Synthetic Studies Towards the Total Synthesis of Hexacyclinic Acid

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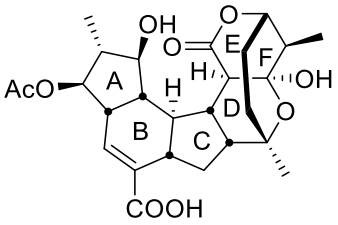
Abstract

Hexacyclinic acid is a polyketide isolated from *Streptomyces cellulosae* in 2000 and is composed of six cycles, a 5/6/5 fused ring system (A, B and C) connected to a bridged tricycle (D, E and F). Hexacyclinic has shown some interesting cytotoxic activities but there has been no total synthesis reported in the literature at present.



In the first chapter of this thesis, published works found in the literature about hexacyclinic acid and FR182877 are reported and commented. A quick summary of the previous work done in the Prunet group is also described.

In the second and third chapter, a more detailed account of the work undertaken during this PhD was given. Firstly, syntheses of two ABC tricycles incorporating *tert*-butyl and (trimethylsilyl)ethyl esters were undertaken. These syntheses include two key steps previously developed in the group, a diastereoselective Michael addition and a Snider cyclisation. Multiple conditions for the hydrolysis of the esters were attempted but none of them gave the desired product.

The main part of this work is focused on the synthesis of a CDEF model and in particular about the development of the key step, the formation of a nine-membered ring. Several DEF fragments were synthesised in short synthetic sequences and as single isomers. Six different synthetic pathways were developed in total and a novel method, a Michael/elimination reaction, was found to be a very efficient way to close the desired medium-size ring. From the nine-membered ring, regioselective reduction and palladium-catalysed allylic substitution led to the formation of the CDF tricycle. Final steps of the synthesis were fruitless and led only to decomposition. A synthesis of a chiral C-ring was also developed during this PhD.

Finally, another project was undertaken, not related to hexacyclinic acid. Methodology developed in the group for the diastereoselective formation of trisubstituted alkenes employing a temporary silicon-tethered ring-closing metathesis was extended to homoallylic alcohols. The first steps of the method were similar to the previous methodology but the end-game had to be modified in favour of an oxidation/reduction sequence to successfully obtain the desired products with the correct geometry.

In the fourth chapter, procedures and analytical data for the synthesised compounds previously described are reported.

Author’s declaration

This thesis represents the original work of Alexandre Audic unless otherwise explicitly stated and referenced in the text. The research was carried out at the University of Glasgow in the Raphael Laboratory under the supervision of Dr Joëlle Prunet during the period from the 1st of October 2012 to 31st of March 2016.

“*Failure is the condiment that gives success its flavor.*” – Truman Capote

Acknowledgments

First of all, I would like to thank my supervisor, Dr Joëlle Prunet, for giving me the opportunity to do my PhD in her group, for the help, guidance and trust she kindly gave me during those 4 years.

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To the entire Marquez group and especially to: Tom “Tommy Cat”, Yezekhiel, Sean “Lepresean”, Alan Sewell, and Colin “super postdoc”.

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To the Clark group, Michael PP, Aurélien Junior, Filo, Laëtitia for her kind help, Sam, Kirsten, Gregor but especially Ludo, with whom I shared worries about the PhD, the writing-

up, post-doc, life in general. We truly started to know each other toward the end but it was great!
I would like to thank all the members of staff that have been of great help during my PhD, especially Ted, Bruce, Karen, Ali, Jim and Harry.

A special thanks to my family and to my mom who supported me from the very beginning, believed in me and has always been here when I needed her.

Abbreviations

Ac: Acetyl

Aq: Aqueous

ACCN: 1,1′-Azobis(cyclohexanecarbonitrile)

AIBN: Azobisisobutyronitrile

BAIB: [Bis(acetoxy)iodo]benzene

BHT: Butylated hydroxytoluene

Bn: Benzyl

brsm: Based on recovered of starting material

Bz: Benzoyl

Cat: Catalytic

COD: 1,5-Cyclooctadiene

CM: Cross-metathesis

Cp*: 1,2,3,4,5-Pentamethylcyclopentadiene

CSA: Camphorsulfonic acid

d: day

dba: Dibenzylideneacetone

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DIAD: Diisopropyl azodicarboxylate

DIBAL-H: Diisobutylaluminium hydride

DIPEA: *N*,*N*-Diisopropylethylamine

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

DMP: Dess-Martin periodinane

DMSO: Dimethyl sulfoxide

dppe: 1,2-*Bis*(diphenylphosphino)ethane

dppf: 1,1′-Ferrocenediyl-*bis*(diphenylphosphine)

dr: Diastereomeric ratio

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

ee: Enantiomeric excess

ent: Enantiomer

Et: Ethyl

Equiv: Equivalent

FGI: Functional group interconversion

GI_{50}: Growth inhibition of 50% of cancer cells

h: hour

HMPA: Hexamethylphosphoramide

HWE: Horner–Wadsworth–Emmons

Hz: Hertz

i: iso

IMDA: Intramolecular Diels-Alder

IMHDA: Intramolecular hetero-Diels-Alder

m: Meta

M: Molar

MBH: Morita-Baylis-Hillman

m-CPBA: meta-Chloroperbenzoic acid

Me: Methyl

Mes: Mesityl

Min: Minute

MS: Molecular sieves

Ms: Mesyl

Mw : Molecular weight

NCS: N-Chlorosuccinimide

NMO: N-Methylmorpholine N-oxide

NMP: N-Methyl-2-pyrrolidone

NMR: Nuclear magnetic resonance

p: Para

Ph: Phenyl

PMB: *p*-Methoxybenzyl ether

ppm: Parts per million

PPTS: Pyridinium *p*-toluenesulfonate

Pr: Propyl

*p*TSA : *p*-Toluenesulfonic acid

Pyr: Pyridine

R: Generalised group

RCEYM: Ring-closing ene-yne metathesis

RCM: Ring-closing metathesis

RRCM: Relay ring-closing metathesis

RT: Room temperature

SM: Starting material

t: Tert

TPAP: Tetrapropylammonium perruthenate

TBAF: Tetra-*n*-butylammonium fluoride

TBDPS: *tert*-Butyldiphenylsilyl

TBS: *tert*-Butyldimethylsilyl

TEAB: Tetraethylammonium bromide

TEMPO: (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

TES: Triethylsilyl

Tf: Triflyl

THF: Tetrahydrofuran

TMANO: Trimethylamine N-oxide

TMDA: Tetramethylethylenediamine

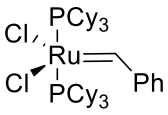
TMS: Trimethylsilyl

TMSE: 2-(Trimethylsilyl)ethyl

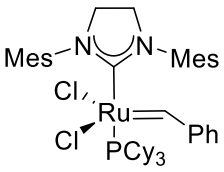
Ts: Tosyl

TTMSS: Tris(trimethylsilyl)silane

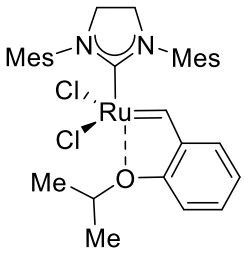
Table of RCM catalysts



Grubbs 1
first generation
of Grubbs' catalyst



Grubbs 2
second generation
of Grubbs' catalyst



Hoveyda-Grubbs 2
second generation of
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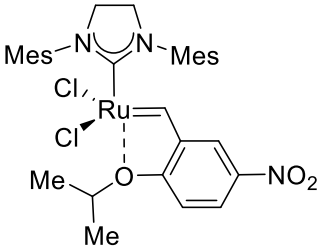

Grela
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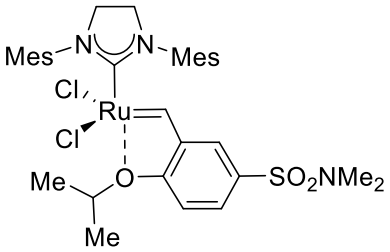
of Hoveyda-Grubbs' catalyst



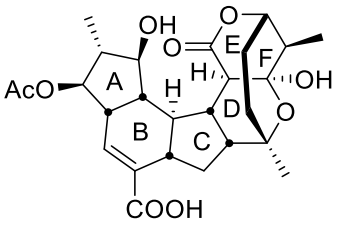
Zhan-1B
modified second generation
of Hoveyda-Grubbs' catalyst

Chapter 1: Introduction

1.1 Presentation of hexacyclinic acid and FR182877

1.1.1 Hexacyclinic acid

Hexacyclinic acid **1.1** is a complex polyketide isolated for the first time by Zeeck *et al.* in 2000 from a bacterium, *Streptomyces cellulosae* (strain S1013).[1] The general structure and relative configuration were elucidated with the aid of several NMR experiments and X-ray analysis; the absolute configuration was successfully determined by Mosher's ester methodology. Hexacyclinic acid **1.1** is composed of six rings, a 5/6/5 fused ring system (A, B and C) connected to a bridged tricycle (D, E and F) with a cyclic hemiketal and a δ-lactone (Figure 1.1).



(**1.1**)

Figure 1.1: Structure of hexacyclinic acid

Hexacyclinic acid **1.1** possesses cytotoxic activities against three cancerous cell lines: HM02 (gastric carcinoma), HEPG2 (hepatocellular carcinoma) and MCF7 (breast carcinoma) with GI_{50} values up to 14.0 µmol.L^{-1}. ^{13}C labelling experiments were undertaken by feeding growing culture with ^{13}C acetate and ^{13}C propionate. These experiments revealed that hexacyclinic acid is built by seven acetate and four propionate units (Figure 1.2).

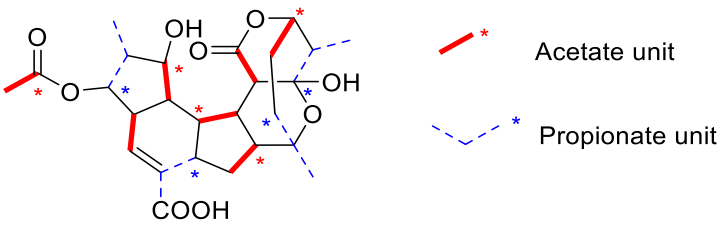
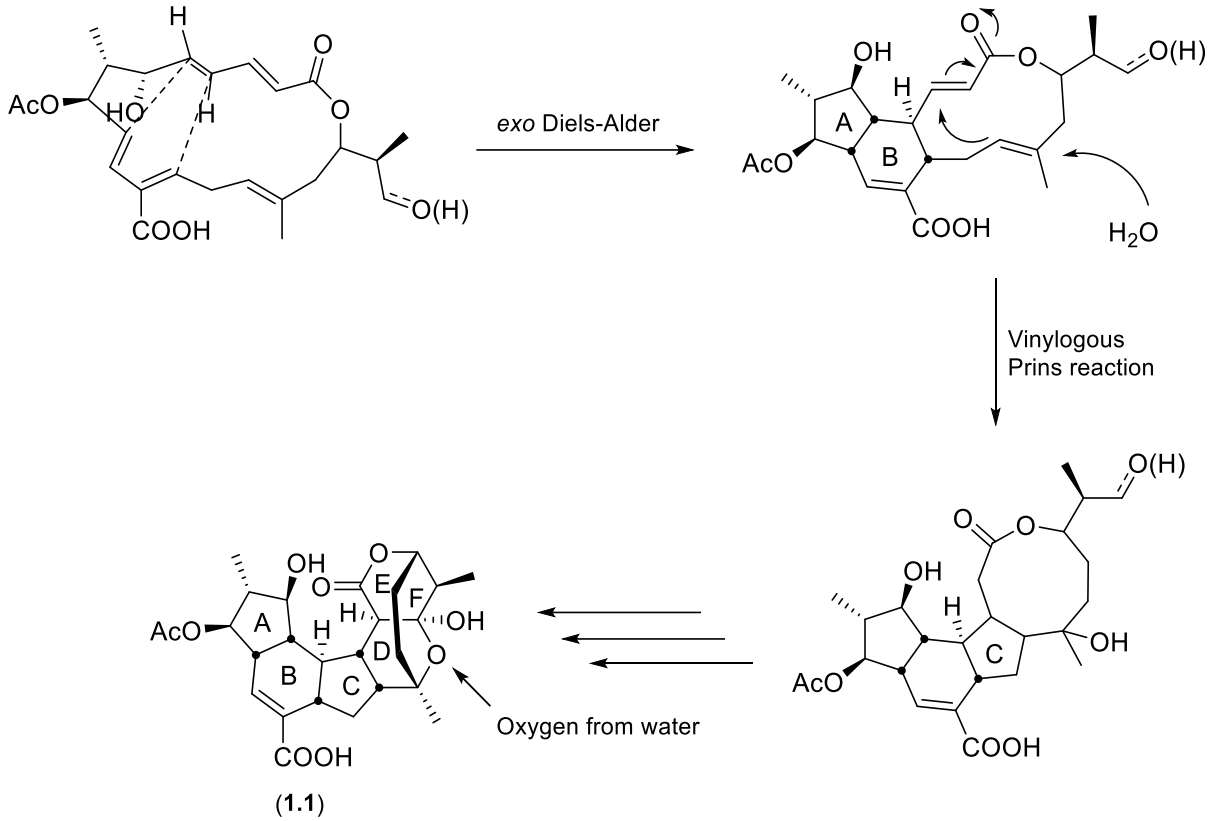


Figure 1.2: ^{13}C labelling experiments

A biosynthesis was proposed: the AB system could be synthesised by an *exo* Diels-Alder and the C ring by a vinylogous Prins reaction with hemiketal oxygen coming from an external source such as water (Scheme 1.1).[1,2]

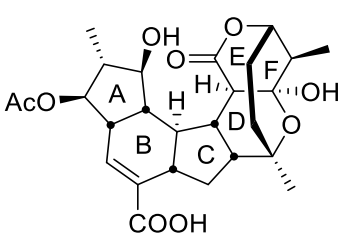


Scheme 1.1: Hypothesised biosynthesis

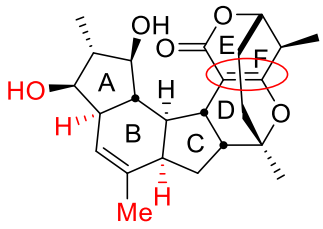
There has been no total synthesis of hexacyclinic acid **1.1** reported in the literature at present.

1.1.2 (−)-FR182877

(−)-FR182877 **1.2**, a cousin compound, was isolated in 1998 by the research group at the Fujisawa Pharmaceutical Co.[3] The first attribution of the absolute configuration of **1.2** was enantiomeric to the actual structure ((+)-FR182877), however this error was later corrected.[4] Compounds **1.1** and **1.2** have very similar structures, but there are some key differences between them: the stereochemistry of the ABC ring junctions, the hemiketal of **1.1** is replaced by a conjugated alkene in **1.2,** the acetate on the A ring, and the carboxylic acid that has been replaced by a methyl group (Figure 1.3).



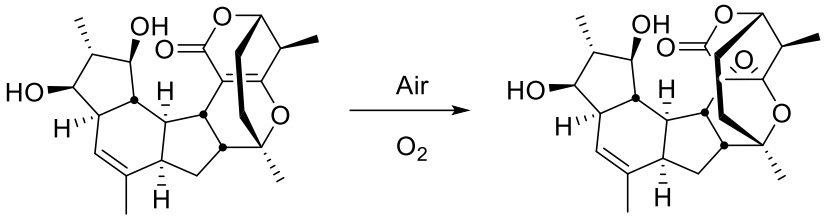
Hexacyclinic acid (**1.1**)



(-)-FR182877 (**1.2**)

Figure 1.3: Comparison between **1.1** and **1.2**

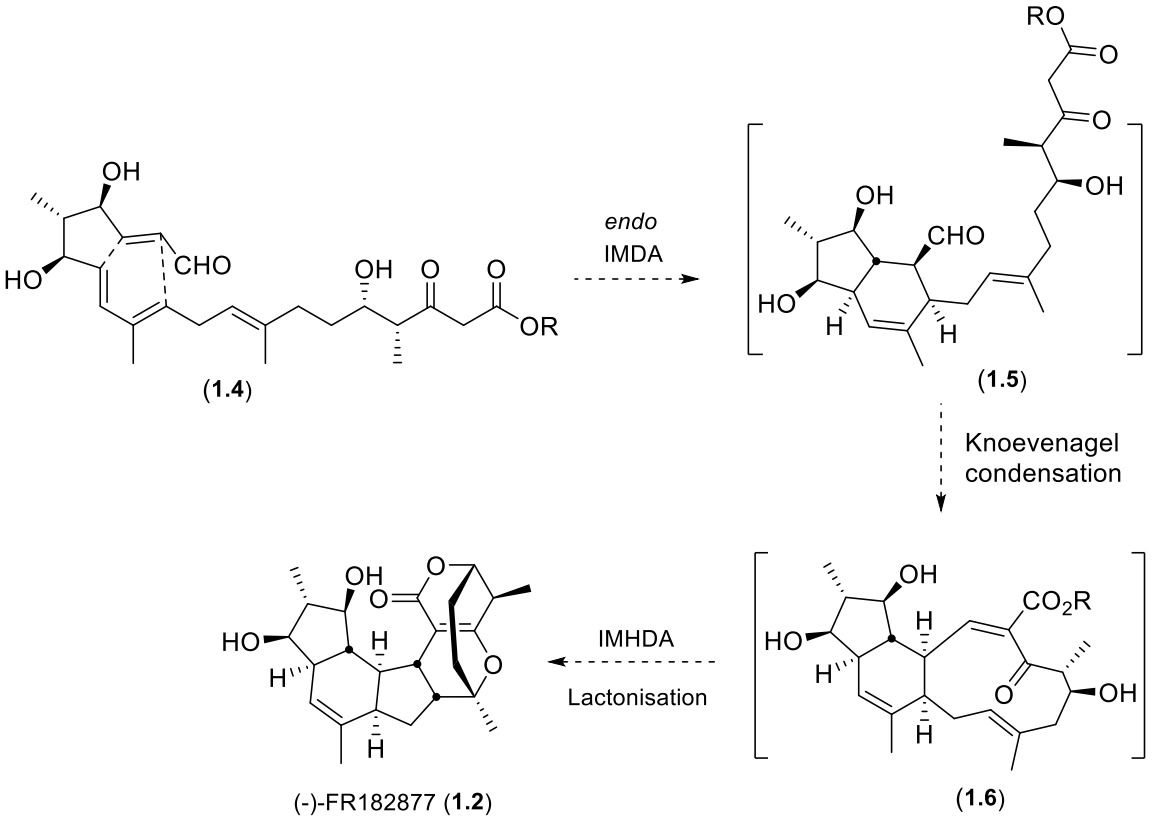
Compound **1.2** exhibits a greater cytotoxicity than hexacyclinic acid **1.1**. For example, the IC_{50} toward P388 cell line (leukemia cells) is 21 ng/mL, which is comparable to the cytotoxic effects of Taxol®. It has been suggested that the potent activity of (–)-FR182877 **1.2** could be due to the strained conjugated alkene, which acts as an excellent Michael acceptor and can react with a wide range of nucleophiles (imidazole, thiols and amines).[5] Indeed, when the alkene was transformed into an epoxide by exposure to dioxygen, compound **1.3** no longer exhibited cytotoxicity (Scheme 1.2).[6]



(**1.2**) (**1.3**)

Scheme 1.2: Reaction between (–)-FR182877 **1.2** and dioxygen

A biosynthesis was hypothesised for FR182877 by Sorensen *et al*.[5,7] The first step described is similar to the biosynthesis of hexacyclinic acid **1.1** as it involves an *endo* intramolecular Diels-Alder (IMDA) to close the AB ring system and installs four new stereocenters. The next steps were thought to be a Knoevenagel condensation followed by an intramolecular hetero Diels-Alder (IMHDA) and lactonisation to give the final product, (–)-FR182877 **1.2** (Scheme 1.3).

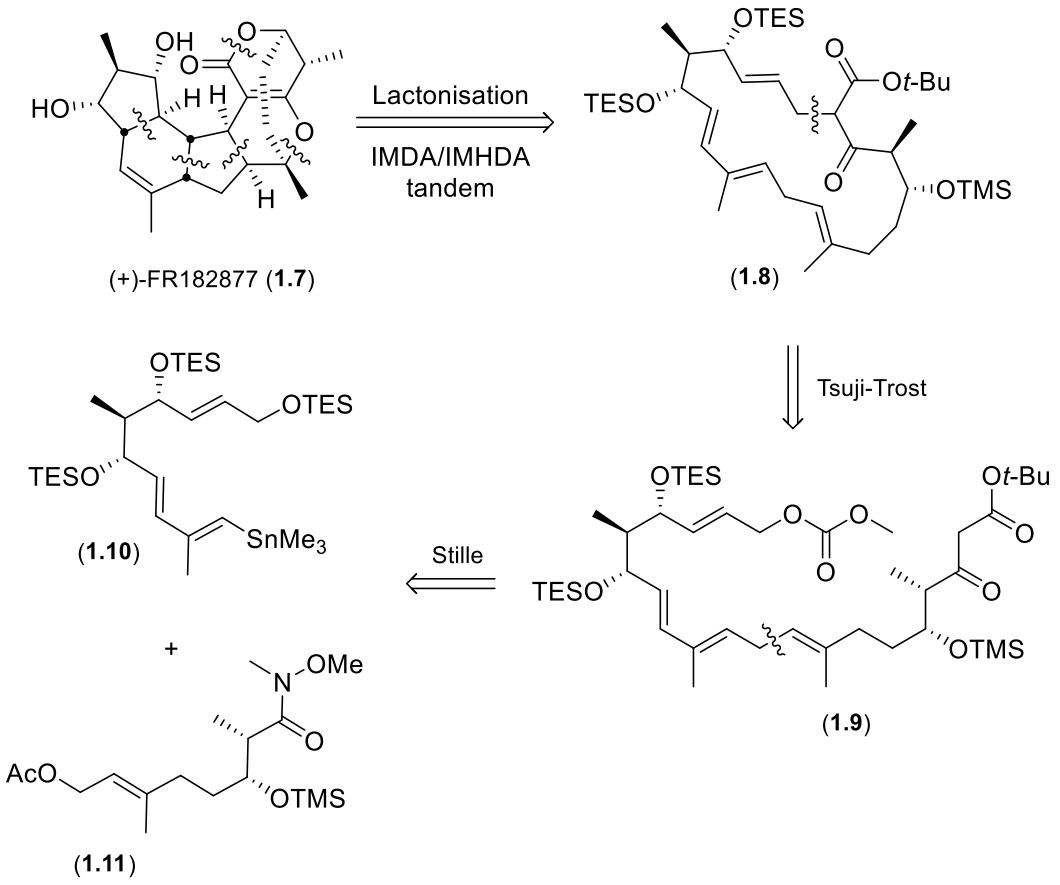


Scheme 1.3: Proposed biosynthesis

1.2 Total syntheses of FR182877

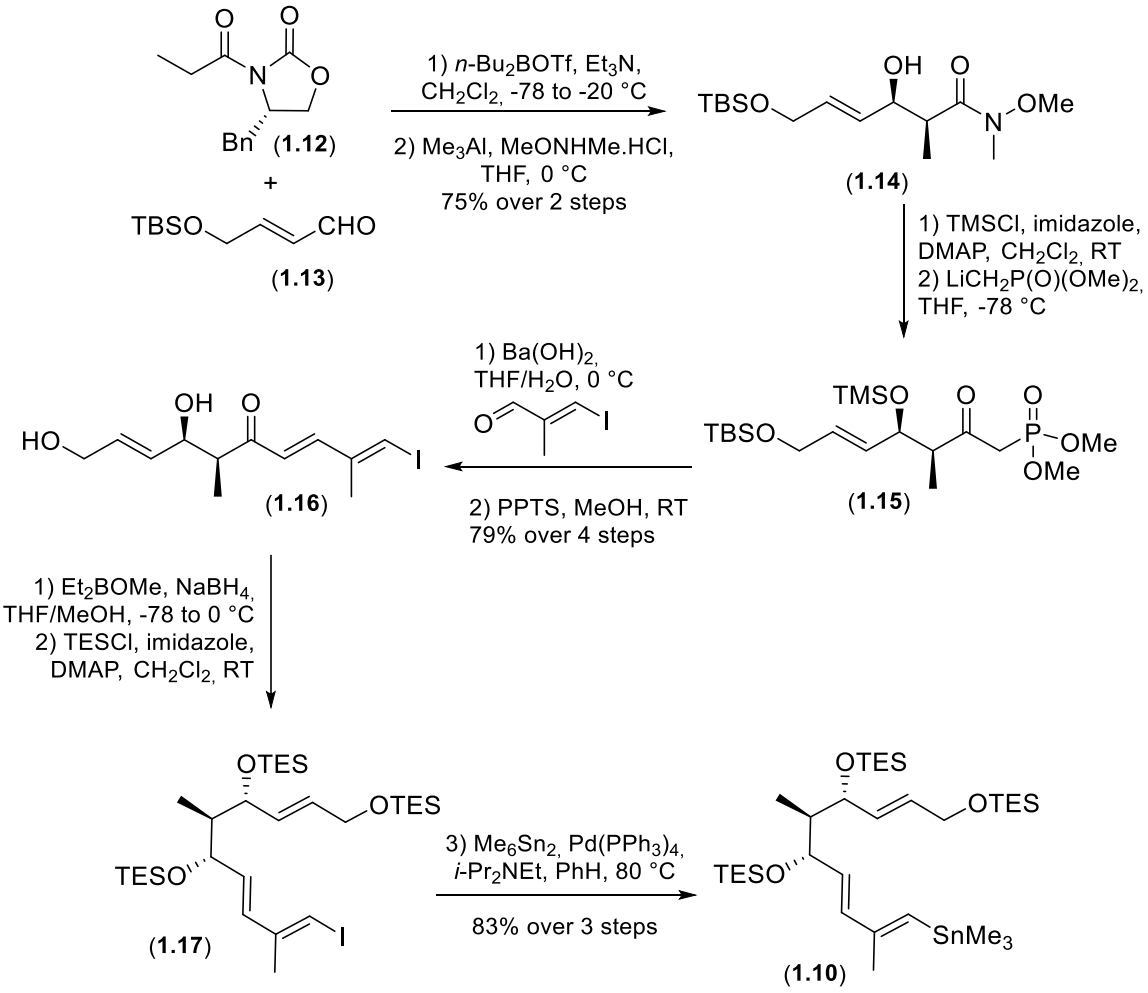
1.2.1 Total synthesis of FR182877 by Sorensen *et al.*

Sorensen *et al.* were the first ones to publish the total synthesis of FR182877 in 2002.[8] At that time, it was still believed that the natural product was (+)-FR182877 **1.7** and therefore, the total synthesis described by Sorensen *et al.* first describes this enantiomer. The synthetic strategy was to use a biomimetic approach. The final key step was planned to be a tandem IMDA/IMHDA to close the ABCDF pentacycle from a nineteen-membered macrocycle **1.8**. The macrocycle **1.8** could be closed from the linear product **1.9** using a Tsuji-Trost cyclisation. Product **1.9** was to be synthesised by a Stille coupling between fragment **1.10** and fragment **1.11** (Scheme 1.4).



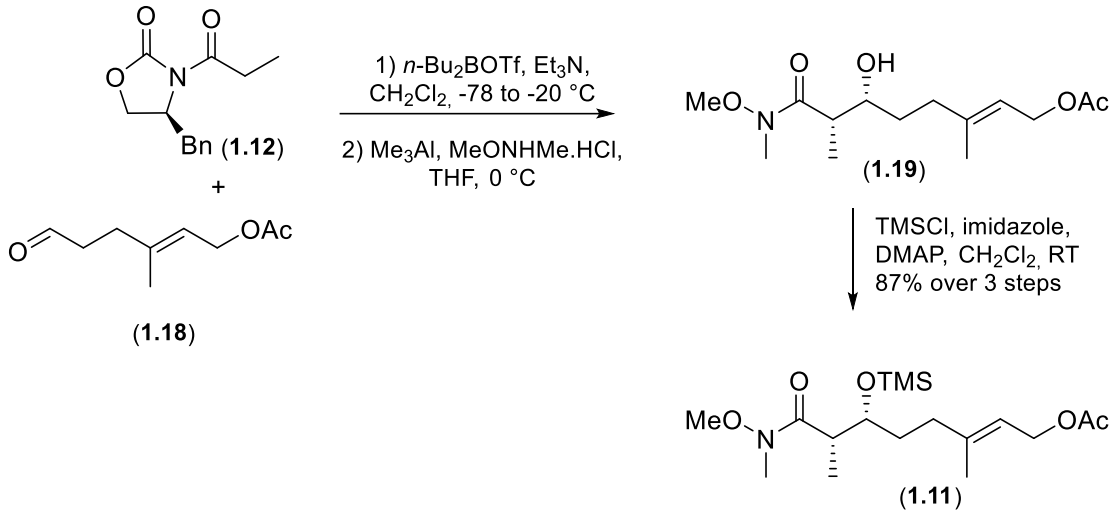
Scheme 1.4: Retrosynthesis of (+)-FR182877

The synthesis of fragment **1.10** started by a diastereoselective aldol reaction between Evans auxiliary **1.12** and aldehyde[9] **1.13** to furnish an aldol as a single isomer that was converted into the corresponding Weinreb amide **1.14**. The following steps were TMS protection of the secondary alcohol then formation of *β*-ketophosphonate **1.15**. Product **1.15** reacted with *β*-iodomethacrolein[10] in a Horner–Wadsworth–Emmons reaction (HWE) using activated barium(II) oxide to produce the *E*-olefin.[11] Both alcohols were deprotected using PPTS to furnish diol **1.17**. 1,3-*Syn* diastereoselective reduction of the *β*-hydroxy ketone[12] followed by complete TES protection of the triol and Stille coupling with hexamethylditin led to the formation of dienylstannane **1.10** in 49% yield over 9 steps (Scheme 1.5).



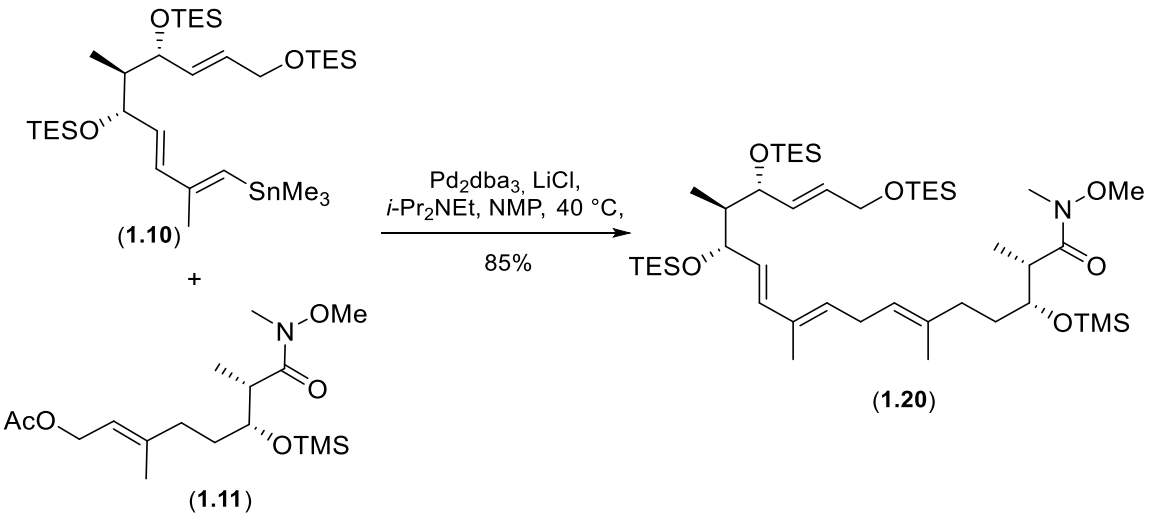
Scheme 1.5: Formation of coupling partner **1.10**

Similar to the previous coupling partner, synthesis of fragment **1.11** started by an Evans aldol reaction this time using aldehyde **1.18**.[13] Weinreb amidation and TMS protection of the resulting product generated amide **1.11** in 87% yield over 3 steps (Scheme 1.6).



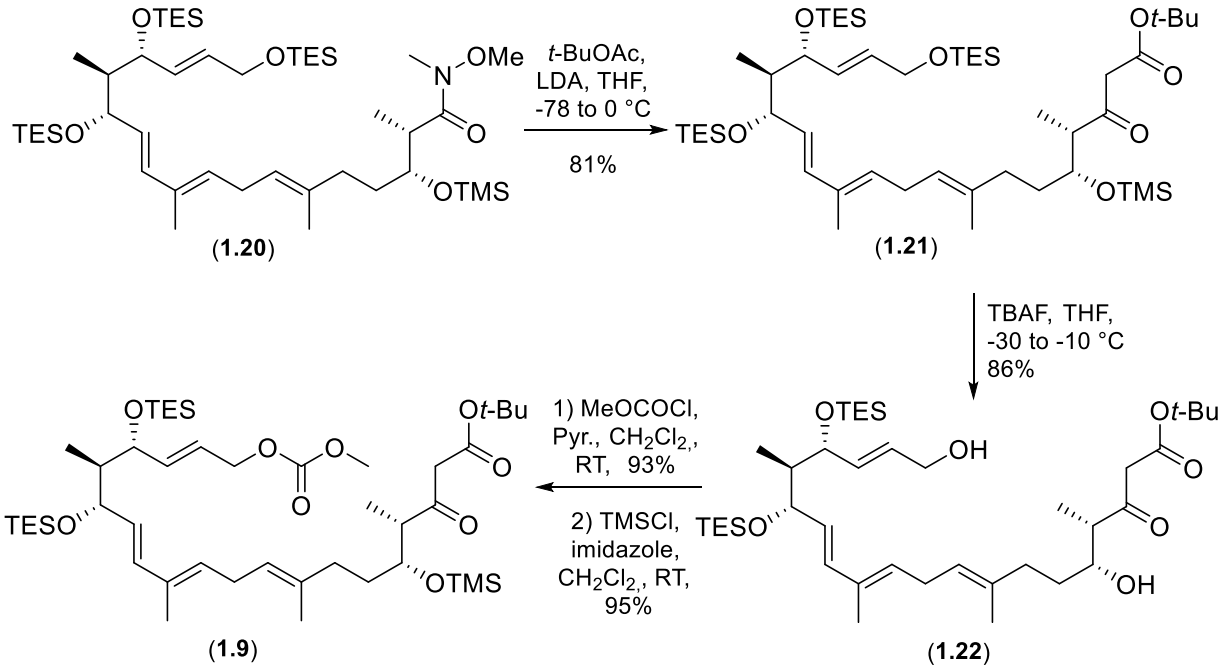
Scheme 1.6: Synthesis of coupling partner **1.8**

Both fragments were then successfully united using a Stille coupling with *tris*(dibenzylideneacetone)dipalladium(0) as a catalyst, lithium chloride and *i*-Pr_2NEt as a paramount additive to avoid protodestannylation of fragment **1.10** (Scheme 1.7).



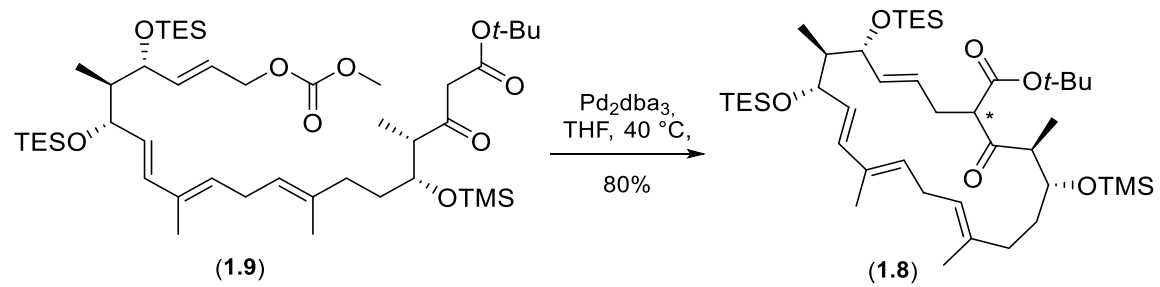
Scheme 1.7: Stille coupling between **1.10** and **1.11**

The next steps were the coupling between **1.20** and the lithium enolate of *tert*-butyl acetate to furnish *β*-ketoester **1.21**, followed by the selective deprotection of the primary TES and secondary TMS protected alcohols with TBAF to give diol **1.22** in 70% yield over 2 steps Primary alcohol **1.22** was transformed into the corresponding carbonate and the secondary alcohol was resilylated to produce Tsuji-Trost precursor **1.9** in excellent yield over 2 steps. (Scheme 1.8).



Scheme 1.8: Synthesis of precursor **1.9**

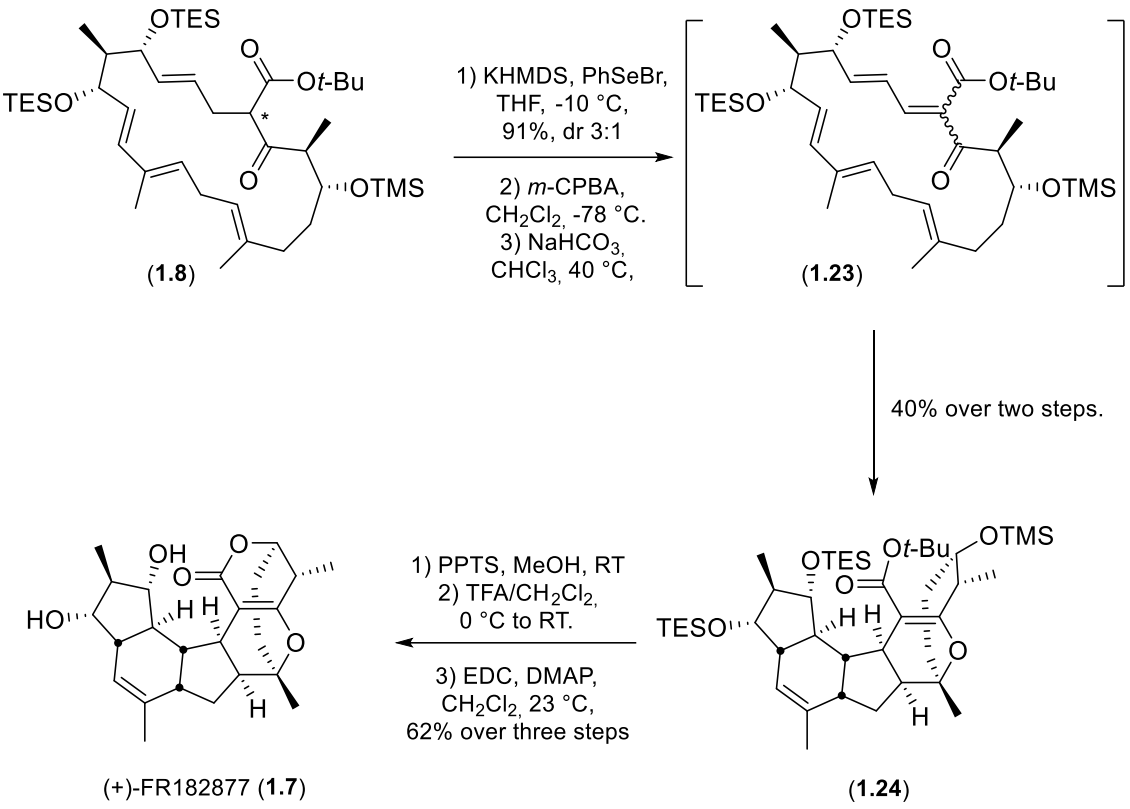
The nineteen-membered ring **1.8** was then closed by a Tsuji-Trost cyclisation using a catalytic amount of *tris*(dibenzylideneacetone)dipalladium(0).[14,15] Macrocycle **1.8** was obtained as a single diastereomer, although the configuration of the stereocenter in the *α* position of the ketoester was not determined (Scheme 1.9).



Scheme 1.9: Formation of macrocycle **1.8**

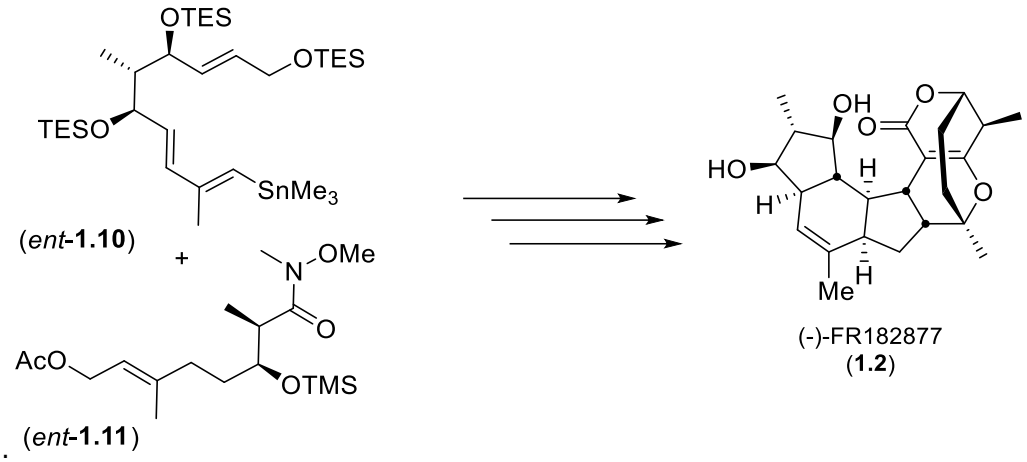
The next step in the synthesis was the installation of a conjugated diene which could react in a tandem IMDA/IMHDA. This diene was produced by *α*-selenylation of the ketoester followed by oxidative deselenylation with *m*-CPBA to afford an equimolar mixture of *E* and *Z* alkenes. Due to its reactivity, this diene was not isolated but used directly in the tandem IMDA/IMHDA reaction without purification to give pentacycle **1.24** as major product in 40% yield. Only the *E* isomer furnished the desired pentacycle **1.24**; the *Z* isomer of the precursor led to the formation of undesired products. The ABCDF ring system and 7 new stereocenters were formed during this step. The end game of the synthesis was the desilylation of the alcohols, TFA acidolysis of the *tert*-butyl ester and finally, lactonisation

using EDC as a coupling agent to give (+)-FR182877 **1.7** in 2% yield over 22 steps (Scheme 1.10).



Scheme 1.10: Final steps of the total synthesis

At the end of the synthesis, Sorensen *et al.* realised that the general structure and relative configuration were a match to the natural product although the absolute configuration was incorrect. This discovery was quickly corroborated by an erratum published by Terano *et al.*[4] Sorensen *et al.* decided to use the previously developed strategy with the enantiomers of the coupling partners, *ent*-**1.10** and *ent*-**1.11** (Scheme 1.11).

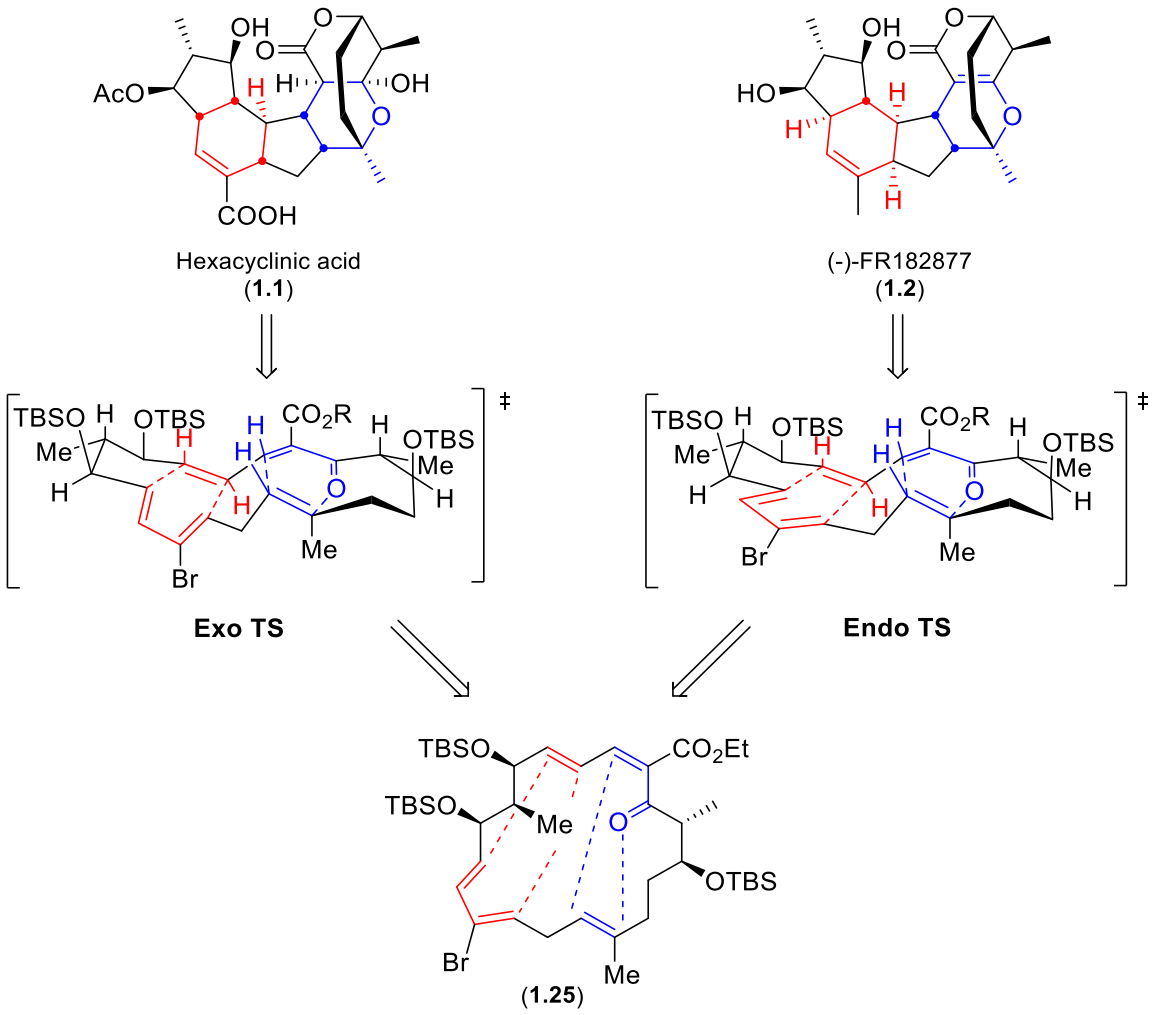


Scheme 1.11: Synthesis of (–)-FR182877

Sorensen *et al.* successfully developed an enantioselective synthesis of FR182877 and were able to produce grams of both enantiomers with comparable yield. However, one of the limitations of this strategy was the loss of half of their material during the double transannular Diels-Alder reaction due to the *Z* isomer of the precursor.

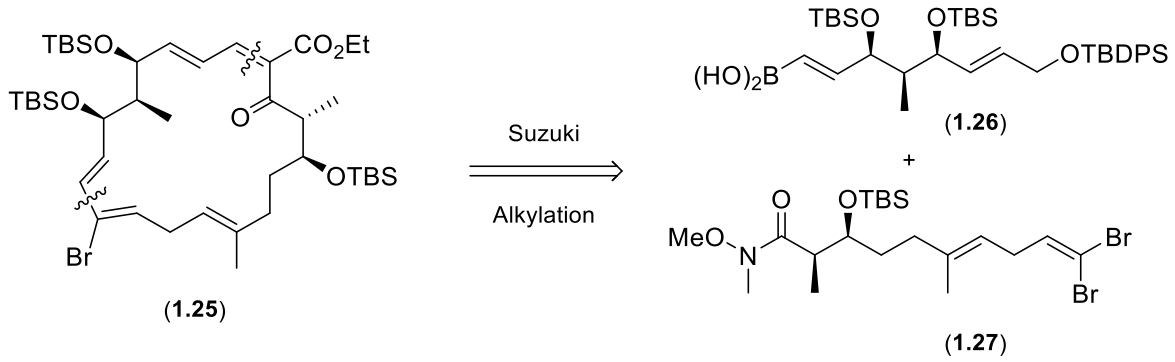
1.2.2 Total synthesis of (–)-FR182877 by Evans *et al.*

Concurrently with Sorensen's efforts, Evans *et al.* developed a very similar strategy: one intramolecular Diels-Alder (IMDA) to close the bicycle AB and an intramolecular hetero Diels-Alder (IMDHA) to give the tricycle CDF.[16] In their strategy, it was thought that it would be possible to complete the synthesis of both hexacyclinic acid **1.1** and (–)-FR182877 **1.2** via the same intermediate, macrocycle **1.25**. The *endo/exo* selectivity during the first cycloaddition would be crucial to achieve the synthesis of **1.1** or **1.2**; *endo* would furnish (−)-FR182877 **1.2**, *exo* would yield hexacyclinic acid **1.1**. Evans *et al.* also planned to introduce either the carboxylic acid or the methyl group from the bromine, by palladium couplings (Scheme 1.12).



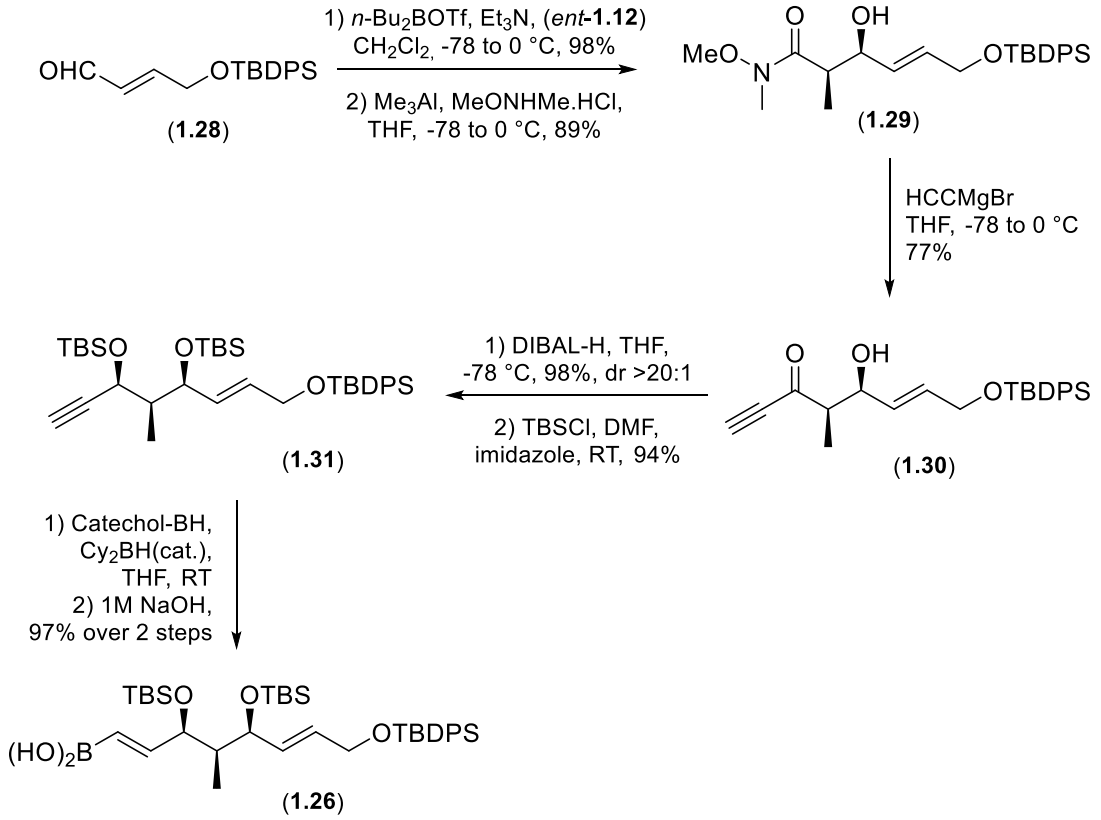
Scheme 1.12: Evans retrosynthesis and proposed Diels-Alder transition states

This macrocycle was to be synthesised using a Suzuki coupling between boronic acid **1.26** and the dibromoalkene product **1.27** and an alkylation reaction between the *β*-ketoester derived from the Weinreb amide and the allylic iodide derived from the TBDPS ether (Scheme 1.13).



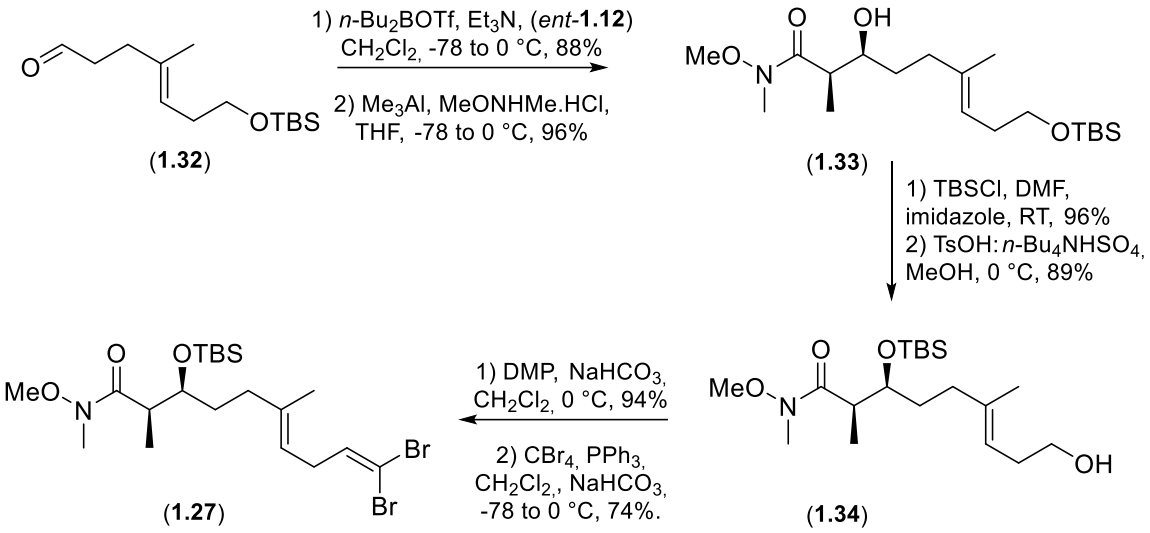
Scheme 1.13: Retrosynthesis of macrocycle **1.25**

Synthesis of fragment **1.26** started by an aldol reaction between Evans auxiliary *ent*-**1.12** and aldehyde **1.28** to produce *syn* aldol adduct **1.29**.[17] Transformation of **1.29** into the Weinreb amide followed by Grignard addition led to the formation of ynone **1.30**. Product **1.30** was submitted to a diastereoselective *syn* reduction[18] to give a diol that was fully protected as TBS ethers furnishing compound **1.31**. The next steps were alkyne hydroboration with catecholborane and saponification to afford boronic acid **1.26** in 62% yield over 6 steps (Scheme 1.14).



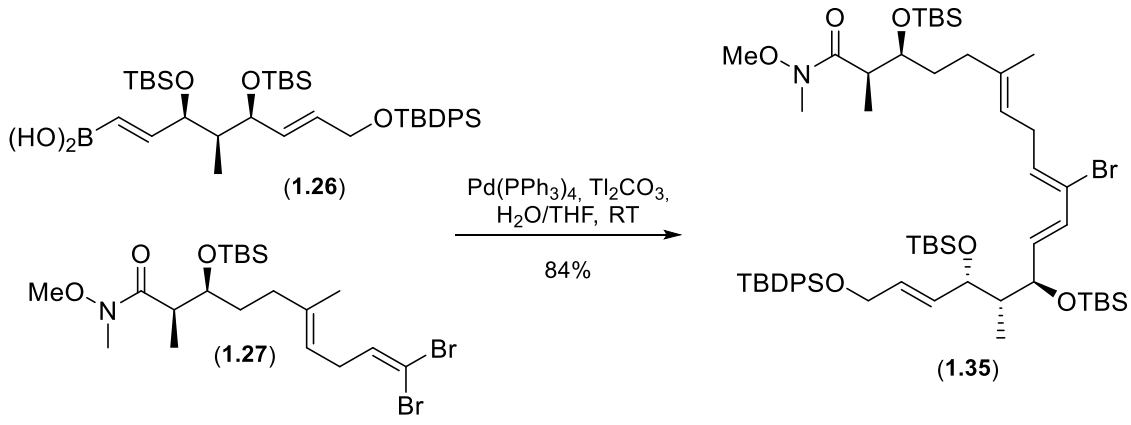
Scheme 1.14: Synthesis of fragment **1.26**

Dibromide fragment **1.27** was synthesised starting with a diastereoselective aldol reaction with aldehyde **1.32** (55% yield over 4 steps from 3-buten-1-ol) followed by conversion into Weinreb amide **1.33** in near quantitative yield. TBS protection of the secondary alcohol and selective desilylation of primary alcohol furnished product **1.34** in very good yield. The primary alcohol was oxidised and converted into dibromide fragment **1.27** using the Ramirez olefination conditions (Scheme 1.15).



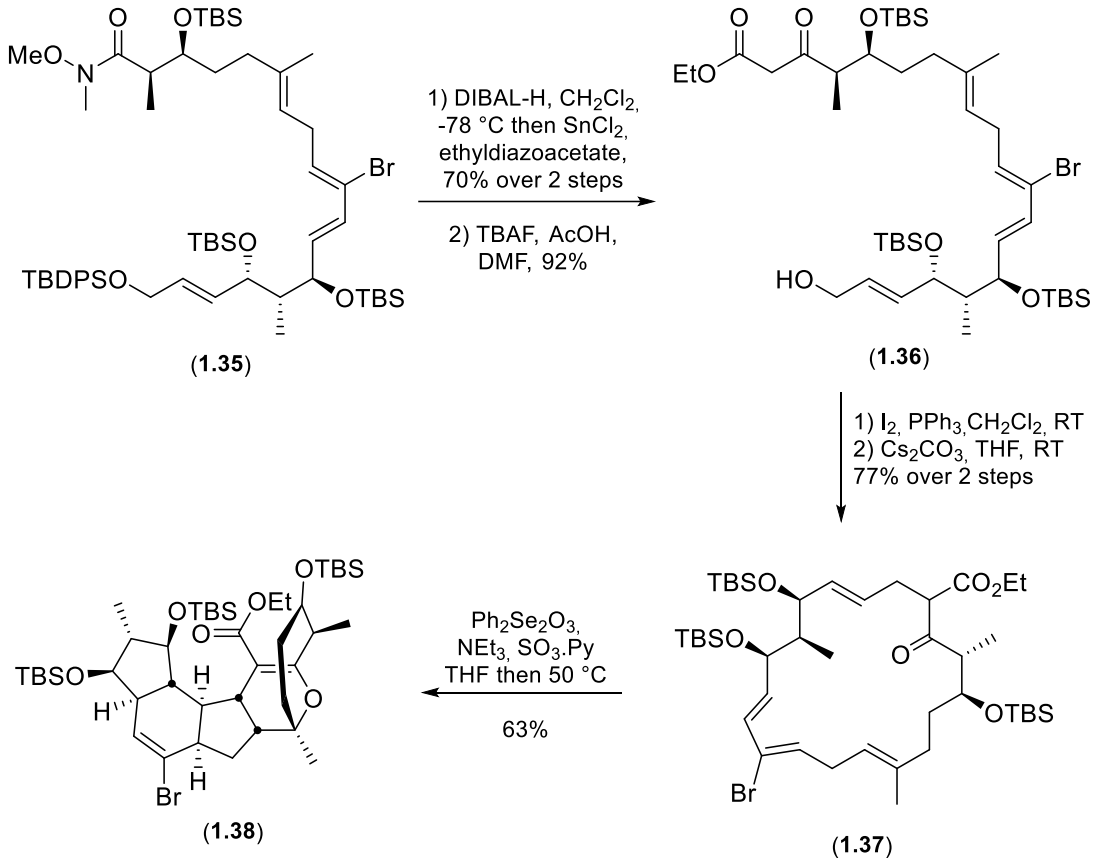
Scheme 1.15: Synthesis of coupling partner **1.27**

With both fragments in hand, Evans *et al.* used a Suzuki coupling to connect them. A wide range of bases and countercations were screened but most of them led to a mixture of product **1.35**, doubly coupled side product and decomposition. Only an unusual base, thallium carbonate, afforded a reasonable rate of reaction with neither formation of side products nor decomposition.[19] Bromodiene **1.35** was formed in 84% yield (Scheme 1.16).



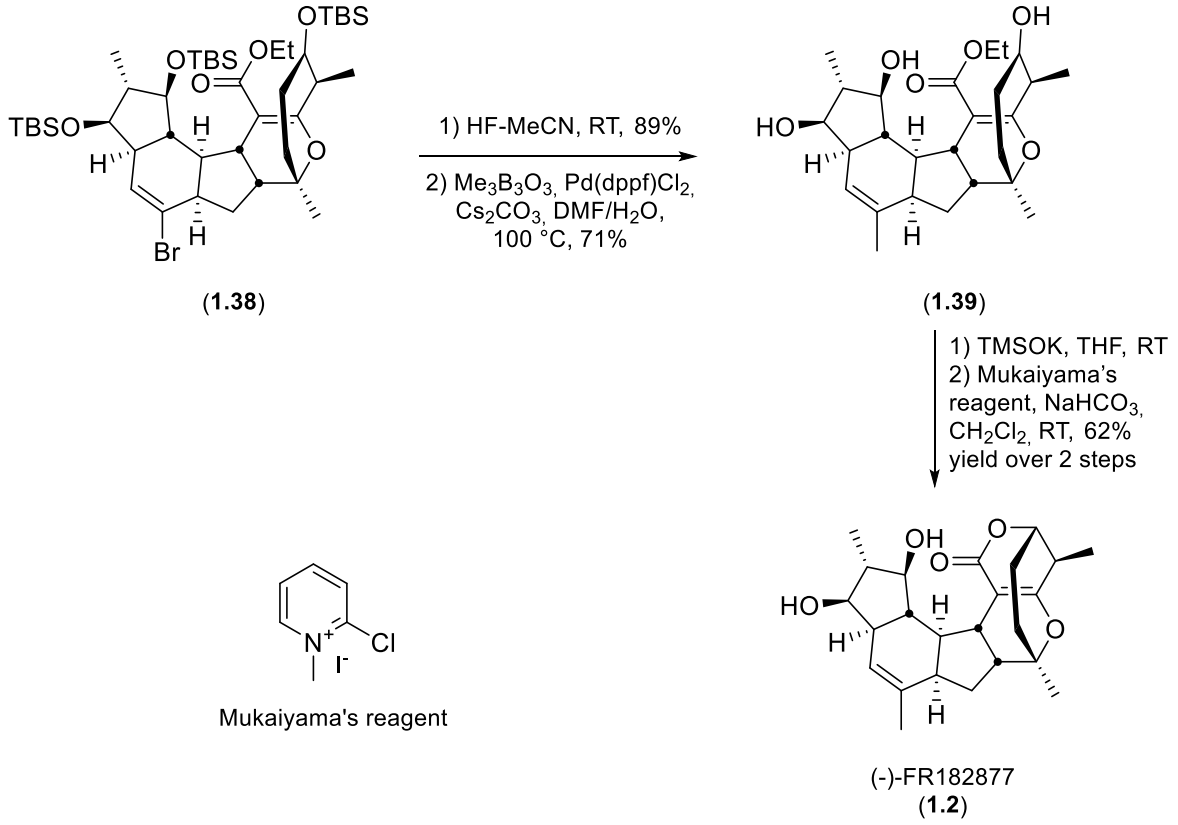
Scheme 1.16: Suzuki coupling

The Weinreb amide was reduced to the corresponding aldehyde, which was subjected to a Roskamp homologation in the presence of ethyldiazoacetate and tin(II) chloride, followed by a selective desilylaton to afford *β*-ketoester **1.36**.[20] The primary alcohol was substituted by an iodine and the resulting allylic iodide was submitted to macrocyclisation to furnish nineteen-membered ring **1.37**. Formation of the alkene in the presence of $Ph_2Se_2O_3$ followed by heating led to the cycloaddition cascade to form product **1.38** as a single diastereomer in good yield (Scheme 1.17).



Scheme 1.17: Formation of pentacycle **1.38**

The final steps of the total synthesis were complete desilylation and Suzuki methylation to give product **1.39**. Saponification and lactonisation with Mukaiyama's reagent afforded natural product (–)-FR182877 **1.2** in 6% yield over 17 steps (Scheme 1.18).

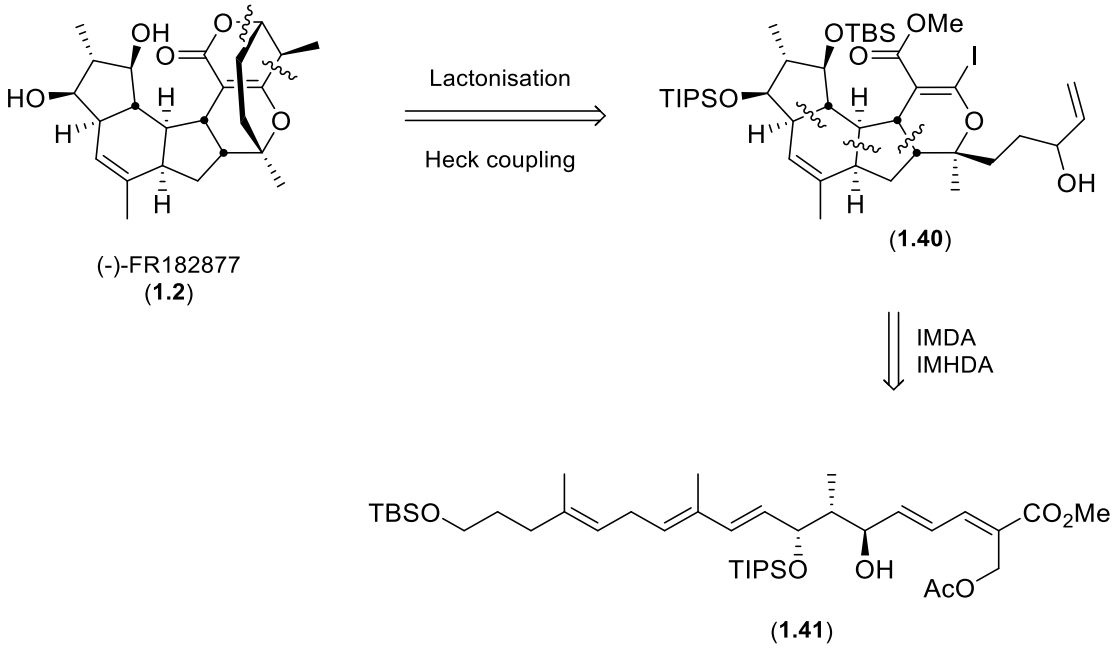


Scheme 1.18: End game of the total synthesis by Evans *et al.*

Evans *et al.* showed that the *endo* transition state was preferred with (–)-FR182877 **1.2** being formed exclusively. Several attempts were made to obtain the *exo* transition state, however no success has been reported to date.

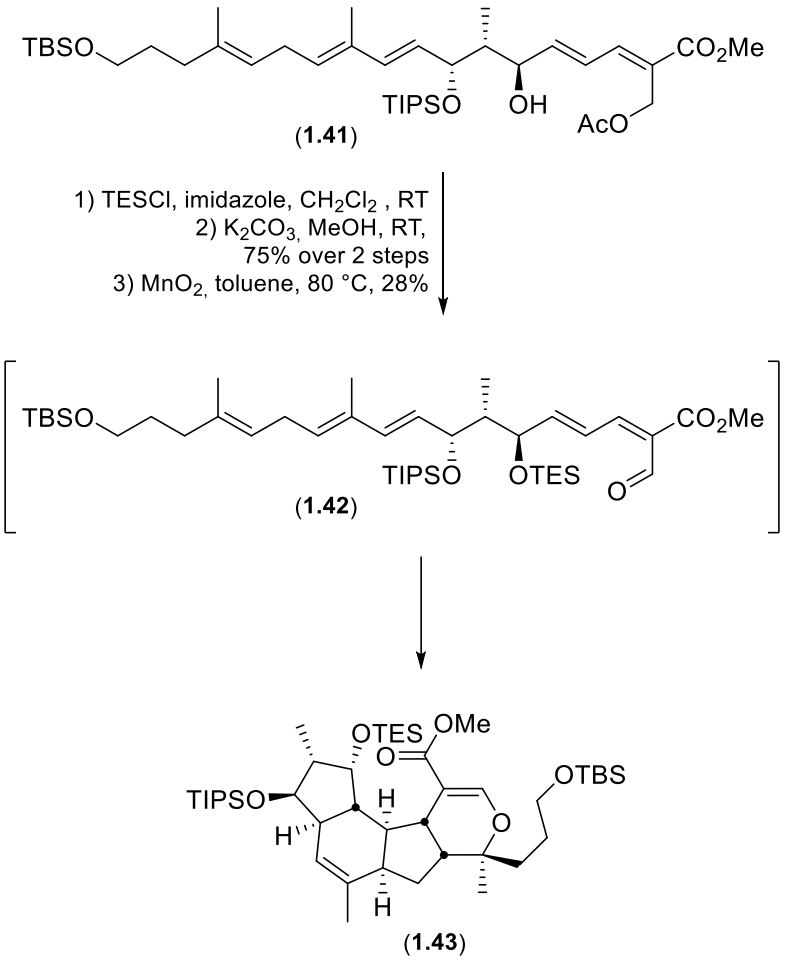
1.2.3 Total synthesis of (–)-FR182877 by Nakada *et al.*

Another synthesis was published more recently by Nakada *et al.*[21] The synthetic strategy was greatly inspired by Sorensen's and Evans' previous work.[5,16] AB and CD ring systems were respectively closed by IMDA and IMHDA from acyclic product **1.41**. The major difference from previous work was the closure of the F ring by a Heck coupling (Scheme 1.19).



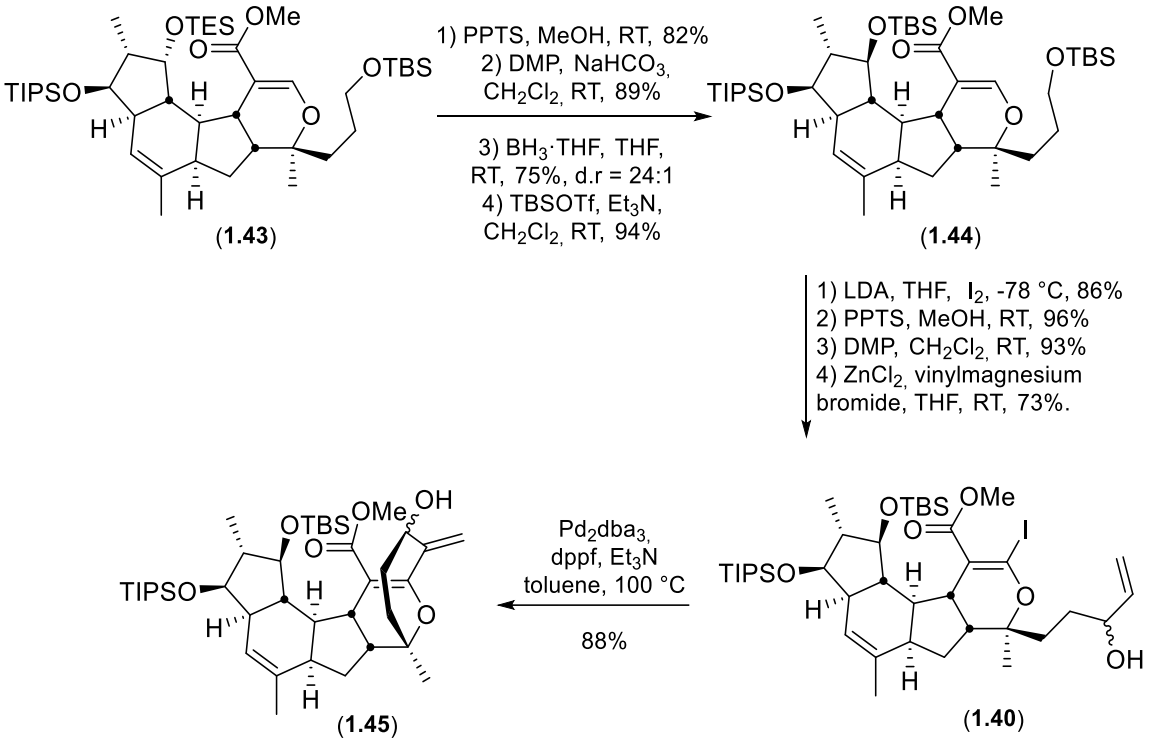
Scheme 1.19: Retrosynthesis of (–)-FR182877 **1.2** by Nakada *et al.*

Product **1.41** was synthesised in 8 steps over the longest linear sequence.[22] From **1.41**, the secondary alcohol was silylated with chlorotriethylsilane and the acetate was saponified to produce the primary alcohol in 75% over 2 steps. The allylic alcohol was then oxidised in presence of manganese(II) oxide and the resulting aldehyde spontaneously reacted in a tandem IMDA/IMHDA to generate ABCD tetracycle **1.43**. It is important to notice the inverted stereochemistry of one of the hydroxyl groups; the incorrect configuration was proved to be of paramount importance in order to achieve the right diastereoselectivity at the ring junctions (Scheme 1.20).



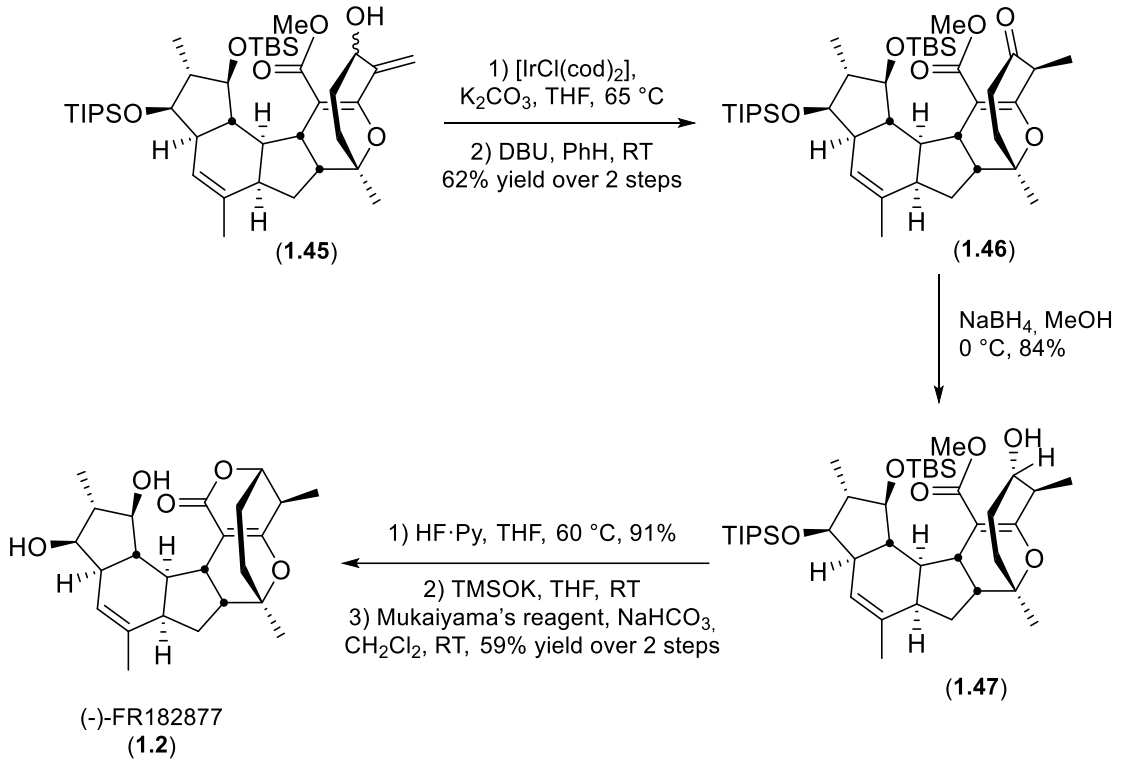
Scheme 1.20: Synthesis of tetracycle **1.43**

The next step of the synthesis was selective desilylation of the TES-protected alcohol followed by oxidation to give the corresponding ketone. The ketone was reduced to give the alcohol with the desired stereochemistry (dr = 24:1), which was protected as a TBS ether to furnish compound **1.44**. Iodination of the double bond, cleavage of the TBS ether followed by oxidation of the resulting alcohol led to the formation of the corresponding aldehyde. Addition of vinylzinc bromide produced allylic alcohol **1.40** in a 1:1 mixture of diastereomers. The Mizoroki-Heck coupling afforded the *7-exo* trig product **1.45** and closed the F ring in excellent yield (Scheme 1.21).



Scheme 1.21: Formation of pentacycle **1.45**

The allylic alcohol moiety was isomerised to the corresponding *α*-methyl ketone using $[IrCl(cod)]_2$ to yield product **1.46** as a mixture of diastereomers. The undesired stereoisomer was epimerised using DBU. The newly formed ketone **1.46** was reduced to the corresponding alcohol **1.47** as a single isomer. Final steps of the synthesis included the complete desilylation of compound **1.47**, saponification of the methyl ester and lactonisation using Mukaiyama's reagent to furnish (–)-FR182877 **1.2** in 59% yield over 2 steps (Scheme 1.22).



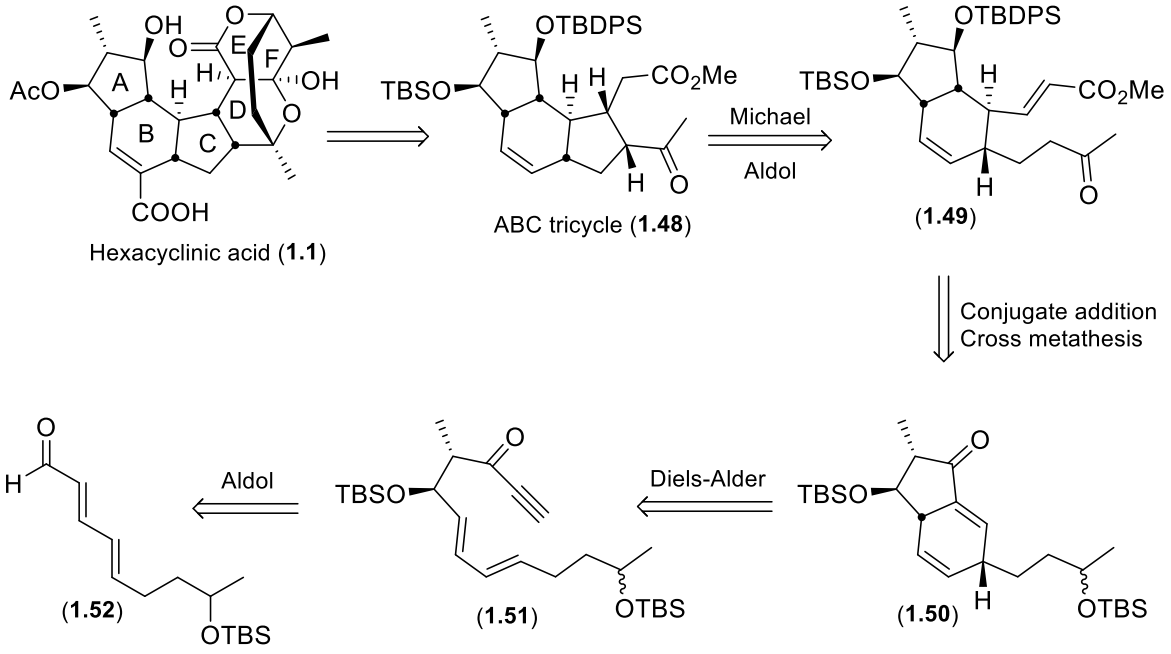
Scheme 1.22: Completion of the total synthesis by Nakada *et al.*

Nakada's synthesis, despite being successful, did not bring a lot of novelty from Sorensen's and Evans' works. It was also a longer synthesis with a lower yield for the key cyclisation step.

1.3 Syntheses of fragments of hexacyclinic acid

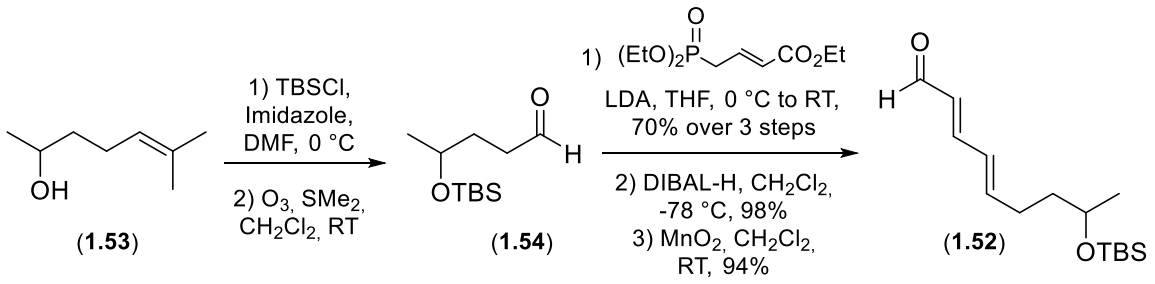
1.3.1 ABC tricycle by Kalesse *et al.*

The first synthesis of the ABC tricycle was published by Kalesse *et al.* in 2004.[2] The proposed retrosynthesis started from the ABC ring system **1.48** installed by a tandem intramolecular Michael-aldol reaction. Compound **1.49** was to be obtained by conjugate addition from **1.50** and cross-metathesis with methyl acrylate. Product **1.50** could be produced by an intramolecular Diels-Alder reaction starting from product **1.51**, which would be synthesised by an asymmetric aldol reaction from aldehyde **1.52** (Scheme 1.23).



