MS (ESI) *m/z* 391 (MNa^+)

HRMS (ESI) – for $C_{20}H_{36}SiO_4Na$: 391.2275, found 391.2271.

***tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-oxohept-6-enoate (113c).**

$C_{17}H_{30}SiO_4$

Mol. Wt. = 326.50 g



In a vacuum-dried two-necked flask, **143** (2.00 g, 5.43 mmol) was dissolved in dry degassed CH_2Cl_2 (108 mL). Grubbs 2nd generation catalyst (230 mg, 0.27 mmol, 5 mol%) was added in one portion and the solution was heated under reflux for 24 h. An additional portion of Grubbs 2nd generation catalyst was added (230 mg, 0.27 mmol, 5 mol%) and the mixture heated under reflux for a further 12 h. Once the reaction had cooled to room temperature, DMSO was added and the mixture was stirred overnight, after which the solvent was removed *in vacuo* and the product purified by column chromatography (8:2 PE/EtOAc) furnishing the product **113c** as a viscous pale brown oil (1.19 g, 67%).

R_f 0.25 (8:2 PE/EtOAc).

$[\alpha]_D^{20}$ + 91 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 2.1 Hz, 1H, H^4), 4.33 (dd *J* = 3.1, 2.1 Hz, 1H, H^3), 2.26 (qd, *J* = 7.5, 3.1 Hz, 1H, H^2), 1.45 (s, 9H, H^9), 1.13 (d, *J* = 7.5 Hz, 3H, H^7) 0.78 (s, 9H, H^{13}), 0.02 (s, 3H, H^{10}), 0.00 (s, 3H, H^{11}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.1 (C^1), 166.0 (C^4), 160.9 (C^6), 137.2 (C^5), 82.2 (C^8), 76.1 (C^3), 52.6 (C^2), 28.8 (C^9), 25.7 (C^{14}), 18.0 (C^{11}), 12.5 (C^7), −4.6 (C^{10}), −4.7 (C^{11}).

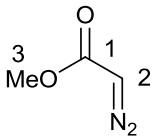
IR 2955 (CH), 2930 (CH), 2858, 1751 (C=O), 1736 (C=O), 1716, 1626 (C=C), 1460, 1342, 1251, 1155 (C-O), 1109, 1072, 1055, 1006 cm^{-1}.

MS (ESI) *m/z* 349 (MNa^+)

HRMS (ESI) for $C_{17}H_{30}SiO_4Na$: 349.1811, found: 349.1806.

Methyl diazoacetate (144).[81]

$C_3H_4N_2O_2$
Mol. Wt. = 100.08 g



In a solution of pentane (500 mL), methyl acetoacetate (8.0 g, 61.5 mmol), **138** (15.8 g, 65.8 mmol, 1.07 equiv) and TBAB (7.93 g, 24.6 mmol, 0.4 equiv) were dissolved and left to stir at 20 °C for 3 min. A 3 M NaOH solution (74 mL, 1.8 equiv NaOH) was added slowly over 10 min and the mixture left to stir for 1 h. Once the reaction was complete the mixture was diluted with H_2O and Et_2O. The organic phase was isolated and aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic extracts were dried over Na_2SO_4. Filtration followed by very careful reduction of the solvent gave the product **144** in ether as yellow solution (0.59 g, 49%). Yield measured by ^{1}H NMR.

R_f 0.2 (98:2 PE/EtOAc)

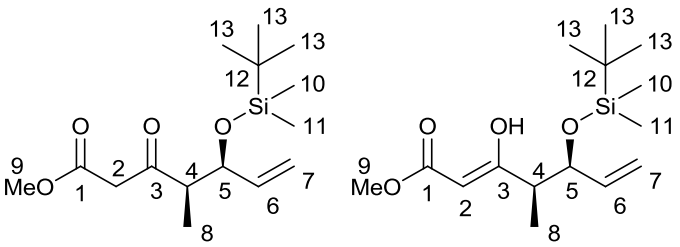
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.75 (br s, 1H, H^2), 3.74 (s, 3H, H^3).

In agreement with literature data.

Methyl (4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-oxohept-6-enoate (145).

$C_{15}H_{28}O_4Si$

Mol Wt = 300.46 g



To a suspension of $SnCl_2$ (0.14 g, 0.75 mmol, 0.5 equiv) in CH_2Cl_2 (10 mL) was added a solution of methyl diazoacetate **144** (>5.0 equiv) in diethyl ether (5 mL), followed by **136** (350 mg, 1.5 mmol) in CH_2Cl_2 (4 mL). The mixture was left to stir at 20 °C for 3 h, filtered and the solvent was reduced *in vacuo*. The product was then purified by flash chromatography (95:5 PE/EtOAc) to give product **145** as a pale yellow oil in a 3:1 ratio with the enol form (315 mg, 70%).

R_f 0.35 **(**95:5 PE/EtOAc)

$[\alpha]_D^{20}$ −41 (*c* = 1.0, $CHCl_3$), lit. −46 (*c* = 1.02, $CHCl_3$).[81]

β-ketoester form

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H, H^6), 5.16 (ddd, *J* = 17.2, 1.4 Hz, 1.4 Hz, 1H, H^7), 5.13 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H, H^7), 4.31–4.25 (m, 1H, H^5), 3.75 (s, 3H, H^9), 3.60 (d, *J* = 16.0 Hz, 1H, H^2), 3.49 (d, *J* = 16.0 Hz, 1H, H^2), 2.88 (qd, *J* = 7.0, 5.6 Hz, 1H. H^4), 1.11 (d, *J* = 7.0 Hz, 3H, H^8), 0.90 (s, 9H, H^{13}), 0.05 (s, 3H, H^{10}), 0.02 (s, 3H, H^{11}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.4 (C^3), 167.6 (C^1), 138.1 (C^6), 116.3 (C^7), 75.4 (C^5), 52.1 (C^9), 52.0 (C^4), 49.7 (C^2), 25.7 (C^{13}), 17.6 (C^{12}), 12.0 (C^8), −4.3 (C^{10}), −4.5 (C^{11}).

IR 2957 (CH), 2931, 2858, 1749 (C=O), 1716 (C=O), 1648 (C=C), 1625, 1472, 1422, 1366, 1307, 1258, 1225, 1154 (C-O), 1073, 1029 cm^{-1}.

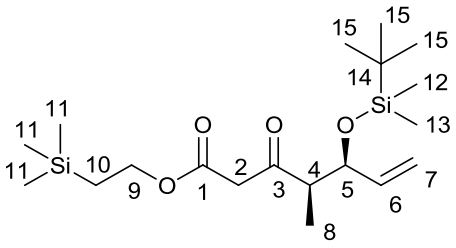
MS (CI) *m/z* 300 (M^+).

HRMS (CI) for $C_{15}H_{28}SiO_4$: 300.4657, found: 300.4655.

2-(Trimethylsilyl)ethyl (4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-oxohept-6-enoate (146).

$C_{19}H_{38}O_4Si_2$

Mol Wt = 386.67 g



To a solution of **145** (250 mg, 0.83 mmol) and 2-(trimethylsilyl)ethanol (0.98 g, 8.3 mmol, 10 equiv) in toluene (5 mL) was added ZnO (14 mg, 0.17 mmol, 20 mol%). The mixture was heated under reflux for 12 hours, after which the solvent was removed *in vacuo* and the crude material was purified by column chromatography (95:5 PE/EtOAc) to furnish the transesterification product **146** (253 mg, 79%)

R_f 0.3 **(**95:5 PE/EtOAc).

$[\alpha]_D^{20}$ −77 (*c* = 1.0, $CHCl_3$).

β-ketoester form

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H, H^6), 5.18 (ddd, *J* = 17.0, 1.4 Hz, 1.4 Hz, 1H, H^7), 5.12 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H, H^7), 4.26 (dd, *J* = 6.7, 6.5 Hz 1H, H^5), 4.20 (dd, *J* = 9.0, 8.3 Hz, 2H, H^9), 3.57 (d, *J* = 15.8 Hz, 1H, H^2), 3.49 (d, *J* = 15.8 Hz, 1H, H^2), 2.87 (qd, *J* = 7.1, 6.7 Hz, 1H, H^4), 1.08 (d, *J* = 7.1 Hz, 3H, H^8), 1.00 (dd, *J* = 9.0, 8.3 Hz, 2H, H^{10}), 0.86 (s, 9H, H^{15}), 0.05 (s, 3H, H^{12}), 0.02 (s, 3H, H^{13}), 0.01 (s, 9H, H^{11}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.5 (C^3), 169.1 (C^1), 139.5 (C^6), 117.8 (C^7), 78.8 (C^5), 65.0 (C^9), 54.3 (C^4), 51.9 (C^2), 29.6 (C^{14}), 27.4 (C^{15}), 18.8 (C^{10}), 13.5 (C^8), 0.00 (C^{11}), −2.9 (C^{12}), −3.6 (C^{13}).

IR 2956 (CH), 2930, 2858, 1745 (CO), 1714 (CO), 1645 (C=C), 1463, 1250, 1224, 1028 cm^{-1}.

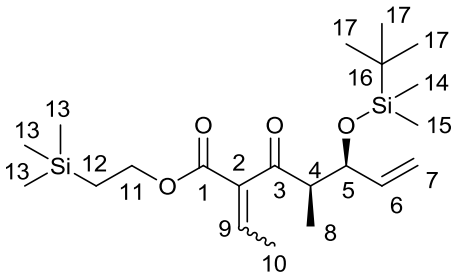
MS (ESI) *m/z* 409 (MNa^+).

HRMS (ESI) for $C_{19}H_{38}Si_2O_4$: 409.2207, found: 409.2210.

2-(Trimethylsilyl)ethyl (4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-2-ethylidene-4-methyl-oxohept-6-enoate (147).

$C_{21}H_{40}O_4Si_2$

Mol Wt = 412.71 g



To a stirred solution of $TiCl_4$ (60 uL, 0.93 mmol, 1.8 equiv) in THF (1 mL) at 0 °C was successfully added freshly distilled acetaldehyde (145 uL, 2.34 mmol, 4.5 equiv), a solution of **146** (200 mg, 0.52 mmol) in THF (3 mL), and pyridine (146 uL, 1.82 mmol, 3.5 equiv). The reaction was allowed to warm to 20 °C and stirred for 3 h. The mixture was then quenched by a slow addition of water and extracted with Et_2O (3 × 10 mL). The organic extracts were then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was then purified by column chromatography (95:5 PE/EtOAc) to furnish the product **147** as a colourless oil (182 mg, 85%). Inseperable 1.7:1 mixture of diastereomers.

R_f 0.4 **(**95:5 PE/EtOAc).

Diastereomer A

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (q, *J* = 7.3 Hz, 1H, H^9), 5.82 (ddd, *J* = 17.2, 10.4, 6.8 Hz 1H, H^6), 5.21–5.04 (m, 2H, H^7), 4.36–4.22 (m, 3H, H^5/H11), 3.11 (quin, *J* = 7.0 Hz, 1H, H^4), 1.87 (d, *J* = 7.3 Hz, 3H, H^{10}), 1.15 (d, *J* = 7.0, 3H, H^8), 1.10–1.00 (m, 2H, H^{12}), 0.88 (s, 9H, H^{17}), 0.06 (s, 9H, H^{13}), 0.04 (s, 3H, H^{14}), 0.02 (s, 3H, H^{15}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.2 (C^3), 166.6 (C^1), 146.6 (C^9), 140.7 (C^6), 140.0 (C^2), 117.1 (C^7), 76.9 (C^5), 65.0 (C^{11}), 53.8 (C^4), 27.4 (C^{17}), 19.8 (C^{16}), 19.0 (C^{12}), 17.2 (C^{10}), 15.2 (C^8), 0.0 (C^{13}), −2.7 (C^{14}), −3.4 (C^{15}).

Diastereomer B

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 (q, *J* = 7.3 Hz, 1H, H^9), 5.75 (ddd, *J* = 17.2, 10.4, 6.8 Hz 1H, H^6), 5.21–5.04 (m, 2H, H^7), 4.36–4.22 (m, 3H, H^5/H11), 3.11 (quin, *J* = 7.0 Hz, 1H, H^4), 1.98 (d, *J* = 7.3 Hz, 3H, H^{10}), 1.14 (d, *J* = 7.0, 3H, H^8), 1.10–1.00 (m, 2H, H^{12}), 0.88 (s, 9H, H^{17}), 0.05 (s, 9H, H^{13}), 0.04 (s, 3H, H^{14}), 0.01 (s, 3H, H^{15}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6 (C^3), 168.1 (C^1), 145.0 (C^9), 140.8 (C^6), 138.3 (C^2), 117.2 (C^7), 76.9 (C^5), 64.9 (C^{11}), 50.5 (C^4), 27.4 (C^{17}), 19.7 (C^{16}), 19.0 (C^{12}), 17.3 (C^{10}), 14.5 (C^8), 0.0 (C^{13}), −2.7 (C^{14}), −3.4 (C^{15}).

IR 2955 (CH), 2857, 1764 (CO), 1726 (CO), 1697 (C=C), 1449, 1387, 1274, 1248, 1131 (C-O), 1057 cm^{-1}.

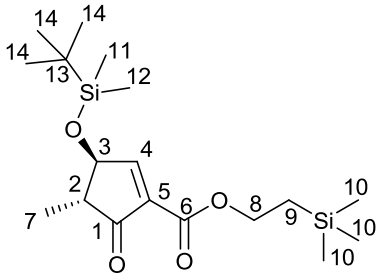
MS (ESI) *m/z* 435 (MNa^+).

HRMS (ESI) for $C_{21}H_{40}Si_2O_4$: 435.2365, found: 435.2373.

2-(Trimethylsilyl)ethyl 5-(*tert*-Butyldimethylsilyloxy)-4-methyl-3-oxohept-6-enoate (113d).

$C_{18}H_{34}Si_2O_4$

Mol. Wt. = 370.63 g



In a vacuum-dried two-necked flask, **147** (108 mg, 0.26 mmol) was dissolved in dry degassed CH_2Cl_2 (10 mL). Grubbs' 2nd generation catalyst (11 mg, 0.013 mmol, 5 mol%) was added in one portion and the solution was heated under reflux for 24 h. Once the reaction had cooled to room temperature, the solvent was removed *in vacuo* and the product purified by column chromatography (92:8 PE/EtOAc) furnishing the product **113d** as a viscous pale brown oil (69 mg, 72%).

R_f 0.25 (92:8 PE/EtOAc).

$[\alpha]_D^{20}$ +113 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* = 2.3 Hz, 1H, H^4), 4.33 (dd *J* = 3.0, 2.3 Hz, 1H, H^3), 4.13 (dd, *J* = 8.9, 8.1 Hz, 2H, H^8), 2.37 (qd, *J* = 7.2, 3.0 Hz, 1H, H^2), 1.14 (d, *J* = 7.2 Hz, 3H, H^7), 0.99 (dd, *J* = 8.9, 8.1 Hz, 2H, H^9), 0.78 (s, 9H, H^{14}), 0.05 (s, 9H, H^{11}), 0.02 (s, 3H, H^{12}), 0.00 (s, 3H, H^{10}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.9 (C^1), 164.7 (C^4), 160.0 (C^6), 134.6 (C^5), 76.1 (C^3), 66.3 (C^8), 51.6 (C^2), 25.7 (C^{14}), 18.9 (C^{13}), 17.4 (C^9), 12.5 (C^7), 0.0 (C^{10}), −4.2 (C^{11}), −4.6 (C^{12}).

IR 2955 (CH), 2930, 2858, 1749 (CO), 1724 (CO), 1621 (C=C), 1460, 1342, 1251, 1155, 1139, 1055, 1012 cm^{-1}.

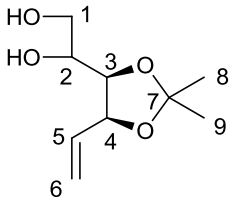
MS (ESI) *m/z* 393 (MNa^+)

HRMS (ESI) for $C_{18}H_{34}Si_2O_4Na$: 393.1893, found: 393.1899.

1-[(4*R*,5*S*)-5-ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]ethan-1,2-diol (151).[42, 82]

$C_9H_{16}O_4$

Mol Wt = 188.10 g



To a stirred suspension of D-ribose (50.0 g, 333 mmol) in acetone (625 mL) was added dropwise concentrated H_2SO_4 (1.5 mL, 28.0 mmol, 0.08 equiv). The mixture was then stirred at room temperature for 3 h until all the solid had gone into solution. The solution was then neutralised with solid $NaHCO_3$, filtered and the solvent reduced *in vacuo* to give the product **152** as a colourless syrup (58.3 g, 93%) which was used in the next step without purification.

To a stirred suspension of methyltriphenylphosphonium bromide (386 g, 1.08 mol, 3.5 equiv) in THF (1.08 L) at 0 °C was added potassium *tert*-butoxide (121 g, 1.08 mol, 3.5 equiv). The bright yellow mixture was then stirred at 0 °C for a further 20 min and then at room temperature for 1 h. The solution was then cooled to 0 °C and a solution of **152** (58.0 g, 308 mmol) in THF (180 mL) was added by cannula and the reaction stirred at 20 °C for 12 h. The mixture was then poured carefully into water (1.0 L) and extracted with ethyl acetate (3 × 500 mL). The organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then purified by column chromatography (2:1 to 2.5:1 EtOAc:PE), followed by trituration with cold Et_2O to remove any remaining solid triphenylphosphine oxide to furnish the product **151** as a pale yellow oil (38.2 g, 68%) contaminated with a little triphenylphosphine oxide.
An analytical sample was prepared by a further column chromatography (2:1 EtOAc/PE) giving the product as a colourless oil.

R_f (2:1 EtOAc/PE)

$[\alpha]_D^{25}$ + 37 (*c* 1.00, $CHCl_3$), lit. + 25 (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.99 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H, H^5), 5.42 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H, H^6), 5.29 (ddd, *J* = 10.4, 1.4, 1.4 Hz, 1H, H^6), 4.68 (br t, *J* = 6.4 Hz, 1H, H^4), 4.06 (dd, *J* = 8.4, 6.4 Hz, 1H, H^3), 3.81-3.64 (m, 3H, H^1/H^2), 2.9 (br s, 2H, OH), 1.44 (s, 3H, H^8), 1.34 (s, 3H, H^9).

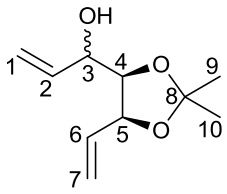
^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.7 (C^5), 118.3 (C^6), 108.9 (C^7), 78.5 (C^4), 77.9 (C^3), 69.9 (C^2), 64.3 (C^1), 27.7 (C^8), 25.3 (C^9).

MS (CI) *m/z* 189 (MH^+).

In agreement with literature data.

1-[(4*R*,5*S*)-5-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (149).[41a]

$C_{10}H_{16}O_3$
Mol Wt = 184.23 g



To a stirring solution of **151** (36.0 g, 198 mmol) in CH_2Cl_2 (750 mL) was added a solution of $NaIO_4$ (63.5, 297 mmol, 1.5 equiv) in distilled water (470 mL). The reaction mixture was then stirred at 20 °C for 1 h. The reaction was then diluted with CH_2Cl_2 and water and the two layers were separated. The organic layer was dried over $MgSO_4$ and carefully evaporated under reduced pressure at 0 °C. The residue was then purified by column chromatography using a very short column (1:1 PE/Et_2O) to yield the product **150** as a colourless oil (17.0 g, 55%). Due to its instability the aldehyde was used immediately in the next step.

