Synthesis of CDEF Ring Systems of Hexacyclinic Acid

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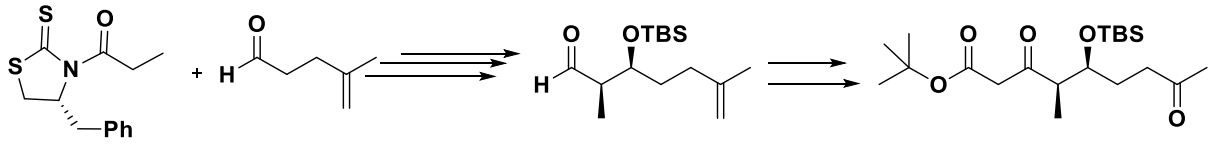
Master's by Research

Abstract

Hexacyclinic acid is a polyketide isolated from *Streptomyces cellulosae* in 2000. It comprises a 5/6/5 fused ring system (A, B and C) connected to a bridged tricycle (D, E and F). Hexacyclinic has demonstrated some notable cytotoxic activities against cancer cells.



160 **115** **162** **DEF fragment**

CDEF ring system plays a crucial role in completing the synthesis of cytotoxic hexacyclinic acid. This strategy was proved to be more efficient than the previous one developed by our group. 4-Benzyl-3-propionylthiazolidine-2-thione **160** was prepared from (*R*)-phenylalanine through reduction, cyclisation, and nucleophilic substitution reaction. Additionally, 4-methylpenten-al **115** was also synthesised from ethyl 4-methylpent-4-enoate to yield an aldol **161**, which was converted to aldehyde **162** over two steps and subsequently used to generate the **DEF** fragment in the next step.

Author's declaration

This thesis is the result of the original research efforts that Bilal Sadiq has undertaken unless it is specifically stated differently and appropriately recognised within the text. The research, which was carried out under the able direction of Dr Joëlle Prunet, was carried out inside the prestigious walls of the Henderson Lab at the University of Glasgow, and it lasted from October 2022 to April 2024.

Acknowledgement

I wish to extend my sincere appreciation to my supervisor, Dr Joëlle Prunet, for her invaluable mentorship, rigorous oversight, and expert guidance throughout the entirety of this research endeavour. Her scholarly insight and methodological expertise have been pivotal in shaping the development and execution of this thesis.

I am also grateful to the members of my thesis committee for their meticulous review and constructive critique, which have enhanced the quality and rigor of this work. Furthermore, I acknowledge the indispensable support of Dr David France and the Chemistry Department University of Glasgow, whose resources and facilities have facilitated the successful completion of this study.

I wish to extend my special thanks to all members of Henderson lab, Clark group and Schmidt group. My gratitude also extends to my whole family for their unwavering support and understanding during this intensive scholarly pursuit. Lastly, I extend my appreciation to all participants and my sponsor whose contributions have enriched the depth and breadth of this research.

Essential list of abbreviations.

Ac: Acetyl

Aq: Aqueous

BAIB: [*bis*(Acetoxy)iodo]benzene

BHT: Butylated hydroxytoluene

Bn: Benzyl

Cat: Catalytic

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)

FGI: Functional group interconversion

HMPA: Hexamethylphosphoramide

HWE: Horner–Wadsworth–Emmons

Hz: Hertz

IMDA: Intramolecular Diels-Alder

IMHDA: Intramolecular hetero-Diels-Alder

RCEYM: Ring closing enyne metathesis

TBDPS: *tert*-Butyldiphenylsilyl

TBS: *tert*-Butyldimethylsilyl

TEAB: Tetraethylammonium bromide

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

TMANO: Trimethylamine N-oxide

TES: Triethylsilyl

THF: Tetrahydrofuran

TMS: Trimethylsilyl

TMSE: 2-(Trimethylsilyl)ether

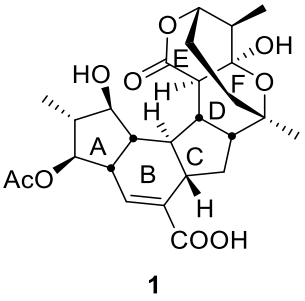
Ts: Toluene sulfonyl

Contents

1 Introduction

1.1 Hexacyclinic acid

Hexacyclinic acid **1** (Figure 1.1), a polyketide, was initially isolated in 2000 from the bacterium *Streptomyces cellulosae* by Zeeck *et al*. Using the one strain many compound (OSMAC) technique, they characterised this natural product **1,** which features a highly intricate molecular architecture.[1] It consists of a fused ring system incorporating a 5/6/5 membered ABC ring system and a bridged DEF ring system that bears hemiketal and lactone functionalities. Hexacyclinic acid demonstrated significant biological activity against cancer cell lines such as gastric carcinoma, hepatocellular carcinoma, and MCF-7.[2]

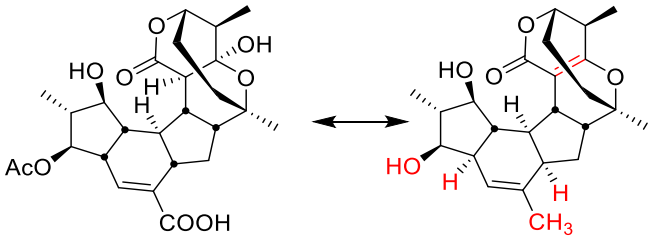


1

Figure 1.1: Hexacyclinic acid

1.2 (-)-FR182877

(-)-FR182877 was isolated in 1998 by Fujisawa Pharmaceutical Co. This compound bears a striking resemblance to hexacyclinic acid, particularly in its hexacyclic ring system (Figure 1.2). Although both compounds have different stereochemical configurations at ABC ring junctions, (-)-FR877182 has been found to possess significant antitumor properties.[3,4]



Hexacyclinic acid **(-) FR182877**

1 **2**

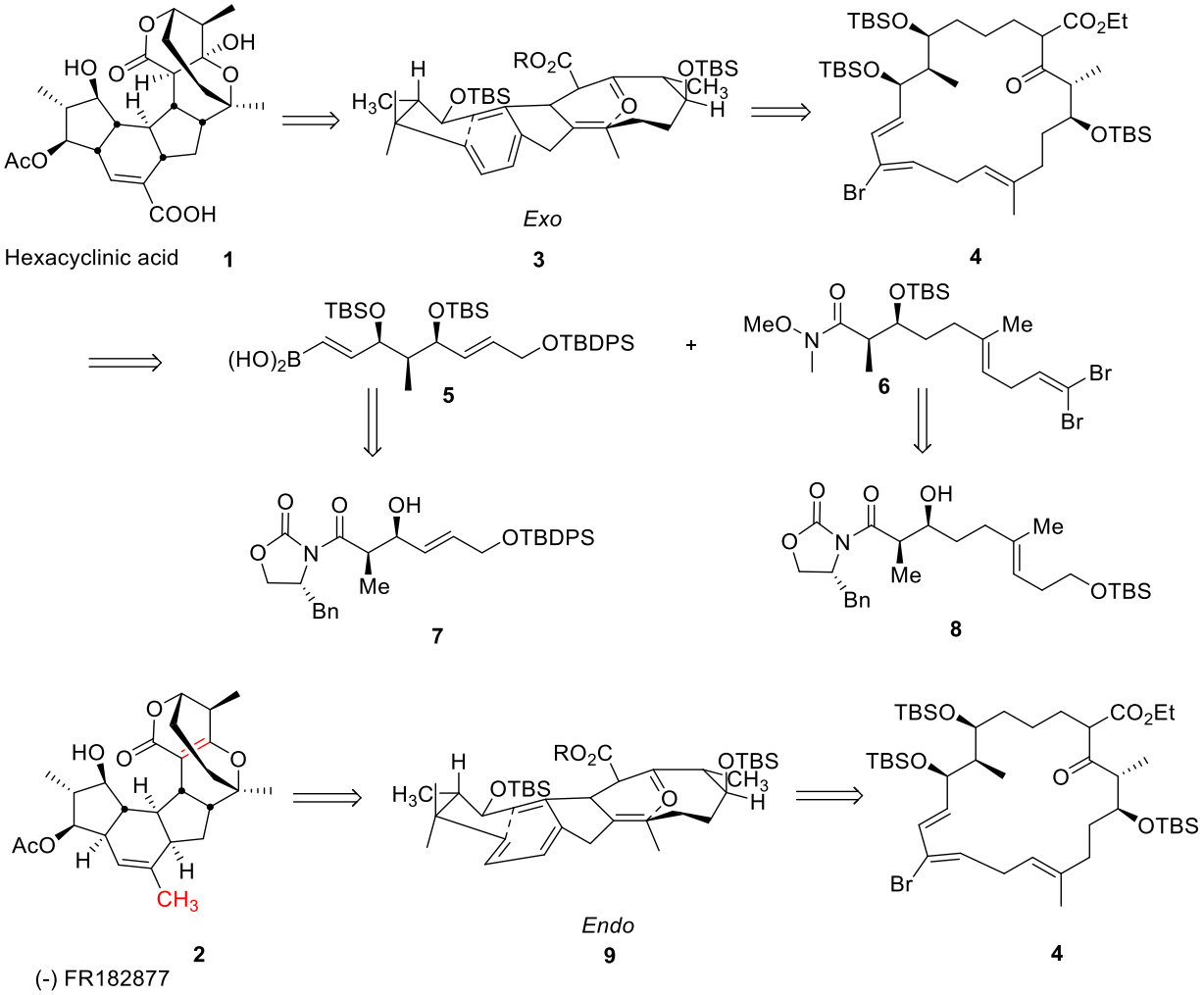
Figure 1.2: Hexacyclinic acid and FR-182877

1.3 Literature review towards the attempted synthesis of hexacyclinic acid

The literature research indicates several efforts have been undertaken to synthesise this natural polyketide, but none have successfully produced compound **1**.

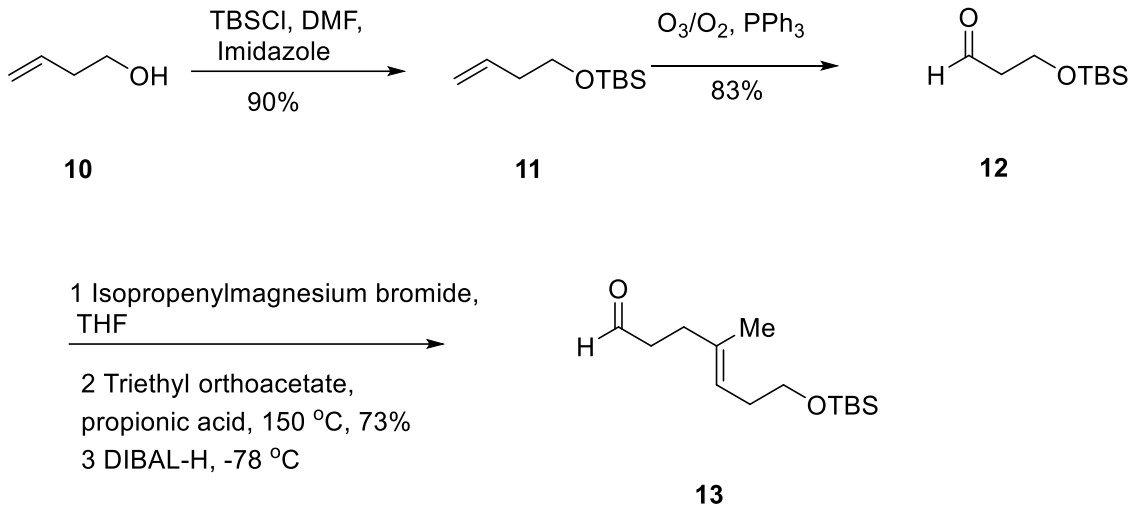
1.3.1 Attempted synthesis of hexacylinic acid and synthesis of (-)-FR182877 by Evans *et al*.

Evans and his co-workers devised a synthetic strategy to construct natural product **1** and (-)-FR182877. Initially, they targeted a 19-membered common macrocyclic intermediate **4** for both **1** and **2**, which would be constructed by the Suzuki coupling of **5** and **6** followed by the macrocyclisation of the resulting ester.[5] The boronic acid **5** would be derived from **7** while dibromide fragment **6** would be generated from **8**. Both fragments **7** and **8** would be formed by an Evans aldol reaction to ensure the stereochemical control.[6] Due to the structural similarities between **1** and **2**, they devised a synthetic plan to generate both natural products using a common intermediate. *Exo* selectivity in the key Diels-Alder cycloaddition of **3** would yield compound **1**, while *endo* selectivity would provide compound **2** from **9** (Scheme 1.1).



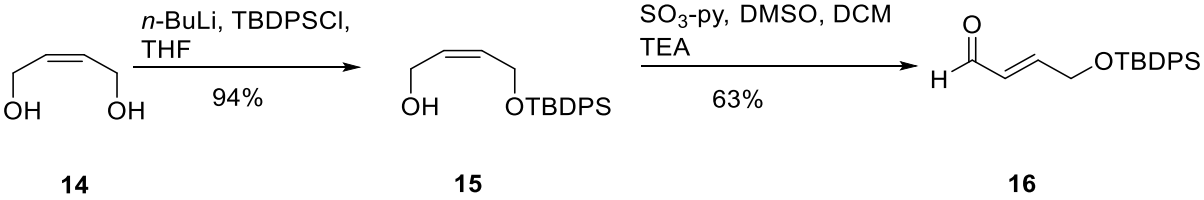
Scheme 1.1: Retrosynthesis of polyketide**1** and **2**

In order to produce the aldol adduct **7**, Evans and his coworkers strategically synthesised two crucial aldehydes, **12** and **13**. The synthesis of aldehyde **12** began by employing TMSCl in DMF to protect 3-buten-1-ol. This protection step was followed by ozonolysis, resulting in the formation of aldehyde **12** with a yield of 83%. Afterwards, aldehyde **12** was reacted with isopropylmagnesium bromide to produce an allylic alcohol, which then underwent a Johnson-Claisen rearrangement to yield an ester. The required aldehyde **13** was obtained by reducing the ester with DIBAL-H (Scheme 1.2).



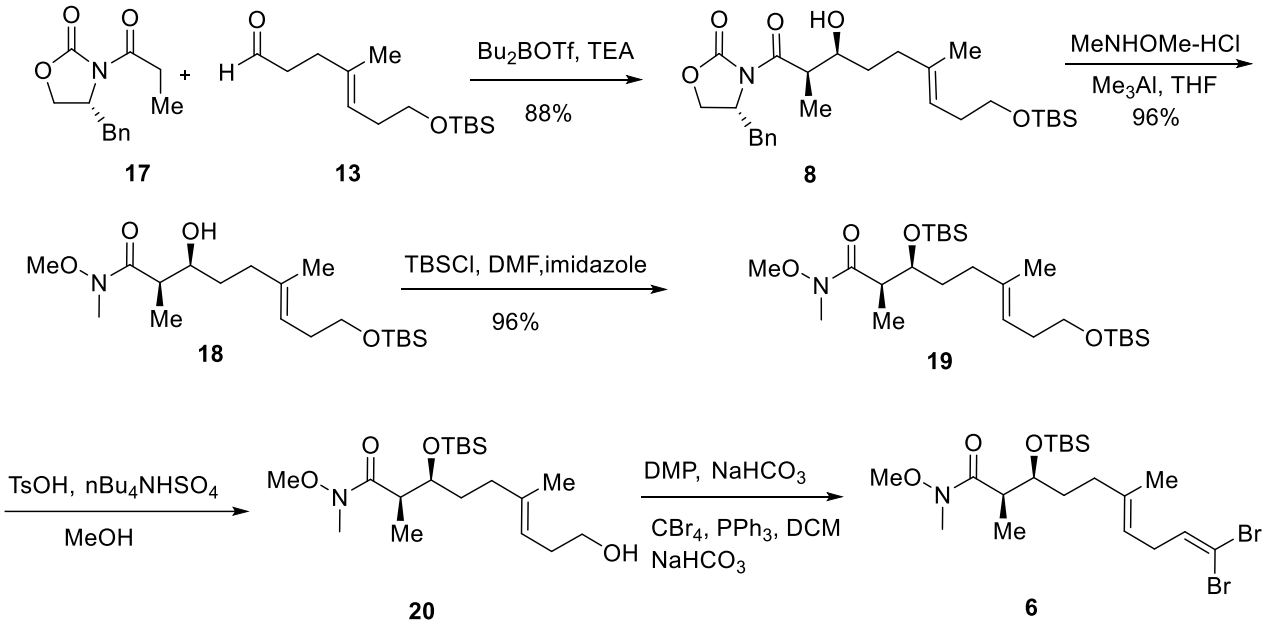
Scheme 1.2: Synthesis of aldehyde **13**

To synthesise aldehyde **16**, the diol **14** was protected by using TBDPSCl in the presence of *n*-BuLi to give the compound **15**. This intermediate was then subjected to Parikh-Doering oxidation to generate the aldehyde **16** after isomerisation of *Z* olefin to *E* olefin during the oxidation (Scheme 1.3).



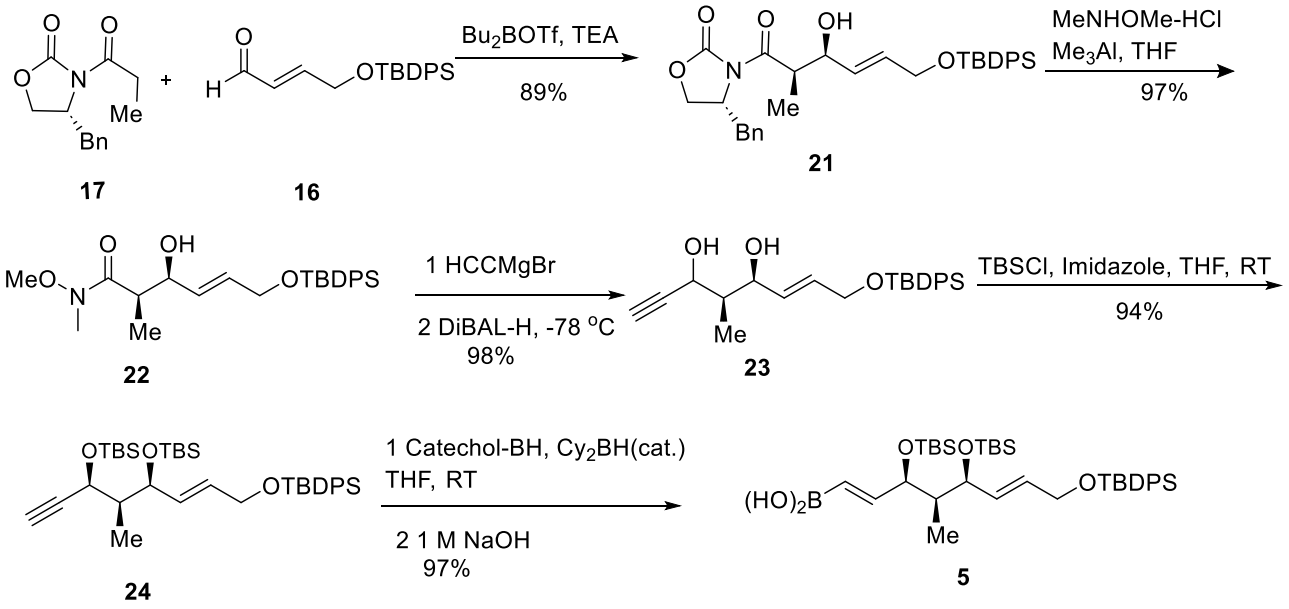
Scheme 1.3: Synthesis of **16** by Parikh-Doering Reaction

The synthesis of **8** began with the aldol addition of the acylated Evans auxiliary **17** to the freshly prepared aldehyde **13**, yielding *syn* aldol **8**. Subsequently, the *syn* aldol **8** was transformed into Weinreb amide **18**. The resulting Weinreb amide **18** was then subjected to silylation to produce **19**, which was followed by desilylation of the protected primary alcohol to furnish **20**. The compound **20** was then oxidised to an aldehyde, which gave **6** under the Corey-Fuchs olefination conditions to afford the desired dibromide fragment (Scheme 1.4).[7]



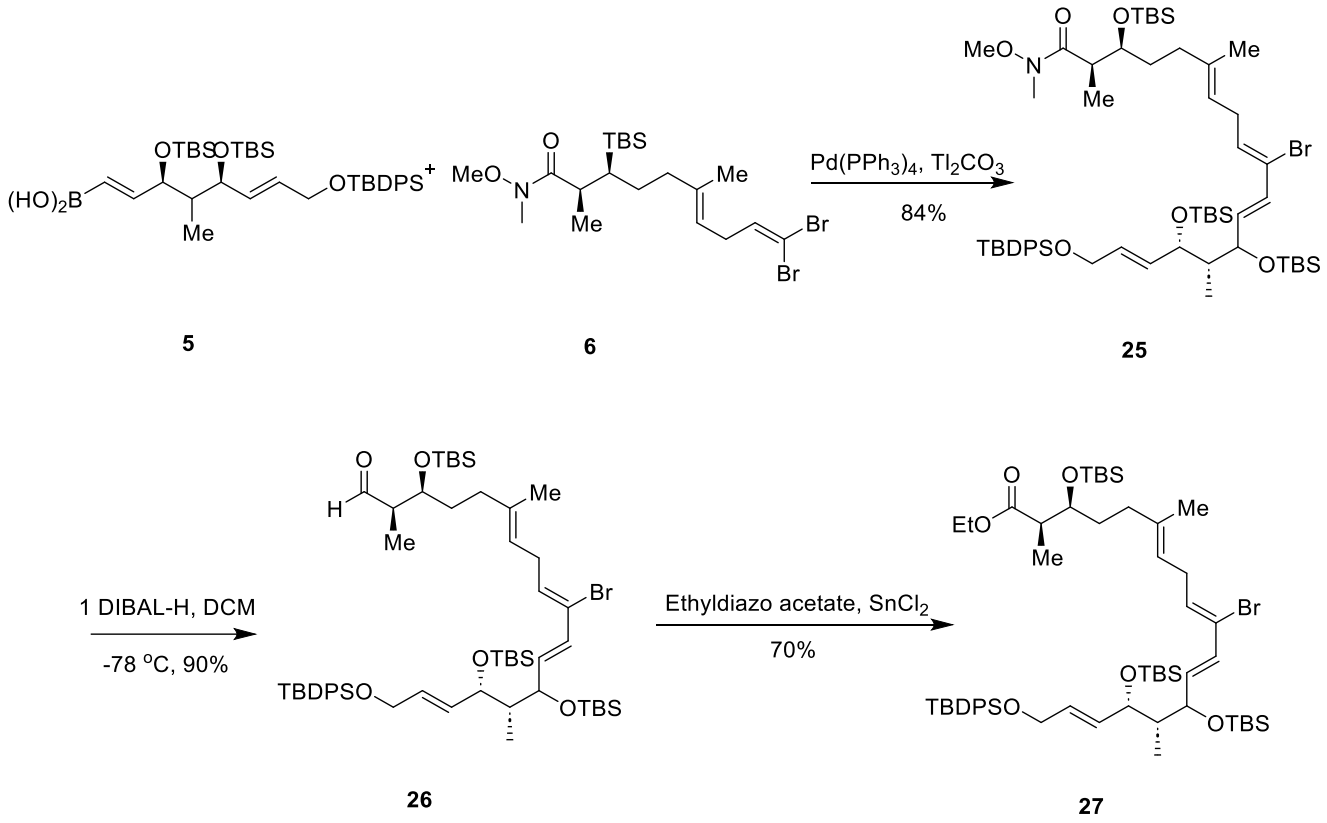
Scheme 1.4: Formation of dibromide fragment

The synthesis of boronic acid **5** was commenced with an aldol reaction between **17** and **16**, yielding the desired *syn* adduct **21**. The adduct **21** was then transformed to amide **22**. The compound **22** was treated with ethynylmegnesium bromide to get the acetylenic ketone, which is reduced by DIBAL-H to produce alcohol **23**. The compound **23** was then subjected to double silylation to afford **24**, followed by hydroboration by using catechol borane to furnish boronic acid **5** (Scheme 1.5).



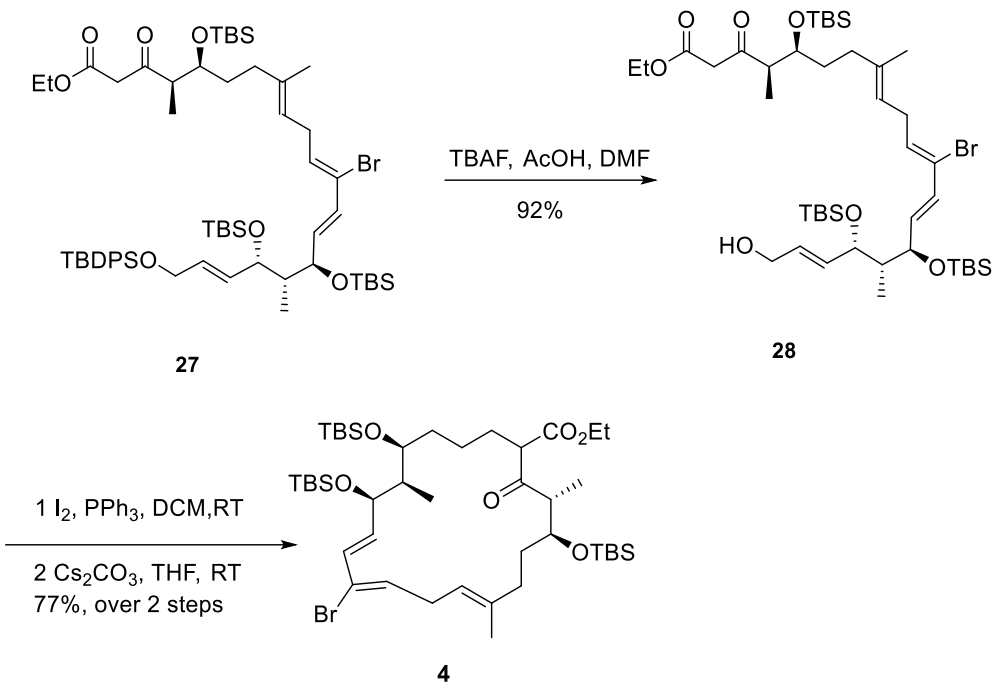
Scheme 1.5: Synthetic pathway towards boronic acid synthesis

The yield of amide **25** was improved through the Suzuki coupling of **5** and **6** in the presence of palladium complex ($Pd(PPh_3)_4$) and Tl_2CO_3. Various bases were tested, but Tl_2CO_3 became the best choice for coupling under optimised conditions. The aldehyde **26** was achieved by the reduction of amide **25** via DIBAL-H (Scheme 1.6). The resulting aldehyde was then subjected to Roskamp homologation by treating it with ethyl diazoacetate in the presence of $SnCl_2$, resulting in the formation of keto ester **27**.



Scheme 1.6: Formation of macrocyclisation precursor

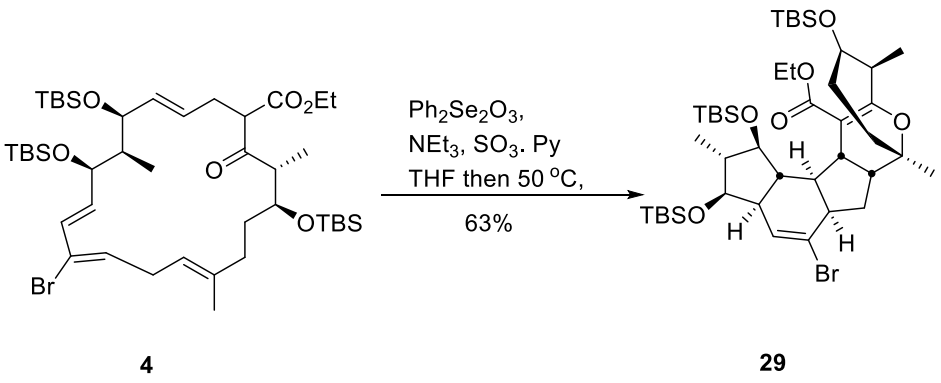
The precursor **28** of macrocyclisation was obtained by the selective deprotection of **27**. The resulting intermediate was then iodinated using iodine in the presence of PPh_3 and DCM at RT. The iodinated intermediate underwent macrocyclisation in the presence of $CsCO_3$ to afford macrolide **4**. The effectiveness of $CsCO_3$ in this step was attributed to its basicity and ability to function under mild conditions, ensuring the integrity of macrolide **4** (Scheme1.7).[8]



27 28 4

Scheme 1.7: Designed and synthesis of 19-membered macrolide

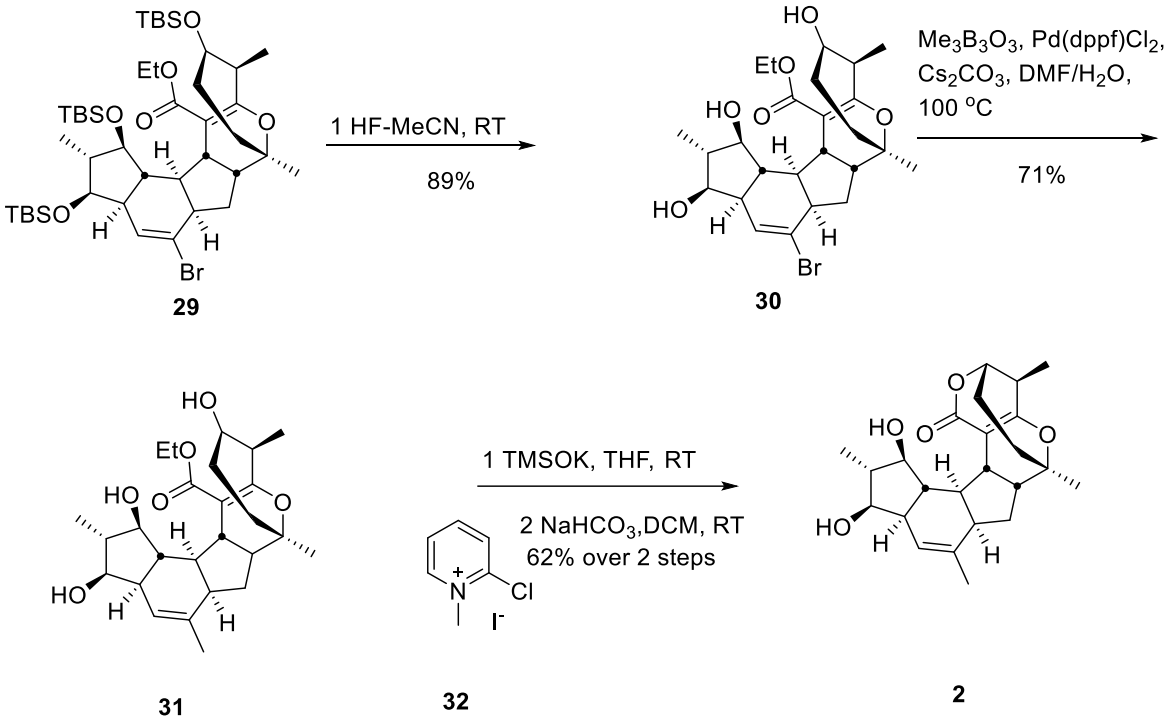
The transformation of **4** to **29** in the presence of $Ph_2Se_2O_3$ involves a sequential process via an intramolecular Diels-alder addition with a 63% yield (Scheme 1.8). In this reaction, $Ph_2Se_2O_3$ facilitates the formation of a reactive intermediate that was necessary for cycloaddition. The IMDA proceeds by forming a cyclic transition state, resulting in the formation of a new carbon-carbon bond within the molecule.



4 29

Scheme 1.8: Formation of pentacyclic ring system

The deprotection of **29** was performed using Gray conditions, resulting in the formation of the desilylation product **30**. The pentacyclic fused ring **30** undergoes methylation to afford **31** by providing Suzuki conditions, which was subjected to saponification and lactonisation in the final step to afford the desired **2** (Scheme 1.9).



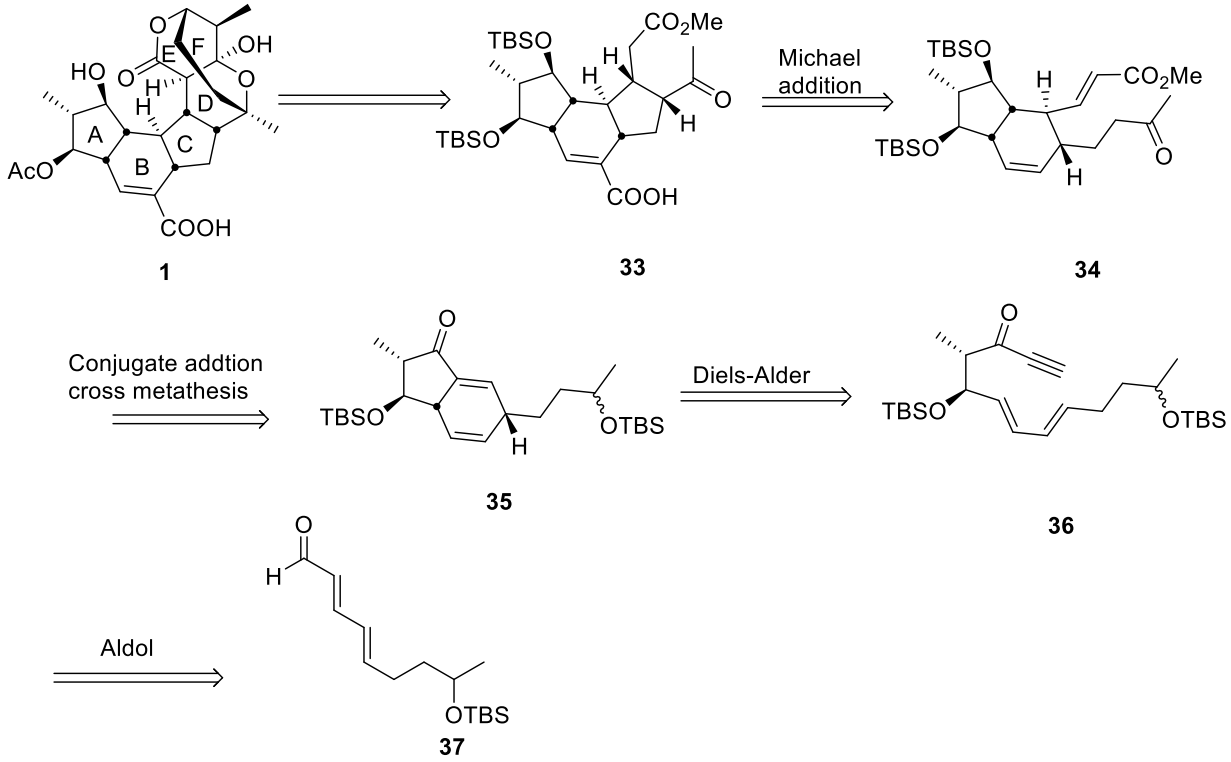
Scheme1.9: Final steps toward the formation of **2**

Evans *et al.* demonstrated that the *endo* transition state was favoured in their synthesis, leading to the exclusive formation of (-)-FR182877.[5] This preference is likely due to the energy barrier associated with the *endo*-transition state, which allows for a more stable transition state in the reaction pathway. Despite extensive efforts to stabilise and attain the *exo* transition state, these endeavours have been unsuccessful.