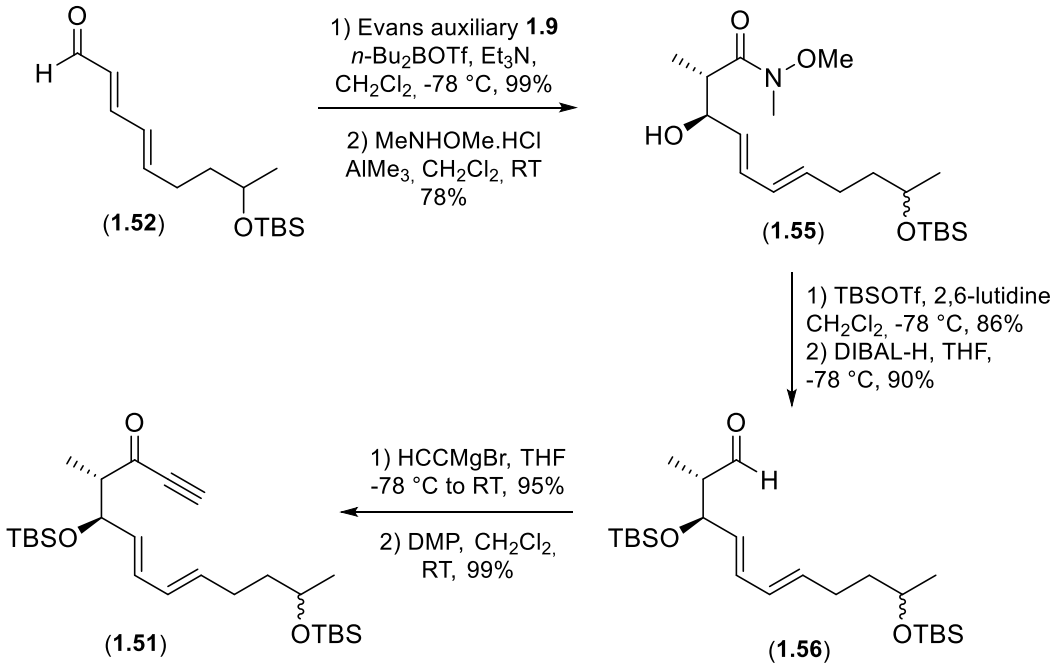
Scheme 1.23: Synthetic strategy for ABC tricycle **1.48**

The synthesis began with racemic alcohol **1.53** that was protected as a TBS ether, before undergoing cleavage of the trisubstituted alkene by ozonolysis to afford aldehyde **1.54**. Olefination of **1.54** using HWE conditions was followed by a DIBAL-H reduction of the ester and oxidation of the resulting allylic alcohol to give the conjugated aldehyde **1.52** in 64% yield over 5 steps (Scheme 1.24).



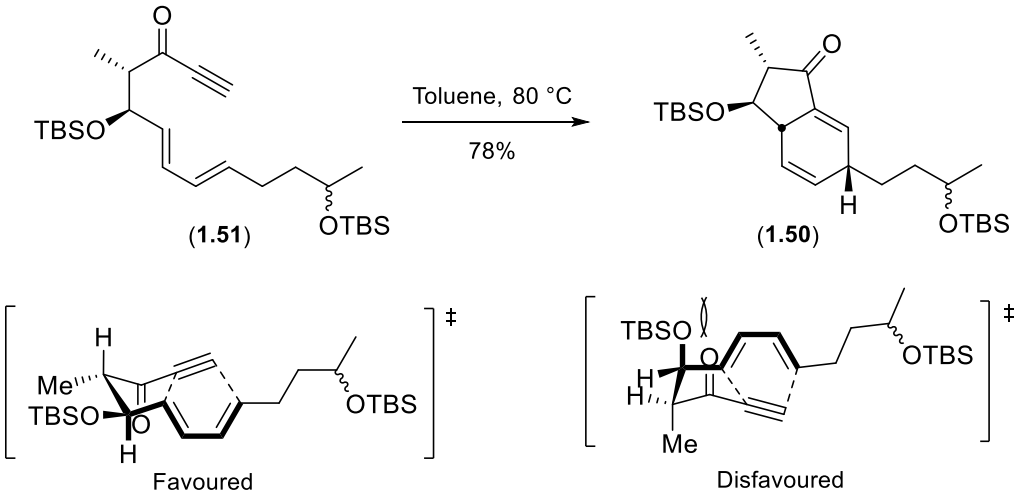
Scheme 1.24: Synthesis of aldehyde **1.52**

The Evans reaction gave the required aldol in excellent yield and as a single isomer, which was converted into corresponding Weinreb amide **1.55**. Silylation of the secondary alcohol and transformation of Weinreb amide generated aldehyde **1.56**. Addition of ethynylmagnesium bromide furnished a propargylic alcohol, which was oxidised using Dess-Martin periodinane to produce Diels-Alder precursor **1.51** (Scheme 1.25).



Scheme 1.25: Formation of Diels-Alder precursor **1.51**

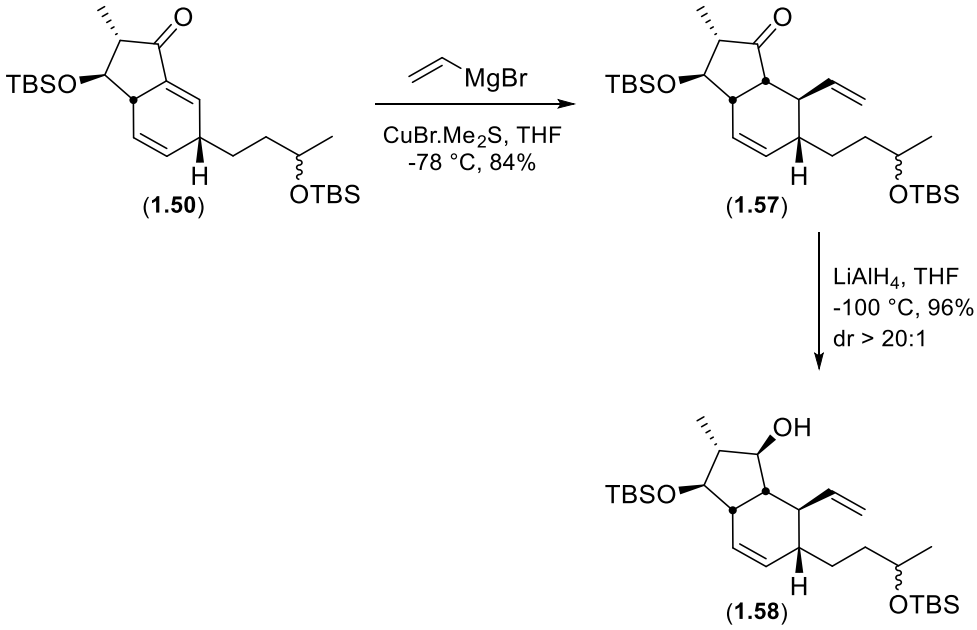
Diels-Alder reaction led to the elaboration of bicycle **1.50**, with the correct configuration at the newly formed stereocenters. The cyclisation supposedly proceeds via a chair-like transition state, with the OTBS and methyl groups remaining in a *pseudo* equatorial position (Scheme 1.26).



Scheme 1.26: Diels-Alder reaction and favoured transition state

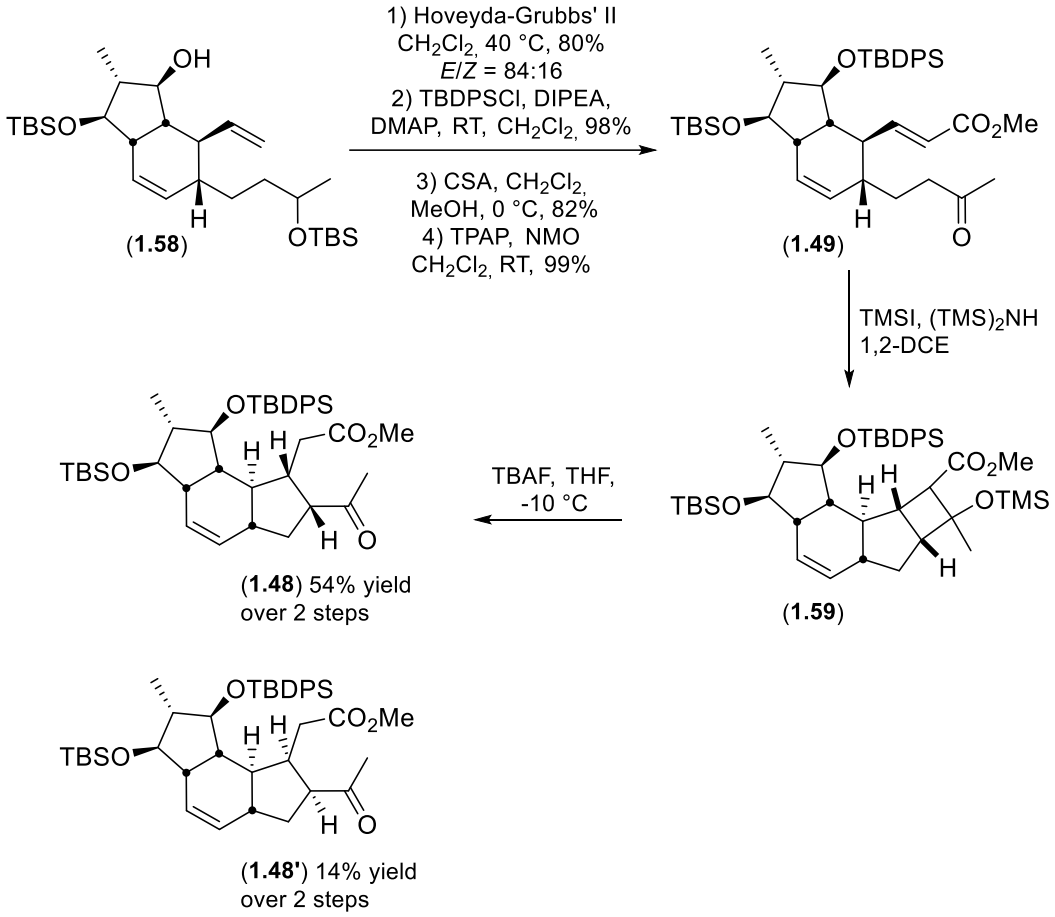
Formation of the vinyl cuprate followed by conjugate addition to enone **1.50** from the convex face gave product **1.57** without formation of the undesired isomer. In order to obtain the desired stereochemistry during the ketone reduction, the hydride source had to come from the most hindered side, (*i.e* the concave face). First attempts using different reducing agents

and, especially bulky reagents such as L-selectride, led to the formation of the undesired isomer, which could not be inverted using Mitsunobu reaction. Pleasingly, lithium aluminium hydride at very low temperature furnished the desired isomer **1.58** with a very good selectivity (Scheme 1.27).



Scheme 1.27: Diastereoselective cuprate addition and reduction

The following steps were cross methathesis between **1.58** and methyl acrylate with Hoveyda-Grubbs' II catalyst to give a mixture of *E* and *Z* conjugated esters. The secondary alcohol was protected as a TBDPS ether, TBS ether was selectively cleaved and the resulting alcohol oxidised using Ley-Griffith conditions to produce compound **1.49**. The next step was a tandem intramolecular Michael-aldol reaction, with formation of the TMS enol ether under thermodynamic control to give the cyclobutane product **1.59**. Finally, cyclobutane **1.59** was opened to establish the ABC ring system **1.48** (and the undesired diastereomer **1.48'**) in 11% overall yield over 20 steps (Scheme 1.28).

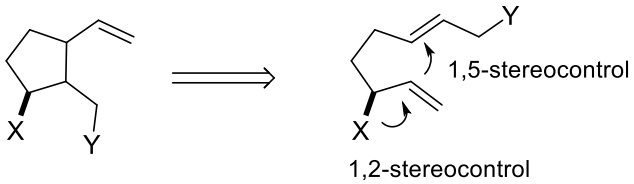


Scheme 1.28: Synthesis of ABC tricycle **1.48**

The Kalesse *et al.* synthesis present an interesting approach of constructing the ABC tricycle with the correct absolute configuration, however there is no mention yet of how to install the allylic carboxylic acid presents in the natural product of hexacyclinic acid.

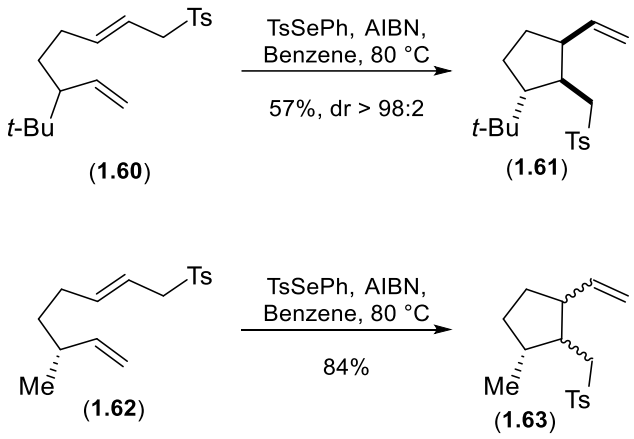
1.3.2 ABC tricycle by Landais *et al.*

In 2004 and 2005, Landais *et al.* published their work regarding the 5-*exo*-trig cyclisations of 1,6-heptadienes.[23,24] Their strategy was based on the radical cascade involving the addition of tosyl radical, 5-*exo*-trig cyclisation and *β*-fragmentation to furnish polysubstituted five-membered rings. They also explored the induction of 1,2 and 1,5-stereocontrol using bulky allylic substituents (Scheme 1.29).



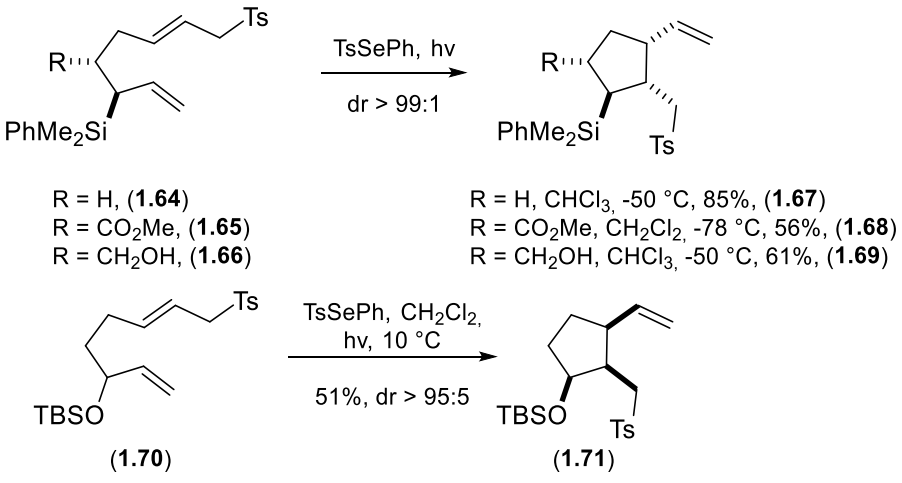
Scheme 1.29: 5-*exo*-trig cyclisation of chiral 1,6-heptadienes

In order to test their theory, several cyclisation precursors were synthesised. Allylic *tert*-butyl diene **1.60** led to the formation of the corresponding cyclopentane **1.61** as a single diastereomer with the *trans*-*cis* stereochemistry. When a smaller methyl group was used instead, a mixture of 4 diastereomers was obtained (Scheme 1.30).



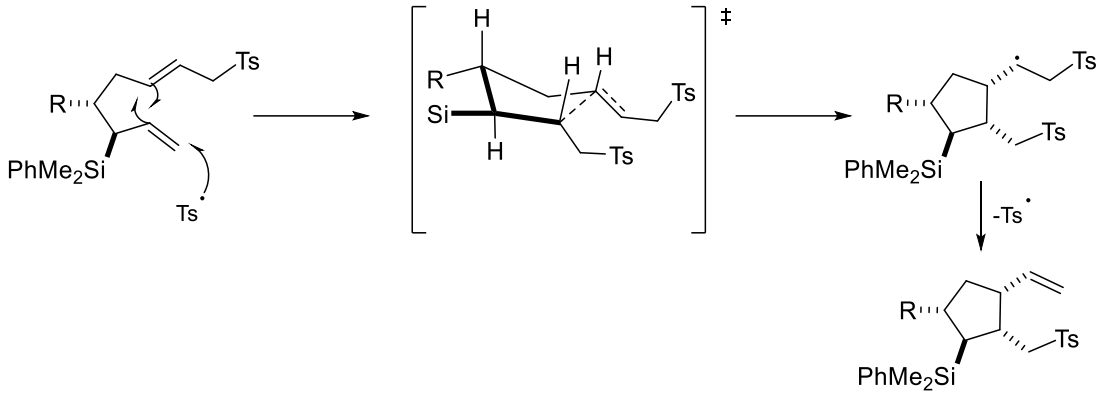
Scheme 1.30: Diastereoselectivity depending on allylic substitution

The reaction was shown to also proceed in the presence of a silyl group and protected alcohols with excellent diastereoselectivity. In the case of a protected allylic alcohol, the selectivity was inverted to give the *cis*-*cis* product **1.68** (Scheme 1.31).



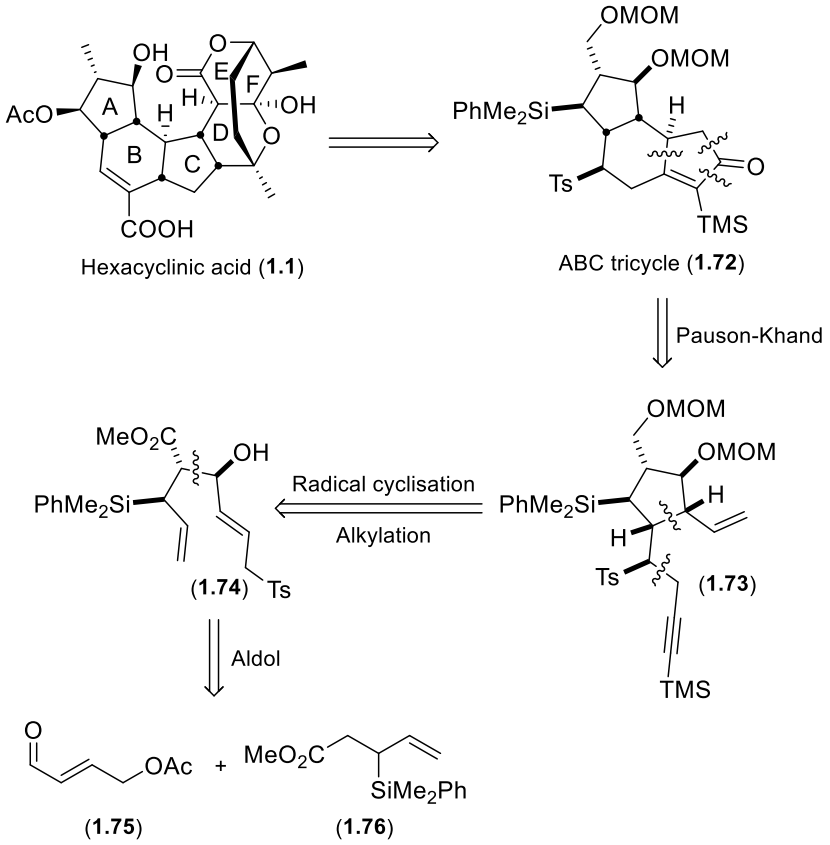
Scheme 1.31: Stereochemistry depending on allylic substitution

The stereochemistry was rationalised using the Beckwith-Houk model; the major isomer arising from a chair-like transition state with the bulky substituents in *pseudo* equatorial position (Scheme 1.32).



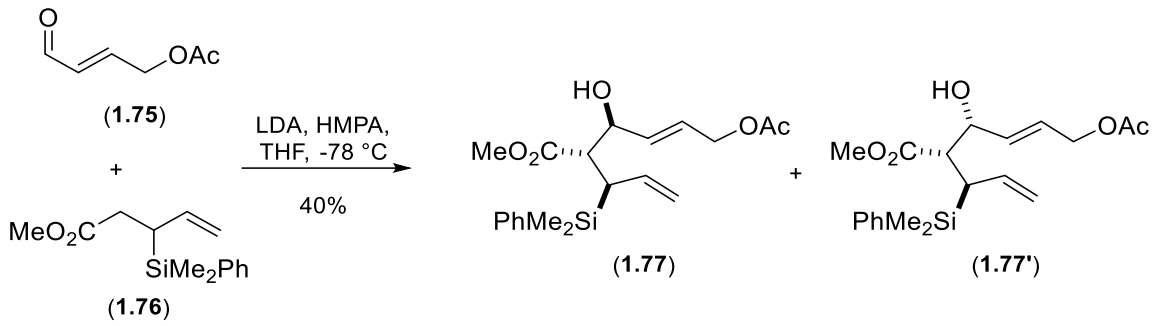
Scheme 1.32: Transition station leading to the formation of the major product

This novel methodology was extended to the racemic synthesis of an ABC ring system of hexacyclinic acid **1.72** where the BC bicycle could be formed by a Pauson-Khand reaction from cyclopentane **1.73**. Cyclopentane **1.73** could be closed from hepta-1,6-diene **1.74** using the new method developed, and diene **1.74** could be synthesised by an aldol reaction between aldehyde **1.75** and ester **1.76** (Scheme 1.33).



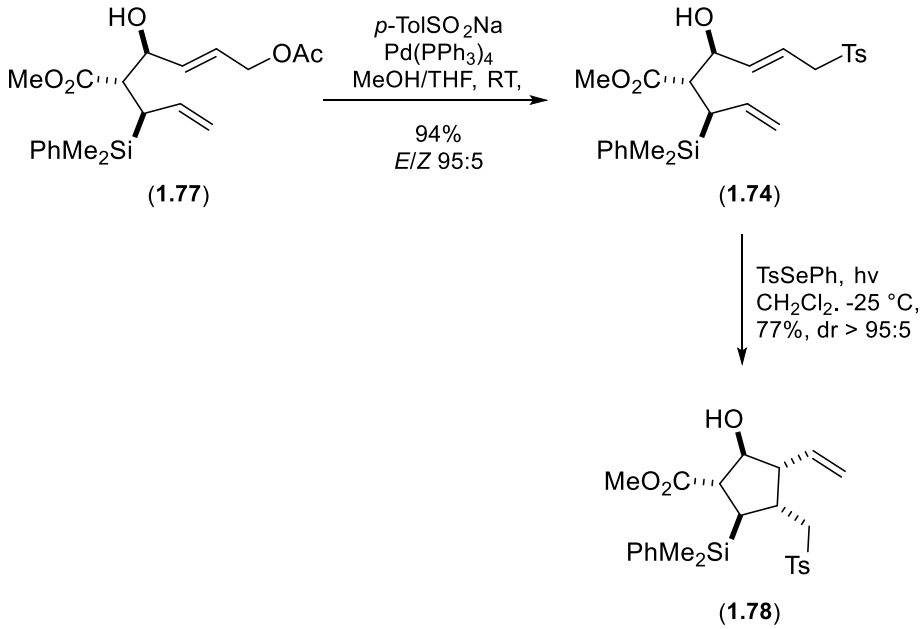
Scheme 1.33: Retrosynthesis of the ABC tricycle by Landais *et al.*

Aldehyde **1.75** was prepared in 3 steps from butyn-1,4-diol and reacted with ester **1.76** in an aldol reaction to furnish products **1.77/1.77'** in a 65:35 mixture of 2 diastereomers (Scheme 1.34).



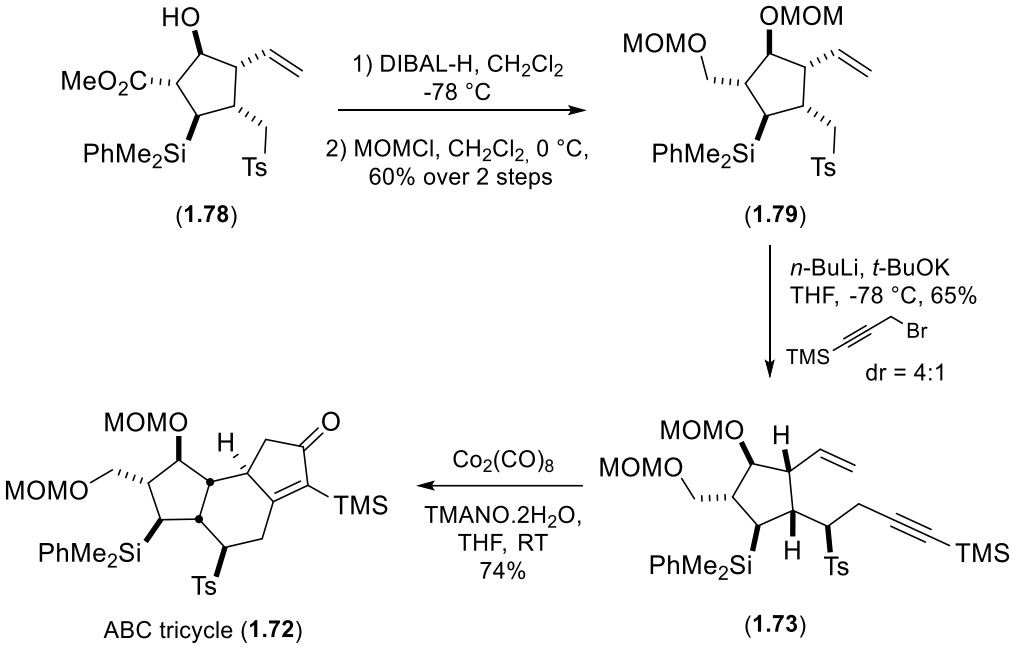
Scheme 1.34: Aldol reaction to furnish **1.77**/**1.77'**

Acetate **1.77** was converted into the corresponding sulfone **1.74** using a palladium-catalysed sulfonylation.[25] Sulfone **1.74** was then closed by a radical cyclisation to give the cyclopentane **1.78** with complete stereocontrol (Scheme 1.35).



Scheme 1.35: Formation of cyclopentane **1.78**

Complete reduction of the ester with DIBAL-H gave the corresponding primary alcohol; MOM protection of the diol furnished product **1.79** in 60% over 2 steps. Deprotonation of compound **1.79** using Schlosser's base gave the corresponding sulfonyl carbanion which was alkylated to produce enyne **1.73**. The final step was a Pauson-Khand reaction promoted by trimethylamine *N*-oxide (TMANO) to give final product **1.72** (Scheme 1.36).

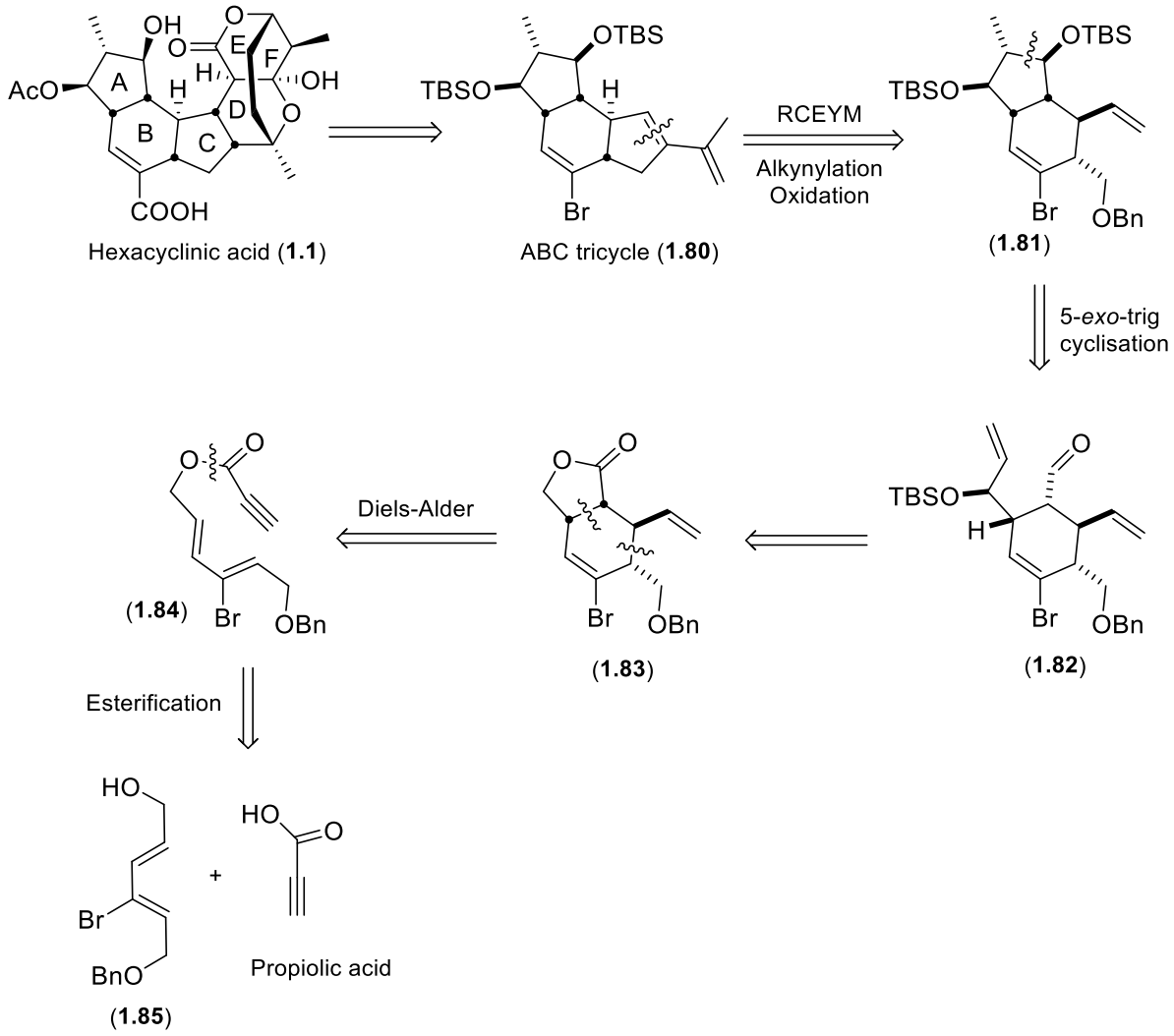


Scheme 1.36: Final steps of the synthesis

The synthesis by Landais *et al.* proved to be an efficient way to construct the ABC tricycle **1.72** in 7 steps from *β*-silylester **1.76**, and to install the correct relative stereochemistry at the AB ring junction. However, the synthesis is racemic and several functional groups are missing, such as the double bond in the B ring and the carboxylic acid. The correct stereochemistry of the BC ring junction also needs to be installed.

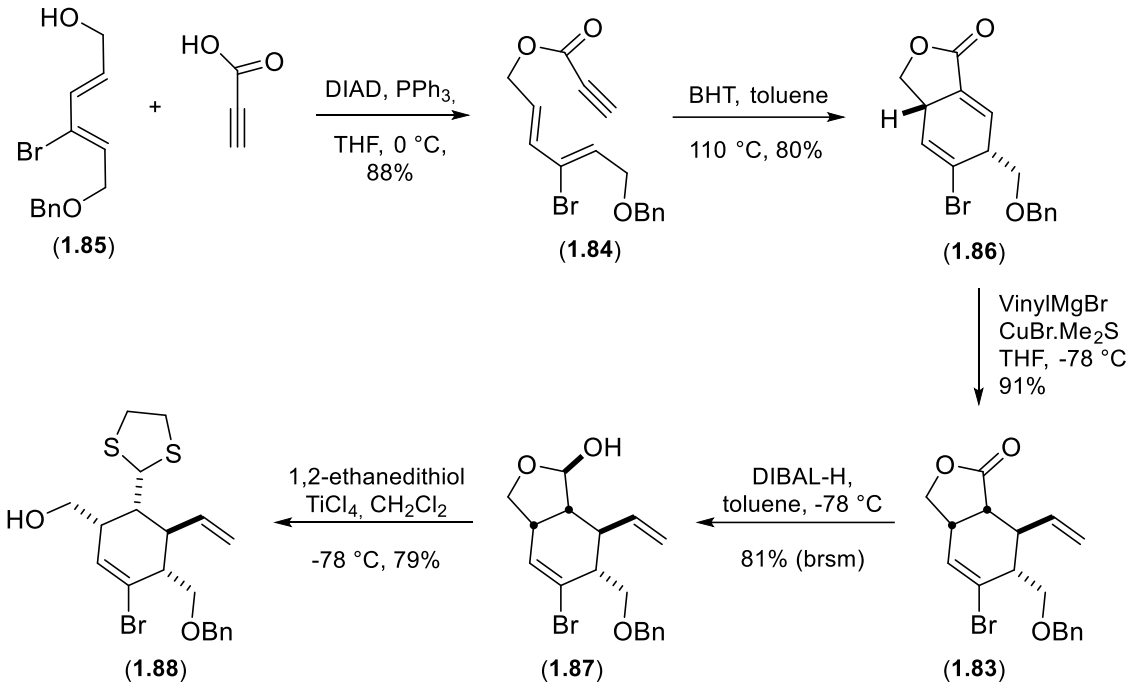
1.3.3 ABC tricycle by Clarke *et al.*

The general strategy developed for the racemic synthesis of the ABC ring system by Clarke *et al*.[26,27] was inspired by the previous work of Kalesse *et al.* The C ring was envisaged to be closed by a ring-closing ene-yne methathesis (RCEYM) from an intermediate which could be produced by oxidation and alkynylation from bicycle **1.81**. A radical cyclisation promoted by samarium(II) iodide would close the A ring from cyclohexene **1.82**. The cyclohexene ring **1.82** could be afforded from lactone **1.83**. The bicycle system **1.83** would be formed by an intramolecular Diels-Alder reaction from diene **1.84**, which could be easily prepared by an esterification reaction between alcohol **1.85** and propiolic acid (Scheme 1.37).



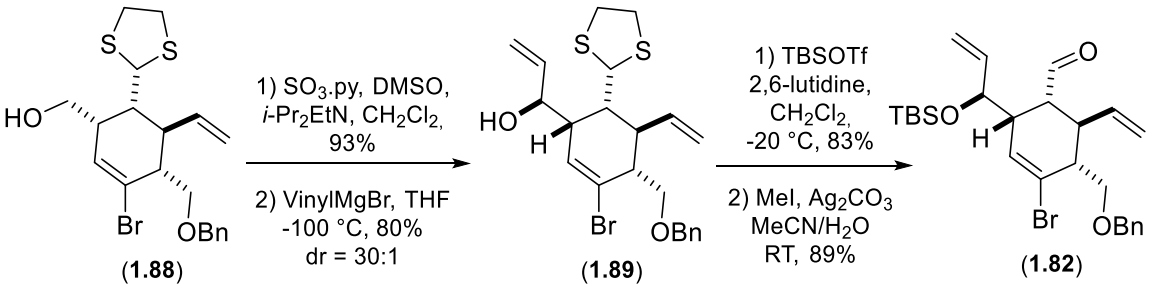
Scheme 1.37: Retrosynthesis proposed by Clarke *et al.*

The synthesis started by a Mitsunobu reaction between propiolic acid and readily available alcohol **1.85**[28] to give ester **1.84**. Ester **1.84** underwent an intramolecular Diels-Alder reaction to furnish bicycle **1.86** in 80% yield and as a single diastereomer. The next step was a diastereoselective addition of vinyl cuprate to furnish product **1.83** with two new stereocenters installed. The diastereoselectivity is explained to be the result of the cuprate addition and reprotonation of the resulting enolate from the less hindedred face. Lactone **1.83** was reduced to the corresponding lactol **1.87** that was transformed into dithiolane **1.88** (Scheme 1.38).



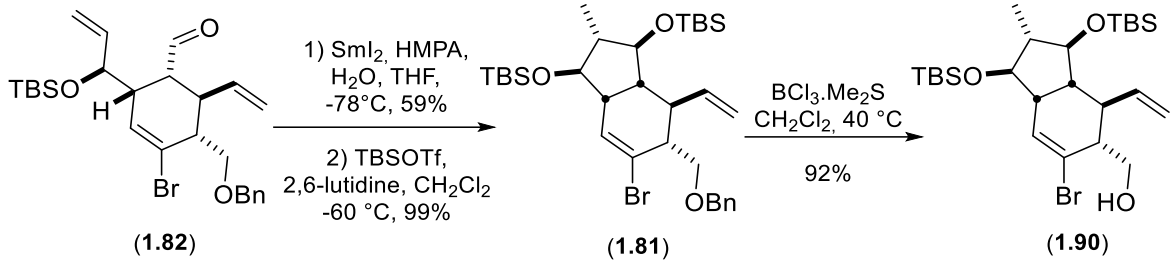
Scheme 1.38: First steps of the synthesis

Alcohol **1.88** was oxidised and the corresponding aldehyde was transformed into allylic alcohol **1.89** by addition of vinyl magnesium bromide in a very good yield and excellent diastereoselectivity. Allylic alcohol **1.89** was protected as a TBS ether and the dithiolane was converted into the unstable aldehyde **1.82** by addition of methyl iodide and silver carbonate (Scheme 1.39).



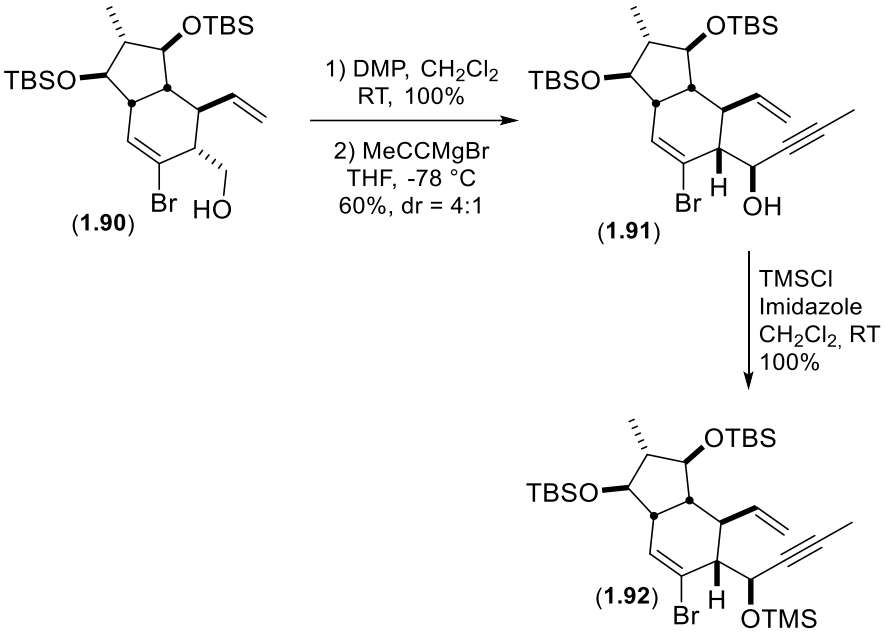
Scheme 1.39: Synthesis of radical cyclisation precursor **1.82**

The reductive cyclisation was promoted by samarium(II) iodide in the presence of HMPA and water to give the desired five-membered ring, with only traces of both the undesired diastereomer and of the dimer product. The newly formed alcohol was silylated with TBSOTf to give product **1.81**. Debenzylation occurred in the presence of boron trichloride to furnish primary alcohol **1.90** (Scheme 1.40).



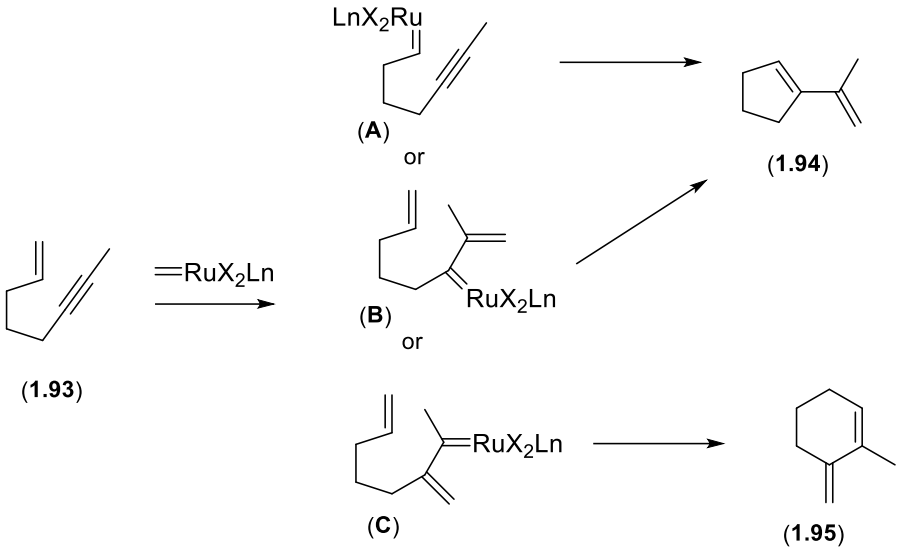
Scheme 1.40: 5-*exo*- trig radical cyclisation and benzyl deprotection

In the next step, the alcohol was oxidised using Dess-Martin periodinane to generate an unstable aldehyde which was immediately alkynylated by propynylmagnesium bromide to furnish propargylic alcohol **1.91** as a 4:1 mixture of diastereomers. The alcohol was finally protected as a TMS ether to give RCEYM precursor **1.92** in quantitative yield (Scheme 1.41).



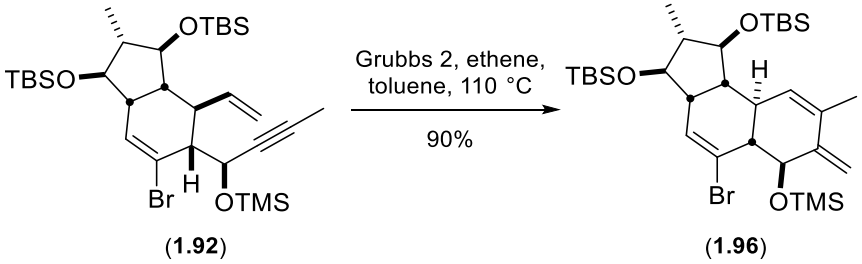
Scheme 1.41: Formation of RCEYM precursor

For the RCEYM, different pathways are possible depending on which unsaturated bond the catalyst attacks first. If the catalyst reacts first with the alkene, a mechanism known as ene-then-yne will occur, with the resulting product being cyclopentene **1.94**. In the case of an yne-then-ene mechanism, two results are possible depending on the regioselectivity during the formation of the ruthenium carbene: the regioisomer **B** with the metallocarbene further away from the methyl would furnish cyclopentene **1.94,** while the one close to the methyl group **C** would give the corresponding cyclohexene **1.95** (Scheme 1.42).



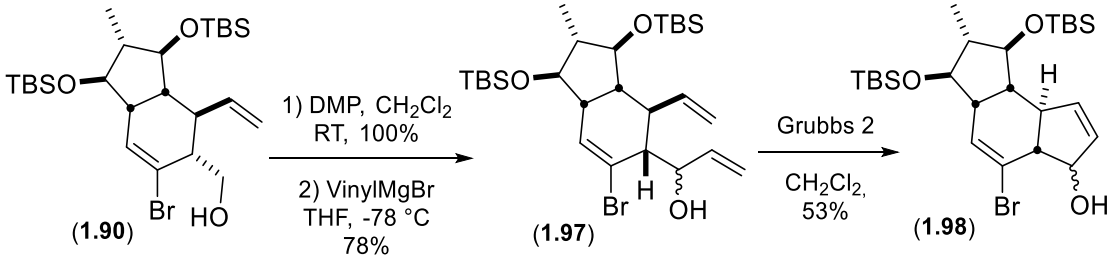
Scheme 1.42: Three possible pathways for the RCEYM

When Clarke *et al.* attempted the RCEYM on substrate **1.92**, disappointingly only the undesired cyclohexene **1.96** was recovered with no traces of the desired cyclopentene **1.80** (Scheme 1.43).



Scheme 1.43: Formation of undesired RCEYM product

The synthetic route to close the C-ring was modified, the previously synthesised alcohol **1.90** was oxidised and the resulting aldehyde reacted with vinylmagnesium bromide to furnish allylic alcohol **1.97**. Diene **1.97** was submitted to RCM conditions to furnish ABC tricycle **1.98** as a mixture of 2 diastereomers (Scheme 1.44).

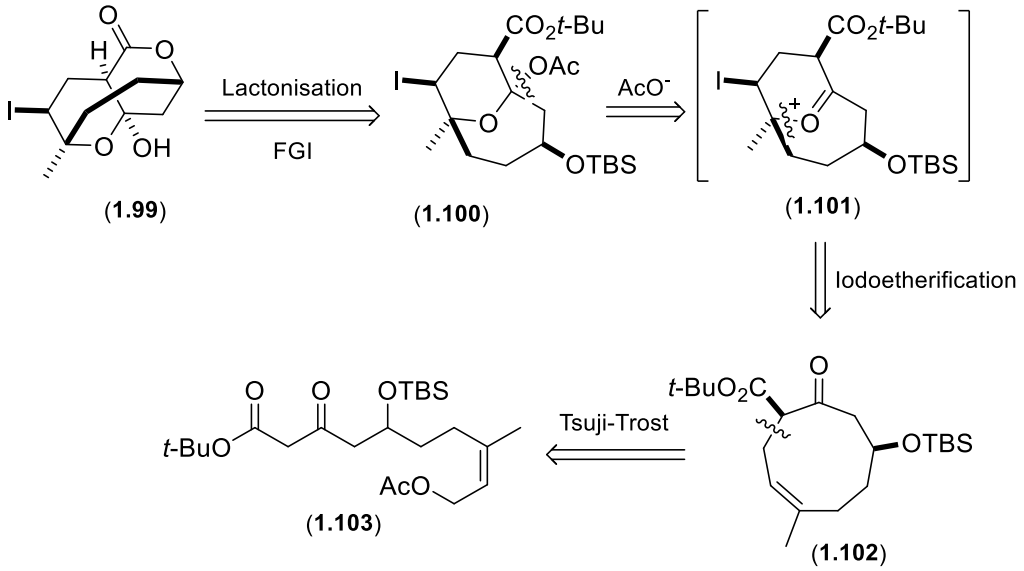


Scheme 1.44: Synthesis of final product **1.98** by RCM

Clarke *et al.* synthesised ABC tricycle in 6% yield over 15 steps and as a racemic mixture. Relative stereochemistry of the AB and BC junctions were efficiently installed and despite the unsuccessful RCEYM, the C-ring was closed by diene RCM.

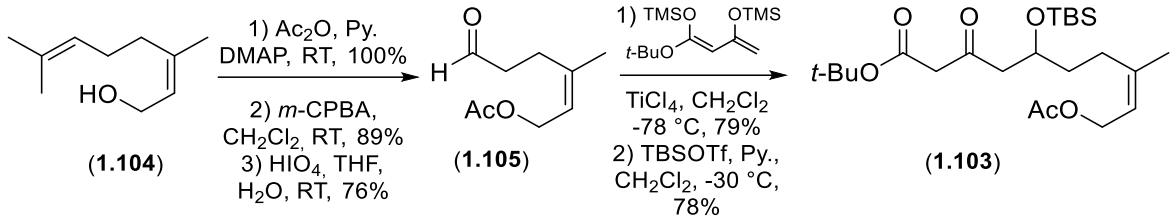
1.3.4 DEF tricycle by Clarke *et al.*

Clarke *et al.* were the first to publish a synthesis of a DEF tricycle model of hexacyclinic acid in 2003.[29] The envisaged retrosynthesis of DEF ring system **1.99** began with the closure of the E-ring by lactonisation and some functionalisation from bicycle **1.100**. Hemiketal **1.100** could be formed by addition of acetate to oxacarbenium **1.101**. The oxacarbenium intermediate could be synthesised by iodoetherification of the nine-membered ring **1.102**. Nine-membered ring **1.102** would be formed from linear chain **1.103** by a Tsuji-Trost cyclisation (Scheme 1.45).



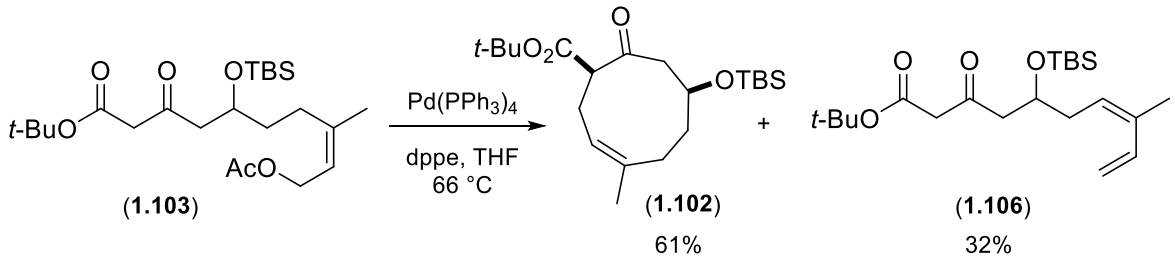
Scheme 1.45: Retrosynthesis of DEF tricycle **1.99**

The synthesis started from nerol **1.104** by acetylation of the primary alcohol, selective epoxidation of one of the trisubstituted alkene and oxidative cleavage of the resulting epoxide to furnish aldehyde **1.105**. Mukaiyama aldol reaction gave *β*-ketoester and the newly formed alcohol was silylated in the presence of TBSOTf to produce compound **1.103** (Scheme 1.46).



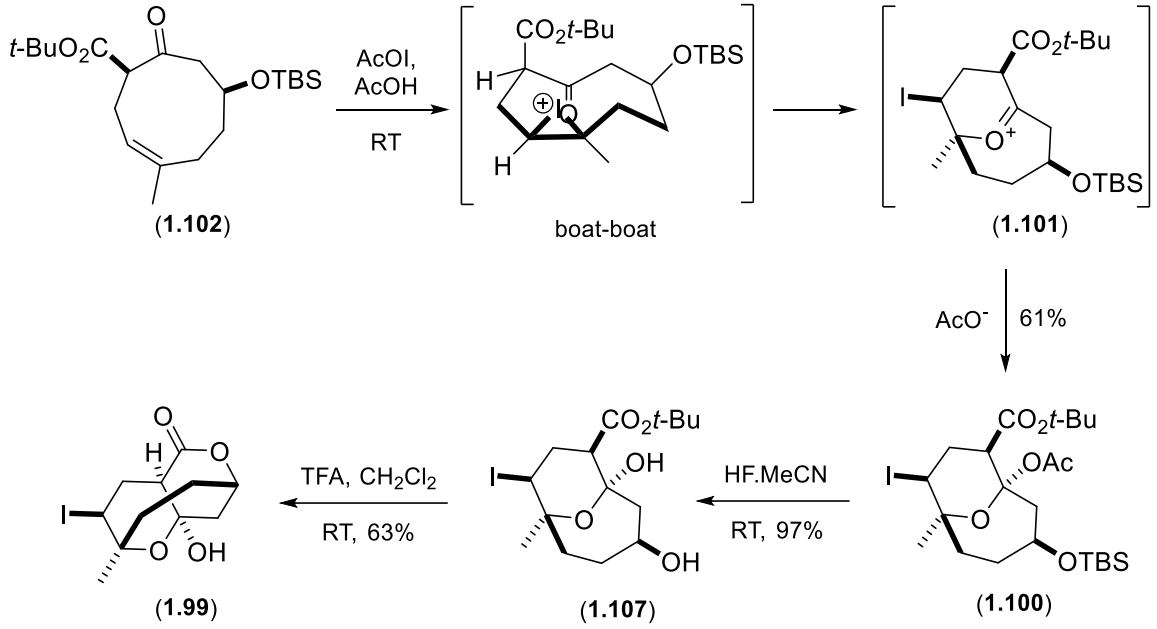
Scheme 1.46: Synthesis of *β*-ketoester **1.103**

The formation of the nine-membered ring was obtained by a palladium catalysed Tsuji-Trost reaction. Clarke *et al.* discovered that 1,2-*bis*(diphenylphosphino)ethane (dppe) was crucial to obtain an adequate ratio (2:1) of the desired product **1.102** and the elimination by-product **1.106**, with only traces of the seven-membered ring (Scheme 1.47).



Scheme 1.47: Formation of nine-membered ring **1.102**

After successful synthesis of **1.102**, the next step was the cyclisation of the DF rings. This reaction proceeded by formation of the iodonium ion in the presence of iodine(I) acetate. The iodonium bridge was then attacked by the carbonyl via a boat-boat conformation to give oxacarbenium **1.101**, which was trapped by an acetate to finally produce DF bicycle **1.100**. Final steps included desilylation of the secondary alcohol and hydrolysis of the acetate to furnish hemiketal **1.107**. TFA acidolysis of *tert*-butyl ester followed by acid-catalysed lactonisation gave the final product, DEF tricycle **1.99** in 9% overall yield over nine steps (Scheme 1.48).

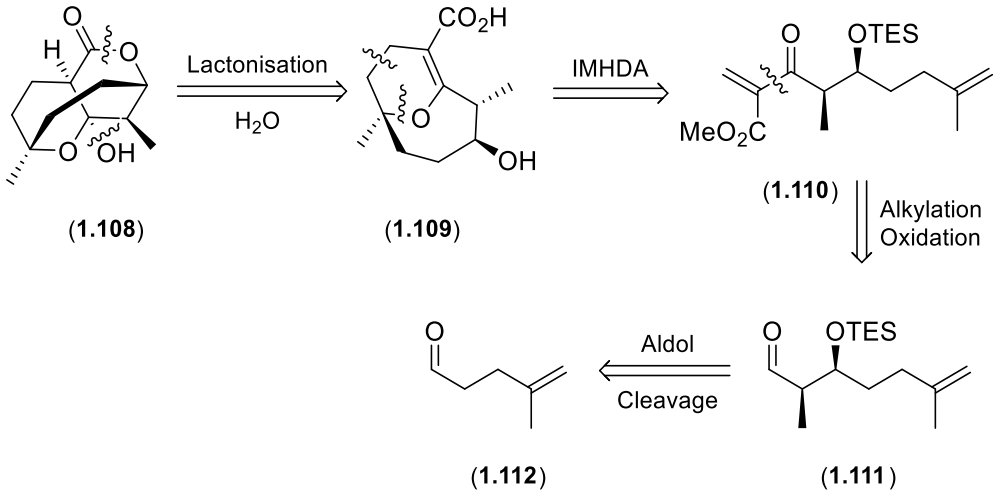


Scheme 1.48: Iodination/cyclisation of product **1.102** and end game of the synthesis

Clarke *et al.* were first to publish the synthesis of a model of DEF tricycle. They synthesised a desmethyl DEF tricycle with the correct relative stereochemistry in a short synthetic sequence and with a very good overall yield. Unfortunately, when they tried the same strategy with the product incorporating a methyl group, the iodoetherification step was unsuccessful. There is also no mention of a general strategy to unite the two models and synthesise an ABCDEF hexacycle.

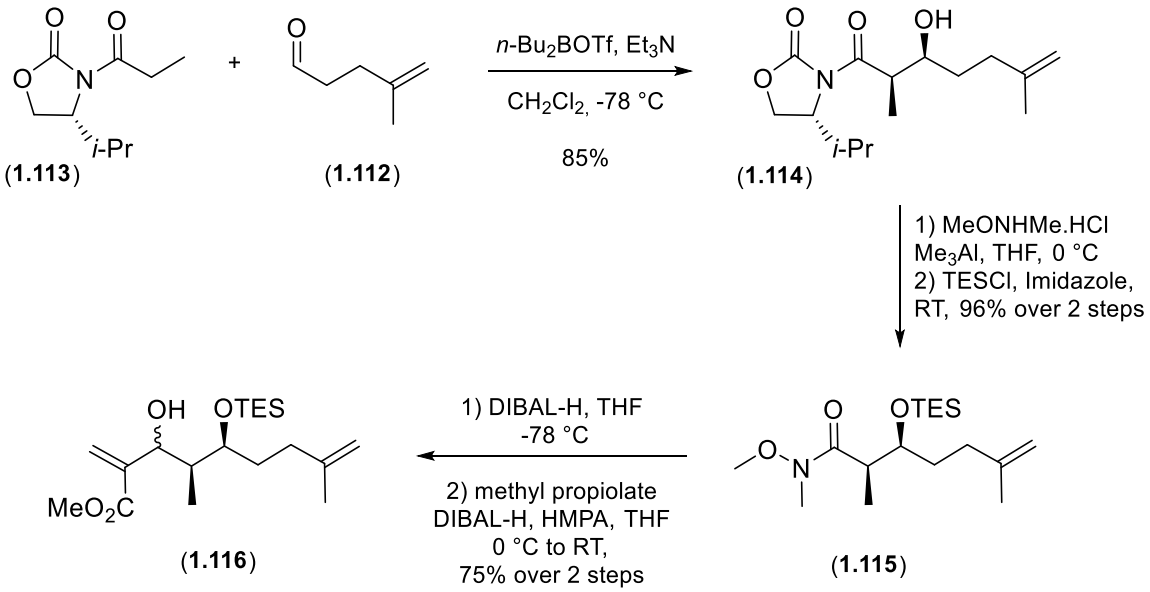
1.3.4 DEF tricycle by Nakada *et al.*

The most recent work published about hexacyclinic acid and its derivatives was from Nakada *et al* in 2012.[30] After the total synthesis of (–)-FR182877, they decided to use a similar strategy to their previous work in order to synthesise the DEF tricycle of (–)-FR182877 and hexacyclinic acid and subsequently evaluate their biological activity. Their envisaged retrosynthesis started from DEF tricycle **1.108**, which could be formed by addition of water and lactonisation from carboxylic acid **1.109**. Bicycle **1.109** could be cyclised by an IMHDA reaction from conjugated ketoester **1.110**. Diels-Alder precursor **1.110** was to be synthesised from aldehyde **1.111** by an alkylation reaction and oxidation. Finally, aldehyde **1.111** could be obtained by an Evans aldol reaction and subsequent auxiliary cleavage from aldehyde **1.112** (Scheme 1.49).



Scheme 1.49: Retrosynthesis for the formation of DEF tricycle **1.108** by Nakada *et al.*

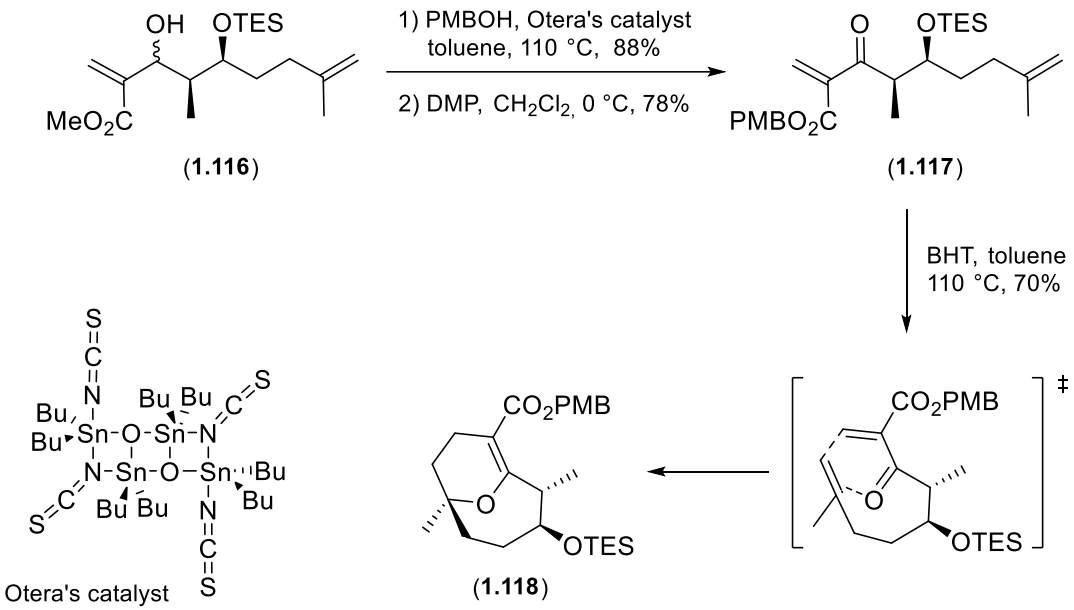
The synthesis started by an Evans aldol reaction using aldehyde **1.112** to give aldol **1.114** in 85% yield as a single isomer. Conversion of aldol **1.114** into the corresponding Weinreb amide, followed by TES protection of the secondary alcohol led to the formation of product **1.115**. Weinreb amide **1.115** was reduced to give the corresponding aldehyde, which was reacted with a vinylaluminium reagent generated *in situ* from methyl propiolate and DIBAL- H to furnish allylic alcohol **1.116** as a 1:1 mixture of diastereomers (Scheme 1.50).[31]



Scheme 1.50: Synthesis of allylic alcohol **1.116**

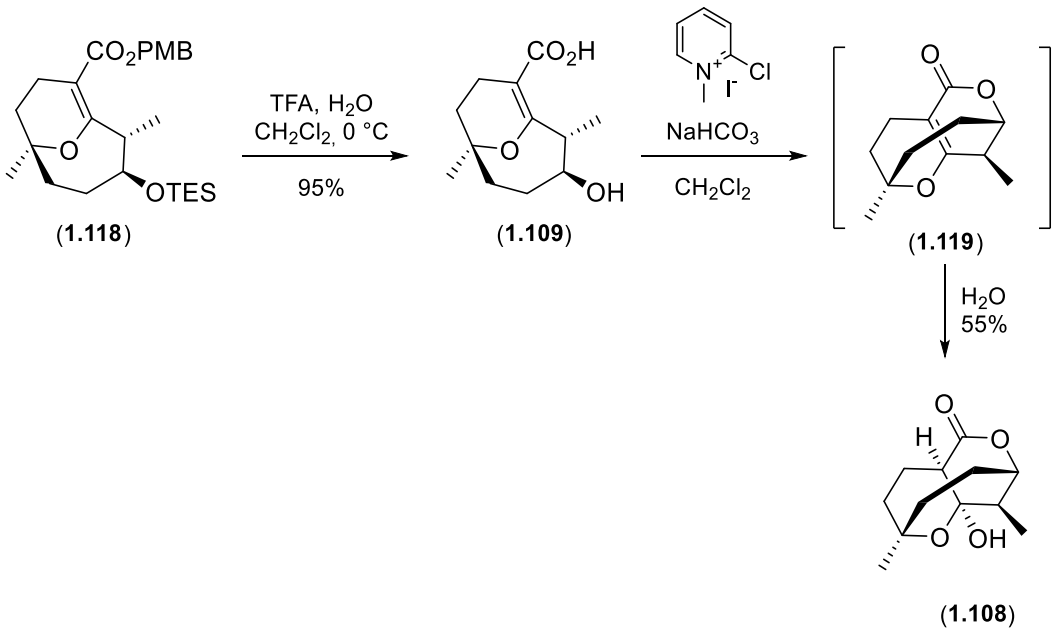
Due to some problems later in the synthesis for the conversion of the methyl ester into a carboxylic acid, ester **1.116** was transformed into the PMB ester using Otera's catalyst.[32] The allylic alcohol was then oxidised to the corresponding enone to produce Diels-Alder

precursor **1.117**. Intramolecular hetero Diels-Alder reaction proceeded slowly over 4 days to furnish the DF bicycle **1.118** as a single diastereomer (Scheme 1.51).



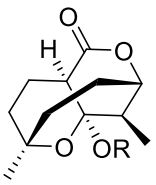
Scheme 1.51: Transesterification and IMHDA cyclisation

Product **1.118** was converted into hydroxy carboxylic acid **1.109** under acidic conditions. Lactonisation using Mukaiyama's reagent furnished (−)-FR182877 DEF tricycle **1.119**, which was not isolated due to its reactivity. Tricycle **1.119** reacted with water during the work-up to give final product **1.108** as a single diastereomer in 14% overall yield over 10 steps (Scheme 1.52).



Scheme 1.52: Final steps of the Nakada's synthesis

Nakada *et al.* synthesised DEF tricycle **1.108** in a concise stereoselective synthesis and with very good overall yield. They also modified the DEF tricycle with the formation of the corresponding acetate **1.120** and benzoate **1.121**. The biological activities of DEF tricycle **1.108** and its derivatives were tested and only very low to moderate effects toward cell cycle arrest were found. This result is an additional proof of the crucial role of the double bond in (–)-FR182877 for the cytotoxicity (Figure 1.4).



(**1.108**) R = H
(**1.120**) R= Ac
(**1.121**) R = Bz

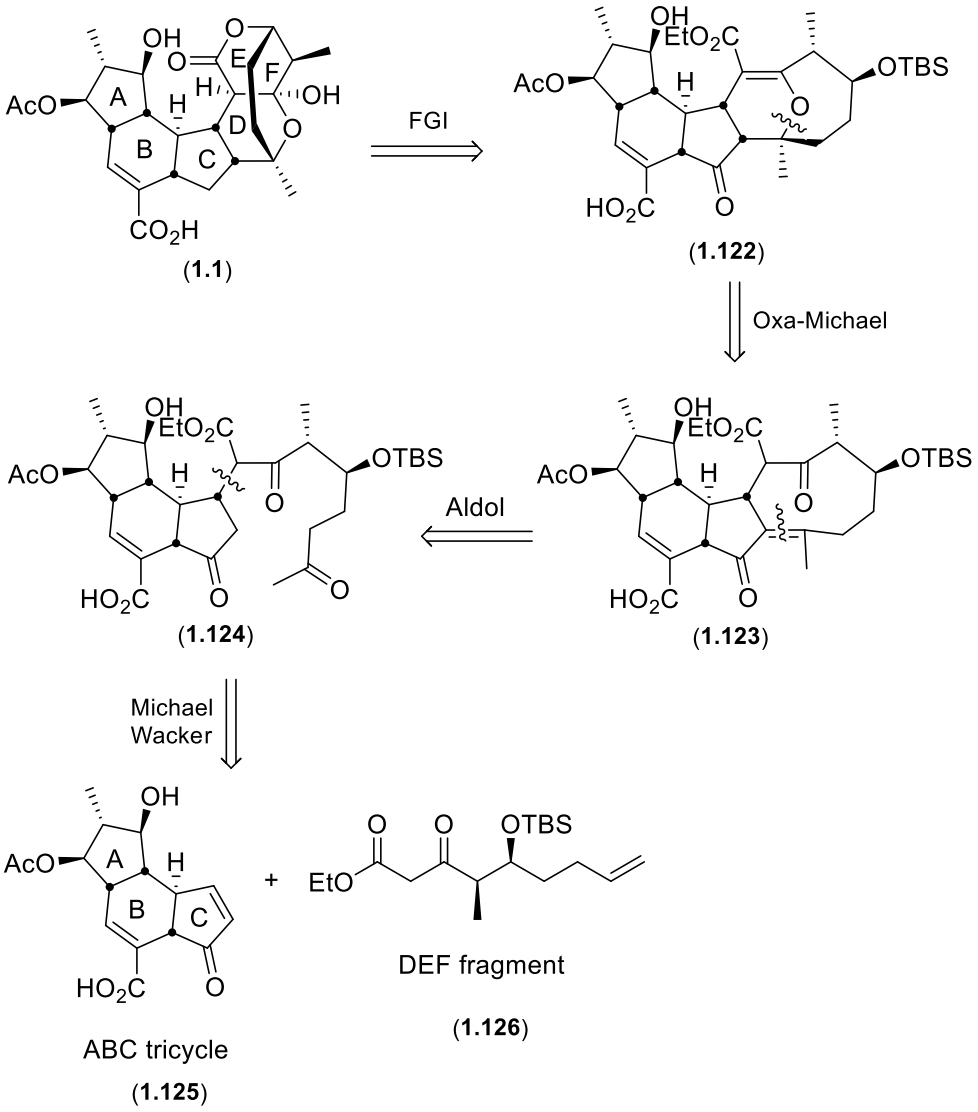
Figure 1.4: DEF tricycle **1.108** and its derivatives

1.4 Previous work in the Prunet group

This work is focused on the synthesis of the ABC tricycle and a CDEF tetracycle model of hexacyclinic acid. This project is based on the previous work done by Julie Toueg, Raphaël Oriez (Ecole Polytechnique, France) and Michael Mathieson (University of Glasgow) during their PhD theses under the supervision of Dr Joëlle Prunet.[33–35]

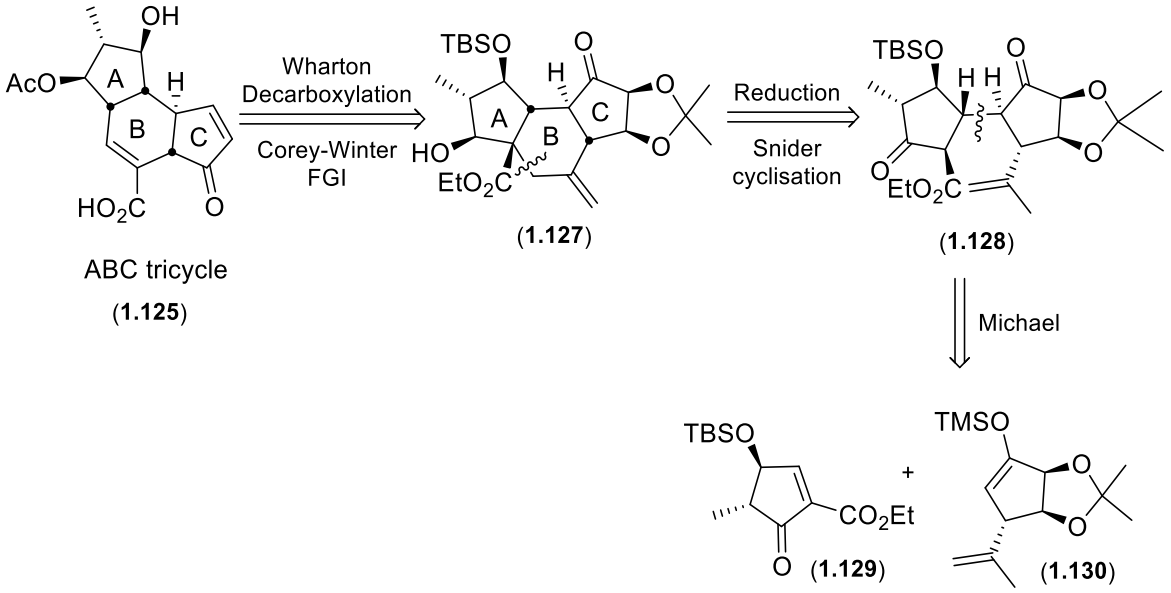
1.4.1 ABC tricycle

The strategy envisaged in the Prunet group to complete the total synthesis of hexacyclinic acid **1.1** started with some functionalisations from pentacycle **1.122**. Pentacycle **1.122** could be formed by an oxa-Michael reaction to close the D-ring from tetracycle **1.123**. Product **1.123** could be produced using an aldol reaction to cyclise the nine-membered ring from compound **1.124**. Product **1.124** was to be synthesised by a Michael reaction between ABC tricycle **1.125** and DEF fragment **1.126** and by a Wacker oxidation (Scheme 1.53).



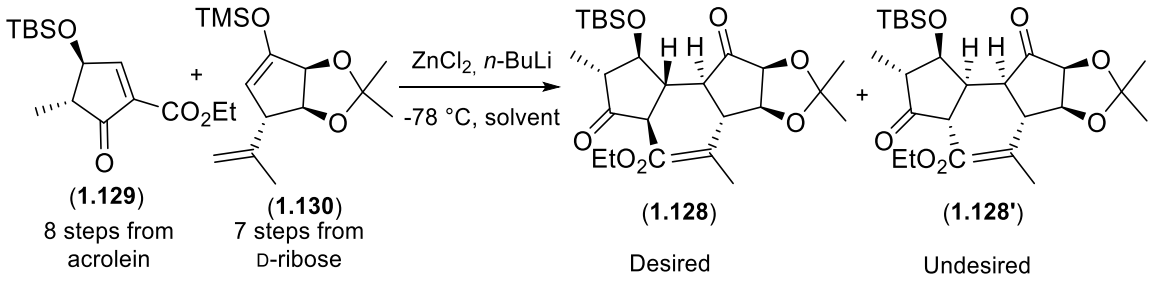
Scheme 1.53: Proposed retrosynthesis

ABC tricycle **1.125** could be synthesised by a Wharton rearrangement, decarboxylation of the ester at the AB ring junction, isomerisation of the exocyclic double bond and a Corey-Winter reaction to give the corresponding enone from intermediate **1.127**. The ketone would be diastereoselectively reduced and the B-ring would be closed by a Snider cyclisation from bicycle **1.128**. Product **1.128** was to be synthesised by a diastereoselective Michael reaction between conjugated ketoester **1.129** and silyl enol ether **1.130** (Scheme 1.54).



Scheme 1.54: Proposed retrosynthesis of ABC tricycle **1.125**

Optimisation of the diastereoselective Michael reaction between **1.129** and **1.130** identified the Lewis acid zinc(II) chloride and *n*-butyllithium as the best conditions for the reaction; however variation of the solvent led to some interesting effects. It appeared that the polarity of the solvent was crucial for the diastereoselectivity. With a low polarity solvent like Et_2O, the major diastereoisomer, with a ratio of 7:1, was the undesired stereoisomer. Surprisingly, the selectivity was completely inverted using a more polar solvent system such as DMF/THF for the reaction (Table 1.1).[36]



Solvent	Yield (%)	Ratio 1.128/1.128’
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 1.1: Effects of the solvent polarity on the yield/diastereoselectivity

These effects could be explained by two possible transition states. In the case of a non-polar solvent, zinc would be complexed preferentially by the oxygens from both reagents, forming an eight-membered transition state and attack of the enolate would occur *trans* to the methyl group of the A-ring. On the other hand, when using a polar solvent, this complexation would be disrupted and the reaction would proceed via an open transition state with the enolate *trans* to the OTBS group (Figure 1.5).

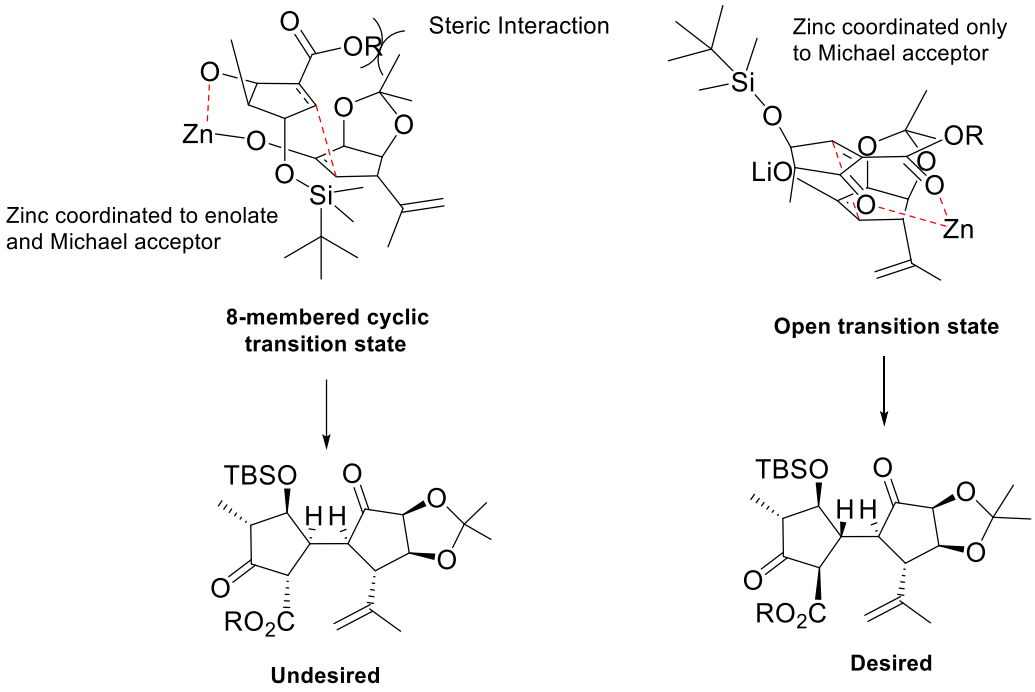
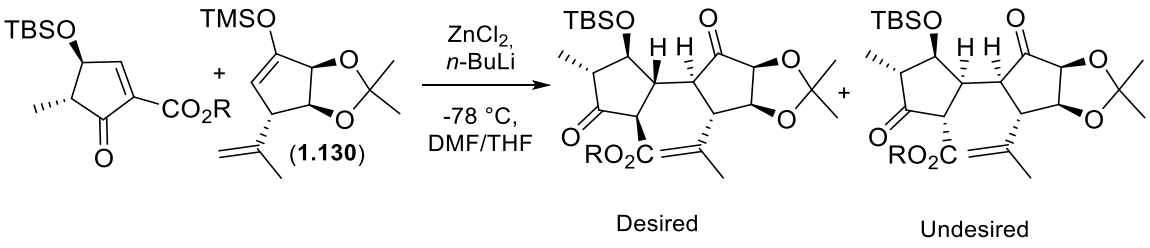


Figure 1.5: Two proposed transition states

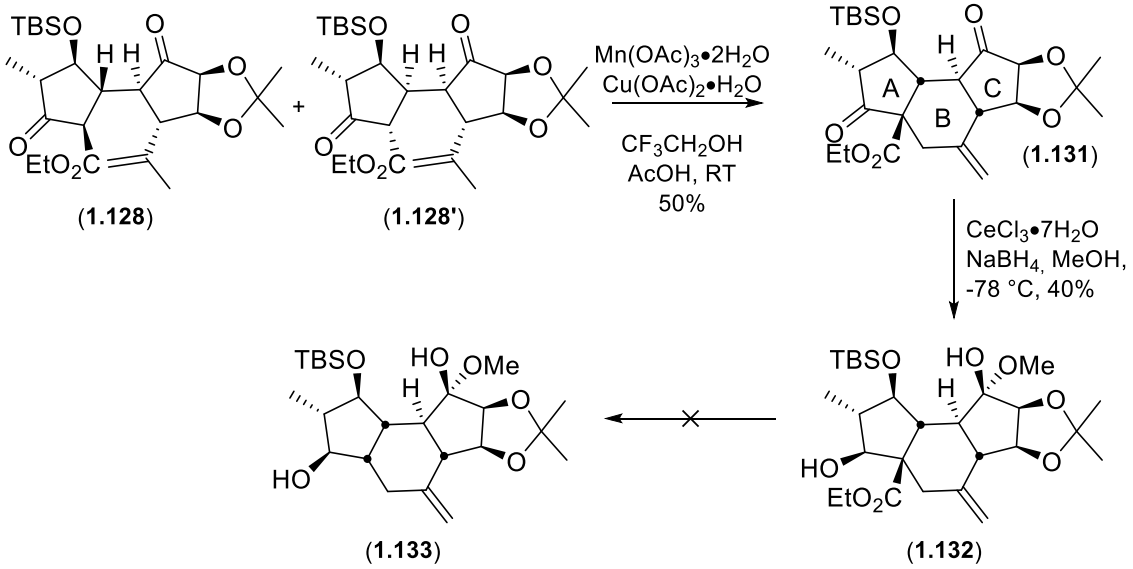
The steric hindrance of the ester was also crucial for the diastereoselectivity of this reaction. By increasing the size of the R group, the diastereomeric ratio increased in favor of the desired diastereomer (Table 1.2).[34,35]



R	Yield (%)	Ratio Desired/Undesired
Me	50	3:1
Et	60	5:1 to 7:1
t-Bu	55	1:0

Table 1.2: Effects of the ester size on the yield/diastereoselectivity

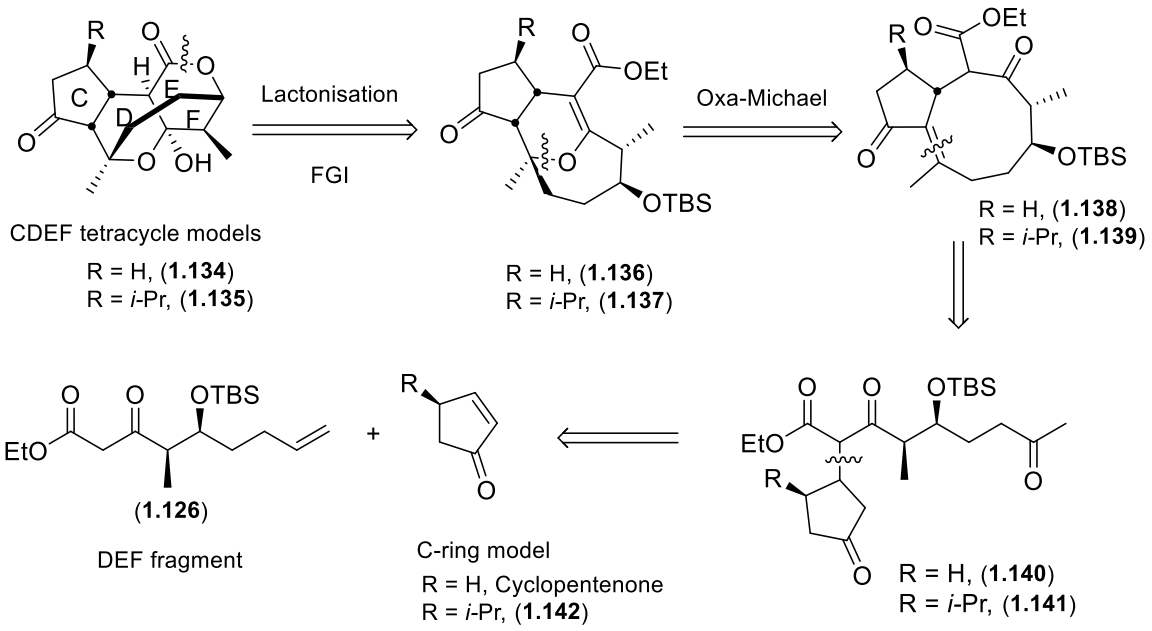
Product **1.128** was then submitted to a Snider cyclisation in the presence of manganese(III) acetate and copper(II) acetate. After optimisation, the best solvent system was found to be a 10:1 mixture of trifluoroethanol/acetic acid. Interestingly, only the desired diastereomer **1.128** underwent cyclisation while the undesired diastereomer solely led to degradation. Tricycle **1.131** was obtained after cyclisation in 50% yield as a single stereoisomer. The following step was the reduction of the ketone moieties; it was hoped that using Luche conditions, cerium(III) chloride would complex the oxygens from the convex face, forcing the hydride source to attack the most hindered concave face to generate the desired diastereomer. Surprisingly, Luche reduction of tricycle **1.131** produced compound **1.132**, converting the ketone of the C-ring into a hemiketal while diastereoselectively reducing the ketone of the A-ring. Decarboxylation of product **1.132**, despite numerous attempts, proved to be unsuccessful (Scheme 1.55).



