Studies Towards the Synthesis of the Decalin Core of Streptosetin A

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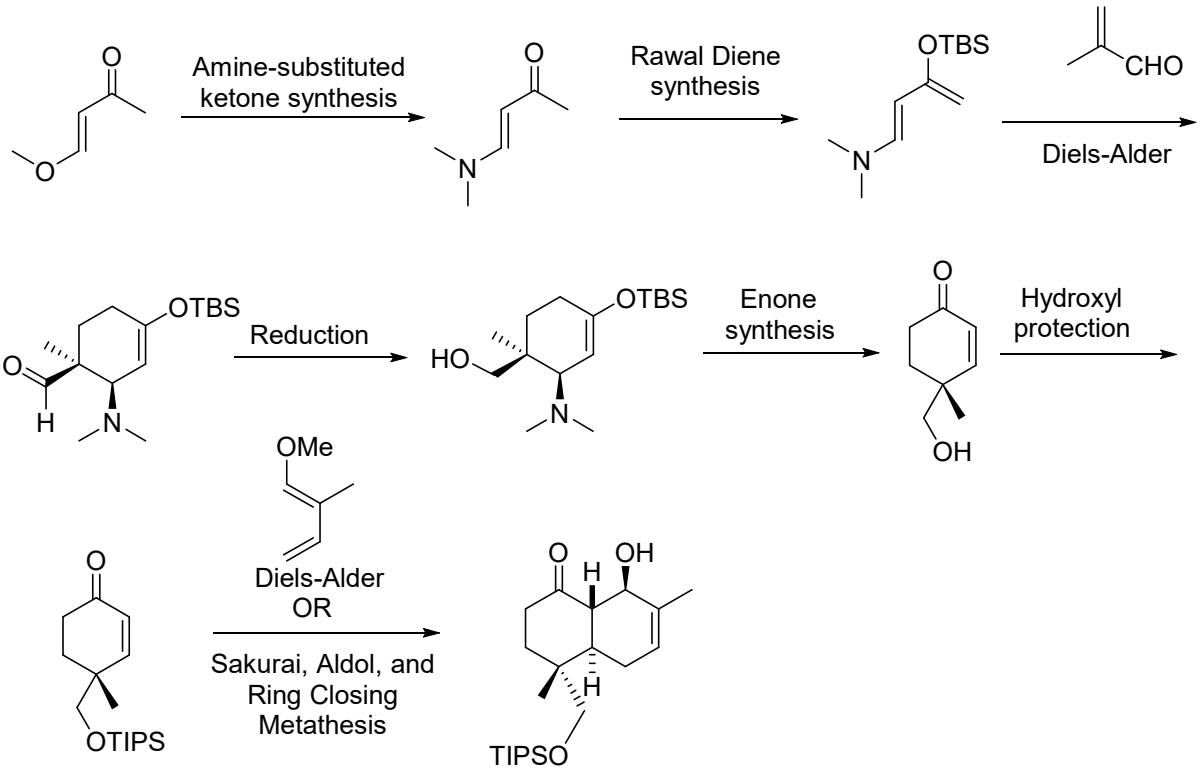
1. **Abstract**

In 2012, Amagata et al. isolated a natural product from a marine-derived actinomycetes. The compound exhibited human class III HDAC (SIRT) inhibition and was named streptosetin A. Structurally, streptosetin A is categorized as a polyketide tetramic acid derivative, produced by an NRPS−PKS hybrid pathway, as reported for equisetin isolated from a *Fusarium equiseti*. This thesis describes the research efforts toward the synthesis of the decalin core of streptosetin A. An asymmetric synthesis of the key enone was achieved in a five-step sequence. The enantioenriched enone core was formed in 79% ee. The synthetic route involved the Diels-Alder cycloaddition reaction of Rawal's diene with a dienophile to generate a Diels-Alder product. Thereafter, the reduction and removal of the OTBS protection group, together with the elimination of dimethylamine afforded an enone compound. Further studies on Diels-Alder and Sakurai reactions were undertaken in an attempt to secure the desired decalin core (**Scheme 1**).



Scheme 1. Formation of the decalin core of streptosetin A

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6. Acknowledgements

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This work would not have been possible without support from technical staff in the department. I would like to thanks to Heather Fish for NMR service, Karl Heaton for mass spectrometry, Adrian Whitwood for X-ray services and Steve and Mike from stores.

7. Declaration

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

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

Suresh Shinde

8. Introduction

8.1 Decalin rings in natural products

A natural product is a substance or chemical compound that is produced by a living organism in nature, and many of these are biologically active. Many bioactive compounds are secondary metabolites produced by the microorganisms for their defence, detoxification, or communication with other organisms.[1,2] Natural products can be prepared by chemical synthesis, and this has historically played an important role in the development of the field of organic chemistry.[3,4]

The decalin motif is found in several secondary metabolites produced by microorganisms, mainly fungi and actinomycetes.[5] It is typically connected to highly multi-functionalized or complex groups, resulting in high structural and functional diversity.

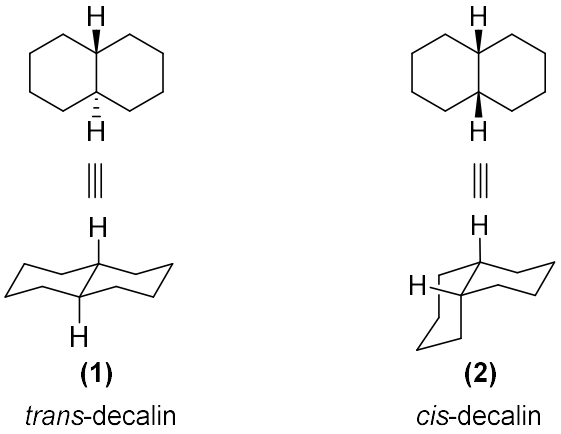


Figure 1. Structures of *trans*-decalin (**1**) and *cis*-decalin (**2**).

Decalin (**Figure 1**) is a fused bicyclic, saturated hydrocarbon (bicyclo[4.4.0]decane). Decalin can exist in two configurations, *trans*-decalin (**1**) and *cis*-decalin (**2**). The ring-junction hydrogens on the same side of the molecule form *cis*-decalin, while those on the opposite sides form *trans*-decalin. In *trans*-decalin, the two rings are joined through two equatorial bonds. On the other hand, in *cis*-decalin, the two rings are joined by axial and equatorial bonds. These units are present in many natural products such as those shown in **Figure 2**.

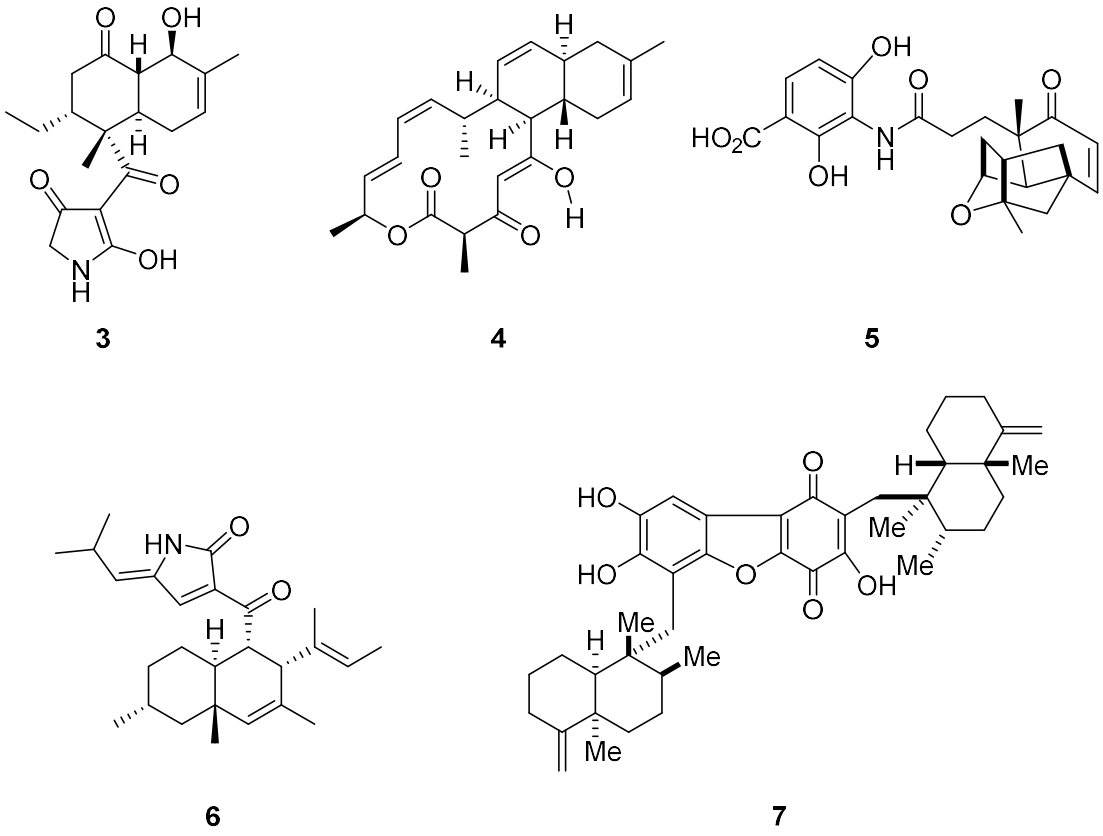


Figure 2. Chemical structures of *streptosetin A* **(3)**,[9] *anthracimycin* **(4)**,[10] *platensimycin* **(5)**,[11] *myceliothermophin E* **(6)**,[12] and *popolohuanone E* **(7)**.[13]

These compounds show various biological activities including antifungal, antibacterial, anticancer, and immunosuppressive activities, and have attracted considerable interest from researchers worldwide in terms of their biosyntheses, chemical syntheses, and varying the properties of the functionalized decalin motif (**Figure 2**).[6–8] For example Streptosetin A (**3**)[9] shows anticancer properties, anthracimycin (**4**)[10] and platensimycin (**5**)[11] are antibiotics, Myceliothermophin E (**6**)[12] shows potent cytotoxic activity against the Chinese hamster ovary cell line, and Popolohuanone E (**7**)[13] shows highly selective cytotoxicity against the A549 human non-small cell lung cancer cells.

Streptosetin A **3** was isolated from a yeast and was identified during the screening of the extract libraries of marine-derived actinomycetes. Streptosetin A shows weak inhibitory activity against yeast Sir2p as well as human SIRT1 and SIRT2.[9]

In 2013, Fenical *et al.* reported the isolation of a natural product from a marine microorganism of *streptomyces* species collected from the deep ocean near Santa Barbara, CA, which showed noteworthy activity against *Bacillus anthracis* as well as vancomycin resistant and methicillin-

resistant *Staphylococcus aureus* (MRSA).[10] The compound was a potent antibiotic and was identified as 14-6-6 membered ring polyketide macrolide **4**[10] (**Figure 2**).

Platensimycin **5**[11] is a potent bacterial type II fatty acid biosynthesis inhibitor, which was isolated from various strains of *Streptomyces platensis,* that were obtained from the soil samples collected in South Africa and Spain. This natural product selectively inhibits *S. aureus* FabF. This enzyme catalyses the initial condensation step in bacterial fatty acid synthesis.[14] It is an antibiotic that is biologically active against gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *vancomycin-resistant Enterococcus* (VRE) with no observed toxicity.

Myceliothermophin E **6**[12] is a new polyketide that contains a tetramic acid, and was isolated from thermophilic fungus, *Myceliophthora thermophila*.[12] Five analogues containing tetramic acid moieties, myceliothermophins A–E, were isolated, through bioassay-guided separation. The cytotoxicity assays of myceliothermophins A–E against four types of cancer cells, human hepatoblastoma (HepG2), human hepatocellular carcinoma (Hep3B), human lung carcinoma (A-549), and human breast adenocarcinoma (MCF-7) have been reported.

Popolohuanone E **7**[13] was isolated from the *Dysidea sp.* of Pohnpei marine sponge by Scheuer *et al*. in 1993. It is a potent inhibitor of topoisomerase II and shows highly selective cytotoxicity against the A549 human non-small cell lung cancer cells.[13,15,16]

The above compounds are examples of naturally occurring complex decalin systems. These decalin cores have different functionalized moieties such as macrolide ring, tetramic acid, aminobenzoic acid units and benzofuran derivatives, affording different biological activities. As these compounds are only available in small quantities from natural sources, the total synthesis of the natural products is important for further investigation of their biological activities and potential as drugs.

8.2 Total synthesis of natural products.

Primary metabolism is the biosynthesis and breakdown of proteins, fats, nucleic acids and carbohydrates, which are essential for all living organisms. The compounds involved in this process are called primary metabolites.[17] Secondary metabolites (natural products) are typically organic compounds produced by the modification of primary metabolite biosynthesis. Secondary metabolites are not essential for the growth, development, or reproduction of a living organism,[17,18] but they are produced for defence against predators or adaptation to the surrounding environment.[17,19]

Natural products have been traditionally used for the treatment of many diseases and illnesses, and play a significant role in drug discovery and development.[20] Many of these natural products have afforded current drug candidates. [20,21] The most well-known example is the synthesis of an anti-inflammatory agent, acetylsalicylic acid (aspirin), derived from salicin, which is a natural product isolated from the bark of the willow tree, *Salix alba L*.[22] Morphine isolated from the plant, *P. somniferum,* is treated with acetic anhydride to yield diacetylmorphine (heroin), which is used as a painkiller.

The isolation of natural products and investigation of their biological activities is possible, but the quantities are not sufficient for their use in medicinal purposes. Hence, the role of total synthesis in the development of natural products is very important.[23] Total synthesis is the chemical synthesis of a molecule, starting from simple, readily available building blocks.

8.3 Biosynthesis of polyketide decalins

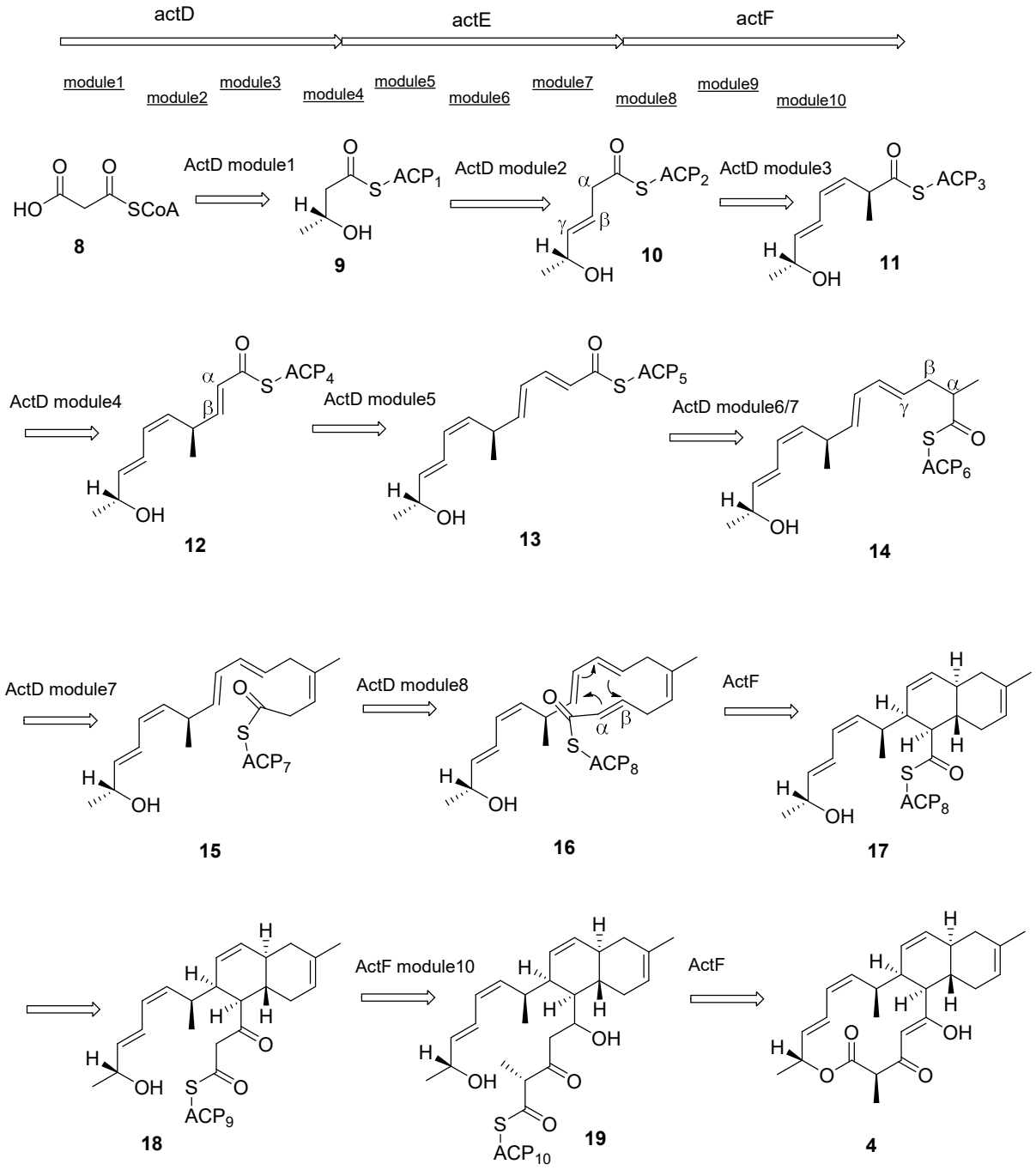
Polyketide synthase (PKS) is an enzyme that produces polyketides, and is divided into three classes: type I, iterative type II, and acyl-carrier protein type III. Type I PKSs comprise β-ketoacyl-ACP synthase, acyltransferase, and acyl carrier protein domains, and are used to select and load carboxylic acid units for condensation in the chain assembly.[24]

For the biosynthesis of the *anthracimycin* polyketide **4**, the enzyme responsible for type I polyketide synthase (PKS) was identified,[25] and it was determined that for the synthesis of the intermediates in the chain elongation process, type I polyketide synthase (PKS) catalysed a series of Claisen-like condensations (**Scheme 2**).[24]

The route for the biosynthesis of anthracimycin **4** may be initiated by the decarboxylation of malonyl residue **8** and addition to acyl CoA, followed by reduction to form the acylated ACP1

metabolite intermediate **9**.[26,27] ACP2 **10** was formed by chain elongation *via* the addition of a β,γ-double bond, formed by a series of addition, reduction, and elimination steps, which could also be introduced in fragment **11** to form a conjugated diene. During the process of chain elongation with the introduction of α,β-double bonds to form fragment **12,** modules **10** and **11** could be characterised.[27] In the next step, the formation of intermediate **14** involved α-methylation and β-keto reduction. After this, a β,γ -shift would occur to install a double bond with cis-geometry.[28] The α,β-unsaturated compound **16** was formed by further chain elongation, and was suitable for the Diels-Alder [4 + 2] cycloaddition, to generate the *trans*-decalin motif of the natural product. An *endo*-transition state could be envisioned to form this *trans*-decalin core. The last two-step sequence of chain elongation would be characterised by a thioesterase (TE) domain to catalyse the macrocyclization and chain release (**Scheme 2**).[25]

The enzymes capable of catalysing [4 + 2] cycloadditions have been characterized for a small number of natural product biosynthetic pathways, for the formation *trans*-decalin scaffolds.[29-35] Recently, in the biosynthetic pathway of pyrroindomycin, Liu and coworkers identified that an FAD-dependent enzyme PyrE3 could catalyse the formation of the *trans*-decalin moiety of this molecule.[36] In addition, in the biosynthesis of the fungal metabolite, lovastatin, the LovB PKS enzyme is responsible for the [4+2] cycloaddition which generates the trans-declain product.[33,34,37] In the biosynthesis of **4**, it is unknown if the intramolecular Diels-Alder reaction is catalysed by an enzyme or is spontaneous to form the *trans*-decalin system. In this cycloaddition, intermediate **16** has a trans-geometry dienophile double bond and a rigidity and orientation, imparted by the presence of two β,γ-shifted double bonds. This decreases the degree of freedom and assists this intramolecular cycloaddition by steric effects rather than being stabilised by any particular transition state explanation.[25]



Scheme 2. Polyketide synthesis of anthracimycin (**4**).

8.4 Chemical syntheses of decalin-cores of natural product

Many natural products such as isoprenoids and polyketides contain the decalin ring system. This motif can be multifunctionalised with the attachment of complex groups, and owing to the diversity of structures, diverse biological activities are observed. Therefore, many researchers worldwide are investigating their chemical syntheses and therapeutic potential.

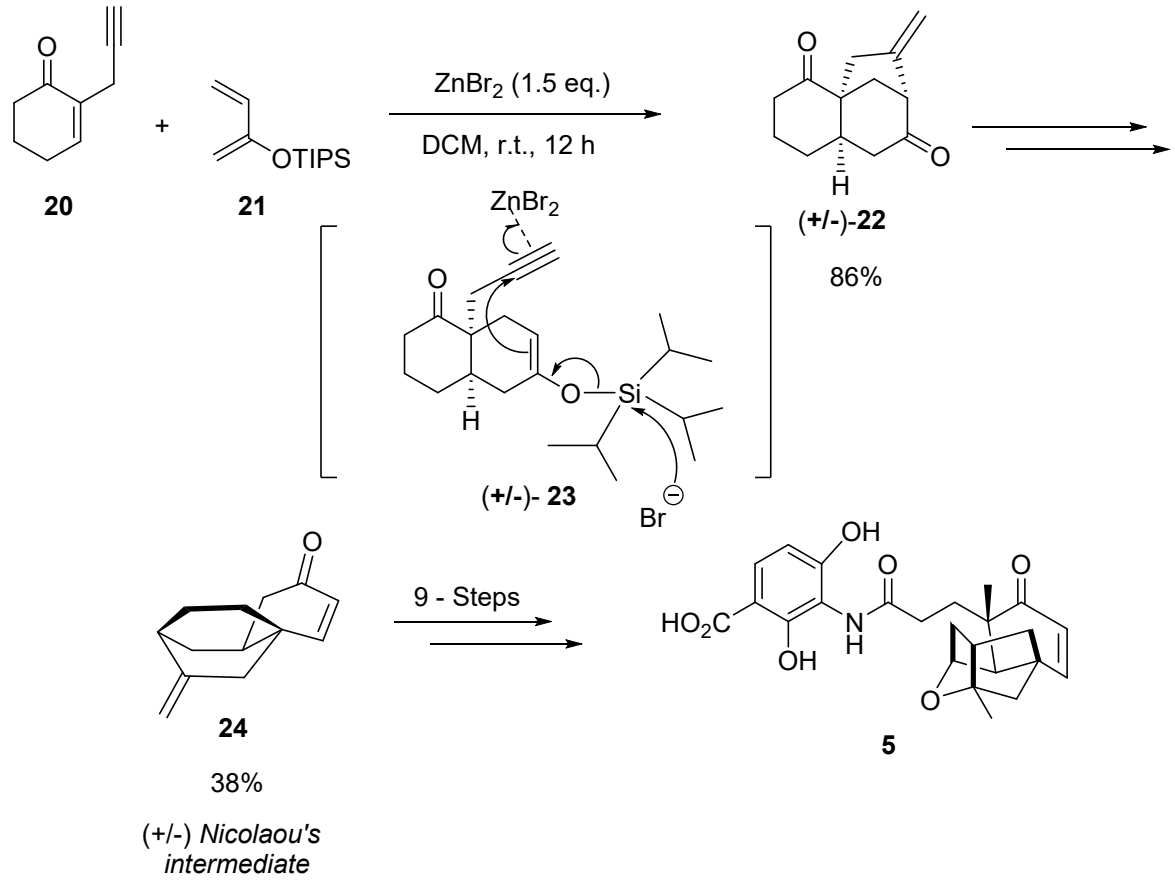
The decalin system has two fused rings, and several methods have been used for its synthesis.[38] The chemical syntheses of decalins mainly involve (a) inter and intramolecular Diels-Alder reactions, (b) nucleophilic and anionic cyclisations, and (c) cation- or radical-induced polyene cyclisations. The chemical syntheses of the decalin cores of a few natural products are discussed below.

8.4.1 Chemical synthesis of decalin core by Diels-Alder reactions

The Diels–Alder cycloaddition is often used for the syntheses of six-membered cyclic compounds. Intermolecular and intramolecular Diels-Alder reactions are the two types that can be used to synthesize the decalin structures.

Intermolecular Diels-Alder reaction

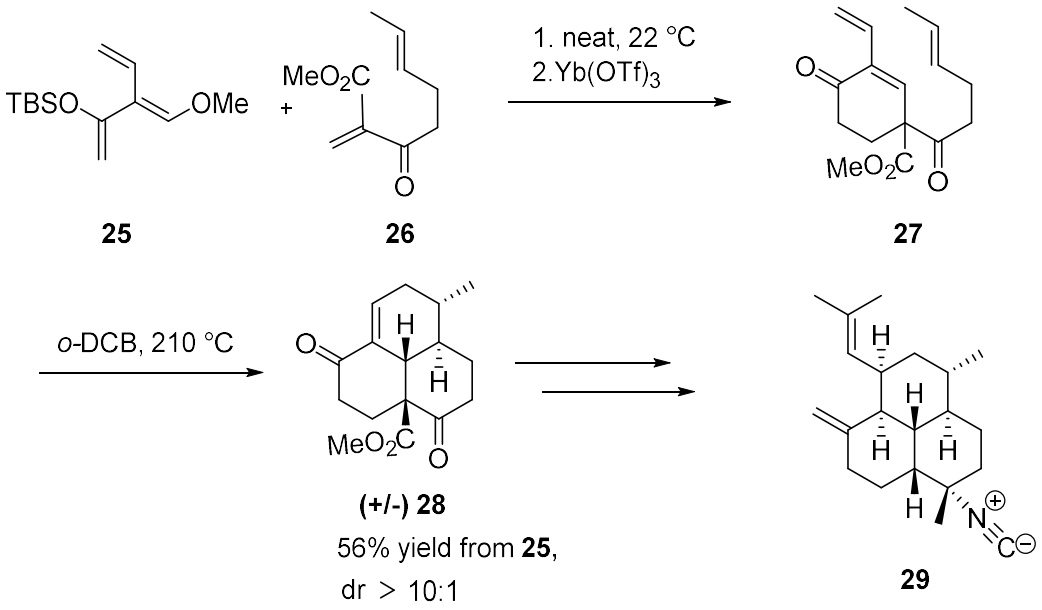
The intermolecular Diels–Alder reaction has been widely applied to the construction of *cis*-decalin frameworks. The tricyclic *ent*-kaurenoid **22** was synthesised by intermolecular Diels-Alder cycloaddition. In this reaction, a mild Lewis acid was used for the σ- complex formation with enone **20**, which was then reacted with diene **21** to form Diels -Alder cycloaddition product **23**. Then, a π-complex was formed with alkyne intermediate **23**, which underwent carbocyclisation, *via*, the breakage of the silyl enol ether bond (O-Si bond) leading to tricyclic product **22**.[39] This cyclic product **22** was used as a building block for the synthesis of platensimycin **5**[11] (**Scheme 3**).