1.3.2 The synthetic route to the ABC ring system of hexacyclinic acid by Kalesse *et al*.

The synthesis of ABC tricyclic ring system of **1** was first reported in 2004 by Kalesse *et al*.[2] The retrosynthesis of **1** commenced with the ABC ring, by using a Michael addition strategy (Scheme 1.10).

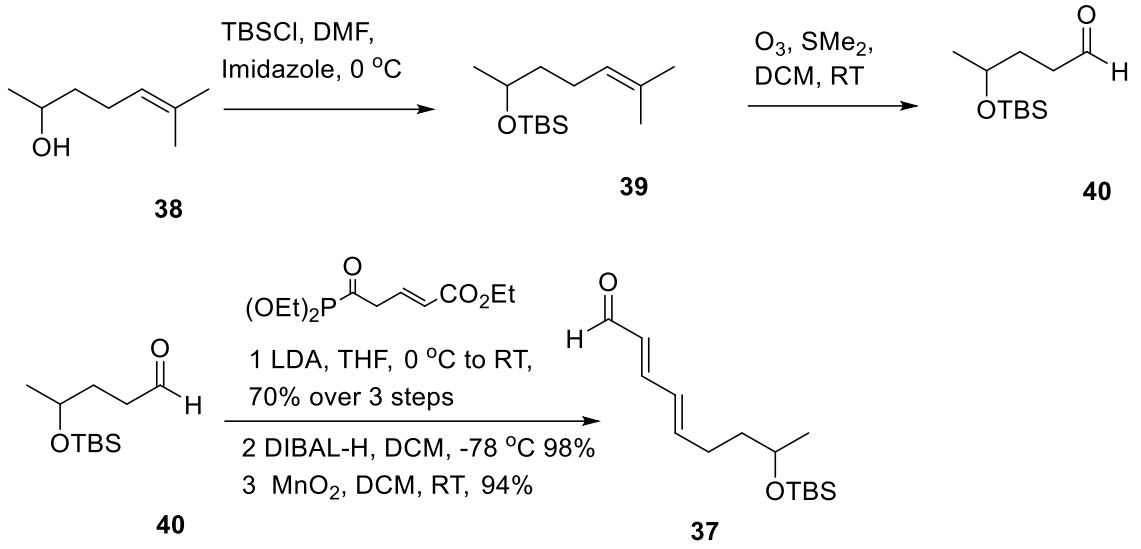
The retrosynthesis began with compound **33** which would be synthesised by using Michael addition of **34**. The compound **34** would be formed from **35** by cross-metathesis reaction. Diels-Alder reaction would be used to afford **35**. The compound **37** would be synthesised *via* aldol condensation.



Scheme 1.10: Proposed retrosynthesis of ABC ring

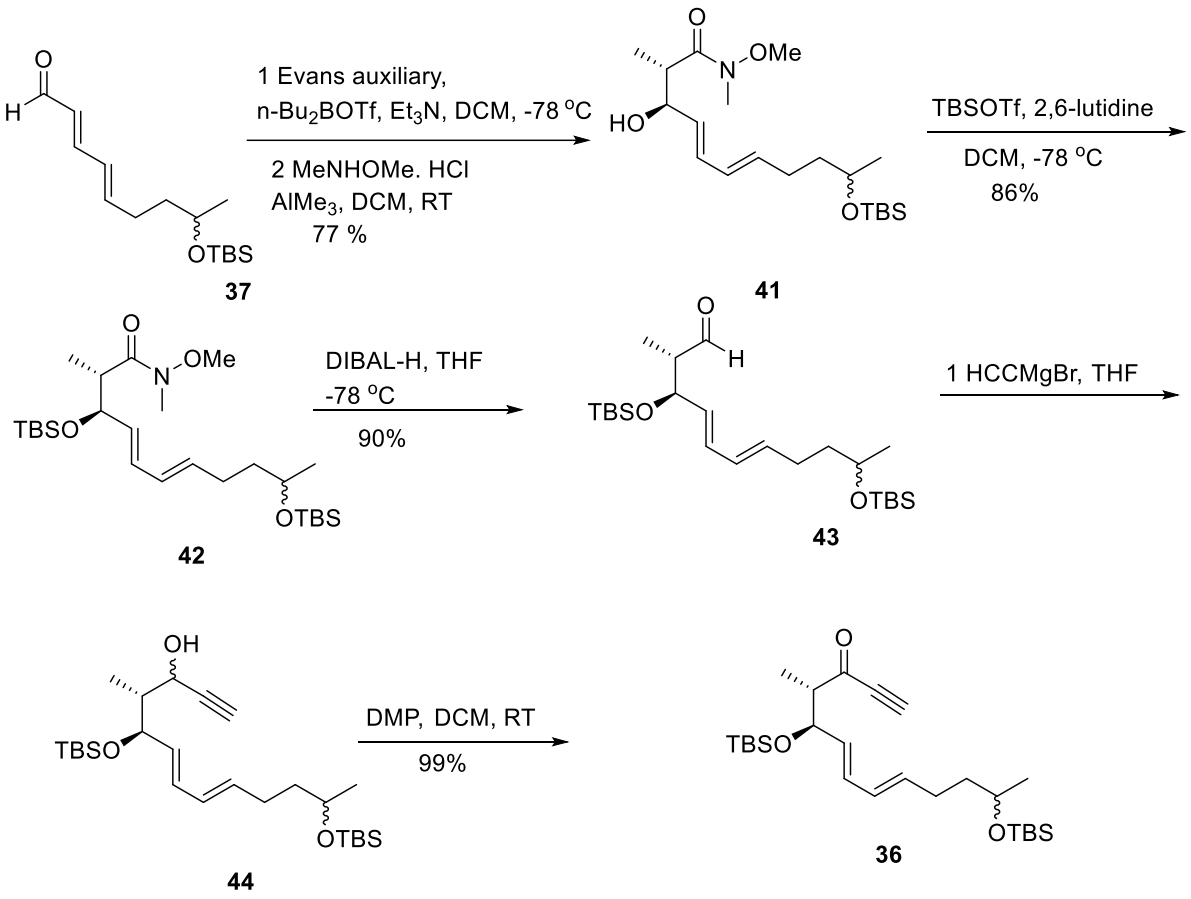
The racemic alcohol **38** was used to synthesise compound **40** (Scheme 1.11), which underwent TBS protection by using TBSCl and imidazole as a base which generated **39**. The compound **39** was then ozonised to yield aldehyde **40**, which was further treated with phosphonate ester under HWE conditions. The resulting ester was reduced by DIBAL-H at -78 ^{o}C and the obtained product was finally oxidised with MnO_2

to produce TBS-protected unsaturated aldehyde **37** with 94% yield.



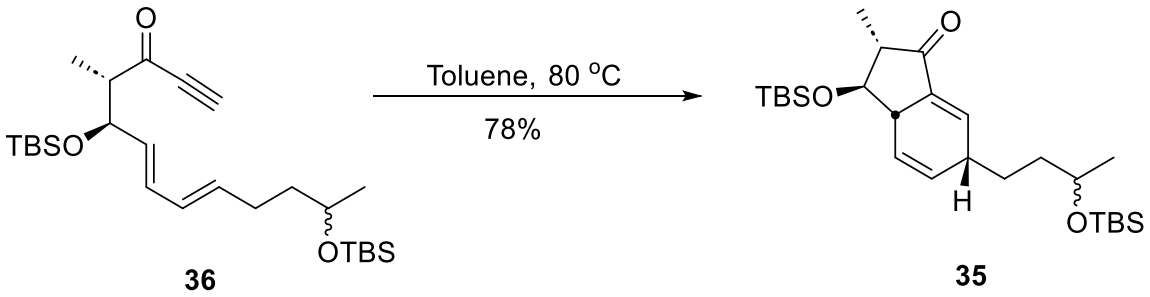
Scheme 1.11: Aldehyde synthesis

The Weinreb amide **41** was synthesised through an Evans aldol reaction of aldehyde **37** with an auxiliary under specific reaction conditions, followed by TBS protection to yield **42**. DIBAL-H mediated reduction of **42** led to the synthesis of **43**, and the addition of alkynylmagnesium bromide generated **44**. This compound was then subjected to oxidation with Dess-Martin periodinane, which led to the formation of **36**, a precursor that was employed for the Diels-Alder reaction in the following step (Scheme 1.12).



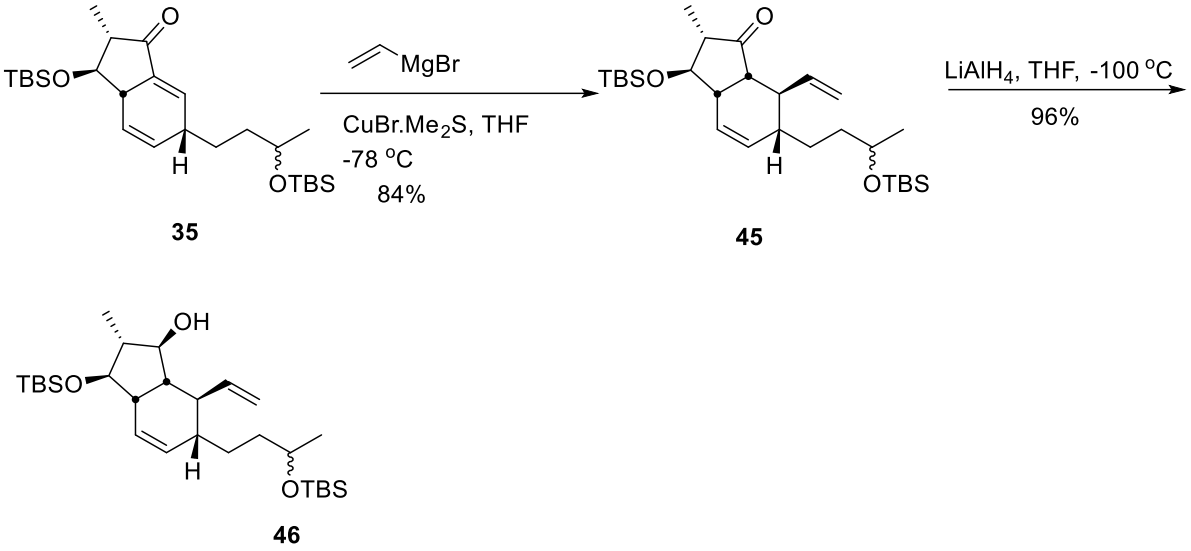
Scheme 1.12: Synthesis of Diels-Alder precursor

The conversion of **36** to bicyclodiene **35** occurred via intramolecular [2+4] cyclisation in toluene at 80 °C, resulting in a yield of 78% (Scheme 1.13).



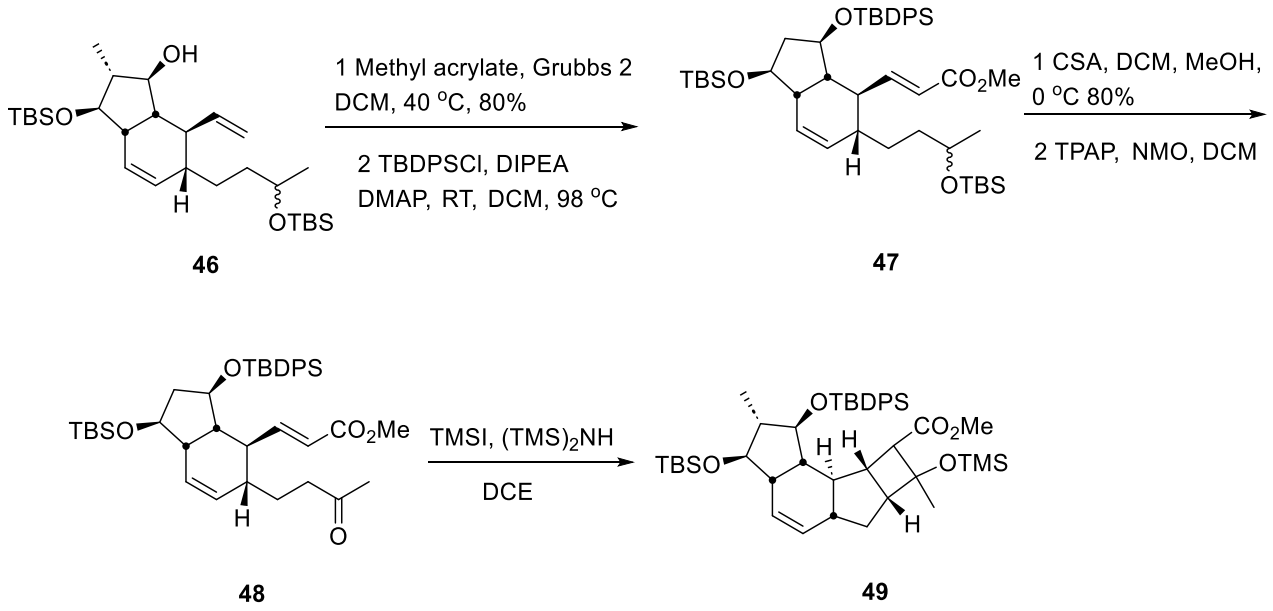
Scheme 1.13: Diels-Alder Reaction

The introduction of a vinyl group on the upper side of the B ring was accomplished by using a copper catalyst at -78°C. This reaction resulted in the formation of the *syn* adduct **45**, which was obtained by a convex face attack. The $LiAlH_4$ was used to reduce **45** to get the desired product **46** with an excellent yield (Scheme 1.14).



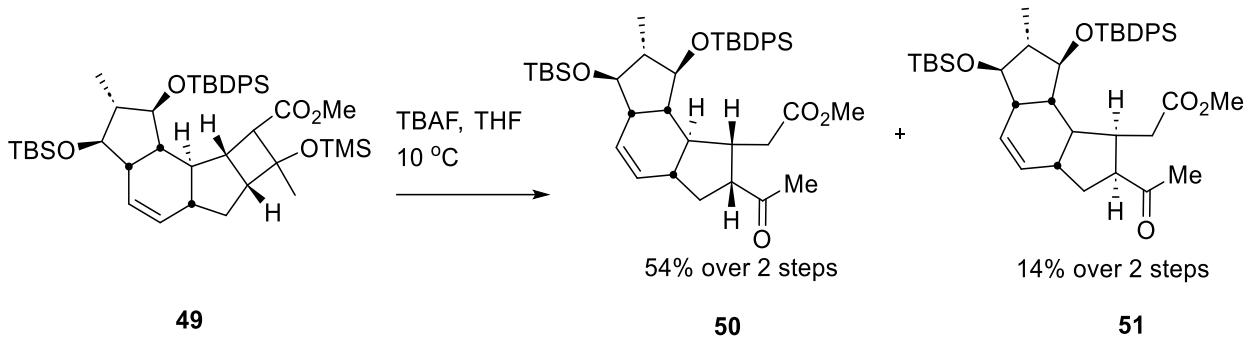
Scheme 1.14: Synthesis of compound **46**

A racemic mixture of esters (*E* and *Z*) was obtained through the cross-metathesis of **46** in the presence of methyl acrylate using Grubbs 2 as a catalyst. The protection of the resulting alcohol was achieved by using a TBDPS ether, and the cleavage of the TBS-ether was achieved in the next step. The resulting compound was then oxidised to **48** with an 80% yield by using Ley-Griffith conditions. The compound **48** was treated with TMSI and $(TMS)_2NH$ to generate an enol that underwent a tandem intramolecular cyclisation reaction in the next step to give the product **49** (Scheme 1.15).



Scheme1.15: Formation of tetracyclic ring System **49**

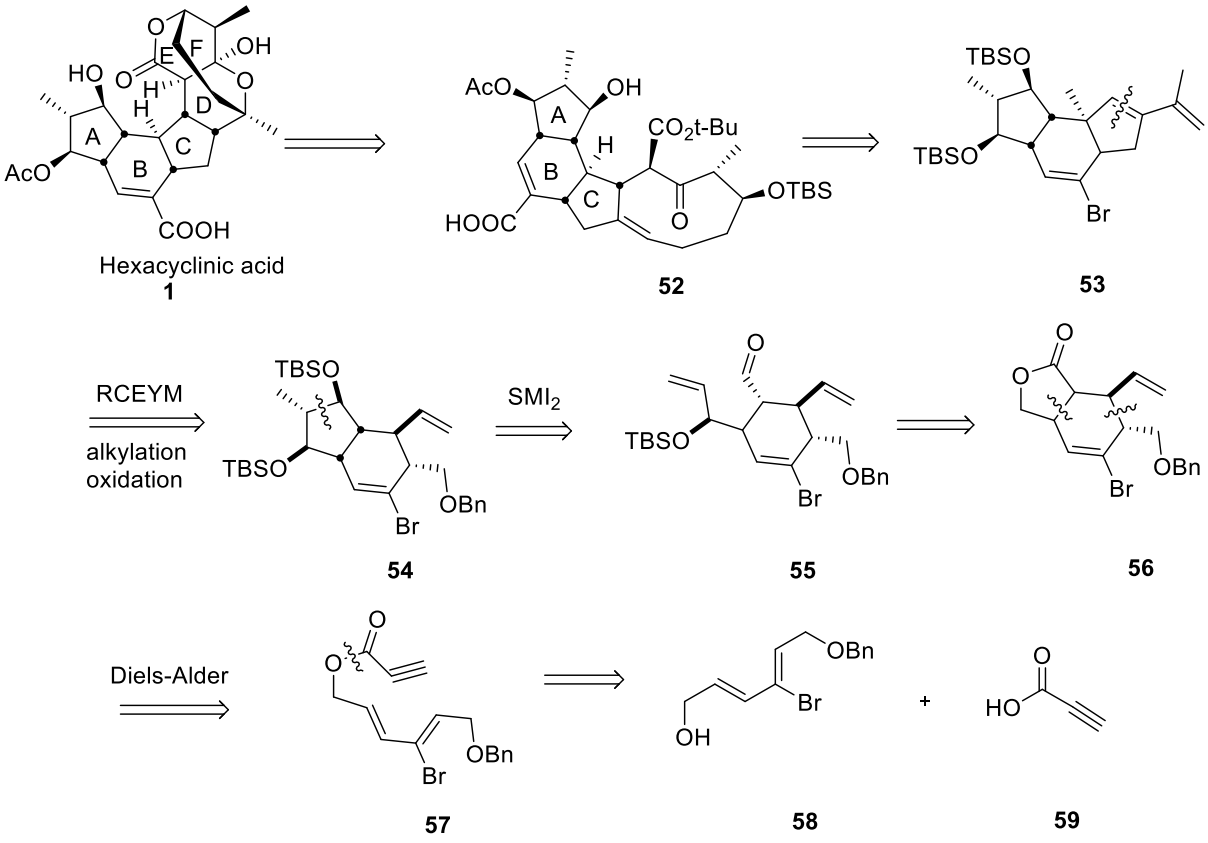
Finally, Compound **49** was converted into the ABC ring system by using TBAF in THF at 10 °C, resulting in the formation of two isomeric products, **50** and **51** (Scheme 1.16).



Scheme 1.16: Synthesis of ABC ring systems

1.3.3 Synthesis of *ABC* ring model by Clarke *et al*.

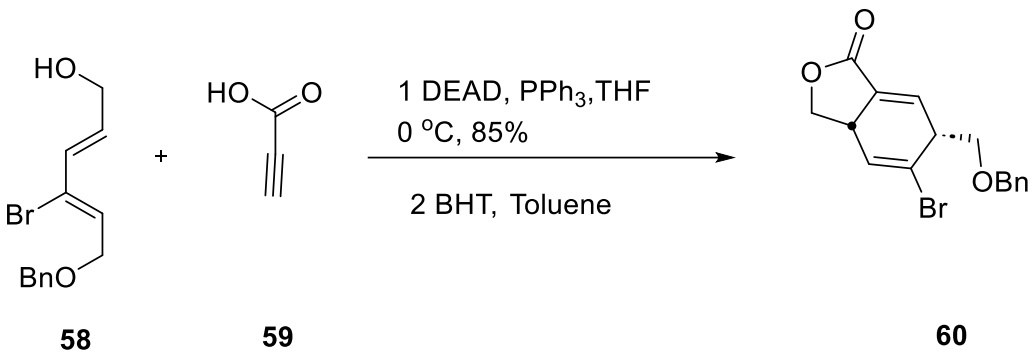
A new approach was adopted by Clarke *et al*. to synthesise the ABC ring system of **1**.[9] The retrosynthetic approach of Clarke *et al.* is outlined below. The 9-membered ring **52** would be achieved via disconnection of lactone and hemiketal, further disconnection of this 9-membered ring led to the formation of the ABC tricycle **53** They utilised a Diels-Alder cyclisation to construct the B ring. The C ring would be formed by an ring closing enyne metathesis (RCEYM) approach through an intermediate which can be built by oxidation and alkylation of **54**. [9,10] Samarium iodide can be a radical cyclisation promoter to close the ring A from cyclohexene **55**. Lactone **56** would be synthesised from the cyclohexene ring **55**. The bicyclic system **56** would be achieved via IMDA reaction from compound **57**, synthesised *via* an esterification approach of **58** with **59** under Mitsunobu reaction conditions. (Scheme 1.17).[11]



Scheme 1.17: Retrosynthesis Proposed by Clarke *et al*.

The synthesis of compound **60** was initiated with a Mitsunobu reaction between compound **59** and alcohol **58** to produce the ester, which was then subjected to an

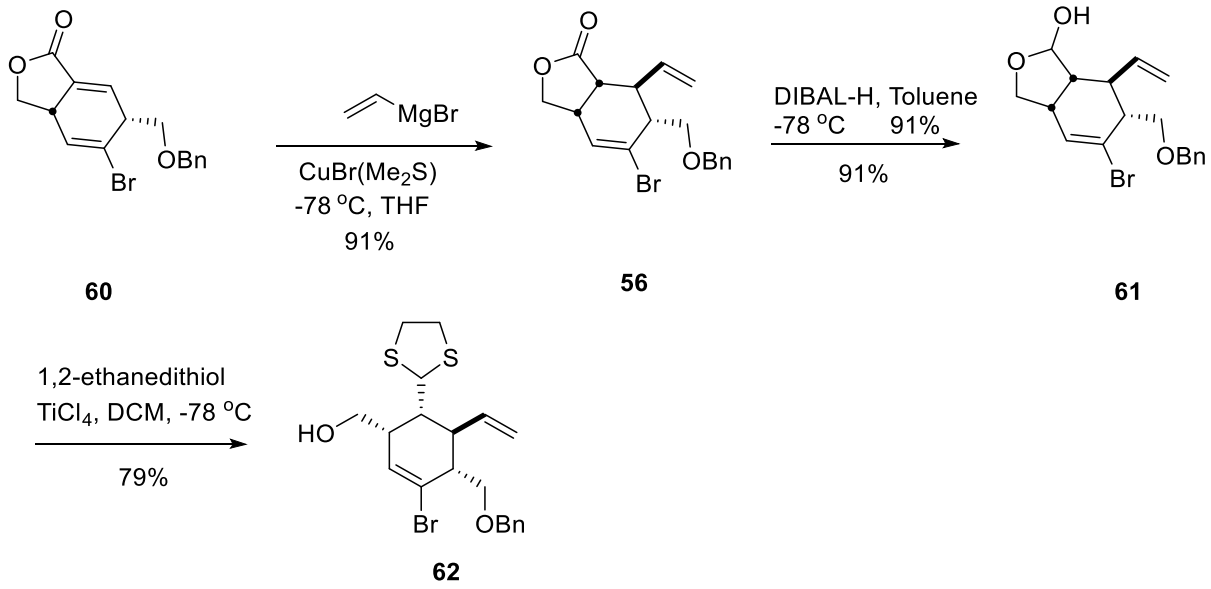
IMDA cyclisation reaction under reflux to furnish bicyclic compound **60** in toluene over a two-step's reaction (Scheme 1.18).



58 **59** **60**

Scheme 1.18: Synthesis of bicyclic compound **60**

The next step was the conversion of **60** into **56** via diastereoselective addition of a Grignard reagent to the α-β unsaturated lactone, catalysed by copper bromide to afford **56**, which was then followed by DIBAL-H reduction to yield the corresponding lactol **61** that was transformed into thiolane **62** in the presence of ethanedithiol and $TiCl_4$ (Scheme 1.19).

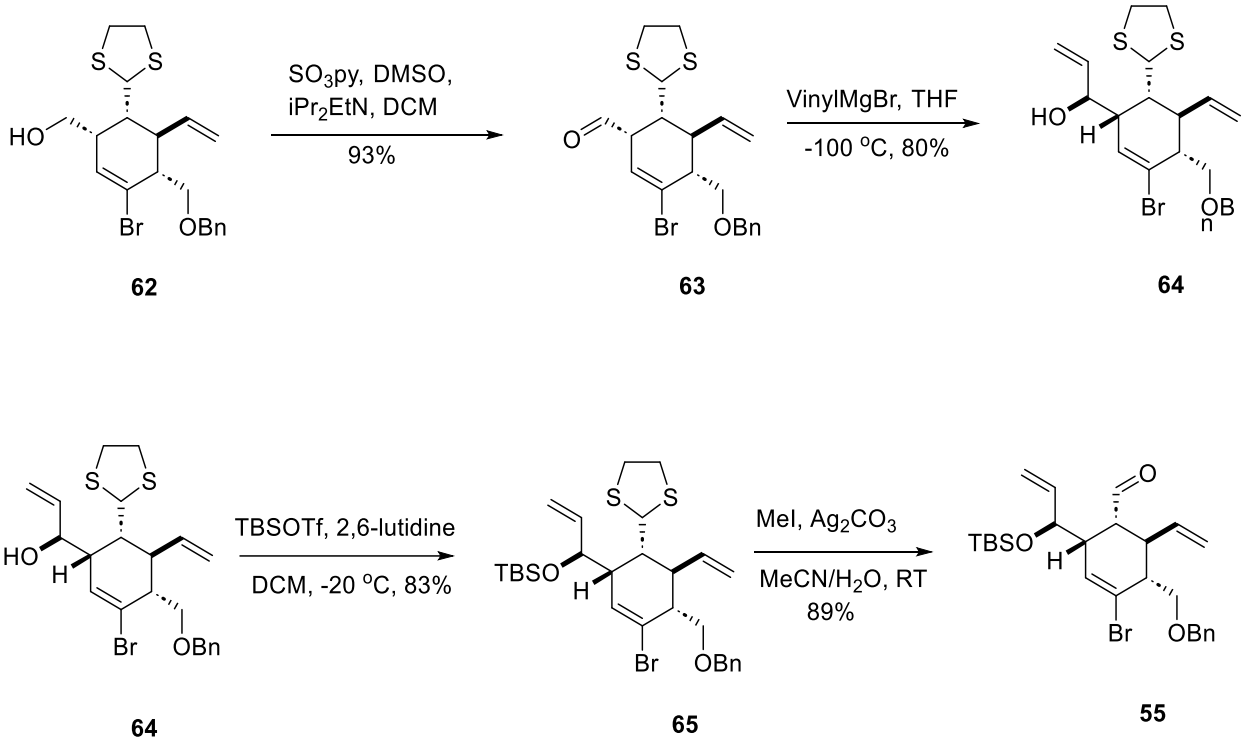


60 **56** **61** **62**

Scheme 1.19: Synthetic route to design fragment **62**

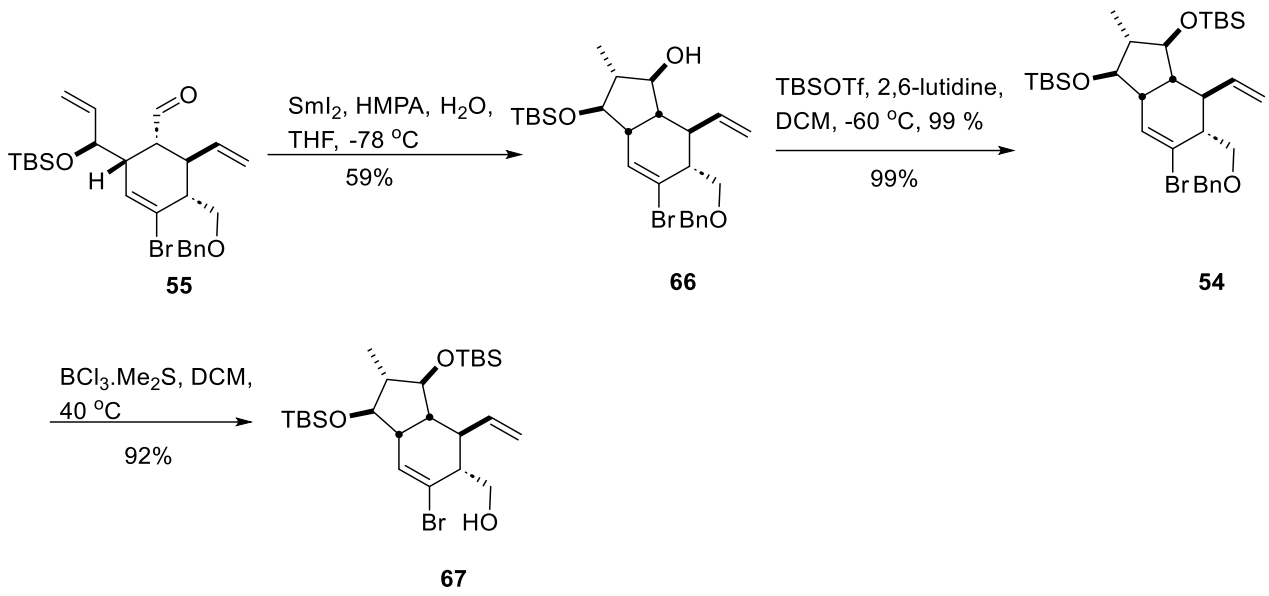
The primary alcohol **62** was oxidised to aldehyde **63** under Parikh-Doering conditions, and then vinylmagnesium bromide was added to convert the resulting aldehyde into the allylic alcohol **64**, yielding a high amount of product in 80% of yield. After that, allylic alcohol **64** was submitted for TBS protection to generate the compound **65**,

which was followed by the removal of the protecting group dithiol to generate the aldehyde **55** (Scheme 1.20).



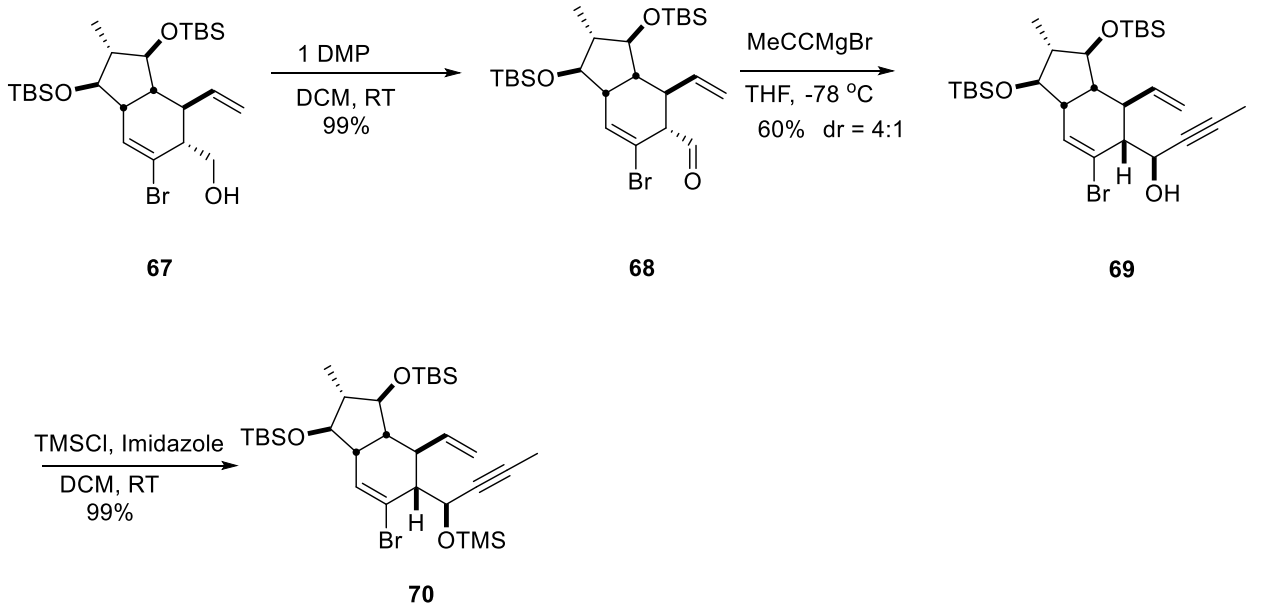
Scheme 1.20: Strategy to design precursor **55**

The desired five-membered ring was formed via a reductive cyclisation approach by using SmI_2 in the presence of catalyst HMPA. This transformation led to formation of trace of undesired diastereomer. The newly formed alcohol **66** was reacted with TBSOTf to yield compound **54**, which was then followed by debenzylation by using boron trichloride to afford the primary alcohol **67** (Scheme 1.21).



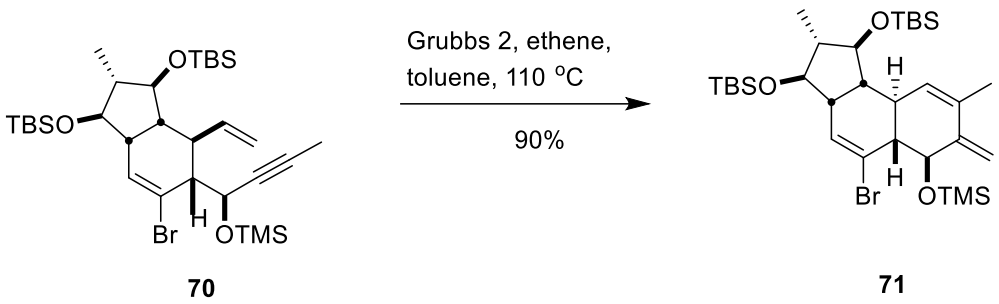
Scheme 1.21: Formation of alcohol **67**

The next step was to oxidise alcohol **67** using DMP, yielding the aldehyde **68**, which was then submitted for alkynylation using a Grignard reagent to afford **69**. The resulting alcohol was then protected by using TMSCl to afford the RCEYM precursor **70** (Scheme 1.22).