Scheme 1.55: Snider cyclisation and following steps

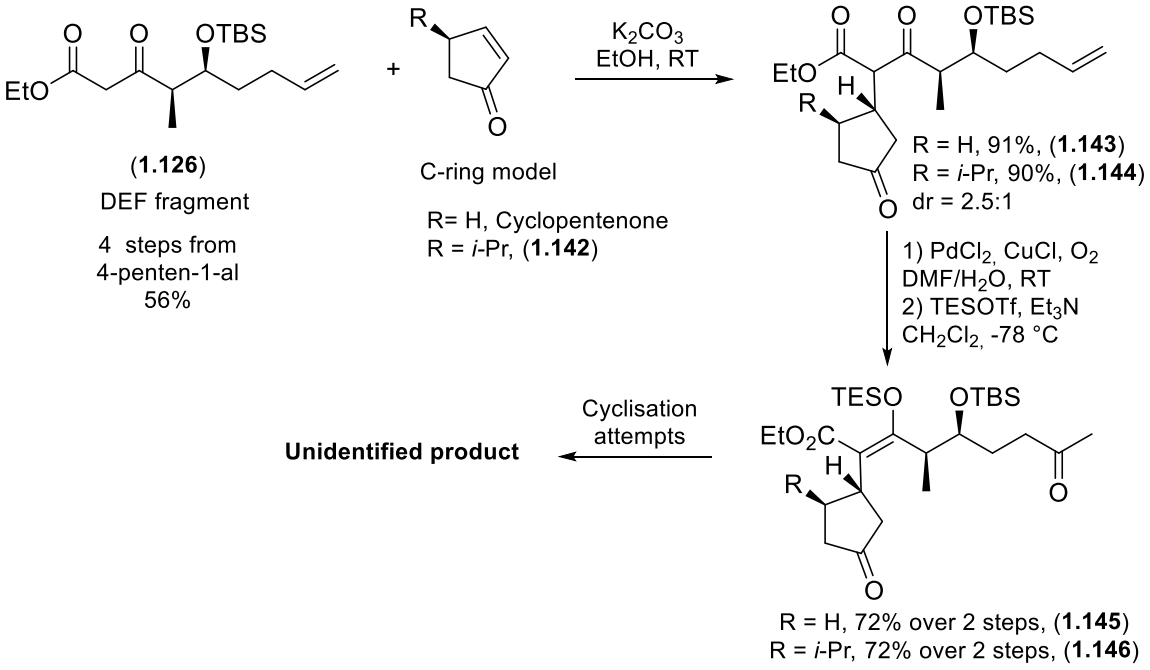
1.4.2 CDEF tetracycle model

In order to complete the total synthesis of hexacyclinic acid **1.1**, it was decided to develop a synthetic strategy for the formation of the DEF tricycle on a model. The synthesis of a CDEF model would furnish a more accessible synthetic pathway instead of using the more valuable ABC tricycle **1.125**. The CDEF tetracycle models **1.134** and **1.135** could be elaborated by lactonisation and several functional group interconversions from tricycles **1.136** and **1.137**. The hemiketal could be formed by an oxa-Michael reaction from the 5,9 ring systems. Nine-membered rings **1.138** and **1.139** would be closed by an aldol reaction from the corresponding linear compounds **1.140** and **1.141**, which could be synthesised by a Wacker oxidation and a Michael addition between DEF fragment **1.126** and different models of the C ring (Scheme 1.56).



Scheme 1.56: Envisaged retrosynthesis of CDEF models

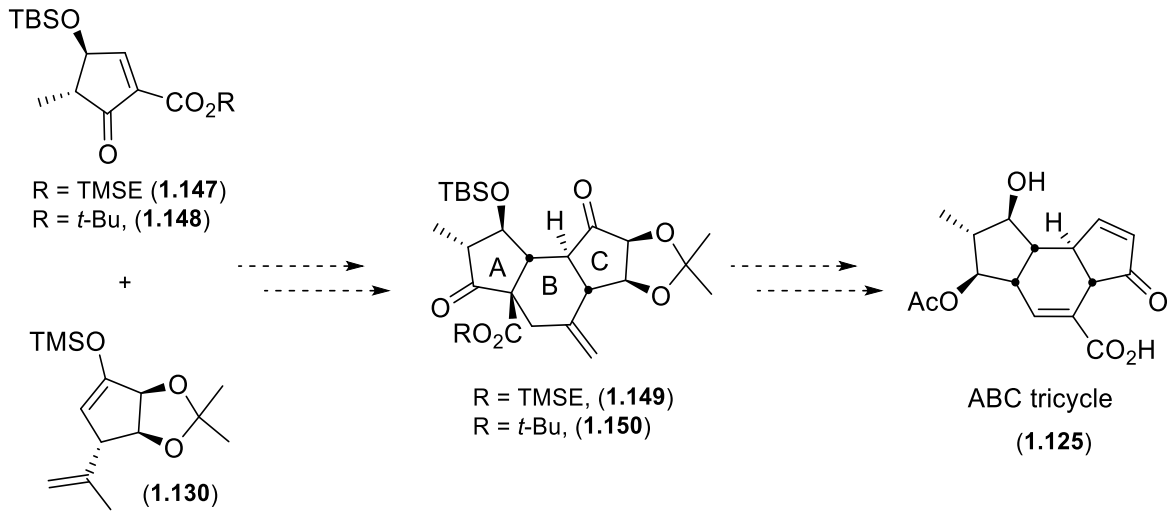
The DEF fragment **1.126** was synthesised in 56% yield in 4 steps as a single diastereomer from 4-penten-1-al.[35] The *β*-ketoester **1.126** reacted with two different C-ring models (cyclopentenone and **1.142**) to give the corresponding addiction products (**1.143** and **1.144**). Wacker oxidation of the alkene and formation of TES silyl enol ether gave two different cyclisation precursors (**1.145** and **1.146**). Unfortunately, attempts to obtain nine-membered rings led only to the formation of an unknown product, which could not be identified at the time as it was produced in only small quantities (Scheme 1.57).



Scheme 1.57: Formation of an unidentified product

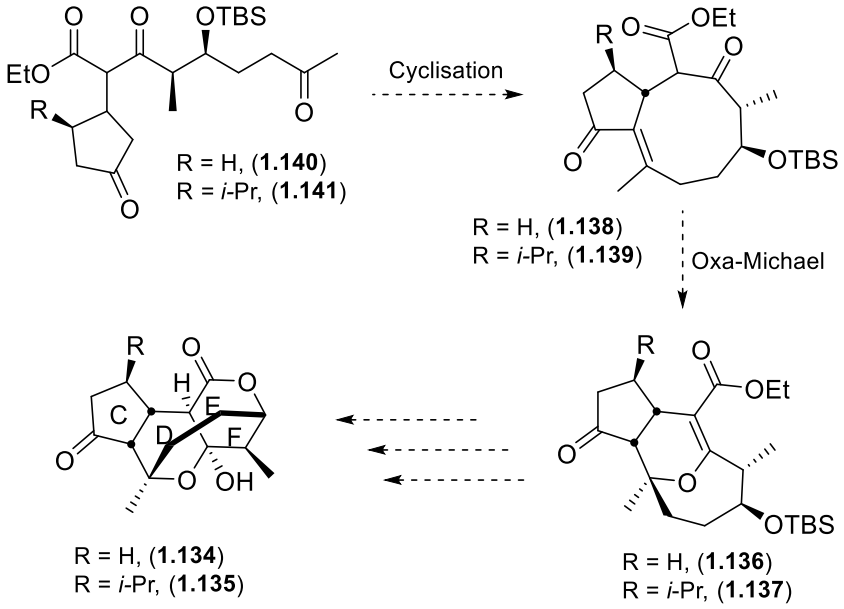
1.4.3 Thesis project

The first objective of this project is to synthesise the ABC tricycles with different esters using the synthesis previously developed in the group.[33–35] Decarboxylation conditions will be explored and the synthesis toward the final ABC tricycle **1.125** will be developed (Scheme 1.58).



Scheme 1.58: Synthesis of ABC tricycle **1.125**

The second objective is to continue the synthesis of different CDEF models. The conditions for the cyclisation of the desired nine-membered rings will be developed; the closure of the DF ring system will be studied leading to the synthesis of CDEF models (Scheme 1.59).

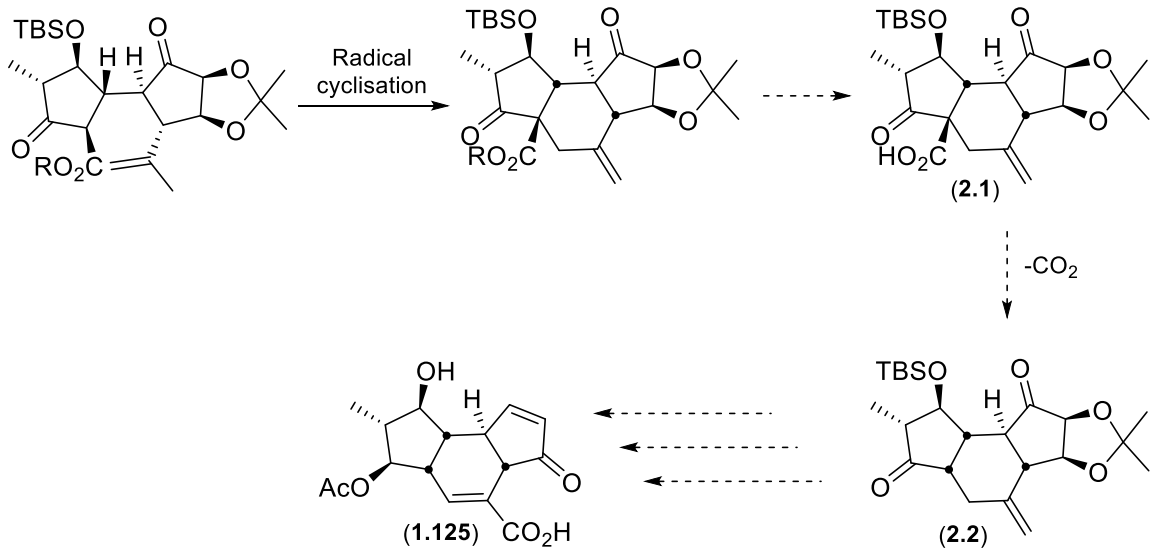


Scheme 1.59: Planned synthesis of CDEF models

Chapter 2: Hexacyclinic acid

2.1 Synthesis of ABC tricycle

One of the aims of the project was to synthesise tricycles with different esters, then subsequently explore decarboxylation methods in order to complete the ABC tricycle **1.125** synthesis. It is known that *β*-ketoacids tend to lose carbon dioxide rapidly in presence of acid. Our goal was to transform the ester into the corresponding carboxylic acid **2.1** and find suitable conditions for the decarboxylation step (Scheme 2.1).

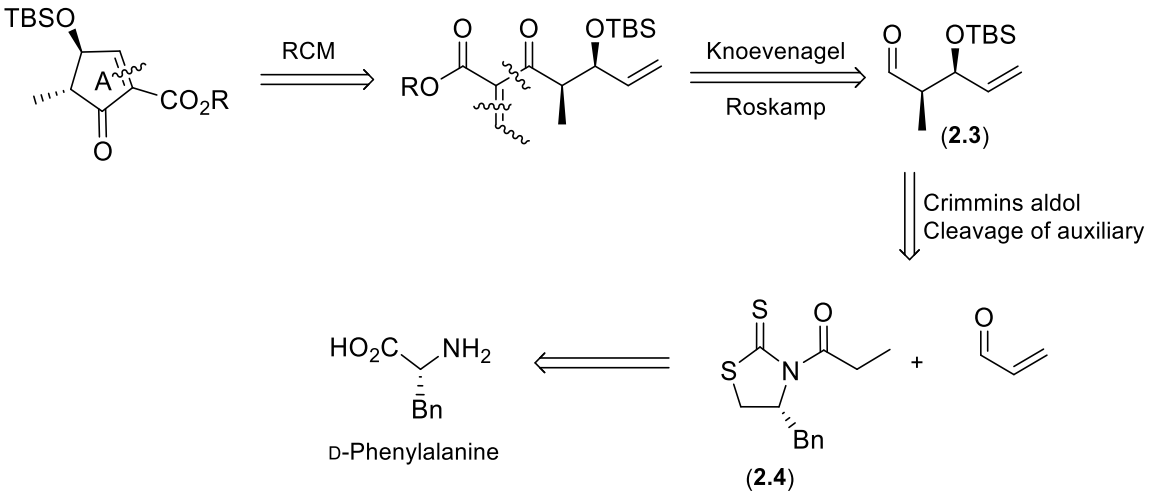


Scheme 2.1: Plan for the synthesis of ABC tricycle

2.1.1 Synthesis of the A ring

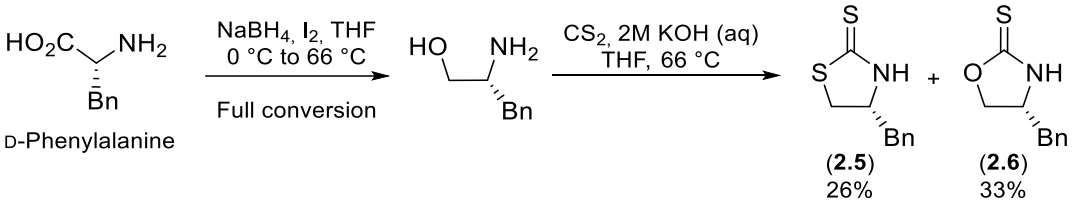
In order to produce the ABC tricycle **1.125**, it was crucial to prepare both A and C rings in multigram scale. The retrosynthesis previously developed in the group started by the formation of A rings with different R groups (**1.147** and **1.148**), which could be closed by a ring-closing metathesis from corresponding conjugated ketoesters **1.153** and **1.154**. The conjugated ketoesters could be produced by a Roskamp homologation with different diazoacetates to generate ester moieties, followed by Knoevenagel condensation with formaldehyde to install the trisubstituted alkenes from aldehyde **2.3**. Aldehyde **2.3** would be synthesised by a Crimmins aldol reaction between Crimmins auxiliary **2.4** and acrolein, followed by formation of the TBS ether from the resulting *β*-hydroxyketone and cleavage of

the auxiliary. Finally, acylated Crimmins auxiliary **2.4** would be obtained in 3 steps from D-Phenylalanine (Scheme 2.2).



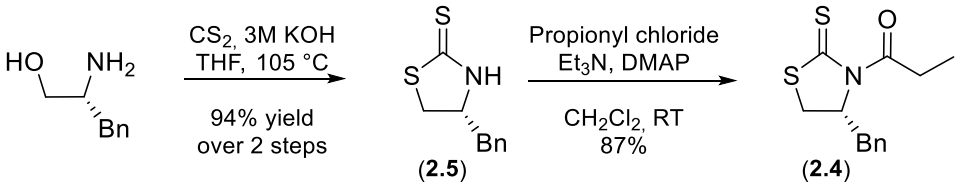
Scheme 2.2: Retrosynthesis of the A ring

The forward synthesis started by the reduction D-Phenylalanine into D-Phenylalaninol using a convenient method for the reduction of carboxylic acids.[37] Sodium borohydride reacted with iodine to generate in situ two equivalents of borane, allowing the reduction of the carboxylic acid into the corresponding alcohol to take place The crude aminoalcohol was then transformed into thiazolidinethione **2.5** in the presence of carbon disulfide and an aqueous solution of potassium hydroxide.[38] Unfortunately, a mixture of thiazolidinethione **2.5** and oxazolidinethione **2.6** was produced (Scheme 2.3).



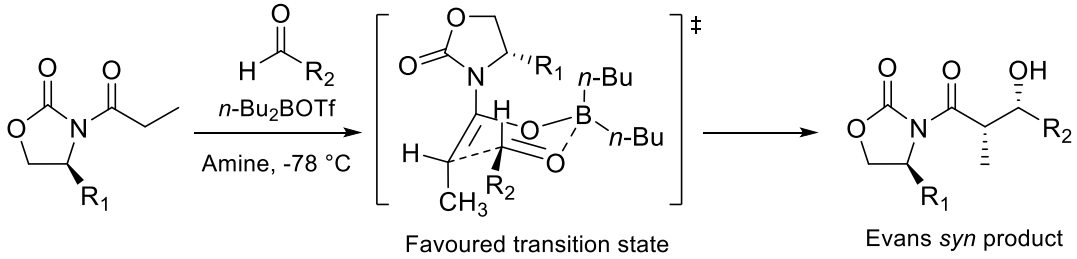
Scheme 2.3: Formation of thiazolidinethione **2.5**

It was hypothesised that the oxazolidinethione resulted from reaction conditions being too mild. More drastic conditions were used (stronger alkaline solution, higher temperature) and the desired heterocycle **2.5** was obtained as the only product. Thiazolidinethione **2.5** was acylated with propionyl chloride, triethylamine and DMAP to give acylated Crimmins auxiliary **2.4** in 82% over 3 steps (Scheme 2.4).



Scheme 2.4: Formation of acylated Crimmins auxiliary **2.4**

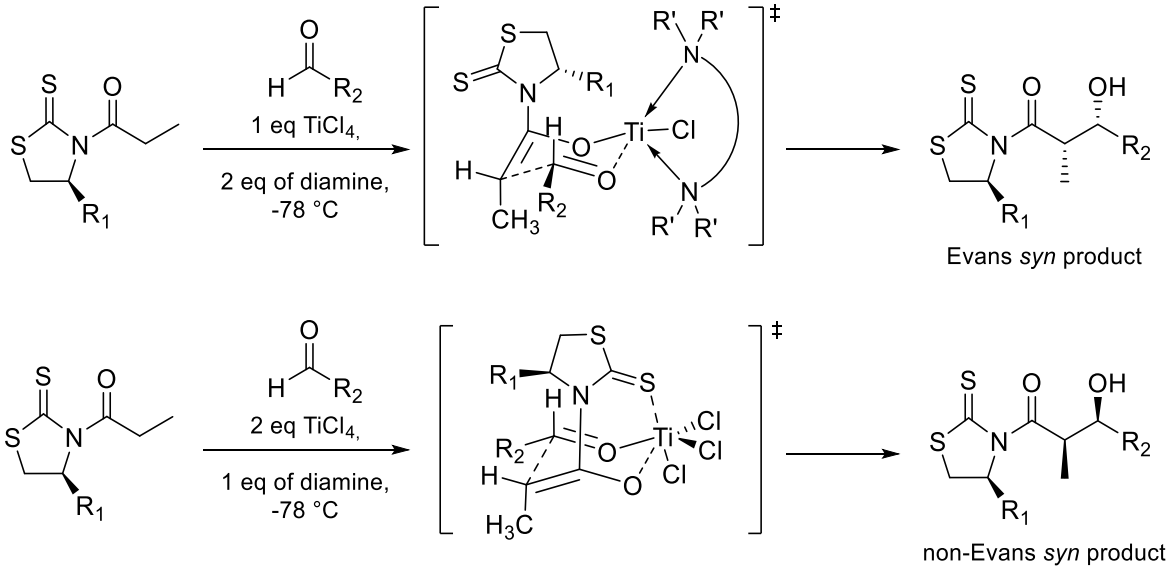
Diastereoselective aldol reactions are very useful tools in organic synthesis to generate asymmetric C-C bonds. A widely used method is the Evans aldol reaction.[39] Evans' method uses a temporary chiral auxiliary to produce chiral boron enolates of *N*-acyl oxazolidinones, and create aldols with high diastereomeric ratios. Titanium enolates of *N*-acyl oxazolidinones were explored but the diastereoselectivity was lower than with boron. The reaction proceeded as described below: in the presence of dibutylboron triflate and an amine, a *Z*-boron enolate was generated. The diastereoselectivty can be rationalised by the formation of a Zimmerman-Traxler transition state where the R group of the aldehyde adopts a pseudo equatorial position and the dipoles are minimised to furnish the Evans *syn* adduct as a major product (Scheme 2.5).



Scheme 2.5: Transition state for Evans aldol reaction

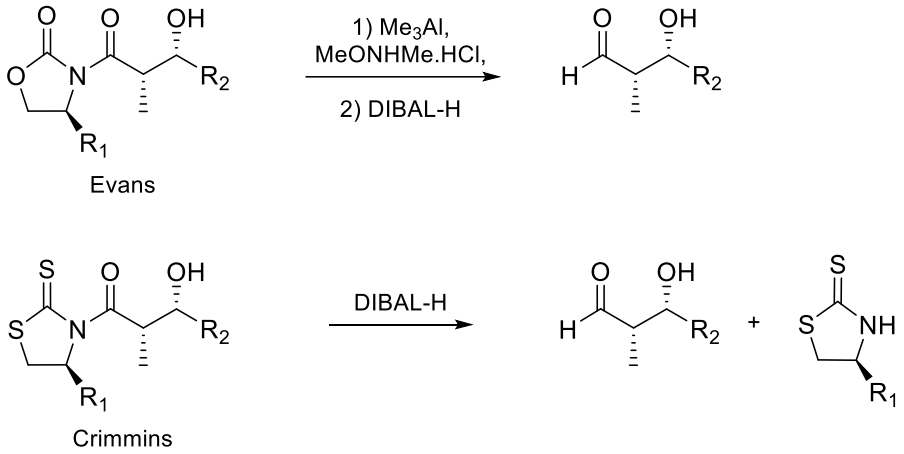
More recently, other chiral auxiliaries were developed. Crimmins *et al.* decided to investigate the use of *N*-acyl thiazolidinethiones and oxazolidinethiones to generate chiral titanium enolates.[40,41] Due to the high affinity of sulfur for titanium, it was shown that, by replacing the oxygen on the auxiliary with a sulfur atom, it was possible to access both Evans *syn* and non-Evans *syn* products with high diastereomeric ratios. Different amine bases were tested and the best results were found when (−)-sparteine was used. Due to (−)-sparteine being quite an expensive reagent, other bidendate bases were explored and TMEDA was discovered to be a potential replacement despite a slight decrease in yield. The diastereoselectivity could be modified by altering the number of equivalents of both reagents. Crimmins aldol reaction using one equivalent of titanium and two equivalents of diamine proceeds in a similar transition state to that of the Evans reaction and furnishes the

Evans *syn* product. When only one equivalent of diamine is used, the sulfur of the auxiliary can coordinate to the metal to produce this time the non-Evans *syn* product (Scheme 2.6).



Scheme 2.6: Possible transition states for Crimmins aldol reaction

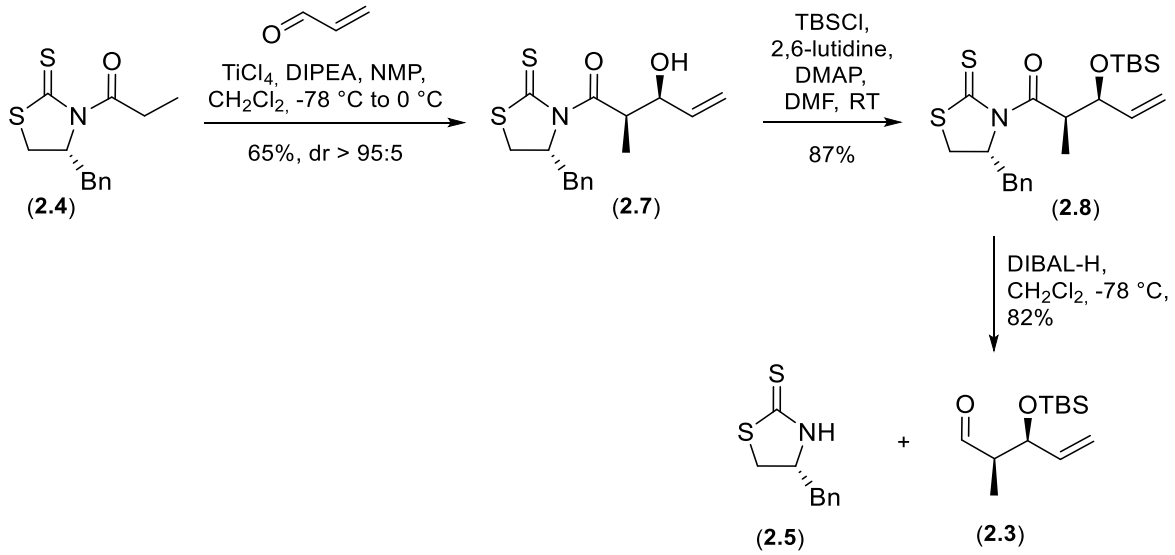
Another difference between Evans' and Crimmins' auxiliaries is the cleavage step. Transformation of the Evans auxiliary into the corresponding aldehyde is usually a two-step process, whereas to convert Crimmins auxiliary into an aldehyde, only one step is required, allowing a higher overall yield and fewer synthetic steps (Scheme 2.7).



Scheme 2.7: Cleavage of Evans' and Crimmins' auxiliaries

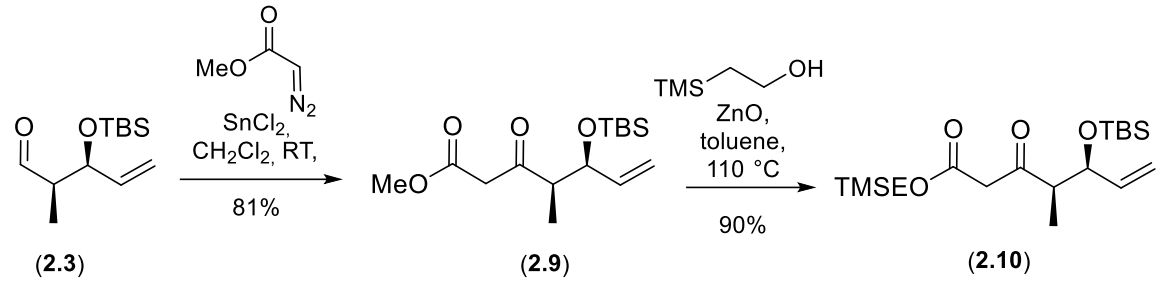
It was decided for our synthesis to use a modified version of the Crimmins aldol reaction with DIPEA and NMP as amine bases.[42] This method is known to give comparable diastereomic ratios and yields as other methods (*e.g.* (−)-sparteine) but for a lesser cost. The previously synthesised acylated Crimmins auxiliary **2.4** reacted with a slight excess of acrolein in the presence of DIPEA and NMP to give aldol **2.7** in good yield and excellent

diastereomeric ratio. Silylation of aldol **2.7** proved to be a slow process; the best conditions found were TBSCl, with 2,6-lutidine as a base and DMAP in DMF at high concentration concentration over three days to furnish TBS protected aldol **2.8**. When imidazole was used instead of 2,6-lutidine, some epimerisation product was obtained. The Crimmins auxiliary was cleaved by DIBAL-H to give aldehyde **2.3** in very good yield and thiazolidinethione **2.5** was recovered (Scheme 2.8).



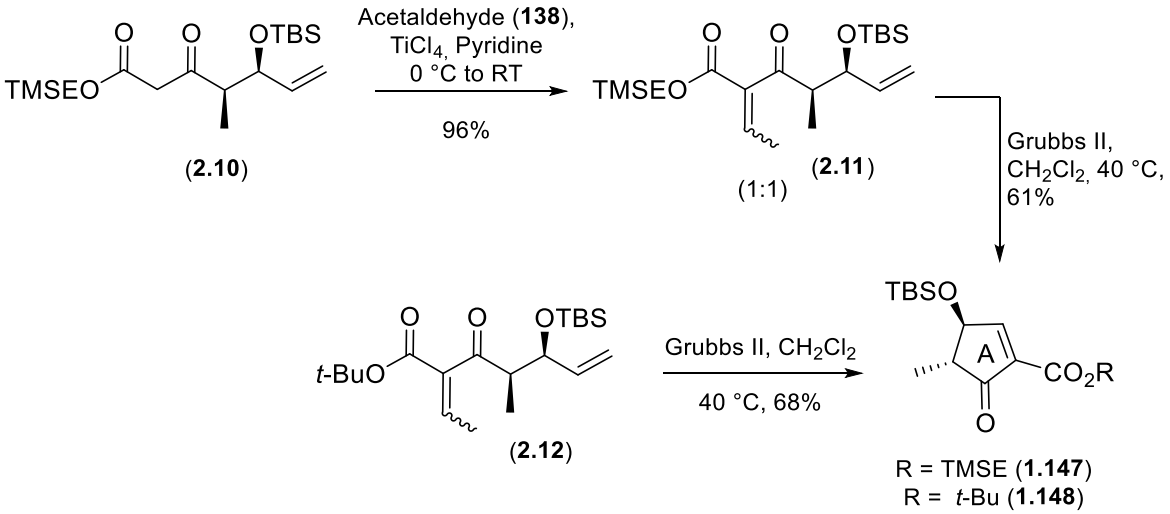
Scheme 2.8: Formation of aldehyde **2.3**

The next step of the synthesis was the conversion of aldehyde **2.3** into *β*-ketoester **2.9** by a Roskamp homologation. It was decided to use methyl diazoacetate as a partner in the Roskamp homologation; several grams of methyl diazoacetate were already available in the lab and a methyl ester would allow the production of a wide range of esters by transesterification later on.[34,35] The reaction proceeded well and *β*-ketoester **2.9** was obtained in 81% yield. Methyl ester **2.9** was then submitted to transesterification conditions using a catalytic amount of ZnO and 2-trimethylsilyl ethanol in refluxing toluene to successfully deliver ester **2.10** (Scheme 2.9).[43]



Scheme 2.9: Roskamp and transesterification steps

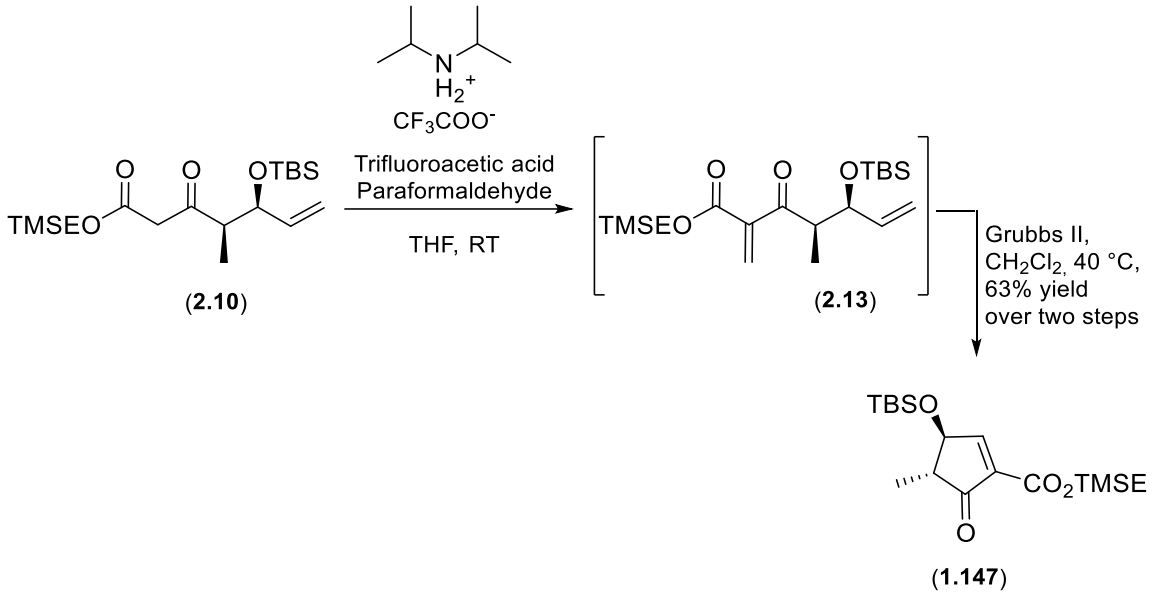
In order to install the trisubstituted alkene, a Knoevenagel condensation with acetaldehyde was performed. In the presence of titanium(IV) chloride, pyridine and acetaldehyde, *β*-ketoester **2.10** was transformed into RCM precursor **2.11** as a 1:1 mixture of diastereomers in excellent yield. Trisubstituted alkene **2.11** underwent RCM, promoted by Grubbs' second generation catalyst, to furnish the A-ring model **1.147** in 61% yield. RCM precursor with *tert*-butyl ester **2.12** (several grams of this product were available in the lab[35]) were submitted to the same conditions and A-ring model **1.148** was synthesised in 68% yield (Scheme 2.10).



Scheme 2.10: Synthesis of both models of the A-ring

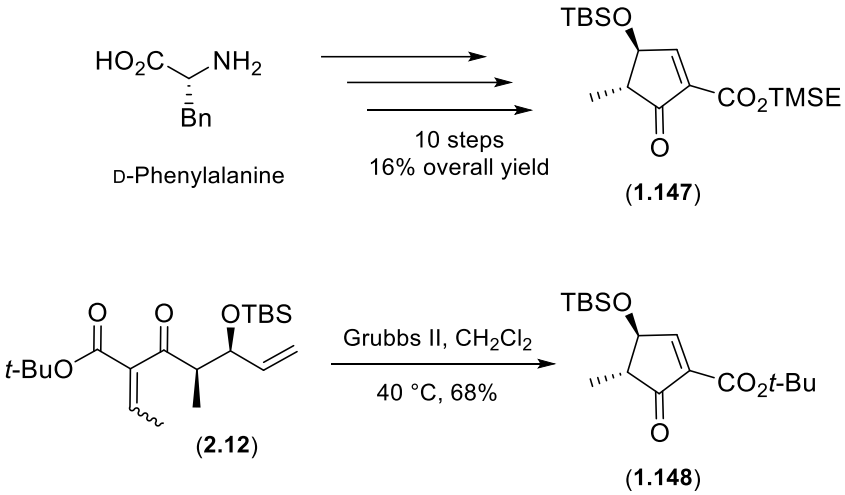
Despite furnishing both A-ring models, the RCM suffers from two limitations: moderate yields and important quantities of expensive catalyst used (7.0 to 10 mol%). These limitations are the results of steric and electronic factors. One of the alkenes being trisubstituted and doubly deactivated due to the conjugation with the two electron withdrawing groups, this problem could be circumvented by installing a *gem*-disubstituted alkene instead of a trisubstituted alkene to limit steric effects. A method developed for direct *α*-methylenation of carbonyls mediated by diisopropylammonium trifluoroacetate was applied to our substrate.[44] Attempts to purify the product only led to complete

decomposition, thus the crude product was used without purification in RCM step. The desired cyclopentene **1.147** was recovered in a comparable yield than the previous method (Scheme 2.11). Without a major increase of the overall yield and due to the difficulty to prepare the new precursor, it was decided to go back to the previously developed method, using the trisubstituted alkene.



Scheme 2.11: RCM with *gem*-disubstituted alkene

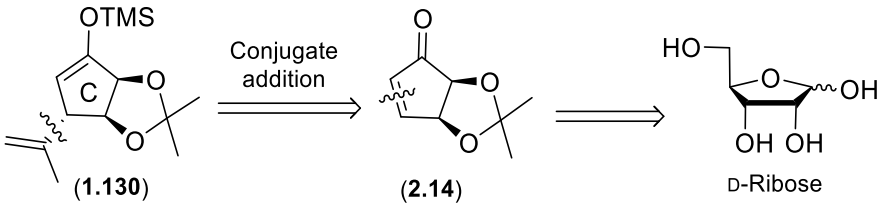
In summary, TMSE A-ring **1.147** was synthesised from D-Phenylalanine in 10 steps in 16% overall yield as a single diastereomer. *tert*-Butyl A-ring **1.148** was synthesised from the available RCM precursor **2.12** in 68% yield (Scheme 2.12).



Scheme 2.12: Formation of two different A rings

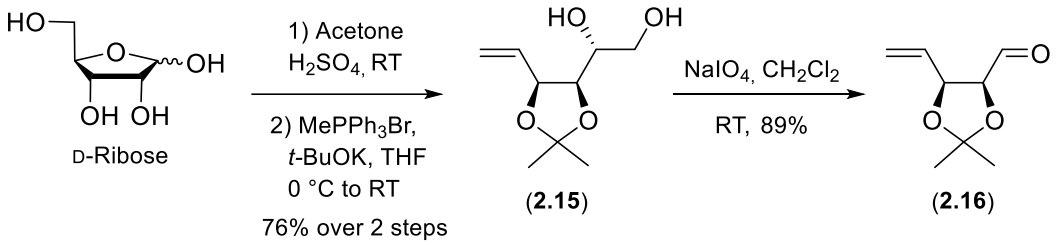
2.1.2 Synthesis of the C ring

Using a method developed in the group, the desired C-ring **1.130** could be formed by a conjugated addition from the known enone **2.14** (Scheme 2.13). [45]



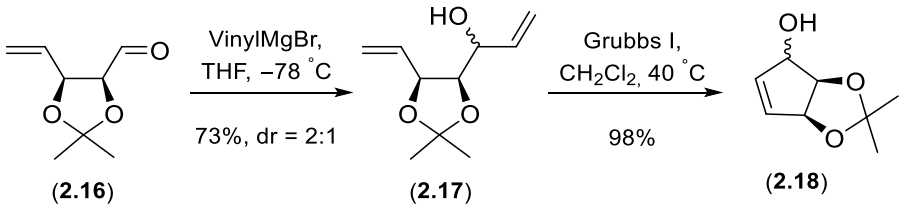
Scheme 2.13: Retrosynthesis of C-ring **1.130**

The synthesis of ketone **2.14** started, as described in the litterature, by the ketal protection of D-Ribose followed by Wittig methylenation to give diol **2.15** in 76% yield over 2 steps. Oxidative cleavage of compound **2.16** furnished the volatile aldehyde **2.16** in very good yield. The yield of this reaction was improved (50–60% to 89%) by the use of Pentane/Et_2O as a solvent system during the purification by flash chromatography (Scheme 2.14).



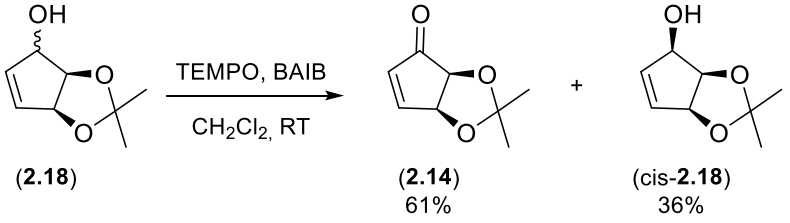
Scheme 2.14: Synthesis of volatile aldehyde **2.16** in 3 steps

Addition of vinylmagnesium bromide to aldehyde **2.16** gave allylic alcohol **2.17**, which was submitted to ring-closing metathesis in presence of Grubbs' first generation catalyst to provide cyclic alcohol **2.18** as a 2:1 mixture of diastereomers in near quantitative yield (Scheme 2.15).



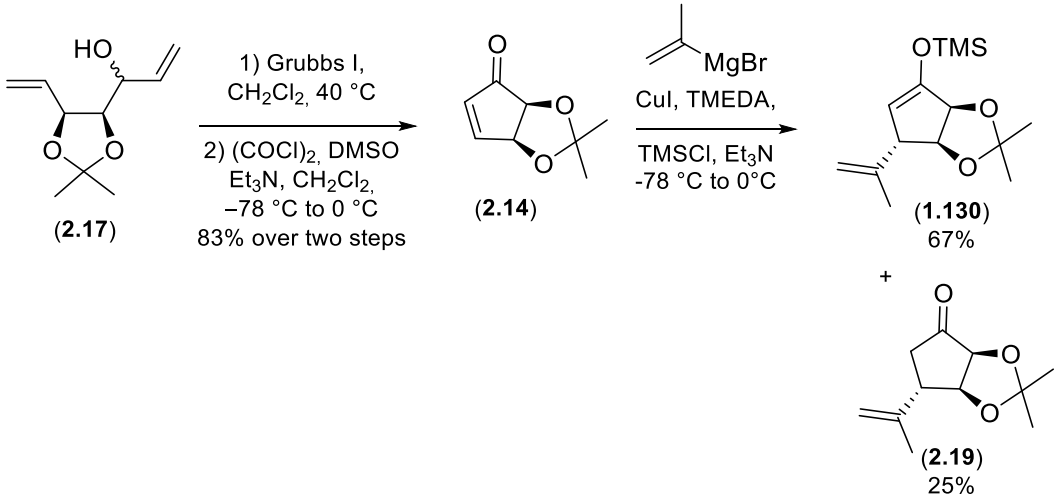
Scheme 2.15: Synthesis of cyclic allylic alcohol **2.18**

Product **2.18** was then submitted to a TEMPO/BAIB oxidation, where TEMPO is the primary oxidant and BAIB ((*bis*(acetoxy)iodo)benzene) the sacrificial or secondary oxidant. Surprisingly, a mixture of ketone **2.14** and starting material was recovered. It appeared that only the *trans* isomer reacted with TEMPO to give ketone **2.14**. This difference in reactivity is most likely due to the steric hindrance of the cyclic ketal, making the *cis* isomer cis-**2.18** less reactive (Scheme 2.16).



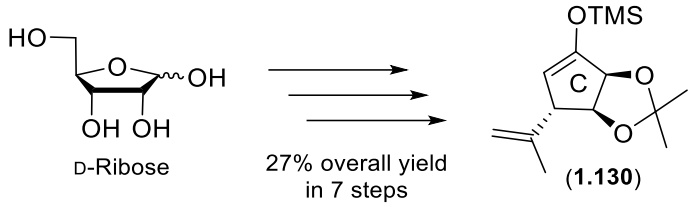
Scheme 2.16: Difference of reactivity between *cis*/*trans* isomers

Submitting acyclic alcohol **2.17** to RCM, followed by a Swern oxidation, provided cyclic ketone **2.14** in very good yield without any traces of unreacted *cis* isomer. The final step for the synthesis of the C-ring was a conjugated addition of isopropenyl magnesium bromide in the presence of copper(I) iodide and TMSCl to furnish silyl enol ether **1.130** and ketone **2.19** with complete stereocontrol. Instability of the silyl enol ether during the purification was limited by the use of an oven-dried silica. Ketone **2.19** can be be easily converted into corresponding silyl enol ether **1.130** in one step (Scheme 2.17).



Scheme 2.17: Production of silyl enol ether **1.130**

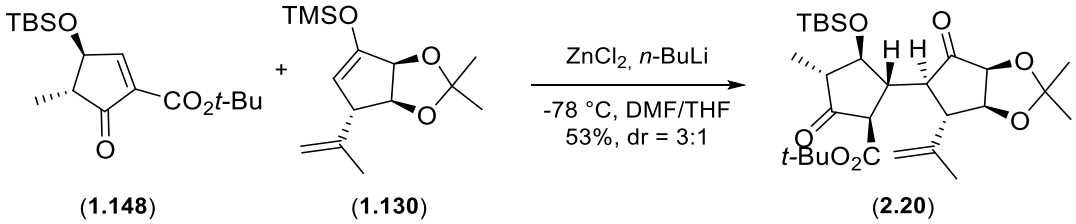
In summary, the C-ring model **1.130** was synthesised from D-Ribose in 27% overall yield over 7 steps, which is a net improvement compared to the previous synthesis (9% overall yield over 7 steps[35]) (Scheme 2.18).



Scheme 2.18: Summary of the synthesis of product **1.130**

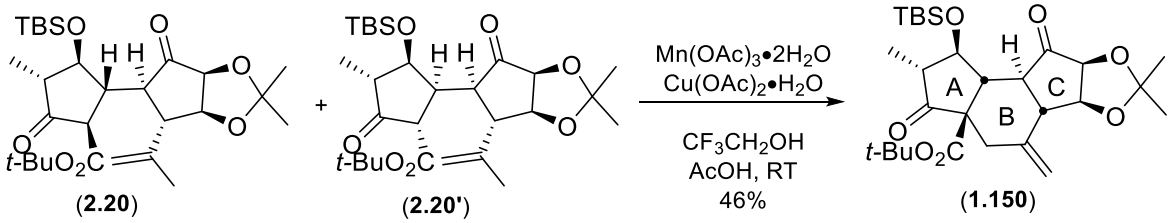
2.1.3 Formation of the ABC tricycle

With both precursors in hand, the next step of the project was a diastereoselective Michael reaction. Previous studies in the group had shown that both steric hindrance of the ester and the polarity of the solvent are paramount for the diastereoselectivity of this reaction.[33–36] Previous reaction with *tert*-butyl ester **1.148** in a 4:1 mixture of DMF/THF exhibited an excellent diastereoselectivity, leading to the synthesis of a single stereoisomer. Surprisingly, when this reaction was repeated, a mixture of two diastereomers with a 3:1 ratio in favor of the desired stereoisomer **2.21** was obtained. The reasons behind the decrease of the diastereoselectivity are unclear and need to be investigated (Scheme 2.19).



Scheme 2.19: Diastereoselective Michael addition

In order to close the B-ring, a Snider cyclisation was performed on the mixture of bicycles **2.20**/**2.20'**. Tricycle **1.150** was obtained in 46% yield and as a single diastereomer after radical cyclisation. The undesired diastereomer decomposed during the Snider cyclisation (Scheme 2.20).



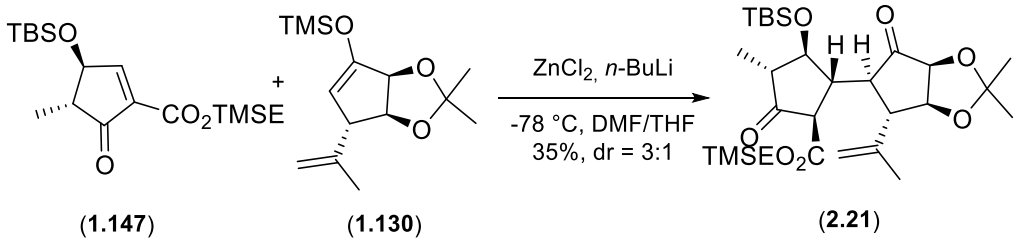
Scheme 2.20: Snider reaction on substrates **2.20**/**2.20**'

A few reaction conditions were then carried out for the cleavage of the *tert*-butyl ester. First of all, treatment with TFA only led to a mixture of starting material and decomposition products. Addition of triethylsilane acting as a cation scavenger to the previous conditions produced a mixture of starting material **1.150** and the TBS ether cleaved product. TMSOTf/2,6–lutidine are well-known conditions for the deprotection of *tert*-butyl esters, ethers and Boc protecting groups.[46] Additionaly, $CeCl_3$/NaI in CH_3CN is also a known method for selective deprotection of *tert*-butyl esters.[47] Both conditions were tested, however only starting material was recovered. Another attempt was made using $ZnBr_2$ in dichloromethane but unfortunately no *β*-ketoacid **2.1** was observed (Table 1.3).[48]

Conditions	Temperature	Results
CH_2Cl_2/TFA (10:1)	RT	SM/decomposition
CH_2Cl_2/TFA (10:1)/Et_3SiH	RT	SM/free hydroxyl (9:1)
TMSOTf/2,6–lutidine/dioxane	RT to 101 °C	SM
$CeCl_3$/NaI/CH_3CN	RT to 82 °C	SM
$ZnBr_2$/CH_2Cl_2	RT	SM

Table 1.3: Attempts for the formation of *β*-ketoacid **2.1**

Due to the unsuccessful formation of *β*-ketoacid **2.1** from *tert*-butyl ester **1.150**, it was then decided to synthesise the corresponding tricycle incorporating a TMSE ester. Previous attempts in the group to produce the bicycle with the TMSE ester moiety only furnished the desired product in very poor yield (<5%).[35] Pleasingly, when the diastereoselective Michael reaction between conjugated ketoester **1.147** and silyl enol ether **1.130** was repeated, bicycle **2.21** was obtained in 35% yield and as a 3:1 mixture of diastereomers (Scheme 2.21).

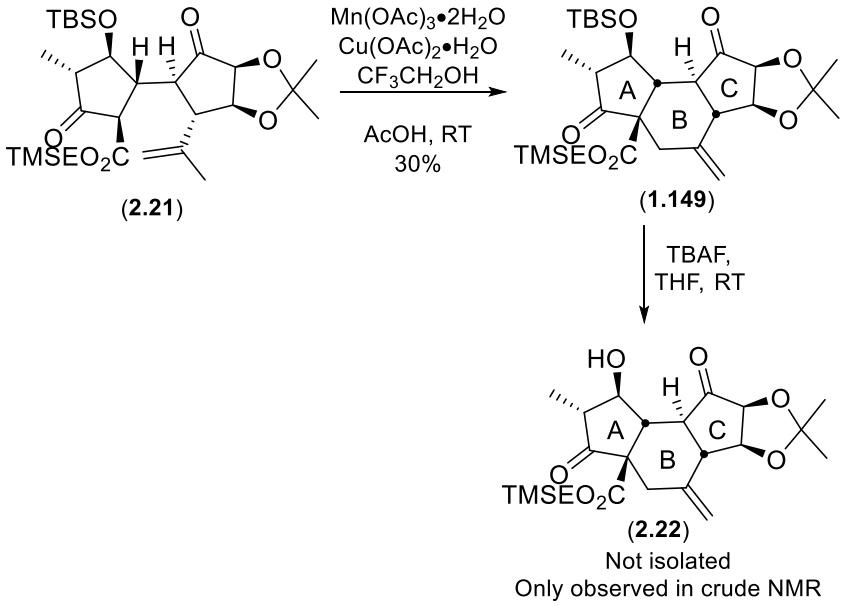


(**1.147**) (**1.130**) (**2.21**)

Scheme 2.21: Diastereoselective Michael reaction to furnish product **2.21**

Radical cyclisation of bicycle **2.21** gave the corresponding tricycle **1.149** in 30% yield and as a single diastereomer. An attempt to cleave the TMSE ester with TBAF was made but

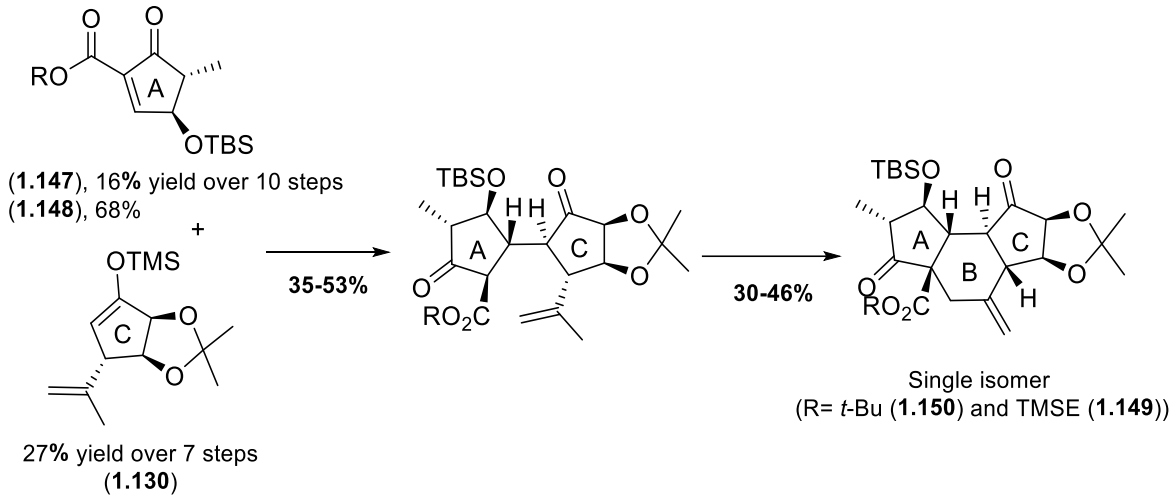
only the deprotected alcohol **2.22** was observed, without any evidence of the formation of the carboxylic acid **2.1** (Scheme 2.22).



Scheme 2.22: Formation of tricycle **1.149** and attempts of fluorolysis of TMSE ester

2.1.4 Conclusion and future work

Unfortunately, due to the production of small of quantities of tricycle **1.149**, no further attempts for the formation of carboxylic acid were made. The synthesis needs to be repeated with larger quantities of starting material. In conclusion, two ABC tricycles with different esters were generated: *tert*-butyl ester tricycle **1.150** was synthesised in 17% yield over 3 steps from available diene **2.12**; TMSE ester tricycle **1.149** was generated as a single diastereomer with an overall yield of 1.7% over 12 steps in the longest linear sequence (Scheme 2.23).

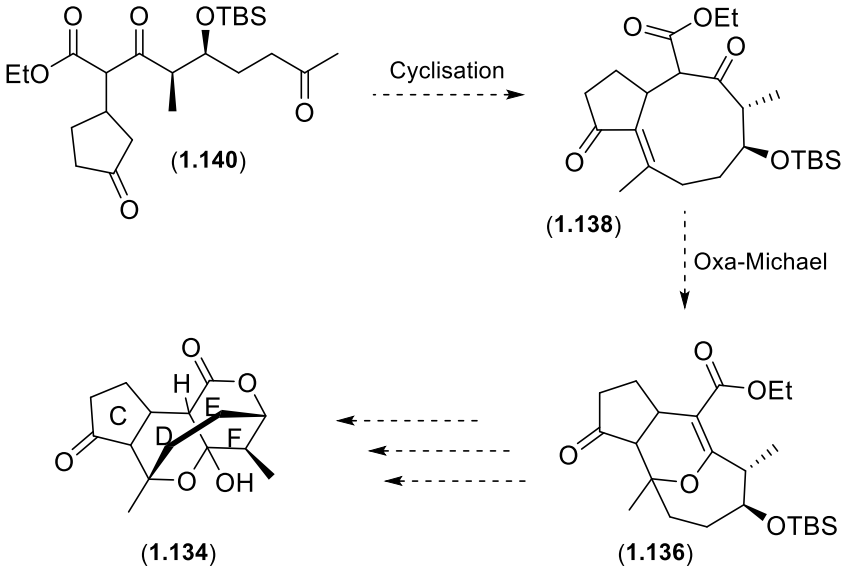


Scheme 2.23: Summary of the ABC tricycle syntheses

The ester cleavage/decarboxylation reaction has proven to be difficult. Further tests are necessary in order to continue the synthesis of the ABC tricycle **1.125**.

2.2 Synthesis of CDEF model

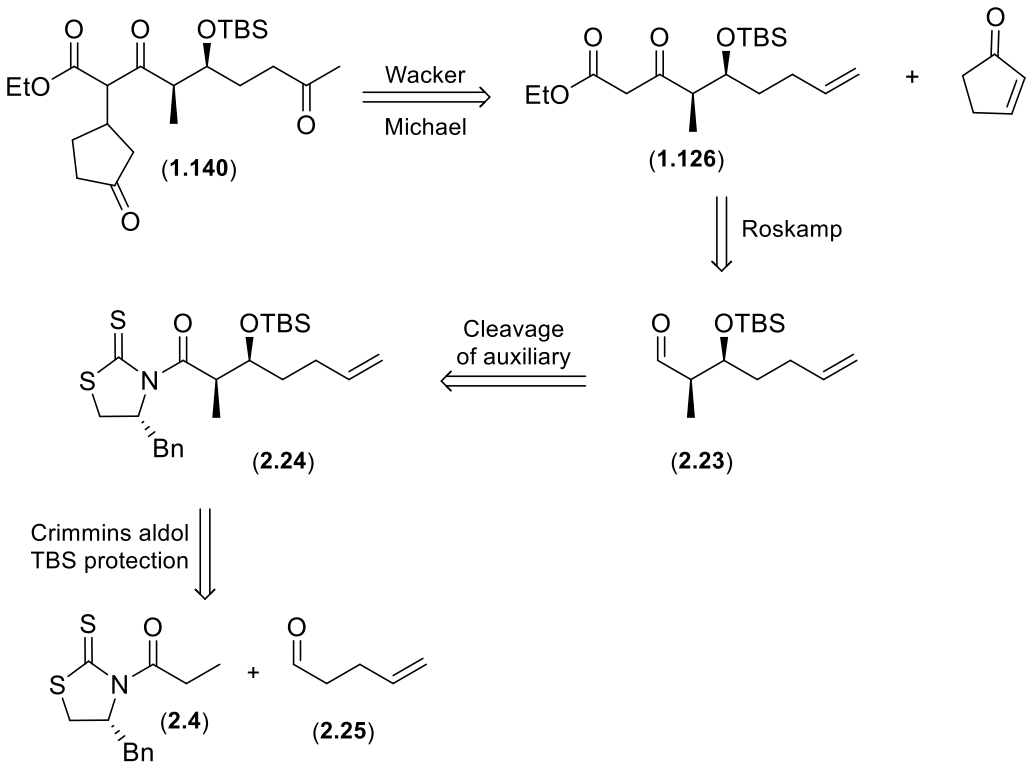
The CDEF model **1.134** could be obtained using a synthetic sequence with two key-steps: the closure of the nine-membered ring followed by an oxa-Michael reaction to give the CDF tricycle **1.136**. Our first efforts were first focused on the development of a method to produce the 5/9 bicycle **1.138** using cyclopentenone as an achiral model C-ring (Scheme 2.24).



Scheme 2.24: Key-steps for the synthesis of CDEF tetracycle **1.134**

2.2.1 Aldol pathway

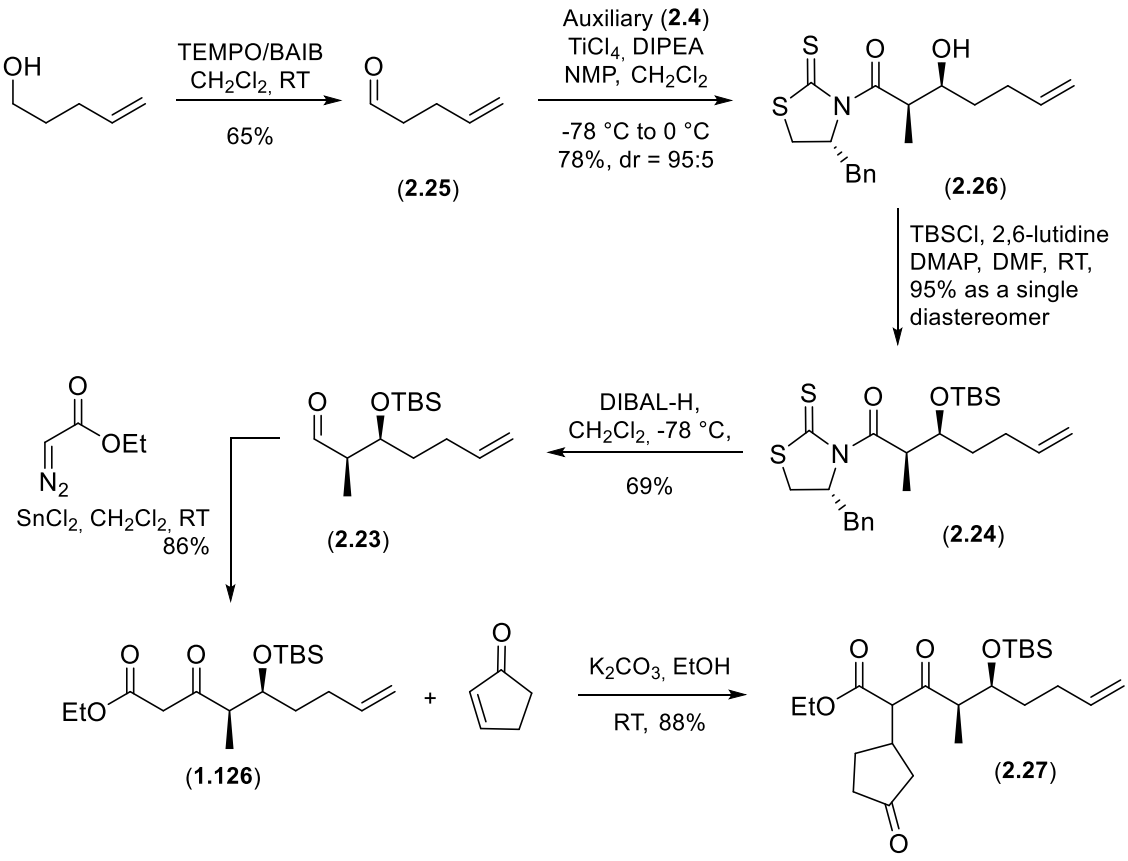
This part of the project started by repeating the work previously developed in the group.[35] The cyclisation precursor **1.140** would be formed by a Michael reaction between fragment **1.126** and cyclopentenone. Ketoester **1.126** could be produced by a Roskamp homologation from aldehyde **2.23**, which would be obtained by cleavage of the auxiliary in aldol **2.24**. Aldol **2.24** would be synthesised by a diastereoselective aldol reaction between the acylated Crimmins auxiliary **2.4** and 4-penten-1-al **2.25** (Scheme 2.25).



Scheme 2.25: Retrosynthesis of precursor **1.140**

4-Penten-1-al was previously synthesised in the group in 60% yield over two steps from glycidol.[35] This method was replaced by a TEMPO/BAIB oxidation of commercially available 4-penten-1-ol to furnish the corresponding aldehyde in 65% yield. 4-Penten-1-al reacted with compound **2.4** to furnish aldol **2.26**, which was then protected as a TBS ether in near quantitative yield. The two diastereomers were separated by flash chromatography as this stage. The protected aldol **2.24** was transformed into the corresponding aldehyde **2.23** by reductive cleavage using DIBAL-H. Aldehyde **2.23** was then submitted to a Roskamp homologation in the presence of ethyl diazoacetate (ethyl diazoacetate was synthesised from ethyl acetoacetate and *p*-ABSA in 51% yield over one step)[49] to give the corresponding ethyl *β*-ketoester **1.126** as a single diastereomer in 26% yield over five steps. The next step was a Michael addition between *β*-ketoester **1.126** and cyclopentenone. Michael reactions

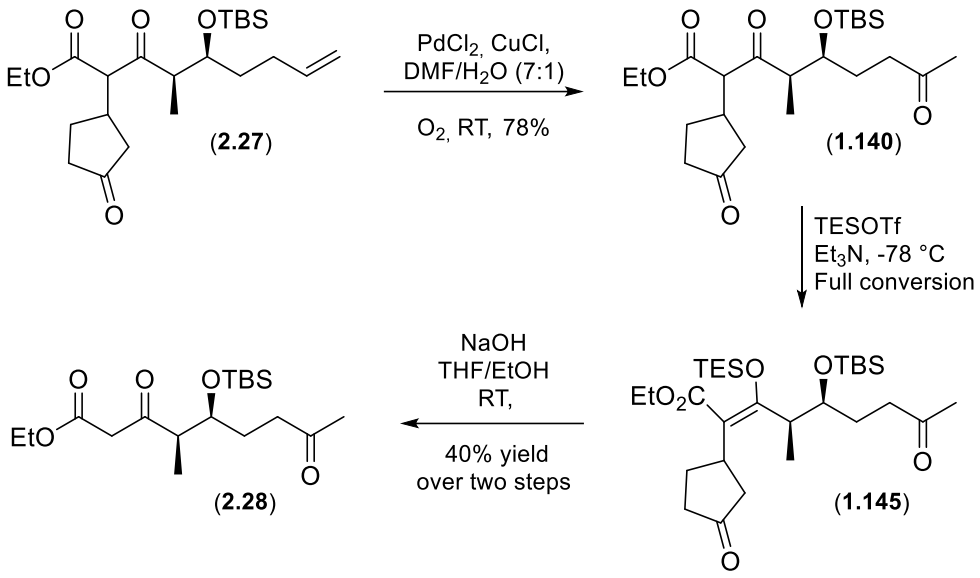
carried out previously in the lab with potassium carbonate usually needed 1.5 equivalents of *β*-ketoester **1.126** and appeared to be difficult to reproduce (7 to 40% yield). Fortunately, after further optimisations, the Michael addition delivered product **2.27** as a mixture of four diastereisomers in a very good yield, using a reasonable amount of fragment **1.126** (1.1 equiv). The order of addition of the reagents was crucial for total conversion of **1.126** (*β*-ketoester/cyclopentenone then catalytic amount of K_2CO_3) (Scheme 2.26).



Scheme 2.26: Synthesis of Wacker oxidation precursor **2.27**

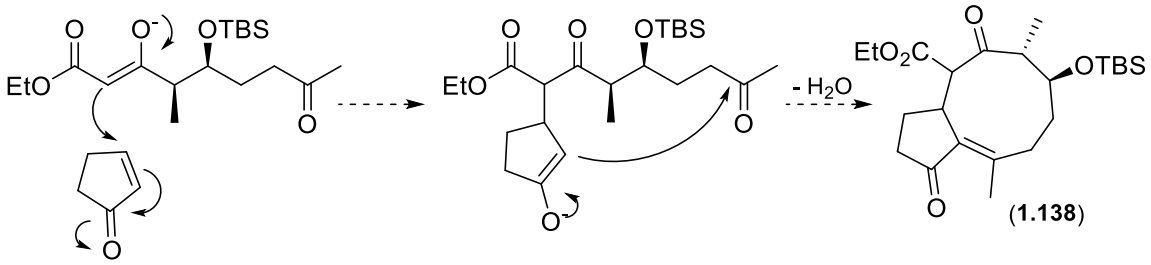
A Wacker oxidation was carried out to transform the terminal alkene into the corresponding ketone. In the presence of $PdCl_2$, CuCl in DMF/H_2O under oxygen atmosphere, product **2.27** was converted into the corresponding ketone **1.140** in 78% yield. Protection of the *β*-ketoester with triethylsilyl trifluoromethanesulfonate at very low temperature led to the formation of the silyl enol ether **1.145**. Due to its instability, compound **1.145** was not purified and used directly in the next step. The geometry of the silyl enol ether was not determined by NMR; it has been previously reported in the literature that treatment of *β*-ketoesters under kinetic conditions led exclusively to of the *Z* silyl enol ethers.[50,51] Different conditions for the formation of the nine-membered ring were attempted; sodium hydroxide in a diluted mixture of THF/EtOH were the only one to give interesting results. Unfortunately, formation of the nine-membered ring was not observed but product **2.28** was obtained in 40% yield.

Generation of compound **2.28** was more likely the result of a retro Michael reaction (Scheme 2.27).



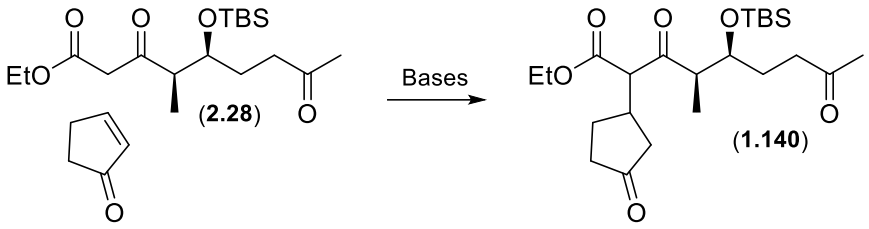
Scheme 2.27: Formation of silyl enol ether **1.145** and retro Michael product **2.28**

Another approach was envisaged, using the retro Michael product **2.28** as a cyclisation precursor in a Michael aldol cascade. First of all, a Michael reaction between **2.28** and cyclopentenone would occur, leading to the formation of the desired enolate. Secondly, this enolate would react in an aldol reaction followed by crotonisation and formation of the nine-membered ring **1.138** (Scheme 2.28).



Scheme 2.28: Mechanism of the envisaged cascade

Different bases (*t*-BuOK, NaH, DBU) were tried, but all of them gave the adduct **1.140** without any traces of nine-membered ring (Scheme 2.29).

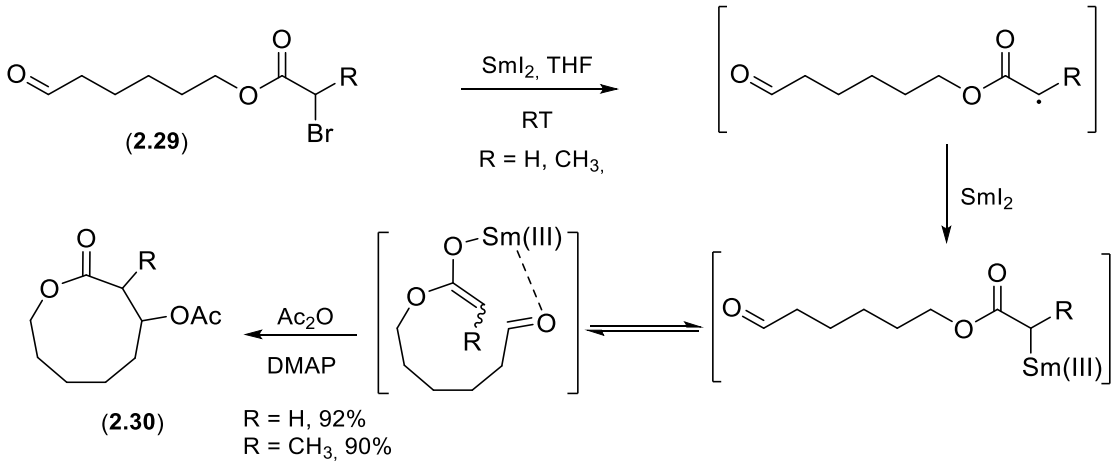


Scheme 2.29: Michael addition between product **2.28** and cyclopentenone

When product **1.140** was directly treated with a base, retro-Michael compound **2.30** was obtained. Due to the aldol pathway being unsuccessful, it was decided to try a new approach for the formation of nine-membered ring **1.138**

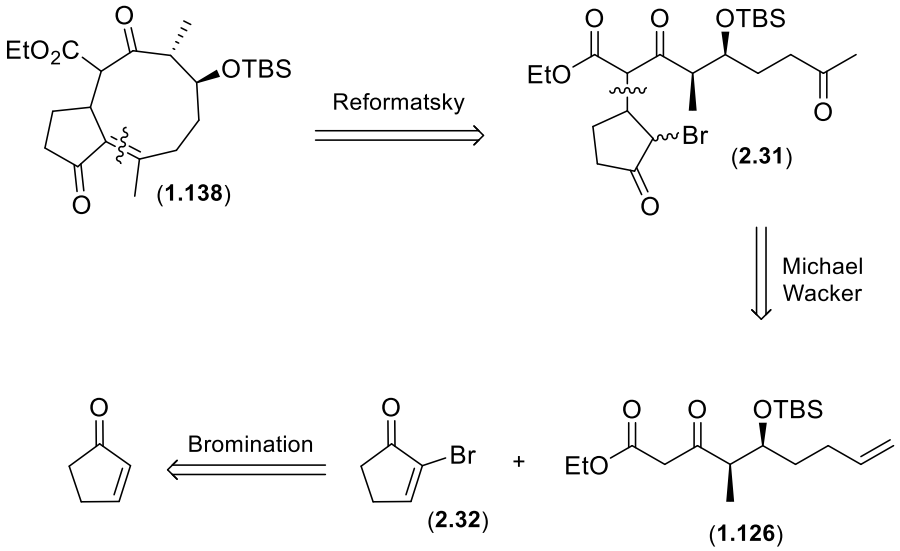
2.2.2 Reformatsky pathway

The Reformatsky reaction is a method where *α*-halo esters react with aldehydes and ketones using different metals, such as zinc or samarium, to produce *β*-hydroxy esters. Formation of medium-size rings and in particular nine-membered rings using the Reformatsky reaction has been previously described in the literature.[52] Inanaga *et al.* published a method to obtain medium- and large-size lactones from *α*-bromo ester with the aid of samarium(II) iodide. The mechanism for the formation of a nine-membered lactone is described below: *α*-bromo ester **2.29** containing an aldehyde moiety at the end of the linear chain reacted with SmI_2 in a single electron transfer to form a radical in the *α* position of the ester. This radical was reduced by another equivalent of SmI_2 to furnish a samarium enolate, which attacked the aldehyde to give the corresponding *β*-hydroxy lactone. The *β*-hydroxy lactone was converted into the corresponding *β*-acetate lactone **2.30** for easier purification (Scheme 2.30).



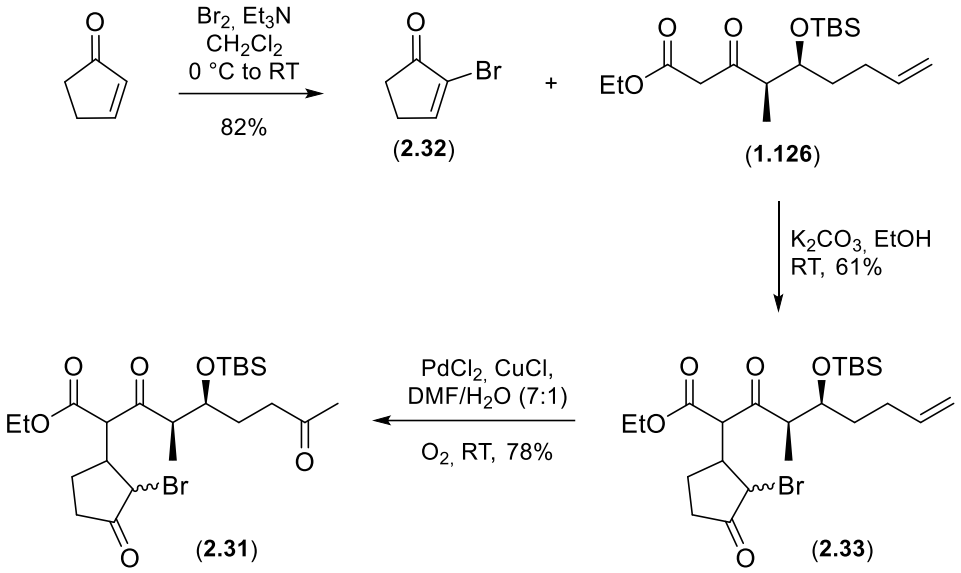
Scheme 2.30: Reformatsky reaction applied to the formation of nine-membered lactone

A Reformatsky reaction to close the desired nine-membered ring **1.138** from *α*-bromo ketone **2.31** was envisaged. *α*-Bromo ketone **2.31** could be obtained by a Wacker oxidation and a Michael addition between fragment **1.126** and bromocyclopentenone **2.32**. Bromocyclopentenone **2.32** would be synthesised from the commercially available cyclopentenone (Scheme 2.31).



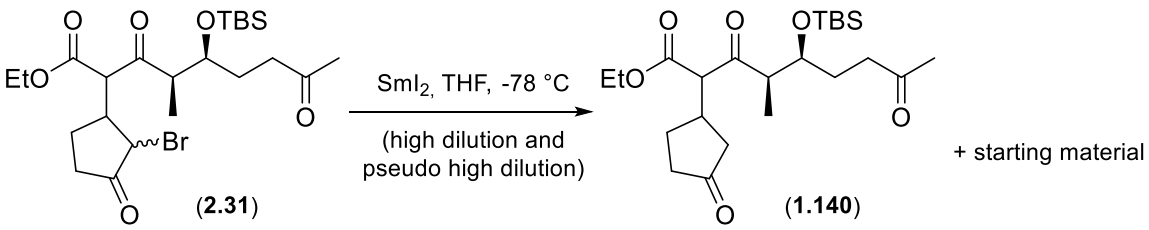
Scheme 2.31: Retrosynthesis of the Reformatsky pathway

Bromocyclopentenone **2.32** was obtained from cyclopentenone in the presence of bromine and triethylamine in 82% yield. Michael reaction between ketoester **1.126** and bromocyclopentenone **2.32** furnished compound **2.33** in good yield. The slight decrease of yield between the Michael reaction with cyclopentenone and bromocyclopentenone **2.32** is probably due to a more acidic proton in the case of the bromoketone. This pKa difference probably slows down the reprotonation step and increases the amount of retro-Michael reaction. The next step was a Wacker oxidation to give Reformatsky precursor **2.31** in very good yield (Scheme 2.32).



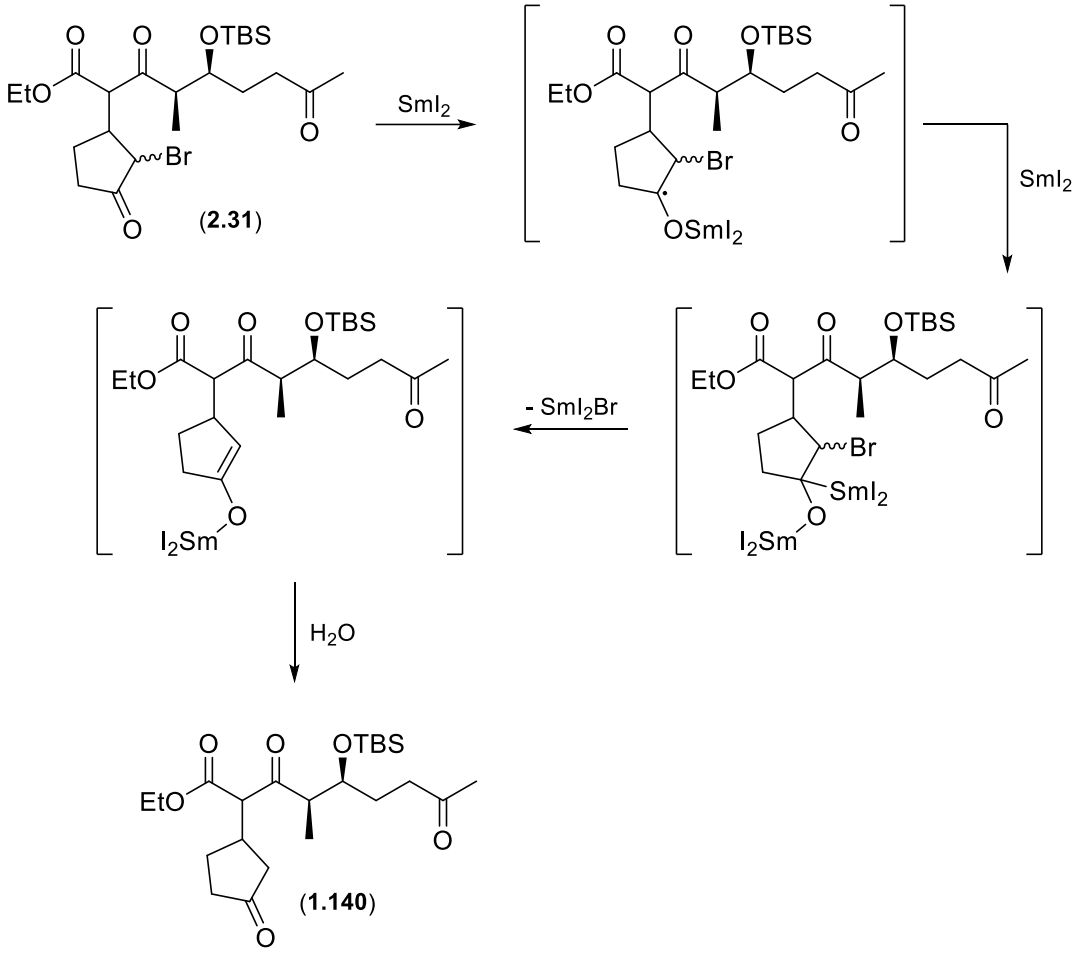
Scheme 2.32: Formation of Reformatsky precursor **2.31**

Samarium-promoted Reformatsky reaction was then attempted. A solution of samarium(II) iodide was prepared by addition of 1,2-diiodoethane to samarium powder, followed by slow addition (pseudo high-dilution) of product **2.31**. Unfortunately, the reaction only gave a mixture of starting material and reduced product **1.140** (Scheme 2.33).



Scheme 2.33: Samarium-promoted Reformatsky

Other conditions were tested, such as $Zn/CeCl_3.7H_2O$ and $SnCl_2/LiAlH_4$.[53,54] Only the starting material was recovered in both cases. Previous experiments with SmI_2 have shown that the *α*-bromo ketone could be reduced to the corresponding ketone, via a radical intermediate (Scheme 2.34).

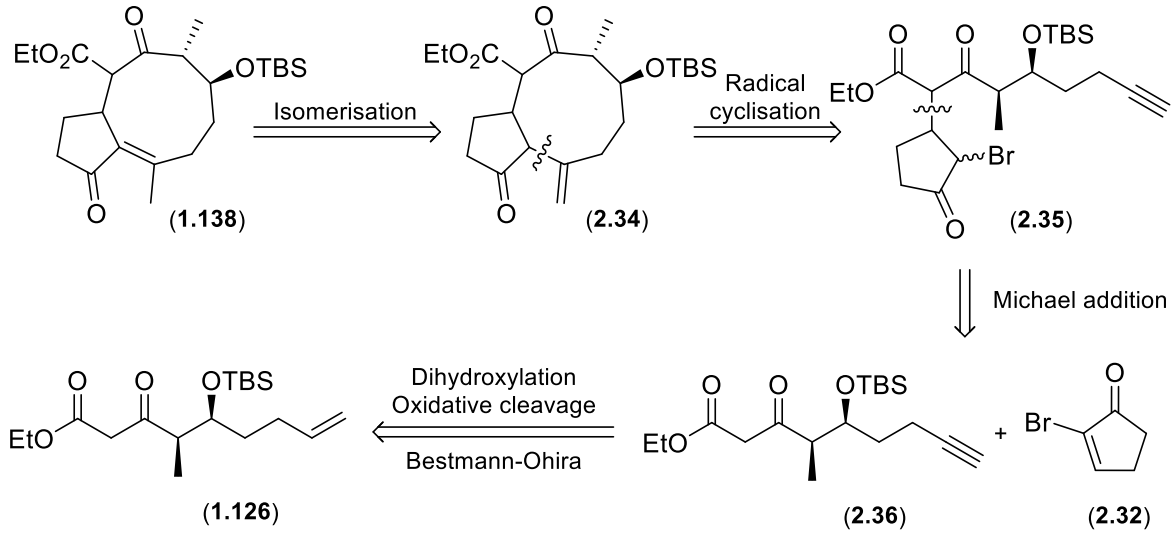


Scheme 2.34: Mechanism for the formation of the reduced bromo ketone

In light of these results, it was decided to change the synthetic pathway and to use the radical intermediate in the cyclisation step.

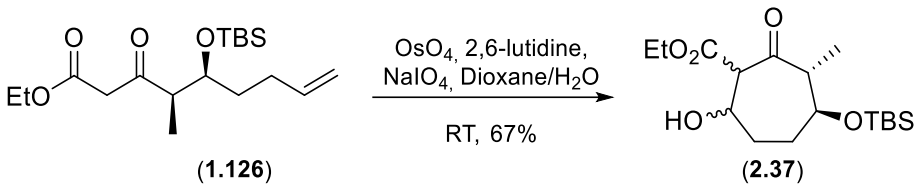
2.2.3 Radical pathway

A new synthetic approach was then considered which involves using an alkyne instead of a ketone. Nine-membered ring **1.138** could be obtained by isomerisation of the alkene from product **2.34**, which would be synthesised by radical cyclisation from product **2.35**. Compound **2.35** could be obtained by a Michael reaction between previously synthesised bromoketone **2.32** and alkyne **2.36**. Alkyne **2.36** could be formed by a dihydroxylation/oxidative cleavage of the alkene from fragment **1.126** followed by a Bestmann-Ohira reaction of the resulting aldehyde (Scheme 2.35).