To a stirred solution of **150** (17.0 g, 108 mmol) in THF (440 mL) at −78 °C was added dropwise a 0.7M solution of vinylmagnesium bromide (231 mL, 162 mmol, 1.5 equiv). The reaction was stirred at −78 °C and then slowly warmed to 0 °C and stirred for a further 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution and warmed to 20 °C. The layers were separated and the aqueous layer extracted with Et_2O (3 × 250 mL). The organic layers were then combined, dried over Na_2SO_4, filtered and reduced *in vacuo*, with the crude material being purified by column chromatography giving the product **149** as a colourless oil as a 2:3 inseparable mix of diastereomers (17.3 g, 80%).

Major diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.08-6.05 (m, 1H, H^6), 5.95 (ddd, J = 17.2, 10.6, 5.4 Hz, 1H, H^6), 5.48-5.25 (m, 4H, H^1/H^7), 4.70 (dd, *J* = 7.5, 6.5 Hz, 1H, H^3), 4.20–4.10 (m, 2H, H^5), 4.20-3.98 (m, 2H, H^4/H^5), 1.55 (s, 3H, H^9), 1.41 (s, 3H, H^{10}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5 (C^2), 133.9 (C^6), 119.9 (C^1), 117.2 (C^7), 108.9 (C^8), 80.5 (C^5), 79.1 (C^3), 71.1 (C^4), 27.2 (C^9), 25.7 (C^{10}).

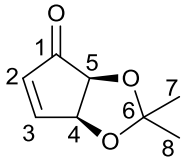
MS (CI) *m/z* 185 (MH^+).

In agreement with literature data.

(3a*S*,6a*S*)-2,2-Dimethyl-2H,3aH,4H,6a*H*-cyclopenta[d][1,3]dioxol-4-one (148).[83]

$C_8H_{10}O_3$

Mol Wt = 154.16 g



To a solution of **149** (7.10 g, 38.6 mmol) in degassed CH_2Cl_2 (500 mL) was added Grubbs' 1st generation catalyst (161 mg, 0.20 mmol, 0.5 mol%) in one portion. The reaction was left to stir at 20 °C for 12 h, after which the solvent was removed *in vacuo*. The residue was then dissolved in EtOAc (275 mL) and IBX (19.5 g, 69.5 mmol, 1.8 equiv) was added in one portion. The reaction was heated under reflux for 3 h, cooled to 0 °C and filtered. The solvent was evaporated *in vacuo* and the crude material was purified by column chromatography (8:2 PE:EtOAc) to furnish the product **148** as a white solid (4.82 g, 81%).

Rf 0.25 (8:2 PE:EtOAc).

$[\alpha]_D^{25}$ +73 (*c* 1.0, $CHCl_3$), lit. +69 (*c* 1.0, $CHCl_3$).

mp - 55–58 °C, lit. 68–69 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (dd, *J* = 5.9, 2.3 Hz, 1H, H^3), 6.21 (dd, *J* = 5.9, 0.6 Hz, 1H, H^2), 5.28 (ddd, *J* = 5.5, 2.3, 0.6 Hz, 1H, H^4) 4.46 (d, *J* = 5.5 Hz, 1H, H^5), 1.42 (s, 3H, H^7), 1.41 (s, 3H, H^8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.3 (C^1), 157.8 (C^3), 132.1 (C^2), 114.7 (C^6), 79.2 (C^4), 72.0 (C^2), 28.5 (C^7), 27.9 (C^8).

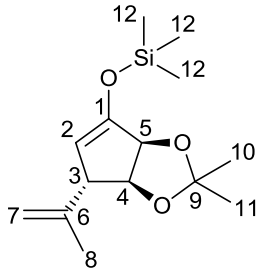
MS (CI) *m/z* 155 (MH^+).

In agreement with literature data.

((3a*S*,6*S*,6a*S*)-6-Isopropenyl-2,2-dimethyl-6,6a-dihydro-3aH-cyclopenta[1,3]dioxol-4-yloxy)trimethylsilane (118).[4f]

$C_{14}H_{24}SiO_3$

Mol. Wt. = 268.42 g



At 0 °C a 0.5 M solution of isopropenylmagnesium bromide (50.4 mL, 25.2 mmol, 1.4 equiv) was subsequently added dry TMEDA (7.55 ml, 50.4 mmol, 2.8 equiv) and CuBr.DMS (370 mg, 1.8 mmol, 0.1 equiv). The mixture was then cooled to −78 °C and a solution of **148** (2.78 g, 18.0 mmol) and TMSCl (6.85 ml, 54.0 mmol, 3 equiv) in THF (50 mL) was added by syringe over 20 minutes, and the reaction was stirred at −78 °C for 1.5 h, and then at −40 °C for 1 h. The reaction was then quenched with saturated aqueous NH_4Cl solution, warmed to room temperature and filtered through Celite® with ether washes. The mixture was the diluted with water and the layers separated. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the organic layers were combined, dried over Na_2SO_4, filtered and reduced *in vacuo*. The crude material was purified by column chromatography using oven dried silica to give a mixture of **118** (1.64g, 34%) and **118'** (2.08g, 59%).

A 0.1 M solution of LDA was prepared by dropwise addition of a 1.6 M *n*-BuLi (8 mL, 12.9 mmol) to a solution of freshly distilled diisopropylamine (2 mL, 14 mmol, 1.1 equiv) in THF (121 mL) at 0 °C.[84] The solution was left to stir at 0 °C for 1 h and then cooled to −78 °C. A solution of **118'** (0.5 g, 2.6 mmol) and TMSCl (1.57 mL, 12 mmol, 5 equiv) in THF (30 mL) was cooled to −78 °C and the LDA solution (91 mL, 9.1 mmol, 3.5 equiv) was added dropwise by syringe. The mixture was stirred at −78 °C for 1 h and then slowly warmed to 0 °C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution, the layers separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using oven dried silica to give the product as a colourless oil (0.63 g, 90%).

R_f 0.5 (95:5 PE:EtOAc)

$[\alpha]_D^{25}$ −32.8 (c 1.00, $CHCl_3$) lit. −54.3 (*c* 1.34, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.80 (dd, *J* = 6.1, 1.4 Hz, 1H, H^4), 4.75 (s, 2H, H^7), 4.62 (m, 1H, H^2), 4.31 (brd, *J* = 6.1, 0.9 Hz, 1H, H^5), 3.20 (brs, 1H, H^3), 1.75 (t, *J* = 1.1 Hz, 3H, H^8), 1.47 (s, 3H, H^{10}), 1.35 (s, 3H, H^{11}), 0.26 (s, 9H, H^{12}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0 (C^1), 146.7 (C^9), 111.0 (C^7), 110.6(C^6), 105.9 (C^2), 82.7 (C^4), 81.0 (C^5), 54.5 (C^3), 27.1 (C^8), 26.2 (C^{10}), 21.0 (C^{11}), 0.0 (C^{12}).

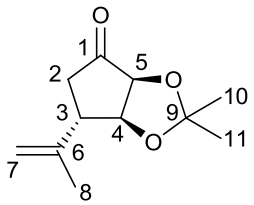
IR 3048, 2995 (CH), 2941 (CH), 1647 (C=C), 1432, 1371, 1281, 1261, 1250, 1200, 1156 (C-O), 1080, 1051 cm^{-1}.

MS (EI) *m/z* 268.

In agreement with literature data.

(3a*S*,6*S*,6a*S*)-6-Isopropenyl-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-one (118').[4f]

$C_{11}H_{16}O_3$
Mol Wt = 196.24 g



R_f 0.25 (95:5 PE:EtOAc)

$[\alpha]_D^{25}$ + 167 (*c* 1.0, $CHCl_3$) lit +188 (*c* 2.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.83 (brs, 1H, H^7) 4.64 (d, *J* = 5.4 Hz, H^5), 4,60 (s, 1H, H^7), 4.11 (dd, *J* = 5.4, 1.0 Hz, 1H, H^4), 2.92 (m, 1H, H^3), 2.70 (dd, *J* = 18.1, 9.3 Hz, 1H, H^2), 2.20 (dd, *J* = 18.1, 0.8 Hz, 1H, H^2), 1.78 (s, 3H, H^8), 1.41 (s, 3H, H^{10}), 1.31 (s, 3H, H^{11}).

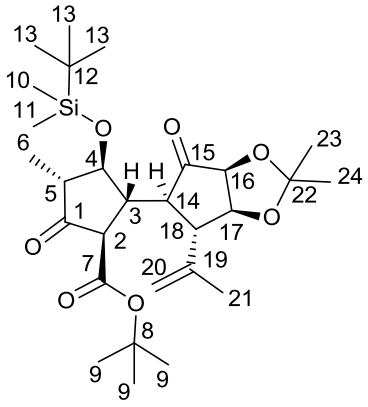
^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.3 (C^1), 144.8 (C^9), 112.3 (C^6), 111.6 (C^7), 80.8 (C^3), 78.0 (C^2), 63.3 (C^4), 39.5 (C^5), 27.3 (C^{10}), 25.2 (C^{11}), 22.0 (C^8).

IR 2896 (C-H), 2934, 1756 (C=O), 1647 (C=C), 1450, 1378, 1241, 1155 (C-O), 1076, 1050 cm^{-1}.

MS (EI) *m/z* 196 (M+).

In agreement with literature data.

***tert*-Butyl (1*S*,2*S*,3*S*,4*R*)-[(3a*S*, 6*S*, 6a*S*)-2,2-dimethyl-4-oxo-6-(prop-1-en-2-yl)-hexahydrochloropenta(d)[1,3]dioxol-5-yl]-3-(tert-butyldimethylsiloxy)-4-methyl-5-oxocyclopentane-1-carboxylate (119c).**



$C_{28}H_{46}O_7Si$

Mol Wt = 522.75 g

To a solution of **118** (620 mg, 2.31 mmol, 3.3 equiv) in THF (1.8 mL) at 0 °C was added dropwise 1.6 M *n*-BuLi (1.43 mL, 2.31 mmol, 3.3 equiv) and the mixture being stirred at 0 °C for a further 1.5 h. Under vacuum $ZnCl_2$ was melted using a Bunsen burner, and a solution of **113c** (230 mg, 0.70 mmol) in DMF (7.5 mL) was added and the solution stirred until all the $ZnCl_2$ had dissolved. The flask containing the THF solution was cooled to −78 °C and the DMF solution was added dropwise by syringe over 30 minutes. The mixture was then stirred at −78 °C for 1 hour and then warmed to −40 °C and stirred for a further hour. The reaction was then warmed slowly to 0 °C over 2 h. Once the reaction had completed by TLC it was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) and THF (5 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were then washed with saturated NaCl solution (1 × 10 mL) and water (2 × 10 mL) sequentially. The organic phase was then dried over Na_2SO_4, filtered and the solvent reduced *in vacuo*. The crude material was purified by column chromatography (8:2 PE:EtOAc) to furnish the product **119c** as a pale yellow oil (183 mg, 50%).

R_f 0.40 (8:2 PE:EtOAc)

$[\alpha]_D^{25}$ −25 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.01 (t, *J* = 0.8 Hz, 1H, H^{20}), 4.94 (s, 1H, H^{20}), 4.57 (dd, *J* = 6.4, 1.2 Hz, 1H, H^{16}), 4.07 (dd, *J* = 6.4, 3.0 Hz, 1H, H^{17}), 3.62 (dd, *J* = 9.0, 8.0 Hz, 1H, H^4), 3.06 (dd, *J* = 8.0, 3.0 Hz, 1H, H^{18}) 3.04 (d, *J* = 1.6 Hz, 1H, H^2), 2.86 (ddd, *J* = 10.0, 3.0, 1.6 Hz, 1H, H^3), 2.71 (dd, *J* = 10.0, 3.0 Hz, 1H, H^{14}), 2.34 (dq, *J* = 9.0, 7.0Hz, 1H, H^5),

1.91 (brs, 3H, H^{21}), 1.57 (s, 6H, H^{23}/H^{24}), 1.37 (s, 9H, H^{9}), 1.16 (d, *J* = 7.0 Hz, 3H, H^{6}), 0.88 (s, 9H, H^{13}), 0.09 (s, 3H, H^{10}), 0.08 (s, 3H, H^{11}).

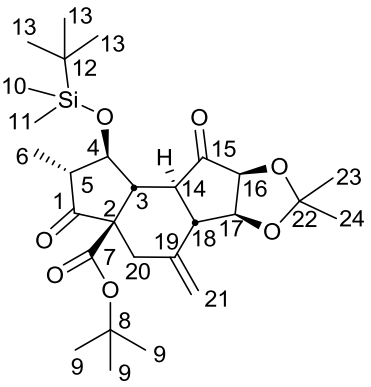
^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.2 (C^{15}), 209.5 (C^{1}), 168.2 (C^{7}), 145.4 (C^{22}), 139.6 (C^{19}), 118.8 (C^{20}), 82.8 (C^{8}), 80.1 (C^{16}), 79.8 (C^{17}), 74.5 (C^{4}), 55.5 (C^{2}), 53.3 (C^{5}), 50.2 (C^{14}), 46.8 (C^{18}), 44.8 (C^{3}), 27.2 (C^{24}), 26.0 (C^{13}), 25.8 (C^{23}), 23.4 (C^{21}), 17.7 (C^{12}), 13.3 (C^{6}), 10.6 (C^{9}), −3.9 (C^{10}), –4.3 (C^{11}).

IR 2945 (CH), 2934, 2860, 1755 (C=O), 1724 (C=O), 1699 (C=O), 1641 (C=C), 1462, 1375, 1311, 1210, 1220, 1147 (C-O), 1041 cm^{-1}.

MS (EI) *m/z* 522 (M^+).

HRMS (EI) calculated for $C_{28}H_{44}O_7Si$: 522.7330, found: 522.7336.

***tert*-Butyl (1*S*,2*R*,3a*R*,5a*S*,5b*S*,8a*S*,9a*S*,9b*R*)-1-[(tert-butyldimethyl)siloxy]-2,7,7-trimethyl-5-methylene-3,9-dioxodecahydro-1H-as-indaceno[2,3-d][1,3]dioxole-3a-carboxylate (157).**



$C_{28}H_{44}O_7Si$

Mol Wt = 520.73 g

To a solution of **119c** (28 mg, 54 umol) in a 10:1 degassed mixture of 2,2,2-trifluoroethanol/acetic acid (0.5 mL) was added $Cu(OAc)_2.H_2O$ (21 mg, 108 umol). The mixture was stirred at 20 °C for 30 minutes until all $Cu(OAc)_2.H_2O$ had dissolved. To the reaction mixture was added $Mn(OAc)_3.2H_2O$ (29 mg, 108 umol) and the reaction was stirred for 1.5 h. The mixture was diluted with water (5 mL) and Et_2O (5 mL), and solid K_2CO_3 was carefully added to neutralise the acetic acid. The layers were separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (9:1 PE:EtOAc) to give the product **157** as a yellow oil (13 mg, 48%).

R_f 0.35 (9:1 PE:EtOAc).

$[\alpha]_D^{25}$ −32.1 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.02–4.98 (m, 2H, H^{21}), 4.79 (dd, *J* = 9.1, 7.8 Hz, 1H, H^{17}), 4.58 (d, *J* = 7.8 Hz, 1H, H^{16}), 3.98 (dd, *J* = 3.0, 2.0 Hz, 1H, H^4), 3.01–2.92 (m, 2H, H^3/H^{14}), 2.90 (d, *J* = 14.8 Hz, 1H, H^{20}). 2.71 (dd, *J* = 9.1, 3.0 Hz, 1H, H^{18}), 2.34–2.22 (m, 2H, H^5/H^{20}), 1.46 (s, 3H, H^{23}), 1.43 (s, 9H, H^9), 1.37 (s, 3H, H^{24}), 1.12 (d, *J* = 7.7 Hz, 3H, H^6), 0.90 (s, 9H, H^{13}), 0.08 (s, 3H, H^{10}), −0.01 (s, 3H, H^{11}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.5 (C^{15}), 209.9 (C^1), 167.7 (C^7), 140.4 (C^{22}), 121.6 (C^{19}), 108.8 (C^{21}), 87.9 (C^8), 80.1 (C^{16}), 79.8 (C^{17}), 75.0 (C^4), 66.2 (C^2), 53.0 (C^{14}), 52.7 (C^5), 48.9 (C^{18}), 48.6 (C^3), 36.5 (C^{20}), 27.7 (C^9), 26.2 (C^{43}), 26.0 (C^{23}), 18.0 (C^{12}), 15.0 (C^{13}), 11.1 (C^6), −4.6 (C^{10}), −5.3 (C^{11}).

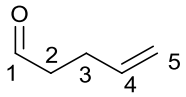
IR 2954 (CH), 2930, 2860, 1758 (C=O), 1740 (C=O), 1670 (C=C), 1473, 1465, 1386, 1650, 1252, 1233, 1160 (C-O), 1042 cm^{-1}.

MS (EI) *m/z* 520 (M^+).

HRMS (EI) calculated for $C_{28}H_{44}O_7Si$: 520.2858, found: 520.2856.

4-Pentenal (176).[53]

C_5H_8O



Mol Wt. = 84.13g

To a solution of glycidol **178** (17.7 mL, 266 mmol) in THF (400 mL) at −78 °C was added by cannula a 2 M solution of allylmagnesium chloride (240 mL, 480 mmol, 1.8 equiv). The mixture was stirred at −78 °C for 30 min and then slowly warmed to 0 °C over 1 h. The reaction was then quenched by addition of a saturated aqueous NH_4Cl solution (300 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 × 150 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to furnish the diol **179** (26.4 g, 86%). The crude **179** was dissolved in a 1:1 mixture of CH_2Cl_2/H_2O (640 mL), and $NaIO_4$ (97 g, 454 mmol, 2 equiv) was added in one portion. The mixture was stirred for 1 h, after which it was quenched by addition of saturated aqueous $NaHCO_3$ solution (200 mL). The layers were separated and the organic layer was washed with 10% aqueous Na_2SO_4 (50 mL). The organic layer was dried over Na_2SO_4, filtered and carefully concentrated *in vacuo* at 0 °C. The crude material was purified by distillation (bp: 102 °C) to afford the aldehyde **176** contaminated with ~5% by weight CH_2Cl_2 (13.6 g, 162 mmol, 71%).

R_f 0.30 (9:1 PE/EtOAc)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (t, *J* = 1.55 Hz, 1H, H^1), 5.76 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H, H^4), 5.12–5.03 (m, 2H, H^5), 2.59–2.54 (m, 2H, H^2), 2.45–2.38 (m, 2H, H^3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.9 (C^1), 136.6 (C^4), 115.9 (C^5), 42.8 (C^2), 26.3 (C^3).

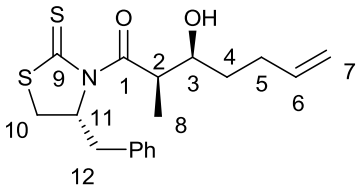
MS (CI) – *m/z* 84 (M+).

In agreement with literature data.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methyl-hept-6-en-1-one (180).