Scheme 3. Intermolecular Diels-Alder/ carbocyclisation reaction sequence reported by Zhang.[39]

Intramolecular Diels-Alder reaction

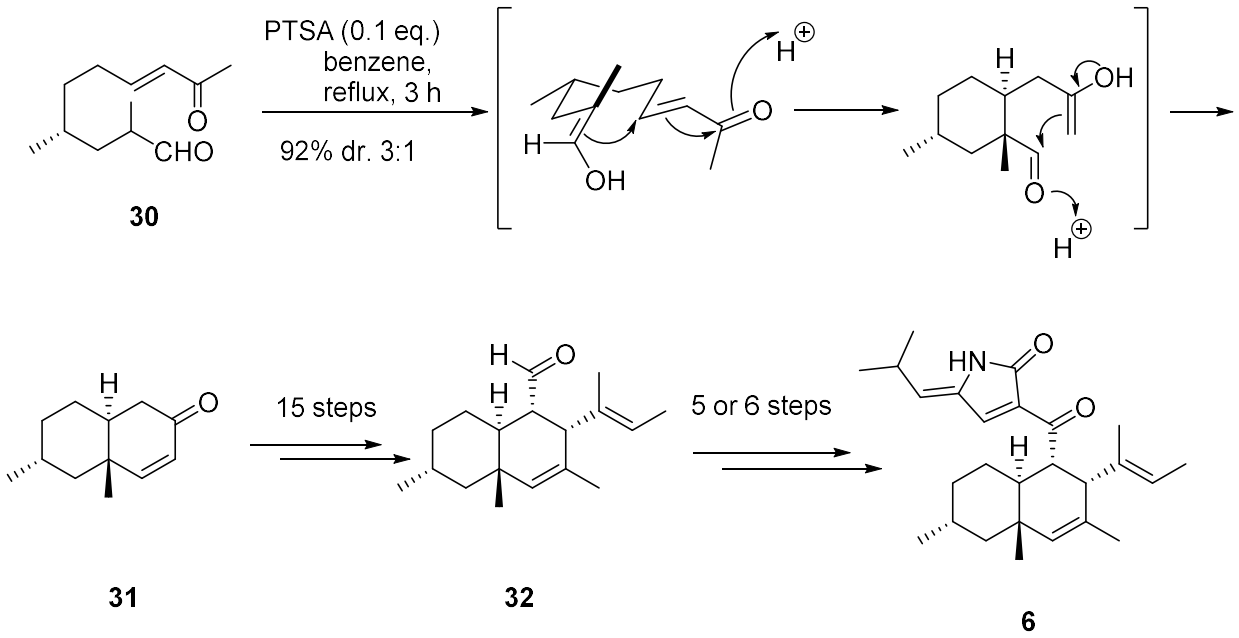
Shenvi (**Scheme 4**) described the total synthesis of racemic amphilectene, a marine nanomolar antimalarial agent.[40] Intermolecular cycloaddition reaction between dendralene **25** and dienophile **26** at ambient temperature, followed by the addition of 5 mol% $Yb(OTf)_3$ afforded an intermediate cross-conjugated enone **27**. After heating in *o*-dichlorobenzene this compound underwent a second Diels-Alder cycloaddition reaction in a microwave to produce **28** in 56% yield with high selectivity (d.r. >10 : 1). Compound **28** was used as a building block for the synthesis of racemic amphilectene **29** (**Scheme 4**).



Scheme 4. Intermolecular Diels-Alder/ carbocyclisation reaction sequence reported by Shenvi. [40]

8.4.2 Nucleophilic and anionic cyclization for the synthesis of decalin system.

The total synthesis of myceliothermophin E **6**, a potent cytotoxic polyketide, was accomplished *via* a cascade reaction affording the *trans*-fused decalin ring **31**.[41]



Scheme 5. Nicolaou's total synthesis of myceliothermophins (**6**)

During this cascade biscyclisation reaction, enolization and intramolecular Michael addition was followed by aldol condensation to afford compound **31** in 92% yield (dr = 3 : 1), in the presence of catalytic amounts of PTSA in refluxing benzene. This enone decalin system **31** was subjected to further reactions to, generate aldehyde intermediate **32** in 15 steps. The final attachment of the pyrrolidinone structural motif to **32** afforded the myceliothermophins **6** (**Scheme 5**).

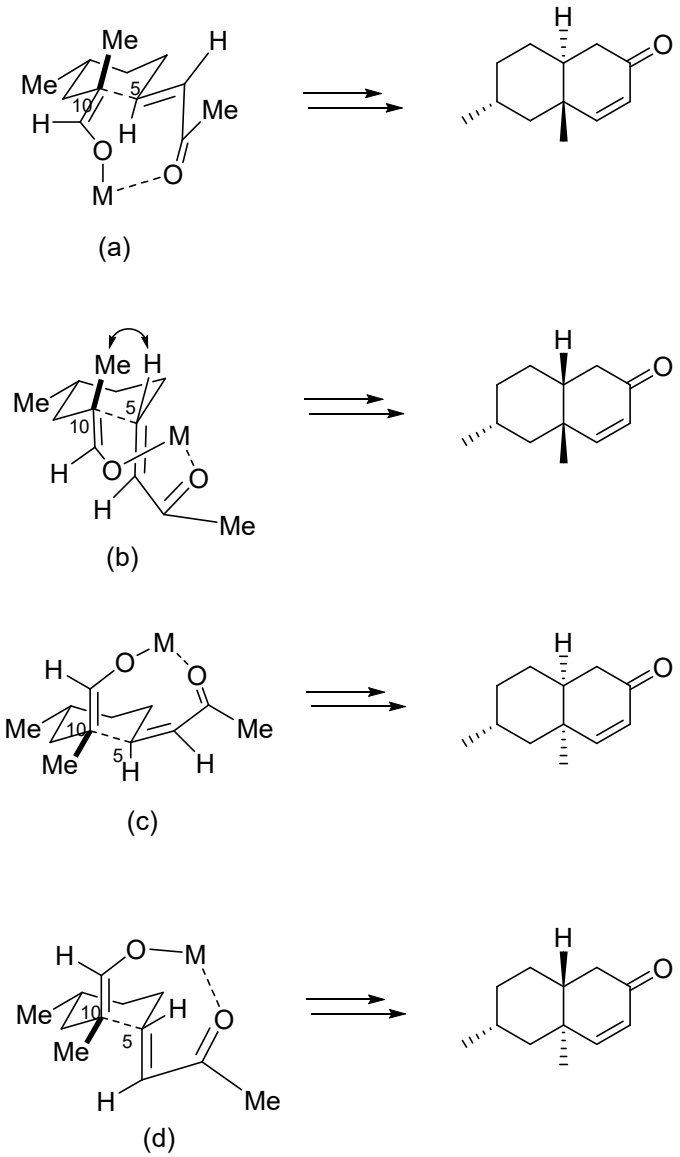


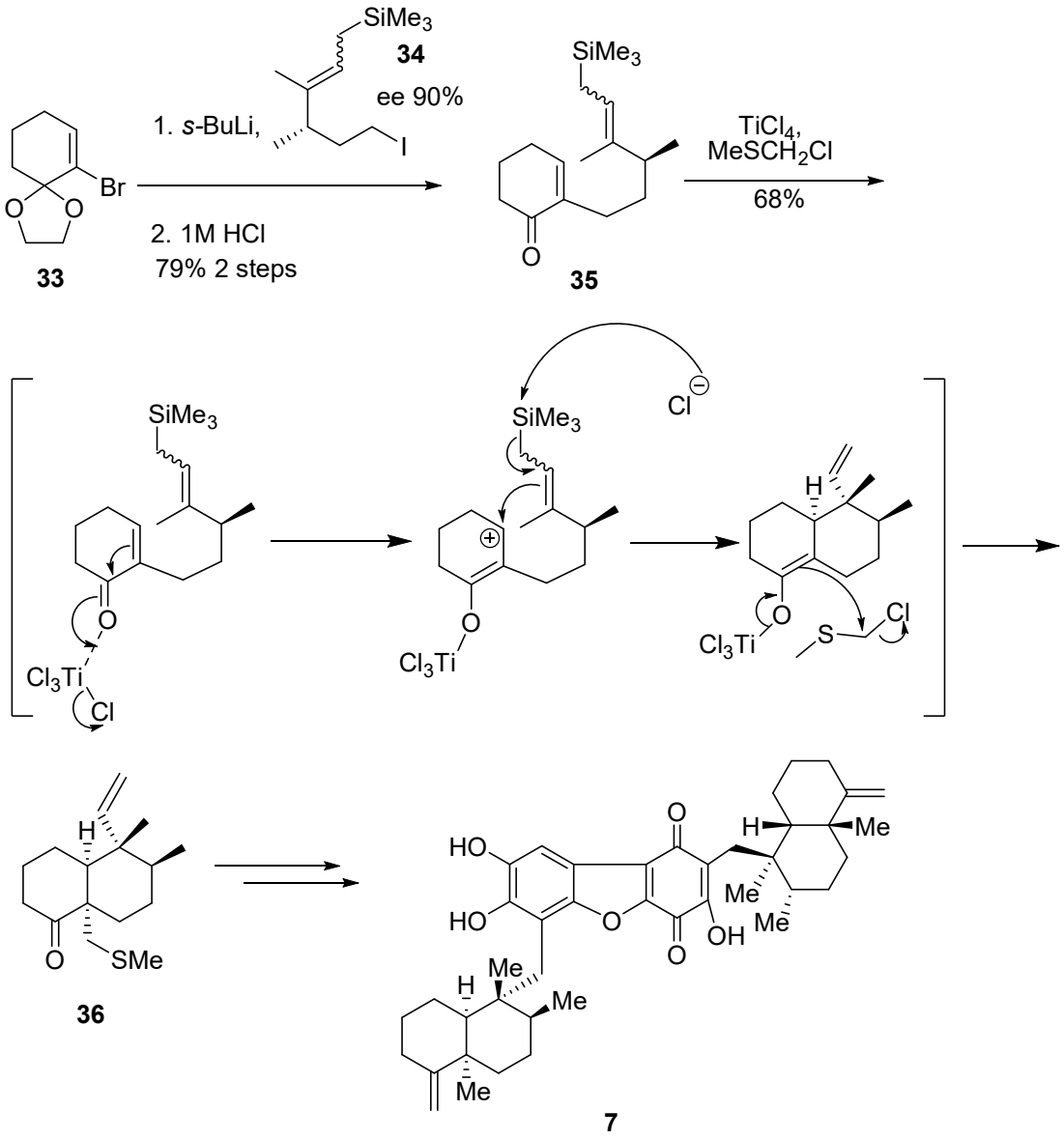
Figure 3. Transition states for different stereochemical configurations of **31**.

Transition state (a) could be used to explain the resultant stereochemistry. As shown in **Figure 3**, transition state (b) with steric interaction between H5 and the methyl group at C10, is unfavourable in comparison to transition state (a). Major diastereomer transition state (a) in which the HOMO of the enolate and the LUMO of the enone are aligned for favourable overlap as compared transition state of minor diastereomer (b). Also, the bulkier carbonyl group are axial at C10 in transition states (c) and (d), which is unfavourable in comparison to transition state (a). The cascade bis-(cyclisation) of the ketoaldehyde afforded decalin **31** in excellent yield and good diastereoselectivity in the presence of catalytic amounts of PTSA in benzene.

Allylation reactions

Intramolecular allylation reactions are examples of nucleophilic cyclisation reactions and have been used in the synthesis of 6'-hydroxyarenarol, the proposed precursor of natural product popolohuanone E **7**[42] (**Scheme 6**). Iodide **34** and vinyl bromide **33** were coupled, and the ketal was deprotected, to yield the precursor to the Hosomi-Sakurai reaction. Treatment of **35** with titanium tetrachloride in the presence of $MeSCH_2Cl$ afforded the desired decalin **36** in 68% yield as a single diastereomer. The *anti*-addition of nucleophiles and electrophiles to an enone is well known.

In addition, the formation of a single diastereomer **36** could be explained by dual stereo-regulation, in terms of orientation and folding-strain stereocontrol (**Figure 4**). Based on the stereocontrol, antiperiplanar transition state (**A**) should be favoured over the synclinal transition state (**B**) if a chair-like conformation is to be assumed. The folding-strain stereocontrol is related to the diastereofacial selection with regard to the C-8 position. In the two possible diastereomeric foldings in the transition states **A** and **C**, transition state (**A**) with a pseudo-equatorial methyl group, is more stable than transition state (**C**), which shows 1,3-allylic repulsion and Gauche interaction.



Scheme 6. Synthesis of 6'- hydroxyarenarol, precursor of popolohuanone E (**7**).[42]

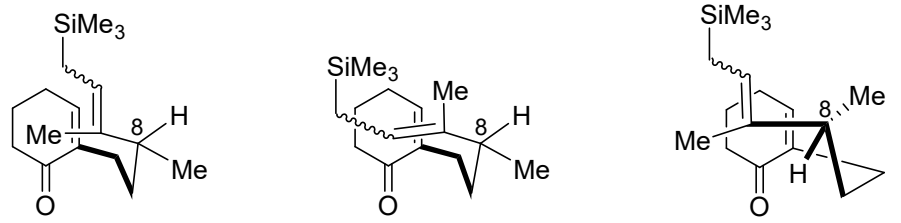
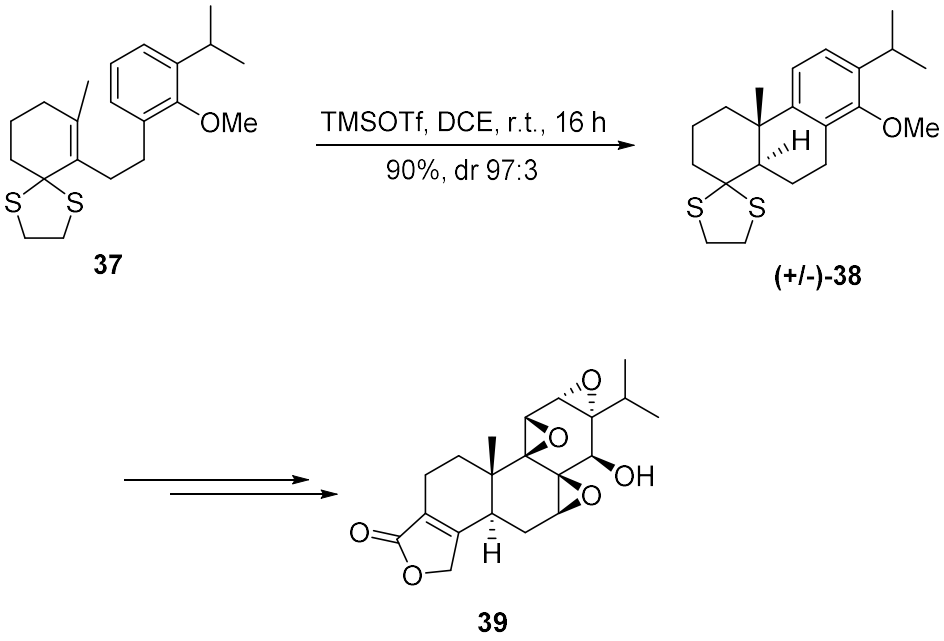


Figure 4. Transition states to explain stereochemistry of **36.**

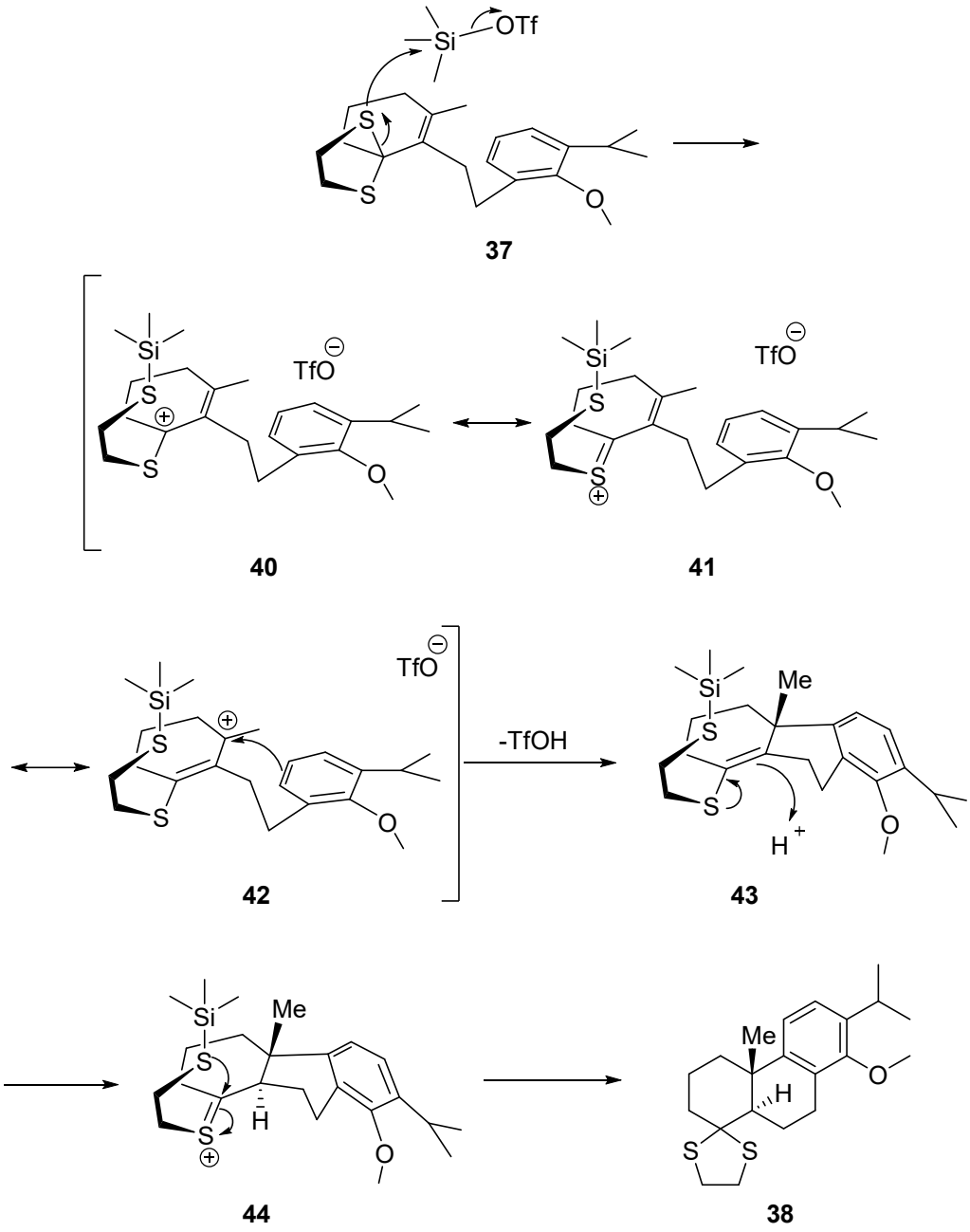
8.4.3. Decalin ring synthesis by the reaction of alkene/alkyne with an electrophilic reagent.

In **Scheme 7**, a highly diastereoselective, cationic 6-*endo*-trig cyclization of 2-alkenyl-1,3-dithiolane **37** formed *trans*-decalin compound **38**, as reported by Baati.[43,44] Furthermore, this decalin compound was used in the synthesis of the natural product, triptolide (**39**)**.**



Scheme 7. Baati's total synthesis of racemic triptolide (**39**).

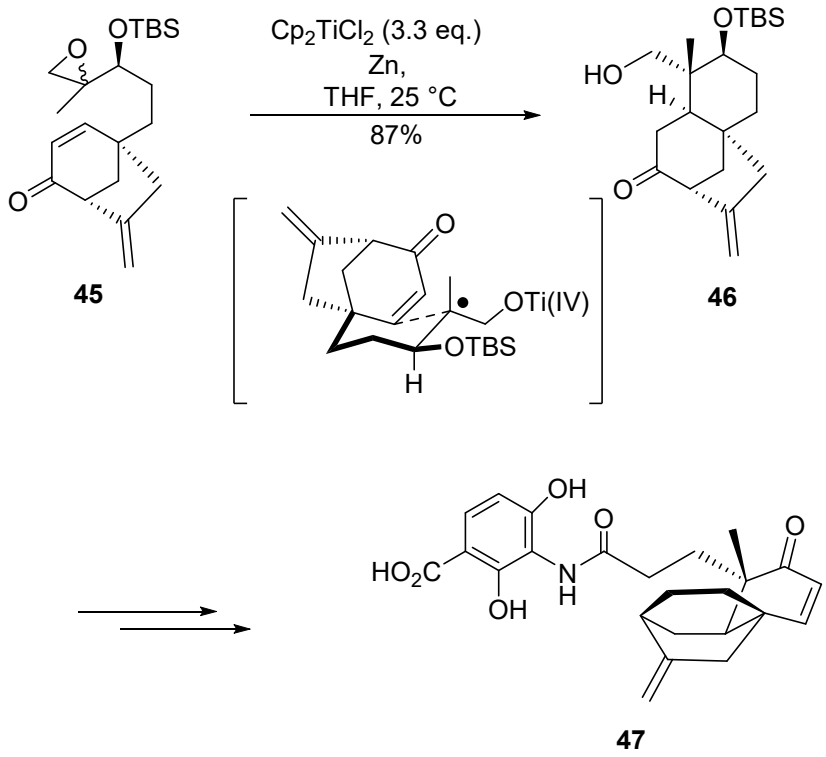
In **Scheme 8**, the plausible reaction mechanism includes the initiation of the reaction by interaction of one sulfur atom of **37** with the electrophilic silicon reagent. Thereafter, the 1,3-dithiolane moiety can temporarily undergo ring opening.[45] This affords a highly electrophilic cationic intermediate **40**, which is stabilized by the mesomeric effect with the conjugated vinyl thionium ion **41** and allylic carbenium ion **42**. Thioenol **43** is then formed by the electrophilic substitution of the aromatic ring and aromatization, followed by the protonation of **43** by TfOH to form the sulfonium ion-containing compound **44**. Subsequent cyclization, regenerates the dithiolane unit, resulting in the formation of compound **38**.[45] The stereochemistry of decalin (+/-) **38** is achieved during the protonation of **43**. The steric hindrance due to the methyl group blocks the β- face of the molecule; therefore, the proton source approaches from the other side (α-face) generating *trans*-decalin **43**.[46]



Scheme 8. Plausible mechanism of 6-*endo*-trig cyclization

8.4.4. Radical reactions for decalin ring synthesis.

Yoshimitsu reported the synthesis of (+/-)-platencin (47) where the key C-C bond formation occurred from a radical addition to an alkene; the radical was generated by a titanium(III)-mediated cyclisation (**Scheme 9**).[47–49] Epoxide **45** underwent homolytic cleavage to generate a radical, which then cyclised to afford the *cis*-decalin ring. Interestingly, both diastereomeric epoxides produced a single stereoisomer, due to the same common radical intermediate.



Scheme 9. Yoshimitsu's synthesis of (+/-)-platencin (**47**).

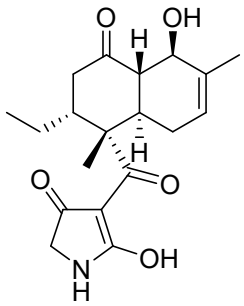
The reaction of compound **45** (mixture of diastereomers) under the above reaction conditions provided the desired tricyclic compound **46** as a single stereoisomer in 87% yield. This implied that both diastereomers of the epoxide generated compound **46**, irrespective of their original stereochemical configurations. This could be explained by the formation of a single radical by the rapid epimerization of the carbon radical centre, which formed the thermodynamically stable chair conformation in the transition state, where the bulkier TBS group was locked at the equatorial position. This explains the stereoselective cyclisation (**Scheme 9**).

The methods summarised indicate a renewed interest in the syntheses of complex decalin ring systems and natural products containing the decalin framework in their molecular architecture. Therefore, the isolation of new natural products containing highly functionalised and substituted decalin ring systems from various sources and investigation of their biological activities have attracted significant attention. The innovation of new methodologies based on cyclisation, inter- and intramolecular Diels-Alder, allylation, and radical reactions can provide opportunities for the rapid, efficient, and stereoselective synthesis of the decalin ring frameworks.

9. Studies Towards the Synthesis of the Decalin Core of Streptosetin A (3).[9]

Streptosetin A **3** (**Figure 5**) is a recently isolated natural product from a marine-derived actinomycetes that exhibits human class III HDAC (SIRT) inhibition. Efforts towards the synthesis of the decalin core of streptosetin A (**3**) are currently underway in our research laboratory.[9]

Sirtins (SIRT) are nicotinamide adenine dinucleotide (NAD)-dependent epigenetic enzymes. The mammalian sirtins SIRT1-SIRT7 are involved in numerous cellular functions such as gene silencing, and control of the cell cycle and apoptosis.[50] In prostate cancer, SIRT1 and SIRT2 are overexpressed, and their inhibition affords an anti-proliferative response in human prostate cancer cells.[51] Streptosetin A (**3**)[9] was obtained from one of the active strains identified through a yeast assay and its structure was elucidated by the analysis of 1D and 2D NMR data. The stereochemistry was determined by X-ray crystal structure analysis and simulation of ECD spectra using time-dependent density functional theory calculations.[9] This compound showed weak inhibitory activities against yeast Sir2p and human SIRT1 and SIRT2. Structurally, streptosetin A (**3**) is categorized as a polyketide tetramic acid derivative produced by the NRPS−PKS hybrid pathway, similar to that reported for equisetin isolated from *Fusarium equiseti*.[52]



3

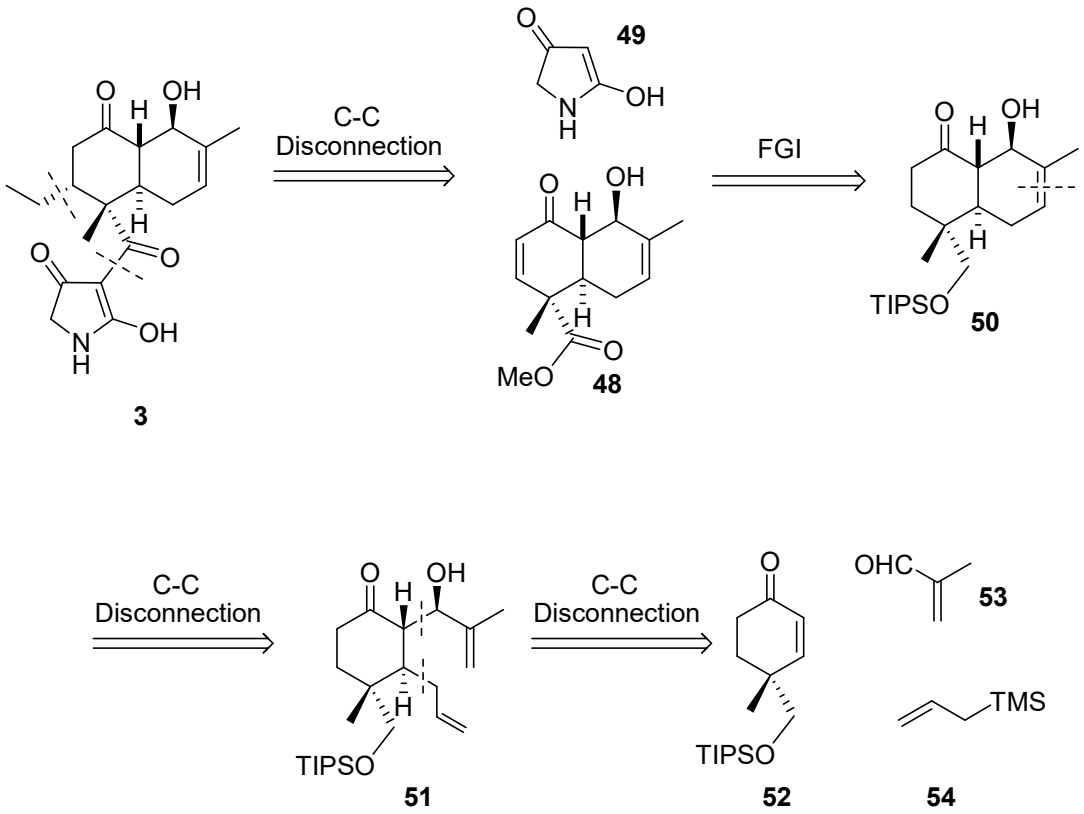
Figure 5. The chemical structure of Streptosetin A (**3**)

9.1 Previous work in the Clarke Group[53,54]

9.1.1 Retrosynthetic Analysis *via* Sakurai Route.

Prior work within our research group showed that the decalin core of streptosetin A (**3**) lacking the quaternary methyl group could be synthesised successfully *via* a ring-closing metathesis route.

Streptosetin A (**3**) would be split into two fragments, the highly functionalised *trans*-decalin core **48** and the tetramic acid **49**, in the proposed retrosynthetic strategy (**Scheme 10**). To form the highly functionalised *trans-decalin* core **50**, the key step would be the Sakurai-aldol reaction and ring closing metathesis. The Sakurai reaction of allyltrimethylsilane **54** and enone **52**, after enolate trapping by reaction with methacrolein **53** would generate **51**. The ring would be closed using a Grubbs catalyst to afford the *trans*-decalin core **50**.