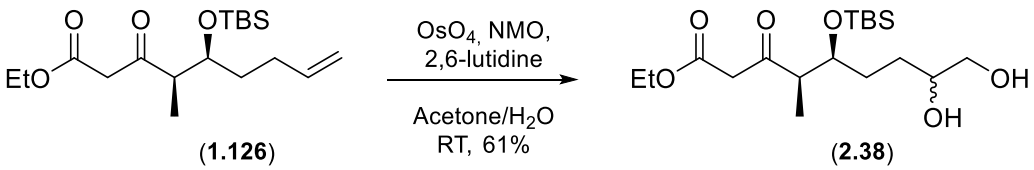
Scheme 2.35: Proposed radical cyclisation route

In order to test this radical cyclisation, transformation of alkene **1.126** into the corresponding alkyne **2.36** was attempted. Surprisingly, when alkene **1.126** was submitted to a one-pot dihydroxylation/oxidative cleavage, instead of obtaining the desired aldehyde, only the cyclic aldol **2.37** was produced (Scheme 2.36).[55]



Scheme 2.36: One-pot dihydroxylation/oxidative cleavage

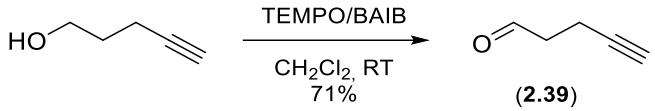
It was decided to investigate and determine which step was responsible for the formation of the undesired seven-membered ring. Isolation of diol **2.38** after an Upjohn dihydroxylation was successful (Scheme 2.37)



Scheme 2.37: Upjohn dihydroxylation

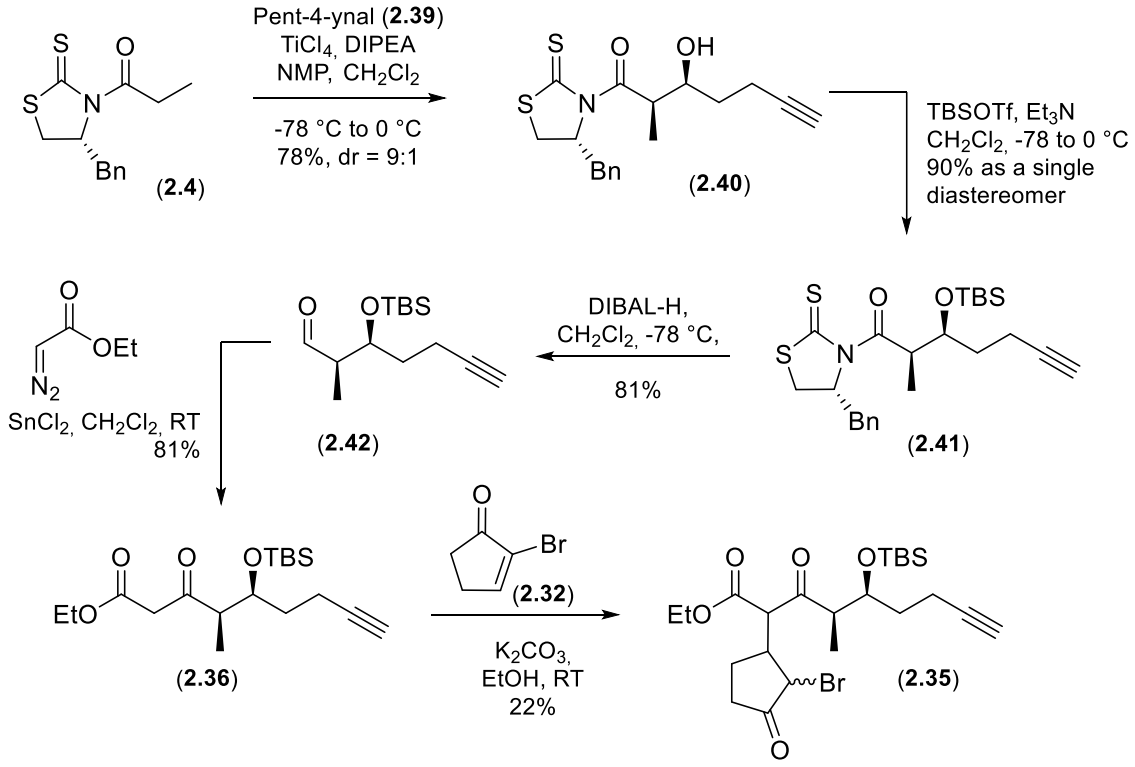
Attempts to cleave diol **2.38** using BAIB or $Pb(OAc)_4$ only led to the formation of cyclic aldol **2.37**.[56,57] Ozonolysis of alkene **1.126** also produced undesired aldol **2.37**. It was then decided to start the synthesis of ester **2.36** by a Crimmins aldol reaction using 4-pentyn-1-

al **2.39**. Aldehyde **2.39** was obtained from the 4-pentyn-1-ol by a TEMPO/BAIB oxidation (Scheme 2.38).



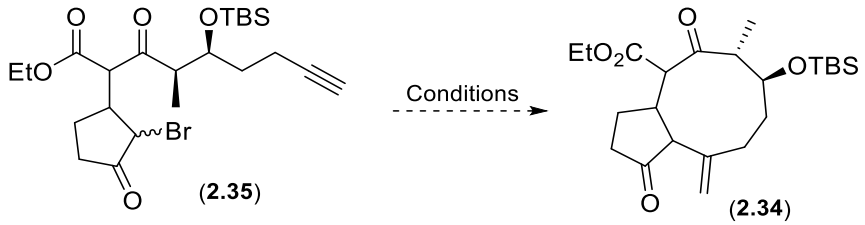
Scheme 2.38: Oxidation of 4-pentyn-1-ol

Diastereoselective Crimmins reaction gave aldol **2.40** in very good yield and diastereomeric ratio. Aldol protection proceeded this time in the presence of TBSOTf and Et_3N to furnish TBS ether **2.41** as a single diastereomer in 90% yield. This new protection method reduced the reaction time (3 days with TBSCl, 2 hours with TBSOTf). Cleavage of the Crimmins auxiliary with DIBAL-H yielded aldehyde **2.42** and Roskamp homologation of aldehyde **2.42** furnished *β*-ketoester **2.36** in very good yield for both steps. Michael reaction between *β*-ketoester **2.36** and bromocyclopentenone **2.32** furnished product **2.35** as a mixture of 8 diastereomers in 10% overall yield over 5 steps. The moderate overall yield is mainly due to the Michael addition step where most of the starting material was left unreacted (Scheme 2.39).



Scheme 2.39: Synthesis of radical cyclisation precursor **2.35**

The cyclisation tests carried out using different conditions are summarised below (Table 2.1).

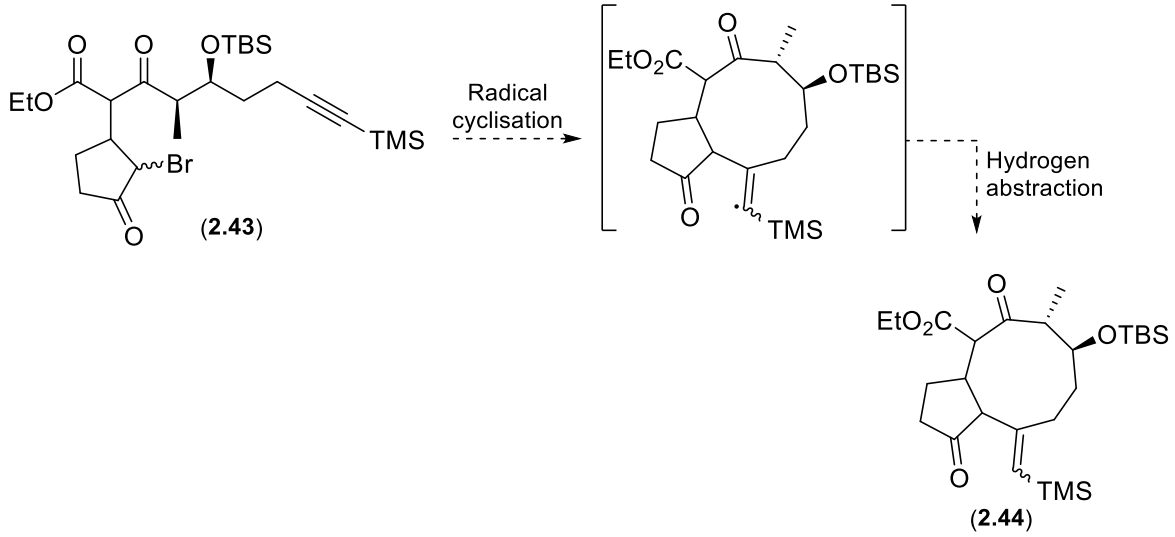


Reagents	Temperature	Addition	Result
Indium(I) iodide, Sonication,CH_3CN[58]	40 °C	Normal	Starting material
TTMSS, ACCN, Benzene	80 °C	Normal	Starting material + reduced product
TTMSS, ACCN, Benzene	80 °C	Slow	Starting material
Bu_3SnH, ACCN, Benzene	80 °C	Normal	Starting material + reduced product
Bu_3SnH, ACCN, Benzene	80 °C	Slow	Starting material + mixture of products

Table 2.1: Conditions for the radical cyclisation

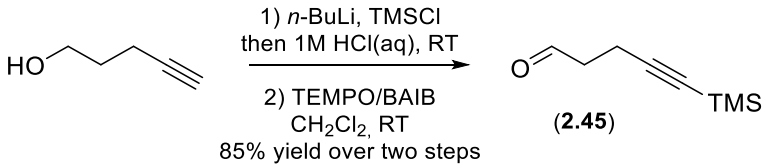
Only tributyltin hydride with ACCN (1,1′-Azo*bis*(cyclohexanecarbonitrile)) as an initiator added very slowly gave interesting results. A mixture of products was obtained, and high resolution mass spectroscopy suggested formation of the desired cyclisation product. Due to the very small quantity of material being obtained, consisting of a complex mixture of diastereomers and a possible mixture of nine- and ten-membered rings, full characterisation was not possible. When this reaction was carried on larger scale the same products were not observed. Unfortunately, this reaction proved to be irreproducible.

It was then decided to modify the route and use the TMS-protected alkyne **2.43**. The TMS group has been shown to stabilise radicals at the *α*-position.[59] The presence of the TMS group should increase the stability of the vinyl radical but also direct the cyclisation to a 9-*exo* dig instead of 10-*endo* dig cyclisation (Scheme 2.40).



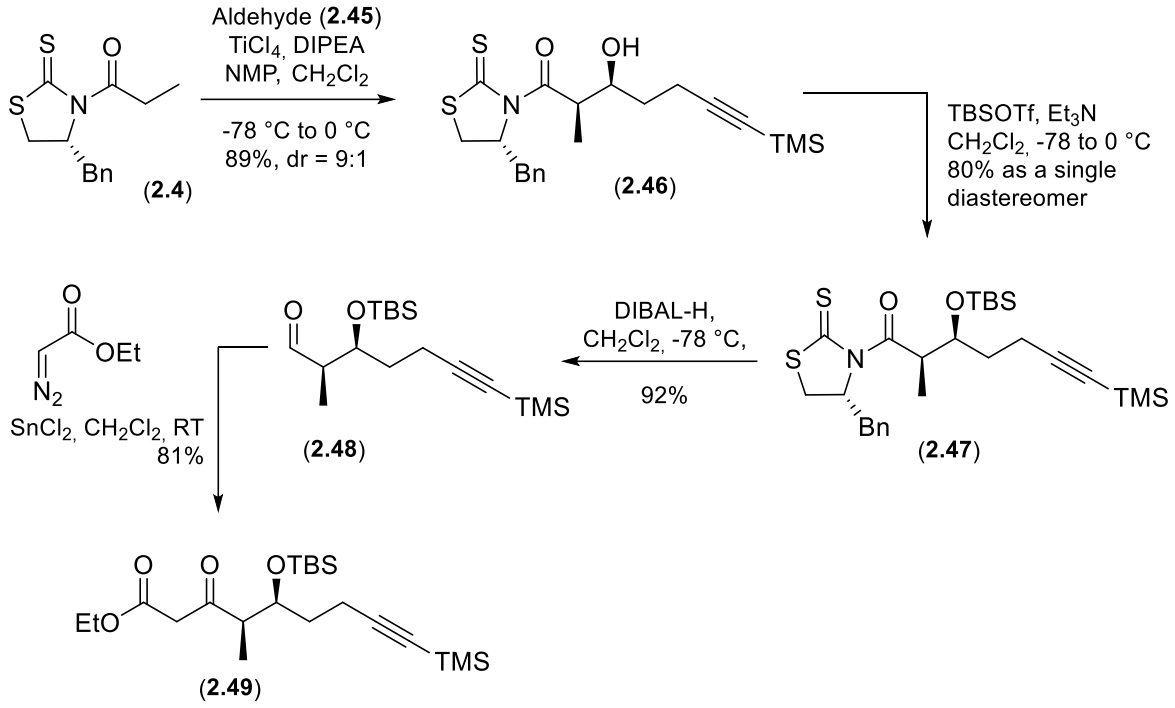
Scheme 2.40: Proposed radical cyclisation with TMS-protected alkyne **2.44**

The coupling partner **2.45** for the Crimmins aldol reaction was synthesised from 4-pentyn-1-ol starting with the addition of *n*-BuLi to deprotonate both alcohol and alkyne. Both positions were silylated by addition of TMSCl then the TMS ether was selectively cleaved by addition of a 1M aqueous solution of HCl. The free alcohol was finally oxidised by a mixture of TEMPO/BAIB to furnish aldehyde **2.45** in excellent yield over 2 steps (Scheme 2.41).



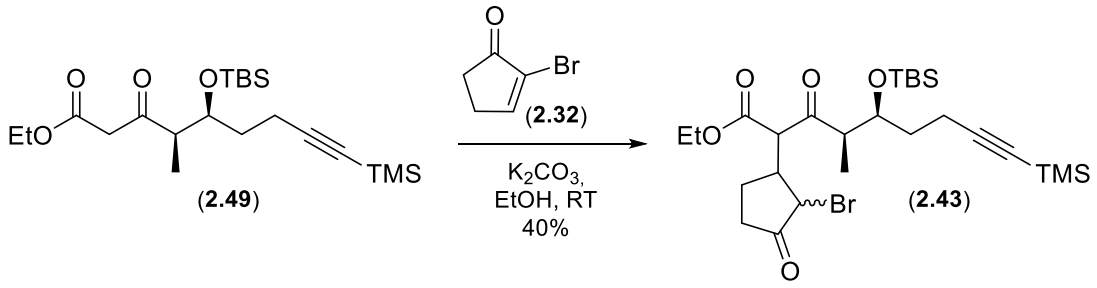
Scheme 2.41: Synthesis of aldol partner **2.45**

Diastereoselective aldol reaction between chiral auxiliary **2.7** and TMS-protected 4-pentyn-1-al **2.45** gave aldol **2.46** in excellent yield and with a good diastereomeric ratio. Formation of TBS ether using TBSOTf gave protected aldol **2.47** as a single diastereomer in 80% yield. Cleavage of the Crimmins auxiliary produced aldehyde **2.48** in excellent yield. The cleavage step was followed by a Roskamp homologation to furnish *β*-ketoester **2.49** as a single diastereomer in 45% yield over 6 steps from 4-pentyn-1-ol (Scheme 2.42).



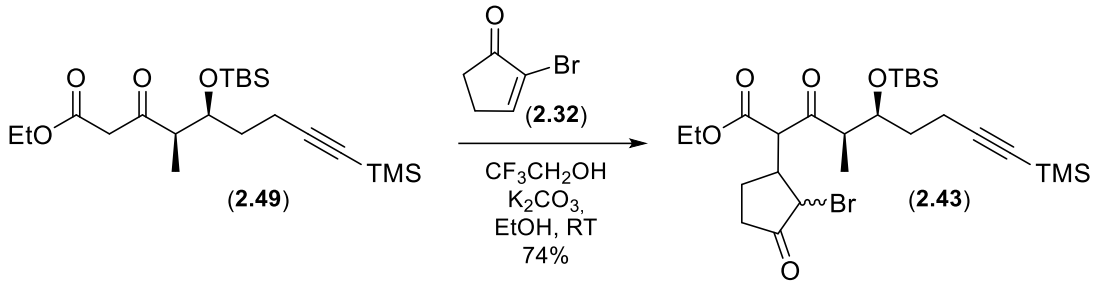
Scheme 2.42: Synthesis of *β*-ketoester **2.49**

Michael addition between *β*-ketoester **2.49** and bromocyclopentenone **2.32** furnished radical cyclisation precursor **2.43** in moderate yield. A part of the starting material was left unreacted (Scheme 2.43).



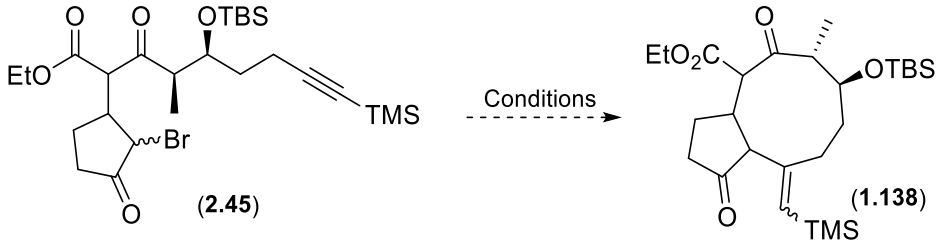
Scheme 2.43: Formation of cyclisation precursor **2.43**

The decrease in yield for the previous Michael addition in the presence of bromocyclopentenone **2.32** was not acceptable; as previously stated, it was believed that this decrease was more likely due to a more acidic proton at the *α*-position of the ester and bromide. This problem could be solved by addition of a cosolvent with a lower pKa, which would accelerate the protonation of the intermediary enolate and avoid a retro-Michael reaction. This theory was later confirmed; addition of one equivalent of trifluorethanol led to the formation of product **2.43** in 74% yield (Scheme 2.44).



Scheme 2.44: Increase of yield by addition of trifluroethanol

With precursor **2.43** in hand, the radical cyclisation was investigated. The previous conditions used with unprotected alkyne were tested on compound **1.138** (Table 2.2).



Reagents	Temperature	Addition	Result
Bu_3SnH, ACCN, Benzene	80 °C	Normal	Starting material
Bu_3SnH, ACCN, Benzene	80 °C	Slow	Starting material
TTMSS, ACCN, Benzene	80 °C	Slow	Starting material + reduced product

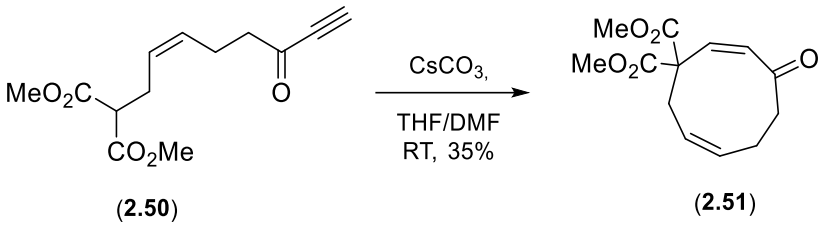
Table 2.2: Increase of yield by addition of trifluroethanol

Unfortunately, only the starting material and traces of the reduced product were observed. With the radical pathway being unsuccessful, it was decided to investigate another synthetic route.

2.2.4 Michael-Isomerisation pathway

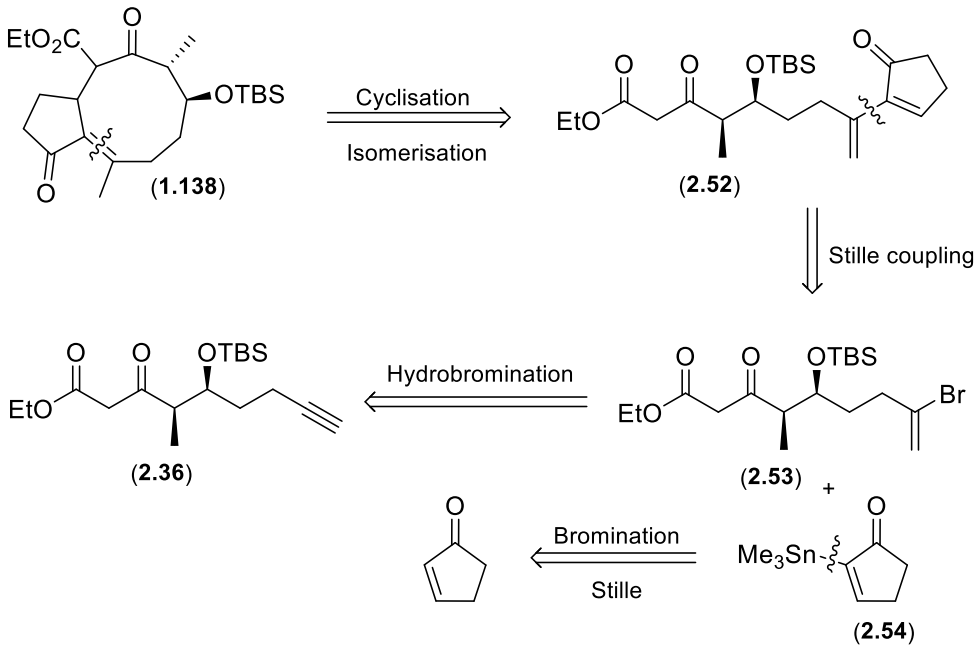
After these disappointing results, another approach was envisaged. In 1986, Deslongchamps and Roy published a synthetic method to produce nine- and ten-membered rings by intramolecular Michael addition of malonate to enones and ynones.[60] The publication showed some interesting results, with the formation of medium size rings in 25–50% yield. One substrate caught our attention: ynone **2.50** was submitted to Michael

addition conditions in the presence of caesium carbonate in a THF/DMF mixture; the result was the formation of nine-membered ring **2.51** in an acceptable 35% yield (Scheme 2.45).



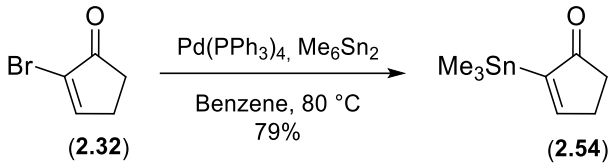
Scheme 2.45: Intramolecular Michael addition

Based on these results, a new retrosynthesis was designed, where the key step would be an intramolecular Michael addition. The nine-membered ring **1.138** could be synthesised by an intramolecular Michael reaction and isomerisation of the double bond from compound **2.52**, which could be prepared by a Stille coupling between bromo alkene **2.53** and *α*-stannylated ketone **2.54**. Bromo alkene **2.53** could be synthesised by selective hydrobromination of alkyne **2.36** and *α*-stannylated ketone **2.54** by bromination Stille coupling of the conjugated double bond of the commercially available cyclopentenone (Scheme 2.46).



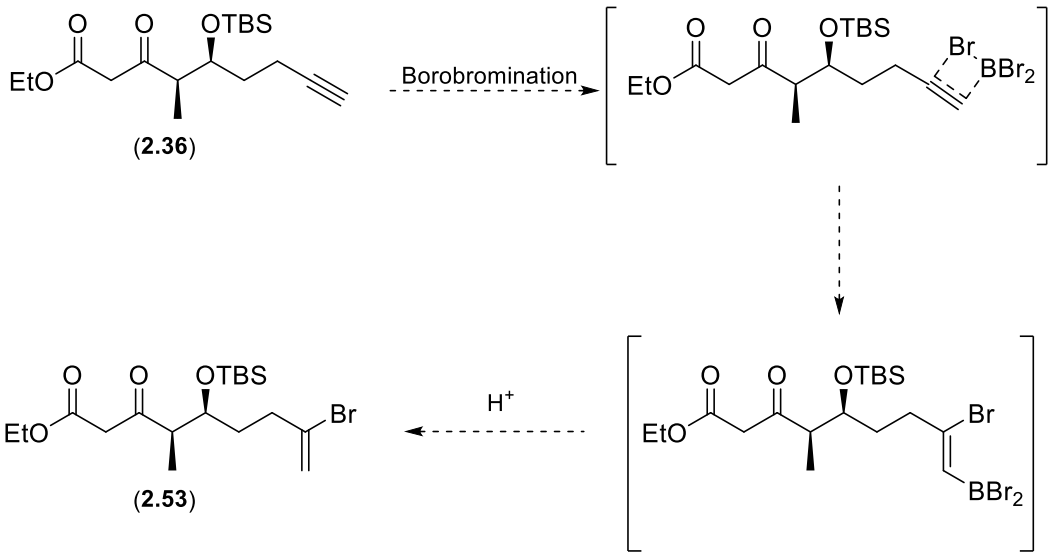
Scheme 2.46: Retrosynthesis for Michael-isomerisation route

The previously synthesised bromoketone **2.32** was submitted to $Pd(PPh_3)_4$ and hexamethyldistannane to give the Stille coupling partner **2.54** in 79% yield (Scheme 2.47).



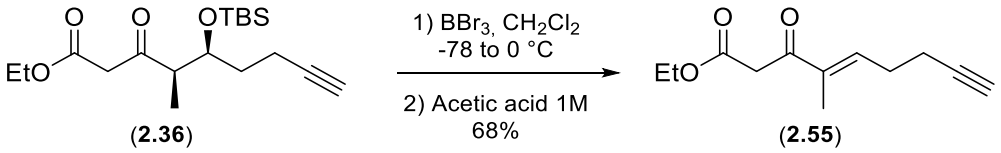
Scheme 2.47: Synthesis of the Stille coupling partner **2.54**

With the stannylated ketone **2.54** in hand, synthesis of the bromo alkene **2.53** was investigated. Conditions for the selective bromination of the alkyne **2.36** to form the *α* isomer were tested. The first try involved boron tribromide followed by addition of acetic acid. The first step of this reaction would be a borobromination of the alkyne followed by protonolysis of the boron to furnish expected bromo alkene product **2.53**.[61] Due to electronic effects, the boron is most likely to attack on the terminal position leading to the desired isomer (Scheme 2.48).



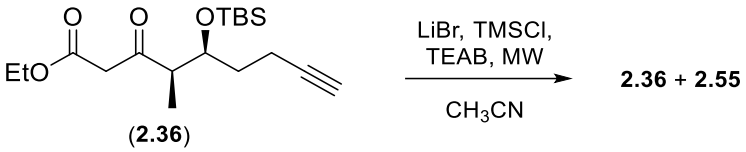
Scheme 2.48: Proposed mechanism for the formation of bromo alkene **2.53**

When alkyne **2.36** was submitted to boron tribromide and acetic acid, only the elimination product **2.55** was observed. This is most likely due to the strong acidic conditions and to the formation of a stable, conjuguated product (Scheme 2.49).



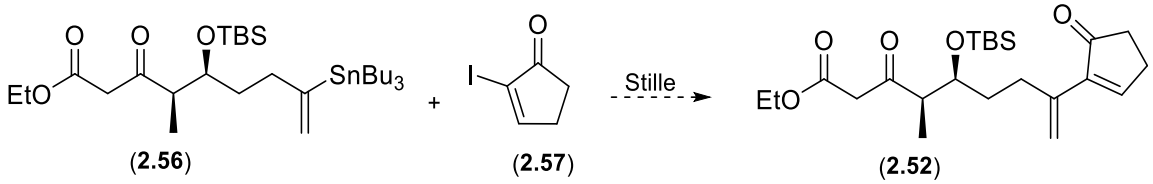
Scheme 2.49: Formation of conjugated alkene **2.55**

Reaction with LiBr, TMSCl and tetraethylammonium bromide in acetonitrile under microwave activation is known to be an efficient way to brominate alkynes.[62] When applied to our substrate, a mixture of starting material and conjuguated alkene **2.55** was recovered (Scheme 2.50).



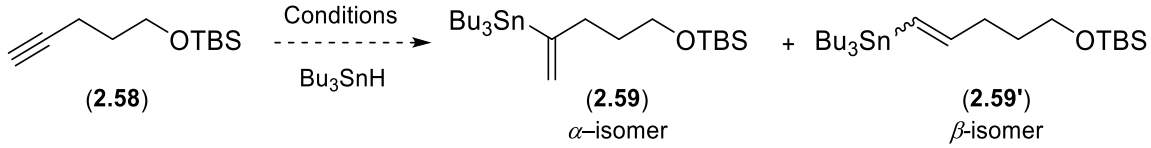
Scheme 2.50: Microwave assisted bromination

The synthetic strategy was modified. It was then decided to swap Stille coupling partners. Iodocyclopentenone **2.57** was easily prepared; the next step was to synthesise the *α*-stannylated alkene **2.56** (Scheme 2.51).



Scheme 2.51: Envisaged Stille coupling

It was first decided to try different methods of hydrostannation on a model alkyne, TBS-protected pent-4-ynol **2.58**, in order to optimise the ratio of *α*/*β* isomers.[63] Three different catalysts were tested in the presence of Bu_3SnH and the results are described below (Table 2.3).[64–66]



Catalyst	Mol%	Solvent	Temperature	Time	SM/*α*/*β*
$Pd(PPh_3)_4$	5	THF	66 °C	12 h	2/1/2
$Mo(CO)_3(NC\text{-}t\text{-}Bu)_3$	20	THF	66 °C	24 h	8/1.25/1
$[(Cp^*)Ru(NCCH_3)_3][PF_6]$	5	CH_2Cl_2	RT	20 min	0/1/0

Table 2.3: Hydrostannation attempts

After 12 h the palladium catalyst after only gave a mixture of starting material **2.58** and *β*-isomer **2.59'** as major products. When the molybdenum catalyst was used, the ratio was slightly in favour of the *α*-isomer **2.59** but a good part of the starting material **2.58** was left unreacted, even after 24 h. In the presence of the ruthenium catalyst, full conversion was observed and the desired isomer **2.59** was obtained as a single product. A mechanism for the ruthenium catalysed hydrostannation is described below and is mostly an extrapolation of the ruthenium-catalysed hydrosilylation mechanism described by Trost *et al*.[67,68] Firstly, the stannane is activated through a *σ*-complex **A**, which reacts in a concerted hydride insertion and oxidative addition to furnish the corresponding η^2-vinylruthenium or metallacyclopropene **B**. The hydride insertion occurs on the less hindered alkyne carbon to furnish the Markovnikov intermediate over the anti-Markovnikov one. The final step is the *α*-stannyl insertion **C** to release the desired stannylated alkene and regenerate the catalyst (Figure 2.1).

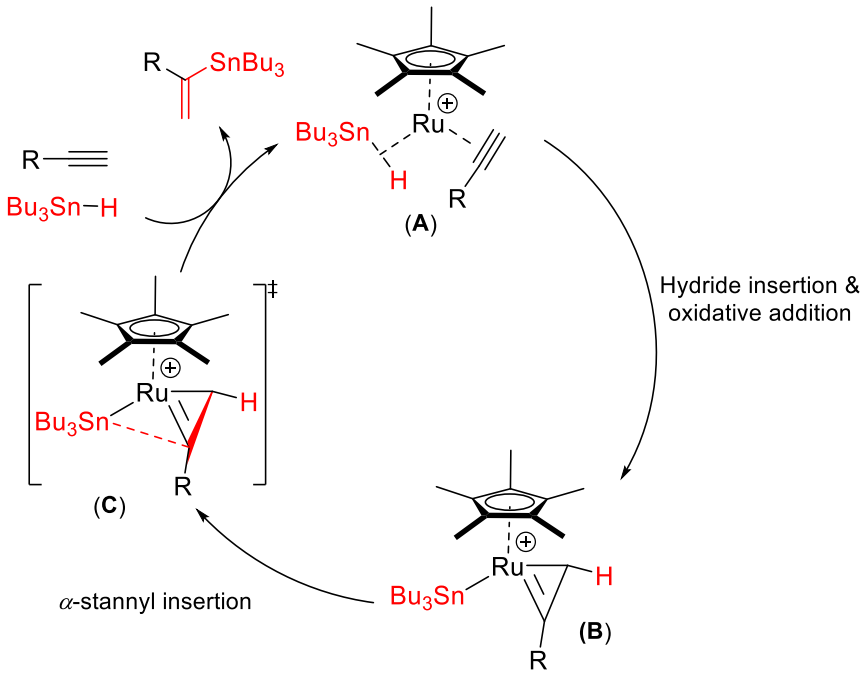
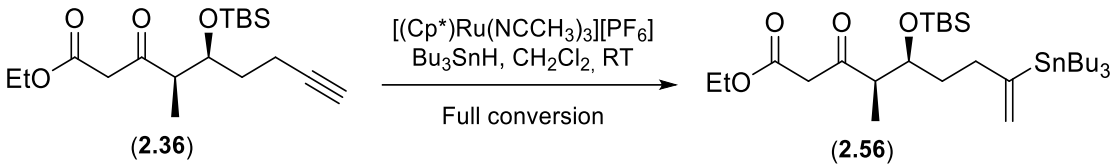


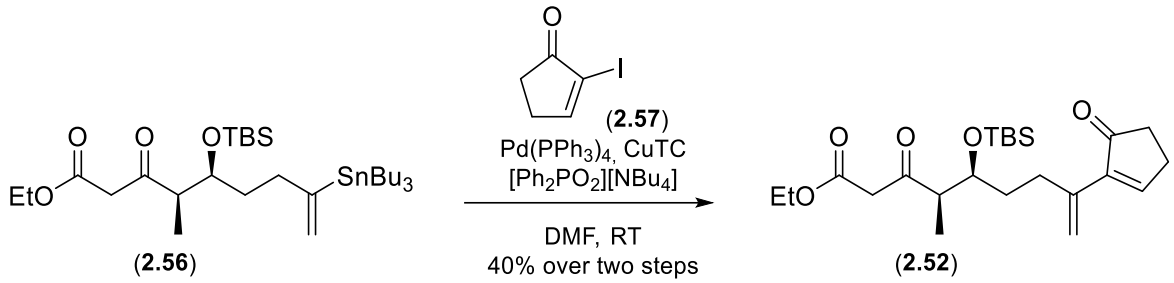
Figure 2.1: Proposed mechanism for the regioselective hydrostannation

The ruthenium-catalysed hydrostannation was applied to our substrate **2.36**. Pleasingly, after 2 h, the starting material was entirely consumed and only the desired product **2.56** was obtained (Scheme 2.52). The product was used in the next step without purification.



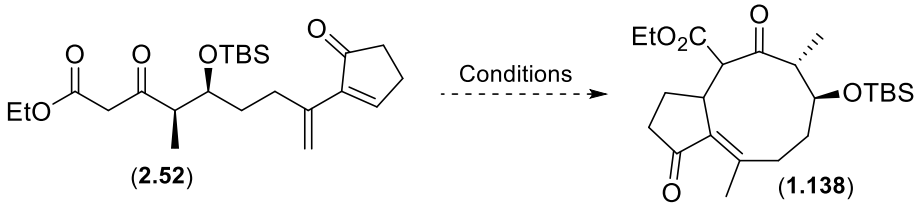
Scheme 2.52: Regioselective hydrostannation on alkyne **2.36**

Different conditions for the Stille coupling were tested; the best conditions were found to be a method developed by Fürstner *et al.* for sensitive substrates.[69] In the presence of copper(I) thiophene-2-carboxylate (CuTc), tetrabutylammonium diphenylphosphinate as additives and iodocyclopentenone **2.57** (synthesised in one step from cyclopentenone using iodine and pyridine), Stille coupling furnished the desired Michael precursor **2.52** in 40% yield over 2 steps (Scheme 2.53).



Scheme 2.53: Modified Stille coupling

Compound **2.52** was then submitted to different test conditions for the intramolecular Michael reaction (Table 2.4).



Reagent	Solvent	Time	Result
K_2CO_3	Ethanol	24 h	SM
Cs_2CO_3	DMF/THF	5 h	SM
$FeCl_3.6H_2O$	CH_2Cl_2	24 h	Decomposition
$Mn(OAc)_3.2H_2O$	Ethanol	24 h	SM

Table 2.4: Tests for the formation of the nine-membered ring

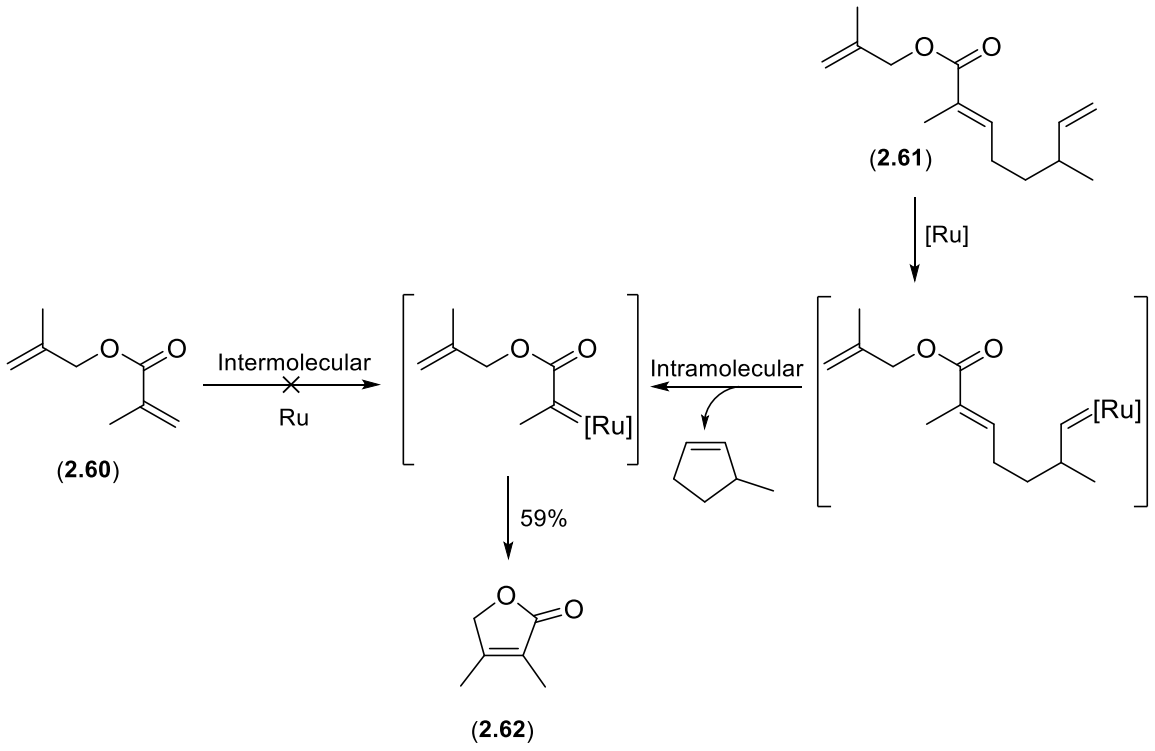
The previous conditions used in our group for Michael additions with a catalytic amount of potassium carbonate in ethanol were attempted. Unfortunately product **2.52** was left unreacted. The conditions reported by Deslongchamps and Roy was applied to our substrate, but only the starting material was recovered after 24 h.[60] In 2000, Christoffers and Oertling published a novel method using iron(III) chloride hexahydrate to catalyse intramolecular Michael reaction for the formation of seven-membered rings. When this method was tried on enone **2.52**, only decomposition was observed.[70] A final test in the presence of manganese(III) acetate led to the recovery of starting material **2.52**.

With the Michael reaction pathway being unsuccessful, it was decided to rethink our strategy for the formation of nine-membered ring **1.138**.

2.2.5 Relay ring-closing metathesis pathway

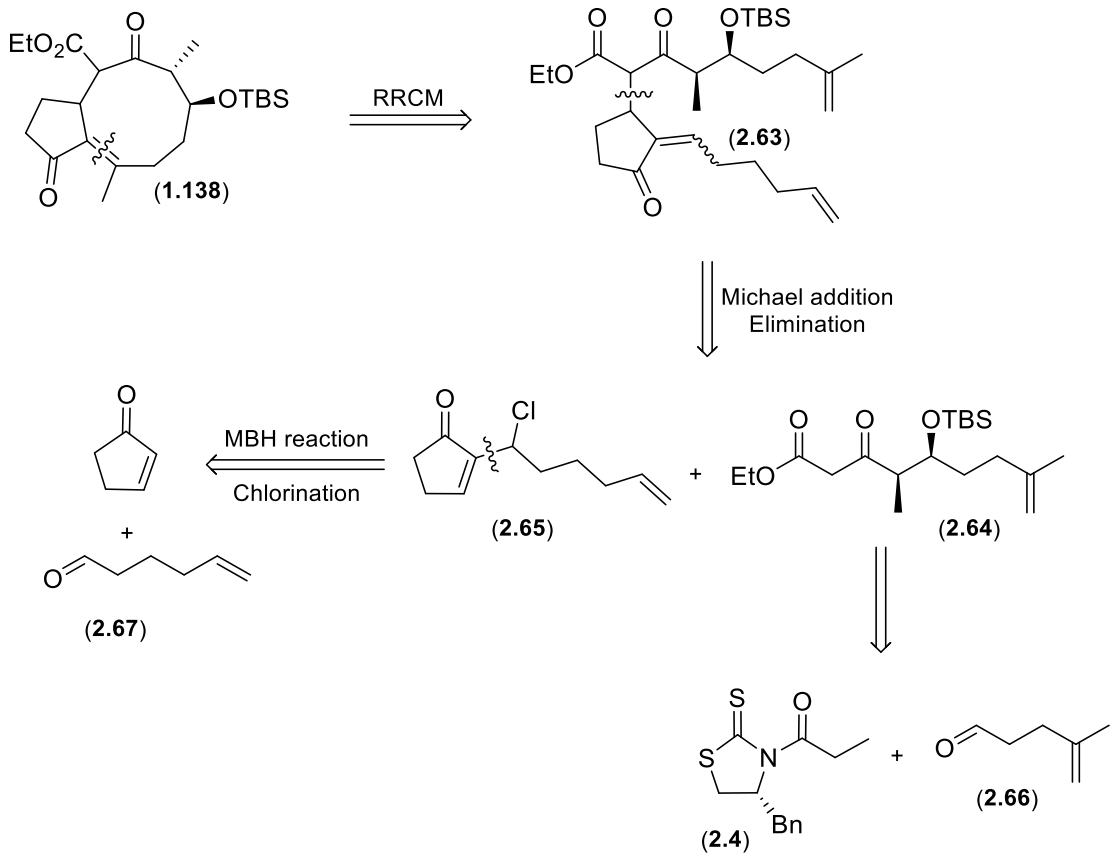
After the previous attempts, it was hypothesised that one of the reason behind these disappointing results might be the reversibility of the key cyclisation step. In all our previous attempts (*e.g.* Michael addition), the formation of the intermediate during the cyclisation was reversible and could go two different pathways: either formation of the desired strained bicycle or return to its previous state. In order to circumvent this difficulty, it was decided to investigate a synthetic strategy where the cyclisation step would be irreversible, pushing the equilibrium towards the formation of the nine-membered ring **1.138**.

RCM is a powerful tool to close rings of different sizes. In most cases, the newly formed double bond is less reactive than the precursors and therefore less likely to react in another metathesis. In our case, due to steric hindrance, the tetrasubstituted alkene would be completely inert towards a secondary metathesis reaction. Unfortunately, a direct RCM between two *gem* disubstituted alkenes to produce a tetrasubstituted alkene can be very difficult, it was then decided to focus our efforts on a relay ring-closing metathesis (RRCM). RRCM is a method recently developed to produce hindered or electronically deactivated alkenes that are difficult to synthesise by direct RCM. Instead of an intermolecular initiation of the catalytic cycle to install the ruthenium carbene on the desired alkene, the metallocarbene is generated by an intramolecular reaction with the aid of a temporary tether incorporating a more reactive olefin.[71] An example is described in more detail below. In order to form the desired butenolide **2.62**, a direct RCM from **2.60** was not feasible due to the steric hindrance of both alkenes and electronic deactivation of the conjugated alkene. Hoye *et al.* decided to install a tether containing a terminal alkene **2.61**, which reacted first with the ruthenium catalyst to produce a metallocarbene.[72] The second step was the kinetically favored formation of a five-membered ring to place the metallocarbene at the *α*-position of the ester, a more hindered and deactivated position. The final step was a classic RCM to regenerate the catalyst and furnish the desired butenolide **2.62** (Scheme 2.54).



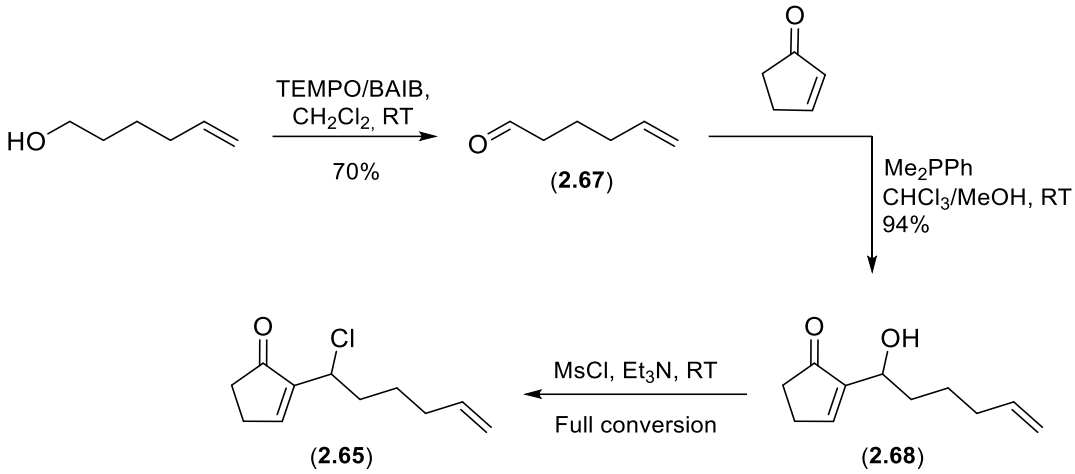
Scheme 2.54: Formation of butenolide **2.62** by RRCM

It was decided to apply RRCM to our strategy. Our envisaged retrosynthesis started by the formation of nine-membered ring **1.138** by RRCM of precursor **2.63**. Product **2.63** could be obtained by a Michael/elimination reaction between *β*-ketoester **2.64** and *β*-chlorocyclopentenone **2.65**. *β*-Ketoester **2.64** would be formed by a series of reactions previously developed, starting from a Crimmins aldol reaction with aldehyde **2.66.** *β*-Chlorocyclopentenone **2.65** would be produced by a Morita-Baylis-Hillman (MBH) reaction between cyclopentenone and aldehyde **2.67** followed by a chlorination (Scheme 2.55).



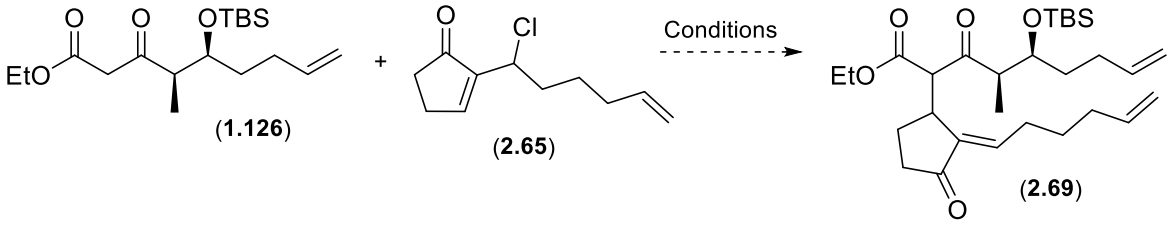
Scheme 2.55: Retrosynthesis for RRCM pathway

The forward synthesis started with the TEMPO/BAIB oxidation of hex-5-en-1-ol to give the corresponding aldehyde **2.67** in 70% yield. The next step was a Morita-Baylis-Hillman reaction between aldehyde **2.67** and commercially available cyclopentenone. The best conditions were found to be the ones developed by Iguchi *et al.* using dimethylphenyl phosphine as a catalyst in a chloroform/methanol mixture.[73] This reaction furnished the desired MBH product **2.68** in an excellent 94% yield in only 1 h. The *β*-hydroxy enone **2.68** was submitted to an addition of mesyl chloride and triethylamine to produce the unstable *β*-chlorocyclopentenone **2.65** that was used in the next step without purifcation (Scheme 2.56).



Scheme 2.56: Formation of fragment **2.65**

With chlorocyclopentenone **2.65** in hand, it was decided to try the Michael addition with the already available *β*-ketoester **1.126** before embarking the synthesis of the desired ketoester **2.64** containing a 1,1-disubstituted alkene. Two sets of conditions were tested and the results are described below (Table 2.5).

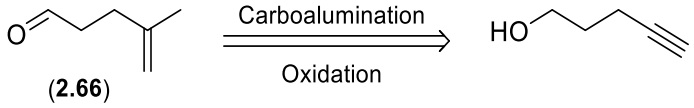


Conditions	Temperature	Time	Results
NaH, THF	RT	24 h	SM recovered
$Pd(PPh_3)_4$, NaH, THF	RT	5 min	Full conversion

Table 2.5: Conditions tested

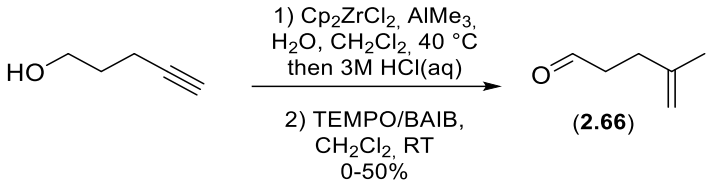
When sodium hydride was added to a mixture of both products, no reaction occured and only the starting materials were recovered after 24 h. Pleasingly, after addition of a catalytic amount of Pd^0 to the crude mixture, the reaction was complete and full conversion was observed by NMR after only 5 min. It was then decided to use this Tsuji-Trost reaction in the synthesis of the envisaged RRCM precursor **2.63**.

Aldehyde **2.66**, crucial partner in the Crimmins aldol reaction, could be formed by a Negishi carboalumination and TEMPO/BAIB oxidation of the commercially available alcohol (Scheme 2.57).



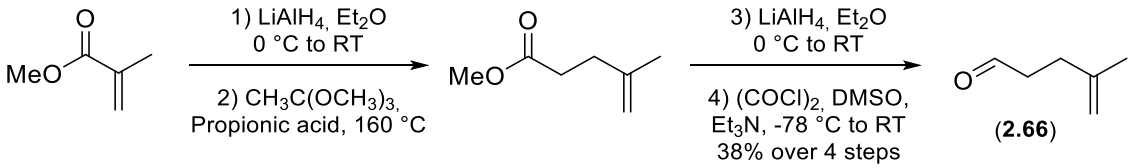
Scheme 2.57: Retrosynthesis of aldehyde **2.66**

After optimisation, the conditions that led to the best results were found to be the addition of a catalytic amount of zirconocene dichloride, trimethylaluminium and 1.5 equivalents of water in refluxing CH_2Cl_2.[74] The crude alcohol was immediately oxidised with a mixture of TEMPO/BAIB to furnish the corresponding aldehyde **2.66**. Unfortunately, in addition to safety concerns during the addition of water in the zirconium/trimethylaluminium mixture, the Negishi carboalumination proved to be quite difficult to reproduce (Scheme 2.58).



Scheme 2.58: 2 steps process for the synthesis of aldehyde **2.66**

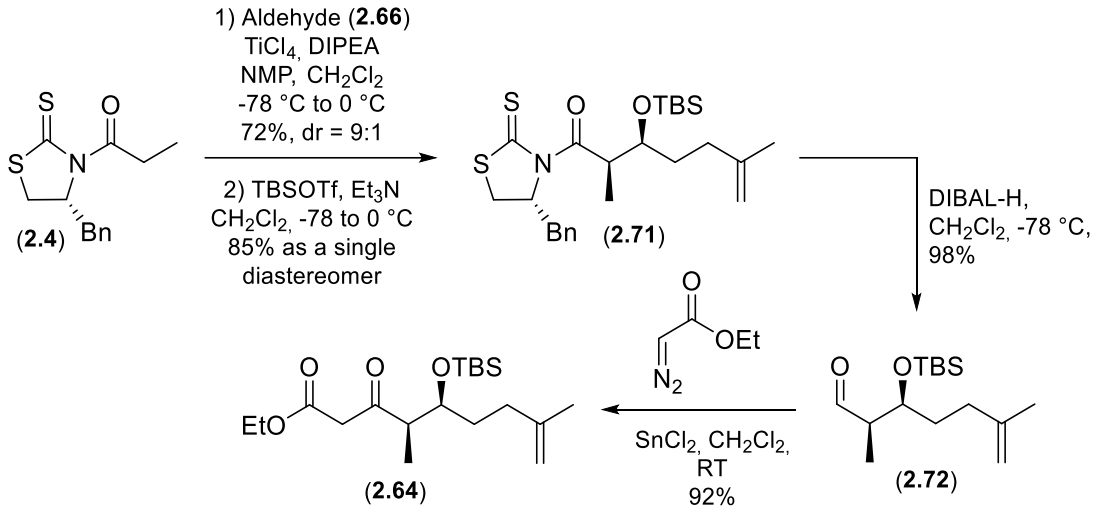
The synthesis was modified and a longer but more reliable route was developed. Reduction of commercially available methacrylate followed by Johnson-Claisen rearrangement furnished the corresponding *γ*,*δ*-unsaturated ester. The ester moiety was reduced by lithium aluminium hydride and the resulting alcohol transformed by Swern oxidation into the desired aldehyde **2.66** in 38% yield over 4 steps (Scheme 2.59).



Scheme 2.59: 4 steps process for the synthesis of aldehyde **2.66**

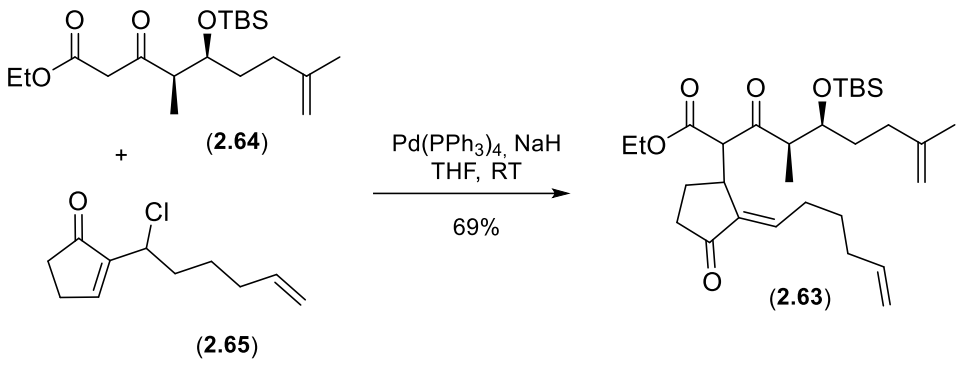
Diastereoselective aldol between acylated Crimmins auxiliary **2.4** and aldehyde **2.66** led to the production of the aldol **2.70** in good yield and diastereomeric ratio. Formation of the TBS ether **2.71** followed by cleavage of the auxiliary furnished aldehyde **2.72** in excellent yield

over 2 steps. Aldehyde **2.72** underwent Roskamp homologation and gave *β*-ketoester **2.64** in 55% yield over 4 steps (Scheme 2.60).



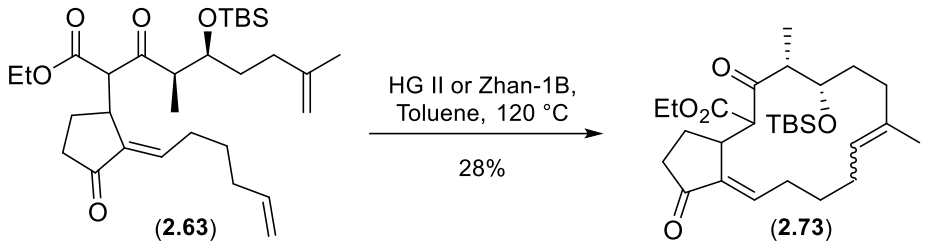
Scheme 2.60: Synthesis of Tsuji-Trost precursor **2.64**

β-Ketoester **2.64** and *β*-chlorocyclopentenone **2.65** reacted together in the presence of Pd^0 to furnish RRCM precursor **2.63** in very good yield and with a perfect regioselectivity (scheme 132). By comparison to published NMR data for similar compounds, the newly formed alkene was determined to be exclusively the *E*-isomer (Scheme 2.61).[75]



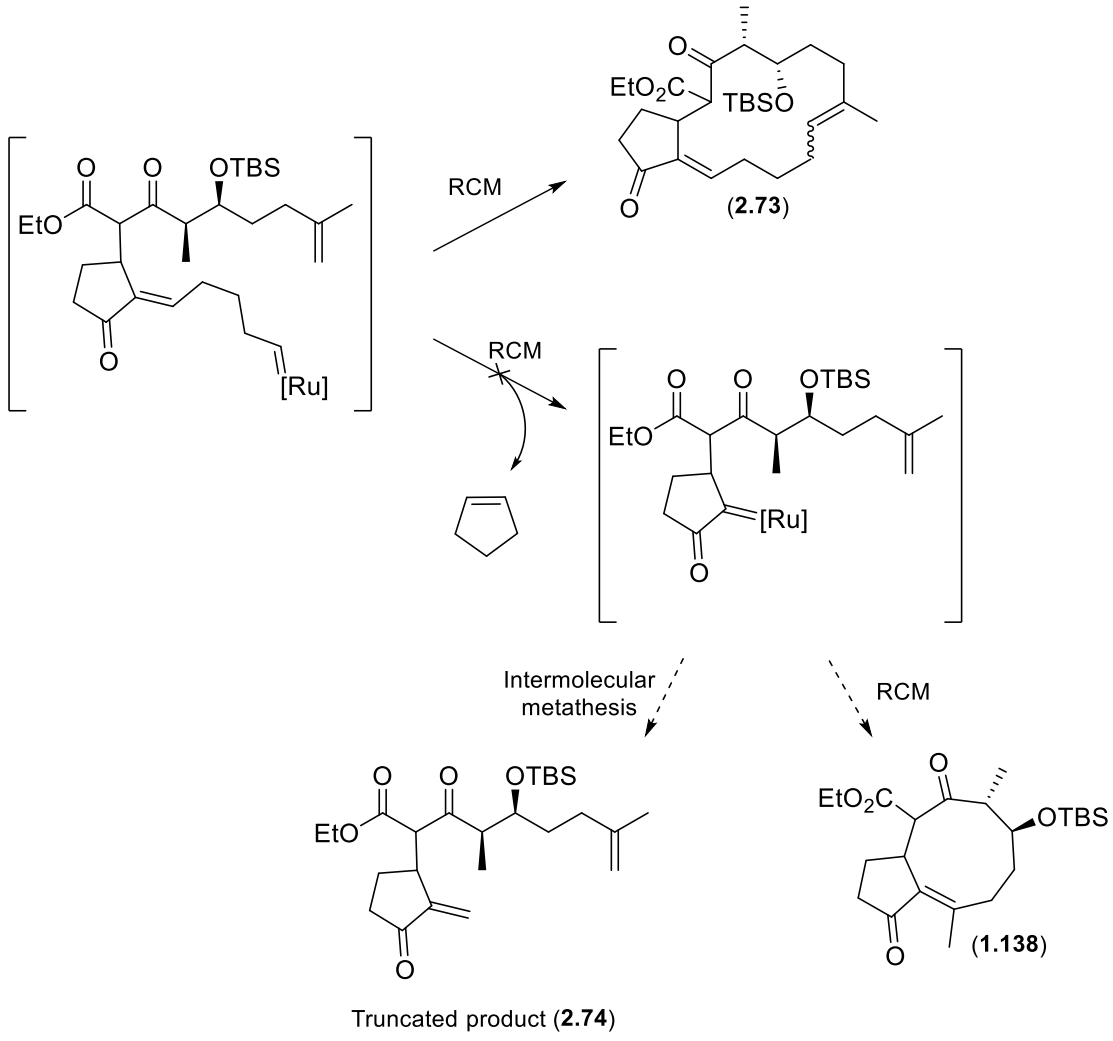
Scheme 2.61: Tsuji-Trost coupling

Product **2.63** was submitted to RRCM conditions using different catalysts such as Hoveyda-Grubbs II catalyst or the more reactive catalyst Zhan-1B, but the fourteen-membered ring **2.73** was obtained exclusively (scheme 2.62).



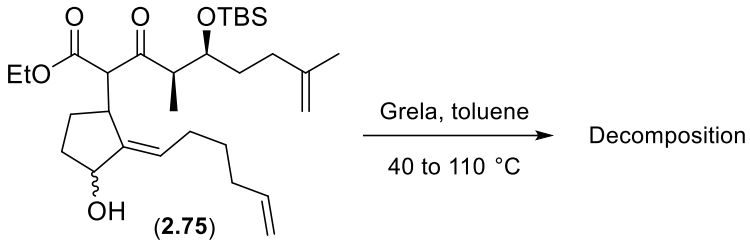
Scheme 2.62: Attempts of RRCM

As expected, the first step of the catalytic cycle was the reaction between the more reactive terminal alkene with the ruthenium catalyst to produce a metallocarbene at the terminal position. The formation of macrocycle **2.73** indicates that the ruthenium carbene at the terminal position reacted preferentially with the most electron-rich gem-disubstituted alkene. The absence of the desired nine-membered ring **1.138** or the truncated product **2.74** confirmed that no reaction occured between the conjugated alkene and the metallocarbene (Scheme 2.63).



Scheme 2.63: Different possible pathways

These results are more likely due to the conjugated alkene being too electron deficient and therefore, unreactive towards metathesis. A possible solution to this problem is the reduction of the enone moiety into the corresponding allylic alcohol. Indeed, allylic alcohols being more electron rich, their reactivities towards metathesis increase. RRCM precursor **2.63** was submitted to Luche reduction conditions using sodium borohydride and cerium(III) chloride heptahydrate. Pleasingly, the enone was selectively reduced to furnish allylic alcohol **2.75** in 66% yield without any sign of the reduced ketoester. The selectivity was hypothesised to be the results of the formation of a cerium enolate, acting as temporary protection against reduction. The allylic alhocol **2.75** reacted with the Grela catalyst at different temperatures and speed of addition but only decomposition was observed (Scheme 2.64).

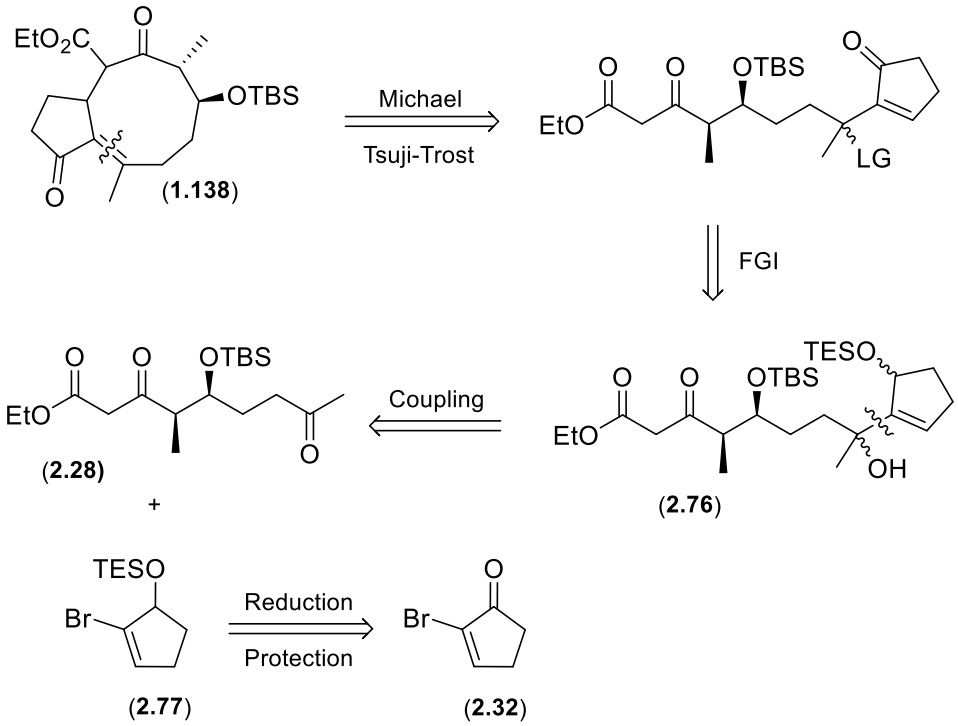


Scheme 2.64: RRCM trials on product **2.75**

These last results have shown that obtention of the nine-membered ring **1.138** using a RRCM as a key-step was not possible and forced us to change our general strategy.

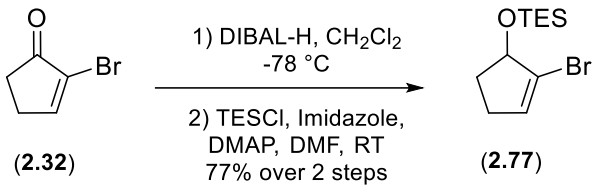
2.2.6 Michael/Tsuji-Trost pathway

During our last synthetic effort, a Michael/Tsuji-Trost reaction was used to produce the RRCM precursor **2.63**. This reaction allowed the formation of the desired product in good yield and with a short reaction time (< 5 min). This method could be applied to the key cyclisation step. Nine-membered ring **1.138** would be closed by a Michael/Tsuji-trost reaction from a precursor containing a leaving group (*e.g.* chloride, acetate) in the *α* position of the enone. This precursor could be formed from the corresponding *bis*-allylic alcohol product **2.76** by several functional group interconversions. This *bis*-allylic alcohol product **2.76** could be obtained by a coupling reaction between readily available retro Michael product **2.28** and a protected bromocyclopentenol **2.77** easily available from bromocyclopentenone **2.32** (Scheme 2.65).



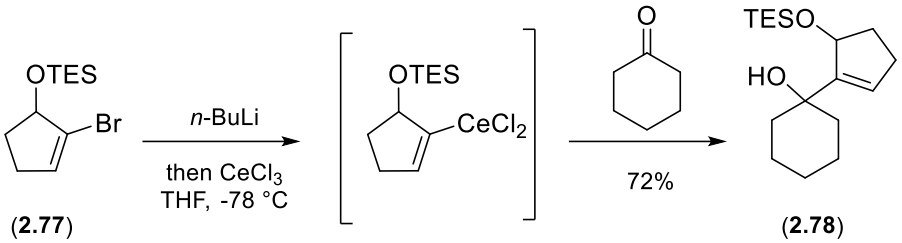
Scheme 2.65: Retrosynthesis for Michael/Tsuji-Trost pathway

Bromoketone **2.32** was reduced using DIBAL-H to furnish the corresponding allylic alcohol, which was immediately converted into TES ether **2.77** in 77% yield over two steps (Scheme 2.66).



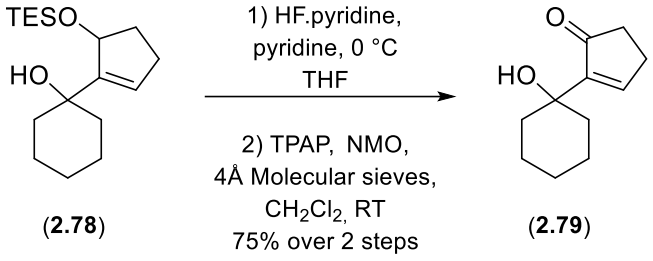
Scheme 2.66: Formation of fragment **2.77**

It was decided to test first the viability of the synthetic route on a model ketone, cyclohexanone. Cerium(III) chloride heptahydrate was slowly dried under high vacuum (120 °C for 2 h, 140 °C for 2 h and 160 °C for 3 h, <1 mbar) to give anhydrous cerium(III) chloride. Bromide/lithium exchange occured between protected bromocyclopentenol **2.77** and *n*-BuLi followed by formation of the corresponding organocerium reagent. When an organocerium reagent is prepared via a Grignard reagent, the reagent formed is an ate complex (R-MgX·$CeCl_3$). In the case of an organocerium prepared from an organolithium source, a true organocerium specie (R-$CeCl_2$) is believed to be formed. Cyclohexanone was added to the newly formed organocerium reagent to produce tertiary allylic alcohol **2.78** in 72% yield (Scheme 2.67).



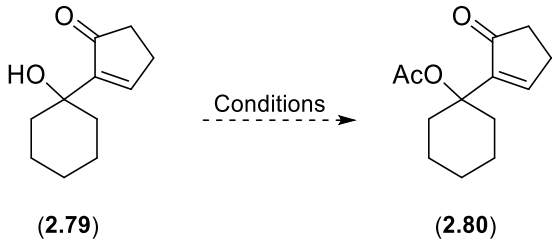
Scheme 2.67: Addition of the organocerium reagent

Clevage of the TES ether was realised in the presence of HF.pyridine with a large excess of pyridine at 0 °C to furnish the corresponding *bis*-allylic alcohol that was used in the next step without purification. Swern oxidation only led to the decomposition of the starting material. Ley-Griffith conditions were found to be the best to produce the desired enone **2.79** in very good yield over two steps (Scheme 2.68).



Scheme 2.68: Deprotection and oxidation of product **2.78**

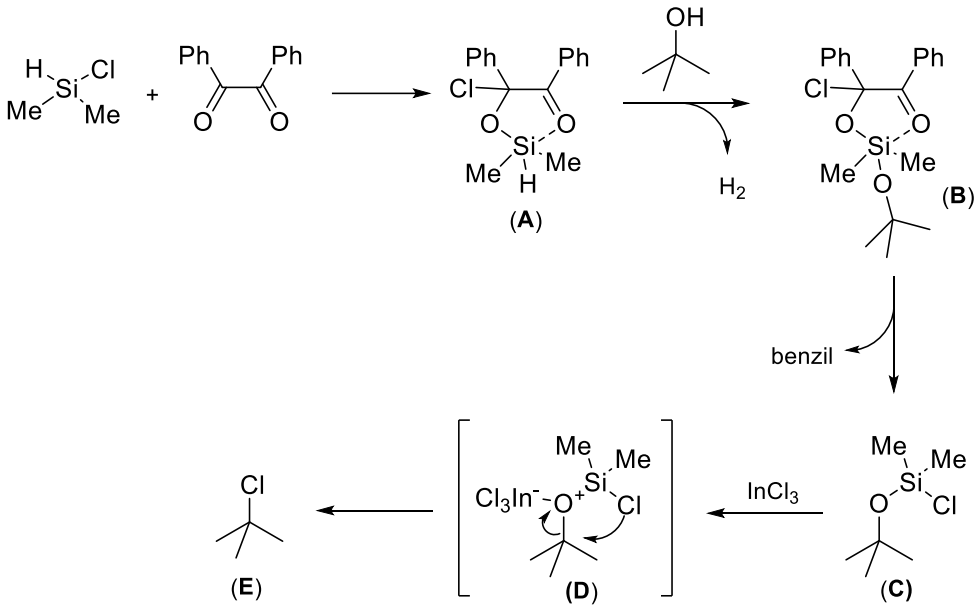
Acetylation of the tertiary alcohol was then attempted and the different tests are described below (Table 2.6). Unfortunately, all the conditions tested led to either formation of the elimination product or decomposition.



Source of acetate	Additives	Solvent	Results
Acetic anhydride	Et_3N/DMAP	/	Elimination
Acetic anhydride	DMAP	Toluene	SM + elimination
Acetic anhydride	$Sc(OTf)_3$	CH_3CN	SM + elimination
Acetyl chloride	*n*-BuLi	THF	SM + decomposition

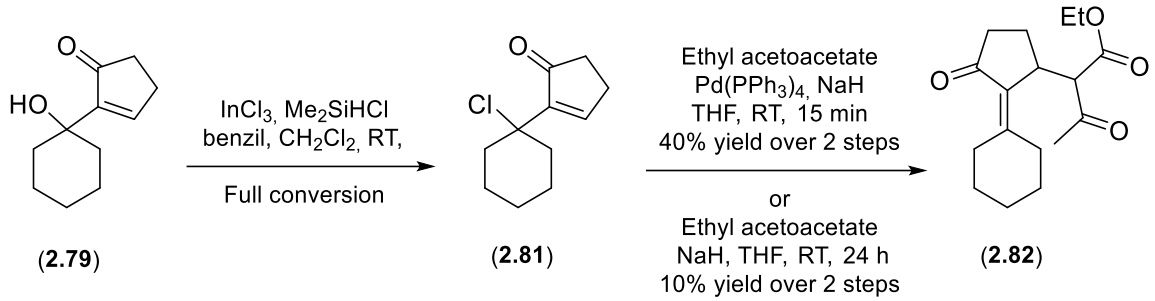
Table 2.6: Conditions tested for the acetylation

It was decided to apply to our substrate a method developed in 2004 by Baba *et al.* for the chlorination of tertiary alcohols.[76] The envisaged mechanism is described in more details below. Dimethylchlorosilane first chlorinates benzil to form intermediate **A**, which reacts with the alcohol to liberate hydrogen and furnish intermediate **B**. Intermediate **B** quickly collapses to produce chlorosilyl ether **C**, which in the presence of indium(III) chloride generates the desired tertiary chloride **E** (Scheme 2.69).



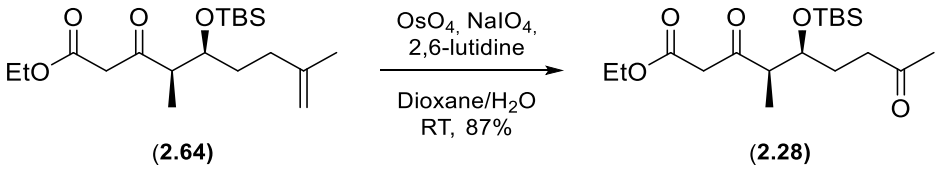
Scheme 2.69: Mechanism for the indium catalysed chlorination

When this chlorination method was applied to compound **2.79**, complete formation of tertiary chloride **2.81** was observed in 15 min. Due to its instability, the product was used in the next step without purification and was immediatly submitted to Tsuji-Trost conditions in the presence of ethyl acetoacetate to give tetrasubstitued alkene product **2.82** in 40% yield over two steps. When the same reaction was attempted without a source of Pd^0, the desired product was obtained after 24 h in 10% yield over two steps (Scheme 2.70).



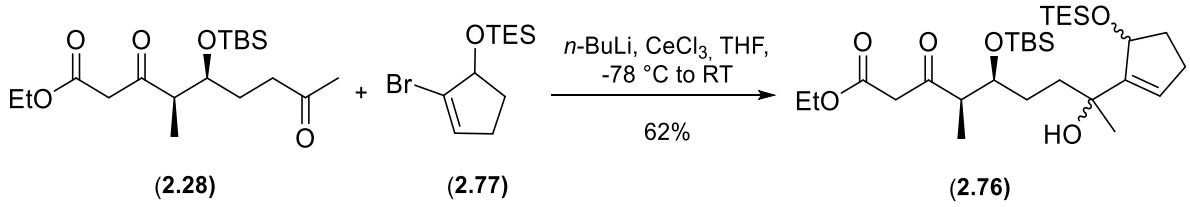
Scheme 2.70: Chlorination followed by Tsuji-Trost reaction

With the synthetic pathway validated on a model system, it was decided to apply this synthesis to our real substrate. The previously synthesised *β*-ketoester **2.64** was quickly converted into fragment **2.28** incorporating a terminal ketone, by a one-pot dihydroxylation/oxidative cleavage. In the presence of osmium(VIII) oxide, sodium periodate and 2,6-lutidine as a buffer, product **2.28** was obtained in 87% yield (Scheme 2.71).



Scheme 2.71: Dihydroxylation/oxidative cleavage

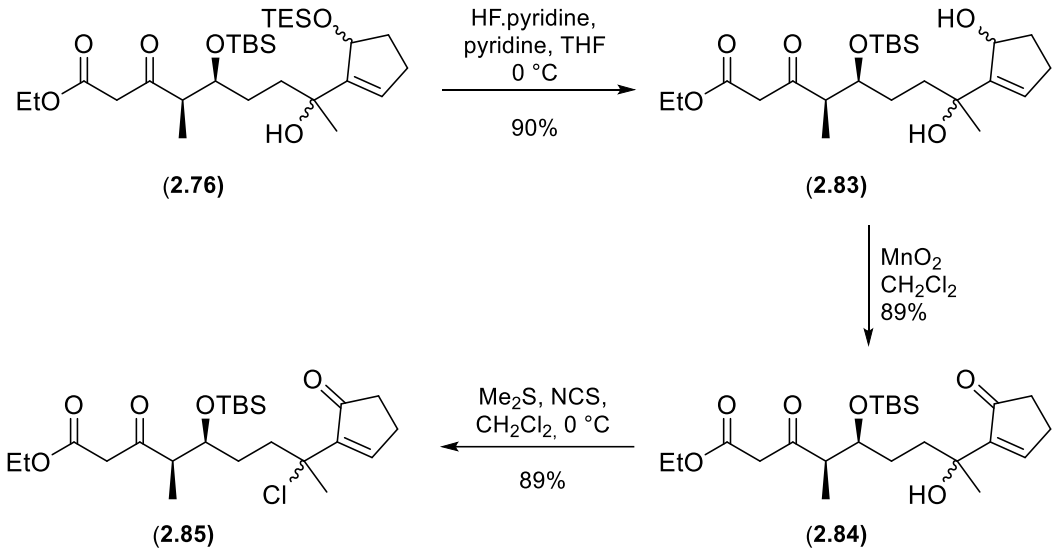
With both fragments in hand, ketone **2.28** and bromo product **2.77** were combined using the previous organocerium reaction to furnish tertiary alcohol compound **2.76** in 62% yield (Scheme 2.72). It is worth noticing that no addition to the ketoester moiety was observed, which suggests once again the formation of a transitory cerium enolate protecting the ketoester.



Scheme 2.72: Organocerium addition

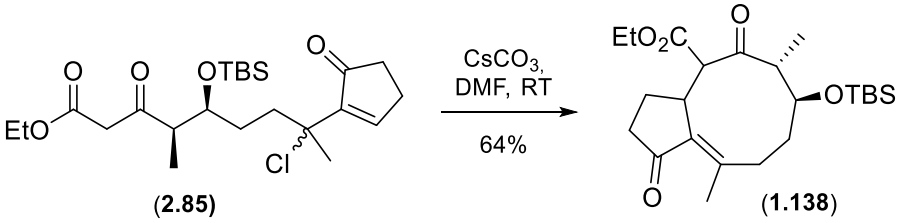
Cleavage of TES ether in the presence of HF.pyridine with an excess of pyridine gave *bis*-allylic alcohol **2.83** in 90% yield. When Ley-Griffith conditions were applied to our substrate, enone **2.84** was obtained in poor yield. Decomposition of product **2.84** occurred during the

purification by flash chromatography. Allylic oxidation using manganese(II) oxide followed by a quick filtration through a short pad of celite to remove inorganic impurities produced enone **2.84** in 89% yield. Enone **2.84** was then submitted to indium-catalysed chlorination conditions, but unfortunately only a mixture of unidentified products was recovered, with no sign of the tertiary chloride. Pleasingly, a second attempt using a mixture of dimethyl sulfide and *N*-chlorosuccinimide led to the formation of the desired product **2.85** in 89% yield. The product was purified by flash chromatography after neutralisation of the silica gel with triethylamine (Scheme 2.73).



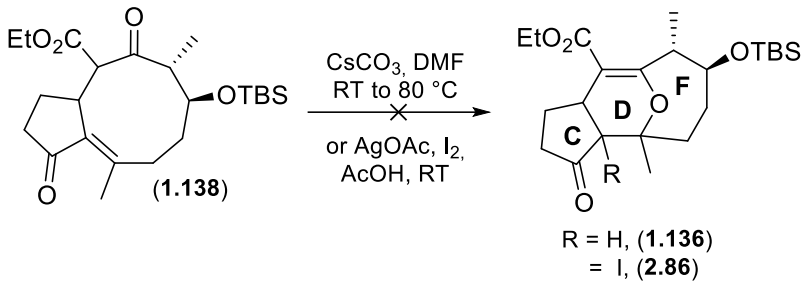
Scheme 2.73: Cleavage, oxidation and chlorination to form product **2.87**

Conditions for the cyclisation step were investigated. Classic Tsuji-Trost using palladium *tetrakis*(triphenylphosphine)palladium(0) and sodium hydride only led to decomposition. Clarke *et al.* have shown that the addition of 1,2-*bis*(diphenylphosphino)ethane (dppe) as a ligand for the Tsuji-Trost reaction greatly improves the yield of nine-membered ring formation.[29] Unfortunately, when product **2.85** was submitted to Clarke's conditions, degradation was observed. Addition of Pd^0 being detrimental to our substrate, it was decided to try a more classic Michael/elimination cascade. In the presence of caesium carbonate in dry DMF, the desired nine-membered product **1.138** was finally obtained as a mixture of 4 diastereomers in 64% yield (Scheme 2.74).



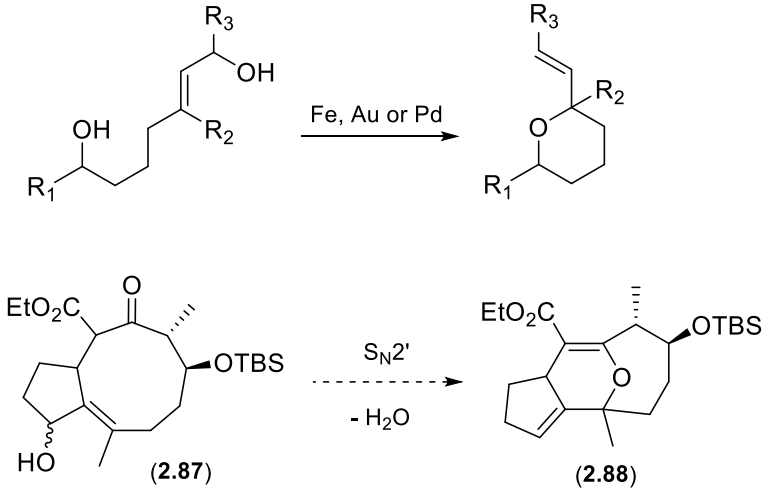
Scheme 2.74: Formation of nine-membered ring **1.138**

With the nine-membered ring in hand, conditions for the formation of the DF-ring system were explored. Formation of the enolate followed by an oxa-Michael addition would give the desired tricycle **1.136**. Unfortunately, when product **1.138** was treated with caesium carbonate in DMF at different temperatures, only the starting material was recovered. When iodoetherification using Clarke's conditions was tried, the starting material was left unreacted (Scheme 2.75).



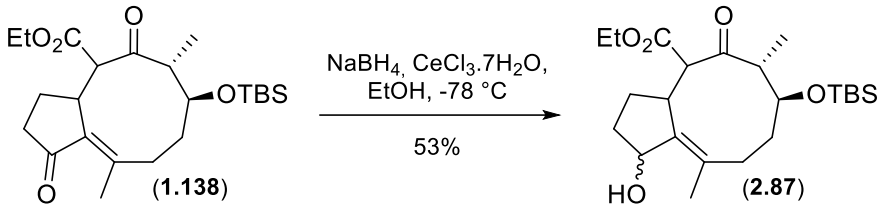
Scheme 2.75: Failed attempts of DF-ring system closure

There are numerous examples in the literature of metal-assisted heterocyclisations using iron, gold or palladium.[77–79] Allylic alcohols can be transformed by a metal-catalysed S_N2' into the corresponding tetrahydropyrans in excellent yields. It was decided to investigate these methods for the formation of the desired tricycle (Scheme 2.76).



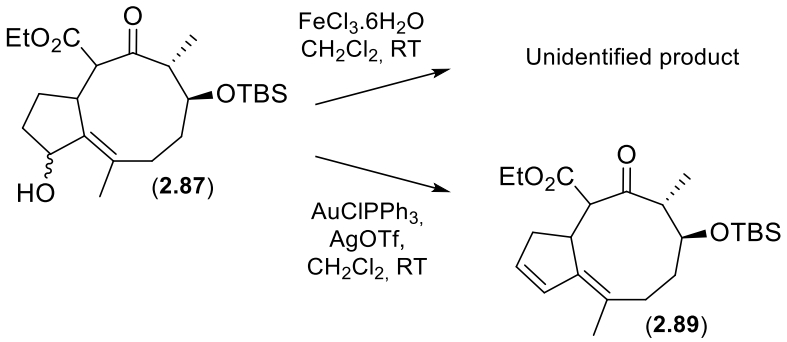
Scheme 2.76: General scheme for metal-assisted heterocyclisations

When nine-membered ring **1.138** was submitted to a Luche reduction, formation of the desired allylic alcohol **2.87** occured in moderate yield (Scheme 2.77).