$C_{18}H_{23}NO_2S_2$

Mol. Wt. = 349.45



To a solution of **127** (780 mg, 2.90 mmol) in CH_2Cl_2 (15 mL) at −10 °C was added dropwise $TiCl_4$ (0.34 mL, 3.10 mmol, 1.05 equiv). This was left to stir for 15 min followed by addition of freshly distilled *N*-diisopropylethylamine (0.51 mL, 2.9 mmol, 1.00 equiv). After stirring for 1 h the flask was cooled to −78 °C and NMP (0.30 mL, 2.9 mmol, 1 equiv) was added dropwise and left to stir for a further 1 h. Aldehyde **176** (0.28 g, 3.3 mmol, 1.1 equiv) was introduced by syringe and the mixture left at −78 °C for 1 h, followed by gradual warming to 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (8:2 PE/EtOAc) product **180** as a yellow oil (0.65 g, 70%).

R_f 0.25 (8:2 PE/EtOAc).

$[\alpha]_D^{25}$ −80 (*c* 0.25, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.12 (m, 5H, H^{Ar}), 5.74 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H, H^6), 5.27–5.21 (m, 1H, H^{11}), 5.06 (ddt, *J* = 17.1, 3.4, 1.4 Hz, 1H, H^7), 4.99 (ddt, *J* = 10.2, 3.4, 1.4 Hz, 1H, H^7), 4.48 (qd, *J* = 6.9, 2.9 Hz, 1H, H^2), 3.88–3.83 (m, 1H, H^3), 3.30 (dd, *J* = 11.5, 7.1 Hz, 1H, H^{10}), 3.05 (dd, *J* = 13.2, 10.5 Hz, 1H, H^{12}), 2.90 (d, *J* = 11.5 Hz, 1H, H^{10}), 2.88 (brs, 1H, OH), 2.71 (d, *J* = 3.1 Hz, 1H, H^{12}), 2.21–2.08 (m, 1H, H^4), 1.80–1.49 (m, 2H, H^4/H^5), 1.45–1.34 (m, 1H, H^5), 1.09 (d, *J* = 6.9 Hz, 3H, H^8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6 (C^9), 178.3 (C^1), 138.2 (C^6), 136.4 (C^{Ar}), 129.4 (C^{Ar}), 129.0 (C^{Ar}), 127.5 (C^{Ar}), 115.1 (C^7), 71.8 (C^{11}), 69.9 (C^3), 43.4 (C^2), 37.0 (C^{10}), 33.5 (C^{12}), 31.9 (C^4), 29.7 (C^5), 10.6 (C^8).

IR 3506 (OH), 2972 (CH), 2924, 2856, 2360, 1712 (CO), 1363, 1342, 1288, 1259, 1130 (C-O), 1107, 1045, 1016 cm^{-1}.

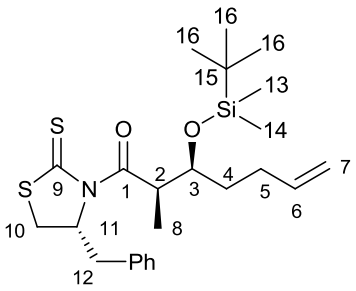
MS (CI) – *m/z* 350 (MH^+).

HRMS (CI) – calculated for $C_{18}H_{24}NO_2S_2$: 350.5213, found: 350.5211.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-*(tert*-butyldimethylsilyloxy)-2-methyl-hept-6-en-1-one (181).

$C_{24}H_{37}NO_2S_2Si$

Mol. Wt. = 463.77 g



A solution of **180** (4.00 g, 11.5 mmol) and TBSCl (6.93 g, 46.0 mmol, 4.0 equiv) in anhydrous DMF (40 mL) was cooled to 0 °C and 2,6-lutidine (6.7 mL, 58 mmol, 5.0 equiv) was added dropwise. The mixture was left to stir at 20 °C for 3 days, followed by dilution with ice water. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous $CuSO_4$ solution (2 × 15 mL). The organic extracts were then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (97:3 PE/EtOAc) furnishing **181** as a bright yellow oil (5.17 g, 97%).

R_f 0.27 (97:3 PE/EtOAc).

$[\alpha]_D^{20}$ −67 (*c* 0.28, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.19 (m, 5H, H^{Ar}), 5.76 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1H, H^6), 5.16–5.10 (m, 1H, H^{11}), 4.99 (ddt, *J* = 17.1, 3.2, 1.5 Hz, 1H, H^7), 4.91 (ddt, *J* = 10.1, 3.2, 1.5 Hz, 1H. H^7), 4.52 (qd, *J* = 6.6, 5.6 Hz, 1H, H^2), 3.98 (dt, *J* = 5.6, 5.6 Hz, 1H, H^3), 3.29–3.20 (m, 2H, H^{10}/H^{12}), 2.98 (dd, *J* = 13.1, 10.6 Hz, 1H, H^{12}), 2.83 (d, *J* = 11.6 Hz, 1H, H^{10}), 2.08–2.00 (m, 2H, H^4/H^5), 1.67–1.57 (m, 1H, H^4), 1.57–1.47 (m, 1H, H^5), 1.20 (d, *J* = 6.6 Hz, 3H, H^8), 0.85 (s, 9H, H^{16}), 0.17 (s, 3H, H^{13}), –0.10 (s, 3H, H^{14}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9 (C^9), 176.8 (C^1), 138.6 (C^6), 136.7 (C^{Ar}), 129.5 (C^{Ar}), 128.9(C^{Ar}), 127.3 (C^{Ar}), 114.6 (C^7), 73.9 (C^{11}), 69.5 (C^3), 44.2 (C^2), 36.6 (C^{10}), 34.4 (C^{12}), 32.1 (C^5), 29.2 (C^4), 25.8 (C^{16}), 18.4 (C^{15}) , 12.6 (C^8), –4.3(C^{13}), –4.5 (C^{14}).

IR 2949 (CH), 2928, 1695 (CO), 1454, 1319, 1340, 1249, 1161, 1134, 1028, 1004 cm^{-1}.

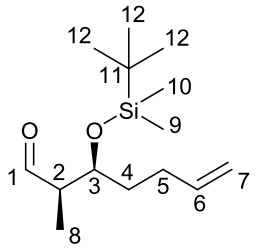
MS (EI) *m/z* 464 (MH^+), 434 (MH^+-S), 210 (**133**$^+$),

HRMS (EI) - calculated for $C_{24}H_{37}NO_2S_2Si$: 463.7750, found: 463.7753.

(2*R*,3*S*)-3-*(tert*-Butyldimethylsilyloxy)-2-methyl-6-heptenal (182).

$C_{14}H_{28}O_2Si$

Mol. Wt. = 256.45g



A solution of **181** (5.10 g, 11.0 mmol) in CH_2Cl_2 (150 mL) was cooled to −78 °C and a 1 M solution of Dibal-H in hexanes (25 mL, 25 mmol, 2.3 equiv) was added dropwise. The mixture was left to stir until the bright yellow colour disappeared, then the reaction was quenched with EtOAc (50 mL). The mixture was then diluted with a 10% aqueous Rochelle's salt solution and stirred for 1 h until the organic phase went clear. The mixture was then extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (98:2 PE/EtOAc) switching up to (8:2 PE/EtOAc) collecting **133** (1.95 g, 85%) and **182** as a colourless oil (2.42 g, 85%).

R_f 0.23 (98:2 PE/EtOAc)

$[\alpha]_D^{25}$ −98 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.73 (d, *J* = 1.0 Hz, 1H, H^1), 5.75 (ddt, *J* = 16.9, 10.4, 6.5 Hz, 1H, H^6), 4.95 (ddt, *J* = 16.9, 3.4, 1.7 Hz, 1H, H^7), 4.91 (ddt, *J* = 10.4, 3.4, 1.7 Hz, 1H, H^7), 4.05 (td, *J* = 6.6, 3.6 Hz, 1H, H^3), 2.40 (qdd, *J* = 7.0, 3.6, 1.0 Hz, 1H, H^2), 2.12–1.95 (m, 2H, H^4/H^5), 1.68–1.50 (m, 2H, H^4/H^5), 0.99 (d, *J* = 7.0 Hz , 3H, H^8), 0.79 (s, 9H, H^{12}), 0.00 (s, 3H, H^{10}), −0.03 (s, 3H, H^9).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.2 (C^1), 138.1 (C^6), 115.0 (C^7), 72.7 (C^3), 51.1 (C^2), 33.6 (C^5), 31.9 (C^4), 25.6 (C^{12}), 14.2 (C^{11}), 7.7 (C^8), −3.0 (C^9), −3.1 (C^{10}).

IR 2948 (CH), 1740 (C=O), 1478, 1295, 1119 (C-O), 1090, 1005 cm^{-1}.

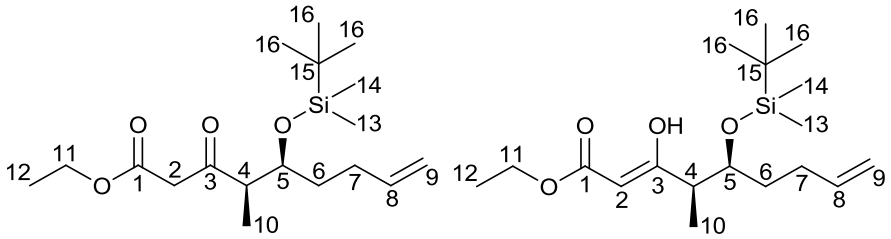
MS (EI) *m/z* 257 (MH^+).

HRMS (EI) calculated for $C_{14}H_{29}O_2Si$: 257.1937, found: 257.1936.

Ethyl (4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-3-oxonon-8-enoate (184/184').

$C_{18}H_{34}SiO_4$

Mol Wt = 342.54 g



To a solution of $SnCl_2$ (0.88 g, 4.8 mmol, 0.5 equivalents) in CH_2Cl_2 (50 mL) was added ethyl diazoacetate (2.76 g, 19.4 mmol, 2.0 equivalents) and **182** (2.48 g, 9.70 mmol) in CH_2Cl_2 (18 mL). The mixture was left to stir at 20 °C for 3 h, filtered and the solvent removed *in vacuo*. The product was then purified by flash chromatography (95:5 PE/EtOAc) to give product **184** as a pale yellow oil. Formed as an inseperable 3:1 ratio with the enol form **184'** (2.48 g, 75%).

R_f 0.25 (95:5 PE/EtOAc).

$[\alpha]_D^{25}$ −187 (*c* 0.17, $CHCl_3$).

β-ketoester form

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71 (ddt, *J* = 17.2, 10.2, 6.5 Hz, 1H, H^8), 4.93 (ddt, *J* = 17.2, 3.4, 1.5 Hz, 1H, H^9), 4.89 (ddt, J = 10.2, 3.4, 1.5, 1H, H^9), 4.10 (q, *J* = 7.1 Hz, 2H, H^{11}), 3.82 (td, *J* = 7.1, 4.4 Hz, 1H, H^5), 3.50 (s, 2H, H^2), 2.76 (qd, *J* = 7.1, 4.4 Hz, 1H, H^4), 2.11–1.95 (m, 2H, H^7), 1.54–1.42 (m, 1H, H^6), 1.40–1.30 (m, 1H, H^6), 1.19 (t, *J* = 7.1 Hz, 3H, H^{12}), 1.00 (d, *J* = 7.1 Hz, 3H, H^{10}), 0.82 (s, 9H, H^{16}), 0.01 (s, 3H, H^{13}), 0.00 (s, 3H, H^{14}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.08 (C^3), 167.41 (C^1), 137.9 (C^8), 114.5 (C^9), 73.2 (C^5), 61.2 (C^{11}), 51.5 (C^4), 49.4 (C^2), 33.54 (C^7), 29.8 (C^6), 25.8 (C^{16}), 17.74 (C^{15}), 14.22 (C^{12}), 11.57 (C^{10}), −4.1 (C^{13}), −4.3 (C^{14}).

IR 3443 (OH), 2953 (CH), 2858, 1745 (CO), 1714 (CO), 1641 (C=C), 1628, 1448, 1381, 1303, 1251, 1226, 1143, 1095, 1032, 1005 cm^{-1}.

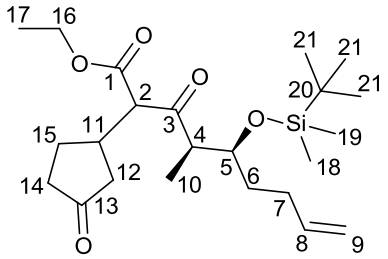
MS (CI) *m/z* 343 (MH^+).

HRMS (CI) – calculated for $C_{18}H_{35}SiO_4$: 343.2305, found: 343.2303.

Ethyl (4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3-oxo-2-(3-oxocyclopentyl) non-8-enoate (186).

$C_{23}H_{40}SiO_5$

Mol. Wt. = 424.64 g



To a solution of **184** (1.33 g, 3.88 mmol, 1.6 equiv) and 2-cyclopentenone (0.20 ml, 2.42 mmol) in anhydrous EtOH (16 mL) was added K_2CO_3 (0.84 g, 6.1 mmol, 0.4 equivalents) in one portion. The mixture was left to stir for 6 h, after which it was diluted with water (20 mL) and Et_2O (20 mL). The two layers were separated and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (8:2 PE:EtOAc) to furnish the product **186** as a colourless oil (1.51 g, 91%). Isolated as an inseperable mixture of 4 diastereomers.

R_f 0.35 (8:2 PE/EtOAc)

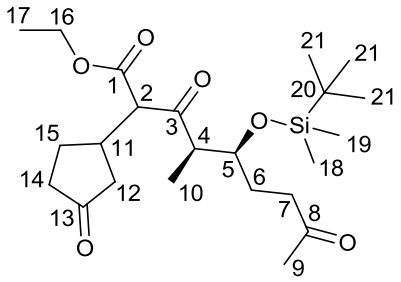
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.68 (m, 1H, H^8), 4.90 (m, 2H, H^9), 4.11 (m, 2H, H^{16}), 3.92 (d, *J* = 8.0 Hz, 1H, H^2), 3.75 (m, 1H, H^5), 3.05−3.00 (m, 1H, H^4), 2.95–2.80 (m, 2H, H^{12}/H^{14}), 2.60-2.11 (m, 3H, H^{12}/H^{13}/H^{14}), 2.09−1.92 (m, 3H, H^7/H^{15}), 1.83–1.78 (m, 1H, H^{11}), 1.65–1.42 (m, 2H, H^6), 1.30–1.25 (m, 3H, H^{17}), 1.17–1.04 (m, 3H. H^{10}), 0.82 (m, 9H, H^{21}), 0.05 (s, 3H. H^{19}), 0.00 (s, 3H, H^{18}).

IR 2950 (C-H), 2932, 1744 (C=O), 1722 (C=O), 1687 (C=O), 1639 (C=C), 1412, 1345, 1264, 1144 (C-O), 1021, 1005 cm^{-1}.

MS (CI) *m/z* 425 (MH^+).

HRMS (CI) calculated for $C_{23}H_{41}SiO_5$: 425.2723, found: 425.2725.

Ethyl(4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3,8-dioxo-2-(3-oxocyclopentyl) nonanoate (187).



$C_{23}H_{40}SiO_6$

Mol. Wt. = 440.64 g

To a 3:1 mixture of DMF/ H_2O (2.1 mL) was added $PdCl_2$ (17 mg, 0.097 mmol, 0.1 equiv) and $CuCl_2$ (96 mg, 0.97 mmol, 1.0 equiv) and oxygen was bubbled through the solution for 1 h. A solution of **186** (0.41 g, 0.97 mmol) in DMF (0.8 mL) was added and the mixture was stirred overnight under an oxygen atmosphere. The mixture was then diluted with H_2O and extracted with Et_2O (3 × 10 mL) then filtered on Celite®. The combined organic layers were washed with saturated aqueous NaCl solution (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (8:2 PE/EtOAc) to furnish the product **187** as a colourless oil (0.30 g, 72%) as an inseperable mixture of 4 diastereomers.

R_f 0.2 (8:2 PE/EtOAc)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12–4.00 (m, 2H, H^{16}), 3.71 (dd, *J* = 9.5, 3.5 Hz, 1H, H^2), 3.66–3.60 (m, 1H, H^5), 2.89–2.82 (m, 1H, H^4), 2.80–2.64 (m, 2H, H^{12}/H^{14}), 2.43–2.00 (m, 3H, H^{12}/H^{14}/H^{15}), 1.99 (s, 3H, H^9), 1.88–1.67 (m, 3H, H^7/H^{15}), 1.67–1.52 (m, 1H, H^{11}), 1.51–1.31 (m, 2H, H^6), 1.17–1.10 (m, 3H, H^{17}), 1.02–0.91 (m, 3H. H^{10}), 0.79–0.74 (m, 9H, H^{21}), −0.05 and −0.10 (2 s, 6H, H^{18}/ H^{19})

IR 2957 (C-H), 2930, 2856, 1739 (C=O), 1710 (C=O), 1472, 1463, 1405, 1361, 1253, 1253, 1191, 1147 (C-O), 1020, 1004 cm^{-1}.

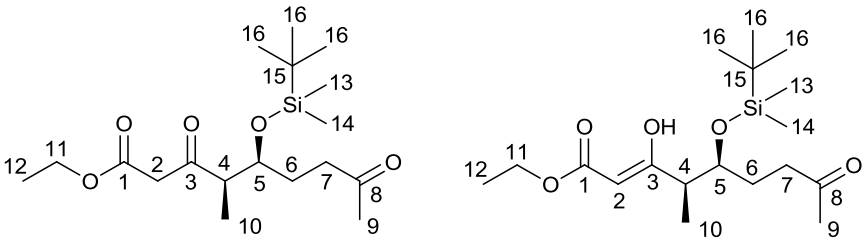
MS (CI) *m/z* 441 (MH^+)

HRMS (CI) calculated for $C_{23}H_{41}SiO_6$: 441.2671, found: 441.2675.

Ethyl (4*R*,5*S*)-5-[*tert*-Butyldimethylsilyl)oxy]-4-methyl-3,8-dioxononanoate (190).

$C_{18}H_{34}SiO_5$

Mol. Wt. = 358.54 g



R_f 0.4 (99:1 PE/EtOAc).

$[\alpha]_D^{20}$ −122 (*c* 1.00, $CHCl_3$).

β-ketoester form

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (q, *J* = 7.1 Hz, 2H, H^{11}), 3.83 (td, *J* = 6.9, 4.8 Hz, 1H, H^5), 3.50 (s, 2H, H^2), 2.74 (qd, *J* = 7.0, 4.8 Hz, 1H, H^4), 2.40–2.29 (m, 2H, H^7), 2.06 (s, 3H, H^9), 1.75-1.65 (m, 1H, H^6), 1.52–1.41 (m, 1H, H^6), 1.20 (t, *J* = 7.1, 3H, H^{12}), 1.02 (d, *J* = 7.0 Hz, 3H, H^{10}), 0.82 (s, 9H, H^{16}), 0.00 (s, 3H, H^{13}), −0.01 (s, 3H, H^{14}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.1 (C^8), 205.2 (C^3), 167.4 (C^1), 72.2 (C^5), 61.2 (C^{11}), 50.7 (C^4), 49.5 (C^2), 38.1 (C^7), 28.9 (C^9), 26.7 (C^6), 24.8 (C^{16}), 17.0 (C^{15}), 13.0 (C^{12}), 12.2 (C^{10}), −5.5 (C^{13}), −5.6 (C^{14}).

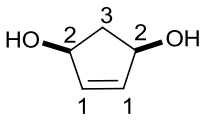
IR 2951 (CH), 2858, 1742 (CO), 1720 (CO), 1709 (CO), 1645 (C=C), 1628, 1333, 1279, 1143, 1095, 1040 cm^{-1}.

MS (CI) *m/z* 359 (MH^+).

HRMS (CI) calculated for $C_{18}H_{35}SiO_5$: 359.2255, found: 359.2259.