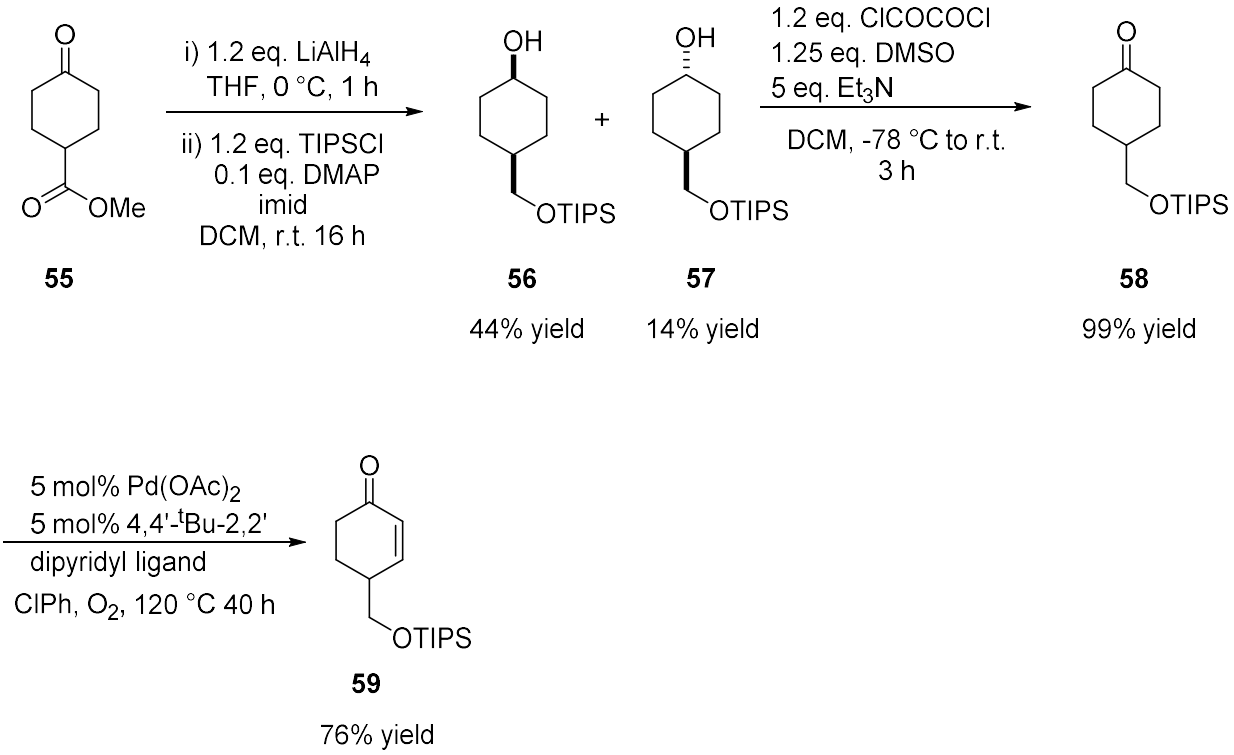


3 **48** **49** **50** **51** **52** **53** **54**

Scheme 10. The retrosynthesis analysis of streptosetin A.

9.1.2 Synthesis of model enone core **59**

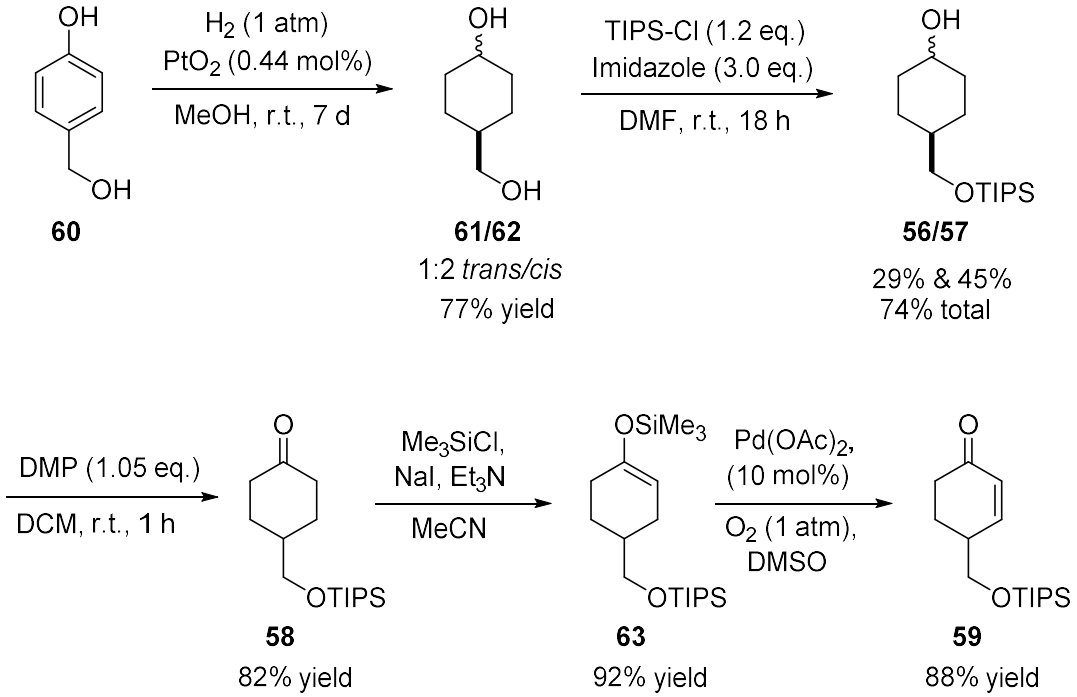
Dr. Ian George, a postdoctoral researcher in the Clarke group, developed the synthesis of enone **59**. Initial work involved the construction of model enone core **59** to determine the feasibility of Sakurai and ring-closing metathesis reactions. In a multi-step total synthesis, the starting materials should not be expensive, but the cyclohexanones with substitution at the 4-position are expensive. Thus, the proposed synthesis began with the reduction of compound **55**, followed by the protection of the primary hydroxyl group with TIPS, which afforded a diastereomeric mixture of alcohols **56** and **57** in 44% and 14% yields, respectively. This was followed by the oxidation of this mixture to a single ketone **58** (99%), and subsequent Ito-Saegusa oxidation, which converted **58** to enone **59** (**Scheme 11**).[55]



Scheme 11. Synthesis of enone **59** by Dr. Ian George.

Enone **59** was also synthesised by J. Smith, a postgraduate student in our research group (**Scheme 12**). The hydrogenation of the aromatic ring of compound **60** using catalyst PtO_2 generated diols **61/62** as a 1:2 inseparable mixture of stereoisomers in 77% yield.[56] Selective protection of the primary alcohol of diols **61/62** by treatment with TIPS-Cl generated compounds **56/57** in 74% total yield. Oxidation of **56/57** *via* a Dess-Martin periodinane

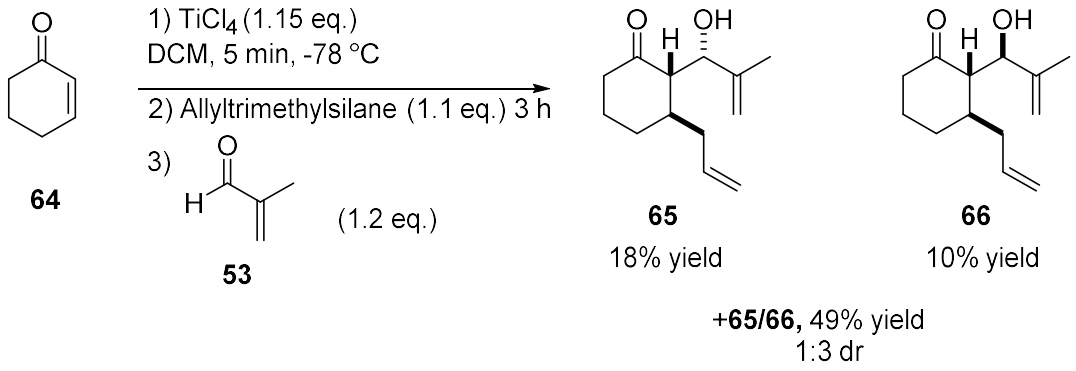
oxidation generated ketone **58** in 82% yield.[57,58] Compound **58** was further converted into the corresponding silyl enol ether **63** by treatment with Me_3SiCl, sodium iodide, and triethylamine in acetonitrile with 92% yield. Then, the Saegusa oxidation of **63** by treatment with $Pd(OAc)_2$ in DMSO generated enone **59** in 88% yield.



Scheme 12. Synthesis of enone **59** by J.Smith

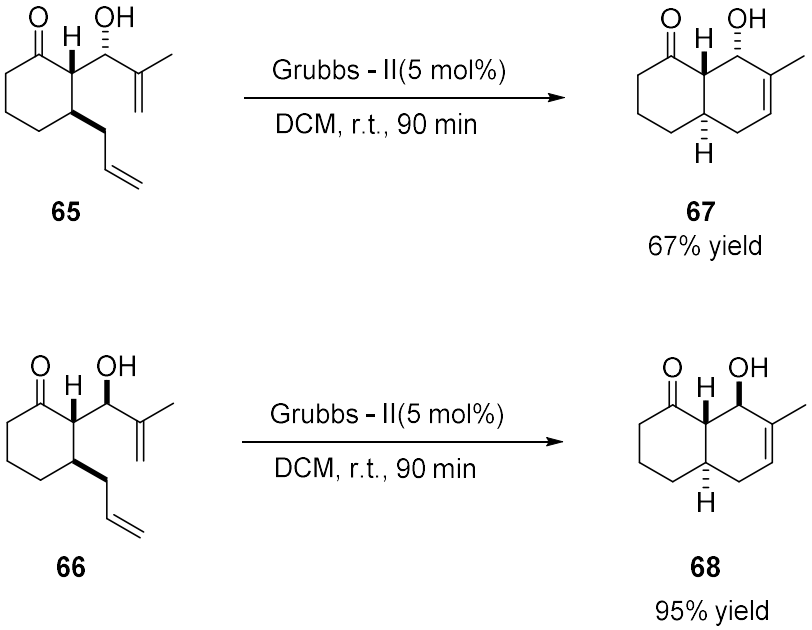
9.1.3 Sakurai, aldol, and ring closing metathesis route to decalin ring formation

J. Smith showed that the decalin core of streptosetin A (**3**) could be synthesised successfully using a ring-closing metathesis reaction. Cyclohexenone, as a model substrate, was subjected to the $TiCl_4$-mediated addition of allyltrimethylsilane to form the intermediate titanium enolate. This enolate was trapped with methacrolein **53**, yielding the aldol products **65** and **66** in 1:3 diastereomeric ratio (**Scheme 13**).



Scheme 13. Sakurai and Aldol reaction to form **65** and **66**.

The decalin ring was formed *via* a ring-closing metathesis reaction. Compounds **65** and **66** were treated with 5 mol% Grubbs 2nd generation catalyst, resulting in the corresponding decalinones **67** and **68** in 67% and 95% yields, respectively (**Scheme 14**).



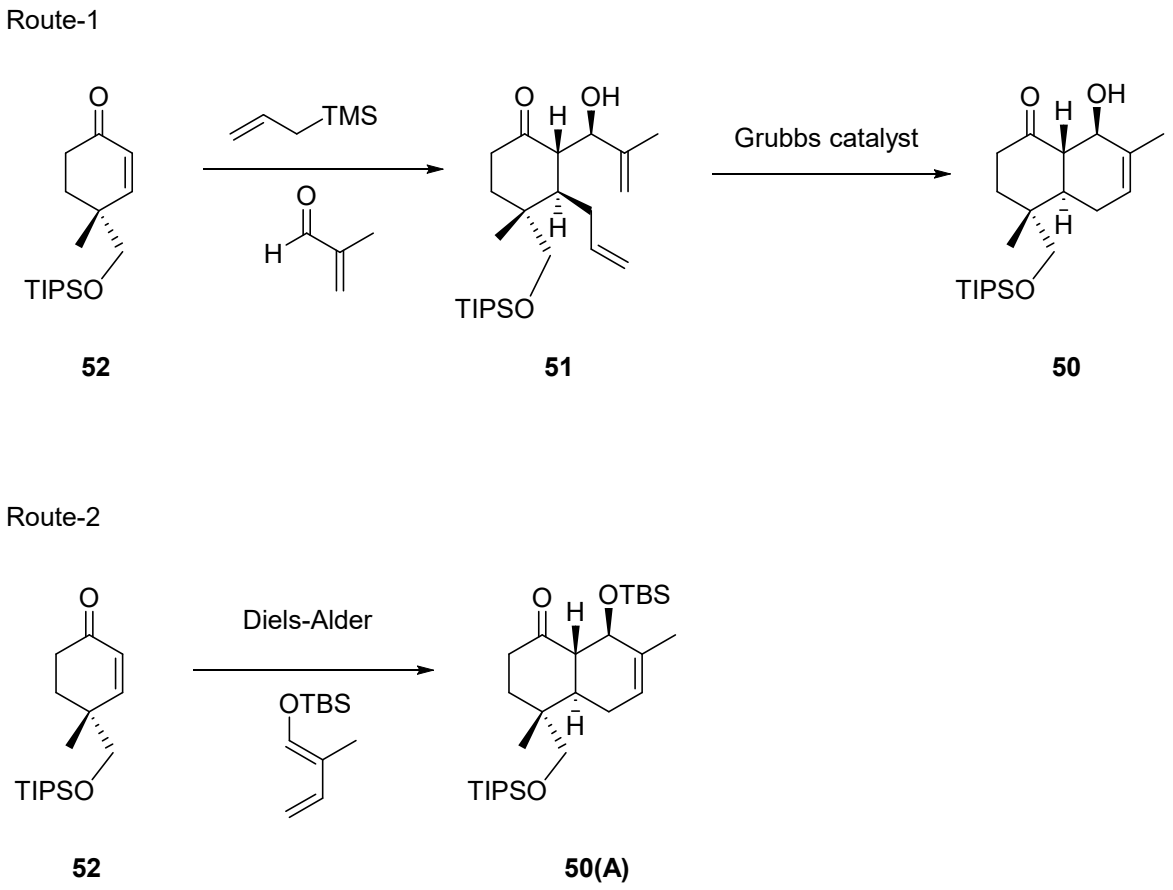
Scheme 14. Ring closing metathesis route to decalin ring formation.

Thus, by employing the routes proposed by J. Smith and Dr. Ian George, who utilized Sakurai, aldol, ring-closing metathesis, and Diels-Alder reactions with enone core **59**, a versatile strategy to build the decalin core streptosetin A **3** can be proposed. These strategies will be discussed in detail in the next chapter.

10. Results and Discussion

10.1 Aim and objectives

The aim of the project was to develop a route for the synthesis of the decalin core of streptosetin A **3**. The proposed routes to the trans-decalin core are summarised in **Scheme 15**. Route 1 would follow a Sakurai and metathesis approach whereas route 2 would explore a Diels-Alder approach. The proposed synthesis of the key enone core **52** of the decalin ring system follows the same route as that published by Rawal *et al*. for the synthesis of racemic and enantioenriched 4-disubstituted enone.

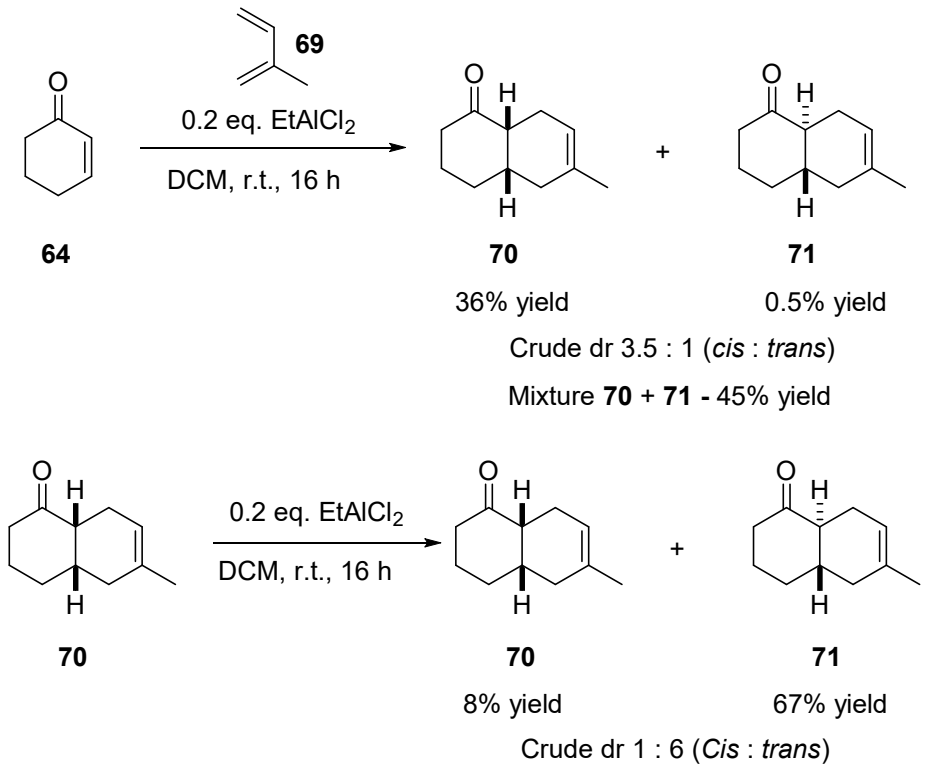


Scheme 15. Proposed routes for the synthesis of the decalin ring of streptosetin A.

10.2 Synthetic efforts towards the *trans*-decalin ring system using Diels-Alder/epimerisation sequence.

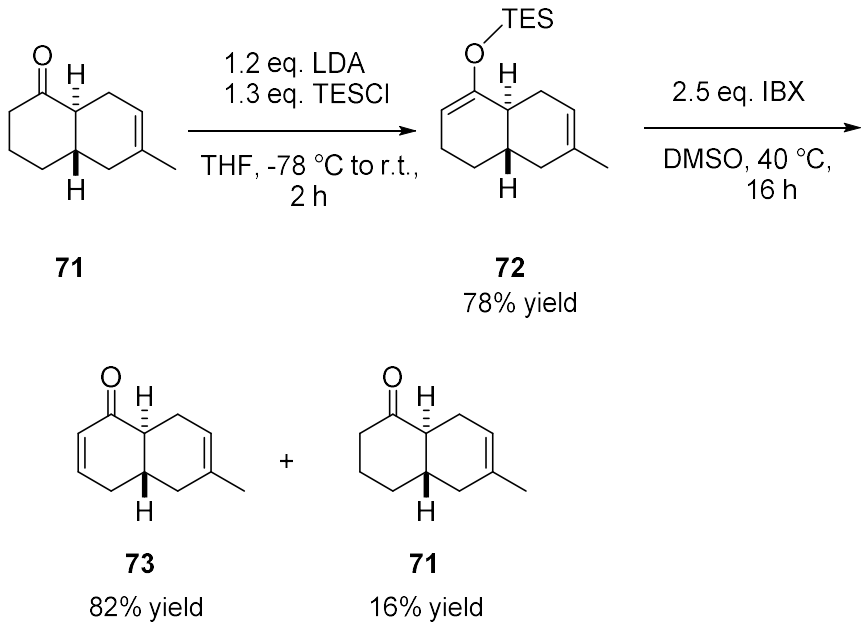
Prior to beginning the synthesis of the core of streptosetin A **3**, initial work was focused on exploring the *trans*-decalin ring system, which was performed by G. Lodovici,[54b] a postgraduate student in the research group.

Using the precedent from G. Lodovici, the cycloaddition of **64** and **69** was performed in the presence of Lewis acid, which generated two decalin products **70** and **71** in a 3.5 : 1 crude ratio (*cis* : *trans*) (**Scheme 16**).[59] Treatment of **70**, under the same Diels-Alder reaction conditions, generated *trans*-diastereoisomer **71** in 1 : 6 ratio (*cis* : *trans*) *via* epimerisation(**Scheme 16**).



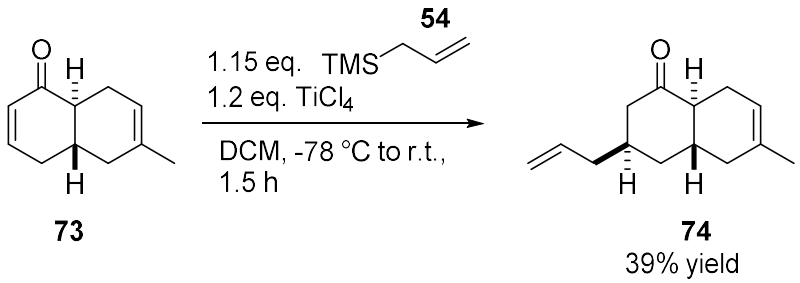
Scheme 16. Diels-Alder/epimerisation sequence to synthesize the *trans*-decalin system with a model compound.

The treatment of the model *trans*-decalin **71** in the presence of LDA at –78 °C and TESCl afforded TES-enol ether **72** in 78% yield,[60] which was then oxidised by IBX at 40 °C. The use of 1.5 eq. of IBX produced the model enone *trans*-decalin **73** in 82% yield and ketone *trans*-decalin **71** in 16% yield.[61] (**Scheme 17**).

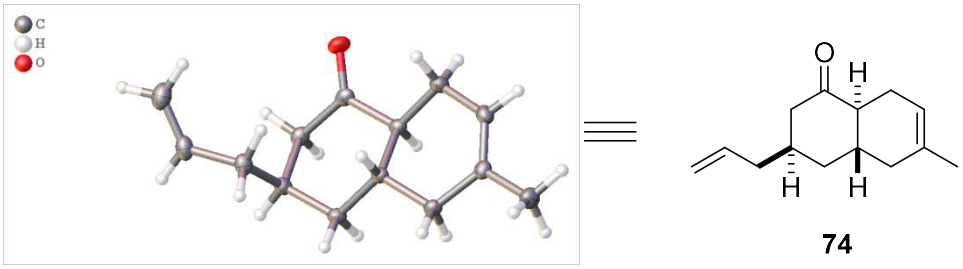


Scheme 17. Synthesis of **73** *via* IBX oxidation.

The Hosomi–Sakurai 1,4-addition[62] between enone *trans*-decalin **73** and allyltrimethylsilane **54** generated a mixture of products; however, only one product could be isolated and characterised as **74** in 39% yield. (**Scheme 18**).



Scheme 18. The Hosomi–Sakurai approach for the synthesis of **74.** [63]



74

Figure 6. The single crystal X-ray diffraction data of **74.**

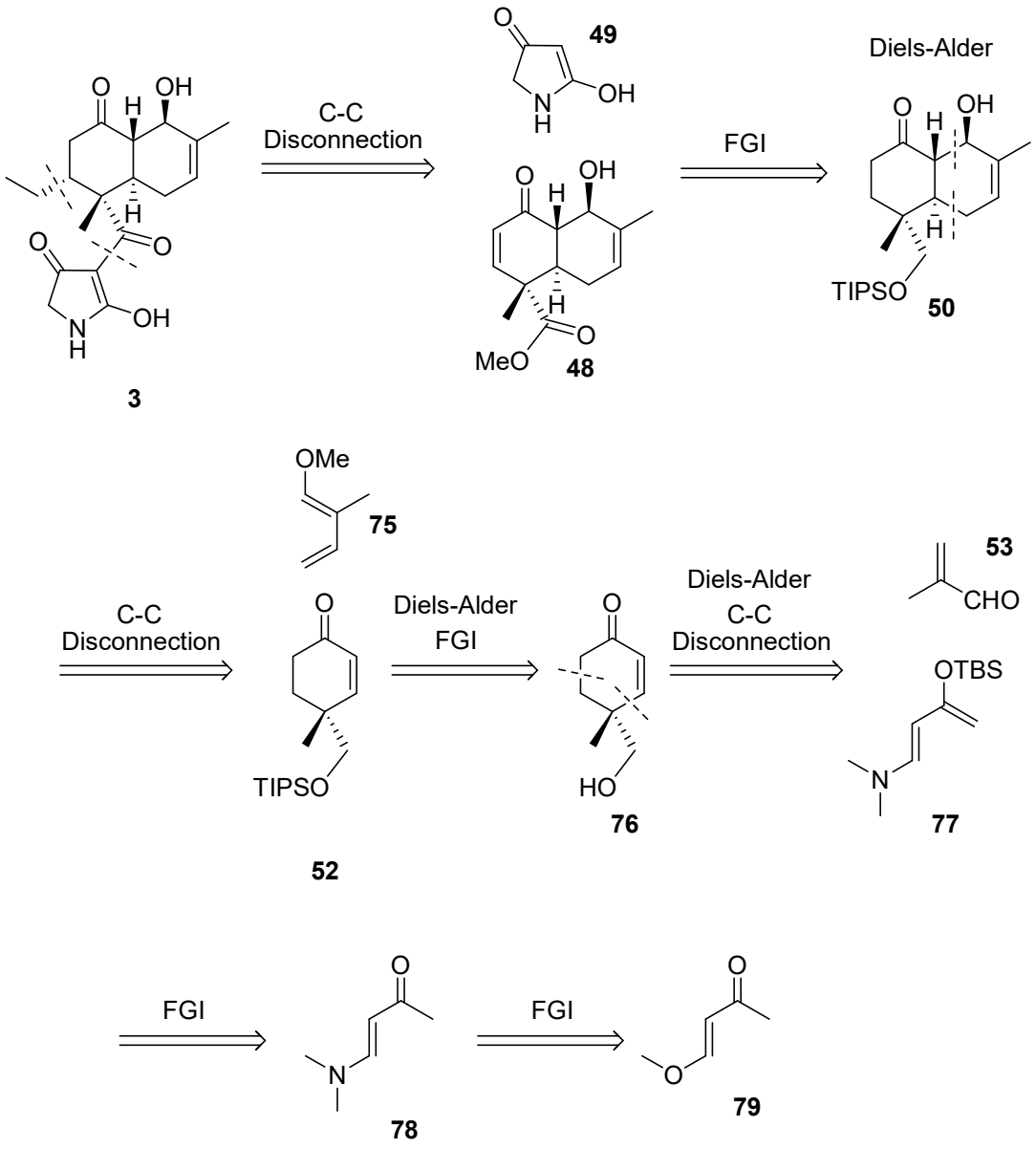
Figure 6 shows the single-crystal X-ray diffraction data of **74** obtained *via* the Hosomi–Sakurai 1,4 addition, affording the relative stereochemistry required for the continuation of the synthesis of anthracimycin **4**, the synthetic efforts toward which are currently underway in our research group.

Before starting work on the actual compound of streptosetin A core, initial work was focused on understanding the *trans*-decalin ring system

10.3 Diels-Alder and Sakurai reaction for the synthesis of *trans*-decalin core of Streptosetin A **3**.

10.3.1. Retrosynthetic analysis Diels-Alder Route

An alternate Diels-Alder route to the construction of the *trans*-decalin ring system of streptosetin A **3** was proposed (**Scheme 19**).



Scheme 19. Retrosynthetic analysis of Streptosetin A **3**.

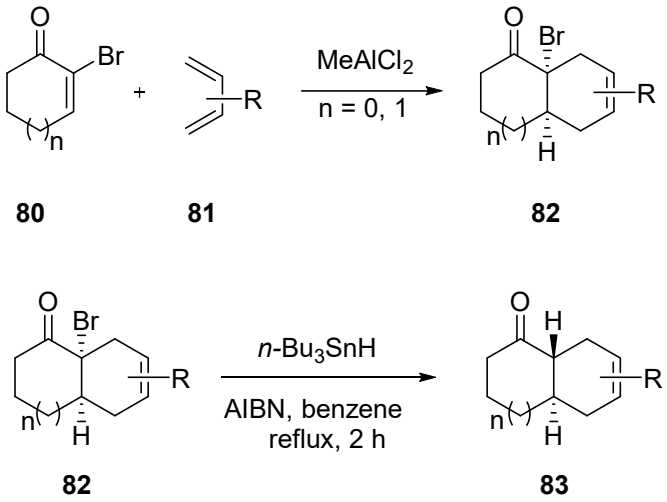
To form the highly-functionalised *trans-decalin* core **48** of streptosetin A **3**, a Diels–Alder reaction between enone **52** and diene **75** was envisioned. The TIPS-protected enone **52** would

be synthesise by the Diels-Alder reaction between Rawal's diene **77** and dienophile methacrolein **53**, followed by reduction and TIPS protection of the primary hydroxyl group (**Scheme 19**).