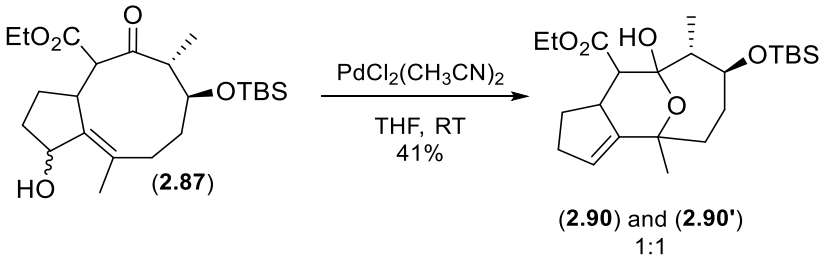
Scheme 2.77: Luche reduction

Allylic alcohol **2.87** was then treated with iron(III) chloride in CH_2Cl_2.[77] A product was obtained but due to the small quantity (<1 mg) and the complexity of the ^1H NMR, it was not possible to clearly identify it. When compound **2.87** was submitted to a mixture of chloro(triphenylphosphine)gold(I) and silver(I) triflate, only the elimination product **2.89** was observed in the crude NMR (Scheme 2.78).[78]



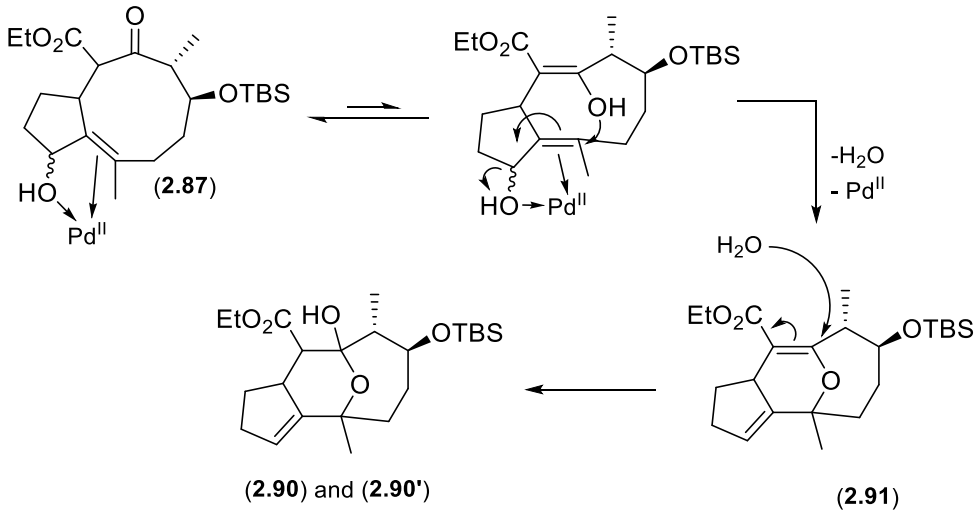
Scheme 2.78: Cyclisation tests with gold/silver and iron

Fortunately, treatement of allylic alcohol **2.87** with *bis*(acetonitrile)dichloropalladium(II) led to the formation of the CDF tricycle containing a bridged hemiketal.[79] This product was obtained as a 1:1 separable mixture of 2 diastereomers (**2.90** and **2.90'**) in 41% yield (Scheme 2.79). It was not possible to determine the relative configuration of the 2 diastereomers using 2D NMR experiments at this stage.



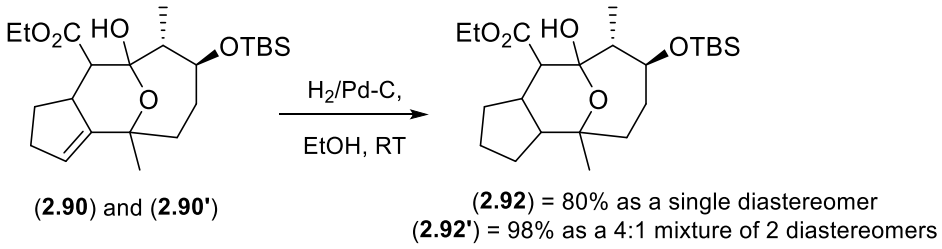
Scheme 2.79: Palladium catalysed formation of CDF tricycle

The mechanism is hypothesised below: first, the alkene and the hydroxyl are coordinated to the palladium. The enol form of the ketone may be responsible for the nucleophilic attack on the olefin, which provokes the elimination of water. Tricycle **2.91** contains an excellent Michael acceptor, which reacts quickly with a molecule of water to furnish the corresponding hemiketal product **2.90** and **2.90'** (Scheme 2.80).



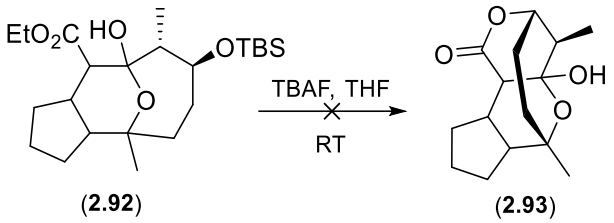
Scheme 2.80: Envisaged mechanism for the formation of CDF tricycle **2.90** and **2.90'**

The next step was the hydrogenation of the double bond to give the corresponding saturated tricycles **2.92** and **2.92'**. The hydrogenation was diastereoselective and furnished the desired product **2.92** as a 4:1 mixture of 2 diastereomers and the major diastereomer was isolated. Product **2.92'** was not purified by flash chromatography and left as a mixture of 2 diastereomers (Scheme 2.81).



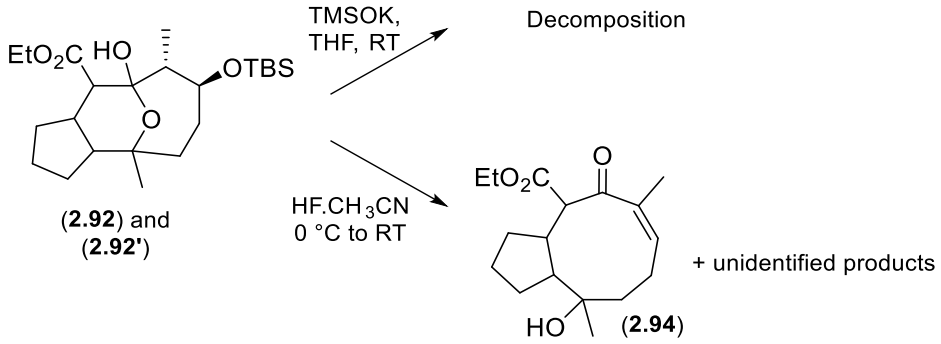
Scheme 2.81: Hydrogenation of **2.90** and **2.90'**

For the last steps of the synthesis, a one-pot TBS cleavage then lactonisation was attempted using TBAF but unfortunately only the starting material was recovered (Scheme 2.82).



Scheme 2.82: Attempts of TBS deprotection/lactonisation

The next attempt was the saponification of the ethyl ester in the presence of potassium trimethylsilanolate to furnish the corresponding carboxylic acid.[80] Only complete decomposition of the starting material **2.92** was observed. When tricycle **2.92** was submitted to TBS cleavage conditions using hydrofluoric acid in acetonitrile, a complex mixture of products was recovered. Only one product (**2.94**) was identified by mass spectrometry and could be the result of an acidic hemiketal opening and OTBS elimination (Scheme 2.83).

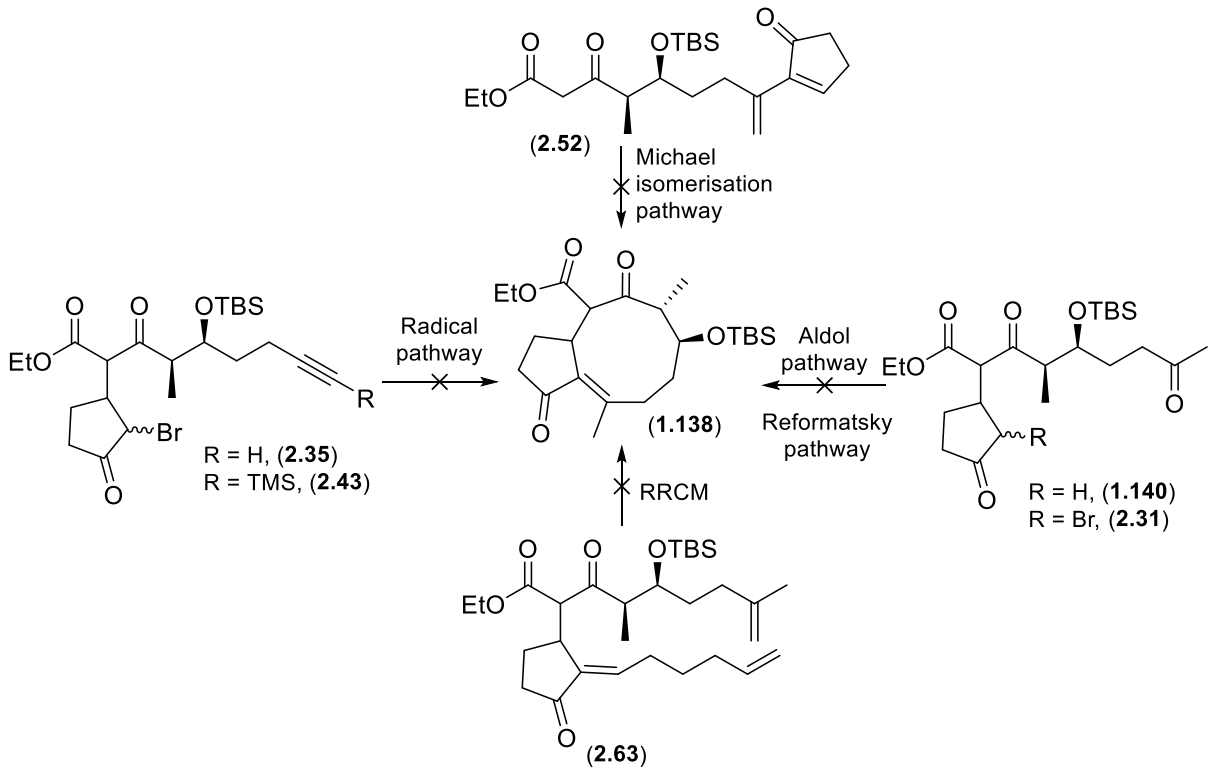


Scheme 2.83: Attempts of saponification and TBS deprotection

Unfortunately, these tests were the only ones I could tried due to very small quantities of product **2.92** and **2.92'** available.

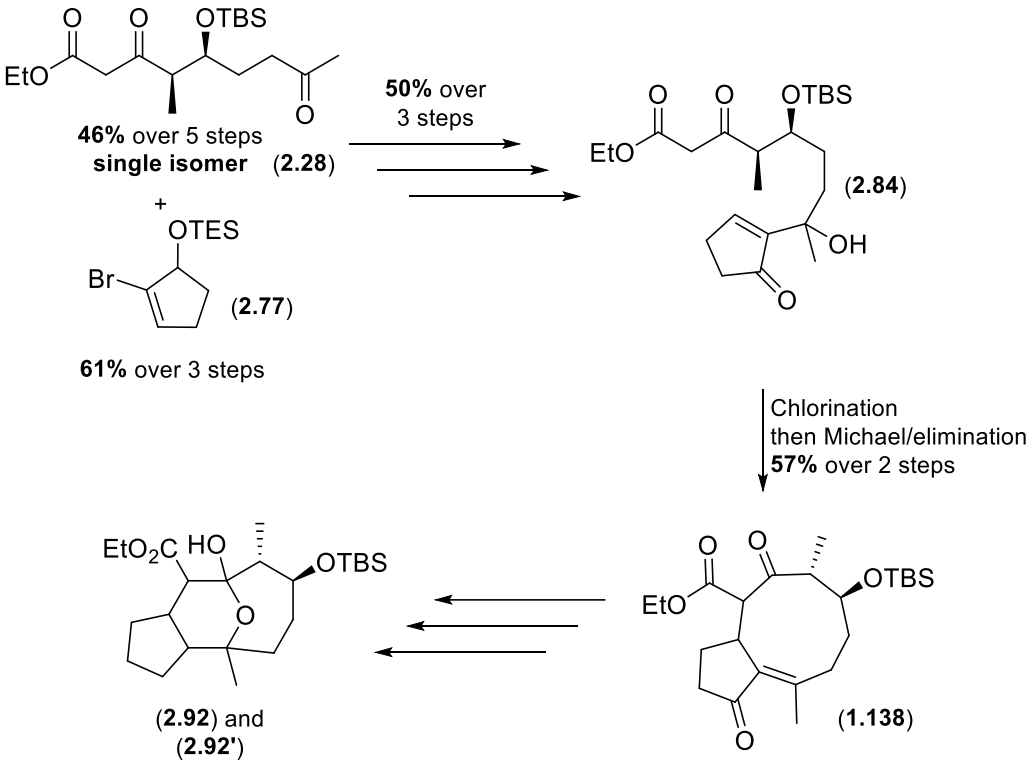
2.2.7 Conclusion and future work

Different approaches to close the nine-membered ring **1.138** were attempted: radical cylisation, Reformatsky reaction, relay ring-closing metathesis, Michael/isomerisation and aldolisation but none of them proved to be successful (Scheme 2.84).



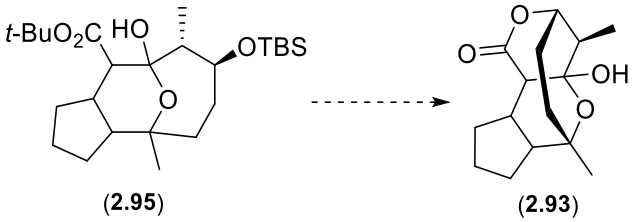
Scheme 2.84: Unsuccessful approaches

A novel method was then developed for the formation of the desired bicycle. The key steps are the selective chlorination of the tertiary alcohol followed by a Michael/elimination reaction to produce the desired bicycle in 57% yield over two steps. The enone was then selectively reduced and a palladium catalysed cyclisation was successful to produce the corresponding CDF tricycle as a mixture of 2 separable diastereomers. Tests were carried out to furnish the final product but unfortunately none of them were conclusive (Scheme 2.85).



Scheme 2.85: Successful synthesis of CDF tricycles **2.92** and **2.92'**

In the future, development of the last steps of the synthesis is necessary to obtain a CDEF tetracycle model **2.93**. A multigram synthesis is also crucial to finalise the synthesis. Hopefully, a crystal structure of one of the the final product could be obtained and X-ray analysis could allow us to determine the relative configuration of tricycle products, which is currently unknown. The ethyl ester would be replaced by a *tert*-butyl ester in order to try conditions developed by Clarke *et al.* for the ester cleavage and lactonisation (Scheme 2.86).[81]

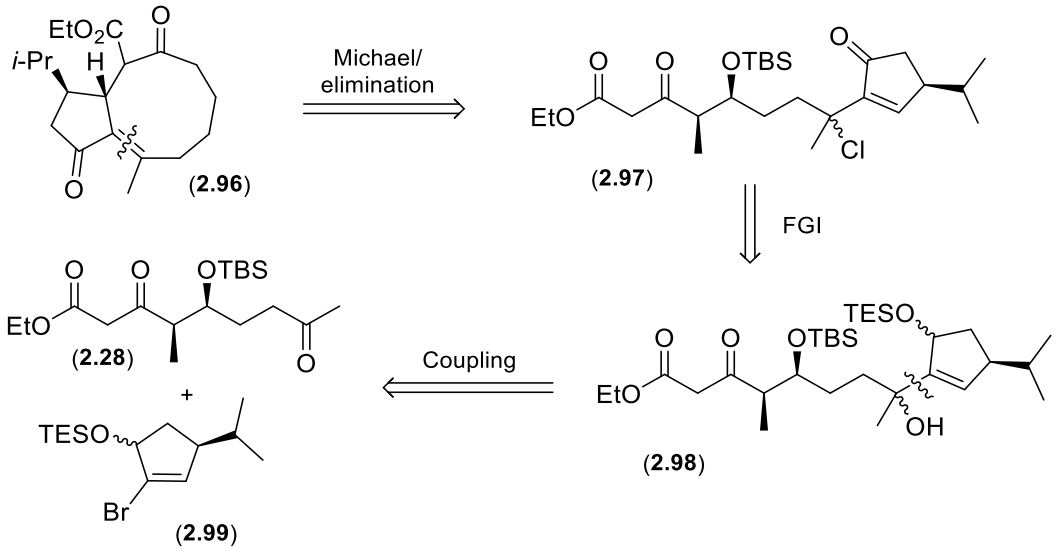


Scheme 2.86: Future work

2.3 Synthesis of a chiral C-ring model

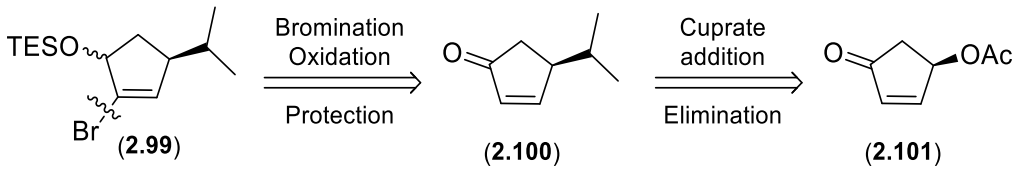
Cyclopentenone was used as a commercially available C-ring model, but the Michael/elimination cyclisation step occurred with no facial selectivity, giving a mixture of 4 diastereomers. In parallel with the synthesis of a CDEF tetracycle model **2.93**, a synthesis

of a chiral C-ring model was envisaged. Diastereoselectivity during the Michael/elimination step would require the use of a hindered group (*e.g* isopropyl) in the *α* position of the conjugated olefin. Diastereoselectivity during this step would hopefully allow the formation later on of a CDF tricycle as a single diastereomer. Nine-membered ring **2.96** could be synthesised following the same retrosynthesis as before (Scheme 2.87).



Scheme 2.87: Retrosynthesis of product **2.96**

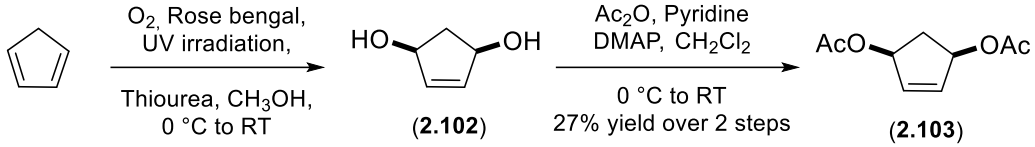
The synthesis of a chiral C-ring has already been investigated in the Prunet group. C-ring **2.99** would be formed by the bromination of the alkene, reduction of the ketone and subsequent formation of TES ether from ketone **2.100**. Ketone **2.100** could be synthesised by a cuprate addition that would produce the *trans* product, followed by elimination of the acetate from compound **2.101**, as described by Trauner *et al.* in 2005.[82]. Ketone **2.101** was readily available from cyclopentanediene (Scheme 2.88).



Scheme 2.88: Retrosynthesis of chiral C-ring **2.99**

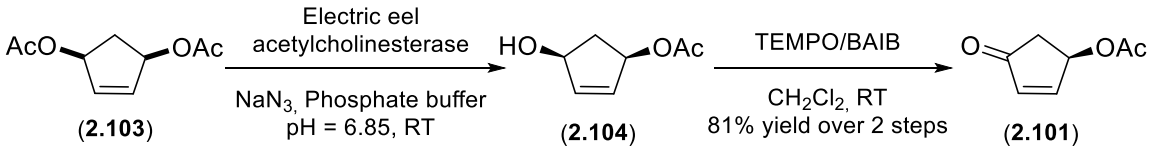
The synthesis began by cracking bicyclopentadiene, to furnish cyclopentadiene *via* a retro Diels-Alder reaction. Cyclopentadiene was then submitted to a mixture of rose bengal as a photosensitizer and singlet oxygen produced by UV irradiation to undergo [4+2] cycloaddition to furnish, after reduction of the endoperoxide by thiourea, diol **2.102**. The reaction mixture was difficult to purify due to residual rose bengal; therefore, the crude

mixture was used in the next step without purification. Diol **2.102** was acetylated using acetic anhydride, pyridine and DMAP to give diacetate **2.103** in 27% yield over two steps (Scheme 2.89).



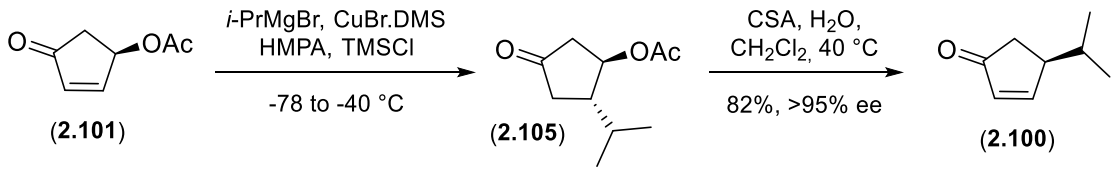
Scheme 2.89: Synthesis of diacetate **2.103**

The next step was the enzymatic desymmetrization of diacetate **2.103**. In the presence of electric eel acetylcholinesterase, sodium azide and an aqueous phosphate buffer (pH = 6.85), one of the acetate was selectively cleaved to produce compound **2.104**, which was used in the next step without purification. The allylic alcohol was converted into the corresponding enone using TEMPO/BAIB conditions. Enone **2.101** was obtained in 81% yield over two steps (Scheme 2.90).



Scheme 2.90: Formation of enone **2.101**

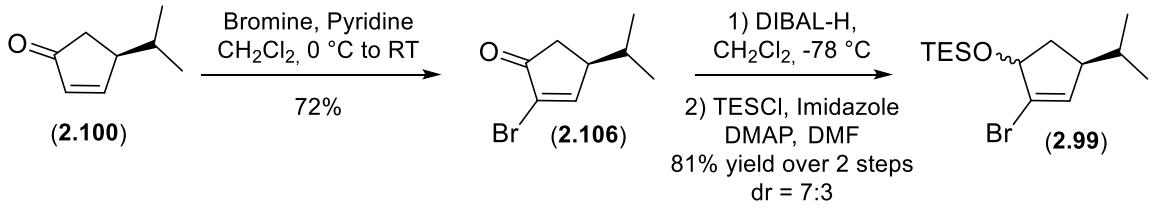
Cuprate addition to enone **2.101** using a mixture of *i*-PrMgBr, CuBr.Me_2S, HMPA and TMSCl in THF led to the formation of intermediate **2.105** with excellent diastereoselectivity. Intermediate **2.105** underwent acetate elimination under acidic conditions to give enone **2.100** in excellent yield and enantiomeric ratio (the enantiomeric ratio was based on the measured optical rotation) (Scheme 2.91).



Scheme 2.91: Cuprate addition followed by elimination to furnish enone **2.100**

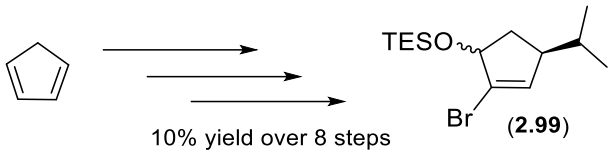
Enone **2.100** was then brominated to produce bromoketone **2.106** in 72% yield. This bromoketone was reduced by DIBAL-H and the resulting alcohol was immediately

transformed into the TES ether, furnishing chiral C-ring **2.199** as a 7:3 mixture of diastereomers in 81% yield over two steps (Scheme 2.92).



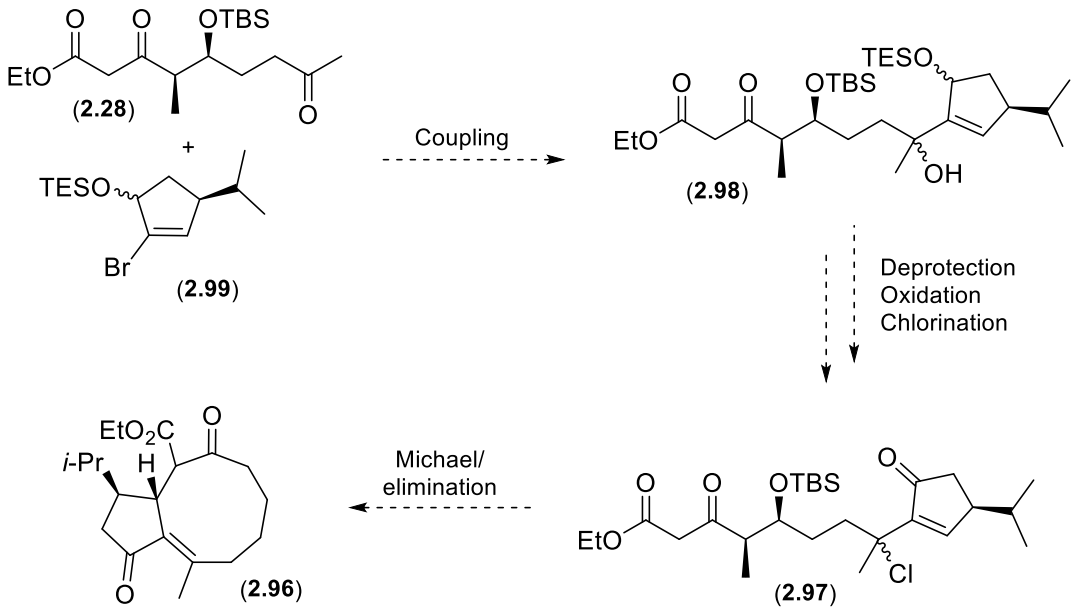
Scheme 2.92: Synthesis of the desired chiral C-ring **2.99**

In summary, chiral C-ring **2.99** was synthesised from cyclopentadiene in 10% yield over 8 steps (Scheme 2.93).



Scheme 2.93: Summary of the synthesis of product **2.99**

In the future, organocerium reaction between fragment **2.28** and product **2.99** will be attempted followed by cleavage of the TES ether, oxidation of the corresponding alcohol and chlorination of the tertiary alcohol to hopefully furnish precursor **2.97**. Finally, cyclisation will be tested and the diastereoselectivity will be assessed (Scheme 2.94).

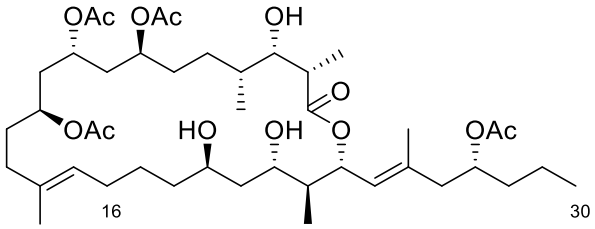


Scheme 2.94: Future work

Chapter 3: Diastereoselective synthesis of trisubstituted olefins by RCM using an O-Si-C tether

3.1 Previous work in the Prunet group

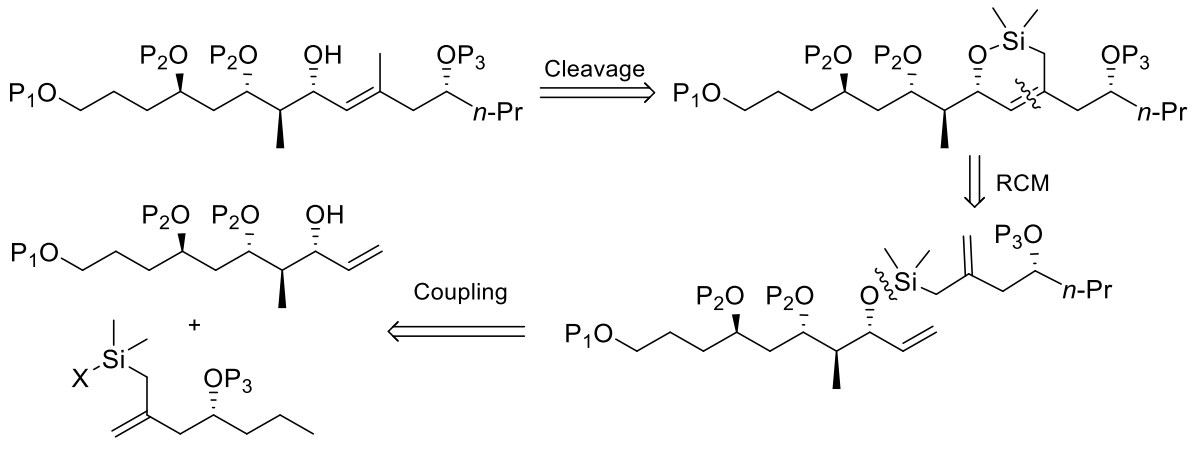
Studies towards the total synthesis of dolabelide C (**3.1**) are currently on progress in the Prunet group (Figure 3.1).[83,84]



Dolabelide C (**3.1**)

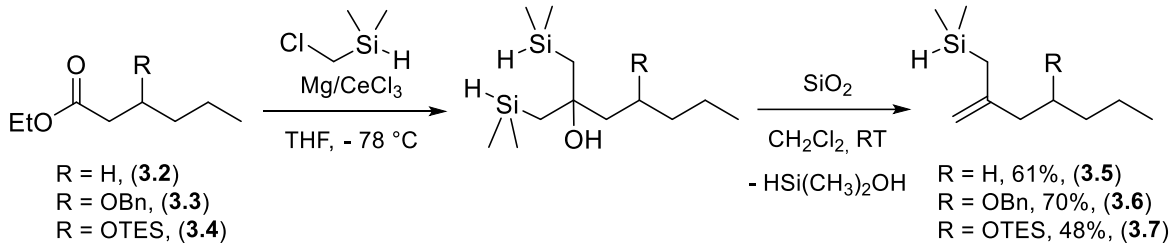
Figure 3.1: Dolabelide C

A novel strategy employing an intramolecular RCM instead of an intermolecular CM, with the aid of a temporary O-Si-C tether, provided the trisubstituted alkene of the C16-C30 fragment with the correct geometry.[85] The C16-C30 fragment could be obtained by cleavage of the O-Si-C tether from a six-membered oxysilanes. The six-membered rings could be closed by a RCM from a diene compounds, which would be produced by a coupling reaction between a silane and an allylic alcohol (Scheme 3.1).



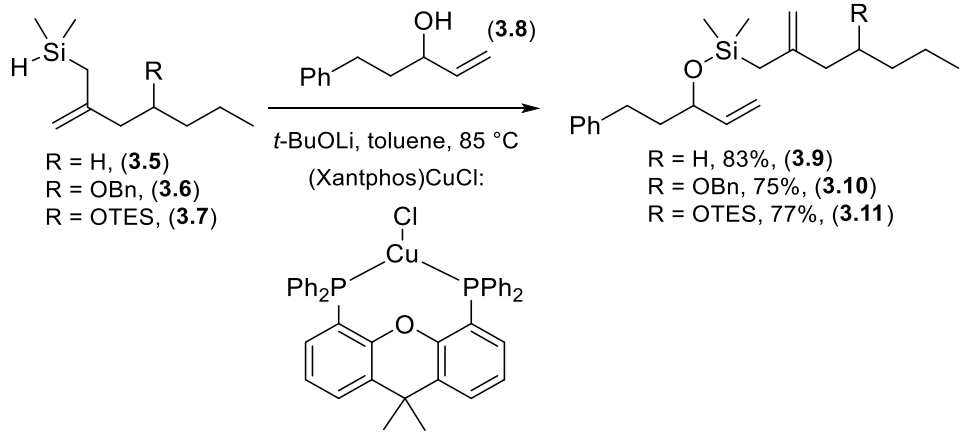
Scheme 3.1: General retrosynthesis for the synthesis of C16-C30 fragment

This methodology was first developed by Stéphane Wittmann on different models.[86] Starting from protected *β*-hydroxyl-esters and ethyl caproate, a novel Peterson olefination using chloromethyl(dimethyl)silane furnished several allysilanes with good yields. The best conditions were found to be the use of an organocerium reagent, which was produced by the addition of a Grignard reagent onto dry cerium(III) chloride. Addition of the organocerium onto different esters led to the formation of tertiary alcohol intermediates, which eliminated in the presence of a slurry of silica in CH_2Cl_2 to furnish the corresponding allylsilanes in moderate to good yields (Scheme 3.2).



Scheme 3.2: Peterson olefinations

The next step was a dehydrogenative coupling between the previously synthesised silanes and allylic alcohol **3.8**.[87,88] In the presence of (Xantphos)CuCl and lithium *tert*-butoxide in toluene, oxysilane were obtained in very good yields (Scheme 3.3).



Scheme 3.3: Dehydrogenative couplings

The mechanism of the dehydrogenative coupling is described below. Addition of the different reagents led to the formation of copper(I) hydride **A** species, which is in equilibrium between dimer **B** and higher aggregates **C**. Hydride **A** reacts in a *σ*-bond metathesis with a free alcohol to produce alkoxocopper(I) **D** and to release dihydrogen. A second metathesis occurs between product **D** and an equivalent of silane to furnish the silylated alcohol and to regenerate copper(I) hydride **A** (Figure 3.2).

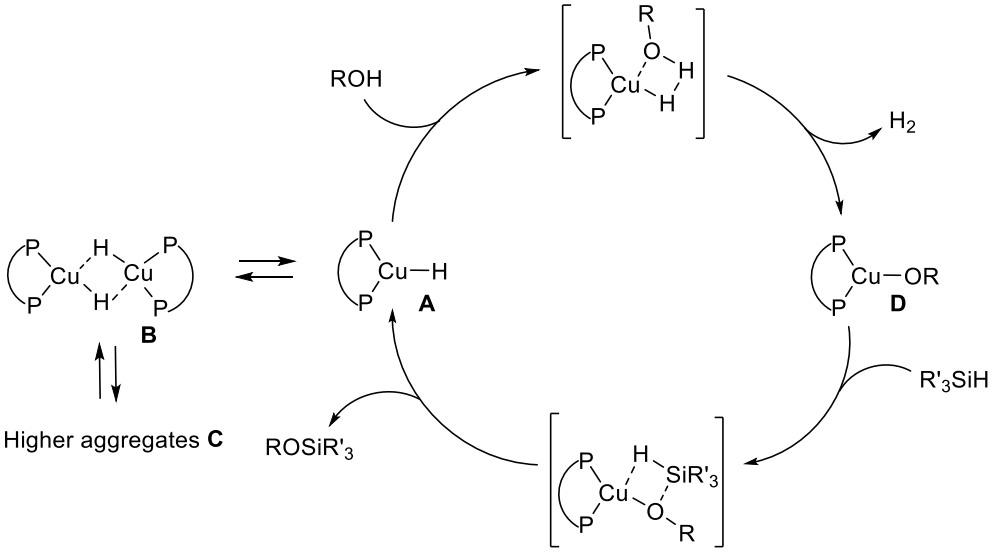
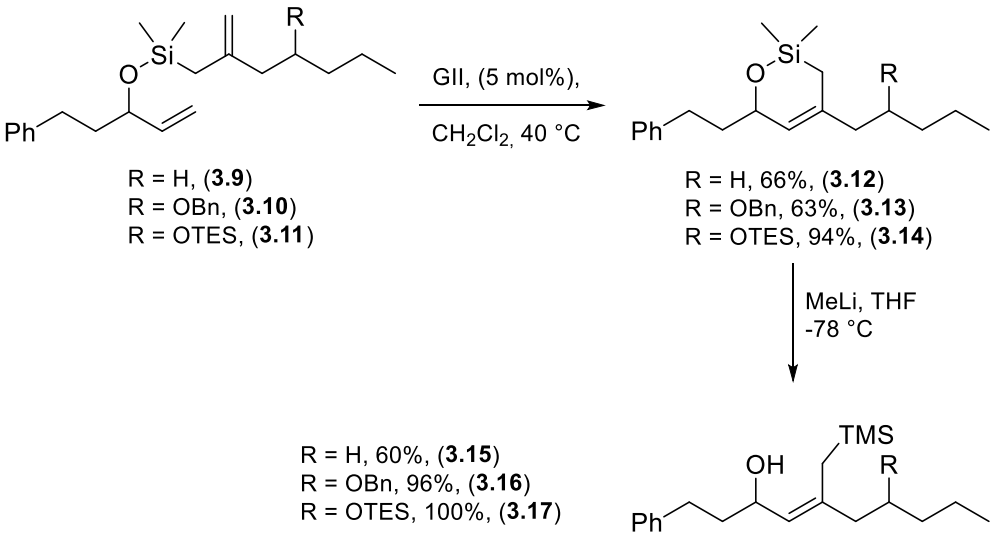


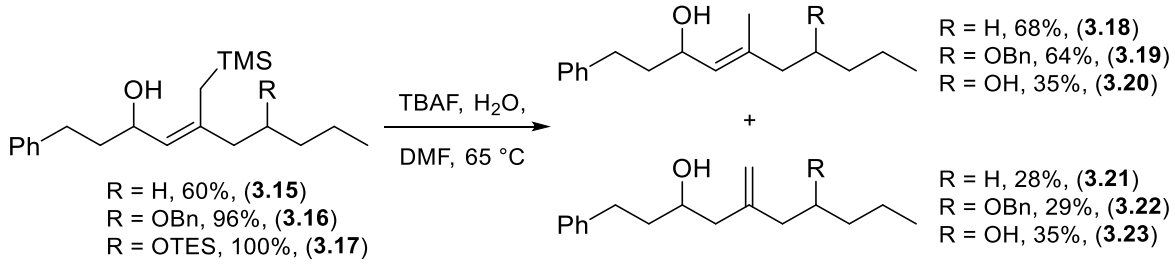
Figure 3.2: Mechanism of the (Xantphos)CuCl catalysed coupling

The newly formed oxysilanes were submitted to RCM conditions using Grubbs' second generation catalyst to generate cyclic alkenes. The six-membered rings were then opened by cleaving the O-Si bond by addition of methyllithium to give TMS substrates in good to excellent yields (Scheme 3.4).



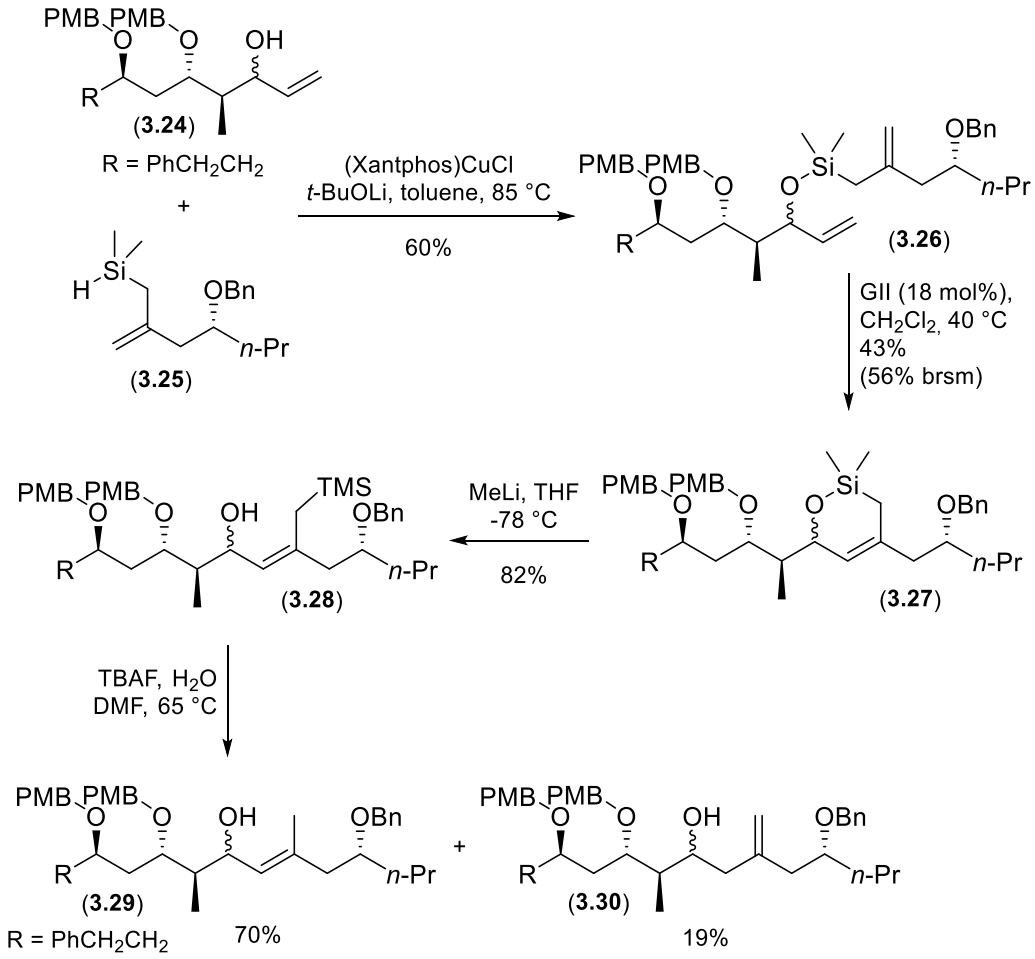
Scheme 3.4: Transformation of oxysilanes into allylic TMS substrates

The final step of this methodology was the TBAF-promoted desilylation to obtain a mixture of desired trisubstituted *E* alkenes and undesired isomerised alkenes (ratios between 1:1 and 2:1) (Scheme 3.5).



Scheme 3.5: Final step of the synthesis

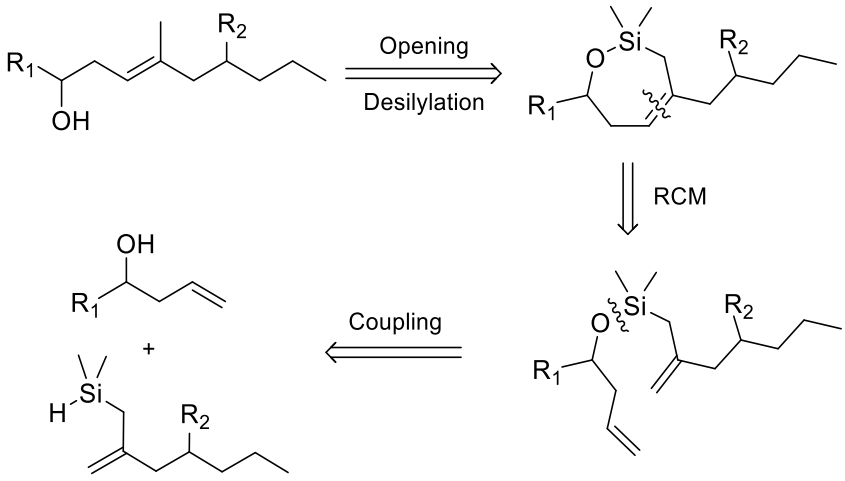
This method was applied to the synthesis of the C16-C30 fragment of dolabelide C (**3.1**). Coupling between alcohol **3.24** and silane **3.25** gave oxysilane **3.26** in 60% yield. Oxysilane **3.26** was subjected to RCM to furnish cyclic product **3.27** in 43% yield. Only one attempt of RCM was made, additional optimisations are necessary. Opening of the oxysilane **3.27** followed by desilylation produced the desired trisubstituted *E* olefin as the major product in 57% yield over two steps (Scheme 3.6).



Scheme 3.6: Application of the methodology to the synthesis of dolabelide C (**3.1**)

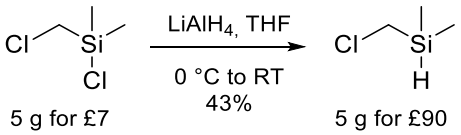
3.2 Application of the methodology to homoallylic alcohols

Development of the methodology was first solely focused on allylic alcohols. The same strategy could be applied to homoallylic alcohols. Homoallylic alcohols with the desired *E* alkenes would be synthesised by oxysilane opening and desilylation from seven-membered rings. The cyclic oxysilanes could be closed by RCM from acyclic precursors, which would be formed by dehydrogenative couplings between homoallylic alcohols and hydrosilanes (Scheme 3.7).



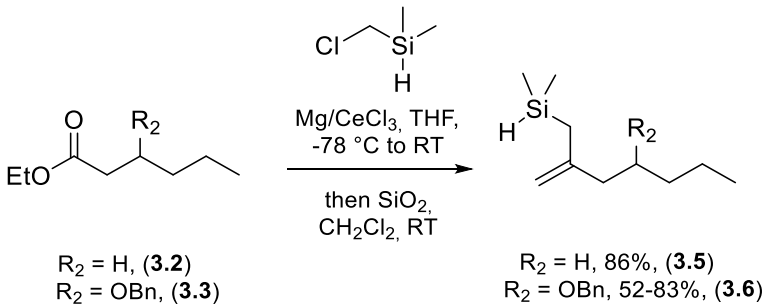
Scheme 3.7: Proposed general retrosynthesis

The first part of the synthesis was the formation of silanes *via* Peterson olefinations. Chloromethyl(dimethyl)silane being a very expensive reagent, it was synthesised by selective reduction of chloro(chloromethyl)dimethylsilane using lithium aluminium hydride (Scheme 3.8).[89]



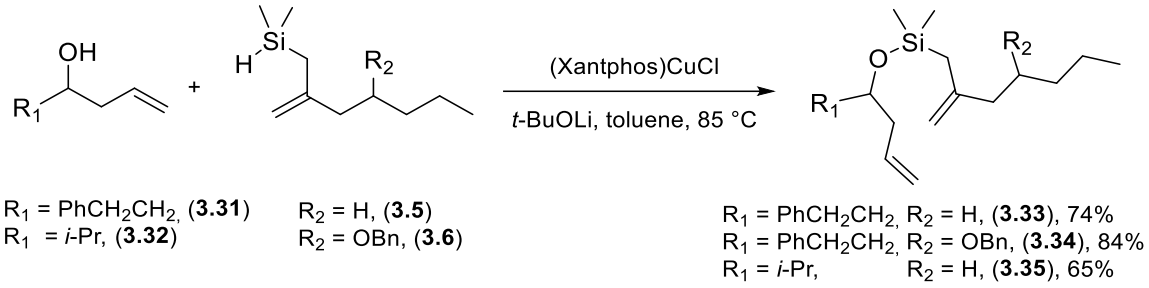
Scheme 3.8: Selective reduction of chloro(chloromethyl)dimethylsilane

Esters **3.2** and **3.3**, which were already available in the laboratory, were subjected to Peterson olefination conditions to obtain the corresponding allylsilanes **3.5** and **3.6** in excellent yield (Scheme 3.9).



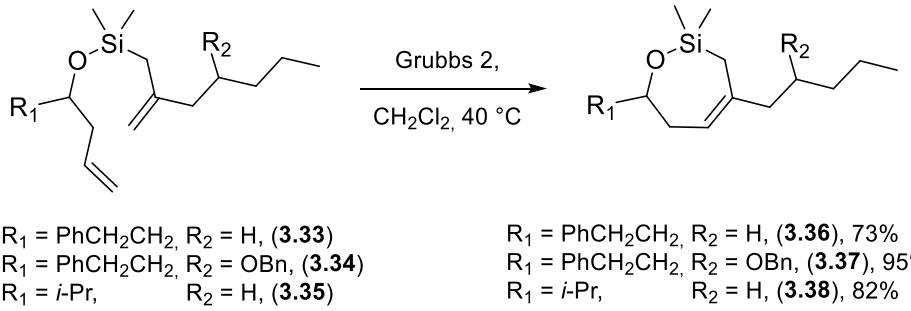
Scheme 3.9: Peterson olefination

Dehydrogenative coupling between homoallylic alcohols (**3.31** and **3.32**) and allysilanes (**3.5** and **3.6**) furnished oxysilanes (**3.33**, **3.34** and **3.35**) in very good yields (Scheme 3.10).



Scheme 3.10: Dehydrogenative coupling

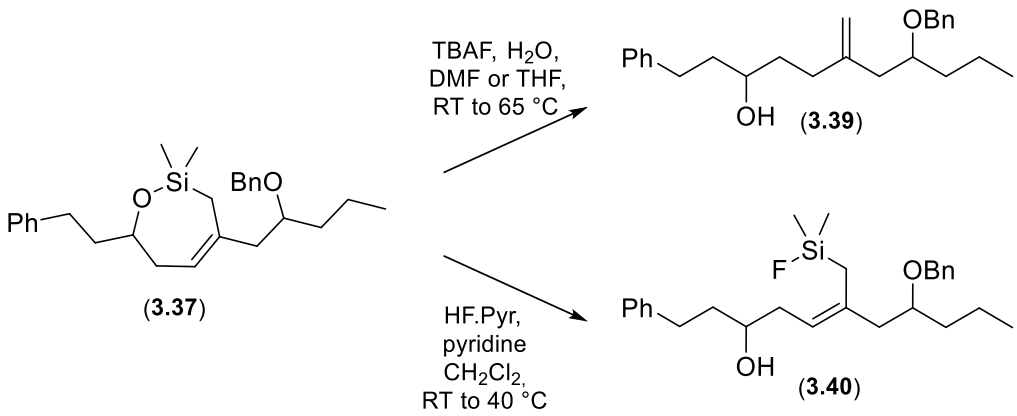
Acyclic oxysilanes (**3.33**, **3.34** and **3.35**) were submitted to RCM conditions to give the corresponding seven-membered rings (**3.36**, **3.37** and **3.38**) in excellent yields (Scheme 3.11).



Scheme 3.11: RCM metathesis

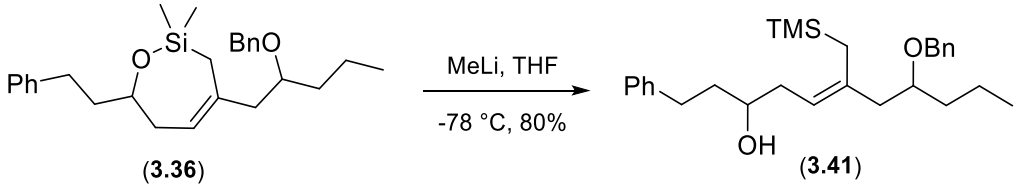
Direct cleavage of the tether and formation of the trisubstituted alkene was then attempted. When **3.37** was submitted to TBAF deprotection conditions, isomerised alkene **3.39** was observed as a major product with only traces of the desired product. When subjected to

HF.pyridine with or without an excess of pyridine, only fluorosilane **3.40** was observed by NMR before rapid decomposition (Scheme 3.12).



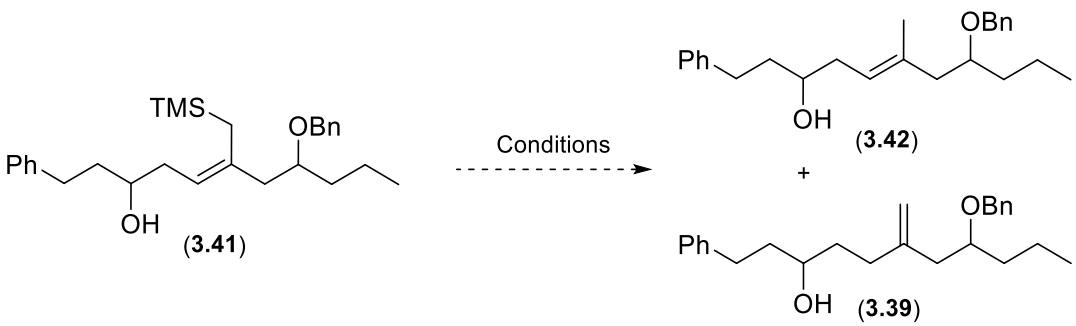
Scheme 3.12: Attempts of direct tether cleavage

Oxysilane **3.37** reacted with methyl lithium to furnish the corresponding opened product **3.41** in very good yield (Scheme 3.13).



Scheme 3.13: Tether cleavage with MeLi

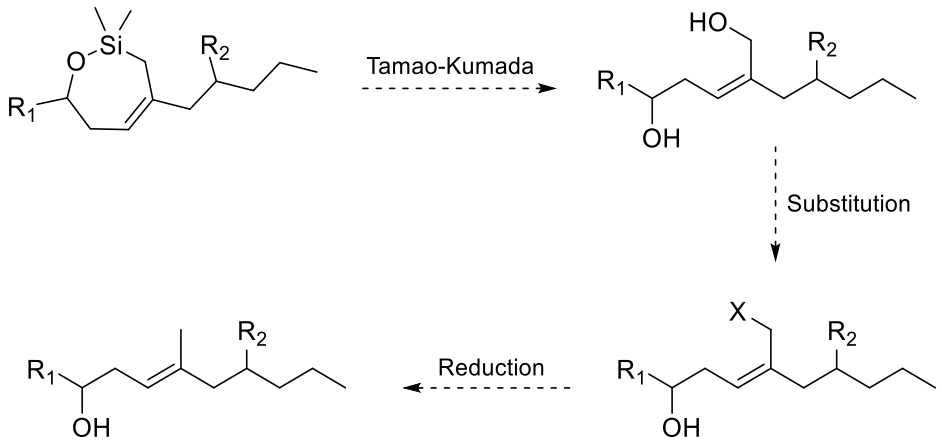
Conditions for the removal of the TMS group were tested. When the previous conditions optimised for the six-membered ring using TBAF/H_2O were tried, a 1:1 mixture of the desired alkene **3.42** and the undesired 1,1-disubstituted alkene **3.39** was obtained. Products **3.42** and **3.39** could not be separated by flash chromatography. More acidic conditions such as HF.pyridine and HF in CH_3CN only led to the formation of the undesired alkene **3.39**. Only starting material was recovered when using potassium carbonate in methanol. Anhydrous caesium fluoride gave a 2:3 mixture of **3.42**/**3.39** in favour of the undesired product. Caesium fluoride with water furnished the same 1:1 ratio than TBAF with water (Table 3.1).



Conditions	Solvent	Temperature	Desired (290)/ Undesired (287)
TBAF/H_2O	DMF	65 °C	1/1
HF.Pyr	CH_2Cl_2	RT	0/1
HF (5%)	CH_3CN	RT	0/1
K_2CO_3	MeOH	65 °C	-
CsF	DMF	RT to 65 °C	2/3
CsF/H_2O	DMF	RT to 65 °C	1/1

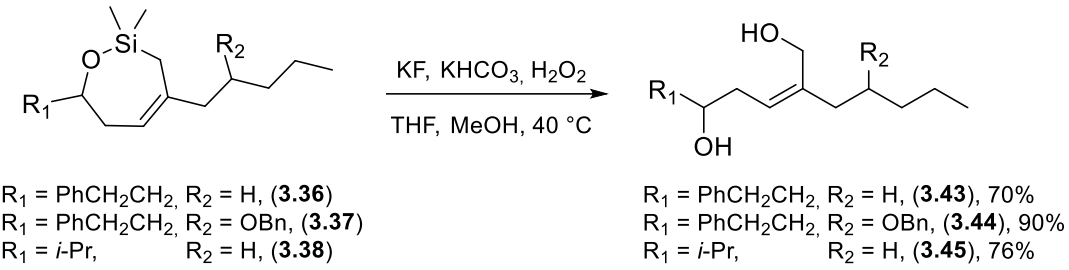
Table 3.1: Results of the desilylation tests

After these unsuccessful attempts, it was decided to modify the end game. In 2001, Takeda *et al.* used a Tamao-Kumada oxidation to convert different seven-membered oxysilanes into the corresponding diols.[90] This method could be used to obtain diol products, where the difference of reactivity between the newly formed primary allylic alcohol and the secondary homoallylic alcohol would allow the selective substitution and reduction of the allylic alcohol. This method would also prevent the formation of the undesired gem-disubstituted alkene (Scheme 3.14).



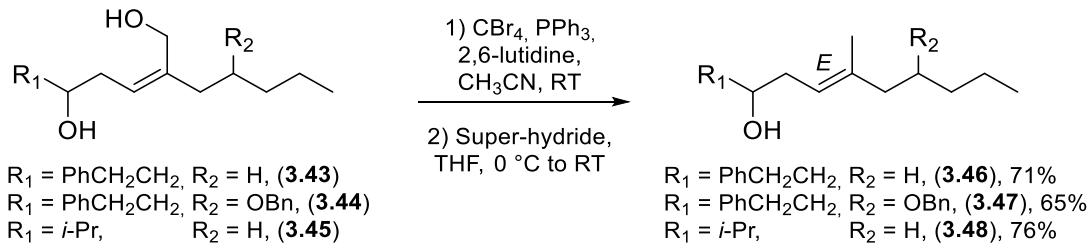
Scheme 3.14: Envisaged end game

Tamao-Kumada oxidation using Takeda's condtions led to the formation of corresponding diols in very good yields (Scheme 3.15).



Scheme 3.15: Tamao-Kumada oxidation

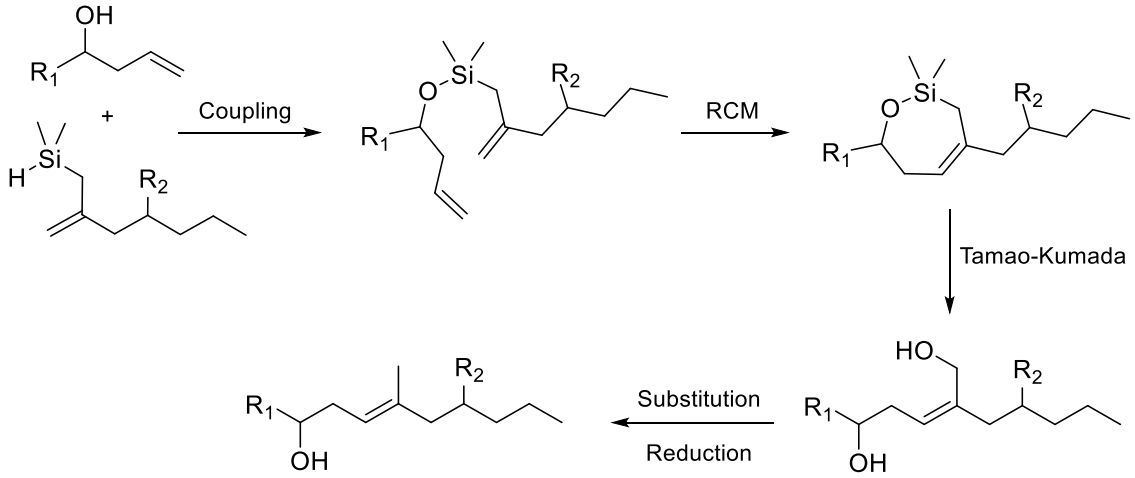
Diols **3.43**, **3.44** and **3.45** were treated with a mixture of carbon tetrabromide, triphenylphosphine and 2,6-lutidine in acetonitrile to furnish the corresponding allylic bromides, which were used in the next step without purification. The crude products were immediately reduced by Super-Hydride® (lithium triethylborohydride) in THF to give the final products **3.46**, **3.47** and **3.48** with the desired *trans* geometry (Scheme 3.16).



Scheme 3.16: Bromination followed by reduction

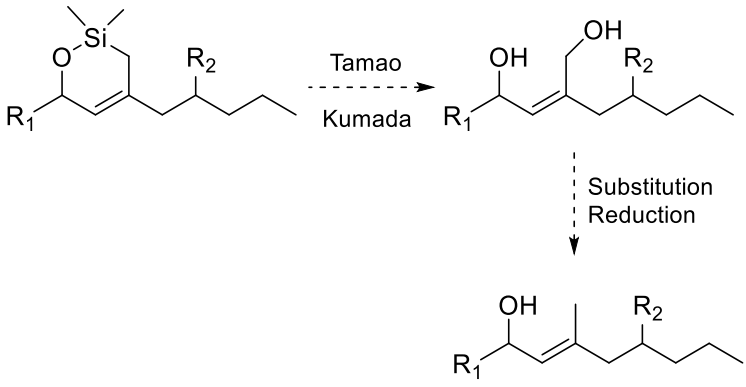
3.3 Conclusion and future work

In summary, it has been shown that the previously developed methodology could be partially applied to homoallylic alcohols. The two-step process using MeLi and TBAF only gave poor results on our substrates for the cleavage of the oxysilanes. A three-step method to remove the tether was developed and permitted the obtention of trisubstituted alkenes with the desired geometry without any sign of isomerised olefins (Scheme 3.17).



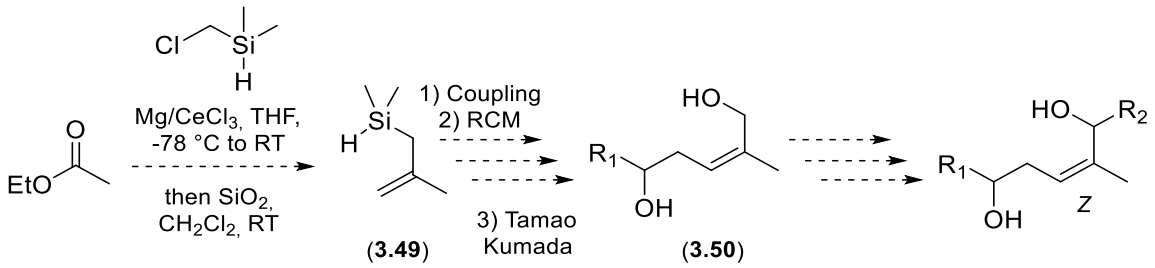
Scheme 3.17: Summary of the work

In the future, the three-step method could be applied to six-membered oxysilanes to prevent the formation of the isomerised product (Scheme 3.18).



Scheme 3.18: Future work

Formation of the allylsilane **3.49** derived from ethyl acetate could also allow the synthesis of trisubstituted *Z* alkenes (Scheme 3.19).



Scheme 3.19: Possible formation of cis alkenes

Chapter 4: Experimental

Apparatus:

NMR spectra were recorded using a Bruker DPX-400 spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz) and a Bruker DPX-500 spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz). Deuterated chloroform ($CDCl_3$) was used as the solvent for both ^{1}H and ^{13}C NMR, with residual solvent peak δ 7.26 being used for calibration of ^{1}H NMR and $CDCl_3$ peak at δ 77.16 for ^{13}C. Signal splitting patterns are described as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), octet (oct), nonet (non), multiplet (m), broad singlet, or any combination of the above. Two dimensional experiments (COSY, HSQC, HMBC, and HMQC) were recorded, where necessary, for assignment. Sn-H and Sn-C couplings were averaged over 117/119Sn. IR spectra were recorded using a Golden Gate™ attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under FAB, ESI and CI conditions by the University of Glasgow analytical service.

Chromatography:

Flash chromatography was executed under forced flow conditions, using the indicated solvent system and the EMD Geduran silica gel 60 as solid support. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 covered aluminium sheets, and monitored by UV-light or by staining with a solution of anisaldehyde or $KMnO_4$ mixture.

Solvents and reagents:

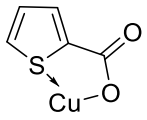
Reactions were collected from an in-house solvent purification system (THF, CH_2Cl_2, Et_2O, CH_3CN, and toluene). Chromatography solvents were HPLC grade solvents, stored in Winchester bottles. All reagents were used directly from supplier, unless prior purification is explicitly stated.

General conditions:

Air or moisture sensitive reactions were carried out in pre-dried glassware; either overnight in an oven (125 °C) or by flame drying under vacuum. Argon was used to create an inert atmosphere. Degassing solvent was done using freeze and thaw method.

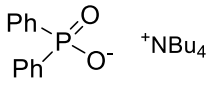
Reagents and catalysts:

Copper-(I)-thiophen-2-carboxylate (CuTc).[91]



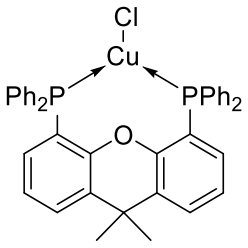
A solution of Cu_2O (2.8 g, 20 mmol) and thiophen-2-carboxylic acid (10 g, 80 mmol, 4 equiv) in toluene (30 mL) was heated to reflux on a Dean-Stark trap overnight. After cooling to RT, the slurry was filtered under argon. The residue was first washed with MeOH (30 mL) and then repeatedly washed with anhydrous Et_2O until the filtrate was completely colorless (~ 1 L). After washing with hexanes (15 mL), the powder was dried to furnish a red powder (5.6 g, 75%).

Tetrabutyl ammoniumdiphenylphosphinate.[92]



Diphenylphosphinic acid (4 g, 18.3 mmol) was dissolved in MeOH (20 mL), a 1 M solution of tetra-*n*-butylammonium hydroxide in MeOH (18.3 mL, 18.3 mmol, 1.00 equiv) was added and the mixture stirred for 5 min. After filtration through a pad of celite, the solvent was removed under reduced pressure to yield a yellow oil, which was recrystallised from diethyl ether to give colorless, hygroscopic needles (4.32 g, 51%). Tetrabutyl ammoniumdiphenylphosphinate was dried prior to use by azeotropic removal of water using benzene.

(Xantphos)CuCl.[88]

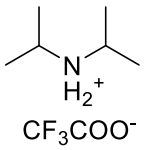


To a suspension of dry CuCl (109 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) was added Xantphos (578 mg, 1.00 mmol) and resultant clear solution was stirred for 10 min. The solvent was removed under vacuum and the precipitated solid was triturated in dry and degassed acetonitrile (3 mL). The suspension was vigorously stirred for 4 h and filtered under Argon atmosphere. The wet cake was washed with acetonitrile (3 x 5 mL) and dried under vacuum to afford an off-white powder (380 mg, 56%).

Samarium(II) iodide.[93]

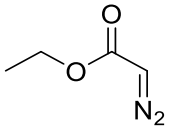
1,2-Diiodoethane (815 mg, 2.89 mmol) was dissolved in Et_2O (30 mL) and the organic solution was washed with a saturated aqueous solution of sodium thiosulfate (25 mL). The phases were separated, the organic layer was dried over magnesium sulfate and concentrated under vacuum. The powder was dried in the dark under high vacuum for 6 h. Samarium (541 mg, 3.61 mmol, 1.25 equiv) was flame dried under high vacuum and let to cool down under argon. 1,2-diiodoethane and THF (29 mL) were subsequently added and the green solution was left to stirr overnight. The dark blue solution of samarium(II) iodide in THF (29 mL, 29 mmol) was used without further manipulation.

Diisopropylammonium 2,2,2-trifluoroacetate



To a stirred mixture of diisopropylamine (1.4 mL, 10 mmol) in Et_2O (10 mL) at 0 °C was added dropwise trifluoroacetic acid (1.1 mL, 10 mmol, 1.0 equiv). The reaction mixture is stirred at 0 °C for 5 min. The crystals were filtered and washed with Et_2O (10 mL), dried under vacuum to afford white crystals (1.8 g, 83%).

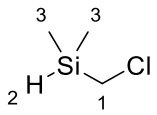
Ethyl 2-diazoacetate.[94]



Ethyl acetoacetate (3.8 mL, 30 mmol), 4-acetamidobenzenesulfonyl azide (7.2 g, 30 mmol, 1.0 equiv) and tetrabutylammonium bromide (0.19 g, 0.60 mmol, 0.02 equiv) were dissolved in pentane (100 mL) and left to stir at RT for 5 min then cooled to 0 °C. Then a 3 M aqueous solution of potassium hydroxide (30 mL) was added slowly (over 10 min) and the mixture left to stir for 4 h at RT. Once the reaction was complete, the mixture was diluted with water (50 mL) and Et_2O (50 mL). The organic phase was isolated and the aqueous layer extracted with Et_2O (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to give the ethyl 2-diazoacetate as a bright yellow oil (1.45 g, 51%).

(Chloromethyl)dimethylsilane.[89]

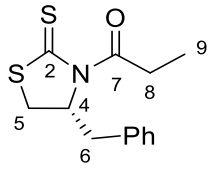
C_3H_9ClSi
Mol. Wt. = 108.64 g/mol



To a mixture of lithium aluminium hydride (1.86 g, 48.9 mmol, 0.500 equiv) in Et_2O (90 mL) at 0 °C was added dropwise (over 4 h) chloro(chloromethyl)dimethylsilane (18.6 mL, 97.8 mmol). The mixture was warmed to RT and left to stir overnight. The reaction was quenched with a 1 M aqueous solution of hydrochloric acid (90 mL) then the layers were separated. The aqueous phase was extracted with Et_2O (3 × 90 mL), dried over magnesium sulfate, filtered and carefully concentrated under vacuum (25 °C, 180 mbar). The crude was purified by distillation (81–83 °C) to furnish (chloromethyl)dimethylsilane (5.56 g, 43%) as a colourless liquid.

(*R*)-4-Benzyl-3-propionylthiazolidine-2-thione (2.4).[35]

$C_{13}H_{15}NOS_2$
Mol. Wt = 265.35 g/mol



In a 3-necked flask, sodium borohydride (13.8 g, 365 mmol, 2.40 equiv) was dissolved in THF (400 mL). (*R*)-Phenylalanine (25.0 g, 150 mmol) was added in one portion then the mixture was cooled to 0 °C. A solution of iodine (38.0 g, 150 mmol, 1.00 equiv) in THF (100 mL) was added dropwise via the addition funnel (over 45 min). After the addition was complete the flask was heated to reflux and left to stir overnight. The flask was then allowed to cool down and methanol was added cautiously until the mixture became clear. The solvent was then removed under vacuum giving a white paste, which was dissolved in a 20% aqueous solution of potassium hydroxide (300 mL). The crude mixture was left to stir at RT for 3 h, then the aqueous phase was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum giving (*R*)-phenylalaninol as a white solid which was used in the next step without purification.

Crude (*R*)-phenylalaninol was dissolved in a 3 M aqueous solution of potassium hydroxide (400 mL) and left to stir for 30 min. Carbon disulfide (45 mL, 0.75 mol, 5.0 equiv) was then added dropwise, the mixture was warmed to 110 °C and stirred overnight. The flask was then cooled to RT and the reaction mixture was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The crude product **2.5** (29 g, 94% over 2 steps) was then used in the next step without further purification.

(The aqueous phase was diluted and the glassware rinsed with a solution of bleach and potassium hydroxide to remove any traces of carbon sulfide).

(*R*)-4-Benzylthiazolidine-2-thione **2.5** (8.1 g, 40 mmol) was dissolved in CH_2Cl_2 (200 mL) followed by addition of freshly distilled triethylamine (14.0 mL, 100 mmol, 2.50 equiv). The reaction was cooled to 0 °C followed by addition of propionyl chloride (5.6 mL, 60 mmol, 1.5 equiv) over 5 min. The reaction was left to stir at RT overnight, after which the mixture was diluted with CH_2Cl_2 (200 mL) and water (400 mL). The aqueous phase was extracted with

CH_2Cl_2 (3 × 200 mL) and the organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by recrystallisation from acetonitrile to furnish **2.4** (8.8 g, 87%) as a bright yellow solid.

Mp: 98–100 °C. lit. 105 °C

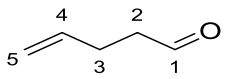
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.29 (m, 5H, H^{Ar}), 5.43–5.38 (m, 1H, H^4), 3.50–3.39 (m, 3H, H^5/H^8), 3.26–3.04 (m, 2H, H^5/H^6), 2.91 (d, *J* = 11.6 Hz, 1H, H^6), 1.22 (t, *J* = 7.3 Hz, 3H, H^9).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 201.1 (C^1), 175.0 (C^7), 136.7 (C^{Ar}), 129.5 (C^{Ar}), 129.0 (C^{Ar}), 127.3 (C^{Ar}), 68.7 (C^4), 36.8 (C^8), 32.4 (C^5), 32.0 (C^6), 8.9 (C^9).

In agreement with literature data.[95]

4-Penten-1-al (2.25).[35]

C_5H_8O
Mol Wt. = 84.13 g/mol



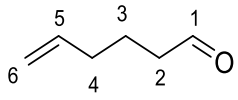
To a solution of 4-penten-1-ol (2.30 mL, 22.3 mmol) in CH_2Cl_2 (100 mL) was added BAIB (7.90 g, 24.5 mmol, 1.10 equiv) and TEMPO (348 mg, 2.23 mmol, 0.100 equiv). The mixture was then stirred at RT for 3 h. The reaction was then diluted with water (100 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 70 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum (28 °C, 180 mbar). The crude mixture was purified by column chromatography (90:10 Pentane/Et_2O) to furnish **2.25** as a colourless liquid (1.19 g, 65%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (t, *J* = 1.6 Hz, 1H, H^1), 5.87 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H, H^4), 5.13–5.04 (m, 2H, H^5), 2.61–2.57 (m, 2H, H^2), 2.46–2.40 (m, 2H, H^3).

In agreement with literature data.[35]

Hex-5-en-1-al (2.67). [96]

$C_6H_{10}O$
Mol Wt. = 98.14 g/mol



Aldehyde **2.67** (colourless liquid) was obtained from the corresponding alcohol according to the procedure described above for aldehyde **2.25**.
Purification by flash column chromatography (90:10 Pentane/Et_2O).
Scale: 39.9 mmol.
Yield: 70%.

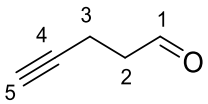
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.78 (t, *J* = 1.7 Hz, 1H, H^1), 5.77 (ddt, *J* = 16.9, 10.2, 7.1 Hz, 1H, H^5), 5.07–4.97 (m, 2H, H^6), 2.45 (td, *J* = 7.3, 1.7 Hz, 2H, H^2), 2.10 (q, *J* = 7.1 Hz, 2H, H^4), 1.74 (p, *J* = 7.4 Hz, 2H, H^3).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.6 (C^1), 137.7 (C^5), 115.7 (C^6), 43.3 (C^2), 33.1 (C^4), 21.3 (C^3).

In agreement with literature data.[96]

Pent-4-ynal (2.39).[97]

C_5H_6O
Mol. Wt. = 82.1 g/mol



Aldehyde **2.39** (colourless liquid) was obtained from the corresponding alcohol according to the procedure described above for aldehyde **2.25**.
Purification by flash column chromatography (90:10 Pentane/Et_2O).
Scale: 32.0 mmol.
Yield: 71%.

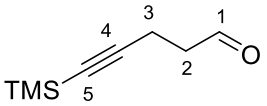
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (t, *J* = 1.1 Hz, 1H, H^1), 2.70–2.62 (m, 2H, H^2), 2.48 (td, *J* = 7.2, 2.7 Hz, 2H, H^3), 1.97 (t, *J* = 2.7 Hz, 1H, H^5).

^{13}C NMR ($CDCl_3$, 101 MHz,) δ 200.1 (C^1), 82.4 (C^4), 69.3 (C^5), 42.4 (C^2), 11.7 (C^3).

In agreement with literature data.[97]

5-(Trimethylsilyl)pent-4-ynal (2.45). [98]

$C_8H_{14}OSi$
Mol. Wt. = 154.28 g/mol



To a solution of pent-4-ynol (4.0 g, 47 mmol) in THF (200 mL) cooled to −78 °C was added dropwise a 2 M solution of *n*-BuLi in hexanes (50.0 mL, 100 mmol, 2.20 equiv). The reaction was stirred for an additional 45 min then trimethylsilyl chloride (13.7 mL, 108 mmol, 2.30 equiv) was added and the mixture was warmed to RT over 1 h 30. A 1:1 solution of 1 M aqueous hydrochloric acid and Et_2O (200 mL) was then added and the mixture stirred overnight. A saturated aqueous solution of sodium bicarbonate (100 mL) was added and the aqueous phase was extracted with Et_2O (3 × 200 mL). The organic phases were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. The product (7.4 g) was used in the next step without further purification.

To a solution of crude alcohol (7.4 g, 47 mmol) in CH_2Cl_2 (60 mL) was added BAIB (16.8 g, 52.2 mmol, 1.10 equiv) and TEMPO (0.74 g, 4.7 mmol, 0.10 equiv). The reaction was stirred for 4 h before being quenched by the addition of water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were combined, dried over magnesium sulfate and concentrated under vacuum. The product was then purified by flash chromatography (95:5 PE/Et_2O) to give **2.45** as a yellow oil (6.2 g, 85% over 2 steps).

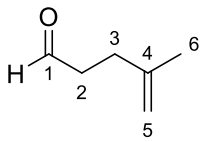
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.81 (s, 1H, H^1), 2.69 (t, *J* = 7.2 Hz, 2H, H^2), 2.56 (t, *J* = 7.2 Hz, 2H, H^3), 0.15 (s, 9H, TMS).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.2 (C^1), 104.5 (C^5), 85.6 (C^4), 42.4 (C^2), 13.0 (C^3), −0.1 (TMS).

In agreement with literature data.[98]

4-Methylpent-4-enal (2.66). [99]

$C_6H_{10}O$
Mol. Wt. = 98.14 g/mol



To a solution of lithium aluminium hydride (9.49 g, 250 mmol, 1.00 equiv) in Et_2O (400 mL) at 0 °C was added slowly methyl methacrylate (26.7 mL, 250 mmol). The mixture was warmed to RT and stirred for 4 h. The reaction was then cooled to 0 °C and cautiously quenched with a 1 M aqueous solution of hydrochloric acid (250 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The organic extract was dried over magnesium sulfate, filtered and concentrated under vacuum (28 °C, 180 mbar) to give methallyl alcohol. The crude product (9.70 g) was used in the next step without further purification.

In a flask connected to a Dean-Stark apparatus, crude methallyl alcohol (9.70 g, 135 mmol) was dissolved in triethyl orthoacetate (120 mL) and propionic acid (6.0 mL, 80 mmol, 0.67 equiv) was added. The reaction was heated to 160 °C for 15 h. The mixture was cooled to RT and was diluted with Et_2O (200 mL). The organic phase was washed with a 2 M aqueous solution of hydrochloric acid (200 mL), a saturated aqueous solution of sodium bicarbonate (2 × 200 mL) and brine (150 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum (28 °C, 180 mbar) to furnish crude ethyl 4-methylpent-4-enoate. The crude product (19.1 g) was used in the next step without further purification.

Ethyl 4-methylpent-4-enoate (19.1 g, 134 mmol) was added dropwise (over 1 h) to a solution of lithium aluminium hydride (5.10 g, 134 mmol, 1.00 equiv) in Et_2O (400 mL) at 0 °C. The slurry was allowed to warm up to RT and was stirred for an additional 40 min. The reaction was cooled to 0 °C and quenched with water (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic layers were combined, dried over magnesium sulfate, filtered and concentrated

under vacuum to yield 4-methylpent-4-en-1-ol (11.5 g) as a colourless liquid that was used without further purification.

Oxalyl chloride (13.6 mL, 161 mmol, 1.40 equiv) in CH_2Cl_2 (400 mL) was cooled to −78 °C then DMSO (23 mL, 0.32 mol, 2.8 equiv) in CH_2Cl_2 (25 mL) was added. The solution was stirred for 20 min and a solution of 4-methylpent-4-en-1-ol (11.5 g, 115 mmol) in CH_2Cl_2 (50 mL) was added dropwise. The reaction was left to stir for 1 h at −78 °C then triethylamine (89 mL, 0.64 mol, 5.6 equiv) was added and the reaction was allowed to warm up to RT over 1 h. The reaction was quenched by addition of a 2 M aqueous solution of hydrochloric acid (250 mL), the layers were separated and the organic phase was washed with a 1 M aqueous solution of hydrochloric acid (2 × 250 mL), a saturated aqueous solution of sodium bicarbonate (500 mL) and brine (300 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum (28 °C, 180 mbar). The crude mixture was then purified by distillation (99–101 °C) to give aldehyde **2.66** (9.36 g, 38% over four steps) as a colourless liquid.

(The aqueous phase was diluted and the glassware rinsed with a solution of bleach and potassium hydroxide to remove any traces of dimethyl sulfide).

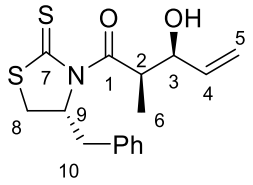
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.78 (t, *J* = 1.7 Hz, 1H, H^1), 4.77 (s, 1H, H^5), 4.68 (s, 1H, H^5), 2.58 (td, *J* = 7.5, 1.7 Hz, 2H, H^2), 2.34 (t, *J* = 7.5 Hz, 2H, H^3), 1.74 (s, 3H, H^6).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 202.3 (C^1), 143.9 (C^4), 110.8 (C^5), 41.9 (C^2), 30.0 (C^3), 22.7 (C^6).

In agreement with literature data.[99]

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylpent-4-en-1-one (2.7).[36]

$C_{16}H_{19}NO_2S_2$
Mol. Wt. = 321.45 g/mol



To a solution of (*R*)-4-Benzyl-3-proponylthiazolidin-2-thione **2.4** (15.0 g, 56.5 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added titanium tetrachloride (6.20 mL, 56.5 mmol, 1.00 equiv). The mixture was stirred 15 min at 0 °C then diisopropylethylamine (9.90 mL, 56.5 mmol, 1.00 equiv) was added. The reaction was stirred for 1 h then cooled to −78 °C and *N*-methyl-2-pyrrolidinone (5.40 mL, 56.5 mmol, 1.00 equiv) was added. The reaction was stirred for 1 h followed by dropwise addition of acrolein (4.10 mL, 62.0 mmol, 1.10 equiv). The reaction was stirred for 1 h at −78 °C then warmed to RT over 1 h. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatrography (80:20 PE/EtOAc) to furnish a yellow oil **2.7** as a single diastereomer (11.8 g, 65%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.22 (m, 5H, H^{Ar}), 5.81 (ddd, *J* = 17.1, 10.6, 5.4 Hz, 1H, H^4), 5.33–5.24 (m, 2H, H^9/H^{5trans}), 5.18 (dt, J = 10.6, 1.3 Hz, 1H, H^{5cis}), 4.54 (dq, *J* = 6.8, 4.1 Hz, 1H, H^2), 4.46–4.42 (m, 1H, H^3), 3.36 (dd, *J* = 11.4, 7.1 Hz, 1H, H^{10}), 3.20 (dd, *J* = 13.2, 3.8 Hz, 1H, H^8), 3.02 (dd, *J* = 13.2, 10.6 Hz, 1H, H^8), 2.87 (d, *J* = 11.4 Hz, 1H, H^{10}), 2.53 (d, *J* = 3.3 Hz, 1H, OH), 1.22 (d, *J* = 6.8 Hz, 3H, H^6).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.6 (C^7), 177.6 (C^1), 137.8 (C^4), 136.6 (C^{Ar}), 129.6 (C^{Ar}), 129.1 (C^{Ar}), 127.4 (C^{Ar}), 116.5 (C^5), 73.7 (C^3), 69.1 (C^9), 44.0 (C^2), 36.9 (C^8), 32.4 (C^{10}), 11.2 (C^6).

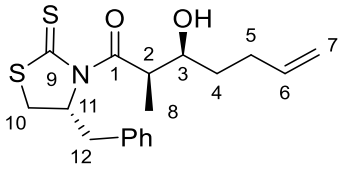
$[\alpha]_D^{25}$ −163.1 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −166 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[36]

(2*R*,3*S*)-1-((*R*)-4'-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methyl-hept-6-en-1-one (2.26).[35]

$C_{18}H_{23}NO_2S_2$

Mol. Wt. = 349.45 g/mol



Aldol **2.26** (yellow oil) was obtained from the corresponding Crimmins auxiliary **2.4** and aldehyde **2.25** according to the procedure described above for aldol **2.7**.