***cis*-4-Cyclopentene-1,3-diol (196).**[85]

$C_5H_8O_2$
Mol. Wt. = 100.12 g



In a 1 L photochemistry apparatus, a solution of freshly distilled cyclopentadiene (6.4 mL, 75 mmol), Rose Bengal (154 mg, 0.152 mmol, 0.002 equiv) and thiourea (3.92 g, 50.2 mmol, 6.7 equiv) in methanol (1 L) was cooled to 0 °C and irradiated with a UV mercury lamp, while oxygen was bubbled through the solution. After 3 h, irradiation and bubbling was stopped and the reaction was stirred in the darkness overnight. The solvent was then evaporated and the residue was dissolved in ethyl acetate, silica (5.0 g) and charcoal (2.5 g) was added and the solvent was reduced *in vacuo*. The resulting powder was then deposited on a silica gel column and the product purified by column chromatography (9:1 CH_2Cl_2/MeOH). Fractions containing the product were combined and evaporated; the residue was then dissolved in water so the Rose Bengal impurities precipitated. After filtration and evaporation of water, the product was dissolved in ethyl acetate, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the product **196** as a dark brown oil (4.5 g, 60%).

R_f 0.3 (9:1 CH_2Cl_2/MeOH).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (d, *J* = 0.3 Hz, 2H, H^1), 4.57 (dd, *J* = 7.3, 5.4 Hz, 2H, H^2), 2.72 (dt, *J* = 13.4, 7.3 Hz, 1H, H^3), 1.41 (dt, *J* = 13.4, 5.4 Hz, 1H, H^3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1 (C^1), 75.3 (C^2), 44.5 (C^3).

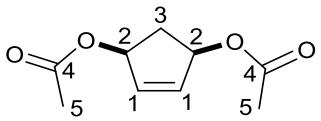
MS (FAB) – *m/z* 100 (M^+).

In agreement with literature data.

***cis*-3,5-Diacetoxy-1-cyclopentene (197).**[85]

$C_9H_{12}O_4$

Mol. Wt. = 184.19 g



Acetic anhydride (19.4 mL, 204 mmol, 4.0 equivalents) was slowly added to a stirred solution of diol **196** (5.10 g, 51.0 mmol), pyridine (41 mL, 510 mmol, 10 equiv) and DMAP (311 mg, 2.55 mmol, 0.05 equiv) in CH_2Cl_2 (250 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then warmed to 20 °C and stirred for a further 5 h, after which the reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution (250 mL). The layers were separated and the organic layer was washed with saturated aqueous $CuSO_4$ solution (3 × 150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The organic residue was then purified by column chromatography (9:1 PE/EtOAc) to furnish the product **197** as a colourless oil (7.42 g, 79%).

R_f 0.3 (9:1 PE/EtOAc)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (d, *J* = 0.8 Hz, 2H, H^1), 4.57 (dd, *J* = 7.5, 3.9 Hz, 2H, H^2), 2.92 (dt, *J* = 14.9, 7.5 Hz, 1H, H^3), 2.09 (s, 6H, H^5), 1.41 (dt, *J* = 14.9, 3.9 Hz, 1H, H^3).

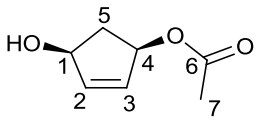
^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (C^4), 134.5 (C^1), 76.5 (C^2), 37.1 (C^3), 21.0 (C^5).

MS (FAB) – *m/z* 184 (M^+).

In agreement with literature data.

(1*S*,4*R*)-*cis*-4-Acetoxy-2-cyclopenten-1-ol (198).[86]

$C_7H_{10}O_3$
Mol. Wt. = 142.15 g



Compound **197** (6.90 g, 37.4 mmol) was added to a slowly stirred solution of electric eel acetylcholineesterase (2.47 mg, 2000 units) and sodium azide (15 mg) in an aqueous phosphate buffer (320 mL) at 20 °C. The buffer was prepared by dissolving anhydrous Na_2HPO_4 (32.8 g) in water (400 mL), adjusting the pH to 6.85 by careful addition of a 2 M aqueous HCl solution. The reaction was stirred at 20 °C overnight, after which it was extracted with 1:1 Et_2O/EtOAc (6 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the product **198** as a white solid (5.15 g, 97%,).

R_f 0.4 (6:4 PE/EtOAc).

mp - 52–53°C, lit. 49–51°C.

$[\alpha]_D^{20}$ +64.3 (*c* 1.00, $CHCl_3$); lit +73.8 (*c* 1.25, $CHCl_3$).

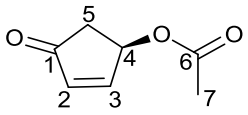
^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.14–6.12 (m, 1H, H^3), 6.02–5.99 (m, 1H, H^2), 5.53–5.49 (m, 1H, H^1), 4.76–4.70 (m, 1H, H^4), 2.84 (dt, *J* = 14.6, 7.4 Hz, 1H, H^5), 2.11 (s, 3H, H^7), 1.70 (dt, *J* = 14.6, 3.9 Hz, 1H, H^5).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (C^1), 138.5 (C^3), 132.7 (C^2), 77.1 (C^1), 74.9 (C^4), 40.6 (C^5), 21.2 (C^7).

MS (CI) – *m/z* 143 (MH^+).

In agreement with literature data.

(4*R*)-4-Acetoxy-2-cyclopenten-2-one (199).[87]



$C_7H_8O_3$

Mol. Wt. = 140.14 g

To a solution of **198** (3.2 g, 23 mmol) in ethyl acetate (450 mL) was added IBX (18.9 g, 67.5 mmol, 3 equiv). The mixture was then stirred vigorously under reflux for 3 h. The reaction was then cooled to 0 °C and the solid residue removed by filtration. The solvent was then concentrated *in vacuo* and the organic residue purified by column chromatography (8:2 PE/EtOAc) to yield **199** as a colourless oil (2.87 g, 91%).

R_f 0.3 (8:2 PE/EtOAc).

$[\alpha]_D^{20}$ +87 (*c* 1.00, $CHCl_3$), lit +100 (*c* 1.4, MeOH).

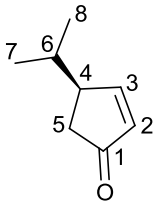
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (dd, *J* = 5.7, 2.4 Hz, 1H, H^3), 6.34 (dd, *J* = 5.7, 1.2 Hz, 1H, H^2), 5.86–5.74 (m, 1H, H^4), 2.84 (dd, *J* = 18.7, 6.3 Hz, 1H, H^5), 2.34 (dd, *J* = 18.7, 2.2 Hz, 1H, H^5), 2.11 (s, 3H, H^7).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.9 (C^1), 169.4 (C^6), 158.9 (C^3), 132.0 (C^2), 72.0 (C^4), 41.0 (C^5), 20.8 (C^7).

MS (CI) – *m/z* 141 (MH^+).

In agreement with literature data.

(4*R*)-4-Isopropyl-2-cyclopenten-2-one (195).[59]



$C_8H_{12}O$

Mol. Wt. = 124.18 g

A solution of isopropylmagnesium bromide was prepared from 2-bromopropane (20.0 mL, 213 mmol) and magnesium (5.44 g, 224 mmol) in THF (180 mL). The solution was standardised using the titration method. Any precipitate formed was redissolved prior to use by gentle heating and swirling. At 0 °C a solution of the Grignard reagent in THF (1.3 M, 25 mL, 32 mmol, 1.4 equiv) was diluted further with THF (75 mL), and dry HMPA (11 mL, 65 mmol, 2.8 equiv) and CuBr.DMS (475 mg, 2.31 mmol, 0.1 equiv) was subsequently added. The mixture was then cooled to −78 °C and a solution of **199** (3.2 g, 23 mmol) and $BF_3.OEt_2$ (8.6 mL, 69 mmol, 3 equiv) in THF (61 mL) was added by syringe over 20 minutes, and the reaction was stirred at −78 °C for 1 hour, and then at −40 °C for 30 minutes. The reaction was then quenched with saturated NH_4Cl solution, warmed to room temperature and filtered through Celite® with ether washings. The mixture was the diluted with water and the layers separated. The aqueous phase was extracted with ether (3 × 80 mL) and the organic layers were combined, dried over Na_2SO_4, and carefully evaporated. The crude material was dissolved in CH_2Cl_2 (50 mL), 1 M acetic acid (15 mL) was added and the mixture was stirred for 2 h. The solution was then diluted with CH_2Cl_2 and $NaHCO_3$ solution, the layers separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and dried over Na_2SO_4, and the solvent was removed very carefully *in vacuo*. The crude material was purified by column chromatography (9:1 PE:Et_2O) and careful evaporation of the fractions containing product **92** was obtained as a colourless oil (2.1 g, 72%).

R_f 0.2 (9:1 PE/Et_2O)

$[\alpha]_D^{20}$ +162 (*c* 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (dd, *J* = 5.7, 2.5 Hz, 1H, H^3), 6.15 (dd, *J* = 5.7, 2.1 Hz, 1H, H^2), 2.83–2.77 (m, 1H, H^4), 2.40 (dd, *J* = 18.8, 6.4 Hz, 1H, H^5), 2.05 (dd, *J* =

18.8, 2.5 Hz, 1H, H^5), 1.75 (oct, *J* = 6.8 Hz, 1H. H^6), 0.94 (d, *J* = 6.8 Hz, 3H, H^7), 0.89 (d, *J* = 6.8 Hz, 3H, H^7).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0 (C^1), 167.5 (C^3), 134.5 (C^2), 49.0 (C^4), 37.5 (C^6), 31.7 (C^5), 20.1 (C^7), 19.8 (C^8).

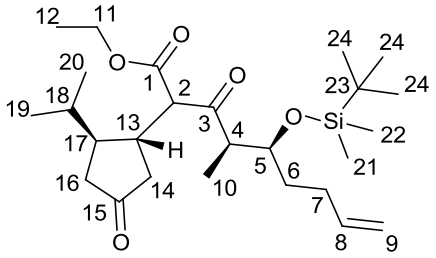
MS (EI) - *m/z* 124 (M^+).

In agreement with literature data.

Ethyl (4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-3-oxo-2-[(1*R*,2*S*)-4-oxo-2-(propan-2-yl)cyclopentyl]non-8-enoate (200).

$C_{26}H_{46}SiO_5$

Mol. Wt = 466.73 g



To a solution of **184** (2.06 g, 6.0 mmol, 1.5 equiv) and **195** (500 mg, 4.00 mmol) in anhydrous EtOH (25 mL) was added K_2CO_3 (0.22 g, 1.6 mmol, 0.4 equiv) in one portion. The mixture was left to stir for 6 h, after which it was diluted with water (100 mL) and Et_2O (50 mL). The two layers were separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (8:2 PE/EtOAc) to furnish the product **200** as a colourless oil (1.68 g, 90%) as an inseperable 3:1 mixture of diastereomers.

R_f 0.3 (8:2 PE/EtOAc).

$[\alpha]_D^{20}$ +37 (*c* 1.0, $CHCl_3$).

Major diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H, H^8), 5.03–4.92 (m, 2H, H^9), 4.20 (q, *J* = 7.1 Hz, 2H, H^{11}), 3.99 (d, *J* = 4.5 Hz, 1H, H^2), 3.76 (dt, *J* = 4.2, 4.2 Hz, 1H, H^5), 2.93 (qd, *J* = 7.0, 4.2 Hz, 1H, H^4), 2.68 (dddd, *J* = 16.9, 12.9, 8,5, 4.5 Hz, 1H, H^{13}), 2.54–2.48 (m, 2H, H^{14}), 2.02–1.80 (m, 6H, H^7/H^{16}/H^{18}), 1.50–1.47 (m, 2H, H^6), 1.28 (t, *J* = 7.1 Hz, 3H, H^{12}), 1.06 (d, *J* = 7.0 Hz, 3H, H^{10}), 0.94 (d, *J* = 6.8 Hz, 3H, H^{20}), 0.92 (s, 9H, H^{24}), 0.83 (d, *J* = 6.8 Hz, 3H, H^{19}), 0.10 (s, 3H, H^{21}), 0.09 (s, 3H, H^{22}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.4 (C^{15}), 206.1 (C^3), 168.8 (C^1), 137.9 (C^8), 114.9 (C^9), 74.2 (C^5), 61.4 (C^{11}), 60.8 (C^2), 51.6 (C^4), 45.5 (C^{18}), 41.8 (C^{16}), 38.8 (C^{14}), 37.1 (C^{13}), 33.2 (C^7), 30.1 (C^6), 28.0 (C^{17}), 25.9 (C^{24}), 21.7 (C^{19}), 18.1 (C^{23}), 16.3 (C^{20}) ,14.2 (C^{12}), 13.1 (C^{10}), −4.2 (C^{21}), –4.5 (C^{22}).

IR 2957 (CH), 2930, 2886, 2843, 1740 (CO), 1712 (CO), 1440, 1463, 1402, 1354, 1253, 1150, 1005 cm^{-1}.

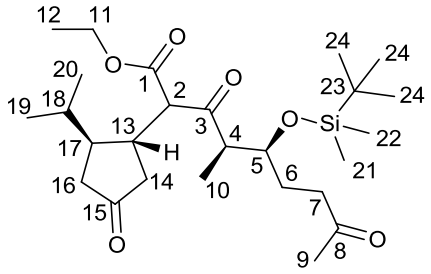
MS (ESI) – *m/z* 489 (MNa^+).

HRMS (ESI) – calculated for $C_{26}H_{46}SiO_5Na$: 489.7183, found: 489.7188.

Ethyl(4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-3,8-dioxo-2-(3-oxocyclopentyl) nonanoate (201).

$C_{26}H_{46}SiO_6$

Mol. Wt = 482.72 g



To a 3:1 mixture of DMF/water (30 mL) was added $PdCl_2$ (148 mg, 0.83 mmol, 0.4 equiv) and $CuCl_2$ (419 mg, 3.12 mmol, 1.5 equivalents) and oxygen was bubbled through the solution for 5 min. A solution of **200** (0.97 g, 2.1 mmol) in DMF (5 mL) was added and the mixture was stirred for 12 h under an oxygen atmosphere. The mixture was then diluted with water and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution (1 × 30 mL) and water (2 × 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography (8:2 PE/EtOAc) to furnish the product **201** as a colourless oil (0.73 g, 72%). Inseparable 3:1 mixture of 2 diastereomers.

R_f 0.2 (8:2 PE/EtOAc).

$[\alpha]_D^{20}$ +57 (*c* 1.0, $CHCl_3$).

Major diastereomer

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (q, *J* = 7.1 Hz, 2H, H^{11}), 4.02 (d, *J* = 4.6 Hz, 1H, H^2), 3.80–3.74 (m, 1H, H^5), 2.84 (qd, *J* = 7.0, 4.5 Hz, 1H. H^4), 2.79-2.74 (m, 1H, H^{17}), 2.63 (dddd, *J* = 17.0, 12.9, 6.4, 4.6 Hz, 1H, H^{13}), 2.56–2.48 (m, 3H, $H^{7/}H^{16}$), 2.43–2.35 (m, 3H, H^7/H^{14}), 2.26-2.16 (m, 1H, H^{18}), 2.13 (s, 3H, H^9), 1.80–1.71 (m, 1H, H^{16}), 1.60–1.70 (m, 1H, H^6), 1.33–1.30 (m, 1H, H^6), 1.28 (t, *J* = 7.1 Hz, 2H, H^{12}), 1.08 (d, *J* = 7.0 Hz, 3H, H^{10}), 0.94 (d, *J* = 6.8 Hz, 3H, H^{19}), 0.92 (s, 9H, H^{24}), 0.84 (d, *J* = 6.8 Hz, 3H, H^{20}), 0.11 (s, 3H, H^{21}), 0.07 (s, 3H, H^{22}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.4 (C^{15}), 208.2 (C^8), 206.5 (C^1), 168.4 (C^3), 71.2 (C^5), 61.5 (C^{11}), 61.2 (C^2), 51.5 (C^4), 45.5 (C^{13}), 41.7 (C^{16}), 39.4 (C^{14}), 38.9 (C^7), 37.1 (C^{17}), 29.9 (C^{18}), 28.2 (C^9), 27.6 (C^6), 25.9 (C^{24}), 21.7 (C^{12}), 17.3 (C^{23}), 16.4 (C^{10}), 14.2 (C^{19}), 13.3 (C^{20}), −4.3 (C^{21}), −4.7 (C^{22}).

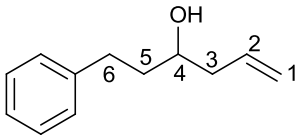
IR 2948 (C-H), 2932, 1745 (C=O), 1710 (C=O), 1689 (C=O), 1465, 1399, 1364, 1252, 1191, 1149 (C-O), 1031, 1005 cm^{-1}.

MS (ESI) *m/z* 505 (MNa^+).

HRMS (ESI) – calculated for $C_{26}H_{46}SiO_6Na$: 505.2961, found: 505.2968.

1-Phenylhex-5-en-3-ol (236).[88]

$C_{12}H_{16}O$
Mol Wt = 176.25 g



To a solution of hydrocinnamaldehyde **235** (5.0 mL, 37.8 mmol), allyl bromide (4.2 mL, 45.4 mmol, 1.2 equiv) and zinc (3.0 g, 45.0 mmol, 1.2 equiv) in THF (50 mL) at 0 °C was added dropwise saturated aqueous NH_4Cl solution (15 mL) over a period of 30 minutes. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was then filtered through a pad of Celite®, washing with Et_2O. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and the solvent reduced *in vacuo*. The crude product was purified by column chromatography (8:2 PE:EtOAc) to give **236** as a yellow oil (5.32 g, 80%).

R_f 0.35 (8:2 PE/EtOAc)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.29 (m, 3H, H^{Ar}), 7.20–7.09 (m, 2H, H^{Ar}), 5.85 (dddd, *J* = 16.1, 9.6, 7.9, 6.5 Hz, 1H, H^2), 5.19–5.09 (m, 2H, H^1), 3.71–3.62 (m, 1H, H^4), 2.85–2.62 (m, 2H, H^6), 2.38–2.20 (m, 2H, H^3), 1.82–1.75 (m, 2H, H^5), 1.65 (brs, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.1 (C^{Ar}), 134.6 (C^{Ar}), 128.7 (C^{Ar}), 128.2 (C^{Ar}), 126.0 (C^2), 118.4 (C^1), 69.9 (C^4), 42.1(C^6), 38.5 (C^3), 31.9 (C^5).

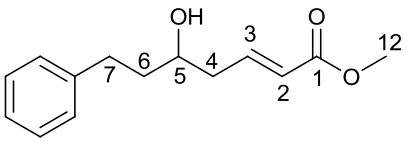
IR 3375 (OH), 3010 (CH), 2951 (CH), 1545, 1096 cm^{-1}.

MS (CI) *m/z* 177 (MH^+).

In agreement with literature data.

(*2E*)-Methyl 5-hydroxy-7-phenylhept-2-enoate (237).[67]

$C_{14}H_{18}O_2$
Mol Wt = 234.29 g



To a solution of **236** (300 mg, 1.7 mmol) and methyl acrylate (0.77 mL, 8.5 mmol, 5 equiv) in degassed CH_2Cl_2 (8 mL) was added in one portion of Grubbs' 2nd generation catalyst (72 mg, 0.09 mmol, 5 mol%). The mixture was stirred under reflux overnight, after which it was cooled to room temperature, and the solvent evaporated. The crude material was purified by column chromatography (8:2 PE:EtOAc) to furnish **237** as a brown oil (370 mg, 93%).