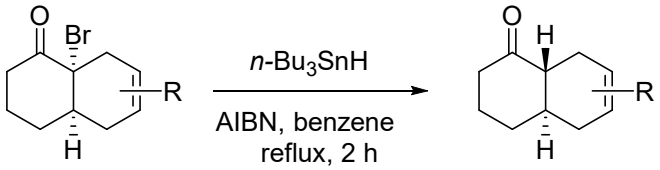
10.3.2. Literature Overview of Diels-Alder reaction

For the construction of six-membered functionalised carbocyclic compounds, Diels-Alder reactions are the most widely used pericyclic reactions. The efficiency of the Diels-Alder reaction has been validated, particularly for complex natural product synthesis.[64] To enhance its rate of reaction, Lewis acids are often used, which decreases the energy gap between the LUMO of the dienophile and HOMO of the diene.[65]

Danishefsky developed a sequence of Lewis-acid-catalysed Diels-Alder reactions to form *cis*-decalin, followed by reductive dehalogenation to generate the *trans*-decalin system.[66] They described the Lewis-acid-catalysed ($MeAlCl_2$) Diels-Alder reaction between 2-bromocyclohex-2-enone **80** and diene **81** to afford a *cis*- fused bicyclic system **82**. Thereafter, using AIBN and n-Bu_3SnH radical reduction was performed to remove the bromine at the bridgehead carbon with inversion of configuration to generate *trans*-decalin **83** (**Scheme 20**). A range of examples are presented in **Table 1**.



Scheme 20. Formation of *cis*-decalin and inversion of configuration from *cis*-to *trans*-decalin *via* radical mechanism.



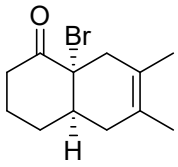
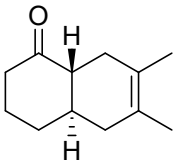
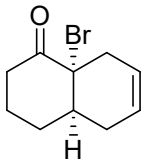
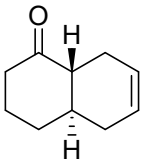
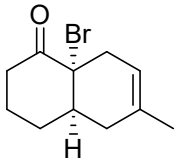
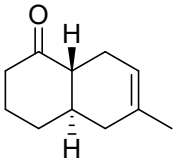
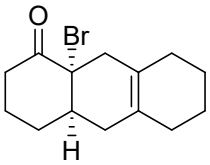
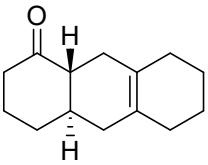
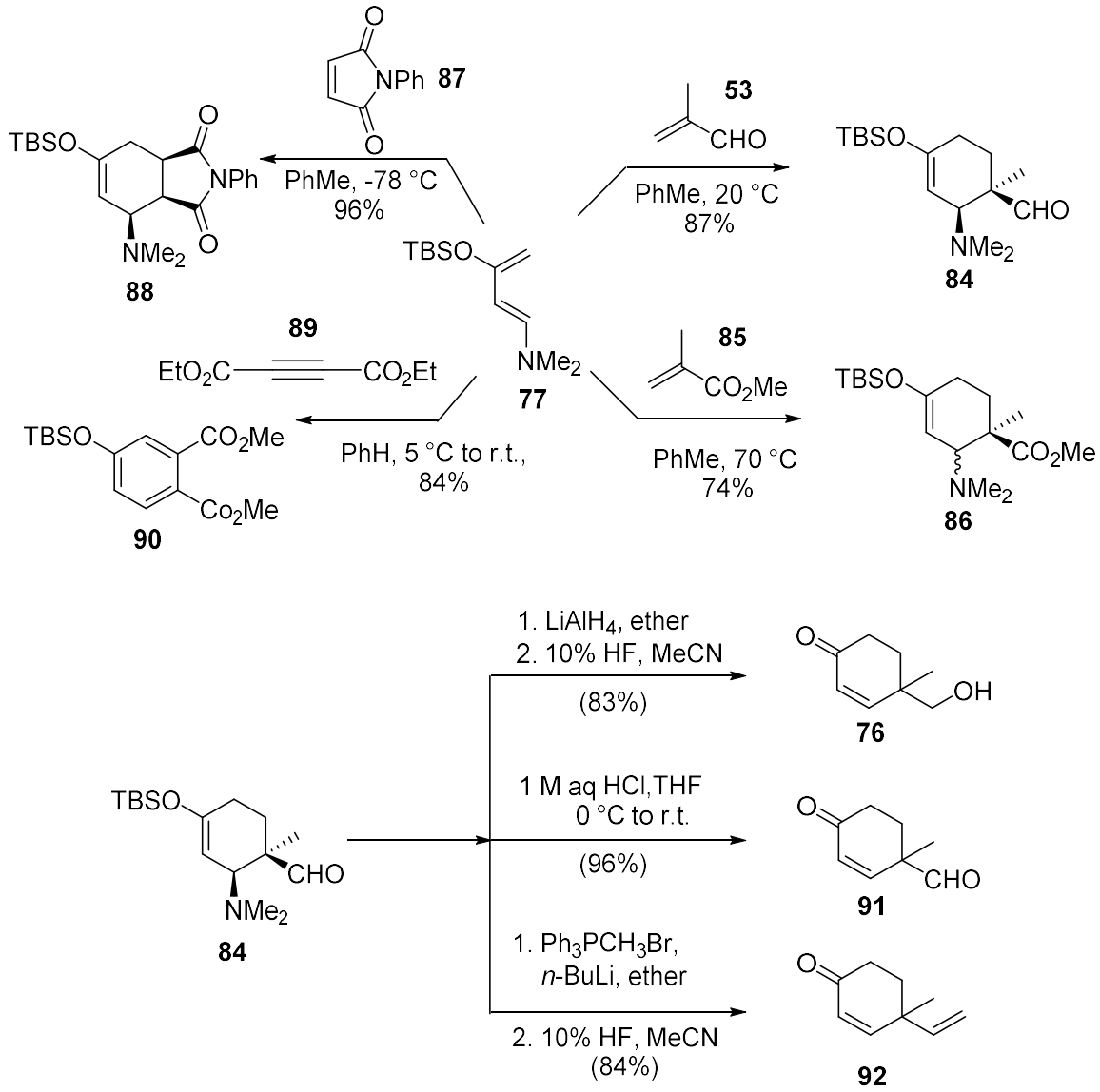
Entry	bromoketone	product	yield (%)	*trans*:*cis*
1			95	25:1
2			97	16:1
3			87	18:1
4			99	18:1

Table 1. Inversion of configuration from *cis*-to *trans*-decalin using AIBN and *n*Bu_3SnH

Inspired by this approach, a similar strategy, was envisioned for the construction of the decalin core, but the synthesis of enone **76** was first required, for which Rawal's chemistry would be employed. Using this Diels-Alder strategy, the formation of functionalised *trans*-decalin of streptosetin A **3** was explored.

Various studies suggest that the modification of the diene and dienophile can expand the synthetic potential of the Diels-Alder reaction.[67] The substitution of the lone-pair-containing heteroatoms on the diene can increase the reaction rate and improve the regioselectivity in cycloaddition reactions.[68] In 1997, Rawal employed a heteroatom-substituted siloxydiene for the Diels-Alder reaction (**Scheme 21**).[69,70] Rawal reported several cycloadducts of the Diels-Alder reaction using diene **77**, which is also known as Rawal's diene, and developed a racemic and asymmetric version of the cycloaddition reaction, including the synthesis of the desired enone **76**, which was a potential key intermediate in our synthetic plan.

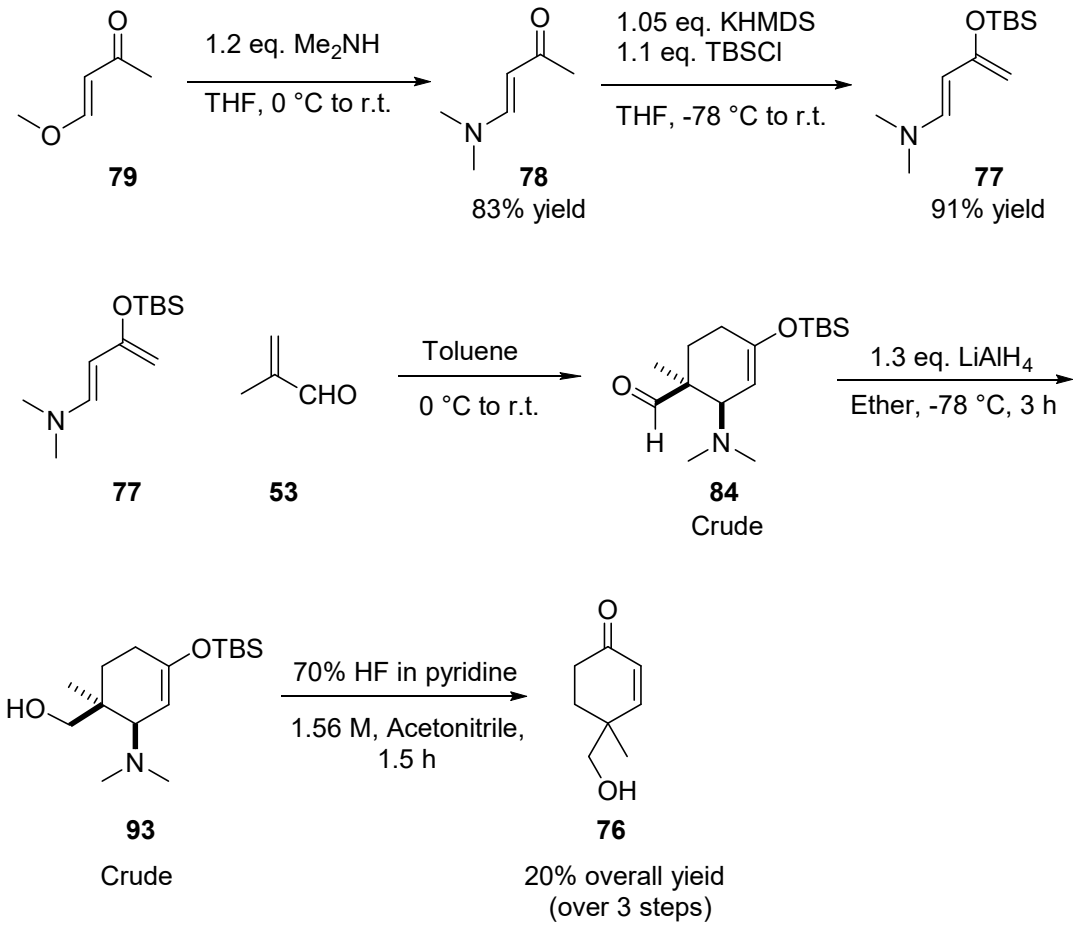


Scheme 21. Diels-Alder reactions of Rawal's diene **77** and the route to **76** and other analogues.

This study suggested that the diene with lone-pair-containing heteroatom substituents is more reactive towards dienophiles and leads to improved regioselectivity in the cycloaddition reaction. Rawal's diene **77** was reacted with *N*-phenylmaleimide **87** at -78 °C for one hour to afford *endo*-adduct **88** in 96% yield. The Diels-Alder reaction of **77** with diethyl acetylenedicarboxylate **89** was performed at 5 °C to yield the aromatised cycloadduct **90**. Slightly high temperatures were used for methacrolein **53** and methyl methacrylate **85**, which yielded cyclised products **84** and **86**, respectively. The products of these Diels-Alder reactions are potentially versatile intermediates. As an example, methacrolein cycloadduct **84** proceeded to react with aqueous HCl in THF to afford **91** in 96% yield. Meanwhile, cycloadduct **84** was subjected to reduction with lithium aluminum hydride ($LiAlH_4$) or Wittig olefination and the resulting products were hydrolysed to produce alcohol **76** and alkene **92**, respectively (**Scheme 21**). Using this chemistry, the synthesis of racemic enone compound **76** was proposed (**Scheme 22**).

10.3.3. Synthesis of racemic enone core **76.**[70]

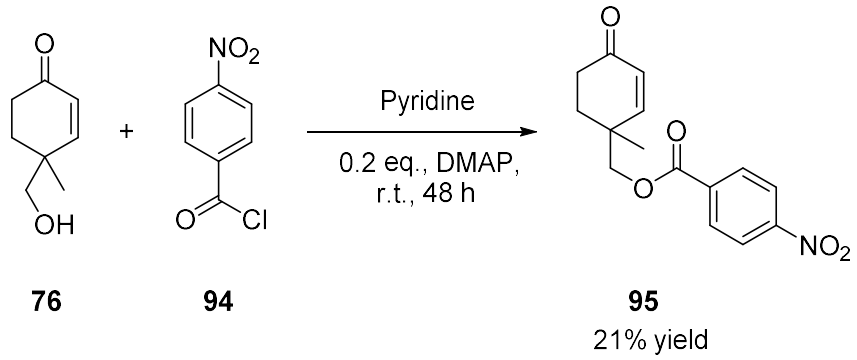
The synthesis of key enone **76** was initiated by preparing Rawal's diene **77**. First, 4-methoxy-3-buten-2-one (**79**) was treated with dimethyl amine to obtain the desired precursor 4-(dimethylamin)-3-butene-2-one (**78**) in 83% yield. Compound **78** was subjected to deprotonation with potassium bis(trimethylsilyl)- amide (KHMDS) and the subsequent trapping of the resulting enolate with *tert*-butyldimethylsilyl chloride (TBSCl) afforded 1-(dimethylamino)-3-siloxy1,3-butadiene (Rawal's diene **77**) in 91% yield. The Diels-Alder cycloaddition was performed with two equivalents of Rawal's diene **77** and methacrolein **53** at 0 °C to room temperature in toluene to generate Diels-Alder product **84**. Crude compound **84** was reduced using $LiAlH_4$, to afford crude alcohol **93**. In the next step, the removal of the OTBS protection group together with the elimination of dimethylamine from crude compound **93**, was achieved by treatment with 2.5 equivalents of 70% HF in pyridine to obtain the desired racemic enone **76** with 20% overall yield in three steps (**Scheme 22**).



Scheme 22. Synthesis of racemic enone core **76**.

10.3.4. HPLC conditions for the analysis of enantioselectivity

Racemic enone **76** is not sufficiently UV-active for direct HPLC analysis. For this reason, a chromophore group needed to be added into compound **76**, and therefore, 4-nitrobenzoyl ester **95** was chosen and formed in 21% yield (**Scheme 23**).

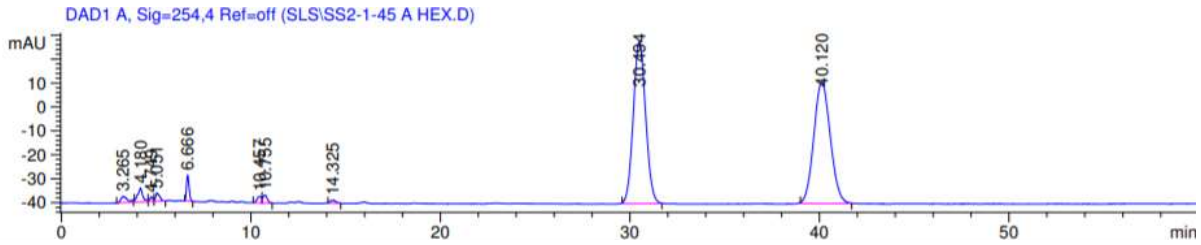


Scheme 23. Formation of UV active racemic enone **95**.

HPLC conditions

The separation of enantiomers was performed using an HPLC system by employing a CHIRALPAK^{TM} IC column with IPA : hexane (50:50) as the mobile phase at a flow rate of 1.0 mL/min at 40 °C, and run time of 60 minutes.

Figure 7, shows the separation of two enantiomers in the racemic mixture of **95** that are indicated by the two peaks observed in the chromatograph.

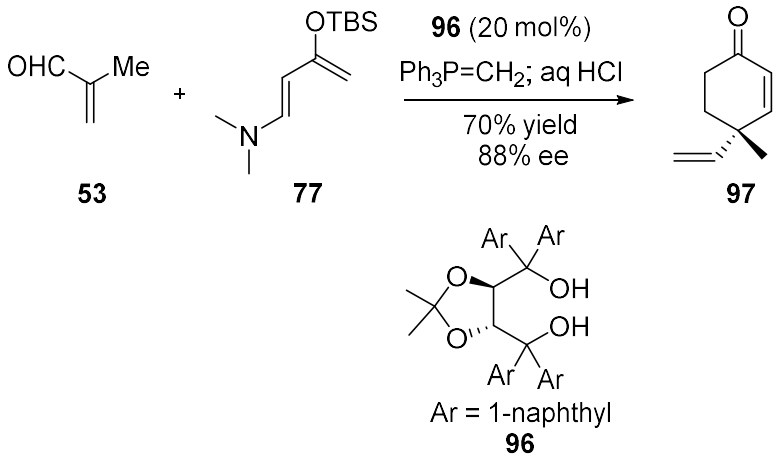


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.265	BB	0.3107	66.82608	2.68226	1.0126
2	4.180	BV	0.2498	106.01608	5.73242	1.6064
3	4.749	VV	0.1623	21.75577	1.94860	0.3297
4	5.051	VB	0.2016	50.05843	3.40429	0.7585
5	6.666	BB	0.1439	102.66496	10.89391	1.5556
6	10.457	BV	0.2440	42.71487	2.67902	0.6472
7	10.755	VB	0.2441	52.83514	3.27690	0.8006
8	14.325	BB	0.2779	23.94479	1.23685	0.3628
9	30.494	BB	0.7024	3071.60474	67.82044	46.5423
10	40.120	BB	0.9220	3061.17725	50.73295	46.3843
Totals :				6599.59810	150.40764	

Figure 7. Chiral separation of two enantiomers of racemic enone **95** by HPLC**.**

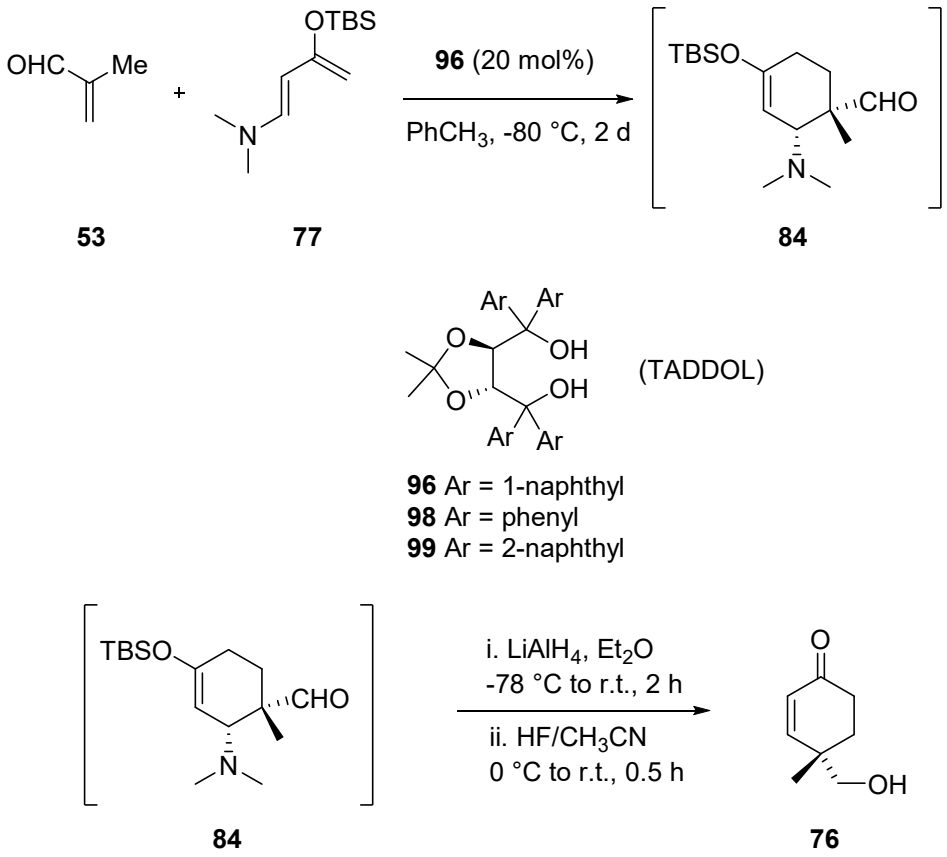
In 2018, Carreira reported the total synthesis of (−)-mitrephorone A, which commenced with TADDOL **96**-catalysed Diels-Alder reaction of Rawal's diene **77** and methacrolein **53**, followed by Wittig methenylation and acidic hydrolysis that generated an enantioenriched enone **97** in 88% ee and 70% overall yield (**Scheme 24**).[71]



Scheme 24. Formation of enantioenriched enone **97**.[71]

In 2004, Rawal reported the asymmetric synthesis of enone **76**.[72] Initially, a solution of TADDOL **96** and methacrolein **53** in toluene at -80 °C was treated with Rawal's diene **77** for two days. The resulting reaction mixture was treated with $LiAlH_4$ at the same temperature, and the mixture was then allowed to warm up to room temperature for 1.5 h. The reaction was quenched at 0 °C with water and filtered followed by evaporation of the filtrate. The resulting oil was dissolved in acetonitrile and treated with HF for 0.5 h at room temperature. Finally, the solvent was evaporated, and the volatiles and residue were purified by silica gel chromatography (30:70% hexanes: EtOAc) to afford a clear, colourless oil **76** in 83% yield and 91% ee (**Scheme 25**).

Rawal *et al*. screened several TADDOL catalysts and showed that different percent yields and enantiomeric excesses were obtained. They screened three commercially available TADDOL catalysts (**96**, **98**, and **99**), and the results showed that the yield and enantioselectivity afforded by the reaction depended on the structure of the TADDOL catalyst. The phenyl-substituted TADDOL **98** and 2-naphthyl-substituted TADDOL **99** afforded 30% and 45% yields with 31% and 33% ee, respectively. 1-Naphthyl TADDOL **96** showed the best result, with 83% yield and excellent enantioselectivity of 91% ee (**Table 2**).[72]



Scheme 25. Synthesis of enantioenriched enone **76** reported by Rawal.[72]

Sr. No.	TADDOL	Yield, %	ee, %
1	**98**	30	31
2	**99**	45	33
3	**96**	83	91

Table 2. Effect of TADDOL structure on the yield and enantiomeric excess of **76**.

The rigidity of the TADDOL conformation is due to the hydrogen bond formation. Dienophile (methacrolein) **53** forms a complex with TADDOL through a two-point interaction. First, the free hydroxyl group of TADDOL forms an intermolecular hydrogen bond with the carbonyl group of the dienophile, which lowers the LUMO energy. The second interaction occurs with an electron-deficient carbonyl double bond that is stabilized by the interaction with the electron-rich 1-naphthyl ring, which selectively shields one face of the dienophile. Thus, the model shows that the *Si*-face of the aldehyde is available to the diene and accurately predicts the absolute configuration of the cycloadduct (**Figure 8**).

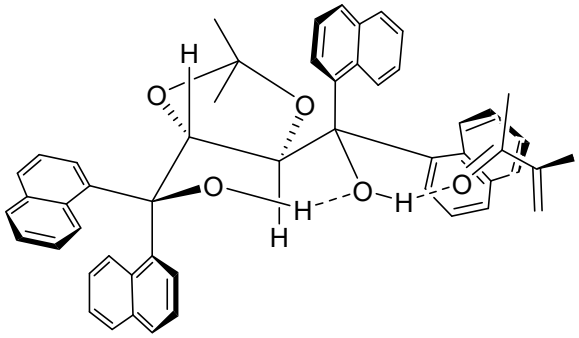
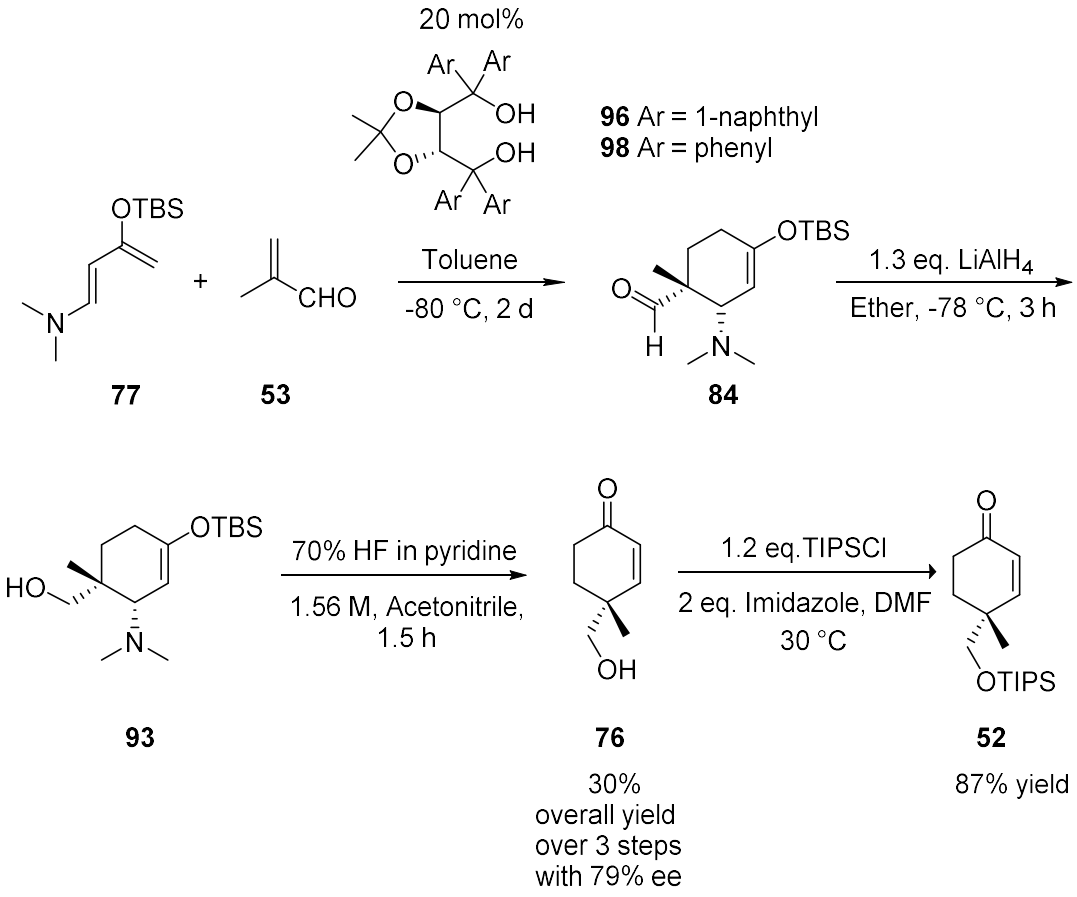


Figure 8. Proposed working model for TADDOL-catalysed Diels-Alder reaction.[72]

Therefore, this chemistry was applied to the asymmetric synthesis of **76**.

10.3.5. Asymmetric synthesis of enone core **76**.[72]



Scheme 26. Asymmetric synthesis of enone core **76**.

1-Amino-3-siloxybutadiene (Rawal's diene **77**) and methacrolein **53** were stirred in toluene at -80 °C for 48 h with 20 mol% of TADDOL **96** as the chiral catalyst to afford cyclised enantioselective product **84** as a crude dark yellow viscous oil. The resulting Diels-Alder cycloadduct **84** was reduced using 1.5 eq. of lithium aluminium hydride ($LiAlH_4$) to generate

compound **93**. Desilylation together with the elimination of dimethylamine was achieved using 70% HF in pyridine to yield the desired asymmetric enantioenriched enone **76** in 30% overall yield in three steps and 79% ee (**Scheme 26**).

Our work confirmed Rawal's observations that the structure of the TADDOL catalyst played a key role in improving the yield and enantioselectivity of the Diels-Alder cycloadduct. An additional observation regarding the purity of our starting materials in Diels-Alder reactions was made as both the crude and Kugelrohr-distilled pure Rawal's diene **77** were used. Four different results were obtained under identical reaction conditions, where the TADDOL was varied which are shown in **Table 3**.