Purification by flash column chromatography (80:20 PE/EtOAc).

Scale: 54.0 mmol.

Yield: 78%, dr = 95:5.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.19 (m, 5H, H^{Ar}), 5.75 (ddt, *J* = 16.6, 10.1, 6.6 Hz, 1H, H^6), 5.28 (ddd, J = 10.5, 7.2, 3.8 Hz, 1H, H^{11}), 4.98 (dq, *J* = 16.6, 1.5 Hz, 1H, H^{7trans}), 4.98 (ddd, *J* = 10.1, 3.0, 1.1 Hz, 1H, H^{7cis}), 4.41 (qd, *J* = 6.9, 3.3 Hz, 1H, H^2), 3.95 (dq, *J* = 7.5, 3.3 Hz, 1H, H^3), 3.33 (dd, *J* = 11.5, 7.2 Hz, 1H, H^{12}), 3.14 (dd, *J* = 13.2, 3.8 Hz, 1H, H^{10}), 2.97 (dd, *J* = 13.2, 10.5 Hz, 1H, H^{10}), 2.83 (d, *J* = 11.5 Hz, 1H, H^{12}), 2.62 (d, *J* = 3.3 Hz, 1H, OH), 2.19−2.12 (m, 1H, H^4), 2.08−2.01 (m, 1H, H^4), 1.62−1.54 (m, 1H, H^5), 1.44−1.37 (m, 1H, H^5), 1.19 (d, *J* = 6.9 Hz, 3H, H^8).

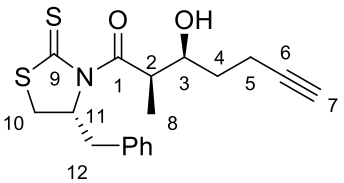
^{13}C NMR ($CDCl_3$, 101 MHz) δ 201.5 (C^9), 178.5 (C^1), 138.2 (C^6), 136.5 (C^{Ar}), 129.6 (C^{Ar}), 129.1 (C^{Ar}), 127.4 (C^{Ar}), 115.2 (C^7), 71.8 (C^{11}), 68.9 (C^3), 43.4 (C^2), 36.9 (C^{10}), 33.5 (C^{12}), 32.2 (C^4), 30.3 (C^5), 10.6 (C^8).

In agreement with literature data.[35]

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylhept-6-yn-1-one (2.40).

$C_{18}H_{21}NO_2S_2$

Mol. Wt. = 347.49 g/mol



Aldol **2.40** (yellow oil) was obtained from the corresponding Crimmins auxiliary **2.4** and aldehyde **2.39** according to the procedure described above for aldol **2.7**.
Purification by flash column chromatography (80:20 PE/EtOAc).
Scale: 18.0 mmol.
Yield: 78%, dr = 90:10.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.27 (m, 5H, H^{Ar}), 5.39 (ddd, *J* = 10.6, 6.9, 3.9 Hz, 1H, H^{11}), 4.47 (qd, *J* = 6.9, 2.9 Hz, 1H, H^{2}), 4.08 (br d, *J* = 9.5 Hz, 1H, H^{3}), 3.42 (dd, *J* = 11.6, 6.9 Hz, 1H, H^{12}), 3.21 (dd, *J* = 13.2, 3.9 Hz, 1H, H^{10}), 3.05 (dd, *J* = 13.2, 10.6 Hz, 1H, H^{10}), 2.91 (d, *J* = 11.6 Hz, 1H, H^{12}), 2.87 (s, 1H, OH), 2.40–2.33 (m, 2H, H^{5}), 1.98 (t, *J* = 2.7 Hz, 1H, H^{7}), 1.77 (ddt, *J* = 13.1, 9.5, 6.5 Hz, 1H, H^{4}), 1.67–1.55 (m, 1H, H^{4}), 1.28 (d, *J* = 6.9 Hz, 3H, H^{8}).

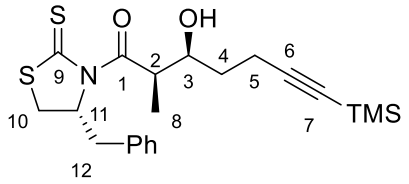
^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.3 (C^{9}), 178.5 (C^{1}), 136.7 (C^{Ar}), 129.8 (C^{Ar}), 129.3 (C^{Ar}), 127.7 (C^{Ar}), 84.2 (C^{6}), 71.4 (C^{11}), 69.3 (C^{7}), 69.0 (C^{3}), 43.7 (C^{2}), 37.2 (C^{10}), 33.2 (C^{12}), 32.5 (C^{4}), 15.6 (C^{5}), 11.15 (C^{8}).

IR (thin film) 3290, 2924, 2854, 1697, 1494, 1340, 1296, 1192, 1163, 1138, 1101 cm^{-1}.

HRMS (ESI) for $C_{18}H_{21}NNaS_2O_2$**:** 370.0906, found**:** 370.0892.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methyl-7(trimethylsilyl) hept-6-yn-1-one (2.46).

$C_{21}H_{29}NO_2S_2Si$
Mol. Wt. = 419.67 g/mol



Aldol **2.46** (yellow oil) was obtained from the corresponding Crimmins auxiliary **2.4** and aldehyde **2.45** according to the procedure described above for aldol **2.7**.
Purification by flash column chromatography (90:10 PE/EtOAc).

Scale: 18.0 mmol.
Yield: 89%, dr = 90:10.

^{1}H NMR ($CDCl_3$, 400 MHz,) δ 7.39–7.28 (m, 5H, H^{Ar}), 5.37 (ddd, *J* = 10.5, 6.7, 4.0 Hz, 1H, H^{11}), 4.52 (qd, *J* = 6.9, 3.0 Hz, 1H, H^2), 4.06 (dq, *J* = 9.6, 3.3 Hz, 1H, H^3), 3.44–3.37 (m, 1H, H^{12}), 3.22 (dd, *J* = 13.1, 4.0 Hz, 1H, H^{10}), 3.05 (dd, *J* = 13.1, 10.5 Hz, 1H, H^{10}), 2.91 (d, *J* = 11.5 Hz, 1H, H^{12}), 2.80 (d, *J* = 3.0 Hz, 1H, OH), 2.46–2.29 (m, 2H, H^5), 1.82–1.70 (m, 1H, H^4), 1.66–1.57 (m, 1H, H^4), 1.27 (d, *J* = 6.9 Hz, 3H, H^8), 0.15 (s, 9H, TMS).

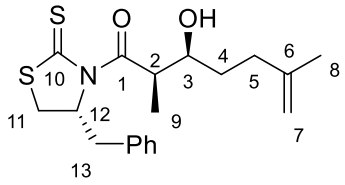
^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.4 (C^9), 178.0 (C^1), 136.5 (C^{Ar}), 129.6 (C^{Ar}), 129.1 (C^{Ar}), 127.4 (C^{Ar}), 106.7 (C^7), 85.6 (C^6), 71.6 (C^{11}), 69.0 (C^3), 43.6 (C^2), 36.9 (C^{10}), 33.3 (C^{12}), 32.2 (C^4), 16.9 (C^5), 10.8 (C^8), 0.27 (TMS).

IR (thin film) 2956, 2173, 1675, 1454, 1340, 1248, 1156, 1136, 1030 cm^{-1}.

HRMS (ESI) for $C_{21}H_{29}NNaO_2S_2Si$**:** 442.1288, found**:** 442.1301.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2,6-dimethylhept-6-en-1-one (2.70).

$C_{19}H_{25}NO_2S_2$
Mol. Wt. = 363.53 g/mol



Aldol **2.70** (yellow oil) was obtained from the corresponding Crimmins auxiliary **2.4** and aldehyde **2.66** according to the procedure described above for aldol **2.7**.
Purification by flash column chromatography (90:10 PE/EtOAc).
Scale: 16.7 mmol.
Yield: 72%, dr = 90:10.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.27 (m, 5H, H^{Ar}), 5.36 (ddd, J = 10.5, 7.1, 3.9 Hz, 1H, H^{12}), 4.73 (s, 1H, H^7), 4.72 (s, 1H, H^7), 4.50 (qd, J = 6.9, 3.0 Hz, 1H, H^2), 3.94 (ddd, J = 7.9, 4.5, 3.0 Hz, 1H, H^3), 3.41 (dd, J = 11.5, 7.1 Hz, 1H, H^{13}), 3.22 (dd, J = 13.2, 3.9 Hz, 1H, H^{11}), 3.05 (dd, J = 13.2, 10.5 Hz, 1H, H^{11}), 2.91 (d, J = 11.5 Hz, 1H, H^{13}), 2.71 (brs, 1H, OH),

2.19 (ddd, J = 15.0, 10.1, 5.5 Hz, 1H, H^5), 2.07 (ddd, J = 15.0, 9.4, 6.2 Hz, 1H, H^5), 1.74 (s, 3H, H^8), 1.72–1.64 (m, 1H, H^4), 1.54 (dddd, J = 14.0, 10.1, 6.2, 4.5 Hz, 1H, H^4), 1.28 (d, J = 6.9 Hz, 3H, H^9).

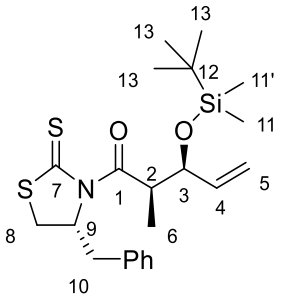
^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.5 (C^{10}), 178.5 (C^1), 145.5 (C^6), 136.5 (C^{Ar}), 129.8 (C^{Ar}), 129.1 (C^{Ar}), 127.4 (C^{Ar}), 110.5 (C^7), 72.1 (C^{12}), 68.9 (C^3), 43.4 (C^2), 37.0 (C^{11}), 34.2 (C^5), 32.3 (C^{13}), 32.2 (C^4), 22.6 (C^8), 10.7 (C^9).

IR (thin film) 3464, 2932, 1690, 1257, 1026 cm^{-1}.

HRMS (CI+) for $C_{19}H_{26}O_2S_2$: 364.1399, found: 364.1405.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-en-1-one (2.8).[36]

$C_{22}H_{24}NO_2S_2Si$
Mol. Wt. = 435.72 g/mol



Method 1:

A solution of **2.7** (10.6 g, 32.9 mmol) and TBSCl (9.92 g, 65.8 mmol, 2.00 equiv) in anhydrous DMF (80 mL) was cooled to 0 °C then freshly distilled 2,6-lutidine (15.3 mL, 132 mmol, 5.00 equiv) and DMAP (0.40 g, 3.3 mmol, 0.10 equiv) were added. The mixture was left to stir at RT for 72 h, followed by dilution with water. The mixture was extracted with Et_2O (3 × 70 mL), and the combined organic extracts were washed with a saturated aqueous solution of copper sulfate (3 × 50 mL). The organic extracts were then dried over magnesium sulfate, filtered and the solvent concentrated under vacuum. The crude product was purified by flash chromatography (97:3 PE/EtOAc) furnishing **2.8** as a bright yellow oil (12.8 g, 87%) and as a single diastereomer.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.27 (m, 5H, H^{Ar}), 5.85 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H, H^4), 5.16 (d, *J* = 17.2 Hz, 1H, H^{5trans}), 5.14–5.07 (m, 2H, H^{5cis}/H^9), 4.59 (quin, *J* = 6.7 Hz, 1H, H^2), 4.32 (t, *J* = 6.7 Hz, 1H, H^3), 3.33–3.25 (m, 2H, H^8/ H^{10}), 3.04 (dd, *J* = 13.2, 10.8 Hz, 1H, H^8), 2.88 (d, *J* = 11.5 Hz, 1H, H^{10}), 1.23 (d, *J* = 6.7 Hz, 3H, H^6), 0.88 (s, 9H, H^{13}), 0.02 (s, 6H, H^{11}/$H^{11'}$).

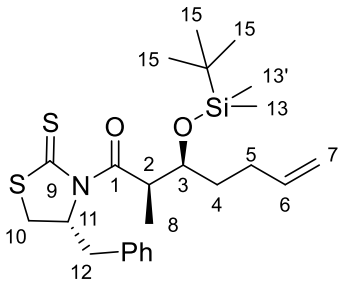
^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.4 (C^7), 176.4 (C^1), 139.4 (C^4), 136.8 (C^{Ar}), 129.6 (C^{Ar}), 129.0 (C^{Ar}), 127.3 (C^{Ar}), 115.9 (C^5), 76.6 (C^3), 69.6 (C^9), 46.0 (C^2), 36.7 (C^8), 32.4 (C^{10}), 25.9 (C^{13}), 18.3 (C^{12}), 12.7 (C^6), −4.2 (C^{11}), −4.9 ($C^{11'}$).

$[\alpha]_D^{25}$ −169.6 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −180.0 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[36]

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-*(tert*-butyldimethylsilyloxy)-2-methylhept-6-en-1-one (2.24). [35]

$C_{24}H_{37}NO_2S_2Si$
Mol. Wt. = 463.77 g



TBS protected aldol **2.24** (yellow oil) was obtained from the corresponding aldol **2.26** according to the procedure (method 1) described above for TBS protected aldol **2.8**.
Purification by flash column chromatography (97:3 PE/EtOAc).
Scale: 14 mmol.
Yield: 95% as a single isomer.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.19 (m, 5H, H^{Ar}), 5.78 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H, H^6), 5.17 (ddd, *J* = 10.8, 6.6, 3.4 Hz, 1H, H^{11}), 5.01 (dq, *J* = 16.9, 1.6 Hz, 1H, H^{7trans}), 4.93 (dq, *J* = 10.2, 1.6 Hz, 1H, H^{7cis}), 4.53 (qd, *J* = 6.7, 5.5 Hz, 1H, H^2), 3.98 (q, *J* = 5.5 Hz, 1H, H^3), 3.33–3.25 (m, 2H, H^{10}/H^{12}), 3.01 (dd, *J* = 13.1, 10.8 Hz, 1H, H^{10}), 2.87 (d, *J* = 11.7 Hz,

1H, H^{12}), 2.09–2.03 (m, 2H, H^4/H^5), 1.69–1.59 (m, 1H, H^4), 1.59–1.49 (m, 1H, H^5), 1.20 (d, *J* = 6.7 Hz, 3H, H^8), 0.87 (s, 9H, H^{15}), 0.04 (s, 3H, H^{13}), 0.02 (s, 3H, $H^{13'}$).

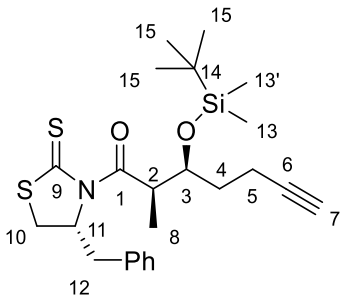
^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.9 (C^9), 176.8 (C^1), 138.6 (C^6), 136.7 (C^{Ar}), 129.6 (C^{Ar}), 129.0 (C^{Ar}), 127.3 (C^{Ar}), 114.6 (C^7), 73.9 (C^{11}), 69.6 (C^3), 44.3 (C^2), 36.6 (C^{10}), 34.6 (C^{12}), 32.2 (C^5), 29.2 (C^4), 25.9 (C^{15}), 18.2 (C^{14}), 12.7 (C^8), -4.0 (C^{13}), -4.5 ($C^{13'}$).

$[\alpha]_D^{25}$ −92.6 (*c* = 0.5, $CHCl_3$), literature **$[\alpha]_D^{25}$** −67.0 (*c* = 0.28, $CHCl_3$).

In agreement with literature data.[35]

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-6-yn-1-one (2.41).

$C_{24}H_{35}NO_2S_2Si$
Mol. Wt. = 461.75 g/mol



Method 2:

A solution of aldol **2.40** (5.27 g, 15.2 mmol) in CH_2Cl_2 (60 mL) was cooled to −78 °C then triethylamine (3.20 mL, 22.7 mmol, 1.50 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.30 mL, 22.7 mmol, 1.50 equiv) were added dropwise to the reaction. The mixture was stirred at −78 °C for 1 h then warmed to 0 °C and stirred for an additional 1 h. The reaction was quenched by addition of water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash column chromatography (95:5 PE/Et_2O) to give product **2.41** (6.31 g, 90%) as a yellow oil and as a single diastereomer.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.27 (m, 5H, H^{Ar}), 5.21 (ddd, *J* = 10.6, 6.7, 3.6 Hz, 1H, H^{11}), 4.58–4.51 (m, 1H, H^2), 4.06 (dd, *J* = 10.5, 5.9 Hz, 1H, H^3), 3.43–3.33 (m, 1H, H^{12}),

3.28 (dd, *J* = 13.1, 3.6 Hz, 1H, H^{10}), 3.05 (dd, *J* = 13.1, 10.6 Hz, 1H, H^{10}), 2.90 (d, *J* = 11.5 Hz, 1H, H^{12}), 2.25 (ddd, *J* = 15.3, 8.4, 2.6 Hz, 2H, H^{5}), 1.96 (t, *J* = 2.6 Hz, 1H, H^{7}), 1.90–1.73 (m, 2H, H^{4}), 1.25 (d, *J* = 6.8 Hz, 3H, H^{8}), 0.89 (s, 9H, H^{15}), 0.09 (s, 3H, H^{13}), 0.06 (s, 3H, $H^{13'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.4 (C^{9}), 176.9 (C^{1}), 137.0 (C^{Ar}), 129.9 (C^{Ar}), 129.3 (C^{Ar}), 127.6 (C^{Ar}), 84.6 (C^{6}), 73.7 (C^{11}), 69.8 (C^{7}), 69.1 (C^{3}), 44.6 (C^{2}), 36.9 (C^{10}), 34.1 (C^{12}), 32.5 (C^{4}), 26.2 (C^{15}), 18.4 (C^{14}), 14.8 (C^{5}), 13.5 (C^{8}), – 4.0 (C^{13}), – 4.2 ($C^{13'}$).

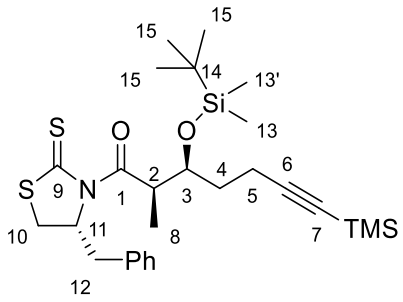
$[\alpha]_D^{25}$ −141.9 (*c* = 0.50, $CHCl_3$).

IR (thin film) 3306, 2953, 2928, 1699, 1361, 1340, 1257, 1192, 1163, 1030 cm^{-1}.

HRMS (ESI) for $C_{24}H_{35}NNaS_2O_2Si$: 484.1771, found: 484.1749.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-7-(trimethylsilyl)hept-6-yn-1-one (2.47).

$C_{27}H_{43}NO_2S_2Si_2$
Mol. Wt. = 533.94 g/mol



TBS protected aldol **2.47** (yellow oil) was obtained from the corresponding aldol **2.46** according to the procedure (method 2) described above for TBS protected aldol **2.41**.
Purification by flash column chromatography (97:3 PE/EtOAc).
Scale: 16.1 mmol.
Yield: 80% as a single diastereomer.

^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.39–7.29 (m, 5H, H^{Ar}), 5.19 (ddd, *J* = 10.5, 6.8, 3.6 Hz, 1H, H^{11}), 4.58 (qd, *J* = 6.8, 4.8 Hz, 1H, H^{2}), 4.05 (dt, *J* = 6.7, 4.8 Hz, 1H, H^{3}), 3.34 (dd, *J* = 11.5,

6.8 Hz, 1H, H^{12}), 3.28 (dd, *J* = 13.1, 3.6 Hz, 1H, H^{10}), 3.04 (dd, *J* = 13.1, 10.5 Hz, 1H, H^{10}), 2.89 (d, *J* = 11.5 Hz, 1H, H^{12}), 2.33–2.21 (m, 2H, H^{5}), 1.88–1.74 (m, 2H, H^{4}), 1.22 (d, *J* = 6.8 Hz, 3H, H^{8}), 0.89 (s, 9H, H^{15}), 0.14 (s, 9H, H^{TMS}), 0.10 (s, 3H, H^{13}), 0.05 (s, 3H, $H^{13'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.1 (C^{9}), 176.6 (C^{1}), 136.8 (C^{Ar}), 129.6 (C^{Ar}), 129.0 (C^{Ar}), 127.3 (C^{Ar}), 107.0 (C^{7}), 85.3 (C^{6}), 73.4 (C^{11}), 69.6 (C^{3}), 44.4 (C^{2}), 36.6 (C^{10}), 33.9 (C^{12}), 32.1 (C^{4}), 25.9 (C^{15}), 18.2 (C^{14}), 16.4 (C^{5}), 12.6 (C^{8}), 0.3 (TMS), -4.2 (C^{13}), -4.5 ($C^{13'}$).

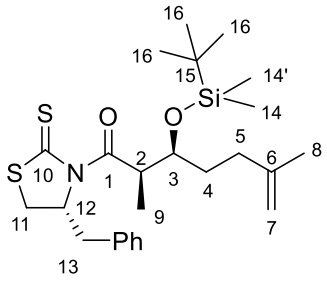
$[\alpha]_D^{25}$ −143.7 (*c* = 1.0, $CHCl_3$).

IR (thin film) 2958, 2857, 2178, 1701, 1341, 1257, 1249, 1028 cm^{-1}.

HRMS (ESI) for $C_{27}H_{43}NNaO_2S_2Si_2$: 556.2166, found: 556.2144.

(2*R*,3*S*)-1-((*R*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2,6-dimethylhept-6-en-1-one (2.71).

$C_{25}H_{39}NO_2S_2Si$
Mol. Wt. = 477.80 g/mol



TBS protected aldol **2.71** (yellow oil) was obtained from the corresponding aldol according to the procedure (method 2) described above for TBS protected aldol **2.41**.
Purification by flash column chromatography (97:3 PE/EtOAc).
Scale: 9.3 mmol.
Yield: 85% as a single diastereomer.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.33 (m, 2H, H^{Ar}), 7.32–7.28 (m, 3H, H^{Ar}), 5.17 (ddd, J = 10.5, 6.8, 3.4 Hz, 1H, H^{12}), 4.69 (s, 1H, H^{7}), 4.68 (s, 1H, H^{7}), 4.56 (app quint, *J* = 6.6 Hz, 1H, H^{2}), 4.04 (app q, J = 5.4 Hz, 1H, H^{3}) , 3.36–3.26 (m, 2H, H^{11}/H^{13}), 3.05 (dd, J = 13.1, 10.5 Hz, 1H, H^{11}), 2.89 (d, J = 11.4 Hz, 1H, H^{13}), 2.07–2.00 (m, 2H, H^{5}), 1.77–1.66 (m, 1H,

H^4), 1.73 (s, 3H, H^8), 1.63–1.56 (m, 1H, H^4), 1.25 (d, J = 6.6 Hz, 3H, H^9), 0.90 (s, 9H, H^{16}), 0.07 (s, 3H, H^{14}), 0.05 (s, 3H, $H^{14'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.1 (C^{10}), 177.0 (C^1), 146.1 (C^6), 136.8 (C^{Ar}), 129.6 (C^{Ar}), 129.1 (C^{Ar}), 127.3 (C^{Ar}), 109.7 (C^7), 74.2 (C^3), 69.6 (C^{12}), 44.2 (C^2), 36.7 (C^{11}), 33.6 (C^4), 33.0 (C^5), 32.3 (C^{13}), 26.0 (C^{16}), 22.8 (C^8), 18.2 (C^{15}), 12.8 (C^9), −4.0 (C^{14}), −4.5 ($C^{14'}$).

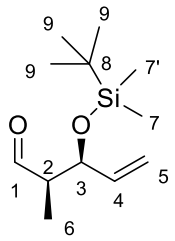
$[\alpha]_D^{25}$ −156.7 (*c* = 1.0, $CHCl_3$).

IR (thin film) 2947, 2855, 1697, 1250, 1088, 1026 cm^{-1}.

HRMS (CI+) for $C_{25}H_{40}NO_2S_2Si$: 478.2264, found: 478.2270.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-enal (2.3).[36]

$C_{12}H_{24}O_2Si$
Mol. Wt. = 228.41 g/mol



A solution of **2.8** (12.8 g, 29.4 mmol) in CH_2Cl_2 (250 mL) was cooled to –78 °C and a 1 M solution of diisobutylaluminium hydride in hexanes (59 mL, 59 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 (40 mL) and warmed to RT. The mixture was then diluted with a 10% Rochelle's salt aqueous solution (250 mL) and stirred for 4 h until the organic phase became clear. The mixture was then extracted with Et_2O (3 × 200 mL), and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (95:5 PE/Et_2O) furnishing **2.3** as a colourless oil (5.42 g, 82%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (d, *J* = 1.4 Hz, 1H, H^1), 5.83 (ddd, *J* = 17.1, 10.4, 6.1 Hz, 1H, H^4), 5.25 (dt, *J* = 17.1, 1.4 Hz, 1H, H^5), 5.17 (dt, *J* = 10.4, 1.3 Hz, 1H, H^5), 4.53 (ddt, *J* = 6.1, 4.2, 1.3 Hz, 1H, H^3), 2.47 (qdd, *J* = 7.0, 4.2, 1.4 Hz, 1H, H^2), 1.07 (d, *J* = 7.0 Hz, 3H, H^6), 0.88 (s, 9H, H^9), 0.05 (s, 3H, H^7), 0.04 (s, 3H, $H^{7'}$).

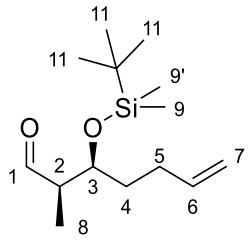
^{13}C NMR ($CDCl_3$, 101 MHz) δ 204.7 (C^1), 138.5 (C^4), 116.1 (C^5), 73.8 (C^3), 52.7 (C^2), 25.9 (C^9), 18.3 (C^8), 8.5 (C^6), −4.1 (C^7), −4.9 ($C^{7'}$).

$[\alpha]_D^{25}$ −88.2 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −87.0 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[36]

(2*R*,3*S*)-3-*(tert*-Butyldimethylsilyloxy)-2-methyl-6-heptenal (2.23).[35]

$C_{14}H_{28}O_2Si$
Mol. Wt. = 256.45 g/mol



Aldehyde **2.23** (colourless oil) was obtained from the corresponding TBS protected aldol **2.24** according to the procedure described above for aldehyde **2.3**.
Purification by flash column chromatography (90:10 PE/Et_2O).
Scale: 13.0 mmol.
Yield: 69%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.70 (d, *J* = 1.0 Hz, 1H, H^1), 5.72 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H, H^6), 4.96 (dq, *J* = 16.9, 1.6 Hz, 1H, H^7), 4.98 (dq, *J* = 10.1, 1.6 Hz, 1H, H^7), 4.05 (td, *J* = 6.6, 3.6 Hz, 1H, H^3), 2.43 (qdd, *J* = 7.0, 3.6, 1.0 Hz, 1H, H^2), 2.12–1.94 (m, 2H, H^4/H^5), 1.62–1.48 (m, 2H, H^4/H^5), 1.02 (d, *J* = 7.0 Hz, 3H, H^8), 0.83 (s, 9H, H^{11}), 0.03 (s, 3H, H^9), 0.00 (s, 3H, $H^{9'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.4 (C^1), 138.0 (C^6), 115.1 (C^7), 71.7 (C^3), 51.3 (C^2), 33.8 (C^5), 30.1 (C^4), 25.9 (C^{11}), 18.2 (C^{10}), 7.9 (C^8), −4.1 (C^9), −4.4 ($C^{9'}$).

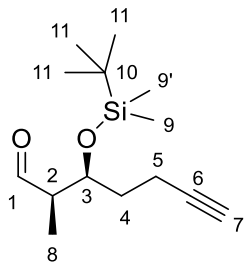
$[\alpha]_D^{25}$ −93.3 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −98.0 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[35]

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-6-ynal (2.42).

$C_{14}H_{26}O_2Si$

Mol. Wt. = 254.44 g/mol



Aldehyde **2.42** (colourless oil) was obtained from the corresponding TBS protected aldol **2.41** according to the procedure described above for aldehyde **2.3**.

Purification by flash column chromatography (90:10 PE/Et_2O).

Scale: 13.6 mmol.

Yield: 81%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.81 (d, *J* = 0.9 Hz, 1H, H^1), 4.26 (ddd, *J* = 7.6, 5.3, 3.8 Hz, 1H, H^3), 2.53 (qdd, *J* = 7.0, 3.8, 0.9 Hz, 1H, H^2), 2.26 (tt, *J* = 7.1, 2.6 Hz, 2H, H^5), 1.99 (t, *J* = 2.6 Hz, 1H, H^7), 1.78–1.65 (m, 2H, H^4), 1.08 (d, *J* = 7.0 Hz, 3H, H^8), 0.88 (s, 9H, H^{11}), 0.12 (s, 3H, H^9), 0.08 (s, 3H, $H^{9'}$).

^{13}C NMR ($CDCl_3$, 126MHz) δ 205.1 (C^1), 83.6 (C^6), 71.1 (C^3), 69.4 (C^7), 51.6 (C^2), 33.1 (C^4), 26.0 (C^{11}), 18.3 (C^{10}), 15.2 (C^5), 8.3 (C^8), −4.16 (C^9) , −4.31 ($C^{9'}$).

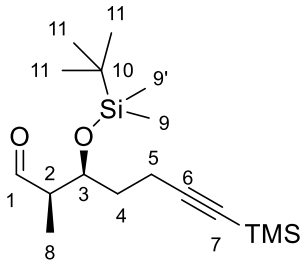
$[\alpha]_D^{25}$ −18.7 (*c* = 0.50, $CHCl_3$).

IR (thin film) 3314, 2955, 2930, 1737, 1366 cm^{-1}.

HRMS (ESI) for $C_{14}H_{26}NaO_2Si$: 277.1594, found: 277.1583.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-7-(trimethylsilyl)hept-6-ynal (2.48).

$C_{17}H_{34}O_2Si_2$
Mol. Wt. = 326.63 g/mol



Aldehyde **2.48** (colourless oil) was obtained from the corresponding TBS protected aldol **2.47** according to the procedure described above for aldehyde **2.3**.
Purification by flash column chromatography (95:5 PE/Et_2O).
Scale: 12.8 mmol.
Yield: 92%.

^{1}H NMR ($CDCl_3$, 400 MHz,) δ 9.81 (d, *J* = 0.8 Hz, 1H, H^1), 4.27 (ddd, *J* = 7.6, 5.6, 3.6 Hz, 1H, H^3), 2.54 (qdd, *J* = 7.0, 3.6, 0.8 Hz, 1H, H^2), 2.29 (t, *J* = 7.0 Hz, 2H, H^5), 1.78–1.60 (m, 2H, H^4), 1.07 (d, *J* = 7.0 Hz, 3H, H^8), 0.88 (s, 9H, H^{11}), 0.16 (s, 9H, H^{TMS}), 0.12 (s, 3H, H^9), 0.08 (s, 3H, $H^{9'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 204.8 (C^1), 106.0 (C^7), 85.5 (C^6), 70.8 (C^3), 51.2 (C^2), 32.7 (C^5), 25.7 (C^{11}), 17.9 (C^{10}), 16.3 (C^4), 7.9 (C^8), -0.03 (TMS), −4.48 (C^9), −4.70 ($C^{9'}$).

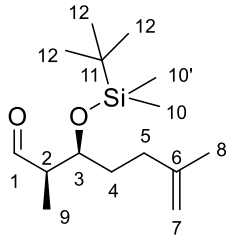
$[\alpha]_D^{25}$ −85.2 (*c* = 1.0, $CHCl_3$).

IR (thin film) 2955, 2928, 2857, 1728, 1250, 839 cm^{-1}.

HRMS (ESI) for $C_{17}H_{34}NaO_2Si_2$: 349.1990, found: 349.1973

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhept-6-enal (2.72).

$C_{15}H_{30}O_2Si$
Mol. Wt. = 270.49 g/mol



Aldehyde **2.72** (colourless oil) was obtained from the corresponding TBS protected aldol **2.71** according to the procedure described above for aldehyde **2.3**.
Purification by flash column chromatography (90:10 PE/Et_2O).
Scale: 15.0 mmol.
Yield: 98%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.79 (d, J = 1.0 Hz, 1H, H^1), 4.74 (s, 1H, H^7), 4.69 (s, 1H, H^7), 4.13 (td, J = 6.5, 3.6 Hz, 1H, H^3), 2.49 (qdd, J = 7.0, 3.6, 1.0 Hz, 1H, H^2), 2.12–2.04 (m, 1H, H^5), 2.01–1.93 (m, 1H, H^5), 1.74 (s, 3H, H^8), 1.72–1.59 (m, 2H, H^4), 1.08 (d, J = 7.0 Hz, 3H, H^9), 0.88 (s, 9H, H^{12}), 0.09 (s, 3H, H^{10}), 0.05 (s, 3H, $H^{10'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.4 (C^1), 145.2 (C^6), 110.4 (C^7), 71.9 (C^3), 51.3 (C^2), 34.0 (C^5), 32.6 (C^4), 25.9 (C^{12}), 22.6 (C^8), 18.2 (C^{11}), 7.8 (C^9), −4.1 (C^{10}), −4.4 ($C^{10'}$).

$[\alpha]_D^{25}$ −41.5 (*c* = 1.0, $CHCl_3$).

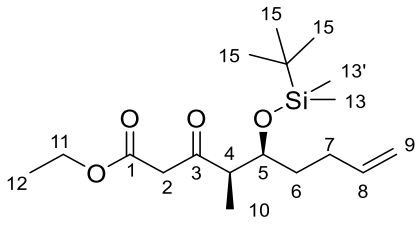
IR (thin film) 2932, 2855, 1728, 833 cm^{-1}.

HRMS (ESI) for $C_{15}H_{30}NaO_2Si$: 293.1907, found: 293.1900.

Ethyl (4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-3-oxonon-8-enoate (1.126).[35]

$C_{18}H_{34}SiO_4$

Mol Wt = 342.54 g/mol



To a solution of ethyl 2-diazoacetate (0.53 mL, 5.0 mmol, 2.0 equiv) in CH_2Cl_2 (15 mL) was added tin(II) chloride (0.24 g, 1.3 mmol, 0.50 equiv). The reaction was stirred at RT for 5 min then a solution of aldehyde **2.23** (0.65 g, 2.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture was left to stir at RT for 3 h. The crude mixture was concentrated under vacuum and purified by flash column chromatography (95:5 PE/Et_2O) to yield a 3:1 mixture of ketoester **1.126** and enol form as a colourless oil (0.75 g, 86%).

Ketoester form is described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71 (ddt, *J* = 17.2, 10.2, 6.5 Hz, 1H, H^8), 4.92–4.85 (m, 2H, H^9), 4.10 (q, *J* = 7.1 Hz, 2H, H^{11}), 3.82 (dt, *J* = 7.1, 4.1 Hz, 1H, H^5), 3.50 (s, 2H, H^2), 2.76 (qd, *J* = 7.1, 4.1 Hz, 1H, H^4), 1.95 (m, 2H, H^7), 1.50 (m, 1H, H^6), 1.35 (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^{15}), 0.01 (s, 3H, H^{13}), 0.00 (s, 3H, $H^{13'}$).

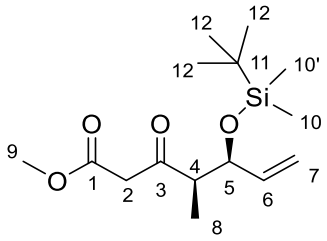
^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.4 (C^3), 167.6 (C^1), 138.1 (C^8), 115.0 (C^9), 73.4 (C^5), 61.3 (C^{11}), 51.8 (C^4), 49.6 (C^2), 33.4 (C^7), 30.0 (C^6), 26.0 (C^{15}), 18.2 (C^{14}), 14.3 (C^{12}), 11.8 (C^{10}), –4.3 (C^{13}), –4.3 ($C^{13'}$).

$[\alpha]_D^{25}$ −63.0 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −187 (*c* = 0.27, $CHCl_3$).

In agreement with literature data.[35]

Methyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxohept-6-enoate (2.9).[36]

$C_{15}H_{28}O_4Si$
Mol. Wt. = 300.47 g/mol



Ketoester **2.9** (colourless oil) was obtained from the corresponding aldehyde **2.3** and methyl 2-diazoacetate according to the procedure described above for ketoester **1.126**.
Purification by flash column chromatography (95:5 PE/Et_2O)
Scale: 7.0 mmol
Yield: 81% as a 3:1 mixture of ketoester **2.9** and enol form.

Ketoester form is described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H, H^6), 5.19 (dt, *J* = 17.1, 1.4 Hz, 1H, H^7), 5.13 (dt, *J* = 10.4, 1.4 Hz, 1H, H^7), 4.26 (ddt, *J* = 6.6, 5.3, 1.2 Hz, 1H, H^5), 3.72 (s, 3H, H^9), 3.60 (d, *J* = 15.9 Hz, 1H, H^2), 3.54 (d, *J* = 15.9 Hz, 1H, H^2), 2.87 (qd, *J* = 7.0, 5.3 Hz, 1H, H^4), 1.09 (d, *J* = 7.0 Hz, 3H, H^8), 0.90 (s, 9H, H^{12}), 0.07 (s, 3H, H^{10}), 0.03 (s, 3H, $H^{10'}$).

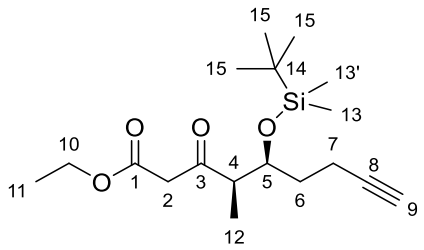
^{13}C NMR ($CDCl_3$, 101 MHz) δ 204.4 (C^3), 167.6 (C^1), 138.2 (C^6), 116.4 (C^7), 75.5 (C^5), 52.2 (C^4), 52.1 (C^9), 49.8 (C^2), 25.8 (C^{12}), 17.8 (C^{11}), 12.1 (C^8), −4.4 (C^{10}), −4.6 ($C^{10'}$).

In agreement with literature data.[36]

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxonon-8-ynoate (2.36).

$C_{18}H_{32}O_4Si$

Mol. Wt. = 340.53 g/mol



Ketoester **2.36** (colourless oil) was obtained from the corresponding aldehyde **2.42** and ethyl 2-diazoacetate according to the procedure described above for ketoester **1.126**.
Purification by flash column chromatography (95:5 PE/Et_2O)
Scale: 8.6 mmol
Yield: 81% as a 3:1 mixture of ketoester **2.36** and enol form.

Ketoester form is described below:

^{1}H NMR ($CDCl_3$, 400MHz) δ 4.20 (q, *J* = 7.1 Hz, 2H, H^{10}), 4.01 (dt, *J* = 8.0, 4.1 Hz, 1H, H^5), 3.60 (s, 2H, H^2), 2.89 (qd, *J* = 7.0, 4.2 Hz, 1H, H^4), 2.29–2.19 (m, 2H, H^7), 1.96 (t, *J* = 2.6 Hz, 1H, H^9), 1.79–1.64 (m, 1H, H^6), 1.59–1.48 (m, 1H, H^6), 1.27 (t, *J* = 7.1 Hz, 3H, H^{11}), 1.08 (d, *J* = 7.0 Hz, 3H, H^{12}), 0.91 (s, 9H, H^{15}), 0.12 (s, 3H, H^{13}) 0.11 (s, 3H, $H^{13'}$).

^{13}C NMR ($CDCl_3$, 126MHz) δ 204.7 (C^3), 167.2 (C^1), 83.4 (C^8), 72.2 (C^5), 68.8 (C^9), 61.0 (C^{10}), 51.4 (C^4), 49.4 (C^2), 32.2 (C^6), 25.6 (C^{15}), 17.8 (C^{14}), 14.6 (C^7), 13.9 (C^{12}), 11.7 (C^{11}), −4.6 (C^{13}), −4.9 ($C^{13'}$).

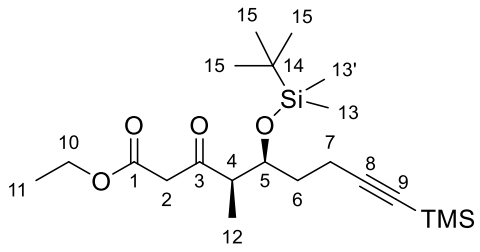
$[\alpha]_D^{25}$ −40.8 (*c* = 0.50, $CHCl_3$).

IR (thin film) 3628, 2955, 2929, 2272, 1749, 1717, 1647, 1636, 1313, 1255, 1026 cm^{-1}.

HRMS (ESI) for $C_{18}H_{32}NaO_4Si$: 363.1962, found: 363.1980.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxo-9-(trimethylsilyl)non-8-ynoate (2.49).

$C_{21}H_{40}O_4Si_2$
Mol. Wt. = 412.71 g/mol



Ketoester **2.49** (colourless oil) was obtained from the corresponding aldehyde **2.48** and ethyl 2-diazoacetate according to the procedure described above for ketoester **1.126**.
Purification by flash column chromatography (90:10 PE/Et_2O)
Scale: 5.9 mmol
Yield: 81% as a 3:1 mixture of ketoester **2.49** and enol form.

Ketoester form is described below:

^{1}H NMR ($CDCl_3$, 500 MHz,) δ 4.20 (q, *J* = 7.2 Hz, 2H, H^{10}), 4.05–4.00 (m, 1H, H^5), 3.61 (s, 2H, H^2), 2.90 (qd, *J* = 7.1, 3.8 Hz, 1H, H^4), 2.34–2.19 (m, 2H, H^7), 1.70–1.63 (m, 1H, H^6), 1.51 (dt, *J* = 14.0, 6.6 Hz, 1H, H^6), 1.28 (t, *J* = 7.2 Hz, 3H, H^{11}), 1.08 (d, *J* = 7.1 Hz, 3H, H^{12}), 0.91 (s, 9H, H^{15}), 0.15 (s, 9H, H^{TMS}), 0.13 (s, 3H, H^{13}), 0.11 (s, 3H, $H^{13'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.1 (C^1), 167.6 (C^3), 90.0 (C^9), 85.7 (C^8), 72.8 (C^5), 61.3 (C^2), 51.9 (C^4), 49.8 (C^{10}), 32.6 (C^7), 26.0 (C^{15}), 18.2 (C^{14}), 16.6 (C^6), 14.3 (C^{11}), 11.9 (C^{12}), 0.2 (TMS), −4.2 (C^{13}), −4.5 ($C^{13'}$).

$[\alpha]_D^{25}$ −60.8 (*c* = 0.50, $CHCl_3$).

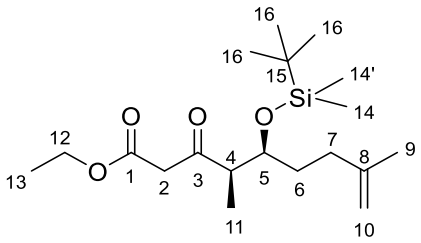
IR (thin film) 2957, 2931, 2897, 1749, 1715, 1626, 1421, 1249, 1097, 1026 cm^{-1}.

HRMS (ESI) for $C_{21}H_{40}NaO_4Si_2$: 435.2357, found: 435.2339.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4,8-dimethyl-3-oxonon-8-enoate (2.64).

$C_{19}H_{36}O_4Si$

Mol. Wt. = 356.58 g/mol



Ketoester **2.64** (colourless oil) was obtained from the corresponding aldehyde **2.72** and ethyl 2-diazoacetate according to the procedure described above for ketoester **1.126**.
Purification by flash column chromatography (95:5 PE/Et_2O)
Scale: 14.8 mmol
Yield: 92% as a 3:1 mixture of ketoester **2.64** and enol form.

Ketoester form is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.72 (s, 1H, H^{10}), 4.67 (s, 1H, H^{10}), 4.19 (q, J = 7.1 Hz, 2H, H^{12}), 3.90 (ddd, J = 7.2, 5.0, 4.2 Hz, 1H, H^5), 3.59 (s, 1H, H^2), 3.59 (s, 1H, H^2), 2.85 (qd, J = 7.0, 4.2 Hz, 1H, H^4), 2.13–2.01 (m, 1H, H^7), 2.01–1.91 (m, 1H, H^7), 1.72 (s, 3H, H^9), 1.67–1.58 (m, 1H, H^6), 1.52–1.43 (m, 1H, H^6), 1.28 (t, J = 7.1 Hz, 3H, H^{13}), 1.09 (d, J = 7.0 Hz, 3H, H^{11}), 0.91 (s, 9H, H^{16}), 0.09 (s, 3H, H^{14}), 0.08 (s, 3H, $H^{14'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.3 (C^3), 167.6 (C^1), 145.4 (C^8), 110.3 (C^{10}), 73.6 (C^5), 61.3 (C^{12}), 51.8 (C^4), 49.6 (C^2), 33.9 (C^7), 32.3 (C^6), 26.0 (C^{16}), 22.7 (C^9), 18.2 (C^{15}), 14.3 (C^{13}), 11.7 (C^{11}), −4.2 (C^{14}), −4.3 ($C^{14'}$).

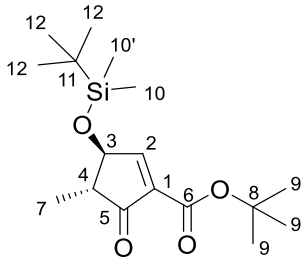
$[\alpha]_D^{25}$ −38.0 (*c* = 1.0, $CHCl_3$).

IR (thin film) 3078, 2932, 2862, 1744, 1713, 1643, 833 cm^{-1}.

HRMS (CI+) for $C_{15}H_{30}NaO_2Si$: 357.2456, found: 357.2461.

tert-Butyl (3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methyl-5-oxocyclopent-1-ene-1-carboxylate (1.148).[34,35]

$C_{17}H_{30}O_4Si$
Mol. Wt. = 326.51 g/mol



Compound **2.12** (2.0 g, 5.4 mmol) was dissolved in dry degassed CH_2Cl_2 (110 mL). Grubbs 2nd generation catalyst (0.23 g, 0.27 mmol, 0.05 equiv) 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 (92 mg, 0.11 mmol, 0.02 equiv) and the mixture heated under reflux for a further 12 h. The solvent was removed under vacuum and the product purified by column chromatography (70:30 PE/Et_2O) furnishing the product **1.148** as a pale brown oil (1.2 g, 68%).

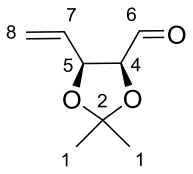
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (d, *J* = 2.1 Hz, 1H, H^2), 4.48 (dd, *J* = 3.1, 2.1 Hz, 1H, H^3), 2.42 (qd, *J* = 7.4, 3.1 Hz, 1H, H^4), 1.54 (s, 9H, H^9), 1.25 (d, *J* = 7.4 Hz, 3H, H^7), 0.93 (s, 9H, H^{12}), 0.17 (s, 3H, H^{10}), 0.15 (s, 3H, $H^{10'}$).

^{13}C NMR ($CDCl_3$, 101MHz) δ 201.0 (C^5), 165.9 (C^6), 160.9 (C^2), 137.3 (C^1), 82.2 (C^8), 76.1 (C^3), 52.6 (C^4), 28.0 (C^9), 25.6 (C^{12}), 18.0 (C^{11}), 12.4 (C^7), −4.7 (C^{10}), −4.7 ($C^{10'}$).

In agreement with literature data.[35]

(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-[1,3]-dioxolane-4-carbaldehyde (2.16).[45]

$C_8H_{12}O_3$
Mol. Wt. = 156.18 g/mol



To a suspension of D-Ribose (24.9 g, 166 mmol) in acetone (300 mL) was added dropwise concentrated sulfuric acid (0.90 mL, 17 mmol, 0.10 equiv). The crude mixture was stirred for 3 h, then solid sodium bicarbonate was added to neutralise the solution. The mixture was then filtered, dried over magnesium sulfate and concentrated under vacuum to furnish the protected product as a yellow oil (31.5 g). The product was used in the next step without further purification.

To a stirred suspension of methyltriphenylphosphonium bromide (86.3 g, 242 mmol, 3.50 equiv) in THF (250 mL) at 0 °C was added potassium *tert*-butoxide (27.1 g, 242 mmol, 3.50 equiv). The yellow mixture was stirred at 0 °C for 30 min then stirred at RT for an additional 1 h. The mixture was cooled to 0 °C and a solution of protected D-Ribose (13 g, 69 mmol) in THF (50 mL) was added dropwise. The reaction was stirred at RT for 12 h then was quenched by addition of water (250 mL). The aqueous phase was extracted with EtOAc (3 × 250 mL), the combined organic phases were dried over magnesium sulfate, filtered then concentrated under vaccum. The crude material was purified by column chromatography (30:70 PE/EtOAc) to furnish a mixture of triphenylphosphine oxide and product **2.15** (9.6 g, 76% over 2 steps) that was used in the next step without further purification.

To a solution of **2.15** (18.6 g, 98.8 mmol) in CH_2Cl_2 (320 mL) was added a solution of sodium periodate (31.7 g, 148 mmol, 1.50 equiv) in water (160 mL). The reaction was stirred at RT for 2 h then was diluted with CH_2Cl_2 (200 mL) and water (100 mL). The two layers were separated and the organic phase was dried over magnesium sulfate, filtered and concentrated carefully under vacuum (25 °C and 180 mbar). The crude material was purified by column chromatography (80:20 Pentane/Et_2O) to furnish compound **2.16** as a pale oil (13.3 g, 89%).

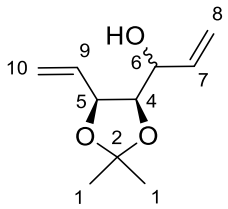
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.57 (d, *J* = 3.1 Hz, 1H, H^6), 5.77 (ddd, *J* = 17.1, 10.4, 6.9 Hz, 1H, H^7), 5.48 (dt, *J* = 17.1, 1.3 Hz, 1H, H^8), 5.34 (dt, *J* = 10.4, 1.3 Hz, 1H, H^8), 4.90–4.85 (m, 1H, H^5), 4.42 (dd, *J* = 7.5, 3.1 Hz, 1H, H^4), 1.64 (s, 3H, H^1), 1.46 (s, 3H, H^1).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.8 (C^6), 131.4 (C^7), 119.9 (C^8), 111.4 (C^2), 82.4 (C^5), 79.2 (C^4), 27.5 (C^1), 25.5 (C^1).

In agreement with literature data.[45]

1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-[1,3]-dioxolan-4-yl)prop-2-en-1-ol (2.17).[45]

$C_{10}H_{16}O_3$
Mol. Wt. = 184.24 g/mol



To a solution of aldehyde **2.16** (13.3 g, 85.1 mmol) in THF (350 mL) at –78 °C was added dropwise a 0.7 M solution of vinylmagnesium bromide in THF (200 mL, 140 mmol, 1.65 equiv). The mixture was stirred at –78 °C for 10 min then warmed to 0 °C and left stirring for 1 h. The reaction was quenched at 0 °C with a saturated aqueous solution of ammonium chloride (300 mL), allowed to warm up to RT, then the aqueous phase extracted with Et_2O (3 × 250 mL). The combined organic phases were dried over magnesium sulfate, filtered then concentrated under vacuum. The crude material was purified by column chromatography (70:30 PE/Et_2O) to furnish **2.17** as a colourless oil and as an inseparable 2:1 mixture of two diastereomers (11.4 g, 73%).

Major diastereomer is described below:

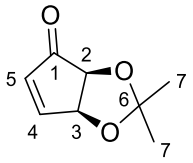
^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.12–5.98 (m, 1H, H^7), 5.86 (ddd, *J* = 17.2, 10.6, 5.4 Hz, 1H, H^9), 5.51–5.19 (m, 4H, H^8/H^{10}), 4.62 (dd, *J* = 7.7, 6.6 Hz, 1H, H^6), 4.16–4.12 (m, 1H, H^5), 4.10 (dd, *J* = 6.6, 5.3 Hz, 1H, H^4), 1.55 (s, 3H, H^1), 1.41 (s, 3H, H^1).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 136.9 (C^7), 134.1 (C^9), 119.6 (C^8 or C^{10}), 117.2 (C^8 or C^{10}), 109.0 (C^2), 80.8 (C^4), 79.1 (C^6), 70.7 (C^5), 27.5 (C^1), 25.1 (C^1).

In agreement with literature data.[45]

(3a*S*,6a*S*)-2,2-Dimethyl-3a,6a-dihydro-4*H*-cyclopenta[d][1,3]dioxol-4-one (2.14).[45]

$C_8H_{10}O_3$
Mol. Wt. = 154.16 g/mol



To a degassed solution of allylic alcohol **2.17** (1.0 g, 5.4 mmol) in CH_2Cl_2 (40 mL) was added Grubbs' 1st generation catalyst (89 mg, 0.11 mmol, 0.020 equiv). The reaction was heated under reflux for 12 h, the crude product was concentrated under vacuum and used in the next step without purification (0.85 g).

To a solution of oxalyl chloride (0.64 mL, 7.6 mmol, 1.4 equiv) in CH_2Cl_2 (20 mL) at –78 °C was added dropwise a mixture of DMSO (1.1 mL, 15 mmol, 2.8 equiv) and CH_2Cl_2 (5 mL). The mixture was stirred at −78 °C for 30 min then a solution of cyclic alcohol **2.18** (0.85 g, 5.4 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was stirred at −78 °C for 1 h, then triethylamine was added (4.2 ml, 30 mmol, 5.6 equiv) and the mixture was allowed to warm up to RT over 1 h. The reaction was quenched with a 1 M aqueous solution of hydrochloric acid (25 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic phases were washed with a 1 M aqueous solution of hydrochloric acid (2 × 50 mL), a saturated aqueous solution of sodium bicarbonate (50 mL), then dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (70:30 PE/Et_2O) to furnish compound **2.14** as a white foam (0.69 g, 83% over 2 steps).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (dd, *J* = 5.9, 2.0 Hz, 1H, H^4), 6.23 (d, *J* = 5.9 Hz, 1H, H^5), 5.28 (dd, *J* = 5.5, 2.0 Hz, 1H, H^3), 4.48 (d, *J* = 5.5 Hz, 1H, H^2), 1.43 (s, 3H, H^7), 1.42 (s, 3H, H^7).

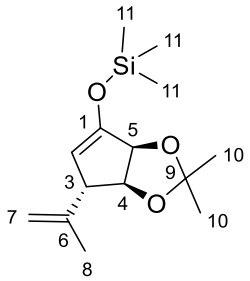
^{13}C NMR ($CDCl_3$, 126 MHz) δ 203.1 (C^1), 159.7 (C^4), 134.5 (C^5), 115.7 (C^6), 78.7 (C^3), 76.7 (C^4), 27.6 (C^7), 26.3 (C^7).

$[\alpha]_D^{25}$ +70.9 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** +73 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[45]

(((3a*S*,4*S*,6a*S*)-2,2-Dimethyl-4-(prop-1-en-2-yl)-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-6-yl)oxy)trimethylsilane (1.130).[36]

$C_{14}H_{24}O_3Si$
Mol. Wt. = 268.43 g/mol



To a suspension of copper(I) iodide (2.23 g, 11.7 mmol, 0.300 equiv) in THF (100 mL) at 0 °C was added TMEDA (12.8 mL, 85.9 mmol, 2.20 equiv). The mixture was cooled to −78 °C, a 0.5 M solution of isopropenyl magnesium bromide in THF (86 mL, 44 mmol, 1.1 equiv) was added and the reaction stirred at −78 °C for 1 h. A mixture of enone **2.14** (6.0 g, 39 mmol) and TMSCl (14.8 mL, 117 mmol, 3.00 equiv) in THF (100 mL) was added dropwise. After 30 min, TMSCl (9.9 mL, 78 mmol, 2.0 equiv) and triethylamine (11 mL, 78 mmol, 2.0 equiv) were added and the crude mixture stirred for 1 h at −78 °C, 1 h at −40 °C and 2 h at 0 °C. The reaction was quenched by addition of a saturated solution of sodium carbonate (150 mL) and the aqueous phase was extracted with Et_2O (3 × 150 mL). The organic phases were washed with brine (5 × 100 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by a very short pad of oven-dried silica gel (silica was dried for 24 h at 150 °C and cooled under inert atmosphere) (95:5 PE/Et_2O) to give silyl enol ether **1.130** (6.95 g, 67%) and **2.19** (1.96 g, 25%) as colourless oils.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.81 (dd, *J* = 6.1, 1.1 Hz, 1H, H^5), 4.78–4.74 (m, 2H, H^7), 4.65–4.63 (m, 1H, H^2), 4.32 (dt, *J* = 6.1, 0.9 Hz, 1H, H^4), 3.21 (m, 1H, H^3), 1.76 (s, 3H, H^8), 1.49 (s, 3H, H^{10}), 1.36 (s, 3H, H^{10}), 0.27 (s, 9H, H^{11}).

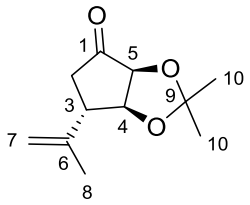
^{13}C NMR ($CDCl_3$, 126 MHz) δ 153.7 (C^1), 146.8 (C^6), 111.1 (C^7), 111.0 (C^9), 106.0 (C^2), 83.0 (C^4), 81.6 (C^5), 54.5 (C^3), 27.6 (C^8), 25.9 (C^{10}), 21.3 (C^{10}), 0.2 (C^{11}).

$[\alpha]_D^{25}$ −28.8 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −32.8 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[36]

(3a*S*,6*S*,6a*S*)-2,2-Dimethyl-6-(prop-1-en-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-4-one (2.19).[36]

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



^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.86 (d, *J* = 0.8 Hz, 1H, H^7), 4.67 (d, *J* = 5.4 Hz, 1H, H^5), 4.64 (s, 1H, H^7), 4.24 (d, *J* = 5.4 Hz, 1H, H^4), 2.96 (d, *J* = 9.1 Hz, 1H, H^2), 2.89–2.81 (m, 1H, H^3), 2.35–2.29 (m, 1H, H^2), 1.83 (s, 3H, H^8), 1.46 (s, 3H, H^{10}), 1.36 (s, 3H, H^{10}).

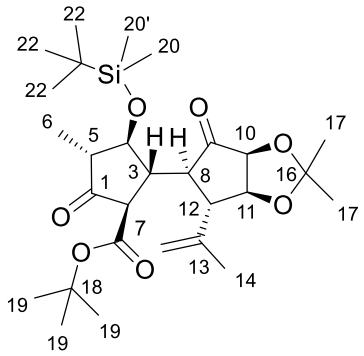
^{13}C NMR ($CDCl_3$, 126 MHz) δ 213.5 (C^1), 145.0 (C^6), 112.4 (C^7), 111.8 (C^9), 80.9 (C^5), 78.2 (C^4), 43.7 (C^3), 39.2 (C^2), 27.0 (C^{10}), 25.0 (C^{10}), 22.3 (C^8).

$[\alpha]_D^{25}$ +131.0 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** +167.0 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[36]

tert-Butyl (1*R*,2*R*,3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((3a*S*,5*R*,6*S*,6a*S*)-2,2-dimethyl-4-oxo-6-(prop-1-en-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-5-yl)-4-methyl-5-oxocyclopentane-1-carboxylate (2.20).[34,35]

$C_{28}H_{46}O_7Si$
Mol. Wt. = 522.75 g/mol



Silyl enol ether **1.130** (0.93 g, 3.5 mmol, 3.0 equiv) was dissolved in THF (5 mL) then cooled to 0 °C and a 2.1 M solution of *n*-BuLi in hexane (1.8 mL, 3.8 mmol, 3.3 equiv) was added dropwise. The reaction was stirred at 0 °C for 1 h then cooled to −78 °C and a mixture of $ZnCl_2$ (174 mg, 1.27 mmol, 1.10 equiv) and enone **1.148** (342 mg, 1.16 mmol) in DMF (15 mL) was added over 30 min to the reaction mixture. The mixture was stirred at −78 °C for 1 h, −40 °C for 1 h, −20 °C for 1 h and 0 °C for 1h. The crude was then quenched with a saturated aqueous solution of ammonium chloride (15 mL) and diluted with THF (15 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), the organic phases combined and dried over magnesium sulfate, filtered then concentrated under vacuum. The crude material was purified by column chromatography (90:10 PE/Et_2O) to furnish a 3:1 mixture of inseparable diastereomers of **2.20**/**2.20'** as a yellow oil (315 mg, 53%).

Major diastereomer is described below:

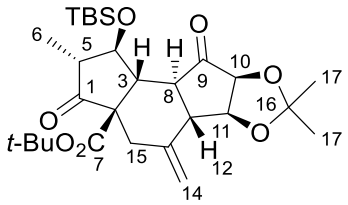
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.01–4.99 (m, 1H, H^{15}), 4.95 (m, 1H, H^{15}), 4.57 (dd, *J* = 6.3, 1.1 Hz, 1H, H^{10}), 4.43 (dd, *J* = 6.3, 3.0 Hz, 1H, H^{11}), 3.83 (t, *J* = 8.2 Hz, 1H, H^4), 3.22–3.11 (m, 2H, H^2/H^3), 2.96 (ddd, *J* = 10.0, 2.9, 1.5 Hz, 1H, H^8), 2.81 (dd, *J* = 10.0, 3.0 Hz, 1H, H^{12}), 2.43 (dq, *J* = 8.9, 7.0 Hz, 1H, H^5), 1.87 (s, 3H, H^{14}), 1.49 (s, 3H, H^{17}), 1.47 (s, 9H, H^{19}), 1.34 (s, 3H, H^{17}), 1.16 (d, *J* = 7.0 Hz, 3H, H^6), 0.88 (s, 9H, H^{22}), 0.09 (s, 3H, H^{20}), 0.08 (s, 3H, $H^{20'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.2 (C^1 or C^9), 208.6 (C^1 or C^9), 167.6 (C^7), 143.7 (C^{13}), 113.7 (C^{15}), 112.9 (C^{16}), 82.2 (C^{18}), 79.3 (C^{10}), 79.2 (C^{11}), 77.5 (C^4), 57.6 (C^2), 52.3 (C^5), 49.6 (C^8), 49.2 (C^{12}), 45.2 (C^3), 27.8 (C^{19}), 26.7 (C^{17}), 25.7 (C^{22}), 25.0 (C^{17}), 20.2 (C^{14}), 17.9 (C^{21}), 12.1 (C^6), −3.6 (C^{20}), −3.9 ($C^{20'}$).

In agreement with literature data.[35]

tert-Butyl (1*S*,2*R*,3a*R*,5a*S*,5b*S*,8a*S*,9a*S*,9b*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2,7,7-trimethyl-5-methylene-3,9-dioxodecahydro-as-indaceno[2,3-d][1,3]dioxole-3a(1H)-carboxylate (1.150).[34,35]

$C_{28}H_{44}O_7Si$
Mol. Wt. = 520.74 g/mol



To a degassed solution of bicycle **2.20**/**2.20'** (204 mg, 0.390 mmol) in a 10:1 mixture of trifluoroethanol/acetic acid (11 mL) was added copper(II) acetate hydrate (156 mg, 0.780 mmol, 2.00 equiv). The mixture was stirred at RT for 30 min and manganese(III) acetate dihydrate (209 mg, 0.780 mmol, 2.00 equiv) was added. The reaction was stirred for 1 h 30, then diluted with water (10 mL) and Et_2O (10 mL) and neutralised with solid potassium carbonate. The aqueous phase was extracted with Et_2O (3 × 10 mL), the organic phases were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (90:10 PE/Et_2O) to give tricycle **1.150** as a colourless oil (93 mg, 46%) and as a single diastereomer.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.09–5.04 (m, 2H, H^{14}), 4.78 (t, *J* = 7.7 Hz, 1H, H^{11}), 4.57 (d, *J* = 7.7 Hz, 1H, H^{10}), 3.98 (dd, *J* = 3.0, 2.0 Hz, 1H, H^4), 3.05 (m, 1H, H^3), 2.90 (d, *J* = 14.8 Hz, 1H, H^{15}), 2.51–2.43 (m, 2H, H^{15} and H^5), 2.34–2.22 (m, 1H, H^{12}), 1.68–1.60 (m, 1H, H^8), 1.50 (s, 3H, H^{17}), 1.42 (s, 9H, OC($\underline{CH_3}$)$_3$), 1.37 (s, 3H, H^{17}), 1.11 (d, *J* = 7.7 Hz, 3H, H^6), 0.91 (s, 9H, SiC($\underline{CH_3}$)$_3$), 0.17 (s, 3H, Si($\underline{CH_3}$)$_2$), 0.14 (s, 3H, Si($\underline{CH_3}$)$_2$).

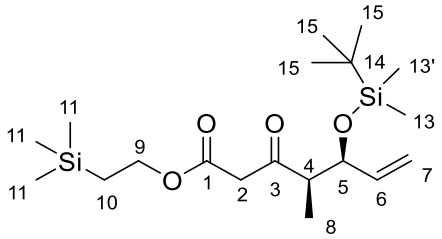
^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.7 (C^1 or C^9), 205.1 (C^1 or C^9), 170.0 (C^7), 140.9 (C^{13}), 115.1 (C^{16}), 108.6 (C^{14}), 82.4 ($O\underline{C}(CH_3)_3$), 78.8 (C^{11}), 77.4 (C^4), 75.3 (C^{10}), 62.0 (C^2), 53.0 (C^8), 50.6 (C^5), 49.4 (C^{12}), 46.7 (C^3), 36.44 (C^{15}), 27.7 ($OC(\underline{C}H_3)_3$), 26.8 (C^{17}), 25.8 ($SiC(\underline{C}H_3)_3$), 25.0 (C^{17}), 18.0 ($Si\underline{C}(CH_3)_3$), 14.4 (C^6), −4.6 ($Si(CH_3)$), −4.8($Si(CH_3)$).

$[\alpha]_D^{25}$ −28.2 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** −31.1 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[35]

2-(Trimethylsilyl)ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxohept-6-enoate (2.10).[35]

$C_{19}H_{38}O_4Si_2$
Mol. Wt. = 386.68 g/mol



To a solution of **2.9** (1.73 g, 5.75 mmol) and 2-(trimethylsilyl)ethanol (8.24 mL, 57.5 mmol, 10 equiv) in toluene (35 mL) was added ZnO (94 mg, 1.2 mmol, 0.20 equiv). The mixture was heated under reflux for 12 h, then the solvent was concentrated under vacuum and the crude material was purified by column chromatography (95:5 PE/EtOAc) to furnish the transesterification product **2.10** (2.0 g, 90%).

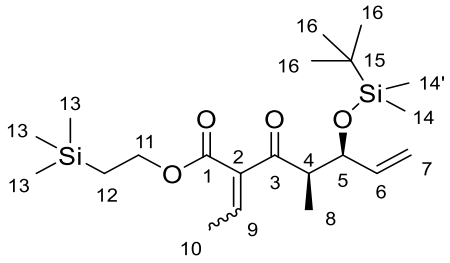
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1H, H^6), 5.18 (dt, *J* = 17.1, 1.4 Hz, 1H, H^7), 5.13 (dt, *J* = 10.4, 1.4 Hz, 1H, H^7), 4.28–4.24 (m, 1H, H^5), 4.23–4.18 (m, 2H, H^9), 3.57 (d, *J* = 15.8 Hz, 1H, H^2), 3.49 (d, *J* = 15.8 Hz, 1H, H^2), 2.87 (qd, *J* = 7.0, 5.4 Hz, 1H, H^4), 1.09 (d, *J* = 7.0 Hz, 3H, H^8), 1.03–0.97 (m, 2H, H^{10}), 0.90 (s, 9H, H^{15}), 0.07 (s, 3H, H^{13}), 0.05 (s, 3H, $H^{13'}$), 0.03 (s, 9H, H^{11}).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.1 (C^3), 167.7 (C^1), 138.1 (C^6), 116.4 (C^7), 75.8 (C^5), 63.6 (C^9), 53.0 (C^4), 50.5 (C^2), 26.0 (C^{15}), 18.3 (C^{14}), 17.5 (C^{10}), 12.4 (C^8), −1.4 (C^{11}), −4.2 (C^{13}), −4.9 ($C^{13'}$).

In agreement with literature data.[35]

(4*S*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-2-(3 (trimethylsilyl)propanoyl)cyclopent-2-en-1-one (2.11).[35]

$C_{21}H_{40}O_4Si_2$
Mol. Wt. = 412.72 g/mol



To a stirred solution of titanium(IV) chloride (1.02 mL, 9.30 mmol, 1.8 equiv) in THF (25 mL) at 0 °C was added freshly distilled acetaldehyde (1.30 mL, 23.3 mmol, 4.50 equiv), a solution of **2.10** (2.00 g, 5.20 mmol) in THF (25 mL), and pyridine (1.46 mL, 18.1 mmol, 3.50 equiv). The reaction was allowed to warm up to RT 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 dried over magnesium sulfate, filtered and the solvent concentrated under vacuum. The crude material was then purified by flash chromatography (95:5 PE/EtOAc) to furnish the product **2.11** as a colourless oil (2.05 g, 96%) as an inseparable 1:1 mixture of diastereomers.

Only one of the diastereomer is described below:

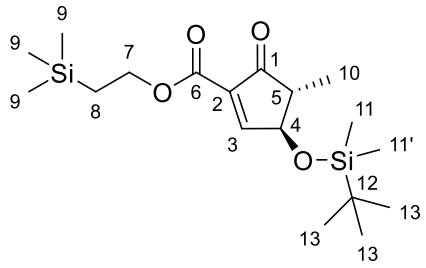
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (q, *J* = 7.4 Hz, 1H, H^9), 5.87–5.78 (m, 1H, H^6), 5.17 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H, H^7), 5.10–5.06 (m, 1H, H^7), 4.37–4.20 (m, 3H, H^3/H^{11}), 3.11 (quint, *J* = 6.9 Hz, 1H, H^4), 1.98 (d, *J* = 7.4 Hz, 3H, H^{10}), 1.15 (d, *J* = 6.9 Hz, 3H, H^8), 1.05–1.00 (m, 2H, H^{12}), 0.88 (s, 9H, H^{16}), 0.06 (s, 9H, H^{13}), 0.04 (s, 3H, H^{14}), 0.00 (s, 3H, $H^{14'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.2 (C^3), 166.7 (C^1), 145.2 (C^9), 139.5 (C^2), 138.7 (C^6), 115.8 (C^7), 75.6 (C^5), 63.6 (C^{11}), 52.5 (C^4), 26.0 (C^{16}), 18.3 (C^{15}), 17.6 (C^{12}), 15.9 (C^{10}), 13.8 (C^8), −1.4 (C^{14}), −4.0 ($C^{14'}$).

In agreement with literature data.[35]

2-(Trimethylsilyl)ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-ethylidene-4-methyl-3-oxohept-6-enoate (1.147).[35]

$C_{18}H_{34}O_4Si_2$
Mol. Wt. = 370.20 g/mol



Cyclic ketoester **1.147** (yellow oil) was obtained from the corresponding ketoester **2.11** according to the procedure described above for cyclic keto-ester **1.148**.
Purification by flash column chromatography (95:5 PE/Et_2O)
Scale: 4.8 mmol
Yield: 61%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, *J* = 2.1 Hz, 1H, H^3), 4.50 (dd, *J* = 3.0, 2.1 Hz, 1H, H^4), 4.34 (td, *J* = 8.3, 1.5 Hz, 2H, H^7), 2.44 (qd, *J* = 7.4, 3.0 Hz, 1H, H^5), 1.25 (d, *J* = 7.4 Hz, 3H, H^{10}), 1.13–1.04 (m, 2H, H^8), 0.92 (s, 9H, H^{13}), 0.16 (s, 3H, H^{11}), 0.15 (s, 3H, $H^{11'}$), 0.06 (s, 9H, H^9).

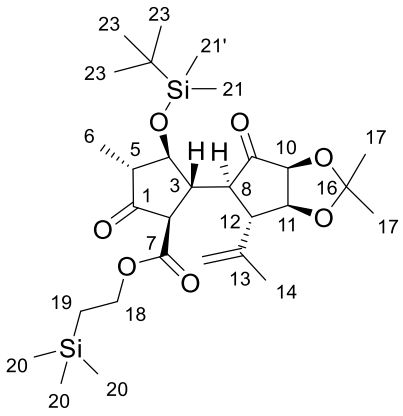
^{13}C NMR ($CDCl_3$, 101 MHz) δ 201.0 (C^1), 166.9 (C^6), 162.0 (C^3), 136.5 (C^2), 76.4 (C^4), 63.8 (C^7), 52.8 (C^5), 25.8 (C^{13}), 18.2 (C^{12}), 17.6 (C^8), 12.6 (C^{10}), −1.4 (C^9), −4.5 (C^{11}/$C^{11'}$).

$[\alpha]_D^{25}$ +113.2 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** +112.0 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[35]

2-(Trimethylsilyl)ethyl (1*R*,2*R*,3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((3a*S*,5*R*,6*S*,6a*S*)-2,2-dimethyl-4-oxo-6-(prop-1-en-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-5-yl)-4-methyl-5-oxocyclopentane-1-carboxylate (2.21).

$C_{29}H_{50}O_7Si_2$
Mol. Wt. = 566.88 g/mol



Bicycle **2.21** (yellow oil) was obtained from the corresponding cyclic keto-ester **1.147** and silyl enol ether **1.130** according to the procedure described above for bicycle **2.20**.
Purification by flash column chromatography (95:5 PE/Et_2O)
Scale: 0.81 mmol
Yield: 35% as a 3:1 mixture of two diastereomers.

Major diastereomer is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.99 (t, *J* = 1.4 Hz, 1H, H^{15}), 4.94 (s, 1H, H^{15}), 4.60–4.52 (m, 1H, H^{10}), 4.43 (dd, *J* = 6.4, 3.0 Hz, 1H, H^{11}), 4.28–4.13 (m, 2H, H^{18}), 3.87 (t, *J* = 8.4 Hz, 1H, H^4), 3.25 (d, *J* = 10.4 Hz, 1H, H^2), 3.16 (ddd, *J* = 10.4, 8.4, 3.2 Hz, 1H, H^3), 2.95 (ddd, *J* = 10.0, 3.2, 1.6 Hz, 1H, H^8), 2.84 (dd, *J* = 10.0, 3.0 Hz, 1H, H^{12}), 2.42 (dq, *J* = 8.6, 7.0 Hz, 1H, H^5), 1.86 (s, 3H, H^{14}), 1.48 (s, 3H, H^{17}), 1.33 (s, 3H, H^{17}), 1.17 (d, *J* = 7.0 Hz, 3H, H^6), 1.06–0.97 (m, 2H, H^{19}), 0.87 (s, 9H, H^{23}), 0.09 (s, 3H, H^{21}), 0.08 (s, 3H, $H^{21'}$), 0.02 (s, 9H, H^{20}).

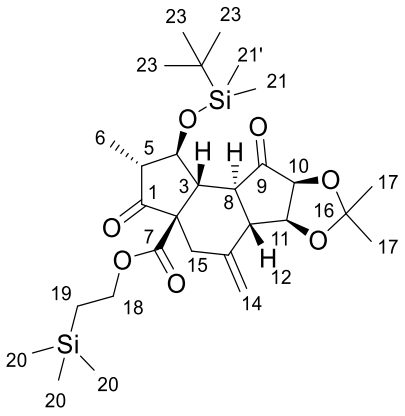
^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.6 (C^1 or C^9), 208.5 (C^1 or C^9), 168.7 (C^7), 143.8 (C^{13}), 114.0 (C^{15}), 113.2 (C^{16}), 80.4 (C^{10}), 79.5 (C^{11}), 77.3 (C^4), 64.3 (C^{18}), 56.7 (C^2), 52.7 (C^5), 49.7 (C^8), 49.4 (C^{12}), 45.5 (C^3), 26.8 (C^{17}), 26.0 (C^{23}), 25.3 (C^{17}), 20.5 (C^{14}), 18.2 (C^{22}), 17.4 (C^{19}), 12.6 (C^6), −1.4 (C^{20}), −3.4 (C^{21}), −3.7 ($C^{21'}$).

IR (thin film) 2954, 2932, 2862, 1754, 1725, 1697, 1641, 1462, 1375, 1147, 1041 cm^{-1}.

HRMS (ESI) for $C_{29}H_{50}NaO_7Si_2$: 589.2987, found: 589.2966.

2-(Trimethylsilyl)ethyl (1*S*,2*R*,3a*R*,5a*S*,5b*S*,8a*S*,9a*S*,9b*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2,7,7-trimethyl-5-methylene-3,9-dioxodecahydro-as-indaceno[2,3-d][1,3]dioxole-3a(1H)-carboxylate (1.149).

$C_{29}H_{48}O_7Si_2$
Mol. Wt. = 564.87 g/mol



Tricycle **1.149** (colourless oil) was obtained from the corresponding bicyclic ketoester **2.21**/**2.21'** according to the procedure described above for tricycle **1.150**.
Purification by flash column chromatography (95:5 PE/Et_2O)
Scale: 0.09 mmol
Yield: 30% as a single diastereomer.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.07 (t, *J* = 1.8 Hz, 1H, H^{14}), 5.04 (t, *J* = 1.8 Hz, 1H, H^{14}), 4.79 (t, *J* = 7.7 Hz, 1H, H^{11}), 4.56 (d, *J* = 7.7 Hz, 1H, H^{10}), 4.17–4.11 (m, 2H, H^{18}), 4.09 (t, *J* = 1.6 Hz, 1H, H^4), 3.00 (t, *J* = 6.0 Hz, 1H, H^3), 2.54–2.49 (m, 1H, H^5), 2.49–2.43 (m, 2H, H^{15}), 2.32 (dd, *J* = 15.0, 7.7 Hz, 1H, H^{12}), 1.62–1.57 (m, 1H, H^8), 1.51 (s, 3H, H^{17}), 1.36 (s, 3H, H^{17}), 1.10 (d, *J* = 8.0 Hz, 3H, H^6), 0.99–0.93 (m, 2H, H^{19}), 0.88 (s, 9H, H^{23}), 0.18 (s, 3H, H^{21}), 0.13 (s, 3H, $H^{21'}$), 0.01 (s, 9H, H^{20}).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 212.4 (C^1 or C^9), 205.4 (C^1 or C^9), 171.9 (C^7), 140.9 (C^{13}), 115.5 (C^{16}), 108.9 (C^{14}), 79.0 (C^{10}), 76.5 (C^4), 75.4 (C^{11}), 64.5 (C^{18}), 61.5 (C^2), 53.0 (C^8),

50.5 (C^5), 49.8 (C^{12}), 48.3 (C^3), 36.8 (C^{15}), 27.1 (C^{17}), 25.9 (C^{23}), 25.2 (C^{17}), 18.0 (C^{22}), 17.3 (C^{19}), 15.1 (C^6), −1.4 (C^{20}), −4.6 (C^{21}), −4.9 ($C^{21'}$).

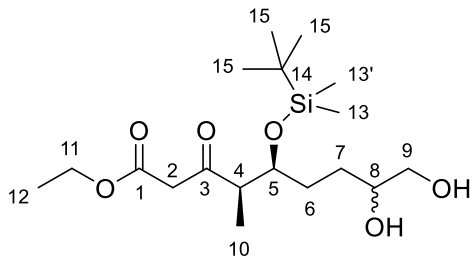
$[\alpha]_D^{25}$ −56.4 (*c* = 1.0, $CHCl_3$).

IR (thin film) 2954, 2932, 2860, 1758, 1740, 1675, 1473, 1465, 1252, 1233, 1160, 1042 cm^{-1}.

HRMS (ESI) for $C_{29}H_{49}O_7Si_2$: 565.3011, found: 565.3004.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8,9-dihydroxy-4-methyl-3-oxononanoate (2.38).

$C_{18}H_{36}O_6Si$
Mol. Wt. = 376.57 g/mol



To a solution of **1.126** (0.17 g, 0.50 mmol) in 10/1 acetone:water (5 mL) at RT were added 2,6-lutidine (0.14 mL, 1.2 mmol, 2.5 equiv), NMO (0.12 g, 1.0 mmol, 2.0 equiv), and a 4% aqueous solution of osmium tetroxide (0.06 mL, 0.01 mmol, 0.02 equiv). After stirring for 2 h, the reaction was quenched with saturated aqueous sodium thiosulfate (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), washed with saturated aqueous copper sulfate (2 × 20 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The crude residue was purified by flash column chromatography (80:20 PE/EtOAc) to give the product **2.38** as a colourless oil (0.12 g, 61%) as an inseparable 1:1 mixture of two diastereomers.

Mixture of diastereomers is described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.16 (q, *J* = 7.1 Hz, 2H, H^{11}), 3.95–3.85 (m, 1H, H^5), 3.67–3.54 (m, 4H, H^2/H^9), 3.40 (dd, *J* = 10.8, 7.4 Hz, 1H, H^8), 2.89–2.79 (m, 1H, H^4), 1.56–1.44 (m,

2H, H^6/H^7), 1.43–1.33 (m, 2H, H^6/H^7), 1.25 (t, *J* = 7.1 Hz, 3H, H^{12}), 1.07 (dd, *J* = 7.0, 3.6 Hz, 3H, H^{10}), 0.91–0.83 (m, 9H, H^{15}), 0.10–0.04 (m, 6H, H^{13}/ $H^{13'}$).

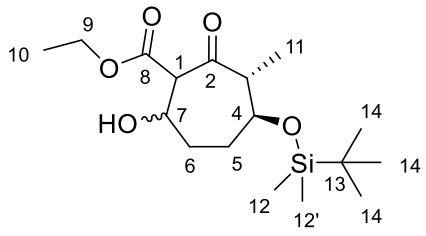
^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.7 (C^3), 167.7 (C^{1a}), 167.6 (C^{1b}), 73.7 (C^{5a}), 73.4 (C^{5b}), 72.2 (C^{8a}), 72.0 (C^{8b}), 66.7 (C^{9a}), 66.6 (C^{9b}), 61.3 (C^{11}), 51.7 (C^4), 49.4 (C^2), 30.3 (C^{7a}), 30.1 (C^{7b}), 28.8 (C^{14}), 25.9 (C^{15}), 18.1 (C^6), 14.1 (C^{12}), 12.3 (C^{10a}), 12.1 (C^{10b}), −4.4 (C^{13a}), −4.4 (C^{13b}), −4.5 ($C^{13a'}$), −4.5 ($C^{13b'}$).

IR (thin film) 3410, 3312, 2953, 2929, 2856, 1739, 1710, 1647, 1627, 1307, 1251, 1224, 1186 cm^{-1}.

HRMS (ESI) for $C_{18}H_{36}NaO_6Si$: 399.2173, found**:** 399.2177.

Ethyl (3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-3-methyl-2-oxocycloheptane-1-carboxylate (2.37).