Scheme 1.22: Formation of compound **70**

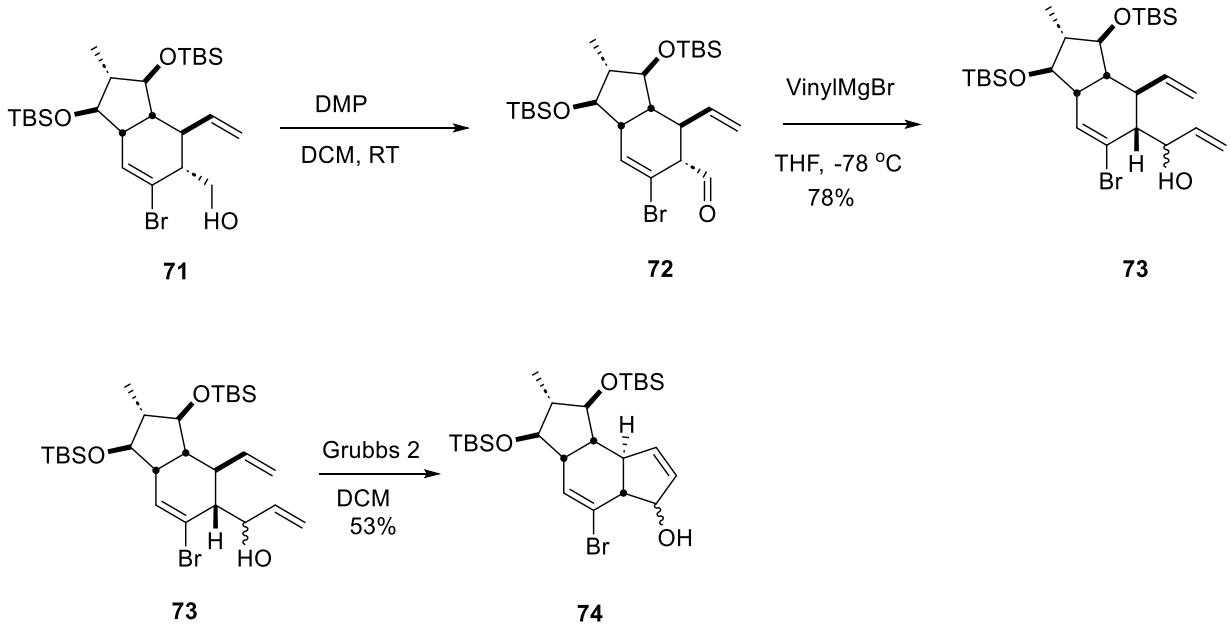
Clarke *et al*. attempted ring closing enyne metathesis on **70**, the undesired cyclohexene **71** was formed (Scheme 1.23).



70 71

Scheme 1.23: Synthesis of **71** by ring closing metathesis

To afford the allylic alcohol, compound **71** was oxidised to aldehyde **72** under given conditions and then treated with vinylmegnesium bromide to achieve an allylic alcohol **73**. The compound **73** was subjected to RCM in the next step to form the ABC system **74** (Scheme 1.24).



71 72 73

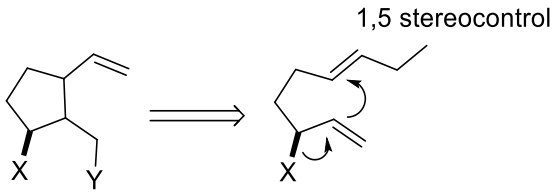
73 74

Scheme 1.24: Synthesis of **74** by RCM

1.3.4 Synthesis of ABC tricycle by Landais *et al.*

To synthesise the ABC tricycle of polyketide **1**, Landais and his co-workers have devised an interesting 5-*exo*-trig radical cyclisation route.[12] This approach employs a 1,6-heptadiene substrate with a bulky allylsilane functionality through a 5-*exo*-trig radical cyclisation. Reasonably high quantities of *trans/cis* isomers were obtained *via*

this radical-mediated method.[12,13] They expanded this tactic to smaller groups in addition to bulky alkyl groups. Smaller alkyl groups promote the formation of more stereoisomers. The allylsilane group was observed to have greater stereocontrol than alkyl and alkoxy groups, indicating that it has an advantage over these groups in terms of stereoselectivity (Scheme 1.25).

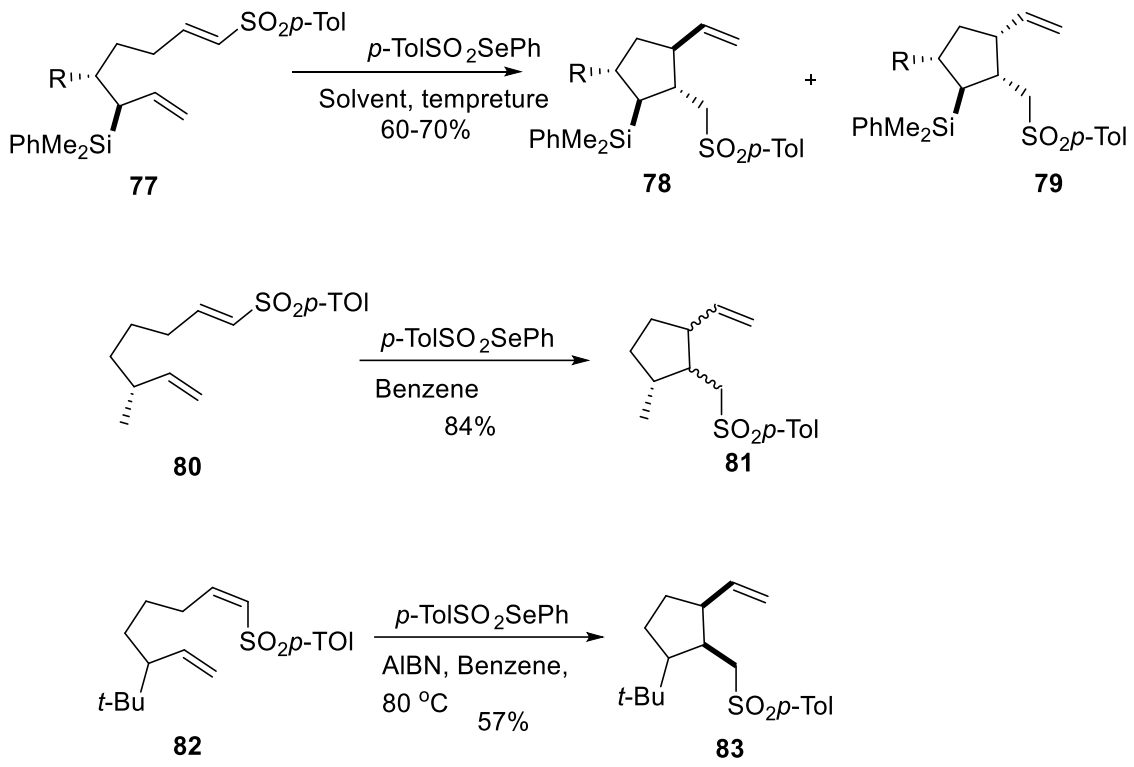


75 **76**

X= SiR_3, Alkyl
Y= *p*-TolSO_2 (Ts)

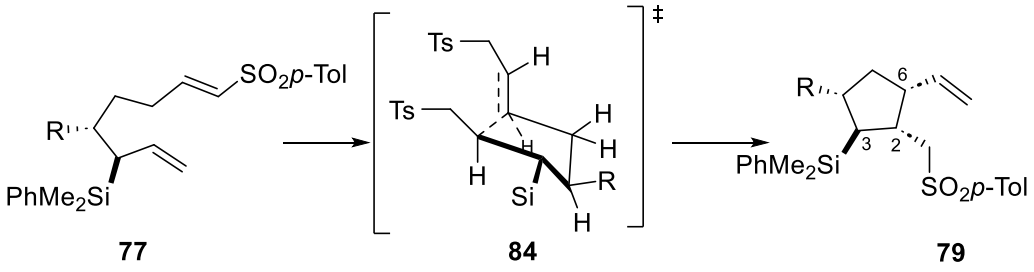
Scheme 1.25: *5-exo* trig cyclisation

To investigate *5-exo* trig radical cyclisation under particular reaction conditions, they first investigated 1,6-diene **77** with a stereogenic centre. Using a catalytic quantity of *p*-TolSO_2SePh, the compound **77** under the 5-*exo* trig cyclisation gives two isomeric products, **78** and **79**, both including *cis*/*trans* and *cis/cis* isomers. To study selectivity more closely, they used compound **80** with a methyl substituent. As predicted, compound **81** was formed as four distinct isomers. The bulky silyl group led to the development of *cis/trans* as the predominant compound. They employed the bulky group *t-Bu* moiety **82**, which provides strong stereocontrol to give the required product **83** (Scheme 1.26).



Scheme 1.26: Examples of *5-exo* trig cyclisation

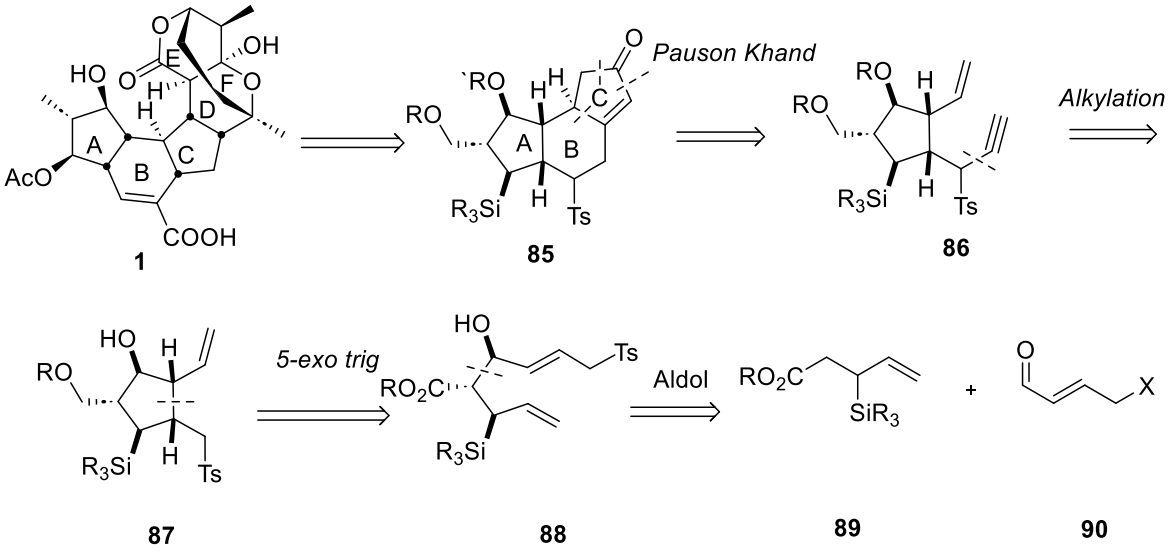
The conversion of compound **77** to compound **79** was shown to exhibit stereoselectivity in the *5-exo* trig cyclisation reaction (Scheme 1.27). This reaction was provided via the transition state **84**, which had a bulky group positioned in the pseudo-equatorial position. This observation aligns with the proposal made by Beckwith and Schiesser.[13]



R= H, CH_2OH, CO_2Me

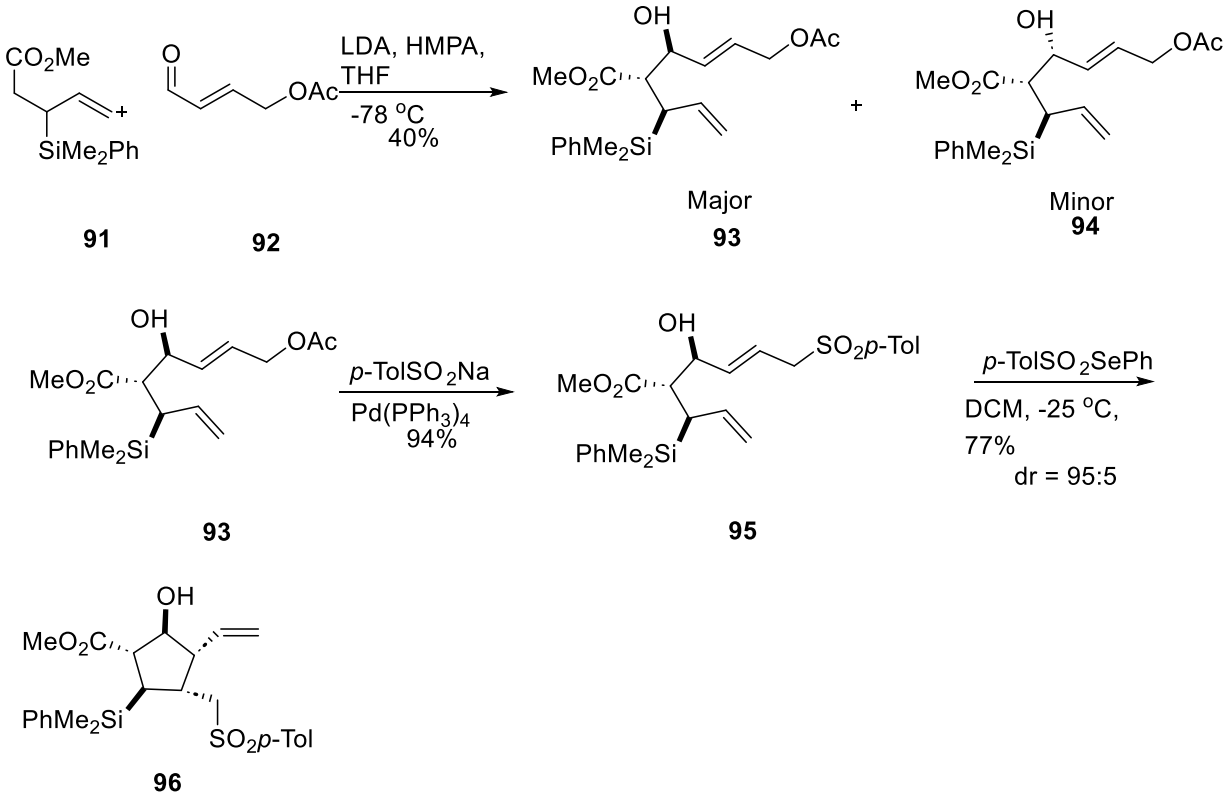
Scheme 1.27: Transition state *5-exo* trig cyclisation

The retrosynthesis of polyketide **1** is initiated with the ABC tricycle **85**, which would be synthesised from **86** by a *5-exo* trigonal cyclisation route and Pauson-Khand reaction. The compound **86** would be synthesised by the alkylation of **87**, which would be produced by a *5-exo* trigonal cyclisation of **88**. The cyclisation precursor **88** would be synthesised by coupling compounds **89** and **90** *via* an aldol reaction (Scheme 1.28).[12]



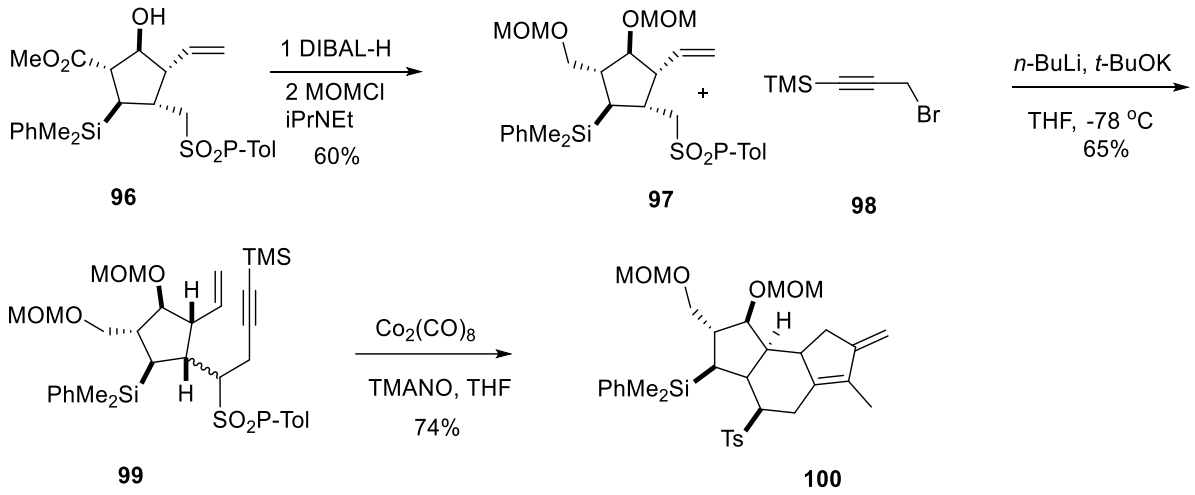
Scheme 1.28: Retrosynthesis of **1** by Landais *et al*.

The aldol reaction between aldehyde **92** and enolate **91** produced a combination of aldol product **93** as a major stereoisomer. In the presence of $Pd(PPh_3)_4$, compound **93** was subjected to sulfonylation by using *p*-$TolSO_2Na$ to generate sulfone **95**. Cyclopentane **96** was the main product of the cyclisation process from the sulfone **95** (Scheme 1.29).



Scheme 1.29: Synthesis of cyclopentane system via 5-*exo* trig cyclisation

The corresponding cyclopentane **96** was converted into MOM-protected cyclopentane **97** before alkylation in a two-step reaction. The initial step involves the reduction of DIBAL-H to produce a diol, which was subsequently protected in the final step. The alkylated cyclopentane **99** was obtained by treating Grignard reagent under the specified conditions (Scheme 1.30). Ultimately, **99** undergoes Pauson-Khand cyclisation, resulting in the generation of the desired ABC ring in the presence of $Co_2(CO)_8$ and trimethylamine N-oxide.

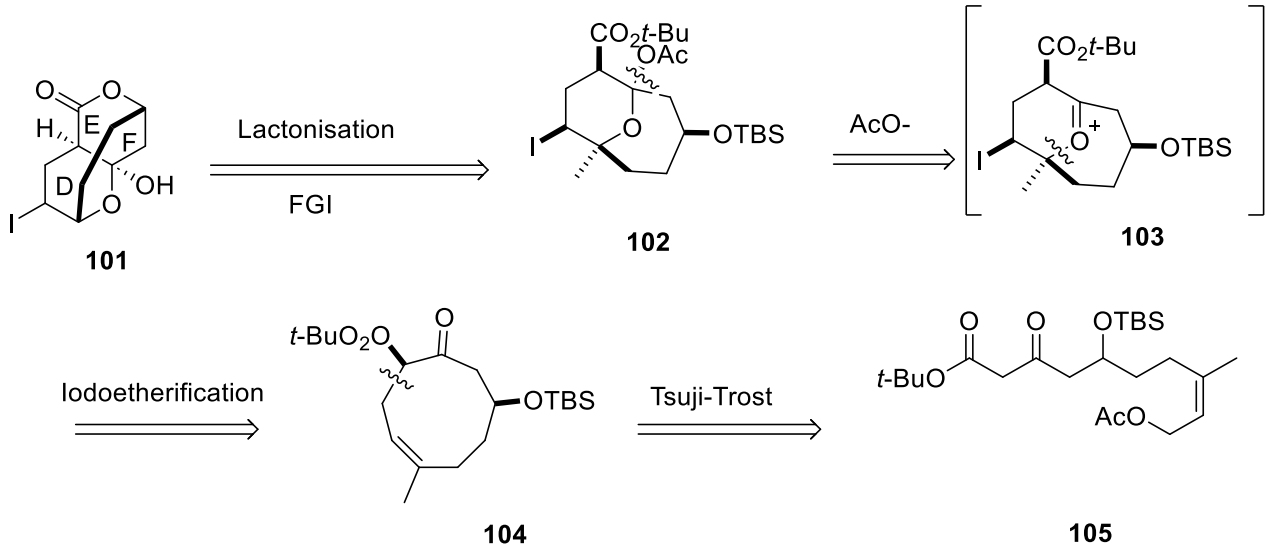


Scheme 1.30: Synthesis of ABC ring system by Landais

The stereoselectivity was presumed to be primarily steric in nature, as evidenced by the entirety of stereocontrol witnessed during the cyclisation. The value of this methodology was ultimately demonstrated through a brief strategy to the extensively modified ABC ring structure of hexacyclinic acid.

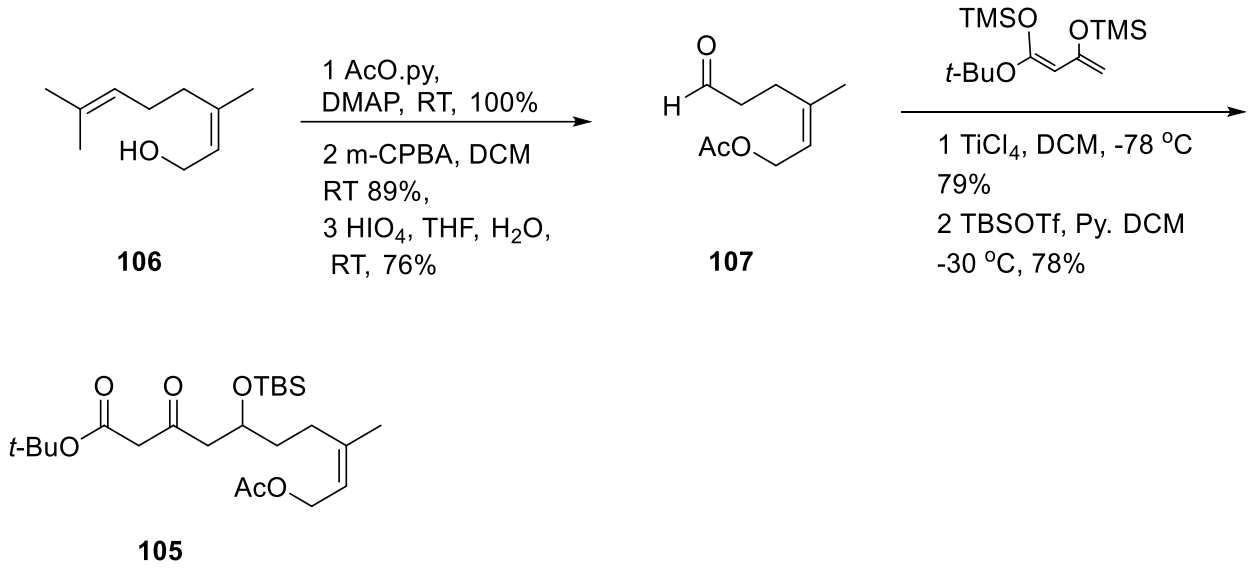
1.3.5 Synthesis of DEF ring by the Clarke Group

In 2005, Clarke *et al.* reported a new route towards DEF ring systems of hexacyclinic acid.[14-16] The retrosynthesis would start with **101**, where the E ring would be formed *via* lactonisation and functional transformations on compound **102**. The formation of this bicyclic hemiketal involves the addition of AcO^- to intermediate **103**, which would be obtained by iodoetherification of compound **104**. The compound **104** would be synthesised using a Tsuji-Trost cyclisation of **105** (Scheme 1.31).



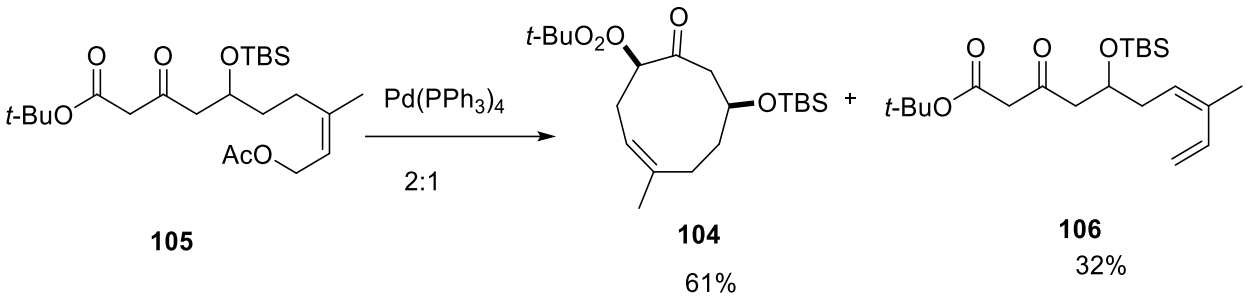
Scheme 1.31: Proposed retrosynthesis of DEF ring systems

Acylation of compound **106** resulted in the presence of pyridine and DMAP, which was converted into an epoxide by using m-CPBA and gave an aldehyde **107** on oxidative cleavage in the next step. The compound **107** underwent Mukaiyama aldol reaction to afford a β-keto ester, which was converted to **105** of the TBS-protection of the resulting compound (Scheme 1.32).



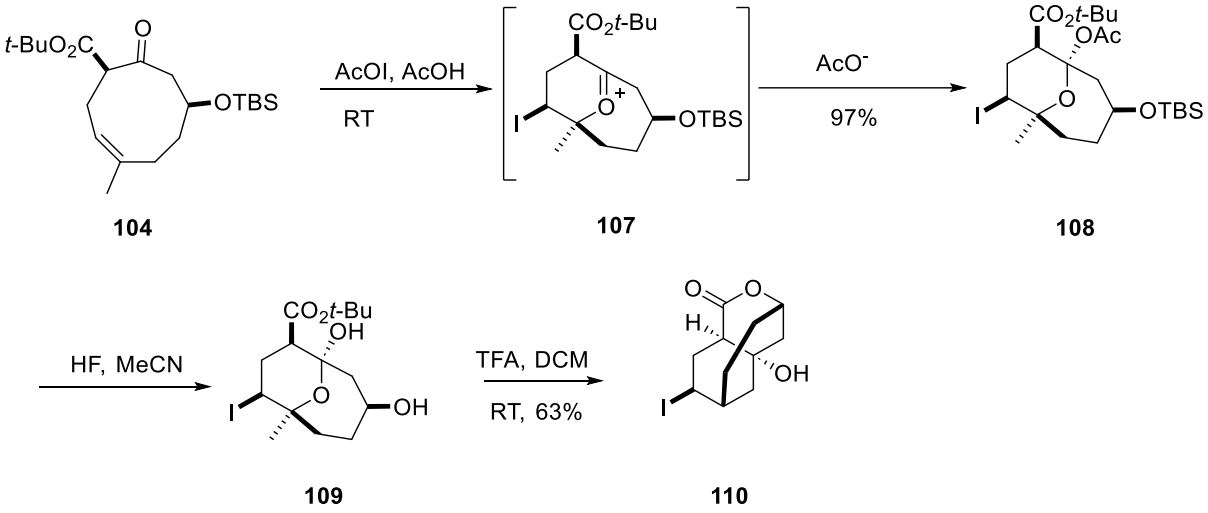
Scheme 1.32: Synthetic strategy to design an ester.

The compound **105** was converted to **104** with a minor amount of **106**, by using Tsuji-Trost (scheme 1.33) reaction, which was catalysed by the corresponding palladium complex ($Pd(PPh_3)_4$.



Scheme 1.33: Formation of compound **104**

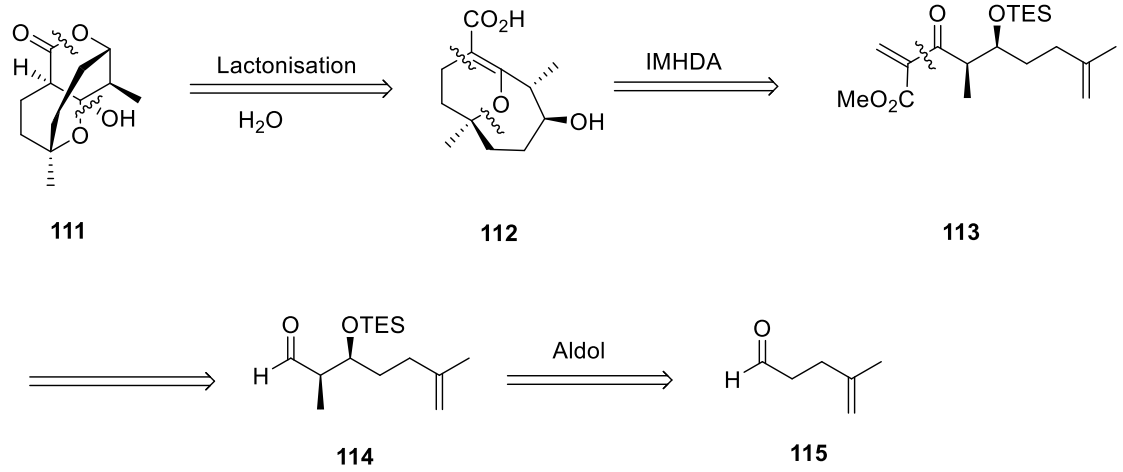
Oxacarbenium **107** was synthesised from **104**. First, AcOI was added to give the iodonium ion, followed by the attack of carbonyl to give oxacarbenium **107**. This compound was then converted to the DF bicycle **108** by the addition of acetate. After treatment with HF, compound **108** was transformed into hemiketal **109**, which then underwent acid-catalysed lactonisation to produce **110** (Scheme 1.34).



Scheme 1.34: Synthesis of **110**

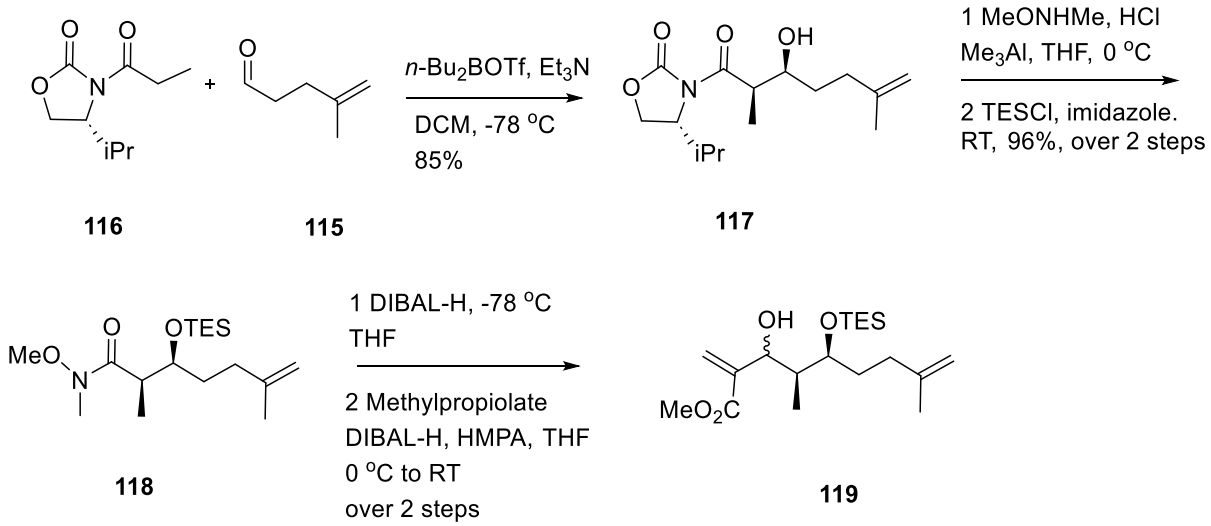
1.3.6 Synthesis of DEF ring by Nakada *et al*.

In 2012, Nakada *et al*. synthesised the DEF ring system of hexacyclinic acid.[17] The retrosynthesis of **111** started by the lactonisation of carboxylic acid **112**, which would be synthesised by cyclisation *via* intramolecular hetero-Diels-Alder rearrangement (IMHDA) from **113**. The compound **113** precursor for the Diels-Alder reaction, would be obtained from aldehyde **114**. Aldehyde **114** would be formed by an Evans aldol reaction from **115** (Scheme 1.35).



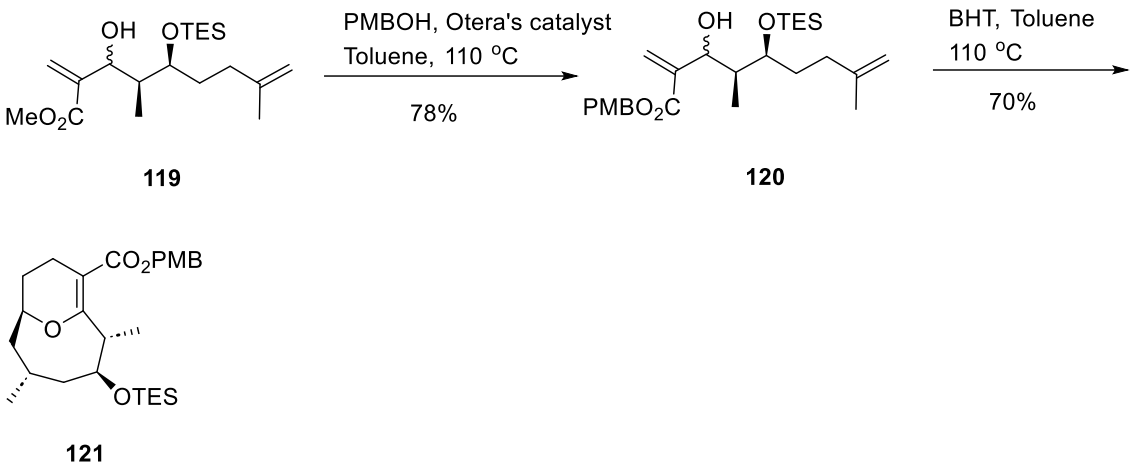
Scheme1.35: Retrosynthesis of **DEF** ring systems by the Nakada group

Aldol **117** was synthesised from aldehyde **115** using an Evans aldol reaction, using *n*-Bu_2BOTf and Et_3N as the base, resulting in a yield of 85%. The aldol **117** underwent conversion into a Weinreb amide, which was then subjected to TES protection in the following phase, resulting in the formation of TES-protected **118**. Compound **118** underwent reduction with DIBAL-H to produce an aldehyde, which was then transformed into alcohol **119** by adding methyl propiolate (Scheme 1.36).[18]



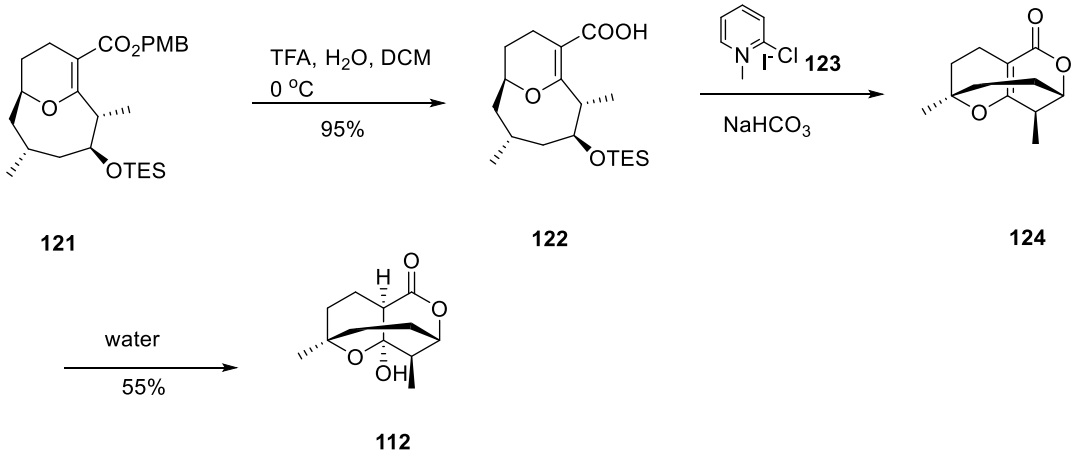
Scheme 1.36: Formation of compound **119**

The conversion of the methyl ester **119** into the PMB ester **120**, which contains an alcoholic group, was achieved using Otera's catalyst.[15] The intended DF bicyclic compound **121** was prepared as the desired isomer by a two-step intramolecular Diels-Alder reaction (Scheme 1.37).