Using phenyl TADDOL catalyst **98** and crude **77** in the Diels-Alder reaction, compound **76** was obtained with 14% ee (Entry 1). However, when 1-naphthyl TADDOL catalyst **96** and crude **77** were used in the Diels-Alder reaction, the enantiopurity of **76** increased to 50% and 67% ee under the same reaction conditions (Entries 2 and, 3). Using freshly prepared pure **77** and 1-naphthyl TADDOL catalyst **96**, 79% ee (Entry 4) was obtained, but this was still lower than that reported by Rawal *et al*. (**Table 3**).

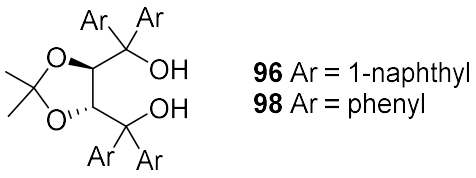


Figure 9. Structure of α, α, α', α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)

Entry	TADDOL	Purity of **77** (by H^1NMR)	Temperature (°C)	Time (h)	ee,%
1	**98**	75%	-80	48	14
2	**96**	64%	-80	48	50
3	**96**	96%	-80	48	67
4	**96**	98%	-80	48	79

Table 3. Effect of TADDOL structure on Diels-Alder reaction.

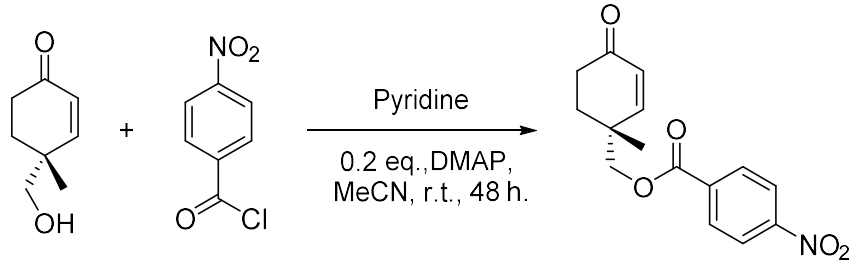
This shows that when freshly prepared pure Rawal's diene is used in the Diels-Alder reaction, the percent enantiomeric excess increased. When the purities of **77** were 64% and 96%, these

afforded 50% and 67% ee, respectively. When freshly prepared **77** was purified by Kugelrohr distillation and the Diels-Alder reaction was performed, an enantioenriched enone **76** in 79% ee was obtained (**Table 3**).

The enantioenriched enone **76** was protected using TIPSCl to generate TIPS-protected compound **52** in 87% yield (**Scheme 26**). Compound **52** was used for the subsequent Diels-Alder reaction to study the formation of the *trans*-decalin moiety.

10.3.6. Determination of the percent enantiomeric excess of enantioenriched enone **95**.

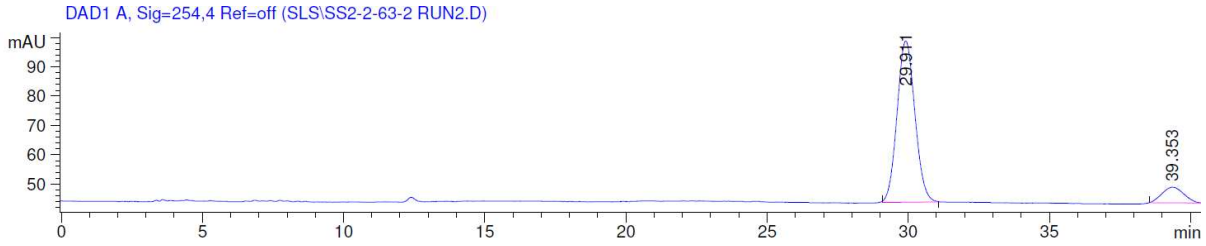
Chiral enone **76** prepared *via* the TADDOL-catalysed Diels-Alder reaction, was reacted with **94** to afford **95** in 79% ee, based on the HPLC analysis (**Scheme 27**).



76 **94** **95**

40% yield

Scheme 27. Acylation of enone **76**.



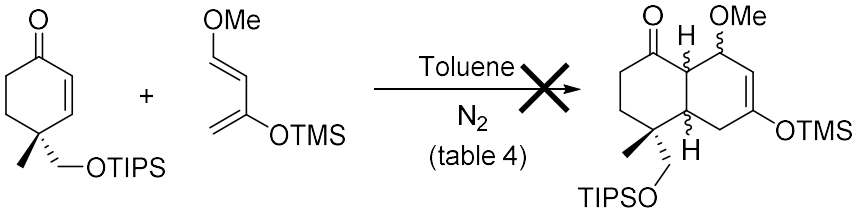
Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.911	BB	0.6680	2416.18701	55.06165	89.4540
2	39.353	BBA	0.6256	284.85043	5.34622	10.5460
Totals :				2701.03745	60.40787	

Figure 10. HPLC data of enantioenriched compound **95**.

10.3.7. The Diels-Alder reaction of enantioenriched enone **52** with Danishefsky's diene **100**.

In the retrosynthetic route (**Scheme 19**) discussed previously, decalin core **48** is an important scaffold in the structure of streptosetin A (**3**), the synthesis of which was proposed using the Diels-Alder strategy. After successful completion of the synthesis of racemic and enantioenriched enone **76**, Diels-Alder reactions between enone **52** and several dienes were investigated. Danishefsky's diene **100** was used because it was highly reactive and had been previously prepared in the group. The Diels-Alder reactions were performed using enantiomerically enriched enone **52** with 1.5 equivalents of Danishefsky's diene **100** in toluene under different conditions, but the cyclised Diels-Alder product **101** was not obtained in any case (**Scheme 28 and Table 4**).



52 **100** **101**

Scheme 28. Diels-Alder reaction of enone **52** and Danishefsky's diene **100**.

Various temperatures and reaction times were examined for the Diels-Alder reaction of enone **52** and Danishefsky diene **100** in toluene (**Table 4**)**.**

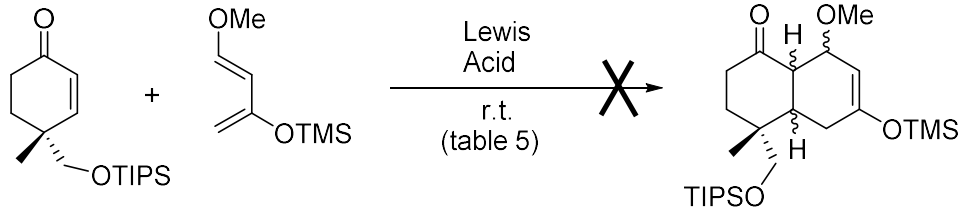
Entry	Equivalents of Danishefsky's diene	Temperature (°C)	Time (h)	Result
1	1.5	r.t.	48	No product formation Both starting materials decomposed
2	1.5	80	78	No product formation Both starting materials decomposed
3	1.5	Reflux	4	No product formation Both starting materials decomposed

Table 4. Diels-Alder reactions of enone **52** and Danishefsky'sdiene **100** under various conditions.

We were unable to recover either of the starting materials due to their decomposition as confirmed by TLC and 1H NMR spectroscopy; the reaction mixture became dark and tarry. This showed that enone **52** and diene **100** were not sufficiently reactive in the absence of a catalyst in the reaction. Therefore, a Lewis acid was employed as a catalyst.

10.3.8. Lewis-acid-catalysed Diels-Alder reaction of enone **52** and Danishefsky's diene **100**.

The Diels-Alder reactions were performed with enantiomerically enriched enone **52** and Danishefsky's diene **100** in the presence of Lewis-acid catalysts (**Scheme 29**), but no traces of cyclised Diels-Alder product **101** were observed (**Table 5**).



52 **100** **101**

Scheme 29. Diels-Alder reaction of enone **52** and diene **100**.

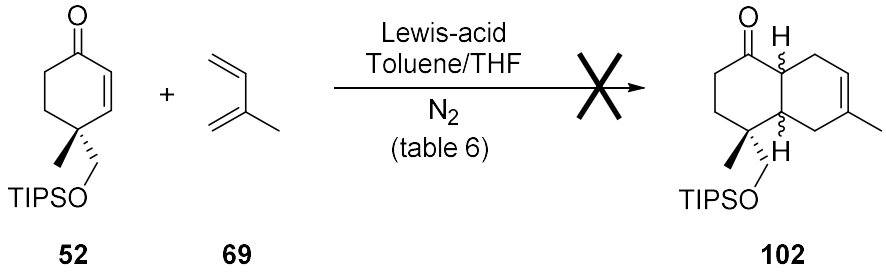
Entry	Lewis acid	Equivalents of Danishefsky diene	Temperature (°C)	Solvent	Time (h)	Result
1	0.2 eq. $EtAlCl_2$	10	r.t.	DCM	19	No product formation Both starting materials decomposed
2	10 mol% $Yb(OTf)_3$	1.2	r.t.	THF	23	No product formation Both starting materials decomposed
3	20 mol% $Yb(OTf)_3$	1.2	r.t.	DCM	16	No product formation Both starting materials decomposed
4	10 mol% BF_3OEt_2	1.2	r.t.	DCM	18	No product formation Both starting materials decomposed

Table 5. Lewis-acid-catalysed Diels-Alder reactions of enone **52** and Danishefsky diene **100**.

Three Lewis-acid catalysts, $EtAlCl_2$, $Yb(OTf)_3$, and BF_3OEt_2, were used but the formation of the cyclised Diels-Alder product was not observed. This could be because of the steric hindrance of enone **52**. Unfortunately, both starting materials decomposed as confirmed by TLC and 1H NMR spectroscopy; and the reaction mixture became dark and tarry.

10.3.9. Diels-Alder reaction of enantioenriched enone **52** with isoprene **69**.

Diels-Alder reactions of enantioenriched enone **52** with isoprene **69** (**Scheme 30**) were also performed in the presence of Lewis-acids at different temperatures, but the Diels-Alder product **102** was not formed as confirmed by TLC and 1H NMR spectroscopy. In all cases, both starting materials could not be isolated (**Table 6**). As mentioned previously, this may be attributed to the steric hindrance of enone **52**. The prior work in the group by G. Lodovici,[54b] showed that the decalin core could be synthesised successfully by the reaction of enone **59** (lacking quaternary methyl group) with isoprene.



52 **69** **102**

Scheme 30. Diels-Alder reaction of enone **52** with diene **69** in presence of Lewis acid at various temperatures.

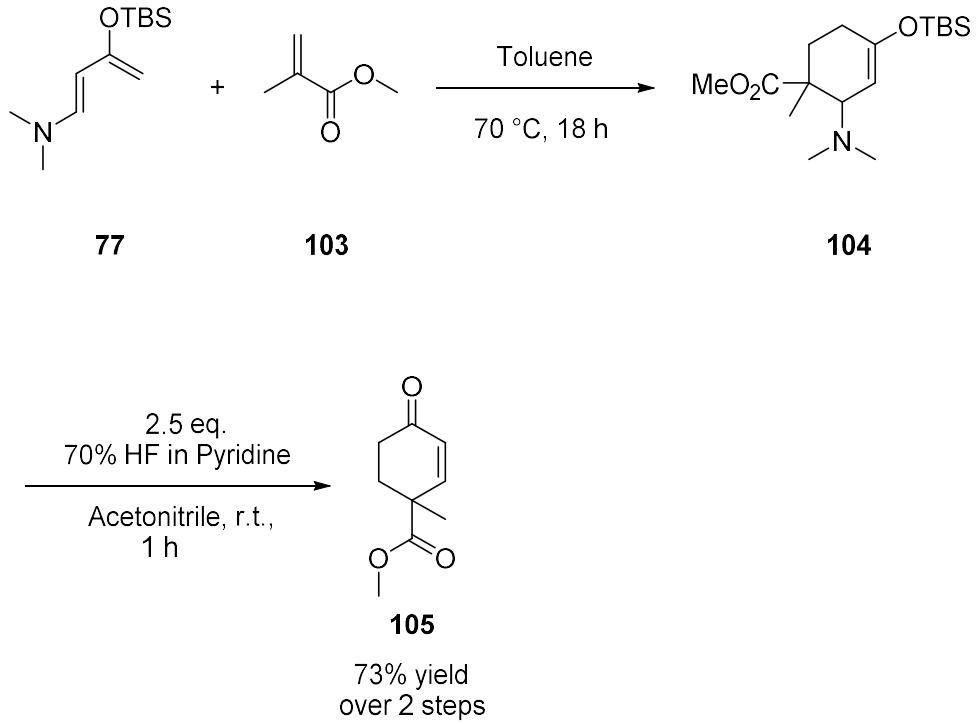
Entry	Lewis acid	Equivalents of diene	Solvent	Temperature (°C)	Time (h)	Result
1	0.25 eq. $EtAlCl_2$	15	Toluene	r.t.	19	No product formation
2	0.25 eq. $EtAlCl_2$	15	Toluene	40	19	No product formation
3	0.25 eq. $EtAlCl_2$	15	Toluene	0-r.t.	18	No product formation
4	10 mol% $Yb(OTf)_3$	15	THF	r.t.	21	No product formation

Table 6. Diels-Alder reaction of enone **52** and isoprene **69** at various temperatures.

10.3.10. Synthesis of racemic enone ester **105**

Rawal synthesised a racemic ester enone **105** (**Scheme 31**), which is less sterically hindered than enone **52**.[70] For this reason, ester enone **105** was prepared for further investigation of the Diels-Alder reaction.

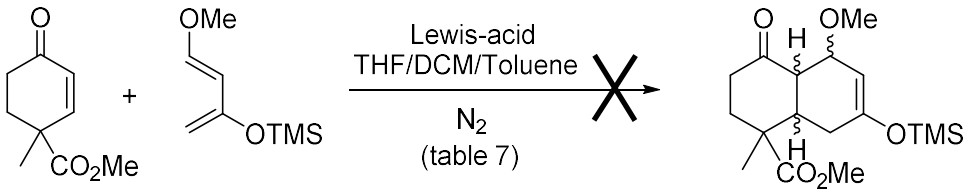
Diels-Alder reaction of Rawal's diene **77** with 1.5 equivalents of methyl methacrylate **103** was performed in toluene at 70 °C to prepare the desired crude cycloadduct **104**. Desilylation together with the elimination of dimethylamine from **104** using 70% HF in pyridine afforded the desired racemic enone **105** in 73% yield (**Scheme 31**).



Scheme 31. Synthesis of racemic enone ester **105**.

10.3.11. Diels-Alder reaction of racemic enone **105** with Danishefsky's diene **100**

The Diels-Alder reactions of racemic enone **105** and Danishefsky's diene **100** were performed in the presence of Lewis acids (**Scheme 32**), but no traces of the Diels-Alder cyclised product were observed (**Table 7**). Attempts to recover both starting materials were made, but decomposition occurred in all cases, as confirmed by TLC and 1H NMR spectroscopy.



105 **100** **106**

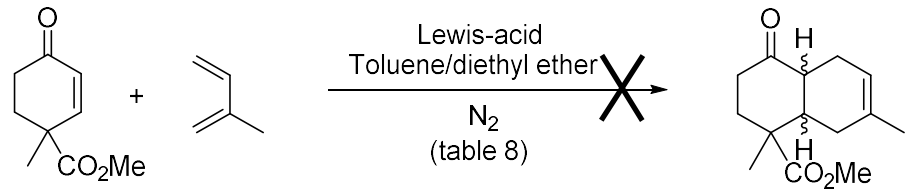
Scheme 32. Diels-Alder reaction of enone **105** with diene **100** in the presence of Lewis acid catalysts.

Entry	Lewis acid	Equivalents of Danishefsky's diene	Solvent	Temperature (°C)	Time (h)	Result
1	10 mol% $Yb(OTf)_3$	1.2	THF	r.t.	43	No product formation Both starting materials decomposed
2	10 mol% BF_3OEt_2	1.2	DCM	r.t.	24	No product formation Both starting materials decomposed
3	-	1.5	Toluene	80	19.5	No product formation Both starting materials decomposed

Table 7. Diels-Alder reaction of enone **105** with diene **100**.

10.3.12. The Diels-Alder reaction of racemic enone **105** with isoprene **69**

The Diels-Alder reaction of racemic enone **105** and isoprene **69** was performed in the presence of Lewis acids, but the Diels-Alder product was still not observed (**Scheme 33**). Both starting materials could not be recovered due to their decomposition, as confirmed by TLC and 1H NMR spectroscopy.



105 **69** **107**

Scheme 33. Diels-Alder reaction of enone **105** with diene **69** in the presence of Lewis acid catalyst.

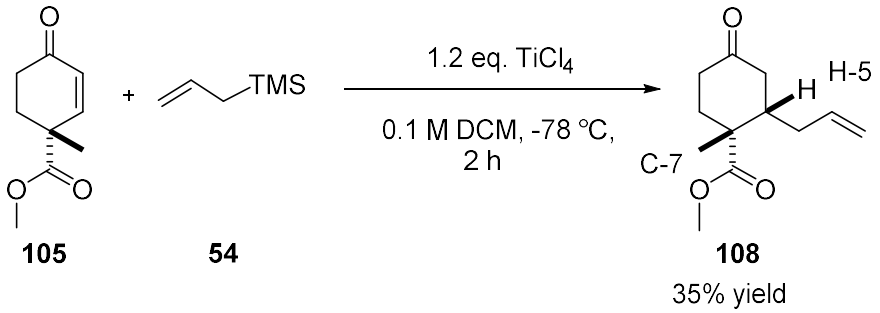
Entry	Lewis acid	Equivalents of diene	Solvent	Temperature (°C)	Time (h)	Result
1	0.25 eq. $EtAlCl_2$	15	Toluene	r.t.	19	No product formation Both starting materials decomposed
2	2 eq. $ZnCl_2$	15	Ether	0 r.t.	1	No product formation Both starting materials decomposed

Table 8. Diels-Alder reactions of enone **105** and isoprene **69** in the presence of Lewis acid catalysts.

Several Diels-Alder reactions between enones **52** and **105** and dienes **69** and **100**, were attempted but the decalin scaffold could not be synthesised. Therefore, an alternate strategy to form the decalin ring of streptosetin A (**3**) was explored.

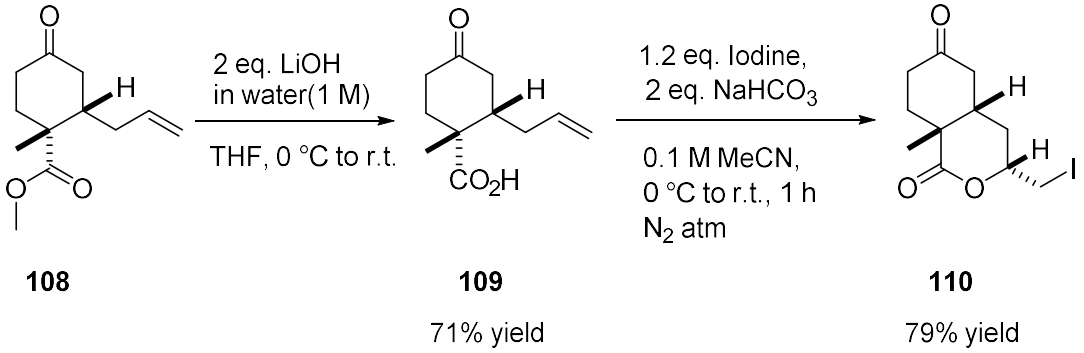
10.3.13. Sakurai approach for the synthesis of streptosetin A core **48**

Owing to the failure of the strategy employing the Diels-Alder reaction, the Sakurai route was investigated. The Hosomi-Sakurai 1,4-addition reaction was performed using racemic ester enone **105** and allyltrimethylsilane **54** to generate **108** in 35% yield (**Scheme 34**).



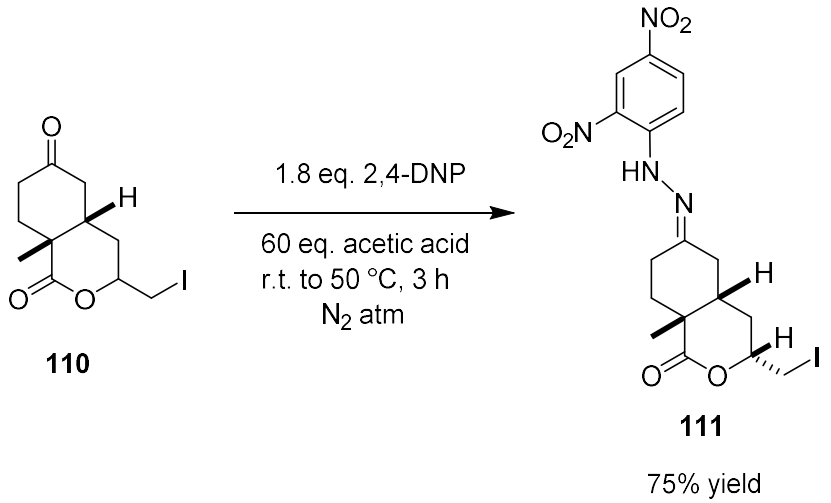
Scheme 34. Sakurai reaction of enone core **108**.

The stereochemistry of **108** was determined *via* saponification of the ester to its corresponding carboxylic acid **109** in 71% yield using aq. lithium hydroxide in THF, followed by iodocyclisation[24] in the presence of I_2 and $NaHCO_3$ to afford bicyclic product **110** in 79% yield (**Scheme 35**).



Scheme 35. Iodocyclisation reaction sequence to determine the stereochemistry of enone core **108**.

Compound **110** was heated with 2,4-dinitrophenylhydrazine in methanol to produce hydrazone **111** in 75% yield (**Scheme 36**). The single-crystal X-ray diffraction data of **111** showed a *syn*-relationship between methyl C-7 and H-5, and the iodomethyl group was oriented in the downward direction opposite to C-7 and H-5. Unfortunately, this did not, correspond to the desired configuration of the natural product (**Figure 5**).



Scheme 36. Hydrazone formation to determine the stereochemistry of **111**.

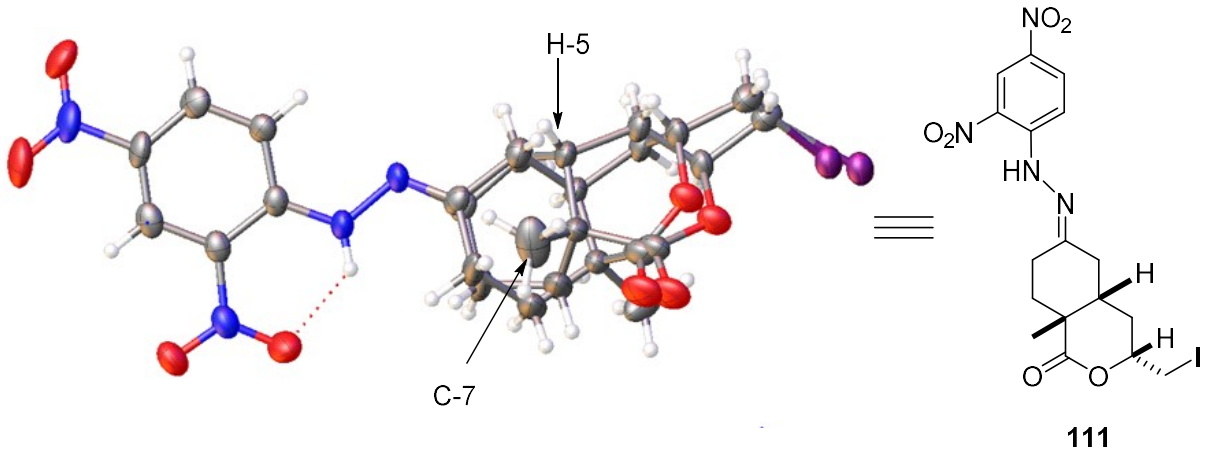


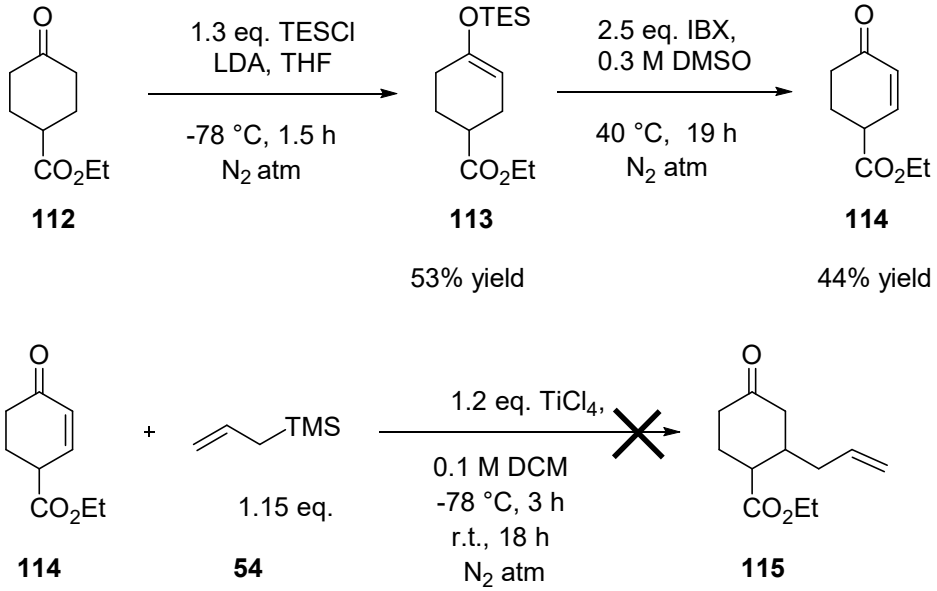
Figure 11. Single-crystal X-ray diffraction data of **111** showing the *syn*-relationship between C-7 and H-5.

The asymmetric unit exists in two possible conformers of the bicyclic portion of the molecule with *E* geometry of the hydrazone. The minor form is an enantiomer of the major form with the 6-membered rings oriented in boat-like conformations. The racemate crystallised with one of each enantiomer in the unit cell. X-ray crystallography was used to determine the stereochemistry, but the data indicated that the desired stereochemical configuration was not obtained. However, only one product crystal could be isolated and characterised as **111**.

10.3.14. Sakurai reaction of enone core **114**

This study was performed because, the Sakurai reaction did not give the stereochemistry needed for the natural product target. Sakurai reaction with **114**, where the enolate could be used to incorporate the methyl group was examined, such that the stereochemistry of compound **115** could be determined.

Treatment of **112** in the presence of LDA at -78 °C and TESCl afforded TES-enol ether **113** in 53% yield, which was then oxidised using 1.5 equivalents of IBX at 40 °C to produce enone **114** in 44% yield**.** Thereafter, the Hosomi-Sakurai 1,4-addition reaction was performed with enone **114** and allyltrimethylsilane **54**, but **115** was not obtained (**Scheme 37**).



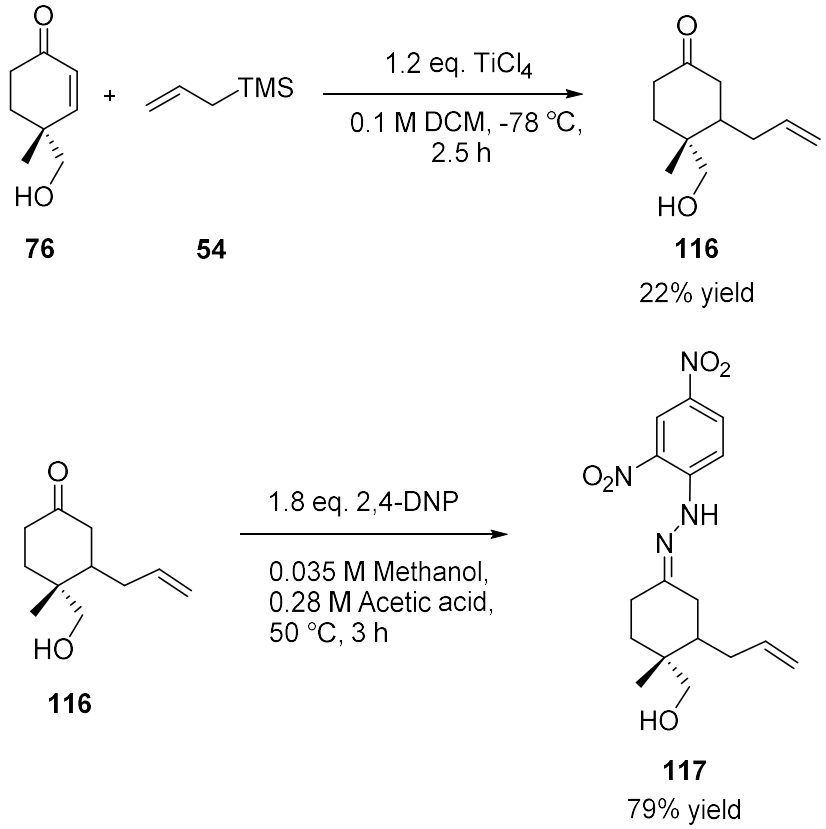
Scheme 37. Sakurai reaction with enone core **114**.