$C_{17}H_{32}O_5Si$
Mol. Wt. = 344.52 g/mol



Ketoester **1.126** (0.1 g, 0.3 mmol) was dissolved in a 3:1 mixture of dioxane/water (8 mL), then 2,6-lutidine (60 µL, 0.60 mmol, 2.0 equiv), a 4% aqueous solution of OsO_4 (50 µL, 6.0 µmol, 0.020 equiv) and sodium periodate (0.25 g, 1.2 mmol, 4.0 equiv) were added. The reaction was stirred at RT for 12 h then the crude reaction was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The crude residue was purified by flash column chromatography (85:15 PE/EtOAc) to give the product **2.37** as a colourless oil (67 mg, 67%) and as an inseparable 7:3 mixture of two diastereomers.

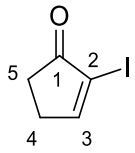
Major diastereomer is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.34 (s, 1H, H^1), 4.31 (t, *J* = 3.2 Hz, 1H, H^7), 4.27–4.15 (m, 2H, H^9), 3.91 (dd, *J* = 6.9, 3.4 Hz, 1H, H^4), 3.19 (s, 1H, OH), 2.60–2.52 (m, 1H, H^3), 2.22–2.13 (m, 1H, H^6), 1.94–1.87 (m, 1H, H^6), 1.75–1.66 (m, 1H, H^5), 1.58–1.49 (m, 1H, H^5), 1.27 (t, *J* = 7.2 Hz, 3H, H^{10}), 1.13 (d, *J* = 7.3 Hz, 3H, H^{11}), 0.92 (s, 9H, H^{14}), 0.09 (s, 6H, H^{12}/$H^{12'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.3 (C^2), 172.0 (C^8), 71.3 (C^4), 67.6 (C^7), 63.6 (C^1), 61.4 (C^9), 54.3 (C^3), 28.2 (C^5), 25.9 (C^{14}), 24.2 (C^6), 18.1 (C^{13}), 14.3 (C^{10}), 14.1 (C^{11}), −4.9 (C^{12}), −5.0 ($C^{12'}$).

2-Iodocyclopent-2-enone (2.57).[100]

C_5H_5IO
Mol. Wt. = 208.0 g/mol



To a mixture of 2-cyclopentenone (0.5 mL, 6 mmol) and pyridine (2.5 mL, 33 mmol, 5.5 equiv) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of iodine (1.8 g, 6.6 mmol, 1.1 equiv) and pyridine (2.5 mL, 33 mmol, 5.5 equiv) in CH_2Cl_2 (10 mL). The reaction was warmed to RT and stirred for an additional 4 h, then quenched with a 1 M aqueous solution of hydrochloric acid (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the organic phases were washed with a saturated aqueous solution of sodium sulfite (2 × 10 mL), dried over magnesium sulfate, filtered then concentrated under vacuum. The product was then purified by flash chromatography (70:30 PE/Et_2O) to furnish 2-iodocyclopent-2-enone **2.57** as a white solid (0.85 g, 68%).

Mp: 66–68 °C. lit. 71 °C

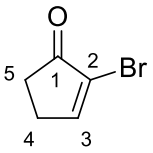
^{1}H NMR ($CDCl_3$, 500 MHz,) δ 8.03 (t, *J* = 2.9 Hz, 1H, H^3), 2.79 (ddd, *J* = 7.4, 2.9, 2.1 Hz, 2H, H^4), 2.58–2.42 (m, 2H, H^5).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 203.9 (C^1), 169.3 (C^3), 102.8 (C^2), 31.1 (C^5), 30.8 (C^4).

In agreement with literature data.[101]

2-Bromocyclopent-2-enone (2.32).[102]

C_5H_5BrO
Mol. Wt. = 161.0 g/mol



A solution of 2-cyclopentenone (0.84 mL, 10 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and a mixture of bromine (0.57 mL, 11 mmol, 1.1 equiv) and CH_2Cl_2 (10 mL) was slowly added. The reaction was warmed to RT and stirred for 1 h 30. Triethylamine (2.2 mL, 16 mmol, 1.6 equiv) was then added and the mixture stirred for an additional 1 h 30. The reaction was quenched by addition of a 1 M aqueous solution of hydrochloric acid (20 mL) and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phases were combined, washed with brine (2 × 20 mL), dried over magnesium sulfate, filtered and concentatred under vacuum. The product was then purified by flash chromatography (90:10 PE/Et_2O) to furnish compound **2.32** as a brown oil (1.34 g, 82%).

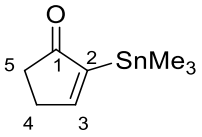
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (t, *J* = 3.0 Hz, 1H, H^3), 2.71 (ddd, *J* = 7.2, 3.0, 2.1 Hz, 2H, H^4), 2.60–2.47 (m, 2H, H^5).

^{13}C NMR ($CDCl_3$, 126 MHz,) δ 202.1 (C^1), 162.1 (C^3), 126.7 (C^2), 32.8 (C^5), 28.4 (C^4).

In agreement with literature data.[102]

2-(Trimethylstannyl)cyclopent-2-en-1-one (2.54).[103]

$C_8H_{14}OSn$
Mol. Wt. = 244.91 g/mol



To a degassed mixture of 2-bromocyclopent-2-enone **2.32** (0.32 g, 2.0 mmol) and *bis*(trimethyltin) (1.2 mL, 4.0 mmol, 2.0 equiv) in benzene (15 mL) was added

tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.10 mmol, 0.05 equiv). The reaction was heated under reflux for 72 h, then diluted with Et_2O (50 mL), filtered through a short pad of celite and concentrated under vacuum. The product was then purified by flash chromatography (95:5 PE/Et_2O) to furnish compound **2.54** as a colourless oil (0.39 g, 79%).

(The aqueous layer was diluted and the glassware was rinsed with a saturated aqueous solution of potassium fluoride to remove any traces of tin byproducts).

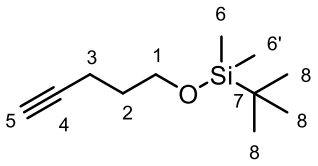
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (t, *J* = 2.5 Hz, $J_{Sn\text{-}H}$ = 31.7 Hz, 1H, H^3), 2.79–2.70 (m, 2H, H^4), 2.34–2.32 (m, 2H, H^5), 0.25 (s, $J_{Sn\text{-}H}$ = 56.5 Hz, 9H, $Sn\underline{Me}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 215.0 (C^1), 173.4 (C^3), 148.8 (C^2), 33.8 (C^5), 31.8 (C^4), -9.8 ($J_{Sn\text{-}C}$ = 352.5 Hz, $Sn\underline{Me}_3$).

In agreement with literature data.[103]

tert-Butyldimethyl(pent-4-ynyloxy)silane (2.58).[63]

$C_{11}H_{22}OSi$
Mol. Wt. = 198.38 g/mol



To a stirred solution of 4-pentyn-1-ol (0.33 mL, 3.5 mmol) in DMF (3 mL) was added imidazole (0.65 g, 4.3 mmol, 1.2 equiv). After all the solid was dissolved, TBSCl (0.59 g, 8.5 mmol, 2.4 equiv) was added. The mixture was stirred at RT for 4 h then quenched by addition of water (3 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with brine (2 × 5 mL), dried over magnesium sulfate and concentrated under vacuum to furnish TBS-protected alcohol **2.58** as a colourless oil (0.69 g, 100%).

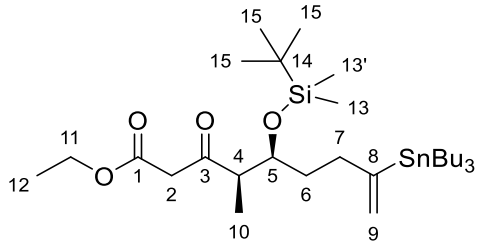
^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.71 (t, *J* = 6.6 Hz, 2H, H^1) 2.28 (td, *J* = 6.6, 2.8 Hz, 2H, H^3) 1.94 (t, *J* = 2.8 Hz, 1H, H^5) 1.73 (quint, *J* = 6.6 Hz, 2H, H^2) 0.90 (s, 9H, H^8) 0.07 (s, 6H, H^6/$H^{6'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 84.3 (C^4), 68.2 (C^5), 61.4 (C^1), 31.5 (C^3), 25.9 (C^8), 18.3 (C^7), 14.8 (C^2), −5.4 (C^6/$C^{6'}$).

In agreement with literature data.[63]

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxo-8-(tributylstannyl)non-8-enoate (2.56).[66]

$C_{30}H_{60}O_4SnSi$
Mol. Wt. = 631.60 g/mol



To a solution of pentamethylcyclopentadienyl*tris* (acetonitrile) ruthenium(II) hexafluorophosphate (36 mg, 0.07 mmol, 0.05 equiv) in CH_2Cl_2 (3.5 mL) was added dropwise a mixture of alkyne **2.36** (484 mg, 1.42 mmol) and tributyltin hydride (0.420 mL, 1.56 mmol, 1.10 equiv) in CH_2Cl_2 (0.5 mL) over 15 min. The reaction was stirred at RT for 2 h then filtered through a short plug of silica and concentrated under vacuum to give stannane **2.56** as a colourless oil. The crude product (430 mg) was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.69–5.66 (m, $J_{Sn\text{-}H}$ = 136.0 Hz, 1H, H^9), 5.12–5.08 (m, $J_{Sn\text{-}H}$ = 59.2 Hz, 1H, H^9), 4.24–4.14 (m, 2H, H^{11}), 3.94 (app q, *J* = 5.5 Hz, 1H, H^5), 3.62 (d, *J* = 15.7 Hz, 1H, H^2), 3.54 (d, *J* = 15.8 Hz, 1H, H^2), 2.84 (qd, *J* = 7.0, 3.8 Hz, 1H, H^4), 2.31–2.04 (m, 2H, H^7), 1.61–1.38 (m, 8H, H^6/Sn<u>Bu</u>$_3$), 1.35–1.24 (m, 9H, H^{12}/Sn<u>Bu</u>$_3$), 1.10 (d, *J* = 7.0 Hz, 3H, H^{10}), 0.92–0.86 (m, 24H, H^{15}/Sn<u>Bu</u>$_3$), 0.04 (s, 3H, H^{13}), −0.00 (s, 3H, $H^{13'}$).

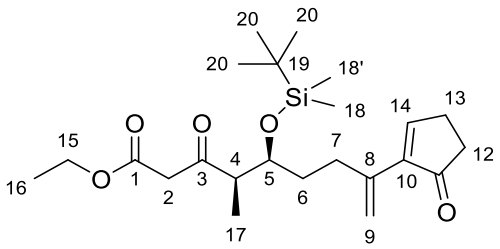
^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.0 (C^3), 173.0 (C^1), 154.7 (C^8), 125.0 (C^9), 73.2 (C^5), 60.1 (C^{11}), 51.9 (C^4), 49.6 (C^2), 36.8 (C^7), 34.4 (C^6), 29.3 ($C^{Sn\underline{Bu}_3}$), 27.6 ($C^{Sn\underline{Bu}_3}$), 26.0 (C^{15}), 18.3 (C^{14}), 14.3 (C^{12}), 13.8 ($C^{Sn\underline{Bu}_3}$), 11.5 (C^{10}), 9.7 ($C^{Sn\underline{Bu}_3}$), −4.2 (C^{13}), −4.5 ($C^{13'}$).

HRMS (ESI) for $C_{30}H_{60}NaO_4SiSn$: 655.3175, found: 655.3155.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxo-8-(5-oxocyclopent-1-en-1-yl)non-8-enoate (2.52).[69]

$C_{23}H_{38}O_5Si$

Mol. Wt. = 422.64 g/mol



To a mixture of tetrabutylammonium diphenylphosphinate (1.25 g, 2.72 mmol, 4.00 equiv) in DMF (5 mL) was added a solution of stannane **2.56** (430 mg, 0.68 mmol) in DMF (10 mL) then 2-iodocyclopent-2-enone (184 mg, 0.88 mmol, 1.30 equiv). *Tetrakis*(triphenylphosphine)palladium(0) (235 mg, 0.200 mmol, 0.300 equiv) and CuTC (389 mg, 2.04 mmol, 3.00 equiv) were quickly added in the same time. The reaction was stirred for 1 h before being quenched with water (15 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), the organic phases were combined, washed with a saturated aqueous solution of lithium chloride (2 × 10 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The product was then purified by flash chromatography (80:20 PE/Et_2O) to give product **2.52** with traces of triphenylphosphine as a pale yellow oil (205 mg, 40% yield over 2 steps).

^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.49 (t, *J* = 2.9 Hz, 1H, H^{14}), 5.94 (m, 1H, H^9), 5.14 (m, 1H, H^9), 4.19 (q, *J* = 7.1 Hz, 2H, H^{15}), 3.91 (dt, *J* = 7.1, 4.5 Hz, 1H, H^5), 3.59 (s, 2H, H^2), 2.87 (qd, *J* = 7.0, 4.5 Hz, 1H, H^4), 2.61 (m, 2H, H^{13}), 2.52–2.46 (m, 2H, H^{12}), 1.75–1.47 (m, 4H, H^6/ H^7), 1.27 (t, *J* = 7.1 Hz, 3H, H^{16}), 1.09 (d, *J* = 7.0 Hz, 3H, H^{17}), 0.92 (s, 9H, H^{20}), 0.09 (s, 3H, H^{18}), 0.09 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.2 (C^3 or C^{11}), 200.8 (C^3 or C^{11}), 168.5 (C^1), 158.1 (C^{14}), 142.9 (C^{10}), 138.2 (C^8), 115.8 (C^9), 73.6 (C^5), 61.3 (C^{15}), 51.9 (C^4), 49.6 (C^2), 36.0 (C^{12}), 32.8 (C^6), 31.3 (C^7), 30.5 (C^{13}), 26.0 (C^{20}), 18.2 (C^{19}), 14.3 (C^{16}), 12.1 (C^{17}), −4.3 (C^{18}/$C^{18'}$).

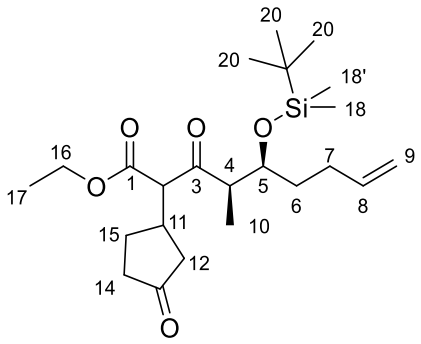
$[\alpha]_D^{25}$ −24.8 (*c* = 0.50, $CHCl_3$).

IR (thin film): 2924, 2855, 1736, 1705, 1250, 1026 cm^{-1}.

HRMS (ESI) for $C_{23}H_{38}NaO_5Si$: 445.2381, found: 445.2363.

Ethyl (4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3-oxo-2-(3-oxocyclopentyl)non-8-enoate (2.27).[35]

$C_{23}H_{40}SiO_5$
Mol. Wt. = 424.64 g/mol



To a solution of **1.126** (0.51 g, 1.5 mmol, 1.1 equiv) and 2-cyclopentenone (0.11 mL, 1.3 mmol) in ethanol (1 mL) was added potassium carbonate (80 mg, 0.50 mmol, 0.40 equiv). The mixture was left to stir overnight and then was diluted with water (5 mL) and Et_2O (5 mL). The two layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude material was purified by column chromatography (90:10 PE:EtOAc) to furnish the product **2.27** as a colourless oil (0.49 g, 88%) as an unseperable mixture of 4 diastereomers.

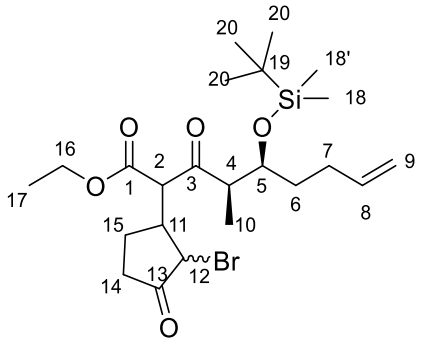
Due to the presence of 4 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.68–5.56 (m, 1H, H^8), 4.89–4.79 (m, 2H, H^9), 4.12–4.06 (m, 2H, H^{16}), 3.75 (d, *J* = 7.6 Hz, 1H, H^2), 3.64–3.56 (m, 1H, H^5), 2.90–2.84 (m, 1H, H^4), 2.80–2.64 (m, 2H, H^{12}/H^{14}), 2.43–2.00 (m, 2H, H^{12}/H^{14}), 1.99–1.77 (m, 4H, H^7/H^{15}), 1.77–1.61 (m, 1H, H^{11}), 1.50–1.32 (m, 2H, H^6), 1.17–1.10 (m, 3H, H^{17}), 1.07–1.04 (m, 3H, H^{10}), 0.82 (s, 9H, H^{20}), 0.05 (s, 3H, H^{18}), −0.02 (s, 3H, $H^{18'}$).

In agreement with literature data.[35]

Ethyl (4*R*,5*S*)-2-(2'-bromo-3'-oxocyclopentyl)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxonon-8-enoate (2.33).

$C_{23}H_{39}BrO_5Si$
Mol. Wt. = 503.5 g/mol



Michael product **2.33** (yellow oil) was obtained from the corresponding ketoester **1.126** and bromoketone **2.32** according to the procedure described above for Michael product **2.27**.
Purification by flash column chromatography (90:10 PE/EtOAc).
Scale: 1.1 mmol
Yield: 61% as 8 inseparable diastereomers.

Due to the presence of 4 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88–5.70 (m, 1H, H^8), 5.09–4.85 (m, 2H, H^9), 4.33–4.12 (m, 2H, H^{16}), 4.02–3.93 (m, 1H, H^{12}), 3.92–3.78 (m, 1H, H^2), 3.70–3.55 (m, 1H, H^5), 2.40−2.20 (m, 2H, H^4/H^{14}) 2.19–1.97 (m, 3H, H^{14}/H^7/H^{11}), 1.96–1.68 (m, 1H, H^{15}) 1.67–1.41 (m, 1H, H^7), 1.37–1.27 (m, 4H, H^{17}/H^{15}), 1.22–1.15 (m, 2H, H^6) 1.12 (d, *J* = 6.9 Hz, 3H, H^{10}), 0.93–0.89 (m, 9H, H^{20}), 0.14–0.03 (m, 6H, H^{18}/ $H^{18'}$).

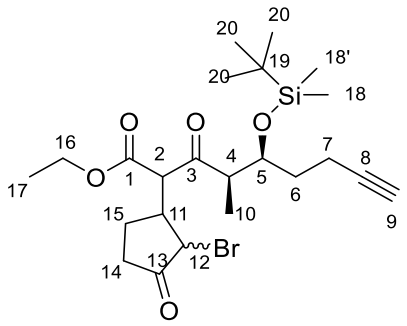
^{13}C NMR ($CDCl_3$, 126 MHz) δ 213.3, 173.6, 172.9, 164.8, 139.0, 138.8, 114.8, 114.1, 113.9, 110.1, 109.9, 105.3, 104.8, 86.5, 83.2, 83.0, 82.8, 84, 73.7, 73.3, 73.0, 63.2, 61.9, 61.1, 59.7, 59.4, 53.6, 51.0, 45.6, 43.5, 41.7, 40.9, 37.6, 35.3, 34.9, 34.5, 33.2, 33.1, 29.7, 28.4, 28.2, 27.5, 27.4, 25.7, 25.6, 25.3, 25.1, 24.6, 23.8, 23.5, 20.8, 18.1 17.5, 17.3, 16.0, 15.8, 15.0, 14.5, 14.1, 13.6, −2.8, −5.2.

IR (thin film) 2955, 2931, 2856, 1755, 1703, 1631, 1462, 1371, 1241, 1224, 1101, 1026 cm^{-1}

HRMS (CI) for $C_{23}H_{39}O_5{}^{79}BrSi$: 503.1828, found: 503.1832.

Ethyl (4*R*,5*S*)-2-(2-bromo-3-oxocyclopentyl)-5-((tert-butyldimethylsilyl)oxy)-4-methyl-3-oxonon-8-ynoate (2.35).

$C_{23}H_{37}BrO_5Si$
Mol. Wt. = 501.53 g/mol



Michael product **2.35** (yellow oil) was obtained from the corresponding ketoester **2.36** according to the procedure described above for Michael product **2.27**.
Purification by flash column chromatography (90:10 PE/EtOAc)
Scale: 2.9 mmol
Yield: 22% as an inseparable mixture of 8 diastereomers.

Due to the presence of 8 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.33–4.09 (m, 2H, H^{16}), 4.00–3.75 (m, 2H, H^2/H^{12}), 3.74–3.41 (m, 1H, H^5), 2.37–2.05 (m, 4H, H^4/H^{14}/H^7), 2.01–1.84 (m, 2H, H^{11}/H^9), 1.80–1.59 (m, 3H, H^6/H^7), 1.34–1.24 (m, 3H, H^{17}), 1.24–1.16 (m, 2H, H^{15}), 1.14 (m, 3H, H^{10}), 0.98–0.82 (m, 9H, H^{20}), 0.18– -0.02 (m, 6H, H^{18}/$H^{18'}$).

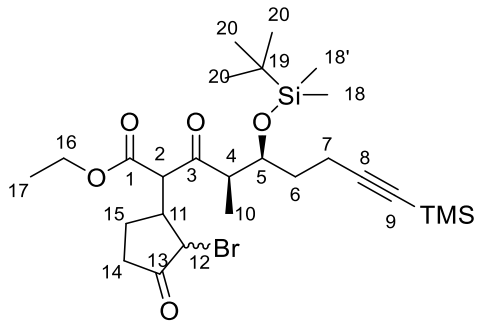
^{13}C NMR ($CDCl_3$, 126 MHz) δ 213.4, 213.3, 210.5, 208.9, 208.6, 208.6, 205.9, 205.2, 173.2, 172.5, 168.2, 167.4, 167.1, 165.4, 164.9, 164.9, 105.8, 105.3, 91.9, 84.9, 84.8, 84.0, 83.9, 83.8, 83.7, 83.1, 82.9, 73.0, 72.5, 72.4, 70.6, 69.2, 68.8, 68.7, 68.2, 63.6, 62.4, 62.2, 62.0, 61.9, 61.5, 60.0, 59.7, 53.9, 53.6, 53.4, 52.4, 52.0, 51.5, 51.3, 51.1, 50.9, 43.7, 43.5, 41.5, 41.0, 40.9, 37.6, 35.0, 34.8, 34.6, 34.4, 32.6, 30.4, 29.8, 28.6, 26.1, 26.0, 25.9, 25.4, 25.3, 18.3, 18.2, 15.8, 15.0, 14.9, 14.7, 14.5, 14.3, 14.2, 12.9, −4.1, −4.5.

IR (thin film) 2955, 2933, 1728, 1709, 1373, 1249, 1226, 1217, 1097, 1030 cm^{-1}.

HRMS (ESI) for $C_{23}H_{37}NaO_5Si79Br$: 523.1486, found: 523.1479.

Ethyl (4*R*,5*S*)-2-(2-bromo-3-oxocyclopentyl)-5-((tert-butyldimethylsilyl)oxy)-4-methyl-3-oxo-9-(trimethylsilyl)non-8-ynoate (2.43).

$C_{26}H_{45}BrO_5Si_2$
Mol. Wt. = 573.71 g/mol



To a solution of **2.43** (0.10 g, 0.24 mmol, 1.1 equiv) and bromoketone **2.32** (0.34 g, 0.21 mmol) in ethanol (2 mL) was added trifluoroethanol (0.15 mL, 0.21 mmol, 1.0 equiv) and potassium carbonate (12 mg, 84 µmol, 0.4 equiv). The mixture was left to stir overnight and then was diluted with water (10 mL) and Et_2O (10 mL). The two layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (80:20 PE:Et_2O) to furnish the product **2.43** as a colourless oil (0.10 g, 74%) and as an inseparable mixture of 8 diastereomers.

Due to the presence of 8 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.29–4.16 (m, 2H, H^{16}), 3.99–3.91 (m, 1H, H^{12}), 3.90–3.85 (m, 1H, H^2), 3.57–3.50 (m, 1H, H^5), 2.37–2.24 (m, 3H, H^4/H^{14}/H^{11}), 2.23–2.12 (m, 2H, H^{14}/H^{15}), 1.77–1.62 (m, 2H, H^{15}/ H^6), 1.49–1.44 (m, 4H, H^6/ H^{17}), 1.28 (m, 2H, H^{15}), 1.14 (d, *J* = 6.9 Hz, 3H, H^{10}), 0.88 (d, *J* = 2.9 Hz, 9H, H^{20}), 0.15–0.13 (m, 9H, H^{TMS}), 0.13–0.11 (m, 6H, H^{18}/ $H^{18'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 213.3, 213.2, 173.4, 172.5, 165.0, 164.9, 107.8, 107.7, 105.94, 105.2, 84.5, 84.4, 83.1, 82.9, 72.8, 72.6, 56.0, 43.7, 43.6, 37.8, 37.6, 35.0, 34.7, 34.6, 34.4,

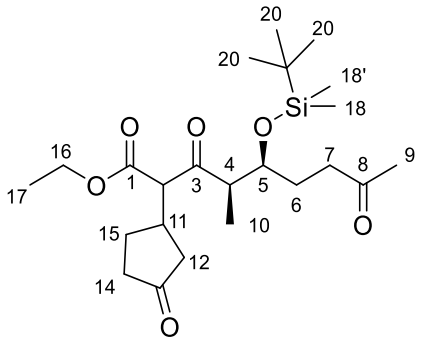
26.1, 26.1, 26.0, 26.0, 25.5, 25.2, 18.2, 18.2, 15.7, 15.3, 14.7, 14.6, 14.5, 0.3, 0.3, 0.2, 0.23, −4.1, −4.1, −4.5, −4.5.

IR 2955, 2928, 2175, 1737, 1710, 1249, 1099, 1060 cm^{-1}.

Ethyl (4*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3,8-dioxo-2-(3-oxocyclopentyl) nonanoate (1.140). [35]

$C_{23}H_{40}SiO_6$

Mol. Wt. = 440.64 g/mol



Palladium(II) chloride (17 mg, 0.097 mmol, 0.10 equiv) and CuCl (96 mg, 0.97 mmol, 1.0 equiv) was added to a 3:1 mixture of DMF/ water (2.1 mL) and oxygen was bubbled through the solution for 1 h. A solution of **2.27** (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 water and extracted with Et_2O (3 x 10 mL) then filtered on celite. The combined organic layers were washed with brine (3 x 10 mL), dried over magnesium sulfate and concentrated under vacuum. The crude material was purified by column chromatography (80:20 PE/EtOAc) to furnish the product **1.140** as a colourless oil (0.33 g, 78%) as an inseparable mixture of 4 diastereomers.

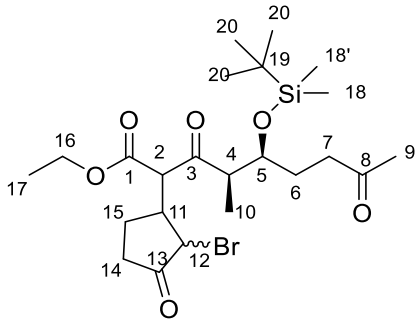
Due to the presence of 4 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12–4.01 (m, 2H, H^{16}), 3.71 (d, *J* = 9.5 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^{20}), –0.05 (s, 3H, H^{18}), –0.10 (s, 3H, $H^{18'}$).

In agreement with literature data.

Ethyl (4*R*,5*S*)-2-(2-Bromo-3-oxocyclopentyl)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3,8-dioxononanoate (2.31).

$C_{23}H_{39}BrO_6Si$
Mol. Wt. = 519.25 g/mol



Ketone **2.31** (colourless oil) was obtained from the corresponding Michael product **2.33** according to the procedure described above for ketone **1.140**.
Purification by flash column chromatography (80:20 PE/EtOAc)
Scale: 0.6 mmol
Yield: 78% as a mixture of 8 inseparable diastereomers.

Due to the presence of 8 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28–4.05 (m, 2H, H^{16}), 3.96–3.74 (m, 2H, H^{12}/ H^2), 3.69–3.45 (m, 1H, H^5), 2.61–2.35 (m, 1H, H^4), 2.37–2.14 (m, 2H, H^{14}), 2.14–2.06 (m, 2H, H^7), 2.03–1.92 (m, 3H, H^9), 1.92–1.79 (m, 1H, H^{11}), 1.80–1.62 (m, 2H, H^6/H^{15}), 1.60–1.45 (m, 2H, H^7/H^{15}), 1.33–1.23 (m, 3H, H^{17}), 1.21 (d, *J* = 6.8 Hz, 3H, H^{10}), 0.95–0.81 (m, 9H, H^{20}), 0.12–−0.04 (m, 6H, H^{18}/$H^{18'}$).

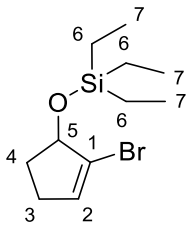
^{13}C NMR ($CDCl_3$) δ 213.7, 213.2, 209.2, 173.5, 172.8, 165.0, 105.7, 105.1, 83.2, 83.0, 73.3, 72.6, 72.3, 63.6, 62.1, 59.9, 59.6, 53.8, 51.4, 43.6, 43.4, 41.0, 39.4, 37.7, 37.5, 37.2, 35.0, 34.6, 34.0, 32.0, 30.4, 30.1, 29.8, 29.5, 28.9, 28.3, 26.1, 25.4, 24.0, 23.7, 22.8, 20.9, 20.7, 18.2, 17.5, 17.4, 17.3, 16.3, 15.8, 15.0 14.4, 14.1, 8.0, −3.9, −4.8, −4.9, −5.2.

IR (thin film) 2955, 2931, 2856, 2360, 1755, 1742, 1703, 1371, 1251, 1224, 1163 cm^{-1}.

HRMS (ESI) for $C_{23}H_{39}NaO_6Si$ 79Br: 541.1591, found: 541.1583.

((2-Bromocyclopent-2-en-1-yl)oxy)triethylsilane (2.77).

$C_{11}H_{21}BrOSi$
Mol. Wt. = 277.28 g/mol



A solution of 2-bromocyclopent-2-enone **2.32** (6.74 g, 41.9 mmol) in CH_2Cl_2 (250 mL) was cooled to −78 °C then a 1 M solution of diisobutylaluminium hydride in heptane (84 mL, 84 mmol, 2.0 equiv) was added dropwise. The reaction was stirred at −78 °C for 1 h then was quenched by addition of a saturated aqueous solution of Rochelle salt (200 mL) and allowed to warm up to RT. The mixture was stirred for 4 h then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL), the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum to furnish the crude allylic alcohol (6.8 g) as a colourless liquid that was used in the next step without further purification.

2-Bromocyclopent-2-en-1-ol (6.80 g, 41.7 mmol) was dissolved in dry DMF (100 mL) then imidazole (8.52 g, 125 mmol, 3.00 equiv) and DMAP (0.51 g, 4.2 mmol, 0.10 equiv) were added. The reaction was cooled to 0 °C then chlorotriethylsilane (10.5 mL, 62.6 mmol, 3.00 equiv) was added dropwise and the reaction was stirred for 5 min. The mixture was warmed to RT and stirred for 1 h. The mixture was then diluted with water (100 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (2 × 300 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (99:1 PE/Et_2O) to give product **2.77** (8.9 g, 77% over 2 steps) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02 (td, *J* = 2.5, 1.1 Hz, 1H, H^2), 4.74–4.69 (m, 1H, H^5), 2.51–2.41 (m, 1H, H^4), 2.35–2.26 (m, 1H, H^3), 2.27–2.17 (m, 1H, H^4), 1.82 (ddt, *J* = 12.6, 8.6, 4.4 Hz, 1H, H^3), 1.01 (t, *J* = 8.0 Hz, 9H, H^7), 0.68 (t, *J* = 8.0 Hz, 6H, H^6).

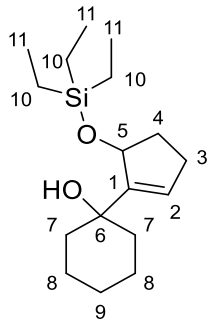
^{13}C NMR ($CDCl_3$, 101MHz) δ 133.7 (C^2), 125.7 (C^1), 79.4 (C^5), 33.4 (C^3), 30.4 (C^4), 7.0 (C^7), 5.0 (C^6).

IR (thin film) 2955, 2878, 1096, 1003 cm^{-1}.

HRMS (ESI) for $C_{21}H_{21}79BrNaOSi$: 299.0437, found: 299.0431.

1-(5-((Triethylsilyl)oxy)cyclopent-1-en-1-yl)cyclohexan-1-ol (2.78).

$C_{17}H_{32}O_2Si$
Mol. Wt. = 296.53 g/mol



Cerium(III) chloride heptahydrate (7.52 g, 20.2 mmol, 2.20 equiv) was finely grinded then stirred under vacuum (P < 1 mbar) and warmed to 120 °C for 2 h, 140 °C for 2 h and 160 °C for 3 h. Cerium(III) chloride was cooled to RT under inert atmosphere then THF (25 mL) was added and the white suspension was stirred vigorously overnight.
((2-Bromocyclopent-2-en-1-yl)oxy)triethylsilane **2.77** (5.10 g, 18.3 mmol, 2.00 equiv) was dissolved in THF (15 mL), the mixture was cooled to −78 °C and a 2.2 M solution of *n*-BuLi in hexane (8.90 mL, 19.3 mmol, 2.10 equiv) was added. The mixture was stirred for 20 min at −78 °C then was added dropwise to the cerium(III) chloride white suspension at −78 °C. The red/brown slurry was stirred for 1 h then cyclohexanone (0.95 mL, 9.2 mmol) in THF (10 mL) was added dropwise (over 30 min). The mixture was stirred at −78 °C for 4 h then quenched with water (50 mL) and allowed to warm up to RT. The layers were separated, the aqueous layer was extracted with Et_2O (3 × 50 mL), the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (95:5 PE/Et_2O) to yield product **2.78** (1.96 g, 72%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.73 (t, *J* = 3.0 Hz, 1H, H^2), 5.10 (td, *J* = 7.0, 1.7 Hz, 1H, H^5), 4.01 (s, 1H, OH), 2.46–2.35 (m, 1H, H^3), 2.30–2.25 (m, 1H, H^4), 2.25–2.17 (m, 1H, H^3), 1.80–1.67 (m, 6H, H^4/H^7/H^9), 1.62–1.47 (m, 5H, H^8/H^9), 0.99 (t, *J* = 7.9 Hz, 9H, H^{11}), 0.66 (q, *J* = 7.9 Hz, 6H, H^{10}).

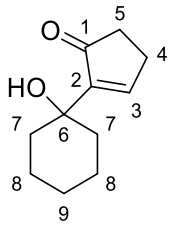
^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.1 (C^1), 126.9 (C^2), 79.0 (C^5), 71.0 (C^6), 36.4 (C^7), 34.5 (C^4), 29.4 (C^3), 26.0 (C^8), 22.3 (C^9), 6.8 (C^{11}), 5.0 (C^{10}).

IR (thin film) 3503, 2932, 2878, 1065, 1003 cm^{-1}.

HRMS (ESI) for $C_{17}H_{32}NaO_2Si$: 319.2064, found: 319.2062.

2-(1-Hydroxycyclohexyl)cyclopent-2-en-1-one (2.79).

$C_{11}H_{16}O_2$
Mol. Wt. = 180.25 g/mol



A solution of **2.78** (1.93 g, 6.51 mmol) in THF (30 mL) in a high-density polyethylene vessel was cooled to 0 °C and pyridine (10.5 mL, 130 mmol, 20 equiv) was added. The mixture was stirred for 10 min followed by addition of HF.pyridine (5.90 mL, 65.1 mmol, 10 equiv). The reaction was stirred at 0 °C for 1 h then was quenched by careful addition of a saturated aqueous solution of sodium bicarbonate (30 mL) and allowed to warm up to RT. The layers were separated and the aqueous layer was extracted with EtOAc (5 x 30 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under vacuum to give the crude diol (1.19 g) as a colourless oil. The crude product was used in the next step without further purification. (The aqueous layer was diluted and the glassware was rinsed with a saturated aqueous solution of calcium(II) chloride to remove any traces of HF).

Crude diol (1.19 g, 6.53 mmol) was dissolved in CH_2Cl_2 (25 mL) and was added to a flask containing both the 4Å molecular sieves and NMO (1.53 g, 13.1 mmol, 2.00 equiv) in CH_2Cl_2 (25 mL). After stirring the mixture for 10 min, TPAP (0.23 g, 0.65 mmol, 0.10 equiv) was added and the reaction was stirred at RT for 1 h. The reaction was then filtered through a short pad of celite and the solvent removed under vacuum. The crude mixture was purified by flash chromatography (70:30 PE/Et_2O) to give enone **2.79** (0.88 g, 75% over 2 steps) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (t, *J* = 2.8 Hz, 1H, H^3), 3.55 (s, 1H, OH), 2.61–2.54 (m, 2H, H^4), 2.46–2.42 (m, 2H, H^5), 1.83–1.77 (m, 2H, H^7), 1.73 (tt, *J* = 12.3, 3.5 Hz, 2H, H^8), 1.68–1.64 (m, 1H, H^9), 1.60 (td, *J* = 12.3, 3.7 Hz, 2H, H^7), 1.51 (dt, *J* = 12.9, 3.7 Hz, 2H, H^8), 1.29–1.19 (m, 1H, H^9).

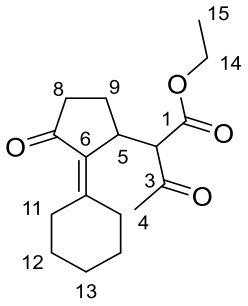
^{13}C NMR ($CDCl_3$, 126 MHz) δ 211.0 (C^1), 156.7 (C^3), 151.3 (C^2), 70.6 (C^6), 36.4 (C^7), 35.7 (C^5), 26.2 (C^4), 25.7 (C^9), 21.5 (C^8).

IR (thin film) 3487, 2932, 2855, 1674, 1312 cm^{-1}.

HRMS (ESI) for $C_{11}H_{16}NaO_2$: 203.1043, found: 203.1040.

Ethyl 2-(2-cyclohexylidene-3-oxocyclopentyl)-3-oxobutanoate (2.82).

$C_{17}H_{24}O_4$
Mol. Wt. = 292.38 g/mol



To a mixture of enone **2.79** (50 mg, 0.28 mmol), benzil (58 mg, 0.28 mmol, 1.0 equiv) and indium(III) chloride (3.1 mg, 0.014 mmol, 0.050 equiv) in CH_2Cl_2 (1 mL) was added dimethylchlorosilane (34 µL, 0.31 mmol, 1.10 equiv). After 15 min the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (1 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated under vacuum to furnish a mixture of the unstable chloro product **2.81** (55 mg) and benzil (58 mg) as a yellow oil that was used in the next step without further purification.

To a solution of **2.81** and benzil (55 and 58 mg) in THF (1 mL) was added *tetrakis*(triphenylphosphine)palladium(0) (32 mg, 0.028 mmol, 0.10 equiv) and the mixture was stirred at RT for 30 min. Ethyl acetoacetate (35 µL, 0.28 mmol, 1.0 equiv) in THF (1

mL) was cooled to 0 °C then sodium hydride (11 mg, 0.28 mmol, 1.0 equiv) was added to the solution. The solution was stirred for 15 min then was added dropwise to the previous mixture (**2.81**/Palladium). The reaction was stirred at RT for 5 min then was quenched with water (2 mL). The layers were separated, the aqueous phase was extracted Et_2O (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The mixture was purified by flash chromatography (70:30 PE/Et_2O) to yield product **2.82** (31 mg, 40% over 2 steps) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.19–4.05 (m, 2H, H^{14}), 3.81 (dt, *J* = 13.2, 7.8 Hz, 1H, H^5), 3.54 (d, *J* = 7.8 Hz, 1H, H^2), 3.07 (dt, *J* = 13.2, 5.4 Hz, 2H, H^{11}), 2.98–2.81 (m, 2H, H^8), 2.74–2.66 (m, 1H, H^{11}), 2.39–2.23 (m, 3H, H^{11}/H^{12}), 2.22 (s, 3H, H^4), 2.18–2.12 (m, 1H, H^9), 2.07–1.94 (m, 1H, H^9), 1.91–1.83 (m, 1H, H^{13}), 1.69–1.59 (m, 2H, H^{12}), 1.59–1.50 (m, 1H, H^{13}), 1.26–1.20 (m, 3H, H^{15}).

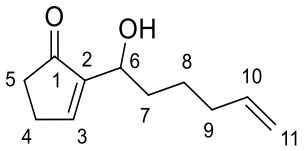
^{13}C NMR (CDCl3, 126 MHz) δ 207.6 (C^3 or C^7), 202.7 (C^3 or C^7), 169.1 (C^1), 157.2 (C^{10}), 129.8 (C^6), 62.1 (C^{14}), 61.7 (C^2), 39.5 (C^8), 37.4 (C^5), 34.0 (C^{11}), 31.1 (C^4), 30.8 (C^5), 30.4 (C^{11}), 29.0 (C^{12}), 28.4 (C^{12}), 26.3 (C^{13}), 14.2 (C^{15}).

IR (thin film) 2931, 1705, 1620, 1172 cm^{-1}.

HRMS (ESI) for $C_{17}H_{24}NaO_4$: 315.1567, found: 315.1556.

2-(1-Hydroxyhex-5-en-1-yl)cyclopent-2-en-1-one (2.68).[73]

$C_{11}H_{16}O_2$
Mol. Wt. = 180.25 g/mol



2-Cyclopenten-1-one (0.10 mL, 1.2 mmol) and hex-5-en-1-al **2.67** (0.24 g, 2.4 mmol, 2.0 equiv) were dissolved in a 3:2 mixture of $CHCl_3$/MeOH (2.5 mL). Dimethylphenylphosphine (17 µL, 0.12 mmol, 0.10 equiv) was added dropwise and the reaction was stirred for 2 h at RT. The solvents were concentrated under vacuum and the resulting crude product was purified by flash chromatography (70:30 PE/Et_2O) to furnish product **2.68** (0.21 g, 94%) as a colourless oil.

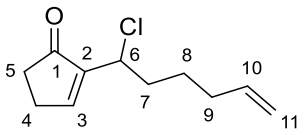
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (td, *J* = 2.7, 1.1 Hz, 1H, H^3), 5.80 (ddt, *J* = 17.1, 10.1, 6.7 Hz, 1H, H^{10}), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H, H^{11}), 4.96 (ddt, *J* = 10.1, 1.7, 1.1 Hz, 1H, H^{11}), 4.48–4.42 (m, 1H, H^6), 2.77 (d, *J* = 5.6 Hz, 1H, OH), 2.64–2.59 (m, 2H, H^4), 2.47–2.43 (m, 2H, H^5), 2.12–2.05 (m, 2H, H^9), 1.74–1.65 (m, 2H, H^7), 1.62–1.56 (m, 1H, H^8), 1.49–1.41 (m, 1H, H^8).

^{13}C NMR (CDCl3, 126 MHz) δ 210.2 (C^1), 157.9 (C^3), 147.9 (C^2), 138.7 (C^{10}), 114.9 (C^{11}), 67.9 (C^6), 35.5 (C^4), 35.4 (C^5), 33.6 (C^9), 26.8 (C^8), 24.9 (C^7).

In agreement with literature data.[104]

2-(1-Chlorohex-5-en-1-yl)cyclopent-2-en-1-one (2.65).

$C_{11}H_{15}ClO$
Mol. Wt. = 198.69 g/mol



To a solution of **2.68** (100 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was added triethylamine (115 µL, 0.830 mmol, 1.50 equiv) and methanesulfonyl chloride (65 µL, 0.83 mmol, 1.5 equiv). The mixture was stirred at RT for 2 h then was quenched by addition of water (3 mL) and the layers were separated. The organic layer was washed with brine (2 × 5 mL), dried over sodium sulfate, filtered and concentrated under vacuum to give the unstable chlorocyclopentenone **2.65** (75 mg) that was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (td, *J* = 2.7, 1.1 Hz, 1H, H^3), 5.78 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H, H^{10}), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H, H^{11}), 4.97 (dt, *J* = 10.2, 1.7 Hz, 1H, H^{11}), 4.68 (ddt, *J* = 7.4, 3.0, 1.3 Hz, 1H, H^6), 2.67–2.62 (m, 2H, H^4), 2.50–2.47 (m, 2H, H^5), 2.15–2.02 (m, 2H, H^9), 2.00–1.91 (m, 1H, H^7), 1.91–1.83 (m, 1H, H^7) 1.65–1.56 (m, 1H, H^8), 1.54–1.46 (m, 1H, H^8).

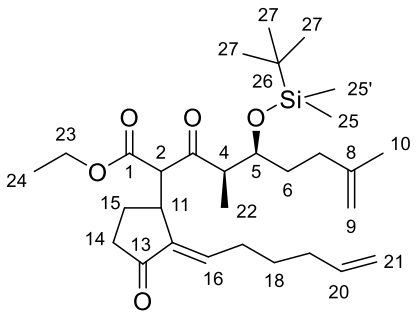
IR (thin film) 3055, 2932, 2862, 1705, 1643 cm^{-1}.

HRMS (CI+) for $C_{11}H_{16}ClO$: 199.0884, found: 199.0890.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-2'-(hex-5'-en-1'-ylidene)-3-oxocyclopentyl)-4,8-dimethyl-3-oxonon-8-enoate (2.63).

$C_{30}H_{50}O_5Si$

Mol. Wt. = 518.81 g/mol



To a solution of chlorocyclopentenone **2.65** (254 mg, 1.27 mmol) in THF (5 mL) was added *tetrakis*(triphenylphosphine)palladium(0) (162 mg, 0.140 mmol, 0.11 equiv) and the reaction was stirred for 20 min at RT. In parallel, sodium hydride (59.0 mg, 1.47 mmol, 1.05 equiv) was added to a solution of ketoester **2.64** (500 mg, 1.40 mmol, 1.10 equiv) in THF (5 mL) and the mixture was stirred for 10 min before dropwise addition to the palladium/chlorocyclopentenone mixture. The reaction was stirred for 5 min then was quenched by addition of a 1 M aqueous solution of hydrochloric acid (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL), the organic phases were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. The mixture was purified by flash chromatography (90:10 PE/Et_2O) to yield product **2.63** (458 mg, 69%) as yellow oil and as an inseparable mixture of 4 diastereomers.

Due to the presence of 4 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.54 (t, *J* = 6.8 Hz, 1H, H^{16}), 5.84–5.71 (m, 1H, H^{20}), 5.05–4.94 (m, 2H, H^{21}), 4.72–4.64 (m, 1H, H^{9}), 4.64 (d, *J* = 1.0 Hz, 1H, H^{9}), 4.18–4.07 (m, 2H, H^{23}), 4.02 (d, *J* = 5.1 Hz, 1H, H^{2}), 3.97–3.90 (m, 1H, H^{5}), 3.73–3.64 (m, 1H, H^{11}), 2.87 (qd, *J* = 7.0, 4.1 Hz, 1H, H^{4}), 2.51–2.38 (m, 1H, H^{14}), 2.33–2.22 (m, 1H, H^{14}), 2.21–2.12 (m, 2H, H^{17}), 2.12–2.02 (m, 3H, H^{15}/H^{19}), 2.02–1.93 (m, 3H, H^{7}/H^{15}), 1.70 (s, 3H, H^{10}), 1.64–1.45 (m, 4H, H^{6}/H^{18}), 1.27–1.19 (m, 3H, H^{24}), 1.09 (d, *J* = 7.0 Hz, 3H, H^{22}), 0.89 (s, 9H, H^{27}), 0.07 (s, 3H, H^{25}), 0.04 (s, 3H, $H^{25'}$).

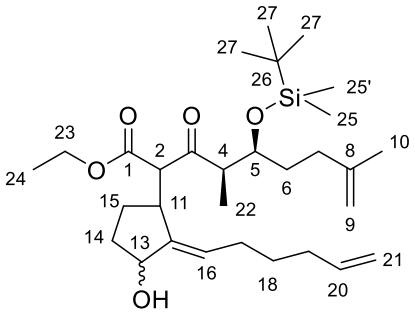
^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.5 (C^3 or C^{13}), 206.3 (C^3 or C^{13}), 168.3 (C^1), 145.5 (C^8 or C^{12}), 139.0 (C^8 or C^{12}), 138.5 (C^{16}), 138.1 (C^{20}), 115.4 (C^{21}), 110.1 (C^9), 72.7 (C^5), 61.6 (C^2), 60.7 (C^{23}), 52.1 (C^4), 38.1 (C^{11}), 35.7 (C^{14}), 34.1 (C^{19}), 33.4 (C^6) 33.1 (C^7), 28.9 (C^{17}), 28.0 (C^{18}), 26.1 (C^{27}), 23.1 (C^{15}), 22.7 (C^{10}), 18.3 (C^{26}), 14.2 (C^{24}), 13.1 (C^{22}), −4.2 (C^{25}), −4.4 ($C^{25'}$).

IR (thin film) 2940, 2862, 1736, 1643, 845 cm^{-1}.

HRMS (CI+) for $C_{30}H_{51}O_5Si$: 519.3500, found: 519.3506.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2'-((*E*)-2-(hex-5'-en-1'-ylidene)-3-hydroxycyclopentyl)-4,8-dimethyl-3-oxonon-8-enoate (2.75).

$C_{30}H_{52}O_5Si$
Mol. Wt. = 520.83 g/mol



Ketone **2.63** (170 mg, 0.330 mmol) and cerium(III) chloride heptahydrate (240 mg, 0.640 mmol, 2.00 equiv) were dissolved in ethanol (2.5 mL) and cooled to 0 °C. The mixture was stirred for 1 h at 0 °C then cooled to −78 °C before addition of sodium borohydride (14 mg, 0.36 mmol, 1.1 equiv). The reaction was left to stir at −78 °C for 1 h, 0 °C for 1 h and RT for 2 h. The crude mixture was diluted with a saturated aqueous solution of ammonium chloride (2.5 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purifed by flash chromatography (70:30 PE/Et_2O) to give allylic alcohol **2.75** (111 mg, 66%) as a colourless oil and as a mixture of 8 diastereomers.

Due to the presence of 8 diastereomers and for purpose of clarity, only the major ones are described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.79 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, H^{20}), 5.71–5.63 (m, 1H, H^{16}), 5.00 (dq, *J* = 16.9, 1.9 Hz, 1H, H^{21}), 4.98–4.93 (m, 1H, H^{21}), 4.68 (s, 1H, H^{9}), 4.64 (s, 1H, H^{9}), 4.33–4.26 (m, 1H, H^{13}), 4.23 (d, *J* = 5.4 Hz, 1H, H^{2}), 4.19–4.12 (m, 2H, H^{23}), 3.98–3.89 (m, 1H, H^{5}), 3.62 (s, 1H, OH), 3.18–3.08 (m, 1H, H^{11}), 2.96–2.88 (m, 1H, H^{4}), 2.13–1.97 (m, 7H, H^{7}/ H^{15}/H^{17}/ H^{19}), 1.91–1.79 (m, 3H, H^{14}/H^{15}), 1.73 (s, 3H, H^{10}), 1.69–1.59 (m, 2H, H^{6}), 1.51–1.43 (m, 2H, H^{18}), 1.27–1.19 (m, 3H, H^{24}), 1.09 (d, *J* = 6.9 Hz, 3H, H^{22}), 0.90 (s, 9H, H^{27}), 0.09 (s, 3H, H^{25}), 0.08 (s, 3H, $H^{25'}$).

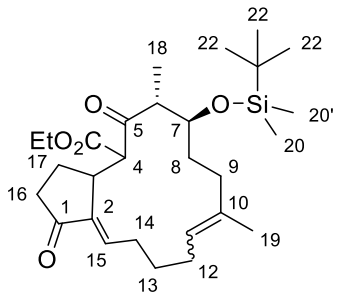
^{13}C NMR ($CDCl_3$, 126 MHz) δ 206.8 (C^{3}), 170.3 (C^{1}), 145.4 (C^{8} or C^{12}), 145.0 (C^{8} or C^{12}), 138.5 (C^{20}), 129.2 (C^{16}), 115.0 (C^{21}), 110.2 (C^{9}), 77.7 (C^{13}), 73.3 (C^{5}), 61.5 (C^{24}), 60.5 (C^{2}), 50.8 (C^{4}), 38.6 (C^{11}), 34.4 (C^{19}), 33.5 (C^{7}), 33.4 (C^{6}), 33.2 (C^{14}), 28.7 (C^{18}), 28.6 (C^{17}), 27.0 (C^{15}), 26.1 (C^{27}), 22.7 (C^{10}), 18.32 (C^{26}), 14.2 (C^{24}), 12.5 (C^{22}), −4.0 (C^{25}), −4.1 ($C^{25'}$).

IR (thin film) 2932, 2855, 1736, 1643, 833 cm^{-1}.

HRMS (ESI) for $C_{30}H_{52}NaO_5Si$: 543.3476, found: 543.3449.

Ethyl (6*R*,7*S*,15*E*)-7-((*tert*-butyldimethylsilyl)oxy)-6,10-dimethyl-1,5-dioxo-2,3,3a,4,5,6,7,8,9,12,13,14-dodecahydro-1H-cyclopenta[14]annulene-4-carboxylate (2.73).

$C_{28}H_{46}O_5Si$
Mol. Wt. = 490.76 g/mol



To a degassed solution of Hoveyda-Grubbs catalyst (7.0 mg, 11 µmol, 0.10 equiv) in toluene (1 mL) was added dropwise (over 3 h) a mixture of product **2.63** (59 mg, 0.11 mmol) in toluene (3 mL) at 110 °C. After addition, the solvent was concentrated under vacuum and the crude was purified by flash chromatography (95:5 PE/Et_2O) to give product **2.73** (15 mg, 28%) as a brown oil and as a mixture of 8 diastereomers (Ratio *E*/*Z* was 73/27).

Mixture of *E* diastereomers is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.65 (td, *J* = 9.0, 2.3 Hz, 1H, H^{15}), 5.38 (t, *J* = 7.4 Hz, 1H, H^{11}), 4.23 (ddd, *J* = 8.6, 4.3, 3.0 Hz, 1H, H^{7}), 4.12 (d, *J* = 3.9 Hz, 1H, H^{4}), 4.02 (q, *J* = 7.2 Hz, 2H, $OC\underline{H_2}CH_3$), 3.41–3.35 (m, 1H, H^{3}), 2.83 (qd, *J* = 6.6, 3.0 Hz, 1H, H^{6}), 2.73 (ddd, *J* = 19.1, 10.7, 8.0 Hz, 1H, H^{16}), 2.73–2.69 (m, 1H, H^{16}) 2.36 (ddt, *J* = 13.8, 10.7, 3.2 Hz, 1H, H^{17}), 2.31–2.23 (m, 2H, H^{9}/ H^{12}), 2.21–2.16 (m, 2H, H^{14}), 2.12 (ddd, *J* = 14.6, 10.5, 3.9 Hz, 1H, H^{9}), 2.06–1.95 (m, 1H, H^{12}), 1.91–1.82 (m, 2H, H^{8}/ H^{17}), 1.74–1.69 (m, 1H, H^{8}), 1.68 (s, 3H, H^{19}), 1.66–1.59 (m, 1H, H^{13}), 1.53–1.47 (m, 1H, H^{13}), 1.17 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H_3}$), 1.06 (d, *J* = 6.6 Hz, 3H, H^{18}), 0.84 (s, 9H, H^{22}), 0.07 (s, 3H, H^{20}), −0.01 (s, 3H, $H^{20'}$).

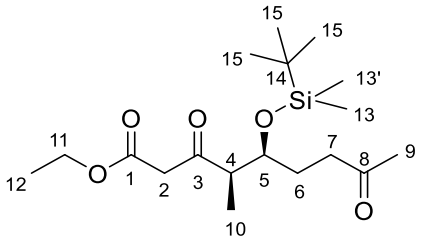
^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.2 (C^{5}), 205.4 (C^{1}), 167.9 ($\underline{C}$(O)OEt), 139.1 (C^{2}), 137.5 (C^{15}), 136.1 (C^{10}), 125.6 (C^{11}), 70.4 (C^{7}), 61.2 ($O\underline{C}H_2CH_3$), 59.4 (C^{4}), 49.1 (C^{6}), 37.2 (C^{3}), 36.9 (C^{16}), 35.4 (C^{9}), 31.7 (C^{8}), 28.9 (C^{13}), 28.0 (C^{14}), 26.7 (C^{12}), 25.9 (C^{22}), 19.9 (C^{17}), 18.2 (C^{21}), 15.5 (C^{19}), 14.2 ($OCH_2\underline{C}H_3$), 8.4 (C^{18}), −3.5 (C^{20}), −4.83 ($C^{20'}$).

IR (thin film) 2932, 2855, 1736, 1643, 1713, 833 cm^{-1}.

HRMS (ESI) for $C_{28}H_{46}NaO_5Si$: 513.3007, found: 513.2889.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3,8-dioxononanoate (2.28).

$C_{18}H_{34}O_5Si$
Mol. Wt. = 358.55 g/mol



Method 1:

A solution of **1.140** (0.353 g, 0.800 mmol) and freshly distilled triethylamine (0.16 mL, 1.2 mmol 1.5 equiv) in CH_2Cl_2 (2 mL) was cooled to −78 °C and stirred for 5 min. Triethylsilyl trifluoromethanesulfonate (0.23 mL, 1.0 mmol, 1.3 equiv) was added dropwise. The mixture was stirred at −78 °C for 1 h then at room temperature for 1 h. The reaction was quenched with a saturated solution of sodium bicarbonate then extracted with pentane (10 mL). The organic layer was dried over Na_2SO_4, concentrated under vacuum to give silyl enol ether **1.145** as a colourless oil that was used in the next step without further purification.

The crude mixture was then dissolved in a 1:1 mixture of THF/EtOH (5 mL) and potassium hydroxide (45 mg, 0.80 mmol, 1.0 equiv) was added. The reaction was stirred at RT for 2 h then was quenched by addition of a 1 M aqueous solution of hydrochloric acid (5 mL) and extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by column chromatography (70:30 PE/Et_2O) to furnish the product **2.28** as a colourless oil (115 mg, 40%).

Method 2:[55]

To a solution of compound **2.64** (1.78 g, 5.04 mmol) in a 5:1 mixture of dioxane/water (70 mL) were added 2,6-lutidine (1.18 mL, 10.1 mmol, 2.00 equiv), OsO_4 (2.5wt% in *tert*-butanol, 1.1 mL, 0.10 mmol, 0.020 equiv), and sodium periodate (4.31 g, 20.1 mmol, 4.00 equiv). The reaction was stirred at RT for 4 h. After the reaction was complete, water (80 mL) and CH_2Cl_2 (150 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with brine (250 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (70:30 PE/Et_2O) to afford ketone **2.38** (1.57 g, 87%) as a colourless oil.
(The aqueous layer was diluted and the glassware rinsed with a saturated solution of sodium sulfite to quench any traces of osmium tetroxide).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.17 (q, J = 7.2 Hz, 2H, H^{11}), 3.91 (td, *J* = 7.2, 4.7 Hz, 1H, H^5), 3.56 (s, 2H, H^2), 2.80 (qd, J = 7.0, 4.7 Hz, 1H, H^4), 2.55–2.38 (m, 2H, H^7), 2.12 (s, 3H, H^9), 1.84–1.72 (m, 1H, H^6), 1.62–1.50 (m, 1H, H^6), 1.26 (t, J = 7.2 Hz, 3H, H^{12}), 1.09 (d, J = 7.0 Hz, 3H, H^{10}), 0.89 (s, 9H, H^{15}), 0.07 (s, 3H, H^{13}), 0.06 (s, 3H, $H^{13'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 208.2 (C^3 or C^8), 205.2 (C^3 or C^8), 167.5 (C^1), 72.7 (C^5), 61.3 (C^{11}), 51.9 (C^4), 49.6 (C^2), 39.3 (C^7), 30.0 (C^9), 27.9 (C^6), 26.0 (C^{15}), 18.1 (C^{14}), 14.2 (C^{12}), 12.3 (C^{10}), −4.3 (C^{13}), −4.5 ($C^{13'}$).

$[\alpha]_D^{25}$ −44.0 (*c* = 1.0, $CHCl_3$).

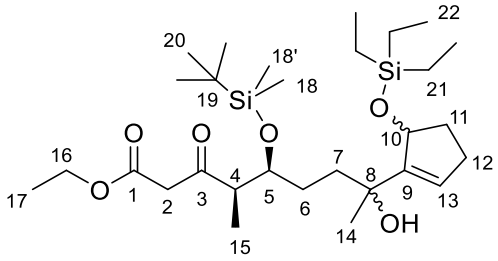
IR (thin film) 2932, 1744, 1713, 1636 cm^{-1}.

HRMS (ESI) for $C_{18}H_{34}NaO_5Si$: 381.2068, found: 381.2051.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-4-methyl-3-oxo-8-(5'-((triethylsilyl)oxy)cyclopent-1'-en-1'-yl)nonanoate (2.76).

$C_{29}H_{56}O_6Si_2$

Mol. Wt. = 556.93 g/mol



Alcohol **2.76** (colourless oil) was obtained from the corresponding ketoester **2.28** and bromo compound **2.77** according to the procedure described above for alcohol **2.78**.
Purification by flash column chromatography (90:10 PE/EtOAc)
Scale: 1.39 mmol
Yield: 62% as an inseparable mixture of 4 diastereomers.

Mixture of diastereomers is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71–5.67 (m, 0.4H, H^{13a}/ H^{13b}), 5.63–5.58 (m, 0.6H, H^{13c}/ H^{13d}), 5.12–5.03 (m, 0.6H, H^{10c}/ H^{10d}), 5.03–4.99 (m, 0.4H, H^{10a}/ H^{10b}), 4.23–4.14 (m, 2H, H^{16}), 4.00–3.85 (m, 1H, H^5), 3.63–3.52 (m, 2H, H^2), 2.86–2.80 (m, 0.6H, H^{4c}/ H^{4d}), 2.79–2.73 (m, 0.4H, H^{4a}/ H^{4b}), 2.46–2.34 (m, 1H, H^{12}), 2.32–2.22 (m, 1H, H^{11}), 2.23–2.12 (m, 1H, H^{12}), 1.83–1.69 (m, 2H, H^7/H^{11}), 1.68–1.57 (m, 2H, H^6/H^7), 1.54–1.40 (m, 1H, H^6), 1.37–1.24 (m, 6H, H^{14}/H^{17}), 1.14–1.04 (m, 3H, H^{15}), 1.04–0.94 (m, 9H, H^{22}), 0.95–0.82 (m, 9H, H^{20}), 0.71–0.63 (m, 6H, H^{21}), 0.12–0.03 (m, 6H, H^{18}/ $H^{18'}$).

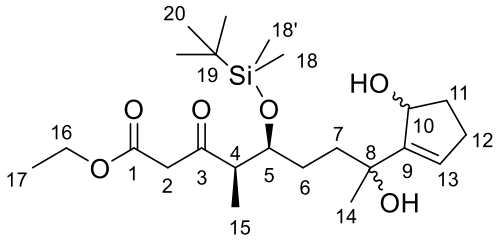
^{13}C NMR ($CDCl_3$, 101 MHz) δ [205.5, 205.4, 205.3, 205.4] (C^3), [173.0, 169.9, 167.7, 167.6] (C^1), [149.3, 149.2, 148.4, 148.2] (C^9), [128.1, 128.0, 126.5, 126.4] (C^{13}), [79.6, 79.5, 79.3, 79.3] (C^{10}), [74.4, 74.4, 74.3, 74.2] (C^5), [72.9, 72.7, 72.5, 72.3] (C^8), [61.3, 61.3, 61.1, 61.0] (C^{16}), [51.9, 51.8, 51.7, 51.6] (C^4), [49.5, 49.3, 49.3, 49.0] (C^2), [38.3, 38.0, 37.7, 37.7] (C^6), [34.8, 34.8, 34.7, 34.6] (C^{11}), 29.5 (C^7), [29.2, 29.2, 29.2] (C^{12}) 28.6 (C^{14}), [26.1, 26.1, 26.0, 26.0] (C^{20}), [18.3, 18.2, 18.2] (C^{19}), 14.2 (C^{17}), [11.4, 11.3] (C^{15}), 7.0 (C^{22}), [5.2, 5.2] (C^{21}), [−4.0, −4.1, −4.1, −4.1, −4.3, −4.4, −4.5] (C^{18}/ $C^{18'}$).

IR (thin film) 3495, 2955, 1744, 1713, 1628 cm^{-1}.

HRMS (ESI) for $C_{29}H_{56}NaO_6Si_2$: 579.3508, found: 579.3485.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-8-(5'-hydroxycyclopent-1'-en-1'-yl)-4-methyl-3-oxononanoate (2.83).

$C_{23}H_{42}O_6Si$
Mol. Wt. = 442.67 g/mol



Diol product **2.83** (colourless oil) was obtained from the corresponding alcohol **2.76** according to the procedure described above for the diol in the procedure for **2.79**.
Purification by flash column chromatography (60:40 PE/EtOAc)
Scale: 0.69 mmol
Yield: 90% as an inseparable mixture of 4 diastereomers.

Mixture of diastereomers is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71–5.59 (m, 1H, H^{13}), 5.00–4.90 (m, 1H, H^{10}), 4.18 (q, *J* = 7.2 Hz, 2H, H^{16}), 3.95–3.84 (m, 1H, H^5), 3.64–3.51 (m, 2H, H^2), 2.87–2.78 (m, 1H, H^4), 2.52–2.43 (m, 1H, H^{12}), 2.30–2.22 (m, 1H, H^{11}), 2.22–2.18 (m, 1H, H^{12}), 1.83–1.73 (m, 2H, H^6/H^{11}), 1.65–1.54 (m, 2H, H^6/H^7), 1.52–1.39 (m, 1H, H^7), 1.33 (s, 3H, H^{14}), 1.26 (t, *J* = 7.2 Hz, 3H, H^{17}), 1.08 (d, J = 7.1 Hz, 3H, H^{15}), 0.89 (s, 9H, H^{19}), 0.08 (s, 3H, H^{18}), 0.07 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ [205.7, 205.6, 205.6] (C^3), [167.8, 167.8, 167.7, 167.7] (C^1), [150.0, 149.9, 149.1, 148.9] (C^9), [129.1, 129.0, 127.8, 127.7] (C^{13}), [77.9, 77.9, 77.7, 77.7] (C^{10}), [74.1, 74.0, 73.9, 73.7] (C^8), [73.6, 73.5, 73.4, 73.4] (C^5), [61.4, 61.4] (C^{16}), [52.0, 51.8, 51.8, 51.7] (C^4), [49.5, 49.4, 49.4] (C^2), [37.8, 37.7, 37.6, 37.5] (C^6), [33.9, 33.8, 33.8, 33.7] (C^{11}), [29.9, 29.9, 29.8, 29.7] (C^{12}), [29.4, 29.3, 28.8, 28.7] (C^{14}), 28.4 (C^7), [26.0, 26.0] (C^{20}), [18.3, 18.2, 18.2, 18.2] (C^{19}), 14.3 (C^{17}), [12.5, 12.3, 12.3, 12.2] (C^{15}), [−4.1, −4.1, −4.2, −4.4, −4.4, −4.4] (C^{18}/ $C^{18'}$).

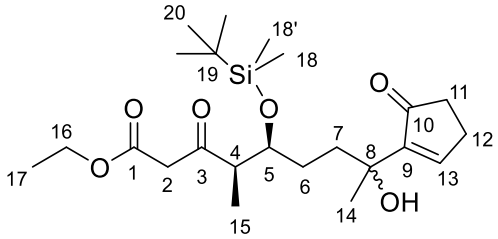
IR (thin film) 3449, 2932, 2855, 1744, 1366, 1227, 1034 cm^{-1}.

HRMS (ESI) for $C_{23}H_{42}NaO_6Si$: 465.2643, found: 465.2622.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-4-methyl-3-oxo-8-(5'-oxocyclopent-1'-en-1'-yl)nonanoate (2.84).

$C_{23}H_{40}O_6Si$

Mol. Wt. = 440.65 g/mol



To a solution of diol **2.83** (20 mg, 0.045 mmol) in CH_2Cl_2 (1 mL) was added activated manganese(II) oxide (80 mg, 0.90 mmol, 20 equiv) and the reaction was stirred at RT for 3 h. The mixture was filtered through a short pad of celite to furnish product **2.84** (17 mg, 89%) as a thick colourless oil and as an inseparable 1:1 mixture of 2 diastereomers.

Mixture of diastereomers is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (q, J = 2.7 Hz, 1H, H^{13}), 4.19 (q, J = 7.1 Hz, 2H, H^{16}), 3.91–3.84 (m, 1H, H^5), 3.56 (s, 1H, H^{2a}), 3.55 (s, 1H, H^{2b}), 2.86–2.76 (m, 1H, H^4), 2.62–2.55 (m, 2H, H^{12}), 2.48–2.43 (m, 2H, H^{11}), 1.88–1.76 (m, 1H, H^7), 1.75–1.69 (m, 1H, H^7), 1.51–1.45 (m, 1H, H^6), 1.44 (s, 3H, H^{14a}), 1.44 (s, 3H, H^{14b}), 1.34–1.30 (m, 1H, H^6), 1.27 (t, J = 7.1 Hz, 3H, H^{17}), 1.06 (d, J = 7.1 Hz, 1.5H, H^{15a}), 1.05 (d, J = 7.1 Hz, 1.5H, H^{15b}), 0.89 (s, 5H, H^{20a}), 0.88 (s, 4H, H^{20b}) 0.06 (s, 3H, H^{18}), 0.06 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 210.5 (C^{3a} or C^{10a}), 210.5 (C^{3b} or C^{10b}), 210.4 (C^{3b} or C^{10b}), 205.6 (C^{3b} or C^{10b}), 167.6 (C^{1a}), 167.6 (C^{1b}), 157.8 (C^{13a}), 157.8 (C^{13b}) 149.9 (C^{9a}), 149.8 (C^{9b}), 73.8 (C^{5a}), 73.8 (C^{5b}), 72.2 (C^{8a}), 72.2 (C^{8b}), 61.3 (C^{16}), 51.7 (C^{4a}), 51.7 (C^{4b}) 49.5 (C^2), 37.0 (C^6), 35.6 (C^{11}), 30.5 (C^{14a}), 28.9 (C^7), 27.0 (C^{14b}), 26.2 (C^{12}), 26.0 (C^{20}), 18.2 (C^{19}), 14.3 (C^{17}), 12.1 (C^{15a}), 12.1 (C^{15b}), −4.2 (C^{18}),−4.4 ($C^{18'}$).

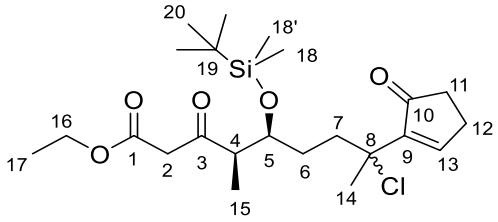
IR (thin film) 2931, 1743, 1690, 1265 cm^{-1}.

HRMS (ESI) for $C_{23}H_{40}NaO_6Si$: 463.2486, found: 463.2465.

Ethyl (4*R*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-8-chloro-4-methyl-3-oxo-8-(5'-oxocyclopent-1'-en-1'-yl)nonanoate (2.85).

$C_{23}H_{39}ClO_5Si$

Mol. Wt. = 459.09 g/mol



N-Chlorosuccinimide (54 mg, 0.40 mmol, 3.0 equiv) was dissolved in CH_2Cl_2 (1 mL) at 0 °C and dimethyl sulfide (31 µL, 0.43 mmol, 3.2 equiv) was added dropwise. The white suspension was stirred at 0 °C for an additional 15 min before dropwise addition of compound **2.84** (59 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL). The reaction was left to stir at 0 °C for 2 h then was quenched by addition of brine (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with brine (3 × 15 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by column chromatography (40:60:1 PE/Et_2O/Et_3N) to afford chloro product **2.85** (54 mg, 89%) as a yellow oil and as an inseparable 1:1 mixture of 2 diastereomers.

Mixture of diastereomers is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (t, *J* = 2.5 Hz, 1H, H^{13}), 4.18 (q, *J* = 7.1 Hz, 1H, H^{16a}), 4.17 (q, *J* = 7.1 Hz, 1H, H^{16b}), 3.92–3.85 (m, 1H, H^5) 3.59–3.52 (m, 2H, H^2), 2.82–2.73 (m, 1H, H^4), 2.62–2.54 (m, 2H, H^{12}), 2.53–2.46 (m, 2H, H^{11}), 2.37–2.11 (m, 1H, H^{7a}/ H^{7b}), 2.10–1.87 (m, 1H, H^{7a}/ H^{7b}), 1.79 (s, 1.5H, H^{14a}), 1.78 (s, 1.5H, H^{14b}), 1.51–1.31 (m, 2H, H^6), 1.29–1.24 (m, 3H, H^{17}), 1.07 (d, *J* = 7.1 Hz, 1.5H, H^{15a}), 1.03 (d, *J* = 7.0 Hz, 1.5H, H^{15b}), 0.89 (s, 9H, H^{20}), 0.08–0.03 (m, 6H, H^{18}/$H^{18'}$).

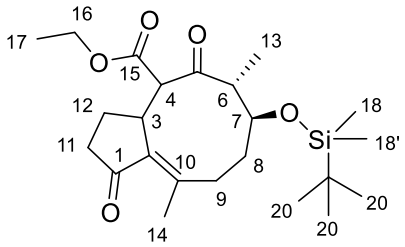
^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.7 (C^{3a} or C^{10a}), 205.6 (C^{3a} or C^{10a}), 205.4 (C^{3b} or C^{10b}), 205.3 (C^{3b} or C^{10b}), 167.6 (C^{1a}), 167.5 (C^{1b}) 161.8 (C^{13a}), 161.6 (C^{13b}), 148.5 (C^{9a}), 148.4 (C^{9b}), 73.4 (C^{5a}), 73.1 (C^{5b}), 71.2 (C^{8a}), 70.9 (C^{8b}), 61.3 (C^{16a}), 61.3 (C^{16b}), 51.6 (C^{4a}), 51.4 (C^{4b}), 49.5 (C^{2a}), 49.5 (C^{2b}), 38.0 (C^{6a}), 37.5 (C^{6b}), 36.7 (C^{11}), 30.8 (C^{14a}), 30.5 (C^{14b}), 30.0 (C^{7a}), 30.0 (C^{7b}) 26.0 (C^{20a}), 26.0 (C^{20b}) 25.7 (C^{12}), 18.2 (C^{19}), 14.3 (C^{17}), 12.2 (C^{15a}), 11.8 (C^{15b}), −4.2 (C^{18a}), −4.2 (C^{18b}), −4.5 ($C^{18a'}$), −4.5 ($C^{18b'}$).

IR (thin film) 1713, 1705, 910, 734 cm^{-1}.

HRMS (ESI) for $C_{23}H_{39}NaO_5Si35Cl$: 481.2147, found: 481.2126.

Ethyl (6*R*,7*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-6,10-dimethyl-1,5-dioxo-1,2,3,3a,4,5,6,7,8,9-decahydrocyclopenta[9]annulene-4-carboxylate (1.138).

$C_{23}H_{38}O_5Si$
Mol. Wt. = 422.64 g/mol



Chloro compound **2.85** (9.5 mg, 0.021 mmol) was dissolved in dry DMF (5 mL) and caesium carbonate (7.0 mg, 0.021 mmol, 1.0 equiv) was added in one portion to the mixture. The reaction was left to stir at RT for 2 h then was diluted with Et_2O (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic phases were combined, washed with a saturated aqueous solution of lithium chloride (2 × 15 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (80:20 PE/Et_2O) to afford the nine-membered ring **1.138** (5.6 mg, 64%) as a thick yellow oil and as an inseparable mixture of diastereomers.

Mixture of diastereomers is described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.30–4.12 (m, 2.4H, H^{7a}/H^{7b}/H^{16}), 4.03–3.94 (m, 0.4H, H^{3a}/H^{3b}), 3.78–3.72 (m, 0.6H, H^{7c}/H^{7d}), 3.73 (d, J = 11.8 Hz, 0.4H, H^{4a}/H^{4b}) 3.65–3.56 (m, 0.6H, H^{3c}/H^{3d}), 3.40 (br d, *J* = 11.3 Hz, 0.6H, H^{4c}/H^{4d}), 3.22–3.12 (m, 0.4H, H^{6a}/H^{6b}) 2.73–2.68 (m, 0.6H, H^{6c}/H^{6d}), 2.38–2.29 (m, 2H, H^{11}), 2.27 (s, 1.2H, H^{14a}/ H^{14b}), 2.18 (s, 1.8H, H^{14c}/ H^{14d}), 2.11–1.97 (m, 3H, H^8/H^{12}), 1.96–1.86 (m, 1H, H^9), 1.78–1.70 (m, 1H, H^8), 1.70–1.61 (m, 1H, H^9), 1.32–1.24 (m, 3H, H^{13}), 1.11 (d, *J* = 6.8 Hz, 1.8H, H^{13c}/H^{13d}), 1.05 (d, *J* = 7.1 Hz, 1.2H, H^{13a}/H^{13b}), 0.91–0.85 (m, 9H, H^{20}), 0.08–0.03 (m, 6H, H^{18}/$H^{18'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ [211.4, 211.1, 209.1] (C^1 or C^5), [206.4, 206.3, 206.1] (C^1 or C^5), [169.4, 168.7, 168.5] (C^{15}), [156.3, 155.0, 152.4] (C^{10}), 132.3 (C^2), [77.4, 73.3, 73.0]

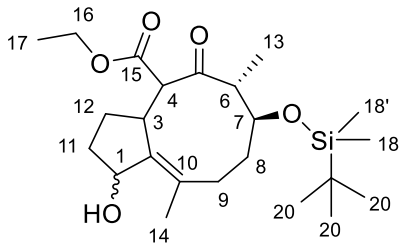
(C^7), [61.9, 61.8] (C^{16}), 61.2 (C^4), 52.8 (C^6), [43.0, 42.2] (C^3), [37.2, 37.2, 37.2] (C^{11}), 34.2 (C^9), [34.0, 33.5] (C^{12}), [26.0, 25.9, 25.9, 25.8] (C^{20}), 25.4 (C^8), [19.7, 19.3] (C^{14}), [18.2, 18.1] (C^{19}), 15.2 (C^{13}), [14.3, 14.2] (C^{17}), [−4.2, −4.2] (C^{18}), [−4.5, −4.7] ($C^{18'}$).

IR (thin film) 2955, 2932, 2862, 1736, 1720, 1705, 1620, 1250, 1173, 1057, 1018 cm^{-1}

HRMS (ESI) for $C_{23}H_{38}NaO_5Si$: 445.2381, found: 445.2361.

Ethyl (6*R*,7*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-6,10-dimethyl-5-oxo-1,2,3,3a,4,5,6,7,8,9-decahydrocyclopenta[9]annulene-4-carboxylate (2.87).

$C_{23}H_{40}O_5Si$
Mol. Wt. = 424.65 g/mol



Cyclononane **1.138** (284 mg, 0.672 mmol) and cerium(III) chloride heptahydrate (661 mg, 1.77 mmol, 2.60 equiv) were dissolved in methanol (15 mL), cooled to −78 °C and stirred for 1 h. Sodium borohydride (27 mg, 0.71 mmol, 1.0 equiv) was then added in small portions. The reaction was left to stir at −78 °C for 2 h. The crude mixture was quenched with a 1 M aqueous solution of hydrochloric acid (15 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purifed by flash chromatography (60:40 PE/Et_2O) to give allylic alcohol **2.87** (150 mg, 53%) as a thick colourless oil and as an inseparable mixture of 4 diastereomers.

A mixture of diastereomers are described below:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.76–4.67 (m, 1H, H^1), 4.23–4.13 (m, 2.6H, H^{7a}/H^{7b}/H^{16}), 3.71 –3.65 (m, 0.4H, H^{7b}/H^{7c}) 3.60 (d, *J* = 11.7 Hz, 1H, H^4), 3.42–3.34 (m, 1H, H^3), 2.76 (dq, *J* = 9.3, 7.1 Hz, 1H, H^6), 2.19–2.08 (m, 2H, H^{12}), 2.08–1.98 (m, 2H, H^8), 1.92–1.84 (m, 2H, H^{11}), 1.82 (s, 3H, H^{14}), 1.81–1.72 (m, 2H, H^9), 1.28 (t, *J* = 7.1 Hz, 3H, H^{17}), 1.10 (d, J = 6.8 Hz,

1.8H, H^{13a}/H^{13b}), 1.06 (d, *J* = 7.1 Hz, 1.2H, H^{13c}/H^{13d}), 0.89 (s, 9H, H^{20}), 0.10–0.04 (m, 6H, $H^{18}/H^{18'}$).

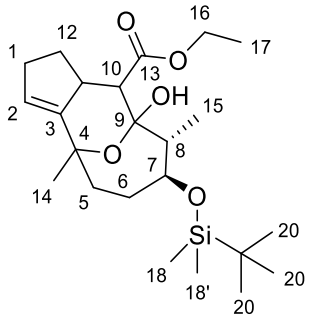
^{13}C NMR ($CDCl_3$, 126 MHz) δ [211.9, 209.5] (C^5), [168.9, 168.7] (C^{15}), [139.8, 139.6] (C^2 or C^{10}), 139.5 (C^2 or C^{10}), [73.3, 72.8] (C^7), 72.1 (C^1), 61.6 (C^{16}), [61.2, 61.1] (C^4), 53.2 (C^6), [43.3, 43.1] (C^3), [34.6, 34.2, 34.0, 33.8] (C^9), [31.1, 30.5, 30.4] (C^{11}), [29.9, 29.8] (C^{12}), 36.0, 25.9 (C^{20}), 19.3 (C^{14}), 19.1 (C^8), [18.2, 18.2] (C^{19}), 15.2 (C^{13}), 14.3 (C^{17}), −4.1 (C^{18}), −4.4 ($C^{18'}$).

IR (thin film) 3510, 2955, 2932, 2862, 1744, 1706, 1250, 1165, 1080, 1026 cm^{-1}

HRMS (ESI) for $C_{23}H_{40}NaO_5Si$: 447.2537, found: 447.2516.

Ethyl (7*S*,8*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-4,8-dimethyl-1,2,4,5,6,7,8,9,10,10a-decahydro-4,9-epoxycyclopenta[9]annulene-10-carboxylate (2.90).

$C_{23}H_{40}O_5Si$
Mol. Wt. = 424.65 g/mol



To a solution of *bis*(acetonitrile)dichloropalladium(II) (5.5 mg, 0.021 mmol, 0.30 equiv) in THF (0.7 mL) was added dropwise a mixture of allylic alcohol **2.87** (27 mg, 0.071 mmol) in THF (0.7 mL). The reaction was stirred at RT for 2 h then was filtered through a short pad of celite. The crude was then purified by flash chromatography (80:20 PE/Et_2O) to afford tricycle **2.90** (11 mg, 41%) as a colourless oil and as a separable 1:1 mixture of 2 diastereomers.