R_f 0.35 (8:2 PE/EtOAc)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.11 (m, 5H, H^{Ar}), 6.91 (dt, *J* = 15.6, 7.6, 1H, H^3), 5.84 (dt, *J* = 15.6 Hz, 1.4 Hz, 1H, H^2), 3.78–3.74 (m, 1H, H^5), 3.66 (s, 3H, H^{12}), 2.77–2.58 (m, 2H, H^7), 2.30–2.25 (m, 2H, H^4), 1.85–1.81 (m, 2H, H^6), 1.54 (br s, 1H, OH).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7 (C^1), 145.2 (C^3), 141.6 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 126.0 (C^{Ar}), 123.7 (C^2), 69.8 (C^5), 51.6 (C^{12}), 40.4 (C^7), 38.7 (C^4), 32.0 (C^6).

IR 3445 (OH), 3043 (CH), 2952 (CH), 1723 (CO), 1642 (C=C), 1473, 1328, 1041 cm^{-1}.

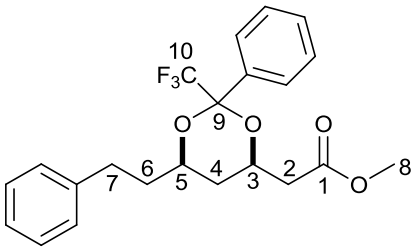
MS (CI) *m/z* 235 (MH^+).

In agreement with literature data.

Methyl 2-(6-phenethyl-2-phenyl-2-(trifluoromethyl)-1,3-dioxan-4-yl)acetate (240).

$C_{22}H_{23}F_3O_2$

Mol Wt = 408.41 g



To a solution of **237** (100 mg, 0.43 mmol) and trifluoroacetophenone **239** (223 mg, 1.3 mmol, 3 equiv) in THF (5 mL) at 0 °C was added KO*t*-Bu (19 mg, 0.17 mmol, 0.4 equiv). The mixture was warmed to room temperature and stirred for a further 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), the layers separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (9:1 PE:EtOAc) to furnish **240** as an off-white solid (149 mg, 85%).

R_f 0.25 (9:1 PE/EtOAc)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (m, 2H, H^{Ar}), 7.34 (m, 3H, H^{Ar}), 7.21 (m, 2H, H^{Ar}), 7.13 (m, 3H, H^{Ar}), 4.19–4.13 (m, 1H, H^3), 3.77 (m, 1H, H^5), 3.70 (s, 3H, H^{12}) 2.90–2.84 (m, 1H, H^7), 2.70–2.61 (m, 2H, H^2/H^7), 2.39 (dd, *J* = 16.0, 5.2 Hz, 1H, H^2), 1.98-1.85 (m, 1H, H^6), 1.80–1.72 (m, 1H, H^6), 1.46 (m, 2H, H^4).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (C^1), 141.4 (C^{Ar}), 140.7 (C^{Ar}), 127.3 (C^{Ar}), 127.1 (C^{Ar}), 123.4 (C^{Ar}), 119.9 (C^{Ar}), 117.9 (C^{Ar}), 112.3 (C^{Ar}), 98.6 (q, *J* = 31 Hz, C^{10}), 91.0 (C^9), 70.0 (C^3), 67.7 (C^5), 52.1 (C^8), 40.7 (C^7), 37.3 (C^2), 35.5 (C^6), 31.0 (C^4).

IR 2949 (CH), 1738 (CO), 1497, 1484, 1398 (CF), 1358, 1337, 1217, 1188, 1177, 1109, 1092, 1061, 1032 cm^{-1}.

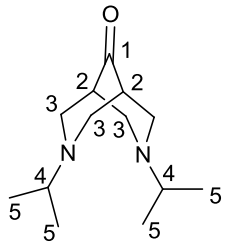
MS (EI) *m/z* 409 (MH^+).

HRMS (EI) calculated for $C_{22}H_{24}F_3O_2$: 409.4254, found: 409.4257.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (245).[76]

$C_{13}H_{24}N_2O$

Mol Wt = 224.19 g



To a solution of *N*-isopropyl-4-piperidone **234** (20 mL, 134 mmol), paraformaldehyde (12.1 g, 402 mmol, 3 equiv) and acetic acid (8 mL) in methanol (190 mL) was added dropwise *i*-propylamine (11.5 mL, 134 mmol, 1 equiv). The mixture was stirred and heated at reflux for 16 h, after which the solvent was removed *in vacuo* and the residue was dissolved in Et_2O (450 mL) and 50% w/v KOH solution (450 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure to give the crude product, which was purified by vacuum distillation (bp 110-113 °C - 1mm Hg) to furnish the product **235** as a colourless oil (18.9 g, 63%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.99 (dd, *J* = 10.5, 2.9 Hz, 4H, H^3), 2.88 (dd, *J* = 10.5, 7.0 Hz, 4H, H^3), 2.82–2.79 (m, 2H, H^4), 2.60–2.58 (m, 2H, H^2), 1.05 (d, *J* = 6.5 Hz, 12H, H^5).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.7 (C1), 53.5 (C^3), 53.4 (C^2), 47.1 (C^4), 18.3 (C^5).

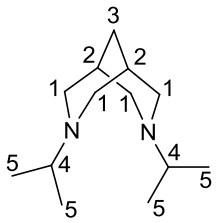
MS (CI) *m/z* 225 (MH^+)

In agreement with literature data.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane (243).[76]

$C_{13}H_{26}N_2$

Mol Wt = 210.36 g



Hydrazine monohydrate (20.2 mL, 369 mmol, 5 equiv) was added dropwise to a solution of **235** (15 g, 67 mmol) and KOH (39.9 g, 777 mmol, 11.6 equiv) in ethylene glycol (385 mL). The mixture was then stirred at heated at 180 °C for 20 h, then cooled to 60 °C and diluted with water. The mixture was then transferred to a separating funnel and extracted with Et_2O (6 × 300 mL). The combined organic extracts were washed with 20% aqueous KOH solution (6 × 100 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by distillation (bp, 105-108 °C – 1mm Hg) to afford the product **233** as a colourless oil (13.1 g, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (hept, *J* = 6.5 Hz, 2H, H^4), 2.50 (dd, *J* = 10.5, 5.5 Hz, 4H, H^1), 2.42 (dd, *J* = 10.5, 2.8 Hz, 4H, H^1), 1.92–1.86 (m, 2H, H^2), 1.43–1.40 (m, 2H, H^3), 0.94 (d, *J* = 6.5 Hz, 12H, H^5).

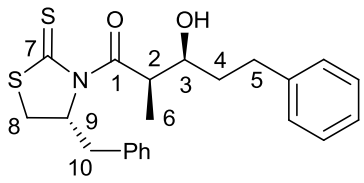
^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.8 (C^1), 52.3 (C^4), 28.1 (C^3), 27.6 (C^2), 18.1 (C^5).

MS (CI) *m/z* 211 (MH^+).

In agreement with literature data.

(2R,3S)-1-[(4R)-4-Benzyl-2-sulfanylidene-1,3-thiazolidin-3-yl]-3-hydroxy-2-methyl-5-phenylpentan-1-one.

$C_{22}H_{25}NO_2S_2$
Mol Wt = 399.13 g



To a solution of **127** (100 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at −10 °C was added dropwise $TiCl_4$ (44 uL, 0.39 mmol, 1.05 equiv). This was left to stir for 15 min followed by addition of freshly distilled bispidine **233** (78 mg, 0.37 mmol, 1.00 equiv). After stirring for 1 h the flask was cooled to −78 °C and NMP (38 uL, 0.37 mmol, 1 equiv) was added dropwise and left to stir for a further 1 h. Hydrocinnamaldehyde **120** (50 mg, 0.37 mmol, 1.1 equiv) was introduced by syringe and the mixture left at −78 °C for 1 h, followed by gradual warming to 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (8:2 PE/EtOAc) affords the product as a yellow solid (106 mg, 72%) with 98:2 dr.

R_f 0.25 (8:2 PE/EtOAc).

$[\alpha]_D^{25}$ −104 (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51–7.04 (m, 10H, H^{Ar}), 5.35−5.29 (m, 1H, H^9), 4.47 (qd, *J* = 6.9, 3.4 Hz, 1H, H^2), 3.98 (dt, *J* = 8.6, 3.4 Hz, 1H, H^3), 3.22 (dd, *J* = 13.0, 3.8 Hz, 1H, H^8), 3.04 (dd, *J* = 13.0, 10.4 Hz, 1H, H^8), 2.90–2.75 (m, 3H, H^5/H^{10}), 2.72–2.63 (m, 1H, H^5), 1.93–1.83 (m, 1H, H^4), 1.75–1.65 (m, 1H, H^4), 1.29 (d, *J* = 6.9 Hz, 3H, H^6).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6 (C^7), 178.3 (C^1), 138.2 (C^{Ar}), 135.4 (C^{Ar}), 129.4 (C^{Ar}), 129.1 (C^{Ar}) 129.0 (C^{Ar}), 127.5 (C^{Ar}), 124.4 (C^{Ar}), 115.1 (C^{Ar}), 71.8 (C^9), 70.7 (C^3), 43.4 (C^2), 37.0 (C^8), 33.5 (C^{10}), 32.3 (C^5), 29.9 (C^4), 15.3 (C^6).

IR 3950 (OH), 2973 (CH), 2949 (CH), 2928, 1710 (CO), 1621 (C=C), 1325, 1250, 1167, 1134, 1011 cm^{-1}.

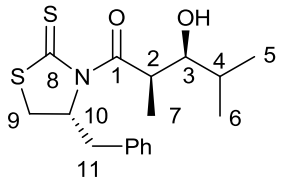
MS (ESI) – *m/z* 422 (MNa^+).

HRMS (ESI) calculated for $C_{22}H_{25}NO_2S_2Na$: 422.1224, found: 422.1230.

(2*R*,3*S*)-1-[(4*R*)-4-Benzyl-2-sulfanylidene-1,3-thiazolidin-3-yl]-3-hydroxy-2,4-dimethylpentan-1-one.[36b]

$C_{17}H_{23}NO_2S_2$

Mol Wt = 337.50 g



To a solution of **127** (100 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at −10 °C was added dropwise $TiCl_4$ (44 uL, 0.39 mmol, 1.05 equiv). This was left to stir for 15 min followed by addition of freshly distilled bispidine **233** (78 mg, 0.37 mmol, 1.0 equiv). After stirring for 1 h the flask was cooled to −78 °C and NMP (38 uL, 0.37 mmol, 1 equiv) was added dropwise and left to stir for a further 1 h. Isobutyraldehyde (26 mg, 0.37 mmol, 1.1 equiv) was introduced by syringe and the mixture left at −78 °C for 1 h, followed by gradual warming to 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (8:2 PE/EtOAc) gives the product as a yellow oil (70 mg, 56%) with >99:1 dr.

R_f 0.25 (8:2 PE/EtOAc)

$[\alpha]_D^{25}$ −69 (*c* 0.25, $CHCl_3$), lit. −39 (c 8.3, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.19 (m, 5H, H^{Ar}), 5.31–5.22 (m, 1H, H^{10}), 4.68 (qd, *J* = 7.0, 2.4 Hz, 1H, H^2), 3.59 (dd, *J* = 8.8, 2.4 Hz, 1H, H^3), 3.33 (m, 2H, H^9/H^{11}), 3.12–3.01 (m, 1H, H^9/H^{11}), 2.87 (d, *J* = 11.8 Hz, 1H, H^{11}), 1.56–1.52 (m, 1H, H^4), 1.10 (d, *J* = 7.0 Hz, 3H, H^7), 1.00 (d, *J* = 6.9 Hz, 3H, H^5), 0.97 (d, *J* = 6.9 Hz, 3H, H^6).

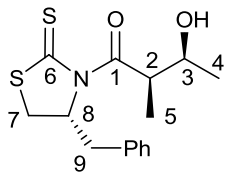
^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2 (C^8), 179.5 (C^1), 136.7 (C^{Ar}), 129.5 (C^{Ar}), 128.9 (C^{Ar}), 127.2 (C^{Ar}), 77.1 (C^3), 68.7 (C^{10}), 46.0 (C^2), 36.5 (C^9), 32.5 (C^{11}), 28.4 (C^4), 19.5 (C^7), 10.2 (C^5), 10.0 (C^6).

MS (CI) – *m/z* 338 (MH^+)

In agreement with literature data.

(2*R*,3*S*)-1-[(4*R*)-4-Benzyl-2-sulfanylidene-1,3-thiazolidin-3-yl]-3-hydroxy-2-methylbutan-1-one.[89]

$C_{15}H_{19}NO_2S_2$
Mol Wt = 309.45 g



To a solution of **127** (100 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at −10 °C was added dropwise $TiCl_4$ (44 uL, 0.39 mmol, 1.05 equiv). This was left to stir for 15 min followed by addition of freshly distilled bispidine **233** (78 mg, 0.37 mmol, 1.0 equiv). After stirring for 1 h the flask was cooled to −78 °C and NMP (38 uL, 0.37 mmol, 1.0 equiv) was added dropwise and left to stir for a further 1 h. Acetaldehyde (21 uL, 0.37 mmol, 1.1 equiv) in CH_2Cl_2 (100 uL) was introduced by syringe and the mixture left at −78 °C for 1 h, followed by gradual warming to 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (8:2 PE/EtOAc) gives the product as a yellow oil (26 mg, 23%) with 97:3 dr.

R_f 0.28 (8:2 PE/EtOAc)

$[\alpha]_D^{20}$ −67 (*c* 0.01, $CHCl_3$) lit −107 (*c* = 18.5, CH_2Cl_2)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.22 (m, 5H, H^{Ar}), 5.34–5.29 (m, 1H, H^8), 4.68 (qd, *J* = 7.2, 2.3 Hz, 1H, H^2), 3.59 (qd, *J* = 6.8, 2.3 Hz, 1H, H^3), 3.25–3.19 (m, 2H, H^7/H^9), 3.08–2.97 (m, 1H, H^9), 2.76–2.71 (m, 1H, H^7), 1.28 (d, *J* = 6.8 Hz, 3H, H^4), 1.21 (d, *J* = 7.2 Hz, 3H, H^5).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.8 (C^8), 178.0 (C^1), 137.0 (C^{Ar}), 129.3 (C^{Ar}), 129.0 (C^{Ar}), 127.4 (C^{Ar}), 71.8 (C^3), 68.7 (C^8), 46.0 (C^2), 36.5 (C^7), 32.5 (C^9), 24.8 (C^4), 11.2 (C^5).

MS (CI) – *m/z* 310 (MH^+)