10.3.15 Sakurai reaction of enone core **76** of streptosetin A

To determine if the Sakurai reaction could be used to obtain the desired stereochemistry, the addition of allylsilane to enone **76** and **52** was investigated.

The Hosomi-Sakurai 1,4-addition reaction was performed between enone **76** and allyltrimethylsilane **54** to generate **116** in 22% yield. A reaction between **116** and 2,4-dinitrophenylhydrazine in methanol was then performed to generate **117** in 79% yield (**Scheme 38**). However, only one product could be isolated and characterised as **117**.

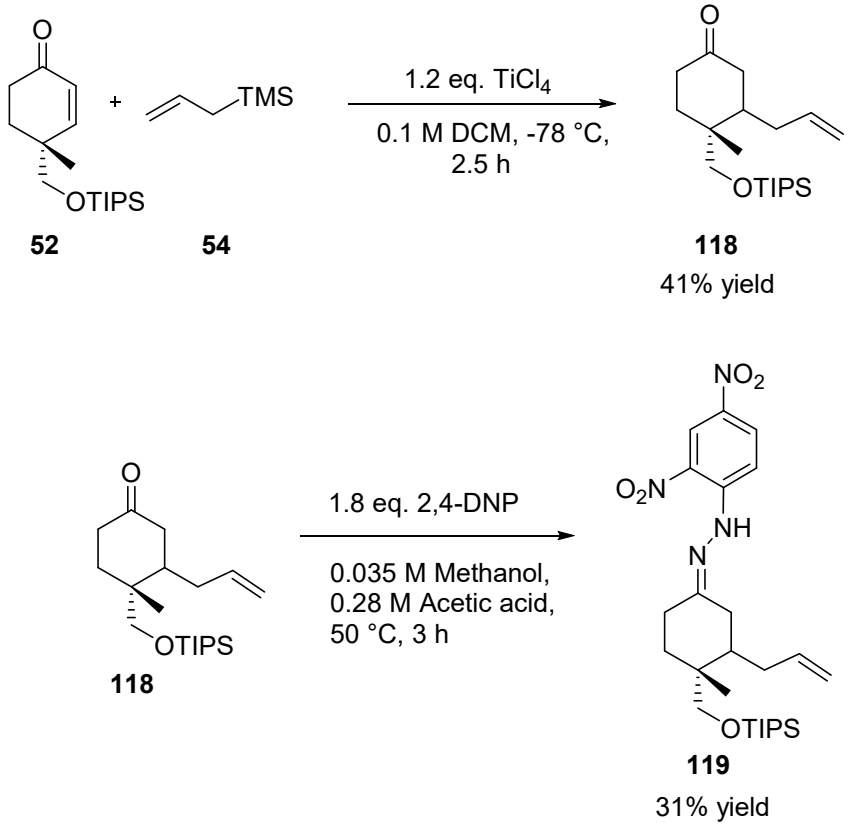
Efforts to obtain a crystal of **117** are underway for stereochemical determination by single-crystal X-ray diffraction.



Scheme 38. Sakurai reaction of enone core **76** and hydrazine formation to generate **117**.

10.3.16. Sakurai reaction strategy for the synthesis of enone core **52** of streptosetin A

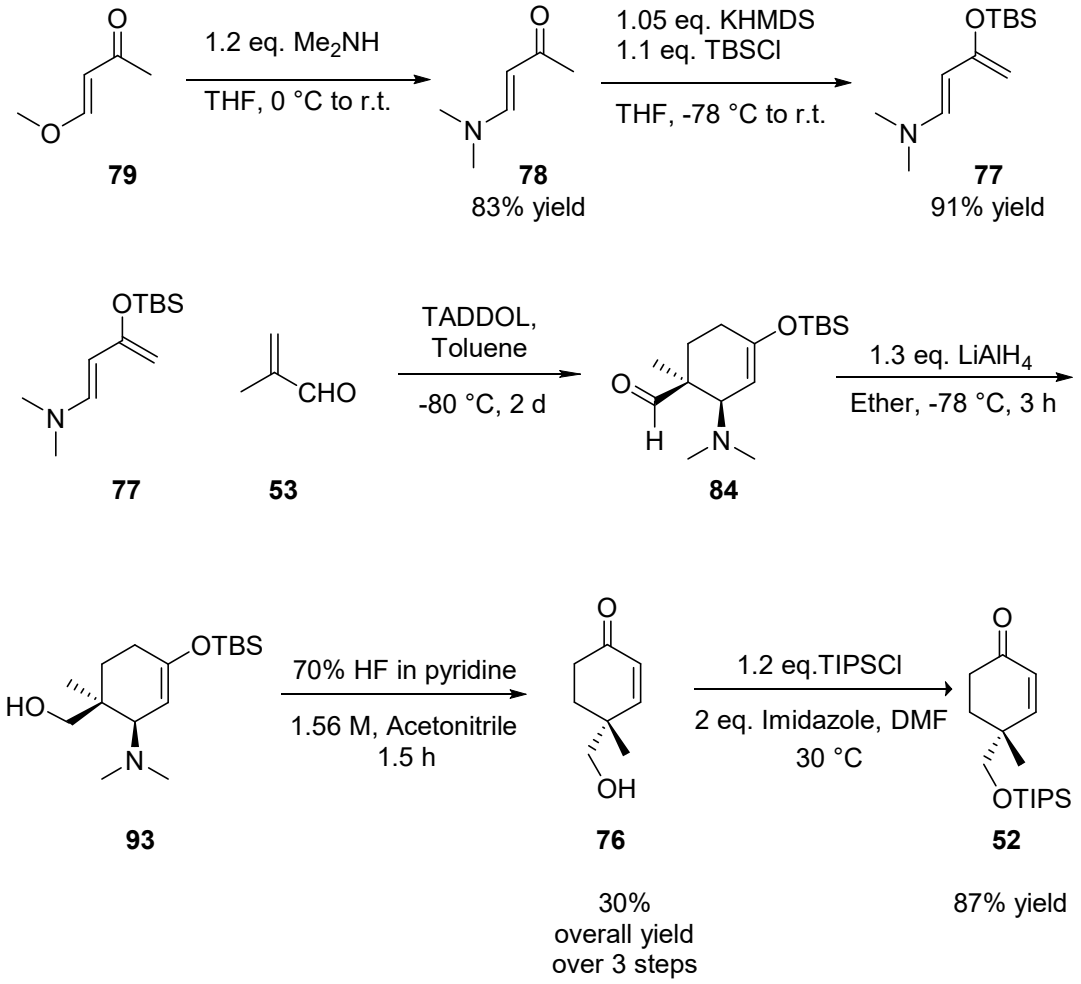
The Hosomi-Sakurai 1,4-addition reaction was performed between enone **52** and allyltrimethylsilane **54** to afford **118** in 41% yield. Compound **118** was treated with 2,4-dinitrophenylhydrazine in methanol to generate **119** in 31% yield (**Scheme 39**). However, only one product could be isolated and characterised as **119**. Efforts to obtain a crystal of **119** are underway for stereochemical determination by single-crystal X-ray diffraction.



Scheme 39. Sakurai reaction of enone core **52** and hydrazone formation to generate **119.**

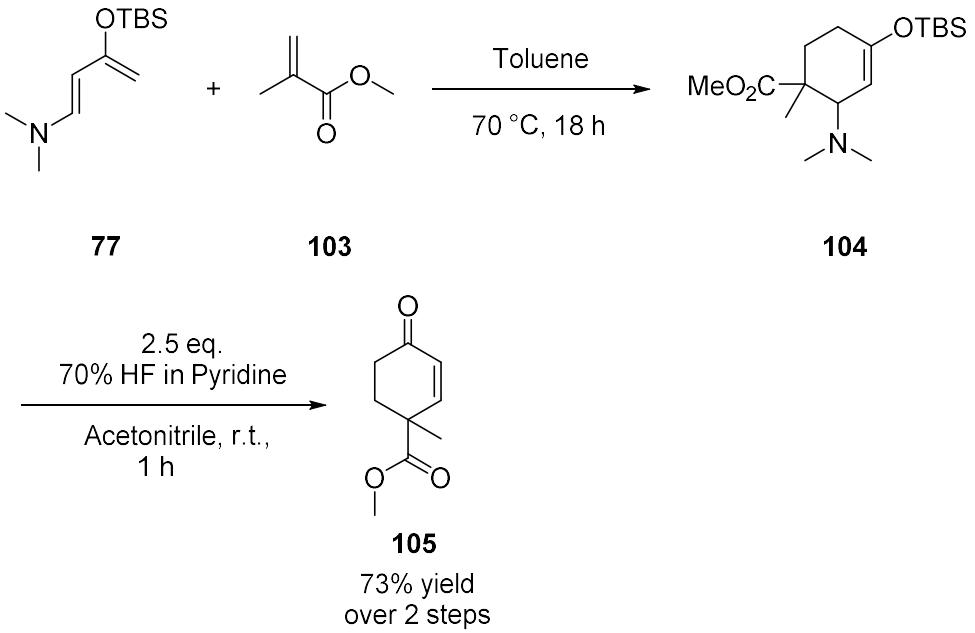
11. Conclusion

The asymmetric synthesis of key enone **76** was achieved in a five-step sequence. The enantioenriched enone core **76** was synthesized in 79% ee. Initially, Rawal's diene **77** was prepared, followed by Diels-Alder cycloaddition with methacrolein **53** in the presence of TADDOL catalyst to generate cyclised Diels-Alder product **84** (crude). This crude product was used in the next step, in which the reduction of the aldehyde group was done to afford crude alcohol **93**. This crude product was further employed in the next step to remove the OTBS protecting group with the elimination of dimethylamine from **93**. The reaction was performed in 70% HF in pyridine to generate the desired enantioenriched enone compound **76** in 30% overall yield over three steps with 79% ee. The enantioenriched enone **76** was protected using TIPSCl to generate TIPS-protected compound **52** in 87% yield (**Scheme 40**). The racemic enone core **76** was also prepared by the Diels-Alder reaction.



Scheme 40. Formation of enone core **76**.

The enone core **76** was protected by the TIPS group to afford compound **52**. This compound was used for the synthesis of the decalin core under various Diels-Alder reaction conditions but the decalin core **50** of the natural product could not be prepared, probably because of the steric hindrance in compound **52**. Another enone core **105** was prepared *via* a two-step sequence, which also did not afford the desired decalin core **50** (**Scheme 41**).

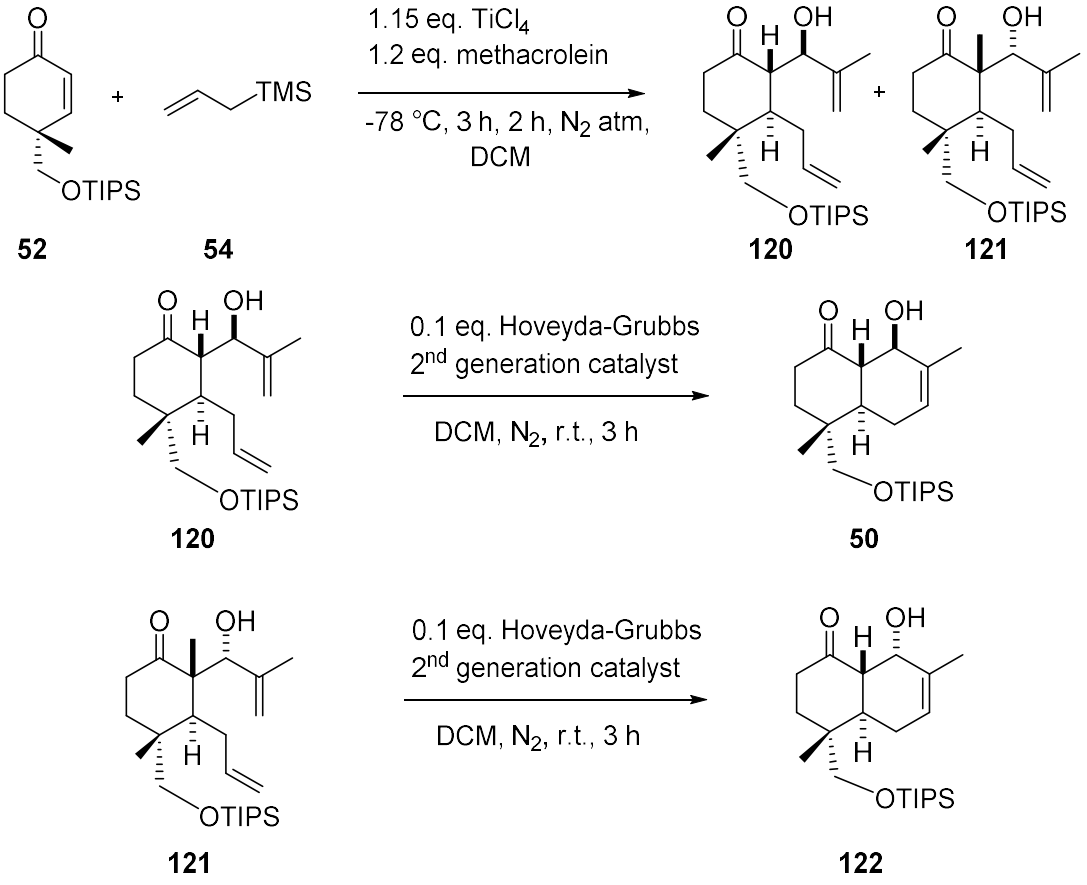


Scheme 41. Formation of ester enone core **105**.

An alternative strategy to form the decalin ring of streptosetin A, employing the Sakurai, aldol, and ring closing metathesis reactions was explored. The Sakurai 1,4-addition reaction between ester enone core **105** and allyltrimethylsilane **54** was performed to afford 35% yield of the product. To investigate the stereochemistry, iodocyclised compound **110** and hydrazine compound **111** were synthesized, followed by their characterisation using X-ray crystallography, but unfortunately, the correct stereochemistry of the product was not obtained. Similarly, Sakurai 1,4-addition reaction was attempted with two other enone cores **76** and **52**, and hydrazones **117** and **119**, respectively, were further synthesised to determine the stereochemistry using single-crystal X-ray crystallography.

12. Future work

The decalin core of Streptosetin A, could be achieved by employing the Sakurai, aldol and ring closing metathesis reactions. Initially, would be the Sakurai reaction of enone **52** and **54** then it will trap the enolate by aldol reaction. It could generate the compound **120** and **121**, further the corresponding compounds will subject to metathesis using Hoveyda-Grubbs 2nd generation catalyst would then allow the completion to form the compound **50** and **122** respectively. To determine the stereochemistry of the hydrazone compounds **117** and **119**, the Sakurai, aldol, and ring closing metathesis reactions will be investigated to study the formation of *trans*-decalin core **50** of Streptosetin A **3** (**Scheme 42**)**.**



Scheme 42. Sakurai, aldol, and ring closing metathesis reactions for the formation of *trans*-decalin core **50** of Streptosetin A **3**

13. Experimental

13.1 General experimental

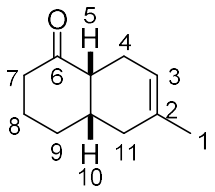
All non-aqueous reactions were carried out under oxygen-free N_2 atmosphere using flame-dried glassware. Distilled water was used, and brine solution constituted the saturated aqueous solution of NaCl. The melting points were measured using a Stuart SMP3 apparatus, while the optical rotation data were obtained using a JASCO-DIP370 polarimeter; the $[\alpha]_D$ values are expressed as 10^{-1}deg.cm^2.g^{-1}. The infra-red spectra were recorded using a ThermoNicolet Avatar 370 FT-IR spectrometer. NMR spectra were recorded employing Jeol ECX-400 and Jeol ECS-400 spectrometers at ambient temperature; chemical shifts are expressed in parts per million (ppm) and referenced using the following solvent peaks: $CDCl_3$ (7.27 ppm), and C_6D_6 (7.16 ppm) for ^{1}H NMR; $CDCl_3$ (77.0 ppm; central line of the triplet), and C_6D_6 (128.4 ppm; central line of triplet) for ^{13}C NMR. ^{13}C NMR spectra were assigned using the DEPT experiments. The coupling constants (J) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI), electron ionisation (EI), and atmospheric pressure chemical ionisation (APCI) techniques.

All the Mass-spectra data were in a 5-ppm error. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich. Hexane, DCM, toluene, THF and Et_2O were all purified using Innovative Technology Solvent Purification System; diisopropylamine was distilled from calcium hydride. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to the IUPAC rules.

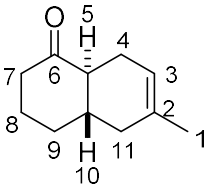
13.2 Methods and Characterisation of Compounds

(5*R**, 10*S**)-2-Methyl-8,9,10,11,4,5-hexahydronaphthalen-6(2H)-one, **70,**

(5*S**, 10*S**)-2-Methyl-8,9,10,11,4,5-hexahydronaphthalen-6(2H)-one, **71**



70



71

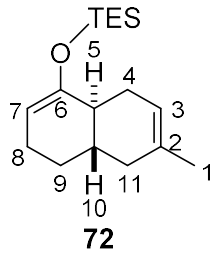
To a solution of cyclohexanone **64** (2.0 mL, 20.8 mmol) in dry DCM (104 mL) was added 1.0 M solution of $EtAlCl_2$ in hexane (4.16 mL, 4.16 mmol), and the reaction mixture was stirred at room temperature for 30 minutes. Isoprene **69** (20.81 mL, 208 mmol) was added, and the mixture was stirred at 30 °C for 14 h. Then, 10% aqueous solution of Rochelle's salt (208 mL) was added, and the mixture was further stirred vigorously for one hour. The reaction mixture was diluted with water (104 mL) and extracted with DCM (3 × 104 mL). The combined organic layers were washed with water (52 mL) followed by brine (52 mL), and then dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (2-5% EtOAc in hexane) to yield **70** (1.21 g, 36%) and **71** (17 mg, 0.5%) as pale-yellow oils, as well as a mixture of **70** and **71** (1.55 g, 45%). The crude product contained a 3.5:1 ratio of **70** and **71** by 1H NMR spectroscopy. (5*R**, 10*S**)-2-methyl-8,9,10,11,4,5-hexahydronaphthalen-6(2H)-one, **70 Rf** =0.42(EtOAc : hexane 5% : 95%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2928, 1708 (C=O), 1445, 1370, 1310, 1152, 1065, 825, 762 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.32 - 5.37 (1 H, m, H-3) 2.64 - 2.70 (1 H, m) 2.42 - 2.45 (1 H, m) 2.35 - 2.41 (2 H, m) 2.24 - 2.33 (1 H, m) 1.94 - 2.04 (3 H, m) 1.85 (3 H, td, *J*=8.77, 3.05 Hz) 1.74 - 1.79 (1 H, m) 1.63 (3 H, s, H-1) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 213.0, 131.8, 118.1, 47.9, 39.9, 36.2, 32.0, 28.4, 24.0, 23.9, 23.7 ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1098. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. (5*R**, 10*S**)-2-methyl-8,9,10,11,4,5-hexahydronaphthalen-6(2H)-one, **71** *trans* decalin. **Rf** = 0.48 (EtOAc : hexane 5% : 95%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2915, 1707 (C=O), 1441, 1376, 1309, 1179, 1149, 1060, 824, 768, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.40 (1 H, br. s. H-3) 2.31 - 2.49 (2 H, m) 2.13 - 2.20 (2 H, m) 2.01 - 2.13 (3 H, m) 1.87 - 1.97 (2 H, m) 1.68 - 1.77 (2 H, m) 1.65 (3 H, s, H-1) 1.40 - 1.52 (1 H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ

212.4, 132.3, 119.9, 50.2, 42.0, 40.4, 38.3, 32.6, 26.1, 24.6, 23.2. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1096. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. Spectroscopic data are consistent with those reported in the literature.[59]

Epimerization Method

To a solution of *cis*-decalin **70** (1.55 g, 9.47 mmol) in dry DCM (47 mL) was added 1.0 M solution of $EtAlCl_2$ in hexane (1.89 mL, 1.89 mmol), and the reaction mixture was stirred for 16 h. Then, 10% aqueous solution of Rochelle's salt (162 mL) was added, and the mixture was stirred vigorously for one hour. The mixture was diluted with water (81 mL) and the organic phase was extracted with DCM (3 × 81 mL). The combined organic layers were washed with water (40 mL) followed by brine (40 mL), and then dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2-5% EtOAc in hexane) to yield **71** as a pale-yellow oil (989 mg, 67%). **71** *trans*- decalin; **Rf** = 0.48 (EtOAc : hexane 5% : 95%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2915, 1707 (C=O), 1441, 1376, 1309, 1179, 1149, 1060, 824, 768, 668 cm^{-1}.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.40 (1 H, br. s. H-3) 2.33 - 2.47 (2 H, m) 2.13 - 2.20 (3 H, m) 2.01 - 2.13 (2 H, m) 1.90 - 1.97 (2 H, m) 1.69 - 1.77 (2 H, m) 1.63 - 1.67 (3 H, m, H-1) 1.40 - 1.53 (1 H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 212.4, 132.3, 119.9, 50.2, 42.0, 40.4, 38.3, 32.6, 26.1, 24.6, 23.2 ppm. **MS** (ESI): m/z 187 ($M+Na^+$); HRMS: found: ($M+Na^+$) 187.1096. $C_{11}H_{16}NaO$ requires ($M+Na^+$) 187.1093. Spectroscopic data are consistent with those reported in the literature.[59]

Triethyl-(((11*S**, 10*S**)-2-methyl,8,9,10,11,4,5-hexahydronaphthalen-6-yl)oxy)silane, **72**

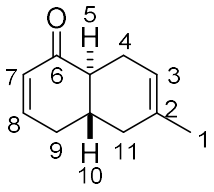


72

To a solution of freshly distilled diisopropylamine (0.6 mL, 4.30 mmol) in dry THF (17.5 mL) at -78 °C, was added *n*-BuLi (3 mL, 1.42 M in hexane, 4.26 mmol), and this solution was stirred at -78 °C for 30 minutes. A solution of model *trans*-decalin **71** (588 mg, 3.58 mmol) in dry THF (17.5 mL) was added to the LDA solution and stirred at -78 °C for one hour. Then, freshly distilled TESCl (0.78 mL, 4.66 mmol) was added, and the reaction mixture was stirred at -78

°C for additional 30 minutes and allowed to warm to room temperature for 30 min. The reaction was quenched by adding water (28 mL), following which it was extracted using Et_2O (235 mL) and the organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield **72** as a pale-yellow oil (784 mg, 78%). **Rf** = 0.88 (EtOAc : hexane 10% : 90%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2959, 2918, 2877, 1661, 1442, 1379, 1245, 1195, 1160, 1015, 978, 885, 800, 735, 689 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.42 (1 H, d, *J*=6.1 Hz, H-3) 4.78 - 4.83 (1 H, m) 2.33 - 2.43 (1 H, m) 2.01 - 2.17 (2 H, m) 1.89 - 2.01 (1 H, m) 1.73 - 1.84 (1 H, m) 1.62 - 1.72 (5 H, m) 1.57 (3 H, s) 0.94 - 1.02 (9 H, m) 0.62 - 0.72 (6 H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 152.6, 133.8, 121.9, 102.8, 41.1, 38.0, 37.4, 29.2, 29.2, 23.7, 23.4, 6.8, 5.0 ppm. **MS** (ESI): m/z 279 ($M+H^+$); HRMS: found: ($M+H^+$) 279.2126. $C_{17}H_{31}OSi$ requires ($M+H^+$) 279.2138. Spectroscopic data are consistent with those reported in the literature.[60]

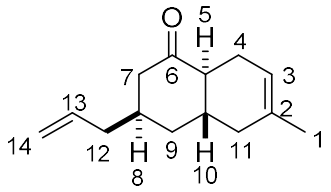
(5*S**, 10*S**)-2-Methyl-10,11,4,5-tetrahydronaphthalen-6(4H)-one, **73**



73

To a solution of TES-enol *trans*-decalin **72** (0.784 g, 2.81 mmol) in dry DMSO (23.4 mL), IBX (1.97 g, 7.03 mmol) was added, and the reaction mixture was stirred at 40 °C for 24 h. Then, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (150 mL), and reaction mixture was extracted with MTBE (3 × 200 mL). The combined organic layers were washed with brine (150 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5-10% EtOAc in hexane) to yield **73** as an orange oil (379 mg, 82%). **Rf** = 0.39 (EtOAc : hexane 10% : 90%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2921, 2849, 1976, 1685 (C=O), 1462, 1375, 1259, 1115, 1018, 792 cm^{-1}.**^{1}H NMR** (400 MHz, $CDCl_3$): δ (1 H, ddd, *J*=9.92, 6.10, 1.53 Hz, H-8) 6.04 (1 H, dd, *J*=9.92, 2.29 Hz, H-7) 5.44 (1 H, d, *J*=2.29 Hz, H-3) 2.46 - 2.58 (2 H, m) 1.97 - 2.23 (6 H, m) 1.64 - 1.73 (3 H, m, H-1)ppm. **MS** (ESI): m/z 163 ($M+H^+$); HRMS: found: ($M+H^+$) 163.1121. $C_{11}H_{15}O$ requires ($M+H^+$) 163.1117. Spectroscopic data are consistent with those reported in the literature.[61]

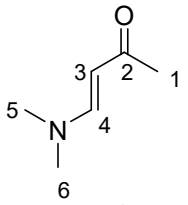
(8*S**, 5*S**, 10*R**)-8-Allyl-2-methyl-8,9,10,11,4,5-hexahydronaphthalen-13(2H)-one,**74**.



74

To a solution of enone *trans*-decalin **73** (240 mg, 1.48 mmol) in dry DCM (14.81 mL) at -78 °C was added $TiCl_4$ (0.19 mL, 1.7 mmol). After five minutes, allyltrimethylsilane **54** (0.27 mL, 1.70 mmol) was added and the reaction mixture was stirred at -78 °C for one hour. Thereafter, the saturated aqueous solution of $NaHCO_3$ (18.48 mL) was added at -78 °C, stirred for 45 minutes and then allowed to warm to room temperature for 30 minutes. The aqueous phase was then extracted with DCM (3 × 55 mL), and the combined organic layers were washed with water (55 mL) and brine (55 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (1% EtOAc in hexanes) to yield **74** as a white coloured solid (116 mg, 39%). **Rf** = 0.27 (EtOAc : hexane 10% : 90%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2910, 2846, 1708 (C=O), 1640, 1440, 1379, 1352, 1150, 1070, 994, 912, cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.72 (1H, ddt, *J*=16.8, J=10.4, *J*=6.9 Hz, H-13), 5.40 (1H, br. s., H-3), 4.97 - 5.09 (2 H, m, H-14), 2.58 -2.63 (2 H, m, H-7), 2.36 – 2.41 (1 H, m, H-8), 2.26 - 2.34 (1 H, m, H-10), 1.95 - 2.08 (3 H, m, H-9 + H-10), 1.83 - 1.94 (3 H, m, H-4 + H-11), 1.59 - 1.71 (4H, m, H-1) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 211.9 (C-6), 136.1 (C-13), 132.4 (C-2), 119.7 (C-3), 116.5 (C-14), 50.2 (C-10), 45.9 (C-7), 38.3 (C-4), 36.9 (C-12), 35.6 (C-5), 35.6 (C-11), 34.8 (C-8), 24.3 (C-9), 23.1 (C-1). **MS** (ESI): m/z 227 ($M+Na^+$); HRMS: found: ($M+Na^+$) 227.1407. $C_{14}H_{20}NaO$ requires ($M+Na^+$) 227.1406. m/z 205 ($M+H^+$); HRMS: found: ($M+H^+$) 205.1586. $C_{14}H_{21}O$ requires ($M+H^+$) 205.1587.