<u>Diastereomer 1</u>:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.36–5.32 (m, 1H, H^{2}), 4.23–4.16 (m, 2H, H^{16}), 3.82 (ddd, *J* = 6.5, 4.7, 1.7 Hz, 1H, H^{7}), 3.29 (d, *J* = 10.3 Hz, 1H, H^{10}), 3.22–3.13 (m, 1H, H^{11}), 2.36–2.30 (m, 2H, H^{1}), 2.30–2.23 (m, 1H, H^{8}), 2.06 (ddd, *J* = 14.4, 9.3, 1.7 Hz, 1H, H^{6}), 1.93–1.83 (m, 1H, H^{6}), 1.66–1.55 (m, 2H, H^{5}), 1.38 (td, *J* = 9.5, 2.4 Hz, 1H, H^{12}), 1.34 (s, 3H, H^{14}), 1.28 (t, *J* = 7.1 Hz, 3H, H^{17}), 1.26–1.23 (m, 1H, H^{12}), 1.01 (d, *J* = 7.1 Hz, 3H, H^{15}), 0.89 (s, 9H, H^{20}), 0.07 (s, 3H, H^{18}), 0.05 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.4 (C^{13}), 150.3 (C^{3}), 119.8 (C^{2}), 98.6 (C^{9}), 74.9 (C^{4}), 72.5 (C^{7}), 60.8 (C^{16}), 54.4 (C^{10}), 48.3 (C^{8}), 42.8 (C^{11}), 36.5 (C^{5}), 32.7 (C^{1}), 31.8 (C^{6}), 29.7 (C^{12}), 29.0 (C^{14}), 26.1 (C^{20}), 18.3 (C^{19}), 14.4 (C^{17}), 13.2 (C^{15}), −4.7 (C^{18}), −4.8 ($C^{18'}$).

$[\alpha]_D^{25}$ +16.7 (*c* = 1.0, $CHCl_3$).

Diastereomer 2:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.34–5.32 (m, 1H, H^{2}), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H, H^{16}), 4.19 (dq, *J* = 10.8, 7.2 Hz, 1H, H^{16}) 3.29 (td, *J* = 9.8, 2.8 Hz, 1H, H^{7}), 3.20–3.11 (m, 1H, H^{11}), 2.54 (d, *J* = 12.6 Hz, 1H, H^{10}), 2.40–2.32 (m, 1H, H^{1}), 2.32–2.25 (m, 1H, H^{1}), 2.04–1.92 (m, 3H, H^{5}/H^{8}), 1.92–1.84 (m, 1H, H^{6}), 1.64 (dddd, *J* = 13.8, 7.8, 3.0, 1.3 Hz, 1H, H^{6}), 1.52–1.44 (m, 2H, H^{6}/H^{12}), 1.36 (s, 3H, H^{14}), 1.30 (t, *J* = 7.1 Hz, 3H, H^{17}), 1.27–1.20 (m, 1H, H^{12}), 0.96 (d, *J* = 7.0 Hz, 3H, H^{15}), 0.88 (s, 9H, H^{20}), 0.06 (s, 3H, H^{18}), 0.05 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.5 (C^{13}), 152.4 (C^{3}), 119.2 (C^{2}), 98.5 (C^{9}), 77.7 (C^{7}), 74.3 (C^{4}), 61.5 (C^{16}), 54.3 (C^{8}), 50.8 (C^{10}), 44.9 (C^{11}), 40.6 (C^{5}), 32.9 (C^{6}), 31.5 (C^{1}), 29.6 (C^{12}), 28.4 (C^{14}), 26.0 (C^{20}), 18.2 (C^{19}), 14.7 (C^{15}), 14.3 (C^{17}), −3.8 (C^{18}), −4.3 ($C^{18'}$).

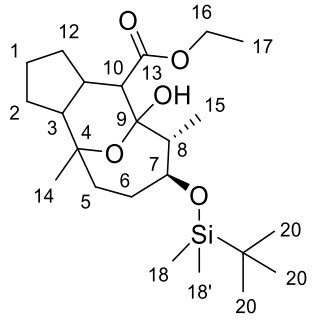
$[\alpha]_D^{25}$ −8.0 (*c* = 1.0, $CHCl_3$).

IR (thin film) 2924, 2855, 1728, 1458, 1259, 1065, 1026, 841 cm^{-1}.

HRMS (ESI) for $C_{23}H_{40}NaO_5Si$: 447.2537, found: 447.2518.

Ethyl (7*S*,8*R*)-7-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-4,8-dimethyldodecahydro-4,9-epoxycyclopenta[9]annulene-10-carboxylate (2.92).

$C_{23}H_{42}O_5Si$
Mol. Wt. = 426.67 g/mol



To a solution of tricycle **2.90** (5 mg, 0.012 mmol) in ethanol (3 mL) under inert atmosphere was added palladium on carbon. Inert atmosphere was purged, replaced with hydrogen and the reaction was stirred at RT for 2 h. The mixture was filtered through a short pad of celite to furnish a separable 4:1 mixture of diastereomers. The crude was then purified by flash chromatography (80:20 PE/Et_2O) to afford saturated tricycle **2.92** (4 mg, 80%) as a white foam and a single diastereomer.

Diastereomer 1:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.22–4.14 (m, 2H, H^{16}), 3.79–3.71 (m, 2H, H^7/H^{10}), 3.41 (s, 1H, OH), 2.55 (tt, *J* = 12.4, 8.0 Hz, 1H, H^{11}), 2.38–2.31 (m, 1H, H^8), 2.32–2.25 (m, 1H, H^3), 2.08–1.98 (m, 2H, H^5/H^{12}), 1.91 (t, *J* = 13.8 Hz, 1H, H^6), 1.79–1.67 (m, 2H, H^2/H^{12}), 1.51 (dd, *J* = 13.8, 6.5 Hz, 1H, H^6), 1.46–1.37 (m, 4H, H^2/H^{14}), 1.35–1.28 (m, 1H, H^1), 1.28–1.24 (m, 3H, H^{17}) 1.24–1.21 (m, 1H, H^5), 1.15–1.05 (m, 1H, H^1), 1.02 (d, *J* = 7.2 Hz, 3H, H^{15}), 0.91 (s, 9H, H^{20}), 0.08 (s, 3H, H^{18}), 0.05 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 174.4 (C^{13}), 97.3 (C^9), 74.2 (C^4), 73.8 (C^7), 60.8 (C^{16}), 50.9 (C^{10}), 47.5 (C^8), 35.1 (C^{11}), 34.4 (C^5), 30.5 (C^{14}), 29.9 (C^1), 29.5 (C^2), 28.9 (C^{12}), 26.1 (C^{20}), 25.8 (C^6), 21.3 (C^3), 18.2 (C^{19}), 14.4 (C^{17}), 12.9 (C^{15}), −4.7 (C^{18}), −5.1 ($C^{18'}$).

$[\alpha]_D^{25}$ −6.0 (*c* = 1.0, $CHCl_3$).

Tricycle **2.92'** was obtained from the corresponding tricycle **2.90'** according to the procedure described above for diastereomer **2.92**.
Scale: 0.012 mmol
Yield: 98% as a 4:1 mixture of 2 diastereomers and some impurities.

Diastereomer 2:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.24–4.16 (m, 2H, H^{16}), 3.36 (ddd, *J* = 10.8, 9.3, 3.2 Hz, 1H, H^{7}), 2.57 (d, *J* = 12.8 Hz, 1H, H^{10}), 2.49–2.39 (m, 1H, H^{11}), 2.33 (td, *J* = 10.7, 7.7 Hz, 1H, H^{3}), 1.99–1.88 (m, 3H, H^{6}/H^{8}/H^{12}), 1.88–1.82 (m, 1H, H^{1}), 1.77–1.65 (m, 2H, H^{2}/H^{6}), 1.51 (dd, *J* = 7.7, 3.5 Hz, 1H, H^{5}), 1.43 (s, 3H, H^{14}), 1.30 (t, *J* = 7.1 Hz, 3H, H^{16}), 1.28–1.19 (m, 4H, H^{1}/H^{2}/ H^{5}/H^{12}), 0.92 (d, *J* = 7.0 Hz, 3H, H^{15}), 0.89 (s, 9H, H^{20}), 0.08 (s, 3H, H^{18}), 0.06 (s, 3H, $H^{18'}$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 175.9 (C^{13}), 97.2 (C^{9}), 77.3 (C^{4}), 74.3 (C^{7}), 61.3 (C^{16}), 54.3 (C^{8}), 48.2 (C^{10}), 47.5 (C^{11}), 37.5 (C^{3}), 33.5 (C^{5}), 32.7 (C^{12}), 32.5 (C^{6}), 30.6 (C^{14}), 29.7 (C^{1}), 28.1 (C^{2}), 25.9 (C^{20}), 18.1 (C^{19}), 14.4 (C^{17}), 14.2 (C^{15}), −3.8 (C^{18}), −4.5 ($C^{18'}$).

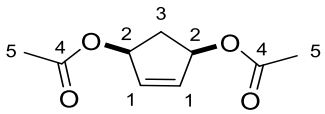
$[\alpha]_D^{25}$ +18.0 (*c* = 1.0, $CHCl_3$).

IR (thin film) 2924, 2855, 1728, 1458, 1250, 1049, 1026, 841, 772 cm^{-1}.

HRMS (ESI) for $C_{23}H_{42}NaO_5Si$: 449.2694, found: 449.2676.

cis-3,5-Diacetoxy-1-cyclopentene (2.103).[105]

$C_9H_{12}O_4$
Mol. Wt. = 184.19 g/mol



In a 1 L photochemistry apparatus, a solution of freshly distilled cyclopentadiene (6.4 mL, 75 mmol), rose Bengal (151 mg, 0.154 mmol, 0.002 equiv) and thiourea (5.7 g, 75 mmol, 1.0 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 were stopped and the reaction was stirred in the dark overnight. The solvent was then evaporated and the crude product **2.102** (3.63 g) was used in the next step without further purification.

Acetic anhydride (13.7 mL, 145 mmol, 4.00 equiv) was slowly added to a stirred solution of **2.102** (3.63 g, 36.0 mmol), pyridine (30.0 mL, 370 mmol, 10.0 equiv) and DMAP (440 mg, 3.60 mmol, 0.100 equiv) in CH_2Cl_2 (250 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 3 h, after which the reaction was quenched by slow addition of a saturated aqueous solution of sodium bicarbonate (50 mL). The layers were separated and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate (2 × 150 mL), a saturated aqueous solution of copper sulfate (3 × 150 mL), brine (150 mL) and water (150 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was then purified by column chromatography (90:10 PE/EtOAc) to furnish the product **2.103** (3.74 g, 27% yield over 2 steps) as a colourless oil.

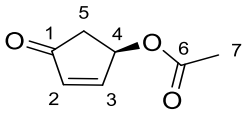
^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (d, *J* = 0.8 Hz, 2H, H^1), 5.59 (m, 2H, H^2), 2.91 (dt, *J* = 15.0, 7.5 Hz, 1H, H^3), 2.09 (s, 6H, H^5), 1.77 (dt, *J* = 15.0, 3.9 Hz, 1H, H^3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6 (C^4), 134.6 (C^1), 76.6 (C^2), 37.2 (C^3), 21.1 (C^5).

In agreement with literature data.[35]

(*R*)-4-Oxocyclopent-2-en-1-yl acetate (2.101).[106]

$C_7H_8O_3$
Mol. Wt. = 140.14 g/mol



Diacetate **2.103** (3.76 g, 20.4 mmol) was added to a slowly stirred (180 rpm) solution of electric eel acetylcholinesterase (3.5 mg, 2000 units) and sodium azide (15 mg) in an aqueous phosphate buffer (150 mL) at RT. The buffer was prepared by dissolving anhydrous sodium hydrogen phosphate (16.4 g) in water (200 mL), adjusting the pH to 6.85 by careful addition of a 2 M aqueous solution of hydrochloric acid. The reaction was stirred at RT overnight; after which it was extracted with EtOAc (6 x 50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under vacuum to give the product **2.104** (2.44 g) as a white solid that was used in the next step without further purification.

To a solution of **2.104** (2.4 g, 17 mmol) in CH_2Cl_2 (75 mL) was added BAIB (6.57 g, 20.4 mmol, 1.20 equiv) and TEMPO (266 mg, 1.70 mmol, 0.100 equiv). The mixture was then stirred at RT for 3 h. The reaction was then diluted by water (75 mL) and the two layers separated. The aqueous layer was extracted by CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude mixture was purified by column chromatography (80:20 PE/EtOAc) to yield **2.101** as a colourless oil (1.93 g, 81% yield over 2 steps).

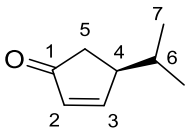
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (dd, *J* = 5.7, 2.4 Hz, 1H, H^3), 6.36 (dd, *J* = 5.7, 1.2 Hz, 1H, H^2), 5.87 (dtd, *J* = 6.3, 2.4, 1.2 Hz, 1H, H^4), 2.85 (dd, *J* = 18.7, 6.3 Hz, 1H, H^5), 2.35 (dd, *J* = 18.7, 2.4 Hz, 1H, H^5), 2.11 (s, 3H, H^7).

^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.0 (C^1), 170.5 (C^6), 159.1 (C^3), 137.1 (C^2), 72.0 (C^4), 41.1 (C^5), 21.0 (C^7).

In agreement with literature data.[35]

(*S*)-4-Isopropylcyclopent-2-en-1-one (2.100).[82]

$C_8H_{12}O$
Mol. Wt. = 124.18 g/mol



A solution of isopropylmagnesium bromide was prepared from freshly distilled isopropyl bromide (4.0 mL, 42 mmol) and magnesium (2.05 g, 84.0 mmol, 2.00 equiv) in THF (42 mL). A 0.65 M solution of the Grignard reagent in THF (8.0 mL, 5.0 mmol, 1.4 equiv) was diluted with additional THF (30 mL) and then cooled to −78 °C. HMPA (1.74 mL, 9.99 mmol, 2.80 equiv) and recrystallized copper(I) bromide dimethyl sulfide complex (73 mg, 0.36 mmol, 0.10 equiv) were added consecutively. A solution of (*R*)-4-acetoxy-2-cyclopenten-1-one **2.101** (500 mg, 3.57 mmol) and TMSCl (1.26 mL, 9.99 mmol, 2.80 equiv) in THF (30 mL) was added dropwise (over 20 min). The mixture was stirred at −78 °C for 1 h and then at −40 °C for 1 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (60 mL). The solution was allowed to warm to RT, filtered through a short pad of celite, diluted with water (30 mL), and extracted with Et_2O (3 x 100 mL). The

combined organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum (28 °C, 180 mbar) to furnish intermediate **2.105** that was used in the next step without further purification.

To a solution of this material in CH_2Cl_2 (30 mL) was added CSA (500 mg) and water (0.5 mL). The mixture was heated at reflux overnight, allowed to cool to RT, diluted with additional CH_2Cl_2 (30 mL), washed with water (2 x 60 mL) and brine (60 mL). The organic layer was dried, filtered, and again carefully concentrated under vacuum (28 °C, 180 mbar). The product was purified by column chromatography (80:20 PE/EtOAc) to furnish **2.100** (363 mg, 82%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (dd, *J* = 5.7, 2.4, Hz, 1H, H^3), 6.18 (dd, *J* = 5.7, 2.4 Hz, 1H, H^2), 2.83–2.76 (m, 1H, H^4), 2.42 (dd, *J* = 18.8, 6.4, 1H, H^5), 2.09 (dd, *J* = 18.8, 2.4 Hz, 1H, H^5), 1.78 (m, 1H, H^6), 0.82 (d, *J* = 6.7 Hz, 3H, H^7), 0.77 (d, *J* = 6.7 Hz, 3H, H^7).

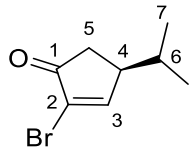
^{13}C NMR ($CDCl_3$, 126 MHz) δ 210.2 (C^1), 167.5 (C^3), 134.5 (C^2), 48.2 (C^4), 38.6 (C^5), 31.7 (C^6), 20.2 (C^7), 19.9 (C^7).

$[\alpha]_D^{25}$ +181 (*c* = 0.61, $CHCl_3$), literature **$[\alpha]_D^{25}$** +174 (*c* = 0.61, $CHCl_3$).

In agreement with literature data.[82]

(*S*)-2-Bromo-4-isopropylcyclopent-2-en-1-one (2.106).

$C_8H_{11}BrO$
Mol. Wt. = 203.08 g/mol



A solution of (*S*)-4-isopropylcyclopent-2-en-1-one **2.100** (28 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and a mixture of bromine (14 µL, 0.27 mmol, 1.2 equiv) and CH_2Cl_2 (1 mL) was slowly added. The reaction was warmed to RT and stirred for 1 h 30. Triethylamine (54 µL, 0.39 mmol, 1.7 equiv) was then added and the mixture stirred for an additional 1 h 30. The reaction was quenched by addition of a 1 M aqueous solution of hydrochloric acid (2 mL) and the aqueous phase was extracted with Et_2O (3 × 2 mL). The organic phases were combined, washed with brine (2 × 2 mL), dried over magnesium

sulfate, filtered and concentrated under vacuum. The product was then purified by flash chromatography (80:20 PE/Et_2O) to furnish compound **2.106** as a brown oil (35 mg, 72%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, *J* = 2.8 Hz, 1H, H^3), 2.76 (tdd, *J* = 6.7, 2.8, 2.1 Hz, 1H, H^4), 2.58 (dd, *J* = 19.0, 6.7 Hz, 1H, H^5), 2.23 (dd, *J* = 19.0, 2.1 Hz, 1H, H^5), 1.79 (oct, *J* = 6.7 Hz, 1H, H^6), 0.97 (d, *J* = 6.7 Hz, 3H, H^7), 0.94 (d, *J* = 6.7 Hz, 3H, H^7).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.5 (C^1), 164.7 (C^3), 126.0 (C^2), 47.2 (C^4), 37.1 (C^5), 31.8 (C^6), 19.9 (C^7), 19.8 (C^7).

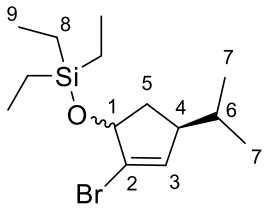
$[\alpha]_D^{25}$ +71.4 (*c* = 0.3, $CHCl_3$).

IR (thin film) 2955, 2870, 1713, 926 cm^{-1}.

HRMS (ESI) for $C_8H_{11}NaO^{79}Br$: 224.9885, found: 224.9879.

(((4*S*)-2-Bromo-4-isopropylcyclopent-2-en-1-yl)oxy)triethylsilane (2.99).

$C_{14}H_{27}BrOSi$
Mol. Wt. = 319.36 g/mol



A solution of **2.106** (368 mg, 1.81 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C then a 1 M solution of diisobutylaluminium hydride in heptane (3.62 mL, 3.62 mmol, 2.00 equiv) was added dropwise. The reaction was stirred at −78 °C for 1 h then was quenched by addition of a saturated aqueous solution of Rochelle salt (20 mL) and allowed to warm up to RT. The mixture was stirred for 4 h then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum to furnish the allylic alcohol (301 mg, dr = 7:3) as a colourless liquid that was used in the next step without further purification.

The crude allylic alcohol (301 mg, 1.47 mmol) was dissolved in dry DMF (10 mL) then imidazole (370 mg, 5.41 mmol, 3.70 equiv) and DMAP (22 mg, 0.18 mmol, 0.12 equiv) were added. The reaction was cooled to 0 °C then chlorotriethylsilane (0.60 mL, 3.6 mmol, 2.4 equiv) was added dropwise and the reaction was stirred for 5 min. The mixture was warmed to RT over 1 h. The mixture was then diluted with water (10 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 30 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (99.5:0.5 PE/Et_2O) to give product **2.99** (464 mg, 81% over 2 steps) as a yellow oil and as a mixture of 2 diastereomers (dr = 7:3).

Major diastereomer is described below.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.99 (dd, *J* = 2.2, 1.3 Hz, 1H, H^3), 4.65 (ddt, *J* = 7.6, 5.9, 1.5 Hz, 1H, H^1), 2.39 (dt, *J* = 12.9, 7.6 Hz, 1H, H^5), 2.24 (app qt, *J* = 7.6, 1.9 Hz, 1H, H^4), 1.56 (oct, *J* = 6.8 Hz, 1H, H^6), 1.49–1.42 (m, 1H, H^5), 1.00 (t, *J* = 7.9 Hz, 9H, H^8), 0.91 (d, *J* = 6.8 Hz, 3H, H^7), 0.87 (d, *J* = 6.8 Hz, 3H, H^7), 0.66 (q, *J* = 7.9 Hz, 6H, H^9).

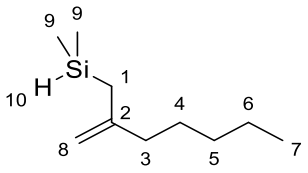
^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.6 (C^3), 126.4 (C^2), 78.4 (C^1), 50.1 (C^4), 38.1 (C^5), 32.6 (C^6), 20.3 (C^7), 20.1 (C^7), 6.8 (C^9), 4.9 (C^8).

IR (thin film) 2955, 2878, 1010, 833 cm^{-1}.

HRMS (ESI) for $C_{14}H_{27}NaOSi^{79}Br$: 341.0907, found: 341.0898.

Dimethyl(2-methyleneheptyl)silane (3.5).[86]

$C_{10}H_{22}Si$
Mol. Wt. = 170.37 g/mol



Cerium(III) chloride heptahydrate (13.0 g, 35.0 mmol, 3.50 equiv) was finely grinded then stirred under vacuum (P < 1 mbar) and warmed to 120 °C for 2 h, 140 °C for 2 h and 160 °C

for 3 h. Cerium(III) chloride was cooled to RT under inert atmosphere then THF (100 mL) was added and the white suspension was stirred vigorously overnight.

To a stirred solution of magnesium (1.70 g, 70.0 mmol, 7.00 equiv) and 1,2-dibromoethane (3 drops) in THF (100 mL) at 65 °C was added slowly a solution of chloromethyldimethylsilane (4.27 mL, 35.0 mmol, 3.50 equiv). The solution was then stirred for 30 min at 65 °C and for 2 h at RT.

The Grignard solution was then added dropwise (over 1 h) at −78 °C to the cerium/THF suspension. The reaction was stirred for 1 h, and then ethyl caproate (1.53 mL, 10.0 mmol) in dry THF (50 mL) was added at −78 °C. The reaction was stirred at −78 °C for 2 h, the flask was then allowed to warm up to RT, and the mixture was stirred for 15 h. A saturated aqueous solution of ammonium chloride (250 mL) was added. The mixture was extracted with Et_2O (3 × 250 mL). The combined ether extracts were washed with brine (2 × 500 mL), then dried over magnesium sulfate, filtered and concentrated under vacuum to give a yellow oil. The crude intermediate was stirred for 72 h with silica gel in CH_2Cl_2. The mixture was then filtered and carefully concentrated under vacuum (28 °C, 180 mbar) to deliver silane **3.5** (1.42 g, 86%), with traces of CH_2Cl_2, as a clear oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.61 (dt, *J* = 2.5, 1.4 Hz, 1H, H^8), 4.56–4.54 (m, 1H, H^8), 3.90 (non, *J* = 3.6 Hz, 1H, H^{10}), 1.98 (t, *J* = 7.4 Hz, 2H, H^3), 1.59 (dd, *J* = 3.6, 1.0 Hz, 2H, H^1), 1.47–1.39 (m, 2H, H^4), 1.35–1.23 (m, 4H, H^5/H^6), 0.89 (t, *J* = 7.1 Hz, 3H, H^7), 0.09 (d, *J* = 3.6 Hz, 6H, H^9).

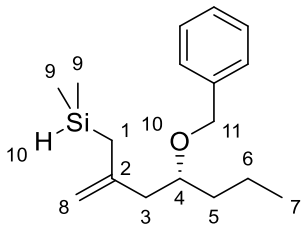
^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.7 (C^2), 107.3 (C^8), 38.0 (C^3), 31.8 (C^5 or C^6), 27.6 (C^4), 24.5 (C^1), 22.7 (C^5 or C^6), 14.2 (C^7), −4.12 (C^9).

In agreement with literature data.[86]

(*R*)-(4-(Benzyloxy)-2-methyleneheptyl)dimethylsilane (3.6').[86]

$C_{17}H_{28}OSi$

Mol. Wt. = 276.49 g/mol



Silane **3.6'** was obtained from the corresponding ester **3.3'** and chloromethyldimethylsilane according to the procedure described above for silane **3.5**.
Scale: 3.22 mmol.
Yield: 83%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.23 (m, 5H, H^{Ar}), 4.72–4.67 (m, 1H, H^{8}), 4.68–4.64 (m, 1H, H^{8}), 4.57 (d, *J* = 11.5 Hz, 1H, H^{11}), 4.50 (d, *J* = 11.5 Hz, 1H, H^{11}), 3.93 (non, *J* = 3.6 Hz, 1H, H^{10}), 3.59–3.51 (m, 1H, H^{4}), 2.37 (ddd, *J* = 14.0, 6.2, 1.4 Hz, 1H, H^{3}), 2.16 (ddd, *J* = 14.0, 6.5, 1.1 Hz, 1H, H^{3}), 1.62 (ddd, *J* = 3.6, 1.4, 1.1 Hz, 2H, H^{1}), 1.54–1.45 (m, 4H, H^{5}/H^{6}), 0.90 (t, *J* = 7.1 Hz, 3H, H^{7}), 0.11 (d, *J* = 3.6 Hz, 3H, H^{9}), 0.10 (d, *J* = 3.6 Hz, 3H, H^{9}).

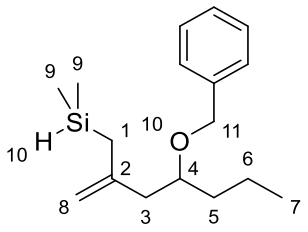
^{13}C NMR ($CDCl_3$, 126 MHz)δ 144.5 (C^{2}), 139.1 (C^{Ar}), 128.4 (C^{Ar}), 127.9 (C^{Ar}), 127.5 (C^{Ar}), 110.4 (C^{8}), 77.7 (C^{4}), 71.1 (C^{11}), 42.8 (C^{3}), 36.6 (C^{5}), 24.8 (C^{1}), 18.8 (C^{6}), 14.4 (C^{7}),−4.2 (C^{9}).

$[\alpha]_D^{25}$ +14.7 (*c* = 1.0, $CHCl_3$), literature **$[\alpha]_D^{25}$** +15.2 (*c* = 1.0, $CHCl_3$).

In agreement with literature data.[86]

(4-(Benzyloxy)-2-methyleneheptyl)dimethylsilane (3.6).[86]

$C_{17}H_{28}OSi$
Mol. Wt. = 276.49 g/mol



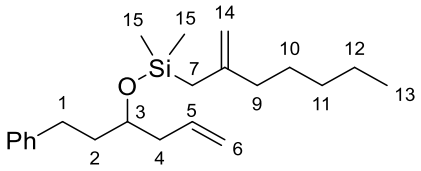
Silane **3.6** was obtained from the corresponding ester **3.3** and chloromethyldimethylsilane according to the procedure described above for silane **3.5.**
Scale: 5.59 mmol.
Yield: 52%.

In agreement with literature data.[86]

Dimethyl(2-methyleneheptyl)((1-phenylhex-5-en-3-yl)oxy)silane (3.33).⁸⁷⁸⁷⁸⁷

$C_{22}H_{36}OSi$

Mol. Wt. = 344.61 g/mol



To a stirred solution of alcohol **3.31** (400 mg, 2.33 mmol), silane **3.5** (327 mg, 2.56 mmol, 1.10 equiv) and Xantphos copper(I) chloride (79 mg, 0.12 mmol, 0.050 equiv) in toluene (100 mL) at 85 °C was added dropwise (over 4 h) a 2.2 M solution of lithium *tert*-butoxide in THF (750 µL, 1.63 mmol, 0.700 equiv) diluted in toluene (20 mL). The solution was stirred for another 30 min at 85 °C. The reaction was cooled to RT, and then was quenched by addition of a saturated aqueous solution of ammonium chloride (80 mL). The mixture was extracted with Et_2O (3 × 80 mL) and the combined organic layers were washed with brine (150 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (99.9:0.01 PE/Et_2O) to give the oxysilane **3.33** (530 mg, 74%) as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.27 (m, 2H, H^{Ar}), 7.21–7.14 (m, 3H, H^{Ar}), 5.81 (ddt, *J* = 17.0, 10.4, 7.3 Hz, 1H, H^5), 5.10–5.02 (m, 2H, H^6), 4.62 (dt, *J* = 2.6, 1.0 Hz, 1H, H^{14}), 4.60–4.54 (m, 1H, H^{14}), 3.76 (p, *J* = 6.0 Hz, 1H, H^3), 2.72 (ddd, *J* = 13.7, 10.3, 6.0 Hz, 1H, H^1), 2.57 (ddd, *J* = 13.7, 10.5, 6.0 Hz, 1H, H^1), 2.26 (ddt, *J* = 7.3, 6.0, 1.3 Hz, 2H, H^4), 2.00 (t, *J* = 7.7 Hz, 2H, H^9), 1.79–1.70 (m, 2H, H^2), 1.63 (dd, *J* = 5.5, 1.0 Hz, 2H, H^7), 1.49–1.39 (m, 2H, H^{10}) 1.36–1.22 (m, 4H, H^{11}/H^{12}), 0.89 (t, *J* = 7.0 Hz, 3H, H^{13}), 0.14 (s, 6H, H^{15}).

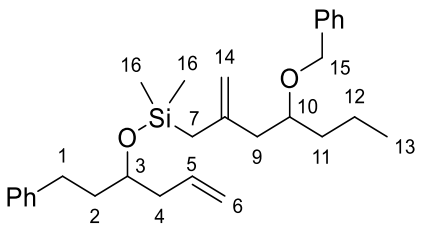
^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.9 (C^8), 143.4 (C^{Ar}), 136.0 (C^5), 129.4 (C^{Ar}), 129.3 (C^{Ar}), 126.7 (C^{Ar}), 118.0 (C^6), 108.6 (C^{14}), 72.9 (C^3), 43.0 (C^4), 39.6 (C^2), 39.3 (C^9), 32.9 (C^1), 32.7 (C^{11} or C^{12}), 28.5 (C^{10}), 28.2 (C^7), 23.6 (C^{11} or C^{12}), 15.1 (C^{13}), 0.00 (C^{15}), −0.13 (C^{15}).

IR (thin film) 2924, 2862, 1250, 1088, 1065 cm^{-1}.

HRMS (ESI) for $C_{22}H_{36}NaOSi$: 367.2428, found: 367.2410.

4-(Benzyloxy)-2-methyleneheptyl)dimethyl((1-phenylhex-5-en-3-yl)oxy)silane (3.34).

$C_{29}H_{42}O_2Si$
Mol. Wt. = 450.74 g/mol



Oxysilane **3.34** (colourless oil) was obtained from the corresponding silane **3.6** and alcohol **3.31** according to the procedure described above for oxysilane **3.33**.
Purification by flash chromatography (99.5:0.05 PE/Et_2O).
Scale: 1.18 mmol.
Yield: 84%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.22 (m, 7H, H^{Ar}), 7.22–7.14 (m, 3H, H^{Ar}), 5.86–5.74 (m, 1H, H^5), 5.08–5.02 (m, 2H, H^6), 4.72 (s, 1H, H^{14}), 4.68 (s, 1H, H^{14}), 4.58 (d, *J* = 11.4 Hz, 1H, H^{15}), 4.49 (d, *J* = 11.4 Hz, 1H, H^{15}), 3.80–3.71 (m, 1H, H^3), 3.56 (app quint, *J* = 6.1 Hz, 1H, H^{10}), 2.75–2.67 (m, 1H, H^1), 2.62–2.52 (m, 1H, H^1), 2.39 (t, *J* = 6.1 Hz, 1H, H^9), 2.30–2.23 (m, 2H, H^4), 2.18 (ddd, *J* = 6.1, 3.6, 1.0 Hz, 1H, H^9), 1.82–1.71 (m, 2H, H^2), 1.67–1.65 (m, 2H, H^7), 1.55–1.46 (m, 3H, H^{11}/H^{12}), 1.41–1.31 (m, 1H, H^{12}), 0.92–0.87 (m, 3H, H^{13}), 0.15 (s, 6H, H^{16}).

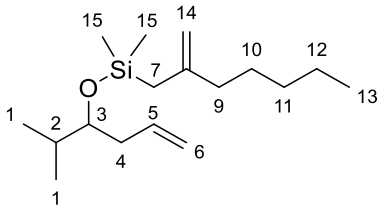
^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.7 (C^8), 142.5 (C^{Ar}), 139.2 (C^{Ar}), 135.1 (C^5), 128.5 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 127.9 (C^{Ar}), 127.5 (C^{Ar}), 125.9 (C^{Ar}), 117.2 (C^6), 110.8 (C^{14}), 77.8 (C^{10}), 72.1 (C^3), 71.1 (C^{15}), 43.3 (C^9), 42.1 (C^4), 38.7 (C^2), 36.6 (C^{11}), 32.1 (C^1), 27.6 (C^7), 18.9 (C^{12}), 14.4 (C^{13}), −0.9 (C^{16}), −1.00 (C^{16}).

IR (thin film) 3071, 3024, 2955, 2932, 1250, 1065, 833 cm^{-1}.

HRMS (ESI) for $C_{29}H_{42}NaO_2Si$: 473.2846, found: 473.2829.

Dimethyl(2-methyleneheptyl)((2-methylhex-5-en-3-yl)oxy)silane (3.35).

$C_{17}H_{34}OSi$
Mol. Wt. = 282.54 g/mol



Oxysilane **3.35** (colourless oil) was obtained from the corresponding silane **3.5** and alcohol **3.32** according to the procedure described above for oxysilane **3.33**.
Purification by flash chromatography (99.9:0.01 PE/Et_2O).
Scale: 2.50 mmol.
Yield: 65%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.81 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H, H^5), 5.07–5.00 (m, 2H, H^6), 4.60 (dt, *J* = 2.5, 1.4 Hz, 1H, H^{14}), 4.55 (dt, *J* = 2.5, 1.0 Hz, 1H, H^{14}), 3.47 (dt, *J* = 6.5, 5.1 Hz, 1H, H^3), 2.21–2.16 (m, 2H, H^4), 1.99 (t, *J* = 7.7 Hz, 2H, H^9), 1.72–1.64 (m, 1H, H^2), 1.62 (app s, 2H, H^7), 1.47–1.39 (m, 2H, H^{10}), 1.35–1.25 (m, 4H, H^{11}/H^{12}), 0.87 (d, *J* = 4.2 Hz, 3H, H^1), 0.89 (t, *J* = 7.1 Hz, 3H, H^{13}), 0.86 (d, *J* = 4.2 Hz, 3H, H^1), 0.12 (s, 3H, H^{15}), 0.11 (s, 3H, H^{15}).

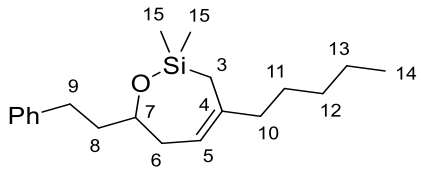
^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.8 (C^8), 136.0 (C^5), 116.6 (C^6), 107.5 (C^{14}), 77.4 (C^3), 39.0 (C^4), 38.4 (C^9), 32.9 (C^2), 31.8 (C^{11} or C^{12}), 27.6 (C^{10}), 27.5 (C^7), 22.8 (C^{11} or C^{12}), 18.9 (C^1), 17.6 (C^1), 14.2 (C^{13}), −0.85 (C^{15}), −1.01 (C^{15}).

IR (thin film) 2963, 2932, 1636, 1466, 1366, 1250, 1050 cm^{-1}.

HRMS (ESI) for $C_{17}H_{34}NaOSi$: 305.2271, found: 305.2260.

2,2-Dimethyl-4-pentyl-7-phenethyl-2,3,6,7-tetrahydro-1,2-oxasilepine (3.36).

$C_{20}H_{32}OSi$
Mol. Wt. = 316.56 g/mol



Oxysilane **3.33** (460 mg, 1.33 mmol) was dissolved in dry degassed CH_2Cl_2 (60 mL). Grubbs 2nd generation catalyst (37 mg, 0.037 mmol, 0.025 equiv) was added in one portion and the solution was heated at reflux for 2 h. The solvent was removed under vacuum and the product purified by column chromatography (99.5:0.05 PE/Et_2O) furnishing the seven-membered ring **3.36** (308 mg, 73%) as a clear oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30–7.24 (m, 2H, H^{Ar}), 7.21–7.14 (m, 3H, H^{Ar}), 5.32 (t, *J* = 7.3 Hz, 1H, H^5), 3.84–3.76 (m, 1H, H^7), 2.74 (ddd, *J* = 14.5, 9.7, 5.2 Hz, 1H, H^9), 2.67–2.55 (m, 1H, H^9), 2.27 (dt, *J* = 15.0, 7.3 Hz, 1H, H^6), 2.19 (ddd, *J* = 15.0, 7.3, 2.3 Hz, 1H, H^6), 1.96 (t, *J* = 7.6 Hz, 2H, H^{10}), 1.87–1.78 (m, 1H, H^8), 1.73–1.67 (m, 2H, H^3/H^8), 1.64–1.59 (m, 1H, H^3), 1.40–1.35 (m, 2H, H^{11}), 1.34–1.22 (m, 4H, H^{12}/H^{13}), 0.89 (t, *J* = 7.2 Hz, 3H, H^{14}), 0.15 (s, 3H, H^{15}), 0.10 (s, 3H, H^{15}).

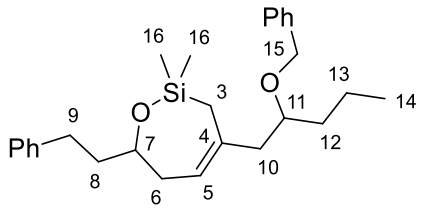
^{13}C NMR ($CDCl_3$, 126 MHz) δ 142.5 (C^4), 141.4 (C^{Ar}), 128.4 (C^{Ar}), 128.2 (C^{Ar}), 125.6 (C^{Ar}), 118.7 (C^5), 72.6 (C^7), 40.7 (C^8), 39.7 (C^{10}), 36.3 (C^6), 32.1 (C^9), 27.0 (C^{11}), 22.5 (C^3), 22.2 (C^{12}), 18.4 (C^{13}), 13.9 (C^{14}), −1.6 (C^{15}), −2.0 (C^{15}).

IR (thin film) 2924, 2862, 1450, 1250, 1096 cm^{-1}.

HRMS (ESI) for $C_{20}H_{32}NaOSi$: 339.2115, found: 339.2099.

4-(2-(Benzyloxy)pentyl)-2,2-dimethyl-7-phenethyl-2,3,6,7-tetrahydro-1,2-oxasilepine (3.37).

$C_{27}H_{38}O_2Si$
Mol. Wt. = 422.68 g/mol



Seven-membered ring **3.37** (yellow oil) was obtained from the corresponding oxysilane **3.34** according to the procedure described above for seven-membered ring **3.36**.
Purification by flash chromatography (99.5:0.05 PE/Et_2O).
Scale: 0.27 mmol.
Yield: 95%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.32 (m, 4H, H^{Ar}), 7.31–7.26 (m, 3H, H^{Ar}), 7.22–7.18 (m, 3H, H^{Ar}), 5.44 (t, *J* = 7.0 Hz, 1H, H^5), 4.55 (d, *J* = 11.6 Hz, 1H, H^{15}), 4.51 (d, *J* = 11.6, 1H, H^{15}), 3.87–3.78 (m, 1H, H^7), 3.56–3.48 (m, 1H, H^{11}), 2.76 (ddd, *J* = 14.5, 9.7, 5.2 Hz, 1H, H^9), 2.68–2.60 (m, 1H, H^9), 2.40–2.26 (m, 2H, H^6/H^{10}), 2.26–2.19 (m, 1H, H^6), 2.16–2.09 (m, 1H, H^{10}), 1.90–1.80 (m, 1H, H^8), 1.75–1.64 (m, 2H, H^3/H^8), 1.55–1.47 (m, 3H, H^{12}/H^{13}), 1.47–1.41 (m, 1H, H^3), 1.40–1.32 (m, 1H, H^{13}), 0.95–0.88 (m, 3H, H^{14}), 0.17 (s, 3H, H^{16}), 0.16 (s, 3H, H^{16}).

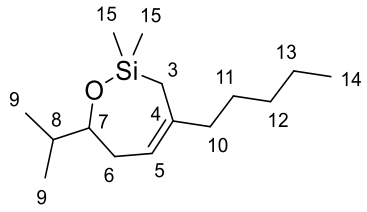
^{13}C NMR ($CDCl_3$, 126 MHz) δ 142.6 (C^4), 139.1 (C^{Ar}), 138.4 (C^{Ar}), 128.7 (C^{Ar}), 128.6 (C^{Ar}), 128.4 (C^{Ar}), 127.9 (C^{Ar}), 127.5 (C^{Ar}), 125.7 (C^{Ar}), 122.2 (C^5), 77.1 (C^{11}), 72.8 (C^7), 71.1 (C^{15}), 46.0 (C^{10}), 40.0 (C^8), 36.8 (C^6), 36.6 (C^{12}), 32.4 (C^9), 23.0 (C^3), 18.9 (C^{13}), 14.4 (C^{14}), −1.7 (C^{16}), −1.8 (C^{16}).

IR (thin film) 3026, 2955, 2930, 2870, 1250, 1096, 1063 cm^{-1}.

HRMS (ESI) for $C_{27}H_{38}NaO_2Si$: 445.2533, found: 445.2512.

7-Isopropyl-2,2-dimethyl-4-pentyl-2,3,6,7-tetrahydro-1,2-oxasilepine 3.38.

$C_{15}H_{30}OSi$
Mol. Wt. = 254.49 g/mol



Seven-membered ring **3.38** (colourless oil) was obtained from the corresponding oxysilane **3.35** according to the procedure described above for seven-membered ring **3.36**.
Purification by flash chromatography (99.9:0.01 PE/Et_2O).
Scale: 1.26 mmol.
Yield: 82%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.33 (td, *J* = 7.6, 1.3 Hz, 1H, H^5), 3.48 (ddd, *J* = 8.4, 6.3, 2.1 Hz, 1H, H^7), 2.28–2.12 (m, 2H, H^6), 1.96 (t, *J* = 7.5 Hz, 2H, H^{10}), 1.66 (s, 2H, H^3), 1.65–1.59 (m, 1H, H^8), 1.43–1.34 (m, 2H, H^{11}), 1.34–1.21 (m, 4H, H^{12}/H^{13}), 0.91–0.84 (m, 9H, H^9/H^{14}), 0.10 (s, 3H, H^{15}), 0.08 (s, 3H, H^{15}).

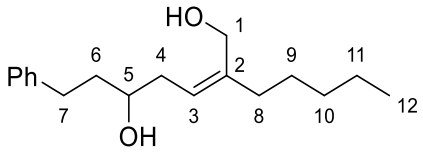
^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.2 (C^4), 119.4 (C^5), 78.8 (C^7), 41.1 (C^{10}), 34.6 (C^8), 33.6 (C^6), 31.8 (C^{12} or C^{13}), 27.3 (C^{11}), 22.8 (C^{12} or C^{13}), 22.6 (C^3), 18.9 (C^9), 18.5 (C^9), 14.2 (C^{14}), 0.1 (C^{15}), −1.8 (C^{15}).

IR (thin film) 2955, 2924, 2862, 1466, 1250, 1042, 833 cm^{-1}.

HRMS (CI+) for $C_{15}H_{31}OSi$: 255.2139, found: 255.2144.

(*Z*)-2-Pentyl-7-phenylhept-2-ene-1,5-diol (3.43).

$C_{18}H_{28}O_2$
Mol. Wt. = 276.42 g/mol



To a solution of seven-membered ring **3.36** (30 mg, 0.095 mmol) in a 1:1 mixture of THF/methanol (4 mL) was added potassium fluoride (28 mg, 0.47 mmol, 5.0 equiv), potassium bicarbonate (22 mg, 0.22 mmol, 2.3 equiv) and a 30% wt aqueous solution of hydrogen peroxide (0.50 mL, 3.79 mmol, 40.0 equiv). The reaction was warmed to 40 °C and stirred for 4 h. Water (5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (50:50 PE/Et_2O) to furnish diol **3.43** (18.5 mg, 70%) as a thick colourless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.27 (m, 2H, H^{Ar}), 7.23–7.17 (m, 3H, H^{Ar}), 5.35 (t, *J* = 8.1 Hz, 1H, H^3), 4.15 (d, *J* = 11.5 Hz, 1H, H^1), 3.97 (d, *J* = 11.5 Hz, 1H, H^1), 3.64 (tdd, *J* = 7.6, 5.1, 3.8 Hz, 1H, H^5), 2.85–2.72 (m, 1H, H^7), 2.74 (brs, 1H, OH), 2.74–2.64 (m, 1H, H^7), 2.34–2.23 (m, 2H, H^4), 2.17–2.09 (m, 2H, H^8), 1.85–1.77 (m, 2H, H^6), 1.48–1.38 (m, 2H, H^9), 1.36–1.23 (m, 4H, H^{10}/H^{11}), 0.89 (t, *J* = 7.1 Hz, 3H, H^{12}).

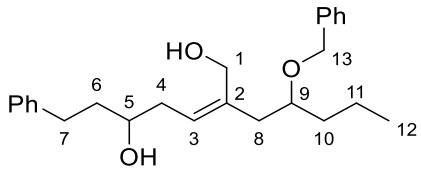
^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.1 (C^2), 142.0 (C^{Ar}), 128.6 (C^{Ar}), 128.5 (C^{Ar}), 126.0 (C^{Ar}), 124.1 (C^3), 70.1 (C^5), 59.9 (C^1), 38.9 (C^6), 36.6 (C^8), 35.6 (C^4), 32.3 (C^7), 31.7 (C^{10} or C^{11}), 28.1 (C^9), 22.7 (C^{10} or C^{11}), 14.2 (C^{12}).

IR (thin film) 3318, 2924, 2855, 1450, 1003 cm^{-1}.

HRMS (ESI) for $C_{18}H_{28}NaO_2$: 299.1982, found: 299.1969.

(*Z*)-2-(2-(Benzyloxy)pentyl)-7-phenylhept-2-ene-1,5-diol (3.44).

$C_{25}H_{34}O_3$
Mol. Wt. = 382.54 g/mol



Diol **3.44** (colourless oil) was obtained from the corresponding seven-membered ring **3.37** according to the procedure described above for diol **3.43**.
Purification by flash chromatography (40:60 PE/Et_2O).
Scale: 0.25 mmol.
Yield: 90%.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.31 (m, 4H, H^{Ar}), 7.31–7.26 (m, 3H, H^{Ar}), 7.23–7.17 (m, 3H, H^{Ar}), 5.43 (t, *J* = 8.0 Hz, 1H, H^3), 4.60–4.48 (m, 2H, H^{13}), 4.18–3.92 (m, 2H, H^1), 3.69–3.62 (m, 1H, H^5), 3.62–3.54 (m, 3H, H^5/H^9), 2.85–2.75 (m, 1H, H^7), 2.73–2.63 (m, 1H, H^7), 2.48–2.39 (m, 1H, H^4), 2.39–2.21 (m, 3H, H^4/H^8), 1.84–1.73 (m, 2H, H^6), 1.66–1.56 (m, 1H, H^{10}), 1.54–1.45 (m, 1H, H^{10}), 1.43–1.33 (m, 2H, H^{11}), 0.91 (t, *J* = 7.3 Hz, 3H, H^{12}).

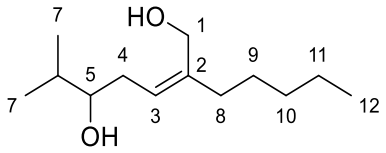
^{13}C NMR ($CDCl_3$, 126 MHz) δ 142.2 (C^2), 139.6 (C^{Ar}), 139.3 (C^{Ar}), 138.2 (C^{Ar}), 128.5 (C^{Ar}), 128.1 (C^{Ar}), 127.9 (C^{Ar}), 127.8 (C^{Ar}), 127.2 (C^3), 125.9 (C^{Ar}), 79.2 (C^9), 71.3 (C^{13}), 70.2 (C^5), 60.6 (C^1), 41.3 (C^4), 39.1 (C^6), 36.1 (C^{10}), 35.8 (C^8), 32.3 (C^7), 18.8 (C^{11}), 14.4 (C^{12}).

IR (thin film) 3356, 3324, 2924, 2862, 1450, 1057, 1003, 741 cm^{-1}.

HRMS (ESI) for $C_{25}H_{34}NaO_3$: 405.2400, found: 405.2386.

(*Z*)-6-Methyl-2-pentylhept-2-ene-1,5-diol (3.45).

$C_{13}H_{26}O_2$
Mol. Wt. = 214.35 g/mol



Diol **3.45** (colourless oil) was obtained from the corresponding seven-membered ring **3.38** according to the procedure described above for diol **3.43**.
Purification by flash chromatography (50:50 PE/Et_2O).
Scale: 0.95 mmol.
Yield: 76%.

^{1}**H NMR** ($CDCl_3$, 500 MHz) δ 5.36 (t, *J* = 8.2 Hz, 1H, H^3), 4.18 (d, *J* = 11.5 Hz, 1H, H^1), 3.92 (d, *J* = 11.5 Hz, 1H, H^1), 3.34 (ddd, *J* = 8.2, 6.5, 2.9 Hz, 1H, H^5), 2.28 (dt, *J* = 14.1, 8.7 Hz, 1H, H^4), 2.23–2.15 (m, 1H, H^4), 2.12 (app q, *J* = 6.9 Hz, 2H, H^8), 1.76–1.63 (oct, *J* = 6.5 Hz, 1H, H^6), 1.47–1.39 (m, 2H, H^9), 1.35–1.23 (m, 4H, H^{10}/H^{11}), 0.95 (d, *J* = 6.5 Hz, 3H, H^7), 0.93 (d, *J* = 6.5 Hz, 3H, H^7), 0.88 (t, *J* = 7.1 Hz, 3H, H^{12}).

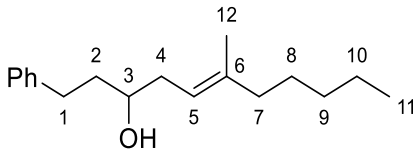
^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.0 (C^2), 124.9 (C^3), 75.7 (C^5), 60.0 (C^1), 36.7 (C^8), 33.7 (C^6), 32.4 (C^4), 31.8 (C^{10} or C^{11}), 28.1 (C^9), 22.7 (C^{10} or C^{11}), 18.8 (C^7), 17.9 (C^7), 14.2 (C^{12}).

IR (thin film) 3310, 2955, 2924, 2870, 1465, 1003 cm^{-1}.

HRMS (ESI) for $C_{13}H_{26}NaO_2$: 237.1825, found: 237.1818.

(*E*)-6-Methyl-1-phenylundec-5-en-3-ol (3.46).

$C_{18}H_{28}O$
Mol. Wt. = 260.42 g/mol



Diol **3.43** (50 mg, 0.18) was dissoled in acetonitrile (3 mL) then triphenylphosphine (57 mg, 0.22 mmol, 1.2 equiv), 2,6-lutidine (21 µL, 0.18 mmol, 1.0 equiv) and carbon tetrabromide (72 mg, 0.22 mmol, 1.2 equiv) were added. The reaction was stirred at RT for 1 h then was quenched with water (3 mL), the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was used in the next step without further purification.
The above crude was dissolved in THF (3 mL), cooled to 0 °C and a 1 M solution of lithium triethylborohydride (0.9 mL, 0.9 mmol, 5 equiv) in THF was added dropwise (over 10 min). The reaction was stirred at 0 °C for 1 h then the reaction was quenched with a 1 M aqueous solution of hydrochloric acid (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL), the combined organic phases were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by flash chromatography (70:30 PE/Et_2O) to afford product **3.46** (33 mg, 71% over 2 steps) as a clear oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31–7.27 (m, 2H, H^{Ar}), 7.24–7.16 (m, 3H, H^{Ar}), 5.19–5.14 (m, 1H, H^5), 3.64 (dt, *J* = 12.6, 6.8 Hz, 1H, H^3), 2.82 (ddd, *J* = 13.7, 9.1, 6.3 Hz, 1H, H^1), 2.69 (ddd, *J* = 13.7, 9.2, 7.2 Hz, 1H, H^1), 2.22 (t, *J* = 6.8 Hz, 2H, H^4), 2.01 (t, *J* = 7.6 Hz, 2H, H^7), 1.83–1.77 (m, 2H, H^2), 1.63 (d, *J* = 1.4 Hz, 3H, H^{12}) 1.40 (quint, *J* = 7.6 Hz, 2H, H^8), 1.35–1.28 (m, 2H, H^{10}), 1.28–1.21 (m, 2H, H^9), 0.89 (t, *J* = 7.2 Hz, 3H, H^{11}).

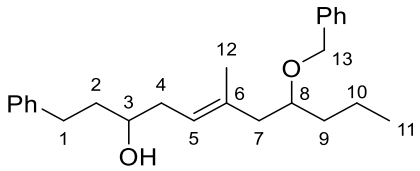
^{13}C NMR ($CDCl_3$, 126 MHz) δ 142.4 (C^{Ar}), 139.7 (C^6), 128.6 (C^{Ar}), 128.5 (C^{Ar}), 125.9 (C^{Ar}), 119.6 (C^5), 71.1 (C^3), 40.0 (C^7), 38.6 (C^2), 36.4 (C^4), 32.3 (C^1), 31.7 (C^9), 27.8 (C^8), 22.7 (C^{10}), 16.4 (C^{12}), 14.2 (C^{11}).

IR (thin film) 3372, 2924, 2855, 1604, 1450, 1049 cm^{-1}.

HRMS (ESI) for $C_{18}H_{28}NaO$: 283.2032, found: 283.2020.

(*E*)-8-(Benzyloxy)-6-methyl-1-phenylundec-5-en-3-ol (3.47).

$C_{25}H_{34}O_2$
Mol. Wt. = 366.55 g/mol



Product **3.47** (colourless oil) was obtained from the corresponding diol **3.44** according to the procedure described above for product **3.46**.
Purification by flash chromatography (70:30 PE/Et_2O).
Scale: 0.11 mmol.
Yield: 65% over 2 steps.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, *J* = 4.1 Hz, 4H, H^{Ar}), 7.30–7.27 (m, 3H, H^{Ar}), 7.22–7.17 (m, 3H, H^{Ar}), 5.24 (app q, *J* = 7.6 Hz, 1H, H^5), 4.51 (d, *J* = 3.4 Hz, 1H, H^{13}), 4.50 (d, *J* = 3.4 Hz, 1H, H^{13}), 3.67–3.58 (m, 1H, H^3), 3.55–3.46 (m, 1H, H^8), 2.84–2.75 (m, 1H, H^1), 2.71–2.63 (m, 1H, H^1), 2.35 (dd, *J* = 13.8, 6.6 Hz, 1H, H^7), 2.24–2.14 (m, 3H, H^4/H^7), 1.81–1.74 (m, 2H, H^2), 1.65 (s, 3H, H^{12}), 1.53–1.41 (m, 3H, H^9/H^{10}), 1.39–1.27 (m, 1H, H^{10}), 0.92–0.83 (m, 3H, H^{11}).

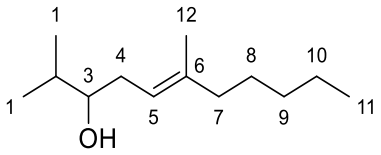
^{13}C NMR ($CDCl_3$, 101 MHz) δ 142.2 (C^6), 138.9 (C^{Ar}), 136.1 (C^{Ar}), 128.4 (C^{Ar}), 128.4 (C^{Ar}), 128.3 (C^{Ar}), 127.7 (C^{Ar}), 127.4 (C^{Ar}), 125.8 (C^{Ar}), 122.5 (C^5), 77.2 (C^8), 70.9 (C^3), 70.8 (C^{13}), 44.7 (C^7), 38.4 (C^2), 36.3 (C^4), 36.2 (C^9), 32.2 (C^1), 18.6 (C^{10}), 16.9 (C^{12}), 14.2 (C^{11}).

IR (thin film) 3352, 2924, 2862, 1451, 1350, 1057, 732 cm^{-1}.

HRMS (ESI) for $C_{25}H_{34}NaO_2$: 389.2451, found: 389.2432.

(*E*)-2,6-dimethylundec-5-en-3-ol (3.48).

$C_{13}H_{26}O$
Mol. Wt. = 198.35 g/mol



Product **3.48** (colourless oil) was obtained from the corresponding diol **3.45** according to the procedure described above for product **3.46**.
Purification by flash chromatography (70:30 PE/Et_2O).
Scale: 0.65 mmol.
Yield: 76% over 2 steps.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.19–5.14 (m, 1H, H^5), 3.34 (dt, *J* = 9.4, 5.1 Hz, 1H, H^3), 2.19–2.10 (m, 2H, H^4), 2.00 (t, *J* = 7.4 Hz, 2H, H^7), 1.73–1.65 (m, 1H, H^2), 1.62 (s, 3H, H^{12}), 1.43–1.36 (m, 2H, H^8), 1.34–1.26 (m, 2H, H^{10}), 1.26–1.19 (m, 2H, H^9), 0.94 (d, *J* = 6.9 Hz, 3H, H^1), 0.92 (d, *J* = 6.9 Hz, 3H, H^1), 0.88 (t, *J* = 7.2 Hz, 3H, H^{11}).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.4 (C^6), 120.3 (C^5), 76.5 (C^3), 40.0 (C^7), 33.2 (C^2), 33.1 (C^4), 31.7 (C^9), 27.8 (C^8), 22.7 (C^{10}), 19.0 (C^1), 17.7 (C^1), 16.3 (C^{12}), 14.2 (C^{11}).

IR (thin film) 3364, 2954, 2924, 2862, 1458, 1381, 1034, 995 cm^{-1}.

HRMS (ESI) for $C_{13}H_{26}NaO$: 221.1876, found: 221.1867.

Chapter 5: Refererences

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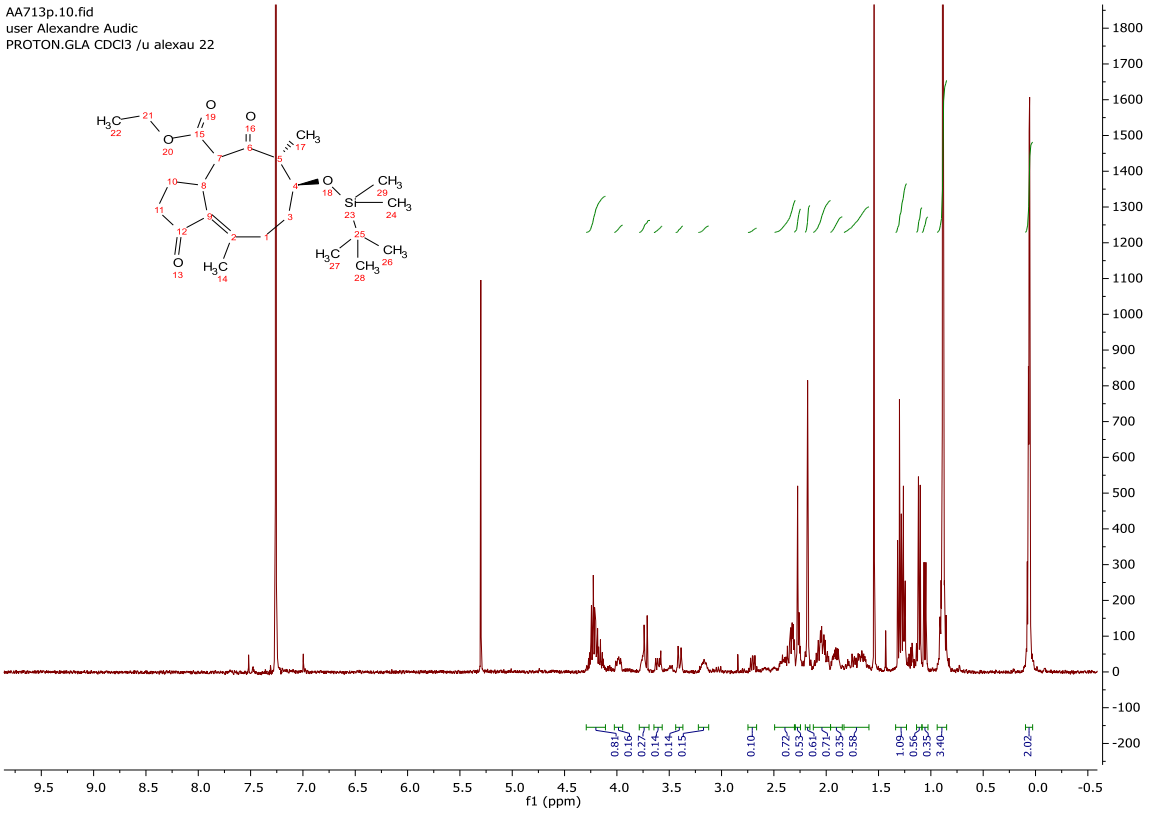
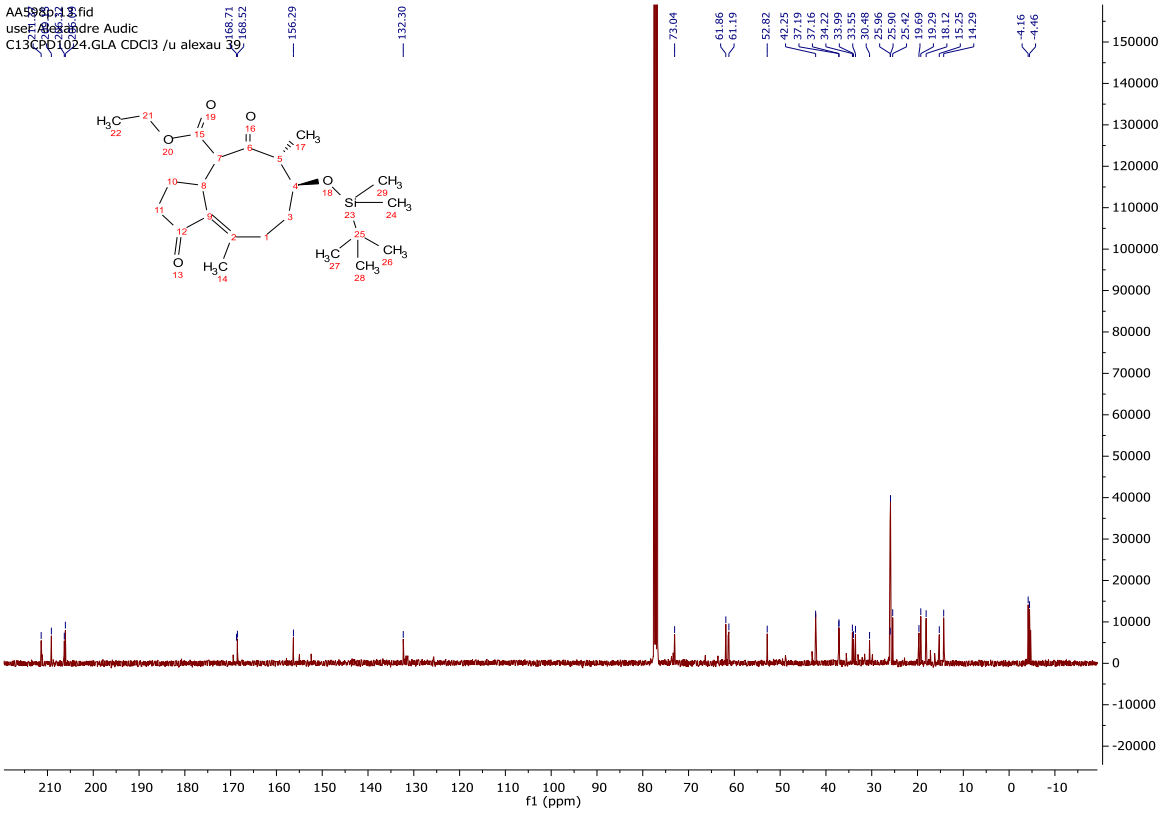
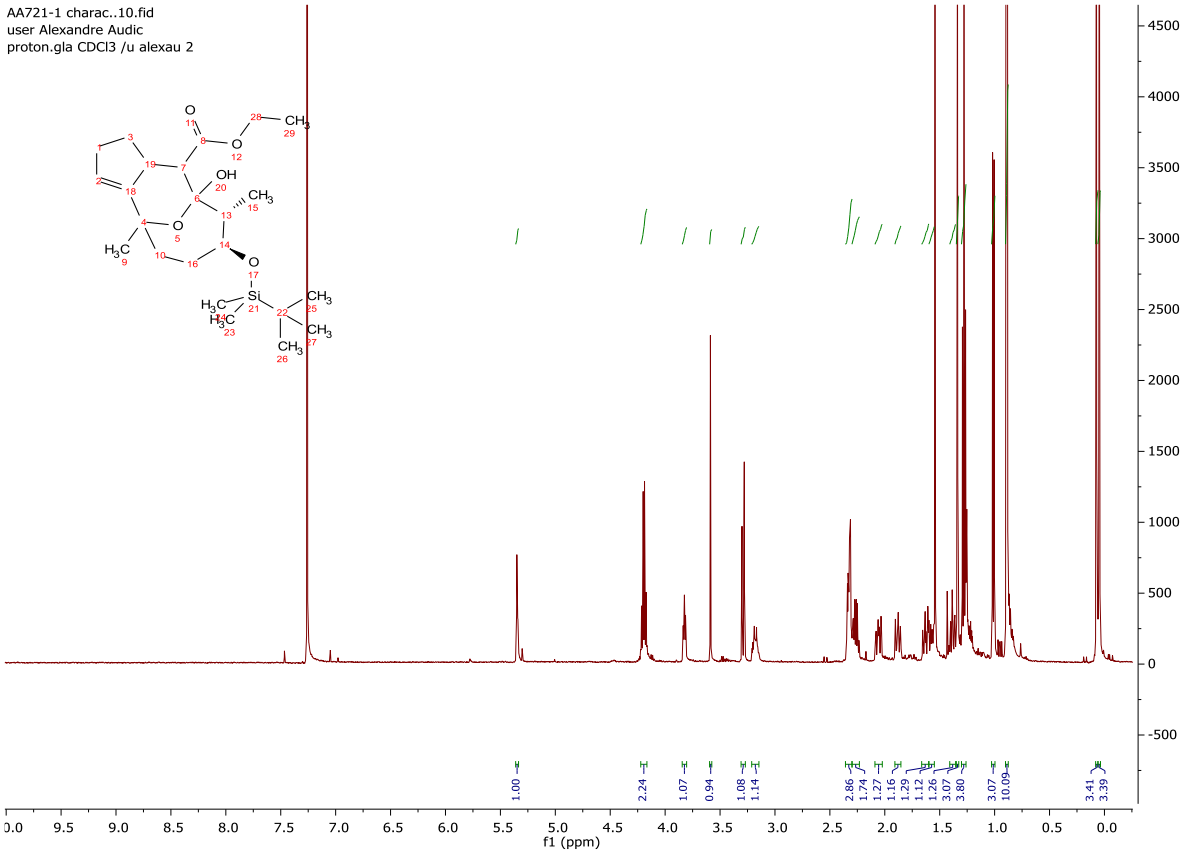
Chapter 6: Appendices



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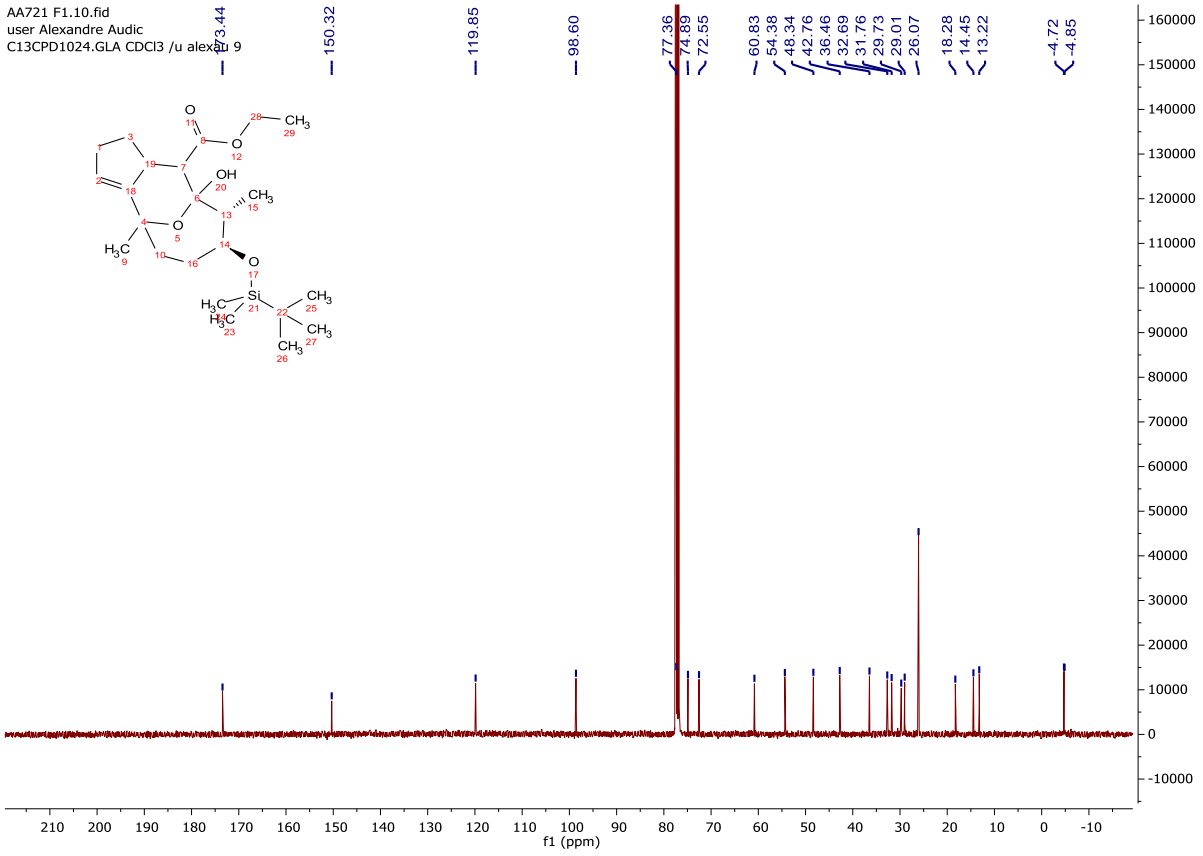
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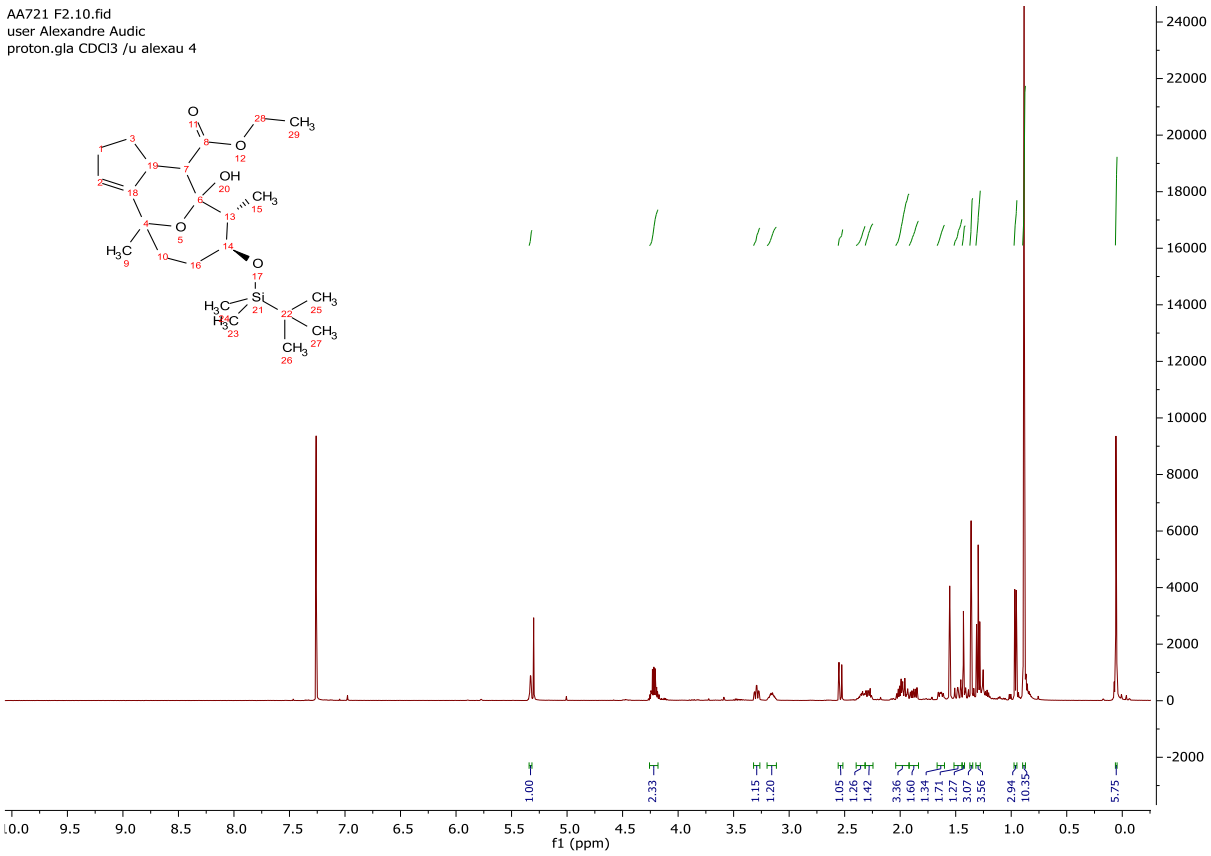
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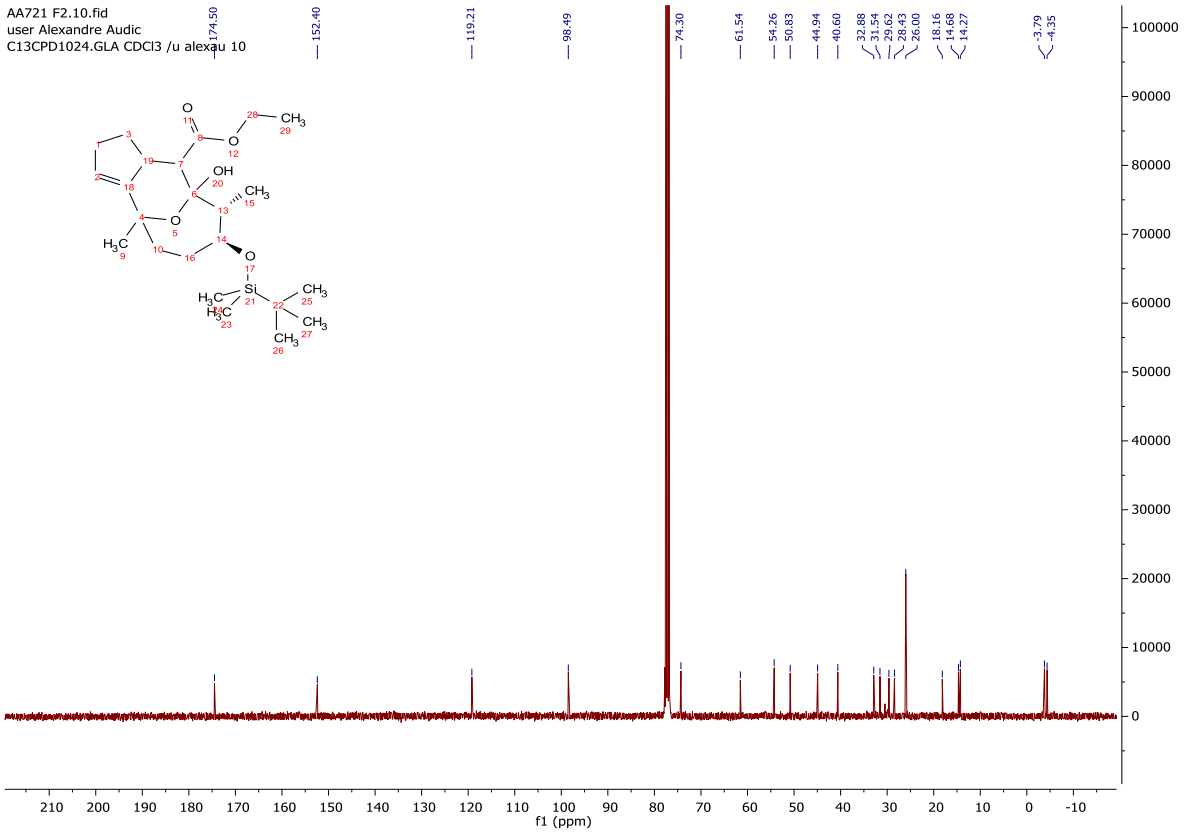
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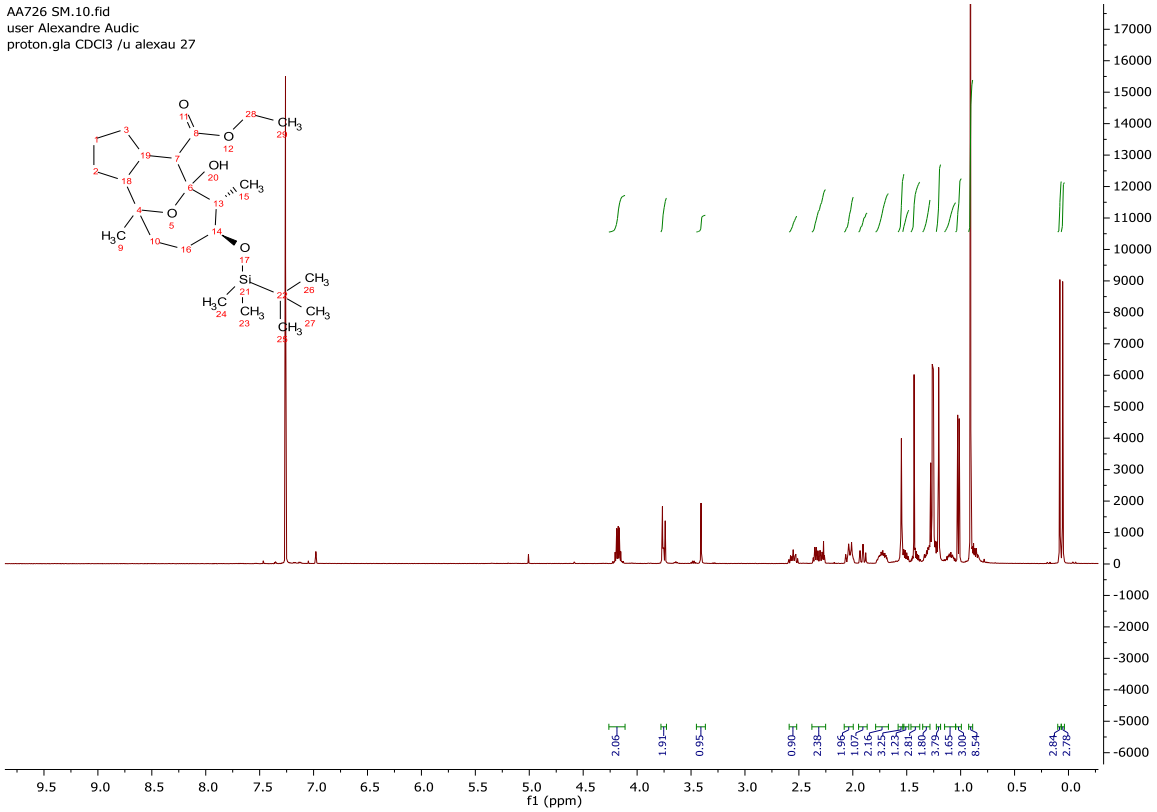
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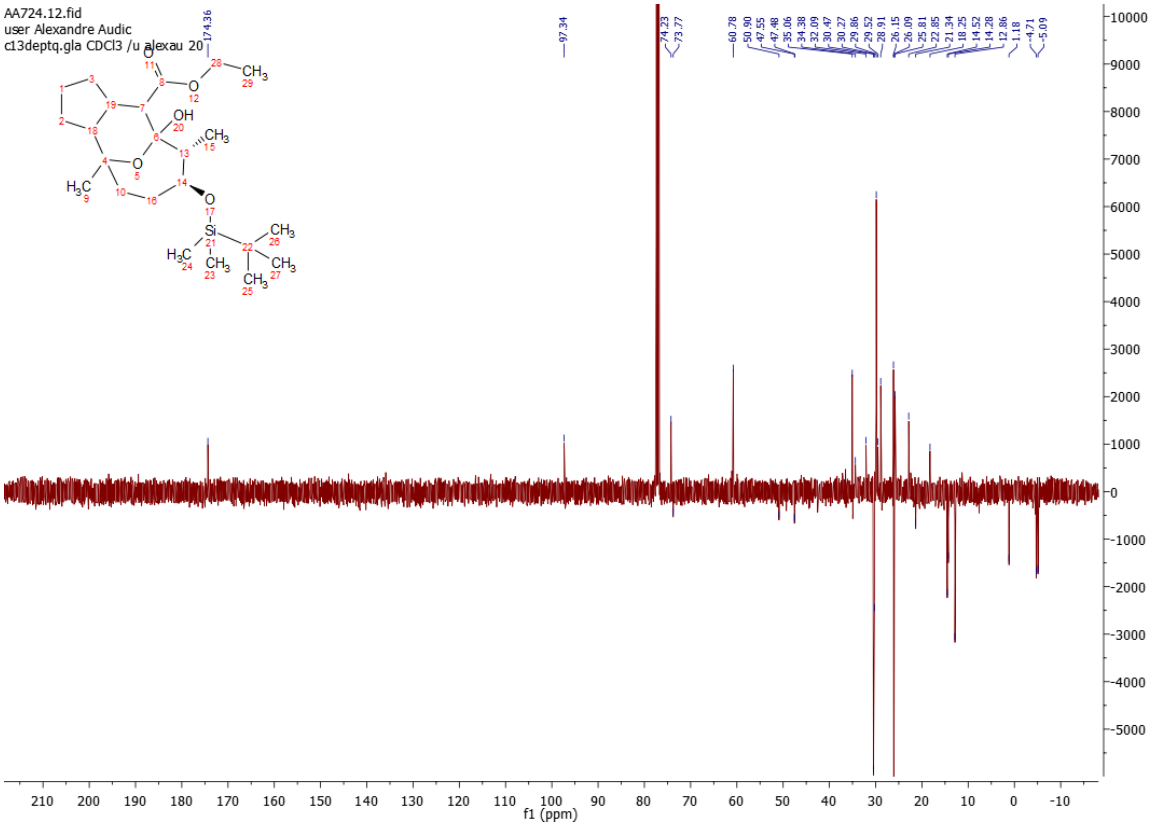
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