In agreement with literature data

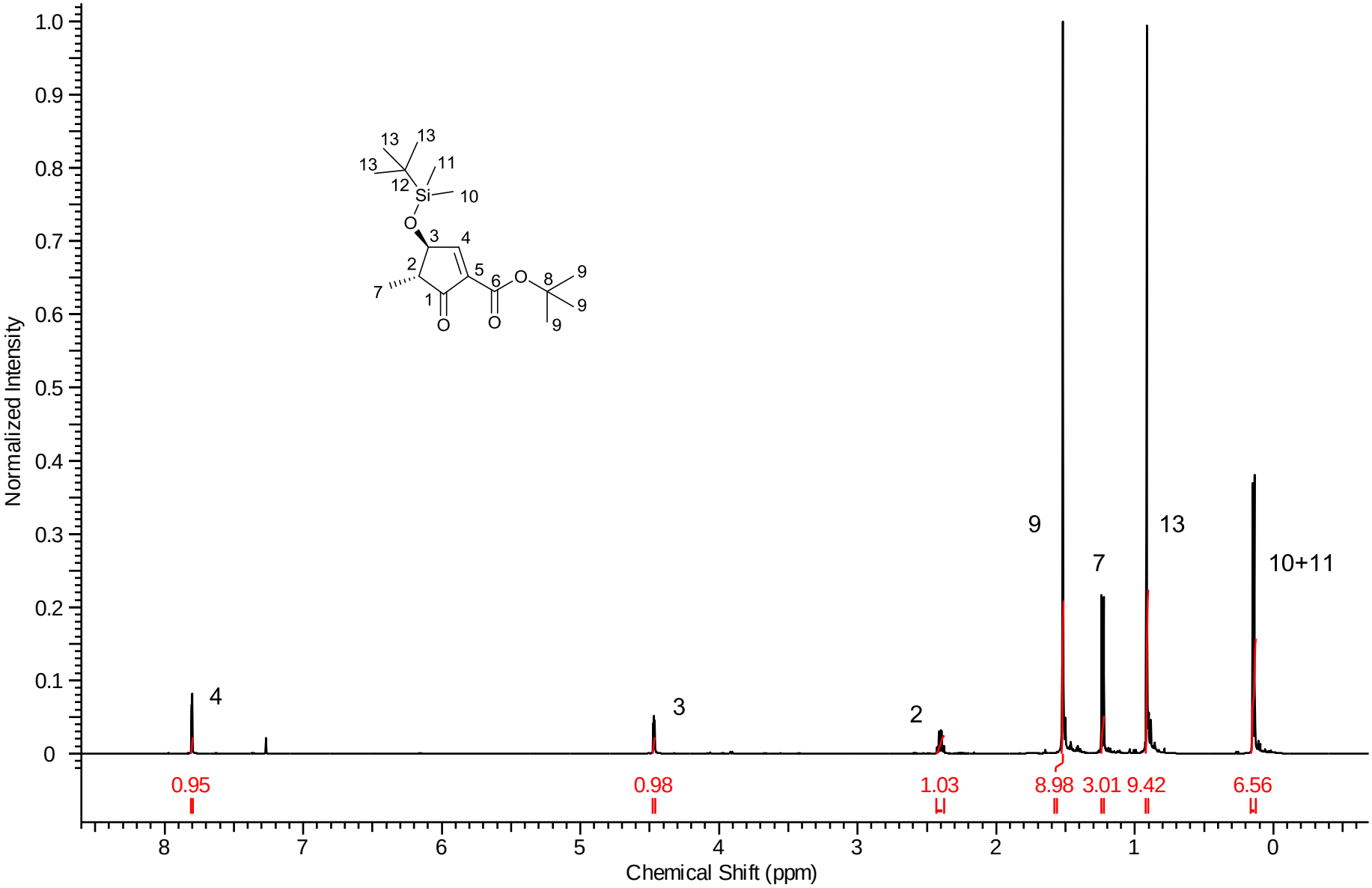
7 - References

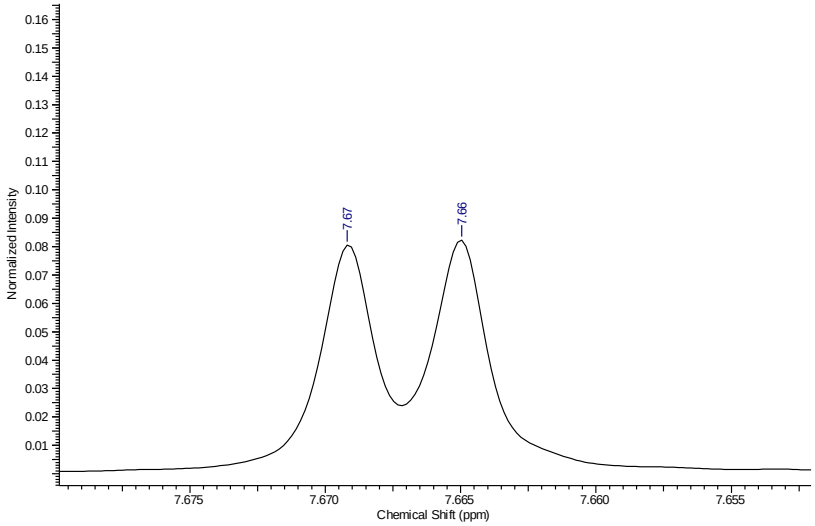
1. Fuchser, J.; Zeeck, A., *Liebigs Ann.* **1997**, *1997*, 87–95.
2. Höfs, R.; Walker, M.; Zeeck, A., *Angew. Chem. Int. Ed.* **2000**, *39*, 3258–3261.
3. Stellfeld, T.; Bhatt, U.; Kalesse, M., *Org. Lett.* **2004**, *6*, 3889–3892.
4. (a) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J., *Tetrahedron* **2005**, *61*, 353–363; (b) Clarke, P. A.; Cridland, A. P., *Org. Lett.* **2005**, *7*, 4221–4224; (c) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C., *Chem. Comm.* **2003**, 1560–1561; (d) Clarke, P. A.; Rolla, G. A.; Cridland, A. P.; Gill, A. A., *Tetrahedron* **2007**, *63*, 9124–9128; (e) Clarke, P. A.; Cridland, A. P.; Rolla, G. A.; Iqbal, M.; Bainbridge, N. P.; Whitwood, A. C.; Wilson, C., *J. Org. Chem.* **2009**, *74*, 7812–7821; (f) Toueg, J.; Prunet, J., *Org. Lett.* **2008**, *10*, 45–48; (g) James, P.; Landais, Y., *Org. Lett.* **2004**, *6*, 325–328.
5. (a) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J., *J. Am. Chem. Soc.* **2003**, *125*, 5393–5407; (b) Evans, D. A.; Starr, J. T., *J. Am .Chem. Soc.* **2003**, *125* (44), 13531-13540; (c) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J., *J. Am. Chem. Soc.* **2002**, *124*, 4552–4553; (d) Evans, D. A.; Starr, J. T., *Angew. Chem. Int. Ed.* **2002**, *41*, 1787–1790; (e) Tanaka, N.; Suzuki, T.; Matsumura, T.; Hosoya, Y.; Nakada, M., *Angew. Chem. Int. Ed.* **2009**, *48*, 2580–2583.
6. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J., *Org. Lett.* **1999**, *1*, 645–648.
7. Roush, W. R.; Koyama, K., *Tetrahedron Lett.* **1992**, *33*, 6227–6230.
8. Baker, R.; Castro, J. L., *J. Chem. Soc.; Perkin Trans. 1* **1990**, 47–65.
9. Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C., *Tetrahedron* **1972**, *28*, 4395–4404.
10. Turner, J. A.; Jacks, W. S., *J. Org. Chem.* **1989**, *54*, 4229–4231.
11. (a) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B., *J. Org. Chem.* **1997**, *62*, 8708–8721; (b) Anderson, J. C.; McDermott, B. P., *Tetrahedron. Lett.* **1999**, *40*, 7135–7138.
12. (a) Hoshino, Y.; Miyaura, N.; Suzuki, A., *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008–3010; (b) Sato, M.; Miyaura, N.; Suzuki, A., *Chem. Lett.* **1989**, *18*, 1405–1408.
13. Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y., *J. Am .Chem. Soc.* **1987**, *109*, 4756-4758.
14. Tanaka, N.; Suzuki, T.; Hosoya, Y.; Nakada, M., *Tetrahedron Lett.* **2007**, *48*, 6488–6492.
15. Suzuki, T.; Tanaka, N.; Matsumura, T.; Hosoya, Y.; Nakada, M., *Tetrahedron Lett.* **2007**, *48*, 6483-6487.
16. Clarke, P. A.; Grist, M.; Ebden, M., *Tetrahedron. Lett.* **2004**, *45*, 927-929.
17. Williams, C. M.; Mander, L. N., *Tetrahedron* **2001**, *57*, 425–447.
18. (a) Gopalan, A. S.; Prieto, R.; Mueller, B.; Peters, D., *Tetrahedron Lett.* **1992**, *33*, 1679–1682; (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y., *J. Org. Chem.* **1986**, *51*, 806–813.
19. James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K., *J. Org. Chem.* **2005**, *70*, 7985–7995.
20. Kobayakawa, Y.; Mori, Y.; Okajima, H.; Terada, Y.; Nakada, M., *Org. Lett.* **2012**, *14*, 2086–2089.
21. Padwa, A.; Kulkarni, Y. S.; Zhang, Z., *J. Org. Chem.* **1990**, *55*, 4144–4153.
22. Tsuda, T.; Yoshida, T.; Saegusa, T., *J. Org. Chem.* **1988**, *53*, 1037–1040.
23. Otera, J.; Danoh, N.; Nozaki, H., *J. Org. Chem.* **1991**, *56*, 5307–5311.
24. Oare, D.; Heathcock, C., *Top. Stereochem.* **1989**, *19*, 227-407.
25. Kwan, E. E.; Evans, D. A., *Org. Lett.* **2010**, *12*, 5124-5127.
26. Li, Z.; Nakashige, M.; Chain, W. J., *J. Am .Chem. Soc.* **2011**, *133*, 6553-6556.

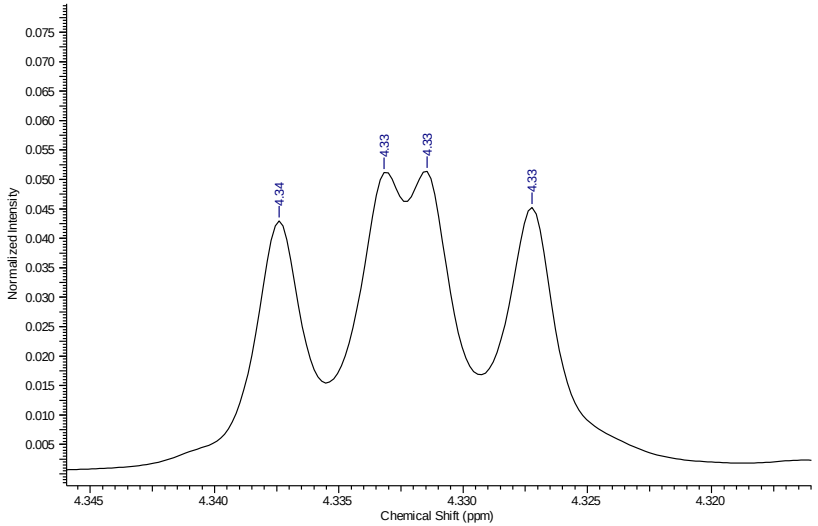
27. Schlegel, B.; Härtl, A.; Dahse, H.-M.; Gollmick, F. A.; Gräfe, U., *J. Antibiot.* **2002**, *55*, 814-817.
28. La Clair, J. J., *Angew. Chem. Int. Ed.* **2006**, *45*, 2769-2773.
29. Rychnovsky, S. D., *Org. Lett.* **2006**, *8*, 2895-2898.
30. Porco, J. A.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D., l. *Angew. Chem. Int. Ed.* **2006**, *45*, 5790-5792.
31. Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Santo Tomas, J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N., *Nature* **2004**, *430*, 900-904.
32. Pericas, À.; Shafir, A.; Vallribera, A., *Tetrahedron* **2008**, *64*, 9258–9263.
33. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M., *J. Org. Chem.* **1993**, *58*, 3568–3571.
34. Delaunay, D.; Toupet, L.; Corre, M. L., *J. Org. Chem.* **1995**, *60*, 6604–6607.
35. (a) Evans, D. A.; Bartroli, J.; Shih, T. L., *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S., *J. Am. Chem. Soc.* **1990**, *112*, 866–868; (c) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L., *Tetrahedron* **1992**, *48*, 2127–2142.
36. (a) Crimmins, M. T.; Chaudhary, K., *Org. Lett.* **2000**, *2*, 775–777; (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K., *J. Org. Chem.* **2001**, *66*, 894–902.
37. Fowles, G. W. A.; Rice, D. A.; Wilkins, J. D., *J. Chem. Soc. A* **1971**, 1920–1923.
38. Crimmins, M. T.; She, J., *Synlett* **2004**, *2004*, 1371–1374.
39. Doering, W. v. E.; DePuy, C. H., *J. Am. Chem. Soc.* **1953**, *75*, 5955–5957.
40. Nicewicz, D. A.; Breteche, G.; Johnson, J. S., *Org. Synth.* **2008**, *85*, 278.
41. (a) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S., *Tetrahedron: Asymmetry* **2002**, *13*, 1189–1193; (b) Johnson, C. R.; Chen, Y. F., *J. Org. Chem.* **1991**, *56*, 3344–3351.
42. Kim, W. H.; Kang, J.-A.; Lee, H.-R.; Park, A.-Y.; Chun, P.; Lee, B.; Kim, J.; Kim, J.-A.; Jeong, L. S.; Moon, H. R., *Carbohyd. Res.* **2009**, *344*, 2317–2321.
43. Ovaa, H.; Lastdrager, B.; Codee, J. D. C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H., *J. Chem. Soc.; Perkin Trans. 1* **2002**, 2370–2377.
44. Grafton, M. W.; Farrugia, L. J.; Senn, H. M.; Sutherland, A., *Chem. Comm.* **2012**, *48*, 7994–7996.
45. More, J. D.; Finney, N. S., *Org. Lett.* **2002**, *4*, 3001–3003.
46. Frigerio, M.; Santagostino, M.; Sputore, S., *J. Org. Chem.* **1999**, *64*, 4537–4538.
47. Snider, B. B.; Yang, K., *J. Org. Chem.* **1992**, *57*, 3615–3626.
48. Toeug, J., *PhD thesis, Ecole Polytechnique* **2007**.
49. Snider, B. B.; McCarthy, B. A., *J. Org. Chem.* **1993**, *58*, 6217–6223.
50. Benelkebir, H.; Hodgkinson, C.; Duriez, P. J.; Hayden, A. L.; Bulleid, R. A.; Crabb, S. J.; Packham, G.; Ganesan, A., *Bioorg. Med. Chem.* **2011**, *19*, 3709–3716.
51. Barton, D. H. R.; Crich, D.; Motherwell, W. B., *Chem. Comm.* **1983**, 939–941.
52. Wharton, P.; Bohlen, D., *J. Org. Chem.* **1961**, *26*, 3615–3616.
53. Crimmins, M. T.; Ellis, J. M., *J. Am. Chem. Soc.* **2005**, *127*, 17200–17201.
54. Holmquist, C. R.; Roskamp, E. J., *J. Org. Chem.* **1989**, *54*, 3258–3260.
55. Ye, W.; Xu, J.; Tan, C.-T.; Tan, C.-H., *Tetrahedron Lett.* **2005**, *46*, 6875–6878.
56. Takano, M.; Umino, A.; Nakada, M., *Org. Lett.* **2004**, *6*, 4897–4900.
57. Li, C.; Yu, X.; Lei, X., *Org. Lett.* **2010**, *12*, 4284–4287.
58. Jung, M. E.; Johnson, T. W., *Tetrahedron* **2001**, *57*, 1449–1481.
59. Hughes, C. C.; Miller, A. K.; Trauner, D., *Org. Lett.* **2005**, *7*, 3425–3428.
60. Lee, P. H.; Cho, M.; Han, I.-S.; Kim, S., *Tetrahedron Lett.* **1999**, *40*, 6975–6978.
61. Iqbal, M.; Black, R. J. G.; Winn, J.; Reeder, A. T.; Blake, A. J.; Clarke, P. A., *Organic & Biomolecular Chemistry* **2011**, *9*, 5062–5078.

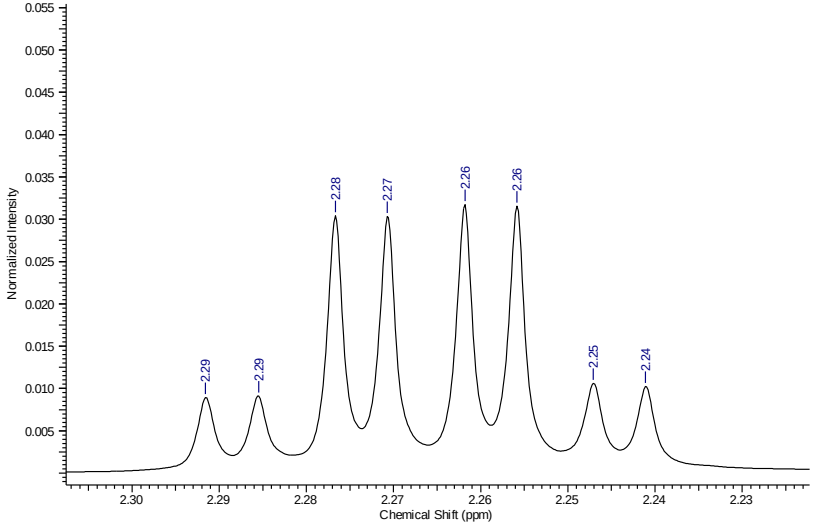
62. Knochel, P.; Brieden, W.; Rozema, M. J.; Eisenberg, C., *Tetrahedron Lett.* **1993**, *34*, 5881-5884.
63. BouzBouz, S.; Cossy, J., *Org. Lett.* **2000**, *2*, 501-504.
64. Esteve, J.; Matas, S.; Pellicena, M.; Velasco, J.; Romea, P.; Urpí, F.; Font-Bardia, M., *Eur. J. Org. Chem.* **2010**, *16*, 3146-3151.
65. Narasaka, K.; Pai, F.-C., *Tetrahedron* **1984**, *40*, 2233-2238.
66. Bode, S. E.; Wolberg, M.; Müller, M., *Synthesis* **2005**, *4*, 557-588.
67. Evans, D. A.; Gauchet-Prunet, J. A., *J. Org. Chem.* **1993**, *58*, 2446–2453.
68. Vincent, A.; Prunet, J., *Synlett* **2006**, 2269–2271.
69. Palimkar, S. S.; Uenishi, J. i.; Ii, H., *J. Org. Chem.* **2011**, *77*, 388–399.
70. Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W., *J. Org. Chem.* **1999**, *64*, 4578–4579.
71. Petrier, C.; Luche, J. L., *J. Org. Chem.* **1985**, *50*, 910–912.
72. Li, C.J., *Tetrahedron* **1996**, *52*, 5643-5668.
73. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H., *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
74. (a) Wu, S.; Lee, S.; Beak, P., *J. Am. Chem. Soc.* **1996**, *118*, 715–721; (b) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K., *Angew. Chem. Int. Ed.* **2007**, *46*, 7491–7494; (c) Muci, A. R.; Campos, K. R.; Evans, D. A., *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076.
75. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J., *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.
76. Barker, G.; O'Brien, P.; Campos, K. R., *Arkivoc* **2011**, 217–229.
77. Huang, M., *J. Am. Chem. Soc.* **1946**, *68*, 2487–2488.
78. Giraldes, J. W.; Akey, D. L.; Kittendorf, J. D.; Sherman, D. H.; Smith, J. L.; Fecik, R. A., *Nat. Chem. Biol.* **2006**, *2* (10), 531-536.
79. Villa, R.; Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D., *Org. Lett.* **2012**, *14*, 5396-5399.
80. Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D., *Synth. Commun.* **1987**, *17*, 1709-1716.
81. Oriez, R., *PhD thesis, Ecole Polytechnique* **2009**.
82. Choi, W. J.; Park, J. G.; Yoo, S. J.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jung, Y. H.; Jeong, L. S., *J. Org. Chem.* **2001,** *66*, 6490–6494.
83. Smith, A. B.; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K., *Org. Lett.* **2005**, *7*, 5075–5078.
84. Paquette, L. A.; Sun, L.-Q.; Friedrich, D.; Savage, P. B., *J. Am. Chem. Soc.* **1997**, *119*, 8438–8450.
85. Johnson, C. R.; Penning, T. D., *J. Am .Chem. Soc.* **1988**, *110*, 4726-4735.
86. Deardorff, D. R.; Windham, C. Q.; Craney, C. L., *Org. Synth.* **1996**, *25*, 73.
87. Singh, G.; Meyer, A.; Aubé, J., *J. Org. Chem.* **2013**, *79*, 452-458.
88. Ghadigaonkar, S.; Koli, M. R.; Gamre, S. S.; Choudhary, M. K.; Chattopadhyay, S.; Sharma, A., *Tetrahedron: Asymmetry* **2012**, *23*, 1093-1099.
89. Crimmins, M. T.; Dechert, A.-M. R., *Org. Lett.* **2012**, *14*, 2366–2369.