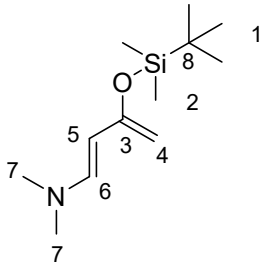
4-(Dimethylamino)but-3-en-2-one **78**



78

To a 2.0 M solution of dimethylamine in THF (29.97 mL, 59.93 mmol) was added *trans*-4-methoxy-3-buten-2-one **79** (5.0 g, 59.94 mmol) at 0 °C over a period of 30 minutes. The light yellow solution was allowed to attain room temperature. After concentrating *in vacuo*, the crude product was purified *via* bulb to bulb distillation (Kugelrohr distillation at 114 °C and 3 mm Hg) to yield **78** as a light -yellow oil (3.43 g, 83% yield). **Rf** = 0.15 (MeOH: DCM 2% : 98%). **IR** (ATR): $\mathbf{\nu}_{max}$ 1654 (C=O), 1555, 1433, 1349, 1255, 1227, 1107, 949, cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (1 H, d, *J*=13.0 Hz, H-4), 5.00 (1 H, d, *J*=13.0 Hz, H-3), 2.64 - 3.13 (6 H, m, H–5, H-6) 2.00 - 2.11 (3 H, m, H-1) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 195.1 (C-2), 152.5 (C-4), 96.5 (C-3), 44.7 (C-5), 36.8 (C-6), 27.8 (C-1). **MS** (ESI): m/z 136 ($M+Na^+$); HRMS: found: ($M+Na^+$) 136.0729. $C_6H_{11}NNaO$ requires ($M+Na^+$) 136.0733. m/z 114 ($M+H^+$); HRMS: found: ($M+H^+$) 114.0908. $C_6H_{12}NO$ requires ($M+H^+$) 114.0913. Spectroscopic data are consistent with those reported in the literature.[70]

(*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-N,N-dimethylbuta-1,3-dien-1-amine **77**

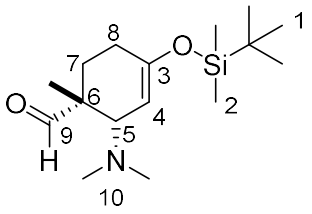


77

To a solution of KHMDS in toluene (0.5 M, 38.4 mL, 19.2 mmol) was added dry THF (35 mL) and it was cooled down to -78 °C. In this solution, dimethylamino-3-buten-2-one **78** (2.07 g, 18.3 mmol) in dry THF (17 mL) was added over a period of 30 minutes and the reaction was then warmed to -30 °C in three hours. Thereafter, the reaction mixture was cooled to -78 °C and *tert*-butyldimethylchlorosilane (3.03 g, 20.1 mmol) in dry THF (15 mL) was further added.

The reaction mixture was allowed to attain room temperature overnight. Finally, the reaction mixture was diluted with diethyl ether (350 mL), filtered through dry Celite, and concentrated *in vacuo* to afford a crude dark orange viscous oil, which was then purified by bulb to bulb distillation (Kugelrohr distillation at 114 °C and 3 mm Hg) to yield **77** as a light yellow oil (3.82 g, 91%). **IR** (ATR): ν_{max} 3371, 2928, 1626, 1556, 1419, 1358, 1258, 1231, 1112, 833, 771 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.58 (1 H, d, *J*=13.0 Hz, H-6) 4.80 (1 H, d, *J*=13.0 Hz, H-5) 3.93 (1 H, s, H-4) 3.84 (1 H, s, H-4) 2.71 (6 H, s, H-7, H-8) 0.96 - 1.00 (9 H, m, H-1) 0.17 - 0.22 (6 H, m, H-2) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 156.4 (C-3), 140.9 (C-6), 95.9 (C-5), 85.8 (C-4), 40.5 (C-7), 25.9 (C-8), 18.3 (C-1), -4.5(C-2) ppm. **MS** (ESI): m/z 228 ($M+H^+$); HRMS: found: ($M+H^+$) 228.1776. $C_{12}H_{26}NOSi$ requires ($M+H^+$) 228.1778. Spectroscopic data are consistent with those reported in the literature.[70]

(1*R*,2*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(dimethylamino)-1-methylcyclohex-3-enecarbaldehyde **84**

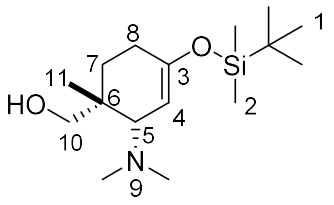


84

Racemic **84**: To a solution of Rawal's diene **77** (200 mg, 0.87 mmol) in dry toluene (0.54 mL) was added methacrolein **53** (43.1 mg, 0.61 mmol) at 0 °C. The reaction mixture was stirred for one hour at 0 °C and then for three hours at room temperature. It was then concentrated *in vacuo.* The crude mass balance of Diels-Alder cycloadduct **84** was 202 mg. **Rf** = 0.2 (MeOH : DCM 5% : 95%).

Asymmetric **84**: To a solution of methacrolein **53** (326.5 mg, 4.65 mmol) in dry toluene (6.9 mL) was added 1-napthyl TADDOL (*R,R*) (**96**; 621 mg, 0.93 mmol) under N_2 atmosphere. The reaction mixture was cooled to -80 °C and Rawal's diene **77** (2.1 g, 9.31 mmol) was added. The reaction was stirred at -80 °C for two days and, concentrated *in vacuo.* The crude mass balance of Diels-Alder cycloadduct **84** was 3.37 g. **Rf** = 0.2 (MeOH : DCM 5% : 95%).

((1*R*,2*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(dimethylamino)-1-methylcyclohex-3-en-1-yl)methanol **93**

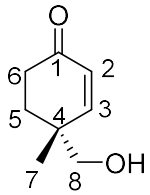


93

Racemic **93**: To a suspension of $LiAlH_4$ (16.4 mg, 0.43 mmol) in dry diethyl ether (1.66 mL) was added the solution of the racemic crude **84** (99 mg) in dry diethyl ether (0.87 mL) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for three hours and diluted by adding diethyl ether (4.3 mL). The reaction was quenched with water (0.13 mL) at -78 °C under N_2 atmosphere. The resulting mixture was allowed to attain the room temperature, following which Na_2SO_4 was added and it was stirred for additional 15 minutes. The organic layer and solid were extracted using diethyl ether (3 × 8.45 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo.* The crude mass balance of compound **93** was 91 mg. **Rf** = 0.1 (MeOH : DCM 5% : 95%).

Asymmetric **93**: To a suspension of $LiAlH_4$ (510 mg, 13.44 mmol) in dry diethyl ether (33.6 mL) was added the solution of crude compound **84** (2.0 g) in dry diethyl ether (17.0 mL) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for three hours and diluted by adding diethyl ether (91 mL). The reaction was quenched with water (4.5 mL) at -78 °C under N_2 atmosphere. The resulting mixture was allowed to attain room temperature, following which Na_2SO_4 was added, and it was stirred for additional 15 minutes. The organic layer and solid were extracted using diethyl ether (3 × 50 mL). The organic layer was dried using Na_2SO_4, filtered and concentrated *in vacuo.* The crude mass balance of compound **93** was 1.72 g. **Rf** = 0.1 (MeOH : DCM 5% : 95%).

(*R*)-4-(Hydroxymethyl)-4-methylcyclohex-2-en-1-one, **76**.



76

Racemic **76**: To a solution of crude compound **93** (46.7 mg) in acetonitrile (0.25 mL) was added 70% HF in pyridine (4.9 µL, 0.39 mmol) under N_2 atmosphere at room temperature. The reaction mixture was stirred at room temperature for two hours. Thereafter, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (20 mL) and the organic phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **76** as a colourless oil (4.4 mg, 20% overall yield over three steps) **Rf** = 0.31 (MeOH : DCM 10% : 90%).

Asymmetric **76**: To a solution of crude compound **93** (1.0 g) in acetonitrile (3.2 mL) was added 70% HF in pyridine (0.09mL, 7.63 mmol) under N_2 atmosphere at room temperature. The reaction mixture was stirred at room temperature for two hours. Thereafter, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (40 mL) and the organic phase was extracted with diethyl ether (3 × 80 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (60 mL) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **76** as a colourless oil (118 mg, 30% overall yield over three steps with 79% ee). **Rf** = 0.31 (MeOH : DCM 10% : 90%). **IR** (ATR): ν_{max} 3426 (OH), 2931, 1663 (C=O), 1393, 1048, 805 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.75 (1 H, d, *J*=10.2 Hz, H-3) 5.97 (1 H, d, *J*=10.2 Hz, H-2) 3.45 - 3.65 (2 H, m, H-8) 2.46 - 2.53 (2 H, m, H-6) 2.25 (1 H, br. s) 2.04 - 2.14 (1 H, m, H-5) 1.70 - 1.80 (1 H, m, H-5) 1.15 (3 H, s, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 199.6 (C-1), 156.0 (C-3), 129.0 (C-2), 69.8 (C-8), 38.1 (C-4), 33.8 (C-6), 30.7 (C-5), 21.7 (C-7) ppm. **MS** (ESI): m/z 163 ($M+Na^+$); HRMS: found: ($M+Na^+$) 163.0726. $C_8H_{12}NaO_2$ requires ($M+Na^+$) 163.0730. m/z 141 ($M+H^+$); HRMS: found: ($M+H^+$) 141.0898. $C_8H_{13}O_2$ requires ($M+H^+$) 141.0837. **Optical Rotation:** $[\alpha]_D^{25.0}$ +27.7 (c = 0.05, $CHCl_3$). Literature value is $[\alpha]_D^{25.0}$ +25.0 (c = 0.333, $CHCl_3$).[70] A % ee of **76** was

determined by CSP-HPLC of the *p*-nitrobenzoate **95**. Spectroscopic data are consistent with those reported in the literature.[70,72]

14%ee of **76**

Asymmetric **84**: To a solution of methacrolein **53** (100 mg, 1.42 mmol) in dry toluene (2.1 mL) was added phenyl TADDOL (*R,R*) (**98**; 113.1 mg, 0.28 mmol) under N_2 atmosphere. The reaction mixture was cooled to -80 °C and Rawal's diene **77** (859 mg, 2.85 mmol) was added. The reaction was stirred at -80 °C for two days and, concentrated *in vacuo.* The crude mass balance of Diels-Alder cycloadduct **84** was 1.1 g. **Rf** = 0.2 (MeOH : DCM 5% : 95%).

Asymmetric **93**: To a suspension of $LiAlH_4$ (70.3 mg, 1.85 mmol) in dry diethyl ether (7.1 mL) was added the solution of crude compound **84** (1.1 g) in dry diethyl ether (3.7 mL) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for three hours and diluted by adding diethyl ether (18.1 mL). The reaction was quenched with water (0.85 mL) at -78 °C under N_2 atmosphere. The resulting mixture was allowed to attain room temperature, following which Na_2SO_4 was added, and it was stirred for additional 15 minutes. The organic layer and solid were extracted using diethyl ether (3 × 27 mL). The organic layer was dried using Na_2SO_4, filtered and concentrated *in vacuo.* The crude mass balance of compound **93** was 924 mg. **Rf** = 0.1 (MeOH : DCM 5% : 95%).

Asymmetric **76**: To a solution of crude compound **93** (849 mg) in acetonitrile (3.0 mL) was added 70% HF in pyridine (0.07mL, 7.08 mmol) under N_2 atmosphere at room temperature. The reaction mixture was stirred at room temperature for two hours. Thereafter, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (20 mL) and the organic phase was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **76** as a colourless oil (181.5 mg, 91% overall yield over three steps with 14% ee). **Rf** = 0.31 (MeOH : DCM 10% : 90%)

50%ee of **76**

Asymmetric **84**: To a solution of methacrolein **53** (50 mg, 0.71 mmol) in dry toluene (1.06 mL) was added 1-napthyl TADDOL (*R,R*) (**96**; 95.1 mg, 0.14 mmol) under N_2 atmosphere. The

reaction mixture was cooled to -80 °C and Rawal's diene **77** (324 mg, 1.42 mmol) was added. The reaction was stirred at -80 °C for two days and, concentrated *in vacuo.* The crude mass balance of Diels-Alder cycloadduct **84** was 664 mg. **Rf** = 0.2 (MeOH : DCM 5% : 95%).

Asymmetric **93**: To a suspension of $LiAlH_4$ (54.1 mg, 1.42 mmol) in dry diethyl ether (3.56 mL) was added the solution of crude compound **84** (664 mg) in dry diethyl ether (1.87 mL) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for three hours and diluted by adding diethyl ether (9.7 mL). The reaction was quenched with water (0.45 mL) at -78 °C under N_2 atmosphere. The resulting mixture was allowed to attain room temperature, following which Na_2SO_4 was added, and it was stirred for additional 15 minutes. The organic layer and solid were extracted using diethyl ether (3 × 15 mL). The organic layer was dried using Na_2SO_4, filtered and concentrated *in vacuo.* The crude mass balance of compound **93** was 444 mg. **Rf** = 0.1 (MeOH : DCM 5% : 95%).

Asymmetric **76**: To a solution of crude compound **93** (444 mg) in acetonitrile (1.56 mL) was added 70% HF in pyridine (0.04mL, 3.7 mmol) under N_2 atmosphere at room temperature. The reaction mixture was stirred at room temperature for two hours. Thereafter, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and the organic phase was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **76** as a colourless oil (43.3 mg, 43% overall yield over three steps with 50% ee). **Rf** = 0.31 (MeOH : DCM 10% : 90%)

67%ee of **76**

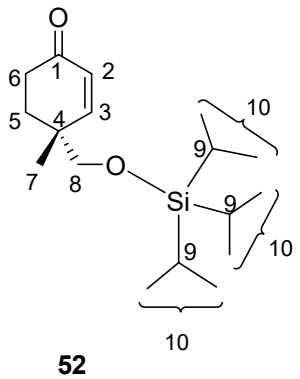
Asymmetric **84**: To a solution of methacrolein **53** (50 mg, 0.71 mmol) in dry toluene (1.06 mL) was added 1-napthyl TADDOL (*R,R*) (**96**; 95.1 mg, 0.14 mmol) under N_2 atmosphere. The reaction mixture was cooled to -80 °C and Rawal's diene **77** (324 mg, 1.42 mmol) was added. The reaction was stirred at -80 °C for two days and, concentrated *in vacuo.* The crude mass balance of Diels-Alder cycloadduct **84** was 410 mg. **Rf** = 0.2 (MeOH : DCM 5% : 95%).

Asymmetric **93**: To a suspension of $LiAlH_4$ (54.1 mg, 1.42 mmol) in dry diethyl ether (3.56 mL) was added the solution of crude compound **84** (410 mg) in dry diethyl ether (1.87 mL) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for three hours and diluted

by adding diethyl ether (9.7 mL). The reaction was quenched with water (0.45 mL) at -78 °C under N_2 atmosphere. The resulting mixture was allowed to attain room temperature, following which Na_2SO_4 was added, and it was stirred for additional 15 minutes. The organic layer and solid were extracted using diethyl ether (3 × 15 mL). The organic layer was dried using Na_2SO_4, filtered and concentrated *in vacuo.* The crude mass balance of compound **93** was 348 mg. **Rf** = 0.1 (MeOH : DCM 5% : 95%).

Asymmetric **76**: To a solution of crude compound **93** (348 mg) in acetonitrile (1.56 mL) was added 70% HF in pyridine (0.02mL, 1.78 mmol) under N_2 atmosphere at room temperature. The reaction mixture was stirred at room temperature for two hours. Thereafter, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (30 mL) and the organic phase was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **76** as a colourless oil (46.5 mg, 47% overall yield over three steps with 67% ee).

(*R*)-4-Methyl-4-(((triisopropylsilyl)oxy)methyl)cyclohex-2-enone, **52**.

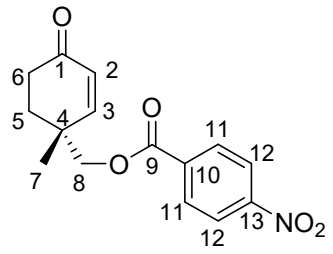


52

To a solution of compound **76** (159 mg, 1.13 mmol) in dry DMF (4.5 mL) were added imidazole (154 mg, 2.27 mmol) and, triisopropylsilyl chloride (0.29 mL, 1.36 mmol) at 30 °C under N_2 atmosphere, and the reaction mixture was stirred at 30 °C for 16 h. Then, an aqueous solution of 2 M HCl (0.4 mL) was added, and the mixture was stirred for additional 15 minutes at room temperature. The organic phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **52** as a colourless oil (294 mg, 87% yield). **Rf** = 0.42

(MeOH : DCM 5% : 95%). **IR** (ATR): ν_{max} 2865, 2947, 1685 (C=O), 1465, 1100, 882, 805, 681 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.77 (1 H, d, *J*=10.4 Hz, H-3) 5.95 (1 H, d, *J*=10.4 Hz, H-2) 3.53 - 3.63 (2 H, m, H-8) 2.49 (2 H, m, *J*=8.0, *J*=5.7 Hz, H-6) 2.09 – 2.06 (1 H, m, H-5) 1.75 - 1.72 (1 H, m, H-5) 1.16 (3 H, s, H-7) 1.03 - 1.08 (18 H, m, H-10) 0.99 - 1.03 (3 H, m, H-9) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 199.5 (C-1), 156.2 (C-3), 128.1 (C-2), 70.1 (C-8), 38.3 (C-4), 33.7 (C-6), 30.7 (C-5), 21.7 (C-7), 17.6 (C-10), 11.5 (C-9) ppm. **MS** (ESI): m/z 319 ($M+Na^+$); HRMS: found: ($M+Na^+$) 319.2058. $C_{17}H_{32}NaO_2Si$ requires ($M+Na^+$) 319.2064. m/z 297 ($M+H^+$); HRMS: found: ($M+H^+$) 297.2237. $C_{17}H_{33}O_2Si$ requires ($M+H^+$) 297.2244. **Optical Rotation:** $[\alpha]_D^{25.0}$ -64 (c = 0.5, $CHCl_3$).

(*R*)-(1-Methyl-4-oxocyclohex-2-en-1-yl)methyl 4-nitrobenzoate, **95**.



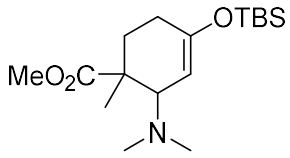
95

Racemic **95**: To a solution of compound **76** (1.74 mg, 0.01 mmol) in pyridine (0.8 mL) was added dimethyl aminopyridine (0.04 mg, 0.0003 mmol), followed by 4-nitrobenzoyl chloride **94** (23 mg, 1.12 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred for 48 h, following which the reaction was quenched by adding diethyl ether (30 mL) and a saturated aqueous $CuSO_4$ solution (5 mL). The reaction mixture was stirred for 15 minutes and the layers were separated. The aqueous layer was extracted using diethyl ether (30 mL) and the combined organic layers were washed with a saturated aqueous $CuSO_4$ solution (2 × 10 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), followed by water (10 mL) and brine (10 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo* to afford a colourless oil. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **95** as a white coloured solid (1.3 mg, 21% yield). **Rf** = 0.5 (MeOH : DCM 5% : 95%).

Asymmetric **95**: To a solution of compound **76** (16 mg, 0.11 mmol) in pyridine (2 mL) was added dimethyl aminopyridine (2.79 mg, 0.02 mmol), followed by 4-nitrobenzoyl chloride **94**

(212 mg, 1.14 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred for 48 h, following which the reaction was quenched by adding diethyl ether (20 mL) and a saturated aqueous $CuSO_4$ solution (5 mL). The reaction mixture was stirred for 15 minutes and the layers were separated. The aqueous layer was extracted using diethyl ether (3 × 20 mL) and the combined organic layers were washed with a saturated aqueous $CuSO_4$ solution (2 × 5 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (7 mL), followed by water (7 mL) and brine (7 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo* to afford a colourless oil. The crude product was purified by silica gel flash column chromatography (100% DCM) to yield **95** as a white coloured solid (13.2 mg, 40% yield). **Melting point** = 123-125 °C. **Rf** = 0.5 (MeOH : DCM 5% : 95%). **IR** (ATR): ν_{max} 3412, 2976, 1639 (C=O), 1484, 1383, 1325, 1163, 1103, 877, 783, 699, 519 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.29 - 8.34 (2 H, m, H-12) 8.16 - 8.22 (2 H, m, H-11) 6.77 (1 H, d, *J*=10.0 Hz, H-3) 6.04 (1 H, d, *J*=10.0 Hz, H-2) 4.38 (1 H, d, *J*=11.4 Hz, H-8) 4.26 (1 H, d=11.4, H-8) 2.53 - 2.60 (2 H, m, H-6) 2.16 - 2.25 (1 H, m, H-5) 1.89 - 1.98 (1 H, m, H-5) 1.32 (3 H, s, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 198.1 (C-1), 164.0 (C-9), 153.3 (C-3), 150.3 (C-13), 134.6 (C-10), 130.3 (C-11), 129.2 (C-2), 123.3 (C-12), 71.1 (C-8), 36.4 (C-4), 33.4 (C-6), 31.0 (C-5), 22.0 (C-7) ppm. **MS** (ESI): m/z 312 ($M+Na^+$); HRMS: found: ($M+Na^+$) 312.0842. $C_{15}H_{15}NNaO_5$ requires ($M+Na^+$) 312.0842. m/z 290 ($M+H^+$); HRMS: found: ($M+H^+$) 290.1023. C15H16NO5 requires ($M+H^+$) 290.1023. **Optical Rotation:** $[\alpha]_D^{25.0}$ +148 (c = 1.0, $CHCl_3$).

Methyl 4-((tert-butyldimethylsilyl)oxy)-2-(dimethylamino)-1-methylcyclohex-3-ene-1-carboxylate **104**

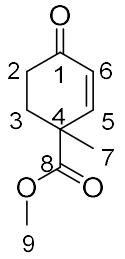


104

To a solution of Rawal's diene **77** (200 mg, 0.87 mmol) in dry toluene (1.0 mL) was added methyl methacrylate **103** (0.14 mg, 1.29 mmol) at room temperature. The reaction mixture was stirred for 18 h at 70 °C, and then concentrated *in vacuo.* The crude mass balance of Diels-Alder cycloadduct **84** was 316 mg. **Rf** = 0.4 (EtOAc : hexane 30% : 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.85 (1 H, d, *J*=6.10 Hz) 3.64 - 3.72 (3 H, m) 3.11 (1 H, d, *J*=5.34 Hz) 2.19 - 2.35 (6 H,

m) 1.99 - 2.10 (2 H, m) 1.54 - 1.63 (4 H, m) 1.15 - 1.24 (3 H, m) 0.89 - 0.99 (9 H, m) 0.10 - 0.20 (6 H, m) ppm. Spectroscopic data are consistent with those reported in the literature.[70]

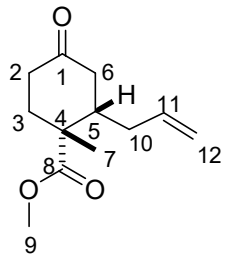
Methyl 1-methyl-4-oxocyclohex-2-enecarboxylate **105**



105

To a solution of crude compound **104** (316 mg) in acetonitrile (0.5 mL) was added 70% HF in pyridine (0.03 mL, 1.19 mmol) under N_2 atmosphere at room temperature. The reaction mixture was stirred at room temperature for 2 h. Then, the reaction was quenched by adding saturated aqueous solution of $NaHCO_3$ (25 mL), and the organic phase was extracted using diethyl ether (3 × 25 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (30% EtOAc in hexane) to yield **105** as a yellow coloured oil (59.6 mg, 73% overall yield over two steps). **Rf** = 0.47 (EtOAc : Hexane 30% : 70%). **IR** (ATR): $\mathbf{\nu}_{max}$ 3000, 1708 (C=O), 1700, 1519, 1440, 1381, 1314, 1214, 1185, 1009, 742, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (1 H, d, *J*=10.0 Hz, H-5) 5.96 (1 H, d, *J*=10.0 Hz, H-6) 3.73 (3 H, s, H-9) 2.40 - 2.55 (3 H, m, H-2, H-3) 1.91 - 2.01 (1 H, m, H-3) 1.43 (3 H, s, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 198.3 (C-1), 174.4 (C-8), 151.5 (C-5), 128.6 (C-6), 52.5 (C-9), 43.7 (C-4), 34.4 (C-2), 32.4 (C-3), 24.7 (C-7) ppm. **MS** (ESI): m/z 191 ($M+Na^+$); HRMS: found: ($M+Na^+$) 191.0675. $C_9H_{12}NaO_3$ requires ($M+Na^+$) 191.0679. Spectroscopic data are consistent with those reported in the literature.[70]

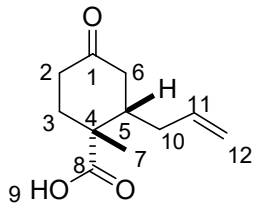
Methyl 2-allyl-1-methyl-4-oxocyclohexanecarboxylate **108**



108

To a solution of compound **105** (37.5 mg, 0.22 mmol) in dry DCM (2.23 mL) was added $TiCl_4$ (0.03 mL, 0.26 mmol) at -78 °C under N_2 atmosphere. The resulting mixture was stirred for 5 minutes at the same temperature and allyltrimethylsilane **54** (0.04 mL, 0.25 mmol) was added at -78 °C under N_2 atmosphere, following which the resulting solution was further stirred for 2 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (3.5 mL) at -78 °C under N_2 atmosphere, and the mixture was allowed to attain room temperature. The organic phase was extracted with DCM (3 × 25 mL), and the combined organic layers were washed with water (20 mL), followed by brine (20 mL, 5 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10-15% EtOAc in hexane) to yield **108** as a colourless oil (16.6 mg, 35% yield). **Rf** = 0.39 (EtOAc: Hexane 30%: 70%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 3020, 1715, (C=O), 1525, 1398, 1214, 929, 743, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.59 - 5.73 (1 H, m, H-11) 4.99 - 5.09 (2 H, m, H-12) 3.74 (3 H,s, H-9) 2.49 - 2.58 (1 H, m, H-2) 2.47 – 2.49 (2 H, m, H-6) 2.25 - 2.41 (2 H, m, H-2, H-3) 1.93 - 2.07 (1 H, m, H-10) 1.97 - 2.05 (1 H, m, H-10) 1.82 - 1.92 (1 H, m, H-5) 1.71 - 1.81 (1 H, m, H-3) 1.40 (3 H, s, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 210.9 (C-1), 175.8 (C-8), 135.9 (C-11), 117.2 (C-12), 51.7 (C-9), 45.1 (C-5), 44.8 (C-4), 41.9 (C-6), 38.1 (C-2), 35.8 (C-10), 34.3 (C-3), 23.8 (C-7). **MS** (ESI): m/z 233 ($M+Na^+$); HRMS: found: ($M+Na^+$) 233.1142. $C_{12}H_{18}NaO_3$ requires ($M+Na^+$) 233.1148. m/z 211 ($M+H^+$); HRMS: found: ($M+H^+$) 211.1322. $C_{12}H_{19}O_3$ requires ($M+H^+$) 211.1329.