Scheme 1.37: Esterification and cyclisation

The compound **121** was transformed into **122** under given reaction conditions, followed by lactonisation by using Mukaiyama's reagent to yield the DEF ring system of (-)-FR182877, which reacted with H_2O and gave final product **112** as a single isomer (Scheme 1.38).

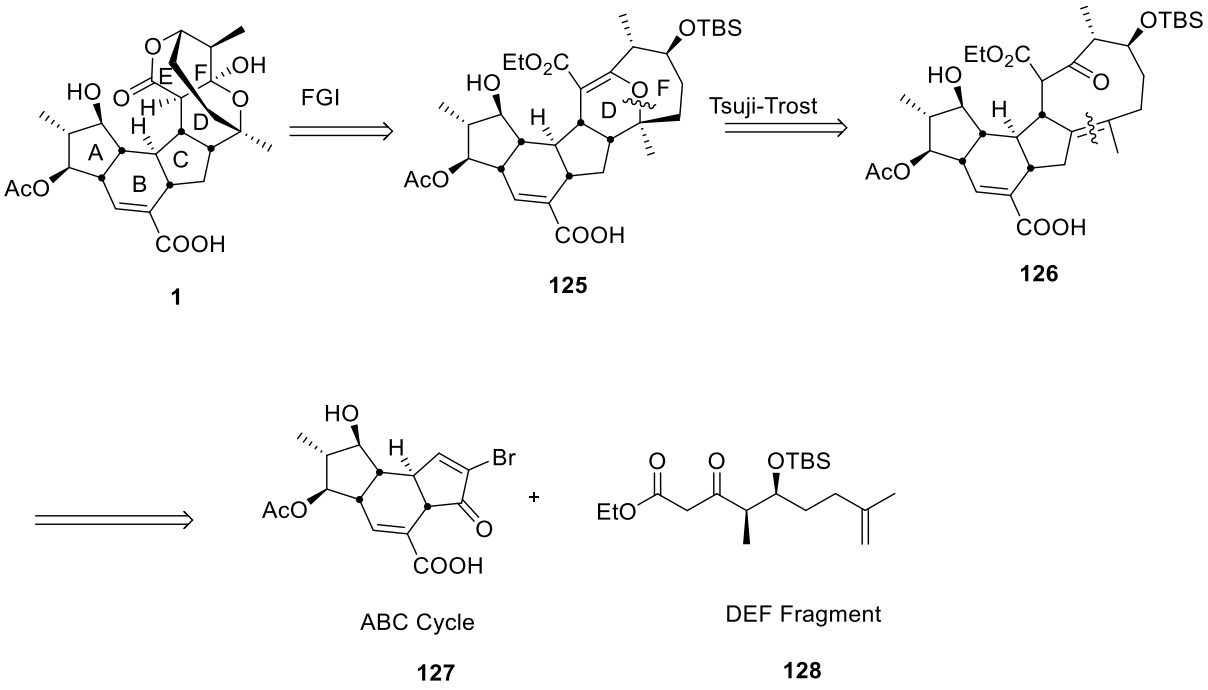


Scheme 1.38: Formation of final Nakada product

2 Previous Work in Prunet Group

2.1 Proposed retrosynthesis

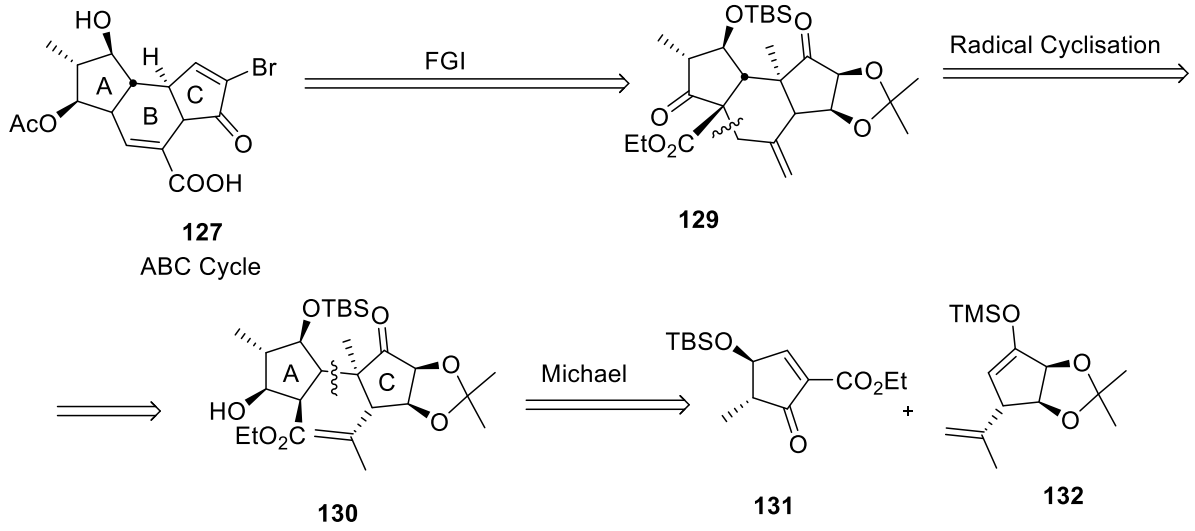
The retrosynthesis of hexacyclinic acid in the Prunet group began with functional group transformation that would form the E-ring lactone. The pentacyclic compound **125** would be synthesised from compound **126** by using Tsuji-Trost reaction (Scheme 1.39).[19,20,21].The compound **126** would be synthesised by a chemoselective addition of the tricycle **127** to **128**.



Scheme 1.39: Proposed synthesis of **1**

Synthesis of the ABC ring system

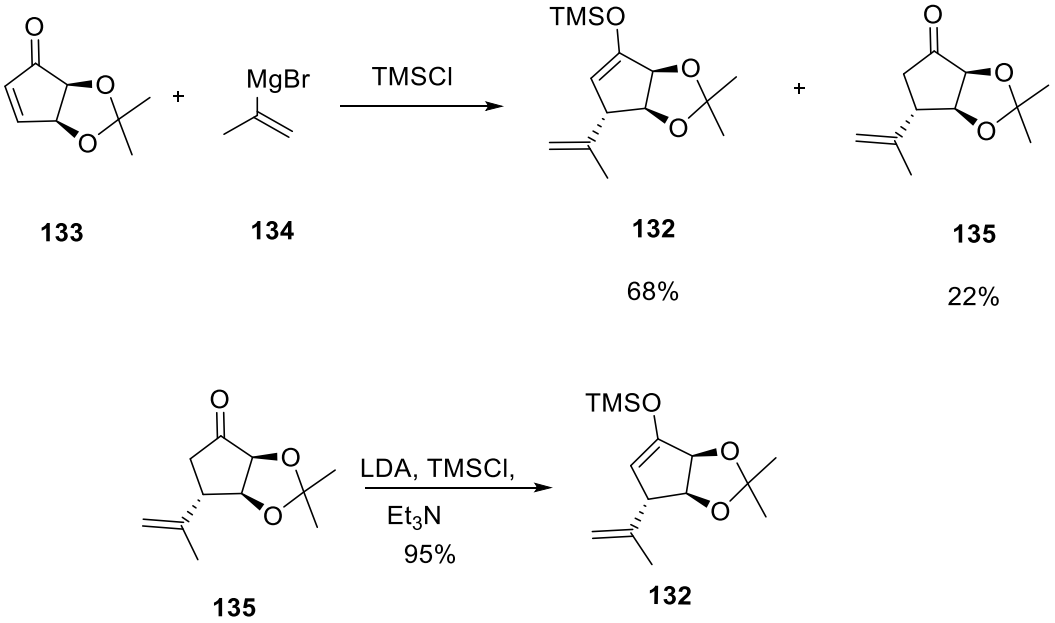
The compound **127** would be formed as the result of functional group interconversions of **129** (scheme1.40), including ester decarboxylation, isomerisation and Corey-Winter reaction. The AB ring would be closed by radical cyclisation of **130**, which would be furnished *via* Michael reaction between keto ester **131** and silyl enol ether **132**.[19]



Scheme 1.40: Retrosynthesis of ABC ring

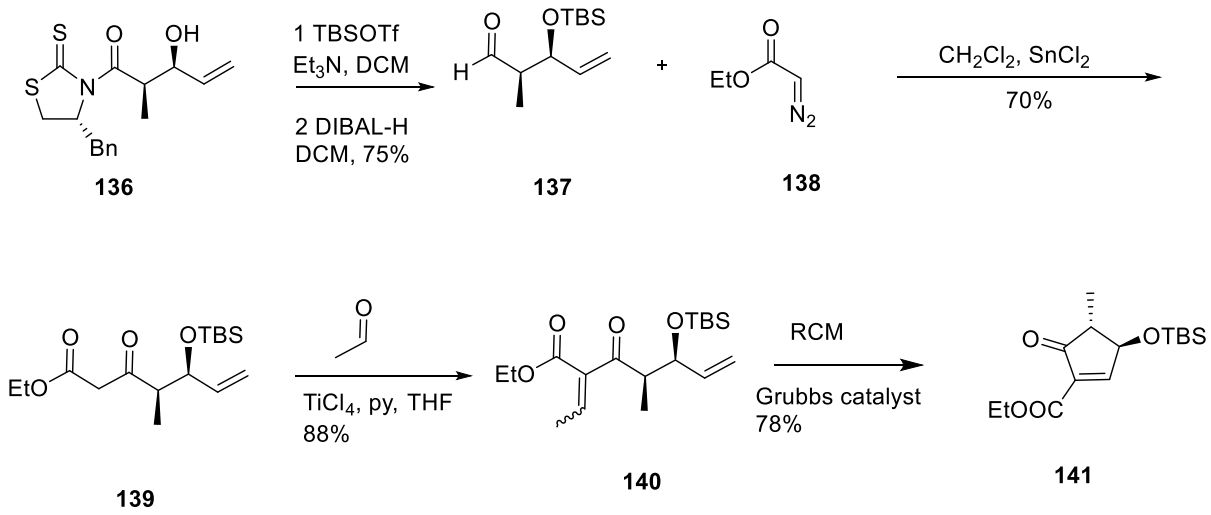
The Michael reaction between compounds **131** and **132** was optimised by using zinc (II) chloride as a source of Lewis acid and *n*-butyllithium to form the corresponding enolate.

The compound **133** was treated with isopropylmagnesium bromide to afford the compound **132**, but it gave a mixture of products, the side product **135** was converted to **132** by using LDA and TMSCl.



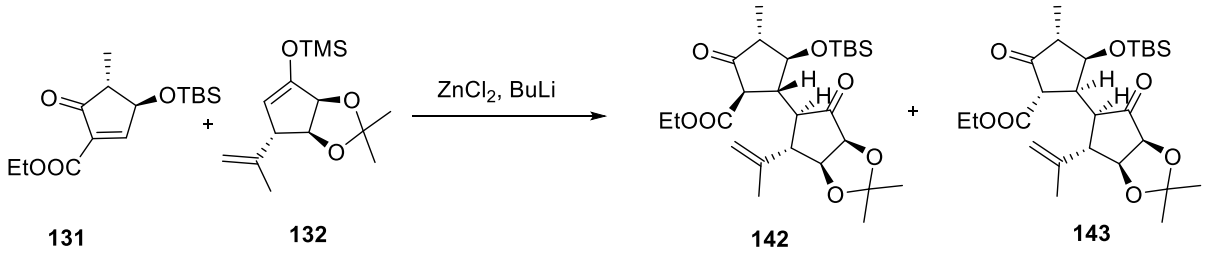
Scheme 1.41. Formation of **132**

Crimmins aldol reaction was used to synthesise Michael precursor **131**. The Crimmins aldol **136** was protected by TBSOTf and then reduced to aldehyde **137** by using DIBAL-H. The compound **137** then underwent Roskamp homologation to give the keto ester **139**, which was further treated with an aldehyde to afford **140**. Finally, the compound **140** underwent RCM to afford **141** (Scheme 1.42).



Scheme 1.42. Synthesis of keto-ester **140**

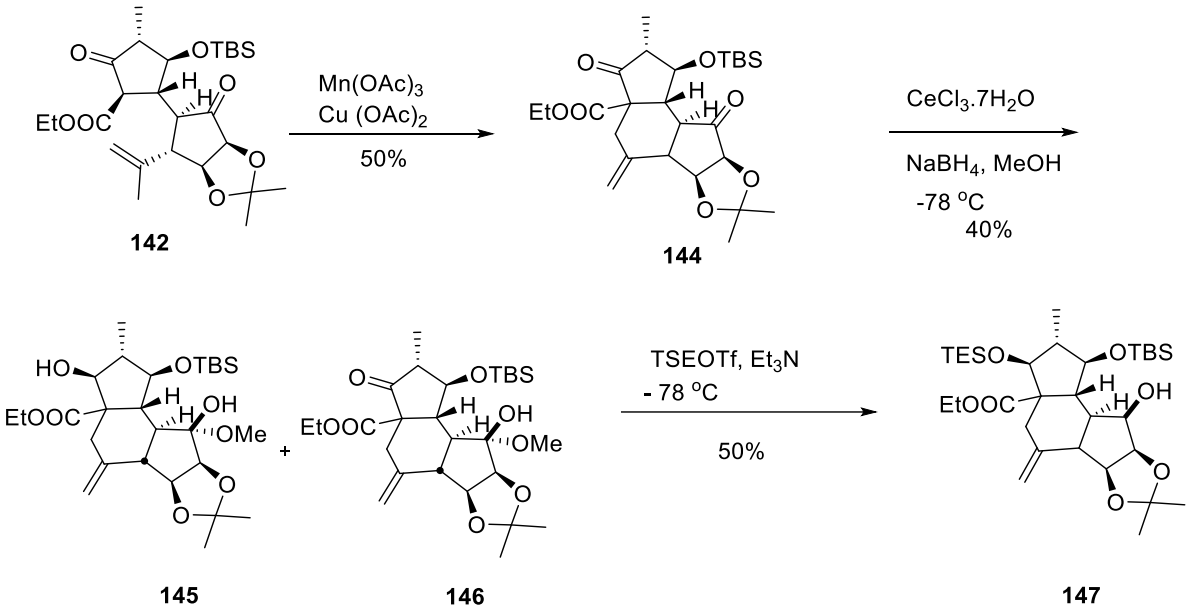
After synthesis of both **131** and **132**, the Michael addition approach was used to connect them by using $ZnCl_2$ and *n*-butyllithium, but it was observed that compound **131** in the presence of *n*-butyllithium gave a mixture of products **142** and **143**. To optimise the reaction selectivity, different solvents were investigated during Michael reaction, DMF/THF gave a good yield with 7:1 ratio of **142** and **143**. The compound **142** gave a stable product as compared to **135**, so they chose the compound **142** for radical cyclisation to afford the ABC tricycle **144** (Scheme 1.43).



Scheme 1.43: Coupling of **142** and **143**

No	Solvent used	Obtained % yield	Ratio
1	Et_2O	60	1:7
2	4:1 THF/Toluene	46	2.5:1
2	4:1 DMF/THF	60	7:1

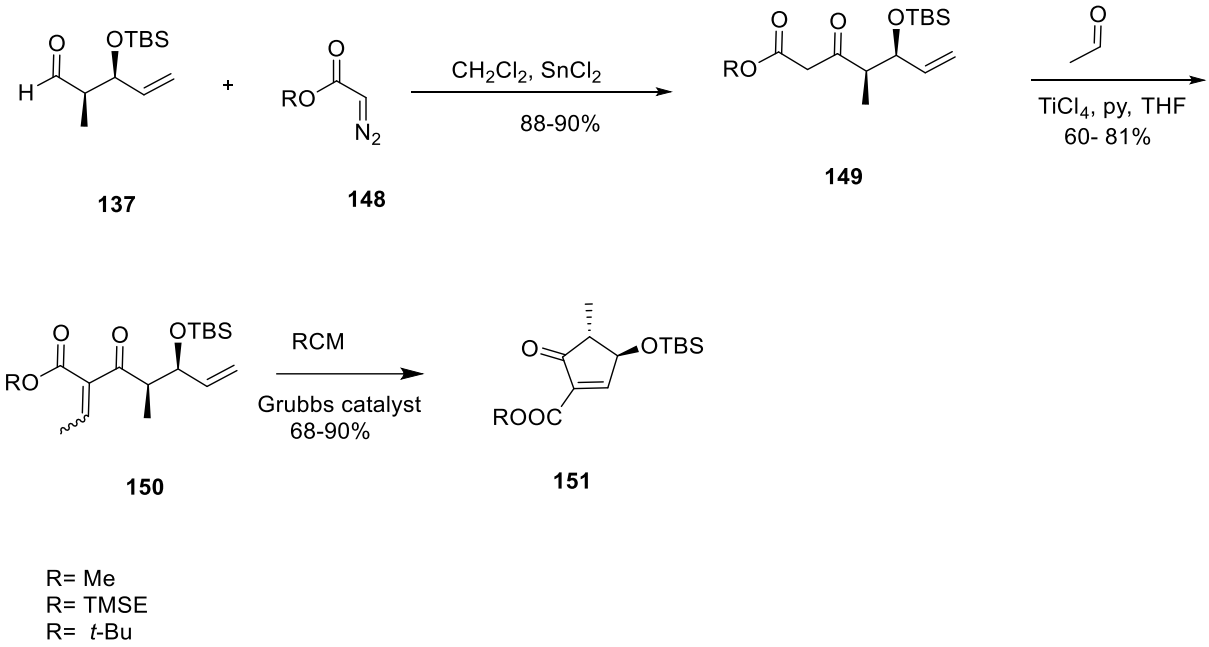
The Michael addition adduct was subjected to radical cyclisation to afford **144**, which was followed by Luche to afford hemiketal **145** and ketone **146**. In the final step, the A ring alcohol was protected as a TES ether (Scheme 1.44).



Scheme 1.44: Formation of **147**

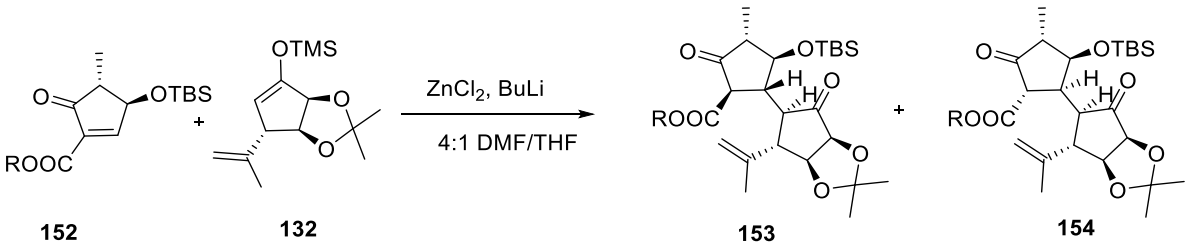
2.2 The significant influence of the ester steric effect on diastereoselectivity

A similar approach was applied to prepare different esters via Roskamp homologation. For this purpose, the aldehyde **137** was subjected to available diazoacetate with different moieties (Me, Et, TMSE, *tert*-butyl). The Roskamp homologation was followed by the Knoevenagel condensation to produce the desired unsaturated β-ketoester **150** (Scheme 1.45**)**. In the next step, the resulting ester was subjected to RCM by using a Grubbs-II catalyst to give the A ring **151**.[22]



Scheme 1.45: RCM of *β-ketoester*

The final step of the study was the Michael addition reaction. Under the previously reported reaction conditions, compound **132** was subjected to Michael addition reaction with different esters. The addition of methyl ester to **132** gave a very poor result of 30% yield, 2:1 ratio of **153** and **154**. While ethyl ester was more convenient to afford a 60% yield and TMSE ester gave 35% yield. Finally, bulky *tert*-butyl ester yields fascinating results without any undesired product. The single isomer obtained *via* this addition yields 55% of the targeted compound. So the steric hindrance played a key role in these conjugate additions (Scheme 1.46).



Scheme 1.46: Michael Addition

No	R	Temp.	Yield	Ratio 153/154
1	Et	-78 ^{o}C	60%	5:1 to 7:1
2	Me	-78 ^{o}C	30-40 %	2:1 to 3:1
3	TMSE	-78 to -20 ^{o}C	35%	3:1
4	*t*-Bu	-78 to -20 ^{o}C	55%	153 only

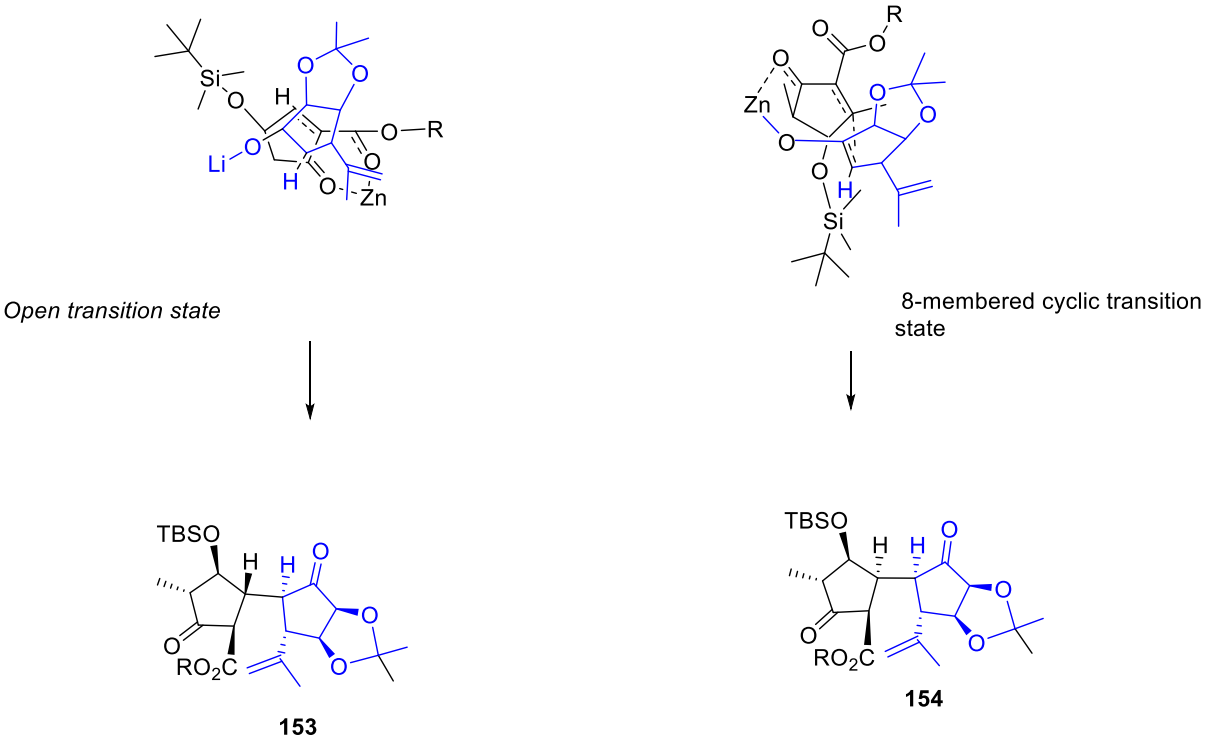
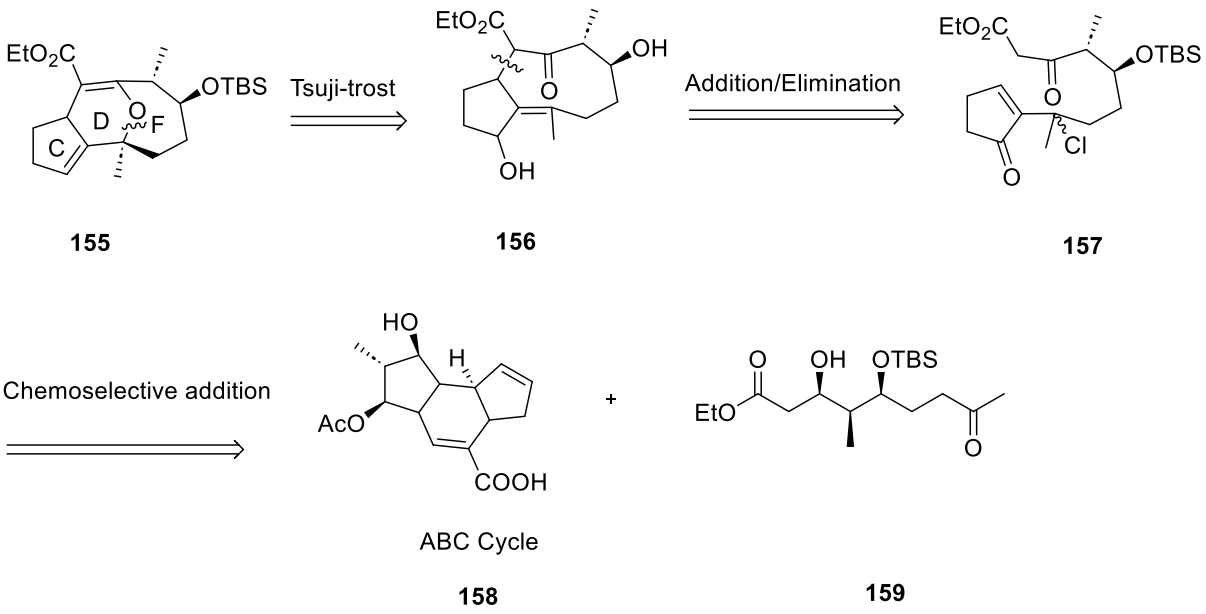


Figure 1.3: Transition states of **153** and **154**

This study revealed that steric hindrance plays a key role in the selectivity of targeted products because transition state leading to the two diastereomers. A bulky group such as *t*-Bu ester gave a better selectivity and the formation of a single product. In contrast, the smaller group with less steric hindrance gave more than one product, so the low selectivity of the less hindrance group was uncovered during this study.

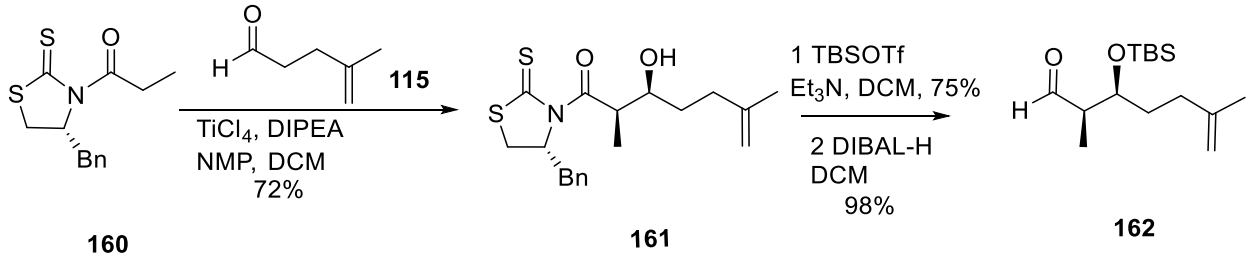
2.3 Synthesis of the CDF ring system in Prunet group

In 2023, the Prunet group published a significant paper on the CDF ring systems of hexacyclinic acid.[23] The combination of these systems was accomplished by using two key reactions: the Michael addition reaction and the Tsuji-Trost reaction. The retrosynthesis began with the formation of **155**, which would be derived from the Tsuji-Trost reaction of the 9-membered ring **156**. This ring would be synthesised from **157** by a Michael elimination process. The compound **157** would be synthesised by linking **158** and **159** using precise reaction conditions.



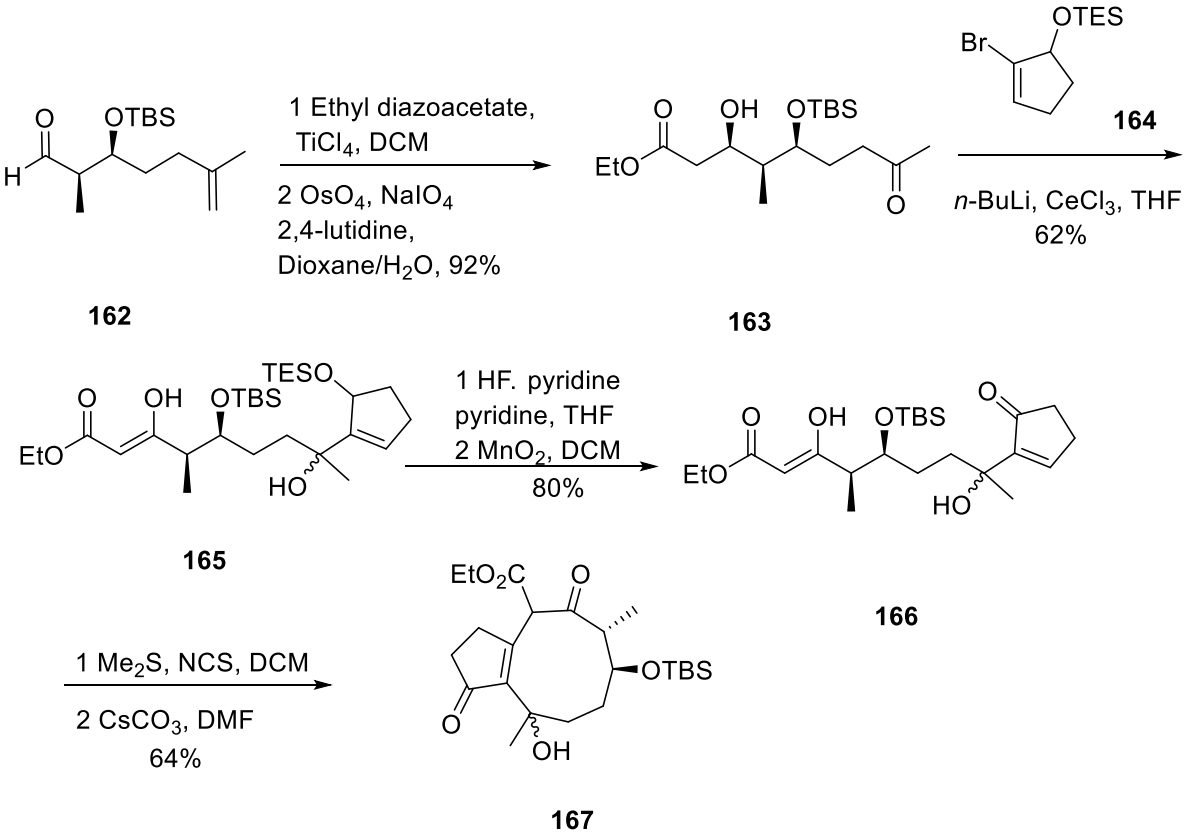
scheme 1.47: Proposed retrosynthesis of CDF ring

To prepare compound **161**, the Crimmins aldol reaction was used, in which compound **160** was treated with an aldehyde **115** in the presence of titanium tetrachloride and N-methyl-2-pyrrolidone. The compound **161** was subjected to TBS protection, followed by DIBAL-H reduction to yield **162** as a single isomer. (Scheme 1.48).