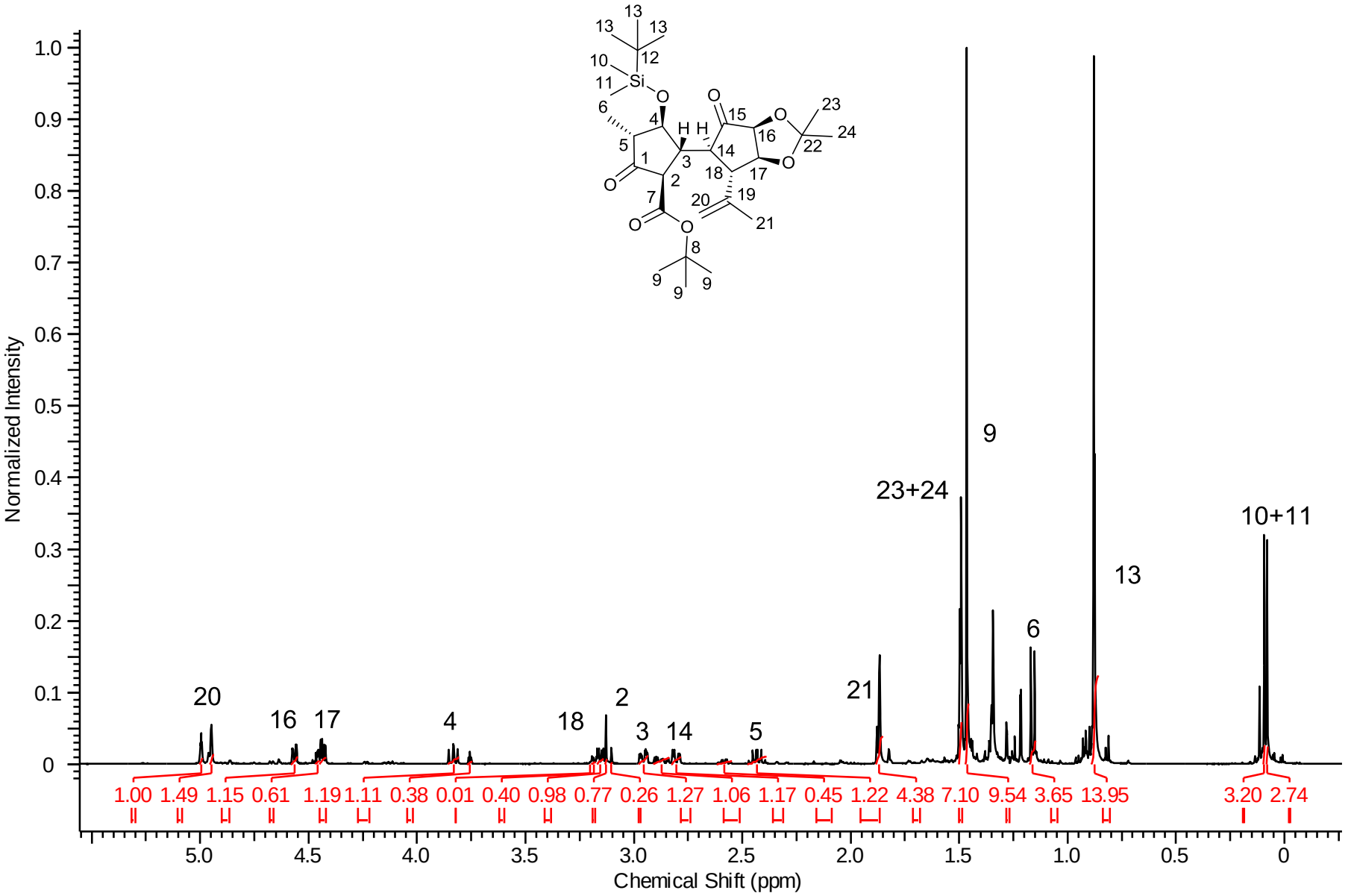
8 - Appendix

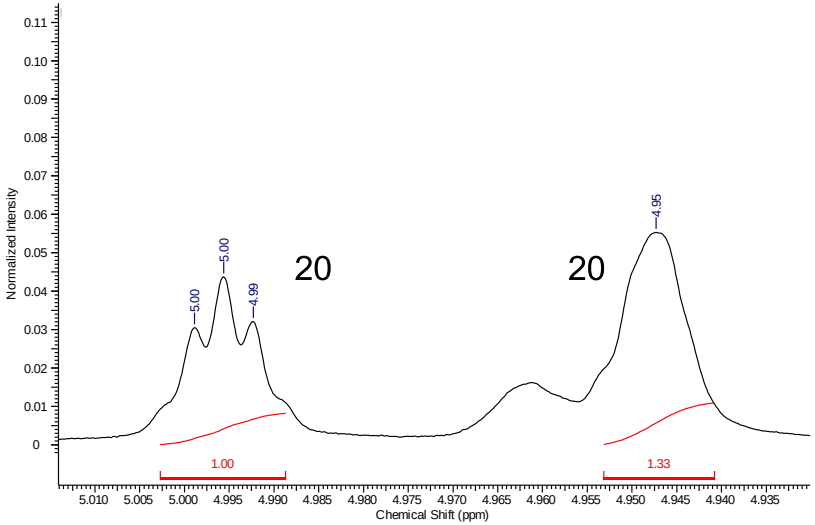

Normalized Intensity
Chemical Shift (ppm)
4
3
2
9
7
13
10+11
0.95
0.98
1.03
8.98
3.01
9.42
6.56

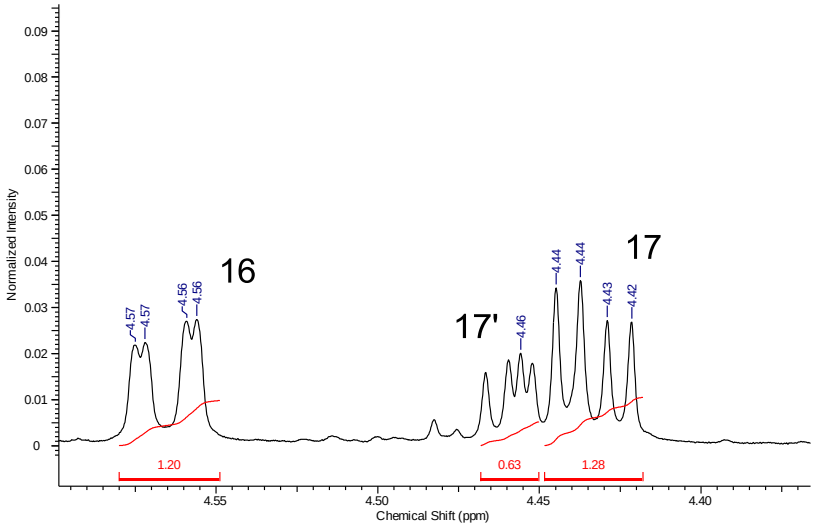

Normalized Intensity
0.16
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
7.67
7.66
7.675
7.670
7.665
7.660
7.655
Chemical Shift (ppm)

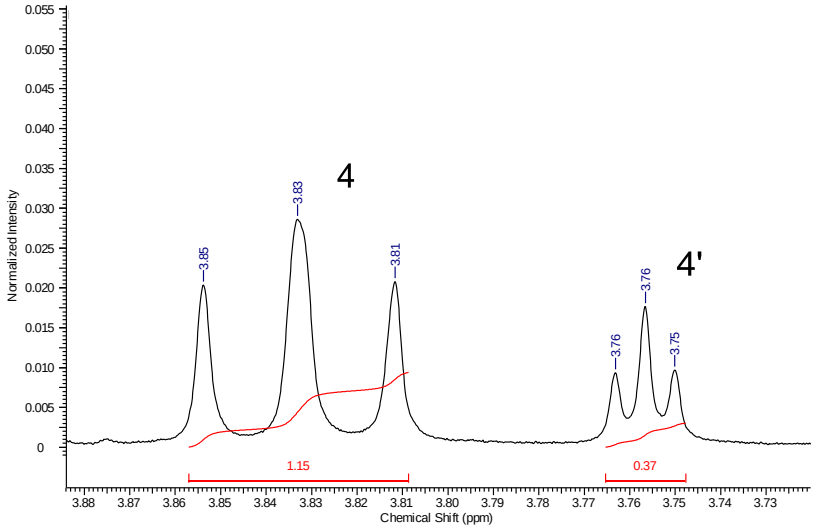

Normalized Intensity
0.075
0.070
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
4.34
4.33
4.33
4.33
4.345
4.340
4.335
4.330
4.325
4.320
Chemical Shift (ppm)

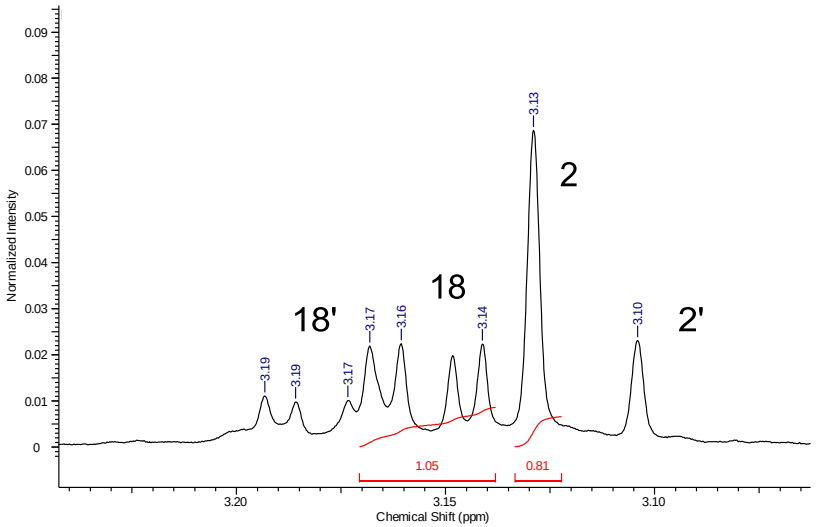

Normalized Intensity
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
2.29
2.29
2.28
2.27
2.26
2.26
2.25
2.24
2.30
2.29
2.28
2.27
2.26
2.25
2.24
2.23
Chemical Shift (ppm)

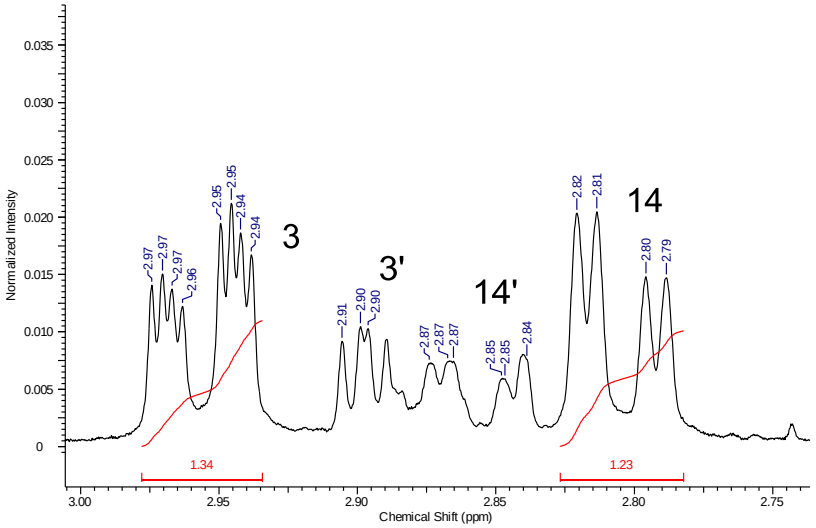

Normalized Intensity
Chemical Shift (ppm)
20
16
17
4
18
2
3
14
5
21
23+24
9
6
13
10+11
1.00 1.49 1.15 0.61 1.19 1.11 0.38 0.01 0.40 0.98 0.77 0.26 1.27 1.06 1.17 0.45 1.22 4.38 7.10 9.54 3.65 13.95 3.20 2.74

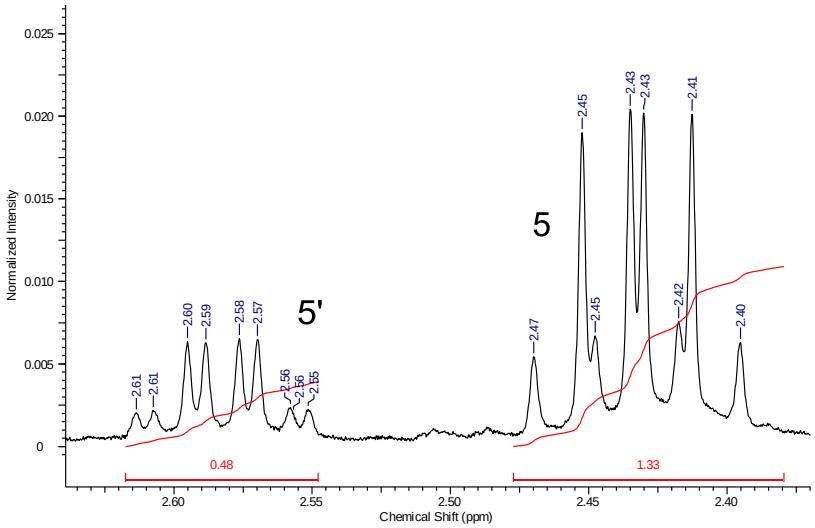

Normalized Intensity
Chemical Shift (ppm)
20
20
5.00
5.00
4.99
4.95
1.00
1.33

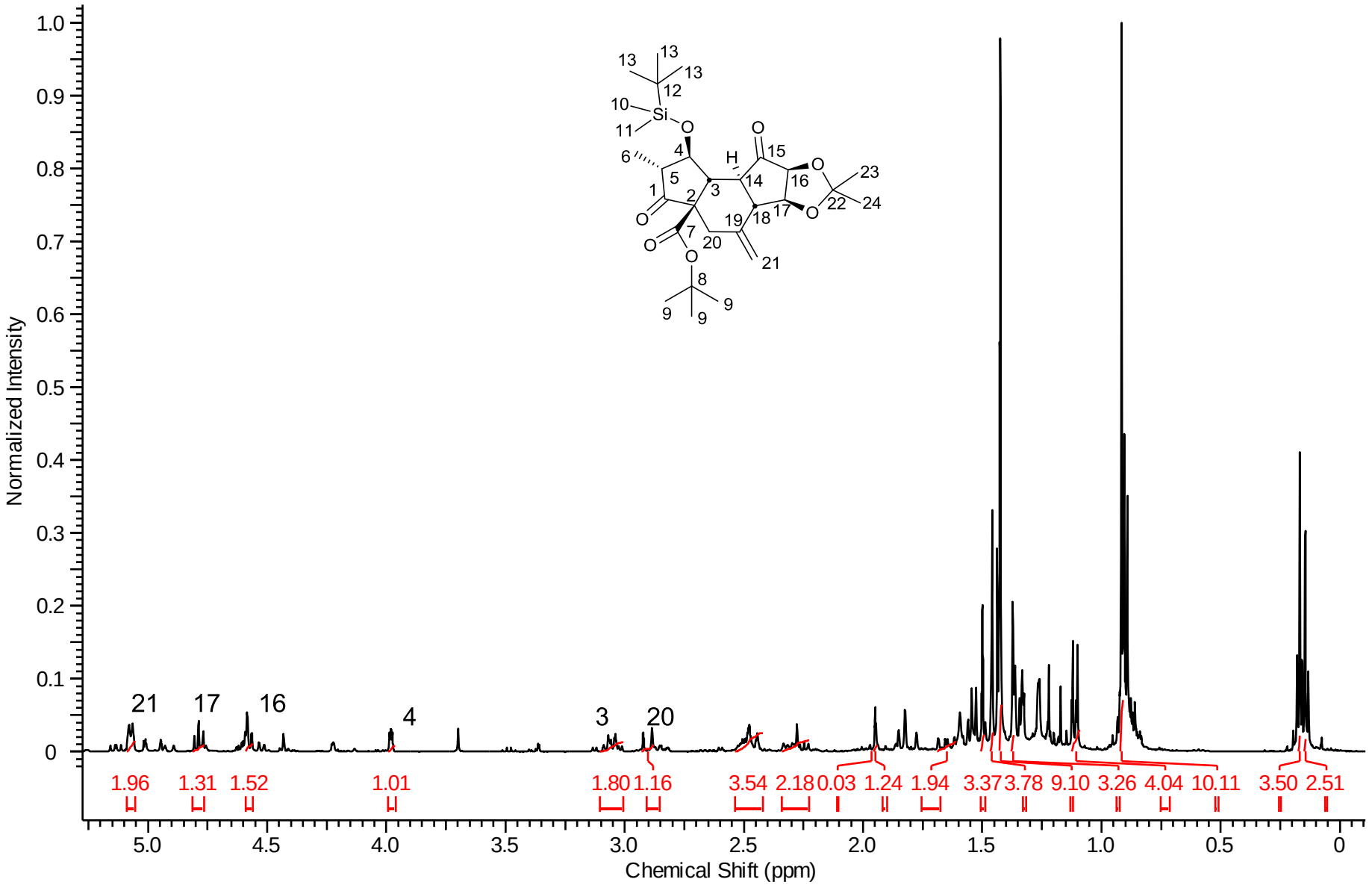

Normalized Intensity
Chemical Shift (ppm)
16
17'
17
4.57
4.57
4.56
4.56
4.46
4.44
4.44
4.43
4.42
1.20
0.63
1.28

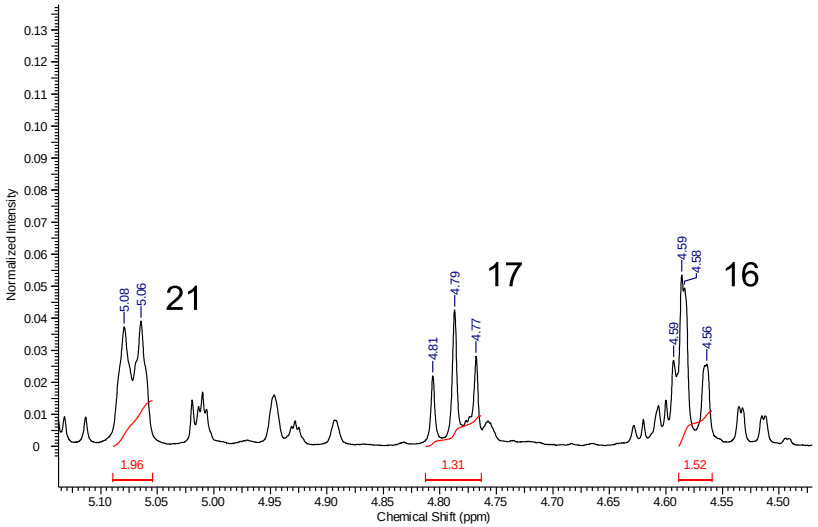

Normalized Intensity
Chemical Shift (ppm)
4
4'
3.85
3.83
3.81
3.76
3.76
3.75
1.15
0.37

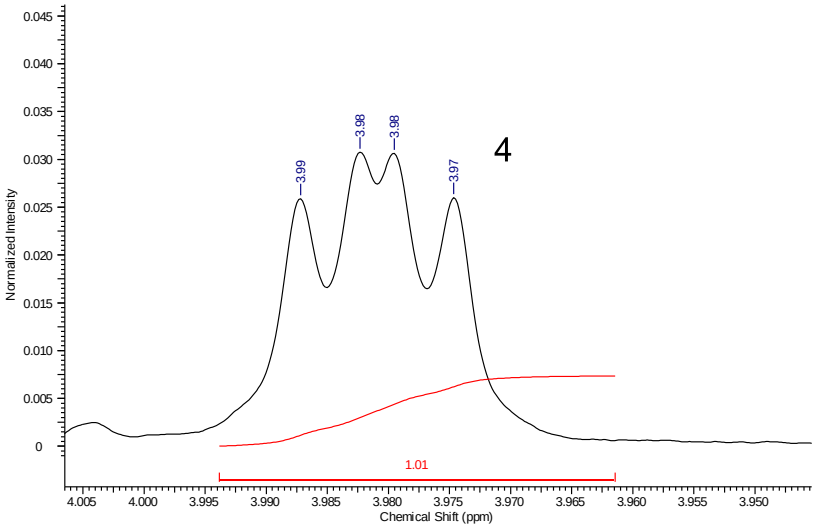

Normalized Intensity
Chemical Shift (ppm)
18'
18
2
2'
3.19
3.19
3.17
3.17
3.16
3.14
3.13
3.10
1.05
0.81