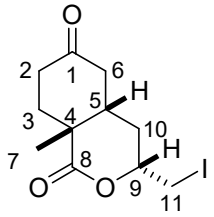
2-Allyl-1-methyl-4-oxocyclohexanecarboxylic acid **109**



109

To a solution of compound **108** (16.6 mg, 0.07 mmol) in THF (0.23 mL) was added an aqueous solution of LiOH (0.23 mL, 0.23 mmol) at 0 °C. The resulting solution was allowed to attain room temperature and stirred for 6 h. The reaction mixture was diluted with diethyl ether (2 mL) and the pH was adjusted to 1-2 by adding aqueous HCl (1.5 mL, 2 M) at room temperature. The resulting solution was extracted with diethyl ether (3 × 15 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (1-10% MeOH in DCM) to yield **109** as a colourless oil (11.6 mg, 71% yield). **Rf** = 0.25 (MeOH: DCM 5%: 95%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2930, 1705, (C=O), 1525, 1110, 1021, 905, 801, 734, 654 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.63 - 5.67 (1 H, m, H-11) 4.97 - 5.14 (2 H, m, H-12) 2.59 (1 H, br. s.) 2.45 - 2.53 (2 H, m) 2.27 - 2.44 (3 H, m) 2.02 - 2.12 (1 H, m) 1.86 - 1.98 (1 H, m) 1.73 - 1.84 (1 H, m) 1.40 - 1.51 (3 H, s) ppm. **MS** (ESI): m/z 219 ($M+Na^+$); HRMS: found: ($M+Na^+$) 219.0988. $C_{11}H_{16}NaO_3$ requires ($M+Na^+$) 219.0992. m/z 197 ($M+H^+$); HRMS: found: ($M+H^+$) 197.1171. $C_{11}H_{17}O_3$ requires ($M+H^+$) 197.1172.

(3*R*,4a*S*,8a*R*)-3-(Iodomethyl)-8a-methylhexahydro-1H-isochromene-1,6(5H)-dione **110**.

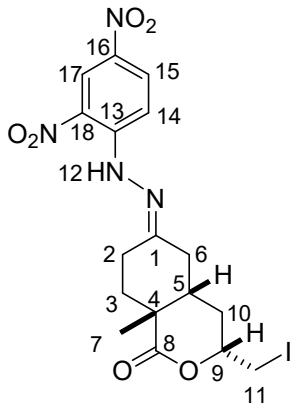


110

To a solution of compound **109** (10 mg, 0.05 mmol) in acetonitrile (0.5 mL) was added iodine (15.5 mg, 0.06 mmol), followed by solid $NaHCO_3$ (8.56 mg 0.10 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was allowed to attain room temperature and stirred for 1 h. The reaction was then quenched with saturated aqueous solution of Na_2CO_3 (2 mL) and the product was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed

with 2 M $HCl_{(aq)}$ (10 mL) followed by brine (10 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (0.5-2% MeOH in DCM) to yield **110** as a yellow coloured oil (13 mg, 79% yield). **Rf** = 0.55 (MeOH: DCM 5%: 95%). **IR** (ATR): ν_{max} 2980, 2252, 1715 (C=O), 1384, 1353, 1229, 1156, 1098, 1005, 905, 727, 648 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.39 - 4.49 (1 H, m, H-9) 3.45 - 3.50 (1 H, m, H-11) 3.39 - 3.44 (1 H, m, H-11) 2.65 - 2.69 (1 H, m, H-6) 2.45 - 2.51 (1 H, m, H-2) 2.38 - 2.44 (2 H, m, H-2, H-3) 2.30 - 2.36 (2 H, m, H-3, H5) 2.23 - 2.28 (1 H, m, H-10) 1.85 (1 H, ddd, *J*=14.3, *J*=4.6, *J*=3.1 Hz, H-10) 1.61 - 1.68 (1 H, m, H-6) 1.47 - 1.52 (3 H, m, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 210.2 (C-1), 174.1 (C-8), 75.5 (C-9), 43.8 (C-2), 42.0 (C-4), 39.9 (C-5), 38.6 (C-6), 35.6 (C-3), 31.0 (C-10), 26.9 (C-7), 9.0 (C-11). **MS** (ESI): m/z 344 ($M+Na^+$); HRMS: found: ($M+Na^+$) 344.9946. $C_{11}H_{15}INaO_3$ requires ($M+Na^+$) 344.9958. m/z 323 ($M+H^+$); HRMS: found: ($M+H^+$) 323.0128. $C_{11}H_{16}IO_3$ requires ($M+H^+$) 323.0139.

(3*R*,4a*R*,8a*R*, *E*)-6-(2-(2,4-Dinitrophenyl)hydrazono)-3-(iodomethyl)-8a-methyloctahydro-1H-isochromen-1-one **111.**

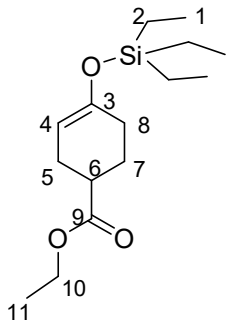


111

To a solution of compound **110** (7.4 mg, 0.02mmol) in dry methanol (0.65 mL) were added 3 Å molecular sieves, followed by 2,4-dinitrophenylhydrazine (8.19 mg, 0.04 mmol) at room temperature under N_2 atmosphere. Then, glacial acetic acid (0.08 mL) was added. The resulting solution was heated to 50 °C and stirred at the same temperature for 3 h. The reaction was subsequently quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (5 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (1% MeOH in DCM) to yield **111** as a yellow coloured solid (8.7 mg, 75% yield). **Rf** = 0.79 (MeOH: DCM 5%: 95%).

IR (ATR): ν_{max} 1731 (C=O), 1618, 1518, 1335, 818, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.13 - 11.26 (1 H, m) 9.11 - 9.14 (1 H, m, H-17) 8.32 (1 H, dd, *J*=9.7, *J*=2.7 Hz, H-15) 7.89 - 8.00 (1 H, m, H-14) 4.51 (1 H, m) 3.37 - 3.54 (2 H, m) 2.58 - 2.87 (3 H, m) 2.35 - 2.49 (2 H, m) 2.21 - 2.31 (2 H, m) 2.13 - 2.20 (1 H, m) 1.92 - 2.03 (1 H, m) 1.54 - 1.61 (1 H, m) 1.45 - 1.52 (3 H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 174.1, 157.6, 145.0, 137.9, 130.0, 123.5, 116.1, 75.3, 53.4, 42.1, 39.3, 37.4, 34.1, 31.1, 26.3, 24.1, 8.7. **MS** (ESI): m/z 525 ($M+Na^+$); HRMS: found: ($M+Na^+$) 525.0238. $C_{17}H_{19}IN_4NaO_6$ requires ($M+Na^+$) 525.0242**. MP –** 168.3 °C.

Ethyl 4-((triethylsilyl)oxy)cyclohex-3-enecarboxylate **113**.

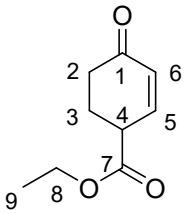


113

To a solution of freshly distilled diisopropylamine (0.99 mL, 7.05 mmol) in dry THF (7.1 mL) at -78 °C was added *n*-BuLi (3.5 mL, 1.98 M in hexane, 6.93 mmol), and this solution was stirred at -78 °C for 30 minutes. A solution of ethyl-4-oxycyclohexane carboxylate **112** (0.92 mL, 5.87 mmol) in dry THF (21.7 mL) was added to the LDA solution and the mixture was stirred at -78 °C for 1 h. Then, freshly distilled TESCl (1.3 mL, 7.63 mmol) was added and the reaction mixture was stirred at the same temperature for additional 30 minutes, after which it was allowed to warm to room temperature for 1.5 h. The reaction was quenched by adding water (36 mL) and the product was extracted with diethyl ether (400 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (100% hexane) to yield **113** as a red coloured oil (896.5 mg, 53% yield). **Rf** = 0.68 (EtOAc: Hexane 20%: 80%). **IR** (ATR): ν_{max} 2894, 1710 (C=O), 1399, 1274, 987, 908, 776,727, 647 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.85 (1 H, t, *J*=3.8 Hz, H-4) 4.13 (2 H, q, *J*=6.8 Hz, H-10) 2.42 - 2.52 (1 H, m, H-6) 2.23 - 2.31 (2 H, m, H-5) 2.06 - 2.21 (2 H, m, H-8) 1.96 - 2.05 (1 H, m, H-7) 1.80 (1 H, m, H-7) 1.21 - 1.29 (3 H, m, H-11) 0.92 - 1.02 (9 H, m, H-1) 0.59 - 0.71 (6 H, m, H-2) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 175.5 (C-9), 150.0 (C-3), 101.9 (C-4), 60.2 (C-10), 39.1 (C-6), 28.8 (C-8), 26.3 (C-5), 25.5 (C-7), 14.1 (C-11), 6.6 (C-1), 4.9 (C-2).

MS (ESI): m/z 307 ($M+Na^+$); HRMS: found: ($M+Na^+$) 307.1691. $C_{15}H_{28}NaO_3Si$ requires ($M+Na^+$) 307.1700. m/z 285 ($M+H^+$); HRMS: found: ($M+H^+$) 285.1872. $C_{15}H_{29}O_3Si$ requires ($M+H^+$) 285.1880.

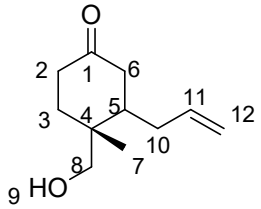
Ethyl 4-oxocyclohex-2-enecarboxylate **114**.



114

To a solution of TES-enol compound **113** (844 mg, 2.96 mmol) in dry DMSO (24.7 mL) was added IBX (2.0 g, 7.41 mmol) at room temperature, and the reaction was stirred at 40 °C for 19 h. Then, the reaction mixture was cooled to room temperature, and the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (161 mL). The product was extracted using MTBE (3 × 250 mL). The combined organic layers were washed with brine (150 mL), dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (20-40% EtOAc in hexane) to yield **114** as an orange coloured oil (219.8 mg, 44% yield). **Rf** = 0.12 (EtOAc: hexane 30%: 70%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 1730 (C=O), 1670, 1371, 1251, 1176, 1091, 965, 936, 842, 756 cm^{-1}. **^{1}H NMR** (400 MHz, benzene-d6) δ 6.23 (1 H, d, *J*=10.0 Hz, H-5) 5.91 (1 H, d, *J*=10.0 Hz, H-6) 3.67 - 3.83 (2 H, m, H-8) 3.50 (1 H, s, H-4) 2.32 - 2.49 (2 H, m, H-2) 1.91 - 2.03 (1 H, m, H-3) 1.79 - 1.91 (1 H, m, H-3) 0.74 (3 H, t, *J*=6.8 Hz, H-10) ppm. **^{13}C NMR** (400 MHz, benzene-d6) δ 196.6 (C-1), 174.0 (C-7), 146.8 (C-5), 130.9 (C-6), 71.7 (C-4), 62.5 (C-8), 34.0 (C-2), 30.2 (C-3), 13.8 (C-9). **MS** (ESI): m/z 207 ($M+K^+$); HRMS: found: ($M+K^+$) 207.0623. $C_9H_{12}KO_3$.

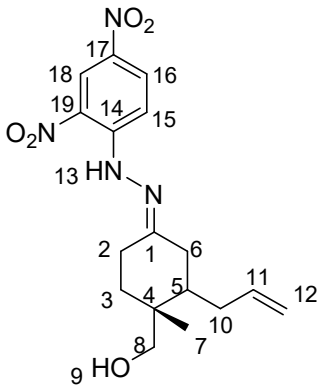
(4*R*)-3-Allyl-4-(hydroxymethyl)-4-methylcyclohexanone **116**.



116

To a solution of compound **76** (29.3 mg, 0.20 mmol) in dry DCM (2.09 mL) was added $TiCl_4$ (0.03 mL, 0.25 mmol) at -78 °C under N_2 atmosphere. The resulting mixture was stirred for 5 minutes at the same temperature and allyltrimethylsilane **54** (0.04 mL, 0.24 mmol) was added at -78 °C under N_2 atmosphere, following which the resulting solution was further stirred for 2.5 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (3 mL) at -78 °C under N_2 atmosphere, and the mixture was allowed to attain room temperature. The organic phase was extracted with DCM (3 × 20 mL), and the combined organic layers were washed with water (20 mL), followed by brine (20 mL mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2% MeOH in DCM) to yield **116** as a colourless oil (8.3 mg, 22% yield). **Rf** = 0.45 (MeOH: DCM 5%: 95%). **IR** (ATR): ν_{max} 2973, 1970 (C=O), 1703, 1640, 1423, 1391, 1244, 1140, 1039, 998, 913 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.59 - 5.78 (1 H, m, H-11) 4.92 - 5.10 (2 H, m, H-12) 3.70 - 3.79 (1 H, m, H-8) 3.63 (1 H, d, *J*=10.6 Hz, H-8) 2.32 - 2.51 (4 H, m) 2.24 (1 H, dd, *J*=15.2, *J*=8.3 Hz) 1.94 - 2.10 (1 H, m) 1.74 - 1.85 (2 H, m) 1.49 (1 H, ddd, *J*=13.7, *J*=10.0, *J*=5.3 Hz) 1.11 - 1.28 (3 H, m, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 212.2, 136.7, 117.1, 66.2, 44.3, 42.2, 37.8, 34.6, 33.3, 23.3, 15.5. **MS** (ESI): m/z 205 ($M+Na^+$); HRMS: found: ($M+Na^+$) 205.1194. $C_{11}H_{18}NaO_2$ requires ($M+Na^+$) 205.1199. m/z 183 ($M+H^+$); HRMS: found: ($M+H^+$) 183.1376. $C_{11}H_{19}O_2$ requires ($M+H^+$) 183.1380.

((1*R*, *E*)-2-Allyl-4-(2-(2,4-dinitrophenyl)hydrazono)-1-methylcyclohexyl)methanol **117**.

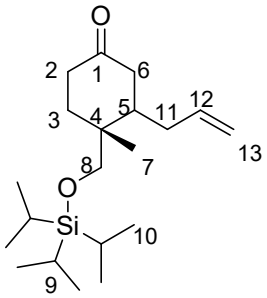


117

To a solution of compound **116** (5 mg, 0.02 mmol) in dry methanol (0.78 mL) was added 3 Å molecular sieves, followed by 2,4-dinitrophenylhydrazine (9.7 mg, 0.05 mmol) at room temperature under N_2 atmosphere. Then, glacial acetic acid (0.1 mL) was added. The resulting

solution was heated to 50 °C and stirred at same temperature for 3 h. The reaction was subsequently quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (20 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (1% Methanol in DCM) to yield **117** as a yellow coloured solid (7.8 mg, 79% yield). **Rf** = 0.59 (MeOH: DCM 5% : 95%). **IR** (ATR): $\boldsymbol{\nu}_{max}$ 2921, 1618, 1588, 1525, 1336, 1229, 1033, 907, 733, 651 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.19 (1 H, d, *J*=6.8 Hz) 9.13 (1 H, d, *J*=2.2 Hz) 8.29 (1 H, dd, *J*=10.0, 2.2 Hz) 7.96 (1 H, dd, *J*=10.0, 2.1 Hz) 5.66 - 5.86 (1 H, m, H-11) 5.07 - 5.18 (2 H, m, H-12) 3.53 - 3.74 (3 H, m) 2.51 - 2.69 (3 H, m) 2.29 - 2.50 (3 H, m) 1.94 - 2.07 (2 H, m) 1.78 - 1.93 (1 H, m) 1.26 (3 H, br. s.) ppm. **MS** (ESI): m/z 385 ($M+Na^+$); HRMS: found: ($M+Na^+$) 385.1487. $C_{17}H_{22}N_4NaO_5$ requires ($M+Na^+$) 385.1482. m/z 363 ($M+H^+$); HRMS: found: ($M+H^+$) 363.1662. $C_{17}H_{23}N_4O_5$ requires ($M+H^+$) 363.1663. m/z 401 ($M+K^+$); HRMS: found: ($M+K^+$) 401.1229. $C_{17}H_{22}KN_4O_5$ requires ($M+K^+$) 401.1222. **MP** – 157-159 °C.

(4*R*)-3-Allyl-4-methyl-4-(((triisopropylsilyl)oxy)methyl)cyclohexanone **118.**

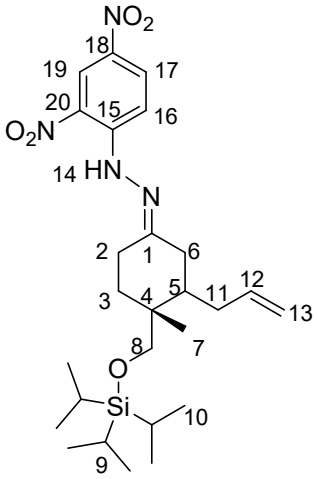


118

To a solution of compound **52** (9 mg, 0.03 mmol) in dry DCM (0.3 mL) was added $TiCl_4$ (4 µL, 0.036 mmol) at -78 °C under N_2 atmosphere. The resulting mixture was stirred for 5 minutes at the same temperature and allyltrimethylsilane **54** (5.5 µL, 0.035 mmol) was added at -78 °C under N_2 atmosphere, following which the resulting solution was further stirred for 45 minutes. The reaction was quenched by addition of a saturated aqueous solution of Na_2HCO_3 (1.5 mL) at -78 °C under N_2 atmosphere, and the mixture was allowed to attain room temperature. The organic phase was extracted with DCM (3 × 10 mL), and the combined organic layers were washed with water (5 mL), followed by brine (2 × 5 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified

by silica gel flash column chromatography (5% EtOAc in hexane) to yield **118** as a colourless oil (4.2 mg, 41% yield). **Rf** = 0.32 (EtOAc : hexane 10% : 90%). **IR** (ATR): ν_{max} 2928, 2868, 1716 (C=O), 1462, 1253, 1097, 1070, 1000, 917, 809, 683 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.61 - 5.73 (1 H, m, H-12) 4.98 - 5.07 (2 H, m, H-13) 3.76 (1 H, d, *J*=10.0 Hz, H-8) 3.63 (1 H, d, *J*=10.0 Hz, H-8) 2.39 - 2.52 (2 H, m, H-6) 2.24 - 2.38 (2 H, m) 1.76 - 1.86 (2 H, m) 1.58 (3 H, s) 1.46 (2 H, d, *J*=4.5 Hz) 1.12 - 1.18 (3 H, m) 1.04 - 1.12 (16 H, m) 0.97 - 1.04 (3 H,m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 212.6 (C-1), 136.8 (C-12), 116.8 (C-13), 67.2 (C-8), 43.9 (C-6), 42.0 (C-2), 37.9 (C-3), 37.5 (C-4), 34.5 (C-11), 33.3 (C-6), 23.7 (C-7), 17.9 (C-10), 11.9 (C-9). **MS** (ESI): m/z 361 ($M+Na^+$); HRMS: found: ($M+Na^+$) 361.2549. $C_{20}H_{38}NaO_2Si$ requires ($M+Na^+$) 361.2533. m/z 339 ($M+H^+$); HRMS: found: ($M+H^+$) 339.2720. $C_{20}H_{39}O_2Si$ requires ($M+H^+$) 339.2714. m/z 377 ($M+K^+$); HRMS: found: ($M+K^+$) 377.2283. $C_{20}H_{38}KO_2Si$ requires ($M+K^+$) 377.2273.

(*E*)-1-((4*R*)-3-Allyl-4-methyl-4-(((triisopropylsilyl)oxy)methyl)cyclohexylidene)-2-(2,4-dinitrophenyl)hydrazine **119**.



119

To a solution of compound **118** (9 mg, 0.02mmol) in dry methanol (0.75 mL) was added 3 Å molecular sieves, followed by 2,4-dinitrophenylhydrazine (9.47 mg, 0.04 mmol) at room temperature under N_2 atmosphere. Then, glacial acetic acid (0.09 mL) was added. The resulting solution was heated to 50 °C and stirred at same temperature for 3 h. The reaction was subsequently quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were washed by brine (20 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (5% EtOAc in hexane) to yield

119 as a yellow coloured solid (4.3 mg, 31% yield). **Rf** = 0.25 (EtOAc: hexane 10% : 90%). **IR** (ATR): $\mathbf{v}_{max}$ 2942, 2866, 1618, 1593, 1520, 1423, 1332, 1310, 1096, 923, 882, 832, 806, 744, 684, 655 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.19 (1 H, d, *J*=8.3 Hz) 9.14 (1 H, d, *J*=3.0 Hz) 8.29 (1 H, dd, *J*=9.5, *J*=2.6 Hz) 7.89 - 8.03 (1 H, m) 5.66 - 5.83 (1 H, m, H-12) 5.10 (2 H, m, H-13) 3.55 - 3.79 (2 H, m) 2.33 - 2.64 (5 H, m) 2.05 (1 H, s) 1.36 - 1.49 (1 H, m) 1.22 - 1.32 (3 H, m) 1.04 - 1.14 (21 H, m) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ 161.3, 145.5, 137.5, 130.2, 124.0, 117.8, 116.4, 68.5, 53.7, 44.3, 38.2, 31.2, 27.6, 24.1, 18.3, 12.2. **MS** (ESI): m/z 519 ($M+H^+$); HRMS: found: ($M+H^+$) 519.3010. $C_{26}H_{43}N_4O_5Si$ requires ($M+H^+$) 519.2997. **MP-**131-133 ^{o}C.

14. Abbreviations

Å	Ångstrom
ACP	acyl carrier protein
AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
$BF_3{\cdot}Et_2O$	borane trifluoride-diethyl etherate
Brsm	based on recovered starting material
n-BuLi	butyl lithium
t-BuOH	*tert*-butanol
CA	california
C-C	carbon-carbon
DCM	dichloromethane
$CHCl_3$	chloroform
CH_3CN	acetonitrile
d	day
D-Ala	D-alanine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
2, 4-DMP	2, 4-dinitrophenylhydazine
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
Dr	diastereomeric ratio
ESI	electrospray ionisation
EI	electron ionisation

Et_2O	diethyl ether
EtOAc	ethylacetate
EtOH	ethanol
Et_3N	triethylamine
FAD	flavin adenine dinucleotide
FGI	functional group interconversion
g	gram
h	hour
H_2	hydrogen
HCC	hepatocellular carcinoma
HCl	hydrochloric acid
HG II	hoveyda-Grubbs 2nd generation catalyst
Hg	mercury
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
I_2	iodine
IBX	2-iodoxy benzoic acid
IC50	half maximal inhibitory concentration
IR	infrared spectroscopy
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LED	light emitting diodie
$LiAlH_4$	lithiumaluminium hydride
LovBPKS	lovastatin B polyketide synthase
LUMO	lowest unoccupied molecular orbital
M	molar
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol

MIC	minimum inhibitory concentration
Min.	minutes
Ms	mesyl (methanesulfonyl)
MsCl	mesylchloride
mg	milligram
MHz	megahertz
MRSA	methicillin resistant bacteria
MS	mass spectrometry
M.S.	molecular sieves
MW	microwaves
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear overhauser effect
$Pd(OAc)_2$	palladium acetate
Pd/C	palladium on carbon
Ph	phenyl
$PhI(OAc)_2$	diacetoxyiodo benzene
PKS	polyketide synthase
PPh_3	triphenylphosphine
PMB	*p*-methoxybenzyl
Py	pyridine
RNA	ribonucleic acid
rt	room temperature
SiO_2	silica
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

TS	transition state
v	vibration frequency (cm^{-1})

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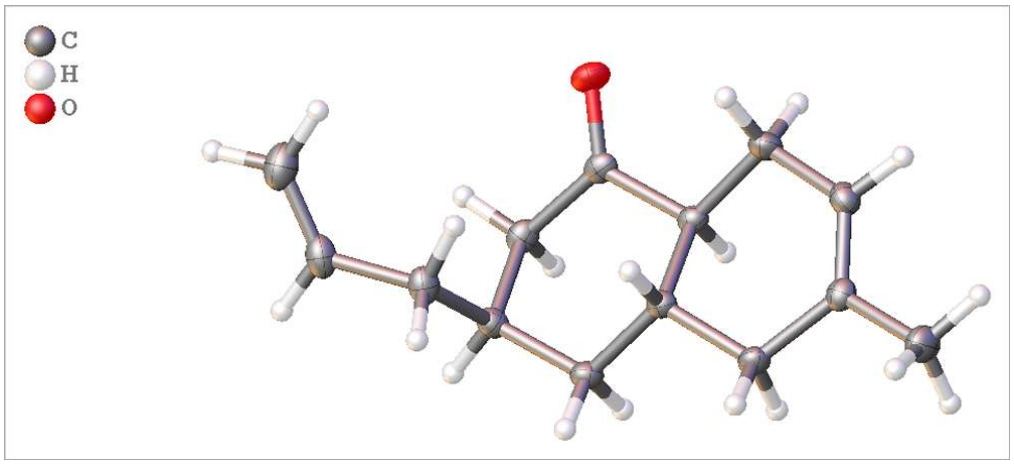
16. Appendices

Appendix A: Crystal data and structure refinement for 74.



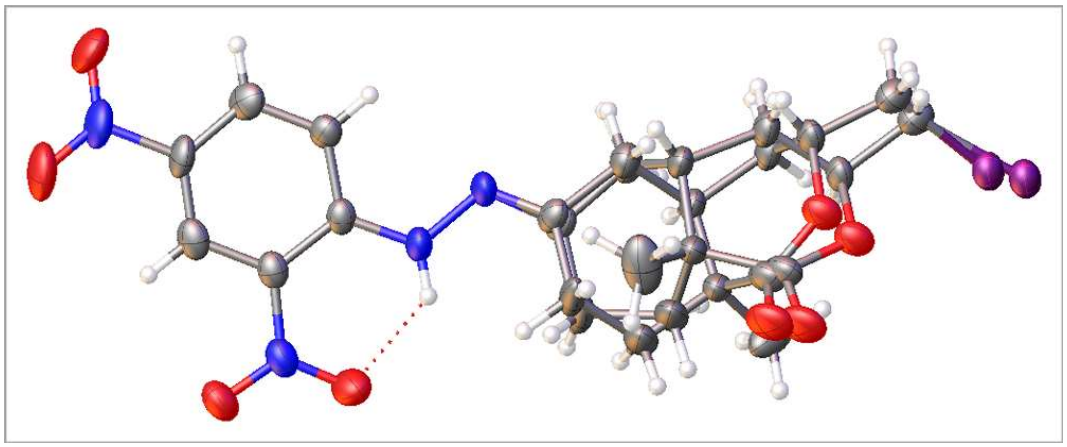
Crystal data and structure refinement for 74.

Identification code	pac1901
Empirical formula	$C_{14}H_{20}O$
Formula weight	204.30
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.9841(3)
b/Å	17.5709(5)
c/Å	9.2686(3)
α/°	90
β/°	114.604(4)
γ/°	90
Volume/Å^3	1182.22(8)
Z	4
ρ_{calc}g/cm^3	1.148

μ/mm^{-1}	0.533
F(000)	448.0
Crystal size/mm^3	0.275 × 0.205 × 0.157
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.068 to 134.11
Index ranges	-9 ≤ h ≤ 7, -20 ≤ k ≤ 20, -11 ≤ l ≤ 10
Reflections collected	3983
Independent reflections	2108 [R_{int} = 0.0143, R_{sigma} = 0.0219]
Data/restraints/parameters	2108/0/217
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0337, wR_2 = 0.0835
Final R indexes [all data]	R_1 = 0.0390, wR_2 = 0.0881
Largest diff. peak/hole / e $Å^{-3}$	0.28/-0.16

Data collected, solved and refined by Adrian C Whitwood

Appendix B: Crystal data and structure refinement for 111.



Crystal data and structure refinement for 111.

Identification code	pac1905
Empirical formula	$C_{17}H_{19}IN_4O_6$
Formula weight	502.26
Temperature/K	110.00(14)
Crystal system	monoclinic
Space group	I2/a
a/Å	11.4622(4)
b/Å	11.7685(4)
c/Å	28.4710(10)
α/°	90
β/°	97.469(3)
γ/°	90
Volume/Å^3	3808.0(2)
Z	8
ρ_{calc}g/cm^3	1.752
μ/mm^{-1}	13.604
F(000)	2000.0

Crystal size/mm^3	0.089 × 0.063 × 0.009
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.14 to 134.128
Index ranges	-13 ≤ h ≤ 13, -10 ≤ k ≤ 14, -26 ≤ l ≤ 34
Reflections collected	6841
Independent reflections	3395 [R_{int} = 0.0275, R_{sigma} = 0.0373]
Data/restraints/parameters	3395/7/304
Goodness-of-fit on F^2	1.230
Final R indexes [I>=2σ (I)]	R_1 = 0.0571, wR_2 = 0.1082
Final R indexes [all data]	R_1 = 0.0658, wR_2 = 0.1117
Largest diff. peak/hole / e $Å^{-3}$	0.97/-0.80

Data collected, solved and refined by Adrian C Whitwood