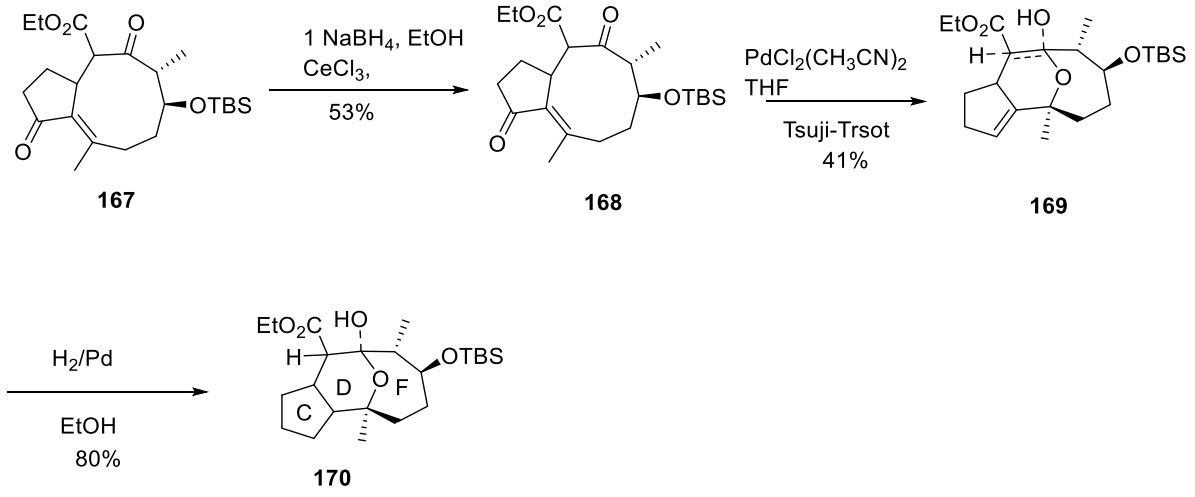
Scheme 1.48: Synthetic route towards formation of TBS-protected aldehyde

The Roskamp homologation, followed by oxidation, was adopted to synthesise the compound **163** from **162**. Then compound **163** was connected with TES-protected 2-bromocyclopentenone to generate **165** by using *n*-butyllithium and activated cerium chloride. In the next step, **165** underwent desilylation to generate *bis*-allylic alcohol, which was followed by oxidation under given conditions to afford **166**. The product **166** underwent chlorination by using Me_2S and NCS, which was then followed by Michael addition/elimination to afford the nine-membered ring **167** (Scheme 1.49).[23]



Scheme 1.49: Synthesis of compound **167**

The 9-membered ring **167** was then reduced to **168**, which was submitted under the Tsuji-Trost conditions in the next step to afford **169**. The compound **169** was submitted to a hydrogenation reaction to achieve the CDF ring system (Scheme 1.50). [23]



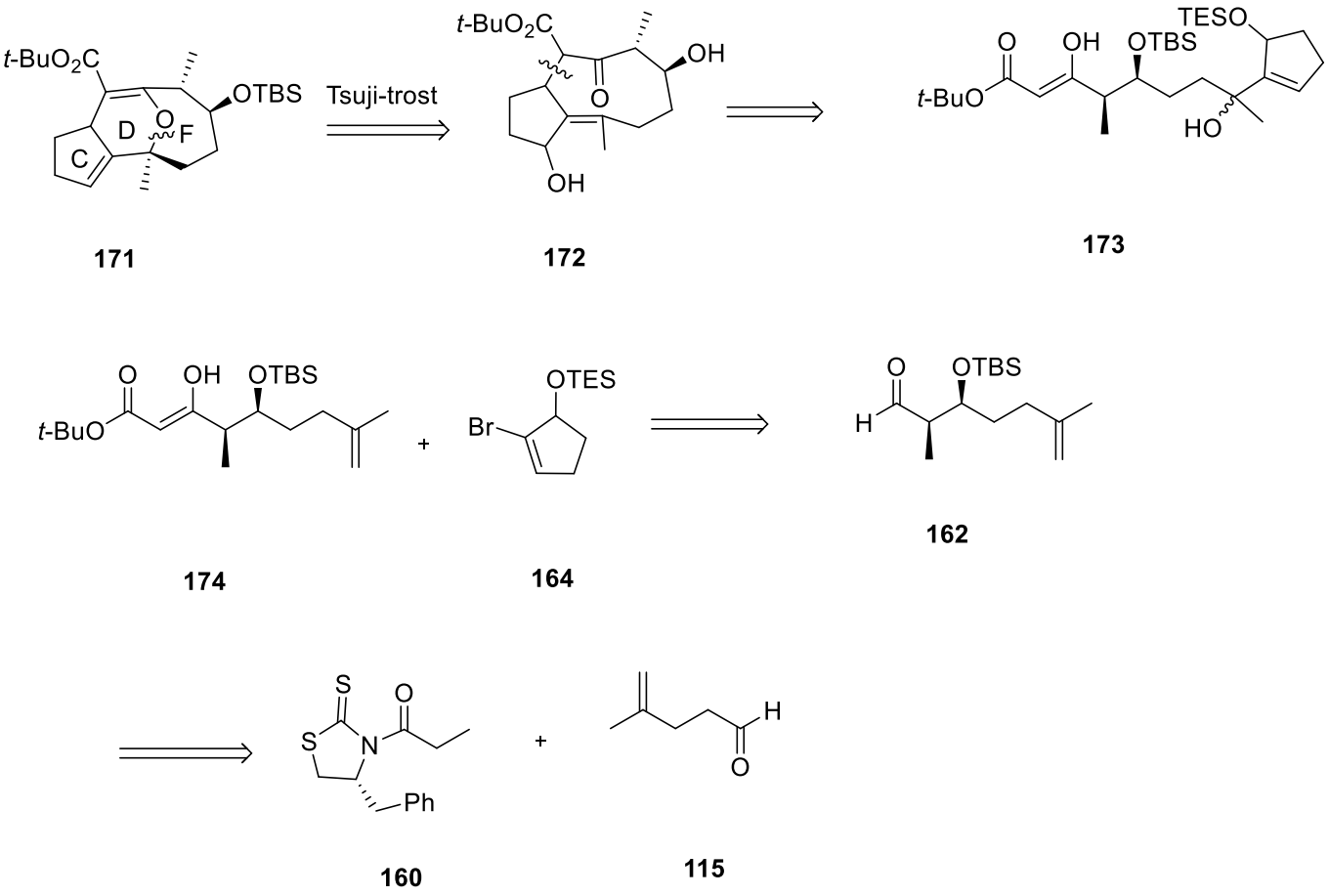
Scheme 1.50: Synthetic route to design CDF ring

3 Aims and Objectives

Project

The basic aim of this project was to synthesise the CDEF fragment of hexacyclinic acid. The CDF ring system was already reported by the Prunet group. To achieve CDEF ring system, the first aim was to construct the precursor of the CDEF fragment to synthesise the E ring we modified the synthetic strategy by using *tert*-butyl ester instead of ethyl ester under acidic conditions which would be a better choice to achieve our targeted E ring lactone as used by the Clarke group. To avoid stereoisomer, we plan to use **164** instead of 2-bromocyclopentenone to obtain a single product because 2-bromocyclopentenone led to formation of undesired stereoisomer.

The first aim was to design the precursor of the CDEF fragment. The compound **171** would be constructed by using acylated Crimmins auxiliary **160** combined with aldehyde **115** to form aldol followed by TBS protection to furnish **162**. The compound **162** would be converted into *tert*-butyl ester by treating it with *tert*-butyldiazo acetate. The final attempt of this project would be the reaction of TES-protected vinyl bromide with **DEF** fragment to generate **171** (Scheme 1.51).



Scheme1.51: Proposed retrosynthesis of **171**

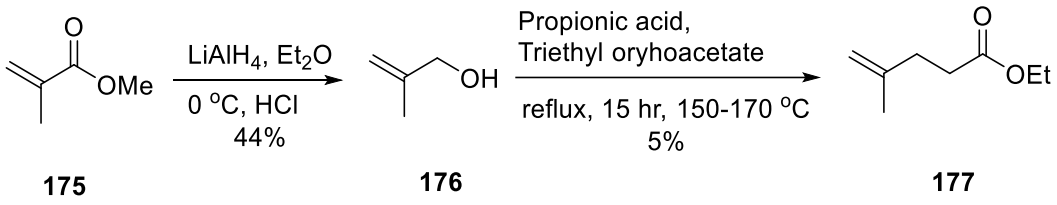
4 Results and Discussion

Synthesis of aldehyde 115

This work was focused on building the CDEF ring system of hexacyclinic acid. The ABC ring system has already been developed by the Prunet group.[21,26]

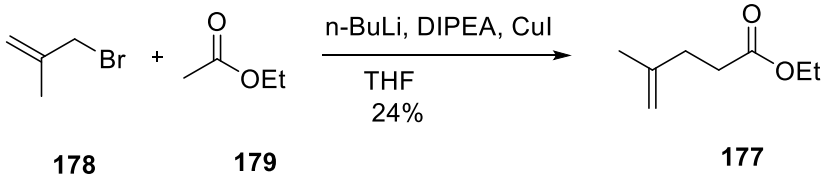
Different synthetic routes were designed to synthesise various fragments of the DEF fragment. The primary objective was to prepare aldehyde **115** for the Crimmins aldol reaction.

To synthesise ethyl 4-methyl pentanoate **177**, methyl methacrylate **175** was reduced to methallyl alcohol **173** by using $LiAlH_4$ with a yield of 44%. In the next step, methallyl alcohol underwent Johnson-Claisen rearrangement to form desired product **177**, but this attempt yielded 5% of compound **177** (Scheme 1.52).



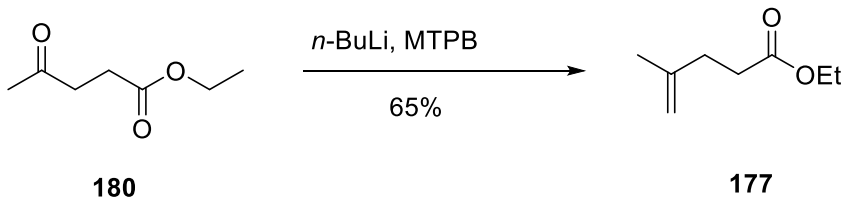
Scheme 1.52: Synthesis of ester

Another attempt was made to form ethyl 4-methyl pentanoate **177** by coupling methallyl bromide **178** with acetate by using *n*-BuLi, DIPEA and CuI (Scheme 1.53).



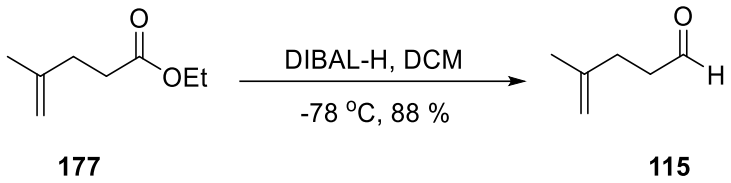
Scheme 1.53: Synthesis of **177**

In a Wittig reaction, ethyl levulinate **180** was converted to an olefin **177** using *n*-butyllithium and methyltriphenylphosphonium bromide. The maximum yield achieved was 65%, sufficient to proceed to the next step (Scheme 1.54).[24]



Scheme 1.54: Wittig reaction

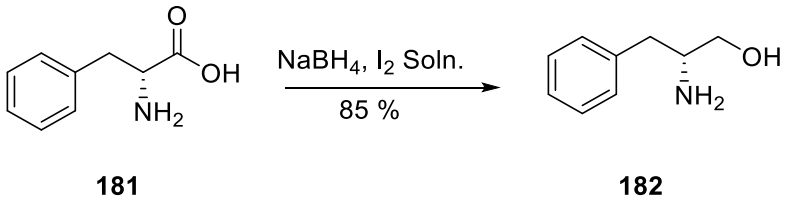
Ethyl 4-methyl pentanoate **177** was subjected to DIBAL-H under given reaction conditions, which led to the formation of the desired aldehyde**115** with 88% yield (Scheme 1.55).[24]



Scheme 1.55: Formation of aldehyde **115**

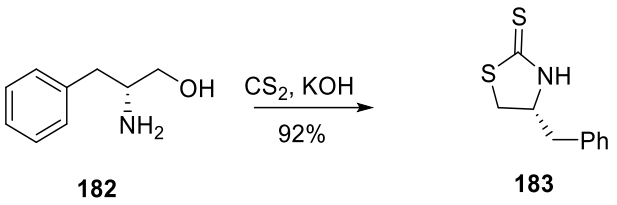
Synthesis of Crimmins auxiliary

(*R*)-4-benzyl-3-propionylthiazolidine-2-thione **160**, the acylated Crimmins auxiliary for the aldol reaction, was constructed in a three-steps reaction. In the first step, (*R*)-phenylalanine **181** was converted to (*R*)-phenylalaninol **182** by sodium borohydride reduction (Scheme 1.56), and the desired alcohol was successfully obtained with 85% yield.



Scheme 1.56: Reduction of phenylalanine

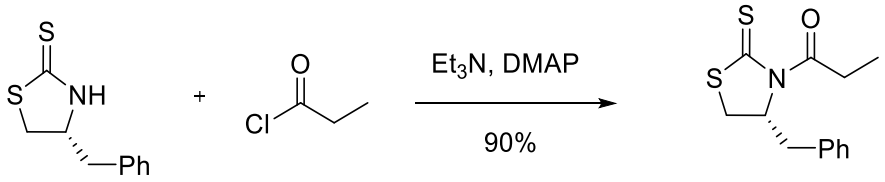
To convert (*R*)-phenylalaninol **182** to (*R*)-4-benzylthiazolidine-2-thione **183**, carbon disulfide was used under basic conditions. The compound **182** underwent cyclisation and yielded the desired product **183** with a 92% yield (Scheme 1.57).



182 **183**

Scheme 1.57: Synthesis of **183**

In the final step, (*R*)-4-benzyl-3-propionylthiazolidine-2-thione **183** was reacted with propionyl chloride in the presence of DMAP and Et_3N. This nucleophilic substitution yields bright yellow crystals of acylated auxiliary **160** (Scheme 1.58). The same three-step procedure was repeated to increase the yield of this reaction. The targeted yield of 90% was successfully achieved.



183 **184** **160**

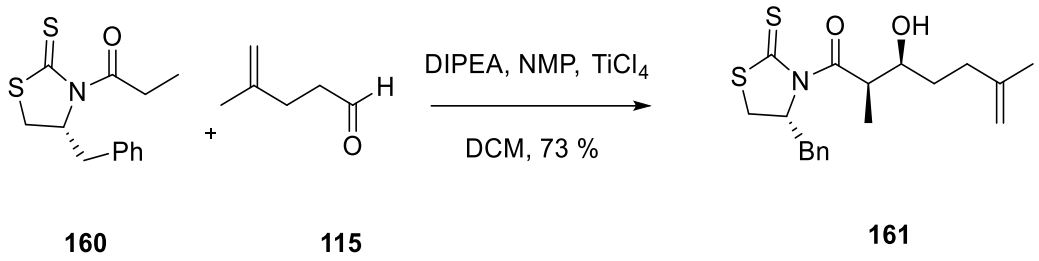
Scheme 1.58: Synthesis of acylated auxiliary **160**

Synthesis of β-keto ester 194

The Crimmins acylated auxiliary **160** was treated with aldehyde **115** in the presence of $TiCl_4$ and DIPEA, resulting in the synthesis of an aldol **161** with a 73 % yield (Scheme 1.49). This aldol reaction proceeded through a transition state (Scheme 1.60).[25]

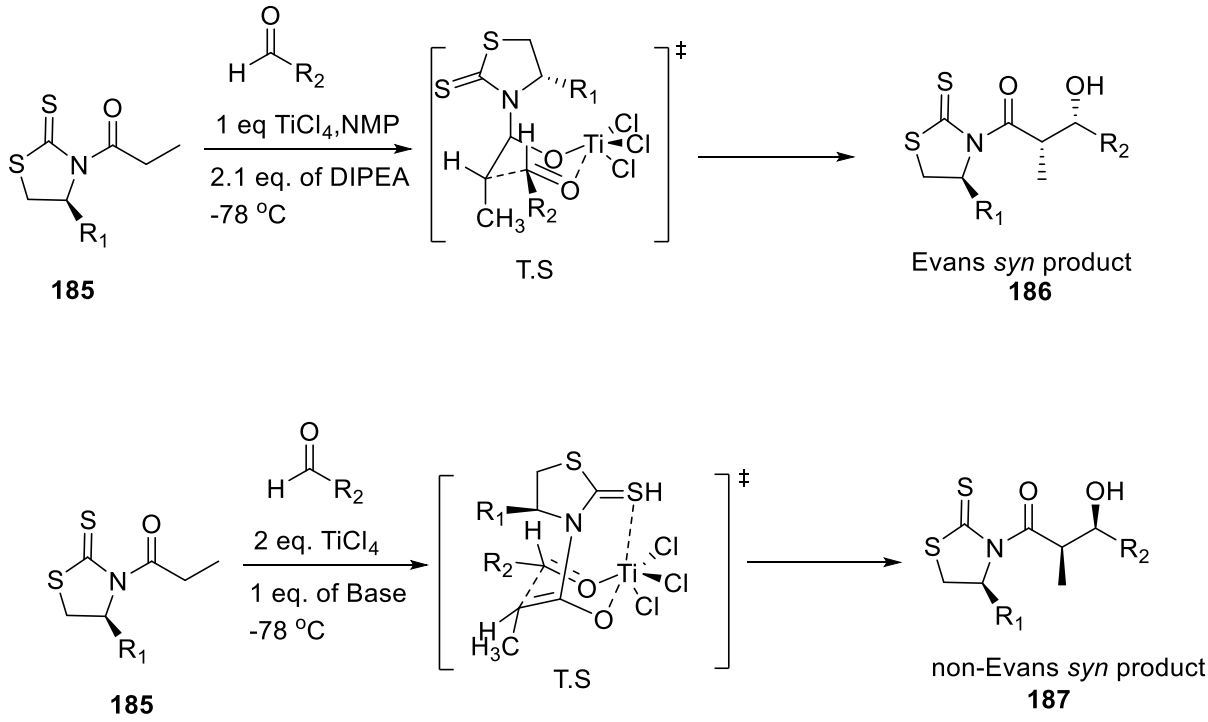
Crimmins *et al*. successfully synthesized auxiliary to afford Evan syn and Evan non-Evan products.[25] The titanium enolate initially synthesised by using N-acyl thiazolidinethiones was more effective as compared to oxazolidinethiones to control the Evans reaction. The initial study revealed that the affinity of the sulfur atom was more than oxygen. The diastereoselectivity of the reaction can be controlled by changing a number of equivalents of base and $TiCl_4$. To synthesise Evans *syn* product

Crimmins used 2 eq. of base and 1 eq. of $TiCl_4$, to afford non-Evan product they used 1:1 of base and $TiCl_4$.



160 **115** **161**

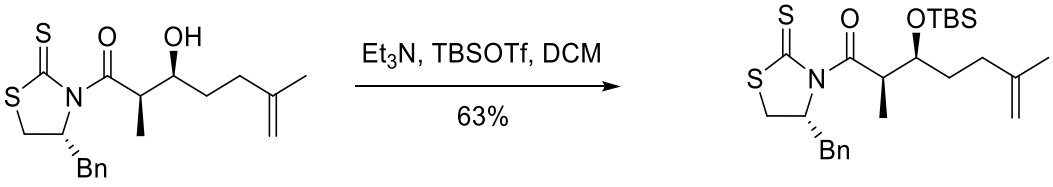
Scheme 1.59: Synthesis of aldol **161**



185 **186** **185** **187**

Scheme 1.60: Mechanism of aldol formation

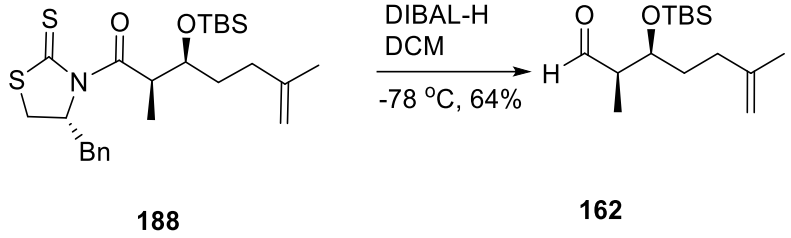
In the next step, the hydroxy group of **161** was protected by TBSOTf by using Et_3N as a base and a 63 % yield of **188** was achieved (Scheme 1.61).[26]



161 **188**

Scheme 1.61: Synthesis of TBS-protected aldol

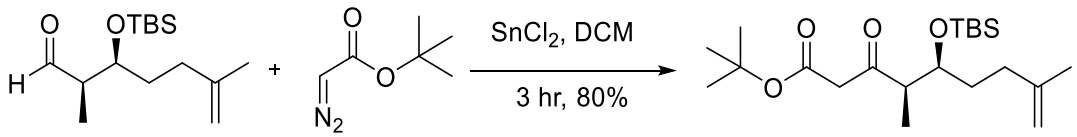
The TBS-protected aldol was reduced to TBS-protected aldehyde **162** with a 64 % yield by using DIBAL-H reduction (Scheme 1.62).



188 **162**

Scheme 1.62: Formation of TBS-protected aldehyde **162**

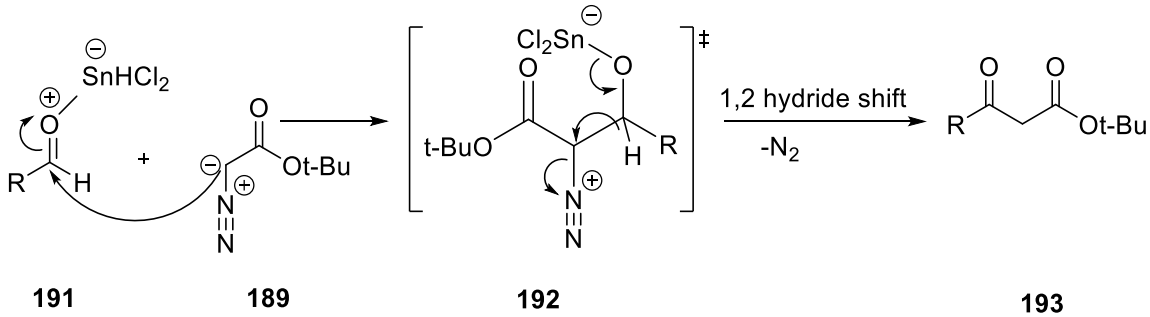
In the Roskamp homologation, the TBS-protected aldehyde was treated with *tert*-butyl diazoacetate in the presence of $SnCl_2$, to produce the desired *β*-keto ester with 80% of a Mixture of keto-ester and enol (3:1) (Scheme 1.63).



162 **189** **190**

Scheme 1.63*:* Synthesis of *tert*-butyl ester **187**

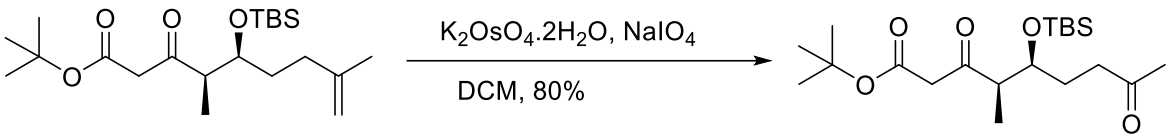
The general mechanism of Roskamp homologation is described below.



191 **189** **192** **193**

Scheme 1.64: Synthesis of ester **191**

After the Roskamp homologation, the resulting mixture was subjected to oxidative cleavage to furnish ketone **194** with an 80% yield, by using potassium osmate dihydrate and sodium periodate (Scheme 1.65).

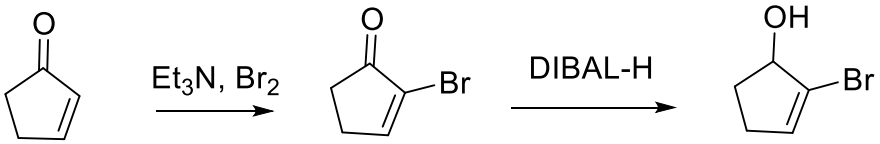


190 **194**

Scheme 1.65: Osmium catalysed oxidation of **194**

Synthesis of TES-protected vinyl bromide

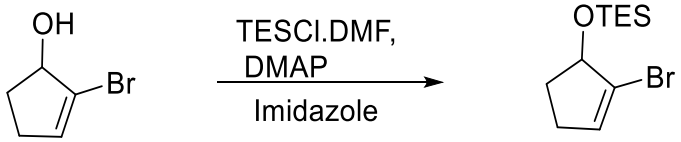
The vinyl bromide **164**, an important part of CDEF fragment was successfully prepared in a three-step reaction scheme. In the first step, the bromination of cyclopentenone was achieved with 70% of yield by using Et_3N and Br_2, which was followed by DIBAL-H reduction in the next step to generate desired 2-bromocyclopent-1-ol **197** with 85% of yield (Scheme1.66).[26]



195 **196** **197**

Scheme 1.66: Formation of bromocyclopent-1-ol

2-Bromocyclopent-1-ol **197** was protected by using TESCl, imidazole and DMAP. yield of 70% was achieved (Scheme 1.67).

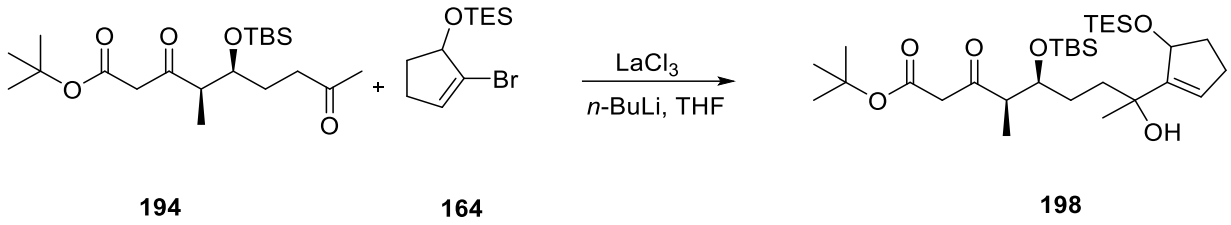


197 **164**

Scheme 1.67: TES-Protection of bromocyclopent-1-ol

Coupling of the two fragments

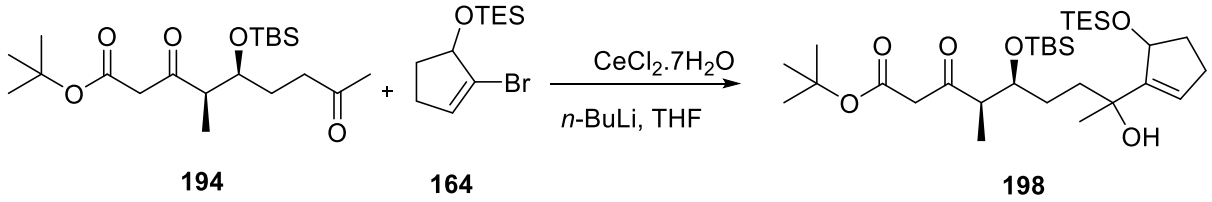
We attempted to couple **164** and **194** using lanthanum chloride solution and *n*-BuLi in THF but did not get the desired product **198** (Scheme 1.68).



194 **164** **198**

Scheme 1.68: Attempted synthesis of **198**

We tried to couple both fragments by using activated $CeCl_2$ and *n*-BuLi but were unable to get **198**. we have made a couple of attempts but were unable to combine two fragments. To synthesise **198,** we added *n*-BuLi with **164** to get lithium halogen exchange, then we added this mixture to the solution of **194** in $LaCl_3$ or $CeCl_2$. The possible reason for the failure of this reaction was the lithium halogen exchange, which was not successfully obtained.



194 **164** **198**

Scheme 1.69: Attempted synthesis of **198**

5 Conclusion

The compounds **160** and 4-methyl-pentanal **115** are precursors to afford the DEF fragment. Synthesis of **160** began with the reduction of phenylalanine to corresponding alcohol **179**, followed by cyclisation to generate **180**, which underwent acylation to afford **160**. The compound **160** was treated with aldehyde **115** via Crimmins aldol reaction to afford **161**.The Crimmins aldol **160** was converted into **162**, followed by DIBAL-H to afford **115**, which was used for Roskamp homologation in the next step to synthesise DEF fragment **194**. TES-protected **164** was also prepared over three steps, was used with DEF fragment to afford nine-membered ring which would be converted into CDEF ring over five steps.

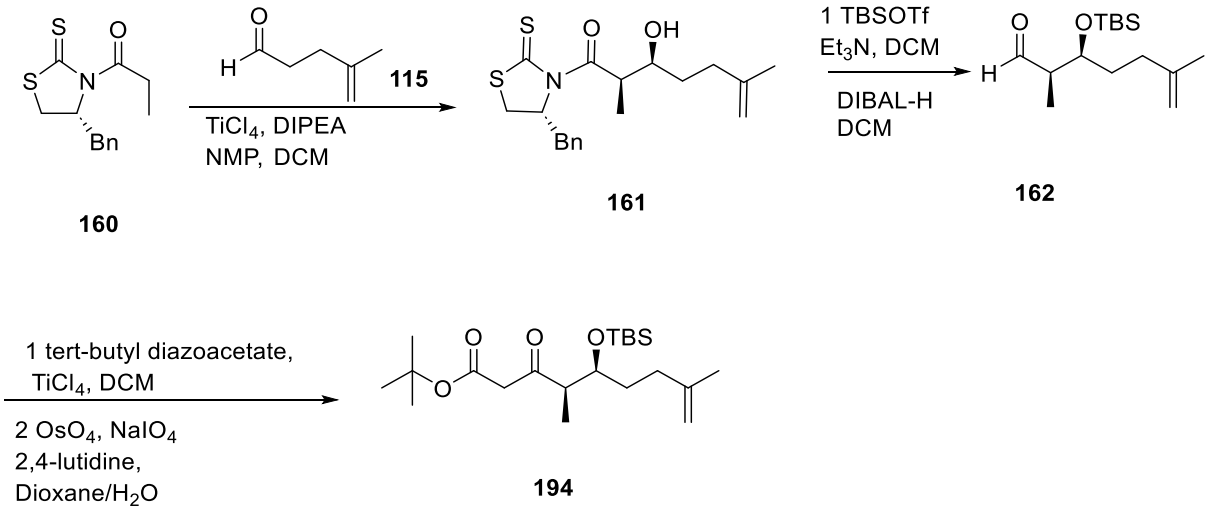
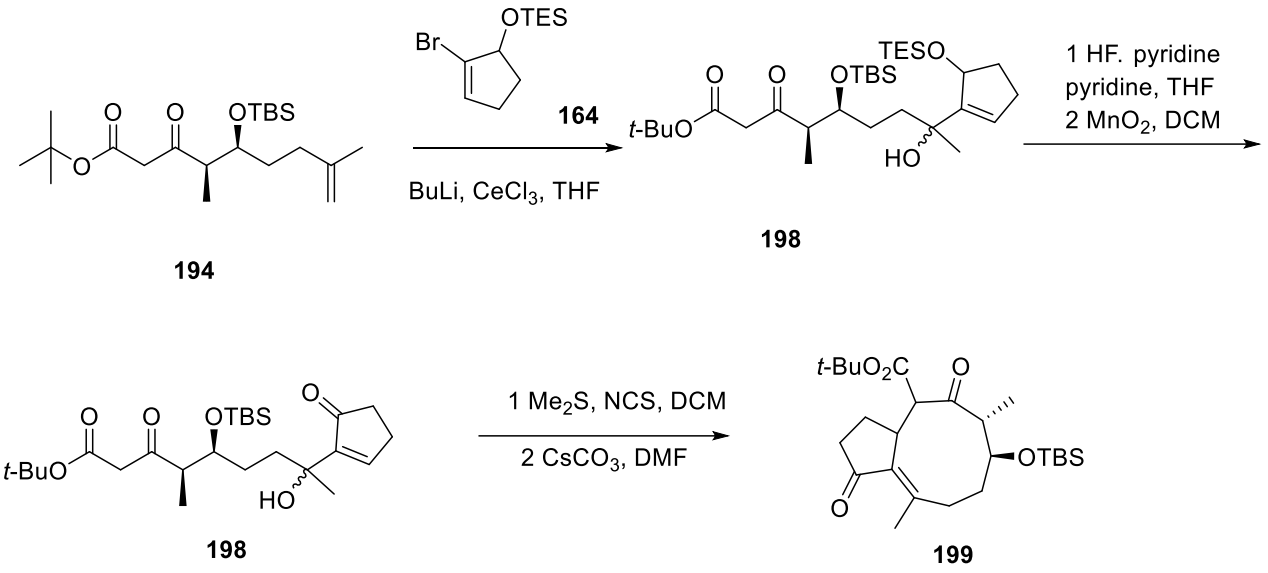


Figure 1.15: Formation of **DEF** fragment

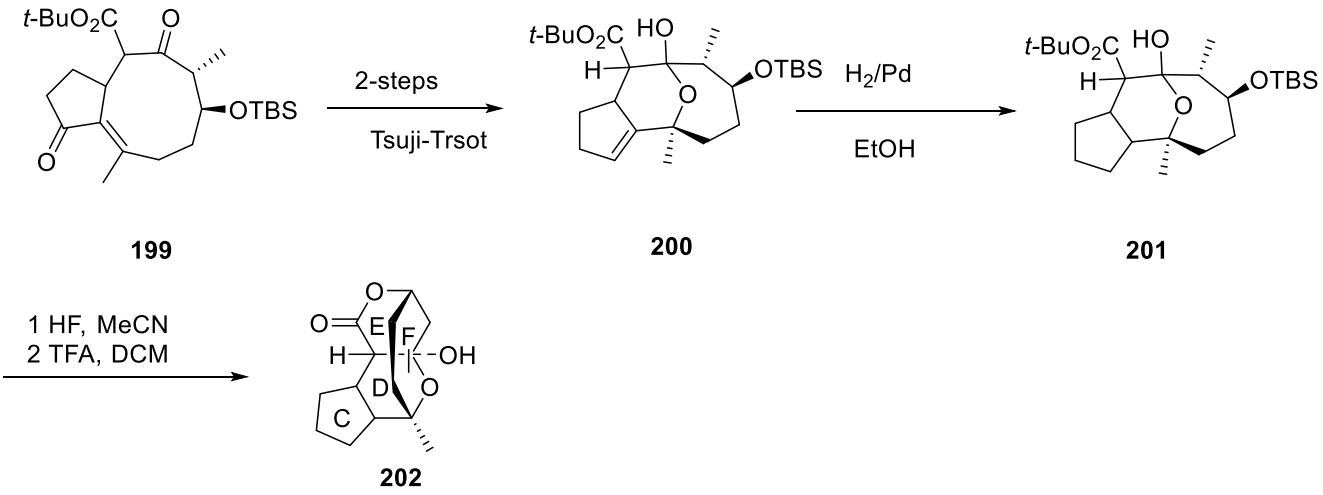
6 Future Work

The future work will be focused on the synthesis of the CDEF ring system. In the next step newly synthesised **199** will be treated with C ring **164** to afford an enol **198**, which would be undergoes cyclisation to nine-membered cyclic compound **199** after a two-step reaction (Scheme 1.58).



Scheme 1.58: Synthetic route to design nine-membered **199**

The bicyclic **199** could be formed by a Tsuji-Trost reaction to afford a CDF tricyclic compound **200**. After hydrogenation of the C ring, resulting compound **201** will be converted to a CDEF ring system **202** of hexacyclinic acid by cleavage of the silyl ether, hydrolysis of the *tert*-butyl ester, and lactonisation using Mukaiyama's reagent (Scheme 1.59).



Scheme 1.59: Formation of **CDEF** ring system

7 General Experimental Section

Instrument

^{1}HNMR of all the compounds was recorded using the Bruker NMR instrument (400 MHz) in the Department of Chemistry. The chemical shifts were shown in PPM (part per million) against the reference solvent $CDCl_3$.The NMR signals were described as S for singlet, d for doublet, t for triplet, q for the quartet, m for multiplet and br for broad signals e.g. OH. The frequency and coupling constant were represented by Hz (hertz) and *J*

^{13}C NMR of all the compounds was recorded in the same instrument at 100 MHz and Chemical shift was represented by PPM.

High-Resolution Mass Spectrometer

The exact mass of the new compounds was determined by using Bruker QTOF high-resolution Agilent 6545Mass spectrometer in the Department of Chemistry. The ESI (Electron spin ionisation) method was adopted to assess the m/z of the samples.

IR

The IR data of the samples were acquired by using Jasco FTIR 4100 spectrometer available in the Department of Chemistry. Jasco FTIR has a wavenumber 7800-350 cm^{-1} and a resolution 0.7 cm^{-1}.

Melting Point

The melting point of solid samples was determined by using eisco 230V, 50-60 Hz melting point apparatus available in Henderson lab.

Optical Rotation

The optical activity of compounds was irradiated in solution with chloroform at 589 wavelength and optical rotation was measured by using the Rudolph polarimeter available in Henderson lab.

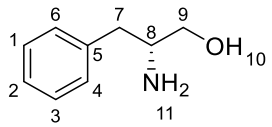
Solvents

All the solvents used for the reactions e.g. dichloromethane, toluene, tetrahydrofuran, and diethyl ether were directly obtained from SPS (Solvent Purifier System) available in the Department of Chemistry. The Solvent used for the chromatography e.g. dichloromethane, ether, diethyl ether, and n-hexane was acquired from the Chemistry store.

Chemical and Reagents

All the required chemical and reagents used in this project was acquired from Sigma, Thermoscientific, key organic, TCI and Fisher Scientific.