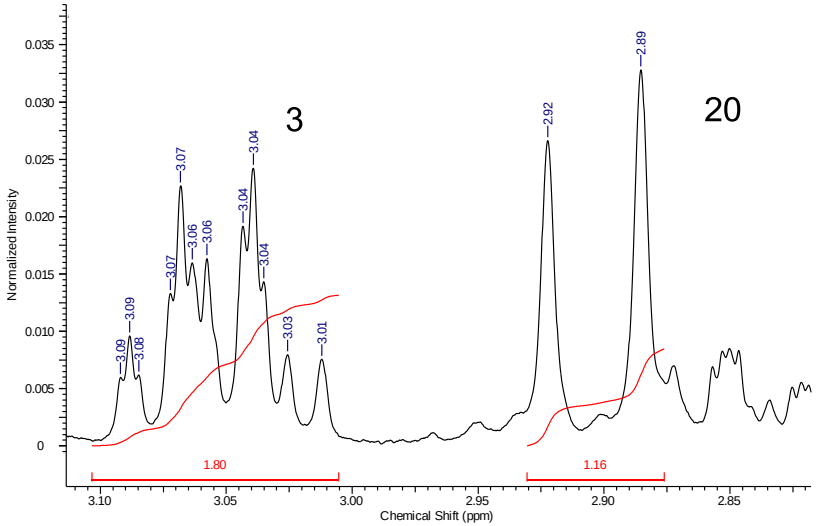

Normalized Intensity
Chemical Shift (ppm)
3
3'
14'
14
1.34
1.23

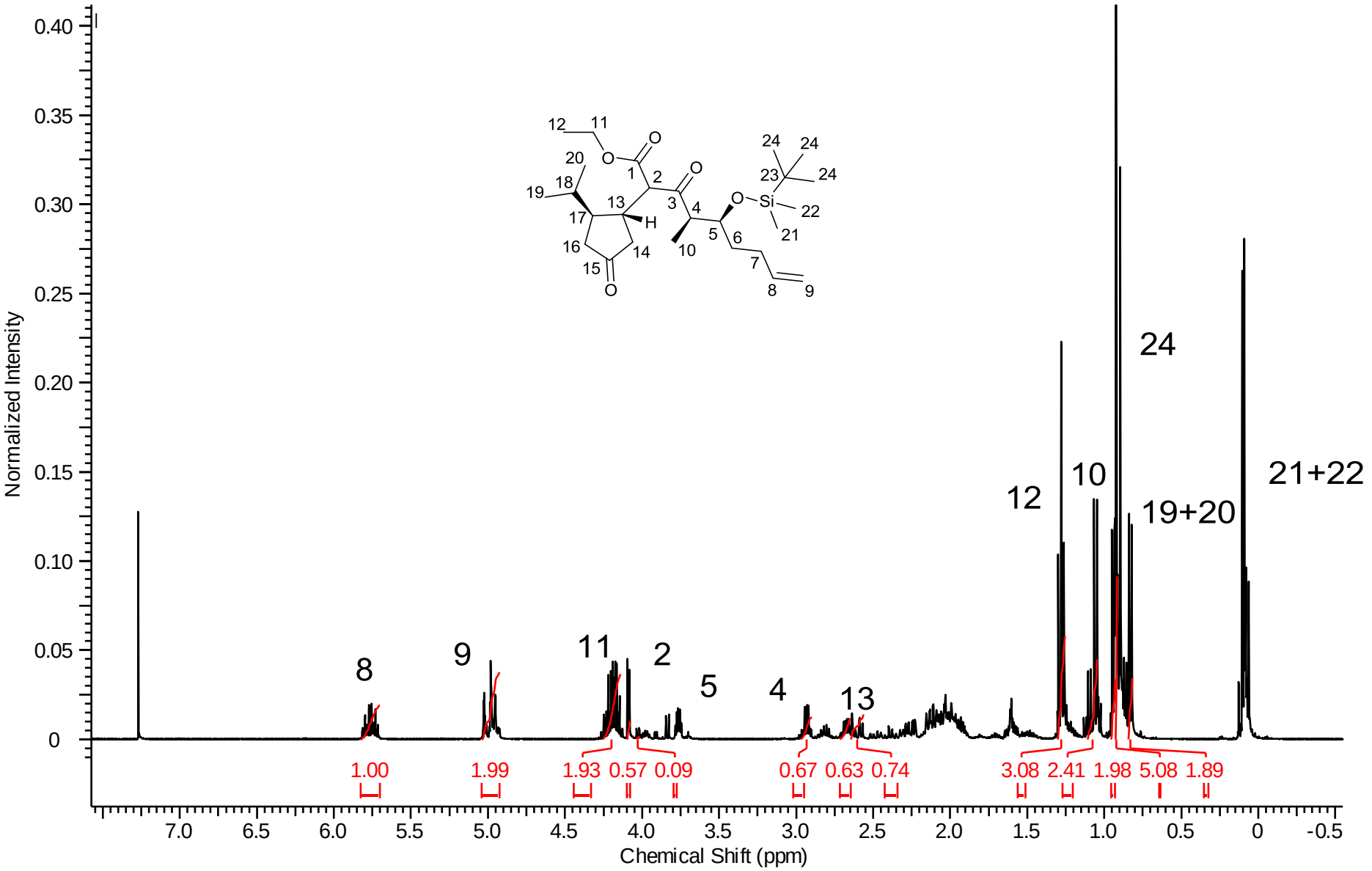

Normalized Intensity
Chemical Shift (ppm)
5
5'
0.48
1.33

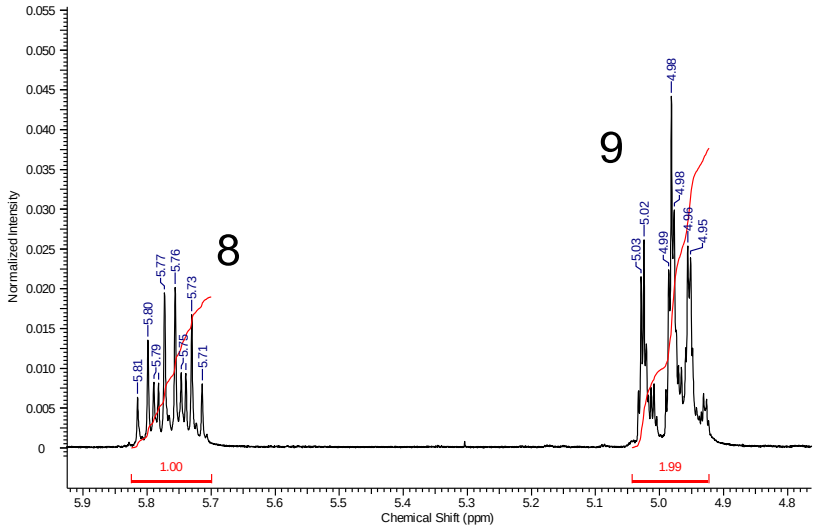

Normalized Intensity
Chemical Shift (ppm)
21
17
16
4
3
20
1.96
1.31
1.52
1.01
1.80
1.16
3.54
2.18
0.03
1.24
1.94
3.37
3.78
9.10
3.26
4.04
10.11
3.50
2.51

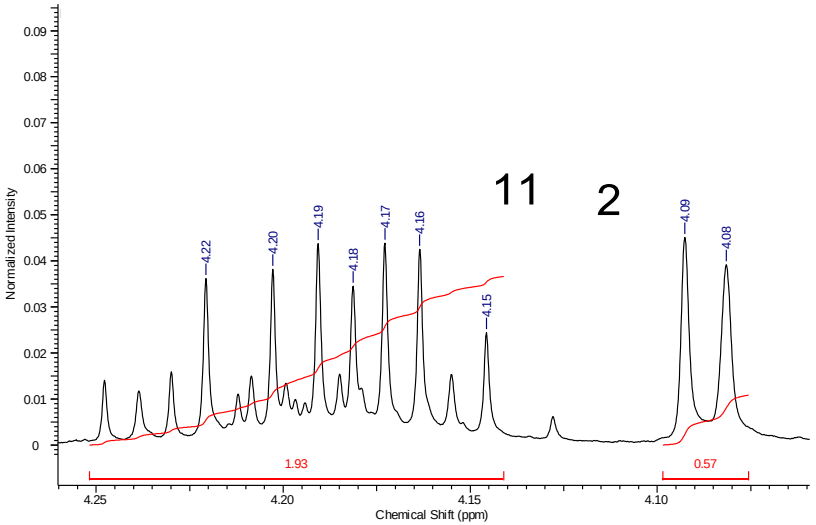

21
17
16
5.08
5.06
4.81
4.79
4.77
4.59
4.58
4.56
1.96
1.31
1.52
Normalized Intensity
Chemical Shift (ppm)

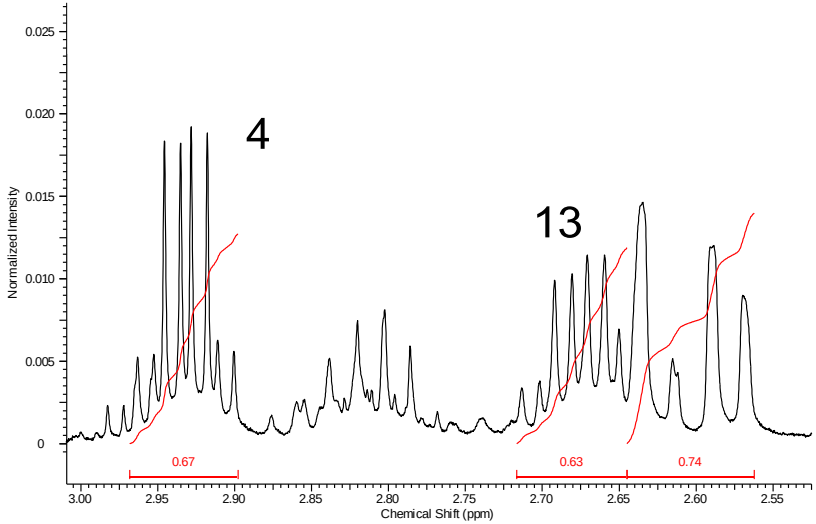

4
3.99
3.98
3.98
3.97
1.01
Normalized Intensity
Chemical Shift (ppm)

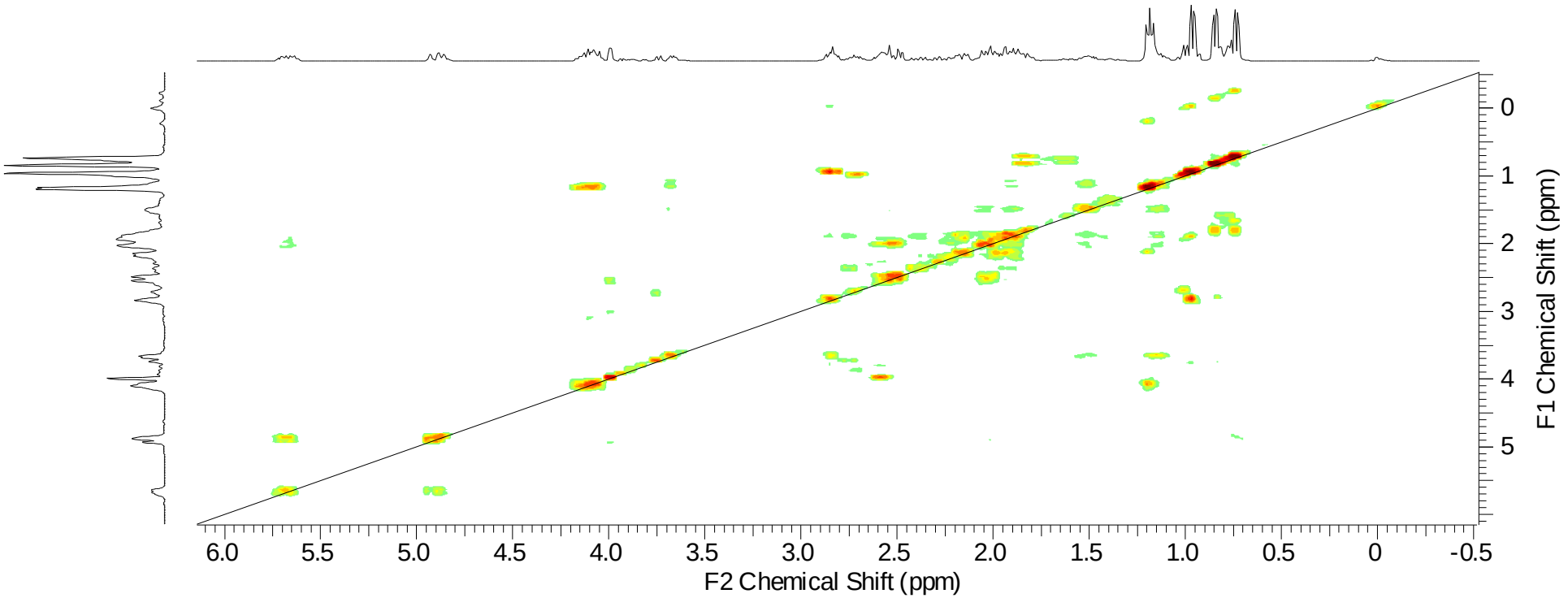

3
20
3.09
3.09
3.08
3.07
3.07
3.06
3.06
3.04
3.04
3.04
3.03
3.01
2.92
2.89
1.80
1.16
Normalized Intensity
Chemical Shift (ppm)

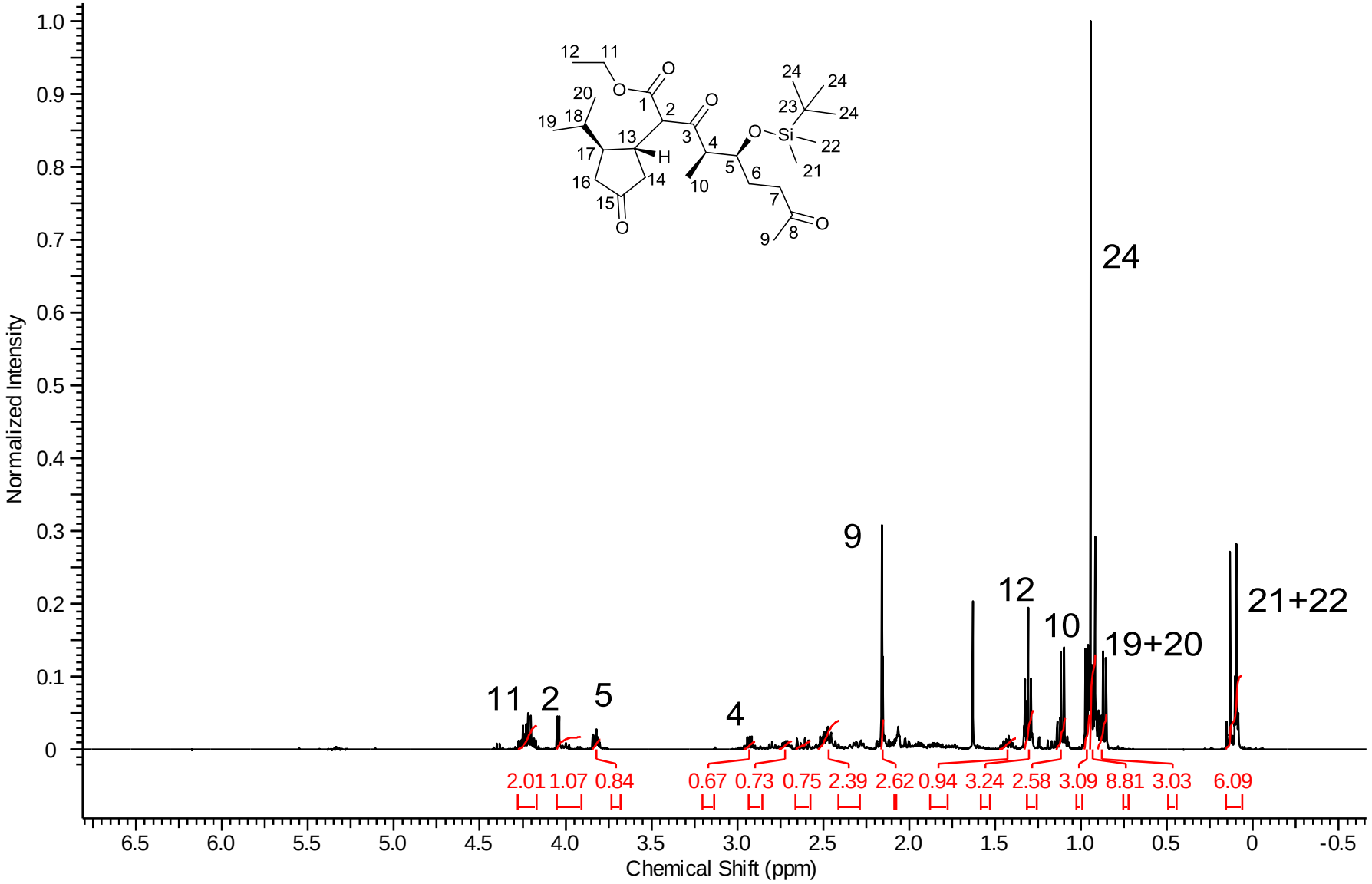

Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
8
9
11
2
5
4
13
12
10
24
19+20
21+22
1.00
1.99
1.93
0.57
0.09
0.67
0.63
0.74
3.08
2.41
1.98
5.08
1.89
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

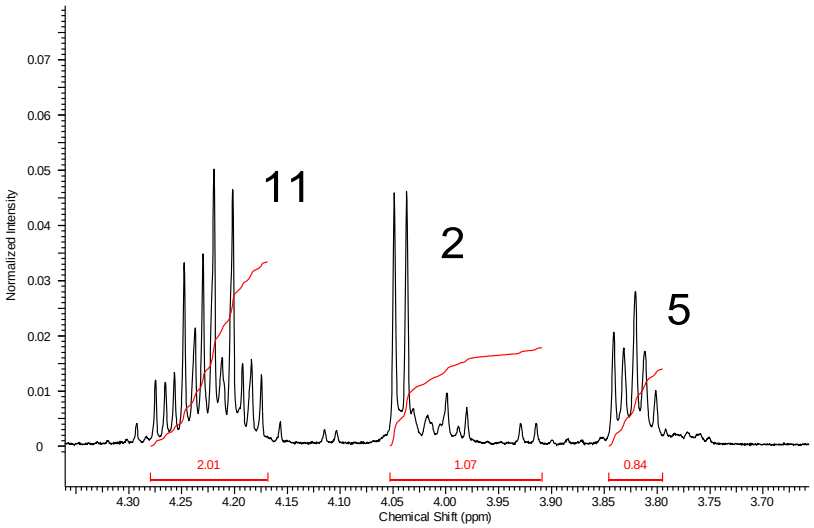

8
9
5.81
5.80
5.79
5.77
5.76
5.75
5.73
5.71
5.03
5.02
4.99
4.98
4.98
4.96
4.95
1.00
1.99
Normalized Intensity
Chemical Shift (ppm)

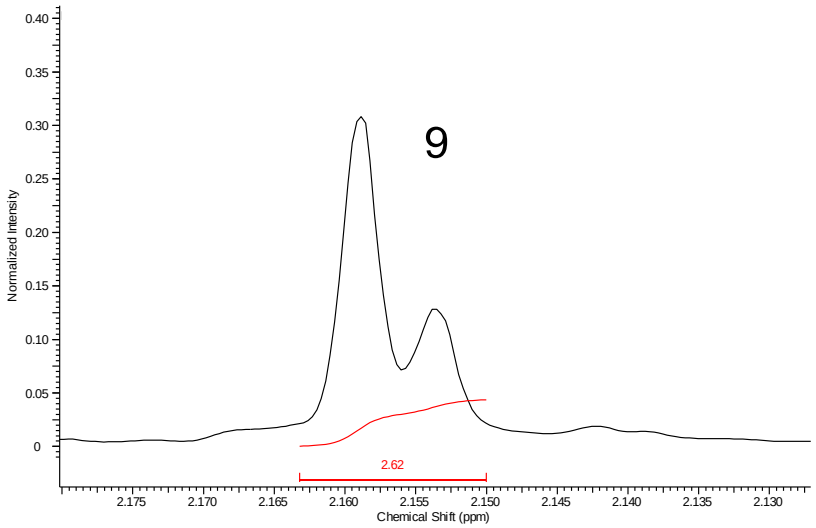

11
2
4.22
4.20
4.19
4.18
4.17
4.16
4.15
4.09
4.08
1.93
0.57
Normalized Intensity
Chemical Shift (ppm)


4
13
0.67
0.63
0.74
Normalized Intensity
Chemical Shift (ppm)


6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
F2 Chemical Shift (ppm)
0
1
2
3
4
5
F1 Chemical Shift (ppm)


Normalized Intensity
Chemical Shift (ppm)
11
2
5
4
9
12
10
19+20
21+22
24
2.01 1.07 0.84
0.67 0.73 0.75 2.39 2.62 0.94 3.24 2.58 3.09 8.81 3.03 6.09


11
2
5
2.01
1.07
0.84
Normalized Intensity
Chemical Shift (ppm)


9
2.62
Normalized Intensity
Chemical Shift (ppm)