(*R*)-Phenylalaninol[26]



182

$C_9H_{13}NO$

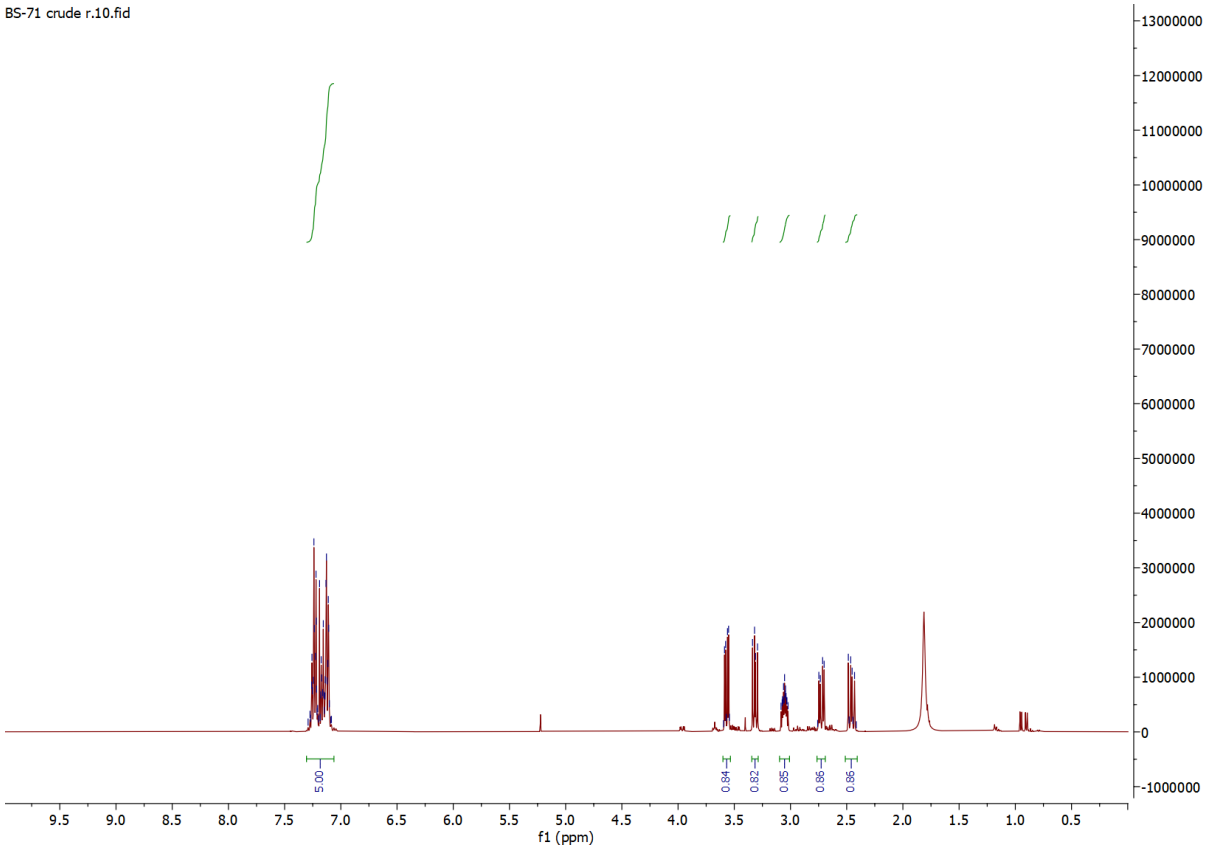
Mol. Wt. 151.21 g/mol

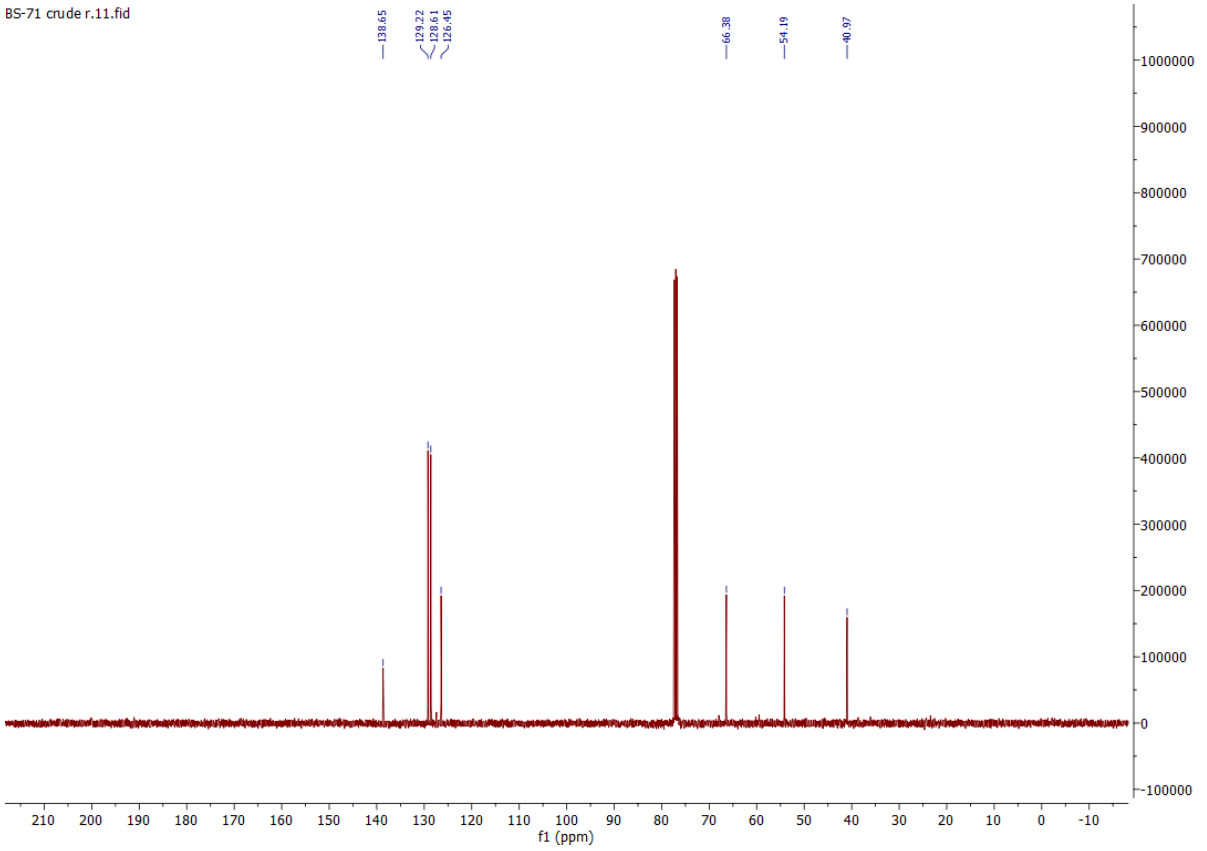
(*R*)-Phenylalanine (6.61 g, 40.0 mmol) was added to a solution of sodium borohydride (3.61 g, 96.0 mmol, 2.4 equiv) in THF (80.0 mL), then the reaction mixture was cooled to 0 °C. An iodine solution (10.1 g, 40.0 mmol, 1 equiv) in THF (50 mL) was added to the reaction mixture over 50 min. The resulting solution was heated at reflux overnight. The reaction mixture was then cooled to room temperature and quenched with methanol, then left to stir until it gave a clear solution, which was then concentrated under vacuum to give a white paste. A 20% aqueous solution of KOH (100 mL) was added to the white paste. The mixture was then left to stir for 3 h and extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under a vacuum to afford phenylalaninol (5.1 g, 85%) as a white solid, which was used for the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35-7.20 (m, 5H, Ar-H), 5.32 (s, 2H, N-H), 3.56 (dd, *J* = 10.4, 3.9 Hz,1H, 9-H), 3.40 (dd, *J* = 10.4, 7.2 Hz, 1H, 9-H), 3.18-3.12 (m, 1H, 8-H), 2.72 (dd, *J* = 13.5, 5.3 Hz, 1H, 7-H), 2.45 (dd, *J* = 13.5, 8.5 Hz, 1H, 7-H), 1.8 (br s, OH).

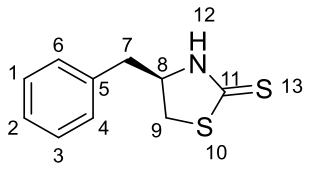
^{13}C NMR ($CDCl_3$, 101 MHz), 138.6 (Ar-C), 129.2 (Ar-C), 128.6 (Ar-C), 126.4 (Ar-C), 66.4 (9-C), 54.2 (8-C), 40.1 (7-C).

In agreement with literature data.[26]


BS-71 crude r.10.fid
5.00
0.84
0.82
0.85
0.86
0.86
f1 (ppm)


BS-71 crude r.11.fid
138.65
129.22
128.61
126.45
66.38
54.19
40.97
f1 (ppm)

(*R*)-4-Benzylthiazolidine-2-thione[26]



183

$C_{10}H_{11}NS_2$

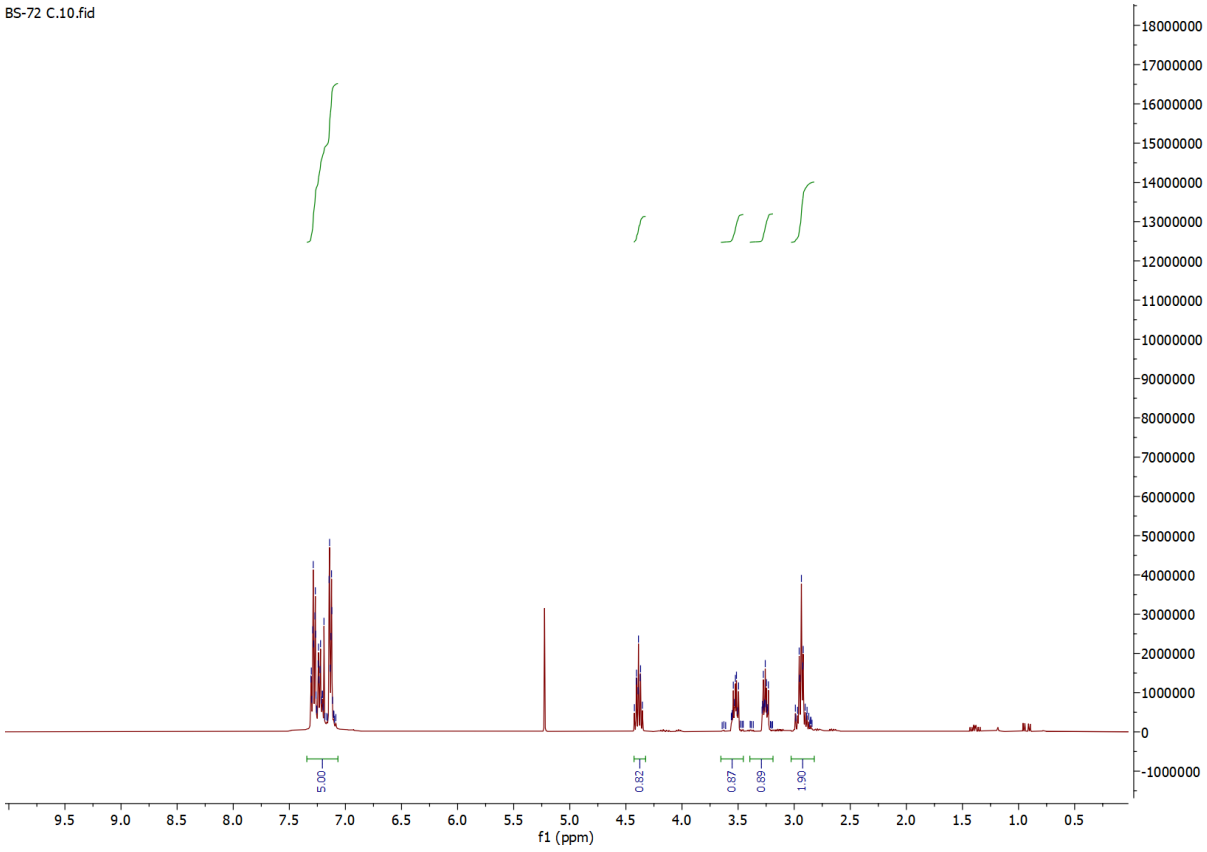
Mol. Wt. 209.33 g/mol

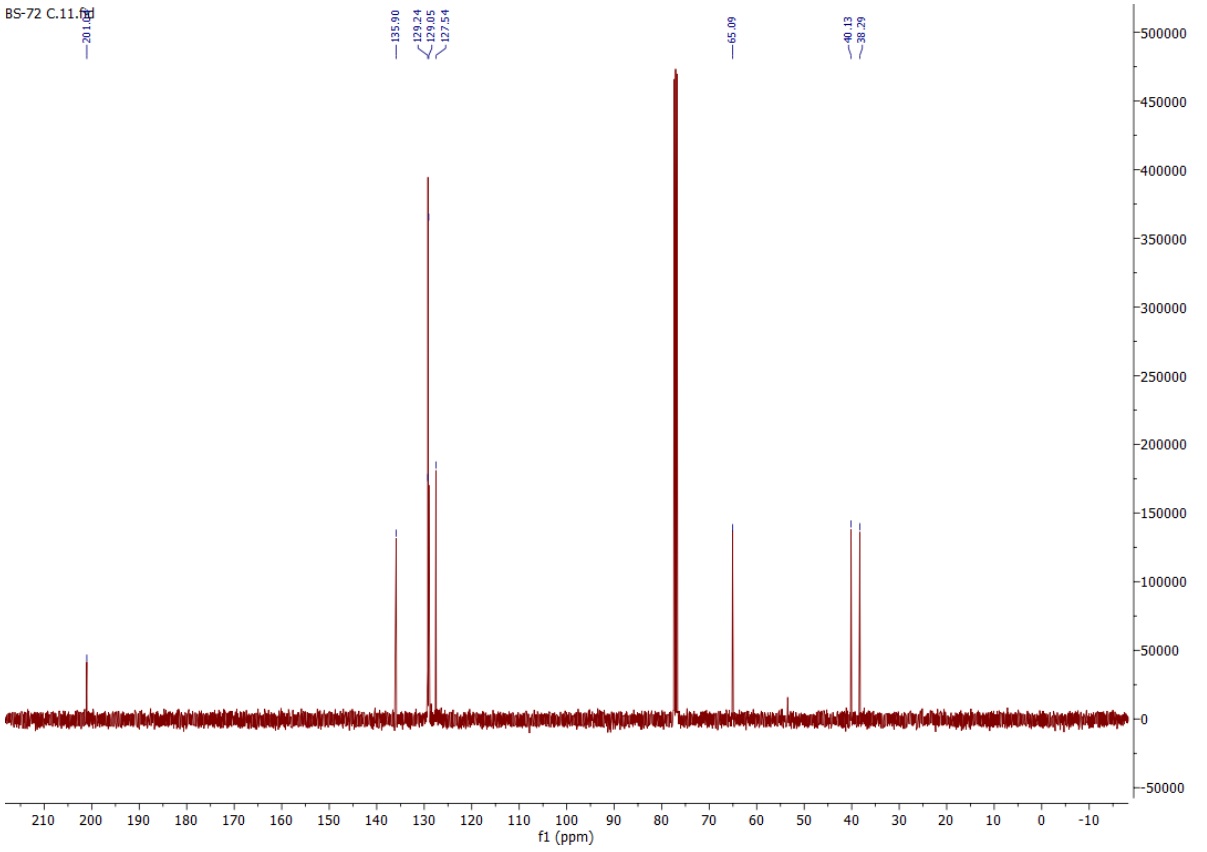
Phenylalaninol (5.0 g, 33 mmol) was added to a 3 M aqueous solution of KOH (100 mL) then the resulting solution was allowed to stir for 30 min. Carbon disulfide (10 mL, 165 mmol, 5.0 equiv) was added dropwise to the reaction solution, and the resulting mixture was heated to 110 °C then left to stir overnight at room temperature. The reaction mixture was cooled to room temperature and extracted with DCM (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to give a crude product (6.3 g, 96%) as a yellow solid, which was used for the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.29-7.11 (m, 5H, Ar-H), 5.2 (s, 1H, 12-H), 4.42-4.35 (m, 1H, 8-H), 3.50 (dd *J* = 11.3, 6.6 Hz, 1H, 7-H), 3.24 (dd, *J* = 11.3, 6.7 Hz, 1H, 7-H), 2.96 (d, *J* = 13.4, 7.7 Hz, 9-H), 2.96 (d, *J* = 13.4, 6.8 Hz, 9-H).

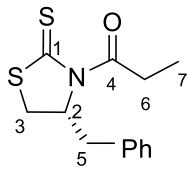
^{13}C NMR ($CDCl_3$, 101 MHz) δ: 201.0 (11-C), 135.9 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 127.5 (Ar-C), 65.1 (8-C), 40.1 (9-C), 38.3 (7-C).

In agreement with literature data.[26]


BS-72 C.10.fid
5.00
0.82
0.87
0.89
1.90
f1 (ppm)


BS-72 C.11.fid
135.90
129.24
129.05
127.54
65.09
40.13
38.29
f1 (ppm)

(*R*)-4-Benzyl-3-propionylthiazolidine-2-thione[26]



160

$C_{13}H_{15}NOS_2$

Mol. Wt. 265.4 g/mol

Melting point 98 ^{o}C, Lit. = 105 ^{o}C.

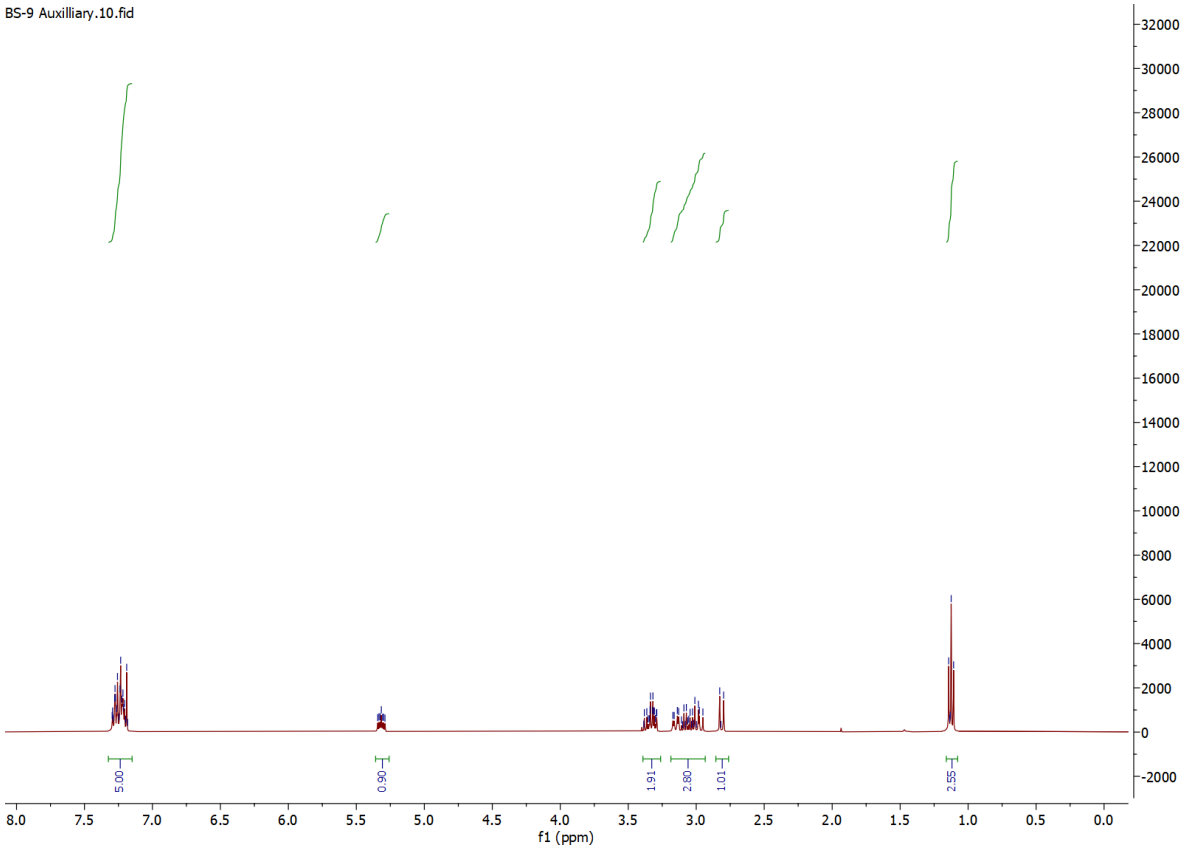
Triethylamine (10.0 mL, 75.0 mmol, 1.5 equiv) was added to a solution of 4-benzylthiazolidine-2-thione (6.30 g, 30.0 mmol), then the reaction mixture was cooled to 0 $^{\circ}$C and treated with propionyl chloride (4.0 mL, 45.0 mmol, 1.5 equiv) over 5 min. The mixture was stirred overnight at room temperature, and then diluted with DCM (50 mL) and water (50 mL). The aqueous phase was extracted with DCM (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. Recrystallisation from acetonitrile gave bright yellow crystals of 4-benzyl-3-propionylthiazolidine-2-thione (7.2 g, 90%).

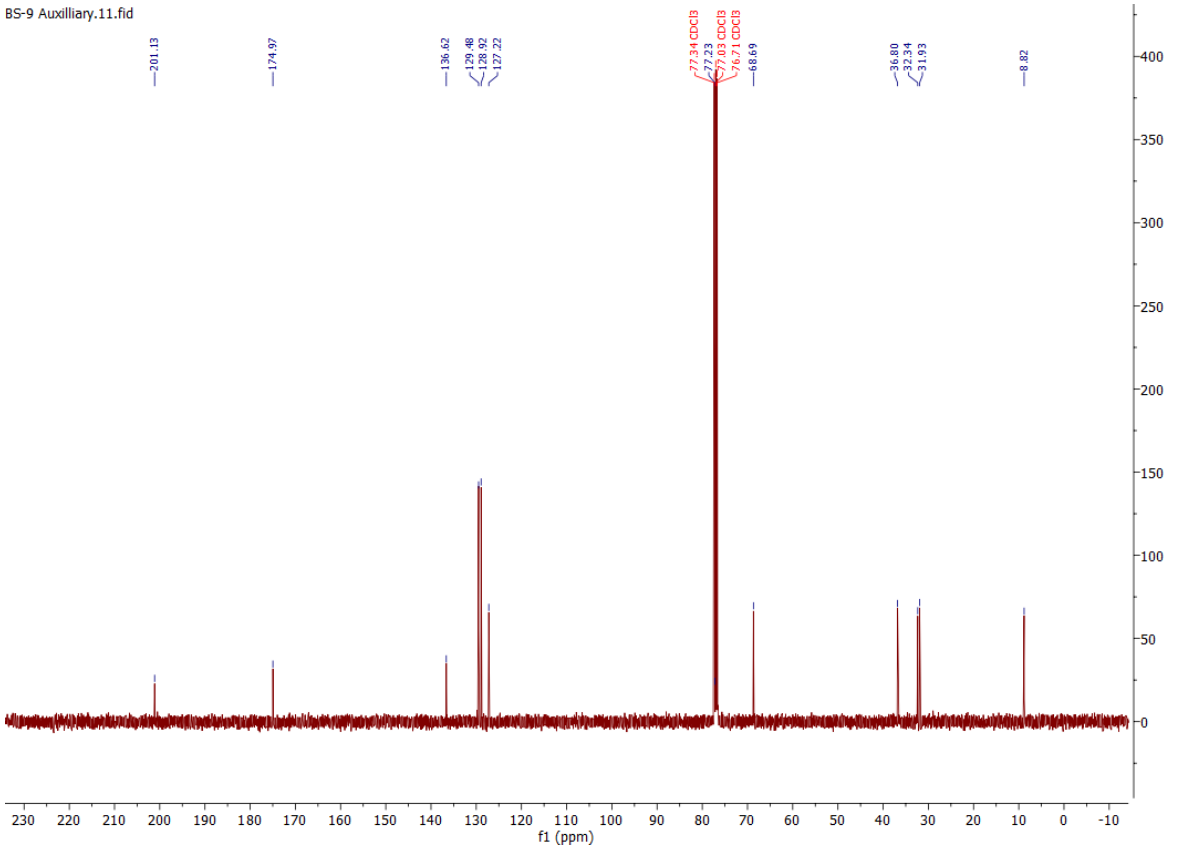
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.38-7.29 (m, 5H, Ar-H), 5.34-5.28 (m, 1H, 3-H), 3.39-3.29 (m, 3H, 4-H/7-H), 3.15 (dd, *J* = 13.1, 3.6 Hz, 1H, 4-H), 3.01-2.95 (m, 2H, 5-H/7-H), 2.81 (d, *J* = 11.1 Hz, 5-H), 1.21 (t, *J* = 6.9 Hz, 3H, 8-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 200.9 (2-C), 174.8 (6-C), 136.5 (Ar-C), 129.4 (Ar-C), 128.8 (Ar-C), 127.2 (Ar-C), 68.6 (3-C), 36.5 (7-C), 32.1(4-C), 31.8 (5-C), 8.6 (8-C).

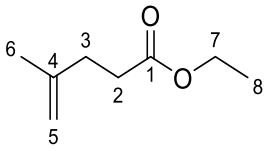
[α]D^{18}= -126.1 (*c* = 0.1 $CHCl_3$) Lit. = -114.0 (*c* = 0.1 $CHCl_3$)

In agreement with literature data.[26]


BS-9 Auxilliary.10.fid
5.00
0.90
1.91
2.80
1.01
2.55
f1 (ppm)


BS-9 Auxilliary.11.fid
201.13
174.97
136.62
129.48
128.92
127.22
77.34 CDCl3
77.23
77.03 CDCl3
76.71 CDCl3
68.69
36.80
32.34
31.93
8.82
f1 (ppm)

Ethyl 4-methylpent-4-enoate[24]



177

$C_8H_{14}O$

Mol. Wt. 142.21 g/Mol

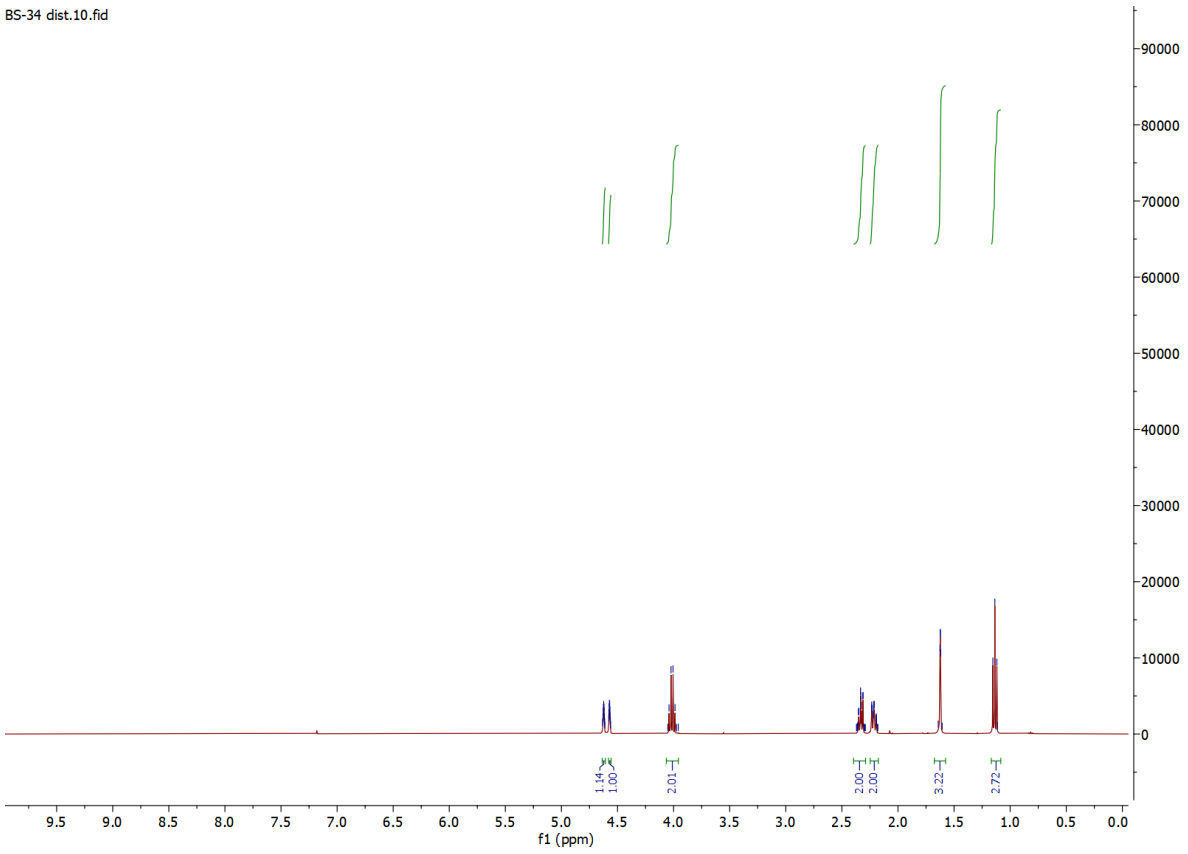
To a solution of methyltriphenylphosphonium bromide (16.71 g, 46.8 mmol, 1.2 equiv) in THF (100 mL) *n*-butyllithium (2.5 M in hexanes, 20.6 mL, 51.5, 1.3 equiv) was added dropwise at 0 ^{o}C under argon. The reaction mixture was left to stir for 30 min before being cooled to -78 ^{o}C, and a solution of ethyl levulinate (5.60 g, 39.0 mmol, 1 equiv) in THF was added dropwise. The reaction mixture was warmed to RT and left to stir for 14 h.

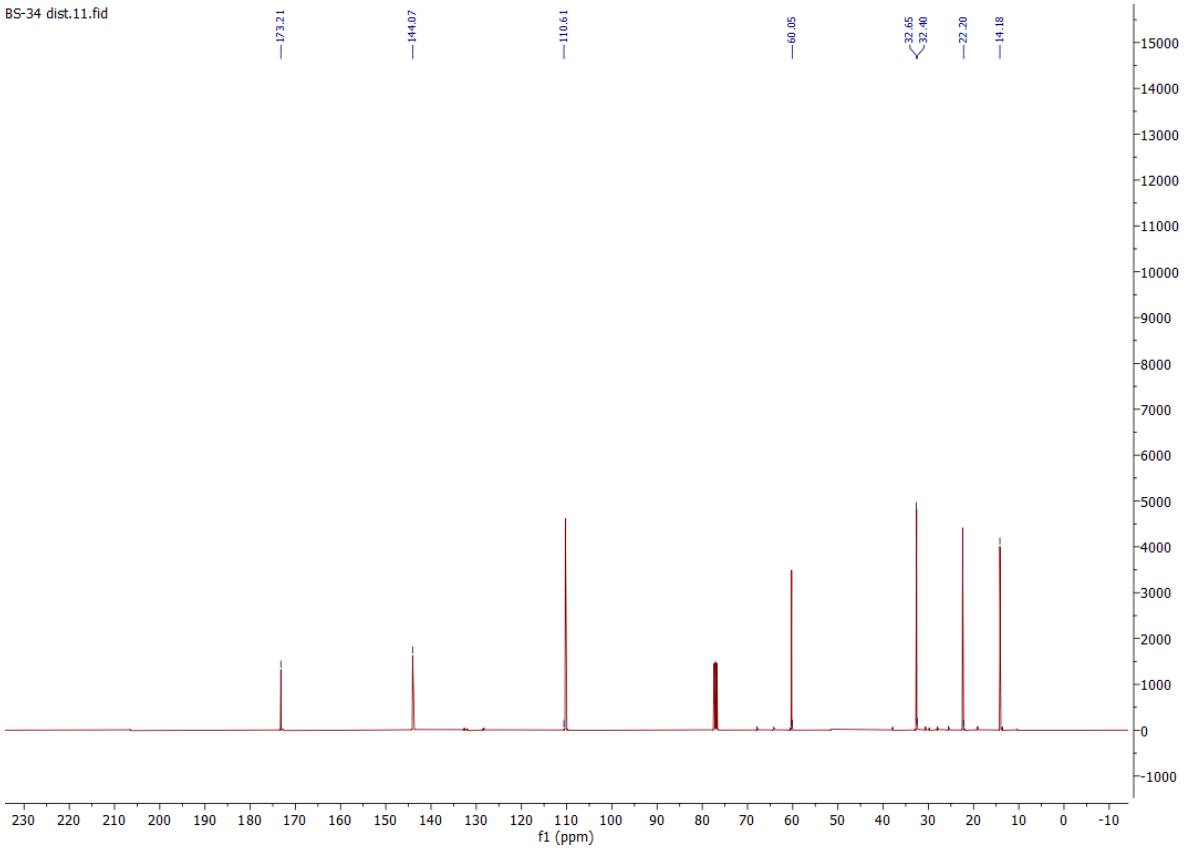
After that, the reaction mixture was quenched with saturated aqueous ammonium chloride and the aqueous phase was extracted with pentane (5 × 20 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and concentrated under vacuum. Vacuum distillation (122 ^{o}C/ 20 mbar) gave the desired ester (3.81 g, 65%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.74 (t, *J* = 0.8 Hz, 1H, 5-H), 4.67 (t, *J* = 0.8 Hz, 1H, 5-H). 4.23 (q, *J* = 7.2 Hz, 2H, 7-H), 2.42 (td, 2H, *J* = 7.6, 1.6 Hz, 3-H), 2.33 (t, 2H, *J* = 8.0 Hz, 2-H), 1.74 (d, 3H, *J* = 0.4 Hz, 6-H), 1.25 (t, 3H, 7.2 Hz, 8-H).

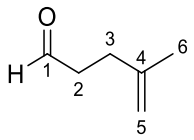
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 173.2 (1-C), 144.1 (4-C),110.6 (5-C), 60.0 (7-C), 32.6 (2-C), 32.4 (3-C), 22.2 (6-C), 14.2 (8-C).

In agreement with literature data.[24]


BS-34 dist.10.fid
1.14
1.00
2.01
2.00
2.00
3.22
2.72
f1 (ppm)


BS-34 dist.11.fid
173.21
144.07
110.61
60.05
32.65
32.40
22.20
14.18
f1 (ppm)

4-Methylpent-4-enal[24]



115

$C_6H_{10}O$

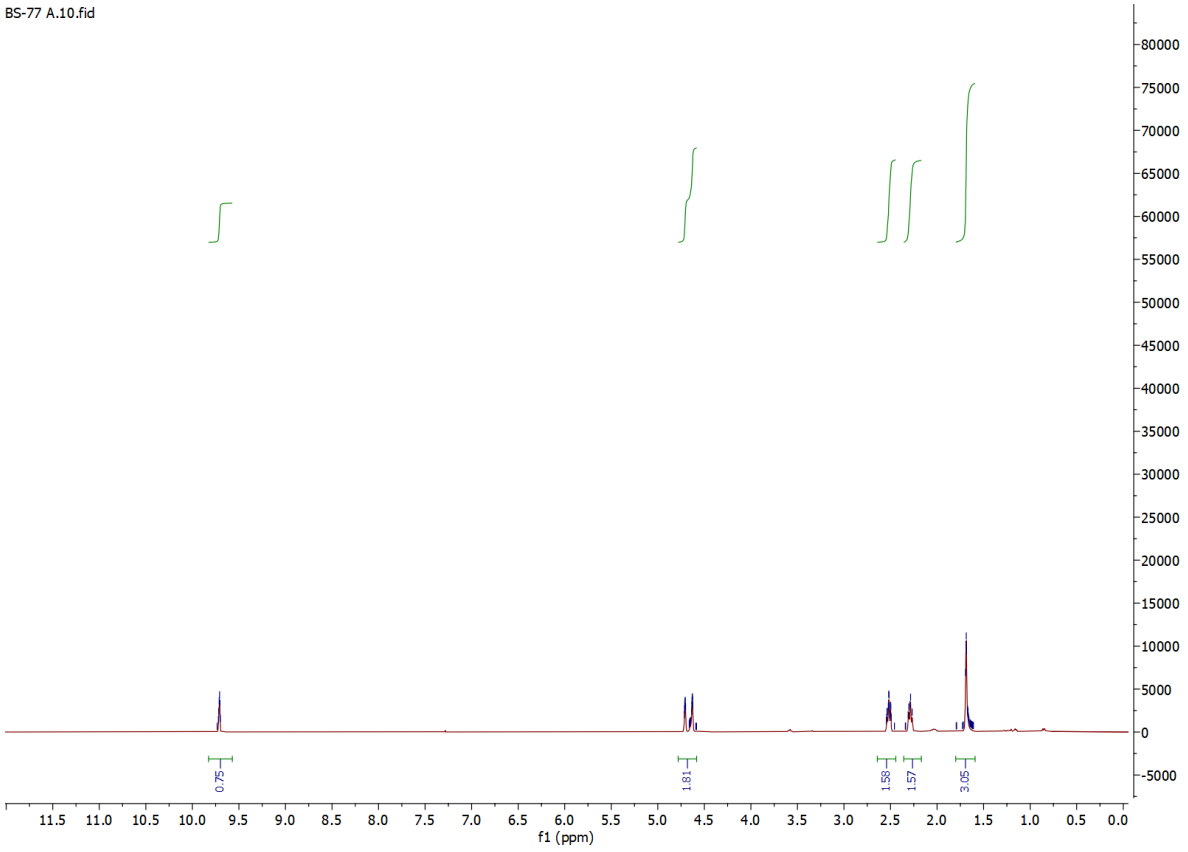
Mol. Wt. 98.14 g/mol

To a solution of ethyl 4-methylpent-4-enoate (3.40 g, 24.0 mmol) in DCM (50 mL) at -78 ^oC under argon was added DIBAL-H (1 M in hexanes, 28.8 mL, 1.2 equiv) dropwise over 30 min. The reaction mixture was left to stir for 4 h under the above conditions, then quenched with methanol (6 mL), 10 mL of Et_2O, 10 mL of Rochelle's salt and the resulting mixture was stirred overnight at room temperature. The layers were separated and the aqueous phase was extracted with DCM (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under a vacuum (180 mbar). The crude product was purified by distillation (120 ^oC/20 mbar) to give (2.31 g, 88%) of the desired product as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.71 (t, *J* = 1.6 Hz, 1H, 1-H), 4.69 (s, 1H, 5-H), 4.61 (s, 1H, 5-H), 2.50 (td, *J* = 7.4, 1.7 Hz, 2H, 2-H), 2.27 (t, *J* = 7.6 Hz, 2H, 3-H), 1.67 (s, 3H, 6-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 202.1 (1-C), 143.7 (4-C), 110.6 (5-C), 41.9 (2-C), 29.8 (3-C), 22.5 (6-C).

In agreement with literature data.[24]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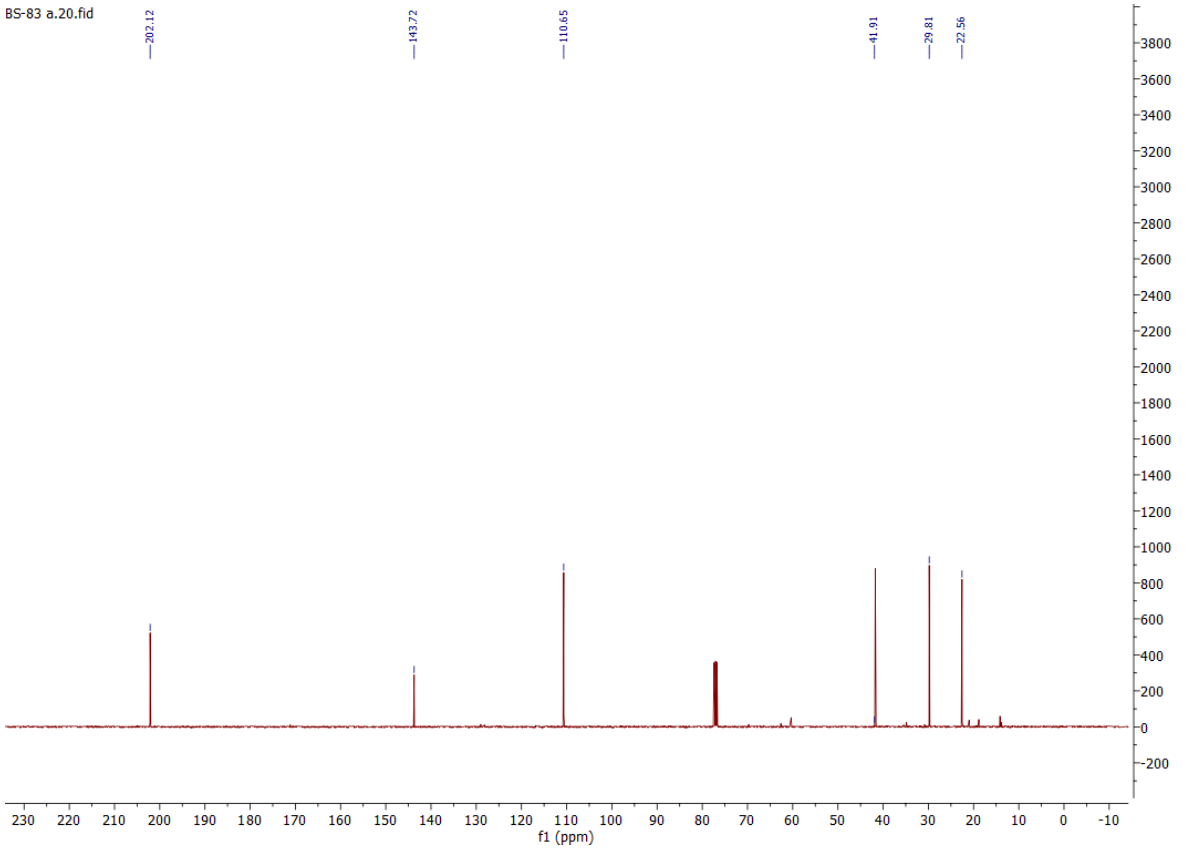
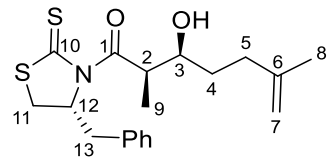
0.75
1.81
1.58
1.57
3.05
f1 (ppm)


BS-83 a.20.fid
202.12
143.72
110.65
41.91
29.81
22.56
f1 (ppm)

4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2,6- dimethylhept-6-en-1-one[27]



161

$C_{19}H_{25}NO_2S_2$

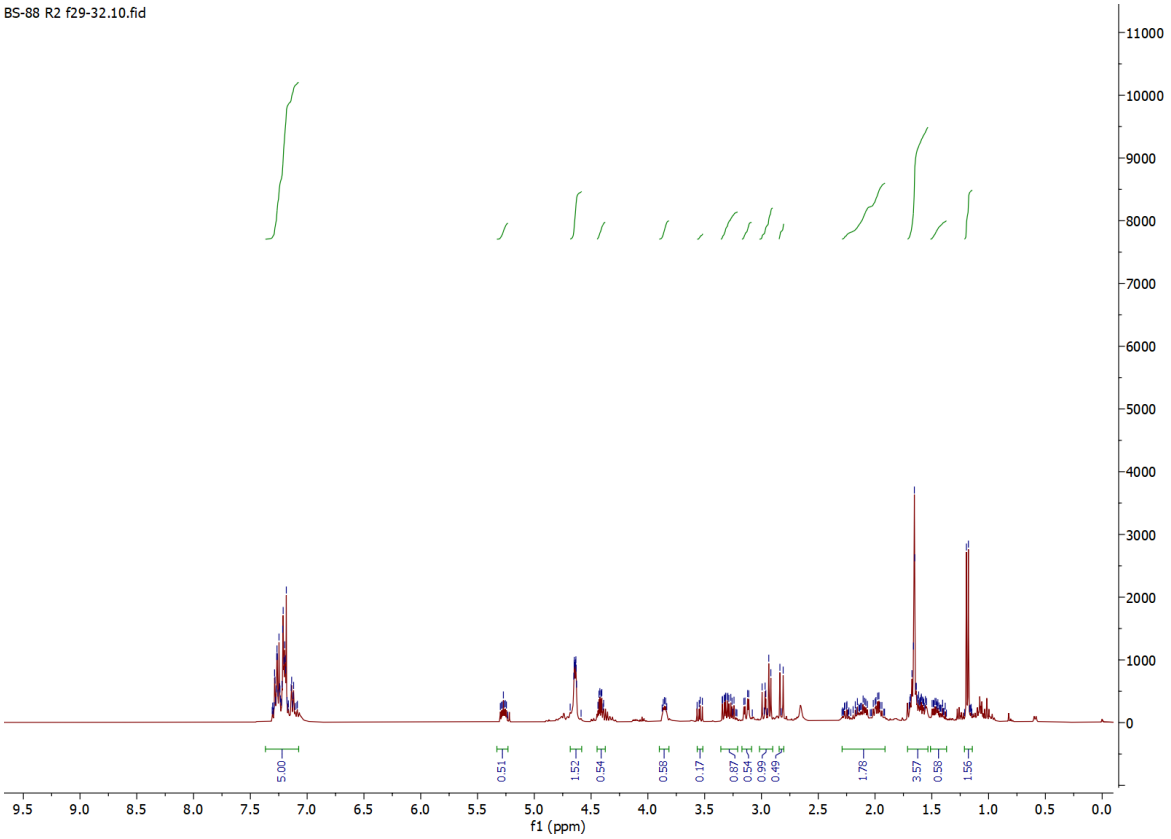
Mol. Wt. 363.53 g/mol

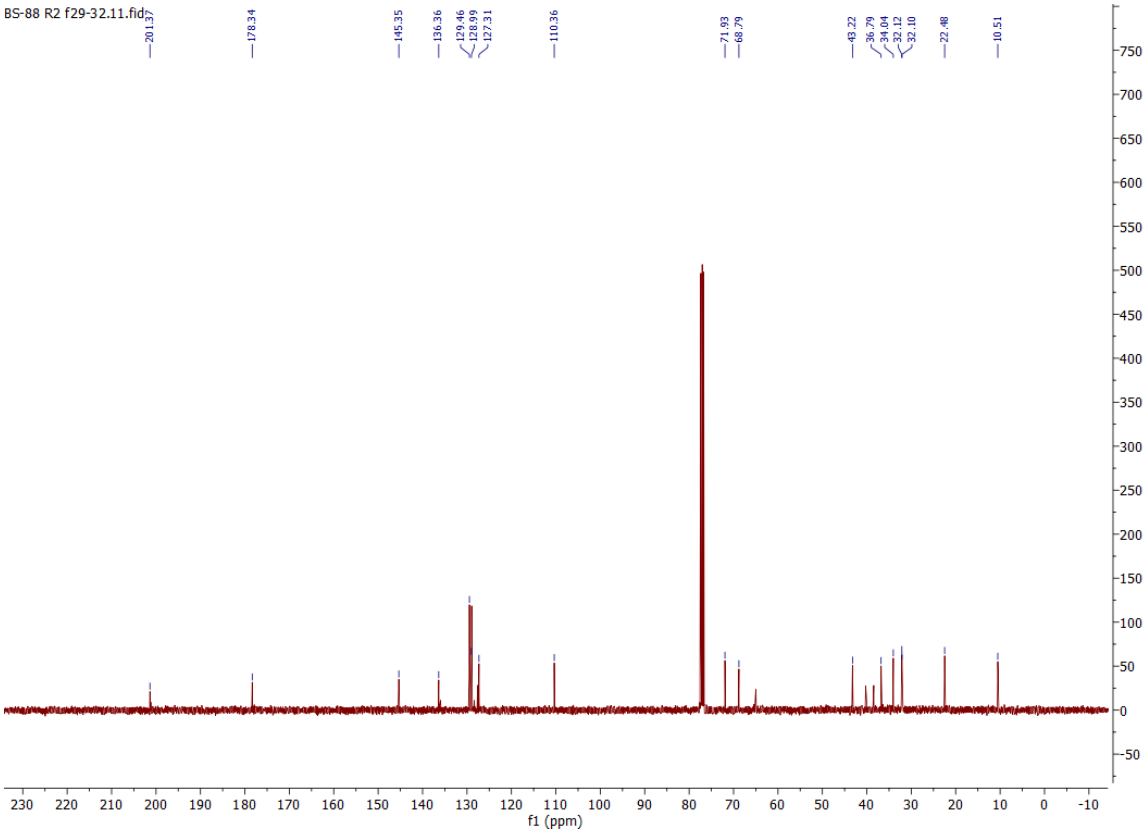
To a solution of the Crimmins acylated auxiliary (0.81 g, 3.0 mmol) in DCM (60 mL) at 0 °C was added $TiCl_4$ (0.3 mL, 3.1 mmol, 1.0 equiv) dropwise. The orange slurry was stirred for 15-20 min at 0°C then diisopropylethylamine (0.36 mL, 2.1 mmol, 2.1 equiv) was added dropwise and the reaction mixture was left to stir for 35 min at the same temperature. After that *N*-methyl-2-pyrrolidinone (0.20 mL, 2.1 mmol, 2.1 equiv) was added dropwise at 0 °C and the reaction mixture was allowed to stir for an additional 10-15 min before being cooled to -78 °C. The freshly prepared aldehyde (0.32, 3.3 mmol) was added dropwise with the help of a syringe. The reaction mixture was left to stir for 1 h at -78 °C then placed in a freezer at -20 ^oC overnight. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (20 mL). The aqueous phase was extracted with DCM (3 × 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (80:20 PE/EtOAc) to furnish a yellow oil (0.82 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31-7.12 (5-H, Ar-H), 5.32 (ddd, *J* = 7.1, 6.6, 3.8 Hz, 1H, 12-H), 4.65 (s, 1H, 7-H), 4.64 (s,1H, 7-H), 4.4 (qd, *J* = 6.4, 3.9 Hz, 1H, 2-H), 3.85 (ddd, *J* = 8.3, 4.6, 3.2 Hz, 1H, 3-H), 3.32 (dd, *J* = 11.6, 6.7 Hz, 1H, 13-H), 3.15 (dd, *J* = 13.17, 3.9 Hz, 1H, 11-H), 2.93 (dd, *J* = 10.3, 6.4 Hz, 1H, 11-H), 2.83 (d, *J* = 11.5 Hz, 1H, 13-H), 2.64 (brs, 1H, OH), 2.15 (ddd, *J* = 14.0, 11.2, 6.0 Hz), 2.02 (m, 1H, 5-H), 1.70-1.62 (m, 1H, 4-H), 1.54 (m, 1H, 4-H), 1.20 (d, *J* = 7.0 Hz, 3H, 9-H).

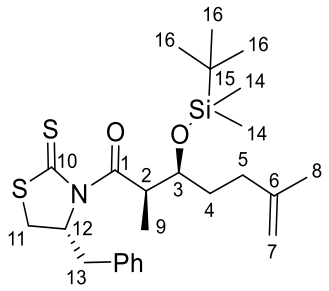
^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 201.4 (10-C), 178.3 (1-C), 145.3 (6-C), 136.2 (Ar-C), 129.2 (Ar-C), 128.9 (Ar-C), 127.3 (Ar-C), 110.4 (7-C), 72.0 (12-C), 68.8 (3-C), 43.2 (2-C), 36.8 (11-C), 34.0 (5-C), 32.1 (C13), 32.4 (11-C), 22.5 (8-C), 10.5 (9-C).

In agreement with literature data.[27]





4-Benzyl-2-thioxothiazolidin-3-yl)-3-((tert-butyldimethylsilyl)oxy)-2,6-dimethylhept-6- en-1-one[27]



188

$C_{25}H_{39}NO_2S_2Si$

Mol. Wt. 477.80 g/mol

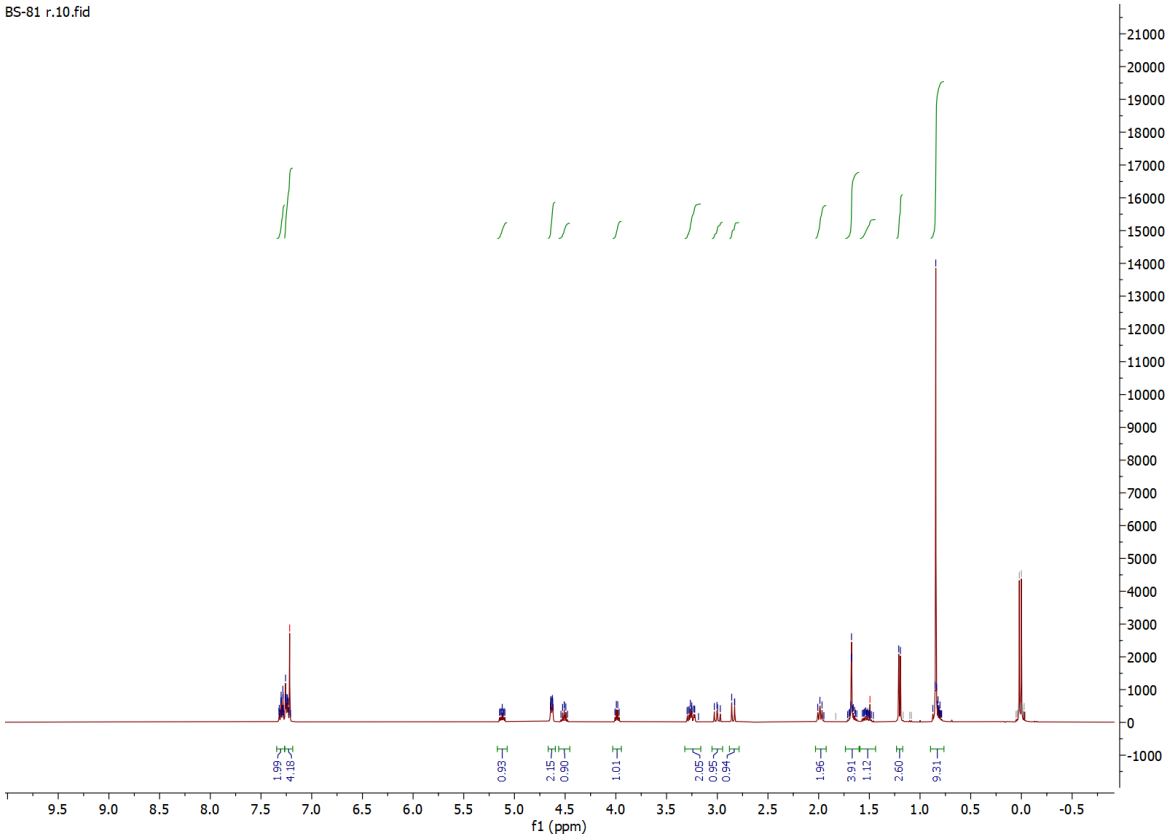
A solution of aldol (0.45 g,1.2 mmol) in DCM (20 mL) was cooled to -78 °C then triethylamine (0.35 mL, 2.5 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.43 mL, 1.8 mmol, 2 equiv.) were added dropwise to the reaction mixture. The reaction mixture was left to stir at -78 °C for 1 h then warmed to 0 °C and stirred for an additional 1 h. The reaction mixture was quenched with methanol (6 mL) and water (10 mL). The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (95:5 PE/Et_2O) to give the product as a yellow oil (0.41 g, 68%).

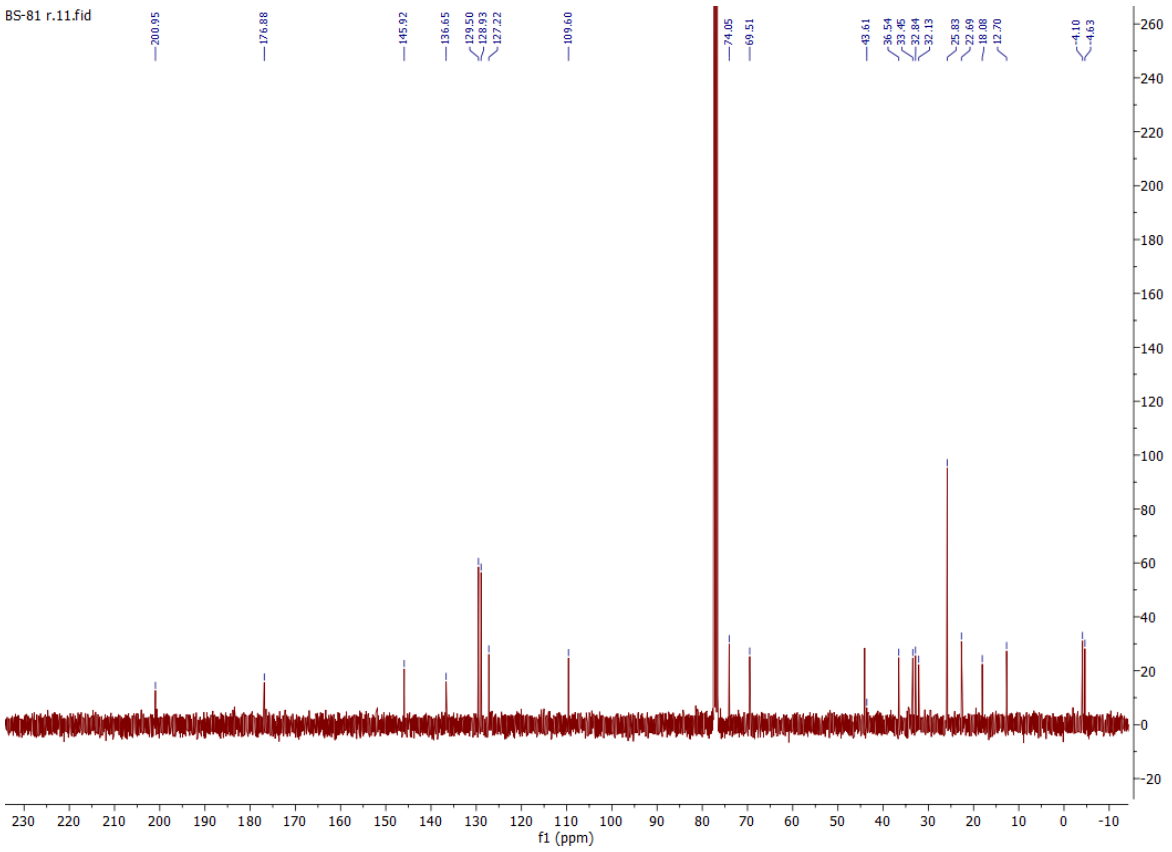
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.32-7.23 (m, 5H, Ar-H), 5.12 (ddd, *J* = 10.5, 6.6, 3.7 Hz, 1H, 12-H), 4.66 (s, 1H, 7-H), 4.65 (s, 1H, 1H, 7-H), 4.53 (app quint, *J* = 6.0 Hz, 1H, 3-H), 3.98 (app quart, *J* = 5.3 Hz, 1H, 3-H), 3.32-3.21 (m, 2H, 11-H, 13-H), 3.02 (dd, *J* = 13.1, 10.5 Hz, 1H, 11-H), 2.86 (d, *J* = 11.3 Hz, 1H, 13-H), 2.03-1.99 (m, 2H, 5-H), 1.72-1.64 (m, 1H, 4-H), 1.70 (s, 3H, 8-H),1.57-1.46 (m, 1h, 4-H), 1.21 (d, *J* = 6.8 Hz, 3H, 9-H), 0.84 (s, 9H, 16-H), 0.03 (s, 3H, 14-H), 0.01 (s, 3H, 14-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 200.9 (10-C), 176.8 (1-C), 145.9 (6-C), 136.6 (Ar-C), 129.5 (Ar-C), 128.9 (Ar-C), 127.2 (Ar-C), 109.5 (7-C), 74.0 (3-C), 69.5 (12-C), 43.6 (2-C), 36.5 (11-C), 33.4 (4-C), 32.8 (5-C), 32.1 (13-C), 25.8 (16-C), 25.6 (16-C), 22.7 (8-C), 18.1 (15-C), 12.7 (9-C), -4.1 (14-C), -4.6 (14-C).

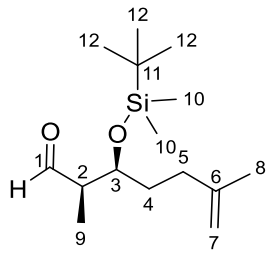
[α]D$^{20.7}$ -136.9 (*c* = 0.1 $CHCl_3$) Lit. - 156.0 (*c* = .0.1 $CHCl_3$)

In agreement with literature data.[27]





3-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhept-6-enal[27]



162

$C_{15}H_{30}O_2Si$

Mol. Wt. 270.49 g/mol

A solution of the TBS-protected aldol (95 mg, 0.20 mmol) in DCM (15 mL) was cooled to -78 °C and DIBAL-H (1 M in hexanes, 0.40 mL, 0.40 mmol, 2.0 equiv) was added dropwise. The reaction mixture was left to stir until the bright yellow colour disappeared, then the reaction mixture was quenched with methanol (2 mL), ethyl acetate (5 mL) and warmed to room temperature. The reaction mixture was then diluted with an aqueous solution of Rochelle's salt (10 mL) and left to stir for 4 h until

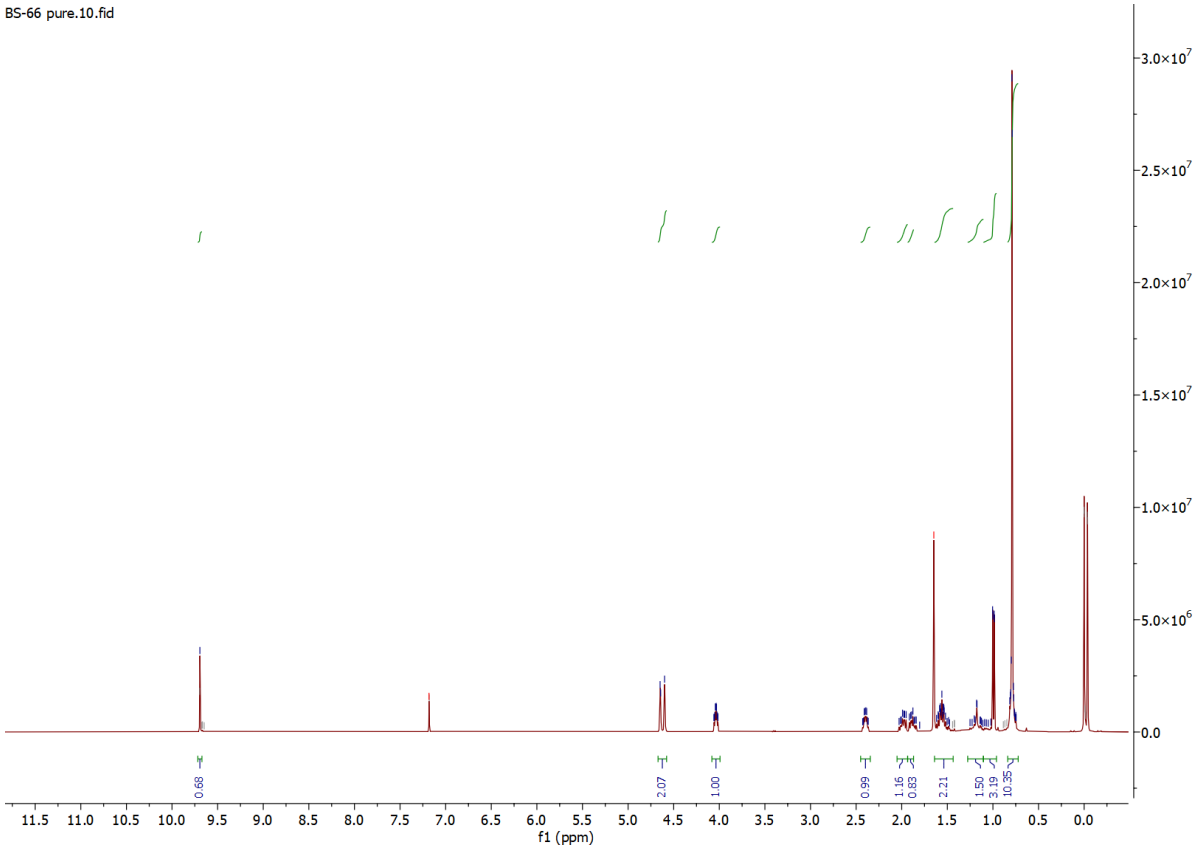
the organic phase became clear. The resulting mixture was then extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography (95:5 PE/Et_2O) to furnish the TBS-protected aldehyde as a colourless oil (35 mg, 64%).

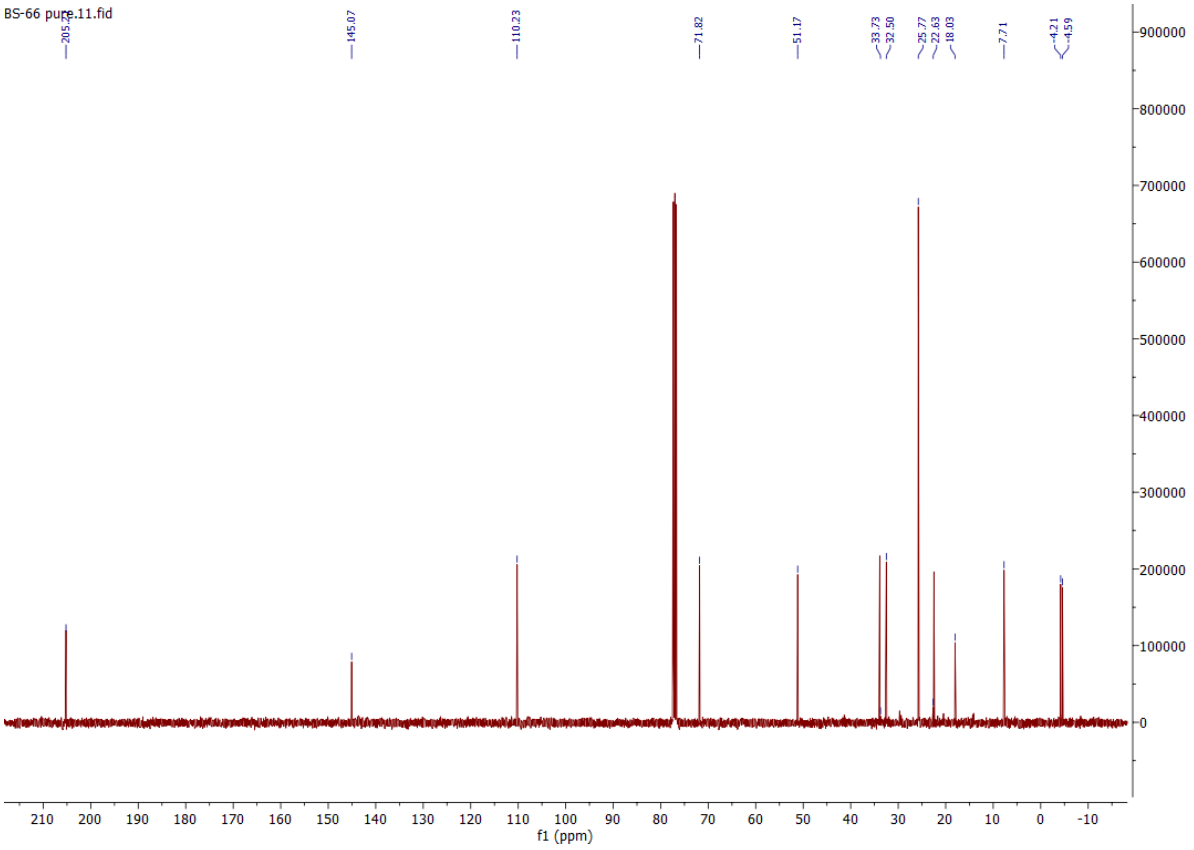
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.70 (d, *J* = 1.6 Hz, 1H, 1-H), 4.64 (s, 1H, 7-H), 4.59 (s, 1H, 7-H), 4.03 (td, *J* = 6.4, 3.4 Hz, 1H, 3-H), 2.39 (qdd, *J* = 7.1, 3.3, 1.0 Hz, 1H, 2-H), 2.03-1.95 (m, 1H, 5-H), 1.91-1.84 (m, 1H, 5-H), 1.64 (s, 3H, 8-H), 1.59-1.51 (m, 2H, 4-H), 0.9 (d, *J* = 6.6 Hz, 3H, 9-H), 0.78 (s, 9H, 12-H), -0.01 (s, 3H, 10-H), -0.04 (s, 3H, 10-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 205.2 (1-C), 145.1 (6-C), 110.2 (7-C), 71.8 (3-C), 51.2 (2-C), 33.7 (5-C), 32.5 (4-C), 25.7 (12-C), 22.6 (8-C), 18.0 (11-C), 7.7 (9-C), -4.2 (10-C), -4.6 (10-C).

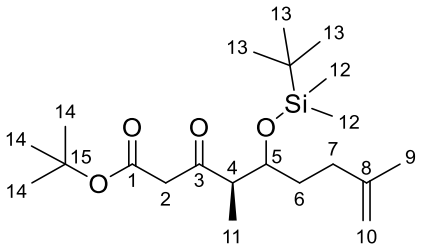
[α]D$^{20.7}$ -47.0 (*c* = 0.1 $CHCl_3$) Lit. - 41.0 (*c* = 0.1 $CHCl_3$)

In agreement with literature data.[27]





tert-Butyl 5-((_tert_-butyldimethylsilyl)oxy)-4,8-dimethyl-3- oxonon-8-enoate[26]



190

$C_{20}H_{40}SiO_4$

Mol.wt = 384.36 g/mol.

To a solution of *tert*-butyl diazoacetate (0.4 mL, 2.8 mmol, 2.0 equiv) in DCM (15 mL) was added tin(II) chloride (132.0 mg, 1.3 mmol, 0.5 equiv). The reaction was stirred at RT for 5 min then a solution of aldehyde (TBS-Protected) (378.0 mg, 0.7 mmol) in DCM (5 mL) was added dropwise and the mixture was left to stir at RT for 3h. The crude mixture was concentrated under vacuum and purified by flash column

chromatography 1:1 n-hex/ ethyl acetate gave 80% of the mixture (3:1) keto ester and enol.

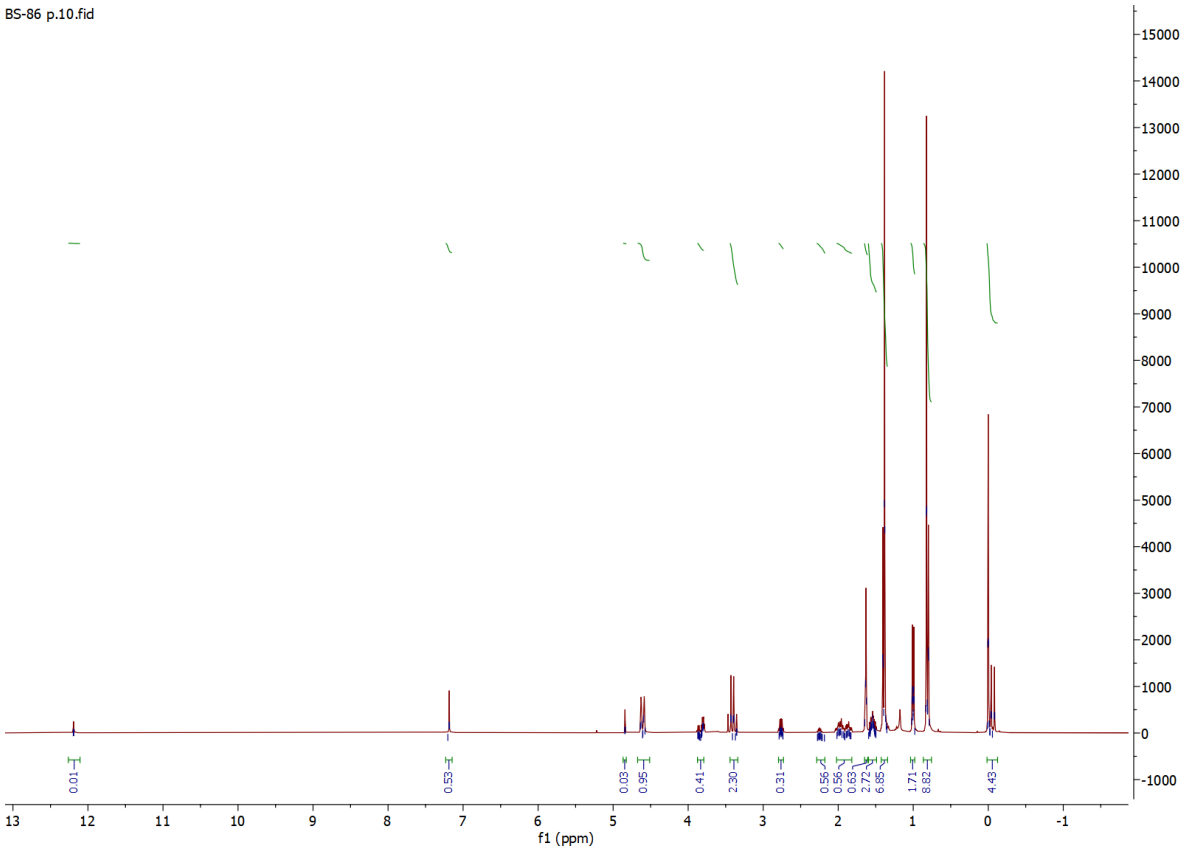
Keto ester spectra.

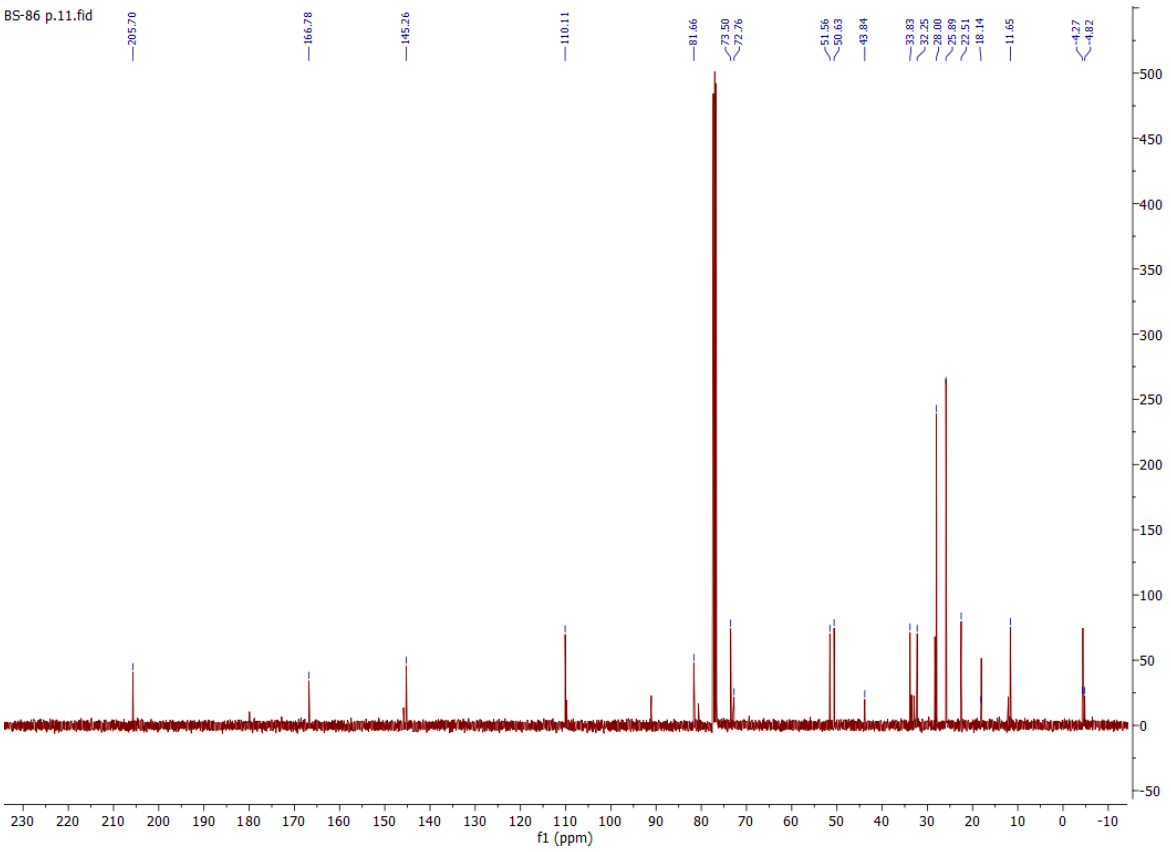
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.63 (s, 1H, 10-H), 4.59 (s, 1H, 10-H), 3.47 (d, *J* = 15.8, 1H, 2-H), 3.39 (d, *J* = 15.6 Hz, 1H, 2-H), 3.81 (dt, *J* = 8.0 Hz, 1H, 5-H), 2.77 (qd, *J* = 8.1, 4.1 Hz,1H, 4-H), 2.04-1.92 m, 2H, 7-H), 1.62, (s, 3H, 9-H), 1.58-1.53 (m, 1H, 6-H), 1.52-1.47 (m, 1H, 6-H), 1.38 (s, 9H, 14-H), 1.02 (d, *J* = 6.8 Hz, 3H, 9-H), 0.82 (s, 9H, 13-H), 0.04 (s, 3H, 12-H), 0.08 (s, 3H, 13-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 205.7 (3-C), 166.8 (1-C), 145.3 (8-C), 110.1 (10-C), 81.6 (15-C), 73.5 (5-C), 72.7 (15-C), 51.6 (2-C), 50.6 (13-C), 43.8 (4-C), 33.8 (6-C), 32.2 (7-C), 28.0 (13-C), 22.5 (9-C), 18.4 (11-C), 11.6 (14-C), -4.2 (12-C), -4.8 (12-C).

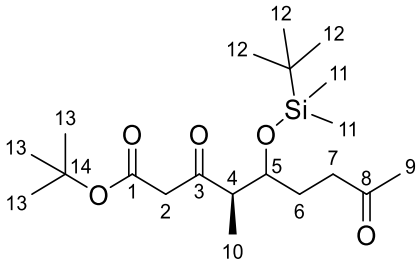
HRMS (Na^+) for $C_{20}H_{40}SiO_4$: 407.2601, Found: 407.2588.
IR (Thin film) 2950, 2932, 2928, 1750, 1710, 1650, 1300, 1180, 1000 cm^{-1}.

In agreement with literature data.[26]





***tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-4-dimethyl-3-8,di oxononanoate**



194

$C_{20}H_{38}SiO_5$

Mol. Wt. 386.36 g/mol

To a solution of (3:1 mixture of ketoester:enol (300 mg, 0.78 mmol) in mixture of dioxane/water 15:3 mL) were added 2,6-lutidine (0.18 mL, 1.56 mmol, 2 equiv), $K_2OsO_4.2H_2O$ (catalytic amount) and $NaIO_4$ (667.4 mg, 3.1 mmol, 4.0 equiv). The

mixture was left to stir for 4 hr. at RT. After completion the reaction mixture was quenched with 26 mL of water and 50 mL of DCM, layers were separated and aqueous layer was extracted with DCM (3 × 30 mL). The organic layer was washed with brine and dried over magnesium sulfate. The crude mixture was concentrated under vacuum and purified by flash column chromatography 1:1 n-hex/DCM giving 80% of the desired products. (The spectrum of ketone is given below)

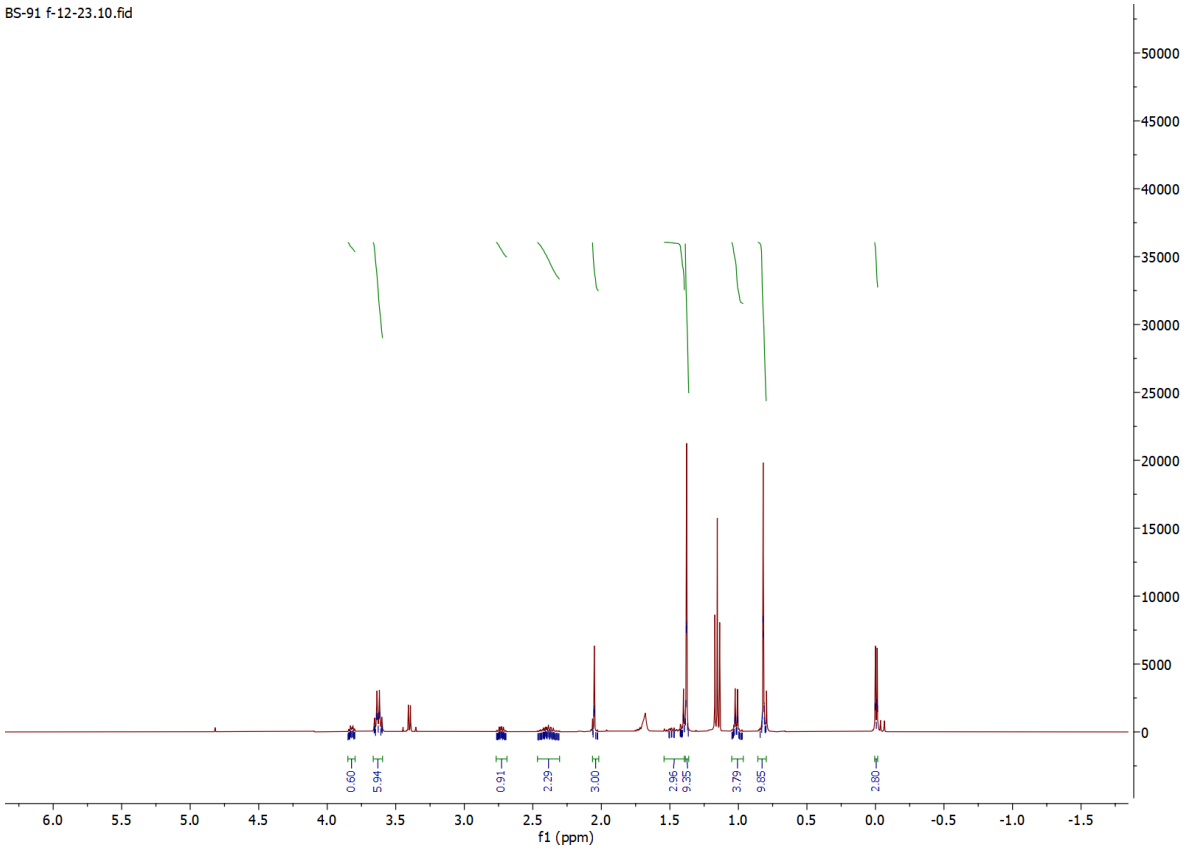
(Aq. layer and glassware were treated with a large excess of sodium sulfite solution to remove traces of osmium)

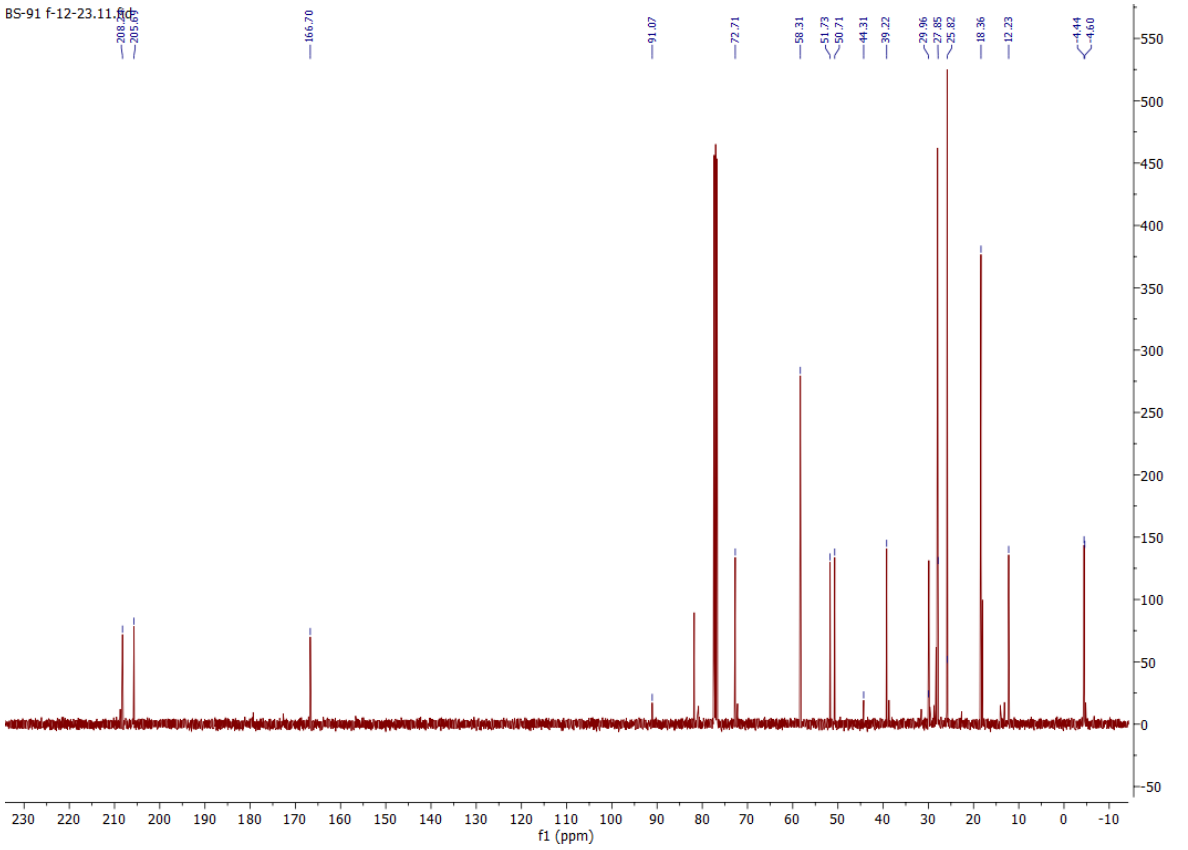
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.82 (td, *J* = 7.1, 2.3 Hz, 5H, 1-H), 3.64(d, *J* = 6.8 Hz, 2H, 1-H), 3.62 (d, *J* = 7.1 Hz, 2H, 1-H), 2.72 (qd, *J* = 7.0, 4.7 Hz, 1H, 4-H), 2.46-2.30 (m, 2H, H-7), 2.04 (s, 3H, H-9), 1.54-1.40 (m, 2H, H-6), 1.37 (s, 9H, 14-H), 1.02 (d, *J* = Hz, 3H, 10-H), 0.87 (s, 9H, H-12), 0.04 (s, 3H, 11-H) -0.02 (s, 3-H, 11-H),

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 208.2 (C-8), 205.6 (C-3), 166.7 (C-1), 91.1 (C-10), (72.7 C-5), 58.3 (14-C), 51.7 (2-C), 50.7 (4-C), 44.3, 39.2 (C-7), 29.9 (C-9), 27.8 (6-C), 25.8 (12-C),18.4 (13-C), 12.2 (10-C), -4.4 (11-C), -4.6 (11-C).

HRMS(Na^+) for $C_{20}H_{38}SiO_5$: 409.2392, Found: 409.2381.

IR (Thin film) 2957, 1714,1461, 1413, 1367, 1251, 1149, 1004 cm^{-1}.


BS-91 f-12-23.10.fid
0.60
5.94
0.91
2.29
3.00
2.96
9.35
3.79
9.85
2.80
f1 (ppm)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205.89
166.70
91.07
72.71
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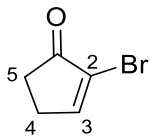
51.73
50.71
44.31
39.22
29.96
27.85
25.82
18.36
12.23
4.44
4.60
f1 (ppm)

2-Bromocyclopent-2-enone[26]



196

C_5H_5BrO

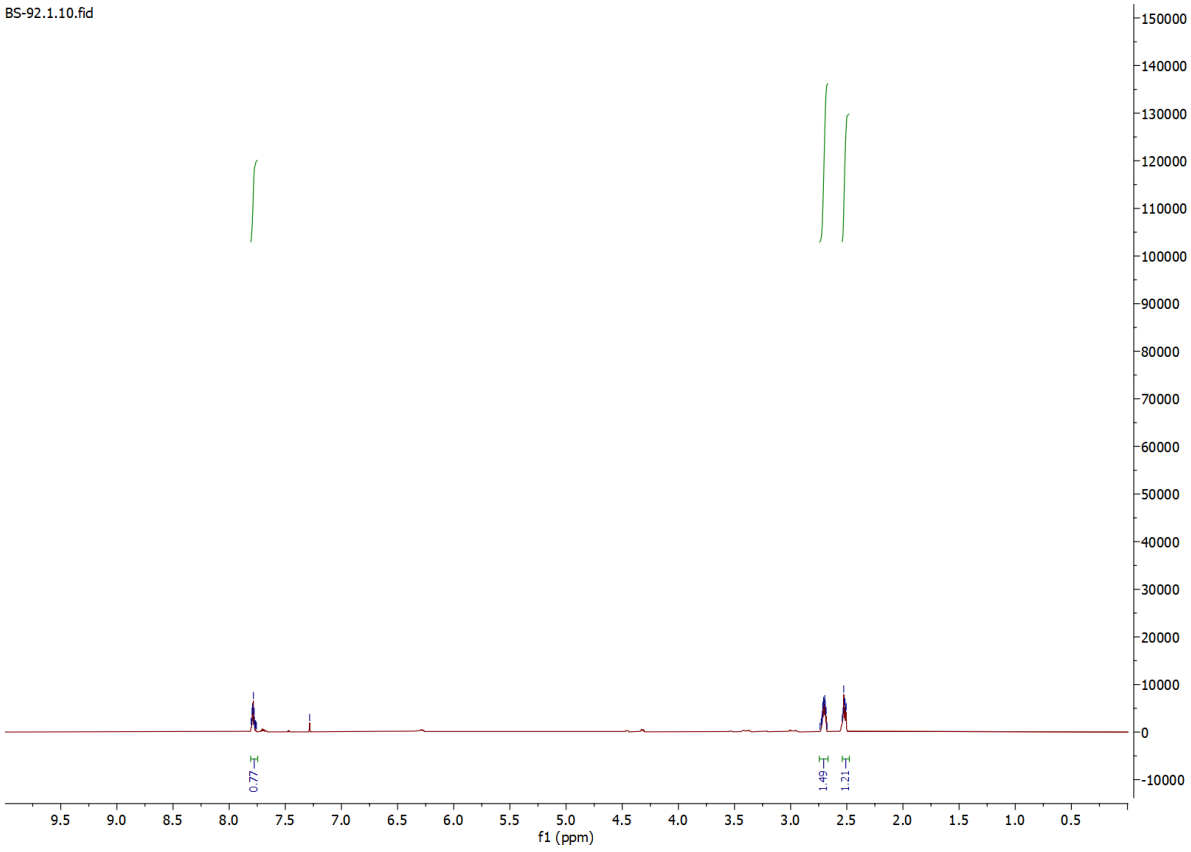
Mol. Wt. 161.0 g/mol

A solution of bromine (1.1 mL, 22.0 mmol, 1.1 equiv) in DCM (15 mL) was added slowly to a solution of 2-cyclopentenone (1.7 mL, 20.0 mmol) at 0 °C. The reaction mixture was warmed to RT and left to stir for 1.5 h. After that time, Et_3N (4.4 mL, 16.0 mmol, 1.6 equiv) was added slowly and the reaction mixture was left to stir for an additional 1.5 h. The reaction mixture was quenched by the addition of a 1 M aqueous solution of hydrochloric acid (40 mL). The aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. Purification by flash chromatography (90:10 PE/Et_2O) gave the product (2.3 g, 71%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.80 (t, *J* = 2.7 Hz, 1H, 3-H), 2.65-2.62 (m, 2H, 4-H), 2.48- 2.45 (m, 2H, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz,) δ 201.8 (C-1), 162.0 (C-3), 126.2 (C-2), 32.4 (C-5), 28.1 (C-4).

In agreement with literature data.[26]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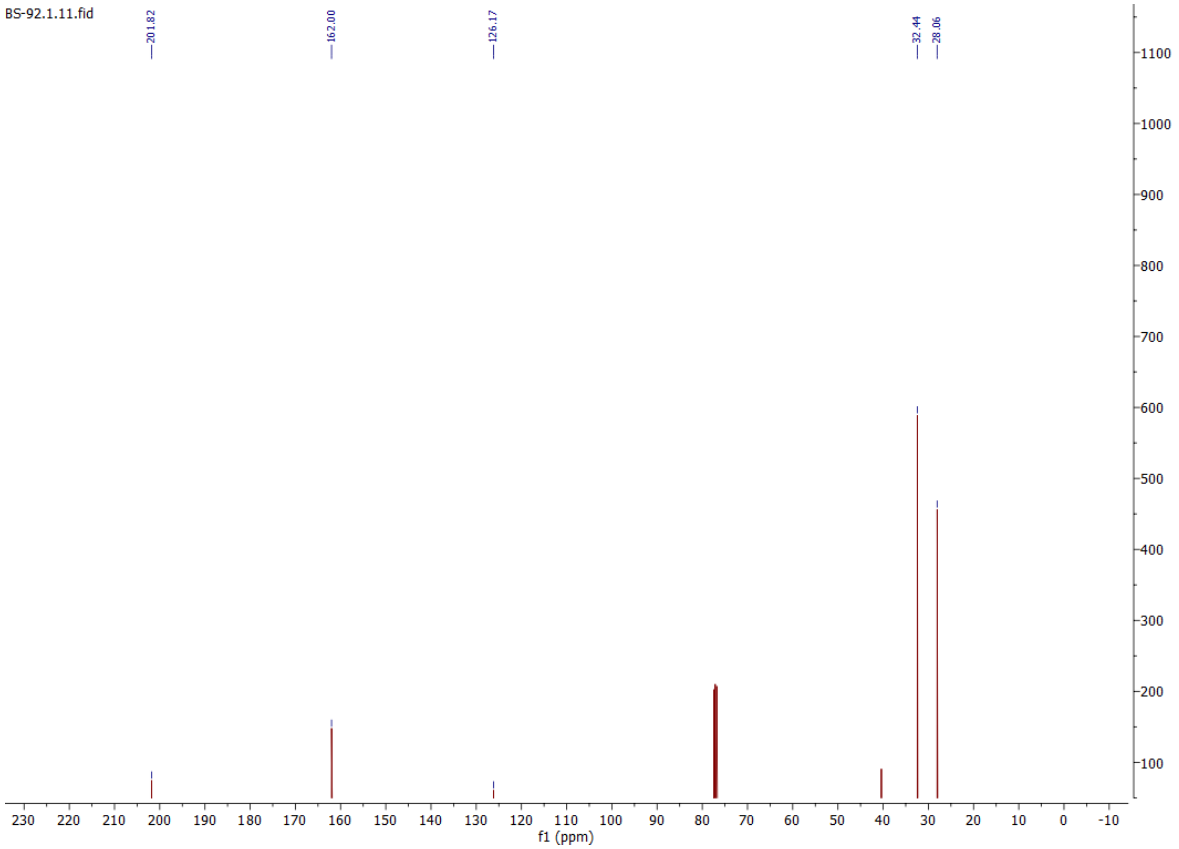
1.49
1.21
f1 (ppm)


BS-92.1.11.fid
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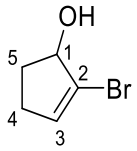
162.00
126.17
32.44
28.06
f1 (ppm)

2-Bromocyclopent-1-ol[26]



197

C_5H_6BrO

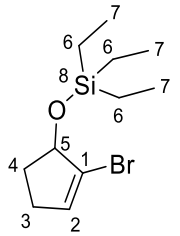
Mol. Wt. 163.0 g/mol

A solution of 2-bromocyclopent-2-enone (0.7 g, 4.5 mmol) in DCM (30 mL) was cooled to - 78 °C and a 1 M DIBAL-H solution in hexanes (9.1 mL, 9.1 mmol, 2.0 equiv) was added dropwise. The reaction mixture was left to stir for 1 h at -78 °C. The reaction mixture was then 39 quenched by adding a saturated aqueous solution of Rochelle salt (100 mL) and left to stir for 4 h. The aqueous layer was extracted with DCM (30 × 3 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to afford the allylic alcohol (0.7 g, 94%) as a colourless liquid, which was used for the next step without purification.

((2-Bromocyclopent-2-en-1-yl)oxy)triethylsilane[26]

$C_{11}H_{21}BrOSi$

Mol. Wt. 277.28 g/mol



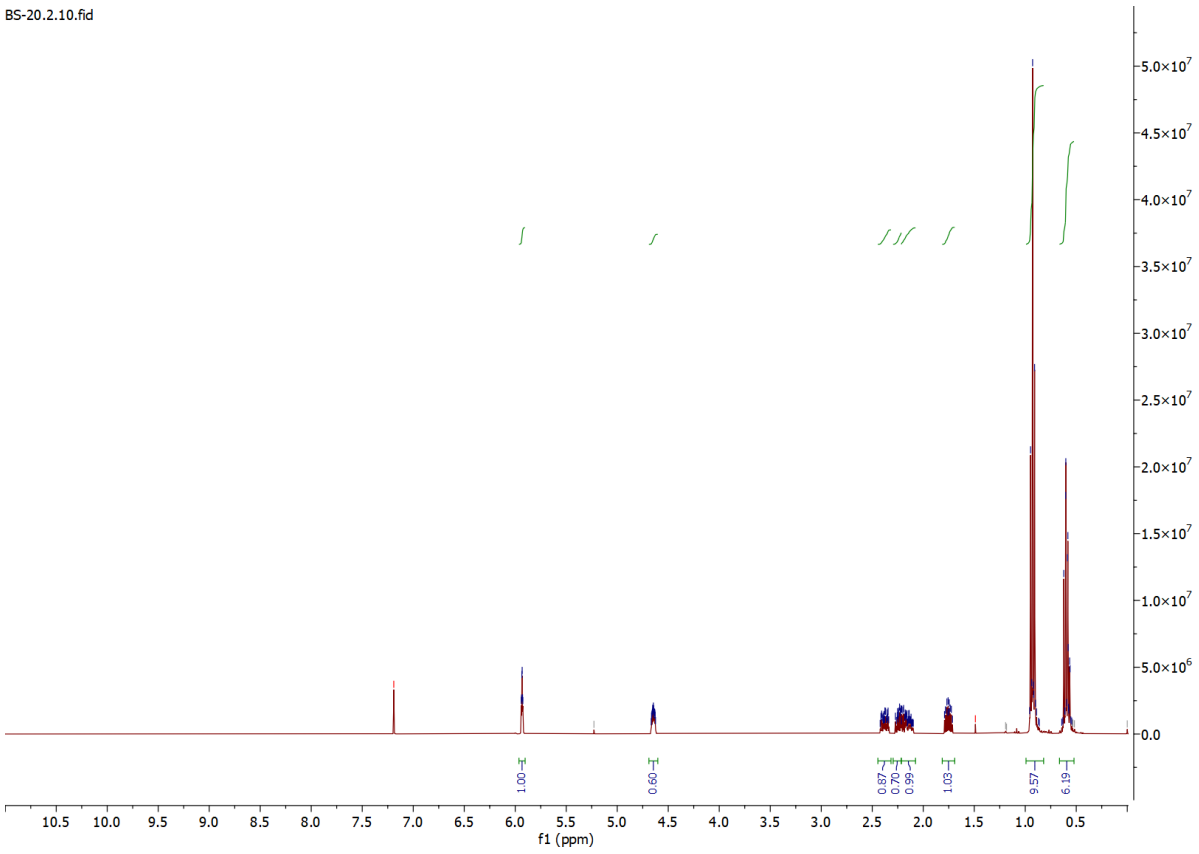
164

2-Bromocyclopent-2-en-1-ol (1.0 g, 6.3 mmol) was dissolved in dry DMF (25 mL) then imidazole (1.3 g, 19.0 mmol, 3.0 equiv) and DMAP (0.76 g, 0.62 mmol, 0.10 equiv) were added. The reaction was cooled to 0 °C then chlorotriethylsilane (1.6 mL, 9.4 mmol, 3.0 equiv) was added dropwise and the reaction was stirred for 10 min. The mixture was warmed to room temperature and left to stir for 1 h. The mixture was then diluted with water (20 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 × 20 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (99:1 PE/Et_2O) to give the product (1.02 g, 59%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.93 (td, *J* = 2.6, 0.7 Hz, 1H, 2-H), 4.68-4.63 (m, 1H, 5-H), 2.42-2.34 (m, 1H, 3-H), 2.26-2.16 (m, 2H, 4-H), 1.79-1.71 (m, 1H, 3-H), 0.94 (t, *J* = 8.1 Hz, 9H, 7-H), 0.60 (q, *J* = 8.0 Hz, 6H, 6-H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 133.5 (2-C), 125.5 (1-C), 79.3 (5-C), 33.3 (3-C), 30.3 (4-C), 6.9 (7-C), 4.6 (6-C).

In agreement with literature data.[26]


BS-20.2.10.fid
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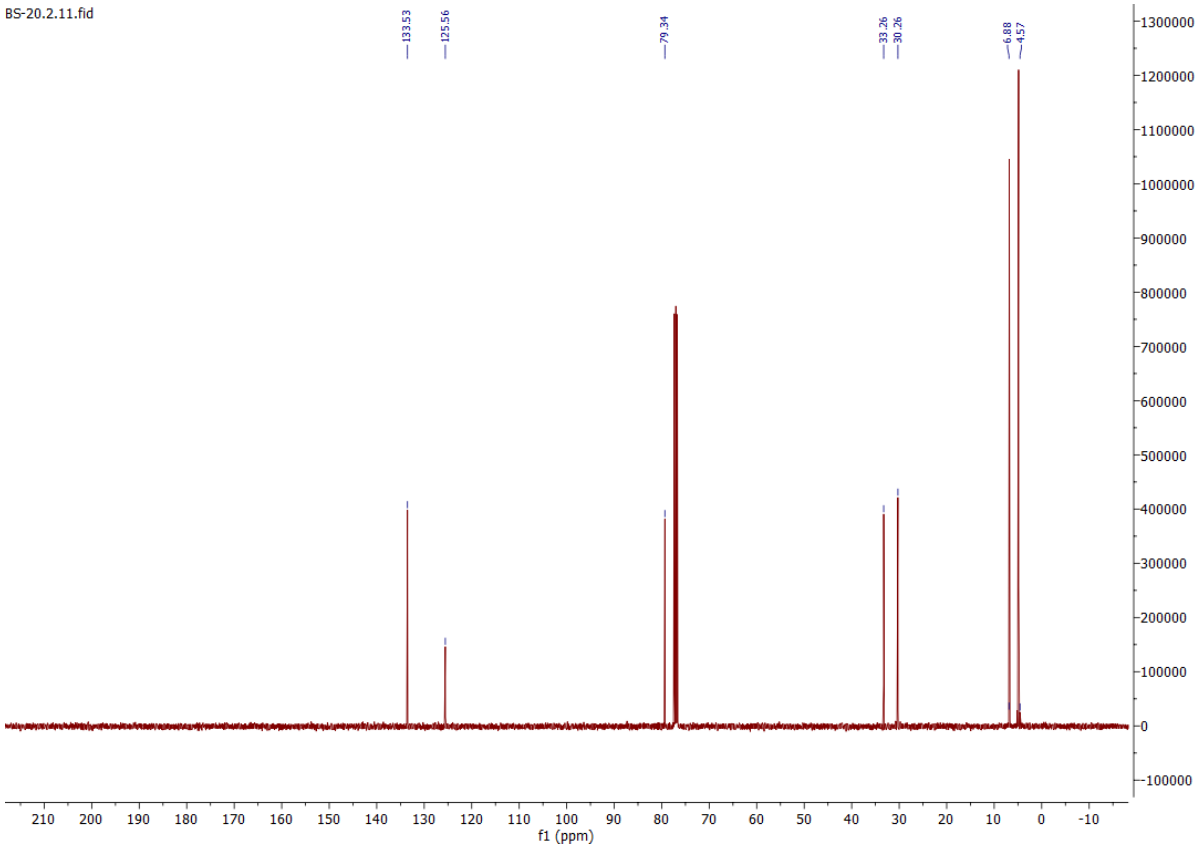
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
1.00
0.60
0.87
0.70
0.99
1.03
9.57
6.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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125.56
79.34
33.26
30.26
6.88
4.57
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

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